SUPPORTING INFORMATION

Acid-Mediated Ring-Expansion of 2,2-Disubstituted Azetidine Carbamates to 6,6-Disubstituted 1,3-Oxazinan-2-ones

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General Experimental Considerations

All non-aqueous reactions were carried out under an inert atmosphere (argon) with flame-dried glassware, using standard techniques. Anhydrous solvents were obtained by filtration through drying columns (CH_2Cl_2, THF, EtOH) or used as supplied (benzene and MeCN). Reactions in sealed tubes were run using Biotage microwave vials (2–5 mL) and aluminium caps with molded butyl (when using benzene) or butyl/PTFE (when using CH_2Cl_2) septa.

Flash chromatography was performed using 230–400 mesh silica, with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography (TLC) was performed on precoated glass-backed silica gel plates. Visualization of the developed chromatogram was performed by UV absorbance (254 nm) and stained with aqueous potassium permanganate solution, a ninhydrin solution in ethanol or a phosphomolybdic acid solution in ethanol.

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

Nuclear magnetic resonance spectra were recorded on 400 or 500 MHz spectrometers. The frequency used to record the NMR spectra is given in each assignment and spectrum (^{1}H NMR at 400 or 500 MHz; ^{13}C NMR at 101 MHz or 126 MHz; ^{19}F NMR at 377 MHz; ^{11}B NMR at 128 MHz). Chemical shifts for ^{1}H NMR spectra are recorded in parts per million with the residual protic solvent resonance as the internal standard ($CDCl_3$: δ = 7.27 ppm, DMSO-*d*$_6$: δ = 2.50 ppm, CD_3OD: δ = 3.35 ppm). Data is reported as follows: chemical shift (multiplicity [s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet and br = broad], coupling constant (in Hz), integration and assignment). ^{13}C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million with the residual protic solvent resonance as the internal standard ($^{13}CDCl_3$: δ = 77.0 ppm, $(^{13}CD_3)_2SO$: δ = 39.5 ppm, $^{13}CD_3OD$: δ = 49.0 ppm). Assignments of ^{1}H and ^{13}C spectra were based upon the analysis of δ and *J* values, as well as DEPT, COSY and HSQC experiments where appropriate. ^{19}F NMR spectra were recorded with or without complete proton decoupling. Decoupling is indicated as ($^{19}F\{^1H\}$) and where relevant this is stated in each assignment and spectrum. ^{19}F NMR spectra are indirectly referenced to $CFCl_3$, automatically *via* direct measurement of the absolute frequency of the deuterium lock signal by the spectrometer hardware.

For clarity NMR spectra are displayed as follows unless this would obscure signals: ^{1}H NMR spectra are displayed between 10 ppm and –0.5 ppm; ^{13}C NMR spectra are displayed between 210 ppm and 0 ppm; ^{19}F NMR spectra are displayed for the full sweep width as acquired.

All *tert*-butyloxycarbonyl (Boc) or carboxybenzyl (Cbz) containing compounds appeared as a mixture of rotamers in the NMR spectra at rt.

Melting points are uncorrected.

The high resolution mass spectrometry (HRMS) analyses were performed using electrospray ion source (ESI) or pneumatically assisted electrospray (pNSI). ESI was performed using a Waters LCT Premier equipped with an ESI source operated in positive ion mode. The software used was MassLynx 4.1, this software does not account for the electron and all the calibrations/references are calculated accordingly, i.e. $[M+H]^+$ is detected and the mass is calibrated to output [M+H]. pNSI was performed using an Orbitrap XL in positive ion mode. Samples are loop injected into or infused in a stream of H_2O/CH_3OH (1:1 at 50 μL/min) using an appropriate solvent for dissolution of the sample. Nebulization was pneumatically assisted by a flow of N_2 through a sheath around the capillary.

All raw and processed data for this manuscript can be found at the Imperial College London Research Data Repository (**DOI**: 10.14469/hpc/4982; https://doi.org/10.14469/hpc/4982).

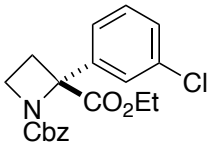
Reagents

Where the synthesis of a reagent is not stated, the reagent was commercially available.
Commercial reagents were used as supplied or purified by standard techniques where necessary.
Trifluoroacetic acid was distilled prior to use.
Catalyst purity: Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] 96% (Aldrich 622623).

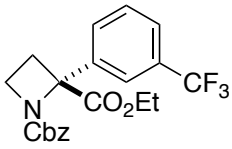
Notes:

- *Although we have not experienced any problems in the handling of azides or diazo reagents, care should be taken when manipulating them due to their potentially explosive nature.*
- *Melting points were not recorded for diazo compounds.*
- *For the diazo compounds synthesized, the resonance for the fully substituted C=N=N carbon in the ^{13}C NMR spectrum is often not seen due to quadrupole coupling to ^{14}N. Unless the ^{13}C resonance was observed it is not reported.*

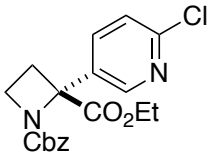
Structures of Additional Compounds in SI



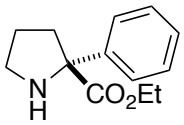
9j



9l



9m



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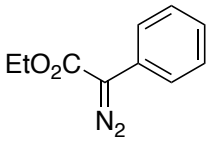
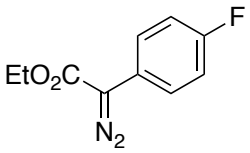
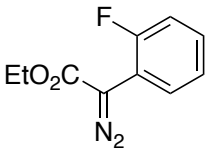
Structures of Diazo Compounds Utilised in the NICE Reaction



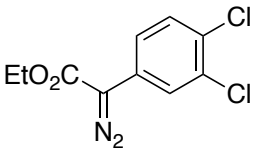
8a



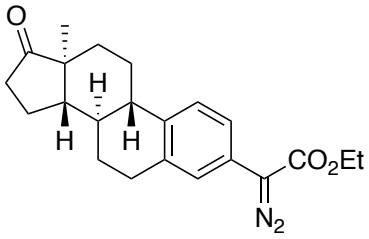
8g



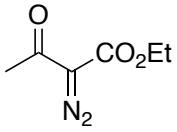
8i



8k



8p



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Synthesis of Protected Amine Starting Materials

tert-Butyl (2-chloroethyl)carbamate **5** was prepared as previously reported.[1]

Benzyl (2-chloroethyl)carbamate **6** was prepared as previously reported,[1] following a procedure by Renaud and co-workers.[2]

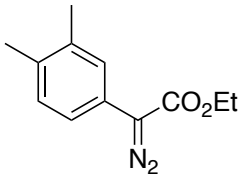
Synthesis of Diazo Compounds

Diazo compounds **8a**–**m** were synthesised as previously reported,[3] using a procedure adapted from Davies and co-workers.[4]

Diazo compound **12** was synthesised as previously reported,[1] using a procedure from Lee and Yuk.[5]

Diazo compound **8p** was synthesised as previously reported,[1] using a procedure adapted from Wang and co-workers.[6]

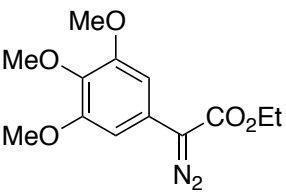
Ethyl 2-diazo-2-(3,4-dimethylphenyl)acetate (8n)



Adapted from a procedure by Wang.[6]
Ethyl 2-diazo-3-oxobutanoate **12** (0.33 mL, 2.4 mmol) was added to a solution of 4-iodo-1,2-dimethylbenzene (464 mg, 2.0 mmol), $Pd(PPh_3)_4$ (116 mg, 0.1 mmol) and dry NaOH* (240 mg, 6.0 mmol) in degassed EtOH (8.0 mL) and stirred at 25 ºC for 18 h. The reaction mixture was filtered through silica, washing with EtOAc (50 mL) and concentrated under reduced pressure. Purification by flash chromatography (2% Et_2O/pentane) afforded ethyl 2-diazo-2-(3,4-dimethylphenyl)acetate **8n** (300 mg, 69%) as an orange solid. R_f 0.21 (2% Et_2O/pentane); ν_{max} (film)/cm^{-1} 2972, 2920, 2079 (C=N=N out-of-phase), 1695 (C=O), 1505, 1372 (C=N=N in-phase), 1345, 1245, 1172, 1111, 892, 805, 706; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.24 (m, 1 H, HC_{Ar}), 7.22 (dd, J = 8.0, 1.9 Hz, 1 H, HC_{Ar}), 7.16 (d, J = 8.0 Hz, 1 H, HC_{Ar}), 4.33 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 2.28 and 2.26 (2 × s, 6 H, 2 × $ArCH_3$), 1.35 (t, J = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6 (C=O), 137.3 (C_{Ar} quat), 134.4 (C_{Ar} quat), 130.2 (C_{Ar}), 125.3 (C_{Ar}), 122.5 (C_{Ar} quat), 121.7 (C_{Ar}), 60.9 (OCH_2CH_3), 19.9 ($ArCH_3$), 19.3 ($ArCH_3$), 14.5 (OCH_2CH_3). The observed characterization data (^{1}H and ^{13}C NMR) was consistent with that previously reported in the literature.[6]

SMILES: CC1=CC(C(C(OCC)=O)=[N+]=[N-])=CC=C1C
InChI = 1S/C12H14N2O2/c1-4-16-12(15)11(14-13)10-6-5-8(2)9(3)7-10/h5-7H,4H2,1-3H3

Ethyl 2-diazo-2-(3,4,5-trimethoxyphenyl)acetate (8o)



Adapted from a procedure by Wang.[6]
Ethyl 2-diazo-3-oxobutanoate **12** (0.33 mL, 2.4 mmol) was added to a solution of 5-iodo-1,2,3-trimethoxybenzene (588 mg, 2.0 mmol), $Pd(PPh_3)_4$ (116 mg, 0.1 mmol) and dry NaOH* (240 mg, 6.0 mmol) in degassed EtOH (8.0 mL) and stirred at 25 ºC for 18 h. The reaction mixture was filtered through silica, washing with EtOAc (50 mL) and concentrated under reduced pressure. Purification by flash chromatography (25% Et_2O/pentane) afforded ethyl 2-diazo-2-(3,4,5-trimethoxyphenyl)acetate **8o** (340 mg, 59%) as an orange solid. R_f 0.24 (20% Et_2O/pentane); ν_{max} (film)/cm^{-1} 2976, 2943, 2078 (C=N=N out-of-phase), 1694 (C=O),

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* NaOH was weighed and then dried over a flame in the reaction vial.

1578, 1509, 1446, 1393, 1378 (C=N=N in-phase), 1280, 1263, 1253, 1176, 1150, 1119, 1081, 1032, 897, 811, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (s, 2 H, 2 × HC_{Ar}), 4.33 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 3.87 (s, 6 H, 2 × OCH_3), 3.84 (s, 3 H, OCH_3), 1.35 (t, J = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3 (C=O), 153.6 (2 × OC_{Ar} quat), 136.1 (OC_{Ar} quat), 120.8 (C_{Ar} quat), 101.5 (2 × C_{Ar}), 63.3 ($C=N_2$ quat), 61.0 (OCH_2CH_3), 60.9 (OCH_3), 56.1 (2 × OCH_3), 14.5 (OCH_2CH_3); HRMS (ESI$^+$) *m/z* Calculated for $C_{13}H_{17}N_2O_5$ [M+H] 281.1137; Found 281.1141. Note: Diazo **8o** was observed to decompose at room temperature.

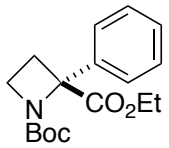
SMILES: COC1=CC(C(C(OCC)=O)=[N+]=[N-])=CC(OC)=C1OC
InChI = 1S/C13H16N2O5/c1-5-20-13(16)11(15-14)8-6-9(17-2)12(19-4)10(7-8)18-3/h6-7H,5H2,1-4H3

Synthesis of Azetidine Carbamates 3a–k and 9a,j,l,m

Azetidines **3b**–**k** and **9a** were synthesised as previously described by our group,[1] in one-pot using a Rh-catalyzed NH insertion and cyclization. Azetidine **1** was synthesised as previously described,[1] from azetidine **3f** by ester hydrolysis and amide coupling.

All *tert*-butyloxycarbonyl (Boc) or carboxybenzyl (Cbz) containing compounds appeared as a mixture of rotamers in the NMR spectra at rt. An asterix * is used to indicate the peaks which are assigned to chemical environments which exist as distinct rotamers at room temperature,

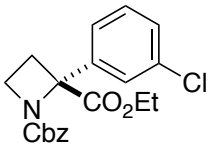
Large scale synthesis of (±)–1-(*tert*-butyl) 2-ethyl 2-phenylazetidine-1,2-dicarboxylate (3a)



$Rh_2(esp)_2$ (56.9 mg, 75 μmol) was added to a solution of *tert*-butyl (2-chloroethyl)carbamate **5** (2.69 g, 15.0 mmol) and ethyl 2-diazo-2-phenylacetate **8a** (4.28 g, 22.5 mmol) in toluene (50.0 mL). The reaction vessel was sealed, purged with Ar and heated at 60 ºC for 2.5 h, then allowed to cool to rt. Tetrabutylammonium bromide (483 mg, 1.5 mmol) was added, followed by $CsOH{\cdot}H_2O$ (5.04 g, 30.0 mmol), and the reaction was stirred at 25 ºC for 18 h. The crude reaction mixture was then filtered through Celite, washing with EtOAc (200 mL), and concentrated under reduced pressure. Purification by flash chromatography (15 to 20% EtOAc/hexane) afforded 1-(*tert*-butyl) 2-ethyl 2-phenylazetidine-1,2-dicarboxylate **3a** (1.97 g, 43%) as a pale yellow oil. R_f 0.18 (10% EtOAc/pentane); ν_{max} (film)/cm^{-1} 2977, 1736 (C=O ester), 1701 (C=O carbamate), 1362, 1230, 1151, 1087, 1022, 766, 696; ^{1}H NMR (400 MHz, $CDCl_3$) 7.50–7.27 (m, 5 H, 5 × HC_{Ph}), 4.34–4.12 (m, 3 H, OCH_2CH_3 and NC*H*), 3.94–3.84 (m, 1 H, NC*H*H), 2.81–2.66 (m, 1 H, NCH_2CH*H*), 2.60–2.45 (m, 1 H, NCH_2CH*H*), 1.55–1.21 (m, 12 H, $C(CH_3)_3$ and OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5 (C=O ester), 155.9 (C=O carbamate), 140.4 (C_{Ph} quat), 127.7 (2 × C_{Ph}), 127.3 (2 × C_{Ph}), 126.4 (C_{Ph}), 80.3* and 80.0* ($C(CH_3)_3$ rotamers), 73.4* and 73.2* (NC quat rotamers), 61.7 (OCH_2CH_3), 46.9* and 45.3* (NCH_2 rotamers), 30.5* and 29.6* (NCH_2CH_2 rotamers), 28.3 ($C(CH_3)_3$), 14.1 (OCH_2CH_3). The observed characterization data was consistent with that previously reported.[1]

SMILES: CC(OC(N1CC[C@@]1(C2=CC=CC=C2)C(OCC)=O)=O)(C)C
InChI = 1S/C17H23NO4/c1-5-21-14(19)17(13-9-7-6-8-10-13)11-12-18(17)15(20)22-16(2,3)4/h6-10H,5,11-12H2,1-4H3

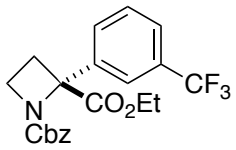
(±)–1-Benzyl 2-ethyl 2-(3-chlorophenyl)azetidine-1,2-dicarboxylate (9j)



$Rh_2(esp)_2$ (3.8 mg, 5.0 μmol) was added to a solution of benzyl (2-chloroethyl)carbamate **6** (214 mg, 1.0 mmol) and ethyl 2-diazo-2-(3-chlorophenyl)acetate **8j** (337 mg, 1.5 mmol) in benzene (3.33 mL). The reaction vessel was sealed, purged with Ar and heated at 60 ºC for 2.5 h, then allowed to cool to rt. Tetrabutylammonium bromide (32 mg, 0.1 mmol) was added, followed by $CsOH{\cdot}H_2O$ (336 mg, 2.00 mmol), and the reaction was stirred at 25 ºC for 18 h. The crude reaction mixture was then filtered through Celite, washing with EtOAc (50 mL), and concentrated under reduced pressure. Purification by flash chromatography (20% EtOAc/hexane) afforded 1-benzyl 2-ethyl 2-(3-chlorophenyl)azetidine-1,2-dicarboxylate **9j** (212 mg, 57%) as a pale yellow oil. R_f 0.25 (20% EtOAc/hexane); ν_{max} (film)/cm^{-1} 2972, 1706 (br s, C=O ester and carbamate), 1446, 1478, 1395, 1339, 1230, 1154, 1124, 777, 764, 739, 696, 689; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.22 (m, 9 H, 5 × HC_{Ph} and 4 × HC_{Ar}), 5.30–5.07 (m, 2 H, OCH_2Ph), 4.32–3.90 (m, 4 H, OCH_2CH_3 and NCH_2), 2.76 (br s, 1 H, NCH_2CH*H*), 2.63–2.46 (m, 1 H, NCH_2CH*H*), 1.26–1.09 (m, 3 H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6 (C=O ester), 156.7* and 156.5* (C=O carbamate rotamers), 142.3* and 141.8* (C_{Ar} quat rotamers), 136.5* and 135.9* (C_{Ph} quat rotamers), 133.9 (ClC_{Ar} quat), 129.2 (C_{Ar}), 128.4 (2 × C_{Ph}), 128.1 (2 × C_{Ph} and 1 × C_{Ar}), 127.7 (C_{Ar}), 126.8 (C_{Ph}), 124.8 (br s, C_{Ar}), 73.1 (NC quat), 67.0 (OCH_2Ph), 62.0 (OCH_2CH_3), 46.8* and 45.7* (NCH_2 rotamers), 30.9*and 30.0* (NCH_2CH_2 rotamers), 13.9 (OCH_2CH_3); HRMS (ESI$^+$) *m/z* Calculated for $C_{20}H_{21}NO_4{}^{35}Cl$ [M+H] 374.1159; Found 374.1164.

SMILES: ClC1=CC=CC([C@](CC2)(C(OCC)=O)N2C(OCC3=CC=CC=C3)=O)=C1
InChI = 1S/C20H20ClNO4/c1-2-25-18(23)20(16-9-6-10-17(21)13-16)11-12-22(20)19(24)26-14-15-7-4-3-5-8-15/h3-10,13H,2,11-12,14H2,1H3

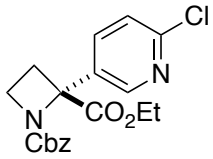
(±)–1-Benzyl 2-ethyl 2-(3-(trifluoromethyl)phenyl)azetidine-1,2-dicarboxylate (9l)



Ethyl 2-diazo-2-(3-(trifluoromethyl)phenyl)acetate **8l** (484 mg, 1.88 mmol) in benzene (1.5 mL) was added slowly *via* syringe pump over 1 h to a solution of benzyl (2-chloroethyl)carbamate **6** (160 mg, 0.75 mmol) and $Rh_2(esp)_2$ (2.8 mg, 3.75 μmol) in benzene (1.0 mL) at 60 ºC. The reaction mixture was stirred at 60 °C for a further 2.5 h, then allowed to cool to rt. Tetrabutylammonium bromide (24 mg, 75.0 μmol) was added, followed by $CsOH{\cdot}H_2O$ (252 mg, 1.50 mmol), and the reaction was stirred at 25 ºC for 18 h. The crude reaction mixture was then filtered through Celite, washing with EtOAc (50 mL), and concentrated under reduced pressure. Purification by flash chromatography (20% EtOAc/pentane) afforded 1-benzyl 2-ethyl 2-(3-(trifluoromethyl)phenyl)azetidine-1,2-dicarboxylate **9l** (227 mg, 74%) as a pale yellow oil. R_f 0.11 (15% EtOAc/pentane); ν_{max} (film)/cm^{-1} 2978, 1707 (s br, 2 × C=O), 1394, 1331, 1226, 1156, 1118, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.19 (m, 9 H, 5 × HC_{Ph} and 4 × HC_{Ar}), 5.29–5.06 (m, 2 H, OCH_2Ph), 4.33–3.91 (m, 4 H, OCH_2CH_3 and NCH_2), 2.86–2.75 (m, 1 H, NCH_2CHH), 2.65–2.47 (m,1 H, NCH_2CHH), 1.23–1.09 (m, 3 H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6 (C=O ester), 156.7 (br s, C=O carbamate), 141.3* and 141.0* (C_{Ar} quat rotamers), 136.3* and 135.8* (C_{Ph} quat rotamers), 130.4*and 130.0* (2 × C_{Ar} rotamers), 128.41*, 128.35*, 128.1* (3 × br s, 5 × C_{Ph} and C_{Ar} rotamers), 124.39* and 124.36* (m, C_{Ar} rotamers), 124.1 (q, J_{C-F} = 271.7 Hz, CF_3), 123.4 (C_{Ar}), 73.2 (NC quat), 67.1 (OCH_2Ph), 62.1 (OCH_2CH_3), 46.8* and 45.8* (NCH_2 rotamers), 30.9* and 30.0* (NCH_2CH_2 rotamers), 13.9 (OCH_2CH_3); ^{19}F{^{1}H} NMR (377 MHz, $CDCl_3$) δ –62.46 and –62.50; HRMS (FTMS + pNSI) *m/z* Calculated for $C_{21}H_{21}NO_4F_3^+$ $[M+H]^+$ 408.1417; Found 408.1413.

SMILES: O=C(N1CC[C@@]1(C2=CC(C(F)(F)F)=CC=C2)C(OCC)=O)OCC3=CC=CC=C3
InChI = 1S/C21H20F3NO4/c1-2-28-18(26)20(16-9-6-10-17(13-16)21(22,23)24)11-12-25(20)19(27)29-14-15-7-4-3-5-8-15/h3-10,13H,2,11-12,14H2,1H3

(±)–1-Benzyl 2-ethyl 2-(6-chloropyridin-3-yl)azetidine-1,2-dicarboxylate (9m)

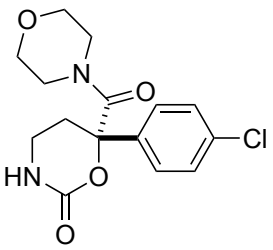


Ethyl 2-(6-chloropyridin-3-yl)-2-diazoacetate **8m** (1.13 g, 5.0 mmol) in benzene (2.17 mL) was added slowly *via* syringe pump over 1 h to a solution of benzyl (2-chloroethyl)carbamate **6** (427 mg, 2.0 mmol) and $Rh_2(esp)_2$ (7.6 mg, 10 μmol) in benzene (4.5 mL) at 60 ºC. The reaction mixture was stirred at 60 °C for a further 2.5 h, then allowed to cool to rt. Tetrabutylammonium bromide (65 mg, 0.2 mmol) was added, followed by $CsOH{\cdot}H_2O$ (672 mg, 4.0 mmol), and the reaction was stirred at 25 ºC for 18 h. The crude reaction mixture was then filtered through Celite, washing with EtOAc (100 mL), and concentrated under reduced pressure. Purification by flash chromatography (30% to 40% EtOAc/pentane) afforded 1-benzyl 2-ethyl 2-(6-chloropyridin-3-yl)azetidine-1,2-dicarboxylate **9m** (133 mg, 18%) as a brown oil. R_f 0.13 (30% EtOAc/pentane); ν_{max} (film)/cm^{-1} 2978, 2900, 1707 (br s, 2 × C=O), 1588, 1457, 1394, 1338, 1238, 1156, 1103, 1014, 738, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (br s, 1 H, HC_{Ar}), 7.84 and 7.67 (2 × d, J = 7.5 Hz, 1 H, HC_{Ar}), 7.49–7.12 (m, 6 H, HC_{Ar} and 5 × HC_{Ph}), 5.25–5.06 (m, 2 H, OCH_2Ph), 4.32–3.85 (m, 4 H, OCH_2CH_3 and NCH_2), 2.80–2.68 (m, 1 H, NCH_2CHH), 2.62–2.43 (m, 1 H, NCH_2CHH), 1.20–1.06 (m, 3 H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1 (C=O ester), 156.8* and 156.3* (C=O carbamate rotamers), 150.4 (ClC_{Ar} quat), 148.0 (C_{Ar}), 137.5* and 137.1* (C_{Ph} quat rotamers), 136.1* and 135.5* (C_{Ar} quat rotamers), 135.0* and 134.5* (C_{Ar} rotamers), 128.4 (2 × C_{Ph}), 128.1 (2 × C_{Ph}), 127.8 (C_{Ph}), 123.3 (C_{Ar}), 71.3* and 71.2* (NC quat rotamers), 67.2* and 67.1* (OCH_2Ph rotamers), 62.3 (OCH_2CH_3), 47.0* and 46.0* (NCH_2 rotamers), 30.5* and 29.5* (NCH_2CH_2 rotamers), 13.8 (OCH_2CH_3); HRMS (ESI^+) *m/z* Calculated for $C_{19}H_{20}N_2O_4{}^{35}Cl$ [M+H] 375.1112; Found 375.1096.

SMILES: ClC(C=C1)=NC=C1[C@](CC2)(C(OCC)=O)N2C(OCC3=CC=CC=C3)=O
InChI = 1S/C19H19ClN2O4/c1-2-25-17(23)19(15-8-9-16(20)21-12-15)10-11-22(19)18(24)26-13-14-6-4-3-5-7-14/h3-9,12H,2,10-11,13H2,1H3

Synthesis of Oxazinanones 2, 4a–l,n–p by 4 to 6 Ring Expansion

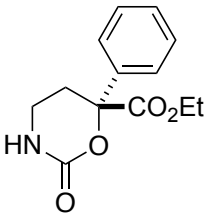
(±)–6-(4-Chlorophenyl)-6-(morpholine-4-carbonyl)-1,3-oxazinan-2-one (2)



Trifluoroacetic acid (0.10 mL) was added to a stirred solution of of *tert*-butyl 2-(4-chlorophenyl)-2-(morpholine-4-carbonyl)azetidine-1-carboxylate **1** (28 mg, 0.075 mmol) in CH_2Cl_2 (0.40 mL) at 0 °C. The reaction mixture was then stirred at 25 °C for 15 h. The solvent was removed under reduced pressure, saturated aq. $NaHCO_3$ (10 mL) and saturated brine (25 mL) was added and the aqueous mixture was extracted with $CHCl_3$:2-propanol (3:1, 6 × 10 mL). The solvent was removed under reduced pressure. Purification by flash chromatography NH_3/MeOH/CH_2Cl_2 (0.05:4.95:95%) afforded 6-(4-chlorophenyl)-6-(morpholine-4-carbonyl)-1,3-oxazinan-2-one **2** (10 mg, 43%) as a yellow solid. R_f 0.18 (0.05:4.95:95 NH_3:MeOH:CH_2Cl_2); mp = 188–190 °C; ν_{max} (film)/cm^{-1} 3283 (br s, NH), 2924, 2858, 1721 (C=O carbamate), 1642 (C=O amide), 1490, 1436, 1319, 1115, 1085, 1006, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.34 (m, 4 H, 2 × HC_{Ar}), 5.77 (br s, 1 H, NH), 3.74–3.56 (m, 6 H, 2 × OC*H*H, HNC*H*HCH_2, NC*H*HCH_2O and NCH_2CH_2O), 3.54–3.46 (m, 1 H, OCH*H*), 3.33–3.25 (m, 1 H, NCH*H*CH_2O), 3.24–3.17 (m, 1 H, HNCH*H*CH_2), 3.16–3.09 (m, 1 H, OCH*H*), 2.77 (dt, 1 H, *J* = 14.0, 4.5 Hz, HNCH_2C*H*H), 2.02–1.92 (m, 1 H, HNCH_2CH*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9 (C=O amide), 152.4 (C=O carbamate), 137.7 (C_{Ar} quat), 134.6 (C_{Ar} quat), 129.3 (2 × C_{Ar}), 125.3 (2 × C_{Ar}), 84.9 (OC quat), 66.7 (O*C*H_2), 66.4 (O*C*H_2), 47.1 (N*C*H_2CH_2O), 43.8 (N*C*H_2CH_2O), 37.7 (HNCH_2), 32.7 (HNCH_2*C*H_2); HRMS (ESI$^+$) *m/z* Calculated for $C_{15}H_{18}N_2O_4{}^{35}Cl$ [M+H] 325.0955; Found 325.0958.

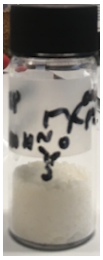
SMILES: O=C1NCC[C@](C2=CC=C(Cl)C=C2)(C(N3CCOCC3)=O)O1
InChI = 1S/C15H17ClN2O4/c16-12-3-1-11(2-4-12)15(5-6-17-14(20)22-15)13(19)18-7-9-21-10-8-18/h1-4H,5-10H2,(H,17,20)/t15-/m0/s1

(±)–Ethyl 2-oxo-6-phenyl-1,3-oxazinane-6-carboxylate (4a)



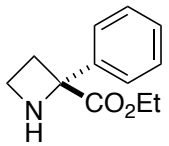
Trifluoroacetic acid (0.19 mL, 2.5 mmol) was added to a stirred solution of 1-(*tert*-butyl) 2-ethyl 2-phenylazetidine-1,2-dicarboxylate **3a** (153 mg, 0.5 mmol) in toluene (0.5 mL) at 25 °C and stirred for 30 min. The reaction mixture was concentrated and purified by flash chromatography (2% to 3% MeOH/CH_2Cl_2) to afford ethyl 2-oxo-6-phenyl-1,3-oxazinane-6-carboxylate **4a** (93 mg, 75%) as an off-white solid. R_f 0.25 (EtOAc); mp = 141–145 °C; ν_{max} (film)/cm^{-1} 3266 (br, NH), 2983, 1710 (s br, 2 × C=O), 1489, 1449, 1408, 1312, 1271, 1203, 1139, 1096, 1074, 1015, 760, 734, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.56 (m, 2 H, 2 × HC_{Ph}), 7.43–7.33 (m, 3 H, 3 × HC_{Ph}), 6.59 (br s, 1 H, NH), 4.27–4.18 (m, 2 H, OCH_2CH_3), 3.41–3.26 (m, 2 H, NCH_2), 2.75 (dt, *J* = 13.8, 4.9 Hz, 1 H, NCH_2C*H*H), 2.33 (ddd, *J* = 13.8, 9.2, 5.9 Hz, 1 H, NCH_2CH*H*), 1.23 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9 (C=O ester), 153.1 (C=O carbamate), 137.4 (C_{Ph} quat), 128.72 (C_{Ph}), 128.66 (2 × C_{Ph}), 124.9 (2 × C_{Ph}), 83.2 (OC quat), 62.4 (O*C*H_2CH$_3$), 37.1 (NCH_2), 29.2 (NCH_2*C*H_2), 13.9 (OCH_2*C*H_3); HRMS (ESI$^+$) *m/z* Calculated for $C_{13}H_{16}NO_4$ [M+H] 250.1079; Found 250.1079.

Gram Scale Synthesis of **4a**



Trifluoroacetic acid (2.87 mL, 37.5 mmol) was added to a stirred solution of 1-(*tert*-butyl) 2-ethyl 2-phenylazetidine-1,2-dicarboxylate **3a** (2.29 g, 7.5 mmol) in toluene (7.5 mL) at 25 °C and stirred for 30 min. The reaction mixture was concentrated and purified by flash chromatography (EtOAc) to afford ethyl 2-oxo-6-phenyl-1,3-oxazinane-6-carboxylate **4a** (1.23 g, 66%) as an off-white solid. The observed characterization data was identical to that reported previously for **4a** above.
SMILES: O=C1NCC[C@@](C2=CC=CC=C2)(C(OCC)=O)O1
InChI = 1S/C13H15NO4/c1-2-17-11(15)13(8-9-14-12(16)18-13)10-6-4-3-5-7-10/h3-7H,2,8-9H2,1H3,(H,14,16)

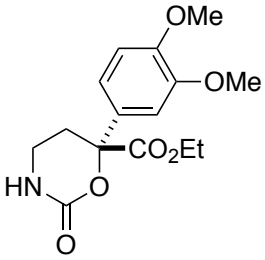
(±)–Ethyl 2-phenylazetidine-2-carboxylate (5a)



4 N HCl in 1,4-dioxane (3.8 mL) was added dropwise to a stirred solution of 1-(*tert*-butyl) 2-ethyl 2-phenylazetidine-1,2-dicarboxylate **3a** (458 mg, 1.5 mmol) in 1,4-dioxane (6.0 mL) at 0 ºC. The reaction mixture was stirred at 25 ºC for 24 h then diluted with 1 M HCl (40 mL). The aqueous reaction mixture was extracted with EtOAc (2 × 40 mL). The aqueous layer was basified with sat. aq. $NaHCO_3$ (50 mL) and extracted with EtOAc (5 × 25 mL). The combined organic layers were dried over Na_2SO_4 and filtered. Concentration under reduced pressure afforded ethyl 2-phenylazetidine-2-carboxylate **5a** (220 mg, 71%) as a yellow oil. R_f 0.36 (EtOAc); ν_{max} (film)/cm^{-1} 3325 (NH), 2974, 2874, 1722 (C=O), 1241, 1103, 1014, 775, 731, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.38 (m, 2 H, 2 × HC_{Ph}), 7.37–7.32 (m, 2 H, 2 × HC_{Ph}), 7.29–7.23 (m, 1 H, HC_{Ph}), 4.28–4.11 (m, 2 H, OCH_2CH_3), 3.69 (td, J = 8.5, 7.4 Hz, 1 H, NC*H*H), 3.34 (ddd, J = 8.5, 7.3, 3.9 Hz, 1 H, NCH*H*), 2.94–2.77 (m, 2 H, NCH_2CH_2), 1.23 (d, J = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.7 (C=O), 143.1 (C_{Ph} quat), 128.1 (2 × C_{Ph}), 127.1 (C_{Ph}), 125.1 (2 × C_{Ph}), 69.4 (NC quat), 61.6 (OCH_2CH_3), 41.8 (NCH_2), 32.4 (NCH_2CH_2), 14.0 (OCH_2CH_3); HRMS (FTMS + pNSI) *m/z* Calculated for $C_{12}H_{16}NO_2^+$ $[M+H]^+$ 206.1176; Found 206.1176.

SMILES: O=C([C@@]1(C2=CC=CC=C2)NCC1)OCC
InChI = 1S/C12H15NO2/c1-2-15-11(14)12(8-9-13-12)10-6-4-3-5-7-10/h3-7,13H,2,8-9H2,1H3

(±)–Ethyl 6-(3,4-dimethoxyphenyl)-2-oxo-1,3-oxazinane-6-carboxylate (4b)

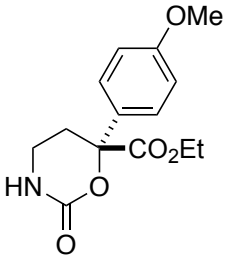


Trifluoroacetic acid (38 μL, 0.50 mmol) was added to a stirred solution of 1-(*tert*-butyl) 2-ethyl 2-(3,4-dimethoxyphenyl)azetidine-1,2-dicarboxylate **3b** (36.5 mg, 0.10 mmol) in toluene (0.10 mL) at 25 ºC and stirred for 30 min. The reaction mixture was concentrated and purified by flash chromatography (3% MeOH/CH_2Cl_2) to afford ethyl 6-(4-methoxyphenyl)-2-oxo-1,3-oxazinane-6-carboxylate **4b** (27 mg, 88%) as a colorless solid. R_f 0.05 (2% MeOH/CH_2Cl_2); mp = 108–111 ºC; ν_{max} (film)/cm^{-1} 3282 (br s, NH), 2939, 1710 (br s, C=O ester/carbamate), 1516, 1460, 1413, 1262, 1202, 1166, 1144, 1090, 1020, 808, 760, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13–7.06 (m, 2 H, 2 × HC_{Ar}), 6.87 (d, J = 8.4 Hz, 1 H, HC_{Ar}), 6.33 (s, 1 H, NH), 4.23 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 3.90 and 3.89 (2 × s, 6 H, 2 × OCH_3), 3.38–3.32 (m, 2 H, NCH_2), 2.75 (dt, J = 13.8, 4.3 Hz, 1 H, NCH_2CHH), 2.37–2.26 (m, 1 H, NCH_2CHH), 1.24 (q, J = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0 (C=O ester), 153.3 (C=O carbamate), 149.3 (OC_{Ar} quat), 149.0 (OC_{Ar} quat), 129.8 (C_{Ar} quat), 117.4 (C_{Ar}), 110.9 (C_{Ar}), 108.2 (C_{Ar}), 83.1 (OC quat), 62.5 (OCH_2CH_3), 56.0 (OCH_3), 55.9 (OCH_3), 37.2 (NCH_2), 29.0 (NCH_2CH_2), 14.0 (OCH_2CH_3); HRMS (ESI^+) *m/z* Calculated for $C_{15}H_{20}NO_6$ [M+H] 310.1291; Found 310.1295.

SMILES: O=C1NCC[C@@](C2=CC(OC)=C(OC)C=C2)(C(OCC)=O)O1

InChI = 1S/C15H19NO6/c1-4-21-13(17)15(7-8-16-14(18)22-15)10-5-6-11(19-2)12(9-10)20-3/h5-6,9H,4,7-8H2,1-3H3,(H,16,18)

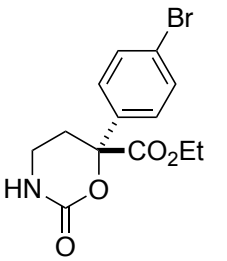
(±)–Ethyl 6-(4-methoxyphenyl)-2-oxo-1,3-oxazinane-6-carboxylate (4c)



Trifluoroacetic acid (38 μL, 0.50 mmol) was added to a stirred solution of 1-(*tert*-butyl) 2-ethyl 2-(4-methoxyphenyl)azetidine-1,2-dicarboxylate **3c** (34 mg, 0.10 mmol) in toluene (0.10 mL) at 25 ºC and stirred for 30 min. The reaction mixture was concentrated and purified by flash chromatography (3% MeOH/CH_2Cl_2) to afford ethyl 6-(4-methoxyphenyl)-2-oxo-1,3-oxazinane-6-carboxylate **4c** (25 mg, 89%) as a colorless solid. R_f 0.21 (3% MeOH/CH_2Cl_2); mp = 175–176 ºC; ν_{max} (film)/cm^{-1} 3241 (br s, NH), 3138, 2942, 1741 (C=O ester), 1702 (C=O carbamate), 1511, 1492, 1462, 1445, 1411, 1326, 1308, 1302, 1254, 1199, 1182, 1145, 1122, 1090, 1031, 1005, 822, 799, 763, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.9 Hz, 2 H, 2 × HC_{Ar}), 6.91 (d, *J* = 8.9 Hz, 2 H, 2 × HC_{Ar}), 6.36 (br s, 1 H, NH), 4.22 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 3.81 (s, 3 H, OCH_3), 3.39–3.26 (m, 2 H, NCH_2), 2.72 (dt, *J* = 13.8, 4.8 Hz, 1 H, NCH_2CHH), 2.32 (ddd, *J* = 13.8, 8.3, 2.6 Hz, 1 H, NCH_2CHH), 1.23 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1 (C=O ester), 159.8 (OC_{Ar} quat), 153.1 (C=O carbamate), 129.5 (C_{Ar} quat), 126.4 (2 × C_{Ar}), 114.0 (2 × C_{Ar}), 83.0 (OC quat), 62.4 (OCH_2CH_3), 55.3 (OCH_3), 37.1 (NCH_2), 29.0 (NCH_2CH_2), 14.0 (OCH_2CH_3); HRMS (ESI$^+$) *m/z* Calculated for $C_{14}H_{18}NO_5$ [M+H] 280.1185; Found 280.1187.

SMILES: O=C1NCC[C@@](C2=CC=C(OC)C=C2)(C(OCC)=O)O1
InChI = 1S/C14H17NO5/c1-3-19-12(16)14(8-9-15-13(17)20-14)10-4-6-11(18-2)7-5-10/h4-7H,3,8-9H2,1-2H3,(H,15,17)

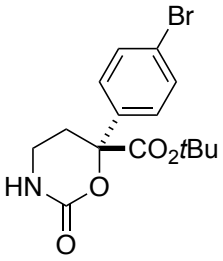
(±)–Ethyl 6-(4-bromophenyl)-2-oxo-1,3-oxazinane-6-carboxylate (4d)



Trifluoroacetic acid (38 μL, 0.50 mmol) was added to a stirred solution of 1-(*tert*-butyl) 2-ethyl 2-(4-bromophenyl)azetidine-1,2-dicarboxylate **3d** (38 mg, 0.10 mmol) in toluene (0.10 mL) at 25 ºC and stirred for 30 min. After 30 min further trifluoroacetic acid (38 μL, 0.50 mmol) was added and the mixture was stirred for a further 30 min. The reaction mixture was concentrated and purified by flash chromatography (80% EtOAc/pentane to EtOAc) to afford ethyl 6-(4-bromophenyl)-2-oxo-1,3-oxazinane-6-carboxylate **4d** (21 mg, 63%) as a colorless solid. R_f 0.23 (3% MeOH/CH_2Cl_2); mp = 122–125 ºC; ν_{max} (film)/cm^{-1} 3241 (br s, NH), 3138, 2980, 2941, 1741 (C=O ester), 1705 (C=O carbamate), 1485, 1462, 1410, 1338, 1324, 1277, 1255, 1199, 1185, 1145, 1122, 1090, 1024, 1007, 967, 820, 779, 723, 700, 685; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.8 Hz, 2 H, 2 × HC_{Ar}), 7.48 (d, *J* = 8.8 Hz, 2 H, 2 × HC_{Ar}), 5.53 (br s, 1 H, NH), 4.28–4.20 (m, 2 H, OCH_2CH_3), 3.43–3.28 (m, 2 H, NCH_2), 2.75 (dt, *J* = 13.9, 4.8 Hz, 1 H, NCH_2CHH), 2.33–2.22 (ddd, *J* = 14.0, 9.4, 6.4 Hz, 1 H, NCH_2CHH), 1.25 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5 (C=O ester), 152.7 (C=O carbamate), 136.5 (C_{Ar} quat), 131.9 (2 × C_{Ar}), 126.8 (2 × C_{Ar}), 123.1 (BrC_{Ar} quat), 82.9 (OC quat), 62.7 (OCH_2CH_3), 37.1 (NCH_2), 29.2 (NCH_2CH_2), 13.9 (OCH_2CH_3); HRMS (ESI$^+$) *m/z* Calculated for $C_{13}H_{15}NO_4{}^{79}Br$ [M+H] 328.0184; Found 328.0184.

SMILES: O=C1NCC[C@@](C2=CC=C(Br)C=C2)(C(OCC)=O)O1
InChI = 1S/C13H14BrNO4/c1-2-18-11(16)13(7-8-15-12(17)19-13)9-3-5-10(14)6-4-9/h3-6H,2,7-8H2,1H3,(H,15,17)

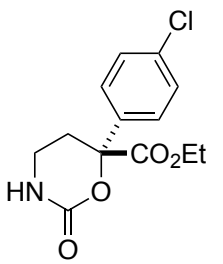
(±)–*tert*-Butyl 6-(4-bromophenyl)-2-oxo-1,3-oxazinane-6-carboxylate (4e)



Trifluoroacetic acid (38 μL, 0.5 mmol) was added to a stirred solution of di-*tert*-butyl 2-(4-bromophenyl)azetidine-1,2-dicarboxylate **3e** (41 mg, 0.10 mmol) in toluene (0.10 mL) at 25 ºC and stirred for 30 min. The reaction mixture was concentrated and purified by flash chromatography (2% MeOH/CH_2Cl_2) to afford *tert*-butyl 6-(4-bromophenyl)-2-oxo-1,3-oxazinane-6-carboxylate **4e** (20 mg, 56%) as a colorless solid. R_f 0.20 (3% MeOH/CH_2Cl_2); mp = 185–188 ºC; ν_{max} (film)/cm^{-1} 3263 (br s, NH), 2979, 1724 (br s, C=O ester/carbamate), 1489, 1397, 1370, 1321, 1160, 1096, 840; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.8 Hz, 2 H, 2 × HC_{Ar}), 7.47 (d, J = 8.8 Hz, 2 H, 2 × HC_{Ar}), 5.94 (br s, 1 H, NH), 3.43–3.30 (m, 2 H, NCH_2), 2.71 (dt, J = 13.8, 4.6 Hz, 1 H, NCH_2CHH), 2.22 (ddd, J = 13.8, 9.7, 6.3 Hz, 1 H, NCH_2CHH), 1.43 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4 (C=O ester), 152.7 (C=O carbamate), 136.9 (C_{Ar} quat), 131.7 (2 × C_{Ar}), 126.8 (2 × C_{Ar}), 122.9 (BrC_{Ar} quat), 83.8 ($C(CH_3)_3$), 83.0 (OC quat), 37.3 (NCH_2), 29.2 (NCH_2CH_2), 27.7 ($C(CH_3)_3$); HRMS (ESI$^+$) *m/z* Calculated for $C_{15}H_{19}NO_4{}^{79}Br$ [M+H] 356.0497; Found 356.0503.

SMILES: O=C1NCC[C@@](C2=CC=C(Br)C=C2)(C(OC(C)(C)C)=O)O1
InChI = 1S/C15H18BrNO4/c1-14(2,3)20-12(18)15(8-9-17-13(19)21-15)10-4-6-11(16)7-5-10/h4-7H,8-9H2,1-3H3,(H,17,19)

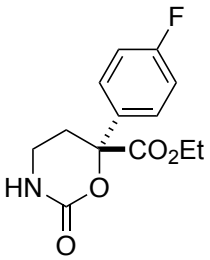
(±)–Ethyl 6-(4-chlorophenyl)-2-oxo-1,3-oxazinane-6-carboxylate (4f)



Trifluoroacetic acid (77 μL, 1.0 mmol) was added to a stirred solution of 1-(*tert*-butyl) 2-ethyl 2-(4-chlorophenyl)azetidine-1,2-dicarboxylate **3f** (68 mg, 0.20 mmol) in toluene (0.20 mL) at 25 ºC and stirred for 30 min. The reaction mixture was concentrated and purified by flash chromatography (2% MeOH/CH_2Cl_2) to afford ethyl 6-(4-chlorophenyl)-2-oxo-1,3-oxazinane-6-carboxylate **4f** (40 mg, 71%) as a colorless solid. R_f 0.23 (3% MeOH/CH_2Cl_2); mp = 116–118 ºC; ν_{max} (film)/cm^{-1} 3242 (br s, NH), 3137, 2981, 2941, 1485, 1462, 1411, 1338, 1324, 1301, 1277, 1255, 1199, 1185, 1145, 1122, 1089, 1024, 1007, 861, 779, 763, 723, 685, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.7 Hz, 2 H, 2 × HC_{Ar}), 7.38 (d, J =, 8.7 Hz, 2 H, 2 × HC_{Ar}), 6.55 (br s, 1 H, NH), 4.23 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 3.40–3.28 (m, 2 H, NCH_2), 2.74 (dt, J = 13.8, 4.7 Hz, 1 H, NCH_2CHH), 2.27 (ddd, J = 14.0, 9.3, 5.9 Hz, 1 H, NCH_2CHH), 1.23 (t, J = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6 (C=O ester), 152.8 (C=O carbamate), 136.0 (C_{Ar} quat), 134.9 (ClC_{Ar} quat), 128.9 (2 × C_{Ar}), 126.5 (2 × C_{Ar}), 82.8 (OC quat), 62.7 (OCH_2CH_3), 37.1 (NCH_2), 29.2 (NCH_2CH_2), 13.9 (OCH_2CH_3); HRMS (ESI$^+$) *m/z* Calculated for $C_{13}H_{15}NO_4{}^{35}Cl$ [M+H] 284.0690; Found 284.0689.

