Supporting Information

C–H Acylation as an Enabling Tool to Tag Phenolic Drugs

*Carlota Girón-Elola and Arkaitz Correa**

University of the Basque Country (UPV/EHU), Department of Organic Chemistry I, Joxe Mari Korta R&D Center, Avda. Tolosa 72, 20018 Donostia-San Sebastián (Spain)

E-mail: arkaitz.correa@ehu.eus

1.-General Considerations

Reagents. Commercially available materials were used without further purification. Estrone was purchased from *Biosynth* and Estradiol from *Gletham Life Sciences*. Palladium acetate and T-Hydro (*tert*-butyl hydroperoxide solution, 70 wt % in water) were purchased from *Sigma-Aldrich*. Ethanol absolute was purchased from *VWR*. Most alcohols were commercially available and were used without further purification.

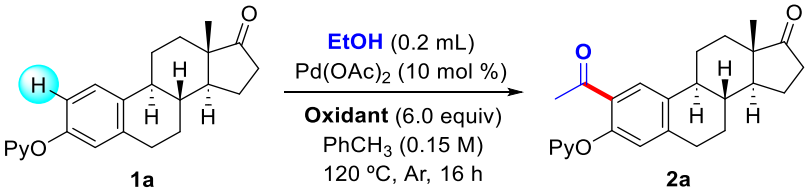
Analytical Methods. ^{1}H NMR and ^{13}C NMR spectra as well as HRMS and melting points (where applicable) are included for all new compounds. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 or 500 MHz unless otherwise indicated. The spectra of compounds housing a Pro unit were recorded in DMSO-d_6 at 80 ^{o}C. All ^{1}H NMR spectra are reported in parts per million (ppm) downfield of TMS and were measured relative to the signals for $CHCl_3$ (7.26 ppm), unless otherwise indicated. All ^{13}C NMR spectra were reported in ppm relative to residual $CHCl_3$ (77 ppm), unless otherwise indicated, and were obtained with ^{1}H decoupling. Coupling constants, *J*, are reported in Hertz. Melting points were measured using open glass capillaries in a Büchi SMP-20 apparatus. High resolution mass spectra (HRMS) were performed by SGIker and were acquired on a LC/Q-TOF mass spectrometer equipped with an electrospray source ESI Agilent Jet Stream. Flash chromatography was performed with EM Science silica gel 60 (230-400 mesh). The yields reported in the manuscript correspond to isolated yields and represent an average of at least two independent runs.

2.-Optimization Details

Pd-Catalyzed Acetylation of 1a with EtOH

A reaction tube containing a stirring bar was charged with the estrone derivative **1a** (0.15 mmol) and $Pd(OAc)_2$ (10 mol %). The reaction tube was then evacuated and back-filled with dry argon (this sequence was repeated up to three times). Then, a commercially available solution of *tert*-butyl hydroperoxide (70 wt % in water) (0.90 mmol), EtOH (3.75 mmol) and benzotrifluoride (1 mL) were added by syringe under argon atmosphere. The reaction tube was next warmed up to 120 °C in a heating block and stirred for 16 hours. The mixture was then allowed to warm to room temperature, evaporated under vacuum and the resulting crude was then purified by column chromatography to afford the corresponding product **2a**. The purity of **2a** was verified by ^{1}H NMR.

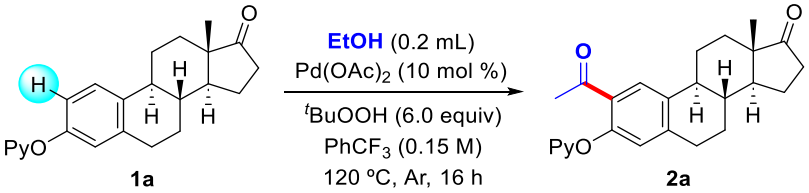
Table S1. Screening of oxidants for the acetylation of estrone derivative 1a[a]



Entry	Oxidant	2a (%)[b]
1	^{t}BuOOH (70% wt in H_2O)	45
2	Dicumyl peroxide (DCP)	0
3	Di-*tert*-butyl peroxide (DTBP)	0
4	Benzoyl peroxide	10
5	$K_2S_2O_8$	0

[a] Reaction conditions: **1a** (0.15 mmol), EtOH (3.75 mmol), $Pd(OAc)_2$ (10 mol %) and oxidant (6.0 equiv) in PhMe (1.0 mL) at 120 °C for 16 h under Ar. [b] Yield of isolated product after column chromatography.

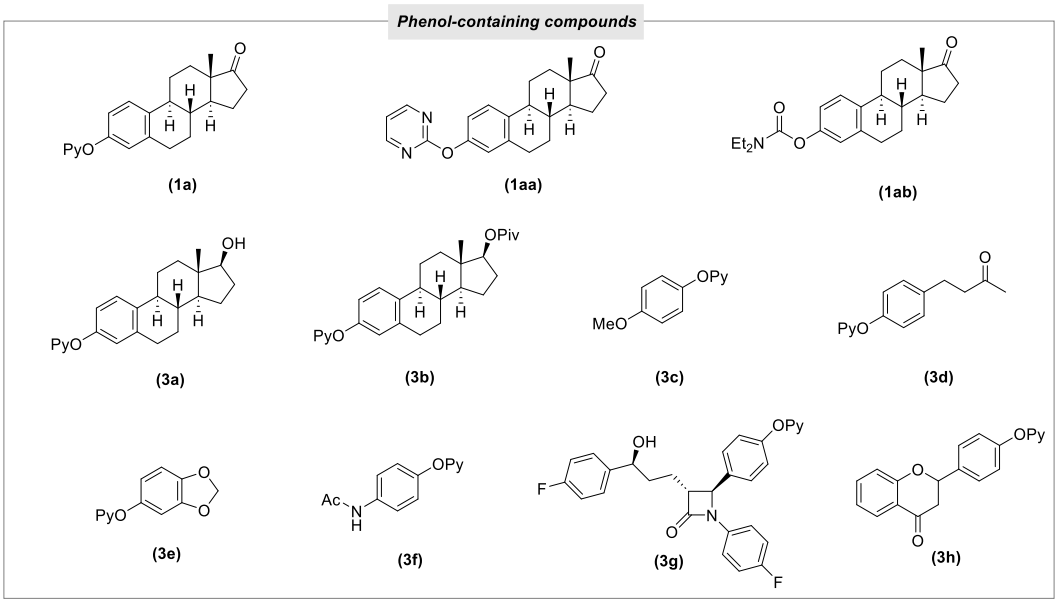
Table S2. Screening of acetylation of estrone derivative 1a[a]



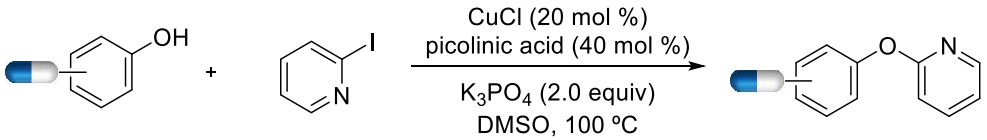
Entry	Variation from the standard conditions	2a (%)[b]
1	none	58 (46)[c]
2	Without $Pd(OAc)_2$	0
3	Without ^{t}BuOOH	0
4	Under air	31
5	EtOH (15 equiv)	27
6	EtOH (5 equiv)	traces
7	^{t}BuOOH (5.0 equiv)	36
8	$PdCl_2$ instead of $Pd(OAc)_2$	26
9	$PdCl_2(MeCN)$ instead of $Pd(OAc)_2$	26
10	$Pd(OPiv)_2$ instead of $Pd(OAc)_2$	43
11	$Pd(TFA)_2$ instead of $Pd(OAc)_2$	traces
12	$PdCl_2(PPh_3)_2$ instead of $Pd(OAc)_2$	traces
13	PheMe as solvent	45
14	PhCl as solvent	30[d]
15	*o*-xylene as solvent	traces
16	Mesitylene as solvent	11[d]
17	*tert*-Butylbenzene as solvent	51
18	Water as solvent	0
19	1,2-DCE as solvent	41[d]
20	HFIP as solvent	traces
21	Cumene as solvent	traces
22	1,4-dioxane as solvent	traces

[a] Reaction conditions: **7a** (0.15 mmol), EtOH (3.75 mmol), $Pd(OAc)_2$ (10 mol %) and T-Hydro (6.0 equiv) in $PhCF_3$ (1.0 mL) at 120 °C for 16 h under Ar. [b] Yield of isolated product after column chromatography. [c] Reaction performed with 1.44 mmol (0.5 g) of **1a**.[d] The yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard.

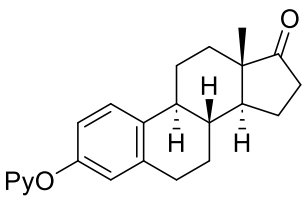
3.-Synthesis of the Starting Materials



General Procedure for the *O*-Arylation of Phenols[1]



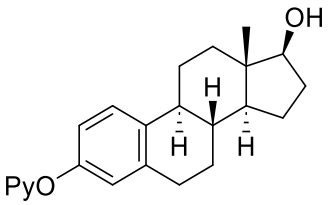
A round-bottom flask containing a stirring bar was charged with the corresponding phenol (1.0 equiv), CuCl (20 mol %), K_3PO_4 (2.0 equiv) and 2-picolinic acid (40 mol %). It was then evacuated and back-filled with dry Ar (this sequence was repeated up to three times). Then DMSO (2.5 mL/mmol of phenol) and 2-iodopyridine (2.0 equiv) were added under argon atmosphere. The reaction tube was next warmed up to 100 °C in a heating block and stirred for 16 h. After cooling down to room temperature, brine was added to the above solution, washed with a saturated aqueous solution of $NaHCO_3$, and extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$ and evaporated under vacuum. The resulting crude was then purified by column chromatography to afford the corresponding product.



(1a)

[1] Chu, J.-H.; Chen, S.-T.; Chiang, M.-F.; Wu, M.-J. *Organometallics* **2015**, *34*, 953–966.

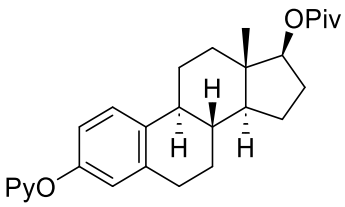
(8*R*,9*S*,13*S*,14*S*)-13-Methyl-3-(pyridin-2-yloxy)-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (1a). Following the general procedure, using commercially available estrone (14.79 mmol, 4.00 g) provided 3.03 g (59% yield) of **1a** as a white solid.[2] Mp 137-138 °C. Column chromatography (Hex/EtOAc 7:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (ddd, *J* = 5.0, 2.1, 0.8 Hz, 1H), 7.66 (ddd, *J* = 8.3, 7.2, 2.0 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 6.96 (ddd, *J* = 7.2, 5.0, 0.9 Hz, 1H), 6.94 – 6.85 (m, 3H), 2.95 – 2.84 (m, 2H), 2.50 (dd, *J* = 18.9, 8.7 Hz, 1H), 2.45 – 2.37 (m, 1H), 2.30 (td, *J* = 10.8, 4.0 Hz, 1H), 2.21 – 1.92 (m, 4H), 1.69 – 1.39 (m, 6H), 0.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.6, 163.7, 151.7, 147.5, 139.1, 137.9, 135.9, 126.4, 121.0, 118.4, 118.0, 111.3, 50.2, 47.7, 44.0, 37.8, 35.6, 31.4, 29.3, 26.2, 25.5, 21.4, 13.6. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{23}H_{25}NO_2$): 347.1885, *found* 347.1885.



(3a)

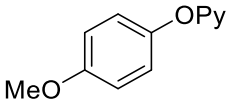
(8*R*,9*S*,13*S*,14*S*,17*S*)-13-Methyl-3-(pyridin-2-yloxy)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-ol (3a). Following the general procedure, using commercially available estradiol (3.67 mmol, 1.00 g) provided 1.02 g (80% yield) of **3a** as a white-yellowish solid.[3] Mp 57-60 °C, (Lit.[3] 203-204 °C). Column chromatography (Hex/EtOAc 7:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (ddd, *J* = 5.0, 2.0, 0.8 Hz, 1H), 7.66 (ddd, *J* = 8.3, 7.2, 2.0 Hz, 1H), 7.31 (dd, *J* = 8.5, 1.1 Hz, 1H), 6.97 (ddd, *J* = 7.2, 5.0, 1.0 Hz, 1H), 6.93 – 6.87 (m, 2H), 6.85 (d, *J* = 2.6 Hz, 1H), 3.73 (dd, *J* = 9.0, 8.0 Hz, 1H), 2.87 (td, *J* = 7.0, 1.9 Hz, 2H), 2.34 (dtd, *J* = 13.4, 4.2, 2.7 Hz, 1H), 2.24 (td, *J* = 11.1, 4.3 Hz, 1H), 2.12 (dtd, *J* = 12.9, 9.3, 5.5 Hz, 1H), 1.96 (ddd, *J* = 12.7, 3.9, 2.7 Hz, 1H), 1.88 (ddt, *J* = 12.7, 5.7, 2.8 Hz, 1H), 1.71 (dddd, *J* = 12.4, 9.8, 7.0, 3.1 Hz, 1H), 1.61 – 1.16 (m, 7H), 0.79 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 151.9, 147.8, 139.5, 138.6, 136.9, 126.7, 121.3, 118.5, 118.3, 111.6, 82.0, 50.2, 44.3, 43.4, 38.7, 36.8, 30.7, 29.8, 27.3, 26.3, 23.3, 11.2. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{23}H_{27}NO_2$): 349.2042, *found* 349.2040.

[2] Chen, X.; Xiao, X.; Sun, H.; Li, Y.; Cao, H.; Zhang, X.; Yang, S.; Lian, Z. *Org. Lett.* **2019**, *21*, 8879–8883.
[3] Sun, M.-R.; Kang, Y.-Y.; Duan, Y.-T.; Liu, H.-M. *Steroids* **2020**, *162*, 108697–108697.



(3b)

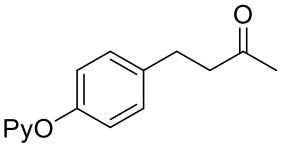
(8*R*,9*S*,13*S*,14*S*,17*S*)-13-Methyl-3-(pyridin-2-yloxy)-7,8,9,11,12,13,14,15,16,17-deca-hydro-6*H*-cyclopenta[*a*]phenanthren-17-yl pivalate (3b). To a solution of the estradiol derivative **3a** (0.48 mmol, 167 mg) and DMAP (0.1 mmol, 12 mg) in CH_2Cl_2 (1.5 mL), at 0 °C, Et_3N (0.72 mmol, 0.1 mL) and pivaloyl chloride (0.72 mmol, 0.09 mL) were carefully added. The resulting mixture was allowed to warm up to room temperature and stirred for 48 h. The reaction was washed with H_2O (5 mL) and extracted with dichloromethane (3 x 5 mL). The organic layers were combined, dried over $MgSO_4$ and evaporated under vacuum. The resulting crude was then purified by column chromatography (Hex/EtOAc 9:1) to afford 112 mg (54% yield) of **3b** as a white solid. Mp 123-124 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (ddd, *J* = 5.0, 2.1, 0.8 Hz, 1H), 7.66 (ddd, *J* = 8.2, 7.2, 2.0 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 6.96 (ddd, *J* = 7.1, 5.0, 1.0 Hz, 1H), 6.92 – 6.87 (m, 2H), 6.85 (d, *J* = 2.5 Hz, 1H), 4.67 (dd, *J* = 9.2, 7.5 Hz, 1H), 2.93 – 2.81 (m, 2H), 2.36 – 2.14 (m, 3H), 1.92-1.85 (m, 2H), 1.80-1.72 (m, 1H), 1.60 – 1.25 (m, 7H), 1.21 (s, 9H), 0.86 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.7, 164.1, 151.8, 147.7, 139.6, 138.5, 136.8, 126.8, 121.3, 118.5, 118.3, 111.6, 82.4, 50.0, 44.2, 43.2, 39.0, 38.4, 37.1, 29.7, 27.7, 27.4, 27.2, 26.2, 23.5, 12.2. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{28}H_{35}NO_3$): 433.2617, *found* 433.2630.



(3c)

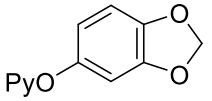
2-(4-Methoxyphenoxy)pyridine (3c). Following the general procedure, using 4-methoxyphenol (16.11 mmol, 2.00 g) provided 2.57 g (79% yield) of **3c** as a white solid.[4] Mp 42-45 °C, (Lit.[4] 42-44 °C). Column chromatography (Hex/EtOAc 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (ddd, *J* = 5.0, 2.0, 0.8 Hz, 1H), 7.64 (ddd, *J* = 8.3, 7.2, 2.0 Hz, 1H), 7.10 – 7.05 (m, 2H), 6.97 – 6.90 (m, 3H), 6.86 (dt, *J* = 8.4, 0.9 Hz, 1H), 3.81 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 156.6, 147.7, 147.4, 139.4, 122.4, 118.1, 114.8, 111.1, 55.6. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{12}H_{11}NO_2$): 201.0790, *found* 201.0784.

[4] Yao, J.; Feng, R.; Wu, Z.; Liu, Z.; Zhang, Y. *Adv. Synth. Catal.* **2013**, *355*, 1517–1522.



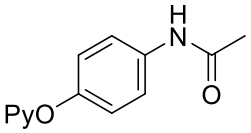
(3d)

4-[4-(Pyridin-2-yloxy)phenyl]butan-2-one (3d). Following the general procedure, using 4-(4-hydroxyphenyl)butan-2-one (6.09 mmol, 1.00 g) provided 761 mg (52% yield) of **3d** as a yellow oil. Column chromatography (Hex/EtOAc 7:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 1H), 7.69 – 7.60 (m, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 8.5 Hz, 2H), 6.96 (ddd, *J* = 7.1, 5.0, 1.0 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 2.89 (t, *J* = 7.6 Hz, 2H), 2.80 – 2.72 (m, 2H), 2.14 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.9, 163.9, 152.4, 147.8, 139.4, 137.3, 129.6, 121.3, 118.4, 111.5, 45.2, 30.2, 29.1. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{15}H_{15}NO_2$): 241.1103, *found* 241.1093.



(3e)

2-(Benzo[*d*][1,3]dioxol-5-yloxy)pyridine (3e). Following the general procedure, using sesamol (3.62 mmol, 500 mg) provided 609 mg (78% yield) of **3e** as a white solid.[5] Mp 38-39 °C, (Lit.[5] 53 °C). Column chromatography (Hex/EtOAc 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (ddd, *J* = 5.0, 2.0, 0.8 Hz, 1H), 7.64 (ddd, *J* = 8.3, 7.2, 2.1 Hz, 1H), 6.95 (ddd, *J* = 7.2, 5.0, 0.9 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 6.66 (d, *J* = 2.3 Hz, 1H), 6.59 (dd, *J* = 8.3, 2.3 Hz, 1H), 5.96 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 148.7, 148.6, 148.0, 145.0, 139.7, 118.6, 114.1, 111.5, 108.6, 104.1, 101.9. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{12}H_9NO_3$): 215.0582, *found* 215.0576.

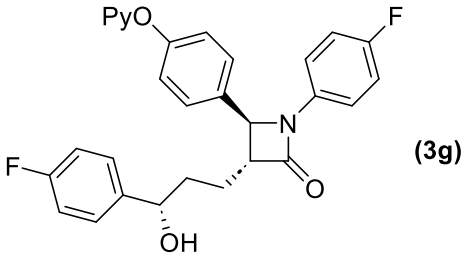


(3f)

***N*-[4-(Pyridin-2-yloxy)phenyl]acetamide (3f)**. Following the general procedure, using acetaminophen (6.62 mmol, 1.00 g) provided 700 mg (46% yield) of **3f** as a white solid. Mp 135-136 °C. Column chromatography (Hex/EtOAc 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 5.0, 1.9 Hz, 1H), 8.06 (s, 1H), 7.71 – 7.62 (m, 1H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 8.5 Hz, 2H), 6.98 (dd, *J* = 7.2, 5.0 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H),

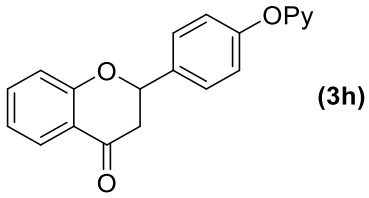
[5] Kinuta, H.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2015**, *137*, 1593–1600.

2.11 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 164.0, 150.3, 147.6, 139.7, 135.0, 121.7, 121.6, 118.6, 111.6, 24.5. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{13}H_{12}N_2O_2$): 228.0899, *found* 228.0897.



(3g)

(3*R*,4*S*)-1-(4-Fluorophenyl)-3-[(*S*)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[4-(pyridin-2-yloxy)phenyl]azetidin-2-one (3g). Following the general procedure, using ezetimibe (3.66 mmol, 1.50 g) provided 980 mg (55% yield) of **3g** as a white solid. Mp 168-171 °C. Column chromatography (Hex/EtOAc 7:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (ddd, *J* = 5.0, 2.0, 0.8 Hz, 1H), 7.68 (ddd, *J* = 8.4, 7.3, 2.1 Hz, 1H), 7.47 (d, *J* = 8.6 Hz, 2H), 7.40 (dd, *J* = 8.5, 5.6 Hz, 2H), 7.24 – 7.17 (m, 2H), 7.09 (d, *J* = 8.6 Hz, 2H), 7.07 – 6.99 (m, 3H), 6.95 – 6.84 (m, 3H), 6.79 (s, 1H), 4.79 (d, *J* = 9.1 Hz, 1H), 4.66 (dd, *J* = 11.4, 2.3 Hz, 1H), 2.50 – 2.33 (m, 2H), 2.27 – 2.18 (m, 1H), 2.11 – 2.02 (m, 1H), 1.76 – 1.65 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 162.3 (d, J_{C-F} = 246.4 Hz), 162.1 (d, J_{C-F} = 246.4 Hz), 158.4, 153.5, 146.6, 140.7, 138.4, 138.1, 133.4, 128.2, 127.6 (d, J_{C-F} = 8.1 Hz), 122.7 (d, J_{C-F} = 8.1 Hz), 121.5, 118.8, 115.5 (d, J_{C-F} = 22.2 Hz), 115.3 (d, J_{C-F} = 21.2 Hz), 112.1, 81.5, 79.3, 53.2, 32.7, 27.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.13, -117.77. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{29}H_{24}F_2N_2O_3$): 486.1755, *found* 486.1755.

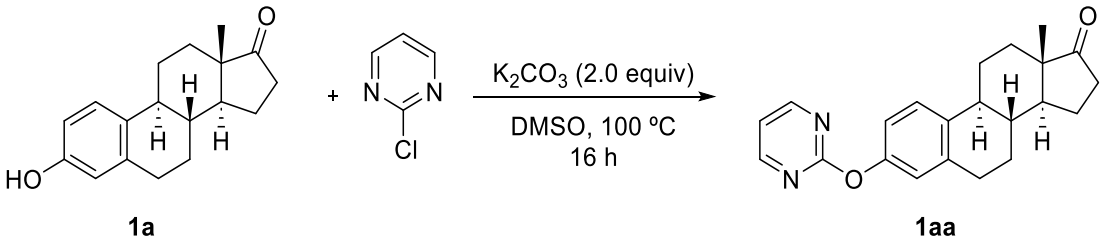


(3h)

2-[4-(Pyridin-2-yloxy)phenyl]chroman-4-one (3h). Following the general procedure, using 4'-hydroxyflavanone (2.08 mmol, 500 mg) provided 138 mg (21% yield) of **3h** as a yellow oil. Column chromatography (Hex/EtOAc 7:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, *J* = 5.2, 2.0 Hz, 1H), 7.94 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.72 (ddd, *J* = 8.3, 7.2, 2.0 Hz, 1H), 7.55 – 7.48 (m, 3H), 7.21 (d, *J* = 8.6 Hz, 2H), 7.10 – 7.01 (m, 3H), 6.96 (d, *J* = 8.3 Hz, 1H), 5.50 (dd, *J* = 13.3, 2.9 Hz, 1H), 3.11 (dd, *J* = 16.9, 13.3 Hz, 1H), 2.92 (dd, *J*

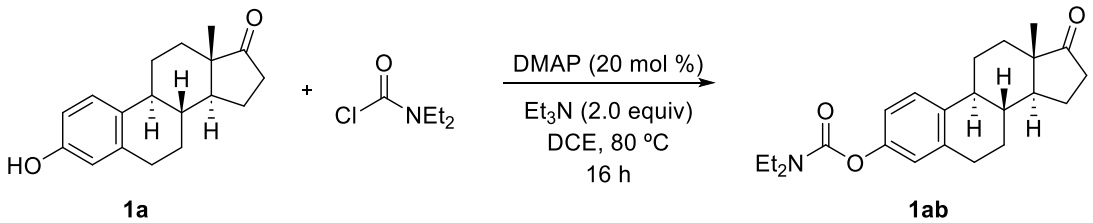
= 16.8, 2.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.4, 163.7, 162.0 154.8, 147.8, 140.4, 136.7, 135.4, 128.2, 127.5, 122.1, 121.9, 121.4, 119.2, 118.6, 112.3, 79.6, 45.1. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{20}H_{15}NO_3$): 317.1052, *found* 317.1051.

Installation of other Directing Groups



1a **1aa**

(8*R*,*9S*,13*S*,*14S*)-13-Methyl-3-(pyrimidin-2-yloxy)-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (1aa). A round-bottom flask containing a stirring bar was charged with estrone (7.40 mmol, 2.00 g), 2-chloropyrimidine (7.40 mmol, 848 mg), and potassium carbonate (14.80 mmol, 2.05 g). Then, dry DMSO (4.5 mL) was added and the reaction was next warmed up to 100 °C and stirred for 16 h. After cooling down to room temperature, the solution was quenched with a saturated solution of NaCl and extracted with EtOAc (3 x 20 mL). The organic layers were combined, dried over $MgSO_4$ and the solvent was evaporated under vacuum. The resulting crude was purified by column chromatography (Hex/EtOAc 1:1) to afford 1.80 g (70% yield) of **1aa** as a white solid. Mp 175-178 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 4.8 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.01 (t, *J* = 4.8 Hz, 1H), 6.95 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.91 (d, *J* = 2.5 Hz, 1H), 2.96 – 2.88 (m, 2H), 2.49 (dd, *J* = 18.7, 8.6 Hz, 1H), 2.44 – 2.36 (m, 1H), 2.30 (td, *J* = 10.9, 4.2 Hz, 1H), 2.18 – 1.92 (m, 4H), 1.68 – 1.39 (m, 6H), 0.90 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 221.1, 165.9, 160.1, 151.1, 138.6, 137.3, 127.0, 121.9, 119.2, 116.4, 50.8, 48.3, 44.6, 38.3, 36.2, 31.9, 29.8, 26.7, 26.0, 22.0, 14.2. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{22}H_{24}N_2O_2$): 348.1838, *found* 348.1823.



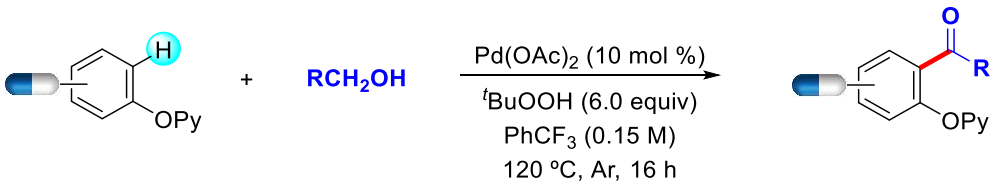
1a **1ab**

(8*R*,9*S*,13*S*,14*S*)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl diethylcarbamate (1ab). A round-bottom flask containing a stirring bar was charged with estrone (7.40 mmol, 2.00 g) and DMAP (1.48 mmol, 181 mg). Then, DCE (22 mL), Et_3N (14.80 mmol, 2.08 mL) and diethylcarbamoyl chloride (11.10 mmol, 1.41 mL) were added by syringe. The reaction mixture was next warmed up to 80 °C and stirred for 16 h. After cooling down to room temperature, the solution was washed with an aqueous solution of HCl 1M and extracted with dichloromethane (3 x 20 mL). The organic layers were combined, dried over $MgSO_4$ and evaporated under vacuum. The resulting crude was triturated with Et_2O to afford 2.12 g (78% yield) of **1ab** as a white solid.[6] Mp 195-196 °C, (Lit. 194.8-195.6 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.4 Hz, 1H), 6.90 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.87 (d, *J* = 2.5 Hz, 1H), 3.42 (q, *J* = 7.6 Hz, 4H), 2.92 (dd, *J* = 8.5, 3.8 Hz, 2H), 2.52 (dd, *J* = 18.8, 8.6 Hz, 1H), 2.46 – 2.38 (m, 1H), 2.30 (td, *J* = 10.6, 4.2 Hz, 1H), 2.21 – 1.94 (m, 4H), 1.68 – 1.39 (m, 6H), 1.31 – 1.16 (m, 6H), 0.92 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 221.0, 154.6, 149.5, 137.8, 136.6, 126.3, 121.9, 119.1, 50.5, 48.1, 44.2, 42.3, 41.9, 38.2, 36.0, 31.6, 29.5, 26.5, 25.9, 21.7, 14.3, 13.9, 13.5. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{23}H_{31}NO_3$): 369.2304, *found* 369.2295.

[6] Bedford, R. B.; Brenner, P. J.; Durrant, S. F.; Gallagher, T.; Méndez-Gálvez, C.; Montgomery, M. *J. Org. Chem.* **2016**, *81*, 3473–3478.

4.- Pd-Catalyzed C(sp^2)–H Acylation of Phenol-Containing Drugs

4.1.- Using Alcohols as Acylating Agents

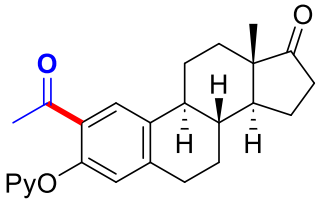


General Procedure A (Acetylation): A reaction tube containing a stirring bar was charged with the corresponding phenol derivative (0.15 mmol) and $Pd(OAc)_2$ (10 mol %). The reaction tube was then evacuated and back-filled with dry argon (this sequence was repeated up to three times). Then, a commercially available solution of *tert*-butyl hydroperoxide (70 wt % in water) (0.90 mmol), **EtOH** (3.75 mmol) and benzotrifluoride (1 mL) were added by syringe under argon atmosphere. The reaction tube was next warmed up to 120 °C in a heating block and stirred for 16 hours. The mixture was then allowed to warm to room temperature, evaporated under vacuum and the resulting crude was then purified by column chromatography to afford the corresponding product.

General Procedure B: A reaction tube containing a stirring bar was charged with the corresponding phenol derivative (0.15 mmol) and $Pd(OAc)_2$ (10 mol %). The reaction tube was then evacuated and back-filled with dry argon (this sequence was repeated up to three times). Then, a commercially available solution of *tert*-butyl hydroperoxide (70 wt % in water) (0.90 mmol), the corresponding ***aliphatic alcohol*** (0.75 mmol) and benzotrifluoride (1 mL) were added by syringe under argon atmosphere. The reaction tube was next warmed up to 120 °C in a heating block and stirred for 16 hours. The mixture was then allowed to warm to room temperature, evaporated under vacuum and the resulting crude was then purified by column chromatography to afford the corresponding product.

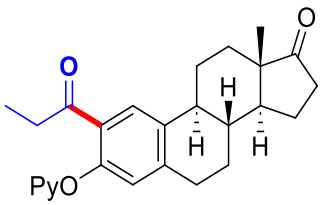
General Procedure C: A reaction tube containing a stirring bar was charged with the corresponding phenol derivative (0.15 mmol) and $Pd(OAc)_2$ (10 mol %). The reaction tube was then evacuated and back-filled with dry argon (this sequence was repeated up to three times). Then, a commercially available solution of *tert*-butyl hydroperoxide (70 wt % in water) (0.90 mmol), the corresponding ***benzyl alcohol*** (0.45 mmol) and benzotrifluoride (1 mL) were added by syringe under argon atmosphere. The reaction

tube was next warmed up to 120 °C in a heating block and stirred for 16 hours. The mixture was then allowed to warm to room temperature, evaporated under vacuum and the resulting crude was then purified by column chromatography to afford the corresponding product.



(2a)

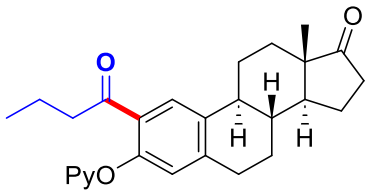
(8*R*,9*S*,13*S*,14*S*)-2-Acetyl-13-methyl-3-(pyridin-2-yloxy)-6,7,8,9,11,12,13,14,15,16-deca-hydro-17*H*-cyclopenta[*a*]phenanthren-17-one (2a). Following the general procedure A, using estrone derivative **1a** (0.15 mmol, 52 mg) and EtOH (3.75 mmol, 0.22 mL) provided 34 mg (58% yield) of **2a** as a white-yellowish solid. Mp 160-162 °C. Column chromatography (Hex/EtOAc 7:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 5.1, 2.0 Hz, 1H), 7.79 (s, 1H), 7.71 (ddd, *J* = 8.3, 7.2, 2.0 Hz, 1H), 7.00 (ddd, *J* = 7.2, 5.0, 0.9 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 1H), 6.82 (s, 1H), 2.90 (dd, *J* = 8.7, 4.0 Hz, 2H), 2.53 – 2.45 (m, 5H), 2.28 (td, *J* = 10.8, 4.4 Hz, 1H), 2.19 – 1.93 (m, 4H), 1.68 – 1.38 (m, 6H), 0.90 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.6, 198.2, 163.4, 150.9, 147.9, 143.4, 139.8, 136.9, 129.2, 127.5, 122.9, 118.8, 111.8, 50.4, 48.0, 44.1, 37.9, 35.9, 31.5, 30.8, 29.5, 26.2, 25.7, 21.6, 13.9. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{25}H_{27}NO_3$): 389.1991, *found* 389.1993. *This reaction was also performed in a **higher scale**: the use of the estrone derivative **1a** (1.44 mmol, 0.5 g), EtOH (36.00 mmol, 2.1 mL) and T-Hydro (8.64 mmol, 1.2 mL) in benzotrifluoride (9.6 mL) provided 260 mg (46% yield) of **2a** as a white-yellowish solid.*



(2b)

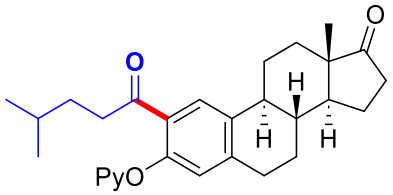
(8*R*,9*S*,13*S*,14*S*)-13-Methyl-2-propionyl-3-(pyridin-2-yloxy)-6,7,8,9,11,12,13,14,15,16-deca-hydro-17*H*-cyclopenta[*a*]phenanthren-17-one (2b). Following the general procedure B, using estrone derivative **1a** (0.15 mmol, 52 mg) and *n*-PrOH (0.75 mmol, 56 µL) provided 33 mg (55% yield) of **2b** as a white solid. Mp 146-148 °C. Column chromatography (Hex/EtOAc 7:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 5.0 Hz, 1H), 7.75 (s, 1H), 7.74 – 7.68 (m, 1H), 7.00 (dd, *J* = 7.2, 5.1 Hz, 1H), 6.96

(d, *J* = 8.2 Hz, 1H), 6.83 (s, 1H), 2.96 – 2.81 (m, 4H), 2.55 – 2.45 (m, 2H), 2.30 (td, *J* = 11.0, 4.3 Hz, 1H), 2.21 – 1.93 (m, 4H), 1.72 – 1.40 (m, 6H), 1.05 (t, *J* = 7.2 Hz, 3H), 0.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.7, 201.8, 163.5, 150.5, 147.9, 142.8, 139.8, 136.9, 127.4, 122.9, 120.1, 118.8, 111.8, 50.5, 48.0, 44.2, 38.0, 36.0, 31.6, 29.5, 26.3, 25.8, 21.7, 13.9, 8.4. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{26}H_{29}NO_3$): 403.2147, *found* 403.2139.



(2c)

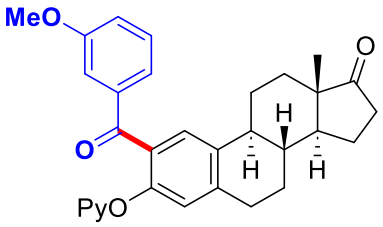
(8*R*,9*S*,13*S*,14*S*)-2-Butyryl-13-methyl-3-(pyridin-2-yloxy)-6,7,8,9,11,12,13,14,15,16-deca-hydro -17*H*-cyclopenta[*a*]phenanthren-17-one (2c). Following the general procedure B, using estrone derivative **1a** (0.15 mmol, 52 mg) and *n*-BuOH (0.75 mmol, 69 µL) provided 35 mg (55% yield) of **2c** as a white-yellowish solid. Mp 114-118 °C. Column chromatography (Hex/EtOAc 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 5.2, 2.0 Hz, 1H), 7.74 – 7.65 (m, 2H), 6.99 (ddd, *J* = 7.2, 5.0, 0.9 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 6.83 (s, 1H), 2.96 – 2.87 (m, 2H), 2.80 (t, *J* = 7.2 Hz, 2H), 2.55 – 2.44 (m, 2H), 2.29 (td, *J* = 11.0, 4.3 Hz, 1H), 2.20 – 1.94 (m, 4H), 1.68 – 1.38 (m, 8H), 0.90 (s, 3H), 0.81 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.6, 201.3, 163.4, 150.3, 147.8, 142.6, 139.7, 136.8, 129.6, 127.2, 122.8, 118.6, 111.6, 50.4, 47.9, 44.5, 44.0, 37.9, 35.8, 31.5, 29.4, 26.9, 25.7, 21.6, 17.7, 13.8, 13.8. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{27}H_{31}NO_3$): 417.2304, *found* 417.2299.



(2d)

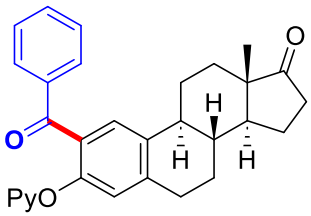
(8*R*,9*S*,13*S*,*14S*)-13-Methyl-2-(4-methylpentanoyl)-3-(pyridin-2-yloxy)-6,7,8,9,11,12,13,14, 15,16-decahydro-*17H*-cyclopenta[*a*]phenanthren-17-one (2d). Following the general procedure B, using estrone derivative **1a** (0.15 mmol, 52 mg) and 4-methylpentan-1-ol (0.75 mmol, 93 µL) provided 40 mg (60% yield) of **2d** as a yellow oil. Column chromatography (Hex/EtOAc 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 5.2, 2.0 Hz, 1H), 7.75 – 7.65 (m, 2H), 7.02 – 6.97 (m, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.83 (s, 1H), 2.91 (dd, *J* = 9.1, 4.3 Hz, 2H), 2.81 (t, *J* = 7.2 Hz, 2H), 2.55 – 2.44 (m, 2H), 2.30 (td, *J* = 11.0, 4.3 Hz, 1H), 2.20 – 1.94 (m, 4H), 1.69 – 1.38 (m, 9H), 0.91 (s, 3H),

0.77 (d, J = 6.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 221.0, 202.1, 163.8, 150.6, 148.2, 143.0, 140.1, 137.2, 130.0, 127.7, 123.2, 119.0, 112.1, 50.8, 48.3, 44.5, 41.2, 38.3, 36.2, 33.4, 31.9, 29.8, 28.2, 26.6, 26.1, 22.7, 22.0, 14.2. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{29}H_{35}NO_3$): 445.2617, *found* 445.2617.



(2e)

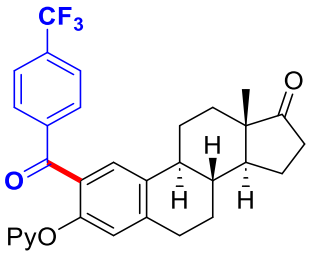
(8*R*,9*S*,13*S*,14*S*)-2-(3-Methoxybenzoyl)-13-methyl-3-(pyridin-2-yloxy)-6,7,8,9,11,12,13,14, 15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (2e). Following the general procedure C, using estrone derivative **1a** (0.15 mmol, 52 mg) and (3-methoxyphenyl)methanol (0.45 mmol, 60 µL) provided 37 mg (51% yield) of **2e** as a yellow solid. Mp 85-88 °C. Column chromatography (Hex/EtOAc 7:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 8.02 (m, 1H), 7.57 – 7.49 (m, 2H), 7.32 – 7.19 (m, 3H), 7.06 – 6.98 (m, 2H), 6.89 (dd, J = 7.2, 5.0 Hz, 1H), 6.61 (d, J = 8.3 Hz, 1H), 3.79 (s, 3H), 3.01 (dd, J = 8.9, 4.3 Hz, 2H), 2.54 (dd, J = 18.8, 8.7 Hz, 1H), 2.43 – 2.30 (m, 2H), 2.23 – 2.02 (m, 3H), 1.97 (dt, J = 12.8, 2.6 Hz, 1H), 1.75 – 1.45 (m, 6H), 0.95 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.8, 195.1, 163.2, 159.5, 149.5, 146.9, 142.0, 139.6, 139.4, 136.7, 129.6, 129.0, 127.9, 123.0, 122.9, 119.6, 118.4, 113.3, 111.7, 55.5, 50.6, 48.1, 44.2, 38.1, 36.0, 31.6, 29.7, 26.4, 25.8, 21.7, 14.0. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{31}H_{31}NO_4$): 481.2253, *found* 481.2257.



(2f)

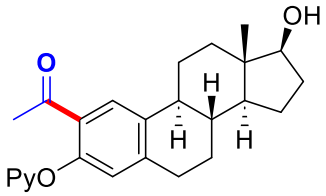
(*8R*,9*S*,13*S*,14*S*)-2-Benzoyl-13-methyl-3-(pyridin-2-yloxy)-6,7,8,9,11,12,13,14,15,16-deca-hydro-17*H*-cyclopenta[*a*]phenanthren-17-one (2f). Following the general procedure C, using estrone derivative **1a** (0.15 mmol, 52 mg) and benzyl alcohol (0.45 mmol, 46 µL) provided 44 mg (65% yield) of **2f** as a white solid. Mp 70-74 °C. Column chromatography (Hex/EtOAc 7:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (ddd, J = 5.1, 2.1, 0.8 Hz, 1H), 7.72 – 7.68 (m, 2H), 7.52 – 7.42 (m, 3H), 7.34 – 7.27 (m, 2H), 6.98 (s, 1H),

6.85 (ddd, *J* = 7.2, 5.0, 1.0 Hz, 1H), 6.53 (dt, *J* = 8.2, 0.9 Hz, 1H), 2.99 (dd, *J* = 9.0, 4.3 Hz, 2H), 2.52 (dd, *J* = 18.7, 8.7 Hz, 1H), 2.42 – 2.31 (m, 2H), 2.24 – 2.02 (m, 3H), 1.95 (dt, *J* = 12.9, 2.5 Hz, 1H), 1.74 – 1.41 (m, 5H), 1.25 (s, 1H), 0.93 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.8, 195.4, 163.2, 149.6, 147.0, 141.9, 139.5, 138.0, 136.7, 132.7, 129.8, 129.6, 128.1, 127.9, 122.8, 118.4, 111.5, 50.6, 48.1, 44.2, 38.1, 36.0, 31.6, 29.7, 26.4, 25.8, 21.7, 14.0. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{30}H_{29}NO_3$): 451.2147, *found* 451.2141.



(2g)

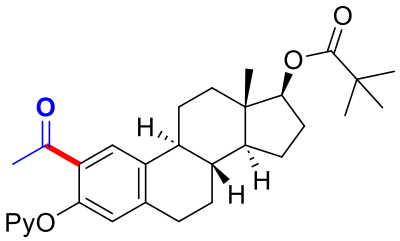
(8*R*,9*S*,13S,14*S*)-13-methyl-3-(pyridin-2-yloxy)-2-[4-(trifluoromethyl)benzoyl]-6,7,8,9,11, 12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (2g). Following the general procedure C, using estrone derivative **1a** (0.15 mmol, 52 mg) and 4-(trifluoromethyl)benzyl alcohol (0.45 mmol, 62 µL) provided 31 mg (40% yield) of **2g** as a yellow solid. Mp 160-163 °C. Column chromatography (Hex/EtOAc 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.95 (m, 1H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.57 – 7.50 (m, 3H), 7.46 (ddd, *J* = 8.3, 7.2, 2.0 Hz, 1H), 6.99 (s, 1H), 6.86 (ddd, *J* = 7.2, 5.0, 1.0 Hz, 1H), 6.45 (dd, *J* = 8.4, 1.0 Hz, 1H), 3.05 – 2.94 (m, 2H), 2.52 (dd, *J* = 18.7, 8.7 Hz, 1H), 2.44 – 2.29 (m, 2H), 2.27 – 2.02 (m, 3H), 2.01 – 1.87 (m, 1H), 1.75 – 1.43 (m, 6H), 0.93 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6 at 80 °C) δ 218.2, 193.1, 162.0, 148.9, 146.3, 142.0, 139.2, 136.2, 131.7 (q, $J_{C\text{-}F}$ = 31.5 Hz), 129.1, 129.0, 126.2, 124.5 (q, $J_{C\text{-}F}$ = 3.8 Hz), 123.3 (q, $J_{C\text{-}F}$ = 273.4 Hz), 122.2, 122.0, 118.3, 110.4, 49.4, 46.8, 42.9, 37.1, 34.8, 30.9, 28.4, 25.1, 24.8, 20.6, 13.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.02. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{31}H_{28}F_3NO_3$): 519.2021, *found* 519.2013.



