Stereospecific radiosynthesis of 3-fluoro amino acids: Access to enantiomerically pure radioligands for positron emission tomography

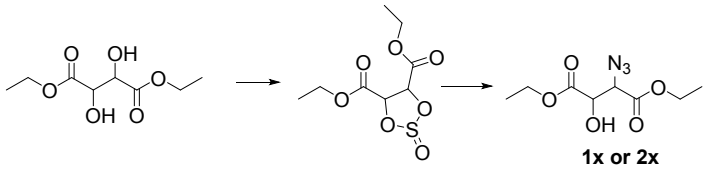
S. Alluri and P.J. Riss

Electronic Supporting Information

General information

All the reactions were carried out in oven-dried glassware and were begun under an atmosphere of nitrogen or argon. All commercially obtained reactants and reagents were used as such without any further purification. Hexanes were distilled prior to use. Anhydrous THF, DMF, DCM, DCE were purchased from Sigma chemicals (Germany, Norway). For lower temperature reactions, ice bath (0°C) and acetone-dry ice bath (-78°C) were used. All the reactions were monitored by TLC using silica gel plates (F-254 indicator) coated with Al_2O_3 backing. The corresponding reaction products were visualized by $KMnO_4$ staining (1.5 g $KMnO_4$, 10 g K_2CO_3, 0.2 g NaOH in 100 mL H_2O). ^1H (400 MHz), ^{13}C (101 MHz), ^{19}F (376 MHz), ^{31}P (162 MHz) NMR were recorded on Bruker AVI 400 instrument. Coupling constant *J* values are reported in Hz. High resolution ESI mass spectra were recorded with a TOF quadruple Micromass QTOF 2 W instrument. Radio-UV HPLC analyses were performed on Agilent 1200 analytical system equipped with UV diode-array detector, Raytest GmBH radioactivity detector and the column Supelco supelcosil ABZ plus C_{18}, 5 µm, 250 x 4.6 mm; [^{18}F]**5a** mobile phase 50-50 CH_3CN-H_2O, 1 mL/minute; [^{18}F]**9a** and [^{18}F]**12a** mobile phase 40-60 CH_3CN-H_2O 1.5 mL/minute. Radio-TLC mobile phase for products 50% ethyl acetate in hexanes. Radio-TLCs were analyzed using a raytest miniGita radioTLC scanner (Raytest GmBH, Straubenhardt, Germany). All other radioactivity measurements during labelling experiments were performed using a Wallac Wizard well counter (PerkinElmer, Oslo, Norway).

Diethyl 2-azido-3-hydroxysuccinate (1x or 2x)



1x or 2x

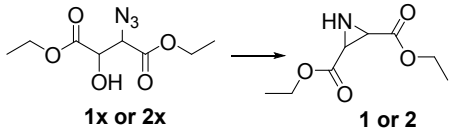
The synthesis was carried out according to the literature protocol[1] with modifications. To a solution of 2R,3R or 2S,3S DET (15 g, 75 mmol) in 15 mL anhydrous dichlormethane at 0°C was added triethylamine (21 mL, 150 mmol) slowly over 30 minutes under argon. Following this time thionyl chloride (5.5 mL, 75 mmol) was added drop wise over 30 minutes and the reaction was warmed to room temperature and stirred for 2 hours. Then the reaction was quenched with 50 mL dichlormethane and 100 mL NaCl and stirred for 10 minutes. The aqueous layer was further extracted with dichloromethane (2X50 mL). The combined organic layers were washed with 75 mL water and dried (Na_2SO_4) and concentrated to obtain the cyclic sulfite **2** as thick yellow oil which was used as such in the next step. Yield (2R,3R) 15 g, 60 mmol, 79%: (2S, 3S) 15.6 g, 62 mmol, 82%

The crude cyclic sulfite (15 g, 60 mmol) was dissolved in dry DMF (60 mL), to which was added sodium azide (8 g, 120 mmol) slowly in portions at room temperature under argon. The reaction was stirred for 24 hours and quenched with 100 mL dichloromethane and 100 mL water. The quenched contents were stirred for 2 hours at room temperature and the layers were separated. The aqueous layer was further extracted with dichloromethane (2X50 mL). The combined organic layers were dried (Na_2SO_4), concentrated and the crude was purified by column

chromatography (0-30% EtOAc in hexanes) to obtain azide derivatives **1x** or **2x** as yellow oils. Yield (2R, 3S) **1x** 6.8 g, 30 mmol, 50%, (2S, 3R) **2x-** 7 g, 30.3 mmol, 51%

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.65 – 4.60 (s, 1H), 4.37 – 4.18 (m, 6H), 3.32 (s, 1H), 1.30 (td, *J* = 7.2, 2.9 Hz, 7H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.57, 166.7, 71.8, 64.2, 62.5, 62.2, 13.8, 13.8
HR-ESIMS: calcd for $[M+Na]^+$ $C_8H_{13}N_3O_5Na$ 254.0855, found 254.0749

Diethyl aziridine-2,3-dicarboxylate (1 or 2)

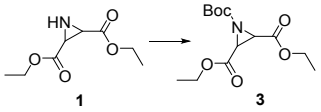


1x or 2x **1 or 2**

To the solution of azide derivative **1x** or **2x (**5 g, 21 mmol**)** in 24 mL anhydrous DMF at 0°C was added PPh_3 (6.8 g, 26 mmol) dissolved in 34 mL of anhydrous DMF over 30 minutes using cannula under argon. The reaction was warmed to room temperature and stirred for 90 minutes after which the reaction was transferred to 90°C oil bath and stirred for 5 hours. Following this time, the excess DMF was evaporated and the crude was purified by column chromatography (0-40% EtOAc in hexanes) to obtain *trans* aziridines **1** or **2** as yellow oils. Yield (2S, 3S) **1-** 2.6 g, 13.8 mmol, 65%; (2R, 3R) **2-** 3 g, 15.9 mmol, 74%

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.19 (ddtd, *J* = 18.0, 10.8, 7.1, 3.0 Hz, 4H), 2.83 (dq, *J* = 8.6, 2.3 Hz, 2H), 1.78 (t, *J* = 8.9 Hz, 1H), 1.27 (dt, *J* = 10.9, 7.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 168.4, 62.1, 61.4, 35.9, 35.1, 13.8; HR-ESIMS: calcd for $[M+Na]^+$ $C_8H_{13}NO_4Na$ 210.0764, found 210.0738

1-(tert-butyl) 2,3-diethyl aziridine-1,2,3-tricarboxylate (3)

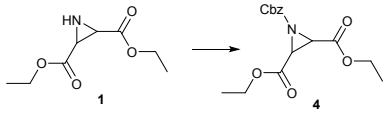


1 **3**

To the aziridine **1** (1.013 g, 5.390 mmol) dissolved in dry THF (6 mL) at 0°C was added boc anhydride (1.76 g, 8.080 mmol) in dry THF (3 mL) followed by the addition of DMAP (0.260 g, 2.155 mmol) in portions. The reaction was warmed to room temperature and stirred for 48 hours which was then quenched with water (15 mL), NaCl (7 mL). The aqueous layer was extracted with EtOAc (3X20 mL). Combined organic layers were dried (Na_2SO_4), concentrated and the crude was purified by column chromatography (0-20% EtOAc in hexanes) to obtain boc derivative **3** as colorless oil. Yield (2S, 3S) **3**- 0.869 g, 3.020 mmol, 56%. Another enantiomer was prepared from **2** in a similar manner to obtain (2R, 3R) **3x-** 1 g, 3.472 mmol, 64%

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.33 – 4.14 (m, 4H), 3.33 (s, 2H), 1.44 (s, 9H), 1.30 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 156.6, 82.6, 62.1, 40.1, 27.6, 13.9; HR-ESIMS: calcd for $[M+Na]^+$ $C_{13}H_{21}NO_6Na$ 310.1188, found 310.1262

1-benzyl 2,3-diethyl aziridine-1,2,3-tricarboxylate (4)



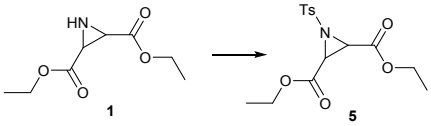
1 **4**

To the aziridine **1** (0.780 g, 4.150 mmol) dissolved in dry THF (5 mL) at 0°C was added anhydrous DIPEA (1.45 mL, 8.300 mmol) slowly over 5 minutes followed by the addition of benzyl chloroformate (0.95 mL, 6.223 mmol) dissolved in dry THF (1 mL) over 5 minutes. The reaction was warmed to room temperature and stirred for 24 hours after which it was quenched with water (20 mL) and extracted with EtOAc (3X15 mL). Combined organic layers were dried (Na_2SO_4), concentrated and the crude was purified by column chromatography (0-25% EtOAc in

hexanes) to obtain -Cbz derivative **4** as colorless oil. Yield (2*S*, 3*S*) **4**- 1.240 g, 3.862 mmol, 97%. Another enantiomer was prepared from **2** in a similar manner to obtain (2R, 3R) **4x**- 1.250 g, 3.894 mmol, 98%

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 (s, 5H), 5.23 – 5.08 (m, 2H), 4.28 – 4.11 (m, 4H), 3.40 (s, 2H), 1.27 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 158.1, 134.8, 128.3, 128.3, 128.3, 68.7, 65.1, 62.2, 40.1, 13.8; HR-ESIMS: calcd for $[M+Na]^+$ $C_{16}H_{19}NO_6Na$ 344.1132, found 344.1105

Diethyl 1-tosylaziridine-2,3-dicarboxylate (5)

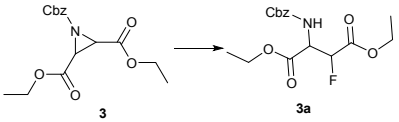


To the azirdine **1** (0.640 g, 3.405 mmol) in anhydrous DCM (10 mL) at 0°C was added (0.540 g, 4.085 mmol) in 5 portions followed by tosyl anhydride (1.450 g, 4.085 mmol) in 5 portions under N_2 and stirred for 2 days at room temperature. Following this time, the reaction was quenched slowly with cold water (15 mL) and extracted with DCM (3X10 mL). The organic layers were dried (Na_2SO_4), concentrated and purified by careful column chromatography (0-25% EtOAc in Hexanes) to obtain **5** as colorless oil. Yield 0.480 g, 1.410 mmol, 42%.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 – 7.82 (d, 2H), 7.38 – 7.28 (d, 2H), 4.26 (qd, *J* = 7.2, 1.4 Hz, 4H), 3.78 (s, 2H), 2.44 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 144.8, 136.4, 129.7, 127.7, 62.6, 43.2, 21.7, 13.9;

HR-ESIMS: calcd for $[M+Na]^+$ $C_{15}H_{19}NO_6Na$ 364.0933, found 364.0825

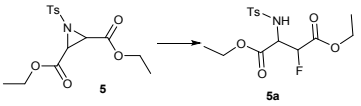
Diethyl 2-(((benzyloxy)carbonyl)amino)-3-fluorosuccinate (3a)



To the compound **3** (0.500 g, 1.558 mmol) dissolved in 4 mL dry dichloroethane in a PE vial at 0°C was pipetted 65% HF-DMPU (0.400 mL, 12.461 mmol) and the reaction was warmed to room temperature and stirred for 36 hours. Following this time the reaction was quenched slowly with 15 mL 1M $NaHCO_3$ at 0°C and extracted with dichloromethane (3X10 mL). The combined organic layers were dried (Na_2SO_4), concentrated and the crude was purified by careful column chromatography (0-25% EtOAc in hexanes) to obtain **3a** as colorless oil. Yield 0.090 g, 0.263 mmol, 24%

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.31 (m, 5H), 5.69 (d, *J* = 8.1 Hz, 1H), 5.24 (dd, *J* = 47.5, 2.4 Hz, 1H), 5.15 (s, 2H), 5.10 – 4.98 (m, 1H), 4.44 – 4.08 (m, 4H), 1.30 (dt, *J* = 27.2, 7.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 165.9, 155.4, 135.6, 128.4, 128.1, 128.1, 89.34- 87.43 (d, $^1J_{CF}$ = 191.95 Hz), 67.3, 62.4, 61.9, 55.9- 55.7 ($^2J_{CF}$ = 21.12 Hz), 13.9, 13.7; ^{19}F NMR (377 MHz, $CDCl_3$) δ -202.74; HR-ESIMS: calcd for $[M+Na]^+$ $C_{16}H_{20}NFO_6Na$ 364.1175, found 364.1167

Diethyl 2-fluoro-3-((4-methylphenyl)sulfonamido)succinate (5a)



To the compound **5** (0.025 g, 0.074 mmol) in 0.5 mL anhydrous acetonitrile was added TBAF(*t*BuOH)$_4$ (0.058 g, 0.109 mmol) at room temperature and stirred at 50°C for 15 minutes

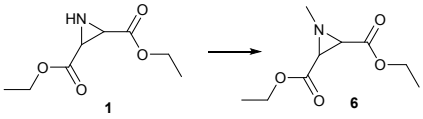
after which the reaction was quenched with cold water (4 mL) and extracted with diethyl ether (2X5 mL). The combined organic layers were dried (Na_2SO_4), concentrated and the crude was purified by careful column chromatography (0-25% EtOAc in hexanes) to obtain **5a** as colorless oil. Yield **5a** 0.008 g, 0.022 mmol, 31% and also ~30% (0.008 g, 0.023 mmol) *cis* isomer of **5** formed.

cis **5**: ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.92 – 7.87 (m, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 4.18 (qd, *J* = 7.2, 1.4 Hz, 4H), 3.55 (s, 2H), 2.46 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.1, 145.6, 133.5, 129.9, 129.7, 128.4, 62.3, 40.6, 21.8, 13.9

5a: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.77 – 7.75 (d, 2H), 7.32 (d, *J* = 8.0 Hz, 1H), 5.50 (d, *J* = 7.8 Hz, 1H), 5.18 (dd, *J* = 47.2, 2.3 Hz, 1H), 4.57 (ddd, *J* = 26.3, 7.8, 2.3 Hz, 1H), 4.31 – 4.06 (m, 4H), 2.43 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1, 136.4, 129.5, 127.3, 89.97-88.67 (d, $^1J_{CF}$ = 89.3 Hz), 63.1, 62.3, 57.58- 57.44 (d, $^2J_{CF}$ = 57.5 Hz), 21.6, 14.06, 13.8

^{19}F NMR (376 MHz, $CDCl_3$) δ -201.50; HR-ESIMS: calcd for $[M+Na]^+$ $C_{15}H_{20}NFO_6Na$ 384.0935, found 384.0888

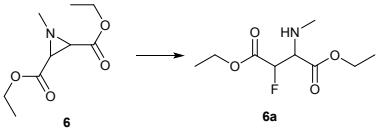
Diethyl 1-methylaziridine-2,3-dicarboxylate (6)



To a stirred solution of **1** (0.950 g, 5.053 mmol) and methyl tosylate (0.920 mL, 6.063 mmol added at 0°C) in dry THF (10 mL) at 0°C was added 0.5 M toluene solution of KHMDS (11.5 mL, 5.053 mmol) slowly over 10 minutes. The reaction was warmed to room temperature and stirred for 6 hours. Following this time, the reaction was quenched with 1M NH_4Cl (3 mL) at 0°C and 15 mL water. The aqueous layer was extracted with EtOAc (3X15 mL). Combined organic layers were dried (Na_2SO_4), concentrated and the crude was purified by careful column chromatography (0-25% EtOAc in hexanes) to obtain **6** as colorless oil. Yield (2S, 3S) **6**- 0.400 g, 1.990 mmol, 40%. Another enantiomer was prepared from **2** in similar manner to obtain (2R, 3R) **6x**- 0.405 g, 2.015 mmol, 41%

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.22 (q, *J* = 7.7 Hz, 4H), 2.97 (d, *J* = 3.2 Hz, 1H), 2.73 (s, 1H), 2.67 (s, 3H), 1.35 – 1.23 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 166.9, 61.6, 44.6, 41.3, 38.4, 14.1; HR-ESIMS: calcd for $[M+Na]^+$ $C_9H_{15}NO_4Na$ 224.1001, found 224.0994

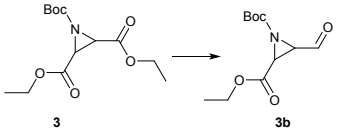
Diethyl 2-fluoro-3-(methylamino)succinate (6a)



To a solution of **6** (0.400 g, 2 mmol) in dichloroethane (2.5 mL) was added Olah's 70% HF (1 mL) in a PE vial at room temperature and stirred at 50°C for 7 days. Following this time, the excess HF was quenched with 1M $NaHCO_3$ (25 mL) and the crude was extracted with diethyl ether (3X10 mL), dried (Na_2SO_4), concentrated and purified by column chromatography (0-50% EtOAc in hexanes). The TLC spots were visualized with $KMnO_4$ staining. Yield **6a-**0.027 g, 0.122 mmol, 6%

^{1}H NMR (100 MHz, Chloroform-*d*) δ 5.23 (dd, *J* = 47.7, 2.8 Hz, 1H), 4.37 – 4.00 (m, 4H), 3.75 (dd, *J* = 24.2, 2.8 Hz, 1H), 2.53 (s, 3H), 1.42 – 1.12 (m, 6H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 167.1, 89.7 (d, $^1J_{CF}$ = 191.0 Hz), 64.5 (d, $^2J_{CF}$ = 21.0 Hz), 61.8 (d, $^2J_{CF}$ = 4.3 Hz), 59.3, 35.4, 14.1; ^{19}F NMR (377 MHz, Chloroform-*d*) δ -199.22

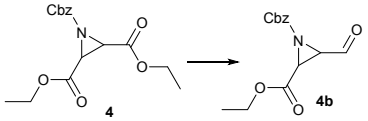
1-(tert-butyl) 2-ethyl 3-formylaziridine-1,2-dicarboxylate (3b)



To the compound **3** (0.800 g, 2.777 mmol) dissolved in dry THF (8 mL) at -78°C was added slowly 1M hexane solution of DIBAL-H (4.300 mL, 3.055 mmol) over 10 minutes. The reaction was stirred for 3 hours at the same temperature and quenched with 0.1 mL water followed by adding diethyl ether (50 mL) and 10% Rochelle's salt (50 mL). The quenched solution was then stirred at room temperature until two clear layers were seen (2 hours). The ether layer was separated and the aqueous layer was further extracted with 25 mL ether. The combined organic layers were dried (Na_2SO_4), concentrated and the crude was purified by column chromatography (0-50% EtOAc in hexanes) to obtain **3b** as thick colorless oil. Yield (2S, 3S) **3b-** 0.360 g, 1.481 mmol, 53%. Another enantiomer was prepared from **3x** to obtain (2R, 3R) **3c-** 0.490 g, 2.016 mmol, 72%

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.10 (d, *J* = 5.3 Hz, 1H), 4.33 – 4.19 (q, 2H), 3.41 (dd, *J* = 5.2, 2.3 Hz, 1H), 3.33 (d, *J* = 2.3 Hz, 1H), 1.46 (s, 9H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.7, 166.3, 156.9, 83.8, 63.0, 46.5, 39.4, 28.3, 14.5; HR-ESIMS: calcd for $[M+Na]^+$ $C_{11}H_{17}NO_5Na$ 266.0926, found 266.0998

1-benzyl 2-ethyl 3-formylaziridine-1,2-dicarboxylate (4b)

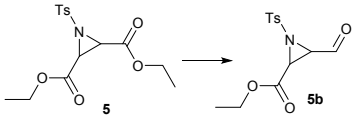


The same reduction procedure above was repeated with **4** or **4x** to obtain **4b** or **4c** as thick colorless oils. Yield (2S, 3S) **4b**-37%; (2R, 3R) **4c-** 34%

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.12 (d, *J* = 5.1 Hz, 1H), 7.39 – 7.32 (s, 5H), 5.18 (q, *J* = 12.0 Hz, 2H), 4.25 – 4.13 (m, 2H), 3.48 (dd, *J* = 5.1, 2.3 Hz, 1H), 3.37 (d, *J* = 2.3 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 193.8, 165.6, 158.1, 134.8, 128.66, 69.2, 62.7, 45.9, 38.9, 13.9

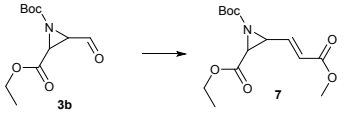
Ethyl 3-formyl-1-tosylaziridine-2-carboxylate (5b)



The same reduction procedure above was repeated with **5** in DCM for 2 hours to obtain **5b** as colorless oil. Yield 28%

^{1}H NMR (400 MHz, Chloroform-d) δ 9.59 (d, J = 6.7 Hz, 1H), 7.91 – 7.83 (m, 2H), 7.41 – 7.31 (m, 2H), 4.21 (q, J = 7.2 Hz, 2H), 4.00 (d, J = 3.5 Hz, 1H), 3.50 (dd, J = 6.8, 3.5 Hz, 1H), 2.46 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, CDCl3) δ 191.7, 164.5, 145.6, 130.1, 134.9, 127.9, 62.7, 50.1, 41.9, 21.7, 13.9; HR-ESIMS: calcd for $[M+Na]^+$ $C_{13}H_{15}NO_5Na$ 320.0571, found 320.0563

1-(tert-butyl) 2-ethyl (*E*)-3-(3-methoxy-3-oxoprop-1-en-1-yl)aziridine-1,2-dicarboxylate (3b)

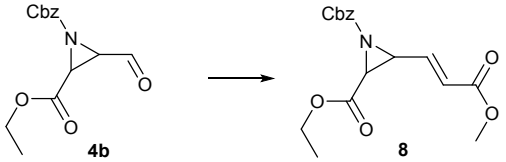


To the aldehyde **3b** (0.185 g, 0.761 mmol) dissolved in 2.5 mL dry THF was added methyl (triphenylphosphoranylidene) acetate (0.450 g, 1.290 mmol) under argon and stirred for 24

hours at room temperature. Following this time the crude was loaded as such on to silica gel column and the product was eluted with 0-25% EtOAc in hexanes. The product **7** (*E*) was obtained as a colorless oil. Yield (2S, 3S) **7-** 0.220 g, 0.755 mmol, 96%; another enantiomer was prepared from **3b** to obtain (2R, 3R) **7x-** 0.221 g, 0.755 mmol, 96%

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.56 (dd, *J* = 15.6, 7.6 Hz, 1H), 6.20 (d, *J* = 15.7 Hz, 1H), 4.29 – 4.19 (m, 2H), 3.74 (d, *J* = 1.7 Hz, 4H), 3.38 (dd, *J* = 7.6, 2.4 Hz, 1H), 3.02 (d, *J* = 2.4 Hz, 1H), 1.45 (s, 9H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 165.8, 157.7, 142.1, 125.0, 82.6, 62.1, 51.8, 42.6, 42.4, 27.8, 14.1; HR-ESIMS: calcd for $[M+Na]^+$ $C_{14}H_{21}NO_6Na$ 299.1269, found 322.1262

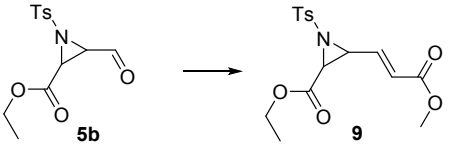
1-benzyl 2-ethyl (*E*)-3-(3-methoxy-3-oxoprop-1-en-1-yl)aziridine-1,2-dicarboxylate (8)



The above Wittig reaction procedure was repeated with **4b** to prepare (*E)* **8** and **8x**. Yield (2S, 3S) **8-**68%; (2R, 3R) **8x-** 70%

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 – 7.31 (m, 5H), 6.59 (dd, *J* = 15.6, 7.4 Hz, 1H), 6.21 (dd, *J* = 15.6, 0.8 Hz, 1H), 5.16 (d, *J* = 7.7 Hz, 2H), 4.21 – 4.14 (m, 2H), 3.74 (s, 3H), 3.45 (ddd, *J* = 7.4, 2.5, 0.7 Hz, 1H), 3.07 (d, *J* = 2.4 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 165.5, 158.9, 141.4, 135.0, 128.33, 128.30, 128.27, 128.2, 125.1, 68.5, 62.1, 51.6, 42.4, 42.2, 13.8
HR-ESIMS: calcd for $[M+Na]^+$ $C_{17}H_{19}NO_6Na$ 356.1126, found 356.1105

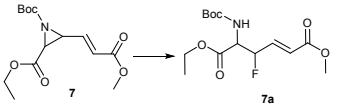
Ethyl (E)-3-(3-methoxy-3-oxoprop-1-en-1-yl)-1-tosylaziridine-2-carboxylate (9)



The above Wittig reaction procedure was repeated with **5b** to prepare (*E)* **9** as colorless oil. Yield 90%

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.82 (d, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.07 (dd, *J* = 15.5, 9.4 Hz, 1H), 6.24 (d, *J* = 15.6 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.65 – 3.59 (m, 2H), 2.44 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H)
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 165.5, 145.6, 138.6, 136.1, 130.2, 128.9, 128.3, 62.9, 52.4, 47.7, 44.6, 22.2, 14.4
HR-ESIMS: calcd for $[M+Na]^+$ $C_{16}H_{19}NSO_6Na$ 376.0933, found 376.0825

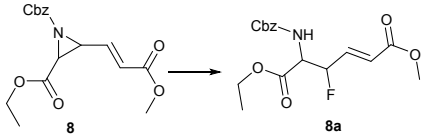
6-ethyl 1-methyl (*E*)-5-((tert-butoxycarbonyl)amino)-4-fluorohex-2-enedioate (7a)



To the compound **7** (0.050 g, 0.167 mmol) in 1.5 mL dry dichloroethane in a PE vial at 0°C was pipetted 65% HF-DMPU (20 µL, 0.669 mmol) and stirred at same temperature for 30 minutes followed by quenching with 5 mL 1M $NaHCO_3$ and 5 mL DCM. The aqueous layer was further extracted with DCM (2X5 mL). The combined organic layers were dried (Na_2SO_4), concentrated and the crude was purified by column chromatography (0-25% EtOAc in hexanes) to obtain **7a** as colorless oil which become white solid upon storage. Yield 0.017 g, 0.053 mmol, 32%

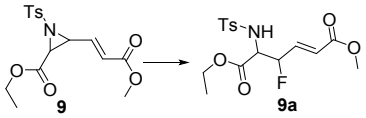
^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.92 (ddd, *J* = 21.4, 15.8, 4.0 Hz, 1H), 6.12 (ddd, *J* = 15.8, 2.0, 1.0 Hz, 1H), 5.48 – 5.30 (m, 2H), 4.69 – 4.57 (m, 1H), 4.28 – 4.16 (m, 2H), 3.76 (s, 3H), 1.45 (s, 9H), 1.28 – 1.22 (t, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.7 (d, $^{3}J_{CF}$ = 5.9 Hz), 165.7, 154.9, 140.4 (d, $^{2}J_{CF}$ = 18.2 Hz), 122.6 (d, $^{3}J_{CF}$ = 11.5 Hz), 90.9 (d, $^{1}J_{CF}$ = 183.6 Hz), 80.6, 62.1, 56.7 (d, $^{2}J_{CF}$ = 22.2 Hz), 51.8, 28.2, 14.1; ^{19}F NMR (377 MHz, $CDCl_3$) δ -193.38 (m)
HR-ESIMS: calcd for $[M+Na]^+$ $C_{14}H_{22}NFO_6Na$ 342.1331, found 342.1324

6-ethyl 1-methyl (*E*)-5-(((benzyloxy)carbonyl)amino)-4-fluorohex-2-enedioate (8a)



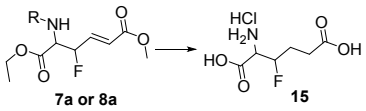
To the compound **8** (0.090 g, 0.270 mmol) in 1.8 mL dry dichloroethane in a PE vial at 0°C was pipetted 65% HF-DMPU (60 µL, 1.351 mmol) and stirred at same temperature for 1 hour followed by quenching with 5 mL 1M $NaHCO_3$ and 5 mL DCM. The aqueous layer was further extracted with DCM (2X10 mL). The combined organic layers were dried (Na_2SO_4), concentrated and the crude was purified by column chromatography (0-30% EtOAc in hexanes) to obtain **8a** as colorless oil which become white solid upon storage. Yield 0.040 g, 0.122 mmol, 43%
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39–7.31 (m, 5H), 6.92 (ddd, *J* = 20.8, 15.7, 3.9 Hz, 1H), 6.18 – 6.08 (d, 1H), 5.61 (d, *J* = 8.5 Hz, 1H), 5.51 – 5.36 (m, 1H), 5.14 (s, 2H), 4.73 (ddd, *J* = 23.1, 8.5, 3.3 Hz, 1H), 4.29 – 4.18 (m, 2H), 3.77 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.30 (d, $^{3}J_{CF}$ = 6.1 Hz), 165.6, 155.62, 139.97 (d, $^{2}J_{CF}$ = 17.98 Hz), 135.8, 130.0 – 126.16 (m), 122.98 (d, $^{3}J_{CF}$ = 10.84 Hz), 90.75 (d, $^{1}J_{CF}$ = 184.4 Hz), 67.4, 62.3 , 57.11 (d, $^{2}J_{CF}$ = 22.3 Hz), 51.9 , 14.1; ^{19}F NMR (377 MHz, $CDCl_3$) δ -195.36 (m); HR-ESIMS: calcd for $[M+Na]^+$ $C_{17}H_{20}NFO_6Na$ 376.1175, found 376.1167

6-ethyl 1-methyl (E)-4-fluoro-5-((4-methylphenyl)sulfonamido)hex-2-enedioate (9a)



To the compound **9** (0.014 g, 0.039 mmol) in 0.5 mL DCE in PE vial at 0°C was added DMPU-65%HF (6 µL) and stirred for 1 hour at rt followed by quenching with ice cold aq.$NaHCO_3$ (3 mL) and extraction with DCM (2X5 mL). The combined organic layers were dried (Na_2SO_4), concentrated and the crude was purified by column chromatography (0-30% EtOAc in hexanes) to obtain **9a** as colorless oil which become white solid upon storage. Yield 0.007 g, 0.019 mmol, 48%
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.74 – 7.71 (d, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 6.82 (ddd, *J* = 21.2, 15.7, 4.1 Hz, 1H), 6.05 (ddd, *J* = 15.9, 2.1, 1.1 Hz, 1H), 5.43 – 5.35 (m, 1.5H), 5.27 (td, *J* = 3.9, 2.0 Hz, 0.5H), 4.25 (ddd, *J* = 21.0, 9.2, 3.7 Hz, 1H), 4.09 – 3.98 (m, 2H), 3.76 (s, 3H), 2.42 (s, 3H), 1.13 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1, 139.2, 129.8, 127.3, 123.5, 91.9-90.3 (d, J_{CF} = 185 Hz), 62.6, 58.52 (d, $^{2}J_{CF}$ = 22.7 Hz), 51.9, 21.6, 13.9
^{19}F NMR (377 MHz, $CDCl_3$) δ -193.59: HR-ESIMS: calcd for $[M+Na]^+$ $C_{16}H_{20}NFSO_6Na$ 396.0935, found 396.0888

2-amino-3-fluorohexanedioic acid (15)



7a or 8a **15**

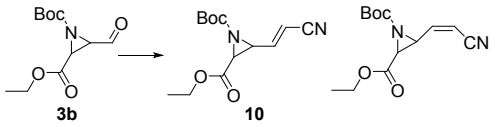
To the compound **7a** or **8a** (0.015 g, 0.042 mmol) dissolved in 1.5 mL absolute EtOH was added 10 mol% Pd/C (10% Pd, 4.600 mg) followed by 20 µL conc. HCl in 0.5 mL EtOH (100 µL $CHCl_3$ can be used instead of HCl). The reaction was bubbled with H_2 balloon for 15 minutes followed by stirring for 30 minutes under the same balloon. Then the crude was diluted with 4 mL MeOH and the Pd was filtered off, the crude was concentrated and suspended in 1 mL 4 N HCl (aq) and refluxed for 20 hours. The crude was freeze dried overnight and triturated with 4 mL diethyl ether to obtain **15** as white solid which contain partially defluorinated 2-amino adipic acid (18%). Yield based on HCl salts-0.009 g, 0.042 mmol, 81%

^{1}H NMR (400 MHz, Deuterium Oxide) δ 5.11 (ddt, *J* = 47.3, 10.5, 2.9 Hz, 1H), 4.40 (dd, *J* = 22.6, 2.6 Hz, 1H), 2.61 (t, *J* = 7.2 Hz, 2H), 2.31 – 1.65 (m, 4H); ^{13}C NMR (101 MHz, Deuterium Oxide) δ 176.9, 168.16 (d, $^3J_{CF}$ = 6.7 Hz), 90.86 (d, $^1J_{CF}$ = 175.8 Hz), 56.07 (d, $^2J_{CF}$ = 21.2 Hz), 29.42 (d, $^2J_{CF}$ = 3.8 Hz), 25.48 (d, $^3J_{CF}$ = 20.8 Hz); ^{19}F NMR (377 MHz, Deuterium Oxide) δ -192.71

HR-ESIMS: calcd for $[M+Na]^+$ $C_6H_{10}NFO_4Na$ 202.0494, found 202.0494

Notes: The reduction of **7a/8a** was carried out with hydrogen gas in presence of 10 mol% of Pd on charcoal or Pt on alumina. Partial elimination (~18%) of fluorine was noticed under the heterogeneous hydrogenation conditions used. The elimination of fluorine probably due to the formation of $\eta^3\pi$-allyl complex. Within 30 minutes, all the starting material was converted to the reduced product with partial elimination of fluorine atom. Using triethyl silane as hydrogen source increased defluorination to ~50% within 15 minutes. Changing the solvents from ethanol to tetrahydrofuran or ethyl acetate or methanol was not useful at all.