SMILES: O=C1NCC[C@@](C2=CC=C(Cl)C=C2)(C(OCC)=O)O1
InChI = 1S/C13H14ClNO4/c1-2-18-11(16)13(7-8-15-12(17)19-13)9-3-5-10(14)6-4-9/h3-6H,2,7-8H2,1H3,(H,15,17)

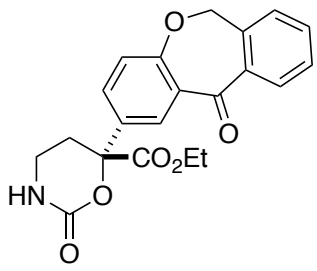
(±)–Ethyl 6-(4-fluorophenyl)-2-oxo-1,3-oxazinane-6-carboxylate (4g)



Trifluoroacetic acid (77 μL, 1.0 mmol) was added to a stirred solution of 1-(*tert*-butyl) 2-ethyl 2-(4-fluorophenyl)azetidine-1,2-dicarboxylate **3g** (65 mg, 0.20 mmol) in toluene (0.20 mL) at 25 ºC and stirred for 30 min. The reaction mixture was concentrated and purified by flash chromatography (3% MeOH/CH_2Cl_2) to afford ethyl 6-(4-fluorophenyl)-2-oxo-1,3-oxazinane-6-carboxylate **4g** (37 mg, 95%) as a colorless solid. R_f 0.28 (3% MeOH/CH_2Cl_2); mp = 115–118 ºC; ν_{max} (film)/cm^{-1} 3236 (br s, NH), 3136, 1732 (C=O ester), 1705 (C=O carbamate), 1511, 1493, 1415, 1332, 1222, 1207, 1142, 1121, 1012, 813, 744, 709; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.55 (m, 2 H, 2 × HC_{Ar}), 7.12–7.05 (m, 2 H, 2 × HC_{Ar}), 6.46 (br s, 1 H, NH), 4.23 (q, J = 7.1 Hz, 2 H, OC*H*$_2$CH$_3$), 3.41–3.28 (m, 2 H, NCH_2), 2.75 (dt, J = 13.8, 4.6 Hz, 1 H, NCH_2CHH), 2.29 (ddd, J = 13.8, 9.2, 6.2 Hz, 1 H, NCH_2CHH), 1.23 (t, J = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7 (C=O ester), 162.8 (d, $J_{C–F}$ = 247.8 Hz, FC_{Ar} quat), 153.0 (C=O carbamate), 133.3 (d, $J_{C–F}$ = 2.9 Hz, C_{Ar} quat), 127.0 (d, $J_{C–F}$ = 8.3 Hz, 2 × C_{Ar}), 115.7 (d, $J_{C–F}$ = 21.9 Hz, 2 × C_{Ar}), 82.9 (OC quat), 62.6 (O*C*H$_2$CH$_3$), 37.1 (NCH_2), 29.2 (NCH_2CH_2), 13.9 (OCH_2CH_3); ^{19}F{^{1}H} NMR (377 MHz, $CDCl_3$) δ –113.0; HRMS (ESI$^+$) *m/z* Calculated for $C_{13}H_{15}NO_4F$ [M+H] 268.0985; Found 268.0993.

SMILES: O=C1NCC[C@@](C2=CC=C(F)C=C2)(C(OCC)=O)O1
InChI = 1S/C13H14FNO4/c1-2-18-11(16)13(7-8-15-12(17)19-13)9-3-5-10(14)6-4-9/h3-6H,2,7-8H2,1H3,(H,15,17)

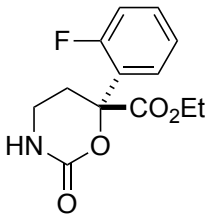
(±)–Ethyl 2-oxo-6-(11-oxo-6,11-dihydrodibenzo[*b*,*e*]oxepin-2-yl)-1,3-oxazinane-6-carboxylate (4h)



Trifluoroacetic acid (38 μL, 0.50 mmol) was added to a stirred solution of 1-(*tert*-butyl) 2-ethyl 2-(11-oxo-6,11-dihydrodibenzo[*b*,*e*]oxepin-2-yl)azetidine-1,2-dicarboxylate **3h** (44 mg, 0.10 mmol) in toluene (0.10 mL) at 25 ºC and stirred for 30 min. The reaction mixture was concentrated and purified by flash chromatography (70% EtOAc/pentane) to afford ethyl 2-oxo-6-(11-oxo-6,11-dihydrodibenzo[b,e]oxepin-2-yl)-1,3-oxazinane-6-carboxylate **4h** (37 mg, 96%) as a colorless solid. R_f 0.20 (70% EtOAc/pentane); mp = 78–80 ºC; ν_{max} (film)/cm^{-1} 3280 (br s, NH), 2982, 1715 (br s, C=O ester and carbamate), 1648 (C=O ketone), 1484, 1297, 1271, 1200, 1092, 1010, 760, 727; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 2.5 Hz, 1 H, HC_{Ar}), 7.88 (dd, J = 7.7, 1.2 Hz, 1 H, HC_{Ar}), 7.78 (dd, J = 8.7, 2.6 Hz, 1 H, HC_{Ar}), 7.58 (td, J = 7.5, 1.4 Hz, 1 H, HC_{Ar}), 7.49 (td, J = 7.6, 1.2 Hz, 1 H, HC_{Ar}), 7.38 (dd, J = 7.6, 0.9 Hz, 1 H, HC_{Ar}), 7.10 (d, J = 8.7 Hz, 1 H, HC_{Ar}), 6.30 (br s, 1 H, NH), 5.21 (s, 2 H, OCH_2Ar), 4.25 (q, J = 7.1 Hz, 2 H, OC*H*$_2$CH$_3$), 3.42–3.36 (m, 2 H, NCH_2), 2.84 (dt, J = 13.8, 4.6 Hz, 1 H, NCH_2CHH), 2.39 (dt, J = 13.8, 7.9 Hz, 1 H, NCH_2CHH), 1.26 (t, J = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.5 (C=O ketone), 170.0 (C=O ester), 161.4 (OC_{Ar} quat), 152.8 (C=O carbamate), 140.3 (C_{Ar} quat), 135.2 (C_{Ar} quat), 132.9 (C_{Ar}), 132.4 (C_{Ar}), 131.3 (C_{Ar} quat), 129.44 (C_{Ar}), 129.37 (C_{Ar}), 128.7 (C_{Ar}), 127.9 (C_{Ar}), 125.0 (C_{Ar} quat), 121.5 (C_{Ar}), 82.8 (OC quat), 73.5 (OCH_2Ar), 62.6 (O*C*H$_2$CH$_3$), 37.2 (NCH_2), 28.7 (NCH_2CH_2), 14.0 (OCH_2CH_3); HRMS (FTMS + pNSI) *m/z* Calculated for $C_{21}H_{20}NO_6^+$ $[M+H]^+$ 382.1285; Found 382.1288.

SMILES: O=C1NCC[C@@](C2=CC(C(C(C=CC=C3)=C3CO4)=O)=C4C=C2)(C(OCC)=O)O1
InChI = 1S/C21H19NO6/c1-2-26-19(24)21(9-10-22-20(25)28-21)14-7-8-17-16(11-14)18(23)15-6-4-3-5-13(15)12-27-17/h3-8,11H,2,9-10,12H2,1H3,(H,22,25)

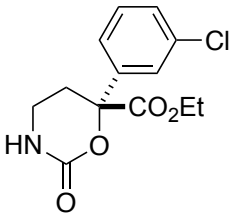
(±)–Ethyl 6-(2-fluorophenyl)-2-oxo-1,3-oxazinane-6-carboxylate (4i)



Trifluoroacetic acid (77 μL, 1.0 mmol) was added to a stirred solution of 1-(*tert*-butyl) 2-ethyl 2-(4-fluorophenyl)azetidine-1,2-dicarboxylate **3i** (65 mg, 0.20 mmol) in toluene (0.20 mL) at 25 °C and stirred for 30 min. The reaction mixture was concentrated and purified by flash chromatography (2% MeOH/CH_2Cl_2) to afford ethyl 6-(2-fluorophenyl)-2-oxo-1,3-oxazinane-6-carboxylate **4i** (4 mg, 15%) as a colorless solid. R_f 0.22 (70% EtOAc/pentane); mp = 170–172 °C; ν_{max} (film)/cm^{-1} 3242 (br s, NH), 3125, 2948, 1748 (C=O ester), 1699 (C=O carbamate), 1491, 1408, 1320, 1276, 1249, 1202, 1147, 1120, 1102, 1079, 1017, 758, 689; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.55 (m, 1 H, HC_{Ar}), 7.41–7.33 (m, 1 H, HC_{Ar}), 7.21 (td, *J* = 7.6, 0.8 Hz, 1 H, HC_{Ar}), 7.08 (m, 1 H, HC_{Ar}), 6.43 (br s, 1 H, NH), 4.31–4.18 (m, 2 H, OCH_2CH_3), 3.46–3.37 (m, 1 H, NC*H*H), 3.24–3.14 (m, 1 H, NCH*H*), 2.82–2.72 (dt, *J* = 13.9, 5.8 Hz, 1 H, NCH_2CHH), 2.50 (ddd, *J* = 13.6, 7.7, 5.2 Hz, 1 H, NCH_2CHH), 1.23 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5 (C=O ester), 159.3 (d, $J_{C–F}$ = 248.6 Hz, FC_{Ar} quat), 152.6 (C=O carbamate), 130.7 (d, $J_{C–F}$ = 8.6 Hz, C_{Ar}), 127.6 (d, $J_{C–F}$ = 2.8 Hz, C_{Ar}), 125.4 (d, $J_{C–F}$ = 11.9 Hz, C_{Ar} quat), 124.4 (d, $J_{C–F}$ = 3.0 Hz, C_{Ar}), 116.3 (d, $J_{C–F}$ = 22.5, C_{Ar}), 81.9 (OC quat), 62.5 (OCH_2CH_3), 36.9 (NCH_2), 27.4 (d, $J_{C–F}$ = 4.7 Hz, NCH_2CH_2), 13.8 (OCH_2CH_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ –112.9 (m); HRMS (ESI$^+$) *m/z* Calculated for $C_{13}H_{15}NO_4F$ [M+H] 268.0985; Found 268.0983.

SMILES: O=C1NCC[C@@](C2=CC=CC=C2F)(C(OCC)=O)O1
InChI = 1S/C13H14FNO4/c1-2-18-11(16)13(7-8-15-12(17)19-13)9-5-3-4-6-10(9)14/h3-6H,2,7-8H2,1H3,(H,15,17)

(±)–Ethyl 6-(3-chlorophenyl)-2-oxo-1,3-oxazinane-6-carboxylate (4j)



*From 1-(tert-butyl) 2-ethyl 2-(3-chlorophenyl)azetidine-1,2-dicarboxylate **3j***

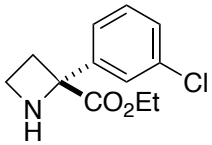
Trifluoroacetic acid (38 μL, 0.50 mmol) was added to a stirred solution of 1-(*tert*-butyl) 2-ethyl 2-(3-chlorophenyl)azetidine-1,2-dicarboxylate **3j** (34 mg, 0.10 mmol) in toluene (0.10 mL) at 25 °C and stirred for 2 h. 1 M aq. HCl (20 mL) was added and the aqueous reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (2% MeOH/CH_2Cl_2) afforded ethyl 6-(3-chlorophenyl)-2-oxo-1,3-oxazinane-6-carboxylate **4j** (2 mg, 6%).

*From 1-benzyl 2-ethyl 2-(3-chlorophenyl)azetidine-1,2-dicarboxylate **9j**:*

TfOH (88 μL, 1.0 mmol) was added to a stirred solution of 1-benzyl 2-ethyl 2-(3-chlorophenyl)azetidine-1,2-dicarboxylate **9j** (37 mg, 0.10 mmol) in toluene (0.50 mL) at 25 °C and stirred for 1 h. Sat. aq. $NaHCO_3$ (20 mL) was slowly added and the aqueous reaction mixture was extracted with EtOAc (5 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (80% EtOAc/pentane) afforded ethyl 6-(3-chlorophenyl)-2-oxo-1,3-oxazinane-6-carboxylate **4j** (17 mg, 61%) as a colorless solid. R_f 0.33 (80% EtOAc/pentane); mp = 151–155 °C; ν_{max} (film)/cm^{-1} 3248 (NH), 3139, 2919, 1728 (C=O ester), 1711 (C=O carbamate), 1492, 1477, 1404, 1327, 1274, 1250, 1226, 1120, 1106, 1078, 1027, 1013, 774, 714; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.61 (m, 1 H, HC_{Ar}), 7.52–7.47 (m, 1 H, HC_{Ar}), 7.37–7.34 (m, 2 H, 2 × HC_{Ar}), 5.75 (br s, 1 H, NH), 4.30–4.21 (m, 2 H, OCH_2CH_3), 3.43–3.29 (m, 2 H, NCH_2), 2.76 (dt, *J* = 13.9, 4.7 Hz, 1 H, NCH_2CHH), 2.29 (ddd, *J* = 13.9, 9.6, 6.0 Hz, 1 H, NCH_2CHH), 1.26 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4 (C=O ester), 152.6 (C=O carbamate), 139.4 (C_{Ar} quat), 134.8 (ClC_{Ar} quat), 130.0 (C_{Ar}), 129.0 (C_{Ar}), 125.4 (C_{Ar}), 123.2 (C_{Ar}), 82.7 (OC quat), 62.8 (OCH_2CH_3), 37.1 (NCH_2), 29.3 (NCH_2CH_2), 13.9 (OCH_2CH_3); HRMS (ESI$^+$) *m/z* Calculated for $C_{13}H_{15}NO_4{}^{35}Cl$ [M+H] 284.0690; Found 284.0703.

SMILES: O=C1NCC[C@@](C2=CC(Cl)=CC=C2)(C(OCC)=O)O1
InChI = 1S/C13H14ClNO4/c1-2-18-11(16)13(6-7-15-12(17)19-13)9-4-3-5-10(14)8-9/h3-5,8H,2,6-7H2,1H3,(H,15,17)

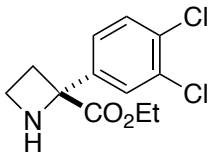
(±)–Ethyl 2-(3-chlorophenyl)azetidine-2-carboxylate (5j)



Trifluoroacetic acid (38 μL, 0.50 mmol) was added to a stirred solution of 1-(*tert*-butyl) 2-ethyl 2-(3-chlorophenyl)azetidine-1,2-dicarboxylate **3j** (34 mg, 0.10 mmol) in toluene (0.10 mL) at 25 ºC and stirred for 2 h. 1 M aq. HCl (20 mL) was added and the aqueous reaction mixture was extracted with EtOAc (3 × 20 mL). The aqueous layer was basified with 1 M NaOH (50 mL) and extracted with EtOAc (6 × 20 mL). The combined organic layers from the second extraction were concentrated to afford ethyl 2-(3-chlorophenyl)azetidine-2-carboxylate **5j** (11 mg, 46%) as a yellow oil. R_f 0.40 (0.05:4.95:95 NH_3:MeOH:CH_2Cl_2); ν_{max} (film)/cm^{-1} 3337 (w, NH), 2979, 1727 (C=O ester), 1596, 1573, 1475, 1247, 1108, 787, 710; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.41 (m, 1 H, HC_{Ar}), 7.30–7.21 (m, 3 H, 3 × HC_{Ar}), 4.28–4.14 (m, 2 H, OC*H*$_2$CH$_3$), 3.74–3.65 (m, 1 H, NC*H*H), 3.33 (ddd, *J* = 12.1, 8.5, 3.7 Hz, 1 H, NCH*H*), 2.89 (ddd, *J* = 11.2, 8.5, 3.7 Hz, 1 H, NCH_2C*H*H), 2.77 (dt, *J* = 11.2, 8.6 Hz, 1 H, NCH_2CH*H*), 1.25 (t, *J* = 7.1 Hz, 3 H, OCH_2C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.2 (C=O), 145.2 (C_{Ar} quat), 134.2 (ClC_{Ar} quat), 129.4 (C_{Ar}), 127.3 (C_{Ar}), 125.7 (C_{Ar}), 123.4 (C_{Ar}), 69.0 (NC quat), 61.9 (O*C*H$_2$CH$_3$), 41.9 (NCH_2), 32.6 (NCH_2*C*H$_2$), 14.0 (OCH_2*C*H$_3$); HRMS (ESI$^+$) *m/z* Calculated for $C_{12}H_{15}NO_2{}^{35}Cl$ [M+H] 240.0791; Found 240.0794.

SMILES: ClC1=CC=CC([C@]2(C(OCC)=O)NCC2)=C1
InChI = 1S/C12H14ClNO2/c1-2-16-11(15)12(6-7-14-12)9-4-3-5-10(13)8-9/h3-5,8,14H,2,6-7H2,1H3

(±)–Ethyl 2-(3,4-dichlorophenyl)azetidine-2-carboxylate (5k)



Trifluoroacetic acid (38 μL, 0.50 mmol) was added to a stirred solution of 1-(*tert*-butyl) 2-ethyl 2-(3,4-dichloromophenyl)azetidine-1,2-dicarboxylate **3k** (37 mg, 0.10 mmol) in toluene (0.10 mL) at 25 ºC and stirred for 30 min. The reaction mixture was concentrated and purified by SCX column† to afford ethyl 2-(3,4-dichlorophenyl)azetidine-2-carboxylate **5k** (12 mg, 44%) as a yellow oil. R_f 0.50 (0.05:4.95:95% NH_3:MeOH:CH_2Cl_2); ν_{max} (film)/cm^{-1} 3324 (w, NH), 2979, 2875, 1727 (C=O ester), 1465, 1247, 1221, 1106, 1030; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 2.1 Hz, 1 H, HC_{Ar}), 7.40 (d, *J* = 8.4 Hz, 1 H, HC_{Ar}), 7.25 (dd, *J* = 8.4, 2.1 Hz, 1 H, HC_{Ar}), 4.29–4.15 (m, 2 H, OC*H*$_2$CH$_3$), 3.74–3.66 (m, 1 H, NC*H*H), 3.32 (ddd, *J* = 8.6, 7.4, 3.7 Hz, 1 H, NCH*H*), 2.88 (ddd, *J* = 11.2, 8.6, 3.7 Hz, 1 H, NCH_2C*H*H), 2.73 (dt, *J* = 11.2, 8.6 Hz, 1 H, NCH_2CH*H*), 1.25 (t, *J* = 7.1 Hz, 3 H, OCH_2C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9 (C=O ester), 143.5 (C_{Ar} quat), 132.3 (ClC_{Ar} quat), 131.3 (ClC_{Ar} quat), 130.1 (C_{Ar}), 127.6 (C_{Ar}), 124.8 (C_{Ar}), 68.6 (NC quat), 62.1 (O*C*H$_2$CH$_3$), 41.8 (NCH_2), 32.8 (NCH_2*C*H$_2$), 14.1 (OCH_2*C*H$_3$); HRMS (ESI$^+$) *m/z* Calculated for $C_{12}H_{14}NO^{35}Cl_2$ [M+H] 274.0402; Found 274.0400.

SMILES: ClC(C=C1)=C(Cl)C=C1[C@]2(C(OCC)=O)NCC2
InChI = 1S/C12H13Cl2NO2/c1-2-17-11(16)12(5-6-15-12)8-3-4-9(13)10(14)7-8/h3-4,7,15H,2,5-6H2,1H3

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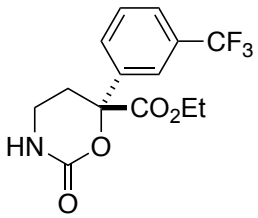
† *Strong Cation Exchange (SCX) Column Procedure*
SCX cartridges (purchased from ThermoScientific) were selected with an appropriate capacity of stationary phase (5% w/v of crude product). The column was washed with three column volumes of methanol. The sample was then loaded onto the column in a minimum amount of solvent (1:1 MeOH/CH_2Cl_2). The column was washed through with three column volumes of MeOH and then with three column volumes of 5% NH_3 (28% aqueous solution)/MeOH to yield the free amine which was concentrated under reduced pressure.

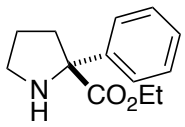
(±)–Ethyl 2-oxo-6-(3-(trifluoromethyl)phenyl)-1,3-oxazinane-6-carboxylate (4l)



TfOH (0.18 mL, 2.0 mmol) was added to a stirred solution of 1-benzyl 2-ethyl 2-(3-(trifluoromethyl)phenyl)azetidine-1,2-dicarboxylate **3l** (82 mg, 0.20 mmol) in toluene (1.0 mL) at 25 °C and stirred for 1 h. Sat. aq. $NaHCO_3$ (20 mL) was slowly added and the aqueous reaction mixture was extracted with EtOAc (5 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (EtOAc) afforded ethyl 2-oxo-6-(3-(trifluoromethyl)phenyl)-1,3-oxazinane-6-carboxylate **4l** (17 mg, 27%) as a colorless solid. R_f 0.30 (EtOAc); mp = 115–117 °C; ν_{max} (film)/cm^{-1} 3250 (NH), 3138, 1744 (C=O ester), 1715 (C=O carbamate), 1327, 1267, 1238, 1167, 1115, 1070; ^{1}H NMR (400 MHz, CD_3OD) δ 7.96–7.90 (m, 2 H, 2 × HC_{Ar}), 7.77–7.73 (m, 1 H, HC_{Ar}), 7.71–7.61 (m, 1 H, HC_{Ar}), 4.33–4.21 (m, 2 H, OCH_2CH_3), 3.40–3.29 (m, 2 H, NCH_2 obscured by residual CH_3OH), 2.95–2.88 (m, 1 H, NCH_2CHH), 2.37 (ddd, *J* = 14.0, 9.6, 6.7 Hz, 1 H, NCH_2CHH), 1.25 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90–7.88 (m, 1 H, HC_{Ar}), 7.85–7.82 (m, 1 H, HC_{Ar}), 7.67–7.64 (m, 1 H, HC_{Ar}), 7.58–7.53 (m, 1 H, HC_{Ar}), 5.23 (br s, 1 H, NH), 4.32–4.20 (m, 2 H, OCH_2CH_3), 3.47–3.34 (m, 2 H, NCH_2), 2.87–2.80 (m, 1 H, NCH_2CHH), 2.31 (ddd, *J* = 13.9, 10.0, 6.1 Hz, 1 H, NCH_2CHH), 1.26 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (101 MHz, CD_3OD) δ 170.7 (C=O ester), 154.9 (C=O carbamate), 140.6 (C_{Ar} quat), 132.1 (q, J_{C-F} = 32.8 Hz, C_{Ar}), 130.8 (C_{Ar}), 130.2 (C_{Ar}), 126.7 (q, *J* = 4.0 Hz, C_{Ar}), 125.4 (q, J_{C-F} = 271.6 Hz, CF_3), 123.1 (q, J_{C-F} = 4.0 Hz, C_{Ar}), 84.3 (OC quat), 63.9 (OCH_2CH_3), 37.8 (NCH_2), 29.9 (NCH_2CH_2), 14.2 (OCH_2CH_3); ^{19}F{^{1}H} NMR (377 MHz, CD_3OD) δ –64.2; HRMS (FTMS + pNSI) *m/z* Calculated for $C_{14}H_{15}NO_4F_3^+$ $[M+H]^+$ 318.0948; Found 318.0950.

SMILES: O=C1NCC[C@@](C2=CC(C(F)(F)F)=CC=C2)(C(OCC)=O)O1
InChI = 1S/C14H14F3NO4/c1-2-21-11(19)13(6-7-18-12(20)22-13)9-4-3-5-10(8-9)14(15,16)17/h3-5,8H,2,6-7H2,1H3,(H,18,20)

(±)–Ethyl 2-phenylpyrrolidine-2-carboxylate (11)

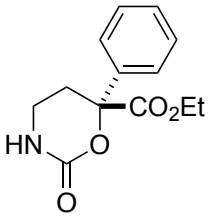


TfOH (44 μL, 0.5 mmol) was added to a stirred solution of 1-benzyl 2-ethyl 2-phenylazetidine-1,2-dicarboxylate **10**[1] (18 mg, 0.05 mmol) in toluene (0.25 mL) at 25 °C and stirred for 1 h. Sat. aq. $NaHCO_3$ (20 mL) was slowly added and the aqueous reaction mixture was extracted with EtOAc (5 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (30% EtOAc/pentane) afforded ethyl 2-phenylpyrrolidine-2-carboxylate **11** (8 mg, 62%) as a colourless oil. R_f 0.27 (40% EtOAc/pentane); ν_{max} (film)/cm^{-1} 3349 (NH), 2980, 2873, 1721 (C=O), 1447, 1242, 1180, 1096, 1025, 729, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.51 (m, 2 H, 2 × HC_{Ph}), 7.35–7.29 (m, 2 H, 2 × HC_{Ph}), 7.28–7.23 (m, 1 H, HC_{Ph}), 4.20–4.09 (m, 2 H, OCH_2CH_3), 3.14–3.05 (m, 2 H, NCH_2), 2.76 (ddd, *J* = 12.7, 8.1, 4.8 Hz, 1 H, $N(CH_2)_2CHH$), 2.07 (dt, *J* = 12.6, 8.5 Hz, 1 H, $N(CH_2)_2CHH$), 1.94–1.75 (m, 2 H, NCH_2CH_2), 1.21 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6 (C=O), 142.9 (C_{Ph} quat), 128.1 (2 × C_{Ph}), 127.1 (C_{Ph}), 126.1 (2 × C_{Ph}), 72.3 (NC quat), 61.5 (OCH_2CH_3), 45.7 (NCH_2), 36.7 ($N(CH_2)_2CH_2$), 24.6 (NCH_2CH_2), 14.1 (OCH_2CH_3); HRMS (ESI^+) *m/z* Calculated for $C_{13}H_{18}NO_2$ $[M+H]$ 220.1338; Found 220.1347.

SMILES: O=C([C@@]1(C2=CC=CC=C2)NCCC1)OCC
InChI = 1S/C13H17NO2/c1-2-16-12(15)13(9-6-10-14-13)11-7-4-3-5-8-11/h3-5,7-8,14H,2,6,9-10H2,1H3

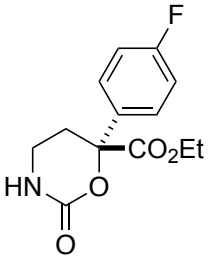
Synthesis of Oxazinanones 4a,g,i,k,n–p by NICE Reaction

(±)–Ethyl 2-oxo-6-phenyl-1,3-oxazinane-6-carboxylate (4a)



$Rh_2(esp)_2$ (1.9 mg, 2.5 μmol) was added to a solution of *tert*-butyl (2-chloroethyl)carbamate **5** (90 mg, 0.50 mmol) and ethyl 2-diazo-2-phenylacetate **8a** (143 mg, 0.75 mmol) in benzene (1.67 mL). The reaction vessel was sealed, purged with Ar and heated at 60 ºC for 2.5 h, then allowed to cool to rt. Tetrabutylammonium bromide (16 mg, 50 μmol) was added, followed by $CsOH·H_2O$ (168 mg, 1.00 mmol), and the reaction was stirred at 25 ºC for 18 h. TFA (0.38 mL, 5.0 mmol) was added and the reaction mixture was stirred for 1 h. Sat. aq. $NaHCO_3$ (40 mL) was slowly added, then the aqueous reaction mixture was extracted with EtOAc (5 × 40 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (2% MeOH/CH_2Cl_2) afforded ethyl 2-oxo-6-phenyl-1,3-oxazinane-6-carboxylate **4a** (48 mg, 38%) as a colorless solid. The observed characterization data was identical to that reported previously for **4a** above (pg S9).

(±)–Ethyl 6-(4-fluorophenyl)-2-oxo-1,3-oxazinane-6-carboxylate (4g)



One-pot procedure

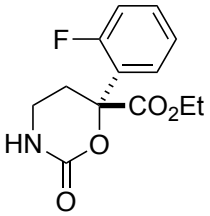
$Rh_2(esp)_2$ (1.9 mg, 2.5 μmol) was added to a solution of *tert*-butyl (2-chloroethyl)carbamate **5** (90 mg, 0.50 mmol) and ethyl 2-diazo-2-(4-fluorophenyl)acetate **8g** (156 mg, 0.75 mmol) in benzene (1.67 mL). The reaction vessel was sealed, purged with Ar and heated at 60 ºC for 2.5 h, then allowed to cool to rt. Tetrabutylammonium bromide (16 mg, 50 μmol) was added, followed by $CsOH·H_2O$ (168 mg, 1.00 mmol), and the reaction was stirred at 25 ºC for 18 h. TFA (0.38 mL, 5.0 mmol) was added and the reaction mixture was stirred for 1 h. Sat. aq. $NaHCO_3$ (40 mL) was slowly added, then the aqueous reaction mixture was extracted with EtOAc (5 × 40 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (2% MeOH/ CH_2Cl_2) afforded ethyl 6-(4-fluorophenyl)-2-oxo-1,3-oxazinane-6-carboxylate **4g** (60 mg, 45%) as a colorless solid. The observed characterization data was identical to that reported previously for **4g** above (pg S12).

Telescoped procedure

$Rh_2(esp)_2$ (1.9 mg, 2.5 μmol) was added to a solution of *tert*-butyl (2-chloroethyl)carbamate **5** (90 mg, 0.50 mmol) and ethyl 2-diazo-2-(4-fluorophenyl)acetate **8g** (156 mg, 0.75 mmol) in benzene (1.67 mL). The reaction vessel was sealed, purged with Ar and heated at 60 ºC for 2.5 h, then allowed to cool to rt. Tetrabutylammonium bromide (16 mg, 50 μmol) was added, followed by $CsOH·H_2O$ (168 mg, 1.00 mmol), and the reaction was stirred at 25 ºC for 18 h. The crude reaction mixture was then filtered through silica, eluting with CH_2Cl_2 (10 mL), and concentrated under reduced pressure. The crude reaction mixture was transferred to a dry reaction flask and concentrated under reduced pressure. TFA (0.19 mL, 2.5 mmol) was added to the crude reaction mixture in toluene (0.50 mL) and stirred at 25 ºC for 0.5 h. The crude reaction mixture was concentrated. Purification by flash chromatography (2% MeOH/CH_2Cl_2) afforded ethyl 6-(4-fluorophenyl)-2-oxo-1,3-oxazinane-6-carboxylate **4g** (57 mg, 43%) as a colorless solid. The observed characterization data was identical to that reported previously for **4g** above (pg S12).

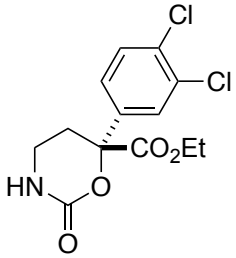
Telescoped procedure on 3.0 mmol scale afforded ethyl 6-(4-fluorophenyl)-2-oxo-1,3-oxazinane-6-carboxylate **4g** (289 mg, 36%).

(±)–Ethyl 6-(2-fluorophenyl)-2-oxo-1,3-oxazinane-6-carboxylate (4i)



$Rh_2(esp)_2$ (1.9 mg, 2.5 μmol) was added to a solution of benzyl (2-chloroethyl)carbamate **6** (90 mg, 0.50 mmol) and ethyl 2-diazo-2-(2-fluorophenyl)acetate **8i** (156 mg, 0.75 mmol) in benzene (1.67 mL). The reaction vessel was sealed, purged with Ar and heated at 60 ºC for 2.5 h, then allowed to cool to rt. Tetrabutylammonium bromide (16 mg, 50 μmol) was added, followed by $CsOH{\cdot}H_2O$ (168 mg, 1.00 mmol), and the reaction was stirred at 25 ºC for 18 h. TfOH (0.44 mL, 5.0 mmol) was added and the reaction mixture was stirred for a further 1.5 h. Sat. aq. $NaHCO_3$ (40 mL) was slowly added and the aqueous reaction mixture was extracted with EtOAc (5 × 40 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (70% EtOAc/pentane) afforded ethyl 6-(2-fluorophenyl)-2-oxo-1,3-oxazinane-6-carboxylate **4i** (26 mg, 19%) as a colorless solid. The observed characterization data was identical to that reported previously for **4i** above (pg S13).

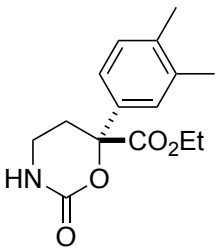
(±)–Ethyl 6-(3,4-dichlorophenyl)-2-oxo-1,3-oxazinane-6-carboxylate (4k)



Ethyl 2-diazo-2-(3,4-dichlorophenyl)acetate **8k** (324 mg, 1.25 mmol) in benzene (1.0 mL) was added slowly *via* syringe pump over 1 h to a solution of benzyl (2-chloroethyl)carbamate **6** (107 mg, 0.50 mmol) and $Rh_2(esp)_2$ (1.9 mg, 2.5 μmol) in benzene (0.67 mL) at 60 ºC. The reaction mixture was stirred at 60 °C for a further 2.5 h, then allowed to cool to rt. Tetrabutylammonium bromide (16 mg, 50 μmol) was added, followed by $CsOH{\cdot}H_2O$ (168 mg, 1.50 mmol), and the reaction was stirred at 25 ºC for 18 h. TfOH (0.45 mL, 5.0 mmol) was added dropwise and the reaction mixture was stirred for 30 min. Sat. aq. $NaHCO_3$ (40 mL) was slowly added and the aqueous reaction mixture was extracted with EtOAc (5 × 40 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (EtOAc) afforded ethyl 6-(3,4-dichlorophenyl)-2-oxo-1,3-oxazinane-6-carboxylate **4k** (78 mg, 45%) as a pale yellow solid. R_f 0.19 (EtOAc); mp = 86–90 ºC; ν_{max} (film)/cm^{-1} 3343 (NH), 2985, 1707 (br s, 2 × C=O), 1256, 1170, 1010, 1033; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75–7.71 (m, 2 H, 2 × HC_{Ar}), 7.58 (br s, 1 H, NH), 7.51 (dd, J = 8.6, 2.3 Hz, 1 H, HC_{Ar}), 4.22–4.12 (m, 2 H, OCH_2CH_3), 3.18–3.05 (m, 2 H, NCH_2), 2.68 (dt, J = 13.8, 4.7 Hz, 1 H, NCH_2CHH), 2.32 (ddd, J = 14.0, 9.2, 6.2 Hz, 1 H, NCH_2CHH), 1.14 (t, J = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.1 (C=O ester), 150.7 (C=O carbamate), 138.9 (C_{Ar} quat), 131.6 (ClC_{Ar} quat), 131.5 (ClC_{Ar} quat), 131.0 (C_{Ar}), 127.3 (C_{Ar}), 125.7 (C_{Ar}), 81.7 (OC quat), 62.3 (OCH_2CH_3), 36.1 (NCH_2), 28.0 (NCH_2CH_2), 13.8 (OCH_2CH_3); HRMS (FTMS + pNSI) *m/z* Calculated for $C_{13}H_{14}NO_4{}^{35}Cl_2^+$ $[M+H]^+$ 318.0294; Found 318.0299.

SMILES: O=C1NCC[C@@](C2=CC(Cl)=C(Cl)C=C2)(C(OCC)=O)O1
InChI = 1S/C13H13Cl2NO4/c1-2-19-11(17)13(5-6-16-12(18)20-13)8-3-4-9(14)10(15)7-8/h3-4,7H,2,5-6H2,1H3,(H,16,18)

(±)–Ethyl 6-(3,4-dimethylphenyl)-2-oxo-1,3-oxazinane-6-carboxylate (4n)

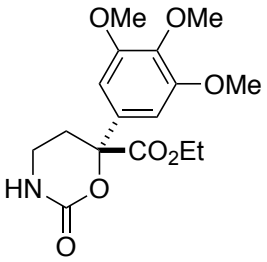


$Rh_2(esp)_2$ (1.9 mg, 2.5 μmol) was added to a solution of *tert*-butyl (2-chloroethyl)carbamate **5** (90 mg, 0.50 mmol) and ethyl 2-diazo-2-(3,4-dimethylphenyl)acetate **8n** (164 mg, 0.75 mmol) in benzene (1.67 mL). The reaction vessel was sealed, purged with Ar and heated at 60 ºC for 2.5 h, then allowed to cool to rt. Tetrabutylammonium bromide (16 mg, 50 μmol) was added, followed by $CsOH{\cdot}H_2O$ (168 mg, 1.00 mmol), and the reaction was stirred at 25 ºC for 18 h. The crude reaction mixture was then filtered through silica, eluting with CH_2Cl_2 (10 mL), and concentrated under reduced pressure. The crude reaction mixture was transferred to a dry reaction flask and concentrated. TFA (0.19 mL, 2.5 mmol) was added to the crude reaction mixture in toluene (0.50 mL) and stirred at 25 ºC for 0.5 h. The crude reaction mixture was concentrated. Purification by flash chromatography (80% EtOAc/hexane) afforded ethyl 6-(3,4-

dimethylphenyl)-2-oxo-1,3-oxazinane-6-carboxylate **4n** (83 mg, 60%) as a colorless solid. R_f 0.31 (EtOAc); mp = 167–169 °C; ν_{max} (film)/cm^{-1} 3236 (NH), 3140, 2916, 1745 (C=O ester), 1713 (C=O carbamate), 1489, 1411, 1327, 1256, 1193, 1121, 1095, 1015, 777; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 1.5 Hz, 1 H, HC_{Ar}), 7.30–7.26 (m, 1 H, HC_{Ar}), 7.15 (d, J = 8.0 Hz, 1 H, HC_{Ar}), 6.25 (br s, 1 H, NH), 4.28–4.16 (m, 2 H, OCH_2CH_3), 3.40–3.26 (m, 2 H, NCH_2), 2.72 (dt, J = 13.8, 5.0 Hz, 1 H, NCH_2CHH), 2.37–2.23 (m, 7 H, NCH_2CH*H* and 2 × $ArCH_3$), 1.24 (t, J = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1 (C=O ester), 153.1 (C=O carbamate), 137.3 (CH_3C_{Ar} quat), 137.1 (CH_3C_{Ar} quat), 134.8 (C_{Ar} quat), 129.9 (C_{Ar}), 126.0 (C_{Ar}), 122.3 (C_{Ar}), 83.2 (OC quat), 62.4 (OCH_2CH_3), 37.2 (NCH_2), 29.1 (NCH_2CH_2), 19.9 ($ArCH_3$), 19.4 ($ArCH_3$), 14.0 (OCH_2CH_3); HRMS (ESI$^+$) *m/z* Calculated for $C_{15}H_{20}NO_4$ [M+H] 278.1392; Found 278.1404.

SMILES: O=C1NCC[C@@](C2=CC(C)=C(C)C=C2)(C(OCC)=O)O1
InChI = 1S/C15H19NO4/c1-4-19-13(17)15(7-8-16-14(18)20-15)12-6-5-10(2)11(3)9-12/h5-6,9H,4,7-8H2,1-3H3,(H,16,18)

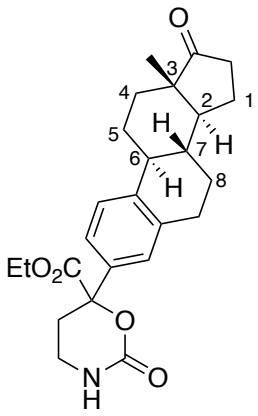
(±)–Ethyl 2-oxo-6-(3,4,5-trimethoxyphenyl)-1,3-oxazinane-6-carboxylate (4o)



$Rh_2(esp)_2$ (1.9 mg, 2.5 μmol) was added to a solution of *tert*-butyl (2-chloroethyl)carbamate **5** (90 mg, 0.50 mmol) and ethyl 2-diazo-2-(3,4,5-trimethoxyphenyl)acetate **8o** (215 mg, 0.75 mmol) in benzene (1.67 mL). The reaction vessel was sealed, purged with Ar and heated at 60 °C for 2.5 h, then allowed to cool to rt. Tetrabutylammonium bromide (16 mg, 50 μmol) was added, followed by $CsOH·H_2O$ (168 mg, 1.00 mmol), and the reaction was stirred at 25 °C for 18 h. The crude reaction mixture was then filtered through silica, eluting with EtOAc (10 mL), and concentrated under reduced pressure. The crude reaction mixture was transferred to a dry reaction flask and concentrated. TFA (0.19 mL, 2.5 mmol) was added to the crude reaction mixture in toluene (0.50 mL) and stirred at 25 °C for 0.5 h. The crude reaction mixture was concentrated. Purification by flash chromatography (EtOAc) afforded ethyl 2-oxo-6-(3,4,5-trimethoxyphenyl)-1,3-oxazinane-6-carboxylate **4o** (98 mg, 58%) as a pale yellow solid. R_f 0.23 (EtOAc); mp = 159–163 °C; ν_{max} (film)/cm^{-1} 3275 (br s, NH), 2940, 1718 (br s, C=O ester/ carbamate), 1591, 1491, 1456, 1416, 1329, 1246, 1125, 1097, 1007; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (s, 2 H, 2 × HC_{Ar}), 6.23 (br s, 1 H, NH), 4.31–4.18 (m, 2 H, OCH_2CH_3), 3.87 (s, 6 H, 2 × OCH_3), 3.85 (s, 3 H, OCH_3), 3.41–3.29 (m, 2 H, NCH_2), 2.74 (dt, J = 13.9, 4.8 Hz, 1 H, NCH_2CHH), 2.29 (ddd, J = 13.9, 9.0, 6.5 Hz, 1 H, NCH_2CH*H*), 1.26 (t, 3 H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8 (C=O ester), 153.3 (2 × OC_{Ar} quat), 152.9 (C=O carbamate), 138.3 (OC_{Ar} quat), 132.9 (C_{Ar} quat), 102.2 (2 × C_{Ar}), 83.1 (OC quat), 62.6 (OCH_2CH_3), 60.8 (OCH_3), 56.3 (2 × OCH_3), 37.2 (NCH_2), 29.5 (NCH_2CH_2), 14.0 (OCH_2CH_3); HRMS (ESI$^+$) *m/z* Calculated for $C_{16}H_{22}NO_7$ [M+H] 340.1396; Found 340.1388.

SMILES: O=C1NCC[C@@](C2=CC(OC)=C(OC)C(OC)=C2)(C(OCC)=O)O1
InChI = 1S/C16H21NO7/c1-5-23-14(18)16(6-7-17-15(19)24-16)10-8-11(20-2)13(22-4)12(9-10)21-3/h8-9H,5-7H2,1-4H3,(H,17,19)

Ethyl 6-((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)-2-oxo-1,3-oxazinane-6-carboxylate (4p) (mixture of diastereomers)



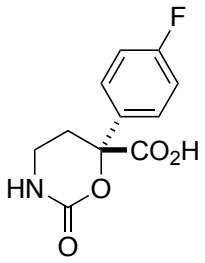
$Rh_2(esp)_2$ (0.8 mg, 1.0 μmol) was added to a solution of *tert*-butyl (2-chloroethyl)carbamate **5** (36 mg, 0.20 mmol) and diazo **8p**[1,6] (110 mg, 0.30 mmol) in benzene (0.67 mL). The reaction vessel was sealed, purged with Ar and heated at 60 ºC for 2.5 h, then allowed to cool to rt. Tetrabutylammonium bromide (6.4 mg, 20 μmol) was added, followed by $CsOH·H_2O$ (67 mg, 0.40 mmol), and the reaction was stirred at 25 ºC for 18 h. The crude reaction mixture was then filtered through silica, eluting with EtOAc (10 mL), and concentrated under reduced pressure. The crude reaction mixture was transferred to a dry reaction flask and concentrated. TFA (0.08 mL, 1.0 mmol) was added to the crude reaction mixture in toluene (0.20 mL) and stirred at 25 ºC for 0.5 h. The crude reaction mixture was concentrated. Purification by flash chromatography (80% EtOAc/hexane) afforded ethyl 6-((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)-2-oxo-1,3-oxazinane-6-carboxylate **4p** (11 mg, 13%) as a colorless solid (the product is assumed to be a 1:1 mixture of diastereomers). R_f 0.13 (70% EtOAc/hexane); mp = 95–97 ºC; ν_{max} (film)/cm^{-1} 3268 (w br, NH), 2929, 1733 (2 × C=O), 1491, 1454, 1407, 1319, 1203, 1096, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.29 (m, 3 H, 3 × HC_{Ar}), 5.96 (s, 1 H, NH), 4.29–4.16 (m, 2 H, OCH_2CH_3), 3.41–3.27 (m, 2 H, NCH_2), 2.97–2.90 (m, 2 H, $ArCH_2$), 2.78–2.69 (m, 1 H, NCH_2CHH), 2.52 (dd, *J* = 19.1, 9.0 Hz, 1 H, ArCH), 2.47–2.37 (m, 1 H, C*H*HCO), 2.36–2.26 (m, 1 H, CH*H*CO), 2.22–1.93 (m, 5 H, 4 × C*H*H and NCH_2CHH), 1.72–1.40 (m, 6 H, 4 × CH*H* and 2 × CH), 1.26 (td, *J* = 7.1, 1.6 Hz, 3 H, OCH_2CH_3), 0.91 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.7 (C=O ketone), 170.0 (C=O ester), 152.9 (C=O carbamate), 140.4 (C_{Ar} quat), 137.0 (C_{Ar} quat), 134.8 (C_{Ar} quat), 125.7 (C_{Ar}), 125.53 and 125.47 (C_{Ar}), 122.26 and 122.23 (C_{Ar}), 83.2 (OC quat), 62.5 (OCH_2CH_3), 50.5 (C_2), 47.9 (C_3 quat), 44.3 (C_6), 37.9 (C_7), 37.3 (NCH_2), 35.8 (CH_2CO), 31.5 (C_4), 29.5, 29.4, 29.3 and 29.2 (CH_2Ar and NCH_2CH_2), 26.4 (C_8), 25.6 (C_5), 21.6 (C_1), 14.0 (OCH_2CH_3), 13.8 (CH_3); HRMS (ESI$^+$) *m/z* Calculated for $C_{25}H_{32}NO_5$ [M+H] 426.2280; Found 426.2282.

SMILES: O=C1CC[C@@]2([H])[C@]3([H])CCC4=C(C=CC([C@]5(CCNC(O5)=O)C(OCC)=O)=C4)[C@@]3([H])CC[C@]12C

InChI = 1S/C25H31NO5/c1-3-30-22(28)25(12-13-26-23(29)31-25)16-5-7-17-15(14-16)4-6-19-18(17)10-11-24(2)20(19)8-9-21(24)27/h5,7,14,18-20H,3-4,6,8-13H2,1-2H3,(H,26,29)/t18-,19-,20+,24+,25?/m1/s1

Functionalization of 6,6-disubstituted 1,3-oxazinan-2-ones

(±)–6-(4-Fluorophenyl)-2-oxo-1,3-oxazinane-6-carboxylic acid (13)

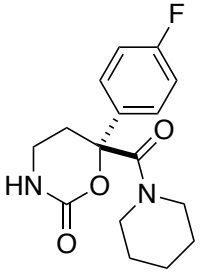


NaOH (2 M aq, 0.2 mL) was added to a solution of ethyl 6-(4-fluorophenyl)-2-oxo-1,3-oxazinane-6-carboxylate **4g** (53.5 mg, 0.2 mmol) in EtOH (1.0 mL). The reaction mixture was heated under reflux for 10 min, then cooled to rt. The solvent was removed under reduced pressure, then 1 M aq. HCl (10 mL) was added and the aqueous mixture was extracted with EtOAc (6 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 6-(4-fluorophenyl)-2-oxo-1,3-oxazinane-6-carboxylic acid **13** (41 mg, 92%) as a colorless solid. R_f 0.38 (EtOAc); mp = 152–153 ºC; ν_{max} (film)/cm^{-1} 3333 (OH), 2919, 2850, 1716 (C=O carbamate), 1661 (br s, C=O carboxylic acid), 1602, 1509, 1459, 1276, 1232, 1224, 1212, 1165, 1118, 1089, 840, 740, 702, 675; ^{1}H NMR (400 MHz, DMSO-*d*^{6}) δ 13.60 (br s, 1 H, CO_2H), 7.60–7.52 (m, 2 H, 2 × HC_{Ar}), 7.42 (br s, 1 H, NH), 7.31–7.23 (m, 2 H, 2 × HC_{Ar}), 3.19–3.07 (m, 2 H, NCH_2), 2.63 (dt, *J* = 13.7, 4.1 Hz, 1 H, NCH_2CHH), 2.29–2.18 (m, 1 H, NCH_2CHH); ^{13}C NMR (101 MHz, DMSO-*d*^{6}) δ 171.2 (C=O carboxylic acid), 160.9 (d, $J_{C–F}$ = 245.1 Hz, FC_{Ar} quat), 151.3 (C=O carbamate), 134.8 (d, $J_{C–F}$ = 2.5 Hz, C_{Ar} quat), 127.5 (d, $J_{C–F}$ = 8.6 Hz, 2 × C_{Ar}), 115.3 (d, $J_{C–F}$ = 21.5 Hz, 2 × C_{Ar}), 81.9 (OC quat), 36.4 (NCH_2), 28.1 (NCH_2CH_2); ^{19}F{^{1}H} NMR (377 MHz, $CDCl_3$) δ –113.8; HRMS (ESI$^-$) *m/z* Calculated for $C_{11}H_9NO_4F$ [M–H] 238.0516; Found 238.0523.