(4a)

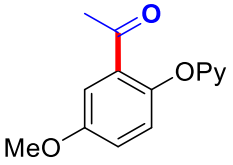
1-[(8*R*,9*S*,13*S*,14*S*,17*S*)-17-Hydroxy-13-methyl-3-(pyridin-2-yloxy)-7,8,9,11,12,13,14,15,16, 17-decahydro-6*H*-cyclopenta[*a*]phenanthren-2-yl]ethan-1-one (4a). Following the general procedure A, using the estradiol derivative (0.15 mmol,

52 mg) and EtOH (3.75 mmol, 0.22 mL) provided 28 mg (47% yield) of **4a** as a white-yellowish solid. Mp 120-123 °C. Column chromatography (Hex/EtOAc 6:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 – 8.14 (m, 1H), 7.81 (s, 1H), 7.75 – 7.66 (m, 1H), 7.00 (dd, *J* = 7.2, 5.0 Hz, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 6.81 (s, 1H), 3.74 (t, *J* = 8.5 Hz, 1H), 2.86 (dd, *J* = 8.8, 4.3 Hz, 2H), 2.54 – 2.37 (m, 4H), 2.32 – 1.95 (m, 4H), 1.93 – 1.84 (m, 1H), 1.74 – 1.14 (m, 7H), 0.78 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.5, 163.4, 150.8, 147.9, 143.8, 139.9, 137.6, 127.6, 122.8, 121.1, 118.8, 111.8, 81.9, 50.2, 44.2, 43.3, 38.5, 36.7, 30.9, 30.6, 29.7, 27.0, 26.2, 23.2, 11.2. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{25}H_{29}NO_3$): 391.2147, *found* 391.2135.



(4b)

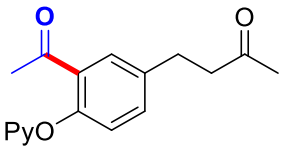
(8*R*,9*S*,13*S*,14*S*,17*S*)-2-Acetyl-13-methyl-3-(pyridin-2-yloxy)-7,8,9,11,12,13,14,15,16,17-de-cahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl pivalate (4b). Following the general procedure A, using protected estradiol derivative **3b** (0.15 mmol, 65 mg) and EtOH (3.75 mmol, 0.22 mL) provided 43 mg (61% yield) of **4b** as a white solid. Mp 160-163 °C. Column chromatography (Hex/EtOAc 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 5.3, 2.1 Hz, 1H), 7.79 (s, 1H), 7.71 (ddd, *J* = 8.2, 7.1, 2.0 Hz, 1H), 7.04 – 6.97 (m, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 6.81 (s, 1H), 4.66 (dd, *J* = 9.2, 7.5 Hz, 1H), 2.87 (dd, *J* = 8.9, 4.3 Hz, 2H), 2.48 (s, 3H), 2.42 – 2.36 (m, 1H), 2.28 – 2.16 (m, 2H), 1.92 – 1.86 (m, 2H), 1.80 – 1.67 (m, 1H), 1.61 – 1.24 (m, 7H), 1.22 (s, 9H), 0.85 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.4, 178.7, 163.4, 150.8, 147.9, 143.7, 139.9, 137.5, 127.6, 122.8, 121.0, 118.8, 111.8, 82.3, 49.9, 47.4, 44.0, 43.1, 38.2, 36.9, 30.9, 29.7, 27.7, 27.4, 27.0, 26.1, 23.4, 12.2. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{30}H_{37}NO_4$): 475.2523, *found* 475.2737.



(4c)

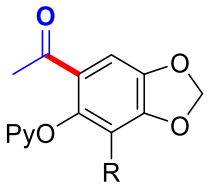
1-[5-Methoxy-2-(pyridin-2-yloxy)phenyl]ethan-1-one (4c). Following the general procedure A, using 2-(4-methoxyphenoxy)pyridine **(3c)** (0.15 mmol, 30 mg) and EtOH

(3.75 mmol, 0.22 mL) provided 28 mg (76% yield) of **4c** as a yellow solid *after 24 h of reaction*.[7] Mp 43-44 °C. Column chromatography (Hex/EtOAc 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 4.8 Hz, 1H), 7.74 – 7.65 (m, 1H), 7.35 (d, *J* = 2.8 Hz, 1H), 7.11 – 7.03 (m, 2H), 7.02 – 6.97 (m, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 3.84 (s, 3H), 2.49 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.2, 163.6, 156.6, 147.9, 146.6, 139.8, 132.4, 124.5, 120.4, 118.8, 113.3, 111.4, 55.8, 30.9. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{14}H_{13}NO_3$): 243.0895, *found* 243.0896.



(4d)

4-[3-Acetyl-4-(pyridin-2-yloxy)phenyl]butan-2-one (4d). Following the general procedure A, using 4-[4-(pyridin-2-yloxy)phenyl]butan-2-one **(3d)** (0.15 mmol, 36 mg) and EtOH (3.75 mmol, 0.22 mL) provided 22 mg (52% yield) of **4d** as a light brown solid. Mp 61-65 °C. Column chromatography (Hex/EtOAc 6:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 4.9 Hz, 1H), 7.75 – 7.68 (m, 1H), 7.65 (d, *J* = 2.4 Hz, 1H), 7.35 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.03 – 7.00 (m, 2H), 6.96 (d, *J* = 8.3 Hz, 1H), 2.92 (t, *J* = 7.5 Hz, 2H), 2.79 (t, *J* = 7.2 Hz, 2H), 2.50 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.5, 198.6, 163.1, 151.3, 147.8, 139.8, 137.8, 133.6, 131.6, 129.6, 123.0, 118.9, 111.7, 44.7, 30.9, 30.1, 28.8. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{17}H_{17}NO_3$): 283.1208, *found* 283.1209.

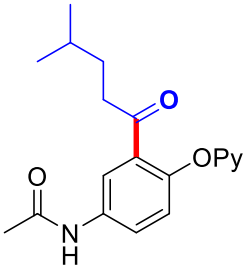


R = H, **4ea**
R = Ac, **4ea'**

1-[6-(Pyridin-2-yloxy)benzo[*d*][1,3]dioxol-5-yl]ethan-1-one (4ea). Following the general procedure A, using the sesamol derivative **3e** (0.15 mmol, 32 mg) and EtOH (3.75 mmol, 0.22 mL) provided 8 mg (21% yield) and 5 mg (11% yield) of **4ea** and **4ea'**, respectively, both of them as a yellow solid. *Both products were separated by column chromatography (*Hex/EtOAc 7:3*) and the following data correspond to the major monofunctionalized product* **4ea**. Mp 104-106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d,

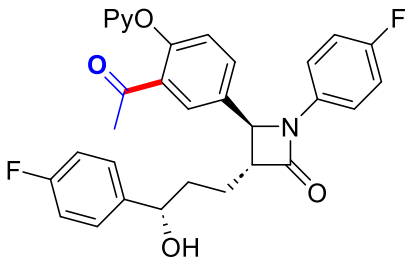
[7] Mohanta, P. R.; Banerjee, A. N.; Santra, S. K.; Behera, A.; Patel, B. K. *Adv. Synth. Catal.* **2016**, *358*, 2047–2052.

J = 5.0 Hz, 1H), 7.78 – 7.69 (m, 1H), 7.37 (s, 1H), 7.08 – 7.00 (m, 1H), 6.98 (d, J = 8.3 Hz, 1H), 6.57 (s, 1H), 6.04 (s, 2H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4, 163.2, 152.0, 149.9, 147.9, 145.3, 140.0, 125.1, 119.1, 111.8, 108.5, 104.1, 102.5, 31.1. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{14}H_{11}NO_4$): 257.0688, *found* 257.0695.



(4f)

***N*-[3-(4-Methylpentanoyl)-4-(pyridin-2-yloxy)phenyl]acetamide (4f).** Following the general procedure B, using the acetaminophen derivative **3f** (0.15 mmol, 34 mg) and 4-methylpentan-1-ol (0.75 mmol, 93 µL) provided 34 mg (70% yield) of **4f** as a white solid *after 1 h of reaction*. Mp 87-88 °C. Column chromatography (Hex/EtOAc 4:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.12 (m, 2H), 7.87 (dd, J = 8.8, 2.7 Hz, 1H), 7.75 – 7.69 (m, 2H), 7.06 (d, J = 8.8 Hz, 1H), 7.04 – 6.99 (m, 1H), 6.96 (d, J = 8.3 Hz, 1H), 2.87 – 2.78 (m, 2H), 2.14 (s, 3H), 1.49 – 1.40 (m, 3H), 0.78 (d, J = 6.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.1, 168.9, 163.3, 148.1, 147.5, 140.0, 135.6, 132.4, 125.0, 123.7, 121.0, 119.0, 111.8, 41.0, 33.0, 27.8, 24.5, 22.4. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{19}H_{22}N_2O_3$): 326.1630, *found* 326.1642.

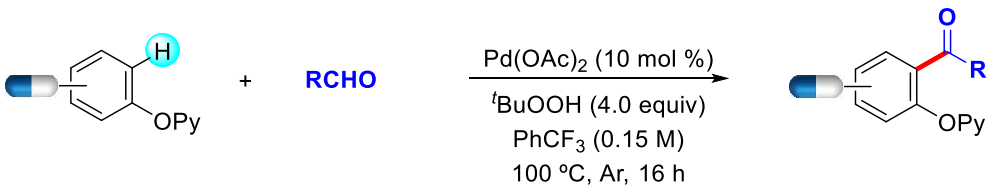


(4ga)

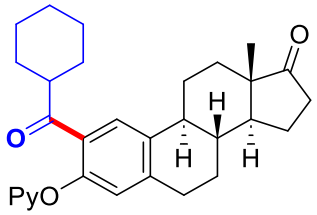
(3*R*,4*S*)-4-[3-Acetyl-4-(pyridin-2-yloxy)phenyl]-1-(4-fluorophenyl)-3-[(*S*)-3-(4-fluorophe-nyl)-3-hydroxypropyl]azetidin-2-one (4ga). Following the general procedure A, using ezetimibe derivative **3g** (0.15 mmol, 73 mg) and EtOH (3.75 mmol, 0.22 mL) provided 30 mg (38% yield) of **4ga** as a white solid. Mp 80-83 °C. Column chromatography (Hex/EtOAc 6:4). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.07 (ddd, J = 5.0, 2.0, 0.8 Hz, 1H), 7.85 (ddd, J = 8.3, 7.2, 2.0 Hz, 1H), 7.79 (d, J = 2.2 Hz, 1H), 7.62 (dd, J = 8.4, 2.3 Hz, 1H), 7.50 – 7.39 (m, 4H), 7.22 – 7.16 (m, 2H), 7.15 – 7.04 (m, 5H), 4.84 (d, J = 10.0 Hz, 1H), 4.72 (dd, J = 11.4, 2.1 Hz, 1H), 2.76 (td, J = 10.8, 4.3 Hz, 1H), 2.36 (s, 3H), 2.24 – 1.97 (m, 3H), 1.62 (qd, J = 12.7, 4.9 Hz, 1H). ^{13}C NMR

(101 MHz, DMSO-d_6) δ 197.8, 171.3, 162.8, 161.6 (d, $J_{C\text{-}F}$ = 246.4 Hz), 158.2 (d, $J_{C\text{-}F}$ = 241.4 Hz), 151.9, 147.5, 140.6, 139.0, 137.6, 135.2, 132.3, 131.5, 128.4, 128.0 (d, $J_{C\text{-}F}$ = 8.1 Hz), 123.4, 121.4 (d, $J_{C\text{-}F}$ = 8.1 Hz), 119.4, 115.4 (d, $J_{C\text{-}F}$ = 24.2 Hz), 115.1 (d, $J_{C\text{-}F}$ = 23.2 Hz), 111.8, 80.4, 78.4, 49.9, 32.4, 30.5, 28.3. ^{19}F NMR (471 MHz, $CDCl_3$ at 50 ºC) δ -115.12, -117.94. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{31}H_{26}F_2N_2O_4$): 528.1861, *found* 528.1856.

4.2.- Using Aldehydes as Acylating Agents

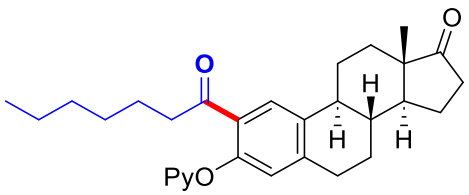


General Procedure D: A reaction tube containing a stirring bar was charged with the corresponding phenol derivative (0.15 mmol) and $Pd(OAc)_2$ (10 mol %). The reaction tube was then evacuated and back-filled with dry argon (this sequence was repeated up to three times). Then, a commercially available solution of *tert*-butyl hydroperoxide (70 wt % in water) (0.60 mmol), the corresponding ***aldehyde*** (0.75 mmol) and benzotrifluoride (1 mL) were added by syringe under argon atmosphere. The reaction tube was next warmed up to 100 °C in a heating block and stirred for 16 hours. The mixture was then allowed to warm to room temperature, evaporated under vacuum and the resulting crude was then purified by column chromatography to afford the corresponding product.



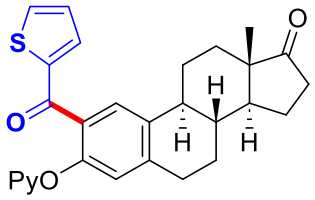
(2h)

(8*R*,9*S*,13*S*,14*S*)-2-(Cyclohexanecarbonyl)-13-methyl-3-(pyridin-2-yloxy)-6,7,8,9, 11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (2h). Following the general procedure D, using estrone derivative **1a** (0.15 mmol, 52 mg) and cyclohexanecarbaldehyde (0.75 mmol, 90 µL) provided 65 mg (95% yield) of **2h** as a white solid. Mp 167-168 °C. Column chromatography (Hex/EtOAc 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.12 (m, 1H), 7.71 (ddd, *J* = 8.9, 7.3, 2.0 Hz, 1H), 7.59 (s, 1H), 7.00 (dd, *J* = 7.2, 5.0 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.85 (s, 1H), 3.03 (tt, *J* = 11.4, 2.8 Hz, 1H), 2.91 (dd, *J* = 9.0, 4.3 Hz, 2H), 2.56 – 2.43 (m, 2H), 2.30 (ddd, *J* = 15.3, 8.5, 4.3 Hz, 1H), 2.20 – 1.94 (m, 4H), 1.80 – 1.72 (m, 2H), 1.71 – 1.41 (m, 9H), 1.35 – 1.23 (m, 2H), 1.17 – 1.02 (m, 3H), 0.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.8, 205.6, 163.5, 149.8, 147.7, 142.1, 139.8, 136.9, 129.8, 127.3, 122.8, 118.7, 111.7, 50.5, 49.6, 48.0, 44.2, 38.0, 35.9, 31.6, 29.5, 29.0, 26.3, 26.0, 25.9, 25.8, 21.7, 13.9. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{30}H_{35}NO_3$): 457.2617, *found* 457.2627.



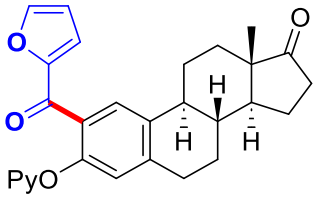
(2i)

(8*R*,9*S*,13*S*,14*S*)-2-Heptanoyl-13-methyl-3-(pyridin-2-yloxy)-6,7,8,9,11,12,13,14,15,16-deca-hydro-17*H*-cyclopenta[*a*]phenanthren-17-one (2i). Following the general procedure D, using estrone derivative **1a** (0.15 mmol, 52 mg) and heptanal (0.75 mmol, 100 µL) provided 41 mg (60% yield) of **2i** as a yellow oil. Column chromatography (Hex/EtOAc 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.13 (m, 1H), 7.74 – 7.67 (m, 2H), 7.02 – 6.96 (m, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 6.83 (s, 1H), 2.90 (dd, *J* = 9.0, 4.3 Hz, 2H), 2.81 (t, *J* = 7.4 Hz, 2H), 2.52 – 2.42 (m, 2H), 2.34 – 2.25 (m, 1H), 2.19 – 1.92 (m, 4H), 1.67 – 1.39 (m, 8H), 1.26 – 1.12 (m, 6H), 0.90 (s, 3H), 0.81 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.7, 201.5, 163.4, 150.3, 147.8, 142.7, 139.8, 136.8, 129.6, 127.3, 122.9, 118.7, 111.7, 50.5, 48.0, 44.1, 42.8, 38.0, 35.9, 31.6, 31.5, 29.5, 29.0, 26.2, 25.7, 24.3, 22.5, 21.6, 14.1, 13.9. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{30}H_{37}NO_3$): 459.2773, *found* 457.2788.



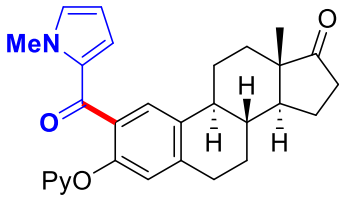
(2j)

(8*R*,9*S*,13S,14*S*)-13-Methyl-3-(pyridin-2-yloxy)-2-(thiophene-2-carbonyl)-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (2j). Following the general procedure D, using estrone derivative **1a** (0.15 mmol, 52 mg) and thiophene-2-carbaldehyde (0.75 mmol, 68 µL) provided 20 mg (29% yield) of **2j** as a white-yellowish solid. Mp 218-220 °C. Column chromatography (Hex/EtOAc 7:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 7.99 (m, 1H), 7.63 – 7.54 (m, 3H), 7.53 (s, 1H), 7.04 (dd, *J* = 4.9, 3.8 Hz, 1H), 6.98 (s, 1H), 6.89 (dd, *J* = 7.2, 5.0 Hz, 1H), 6.75 (d, *J* = 8.3 Hz, 1H), 2.98 (dd, *J* = 9.0, 4.3 Hz, 2H), 2.52 (dd, *J* = 18.8, 8.7 Hz, 1H), 2.44 – 2.28 (m, 2H), 2.24 – 2.00 (m, 3H), 1.96 (dt, *J* = 12.9, 2.5 Hz, 1H), 1.73 – 1.42 (m, 6H), 0.93 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 221.0, 187.3, 163.7, 149.5, 147.4, 144.8, 142.0, 140.0, 136.9, 135.4, 134.7, 130.0, 128.2, 127.6, 123.2, 118.8, 112.1, 50.8, 48.4, 44.5, 38.4, 36.3, 31.9, 30.0, 26.7, 26.2, 22.0, 14.3. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{28}H_{27}NO_3S$): 457.1732, *found* 457.1712.



(2k)

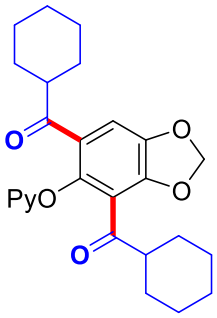
(8*R*,9*S*,13*S*,14*S*)-2-(Furan-2-carbonyl)-13-methyl-3-(pyridin-2-yloxy)-6,7,8,9,11,12, 13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (2k). Following the general procedure D, using estrone derivative **1a** (0.15 mmol, 52 mg) and furan-2-carbaldehyde (0.75 mmol, 62 µL) provided 38 mg (57% yield) of **2k** as a yellow solid. Mp 215-218 °C. Column chromatography (Hex/EtOAc 7:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 8.01 (m, 1H), 7.59 (ddd, *J* = 8.7, 7.2, 1.9 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.10 (d, *J* = 3.5 Hz, 1H), 6.97 (s, 1H), 6.90 (dd, *J* = 7.2, 5.0 Hz, 1H), 6.78 (d, *J* = 8.3 Hz, 1H), 6.46 (dd, *J* = 3.6, 1.7 Hz, 1H), 2.96 (dd, *J* = 8.9, 4.3 Hz, 2H), 2.51 (dd, *J* = 18.8, 8.6 Hz, 1H), 2.45 – 2.28 (m, 2H), 2.22 – 2.00 (m, 3H), 1.96 (dt, *J* = 12.9, 3.1 Hz, 1H), 1.72 – 1.39 (m, 6H), 0.92 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.7, 182.0, 163.4, 152.8, 149.4, 147.1, 142.0, 139.7, 136.6, 128.9, 127.4, 126.2, 122.9, 120.2, 118.5, 112.3, 111.8, 50.5, 48.0, 44.2, 38.0, 36.0, 31.6, 29.7, 26.3, 25.8, 21.7, 14.0. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{28}H_{27}NO_4$): 441.1940, *found* 441.1963.



(2l)

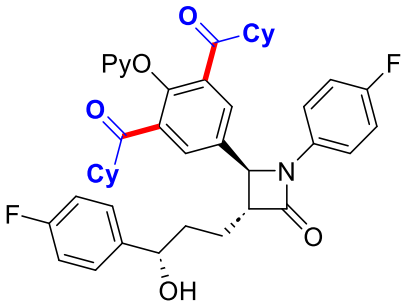
(8*R*,9*S*,13*S*,14*S*)-13-Methyl-2-(1-methyl-1*H*-pyrrole-2-carbonyl)-3-(pyridin-2-yloxy)-6,7,8, 9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (2l). Following the general procedure D, using estrone derivative **1a** (0.15 mmol, 52 mg) and 1-methyl-1*H*-pyrrole-2-carbaldehyde (0.75 mmol, 76 µL) provided 25 mg (37% yield) of **2l** as a yellow solid. Mp 182-185 °C. Column chromatography (Hex/EtOAc 6:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (ddd, *J* = 5.1, 2.1, 0.8 Hz, 1H), 7.59 (ddd, *J* = 8.4, 7.2, 2.0 Hz, 1H), 7.48 (s, 1H), 6.94 – 6.87 (m, 2H), 6.80 – 6.74 (m, 2H), 6.67 (dd, *J* = 4.1, 1.7 Hz, 1H), 6.06 (dd, *J* = 4.1, 2.5 Hz, 1H), 3.83 (s, 3H), 2.95 (dd, *J* = 9.0, 4.3 Hz, 2H), 2.52 (dd, *J* = 18.8, 8.6 Hz, 1H), 2.43 – 2.28 (m, 2H), 2.21 – 2.00 (m, 3H), 1.98 – 1.90 (m, 1H), 1.72 – 1.41 (m, 6H), 0.93 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.9, 184.4, 163.8, 149.3, 147.3, 140.5, 139.4, 136.1, 131.4, 131.3, 131.0, 127.4, 123.3, 122.6, 118.2,

111.7, 108.2, 50.6, 48.1, 44.2, 38.1, 37.3, 36.0, 31.6, 29.6, 26.4, 25.8, 21.7, 14.0. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{29}H_{30}N_2O_3$): 454.2256, *found* 454.2264.



(4eb)

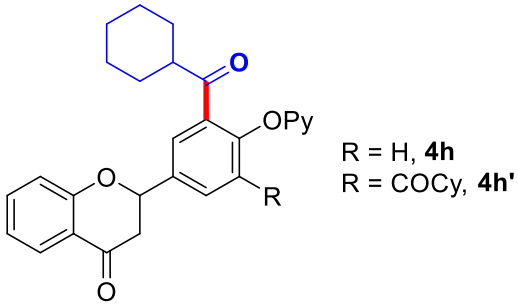
[5-(Pyridin-2-yloxy)benzo[*d*][1,3]dioxole-4,6-diyl]bis(cyclohexylmethanone) (4eb). Following the general procedure D, using the sesamol derivative **3e** (0.15 mmol, 52 mg) and cyclohexanecarbaldehyde (0.75 mmol, 90 µL) provided 63 mg (97% yield) of **4eb** as a white-yellowish solid *after 1 h of reaction*. Mp 145-146 °C. Column chromatography (Hex/EtOAc 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 7.99 (m, 1H), 7.73 – 7.63 (m, 1H), 7.16 (s, 1H), 6.94 (m, 2H), 6.10 (s, 2H), 3.03 – 2.81 (m, 2H), 1.83 – 1.50 (m, 10H), 1.34 – 0.98 (m, 10H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.2, 202.3, 163.5, 148.9, 147.3, 145.5, 139.8, 118.8, 111.6, 111.2, 110.1, 108.7, 102.9, 102.4, 50.7, 49.4, 29.1, 28.3, 25.9, 25.8, 25.8. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{26}H_{29}NO_5$): 435.2046, *found* 435.2057.



(4gb)

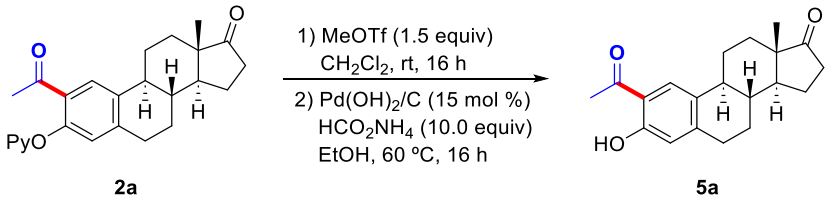
{5-{(2*S*,3*R*)-1-(4-Fluorophenyl)-3-[(*S*)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-azetidin-2-yl}-2-(pyridin-2-yloxy)-1,3-phenylene}bis(cyclohexylmethanone) (4gb). Following the general procedure D, using ezetimibe derivative **3g** (0.15 mmol, 73 mg) and cyclohexanecarbaldehyde (0.75 mmol, 90 µL) provided 72 mg (68% yield) of **4gb** as a white solid. Mp 85-88 °C. Column chromatography (Hex/EtOAc 7:3). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (s, 1H), 7.96 (dd, J = 5.0, 1.9 Hz, 1H), 7.83 (ddd, J = 9.0, 7.2, 2.0 Hz, 1H), 7.69 (s, 2H), 7.50 – 7.42 (m, 4H), 7.22 – 7.16 (m, 2H), 7.11 – 7.02 (m, 4H), 4.89 (d, J = 10.0 Hz, 1H), 4.75 (dd, J = 11.4, 2.2 Hz, 1H), 2.86 – 2.74 (m, 3H), 2.23 –

2.11 (m, 2H), 2.09 – 2.00 (m, 1H), 1.63 (td, J = 12.2, 4.8 Hz, 1H), 1.54 – 1.38 (m, 10H), 1.11 – 0.88 (m, 10H). ^{13}C NMR (101 MHz, DMSO) δ 204.5, 171.0, 162.5, 161.4 (d, $J_{C\text{-}F}$ = 243.4 Hz), 158.0 (d, $J_{C\text{-}F}$ = 240.4 Hz), 147.0, 146.8, 140.4, 138.7, 137.9, 135.0, 133.8, 130.0, 127.7 (d, $J_{C\text{-}F}$ = 8.1 Hz), 120.8 (d, $J_{C\text{-}F}$ = 8.1 Hz), 119.2, 115.1 (d, $J_{C\text{-}F}$ = 22.2 Hz), 115.0 (d, $J_{C\text{-}F}$ = 21.2 Hz), 110.9, 79.8, 78.3, 49.8, 48.5, 32.1, 28.2, 27.9, 25.3, 25.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.90, -117.76. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{43}H_{44}F_2N_2O_5$): 706.3218, *found* 706.3219.



2-[3-(Cyclohexanecarbonyl)-4-(pyridin-2-yloxy)phenyl]chroman-4-one (4h). Following the general procedure D, using the 4'-hydroxyflavanone derivative **3h** (0.15 mmol, 48 mg) and cyclohexanecarbaldehyde (0.75 mmol, 90 µL) provided 37 mg (58% yield) and 20 mg (25% yield) of **x** and **x'**, respectively, both of them as a yellow oil. *Both products were separated by column chromatography* (Hex/EtOAc 8:2) *and independently characterized*. **Monofunctionalized 4h:** ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (ddd, J = 4.9, 2.0, 0.8 Hz, 1H), 7.90 (ddd, J = 8.3, 7.2, 2.0 Hz, 1H), 7.84 – 7.79 (m, 2H), 7.77 (dd, J = 8.4, 2.3 Hz, 1H), 7.62 (ddd, J = 8.7, 7.1, 1.8 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.18 – 7.10 (m, 4H), 5.77 (dd, J = 13.1, 2.8 Hz, 1H), 3.42 – 3.28 (m, 1H), 3.04 (tt, J = 11.0, 3.3 Hz, 1H), 2.91 (dd, J = 16.8, 2.9 Hz, 1H), 1.75 – 1.51 (m, 5H), 1.27 – 1.01 (m, 5H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 204.4, 191.5, 162.7, 161.0, 151.3, 147.3, 140.4, 136.4, 135.7, 132.1, 130.9, 127.8, 126.4, 123.6, 121.6, 120.7, 119.3, 118.1, 111.5, 78.1, 48.6, 43.3, 28.4, 25.4, 25.1. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{27}H_{25}NO_4$): 427.1784, *found* 427.1772. **Difunctionalized 4h':** ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (ddd, J = 4.6, 1.9, 0.9 Hz, 1H), 7.95 (s, 2H), 7.88 (ddd, J = 8.4, 7.3, 2.0 Hz, 1H), 7.82 (dd, J = 7.8, 1.7 Hz, 1H), 7.63 (ddd, J = 8.8, 7.3, 1.8 Hz, 1H), 7.19 – 7.09 (m, 4H), 5.82 (dd, J = 13.2, 2.8 Hz, 1H), 3.43 (dd, J = 16.8, 13.2 Hz, 1H), 3.01 – 2.92 (m, 3H), 1.67 – 1.46 (m, 10H), 1.17 – 1.01 (m, 10H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 204.4, 191.4, 162.5, 160.9, 147.7, 146.8, 140.5, 136.4, 136.3, 134.4, 129.9, 126.4, 121.7, 120.6, 119.2, 118.1, 111.1, 77.8, 48.4, 43.1, 28.3, 25.3, 25.0. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{34}H_{35}NO_5$): 537.2515, *found* 537.2513.

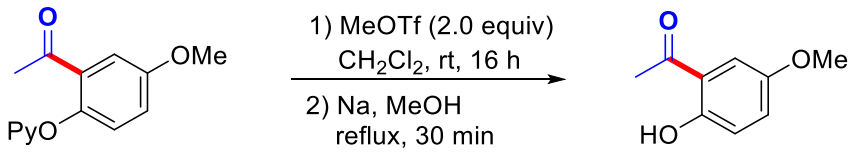
5.- Cleavage of the Directing Group



2a **5a**

(8*R*,9*S*,13*S*,14*S*)-2-Acetyl-3-hydroxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (5a). Following a reported protocol,[8] a reaction tube containing a stirring bar was charged with the acetylated estrone **2a** (0.50 mmol, 195 mg). The reaction tube was then evacuated and back-filled with dry argon (this sequence was repeated up to three times). Dichloromethane (2 mL) was added via syringe under argon atmosphere and the resulting solution was cooled to 0 °C, then methyl trifluoromethanesulfonate (0.75 mmol, 85 µL) was added. The reaction mixture was allowed to stir at room temperature for 16 h. Then, the solvent was eliminated under reduced pressure and $Pd(OH)_2/C$ (20% wt) (0.075 mmol, 53 mg) and ammonium formate (5.00 mmol, 317 mg) were added. The reaction tube was again evacuated and back-filled with dry argon and ethanol (1 mL) was added by syringe under argon atmosphere. The reaction tube was next warmed up to 60 °C in a heating block and stirred for 16 hours. The mixture was then allowed to cool to room temperature, diluted with dichloromethane, filtered through a pad of celite and evaporated under vacuum. The resulting crude was then purified by column chromatography (Hex/EtOAc 8:2) to afford 77 mg (50% yield) of **5a** as a white solid.[9] Mp 158-159 °C, (Lit.[9] 160-162 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.04 (s, 1H), 7.60 (s, 1H), 6.70 (s, 1H), 2.93 – 2.86 (m, 2H), 2.60 (s, 3H), 2.51 (dd, *J* = 18.8, 8.7 Hz, 1H), 2.45 – 2.37 (m, 1H), 2.28 – 1.95 (m, 5H), 1.71 – 1.38 (m, 6H), 0.92 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.7, 204.2, 160.2, 147.0, 131.0, 127.4, 118.0, 117.8, 50.5, 48.0, 43.6, 38.2, 35.9, 31.5, 29.9, 26.6, 26.2, 26.0, 21.7, 13.9. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{20}H_{24}O_3$): 312.1725, *found* 312.1726.

[8] Urruzuno, I.; Andrade-Sampedro, P.; Correa, A. *Eur. J. Org. Chem.* **2023**, *26*, e20220148.
[9] Xie, R.-G.; Deng, L.; Gu, H.; Fan, Y.; Zhao, H. *Steroids* **1982**, *40*, 389-392.



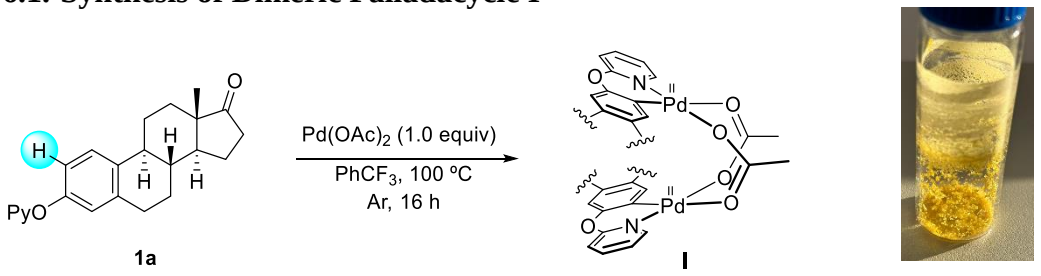
4c **5c**

1-(2-Hydroxy-5-methoxyphenyl)ethan-1-one (5c). A reaction tube containing a stirring bar was charged with the acetylated mequinol **4c** (0.41 mmol, 100 mg). The reaction tube was then evacuated and back-filled with dry argon (this sequence was repeated up to three times). Dichloromethane (1.65 mL) was added via syringe under argon atmosphere and the resulting solution was cooled to 0 °C, then methyl trifluoromethanesulfonate (0.82 mmol, 93 µL) was added. The reaction mixture was allowed to stir at room temperature for 16 h. Then, the solvent was eliminated under reduced pressure and, without further purification, a mixture of Na (10.25 mmol, 236 mg) in dry MeOH (8.2 mL) was added to the crude pyridinium under argon atmosphere. The reaction tube was next warmed up to 80 °C in a heating block and stirred for 30 min. The mixture was then allowed to cool to room temperature and H_2O (6 mL) was added. Then a 2M HCl aqueous solution was added to acidify the reaction system and the resulting mixture was extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$ and evaporated under vacuum. The resulting crude was then purified by column chromatography (CH_2Cl_2/MeOH 95:5) to afford 53 mg (77% yield) of **5c** as a yellow solid.[10] Mp 45-47 °C, (Lit.[10] 46 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.85 (s, 1H), 7.16 (d, *J* = 3.0 Hz, 1H), 7.11 (dd, *J* = 9.1, 3.1 Hz, 1H), 6.92 (d, *J* = 9.0 Hz, 1H), 3.80 (s, 3H), 2.61 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.0, 156.8, 151.7, 124.2, 119.2, 113.5, 56.0, 26.8. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_9H_{10}O_3$): 166.0630, *found* 166.0626.

[10] Boyer, J. L.; Krum, J. E.; Myers, M. C.; Wigal, C. T. *J. Org. Chem.* **2000**, *65*, 4712–4714.

6- Mechanistic Studies

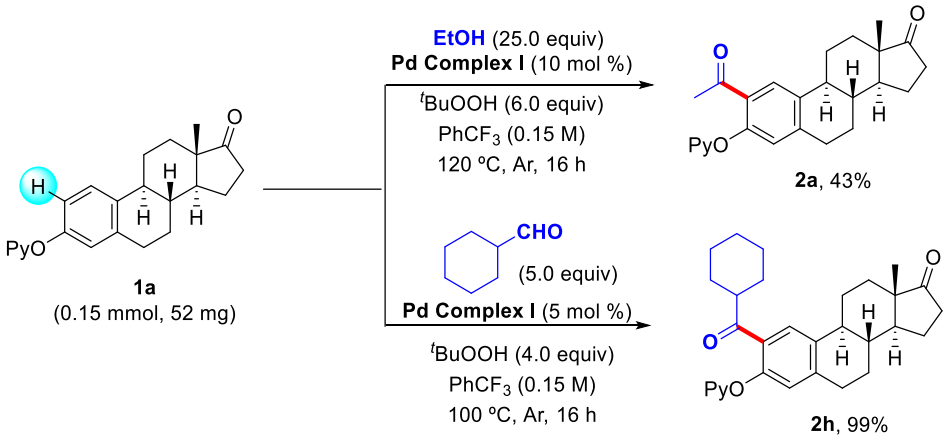
6.1.-Synthesis of Dimeric Palladacycle I



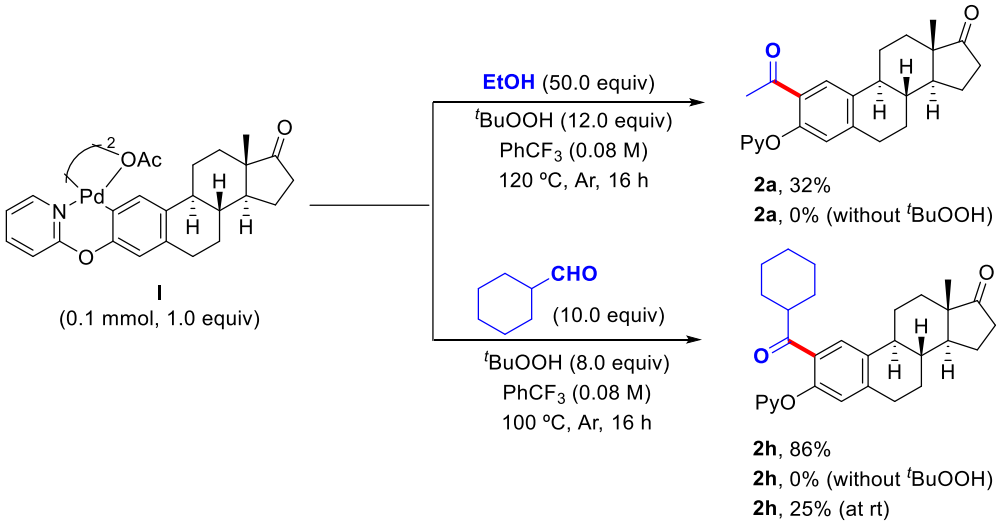
A flask containing a stirring bar was charged with estrone derivative **1a** (1.15 mmol, 400 mg) and stoichiometric amount of $Pd(OAc)_2$ (1.15 mmol, 258 mg). It was then evacuated and back-filled with dry Ar (this sequence was repeated up to three times). Then $PhCF_3$ (58 mL) was added under argon atmosphere. The reaction tube was next warmed up to 100 °C and stirred for 16 h. After cooling down to room temperature, the reaction solution was diluted with CH_2Cl_2 filtered with celite and evaporated under vacuum. The resulting crude mixture was dissolved in CH_2Cl_2/Hex and recrystallized to obtain 447 mg (76% yield) of pure **I** as yellow crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, J = 6.1, 1.8 Hz, 2H), 7.54 (ddd, J = 8.7, 7.1, 1.8 Hz, 2H), 6.87 – 6.79 (m, 2H), 6.67 (s, 2H), 6.57 (ddd, J = 7.2, 6.0, 1.4 Hz, 2H), 6.37 (s, 2H), 2.86 – 2.67 (m, 4H), 2.50 (dd, J = 18.9, 8.6 Hz, 2H), 2.29 – 2.12 (m, 4H), 2.09 (s, 6H), 2.06 – 1.86 (m, 8H), 1.51 – 1.20 (m, 12H), 0.87 (s, 6H).

6.2.- Control Experiments with Palladium Complex I

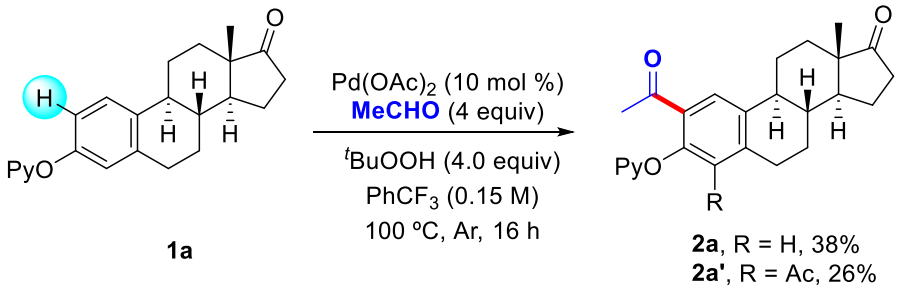
A) Catalytic Control Experiments



B) Stoichiometric Control Experiments



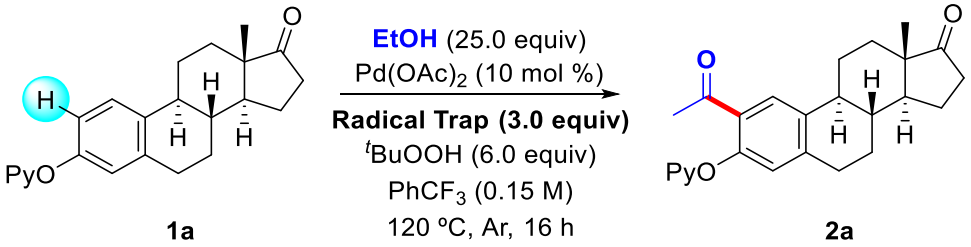
6.3.-Reaction with MeCHO



(8*R*,9*S*,13*S*,14*S*)-2-Acetyl-13-methyl-3-(pyridin-2-yloxy)-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (8a). Following the general procedure for the acylation with aldehydes, using the estrone derivative (0.15 mmol, 52 mg) and MeCHO (0.60 mmol, 34 µL) provided 22 mg (38% yield) of **2a** as a white-yellowish solid and 17 mg (26% yield) of **2a'** as a white solid. *Both products were separated by column chromatography (Hex/EtOAc 7:3) and independently characterized.* The spectroscopic data of the monofunctionalized product is consistent with the one previously described for **2a**. **Difunctionalized 2a':** Mp 78-80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 5.1, 1.9 Hz, 1H), 7.78 (s, 1H), 7.69 (ddd, *J* = 8.3, 7.2, 2.0 Hz, 1H), 6.98 (ddd, *J* = 7.2, 5.0, 0.9 Hz, 1H), 6.92 (dd, *J* = 8.4, 0.9 Hz, 1H), 2.84 – 2.77 (m, 2H), 2.57 – 2.44 (m, 2H), 2.40 – 2.29 (m, 7H), 2.22 – 1.95 (m, 4H), 1.72 – 1.37 (m, 6H), 0.92 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 219.5, 203.6, 197.4, 162.5, 146.9, 144.4, 140.3, 137.9, 137.7, 136.3, 130.2, 127.0, 119.0, 111.0, 49.4, 47.2, 43.6, 36.7, 35.4, 31.6, 31.3, 29.5, 26.0, 25.3, 25.3, 21.1, 13.5. HRMS (ESI-TOF) m/z: (M^+) *calcd.* for ($C_{27}H_{29}NO_4$): 431.2097, *found* 431.2074.

6.4.-Control Experiments with Radical Traps

Table S3. Influence of Radical Traps[a]

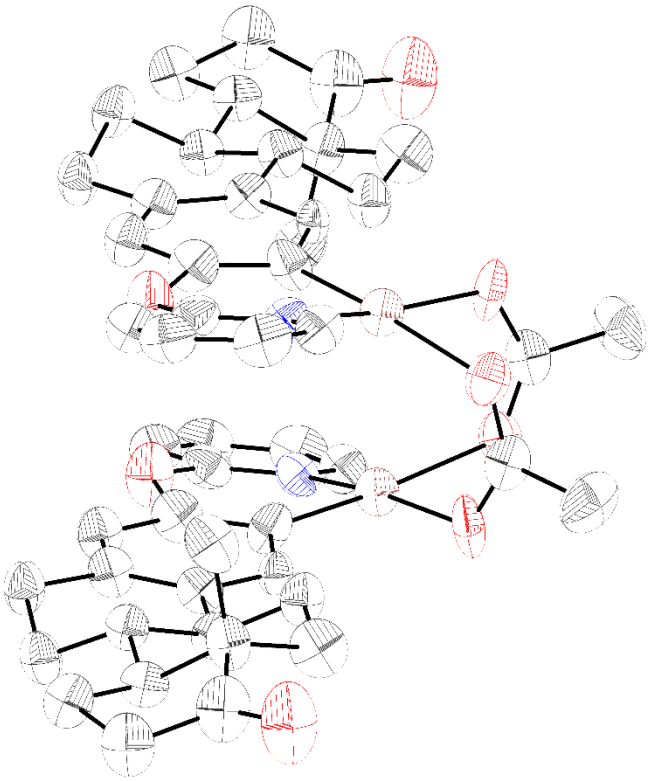


Entry	Radical trap	Yield (%)[b]
1	none	58
2	BHT	29
3	TEMPO	0
4	1,1-Diphenylethylene	34

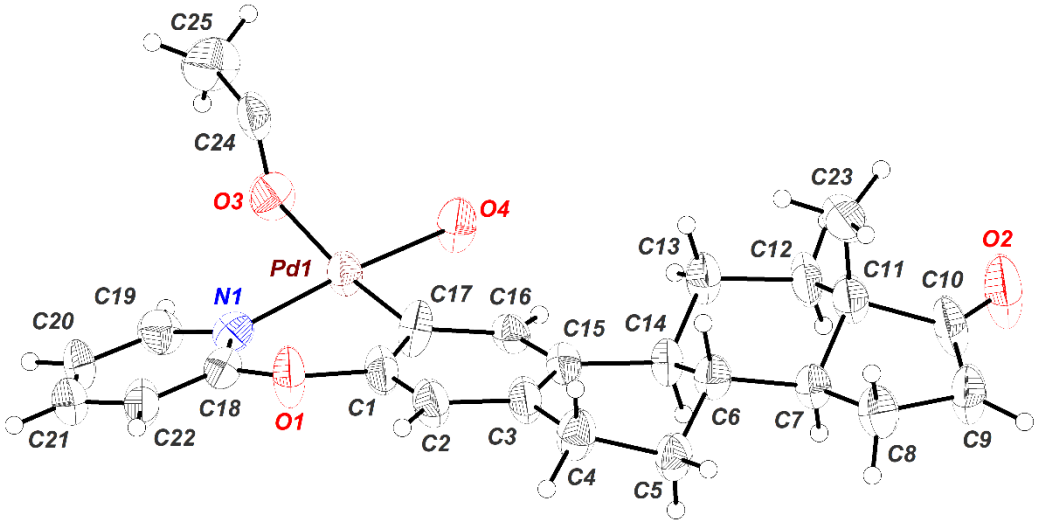
[a] Reaction conditions: **1a** (0.15 mmol), EtOH (3.75 mmol), $Pd(OAc)_2$ (10 mol %), T-Hydro (6.0 equiv) and radical Trap (3.0 equiv) in $PhCF_3$ (1.0 mL) at 120 °C for 16 h under Ar. [b] Isolated yield after column chromatography.