1-(tert-butyl) 2-ethyl (*E*)-3-(2-cyanovinyl)aziridine-1,2-dicarboxylate (10)



3b **10**

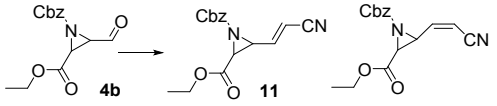
To the compound **3b** (0.150 g, 0.617 mmol) in 2 mL dry THF was added (triphenylphosphoranylidene) acetonitrile (0.315 g, 1.111 mmol) at room temperature and stirred for 36 hours. Following this time the crude was loaded as such onto silica gel column and the products eluted using 0-30% EtOAc in hexanes. The products (*trans, cis*) obtained as colorless oils. Yield (2S, 3S) **10-** *trans* 0.135 g, 0.507 mmol, 80%; *cis* 0.010g, 0.037 mmol, 6%; another enantiomer was prepared from **3x** to obtain (2R, 3R) **10x**-(*E)* 0.125 g, 0.469 mmol, 76%, *(Z)* 0.008 g, 0.030 mmol, 5%

E ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.47 (dd, *J* = 16.1, 6.4 Hz, 1H), 5.74 (dd, *J* = 16.2, 0.9 Hz, 1H), 4.34 – 4.19 (m, 2H), 3.39 (ddd, *J* = 6.4, 2.4, 0.9 Hz, 1H), 2.98 (d, *J* = 2.4 Hz, 1H), 1.46 (s, 9H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.4, 157.3, 148.1, 116.2, 103.6, 83.1, 62.4, 43.1, 42.1, 27.8, 14.1

Z ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.01 (dd, *J* = 11.1, 8.9 Hz, 1H), 5.60 (d, *J* = 11.1 Hz, 1H), 4.33 – 4.18 (m, 3H), 3.74 (dd, *J* = 8.9, 2.3 Hz, 1H), 3.09 (d, *J* = 2.3 Hz, 1H), 1.47 (s, 9H), 1.33 (t, *J* = 7.2 Hz, 3H): ^{13}C NMR (101 MHz, Chloroform-*d*) δ 148.2, 103.9, 62.3, 41.8, 41.6, 27.8, 14.1

HR-ESIMS: calcd for $[M+Na]^+$ $C_{13}H_{18}N_2O4Na$ 289.1167, found 289.1159

1-benzyl 2-ethyl (*E*)-3-(2-cyanovinyl)aziridine-1,2-dicarboxylate (11)



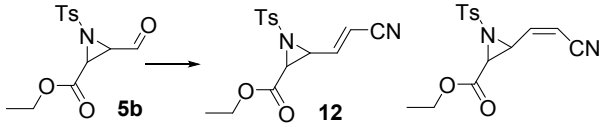
4b **11**

The above Wittig procedure was repeated with **4b** to obtain **11** *trans, cis* as colorless oils that became solids upon drying and storage. Yield (2S, 3S) **11-** *(E)* 62%, *(Z)* 8%; (2R, 3R) **11x-** *(E)* 68%, *(Z)* 15%

E ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.30 (m, 5H), 6.46 (dd, *J* = 16.1, 6.3 Hz, 1H), 5.74 (dd, *J* = 16.1, 0.9 Hz, 1H), 5.22 – 5.09 (q, 2H), 4.23 – 4.12 (q, 2H), 3.45 (ddd, *J* = 6.3, 2.4, 0.9 Hz, 1H), 3.04 (d, *J* = 2.4 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.1, 158.5, 147.2, 134.7, 130.94 – 125.52 (m), 115.8, 103.7, 68.7, 62.3, 42.7, 42.1, 13.8

Z ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.33 (m, 5H), 6.01 (dd, *J* = 11.1, 8.8 Hz, 1H), 5.59 (dd, *J* = 11.2, 0.9 Hz, 1H), 5.18 (d, *J* = 1.3 Hz, 2H), 4.33 – 4.05 (q, 2H), 3.80 (ddd, *J* = 8.7, 2.4, 0.9 Hz, 1H), 3.14 (d, *J* = 2.4 Hz, 1H), 1.28 – 1.24 (t, 3H); HR-ESIMS: calcd for $[M+Na]^+$ $C_{16}H_{16}N_2O4Na$ 323.1100, found 323.1003

Ethyl (E)-3-(2-cyanovinyl)-1-tosylaziridine-2-carboxylate (12)

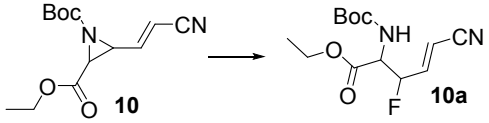


The same Wittig procedure was repeated with **5b** in DCM for 15 hours to obtain **12** *(E), (Z)* as colorless oils. Yield *(E)* 46%, *(Z)* 41%

E ^{1}H NMR (400 MHz, Chloroform-d) δ 7.84 (d, J = 8.3 Hz 2H), 7.42 – 7.31 (d, 2H), 6.82 (dd, J = 11.0, 10.2 Hz, 1H), 5.75 (dd, J = 11.0, 0.7 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.98 (ddd, J = 10.2, 3.6, 0.7 Hz, 1H), 3.68 (d, J = 3.6 Hz, 1H), 2.46 (s, 3H), 1.32 – 1.18 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1, 145.5, 143.8, 135.1, 129.9, 127.8, 114.4, 106.6, 62.5, 45.7, 44.1, 21.7, 13.9

Z ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.82 (d, 2H), 7.40 – 7.32 (d, 2H), 6.92 (dd, *J* = 16.1, 9.5 Hz, 1H), 5.78 (d, *J* = 16.1 Hz, 1H), 4.20 (qd, *J* = 7.1, 0.8 Hz, 2H), 3.65 – 3.54 (m, 2H), 2.46 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 145.5, 144.7, 135.1, 129.9, 127.9, 115.6, 106.8, 62.6, 46.8, 44.2, 21.7, 13.9; HR-ESIMS: calcd for $[M+Na]^+$ $C_{15}H_{16}N_2SO_4Na$ 43.0831, found 343.0723

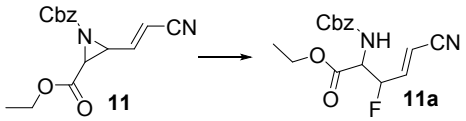
Ethyl (*E*)-2-((tert-butoxycarbonyl)amino)-5-cyano-3-fluoropent-4-enoate (10a)



To the *trans* compound **10** (0.045 g, 0.169 mmol) in 1 mL dry dichloroethane in a PE vial at 0°C was pipetted 65% HF-DMPU (20 µL, 0.676 mmol) and stirred at same temperature for 30 minutes followed by quenching with 5 mL 1M $NaHCO_3$ and 5 mL DCM. The aqueous layer was further extracted with DCM (2X8 mL). The combined organic layers were dried (Na_2SO_4), concentrated and the crude was purified by careful column chromatography (0-25% EtOAc in hexanes) to obtain **10a** as colorless oil which become white solid upon storage. Yield 0.010 g, 0.035 mmol, 21%

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.76 (ddd, *J* = 20.2, 16.4, 3.5 Hz, 1H), 5.69 (ddd, *J* = 16.3, 2.2, 1.3 Hz, 1H), 5.47 – 5.29 (m, 2H), 4.58 (dd, *J* = 25.1, 8.0 Hz, 1H), 4.31 – 4.21 (q, 2H), 1.46 (s, 9H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.60 (d, $^3J_{CF}$ = 5.5 Hz), 155.5, 147.4 (d, $^2J_{CF}$ = 18.1 Hz), 116.4, 102.1, 91.35 (d, $^1J_{CF}$ = 186.6 Hz), 81.5, 62.9, 57.0, 43.03 (d, $^2J_{CF}$ = 94.4 Hz), 28.7, 14.6; ^{19}F NMR (377 MHz, Chloroform-*d*) δ -197.97

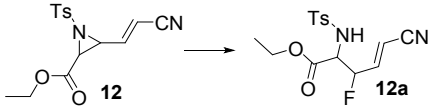
Ethyl (*E*)-2-(((benzyloxy)carbonyl)amino)-5-cyano-3-fluoropent-4-enoate (11a)



To the *trans* compound **11** (0.130 g, 0.433 mmol) in 2 mL dry dichloroethane in a PE vial at 0°C was pipetted 65% HF-DMPU (80 µL, 2.600 mmol) and stirred at same temperature for 60 minutes followed by quenching with 5 mL 1M $NaHCO_3$ and 5 mL DCM. The aqueous layer was further extracted with DCM (5X2 mL). The combined organic layers were dried (Na_2SO_4), concentrated and the crude was purified by column chromatography (0-30% EtOAc in hexanes) to obtain **11a** as colorless oil which become white solid upon storage. Yield 0.062 g, 0.193 mmol, 45%

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.32 (m, 5H), 6.75 (ddd, *J* = 20.4, 16.3, 3.5 Hz, 1H), 5.73 – 5.60 (m, 2H), 5.42 (dq, *J* = 46.5, 3.3, 2.7 Hz, 1H), 5.14 (s, 2H), 4.67 (ddd, *J* = 24.8, 7.9, 3.1 Hz, 1H), 4.25 (q, 2H), 1.30 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.58 (d, $^3J_{CF}$ = 5.5 Hz), 155.3, 146.41 (d, $^2J_{CF}$ = 17.4 Hz), 135.4, 129.80 – 126.79 (m), 115.7, 101.65 (d, $^3J_{CF}$ = 15.6 Hz), 90.43 (d, $^1J_{CF}$ = 187.0 Hz), 67.4, 62.4, 56.61 (d, $^2J_{CF}$ = 21.6 Hz), 13; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -198.25; HR-ESIMS: calcd for $[M+Na]^+$ $C_{16}H_{17}N_2FO_4Na$ 343.1072, found 343.1065

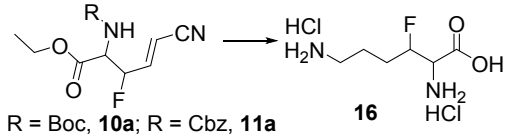
Ethyl (E)-5-cyano-3-fluoro-2-((4-methylphenyl)sulfonamido)pent-4-enoate (12a)



To the compound **12** (0.011 g, 0.015 mmol) in 0.3 mL dry acetonitrile was added TBAF(*t*BuOH)$_4$ (0.024 g, 0.021 mmol) at room temperature and stirred for 10 minutes at 50°C followed by quenching with 3 mL cold water and 5 mL diethyl ether. The aqueous layer was further extracted with 3 mL ether. The combined organic layers were dried (Na_2SO_4), concentrated and the crude was purified by column chromatography (0-30% EtOAc in hexanes) to obtain **12a** as an oil. Yield 0.002 g, 0.006 mmol, 17%

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.77 – 7.73 (d, 2H), 7.34 – 7.29 (d, 2H), 6.50 (ddd, *J* = 13.1, 11.5, 7.5 Hz, 1H), 5.63 (dt, *J* = 11.5, 1.4 Hz, 1H), 5.53 (ddd, *J* = 7.5, 4.6, 1.3 Hz, 0.5H), 5.43 – 5.36 (m, 1.5H), 4.36 – 4.25 (m, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 2.43 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 3H)
^{19}F NMR (376 MHz, $CDCl_3$) δ -186.27
HR-ESIMS: calcd for $[M+Na]^+$ $C_{15}H_{17}N_2FSO_4Na$ 363.0893, found 363.0786

2,6-diamino-3-fluorohexanoic acid (16)

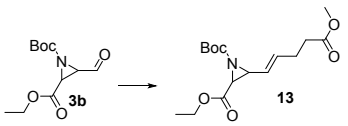


To the fluorinated compounds **10a** or **11a** (0.045 g, 0.140 mmol) dissolved in 1.5 mL absolute ethanol was added 10 mol% Pt on alumina (5 wt% Pt) and 0.5 mL of ethanolic HCl (40 µL conc. HCl). The reaction was then bubbled with hydrogen balloon for 15 minutes and stirred further for 45 minutes under the same balloon. Following this time, the crude was diluted with 4 mL MeOH and the Pt was filtered off, the crude was concentrated and triturated with cold diethyl ether (2X2 mL) to obtain the reduced compounds as white solids which were dissolved in 1 mL 4 N HCl (aq) and refluxed for 12 hours. The crude was then freeze dried and triturated with 3 mL diethyl ether to obtain **16** as white solid which contain partially defluorinated lysine (19%). Yield based on the weight of HCl salts over two steps- 0.012 g, 0.051 mmol, 36%

^{1}H NMR (400 MHz, Deuterium Oxide) δ 5.18 – 4.98 (m, 1H), 4.30 (dd, *J* = 22.5, 2.7 Hz, 1H), 3.05 (dt, *J* = 19.5, 7.6 Hz, 2H), 2.04 – 1.68 (m, 4H); ^{13}C NMR (101 MHz, Deuterium Oxide) δ 91.44 (d, $^{1}J_{CF}$ = 175.5 Hz), 56.4 (d, $^{2}J_{CF}$ = 21.6 Hz), 38.8, 29.3, 27.1, 23.1; HR-ESIMS: calcd for $[M+H]^{+}$ $C_6H_{14}N_2FO_2Na$ 165.1061, found 165.1034

Notes: The hydrogenation reaction of **10a/11a** was carried out in presence of conc.HCl with 0.15 mol% Pt on Alumina to reduce the olefin as well as the nitrile to primary amine. Partial defluorination (~19%) was also noticed during the reduction conditions used. Acidic conditions are necessary for this type of hydrogenation reaction to avoid the formation of secondary or tertiary amine side products and also the lactam formation via intra-molecular cyclization reaction[2]. The acidic alumina also adsorbs the primary amines to some extent as they formed from nitrile reduction. Using Pd/C or platinum (IV) oxide catalysts even in acidic reaction conditions gave desired primary amine products as well as complex mixture of products which were assumed to be the 2° or 3° amine products.

1-(tert-butyl) 2-ethyl (2S,3S)-3-((E)-5-methoxy-5-oxopent-1-en-1-yl)aziridine-1,2-dicarboxylate (13)

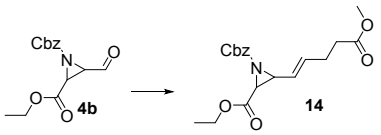


[3-(Methoxycarbonyl)propyl]triphenylphosphonium bromide:
To a solution of methyl-4-bromobutanoate (0.500 g, 2.800 mmol) in 6 mL anhydrous acetonitrile was added 4 mL acetonitrile solution of PPh_3 (0.730 g, 2.800 mmol) at room temperature and refluxed for 24 hours. Following this time acetonitrile was evaporated and the crude was added to 10 mL ether and the white precipitate was filtered off and washed with cold ether (2X5 mL) to obtain the corresponding Wittig reagent as white solid. Yield 1.100 g, 90%
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 – 7.73 (m, 15H), 3.61 (s, 3H), 2.58 (t, *J* = 7.0 Hz, 2H), 1.84 – 1.70 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.16 (d, *J* = 1.6 Hz), 134.95 (d, *J* = 3.0 Hz), 133.55 (d, *J* = 10.2 Hz), 130.26 (d, *J* = 12.5 Hz), 118.28 (d, *J* = 85.9 Hz), 51.54, 33.41 , 19.80 (d, *J* = 51.5 Hz), 17.66 (d, *J* = 3.1 Hz); ^{31}P NMR (162 MHz, DMSO) δ 37.12

To a suspension of [3-(Methoxycarbonyl)propyl]triphenylphosphonium bromide (0.2 g, 0.450 mmol) in dry THF (3 mL) was added drop-wise 0.5 M toluene solution of KHMDS (0.600 mmol) at room temperature and stirred for 30 minutes. Following this time, **3b** (0.1 g, 0.400 mmol) in 1 mL dry THF was added to the orange solution at -78°C and stirred for 6 hours at room temperature. After the reaction completion, it was quenched with 1 M NH_4Cl (6 mL), water (10 mL) at 0°C and extracted with EtOAc (3X10 mL). Combined organic layers were concentrated and the crude was purified by column chromatography to obtain **13** as colorless oil. Yield *(E)* 0.094 g, 0.288 mmol, 70%, *(Z)* 0.003 g, 0.008 mmol, 2%
E ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.72 (dtd, *J* = 11.1, 7.6, 1.0 Hz, 1H), 5.02 (ddt, *J* = 10.5, 8.9, 1.5 Hz, 1H), 4.30 – 4.18 (m, 2H), 3.67 (s, 3H), 3.48 (ddd, *J* = 8.9, 2.6, 1.0 Hz, 1H), 2.94 (d, *J* = 2.6 Hz, 1H), 2.58 – 2.38 (m, 4H), 1.44 (s, *J* = 2.3 Hz, 9H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.9, 167.8, 158.4, 134.9, 125.7, 82.0, 61.8, 51.6, 41.7, 40.7, 33.6, 27.9, 23.1, 14.1
Z ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.93 (ddd, *J* = 15.3, 6.3, 4.1 Hz, 1H), 5.21 – 5.14 (m, 1H), 4.25 (m, 2H), 3.67 (s, 3H), 3.23 (dd, *J* = 7.8, 2.6 Hz, 1H), 2.92 (d, *J* = 2.5 Hz, 1H), 2.61 – 2.32 (m, 4H), 1.44 (d, *J* = 2.3 Hz, 9H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.9, 167.5, 158.3, 134.6, 125.7, 81.7, 61.5, 51.4, 44.2, 41.6, 32.9, 27.2, 23.0, 14.0

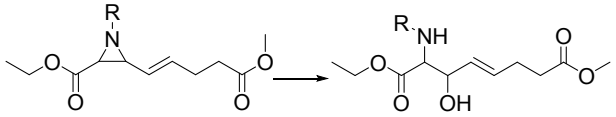
HR-ESIMS: calcd for $[M+Na]^+$ $C_{16}H_{25}NO_6Na$ 350.1582, found 350.1574

1-benzyl 2-ethyl (2S,3S)-3-((E)-5-methoxy-5-oxopent-1-en-1-yl)aziridine-1,2-dicarboxylate (14)



Above procedure was repeated with **4b** to obtain **14** as colorless oil. Yield *(E)* 75%, *(Z)* 3%
E ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 – 7.31 (m, 5H), 5.71 (dtd, *J* = 10.9, 7.6, 1.0 Hz, 1H), 5.15 (q, *J* = 6.1 Hz, 2H), 5.03 (ddt, *J* = 10.4, 8.7, 1.5 Hz, 1H), 4.18 (m, 2H), 3.66 (d, *J* = 2.6 Hz, 3H), 3.55 (ddd, *J* = 8.7, 2.7, 1.0 Hz, 1H), 3.00 (d, *J* = 2.6 Hz, 1H), 2.57 – 2.34 (m, 4H), 1.26 (t, *J* = 7.2 Hz, 3H)
^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.7, 167.4, 159.5, 135.2, 135.0, 128.48 – 128.07 (m), 125.2, 68.2, 61.7, 51.4, 41.5, 40.7, 33.3, 23.0, 13.8
Z ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.31 (m, 5H), 6.02 – 5.87 (m, 1H), 5.15 (q, 2H), 4.70 (d, *J* = 5.9 Hz, 1H), 4.18 (m, 4H), 3.67 (s, 3H), 3.32 – 3.27 (m, 1H), 2.97 (d, *J* = 2.6 Hz, 1H), 2.57 – 2.38 (m, 4H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.8, 167.3, 159.5, 135.3, 135.0, 128.45 – 127.93 (m), 125.3, 68.2, 61.7, 51.4, 44.4, 41.6, 32.9, 27.2, 13.8

1-ethyl 8-methyl (E)-2-((tert-butoxycarbonyl)amino)-3-hydroxyoct-4-enedioate (13a)
1-ethyl 8-methyl (E)-2-(((benzyloxy)carbonyl)amino)-3-hydroxyoct-4-enedioate (14a)



R = Boc, **13**; R = Cbz, **14** R = Boc, **13a**; R = Cbz, **14a**

To the compound **13** or **14** (0.050 g) in 1 mL DCE in a PE vial at 0°C was added DMPU.65%HF or Olah's.70%HF (2 eq) and stirred for 30 minutes at same temperature after which the reaction was quenched with aq.$NaHCO_3$ (1 mL) and water (4 mL) and extracted with DCM (2X5 mL). The combined organic layers were dried (Na_2SO_4), concentrated and purified by column chromatography (0-50% EtOAc in Hexanes) to obtain **13a** or **14a** as colorless oils (diastereomeric mixture). Yield **13a** 0.024 g, 0.07 mmol, 46%, **14a** 0.026 g, 0.068 mmol, 52%
13a ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.77 (dd, *J* = 3.7, 2.5 Hz, 2H), 5.21 (d, *J* = 8.3 Hz, 1H), 4.83 (d, *J* = 7.9 Hz, 1H), 4.21 (dddd, *J* = 12.2, 9.6, 6.7, 3.1 Hz, 3H), 3.67 (s, 3H), 2.48 – 2.37 (m, 2H), 1.95 – 1.72 (m, 2H), 1.44 (s, 13H), 1.28 (t, *J* = 7.1 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 170.7, 135.3, 128.3, 125.7, 70.88, 70.81, 61.8, 54.9, 51.7, 31.6, 29.82, 29.80, 28.3, 14.1
HR-ESIMS: calcd for $[M+Na]^+$ $C_{16}H_{27}NO_7Na$ 368.1788, found 368.1687

14a ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 – 7.27 (m, 5H), 5.78 (d, *J* = 3.7 Hz, 2H), 5.50 (d, *J* = 8.4 Hz, 1H), 5.12 (s, 2H), 5.00 – 4.88 (m, 2H), 4.21 (qd, *J* = 8.9, 6.9, 4.1 Hz, 4H), 3.67 (s, 3H), 2.42 (t, *J* = 7.1 Hz, 2H), 2.14 (s, 1H), 1.93 – 1.74 (m, 2H), 1.33 – 1.21 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.34, 174.29, 155.48, 136.16, 135.64, 130.62, 128.56, 128.54, 128.29, 128.23, 128.17, 128.14, 125.29, 78.95, 70.83, 70.70, 67.24, 67.12, 62.24, 61.98, 55.26, 51.76, 31.60, 31.53, 29.84, 29.79, 14.1; HR-ESIMS: calcd for $[M+Na]^+$ $C_{19}H_{25}NO_7Na$ 402.1631, found 402.1523

Radiochemistry

Cyclotron produced aqueous ^{18}F ($H_2{}^{18}O$) was trapped on QMA cartridge and eluted into a 5 mL v-vial with either of the different bases/phase transfer catalysts as mentioned below.

i. 1.8 mg K_2CO_3/100 µL water and 10 mg K_{222}/600 µL acetonitrile;

ii. 1.8 mg $KHCO_3$/100 µL water and 7 mg K_{222}/600 µL acetonitrile;
iii. 8 mg $TEAHCO_3^-$/100 µL water + 600 µL acetonitrile;
iv. 2 mg Cs_2CO_3/ 100 µL water + 600 µL acetonitrile;
v. 2.5 mg $K_2C_2O_4$/100 µL water and 14 mg K_{222}/600 µL acetonitrile;
vi. 20 µL 40% TBAOH in 80 µL water + 600 µL acetonitrile

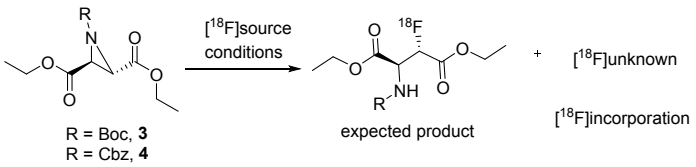
[Pottassium carbonate (K_2CO_3), Potaium hydrogen carbonate ($KHCO_3$), Tetraethylammonium bicarbonate ($TEAHCO_3^-$), Tetrabutylammonium hydroxide (TBAOH), Cesium carbonate (Cs_2CO_3), potassium oxalate ($K_2C_2O_4$)]

The eluted ^{18}F fractions then azeotropically dried 3 times (1X3 mL ACN) at 80°C under a stream of nitrogen. The dried ^{18}F was then dissolved in the chosen solvent and was added with aziridine precursors. Pyridine.H^{18}F and DMAP.H^{18}F were prepared as described elsewhere[3, 4].

Initially, aziridines **3** and **4** were reacted with standard [^{18}F]KF(K_{222})(K_2CO_3) or [^{18}F]KF(K_{222})($KHCO_3$) systems in various solvents and temperatures with conventional heating (table). The ^{18}F incorporation was noticed in most of the labelings shown by radio-TLC, but the labeled products were not the desired products. The labeled products were turned out to be relatively polar to that of free [^{18}F]fluoride. Excess methanol in dichloromethane as mobile phase in normal phase radio-TLC, shown the separation of ^{18}F labeled product from free [^{18}F]fluoride. This TLC conditions are compared with reference free [^{18}F]fluoride TLC conditions.

It was assumed that the undesired labeled products resulting from basic K_2CO_3/K_{222}, $KHCO_3/K_{222}$ reagents. Therefore a relatively weak basic tetraethyl ammonium bicarbonate ($TEAHCO_3^-$) was used to prepare anhydrous [^{18}F]TEAF($TEAHCO_3^-$) system. The precursors **3**, **4** were again reacted with [^{18}F]TEAF($TEAHCO_3^-$) under various labeling reaction conditions. Table 1 below shows the labeling of **3** and **4** with various ^{18}F systems, and the ^{18}F incorporated yields ([^{18}F]unknown) based on radio-TLC at different time intervals, temperature, solvents.

SI T1: Initial [^{18}F]fluoride labeling of **3, 4**



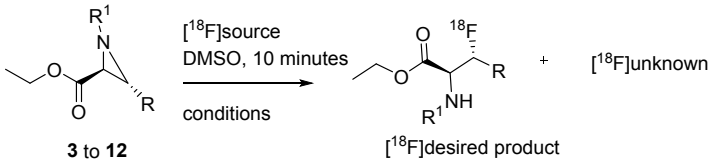
Entry	^{18}F system base	Aziridine	Solvent	Temperature (°C)	Time (min)	[^{18}F] incorporation[a] (%)
1	K_2CO_3/K_{222} or $KHCO_3/K_{222}$	**3**	DMSO	rt	15	10±5
2	K_2CO_3/K_{222} or $KHCO_3/K_{222}$		DMSO	85	5 10 15 20	10±4 15±4 18±4 15±5
3	K_2CO_3/K_{222} or $KHCO_3/K_{222}$		DMSO	100	5 10 15 25	15±5 15±4 20±5 20±5
4	$TEAHCO_3^-$	**3**	DMSO	85	5 10 15 20	30±9 30±5 30±5 25±5
5			DMSO	100	5	30±4

					10	34±5
					15	30±4
6	$TEAHCO_3^-$	**4**	DMSO	rt	10	5±5
					20	10±5
				85	5	20±4
					10	20±6
				100	5	25±8
					10	25±5
9	$TEAHCO_3^-$	**4**	ACN	0	20	5±5
				rt	5	10±5
					10	10±5
					15	15±5
				50	5	15±6
					10	20±6
					15	20±5
				85	5	20±5
					10	22±5
					15	22±5
10	$TEAHCO_3^-$	**3**	ACN	Rt	30	10±7
				50	10	20±5
					20	20±5
				85	5	21±4
					10	22±5
11	$TEAHCO_3^-$	**3**	DMF	rt	5	10±4
					10	12±5
					20	12±5
				85	5	25±4
					10	30±5
12	$TEAHCO_3^-$	**4**	DMF	rt	5	10±4
					15	12±5
					25	12±5
				85	5	20±4
					10	28±5

Data corresponds to the labelings performed with ^{18}F (0.2 to 1.2 GBq), aziridine (10 µmol), base (10 µmol), solvent (0.3 to 0.5 mL); [a]40%MeOH in DCM ; For base concentration screen- 5, 10, 15 20 µmol K_2CO_3; 10, 12, 16, 20 µmol $KHCO_3$; 5, 10, 15, 25, 40 µmol $TEAHCO_3^-$ used

Two reaction solvents DMF, acetonitrile were seemed to be giving more or less same [^{18}F]fluoride incorporation yields between the temperatures 50 and 100 °C. But DMSO has shown somewhat higher ^{18}F incorporation yields compared to that of DMF and acetonitrile. Therefore further labeling experiments were done mainly in DMSO at temperatures 50°C or 80°C for 10 minutes. The same substrates **3, 4** were then reacted with other [^{18}F]fluoride systems such as [^{18}F]TBAF[TBAOH], [^{18}F]CsF(Cs_2CO_3), [^{18}F]KF(K_{222})($K_2C_2O_4$) and [^{18}F]KF(18C6)($KHCO_3$). Similar undesired results were obtained even after changing the ^{18}F fluoride system. Other aziridines **6, 7, 8, 10** and **11** were also reacted with above ^{18}F fluoride systems that gave the undesired labeling products as well. These undesired results are in line with the non-radioactive fluorination experiments (Table 2, article). Table 2 below shows various 18F systems, aziridines and the 18F incorporated yields based on radio-TLC. Only the –tosyl activated aziridnes **5, 9** and **12** were labeled as expected giving the desired ^{18}F intermediate products.

