Synthesis of new fluorinated proline analogs from polyfluoroalkyl β-ketoacetals and ethyl isocyanoacetate

N. A. Tolmachova,[a,*] I. S. Kondratov,[a,b] V. G. Dolovanyuk,[b] S. O. Pridma,[a] A. V. Chernykh,[a] C. G. Daniliuc,[c] and G. Haufe[c,d,*]

a. *Enamine Ltd, Chervonotkatska St 78, Kyiv, 02094, Ukraine.*

b. *Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine, Murmanska Str. 1, Kyiv, 02660, Ukraine*

c. *Organisch-Chemisches Institut, Universität Münster, Corrensstraße 40, Münster 48149, Germany.*

d. *Cells-in-Motion Cluster of Excellence, Universität Münster, Waldeyerstraße 15, 48149 Münster, Germany.*

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1. General

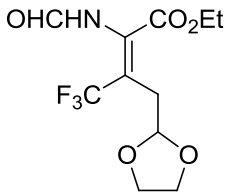
Solvents were purified according to standard procedures. Starting materials were purchased from Acros, Sigma-Aldrich, Merck, ABCR and Enamine at the highest commercial quality and were used without further purification. Melting points are uncorrected. Bruker Avance II at 300 and 400 MHz, Bruker DRX at 300 MHz and Agilent DD2 at 500 and 600 MHz (^{1}H), at 25 °C. TMS (for ^{1}H and ^{13}C NMR) and CCl_3F (for ^{19}F NMR) were used as internal standards. Mass spectra (ESI-MS) were measured on a MicroTof Bruker Daltonics. The progress of reactions was monitored by TLC-plates (silica gel 60 F254, Merck). Column chromatography was carried out on silica gel 60 (Merck, particle size 0.040–0.063 mm).

Compounds **2a-e** were synthesized according to the literature procedures.[1]

2. Synthetic procedures and compound characterization

2.1. Reaction of ketoacetals 2a,b with ethyl isocyanoacetate

(Z)-Ethyl 3-[(1,3-dioxolan-2-yl)methyl]-4,4,4-trifluoro-2-formamidobut-2-enoate (3a). Ethyl



isocyanoacetate (1.13 g, 10 mmol) in anhydrous THF (10 mL) was added dropwise via a syringe to a solution of *t*-BuOK (1.12 g, 10 mmol) in anhydrous THF (10 mL) at –78 °C. After the addition was complete, the solution was stirred at –78 °C for further 30 min. Then a solution of ketoacetal **2a** (1.47 g, 8 mmol) in THF (5 mL) was added dropwise via a syringe. The mixture was stirred at –78 °C for 1 h and warmed up to r.t. during 1–2 h. Aqueous HCl (1 N, 10 mL) was added and the mixture was stirred for 30 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The products were separated and purified by column chromatography (EtOAc/cHex 1:2, R_f = 0.62). Yield: 1.59 g (67%). Colorless solid, mp 82-84 °C

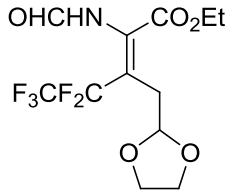
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (t, 3H, J_{HH} = 7.2 Hz, CH_3), 2.86 (d, 2H, J_{HH} = 4.2 Hz), 3.80-3.96 (m, 4H, $2CH_2O$), 4.32 (q, 2H, J_{HH} = 7.2 Hz), 5.05 (t, 1H, J_{HH} = 4.2 Hz, CHO_2), 7.83 (br. s, 1H, NH), 8.18 (s, 1H, CHO) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 30.9, 62.3, 65.0, 102.4, 116.7 (q, J_{CF} = 30.0 Hz), 123.6 (q, J_{CF} =275.0 Hz), 133.2 (q, J_{CF} = 3.2 Hz), 158.7, 162.7 ppm.

^{19}F NMR (282.5 MHz, $CDCl_3$): δ = – 60.60 (s, CF_3) ppm.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd. for $C_{11}H_{14}F_3NNaO_5^+$ (320.0716). Found: 320.0709.

(Z)-ethyl 3-[(1,3-dioxolan-2-yl)methyl]-4,4,5,5,5-pentafluoro-2-formamidopent-2-enoate (3b) was



synthesized from ketoacetal **2b** (1.87 g, 8mmol) by the same method as compound **3a** with the following modification: the reaction mixture was stirred at –78 °C for 2 h and then left overnight at –20 °C. Then it was heated to –5 °C. Aqueous HCl (1 N, 10 mL) was added and the mixture was stirred for 30 min at 5-10 °C and the cold solution was extracted with CH_2Cl_2. The organic layers were combined, dried over

Na_2SO_4, filtered and concentrated under reduced pressure. The products were separated and purified by column chromatography (EtOAc/cHex, 1:1, R_f = 0.63). Yield: 1.69 g (61%). Colorless solid, mp 93-95 °C.

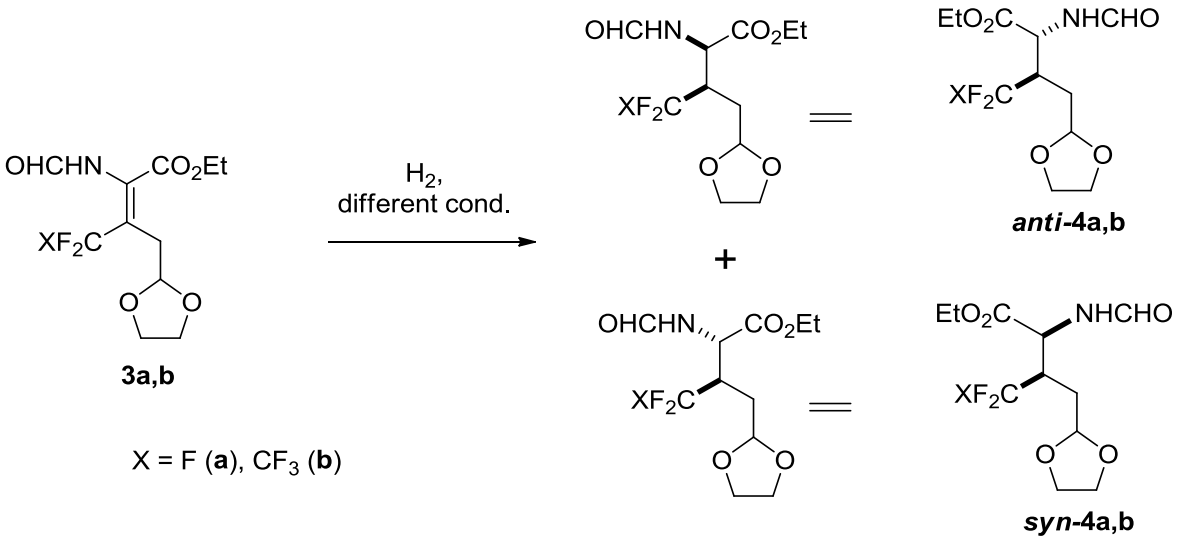
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (t, 3H, J_{HH} = 7.2 Hz, CH_3), 2.86 (d, 2H, J_{HH} = 4.3 Hz, CH_2), 3.79-3.94 (m, 4H, $2CH_2O$), 4.32 (q, 2H, J_{HH} = 7.2 Hz, CH_2O), 5.03 (t, 1H, J_{HH} = 4.3 Hz, CHO_2), 7.68 (br. s, 1H, NH), 8.16 (s, 1H, CHO) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 31.2, 62.3, 65.0, 102.6, 114.0 (t, J_{CF} = 19.8 Hz), 135.2, 158.4, 162.5 ppm. Low intensity, highly multiplicity signals of C_2F_5-group carbons are located in the area 112-125 ppm.

^{19}F NMR (282.5 MHz, $CDCl_3$): δ = – 84.27 (t, 3F, J_{FF} = 3.2 Hz, CF_3), –111.59 (q, 2F, J_{FF} = 3.2 Hz, CF_2) ppm.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd. for $C_{12}H_{14}F_5NNaO_5^+$ (370.0684). Found: 370.0691.

2.2 Hydrogenation of compounds 3a,b



Scheme S1. Hydrogenation of compounds **3a,b**

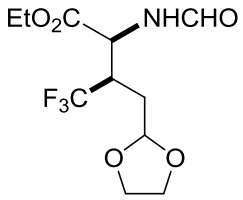
Table S1. Hydrogenation of compounds **3a,b**: yields and conditions.

Entry	Starting compound	Conditions	Share of **3** [%][a]	Product	Isomer ratio ***anti*/syn**[b] (isolated yield, %)
1	**3a**	10% Pd /C, 3 bar, r.t., EtOH, 12h	45	**4a**	73 / 27 (-)
2	**3a**	10% Pd /C, 3 bar, r.t., EtOH, 12 h	33	**4a**	70 / 30 (-[d])
3	**3a**	10% Pd /C, 20 bar, r.t., EtOH, 8 h	-[c]	**4a**	75 / 25 (64/20)
4	**3a**	5% Rh /C, 20 bar, r.t., EtOH, 8 h	-[c]	**4a**	74 /26 (-[d])
5	**3a**	10% Pt /C, 20 bar, r.t., EtOH, 8 h	5	**4a**	71 /29 (-[d])
6	**3a**	10% Pd /C, 20 bar, r.t., THF, 8 h	-[c]	**4a**	93 / 7 (-[d])
7	**3a**	10% Pd /C, 20 bar, r.t., EtOAc, 8 h	-[c]	**4a**	94 / 6 (84/-[e])
8	**3a**	(+)-COD-Rh-DuPhos, 20 bar, EtOH, 50 °C, 12 h	-[c]	**4a**	96 / 4 (-[d]) ee < 10%
9	**3b**	10% Pd /C, 20 bar, r.t., EtOH, 8h	85	**4b**	67 / 33 (-[d])
10	**3b**	10% Pd /C, 50 bar, 50 °C, EtOH, 24 h	5	**4b**	67 / 33 (56 /23)

[a] The conversion was calculated from ^{19}F NMR spectra of the crude mixture. [b] The ratio was calculated from ^{19}F NMR spectra of the crude mixture. [c] Compound **3** was not observed in the reaction mixture. [d] The mixture was not purified. [e] Isomer ***syn*-4** was not isolated.

Ethyl anti- and syn-3-[(1,3-dioxolan-2-yl)methyl]-4,4,4-trifluoro-2-formamidobutanoate (anti-4a and syn-4a). To a solution of compound **3a** (1.49 g, 5 mmol) in EtOH (50 mL) 10% Pd /C (35 mg) was added and the reaction mixture was stirred under hydrogen atmosphere (20 atm) in an autoclave at r.t. for 8 h. The reaction progress was monitored by TLC. After complete hydrogenation, the mixture was filtered and the solution was concentrated under reduced pressure. The obtained mixture of diastereomers ***anti-4a*** and ***syn-4a*** (75:25) was purified by column chromatography (EtOAc/cHex, 1:1).

Ethyl syn-3-[(1,3-dioxolan-2-yl)methyl]-4,4,4-trifluoro-2-formamidobutanoate (syn-4a) was isolated by column chromatography (eluent: EtOAc/cHex, 1:1, R_f = 0.41). Yield: 0.30 g (20%).Colorless solid, mp 57-59 °C.



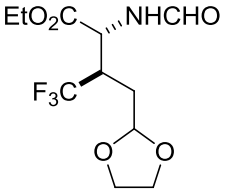
^{1}H NMR (400 MHz, CD_2Cl_2): δ = 1.28 (t, 3H, J_{HH} = 7.2 Hz, CH_3), 1.90 (ddd, 1H, J_{1HH} = 14.9 Hz, J_{2HH} = 4.3 Hz, J_{3HH} = 3.6 Hz, H_A of CH_2), 2.03 (ddd, J_{1HH} = 14.9 Hz, J_{2HH} = 8.8 Hz, J_{3HH} = 4.3 Hz, H_B of CH_2), 3.19-3.32 (m, 1H, $CHCF_3$), 3.85-4.05 (m, 4H, $2CH_2O$), 4.19-4.26 (m, 2H, CH_2O), 5.10 (t, 1H, J_{HH} = 4.3 Hz, CHO_2), 5.20 (dd, 1H, J_{1HH} = 9.7 Hz, J_{2HH} = 3.2 Hz, CH), 6.39 (d, 1H, J_{HH} = 9.7 Hz, NH), 8.29 (s, 1H, CHO) ppm.

^{13}C NMR (100 MHz, CD_2Cl_2): δ = 14.2, 29.3, 41.4 (q, J_{CF} = 25.4 Hz), 49.4 (q, J_{CF} = 2.1 Hz), 62.7, 65.5, 65.6, 102.0, 127.4 (q, J_{CF} = 281.2 Hz), 161.7, 169.8 ppm.

^{19}F NMR (282.5 MHz, CD_2Cl_2): δ = – 67.15 (d, J_{FH} = 9.6 Hz, CF_3) ppm.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd. for $C_{11}H_{16}F_3NNaO_5^+$ (322.0873). Found: 322.0870.

Ethyl anti-3-[(1,3-dioxolan-2-yl)methyl]-4,4,4-trifluoro-2-formamidobutanoate (anti-4a) was isolated by column chromatography (eluent: EtOAc/cHex, 1:1, R_f = 0.30). Yield: 0.96 g (64%). Colorless oil.



^{1}H NMR (400 MHz, CD_2Cl_2): δ = 1.21 (t, 3H, J_{HH} = 7.1 Hz, CH_3), 2.01 (ddd, 1H, J_{1HH} = 14.9 Hz, J_{2HH} = 9.5 Hz, J_{3HH} = 5.0 Hz, H_A of CH_2), 2.03 (ddd, J_{1HH} = 14.9 Hz, J_{2HH} = 3.9 Hz, J_{3HH} = 3.1 Hz, H_B of CH_2), 3.11-3.36 (m, 1H, $CHCF_3$), 3.78-4.01 (m, 4H, $2CH_2O$), 4.17-4.24 (m, 2H, CH_2O), 5.25 d, 1H, J_{1HH} = 5.0 Hz, J_{2HH} = 3.1 Hz, CHO_2), 5.25 (dd, 1H, J_{1HH} = 9.6 Hz, J_{2HH} = 2.4 Hz, CH), 6.63 (d, 1H, J_{HH} = 9.6 Hz, NH), 8.24 (s, 1H, CHO) ppm.

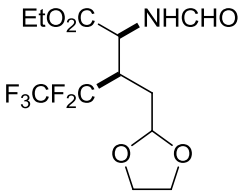
^{13}C NMR (100 MHz, CD_2Cl_2): δ = 14.3, 28.3, 40.7 (q, J_{CF} = 25.1 Hz), 48.0 (q, J_{CF} = 2.5 Hz), 62.7, 65.2, 65.5, 101.8, 127.4 (q, J_{CF} = 279.9 Hz), 160.8, 169.9 ppm.

^{19}F NMR (282.5 MHz, CD_2Cl_2): δ = – 70.25 (d, J_{FH} = 9.5 Hz, CF_3) ppm.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd. for $C_{11}H_{16}F_3NNaO_5^+$ (322.0873). Found: 322.0878.

Ethyl anti- and syn-3-[(1,3-dioxolan-2-yl)methyl]-4,4,5,5,5-pentafluoro-2-formamidopentanoate (anti-4b and syn-4b). A solution of compound **3b** (1.39 g, 4 mmol) in EtOH and 10% Pd /C (35 mg) was stirred under hydrogen atmosphere (50 atm) in an autoclave at 50 °C for 8 h. The reaction progress was monitored by TLC. After complete hydrogenation, the mixture was filtered and the solution was concentrated under reduced pressure. The obtained diastereomers ***anti-4b*** and ***syn-4b*** (67:33) were separated and purified by column chromatography (EtOAc/cHex, 1:1).

Ethyl syn-3-((1,3-dioxolan-2-yl)methyl)-4,4,5,5,5-pentafluoro-2-formamidopentanoate (syn-4b). was isolated by column chromatography (eluent: EtOAc/cHex, 1:1, R_f = 0.50). Yield: 0.32 g (23%). Colorless solid, mp 73-75 °C.



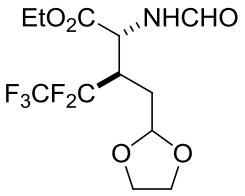
^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.28 (t, 3H, J_{HH} = 7.2 Hz, CH_3), 1.94 (ddd, J_{1HH} = 15.2 Hz, J_{2HH} = 3.8 Hz, J_{3HH} = 2.4 Hz, H_A of CH_2), 2.11 (ddd, J_{1HH} = 15.2 Hz, J_{2HH} = 9.7 Hz, J_{3HH} = 3.8 Hz, H_B of CH_2), 3.45 (ddq, J_{1HF} = 28.1 Hz, J_{2HH} = 9.7 Hz, $J_{3HH(HF)}$ = 2.4 Hz, $CHCF_2$), 3.88-4.07 (m, 4H, $2CH_2O$), 4.17-4.32 (m, 2H, CH_2O), 5.13 (t, 1H, J_{HH} = 3.8 Hz, CHO_2), 5.41 (dd, 1H, J_{1HH} = 9.7 Hz, J_{2HH} = 2.4 Hz, CH), 6.23 (d, 1H, J_{HH} = 9.7 Hz, NH), 8.37 (s, 1H, CHO) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.9, 28.4, 38.0 (t, J_{CF} = 19.0 Hz), 49.6, 62.3, 65.1, 65.2, 101.7, 161.5, 169.4 ppm. Low intensity, highly multiplicity signals of C_2F_5-group carbons are located in the area 112-125 ppm.

^{19}F NMR (282.5 MHz, $CDCl_3$): δ = – 84.01 (s, 3F, CF_3), –113.12 (dd, 1F, J_{FF} = 274.5 Hz, J_{FH} = 2.4 Hz, F_A of CF_2), –119.42 (dd, 1F, J_{FF} = 274.5 Hz, J_{FH} = 28.1 Hz, F_B of CF_2) ppm.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd. for $C_{12}H_{16}F_5NNaO_5^+$ (372.0841). Found: 372.0838.

Ethyl anti-3-[(1,3-dioxolan-2-yl)methyl]-4,4,5,5,5-pentafluoro-2-formamidopentanoate (anti-4b) was isolated by column chromatography (eluent: EtOAc/cHex, 1:1, R_f = 0.37). Yield: 0.78 g (56%). Colorless oil.



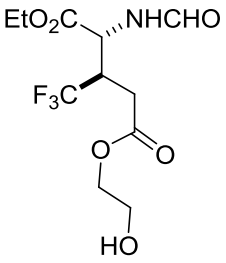
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 = (t, 3H, J_{HH} = 7.1 Hz, CH_3), 2.01-2.23 (2H, m, CH_2), 3.24-3.47 (1H, m, $CHCF_2$), 3.81-4.05 (m, 4H, $2CH_2O$), 4.23 (q, 2H, J_{HH} = 7.1 Hz, CH_2O), 4.97 (t, 1H, J_{HH} = 3.8 Hz, CHO_2), 5.41 (dd, 2H, J_{1HH} = 9.5 Hz, J_{2HH} = 2.4 Hz, CH), 6.68 (d, 1H, J_{HH} = 9.5 Hz, NH), 8.28 (s, 1H, CHO) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.0, 27.4, 38.0 (t, J_{CF} = 20.5 Hz), 47.4, 62.3, 64.7, 65.1, 101.4, 160.5, 169.8 ppm. Low intensity, highly multiplicity signals of C_2F_5-group carbons are located in the area 112-125 ppm.

^{19}F NMR (282.5 MHz, $CDCl_3$): δ = – 82.27 (s, 3F, CF_3), –115.60 (dd, 1F, J_{FF} = 274.5 Hz, J_{FH} = 10.5 Hz, F_A of CF_2), –120.40 (dd, 1F, J_{FF} = 274.5 Hz, J_{FH} = 21.6 Hz, F_B of CF_2) ppm.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd. for $C_{12}H_{16}F_5NNaO_5^+$ (372.0841). Found: 372.0848.

2.3. Synthesis of *trans*-3-CF_3-pyroglutamate *trans*-6a



1-Ethyl anti-5-(2-hydroxyethyl) 2-formamido-3-(trifluoromethyl)pentanedioate (anti-5a). A solution of compound ***anti*-4a** (0.30 g, 1 mmol) in EtOAc (30 mL) was cooled to –78 °C and generated ozone was bubbled for 1 h. Then oxygen was bubbled for 30 min in order to remove ozone and the mixture was heated to r.t. and concentrated under reduced pressure. The residue was purified by column chromatography. (EtOAc/cHex, 1:1, R_f = 0.22). Yield: 0.27 g (87%). Colorless oil.

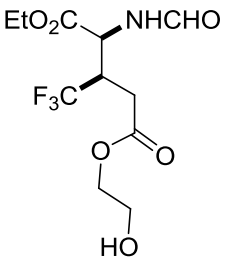
^{1}H NMR (400 MHz, CD_3OD): δ = 1.30 (t, 3H, J_{HH} = 7.1 Hz, CH_3), 2.71 (dd, 1H, J_{1HH} = 17.2 Hz, J_{2HH} = 7.1 Hz, H_A of CH_2), 2.77 (dd, 1H, J_{1HH} = 17.2 Hz, J_{2HH} = 5.7 Hz, H_B of CH_2), 3.46-3.57 (m, 1H, $CHCF_3$), 3.72-3.76 (m, 2H, CH_2O), 4.16-4.20 (m, 2H, CH_2O), 4.22 (q, 2H, J_{HH} = 7.1 Hz, CH_2O), 5.12 (d, 1H, J_{HH} = 3.2 Hz, CH), 8.14 (s, 1H, CHO) ppm.

^{13}C NMR (100 MHz, CD_3OD): δ = 14.4, 30.4, 42.9 (q, J_{CF} =24.5 Hz), 47.5, 61.0, 63.6, 67.9, 127.9 (q, J_{CF} = 279.8 Hz), 163.7, 170.4, 171.8 ppm.

^{19}F NMR (282.5 MHz, $CDCl_3$): δ = – 71.28 (d, J_{FH} = 9.1 Hz, CF_3).

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd. for $C_{11}H_{16}F_3NNaO_6^+$ (338.0822). Found: 338.0831

1-Ethyl syn-5-(2-hydroxyethyl) 2-formamido-3-(trifluoromethyl)pentanedioate (syn-5a) was obtained by the same approach as compound ***anti*-5a** starting from compound ***syn*-4a** (0.30 g, 1 mmol). The residue was purified by column chromatography. (EtOAc/cHex, 1:1, R_f = 0.22). Yield: 0.25 g (79%).Colorless oil.



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (t, 3H, J_{HH} = 7.1 Hz, CH_3), 2.62 (dd, 1H, J_{1HH} = 17.5 Hz, J_{2HH} = 11.6 Hz, H_A of CH_2), 2.72 (dd, 1H, J_{1HH} = 17.5 Hz, J_{2HH} = 3.7 Hz, H_B of CH_2), 3.53-3.67 (m, 1H, $CHCF_3$), 3.70 (ddd, 1H, J_{1HH} = 12.6 Hz, J_{2HH} = 5.9, Hz, J_{3HH} = 2.3 Hz, H_A of CH_2O), 3.91-4.05 (m, 2H, CH_2O), 4.21-4.36 (m, 2H, CH_2O), 4.68 (ddd, 1H,

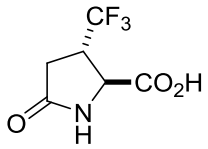
J_{1HH} = 11.2 Hz, J_{2HH} = 5.9, Hz, J_{3HH} = 2.3 Hz, H_A of CH_2O), 5.19 (dd, 1H, J_{1HH} = 9.1 Hz, J_{2HH} = 2.5 Hz, CH), 6.56 (d, 1H, J_{HH} = 9.1 Hz, NH), 8.30 (s, 1H, CHO) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 30.1, 42.7 (q, J_{CF} =24.9 Hz), 47.9, 60.5, 62.9, 67.2, 126.2 (q, J_{CF} = 280.9 Hz), 161.9, 169.0, 170.2 ppm.

^{19}F NMR (282.5 MHz, $CDCl_3$): δ = – 67.56 (d, J_{FH} = 8.6 Hz, CF_3) ppm.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd. for $C_{11}H_{16}F_3NNaO_6^+$ (338.0822). Found: 338.0818

***trans*-5-Oxo-3-(trifluoromethyl)pyrrolidine-2-carboxylic acid (*trans*-6a)**. $LiOH·H_2O$ (21 mg, 0.5 mmol) was added to a solution of compound ***anti*-5a** (158 mg, 0.5 mmol) in EtOH (10 mL) and the resulting mixture was stirred overnight. Then solvent was concentrated under reduced pressure. Then the residue was dissolved in water (50 mL) and 1N aq. HCl was added (~0.5 mL, until pH 4-5). The organic layers were combined, washed by brine,dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by crystallization from cyclohexane. Yield 80 mg (81%):



Also compound ***trans*-6a** was obtained starting from compound ***syn*-5a** (158 mg, 0.5 mmol) by the same procedure. Yield: 73 mg (74%)

Colorless solid, mp 174-176 °C. (Lit.: 174 °C)[2a]

^{1}H NMR (300 MHz, CD_3OD): δ = 2.40 (dd, 1H, J_{1HH} = 18.0 Hz, J_{2HH} = 3.8 Hz, H_A of CH_2), 2.76 (dd, 1H, J_{1HH} = 18.0 Hz, J_{2HH} = 10.3 Hz, H_B of CH_2), 3.41-3.57 (m, 1H, $CHCF_3$), 4.32 (d, 1H, J_{HH} = 3.2 Hz) ppm.

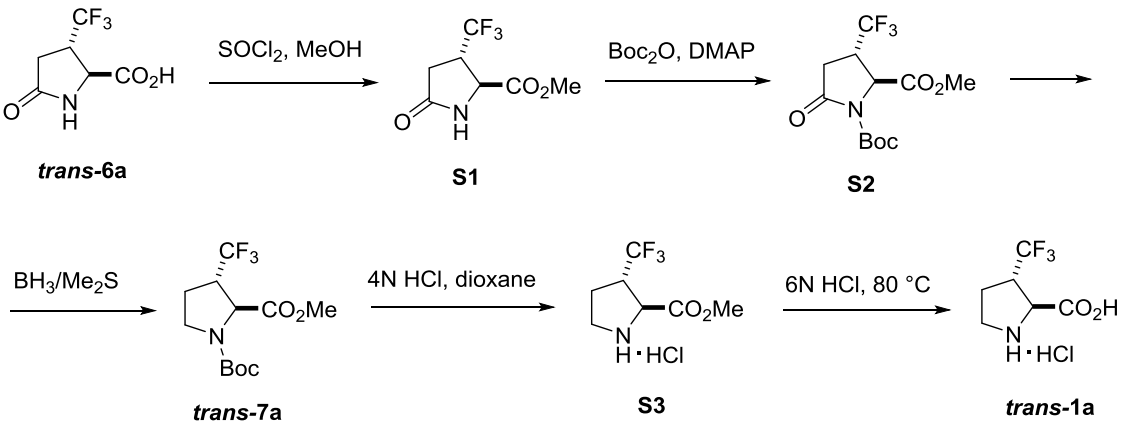
^{13}C NMR (75 MHz, CD_3OD): δ = 30.8 (q, J_{CF} = 2.4 Hz), 42.8 (q, J_{CF} = 29.6 Hz), 56.9 (q, J_{CF} = 2.8 Hz), 128.2 (q, J_{CF} = 276.8 Hz), 173.3, 177.4 ppm.

^{19}F NMR (282.5 MHz, CD_3OD): δ = – 73.45 (d, J_{FH} = 9.5 Hz, CF_3) ppm.

HRMS (ESI-TOF) *m/z*: $[M - H]^-$ calcd. for $C_6H_5F_3NO_3^-$ (196.0227). Found: 196.0214.

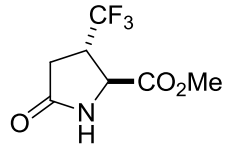
For literature data see[2a]

2.4. Synthesis of *trans*-3-CF_3-proline *trans*-1a from *trans*-6a



Scheme S2. Synthesis of compound ***trans*-1a** from ***trans*-6a.**

***trans*-Methyl 5-oxo-3-(trifluoromethyl)pyrrolidine-2-carboxylate(S1,** see Scheme S2**).** Thionyl chloride (2.26 g, 1.38 mL, 19 mmol) was added dropwise to methanol (150 mL) at 5-10° C. When the addition was complete and the mixture was cooled to 0-5° C and compound ***trans*-6a** (1.50 g, 7.60 mmol) was added in one portion. The reaction mixture was stirred at ambient temperature for 16 hours and then was concentrated under reduced pressure and the residue was treated with EtOAc (300 mL) and 2M solution of Na_2CO_3 (40 mL) and stirred at r.t. for 1 h. The mixture was extracted with EtOAc (3 × 100 mL). The organic fractions were combined and reduced on the rotary evaporator to give ~1.61 g of compound **S1** which was used for the next step without purification.



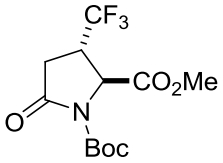
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.50 (dd, 1H, J_{1HH} = 18.0 Hz, J_{2HH} = 4.5 Hz, H_A of CH_2), 2.68 (dd, 1H, J_{1HH} = 18.0 Hz, J_{2HH} = 10.1 Hz, H_B of CH_2), 3.31-3.46 (m, 1H, $CHCF_3$), 3.81 (s, 3H, CH_3O), 4.32 (d, 1H, J_{HH} = 3.3 Hz, CH) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.5, 41.0 (q, J_{CF} = 30.5 Hz), 53.3, 55.3 (q, J_{CF} = 2.5 Hz), 126.1 (q, J_{CF} = 277.5 Hz), 170.2, 174.9 ppm.

^{19}F NMR (282.5 MHz, $CDCl_3$): δ = – 73.73 (d, J_{FH} = 9.4 Hz, CF_3) ppm.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd. for $C_7H_8F_3NNaO_3^+$ (234.0348). Found: 234.0356.

***trans*-1-*tert*-Butyl 2-methyl 5-oxo-3-(trifluoromethyl)pyrrolidine-1,2-dicarboxylate (S2,** see Scheme S2). Obtained compound **S1** (1.60 g) was dissolved in CH_3CN. Then Boc-anhydride (1.99 g, 9.1 mmol) and DMAP (12 mg, 0.1 mmol) were added and the resulting solution was stirred overnight under Argon atmosphere at r.t. Then the solvent was concentrated under reduced pressure and the residue was purified by column chromatography (EtOAc/Hex, 1:3, R_f = 0.28) giving pure target compound **S2**. Yield: 1.75 g (74% upon two stages). Colorless solid, mp 63-65 °C.



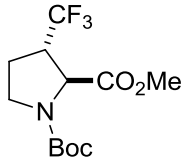
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50 (s, 9H, $3CH_3$), 2.67 (dd, 1H, J_{1HH} = 18.0 Hz, J_{2HH} = 2.8 Hz, H_A of CH_2), 2.89 (dd, 1H, J_{1HH} = 18.0 Hz, J_{2HH} = 10.0 Hz, H_B of CH_2), 2.91-3.01 (m, 1H, $CHCF_3$), 3.83 (s, 3H, CH_3O), 4.71 (d, 1H, J_{HH} = 2.2 Hz, CH) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.8, 31.3 (q, J_{CF} = 1.6 Hz), 38.1 (q, J_{CF} = 30.5 Hz), 58.2 (q, J_{CF} = 2.5 Hz), 84.6, 125.6 (q, J_{CF} = 279.5 Hz), 148.5, 169.2, 169.7 ppm.

^{19}F NMR (282.5 MHz, $CDCl_3$): δ = – 74.06 (d, J_{FH} = 9.1 Hz, CF_3) ppm.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd. for $C_{12}H_{16}F_3NNaO_5^+$ (334.0873). Found: 334.0886.

1-*tert*-Butyl *trans*-2-methyl 3-(trifluoromethyl)pyrrolidine-1,2-dicarboxylate (*trans*-7a). Obtained compound **S2** (1.71 g, 5.5 mmol) was dissolved in THF (100 mL) and cooled to 0°C. Then solution of $BH_3{\cdot}Me_2S$ (2.0 M in THF, 5.5 mL, 11 mmol) was added dropwise under stirring under Argon atmosphere. The solution was allowed to warm to 50 °C and stirred for additional 3 days. Then the solution was cooled to 0 °C and the reaction mixture was quenched with MeOH (10 mL). The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (EtOAc/Hex 1:4, Rf = 0.46) giving compound ***trans*-7a.** Yield: 605 mg (37%). Colorless oil.



NMR-spectra contain overlapping signals of both rotamers in ratio ~2:3.

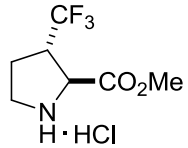
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 5.4H, $3CH_3$, major rotamer), 1.43 (s, 3.6H, $3CH_3$, minor rotamer), 2.01-2.25 (m, 2H, CH_2), 2.83-3.01 (m, 1H, $CHCF_3$), 3.74 (s, 3H, CH_3O), 4.32 (d, 0.6H, J_{HH} = 4.0 Hz, CH, major rotamer), 4.47 (d, 0.64H, J_{HH} = 3.0 Hz, CH, minor rotamer) ppm.

^{13}C NMR (100 MHz, $CDCl_3$, signals of both rotamers): δ = 24.0, 24.7, 28.2, 28.3, 45.3, 45.4, 46.4 (q, J_{CF} = 28.9 Hz), 47.6 (q, J_{CF} = 28.9 Hz), 52.5, 52.7, 58.8, 59.0, 80.6, 80.8, 126.1 (q, J_{CF} = 277.0 Hz), 126.3 (q, J_{CF} = 277.0 Hz),153.1, 153.9, 171.6, 171.8 ppm.

^{19}F NMR (282.5 MHz, $CDCl_3$): δ = – 71.81 (d, 0.6F, J_{FH} = 9.6 Hz, CF_3, major rotamer), – 71.93 (d, 0.4F, J_{FH} = 9.6 Hz, CF_3, minor rotamer), ppm.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd. for $C_{12}H_{18}F_3NNaO_4^+$ (320.1080). Found: 320.1088.

Methyl *trans*-3-(trifluoromethyl)pyrrolidine-2-carboxylate hydrochloride (S3, see scheme S2**).**



Compound ***trans*-7a** (595 mg, 2 mmol) was dissolved in a 4 N HCl in dioxane (20 mL) and then the residue was stirred at r.t. for 10 hours, then concentrated under reduced pressure giving ~460 mg of compound **S3**, which was used for the next step without purification. Colorless oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.98-2.09 (m, 1H, H_A of CH_2), 2.25-2.37 (m, 1H, H_B of CH_2), 3.26-3.32 (m, 1H, $CHCF_3$), 3.61-3.74 (m, 2H, CH_2N), 3.78 (s, 3H, CH_3O), 4.52 (d, 1H, J_{HH} = 5.3 Hz, CH), 10.42 (br. s, 2H, NH_2) ppm.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 25.3, 44.3 (q, J_{CF} = 28.7 Hz), 45.9, 54.0, 58.0 (q, J_{CF} = 2.0 Hz), 126.7 (q, J_{CF} = 278.3 Hz), 167.5 ppm.

^{19}F NMR (282.5 MHz, CD_3OD): δ = – 70.93 (d, J_{FH} = 9.5 Hz, CF_3) ppm.

***trans*-3-(Trifluoromethyl)pyrrolidine-2-carboxylic acid hydrochloride (*trans*-1a).** The obtained *trans*-methyl 3-(trifluoromethyl)pyrrolidine-2-carboxylate hydrochloride was dissolved in an aq. 6N HCl (20 mL) and was stirred at 80 °C for 8 h. Then the solution was concentrated under reduced pressure and dried under vacuum of oil pump (10^{-3} mm Hg) giving pure product ***trans*-1a** which did not require any additional purification. Yield: 420 mg (96% upon 2 stages). Colorless solid, mp >200 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.94-2.10 (m, 1H, H_A of CH_2), 2.20-2.33 (m, 1H, H_B of CH_2), 3.12-3.32 (m, 2H, CH_2N), 3.44-3.62 (m, 1H, $CHCF_3$), 4.53 (d, 1H, J_{HH} = 6.2 Hz, CH) ppm.

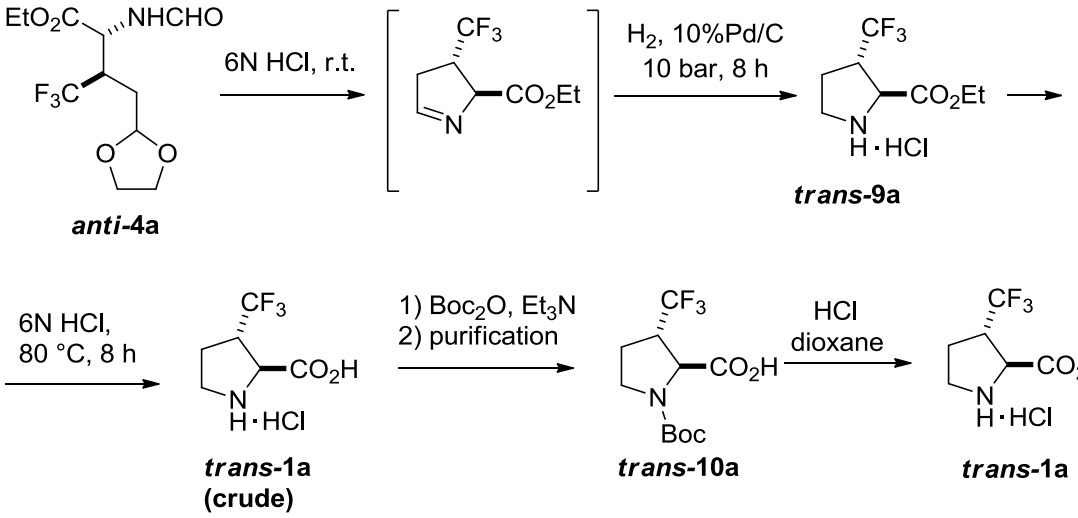
^{13}C NMR (125 MHz, DMSO-d_6): δ = 25.4, 44.8 (q, J_{CF} = 29.5 Hz), 45.9, 58.6, 127.1 (q, J_{CF} = 277.5 Hz), 168.7 ppm.

^{19}F NMR (282.5 MHz, CD_3OD): δ = – 72.43 (d, J_{FH} = 9.0 Hz, CF_3) ppm.

HRMS (ESI-TOF) *m/z*: $[M – H]^-$ calcd. for $C_6H_7F_3NO_2^-$ (182.0434). Found: 182.0442.

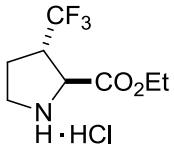
2.5. Synthesis of *trans/cis*-3-CF_3-/C_2F_5-proline *trans*-/cis-1a,b from *anti-/syn-3*a,b

2.5.1. Synthesis of trans-3-CF_3-proline ***trans-1a***



Scheme S3. Synthesis of compound ***trans*-1a.**

Ethyl *trans*-3-(trifluoromethyl)pyrrolidine-2-carboxylate (*trans*-9a). 6N HCl (20 mL) was added to a solution of compound ***anti*-4a** (299 mg, 1 mmol) in EtOH (20 mL). The resulting mixture was stirred at r.t. for 8 h. Then 10% Pd/C (20 mg) was added to the solution and the resulting solution was was stirred under hydrogen atmosphere (20 atm) in an autoclave at r.t. for 8 h. The reaction progress was monitored by TLC. After complete hydrogenation, the mixture was filtered and the solution was concentrated under reduced pressure giving ~190 mg of crude compound ***trans*-9a** (contains ~15% of compound ***trans*-1a** and ethylene glycol) which was used for further stage without purification. Colorless oil.

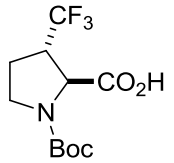


^{1}H NMR (300 MHz, D_2O): δ = 1.19 (t, 3H, J_{HH} = 7.0 Hz, CH_3), 2.10-2.40 (m, 2H, CH_2), 3.32-3.64 (m, 3H, CH_2N and $CHCF_3$), 4.24 (q, 2H, J_{HH} = 7.0 Hz, CH_2O), 4.67 (d, 1H, J_{HH} = 5.1 Hz, CH) ppm.

^{19}F NMR (282.5 MHz, D_2O): δ = – 71.30 (d, J_{FH} = 9.3 Hz, CF_3) ppm.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_8H_{13}F_3NO_2^+$ (212.0893). Found: 212.0901.

***trans*-1-(*tert*-Butoxycarbonyl)-3-(trifluoromethyl)pyrrolidine-2-carboxylic acid (*trans*-10a)**. Obtained amount of crude compound ***trans*-9a** (190 mg) was dissolved in 6N HCl (20 mL) and the resulting solution was stirred for 10 h at 80 °C. Then the cooled mixture was washed by EtOAc (2 × 30 mL) and the water layer was concentrated under reduced pressure and the residue was dried in vacuum of oil pump (10^{-3} mm Hg) for 5 h giving crude compound ***trans*-1a** (~130 mg) which was used for the next step without purification.



A solution of crude compound ***trans*-1a** (~110 mg) in dioxane (10 mL) was cooled to 0 °C and then triethylamine (0.21 mL, 152mg, 1.5 mmol) and Boc-anhydride (153 mg, 0.7 mmol) were consequently added portionwise under stirring. The mixture was stirred for 1 h at 0-5 °C and left stirring overnight at r.t. Then dioxane was evaporated and the resulting aqueous solution was acidified with 1N HCl solution

to pH ~2-3 at 0-5 °C. The aqueous layer was extracted with ethyl acetate (4×50 mL) and combined organic layers were washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/cHex 1:2, R_f = 0.11). Yield: 186 mg (54% upon three steps starting from ***anti*-4a**). Colorless solid, mp > 200 °C.

NMR spectra contain overlapping signals of two rotamers in ratio ~3:2 (DMSO-d_6) or ~7:3 ($CDCl_3$).

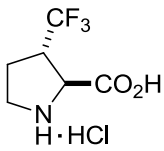
^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.36 (s, 5.4H, $3CH_3$, major rotamer), 1.40 (s, 3.6H, $3CH_3$, minor rotamer), 1.94-2.25 (m, 2H, CH_2), 3.24-3.51 (m, 3H, CH_2N and $CHCF_3$), 4.12 (d, J_{HH} = 3.7 Hz, CH, major rotamer), 4.19 (d, J_{HH} = 3.7 Hz, CH, minor rotamer), 13.11 (br. s, 1H, CO_2H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6, both rotamers): δ = 23.4, 24.2, 27.8, 27.9, 44.9 (q, J_{CF} = 28.0 Hz), 45.0, 45.1, 46.0(q, J_{CF} = 28.0 Hz), 79.5 (q, J_{CF} = 278.3 Hz), 152.6, 153.2, 171.5, 172.0 ppm.

^{19}F NMR (285 MHz, $CDCl_3$): δ = –71.53 (d, 0.7F, J_{CF} = 9.4 Hz, CF_3, major rotamer), –71.80 (d, 0.3F, J_{CF} = 9.4 Hz, CF_3, minor rotamer) ppm.

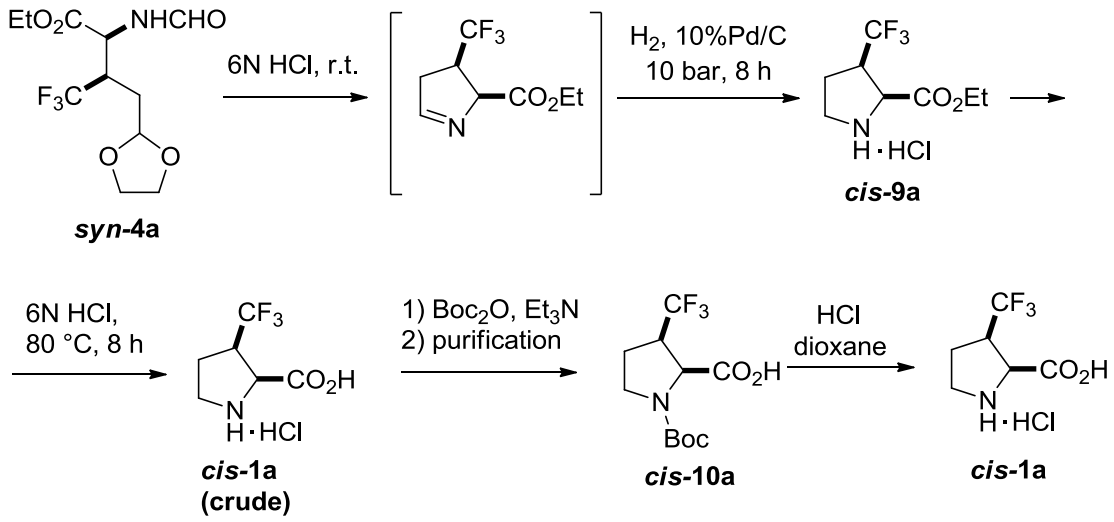
HRMS (ESI-TOF) *m/z*: $[M - H]^-$ calcd. for $C_{11}H_{15}F_3NO_4^-$ (282.0959). Found: 282.0965.

***trans*-3-(Trifluoromethyl)pyrrolidine-2-carboxylic acid hydrochloride (*trans*-1a)**. Compound ***trans*-10a** (170 mg, 0.6 mmol) was dissolved in a 4 N HCl in dioxane (10 mL) and then the residue was stirred at r.t. for 10 hours then concentrated under reduced pressure giving pure compound ***trans*-1a**.Yield: 124 mg (94%)



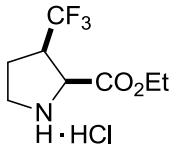
Analytical data are presented above.

*2.5.2. Synthesis of trans-3-CF_3-proline **cis-1a***



Scheme S4. Synthesis of compound ***cis*-1a.**

***cis*-Ethyl 3-(trifluoromethyl)pyrrolidine-2-carboxylate hydrochloride (*cis*-9a)**. was synthesized by the same approach as compound ***trans*-10a** starting from compound ***syn*-4a** (299 mg, 1 mmol). Isolated ~180 mg of the crude product (contains ~20% of compound ***cis*-1a** and ethylene glycol) was used for further stage without purification. Colorless oil.

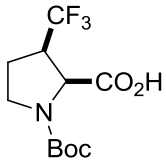


^{1}H NMR (300 MHz, D_2O): δ = 1.20 (t, 3H, J_{HH} = 7.1 Hz, CH_3), 2.17-2.53 (m, 2H, CH_2), 3.34-3.47 (m, 1H, $CHCF_3$), 3.57-3.83 (m, 2H, CH_2N), 4.24 (q, 2H, J_{HH} = 7.1 Hz, CH_2O), 4.67 (d, 1H, J_{HH} = 8.1 Hz, CH) ppm.

^{19}F NMR (282.5 MHz, D_2O): δ = – 67.83 (d, J_{FH} = 9.3 Hz, CF_3) ppm.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_8H_{13}F_3NO_2^+$ (212.0893). Found: 212.0904.

***cis*-1-(*tert*-Butoxycarbonyl)-3-(trifluoromethyl)pyrrolidine-2-carboxylic acid (*cis*-10a)** was synthesized by the same approach as compound ***trans*-10a** starting from crude compound ***cis*-9a** (110 mg, 0.5 mmol) and purified by column chromatography (EtOAc/cHex, R_f = 0.12). Yield: 119 mg (55% upon 3 steps starting from compound ***syn*-4a**). Colorless solid, mp 122-124 °C.



NMR spectra contain overlapping signals of two rotamers in ratio ~1:2 ($CDCl_3$).

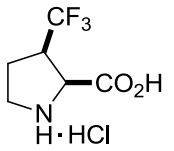
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 6H, $3CH_3$, major rotamer), 1.43 (s, 3H, $3CH_3$, minor rotamer), 2.05-2.36 (m, 2H, CH_2), 3.02-3.22 (m, 1H, $CHCF_3$), 3.36-3.47 (m, 1H, H_A of CH_2N), 3.66-3.86 (m, 1H, H_B of CH_2N), 4.43 (d, J_{HH} = 8.2 Hz, CH, major rotamer), 4.53 (d, J_{HH} = 8.2 Hz, minor rotamer), 10.73 (br. s, 1H, CO_2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$, both rotamers): δ = 23.2, 24.1, 28.1, 28.3, 44.9, 45.1, 46.0 (q, J_{CF} = 30.1 Hz), 46.9 (q, J_{CF} = 30.1 Hz), 57.9, 58.3, 81.1, 81.5, 124.7 (q, J_{CF} = 278.3 Hz), 124.8 (q, J_{CF} = 278.3 Hz), 153.4, 154.2, 174.7, 175.8 ppm.

^{19}F NMR (285 MHz, $CDCl_3$): δ = –68.10 (d, 0.33F, J_{FH} = 8.4 Hz, CF_3, minor rotamer), –68.27 (d, 0.64F, J_{FH} = 8.4 Hz, CF_3, major rotamer) ppm.

HRMS (ESI-TOF) *m/z*: $[M - H]^-$ calcd. for $C_{11}H_{15}F_3NO_4^-$ (282.0959). Found: 282.0967.

***cis*-3-(Trifluoromethyl)pyrrolidine-2-carboxylic acid hydrochloride (*cis*-1a)** was synthesized by the same approach as compound ***trans*-1a** (see section 2.5.1) starting from compound ***trans*-10a** (113 mg, 0.4 mmol). Yield: 85 mg (97%). Colorless oil.



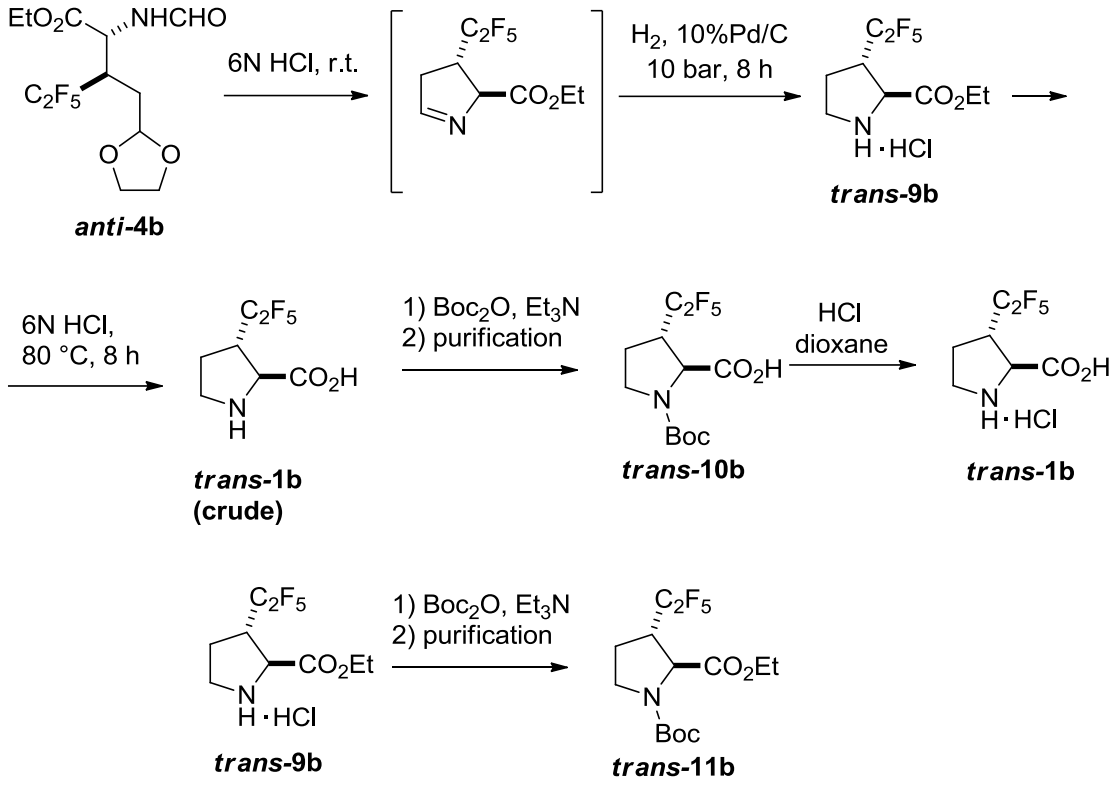
^{1}H NMR (400 MHz, D_2O): δ = 2.17-2.50 (m, 2H, CH_2), 3.28-3.66 (m, 3H, $CHCF_3$ and CH_2N), 4.47 (d, 1H, J_{HH} = 8.0 Hz, CH) ppm.

^{13}C NMR (100 MHz, D_2O): δ = 24.6 (q, J_{CF} = 1.8 Hz), 44.0, 44.3 (q, J_{CF} = 29.1 Hz), 66.1, 125.6 (q, J_{CF} = 279.1 Hz), 168.7 ppm.

^{19}F NMR (285 MHz, D_2O): δ = 67.74 (d, J_{FH} = 9.5 Hz, CF_3) ppm.

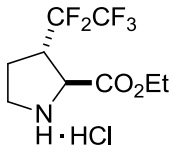
HRMS (ESI-TOF) *m/z*: $[M – H]^-$ calcd. for $C_6H_7F_3NO_2^-$ (182.0434). Found: 182.0444.

*2.5.3. Synthesis of trans-3-C_2F_5-proline **trans-1b** and compound **trans-11b***



Scheme S5. Synthesis of compounds ***trans*-1b** and ***trans*-11b.**

Ethyl *trans*-3-(perfluoroethyl)pyrrolidine-2-carboxylate hydrochloride (*trans*-9b) was synthesized by the same approach as compound ***trans*-9a** starting from compound ***anti*-4b** (349 mg, 1 mmol). Isolated ~210 mg of the crude product (contains ~10% of compound ***trans*-1b** and ethylene glycol) was used for further stage without purification. Colorless oil.

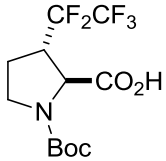


^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, 3H, J_{HH} = 7.2 Hz, CH_3), 2.14-2.31 (m, 1H, H_A of CH_2), 2.39-2.53 (m, 1H, H_B of CH_2), 3.34-3.47 (m, 1H, H_A of CH_2N), 3.50-3.77 (m, 2H, H_B of CH_2N and $CHCF_2$), 4.36 (q, 2H, J_{HH} = 7.2 Hz, CH_2O), 4.76 (d, 1H, J_{HH} = 5.5 Hz, CH) ppm.

^{19}F NMR (282.5 MHz, CD_3OD): δ = – 84.51 (s, 3F, CF_3), –118.38 (dd, 1F, J_{FF} = 273.0 Hz, J_{FH} = 13.1 Hz, F_A of CF_2), –124.13 (dd, 1F, J_{FF} = 273.0 Hz, J_{FH} = 19.2 Hz, F_B of CF_2) ppm.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_9H_{13}F_5NO_2^+$ (262.0861). Found: 262.0871.

***trans*-1-(*tert*-Butoxycarbonyl)-3-(perfluoroethyl)pyrrolidine-2-carboxylic acid (*trans*-10b)** was synthesized by the same approach as compound ***trans*-10a** starting from compound ***trans*-9b** (~135 mg) and purified by column chromatography (EtOAc/cHex 1:2, R_f = 0.15). Yield: 133 mg (52% upon 3 steps starting from compound ***anti*-4b**). Colorless solid, mp 103-104 °C



NMR spectra contain overlapping signals of two rotamers in ratio ~2:3 ($CDCl_3$)

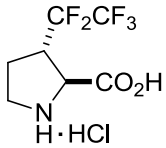
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 3.6H, $3CH_3$, minor rotamer), 1.46 (s, 5.4H, $3CH_3$, major rotamer), 1.99-2.27 (2H, m, CH_2), 2.97-3.14 (m, 0.4H, $CHCF_2$, minor rotamer), 3.29-3.55 (1.6H, H_A of CH_2N and $CHCF_2$, major rotamer), 3.56-3.77 (m, 1H, H_B of CH_2N), 4.46 (d, 0.4H, J_{HH} = 4.0 Hz, CH, minor rotamer), 4.60 (d, 0.6H, J_{HH} = 4.0 Hz, CH, major rotamer), 9.58 (br. s, 1H, CO_2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$, both rotamers): δ = 24.2, 24.5, 28.1, 28.3, 42.7 (t, J_{CF} = 21.2 Hz), 45.4 (t, J_{CF} = 21.2 Hz), 45.6, 46.0, 58.3, 58.7, 81.6, 82.7, 153.2, 156.1, 172.3, 176.4 ppm. Low intensity, highly multiplicity signals of C_2F_5-group carbons are located in the area 112-125 ppm.

^{19}F NMR (282.5 MHz, $CDCl_3$): δ = – 83.50 (s, 3F, CF_3), –115.90 (dd, 0.4F, J_{FF} = 270.7 Hz, J_{FH} = 11.1 Hz, F_A of CF_2, minor rotamer), –117.20 (dd, 0.6F, J_{FF} = 270.7 Hz, J_{FH} = 9.5 Hz, F_A of CF_2, major rotamer), –123.59 (dd, 0.6F, J_{FF} = 270.7 Hz, J_{FH} = 19.0 Hz, F_B of CF_2, major rotamer), –125.60 (dd, 0.4F, J_{FF} = 270.7 Hz, J_{FH} = 19.0 Hz, F_B of CF_2, minor rotamer) ppm.

HRMS (ESI-TOF) *m/z*: $[M - H]^-$ calcd. for $C_{12}H_{15}F_5NO_4^-$ (332.0927). Found: 332.0916.

***trans*-3-(Perfluoroethyl)pyrrolidine-2-carboxylic acid hydrochloride (*trans*-1b)** was synthesized by the same approach as compound ***trans*-1a** (see section 2.5.1) starting from compound ***trans*-10b** (100 mg, 0.3 mmol). Yield: 75 mg (93%). Colorless solid, mp > 200 °C.



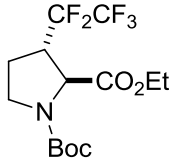
^{1}H NMR (600 MHz, CD_3OD): δ = 2.19-2.27 (m, 1H, H_A of CH_2), 2.41-2.50 (m, 1H, H_B of CH_2), 3.36-3.44 (m, 1H, H_A of CH_2N), 3.50-3.57 (m, 1H, H_B of CH_2N), 3.62- 3.72 (m, 1H, $CHCF_2$), 4.73 (d, 1H, J_{HH} = 5.4 Hz, CH) ppm.

^{13}C NMR (150 MHz, CD_3OD): δ = 26.1, 44.3 (t, J_{CF} = 21.7 Hz), 47.5, 59.4, 169.4 ppm. Low intensity, highly multiplicity signals of C_2F_5-group carbons are located in the area 112-125 ppm.

^{19}F NMR (282.5 MHz, CD_3OD): δ = – 84.63 (s, 3F, CF_3), –118.33 (dd, 1F, J_{FF} = 273.0 Hz, J_{FH} = 12.3 Hz, F_A of CF_2), –124.53 (dd, 1F, J_{FF} = 273.0 Hz, J_{FH} = 19.0 Hz, F_B of CF_2) ppm.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_7H_9F_5NO_2^+$ (234.0548). Found: 234.0561.

***trans*-1-(*tert*-Butoxycarbonyl)-3-(perfluoroethyl)pyrrolidine-2-carboxylic acid (*trans*-11b).** A solution of crude compound ***trans*-9a** (~210 mg) in dioxane (10 mL) was cooled to 0°C and then triethylamine (0.42 mL, 304 mg, 3 mmol) and Boc-anhydride (314 mg, 1.4 mmol) were consequently added portionwise under stirring. The mixture was stirred for 1 h at 0-5 °C and left stirring overnight at r.t. Then dioxane was evaporated and the residue was acidified with 1N HCl solution to pH ~2-3 at 0-5 °C. The aqueous layer was extracted with ethyl acetate (4×50 mL) and combined organic layers were washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/cHex 1:2, R_f = 0.61). Yield: 245 mg (68% upon two stages, starting from ***anti*-4b**). Colorless oil.



NMR spectra contain overlapping signals of two rotamers in ratio ~2:3 ($CDCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.27 (t, 3H, J_{HH} = 7.1 Hz, CH_3), 1.41 (s, 5.4H, $3CH_3$, major rotamer), 1.44 (s, 3.6H, $3CH_3$, minor rotamer), 2.02-2.20 (m, 2H, CH_2), 2.89-3.05 (m, 1H, $CHCF_2$), 3.45-3.54 (m, 1H, H_A of

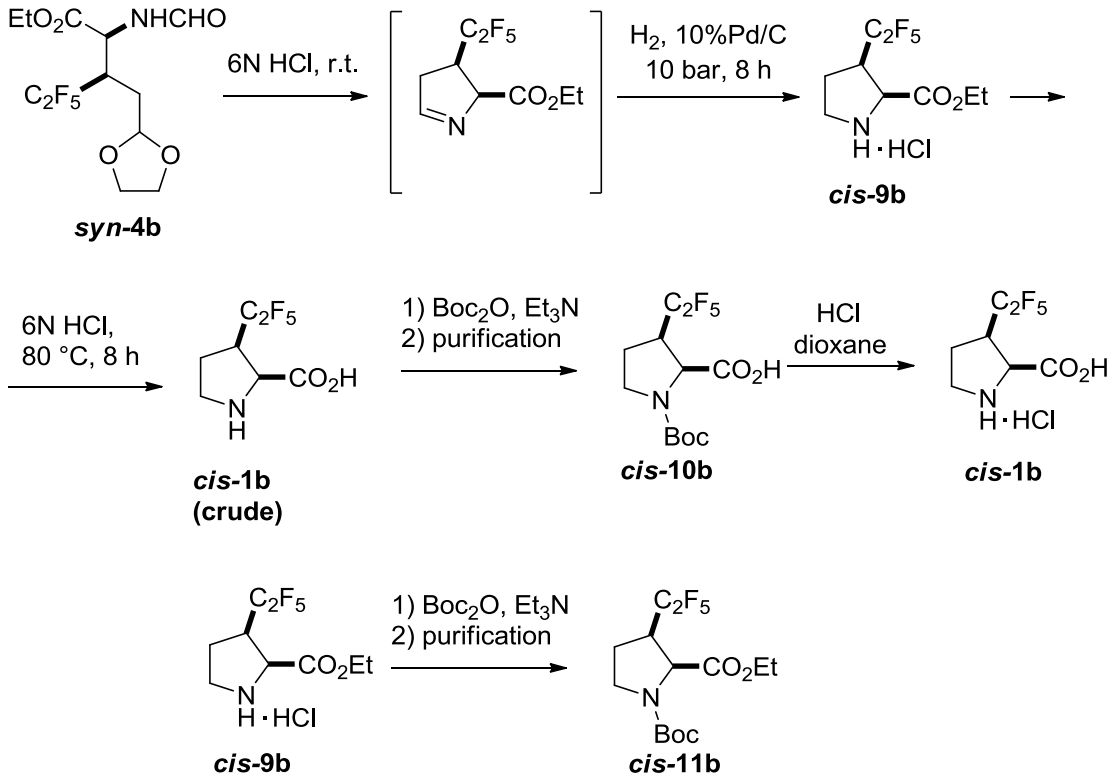
CH_2N), 3.57-3.77 (m, 1H, H_B of CH_2N), 4.11-4.28 (m, 2H, CH_2O), , 4.42 (d, 0.6H, J_{HH} = 5.2 Hz, CH, major rotamer), 4.54 (d, 0.4H, J_{HH} = 5.2 Hz, CH, minor rotamer) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, both rotamers): δ = 14.0, 24.2, 24.8, 28.1, 28.2, 44.3 (t, J_{CF} = 21.5), 45.5 (t, J_{CF} = 21.5), 45.6, 45.7, 58.4, 61.6, 61.5, 80.6, 80.8, 153.1, 153.8, 171.4, 171.6 ppm. Low intensity, highly multiplicity signals of C_2F_5-group carbons are located in the area 112-125 ppm.

^{19}F NMR (282.5 MHz, $CDCl_3$): δ = –83.04 (s, 1.2F, CF_3, minor rotamer), –83.07 (s, 1.8F, CF_3, major rotamer), –115.64 (dd, 0.6F, J_{FF} = 272.5 Hz, J_{FH} = 8.3 Hz, F_A of CF_2, major rotamer), –116.51 (dd, 0.4F, J_{FF} = 272.5 Hz, J_{FH} = 11.4 Hz, F_A of CF_2, minor rotamer), –124.14 (dd, 0.4F, J_{FF} = 272.5 Hz, J_{FH} = 19.0 Hz, F_B of CF_2, minor rotamer), –124.88 (dd, 0.6F, J_{FF} = 272.5 Hz, J_{FH} = 20.3 Hz, F_B of CF_2, major rotamer) ppm.

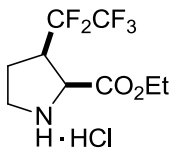
HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd. for $C_{14}H_{20}F_5NNaO_4$+ (384.1205). Found: 384.1212.

2.5.4. Synthesis of cis-3-C_2F_5-proline ***cis-1b***



Scheme S6. Synthesis of compounds ***cis*-1b** and ***cis*-11b**

Ethyl *cis*-3-(perfluoroethyl)pyrrolidine-2-carboxylate hydrochloride (*cis*-9b) was synthesized by the same approach as compound ***trans*-9a** starting from compound ***syn*-4b** (349 mg, 1mmol). Isolated ~200 mg of the crude product (contains ~10% of compound ***cis*-1b** and ethylene glycol) was used for further stage without purification.



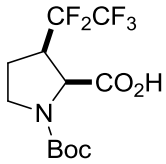
Colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (t, 3H, J_{HH} = 7.2 Hz, CH_3), 2.20-2.37 (m, 1H, H_A of CH_2), 2.41-2.54 (m, 1H, H_B of CH_2), 3.45-3.79 (m, 3H, CH_2N and $CHCF_2$), 4.27-4.39 (m, 2H, CH_2O), 4.73 (d, 1H, J_{HH} = 7.5 Hz, CH) ppm.

