Sustainable continuous flow synthesis of β-aminocarbonyls via acid-catalyzed hydration of N-Boc-2-azetines

Supporting information

Michael Andresini,[a] Marco Colella,[a] Roberta Savina Dibenedetto,[a] Elena Graziano,a Giuseppe Romanazzi,[b] Andrea Aramini,[c] Leonardo Degennaro,[a,*] Renzo Luisi[a,*]

[a]FLAME-Lab, Flow Chemistry and Microreactor Technology Laboratory Department of Pharmacy– Drug Sciences University of Bari "A. Moro" Via E. Orabona 4 – 70125 Bari, Italy. [b]DICATECh, Politecnico di Bari, Bari, 70125, Italy. [c]Department of Discovery, Dompé Farmaceutici S.p.A., Via Campo di Pile, L'Aquila I-67100, Italy.

e-mail: leonardo.degennaro@uniba.it; renzo.luisi@uniba.it

Table of contents

1. General information

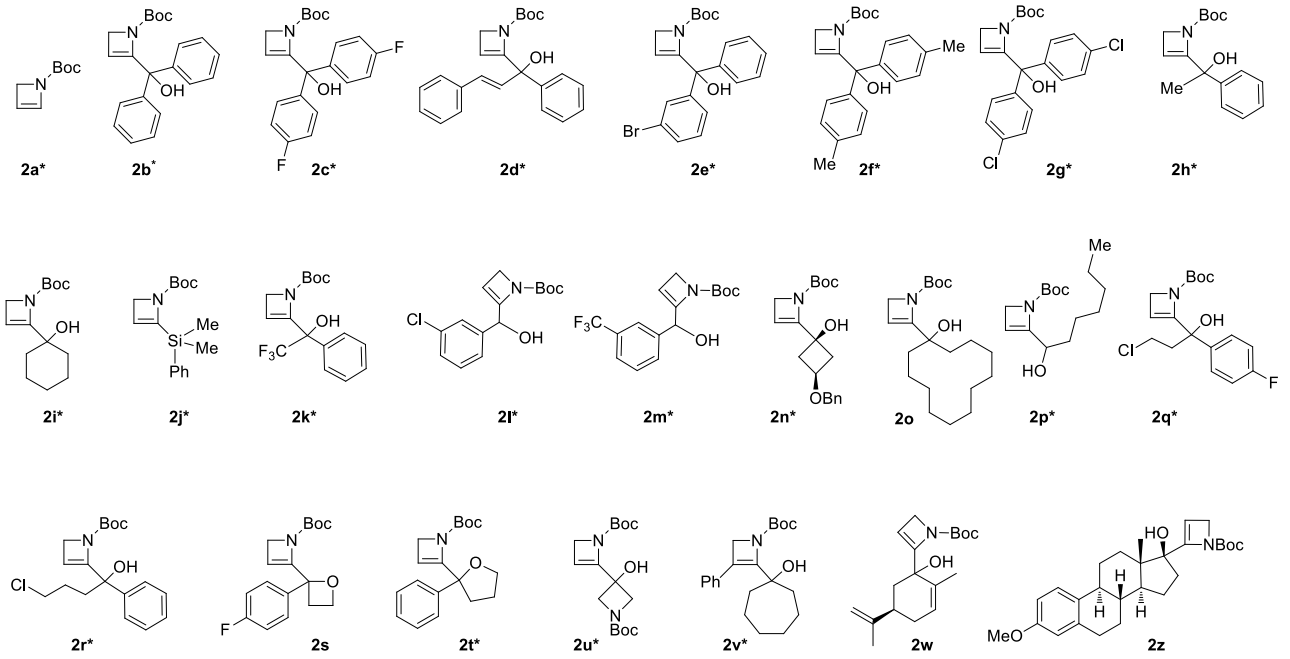
All the chemicals were purchased from Alfa Aesar, Sigma-Aldrich, Fluorochem, and TCI Europe, and used without further purification. An Agilent 500 spectrometer (with frequencies of 500 MHz for ^{1}H, 126 MHz for ^{13}C, and 470 MHz for ^{19}F), and a Bruker Ascend 400 spectrometer (with frequencies of 101 MHz for ^{13}C, and 377 MHz for ^{19}F) were used to record the ^{1}H, ^{13}C, and ^{19}F NMR spectra, which were reported in parts per million (ppm) relative to residual $CHCl_3$ (^{1}H: δ = 7.26 ppm) and relative to $CDCl_3$ (^{13}C: δ = 77.16 ppm). The signals' multiplicity was indicated by s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), bs (broad signal), or m (multiplet), and spin-spin coupling constants (*J*) were given in Hz. To ensure complete and unambiguous assignment of resonances, 2D NMR techniques (i.e. HSQC and COSY experiments) were combined. NOESY experiments were performed for structural evaluations of the products. The NMR spectra of azetines were recorded with $CDCl_3$ treated with solid K_2CO_3 to minimize decomposition. PerkinElmer 283 spectrometer was used to obtain the infrared spectra, while high-resolution mass spectrometry (HRMS) spectra were recorded using the Agilent 6530 accurate mass Q-TOF instrument and Excalibur data system. Flash column chromatography was performed using 230-400 mesh silica under the reported conditions for each compound and using standard techniques, and solutions were concentrated under reduced pressure with a rotary evaporator. Thin layer chromatography (TLC) was conducted using aluminum sheets precoated with silica gel 60F254 (Merck), and the spots were visualized under UV light (λ = 254 nm) or by oxidation with $KMnO_4$ (aq.).

Flow equipment

The customized flow microreactor system was assembled using a peek T-shaped micromixer with an inner volume of 500 µL and PTFE microtube (ϕ = 1 mm) reactors and loops were used. The microtubes were cut to the required length and connected to the micromixers using peek fittings. Harvard PHD 2000 syringe pumps equipped with gastight syringes were used to inject the reaction components into the flow microreactor system. A Gilson Miniplus3 peristaltic pump was used for the inline recycle of the aqueous acidic solution. For the inline liquid-liquid extraction a Zaiput SEP-10 device equipped with a hydrophobic PTFE OB-900 pore size membrane was employed. The reactor was kept at the desired temperature with a heated bath and a hotplate equipped with a temperature probe.

2. Azetines collection

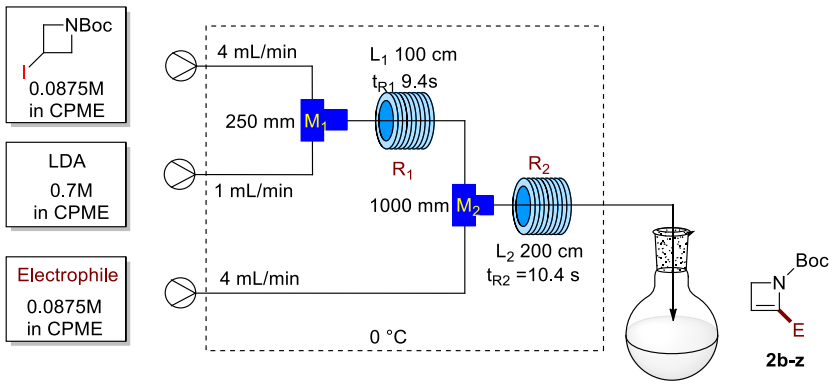
Azetine **2a** was prepared according to the reported procedure.[1] 2-Substituted *N*-Boc-2-azetines **2b-2z** were prepared according to our previously reported flow procedure (**GP1**)[2] unless otherwise specified. The 2,3-substituted *N*-Boc-2-azetine **2v** was synthesized starting from *tert*-Butyl 3-methoxy-3-phenylazetidine-1-carboxylate[3] according to the reported continuous flow method.[4]



*data consistent with literature [2,4]

***Scheme S1**. List of utilized 2-substituted N-Boc-2-azetines.*

2.1 General procedure for the preparation of 2-substituted N-Boc-2-azetines 2b-2z (GP1)[2]

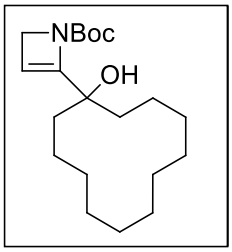


The used flow system made of two T-shaped micromixers (**M1, M2**), two microtube reactors (**R1, R2**), and three tube precooling units (**P1**, **P2** and **P3**) was dipped in a cooling bath at 0 °C. A solution of 1-Boc-3-iodoazetidine (0.0875M in CPME, flow rate: 4 mL/min) and a solution of lithium diisopropylamide (0.7M in CPME, flow rate: 1 mL/min) were introduced into **M1** by means of syringe pumps. The resulting solution passed through the first tubular reactor R1 (9.4 s) and then introduced to mixer **M2**, where it was mixed with the electrophile. The resulting solution passed through the second reactor R2 (10.4 s). After reaching the steady state (1 min), the outcoming solution was collected for 3 minutes while being quenched with water.

The reaction mixture was extracted with AcOEt (3 x 5 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under vacuum. The desired 2-azetine was obtained by washing the reaction crude with hexane/diethyl ether 9:1 (v/v) or after flash column chromatography.

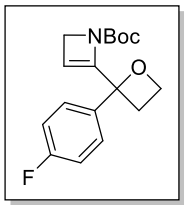
2.2 Characterization of unreported 2-substituted N-Boc-2-azetines

tert-butyl 4-(1-hydroxycyclododecyl)azete-1(*2H*)-carboxylate 2o



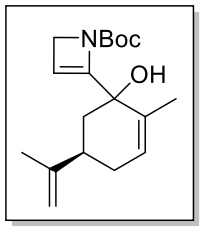
Prepared according to **GP1** with cyclododecanone as electrophile, compound **2o** was obtained as white waxy solid after flash column chromatography (63%, 223 mg, R_f = 0.5, hexane/AcOEt 9:1 + Et_3N 1%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.31 (s, 1H, C=CH), 4.20 (s, 1H, NCH_2), 1.78 – 1.65 (m, 4H), 1.47 (s 9H, 3 x CH_3), 1.46 – 1.29 (m, 18H). **^{13}C{1H} NMR** (126 MHz, $CDCl_3$) δ 156.6, 106.2, 81.2, 71.9, 55.7, 31.5, 26.5, 26.2, 22.7, 22.4, 19.5. **IR** (film)/cm^{-1} 3398, 2930, 2863, 1704, 1673, 1410, 1130, 723. **HRMS** calcd for $C_{20}H_{35}NNaO_3$ $[M+Na]^+$ 360.2515; found 360.2530.

tert-Butyl 4-(2-(4-fluorophenyl)oxetan-2-yl)azete-1(*2H*)-carboxylate 2s



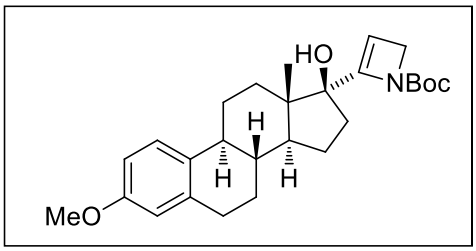
To a solution of *tert*-butyl 4-(3-chloro-1-(4-fluorophenyl)-1-hydroxypropyl)azete-1(2H)-carboxylate[2] (0.6 mmol, 205 mg) in THF (6 mL), potassium *tert*-butoxide (1.8 mmol, 202 mg) was added. After stirring for 2 hours, the reaction crude was diluted with water (6 mL). The mixture was extracted with EtOAc (3 x 6 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Compound **2r** was obtained as a pale yellow oil (91 %, 167 mg) after flash column chromatography (R_f = 0.4, hexane/AcOEt 8:2 + Et_3N 1%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.58 – 7.5 (m, 2H, Ar-H), 7.06 (t, *J* = 8.8 Hz, 2H, Ar-H), 5.59 (s, 1H, C=CH), 4.74 (ddd, *J* = 8.6, 7.0, 5.9 Hz, 1H, OCH_2), 4.59 (dt, *J* = 8.8, 6.1 Hz, 1H, OCH_2), 4.33 – 4.21 (m, 2H, NCH_2), 3.31 – 3.21 (m, 1H, OCH_2CH_2), 2.95 – 2.85 (m, 1H, OCH_2CH_2), 1.31 (s, 9H, 3 x CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 162.4 (d, $^1J_{CF}$ = 246.2 Hz), 152.8, 151.4, 138.8 (d, $^4J_{CF}$ = 3.2 Hz), 127.6 (d, $^3J_{CF}$ = 8.2 Hz), 115.0 (d, $^2J_{CF}$ = 21.5 Hz), 108.7, 83.7, 80.5, 66.3, 55.1, 33.6, 28.4. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -117.50 (s). **IR** (film)/cm^{-1} 2917, 1704, 1602, 1508, 1392.1367, 1232, 1149, 964, 833, 672. **HRMS** calcd for $C_{17}H_{20}FNNaO_3$ $[M+Na]^+$ 328.1325; found 328.1339.

tert-Butyl 4-((5*R*)-1-hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-yl)azete-1(*2H*)-carboxylate 2w



Prepared according to **GP1** with (*R*)-carvone as electrophile, compound **2v** was obtained as white waxy solid (50 %, 160 mg, dr > 95:5, absolute stereochemistry not assigned) after flash column chromatography (R_f = 0.5, hexane/Et_2O 9:1 + Et_3N 1%), $[\alpha]^{20}_D$ = -97.8° (c = 1, $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$) 5.67 – 5.60 (m, 1H, C=C*H*CH_2CH), 5.27 (s, 1H, NC=CH), 4.73 – 4.69 (m, 2H, C=CH_2), 4.24 - 4.17 (m, 2H, NCH_2), 2.26 – 2.22 (m, 1H, cyclohexenyl-CH_2), 2.14 – 2.06 (m, 1H, cyclohexenyl-CH_2), 1.96 – 1.87 (m, 1H, cyclohexenyl-CH_2), 1.81 – 1.78 (m, 3H, CH_3), 1.71 (s, 3H, CH_3), 1.48 (s, 9H, $C(CH_3)_3$). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 153.9, 148.9, 133.5, 128.4, 126.5, 109.2, 108.1, 81.4, 72.3, 55.2, 40.3, 39.0, 31.2, 28.5, 20.7, 18.4. **IR** (film)/cm^{-1} 3353, 2975, 2924, 1669, 1415, 1368, 1204, 1158, 1131, 1038, 1022, 861, 765. **HRMS** calcd for $C_{18}H_{27}NNaO_3$ $[M+Na]^+$ 328.1889; found 328.1892.

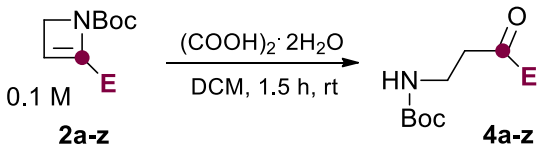
***tert*-butyl 4-((8*R*,9*S*,13*S*,14*S*,17*S*)-17-hydroxy-3-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[*a*]phenanthren-17-yl)azete-1(*2H*)-carboxylate 2z**



Prepared according to **GP1** with (8*R*,9*S*,13*S*,14*S*)-3-methoxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one as electrophile, compound **2z** was obtained as white waxy solid after flash column chromatography (55%, 264 mg, Rf = 0.3, hexane/EtOAc 9:1 + Et_3N 1%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.6 Hz, 1H, Ar-H), 6.70 (dd, *J* = 8.6, 2.7 Hz, 1H, Ar-H), 6.62 (d, *J* = 2.4 Hz, 1H, Ar-H), 5.39 (s, 1H), 5.29 (d, *J* = 7.8 Hz, 1H), 4.30 (d, *J* = 11.6 Hz, 1H), 4.22 – 4.17 (m, 2H), 3.77 (s, 3H, OCH_3), 2.94 – 2.76 (m, 2H), 2.32 – 2.22 (m, 1H), 2.16 – 1.87 (m, 5H), 1.69 – 1.59 (m, 1H), 1.48 (s, 9H, 3 x CH_3), 1.44 – 1.27 (m, 5H), 0.95 (s, 3H, CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 157.6, 156.7, 138.1, 132.9, 126.5, 114.0, 111.6, 110.2, 107.8, 104.1, 81.8, 55.4, 50.0, 48.2, 43.7, 39.6, 35.1, 32.8, 30.0, 28.5, 27.7, 26.9, 26.7, 23.1, 13.9. **IR** (film)/cm^{-1} 3342, 2917, 1669, 1424, 1255, 1162, 1132, 1044, 863. **HRMS** calcd for $C_{27}H_{30}NNaO_4$ $[M+Na]^+$ 462.2620; found 462.2619.

3. General procedures

3.1 General procedure for the oxalic acid-promoted ring opening of 2-azetines. Preparation of products 4a-4z (GP2)



To a stirred solution of azetine **2a-z** (0.25 mmol, 1.0 equiv) in dichloromethane (2.5 mL), oxalic acid dihydrate (0.125 mmol, 0.5 equiv) was added. After 1.5 hours, the reaction mixture was filtered, and the solvent was removed under reduced pressure obtaining the desired products **4a-z** without further purification.

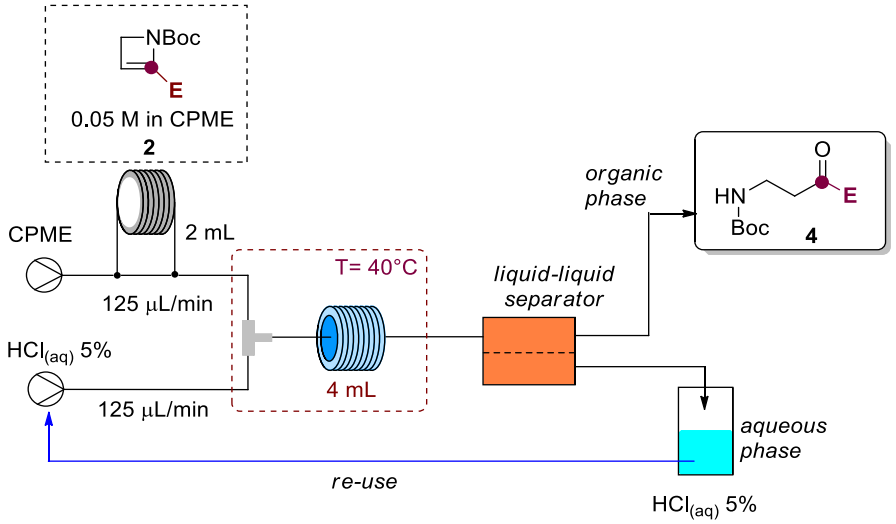
Example: Synthesis of **4b**
To a stirred solution of azetine **2b** (0.25 mmol, 84 mg, 1.0 equiv) in dichloromethane (2.5 mL), oxalic acid dihydrate (0.125 mmol, 16 mg, 0.5 equiv) was added. After 1.5 hours, the reaction mixture was filtered, and the solvent was removed under reduced pressure obtaining the desired products **4b** without further purification (87 mg, 98%).

3.2 Gram-scale synthesis of 4a and 4b

To a stirred solution of azetine **2b** (3.0 mmol, 1.0 equiv) in dichloromethane (30 mL), oxalic acid dihydrate (1.5 mmol, 0.5 equiv) was added. After 1.5 hours, the reaction mixture was filtered, and the solvent was distilled obtaining the desired products **4b** without further purification unless otherwise specified (1043 mg, 98%). The 95% of DCM could be recovered by distillation (37.9 g).

Compound **4a** could be obtained following the same procedure employing azetine **2a**, 3.0 mmol in 30 mL DCM (493 mg, 95%).

3.3 General procedure for the continuous flow acid-promoted ring opening of 2-azetines with inline liquid-liquid extraction (GP3).



Flow set-up

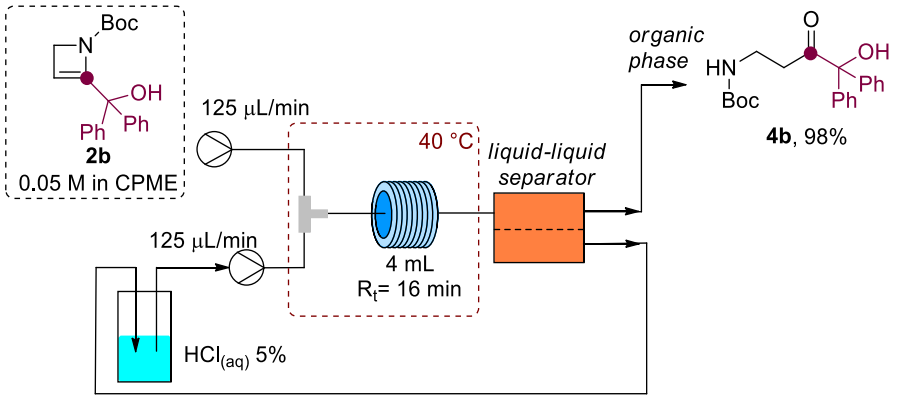
A peek T-shaped micromixer (inner volume = 500 µL), a PTFE microtube loop (ϕ = 1 mm, 2 mL, length = 254 cm) and a PTFE microtube reactor (4 mL, ϕ = 1 mm, length = 508 cm) were employed.

The flow microreactor was dipped in a heated bath (40 °C). The solution of azetine **2** (0.05 M in CPME) was loaded into the loop (2 mL). The solution of **2** (125 µL/min) and the solution of HCl (5% in H_2O, 125 µL/min) were delivered into the T-shaped peek micromixer by syringe pumps (solution of **2** was injected by fluxing fresh CPME). The resulting solution passed through R_1 (4 mL, 16 min) and then was introduced to the Zaiput Zaiput SEP-10 device equipped with a hydrophobic PTFE OB-900 pore size membrane. The resulting aqueous and organic phases were collected separately. Evaporation of the organic solvent with a rotary evaporator furnished the desired products **4b**, **4g**, **4h**, **4m**, **4o**, **4t**, **4u**, **4w** and **4z** as described in Section7.

Example: Continuous flow synthesis of **4b**

The flow microreactor was dipped in a heated bath (40 °C). The solution of azetine **2b** (0.05 M in CPME, 33.7 mg in 2 mL CPME) was loaded into the loop (2 mL). The solution of **2** (125 µL/min) and the solution of HCl (5% in H_2O, 125 µL/min) were delivered into the T-shaped peek micromixer by syringe pumps (solution of **2b** was injected by fluxing fresh CPME). The resulting solution passed through R_1 (4 mL, 16 min) and then was introduced to the Zaiput Zaiput SEP-10 device equipped with a hydrophobic PTFE OB-900 pore size membrane. The resulting aqueous and organic phases were collected separately. Evaporation of the organic solvent with a rotary evaporator furnished the desired product **4b** in 98% yield (35 mg).

3.4 Continuous flow acid-promoted ring opening of azetine 2b with inline liquid-liquid extraction and closed-loop recycle of the acidic solution (2.0 mmol scale).



Flow set-up

A peek T-shaped micromixer (inner volume = 500 µL), a PTFE microtube loop (ϕ = 1 mm, 2 mL, length = 254 cm) and a PTFE microtube reactor (4 mL, ϕ = 1 mm, length = 508 cm) were employed.

The flow microreactor was dipped in a heated bath (40 °C). The solution of azetine **2** (42 mL, 0.05 M in CPME) was delivered into the system using a Harvard PHD 2000 syringe pump (125 µL/min) and the solution of HCl (5% in H_2O, 12 mL) was delivered employing a peristaltic pump (Gilson Miniplus3 pump, 125 µL/min). The organic and aqueous solution were mixed into a T-shaped peek mixer (inner volume = 500 µL), the resulting segmented flow passed through R_1 (4 mL, 16 min, 40 °C) and then introduced to the Zaiput SEP-10 device equipped with a hydrophobic PTFE OB-900 pore size membrane. After 16 minutes from the start of the process, the organic phase was collected in a round bottom flask, while the aqueous solution was reintroduced into the HCl(aq) 5% feedstock through a PTFE microtube. The outcoming organic solution was collected for 320 min (40 mL). Distillation of the organic solvent furnished the desired product **4b** in 98% yield (696 mg). The 99.3% of CPME was recovered by distillation (34.27 g).

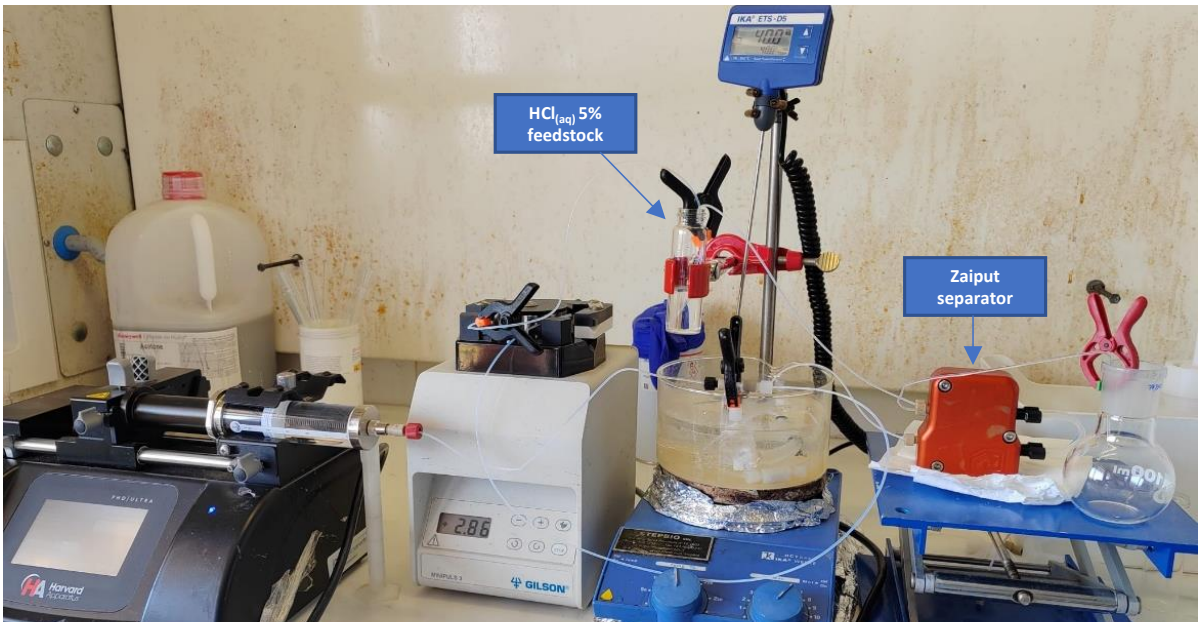
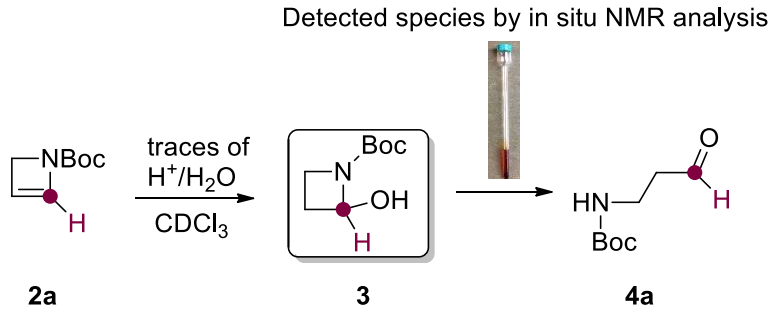


***Figure S1**. Continuous flow set-up – Synthesis of **4b** with direct recycle of $HCl_{(aq)}$ 5%* after inline liquid-liquid extraction.

4. Mechanistic investigations on the acid-promoted ring opening of 2-azetines

4.1 Ring Opening Studies on 2a – Formation of the emiaminal intermediate 3

An NMR tube charged with 2-azetine **2a** (10 mg, 0.06 mmol) in 0.6 mL of $CDCl_3$ was introduced into a 500 MHz NMR machine with the probe at 25 °C. The first spectrum (t =0 in Figure S2) was taken soon after the introduction of the sample into the probe. The ^1H NMR spectra were acquired using 8 scans (ns) and 1s relaxation delay (d1) and processed using MestReNova (Version 6.0.2). The reaction was monitored every 30 minutes, and selected spectra (0, 6h, 9h, 12h) reported in Figure S2. After 6h, the NMR spectrum reveals the presence of the product **4a** (labelled in blue) along with the signal of the putative intermediate **3** (labelled in green). After 9h, the signals of the starting azetine **2a** (labelled in red) disappeared resulting in a mixture of intermediate **3** and product **4a**. This mixture was subjected to a HSQC NMR experiment (see Figure S3) that allowed to confirm the identity of intermediate **3**. Complete conversion of **3** into **4** is observed after 12h supporting the hypothesis that **3** is a transient species in this process (Figure S2).



Long run NMR analysis

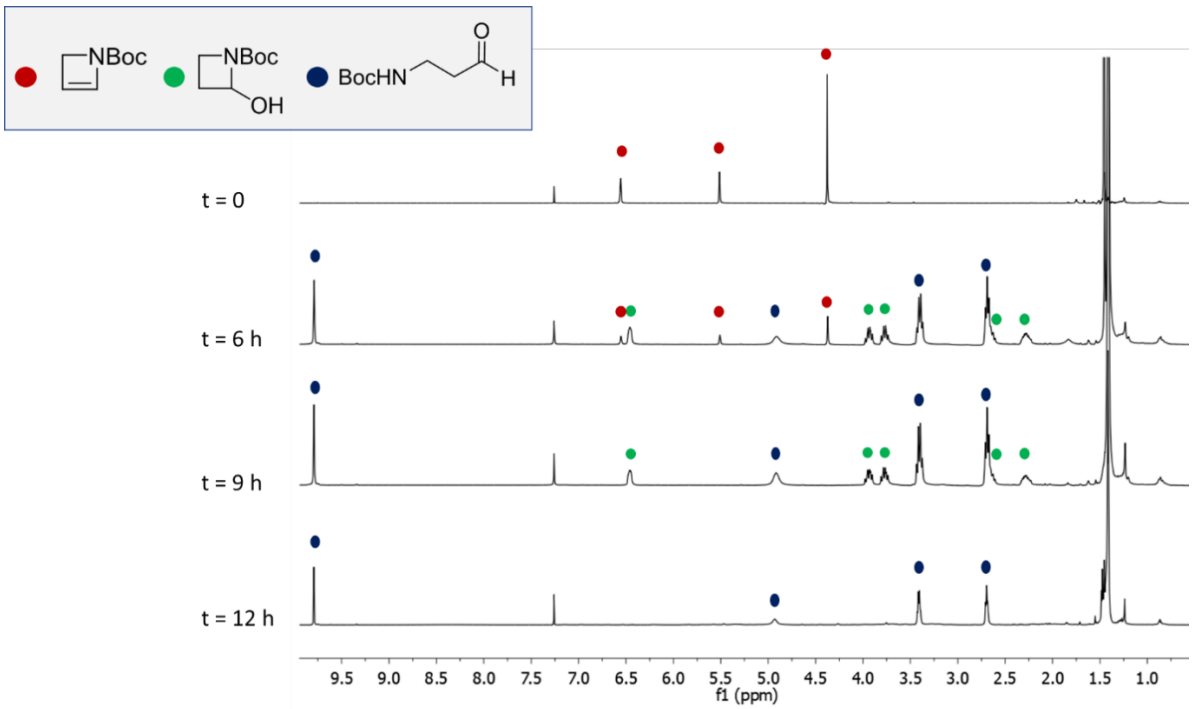


Figure S2. *Transformation **2a** → **4a** by in situ NMR analysis.*

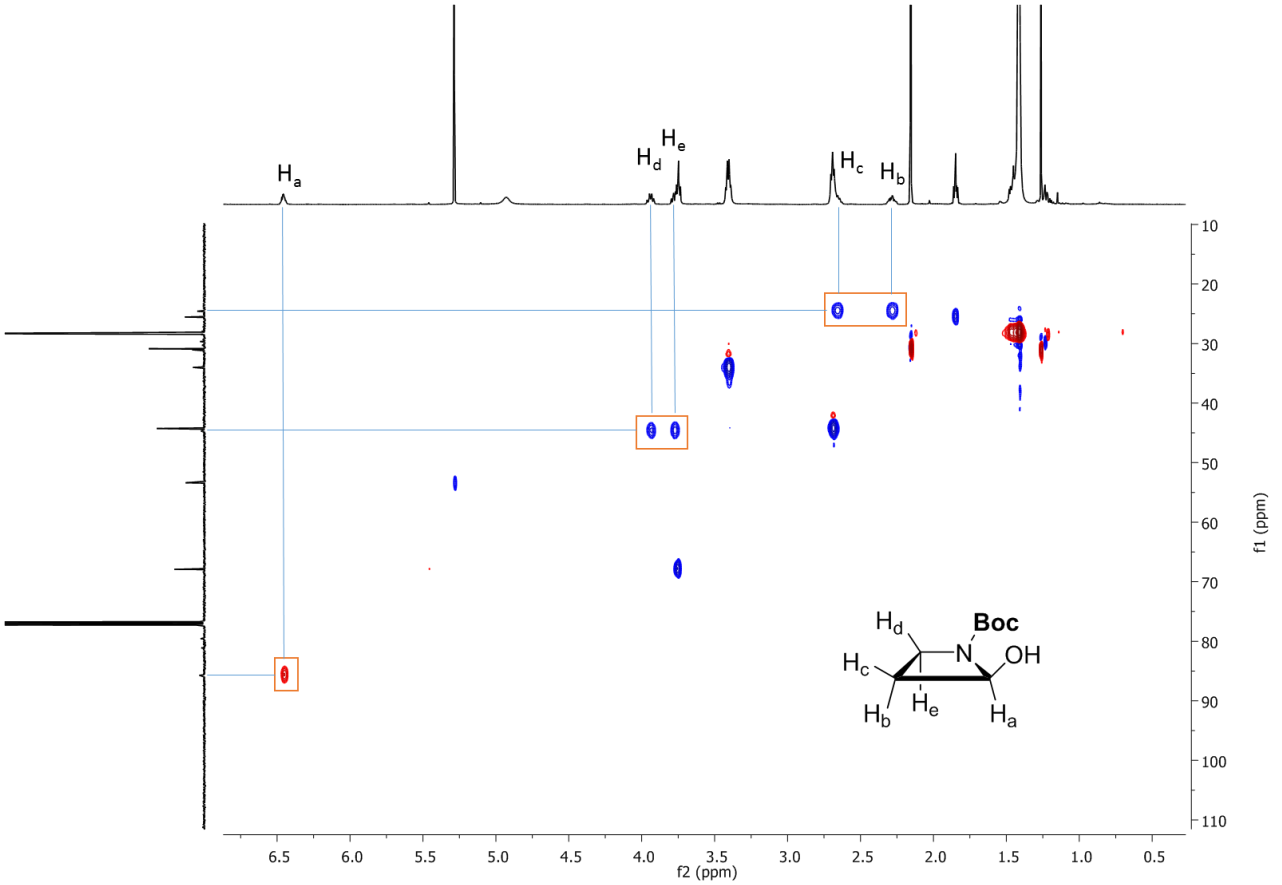


Figure S3. *500 MHz HSQC NMR analysis of a mixture* ***3/4a****.*

4.2 Ring Opening Studies on 2b - Assessing the role of acid catalyst and water

To assess the role of water in the ring-opening reaction, commercial $CDCl_3$ was previously dried by treatment with CaH_2, filtered and stored under molecular sieves (Figure S4). Residual content of water and acid was removed.

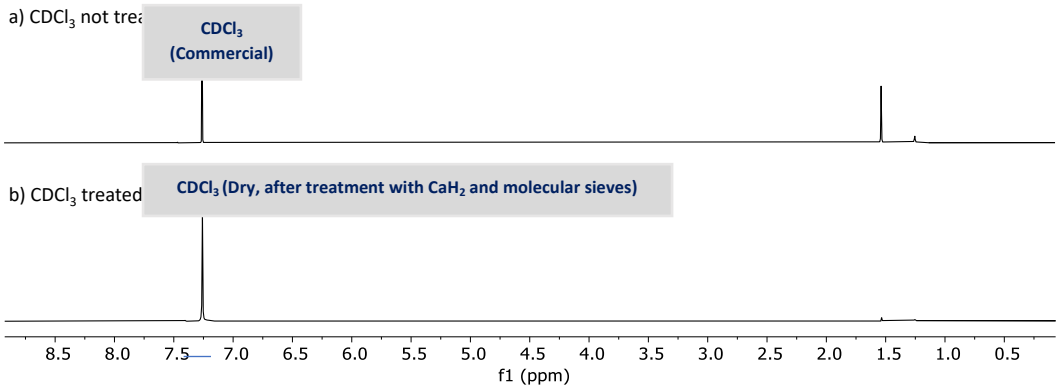


Figure S4. *^{1}H NMR spectra of commercial (top) and dry (bottom) $CDCl_3$.*

An NMR tube was charged with a solution of azetine **2b** (10 mg, 0.06 mmol) and 0.1 equiv of p-TsOH (0,006 mmol) in dry $CDCl_3$. The sealed tube was introduced in a 500 MHz NMR machine with the probe at 25 °C, and the first spectrum (Figure S5, t =0) acquired using 8 scans (ns), 1 s relaxation delay (d1) and processed using MestReNova (Version 6.0.2). The progress of the reaction was executed acquiring a ^{1}H NMR spectrum every 30 min. After 72h of acquisition, only negligible changes were observed (Figure S5, a and b) testifying that

the reaction doesn't proceed in the absence of water. Then, 20µL of water were added to the reaction mixture, and recording the spectrum after 2 h we observed the formation of the product **4b** (40% yield, spectrum d). The reaction was monitored up to 4h but the consumption of the starting material stopped. To access the role of the acid in the reaction, we decided to add an equimolar amount of *p*-TsOH to the reaction mixture (2,6 mg in 0.1 mL of $CDCl_3$). Recording the spectra every 30 min up to 2 h, after addition of acid, the conversion of the substrate reached 80% (spectrum e). This graphical comparison suggests that equimolar amount of water and acid are mandatory for the success of the reaction.

