Supporting Information

Racemization-free peptide bond formation via 2-nitrobenzensulfonyl strategy for diastereoselective synthesis of (*Z*)-fluoroalkene peptidomimetics

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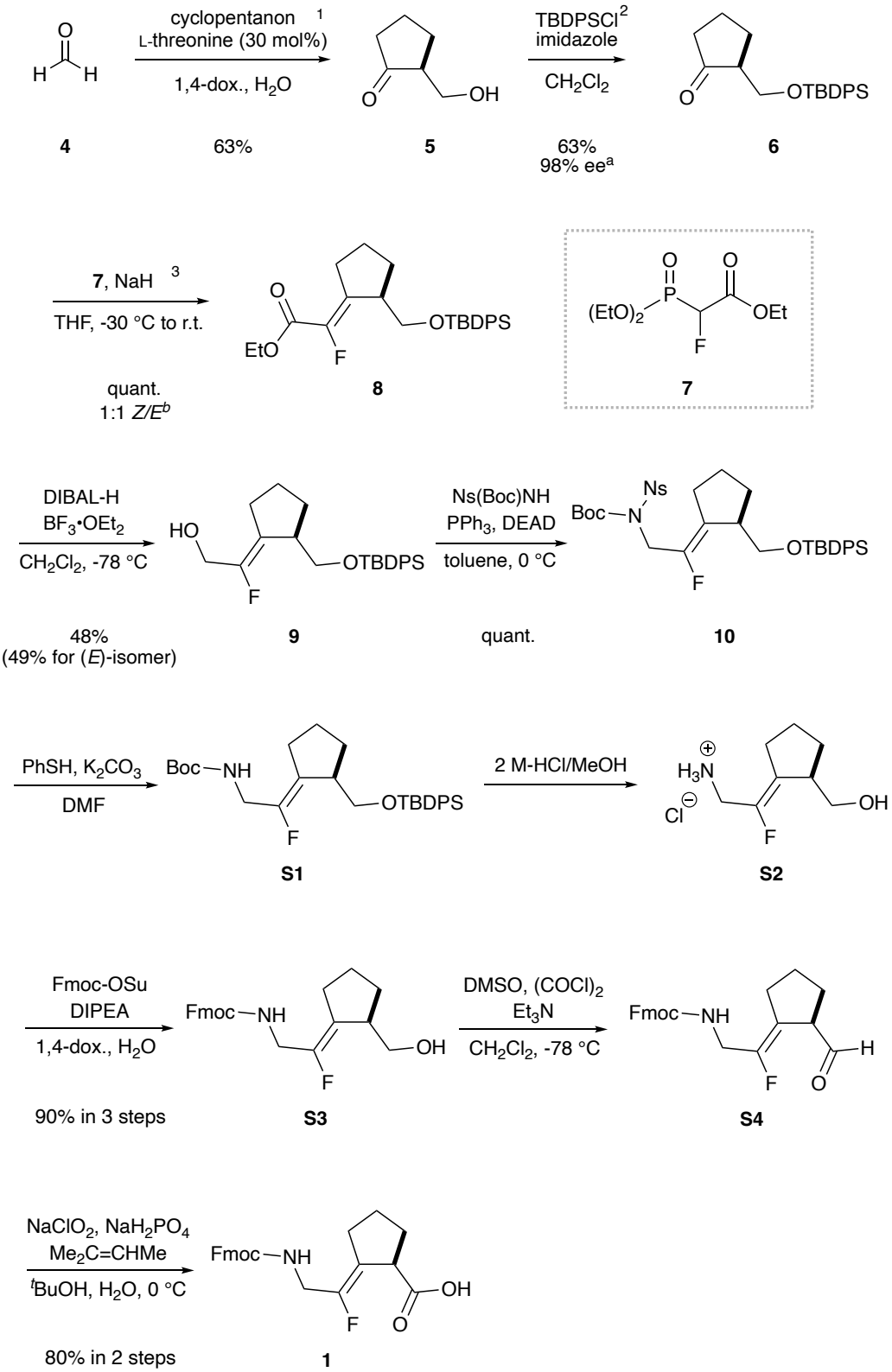
I. General information

General methods. All reactions utilizing air- or moisture-sensitive reagents were performed in dried glassware under an atmosphere of nitrogen, using commercially supplied solvents and reagents unless otherwise noted. An oil bath was used as the heat source for reactions that required heating. Thin-layer chromatography (TLC) was performed on Merck $60F_{254}$ precoated silica gel plates and was visualized by fluorescence quenching under UV light and by staining with phosphomolybdic acid, *p*-anisaldehyde, or ninhydrin, respectively. Flash column chromatography was carried out using silica gel PSQ60B (Fuji Silysia Chemical, Ltd.).

Characterization data. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) and ^{19}F NMR (376 MHz) spectra were recorded using a Bruker Biospin AVANCE III HD. Chemical shifts are reported in δ (ppm) relative to Me_4Si (in $CDCl_3$ for ^{1}H NMR and ^{13}C NMR) and FPh (in $CDCl_3$ for ^{19}F NMR) as an internal standard. Structural assignments were made with additional information from COSY and NOESY experiments. Infrared (IR) spectra were recorded on a JASCO FT/IR 6300 with the ATR method and are reported as wavenumbers (cm^{-1}). Low- and high-resolution mass spectra were recorded on a Bruker Daltonics compact (ESI-Q-TOF) spectrometer in the positive and negative detection mode. Optical rotations were measured on a JASCO DIP-polarimeter operating at the sodium D line with a 100 mm path length cell and were reported as follows: $[\alpha]_D$ (concentration (g/100 mL), solvent).

HPLC condition. For HPLC separations, a Cosmosil $5C_{18}$-AR-II analytical column (Nacalai Tesque, 4.6 × 250 mm, flow rate 1.0 mL min^{-1}) and a Cosmosil $5C_{18}$-AR-II analytical column (Nacalai Tesque, 20 × 250 mm, flow rate 8.0 mL min^{-1}) were employed, and eluting products were detected by UV at 220 nm. A solvent system consisting of 0.1% TFA aqueous solution (v/v, solvent A) and 0.1% TFA in MeCN (v/v, solvent B) was used for HPLC elution.

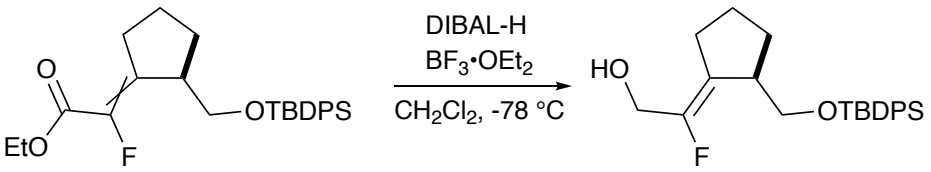
II. Synthetic procedure of Fmoc-protected FADI (1)



Scheme S1. Synthesis of Fmoc-protected FADI (**1**).

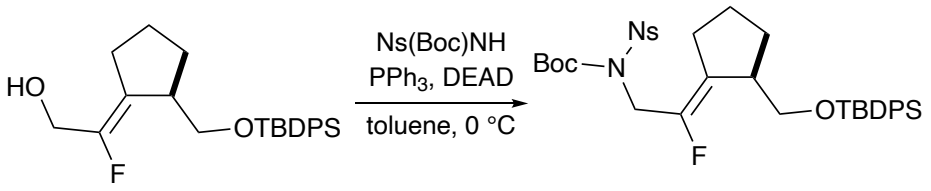
a. Enantiomeric excess (*ee*) was determined by chiral-phase HPLC (Daicel-IC, Hexane/2-PrOH = 100:1, flow rate 0.5 mL/min, λ=254 nm); t_R = 12.41 (*R*), 15.80 (*S*) min.

b. *E/Z* ratio was determined by ^{1}H NMR analysis of the crude sample.



8 48% (49% for (*E*)-isomer) **9**

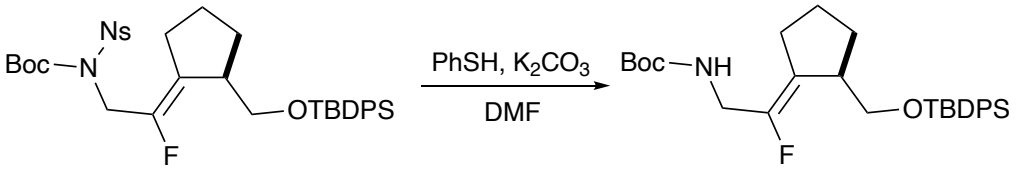
(*R*,*Z*)-2-(2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)cyclopentylidene)-2-fluoroethan-1-ol (9): To a solution of geometrical mixture of α,β-unsaturated ester **8**[3] (3.66 g, 8.30 mmol, 1:1 *E*/*Z*) and $BF_3 \cdot OEt_2$ (4.17 mL, 33.2 mmol) in CH_2Cl_2 (27.7 mL) was added dropwise a solution of DIBAL-H in toluene (1.00 M, 49.8 mL, 49.8 mmol) at −78 °C under nitrogen, and the mixture was stirred at −78 °C for 4 h. The reaction was quenched by MeOH (1.34 mL, 33.2 mmol) and saturated aqueous solution of Rochelle salt. The reaction mixture was extracted with ethyl acetate, washed with brine, and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with Hex.-EtOAc (9:1) gave the title compound **9** as a colorless oil (1.59 g, 48%): $[\alpha]_D^{20.9}$ = -41.3 (*c* 1.11, $CHCl_3$); IR (ATR) ν 3305 (OH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70−7.61 (m, 4H), 7.46−7.32 (m, 6H), 4.24−4.08 (m, 5H), 3.85−3.77 (m, 1H), 3.58−3.49 (m, 1H), 3.10−3.01 (m, 1H), 2.32−2.19 (m, 2H), 1.97−1.89 (m, 1H), 1.83−1.78 (m, 1H), 1.71−1.66 (m, 1H), 1.64−1.54 (m, 2H), 1.05 (s, 9H); $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$) δ 151.3 (d, *J* = 243.9 Hz), 135.6 (4C), 133.9 (2C), 129.5 (2C), 127.6 (4C), 123.2 (d, *J* = 15.0 Hz), 64.5, 59.6 (d, *J* = 30.3 Hz), 43.2, 29.3, 28.5, 26.9 (3C), 24.7, 19.3; $^{19}F\{^1H\}$ (376 MHz, $CDCl_3$) δ -121.0 (t, *J* = 21.1 Hz); HRMS (ESI), *m/z* calcd for $C_{24}H_{31}FNaO_2Si$ $[M+Na]^+$ 421.1975, found 421.1972.



9 quant. **10**

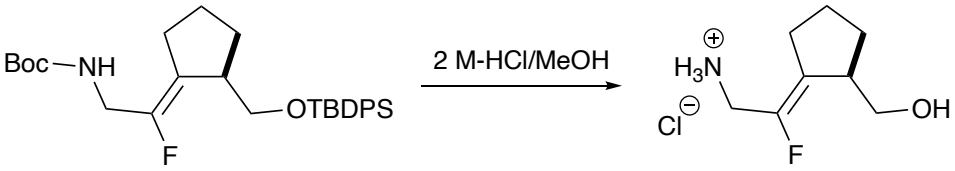
***tert*-Butyl (*R*,*Z*)-(2-(2-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclopentylidene)-2-fluoroethyl)((4-nitrophenyl)sulfonyl)carbamate (10):** To a solution of **9** (1.18 g, 2.96 mmol), Ns(Boc)NH (1.07 g, 3.55 mmol) and PPh_3 (1.08 mg, 4.14 mmol) in toluene (29.6 mL) was added a solution of dietyl azodicalboxylate (DEAD) in toluene (2.2 M, 1.9 mL, 4.1 mmol) at 0 °C under nitrogen. After being stirred at room temperature for 30 min, concentration under reduced pressure followed by flash chromatography over silica gel with Hex.−EtOAc (3:1) gave the title compound **10** as a colorless oil (2.03 g, quant.): $[\alpha]_D^{21.7}$ = -28.4 (*c* 1.09, $CHCl_3$); IR (ATR) ν 2957 (NH), 1732 (CO), 1542 (NO_2), 1368 (SO_2NH), 1151 (SO_2NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25−8.22 (m, 1H), 7.74−7.63 (m, 6H), 7.61−7.55 (m, 1H), 7.45−7.33 (m, 6H), 4.52 (d, *J* = 17.5 Hz, 2H), 3.88−3.79 (m, 1H), 3.57−3.47 (m, 1H), 3.15-3.09 (m, 1H), 2.48−2.37 (m, 1H), 2.36-2.26 (m, 1H), 1.98−1.87 (m, 1H), 1.86 (m, 1H), 1.74−1.55 (m, 2H), 1.28 (s, 9H), 1.06 (s, 9H); ^{13} C NMR (100 MHz, $CDCl_3$) δ 150.1, 147.7, 147.2 (d, *J* = 245.2 Hz), 135.7 (4C), 134.2, 134.0 (2C), 133.5, 133.0, 131.9, 129.6 (2C), 127.7 (4C), 124.2, 124.2 (d, *J* = 37.9 Hz), 85.3, 64.5, 45.4 (d, *J* = 28.2 Hz), 43.7, 29.4, 28.6, 27.8 (3C), 27.0 (3C), 24.8, 19.4.;

$^{19}F\{^{1}H\}$ (376 MHz, $CDCl_3$) δ -119.6 (t, J = 17.3 Hz); HRMS (ESI), *m/z* calcd for $C_{35}H_{43}FN_2NaO_7SSi$ $[M+Na]^+$ 705.2436, found 705.2435.



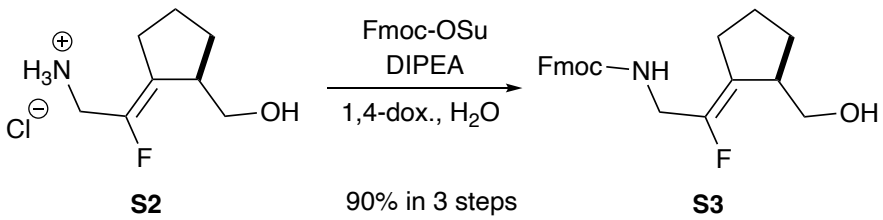
10 **S1**

***tert*-Butyl (*R*,*Z*)-(2-(2-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclopentylidene)-2-fluoroethyl)carbamate (S1):** To a solution of **10** (2.03 g, 2.96 mmol) in DMF (4.00 mL) was added a solution of K_2CO_3 (2.45 g, 17.8 mmol) and PhSH (1.20 mL, 11.8 mmol) in DMF (5.92 mL), and the reaction was stirred for 20 min. The reaction mixture was diluted with EtOAc, washed with water, and dried over Na_2SO_4. The reaction mixture was concentrated under reduced pressure to give the deprotected carbamate as a yellow oil, which was used immediately in the next step without purification.



S1 **S2**

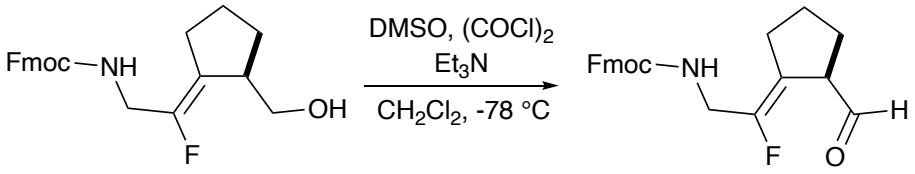
(*R*,*Z*)-2-Fluoro-2-(2-(hydroxymethyl)cyclopentylidene)ethan-1-aminium chloride (S2): To above carbamate (**S1**) (1.47 g, 2.96 mmol) was added 2 M HCl/MeOH (9.87 mL). After being stirred for 18 h, the mixture was concentrated under reduced pressure to give the amino alcohol hydrochloride (**S2**) as a yellow oil, which was used immediately in the next step without purification.



S2 90% in 3 steps **S3**

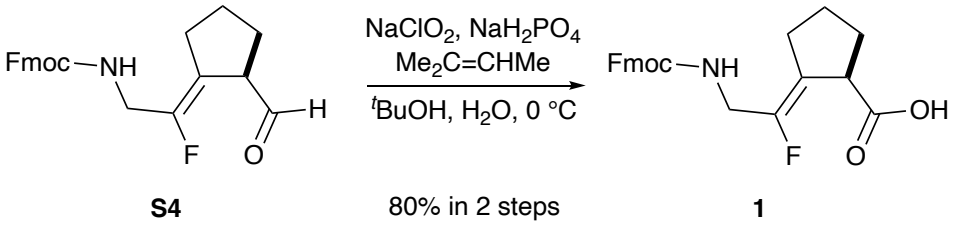
(9*H*-Fluoren-9-yl)methyl (*R*,*Z*)-(2-fluoro-2-(2-(hydroxymethyl)cyclopentylidene)ethyl)carbamate (S3): To a stirred solution of the above ammonium hydrochloride (**S2**) (2.96 mmol) in 1,4-dox. (11.5 mL) and H_2O (8.00 mL) was added DIPEA (1.70 μL, 14.8 mmol) and Fmoc-OSu (1.10 g, 3.26 mmol). After being stirrred for 6 h at room temperature, the reaction was quenched with aqueous 1 M solution of HCl. The mixture was extracted with EtOAc, washed with brine and dried over $NaSO_4$. Concentration

under reduced pressure followed by flash chromatography over silica gel with Hex.−EtOAc (3:1) gave the title compound (**S3**) (1.02 g, 90%) as colorless amorphos; $[\alpha]_D^{22.9}$ = -13.3 (*c* 1.14, $CHCl_3$); IR (ATR) ν 3354 (OH), 3295 (NH), 1704 (CO) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.6 Hz, 2H), 7.58 (d, *J* = 7.3 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 5.13 (t, *J* = 5.9 Hz, 1H), 4.41 (d, *J* = 7.0 Hz, 2H), 4.21 (t, *J* = 7.0 Hz, 1H), 4.06−3.84 (m, 2H), 3.72−3.63 (m, 1H), 3.60−3.51 (m, 1H), 3.03−2.95 (m, 1H), 2.43−2.30 (m, 2H), 1.88−1.58 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 149.2 (d, *J* = 243.9 Hz), 143.9 (2C), 141.3 (2C), 127.7 (2C), 127.1 (2C), 125.0 (2C), 122.9−122.1 (d, *J* = 14.2 Hz), 120.0 (2C), 66.9, 64.3, 47.2, 43.7, 40.3 (d, *J* = 29.4 Hz), 29.7, 28.6, 24.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -118.5 (t, *J* = 19.9 Hz) ; HRMS (ESI), *m/z* calcd for $C_{23}H_{24}FNNaO_3$ $[M+Na]^+$ 404.1627, found 404.1621



S3 **S4**

(9*H*-Fluoren-9-yl)methyl (*R*,*Z*)-(2-fluoro-2-(2-formylcyclopentylidene)ethyl)carbamate (S4): To a solution of $(COCl)_2$ (1.85 mL, 21.6 mmol) in CH_2Cl_2 (21.6 mL) was added dropwise a solution of DMSO (3.07 mL, 43.2 mmol) in CH_2Cl_2 (4.32 mL) at -78 °C. After being stirred for 20 min at -78 °C under nitrogen, to the suspension was added dropwise a solution of **S3** (826 mg, 2.16 mmol) in CH_2Cl_2 (13.5 mL), and the reaction mixture was stirred for 20 min at -78 °C. To the solution of sulfonium chloride was added Et_3N (8.98 mL, 64.8 mmol), and the reaction was stirred for 20 min at -78 °C. The reaction was quenched by saturated aqueous solution of $NaHCO_3$. The reaction mixture was extracted with ethyl acetate, washed with brine, and dried over $MgSO_4$. The reaction mixture was concentrated under reduced pressure to give the aldehyde (**S4**) as a colorless oil, which was used immediately in the next step without purification.

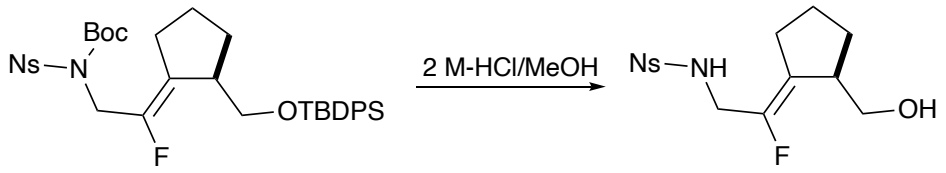


S4 80% in 2 steps **1**

(9*H*-Fluoren-9-yl)methyl (*R*,*Z*)-(2-fluoro-2-(2-formylcyclopentylidene)ethyl)carbamate (1): To a solution of above aldehyde (**S4**) (2.16 mmol), NaH_2PO_4 (389 mg, 3.24 mmol), and 2-methyl-2-butene (1.38 mL, 13.0 mmol) in ^tBuOH (21.6 mL) and H_2O (4.32 mL) was added $NaClO_2$ (1.17 g, 13.0 mmol) at 0 °C, and the reaction was stirred for 4 h at room temperature. The reaction was quenched by saturated aqueous solution of NaS_2O_3. The reaction mixture was extracted with ethyl acetate, washed with brine, and dried over Na_2SO_4. Concentration under reduced pressure followed by flash chromatography over silica gel with Hex.−EtOAc (3:2) gave the title compound (**1**) (729 mg, 80%) as colorless amorphos; $[\alpha]_D^{20.7}$ = -1.91 (*c* 1.04, $CHCl_3$);

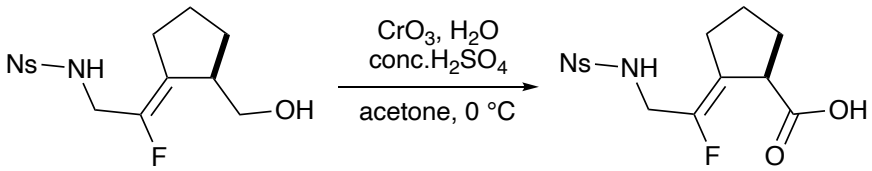
IR (ATR) ν 3374 (NH), 1706 (CO) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.5 Hz, 2H), 7.57 (d, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 5.20−5.08 (m, 1H), 5.21−5.03 (m, 2H), 4.39 (dd, *J* = 7.0 Hz, 7.0 Hz, 2H), 4.20 (t, *J* = 7.0 Hz, 1H), 4.14−3.81 (m, 2H), 3.62−3.53 (m, 1H), 2.54−2.39 (m, 1H), 2.12−1.84 (m, 3H), 1.75−1.64 (m, 1H); ^{13} C NMR (100 MHz, CDCl3) δ 179.7, 156.3, 150.1 (d, *J* = 248 Hz), 143.9 (2C), 141.3 (2C), 127.7 (2C), 127.1 (2C), 125.1 (2C) 120.5 (d, *J* = 42.4 Hz), 120.0 (2C), 67.0, 47.2, 45.4, 40.0 (d, *J* = 28.4 Hz), 31.7, 28.4, 25.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.1 (t, *J* = 20.7 Hz); HRMS (ESI), *m/z* calcd for $C_{23}H_{22}FNNaO_4$ $[M+Na]^+$ 418.1425, found 418.1425.

III. Synthesis of Ns-protected Gly-Pro-type FADI (12)



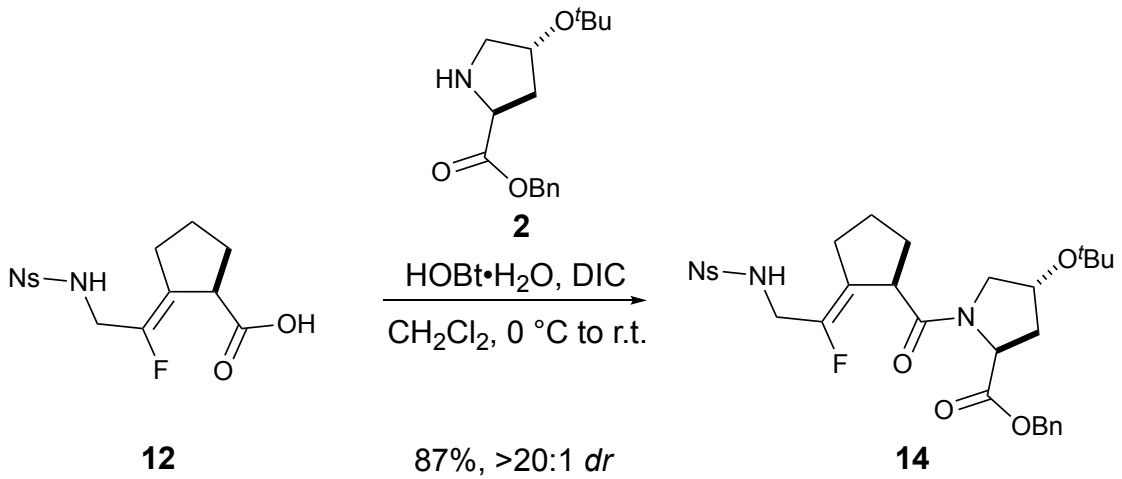
10 90% **11**

(*R*,*Z*)-*N*-(2-fluoro-2-(2-(hydroxymethyl)cyclopentylidene)ethyl)-4-nitrobenzenesulfonamide (S11): To a compound **10** (413.1 mg, 3.29 mmol) was added 2 M-HCl/MeOH (12.0 mL). After being stirred for 16 hour at r.t., the reaction mixture was concentrated under reduced pressure followed by flash chromatography over silica gel with Hex.-EtOAc (3:2) gave the title compound (**11**) (906.3 mg, 80%) as colorless amorphos; $[\alpha]_D^{19.0}$ = -25.0 (*c* 0.95, $CHCl_3$); IR (ATR) ν 3365 (OH), 1542 (NO_2), 1348 (SO_2NH), 1212 (CF), 1162 (SO_2NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15−8.05 (m, 1H), 7.97−7.87 (m, 1H), 7.80−7.69 (m, 2H), 6.02−5.92 (m, 1H), 4.06−3.82 (m, 2H), 3.47−3.38 (m, 1H), 3.32−3.23 (m, 1H), 2.73−2.62 (m, 1H), 2.36−2.17 (m, 2H), 1.78−1.53 (m, 5H); ^{13} C NMR (100 MHz, $CDCl_3$) δ 179.3, 147.7, 147.3 (d, *J* = 65 Hz), 134.3, 133.7, 132.8, 130.8, 125.7, 121.6 (d, *J* = 14 Hz), 63.8, 43.4, 42.8 (d, *J* = 29 Hz), 29.3, 28.7, 24.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -118.4 (t, *J* = 18.8 Hz); HRMS (ESI), *m/z* Calcd for $C_{14}H_{17}FN_2NaO_5S$ $[M+Na]^+$ 367.0734, found 367.0733.



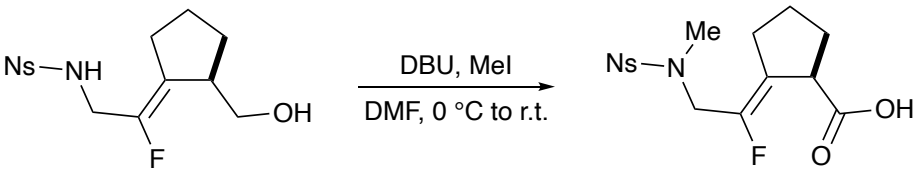
11 80% **12**

(*R*,*Z*)-2-(1-fluoro-2-((4-nitrophenyl)sulfonamido)ethylidene)cyclopentane-1-carboxylic acid (12): To a solution of CrO_3 (600 mg, 6.00 mmol) in H_2O (1.60 mL) was added dropwise H_2SO_4 (545 μL) at 0 °C. After being stirred for 5 min at 0 °C, to the solution was added a solution of **11** (413.1 mg, 1.20 mmol) in acetone (12.0 mL), and the reaction mixture was stirred for 20 min at 0 °C. The reaction was quenched by 2-propanol. The reaction mixture was extracted with ethyl acetate, washed with brine, and dried over Na_2SO_4. Concentration under reduced pressure followed by flash chromatography over silica gel with Hex.−EtOAc (3:2) gave the title compound (**12**) (344.1 mg, 80%) as colorless amorphos; $[\alpha]_D^{10.6}$ = -139.6 (*c* 0.53, $CHCl_3$); IR (ATR) ν 3338 (OH), 1702 (CO), 1535 (NO_2), 1345 (SO_2NH), 1162 (SO_2NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14−8.06 (m, 1H), 7.94−7.83 (m, 1H), 7.77−7.67 (m, 2H), 5.92−5.84 (m, 1H), 4.14−3.91 (m, 2H), 3.33−3.24 (m, 1H), 2.42−2.29 (m, 2H), 2.07−1.79 (m, 3H), 1.73−1.60 (m, 1H); ^{13} C NMR (100 MHz, $CDCl_3$) δ 179.3, 148.4 (d, *J* = 249 Hz), 147.8, 134.2, 133.7, 133.0, 130.6, 125.7, 121.5 (d, *J* = 14 Hz), 45.2 (d, *J* = 21.9 Hz), 42.5 (d, *J* = 28.4 Hz), 31.5, 28.4, 25.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.1 (t, *J* = 18.8 Hz); HRMS (ESI), *m/z* Calcd for $C_{14}H_{15}FN_2NaO_6S$ $[M+Na]^+$ 381.0527, found 381.0527.