SI T2: Further ^{18}F labeling of all aziridine precursors



3 to **12**

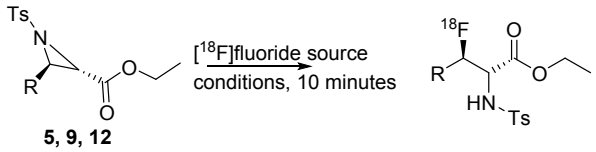
[18F]desired product

Entry	18F system base	Aziridine	Temperature (°C)	[18F]unknown[b] (%)	[18F]desired[a] (%)
1	$KHCO_3$/18C6	**3**	80	5±4	
2	CS_2CO_3	**3**	80	10±3	
3	$K_2C_2O_4/K_{222}$	**3**	80	3±2	
4	$KHCO_3$/18C6	**4**	80	7±4	
5	CS_2CO_3	**4**	80	13±3	
6	$K_2C_2O_4/K_{222}$	**4**	80	3±2	
7	$KHCO_3/K_{222}$	**5**	50	5±4	60±6 ([18F]**5a**)
			80	8±4	55±5 ([18F]**5a**)
8	$TEAHCO_3^-$	**5**	50	5±4	70±4 ([18F]**5a**)
			80	6±4	68±5 ([18F]**5a**)
9	TBAOH	**5**	rt	-	30±5 ([18F]**5a**)
			50	6±5	50±5 ([18F]**5a**)
10	$TEAHCO_3^-$	**7**	80	17±4	
11	$TEAHCO_3^-$	**8**	80	22±3	
12	$KHCO_3/K_{222}$	**9**	50	16±6	26±4 ([18F]**9a**)
			80	20±5	25±6 ([18F]**9a**)
13	$TEAHCO_3^-$	**9**	80	28±5	30±4 ([18F]**9a**)
14	$TEAHCO_3^-$	**10**	rt	-	
			80	14±1	
15	$KHCO_3/K_{222}$	**10**	80	19±5	
16	$TEAHCO_3^-$	**11**	50	13±4	
			80	17±2	
17	$KHCO_3/K_{222}$	**11**	50	14±4	
			80	20±5	
18	$K_2C_2O_4/K_{222}$	**11**	80	10±5	
19	$KHCO_3$/18C6	**11**	80	5±4	
20	K_2CO_3/K_{222}	**11**	80	12±4	
21	$KHCO_3/K_{222}$	**12**	50	5±3	20±4 ([18F]**12a**)
			80	10±5	27±6 ([18F]**12a**)
22	$TEAHCO_3^-$	**12**	50	4±2	25±3 ([18F]**12a**)
			80	7±3	24±4 ([18F]**12a**)

Data corresponds to the labelings performed with 18F (0.2 to 1.2 GBq), aziridine (10 µmol), base (10 µmol), solvent (0.3 mL); [a]40%MeOH in DCM; [b]50%EtOAc in hexanes: For base concentration screen- 6, 10 µmol Cs_2CO_3; 10, 12, 16, 20 µmol $KHCO_3$; 10, 15 µ $K_2C_2O_4$; 5, 10, 15, 25, 40 µmol $TEAHCO_3^-$ used

Having noticed the formation of desired 18F intermediates with tosyl aziridines, labeling conditions were further optimized. Three different fluoride systems [18F]KF(K_{222})($KHCO_3$), [18F]TEAF($TEAHCO_3^-$), [18F]TBAF(TBAOH) were used to ring open the tosyl aziridines. All of them gave the desired 18F labeled intermediates and also [18F]tosyl fluoride (TsF) as a minor product. The optimization conditions are shown in the table 3.

SI T3: Optimization of labeling conditions of tosyl aziridines



Entry	^{18}F base	Aziridine	Solvent	Temperature (°C)	TLC yield (%)	Product
1	$TEAHCO_3^-$	**5**	DMSO	rt	35±4	
				50	70±5	[^{18}F]**5a**
				80	68±5	
				100	60±6	
2	$TEAHCO_3^-$	**5**	ACN	50	66±4	[^{18}F]**5a**
				80	60±5	
3	$TEAHCO_3^-$	**5**	DMF	50	47±5	[^{18}F]**5a**
				80	38±4	
4	$KHCO_3/K_{222}$	**5**	DMSO	rt	35±5	[^{18}F]**5a**
				50	60±6	
				80	55±5	
5	TBAOH	**5**	DMSO	rt	30±5	([^{18}F]**5a**)
				50	50±5	
6	$TEAHCO_3^-$	**9**	DMSO	rt	7±3	([^{18}F]**9a**)
				50	28±6	
				80	30±4	
7	$KHCO_3/K_{222}$	**9**	DMSO	50	26±4	([^{18}F]**9a**)
				80	25±6	
8	$KHCO_3/K_{222}$	**12**	DMSO	50	20±4	([^{18}F]**12a**)
				80	27±6	
9	$TEAHCO_3^-$	**12**	DMSO	rt	8±3	([^{18}F]**12a**)
				50	25±3	
				80	24±4	

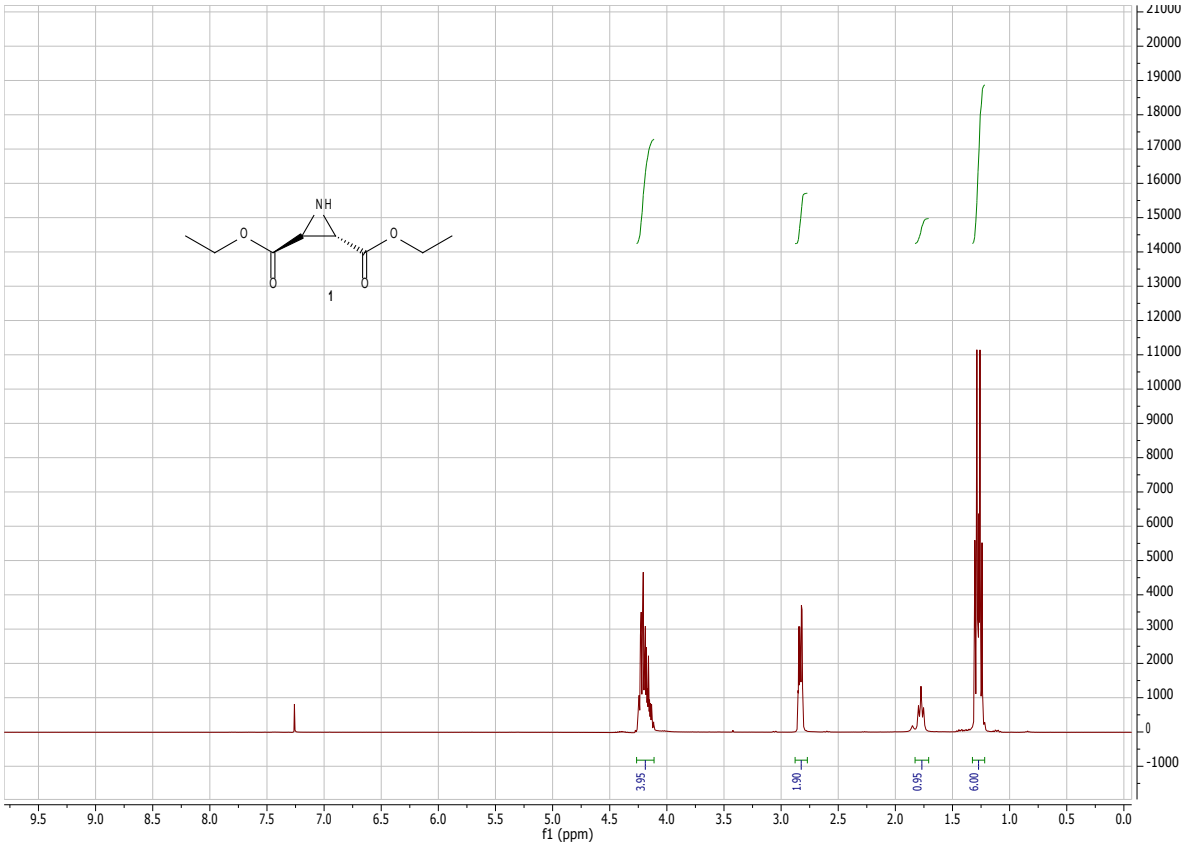
Data corresponds to the labelings performed with ^{18}F (0.2 to 1.2 GBq), aziridine (10 µmol), base (10 µmol), solvent (0.3 mL); [b]50%EtOAc in hexanes; For base concentration screen 5, 10, 15, 25, 40 µmol $TEAHCO_3^-$ used; Better conditions are shown in red color

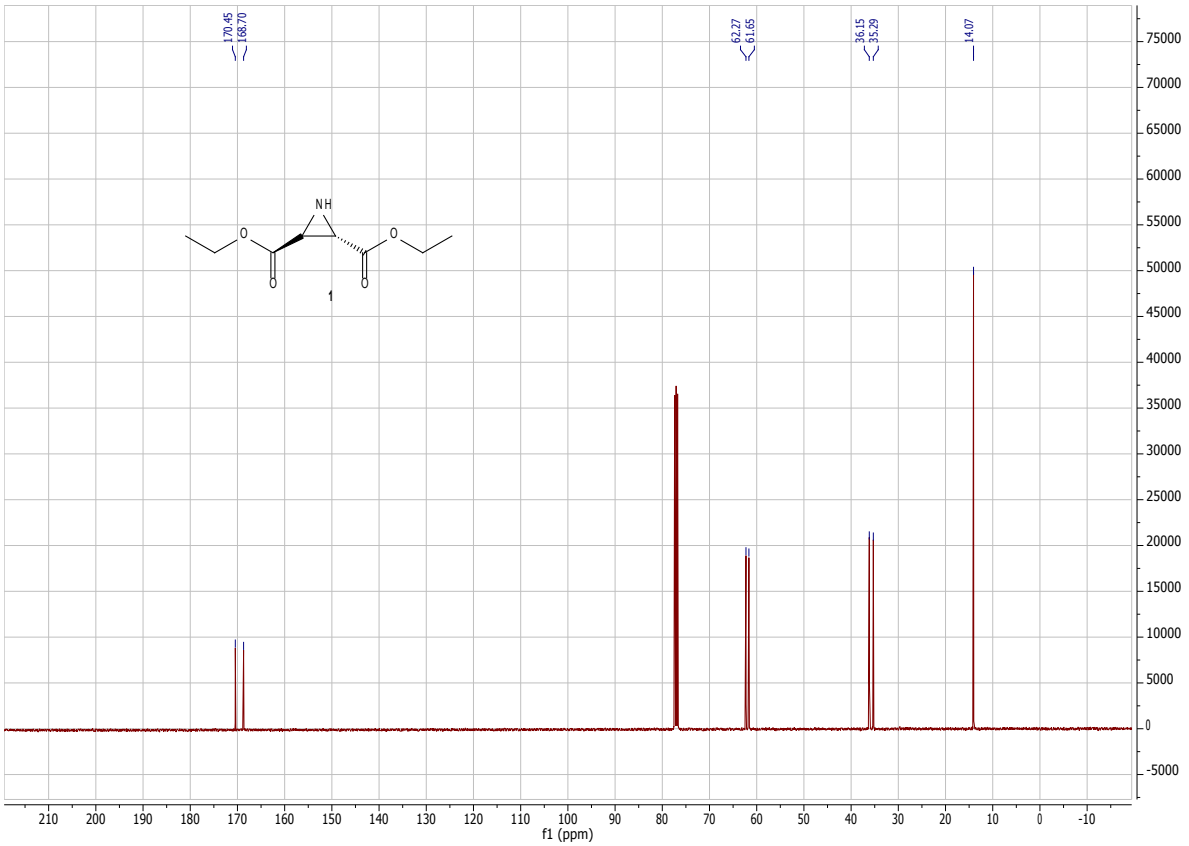
Labeling procedure and product purification:

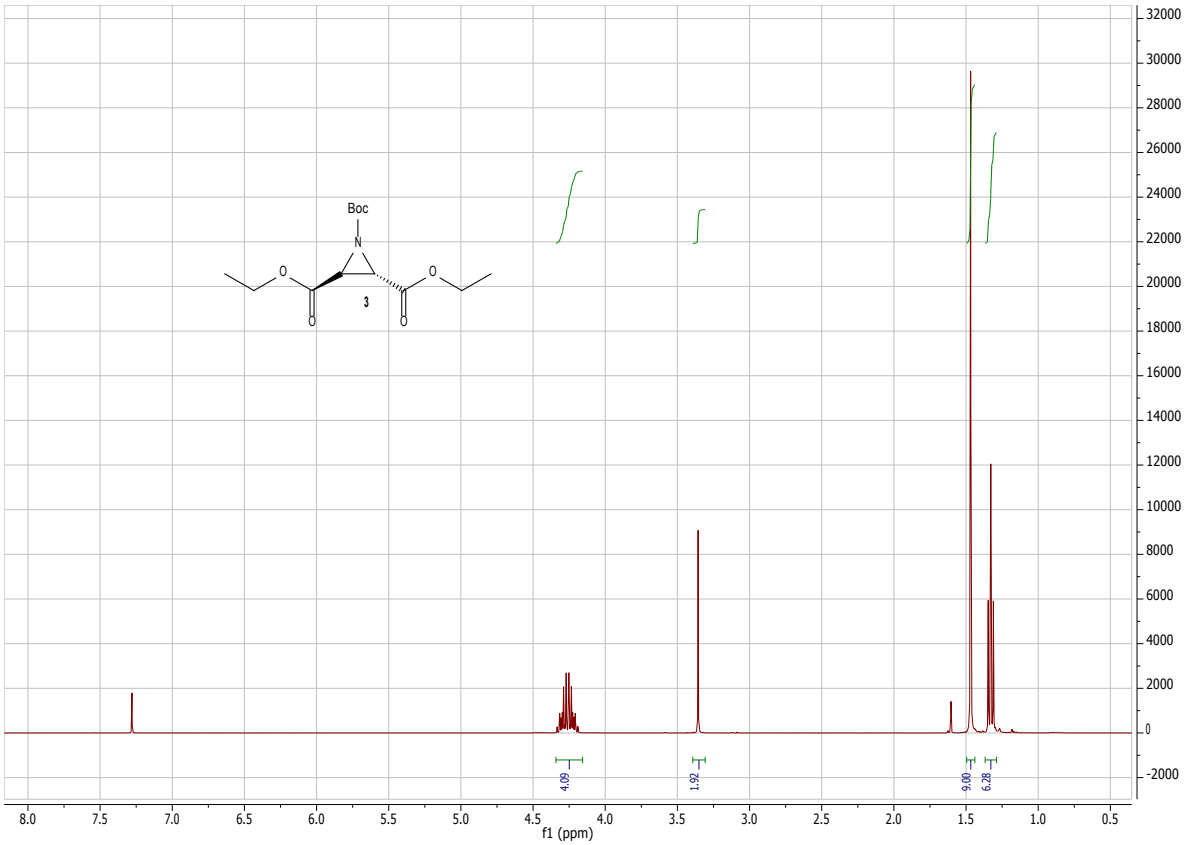
The QMA trapped 1.20 GBq ^{18}F was eluted with 700 µL $TEAHCO_3^-$ (10 mg in 100 µL water + 600 µL acetonitrile) into 5 mL v-vial (≥95% elution). Then the solution was dried azeotropically with acetonitrile (3X1 mL) over 15 minutes. The dried [^{18}F]TEAF($TEAHCO_3^-$) was cooled and then dissolved in 600 µL anhydrous DMSO and separated into three 200 µL fractions. Aziridine precursor (~2 mg in 0.1 mL DMSO) was added to the above 0.2 mL ^{18}F solution at room temperature and stirred at 50°C on aluminum block for 10 minutes. Following this time, the vial was cooled and quenched with 1 mL 1 M NH_4Cl and 4 mL water.

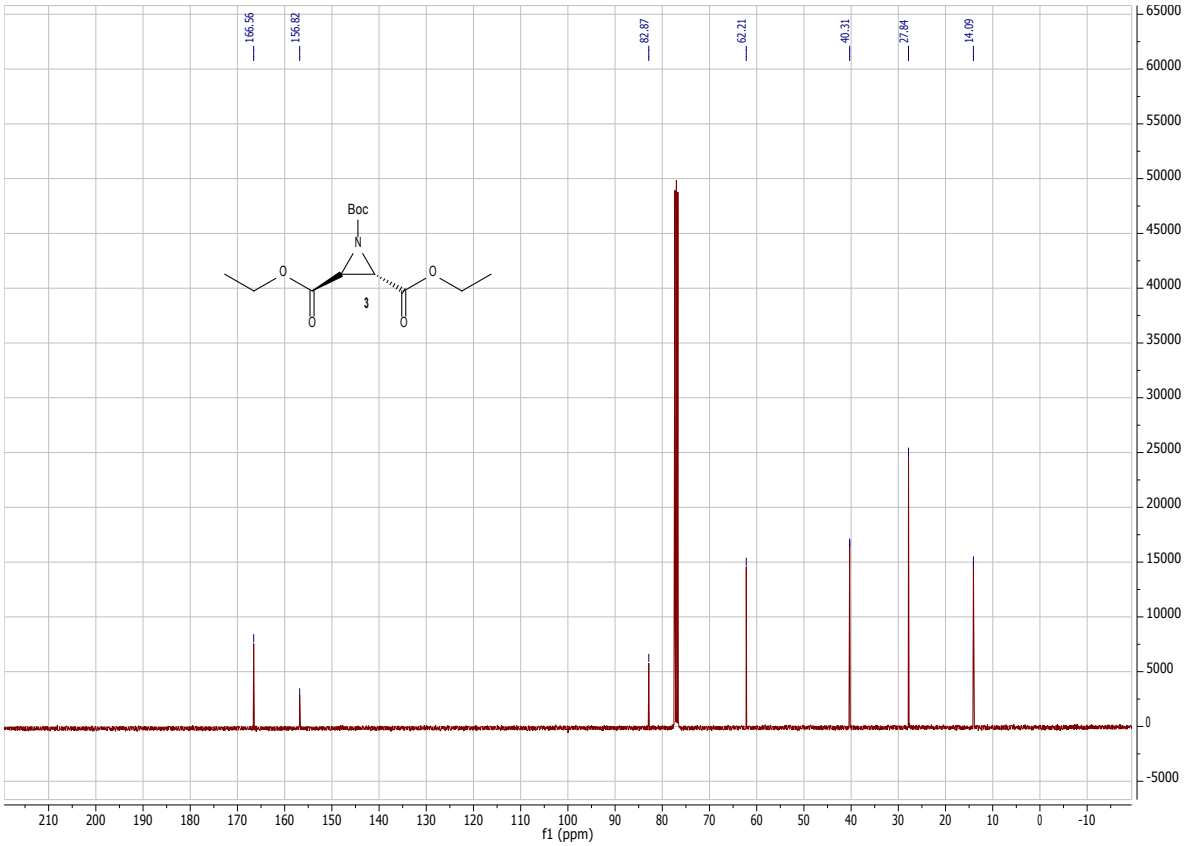
This solution was passed through a C_{18} cartridge (pre activated with 5 mL ACN and 5 mL water) and the cartridge was again rinsed with 10 mL water and 10 mL air. The C_{18} cartridge was then connected to a silica cartridge (preactivated with 10 mL hexanes) and 2 mL dichloromethane (followed by 1 mL air) was passed through both the cartridges. The eluted fraction ([^{18}F]TsF] was collected in a separate vial. The products trapped on C_{18}, silica cartridge were later eluted with 1 mL acetonitrile followed by 1 mL air ([^{18}F]**5a**) or 1 mL THF followed by 1 mL air ([^{18}F]**9a,** [^{18}F]**12a**) into another vial. From this eluted fraction, 50 µL was mixed with 50

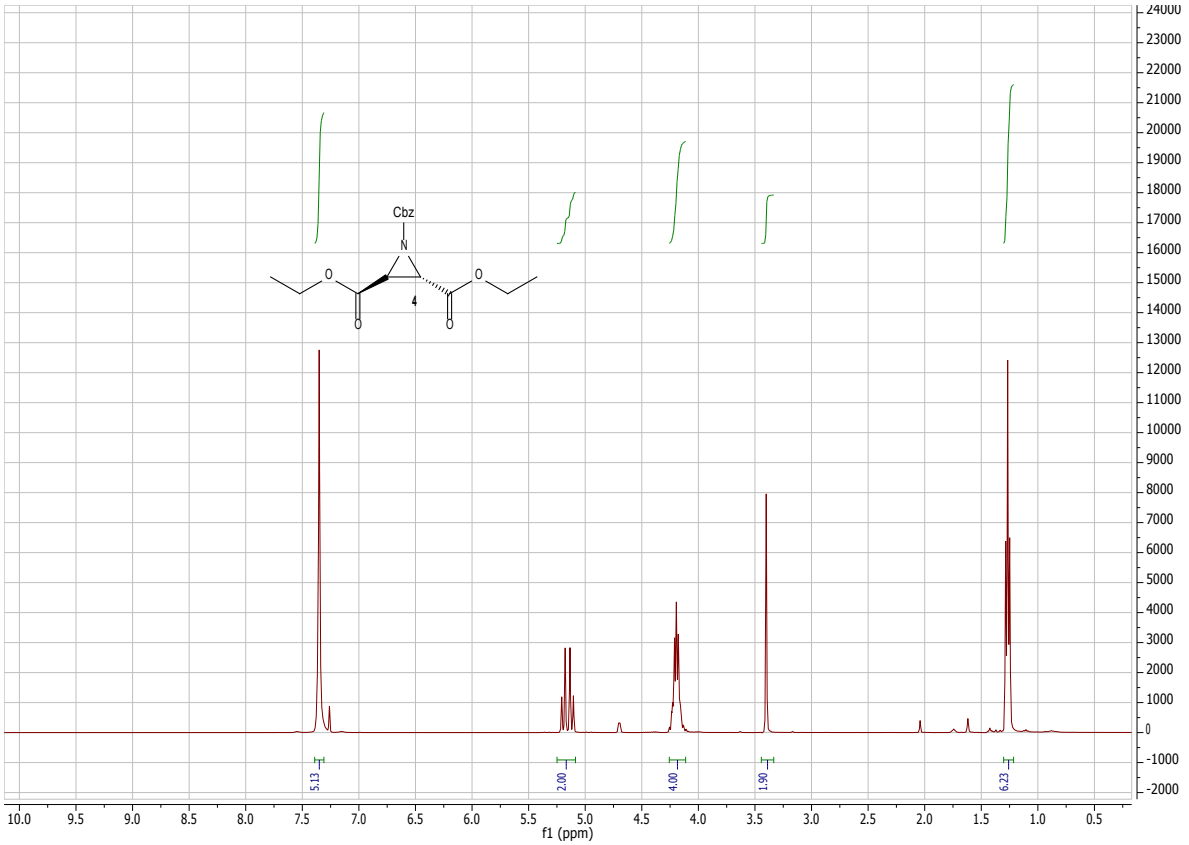
µL water and 10 µL was injected into an analytical HPLC for the identification of products (HPLC sample was spiked with reference compounds).

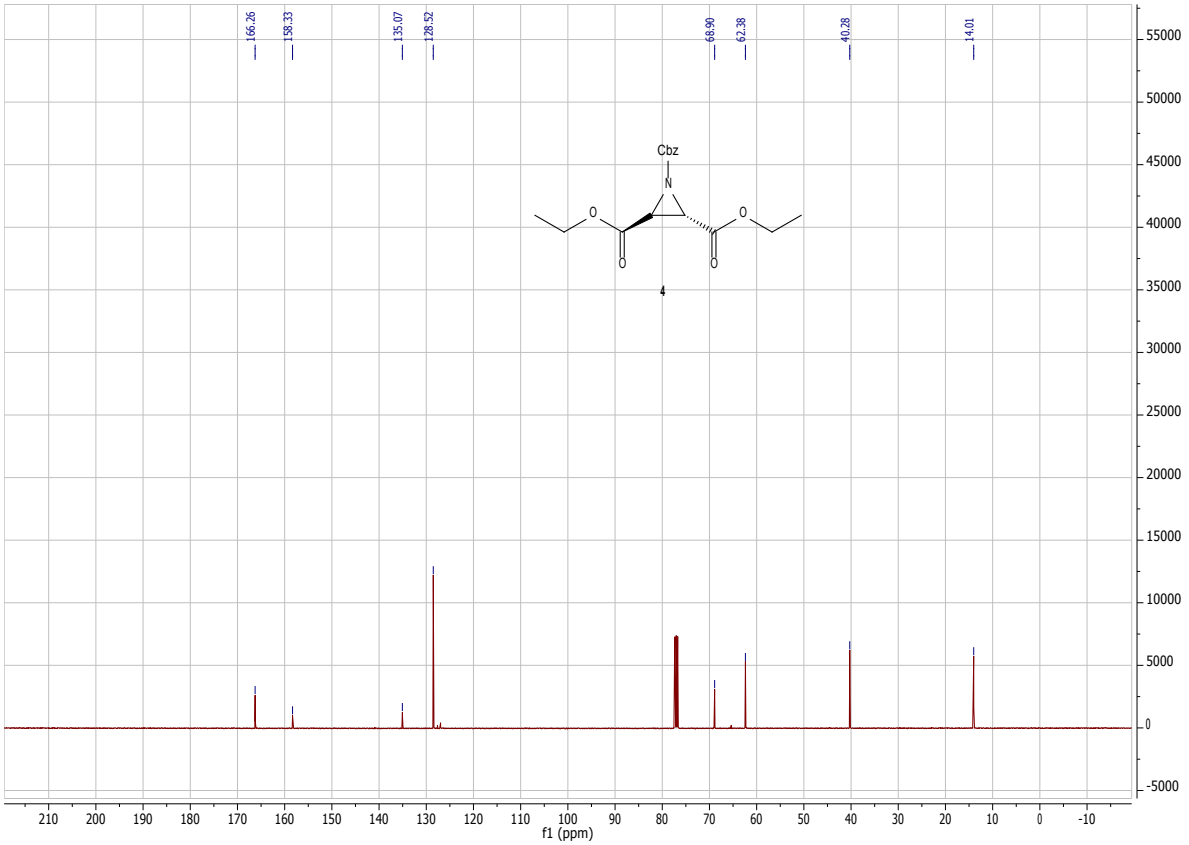


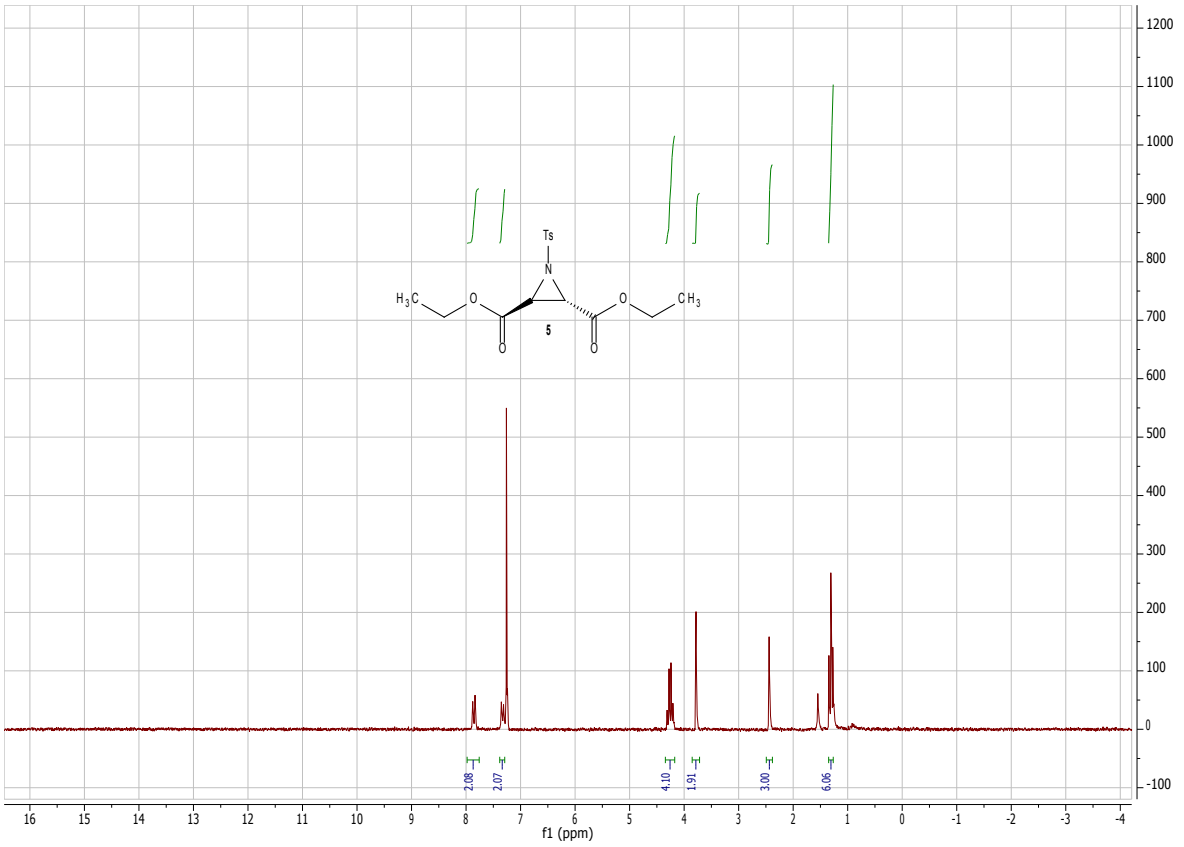


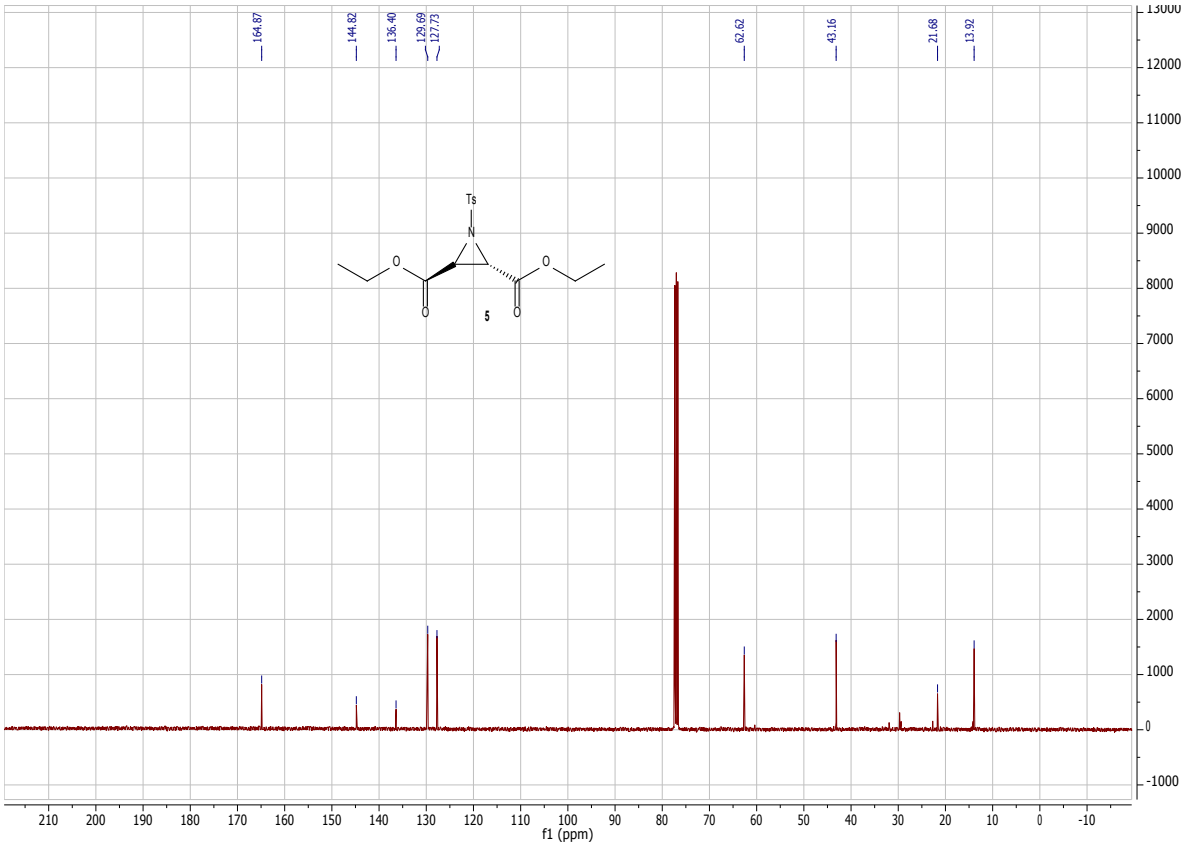

Boc
N
O
O
O
O
3
4.09
1.92
9.00
6.28
f1 (ppm)