SMILES: O=C1NCC[C@@](C2=CC=C(F)C=C2)(C(O)=O)O1

InChI = 1S/C11H10FNO4/c12-8-3-1-7(2-4-8)11(9(14)15)5-6-13-10(16)17-11/h1-4H,5-6H2,(H,13,16)(H,14,15)

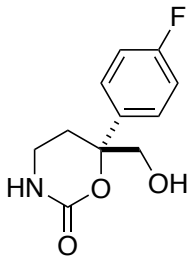
(±)–6-(4-Fluorophenyl)-6-(piperidine-1-carbonyl)-1,3-oxazinan-2-one (14)



DIPEA (0.1 mL) was added to a solution of HATU (80 mg, 0.21 mmol), piperidine (21 μL) and 6-(4-fluorophenyl)-2-oxo-1,3-oxazinane-6-carboxylic acid **13** (42 mg, 0.18 mmol) in DMF (0.72 mL). The reaction mixture was stirred at 40 ºC for 24 h then H_2O (20 mL) was added. EtOAc (20 mL) was added to the aqueous mixture and the layers were separated. Sat. brine (10 mL) was added to aid separation. The aqueous layer was extracted with EtOAc (5 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (2% MeOH/CH_2Cl_2 followed by EtOAc) afforded 6-(4-fluorophenyl)-6-(piperidine-1-carbonyl)-1,3-oxazinan-2-one **14** (39 mg, 64%) as a colorless solid. R_f 0.28 (EtOAc); mp = 177–180 ºC; ν_{max} (film)/cm^{-1} 3279 (br s, NH), 2937, 2859, 1718 (C=O carbamate), 1634 (C=O amide), 1509, 1444, 1318, 1229, 1025, 1086, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.40 (m, 2 H, 2 × HC_{Ar}), 7.13–7.06 (m, 2 H, 2 × HC_{Ar}), 5.69 (br s, 1 H, NH), 3.68–3.57 (m, 2 H, 2 × $NCHH$), 3.52–3.43 (m, 2 H, 2 × NCH_2), 3.37–3.28 (m, 1 H, $NHCHH$), 3.22–3.15 (m, 1 H, $NHCH_2$), 2.78 (dt, *J* = 13.9, 4.4 Hz, 1 H, $NHCH_2CHH$), 1.95 (ddd, *J* = 14.0, 9.7, 6.0 Hz, 1 H, $NHCH_2CHH$), 1.60–1.44 (m, 4 H, 2 × NCH_2CH_2), 1.43–1.33 (m, 1 H, $N(CH_2)_2CHH$), 0.98–0.85 (m, 1 H, $N(CH_2)CHH$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6 (C=O amide), 162.4 (d, $J_{C–F}$ = 247.7 Hz, FC_{Ar} quat), 152.8 (C=O carbamate), 135.6 (d, $J_{C–F}$ = 3.0 Hz, C_{Ar} quat), 125.8 (d, $J_{C–F}$ = 8.3 Hz, 2 × C_{Ar}), 115.9 (d, $J_{C–F}$ = 21.8 Hz, 2 × C_{Ar}), 85.1 (OC quat), 47.3 (NCH_2), 44.7 (NCH_2), 37.8 ($NHCH_2$), 33.1 ($NHCH_2CH_2$), 25.7 (NCH_2CH_2), 25.6 (NCH_2CH_2), 24.3 ($N(CH_2)_2CH_2$); ^{19}F NMR (377 MHz, $CDCl_3$) δ –113.6 (m); HRMS (ESI$^+$) *m/z* Calculated for $C_{16}H_{20}NO_3F$ [M+H] 307.1458; Found 307.1466.

SMILES: O=C1NCC[C@](C(N2CCCCC2)=O)(C3=CC=C(F)C=C3)O1
InChI = 1S/C16H19FN2O3/c17-13-6-4-12(5-7-13)16(8-9-18-15(21)22-16)14(20)19-10-2-1-3-11-19/h4-7H,1-3,8-11H2,(H,18,21)/t16-/m1/s1

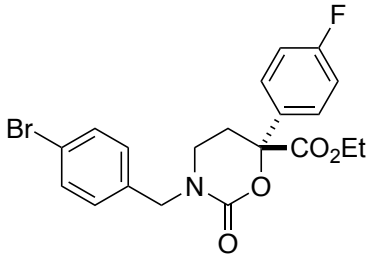
(±)–6-(4-Fluorophenyl)-6-(hydroxymethyl)-1,3-oxazinan-2-one (15)



$LiAlH_4$ (4.1 mg, 0.11 mmol) in 1.8:1 Et_2O:THF (2.8 mL) was added dropwise over 10 min to a solution of ethyl 6-(4-fluorophenyl)-2-oxo-1,3-oxazinane-6-carboxylate **4g** (27 mg, 0.1 mmol) in Et_2O (0.2 mL) at 0 ºC. The reaction mixture was stirred for a further 50 min at 25 ºC then sat. aq. NH_4Cl (20 mL) was added and the mixture was filtered into a separating funnel. The aqueous reaction mixture was extracted with EtOAc (4 × 20 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (5% MeOH/CH_2Cl_2) afforded 6-(4-fluorophenyl)-6-(hydroxymethyl)-1,3-oxazinan-2-one **15** (15 mg, 67%) as a colorless solid. R_f 0.10 (5% MeOH/CH_2Cl_2); mp = 185–187 ºC; ν_{max} (film)/cm^{-1} 3443 (br s, OH), 3242 (NH), 2917, 1720 (C=O), 1656, 1601, 1491, 1479, 1441, 1330, 1163, 1136, 1113, 1076, 1049, 982, 841, 768; ^{1}H NMR (400 MHz, CD_3OD) δ 7.50–7.45 (m, 2 H, 2 × HC_{Ar}), 7.22–7.15 (m, 2 H, 2 × HC_{Ar}), 3.73 (d, *J* = 12.2 Hz, 1 H, C*H*HOH), 3.68 (d, *J* = 12.2 Hz, 1 H, CH*H*OH), 3.33–3.27 (m, 1 H, NC*H*H), 2.98–2.90 (m, 1 H, NCH*H*), 2.45–2.39 (m, 2 H, NCH_2CH_2); ^{13}C NMR (101 MHz, CD_3OD) δ 163.9 (d, J_{C-F} = 245.2 Hz, FC_{Ar}), 156.7 (C=O), 137.2 (d, J_{C-F} = 3.1 Hz, C_{Ar}), 128.6 (d, J_{C-F} = 8.1 Hz, 2 × C_{Ar}), 116.5 (d, J_{C-F} = 21.8 Hz, 2 × C_{Ar}), 86.3 (OC quat), 70.1 (CH_2OH), 37.2 (NCH_2), 26.7 (NCH_2CH_2); ^{19}F NMR (377 MHz, CD_3OD) δ –116.8 (m); HRMS (ESI$^+$) *m/z* Calculated for $C_{11}H_{13}NO_3F$ [M+H] 226.0879; Found 226.0890.

SMILES: O=C1NCC[C@](CO)(C2=CC=C(F)C=C2)O1
InChI = 1S/C11H12FNO3/c12-9-3-1-8(2-4-9)11(7-14)5-6-13-10(15)16-11/h1-4,14H,5-7H2,(H,13,15)/t11-/m0/s1

(±)–Ethyl 3-(4-bromobenzyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinane-6-carboxylate (16)

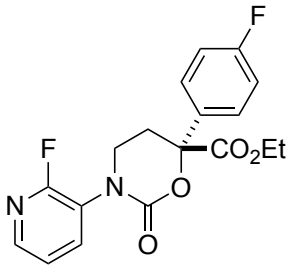


A solution of ethyl 6-(4-fluorophenyl)-2-oxo-1,3-oxazinane-6-carboxylate **4g** (27 mg, 0.1 mmol), 4-bromobenzyl bromide (30 mg, 0.12 mmol), KI (1.7 mg, 10 μmol) and K_2CO_3 (42 mg, 0.3 mmol) in MeCN (0.25 mL) was stirred at 50 ºC for 20 h. The reaction was allowed to cool to rt and H_2O (25 mL) was added. The aqueous reaction mixture was extracted with EtOAc (3 × 25 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (25% to 40% EtOAc/pentane) followed by purification by flash chromatography (2% Et_2O/CH_2Cl_2) afforded ethyl 3-(4-bromobenzyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinane-6-carboxylate **16** (15 mg, 34%) as a colorless solid. R_f 0.18 (1% Et_2O/CH_2Cl_2); mp = 105–107 ºC; ν_{max} (film)/cm^{-1} 3049, 2974, 2929, 1737 (C=O ester), 1692 (C=O carbamate), 1513, 1439, 1267, 1170, 1010, 824, 753; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.54 (m, 2 H, 2 × HC_{Ar}), 7.44 (d, *J* = 8.4 Hz, 2 H, 2 × HC_{Ar}), 7.15–7.05 (m, 4 H, 4 × HC_{Ar}), 4.59 (d, *J* = 15.0 Hz, 1 H, NC*H*HAr), 4.44 (d, *J* = 15.0 Hz, 1 H, NCH*H*Ar), 4.23–4.11 (m, 2 H, OCH_2CH_3), 3.25–3.17 (m, 1 H, NC*H*H), 3.16–3.08 (m, 1 H, NCH*H*), 2.80–2.72 (m, 1 H, NCH_2CHH), 2.33 (ddd, *J* = 13.9, 9.7, 6.1 Hz, 1 H, NCH_2CHH), 1.19 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8 (C=O ester), 162.9 (d, J_{C-F} = 248.3 Hz, FC_{Ar} quat), 152.1 (C=O carbamate), 135.2 (C_{Ar} quat), 133.1 (d, J_{C-F} = 2.7 Hz, C_{Ar} quat), 131.8 (2 × C_{Ar}), 129.7 (2 × C_{Ar}), 127.0 (d, J_{C-F} = 8.4 Hz, 2 × C_{Ar}), 121.8 (BrC_{Ar} quat), 115.6 (d, J_{C-F} = 21.7 Hz, 2 × C_{Ar}), 82.5 (OC quat), 62.6 (OCH_2CH_3), 52.0 (NCH_2Ar), 41.8 (NCH_2), 30.0 (NCH_2CH_2), 13.9 (OCH_2CH_3); ^{19}F{^{1}H} NMR (377 MHz, $CDCl_3$) δ –112.8; HRMS (ESI$^+$) *m/z* Calculated for $C_{20}H_{20}NO_4F^{79}Br$ [M+H] 436.0560; Found 436.0554.

SMILES: O=C1N(CC2=CC=C(Br)C=C2)CC[C@@](C3=CC=C(F)C=C3)(C(OCC)=O)O1

InChI = 1S/C20H19BrFNO4/c1-2-26-18(24)20(15-5-9-17(22)10-6-15)11-12-23(19(25)27-20)13-14-3-7-16(21)8-4-14/h3-10H,2,11-13H2,1H3

(±)–Ethyl 6-(4-fluorophenyl)-3-(2-fluoropyridin-3-yl)-2-oxo-1,3-oxazinane-6-carboxylate (17)



A solution of ethyl 6-(4-fluorophenyl)-2-oxo-1,3-oxazinane-6-carboxylate **4g** (27 mg, 0.1 mmol), 2-fluoro-3-iodopyridine (44 mg, 0.2 mmol), CuI (1.9 mg, 10 μmol), K_2CO_3 (28 mg, 0.2 mmol) and cyclohexan-1,2-diamine (2.4 μL, 20 μmol) in 1,4-dioxane was stirred at 110 ºC for 24 h. The reaction mixture was allowed to cool to rt, then the mixture was filtered through celite washing with EtOAc (20 mL) and the crude product was concentrated under reduced pressure. Purification by flash chromatography (60% EtOAc/pentane) afforded ethyl 6-(4-fluorophenyl)-3-(2-fluoropyridin-3-yl)-2-oxo-1,3-oxazinane-6-carboxylate **17** (20 mg, 55%) as a colorless solid. R_f 0.13 (50% EtOAc/pentane); mp = 139–141 ºC; ν_{max} (film)/cm^{-1} 3064, 2907, 2967, 1703 (s br, 2 × C=O), 1603, 1577, 1450, 1323, 1252, 1223, 1159, 1092, 1006, 965, 917, 828; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (m, 1 H, HC_{Ar}), 7.81–7.75 (m, 1 H, HC_{Ar}), 7.67–7.61 (m, 2 H, 2 × HC_{Ar}), 7.27–7.25 (m, 1 H, HC_{Ar}), 7.16–7.09 (m, 2 H, 2 × HC_{Ar}), 4.36–4.24 (m, 2 H, OCH_2CH_3), 3.74–3.66 (m, 1 H, $NCHH$), 3.61–3.54 (m, 1 H, $NCHH$), 2.97 (ddd, J = 13.9, 5.2, 4.1 Hz, 1 H, NCH_2HH), 2.55 (ddd, J = 13.9, 10.1, 5.9 Hz, 1 H, NCH_2CHH), 1.29 (t, J = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6 (C=O ester), 163.0 (d, J = 249.0 Hz, FC_{Ar} quat), 158.6 (d, J = 241.6 Hz, $FC_{Ar}N$ quat), 150.7 (C=O carbamate), 139.9 (d, $J_{C–F}$ = 2.9 Hz, C_{Ar} quat), 132.8 (d, $J_{C–F}$ = 2.9 Hz, C_{Ar} quat), 127.0 (d, $J_{C–F}$ = 8.4 Hz, 2 × C_{Ar}), 124.5 (d, $J_{C–F}$ = 27.7 Hz, C_{Ar}), 122.2 (d, $J_{C–F}$ = 4.2 Hz, C_{Ar}), 115.8 (d, $J_{C–F}$ = 21.8 Hz, 2 × C_{Ar}), 83.5 (OC quat), 63.0 (OCH_2CH_3), 45.4 (NCH_2), 30.4 (NCH_2CH_2), 14.0 (OCH_2CH_3) (the peak due to NC_{Ar} quat was not observed); ^{19}F{^{1}H} NMR (377 MHz, $CDCl_3$) δ –74.9, –112.5; HRMS (ESI$^+$) *m/z* Calculated for $C_{18}H_{17}N_2O_4F_2$ [M+H] 363.1156; Found 363.1154.

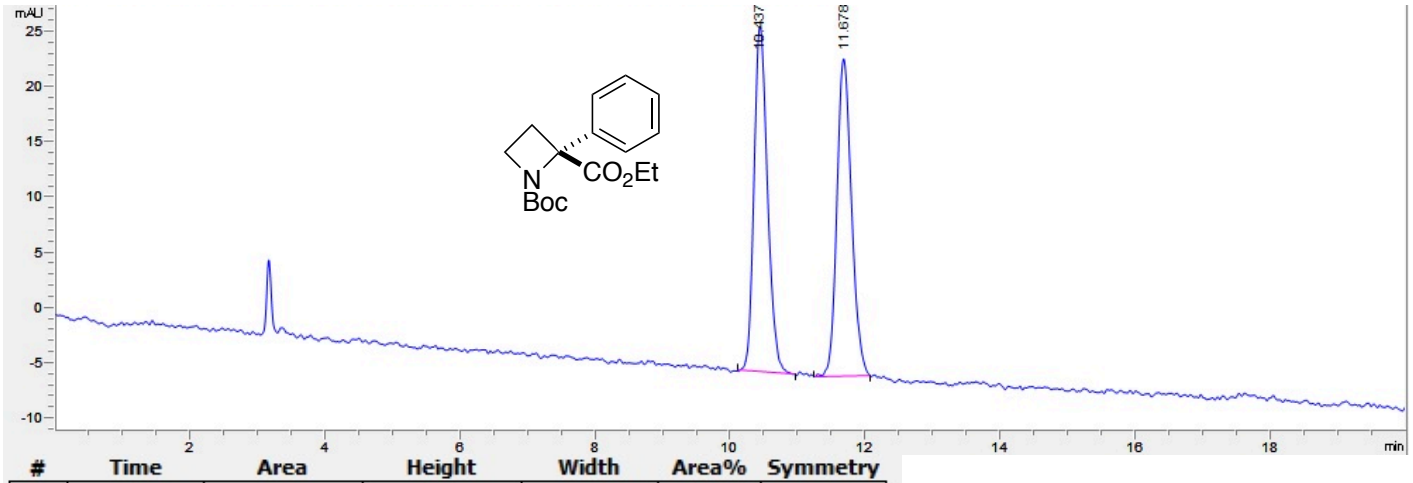
SMILES: O=C1N(C2=C(F)N=CC=C2)CC[C@@](C3=CC=C(F)C=C3)(C(OCC)=O)O1

InChI = 1S/C18H16F2N2O4/c1-2-25-16(23)18(12-5-7-13(19)8-6-12)9-11-22(17(24)26-18)14-4-3-10-21-15(14)20/h3-8,10H,2,9,11H2,1H3

HPLC Data

(±)-1-(*tert*-Butyl) 2-ethyl 2-phenylazetidine-1,2-dicarboxylate 3a

Conditions: Chiralpak IE 3-column, 95:5 *n*-hexane:*i*-PrOH, flow rate: 1 mL·min^{-1}, 35 ºC. UV detection wavelength: 210.4 nm.



#	Time	Area	Height	Width	Area%	Symmetry
1	10.437	441	31.5	0.2155	50.153	0.762
2	11.678	438.3	28.9	0.2311	49.847	0.837

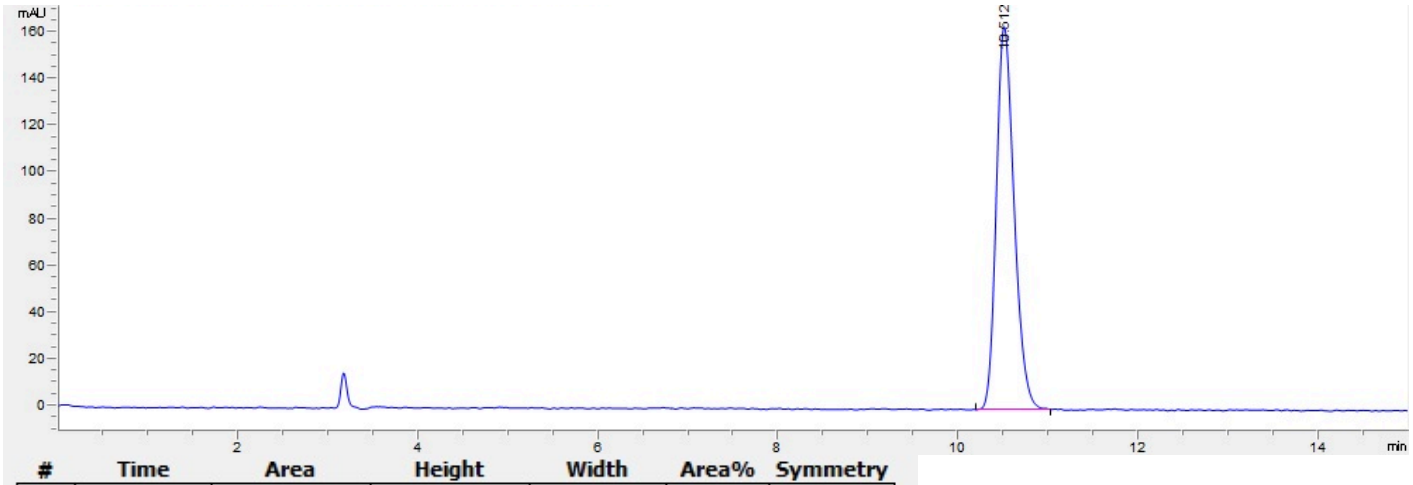
Separation of enantiomers of (±)-1-(*tert*-Butyl) 2-ethyl 2-phenylazetidine-1,2-dicarboxylate 3a

A racemic mixture of 1-(*tert*-Butyl) 2-ethyl 2-phenylazetidine-1,2-dicarboxylate **3a** was separated by chiral HPLC.

Conditions: Chiralpak IE 3-column, 95:5 *n*-hexane:*i*-PrOH, flow rate: 1 mL·min^{-1}, 35 ºC. UV detection wavelength: 210.4 nm.

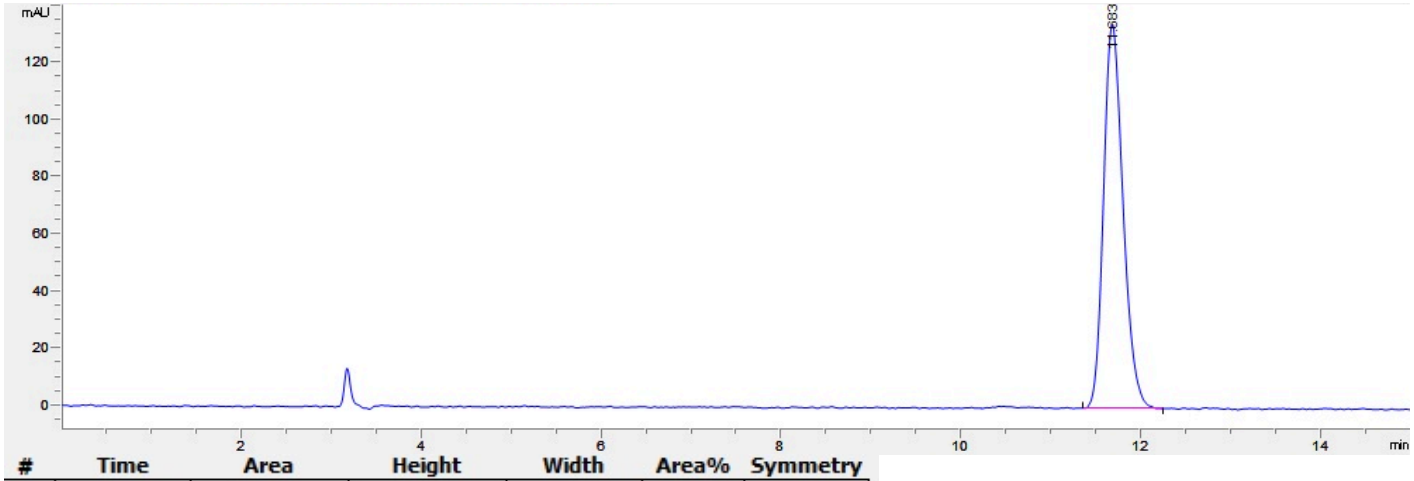
A 10 mg/mL solution of 1-(*tert*-Butyl) 2-ethyl 2-phenylazetidine-1,2-dicarboxylate **3a** was injected and the HPLC outlet was collected in vials, changing every 15 s. This was repeated to afford 3 mg each of the two enantiomers with high enantiopurity.

Enantiomer at t = 10.5 min



#	Time	Area	Height	Width	Area%	Symmetry
1	10.512	2269.8	164.6	0.2109	100.000	0.751

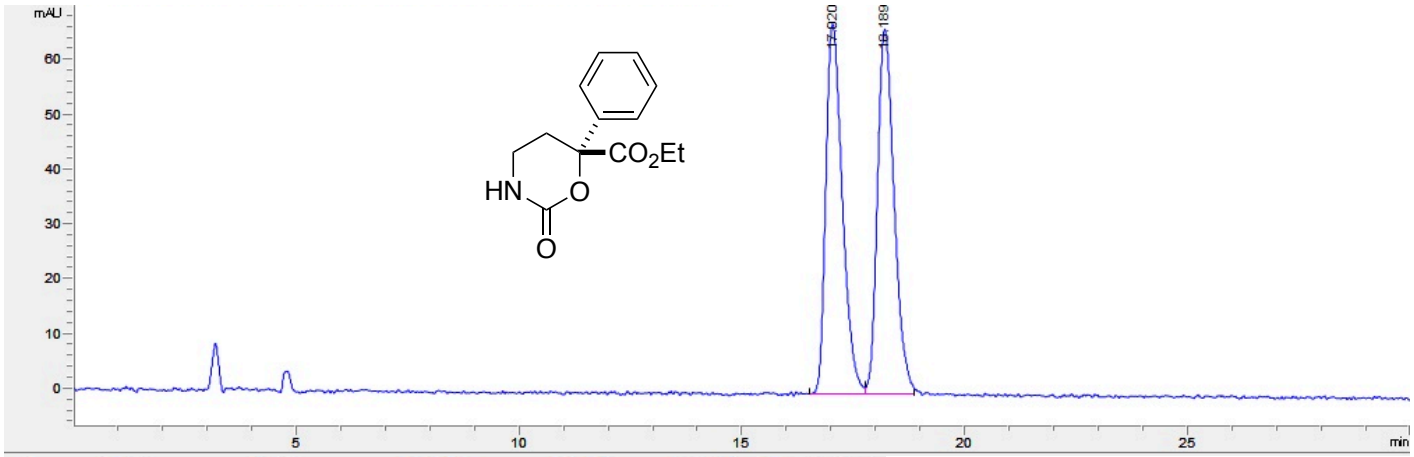
Enantiomer at t = 11.7 min



#	Time	Area	Height	Width	Area%	Symmetry
1	11.683	2026.8	134.3	0.2321	100.000	0.765

(±)-Ethyl 2-oxo-6-phenyl-1,3-oxazinane-6-carboxylate 4a

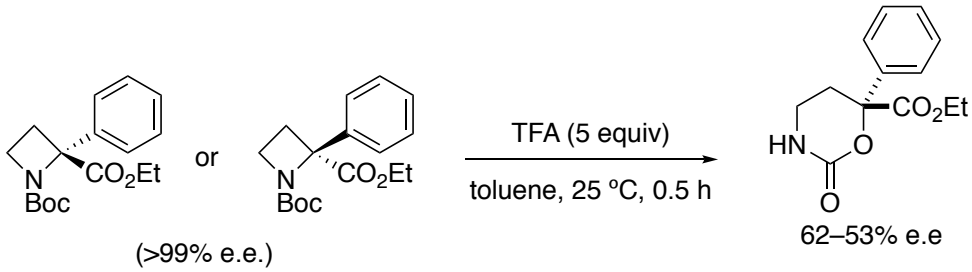
Conditions: Chiralpak ID 3-column, 80:20 *n*-hexane:*i*-PrOH, flow rate: 1 mL·min^{-1}, 35 °C. UV detection wavelength: 210.4 nm.



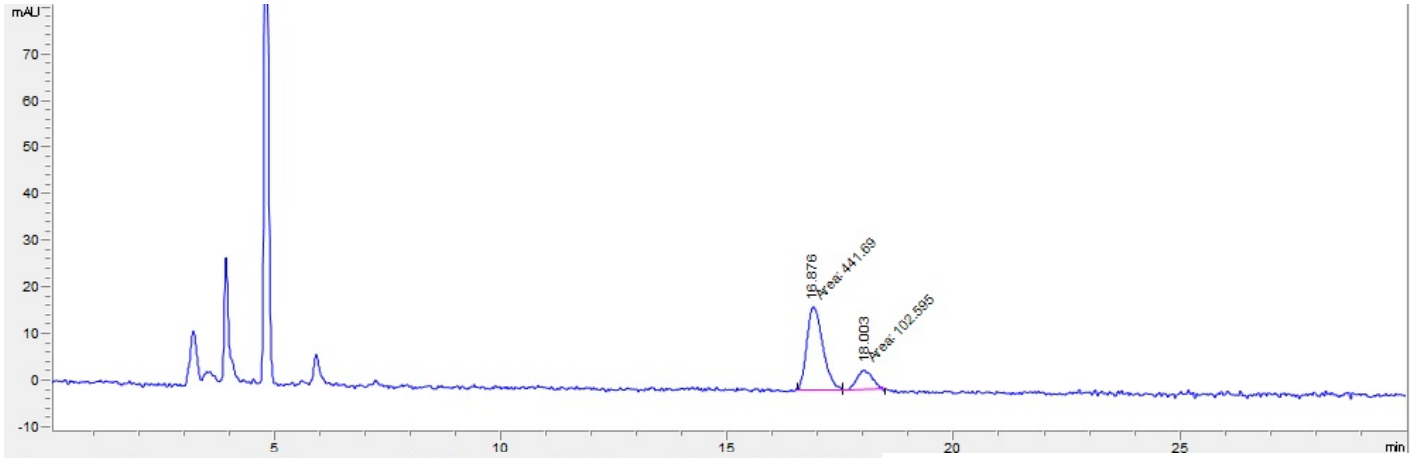
#	Time	Area	Height	Width	Area%	Symmetry
1	17.02	1740.1	67.4	0.3751	49.990	0.643
2	18.189	1740.9	66.6	0.3931	50.010	0.72

Subjection of enantiomer of 1-(*tert*-butyl) 2-ethyl 2-phenylazetidine-1,2-dicarboxylate to reaction conditions

A stock solution of trifluoroacetic acid in toluene (10 μL, 0.38 mL TFA/ 1 mL toluene) was added to a solution of 1-(*tert*-butyl) 2-ethyl 2-phenylazetidine-1,2-dicarboxylate (e.e. > 99%) (3 mg) at 25 °C and stirred for 30 min. The reaction mixture was concentrated under reduced pressure and a sample taken for HPLC analysis.

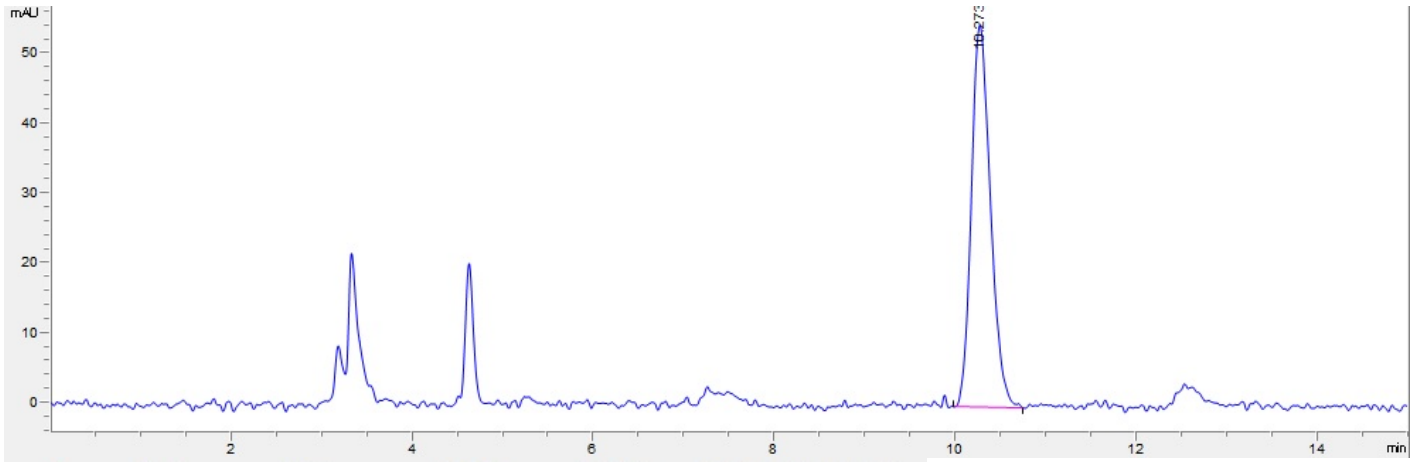


HPLC trace of ethyl 2-oxo-6-phenyl-1,3-oxazinane-6-carboxylate formed



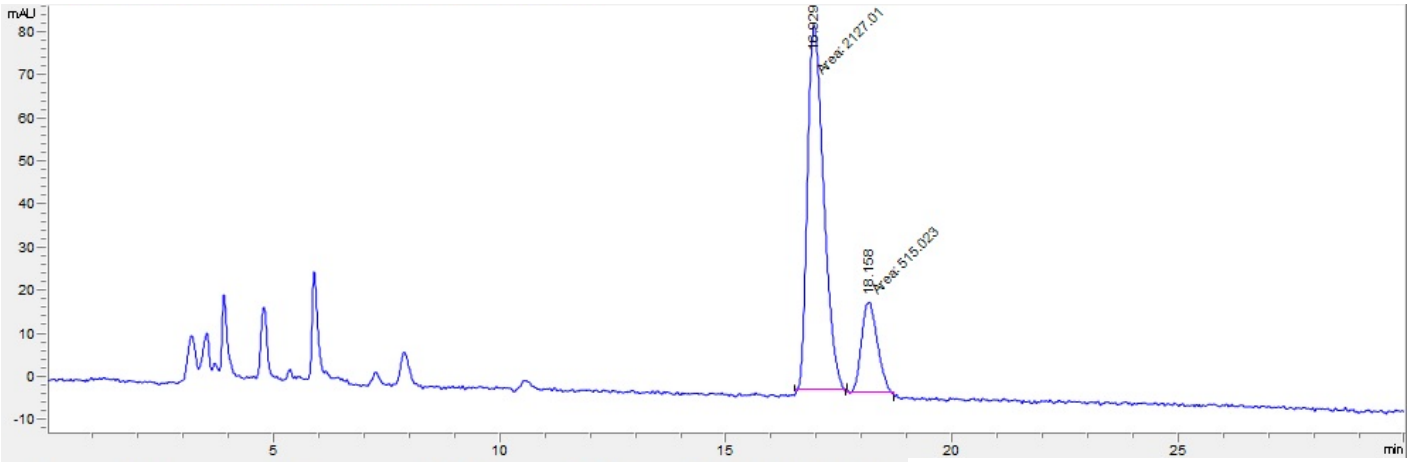
#	Time	Area	Height	Width	Area%	Symmetry
1	16.876	441.7	17.9	0.4119	81.151	0.66
2	18.003	102.6	4.3	0.3993	18.849	0.909

HPLC trace of remaining starting material



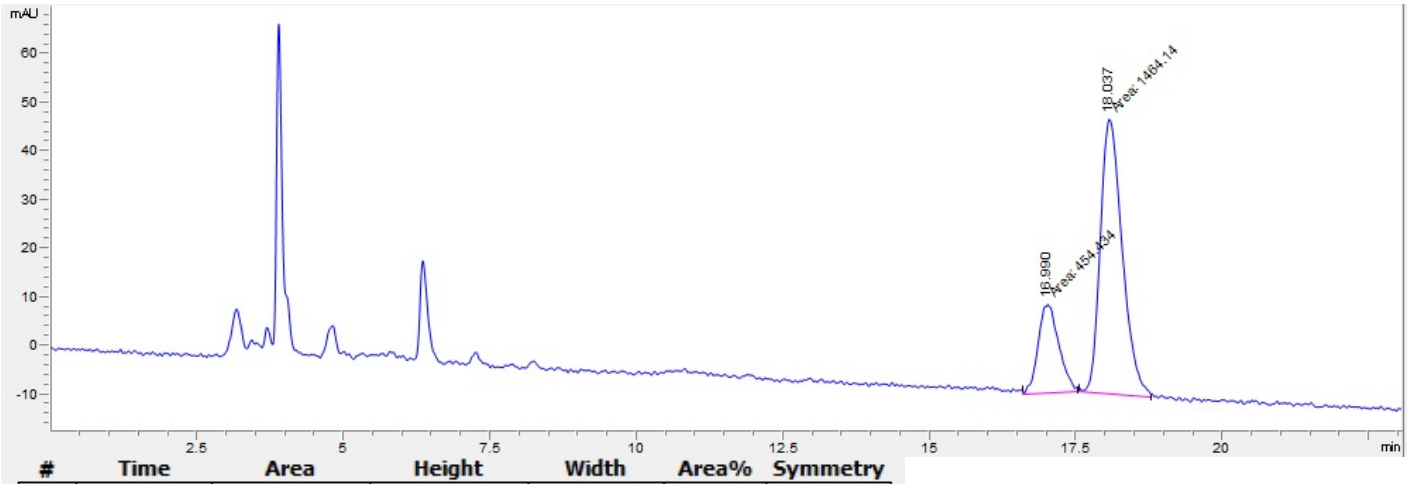
#	Time	Area	Height	Width	Area%	Symmetry
1	10.273	811	54.9	0.2084	100.000	0.762

HPLC trace of product formed resubjected to reaction condtions



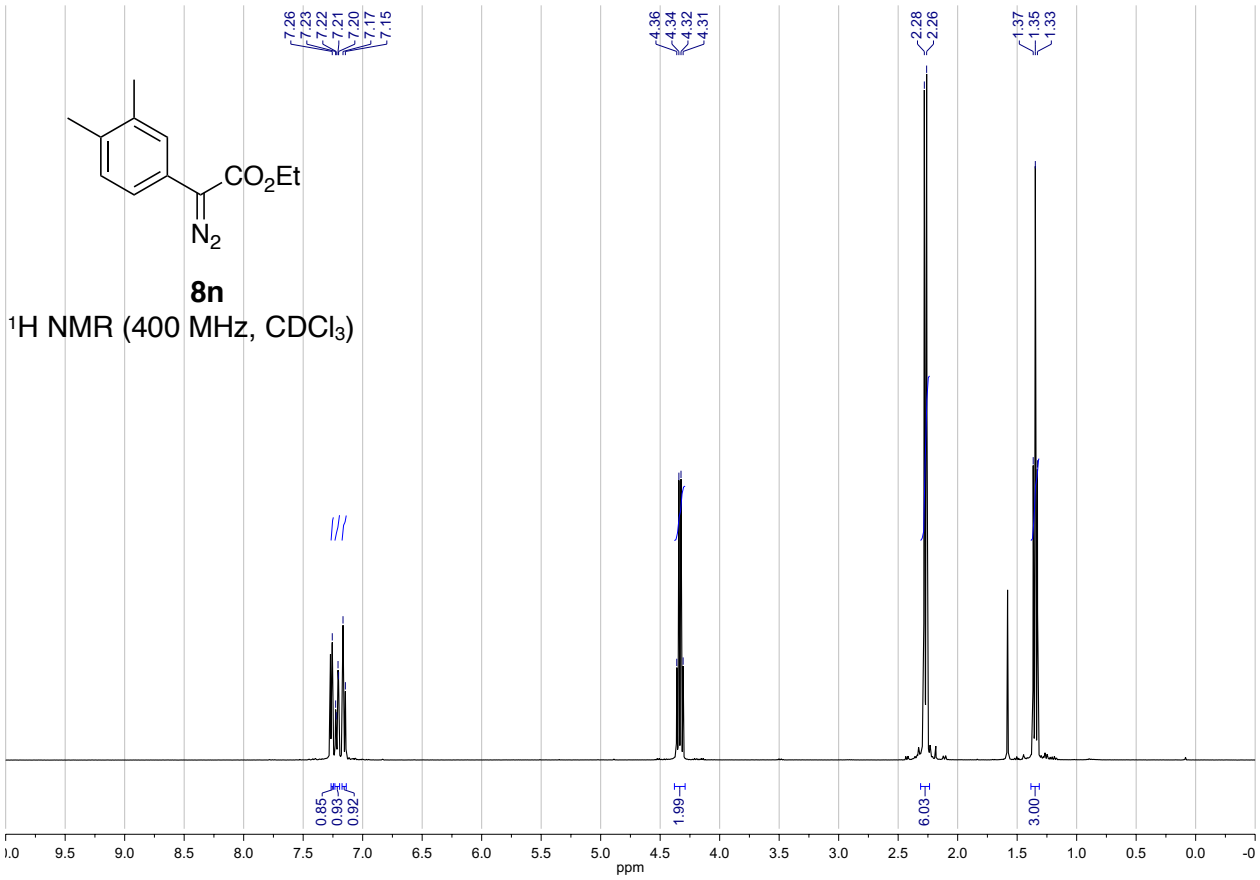
#	Time	Area	Height	Width	Area%	Symmetry
1	16.929	2127	84.7	0.4183	80.507	0.646
2	18.158	515	21.1	0.4076	19.493	0.982

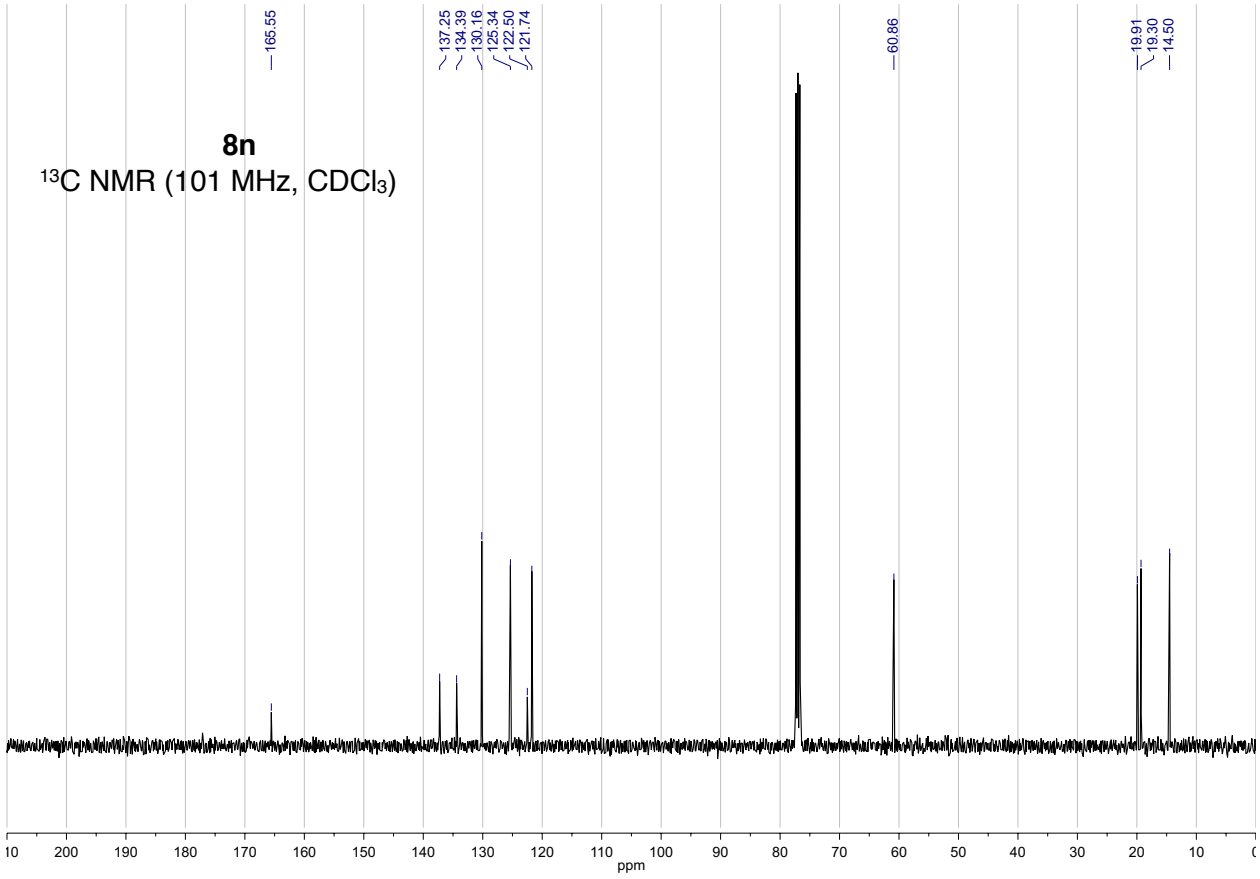
HPLC when opposite enantiomer is subjected to reaction conditions

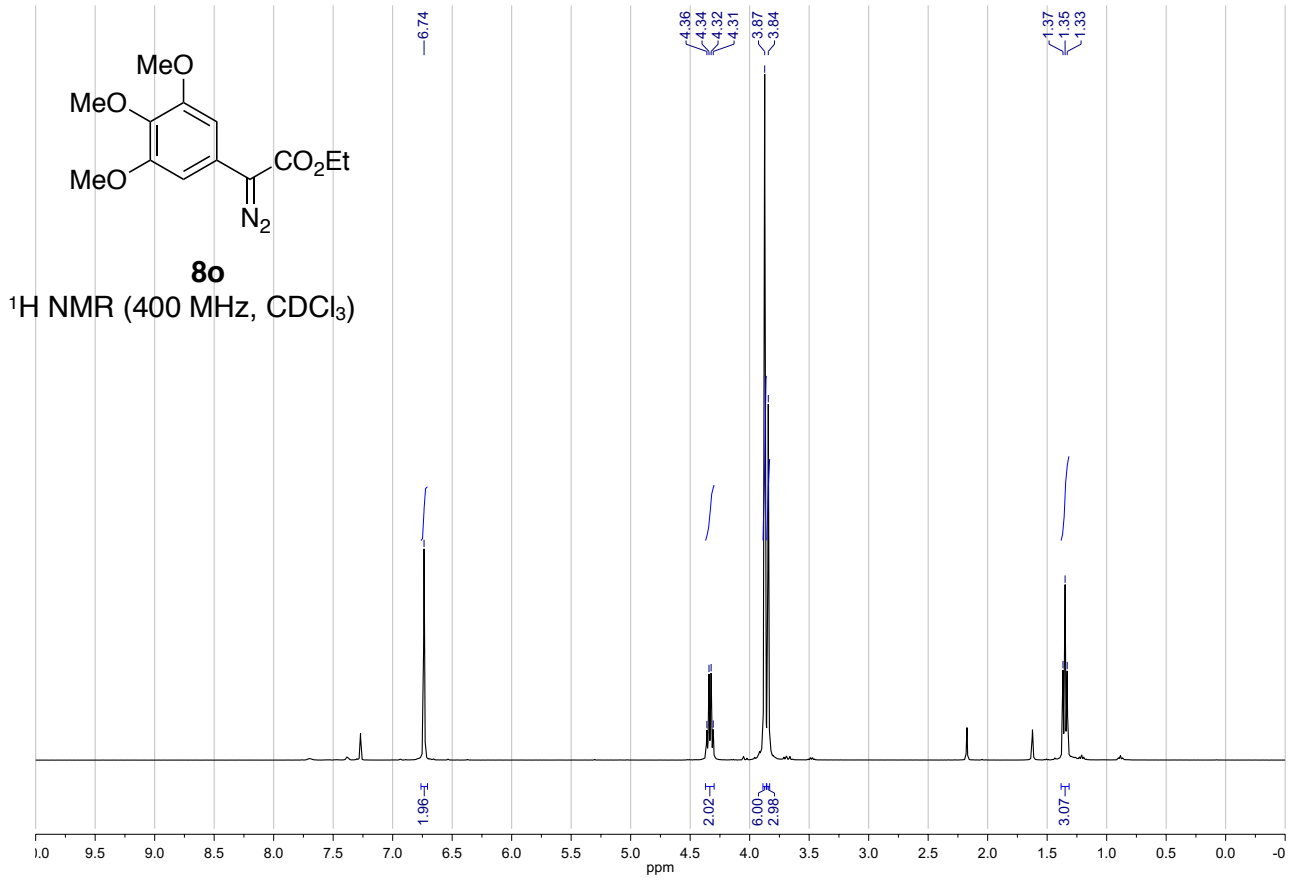


#	Time	Area	Height	Width	Area%	Symmetry
1	16.99	454.4	18.3	0.4133	23.686	0.855
2	18.037	1464.1	56.3	0.4335	76.314	0.667

^{1}H and ^{13}C NMR Spectra of Selected Compounds

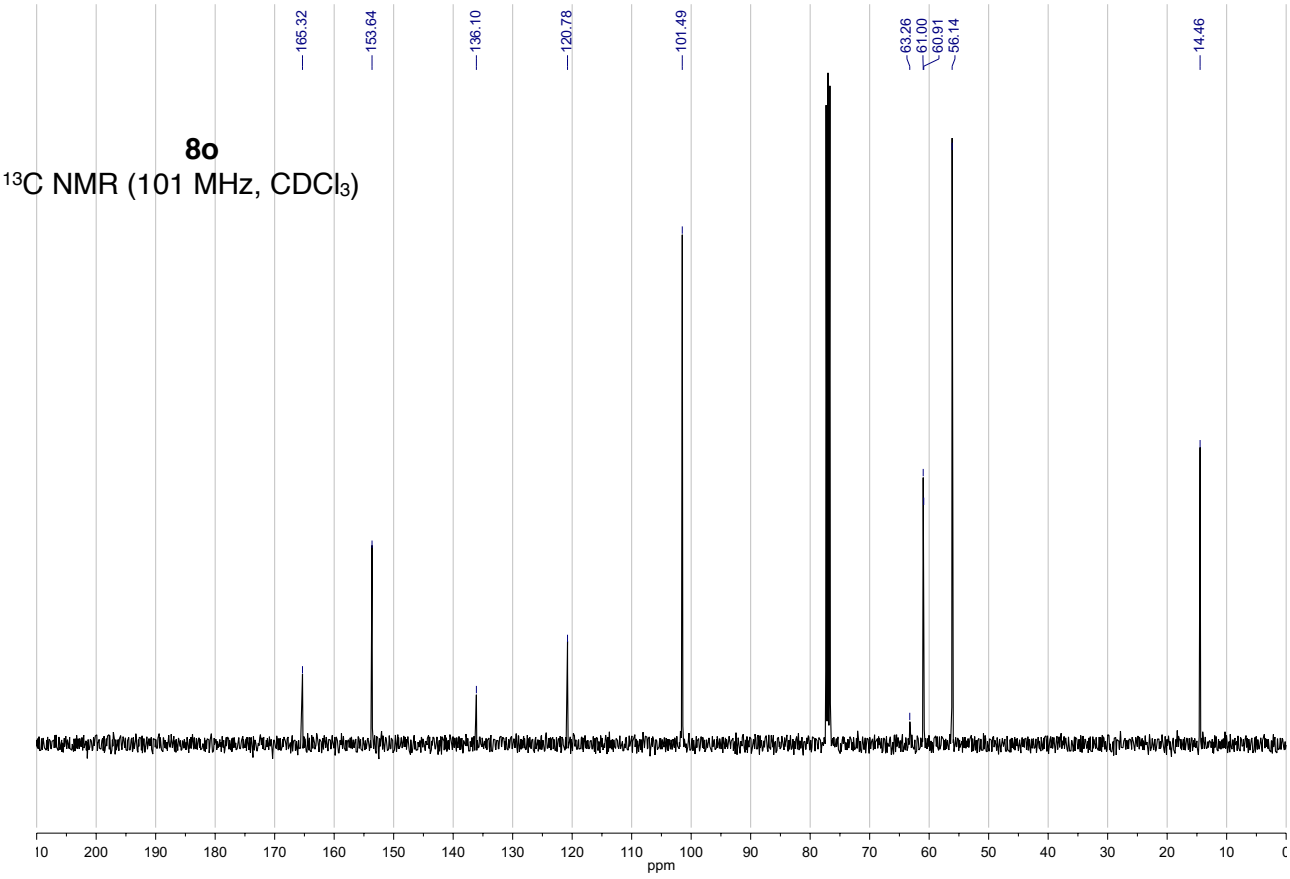

7.26
7.23
7.22
7.21
7.20
7.17
7.15
4.36
4.34
4.32
4.31
2.28
2.26
1.37
1.35
1.33
CO2Et
N2
8n
1H NMR (400 MHz, CDCl3)
0.85
0.93
0.92
1.99
6.03
3.00
ppm