7. X-Ray Crystallography

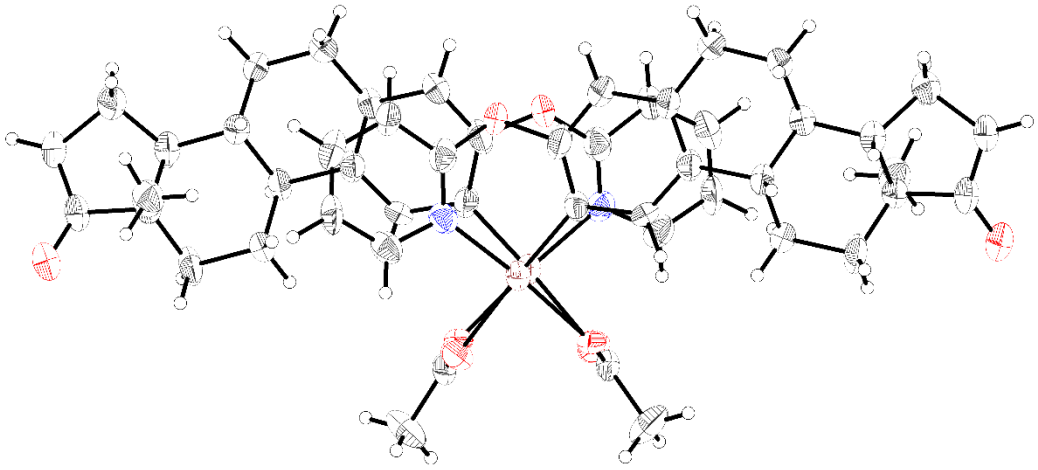
Intensity data were collected on an Agilent Technologies Super-Nova diffractometer, which was equipped with monochromated Cu k_α radiation (λ= 1.54184 Å) and Atlas CCD detector. Measurement was carried out at 150.00(10) K with the help of an Oxford Cryostream 700 PLUS temperature device. Data frames were processed (united cell determination, analytical absorption correction with face indexing, intensity data integration and correction for Lorentz and polarization effects) using the Crysalis software package. The structure was solved using SHELXT and refined by full-matrix least-squares with SHELXL-97. Final geometrical calculations were carried out with Mercury and PLATON as integrated in WinGX. Analysis of the absolute structure using likelihood methods (Hooft, Straver & Spek, 2008) was performed using PLATON (Spek, 2010). The Friedel pair coverage of the experiment is almost complete (83%). The results indicated that the absolute structure had been correctly assigned. The method calculated that the probability that the structure is inverted is smaller than 10^{-169}. The absolute structure parameter y (Hooft, Straver & Spek, 2008) was calculated using PLATON (Spek, 2010). The resulting value was y=-0.026(18), which together with Flack parameter value, indicate that the absolute structure has probably been determined correctly.



ORTEP of dimeric **complex I**
See CIF file attached (**2386321**)



ORTEP of **complex I** illustrating the monomer unit



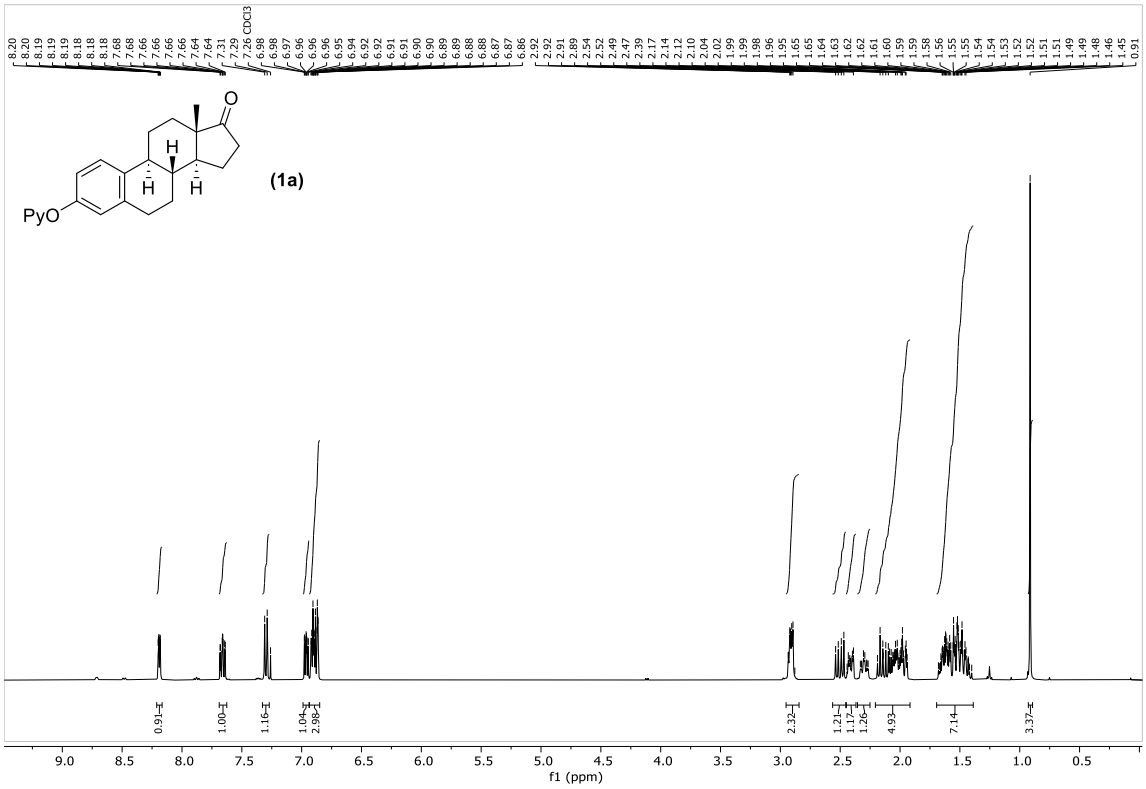
See CIF file attached (**2386321**)

Empirical formula	$C_{50}H_{52}N_2O_8Pd_2$
Formula weight	1021.73
Temperature/K	170.00(10)
Crystal system	monoclinic
Space group	C2
a/Å	22.8188(9)
b/Å	11.1547(4)
c/Å	8.7813(3)
α/°	90.0
β/°	90.733(4)
γ/°	90.0
Volume/Å3	2234.98(15)
Z	2
ρcalcg/cm^3	1.517
μ/mm^{-1}	0.860
F(000)	1044.0
Crystal size/mm^3	0.286 × 0.188 × 0.113

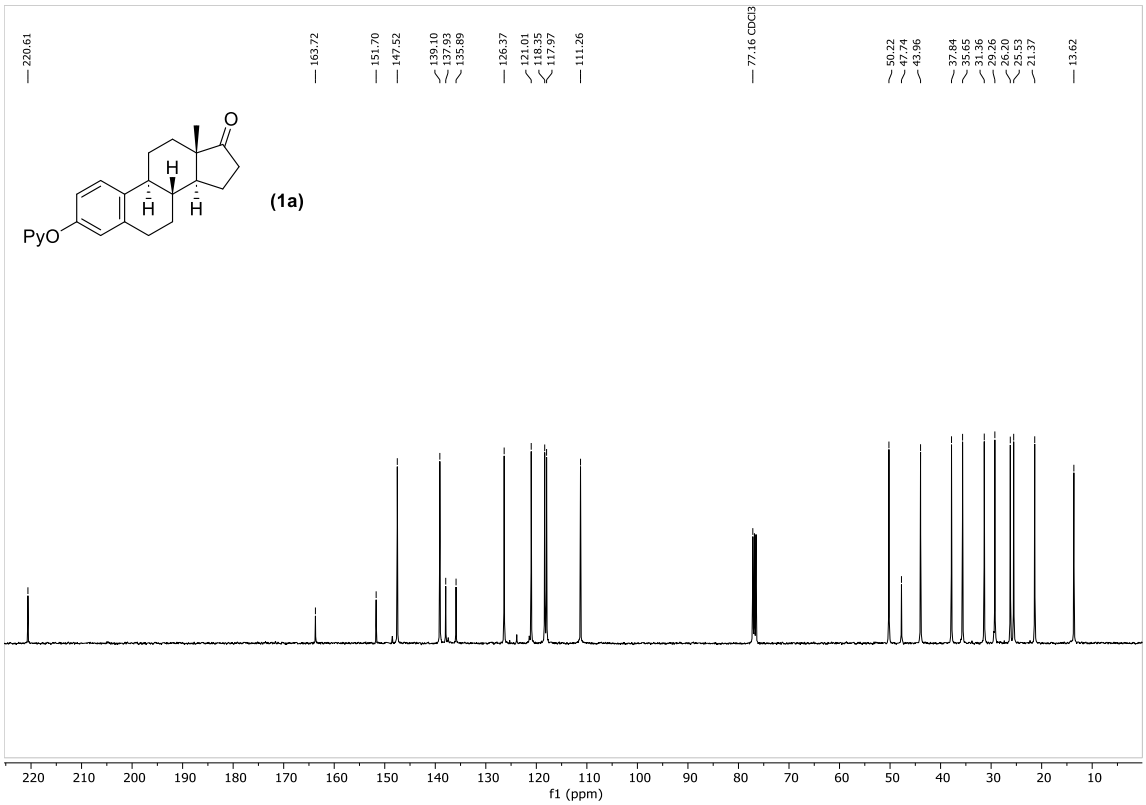
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	4.062 to 53.996
Index ranges	$-29 \leq h \leq 28$, $-14 \leq k \leq 13$, $-11 \leq l \leq 11$
Reflections collected	9641
Independent reflections	4450 [R_{int} = 0.0439, R_{sigma} = 0.0568]
Data/restraints/parameters	4450/1/282
Goodness-of-fit on F2	1.135
Final R indexes [I>=2σ (I)]	R_1 = 0.0698, wR_2 = 0.1635
Final R indexes [all data]	R_1 = 0.1000, wR_2 = 0.1874
Largest diff. peak/hole / e Å^{-3}	3.18/-1.25
Flack parameter	-0.08(4)
Bijvoet Pairs Covarage	83%
Hooft y	-0.026(18)
P3 false	$\leq 10^{-186}$

8.-^{1}H NMR, ^{13}C NMR and ^{19}F NMR Spectra

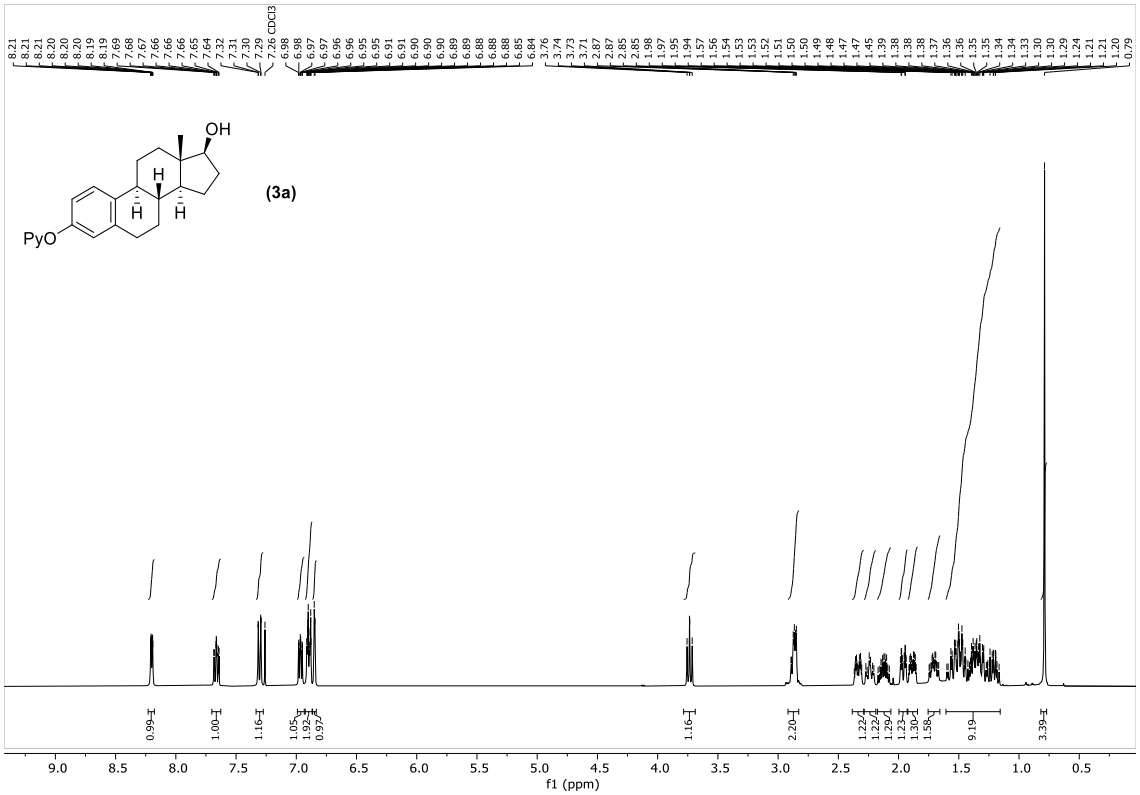
^{1}H NMR (400 MHz, $CDCl_3$)



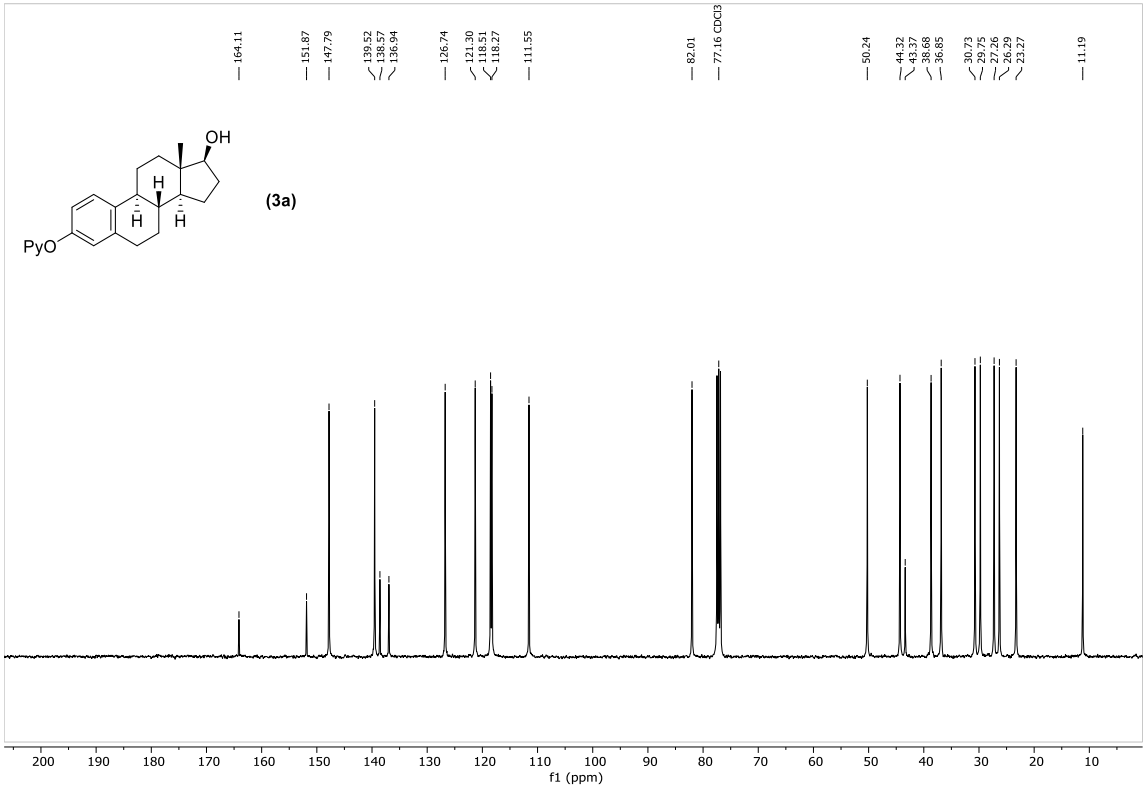
^{13}C NMR (101 MHz, $CDCl_3$)



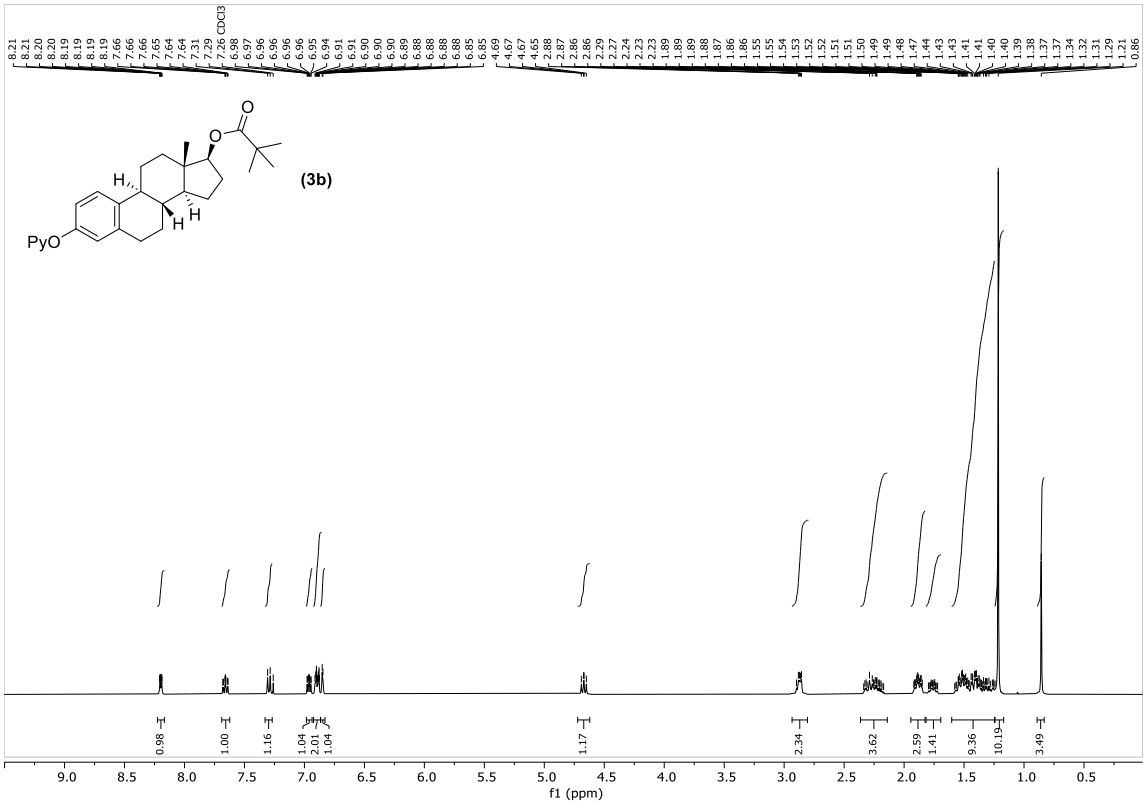
^{1}H NMR (400 MHz, $CDCl_3$)



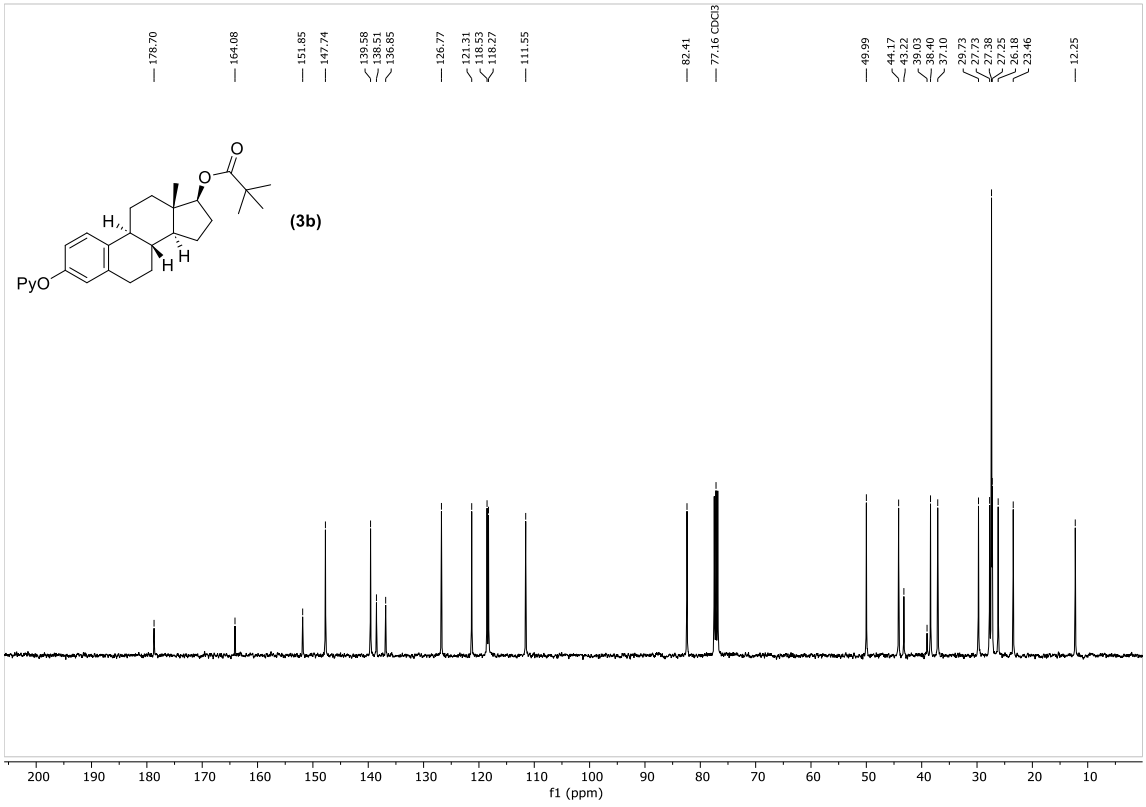
^{13}C NMR (101 MHz, $CDCl_3$)



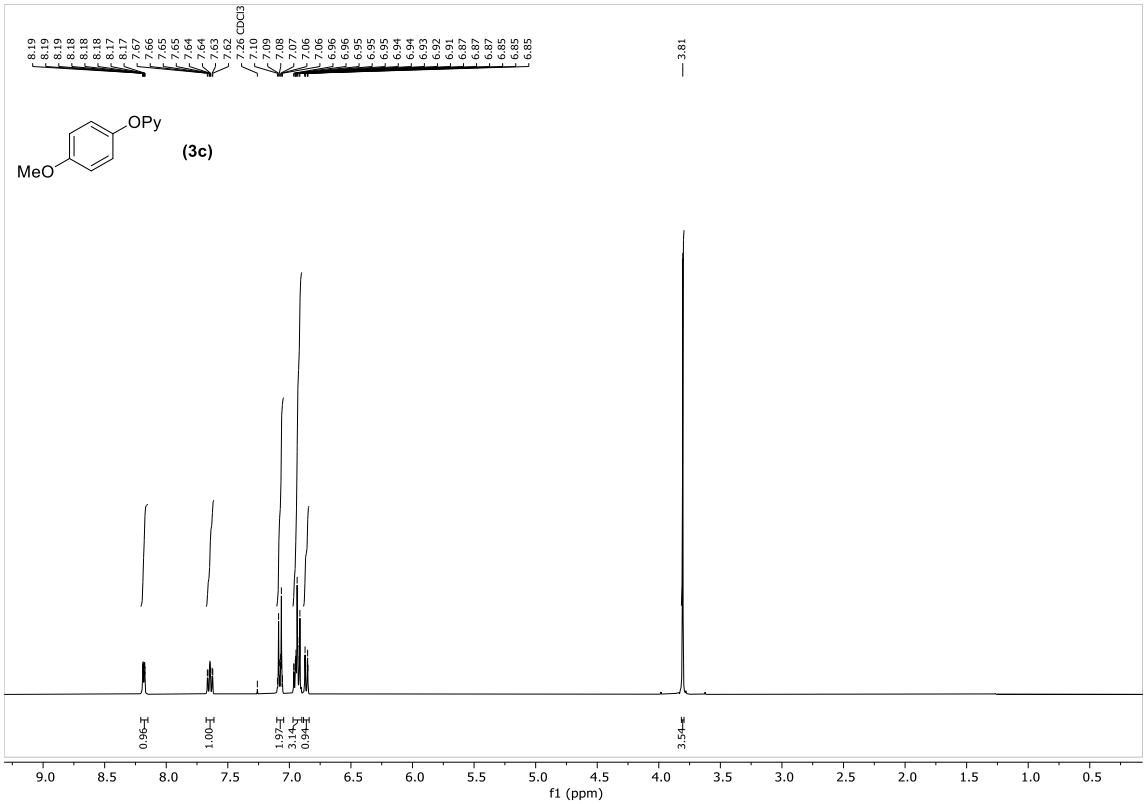
^{1}H NMR (400 MHz, $CDCl_3$)



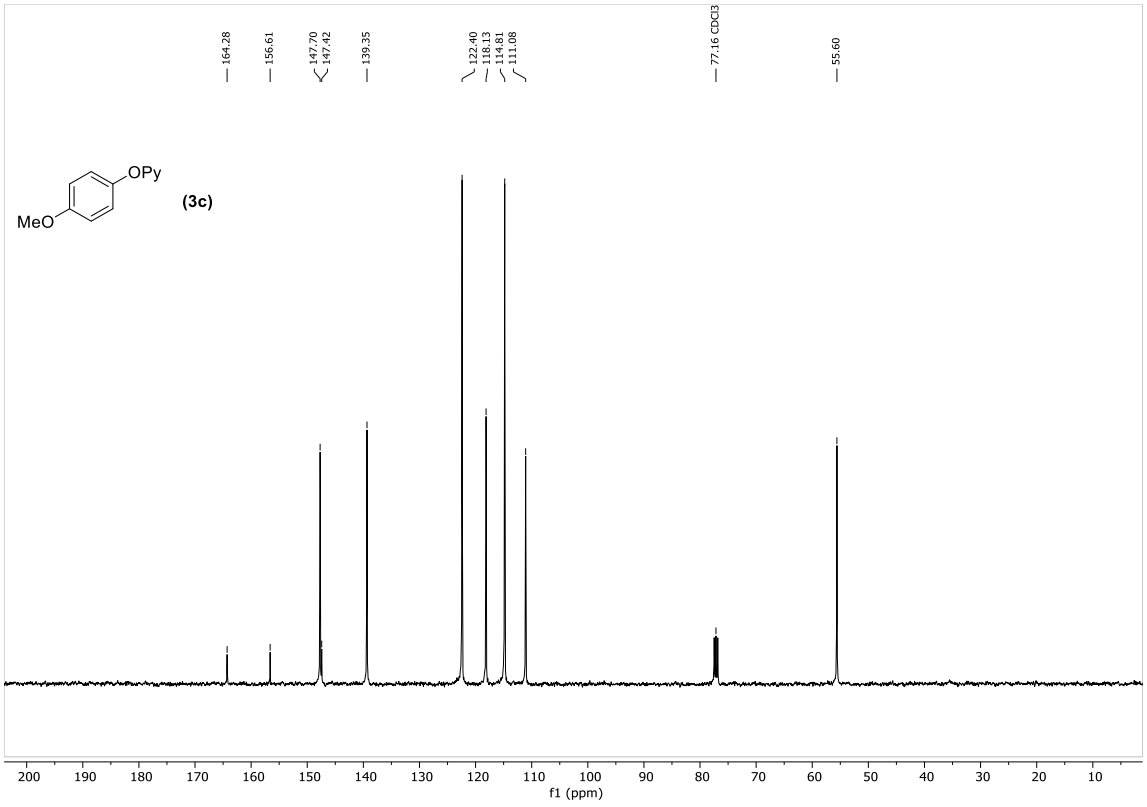
^{13}C NMR (101 MHz, $CDCl_3$)



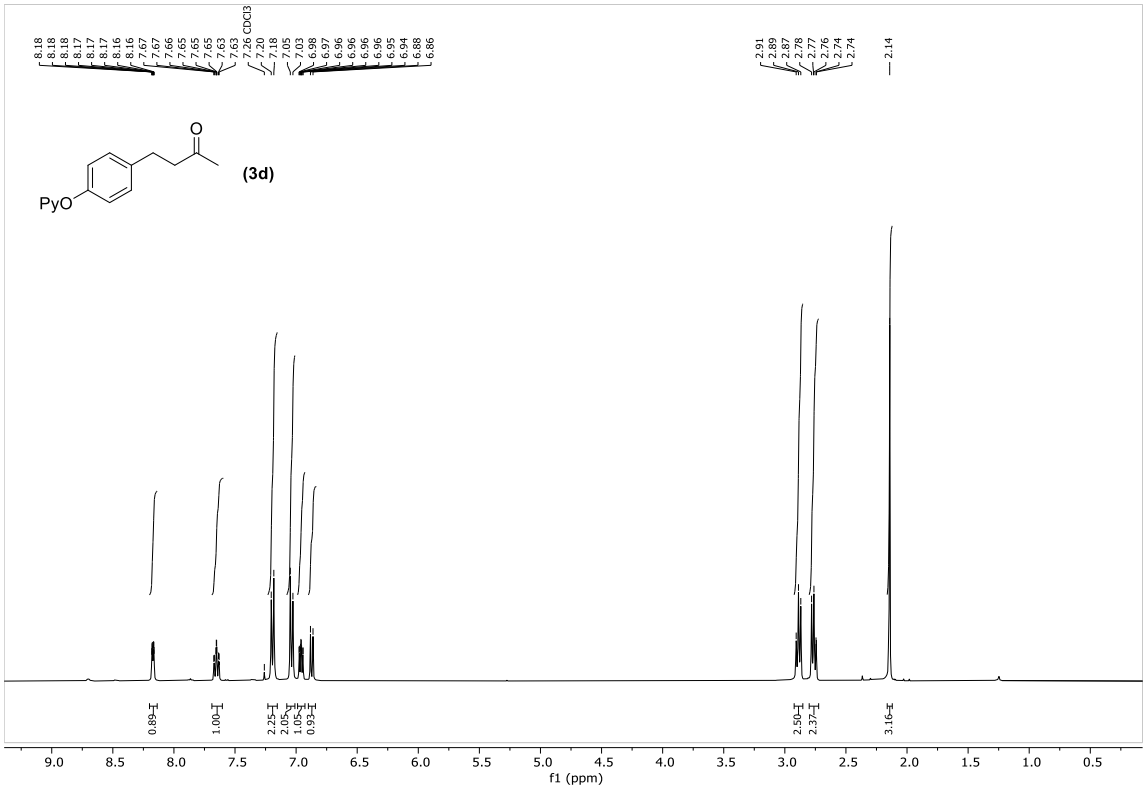
^{1}H NMR (400 MHz, $CDCl_3$)



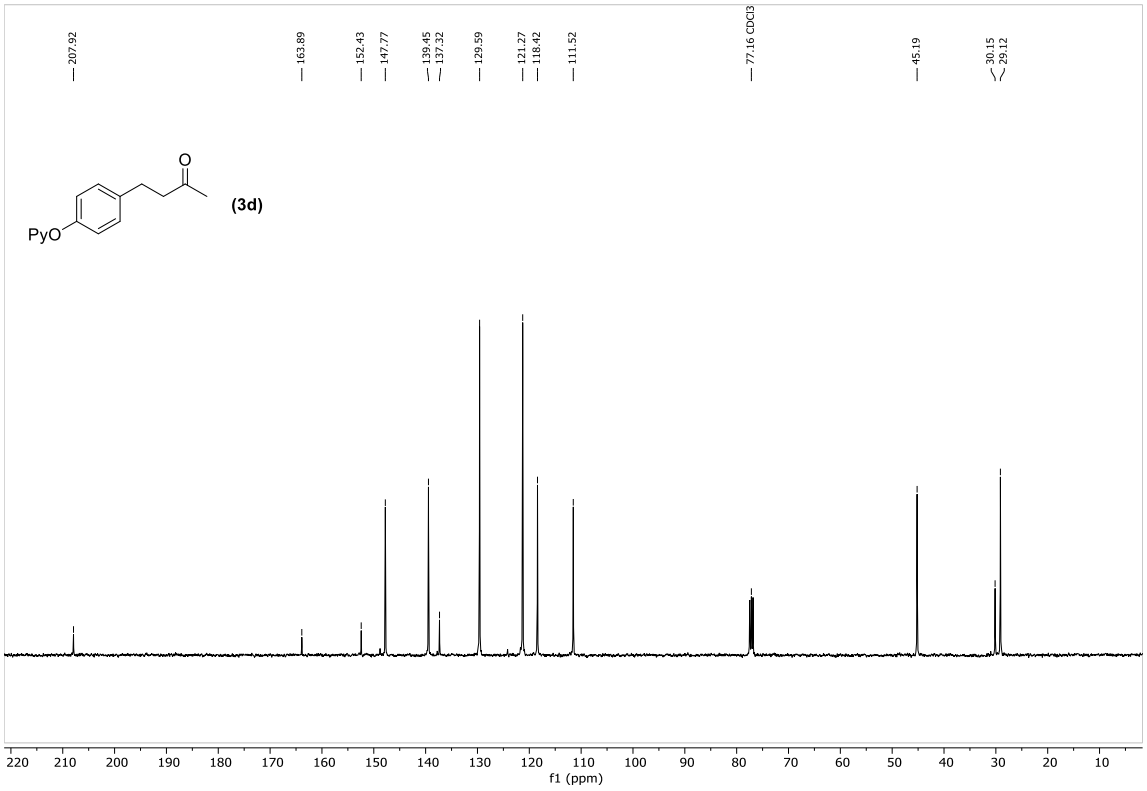
^{13}C NMR (101 MHz, $CDCl_3$)



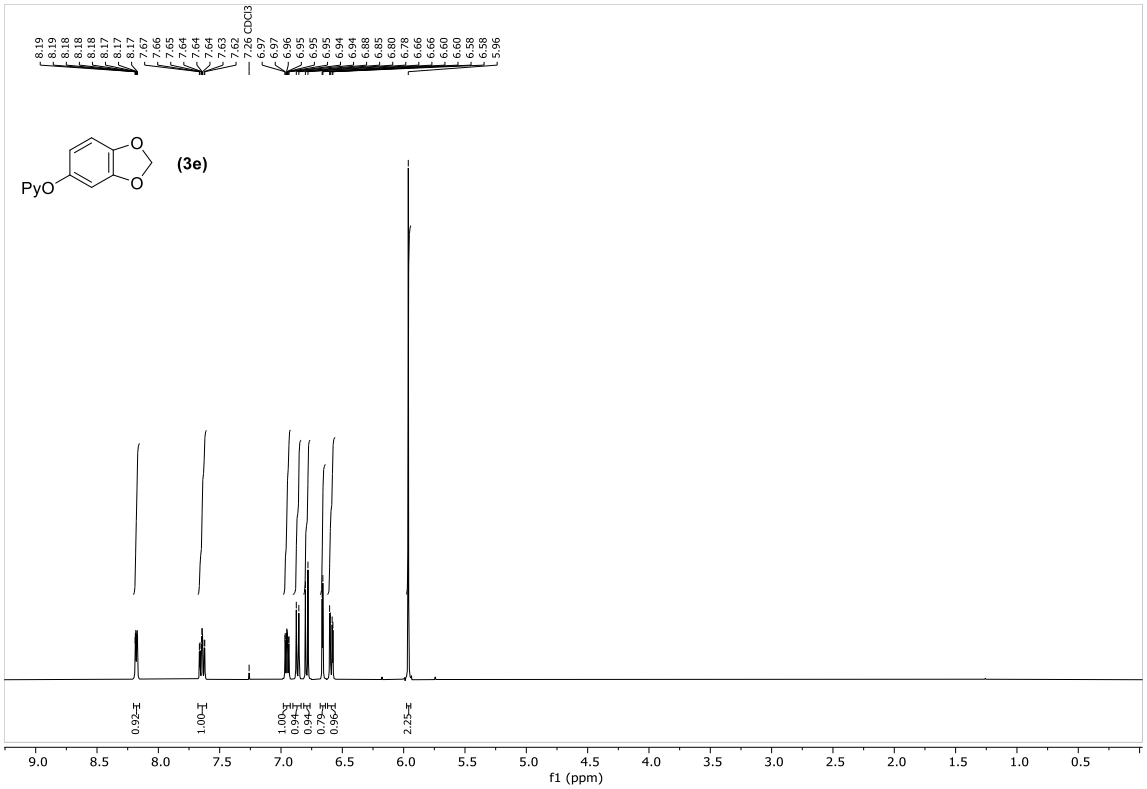
^{1}H NMR (400 MHz, $CDCl_3$)



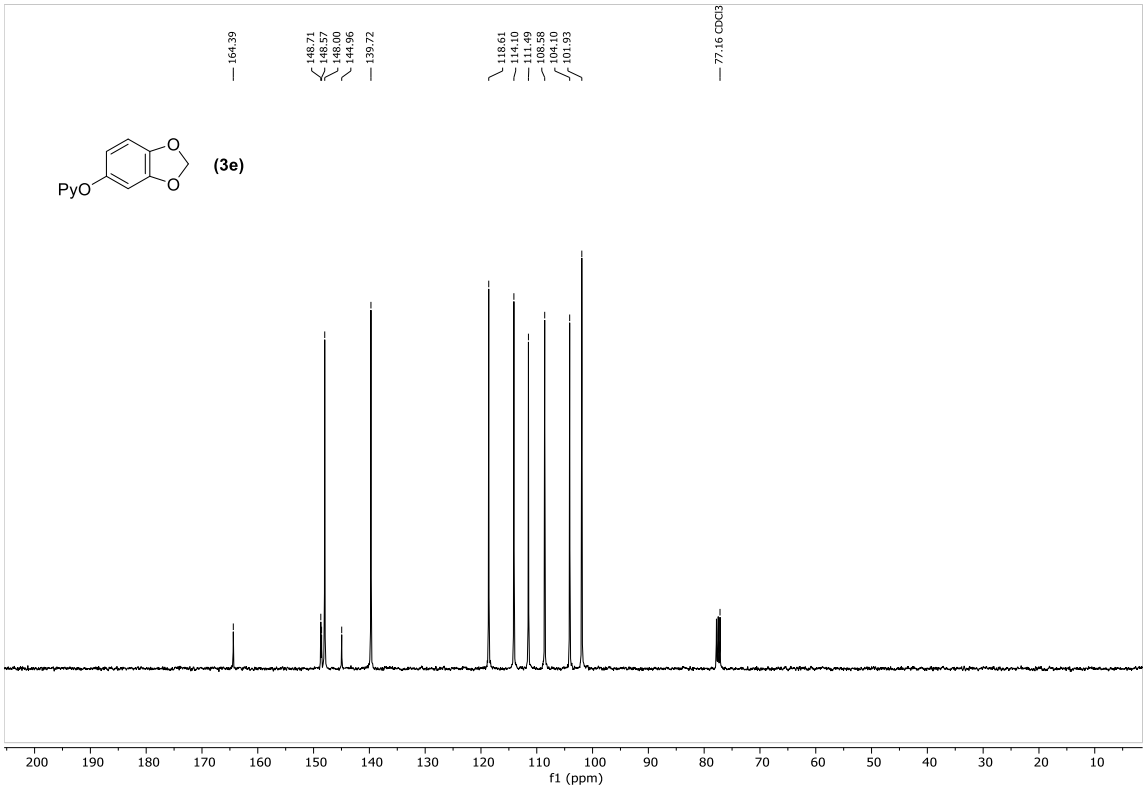
^{13}C NMR (101 MHz, $CDCl_3$)



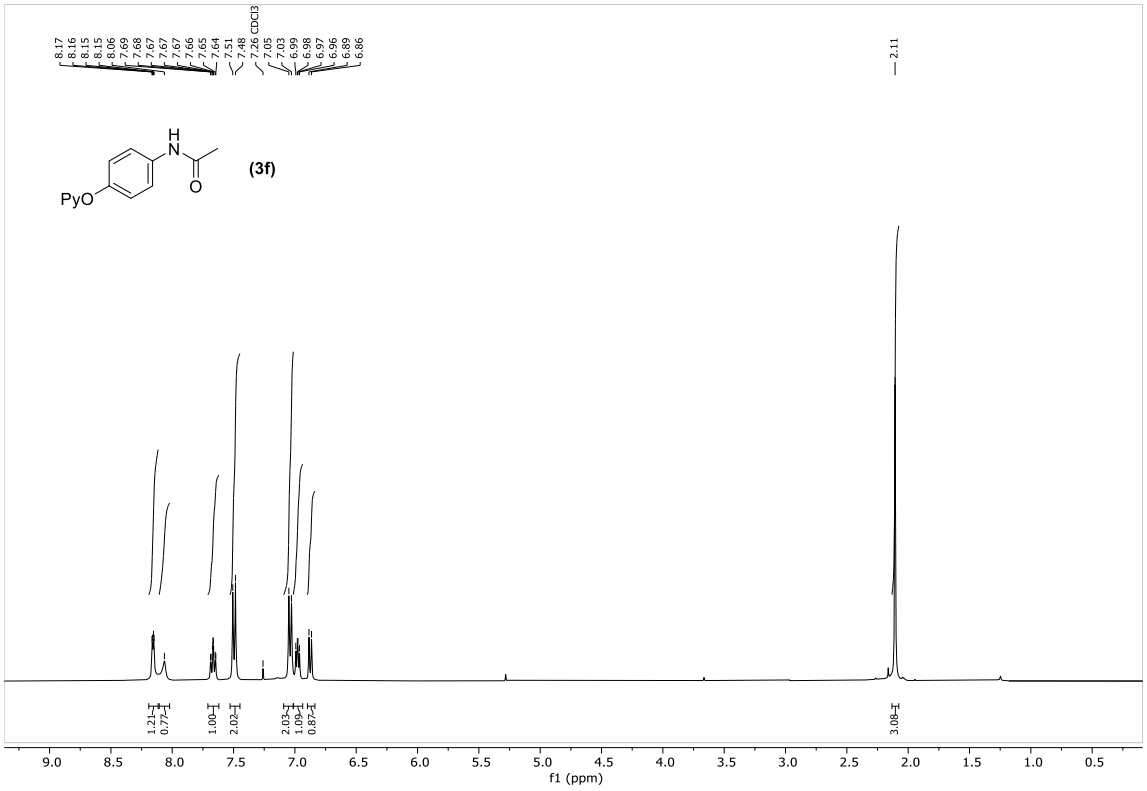
^{1}H NMR (400 MHz, $CDCl_3$)