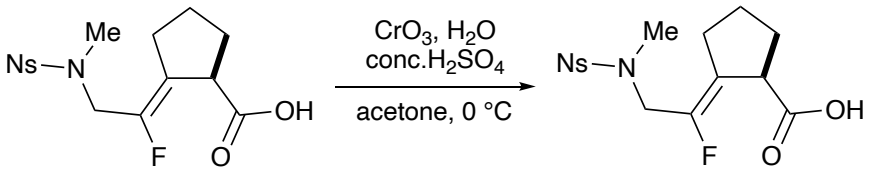
benzyl (2*S*,4*R*)-4-(*tert*-butoxy)-1-((*R*,*Z*)-2-(1-fluoro-2-((4-nitrophenyl)sulfonamido)ethylidene)cyclopentane-1-carbonyl)pyrrolidine-2-carboxylate (14): To a solution of **12** (120 mg, 0.335 mmol) and HOBt (153 mg, 1.00 mmol) in CH_2Cl_2 (1.00 mL) was added DIC (153 μL, 1.00 mmol) at 0 °C. After being stirred for 5 min at 0 °C, to the suspension was added H-Hyp(*t*Bu)-OBn (**2**) (277 mg, 1.00 mmol) in CH_2Cl_2 (2.35 mL), and the reaction mixture was stirred for 16 h at r.t. The reaction mixture was extracted with ethyl acetate, washed with 0.1 M-HCl aq., $NaHCO_3$ aq. and brine, and dried over Na_2SO_4. Concentration under reduced pressure followed by flash chromatography over silica gel with Hex.−EtOAc (1:1) gave the title compound (**14**) (180 mg, 87%) as colorless oil; $[\alpha]_D^{19.3}$ = -39.8 (*c* 0.965, $CHCl_3$); IR (ATR) ν 1740 (CO), 1622 (CO), 1542 (NO_2), 1360 (SO_2NH), 1219 (CF), 1162 (SO_2NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.2 Hz, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.79−7.62 (m, 2H), 7.41−7.26 (m, 5H), 5.92−5.85 (m, 1H), 5.17 (d, *J* = 12.4 Hz, 1H), 5.08 (d, *J* = 12,4 Hz, 1H), 4.59 (t, *J* = 5.2 Hz, 1H), 4.32−4.21 (m, 2H), 4.11−3.94 (m, 1H), 3.93 −3.79 (m, 1H), 3.77−3.68 (m, 1H), 3.35 (t, *J* = 8 Hz, 1H), 3.30−3.21 (m, 1H), 2.43−2.29 (m, 2H), 1.97−1.86 (m, 2H), 1.85−1.76 (m, 1H), 1.68−1.47 (m, 1H), 1.14 (s, 9H); ^{13} C NMR (100 MHz, $CDCl_3$) δ 172.3, 172.1, 148.1 (d, *J* = 54 Hz), 145.9, 135.7, 134.2, 133.5, 132.9, 130.9, 128.6 (2C), 128.3, 128.1 (2C), 125.6, 123.7 (d, *J* = 15 Hz), 74.1, 69.2, 66.8, 57.5, 53.6, 44.0, 42.5 (d, *J* = 29 Hz), 42.1, 31.0, 29.0, 28.2 (3C), 25.8, 23.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.6−-115.1 (dd, *J* = 11.3 Hz, *J* = 15 Hz); HRMS (ESI), *m/z* Calcd for $C_{30}H_{36}FN_3NaO_8S$ $[M+Na]^+$ 640.2099, found 640.2099.

IV. Synthesis of *N*-methylated Gly-Pro-type FADI (13)



11 **S5**

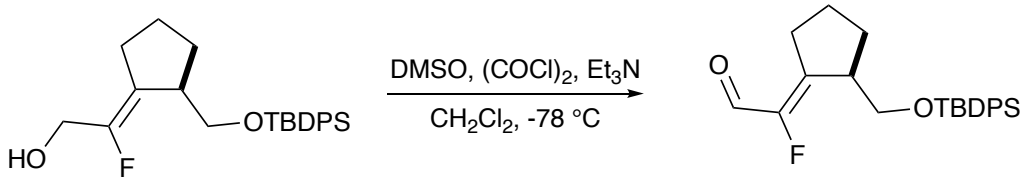
(*R*,*Z*)-2-(1-fluoro-2-((*N*-methyl-4-nitrophenyl)sulfonamido)ethylidene)cyclopentane-1-carboxylic acid (S5):To a solution of **11** (237.6 mg, 0.69 mmol) in DMF (6.90 mL) was added DBU (820 μL, 5.50 mmol). After being stirred for 10 min at 0 °C, to a suspension was added MeI (342 μL, 5.50 mmol), and the reaction was stirred for 5 h. The reaction mixture was extracted with ethyl acetate, washed with brine, and dried over Na_2SO_4. The reaction mixture was concentrated under reduced pressure to give the title compound (**S5**) as a colorless oil, which was used immediately in the next step without purification.



S5 72% in 2 steps **13**

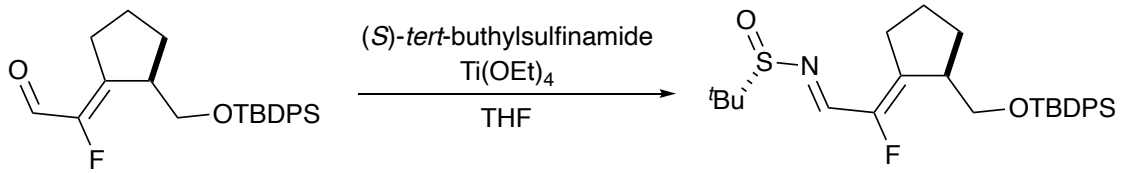
To a solution of CrO_3 (345 mg, 3.45 mmol) in H_2O (0.932 mL) was added dropwise H_2SO_4 (0.313 mL) at 0 °C. After being stirred for 5 min at -0 °C, to the solution was added a solution of **S5** (0.690 mmol) in acetone (6.90 mL), and the reaction mixture was stirred for 20 min at 0 °C. The reaction was quenched by 2-propanol. The reaction mixture was extracted with ethyl acetate, washed with brine, and dried over Na_2SO_4. Concentration under reduced pressure followed by flash chromatography over silica gel with Hex.−EtOAc (3:2) gave the title compound **13** (268 mg, 72%) as colorless amorphos;-$[\alpha]_D^{6.0}$ = -153.15 (*c* 3.00, $CHCl_3$); IR (ATR) ν 3345 (OH), 1702 (CO), 1538 (NO_2), 1345 (SO_2NH), 1219 (CF), 1165 (SO_2NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03−7.96 (m, 1H), 7.70−7.69 (m, 3H), 4.23−3.96 (m, 2H), 3.60 −3.56 (m, 1H), 2.94 (s, 3H), 2.51−2.35 (m, 1H), 2.15−1.84 (m, 3H), 1.79−1.64 (m, 1H); ^{13} C NMR (100 MHz, $CDCl_3$) δ 179.7, 148.5 (d, *J* = 149 Hz), 147.2, 133.7, 132.4, 131.7, 130.9, 124.2, 123.4 (d, *J* = 14 Hz), 48.5 (d, *J* = 29 Hz), 45.5, 34.6, 31.6, 28.5, 25.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.6 (t, *J* = 18.8 Hz); HRMS (ESI), *m/z* Calcd for $C_{15}H_{18}FN_2O_6S$ $[M+H]^+$ 373.0864, found 373.0864.

V. Synthetic procedure of *N*-Ns-protected Val-Pro-type FADI (24)



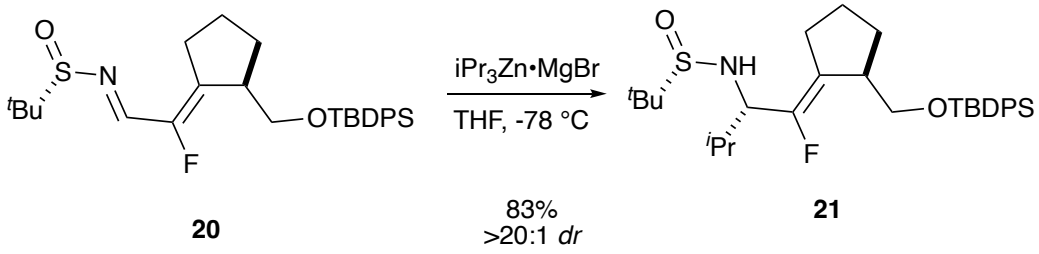
9 **S6**

(*R*,*Z*)-2-(2-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclopentylidene)-2-fluoroacetaldehyde (S6): To a solution of $(COCl)_2$ (700 μL, 8.04 mmol) in CH_2Cl_2 (26.8 mL) was added dropwise a solution of DMSO (1.14 mL, 16.1 mmol) in CH_2Cl_2 (16.8 mL) at -78 °C. After being stirred for 20 min at -78 °C under nitrogen, to the suspension was added dropwise a solution of **9** (1.07 g, 2.68 mmol) in CH_2Cl_2 (5.36 mL), and the reaction mixture was stirred for 20 min at -78 °C. To the solution of sulfomium chloride was added Et_3N (3.30 mL, 24.1 mmol), and the reaction mixture was stirred for 20 min at -78 °C. The reaction was quenched by saturated aqueous solution of $NaHCO_3$. The reaction mixture was extracted with CH_2Cl_2, washed with brine, and dried over $MgSO_4$. The reaction mixture was concentrated under reduced pressure to give the aldehyde (**S6**) as a colorless oil, which was used immediately in the next step without purification.



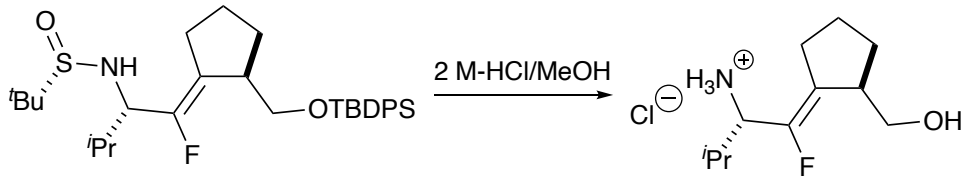
S6 87% in 2 steps **20**

(*R*)-*N*-((1*E*,2*Z*)-2-((*R*)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclopentylidene)-2-fluoroethylidene)-2-methylpropane-2-sulfinamide (20): To a suspension of the above aldehyde (**S6**) (2.68 mmol) and (*S*)-*tert*-buthylsulfinamide (487 mg, 4.02 mmol) in THF (13.4 mL) was added dropwise $Ti(OEt)_4$ (2.14 mmol). After stirring at r.t. for 4 h, the reaction was quenched with H_2O. After celite filterelation, the reaction mixture was extracted with EtOAc, washed with brine, and dried over Na_2SO_4. Concentration under reduced pressure followed by flash chromatography over silica gel *n*-hexane-EtOAc (9:1) gave the title compound **20** as a colorless oil (1.16 mg, 87%) : $[a]_D^{29.6}$ = +198.4 (*c* 1.20, $CHCl_3$); IR (ATR) ν 2961 (CH), 1581 (C=N), 1276 (CF), 1108 (SO_2NH), 750 (Ph-H) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, $J_{C\text{-}F}$ = 19.7 Hz, 1H), 7.68 – 7.59 (m, 4H), 7.46 – 7.32 (m, 6H), 3.89 – 3.85 (m, 1H), 3.72 – 3.63 (m, 1H), 3.29 – 3.18 (m, 1H), 2.74 – 2.55 (m, 2H), 2.07 – 1.95 (m, 1H), 1.95 – 1.80 (m, 2H), 1.78 – 1.68 (m, 1H), 1.22 (s, 9H), 1.05 (s, 9H); $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$) δ 152.8 – 152.2 (d, *J* = 20 Hz), 149.0 (d, *J* = 250 Hz) , 142.6 – 141.8 (d, *J* = 20 Hz), 135.6 (4C), 133.6 (2C), 129.7 (2C), 128.0 (4C), 64.1, 57.8, 45.4, 29.6, 28.9, 26.9 (3C), 24.9, 22.5 (3C), 19.3; $^{19}F\{^1H\}$ (376 MHz, $CDCl_3$) δ -126.9 (d, *J* = 19.7 Hz,1H); HRMS (ESI), *m/z* calcd for $C_{28}H_{39}FNO_2SSi$ $[M+H]^+$ 500.2449, found 500.2448.



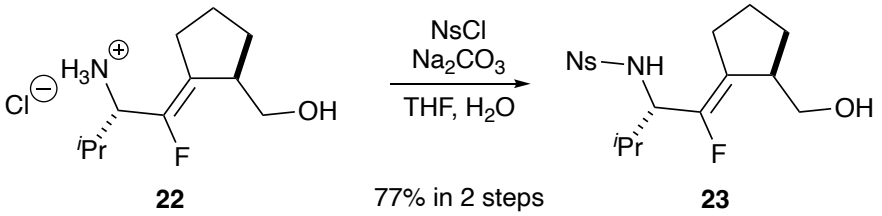
20 **21**

(*S*)-*N*-((*S*,*Z*)-1-((*R*)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)cyclopentylidene)-1-fluoro-3-methylbutan-2-yl)-2-methylpropane-2-sulfinamide (21): To a suspension of $ZnCl_2$ (214 mg, 1.57 mmol) in THF (7.0 mL) was added dropwise a solution of isopropylmagnesium bromide in THF (0.400 M, 11.8 mL, 4.73 mmol) at −78 °C, and the mixture was stirred at -78 °C for 30 min to provide ca. 0.252 M solution of triisopropyl zincate in THF. To the solution of above triisopropyl zincate was added dropwise a solution of **20** (524 mg, 1.05 mmol) in THF (7.0 mL) at −78 °C. After stirring at −78 °C for 2.5 h, the reaction was quenched by adding a 3:2 mixture of saturated aqueous NH_4Cl solution and 28% NH_3 aqueous solution, followed by additional stirring at room temperature for 1 h. The reaction mixture was extracted with EtOAc, and the extract was washed with brine and dried over Na_2SO_4. Concentration under reduced pressure followed by flash chromatography over silica gel *n*-hexane-EtOAc (4:1) gave the title compound **21** as a colorless oil (471 mg, 83%, >20:1 *dr*): $[a]_D^{25.2}$ = +43.6 (*c* 0.92, $CHCl_3$); IR (ATR) ν 2954 (CH), 1217 (CF), 1105 (SO_2NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.62 (m, 4H), 7.45 – 7.32 (m, 6H), 3.81 – 3.73 (m, 1H), 3.61 – 3.54 (m, 1H), 3.50 – 3.47 (m, 1H), 3.16 – 3.08 (m, 1H), 2.50 – 2.39 (m, 1H), 2.27 – 2.16 (m, 1H), 1.90 – 1.77 (m, 3H), 1.76 – 1.63 (m, 2H), 1.22 (s, 9H), 1.04 (s, 9H), 0.99 – 0.95 (m, 3H), 0.88 – 0.84 (m, 3H); $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$) δ 151.2 (d, *J* = 250 Hz), 135.6 (4C), 134.1, 133.9, 129.6 (2C), 127.6 (4C), 122.2, 64.7, 62.5 (d, *J* = 70 Hz), 56.5, 43.4, 31.9, 29.3, 28.8 (d, *J* = 10 Hz), 26.9 (3C). 24.9, 22.7 (3C), 19.7, 19.4, 19.3; $^{19}F\{^1H\}$ (376 MHz, $CDCl_3$) δ -128.5 (d, *J* = 37.6 Hz); HRMS (ESI), *m/z* calcd for $C_{31}H_{47}FNO_2SSi$ $[M+H]^+$ 544.3075, found 544.3075.

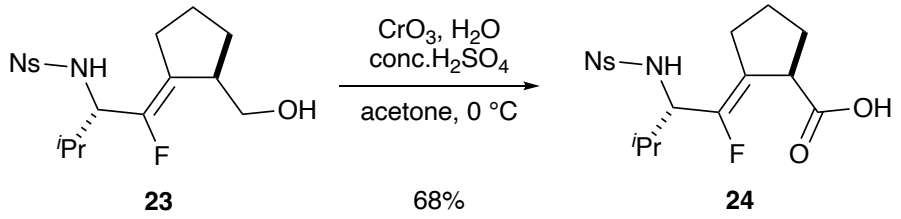


21 **22**

***N*-((*S*,*Z*)-1-Fluoro-1-((*R*)-2-(hydroxymethyl)cyclopentylidene)-3-methylbutan-2-yl)-2-nitrobenzenesulfonamide (S16):** To a solution of **21** (113.4 mg. 0.209 mmol) was added 2 M HCl/MeOH (2.09 mL), and the mixture was stirred at room temperature for 13 h. The reaction mixture was concentrated under reduced pressure to give the amine as a brown oil, which was used immediately in the next step without purification.



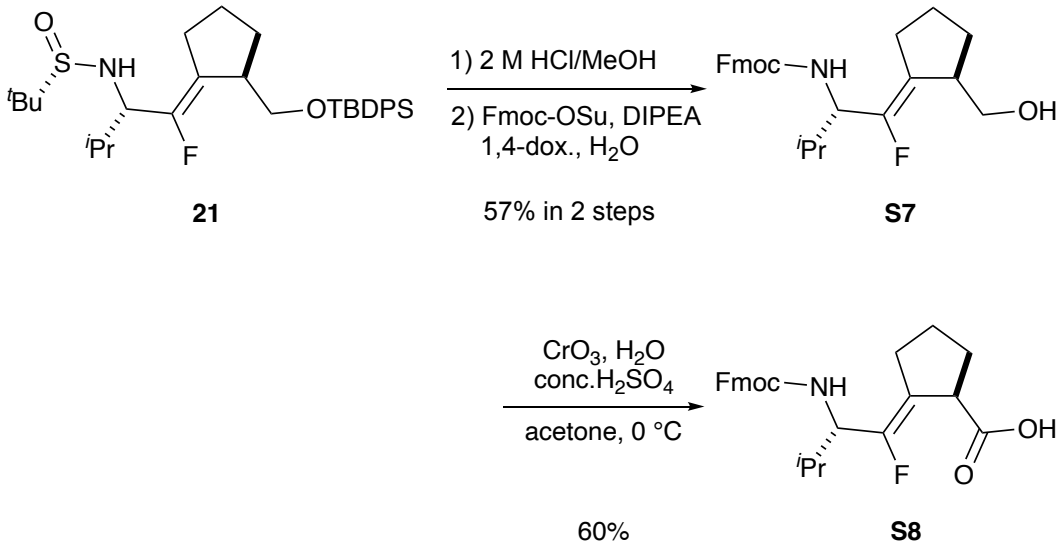
***N*-((*S*,*Z*)-1-Fluoro-1-((*R*)-2-(hydroxymethyl)cyclopentylidene)-3-methylbutan-2-yl)-4-nitrobenzenesulfonamide** (**23**): To a stirred solution of the above ammonium hydrochloride (**22**) (0.209 mmol) and Na_2CO_3 (68.1 mg, 0.643 mmol) in H_2O (2.09 mL) was added a solution of 2-nitrobenzensulfonyl chloride (60.2 mg, 0.272 mmol) in THF (2.09 mL). After being stirrred for 8 h at room temperature, the reaction was quenched with aqueous 1 M solution of HCl. The mixture was extracted with EtOAc, washed with brine and dried over $NaSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with Hex.−EtOAc (2:1) gave the title compound (**23**) (62.1 mg, 77% in 2 steps) as colorless oil: $[a]_D^{29.0}$ = -206.0 (*c* 2.65, $CHCl_3$); IR (ATR) ν 3565 (OH), 2961 (CH), 1352 (SO_2NH), 1217 (CF), 1167 (SO_2NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 – 8.00 (d, *J* = 8.0 Hz, 1H), 7.99 – 7.92 (d, *J* = 8 Hz, 1H), 7.78 – 7.63 (tt, *J* = 8 Hz, *J* = 8 Hz, 2H), 5.87 (d, *J* = 12 Hz, 1H), 3.99 – 3.81 (dt, *J* = 12 Hz, *J* = 28 Hz, 1H), 3.56 – 3.48 (m, 1H), 3.38 – 3.27 (m, 1H), 2.27 (m, 2H), 2.22 – 2.10 (m, 1H), 1.97 – 1.83 (m, 1H), 1.76 – 1.46 (m, 5H); $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$) δ 148.4 (d, *J* = 240.0 Hz), 147.5, 134.8, 133.5, 132.5, 130.5, 125.7, 123.2 (d, *J* = 10.0 Hz), 63.7, 59.8 (d, *J* = 20.0 Hz), 43.3, 31.2, 29.2, 28.6, 24.8, 19.5, 19.0; $^{19}F\{^1H\}$ (376 MHz, $CDCl_3$) δ -127.2 − -127.4 (m, 1F); HRMS (ESI), *m/z* calcd for $C_{17}H_{24}FN_2O_5S$ $[M+H]^+$ 387.1384, found 387.1384.



(*R*,*Z*)-2-((*S*)-1-Fluoro-3-methyl-2-((2-nitrophenyl)sulfonamido)butylidene)cyclopentane-1-carboxylic acid (**24**): To a solution of CrO_3 (77.0 mg, 0.770 mmol) in H_2O (208 μL) was added dropwise H_2SO_4 (70.0 μL) at 0 °C and the reaction mixture stirred for 5 min at 0 °C. To the solution was added a solution of **23** (59.6 mg, 0.154 mmol) in acetone (1.54 mL), and the reaction mixture was stirred for 10 min at 0 °C. The reaction was quenched by 2-propanol. The reaction mixture was extracted with ethyl acetate, washed with brine, and dried over Na_2SO_4. Concentration under reduced pressure followed by flash chromatography over silica gel with Hex.−EtOAc (1:1) gave the title compound (**24**) as colorless amorphous (41.9 mg, 68%): $[a]_D^{22.0}$ = -195.2 (*c* 1.85, $CHCl_3$); IR (ATR) ν 3019 (CH), 1712 (CO), 1359 (SO_2NH), 1217 (CF) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 – 7.99 (d, *J* = 8 Hz, 1H), 7.98 – 7.91 (d, *J* = 8 Hz, 1H), 7.78 – 7.63 (m, *J* = 8 Hz, *J* = 8 Hz, 2H), 5.88 – 5.81 (d, *J* = 8 Hz, 1H), 3.98 – 3.82 (dt, J = 28 Hz, 8 Hz, 1H), 2.87 – 2.79 (m, 1H), 2.42 – 2.21 (m, 2H), 1.99 – 1.76 (m, 4H), 1.62 – 1.47 (dq, *J* = 8 Hz, 4 Hz, 1H), 1.10 – 1.01 (d, *J* = 4 Hz, 3H), 1.00 – 0.89 (d, *J* = 4 Hz, 3H); $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$) δ 179.4, 149.7 (d, *J* = 250.0 Hz), 147.6, 134.8, 133.6, 132.4, 130.4, 125.8, 120.8 (d, *J* = 10.0 Hz), 59.6 (d, *J* = 20.0 Hz), 45.1, 31.5 (2C), 28.5, 25.8, 19.5, 18.7; $^{19}F\{^1H\}$ (376 MHz, $CDCl_3$) δ -122.2 (d, *J* = 38 Hz); HRMS (ESI), *m/z* calcd for $C_{17}H_{22}FNO_6S$ $[M+H]^+$

401.1177, found 401.1174.

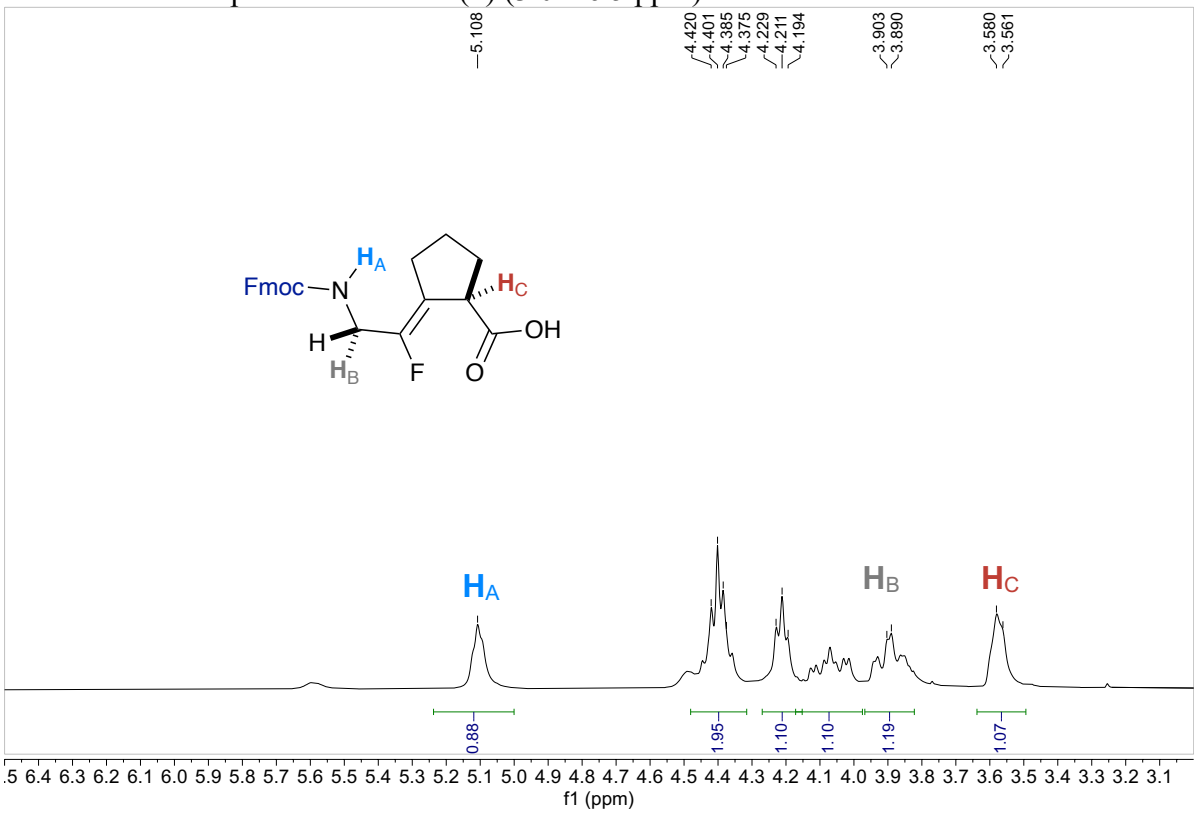
VI. Synthetic procedure of *N*-Fmoc-protected Val-Pro-type FADI (S8)[3]



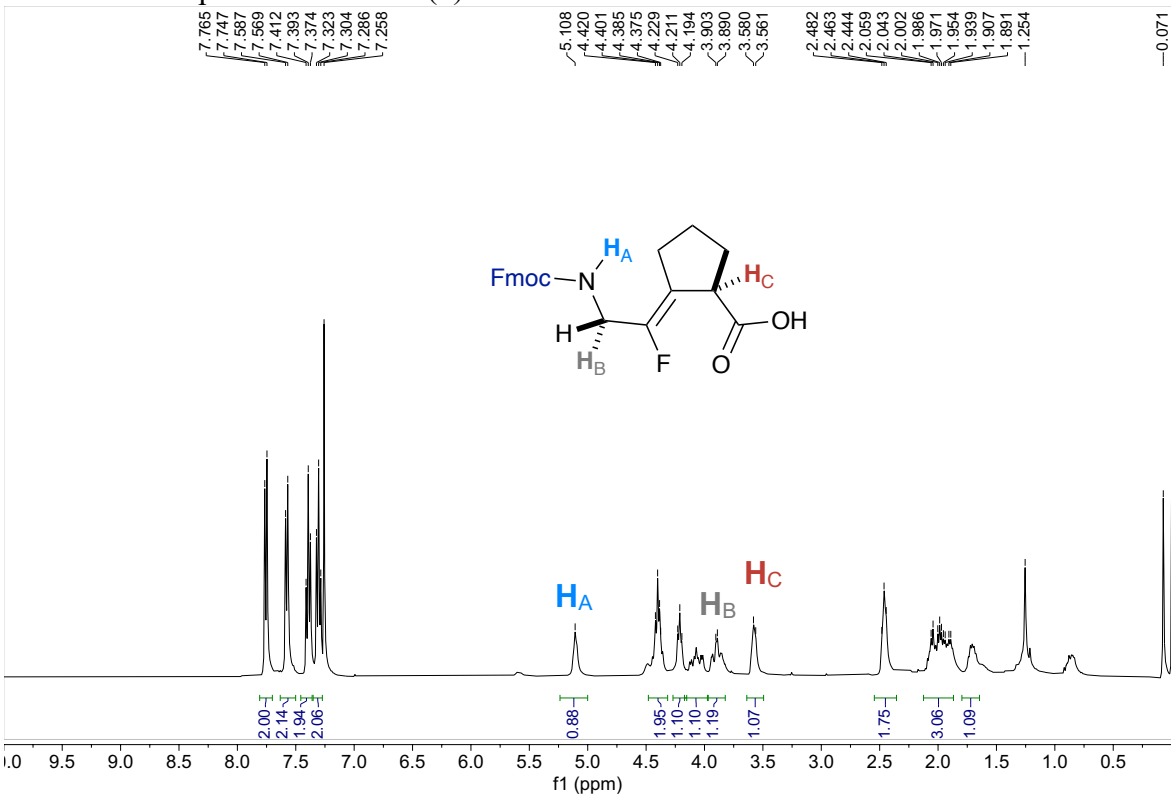
Scheme S5. Synthesis of N-Fmoc-protected Val-Pro-type FADI (**S8**)