165.55
137.25
134.39
130.16
125.34
122.50
121.74
60.86
19.91
19.30
14.50
8n
13C NMR (101 MHz, CDCl3)
ppm



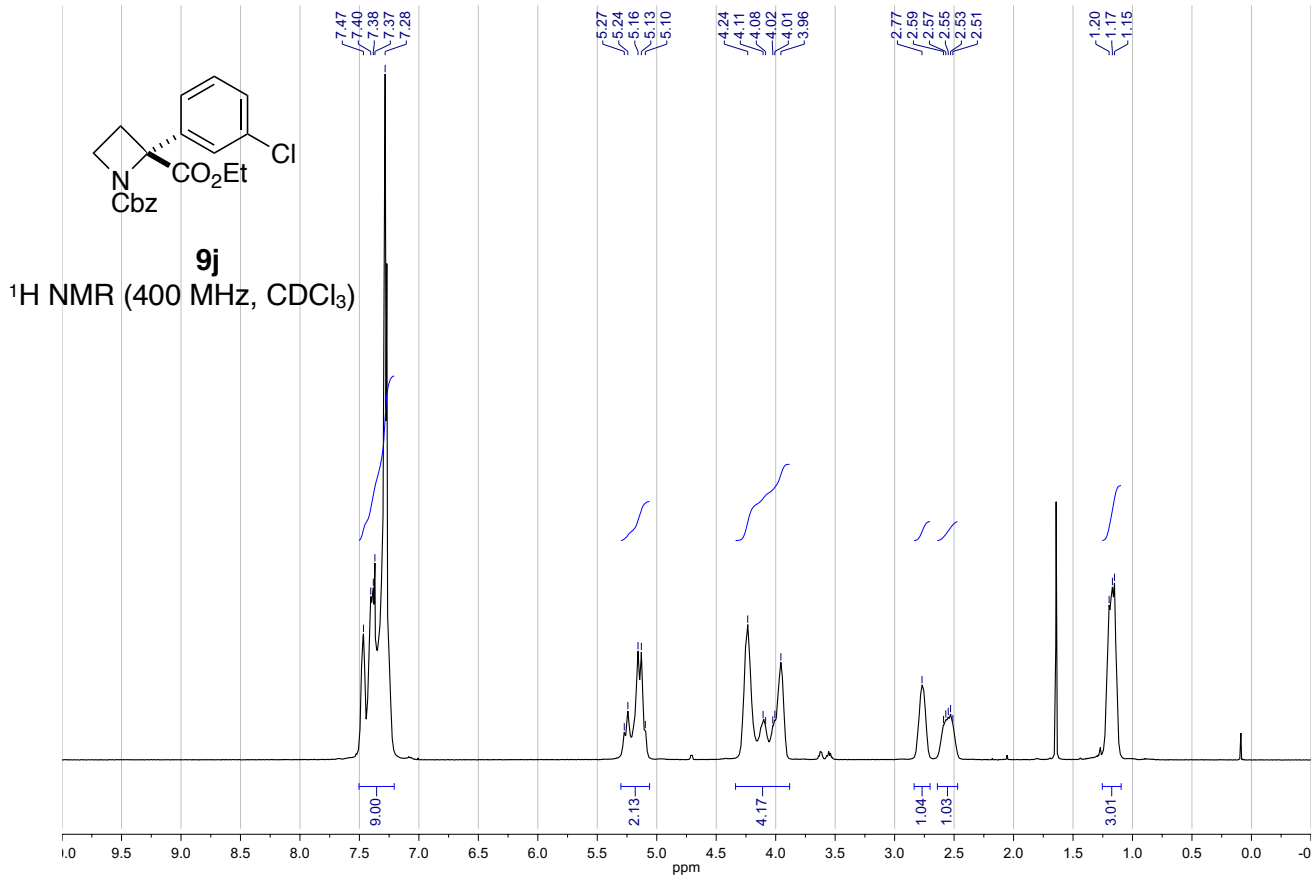
8o

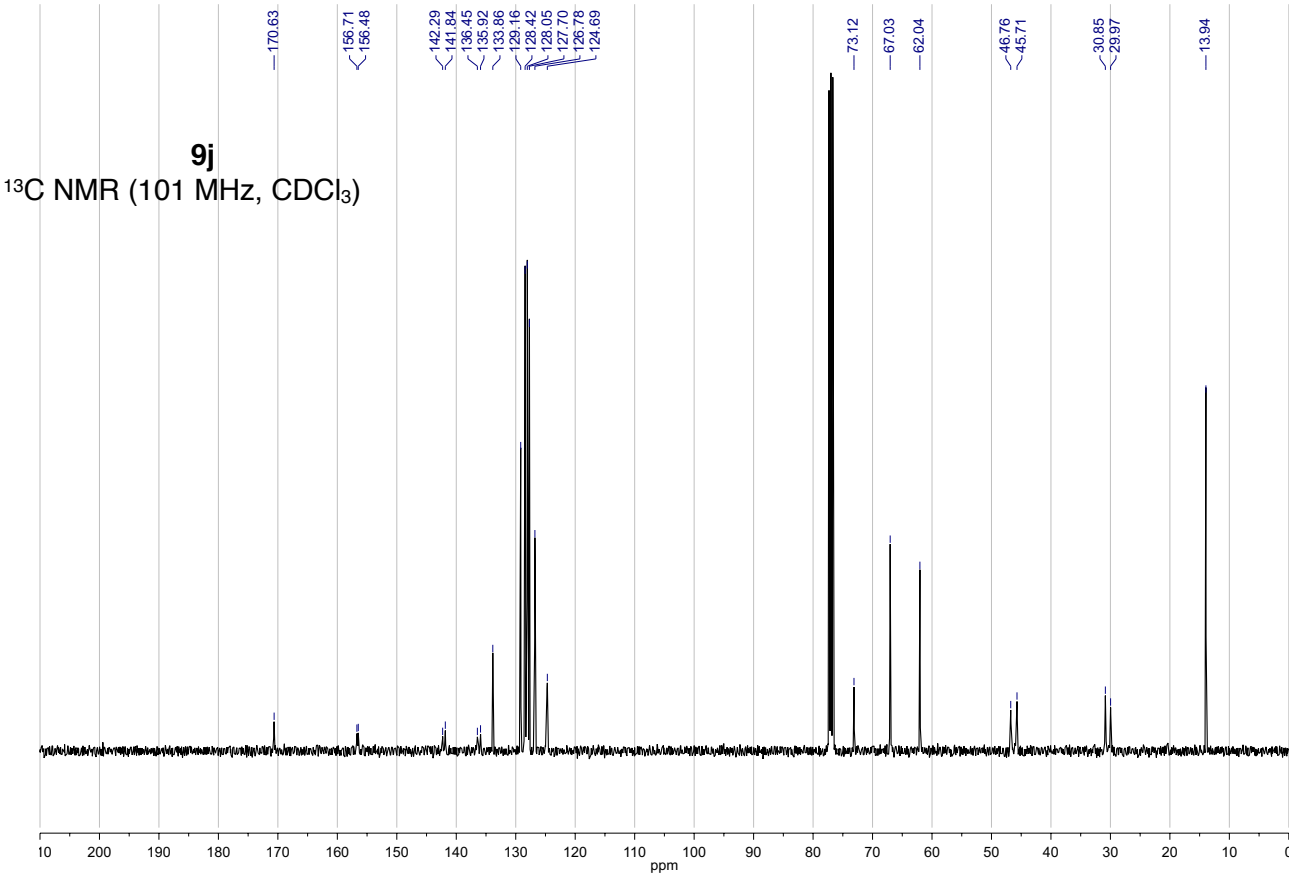
^{1}H NMR (400 MHz, $CDCl_3$)

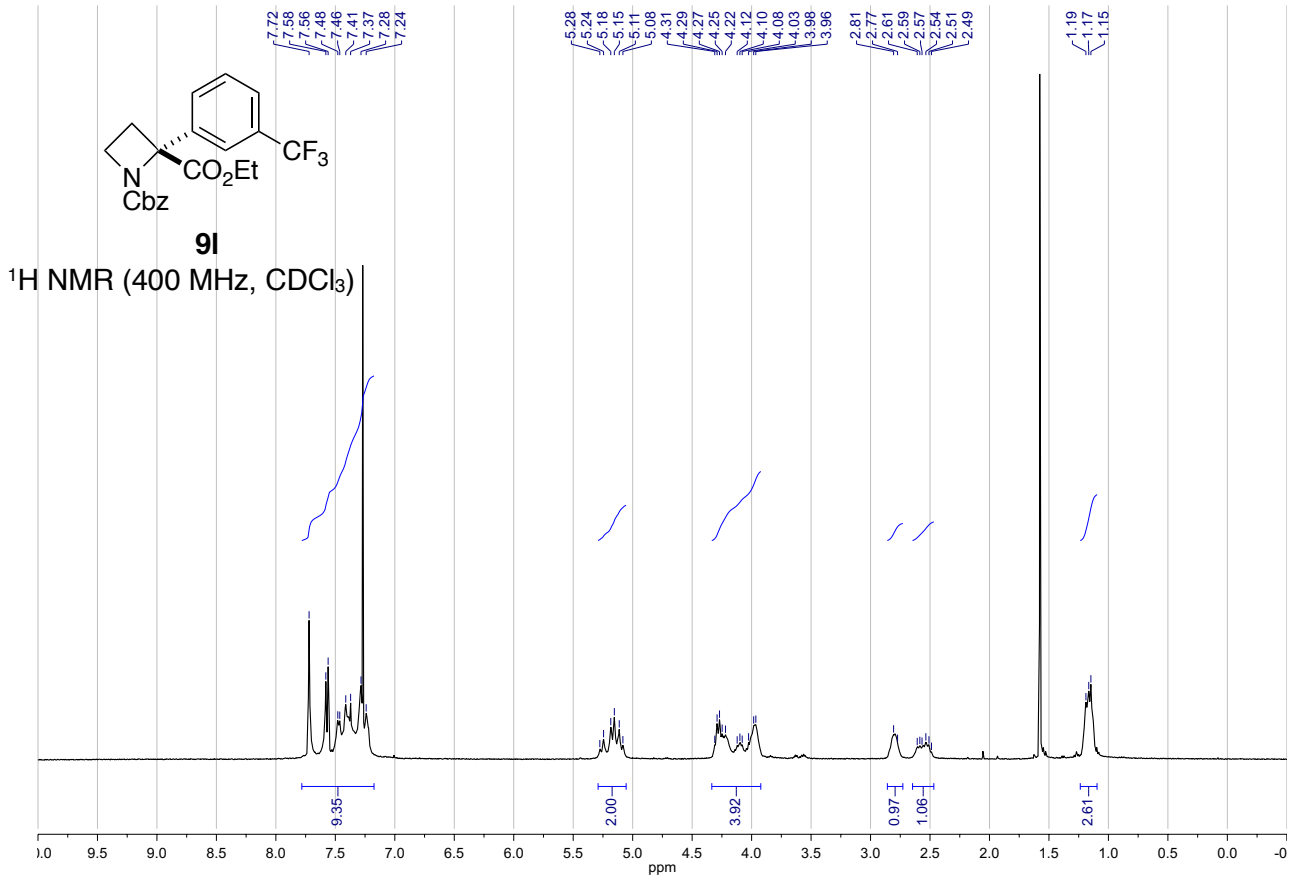


8o

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

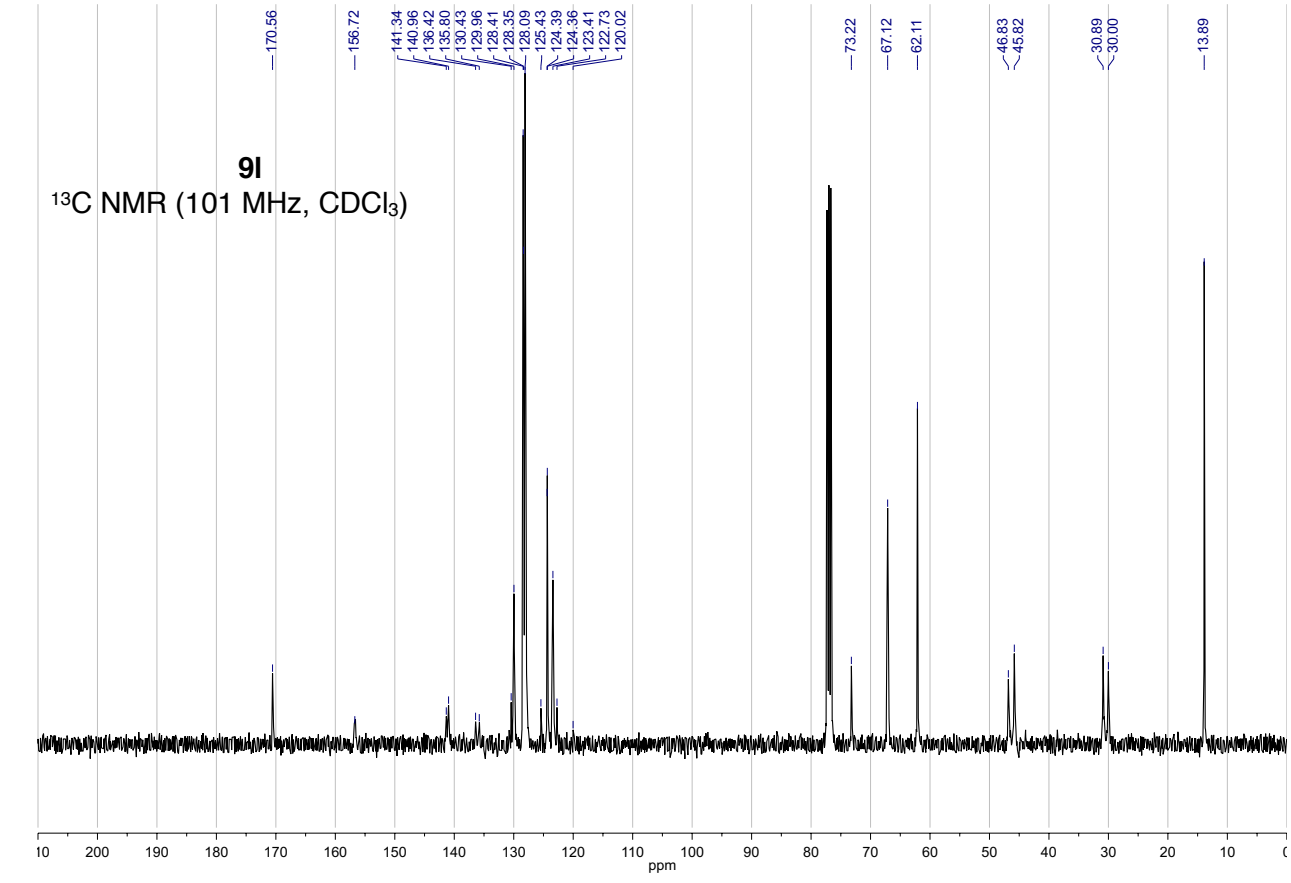

Cl
CO2Et
N
Cbz
9j
1H NMR (400 MHz, CDCl3)
7.47
7.40
7.38
7.37
7.28
5.27
5.24
5.16
5.13
5.10
4.24
4.11
4.08
4.02
4.01
3.96
2.77
2.59
2.57
2.55
2.53
2.51
1.20
1.17
1.15
9.00
2.13
4.17
1.04
1.03
3.01
ppm


9j
13C NMR (101 MHz, CDCl3)
170.63
156.71
156.48
142.29
141.84
136.45
135.92
133.86
129.16
128.42
128.05
127.70
126.78
124.69
73.12
67.03
62.04
46.76
45.71
30.85
29.97
13.94
ppm



9l

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

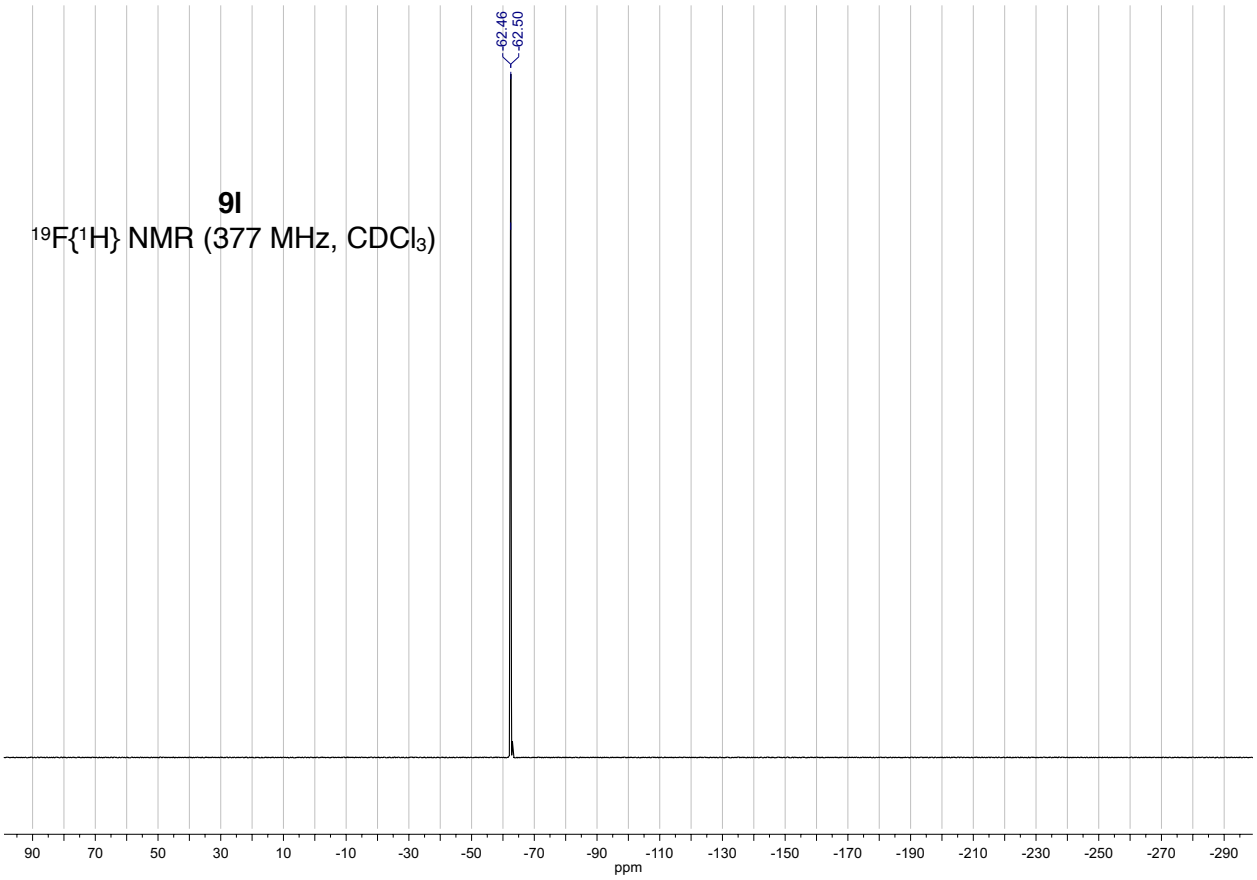


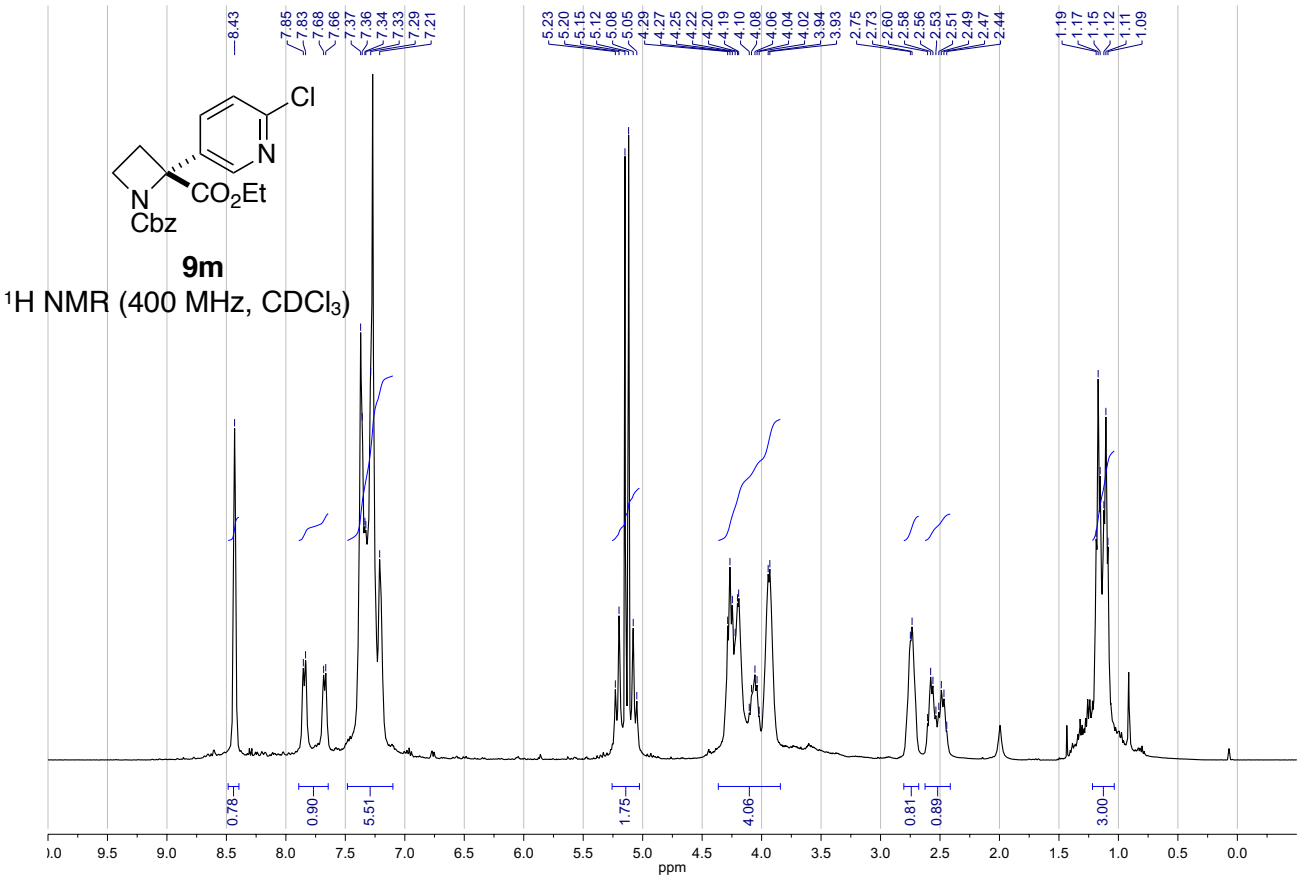
9l

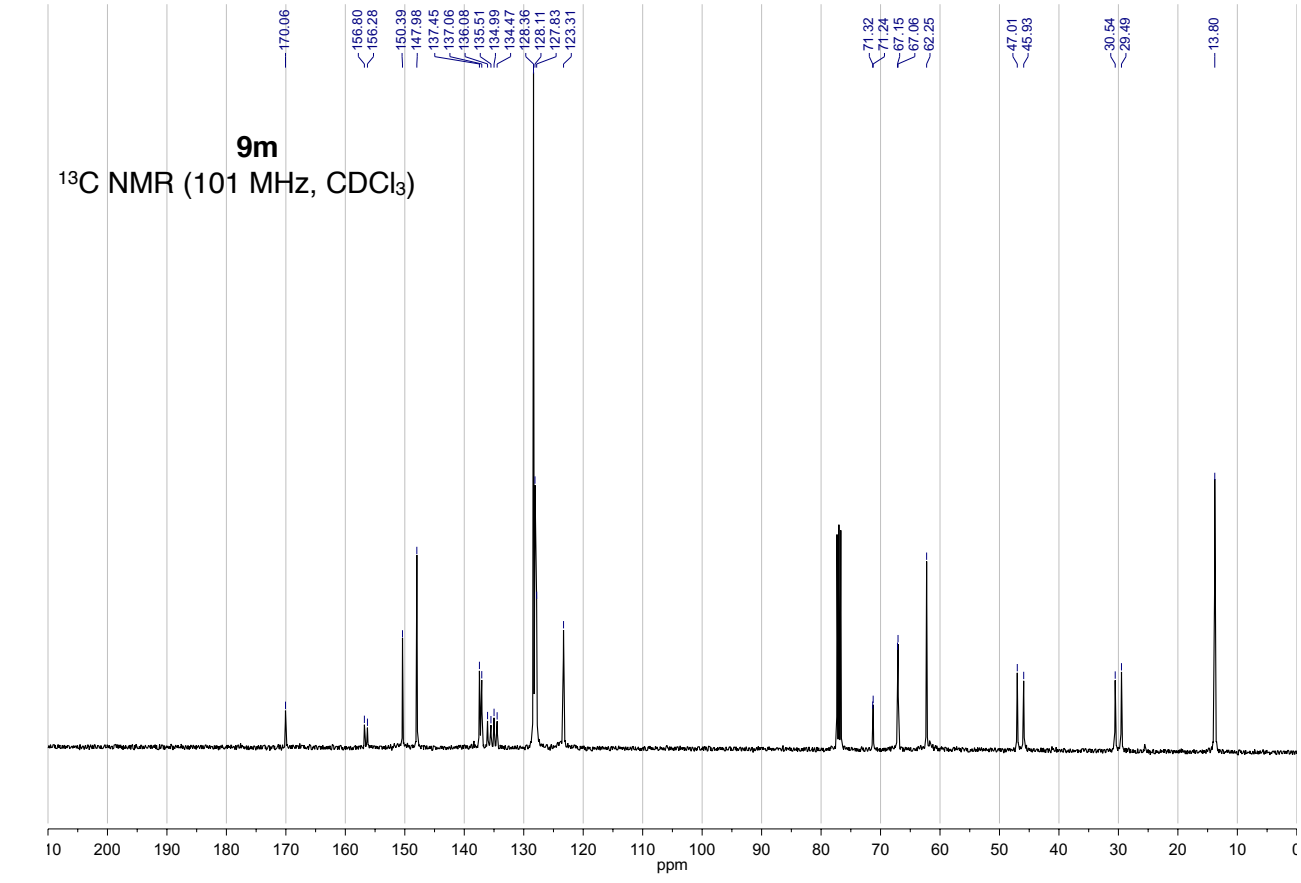
^{13}C NMR (101 MHz, $CDCl_3$)

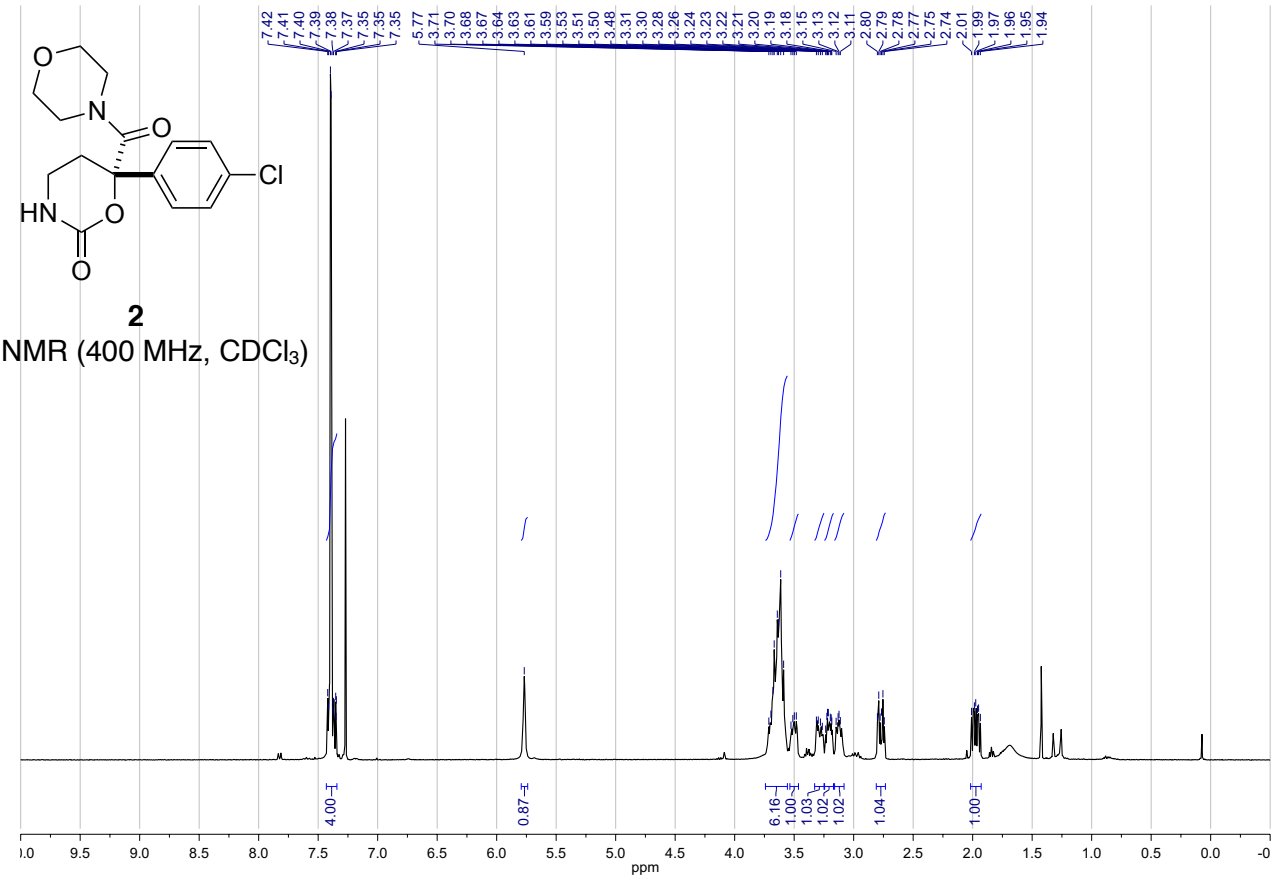
9l

$^{19}F\{^{1}H\}$ NMR (377 MHz, $CDCl_3$)



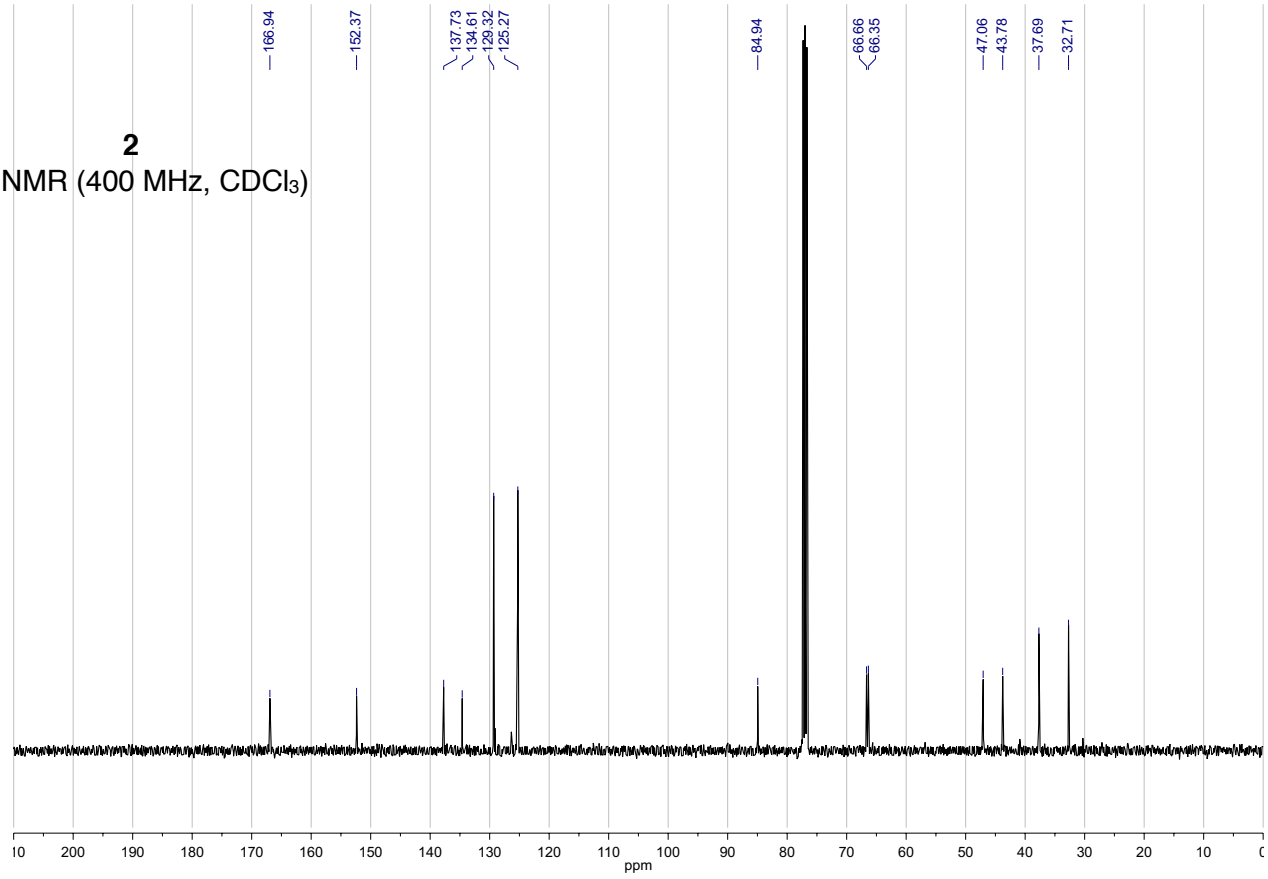

Cl
N
N
CO2Et
Cbz
9m
1H NMR (400 MHz, CDCl3)
ppm


9m
13C NMR (101 MHz, CDCl3)
ppm



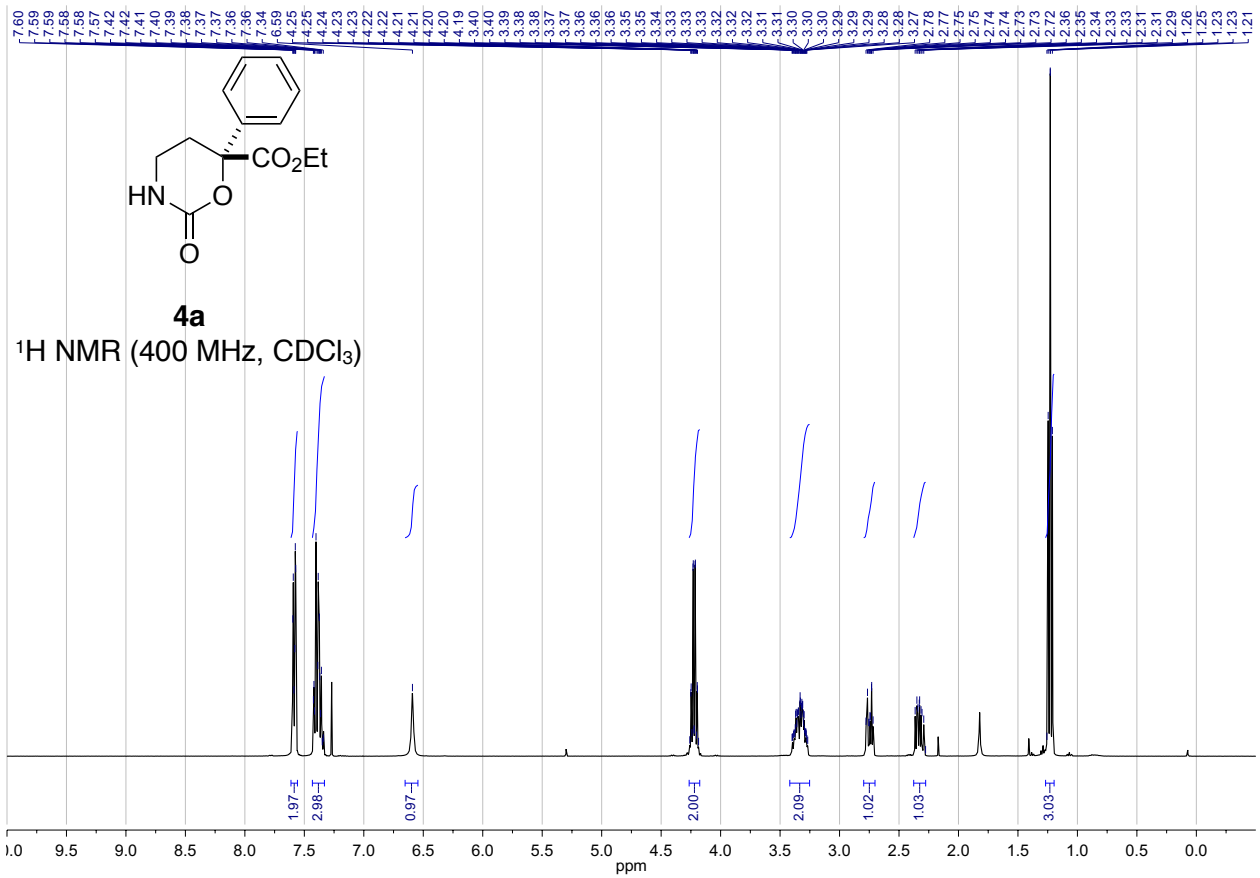
2

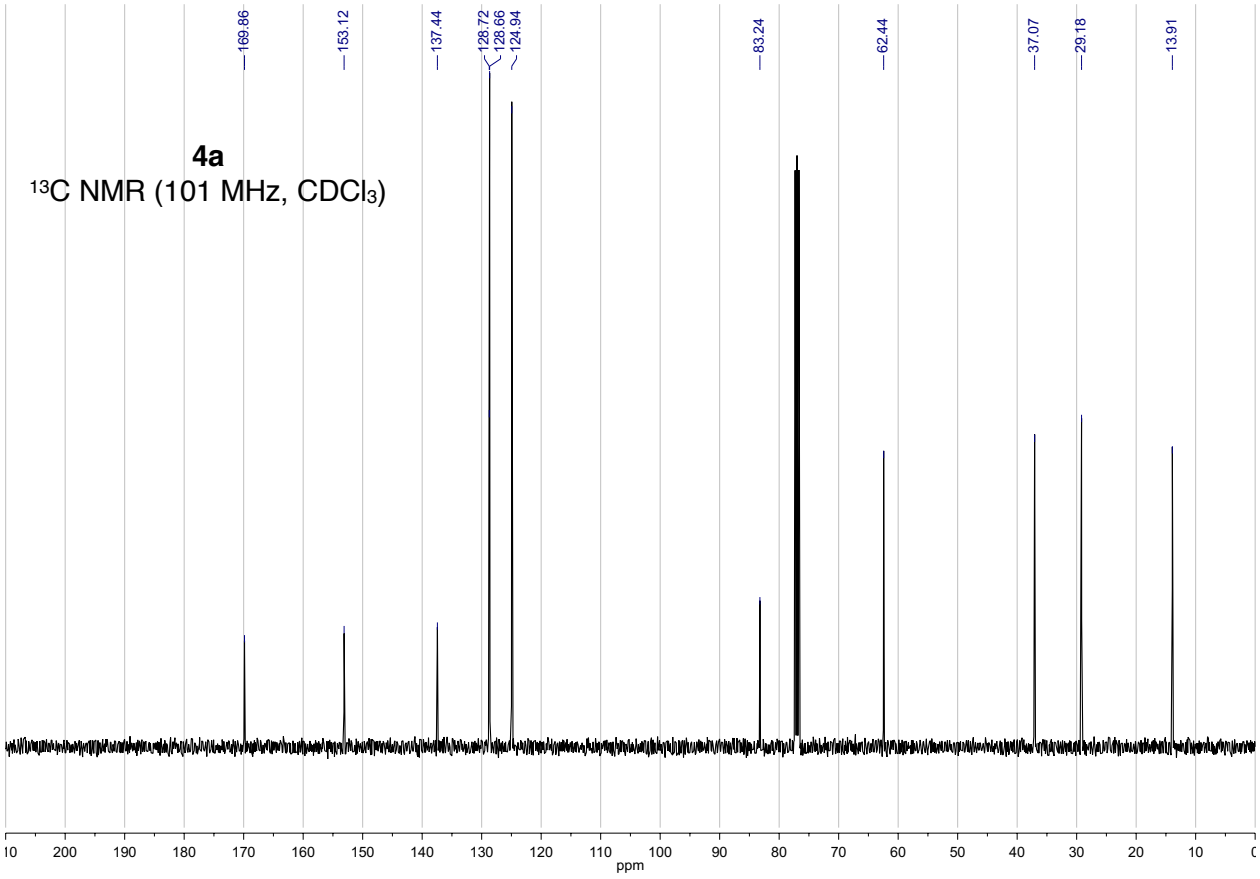
^{1}H NMR (400 MHz, $CDCl_3$)

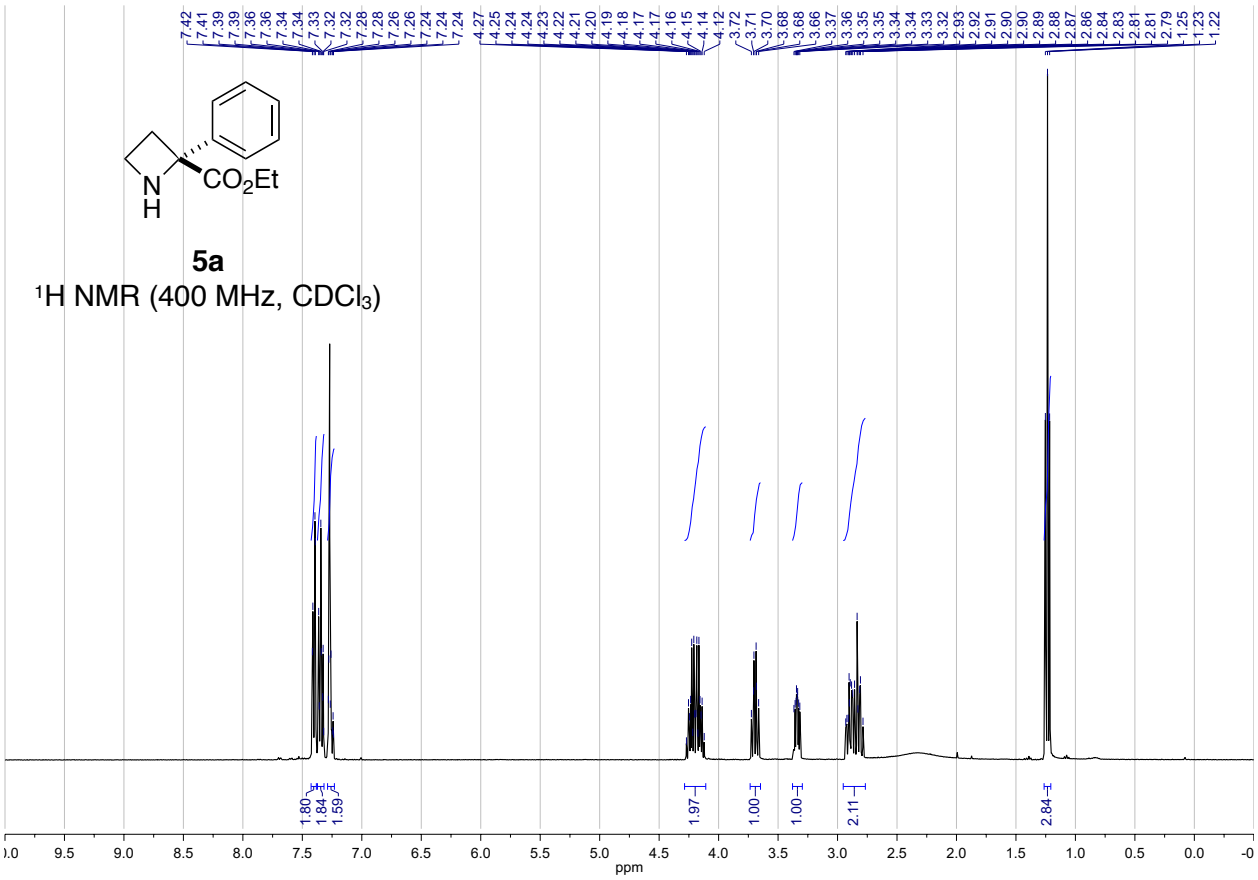


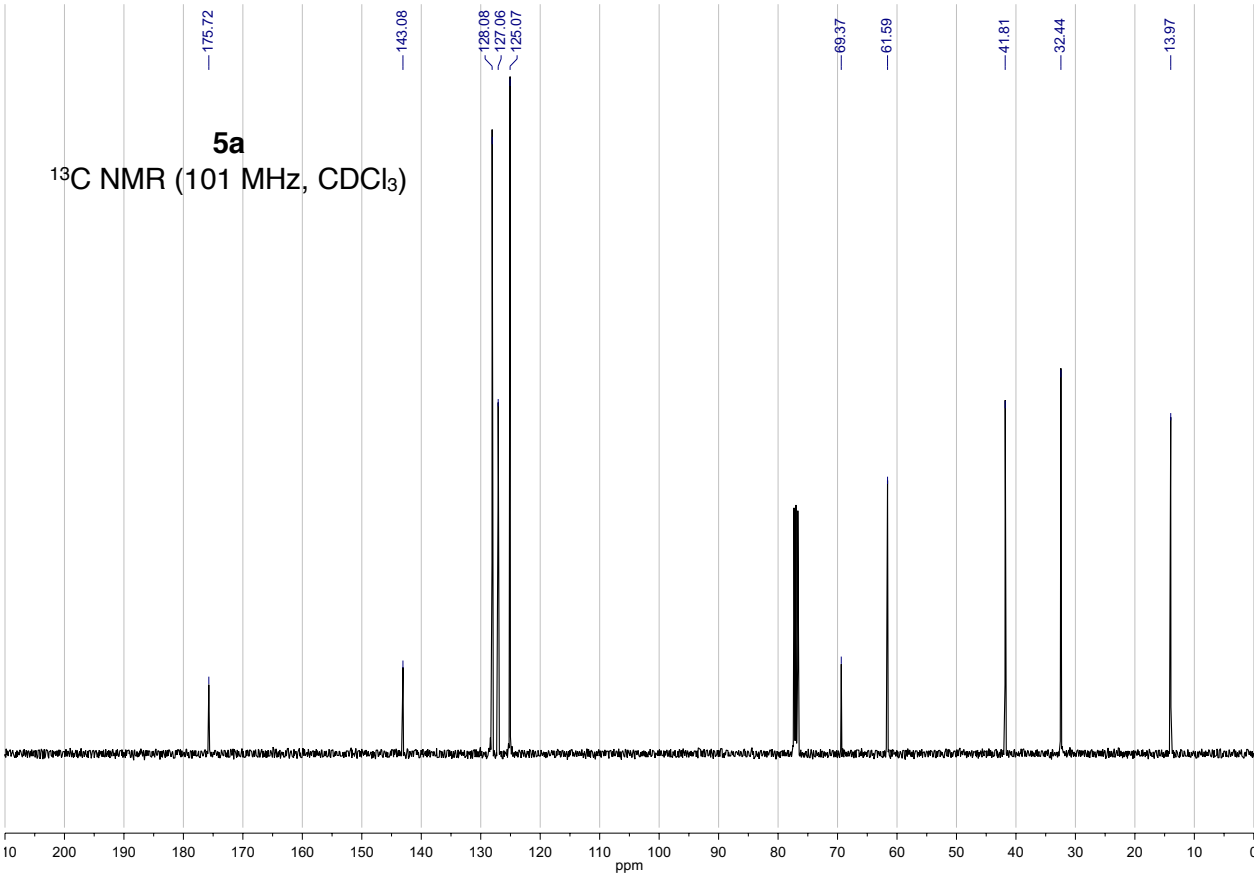
2

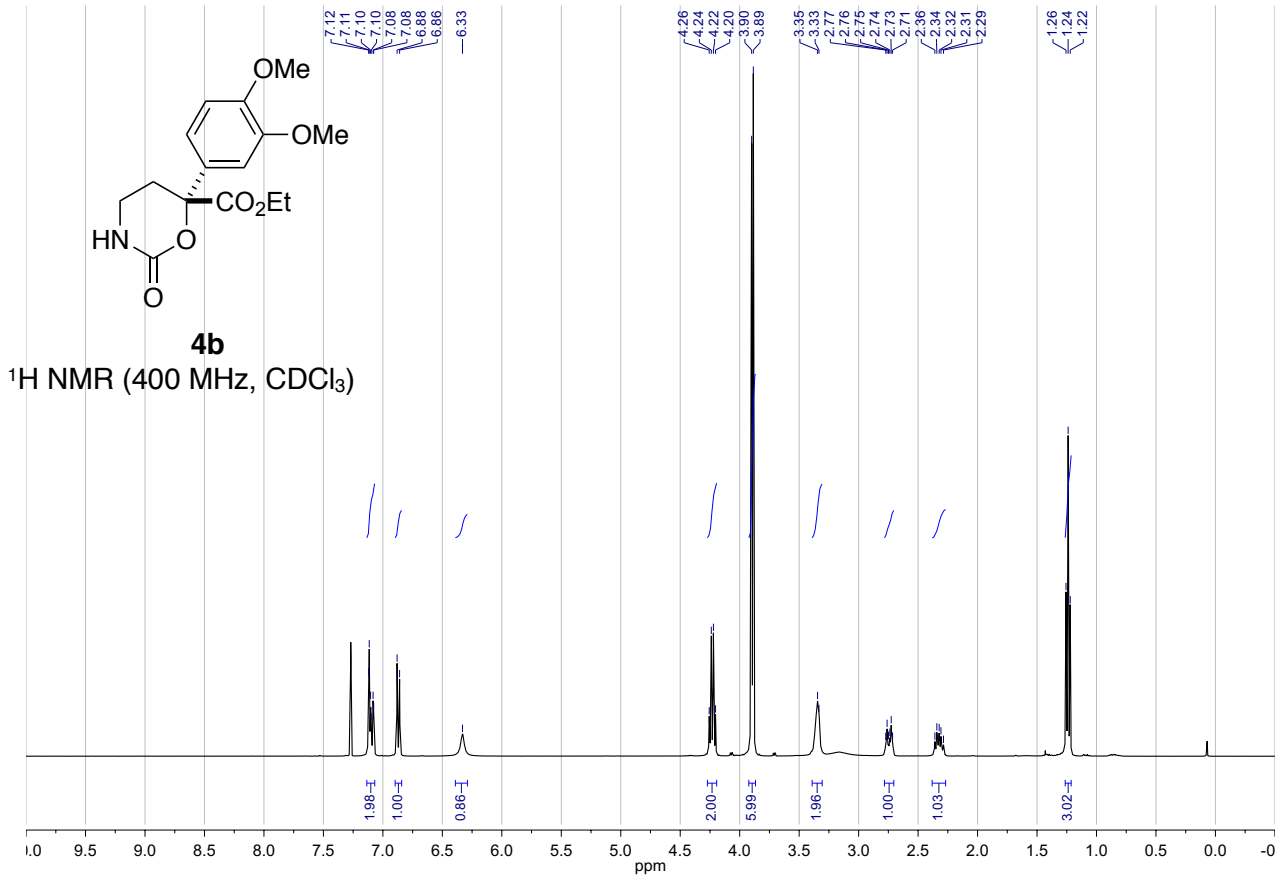
^{13}C NMR (400 MHz, $CDCl_3$)