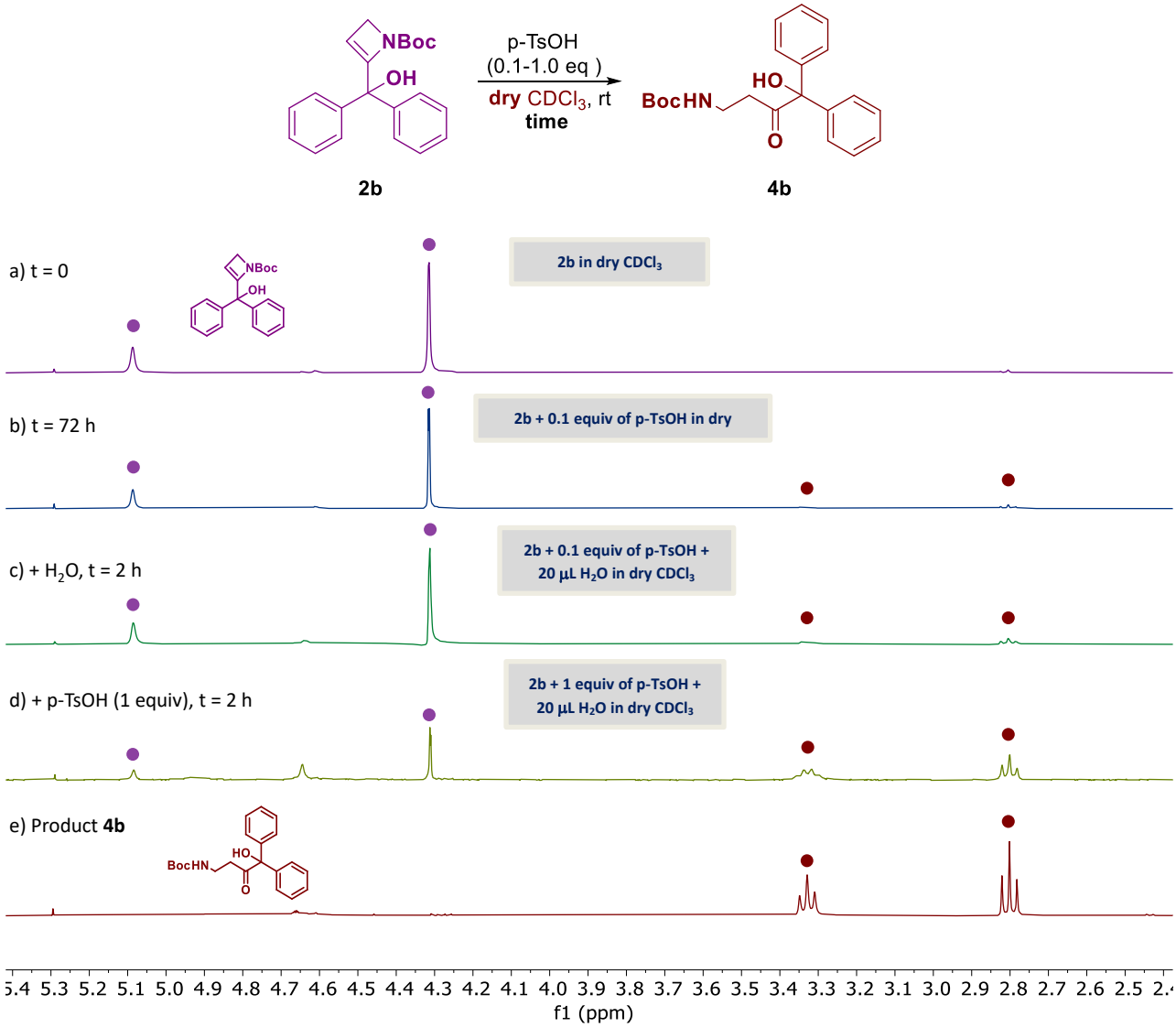


Figure S5. *^{1}H NMR spectra for the ring opening reaction, assessing the role of water and acid catalyst.*

5. Calculation of Green Metrics

The calculation of green metrics for the batch and continuous flow methods was performed following the reported equations.[5,6,*]

AE (Atom economy) = $\frac{mass\ of\ desired\ product}{mass\ of\ total\ products}$

MRP (Materia Recovery Parameter) = $\frac{1}{1+\frac{\varepsilon \cdot AE \cdot (c+s+w)}{SF \cdot m_{cp}}}$

RME (Reaction Mass Efficiency) = $\frac{\varepsilon \cdot \mathrm{AE} \cdot \mathrm{MRP}}{SF}$

STY (Space Time Yield) = $\frac{\mathrm{mass\ of\ product}}{Reactor\ volume \cdot Reaction\ time}$

Were ε = reacton yield

SF = stoichiometric factor

c = mass of not recovered catalysts

s = mass of not recovered solvents

w = mass of all the post-reaction materials employed

m_{cp} = mass of the collected target product

E-factor= $\frac{mass\ of\ total\ waste}{mass\ of\ product}$

Flow protocol (HCl). MRP = $\frac{1}{1+\frac{0.98 \cdot 1 \cdot (0.241)}{1 \cdot 0.696}}$ = 0.747

were s = 0,241 g (not recovered CPME), m_{cp}= 0.696 g

Batch protocol (oxalic acid). MRP = $\frac{1}{1+\frac{0.98 \cdot 1 \cdot (0.270\ g+1.815\ g)}{1.043\ g}}$ = 0.338

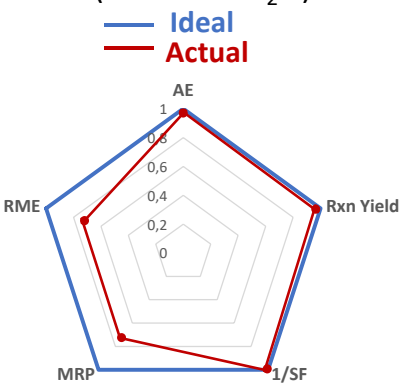
were s = 1,815 g (not recovered DCM), c = 0.270 g (not recovered oxalic acid) m_{cp}= 1.043 g

Flow protocol (HCl). E-factor = $\frac{0.241}{0.696}$ = 0.346

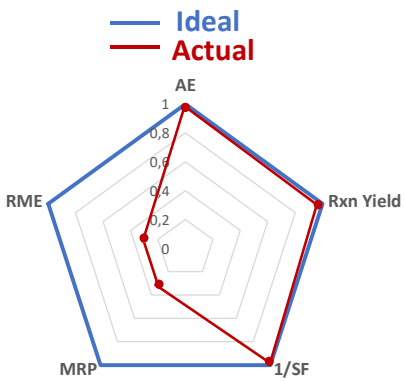
Batch protocol (oxalic acid). E-factor = $\frac{0.177}{0.086}$ = 2.058

[*] The exceeding 2mL of CPME solution (continuous flow 2.0 mmol scale reaction) employed for pushing out the desired product from the reactor was not considered for the calculation of green metrics.

Flow (HCl 5% in H_2O)



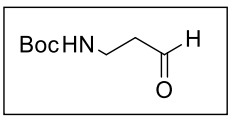
Batch ($(COOH)_2 \bullet 2H_2O$)



Parameter	Actual (Flow)	Ideal (Flow)	Parameter	Actual (Batch)	Ideal (Batch)
AE	1	1	**AE**	1	1
Rxn Yield	0.98	1	**Rxn Yield**	0.98	1
1/SF	1	1	**1/SF**	1	1
MRP	0.747	1	**MRP**	0.338	1
RME	0.731	1	**RME**	0.331	1
STY	32.62 g/L*h	-	**STY**	23.69 g/L*h	-
E-factor	0.346	0	**E-factor**	2.058	0

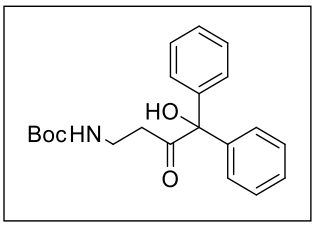
6. Characterization of products 4a-z

***tert*-Butyl (3-oxopropyl)carbamate 4a**



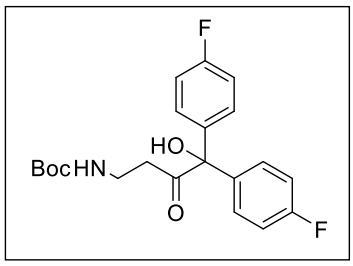
Following **GP2** with tert-butyl azete-1(*2H*)-carboxylate **2a** as starting material, compound **4a** was obtained as colorless oil (97%, 77 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.79 (s, 1H, CO*H*), 4.93 (bs, 1H, NH), 3.44 – 3.37 (m, 2H, NC$H_2$$CH_2$), 2.70 (t, *J* = 5.6 Hz, 2H, NCH_2CH_2), 1.42 (s, 9H, 3 × CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 201.6, 156.0, 79.7, 44.4, 34.2, 28.5. **IR** (film)/cm^{-1} 3363, 2978, 2932, 1694, 1515, 1453, 1367, 1251, 1168, 915, 733. **HRMS** calcd for $C_8H_{15}NNaO_3$ $[M+Na]^+$ 196.0950; found 196.0954.

***tert*-Butyl (4-hydroxy-3-oxo-4,4-diphenylbutyl)carbamate 4b**



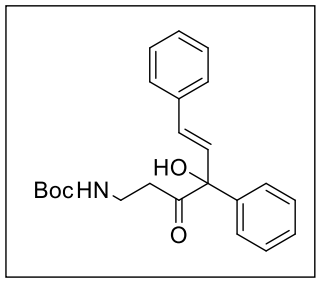
Following **GP2** with *tert*-Butyl 4-(Hydroxydiphenylmethyl)azete-1(*2H*)-carboxylate **2b** as starting material, compound **4b** was obtained as a white waxy solid (97%, 86 mg). Compound **4g** was obtained in 98% yield (35 mg) following **GP3**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 10H, Ar-H), 4.90 (bs, 1H, NH), 4.60 (s, 1H, OH), 3.37 – 3.29 (m, 2H, NC$H_2$$CH_2$), 2.80 (t, *J* = 5.7 Hz, 2H, NCH_2CH_2), 1.41 (s, 9H, 3 × CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 210.7, 155.7, 141.4, 128.5, 128.3, 127.9, 85.4, 79.4, 38.9, 35.6, 28.4. **IR** (film)/cm^{-1} 3401, 2917, 1713, 1682, 1525, 1447, 1367, 1274, 1165, 1050, 700. **HRMS** calcd for $C_{21}H_{25}NNaO_4$ $[M+Na]^+$ 378.1681; found 378.1682.

***tert*-Butyl (4,4-bis(4-fluorophenyl)-4-hydroxy-3-oxobutyl)carbamate 4c**



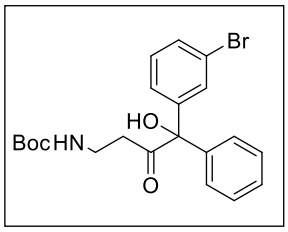
Following **GP2** with *tert*-Butyl 4-(bis(4-fluorophenyl)(hydroxy)methyl)azete-1(*2H*)-carboxylate **2c** as starting material, compound **4c** was obtained as a white waxy solid (96%, 94 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 4H, Ar-H), 7.08 – 7.03 (m, 4H, Ar-H), 4.86 (bs, 1H, NH), 4.56 (s, 1H, OH), 3.38 – 3.32 (m, 2H, NC$H_2$$CH_2$), 2.78 (t, *J* = 5.8 Hz, 2H, NCH_2CH_2), 1.41 (s, 9H, 3 × CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 207.1, 162.7 (d, $^1J_{CF}$ = 248.5 Hz), 156.0, 137.2 (d, $^4J_{CF}$ = 3.3 Hz), 129.8 (d, $^3J_{CF}$ = 8.2 Hz), 115.7 (d, $^2J_{CF}$ = 21.6 Hz), 84.6, 79.8, 39.0, 35.8, 28.5. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -113.31 (s). **IR** (film)/cm^{-1} 3400, 2979, 2917, 1693, 1506, 1393, 1367, 1230, 1161, 1068, 836. **HRMS** calcd for $C_{21}H_{23}F_2NNaO_4$ $[M+Na]^+$ 414.1493; found 414.1485.

***tert*-Butyl *(E)*-(4-hydroxy-3-oxo-4,6-diphenylhex-5-en-1-yl)carbamate 4d**



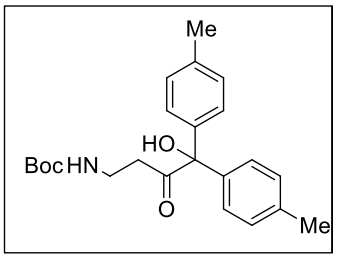
Following **GP2** with *tert*-Butyl *(E)*-3-(1-Hydroxy-1,3-diphenylallyl)azetidine-1-carboxylate **2d** as starting material, compound **4d** was obtained as a white waxy solid (95%, 90 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 – 7.27 (m, 10 H, Ar-H), 6.99 (d, *J* = 15.7 Hz, 1H, CH=CH), 6.81 (d, *J* = 15.7 Hz, 1H, CH=CH), 4.85 (bs, 1H, NH), 4.62 (bs, 1H, OH), 3.38 – 3.33 (m, 2H, N$CH_2$$CH_2$), 2.85 – 2.80 (m, 1H), 2.72 – 2.66 (m, 1H), 1.36 (s, 9H, 3 × CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 209.0, 155.9, 140.9, 136.3, 132.9, 129.1, 128.8, 128.6, 128.4, 127.1, 127.0, 126.8, 83.3, 79.6, 37.8, 35.7, 28.5. **IR** (film)/cm^{-1} 3435, 2977, 2917, 1710, 1495, 1449, 1366, 1266, 1168, 1073, 739.**HRMS** calcd for $C_{23}H_{27}NNaO_4$ $[M+Na]^+$ 404.1838; found 404.1844.

***tert*-Butyl (4-(3-bromophenyl)-4-hydroxy-3-oxo-4-phenylbutyl)carbamate 4e**



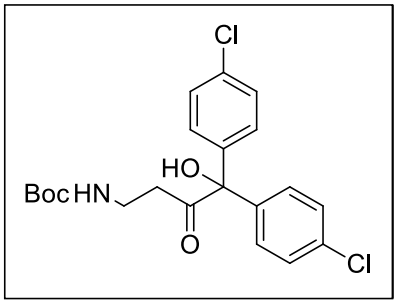
Following **GP2** with *tert*-Butyl 4-((3-bromophenyl)(hydroxy)(phenyl)methyl)azete-1(*2H*)-carboxylate **2e** as starting material, compound **4e** was obtained as a white waxy solid (95%, 103 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.58 – 7.56 (m, 1 H, Ar-H), 7.50 – 7.46 (m, 1H, Ar-H), 7.40 – 7.35 (m, 3H, Ar-H), 7.31 – 7.27 (m, 2H, Ar-H), 7.26 – 7.21 (m, 2H, Ar-H overlapping $CHCl_3$ signal), 4.90 (bs, 1H, NH), 4.58 (s, 1H, OH), 3.39 – 3.32 (m, 2H, NCH_2CH$_2$), 2.86 (dt, *J* = 18.4, 5.7 Hz, 1H, NCH$_2$CH*H*), 2.75 (dt, *J* = 18.2, 5.8 Hz, 1H, NCH$_2$CH_2), 1.41 (s, 9H, 3 × CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 210.2, 156.0, 143.7, 141.1, 131.6, 131.1, 130.1, 128.9, 128.7, 127.9, 126.8, 122.9, 85.1, 79.7, 39.2, 35.7, 28.5. **IR** (film)/cm^{-1} 3413, 2975, 2924, 1691, 1510, 1448, 1366, 1250, 1167, 1060, 698. **HRMS** calcd for $C_{21}H_{24}BrNNaO_4$ $[M+Na]^+$ 456.0786; found 456.0784.

***tert*-Butyl (4-hydroxy-3-oxo-4,4-di-*p*-tolylbutyl)carbamate 4f**



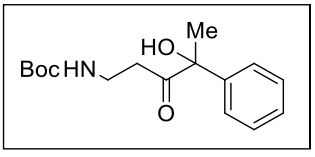
Following **GP2** with *tert*-Butyl 4-(Hydroxydi-p-tolylmethyl)azete-1(*2H*)-carboxylate **2f** as starting material, compound **4f** was obtained as a white waxy solid (96%, 92 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.3 Hz, 4 H, Ar-H), 7.16 (d, *J* = 8.1 Hz, 4 H, Ar-H), 4.89 (bs, 1H, NH), 4.50 (s, 1H, OH), 3.35 – 3.29 (m, 2H, NCH_2CH$_2$), 2.79 (t, *J* = 5.7 Hz, 2H, NCH$_2$CH_2), 2.35 (s, 6H, 2 × Ar-CH_3) 1.41 (s, 9H, 3 × CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 211.0, 155.7, 138.5, 138.0, 129.1, 127.8, 85.1, 79.3, 38.6, 35.6, 28.4, 21.1. **IR** (film)/cm^{-1} 3414, 2976, 2924, 1706, 1509, 1454, 1366, 1279, 1168, 1068, 816. **HRMS** calcd for $C_{23}H_{29}NNaO_4$ $[M+Na]^+$ 406.1994; found 406.1999.

***tert*-Butyl (4,4-bis(4-chlorophenyl)-4-hydroxy-3-oxobutyl)carbamate 4g**



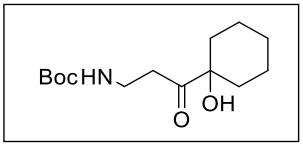
Following **GP2** with *tert*-Butyl 4-(bis(4-chlorophenyl)(hydroxy)methyl)azete-1(*2H*)-carboxylate **2g** as starting material, compound **4g** was obtained as white waxy solid (95%, 100 mg). Compound **4g** was obtained in 96% yield (41 mg) following **GP3**. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 4H, Ar-H), 7.30 – 7.23 (m, 4H, Ar-H overlapping $CHCl_3$ signal), 4.87 (bs, 1H, NH), 4.61 (s, 1H, OH), 3.40 – 3.29 (m, 2H, NCH_2CH$_2$), 2.78 (t, *J* = 5.8 Hz, 2H, NCH$_2$CH_2), 1.41 (s, 9H, 3 × CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 209.8, 156.0, 139.7, 134.7, 129.3, 129.0, 84.7, 79.9, 39.1, 35.8, 28.5. **IR** (film)/cm^{-1} 3401, 2917, 2849, 1688, 1490, 1400, 1366, 1283, 1167, 1093, 823. **HRMS** calcd for $C_{21}H_{23}Cl_2NNaO_4$ $[M+Na]^+$ 446.0902; found 446.0906.

***tert*-Butyl (4-hydroxy-3-oxo-4-phenylpentyl)carbamate 4h**



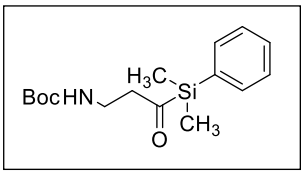
Following **GP2** with *tert*-Butyl 4-(1-Hydroxy-1-phenylethyl)azete-1(*2H*)-carboxylate **2h** as starting material, compound **4h** was obtained as a pale yellow oil (96%, 70 mg). Compound **4h** was obtained in 98% yield (29 mg) following **GP3**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 – 7.40 (m, 2 H, Ar-H), 7.39 – 7.34 (m, 2H, Ar-H), 7.32 – 7.28 (m, 1 H, Ar-H), 4.81 (bs, 1H, NH), 3.35 – 3.23 (m, 2H, NCH_2CH$_2$), 2.73 – 2.65 (m, 1H, NCH$_2$CH_2), 2.57 – 2.48 (m, 1H, NCH$_2$CH_2), 1.74 (s, 3H, CH_3), 1.37 (s, 9H, 3 × CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 211.3, 155.8, 141.1, 128.7, 128.1, 125.8, 80.0, 79.4, 36.2, 35.6, 28.3, 24.3. **IR** (film)/cm^{-1} 3408, 2978, 2933, 1709, 1515, 1448, 1367, 1281, 1170, 1073, 701. **HRMS** calcd for $C_{16}H_{23}NNaO_4$ $[M+Na]^+$ 316.1525; found 316.1523.

***tert*-Butyl (3-(1-hydroxycyclohexyl)-3-oxopropyl)carbamate 4i**



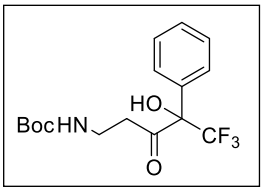
Following **GP2** with *tert*-Butyl 4-(1-Hydroxycyclohexyl)azete-1(*2H*)-carboxylate **2i** as starting material, compound **4i** was obtained as a pale yellow oil (95%, 64 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.94 (bs, 1H, NH), 3.44 – 3.36 (m, 2H, NC*H*$_2$CH$_2$), 2.81 (t, *J* = 5.7 Hz, 2H, NCH$_2$C*H*$_2$), 1.76 – 1.60 (m, 7H, cyclohexyl-CH$_2$), 1.49 – 1.44 (m, 2H, cyclohexyl-CH$_2$), 1.41 (s, 9H, 3 × CH$_3$), 1.30 – 1.21 (m, 1H, cyclohexyl-CH$_2$). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 214.4, 155.9, 79.4, 78.1, 36.2, 35.5, 33.7, 28.3, 25.2, 21.0. **IR** (film)/cm^{-1} 3390, 2977, 2933, 1704, 1694, 1519, 1506, 1367, 1252, 1170, 986. **HRMS** calcd for $C_{14}H_{25}NNaO_4$ [M+Na]$^+$ 294.1681; found 294.1670.

***tert*-Butyl (3-(dimethyl(phenyl)silyl)-3-oxopropyl)carbamate 4j**



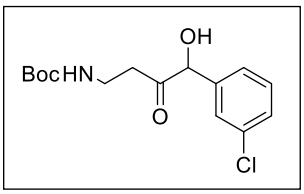
Following **GP2** with *tert*-Butyl 4-(dimethyl(phenyl)silyl)azete-1(*2H*)-carboxylate **2j** as starting material, compound **4j** was obtained as a pale yellow oil (95%, 73 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 – 7.51 (m, 2H, Ar-H), 7.44 – 7.37 (m, 3 H, Ar-H), 4.86 (bs, 1H, NH), 3.32 – 3.23 (m, 2H, NC*H*$_2$CH$_2$), 2.79 (t, *J* = 5.7 Hz, 2H, NCH$_2$C*H*$_2$), 1.39 (s, 9H, 3 × CH$_3$), 0.49 (s, 6H, Si(CH$_3$)$_2$). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 246.4, 156.0, 134.1, 134.0, 130.2, 128.4, 79.3, 48.5, 34.3, 28.5, – 4.8. **IR** (film)/cm^{-1} 3393, 2849, 1712, 1639, 1505, 1365, 1249, 1170, 1111, 835, 699. **HRMS** calcd for $C_{16}H_{25}NNaO_3Si$ [M+Na]$^+$ 330.1501; found 330.1509.

***tert*-Butyl (5,5,5-trifluoro-4-hydroxy-3-oxo-4-phenylpentyl)carbamate 4k**



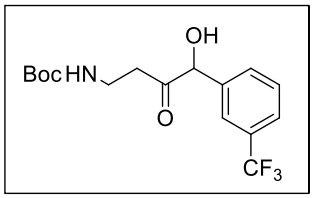
Following **GP2** with *tert*-butyl 4-(2,2,2-trifluoro-1-hydroxy-1-phenylethyl)azete-1(*2H*)-carboxylate **2k** as starting material, compound **4k** was obtained as white waxy solid (96%, 83 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56 –7.53 (m, 2H, Ar-H), 7.45 – 7.38 (m, 3H, Ar-H), 5.30 (s, 1H), 4.82 (s, 1H), 3.45 – 3.29 (m, 2H, NCH$_2$), 2.80 – 2.71 (m, 2H, NCH$_2$C*H*$_2$), 1.39 (s, 9H, 3 × CH$_3$). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 203.3, 156.1, 132.8, 129.5, 129.0, 126.4, 123.4 (q, $^1J_{CF}$ = 286.3 Hz), 82.4 (q, $^2J_{CF}$ = 28.2 Hz), 80.0, 38.5, 35.9, 28.3. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -73.46 (s). **IR** (film)/cm^{-1} 3429, 2980, 2931, 1726, 1694, 1515, 1453, 1368, 1276, 1169, 919. **HRMS** calcd for $C_{16}H_{20}F_3NNaO_4$ [M+Na]$^+$ 370.1242; found 370.1248.

***tert*-Butyl (4-(3-chlorophenyl)-4-hydroxy-3-oxobutyl)carbamate 4l**



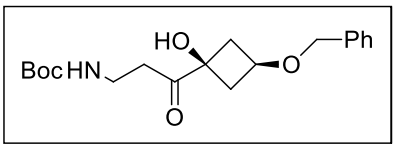
Following **GP2** with *tert*-Butyl 4-((3-chlorophenyl)(hydroxy)methyl)azete-1(*2H*)-carboxylate **2l** as starting material, compound **4l** was obtained as a pale yellow oil (95%, 74 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 – 7.31 (m, 3H, Ar-H), 7.24 – 7.20 (m, 1H, Ar-H), 5.06 (d, *J* = 4.1 Hz, OH), 4.81 (bs, 1H, NH), 4.22 (d, *J* = 4.1 Hz, 1H, C*H*OH), 3.38 – 3.31 (m, 2H, NC*H*$_2$CH$_2$), 2.71 – 2.63 (m, 1H, NCH$_2$C*H*$_2$), 2.52 (dt, *J* = 17.8, 5.7 Hz, 1H, NCH$_2$C*H*$_2$), 1.39 (s, 9H, 3 x CH$_3$). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 208.1, 155.7, 139.6, 135.1, 130.3, 129.0, 127.3, 125.5, 79.6, 79.2, 38.3, 35.1, 28.3. **IR** (film)/cm^{-1} 3452, 2980, 2928, 1709, 1507, 1393, 1367, 1250, 1168, 910, 734. **HRMS** calcd for $C_{15}H_{20}ClNNaO_4$ [M+Na]$^+$ 336.0979; found 336.0976.

***tert*-Butyl (4-(3-chlorophenyl)-4-hydroxy-3-oxobutyl)carbamate 4m**



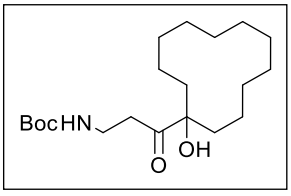
Following **GP2** with *tert*-Butyl 4-((3-trifluoromethylphenyl)(hydroxy)methyl)azete-1(*2H*)-carboxylate **2m** as starting material, compound **4m** was obtained as a pale yellow oil (96%, 83 mg). Compound **4m** was obtained in 95% yield (33 mg) following **GP3**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63 – (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 5.3 Hz, 1H), 5.16 (d, *J* = 3.9 Hz, 1H), 4.84 (s, 1H), 4.31 (d, *J* = 4.0 Hz, 1H), 3.35 (dd, *J* = 11.3, 5.5 Hz, 1H), 2.74 – 2.63 (m, 1H), 2.50 (dt, *J* = 18.0, 5.7 Hz, 1H), 1.39 (s, 5H). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.86. **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 208.3, 156.0, 138.9, 131.7 (q, *J* = 32.6 Hz), 130.8, 129.7, 125.8 (q, *J* = 3.6 Hz), 124.1, 123.9 (q, *J* = 272.4 Hz), 79.8, 79.5, 38.4, 35.2, 28.4. **IR** (film)/cm^{-1} 3374, 2979, 2931, 1694, 1124, 1072, 736, 702. **HRMS** calcd for $C_{16}H_{20}F_3NNaO_4$ $[M+Na]^+$ 370.1242; found 370.1240.

***tert*-Butyl (3-(1-hydroxy-3-phenoxycyclobutyl)-3-oxopropyl)carbamate 4n**



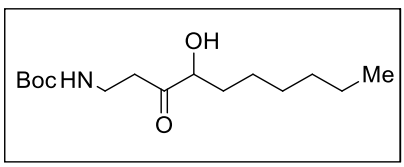
Following **GP2** with *tert*-Butyl 4-(3-(Benzyloxy)-1-hydroxycyclobutyl)azete-1(*2H*)-carboxylate **2n** as starting material, compound **4n** was obtained as a white waxy solid (96%, 83 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H, Ar-H), 4.96 (bs, 1H, NH), 4.45 (s, 2H, OCH_2), 3.96 (quin, *J* = 6.8 Hz, 1H, C*H*OCH_2), 3.46 – 3.40 (m, 2H, NCH_2CH_2), 2.83 – 2.75 (m, 4H, 2H NCH_2CH_2 and 2H $COHCH_2$), 2.33 – 2.26 (m, 2H, $COHCH_2$), 1.42 (s, 9H, 3 × CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 211.9, 156.0, 137.7, 128.4, 127.8, 127.8, 79.6, 73.6, 70.5, 64.6, 43.0, 36.4, 35.5, 28.3. **IR** (film)/cm^{-1} 3391, 2927, 2855, 1692, 1514, 1454, 1366, 1247, 1168, 1069, 736. **HRMS** calcd for $C_{19}H_{27}NNaO_5$ $[M+Na]^+$ 372.1787; found 372.1797.

***tert*-Butyl (3-(1-hydroxycyclododecyl)-3-oxopropyl)carbamate 4o**



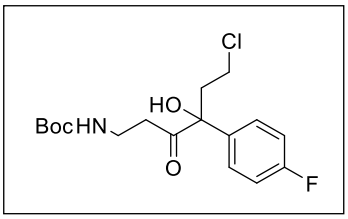
Following **GP2** with *tert*-Butyl 4-(1-hydroxycyclododecyl)azete-1(*2H*)-carboxylate **2o** as starting material, compound **4o** was obtained as a white waxy solid (96%, 85 mg). Compound **4o** was obtained in 97% yield (35 mg) following **GP3**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.96 (bs, 1H, NH), 3.42 – 3.35 (m, 2H, NCH_2), 2.90 (s, 1H, OH), 2.80 (t, *J* = 5.8 Hz, 2H, NCH_2CH_2), 1.66 – 1.61 (m, 4H, cyclododecyl-CH_2), 1.42 (s, 9H, 3 × CH_3), 1.36 (bs, 18H, cyclododecyl-CH_2). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 214.6, 156.1, 81.4, 79.5, 37.9, 35.7, 32.3, 28.6, 26.5, 26.0, 22.8, 22.4, 19.6. **IR** (film)/cm^{-1} 3466, 2917, 2849, 1688, 1515, 1471, 1365, 1248, 1166, 1080, 968. **HRMS** calcd for $C_{20}H_{37}NNaO_4$ $[M+Na]^+$ 378.2620; found 378.2639.

***tert*-Butyl (4-hydroxy-3-oxodecyl)carbamate 4p**



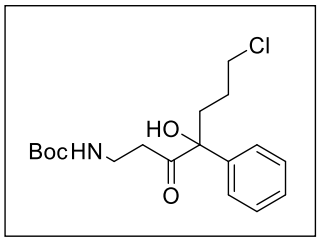
Following **GP2** with *tert*-Butyl 4-(1-Hydroxyheptyl)azete-1(*2H*)-carboxylate **2p** as starting material, compound **4p** was obtained as a pale yellow oil (95%, 68 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.95 (bs, 1H, NH), 4.19 – 4.13 (m, 1H, C*H*OH), 3.45 – 3.39 (m, 2H, NCH_2CH_2), 3.35 (d, *J* = 4.8 Hz, 1H, OH), 2.77 (dt, *J* = 17.9, 5.8 Hz, 1H, NCH_2CH_2), 2.65 (dt, *J* = 17.5, 5.6 Hz, 1H, NCH_2CH_2), 1.84 – 1.76 (m, 1H, CH_2), 1.57 – 1.49 (m, 1H, CH_2), 1.43 (s, 9H, 3 × CH_3), 1.35 – 1.24 (m, 8H, 4 × CH_2), 0.90 – 0.85 (m, 3H, CH_2CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 211.8, 155.9, 79.5, 76.6, 38.1, 35.1, 33.6, 31.6, 29.1, 28.3, 24.7, 22.5, 14.0. **IR** (film)/cm^{-1} 3391, 2956, 2930, 1712, 1514, 1456, 1366, 1251, 1171, 1085, 962. **HRMS** calcd for $C_{15}H_{29}NNaO_4$ $[M+Na]^+$ 310.1994; found 310.1996.

tert-Butyl (6-chloro-4-(4-fluorophenyl)-4-hydroxy-3-oxohexyl)carbamate 4q



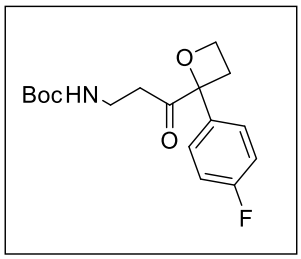
Following **GP2** with *tert*-Butyl 4-(3-Chloro-1-(4-fluorophenyl)-1-hydroxypropyl)- azete-1(*2H*)-carboxylate **2q** as starting material, compound **4q** was obtained as a white waxy solid (96%, 86 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 – 7.39 (m, 2H, Ar-H), 7.09 – 7.02 (m, 2H, Ar-H), 4.78 (bs, 1H, NH), 3.62 – 3.51 (m, 2H, CH_2CH_2Cl), 3.31– 3.25 (m, 2H, NCH_2CH_2), 2.73 – 2.59 (m, 4H, 2H NCH_2CH_2 and 2H CH_2CH_2Cl), 1.38 (s, 9H, 3 × CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 209.7, 162.5 (d, $^{1}J_{CF}$ = 248.0 Hz), 156.0, 135.3, 127.5 (d, $^{3}J_{CF}$ = 8.2 Hz), 115.8 (d, $^{2}J_{CF}$ = 21.6 Hz), 81.3, 79.7, 40.1, 39.4, 36.4, 35.7, 28.3. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -113.72 (s). **IR** (film)/cm^{-1} 3411, 2978, 2933, 1710, 1688, 1602, 1507, 1367, 1237, 1162, 836. **HRMS** calcd for $C_{17}H_{23}ClFNNaO_4$ $[M+Na]^+$ 382.1197; found 382.1192.

***tert*-Butyl (7-chloro-4-hydroxy-3-oxo-4-phenylheptyl)carbamate 4r**



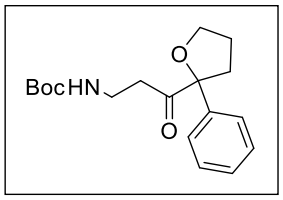
Following **GP2** with *tert*-Butyl 4-(4-chloro-1-hydroxy-1-phenylbutyl)azete-1(*2H*)-carboxylate **2r** as starting material, compound **4r** was obtained as white waxy solid (95%, 84 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46 – 7.43 (m, 2H, Ar-H), 7.39 – 7.36 (m, 2H, Ar-H), 7.32 – 7.29 (m, 1H, Ar-H), 4.76 (bs, 1H, NH), 4.47 (s, 1H, OH), 3.60 – 3.56 (m, 2H, CH_2CH_2Cl), 3.33 – 3.25 (m, 2H, NCH_2CH_2), 2.69 – 2.66 (m, 1H, NCH_2CH_2), 2.62 – 2.57 (m, 1H, NCH_2CH_2), 2.36 – 2.31 (m, 1H, $CH_2CH_2CH_2Cl$), 2.29 – 2.21 (m, 1H, $CH_2CH_2CH_2Cl$), 1.95 – 1.84 (m, 1H, CH_2CH_2Cl), 1.75 – 1.66 (m, 1H, CH_2CH_2Cl), 1.38 (s, 9H, 3 × CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 210.9, 156.0, 140.0, 129.0, 128.3, 126.2, 82.4, 79.7, 45.3, 36.5, 35.7, 34.2, 28.5, 26.7. **IR** (film)/cm^{-1} 3413, 2918, 2849, 1694, 1514, 1448, 1366, 1251, 1169, 1073, 756. **HRMS** calcd for $C_{18}H_{26}ClNNaO_4$ $[M+Na]^+$ 378.1448; found 378.1419.

***tert*-Butyl (3-(2-(4-fluorophenyl)oxetan-2-yl)-3-oxopropyl)carbamate 4s**



Following **GP2** with *tert*-Butyl 4-(2-(4-fluorophenyl)oxetan-2-yl)azete-1(*2H*)-carboxylate **2s** as starting material, compound **4s** was obtained as white waxy solid (95%, 77mg).**^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.36 (m, 2H, Ar-H), 7.09 – 7.06 (m, 2H, Ar-H), 4.81 (bs, 1H, NH), 4.61 – 4.54 (m, 2H, OCH_2), 3.32 – 3.31 (m, 3H, 2H NCH_2 and 1H OCH_2CH_2), 2.95 (dt, *J* = 18.3, 5.8 Hz, 1H, NCH_2CH_2), 2.73 – 2.65 (m, 1H, OCH_2CH_2), 2.56 – 2.47 (m, 1H, NCH_2CH_2), 1.38 (s, 9H, 3 × CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 210.7, 162.6 (d, $^{1}J_{CF}$ = 247.4 Hz), 155.8, 136.2 (d, $^{4}J_{CF}$, *J* = 3.0 Hz), 126.2 (d, $^{3}J_{CF}$ = 8.4 Hz), 115.8 (d, $^{2}J_{CF}$, *J* = 21.7 Hz), 90.8, 79.4, 66.2, 35.9, 32.4, 29.9, 28.5. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -114.17 (s). **IR** (film)/cm^{-1} 3398, 2918, 2850, 1713, 1646, 1506, 1366, 1236, 1169. **HRMS** calcd for $C_{17}H_{22}FNNaO_4$ $[M+Na]^+$ 346.1431; 346.1434 found.