VII. ^{1}H NMR monitoring of reaction intermediate of FADI (1)

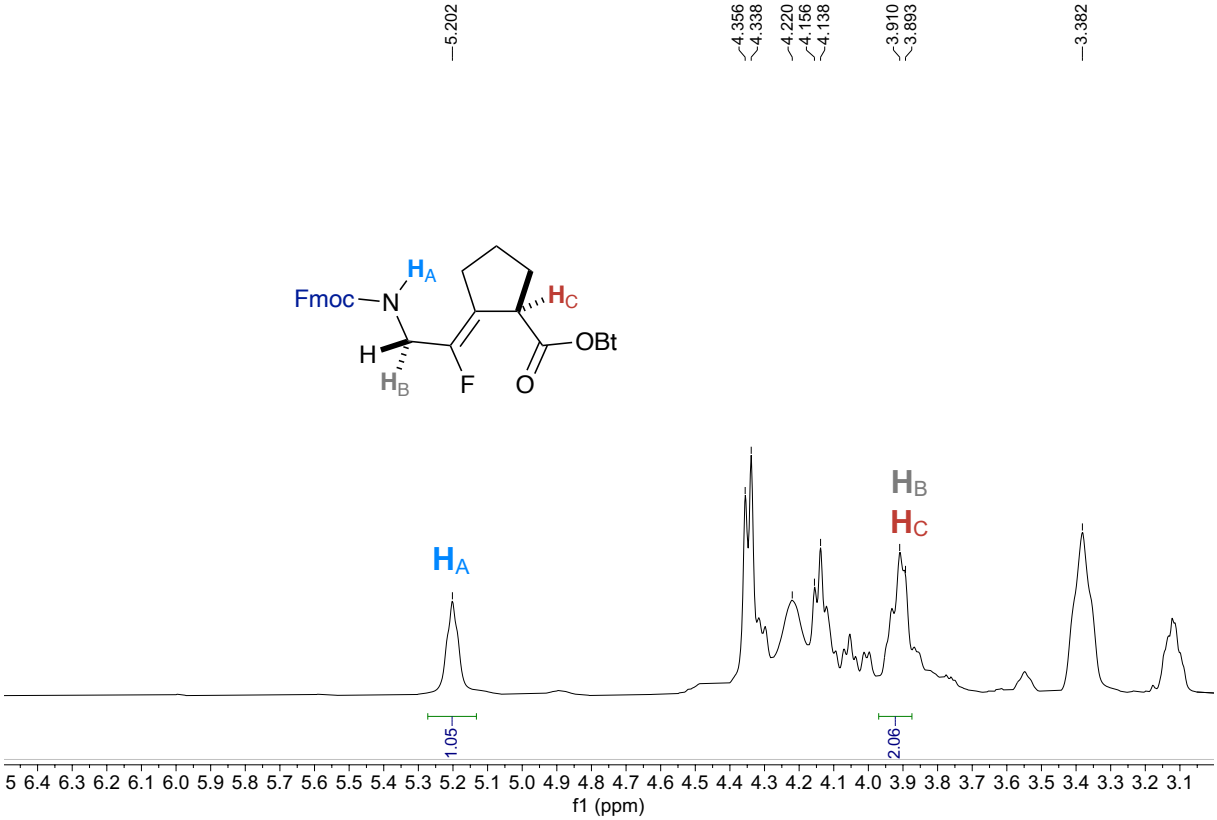
Partial ^{1}H NMR spectrum of FADI (**1**) (3.0 – 6.5 ppm)



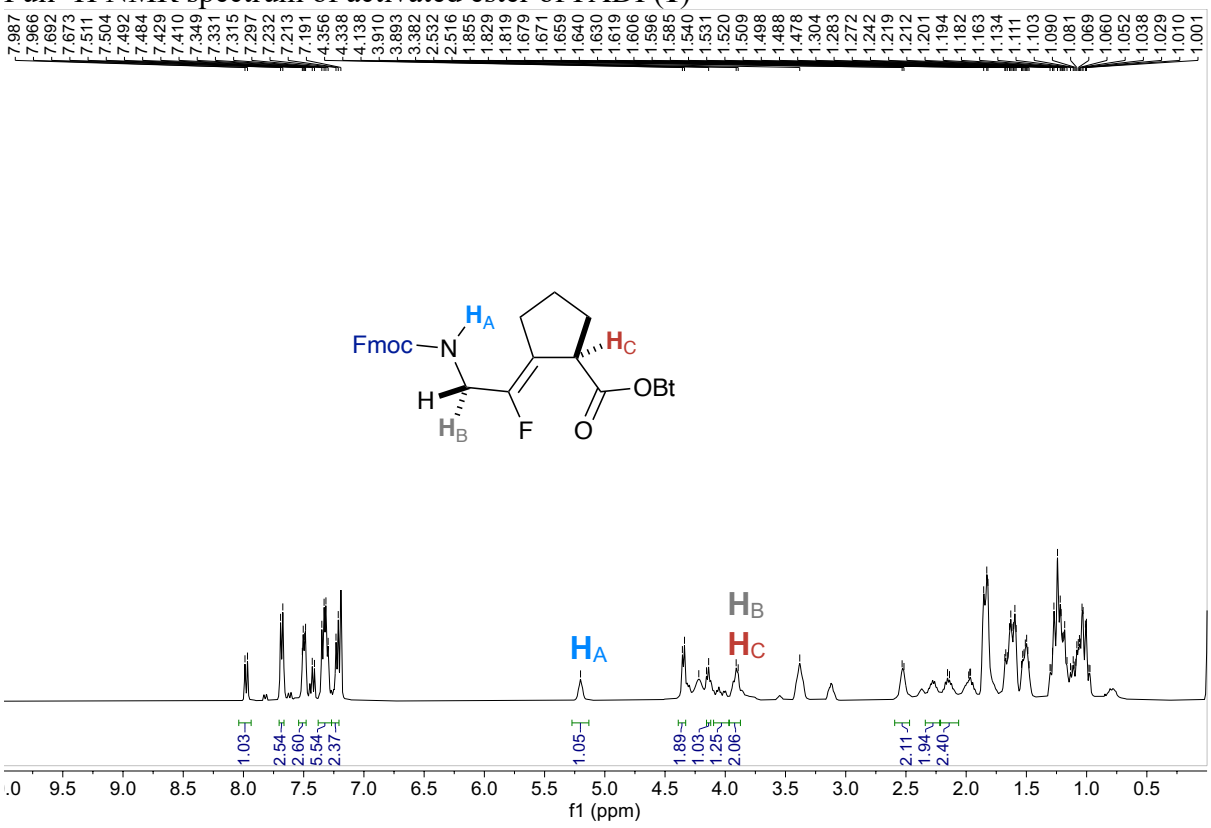
Full ^{1}H NMR spectrum of FADI (**1**)



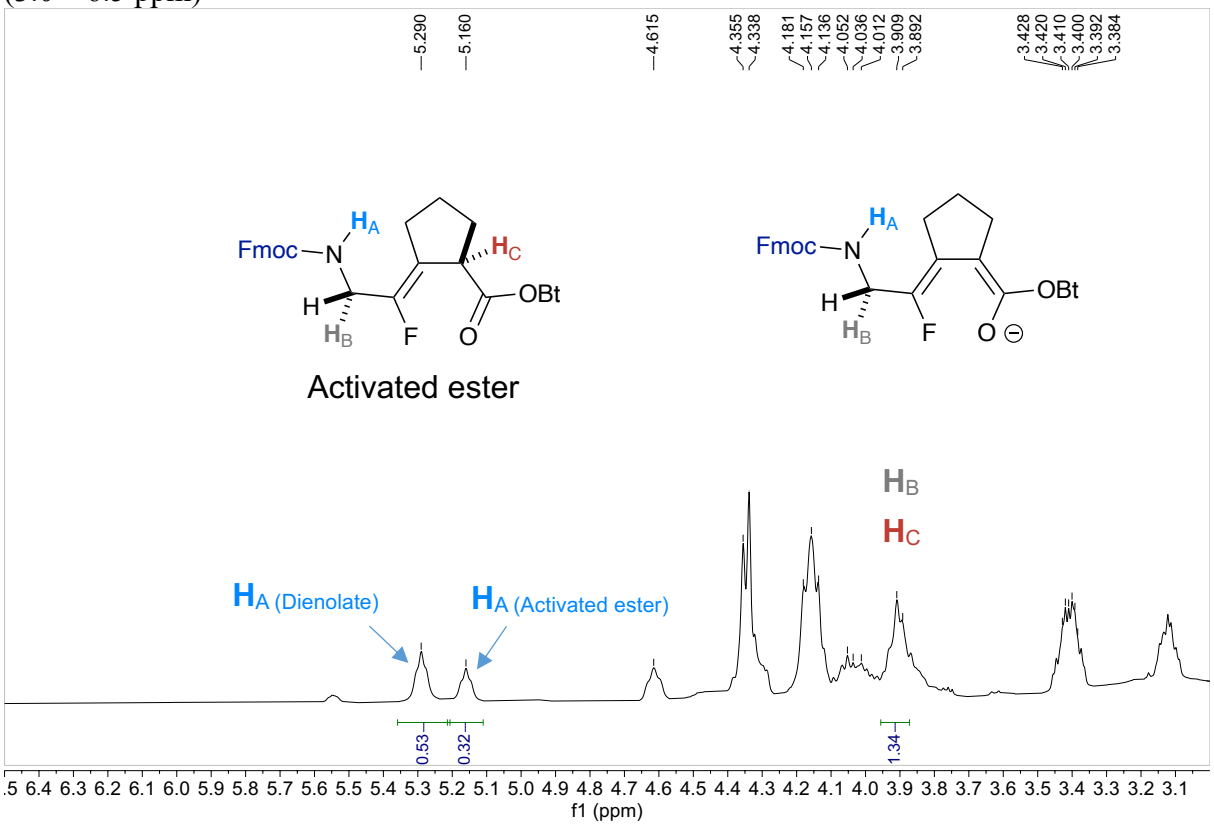
Partial ^{1}H NMR spectrum of activated ester of FADI (**1**) (3.0 – 6.5 ppm)



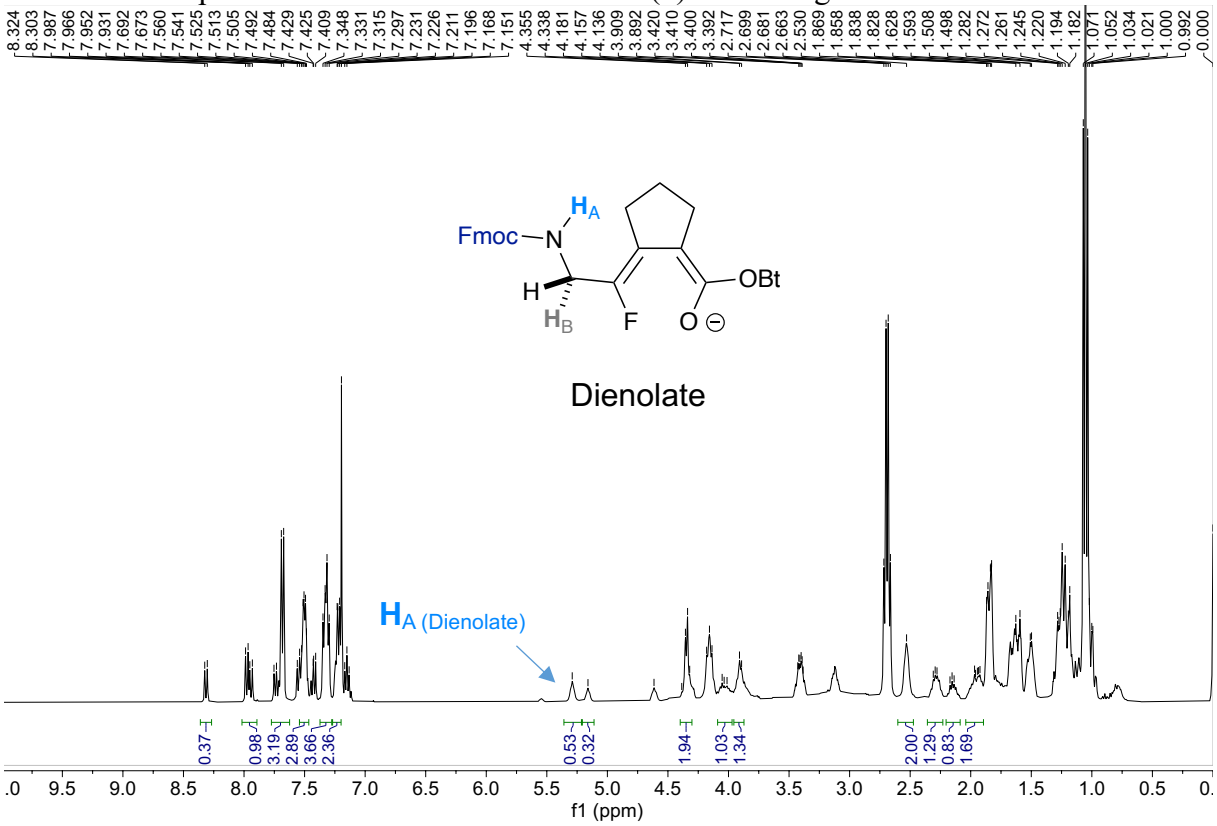
Full ^{1}H NMR spectrum of activated ester of FADI (**1**)



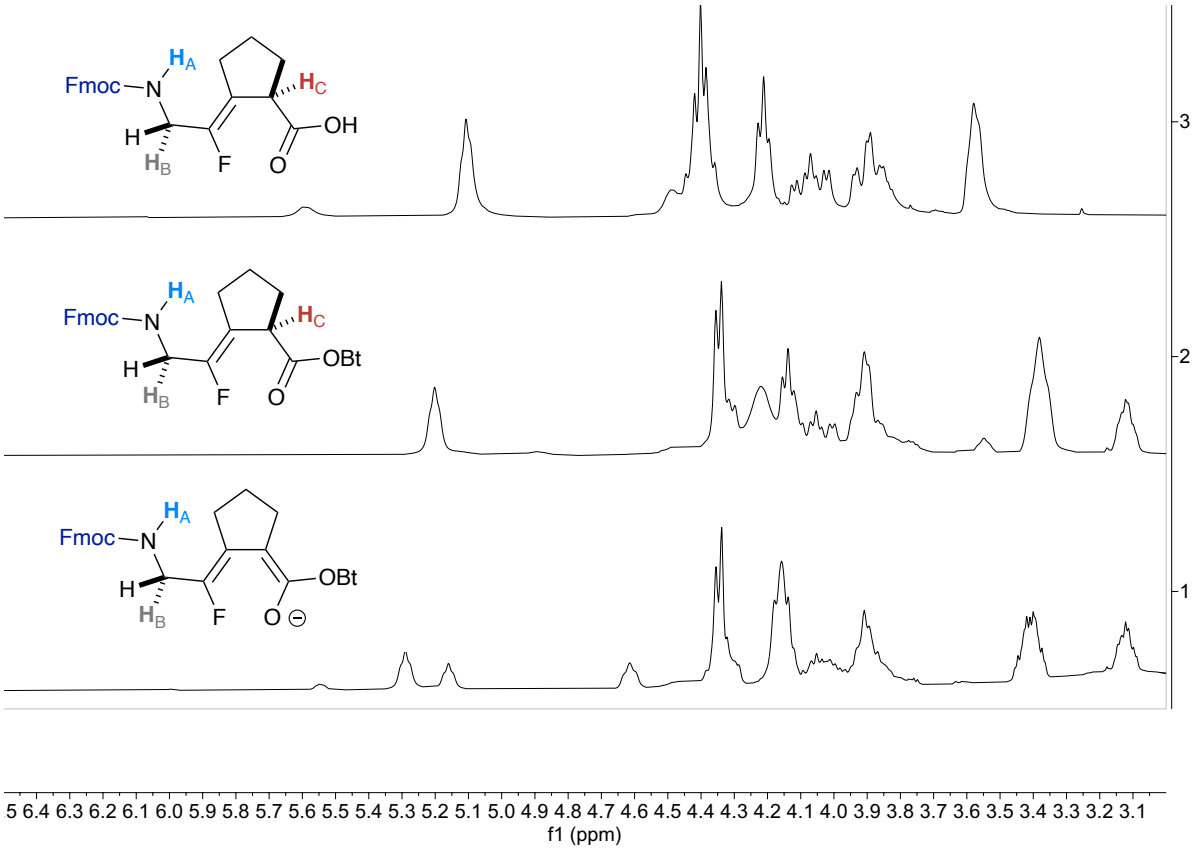
Partial ^{1}H NMR spectrum of dienolate anion of FADI (**1**) containing 30% of activated ester (3.0 – 6.5 ppm)



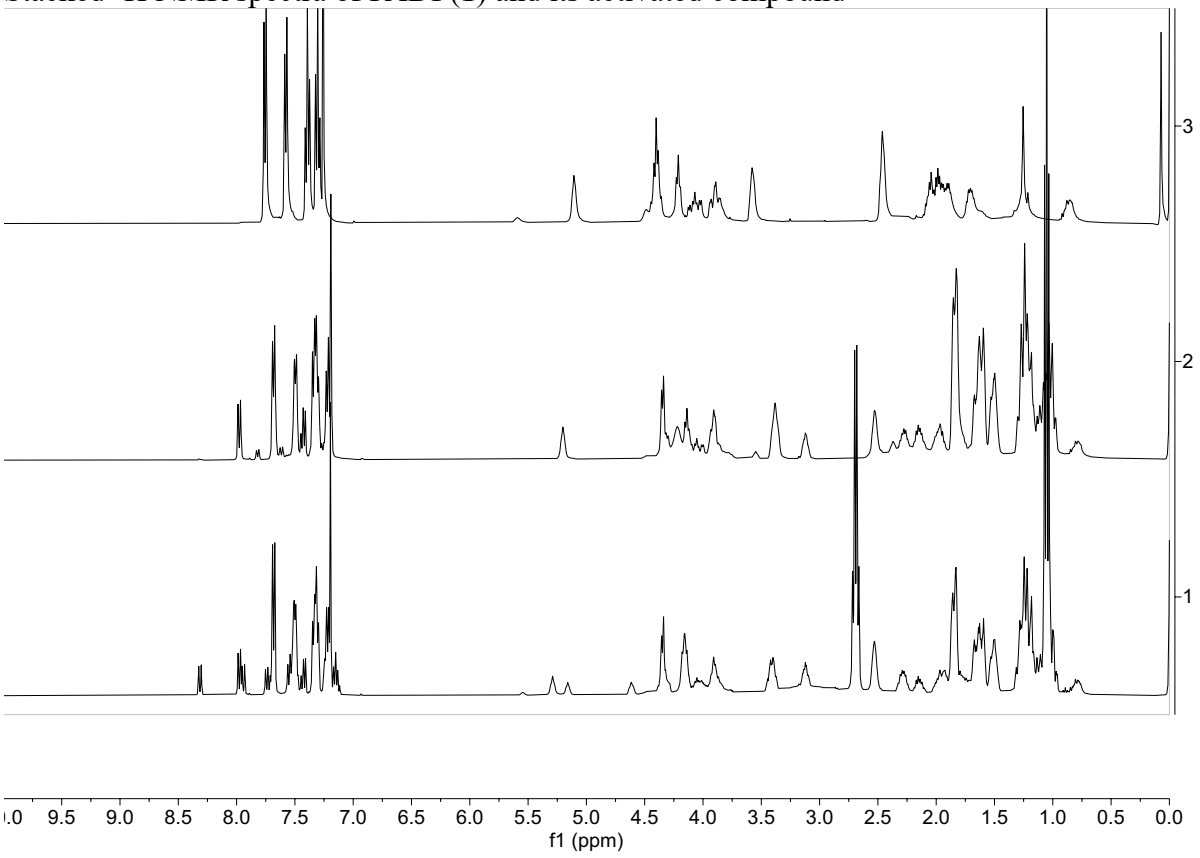
Full ^{1}H NMR spectrum of dienlate anion of FADI (**1**) containing 30% of activated ester



Stacked ^{1}H NMR spectra of FADI (**1**) and its activated compound (3.0– 6.5 ppm)

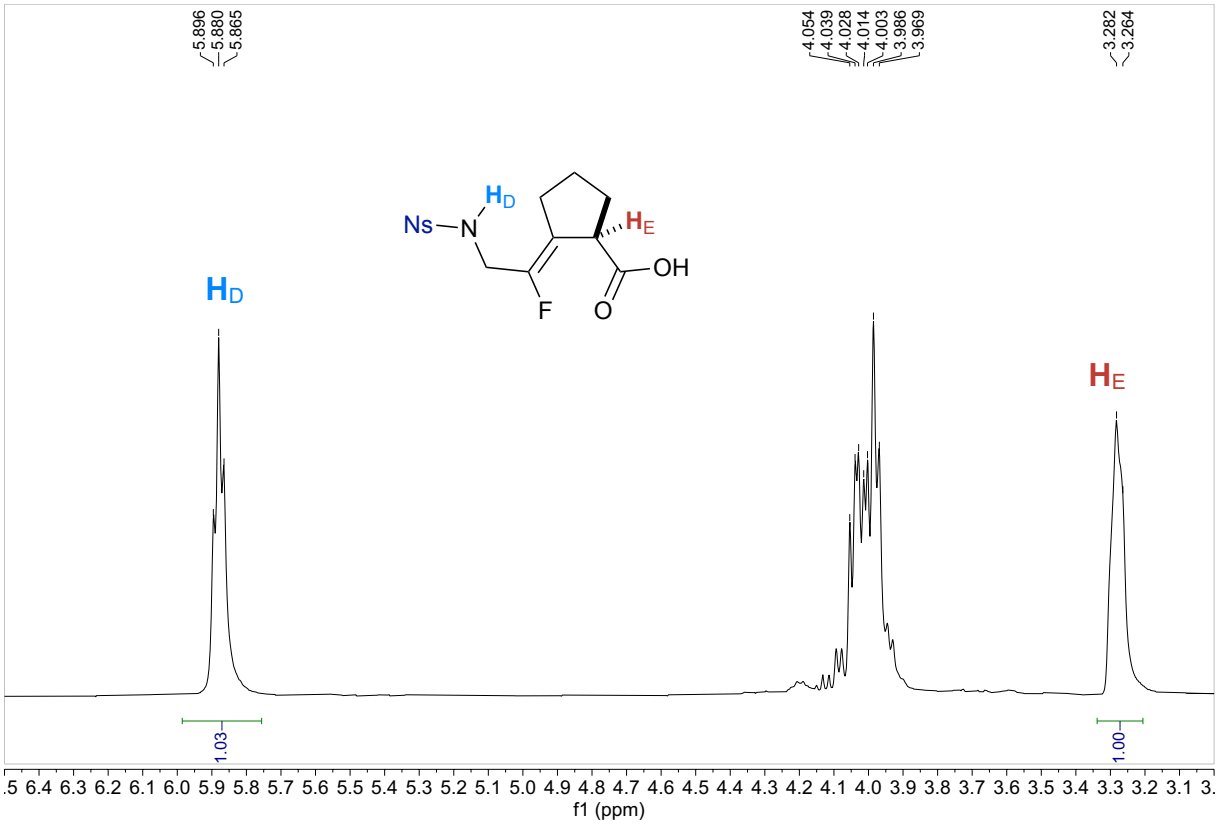


Stacked ^{1}H NMR spectra of FADI (**1**) and its activated compound

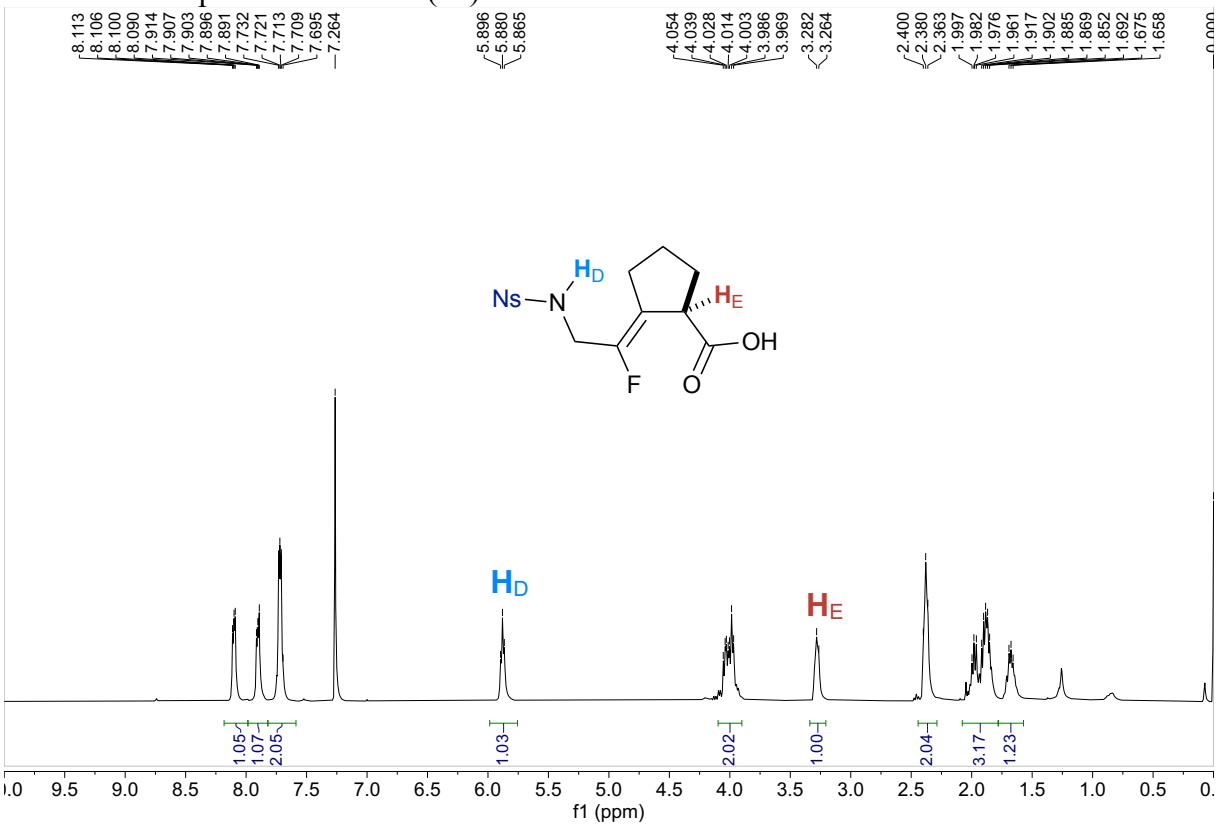


VIII. ^{1}H NMR monitoring of reaction intermediate of FADI (12)

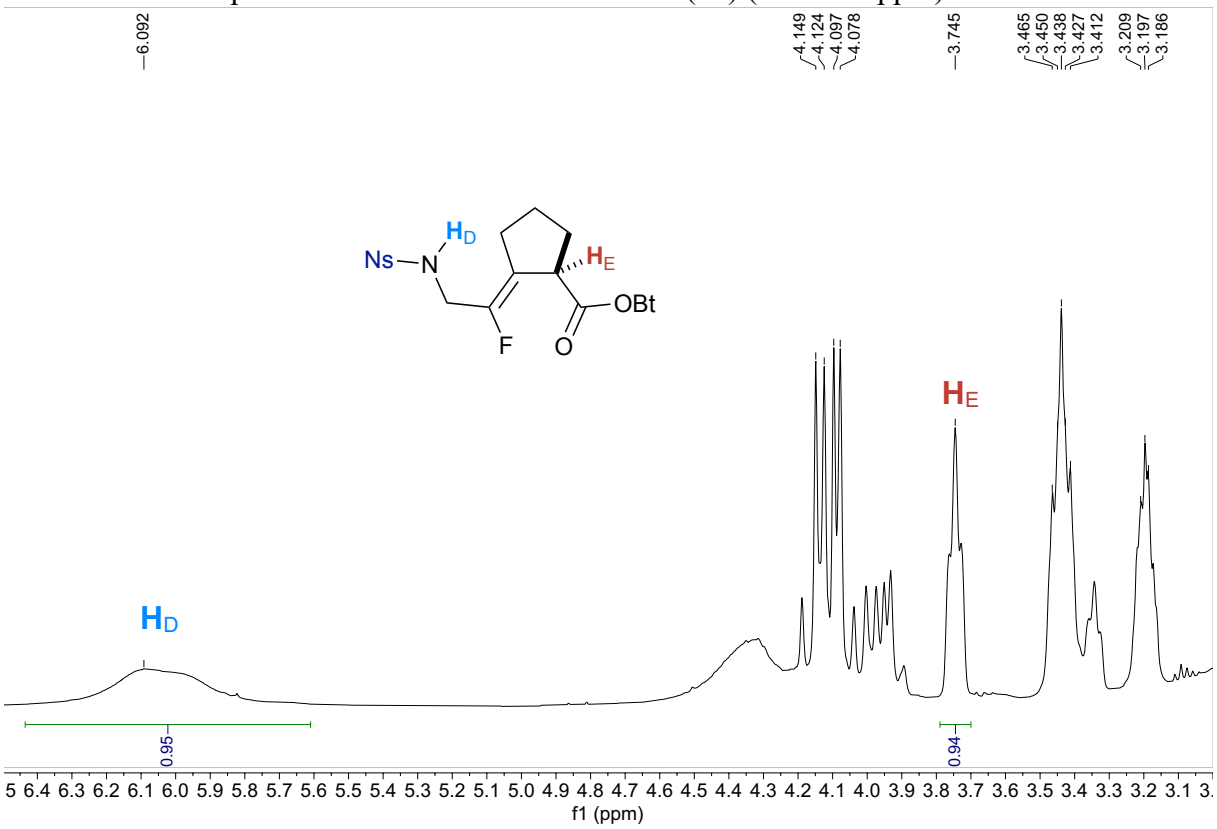
Partial ^{1}H NMR spectrum of FADI (**12**) (3.0 – 6.5 ppm)