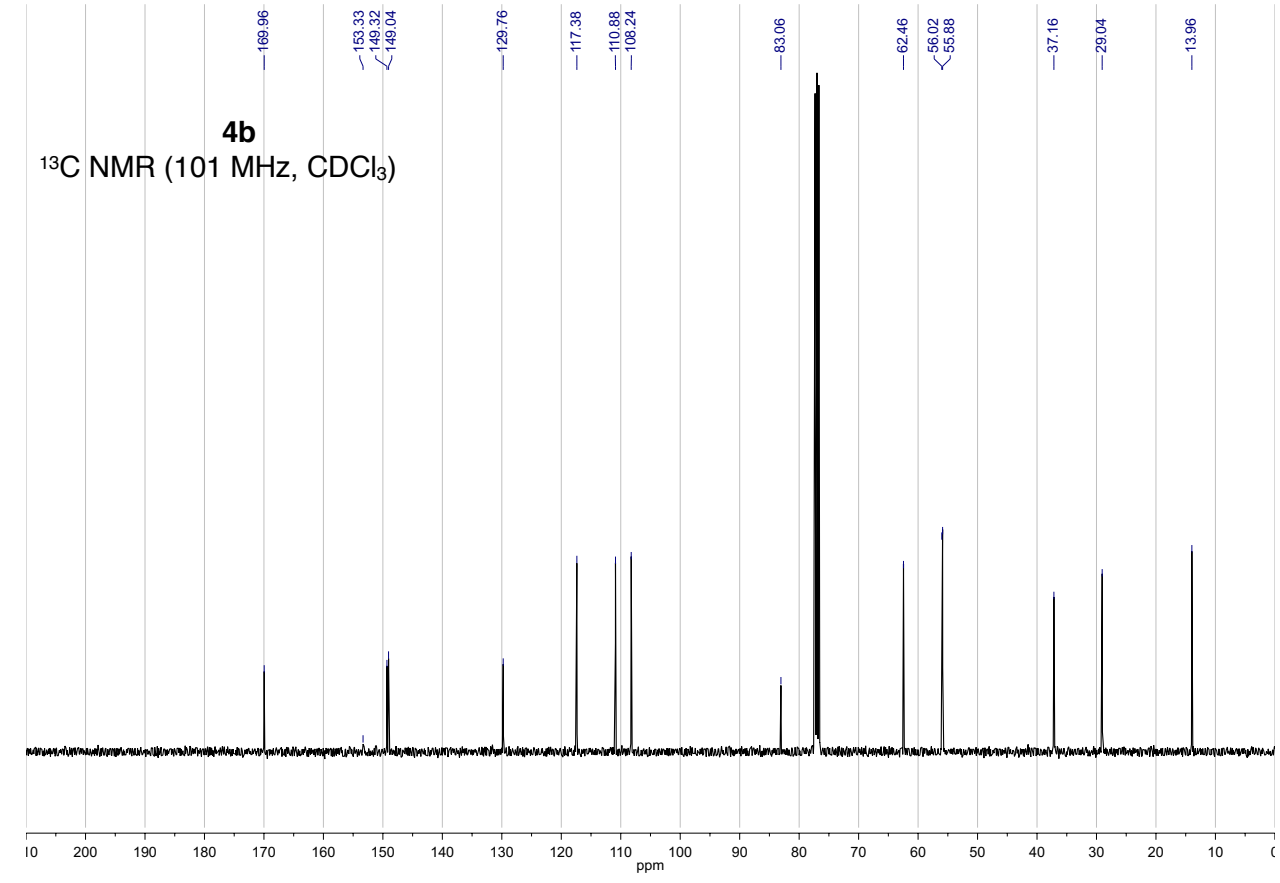

CO2Et
HN
O
O
4a
1H NMR (400 MHz, CDCl3)
1.97
2.98
0.97
2.00
2.09
1.02
1.03
3.03
ppm

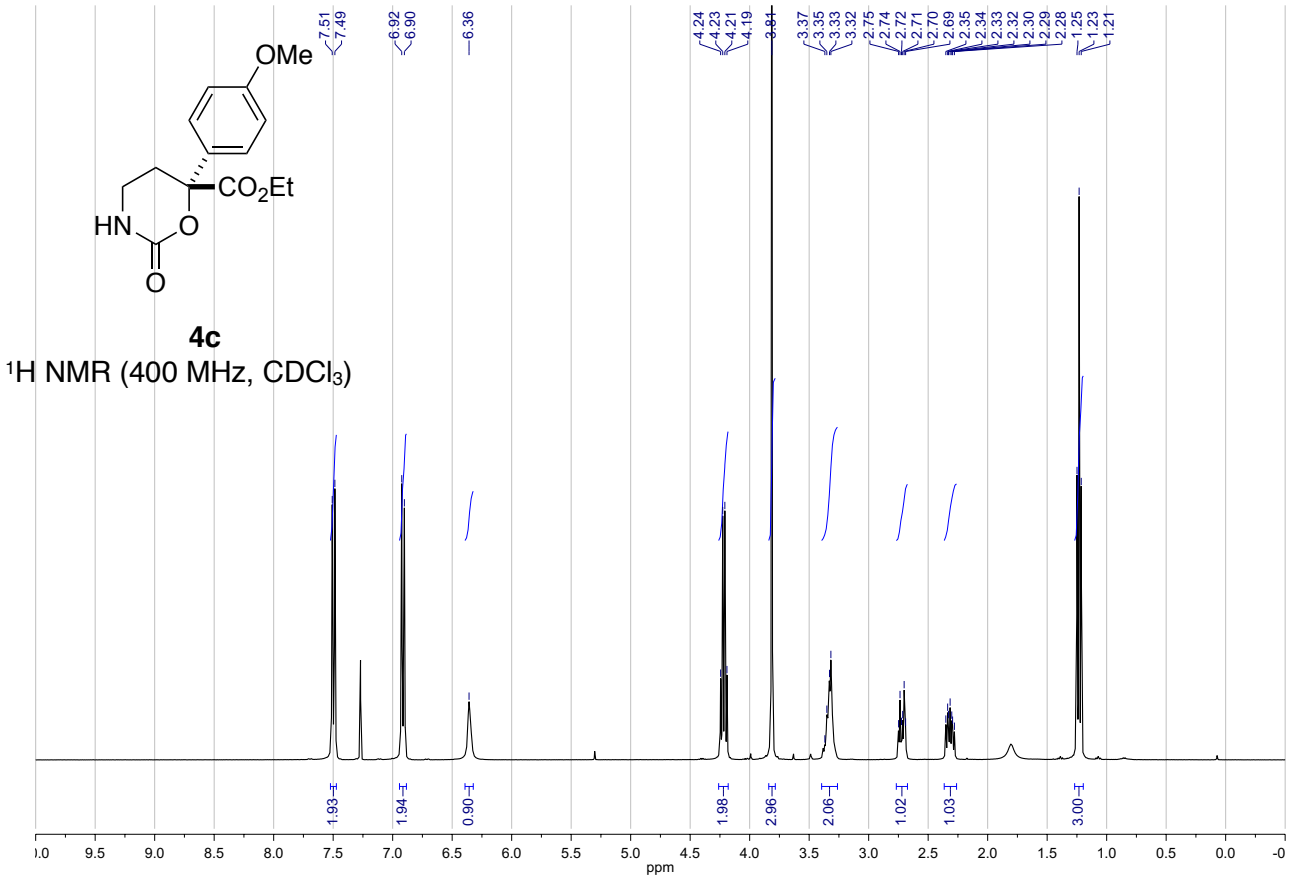

169.86
153.12
137.44
128.72
128.66
124.94
83.24
62.44
37.07
29.18
13.91
4a
13C NMR (101 MHz, CDCl3)
ppm


7.42 7.41 7.39 7.39 7.36 7.36 7.34 7.34 7.33 7.32 7.32 7.28 7.28 7.26 7.26 7.24 7.24 7.24
4.27 4.25 4.24 4.24 4.23 4.22 4.21 4.20 4.19 4.18 4.17 4.17 4.16 4.15 4.14 4.12
3.72 3.71 3.70 3.68 3.68 3.66 3.37 3.36 3.35 3.35 3.34 3.34 3.33 3.32 2.93 2.92 2.91 2.90 2.90 2.89 2.88 2.87 2.86 2.84 2.83 2.81 2.81 2.79 1.25 1.23 1.22
N
H
CO2Et
5a
1H NMR (400 MHz, CDCl3)
1.80 1.84 1.59 1.97 1.00 1.00 2.11 2.84
ppm


175.72 143.08 128.08 127.06 125.07 69.37 61.59 41.81 32.44 13.97
5a
13C NMR (101 MHz, CDCl3)
ppm

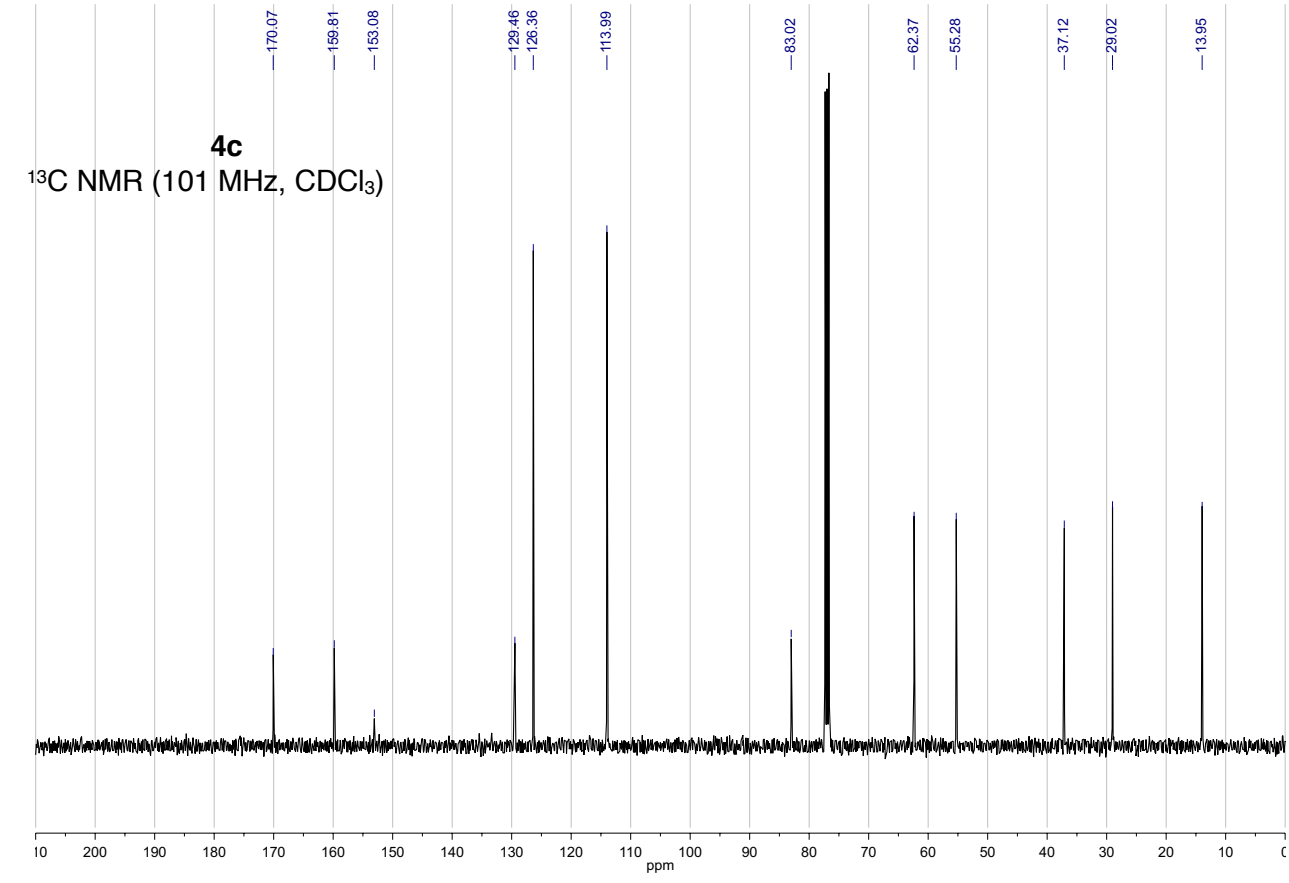

OMe
OMe
CO2Et
HN
O
O
4b
1H NMR (400 MHz, CDCl3)
ppm


4b
13C NMR (101 MHz, CDCl3)
ppm



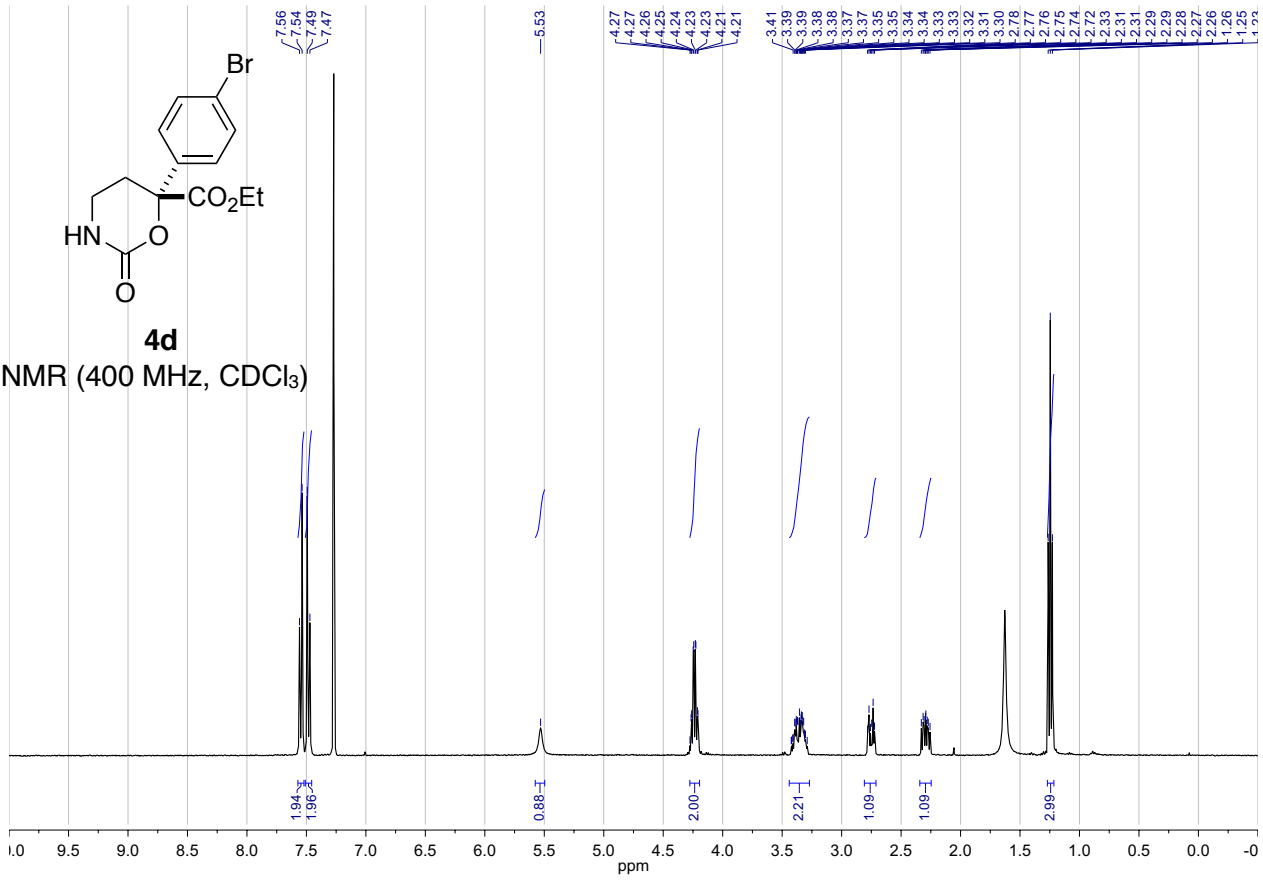
4c

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



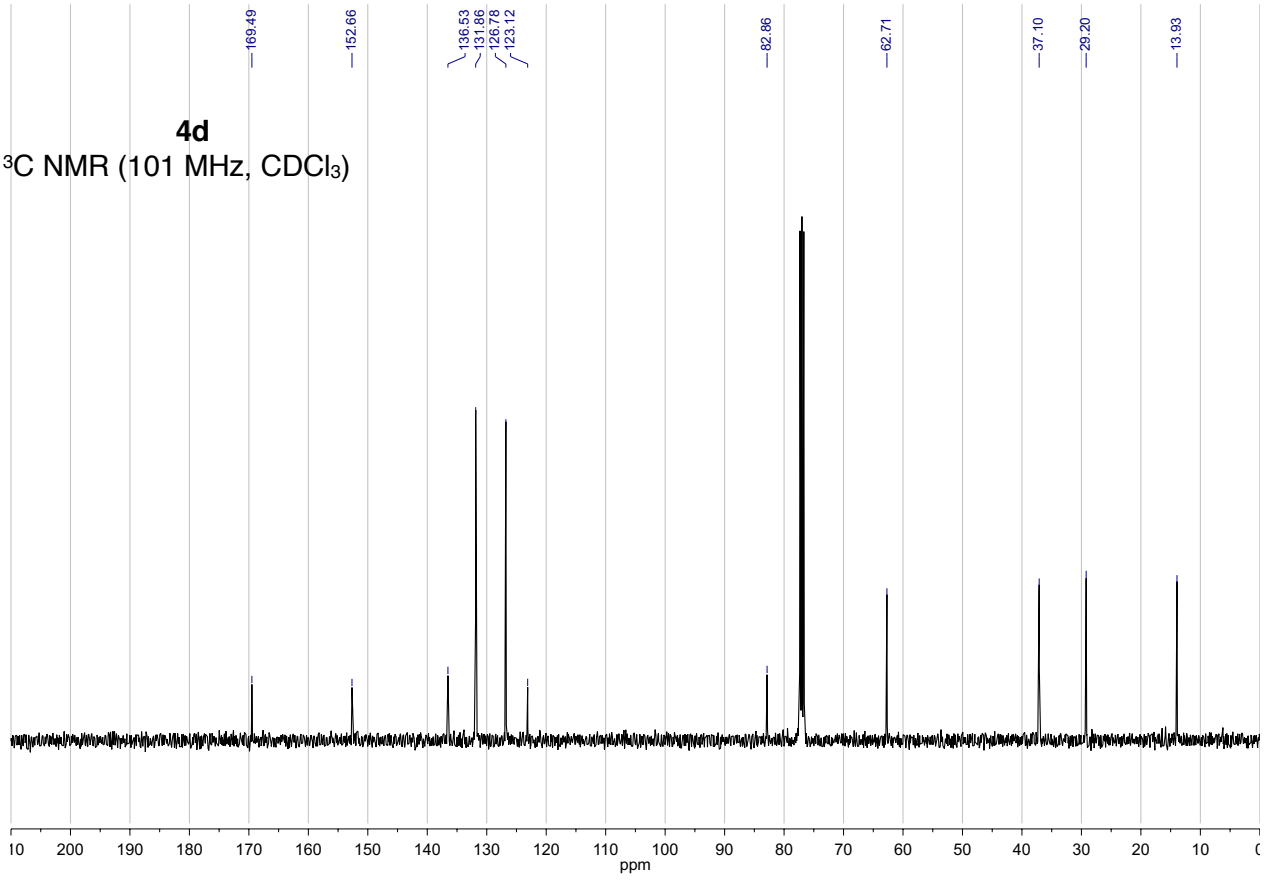
4c

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



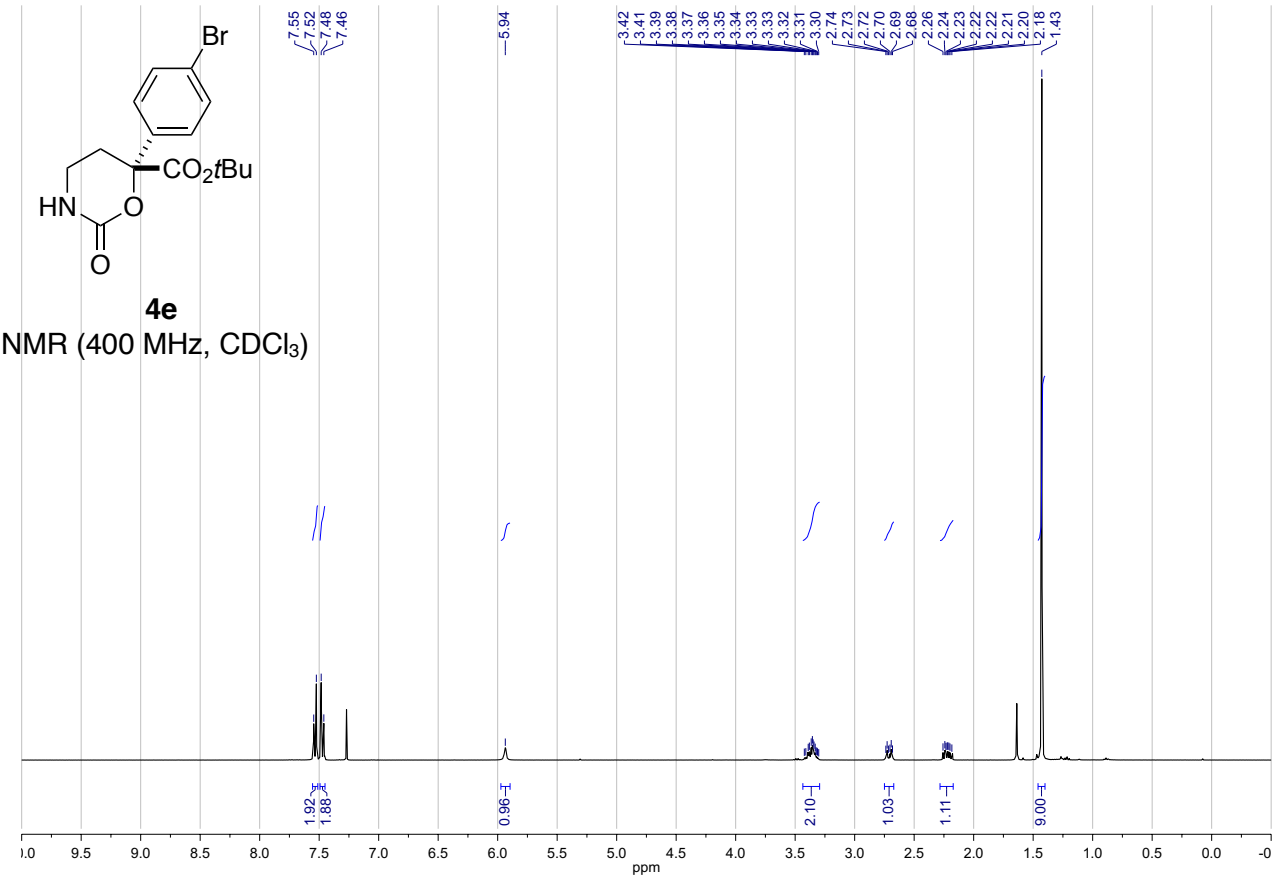
4d

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



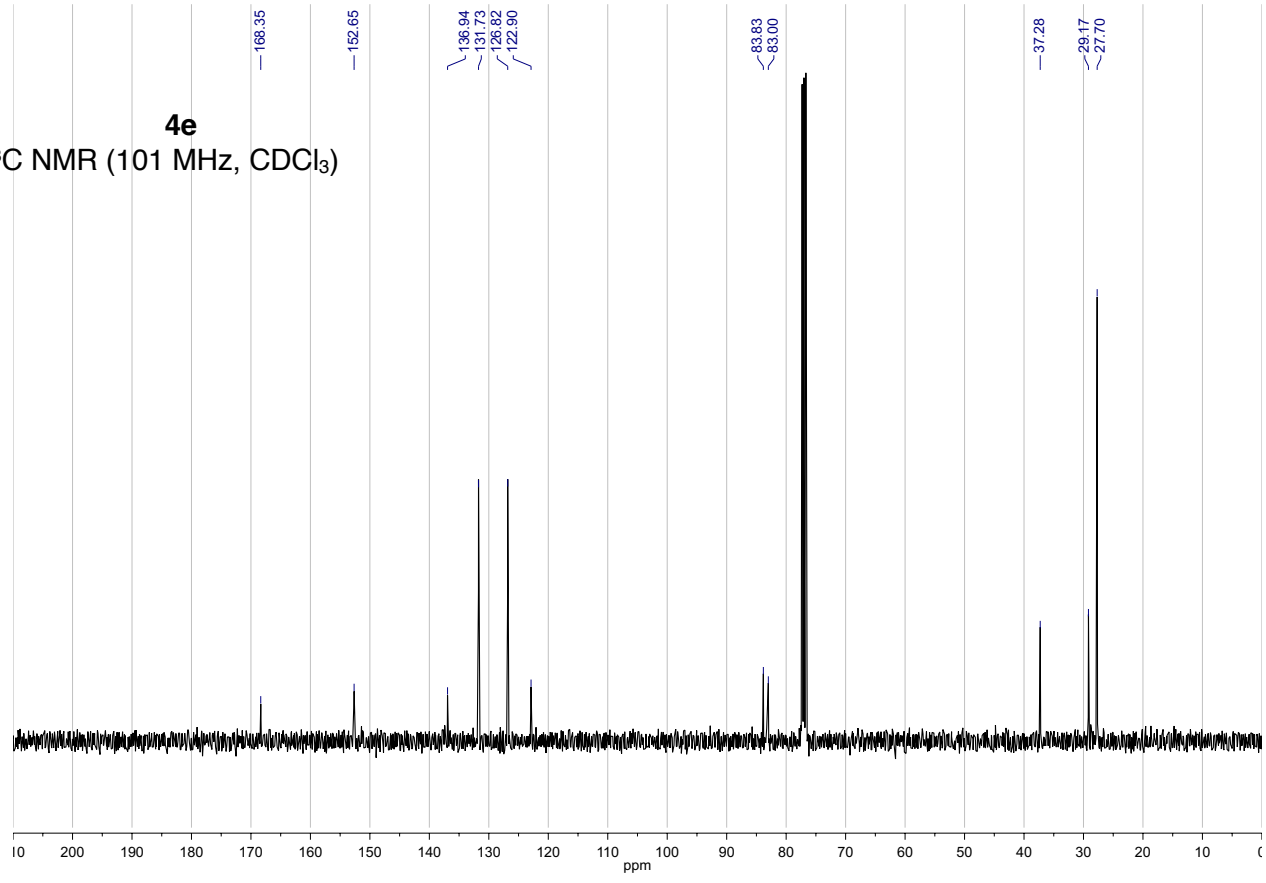
4d

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



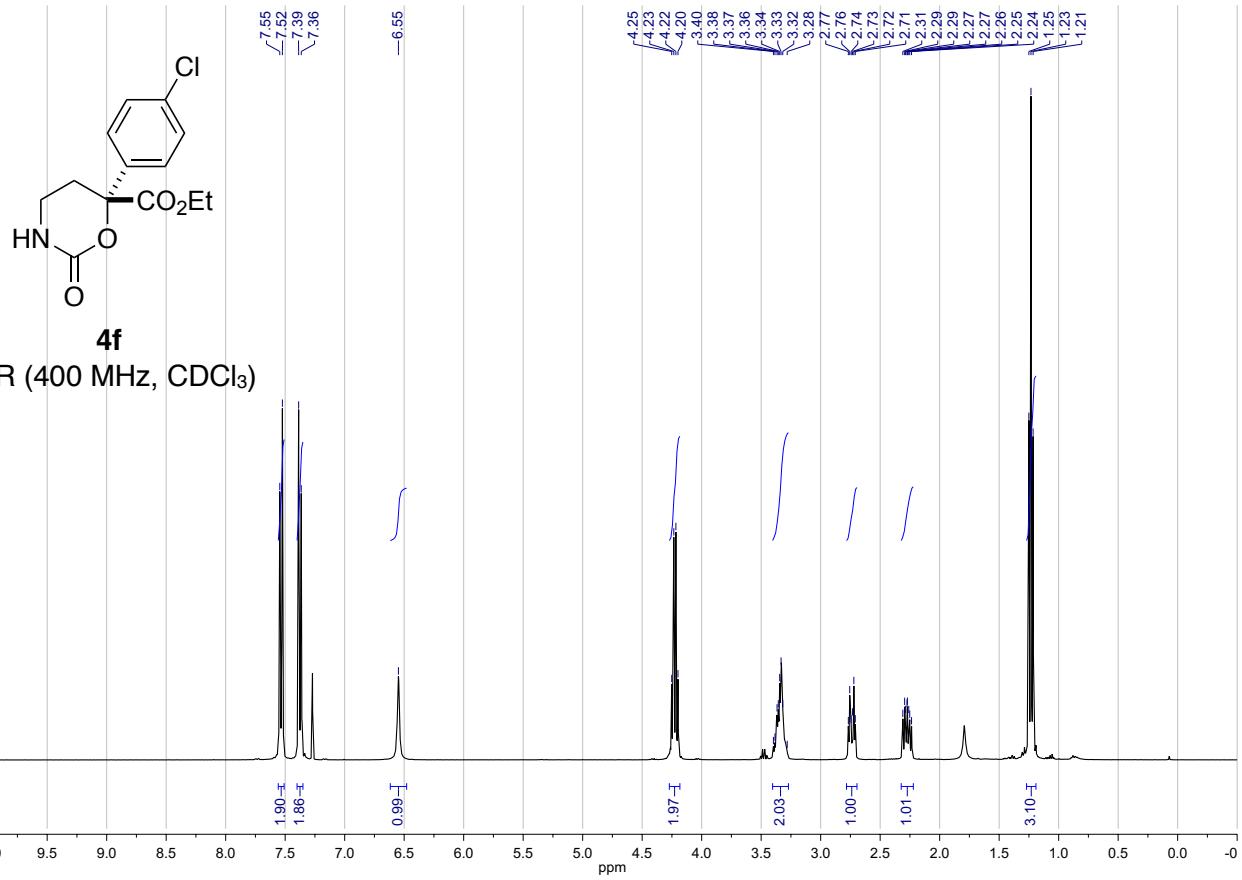
4e

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



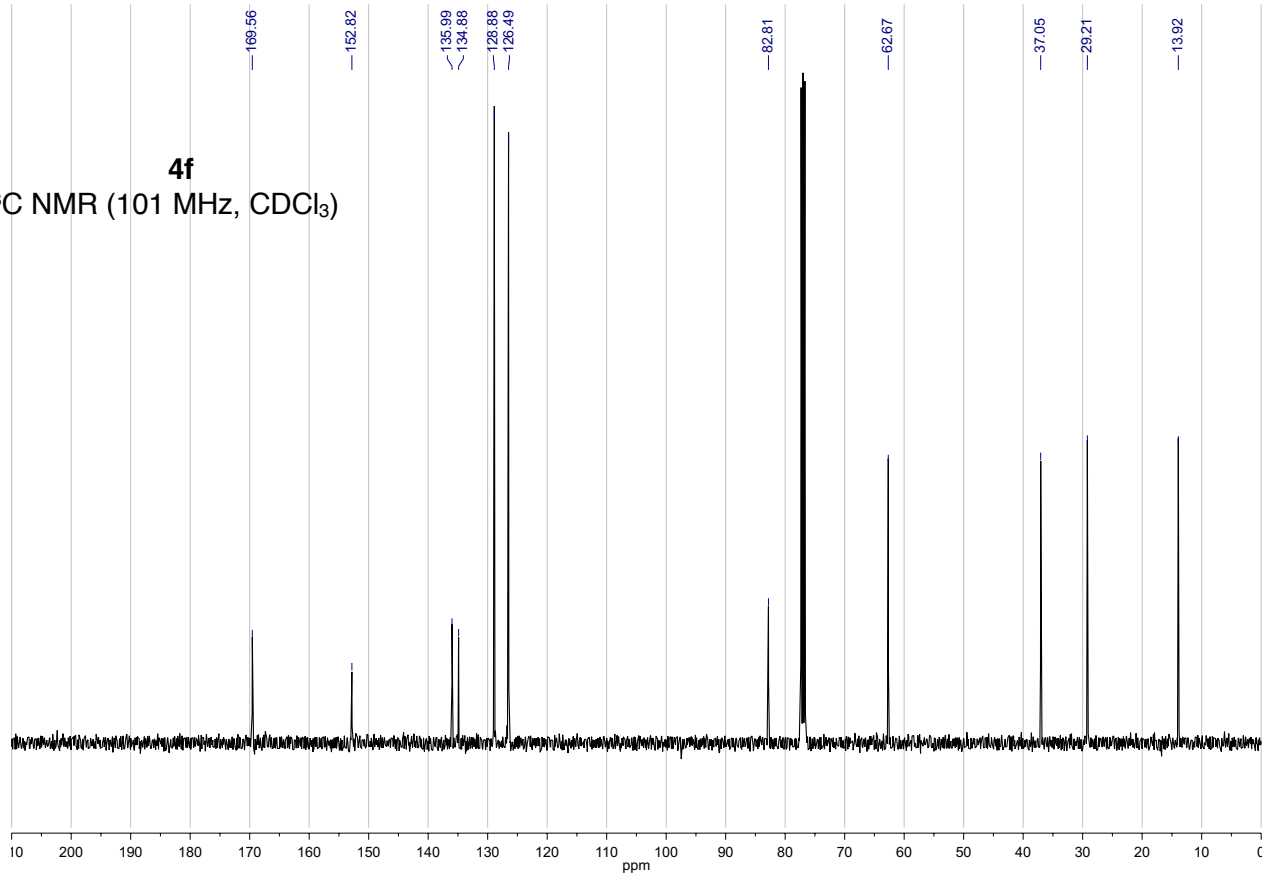
4e

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



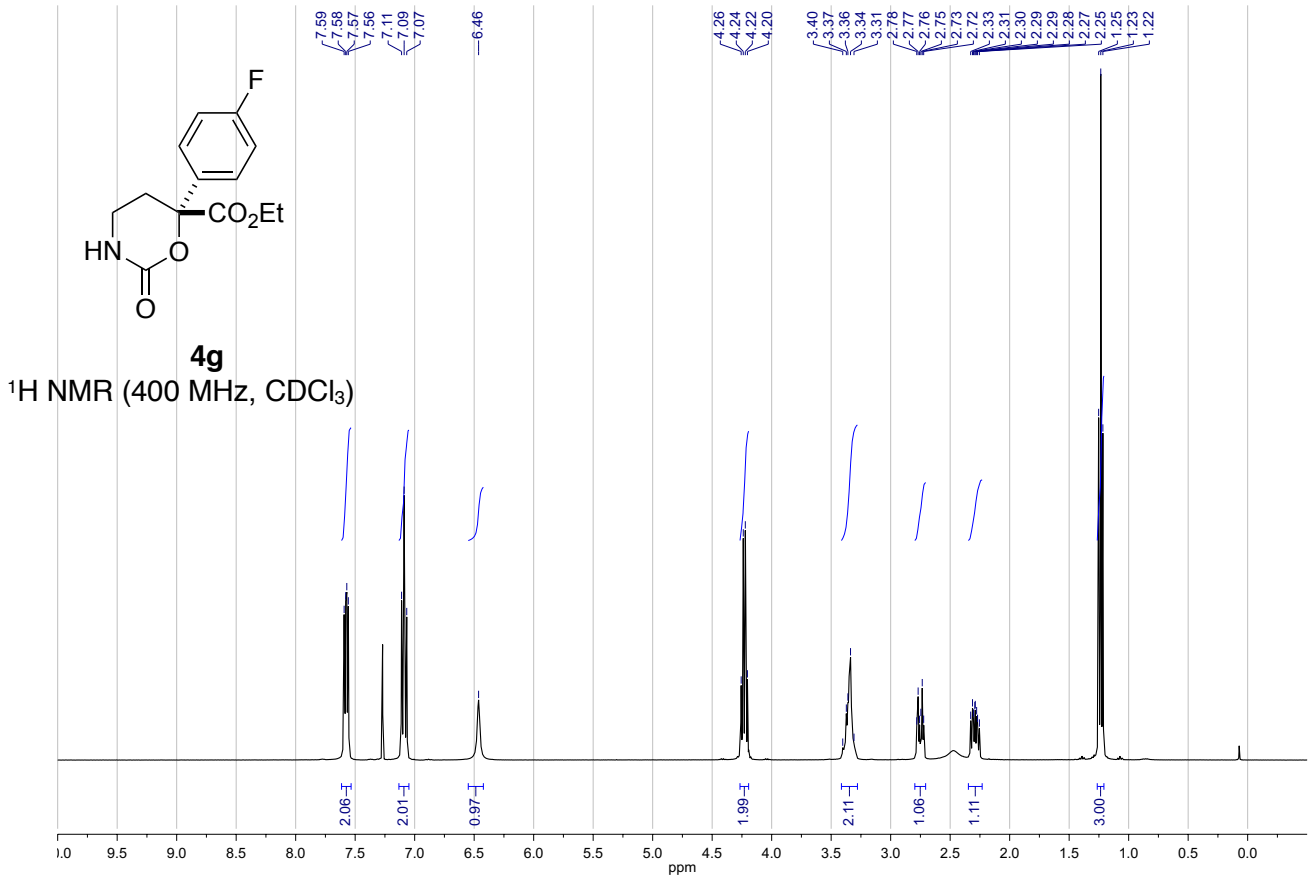
4f

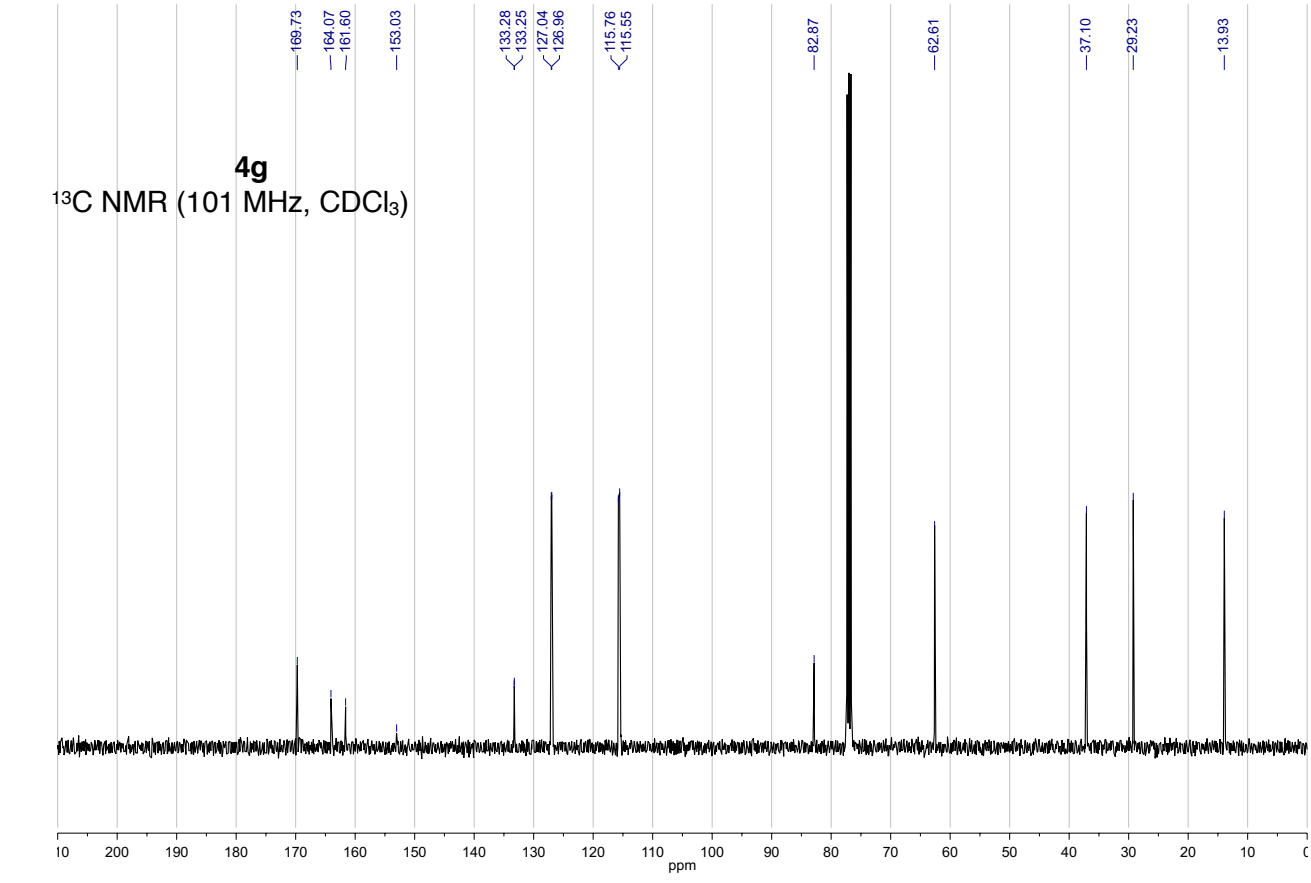
^{1}H NMR (400 MHz, $CDCl_3$)