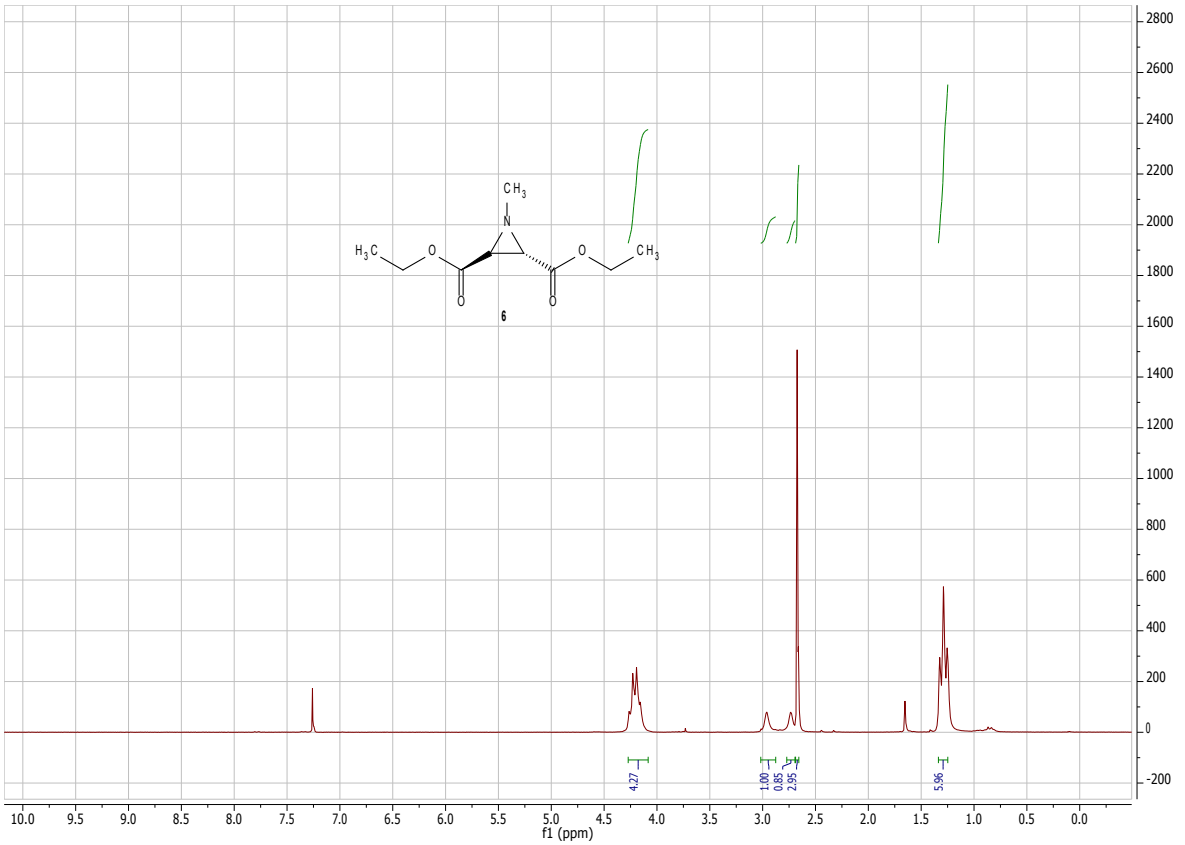

166.56
156.82
82.87
62.21
40.31
27.84
14.09
Boc
N
O
O
O
O
3
f1 (ppm)

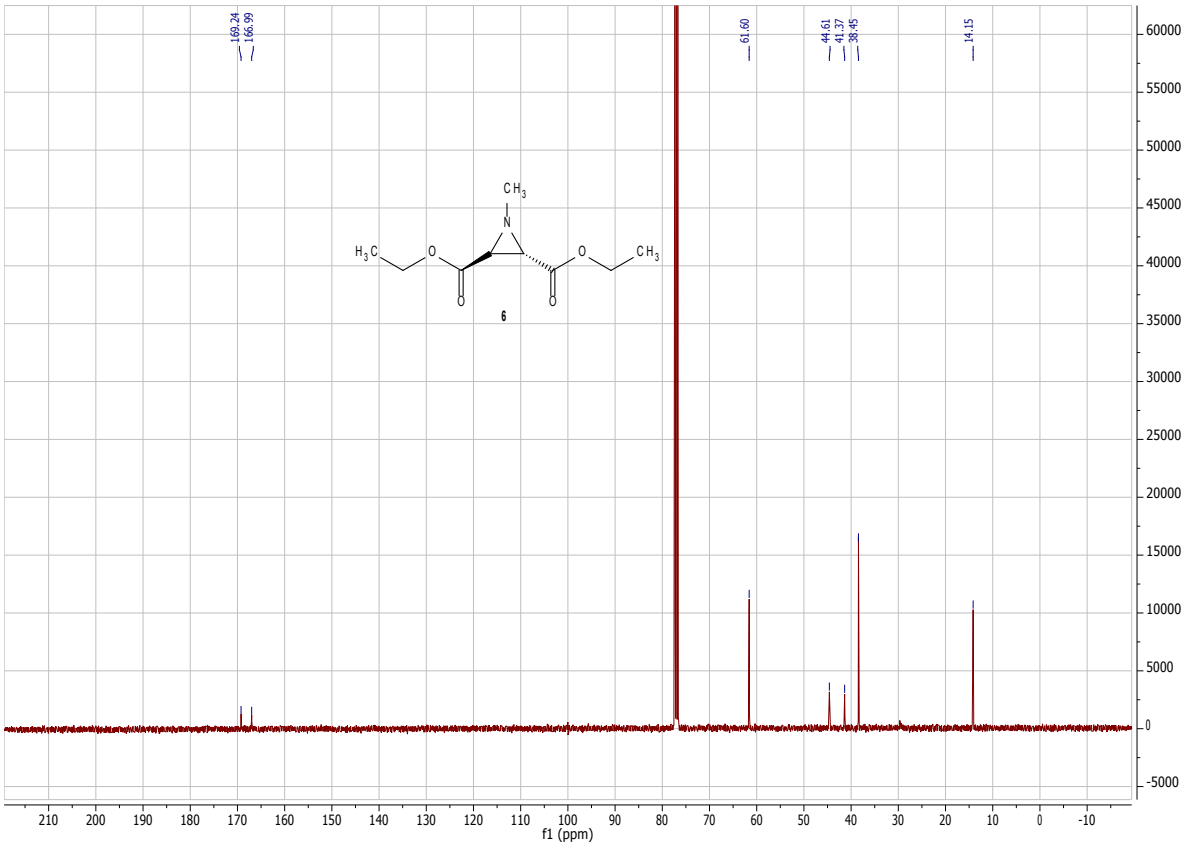

Cbz
N
O
O
O
O
4
5.13
2.00
4.00
1.90
6.23
f1 (ppm)

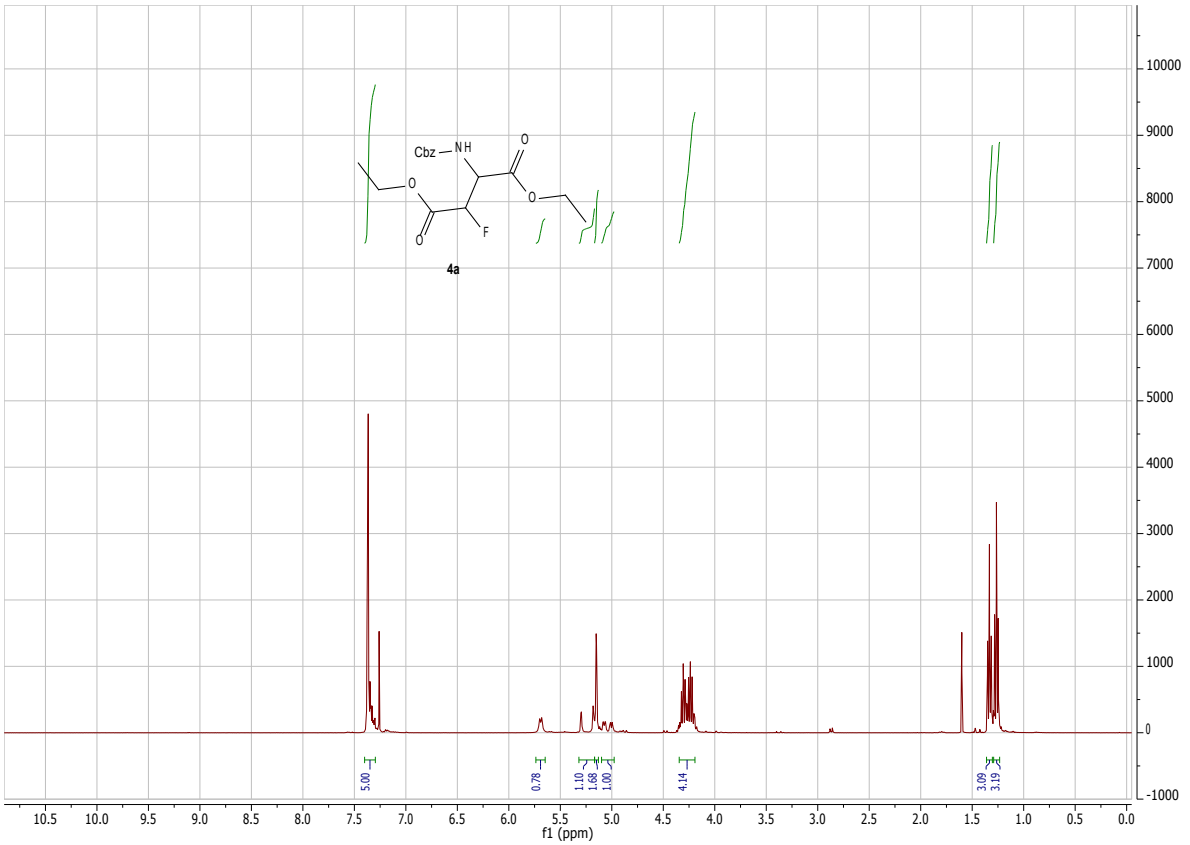

166.26
158.33
135.07
128.52
68.90
62.38
40.28
14.01
Cbz
N
O
O
O
O
4
f1 (ppm)

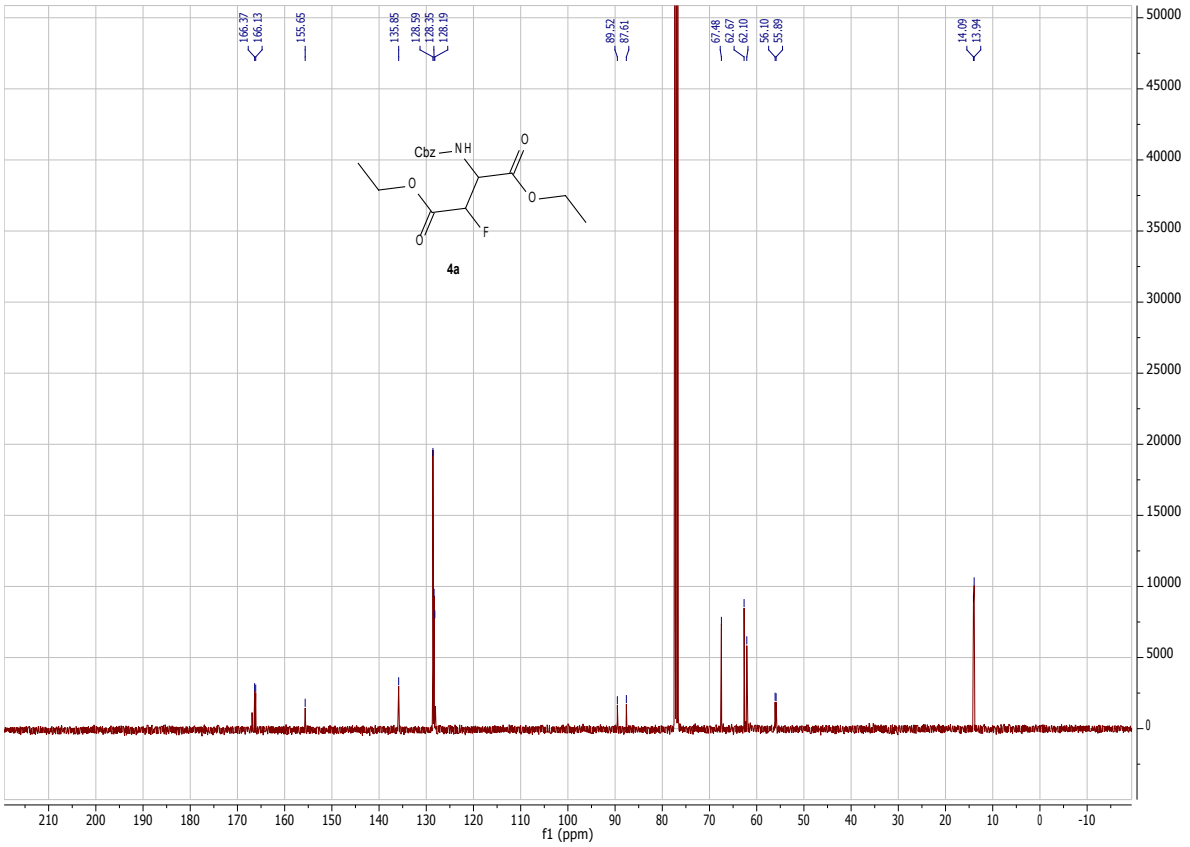

Ts
N
H3C
O
O
O
CH3
5
2.08
2.07
4.10
1.91
3.00
6.06
f1 (ppm)

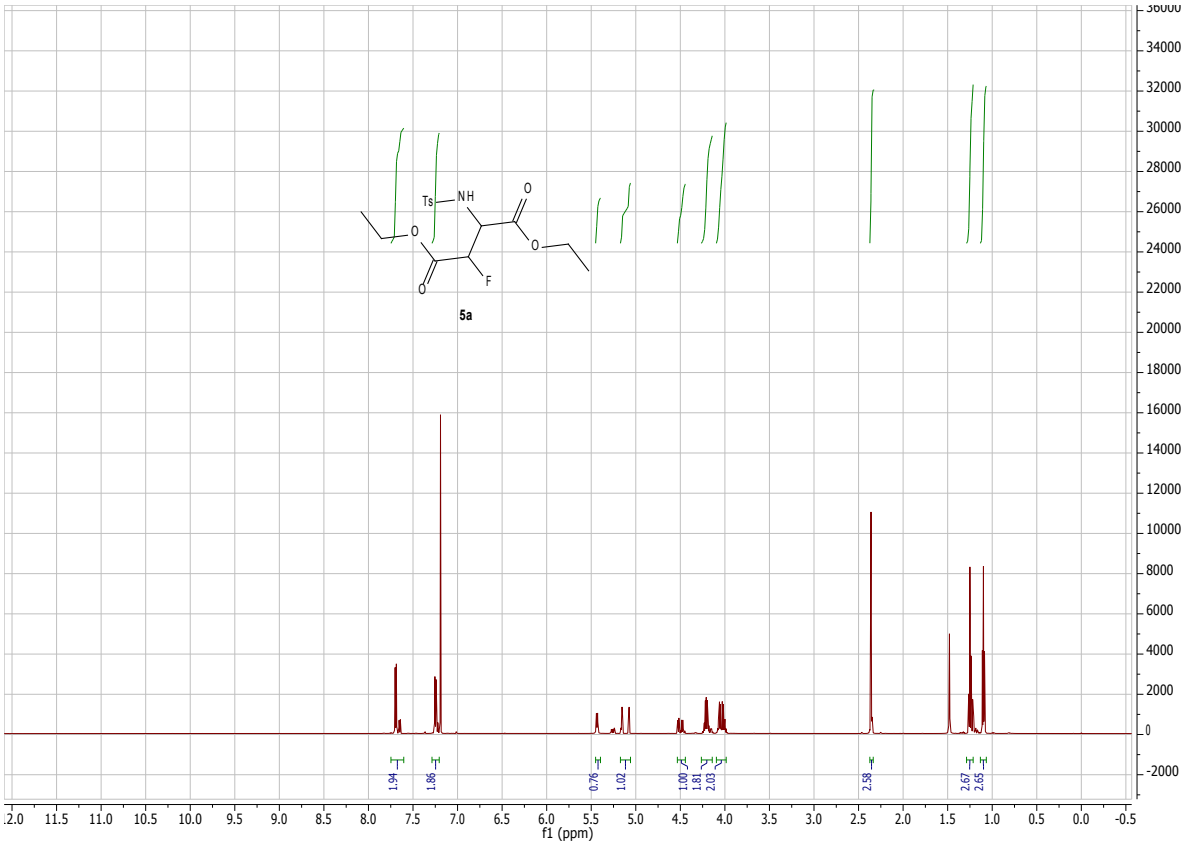

164.87
144.82
136.40
129.69
127.73
62.62
43.16
21.68
13.92
Ts
N
O
O
O
O
5
f1 (ppm)

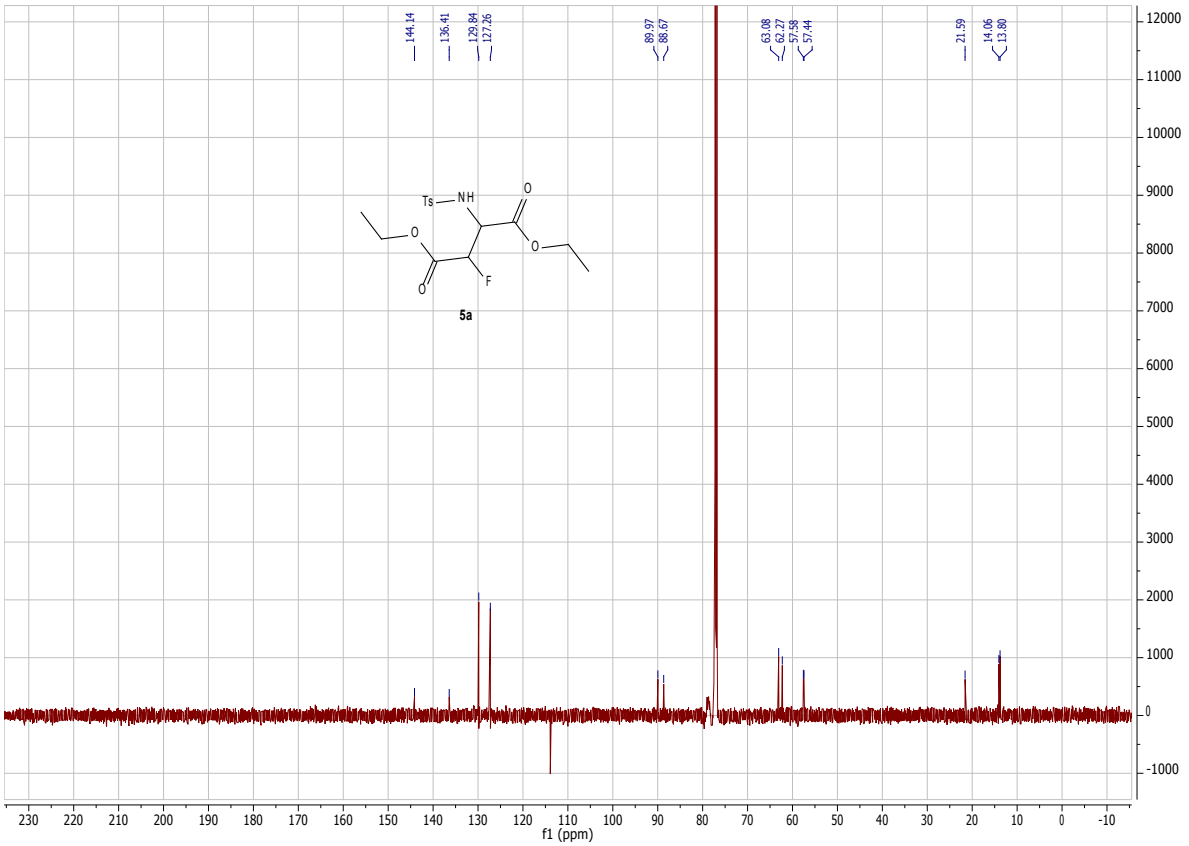

CH3
N
H3C
O
O
O
CH3
6
4.27
1.00
0.85
2.95
5.96
f1 (ppm)

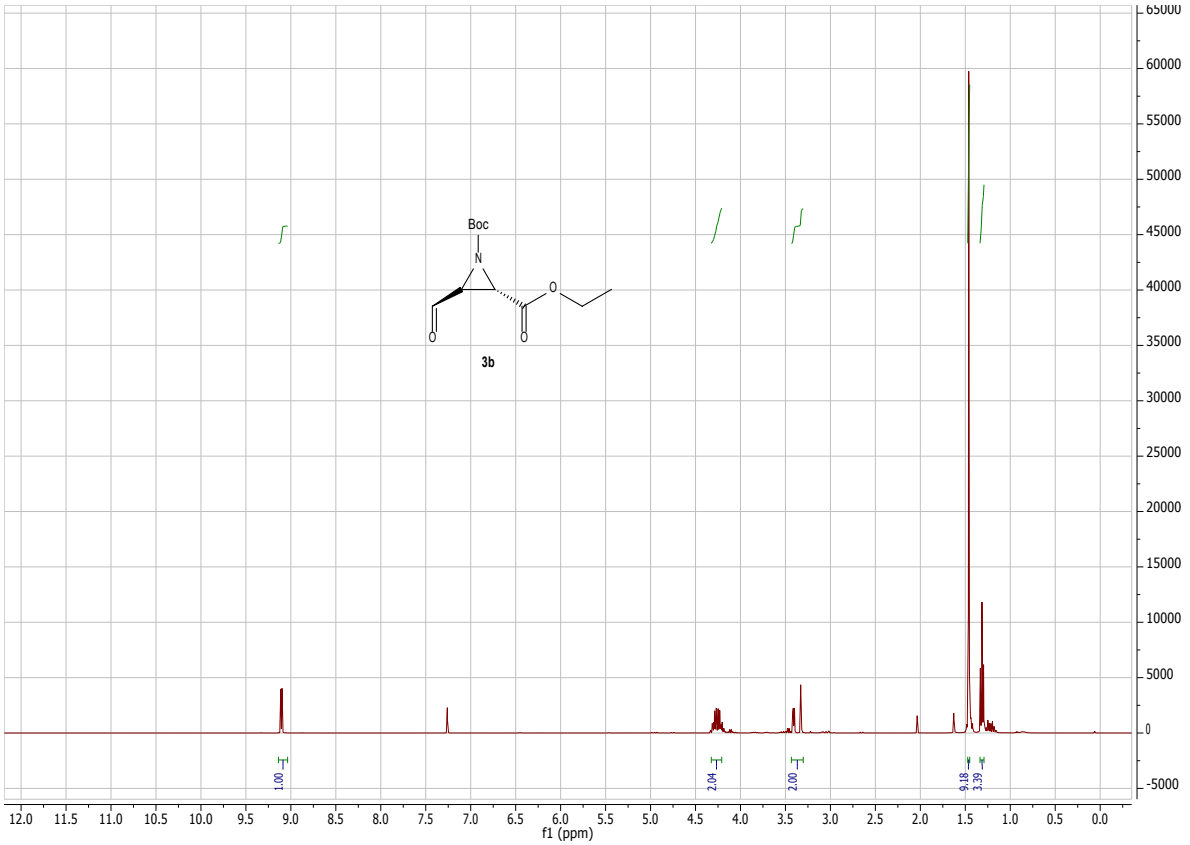

169.24
166.99
61.60
44.61
41.37
38.45
14.15
CH3
N
H3C
O
O
O
CH3
6
f1 (ppm)

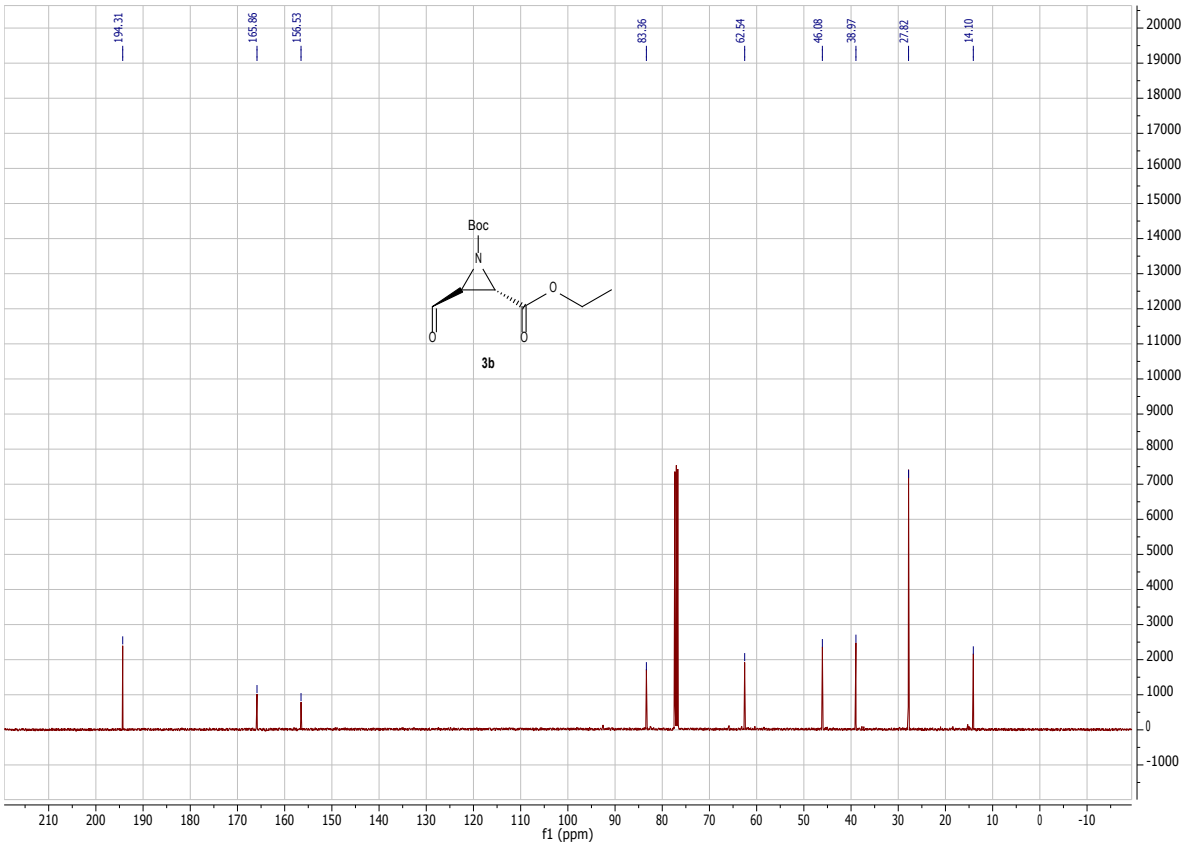

Cbz
NH
O
O
O
O
F
4a
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
5.00
0.78
1.10
1.68
1.00
4.14
3.09
3.19
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

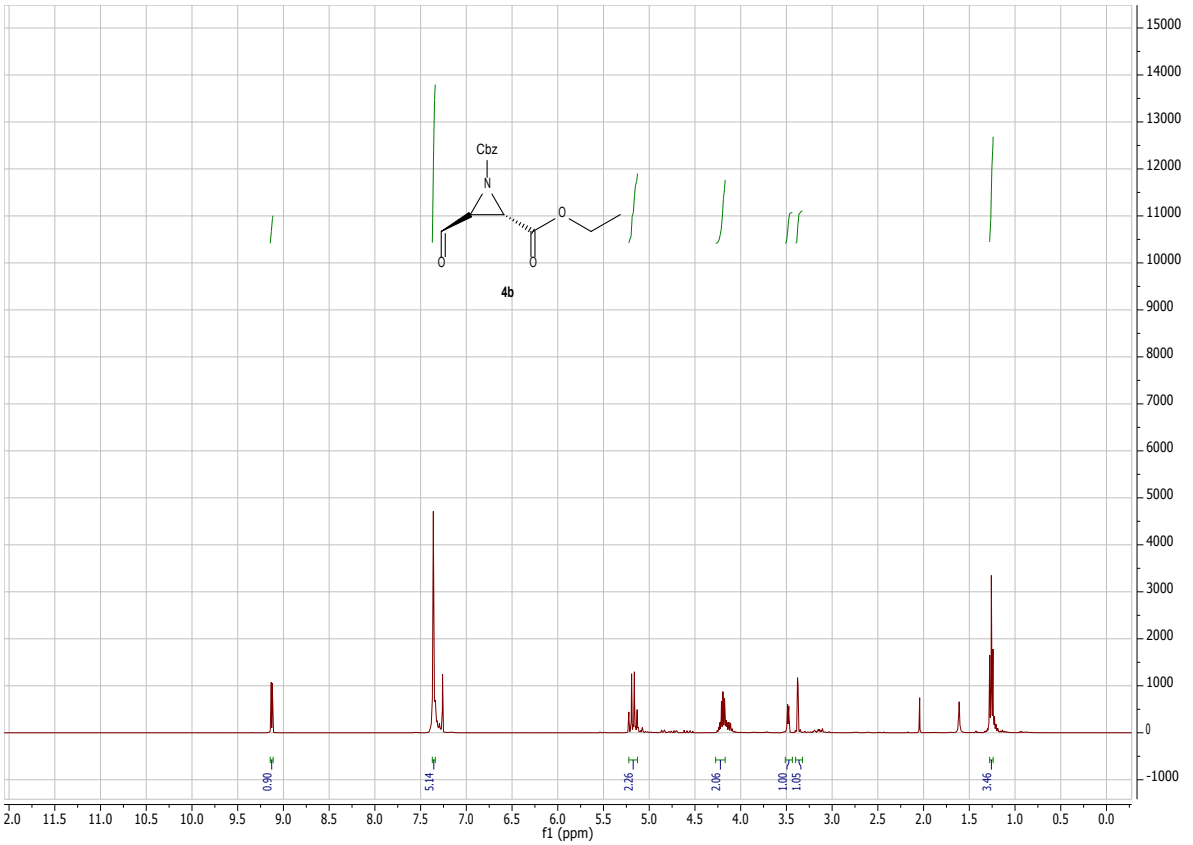

166.37
166.13
155.65
135.85
128.99
128.35
128.19
89.52
87.61
67.48
62.67
62.10
56.10
55.89
14.09
13.94
Cbz
NH
O
O
O
O
F
4a
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

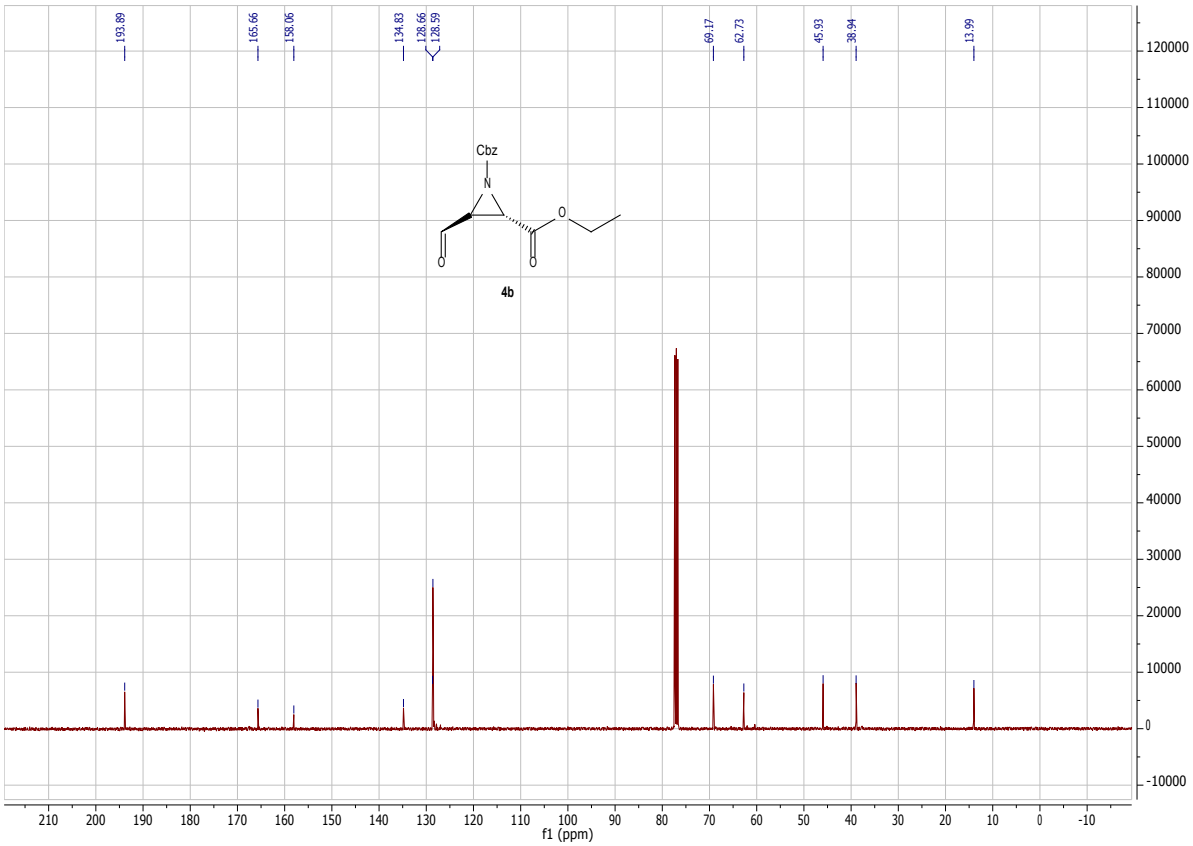

Ts
NH
O
O
O
O
F
5a
1.94
1.86
0.76
1.02
1.00
1.81
2.03
2.58
2.67
2.65
f1 (ppm)