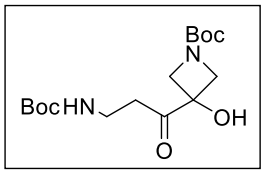
***tert*-Butyl (3-oxo-3-(2-phenyltetrahydrofuran-2-yl)propyl)carbamate 4t**



Following **GP2** with *tert*-Butyl 4-(2-phenyltetrahydrofuran-2-yl)azete-1(*2H*)-carboxylate **2t** as starting material, compound **4t** was obtained as white waxy solid (96%, 77 mg). Compound **4t** was obtained in 98% yield (31 mg) following **GP3**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 – 7.40 (m, 2H, Ar-H), 7.35 – 7.31 (m, 2H, Ar-H), 7.28 – 7.24 (m, 1H, Ar-H overlapping $CHCl_3$ signal), 4.78 (bs, 1H, NH), 4.07 – 3.96 (m, 2H, OCH_2), 3.27 – 3.19 (m, 2H, NCH_2), 2.91 – 2.79 (m, 2H, 1H NCH_2CH_2 and 1H $OCH_2CH_2CH_2$), 2.64 – 2.55 (m, 1H, NCH_2CH_2), 2.02 – 1.94 (m, 1H, $OCH_2CH_2CH_2$), 1.91 – 1.82 (m, 2H OCH_2CH_2), 1.37 (s, 9H, 3 × CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 211.0, 155.7, 140.8, 128.5, 127.6, 125.0, 92.4, 79.2,

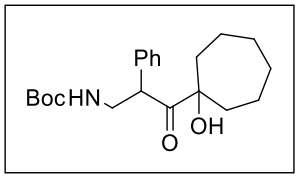
79.0, 68.8, 36.9, 35.6, 35.4, 28.5, 25.9. **IR** (film)/cm^{-1} 3400, 2917, 2849, 1714, 1505, 1447, 1365, 1249, 1170, 1060, 700. **HRMS** calcd for $C_{18}H_{25}NNaO_4$ [M+Na]$^+$ 342.1681; found 342.1678.

***tert*-Butyl 3-(3-((tert-butoxycarbonyl)amino)propanoyl)-3-hydroxyazetidine-1-carboxylate 4u**



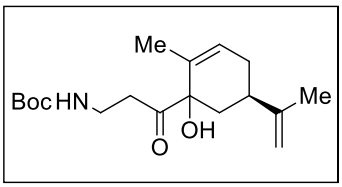
Following **GP2** with *tert*-Butyl 4-(1-(tert-Butoxycarbonyl)-3-hydroxyazetidin-3-yl)-azete-1(*2H*)-carboxylate **2u** as starting material, compound **4u** was obtained as a pale yellow oil (95%, 82 mg). Compound **4u** was obtained in 93% yield (32 mg) following **GP3**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.99 (bs, 1H, NH), 4.12 and 4.01 (2 × d, AB system, *J* = 9.5 Hz, 4H, azetidine-CH_2), 3.52 – 3.45 (m, 2H, NHC*H*$_2$), 2.99 (t, *J* = 5.6 Hz, 2H, NCH_2CH_2), 1.45 (s, 9H, 3 × CH_3), 1.42 (s, 9H, 3 × CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 208.7, 156.4, 156.0, 80.6, 79.9, 73.7, 59.7, 35.9, 35.5, 28.3, 28.3. **IR** (film)/cm^{-1} 3366, 2979, 2935, 1691, 1516, 1506, 1478, 1368, 1252, 1167, 914. **HRMS** calcd for $C_{16}H_{28}N_2NaO_6$ [M+Na]$^+$ 367.1845; found 367.1846.

***tert*-Butyl (3-(1-hydroxycycloheptyl)-3-oxo-2-phenylpropyl)carbamate 4v**



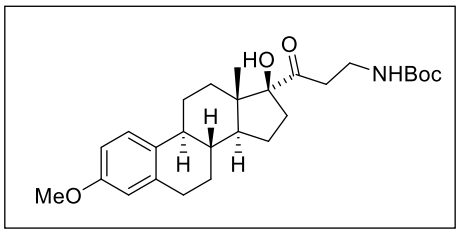
Following **GP2** with *tert*-Butyl 4-(1-hydroxycycloheptyl)-3-phenylazete-1(*2H*)-carboxylate **2v** as starting material, compound **4v** was obtained as a white waxy solid (96%, 87 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 2H, Ar-H), 7.29 – 7.24 (m, 3H, Ar-H overlapping $CHCl_3$ signal), 4.76 (bs, 1H, NH), 4.67 – 4.61 (m, 1H, NCH_2CH), 3.51 – 3.40 (m, 2H, NCH_2), 3.11 (bs, 1H, OH), 1.99 – 1.93 (m, 1H, cycloheptyl-CH_2), 1.69 – 1.45 (m, 10H, cycloheptyl-CH_2 overlapping H_2O signal), 1.42 (s, 9H, 3 × CH_3), 1.33 – 1.28 (m, 1H, cycloheptyl-CH_2). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 214.4, 156.0, 136.1, 129.2, 128.4, 127.9, 82.2, 79.8, 52.1, 44.9, 37.9, 37.2, 29.2, 29.1, 28.5, 23.0, 22.9. **IR** (film)/cm^{-1} 3401, 2976, 2927, 1698, 1506, 1455, 1366, 1278, 1251, 1170, 945. **HRMS** calcd for $C_{21}H_{31}NNaO_4$ [M+Na]$^+$ 384.2151; found 384.2141.

***tert*-Butyl (3-((5*R*)-1-hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-yl)-3-oxopropyl)carbamate 4w**



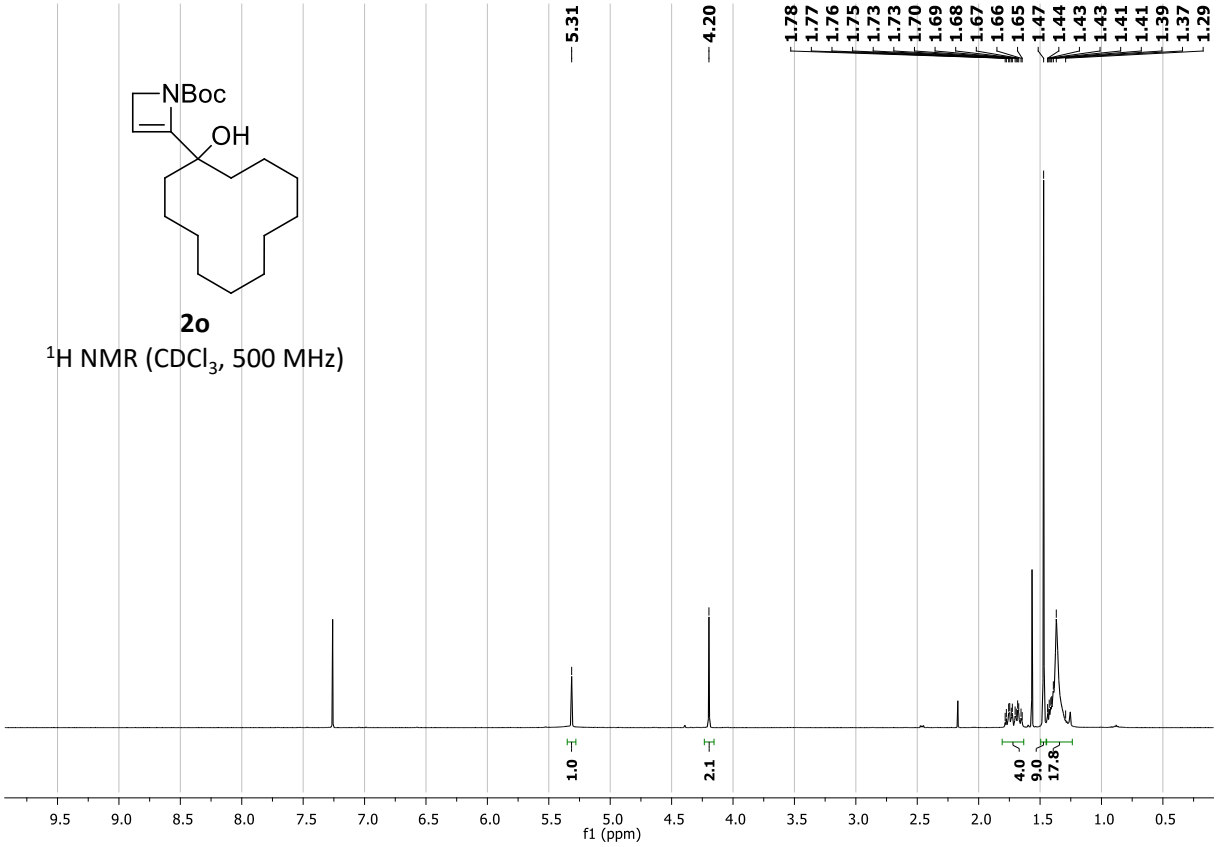
Following **GP2** with *tert*-Butyl 4-((5R)-1-hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-yl)azete-1(*2H*)-carboxylate **2w** as starting material, the title compound **4w** was obtained as white waxy solid (95%, 77 mg, dr = 95:5, absolute stereochemistry not assigned, $[\alpha]^{20}_D$ = -123,0° (c = 1, $CHCl_3$). Compound **4w** was obtained in 98% yield (32 mg) following **GP3**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.83 – 5.80 (m, 1H, C=*CH*), 4.97 (bs, 1H, NH), 4.77 – 4.72 (m, 2H, $C=CH_2$), 3.92 (s, 1H, OH), 3.43 – 3.37 (m, 2H, NCH_2), 2.91 (dt, *J* = 18.5, 5.9 Hz, 1H, NCH_2CH_2), 2.74 (dt, *J* = 18.6, 5.3 Hz, 1H, NCH_2CH_2), 2.58 – 2.50 (m, 1H, CH), 2.27 – 2.20 (m, 1H, C=CHC*H*$_2$), 2.10 – 2.02 (m, 1H, C=CHC*H*$_2$), 1.93 – 1.88 (m, 1H, OHCC*H*$_2$), 1.83 (d, *J* = 12.9 Hz, 1H, OHCC*H*$_2$), 1.72 (s, 3H, $CH_3C=CH_2$), 1.52 – 1.50 (m, 3H, $CH_3C=CH$), 1.41 (s, 9H, 3 × CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 213.2, 156.0, 147.8, 133.2, 128.7, 110.1, 80.3, 79.6, 39.7, 39.3, 38.1, 35.4, 30.2, 28.5, 20.7, 17.5. **IR** (film)/cm^{-1} 3407, 2976, 2920, 1694, 1506, 1451, 1366, 1282, 1251, 1172, 890. **HRMS** calcd for $C_{18}H_{29}NNaO_4$ [M+Na]$^+$ 346.1994; found 346.2001.

***tert*-Butyl (3-((8*R*,9*S*,13*S*,14*S,17S*)-17-hydroxy-3-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl)-3-oxopropyl)carbamate 4z**



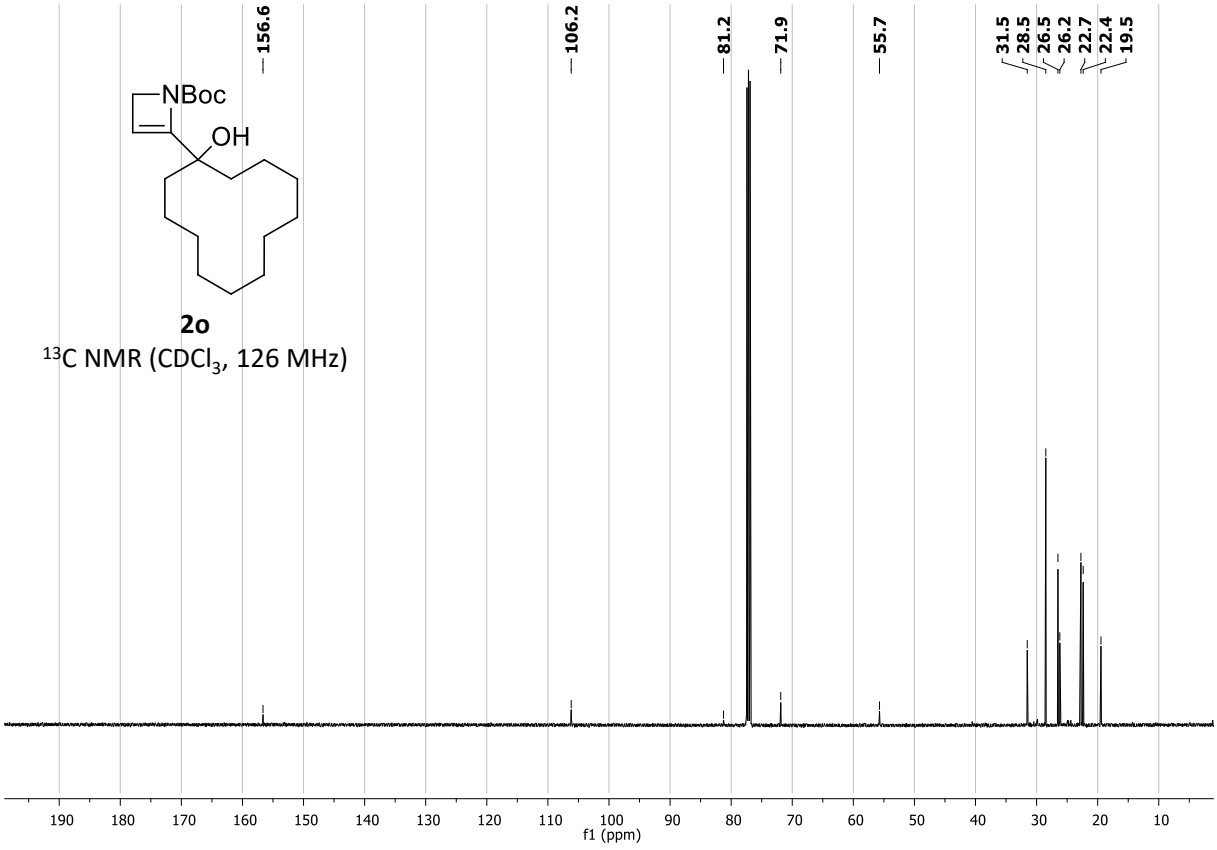
Following **GP2** with *tert*-Butyl 4-((8*R*,9*S*,13*S*,14*S,17S*)-17-hydroxy-3-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl)azete-1(2H)-carboxylate **2z** as starting material, compound **4z** was obtained as a white waxy solid (95%, 109 mg) $[\alpha]^{20}_{D}$ = +6,6° (c = 0.4, $CHCl_3$). Compound **4z** was obtained in 96% yield (44 mg) following **GP3**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.6 Hz, 1H, Ar-H), 6.69 (dd, *J* = 8.6, 2.7 Hz, 1H, Ar-H), 6.62 (d, *J* = 2.6 Hz, 1H, Ar-H), 5.03 (bs, 1H, NH), 3.77 (s, 3H, OCH_3), 3.50 – 3.33 (m, 2H, NCH_2), 2.98 – 2.90 (m, 1H, NCH_2CH_2), 2.87 – 2.78 (m, 3H, 1H NCH_2CH_2 and 2H CH_2), 2.69 (bs, 1H, OH), 2.37 – 2.29 (m, 1H, CH_2), 2.29 – 2.23 (m, 1H, CH_2), 2.16 – 2.09 (m, 1H, CH), 1.93 – 1.87 (m, 1H, CH_2), 1.86 – 1.74 (m, 2H, CH_2), 1.71 – 1.65 (m, 1H, CH), 1.64 – 1.61 (m, 1H, CH_2), 1.52 – 1.35 (m, 13H, 1H CH, 3H CH_2 and 9H $C(CH_3)_3$), 1.13 – 1.06 (m, 1H, CH_2), 0.96 (s, 3H, CH_3). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 216.0, 157.7, 156.2, 138.1, 132.4, 126.3, 114.0, 111.7, 91.1, 79.5, 55.4, 48.7, 48.5, 43.5, 40.9, 39.5, 36.1, 36.0, 33.5, 28.6, 27.5, 26.5, 24.5, 14.3. **IR** (film)/cm^{-1} 3401, 2918, 1692, 1609, 1501, 1392, 1366, 1254, 1170, 1047, 730. **HRMS** calcd for $C_{27}H_{39}NNaO_5$ $[M+Na]^+$ 480.2726; found 480.2734.

7. Copy of NMR spectra



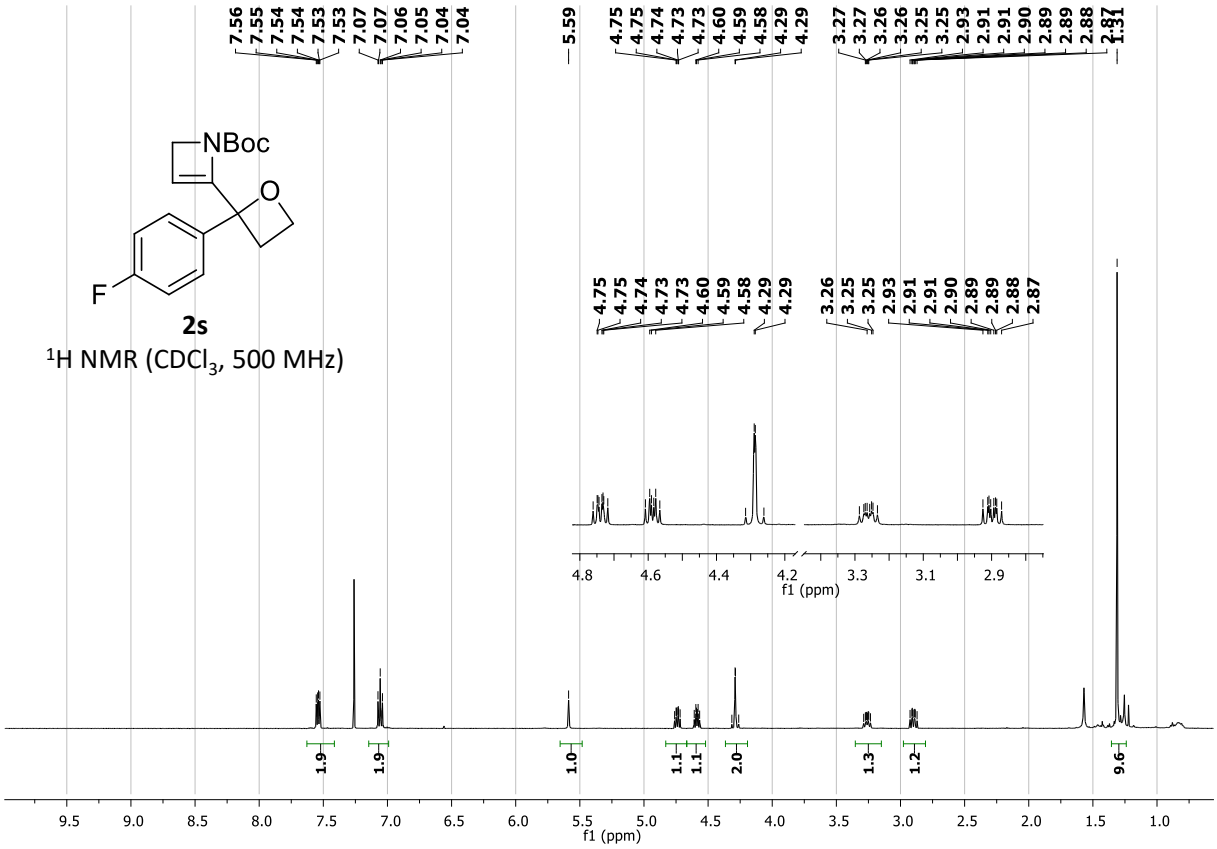
2o

^{1}H NMR ($CDCl_3$, 500 MHz)



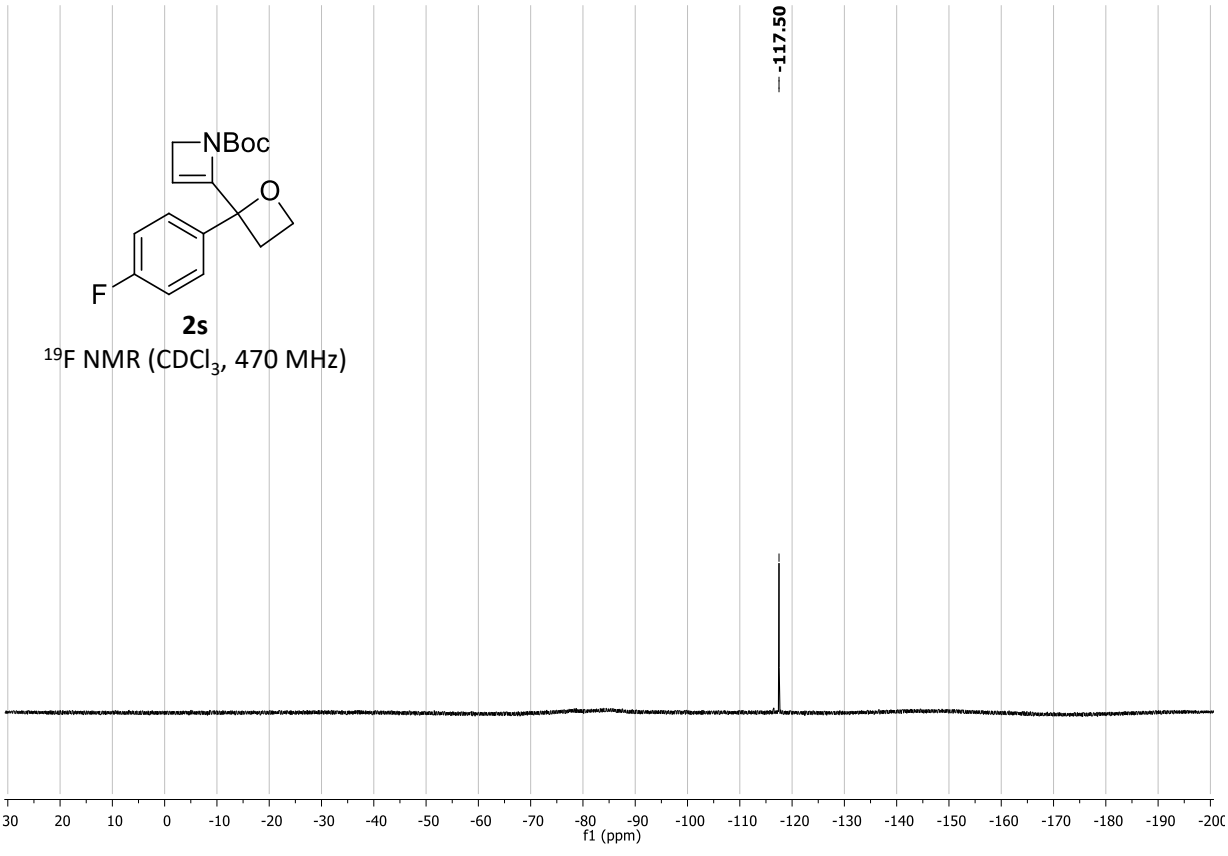
2o

^{13}C NMR ($CDCl_3$, 126 MHz)



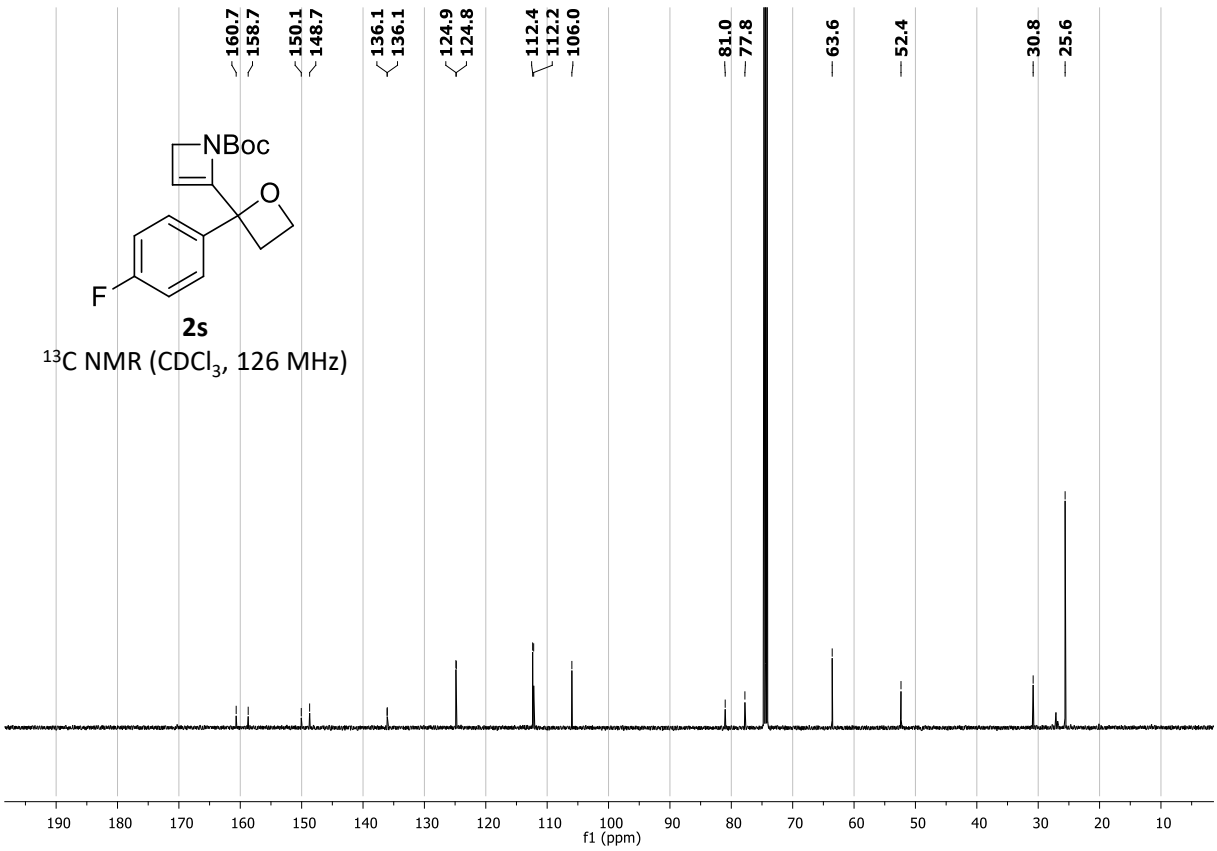
2s

^{1}H NMR ($CDCl_3$, 500 MHz)



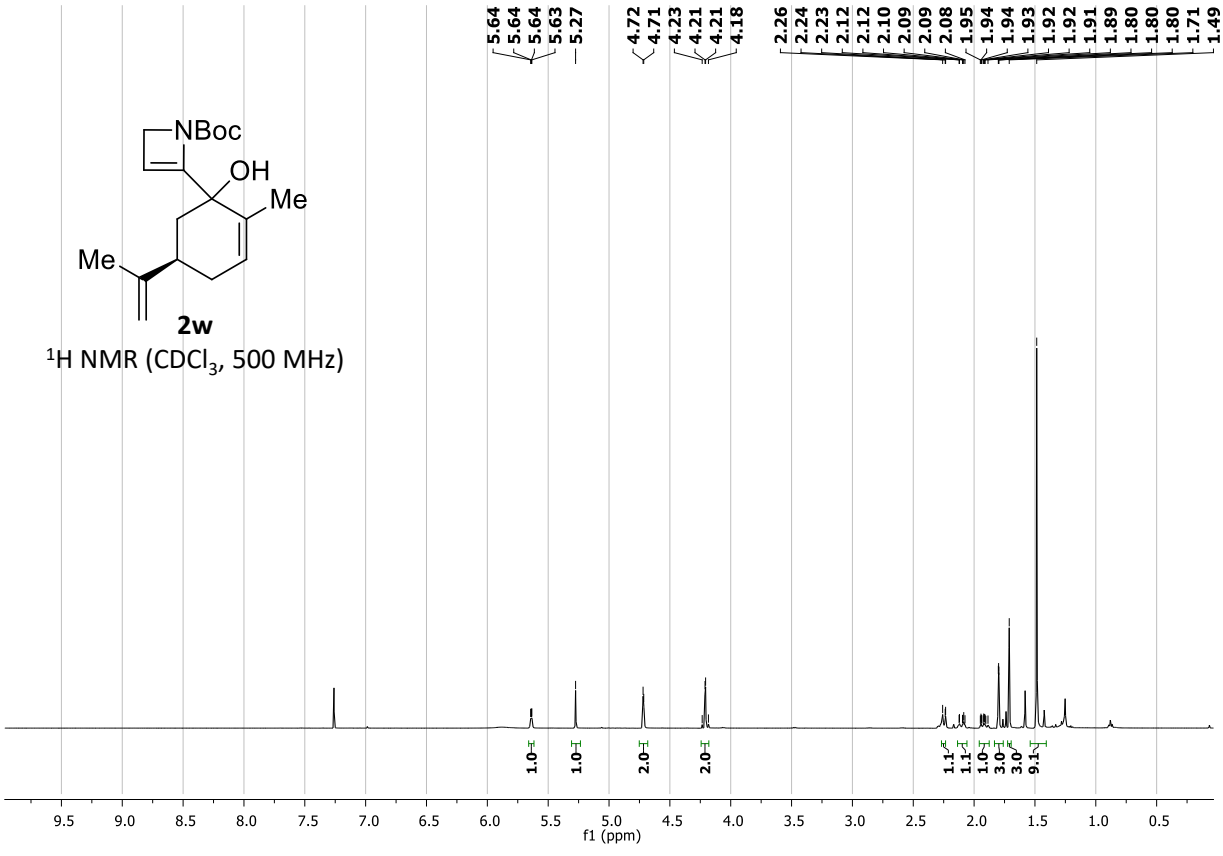
2s

^{19}F NMR ($CDCl_3$, 470 MHz)



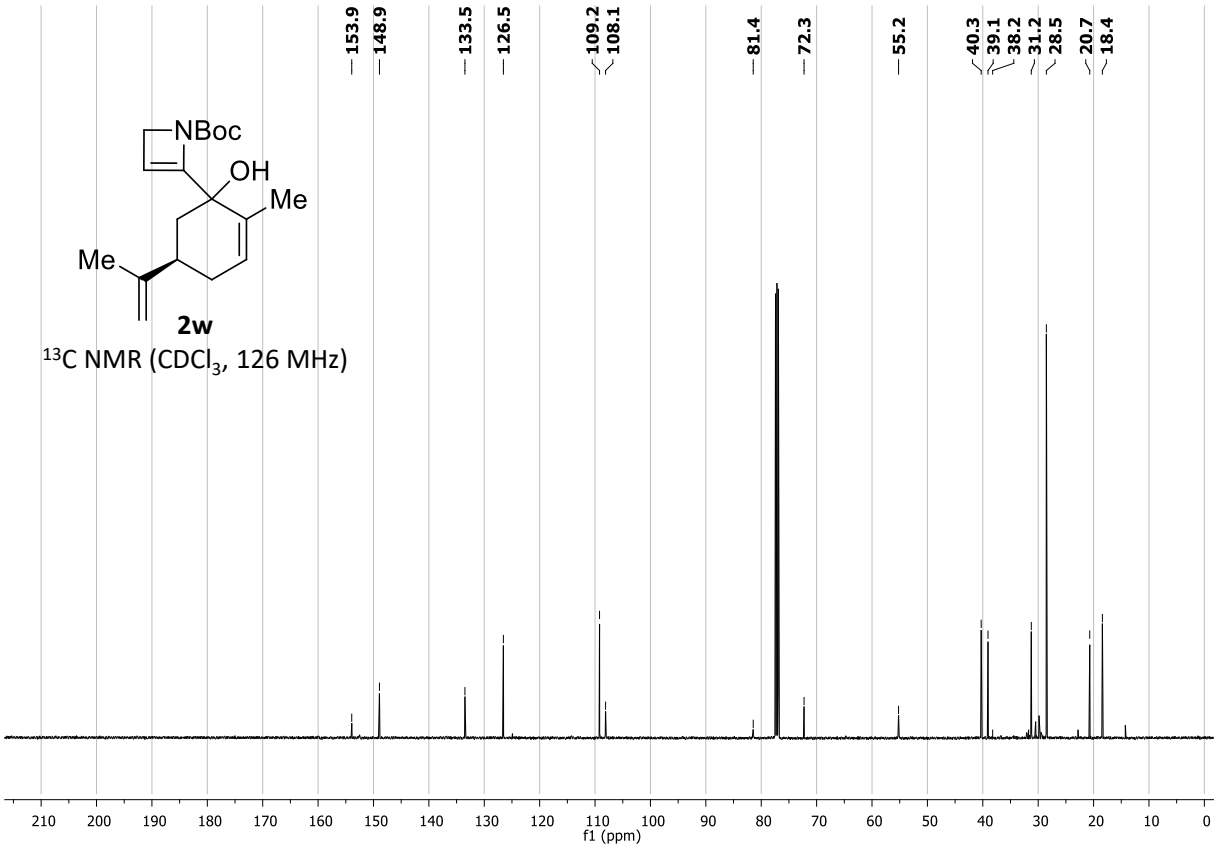
2s

^{13}C NMR ($CDCl_3$, 126 MHz)



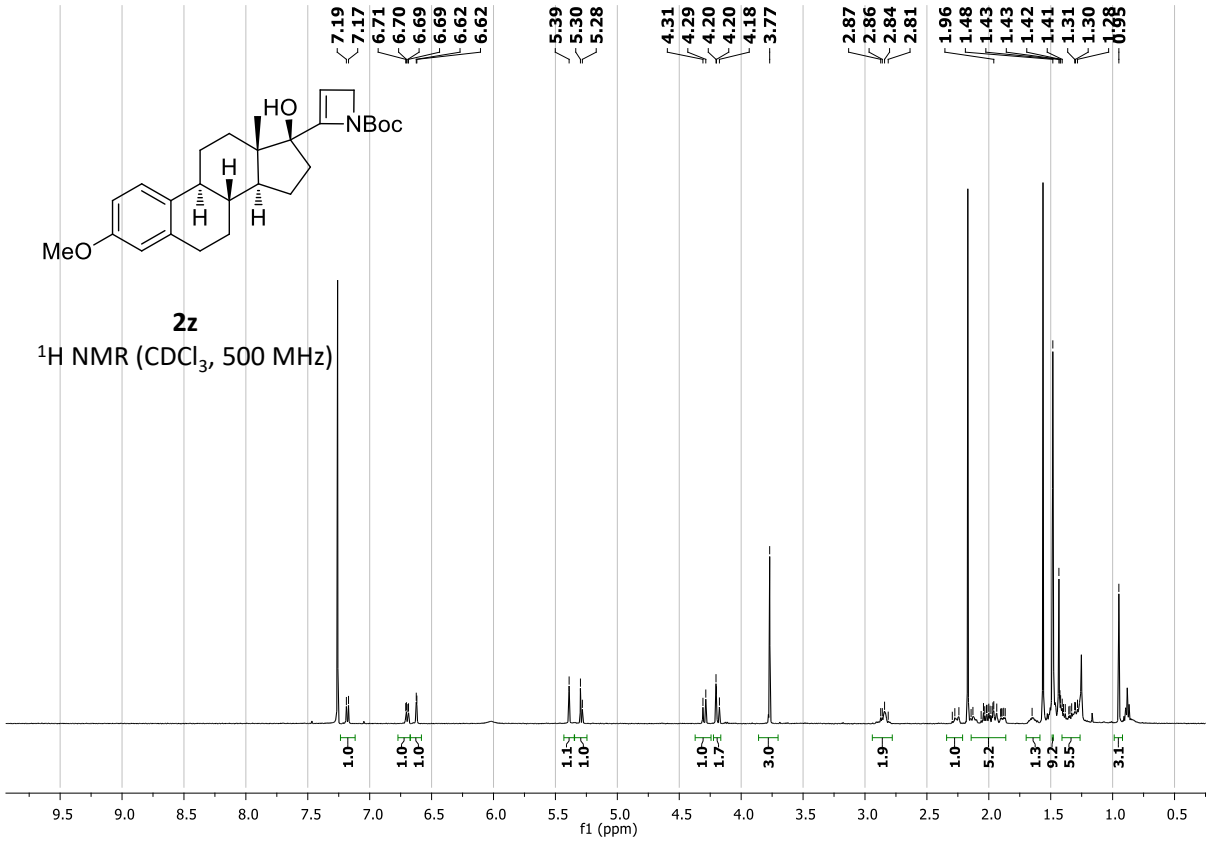
2w

^{1}H NMR ($CDCl_3$, 500 MHz)



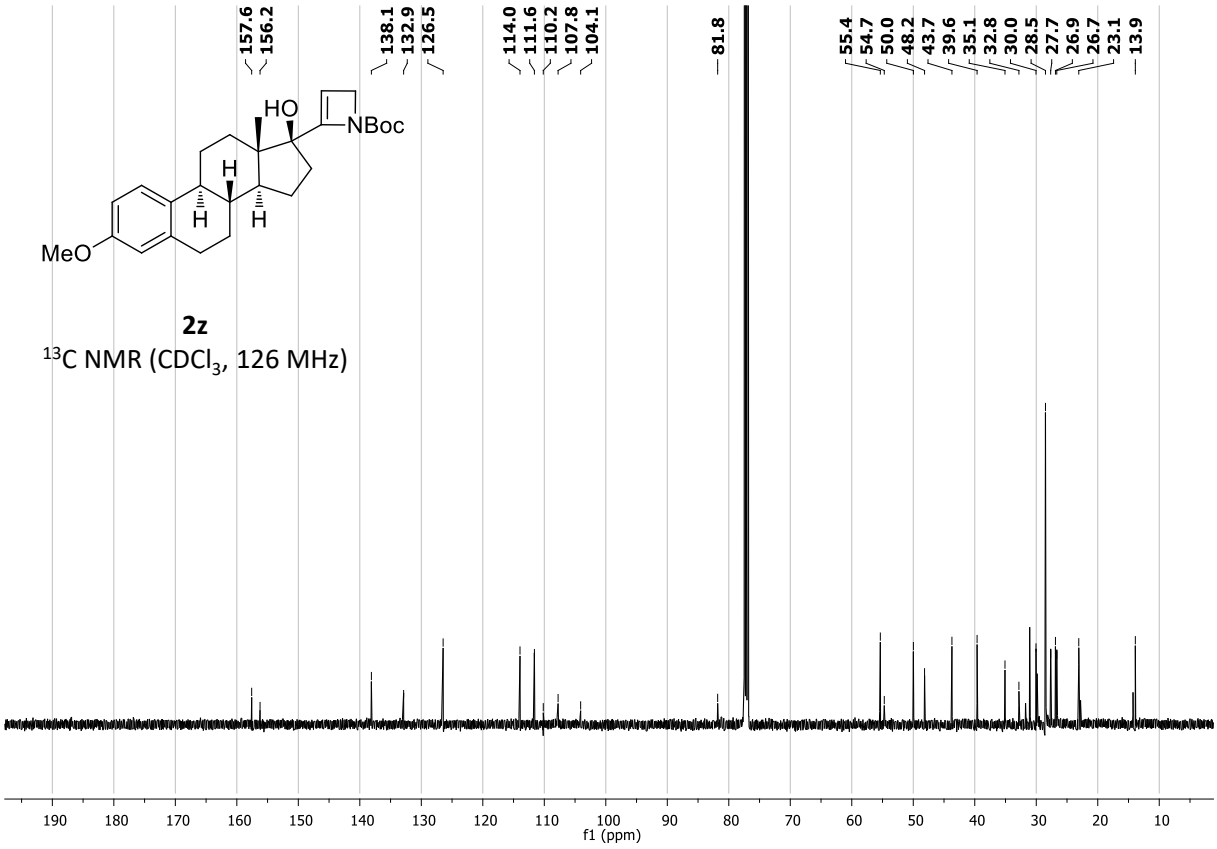
2w

^{13}C NMR ($CDCl_3$, 126 MHz)