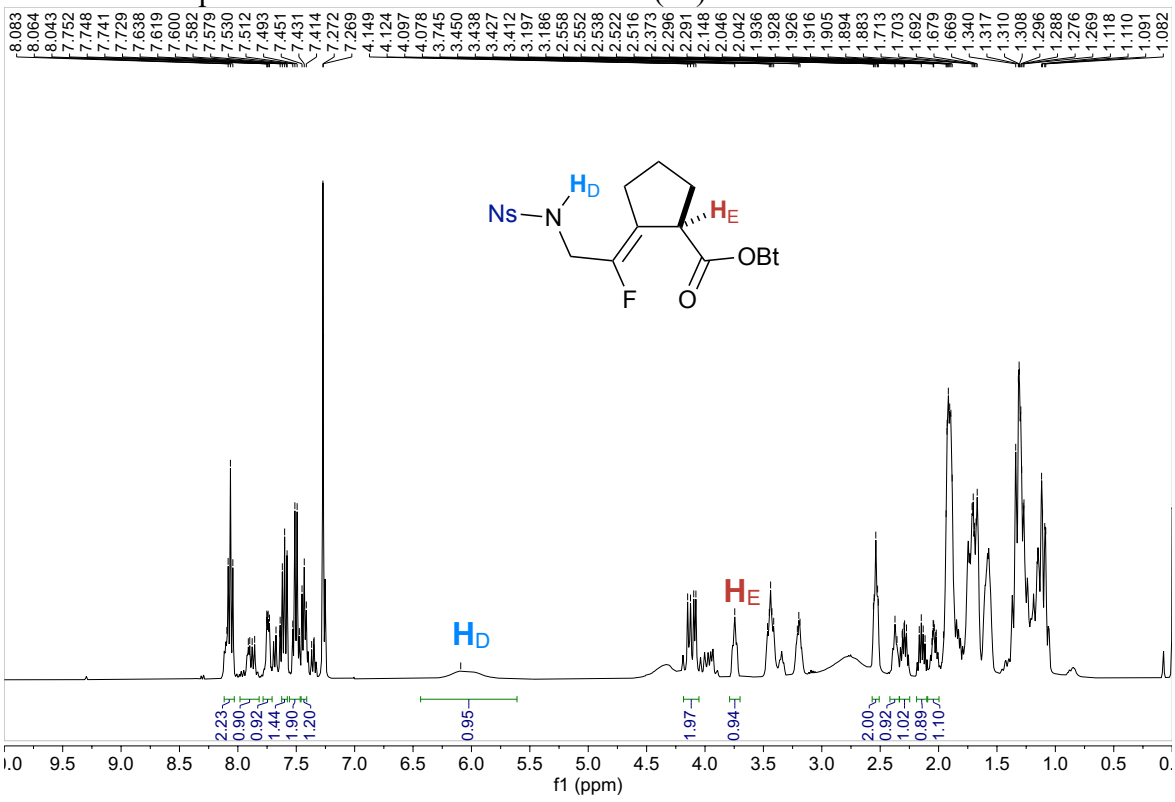
Full ^{1}H NMR spectrum of FADI (**12**)



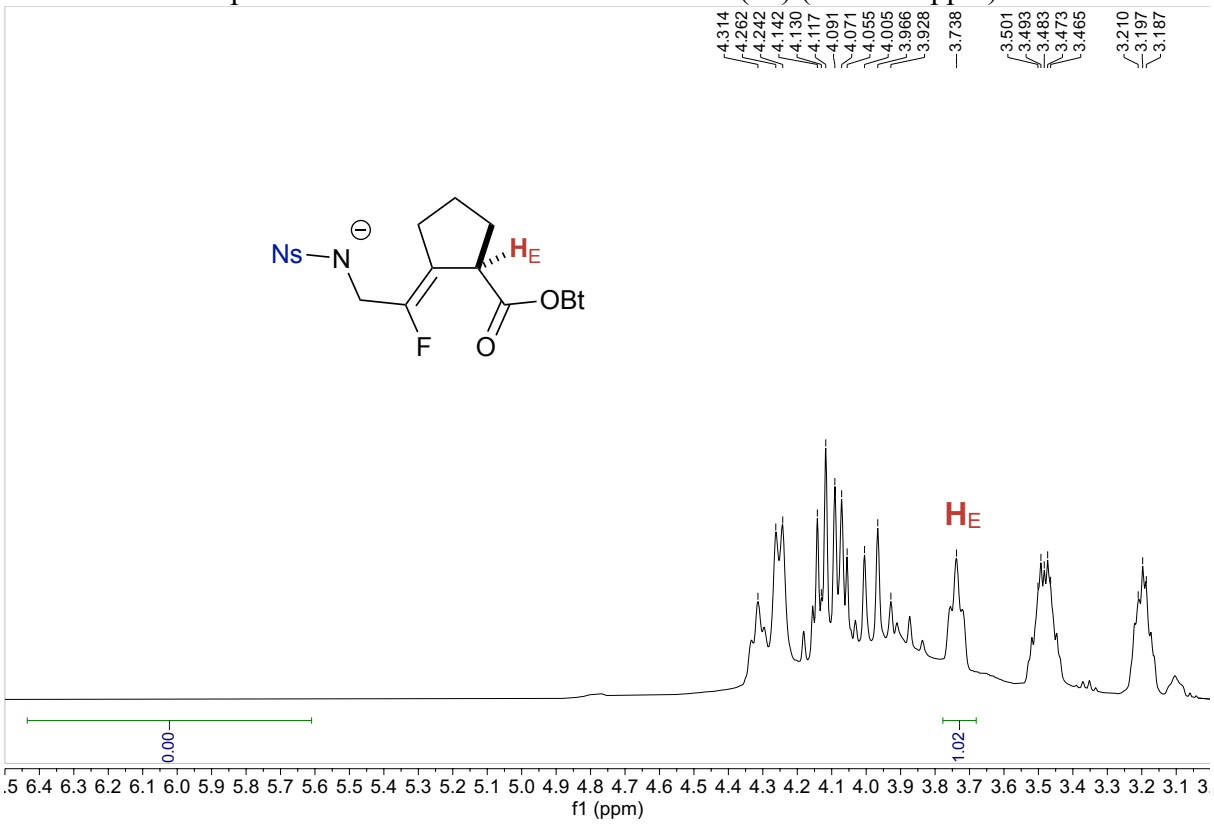
Partial ^{1}H NMR spectrum of activated ester of FADI (**12**) (3.0 – 6.5 ppm)



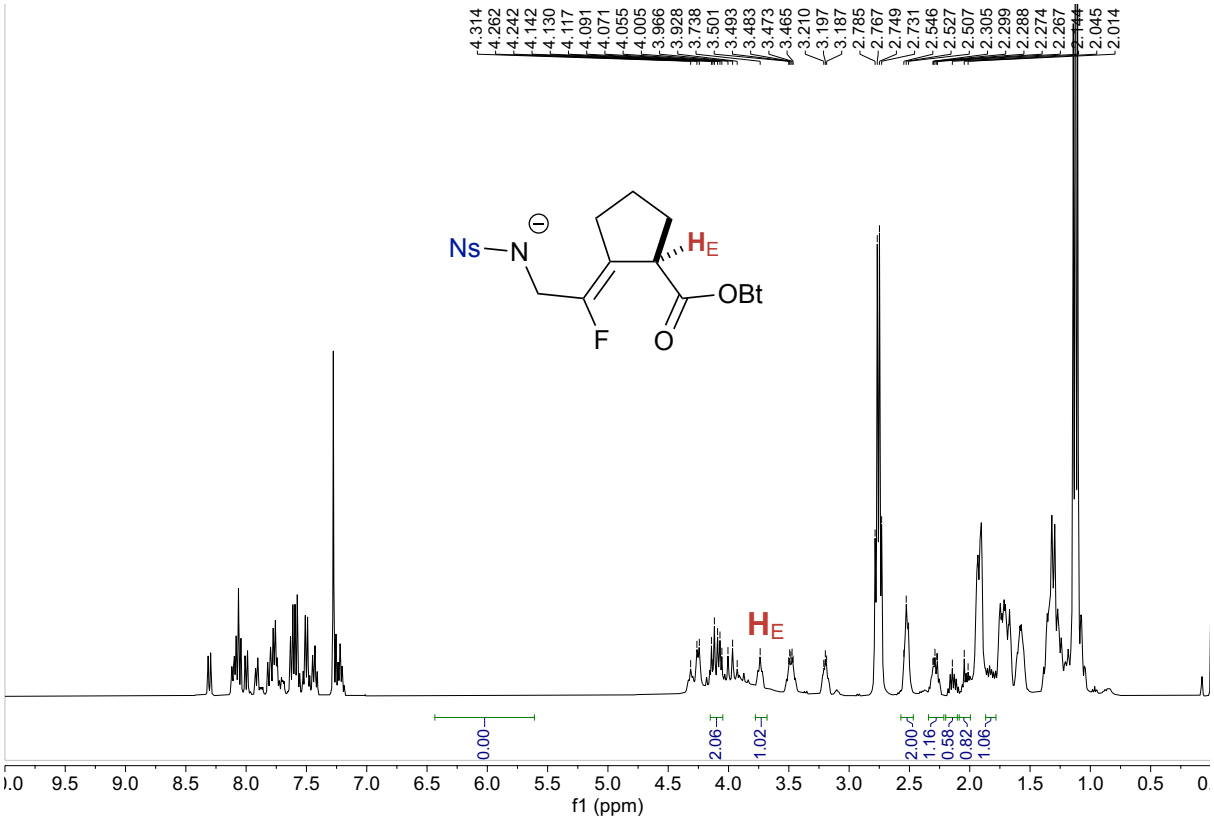
Full ^{1}H NMR spectrum of activated ester of FADI (**12**)



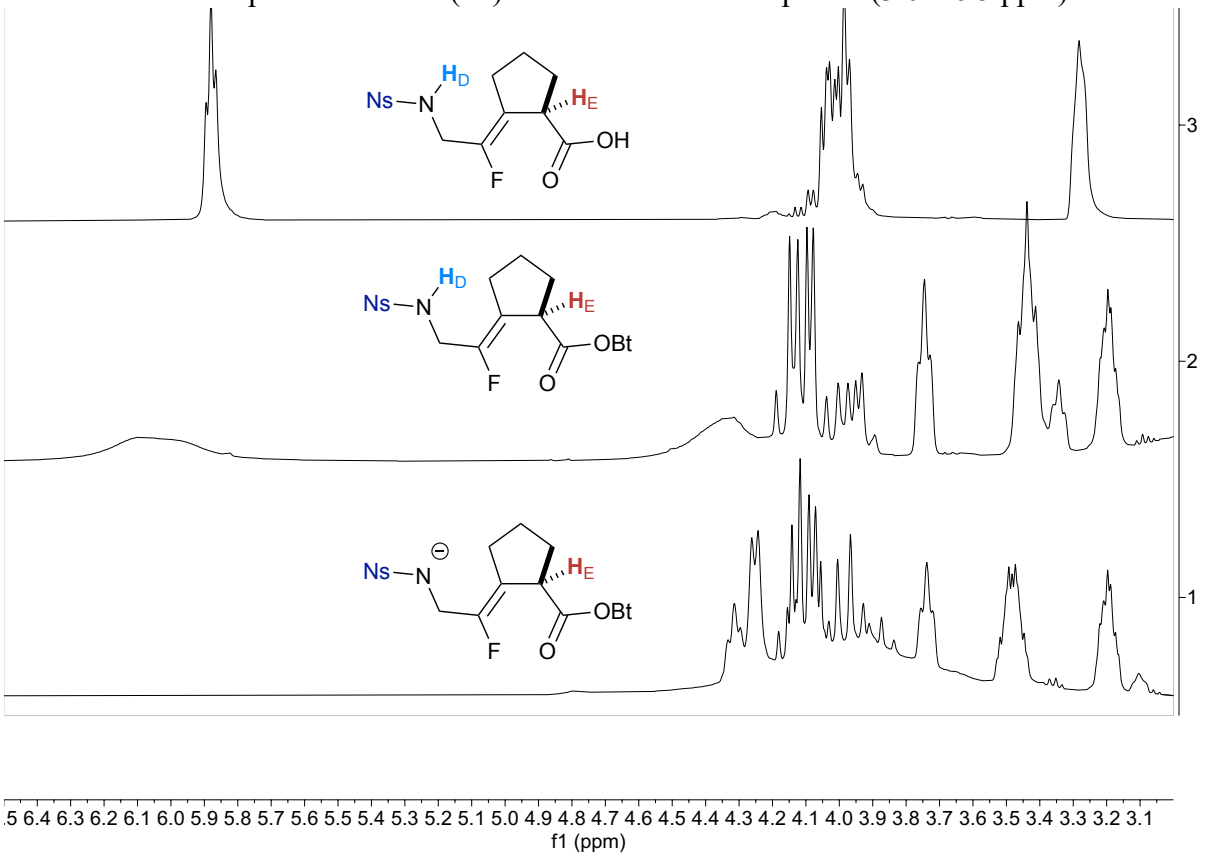
Partial ^{1}H NMR spectrum of sulfonamide anion of FADI (**12**) (3.0 – 6.5 ppm)



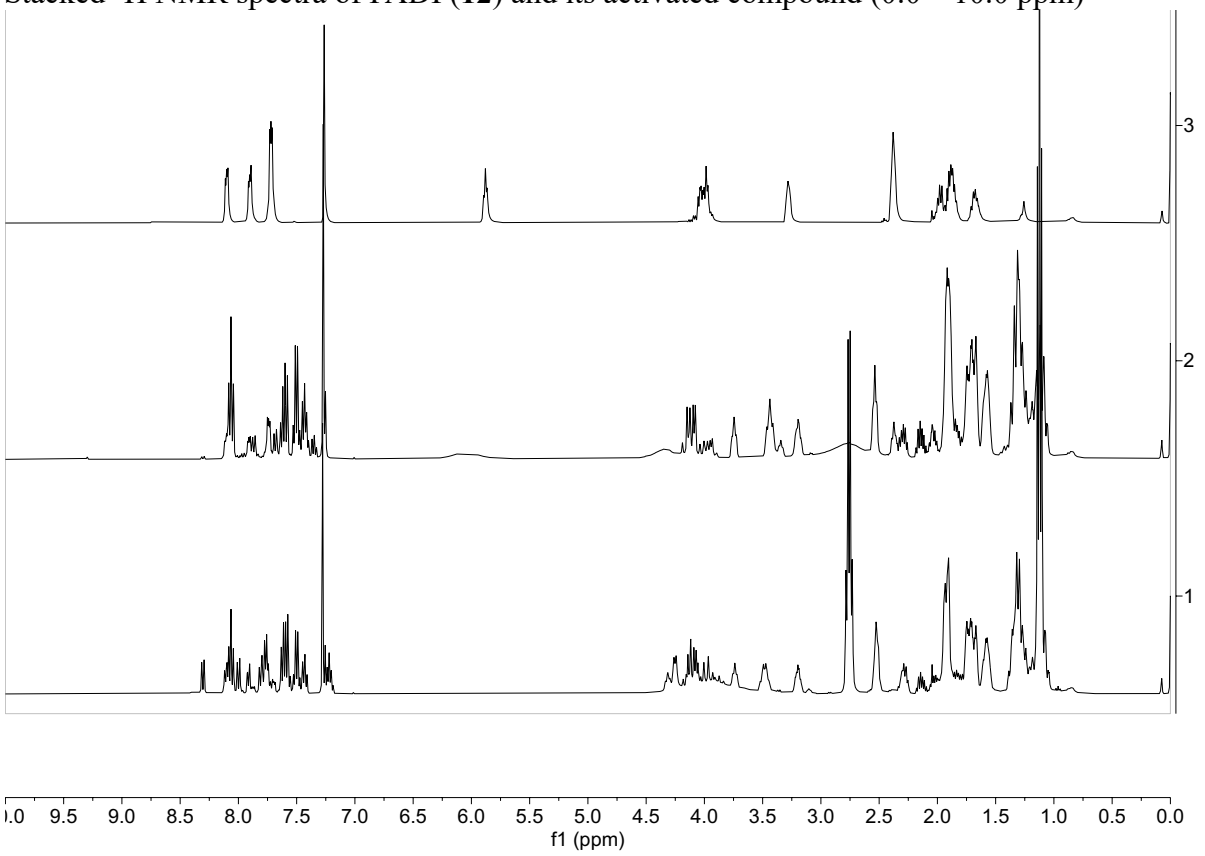
Full ^{1}H NMR spectrum of sulfonamide anion of FADI (**12**)



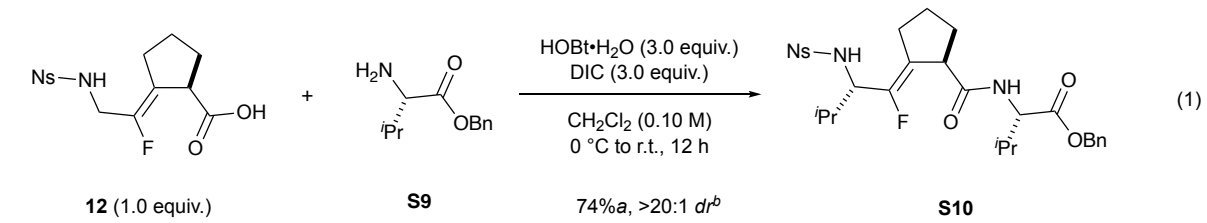
Stacked ^{1}H NMR spectra of FADI (**12**) and its activated compound (3.0 – 6.5 ppm)



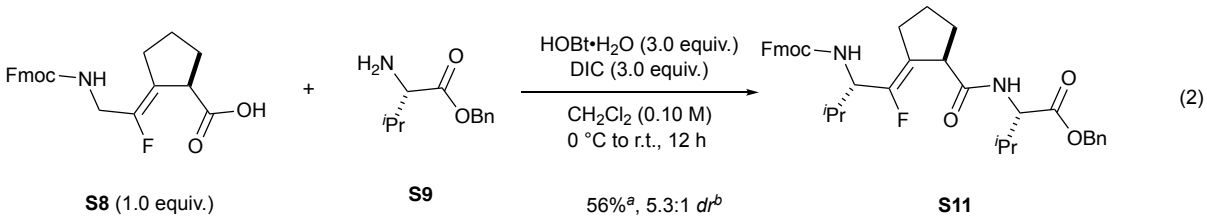
Stacked ^{1}H NMR spectra of FADI (**12**) and its activated compound (0.0 – 10.0 ppm)



IX. Control experiments: coupling reactions with Val-Pro-type FADI



12 (1.0 equiv.) **S9** 74%*a*, >20:1 *dr*[b] **S10** (1)



S8 (1.0 equiv.) **S9** 56%[a], 5.3:1 *dr*[b] **S11** (2)

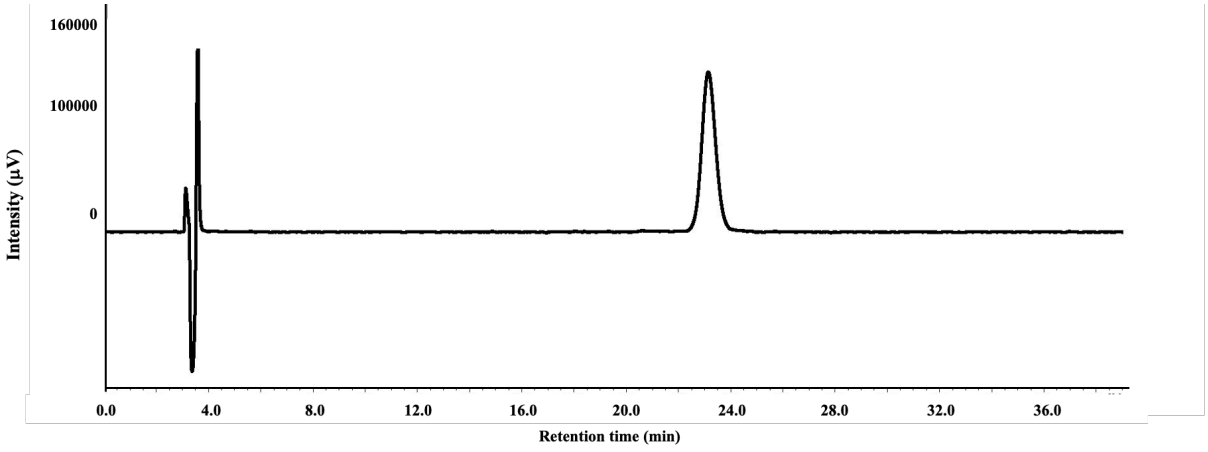
[a] NMR yields. [b] diastereomeric ratios were determined ^{19}F NMR.

X. Synthesis of fluoroalkene-type collagen peptidomimetic

18. Ac-Gly-Pro-Hyp-Gly-Pro-Hyp-Gly-Pro-Hyp-Gly-Ψ[(*Z*)-CF=C]-Pro-Hyp-Gly-Pro-Hyp-Gly-Pro-Hyp-Gly-Pro-Hyp-Gly-Gly-Tyr-NH_2:

Rink Amide Chem Matrix resin was used. On this resin (0.42 mmol amine/g, 118.7 mg, 0.049 mmol) was coupled Fmoc-Tyr(^{t}Bu)-OH (3.0 equiv), Fmoc-Gly-OH (3.0 equiv), Fmoc-Gly-OH (3.0 equiv), Fmoc-Hyp(^{t}Bu)-OH (3.0 equiv), Fmoc-Pro-OH (3.0 equiv), Fmoc-Gly-OH (3.0 equiv), Fmoc-Hyp(^{t}Bu)-OH (3.0 equiv), Fmoc-Pro-OH (3.0 equiv), Fmoc-Gly-OH (3.0 equiv), Fmoc-Hyp(^{t}Bu)-OH (3.0 equiv), Fmoc-Pro-OH (3.0 equiv), Fmoc-Gly-OH (3.0 equiv), and Fmoc-Hyp(^{t}Bu)-OH (3.0 equiv), with the aid of DIC (3.0 equiv) and Oxyma Pure® (3.0 equiv) in DMF at room temperature for 1 h. Then Fmoc removal was performed with 20% (v/v) piperidine/DMF to give a Hyp-Gly-Pro-Hyp-Gly-Pro-Hyp-Gly-Pro-Hyp-Gly-Pro-Hyp-Gly-Gly-Tyr incorporated resin (**16**). The resulting resin was treated with an Ns-Gly-Ψ[(*Z*)-CF=C]-Pro-OH (**12**, 3.0 equiv), HOBt·H_2O (3.0 equiv), and DIC (3.0 equiv) to yield the resin containing the Gly-Pro-type FADI (**17**). Then, Ns group removal was performed with PhSH (20 equiv.) and K_2CO_3 (20 equiv.)/DMF to give a H-Gly-Ψ[(*Z*)-CF=C]-Pro-Hyp-Gly-Pro-Hyp-Gly-Pro-Hyp-Gly-Pro-Hyp-Gly-Pro-Hyp-Gly-Gly-Tyr-incorporated resin. On these resins, standard Fmoc SPPS was performed for the chain elongation to give a protected peptide resin for the pseudopeptide (**18**). On these resins, standard Fmoc SPPS and acetylation with Ac_2O (10 equiv.) and pyridine (10 equiv.) were performed to give a protected peptide resin for the peptidomimetic (**18**). The resulting completed resin was treated with TFA-triisopropylsilane-H_2O (95:2.5:2.5 (v/v), 50 μL/1 mg resin) at room temperature for 2 h. The resin in the reaction mixture was filtrated off. To the resulting filtrate was added cooled Et_2O to give a precipitate. The formed precipitate was collected by centrifugation and thoroughly washed with Et_2O to afford crude pseudopeptide (**18**). The crude pseudopeptide (**18**) was purified by preparative HPLC gave the title pseudopeptide (**18**) as a colorless freeze-dried powder.

18 Analytical HPLC conditions: COSMOSIL 5C_{18}-AR-II analytical column with an isocratic of 0.1% TFA-MeCN in 0.1% TFA aq., 12% over 40 min, detected at 220 nm, retention time = 23.95 min, HRMS (ESI) *m*/*z* calcd ([M + 2H]$^+$) 1238, found 1238.

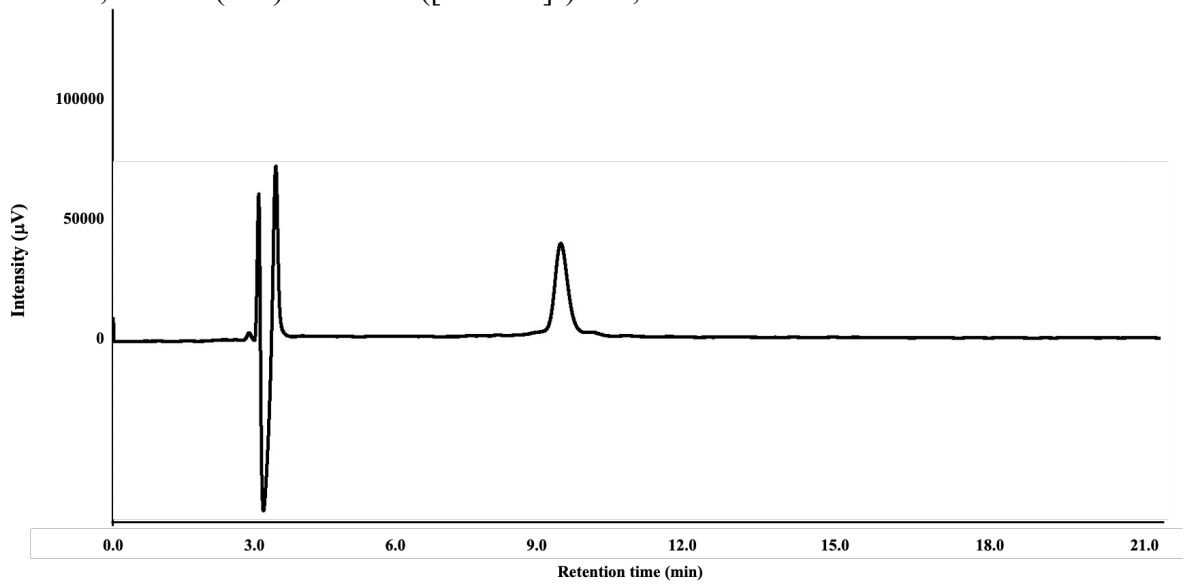


XI. Synthesis of fluoroalkene-type R3 peptidomimetic (27)

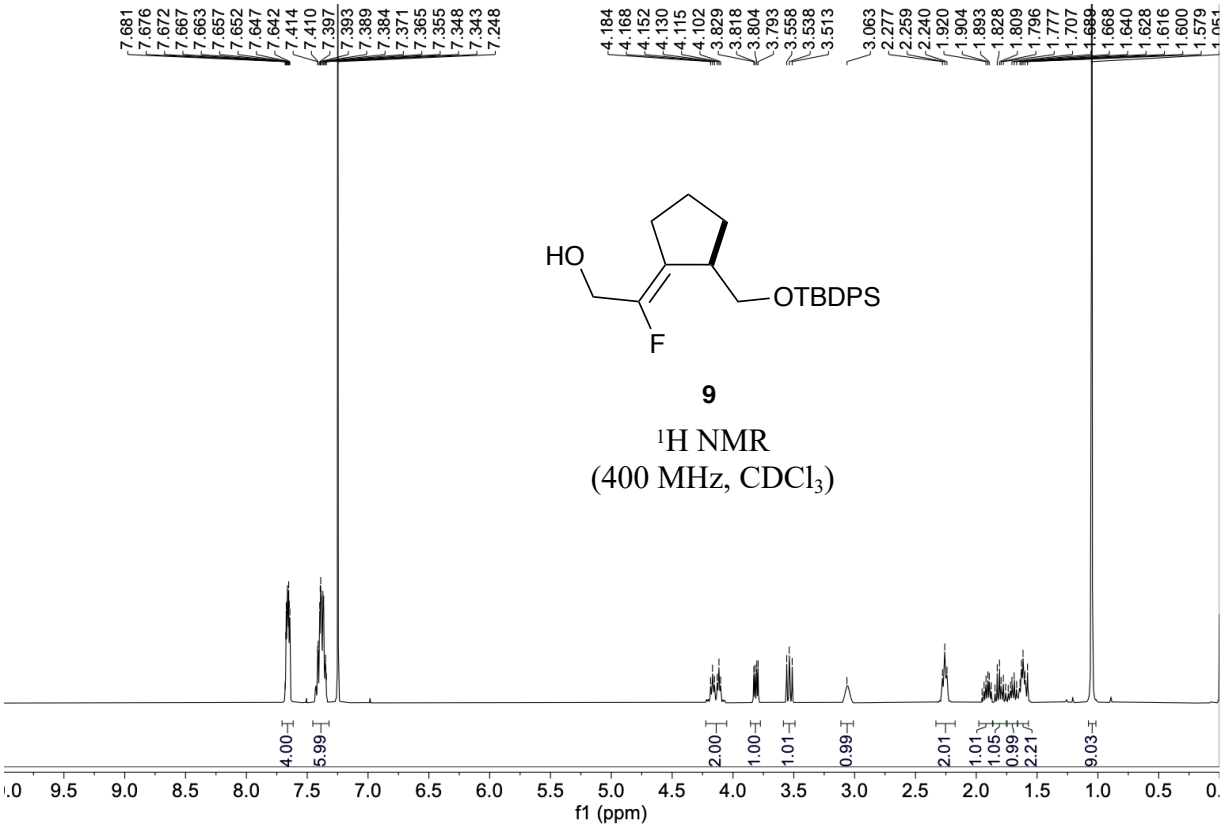
15. Ac-Val-Gln-Ile-Val-Tyr-Val-Ψ[(*Z*)CF=C]-Pro-Val-Asp-Leu-Ser-Lys-Val-Thr-Ser-Lys-Cys-Gly-Ser-Leu-Gly-Asn-Ile-His-His-Lys-Pro-Gly-Gly-Gly-Gln-NH_2:

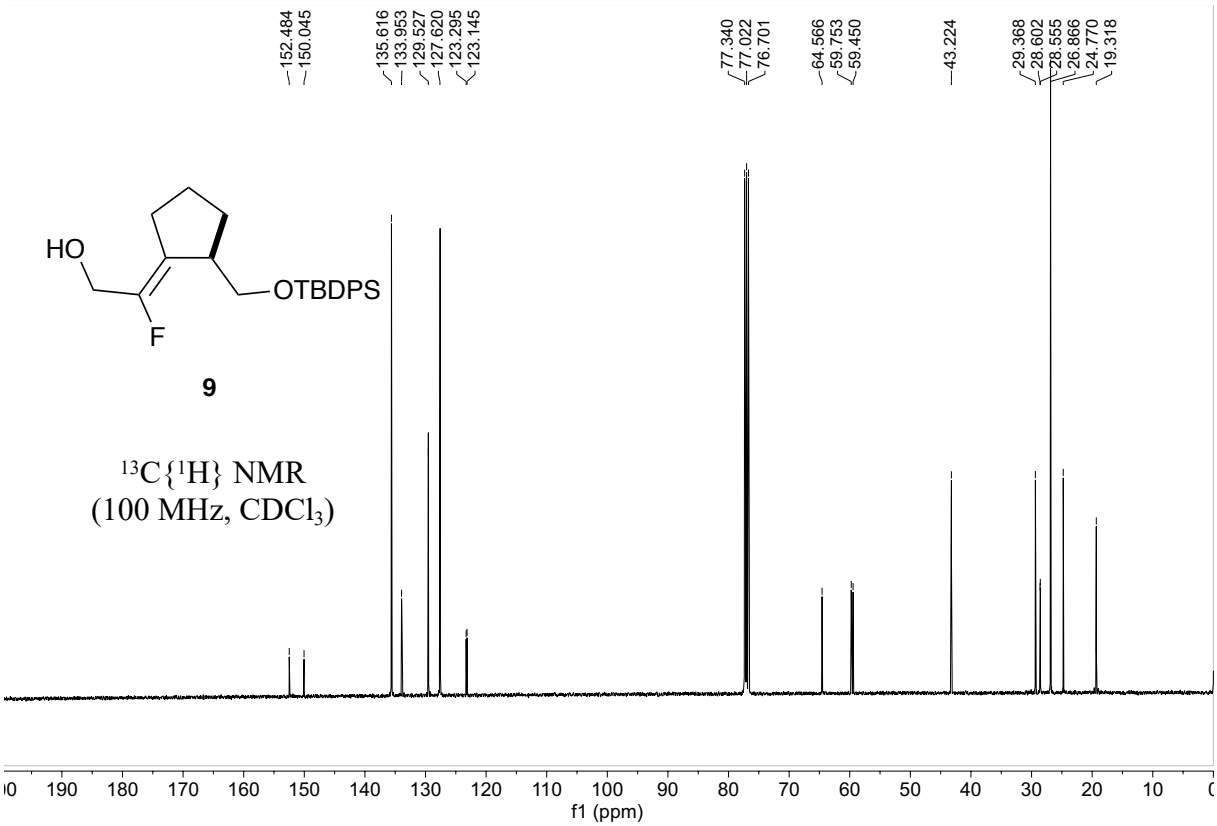
Rink Amide NovaSyn TGR® resin was used. On this resin (0.22 mmol amine/g, 227 mg, 0.050 mmol) was coupled Fmoc-Val-OH (3.0 equiv), Fmoc-Gln(Trt)-OH (3.0 equiv), Fmoc-Gly-OH (3.0 equiv), Fmoc-Gly-OH (3.0 equiv), Fmoc-Gly-OH (3.0 equiv), Fmoc-Pro-OH (3.0 equiv), Fmoc-Lys(Boc)-OH (3.0 equiv), Fmoc-His(Boc)-OH (3.0 equiv), Fmoc-His(Boc)-OH (3.0 equiv), Fmoc-Ile-OH (3.0 equiv), Fmoc-Asn(Trt)-OH (3.0 equiv), Fmoc-^{Dmb}Gly-OH (3.0 equiv), Fmoc-Leu-OH (3.0 equiv), Fmoc-Ser(^{t}Bu)-OH (3.0 equiv), Fmoc-^{Dmb}Gly-OH (3.0 equiv), Fmoc-Cys(Trt)-OH (3.0 equiv), Fmoc-Lys(Boc)-OH (3.0 equiv), Fmoc-Ser(^{t}Bu)-OH (3.0 equiv), Fmoc-Thr(^{t}Bu)-OH (3.0 equiv), Fmoc-Val-OH (3.0 equiv), Fmoc-Lys(Boc)-OH (3.0 equiv), Fmoc-Ser(^{t}Bu)-OH (3.0 equiv), Fmoc-Leu-OH (3.0 equiv), Fmoc-Asp(^{t}Bu)-OH (3.0 equiv), and Fmoc-Val-OH (3.0 equiv) with the aid of diisopropylcarbodiimide (DIC: 3.0 equiv) and Oxyma Pure® (3.0 equiv) in DMF at room temperature for 1 h. Then Fmoc removal was performed with 20% (v/v) piperidine/DMF to give a H-Pro-Val-Asp-Leu-Ser-Lys-Val-Thr-Ser-Lys-Cys-Gly-Ser-Leu-Gly-Asn-Ile-His-His-Lys-Pro-Gly-Gly-Gly-Gln- incorporated resin (**25**). The resulting resin was treated with an Ns-Val-Ψ[(*Z*)-CF=C]-Pro-OH (**24**, 3.0 equiv), HOBt·H_2O (3.0 equiv), and DIC (3.0 equiv) at seven times to yield the resin containing the Val-Pro-type (*Z*)-FADI (**26**). Then, Ns group removal was performed with PhSH (20 equiv.) and K_2CO_3 (20 equiv.)/DMF to give a H-Val-Ψ[(*Z*)-CF=C]-Pro-Val-Asp-Leu-Ser-Lys-Val-Thr-Ser-Lys-Cys-Gly-Ser-Leu-Gly-Asn-Ile-His-His-Lys-Pro-Gly-Gly-Gly-Gln- incorporated resin. On these resins, standard Fmoc SPPS and acetylation with Ac_2O (10 equiv.) and pyridine (10 equiv.) were performed to give a protected peptide resin for the peptidomimetic (**27**). The resulting completed resin was treated with TFA-triisopropylsilane-H_2O (95:2.5:2.5 (v/v), 50 μL/1 mg resin) at room temperature for 2 h. The resin in the reaction mixture was filtrated off. To the resulting filtrate was added cooled Et_2O to give a precipitate. The formed precipitate was collected by centrifugation and thoroughly washed with Et_2O to afford crude peptidomimetic (**27**). The crude peptidomimetic (**27**) was purified by preparative HPLC gave the title peptidomimetic (**27**) as a colorless freeze-dried powder.

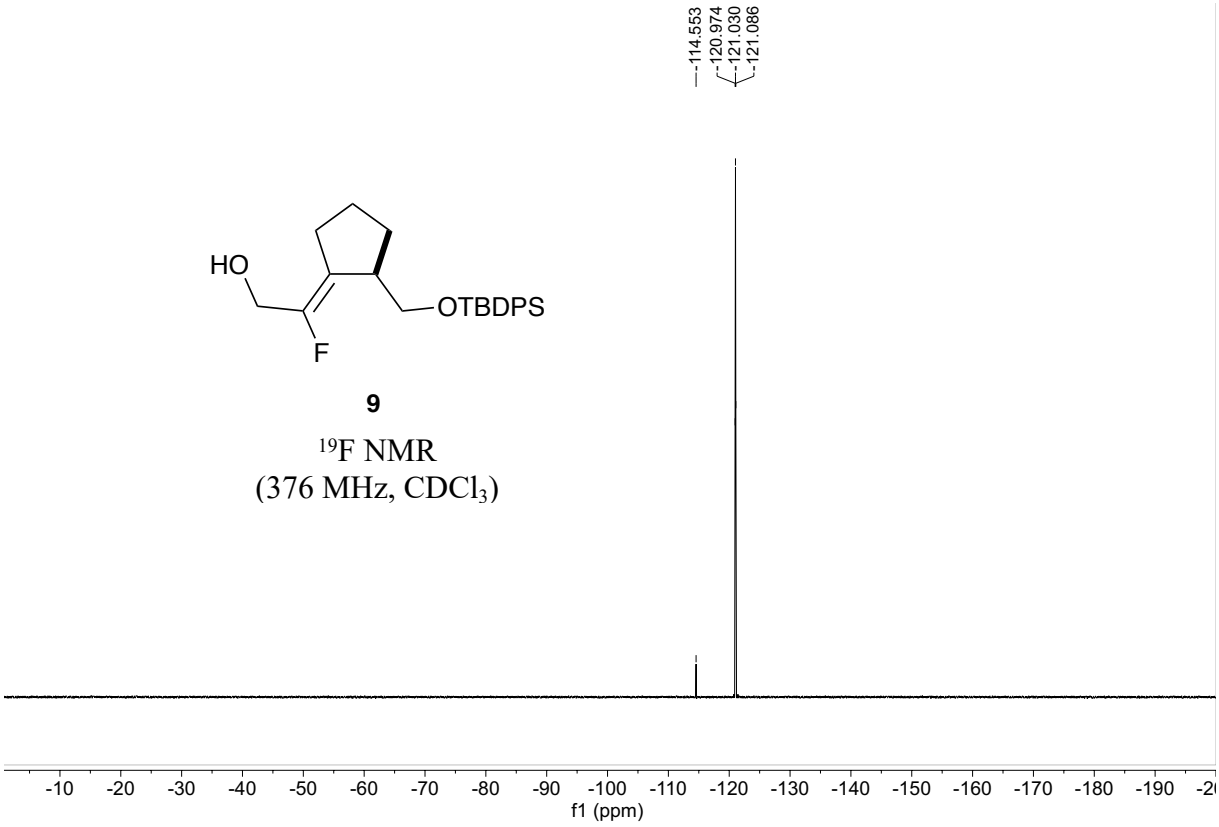
27 Analytical HPLC conditions: COSMOSIL 5C_{18}-AR-II analytical column with an isocratic of 0.1% TFA-MeCN in 0.1% TFA aq., 30% over 30 min, detected at 220 nm, retention time = 9.06 min, HRMS (ESI) *m*/*z* calcd ($[M + 4H]^+$) 815, found 815.



XII. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR charts

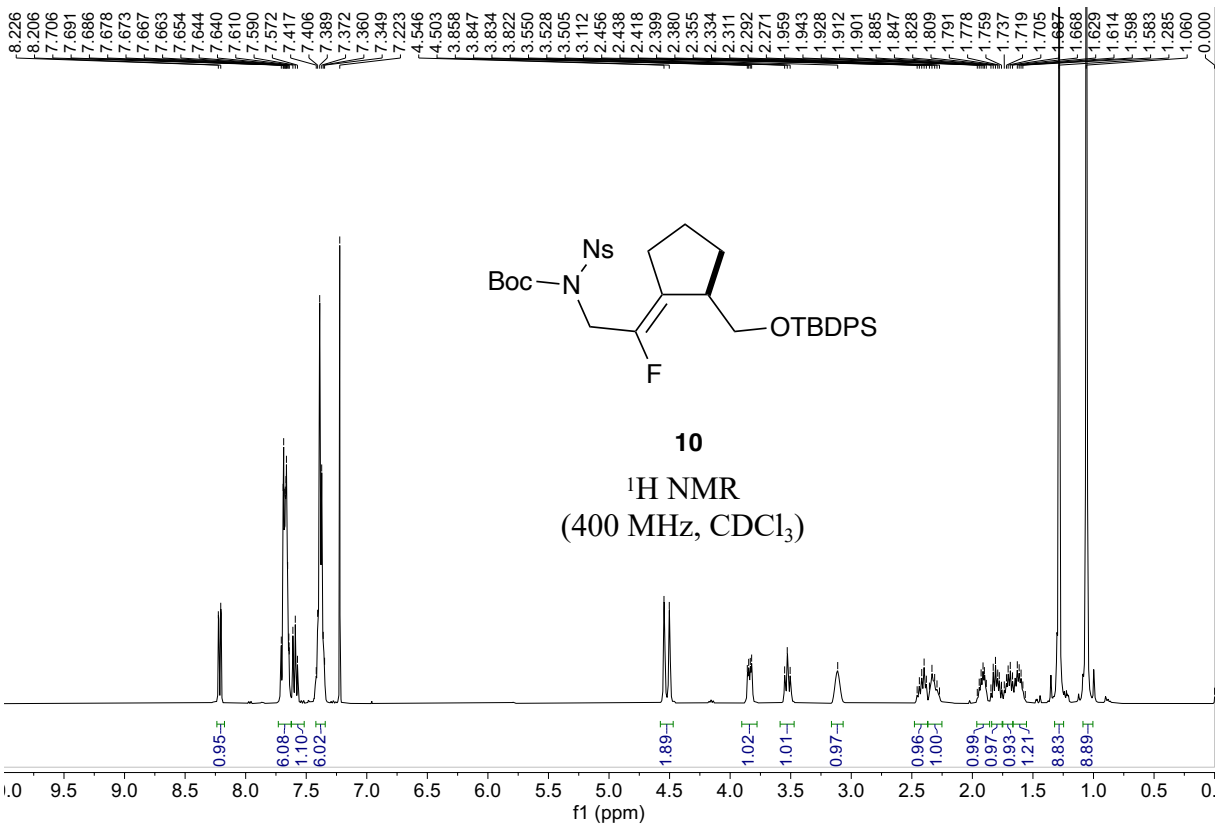






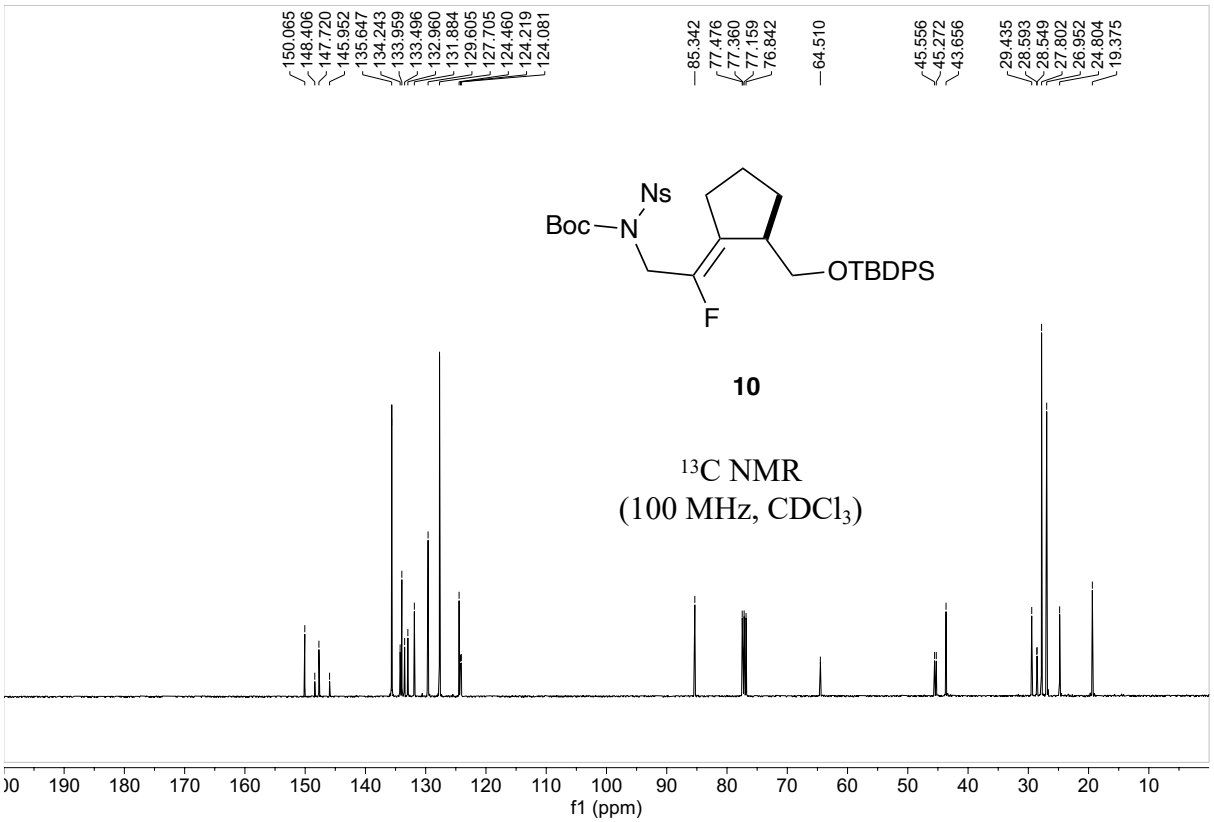
9

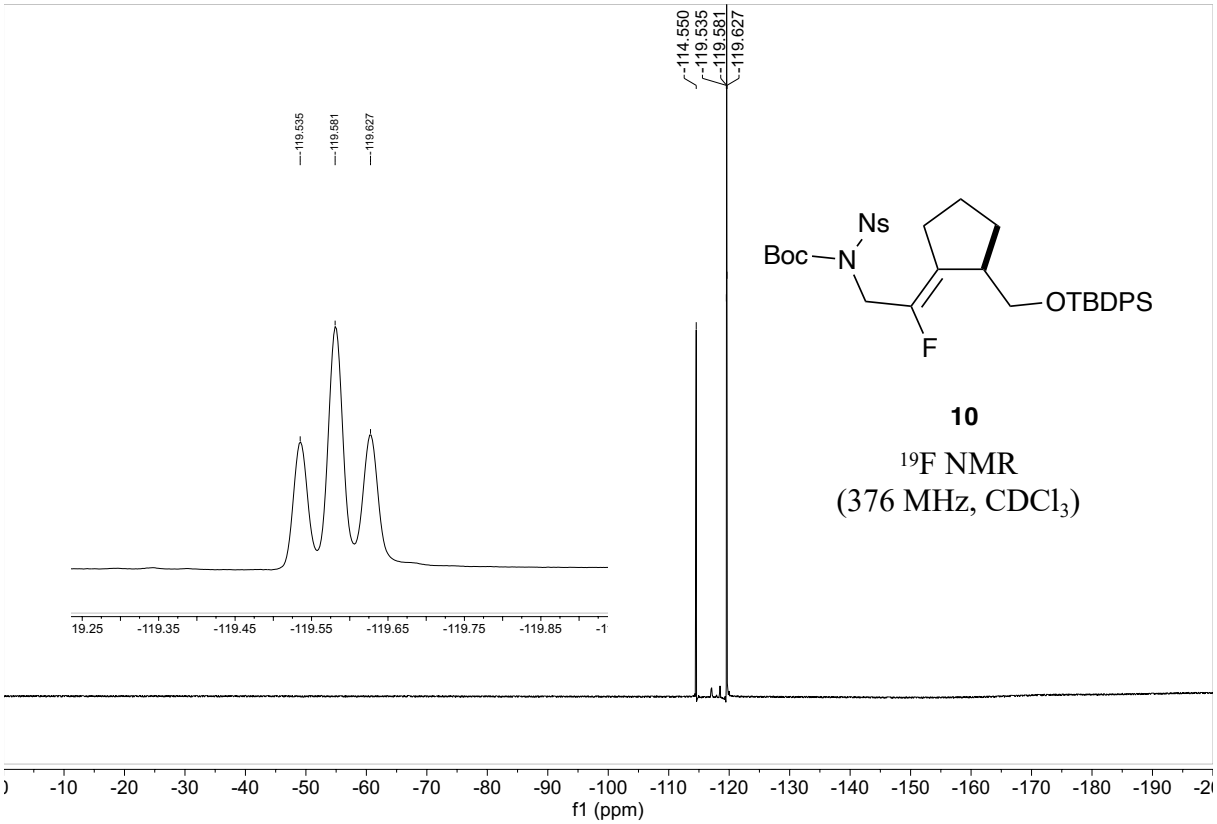
^{19}F NMR
(376 MHz, $CDCl_3$)

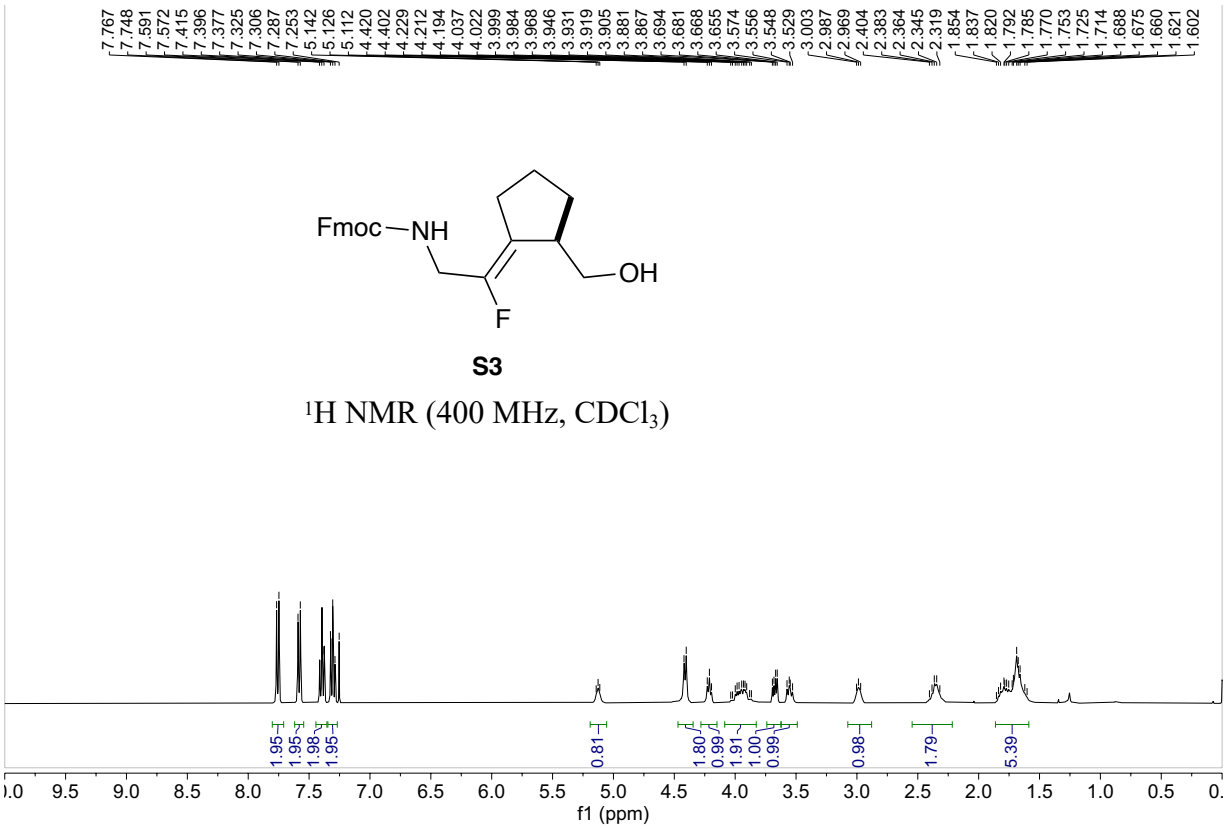


10

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

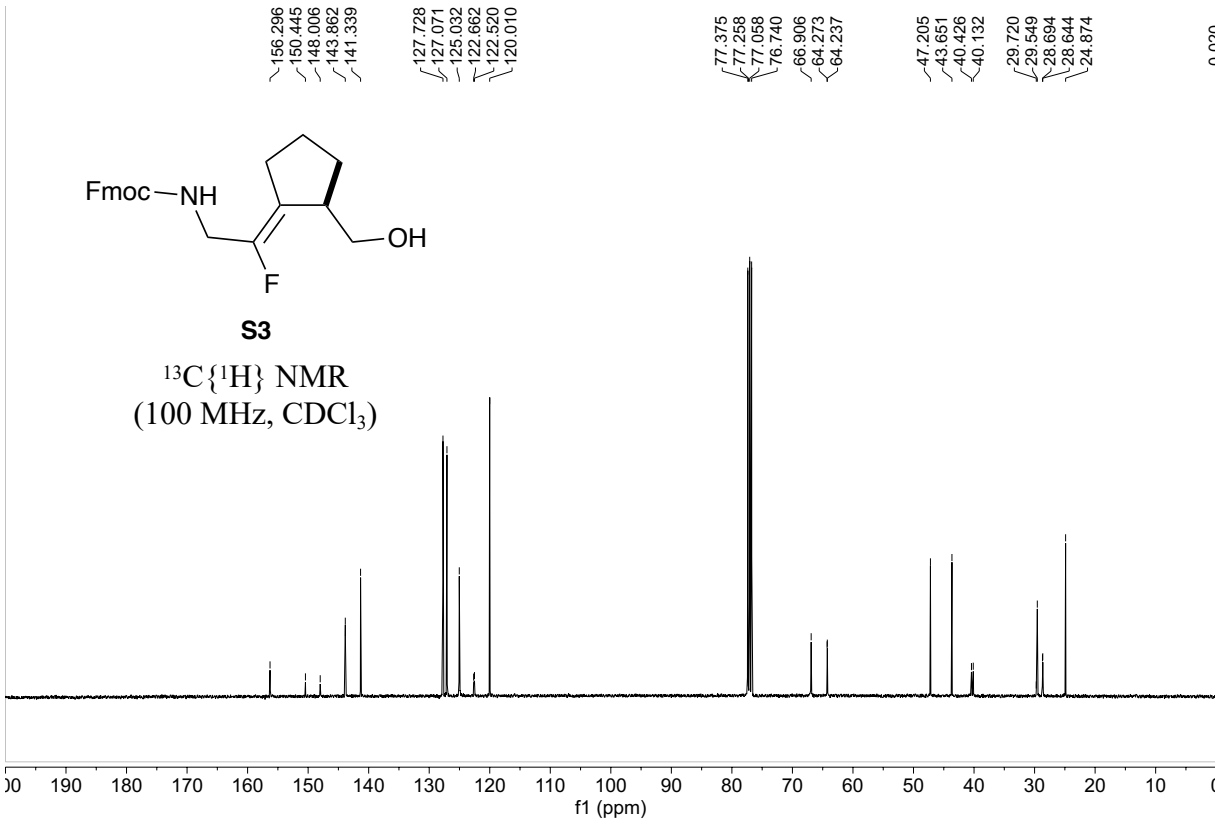

150.065
148.406
147.720
145.952
135.647
134.243
133.959
133.496
132.960
131.884
129.605
127.705
124.460
124.219
124.081
85.342
77.476
77.360
77.159
76.842
64.510
45.556
45.272
43.656
29.435
28.593
28.549
27.802
26.952
24.804
19.375
Ns
Boc
N
OTBDPS
F
10
13C NMR
(100 MHz, CDCl3)
f1 (ppm)


114.550
119.535
119.581
119.627
119.535
119.581
119.627
19.25
-119.35
-119.45
-119.55
-119.65
-119.75
-119.85
Ns
Boc
N
OTBDPS
F
10
19F NMR
(376 MHz, CDCl3)
f1 (ppm)



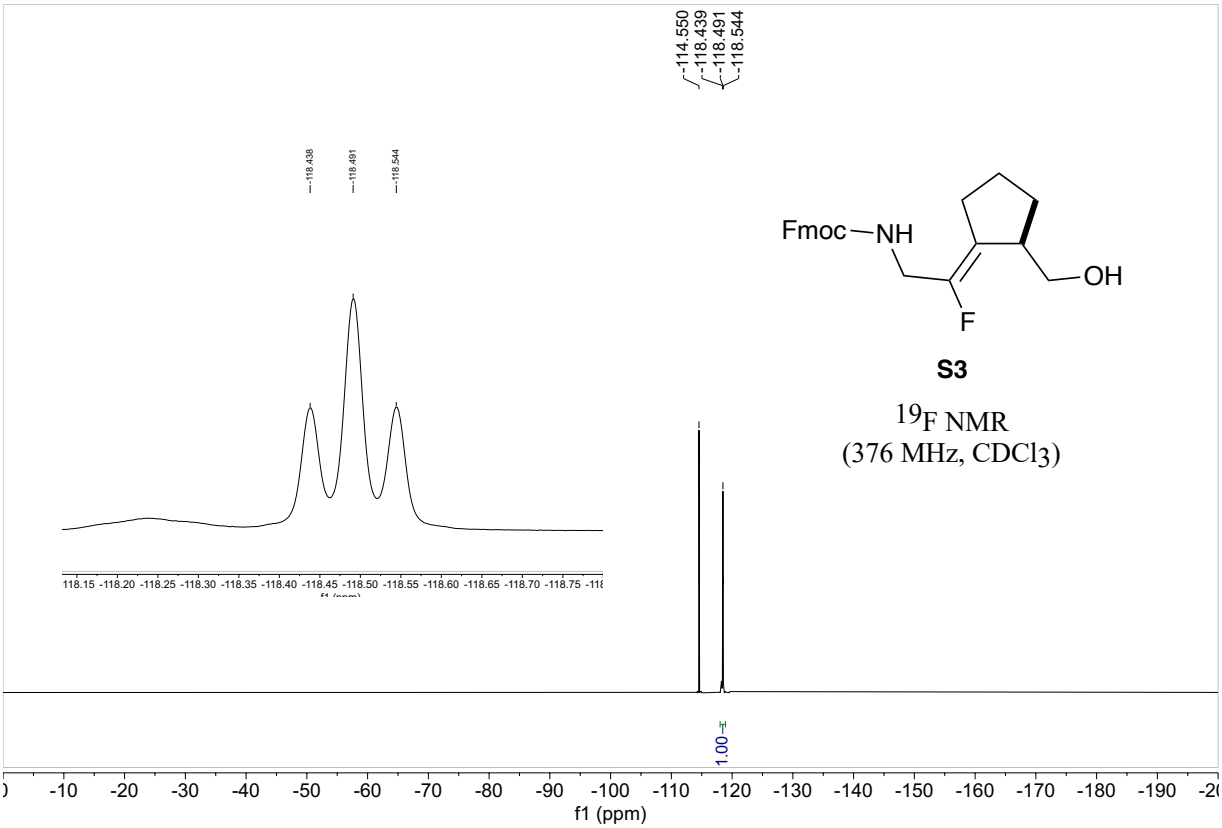
S3

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



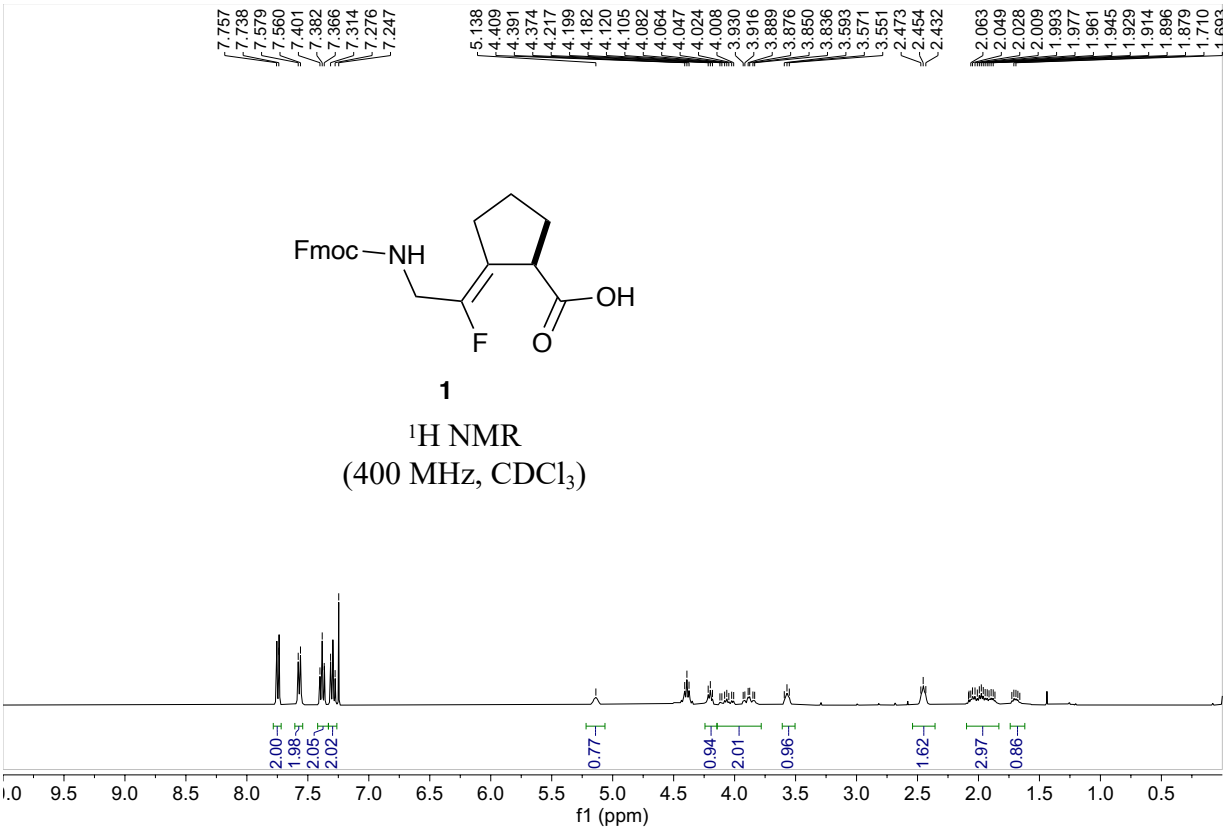
S3

^{13}C{^{1}H} NMR
(100 MHz, $CDCl_3$)