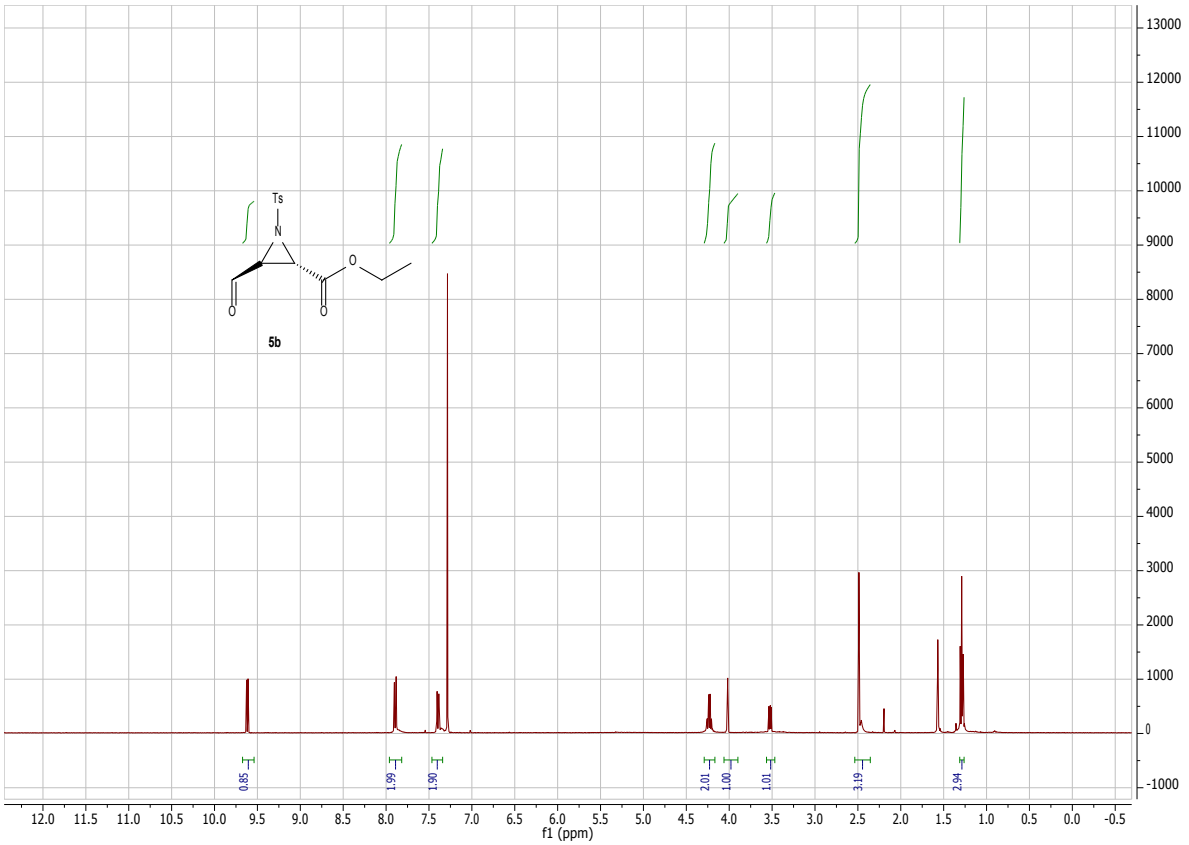

144.14
136.41
129.84
127.26
89.97
88.67
63.08
62.27
57.58
57.44
21.59
14.06
13.80
Ts
NH
O
O
O
O
F
5a
f1 (ppm)

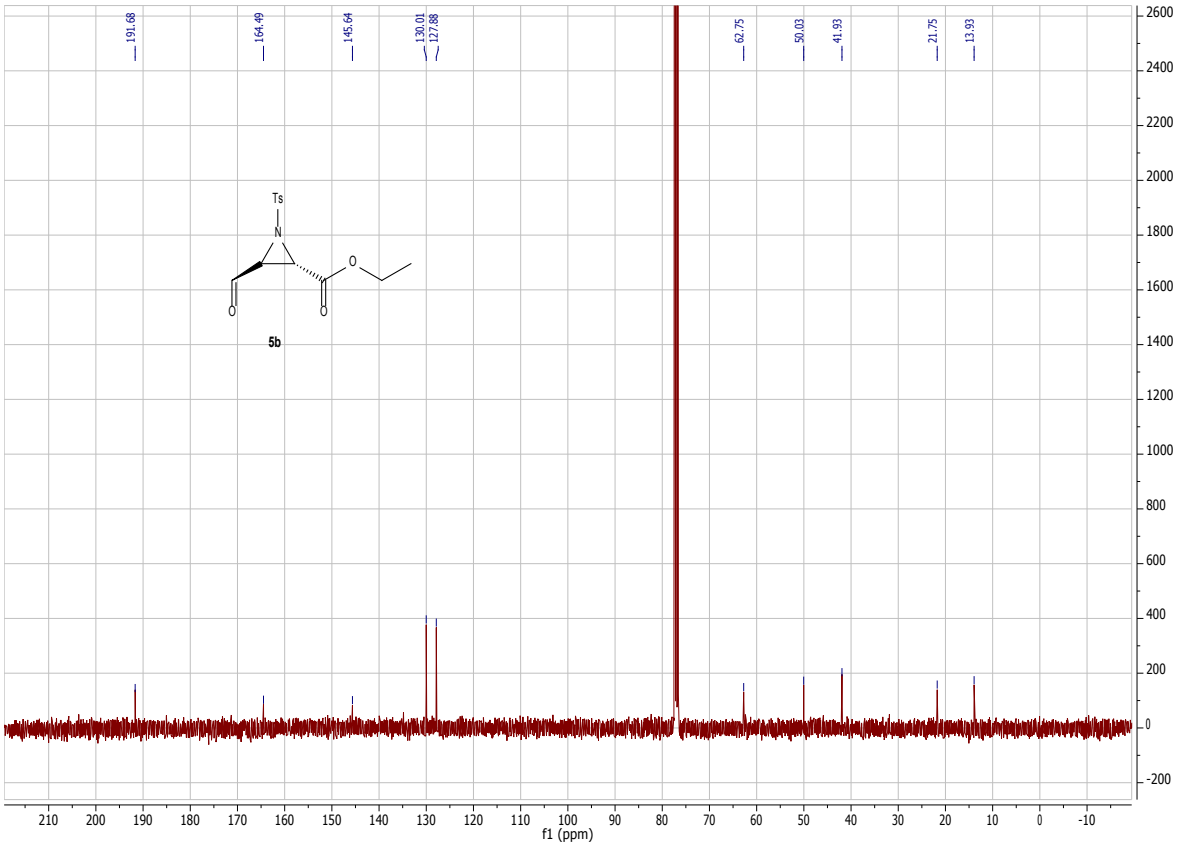

Boc
N
O
O
O
3b
1.00
2.04
2.00
9.18
3.39
f1 (ppm)

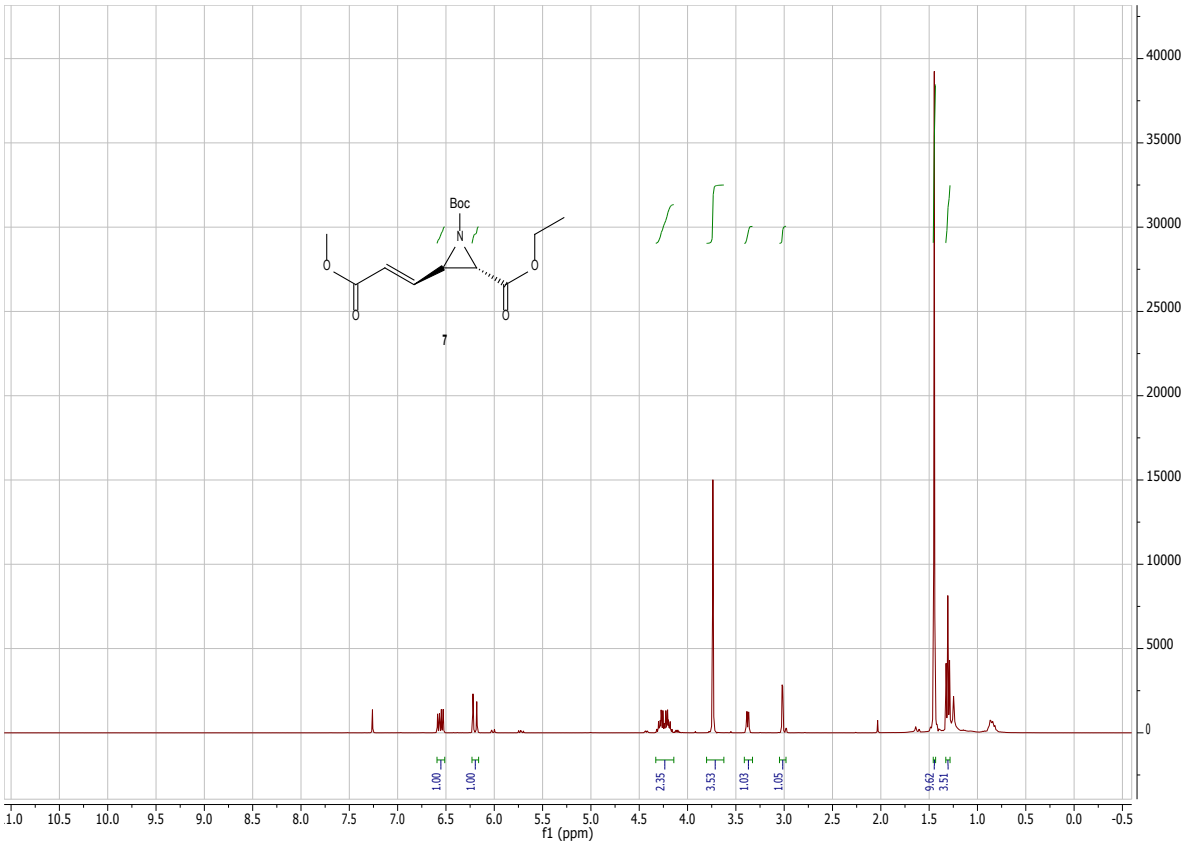

194.31
165.86
156.53
83.36
62.54
46.08
38.97
27.82
14.10
Boc
N
O
O
O
3b
f1 (ppm)

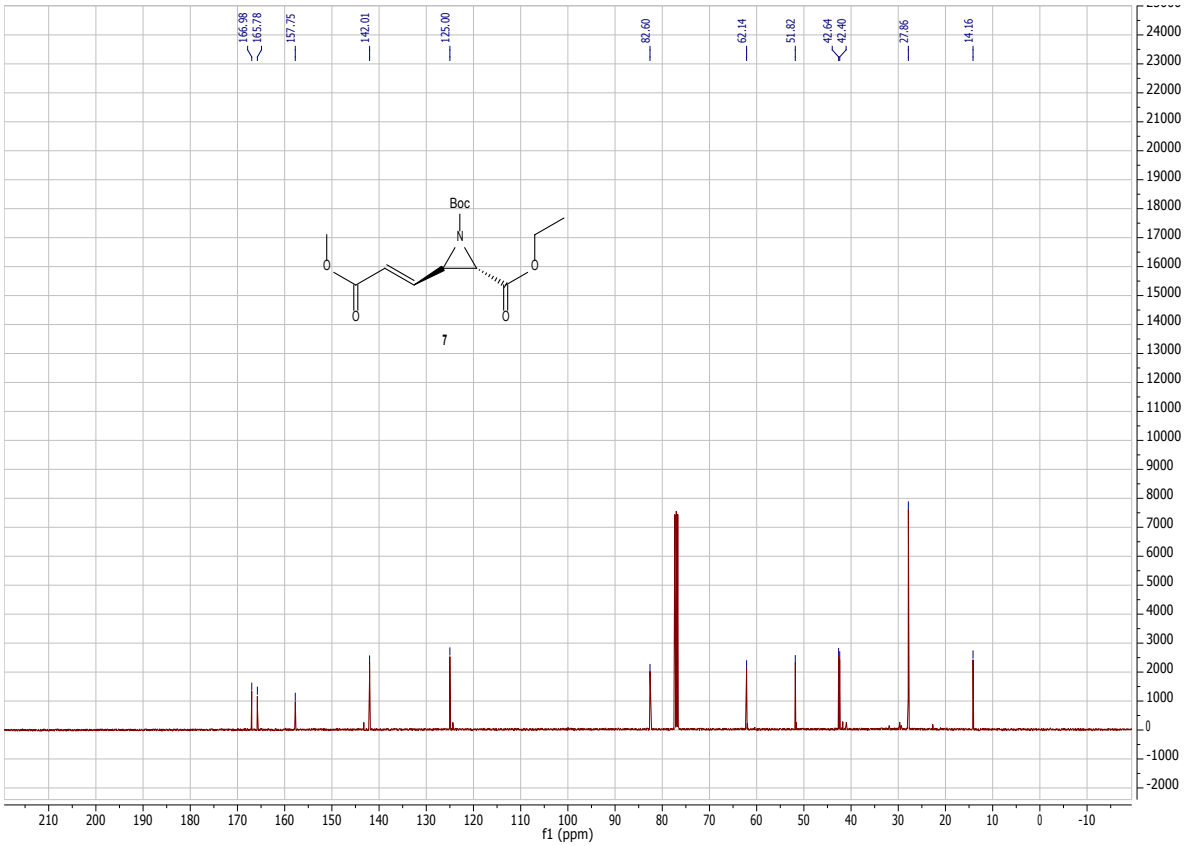

Cbz
N
O
O
O
4b
0.90
5.14
2.26
2.06
1.00
1.05
3.46
f1 (ppm)

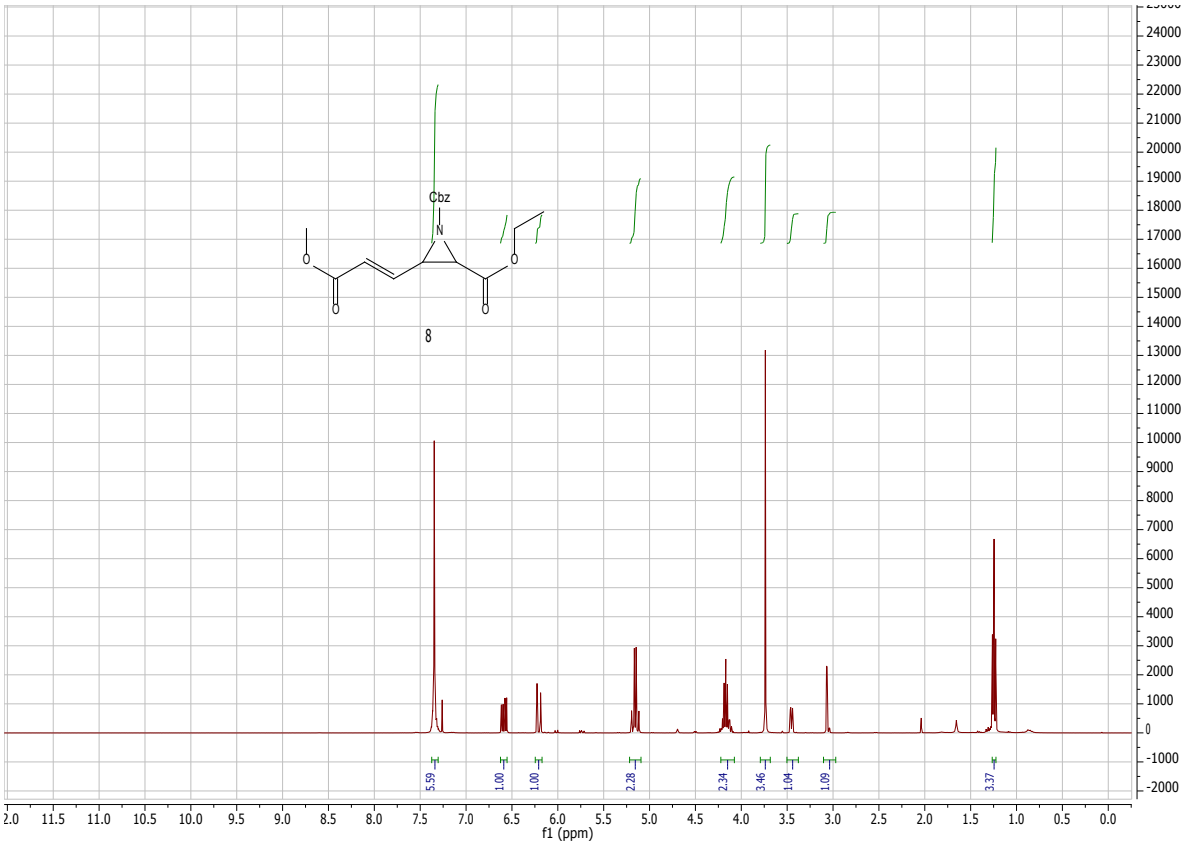

193.89
165.66
158.06
134.83
128.66
128.59
69.17
62.73
45.93
38.94
13.99
Cbz
N
O
O
O
4b
f1 (ppm)

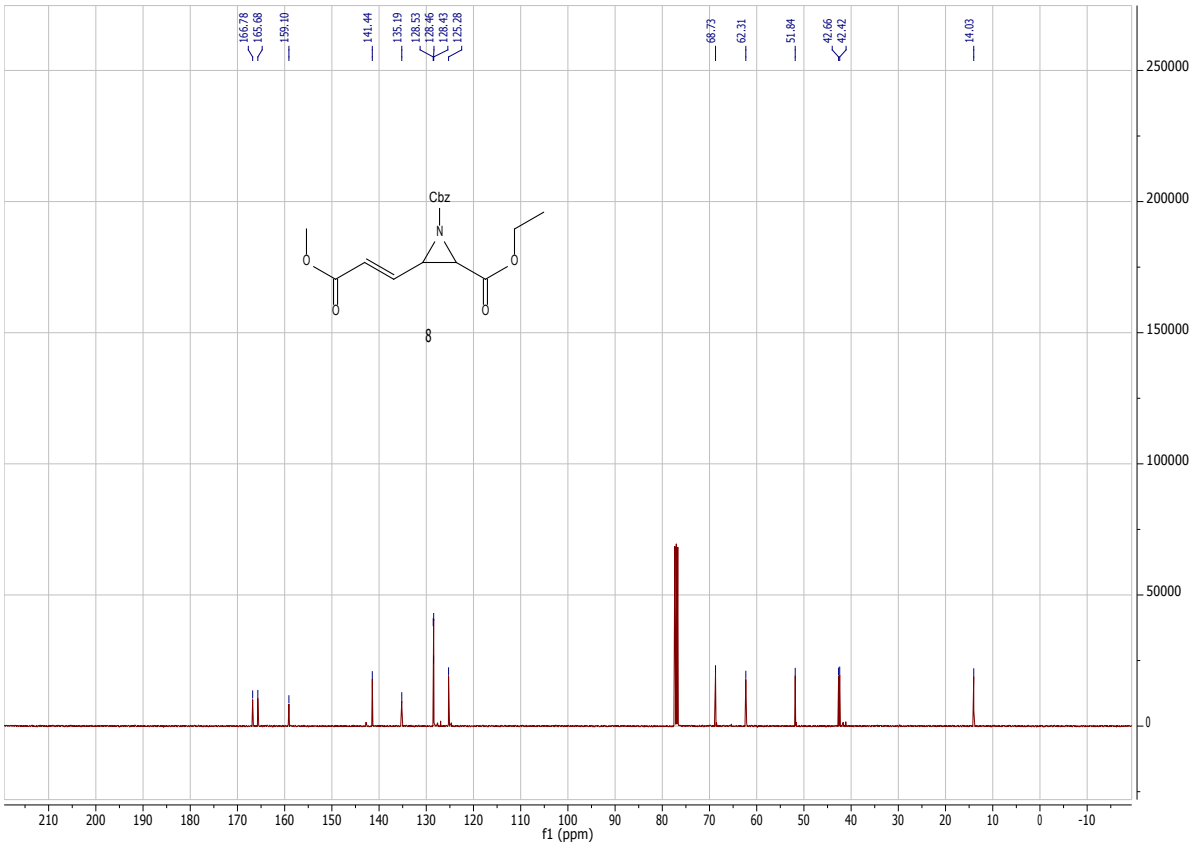

Ts
N
O
O
O
5b
0.85
1.99
1.90
2.01
1.00
1.01
3.19
2.94
f1 (ppm)

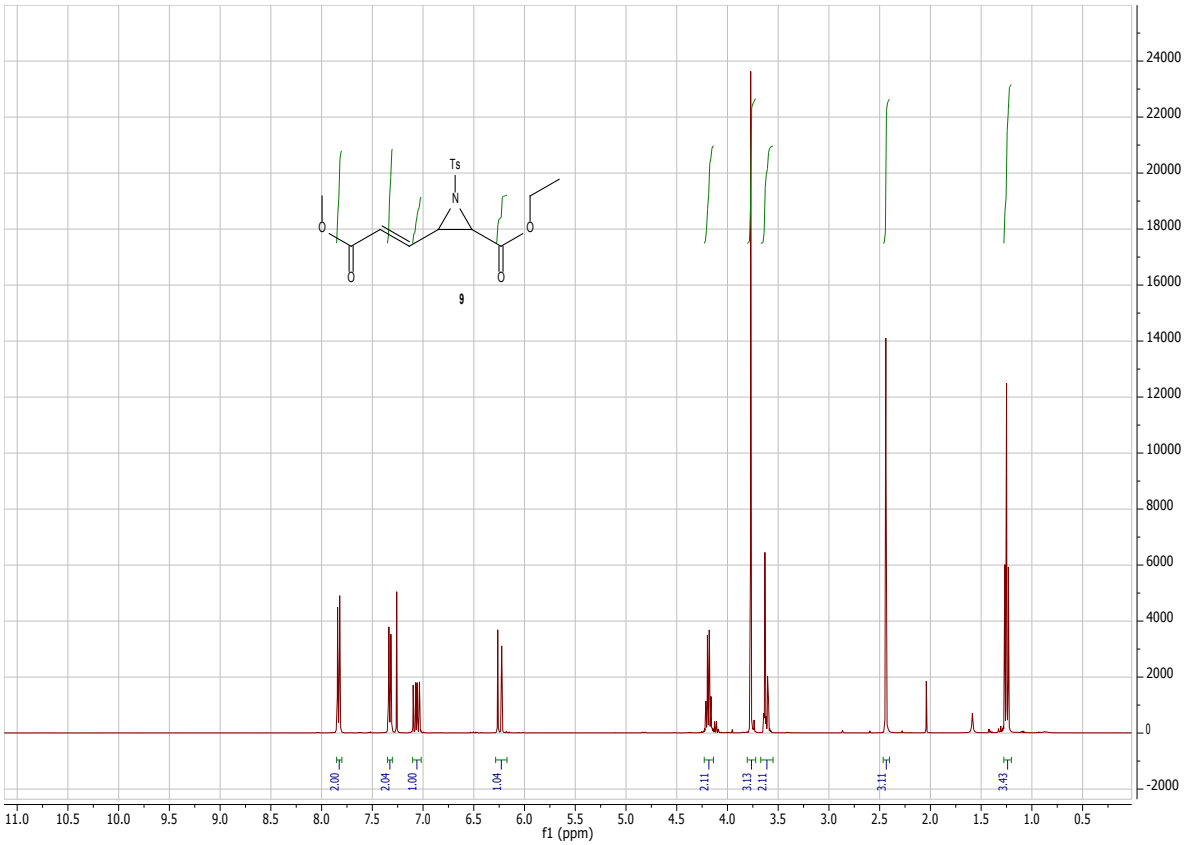

191.68
164.49
145.64
130.01
127.88
62.75
50.03
41.93
21.75
13.93
Ts
N
O
O
O
5b
f1 (ppm)

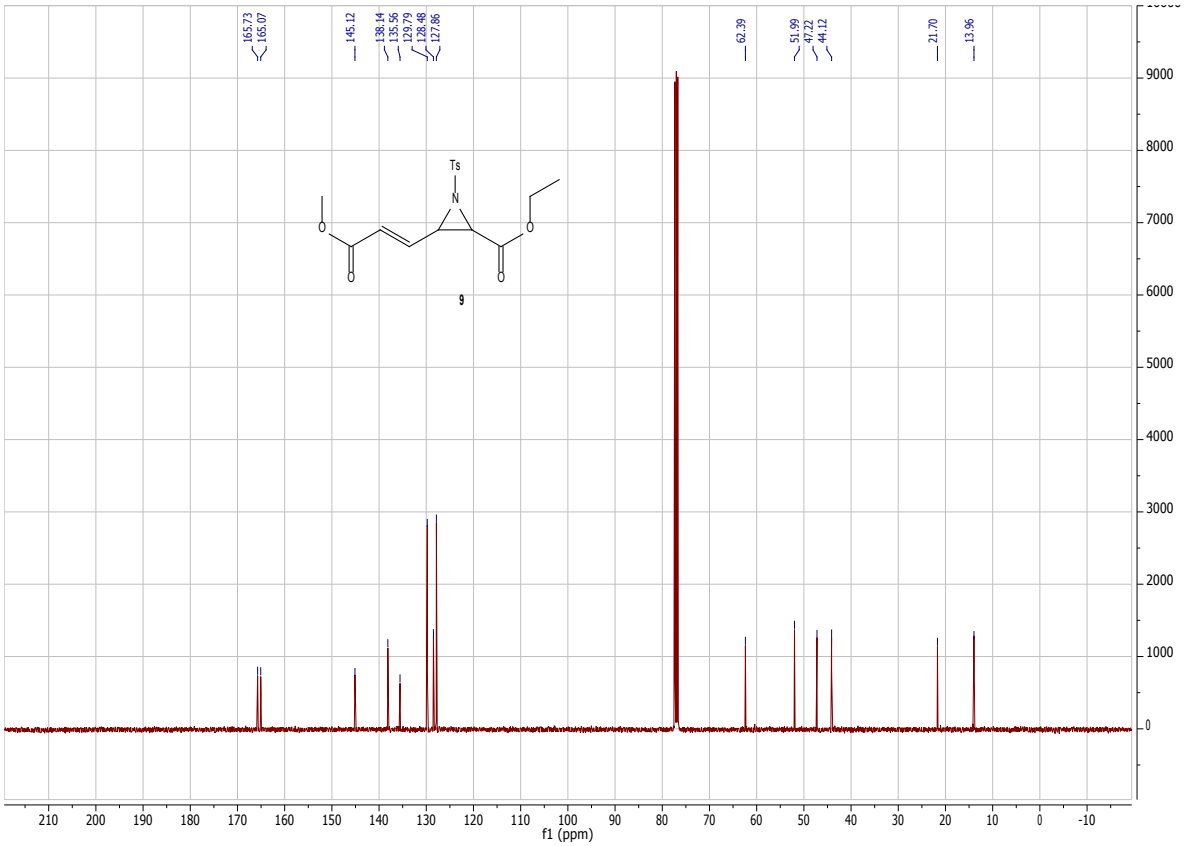

Boc
N
O
O
O
O
7
1.00
1.00
2.35
3.53
1.03
1.05
9.62
3.51
f1 (ppm)

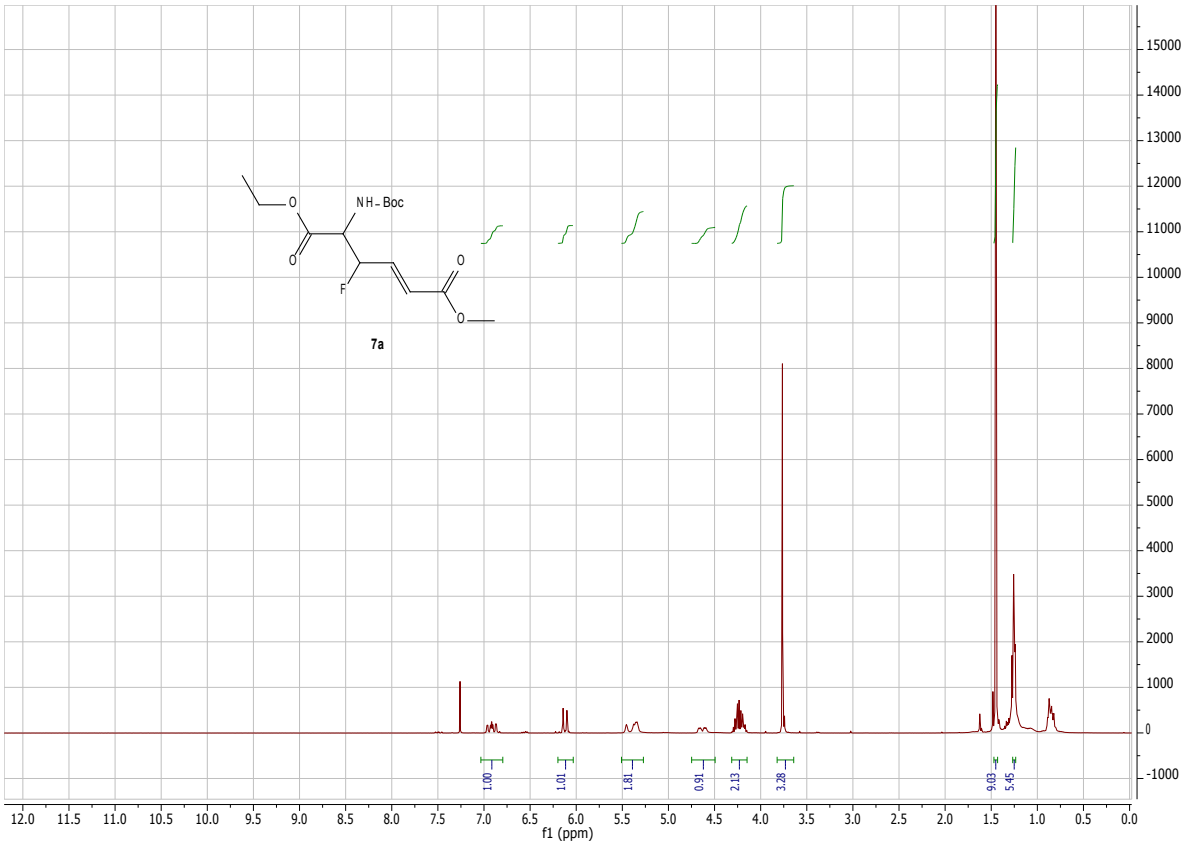

166.98
165.78
157.75
142.01
125.00
82.60
62.14
51.82
42.64
42.40
27.86
14.16
Boc
N
O
O
O
O
7
f1 (ppm)