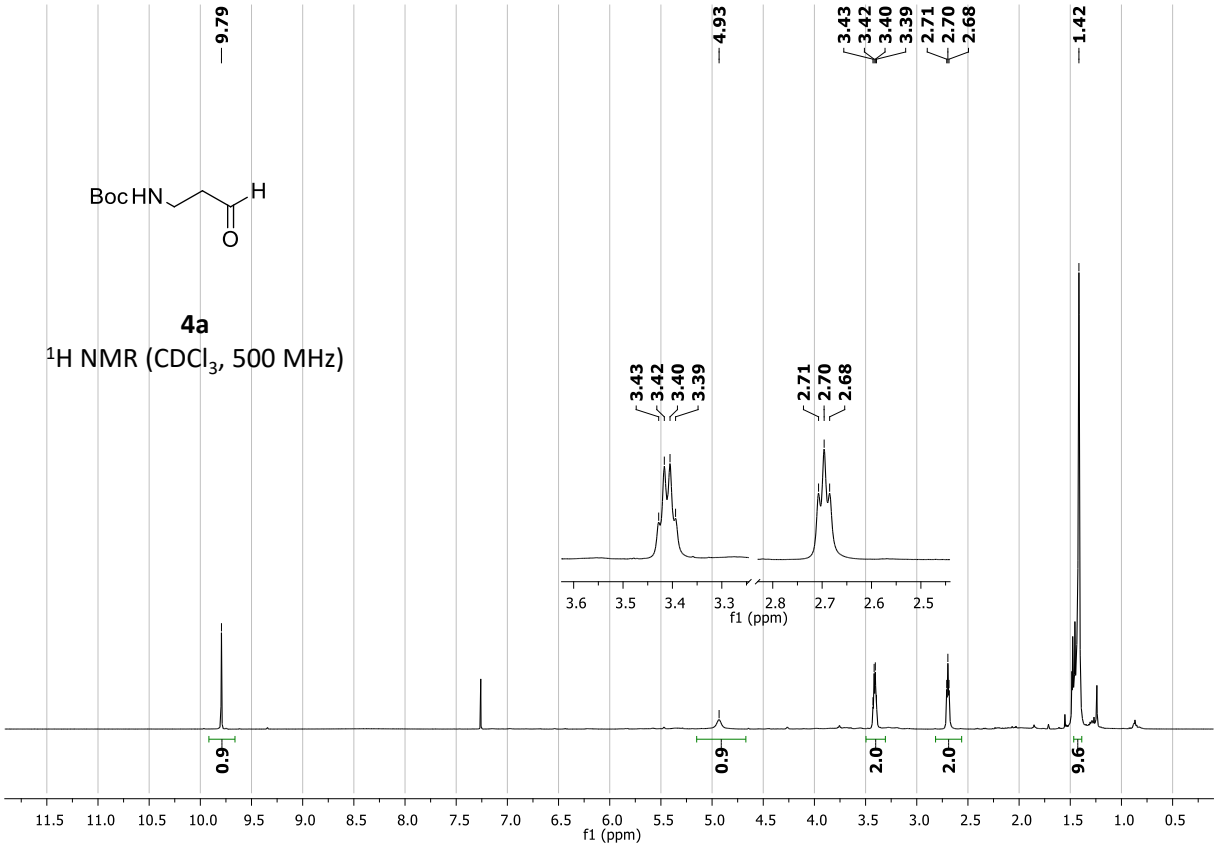
2z

^{1}H NMR ($CDCl_3$, 500 MHz)



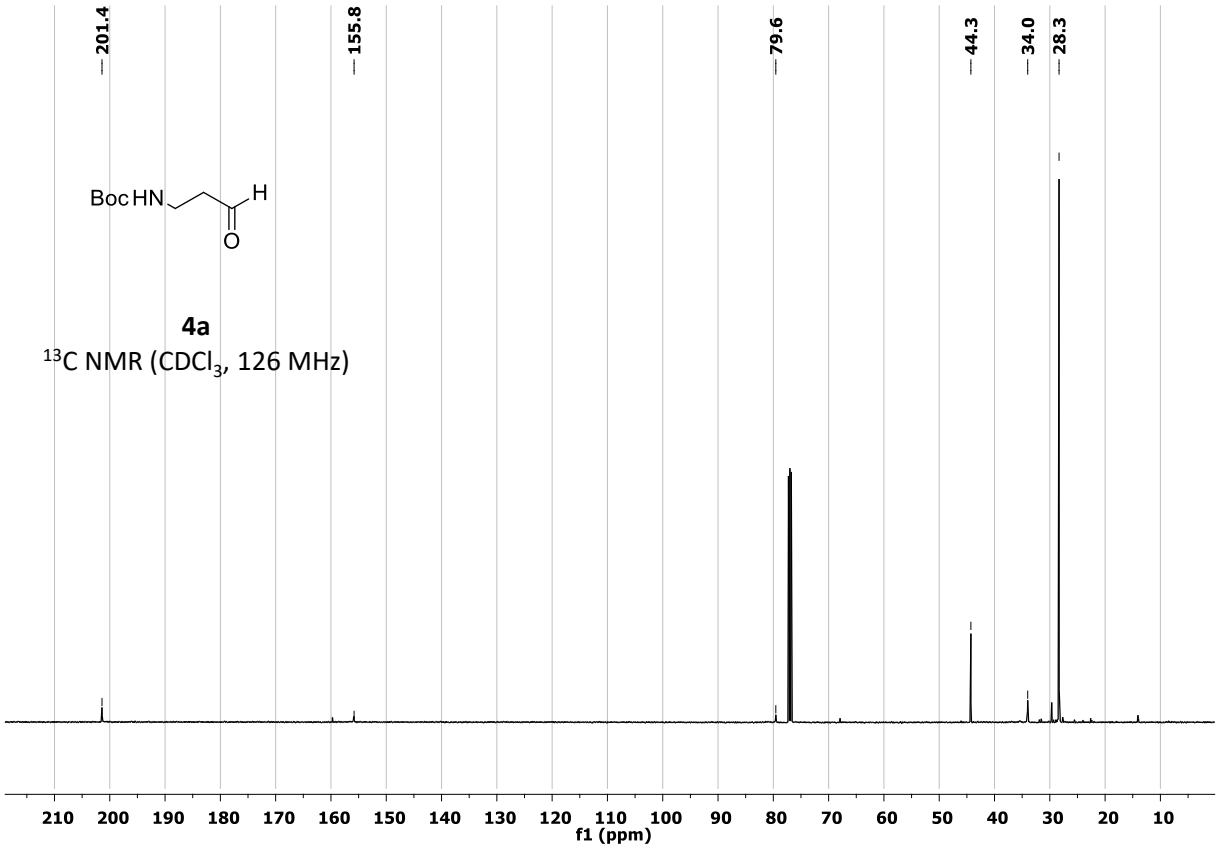
2z

^{13}C NMR ($CDCl_3$, 126 MHz)



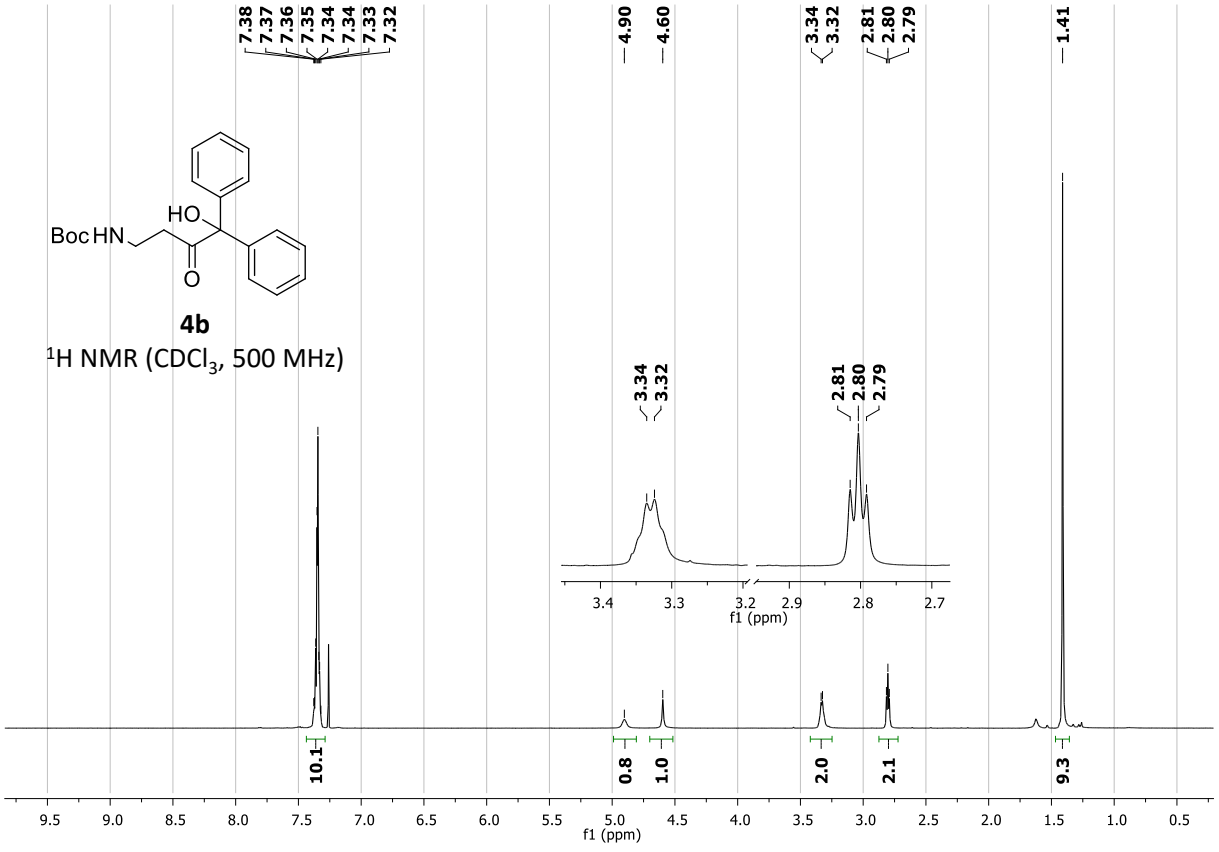
4a

^{1}H NMR ($CDCl_3$, 500 MHz)



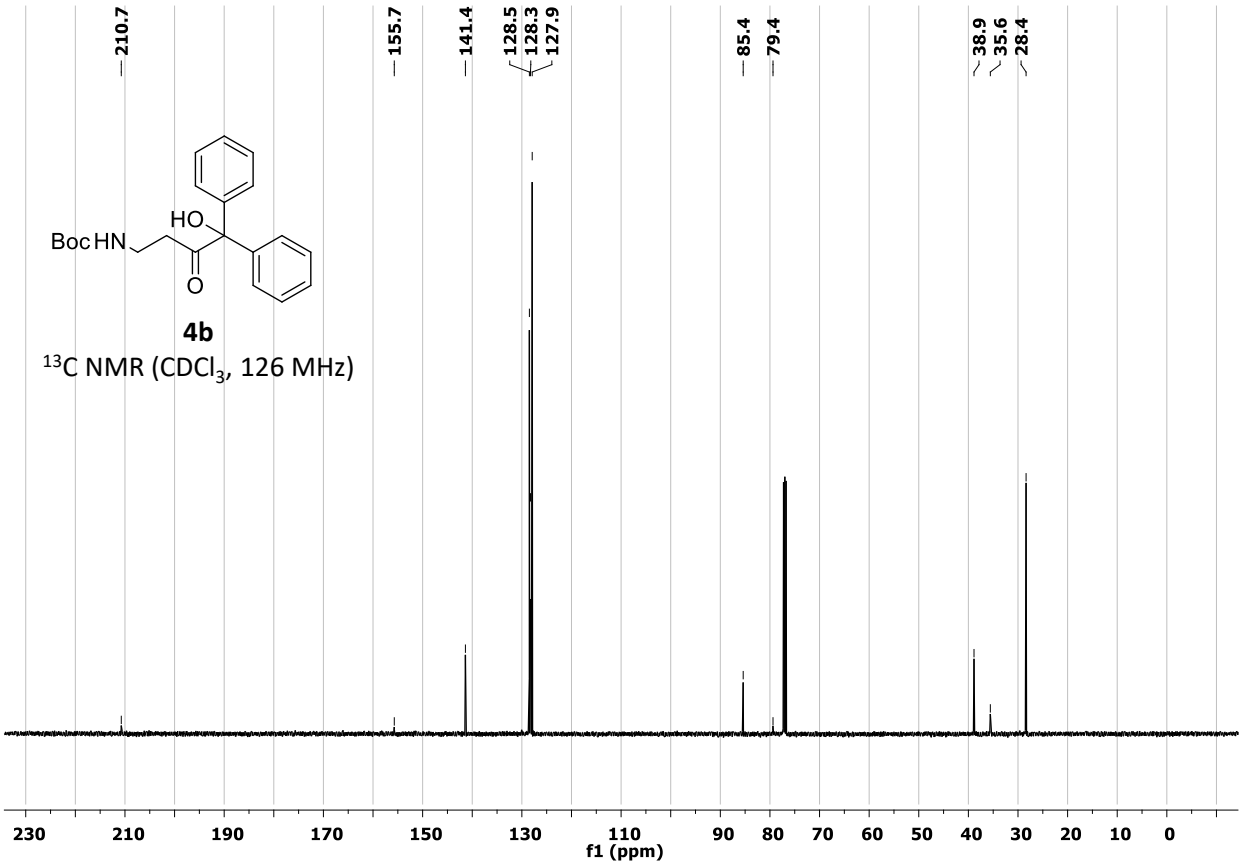
4a

^{13}C NMR ($CDCl_3$, 126 MHz)



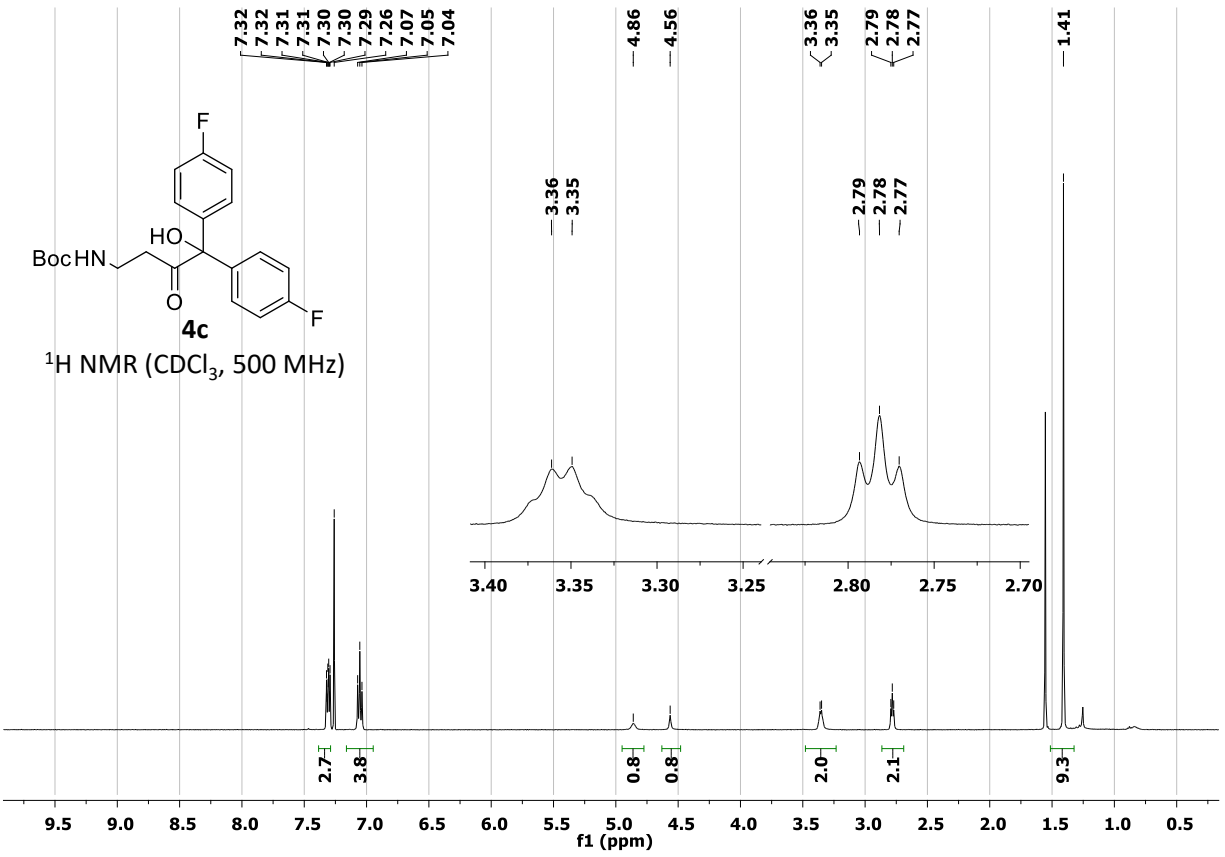
4b

^{1}H NMR ($CDCl_3$, 500 MHz)



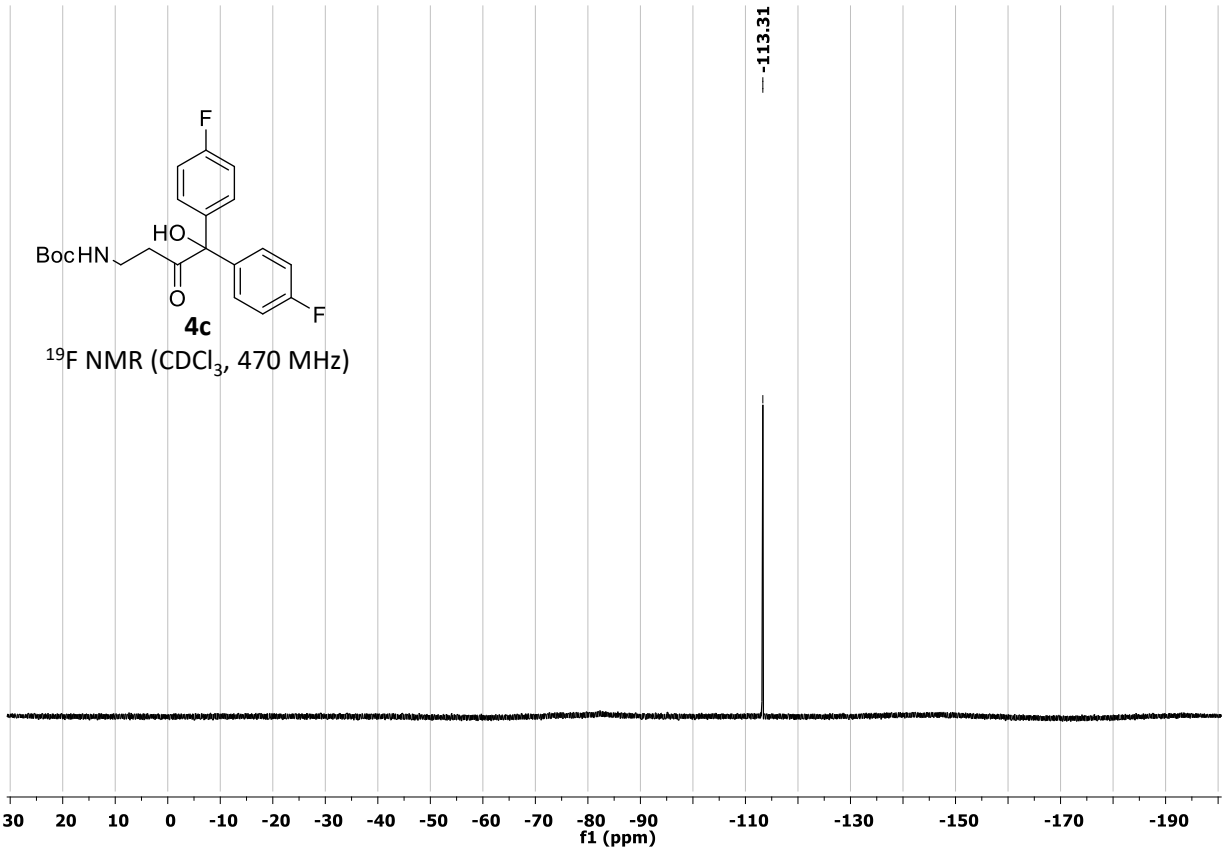
4b

^{13}C NMR ($CDCl_3$, 126 MHz)

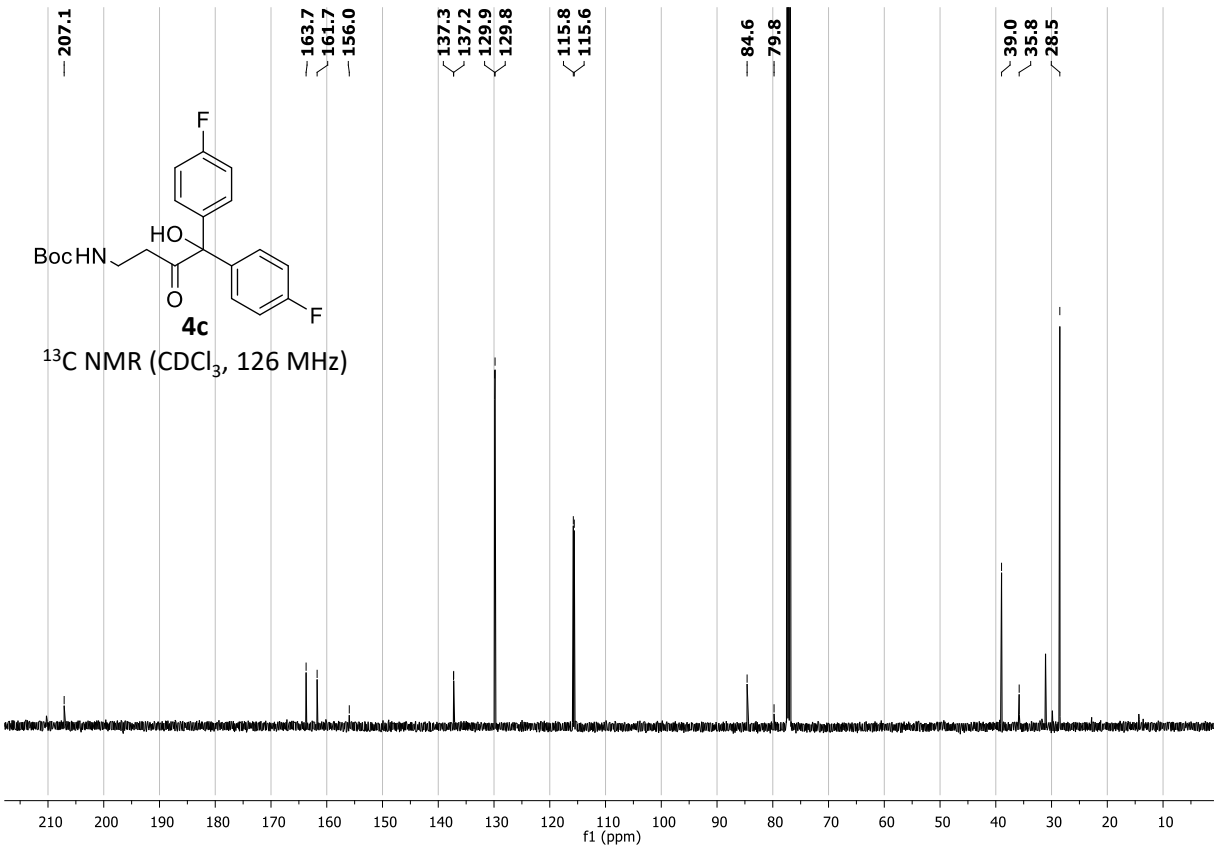


4c

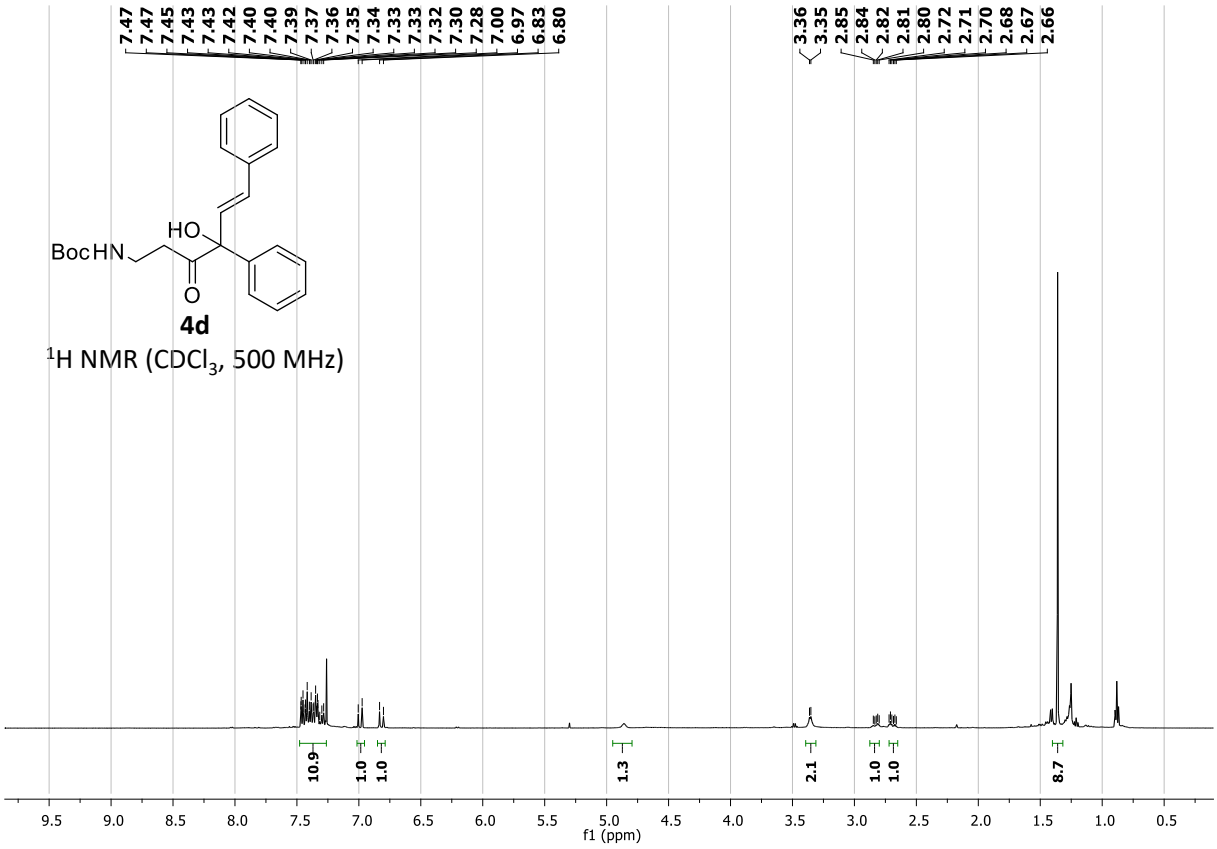
^{1}H NMR ($CDCl_3$, 500 MHz)



^{19}F NMR ($CDCl_3$, 470 MHz)

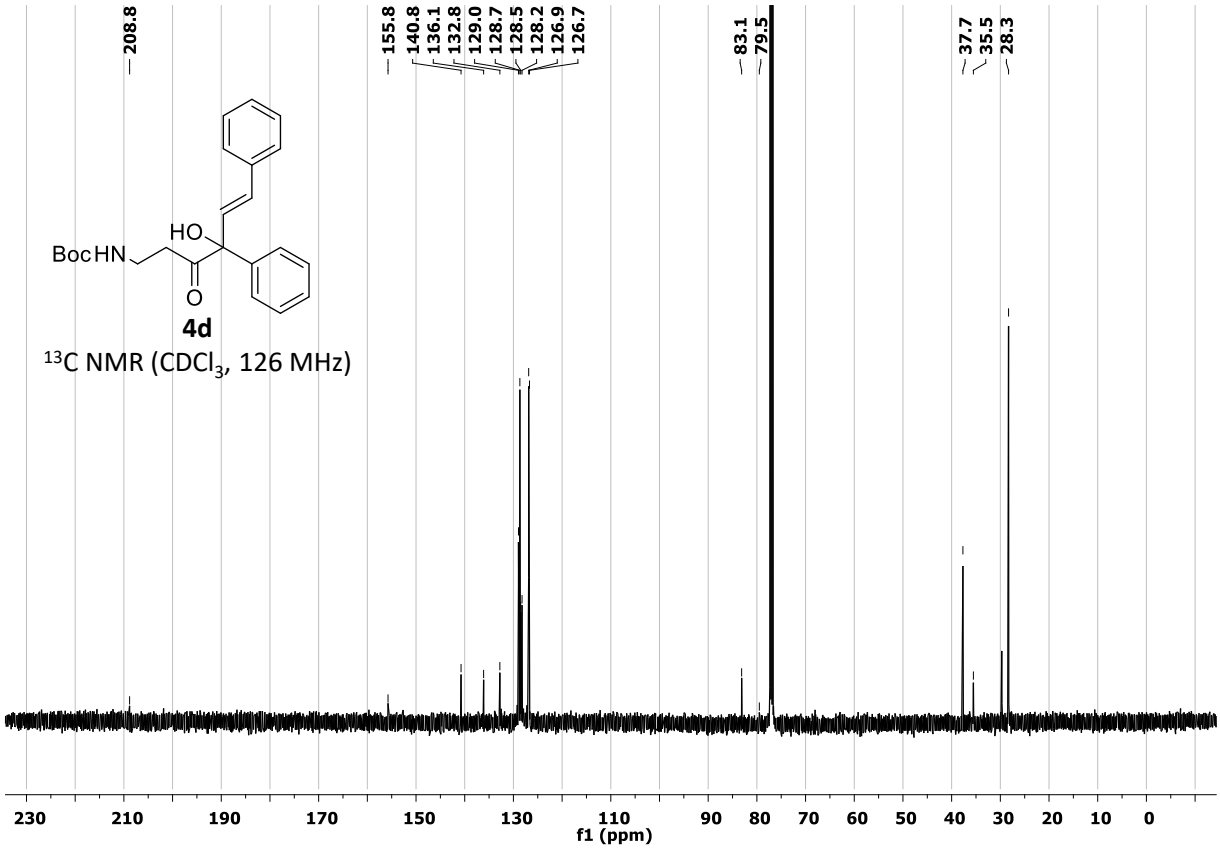


^{13}C NMR ($CDCl_3$, 126 MHz)



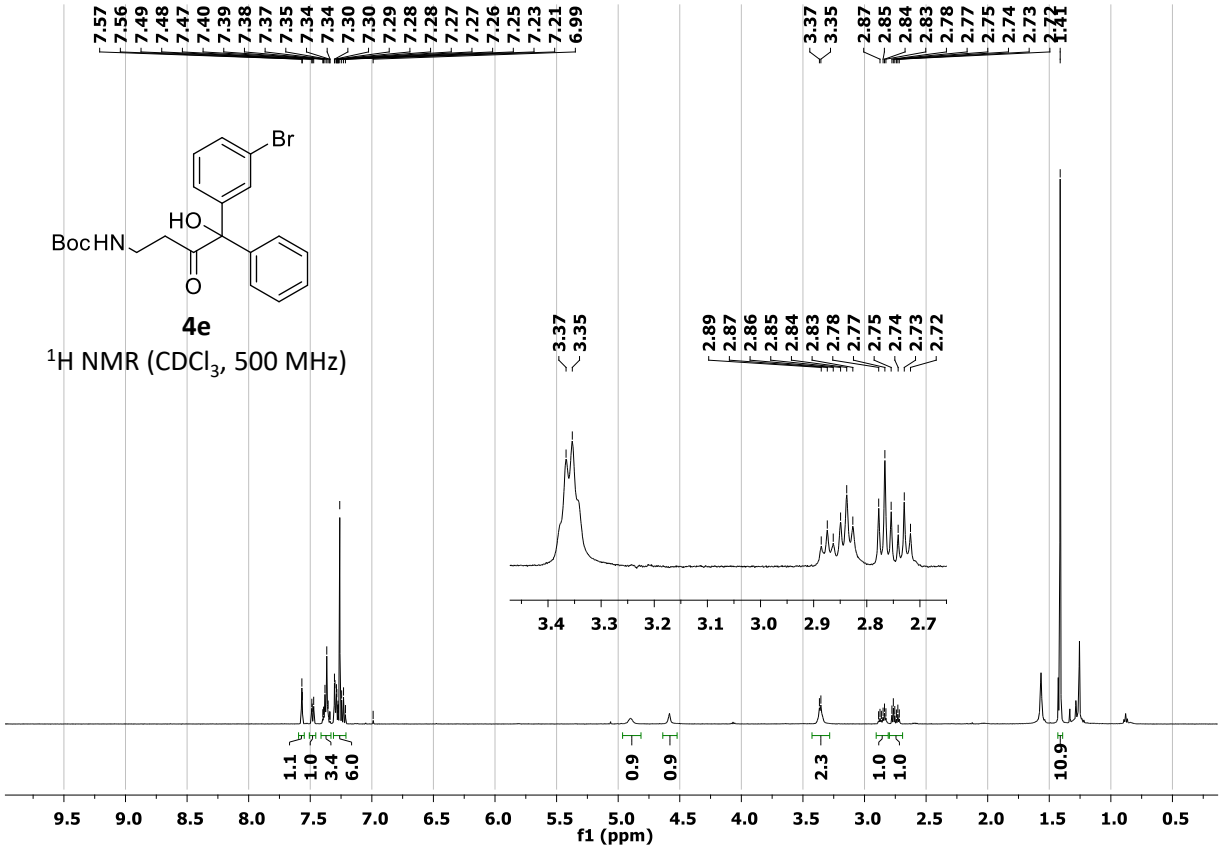
4d

^{1}H NMR ($CDCl_3$, 500 MHz)



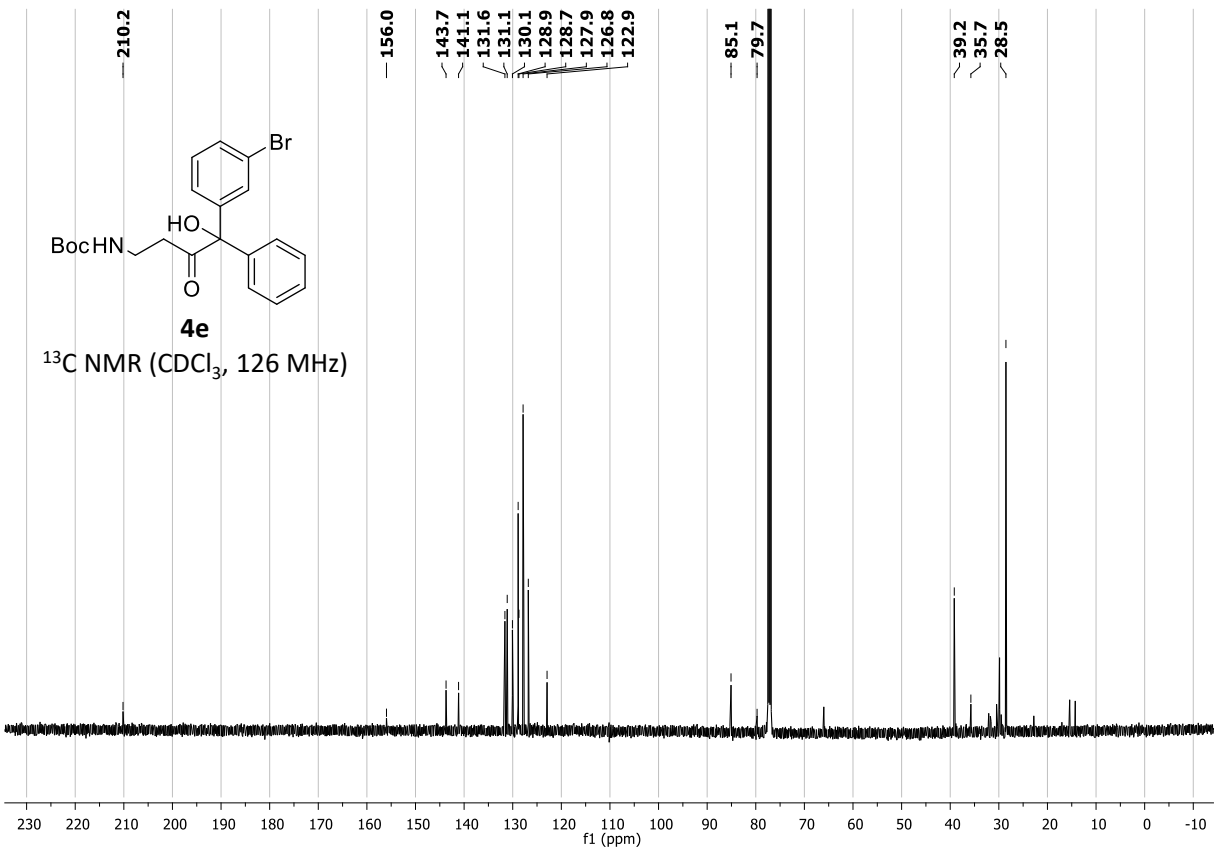
4d

^{13}C NMR ($CDCl_3$, 126 MHz)