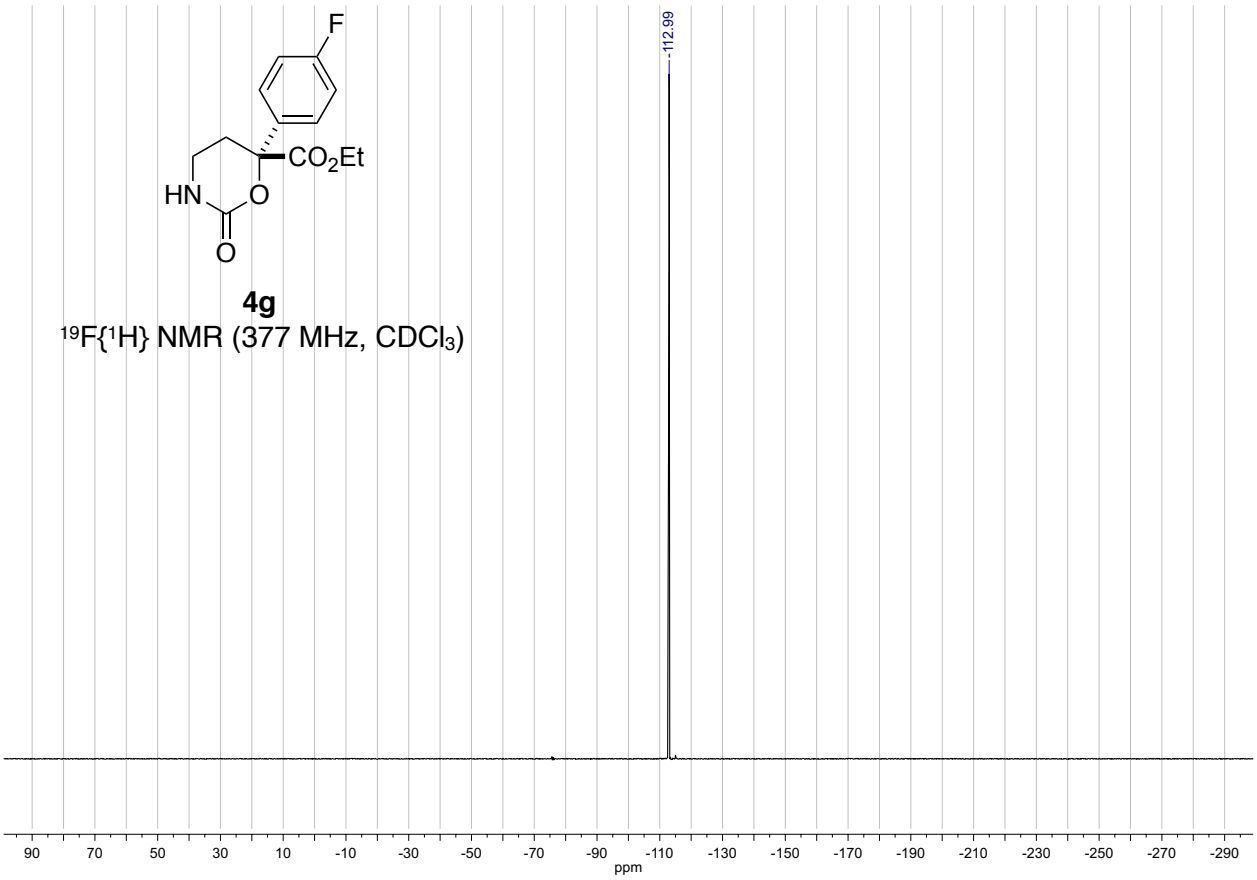


4f

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

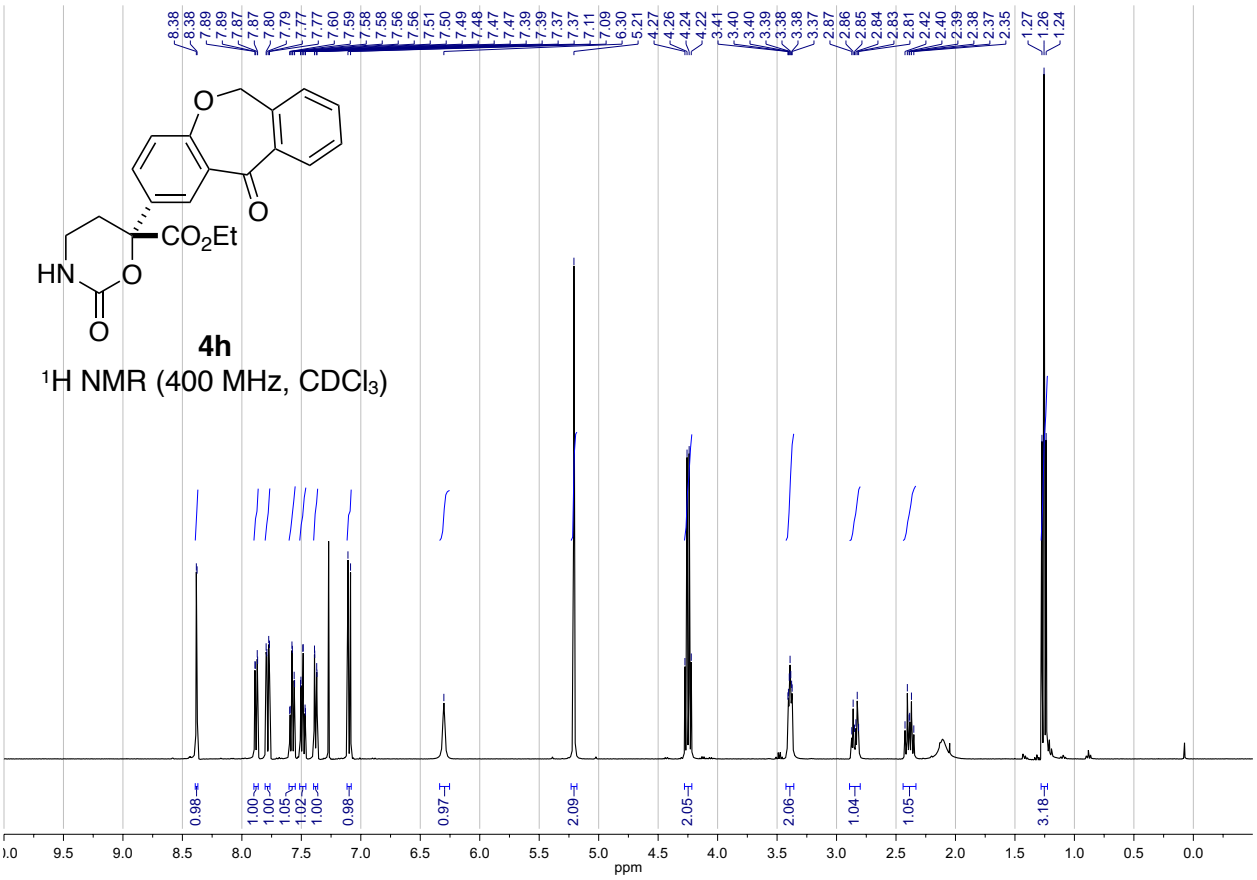

F
CO2Et
HN
O
O
4g
1H NMR (400 MHz, CDCl3)
7.59
7.58
7.57
7.56
7.11
7.09
7.07
6.46
4.26
4.24
4.22
4.20
3.40
3.37
3.36
3.34
3.31
2.78
2.77
2.76
2.75
2.73
2.72
2.33
2.31
2.30
2.29
2.29
2.28
2.27
2.25
1.25
1.23
1.22
2.06
2.01
0.97
1.99
2.11
1.06
1.11
3.00
ppm

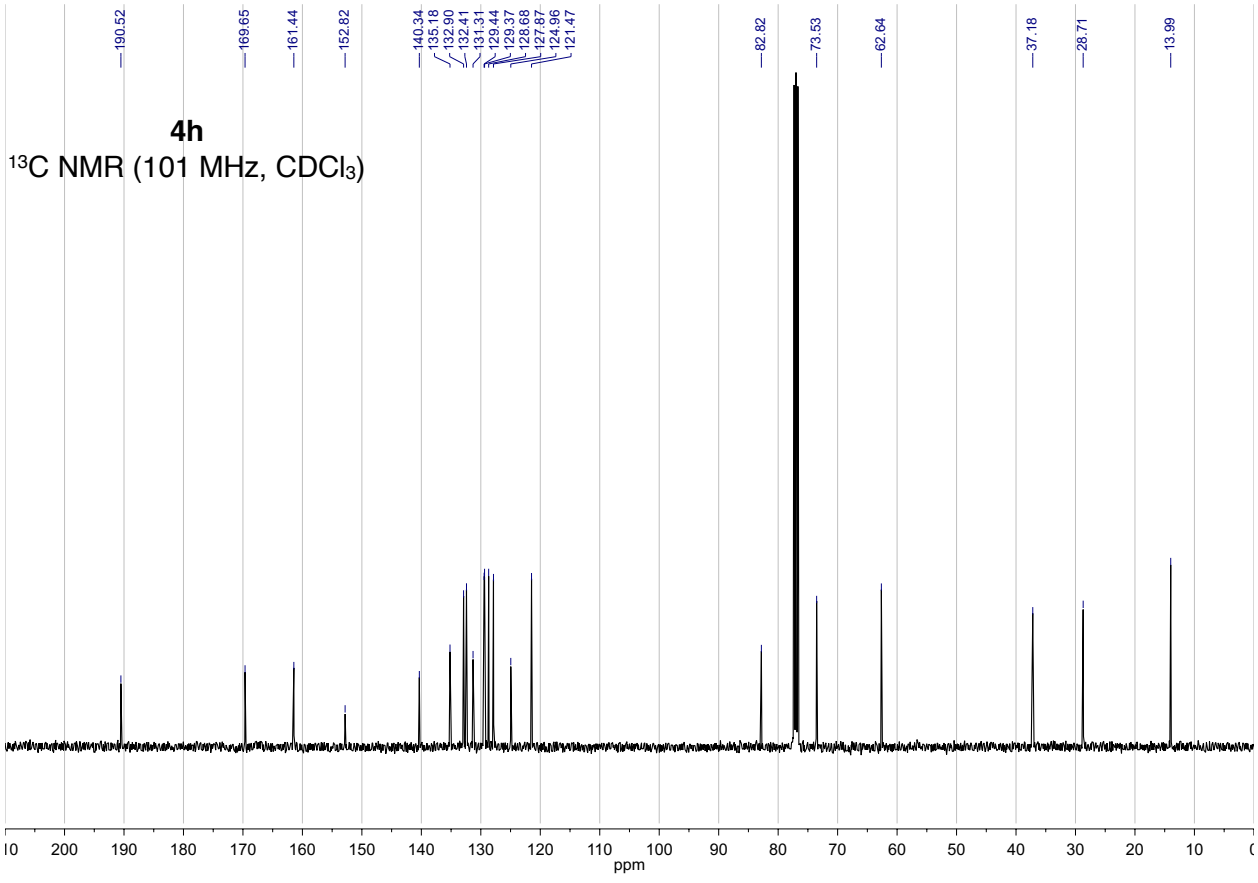

4g
13C NMR (101 MHz, CDCl3)
169.73
164.07
161.60
153.03
133.28
133.25
127.04
126.96
115.76
115.55
82.87
62.61
37.10
29.23
13.93
ppm

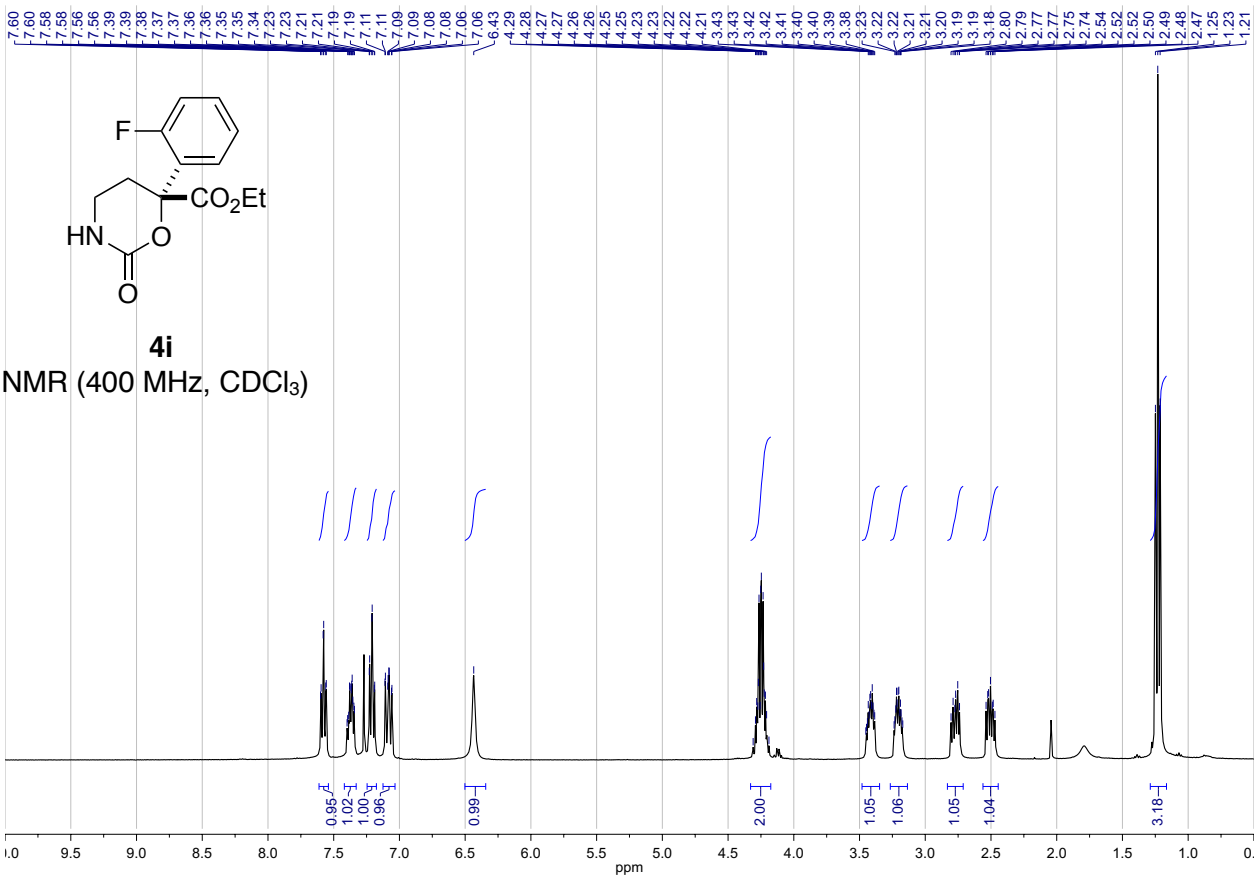


4g

$^{19}F\{^{1}H\}$ NMR (377 MHz, $CDCl_3$)

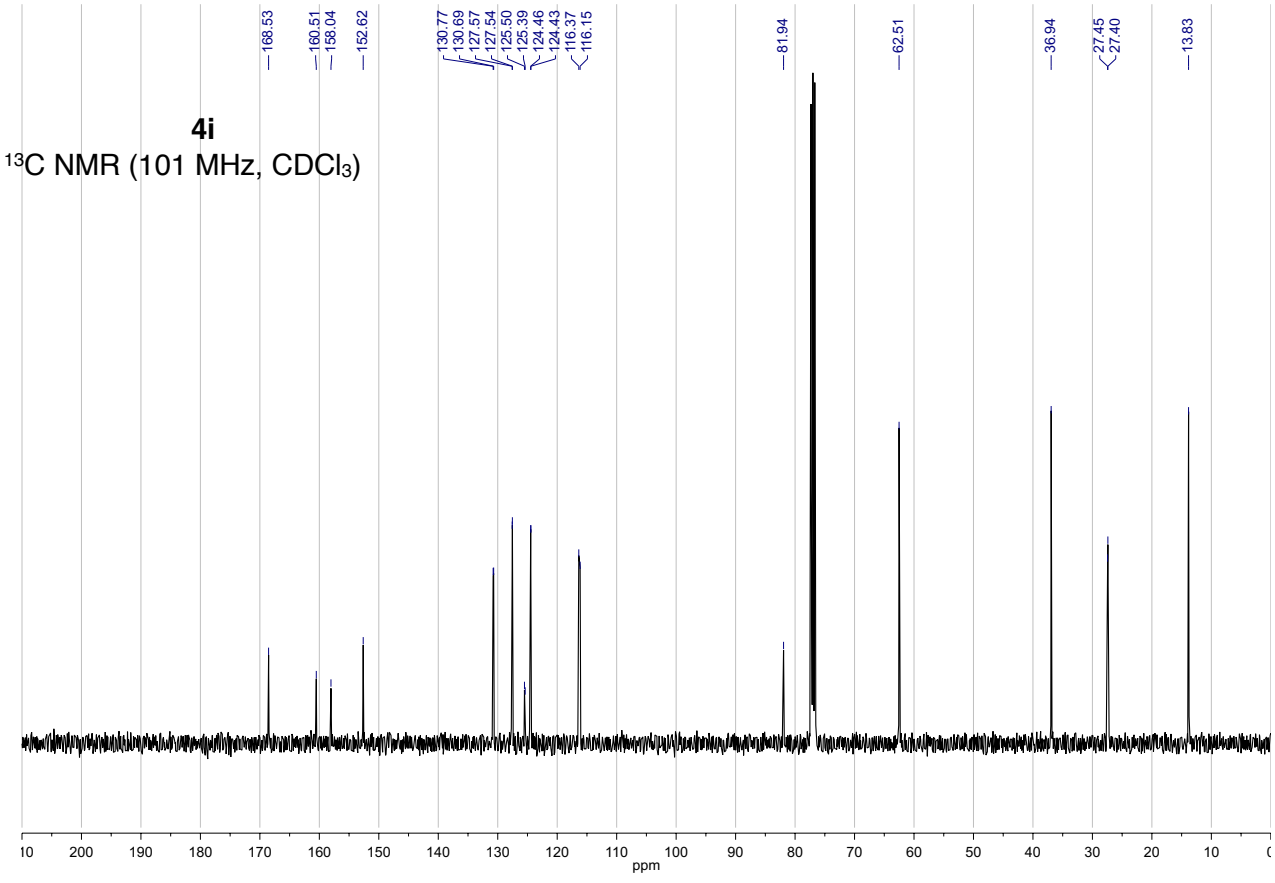

8.38
8.38
7.89
7.89
7.87
7.87
7.80
7.79
7.77
7.77
7.60
7.59
7.58
7.58
7.56
7.56
7.51
7.50
7.49
7.48
7.47
7.47
7.39
7.39
7.37
7.37
7.11
7.09
6.30
5.21
4.27
4.26
4.24
4.22
3.41
3.40
3.40
3.39
3.38
3.38
3.37
2.87
2.86
2.85
2.84
2.83
2.81
2.42
2.40
2.39
2.38
2.37
2.35
1.27
1.26
1.24
O
O
CO2Et
HN
O
O
4h
1H NMR (400 MHz, CDCl3)
0.98
1.00
1.00
1.05
1.02
1.00
0.98
0.97
2.09
2.05
2.06
1.04
1.05
3.18
ppm


190.52
169.65
161.44
152.82
140.34
135.18
132.90
132.41
131.31
129.44
129.37
128.88
127.87
124.96
121.47
82.82
73.53
62.64
37.18
28.71
13.99
4h
13C NMR (101 MHz, CDCl3)
ppm



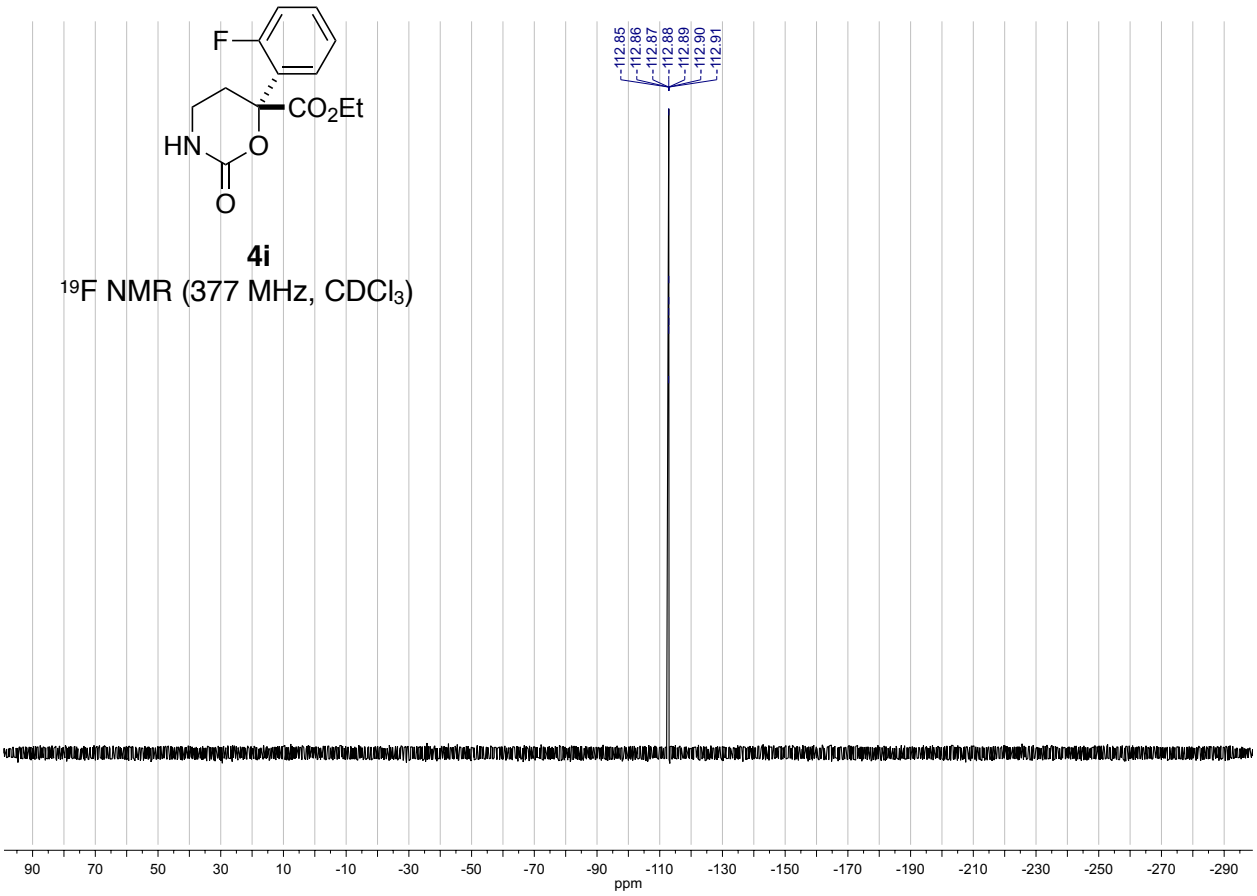
4i

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



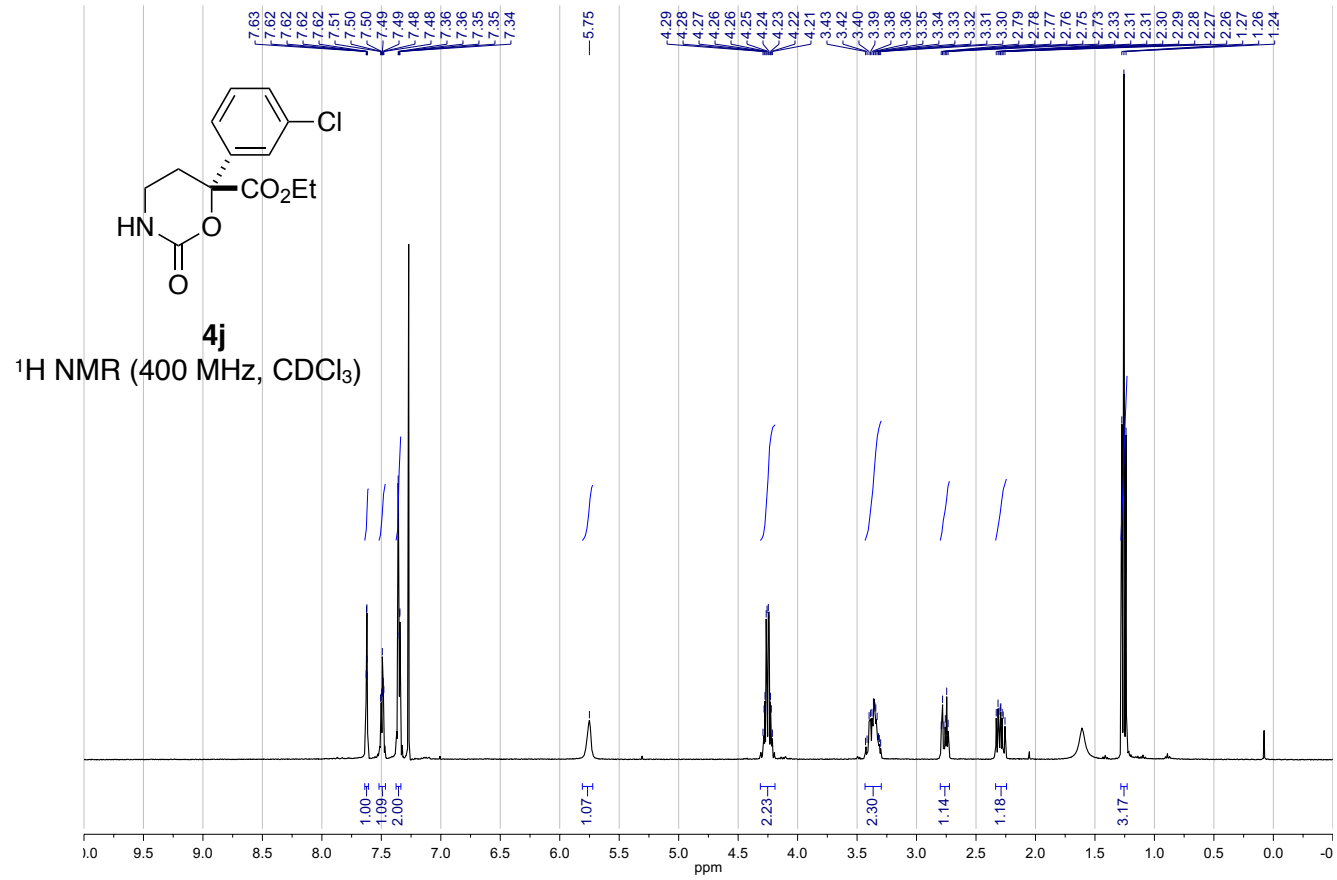
4i

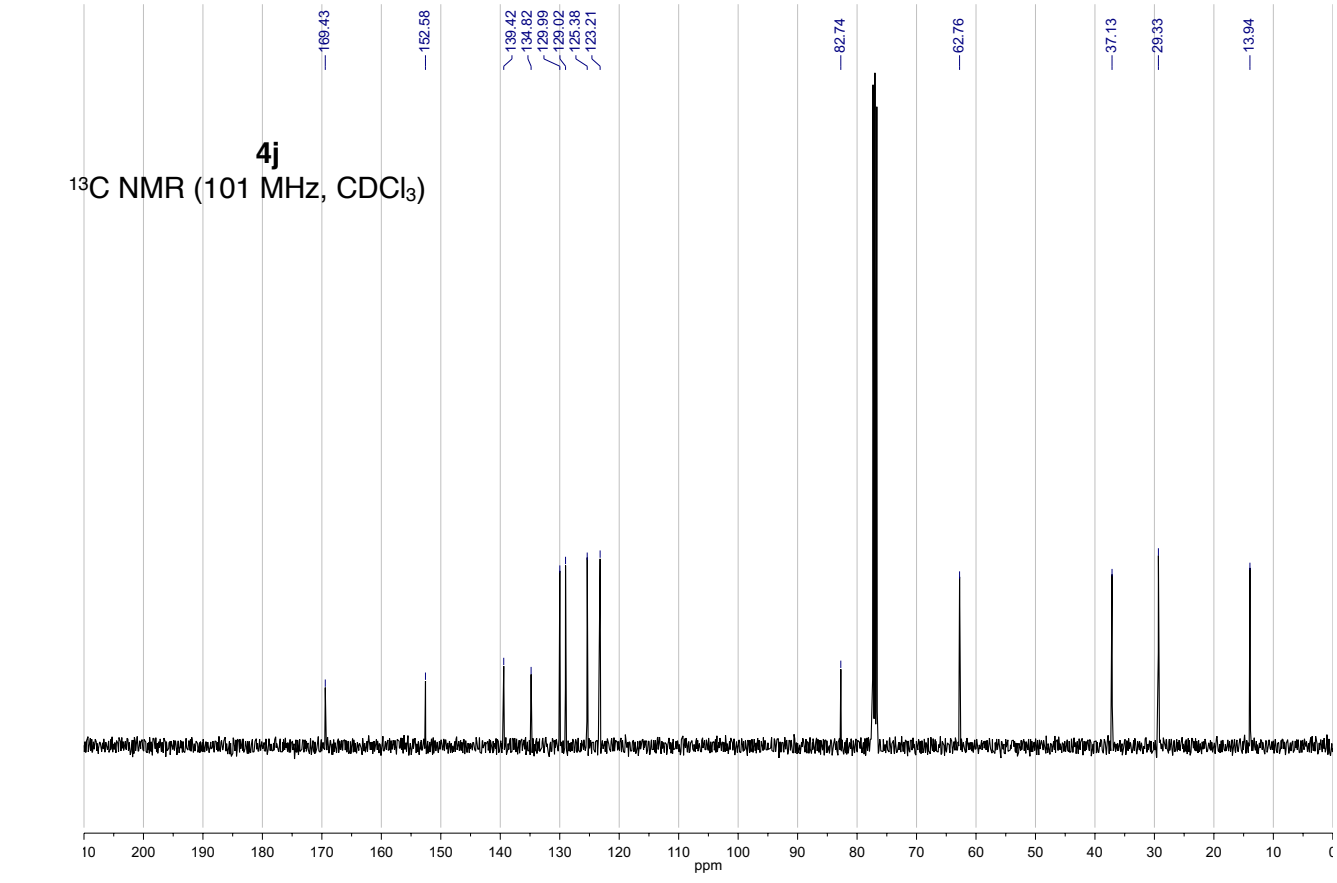
^{13}C NMR (101 MHz, $CDCl_3$)

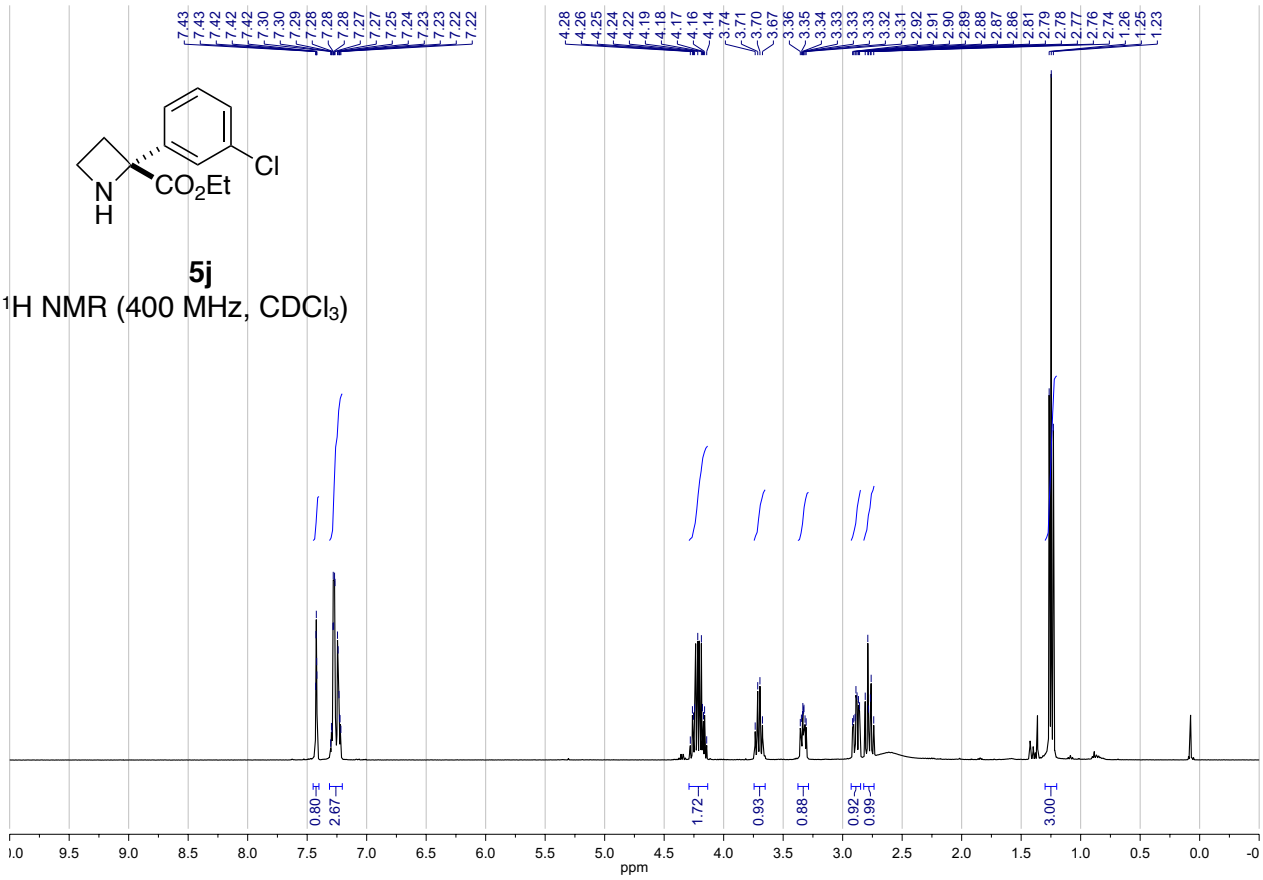


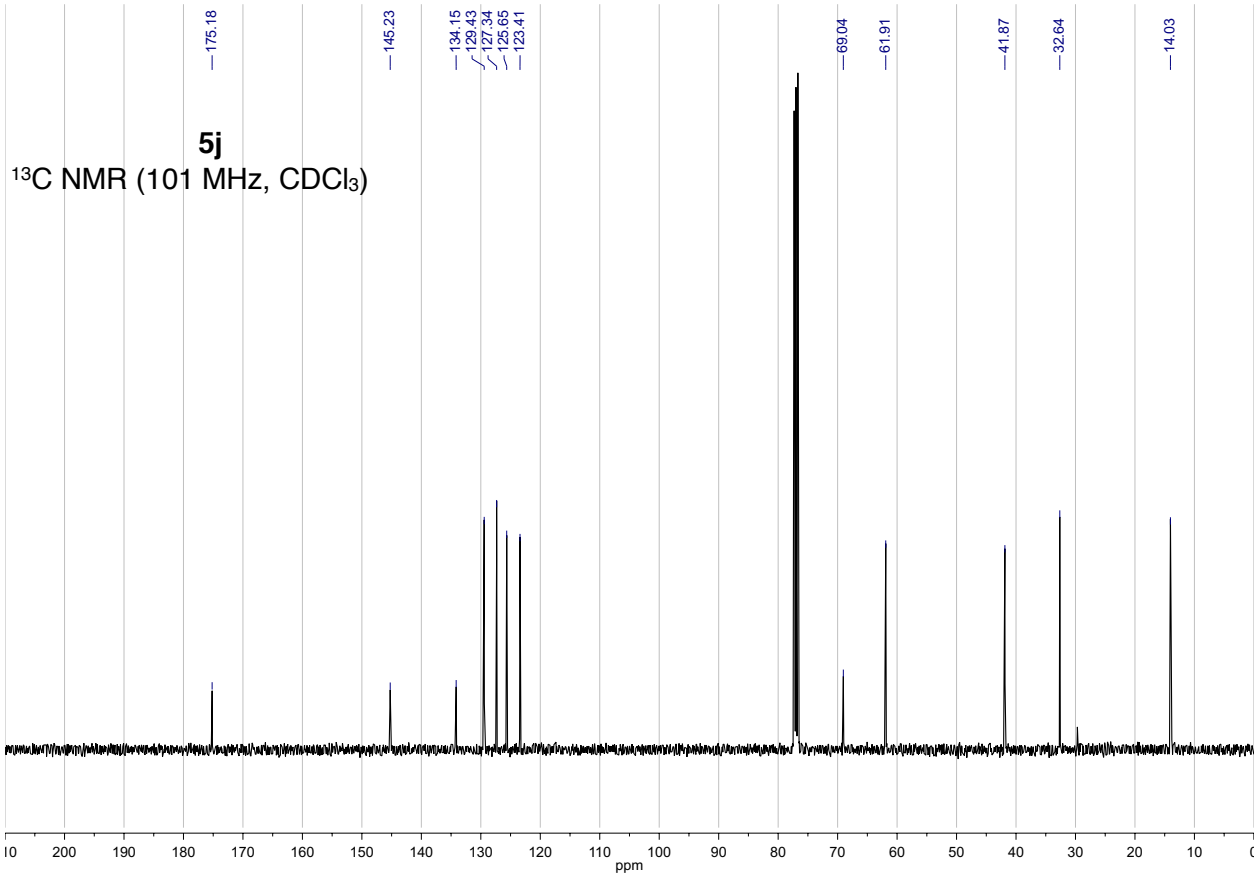
4i

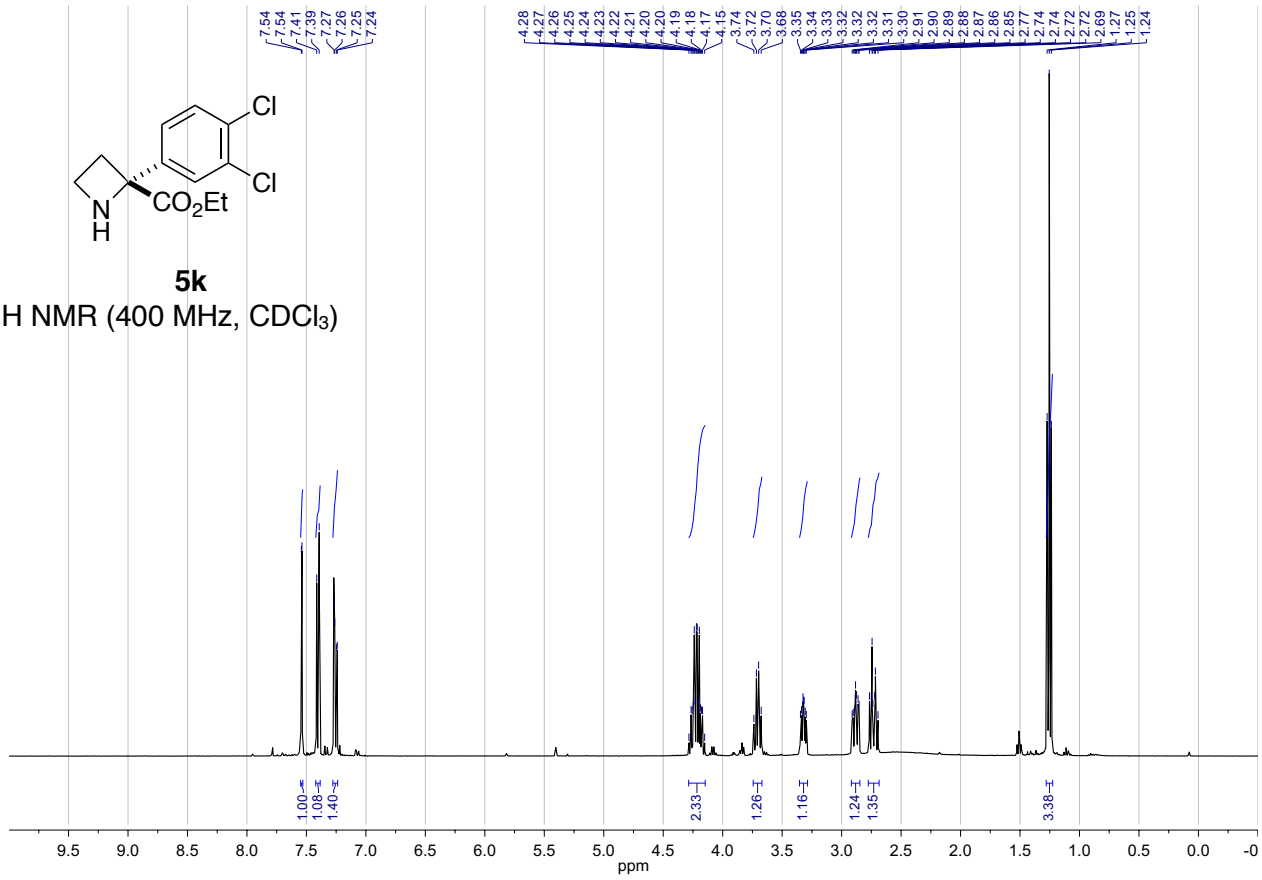
^{19}F NMR (377 MHz, $CDCl_3$)


Cl
CO2Et
HN
O
O
4j
1H NMR (400 MHz, CDCl3)
ppm


4j
13C NMR (101 MHz, CDCl3)
ppm

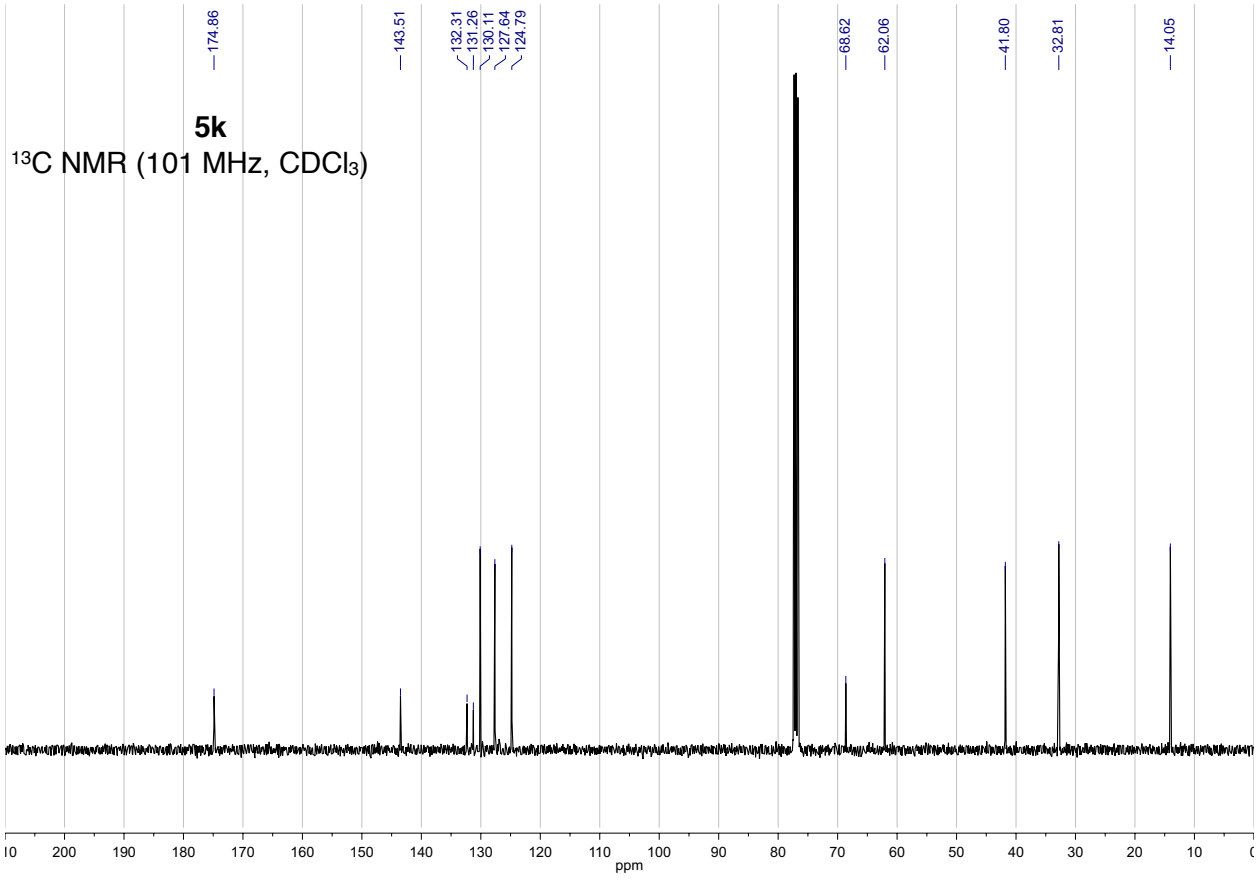

Cl
CO2Et
N
H
5j
1H NMR (400 MHz, CDCl3)
ppm


5j
13C NMR (101 MHz, CDCl3)
ppm



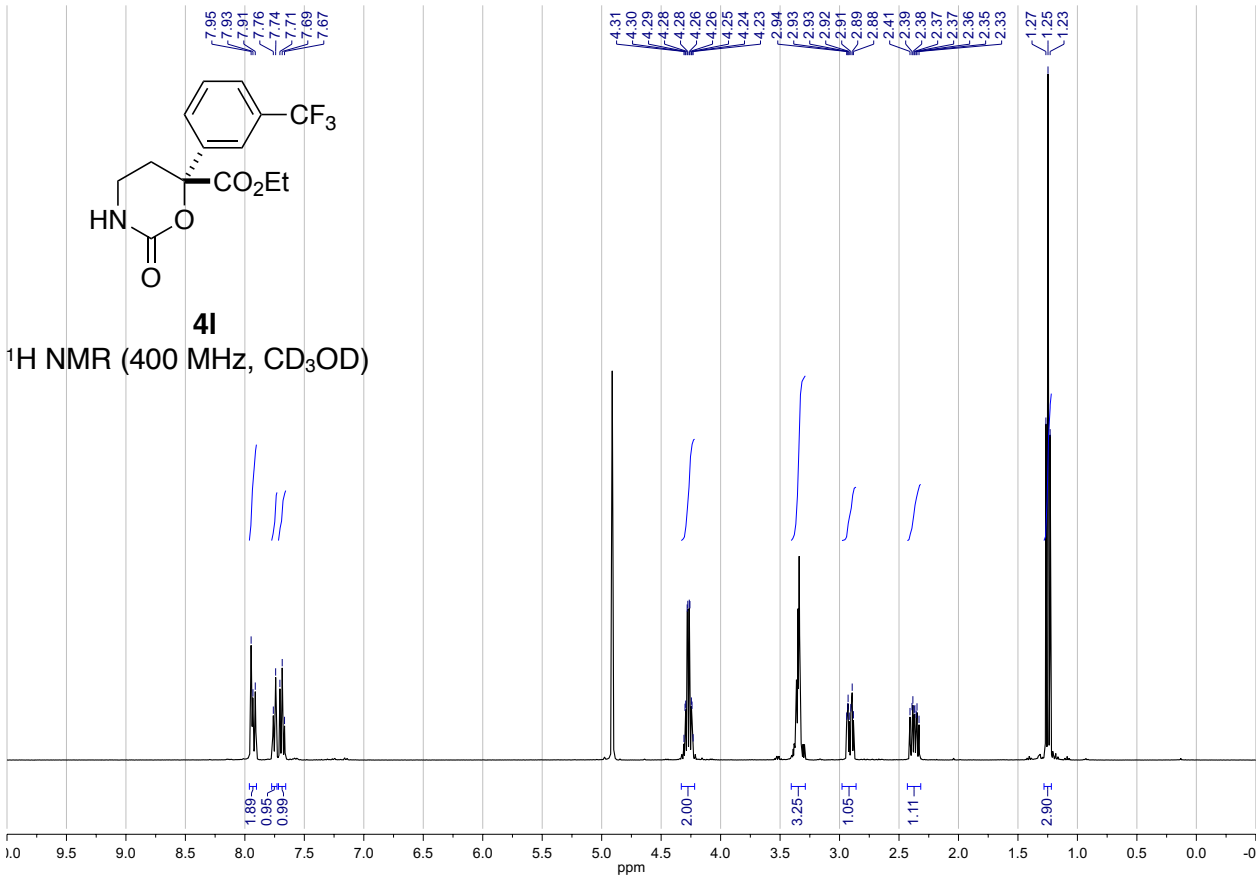
5k

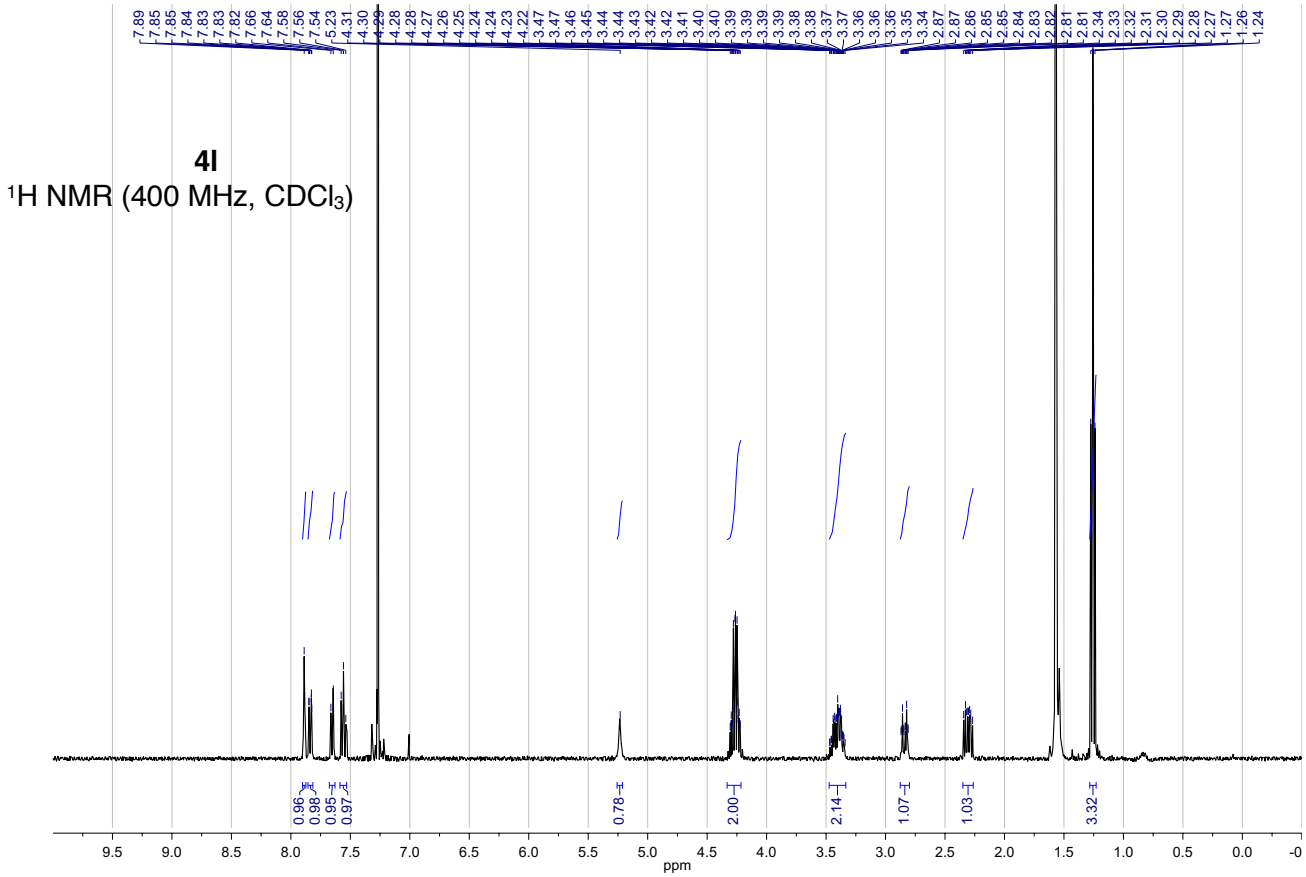
^{1}H NMR (400 MHz, $CDCl_3$)