^{19}F NMR (282.5 MHz, CD_3OD): δ = – 84.94 (s, 3F, CF_3), –114.71 (dd, 1F, J_{FF} = 274.9 Hz, J_{FH} = 6.5 Hz, F_A of CF_2), –123.72 (dd, 1F, J_{FF} = 276.7 Hz, J_{FH} = 28.9 Hz, F_B of CF_2) ppm.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_9H_{13}F_5NO_2^+$ (262.0861). Found: 262.0868

***cis*-1-(*tert*-Butoxycarbonyl)-3-(perfluoroethyl)pyrrolidine-2-carboxylic acid (*cis*-10b)** was synthesized by the same approach as compound ***trans*-9a** starting from compound ***cis*-10b** (135 mg, 0.5 mmol) and purified by column chromatography (EtOAc/cHex 1:2, R_f = 0.16). Yield: 151 mg (56% upon 3 stages starting from compound ***syn*-4b**). Colorless solid, mp 166-168 °C.



NMR spectra contain overlapping signals of two rotamers in ratio ~1:2 ($CDCl_3$).

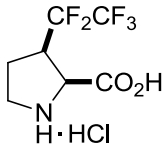
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 5.4H, $3CH_3$, major rotamer), 1.43 (s, 3.6H, $3CH_3$, minor rotamer), 2.06-2.43 (m, 2H, CH_2), 2.94-3.17 (m, 1H, $CHCF_2$), 3.35-3.47 (m, 1H, H_A of CH_2), 3.68-3.86 (m, 1H, H_B of CH_2), 4.48 (d, 0.6H, J_{HH} = 7.5 Hz, CH, major rotamer), 4.59 (d, 0.4H, J_{HH} = 7.5 Hz, CH, minor rotamer), 8.67 (br. s, 1H, CO_2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$, both rotamers): δ = 22.9, 23.7, 28.1, 28.3, 43.4 (t, J_{CF} = 20.7 Hz), 44.4 (t, J_{CF} = 20.7 Hz), 45.1, 45.2, 57.9, 58.3, 81.1, 81.4, 153.3, 154.1, 174.7, 175.8 ppm. Low intensity, highly multiplicity signals of C_2F_5-group carbons are located in the area 112-125 ppm.

^{19}F NMR (282.5 MHz, $CDCl_3$): δ = –84.37 (s, 1.8F, CF_3, major rotamer), –84.43 (s, 1.2F, CF_3, minor rotamer), –115.95 (dd, 0.6F, J_{FF} = 274.5 Hz, J_{FH} = 8.5 Hz, F_A of CF_2, major rotamer), –116.26 (dd, 0.4F, J_{FF} = 274.5 Hz, J_{FH} = 8.5 Hz, F_A of CF_2, minor rotamer), –123.02 (dd, 0.4F, J_{FF} = 274.5 Hz, J_{FH} = 21.5 Hz, F_B of CF_2, minor rotamer), –124.41 (dd, 0.6F, J_{FF} = 274.5 Hz, J_{FH} = 21.5 Hz, F_B of CF_2, major rotamer) ppm.

HRMS (ESI-TOF) *m/z*: $[M - H]^-$ calcd. for $C_{12}H_{15}F_5NO_4^-$ (332.0927). Found: 332.0911.

***cis*-3-(Perfluoroethyl)pyrrolidine-2-carboxylic acid hydrochloride (*cis*-1b)** was synthesized by the same approach as compound ***trans*-1a** (see section 2.5.1) starting from compound ***cis*-10b** (100 mg, 0.3 mmol). Yield: 77 mg (96%). Colorless oil.



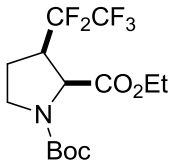
^{1}H NMR (300 MHz, CD_3OD): δ = 2.22-2.55 (m, 2H, CH_2), 3.41-3.77 (m, 3H, CH_2N and $CHCF_2$), 4.66 (d, 1H, J_{HH} = 7.5 Hz, CH) ppm.

^{13}C NMR (150 MHz, CD_3OD): δ = 25.0, 44.1 (t, J_{CF} = 20.5 Hz), 45.7, 60.6, 169.4 ppm. Low intensity, highly multiplicity signals of C_2F_5-group carbons are located in the area 112-125 ppm.

^{19}F NMR (282.5 MHz, CD_3OD): δ = – 85.01 (s, 3F, CF_3), –114.65 (dd, 1F, J_{FF} = 276.7 Hz, J_{FH} = 6.5 Hz, F_A of CF_2), –123.98 (dd, 1F, J_{FF} = 276.7 Hz, J_{FH} = 28.9 Hz, F_B of CF_2) ppm.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_7H_9F_5NO_2^+$ (234.0548). Found: 234.0559.

***cis*-1-(*tert*-Butoxycarbonyl)-3-(perfluoroethyl)pyrrolidine-2-carboxylic acid (*cis*-11b)** was synthesized by the same approach as compound ***trans*-10b** starting from compound ***cis*-9b** (~200 mg) and purified by column chromatography (EtOAc/cHex 1:2, R_f = 0.57). Yield: 225 mg (62% upon two stages starting from compound ***syn*-4a**). Colorless oil.



NMR spectra contain overlapping signals of two rotamers in ratio ~2:3 ($CDCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.25 (t, 1.2H, J_{HH}= 7.0 Hz, CH_3, minor rotamer), 1.27 (t, 1.8H, J_{HH} = 7.0 Hz, CH_3, major rotamer), 1.40 (s, 5.4H, $3CH_3$, major rotamer), 1.44 (s, 3.6H, $3CH_3$, minor rotamer), 2.07-2.14 (m, 1H, H_A of CH_2), 2.22-2.38 (m, 1H, H_B of CH_2), 2.91-3.10 (m, 1H, CH), 3.36-3.45 (m, 1H, H_A of CH_2N), 3.75 (t, 0.4H, J_{HH} = 9.2 Hz, H_B of CH_2N, minor rotamer), 3.83 (t, 0.6H, J_{HH} = 10.0 Hz, H_B of CH_2N, major rotamer), 4.11-4.26 (m, 2H, CH_2O), 4.46 (d, 0.6H, J_{HH} = 7.6 Hz, CHN, major rotamer), 4.57 (d, 0.4H, J_{HH} = 7.6 Hz, CHN, minor rotamer) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, both rotamers): δ = 13.7, 13.9, 22.8, 23.6, 28.2, 28.3, 43.2 (t, J_{CF} = 21.2), 44.0 (t, J_{CF} = 21.2), 45.0, 45.1, 58.0, 58.4, 61.4, 61.5, 80.6, 80.7, 153.2, 153.9, 170.2, 170.3 ppm. Low intensity, highly multiplicity signals of C_2F_5-group carbons are located in the area 112-125 ppm.

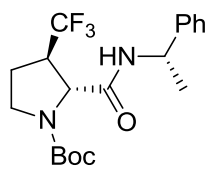
^{19}F NMR (282.5 MHz, $CDCl_3$): δ = –83.79 (s, 3F, CF_3), –115.44 (dd, 0.6F, J_{FF} = 274.7 Hz, J_{FH} = 8.1 Hz, F_A of CF_2, major rotamer), –115.80 (dd, 0.4F, J_{FF} = 274.7 Hz, J_{FH} = 8.1 Hz, F_A of CF_2, minor rotamer), –122.87 (dd, 0.4F, J_{FF} = 274.7 Hz, J_{FH} = 21.9 Hz, F_B of CF_2, major rotamer), –123.28 (dd, 0.6F, J_{FF} = 274.7 Hz, J_{FH} = 21.9 Hz, F_B of CF_2, major rotamer) ppm.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd. for $C_{14}H_{20}F_5NNaO_4$+ (384.1205). Found: 384.1214.

2.6. Enantiomer separation of compounds *trans-/cis*-10a

(*2S,3S*)-and (*2R,3R*)-*tert*-Butyl 2-[((*S*)-1-phenylethyl)carbamoyl]-3-(trifluoromethyl)pyrrolidine-1-carboxylate ((*2S,3S*)- and (*2R,3R*)-12a). Triethylamine (0.25 mL ,182 mg, 1.8 mmol), HBTU (606 mg, 1.6 mmol) and (*S*)-PEA (194 mg, 1.6 mmol) were consequently added to a stirred solution of compound ***trans*-10a** (500 mg, 1.5 mmol) in dry acetonitrile (20 mL) at 0 °C. The mixture was stirred at 0-5 °C for 1h and then left stirring overnight at r.t. Then the solution was concentrated under reduced pressure, Dissolved in EtOAc (10 mL) and consequently washed with 1N HCl (2 × 25 mL), saturated solution of $NaHCO_3$ (2 × 25 mL) and brine (25 mL). The organic layer was dried under over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/cHex, 1:3) giving pure diastereomer **(*2S,3S*)-** and **(*2R,3R*)-12a.**

(*2R,3R*)- *tert*-Butyl 2-[((*S*)-1-phenylethyl)carbamoyl]-3-(trifluoromethyl)pyrrolidine-1-carboxylate ((*2R,3R*)-12a) isolated by column chromatography (EtOAc/cHex, 1:2, R_f = 0.35). Yield: 249 mg (43%). Colorless solid, mp 102-104 °C. $[\alpha]_D^{20}$ = –59.5 (*c*, 1.0, MeOH).



NMR-spectra contain overlapping signals of both rotamers in ratio ~1:4 ($CDCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33-1.54 (m, 12H, $4CH_3$), 2.04-2.26 (m, 2H, CH_2),3.21-3.71 (m, 3H, CH_2N and $CHCF_3$), 4.38 (br. s, 0.2H, CHN, minor rotamer), 4.57 (br. s, 0.8H, CHN, major rotamer), 4.99-5.10 (m, 1H, CHN), 6.39 (br. s, 0.2H, NH, minor rotamer), 7.18-7.37 (m, 5H, Ph), 7.77 (br. s, 0.8H, NH, major rotamer) ppm.

^{13}C NMR (100 MHz, $CDCl_3$, signals of major rotamer only): δ = 22.9, 24.7, 28.2, 43.1 (q, J_{CF} = 28.6 Hz), 45.8, 49.2, 59.7, 81.3, 125.8, 127.1, 128.6, 143.5, 155.8, 168.2. Low intensive signal of CF_3-Carbon is located in the area 120-125 ppm.

^{19}F NMR (282.5 MHz, $CDCl_3$): δ = –71.36 (d, J_{FH} = 9.7 Hz, 0.8F, major rotamer), –71.68.. –71.86 (m, 0.2F, minor rotamer) ppm.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd. for $C_{19}H_{25}F_3N_2NaO_3^+$ (409.1709). Found: 409.1720

(*2S,3S*)- *tert*-Butyl 2-[((*S*)-1-phenylethyl)carbamoyl]-3-(trifluoromethyl)pyrrolidine-1-carboxylate ((*2S,3S*)-12a) isolated by column chromatography (EtOAc/cHex, 1:2, R_f = 0.30). Spectra contain overlapping signals of both rotamers in ratio ~1:3. Yield 214 mg (37%). Colorless solid, mp 119-121 °C. $[\alpha]_D^{20}$ = –83.0 (*c*, 1.0, MeOH).

NMR-spectra contain overlapping signals of both rotamers in ratio ~1:3 ($CDCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33-1.54 (m, 12H, $4CH_3$), 2.04-2.26 (m, 2H, CH_2), 3.21-3.71 (m, 3H, CH_2N and $CHCF_3$), 4.38 (s, 0.25H, CH, minor rotamer), 4.57 (s, 0.75H, CH, major rotamer), 4.99-5.10 (m, 1H, CHN), 6.39 (br. s, 0.25H, NH, minor rotamer), 7.18-7.37 (m, 5H, Ph), 7.77 (br. s, 0.75H, major rotamer).

^{13}C NMR (100 MHz, $CDCl_3$, signals of major rotamer only): δ = 22.3, 24.8, 28.3, 43.3 (q, *J* = 27.5 Hz), 45.8, 81.3, 115.9 (q, *J* = 267.0 Hz), 126.0, 127.3, 128.7, 143.1, 155.8, 168.5 ppm.

^{19}F NMR (282.5 MHz, $CDCl_3$): δ = δ = –71.35 (d, J_{HF} = 9.7 Hz, 0.75F, major rotamer), –71.74.. –71.97 (m, 0.25F, minor rotamer) ppm.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd. for $C_{19}H_{25}F_3N_2NaO_3^+$ (409.1709). Found: 409.1727

(*2S,3R*)-and (*2R,3S*)-*tert*-Butyl 2-[((*S*)-1-phenylethyl)carbamoyl]-3-(trifluoromethyl)pyrrolidine-1-carboxylate ((*2S,3R*)- and (*2R,3S*)-12a). The mixture of diastereomers was obtained by the same method as **(*2S,3S*)-** and **(*2R,3R*)-12a** starting from ***cis*-10a** (500 mg, 1.5 mmol) and were separated by column chromatography.

(*2S,3R*)- *tert*-Butyl 2-[((*S*)-1-phenylethyl)carbamoyl]-3-(trifluoromethyl)pyrrolidine-1-carboxylate ((*2S,3R*)-12a). Isolated by column chromatography. (EtOAc/cHex, 1:3, R_f = 0.37). Yield: 220 mg (38%). Colorless solid, mp 172-174 °C. $[\alpha]_D^{20}$ = –142.3 (*c*, 1.0, MeOH).

NMR spectra contain overlapping signals of two rotamers in ratio ~2:3 ($CDCl_3$)

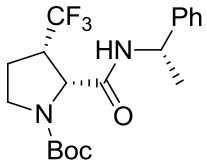
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.05-1.53 (12H, m, 4CH3), 2.08-2.15 (m, 1H, H_A of CH_2), 2.24-2.58 (m, 1H, H_B of CH_2), 2.94-3.11 (m, 1H, H_A of CH_2N), 3.37-3.47 (m, 1H, $CHCF_3$), 3.69-3.82 (m, 1H, H_B of CH_2N), 4.15-4.39 (m, 1H, CH), 5.03-5.23 (m, 1H, CH), 5.73-6.17 (m, 1H, NH), 7.12-7.43 (5H,m, Ph) ppm.

^{13}C NMR (126 MHz, $CDCl_3$, major rotamer): δ = 20.6, 23.4, 28.2, 45.3, 45.6-47.5 (m), 59.7, 80.7, 125.2 (q, J_{CF} = 280.0 Hz), 126.3, 127.5, 128.6, 142.6, 153.6, 167.5 ppm.

^{19}F NMR (282.5 MHz, $CDCl_3$): δ = –66.54 (br.s, 0.4F, CF_3, minor rotamer), –67.07 (br.s, 0.6F, CF_3, major rotamer) ppm.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd. for $C_{19}H_{25}F_3N_2NaO_3^+$ (409.1709). Found: 409.1714

(*2R,3S*)- *tert*-Butyl 2-[((*S*)-1-phenylethyl)carbamoyl]-3-(trifluoromethyl)pyrrolidine-1-carboxylate ((*2R,3S*)-12a). Isolated by column chromatography. (EtOAc/cHex, 1:3, R_f = 0.25). Yield: 255 mg (44%). Colorless solid, mp 104-106 °C. $[\alpha]_D^{20}$ = –60.2 (*c*, 1.0, MeOH).



NMR spectra contain overlapping signals of two rotamers.

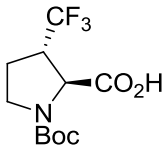
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.19-1.45 (m, 9H, $3CH_3$), 1.52 (d, 3H, J_{HH} = 7.0 Hz, CH_3), 2.07-2.16 (m, 1H, H_A of CH_2), 2.19-2.46 (m, 1H, H_B of CH_2), 2.95-3.11 (m, 1H, H_A of CH_2N), 3.39-3.51 (m, 1H, $CHCF_3$), 3.70-3.77 (m, 1H, H_B of CH_2N), 4.23-4.36 (m, 1H, CH), 5.08-5.17 (m, 1H, CH), 5.79-6.22 (m, 1H, NH), 7.15-7.40 (5H,m, Ph) ppm.

^{13}C NMR (126 MHz, $CDCl_3$, major rotamer): δ = 21.0, 26.9, 28.2, 45.5, 45.7-47.0 (m), 49.0, 60.0, 80.9, 125.2 (q, J_{CF} = 279.5 Hz), 126.4, 127.5, 128.6, 142.3, 153.9, 167.5 ppm

^{19}F NMR (282.5 MHz, $CDCl_3$): δ = –66.38,–67.55 (m,CF_3) ppm.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd. for $C_{19}H_{25}F_3N_2NaO_3^+$ (409.1709). Found: 409.1718

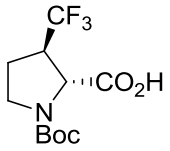
(*2S,3S*)-1-(*tert*-Butoxycarbonyl)-3-(trifluoromethyl)pyrrolidine-2-carboxylic acid ((*2S,3S*)-10a)). 6N HCl (5 mL) was added to the solution of compound **(*2S,3S*)-12a** (193 mg, 0.5 mmol) in dioxane (5 mL) and the resulting mixture was stirred under reflux for 12h. The reaction progress was monitored by TLC. Then the mixture was concentrated under reduced pressure and dried under vacuum of oil pump (10^{-3} mm Hg). The residue was dissolved in dioxane and cooled to 0°C. Then Et_3N (0.21 mL, 152 mg, 1.5 mmol) and Boc-anhydride (218 mg, 1 mmol) were added consequently portionwise under stirring. The mixture was stirred at 0-5 °C for 1 h and left stirring at r.t. overnight. Then dioxane was evaporated and the resulting aqueous solution was acidified with 1N HCl solution to pH ~2-3 at 0-5 °C. The aqueous layer was extracted with ethyl acetate (4×50 mL) and combined organic layers were washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/cHex 1:2, R_f = 0.11). Yield: 96 mg (68%). Colorless solid, mp >200 °C. $[\alpha]_D^{20}$ = –26.5 (c, 1.0, MeOH).



See NMR-spectra description above for ***trans*-10a**.

HRMS (ESI-TOF) *m/z*: $[M - H]^-$ calcd. for $C_{11}H_{15}F_3NO_4^-$ (282.0959). Found: 282.0986

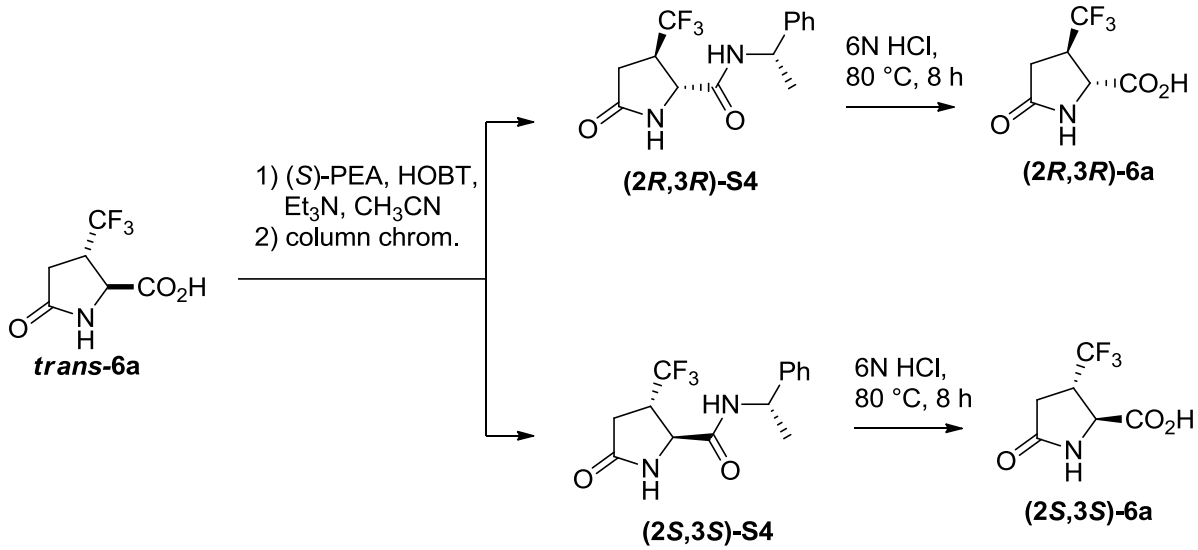
(*2R,3R*)-1-(*tert*-Butoxycarbonyl)-3-(trifluoromethyl)pyrrolidine-2-carboxylic acid ((*2R,3R*)-10a)) was synthesized by the same method as compound **(*2S,3S*)-10a** starting from compound **(*2R,3R*)-10a** (193 mg, 0.5 mmol) and purified by column chromatography (EtOAc/cHex 1:2, R_f = 0.11). Yield: 99 mg (70%). Colorless solid, mp >200 °C. $[\alpha]_D^{20}$ = +27.8 (MeOH).



See NMR-spectra description above for ***trans*-10a**.

HRMS (ESI-TOF) *m/z*: $[M - H]^-$ calcd. for $C_{11}H_{15}F_3NO_4^-$ (282.0959). Found: 282.0969

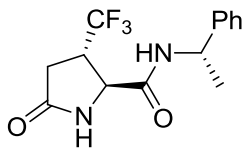
2.7. Enantiomer separation of compounds *trans*-6a



Scheme S7. Enantiomer separation of compounds ***trans*-6a**

***(2S,3S)*- and *(2R,3R)*-5-Oxo-*N*-((*S*)-1-phenylethyl)-3-(trifluoromethyl)pyrrolidine-2-carboxamide (*(2S,3S)*- and *(2R,3R)*-S4)**. The mixture of diastereomers was obtained by the same method as **(*2S,3S*)-** and **(*2R,3R*)-12a** starting from ***trans*-6a** (296 mg, 1.5 mmol) and were separated by column chromatography.

***(2S,3S)*- 5-Oxo-*N*-((*S*)-1-phenylethyl)-3-(trifluoromethyl)pyrrolidine-2-carboxamide (*(2S,3S)*- S4)** was separated by column chromatography (Et_2O/ EtOH, 97:3, R_f = 0.16). Yield: 158 mg (35%). Colorless solid, mp = 166-168 °C. $[\alpha]_D^{20}$ = –50.0 (*c*, 1.0, MeOH).



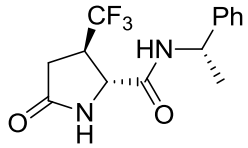
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 (d, 3H, J_{HH} = 6.9 Hz, CH_3), 2.37 (dd, 1H, J_{1HH} = 18.0 Hz, J_{2HH} = 4.3 Hz, H_A of CH_2), 2.53 (dd, 1H, J_{1HH} = 18.0 Hz, J_{2HH} = 10.2 Hz, H_B of CH_2), 3.23-3.37 (m, 1H, $CHCF_3$), 4.13 (d, 1H, J_{HH} = 2.9 Hz, CH), 5.01-5.11(m, 1H, CH), 7.22 (d, 1H, J_{HH} = 7.4 Hz, NH), 7.23-7.35 (m, 5H, Ph), 7.41 (br. s, 1H, NH) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 29.7, 41.6 (q, J_{CF} = 29.9 Hz), 49.5, 56.6, 126.2, 126.3 (q, J_{CF} = 279.8 Hz), 127.6, 128.7, 142.6, 168.4, 175.5 ppm.

^{19}F NMR (282.5 MHz, $CDCl_3$): δ = – 73.60 (s, CF_3) ppm.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd. for $C_{14}H_{15}F_3N_2NaO_2^+$ (323.0978). Found: 323.0968.

(2R,3R)- **5-Oxo-*N*-((*S*)-1-phenylethyl)-3-(trifluoromethyl)pyrrolidine-2-carboxamide (*(2R,3R)*-24a)** was separated by column chromatography (Et_2O/ EtOH, 97:3, R_f = 0.28). Yield: 167 mg (37%). Colorless solid, mp = 130-132 °C. $[\alpha]_D^{20}$ = –179.3 (*c*, 1.0, MeOH).



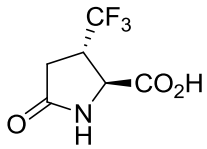
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 (d, 3H, J_{HH} = 7.0 Hz, CH_3), 2.34 (dd, 1H, J_{1HH} = 18.0 Hz, J_{2HH} = 5.2 Hz, H_A of CH_2), 2.43 (dd, 1H, J_{1HH} = 18.0 Hz, J_{2HH} = 10.2 Hz, H_B of CH_2), 3.23-3.35 (m, 1H, $CHCF_3$), 4.17 (d, 1H, J_{HH} = 3.3 Hz, CH), 5.08 (qwint, 1H, J_{HH} = 7.0 Hz, CH), 6.91 (d, 1H, J_{HH} = 7.0 Hz, NH), 7.21-7.32 (m, 5H, Ph), 7.43 (br. s, 1H, NH) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 29.5, 42.7 (q, J_{CF} = 30.0 Hz), 49.6, 56.6, 126.1, 126.2 (q, J_{CF} = 279.8 Hz), 127.7, 128.8, 142.4, 168.2, 175.7 ppm.

^{19}F NMR (282.5 MHz, $CDCl_3$): δ = – 73.48 (s, CF_3) ppm.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd. for $C_{14}H_{15}F_3N_2NaO_2^+$ (323.0978). Found: 323.0980

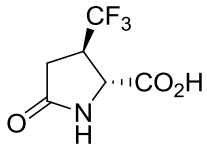
(*2S,3S*)-5-oxo-3-(trifluoromethyl)pyrrolidine-2-carboxylic acid (*(2S,3S)*- 6a). 6N HCl (5 mL) was added to the solution of compound **(*2S,3S*)-S4** (150 mg, 0.5 mmol) in dioxane (5 mL) and the resulting mixture was stirred under reflux for 12h. The reaction progress was monitored by TLC. Then the mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (30 mL), washed with water (2 × 25 mL), dried under $MgSO_4$, concentrated under reduced pressure and crystallized from cyclohexane. Yield: 78 mg (79%). Colorless solid, mp 119-120 °C, (Lit.: 120-122 °C).[2b] $[\alpha]_D^{20}$ = +24.7 (*c*, 1.0, MeOH) {Lit.: $[\alpha]_D^{20}$ = +25.3 (*c*, 1.2, MeOH),[2b] +24.9 (*c*, 0.5, MeOH) [2c]}



See NMR-spectra description above for racemic ***trans*-6a**.

HRMS (ESI-TOF) *m/z*: $[M - H]^-$ calcd. for $C_6H_5F_3NO_3^-$ (196.0227). Found: 196.0204.

(*2R,3R*)-5-oxo-3-(trifluoromethyl)pyrrolidine-2-carboxylic acid (*(2R,3R)*- 6a) was synthesized by the same method as compound **(*2S,3S*)-6a** starting from compound **(*2R,3R*)-S4** (150 mg, 0.5 mmol) and purified by column chromatography. Yield: 81 mg (82%). Colorless solid, mp = 123-124 °C. $[\alpha]_D^{20}$ = –26.3 (c, 0.5, MeOH).

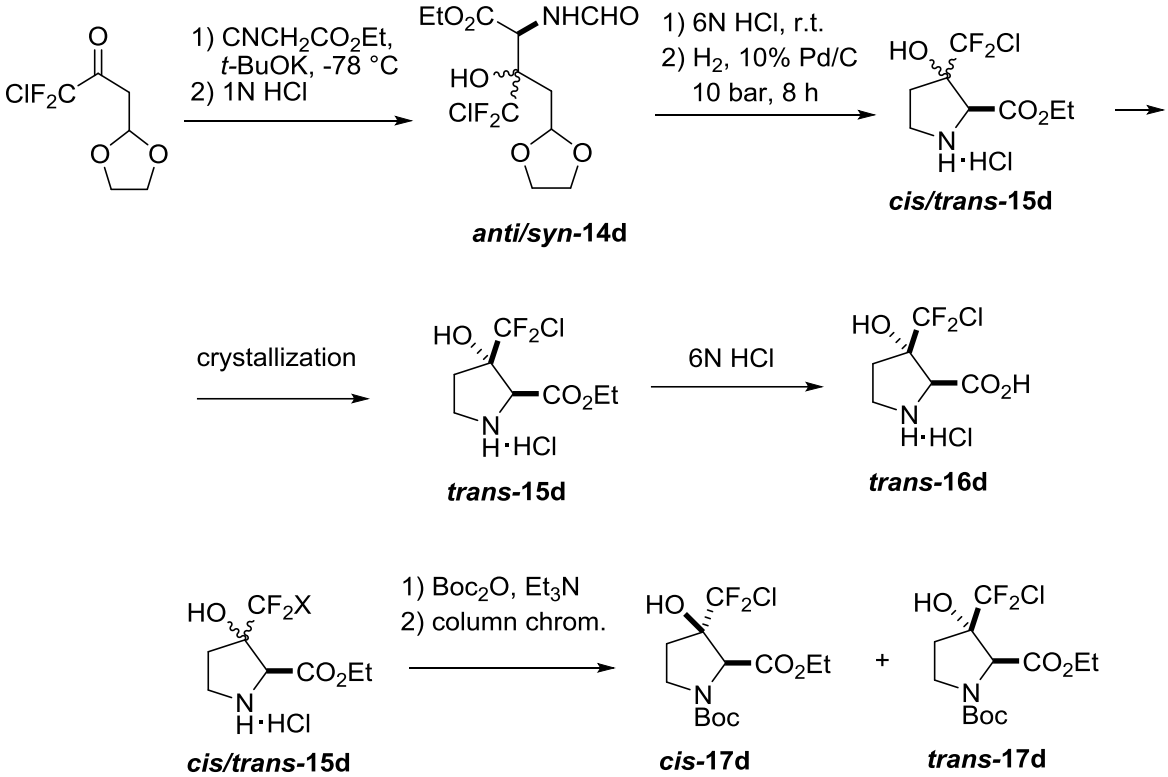


See NMR-spectra description above for ***trans*-6a**.

HRMS (ESI-TOF) *m/z*: $[M - H]^-$ calcd. for $C_6H_5F_3NO_3^-$ (196.0227). Found: 196.0211.

2.8. Reactions of ketoacetals 2d,e with ethyl isocyanoacetate. Synthesis of 3-hydroxy-polyfluoroalkyl prolines 16c-e

*2.8.1. Synthesis of compounds **trans-16d** and **trans-/cis-17d***



anti/syn*-Ethyl 3-[(1,3-dioxolan-2-yl)methyl]-4-chloro-4,4-difluoro-2-formamido-3-hydroxybutanoate (*anti/syn*-14d).** The mixture of diastereomers was obtained by the same procedure as compounds ***trans-/cis-3a,b(see section 2.1)**,** starting from ketoacetal **2d** (1.60 g, 8.0 mmol) and purified by column chromatography (without separation, EtOAc/cHex, 1:1, R_f = 0.21) giving ~1.3 g of compound ***anti/syn*-14d** Even after column chromatography the compounds is ~70% purity and contains EtOAc. Colorless oil.

NMR spectra contain overlapping signals of both diastereomers in ratio ~1:9.

^{1}H NMR (300 MHz, $CDCl_3$, signals of major diastereomer only): δ = 1.32 (t, 3H, *J* = 7.2 Hz, CH_3), 2.15 (dd, 1H, J_1 = 15.0 Hz, J_2 = 5.2 Hz, H_A of CH_2), 2.38 (dd, 1H, J_1 = 15.0 Hz, J_2 = 4.1 Hz, H_B of CH_2), 3.85-4.05 (m, 4H, $2CH_2O$), 4.26 (q, 2H, *J* = 7.2 Hz, CH_2O), 5.04 (s, 1H, OH), 5.17-5.28 (m, 2H, CH and CHO_2), 6.69 (d, 1H, *J* = 7.7 Hz, NH), 8.26 (s, 1H, CHO) ppm.

^{19}F NMR (282.5 MHz, $CDCl_3$): δ = – 62.50 (d, 0.9F, J_{CF} = 170.0 Hz, F_A of CF_2Cl, major diastereomer), –62.91 (d, 0.1F, J_{CF} = 172.0 Hz, F_A of CF_2Cl, minor diastereomer), – 63.16 (d, 0.9F, J_{CF} = 170.0 Hz, F_B of CF_2Cl, major diastereomer), –63.71 (d, 0.1F, J_{CF} = 172.0 Hz, F_B of CF_2Cl, minor diastereomer),

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd. for $C_{11}H_{16}ClF_2NNaO_6^+$ (354.0526). Found: 354.0535.

***trans-/cis*-Ethyl 3-(chlorodifluoromethyl)-3-hydroxypyrrolidine-2-carboxylate hydrochloride(*trans-/cis*-15d)** was synthesized by the same approach as compound ***trans*-9a** starting from the crude mixture of compounds ***anti-/syn*-14d** (1.3 g) giving ~1.0 g of the crude mixture of compounds ***trans-/cis*-15d**. Colorless oil.

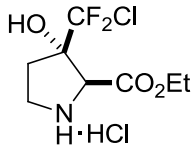
NMR spectra contain signals of ***trans*-** and ***cis*-15d** in ratio 9:1 (by ^{19}F NMR).

^{1}H NMR (300 MHz, CD_3OD): δ = 1.32 (t, 2.7H, J_{HH} = 7.2 Hz, CH_3, major diastereomer), 1.36 (t, 0.3H, J_{HH} = 7.2 Hz, CH_3, minor diastereomer), 2.29-2.39 (m, 1H, H_A of CH_2), 2.44-2.57 (m, 1H, H_B of CH_2), 3.57-3.68 (m, 1H, H_A of CH_2N), 3.77-3.78 (m, 1H, H_B of CH_2N), 4.22-4.35 (m, 2H, CH_2O), 4.37 (s, 0.9H, CH, major diastereomer), 4.66 (s, 0.1H, CH, minor diastereomer) ppm.

^{19}F NMR (282.5 MHz, CD_3OD): δ = –62.87 (d, 0.9F, J_{FF} = 172.0 Hz, F_A of CF_2Cl, major diastereomer), –64.68 (d, 0.9F, J_{FF} = 172.0 Hz, F_B of CF_2Cl, major diastereomer), –64.94 (d, 0.1F, J_{FF} = 169.0 Hz, F_A of CF_2Cl, minor diastereomer), –66.00 (d, 0.1F, J_{FF} = 169 Hz, F_B of CF_2Cl, minor diastereomer) ppm.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_8H_{13}ClF_2NO_3^+$ (244.0547). Found: 244.0540.

***trans*-Ethyl 3-(chlorodifluoromethyl)-3-hydroxypyrrolidine-2-carboxylate hydrochloride(*trans*-15d)** was isolated by crystallization from EtOH. Yield: 580 mg (26%, upon 2 stages starting from compound **2d**). Colorless solid, mp 112-114 °C.



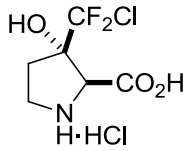
^{1}H NMR (400 MHz, D_2O): δ = 1.22 (t, 3H, *J* = 7.2 Hz, CH_3), 2.32 (ddd, 1H, J_{1HH} = 14.0 Hz, J_{2HH} = 6.1 Hz, J_{3HH} = 2.5 Hz, H_A of CH_2), 2.54 (dt, 1H, J_1 = 14.0 Hz, J_2 = 9.8 Hz, H_B of CH_2), 3.57-3.66 (m, 1H, H_A of CH_2N), 3.78 (ddd, 1H, J_{1HH} = 12.0 Hz, J_{2HH} = 9.8 Hz, J_{3HH} = 2.5 Hz, H_B of CH_2N), 4.19-4.28 (m, 2H, CH_2O), 4.46 (s, 1H, CH)

^{13}C NMR (100 MHz, D_2O): δ = 12.9, 31.0, 43.5, 64.5, 65.7, 85.7 (t, J_{CF} = 27.0 Hz), 122.7 (t, J_{CF} = 299.0 Hz), 166.2 ppm.

^{19}F NMR (282.5 MHz, D_2O): δ = – 62.34 (d, 1F, J_{FF} = 172.5 Hz, F_A of CF_2Cl), – 64.33 (d, 1F, J_{FF} = 172.5 Hz, F_B of CF_2Cl) ppm.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_8H_{13}ClF_2NO_3^+$ (244.0547). Found: 244.0552.

***trans*-3-(Chlorodifluoromethyl)-3-hydroxypyrrolidine-2-carboxylic acid hydrochloride (*trans*-16d).** Compound ***trans*-15d** (~560 mg, 2mmol) was dissolved in 6N HCl (20 mL) and the resulting solution was stirred for 10 h at 80 °C. Then the cooled mixture was washed by EtOAc (2 × 30 mL) and the water layer was concentrated under reduced pressure and the residue was dried in vacuum of oil pump (10^{-3} mm Hg) for 5 h giving pure compound ***trans*-16d**. Yield: 368 mg (73%). Colorless oil.



^{1}H NMR (300 MHz, D_2O): δ = 2.27 (dddd, 1H, J_{1HH} = 13.8 Hz, J_{2HH} = 7.6 Hz, J_{3HH} = 2.0 Hz, J_{4HH} = 1.1 Hz, H_A of CH_2), 2.53 (dt, 1H, J_{1HH} = 13.8 Hz, J_{2HH} = 10.1 Hz, H_B of CH_2), 3.55 (ddd, 1H, J_{1HH} = 11.0 Hz, J_{2HH} = 10.1, J_{3HH} = 7.6 Hz, H_A of CH_2N), 3.79 (ddd, 1H, J_{1HH} = 11.0 Hz, J_{2HH} = 10.1 Hz, J_{3HH} = 2.0 Hz, H_B of CH_2N), 4.06 (d, 1H, *J* = 1.1 Hz, CH) ppm.

^{13}C NMR (125 MHz, D_2O): δ = 31.4, 48.1, 68.1, 85.4, (dd, J_{1CF} = 28.0 Hz, J_{2CF} = 26.5 Hz), 128.1 (dd, J_{1CF} = 299.0 Hz, J_{2CF} = 296.1 Hz), 169.1 ppm.

^{19}F NMR (282.5 MHz, D_2O): δ = –61.38 (d, 1F, J_{FF} = 171.5 Hz, F_A of CF_2Cl), –63.12 (d, 1F, J_{FF} = 171.5 Hz, F_B of CF_2Cl) ppm.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_6H_9ClF_2NO_3^+$ (216.0234). Found: 216.0236.

***trans*- and *cis*-1-*tert*-Butyl 2-ethyl 3-(chlorodifluoromethyl)-3-hydroxypyrrolidine-1,2-dicarboxylate (*trans*- and *cis*-17d).** A solution of crude diastereomeric mixture ***trans-/cis*-15d** (~1.0 g) in dioxane (10 mL) was cooled to 0°C and then triethylamine (0.40 mL ,300 mg, 3 mmol) and Boc-anhydride (327 mg, 1.5 mmol) were consequently added in portions under stirring. The mixture was stirred for 1 h at 0-5°C and left stirring overnight at r.t. Then dioxane was evaporated and the resulting aqueous solution was acidified with 1N HCl solution to pH ~2-3 at 0-5 °C. The aqueous layer was extracted with ethyl acetate (4×50 mL) and combined organic layers were washed with saturated $NaHCO_3$ (25 mL) and water (25 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue contained diastereomers ***trans*-** and ***cis*-17d** in ratio 9:1 which were separated and purified by column chromatography.

***cis*-1-*tert*-Butyl 2-ethyl 3-(chlorodifluoromethyl)-3-hydroxypyrrolidine-1,2-dicarboxylate (*cis*-17d)** was purified by column chromatography (EtOAc/cHex, 1:4, R_f = 0.37). Yield: 82 mg (3% upon 3 steps starting from **2d**). Colorless oil.

NMR-spectra contain overlapping signals of both rotamers in ratio ~2:3.

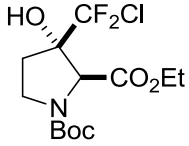
^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.29 (t, 3H, J_{HH} = 7.0 Hz, CH_3), 1.35-1.46 (m, 9H, $3CH_3$), 2.11-2.19 (m, 1H, Ha of CH_2), 2.35 (t, 0.6H, J_{HH} = 8.0 Hz, H_b of CH_2, major rotamer), 2.38 (t, 0.4H, J_{HH} = 8.0 Hz, H_b of CH_2, minor rotamer), 3.56 (br. s, 0.6H, OH, major rotamer), 3.59-3.68 (m, 2H, CH_2N), 3.84 (br. s, 0.4H, OH, minor rotamer), 4.17-4.33 (m, 2H, CH_2O), 4.48 (s, 0.6H, CH, major rotamer), 4.56 (s, 0.4H, CH, minor rotamer).

^{13}C NMR (151 MHz, $CDCl_3$): δ =13.9, 14.0, 28.2, 28.3, 44.2, 44.5, 62.0, 62.2, 62.5, 63.1, 80.8, 81.1, 83.6 (t, J_{CF} = 27.0 Hz), 84.8 (t, *J* =27.0 Hz), 129.7 (t, J_{CF} = 298.5 Hz), 153.1, 153.8, 169.7 ppm

^{19}F NMR (282.5 MHz, $CDCl_3$): δ = –65.80 (d, 0.4F, J_{FF} = 167.0 Hz, F_A of CF_2Cl, minor rotamer), –65.87 (d,0.6F, J_{FF} = 168.5 Hz, F_A of CF_2Cl, major rotamer), –66.47 (d, 0.4F, J_{FF} = 167.0 Hz, F_B of CF_2Cl, minor rotamer), –66.59 (d, 0.6F, J_{FF} = 168.5 Hz, F_B of CF_2Cl, major rotamer) ppm.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd. for $C_{13}H_{20}ClF_2NNaO_5^+$ (366.0890). Found: 366.0884.

***trans*-1-*tert*-Butyl 2-ethyl 3-(chlorodifluoromethyl)-3-hydroxypyrrolidine-1,2-dicarboxylate (*trans*-17d)**



was purified by column chromatography chromatography (EtOAc/cHex, 1:4, R_f = 0.21). Yield: 1.07 g (39% upon 3 steps starting from compound **2d**). Colorless solid, mp 141-143 °C.

Spectra contain overlapping signals of both rotamers in ratio ~2:3.

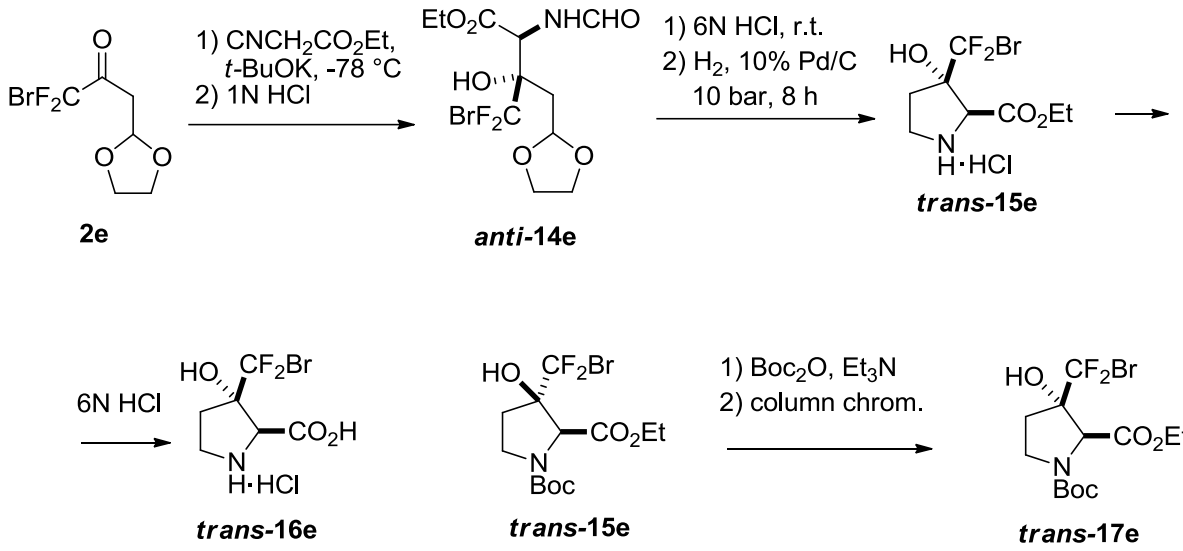
^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.25 (t, 1.2H, J_{HH} = 7.1 Hz, CH_3, minor rotamer), 1.27 (t, 1.8H, J_{HH} = 7.1 Hz, CH_3, major rotamer), 1.37-1.45 (m, 9H, $3CH_3$), 1.98-2.03 (m, 1H, H_A of CH_2), 2.39-2.47 (m, 1H, H_B of CH_2), 3.18 (br. s, 1H, OH), 3.54-3.62 (m, 1H, H_A of CH_2N), 3.76 (t, 0.4H, J_{HH} = 9.7 Hz, H_B of CH_2N, minor rotamer), 3.83 (t, 0.6H, J_{HH} = 9.7 Hz, H_B of CH_2N, major rotamer),4.12-4.21 (m, 2H, CH_2O), 4.25 (s, 0.6H, CH, major rotamer), 4.27 (s, 0.4H, CH, minor rotamer) ppm.

^{13}C NMR (151 MHz, $CDCl_3$): δ = 13.7, 13.9, 28.2, 28.3, 30.8, 31.3, 43.6, 44.0, 61.8, 61.9, 66.8, 67.1, 80.8, 80.9, 84.8 (t, J_{CF} = 27.5 Hz), 85.7 (t, J_{CF} = 27.5 Hz), 128.5 (t, J_{CF} = 298.0 Hz), 153.5, 154.3, 168.7 ppm.

^{19}F NMR (282.5 MHz, $CDCl_3$): δ = –61.95 (d, 0.4H, J_{FF} = 170.0 Hz, F_A of CF_2Cl, minor rotamer), –62.13 (d, 0.6H, J_{FF} = 170.0 Hz, F_A of CF_2Cl, major rotamer), –64.02 (d, 0.4H, J_{FF} = 170.0 Hz, F_b of CF_2Cl, minor rotamer), –64.12 (d, 0.6H, J_{FF} = 170.0 Hz, F_B of CF_2Cl, major rotamer) ppm.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd. for $C_{13}H_{20}ClF_2NNaO_5^+$ (366.0890). Found: 366.0881.

*2.8.2. Synthesis of compounds **trans-16e** and **trans-17e***



Ethyl *anti*-3-[(1,3-dioxolan-2-yl)methyl]-4-bromo-4,4-difluoro-2-formamido-3-hydroxybutanoate (*anti*-26e) The mixture of diastereomers was obtained by the same procedure as compounds ***anti-/syn-14b*** starting from ketoacetal **7e** (1.96 g, 8 mmol) and purified by column chromatography (EtOAc/cHex, 1:1, R_f = 0.31). Yield: 1.59 g (53%). Colorless oil.

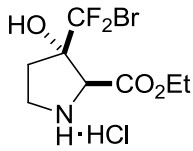
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, 3H, J_{HH} = 7.0 Hz, CH_3), 2.19 (dd, 1H, J_{1HH} = 15.4 Hz, J_{2HH} = 6.5 Hz, H_A of CH_2), 2.42 (dd, 1H, J_{1HH} = 15.4 Hz, J_{2HH} = 6.5 Hz, H_B of CH_2), 3.85-4.08 (m, 4H, $2CH_2O$), 4.27 (q, 2H, J_{HH} = 7.0 Hz CH_2O), 5.08 (br. s, 1H, OH), 5.21-5.30 (m, 2H, CH and CHO_2), 6.8 (d, 1H, J_{HH} = 8.7 Hz, NH), 8.27 (s, 1H, CHO) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 36.1, 53.6, 62.5, 64.8, 65.0, 79.1 (t, J_{CF} = 21.0 Hz), 100.8, 126.4 (t, J_{CF} = 316.0 Hz), 160.9, 168.8 ppm

^{19}F NMR (282.5 MHz, $CDCl_3$): δ = – 56.45 (s, CF_2Br) ppm.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd. for $C_{11}H_{16}BrF_2NNaO_6^+$ (398.0021 and 400.0001). Found: 398.0030 and 400.0010.

***trans*-Ethyl 3-(bromodifluoromethyl)-3-hydroxypyrrolidine-2-carboxylate hydrochloride (*trans*-15e)** was synthesized by the same approach as compound ***trans*-9a** (see section 2.5.1) starting from compound ***anti*-26e** (376 mg, 1.0 mmol) and purified by crystallization from EtOH. Yield: 243 mg (75%). Colorless solid, mp 105-107 °C.



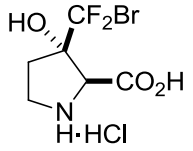
^{1}H NMR (400 MHz, CD_3OD): δ = 1.35 (t, 3H, J_{HH} = 7.2 Hz, CH_3), 2.36 (ddd, 1H, J_{1HH} = 14.0 Hz, J_{2HH} = 8.0 Hz, J_{3HH} = 1.9 Hz H_A of CH_2), 2.52 (dt, 1H, J_{1HH} = 14.0 Hz, J_{2HH} = 10.2 Hz, H_B of CH_2), 3.61-3.69 (m, 1H, H_A of CH_2N), 3.85 (td, J_{1HH} = 10.2 Hz, J_{2HH} = 1.9 Hz, H_B of CH_2N), 4.23-4.36 (m, 2H, CH_2O), 4.38 (s, 1H, CH) ppm.

^{13}C NMR (100 MHz, CD_3OD): δ = 12.6, 30.8, 43.3, 62.9, 65.5, 86.3 (t, J_{CF} = 24.5 Hz), 122.2 (t, J_{CF} = 311.0 Hz), 165.9 ppm.

^{19}F NMR (282.5 MHz, CD_3OD): δ = – 57.41 (d, 1F, J_{FF} = 171.8 Hz, F_A of CF_2Br), – 59.44 (d, 1F, J_{FF} = 171.8 Hz, F_B of CF_2Br) ppm.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_8H_{13}BrF_2NO_3^+$ (288.0041 and 290.0021). Found: 288.0054 and 290.0034.

***trans*-3-(Bromodifluoromethyl)-3-hydroxypyrrolidine-2-carboxylic acid hydrochloride (*trans*-16e)** was synthesized by the same hydrolysis method as compound ***trans*-16d** above starting from compound ***trans*-15e** (162 mg, 0.5 mmol). Yield: 108 mg (73%). Colorless oil.



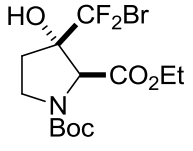
^{1}H NMR (600 MHz, CD_3OD): δ = 2.34 (dd, 1H, *J* = 13.5 Hz, J_{HH} = 7.6 Hz, H_A of CH_2), 2.51 (dt, 1H, J_{HH} = 13.5 Hz, *J* = 10.2 Hz, H_B of CH_2), 3.57-3.65 (m, 1H, H_A of CH_2N), 3.81 (t, 1H, J_{HH} = 10.2 Hz, H_B of CH_2N), 4.31 (s, 1H, CH) ppm.

^{13}C NMR (125 MHz, CD_3OD): δ = 32.6, 44.8, 67.1, 87.9 (t, J_{CF} = 25.5 Hz), 123.9 (t, J_{CF} = 309.0 Hz), 168.4 ppm.

^{19}F NMR (282.5 MHz, CD_3OD): δ = –58.93 (d, 1F, J_{FF} = 172.5 Hz, F_A of CF_2Br), –56.81 (d, 1F, J_{FF} = 172.5 Hz, F_B of CF_2Br) ppm.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_6H_9BrF_2NO_3^+$ (259.9729 and 261.9708). Found: 259.9717 and 261.9701.

***trans*-1-*tert*-Butyl 2-ethyl 3-(bromodifluoromethyl)-3-hydroxypyrrolidine-1,2-dicarboxylate (*trans*-17e)** was synthesized by the same approach as compound ***trans-/cis*-17d** above starting from compound ***trans*-15e** (325 mg, 1.0 mmol) and purified by column chromatography (EtOAc/cHex, 1:2, R_f = 0.45). Yield: 330 mg (85%). Colorless solid, mp 115-117 °C.



NMR-spectra contain overlapping signals of both rotamers in ratio ~2:3.

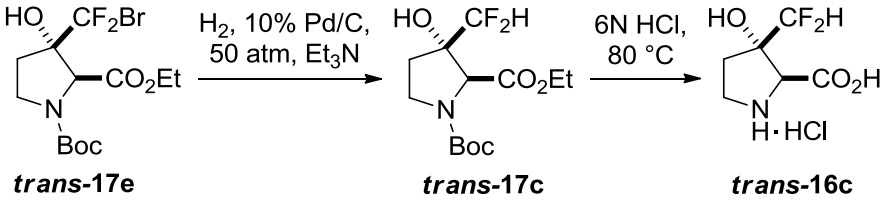
^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.27 (t, 1.2H, J_{HH} = 7.1 Hz, CH_3, minor rotamer), 1.28 (t, 1.8H, J_{HH} = 7.1 Hz, CH_3, major rotamer), 1.40 (s, 3.6H, $3CH_3$, minor rotamer), 1.45 (s, 5.4H, $3CH_3$, major rotamer), 2.01-2.07 (m, 1H, H_A of CH_2), 2.39-2.47 (m, 1H, H_B of CH_2), 3.55-3.65 (m, 1H, H_A of CH_2N), 3.77 (t, 0.4H, J_{HH} = 10.0 Hz, H_B of CH_2N, minor rotamer), 3.82 (br. s, 1H, OH), 3.84 (t, 0.6H, J_{HH} = 10.0 Hz, H_B of CH_2N, major rotamer), 4.13-4.23 (2H, m, CH_2O), 4.28 (s, 0.6H, CH, major rotamer), 4.41 (s, 0.4H, CH, minor rotamer) ppm.

^{13}C NMR (151 MHz, $CDCl_3$): δ = 13.7, 13.9, 28.2, 28.3, 31.0, 31.4, 43.6, 44.0, 61.7, 61.8, 66.5, 66.9, 80.9, 81.1, 85.5 (t, J = 24.5 Hz), 86.4 (t, J_{CF} = 24.5 Hz), 123.0 (t, J_{CF} = 312.0 Hz), 123.2 (t, J_{CF} = 312.0 Hz), 153.8, 154.4, 168.9 ppm.

^{19}F NMR (282.5 MHz, $CDCl_3$): δ = –55.58 (d, 0.4F, J_{FF} = 168.0 Hz, F_A of CF_2Br, minor rotamer), –55.75 (d, 0.6F, J_{FF} = 168.0 Hz, F_A of CF_2Br, major rotamer), –57.76 (d, 0.4F, J_{FF} = 168.0 Hz, F_B of CF_2Br, minor rotamer), –57.88 (d, 0.6F, J_{FF} = 168.0 Hz, F_B of CF_2Br, major rotamer) ppm.

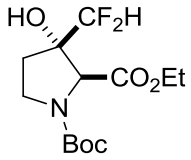
HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd. for $C_{13}H_{20}BrF_2NNaO_5^+$ (410.0386 and 412.0365). Found: 410.0390 and 412.0369.

*2.8.3. Synthesis of compounds **trans-16c** and **trans-17c***



***trans*-17e** ***trans*-17c** ***trans*-16c**

trans-1-_tert_-Butyl 2-ethyl 3-(difluoromethyl)-3-hydroxypyrrolidine-1,2-dicarboxylate (_trans_-17c).



Compound ***trans*-17e** (194 mg, 0.5 mmol) was dissolved in EtOH (20 mL) then Et_3N (0.08 mL, 61 mg, 0.6 mmol) and 10% Pd/C (5 mg) were added and the solution was stirred under hydrogen atmosphere (50 atm) in an autoclave at r.t. for 8 h. The reaction progress was monitored by TLC. After complete hydrogenation, the mixture was filtered and the solution was concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/cHex, 1:2, R_f = 0.33). Yield: 136 mg (88%). Colorless solid, mp 150-152 °C.

NMR-spectra contain overlapping signals of both rotamers in ratio ~2:3.

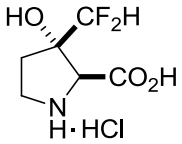
^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.27 (t, 1.2H, J_{HH} = 6.8 Hz, CH_3, minor rotamer), 1.29 (t, 1.8H, J_{HH} = 6.8 Hz, CH_3, major rotamer), 1.41 (s, 5.4H, $3CH_3$, major rotamer), 1.46 (s, 3.6H, $3CH_3$, minor rotamer), 1.87-1.93 (m, 1H, H_A of CH_2), 2.25-2.33 (m, 1H, H_B of CH_2), 2.66 (br. s, 1H, OH), 3.55-3.63 (m, 1H, H_A of CH_2N), 3.74 (t, 0.4H, J_{HH} = 9.5 Hz, H_B of CH_2N), 3.81 (t, 0.6H, J_{HH} = 9.5 Hz, H_B of CH_2N), 4.14-4.23 (m, 2H, CH_2O), 4.22 (s, 0.6H, CH, major rotamer), 4.31 (s, 0.4H, CH, minor rotamer), 5.79 (t, 0.6H, J_{HF} = 55.5 Hz, major rotamer), 5.81 (t, 0.4H, J_{HF} = 55.5 Hz, minor rotamer) ppm.

^{13}C NMR (151 MHz, $CDCl_3$): δ = 13.9, 14.0, 28.2, 28.3, 30.1, 30.7, 43.7, 44.0, 61.6, 61.7, 66.9, 67.2, 80.5, 80.6, 80.9 (t, J_{CF} = 22.5 Hz), 82.0 (t, J_{CF} = 22.5 Hz), 113.7 (t, J_{CF} = 245.0 Hz), 113.8 (t, J_{CF} = 245.0 Hz), 153.5, 154.5, 169.1, 169.2 ppm.

^{19}F NMR (282.5 MHz, $CDCl_3$): δ = – 129.05 (dd, 1F, J_{FF} = 290.0 Hz, J_{HF} = 55.5 Hz, F_A of CHF_2), – 130.71 (dd, 0.4F, J_{FF} = 290.0 Hz, J_{HF} = 55.5 Hz, F_B of CHF_2, minor rotamer), – 130.96 (dd, 0.6F, J_{FF} = 290.0 Hz, J_{HF} = 55.5 Hz, F_B of CHF_2, major rotamer) ppm.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd. for $C_{13}H_{21}F_2NNaO_5^+$ (332.1280). Found: 332.1283.

trans*-3-(Difluoromethyl)-3-hydroxypyrrolidine-2-carboxylic acid hydrochloride (*trans*-16c).** Compound ***trans*-17c** (93 mg, 0.3 mmol) was dissolved in dioxane (5 mL). 6N HCl (5 mL) was added and the resulting mixture was stirred for 10 h at 80 °C. Then the cooled mixture was washed by EtOAc (2 × 30 mL) and the water layer was concentrated under reduced pressure and the residue was dried in vacuum of oil pump (10^{-3} mm Hg) for 5 h giving pure compound (trans*-16c**). Yield: 55 mg (84%). Colorless oil.



^{1}H NMR (600 MHz, CD_3OD): δ = 2.16 (dd, 1H, J_{1HH} = 13.5 Hz, J_{2HH} = 6.2 Hz, H_A of CH_2), 2.33 (dt, 1H, J_{1HH} = 13.5 Hz, J_{2HH} = 9.3 Hz, H_B of CH_2), 3.54 (m, 1H, H_A of CH_2N), 3.65 (t, 1H, J_{1HH} = 9.3 Hz, H_B of CH_2N), 4.33 (s, 1H, CH), 6.11 (t, 1H, J_{HF} = 54.5 Hz, CHF_2) ppm.

^{13}C NMR (151 MHz, CD_3OD): δ = 31.8, 45.0, 68.2, 82.3 (t, J_{CF} = 24.0 Hz), 115.5 (t, J_{CF} = 241.5 Hz), 168.2 ppm.

^{19}F NMR (282.5 MHz, CD_3OD): δ = –129.05 (dd, 1F, J_{FF} = 290 Hz, J_{FH} = 54.5 Hz, F_A of CHF_2), –132.61 (dd, 1F, J_{FF} = 290 Hz, J_{FH} = 54.5 Hz, F_B of CHF_2) ppm.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd. for $C_6H_{10}F_2NO_3^+$ (182.0623). Found: 182.0634.

3. X-ray crystallography data

3.1. General

For compound ***trans*-17d** data sets were collected with a Nonius Kappa CCD diffractometer. Programs used: data collection, COLLECT;[3] data reduction Denzo-SMN;[4] absorption correction, Denzo;[5] structure solution SHELXS-97;[6] structure refinement SHELXL-97.[6] Data sets for compounds **(*2S,3S*)-12a**, **(*2R,3S*)-12a** and ***trans*-15d** were collected with a D8 Venture CMOS diffractometer. For compounds ***trans*-1b** and ***trans*-6a** data sets were collected with a Bruker APEX II CCD diffractometer. Programs used: data collection: APEX3 V2016.1-0;[7] cell refinement: SAINT V8.37A;[7] data reduction: SAINT V8.37A;[7] absorption correction, SADABS V2014/7;[7] structure solution SHELXT-2015;[8] structure refinement SHELXL-2015.[8] *R*-values are given for observed reflections, and wR^2 values are given for all reflections.
Exceptions and special features: For compound **(*2S,3S*)-12a** one O-*t*Bu group and for compound ***trans*-15d** two ethoxy and one CF_2Cl were found disordered over two positions in the asymmetric unit. Several restraints (SADI, SAME, ISOR and SIMU) were used in order to improve refinement stability.

3.2 X-ray crystal structure analysis of *trans*-1b

A colorless plate-like specimen of $C_7H_9ClF_5NO_2 \cdot H_2O$, approximate dimensions 0.040 mm x 0.150 mm x 0.150 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 1276 frames were collected. The total exposure time was 19.87 hours. The frames were integrated with the Bruker SAINT software package using a wide-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 14163 reflections to a maximum θ angle of 66.80° (0.84 Å resolution), of which 1940 were independent (average redundancy 7.301, completeness = 99.1%, R_{int} = 5.07%, R_{sig} = 2.85%) and 1700 (87.63%) were greater than $2\sigma(F^2)$. The final cell constants of a = 11.5790(5) Å, b = 10.2974(4) Å, c = 9.8109(4) Å, β = 109.426(2)°, volume = 1103.19(8) $Å^3$, are based upon the refinement of the XYZ-centroids of 5379 reflections above 20 σ(I) with 8.096° < 2θ < 133.6°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.782. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.6000 and 0.8630. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group $P2_1/c$, with Z = 4 for the formula unit, $C_7H_9ClF_5NO_2 \cdot H_2O$. The final anisotropic full-matrix least-squares refinement on F^2 with 174 variables converged at R1 = 3.05%, for the observed data and wR2 = 7.35% for all data. The goodness-of-fit was 1.083. The largest peak in the final difference electron density synthesis was 0.281 $e^-/Å^3$ and the largest hole was -0.237 $e^-/Å^3$ with an RMS deviation of 0.053 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.732 g/cm^3 and F(000), 584 e^-.

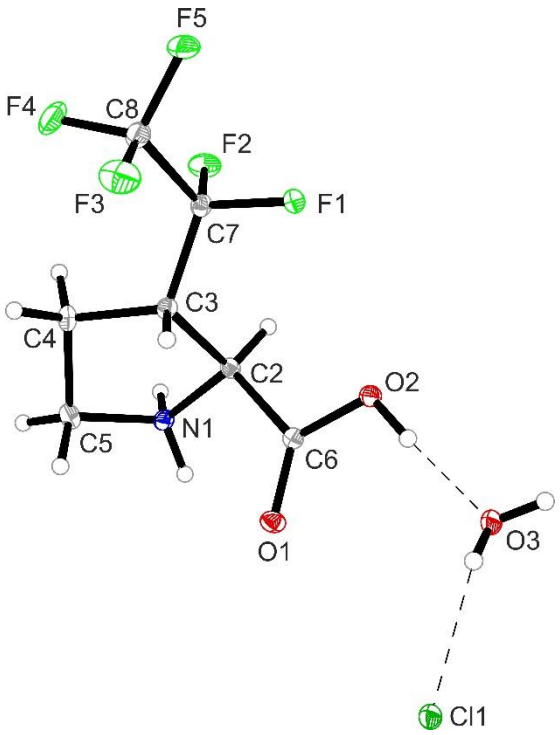


Figure S1. Crystal structure of compound ***trans*-1b**.
Thermal ellipsoids are shown at 30 % probability.

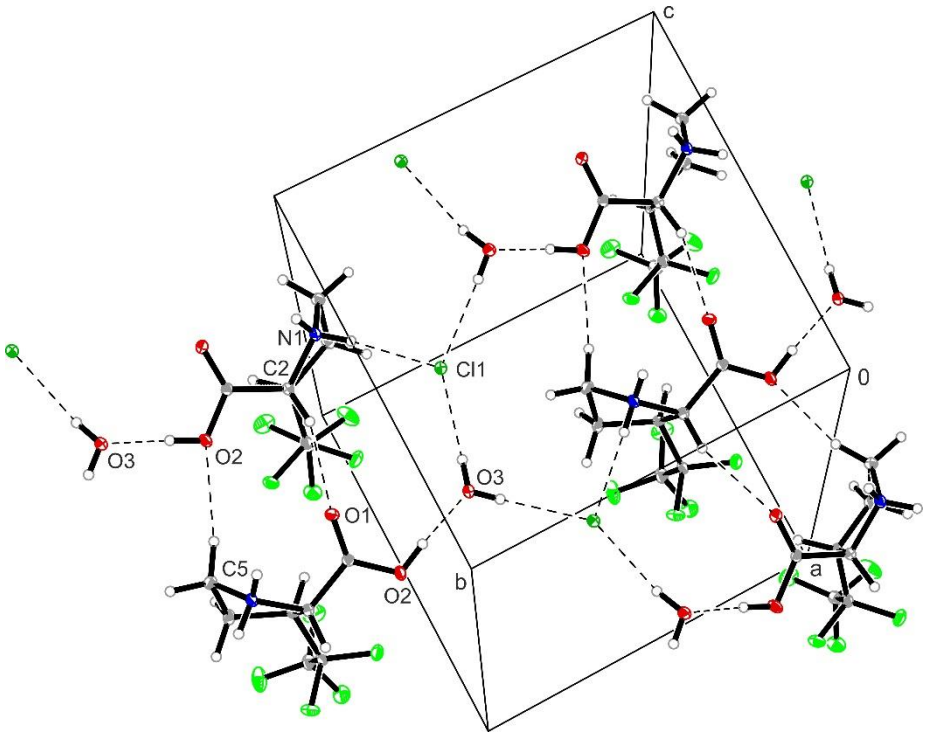


Figure S2. Excerpt of the packing diagram of ***trans*-1b** presenting the formations of various types of hydrogen bonds interactions (OH···O, OH···Cl, NH···Cl, CH···O hydrogen bonds).