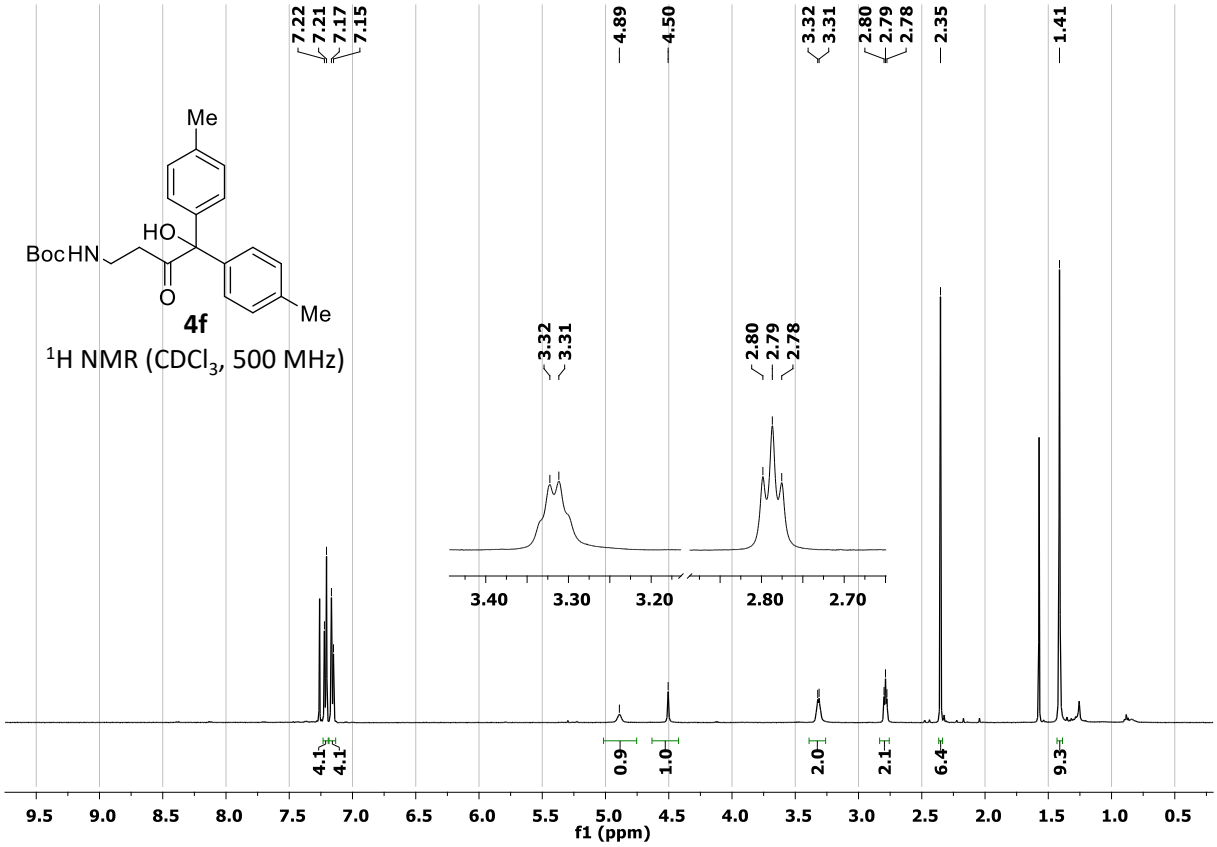
4e

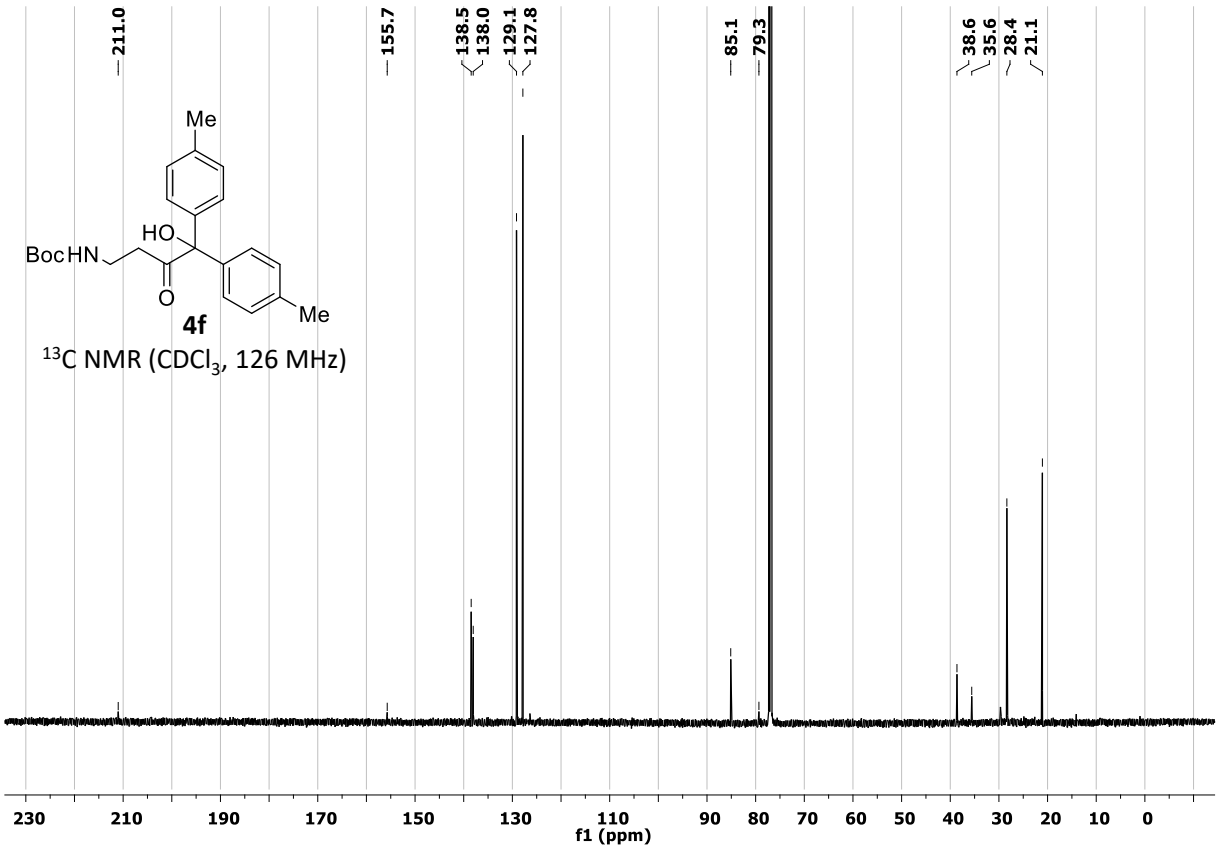
^{1}H NMR ($CDCl_3$, 500 MHz)

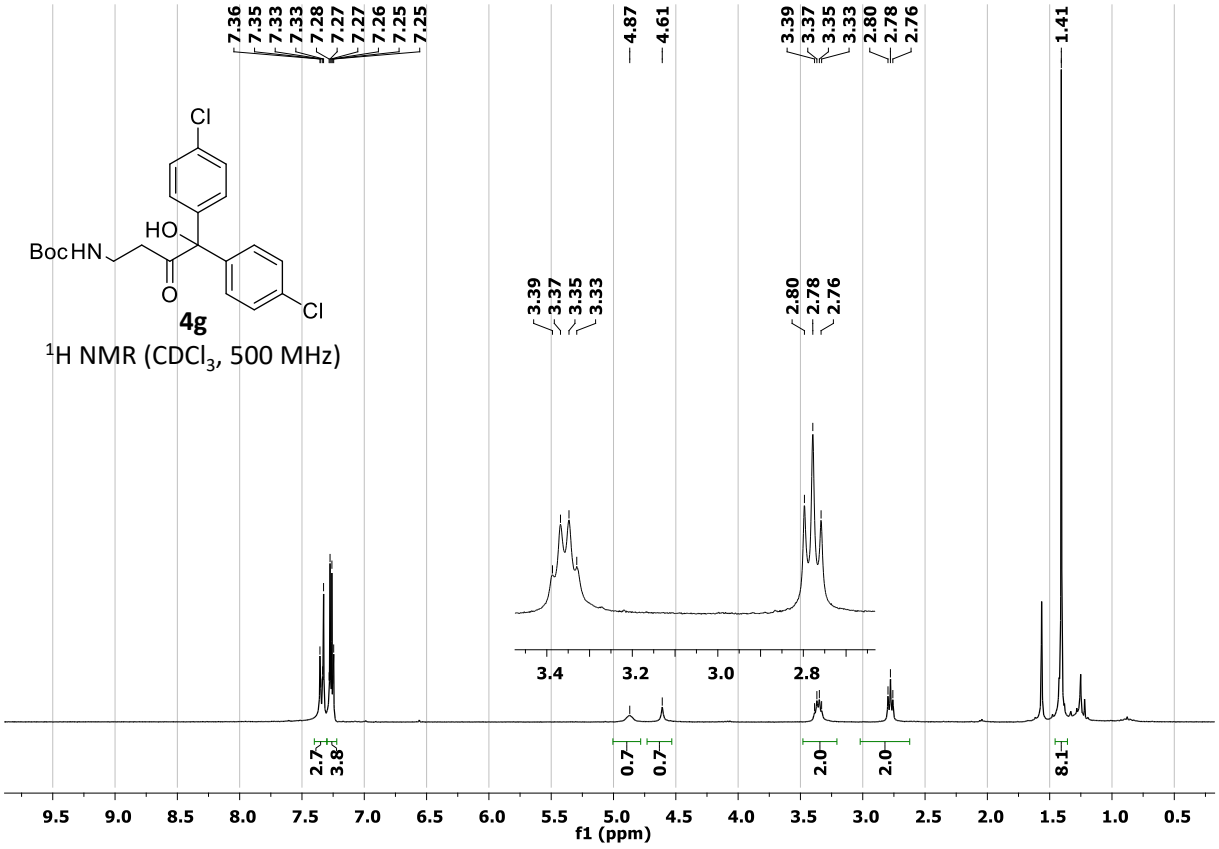


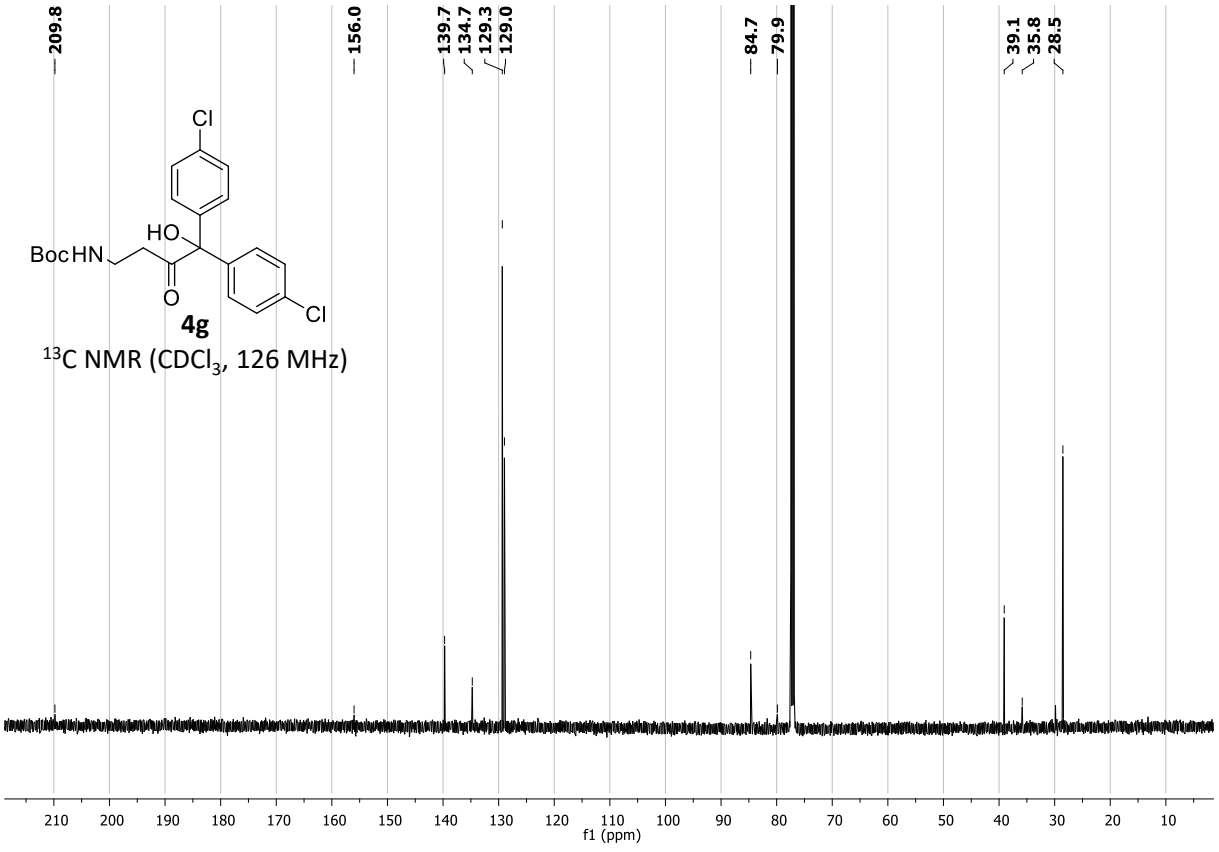
4e

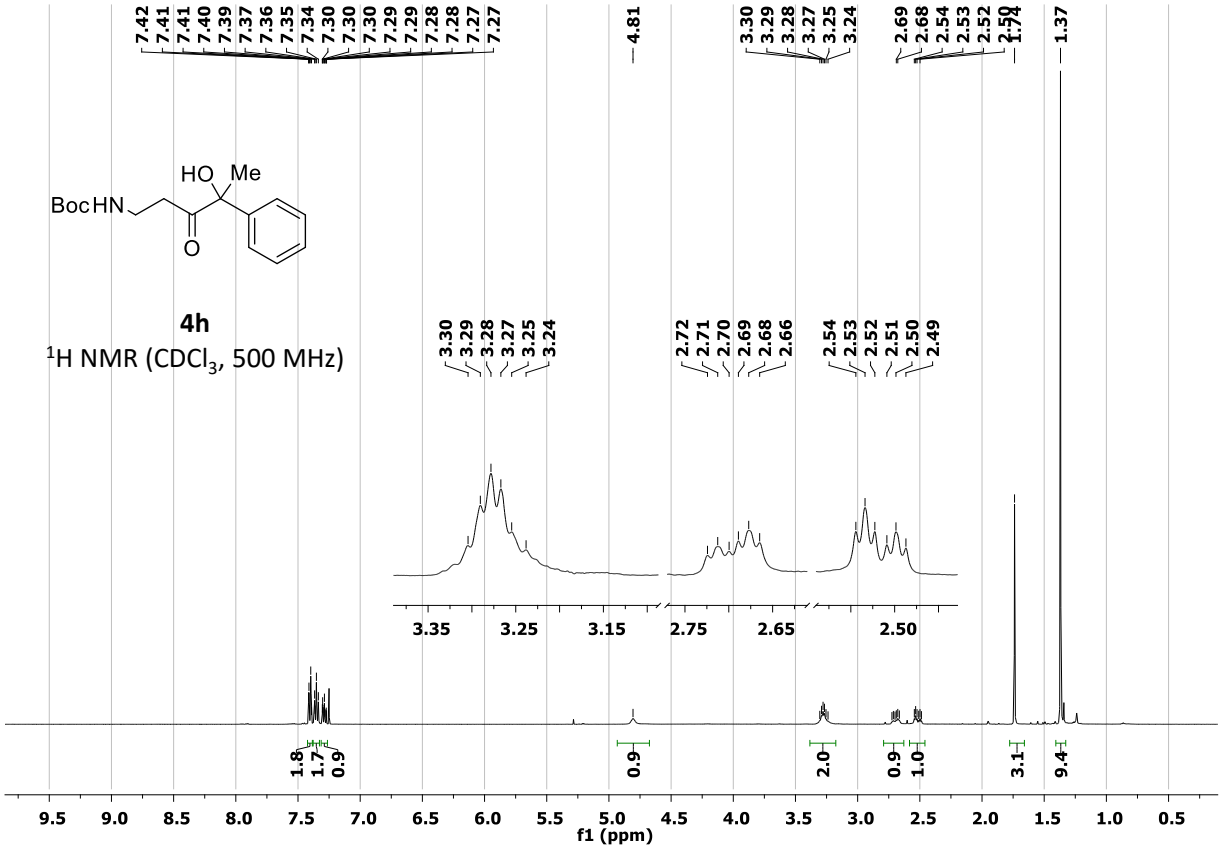
^{13}C NMR ($CDCl_3$, 126 MHz)

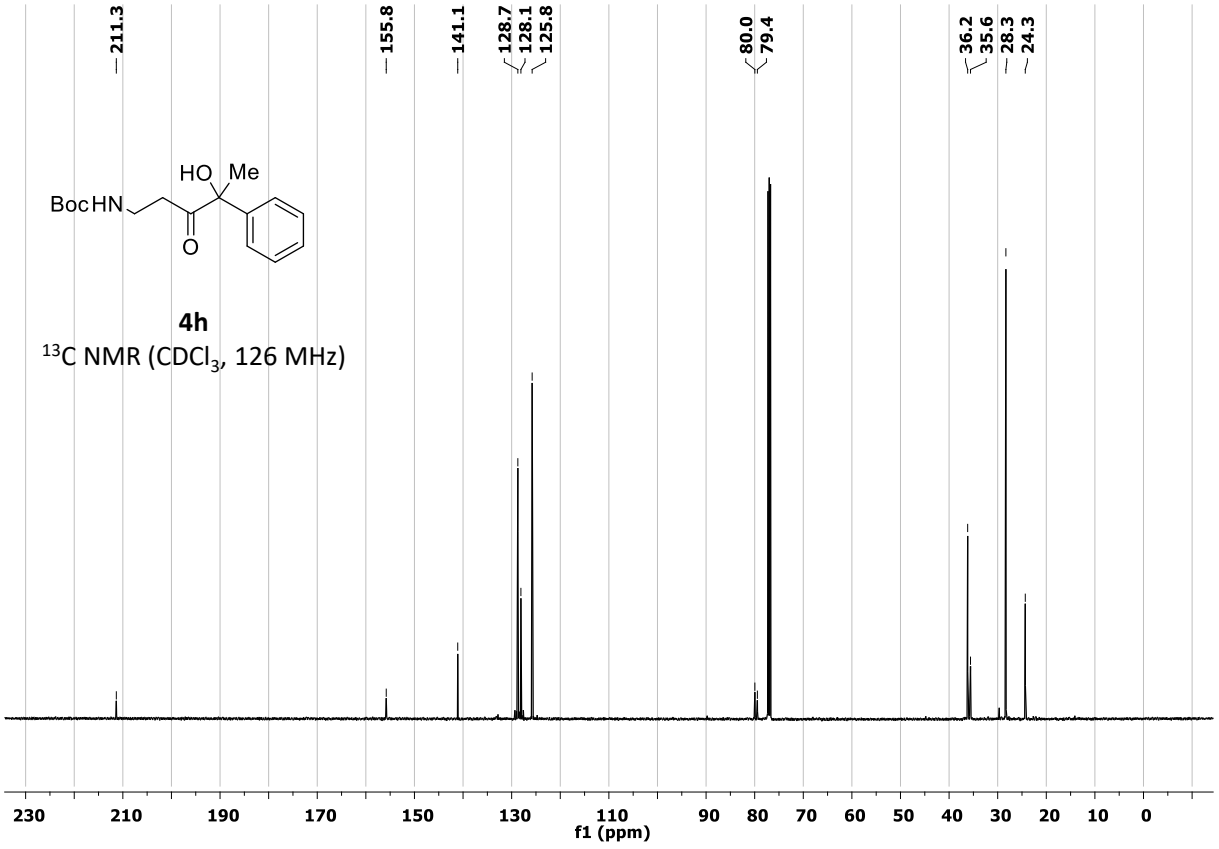

Me
HO
BocHN
O
Me
4f
^{1}H NMR ($CDCl_3$, 500 MHz)
7.22
7.21
7.17
7.15
4.89
4.50
3.32
3.31
2.80
2.79
2.78
2.35
1.41
4.1
4.1
0.9
1.0
2.0
2.1
6.4
9.3
f1 (ppm)

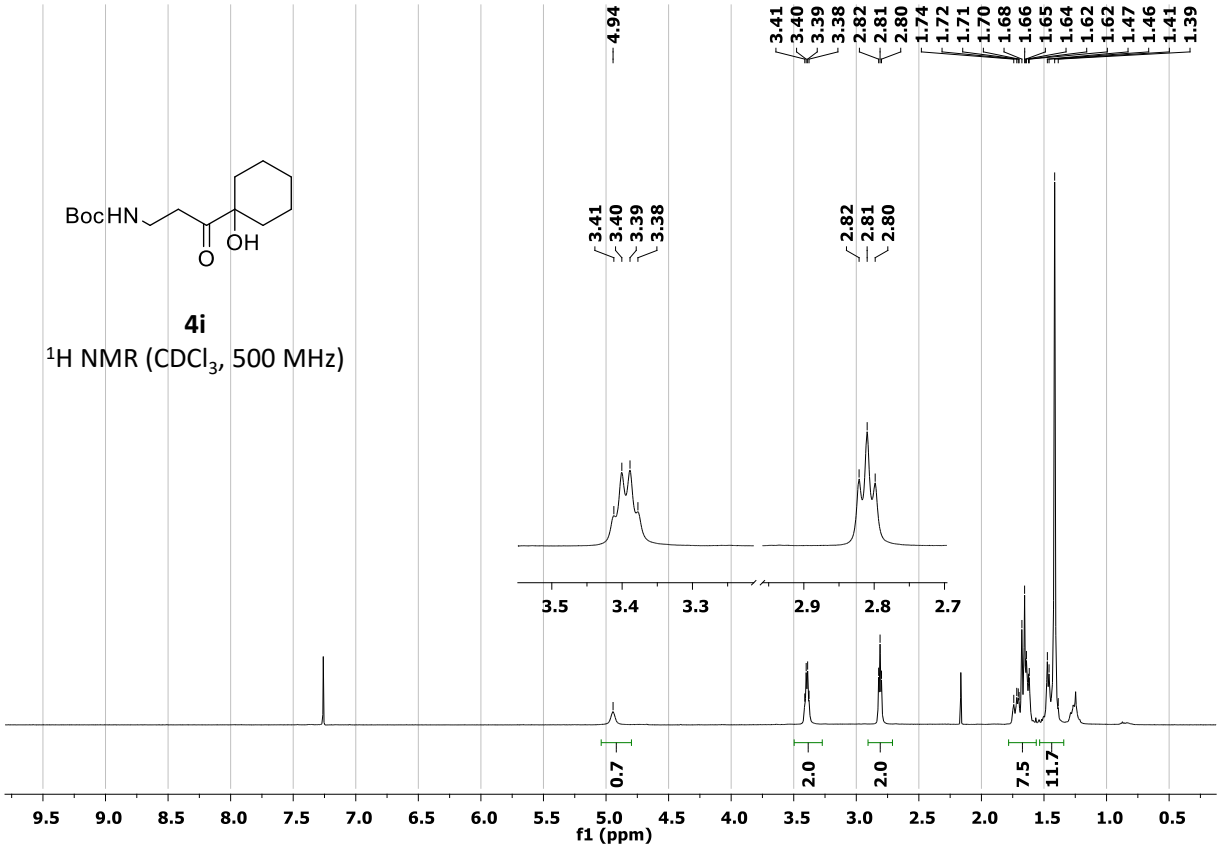

Me
HO
BocHN
O
Me
4f
^{13}C NMR ($CDCl_3$, 126 MHz)
211.0
155.7
138.5
138.0
129.1
127.8
85.1
79.3
38.6
35.6
28.4
21.1
f1 (ppm)


7.36
7.35
7.33
7.33
7.28
7.27
7.27
7.26
7.25
7.25
4.87
4.61
3.39
3.37
3.35
3.33
2.80
2.78
2.76
1.41
Cl
HO
BocHN
O
Cl
4g
^{1}H NMR ($CDCl_3$, 500 MHz)
2.7
3.8
0.7
0.7
2.0
2.0
8.1
f1 (ppm)


209.8
156.0
139.7
134.7
129.3
129.0
84.7
79.9
39.1
35.8
28.5
Cl
HO
BocHN
O
Cl
4g
^{13}C NMR ($CDCl_3$, 126 MHz)
f1 (ppm)

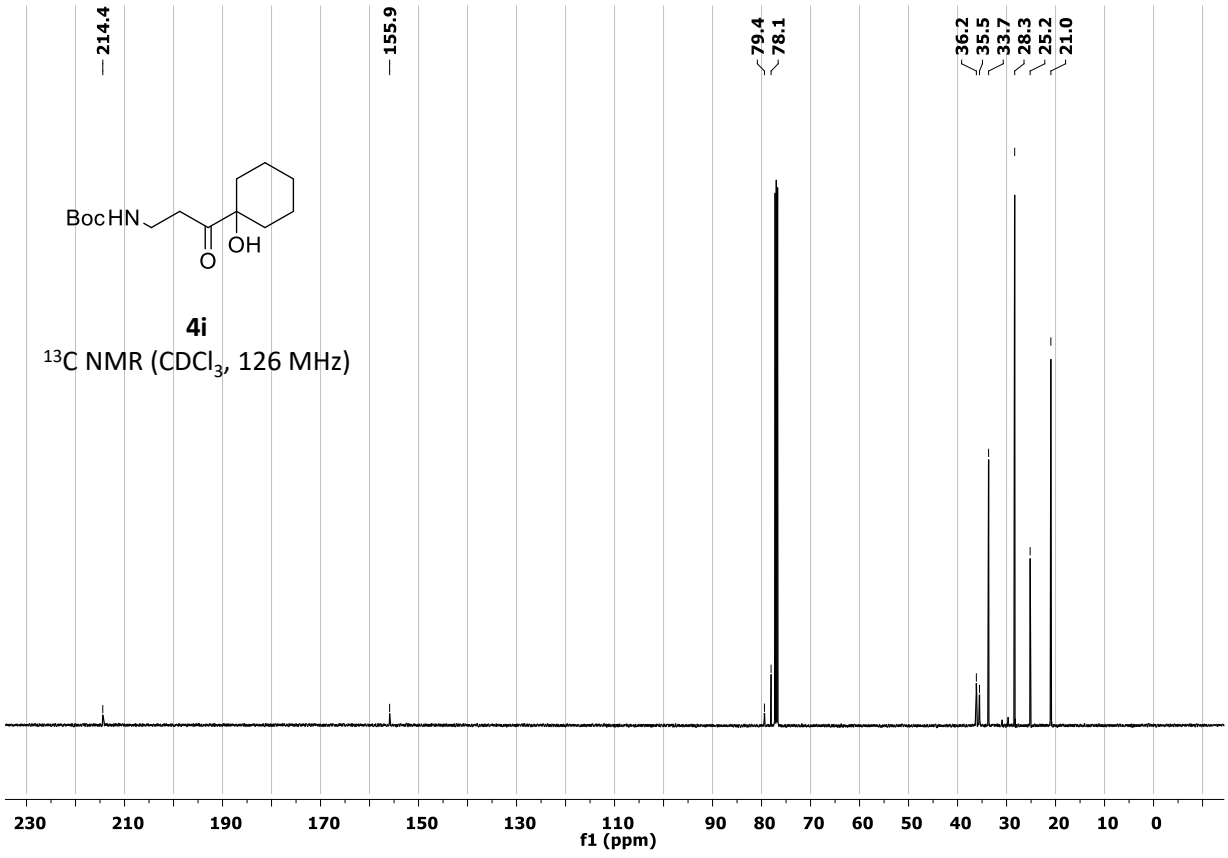

HO Me
BocHN
O
4h
1H NMR (CDCl3, 500 MHz)
f1 (ppm)


HO Me
BocHN
O
4h
13C NMR (CDCl3, 126 MHz)
f1 (ppm)



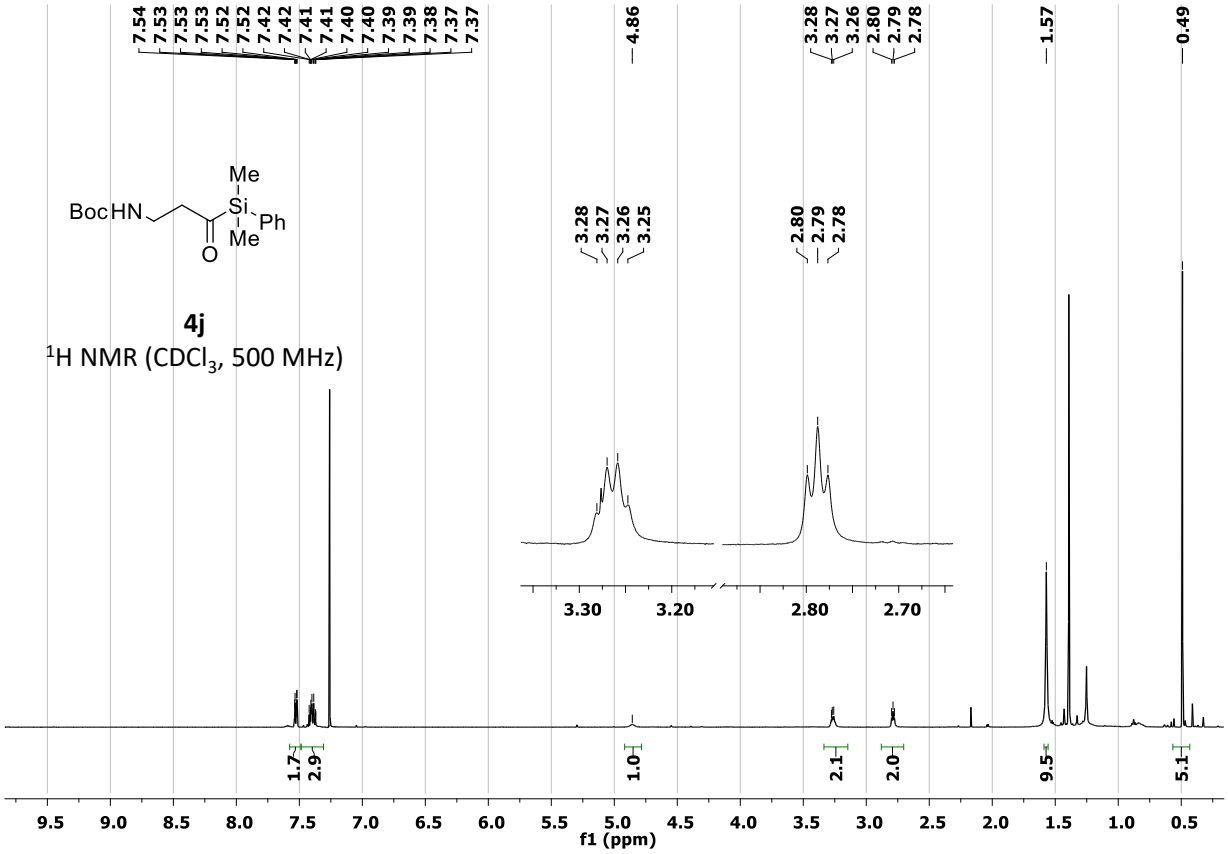
4i

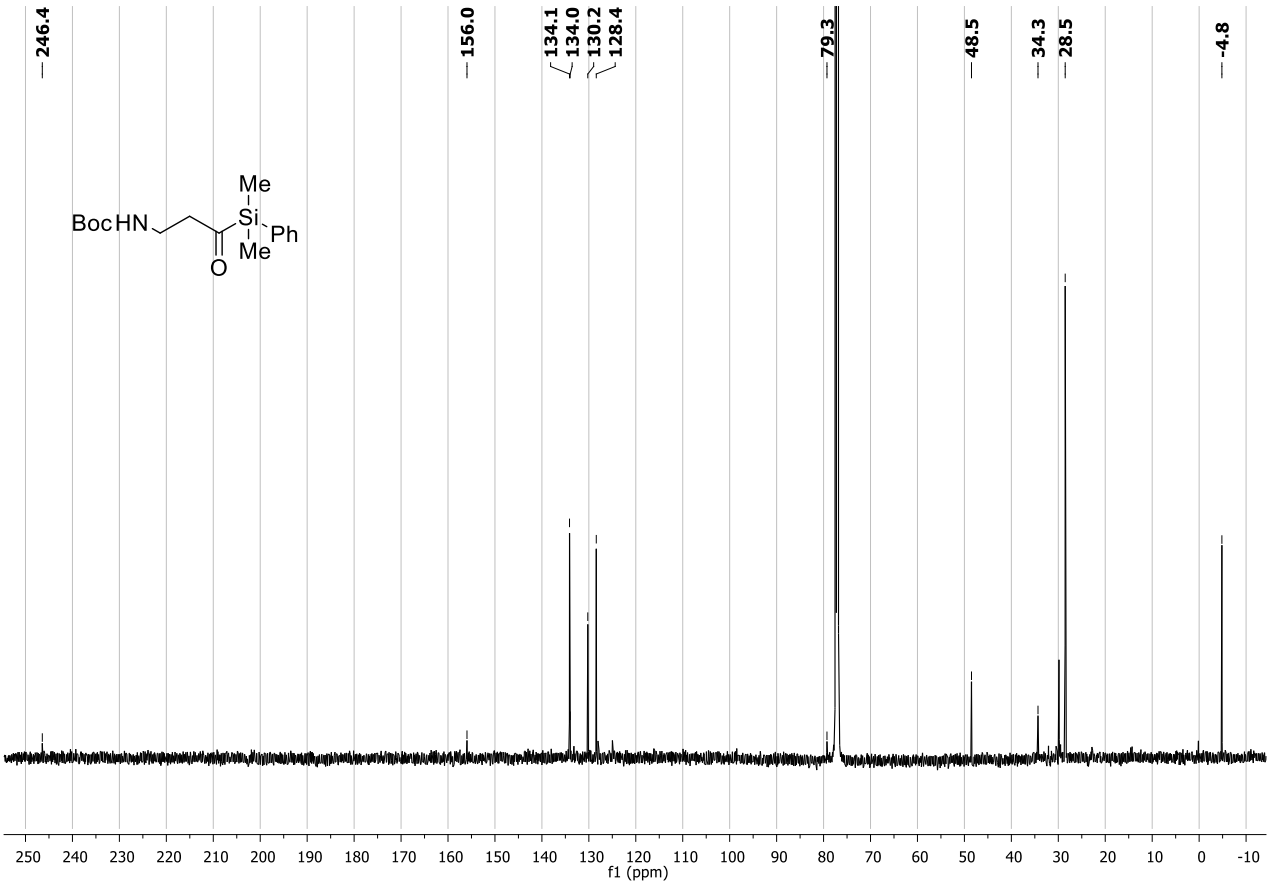
^{1}H NMR ($CDCl_3$, 500 MHz)