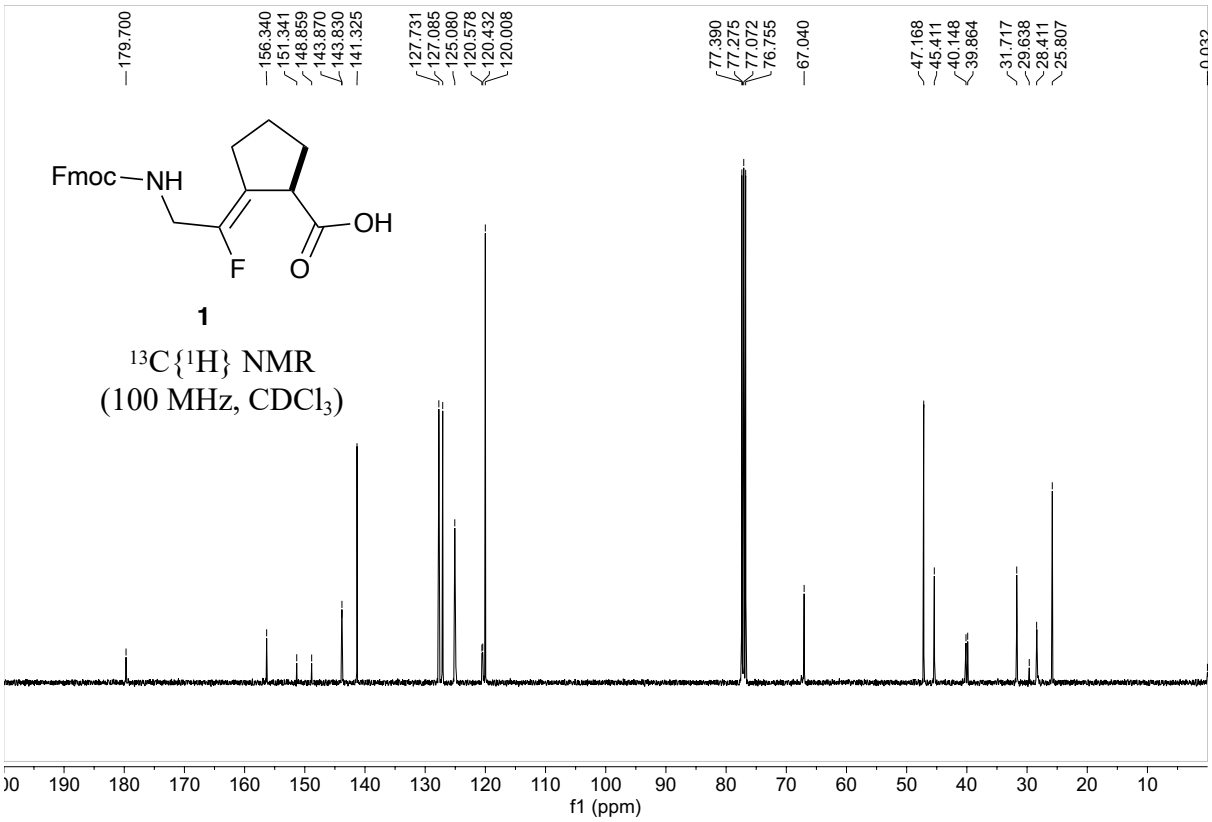
S3

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



1

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


179.700
156.340
151.341
148.859
143.870
143.830
141.325
127.731
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125.080
120.578
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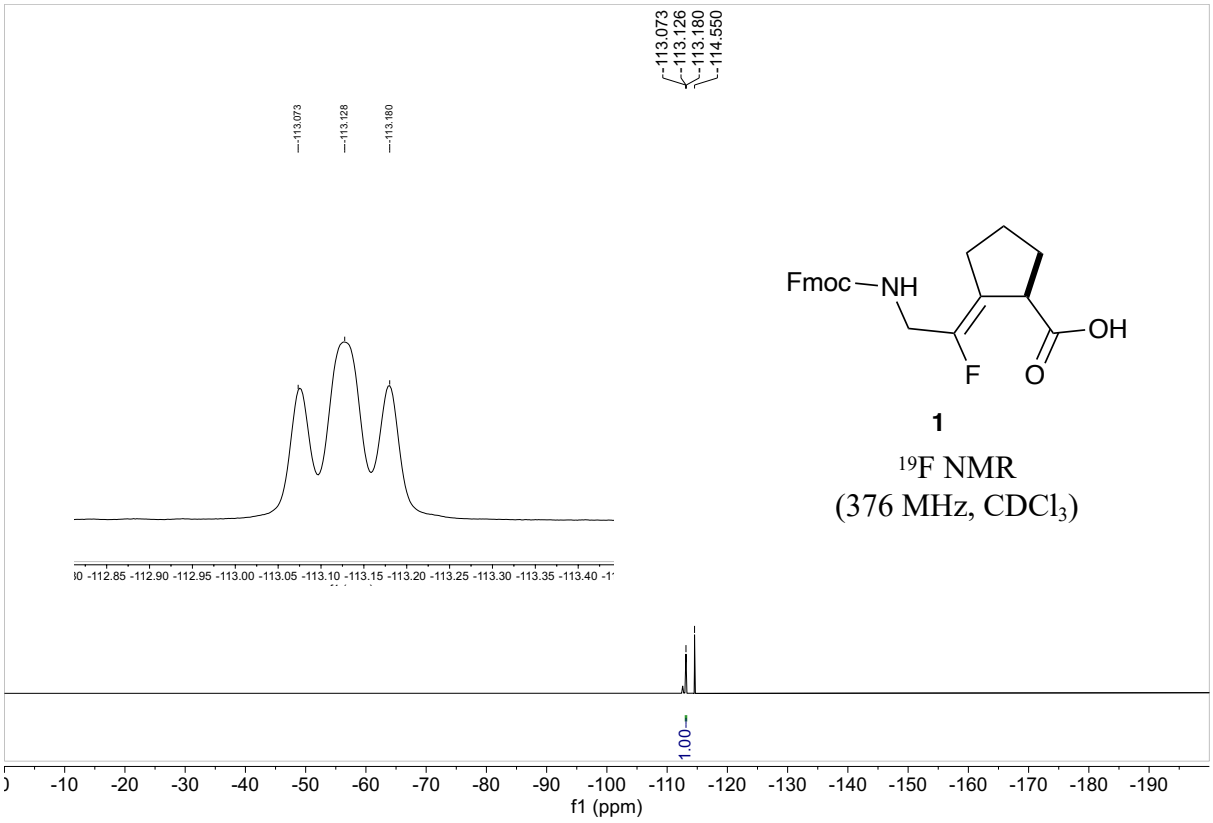
77.390
77.275
77.072
76.755
67.040
47.168
45.411
40.148
39.864
31.717
29.638
28.411
25.807
Fmoc—NH
OH
F
O
1
13C{1H} NMR
(100 MHz, CDCl3)
f1 (ppm)


113.073
113.126
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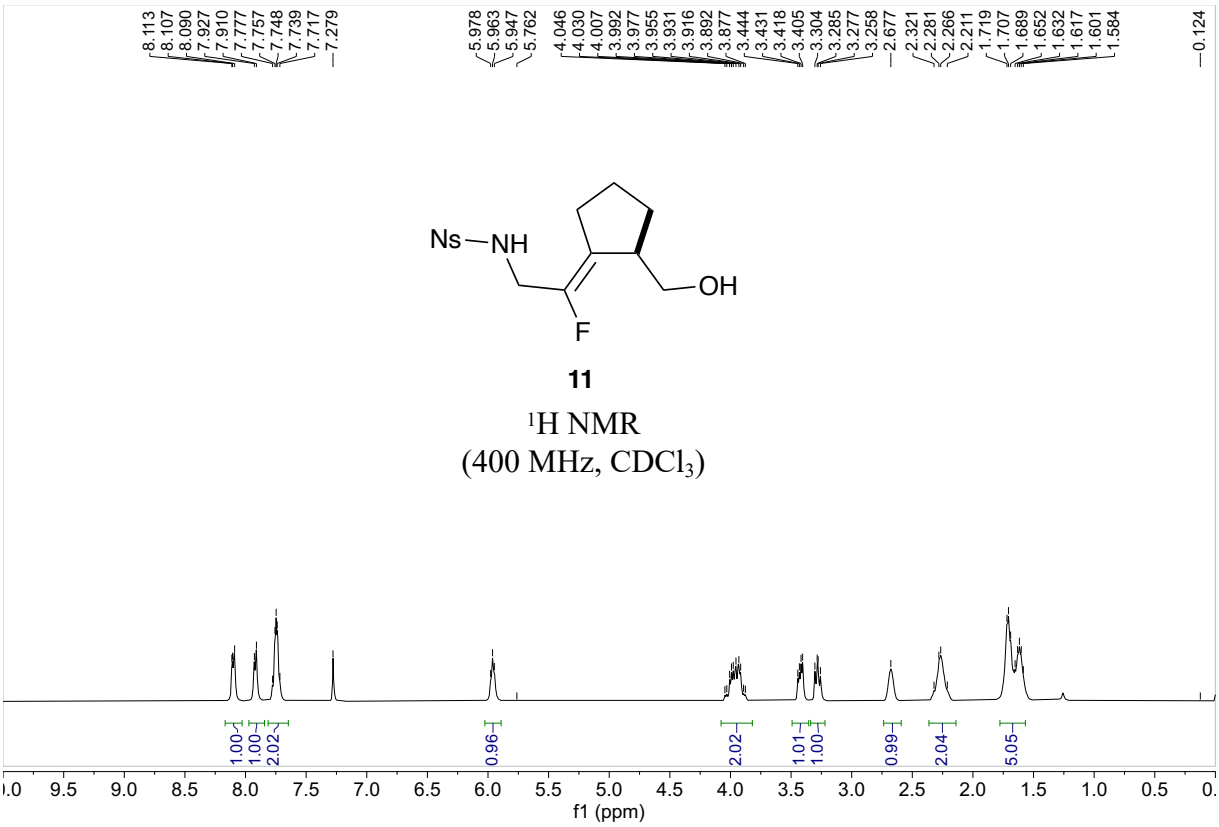
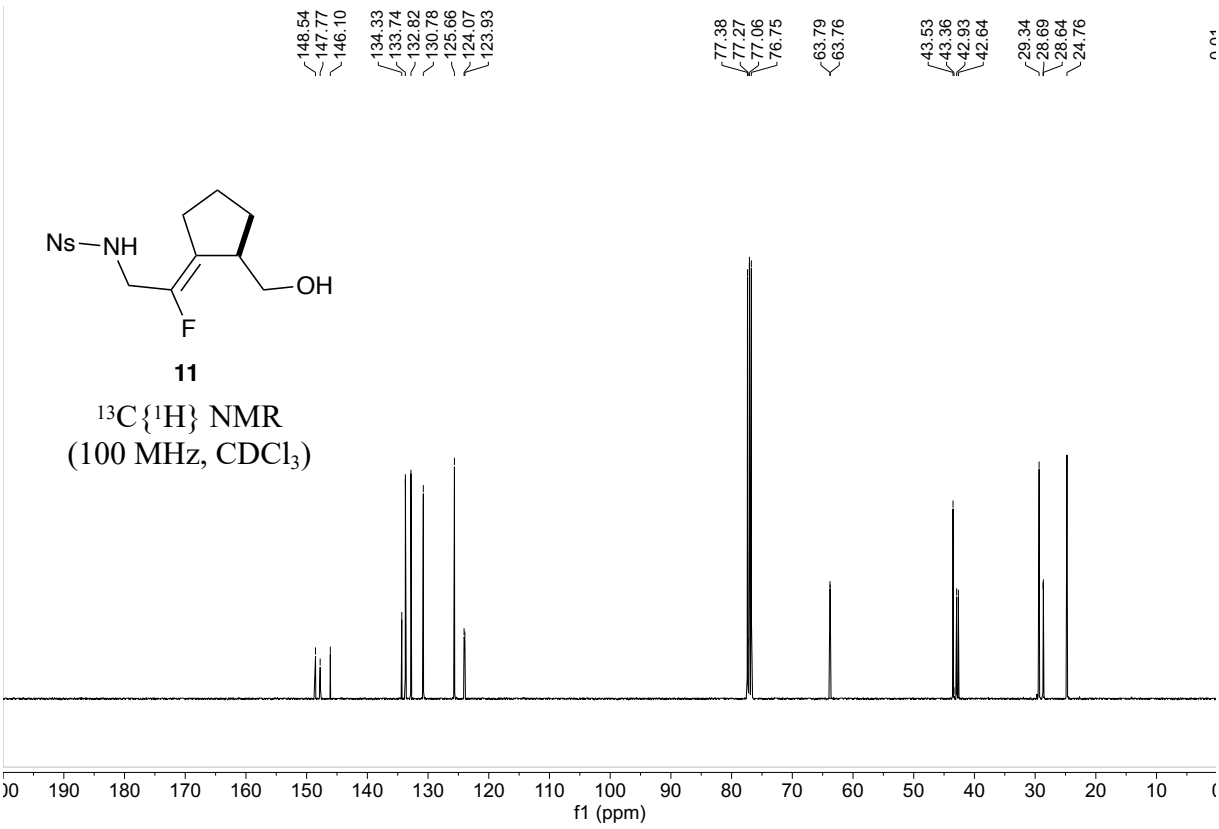
114.550
Fmoc—NH
OH
F
O
1
19F NMR
(376 MHz, CDCl3)
1.00
f1 (ppm)



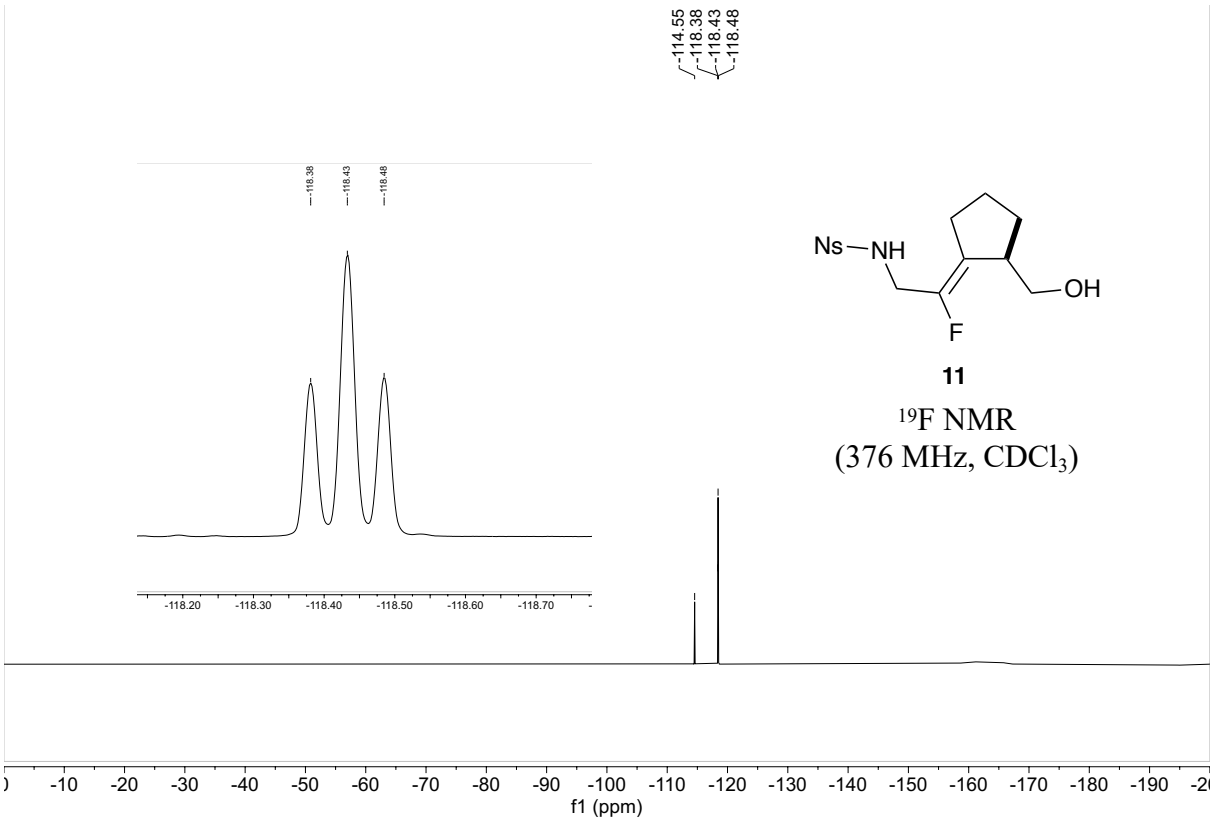
11

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



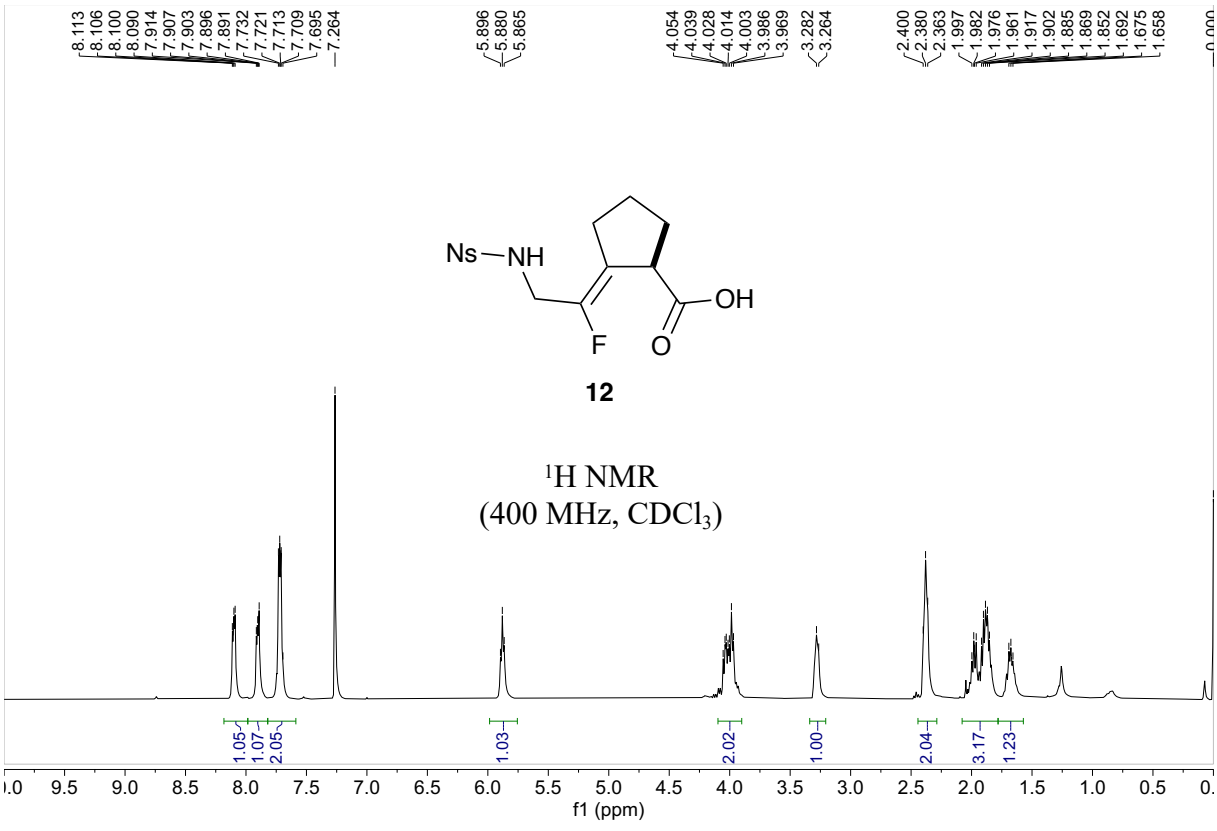
11

^{13}C{^{1}H} NMR
(100 MHz, $CDCl_3$)