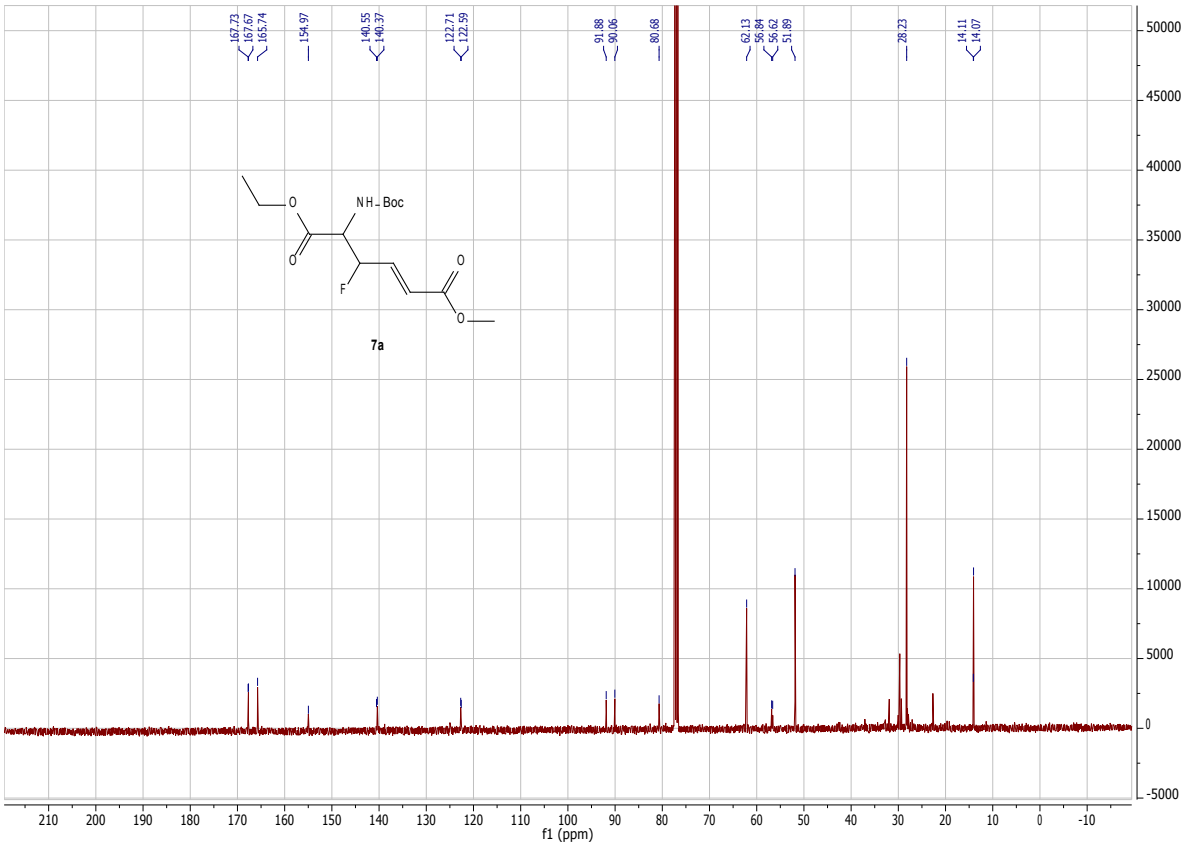

Cbz
N
O
O
O
O
8
5.59
1.00
1.00
2.28
2.34
3.46
1.04
1.09
3.37
f1 (ppm)

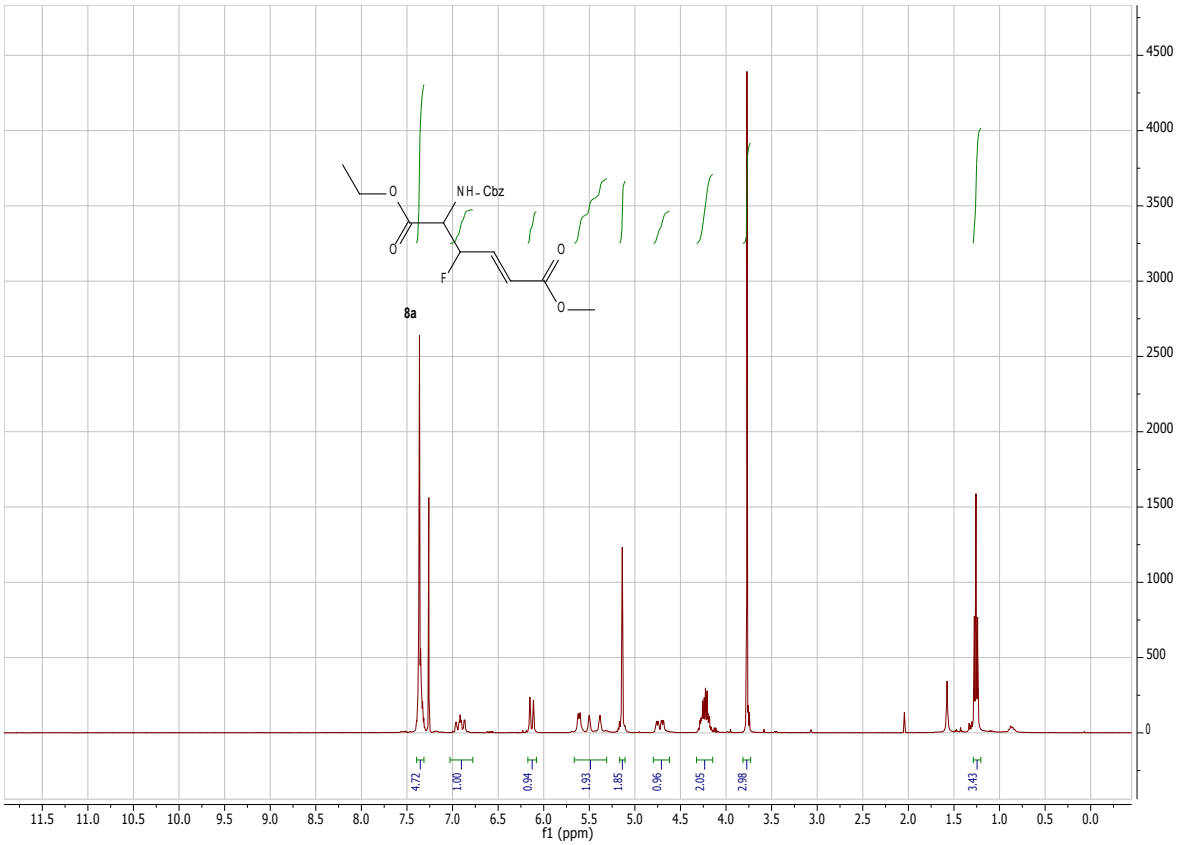

166.78
165.68
159.10
141.44
135.19
128.53
128.46
128.43
125.28
68.73
62.31
51.84
42.66
42.42
14.03
Cbz
N
O
O
O
O
8
f1 (ppm)

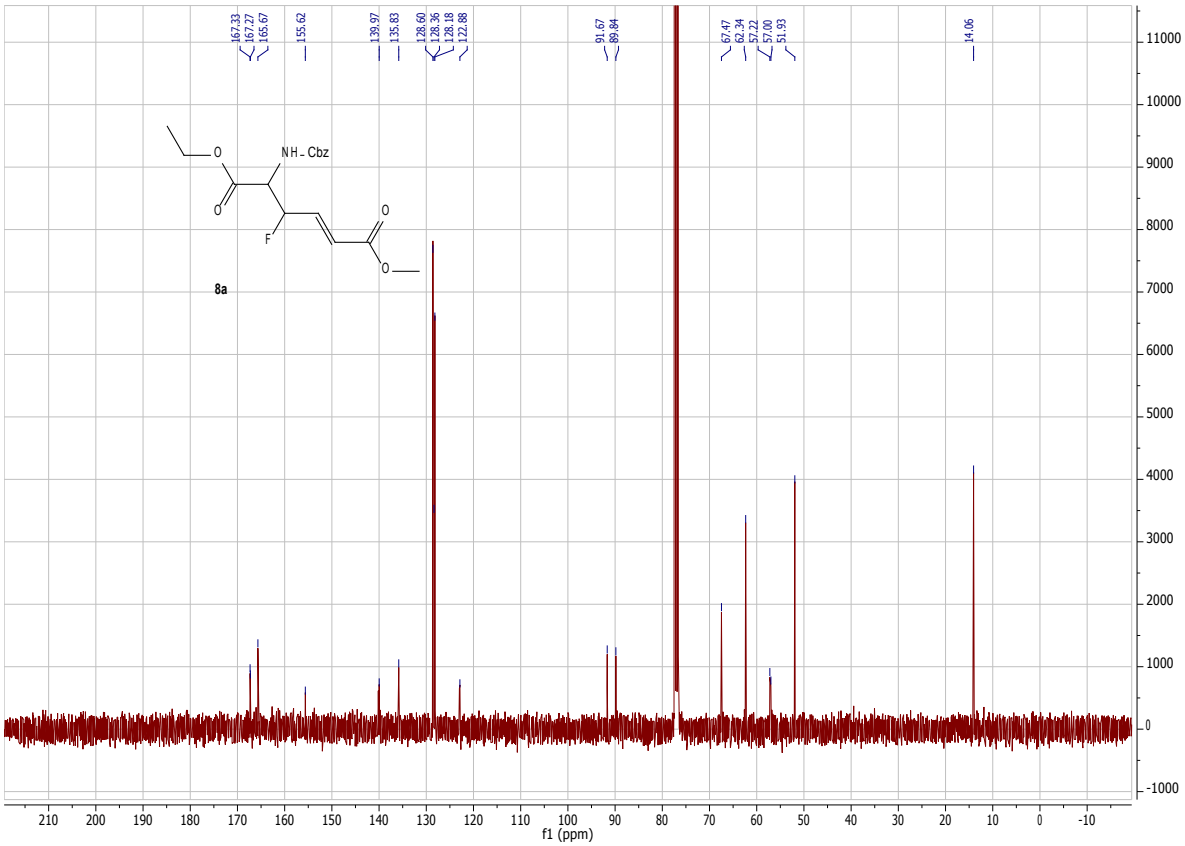

Ts
N
O
O
O
O
9
2.00
2.04
1.00
1.04
2.11
3.13
2.11
3.11
3.43
f1 (ppm)

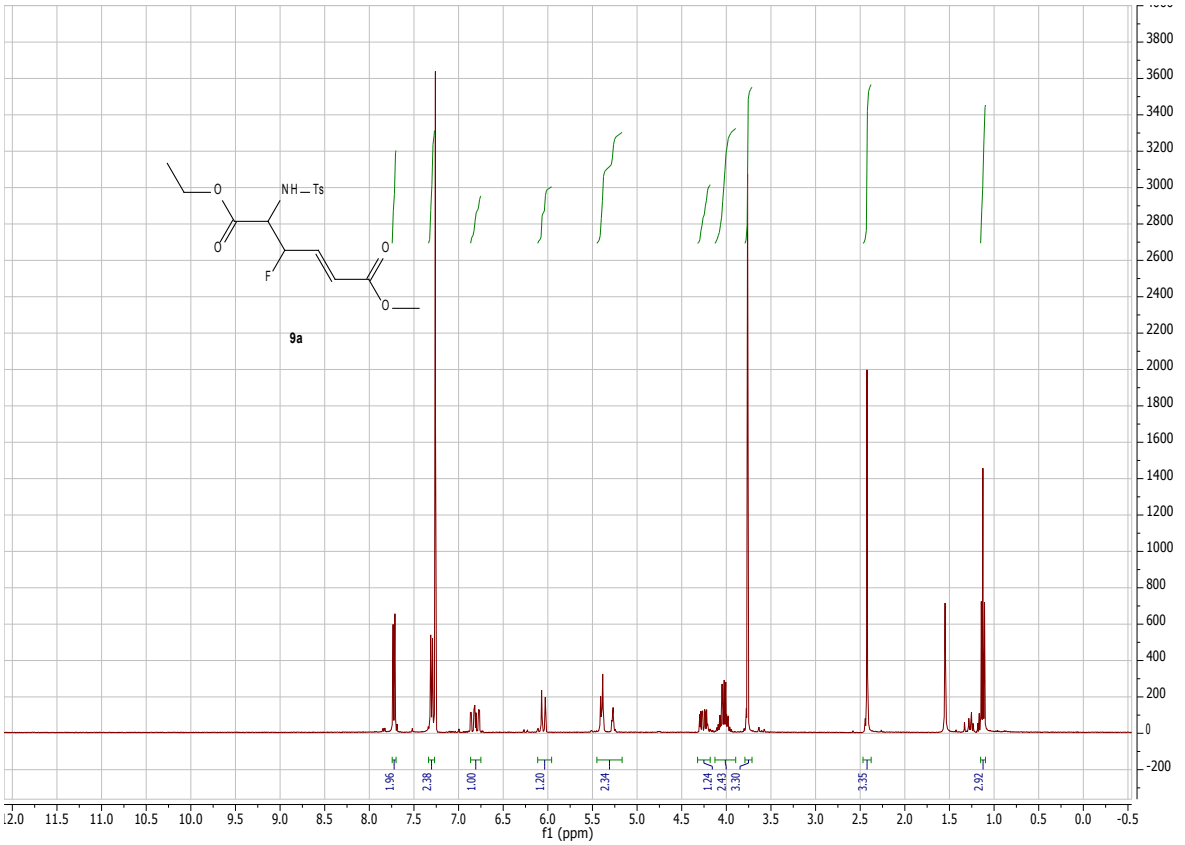

165.73
165.07
145.12
138.14
135.56
129.79
128.48
127.86
62.39
51.99
47.22
44.12
21.70
13.96
Ts
N
O
O
O
O
9
f1 (ppm)

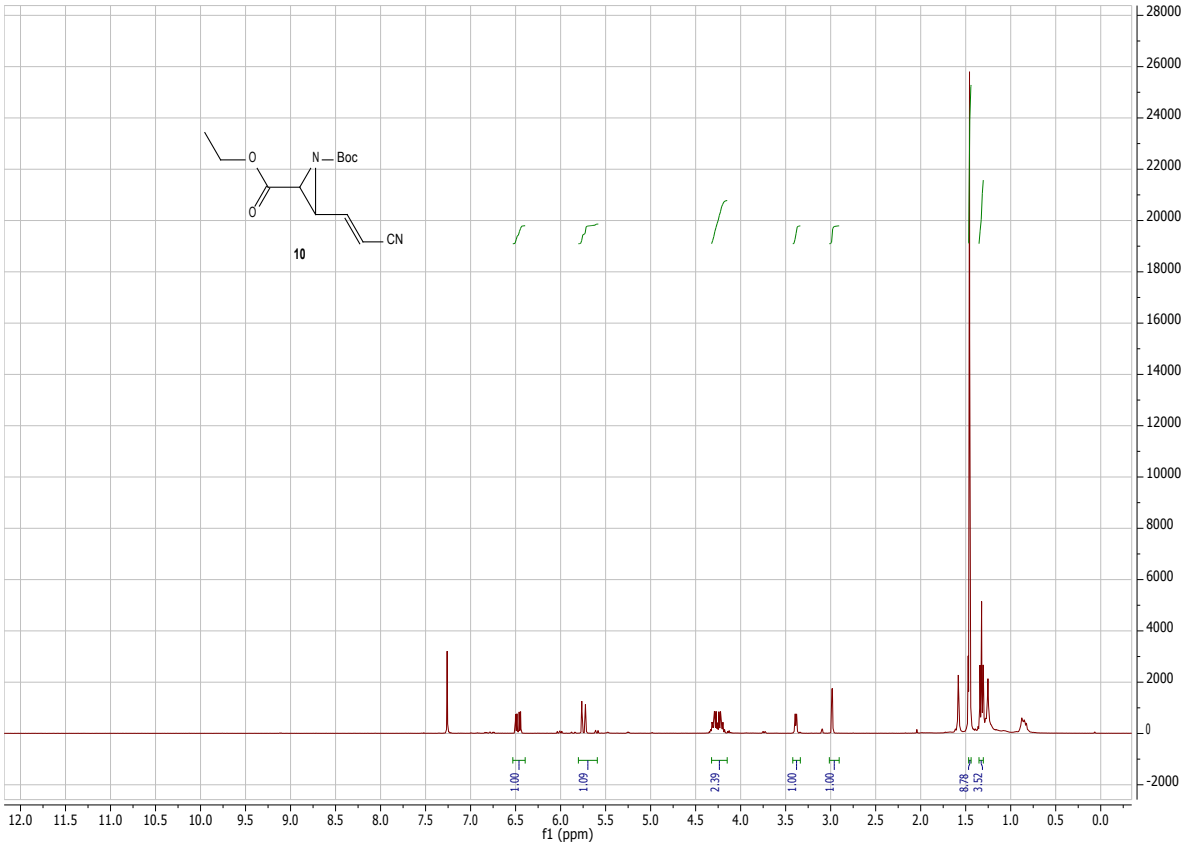

NH-Boc
O
O
F
O
O
7a
1.00
1.01
1.81
0.91
2.13
3.28
9.03
5.45
f1 (ppm)

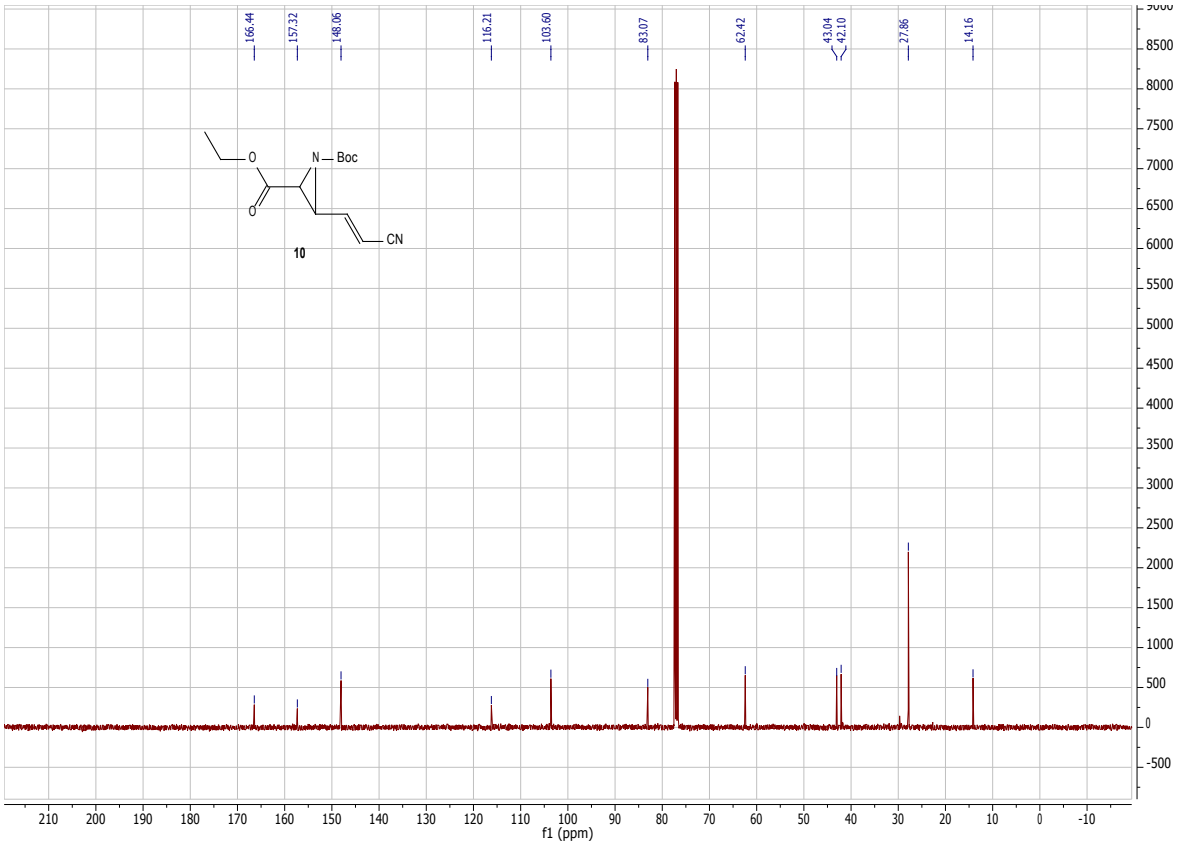

167.73
167.67
165.74
154.97
140.55
140.37
122.71
122.59
91.88
90.06
80.68
62.13
56.84
56.62
51.89
28.23
14.11
14.07
NH-Boc
O
O
F
O
O
7a
f1 (ppm)

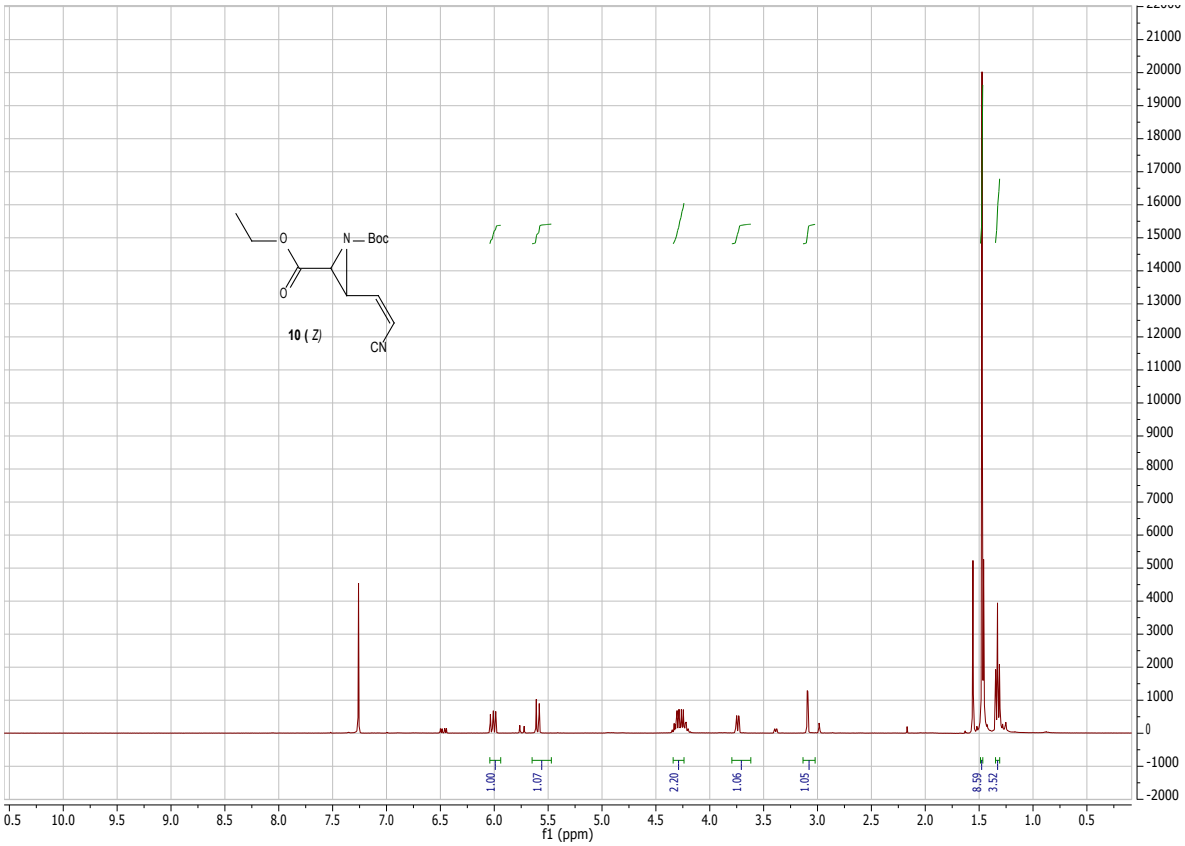

NH - Cbz
O
O
F
O
O
8a
4.72
1.00
0.94
1.93
1.85
0.96
2.05
2.98
3.43
f1 (ppm)

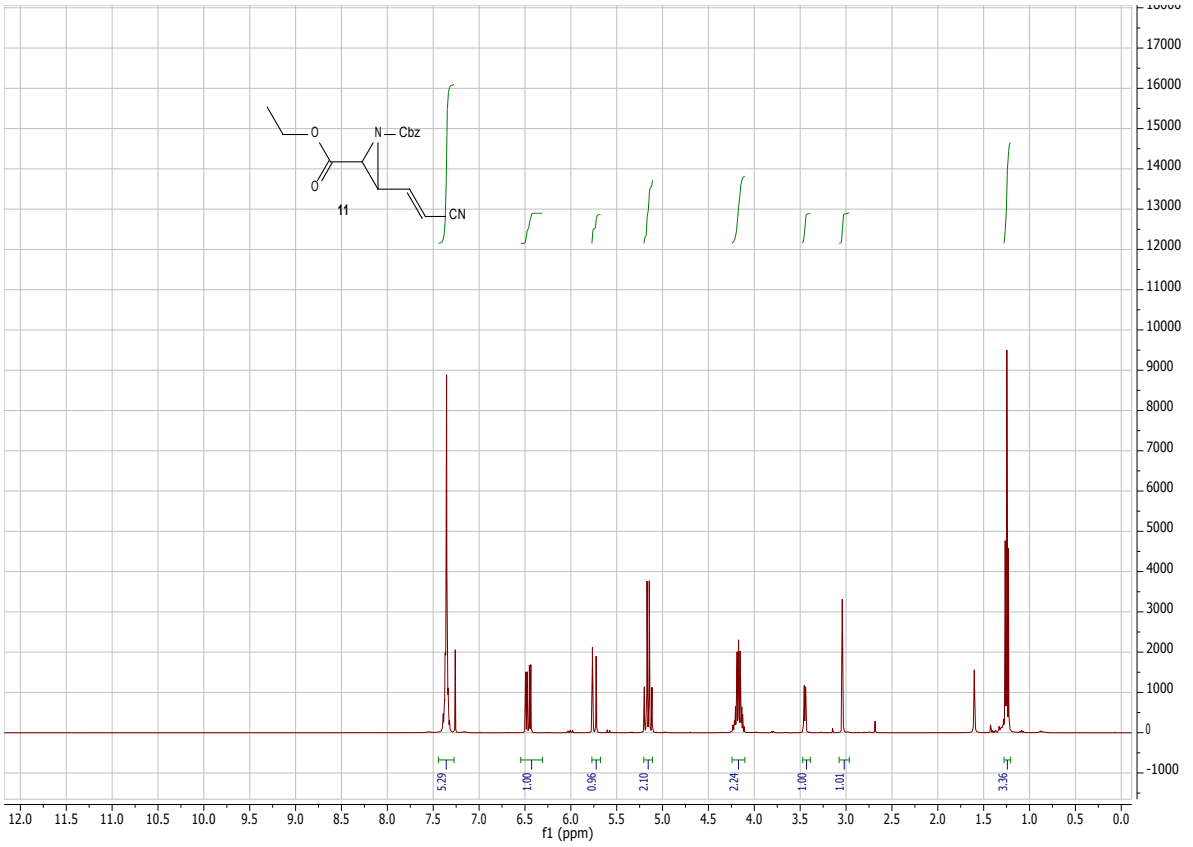

167.33
167.27
165.67
155.62
139.97
135.83
128.60
128.36
128.18
122.88
91.67
89.84
67.47
62.34
57.22
57.00
51.93
14.06
NH - Cbz
O
O
F
O
O
8a
f1 (ppm)

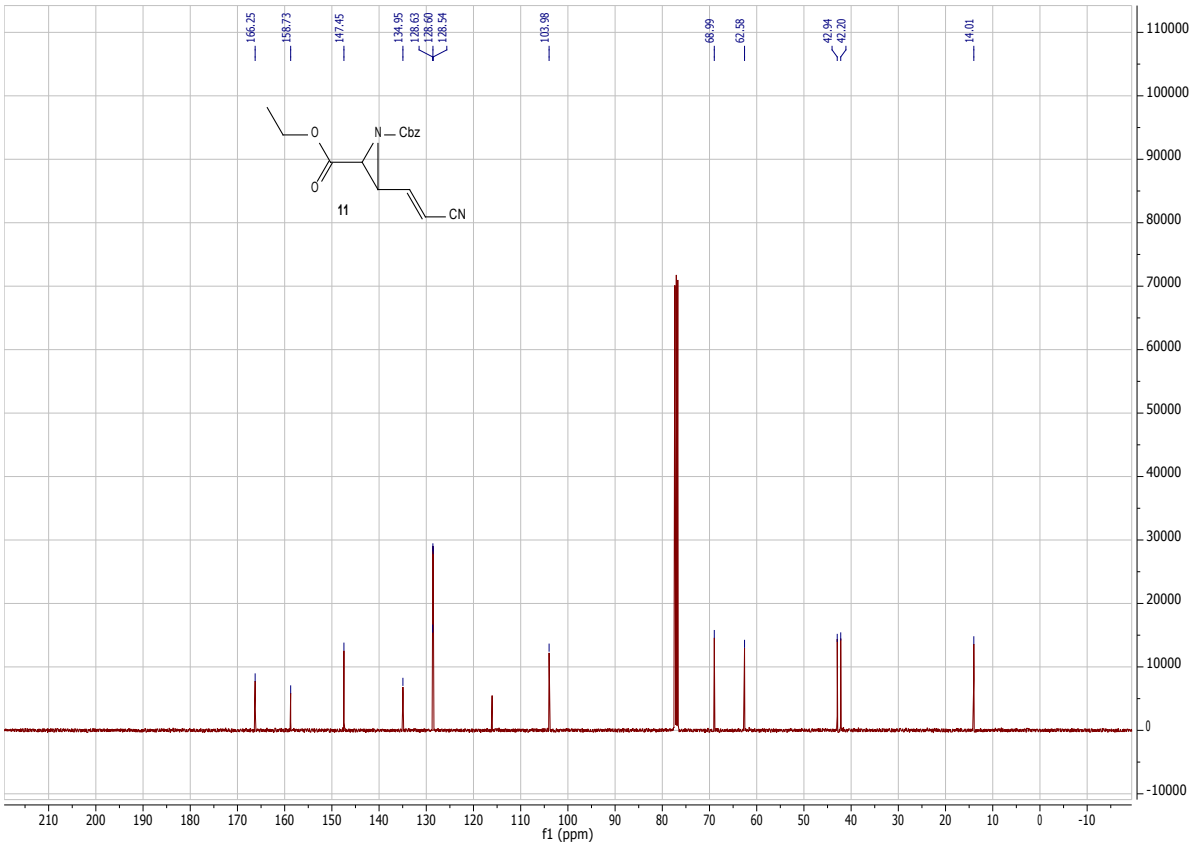

NH—Ts
O
O
F
O
O
9a
1.96
2.38
1.00
1.20
2.34
1.24
2.43
3.30
3.35
2.92
f1 (ppm)

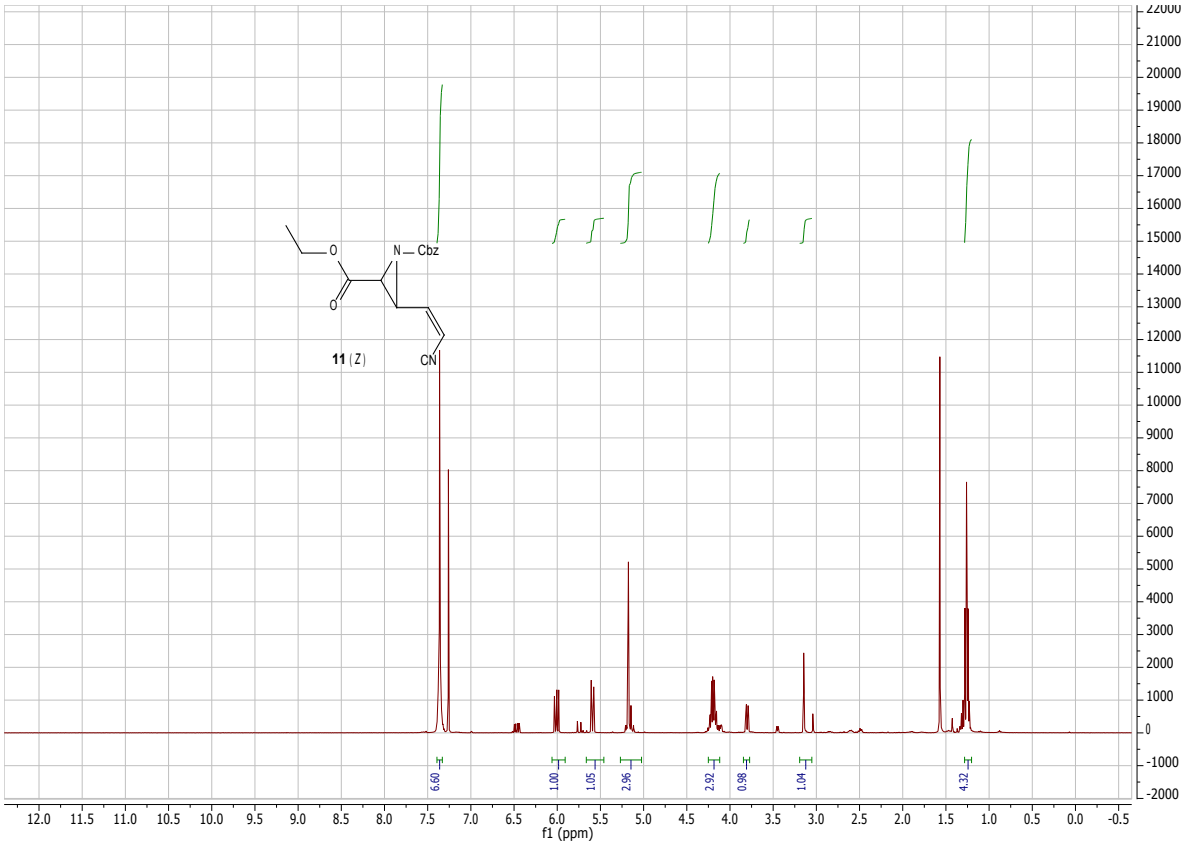

N—Boc
O
O
CN
10
1.00
1.09
2.39
1.00
1.00
8.78
3.52
f1 (ppm)