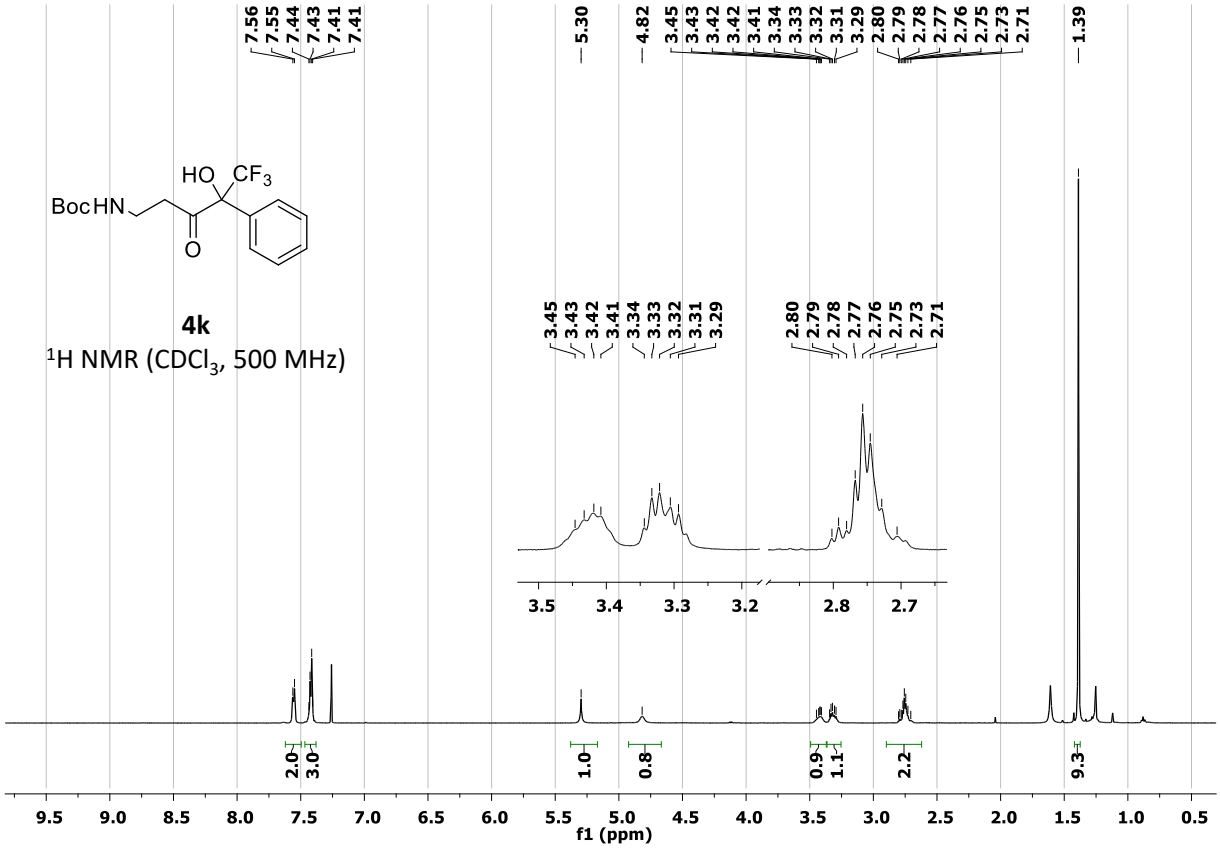


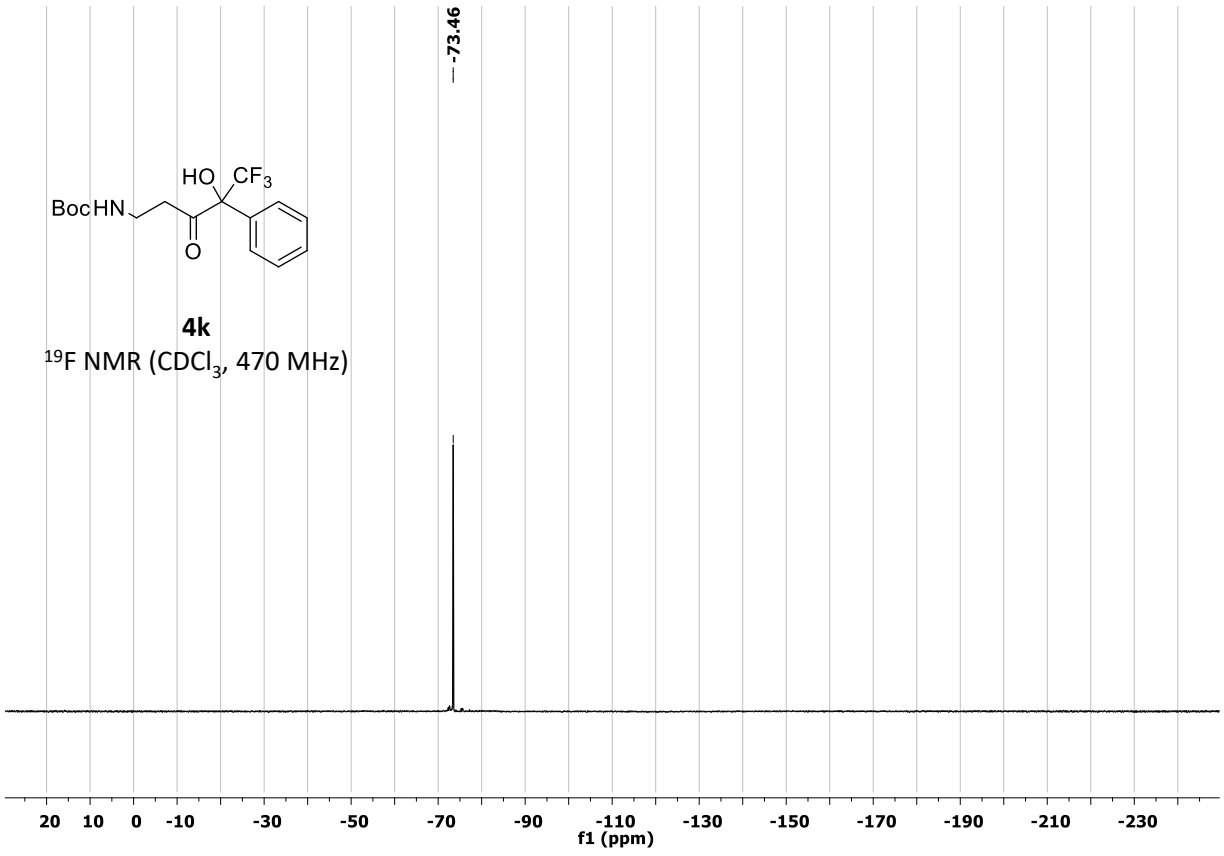
4i

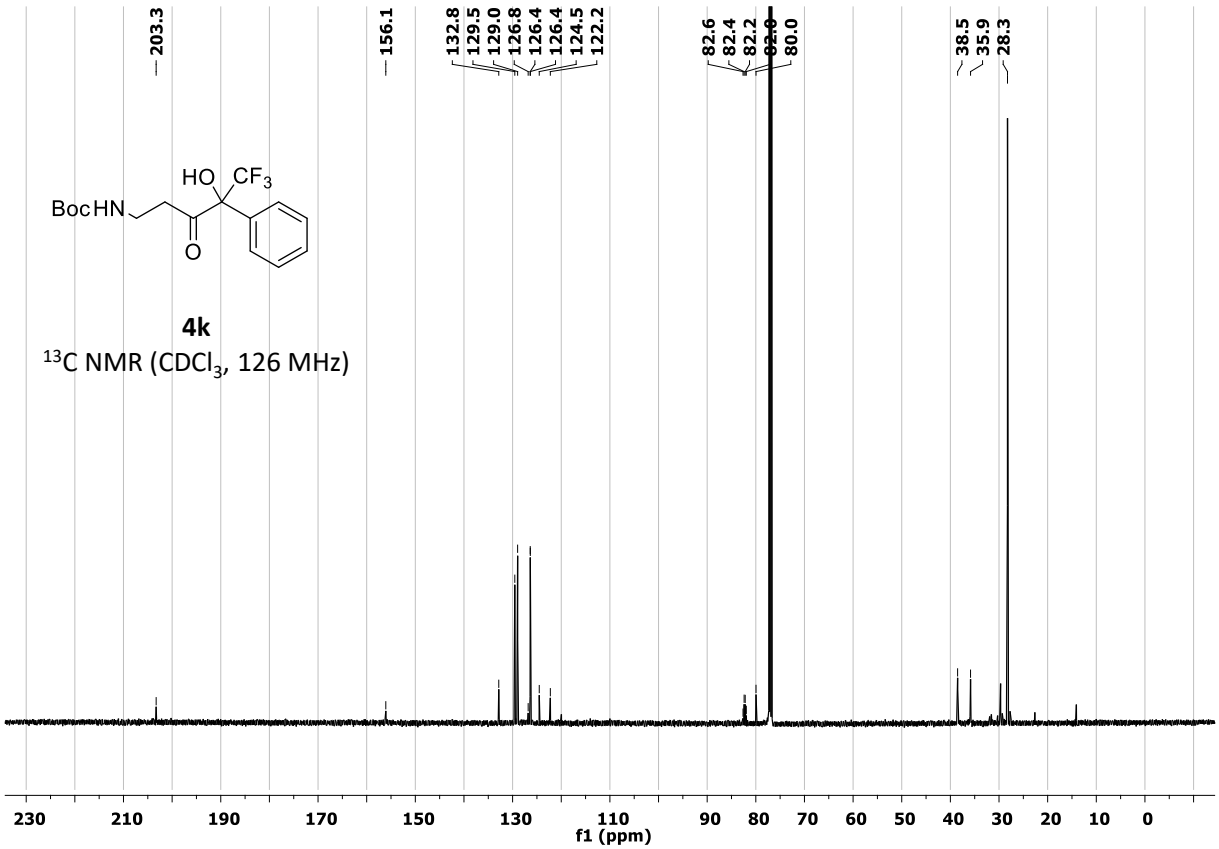
^{13}C NMR ($CDCl_3$, 126 MHz)


7.54 7.53 7.53 7.53 7.52 7.52 7.42 7.42 7.41 7.41 7.40 7.40 7.39 7.39 7.38 7.37 7.37
4.86
3.28 3.27 3.26 2.80 2.79 2.78
1.57
0.49
Me
BocHN
Si
Ph
Me
O
4j
1H NMR (CDCl3, 500 MHz)
3.28 3.27 3.26 3.25
2.80 2.79 2.78
3.30 3.20 2.80 2.70
1.7 2.9 1.0 2.1 2.0 9.5 5.1
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


246.4
156.0
134.1 134.0 130.2 128.4
79.3
48.5
34.3
28.5
-4.8
Me
BocHN
Si
Ph
Me
O
250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

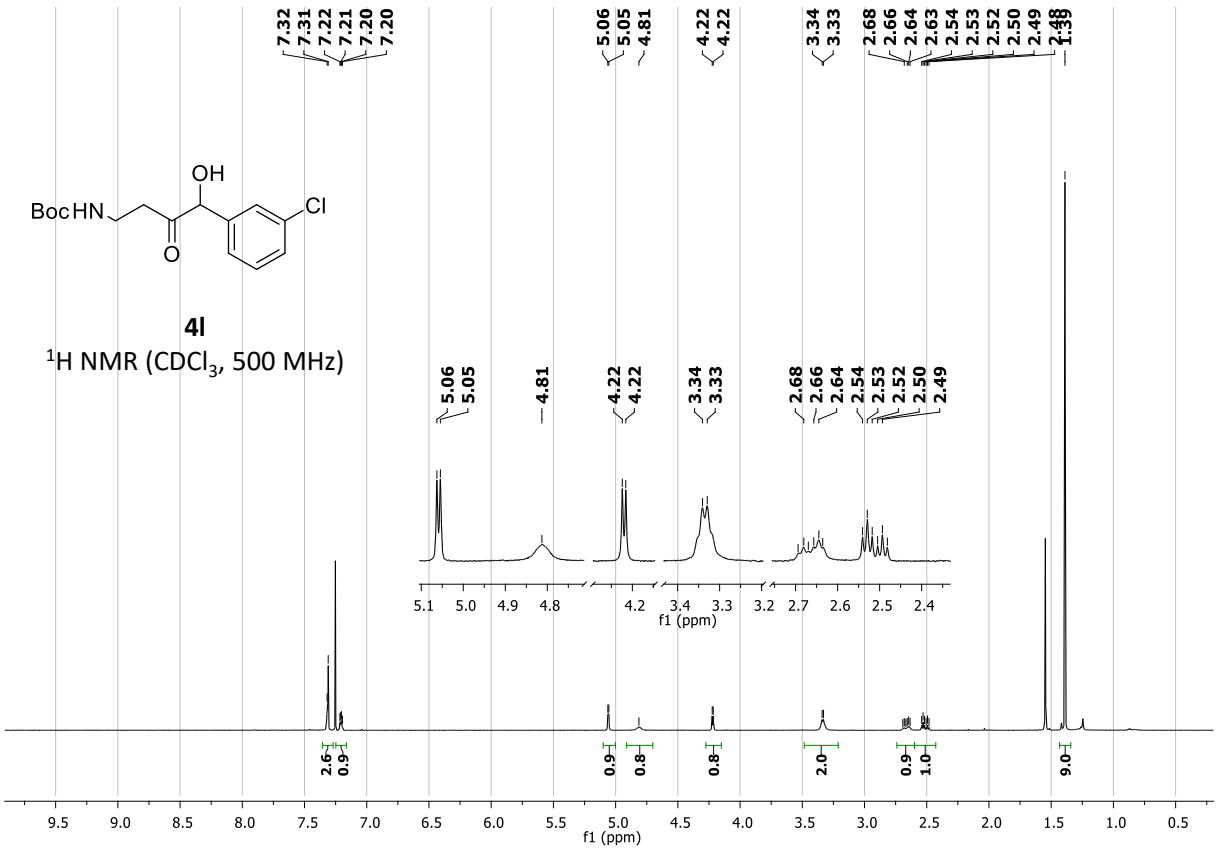

HO
CF3
BocHN
O
4k
1H NMR (CDCl3, 500 MHz)
7.56
7.55
7.44
7.43
7.41
7.41
5.30
4.82
3.45
3.43
3.42
3.42
3.41
3.34
3.33
3.32
3.31
3.29
2.80
2.79
2.78
2.77
2.76
2.75
2.73
2.71
1.39
2.0
3.0
1.0
0.8
0.9
1.1
2.2
9.3
f1 (ppm)


HO
CF3
BocHN
O
4k
19F NMR (CDCl3, 470 MHz)
-73.46
f1 (ppm)



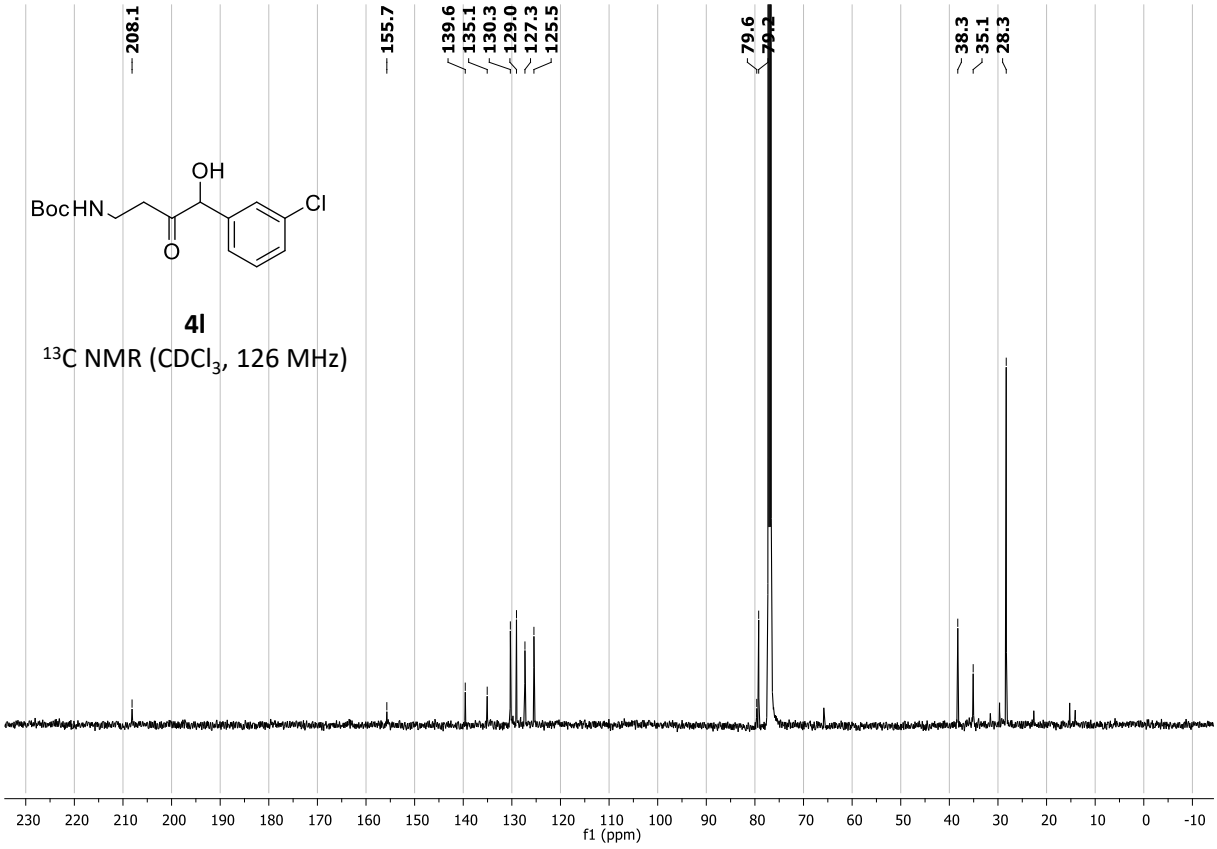
4k

^{13}C NMR ($CDCl_3$, 126 MHz)



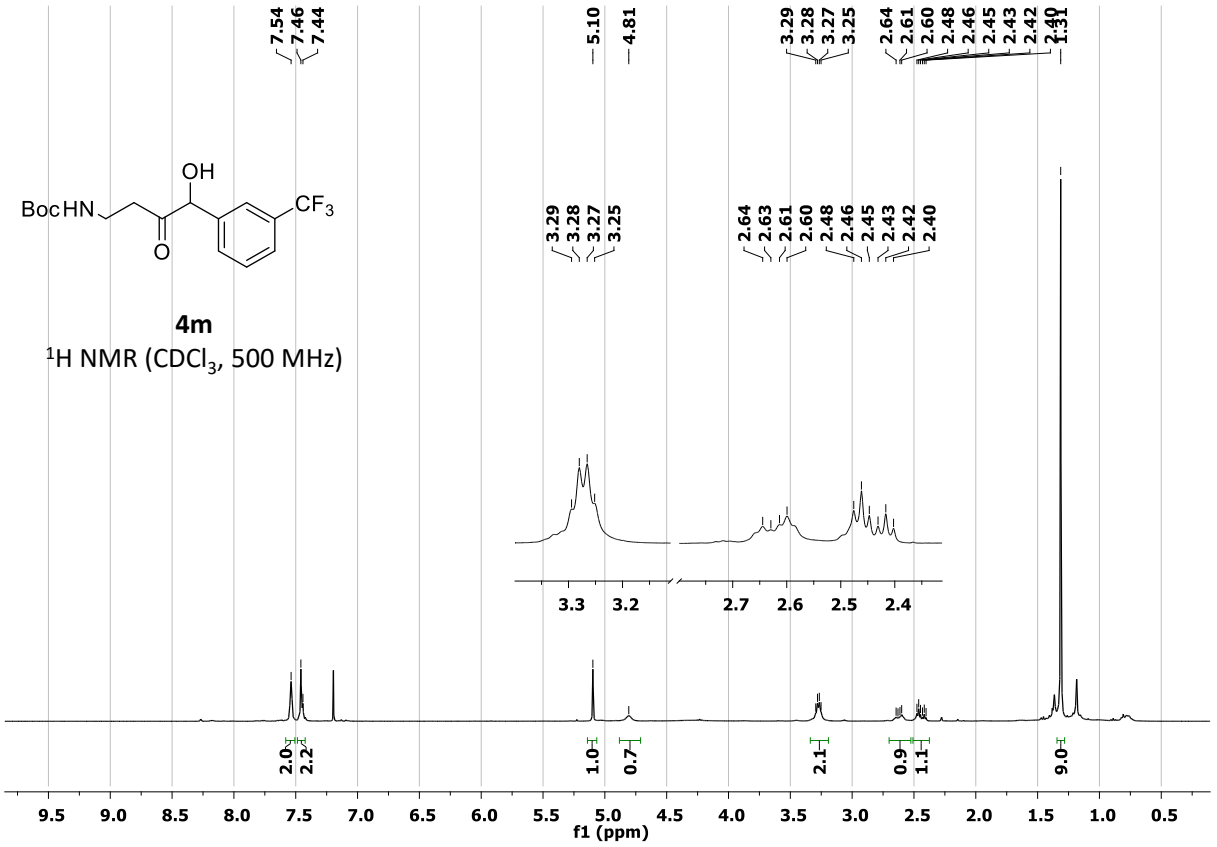
4l

^{1}H NMR ($CDCl_3$, 500 MHz)



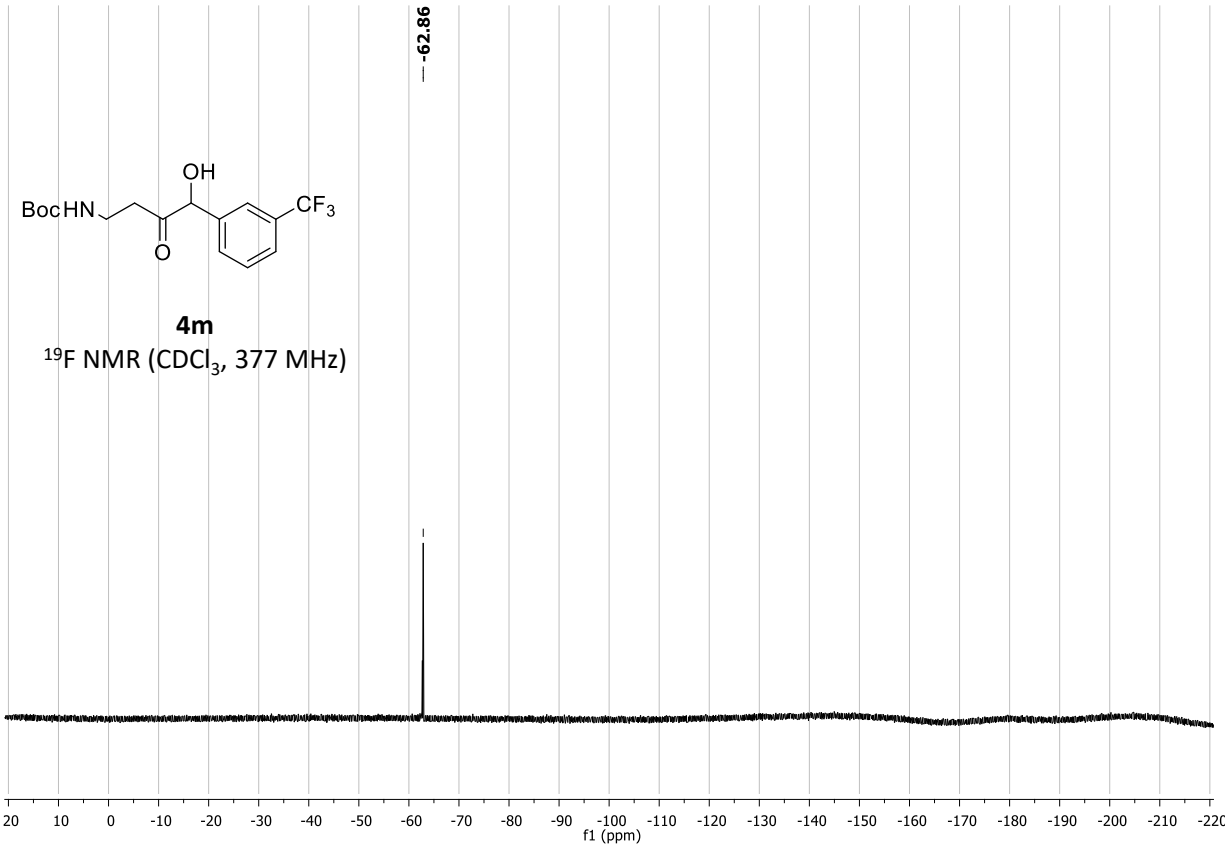
4l

^{13}C NMR ($CDCl_3$, 126 MHz)



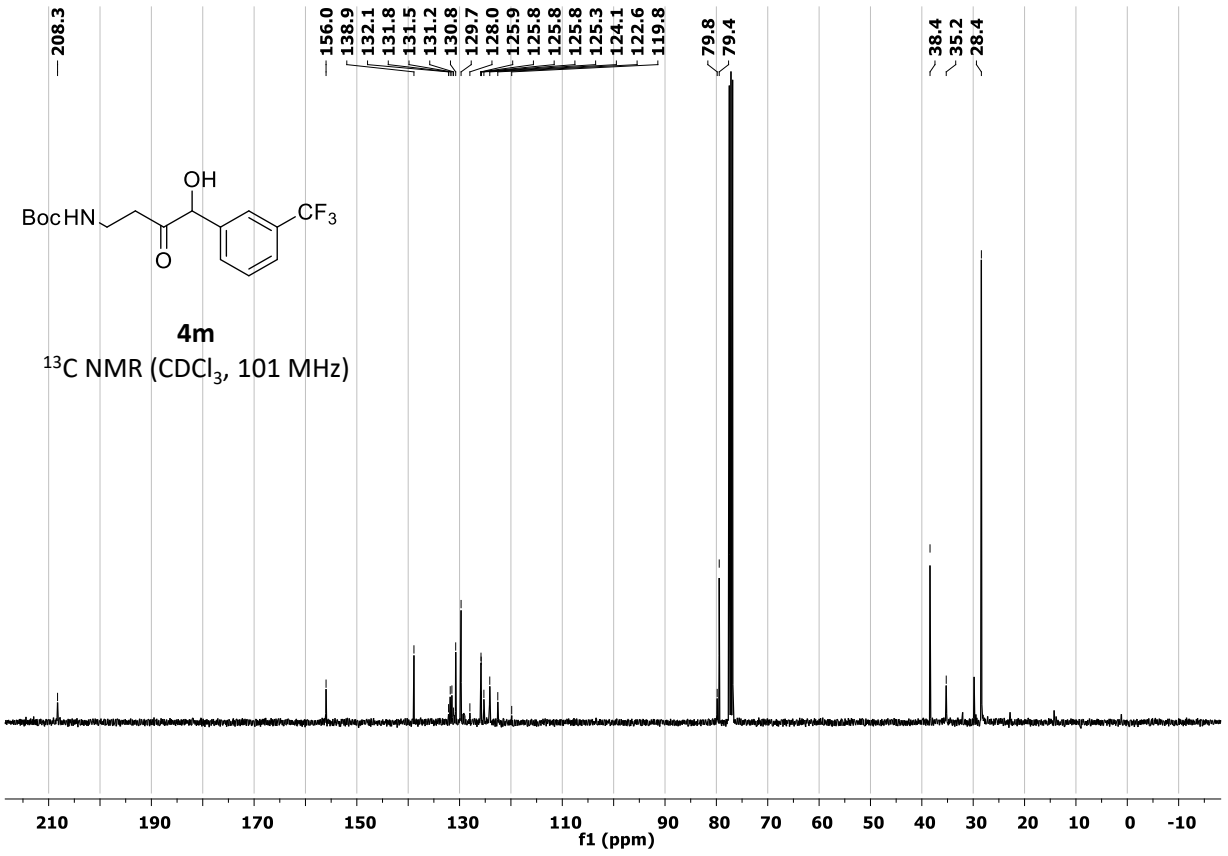
4m

^{1}H NMR ($CDCl_3$, 500 MHz)



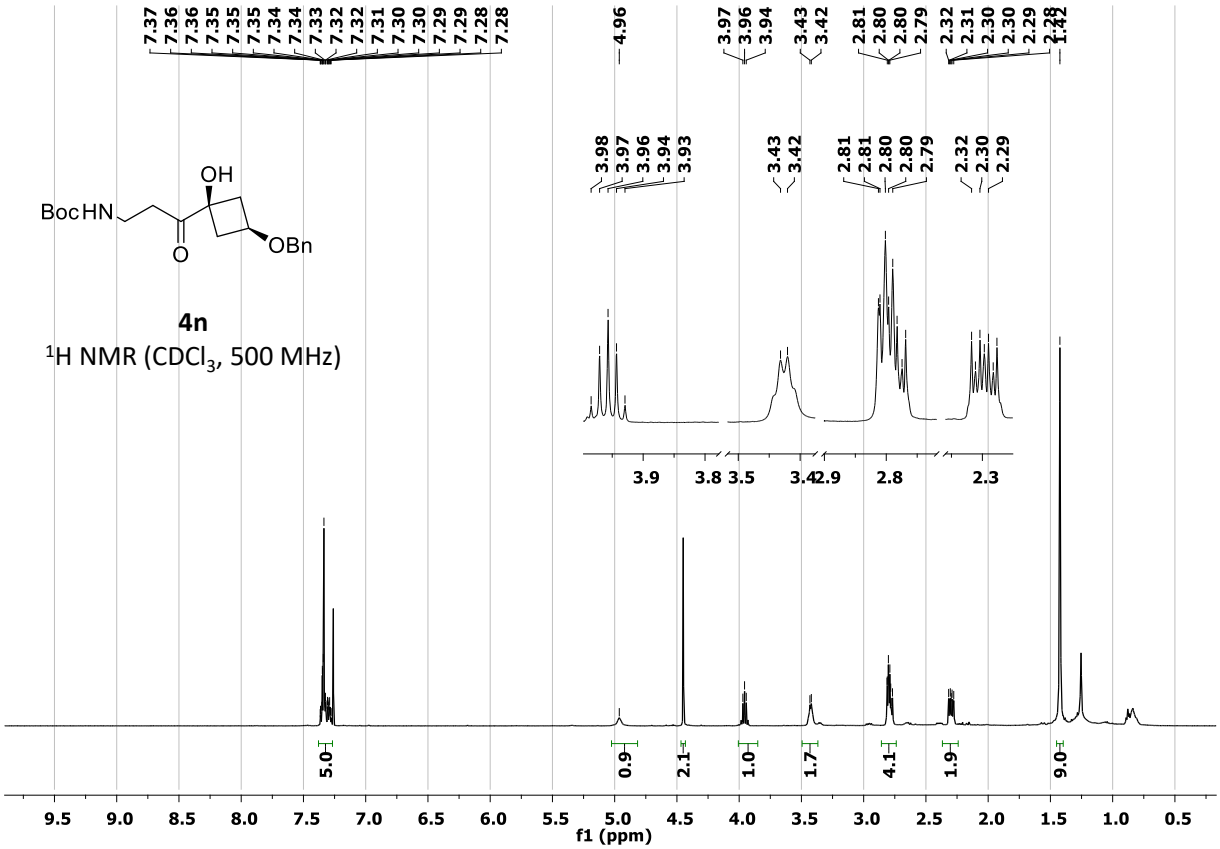
4m

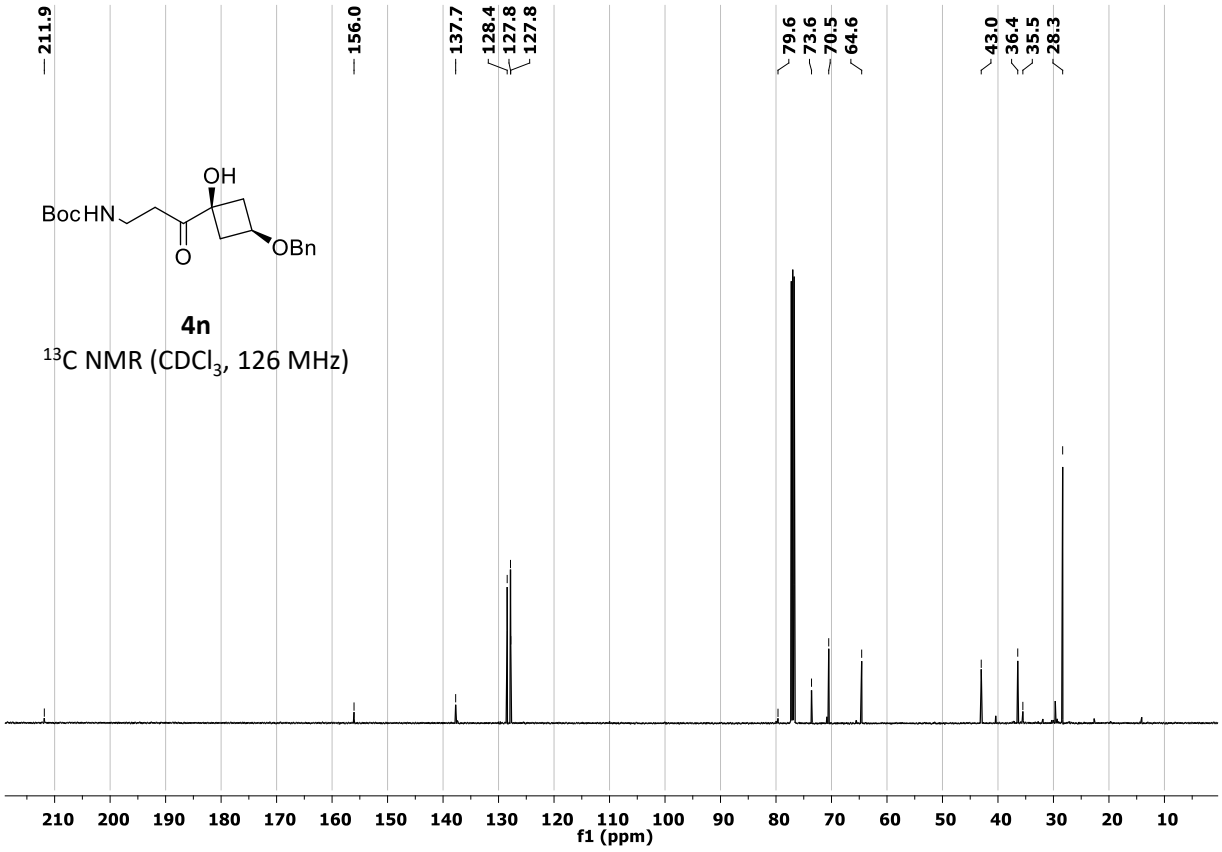
^{19}F NMR ($CDCl_3$, 377 MHz)

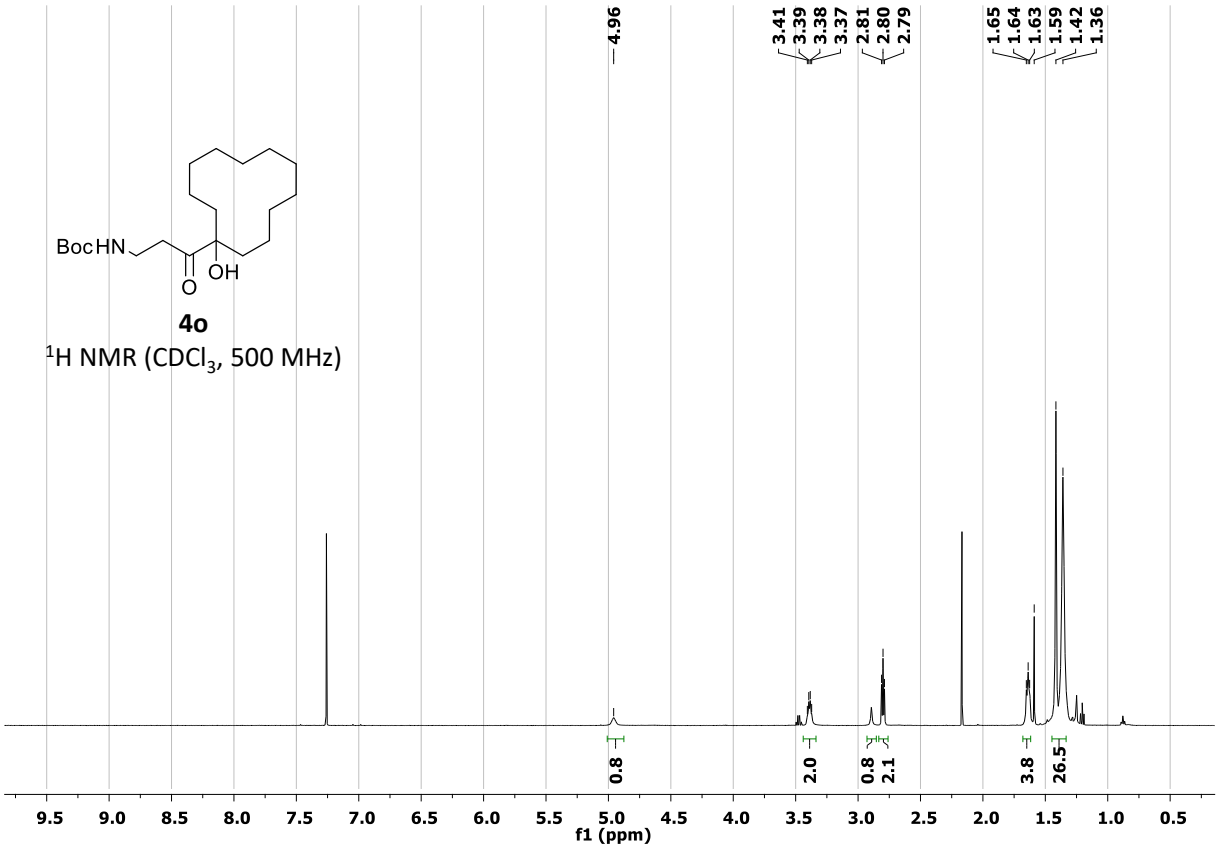


4m

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

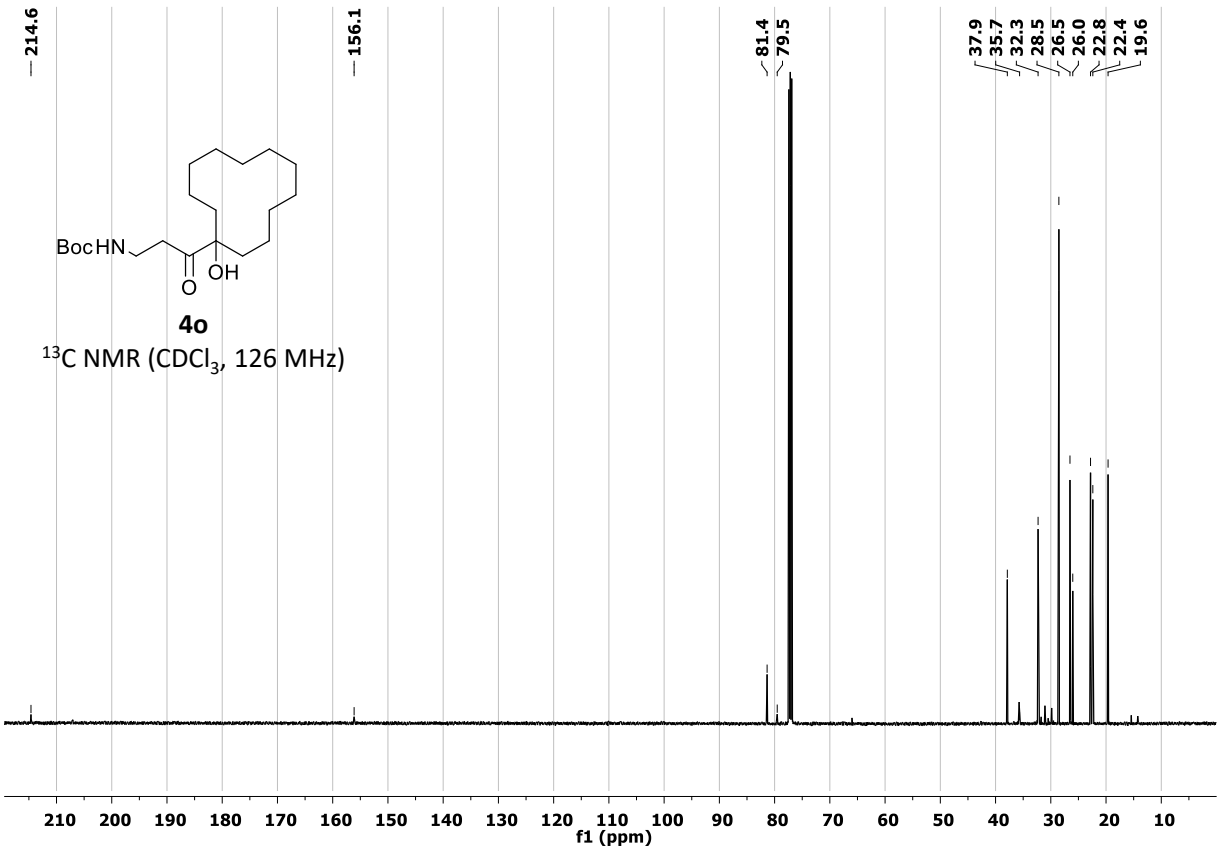

BocHN
OH
O
OBn
4n
^{1}H NMR ($CDCl_3$, 500 MHz)
f1 (ppm)