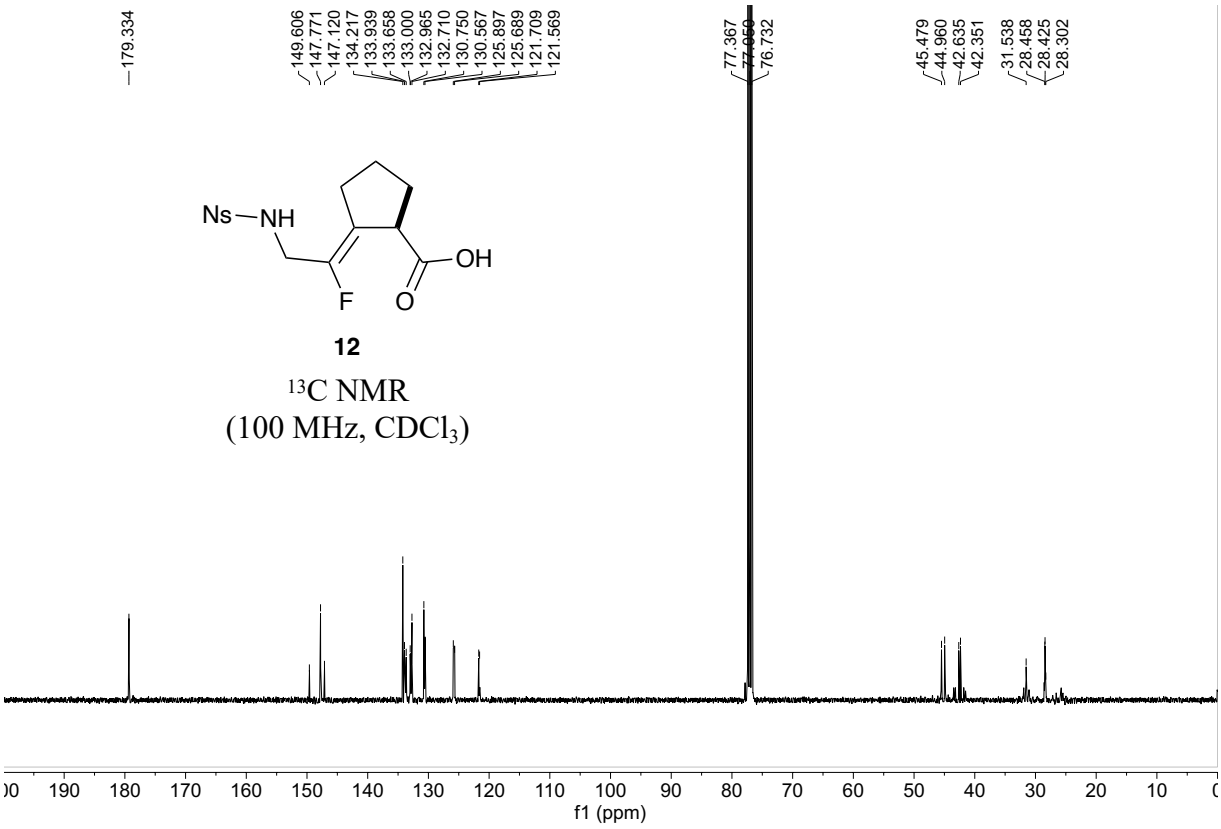
11

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



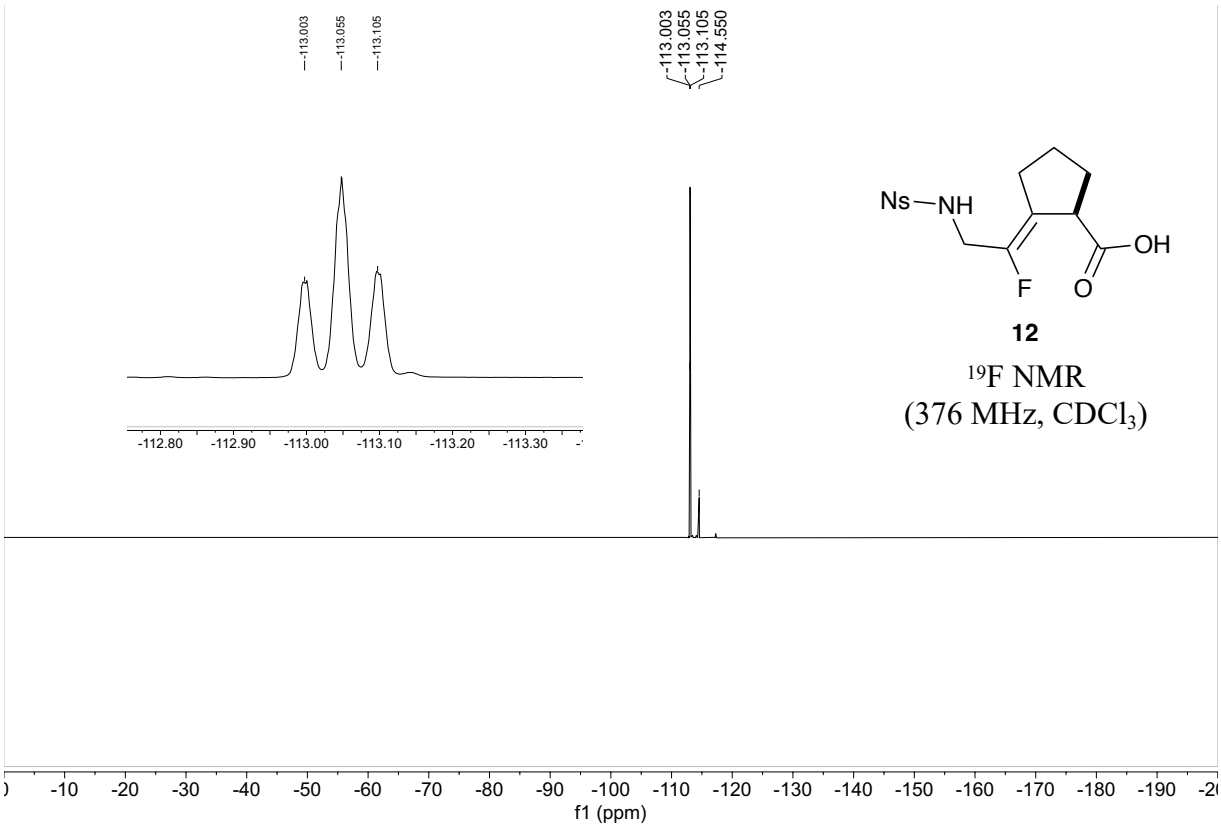
12

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



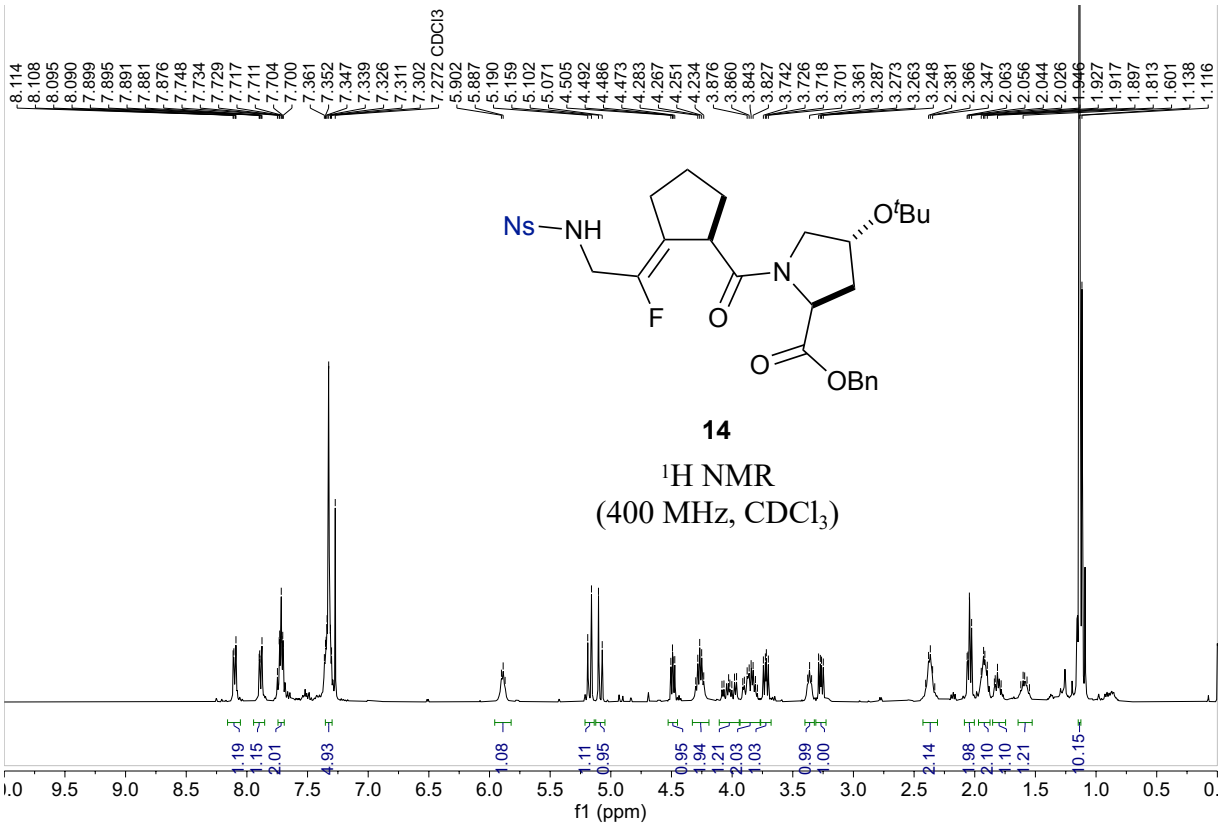
12

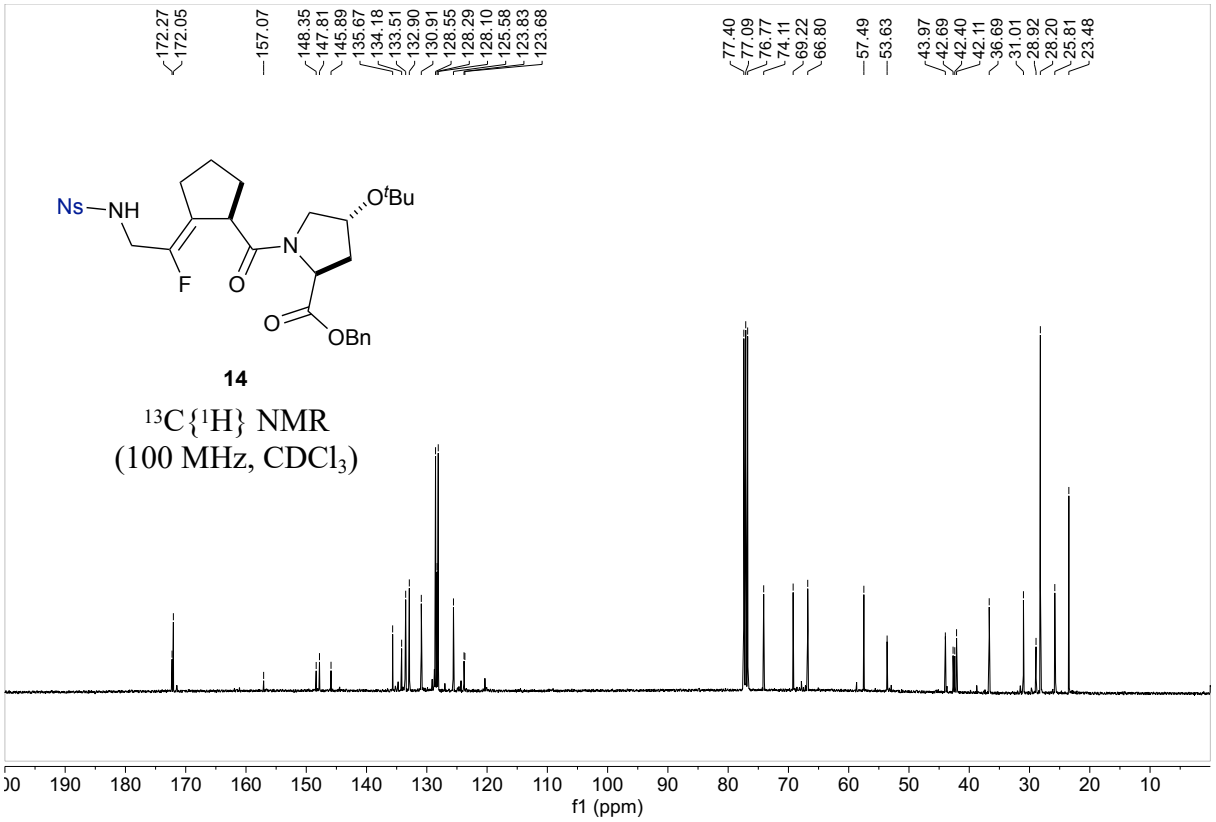
^{13}C NMR
(100 MHz, $CDCl_3$)

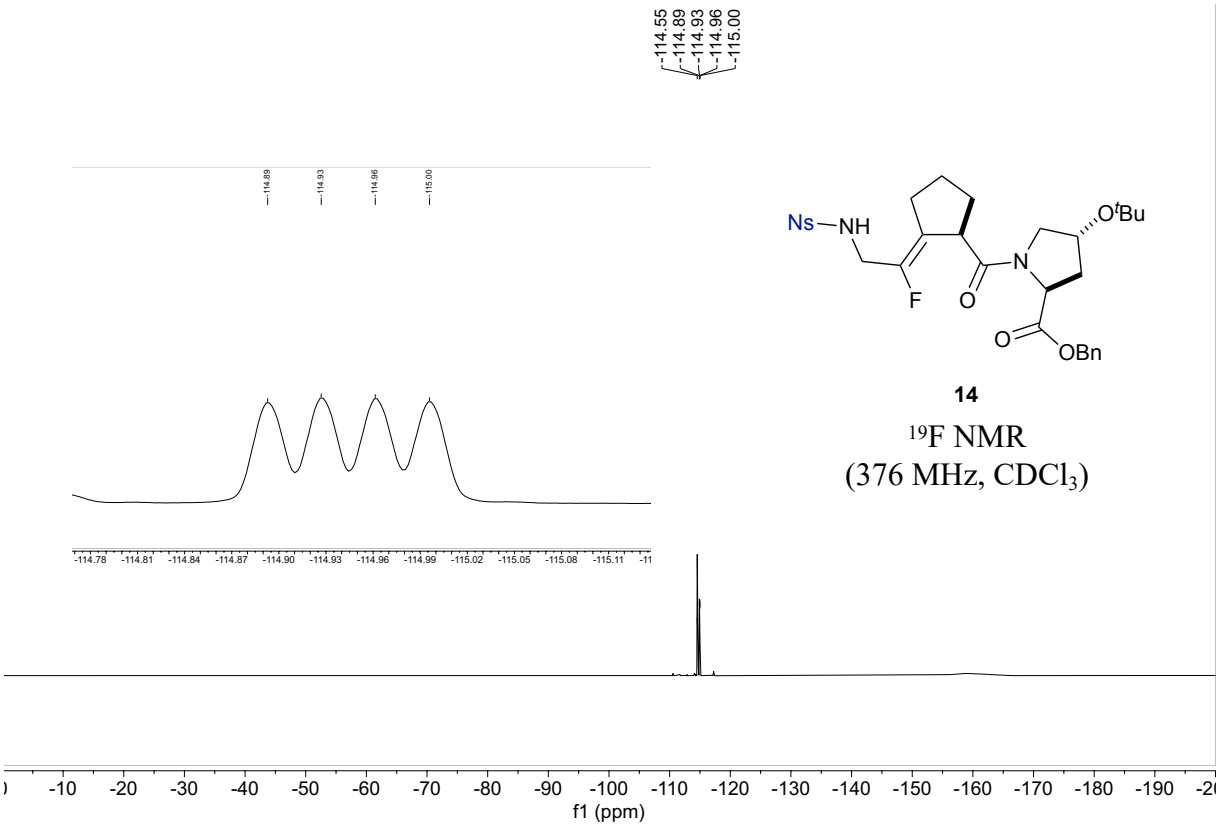


12

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

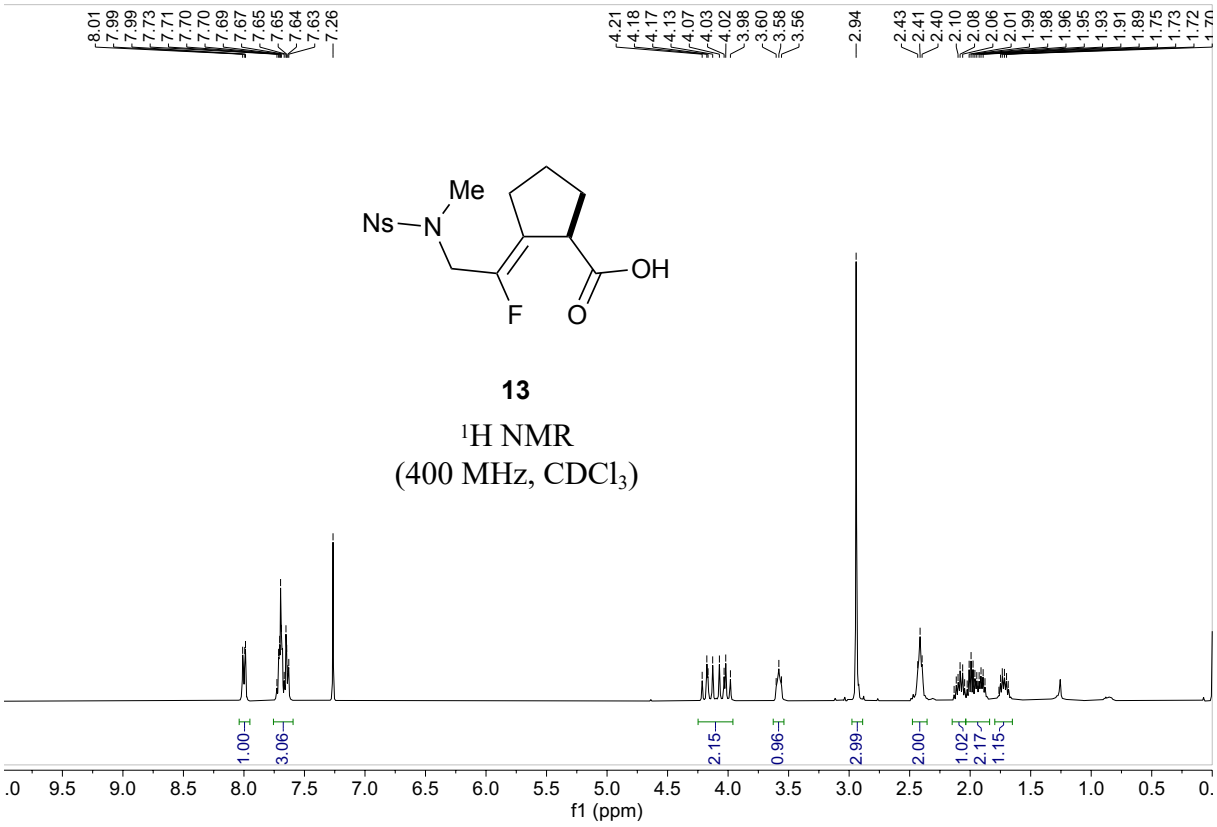

Ns—NH
O^{t}Bu
N
F
O
O
OBn
14
^{1}H NMR
(400 MHz, $CDCl_3$)
f1 (ppm)


Ns—NH
O^{t}Bu
N
F
O
O
OBn
14
^{13}C{^{1}H} NMR
(100 MHz, $CDCl_3$)
f1 (ppm)



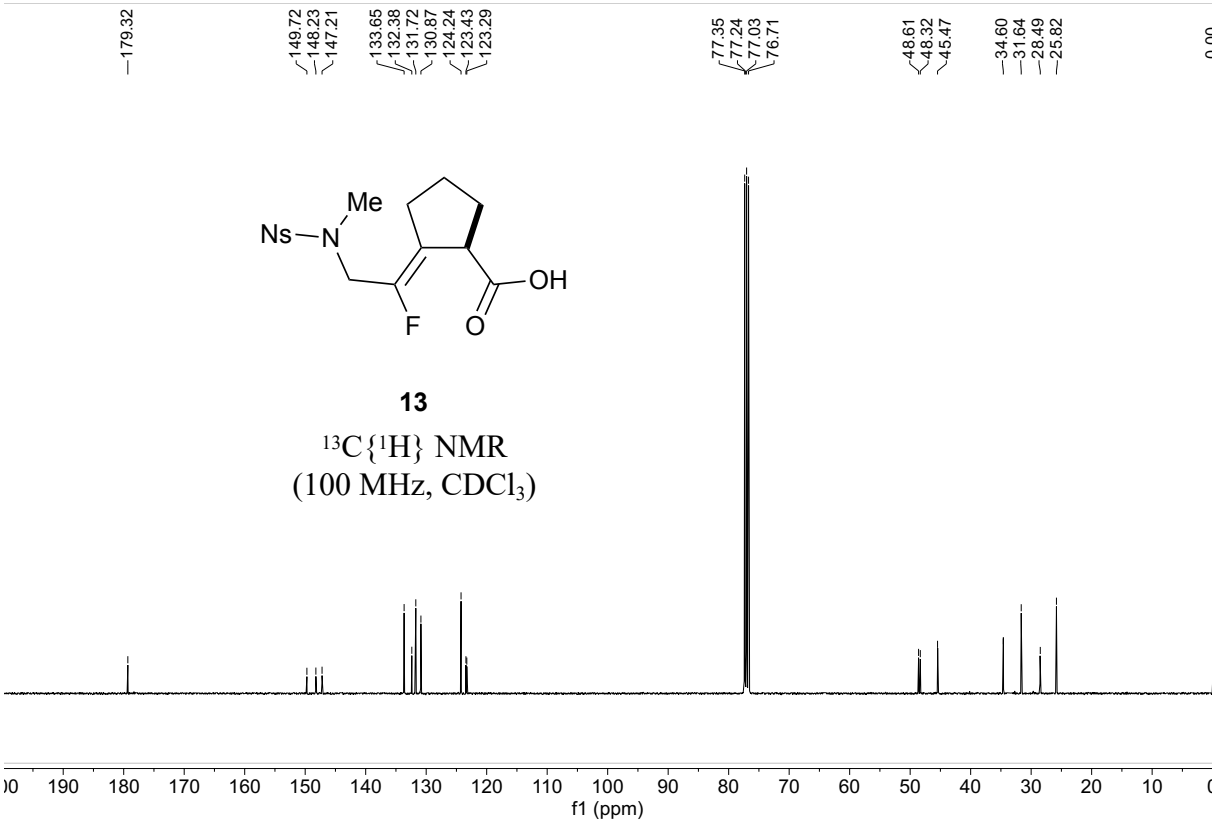
14

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



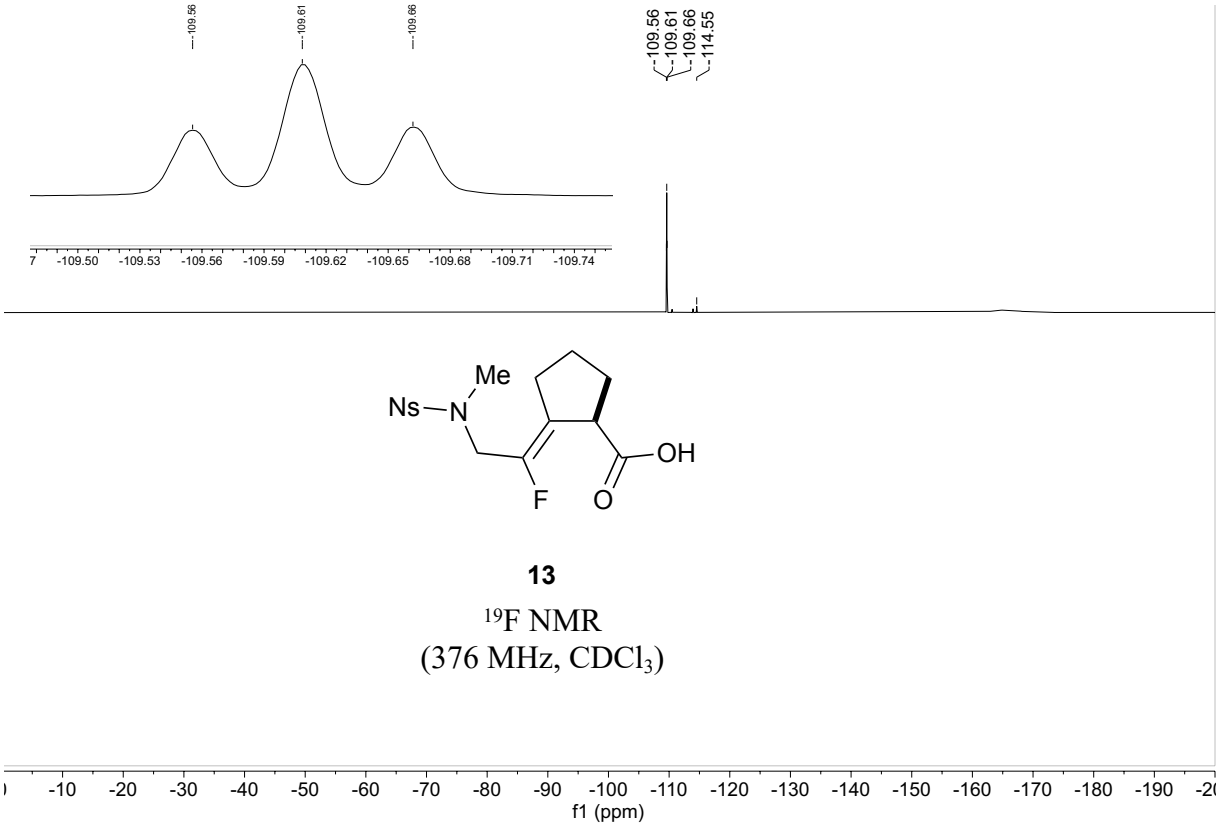
13

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



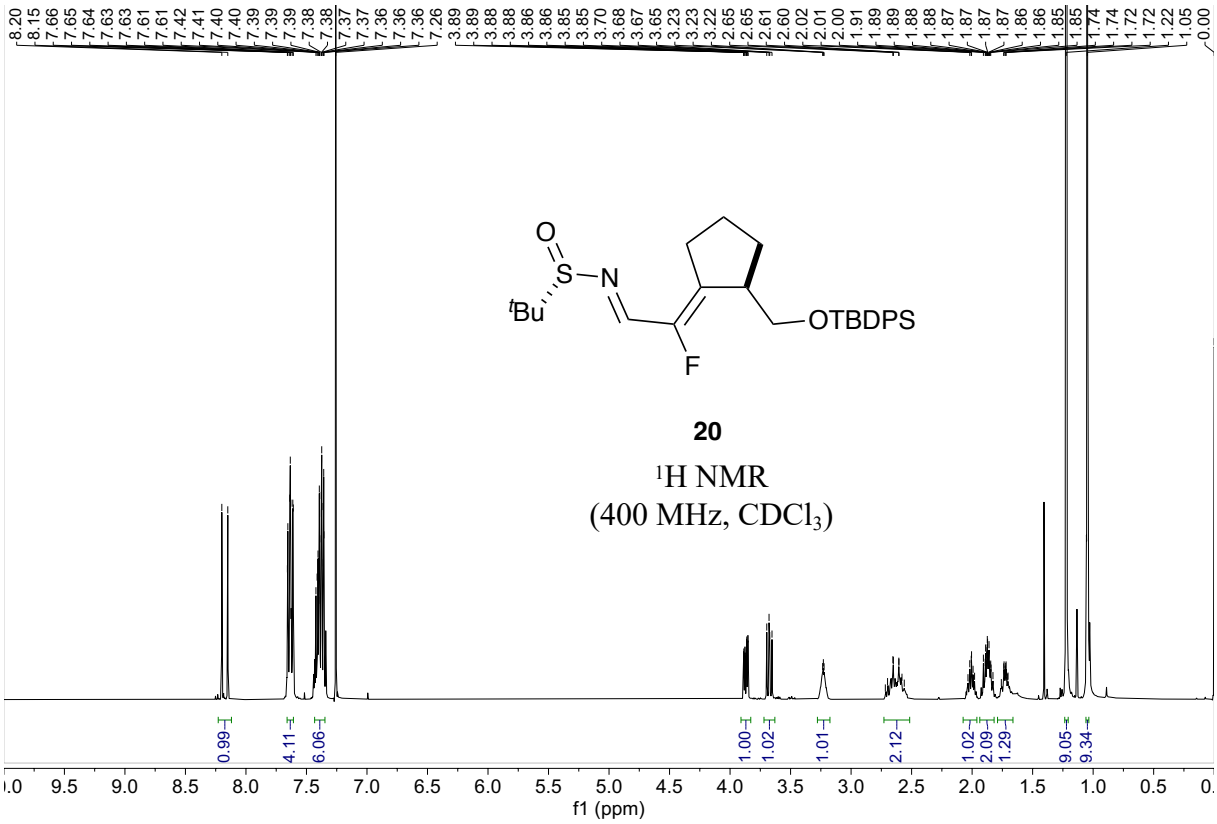
13

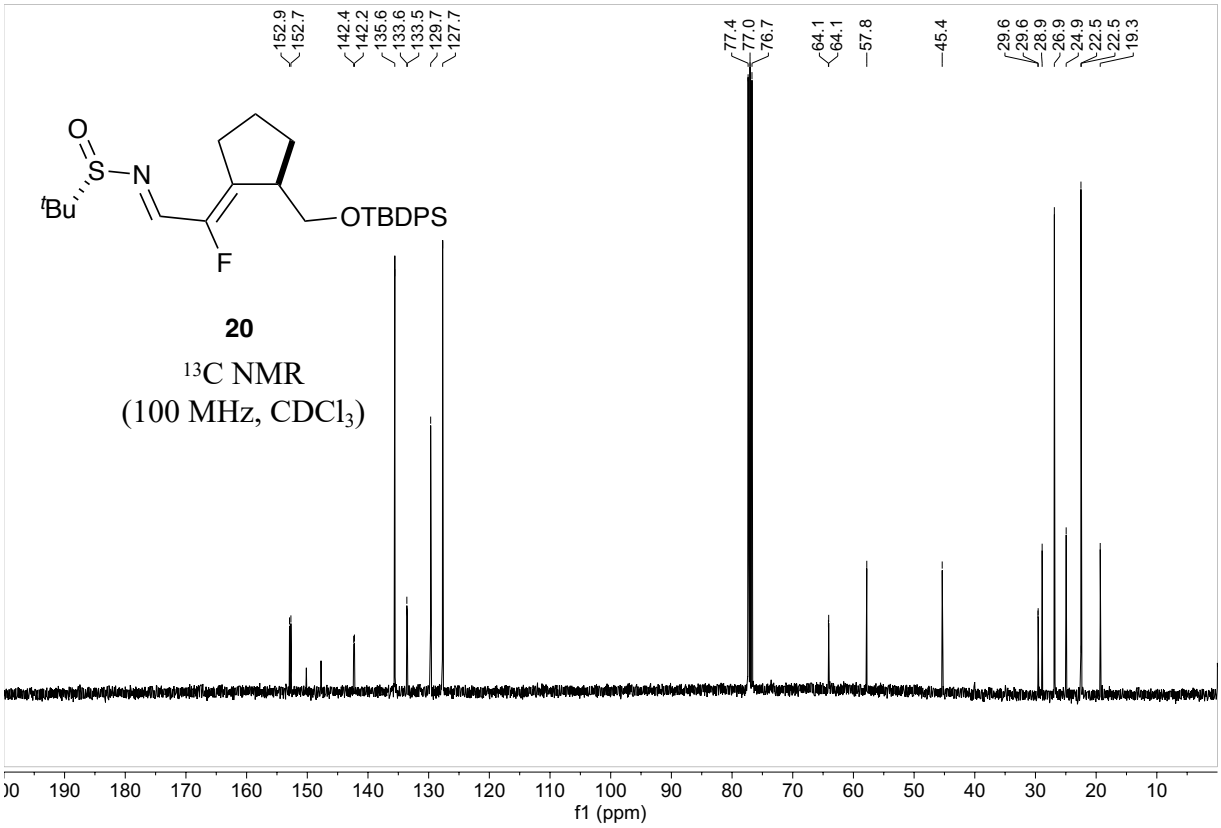
$^{13}C\{^{1}H\}$ NMR
(100 MHz, $CDCl_3$)