Table S2. Hydrogen bond interactions in compound ***trans*-1b** (Å and deg)[a]

D-H···*A*	*d*(*D*-H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*DHA*)
C2-H2···O1[#1]	1.00	2.44	3.404(2)	161.4
C3-H3···F2[#2]	1.00	2.50	3.344(2)	141.5
C5-H5A···O2[#2]	0.99	2.42	3.350(2)	155.6
C5-H5B···Cl1[#3]	0.99	2.97	3.902(2)	156.9
N1-H1A···Cl1[#1]	0.89(3)	2.24(3)	3.087(2)	157(2)
N1-H1B···O3[#4]	0.87(3)	2.08(3)	2.926(2)	163(2)
O2-H2A···O3	0.87(3)	1.68(3)	2.550(2)	174(3)
O3-H3A···Cl1[#5]	0.77(3)	2.32(3)	3.089(2)	176(3)
O3-H3B···Cl1	0.85(3)	2.24(3)	3.045(2)	157(3)

Symmetry transformations used to generate equivalent atoms: [#1] x, 1.5-y, -0.5+z; [#2] x, 1.5-y, 0.5+z; [#3] x, 1+y, z; [#4] -x, 0.5+y, 0.5-z; [#5] x, 0.5-y, -0.5+z.

3.3. X-ray crystal structure analysis of *trans*-6a

A colorless plate-like specimen of $C_6H_6F_3NO_3$, approximate dimensions 0.020 mm x 0.200 mm x 0.200 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 1831 frames were collected. The total exposure time was 39.82 hours. The frames were integrated with the Bruker SAINT software package using a wide-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 18311 reflections to a maximum θ angle of 66.71° (0.84 Å resolution), of which 2632 were independent (average redundancy 6.957, completeness = 98.3%, R_{int} = 10.00%, R_{sig} = 7.38%) and 1810 (68.77%) were greater than $2\sigma(F^2)$. The final cell constants of a = 11.4217(13) Å, b = 20.9410(19) Å, c = 6.3348(6) Å, β = 94.730(7)°, volume = 1510.0(3) Å^3, are based upon the refinement of the XYZ-centroids of 3472 reflections above 20 σ(I) with 8.444° < 2θ < 130.9°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.705. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.7330 and 0.9680. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group $P2_1/c$, with Z = 8 for the formula unit, $C_6H_6F_3NO_3$. The final anisotropic full-matrix least-squares refinement on F^2 with 246 variables converged at R1 = 5.32%, for the observed data and wR2 = 13.64% for all data. The goodness-of-fit was 1.034. The largest peak in the final difference electron density synthesis was 0.328 e^-/Å^3 and the largest hole was -0.278 e^-/Å^3 with an RMS deviation of 0.062 e^-/Å^3. On the basis of the final model, the calculated density was 1.734 g/cm^3 and F(000), 800 e^-.

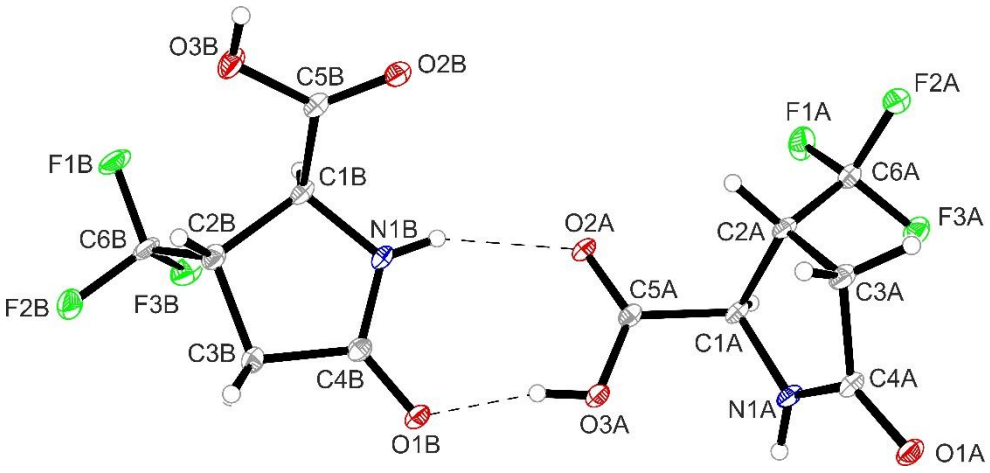


Figure S3. Asymmetric unit of compound ***trans*-6a** presenting the formation of pair unit trough N-H···O and O-H···O hydrogen bonds involving the carboxylic group of molecule "A" and the proline derivative ring of molecule "B".
Thermal ellipsoids are shown at 15 % probability.

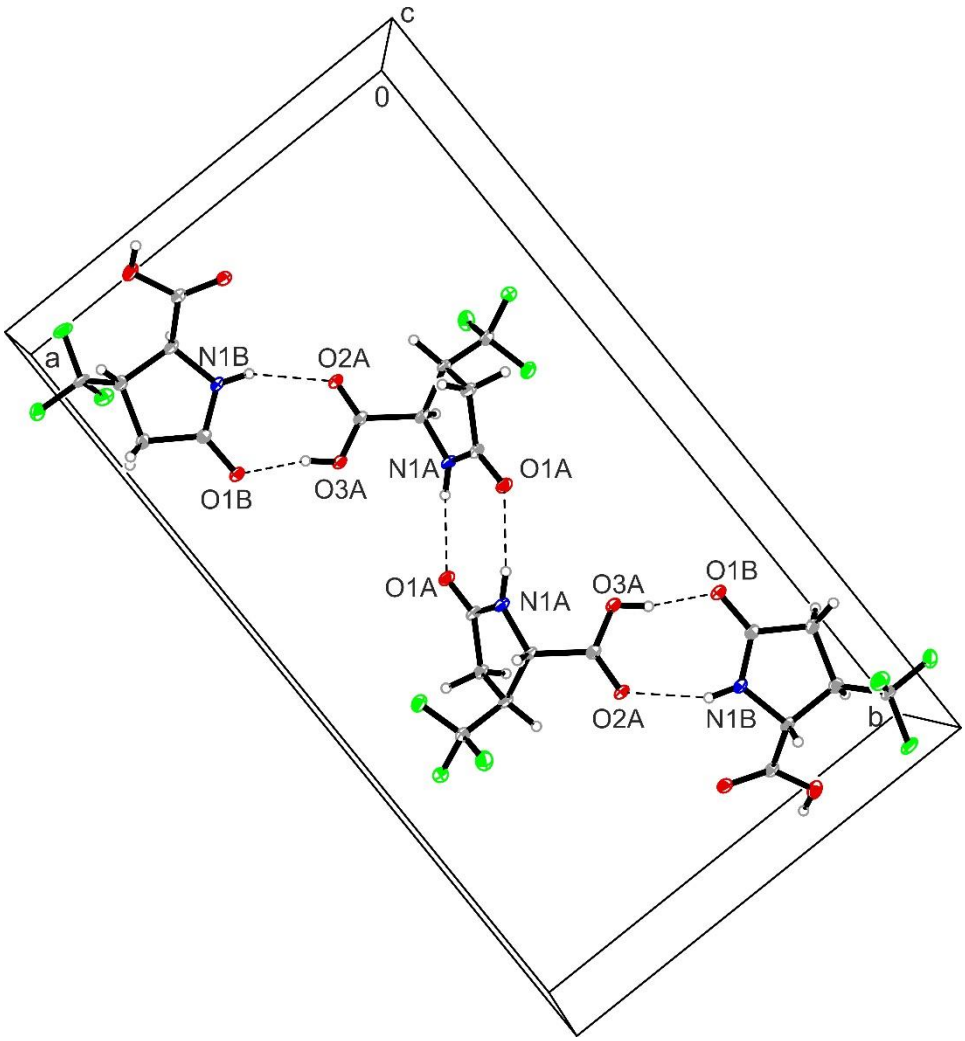


Figure S4. Dimer structure formation between the pair units of compound ***trans*-6a** involving N-H···O hydrogen bonds of two proline derivative rings from the molecules "A".

Table S3. Hydrogen bond interactions in compound ***trans*-6a** (Å and deg)[a]

D-H···*A*	*d*(*D*-H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*DHA*)
N1A-H1···O1A$^{\#1}$	0.86(4)	2.06(4)	2.897(4)	162(4)
O3A-H3A···O1B	0.84	1.71	2.538(3)	166.8
N1B-H2···O2A	0.84(4)	2.17(4)	2.961(4)	157(3)
C3A-H301···F2B$^{\#2}$	0.99	2.53	3.496(4)	164.5
O3B-H3B···O1A$^{\#3}$	0.84	1.76	2.597(3)	170.2

Symmetry transformations used to generate equivalent atoms: $^{\#1}$ 1-x, 2-y, 1-z; $^{\#2}$ -1+x, 1.5-y, 0.5+z; $^{\#3}$ 1-x, -0.5+y, 1.5-z.

3.4. X-ray crystal structure analysis of (*2S,3S*)-12a

A colorless plate-like specimen of $C_{19}H_{25}F_3N_2O_3$, approximate dimensions 0.038 mm x 0.203 mm x 0.214 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. The integration of the data using a monoclinic unit cell yielded a total of 37191 reflections to a maximum θ angle of 65.05° (0.85 Å resolution), of which 12106 were independent (average redundancy 3.072, completeness = 95.1%, R_{int} = 5.42%, R_{sig} = 6.38%) and 10067 (83.16%) were greater than 2σ(F^2). The final cell constants of a = 9.4312(2) Å, b = 44.5944(10) Å, c = 9.6364(2) Å, β = 93.151(2)°, volume = 4046.74(15) Å^3, are based upon the refinement of the XYZ-centroids of reflections above 20 σ(I). The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.8330 and 0.9670. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group $P2_1$, with Z = 8 for the formula unit, $C_{19}H_{25}F_3N_2O_3$. The final anisotropic full-matrix least-squares refinement on F^2 with 1054 variables converged at R1 = 5.65%, for the observed data and wR2 = 10.38% for all data. The goodness-of-fit was 1.079. The largest peak in the final difference electron density synthesis was 0.222 e^-/Å^3 and the largest hole was -0.234 e^-/Å^3 with an RMS deviation of 0.047 e^-/Å^3. On the basis of the final model, the calculated density was 1.268 g/cm^3 and F(000), 1632 e^-. Flack parameter was refined to 0.09(8).

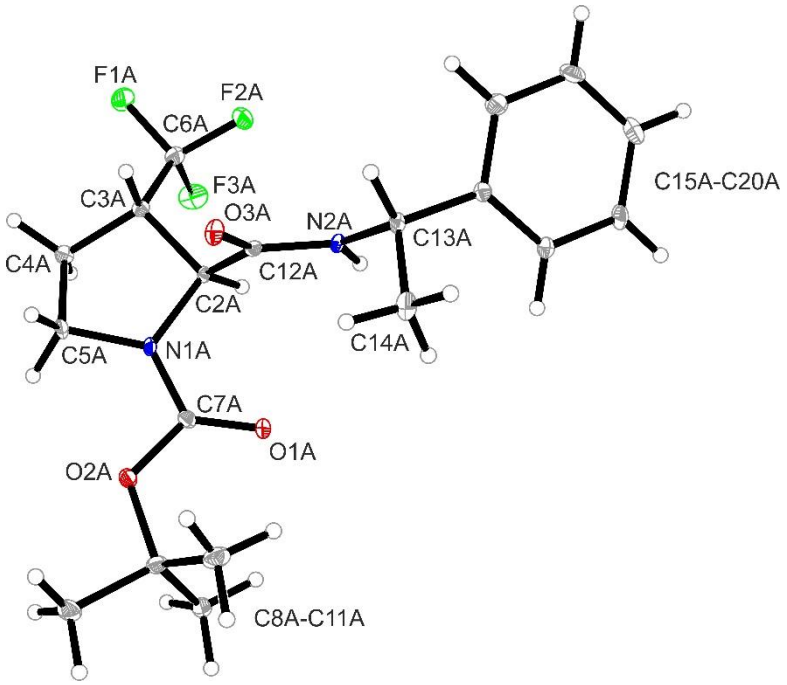


Figure S5. Crystal structure of compound **(*2S,3S*)-12a**. Only one molecule (molecule "A") of four found in the asymmetric unit is shown. Thermal ellipsoids are shown at 15 % probability.

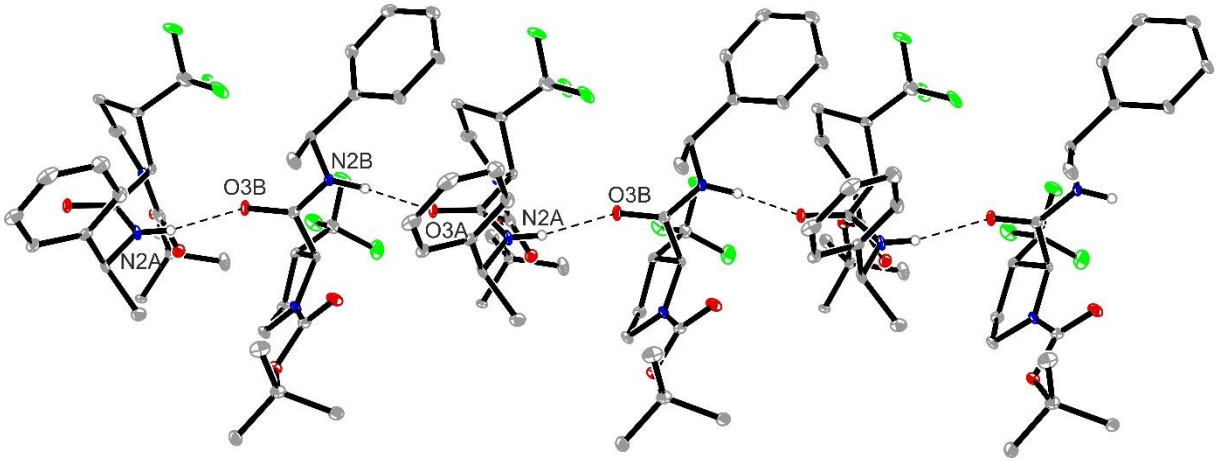


Figure S6. Linear chains containing alternate molecules "A" and "B" involving N-H···O hydrogen bonds in compound **(*2S,3S*)-12a**.

Table S4. Hydrogen bond interactions in compound **(2S,3S)-12a** (Å and deg)[a]

D-H···*A*	*d*(*D*-H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*DHA*)
N2A-H1···O3B$^{\#1}$	0.93(7)	1.94(7)	2.845(6)	163(5)
N2B-H2···O3A	0.86(6)	1.99(6)	2.832(6)	167(6)
N2C-H3···O3D	0.93(5)	1.93(6)	2.859(6)	174(5)
N2D-H4···O3C$^{\#2}$	1.00(5)	1.80(5)	2.792(5)	171(4)

Symmetry transformations used to generate equivalent atoms: $^{\#1}$ -1+x, y, z; $^{\#2}$ x, y, 1+z.

3.5. X-ray crystal structure analysis of (*2R,3S*)-12a

A colorless needle-like specimen of $C_{19}H_{25}F_3N_2O_3$, approximate dimensions 0.048 mm x 0.091 mm x 0.175 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 1233 frames were collected. The total exposure time was 24.12 hours. The frames were integrated with the Bruker SAINT software package using a wide-frame algorithm. The integration of the data using an orthorhombic unit cell yielded a total of 22784 reflections to a maximum θ angle of 68.26° (0.83 Å resolution), of which 3580 were independent (average redundancy 6.364, completeness = 99.4%, R_{int} = 6.71%, R_{sig} = 3.87%) and 3292 (91.96%) were greater than $2\sigma(F^2)$. The final cell constants of a = 8.9485(2) Å, b = 11.2537(3) Å, c = 19.5558(4) Å, volume = 1969.34(8) Å^3, are based upon the refinement of the XYZ-centroids of 9983 reflections above 20 σ(I) with 9.044° < 2θ < 136.2°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.884. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.8570 and 0.9580. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group $P2_12_12_1$, with Z = 4 for the formula unit, $C_{19}H_{25}F_3N_2O_3$. The final anisotropic full-matrix least-squares refinement on F^2 with 252 variables converged at R1 = 3.59%, for the observed data and wR2 = 7.49% for all data. The goodness-of-fit was 1.120. The largest peak in the final difference electron density synthesis was 0.152 e$^-$/Å^3 and the largest

hole was -0.206 $e^-/Å^3$ with an RMS deviation of 0.043 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.303 g/cm^3 and F(000), 816 e^-. Flack parameter was refined to 0.1(1).

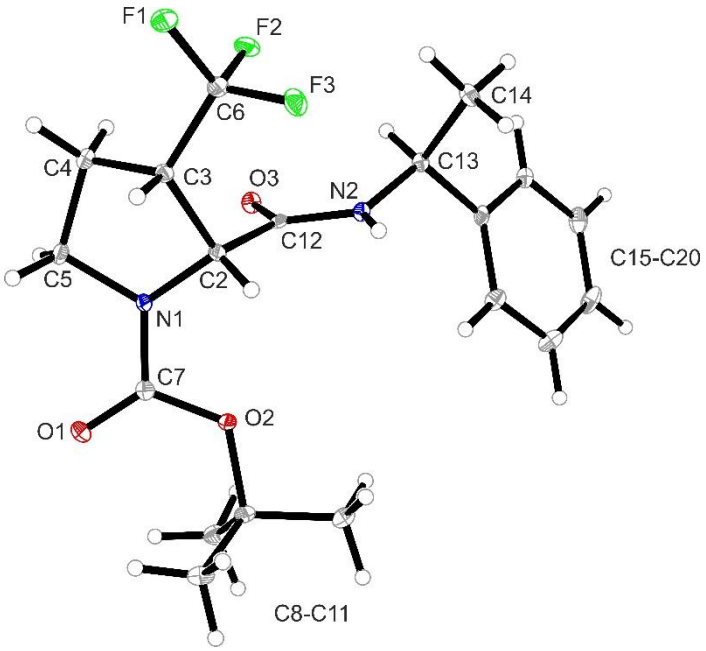


Figure S7. Crystal structure of compound **(2R,3S)-23a**.
Thermal ellipsoids are shown at 30 % probability.

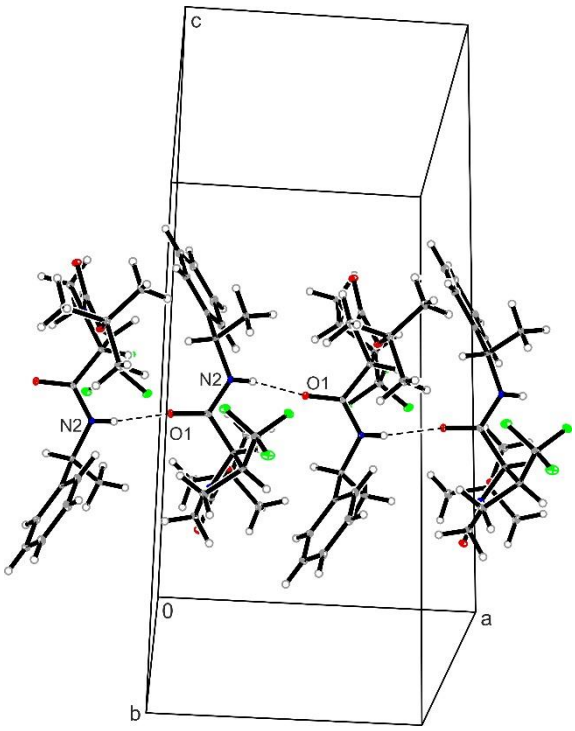


Figure S8. Linear chains along "a"-axis involving N-H···O hydrogen bonds in compound **(*2R,3S*)-12a**.

Table S5. Hydrogen bond interactions in compound **(*2R,3S*)-12a** (Å and deg)[a]

D-H···*A*	*d*(*D*-H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*DHA*)
N2-H1A···O1[#1]	0.75(3)	2.17(3)	2.890(3)	161(3)

Symmetry transformations used to generate equivalent atoms: [#1] 0.5+x, 1.5-y, 1-z.

3.6. X-ray crystal structure analysis of *trans*-15d

A colorless plate-like specimen of $C_8H_{13}Cl_2F_2NO_3 \cdot 1.25$ x H_2O, approximate dimensions 0.120 mm x 0.261 mm x 0.320 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 2709 frames were collected. The total exposure time was 45.15 hours. The frames were integrated with the Bruker SAINT software package using a wide-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 33870 reflections to a maximum θ angle of 68.37° (0.83 Å resolution), of which 4837 were independent (average redundancy 7.002, completeness = 98.9%, R_{int} = 5.16%, R_{sig} = 3.51%) and 4616 (95.43%) were greater than $2\sigma(F^2)$. The final cell constants of a = 32.3706(15) Å, b = 5.5808(3) Å, c = 32.0773(15) Å, β = 113.0500(10)°, volume = 5332.2(5) $Å^3$, are based upon the refinement of the XYZ-centroids of 9849 reflections above 20 σ(I) with 6.577° < 2θ < 136.6°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.601. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.3150 and 0.6020. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group *C*2/c, with Z = 16 for the formula unit, $C_8H_{13}Cl_2F_2NO_3 \cdot 1.25$ x H_2O. The final anisotropic full-matrix least-squares refinement on F^2 with 414 variables converged at R1 = 5.50%, for the observed data and wR2 = 13.86% for all data. The goodness-of-fit was 1.080. The largest peak in the final difference electron density synthesis was 0.737 $e^-/Å^3$ and the largest hole was -0.746 $e^-/Å^3$ with an RMS deviation of 0.073 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.508 g/cm^3 and F(000), 2504 e^-.

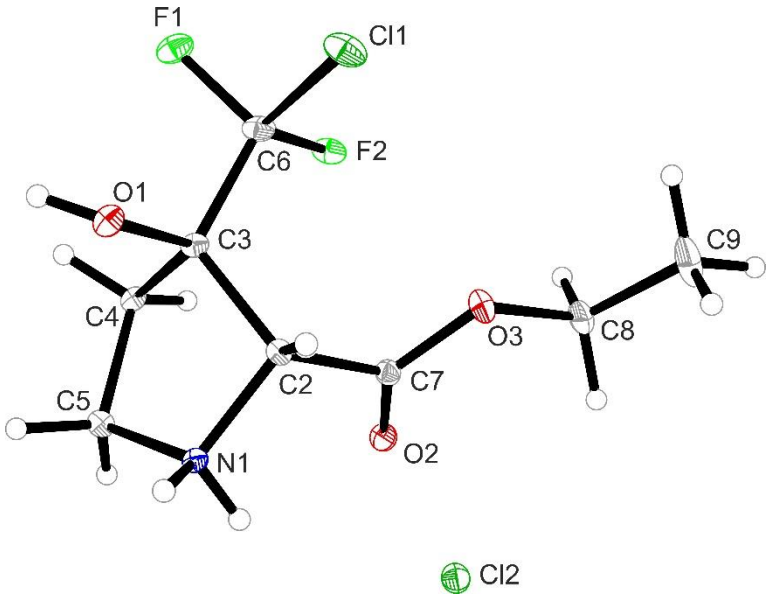


Figure S9. Crystal structure of compound ***trans*-15d**.
Thermal ellipsoids are shown at 15 % probability.

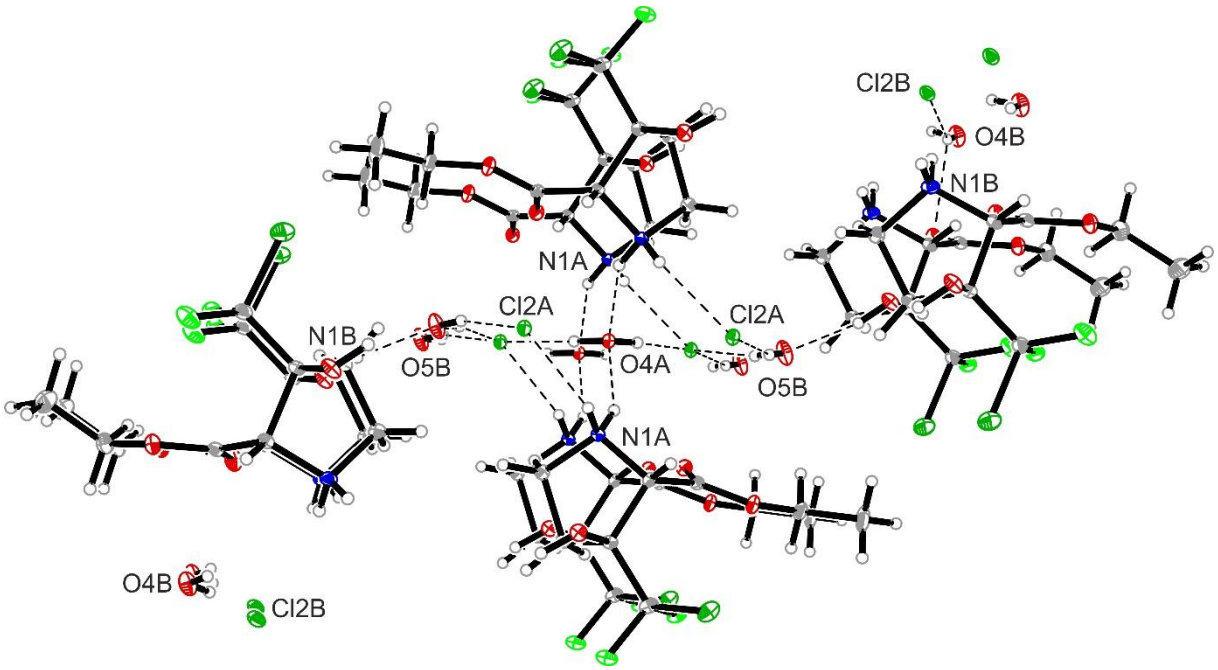


Figure S10. Excerpt of the packing diagram of ***trans*-15d** presenting the formations of various types of hydrogen bonds interactions (O-H···O, O-H···Cl, N-H···Cl, N-H···O hydrogen bonds).

Table S6. Hydrogen bond interactions in compound ***trans*-15d** (Å and deg)[a]

D-H···*A*	*d*(*D*-H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*DHA*)
N1A-H1A···O4A	0.86(2)	2.03(2)	2.824(3)	153(3)
N1A-H1B···Cl2A$^{\#1}$	0.86(2)	2.29(2)	3.087(3)	154(4)
O1A-H1···O4B$^{\#2}$	0.86(2)	1.78(2)	2.635(4)	172(4)
O4A-H4A···Cl2A$^{\#3}$	0.86(2)	2.28(2)	3.125(2)	166(3)
N1B-H1C···Cl2B$^{\#5}$	0.87(2)	2.24(2)	3.109(3)	173(4)
N1B-H1D···Cl2B	0.87(2)	2.48(4)	3.152(3)	134(4)
O1B-H2···O5B$^{\#4}$	0.85(2)	1.82(2)	2.650(3)	165(4)
O4B-H4C···Cl2B	0.85(2)	2.50(3)	3.265(3)	150(4)
O4B-H4C···O2B	0.85(2)	2.55(4)	3.081(4)	122(4)
O4B-H4D···Cl2B$^{\#3}$	0.86(2)	2.25(2)	3.109(3)	174(5)
O5B-H5A···Cl2A	0.86(2)	2.36(2)	3.210(3)	168(4)
O5B-H5B···Cl2A$^{\#3}$	0.86(2)	2.40(2)	3.240(3)	166(4)

Symmetry transformations used to generate equivalent atoms: $^{\#1}$ 2-x, y, 0.5-z; $^{\#2}$ 0.5+x, -0.5-y, -z; $^{\#3}$ x, 1+y, z; $^{\#4}$ 1.5-x, -0.5+y, 0.5-z; $^{\#5}$ x, -1+y, z.

3.7. X-ray crystal structure analysis of *trans*-17d.

Formula $C_{13}H_{20}ClF_2NO_5$, M = 343.75, colourless crystal, 0.23 x 0.18 x 0.04 mm, a = 19.3791(4), b = 9.2260(2), c = 19.4047(4) Å, β = 105.322(1)°, V = 3346.1(1) Å^3, ρ_{calc} = 1.365 gcm^{-3}, μ = 0.269 mm^{-1}, empirical absorption correction (0.940 ≤ T ≤ 0.989), Z = 8, monoclinic, space group $P2_1/n$ (No. 14), λ = 0.71073 Å, T = 173(2) K, ω and ϕ scans, 21562 reflections collected (±h, ±k, ±l), 5760 independent (R_{int} = 0.050) and 4993 observed reflections [I>2σ(I)], 408 refined parameters, R = 0.086, wR^2 = 0.271, max. (min.) residual electron density 0.53 (-0.61) e.Å^{-3}, the hydrogen atoms were calculated and refined as riding atoms.

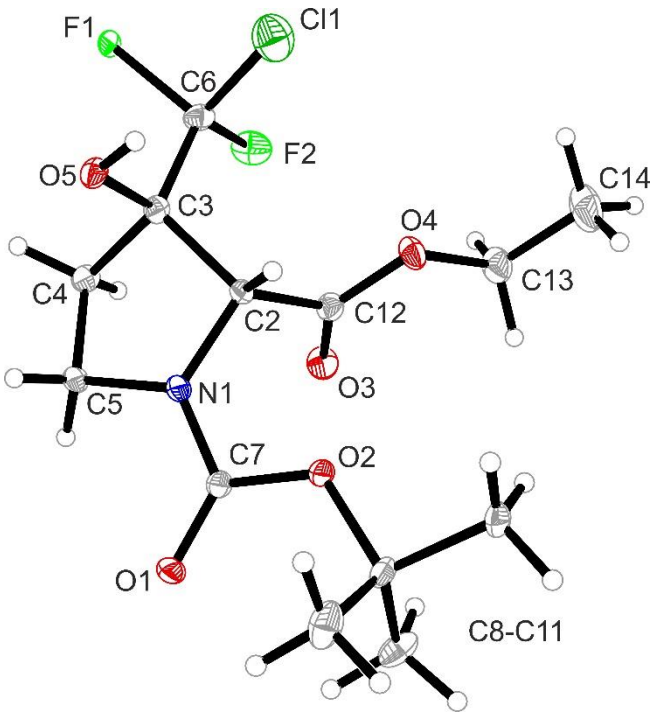


Figure S11. Crystal structure of compound ***trans*-17d**.
Only one molecule of two found in the asymmetric unit is shown.
Thermal ellipsoids are shown at 15 % probability.

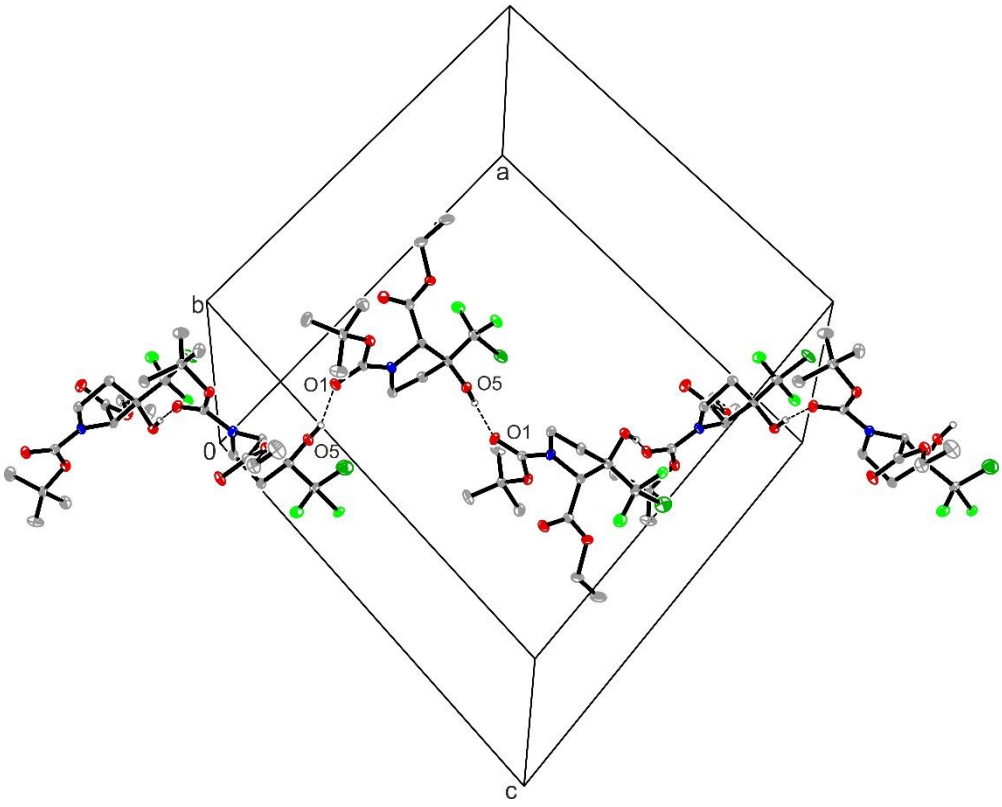


Figure S12. Wave chains perpendicular to ac-diagonal involving O-H···O hydrogen bonds in compound ***trans*-17d**.

Table S7. Hydrogen bond interactions in compound ***trans*-17d** (Å and deg)[a]

D-H···*A*	*d*(*D*-H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*H*A*)
O5A-H5C···O1	0.84	1.85	2.691(6)	173.4
O5-H5···O1A[#1]	0.89	1.89	2.705(6)	162.1

Symmetry transformations used to generate equivalent atoms: [#1] 0.5+x, 1.5-y, 0.5+z.

4. References

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[3] R. W. W. Hooft, *COLLECT, Program for Collecting Data on CCD Area Detectors* Bruker AXS, 2008, Delft, The Netherlands.

[4] Z. Otwinowski, W. Minor, *Methods Enzymol*., 1997, **276**, 307.

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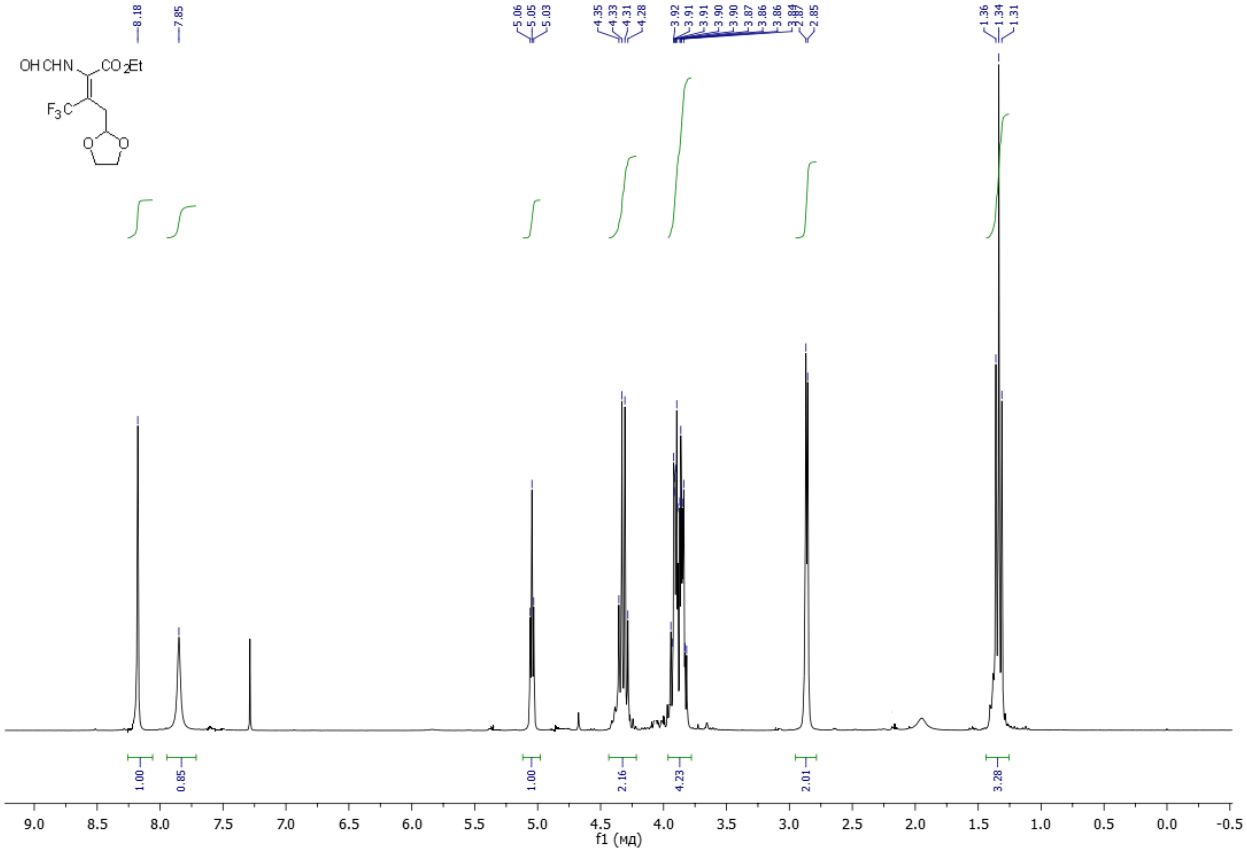
[6] *SHELX* software (2008). G. M. Sheldrick, G. M. *Acta Cryst.* 2008, A**64**, 112.

[7] *XP – Interactive molecular graphics, Version 5.1,* Bruker AXS Inc., Madison, Wisconsin, USA, 1998; *APEX3* (2016), *SAINT* (2015) and *SADABS* (2014), Bruker AXS Inc., Madison, Wisconsin, USA.

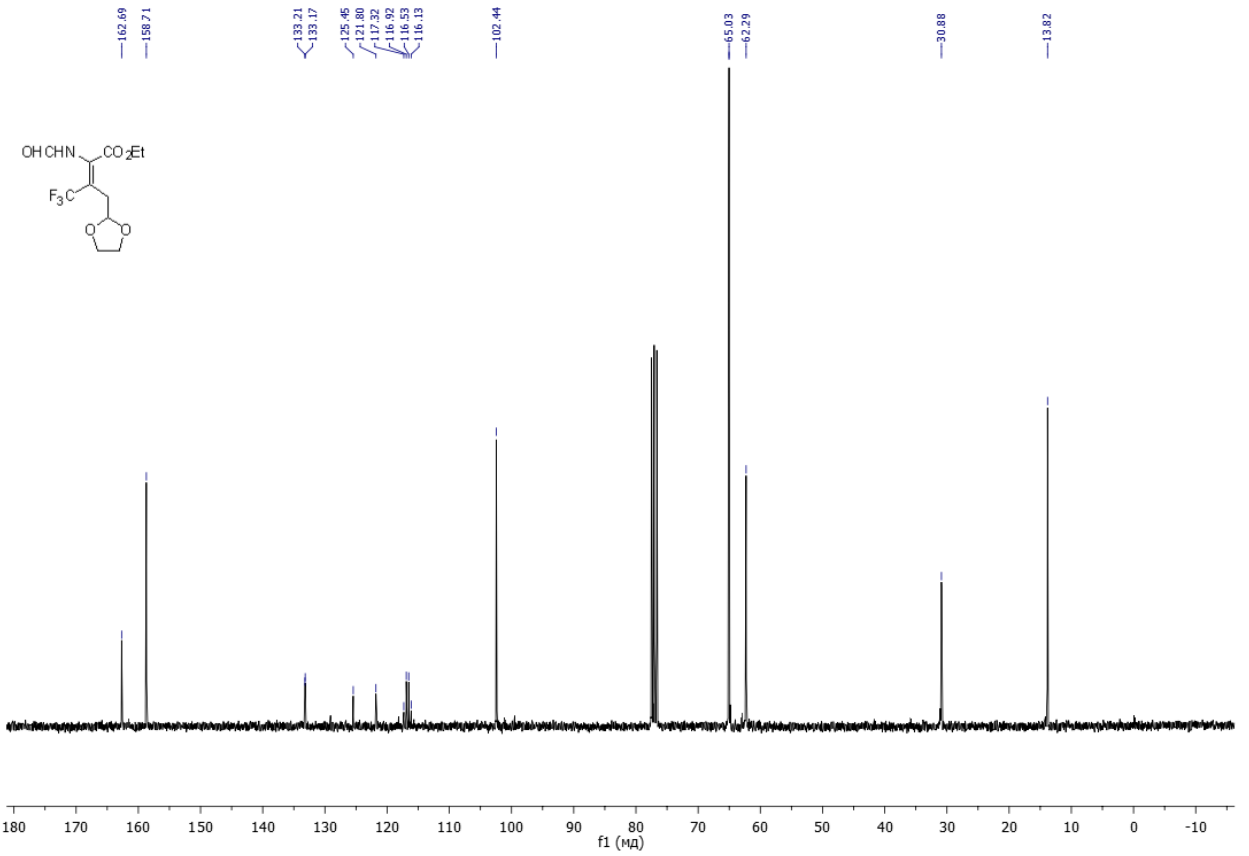
[8] *SHELX* software: G. M. Sheldrick, *Acta Cryst.,* 2015, **A71**, 3.

5. Copies of ^{1}H, ^{13}C and ^{19}F NMR-spectra

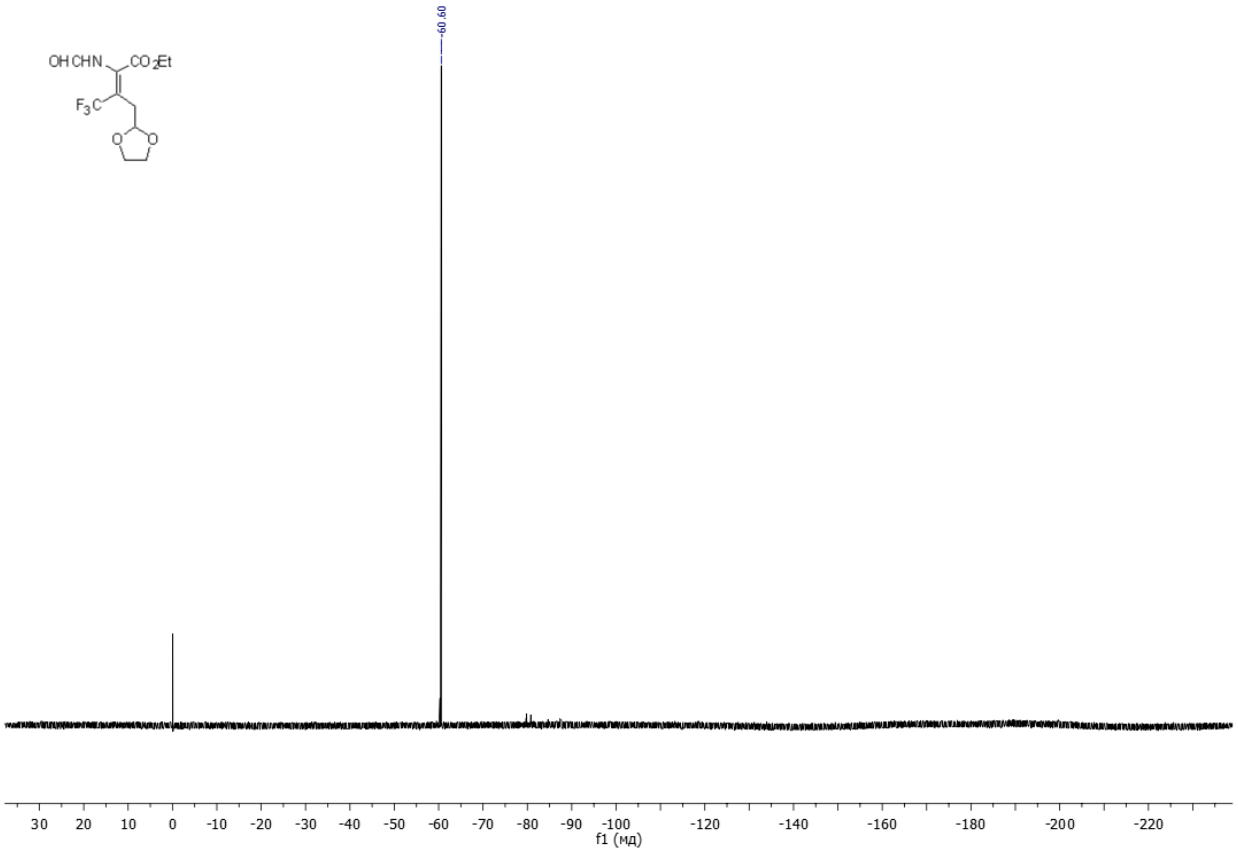
^{1}H NMR, compound **3a**



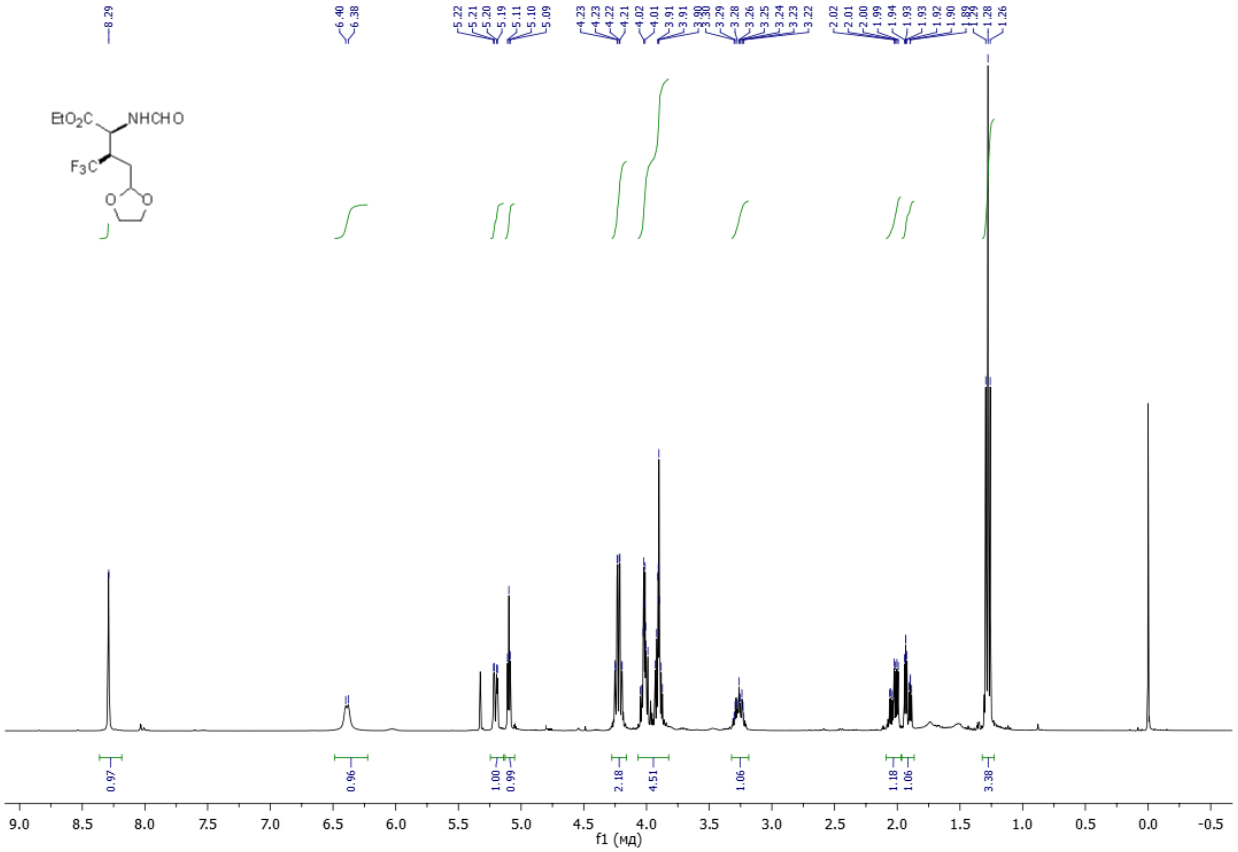
^{13}C NMR, compound **3a**



^{19}F NMR, compound **3a**



^{1}H NMR, compound ***syn*-4a**



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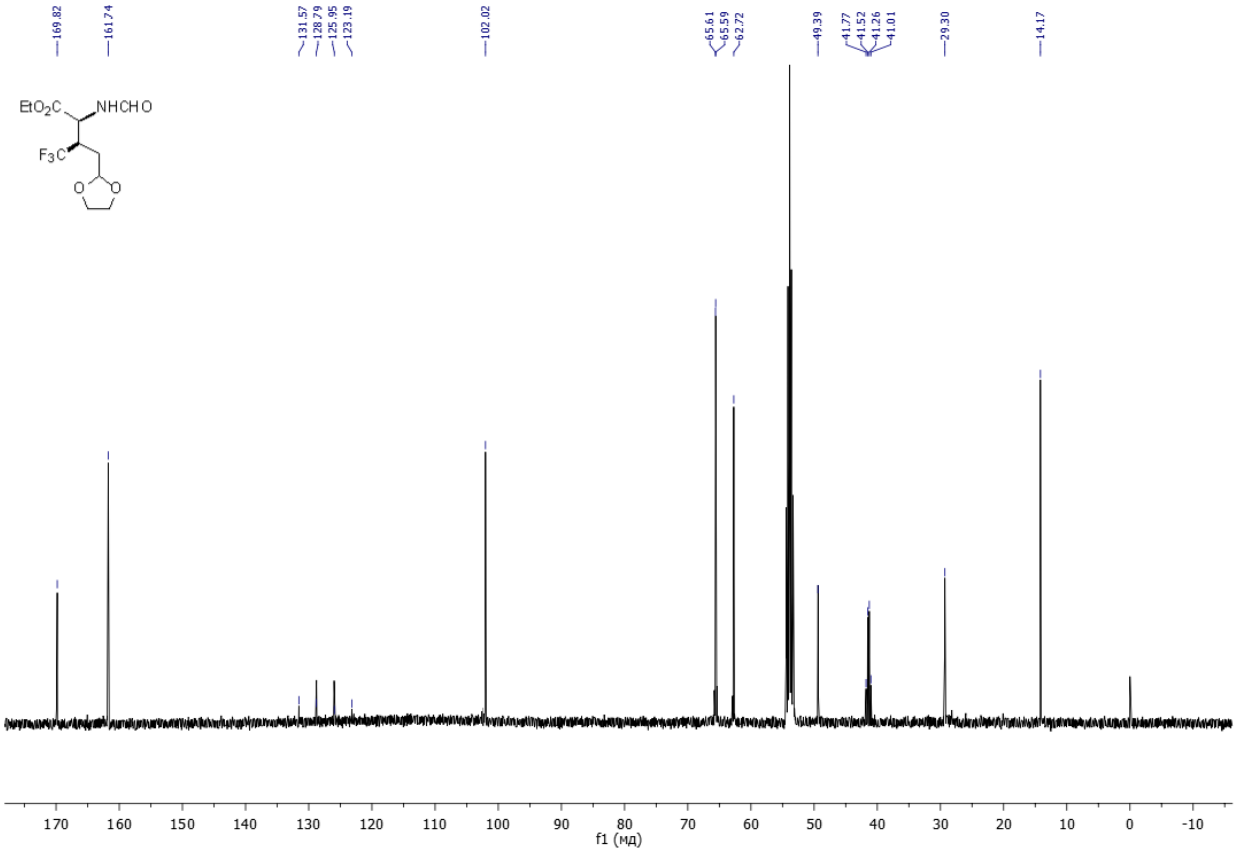
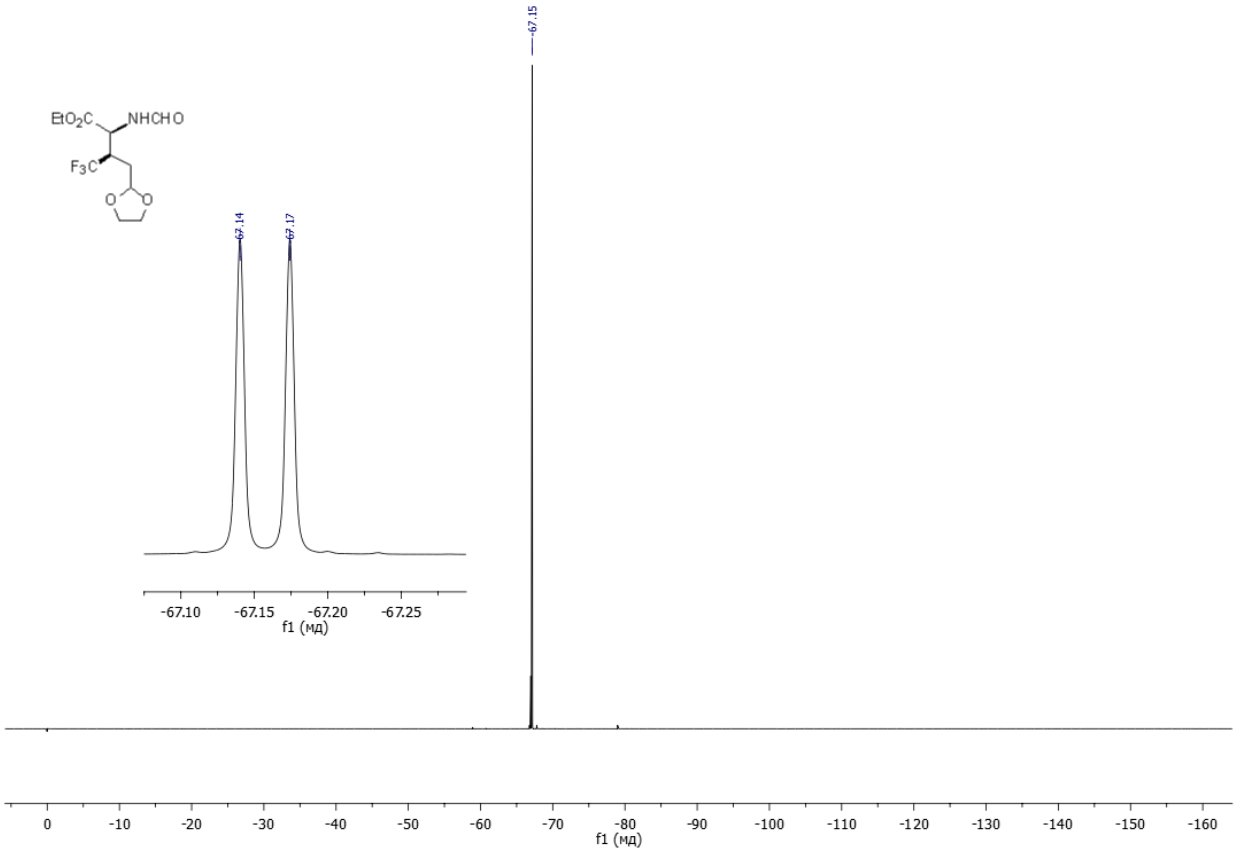
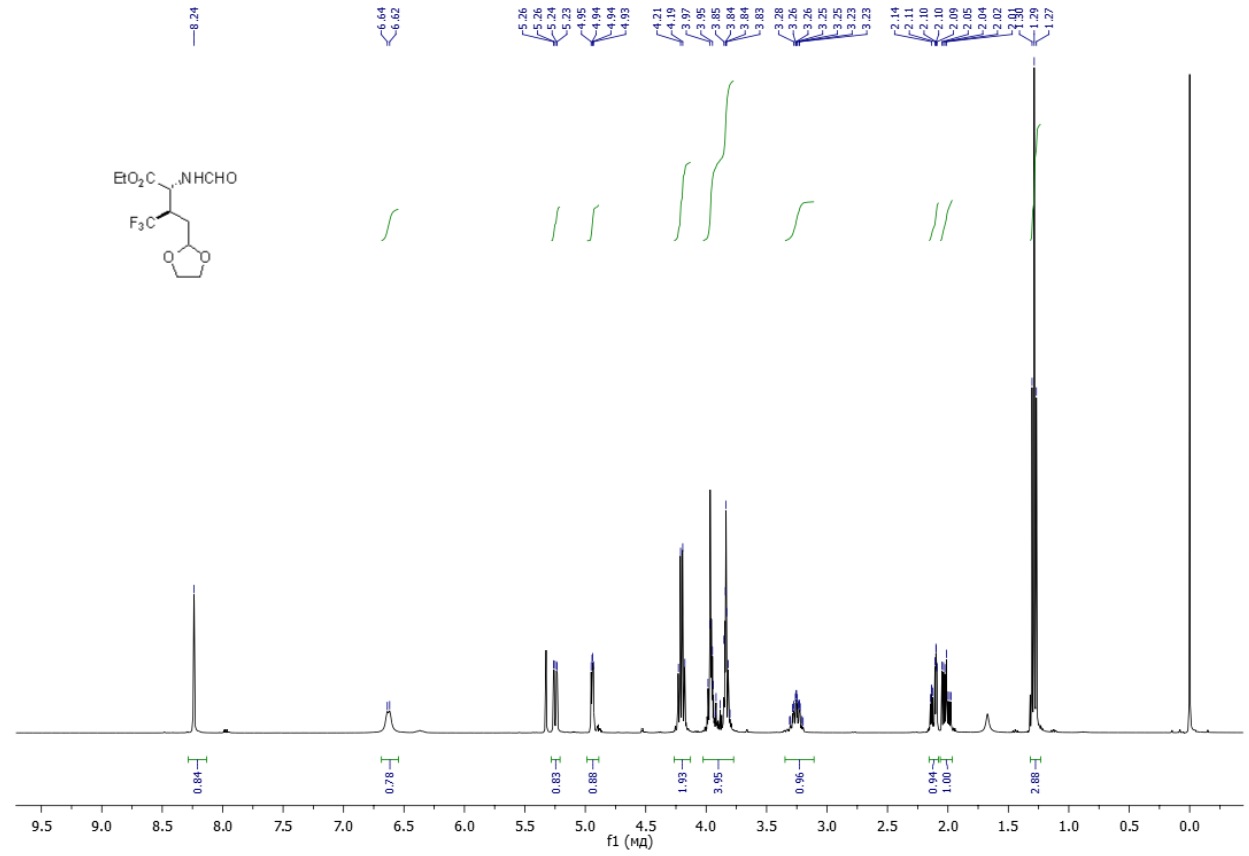