BocHN
OH
O
OBn
4n
^{13}C NMR ($CDCl_3$, 126 MHz)
f1 (ppm)



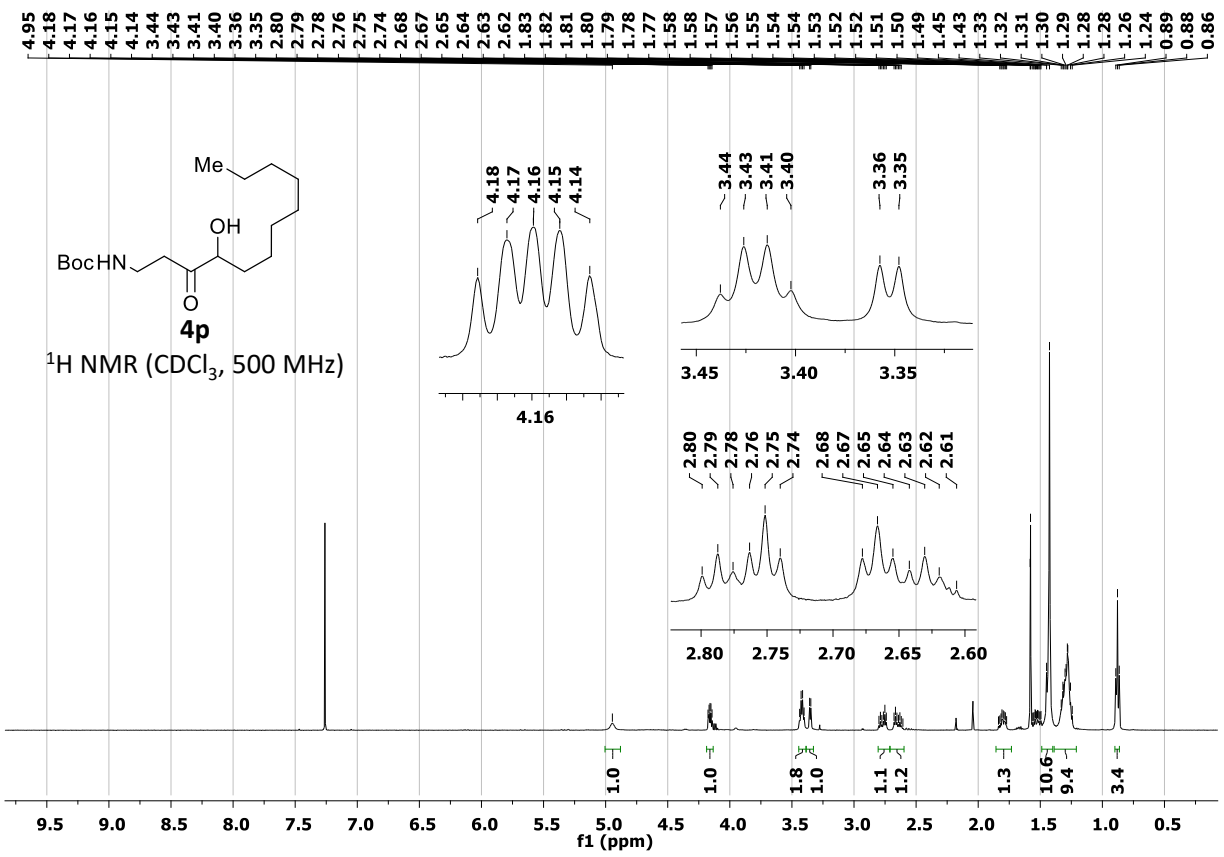
4o

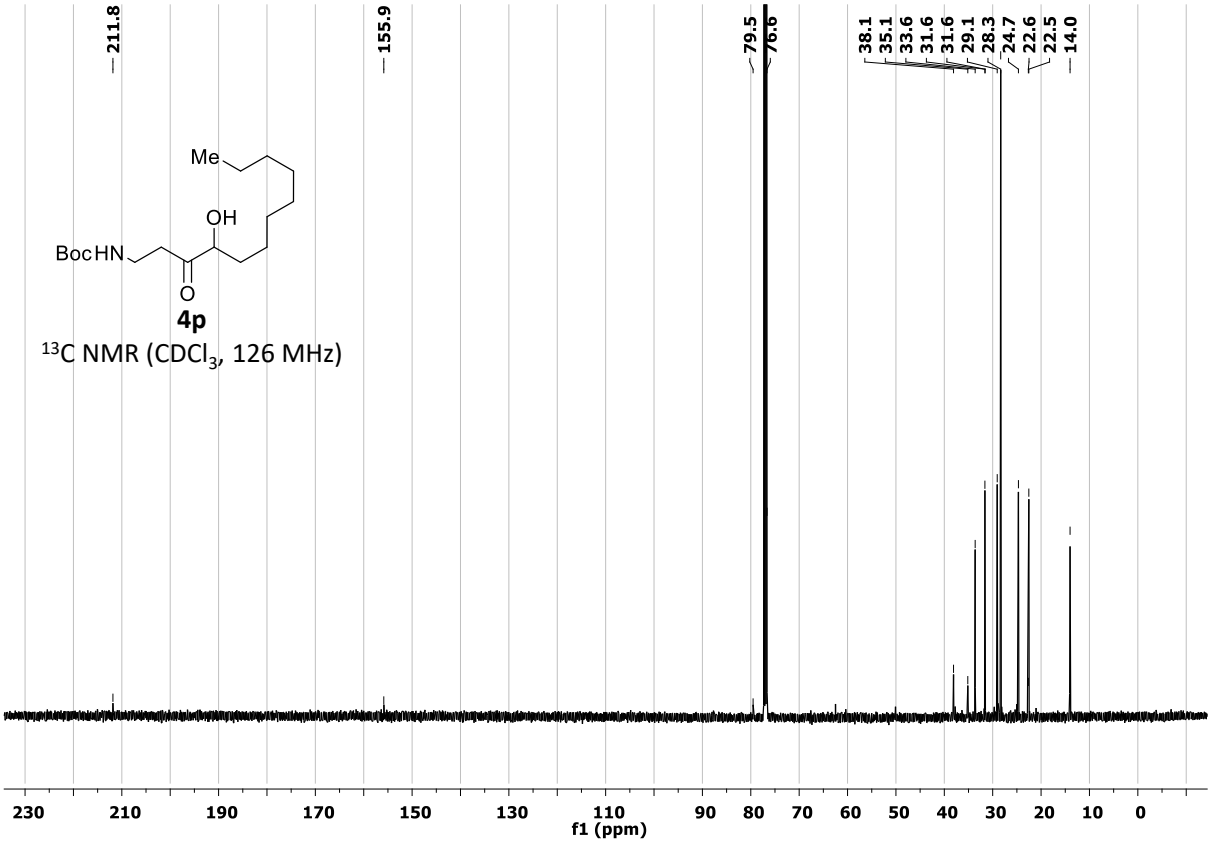
^{1}H NMR ($CDCl_3$, 500 MHz)

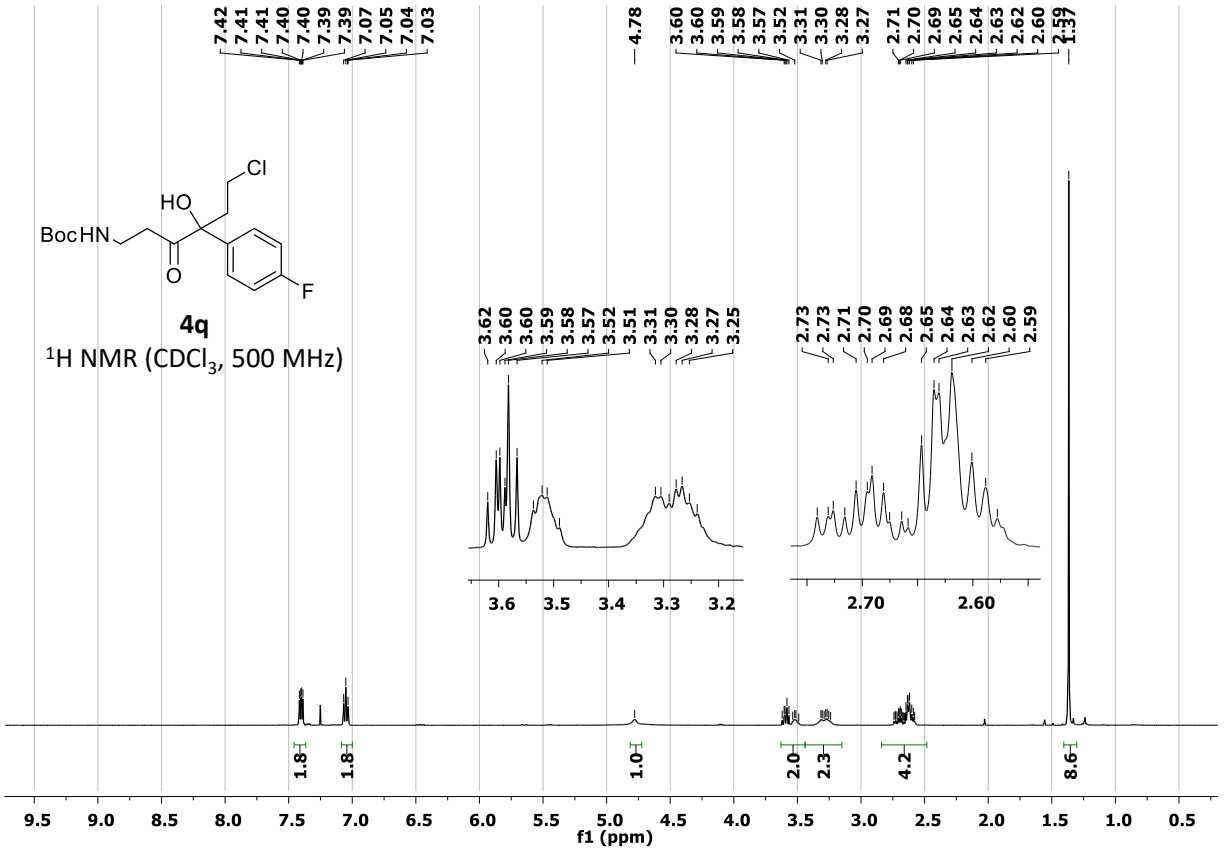


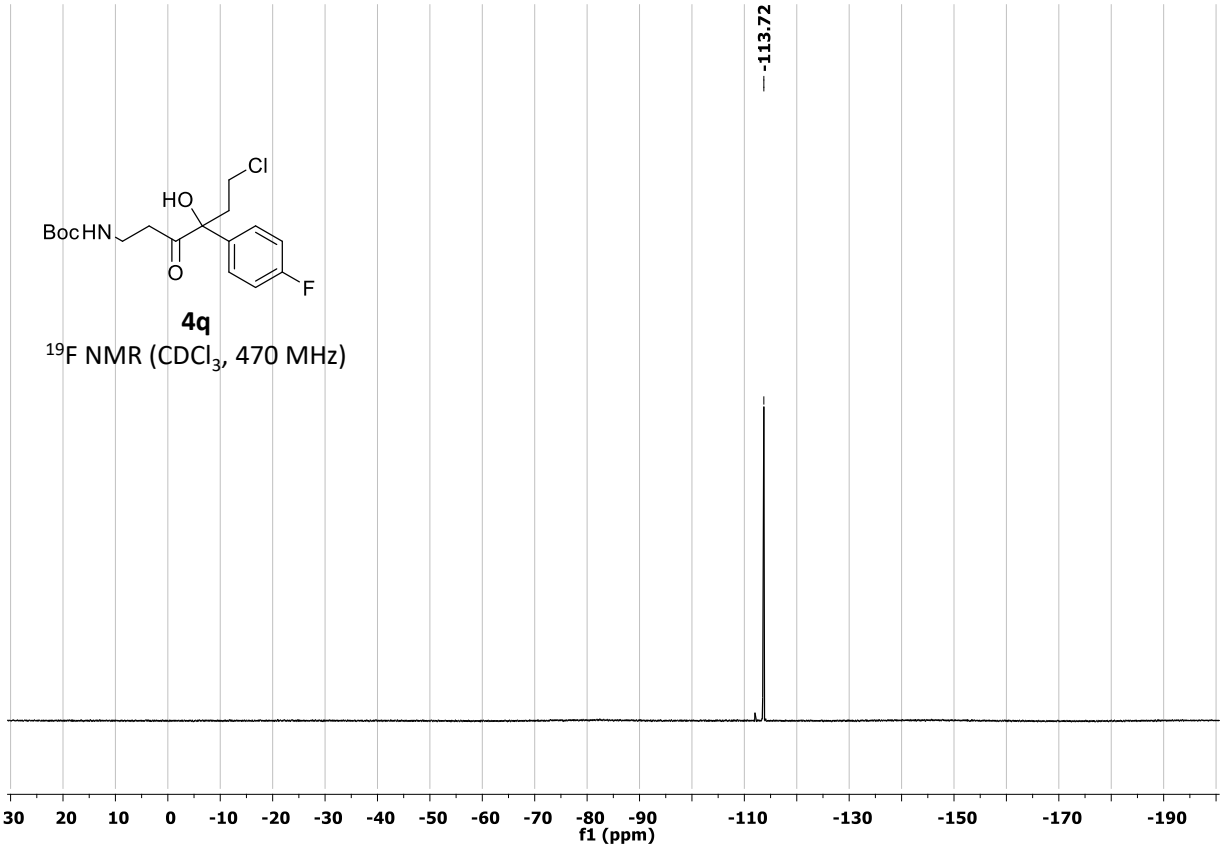
4o

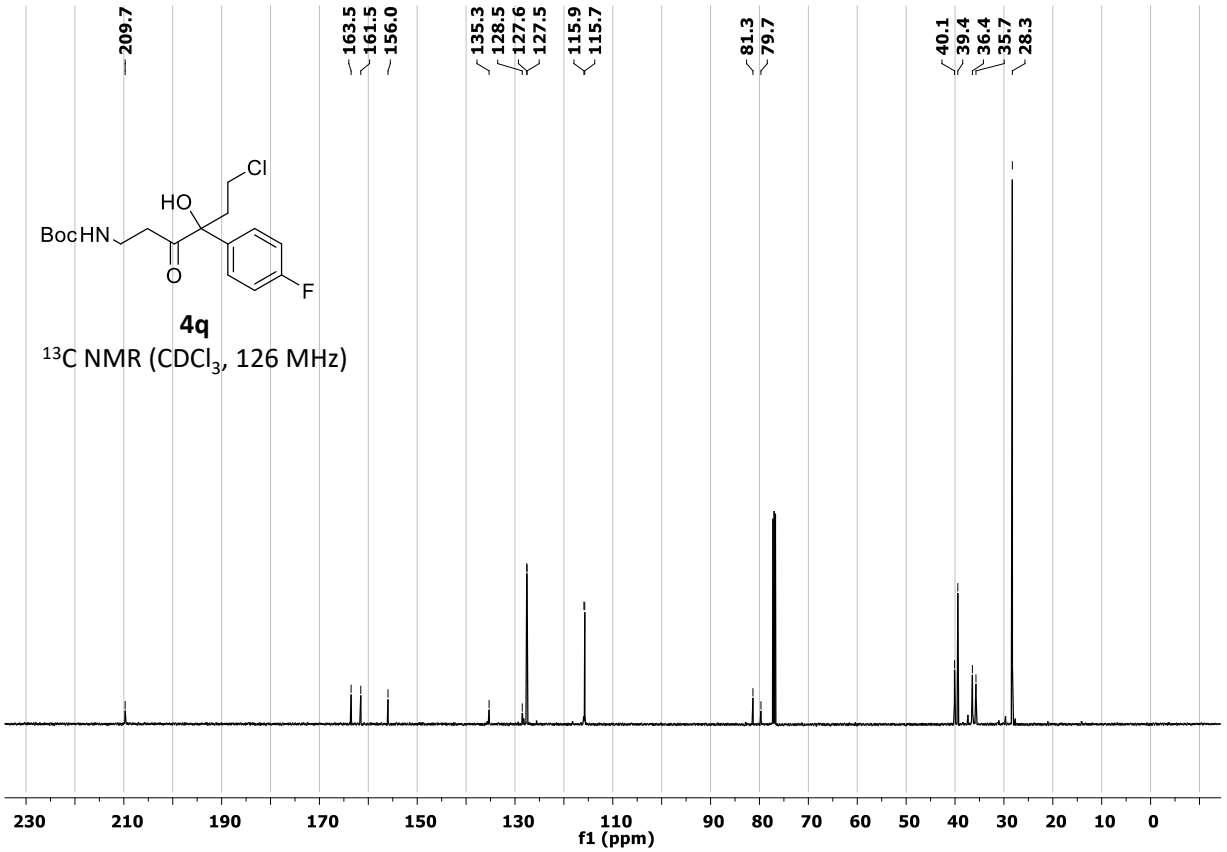
^{13}C NMR ($CDCl_3$, 126 MHz)


Me
OH
BocHN
O
4p
1H NMR (CDCl3, 500 MHz)
f1 (ppm)


Me
OH
BocHN
O
4p
13C NMR (CDCl3, 126 MHz)
f1 (ppm)

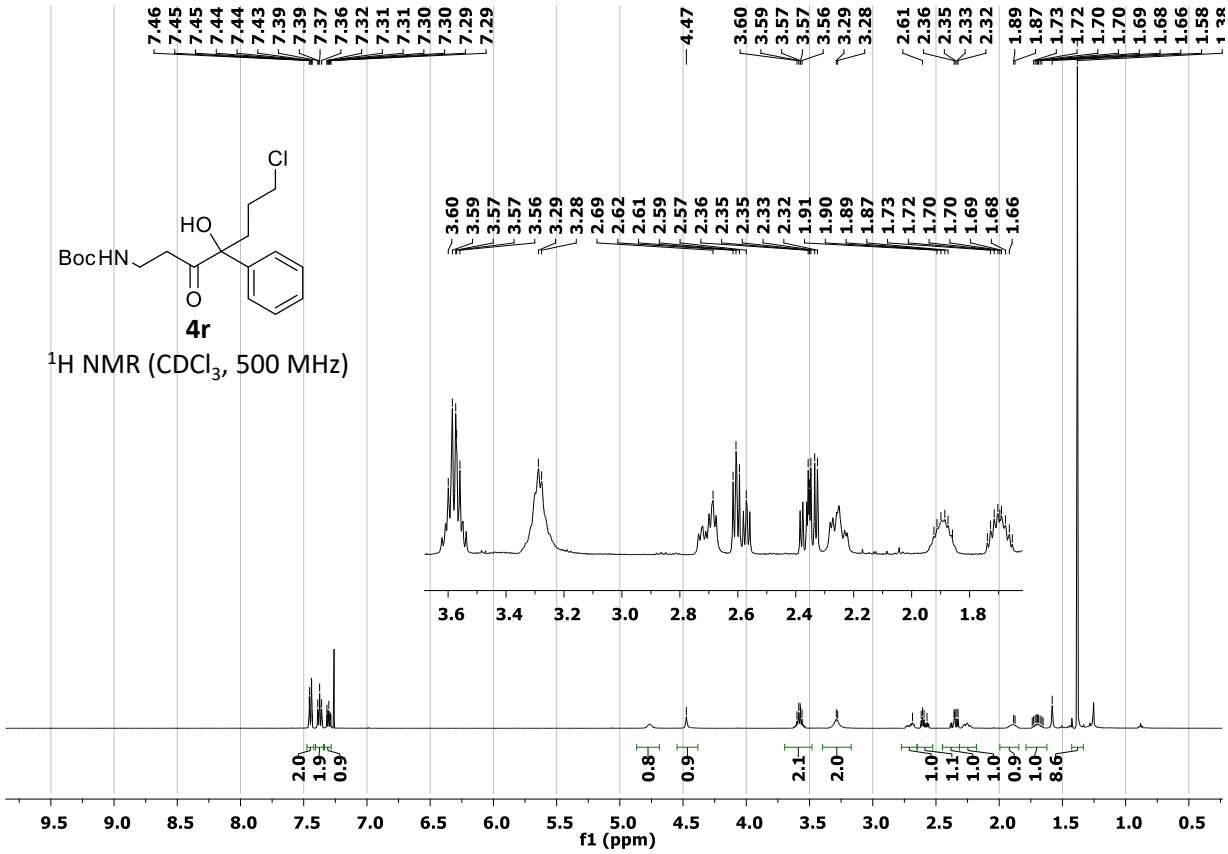

Cl
HO
BocHN
O
F
4q
1H NMR (CDCl3, 500 MHz)
7.42 7.41 7.41 7.40 7.40 7.39 7.39 7.07 7.05 7.04 7.03
4.78
3.60 3.60 3.59 3.58 3.57 3.52 3.31 3.30 3.28 3.27
2.71 2.70 2.69 2.65 2.64 2.63 2.62 2.60 2.59 1.37
3.62 3.60 3.60 3.59 3.58 3.57 3.52 3.51 3.31 3.30 3.28 3.27 3.25
2.73 2.73 2.71 2.70 2.69 2.68 2.65 2.64 2.63 2.62 2.60 2.59
1.8 1.8 1.0 2.0 2.3 4.2 8.6
f1 (ppm)


Cl
HO
BocHN
O
F
4q
19F NMR (CDCl3, 470 MHz)
-113.72
f1 (ppm)



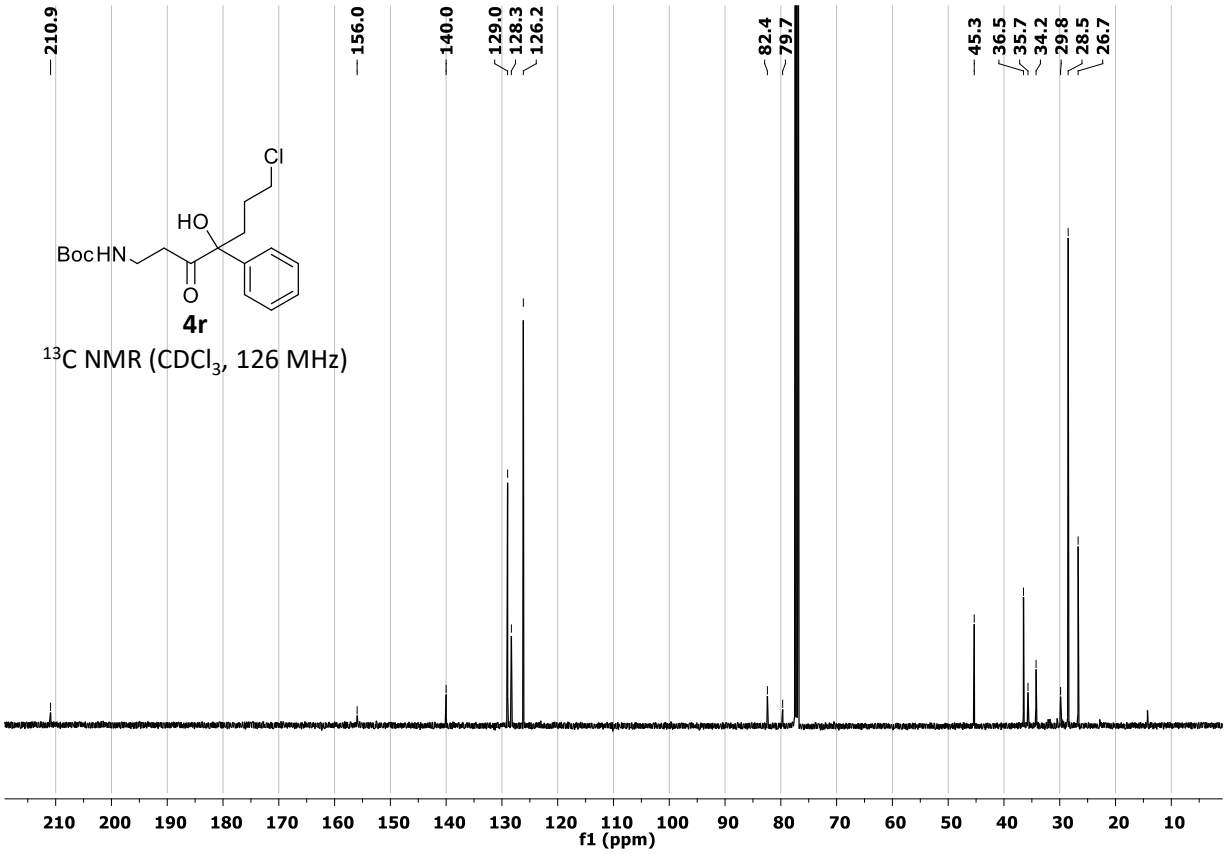
4q

^{13}C NMR ($CDCl_3$, 126 MHz)



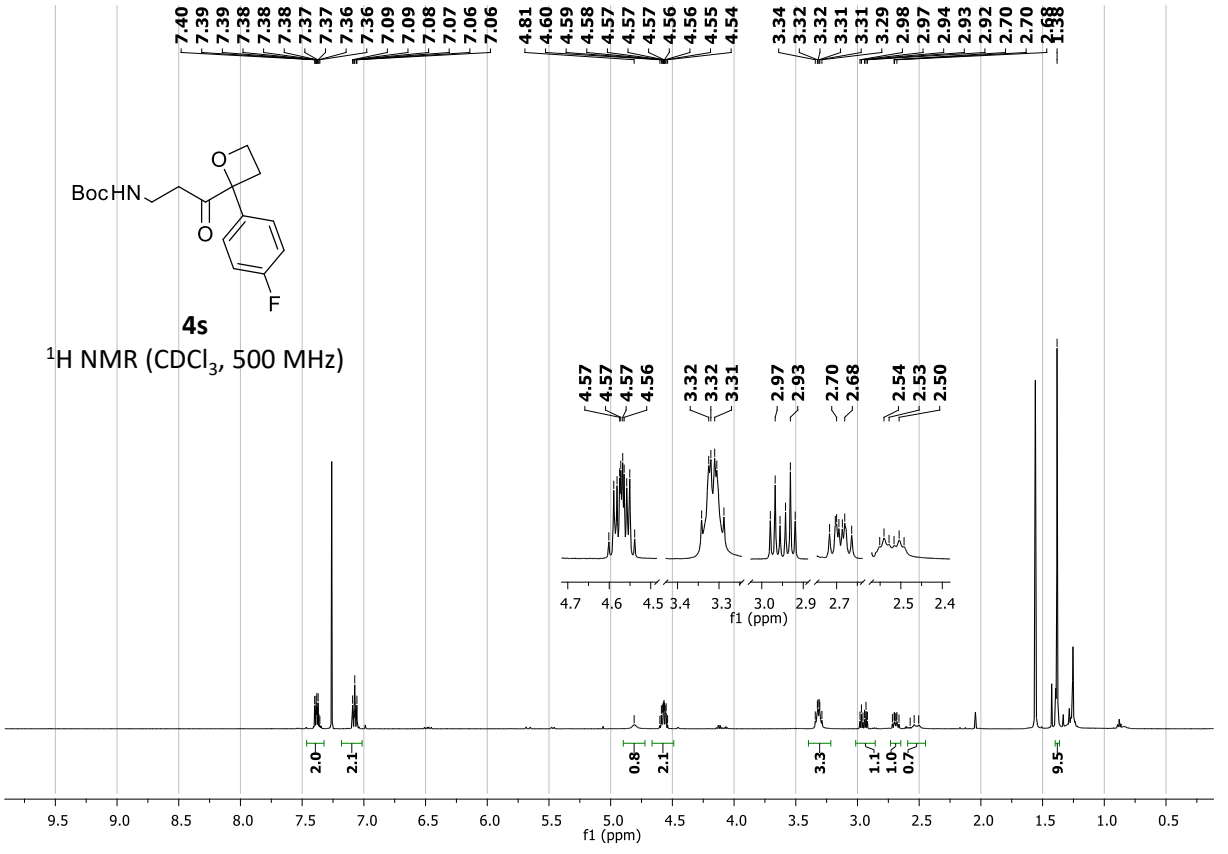
4r

^{1}H NMR ($CDCl_3$, 500 MHz)



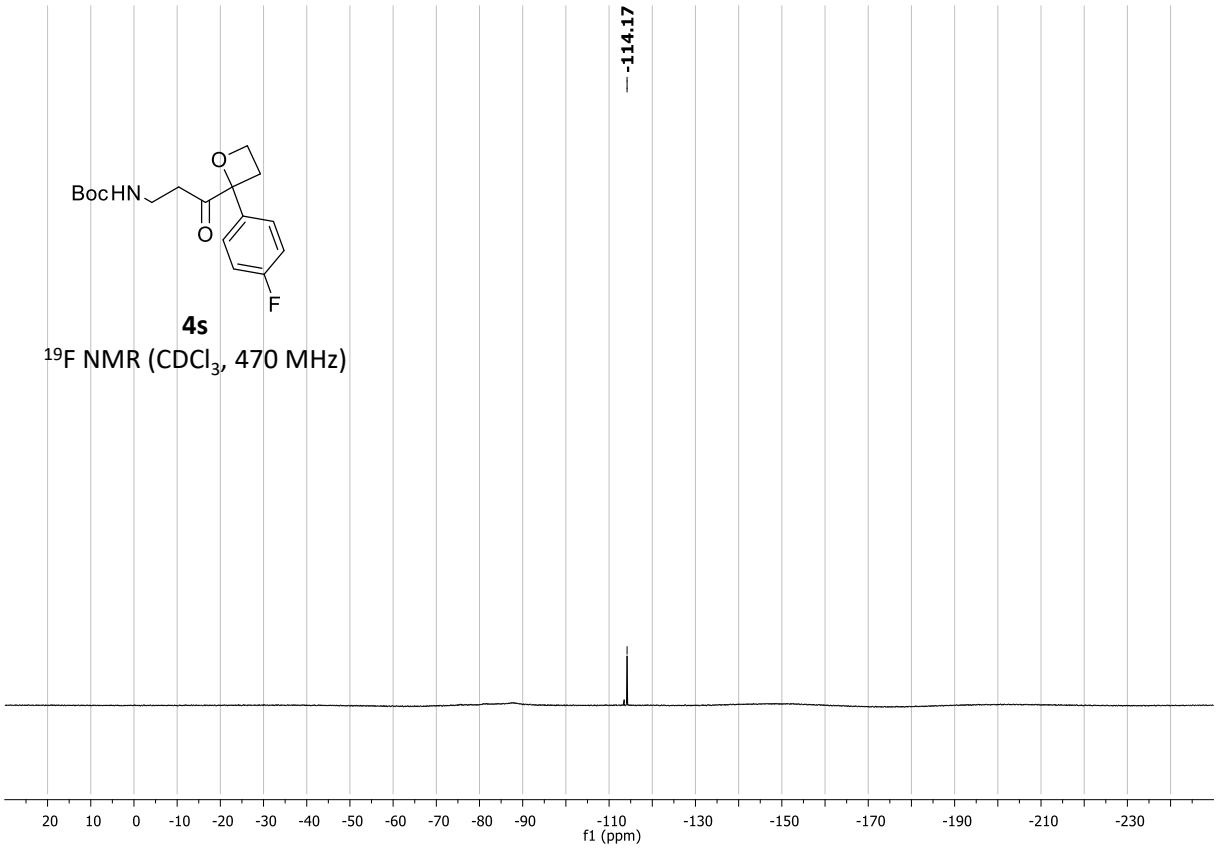
4r

^{13}C NMR ($CDCl_3$, 126 MHz)



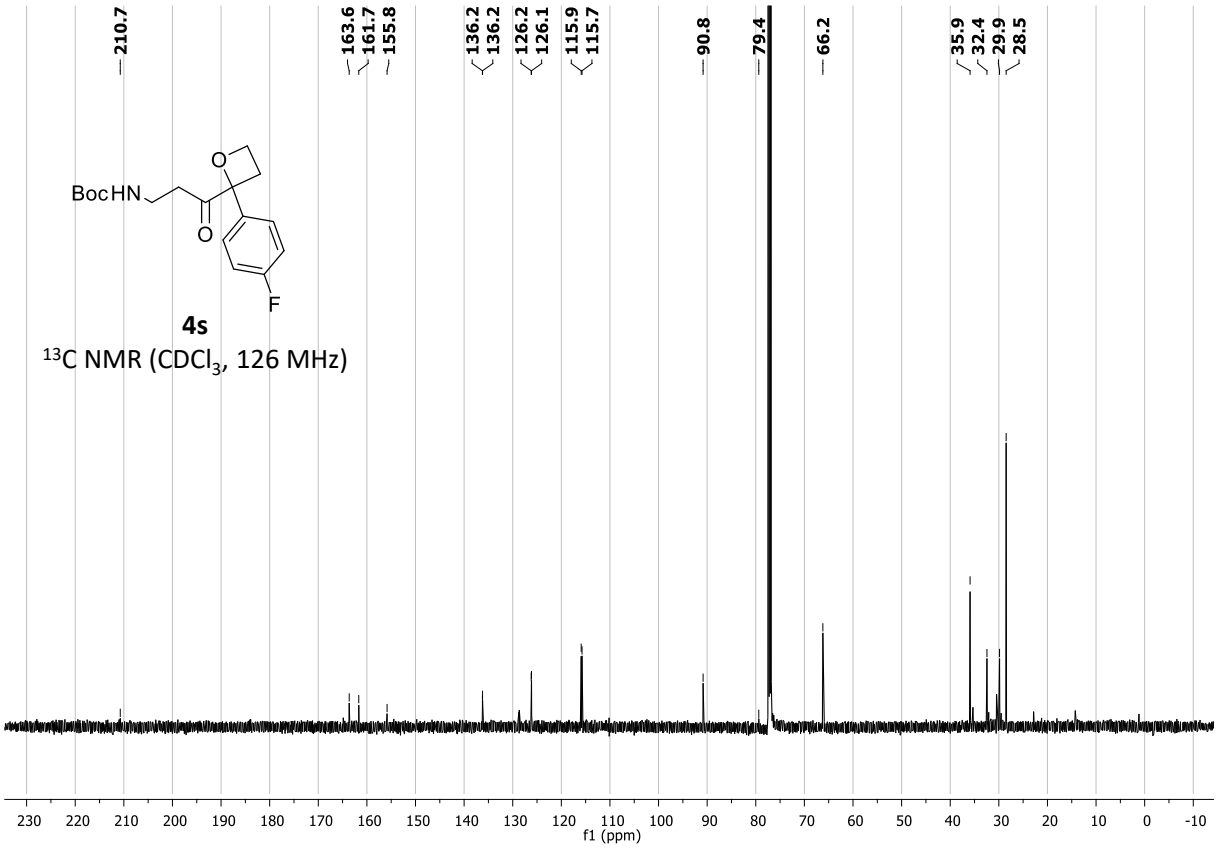
4s

^{1}H NMR ($CDCl_3$, 500 MHz)



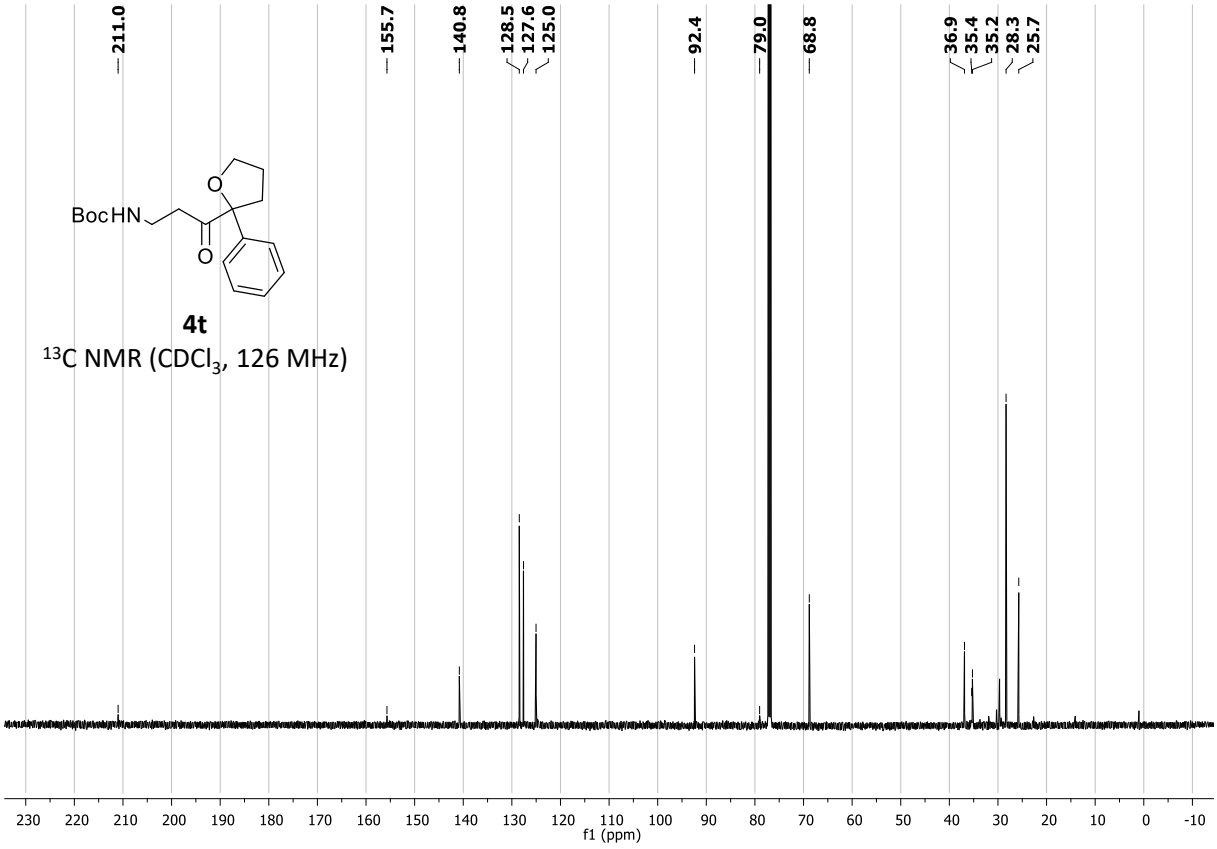
4s

^{19}F NMR ($CDCl_3$, 470 MHz)