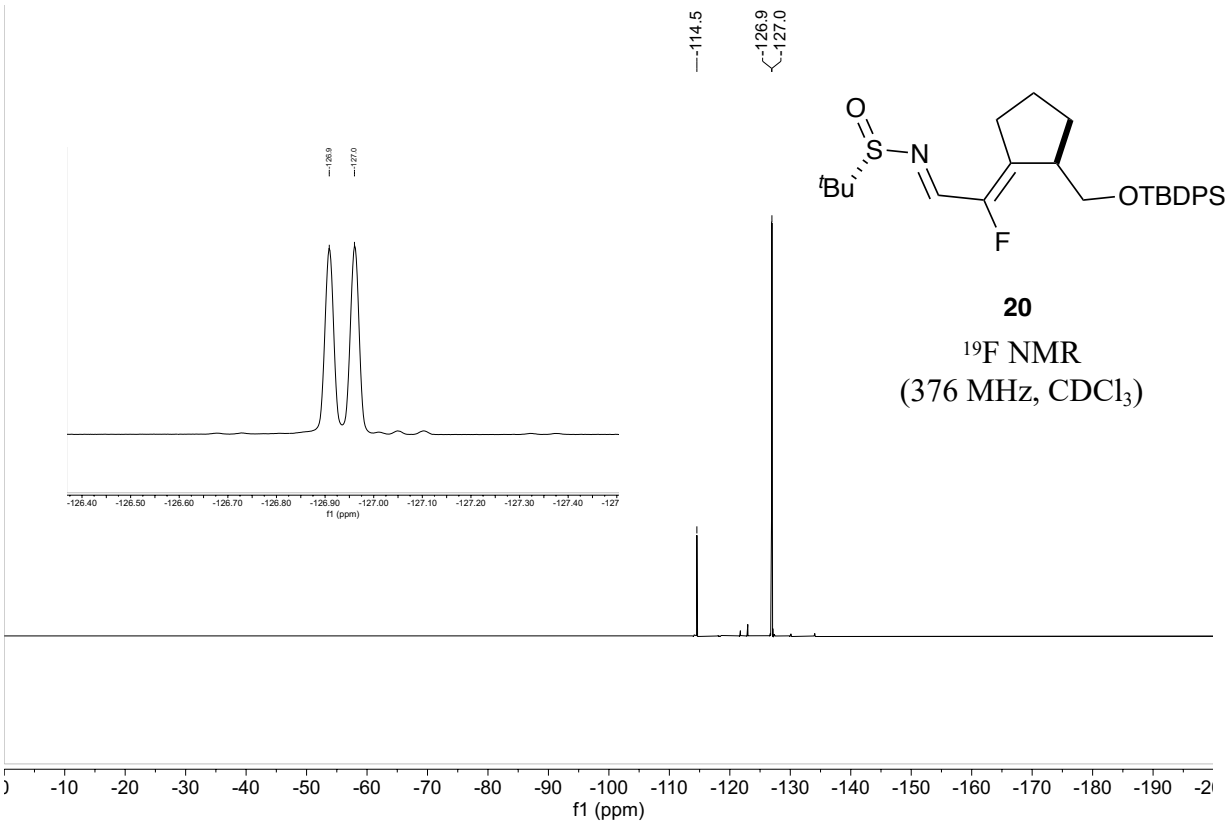


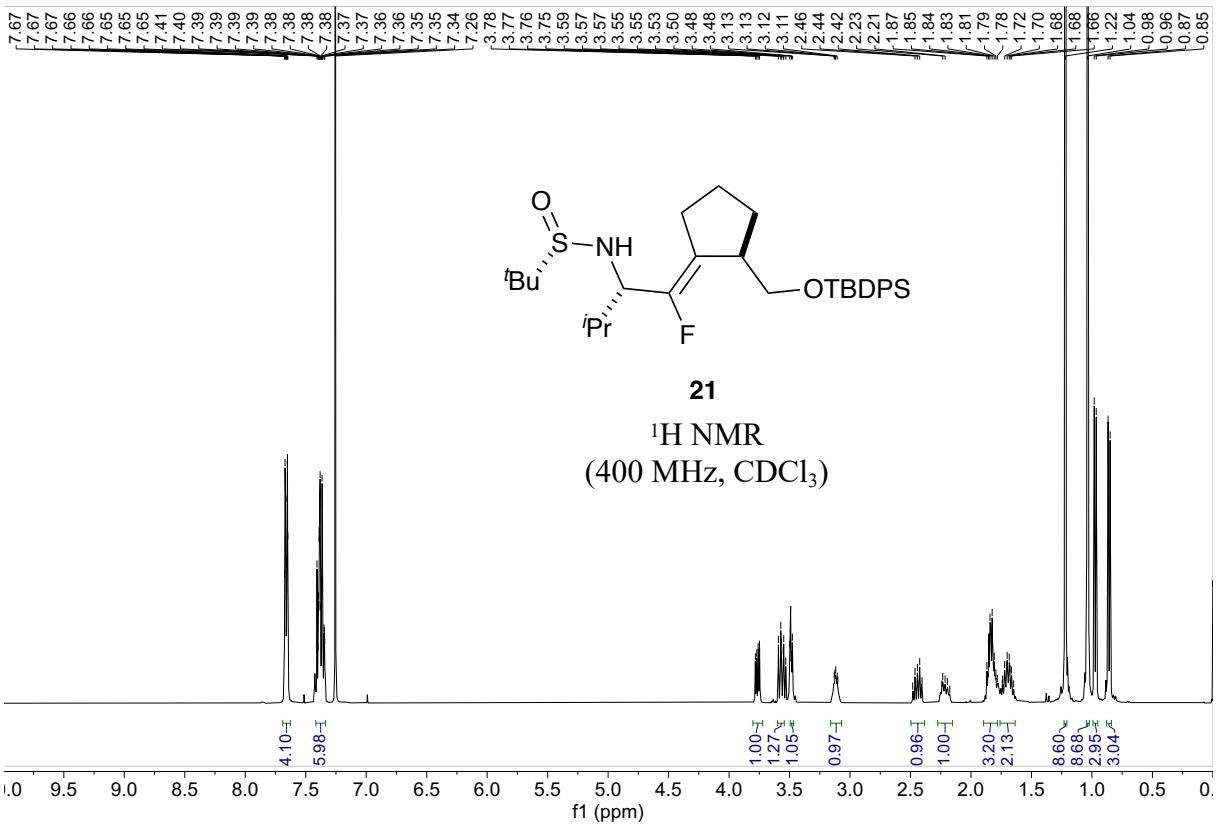
13

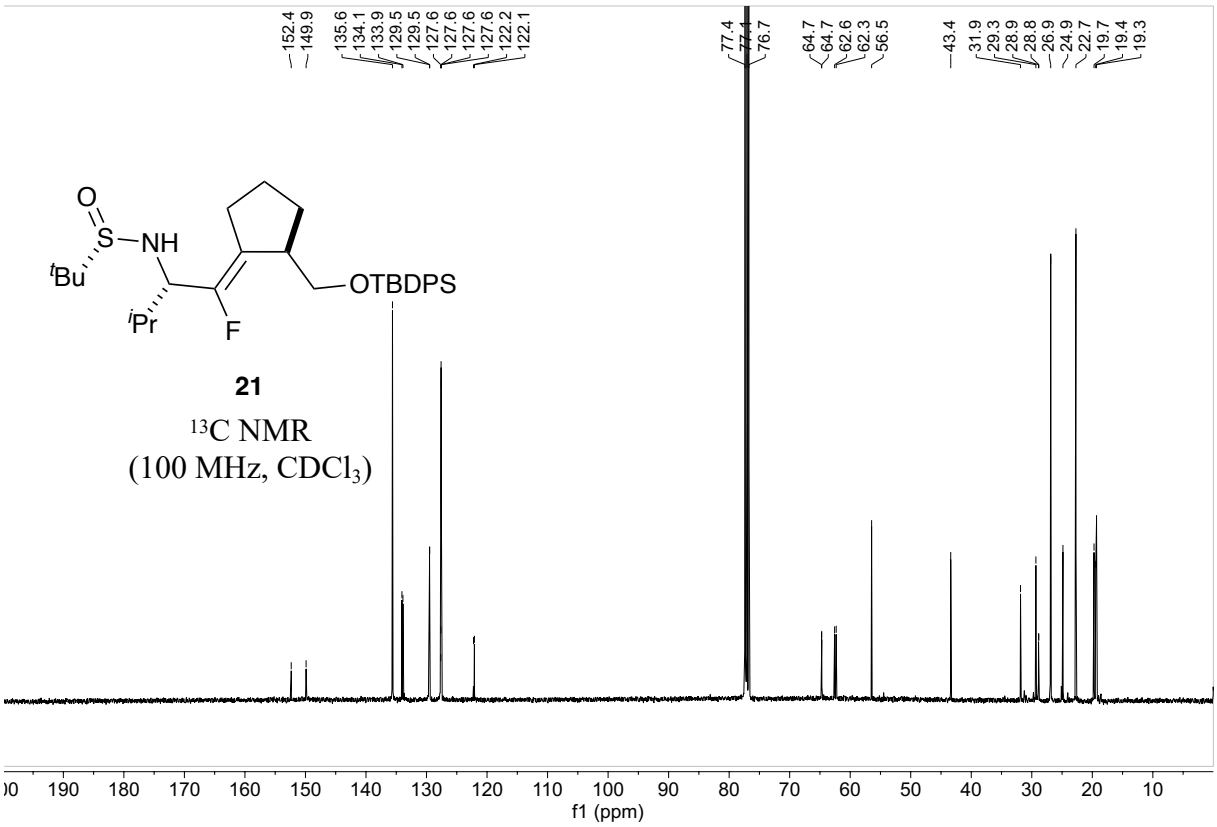
^{19}F NMR
(376 MHz, $CDCl_3$)

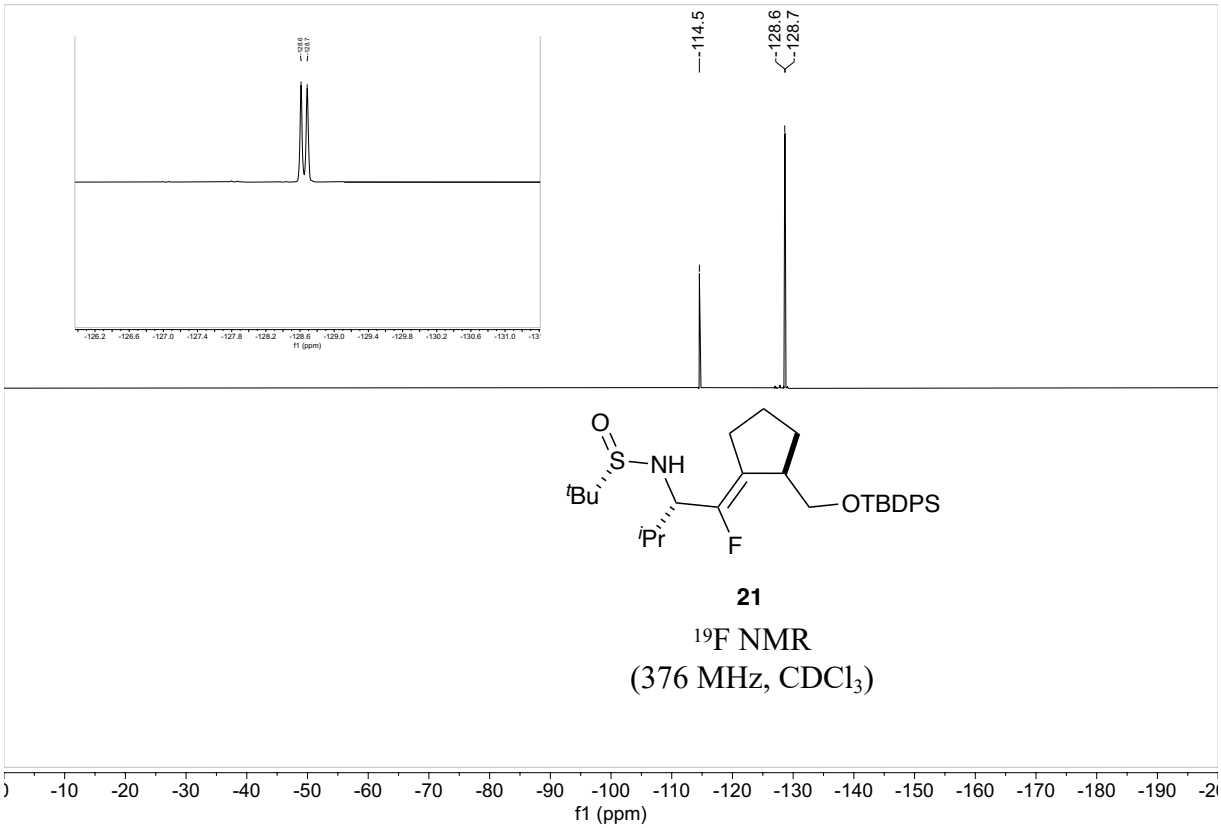

O
S
N
tBu
OTBDPS
F
20
1H NMR
(400 MHz, CDCl3)
f1 (ppm)

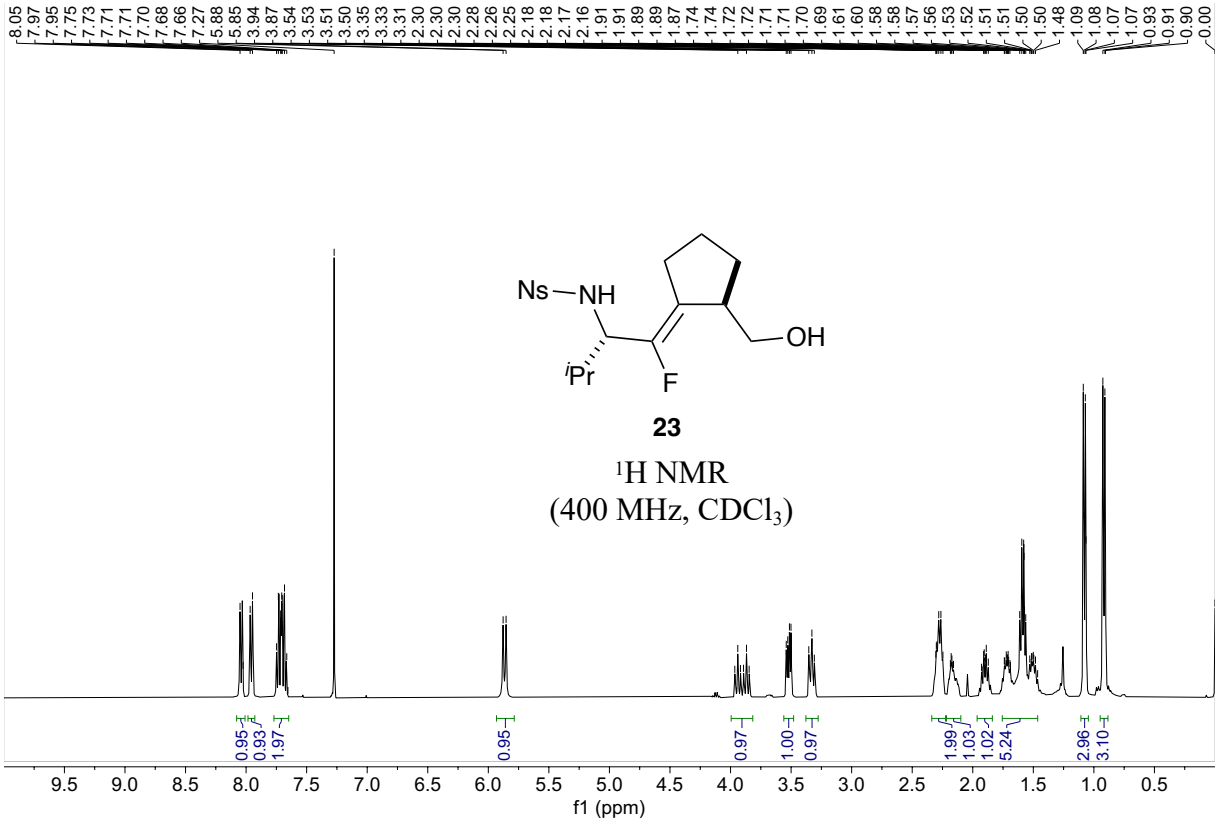

O
S
N
tBu
OTBDPS
F
20
13C NMR
(100 MHz, CDCl3)
f1 (ppm)

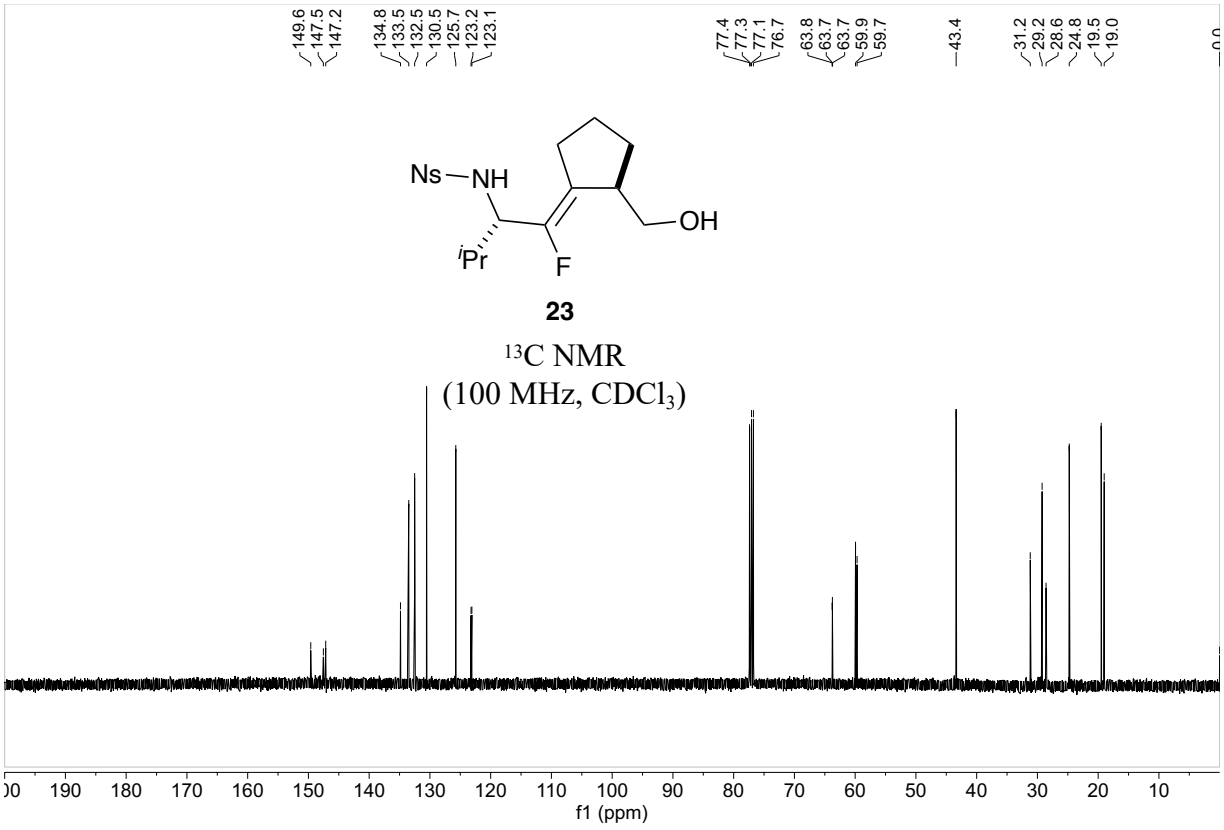

-114.5
-126.9
-127.0
O
S
N
tBu
OTBDPS
F
20
19F NMR
(376 MHz, CDCl3)
f1 (ppm)

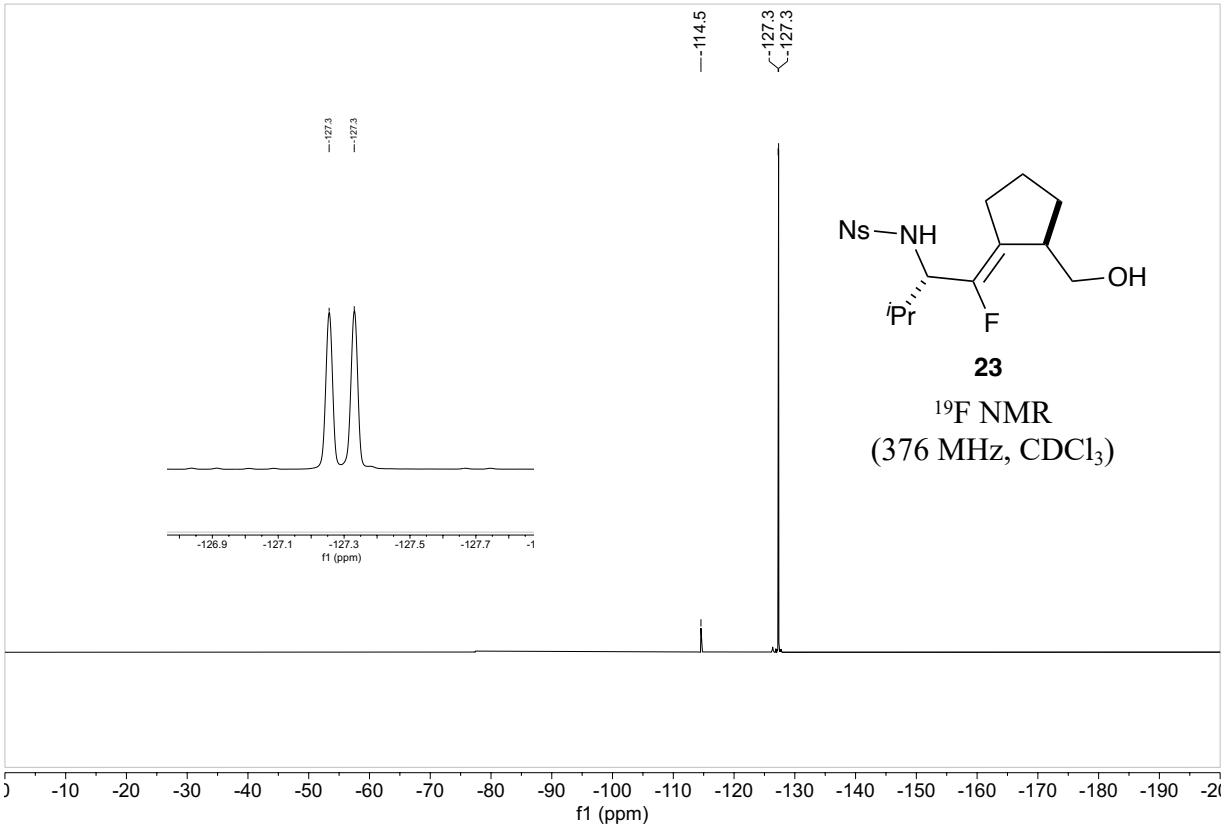

O
S
NH
tBu
iPr
OTBDPS
F
21
1H NMR
(400 MHz, CDCl3)
f1 (ppm)

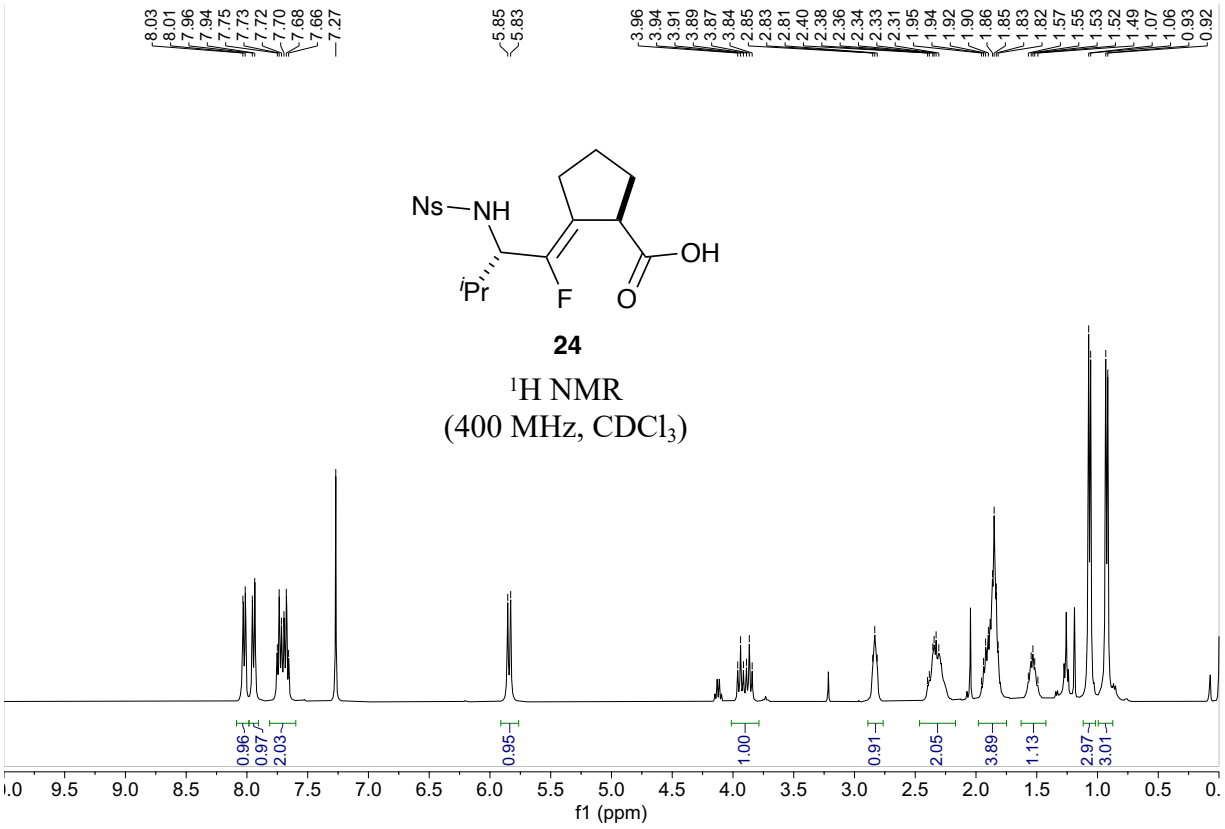

152.4
149.9
135.6
134.1
133.9
129.5
129.5
127.6
127.6
127.6
127.6
122.2
122.1
77.4
77.4
76.7
64.7
64.7
62.6
62.3
56.5
43.4
31.9
29.3
28.9
28.8
26.9
24.9
22.7
19.7
19.4
19.3
O
S
NH
tBu
iPr
F
OTBDPS
21
13C NMR
(100 MHz, CDCl3)
f1 (ppm)

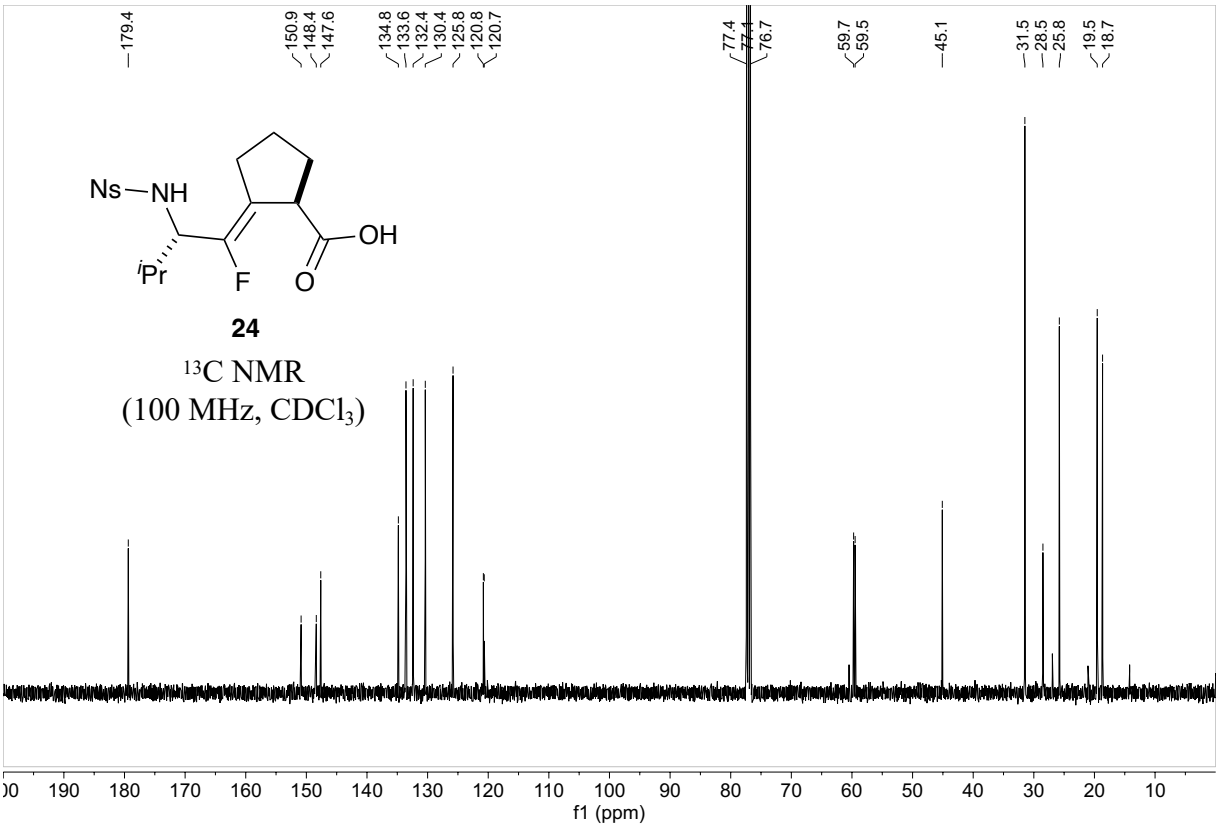

114.5
128.6
128.7
O
S
NH
tBu
iPr
F
OTBDPS
21
19F NMR
(376 MHz, CDCl3)
f1 (ppm)


Ns—NH
OH
iPr
F
23
1H NMR
(400 MHz, CDCl3)
f1 (ppm)


Ns—NH
OH
iPr
F
23
13C NMR
(100 MHz, CDCl3)
f1 (ppm)

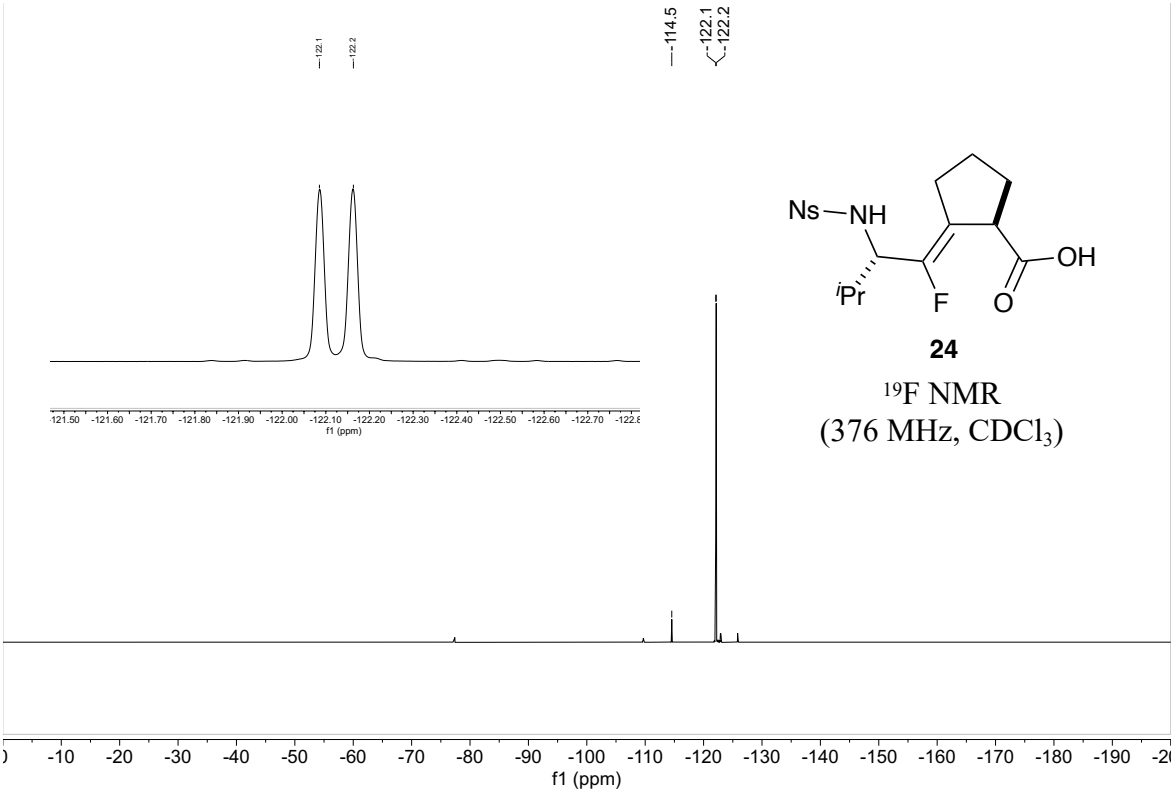

-114.5
-127.3
-127.3
Ns—NH
OH
iPr
F
23
19F NMR
(376 MHz, CDCl3)
f1 (ppm)


Ns—NH
OH
iPr
F
O
24
1H NMR
(400 MHz, CDCl3)
f1 (ppm)



24

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



24

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

XIII. References

1. Mase, N.; Inoue, A.; Nishio, M.; Takabe, K. *Bioorganic Med. Chem. Lett.* **2009**, *19*, 3955−3958
2. Chang, W.; Mosley, R. T.; Bansal, S.; Keilman, M.; Lam, A. M.; Furman, P. A.; Otto, M. J.; Sofia, M. J. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2938–2942
3. Villie, E.; Couve-Bonnaire, S.; Cahard, D.; Pannecoucke, X. *Tetrahedron* **2015**, *71*, 7054−7062