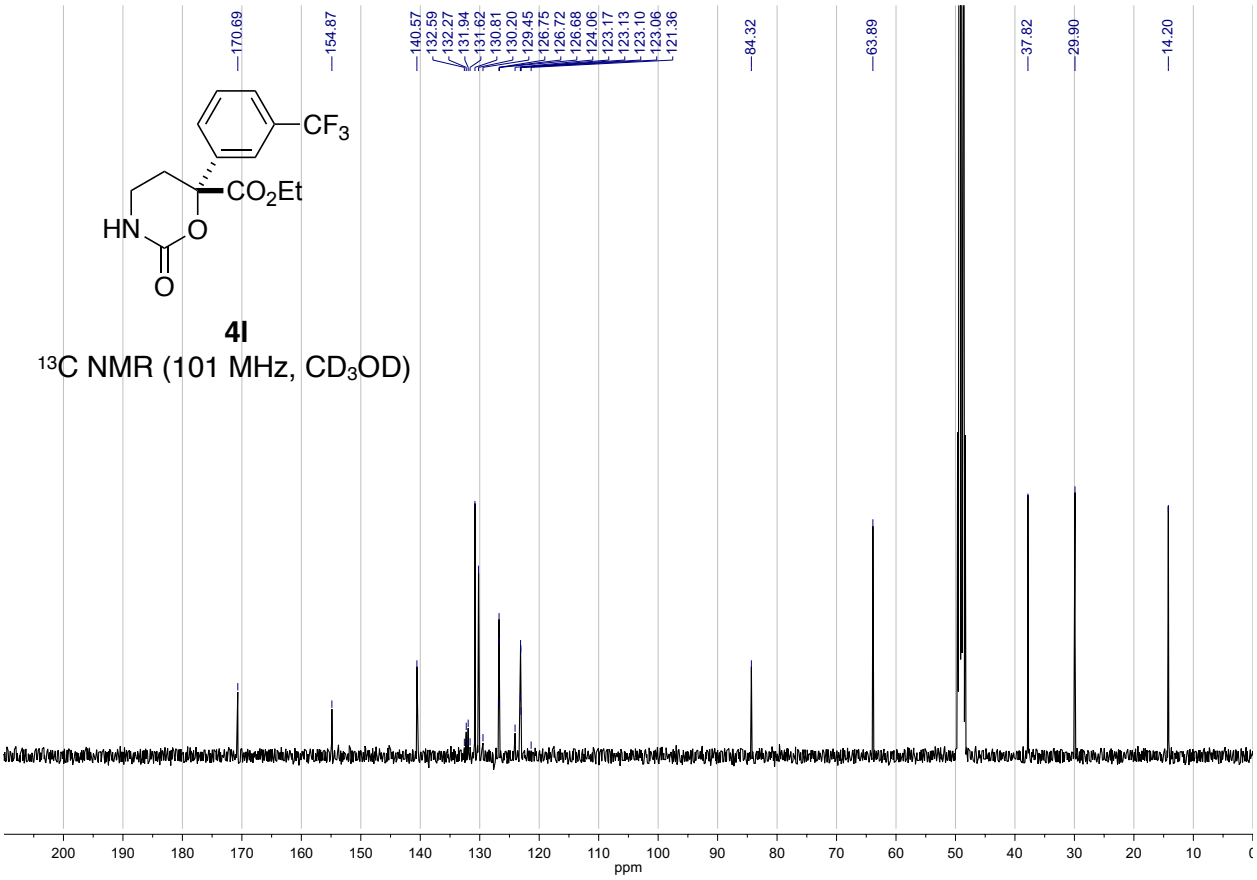


5k

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

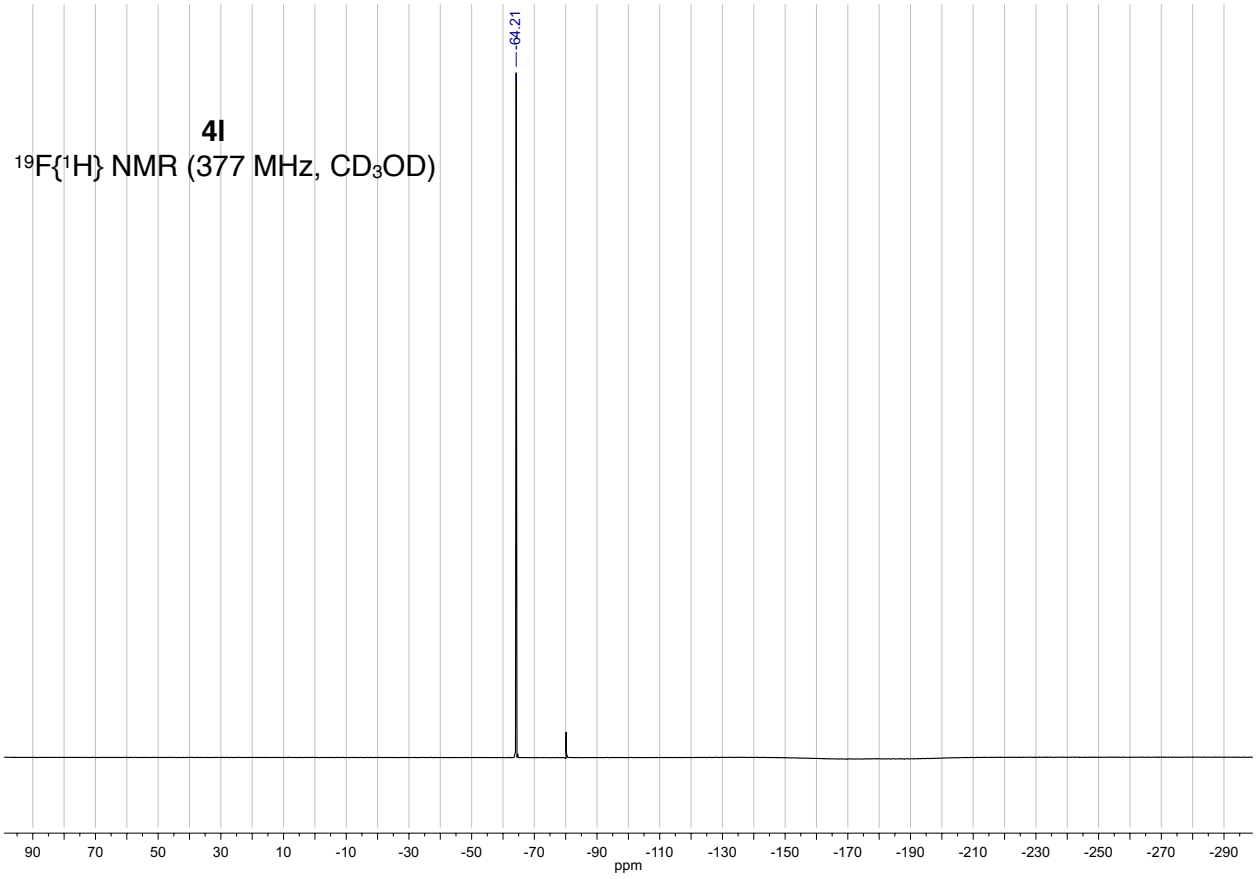

CF3
CO2Et
HN
O
O
4l
1H NMR (400 MHz, CD3OD)
ppm


4l
1H NMR (400 MHz, CDCl3)
ppm



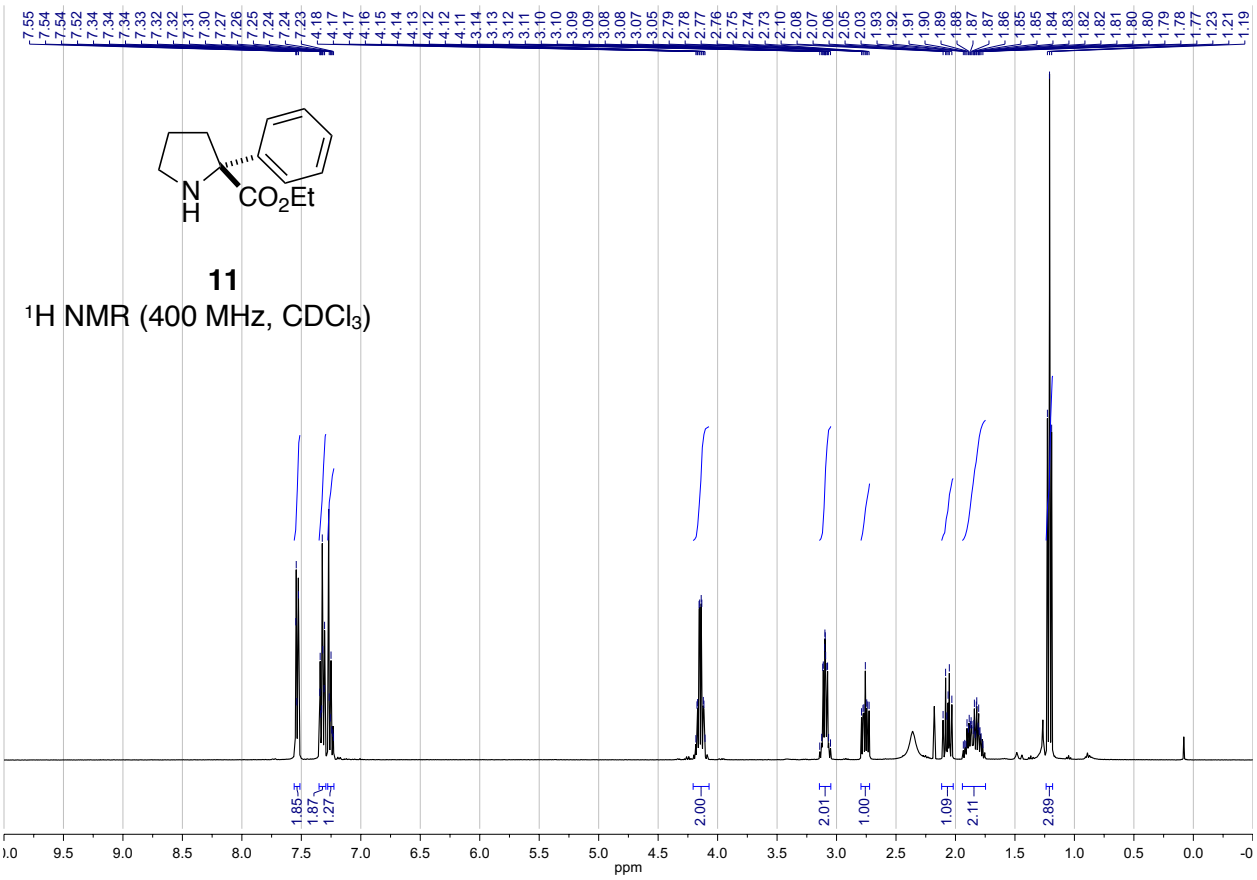
4l

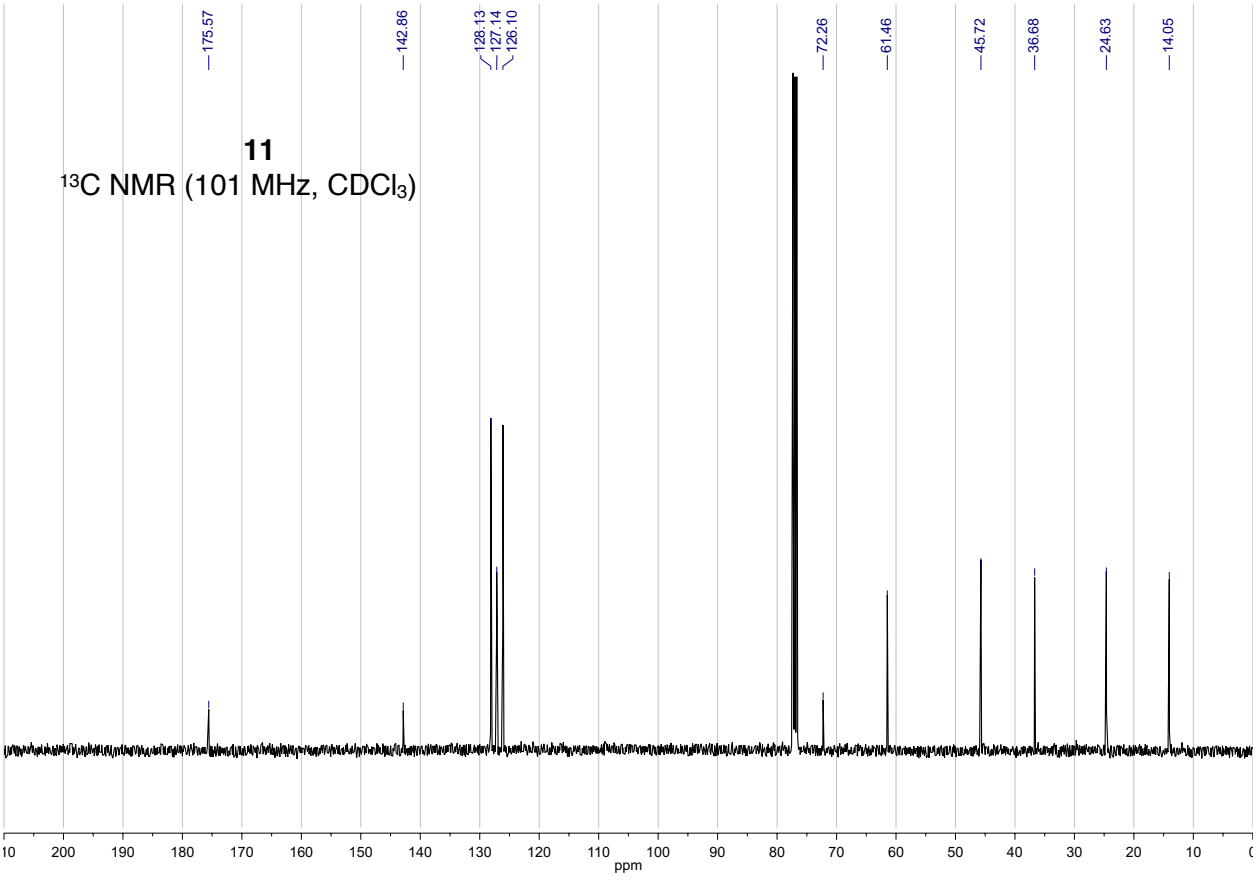
^{13}C NMR (101 MHz, CD_3OD)

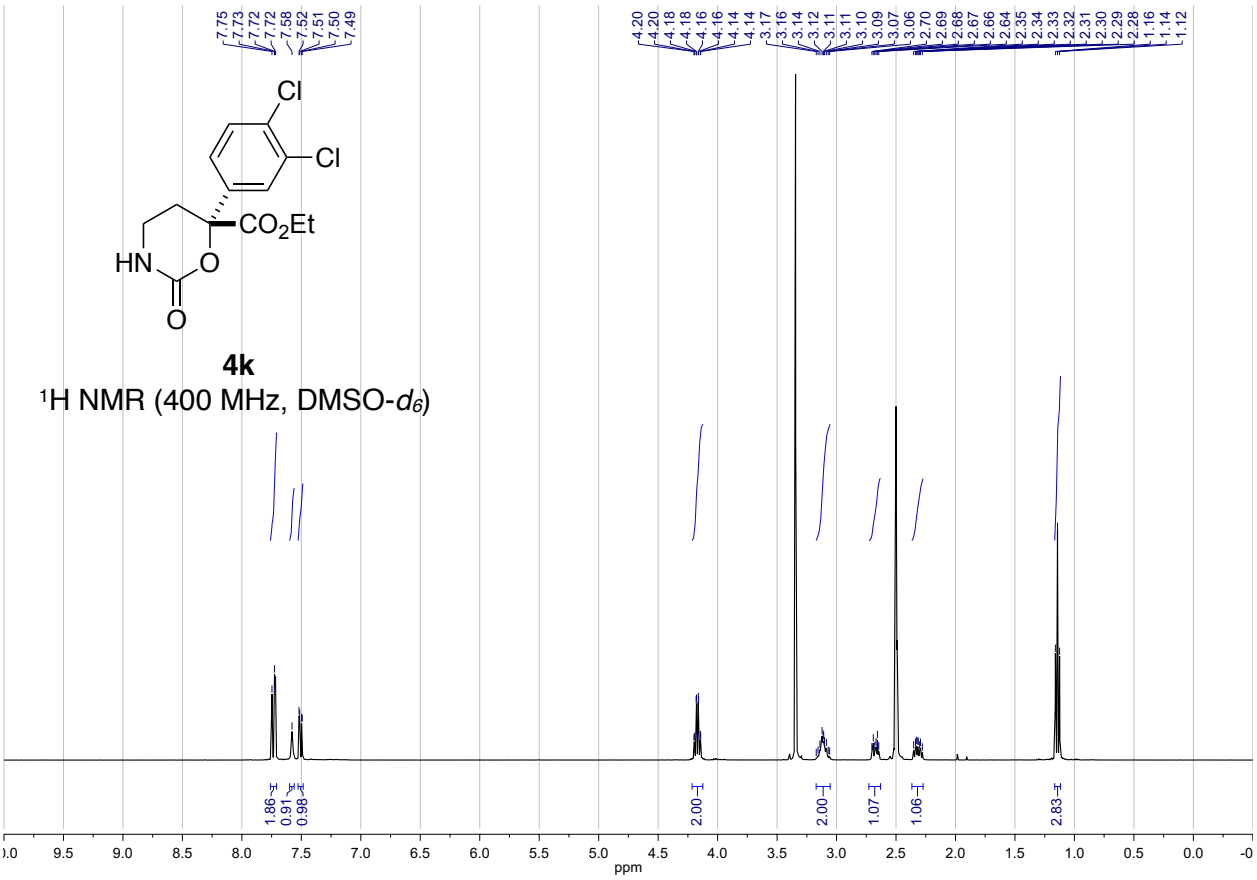


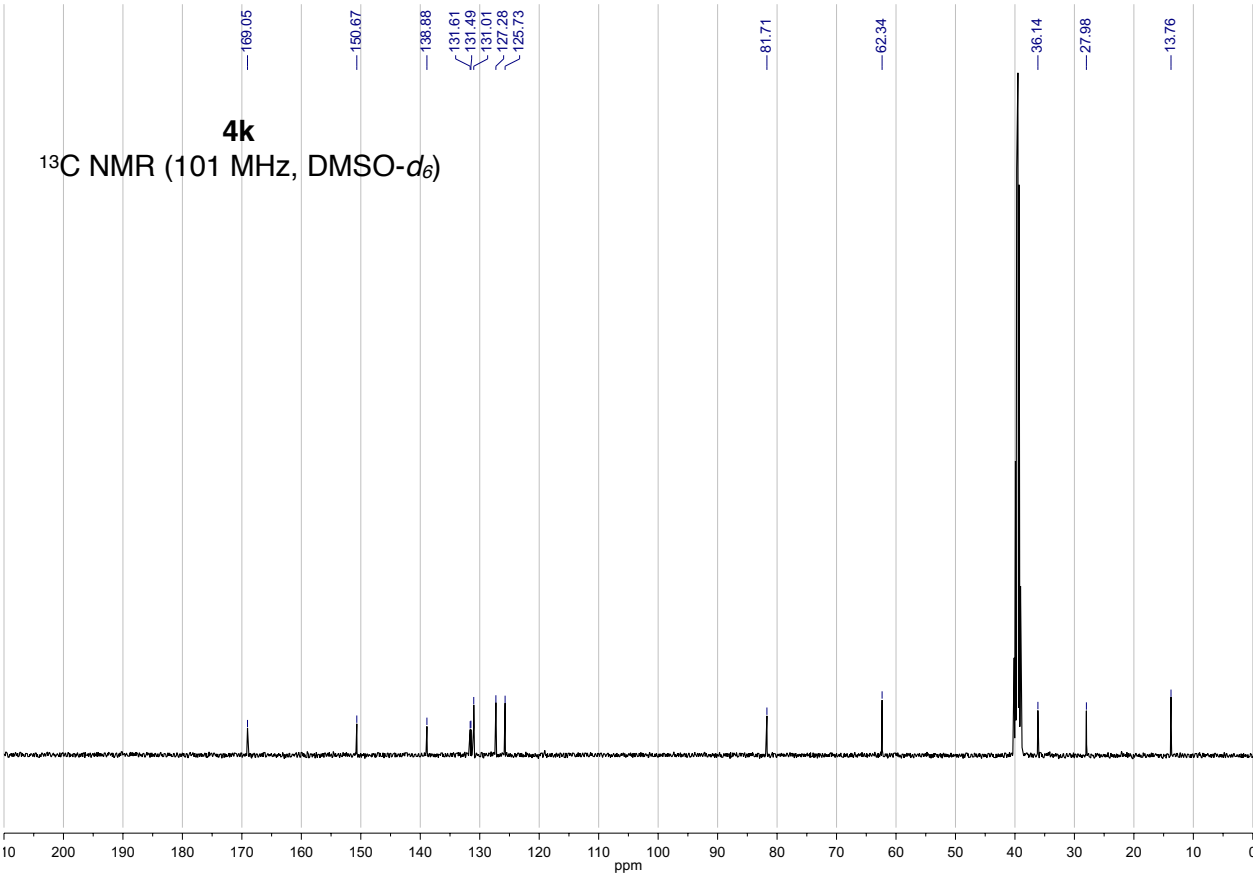
4l

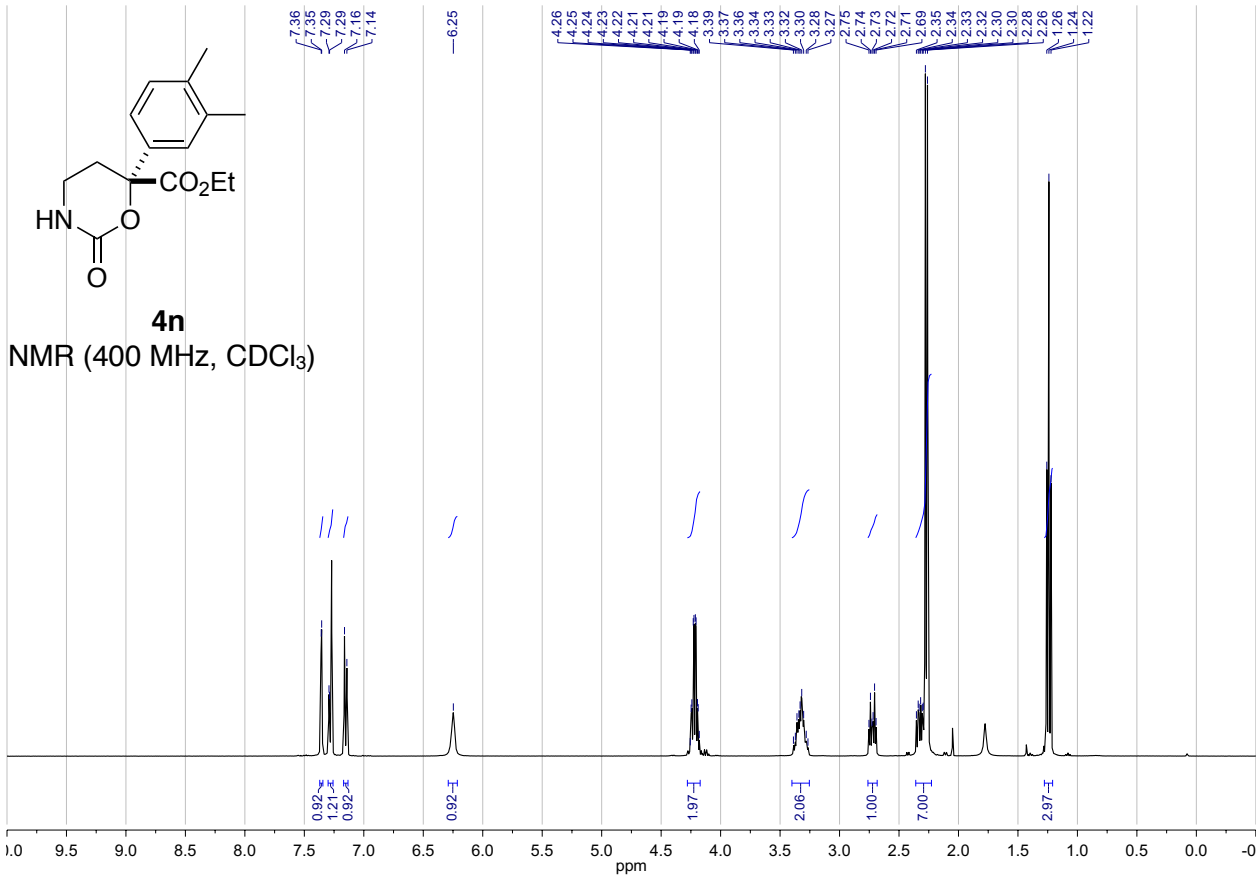
$^{19}F\{^{1}H\}$ NMR (377 MHz, CD_3OD)


N
H
CO2Et
11
1H NMR (400 MHz, CDCl3)
ppm


11
13C NMR (101 MHz, CDCl3)
175.57
142.86
128.13
127.14
126.10
72.26
61.46
45.72
36.68
24.63
14.05
ppm

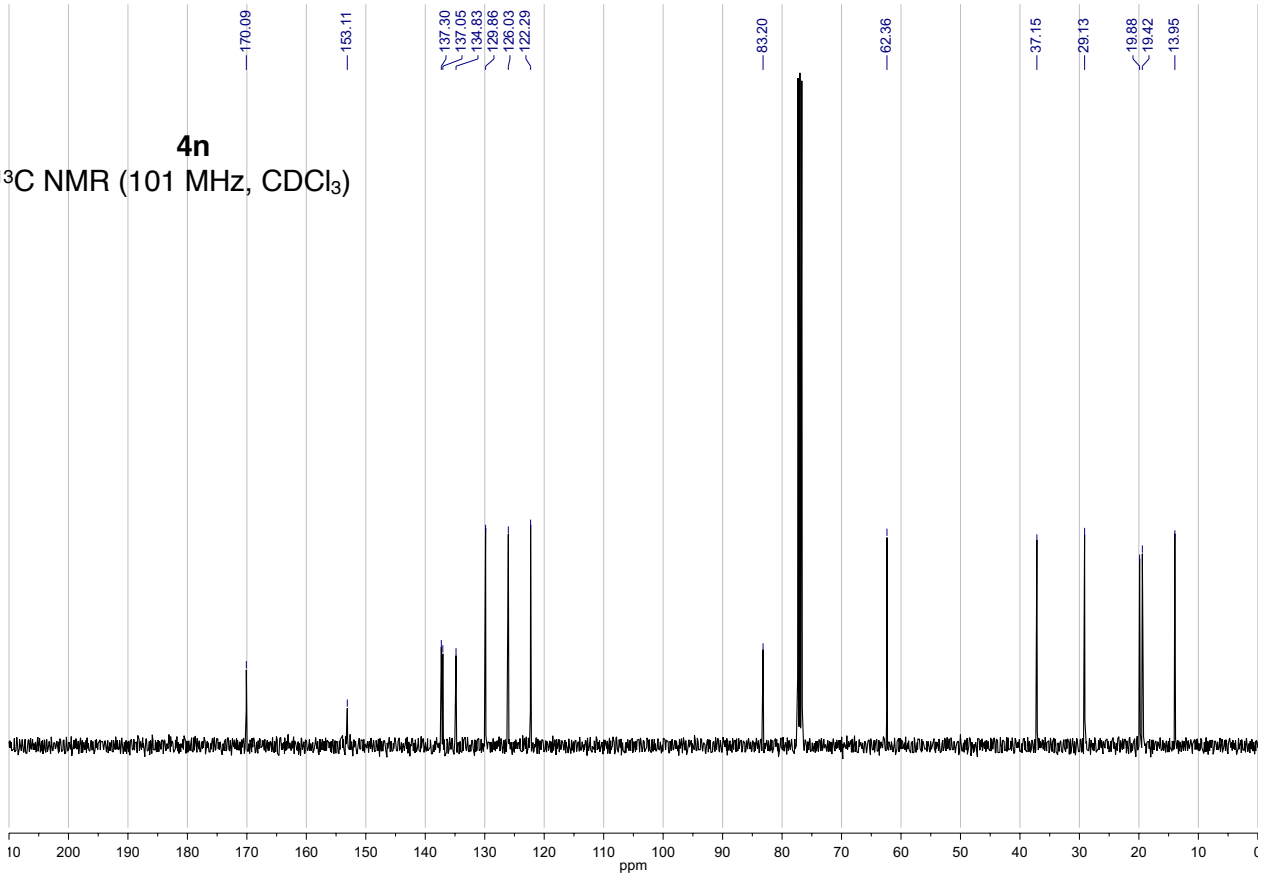

Cl
Cl
CO2Et
HN
O
O
4k
1H NMR (400 MHz, DMSO-d6)
ppm


4k
13C NMR (101 MHz, DMSO-d6)
ppm



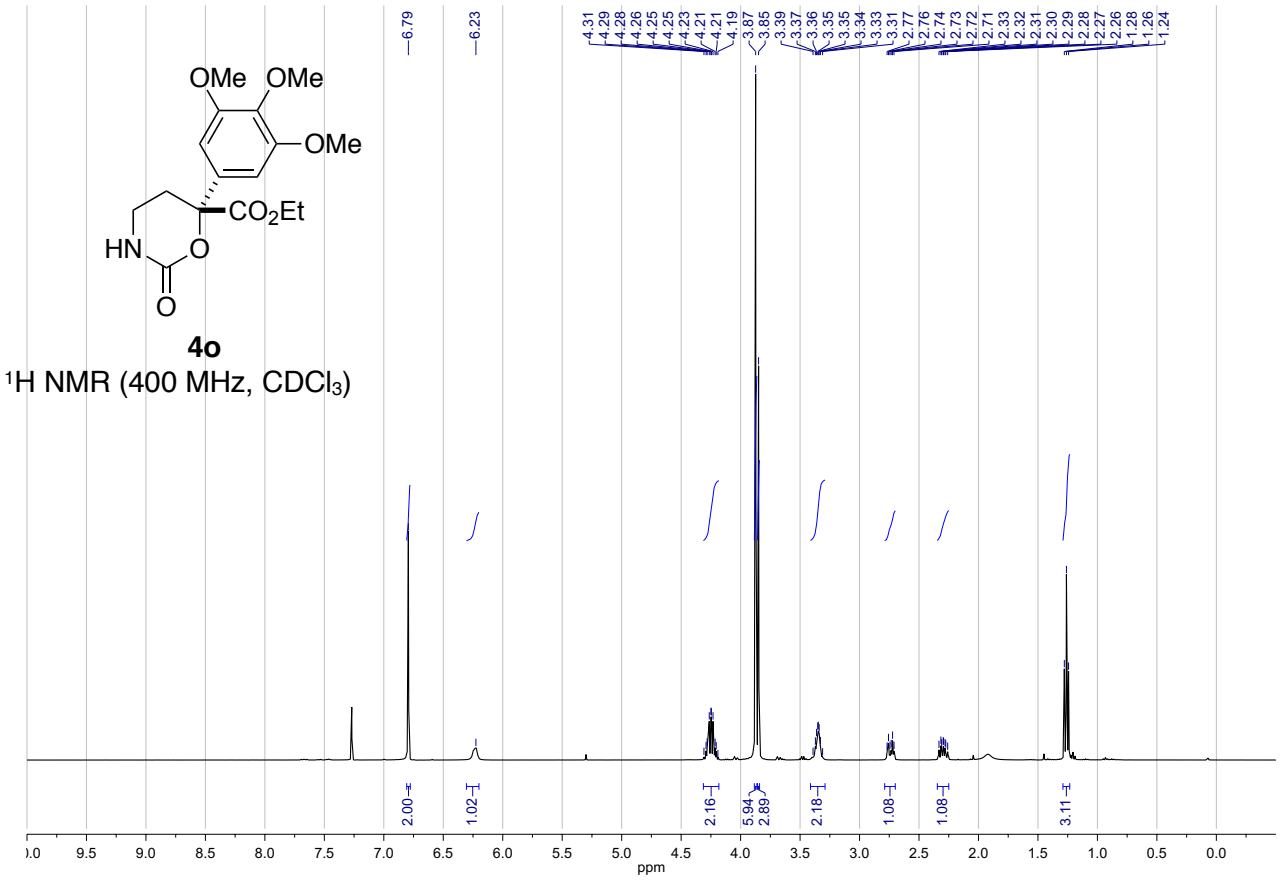
4n

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



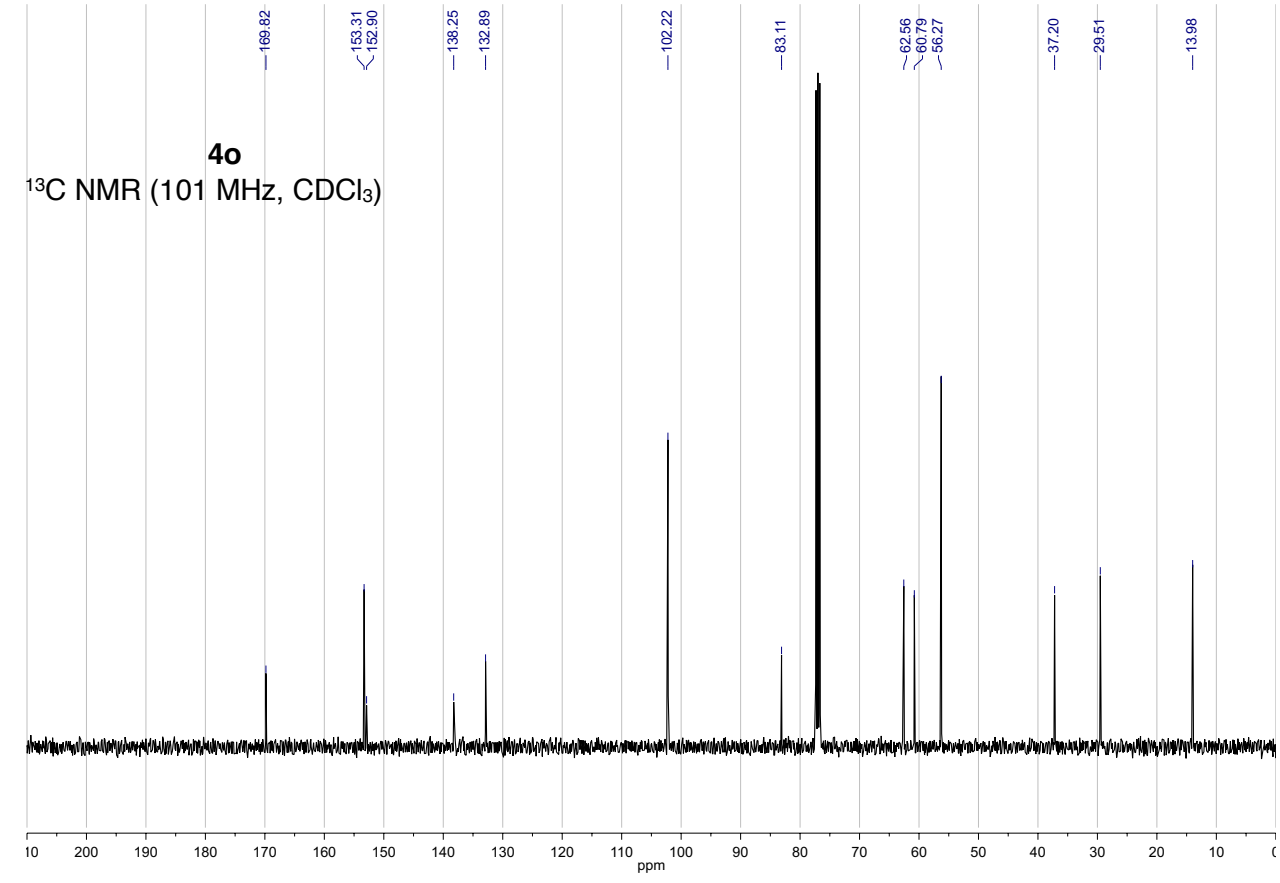
4n

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



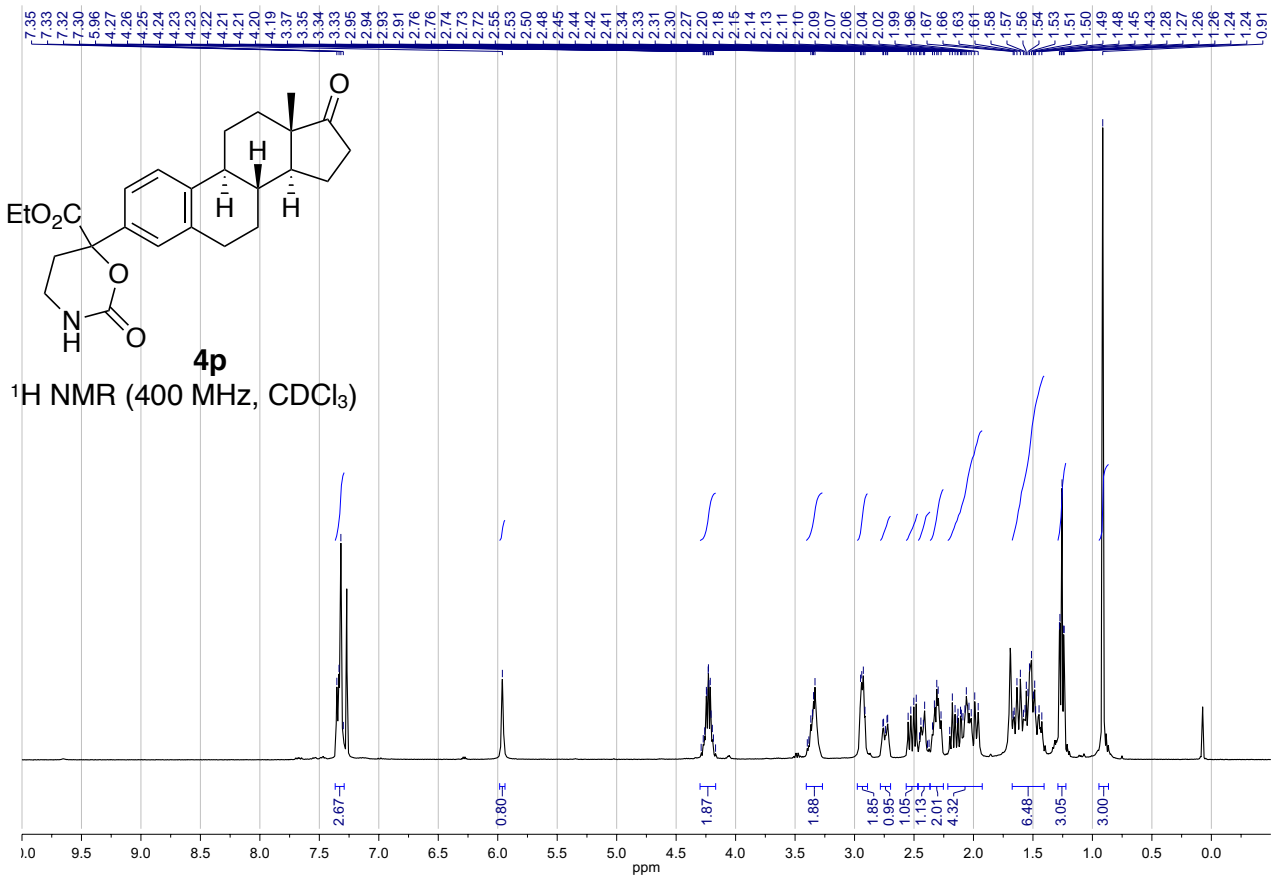
4o

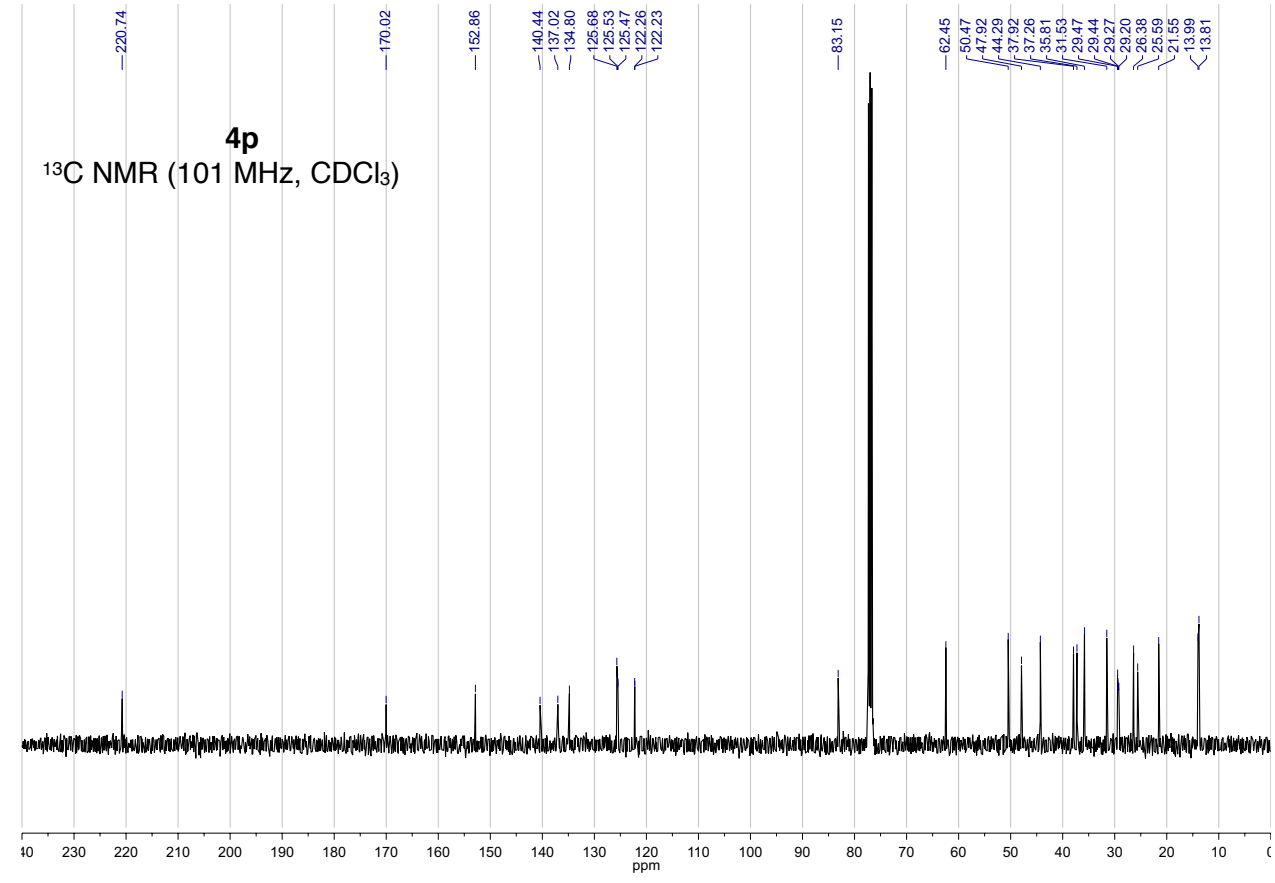
^{1}H NMR (400 MHz, $CDCl_3$)

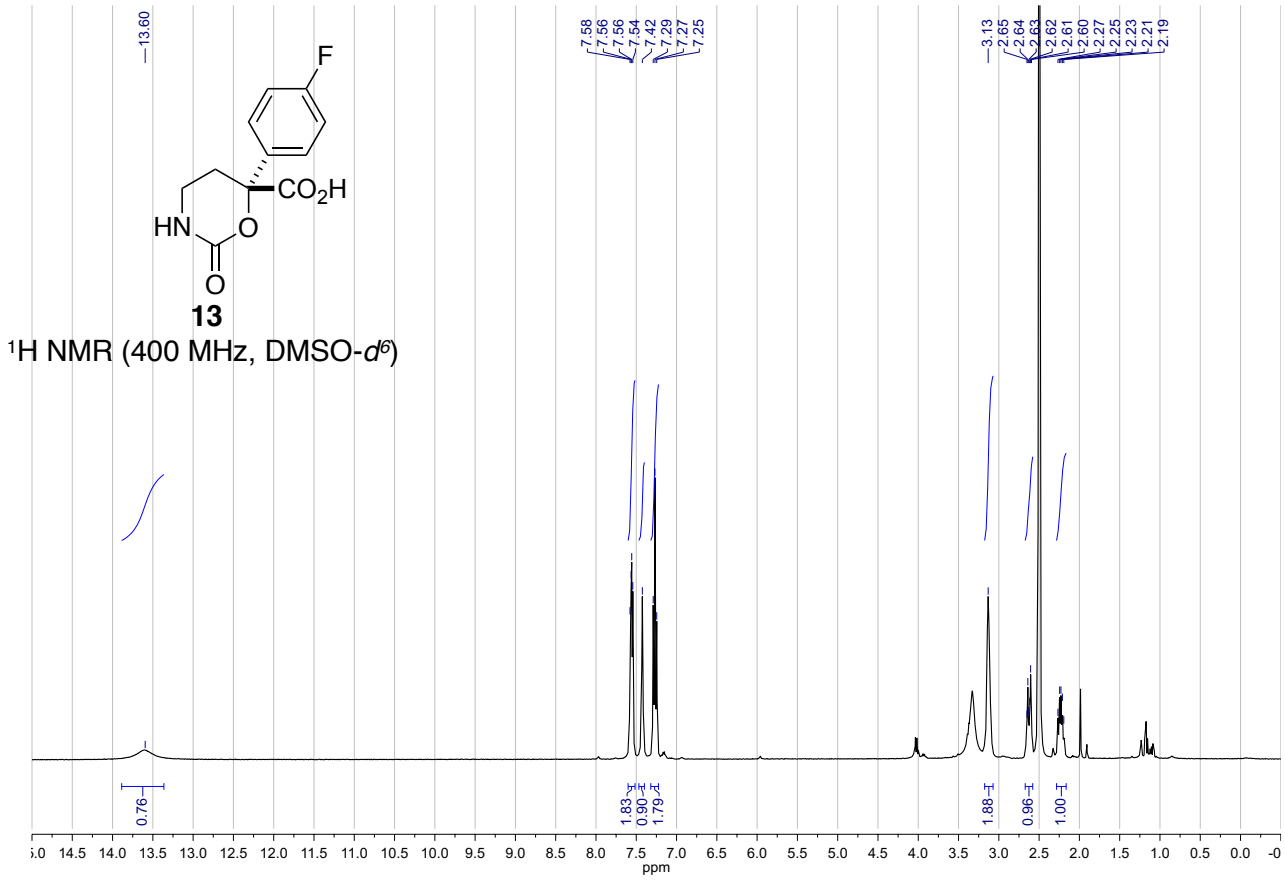


4o

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

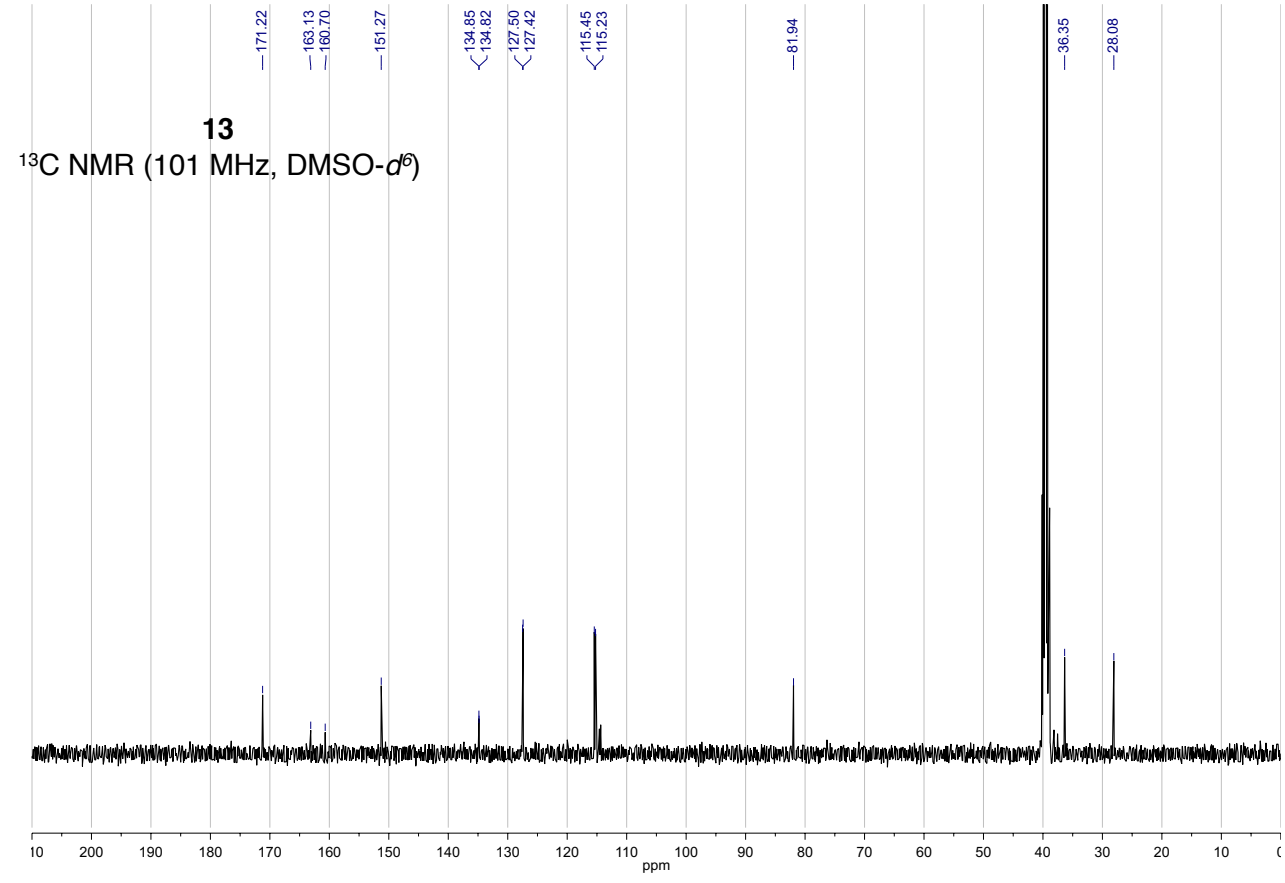

EtO2C
O
H
H
H
O
N
H
O
4p
1H NMR (400 MHz, CDCl3)
ppm


4p
13C NMR (101 MHz, CDCl3)
ppm



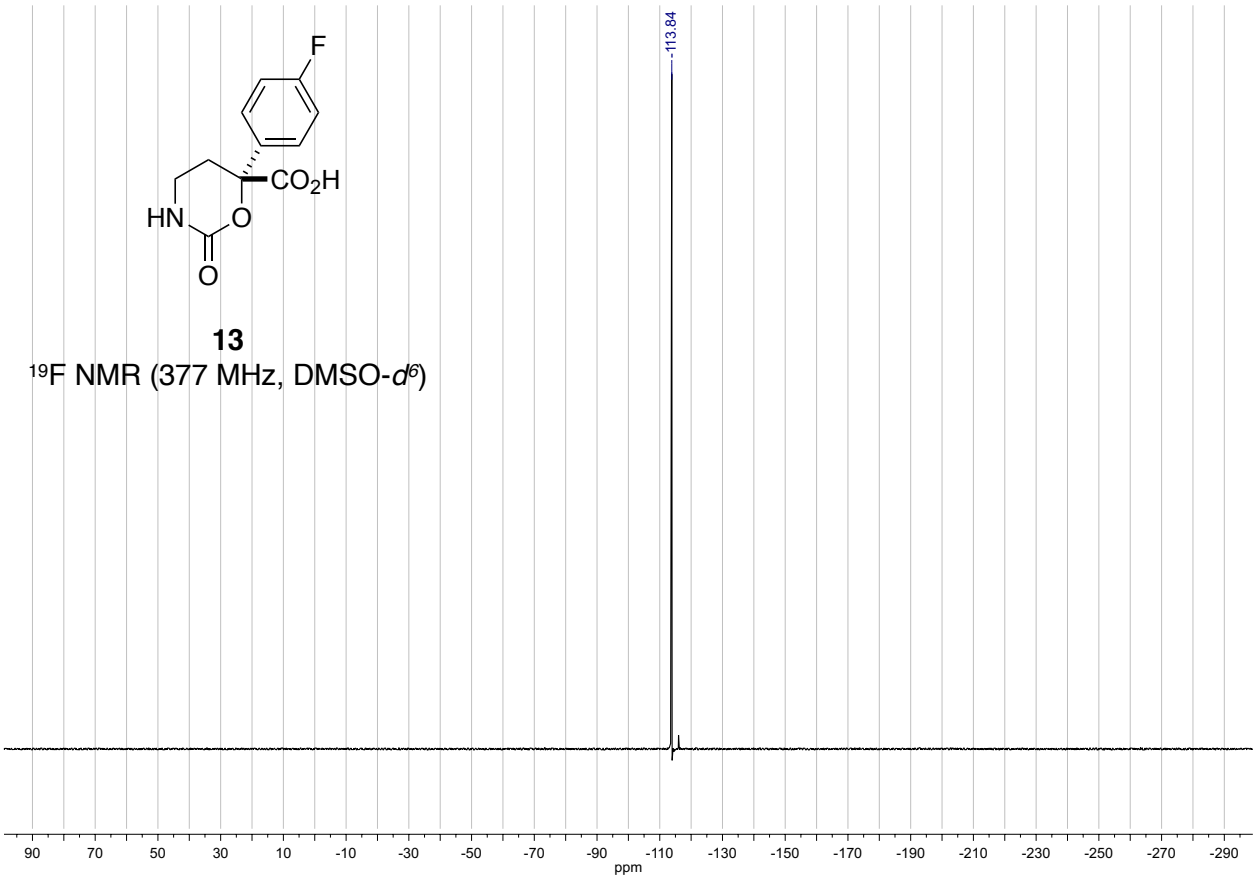
13

^{1}H NMR (400 MHz, DMSO-*d*^{6})