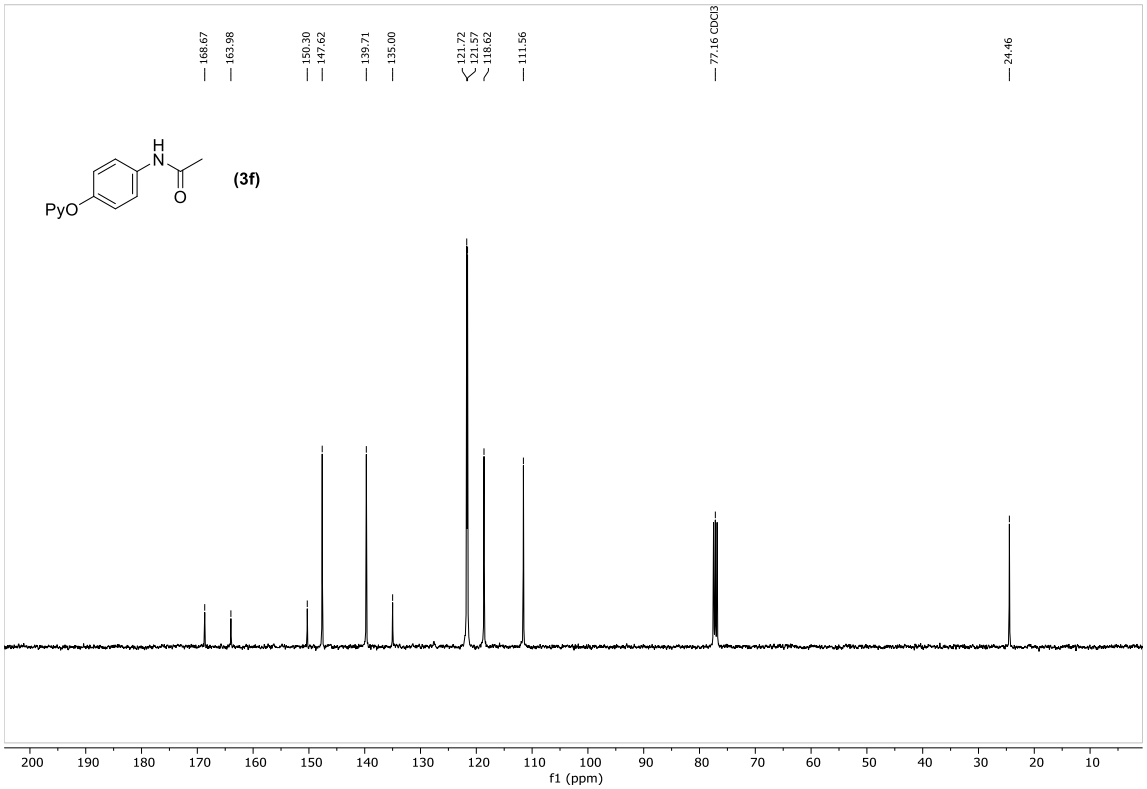
^{13}C NMR (101 MHz, $CDCl_3$)



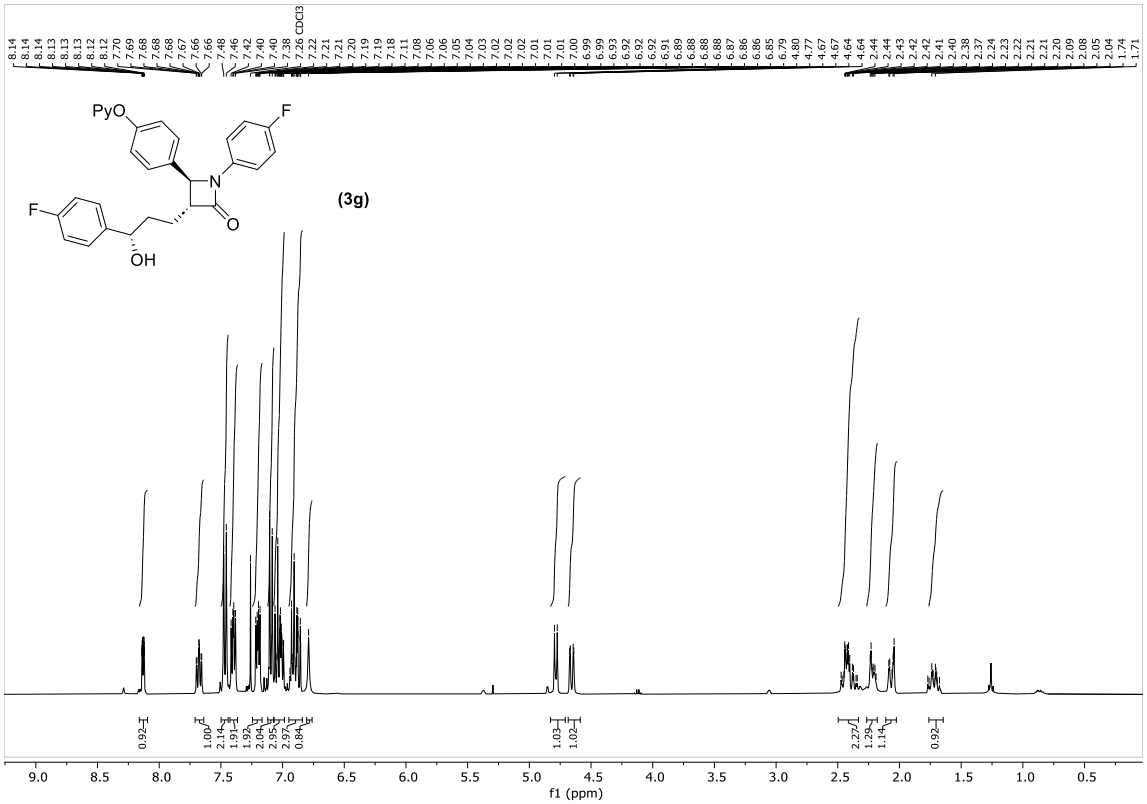
^{1}H NMR (400 MHz, $CDCl_3$)



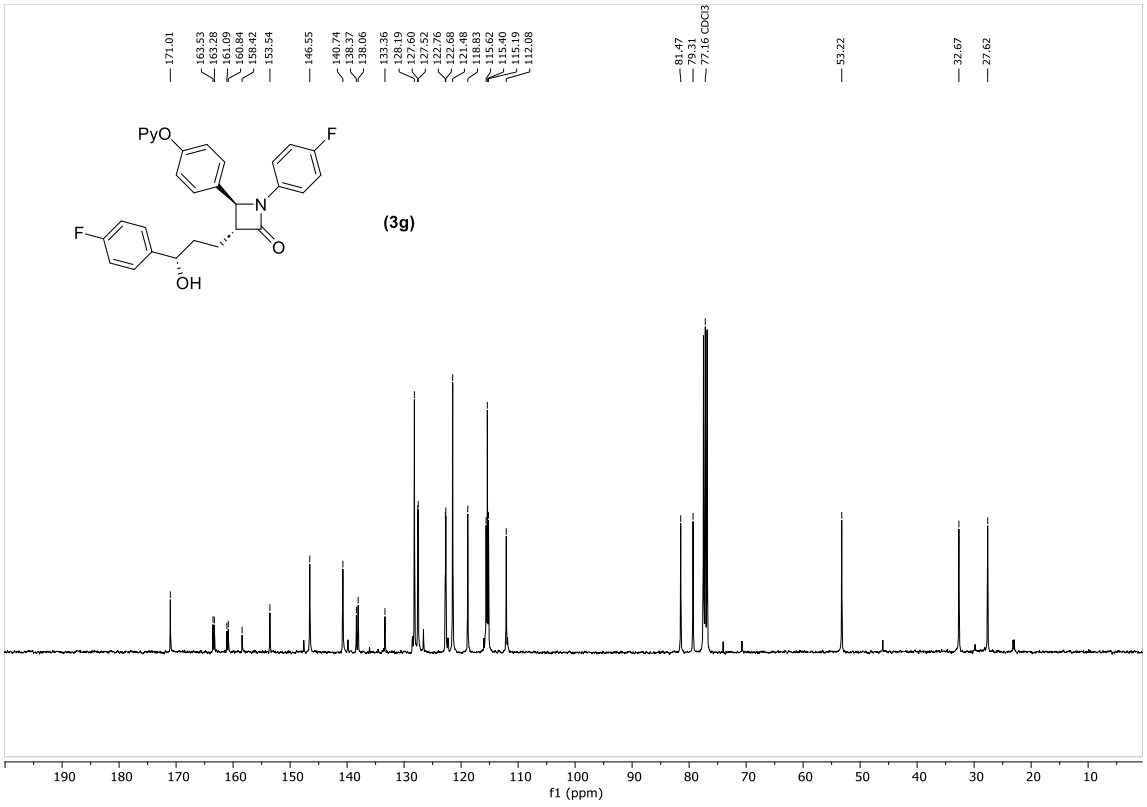
^{13}C NMR (101 MHz, $CDCl_3$)



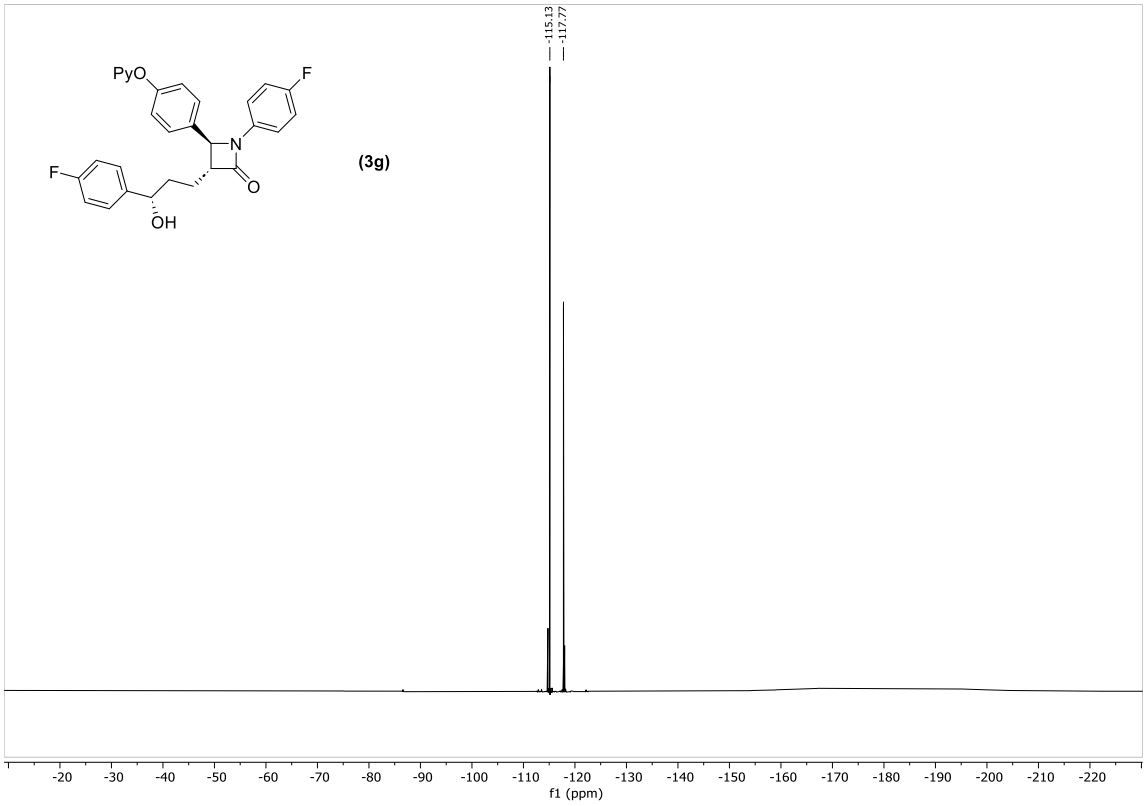
^{1}H NMR (400 MHz, $CDCl_3$)



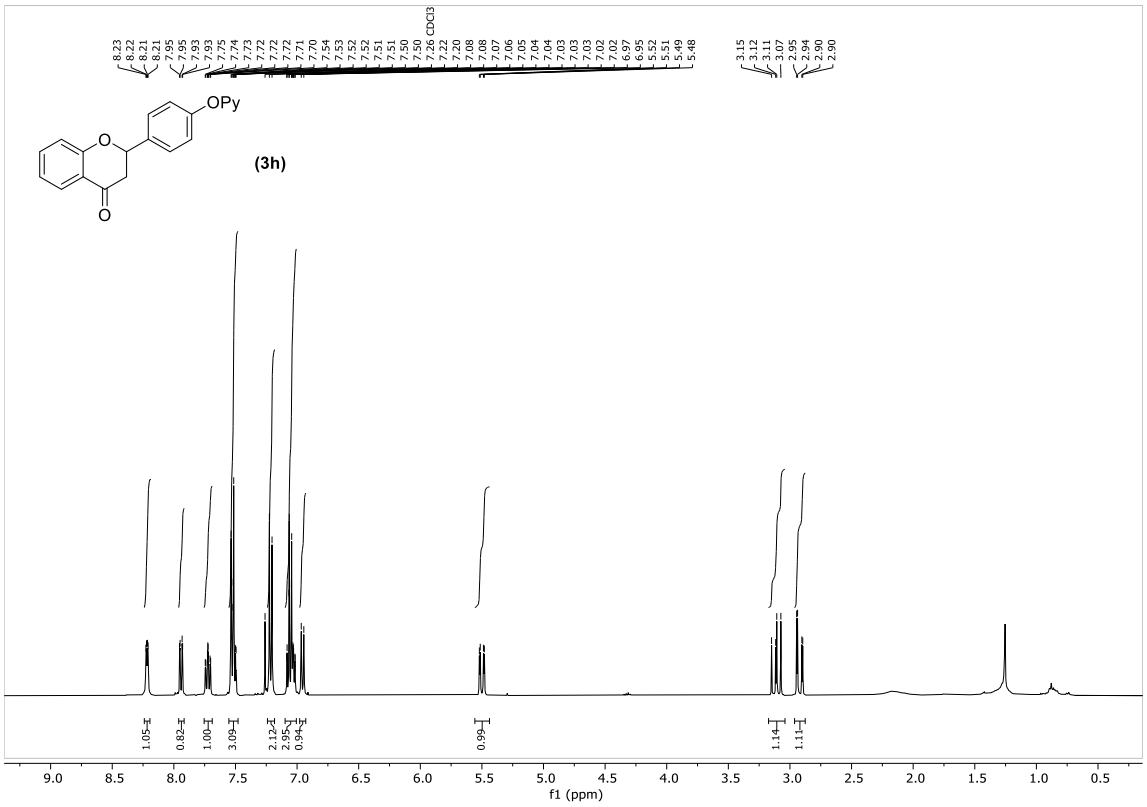
^{13}C NMR (101 MHz, $CDCl_3$)



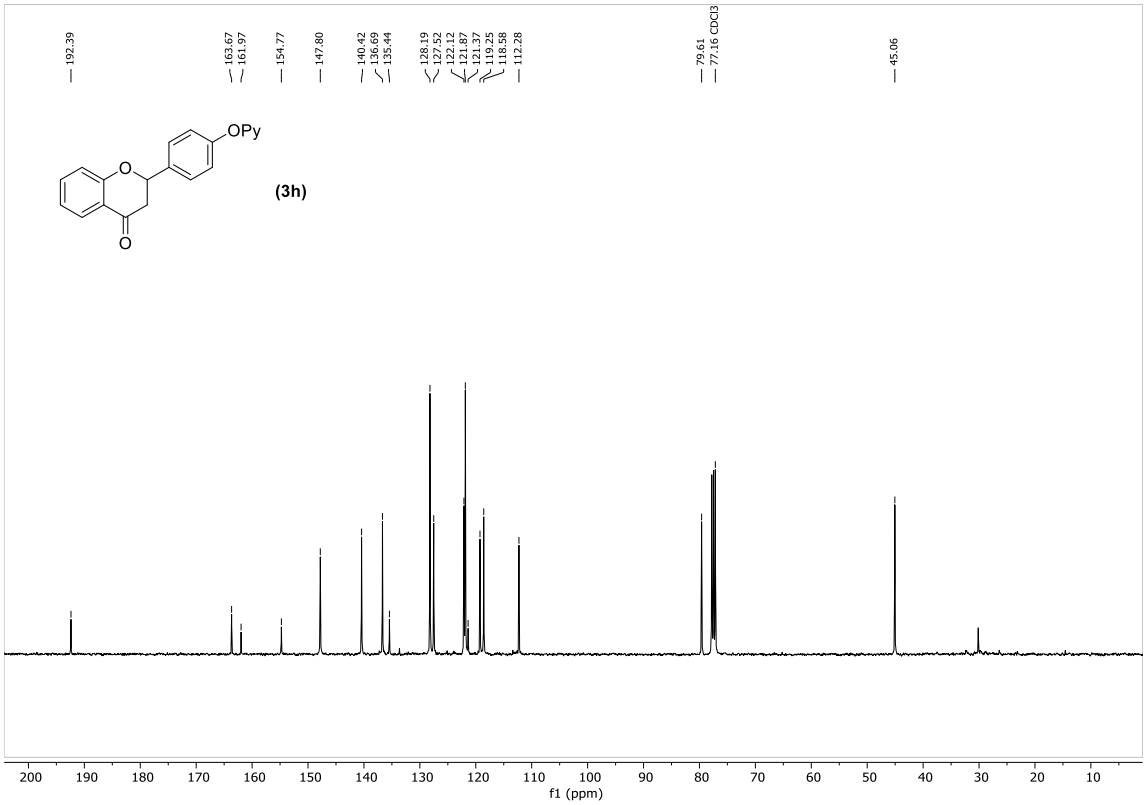
^{19}F NMR (376 MHz, $CDCl_3$)



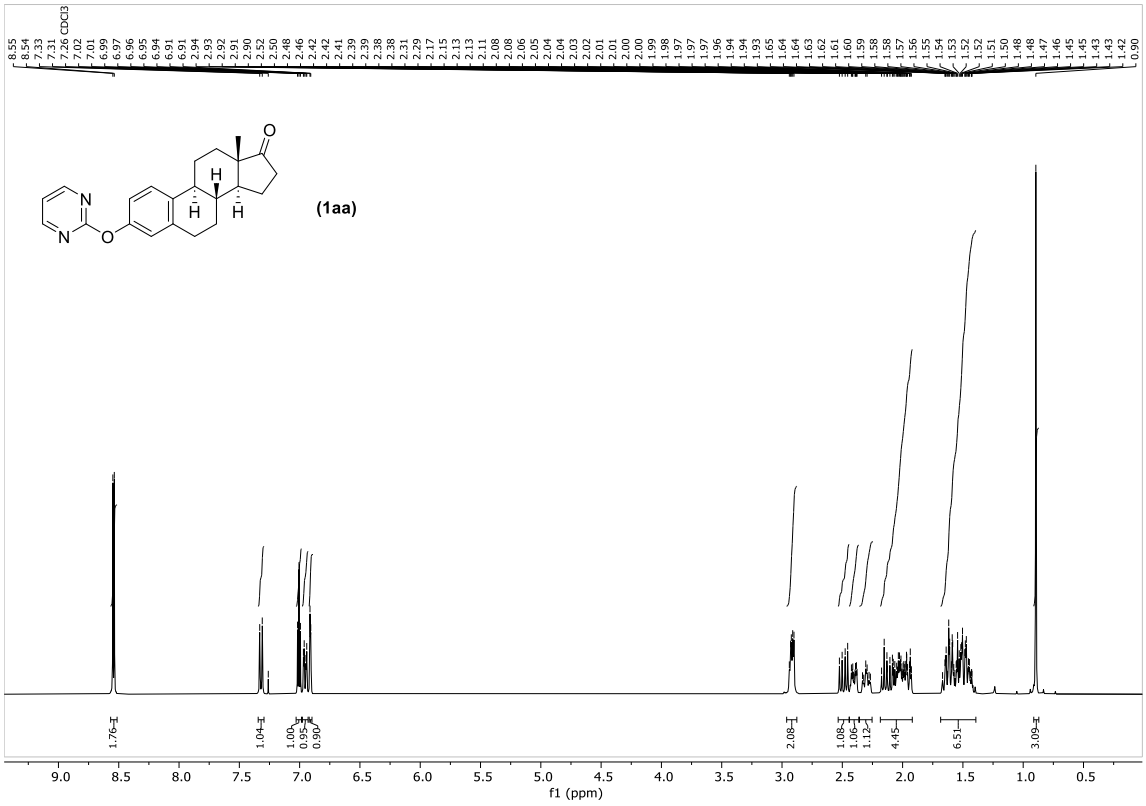
^{1}H NMR (400 MHz, $CDCl_3$)



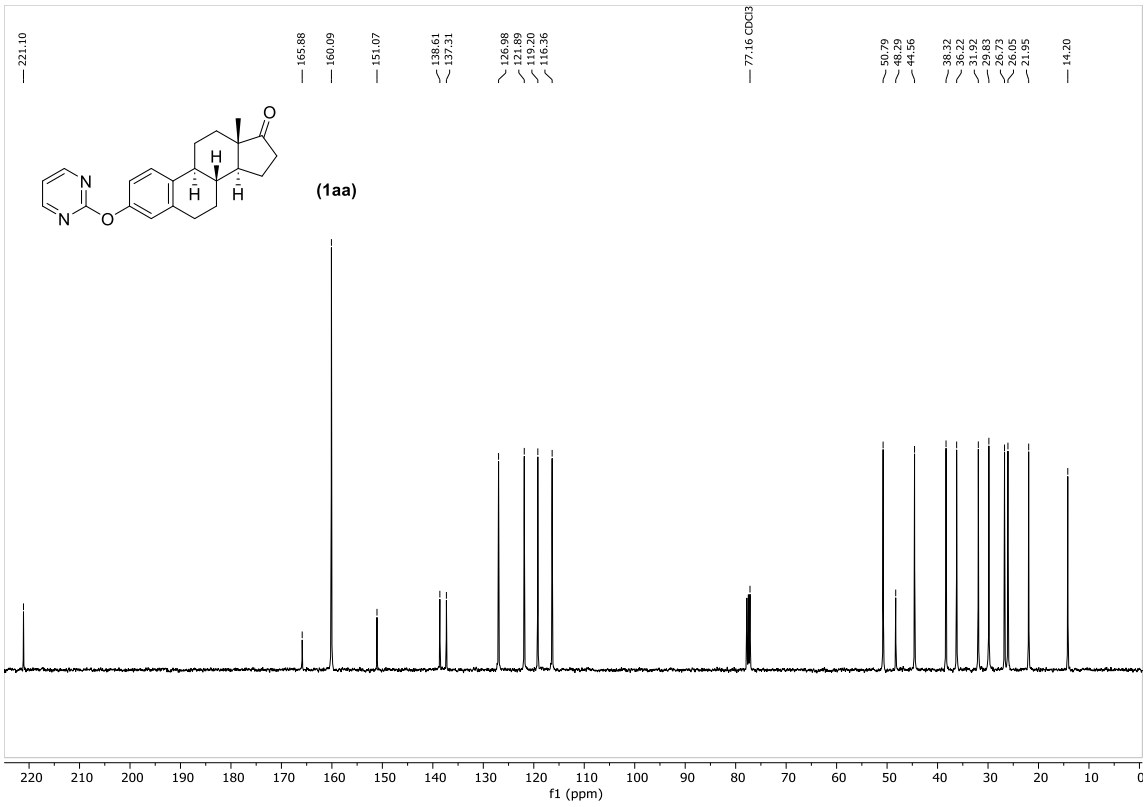
^{13}C NMR (101 MHz, $CDCl_3$)



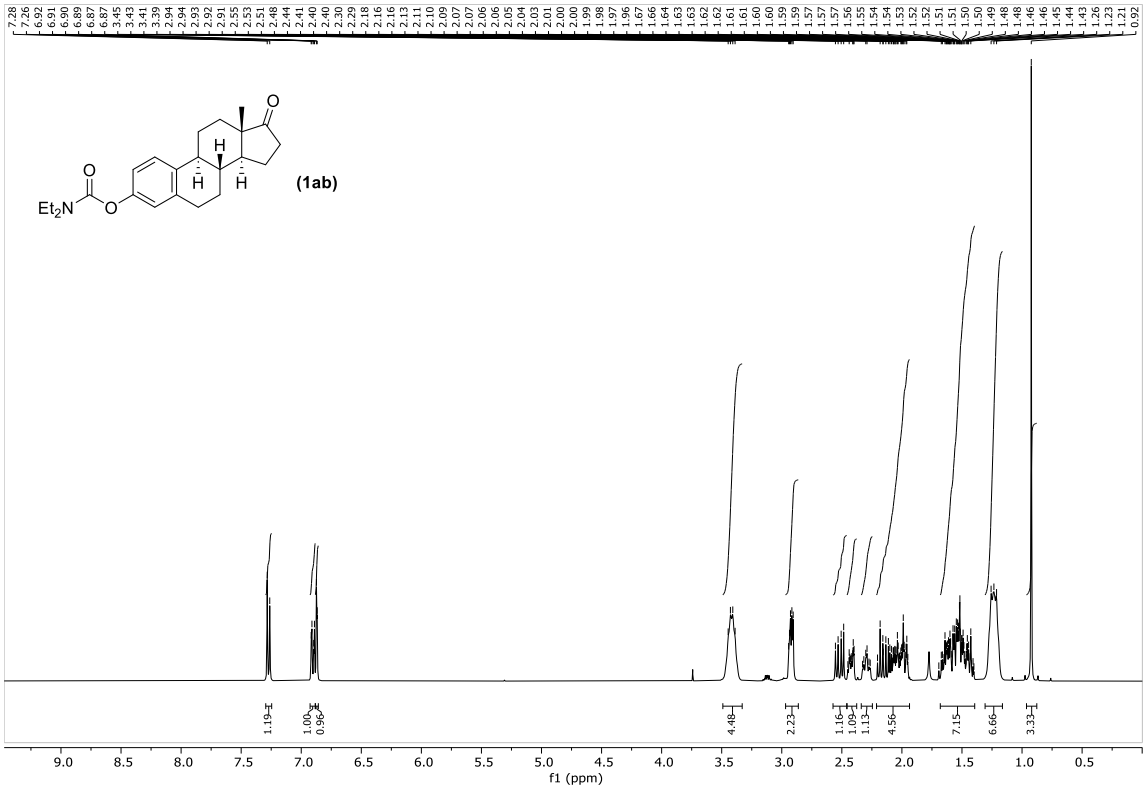
^{1}H NMR (400 MHz, $CDCl_3$)



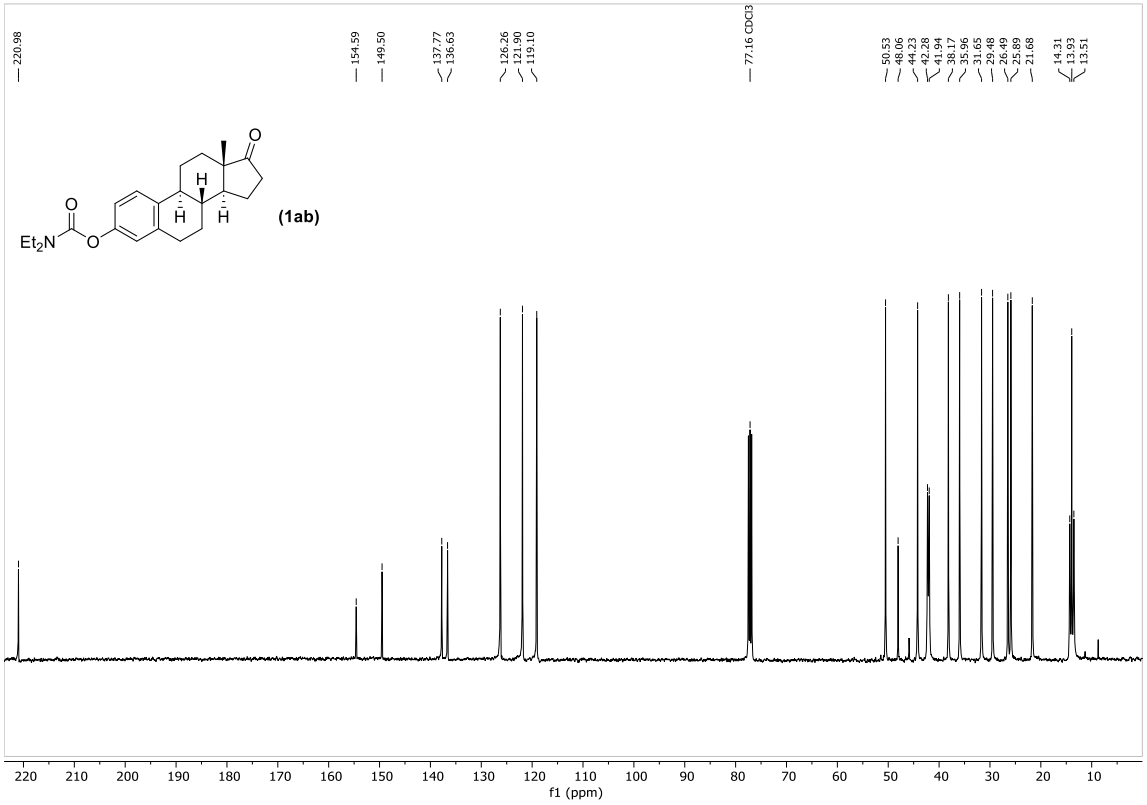
^{13}C NMR (101 MHz, $CDCl_3$)



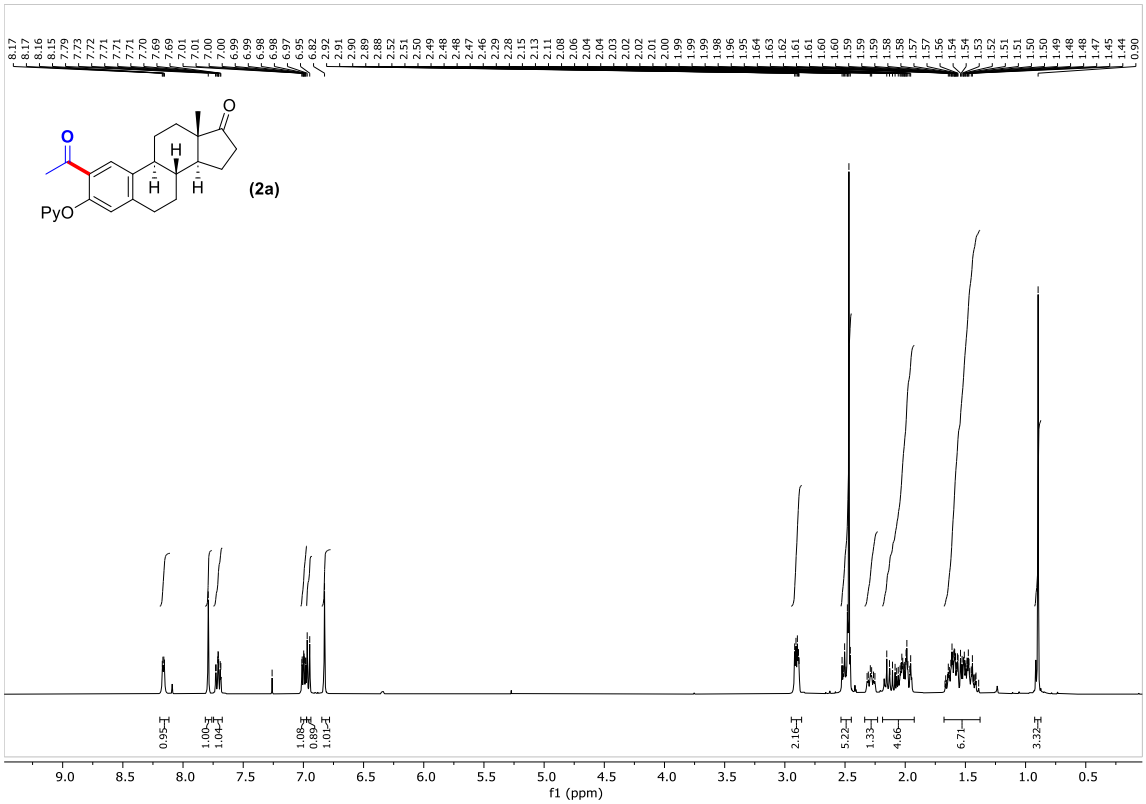
^{1}H NMR (400 MHz, $CDCl_3$)



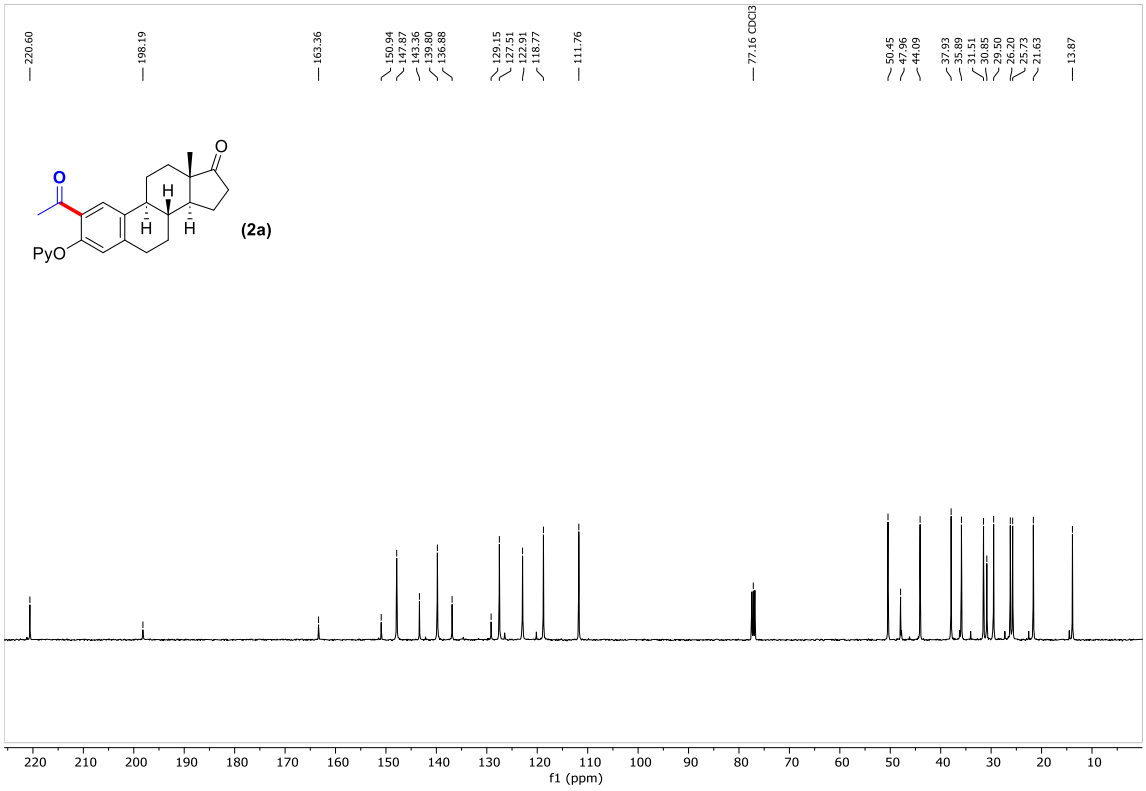
^{13}C NMR (101 MHz, $CDCl_3$)



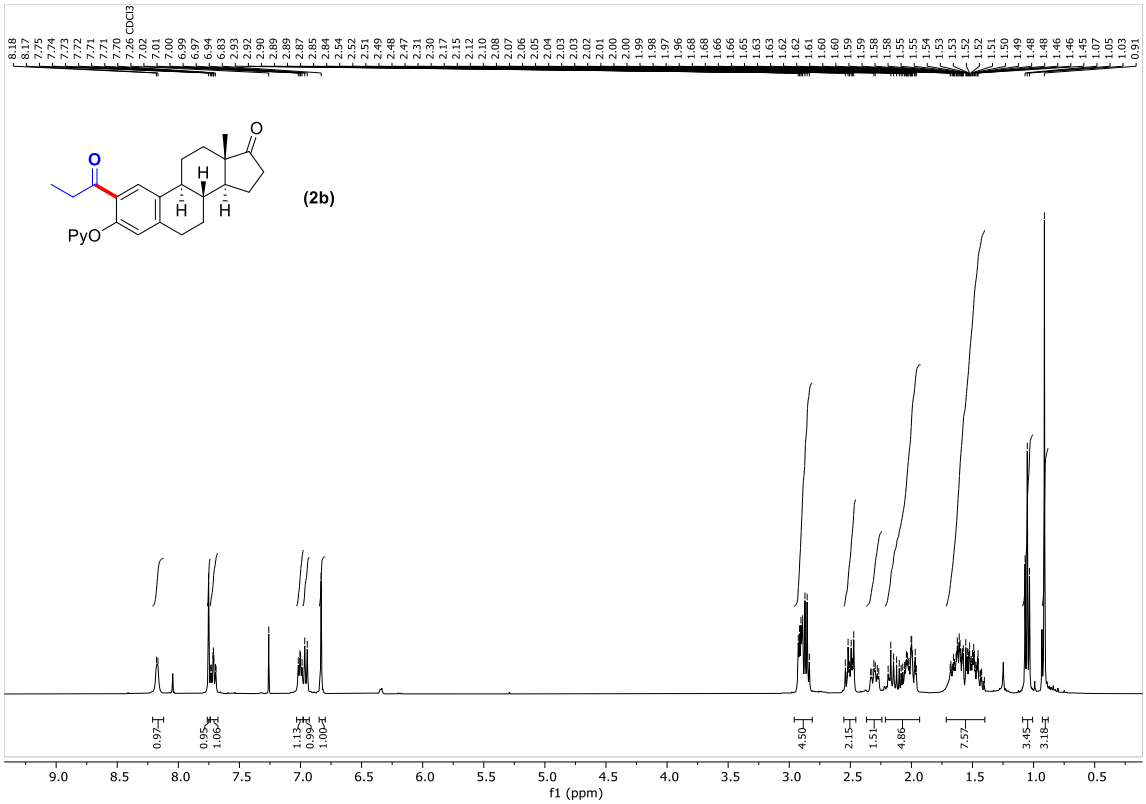
^{1}H NMR (400 MHz, $CDCl_3$)



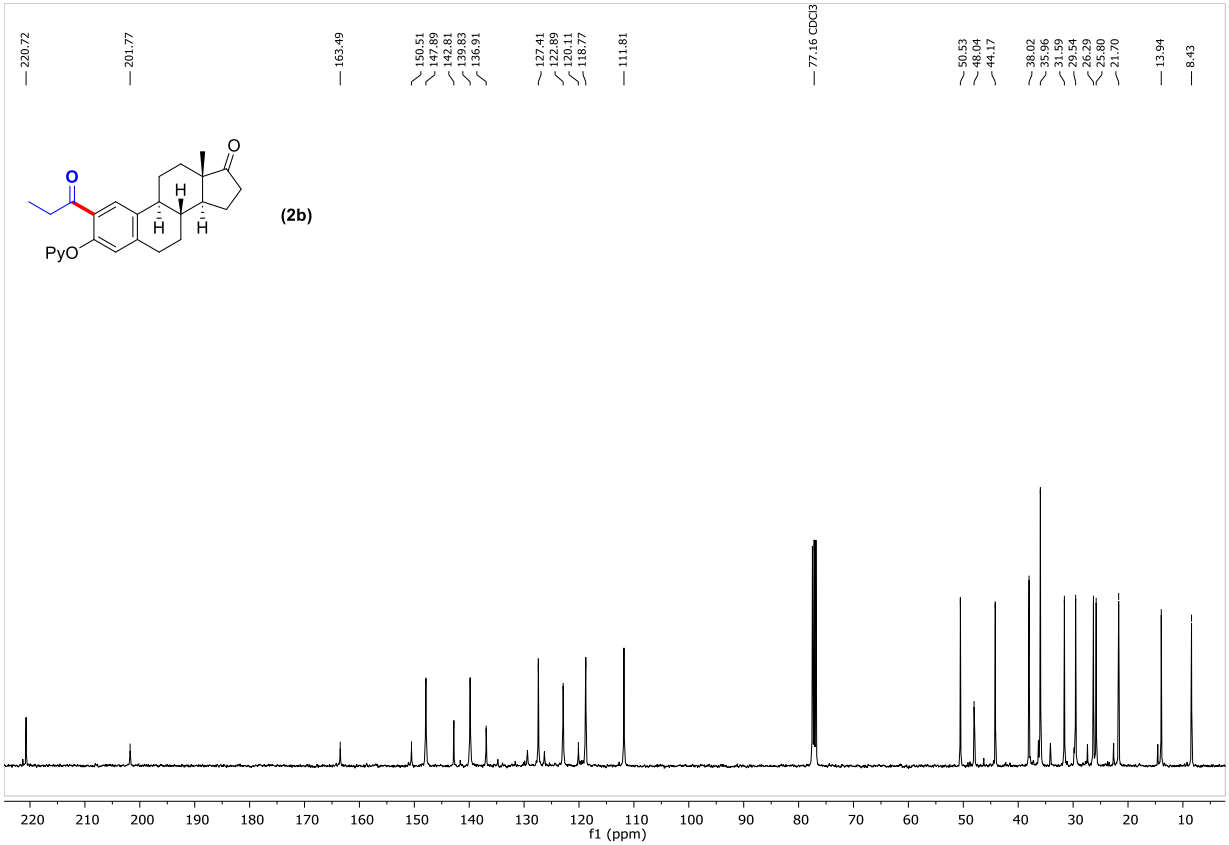
^{13}C NMR (101 MHz, $CDCl_3$)



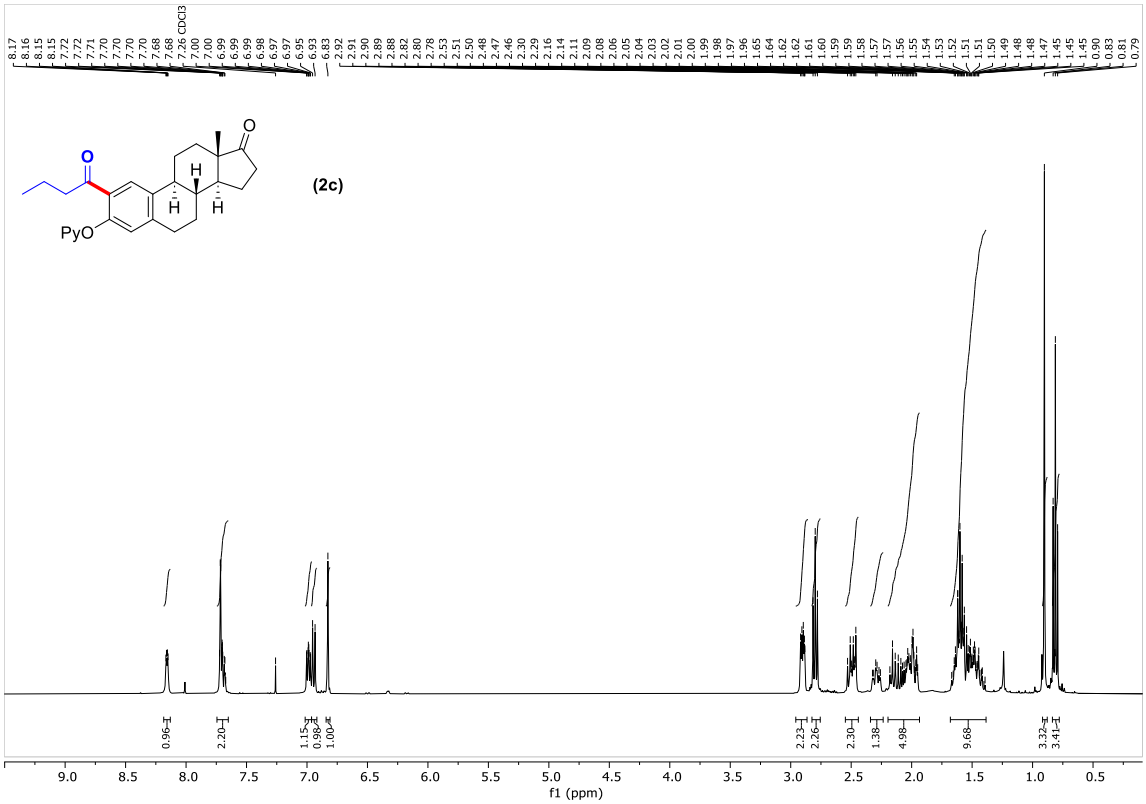
^{1}H NMR (400 MHz, $CDCl_3$)



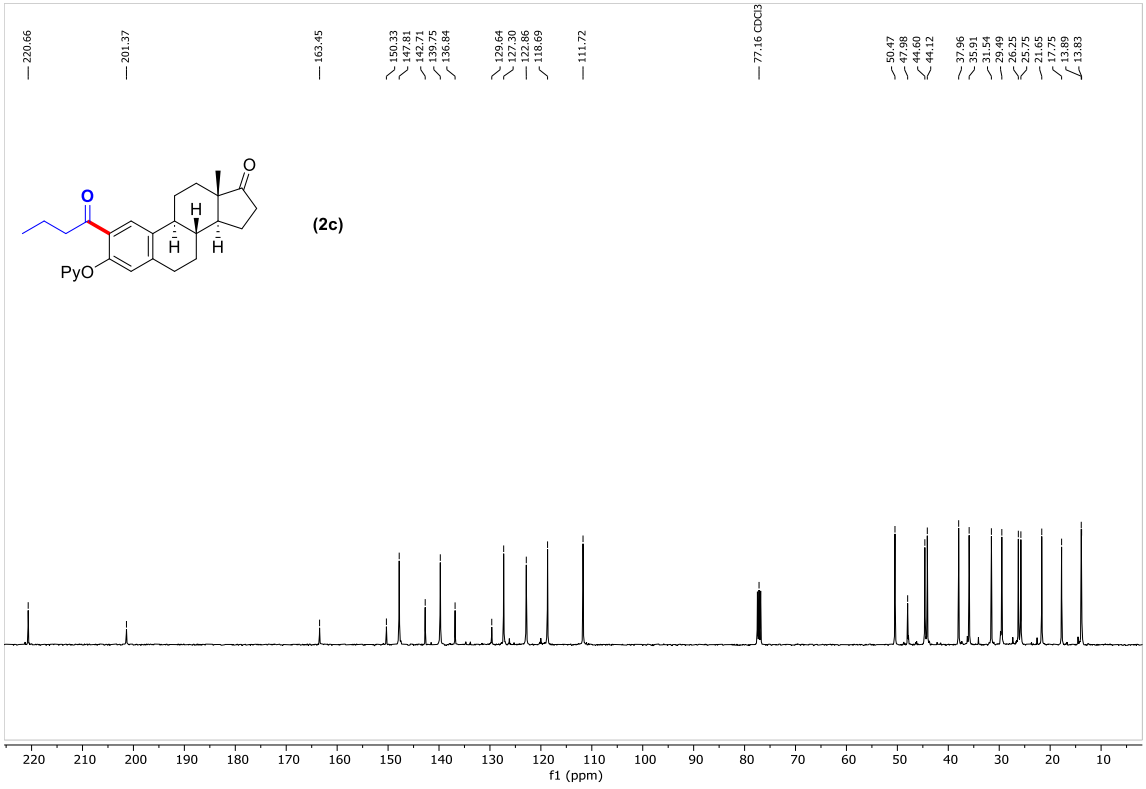
^{13}C NMR (101 MHz, $CDCl_3$)