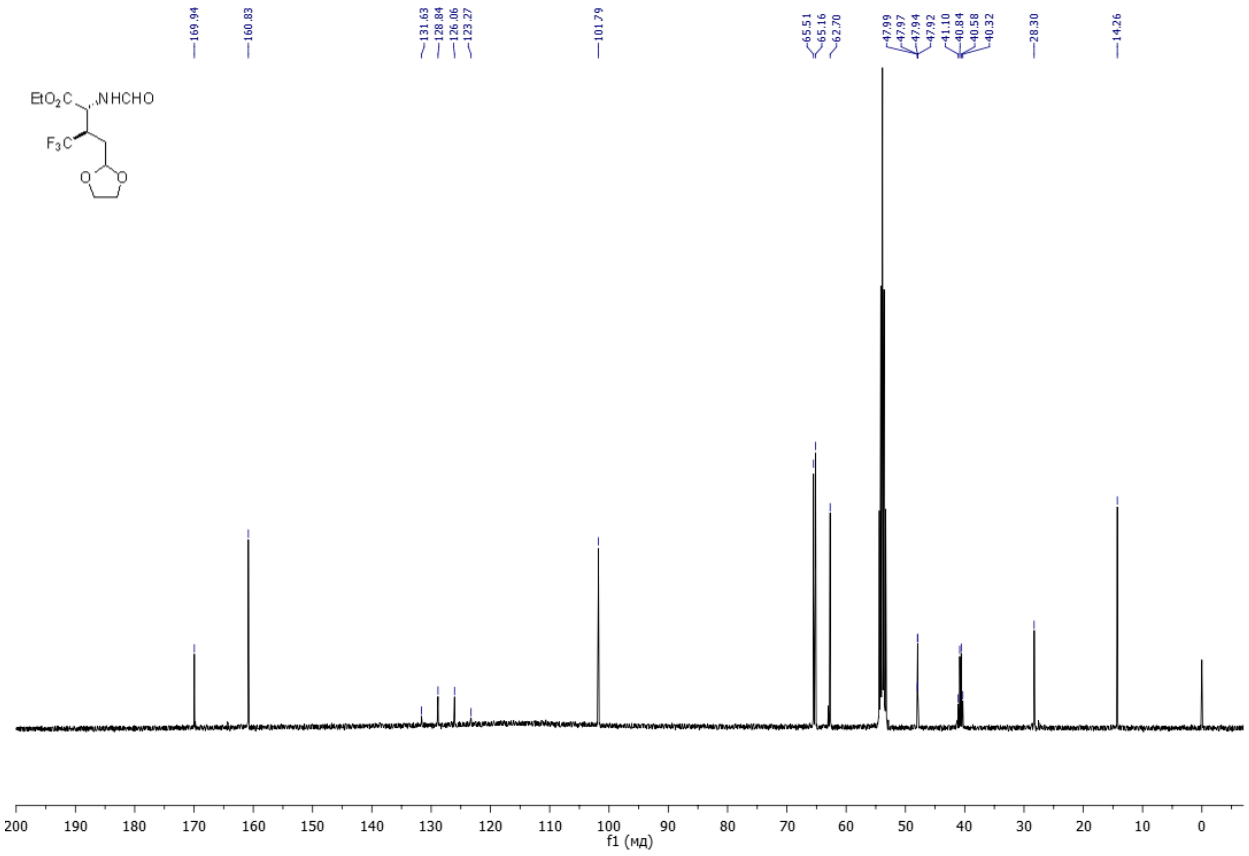
^{19}F NMR, compound ***syn*-4a**



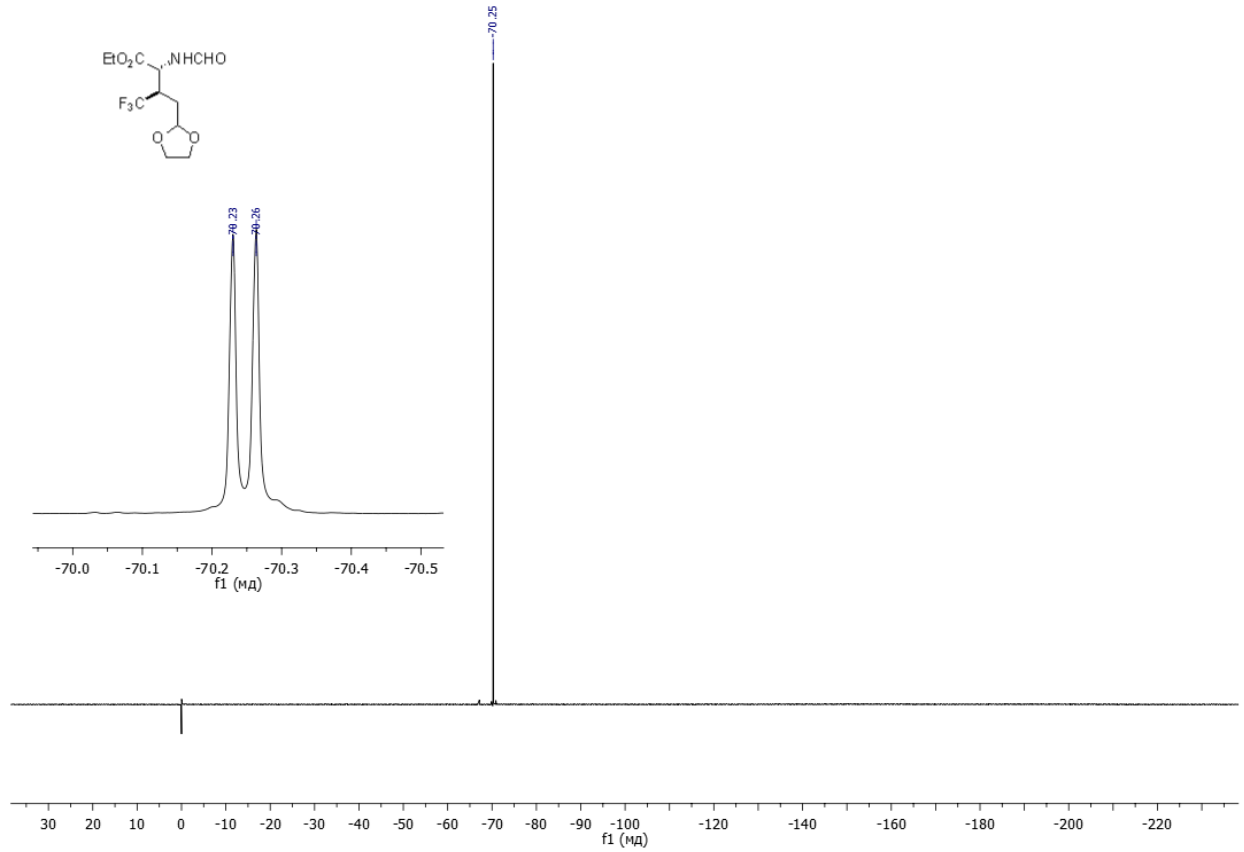
^{1}H NMR, compound ***anti*-4a**



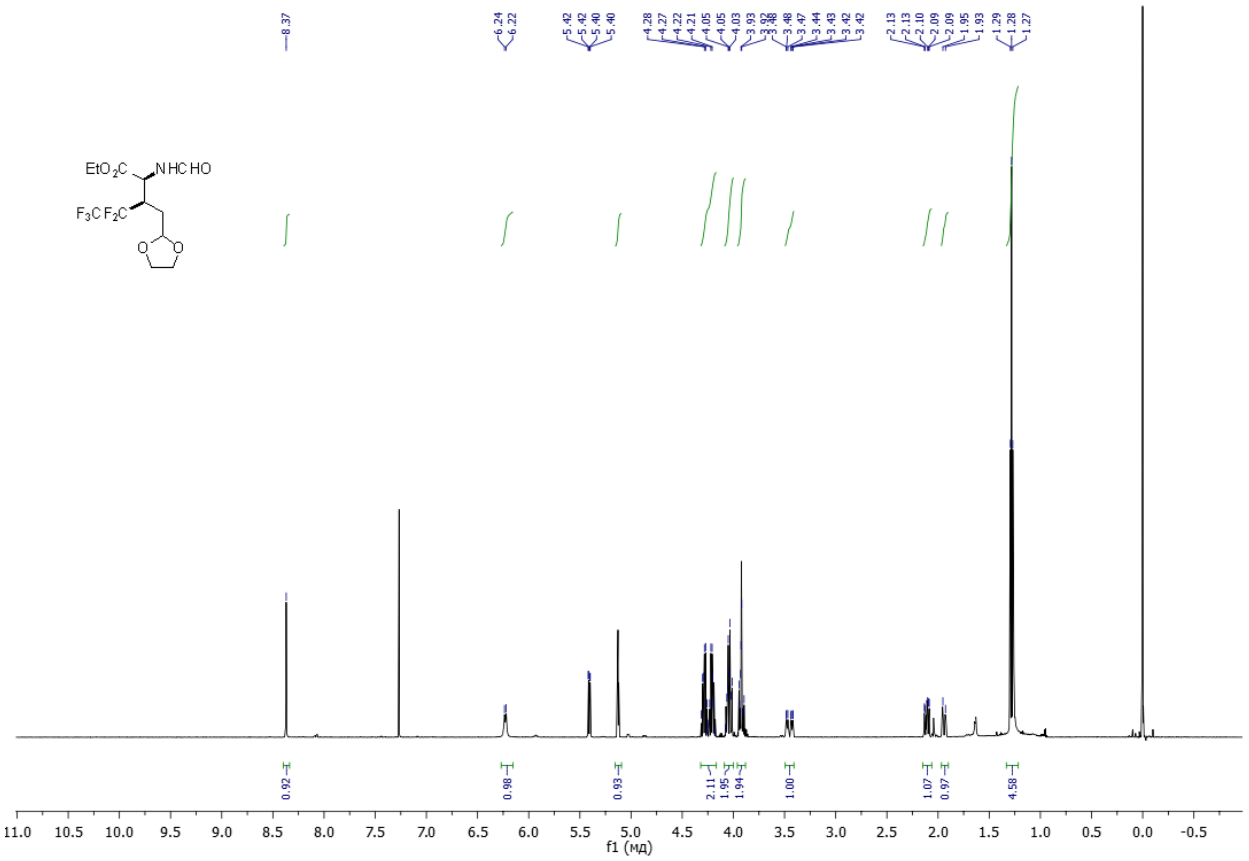
^{13}C NMR, compound ***anti*-4a**



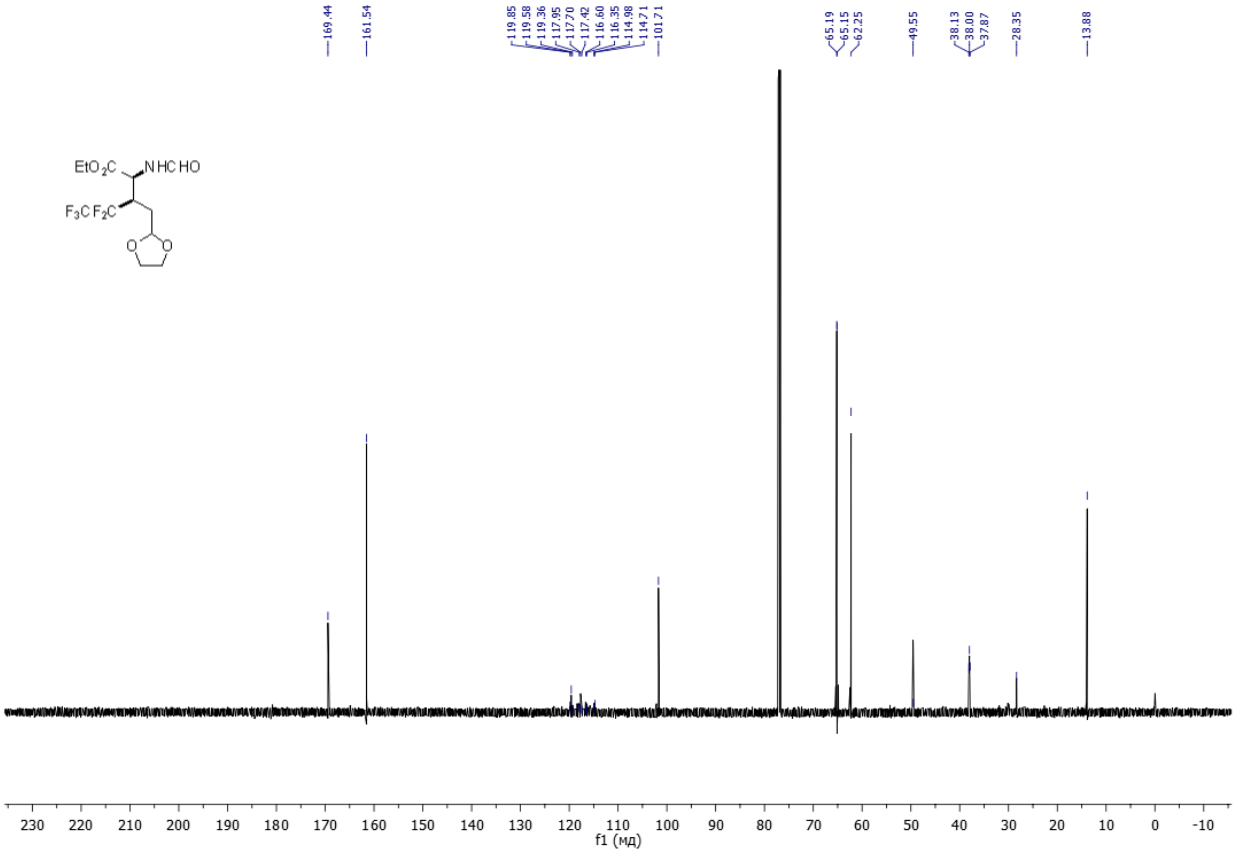
^{19}F NMR, compound ***anti*-4a**



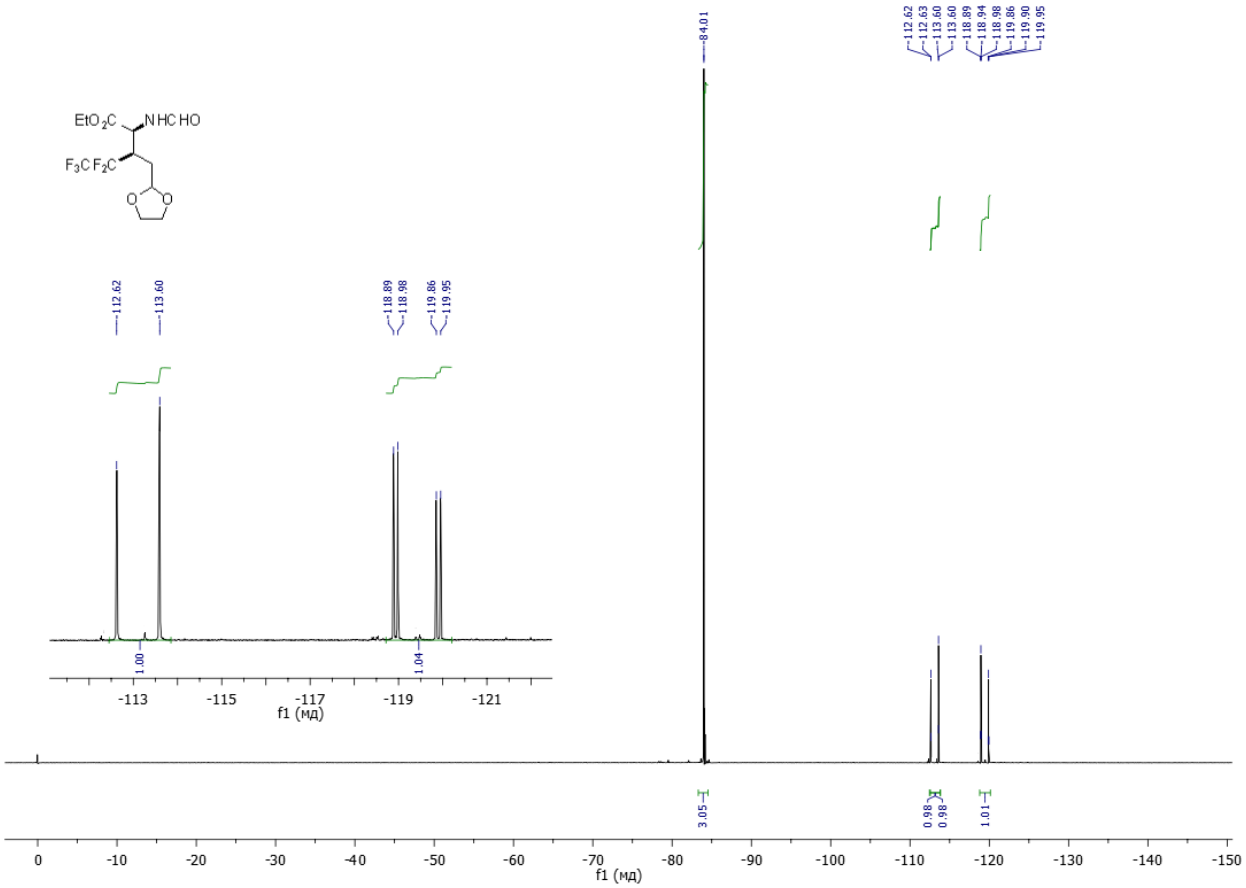
^{1}H NMR, compound ***syn*-4b**



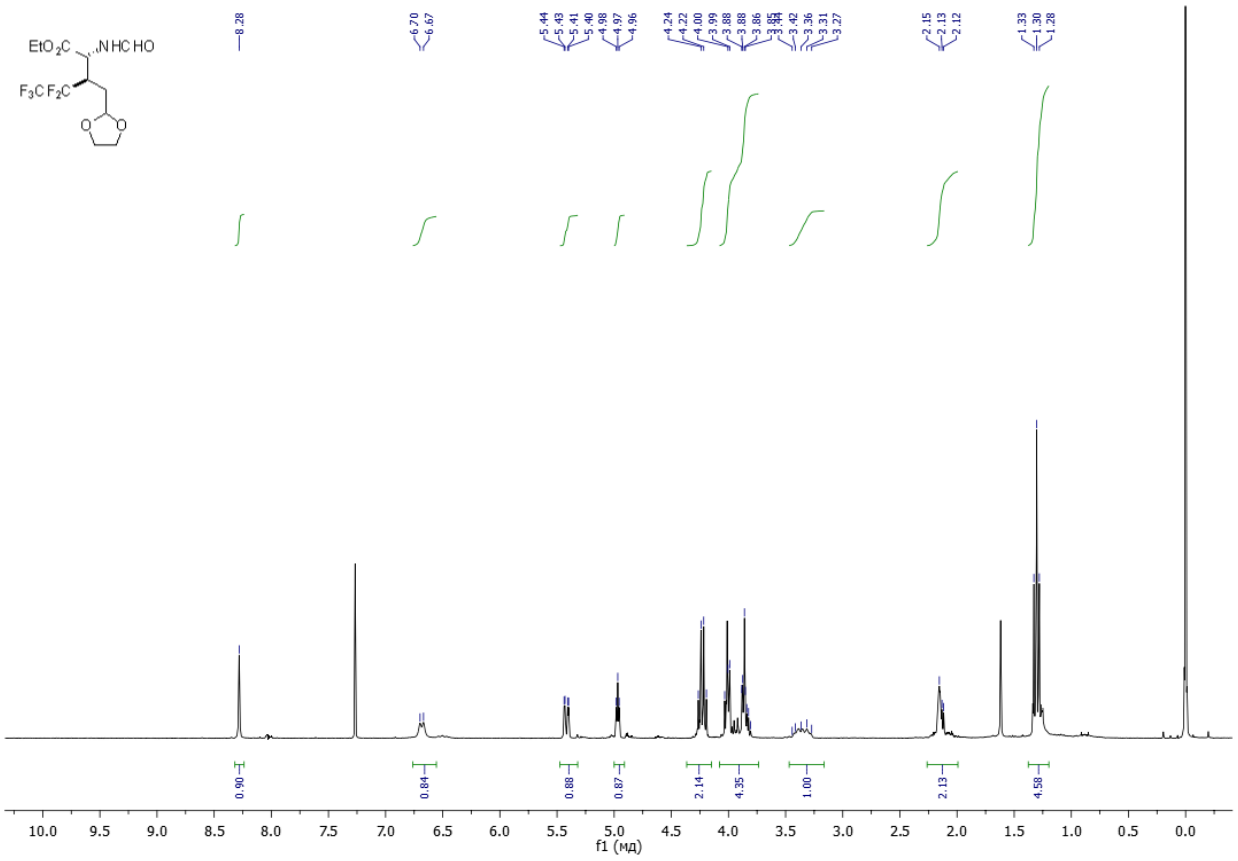
^{13}C NMR, compound ***syn*-4b**



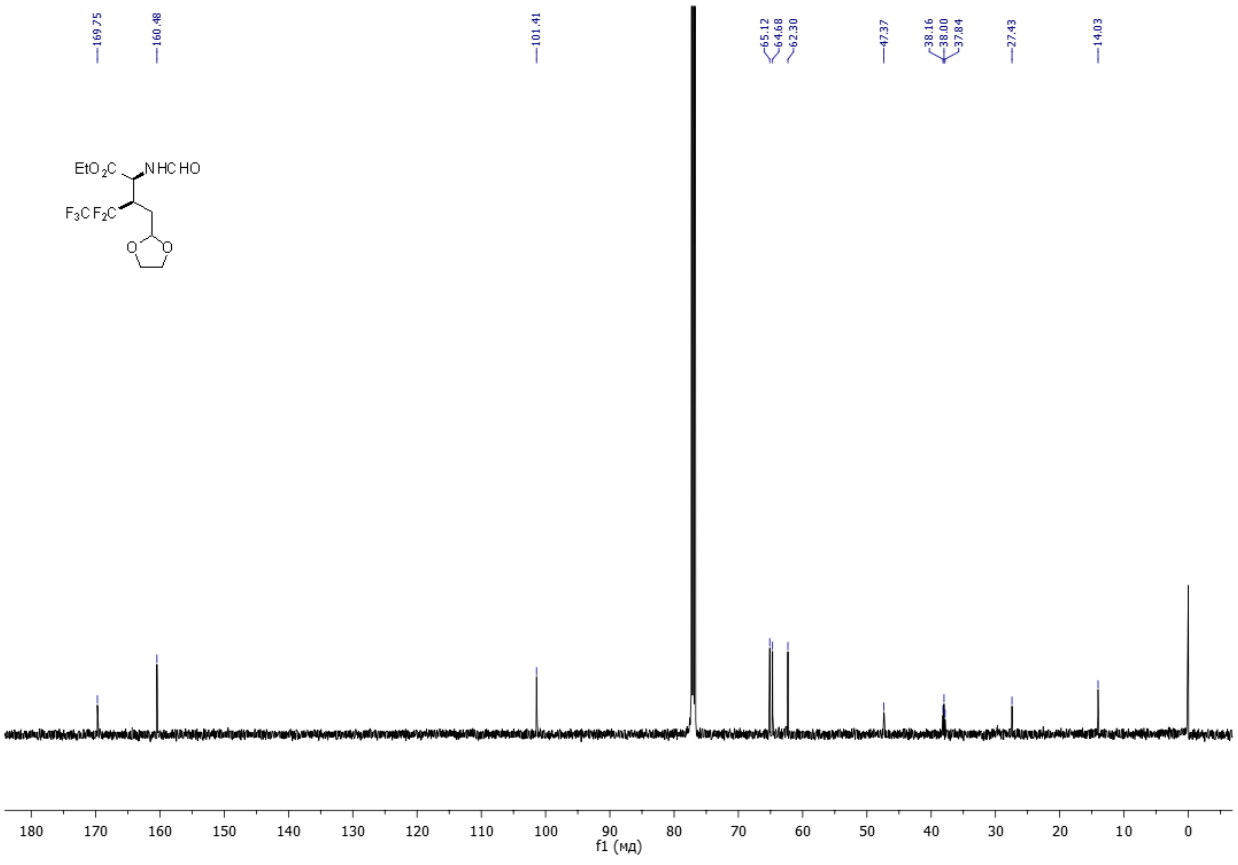
^{19}F NMR, compound ***syn*-4b**



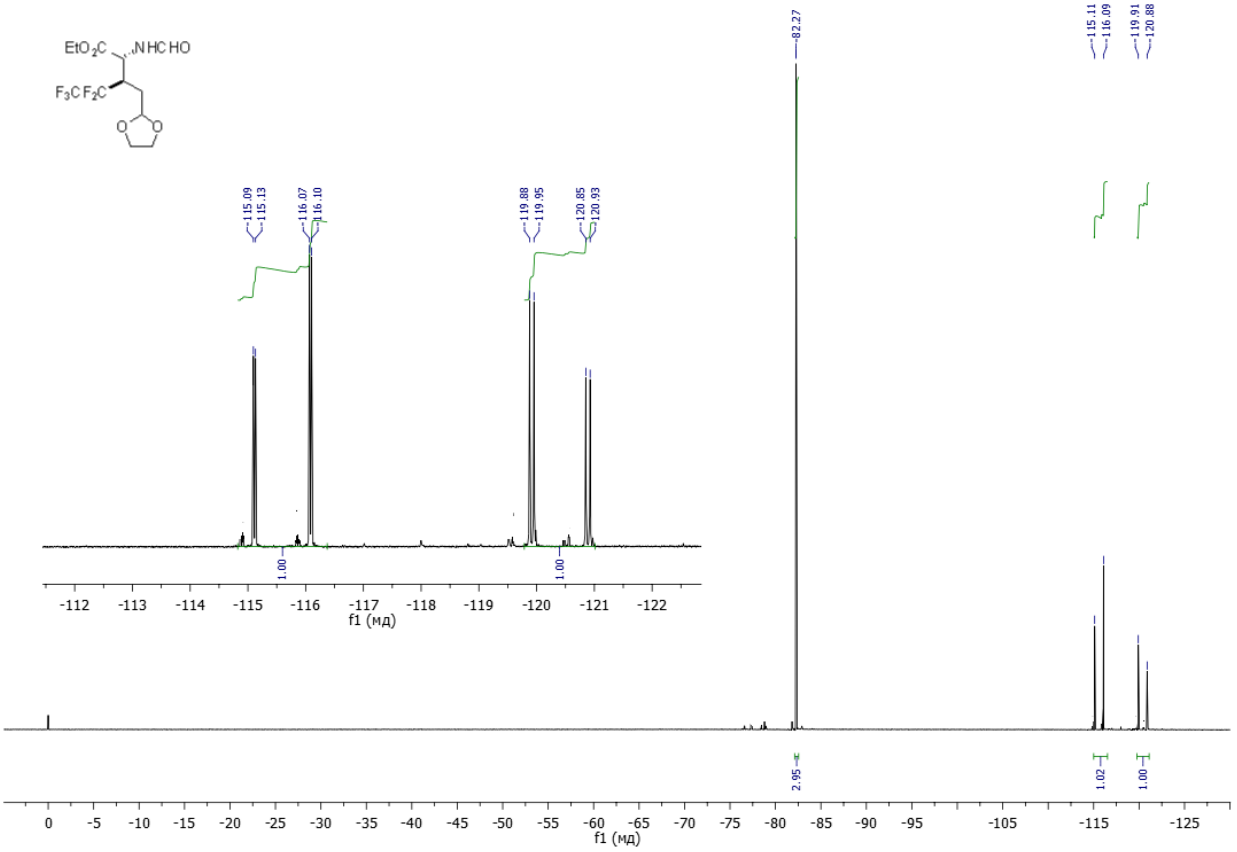
^{1}H NMR, compound ***anti*-4b**



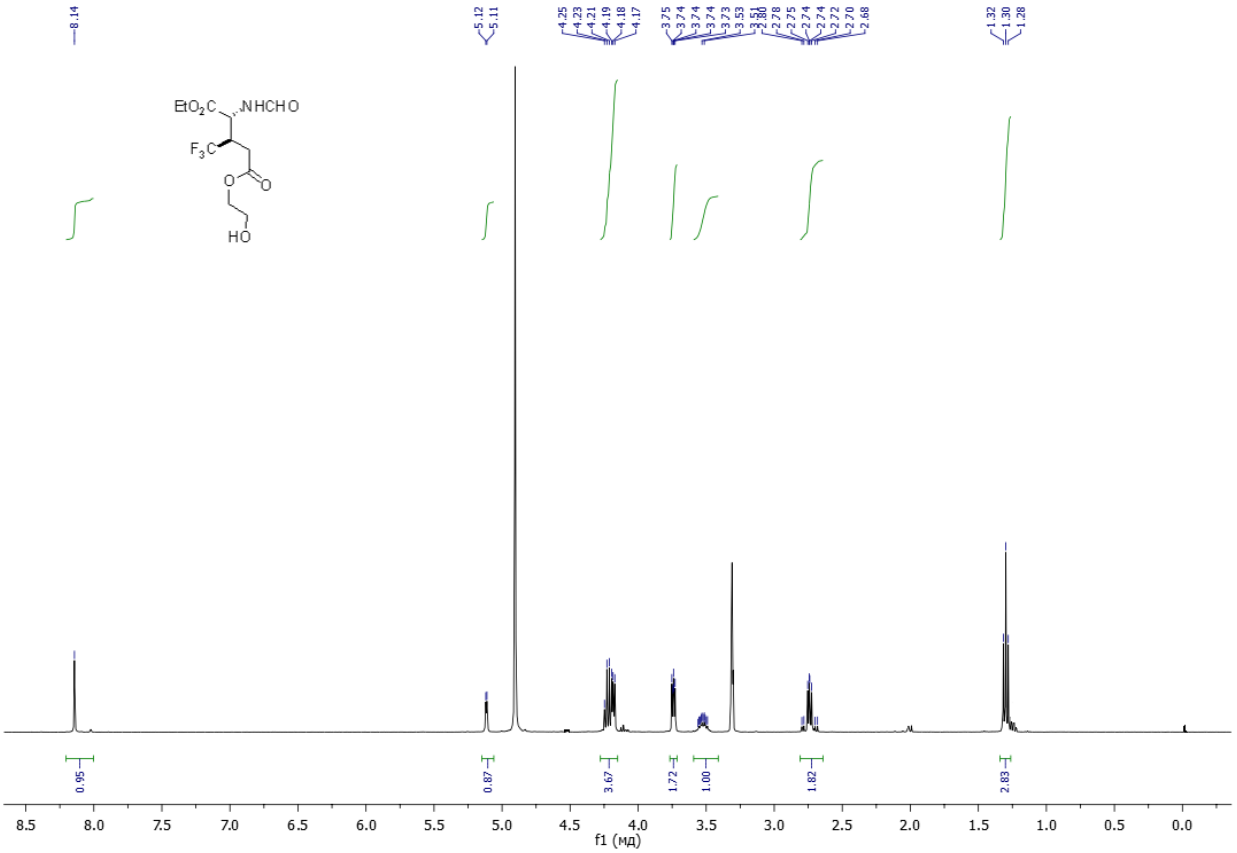
^{13}C NMR, compound ***anti*-4b**



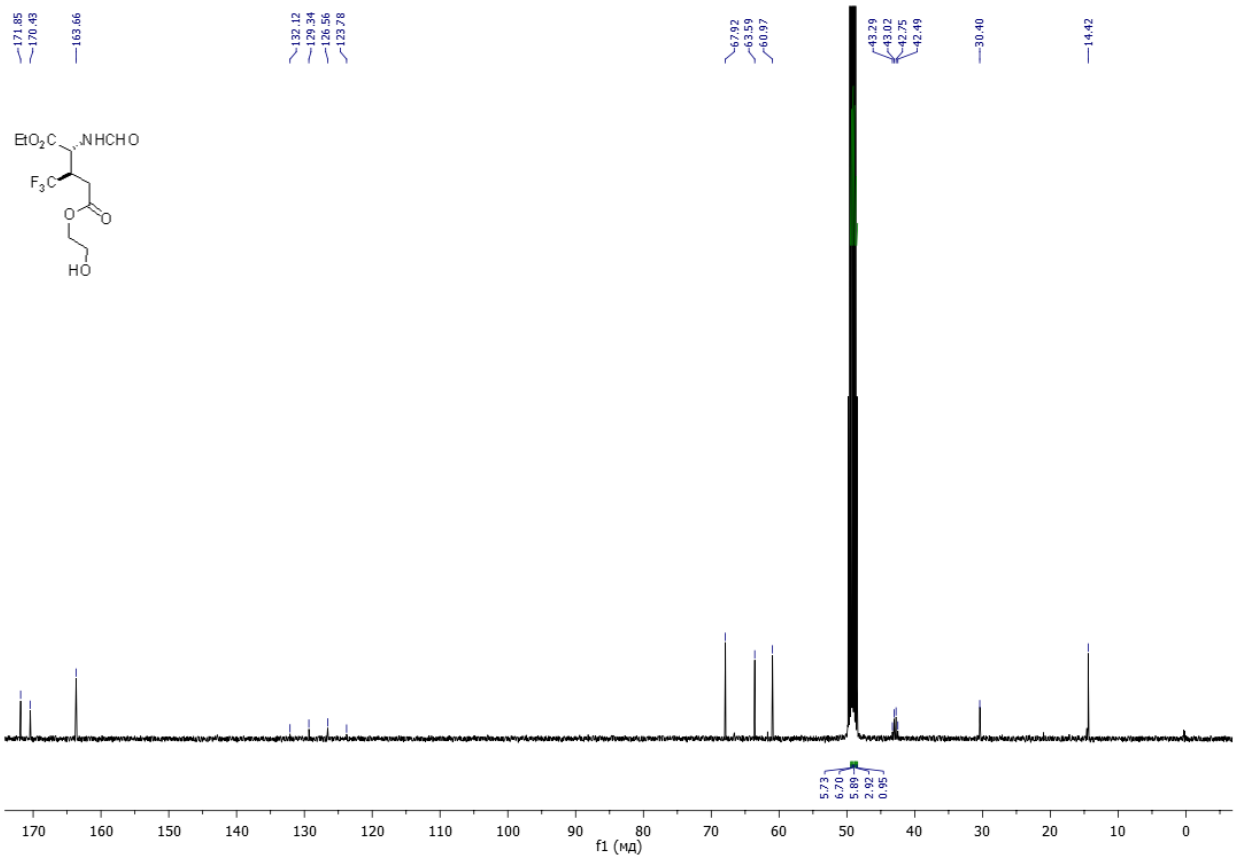
^{19}F NMR, compound ***anti*-4b**



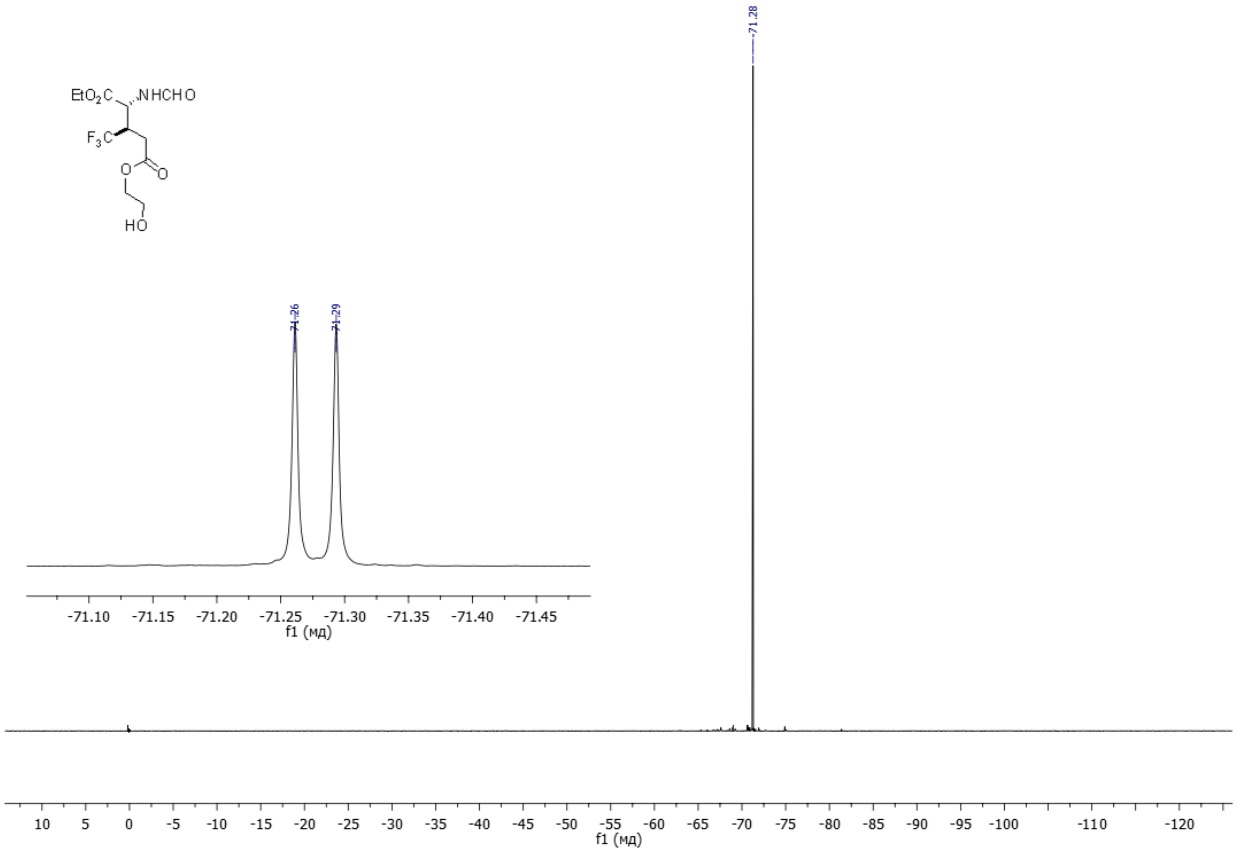
^{1}H NMR, compound ***anti*-5a**



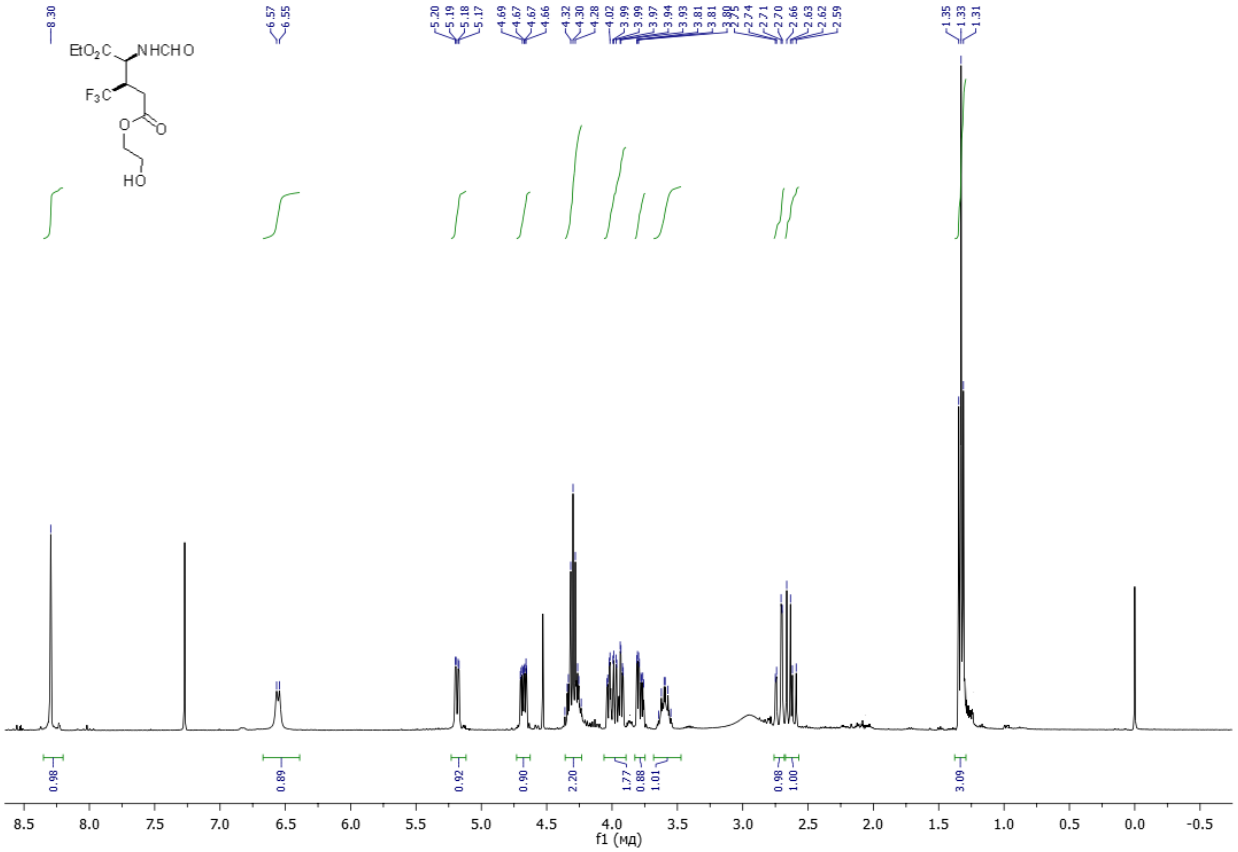
^{13}C NMR, compound ***anti*-5a**



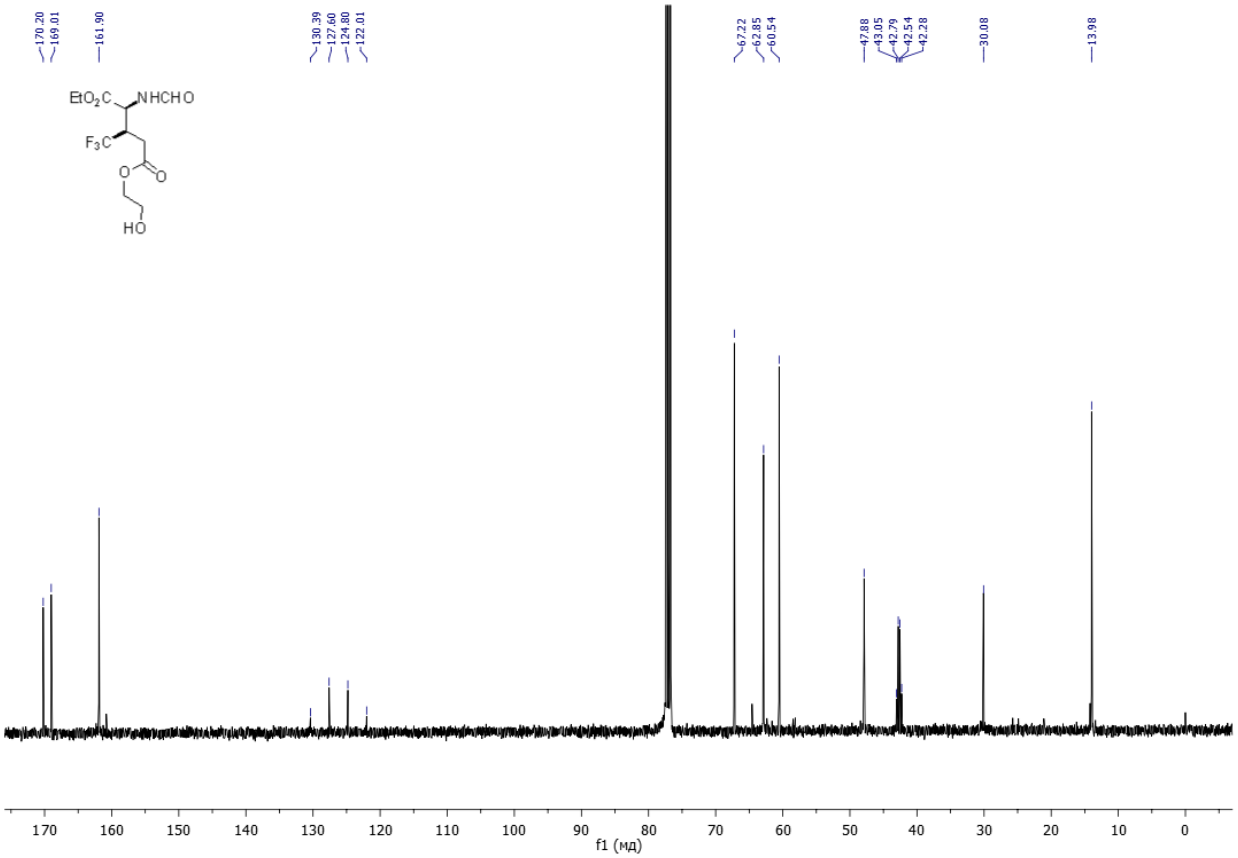
^{19}F NMR, compound ***anti*-5a**



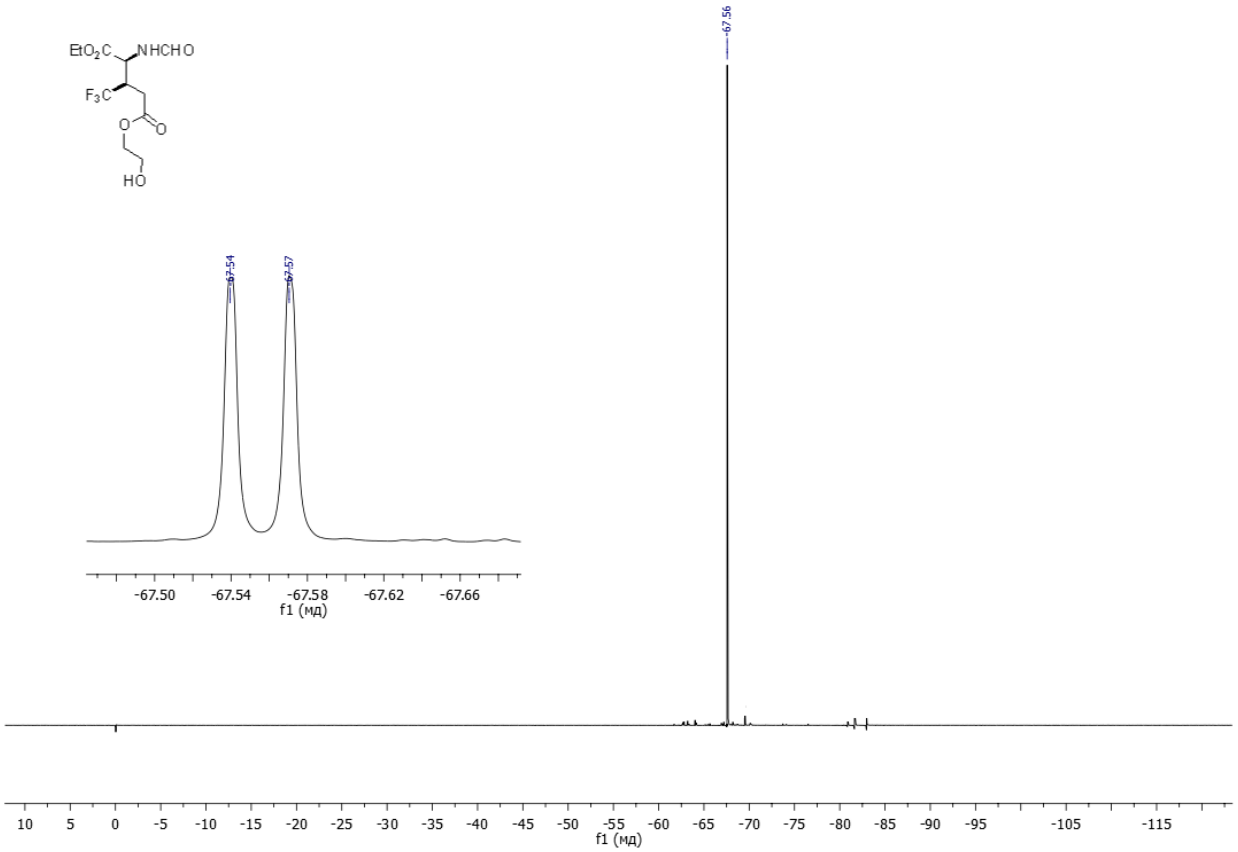
^{1}H NMR, compound ***syn*-5a**



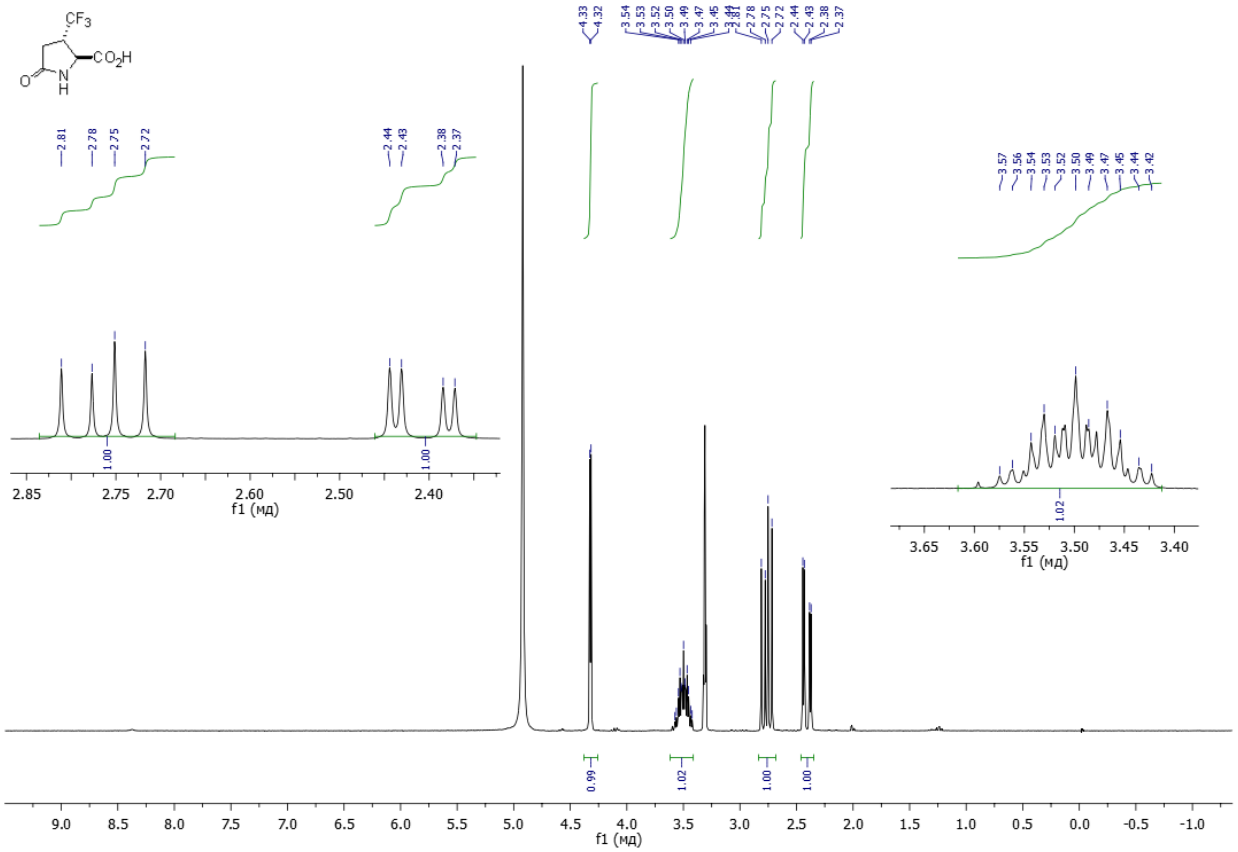
^{13}C NMR, compound ***syn*-5a**



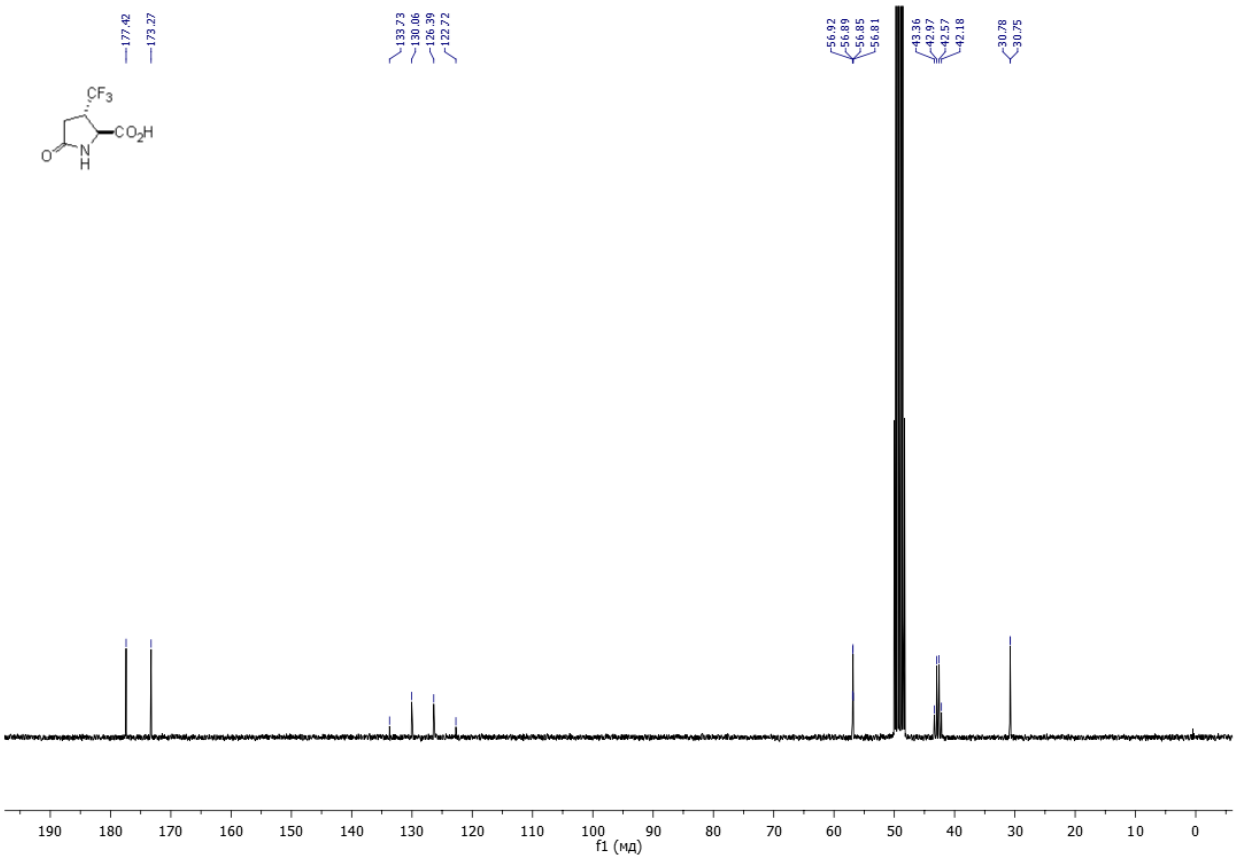
^{19}F NMR, compound ***syn*-5a**



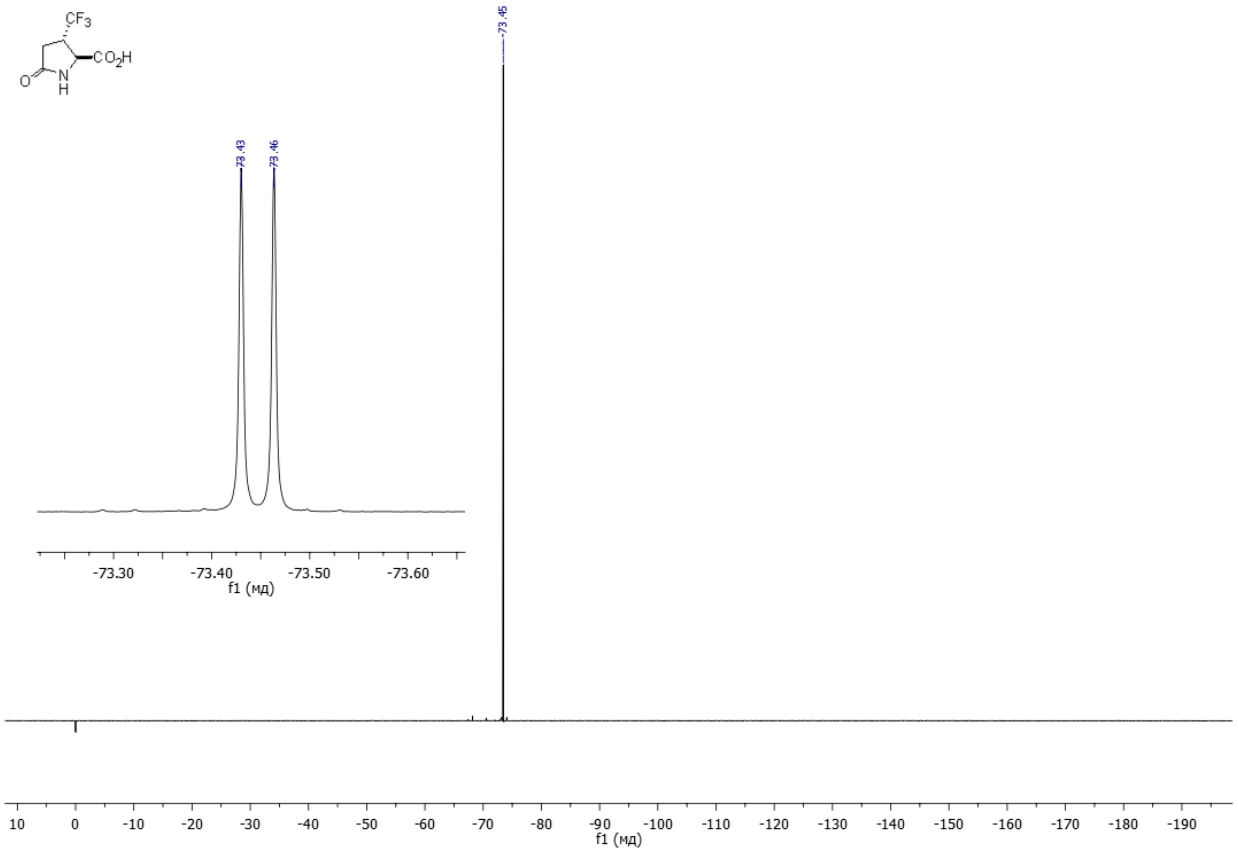
^{1}H NMR, compound ***trans*-6a**



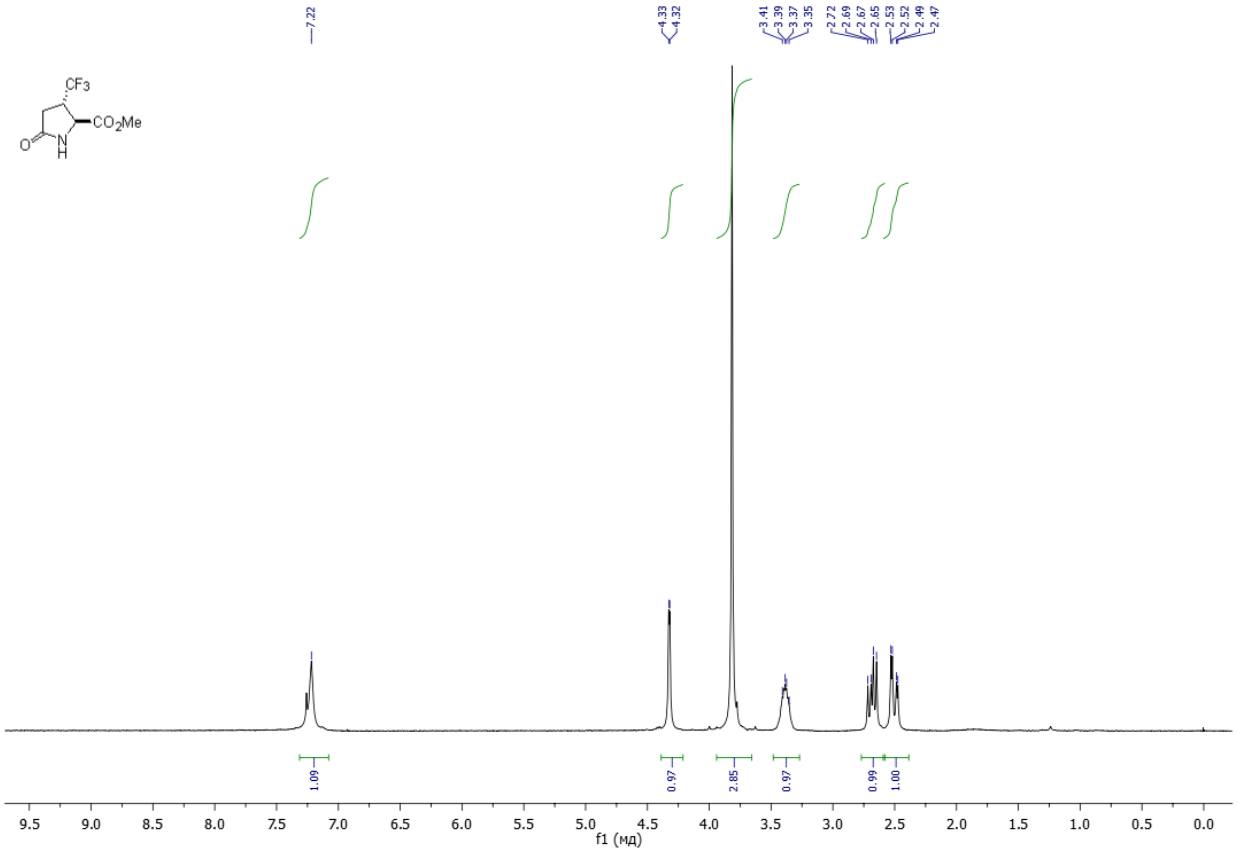
^{13}C NMR, compound ***trans*-6a**



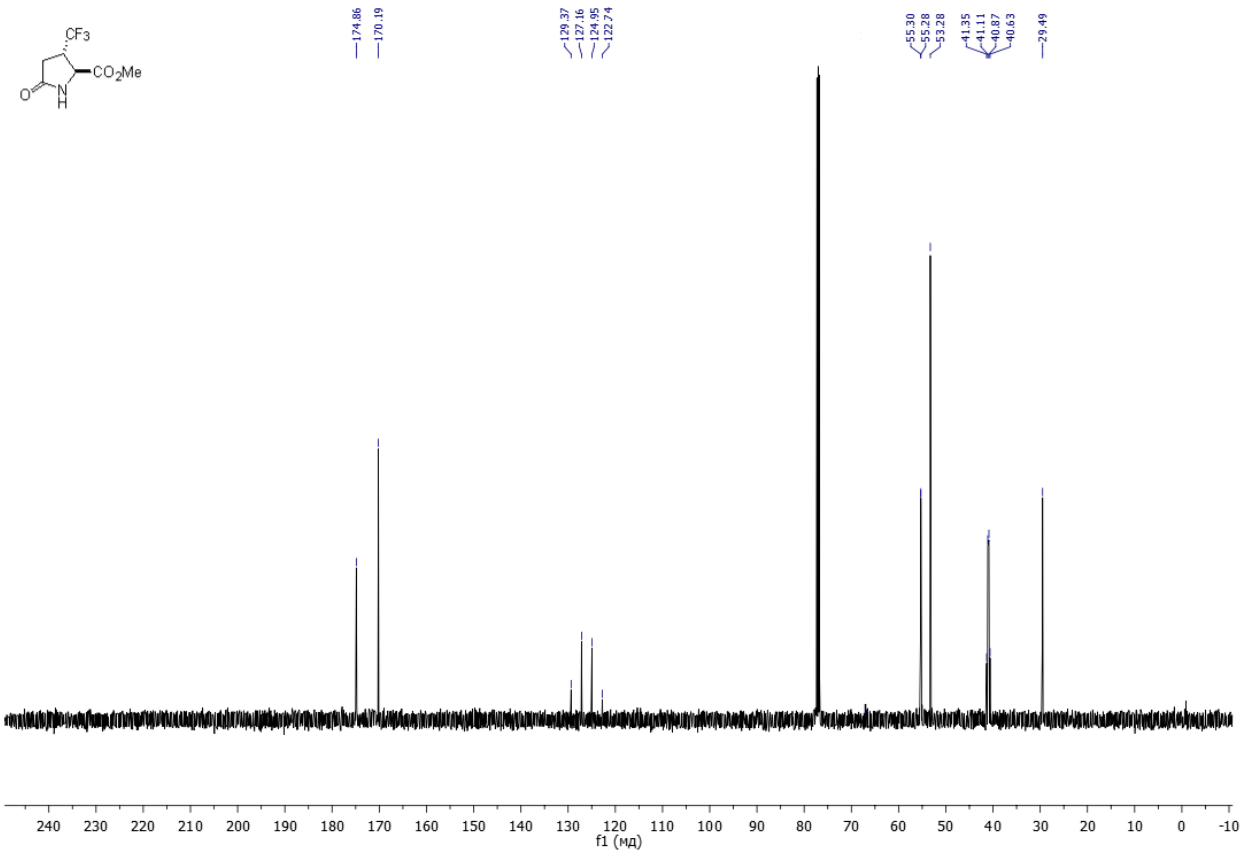
^{19}F NMR, compound ***trans*-6a**



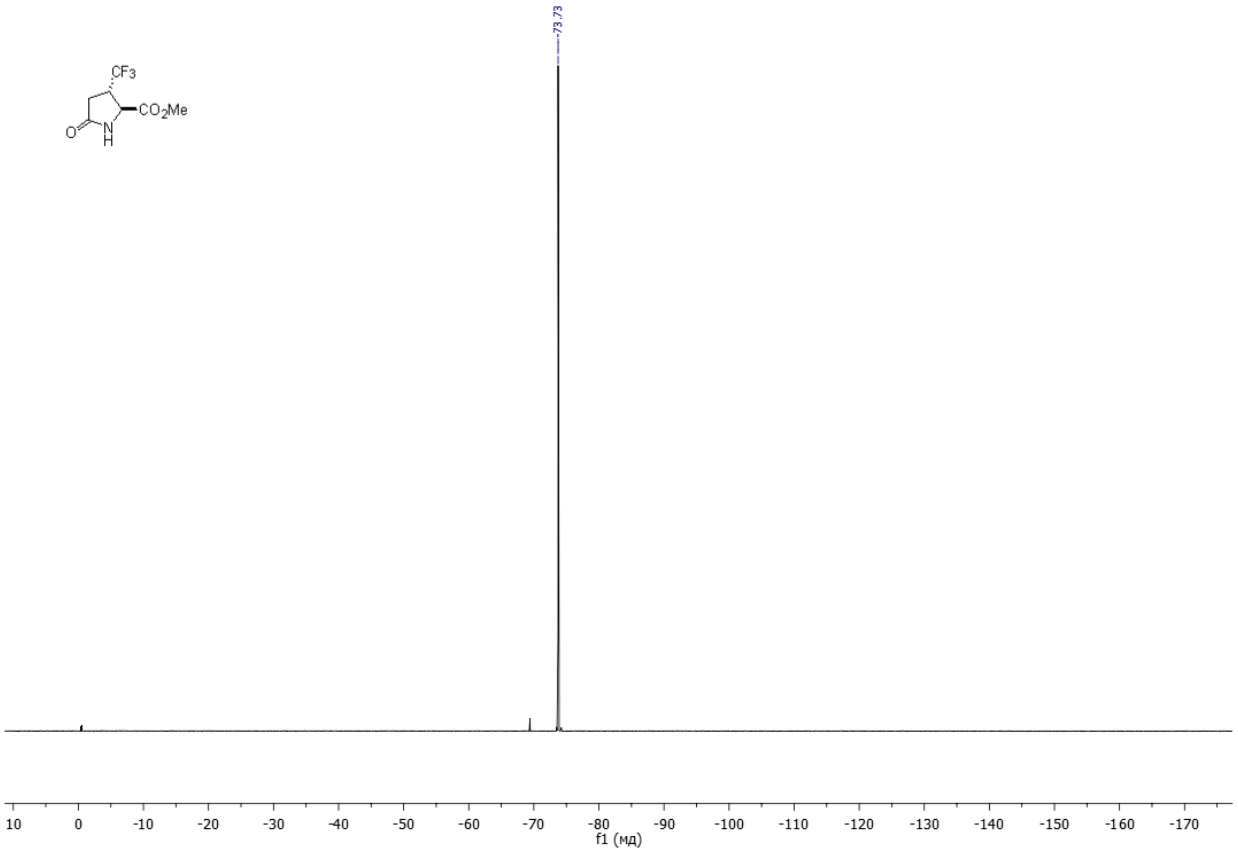
^{1}H NMR, Compound **S1** (see Scheme S2)



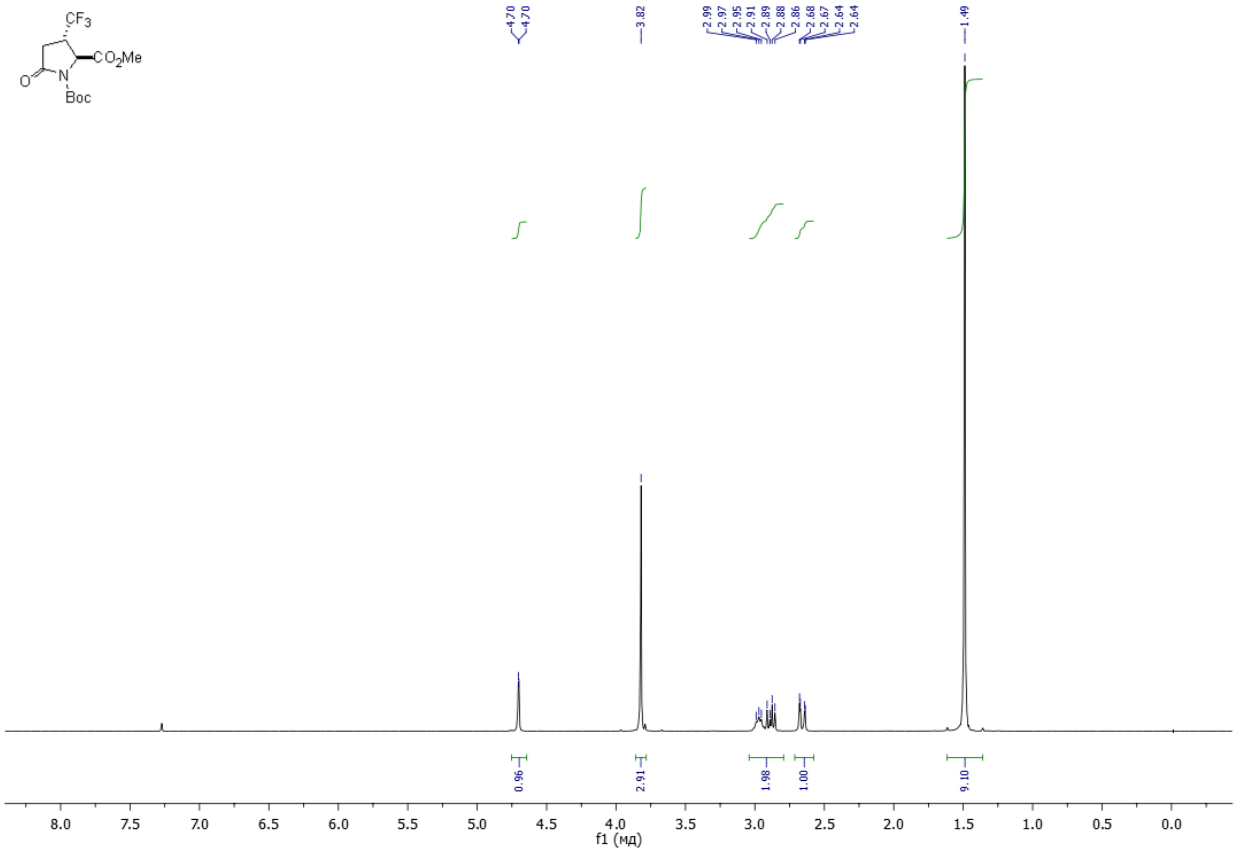
^{13}C NMR, Compound **S1** (see Scheme S2)