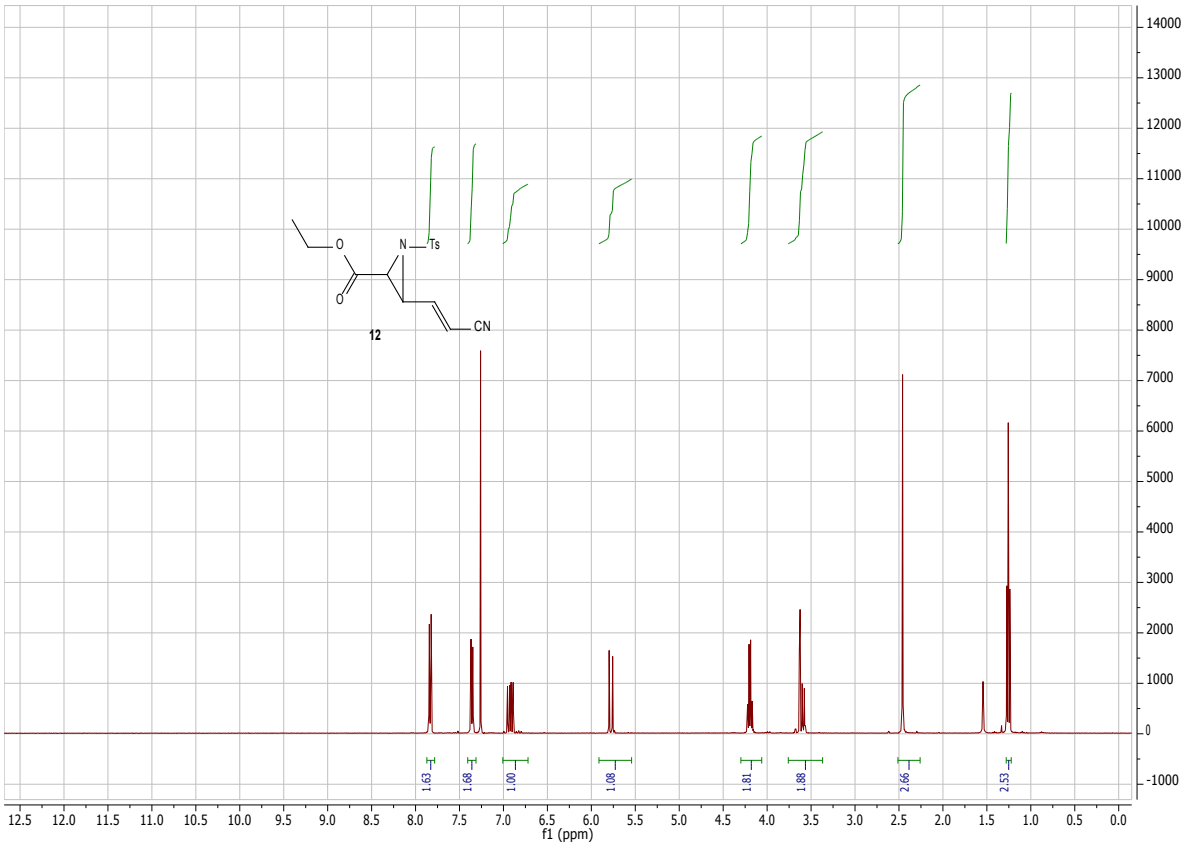

166.44
157.32
148.06
116.21
103.60
83.07
62.42
43.04
42.10
27.86
14.16
O
N — Boc
O
CN
10
f1 (ppm)

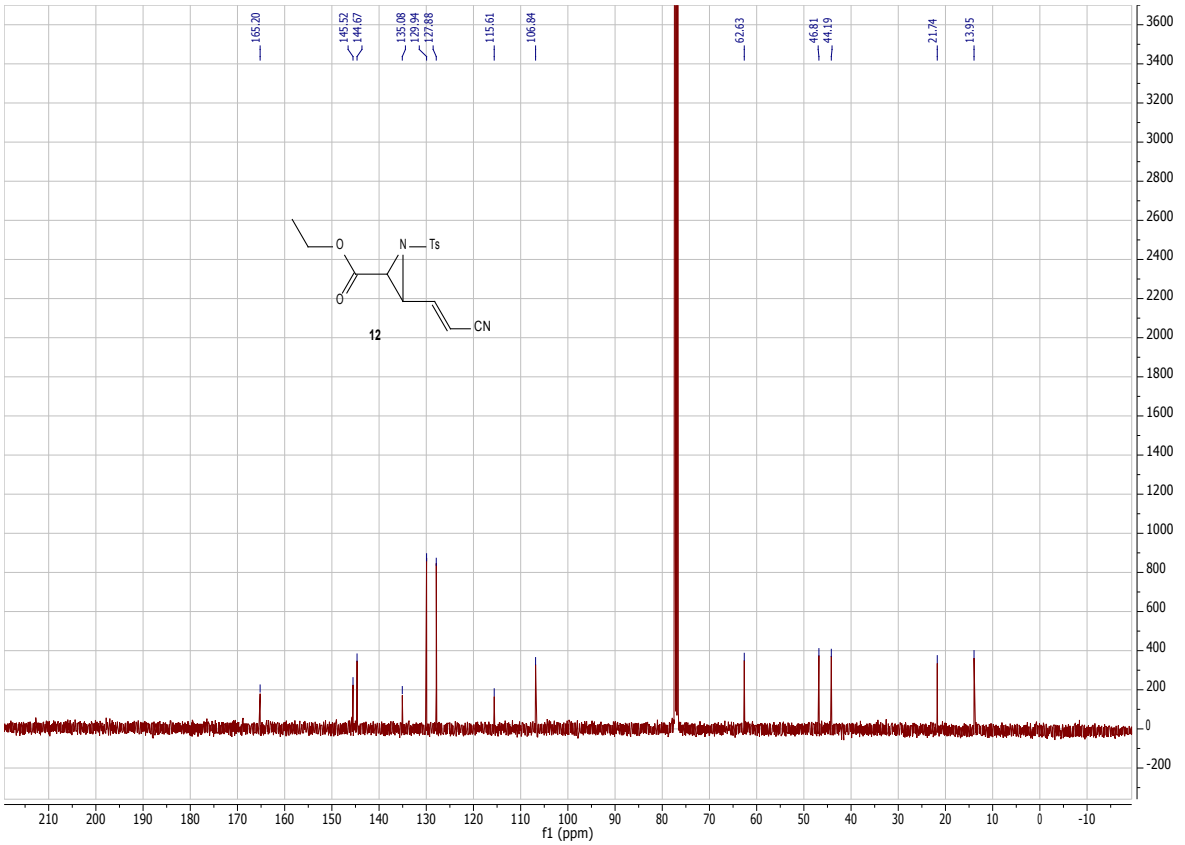

O
N — Boc
O
CN
10 (Z)
1.00
1.07
2.20
1.06
1.05
8.59
3.52
f1 (ppm)

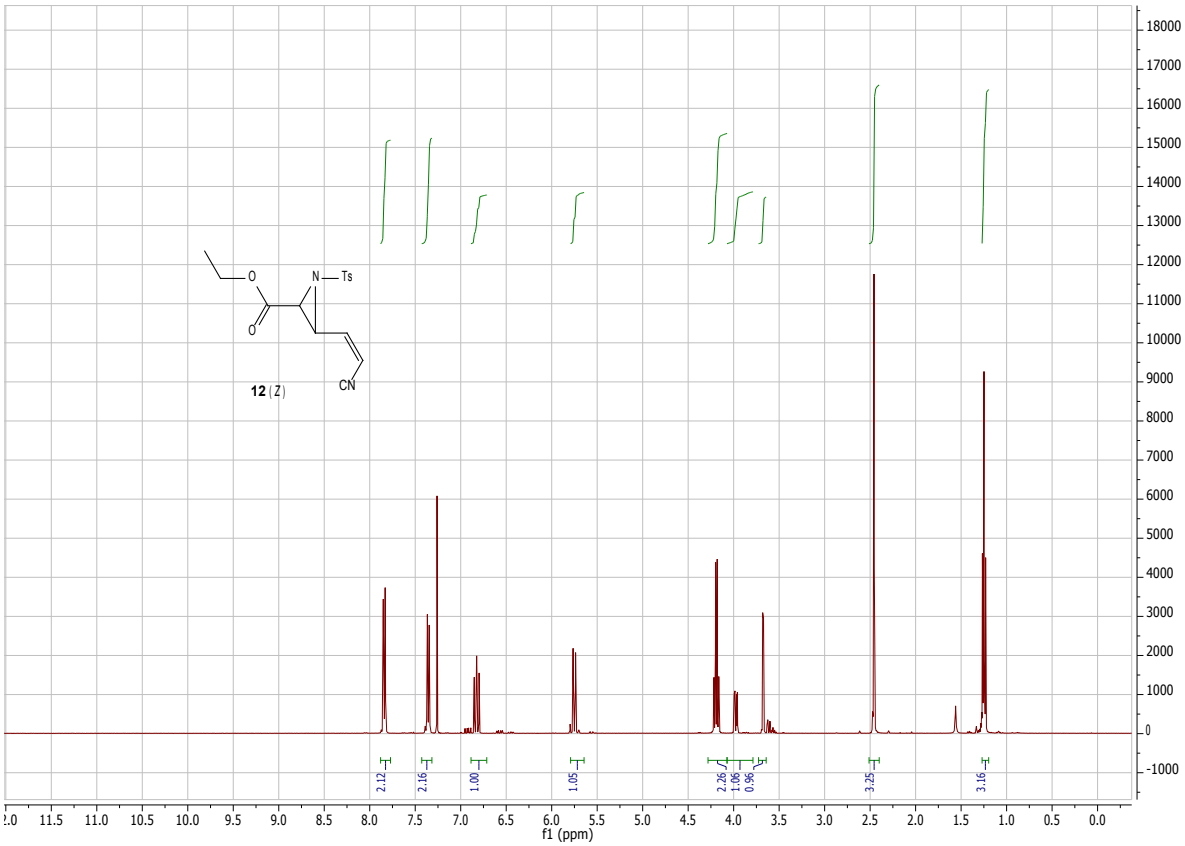

O
N — Cbz
O
11
CN
5.29
1.00
0.96
2.10
2.24
1.00
1.01
3.36
f1 (ppm)

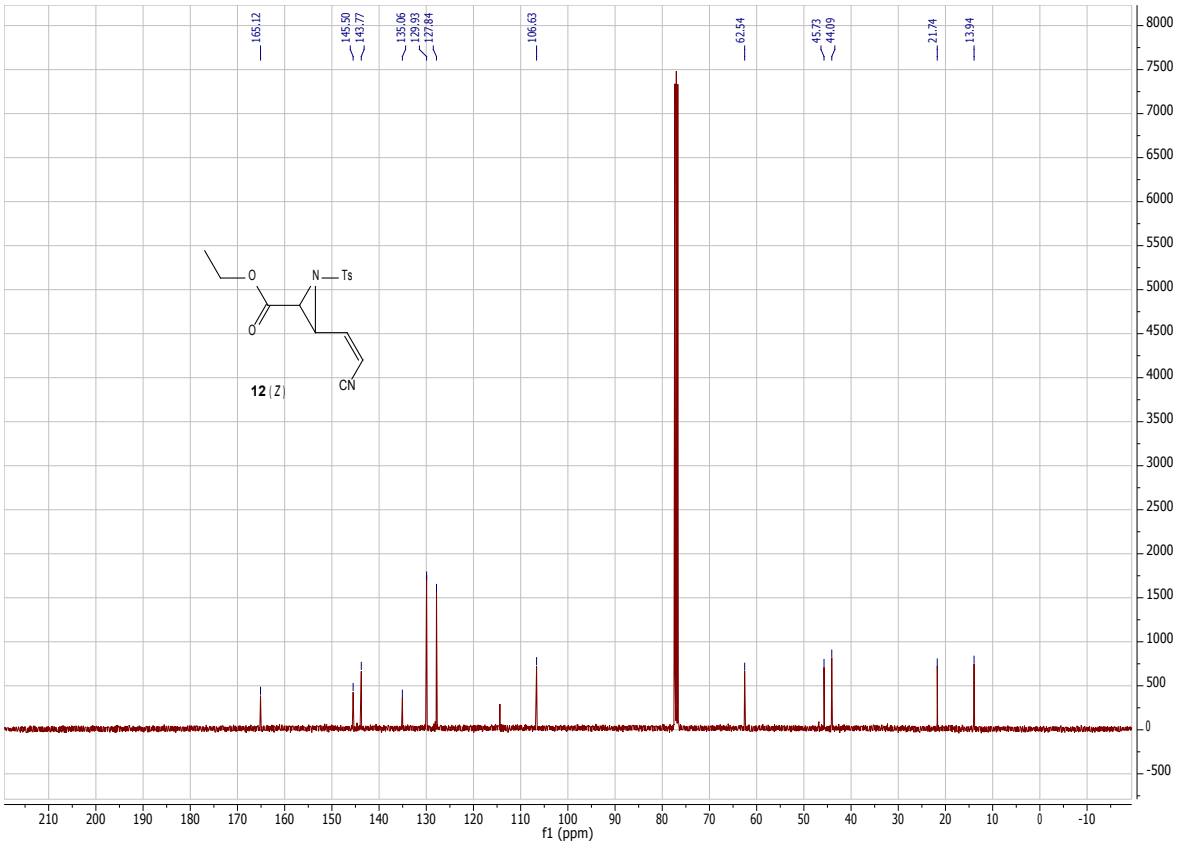

166.25
158.73
147.45
134.95
128.63
128.60
128.54
103.98
68.99
62.58
42.94
42.20
14.01
O
N — Cbz
O
11
CN
f1 (ppm)

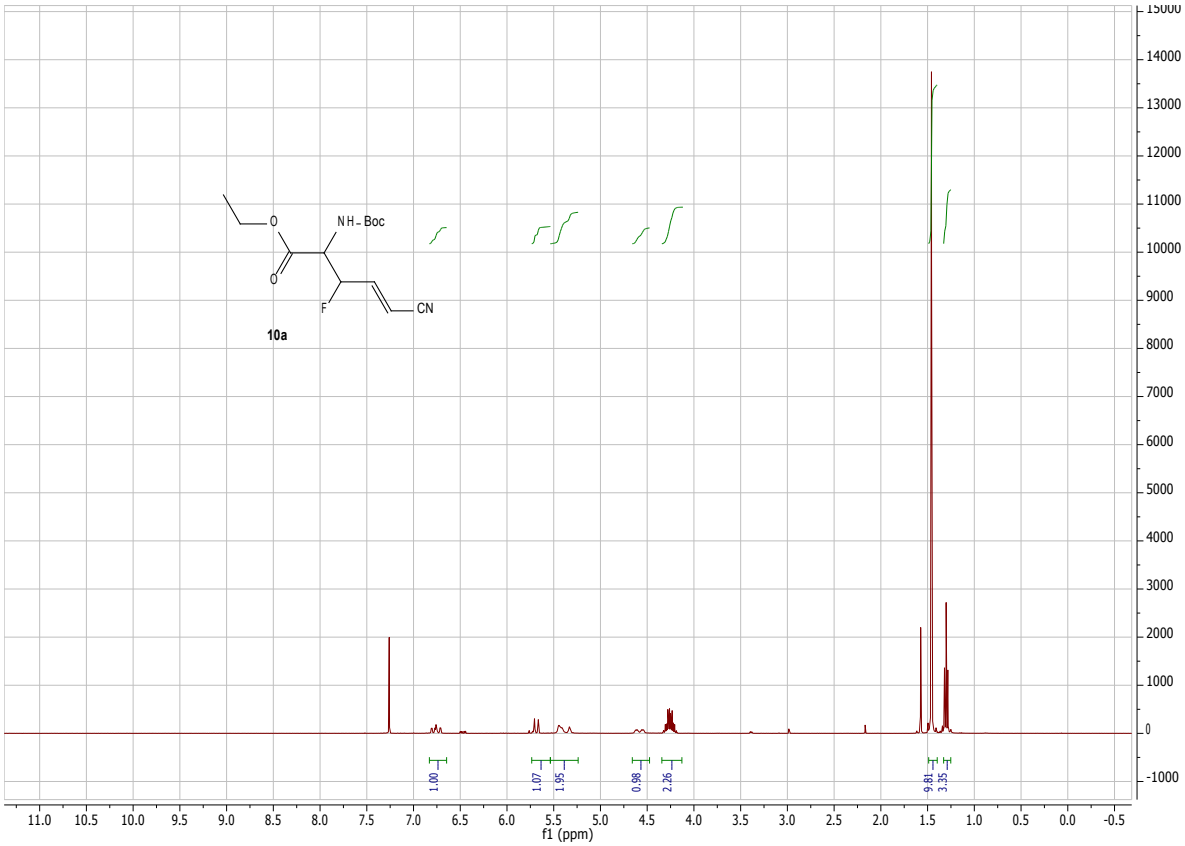

O
N — Cbz
O
11 (Z)
CN
6.60
1.00
1.05
2.96
2.92
0.98
1.04
4.32
f1 (ppm)

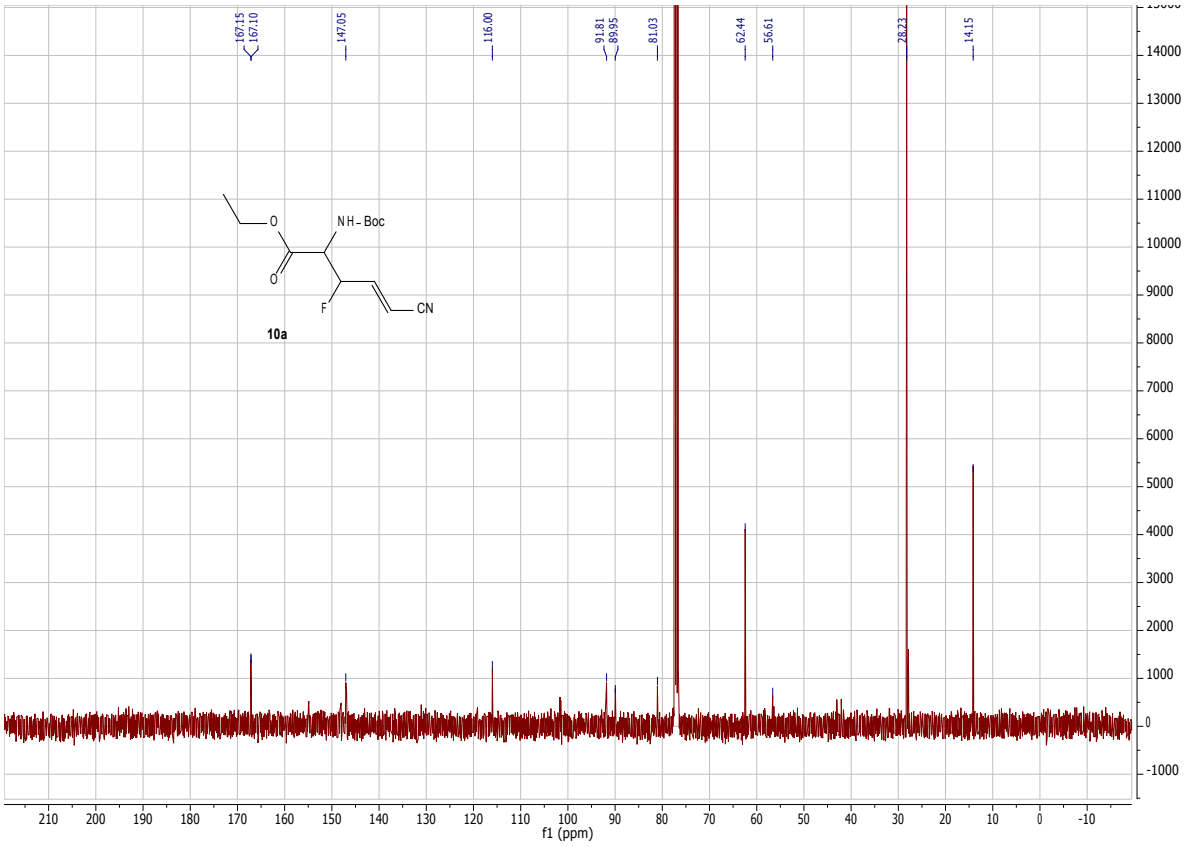

O
N — Ts
O
12
CN
1.63
1.68
1.00
1.08
1.81
1.88
2.66
2.53
f1 (ppm)

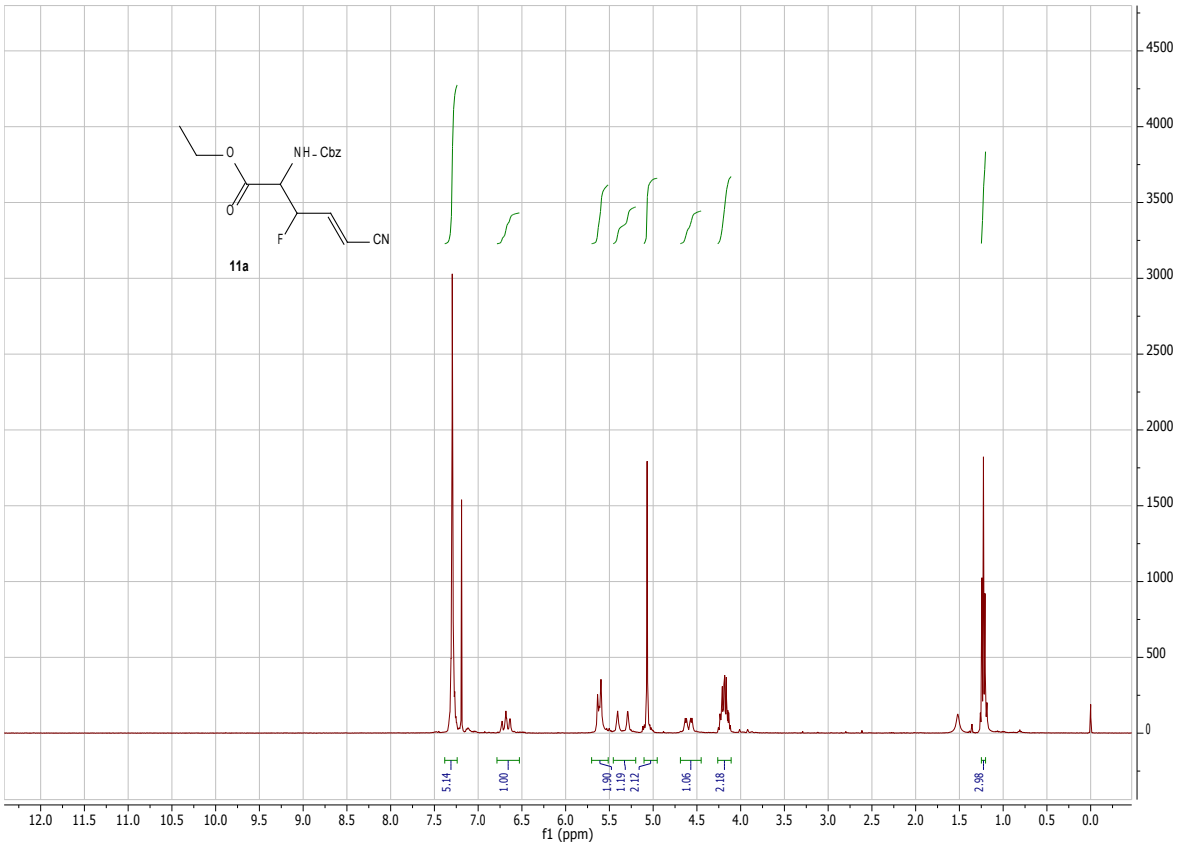

165.20
145.52
144.67
135.08
129.94
127.88
115.61
106.84
62.63
46.81
44.19
21.74
13.95
O
N
Ts
O
CN
12
f1 (ppm)

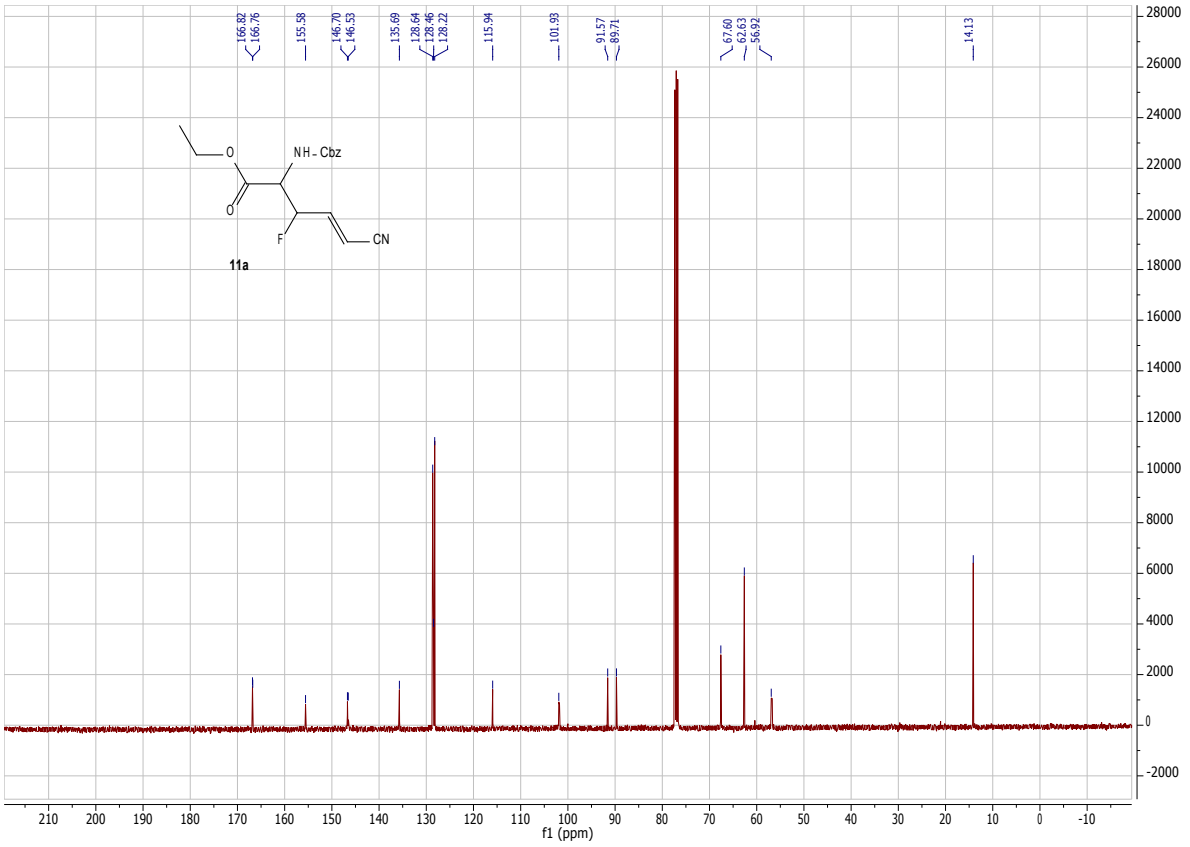

O
N
Ts
O
CN
12 (Z)
2.12
2.16
1.00
1.05
2.26
1.06
0.96
3.25
3.16
f1 (ppm)

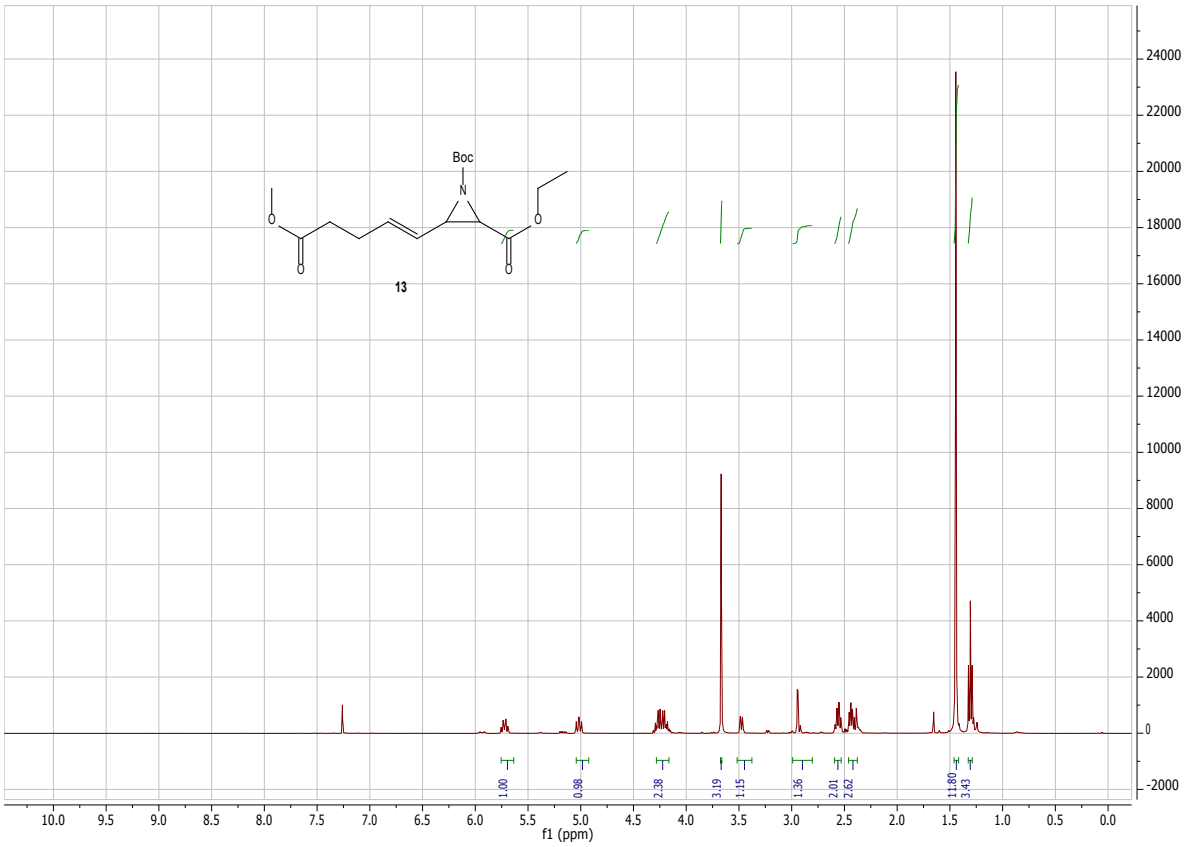

165.12
145.50
143.77
135.06
129.93
127.84
106.63
62.54
45.73
44.09
21.74
13.94
O
N
Ts
O
CN
12 (Z)
f1 (ppm)