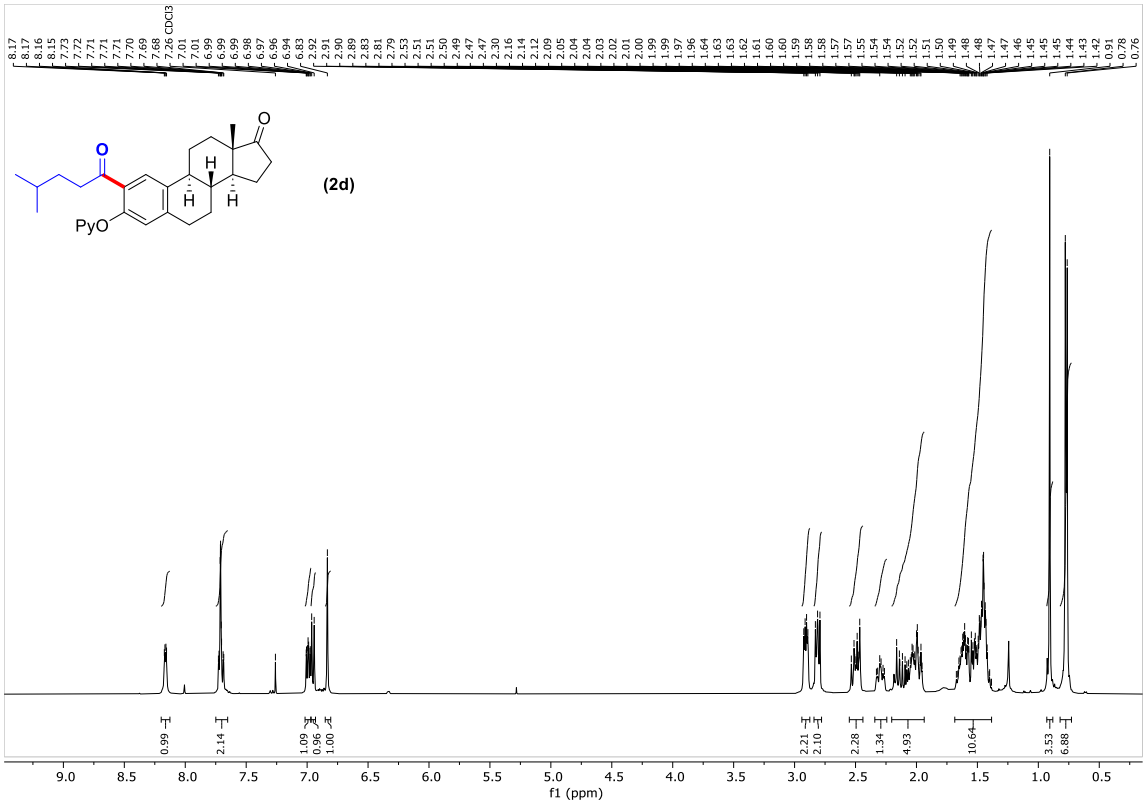
^{1}H NMR (400 MHz, $CDCl_3$)



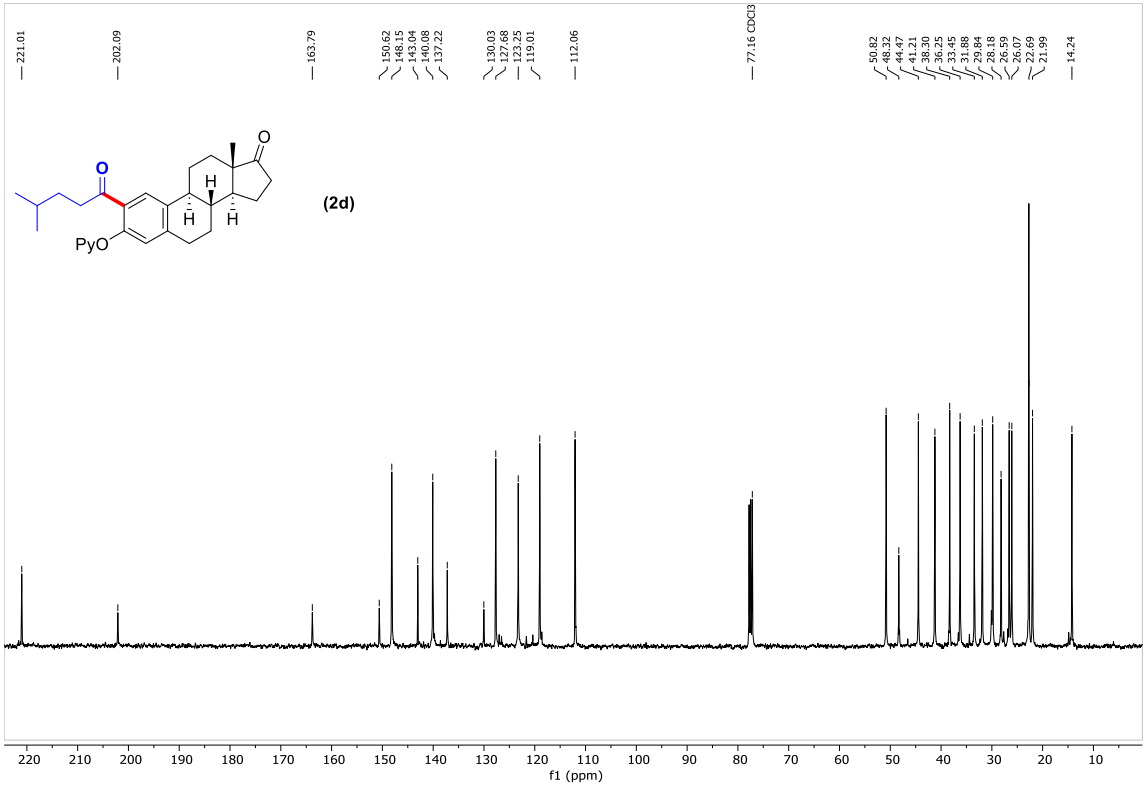
^{13}C NMR (101 MHz, $CDCl_3$)



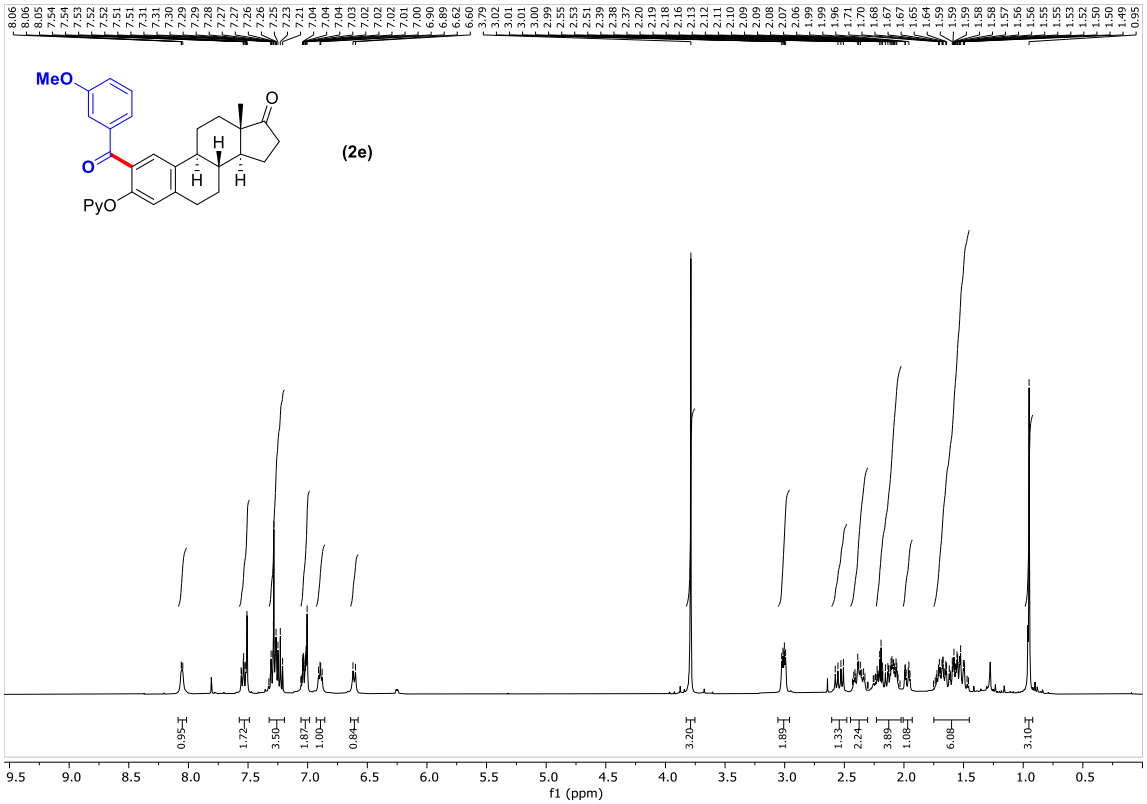
^{1}H NMR (400 MHz, $CDCl_3$)



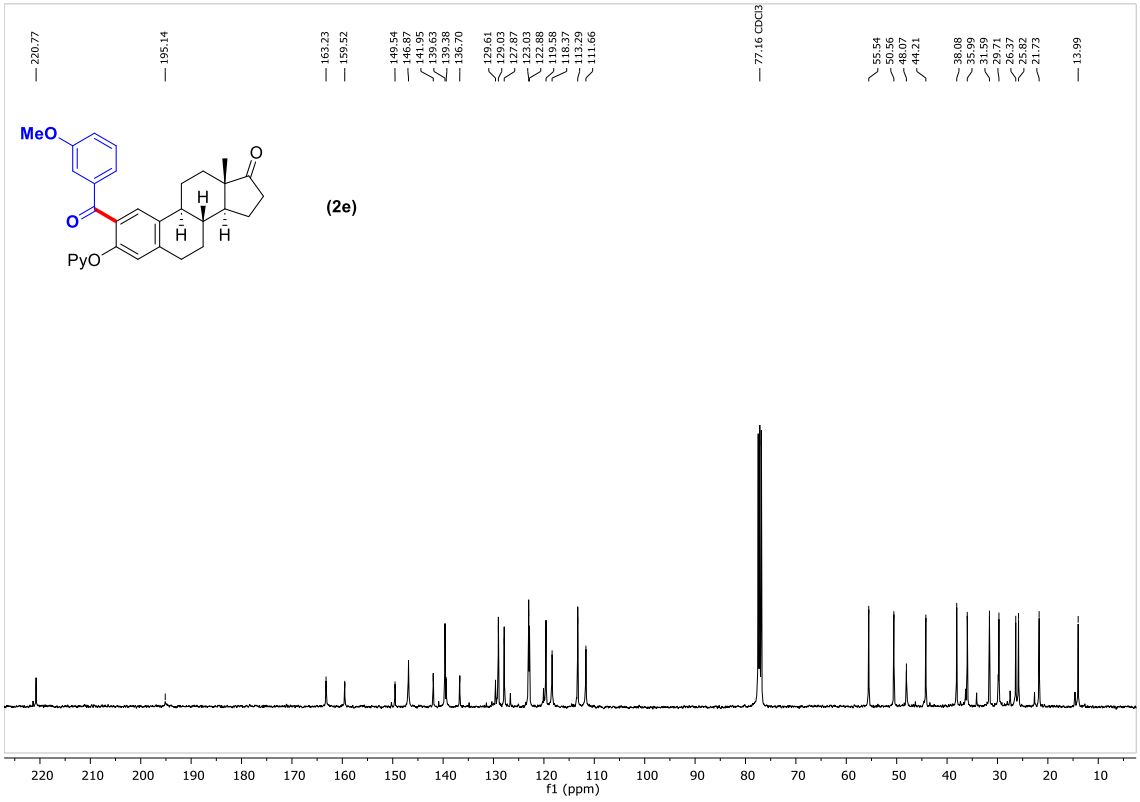
^{13}C NMR (101 MHz, $CDCl_3$)



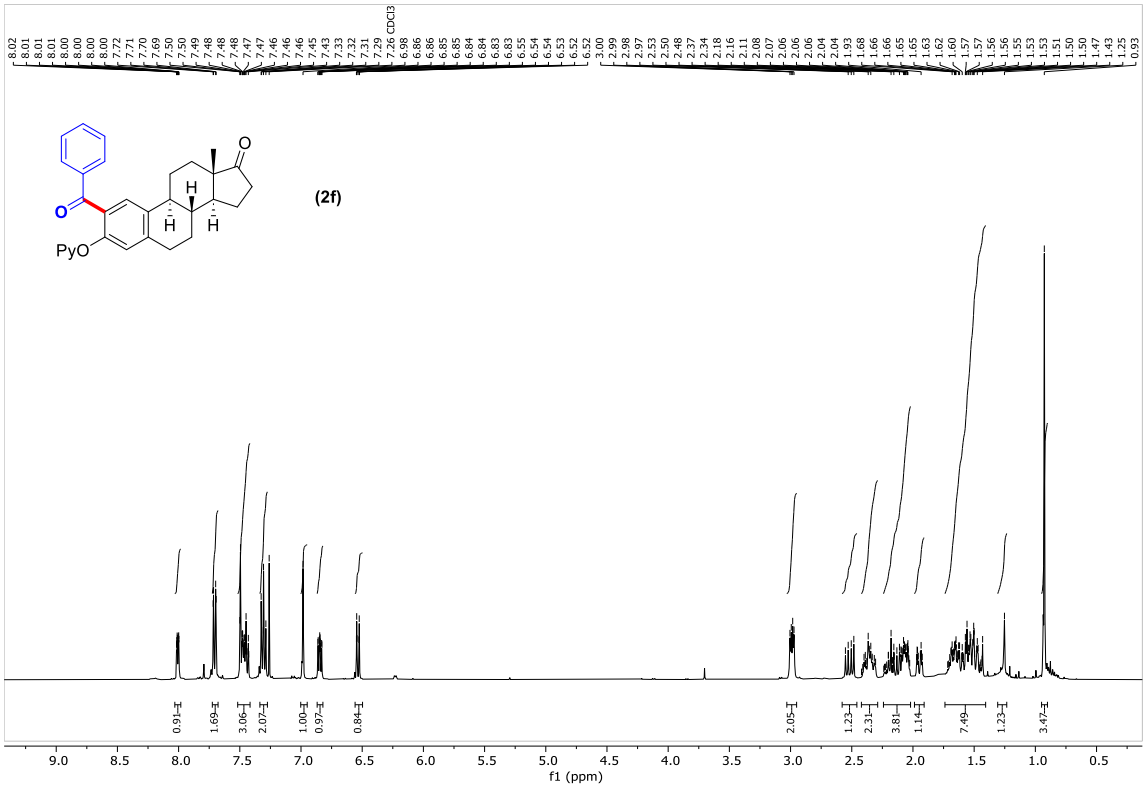
^{1}H NMR (400 MHz, $CDCl_3$)



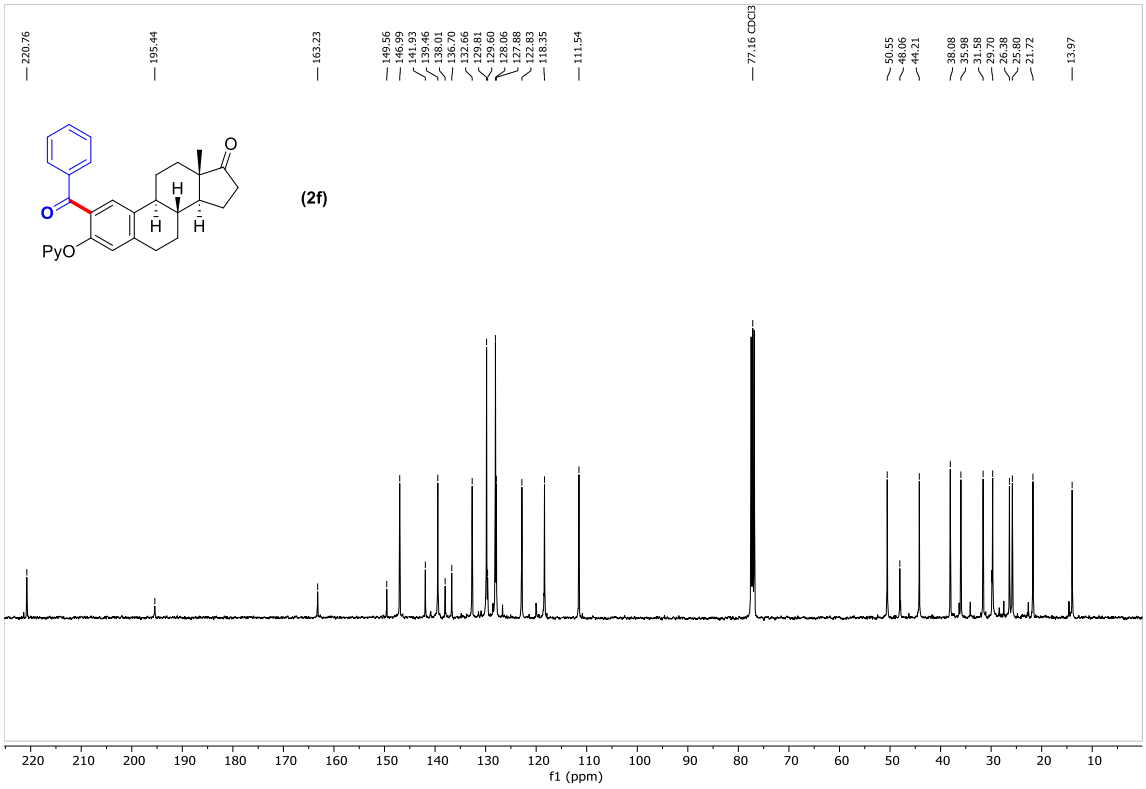
^{13}C NMR (101 MHz, $CDCl_3$)



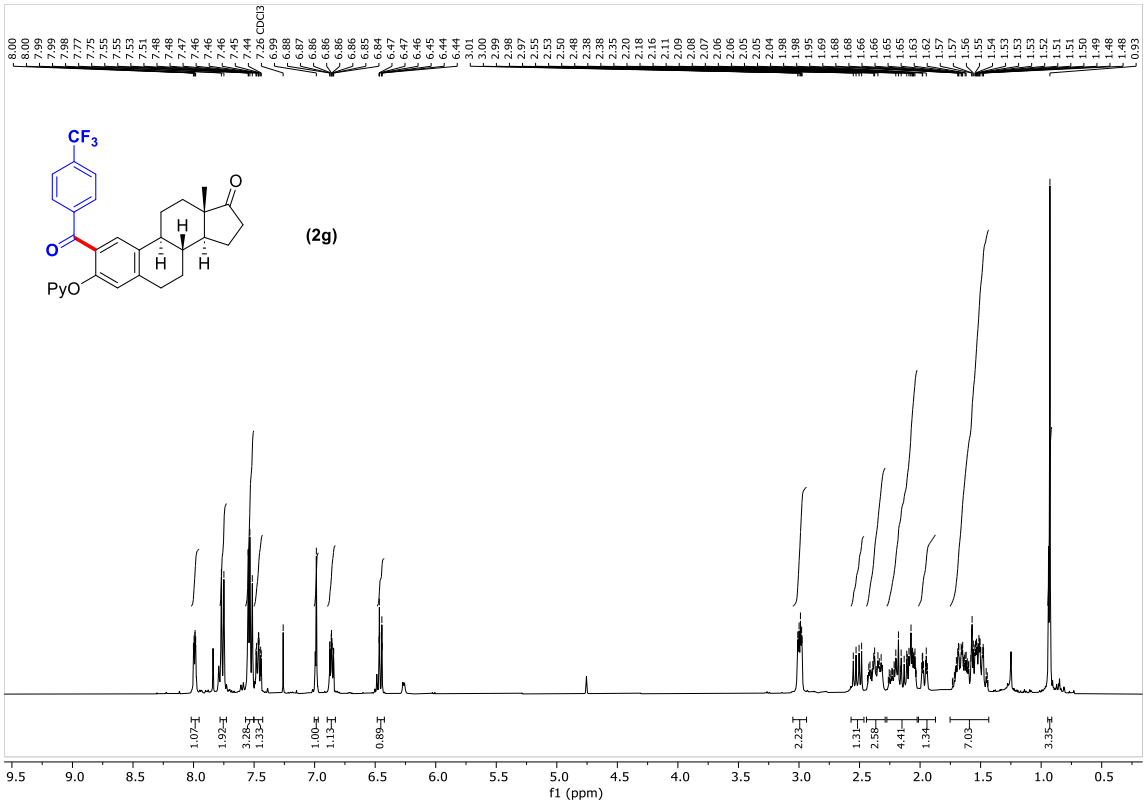
^{1}H NMR (400 MHz, $CDCl_3$)



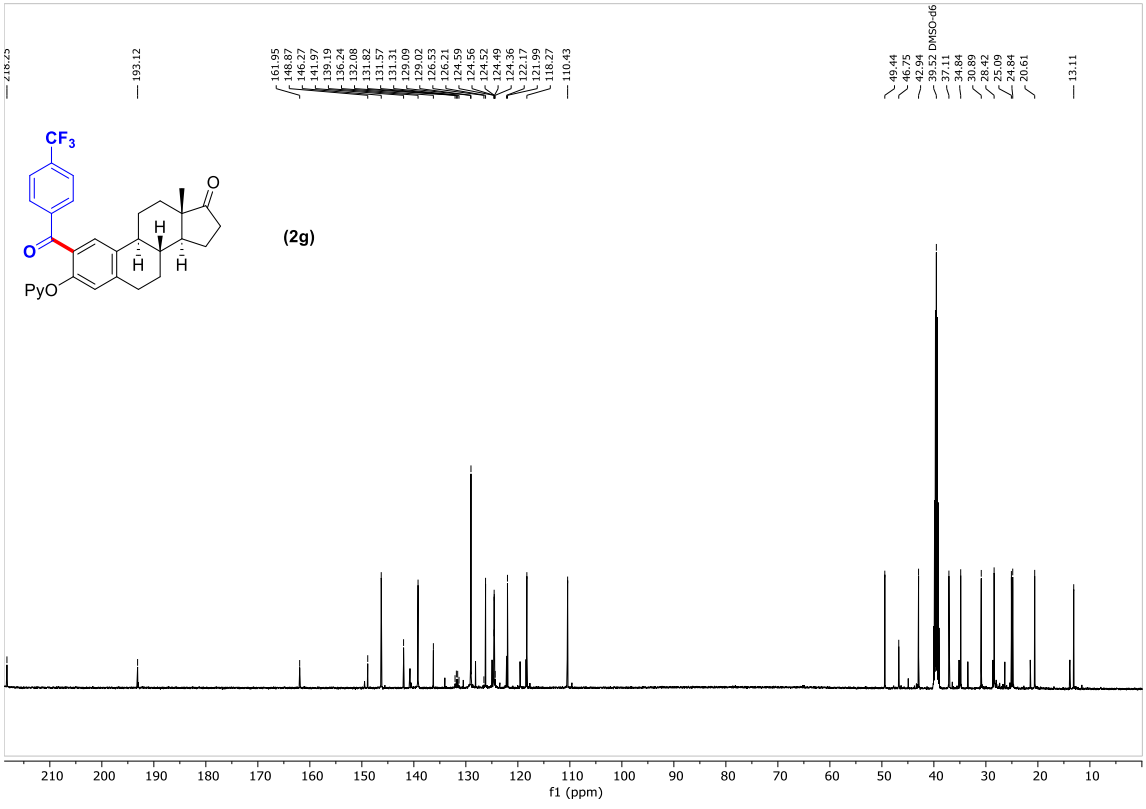
^{13}C NMR (101 MHz, $CDCl_3$)



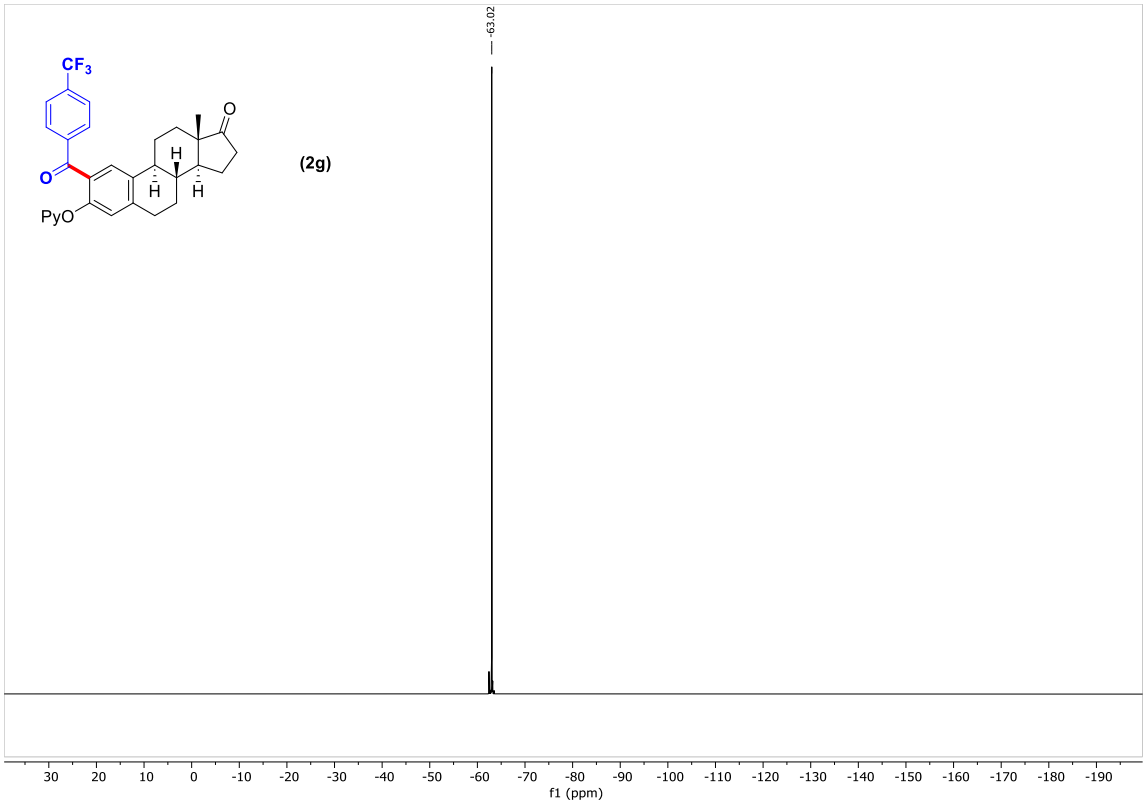
^{1}H NMR (400 MHz, $CDCl_3$)



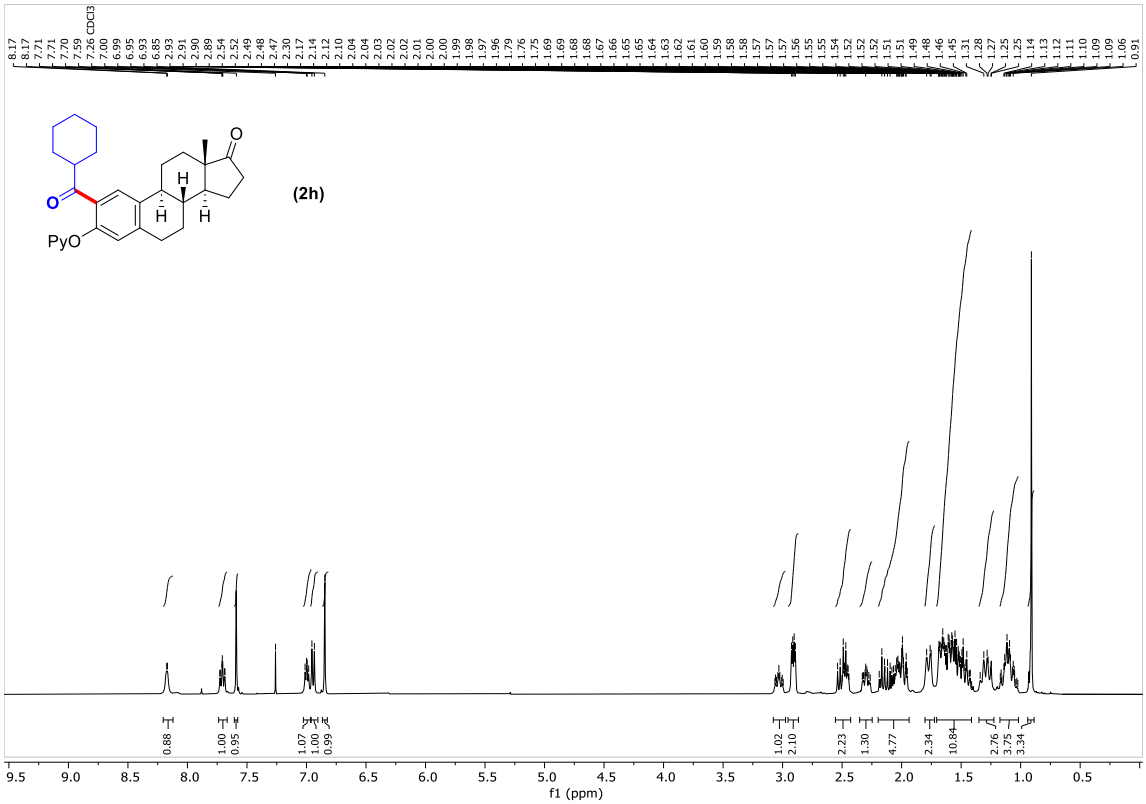
^{13}C NMR (126 MHz, DMSO-d_6 at 80 °C)



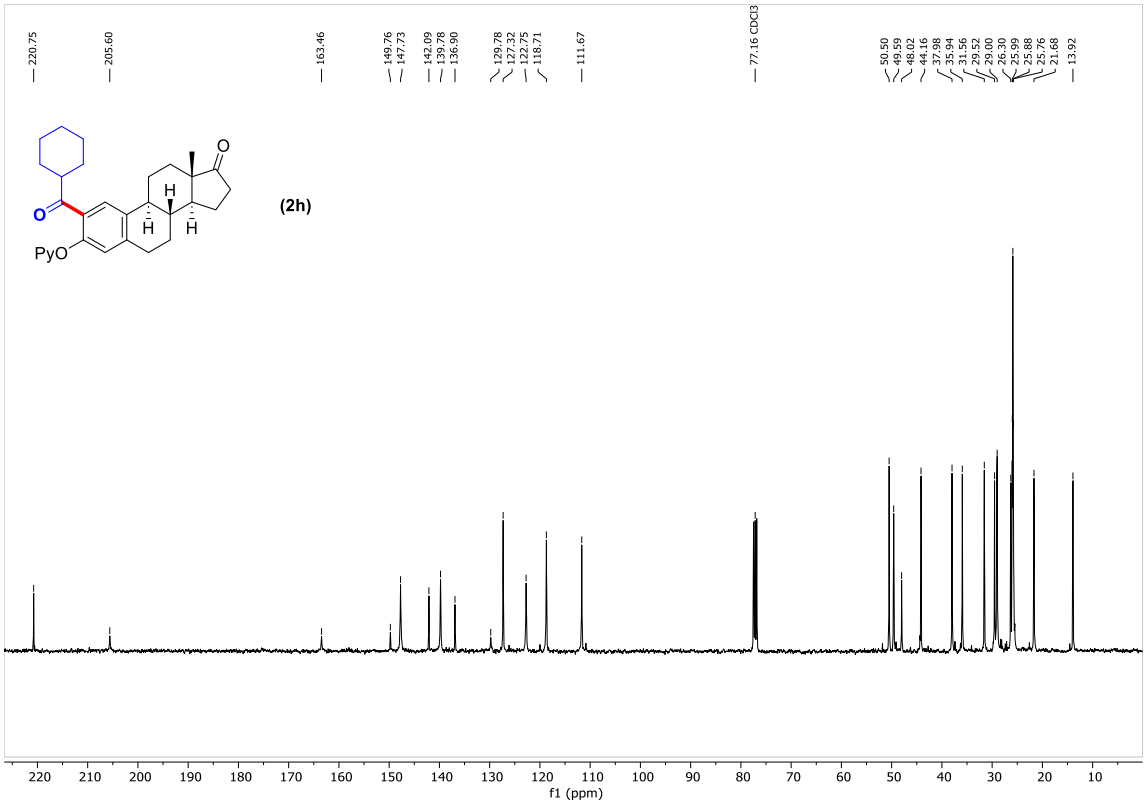
^{19}F NMR (376 MHz, $CDCl_3$)



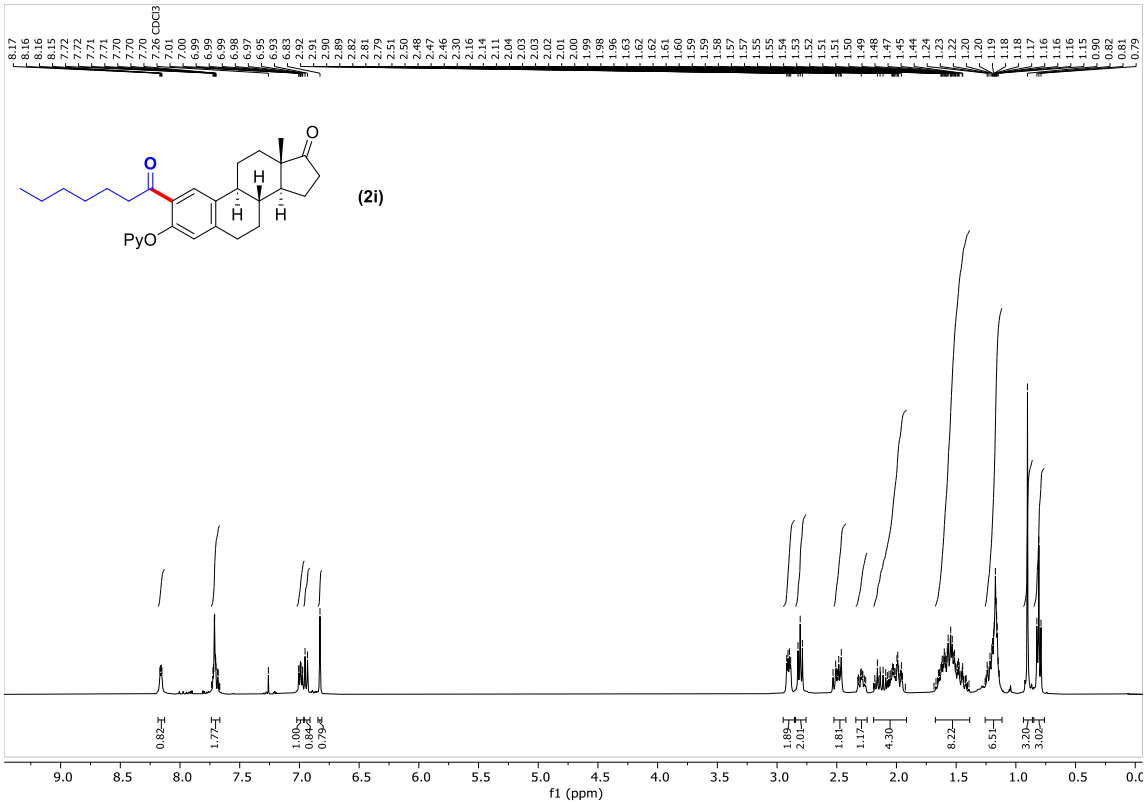
^{1}H NMR (400 MHz, $CDCl_3$)



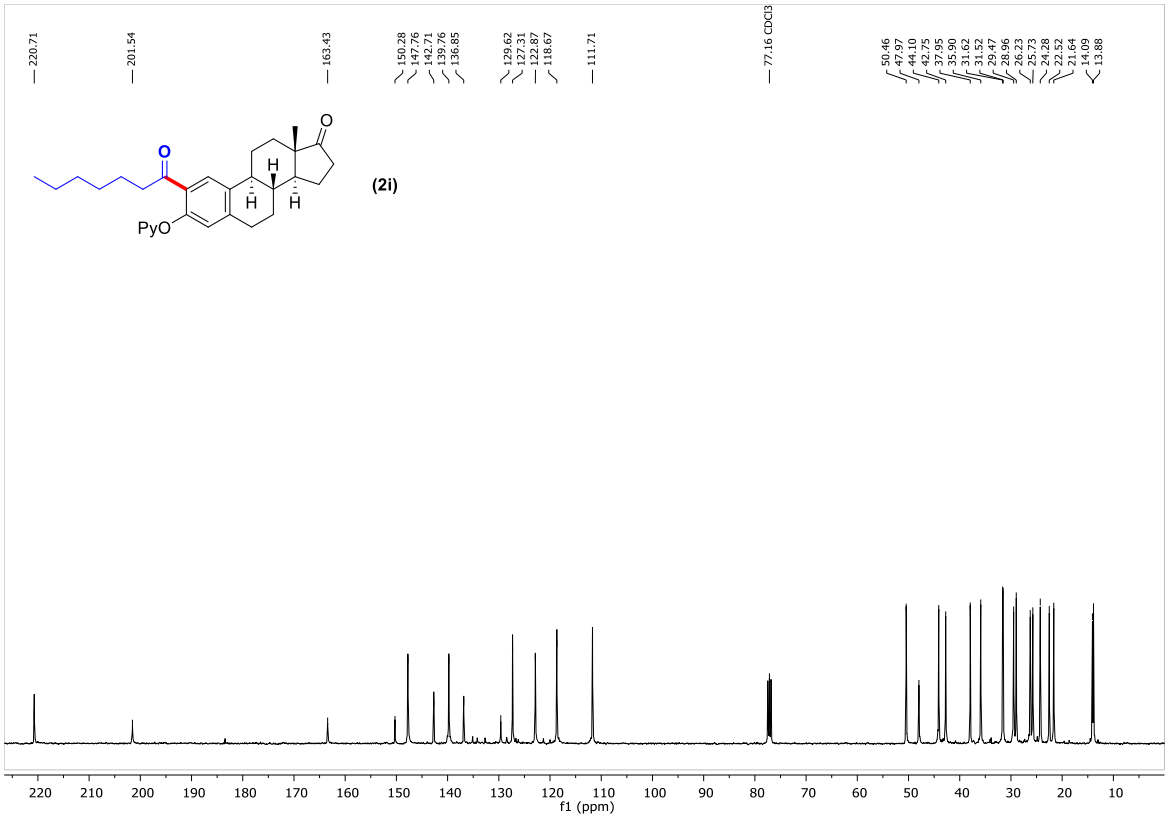
^{13}C NMR (101 MHz, $CDCl_3$)



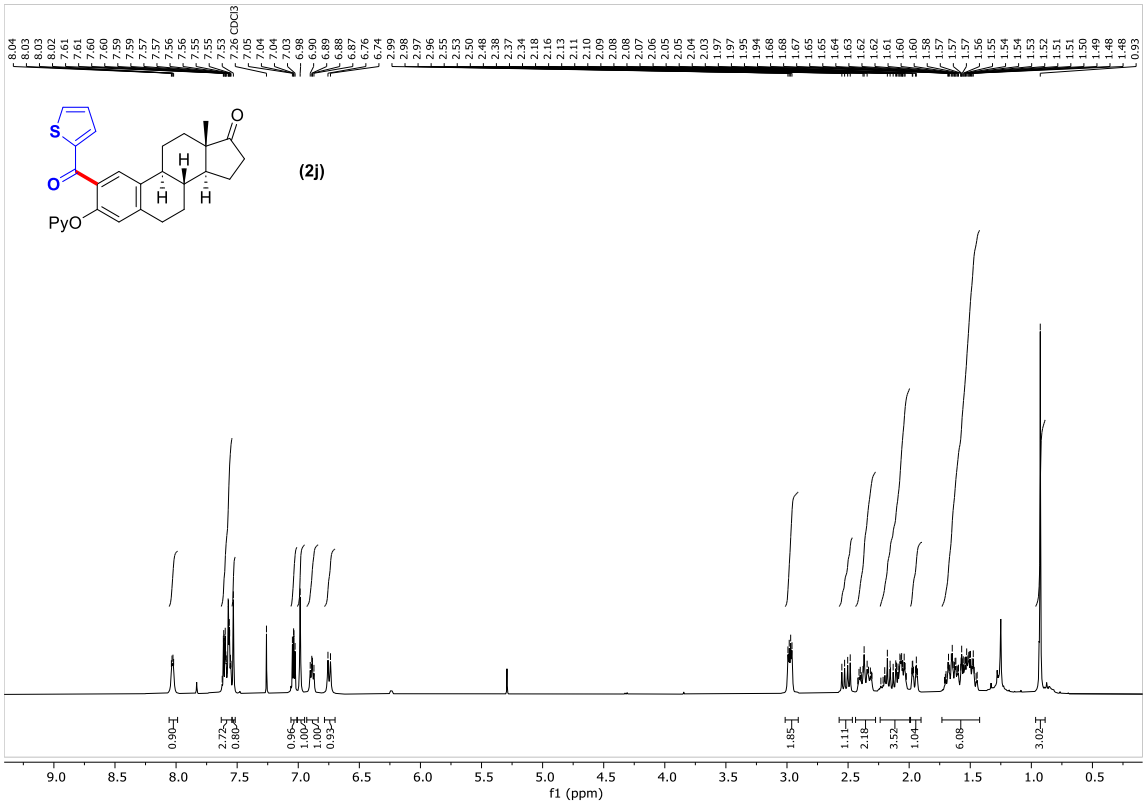
^{1}H NMR (400 MHz, $CDCl_3$)



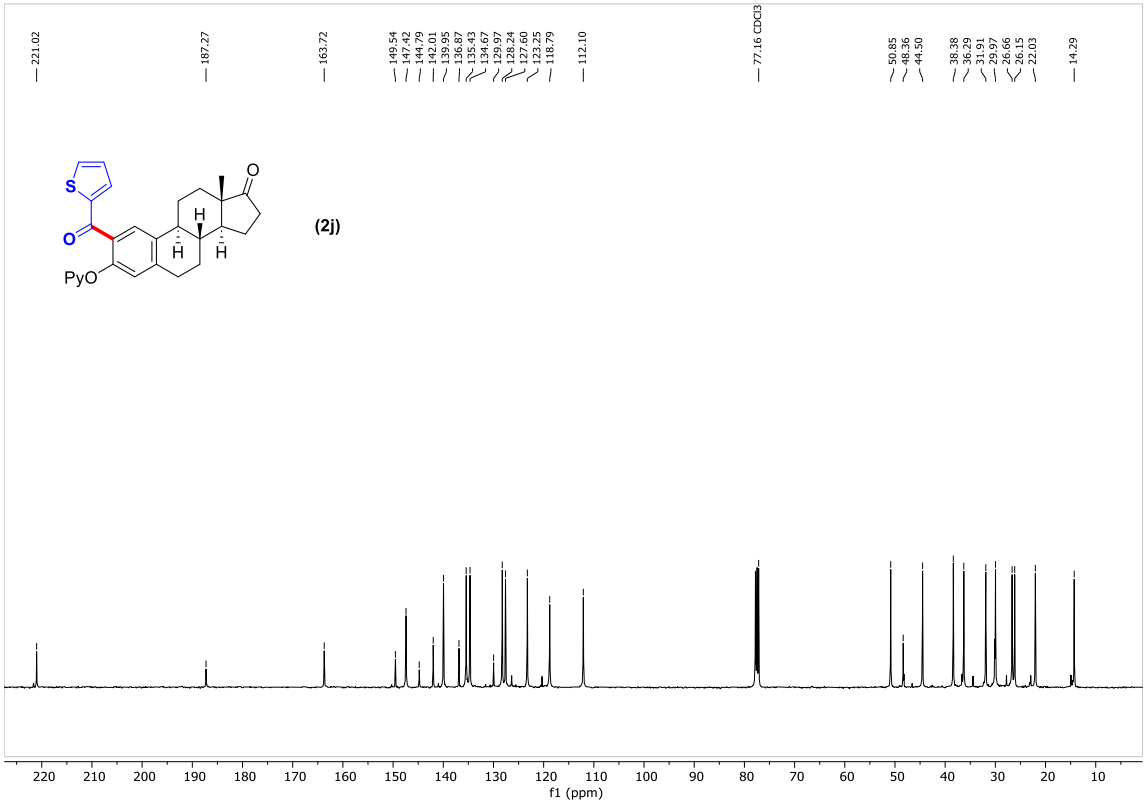
^{13}C NMR (101 MHz, $CDCl_3$)