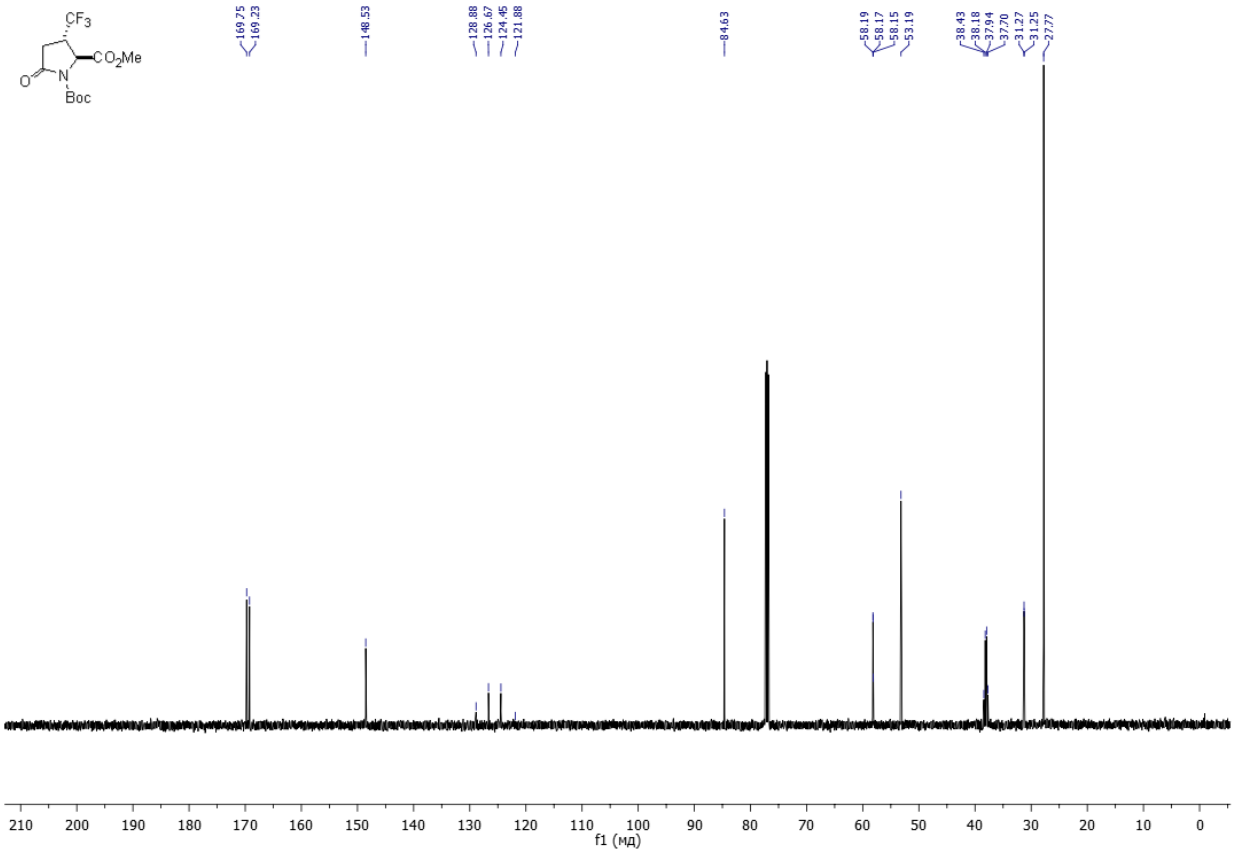
^{19}F NMR Compound **S1** (see Scheme S2)



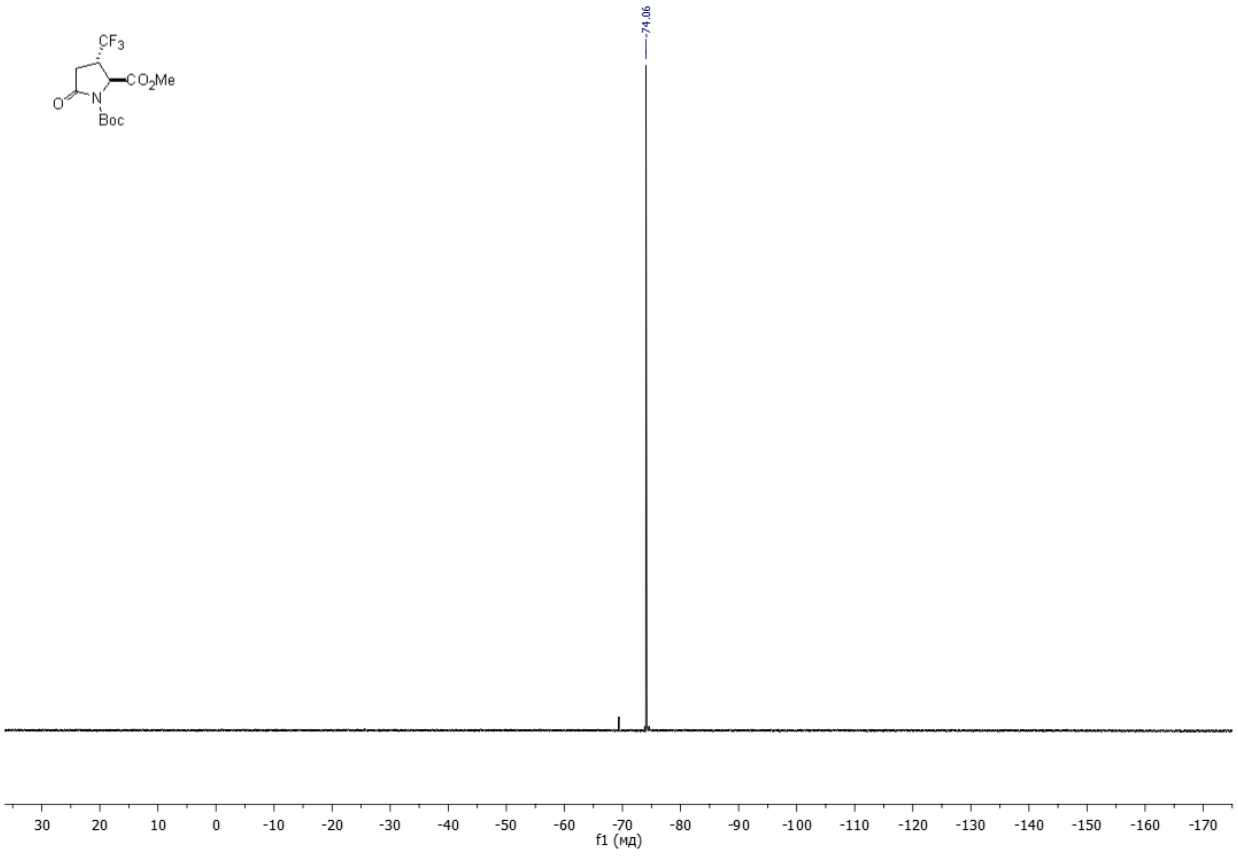
^{1}H NMR, Compound **S2** (see Scheme S2)



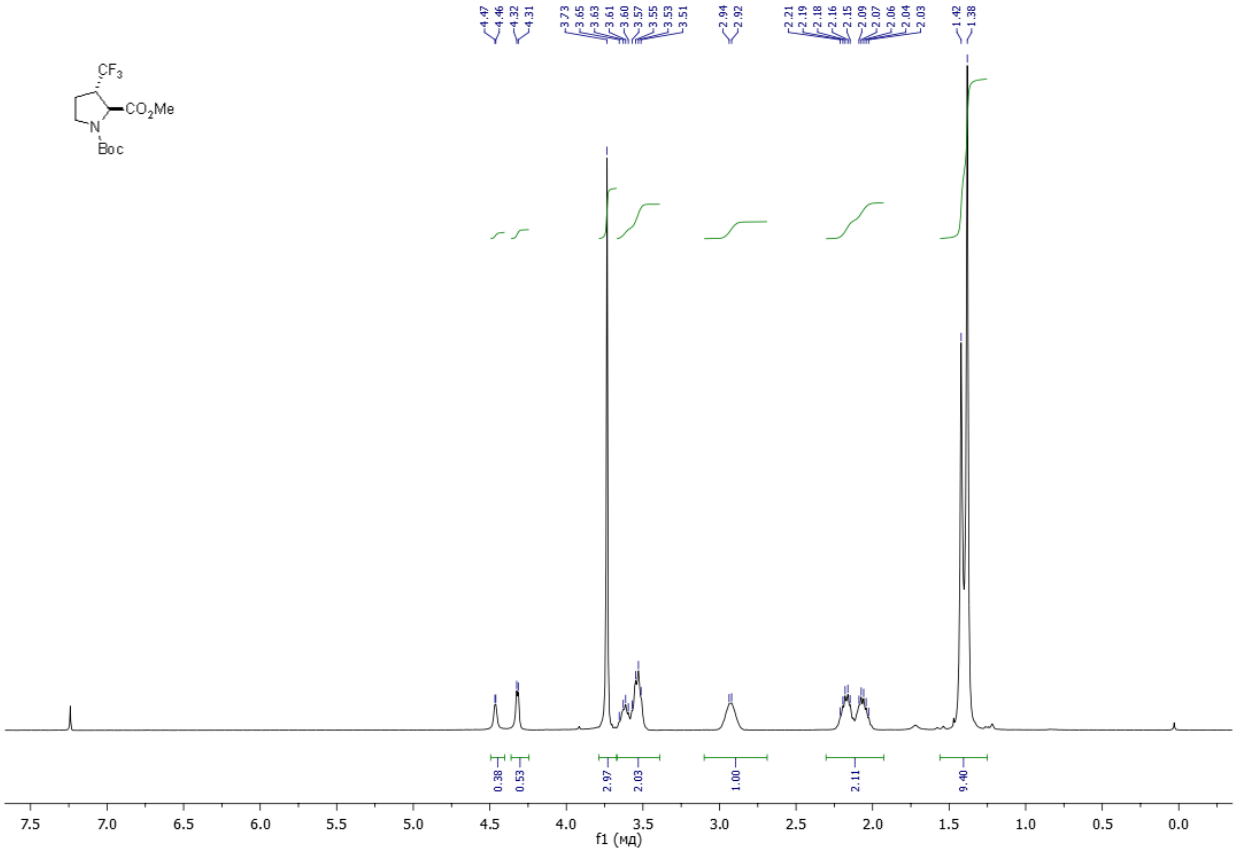
^{13}C NMR, Compound **S2** (see Scheme S2)



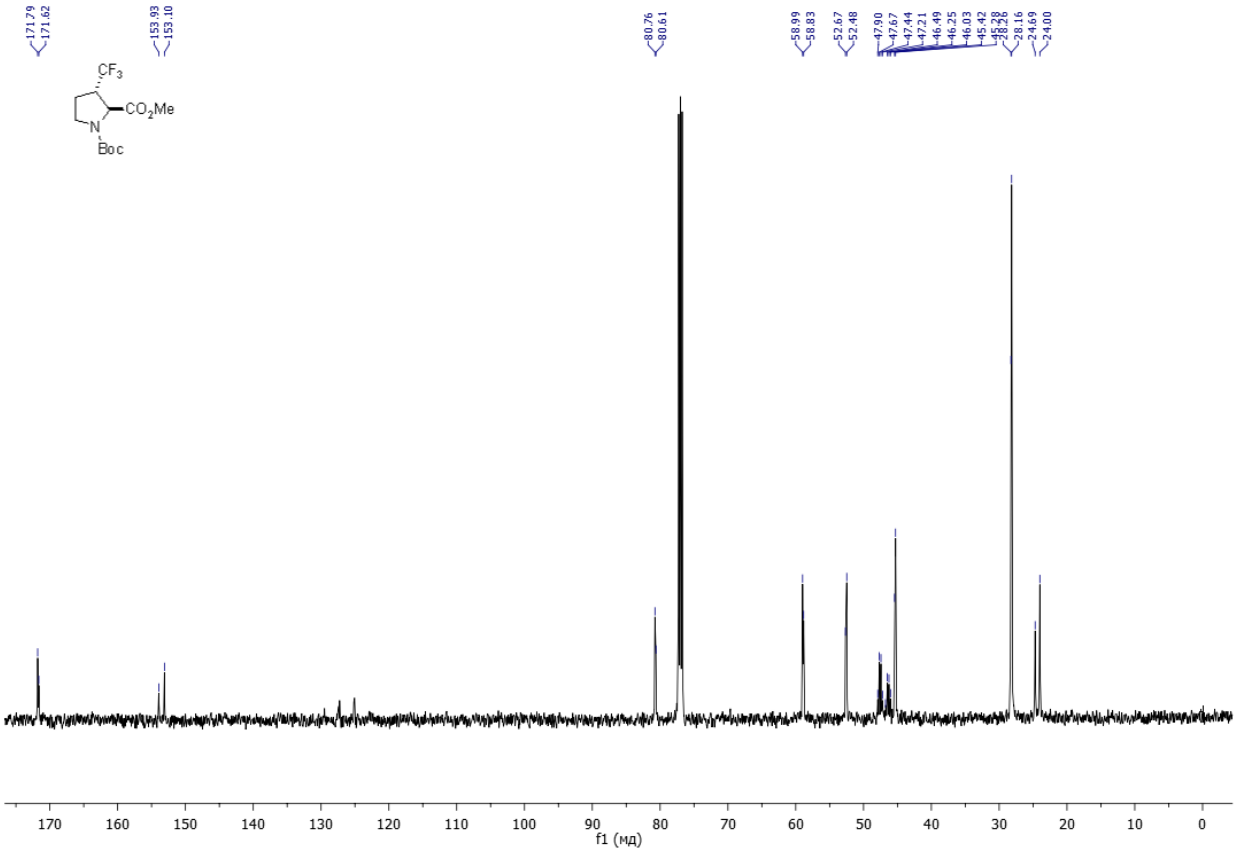
^{19}F NMR, Compound **S2** (see Scheme S2)



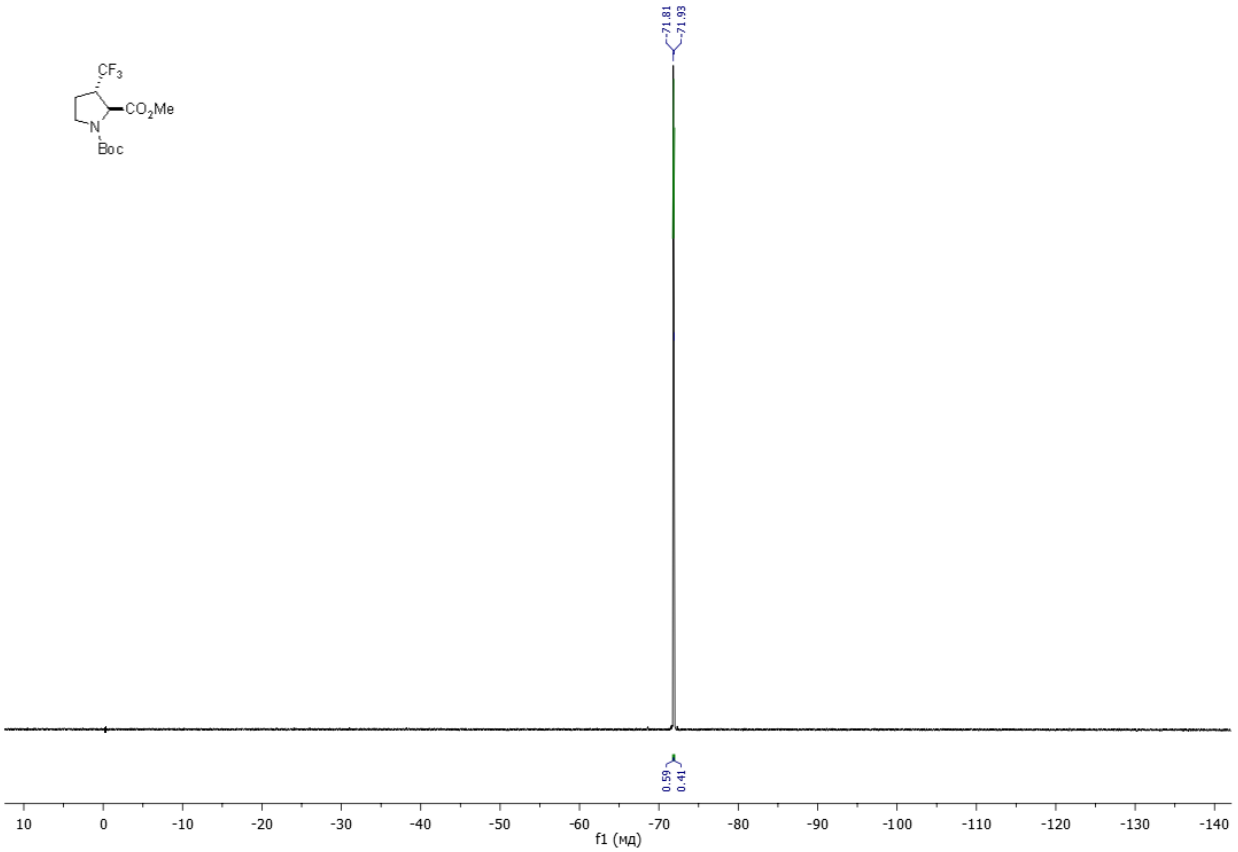
^{1}H NMR, Compound ***trans*-7a**



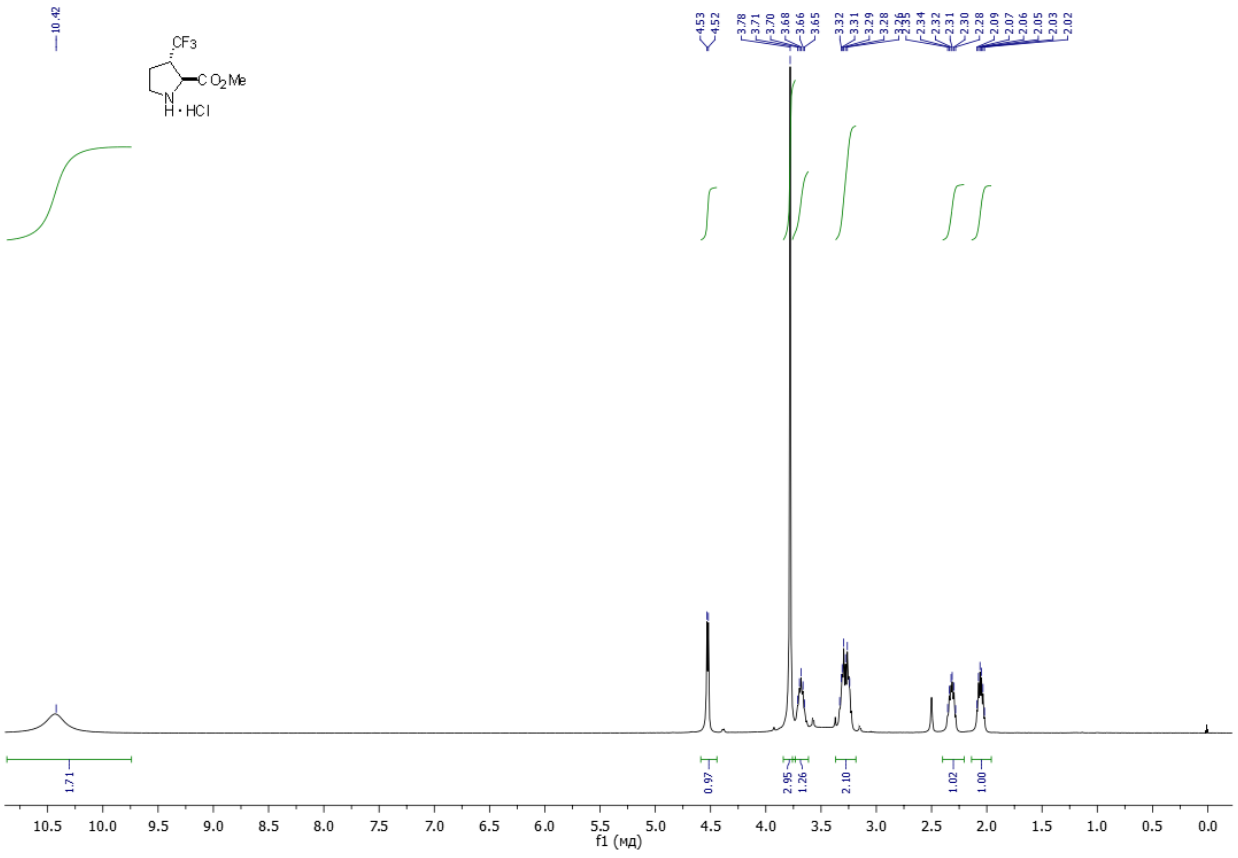
^{13}C NMR, Compound ***trans*-7a**



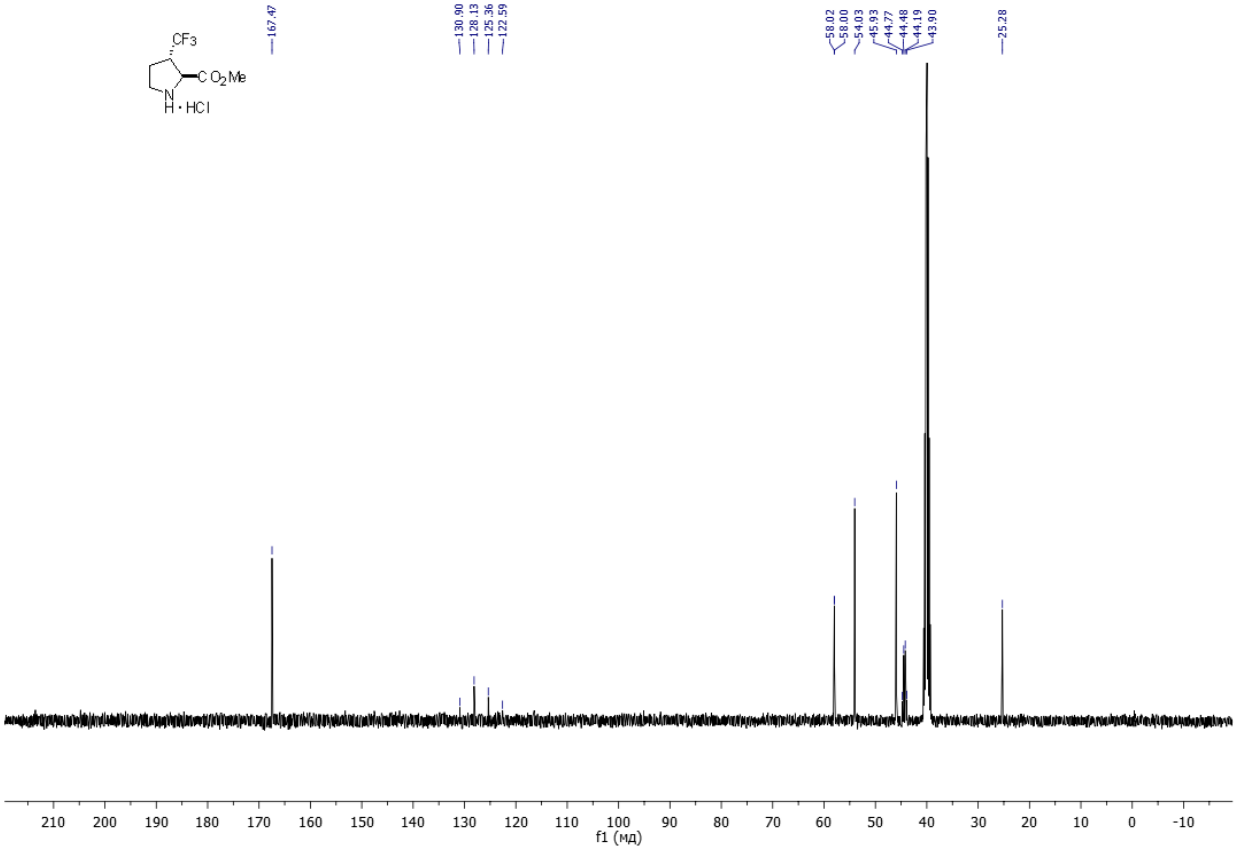
^{19}F NMR, Compound ***trans*-7a**



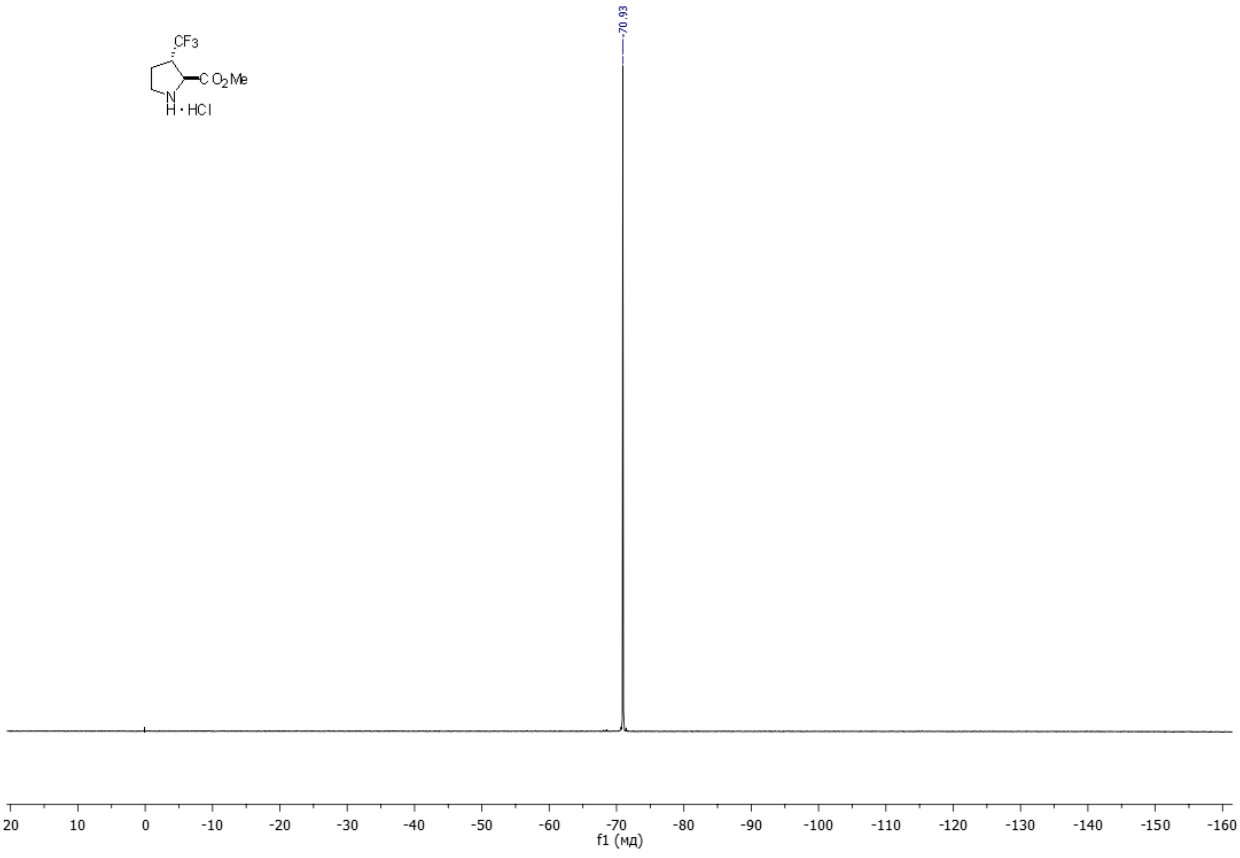
^{1}H NMR, compound **S3** (See scheme S2)



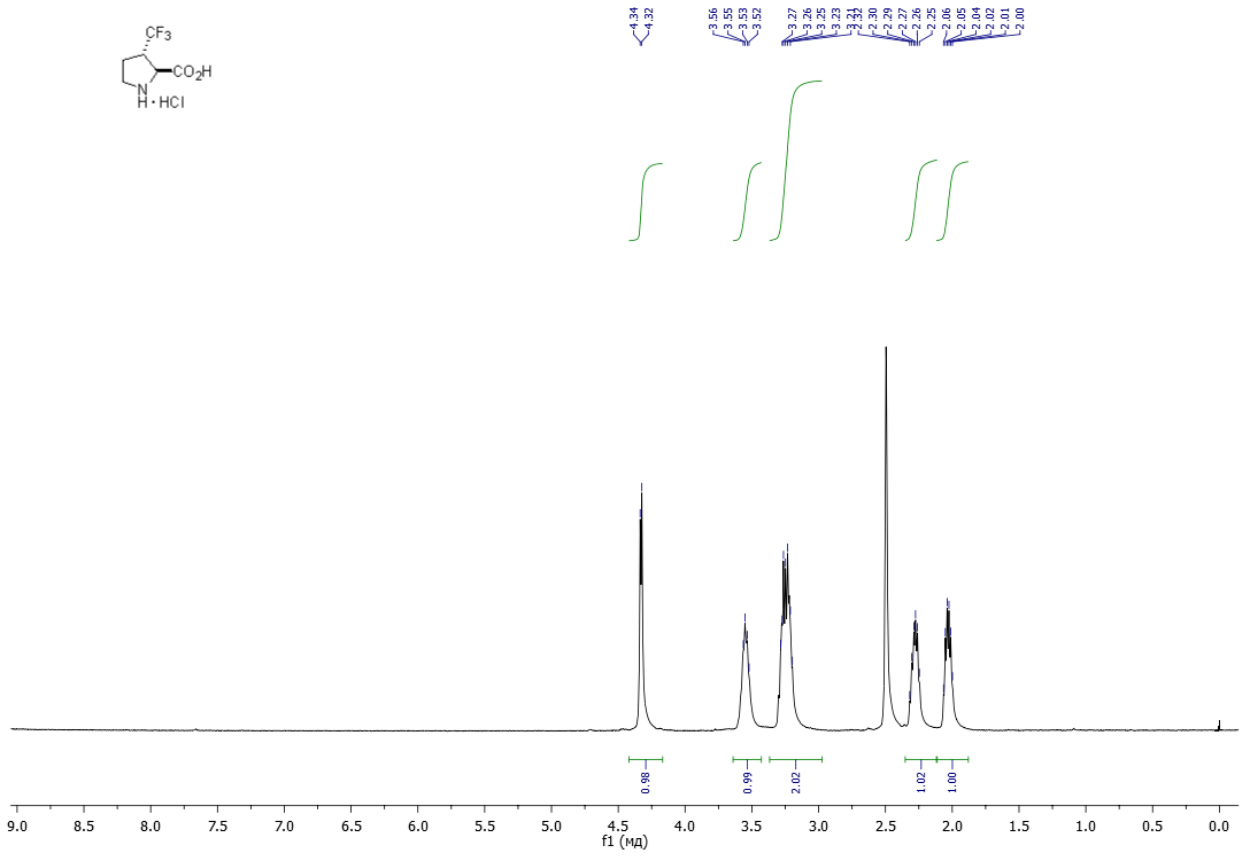
^{13}C NMR, compound **S3** (See scheme S2)



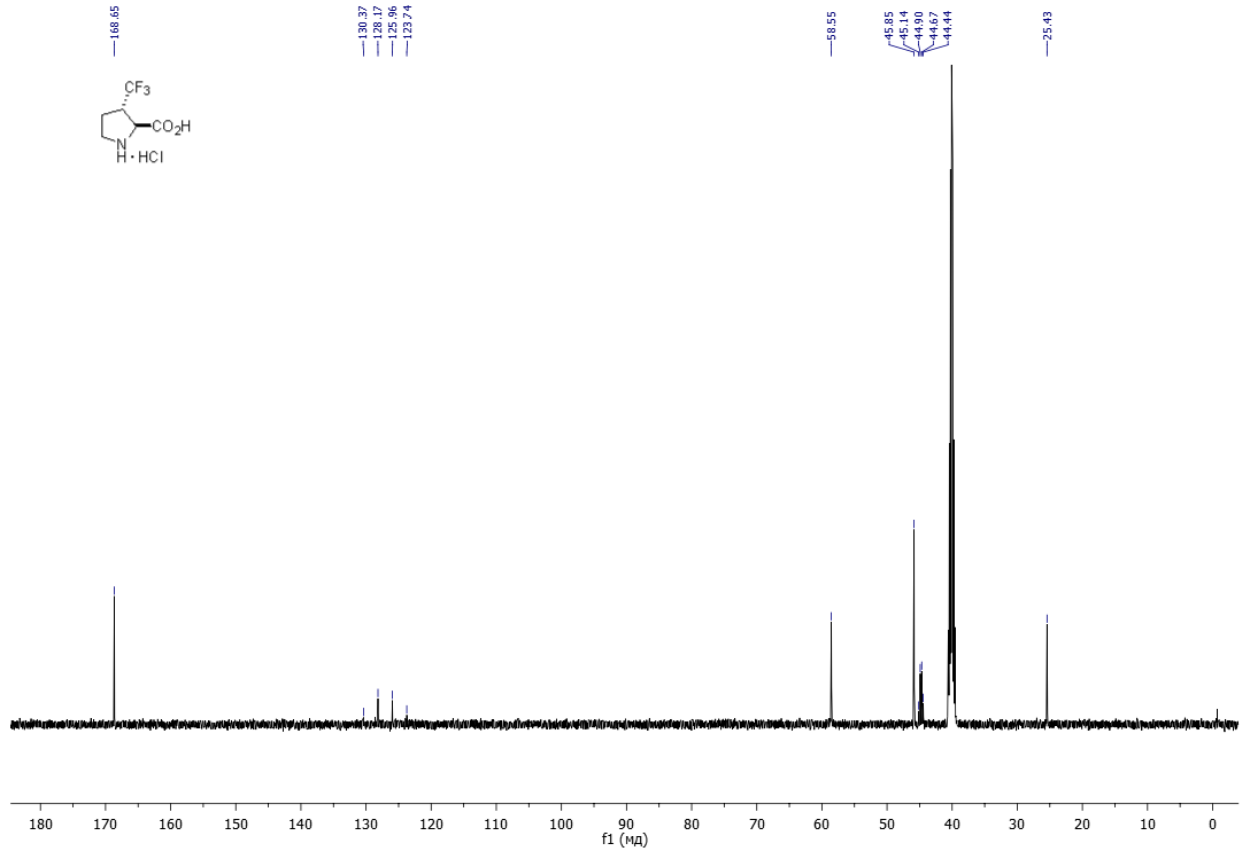
^{19}F NMR, compound **S3** (See scheme S2)