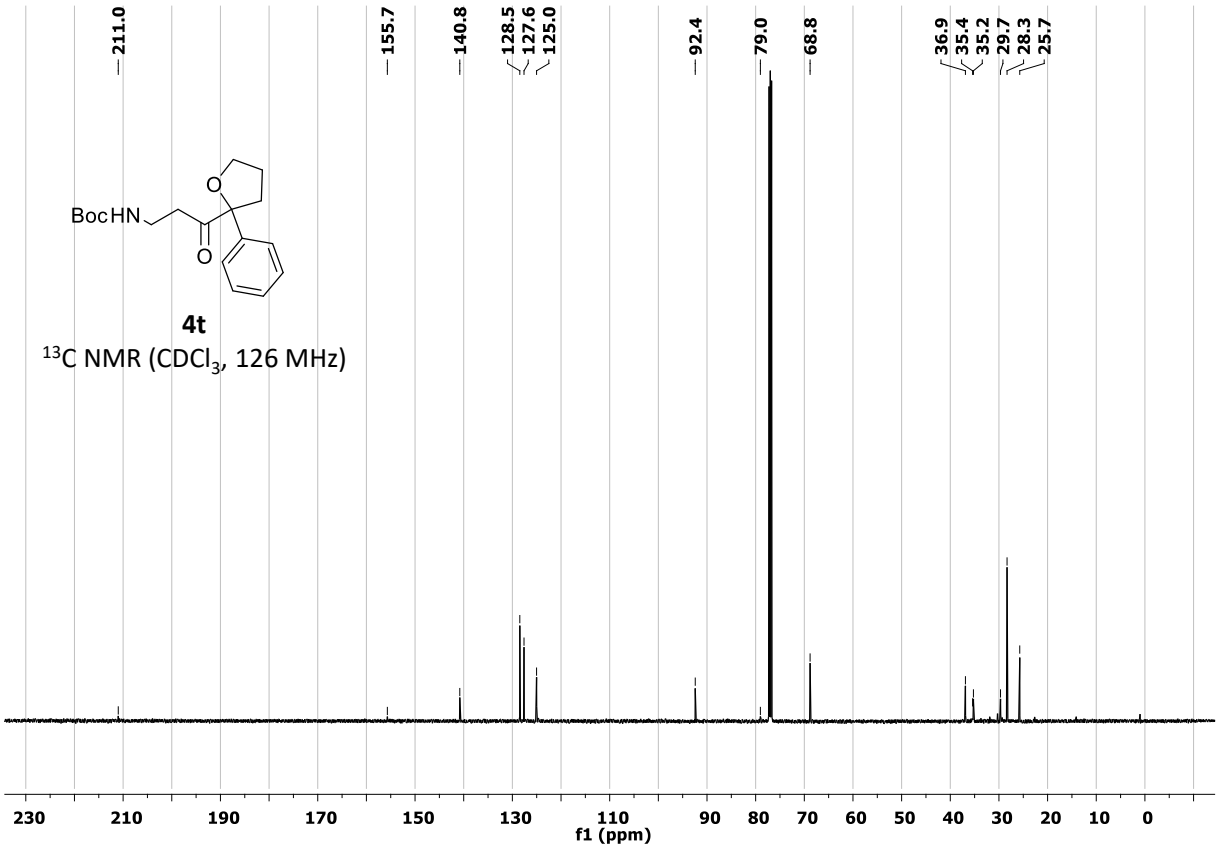
4s

^{13}C NMR ($CDCl_3$, 126 MHz)



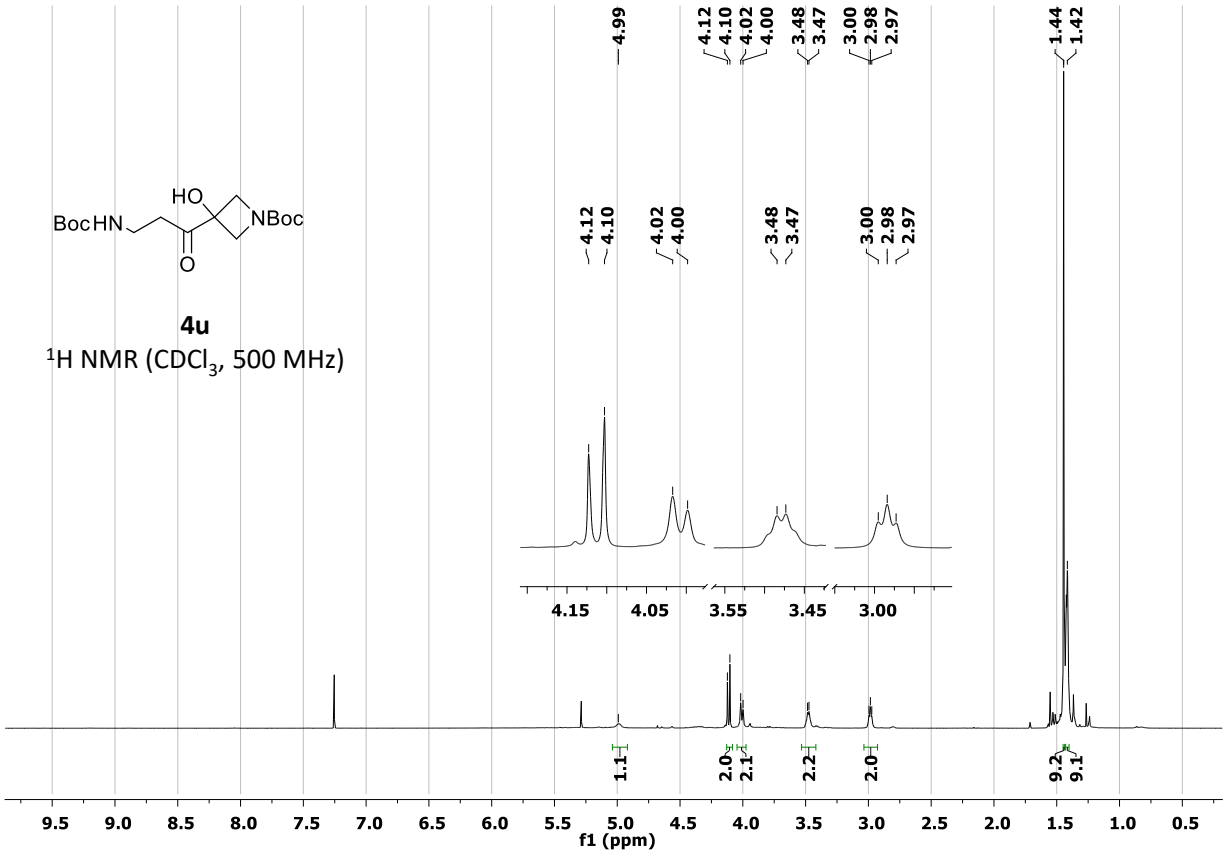
4t

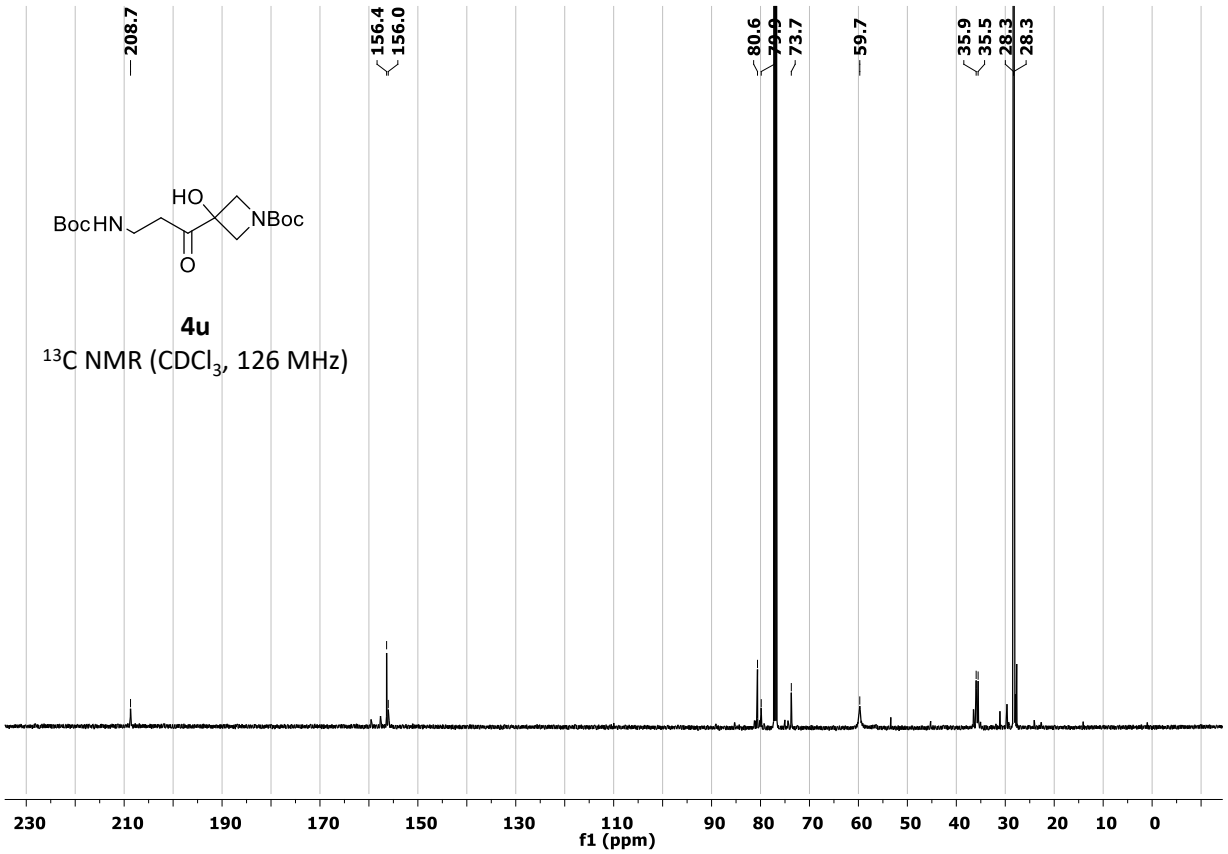
^{13}C NMR ($CDCl_3$, 126 MHz)

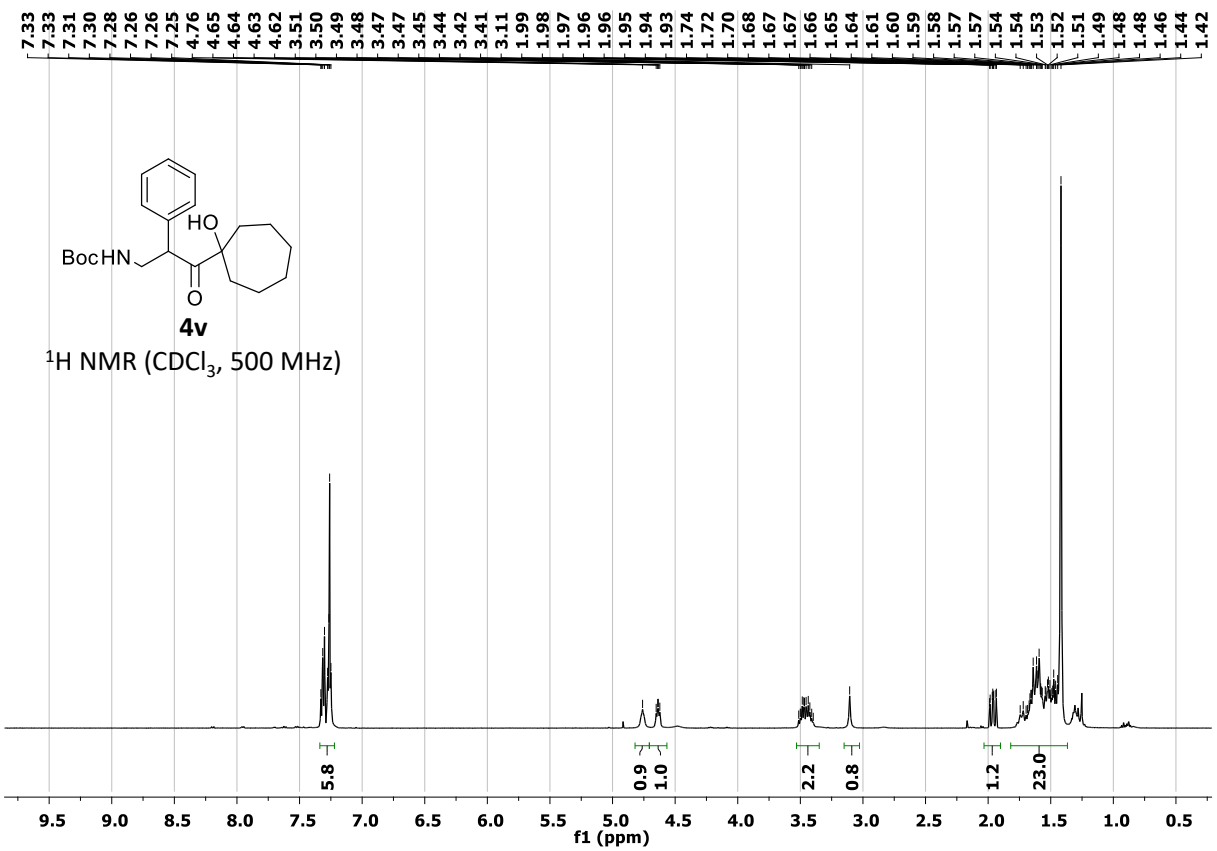


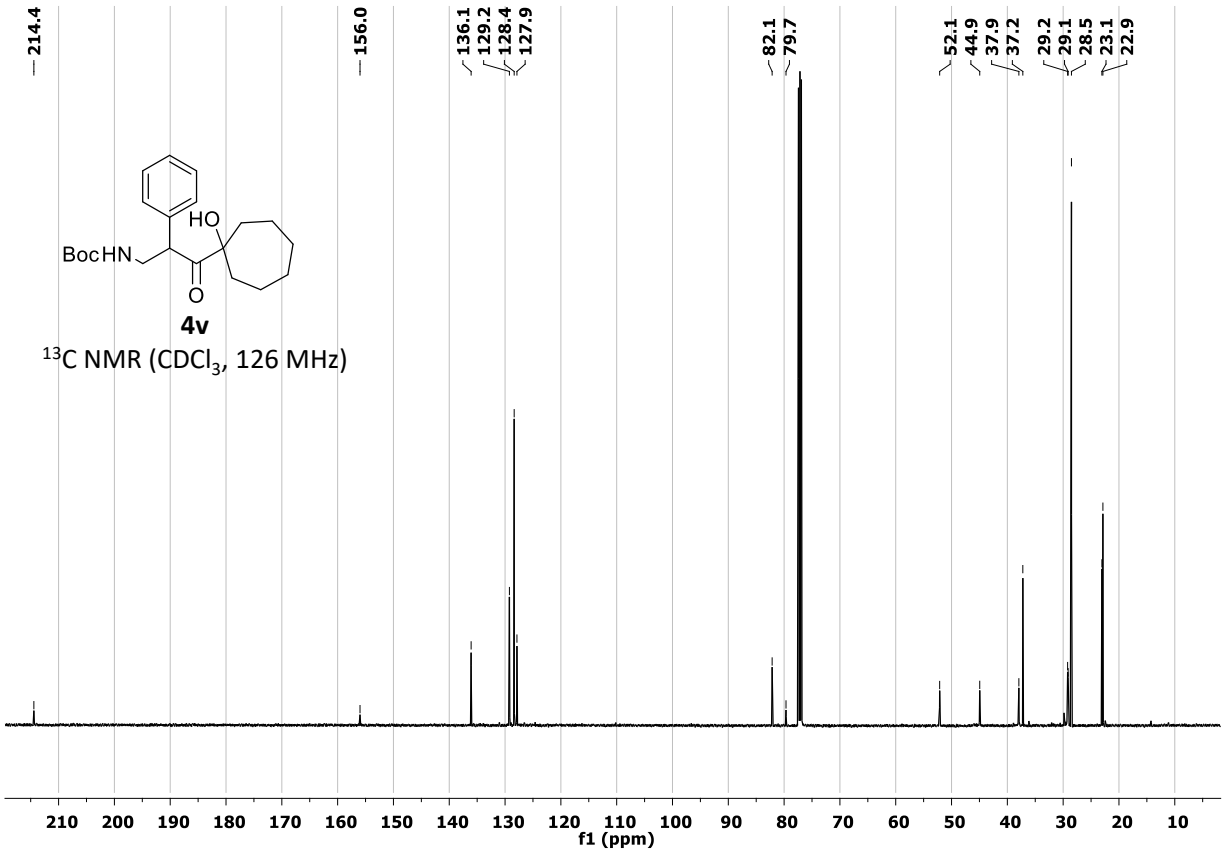
4t

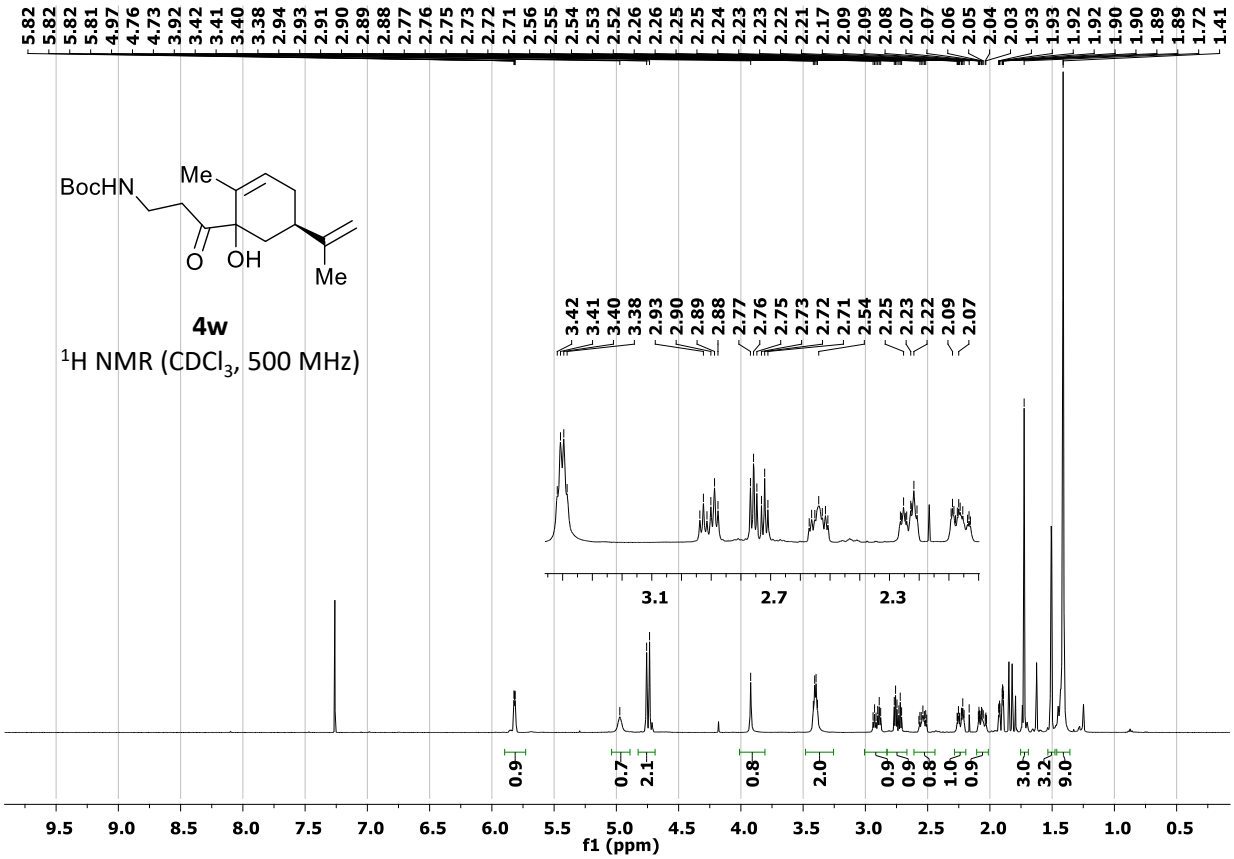
^{13}C NMR ($CDCl_3$, 126 MHz)

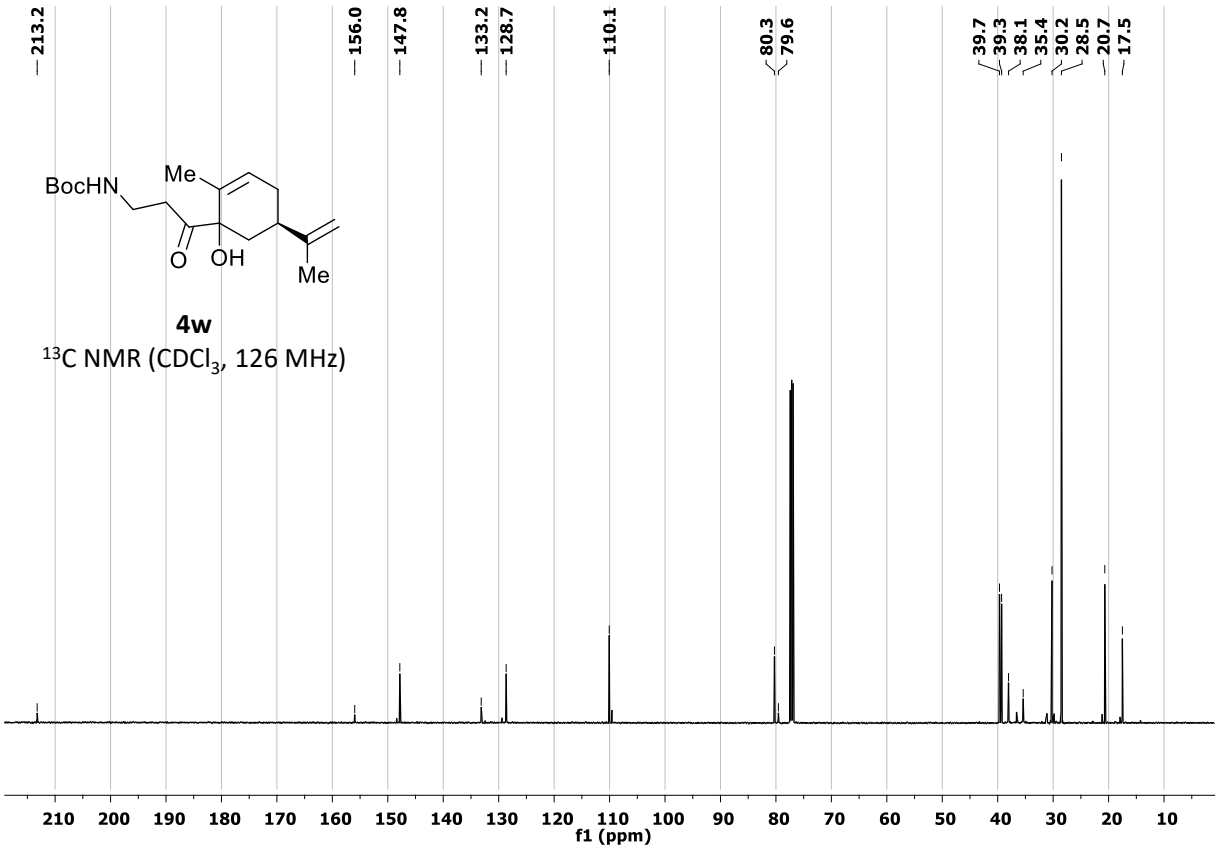

HO
BocHN
NBoc
O
4u
1H NMR (CDCl3, 500 MHz)
4.99
4.12
4.10
4.02
4.00
3.48
3.47
3.00
2.98
2.97
1.44
1.42
4.15
4.05
3.55
3.45
3.00
1.1
2.0
2.1
2.2
2.0
9.2
9.1
f1 (ppm)

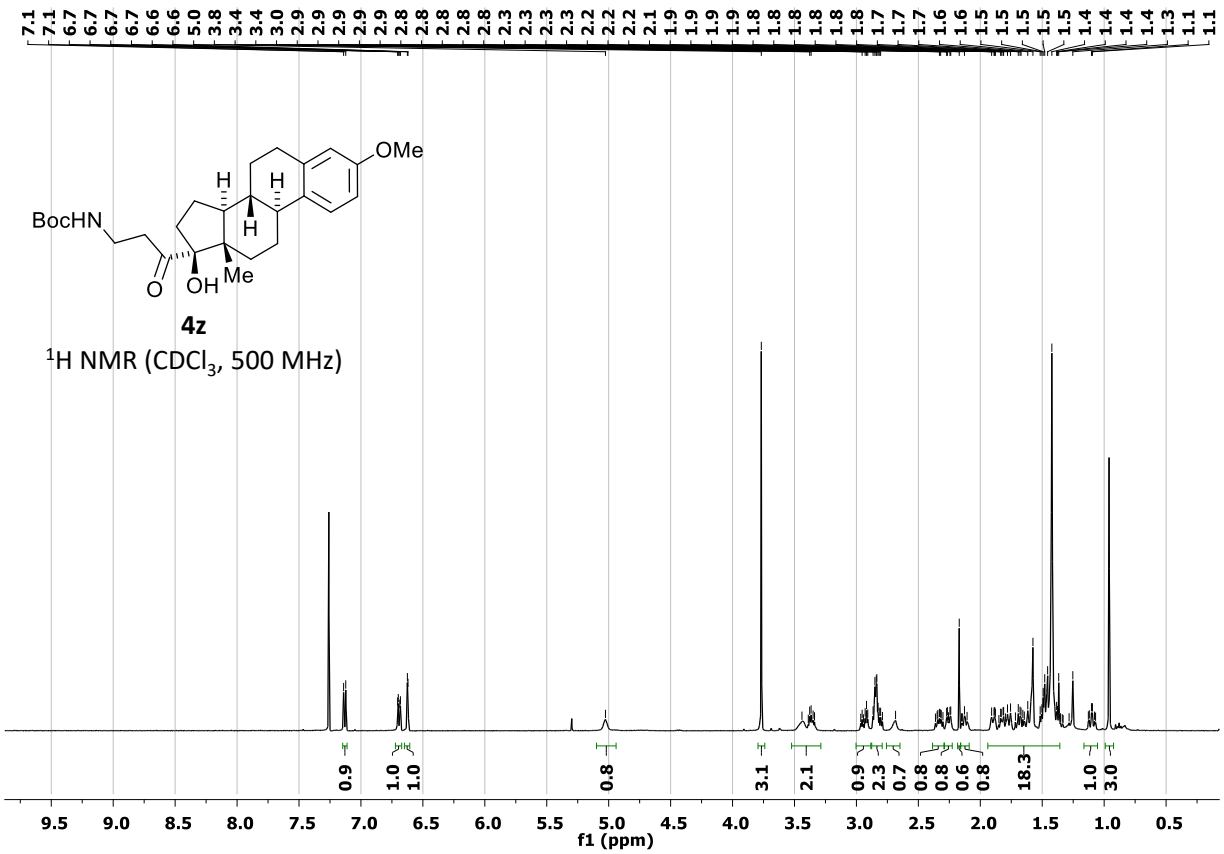

HO
BocHN
NBoc
O
4u
13C NMR (CDCl3, 126 MHz)
208.7
156.4
156.0
80.6
79.9
73.7
59.7
35.9
35.5
28.3
28.3
f1 (ppm)

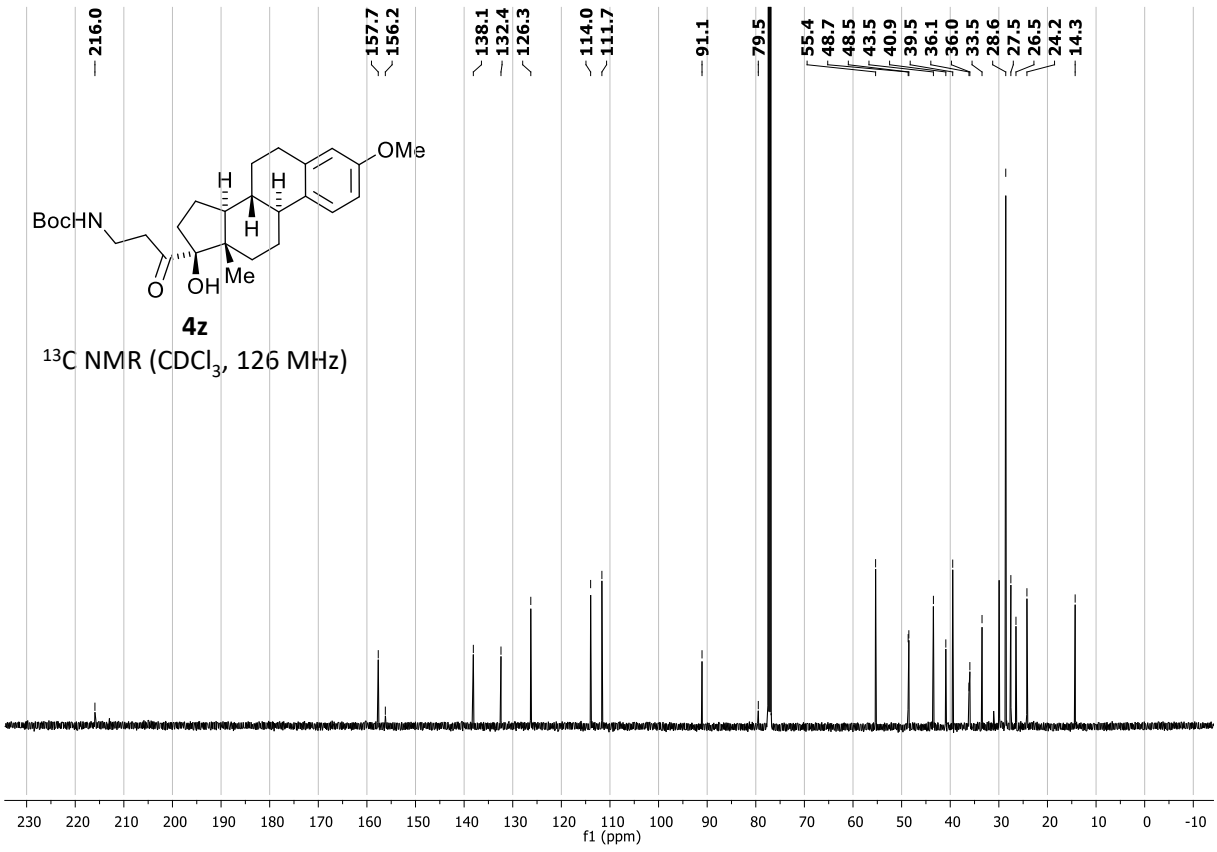

7.33 7.33 7.31 7.30 7.28 7.26 7.25 4.76 4.65 4.64 4.63 4.62 3.51 3.50 3.49 3.48 3.47 3.47 3.45 3.44 3.42 3.41 3.11 1.99 1.98 1.97 1.96 1.96 1.95 1.94 1.93 1.74 1.72 1.70 1.68 1.67 1.67 1.66 1.65 1.64 1.61 1.60 1.59 1.58 1.57 1.57 1.54 1.54 1.53 1.52 1.51 1.49 1.48 1.48 1.46 1.44 1.42
HO
BocHN
O
4v
1H NMR (CDCl3, 500 MHz)
5.8
0.9
1.0
2.2
0.8
1.2
23.0
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

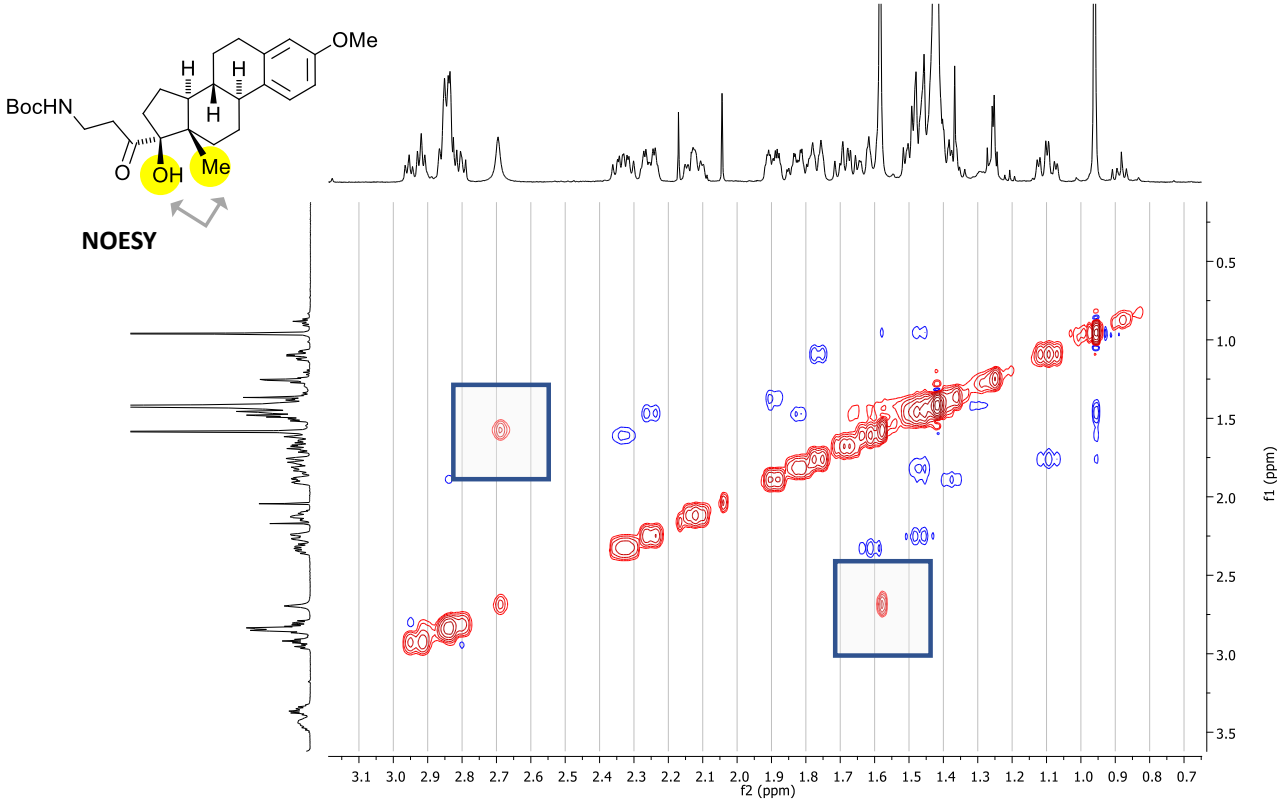

214.4
156.0
136.1
129.2
128.4
127.9
82.1
79.7
52.1
44.9
37.9
37.2
29.2
29.1
28.5
23.1
22.9
HO
BocHN
O
4v
13C NMR (CDCl3, 126 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


BocHN
Me
O
OH
Me
4w
1H NMR (CDCl3, 500 MHz)
f1 (ppm)


BocHN
Me
O
OH
Me
4w
13C NMR (CDCl3, 126 MHz)
f1 (ppm)


OMe
H
H
H
BocHN
O
OH
Me
4z
^{1}H NMR ($CDCl_3$, 500 MHz)
f1 (ppm)


OMe
H
H
H
BocHN
O
OH
Me
4z
^{13}C NMR ($CDCl_3$, 126 MHz)
f1 (ppm)



References

[1] D. M. Hodgson, C. I. Pearson and M. Kazmi *Org. Lett.* **2014**, *16*, 856-859.

[2] M. Colella, P. Musci, D. Cannillo, M. Spennacchio, A. Aramini, L. Degennaro and R. Luisi *J. Org. Chem*. **2021**, *86*, 13943-13954.

[3] 3-methoxy-3-phenylazetidine-1-carboxylate was prepared according to a procedure reported here: A. N. Baumann, M. Eisold, A. Music, G. Haas, Y. M. Kiw and D. Didier *Org. Lett*. **2017**, *19*, 5681–5684,

[4] E. Graziano, D. Cannillo, M. Spennacchio, P. Musci, L. Pisano, M. Andresini, M. Colella, *Tetrahedron Green Chem*, **2023**, *1*, 100003. https://doi.org/10.1016/j.tgchem.2023.100003.

[5] J. Andraos and A. Hent, *J. Chem. Educ.*, **2015**, *92*, 1820–1830.

[6] J. Andraos and M. Sayed, *J. Chem. Educ.*, **2007**, *84*, 1004.