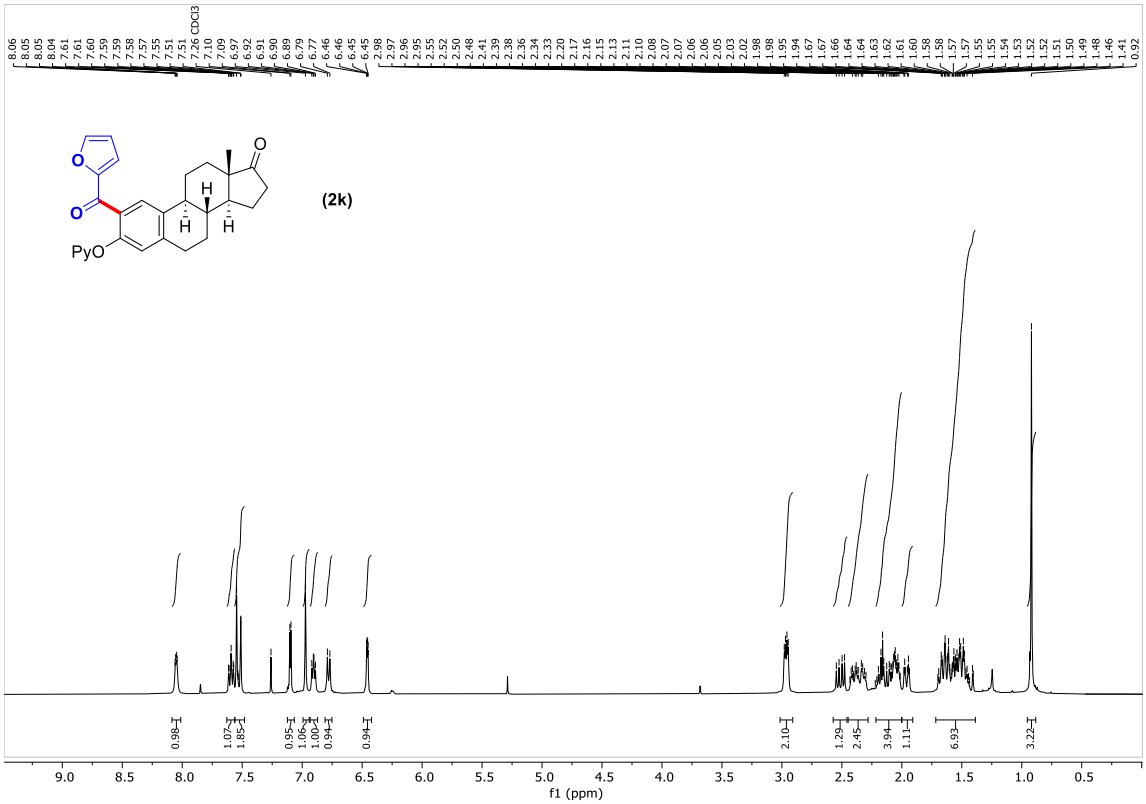
^{1}H NMR (400 MHz, $CDCl_3$)



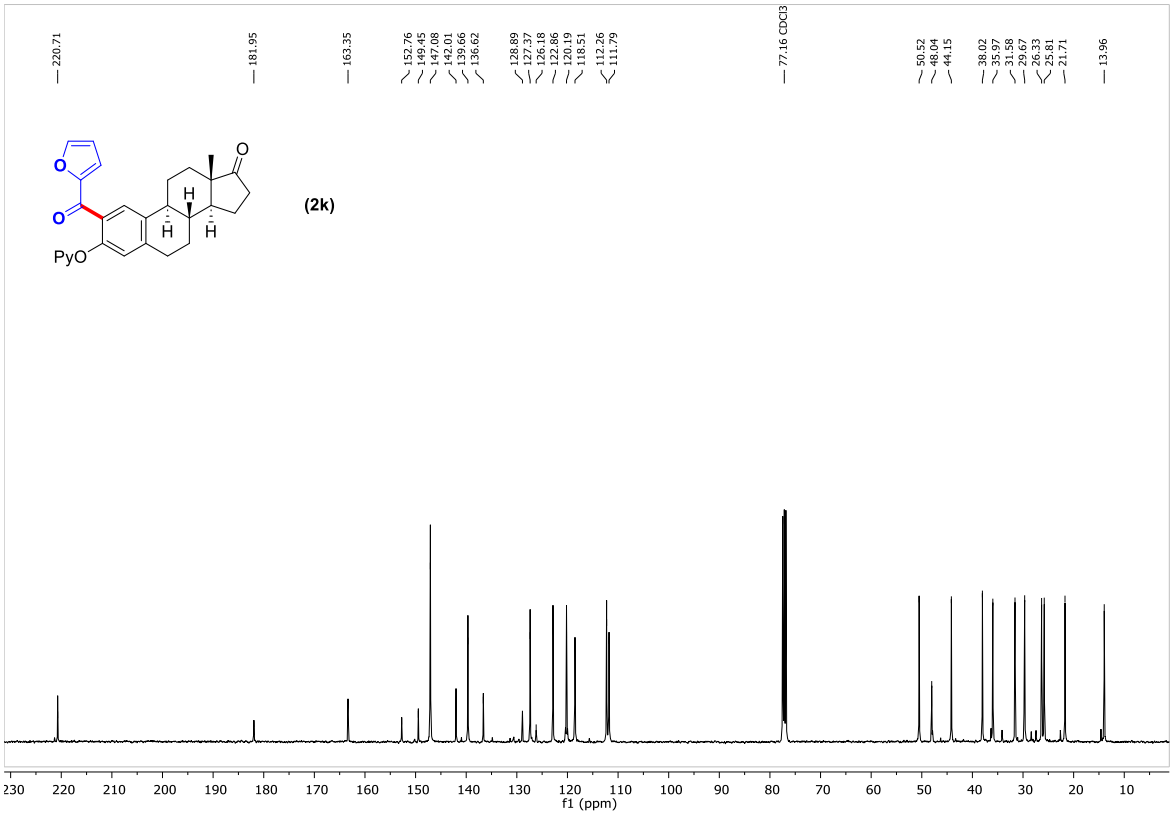
^{13}C NMR (101 MHz, $CDCl_3$)



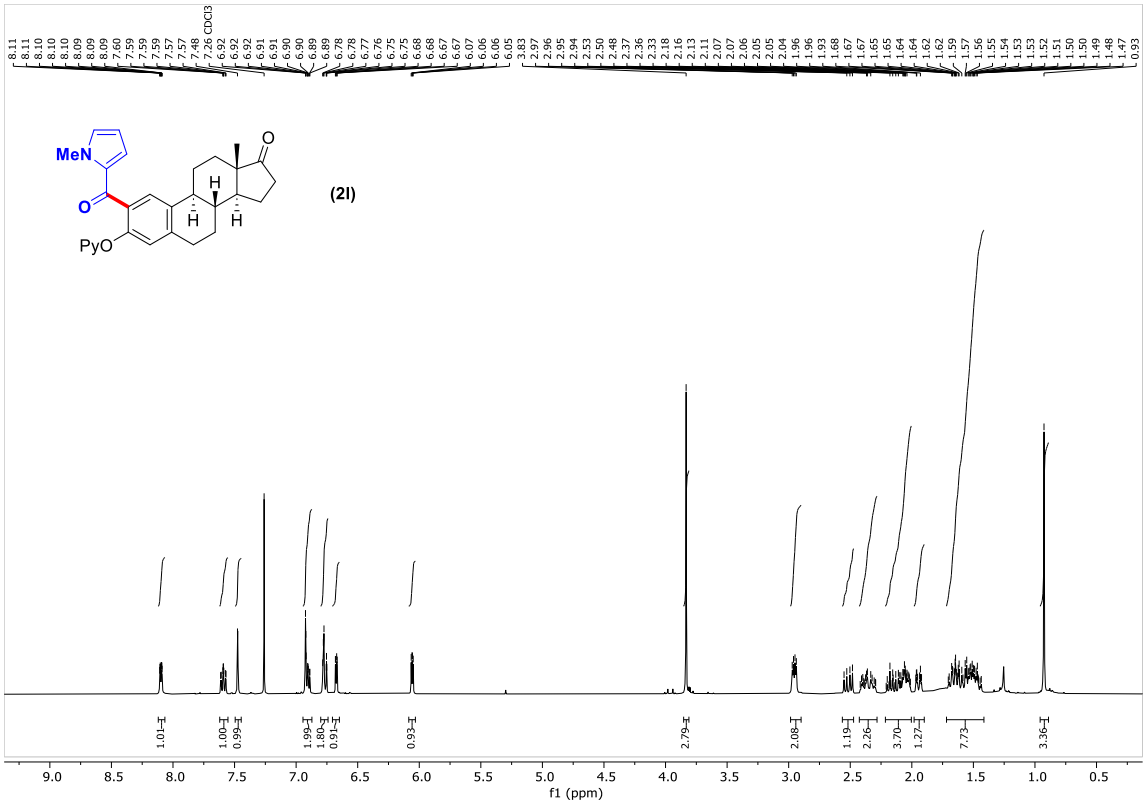
^{1}H NMR (400 MHz, $CDCl_3$)



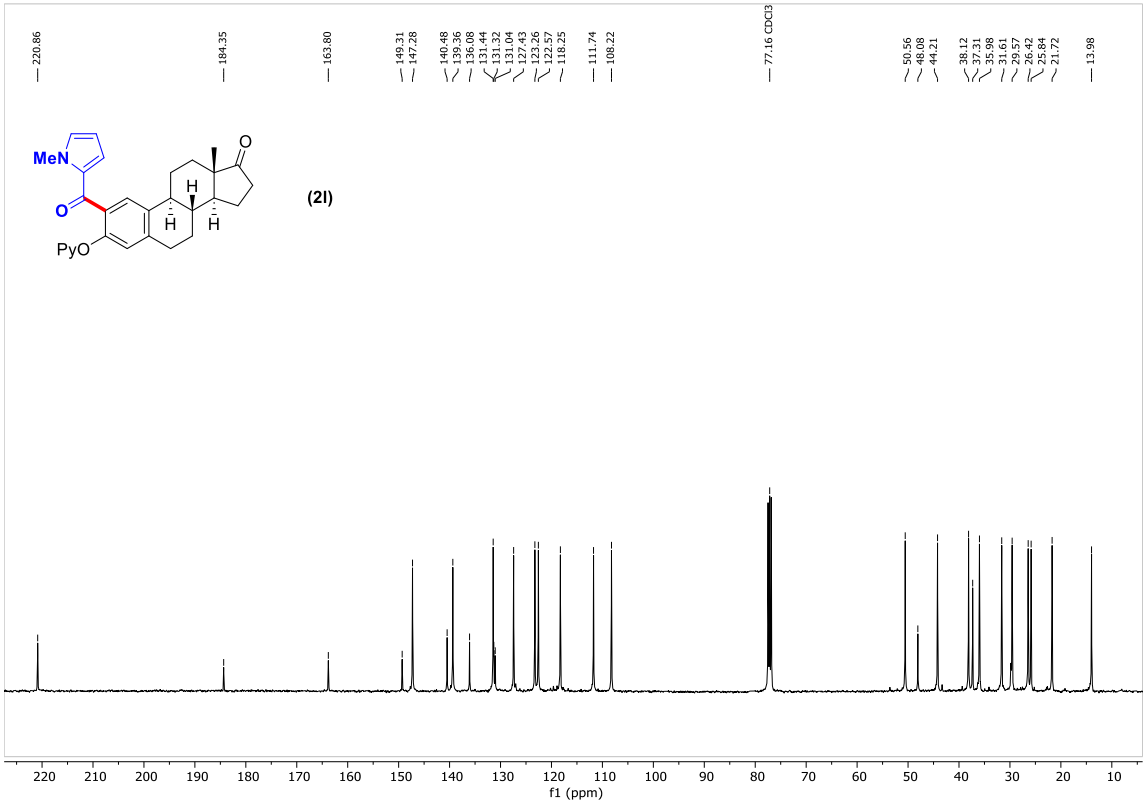
^{13}C NMR (101 MHz, $CDCl_3$)



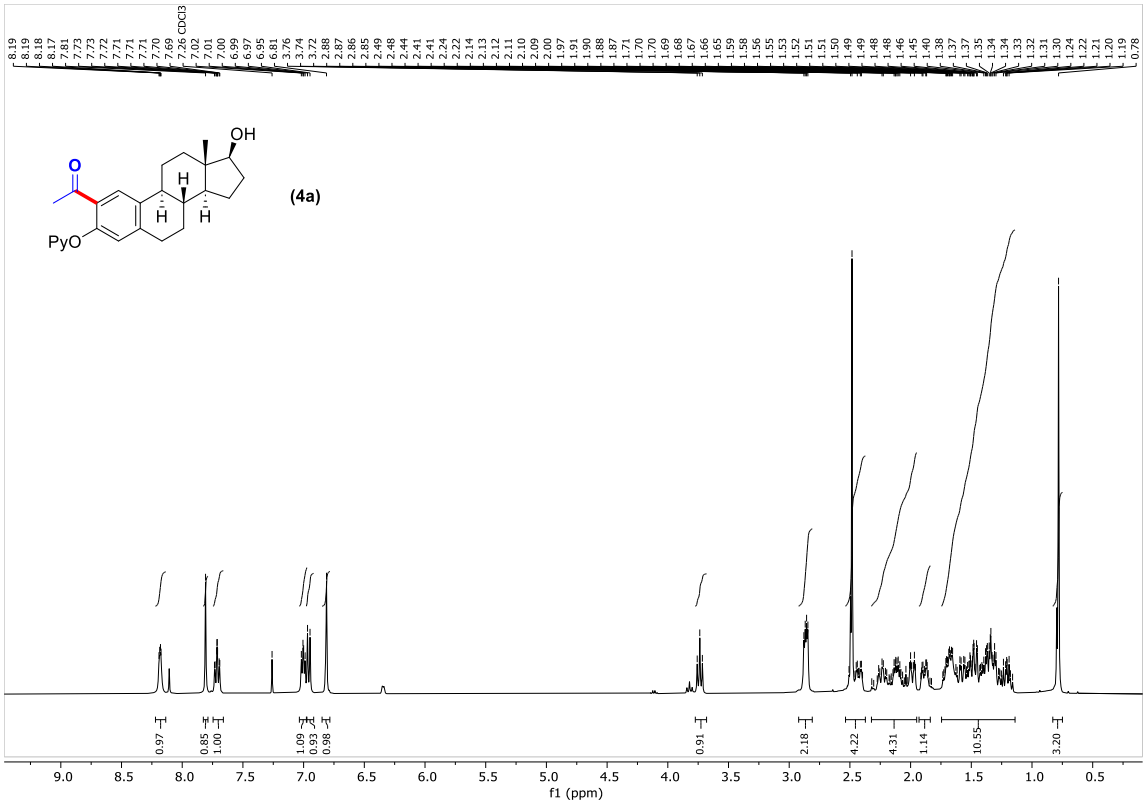
^{1}H NMR (400 MHz, $CDCl_3$)



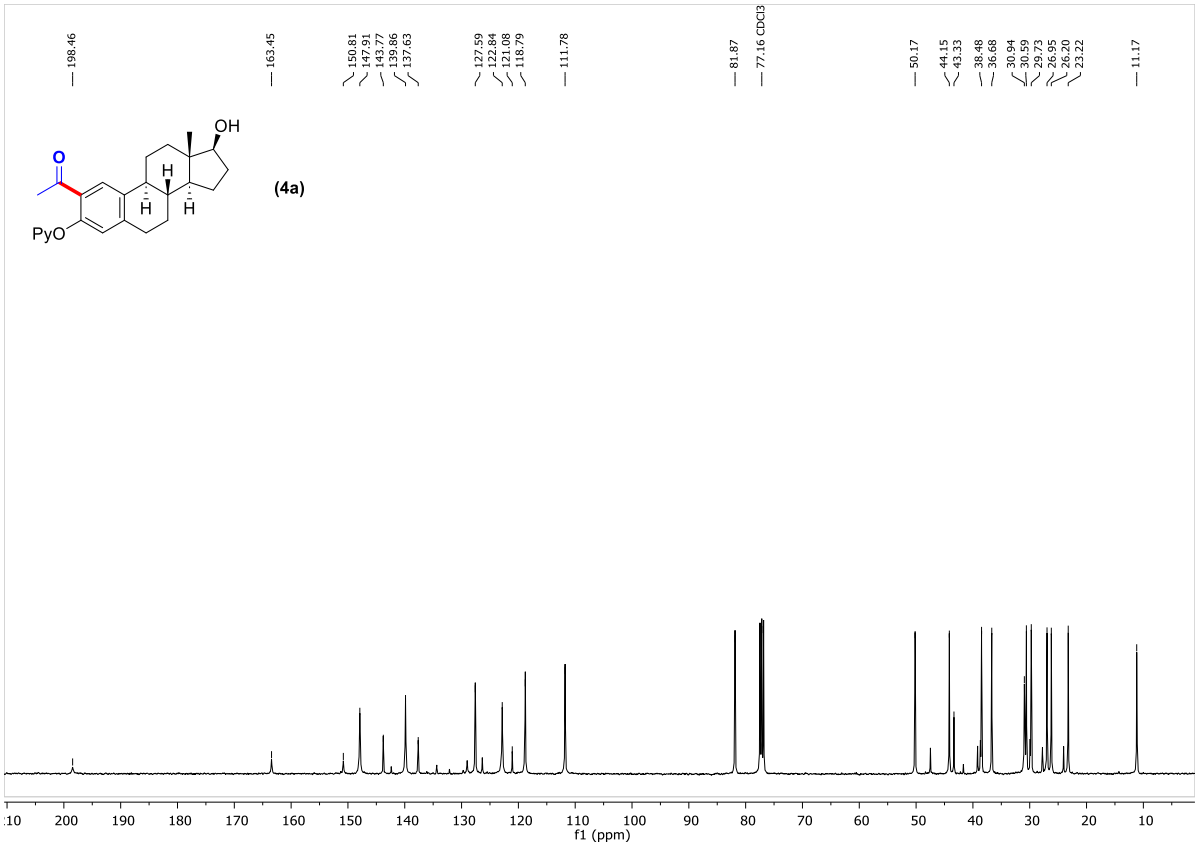
^{13}C NMR (101 MHz, $CDCl_3$)



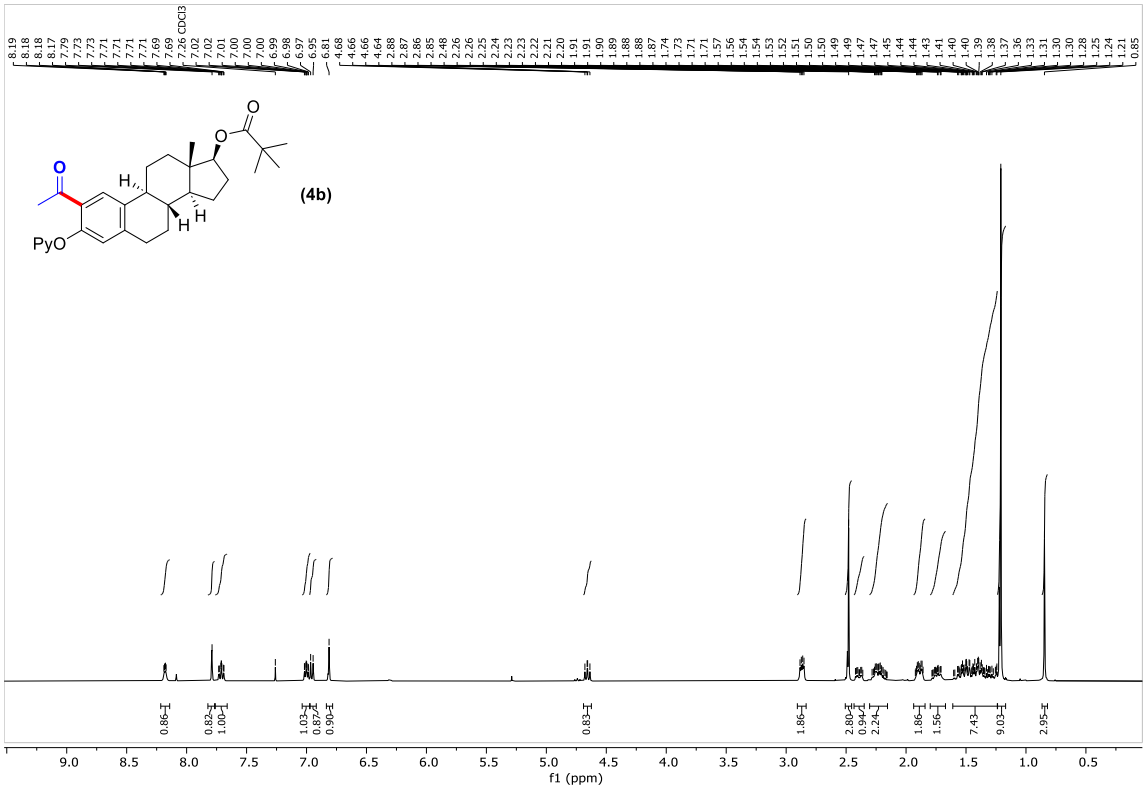
^{1}H NMR (400 MHz, $CDCl_3$)



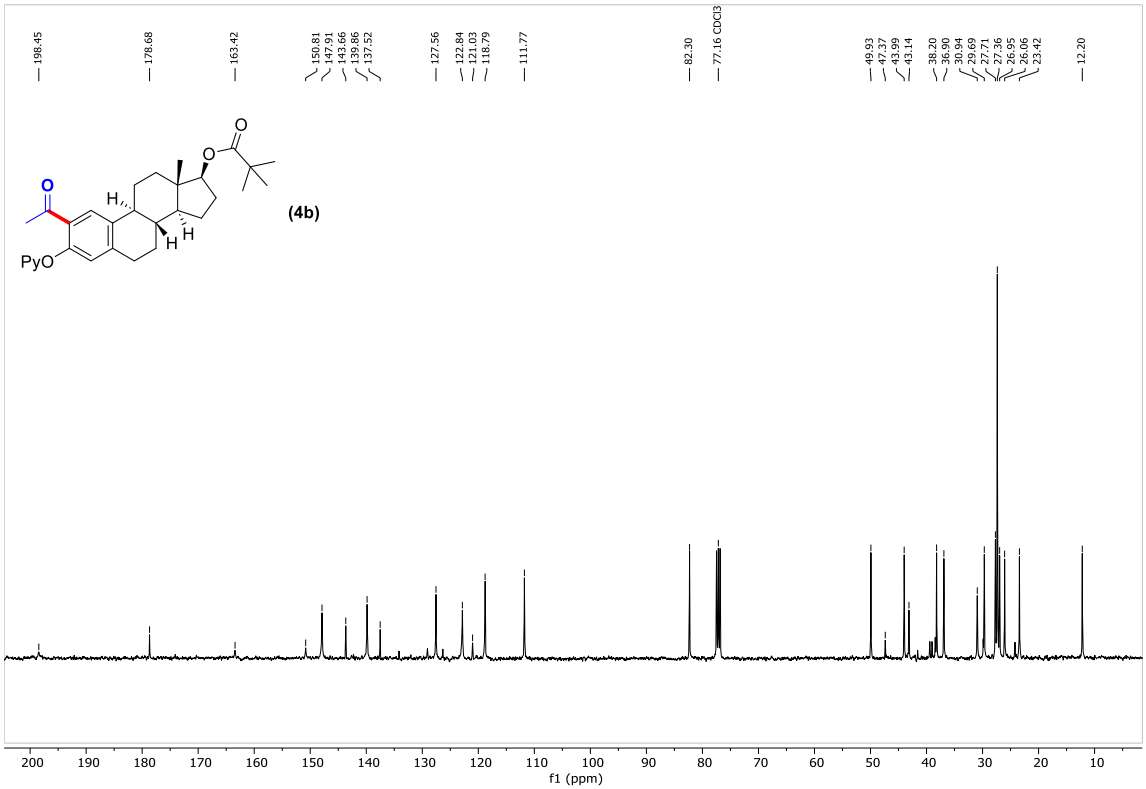
^{13}C NMR (101 MHz, $CDCl_3$)



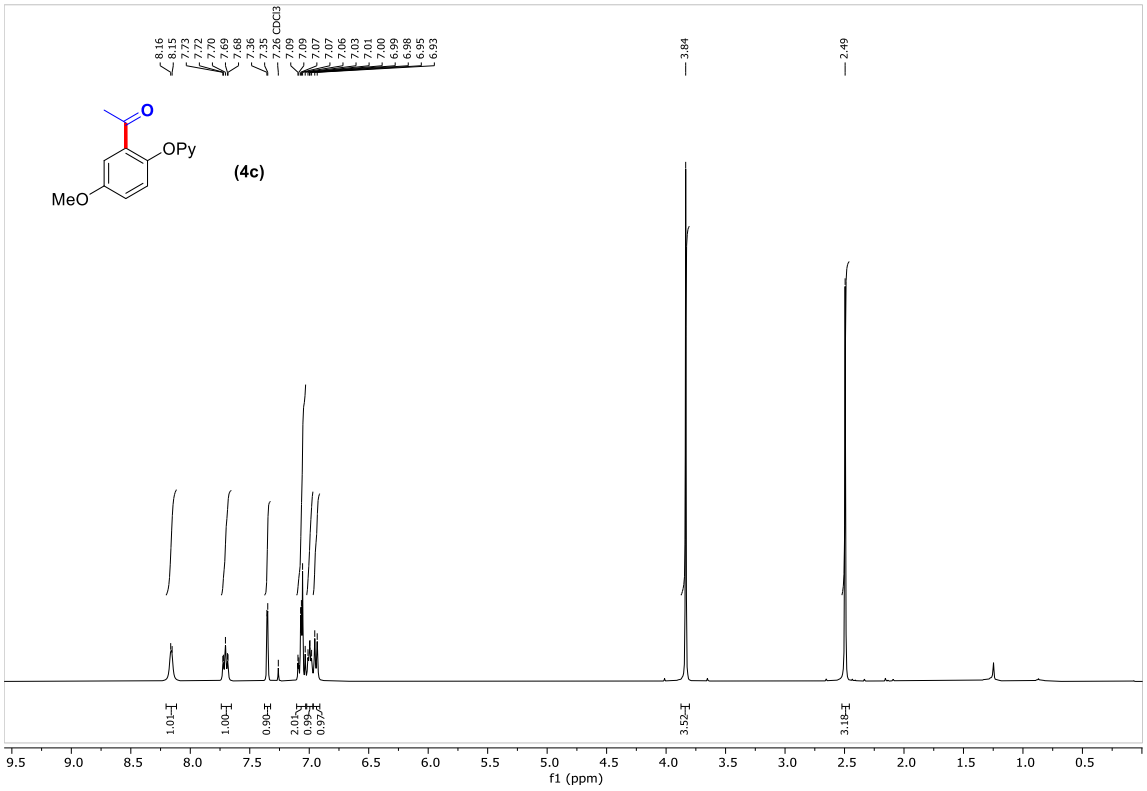
^{1}H NMR (400 MHz, $CDCl_3$)



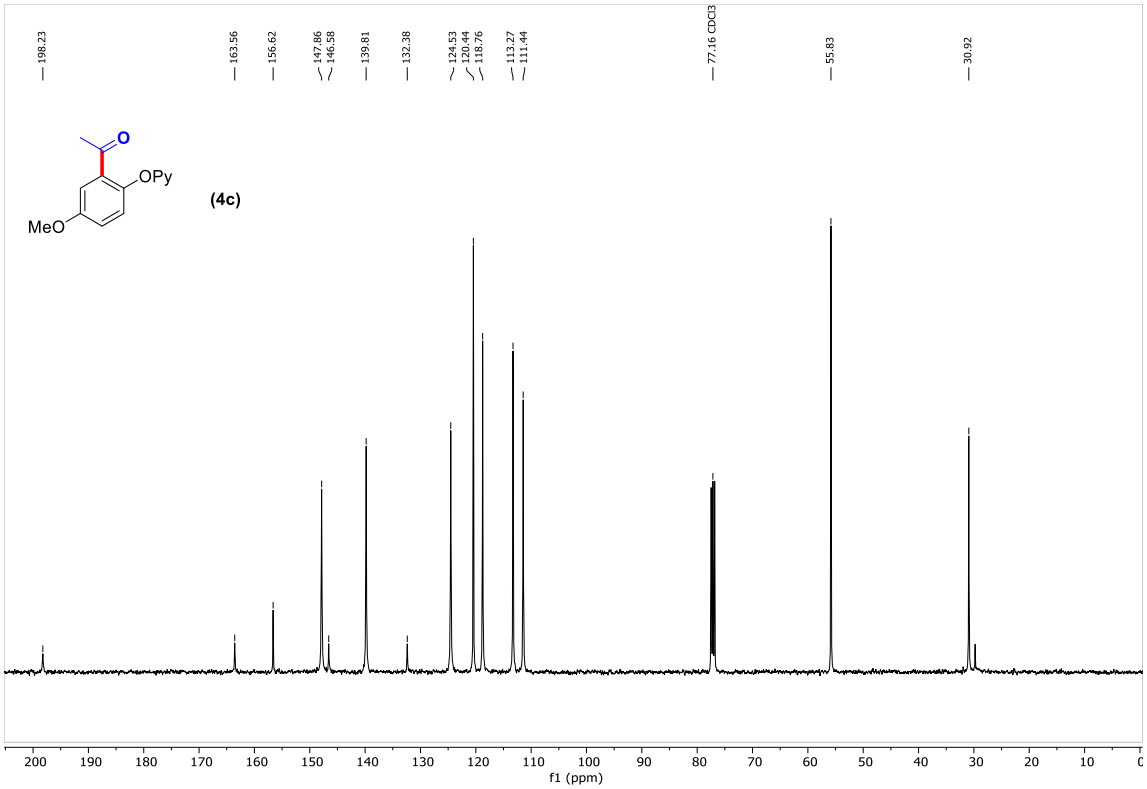
^{13}C NMR (101 MHz, $CDCl_3$)



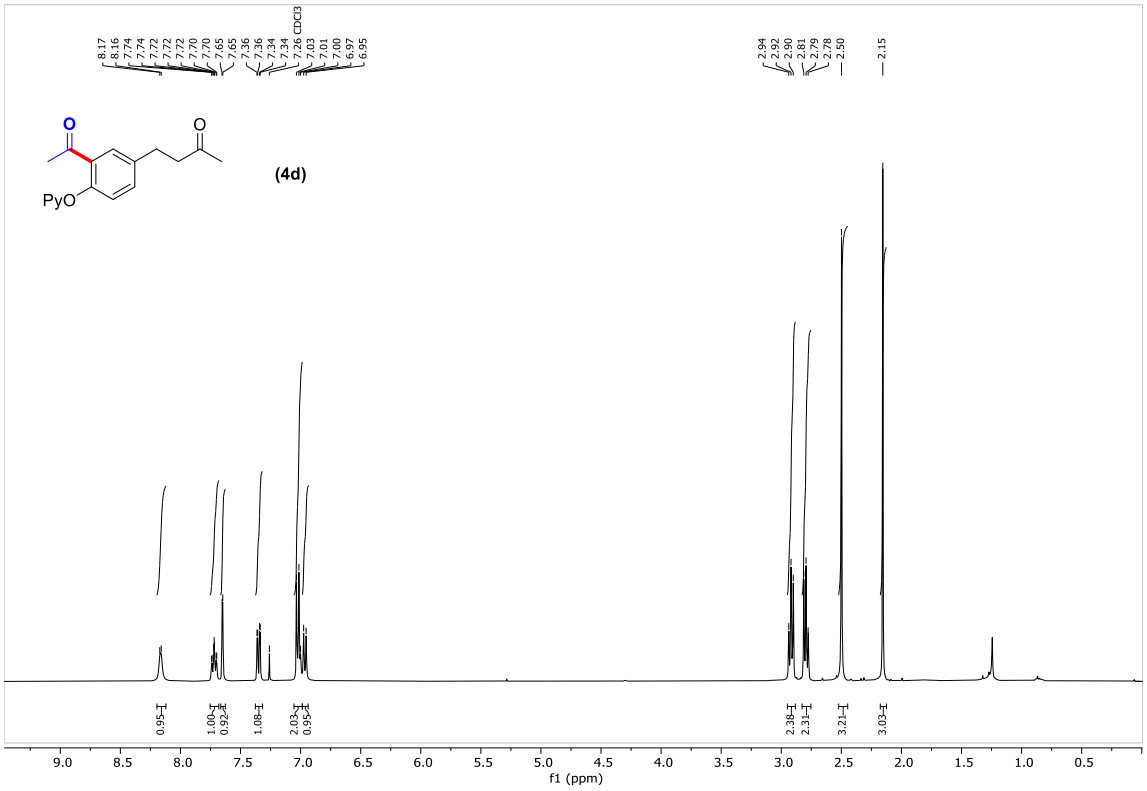
^{1}H NMR (400 MHz, $CDCl_3$)



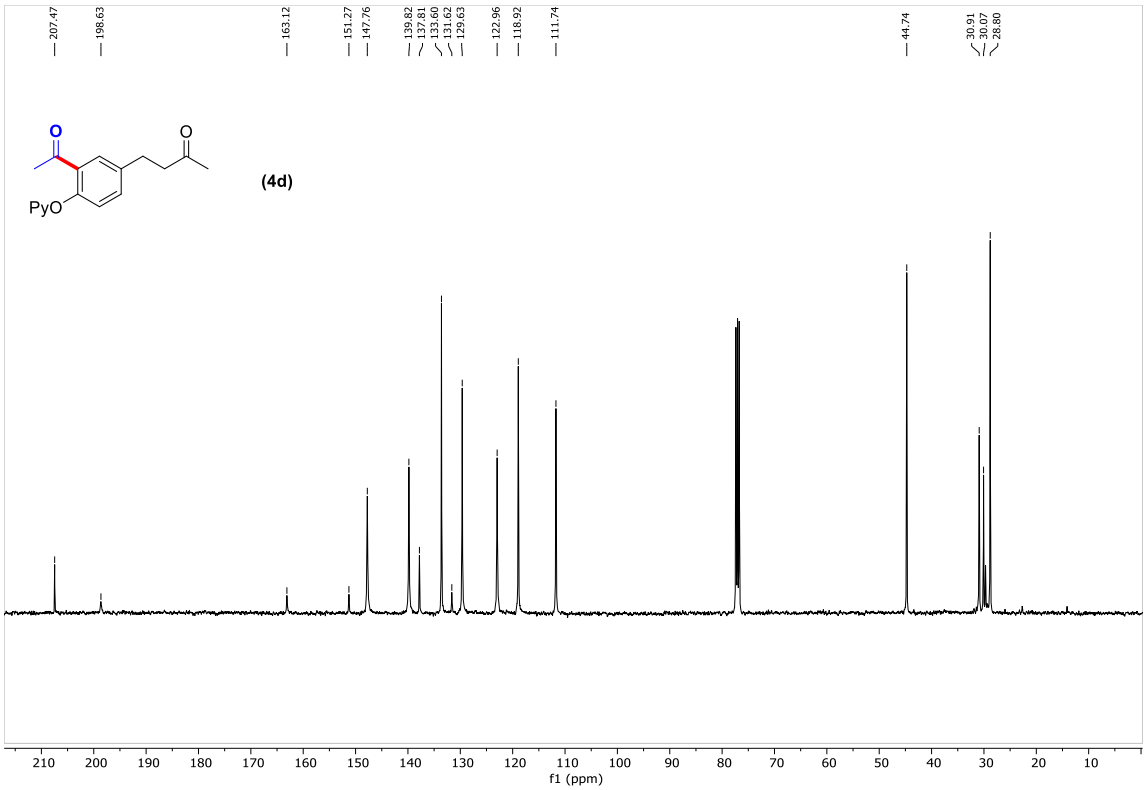
^{13}C NMR (101 MHz, $CDCl_3$)



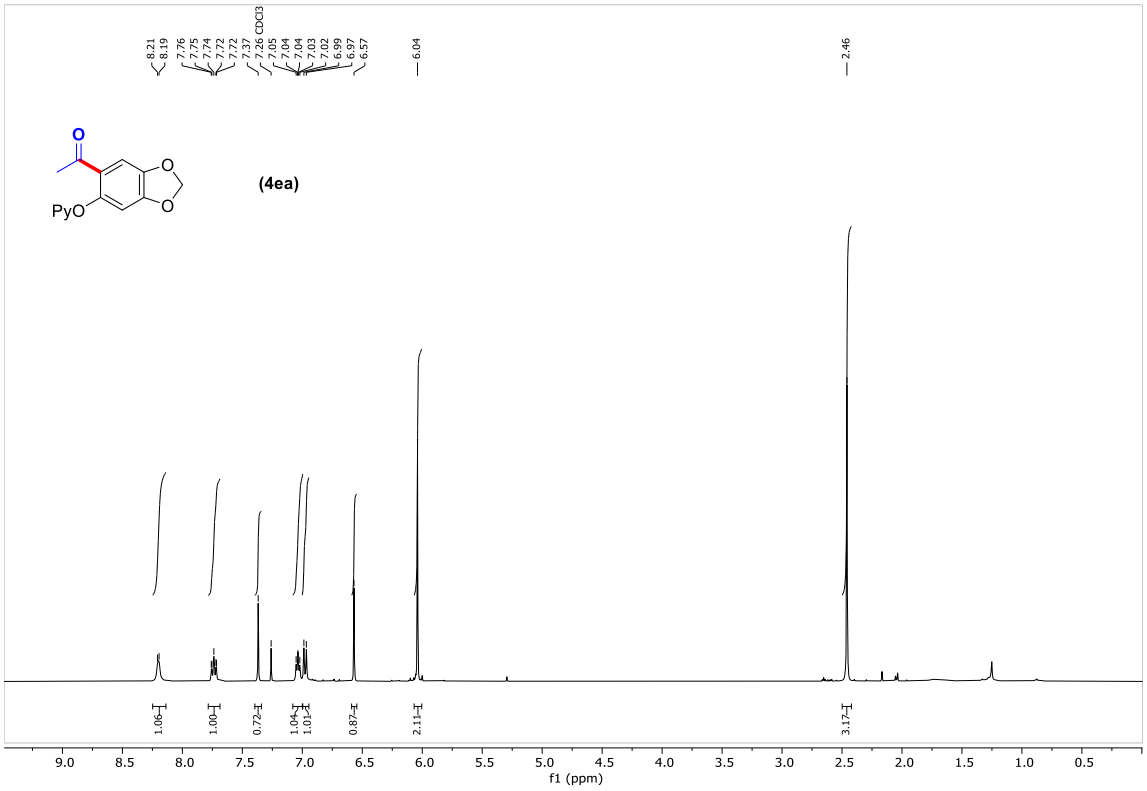
^{1}H NMR (400 MHz, $CDCl_3$)



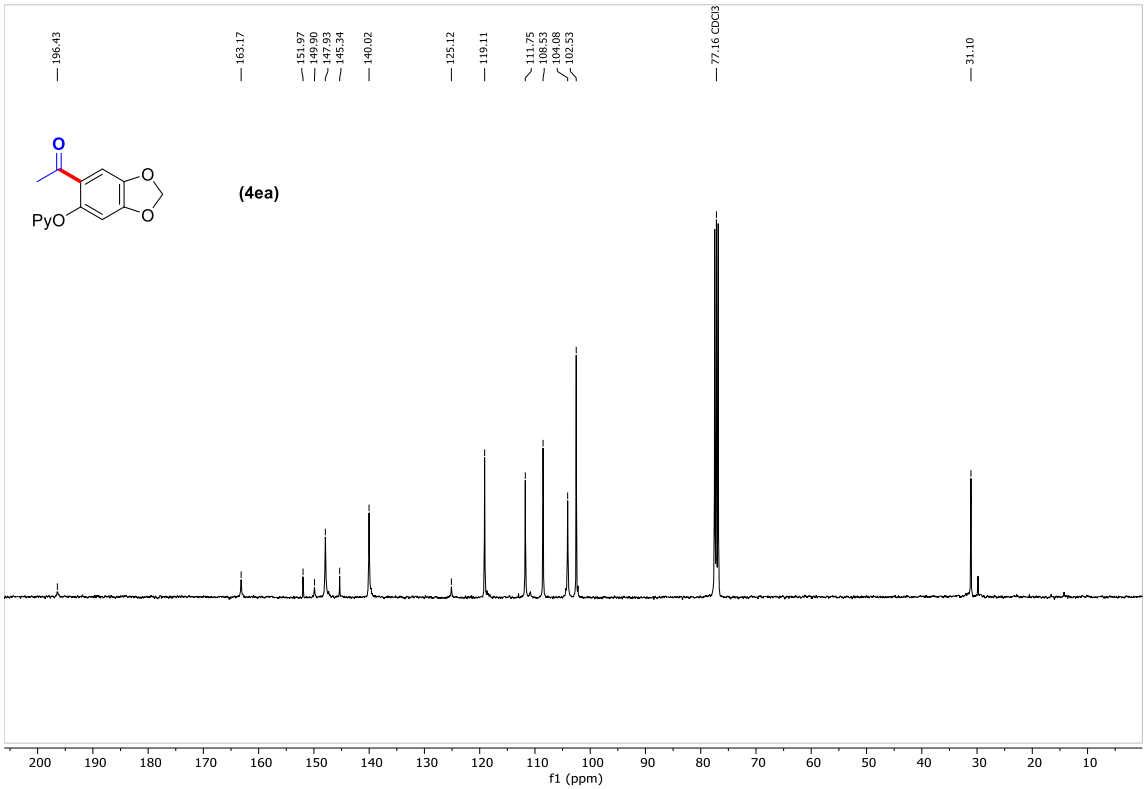
^{13}C NMR (101 MHz, $CDCl_3$)



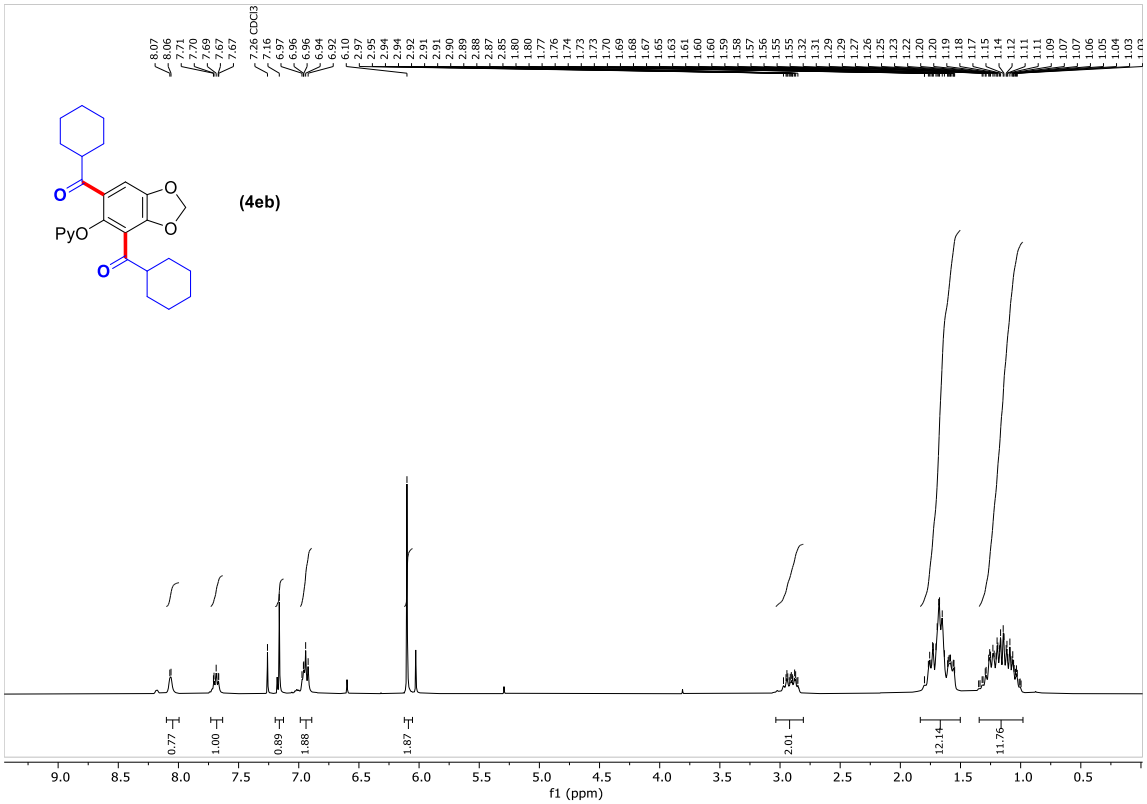
^{1}H NMR (400 MHz, $CDCl_3$)