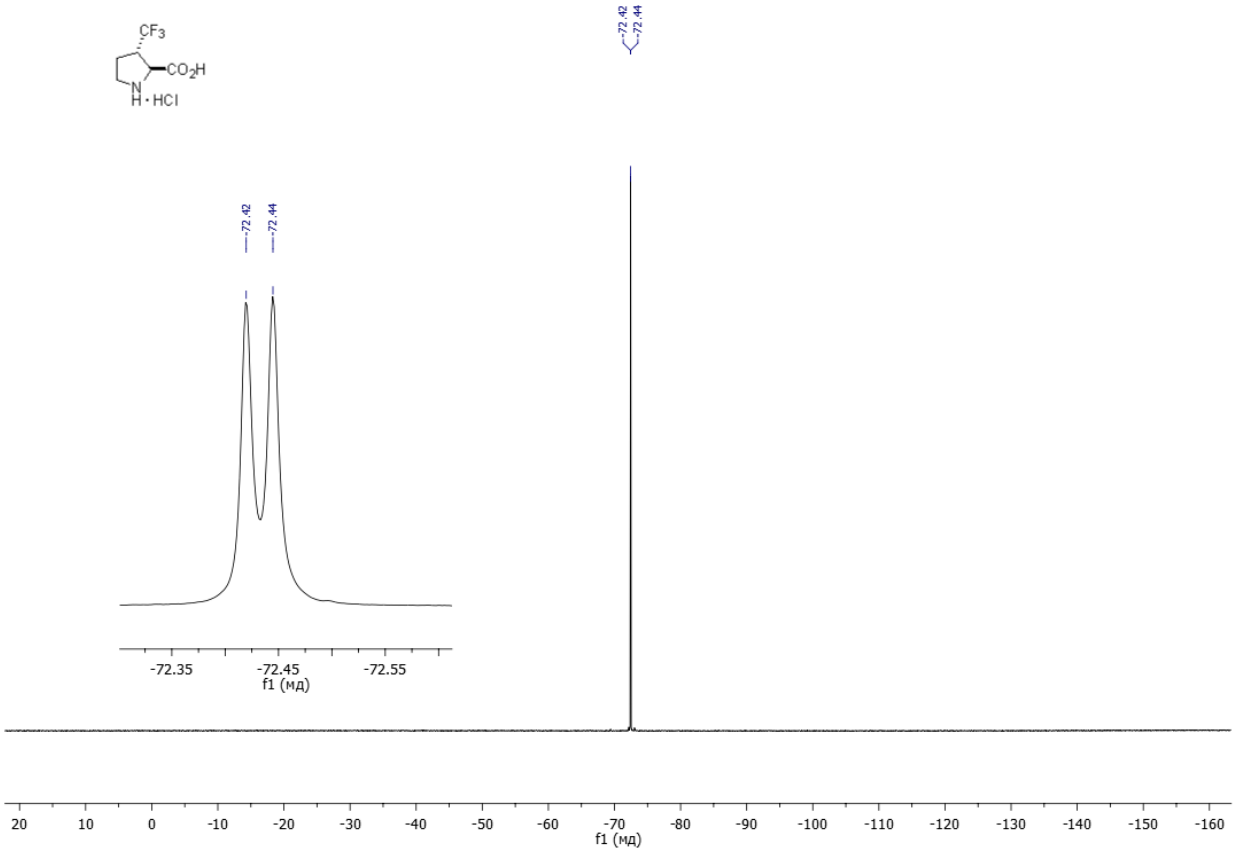
^{1}H NMR, compound ***trans*-1a**



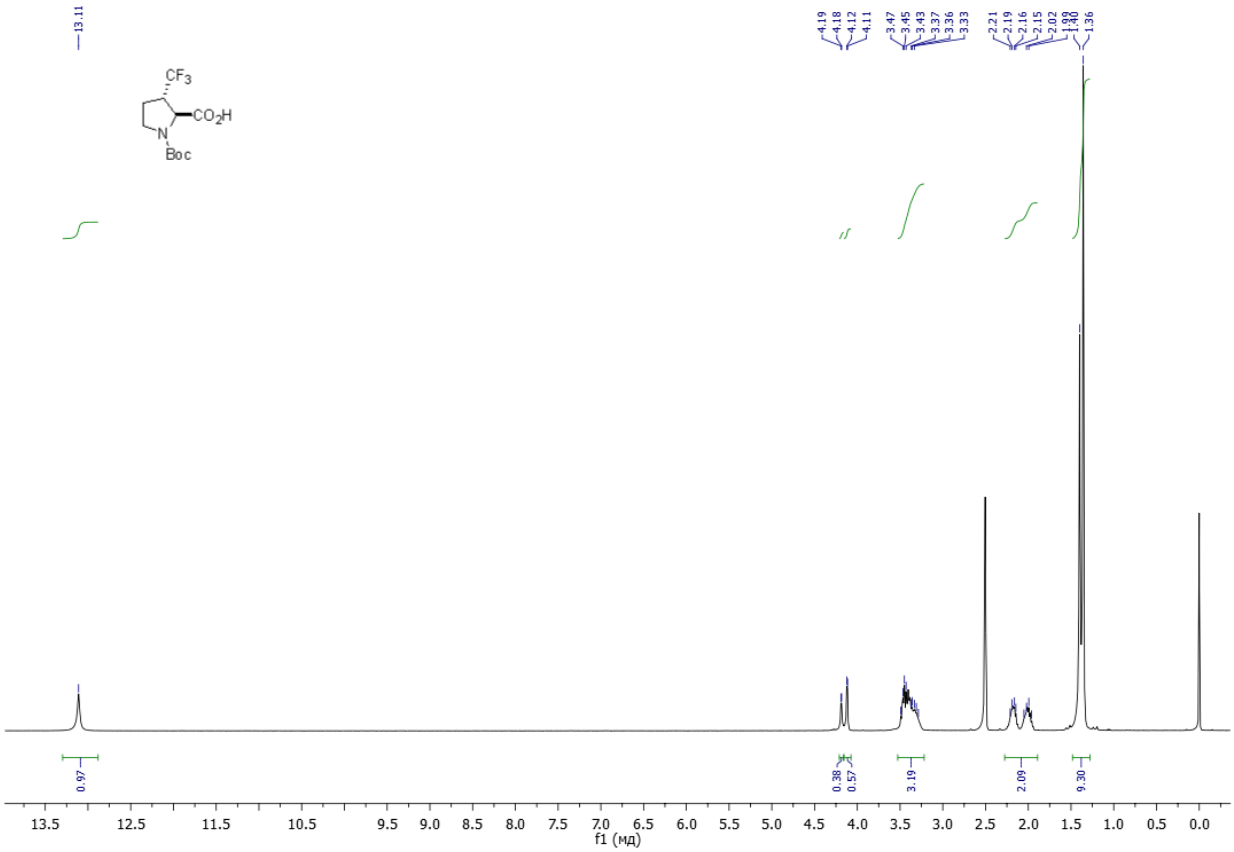
^{13}C NMR, compound ***trans*-1a**



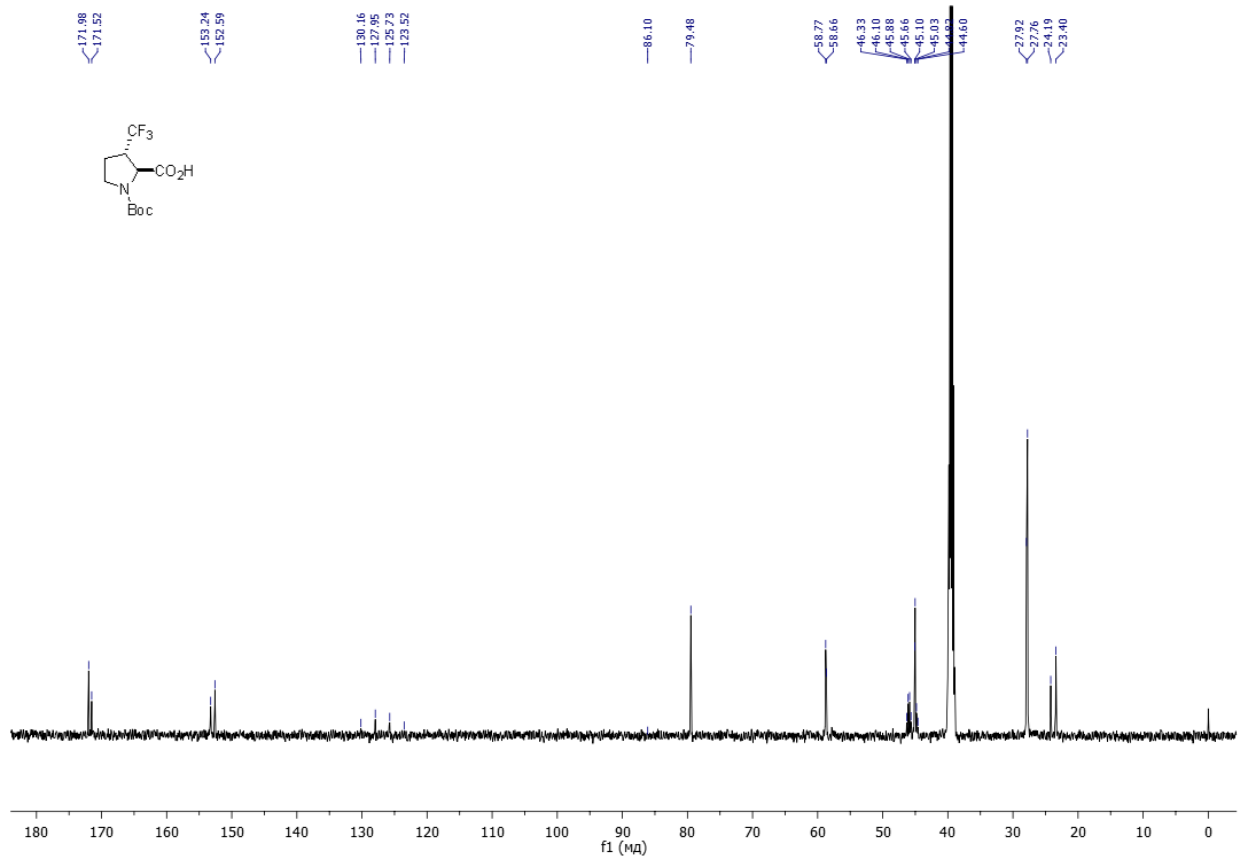
^{19}F NMR, compound ***trans*-1a**



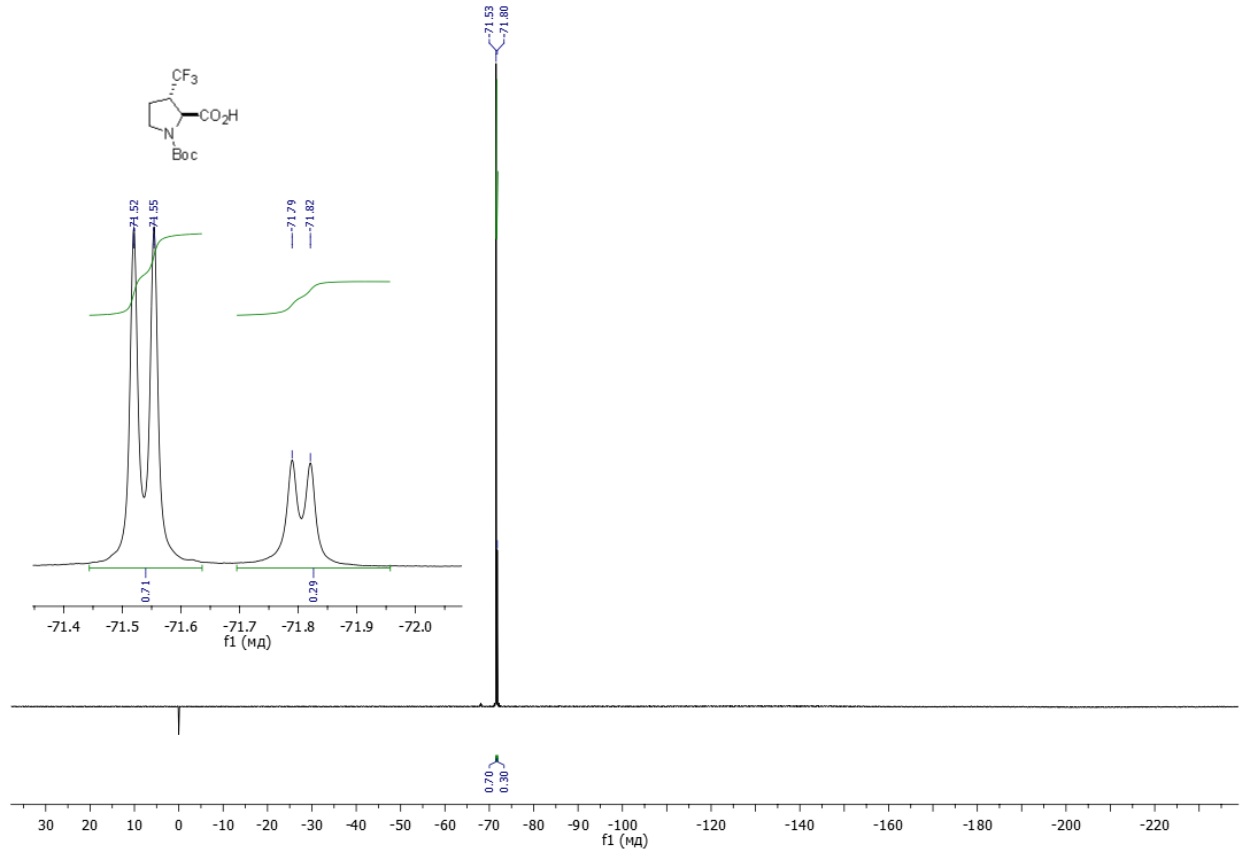
^{1}H NMR, compound ***trans*-10a**



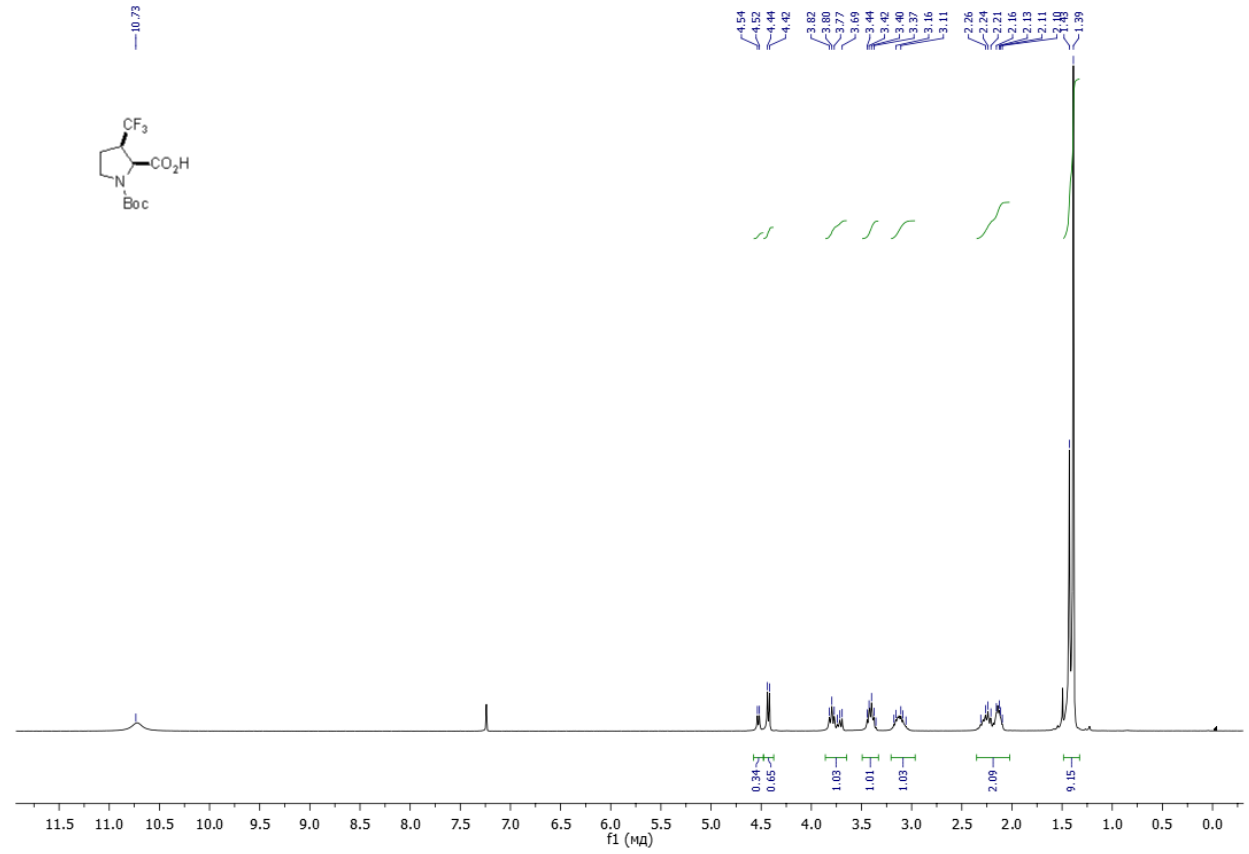
^{13}H NMR, compound ***trans*-10a**



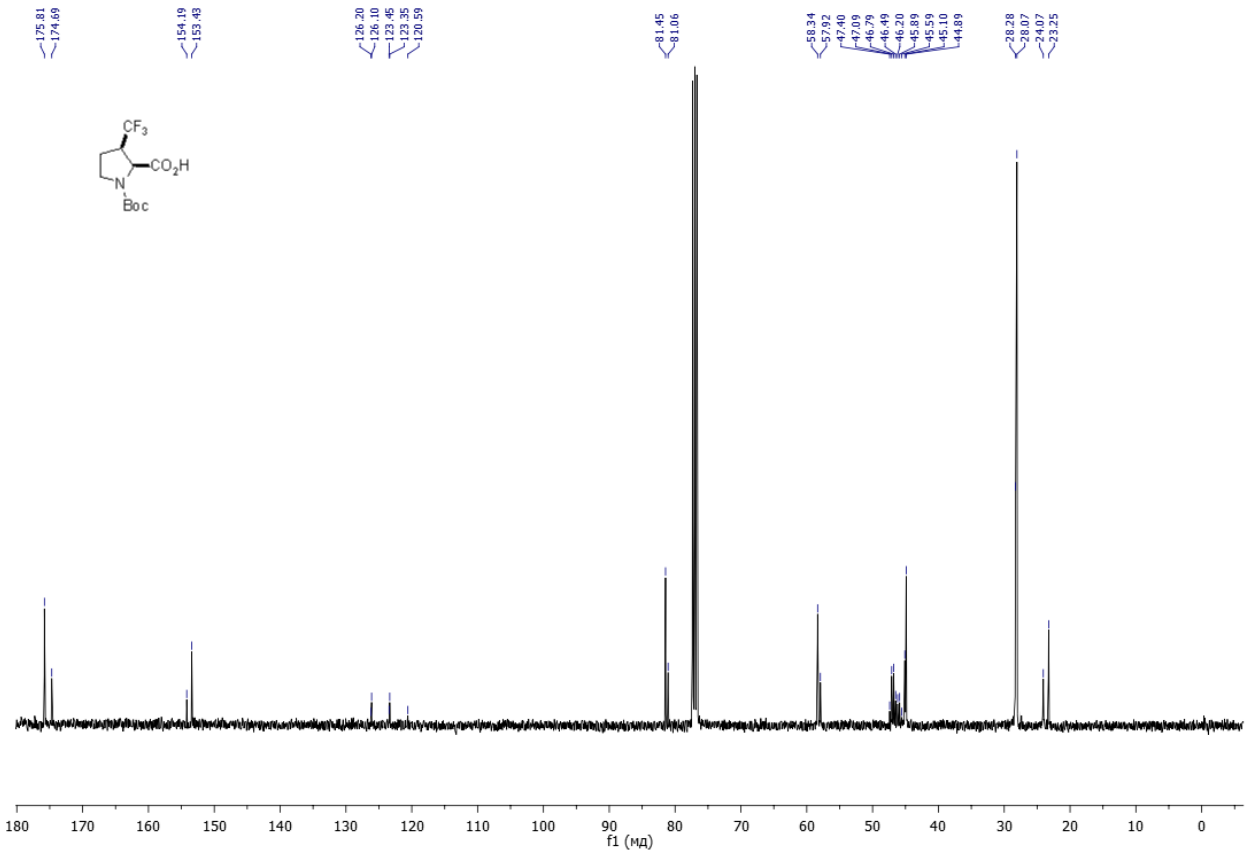
^{19}F NMR, compound ***trans*-10a**



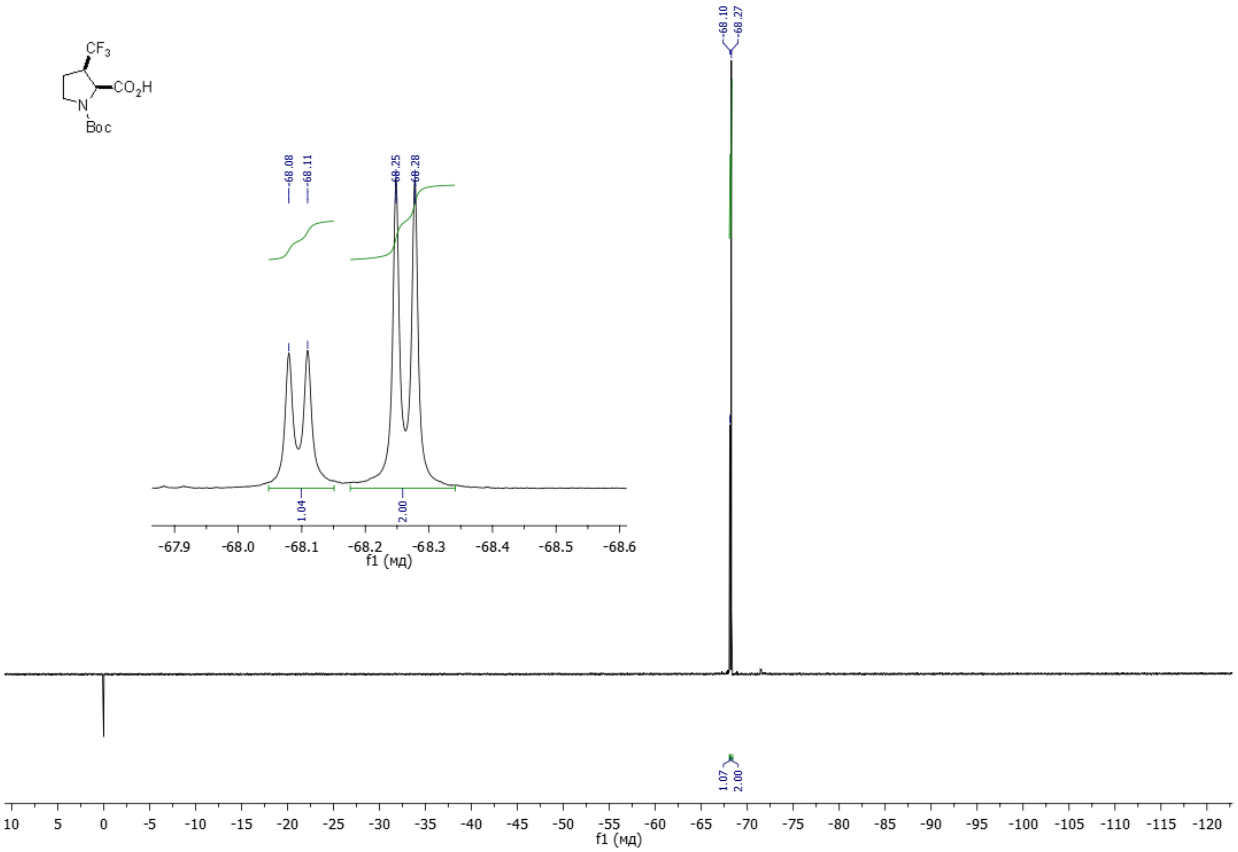
^{1}H NMR, compound ***cis*-10a**



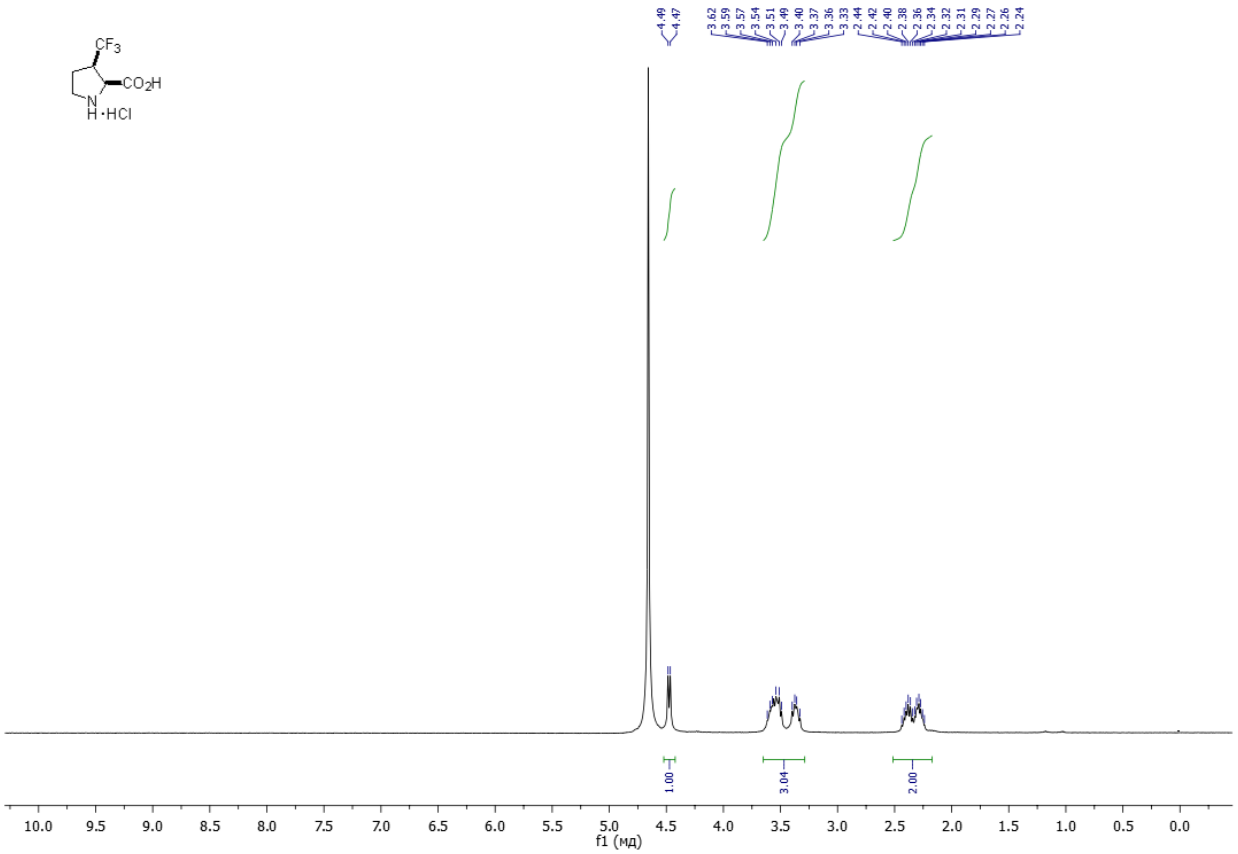
^{13}C NMR, compound ***cis*-10a**



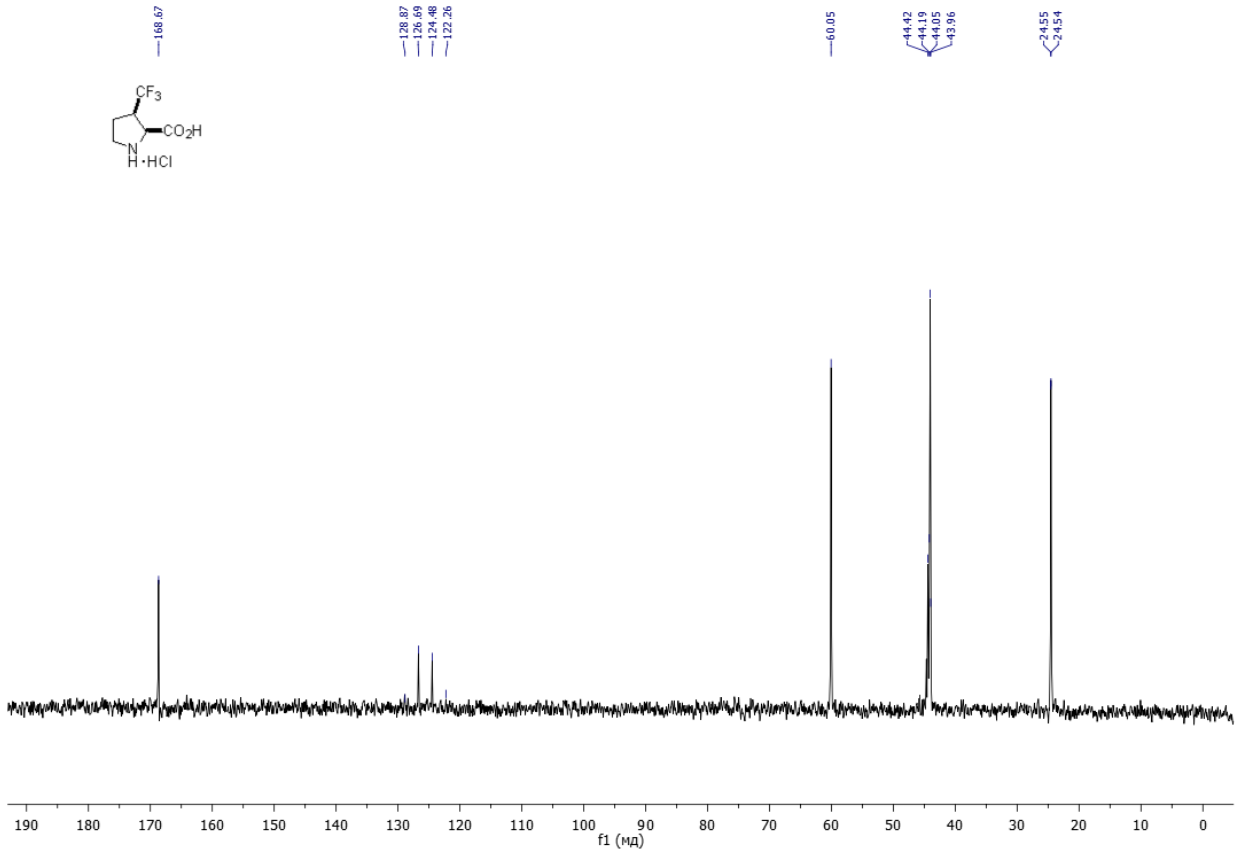
^{19}F NMR, compound ***cis*-10a**



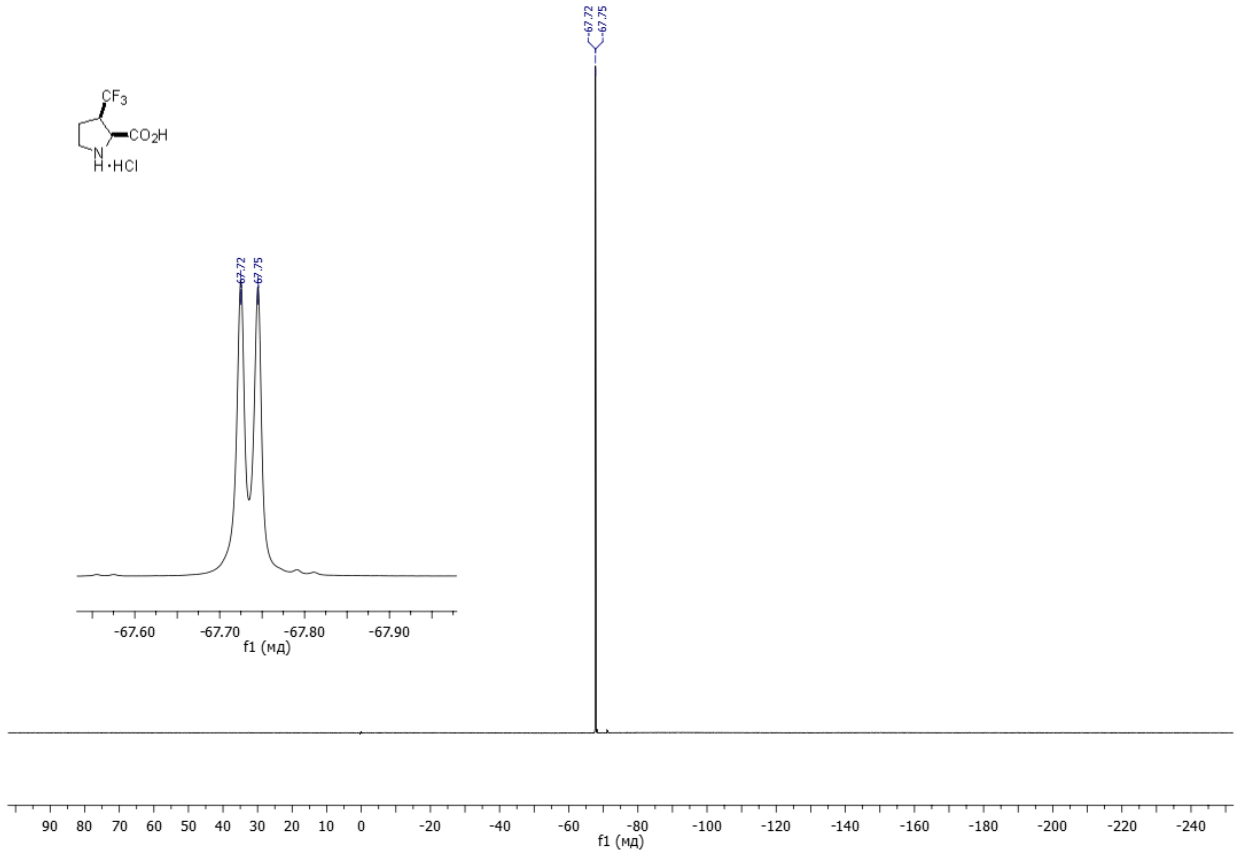
^{1}H NMR, compound ***cis*-1a**



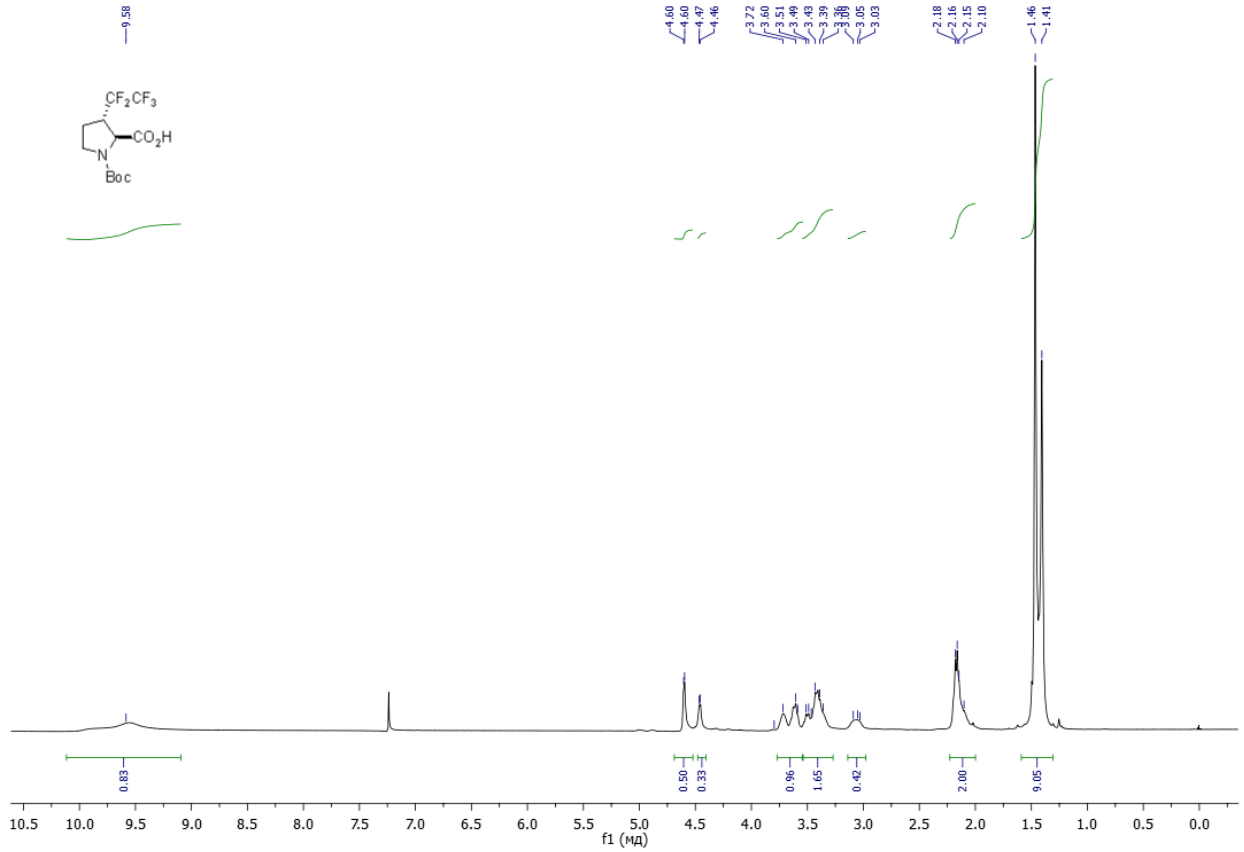
^{13}C NMR, compound ***cis*-1a**



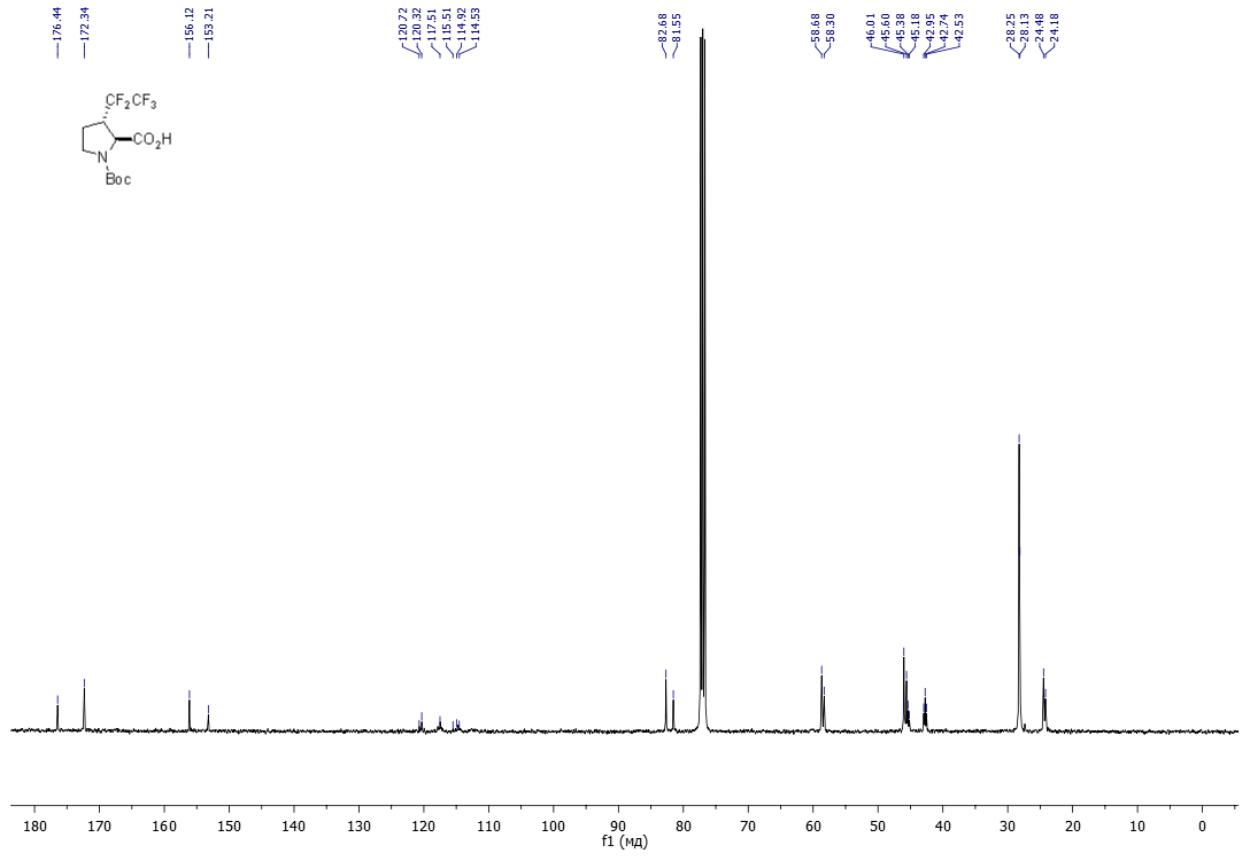
^{19}F NMR, compound ***cis*-1a**



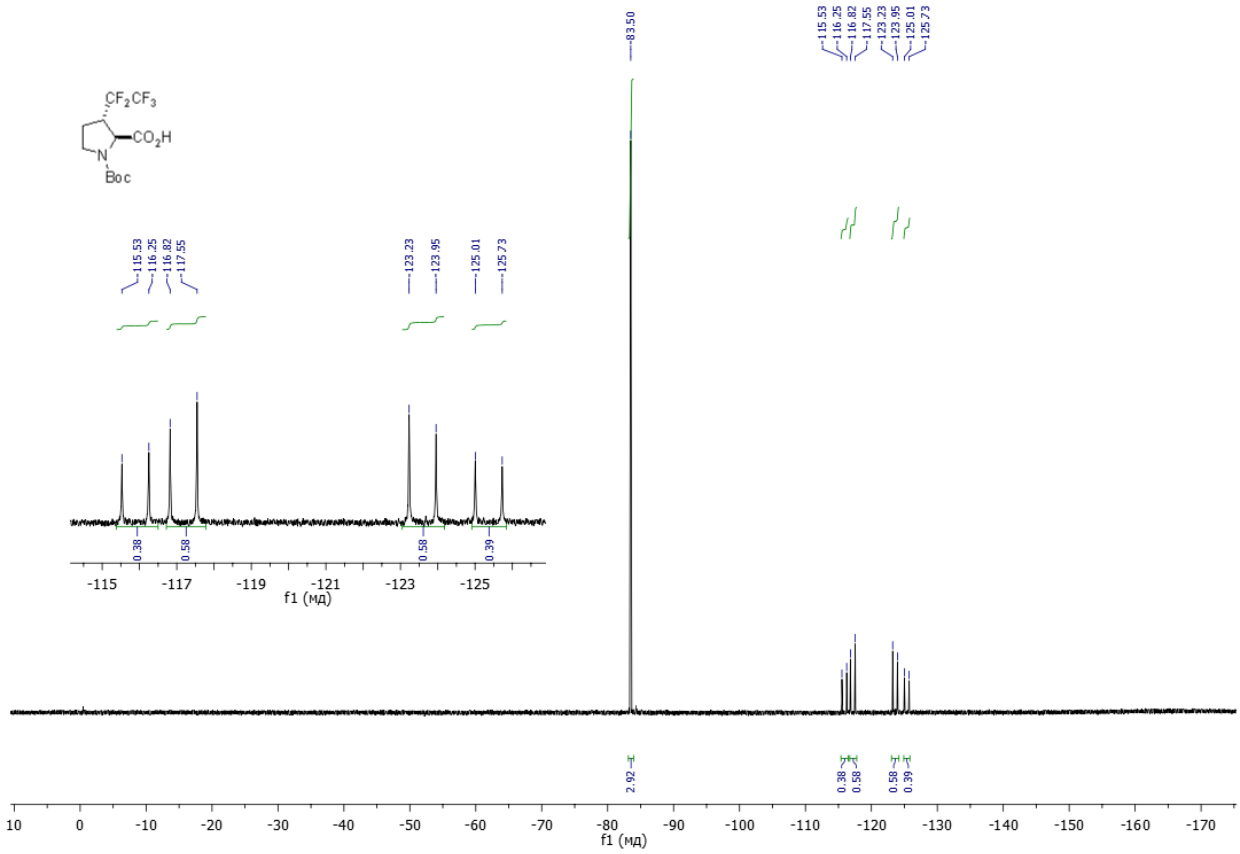
^{1}H NMR, compound ***trans*-10b**



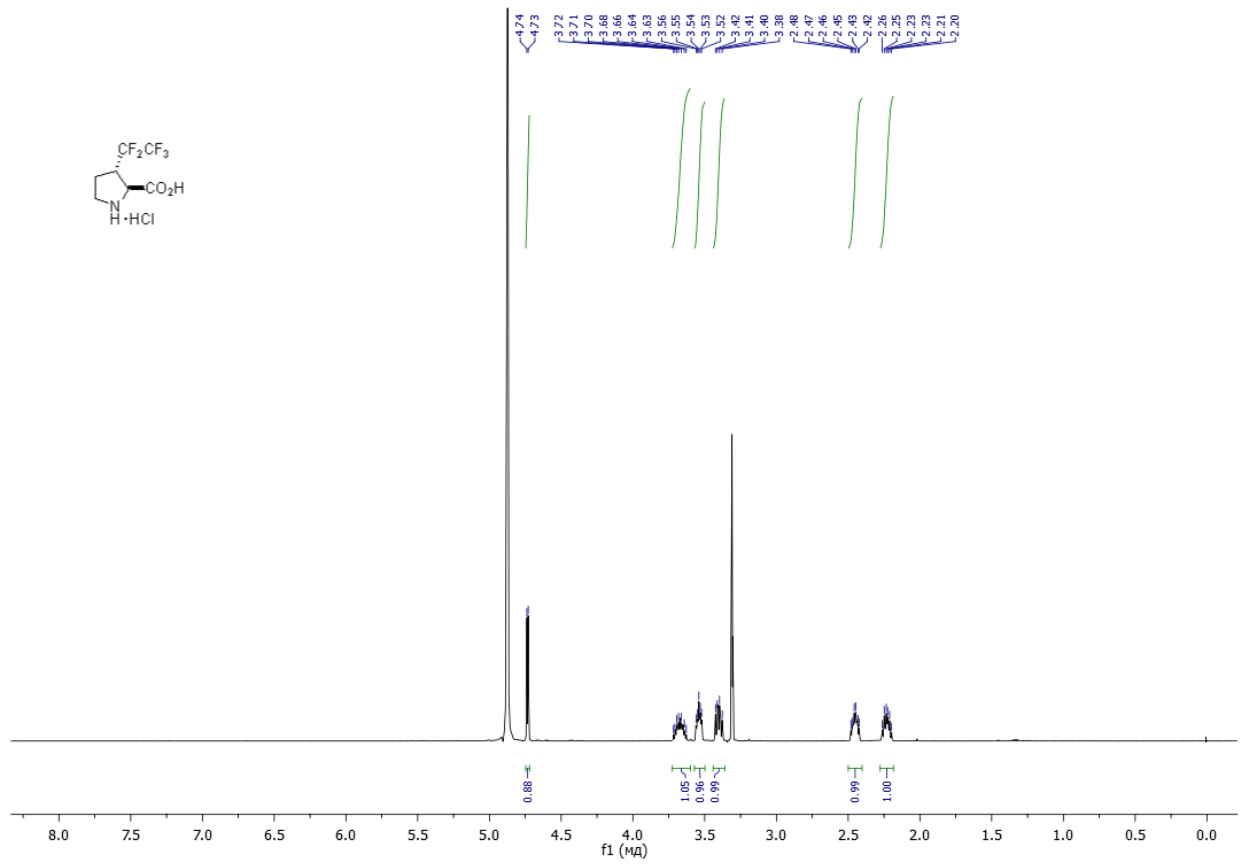
^{13}C NMR, compound ***trans*-10b**



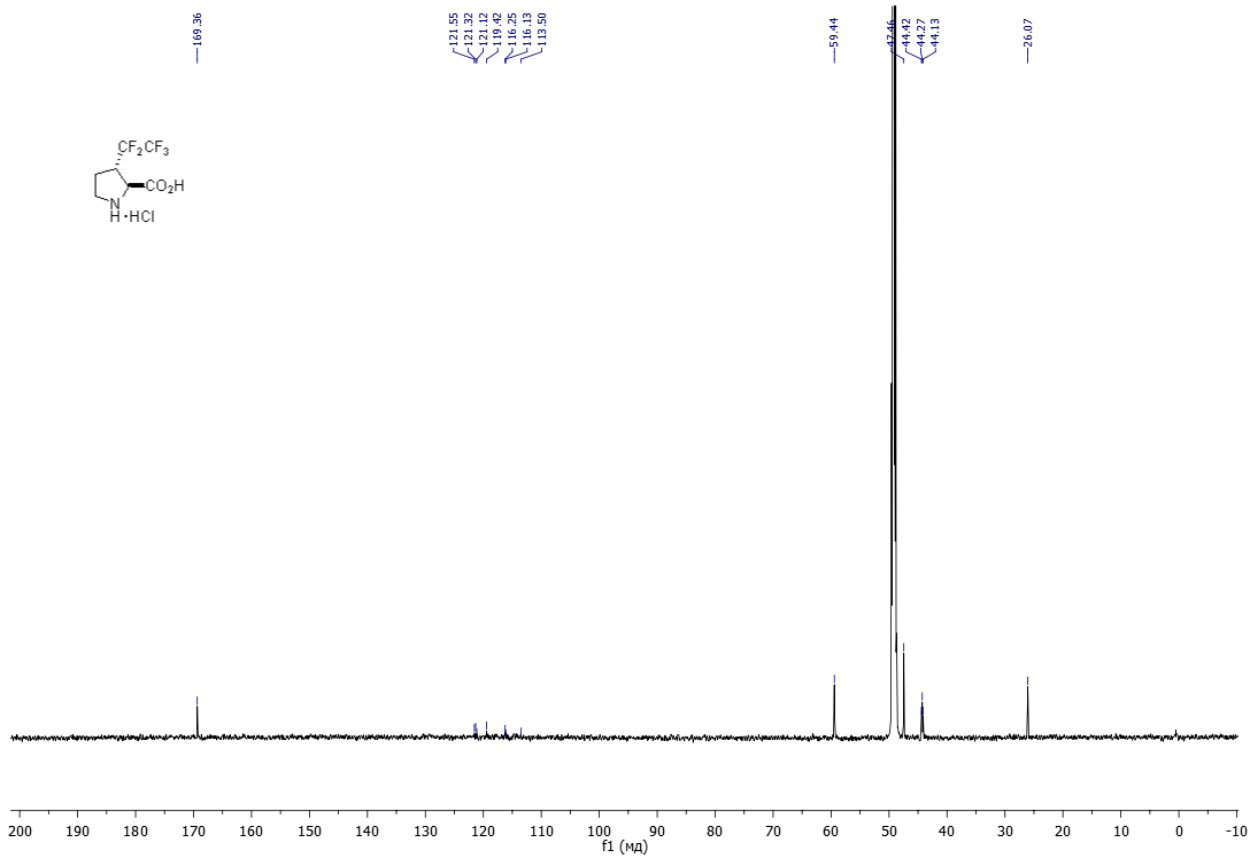
$^{19}F\{^{1}H\}$ NMR, compound ***trans*-10b**