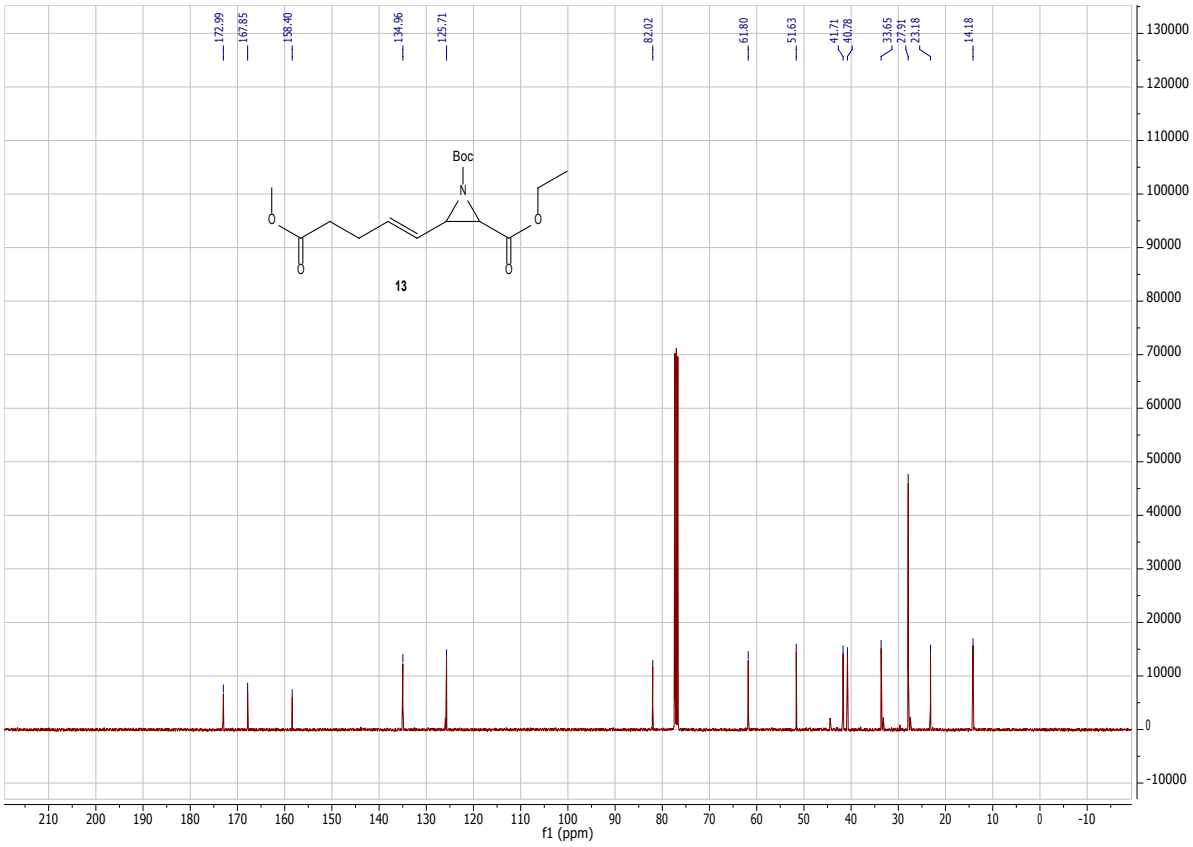

O
NH-Boc
O
F
CN
10a
1.00
1.07
1.95
0.98
2.26
9.81
3.35
f1 (ppm)

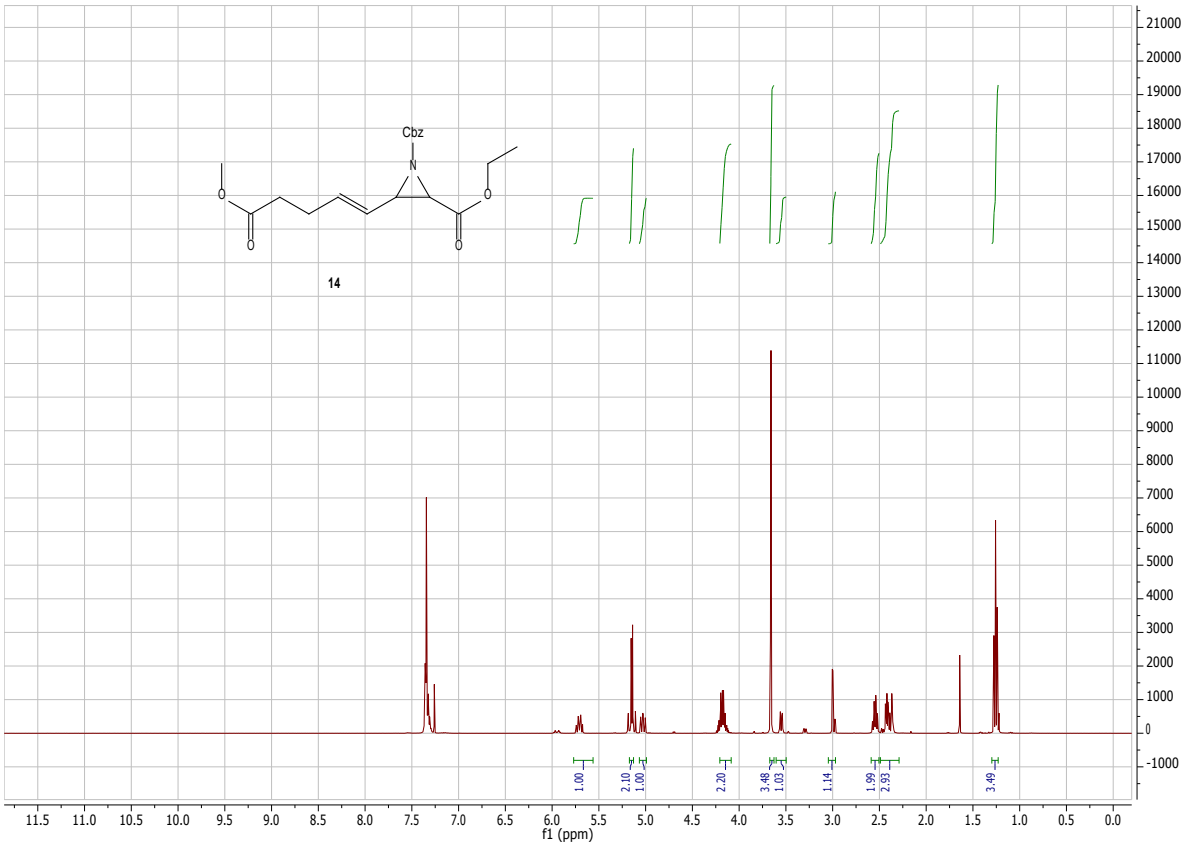

167.15
167.10
147.05
116.00
91.81
89.95
81.03
62.44
56.61
28.23
14.15
O
NH-Boc
O
F
CN
10a
f1 (ppm)

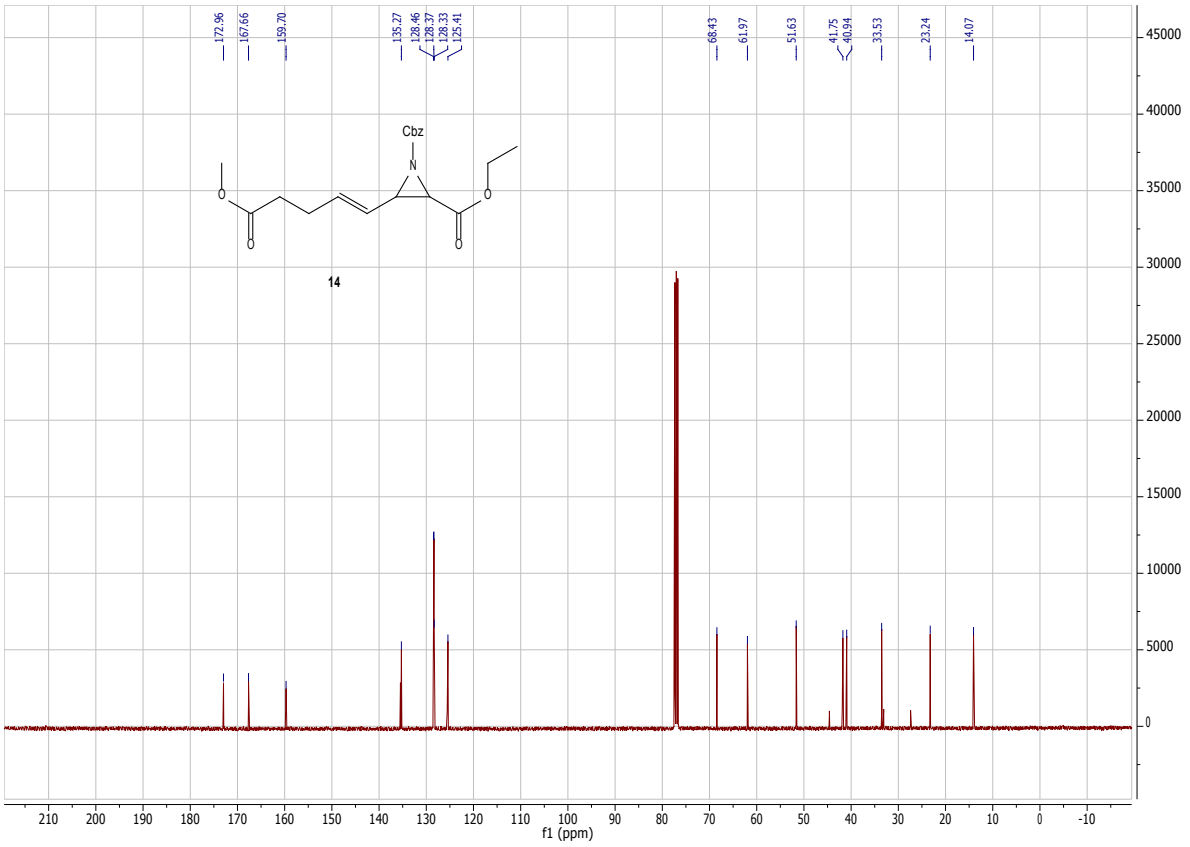

O
NH-Cbz
O
F
CN
11a
5.14
1.00
1.90
1.19
2.12
1.06
2.18
2.98
f1 (ppm)

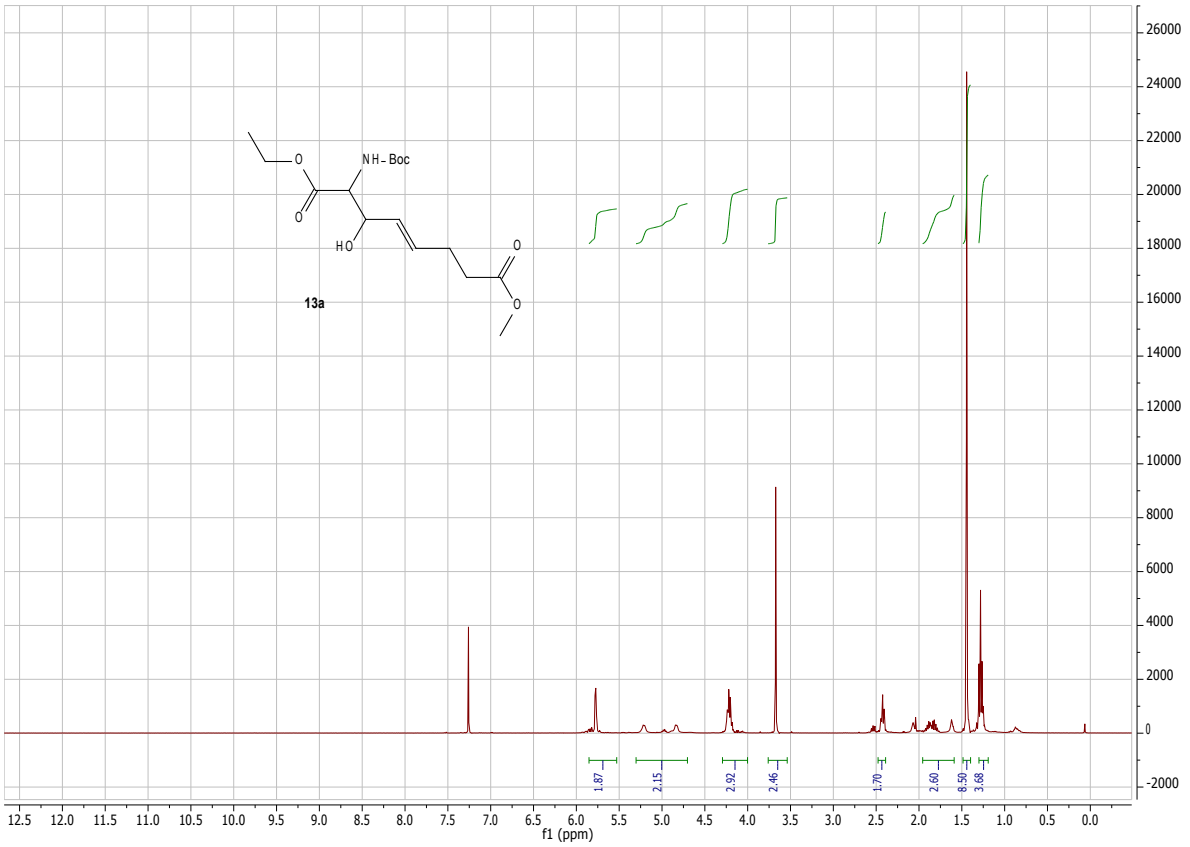

166.82
166.76
155.58
146.70
146.53
135.69
128.64
128.46
128.22
115.94
101.93
91.57
89.71
67.60
62.63
56.92
14.13
O
NH-Cbz
O
F
CN
11a
f1 (ppm)

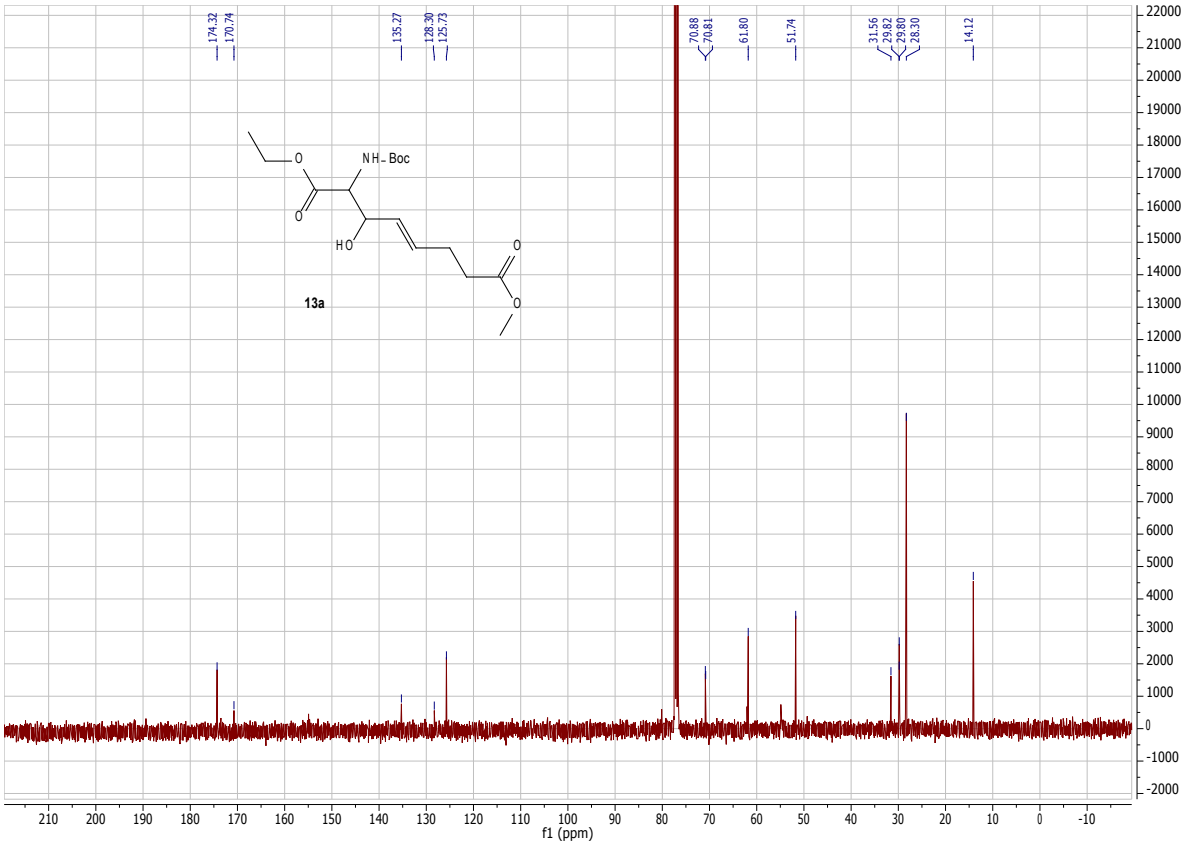

Boc
N
O
O
O
O
13
1.00
0.98
2.38
3.19
1.15
1.36
2.01
2.62
11.80
3.43
f1 (ppm)

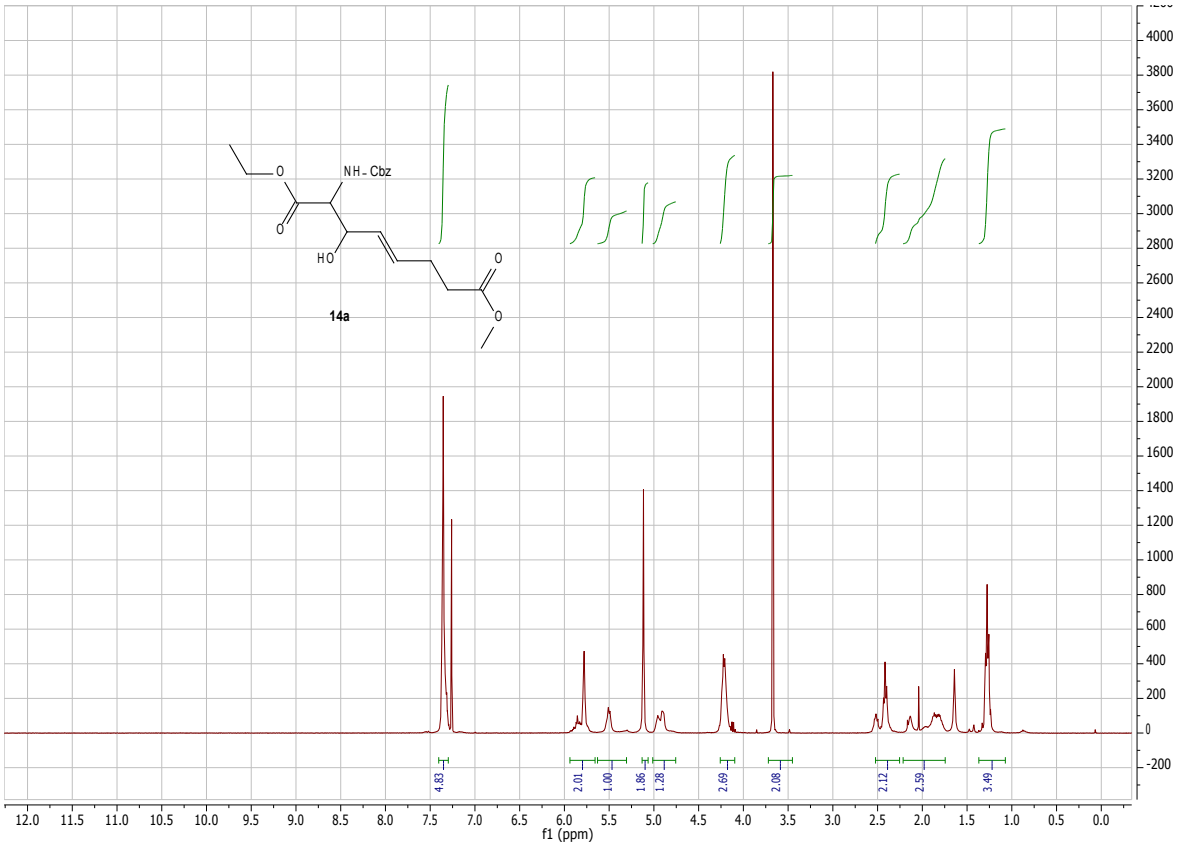

172.99
167.85
158.40
134.96
125.71
82.02
61.80
51.63
41.71
40.78
33.65
27.91
23.18
14.18
Boc
N
O
O
O
O
13
f1 (ppm)

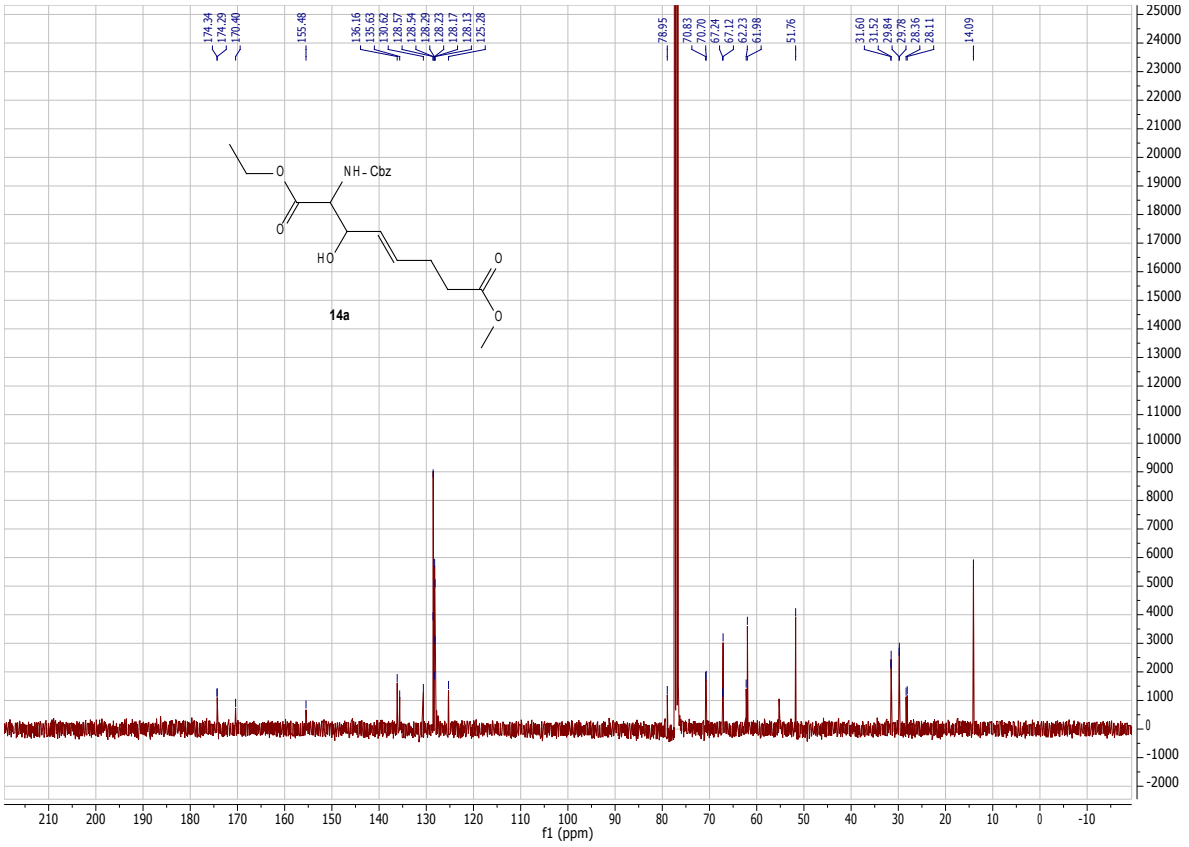

Cbz
N
O
O
O
O
14
1.00
2.10
1.00
2.20
3.48
1.03
1.14
1.99
2.93
3.49
f1 (ppm)

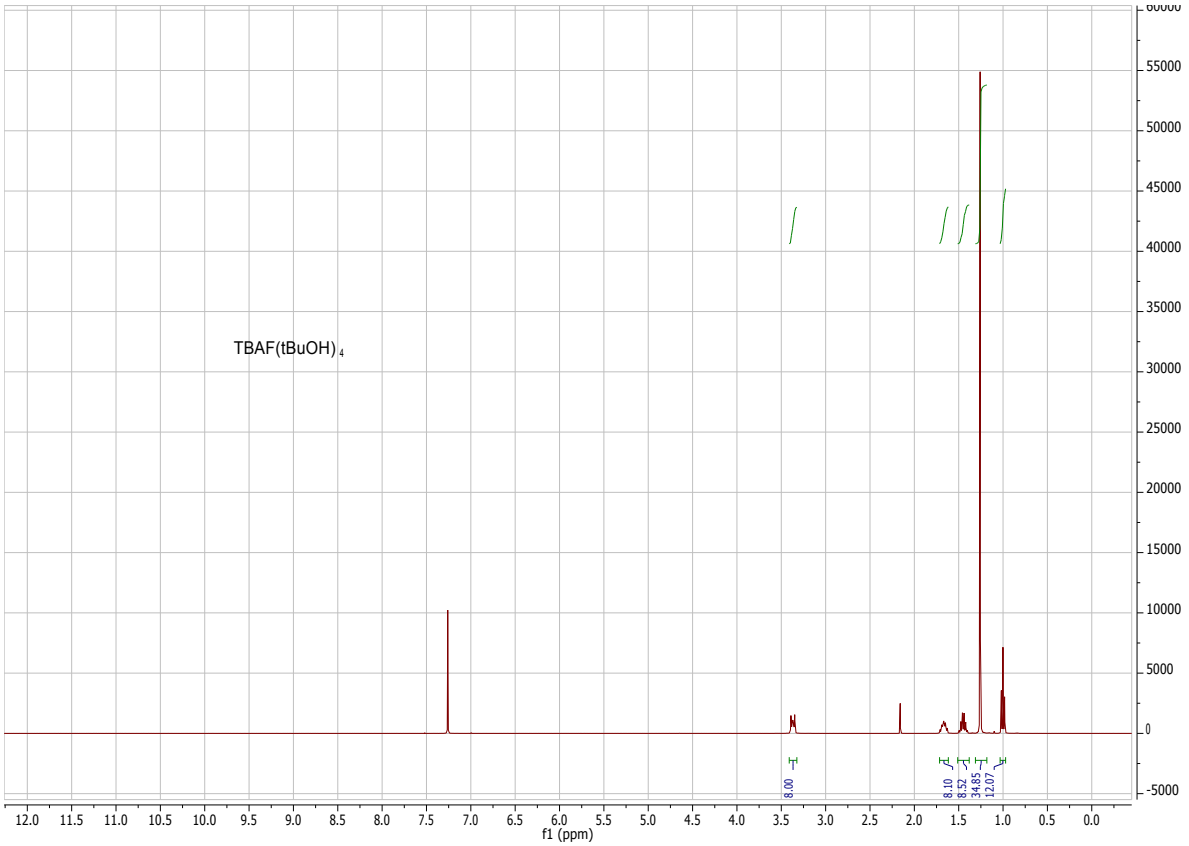

172.96
167.66
159.70
135.27
128.46
128.37
128.33
125.41
68.43
61.97
51.63
41.75
40.94
33.53
23.24
14.07
Cbz
N
O
O
O
O
14
f1 (ppm)

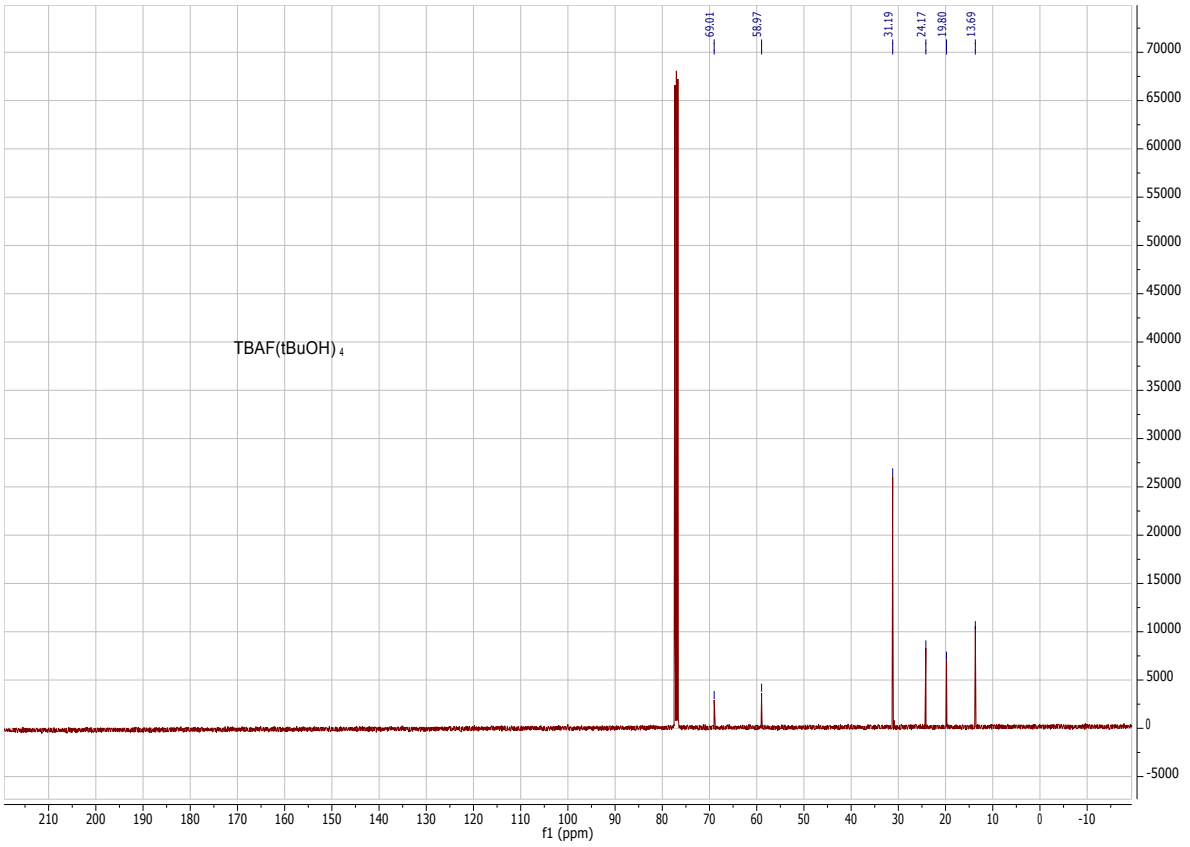

NH-Boc
O
O
HO
O
O
13a
1.87
2.15
2.92
2.46
1.70
2.60
8.50
3.68
f1 (ppm)


174.32
170.74
135.27
128.30
125.73
70.88
70.81
61.80
51.74
31.56
29.82
29.80
28.30
14.12
NH-Boc
HO
13a
f1 (ppm)


NH-Cbz
HO
14a
4.83
2.01
1.00
1.86
1.28
2.69
2.08
2.12
2.59
3.49
f1 (ppm)


174.34
174.29
170.40
155.48
136.16
135.63
130.62
128.57
128.54
128.29
128.23
128.17
128.13
125.28
78.95
70.83
70.70
67.24
67.12
62.23
61.98
51.76
31.60
31.52
29.84
29.78
28.36
28.11
14.09
NH - Cbz
HO
14a
f1 (ppm)


TBAF(tBuOH)4
8.00
8.10
8.52
34.85
12.07
f1 (ppm)



References

1. Alexander Breuning, Radim Vicik, Tanja Schirmeister, *Tetrahedron: Asymmetry.*, 2003**, 14**, 3301–3312 and references therein
2. Barrault, J.; Pouilloux, Y., *Catal. Today* **1997**, *37* (2), 137–153.
3. Andrew V. Mossine, Allen F. Brooks, Naoko Ichiishi, Katharina J. Makaravaga, Melani S. Sanford, Peter J. H. Scott, *Sci.Rep.* 2017**, 7**, 233
4. Olivier Josse, Daniel Labar, Benoit Georges, Vincent Gregoire, Jacqueline M B, *Bioorg & Med. Chem.,* 2001, **9**, 665-675