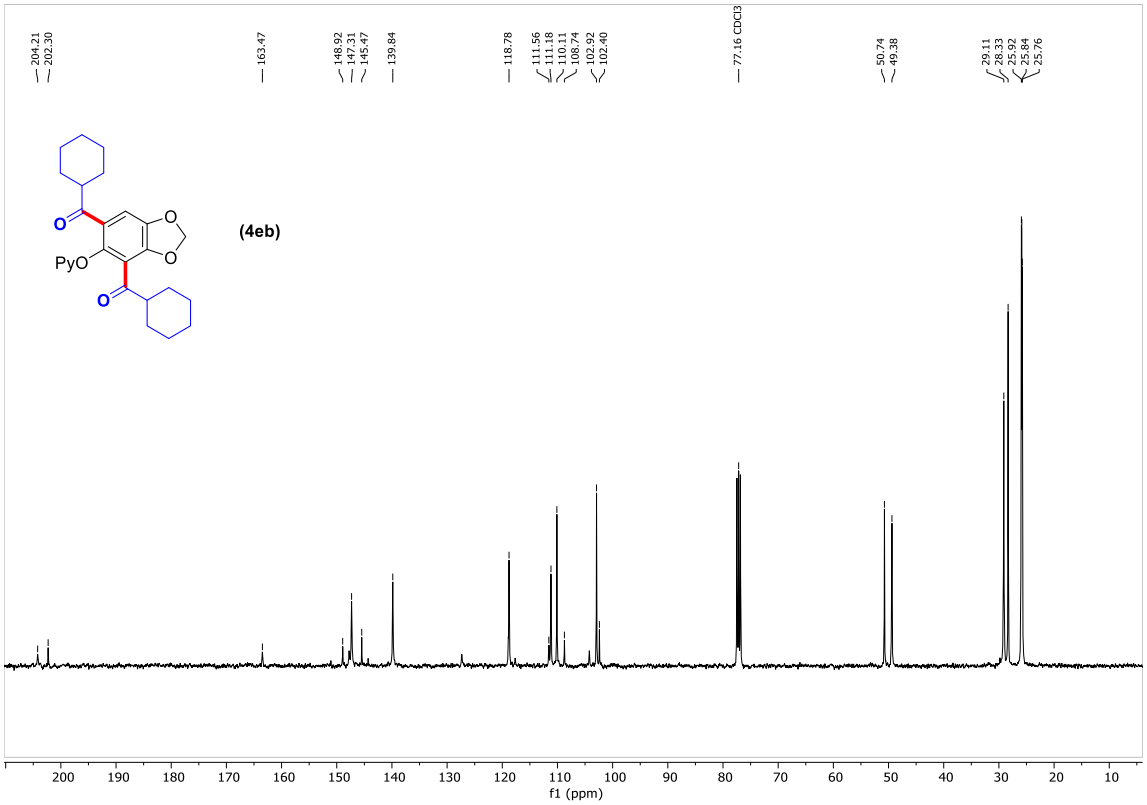
^{13}C NMR (101 MHz, $CDCl_3$)



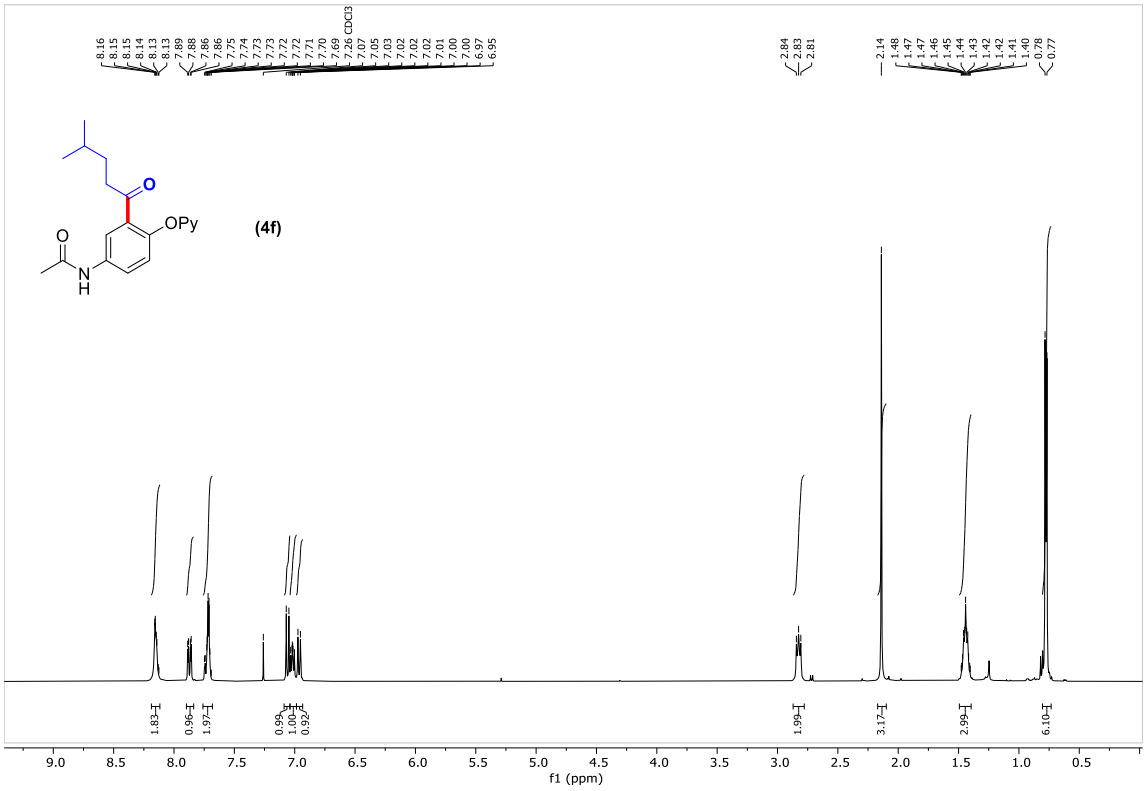
^{1}H NMR (400 MHz, $CDCl_3$)



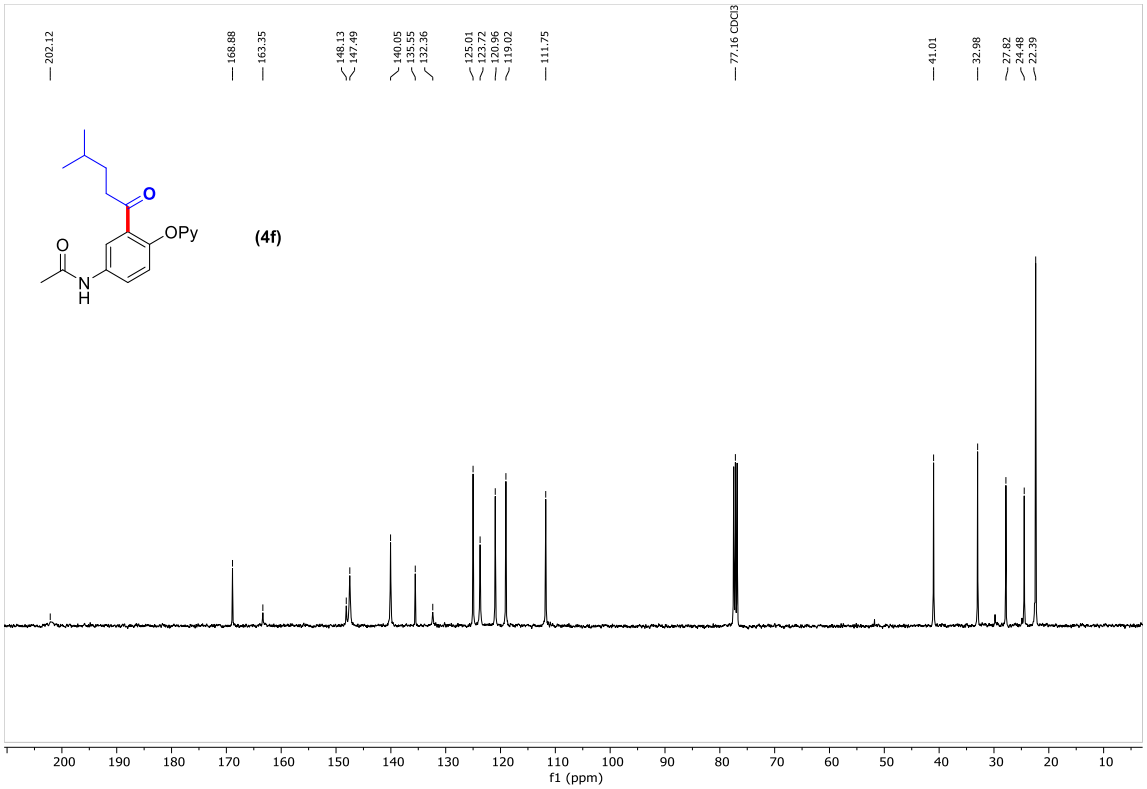
^{13}C NMR (101 MHz, $CDCl_3$)



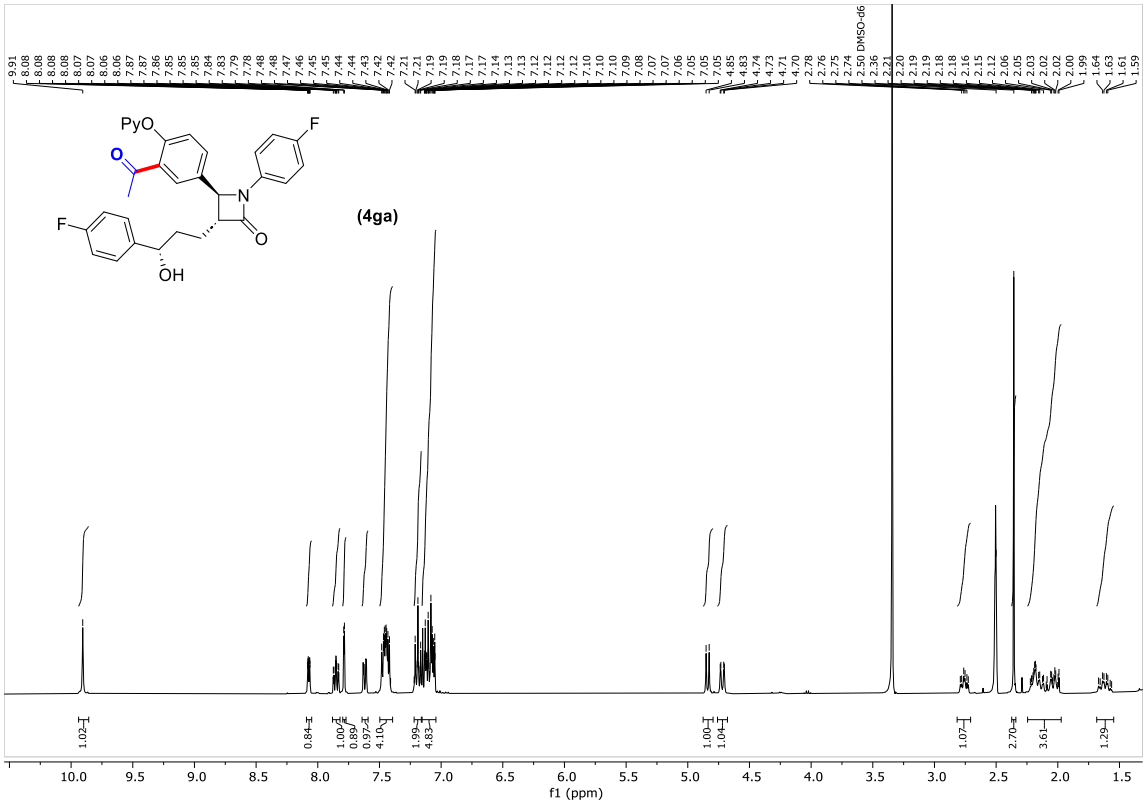
^{1}H NMR (400 MHz, $CDCl_3$)



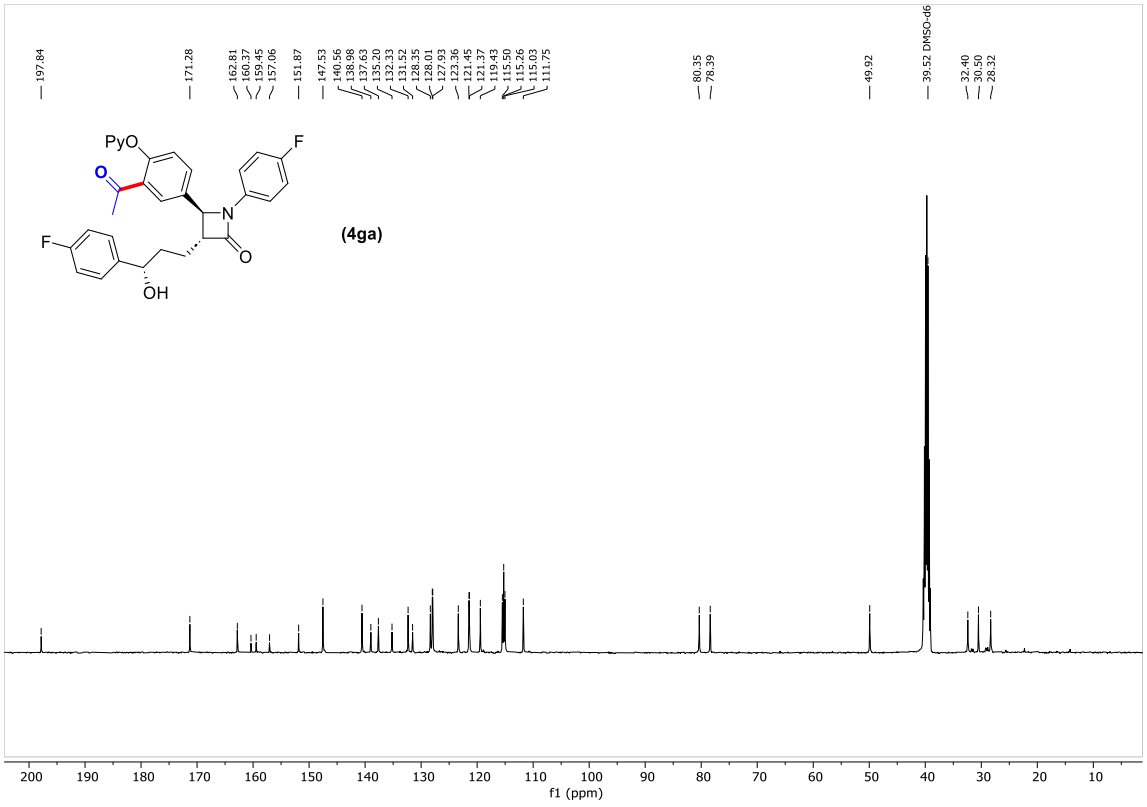
^{13}C NMR (101 MHz, $CDCl_3$)



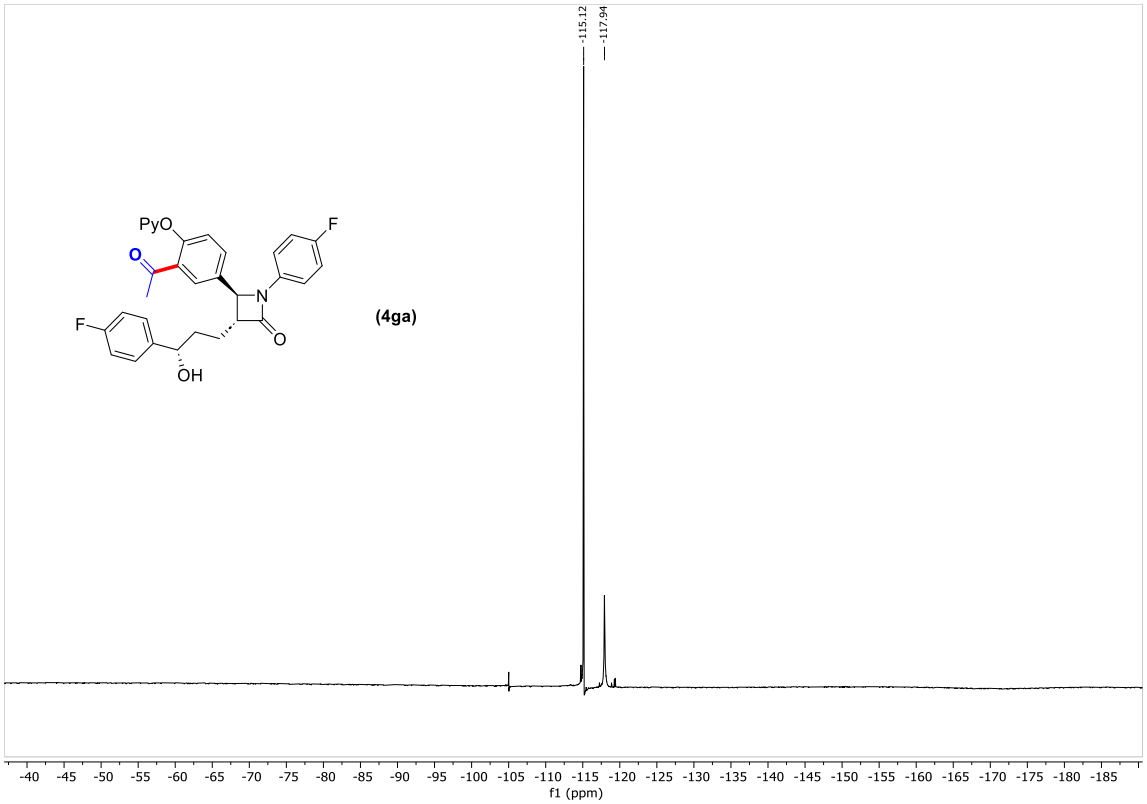
^{1}H NMR (400 MHz, DMSO-d_6)



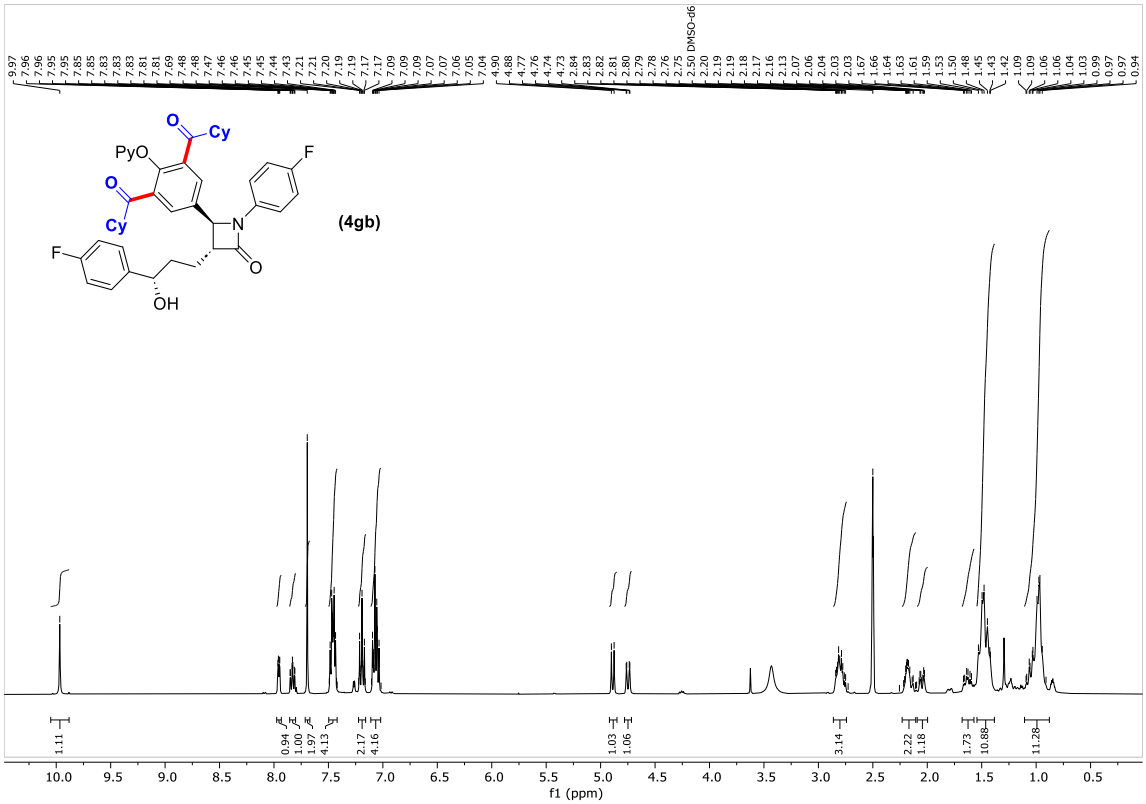
^{13}C NMR (101 MHz, DMSO-d_6)



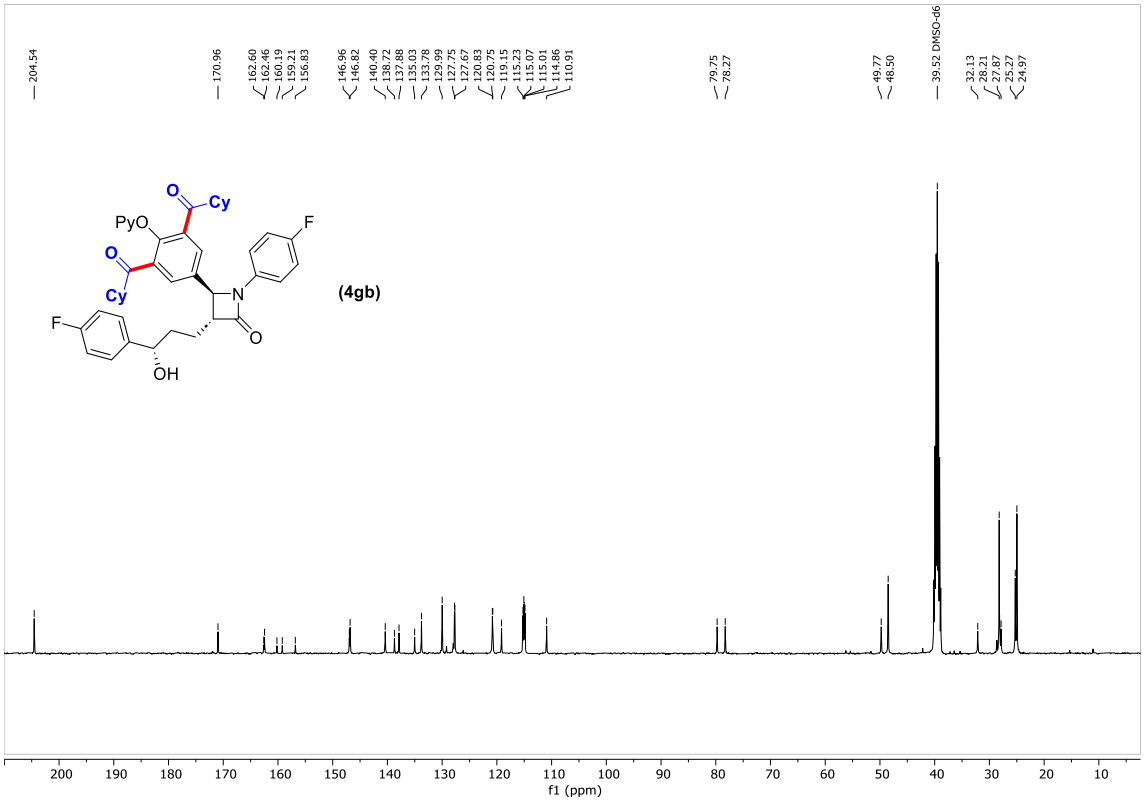
^{19}F NMR (471 MHz, $CDCl_3$ at 50 ºC)



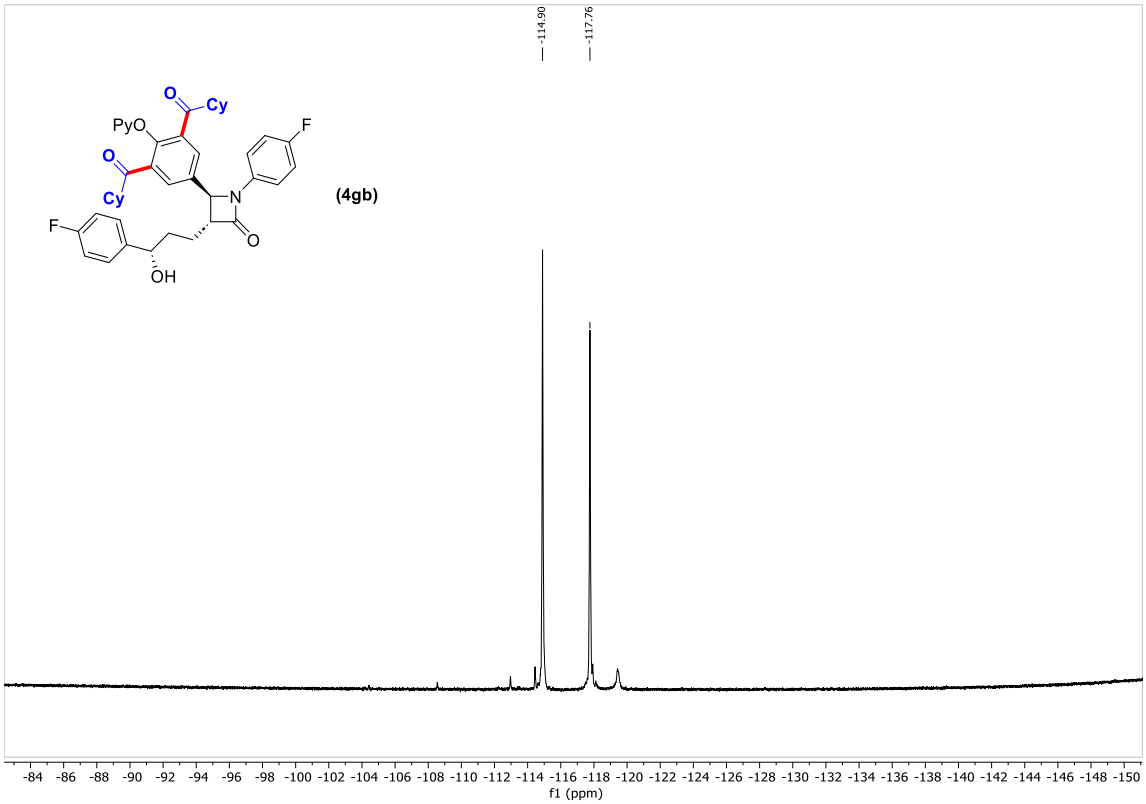
^{1}H NMR (400 MHz, DMSO-d_6)



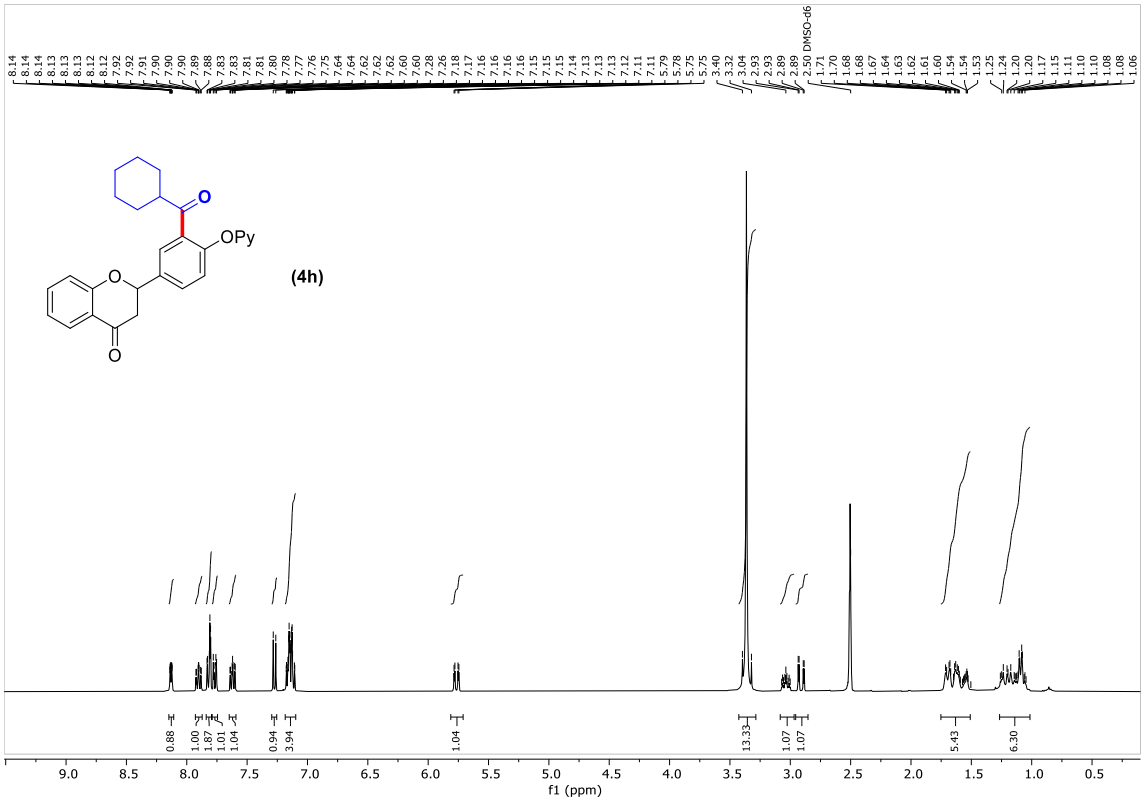
^{13}C NMR (101 MHz, DMSO-d_6)



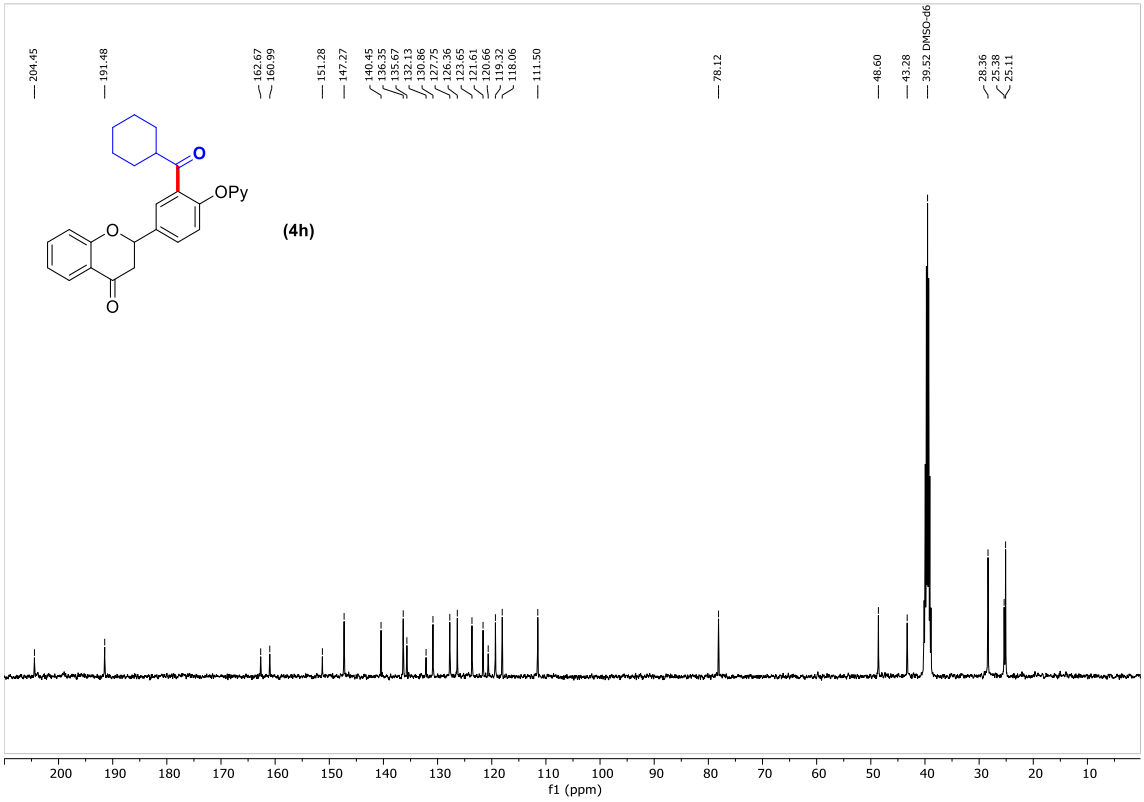
^{19}F NMR (376 MHz, $CDCl_3$)



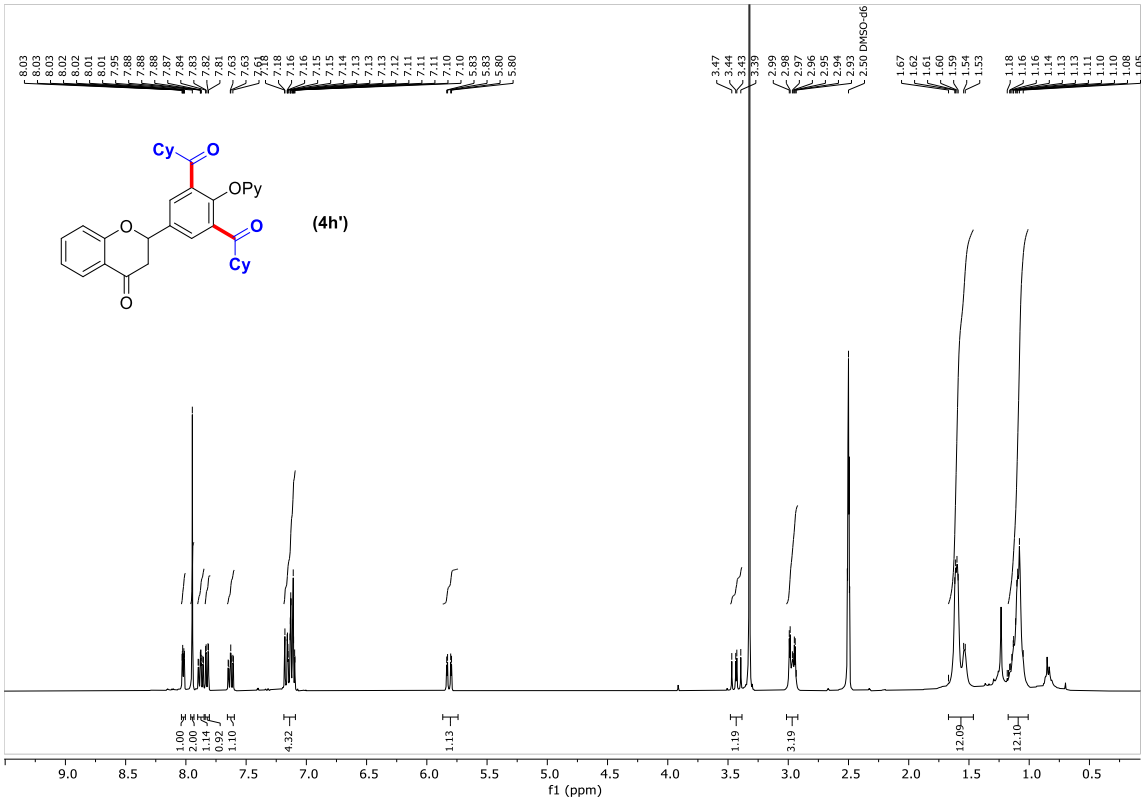
^{1}H NMR (400 MHz, DMSO-d_6)



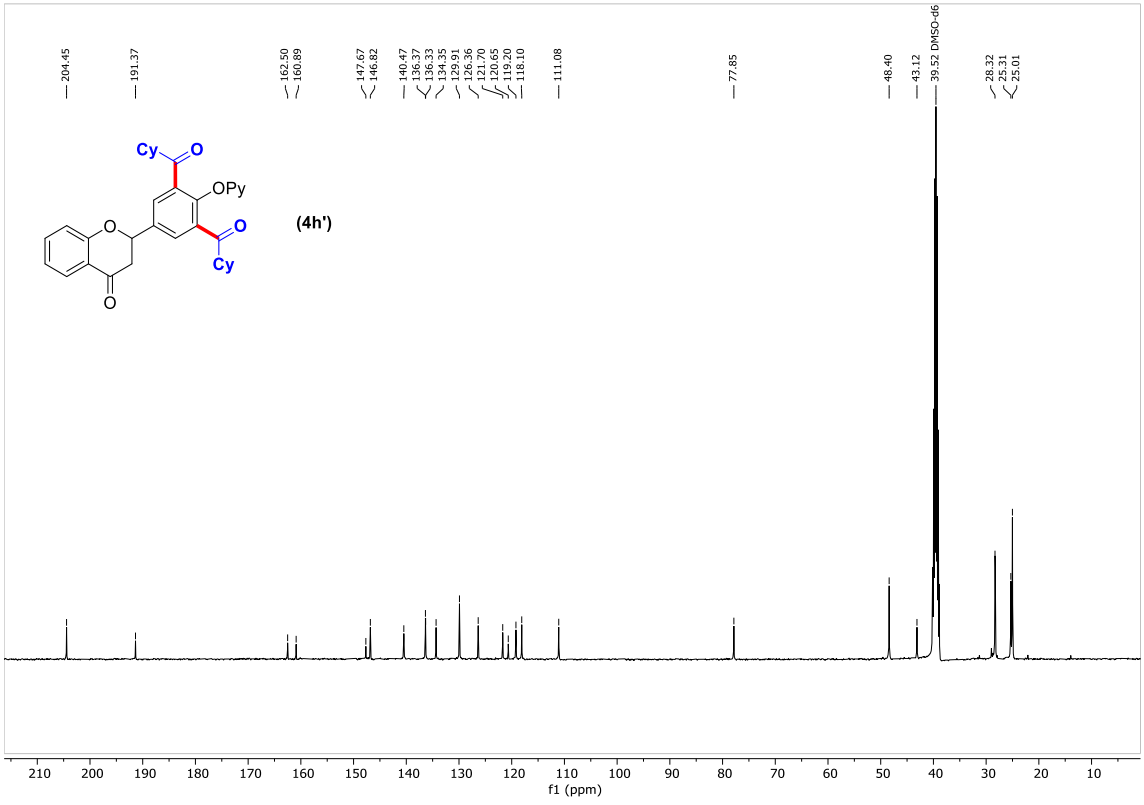
^{13}C NMR (101 MHz, DMSO-d_6)



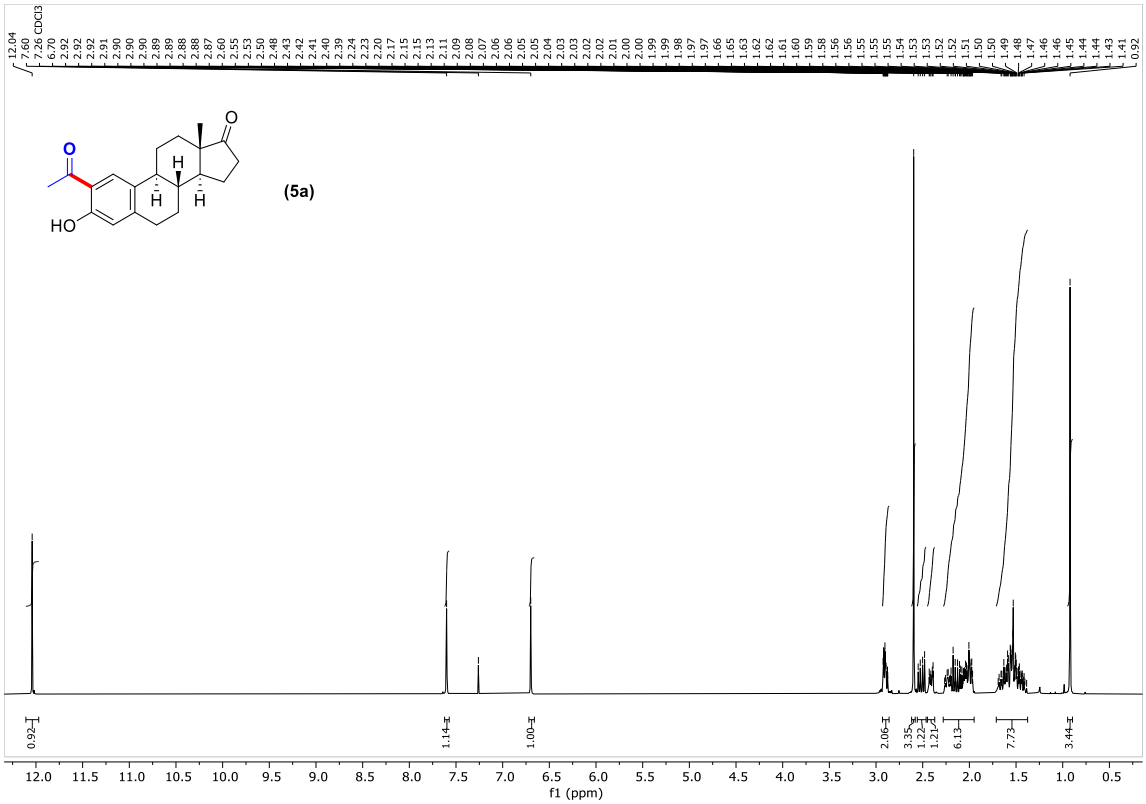
^{1}H NMR (400 MHz, DMSO-d_6)



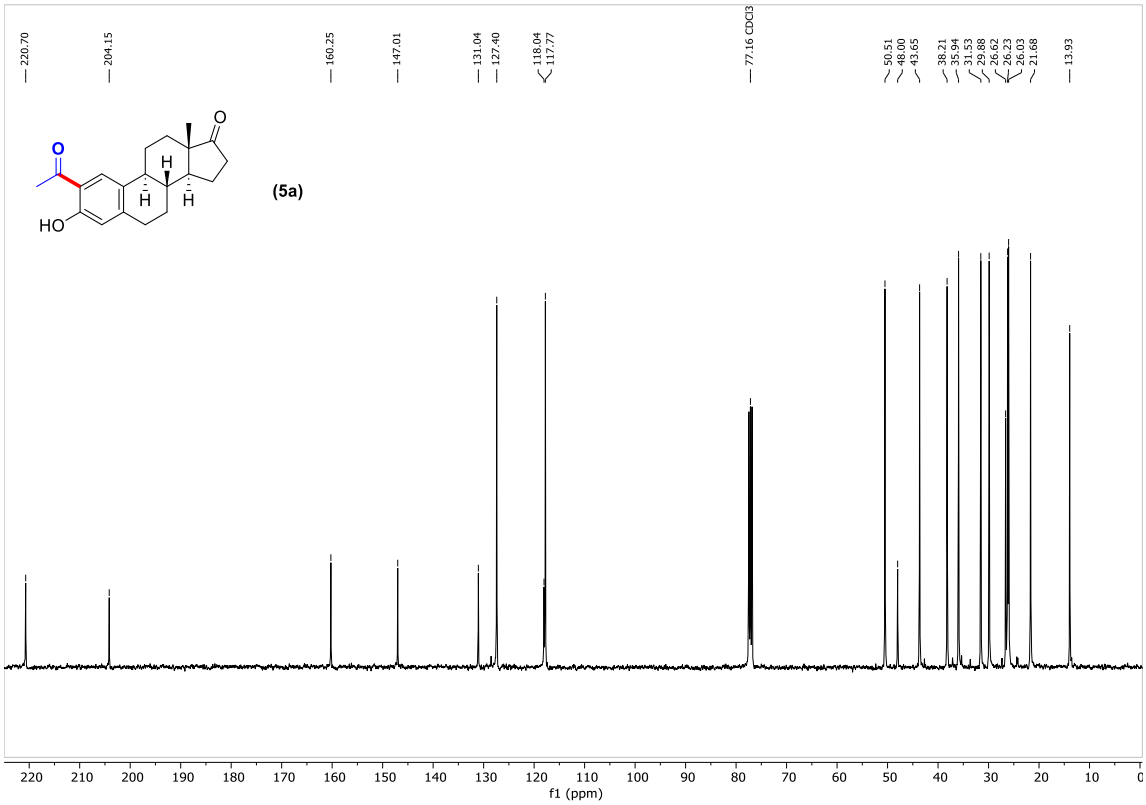
^{13}C NMR (101 MHz, DMSO-d_6)



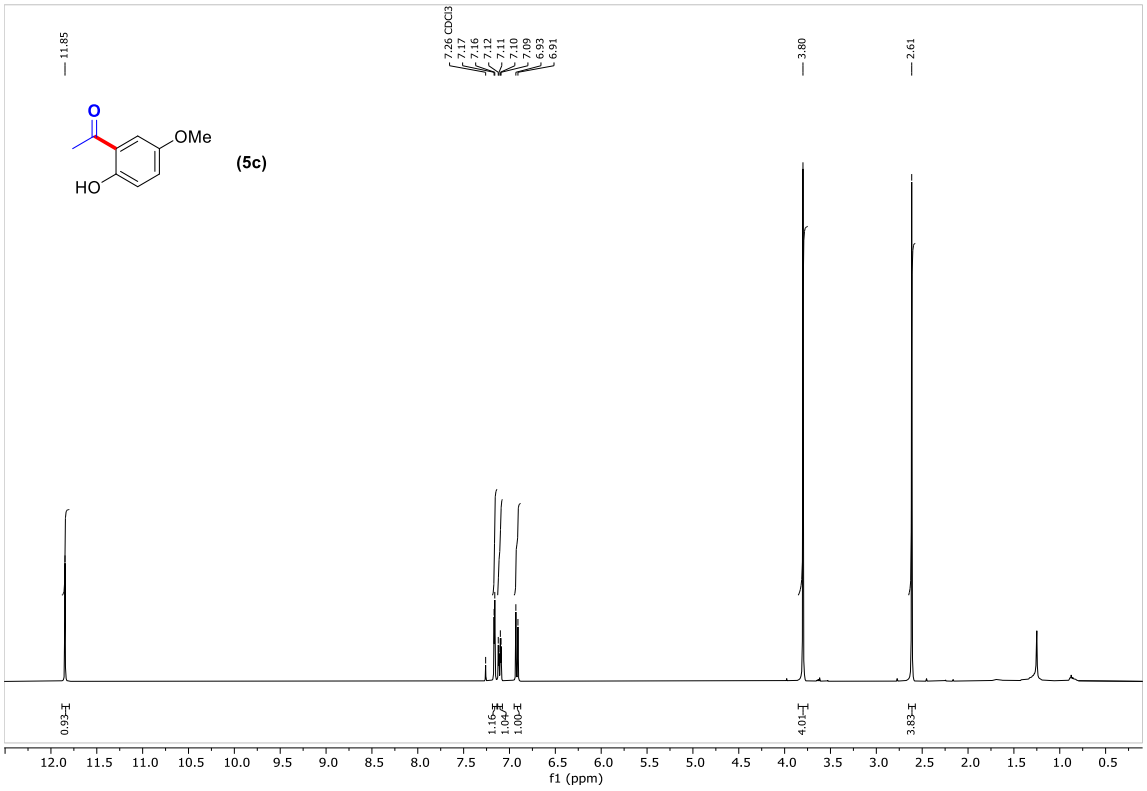
^{1}H NMR (400 MHz, $CDCl_3$)