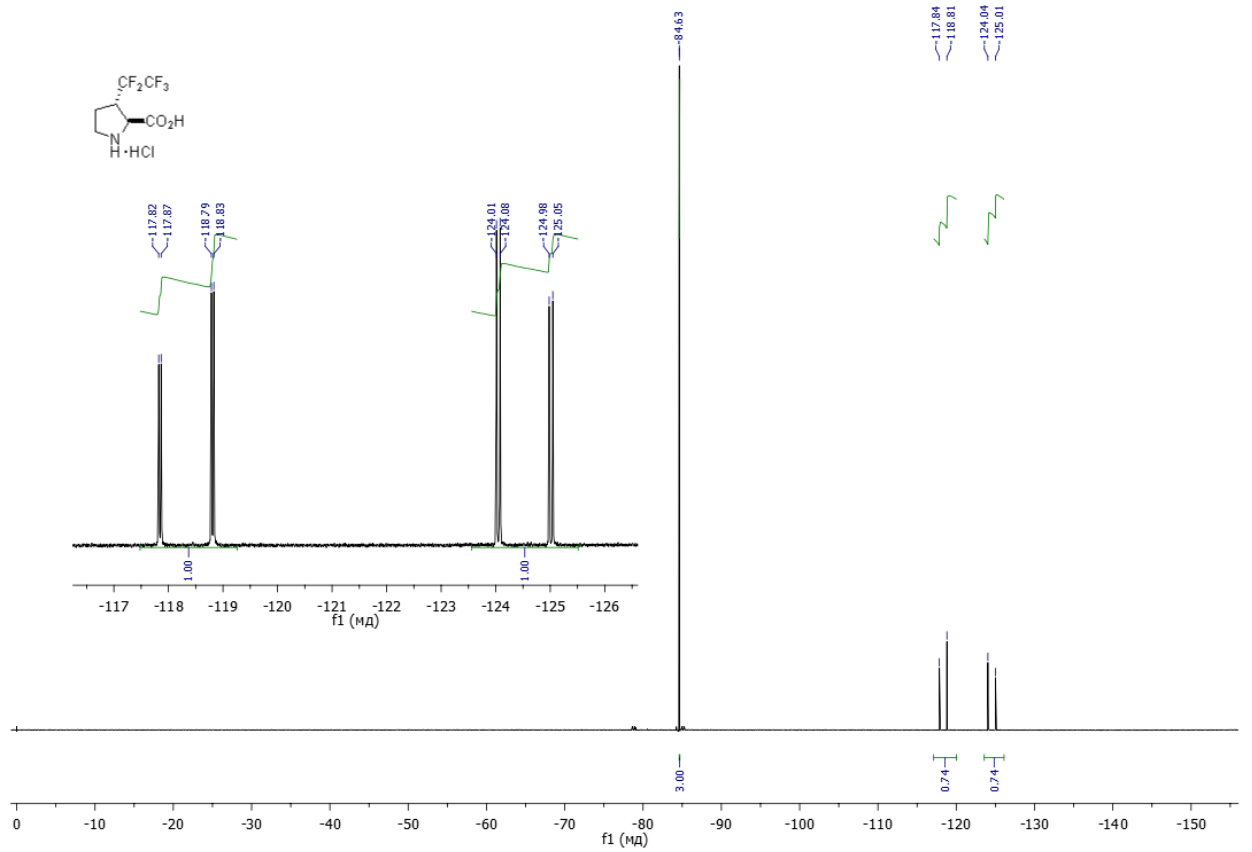
^{1}H NMR, compound ***trans*-1b**



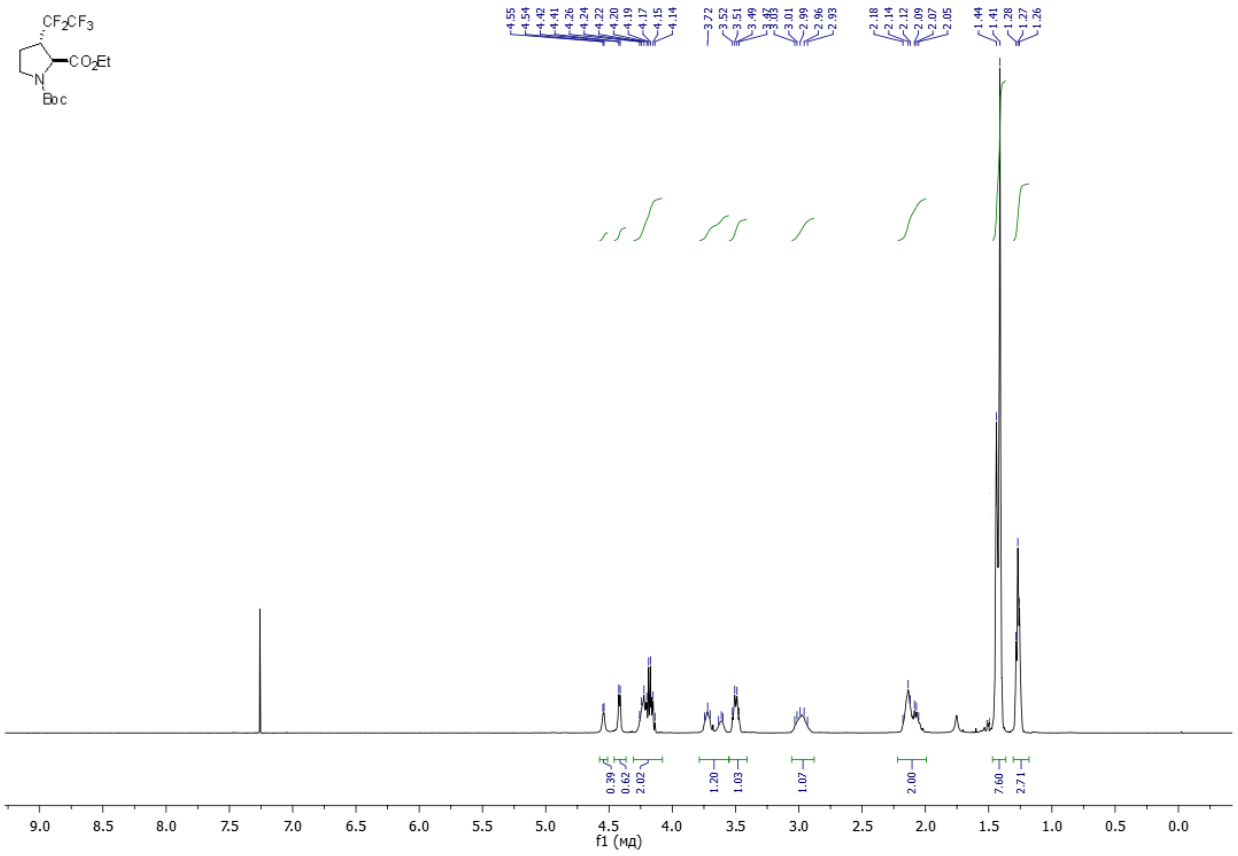
^{13}C NMR, compound ***trans*-1b**



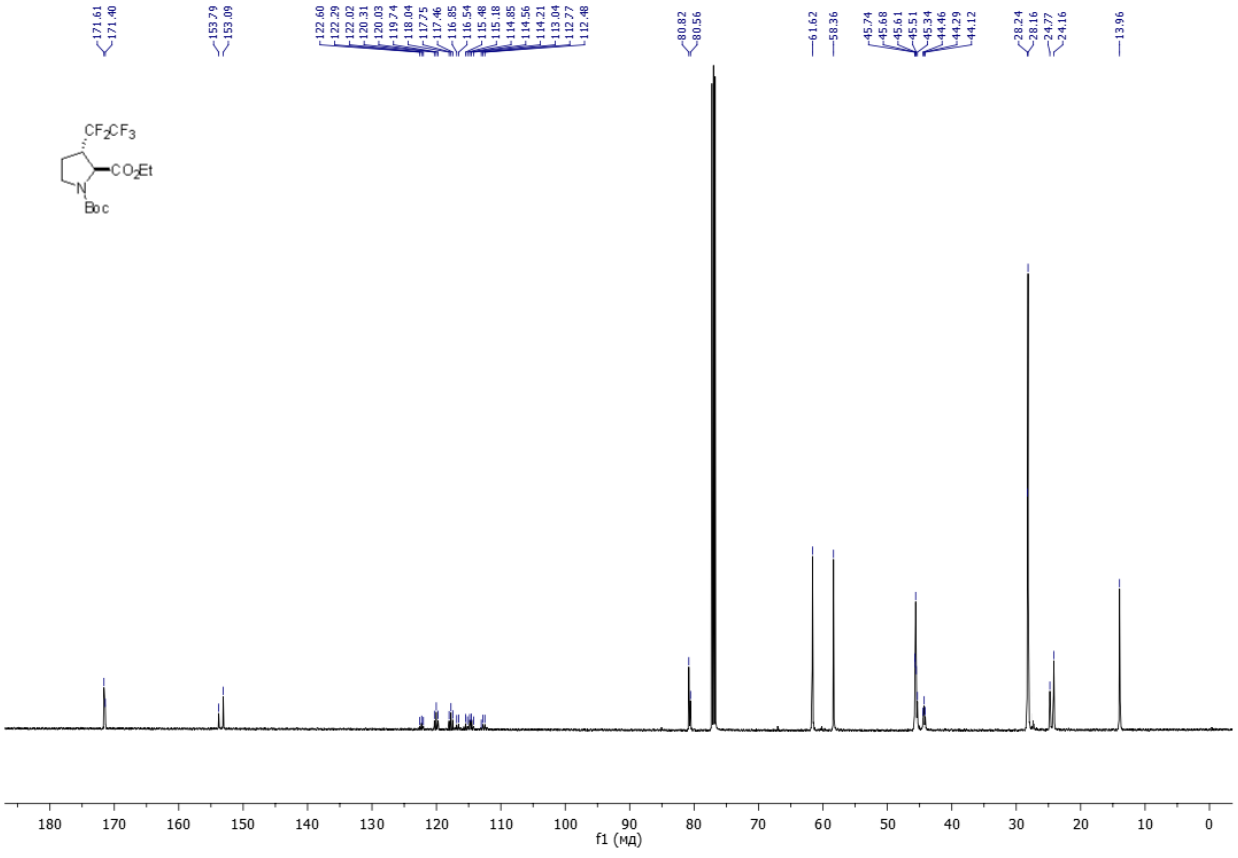
^{19}F NMR, compound ***trans*-1b**



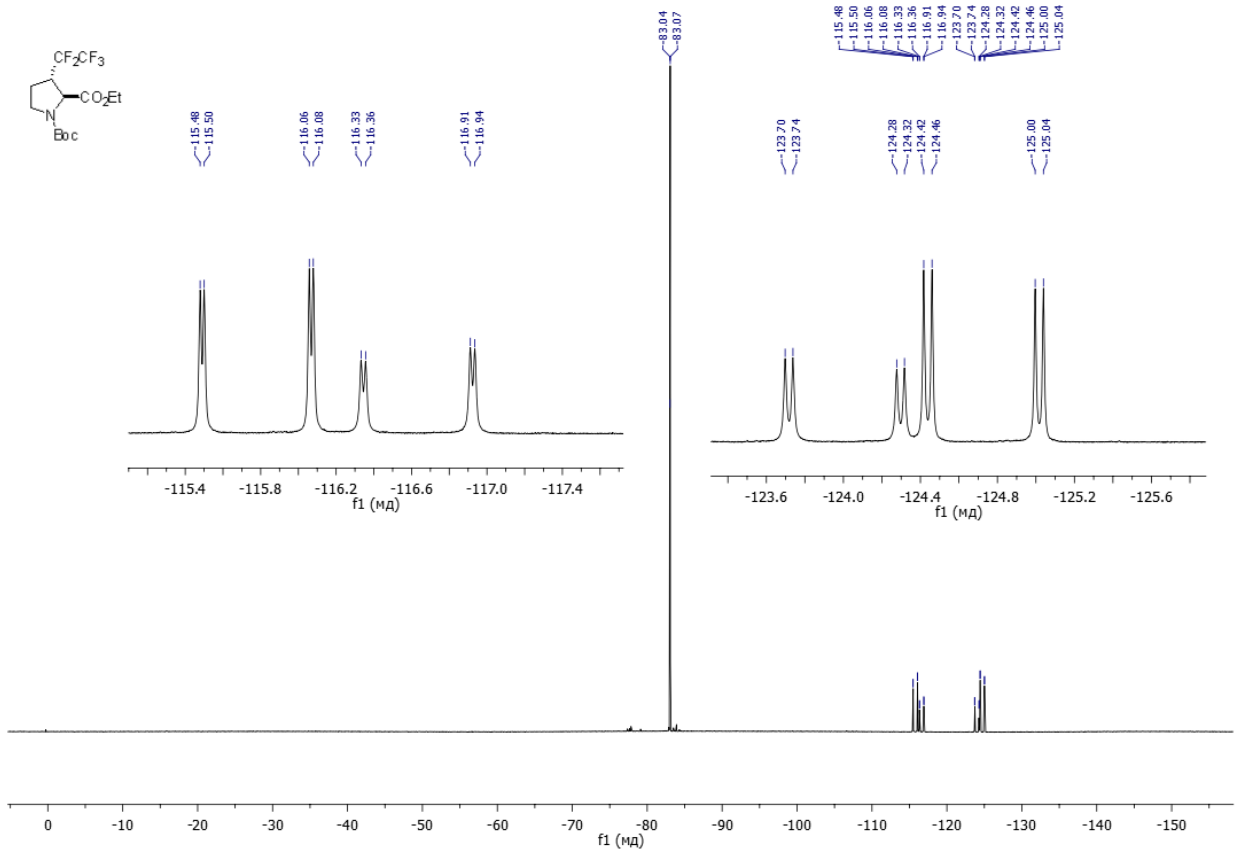
^{1}H NMR, compound ***trans*-11b**



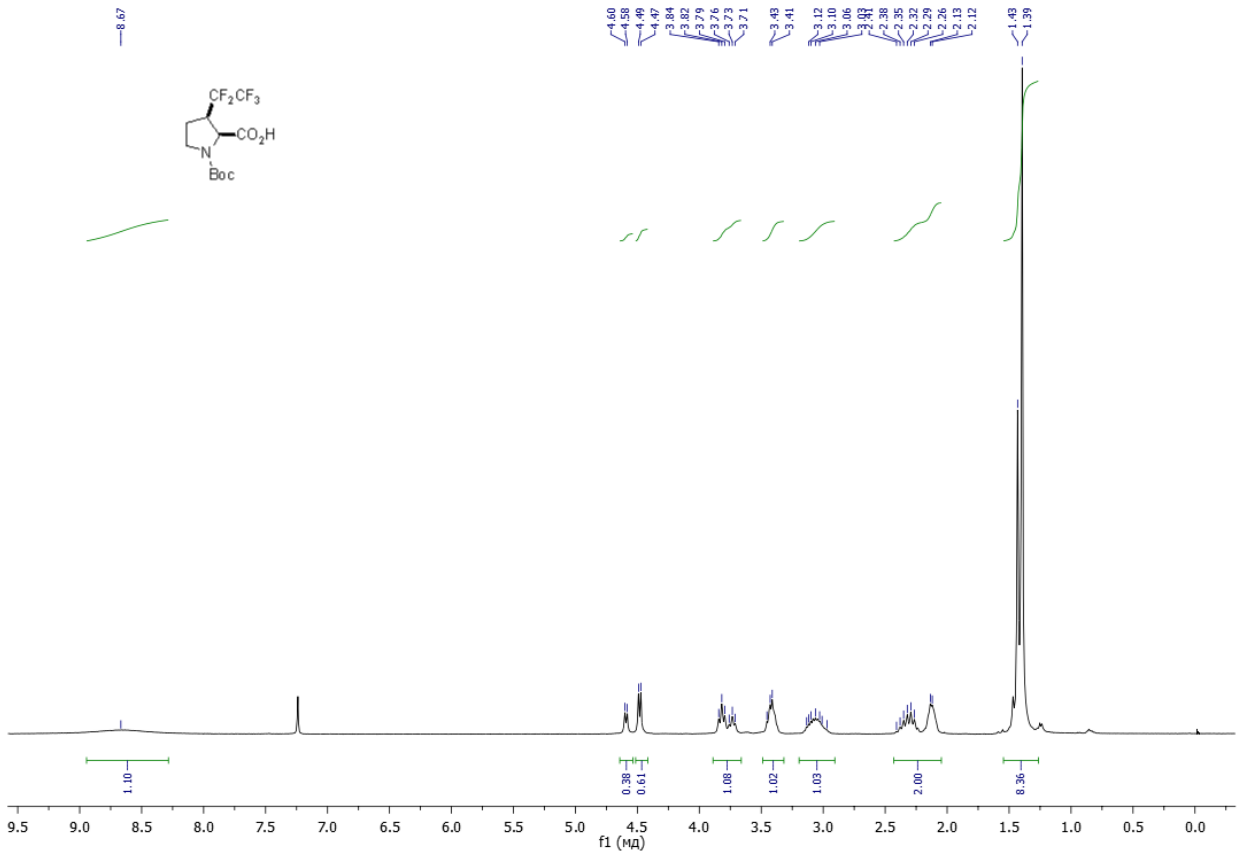
^{13}C NMR, compound ***trans*-11b**



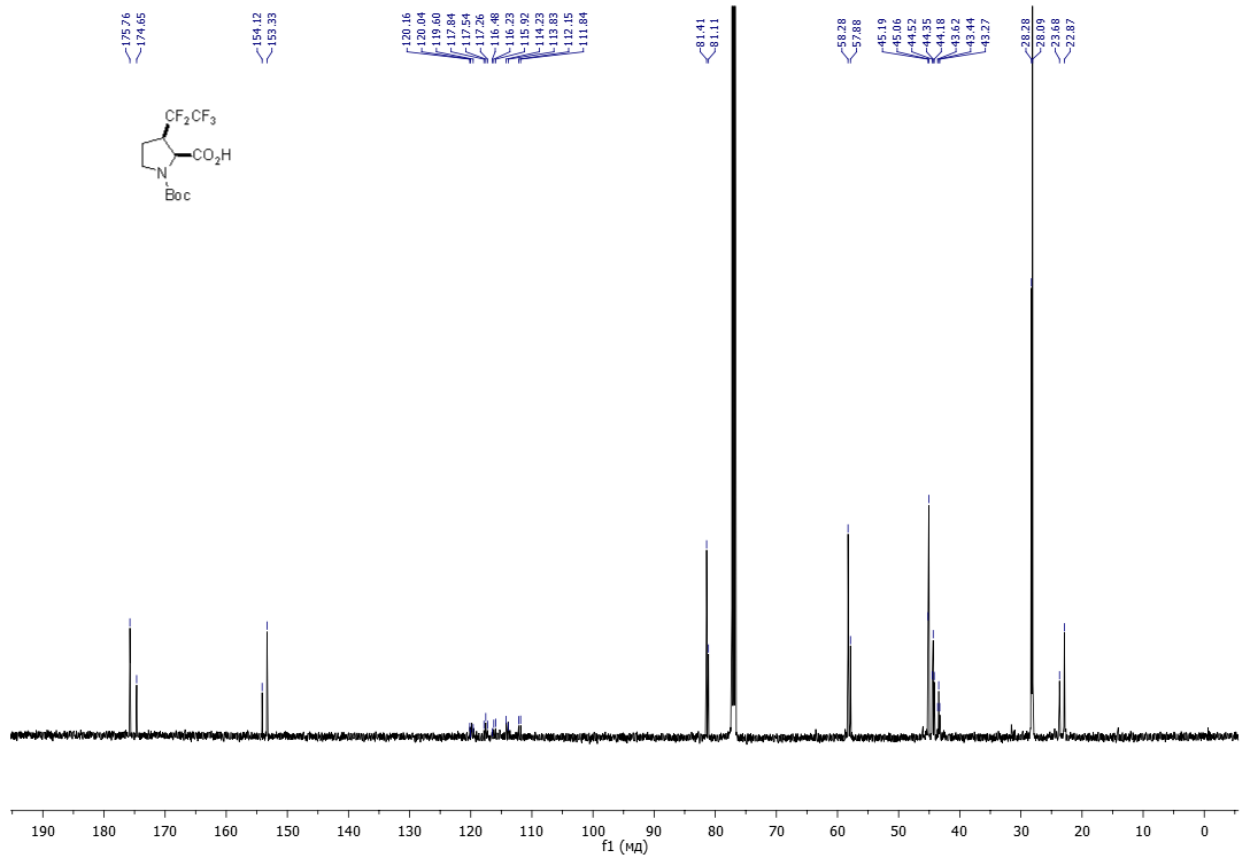
^{19}F NMR, compound ***trans*-11b**



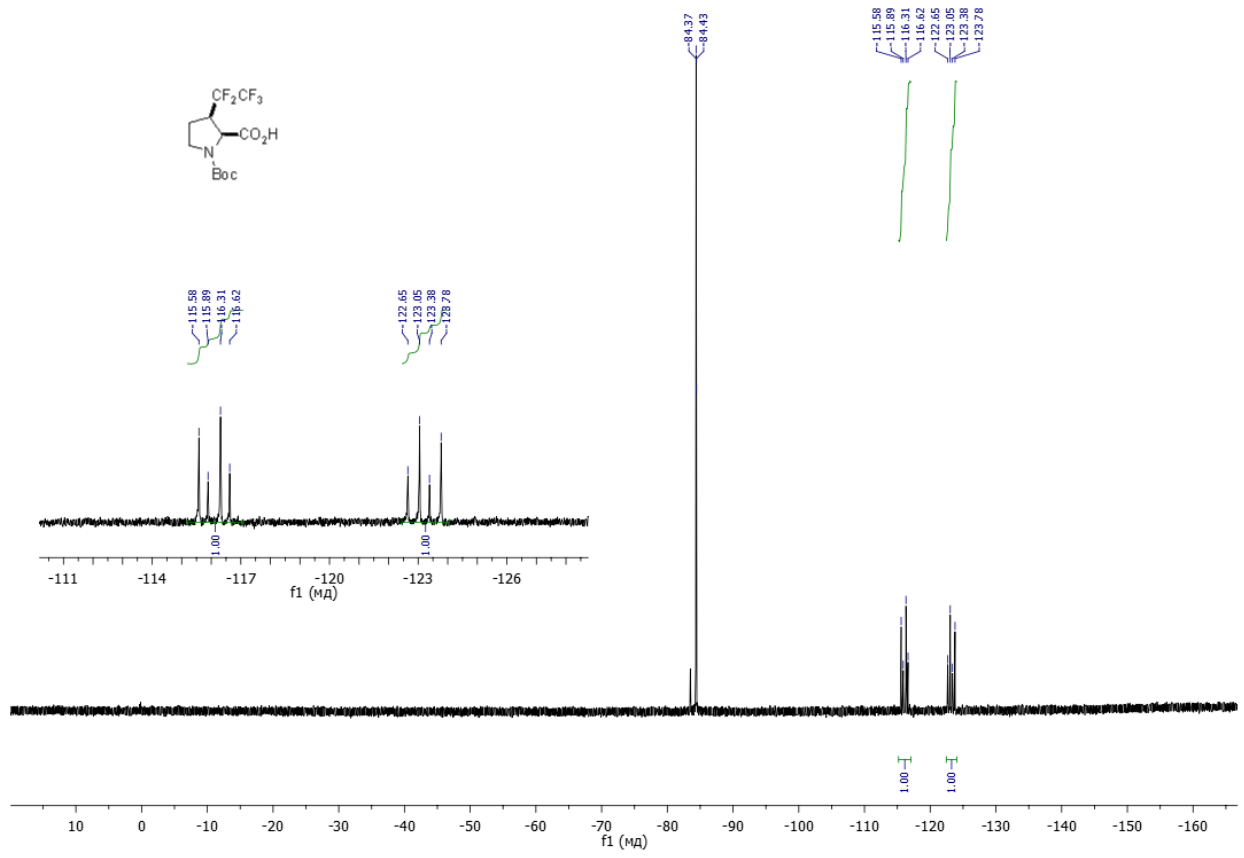
^{1}H NMR, compound ***cis*-10b**



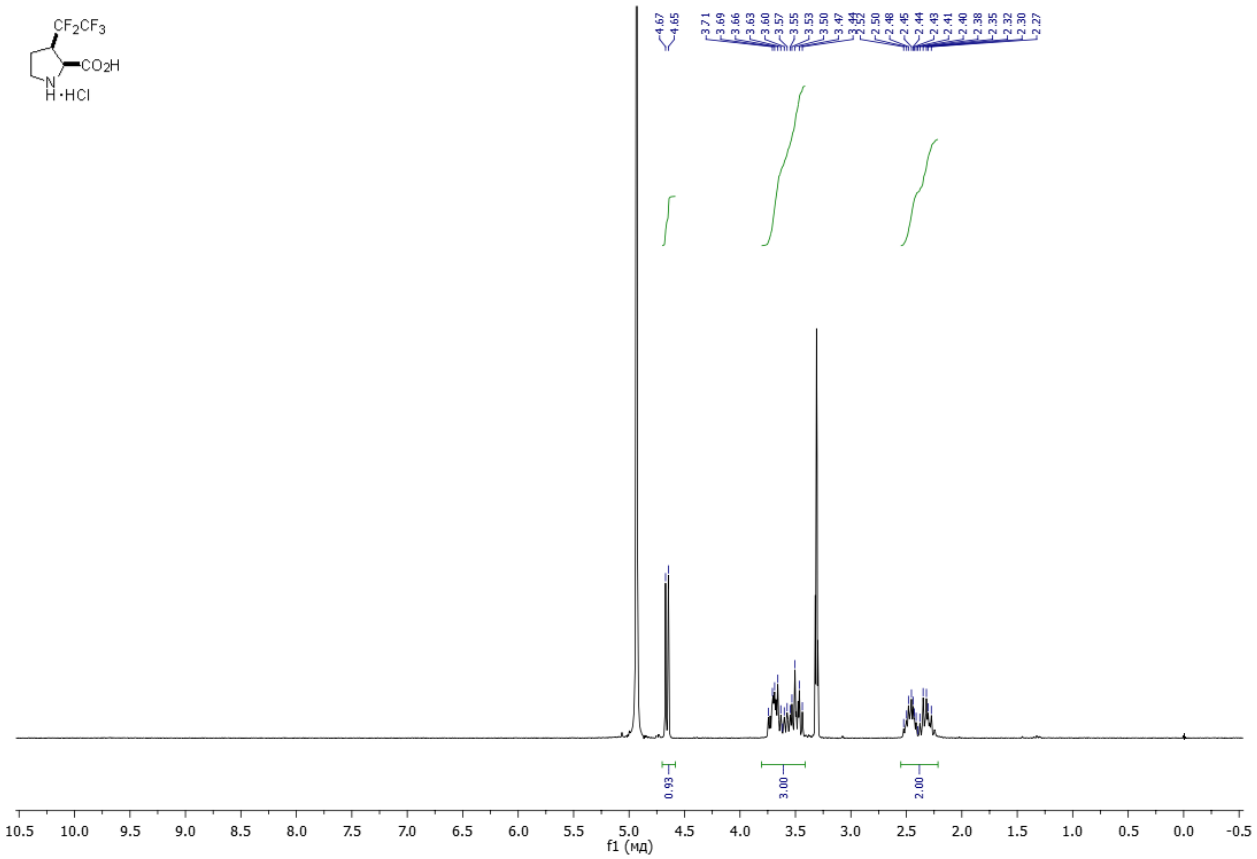
^{13}C NMR, compound ***cis*-10b**



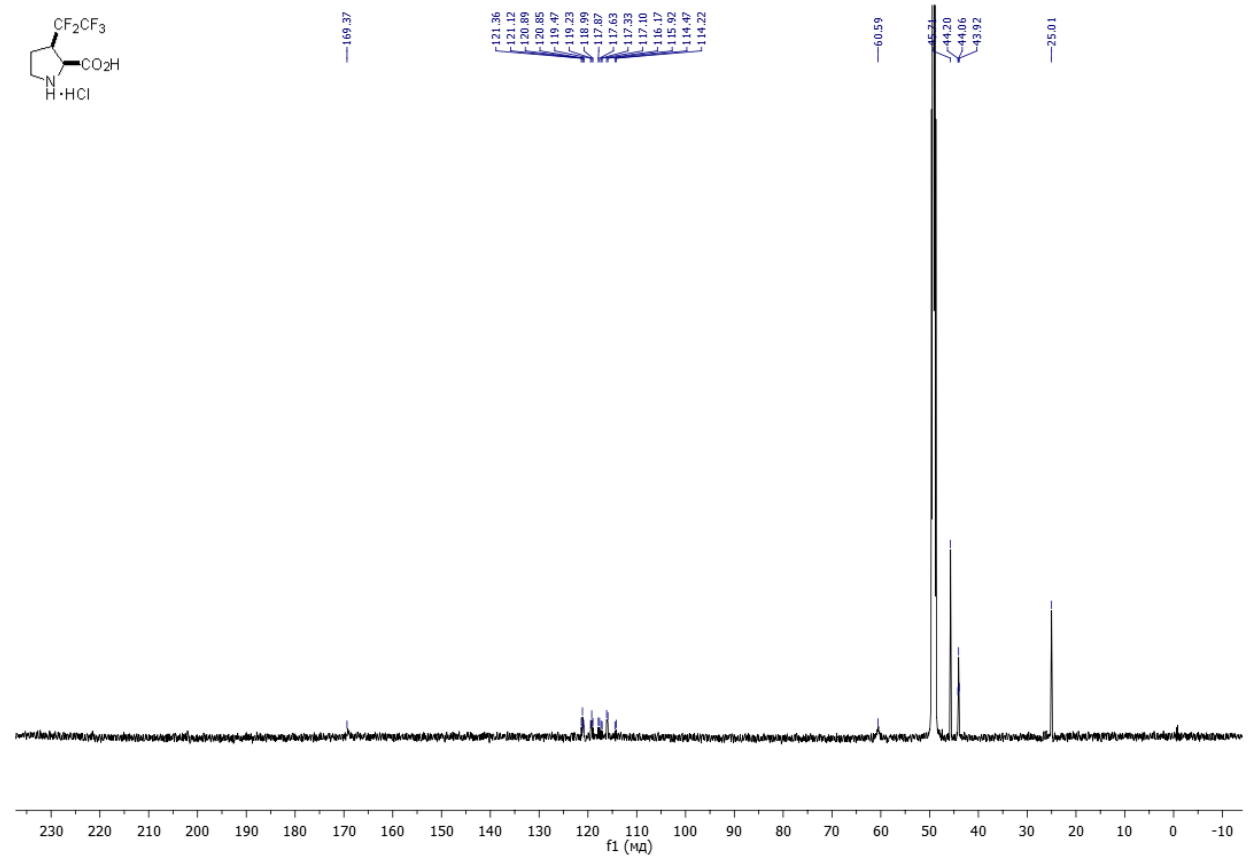
^{19}F NMR, compound ***cis*-10b**



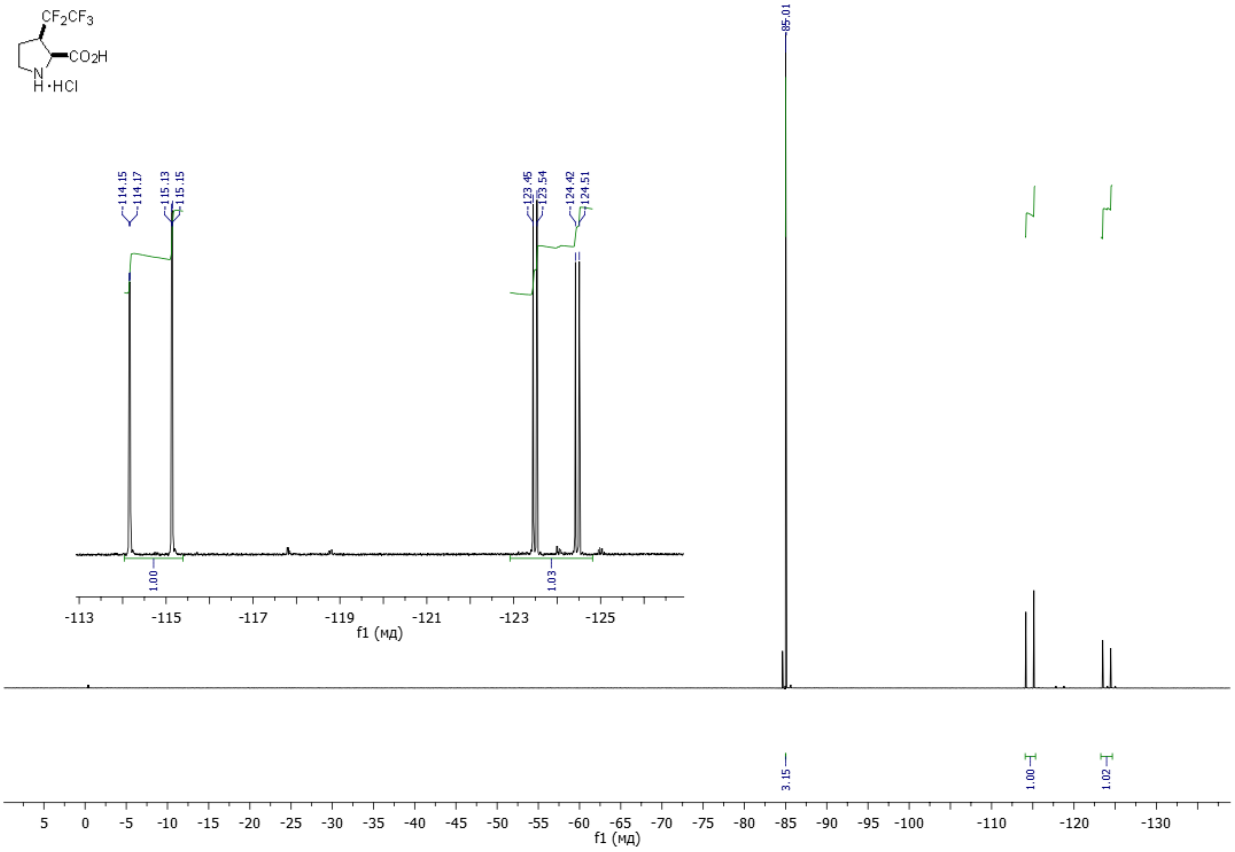
^{1}H NMR, compound ***cis*-1b**



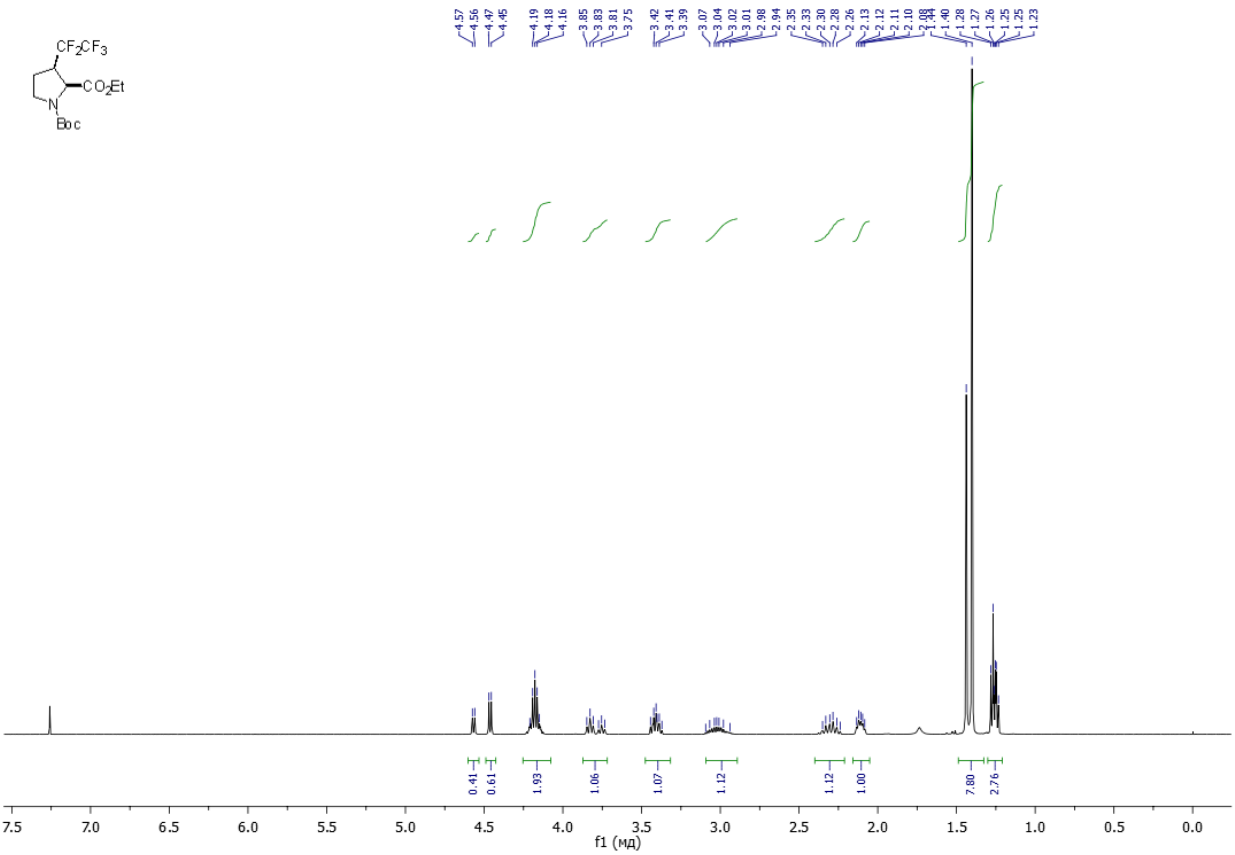
^{13}C NMR, compound ***cis*-1b**



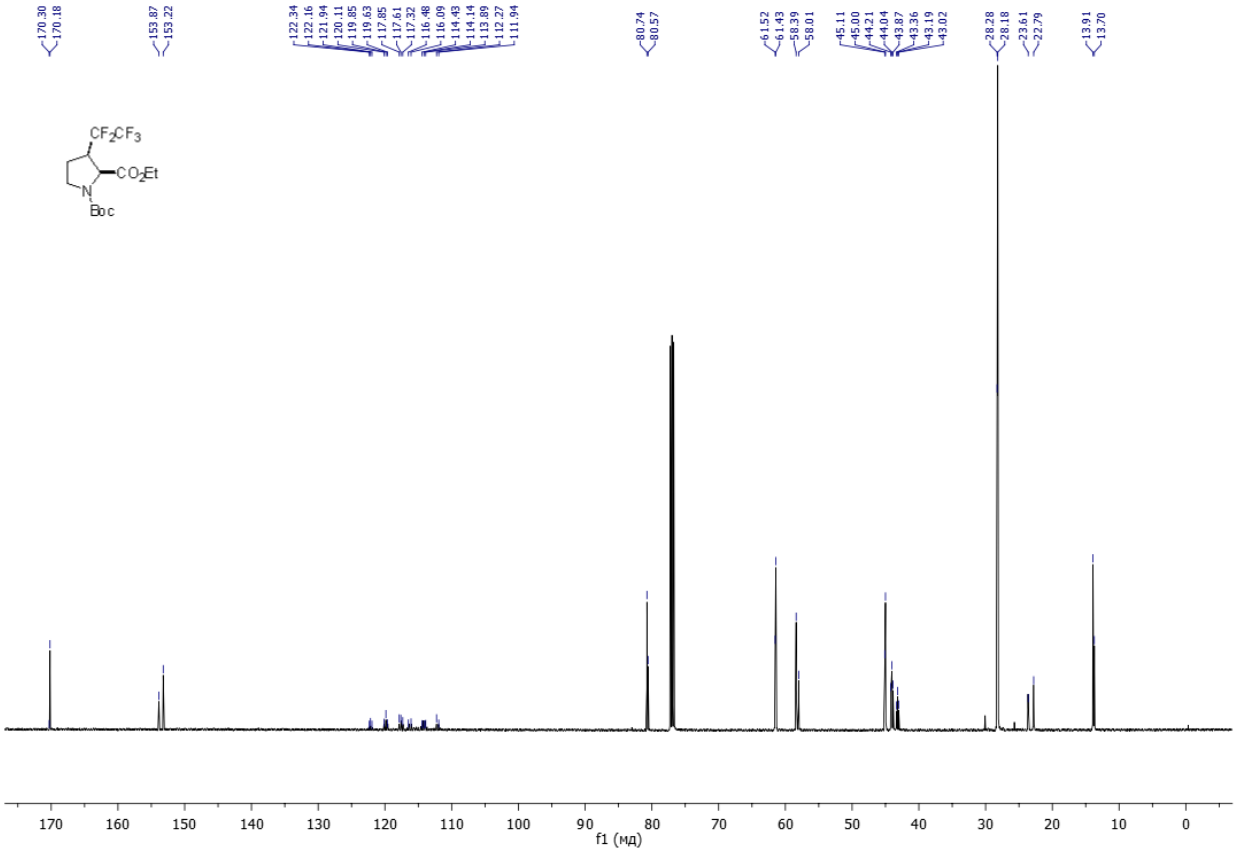
^{19}F NMR, compound ***cis*-1b**



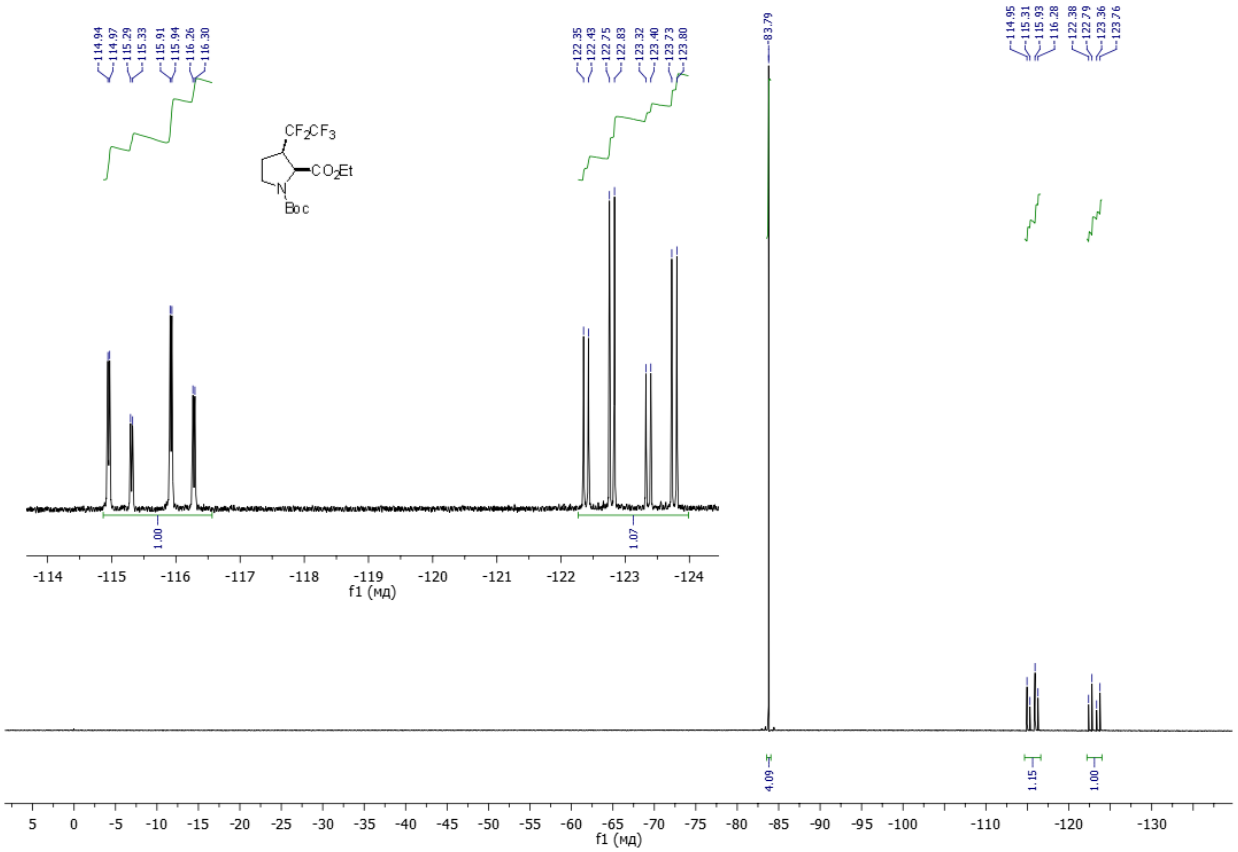
^{1}H NMR, compound ***cis*-11b**



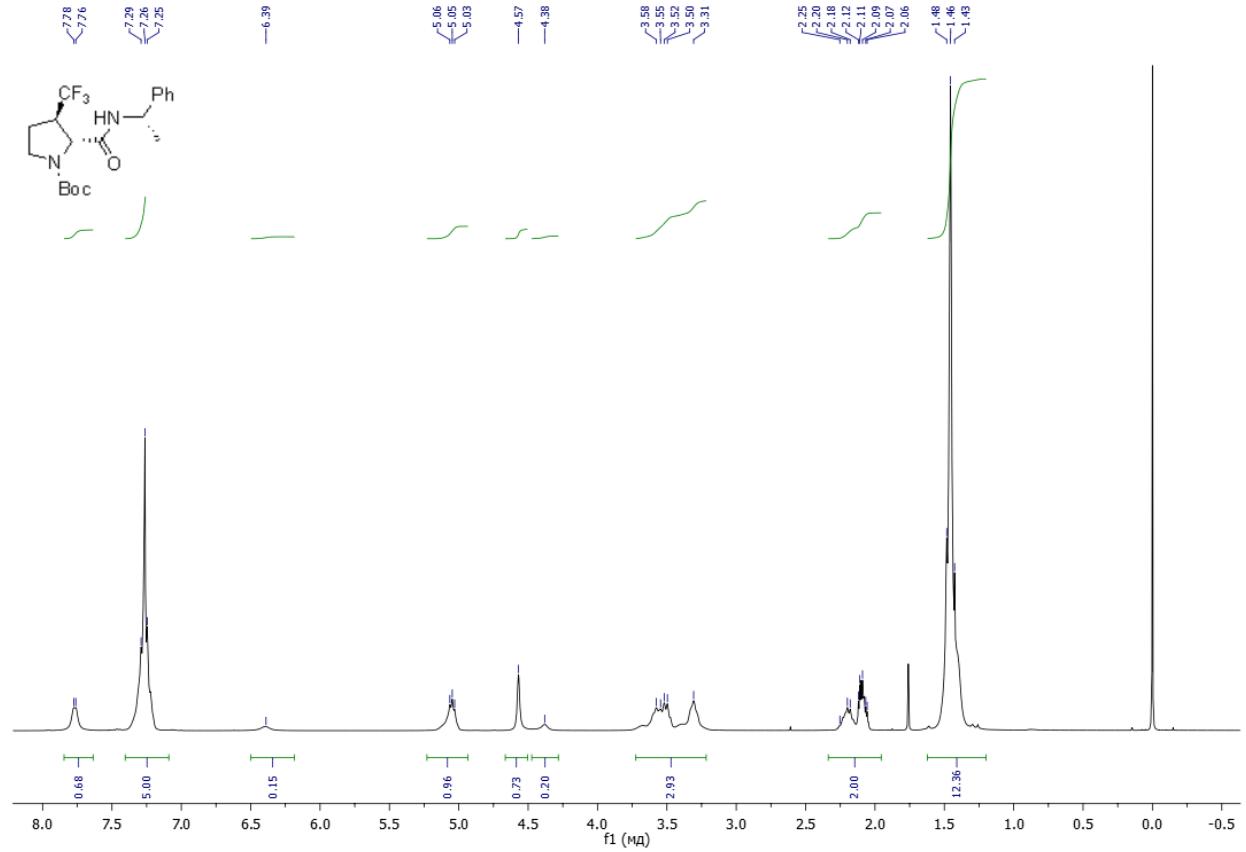
^{13}C NMR, compound ***cis*-11b**



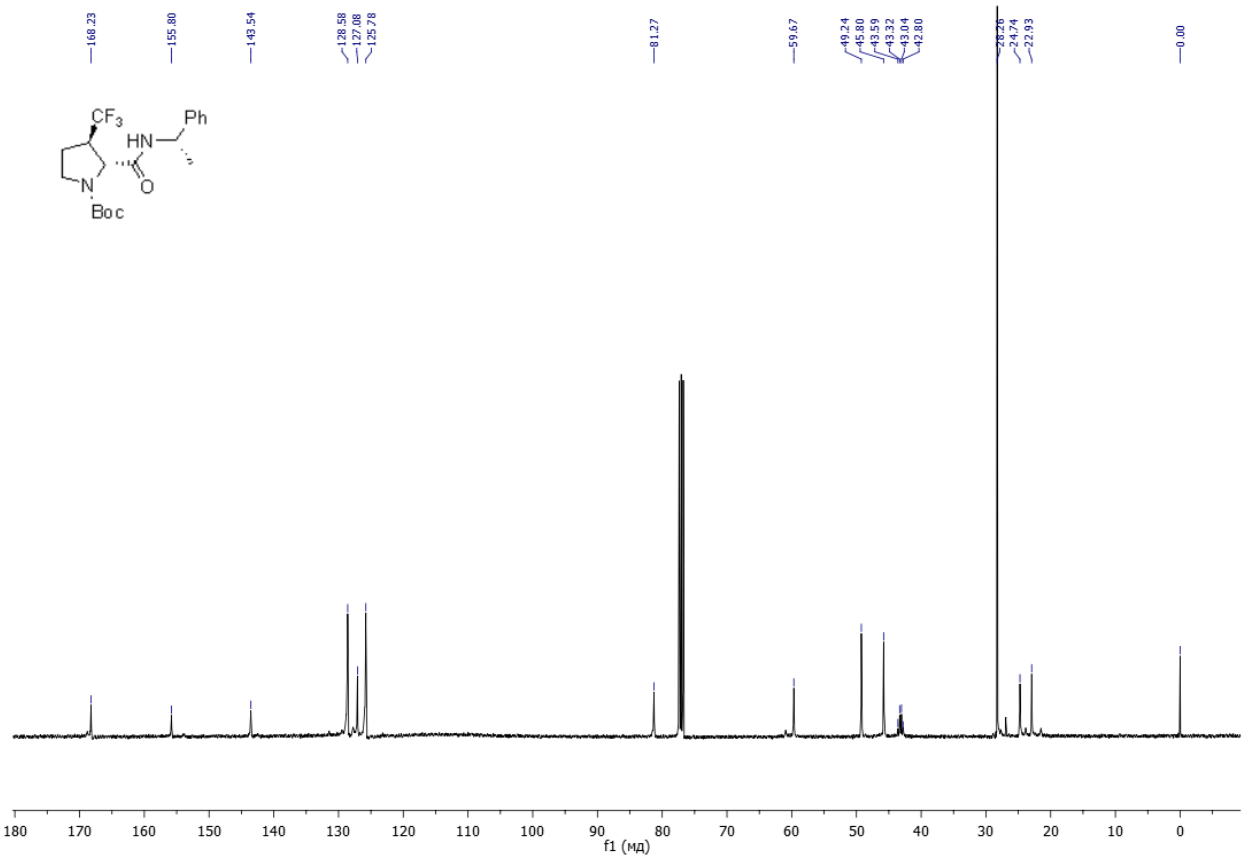
^{19}F NMR, compound ***cis*-11b**



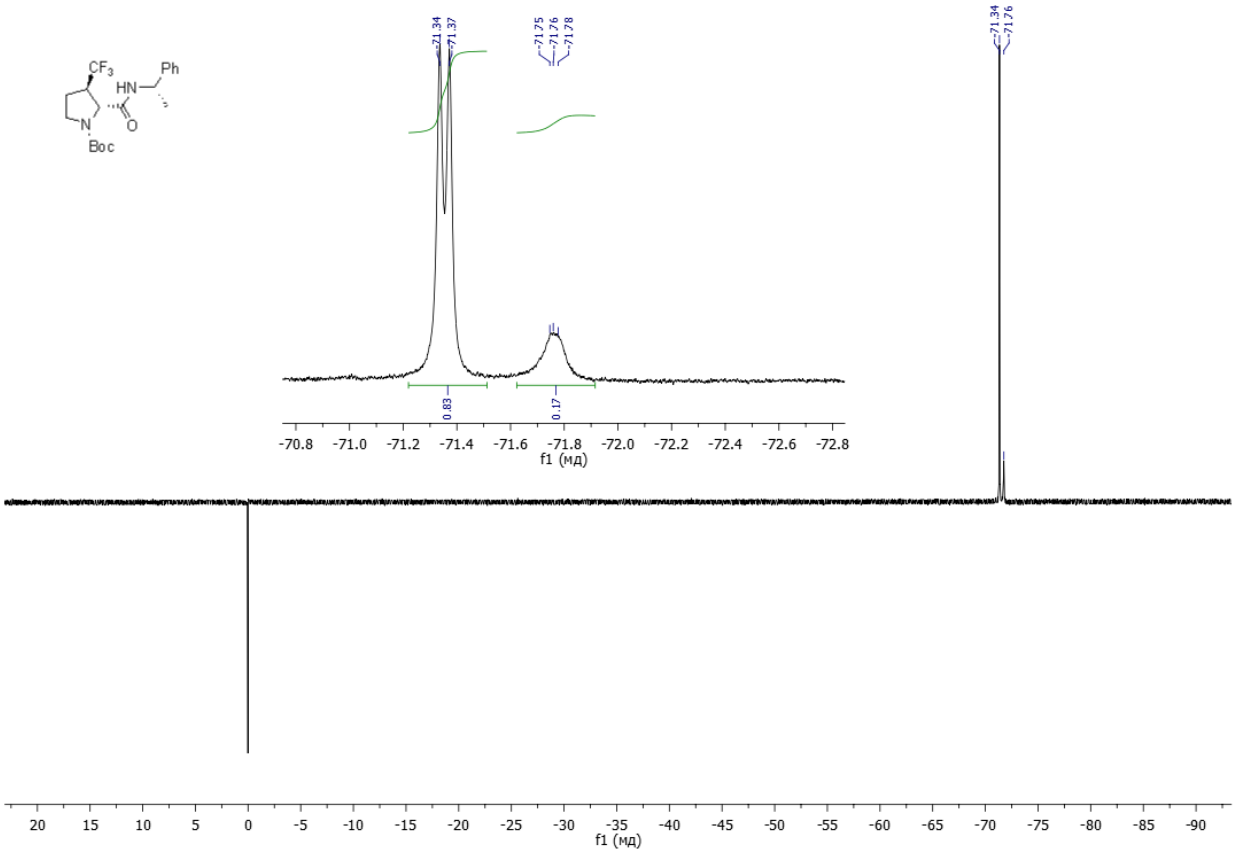
^{1}H NMR, compound **(*2R,3R*)-12a**



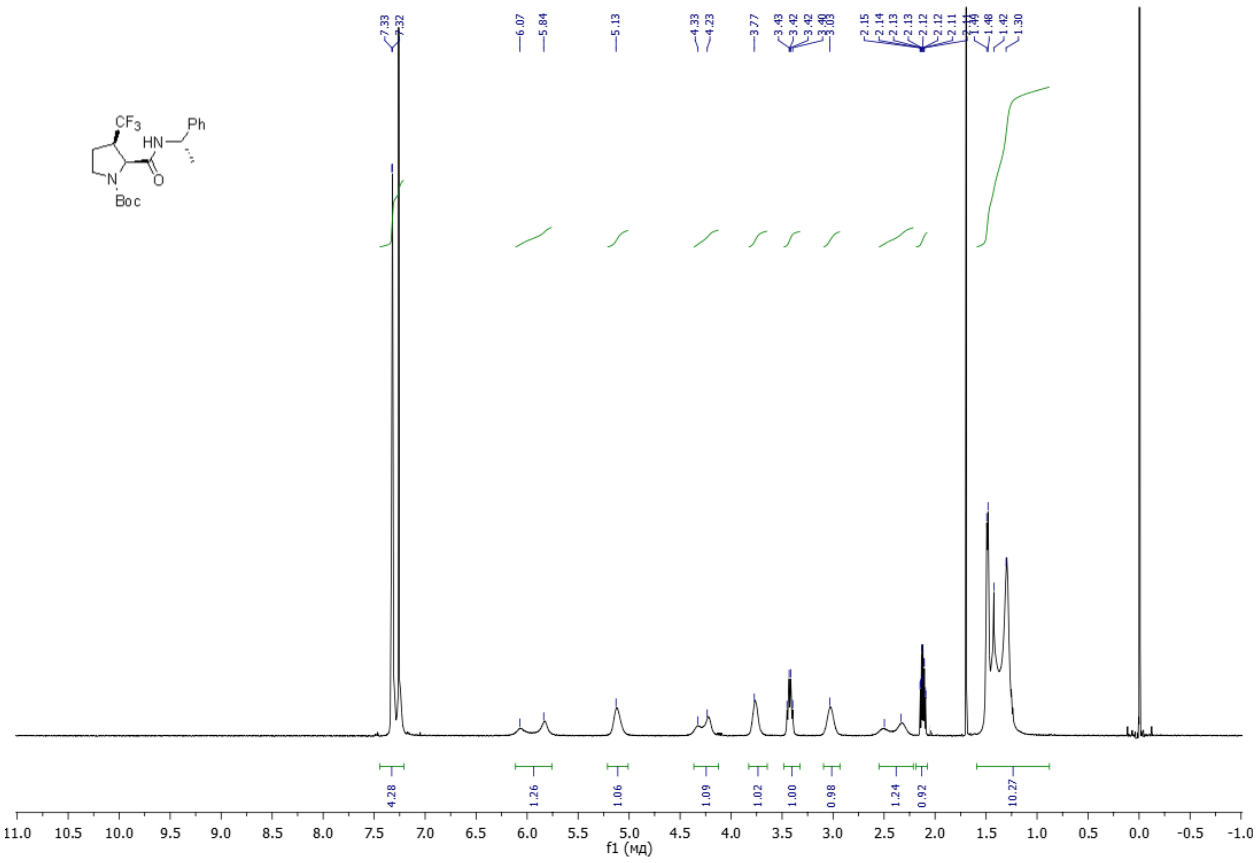
^{13}C NMR, compound **(*2R,3R*)-12a**



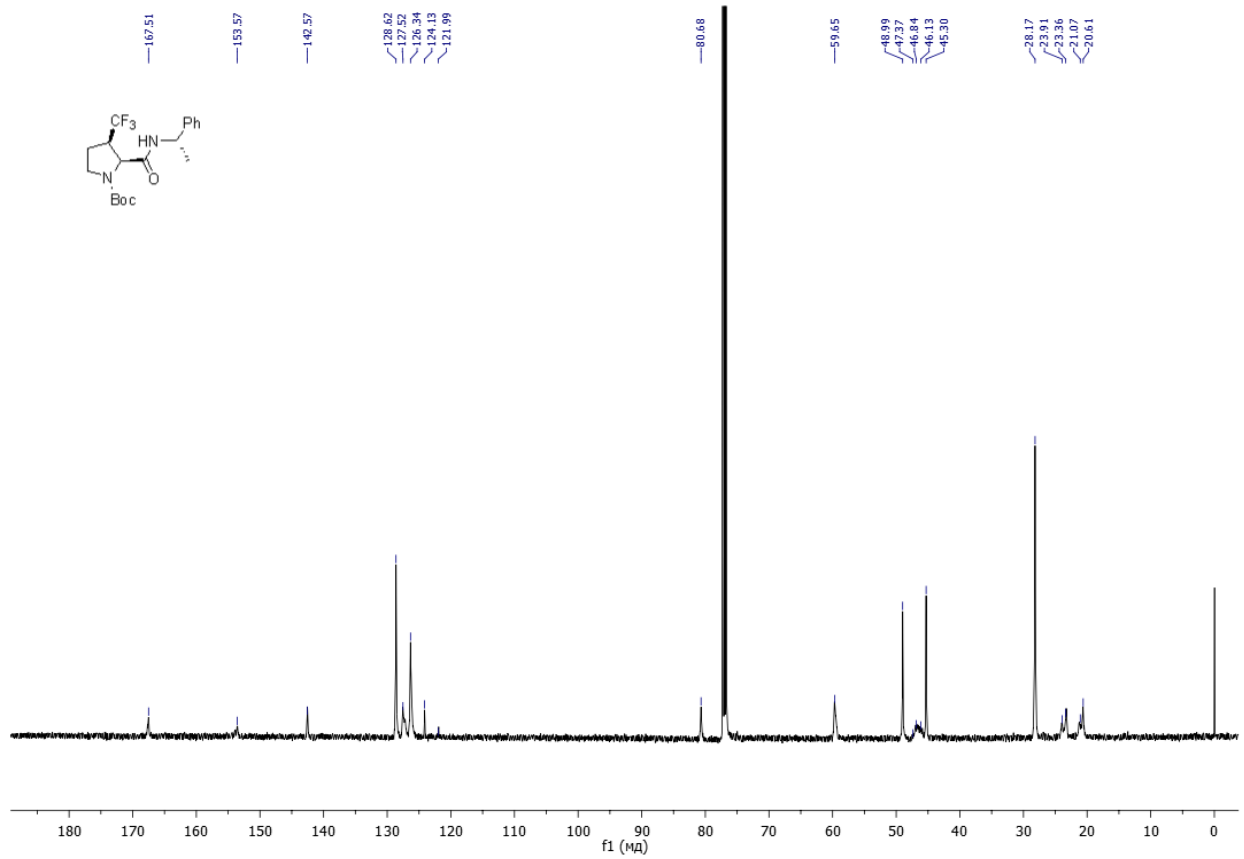
^{19}F NMR, compound **(*2R,3R*)-12a**



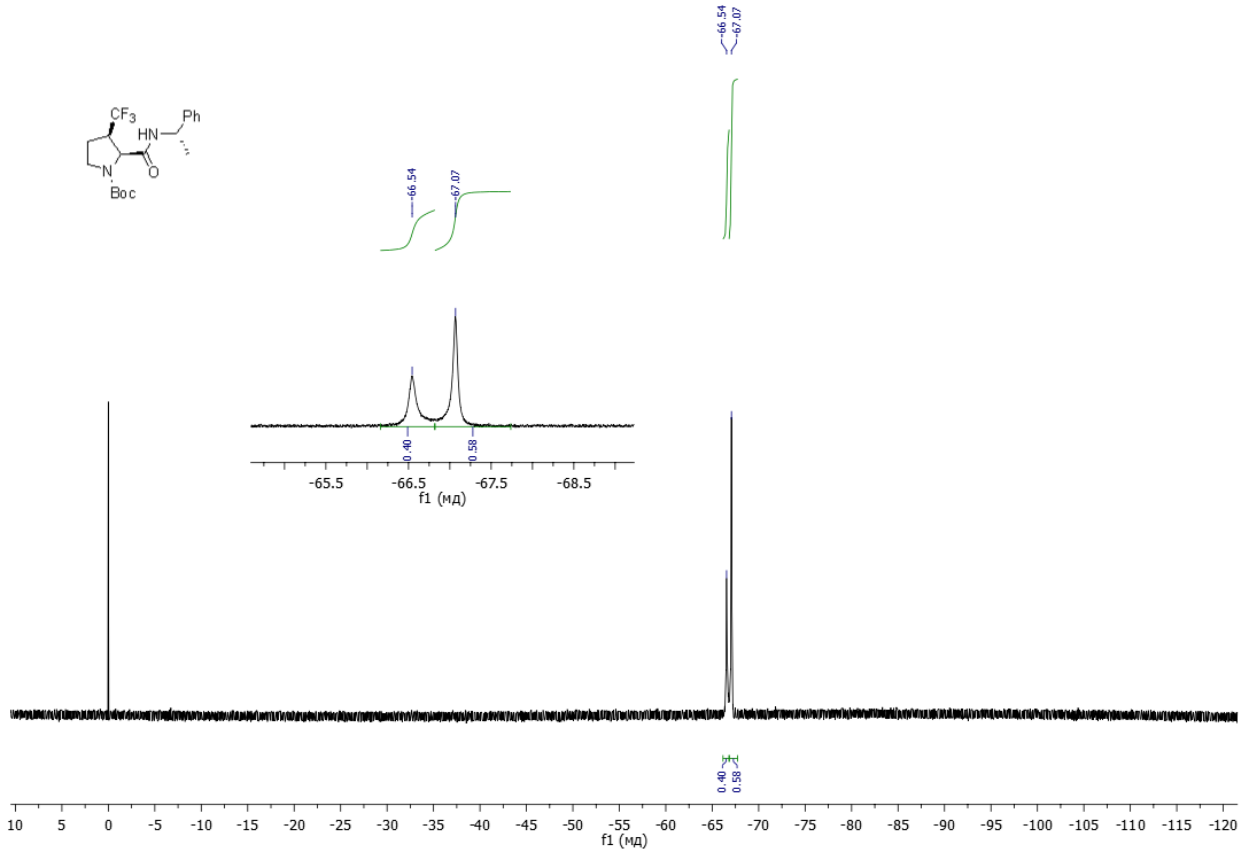
^{1}H NMR, compound **(*2S,3R*)-12a**



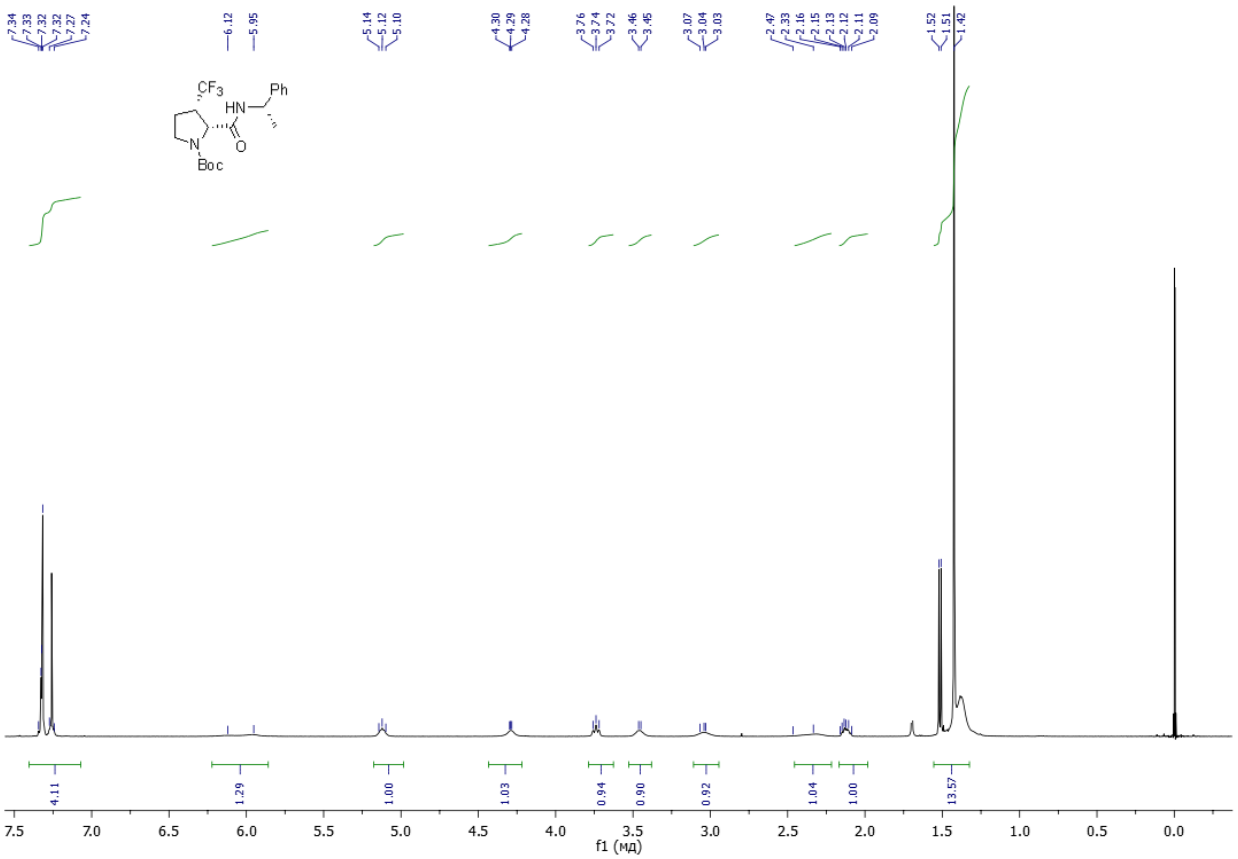
^{13}C NMR, compound **(*2S,3R*)-12a**



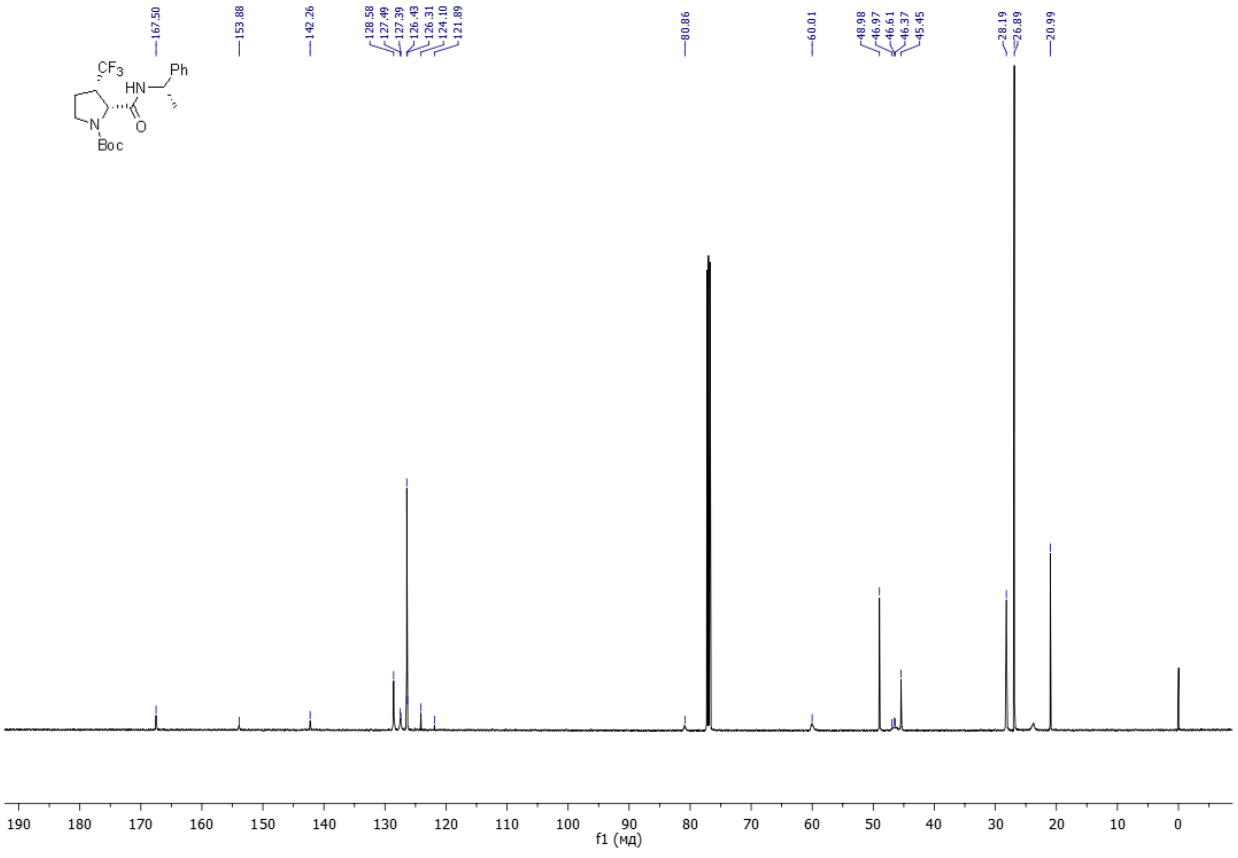
^{19}F NMR, compound **(*2S,3R*)-12a**



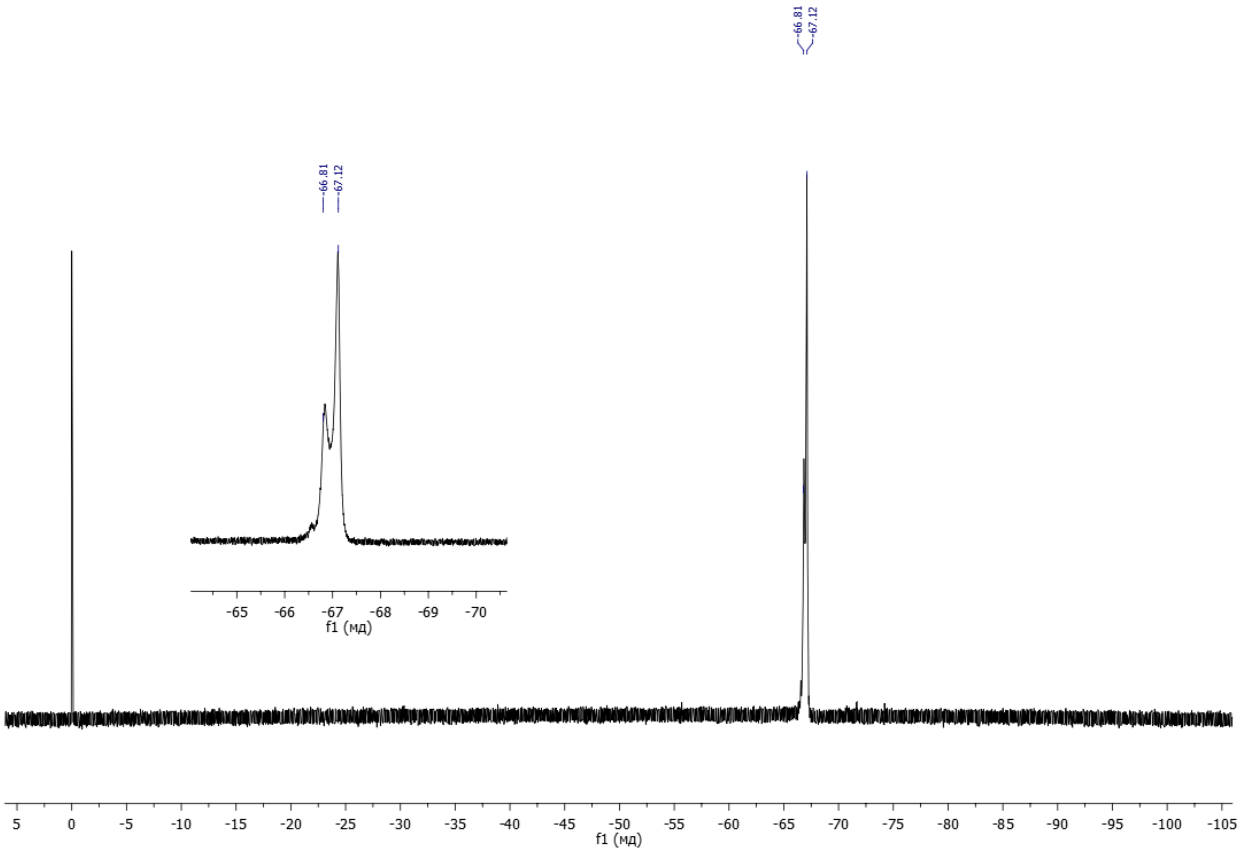
^{1}H NMR, compound **(*2R,3S*)-12a**



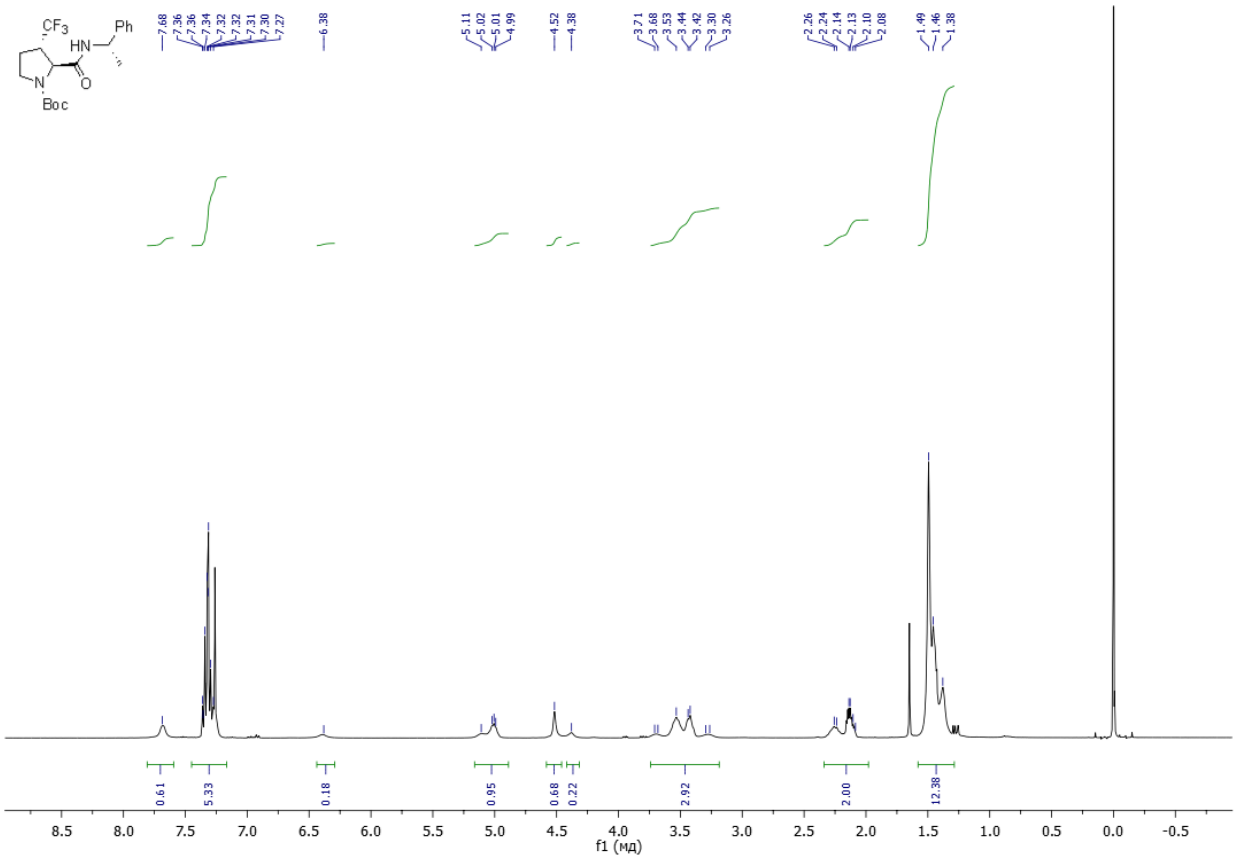
^{13}C NMR, compound **(*2R,3S*)-12a**



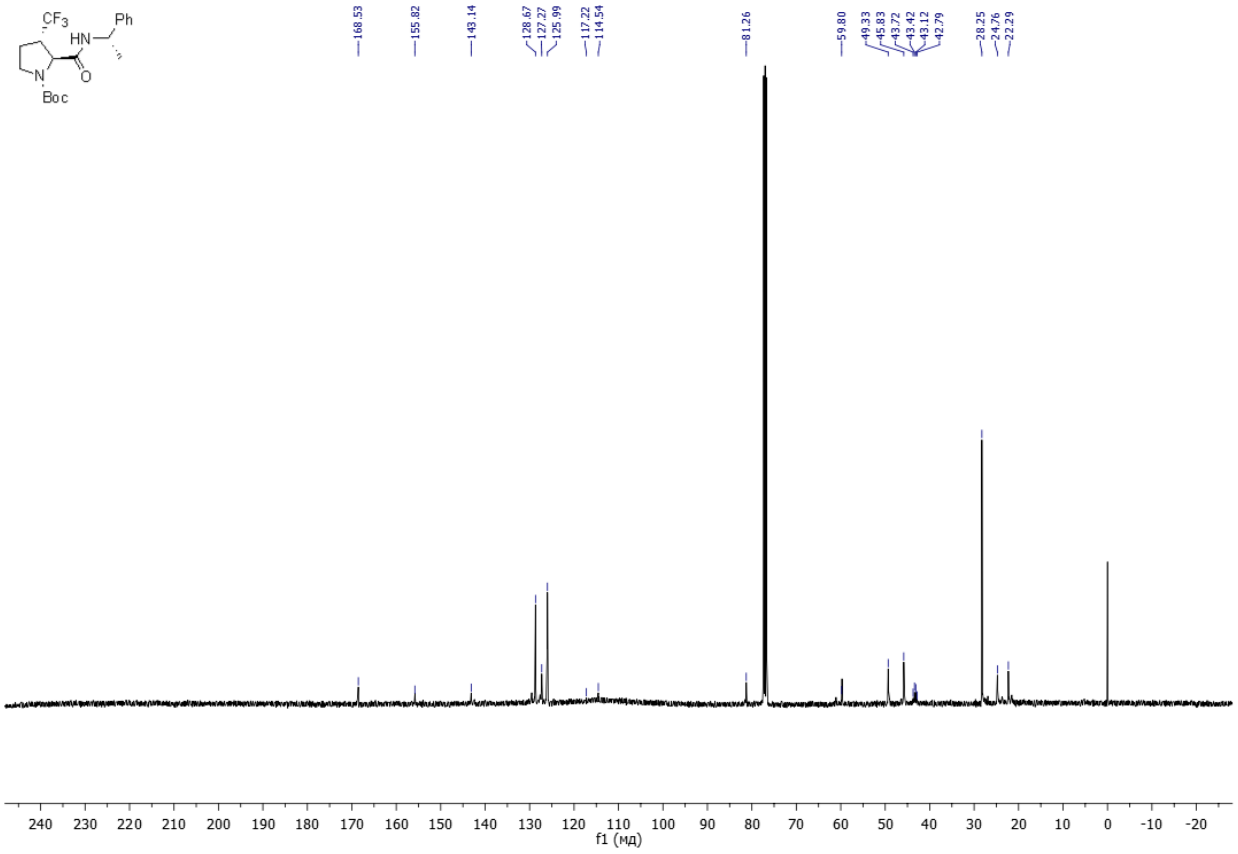
^{19}F NMR, compound **(*2R,3S*)-12a**



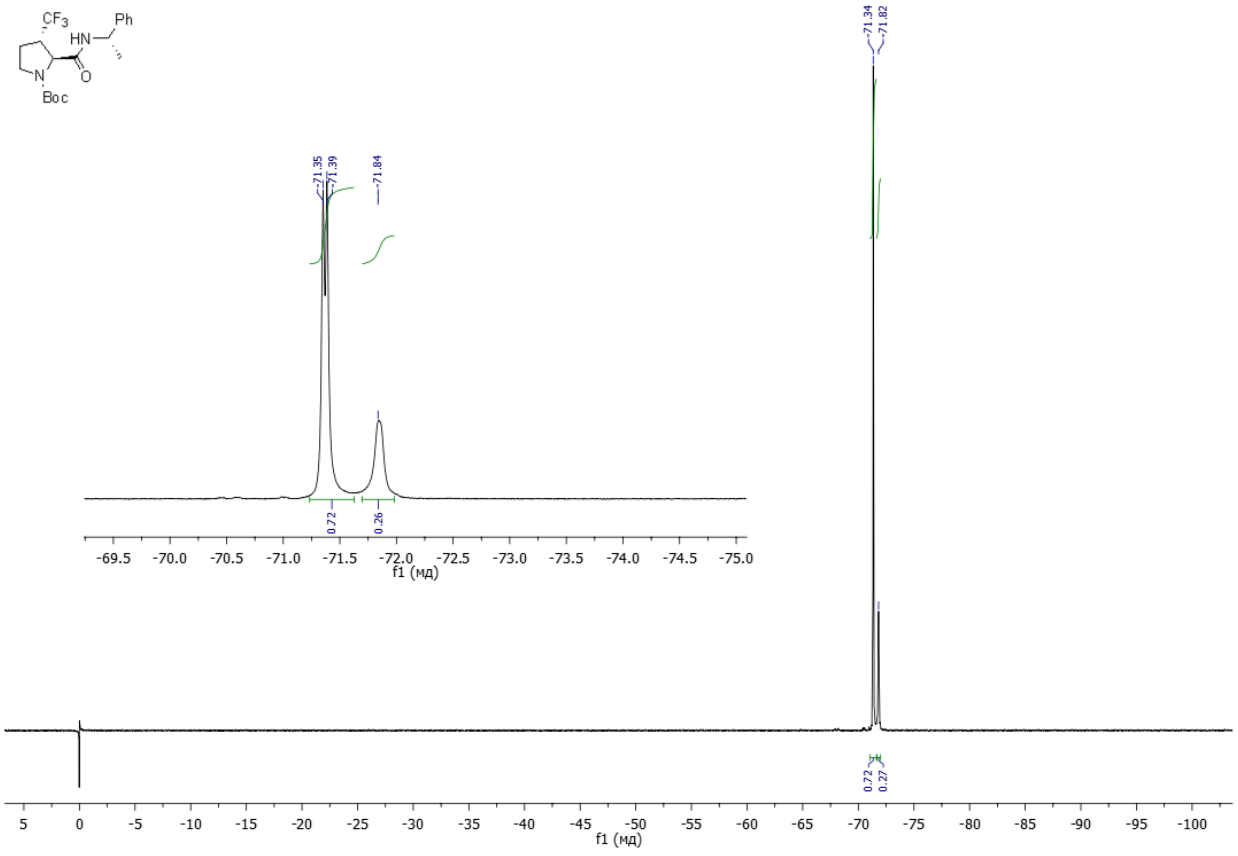
^{1}H NMR, compound **(*2S,3S*)-12a**



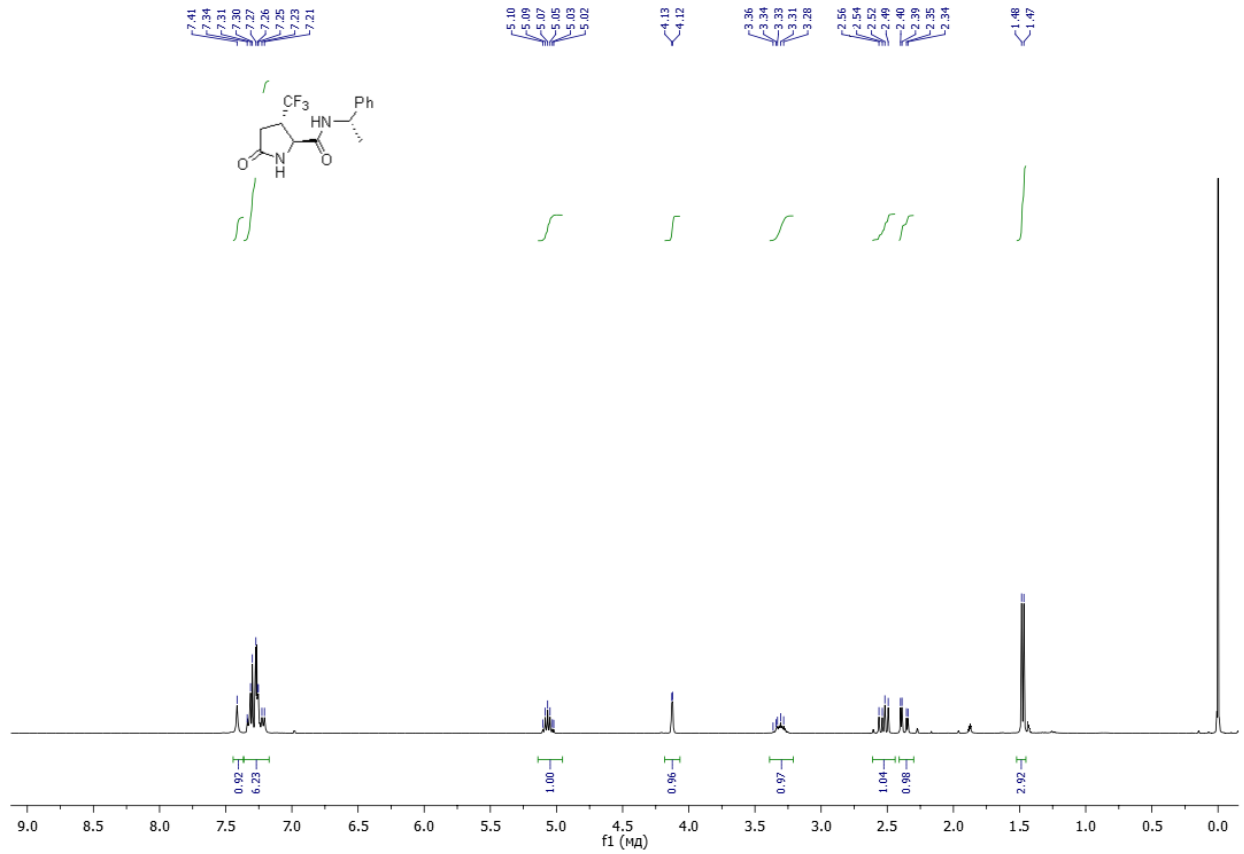
^{13}C NMR, compound **(*2S,3S*)-12a**



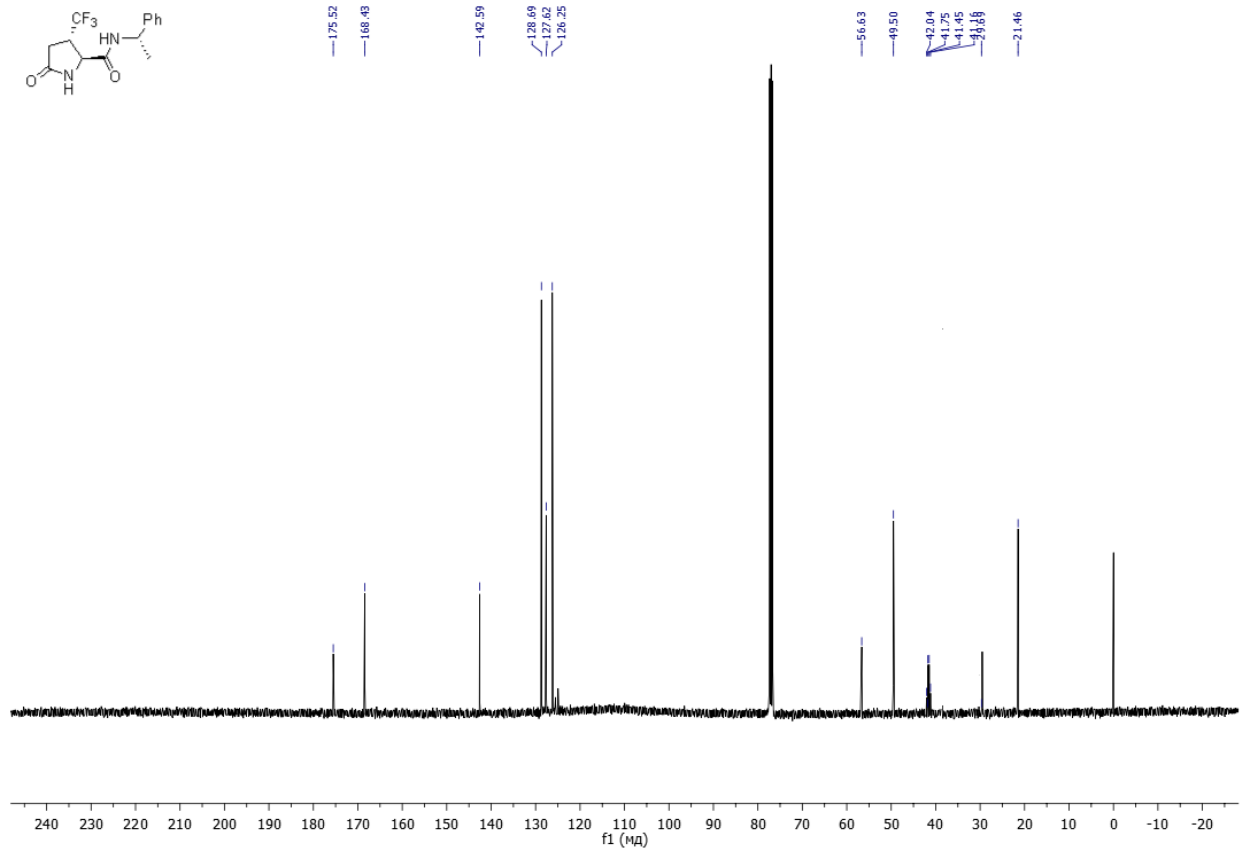
^{19}F NMR, compound **(*2S,3S*)-12a**



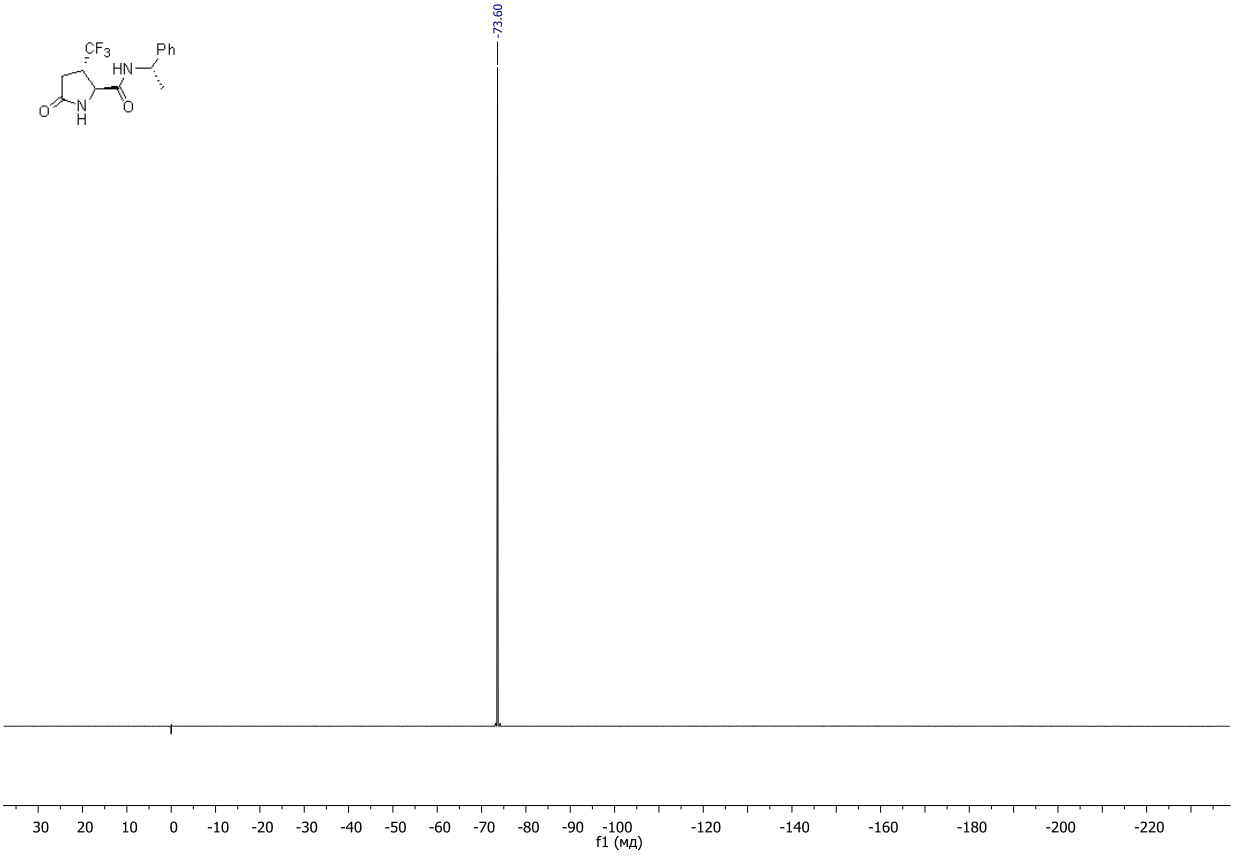
^{1}H NMR, compound ***(2S,3S)*- S4** (Scheme S7)



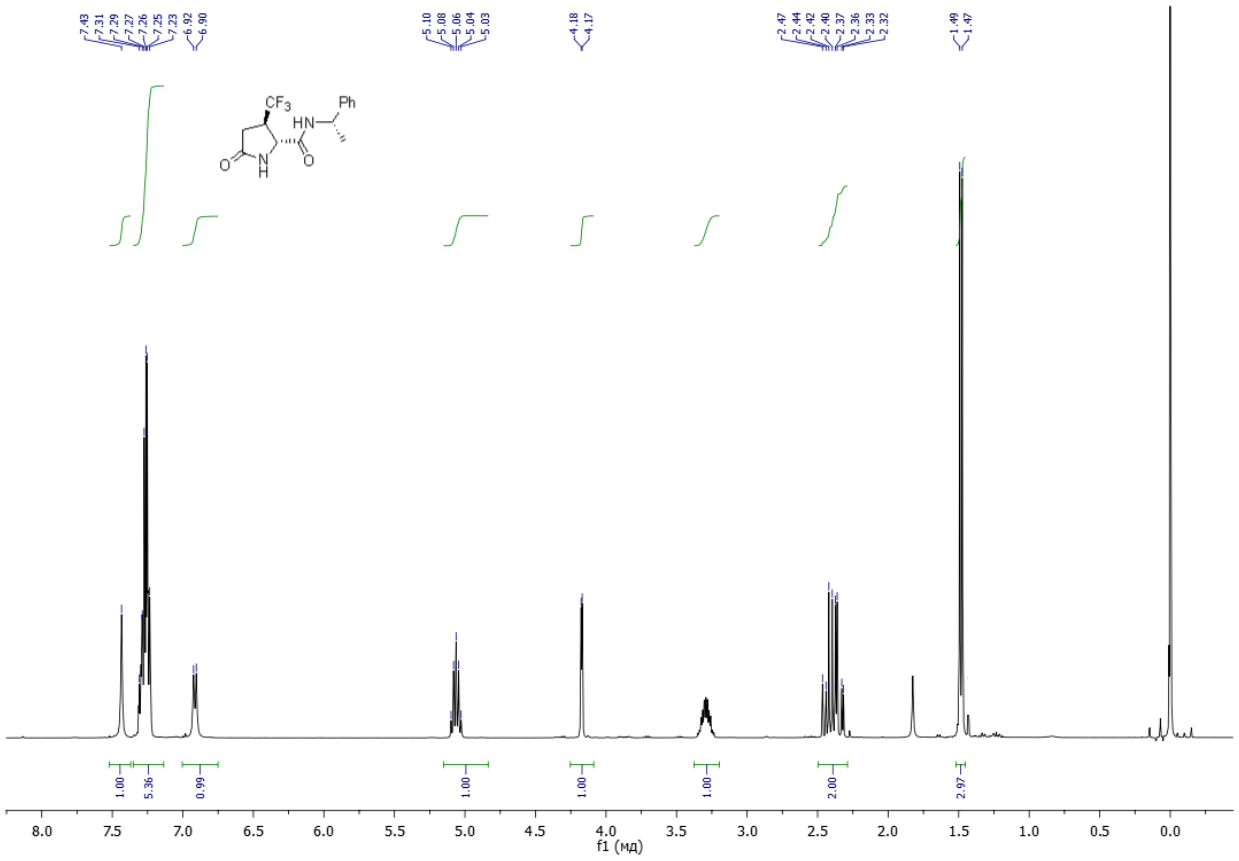
^{13}C NMR, compound ***(2S,3S)*- S4** (Scheme S7)



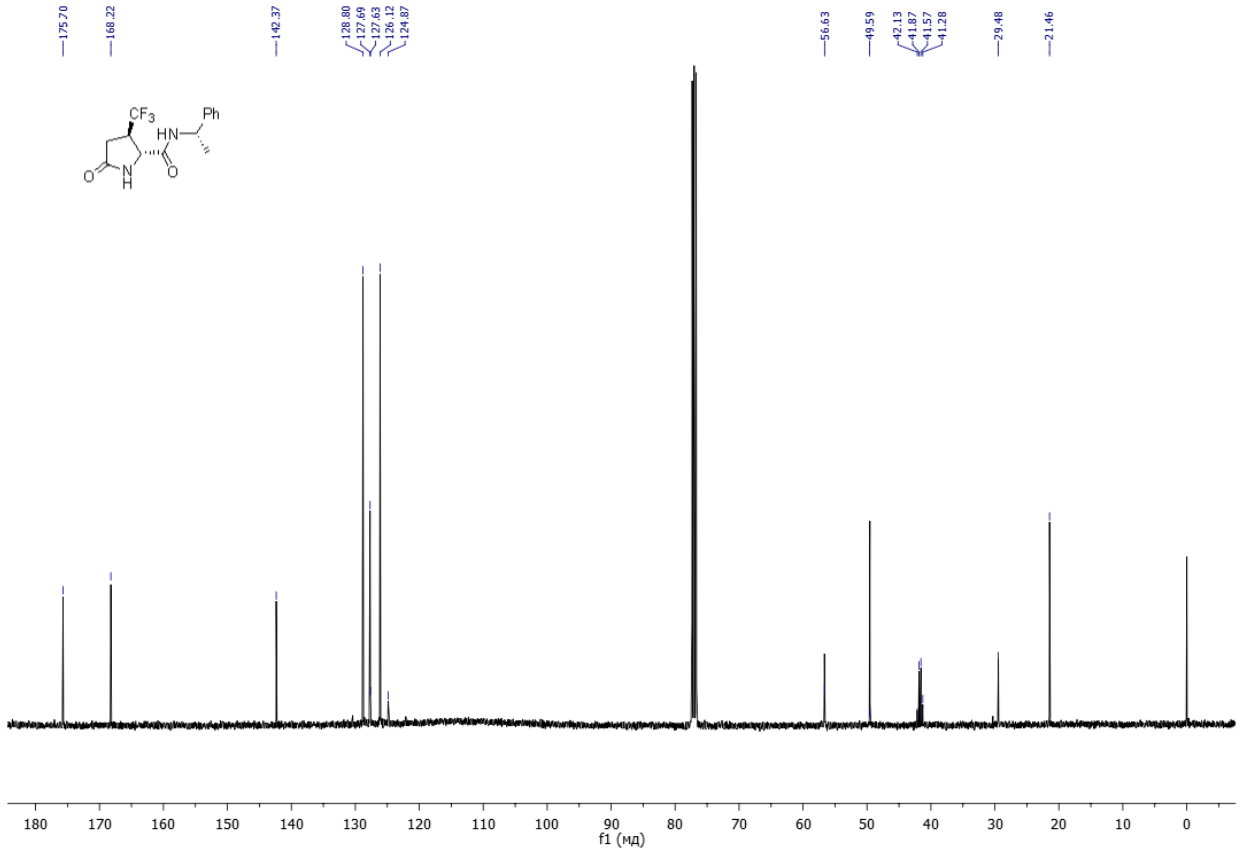
^{19}F NMR, compound ***(2S,3S)*- S4** (Scheme S7)



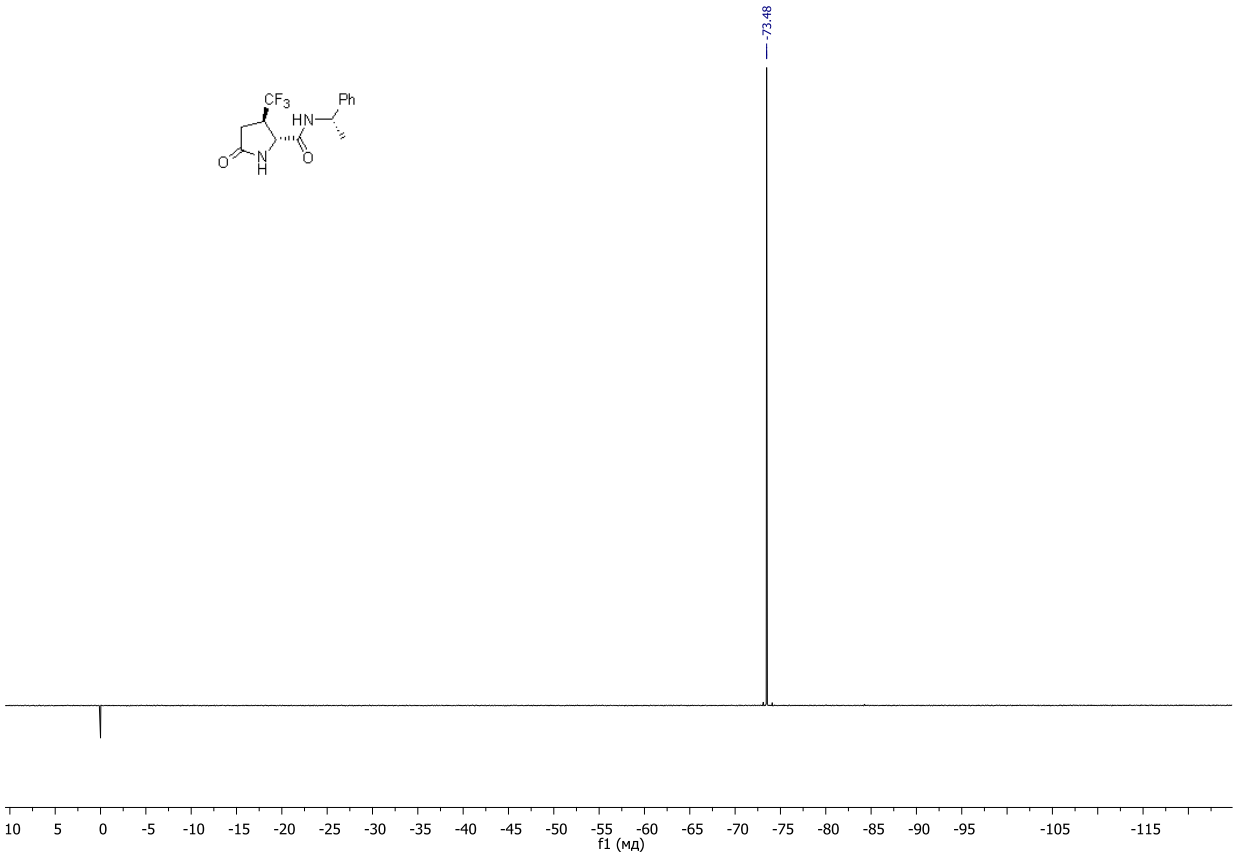
^{1}H NMR, compound ***(2R,3R)*- S4** (Scheme S7)



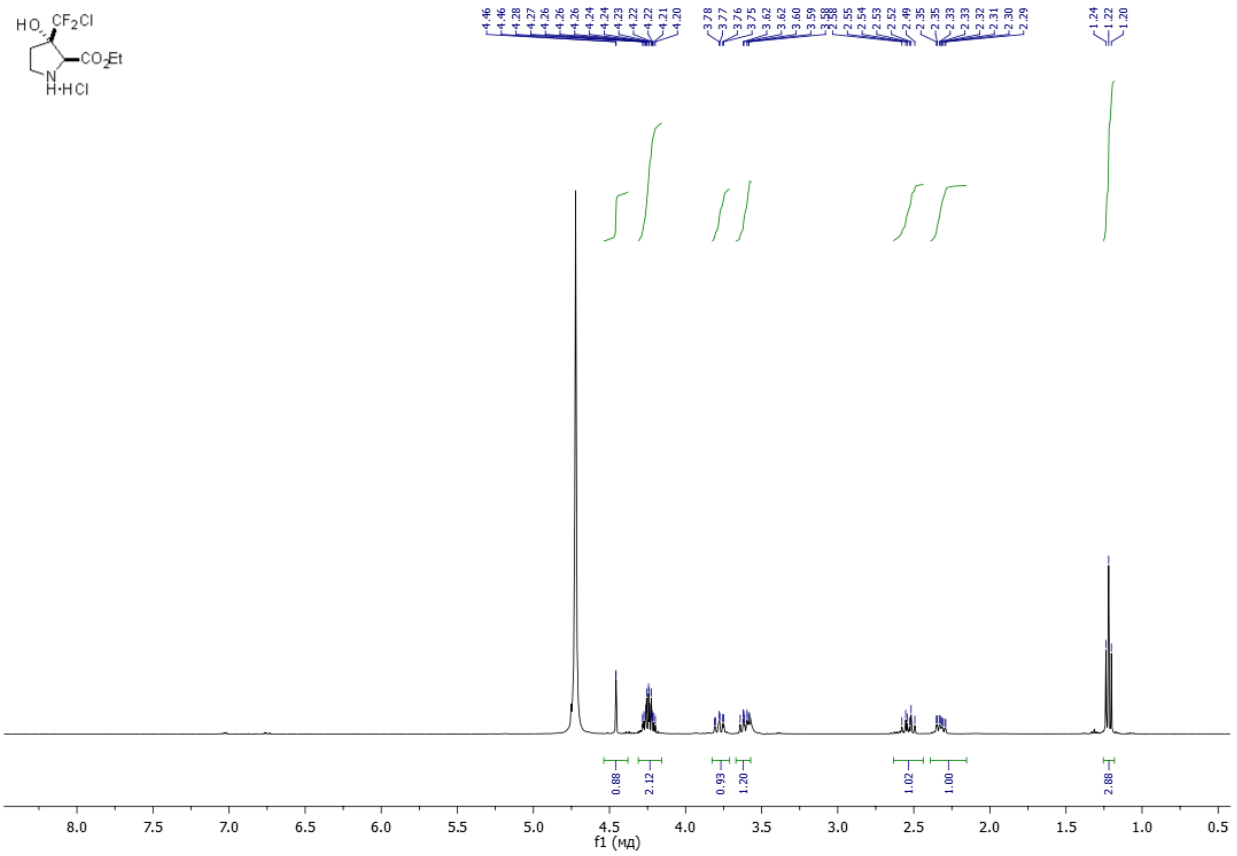
^{13}C NMR, compound ***(2R,3R)- S4*** (Scheme S7)



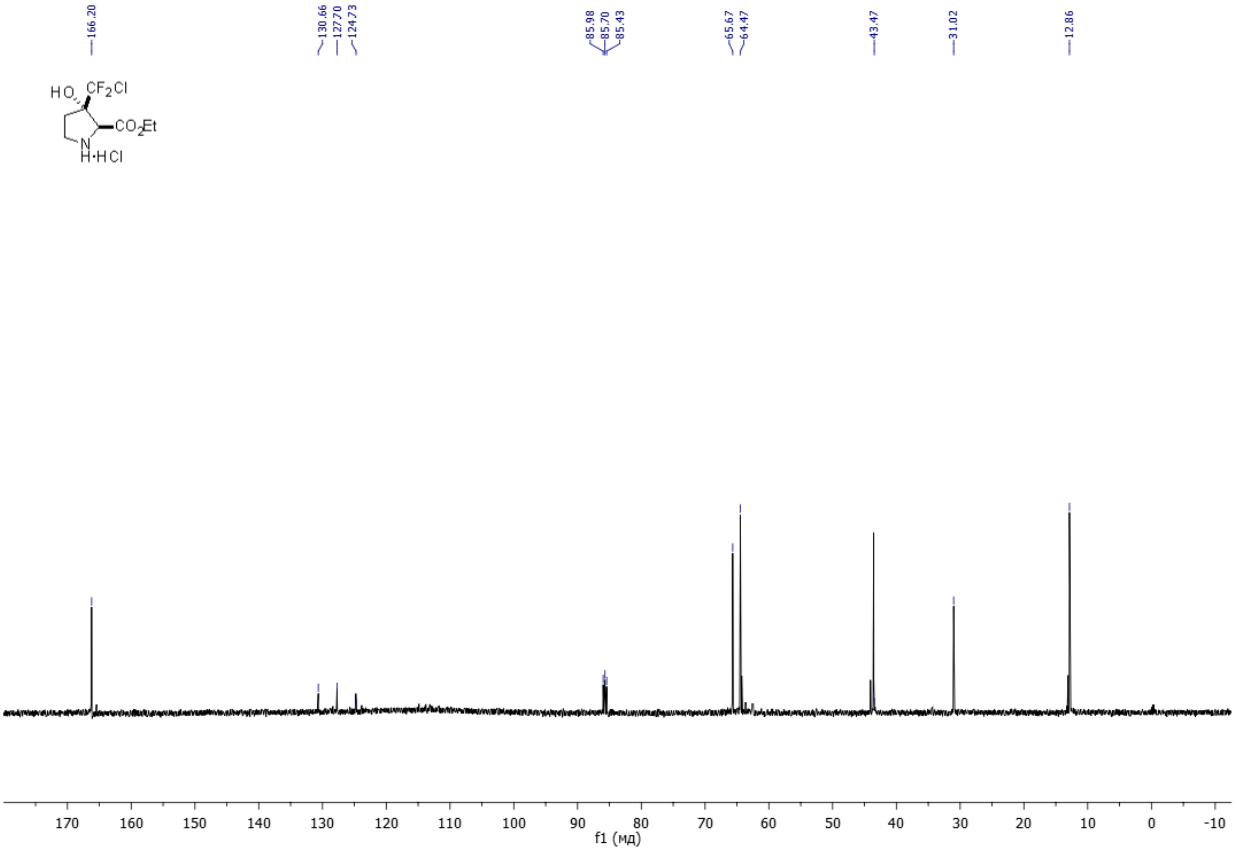
^{19}F NMR, compound ***(2R,3R)- S4*** (Scheme S7)