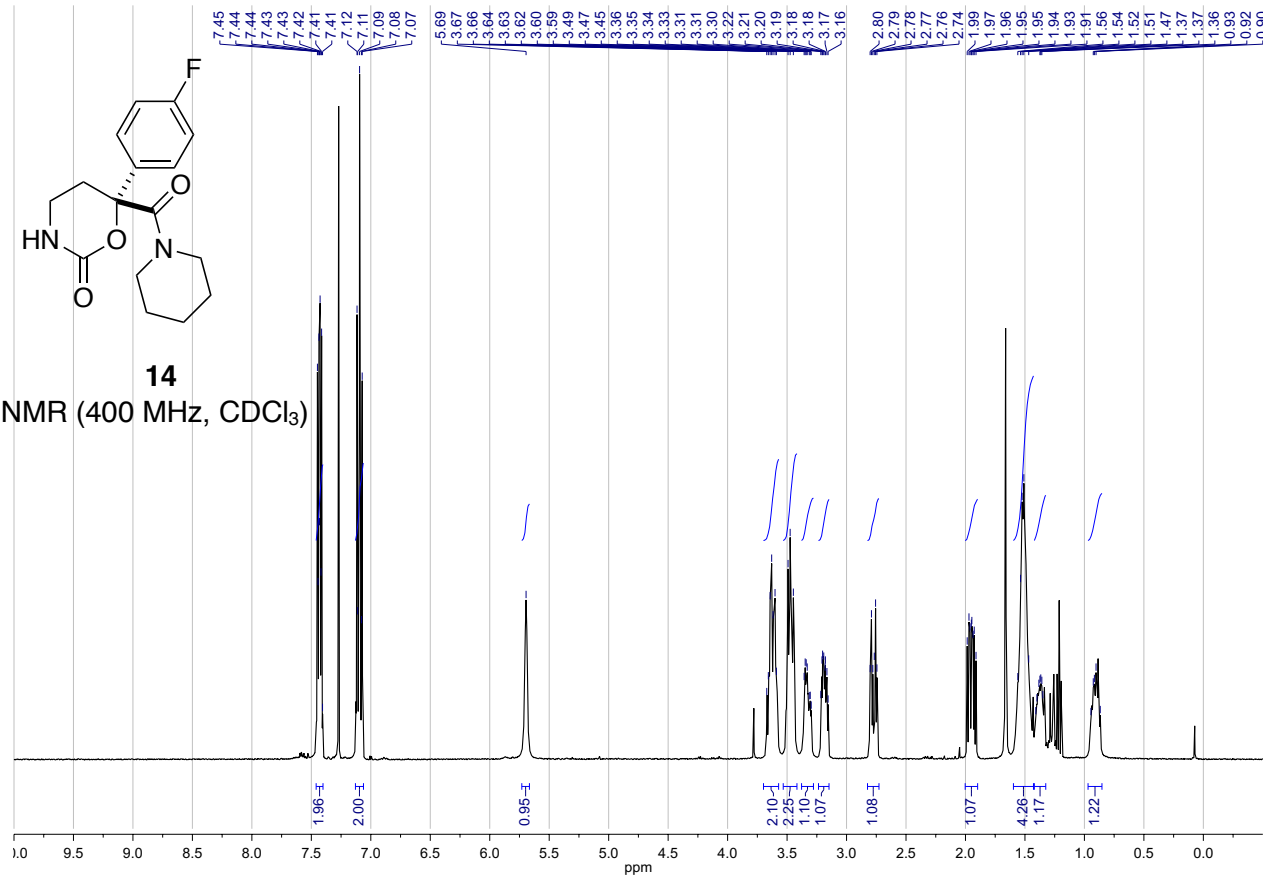
13

^{13}C NMR (101 MHz, DMSO-*d*^{6})



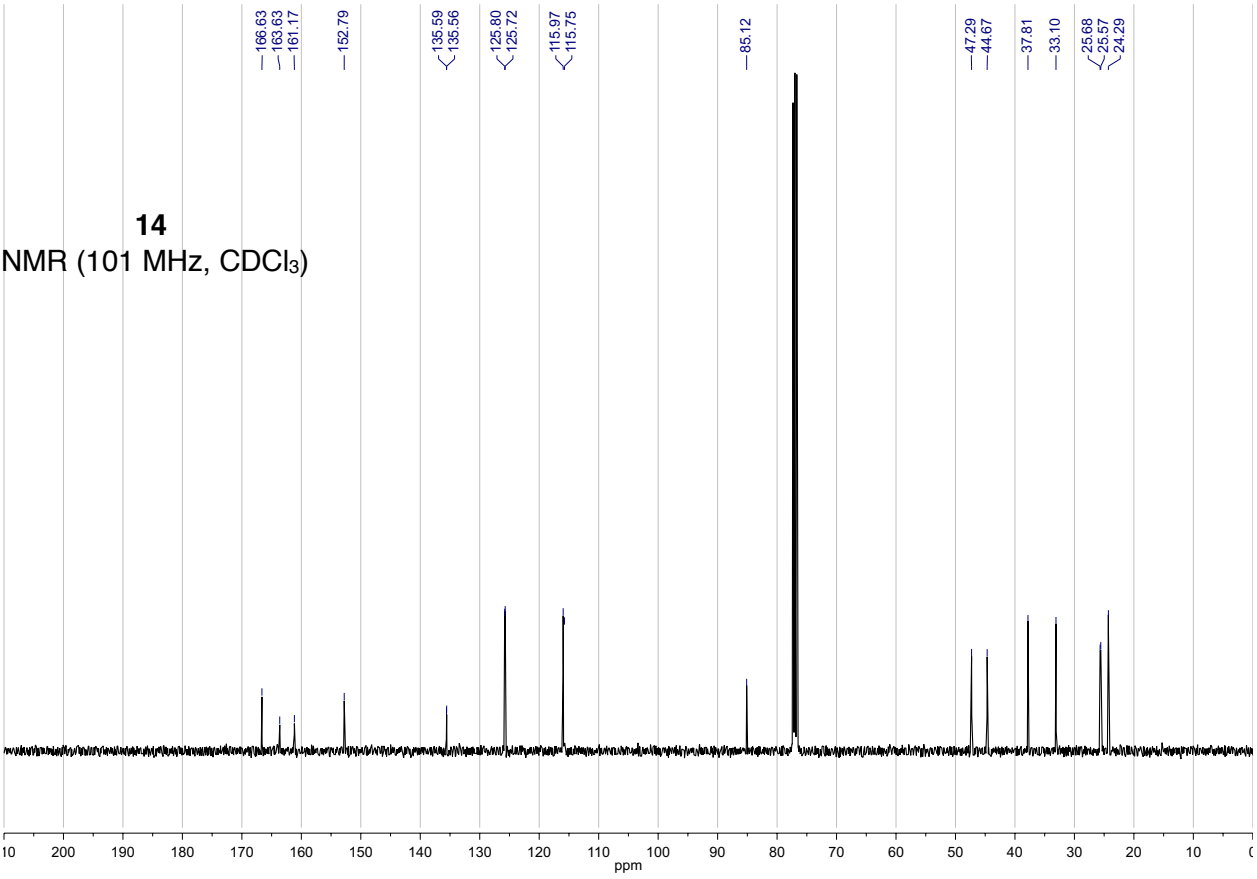
13

^{19}F NMR (377 MHz, DMSO-*d*^{6})



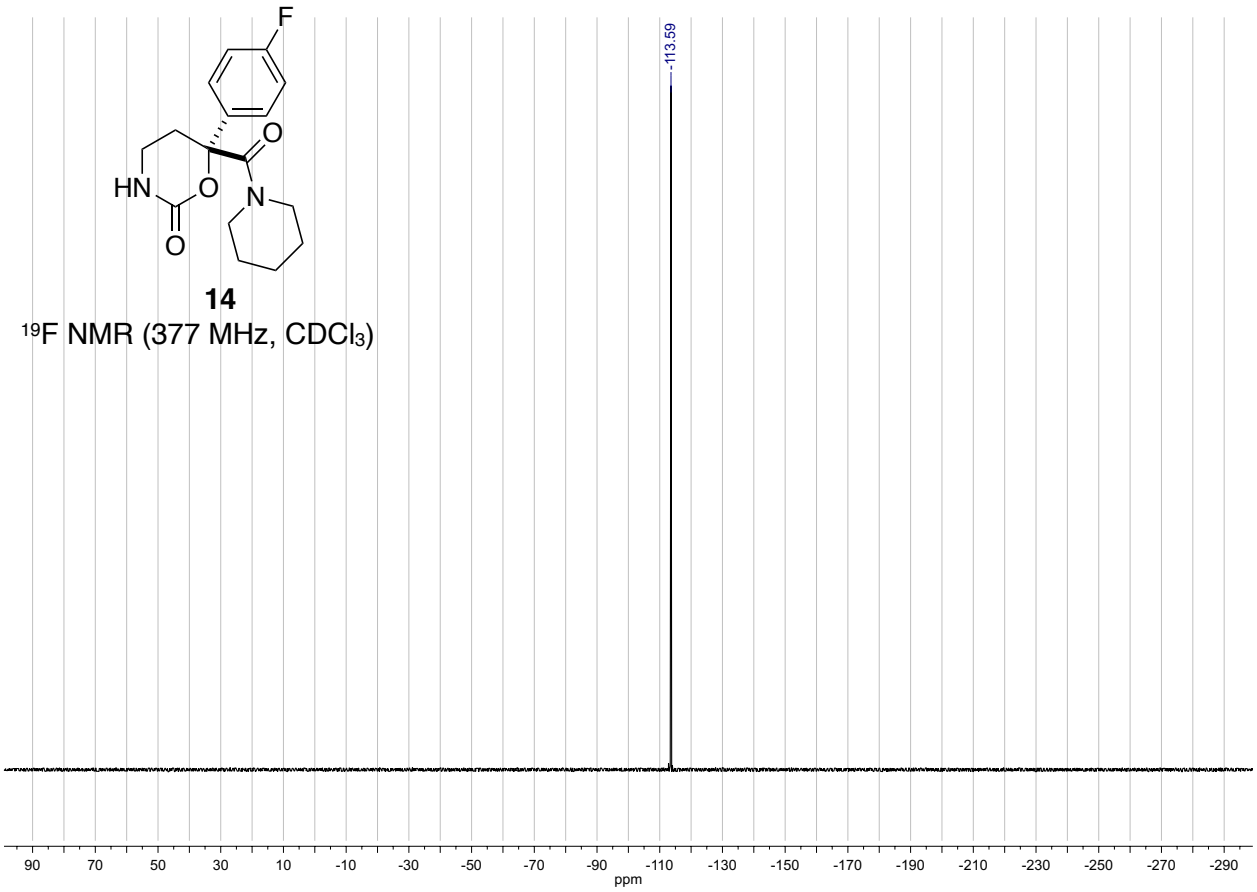
14

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



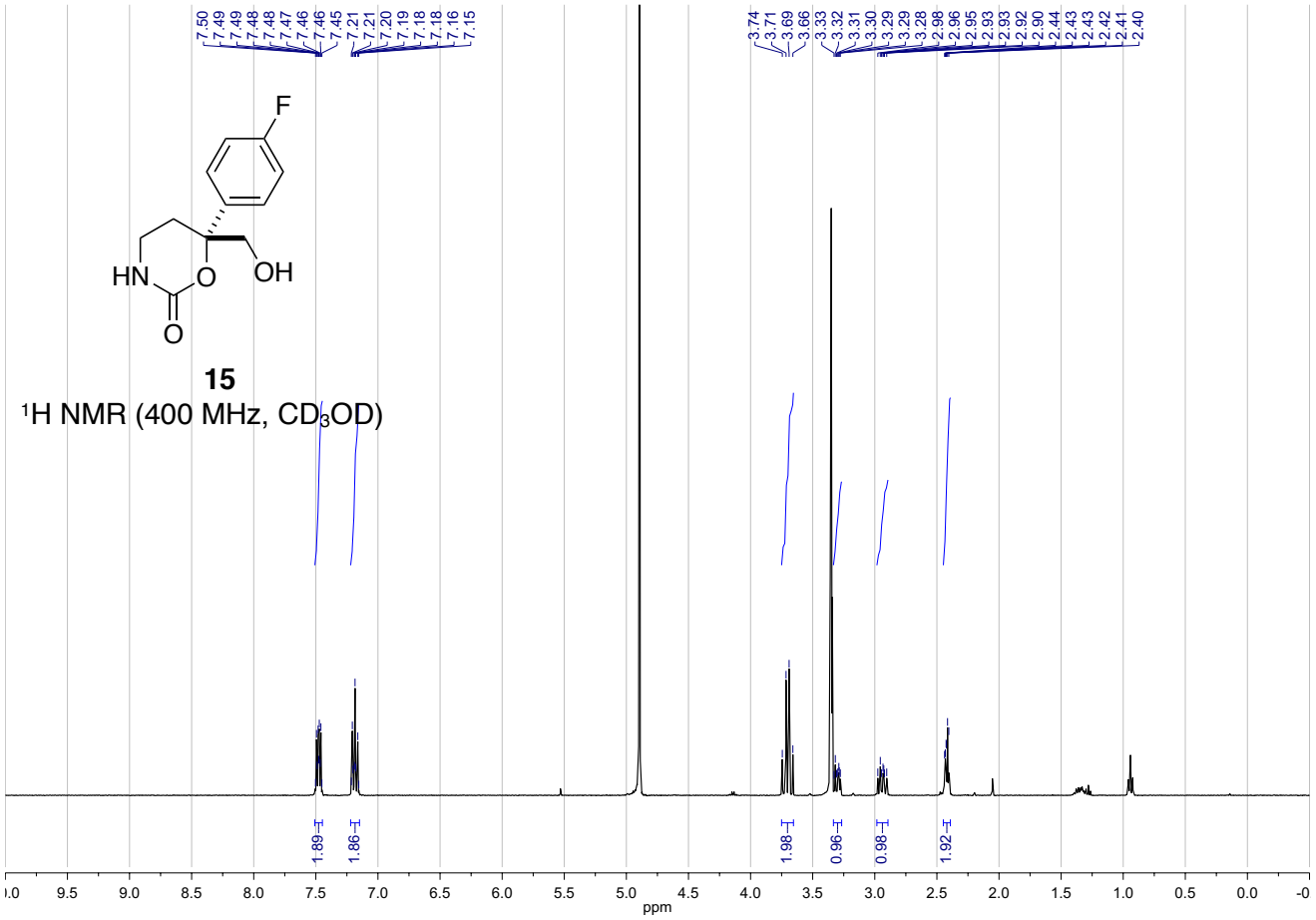
14

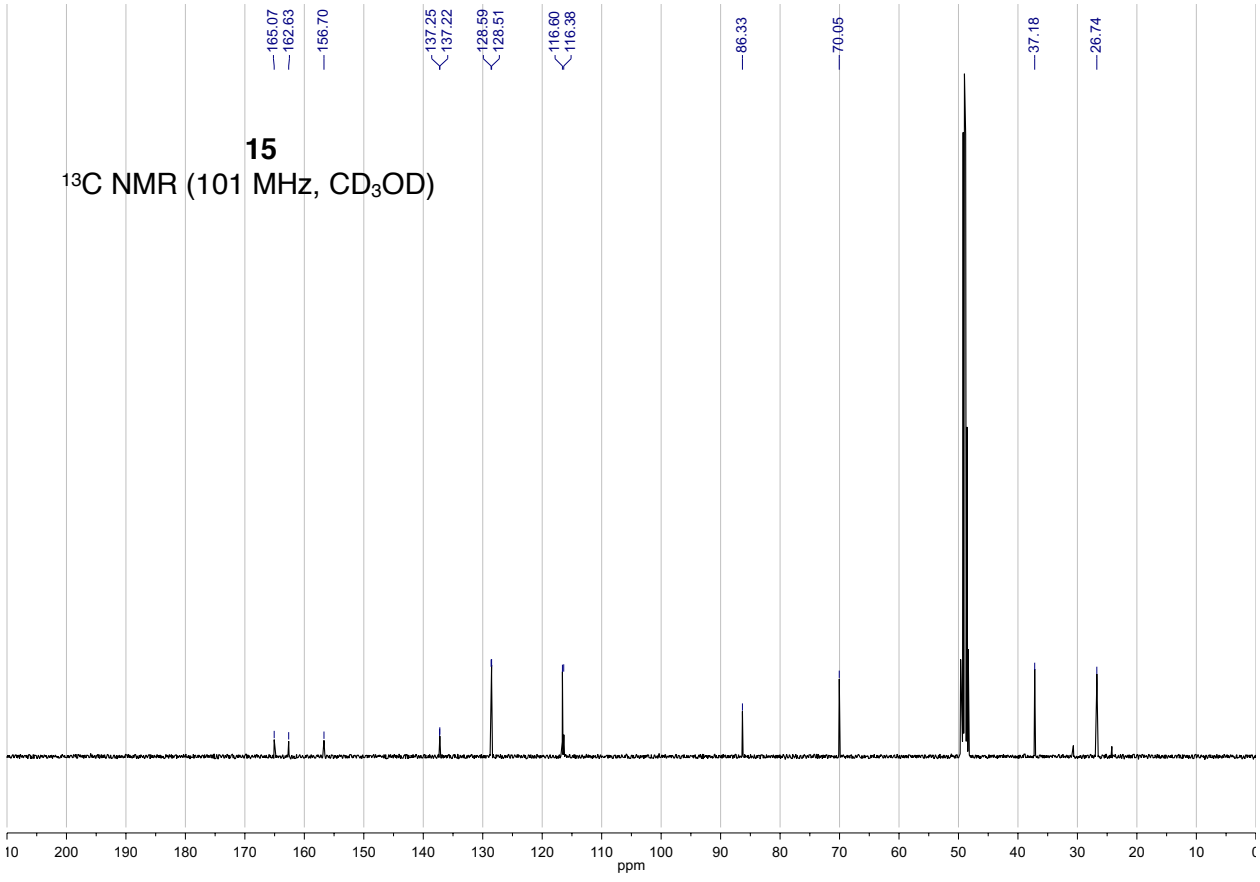
^{13}C NMR (101 MHz, $CDCl_3$)

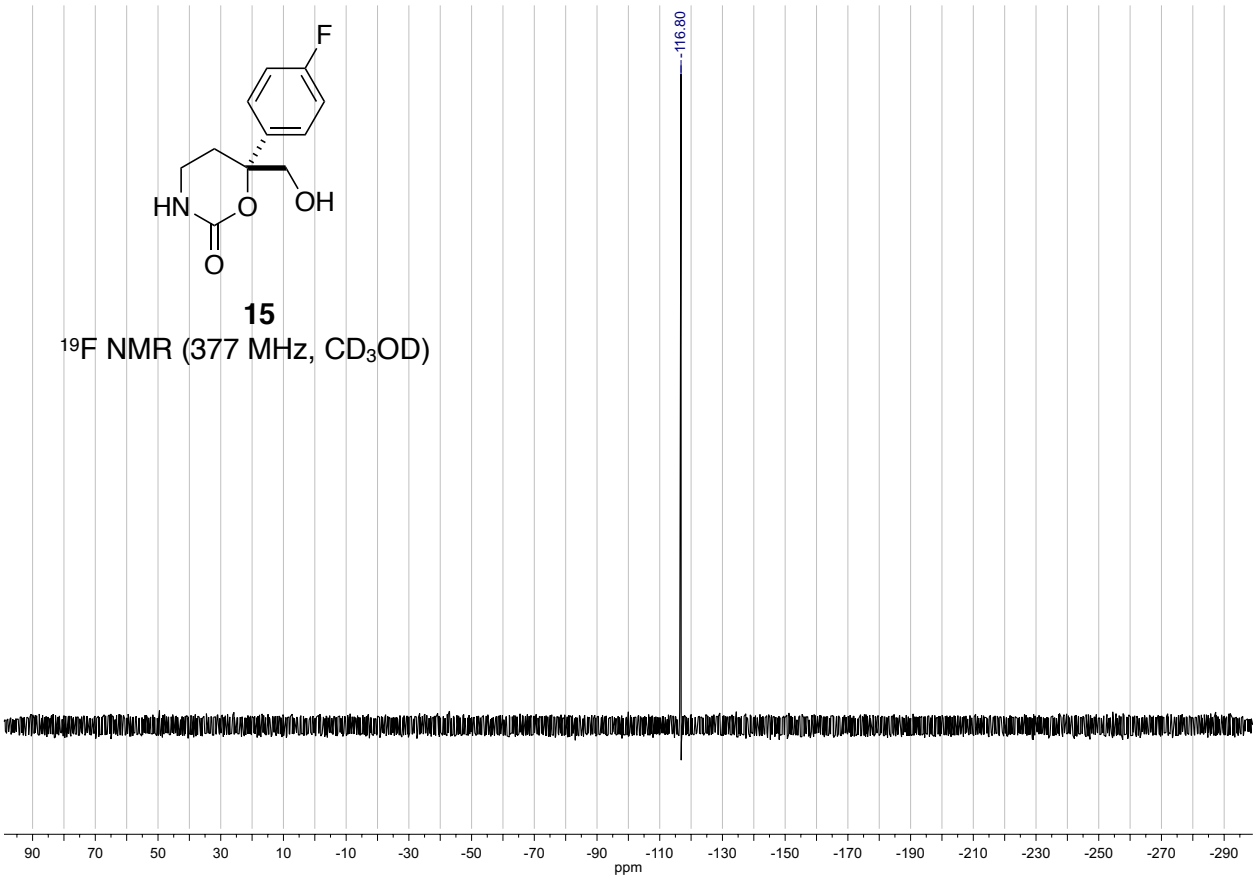


14

^{19}F NMR (377 MHz, $CDCl_3$)

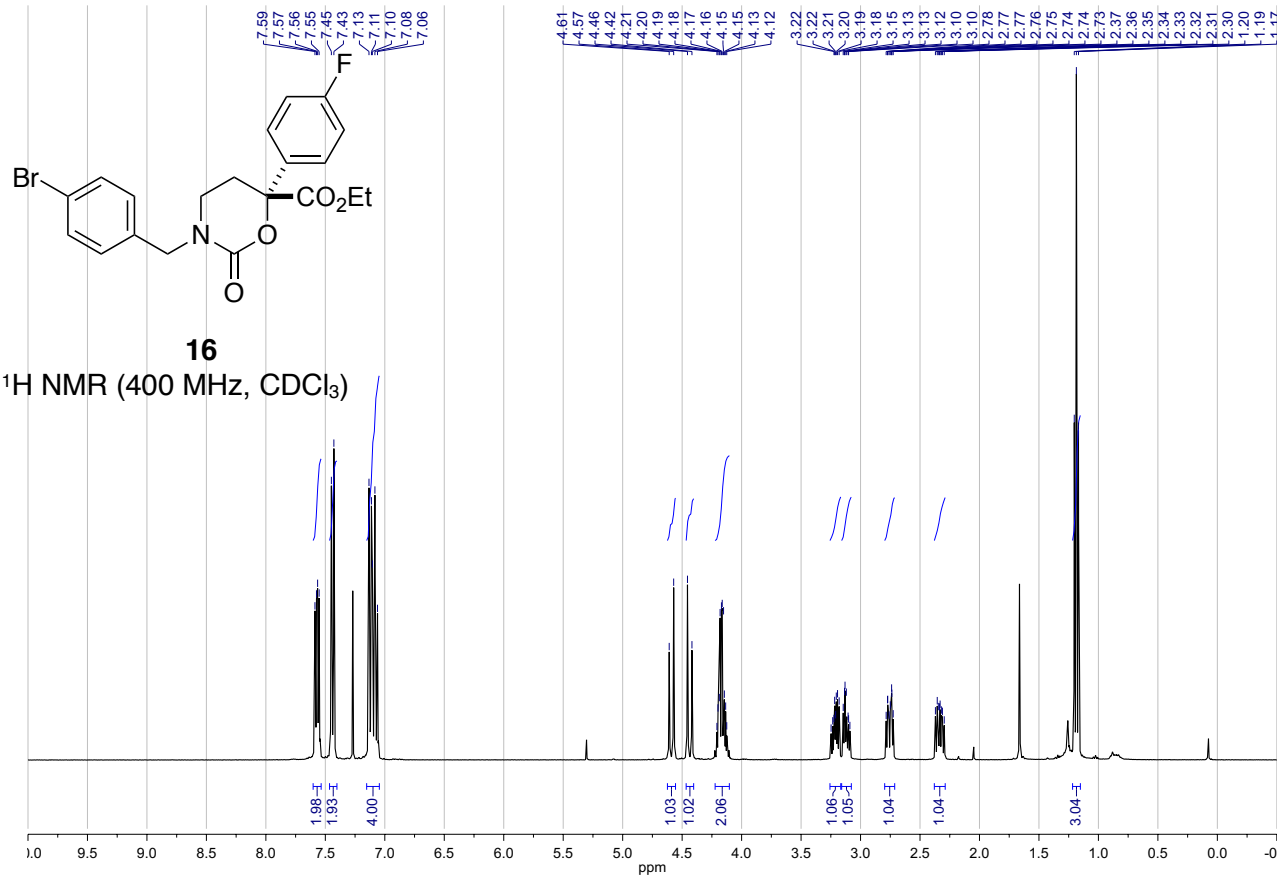

F
HN
O
OH
O
15
^{1}H NMR (400 MHz, CD_3OD)
ppm

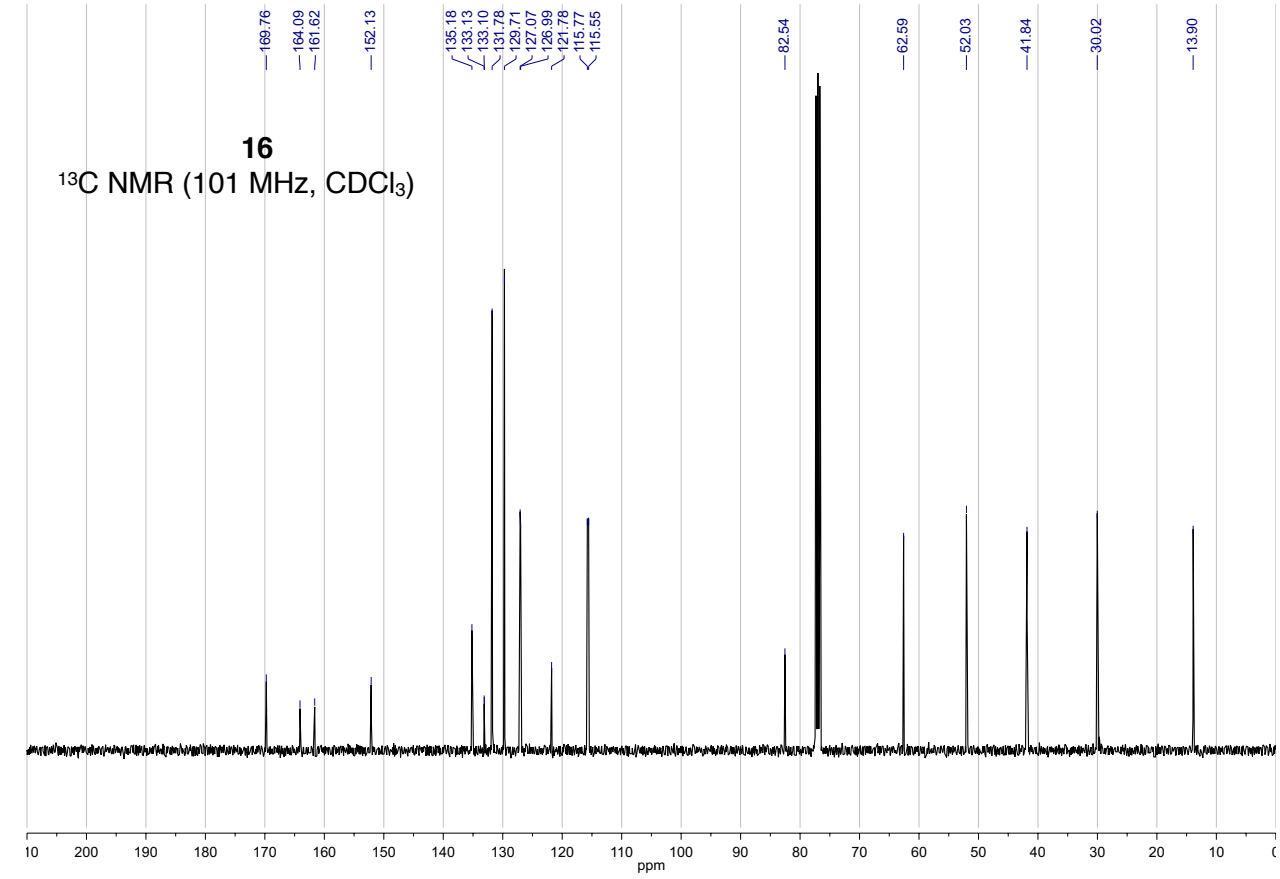

15
^{13}C NMR (101 MHz, CD_3OD)
ppm

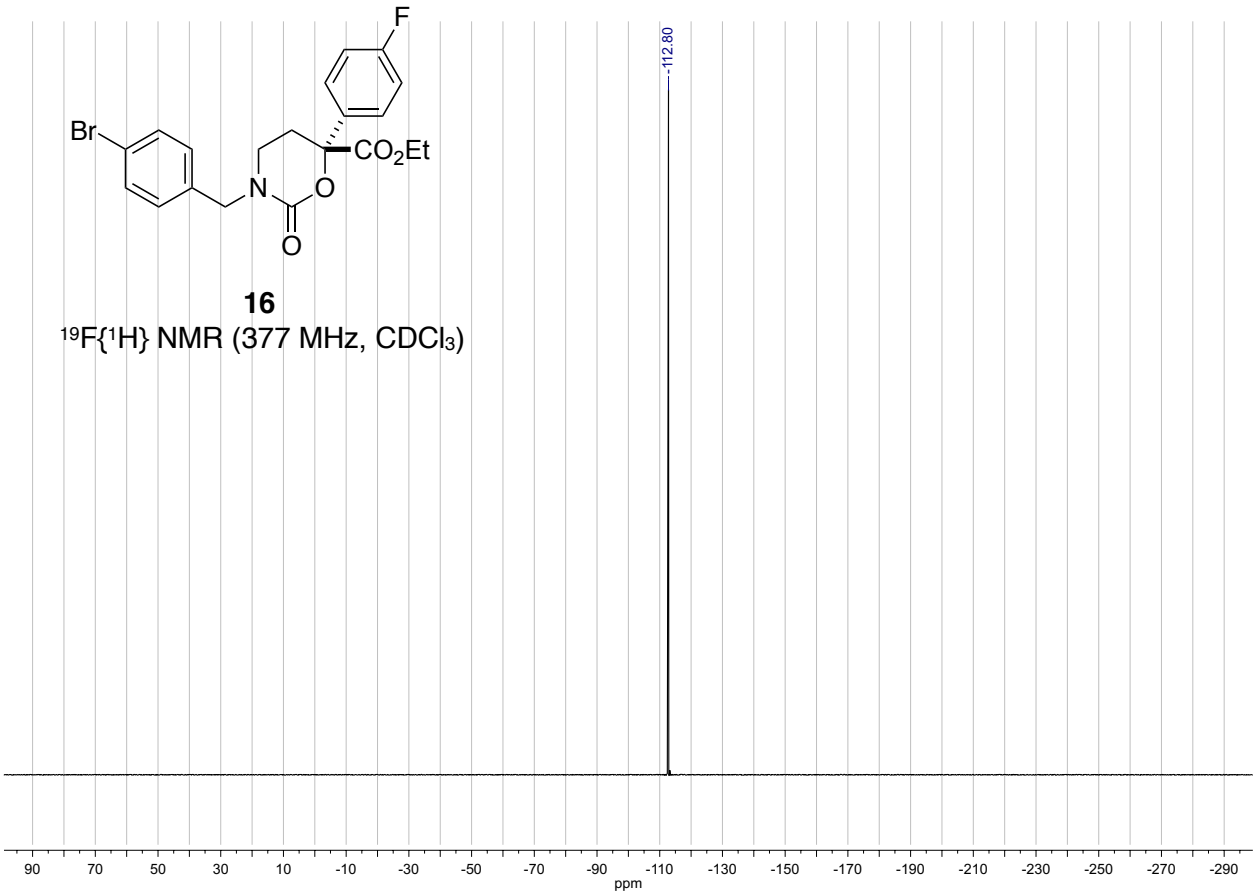


15

^{19}F NMR (377 MHz, CD_3OD)

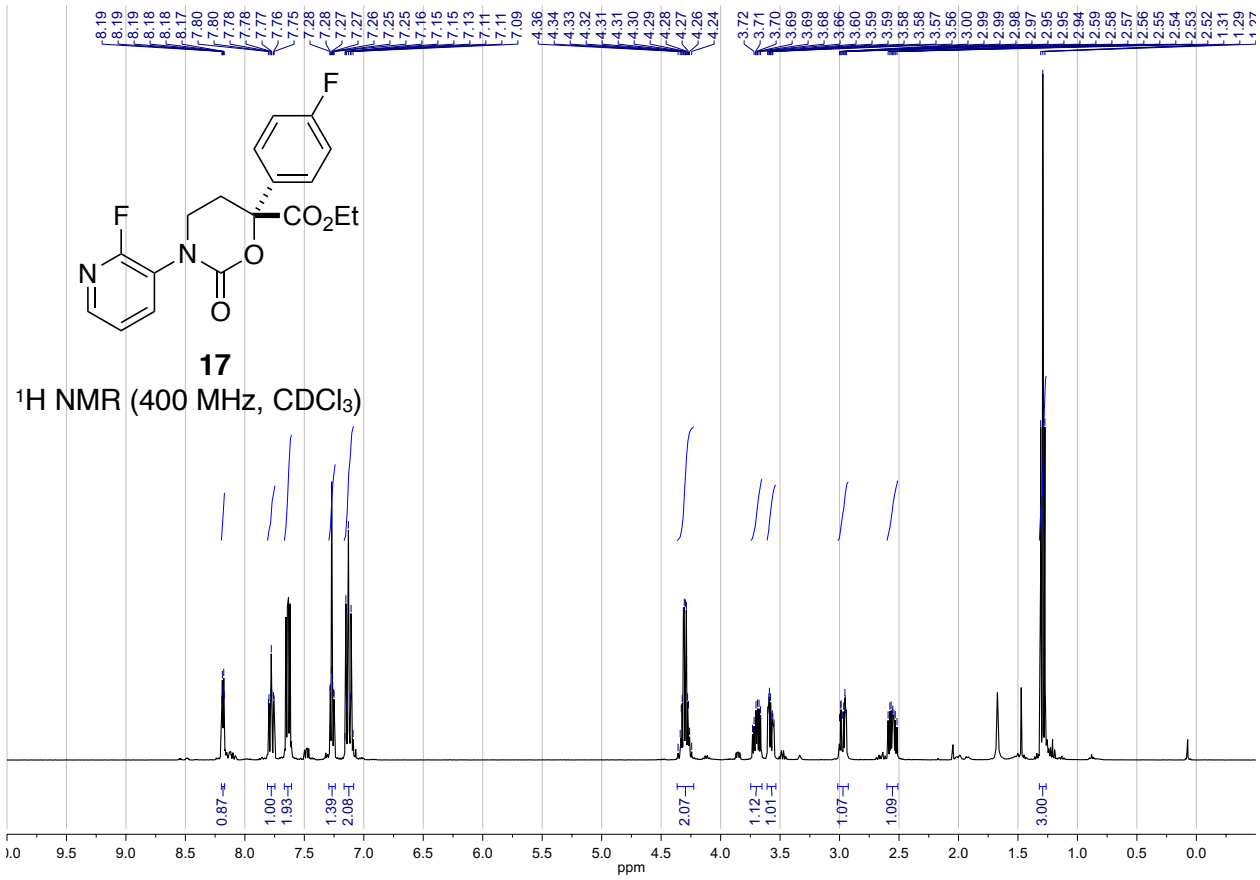

F
Br
CO_2Et
N
O
O
16
^{1}H NMR (400 MHz, $CDCl_3$)
ppm

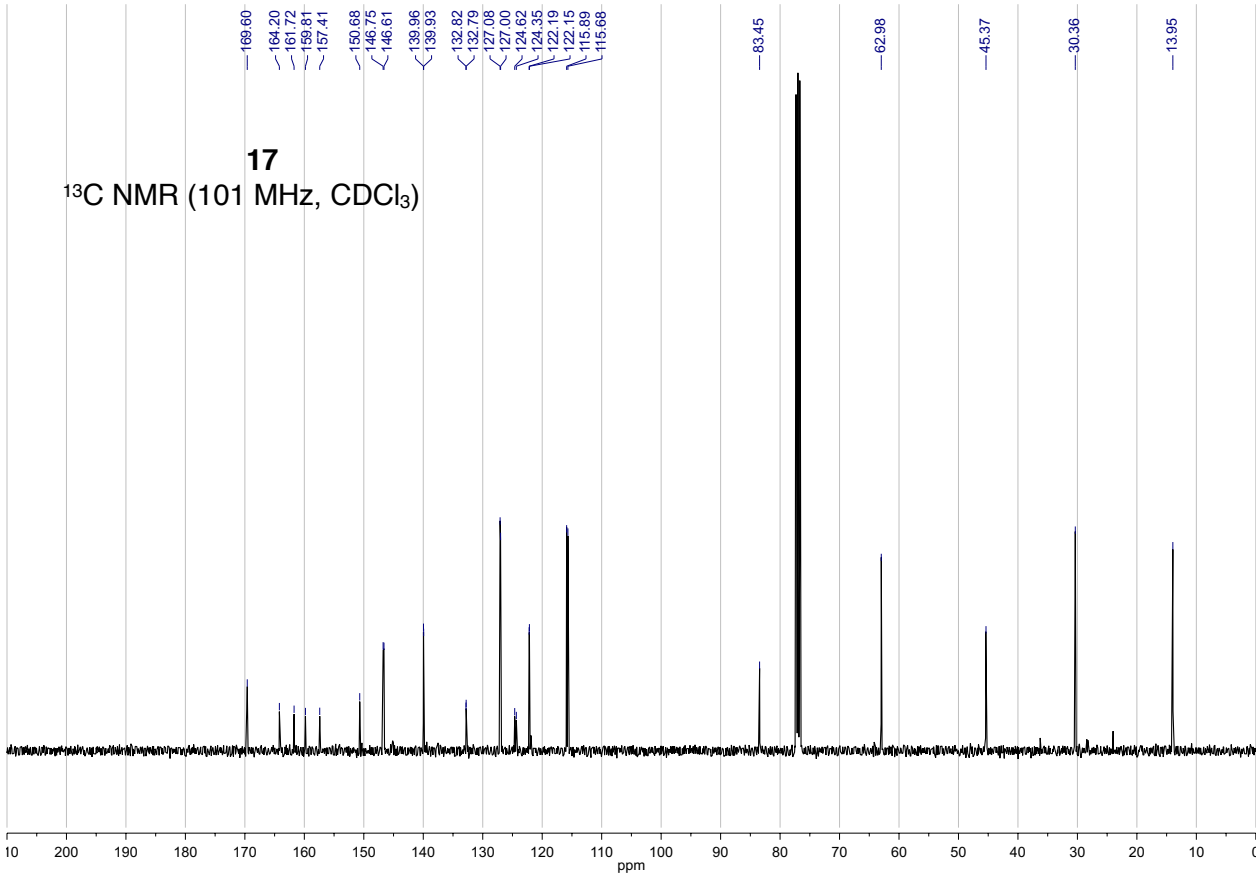

16
^{13}C NMR (101 MHz, $CDCl_3$)
ppm

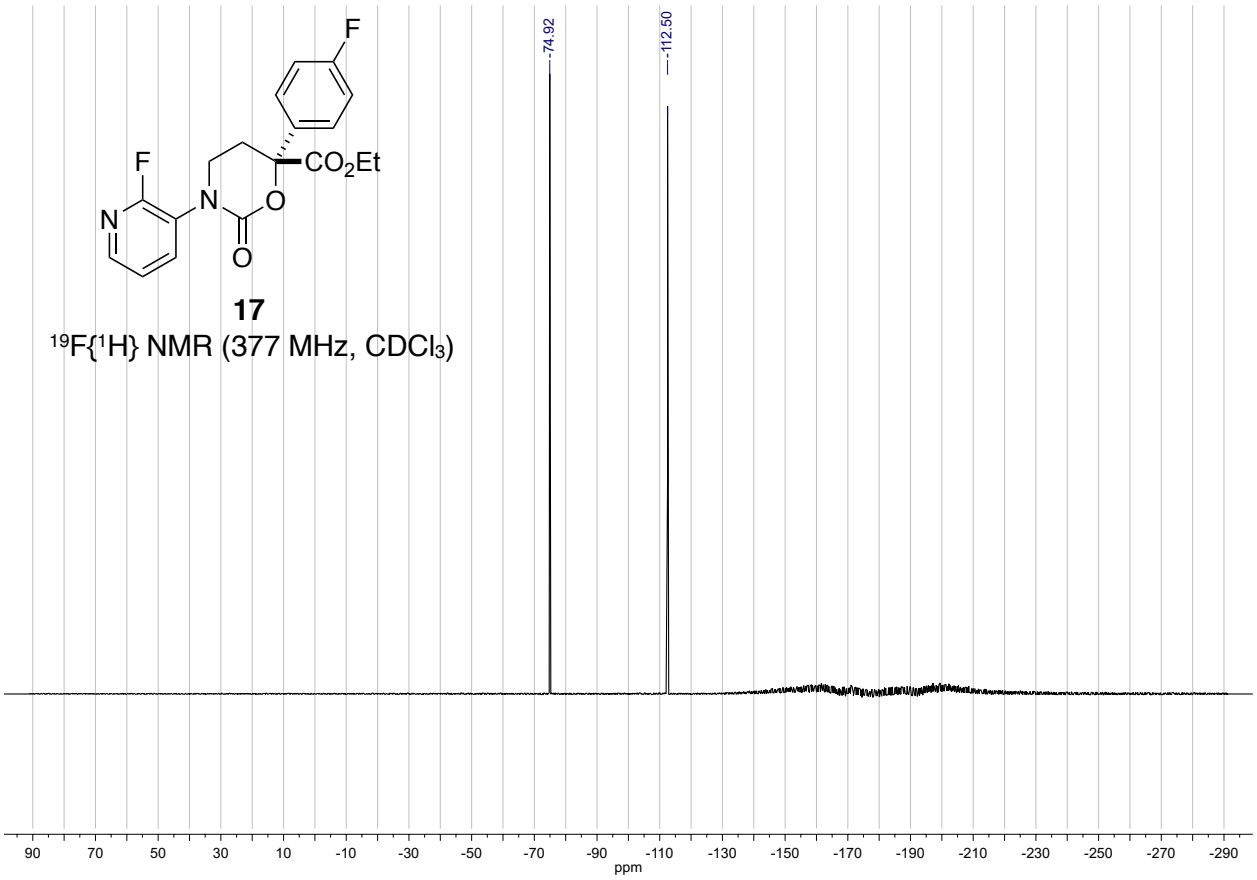


16

$^{19}F\{^{1}H\}$ NMR (377 MHz, $CDCl_3$)


F
F
CO2Et
N
N
O
O
17
1H NMR (400 MHz, CDCl3)
ppm


17
13C NMR (101 MHz, CDCl3)
ppm



17

$^{19}F\{^{1}H\}$ NMR (377 MHz, $CDCl_3$)

References

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