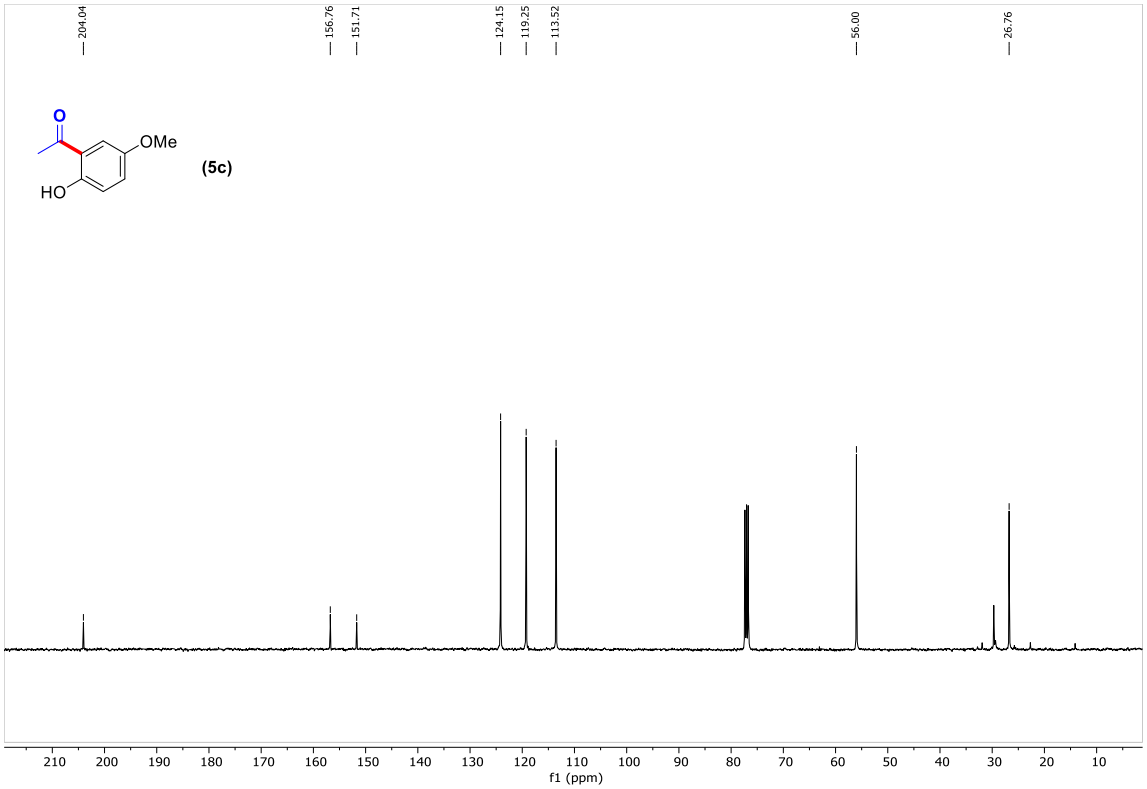
^{13}C NMR (101 MHz, $CDCl_3$)



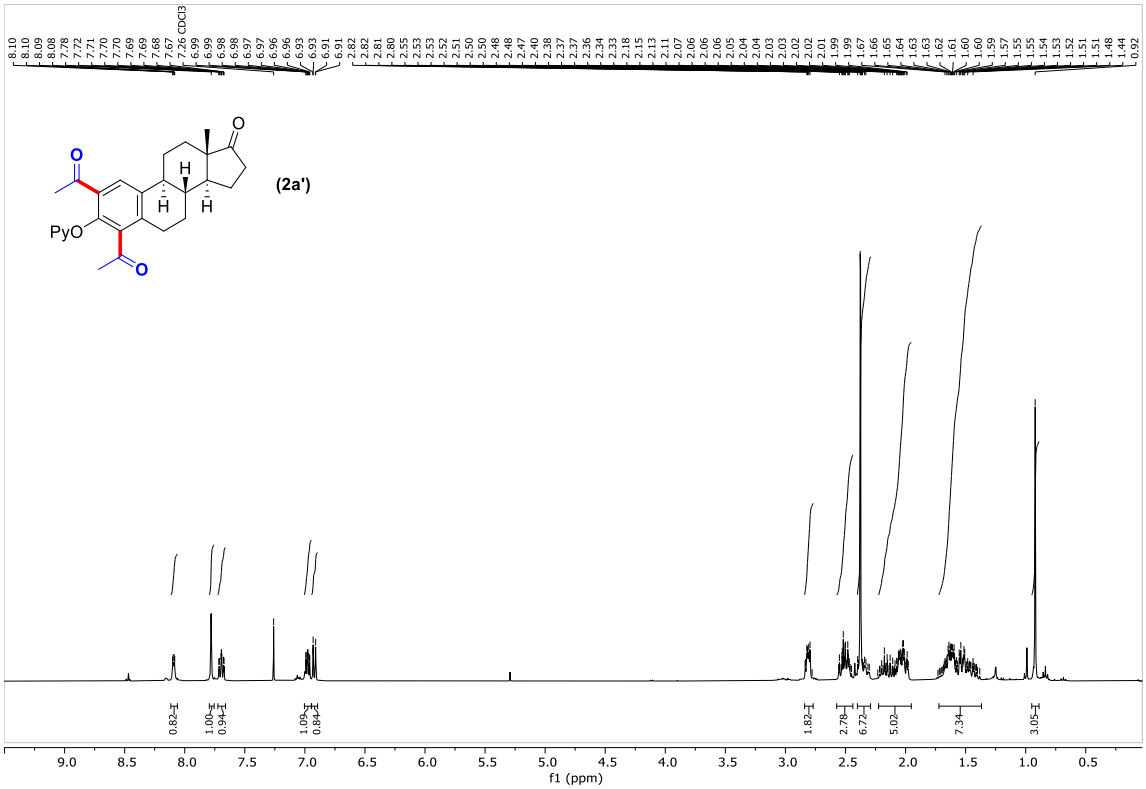
^{1}H NMR (400 MHz, $CDCl_3$)



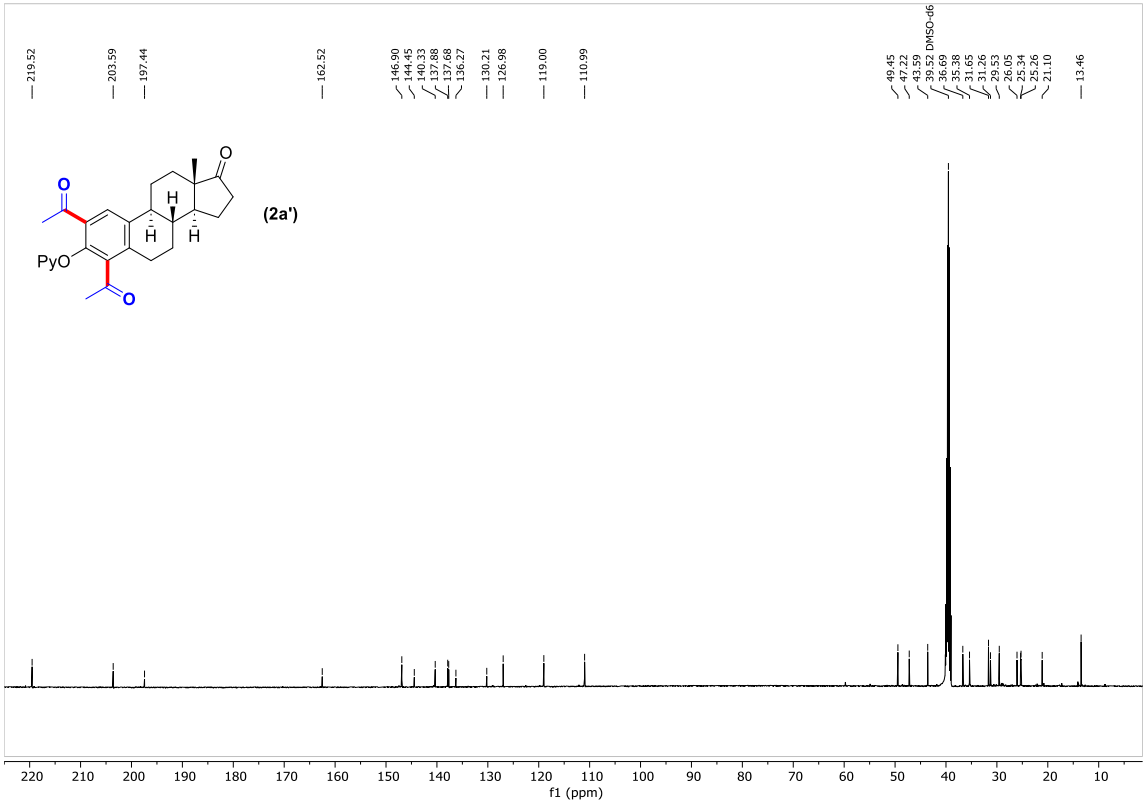
^{13}C NMR (101 MHz, $CDCl_3$)



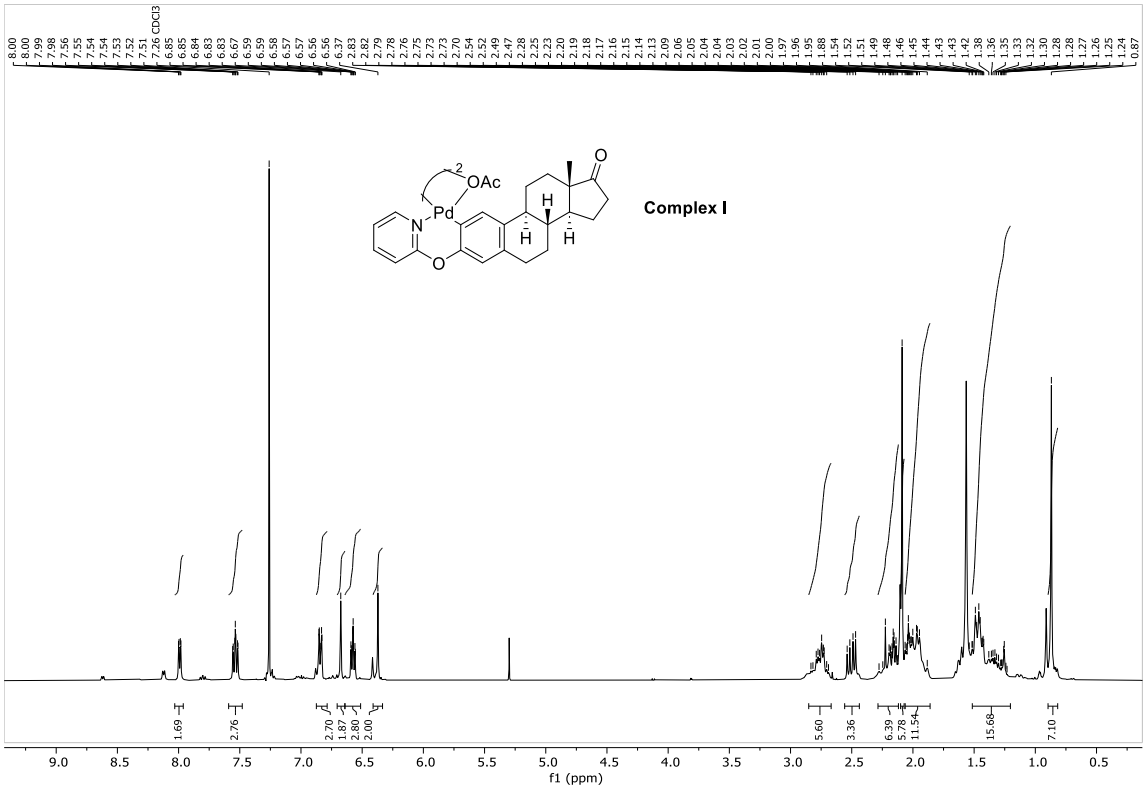
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (126 MHz, DMSO-d_6)

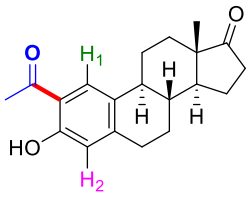


^{1}H NMR (400 MHz, $CDCl_3$)

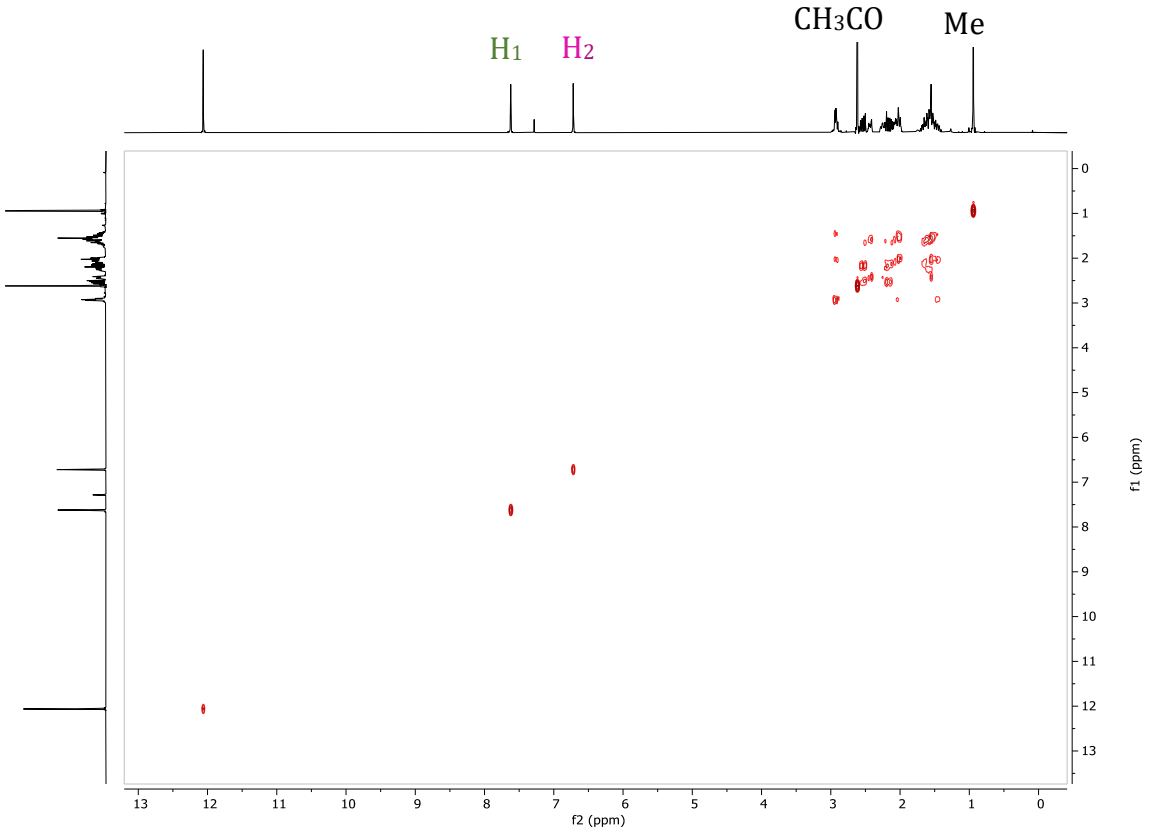


9.-2D NMR Spectra

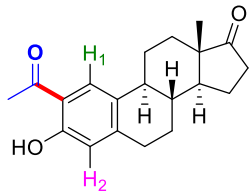
NMR (400 MHz, $CDCl_3$) **COSY EXPERIMENT**



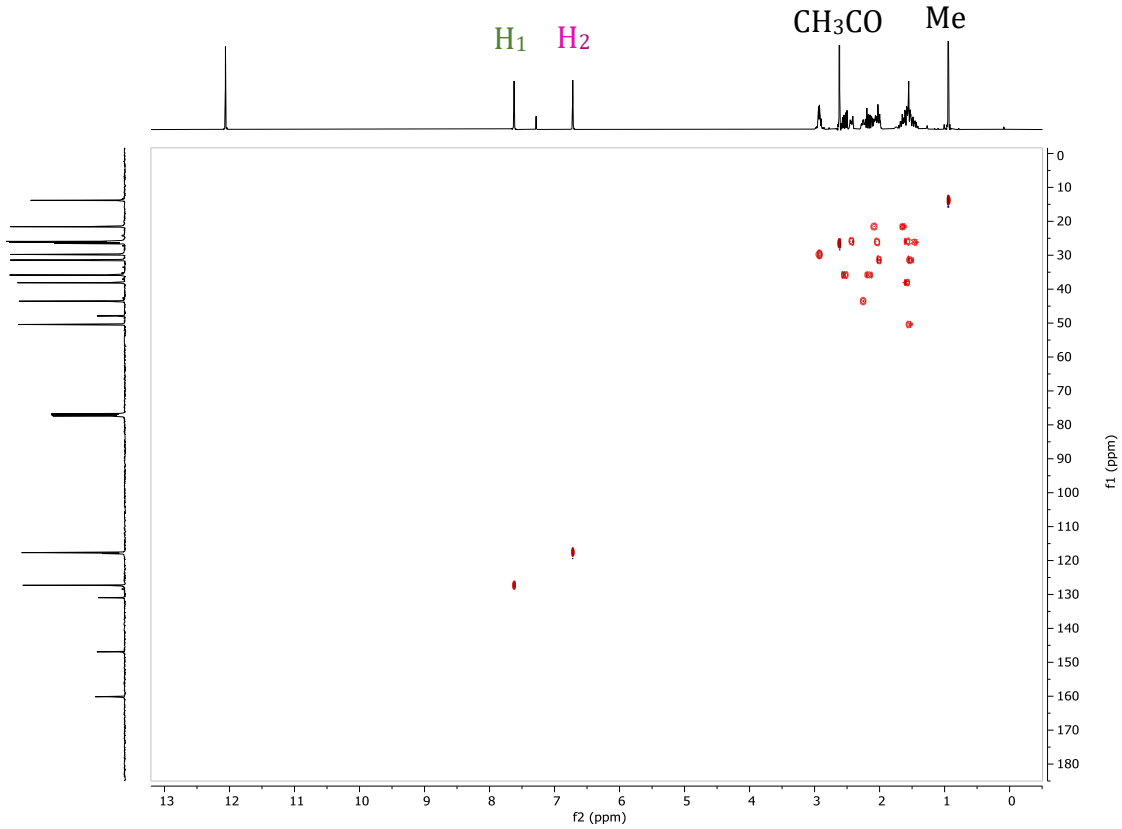
(5a)



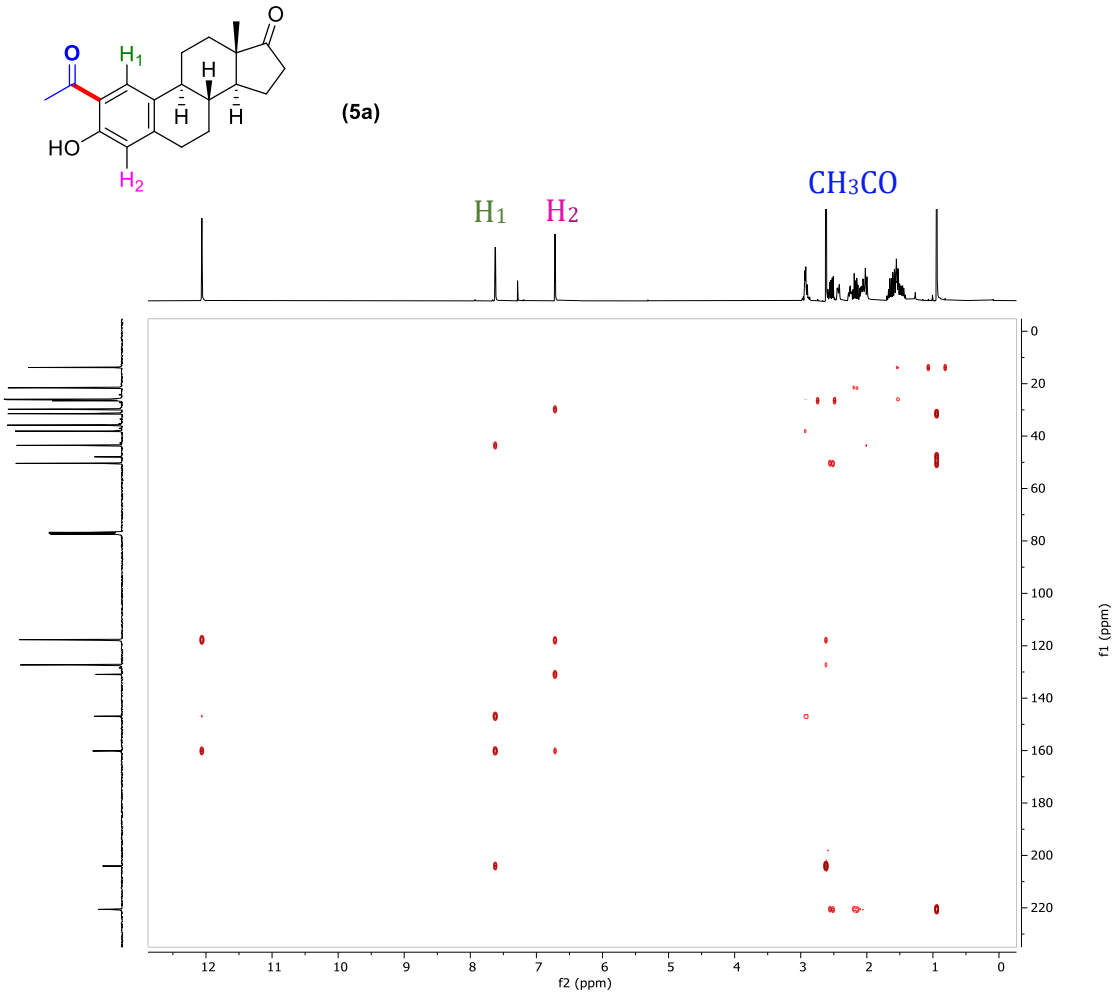
NMR (400 MHz, $CDCl_3$) **HSQC EXPERIMENT**



(5a)

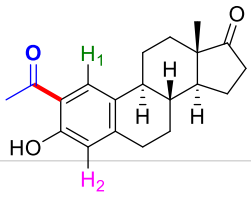


NMR (500 MHz, $CDCl_3$) **HMBC EXPERIMENT**

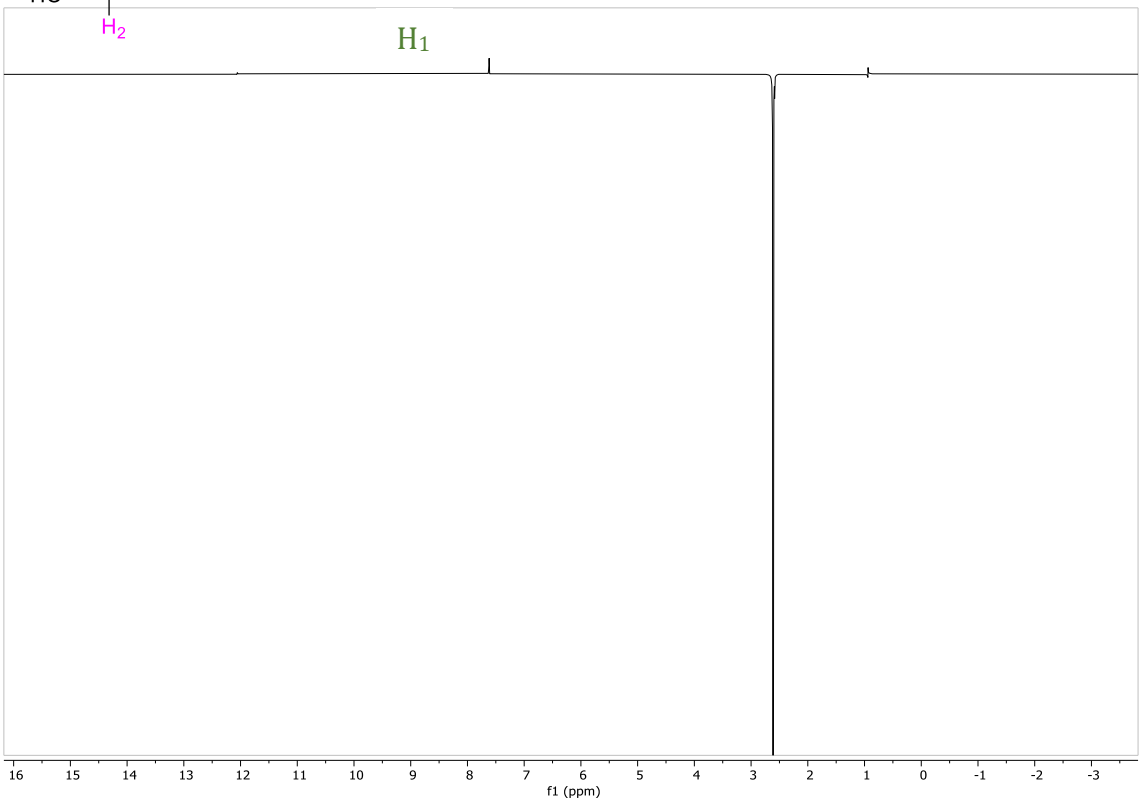


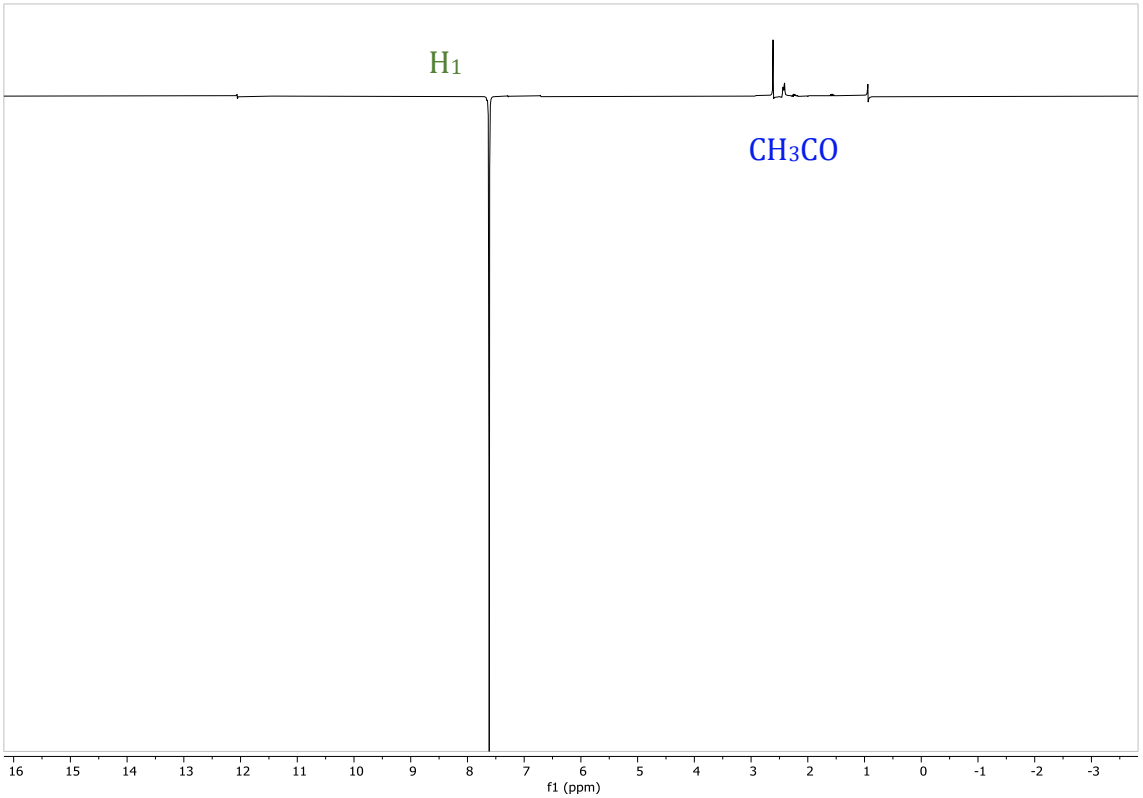
Along these experiments with compound 5a, H_1 is coupled within a 3-bond distance with the installed acetyl group. Conversely. H_2 is not.

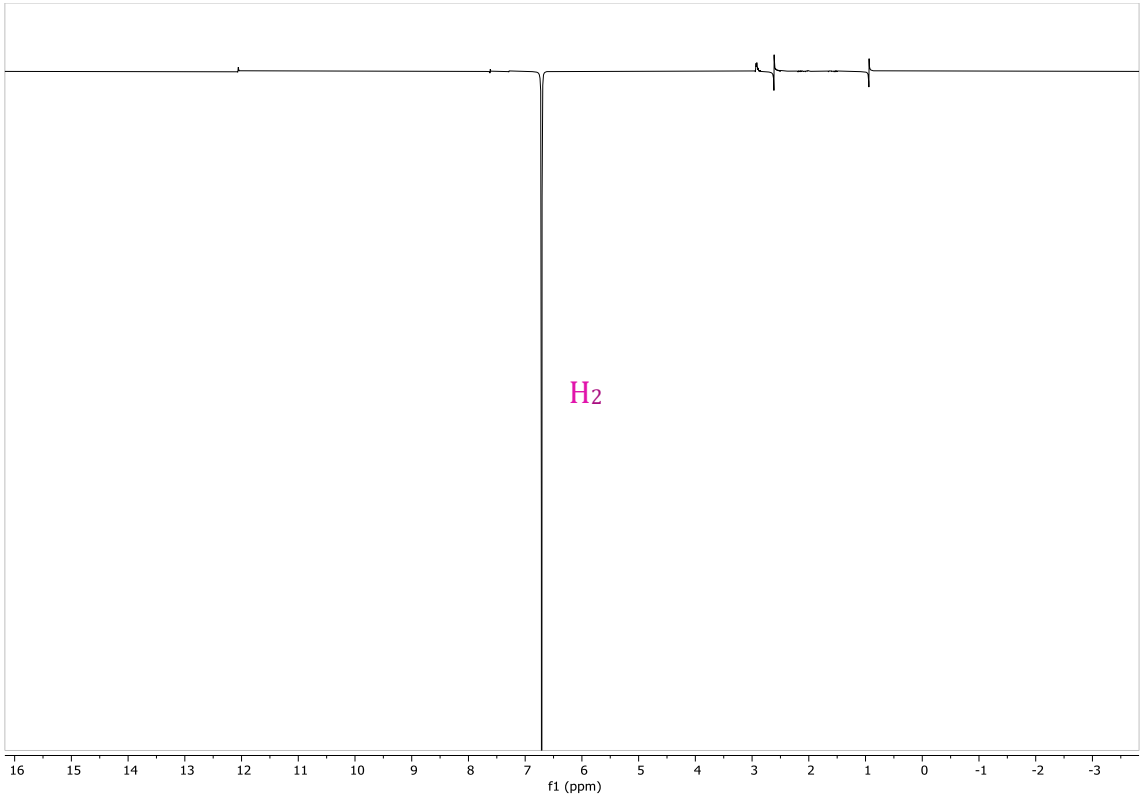
NMR (500 MHz, $CDCl_3$) **NOE EXPERIMENTS with H_1 and H_2**



(5a)

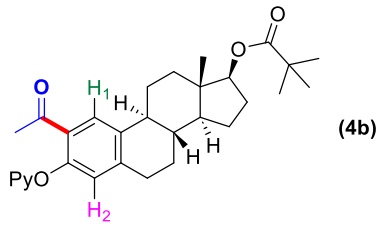




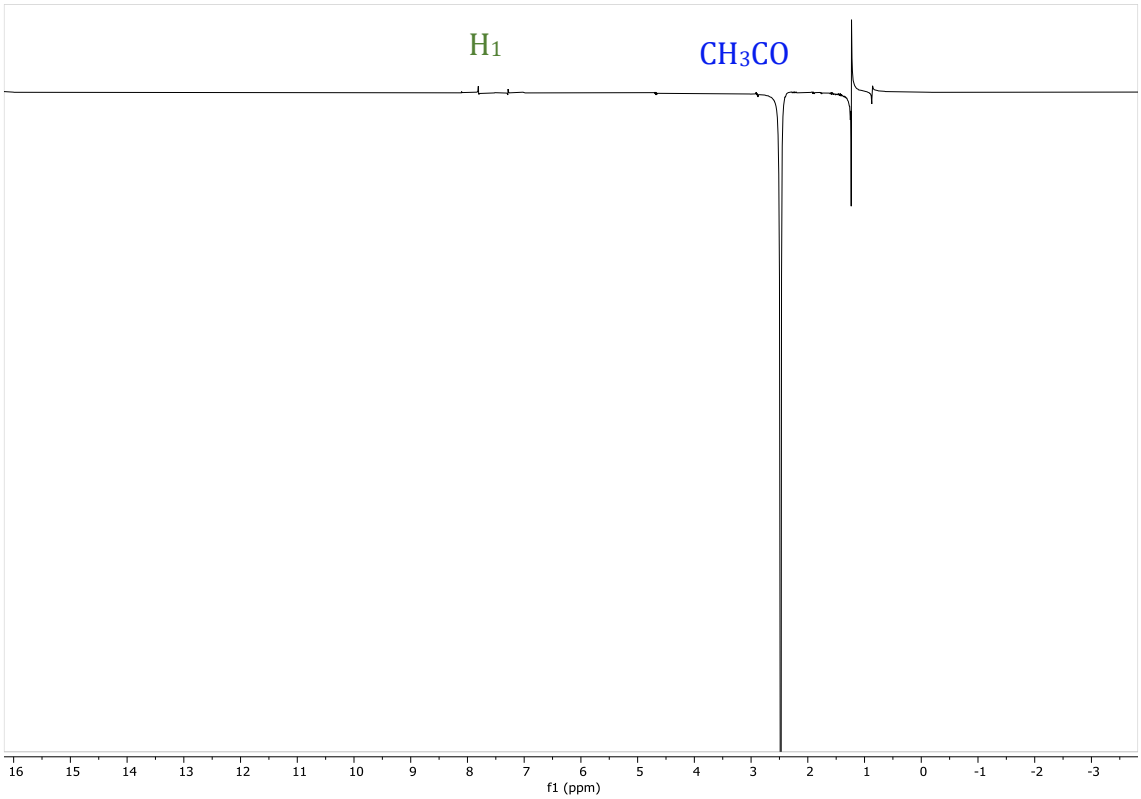


Along these NOE experiments of compound 5a, it is observed a NOE effect between H_1 and the acetyl group, which indicates that they are close within the aryl ring. Conversely, we do not see a NOE effect between H_2 and the corresponding acetyl group. Accordingly, we can verify the regioselectivity of the reaction toward the less hindered ortho-position.

NMR (500 MHz, $CDCl_3$) **NOE EXPERIMENTS with H_1 and H_2**

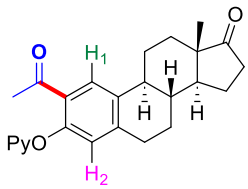


(4b)

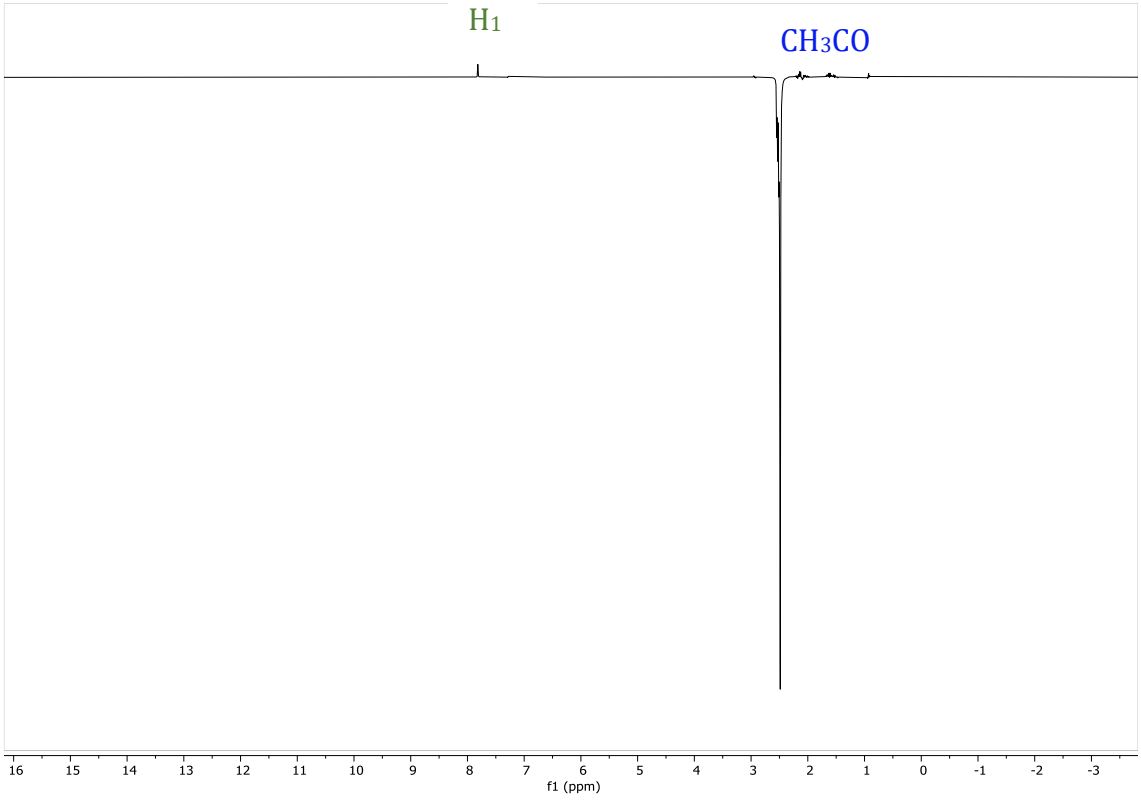


Along this NOE experiment of compound 4b, it is observed a NOE effect between H_1 and the acetyl group, which indicates that they are close within the aryl ring.

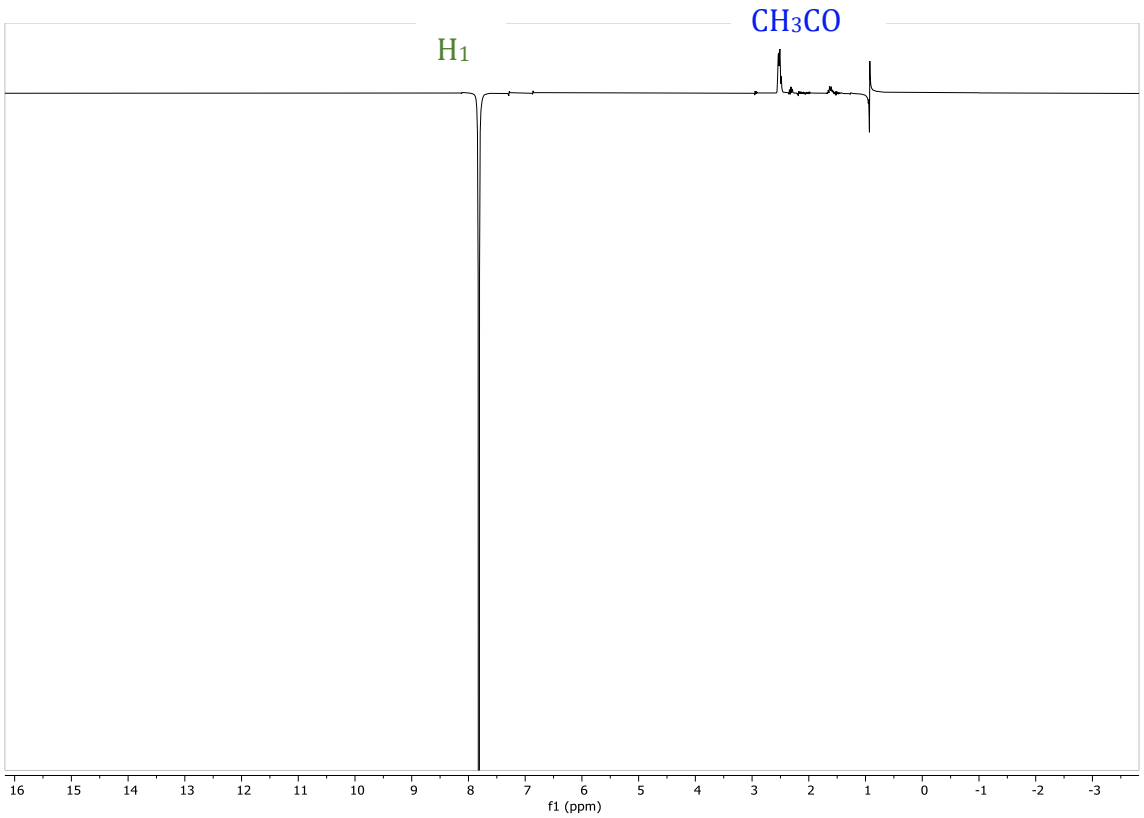
NMR (500 MHz, $CDCl_3$) **NOE EXPERIMENTS with H_1 and H_2**

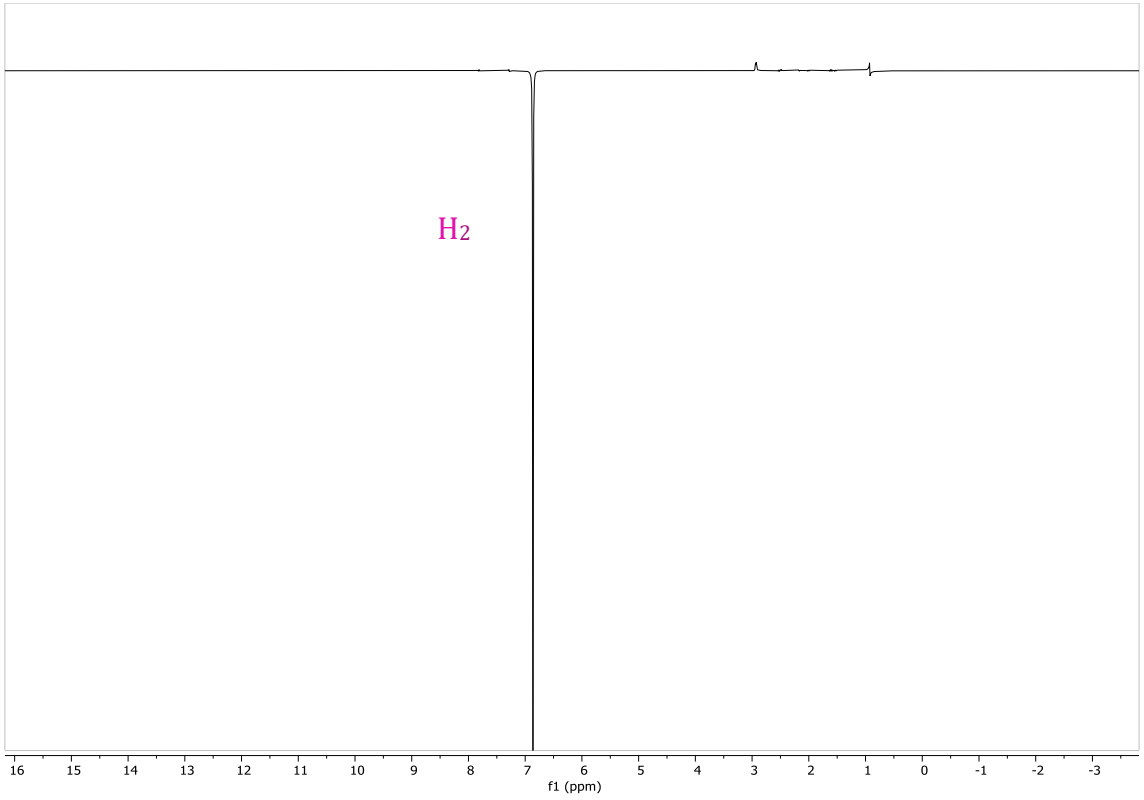


(2a)



Along these NOE experiments of compound 2a, it is observed a NOE effect between H_1 and the acetyl group, which indicates that they are close within the aryl ring. Conversely, we do not see a NOE effect between H_2 and the corresponding acetyl group. Accordingly, we can verify the regioselectivity of the reaction toward the less hindered ortho-position.


CH3CO
H1
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)


H2
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)