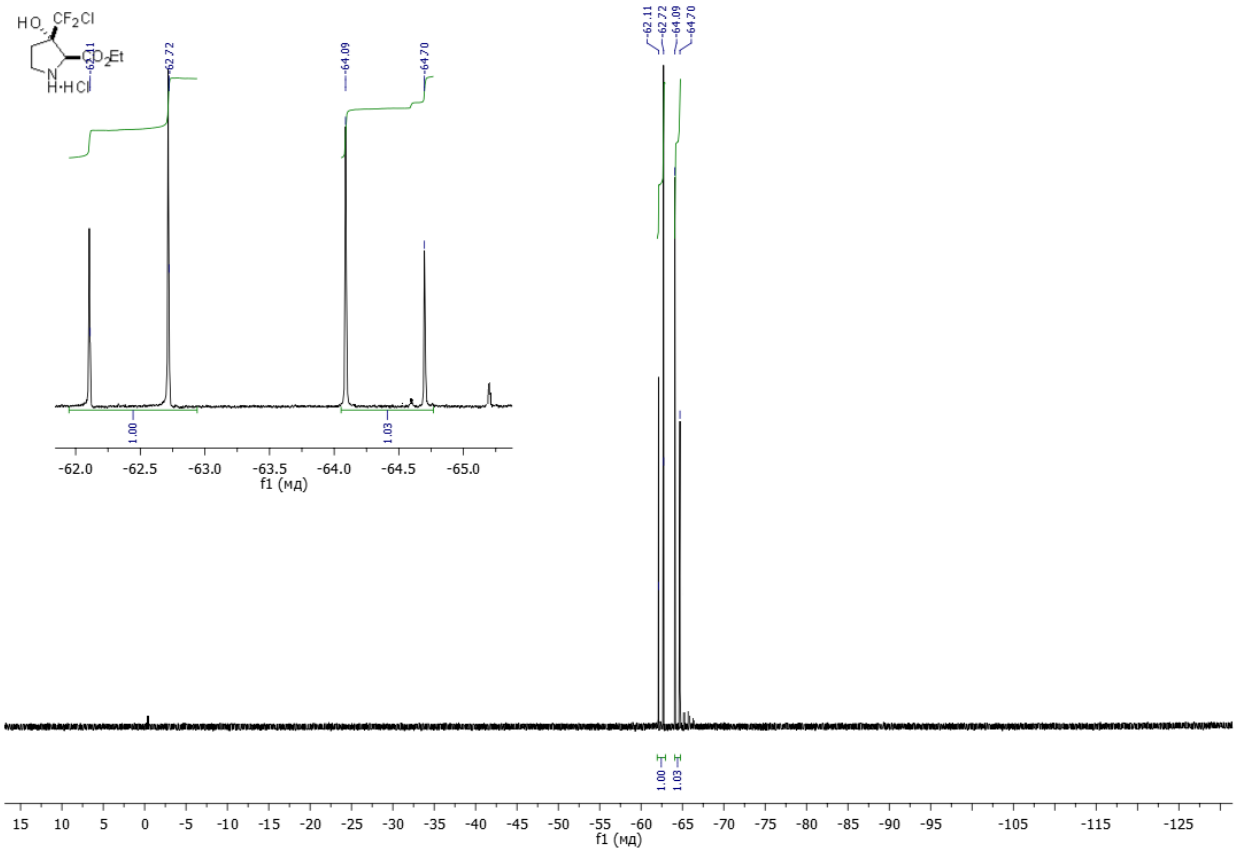
^{1}H NMR, compound ***trans*-15d**



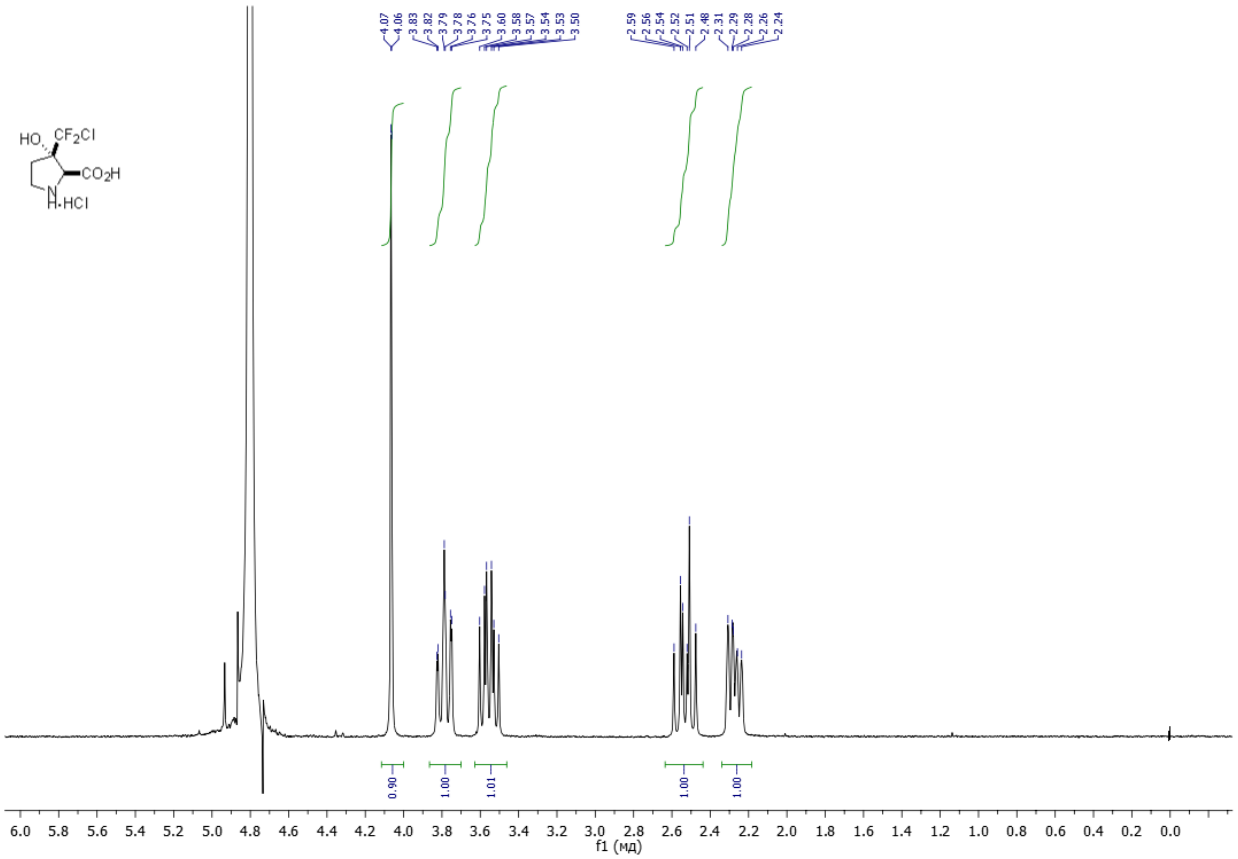
^{13}C NMR, compound ***trans*-15d**



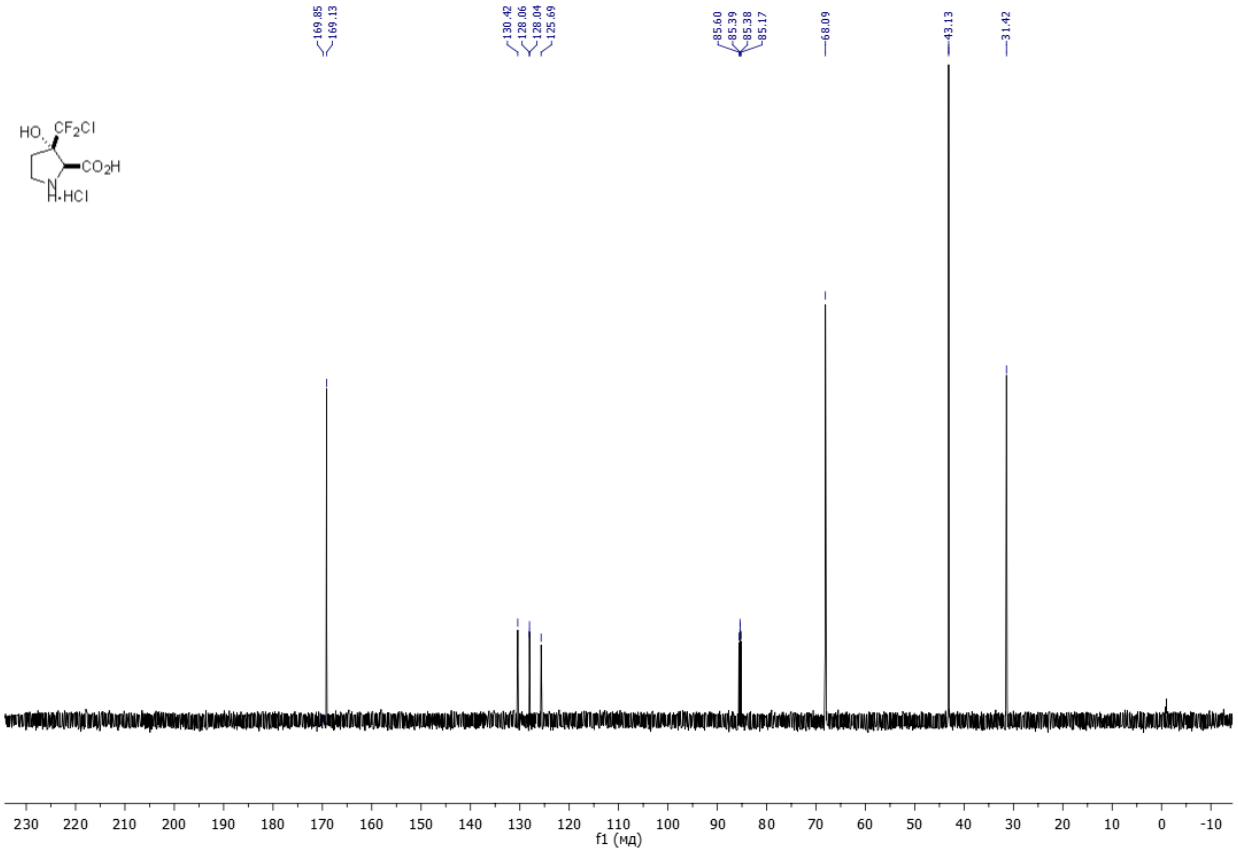
^{19}F NMR, compound ***trans*-15d**



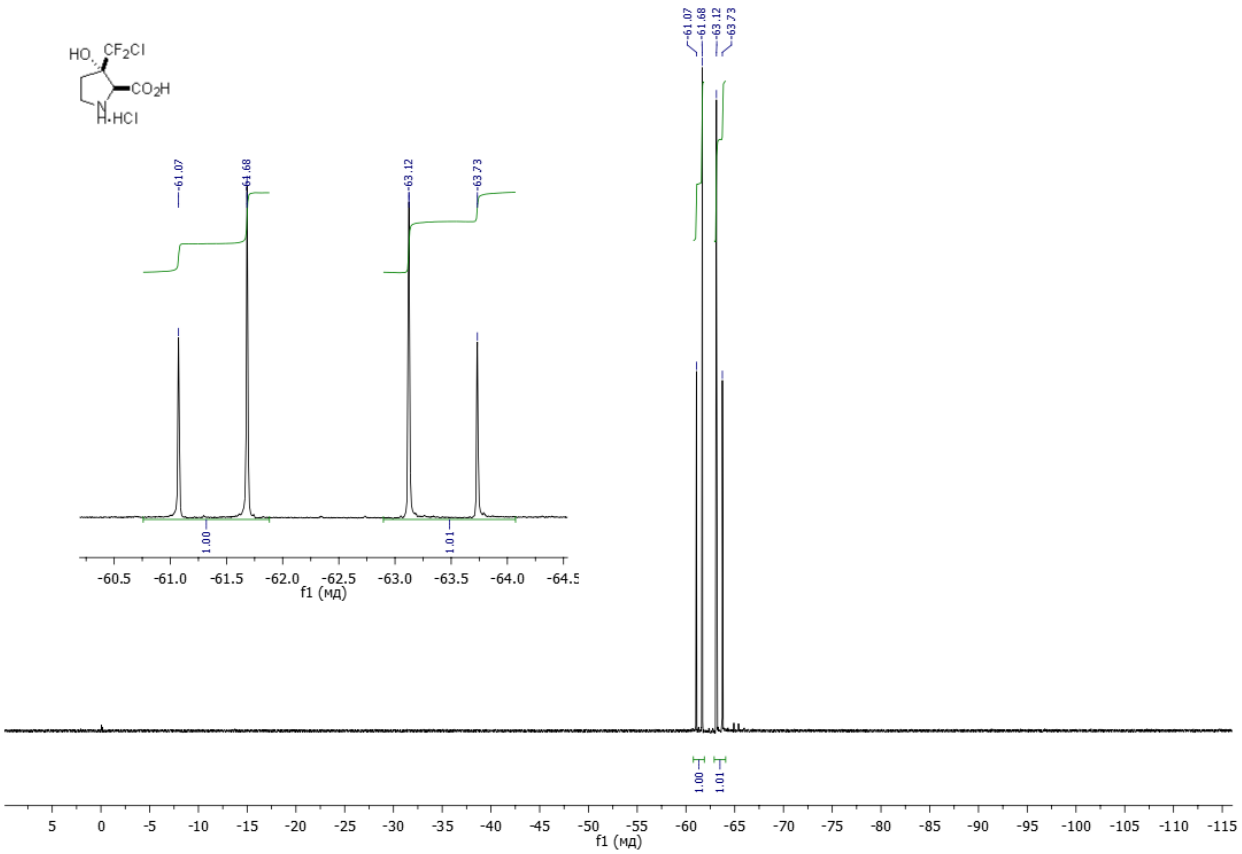
^{1}H NMR, compound ***trans*-16d**



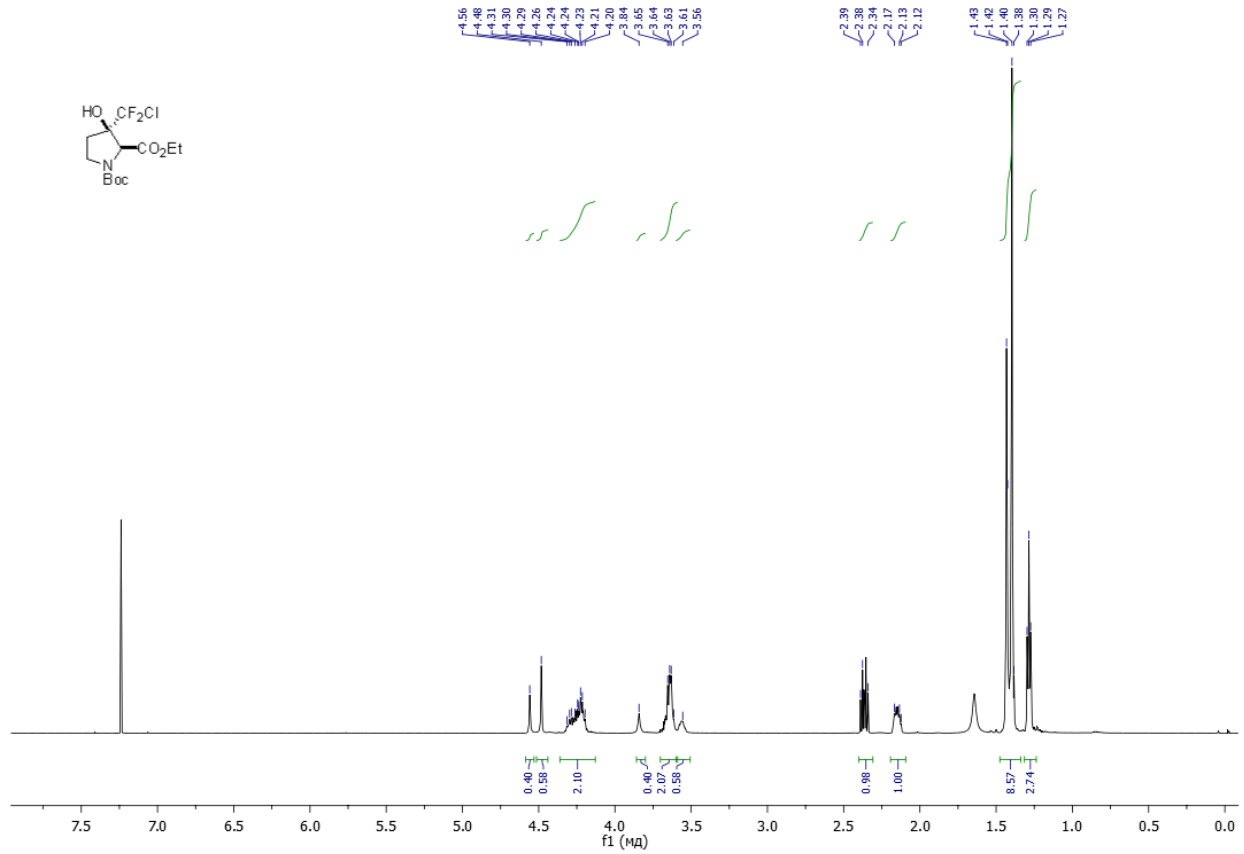
^{13}C NMR, compound ***trans*-16d**



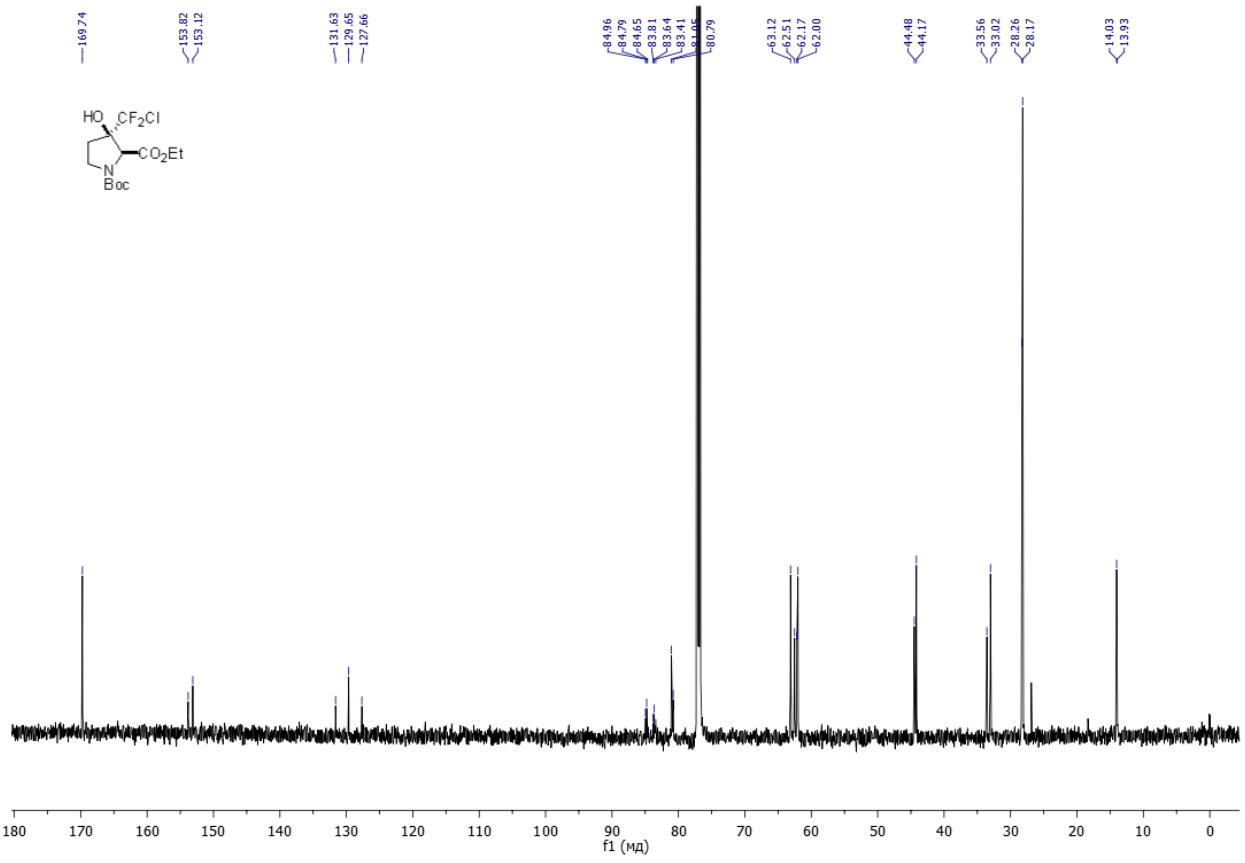
^{19}F NMR, compound ***trans*-16d**



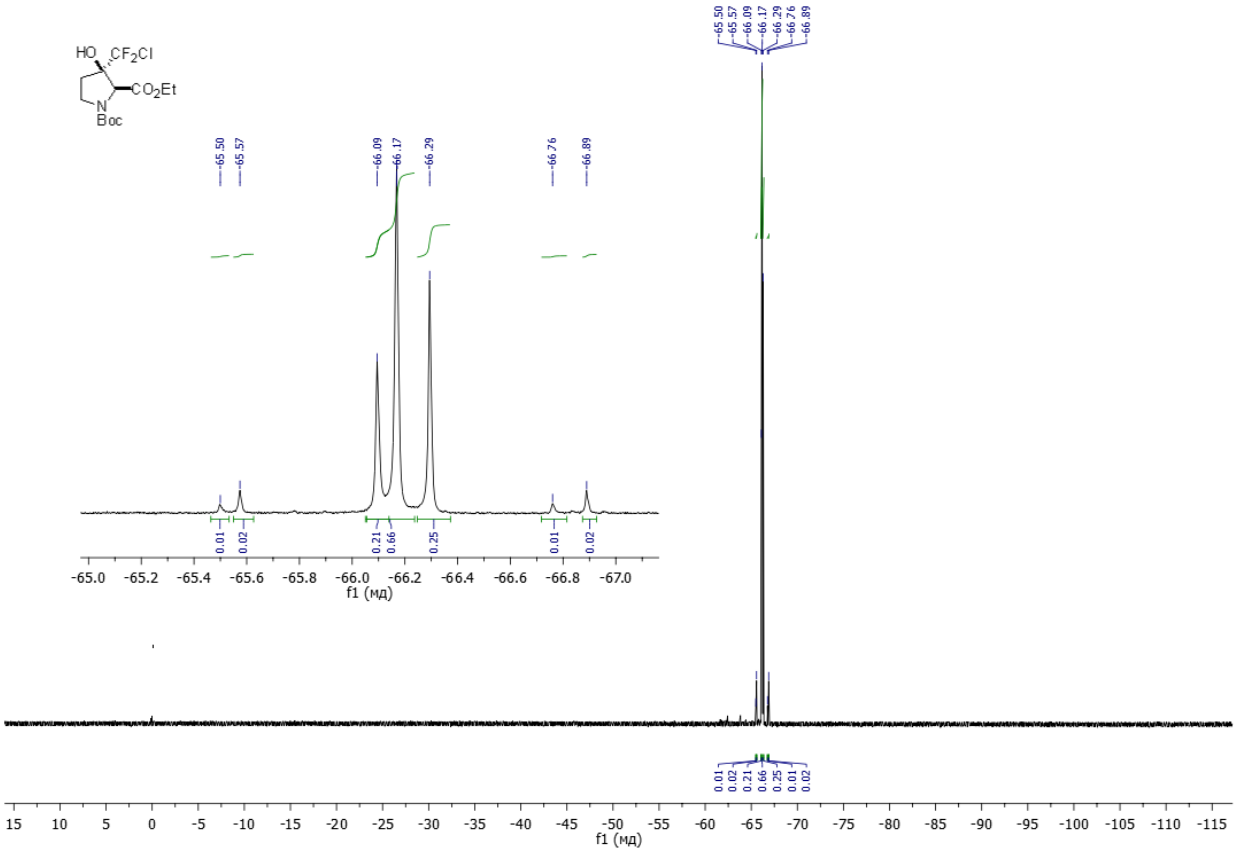
^{1}H NMR, compound ***cis*-17d**



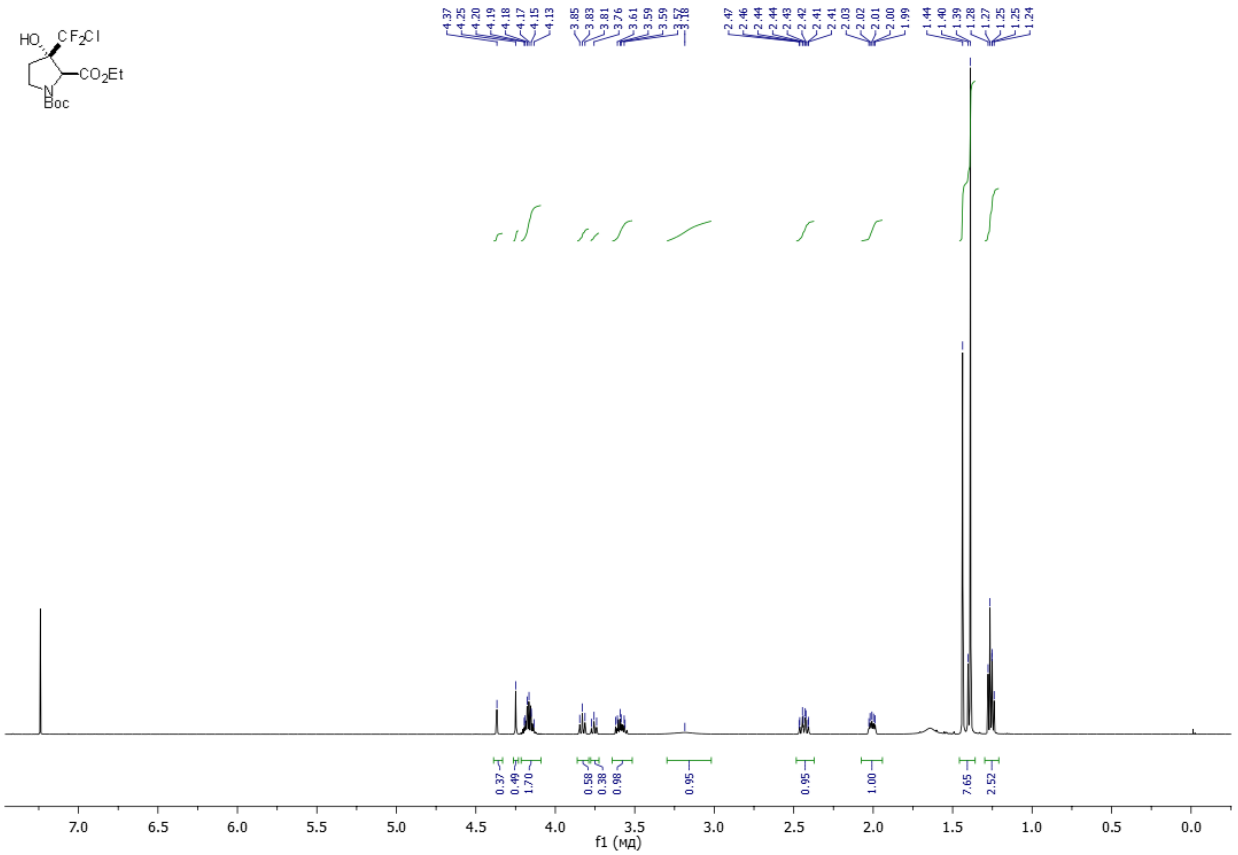
^{13}C NMR, compound ***cis*-17d**



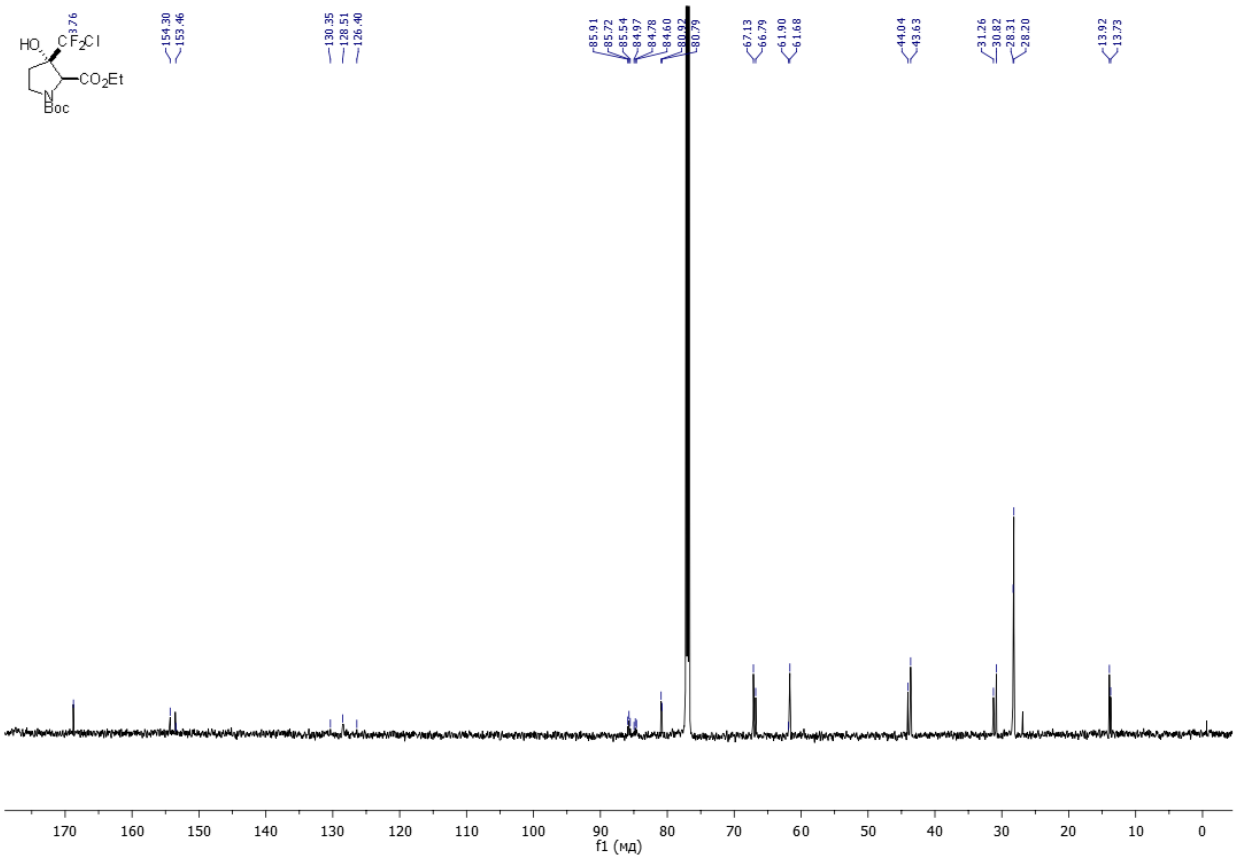
^{19}F NMR, compound ***cis*-17d**



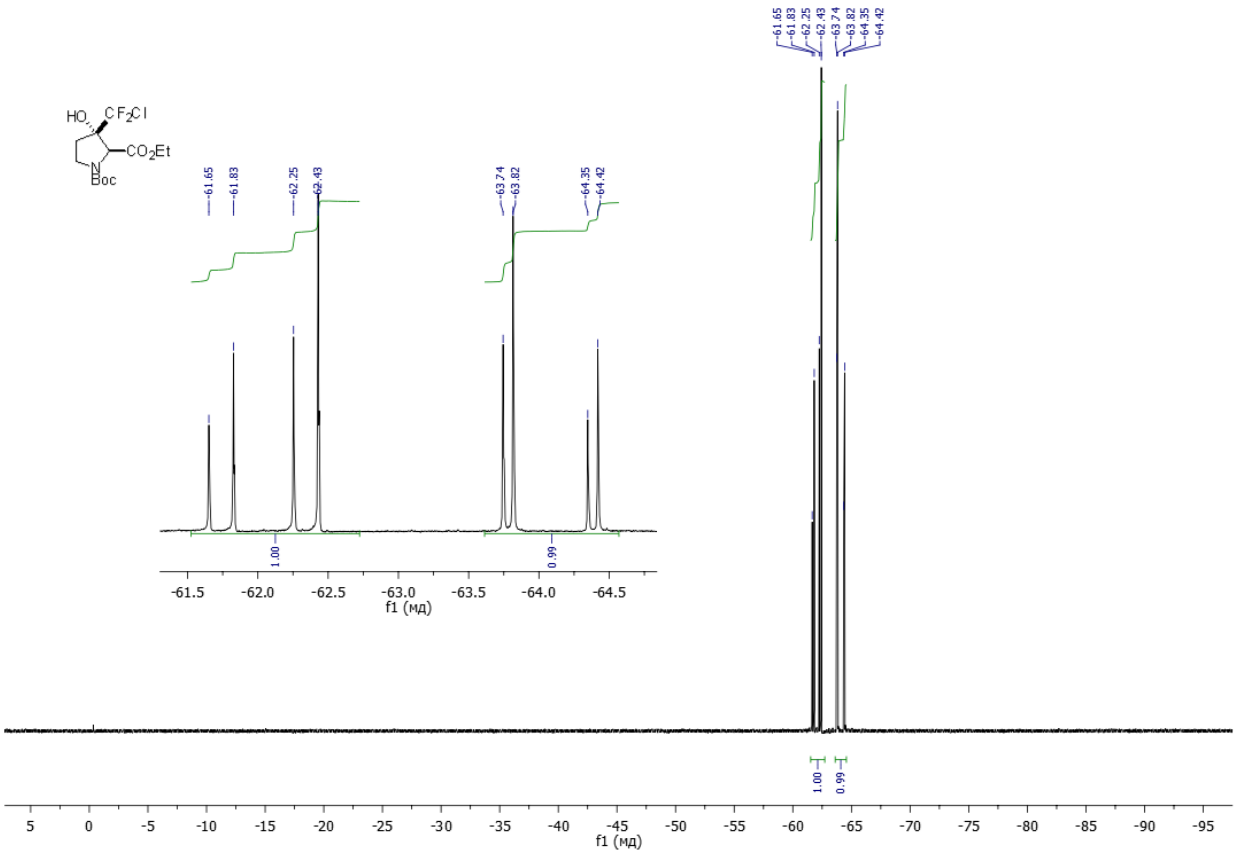
^{1}H NMR, compound ***trans*-17d**



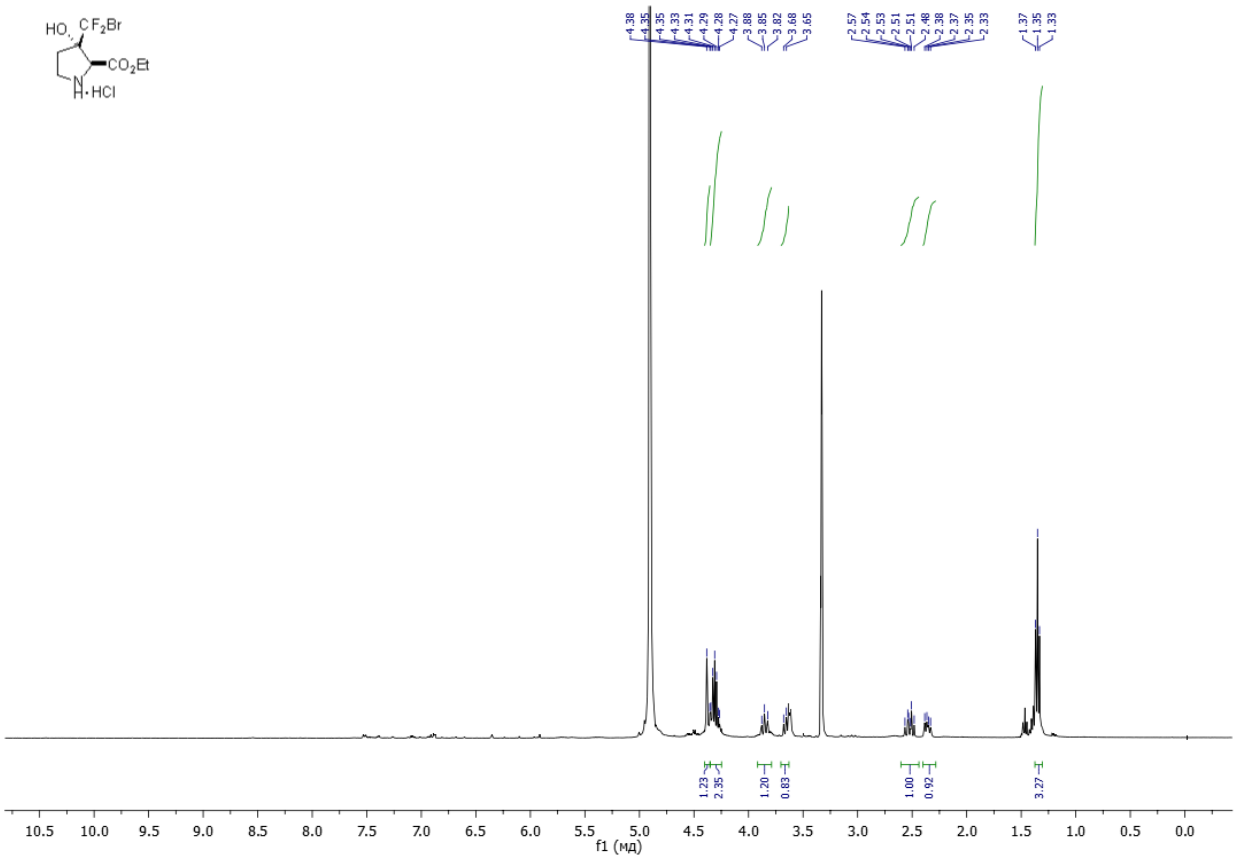
^{13}C NMR, compound ***trans*-17d**



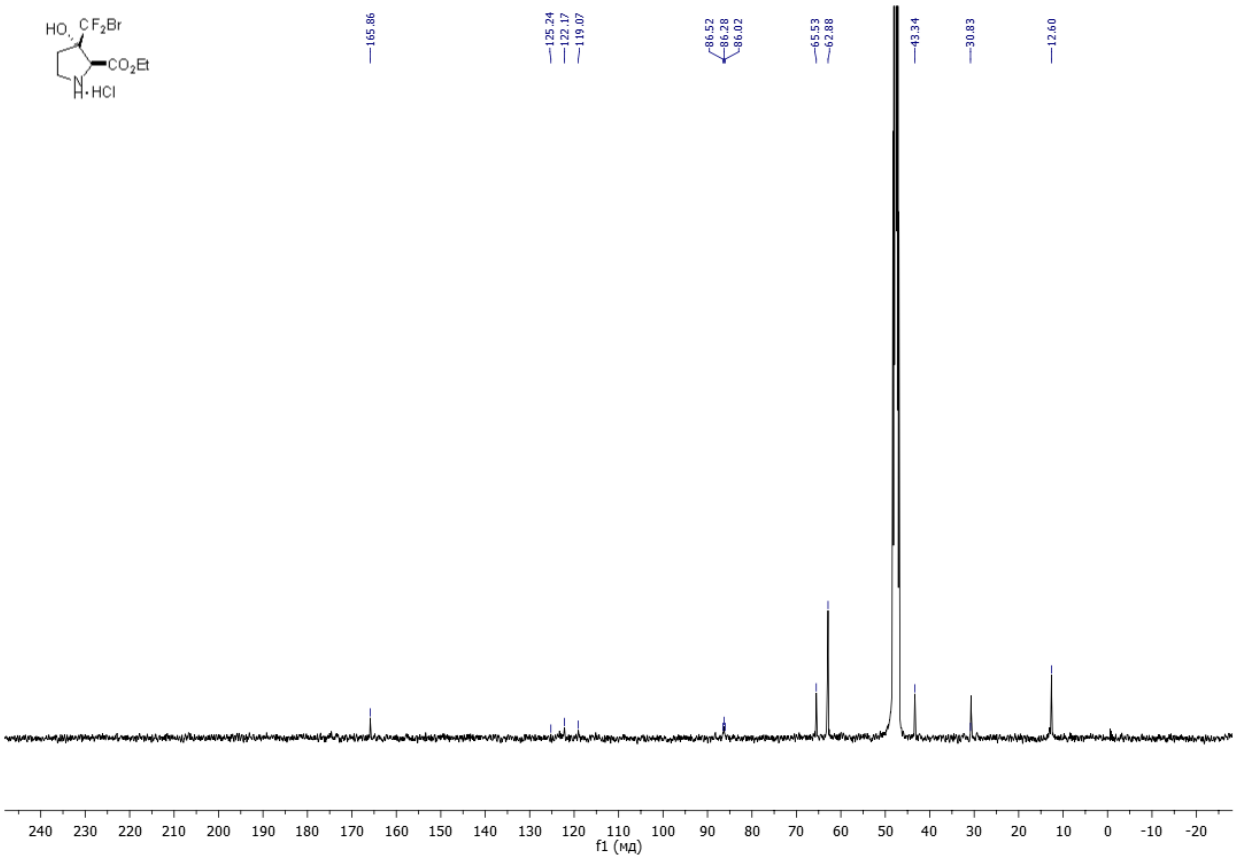
^{19}F NMR, compound ***trans*-17d**



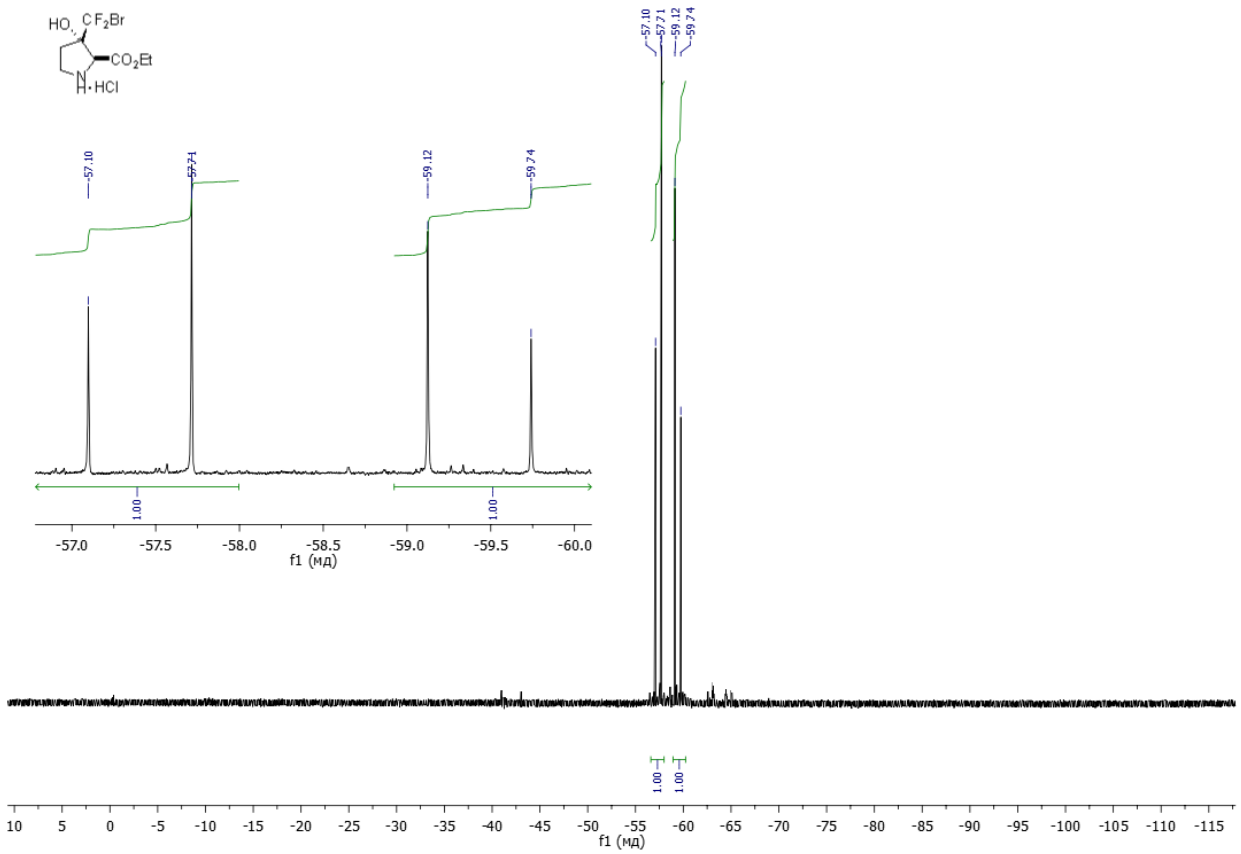
^{1}H NMR, compound ***trans*-15e**



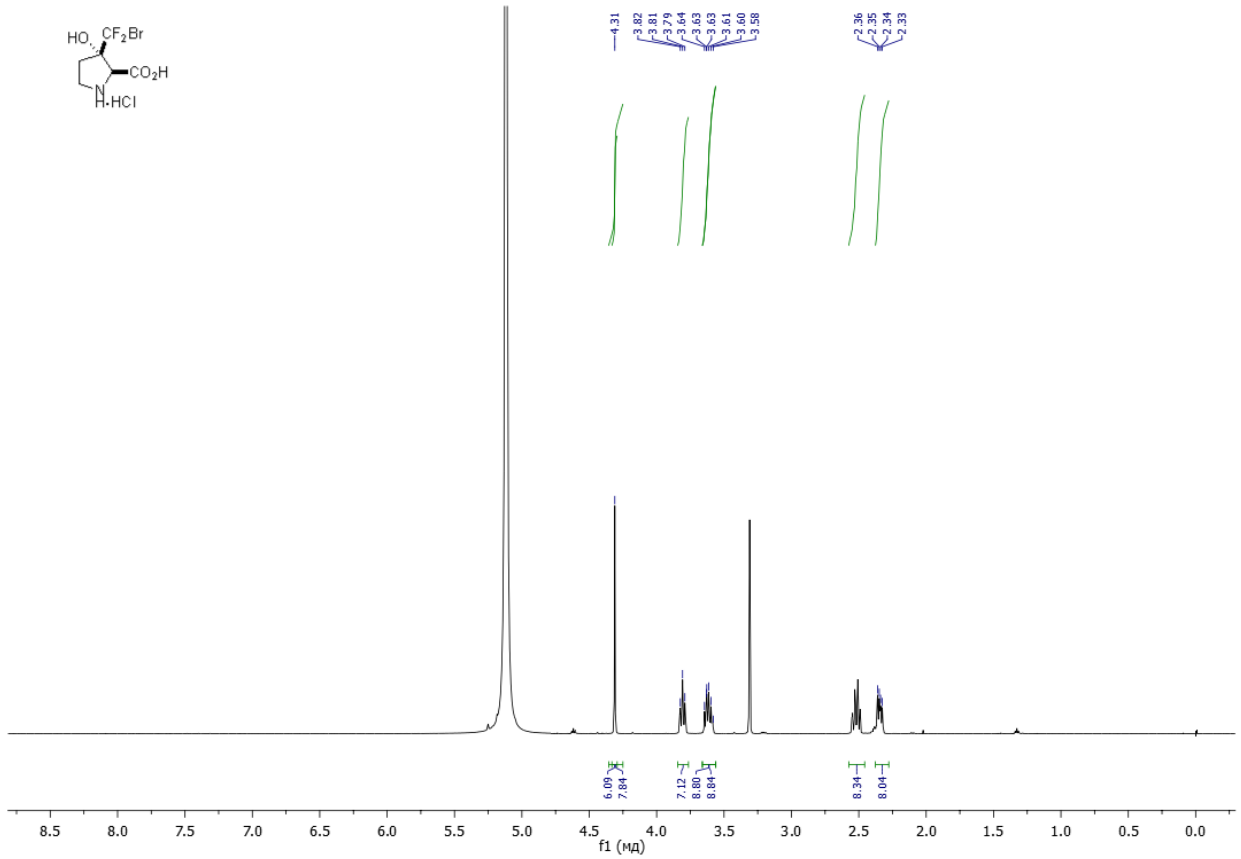
^{13}C NMR, compound ***trans*-15e**



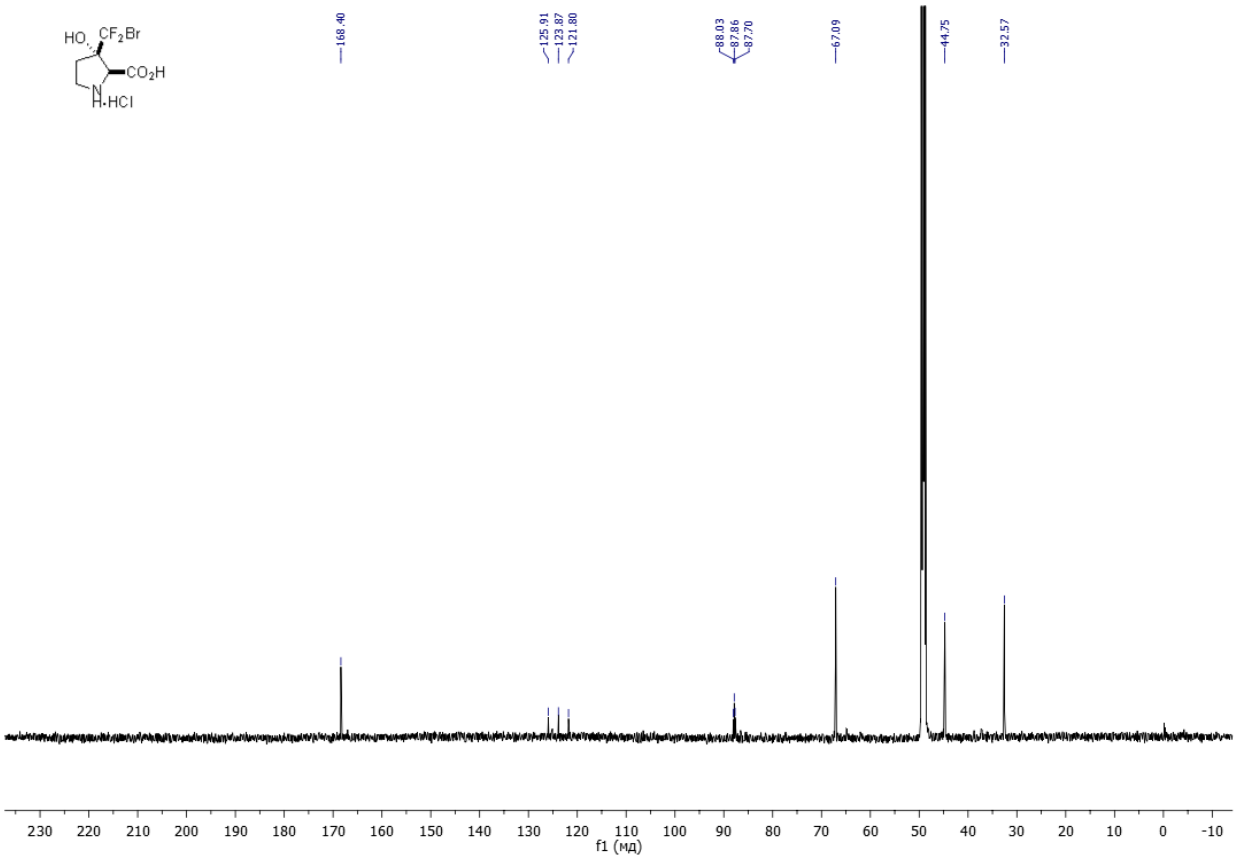
^{19}F NMR, compound ***trans*-15e**



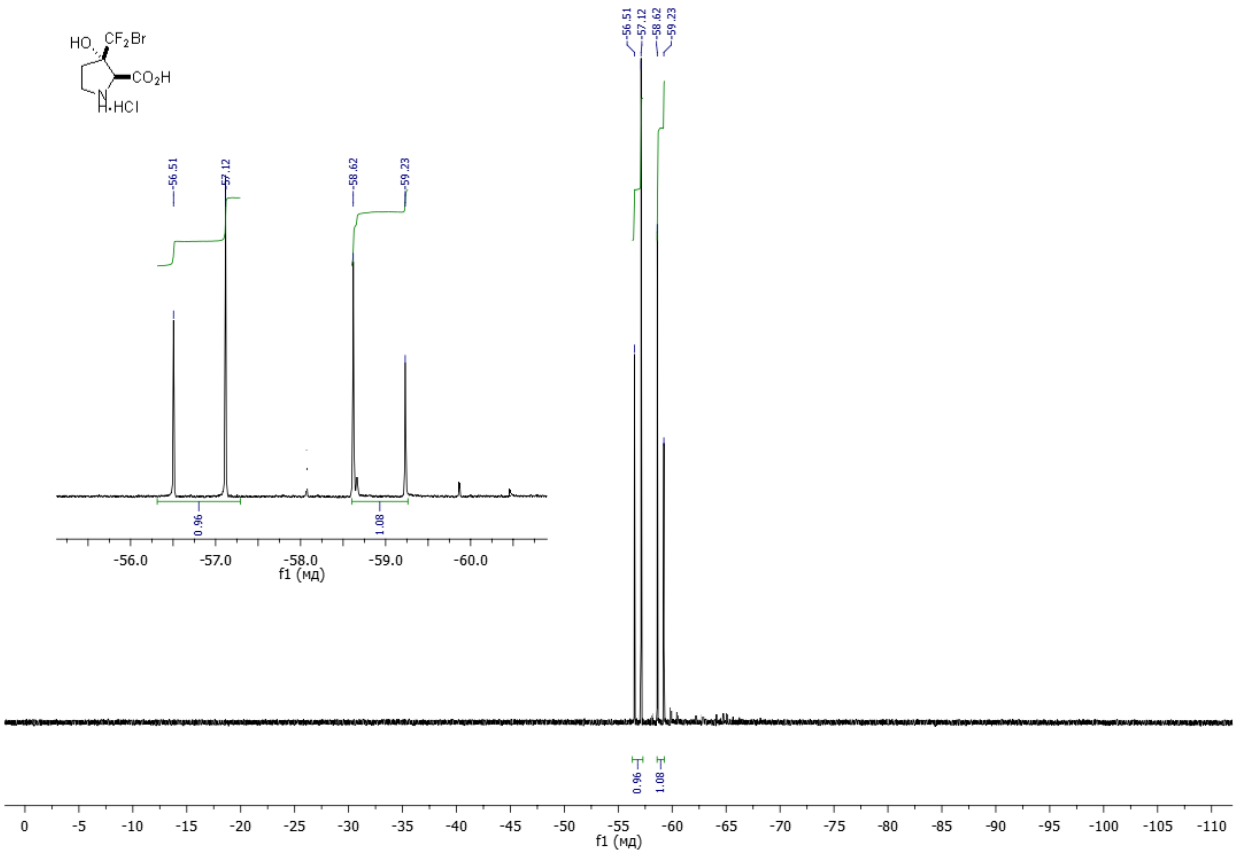
^{1}H NMR, compound ***trans*-16e**



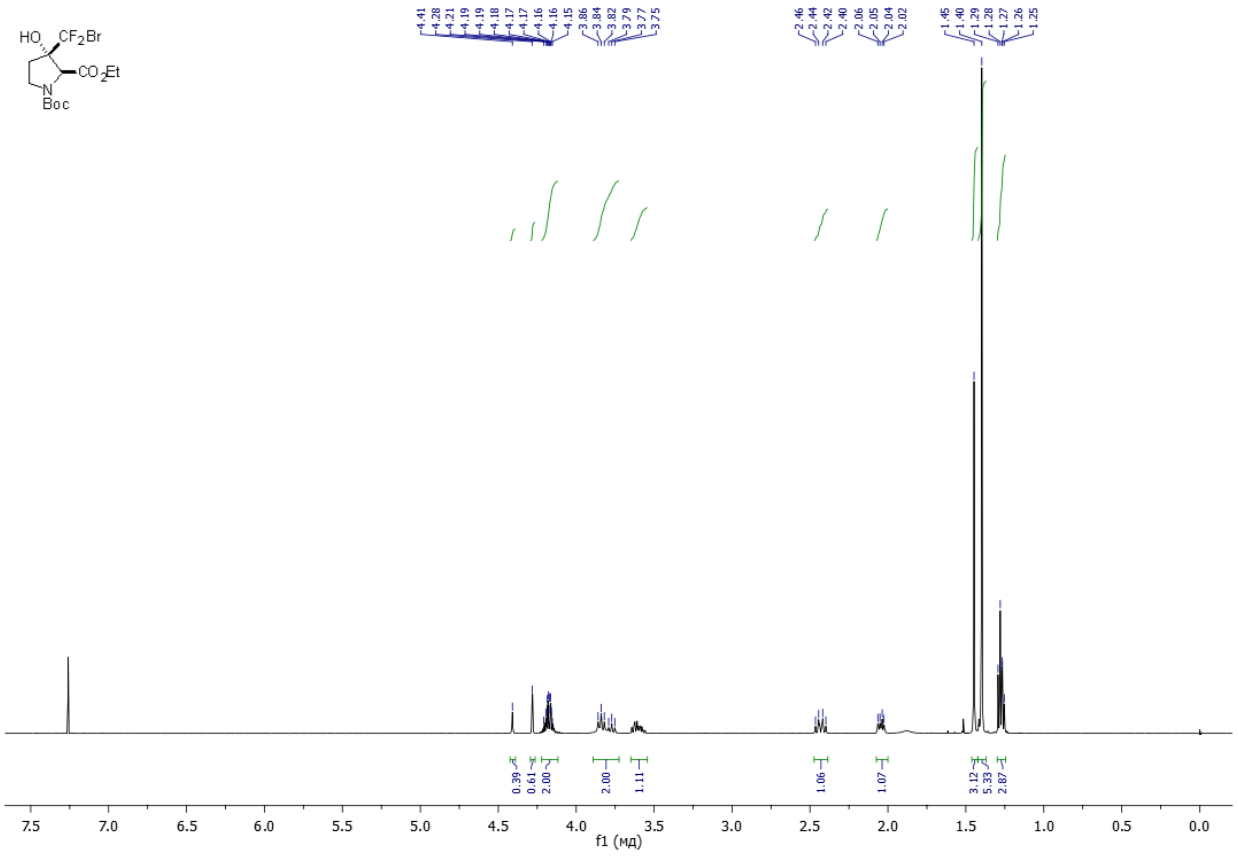
^{13}C NMR, compound ***cis*-16e**



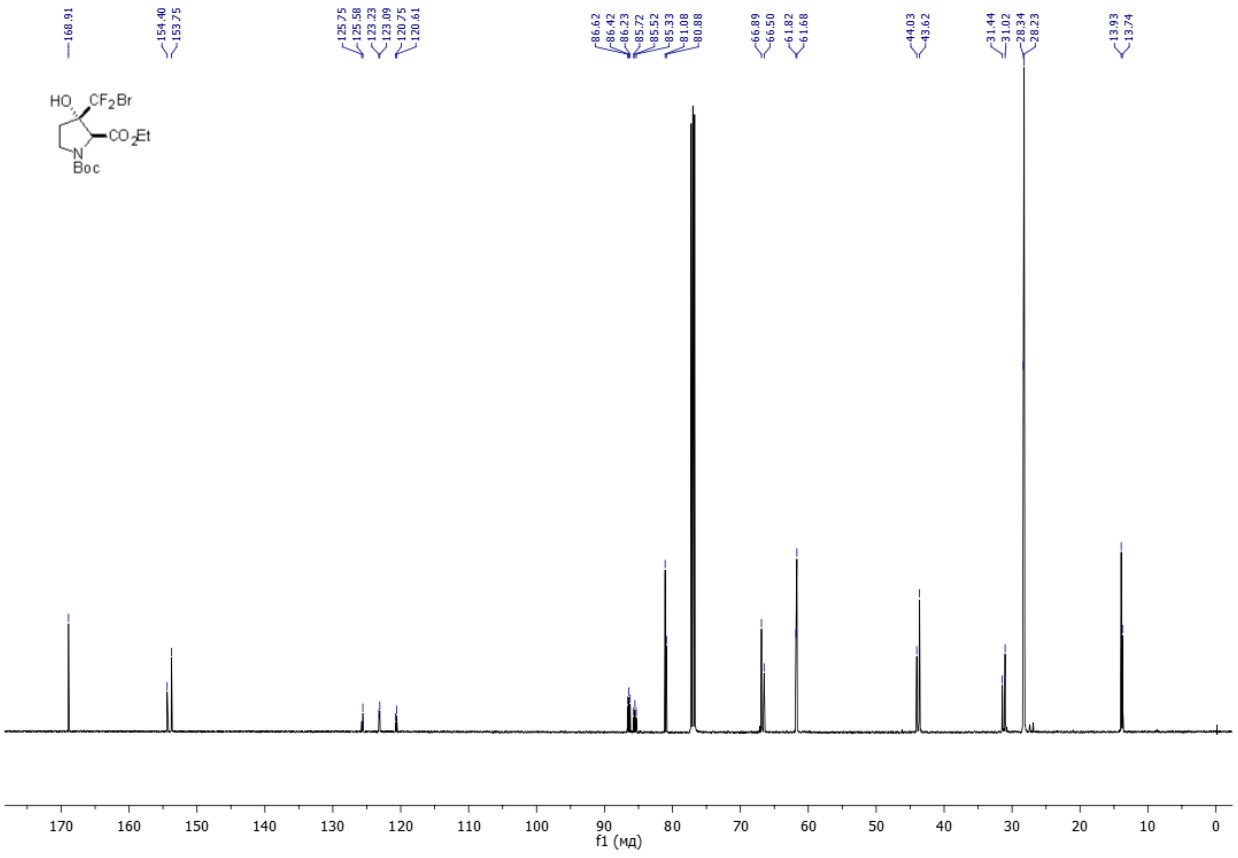
^{19}F NMR, compound ***cis*-16e**



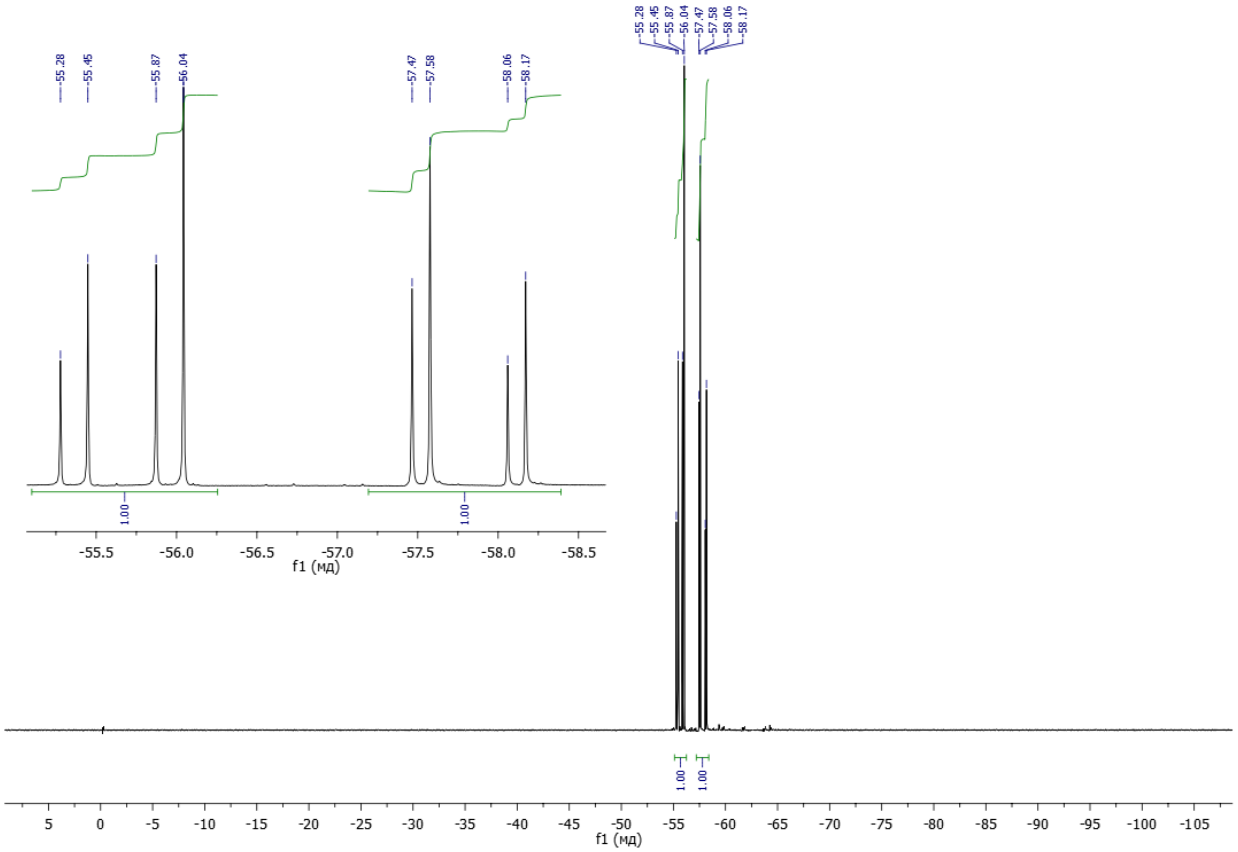
^{1}H NMR, compound ***trans*-17e**



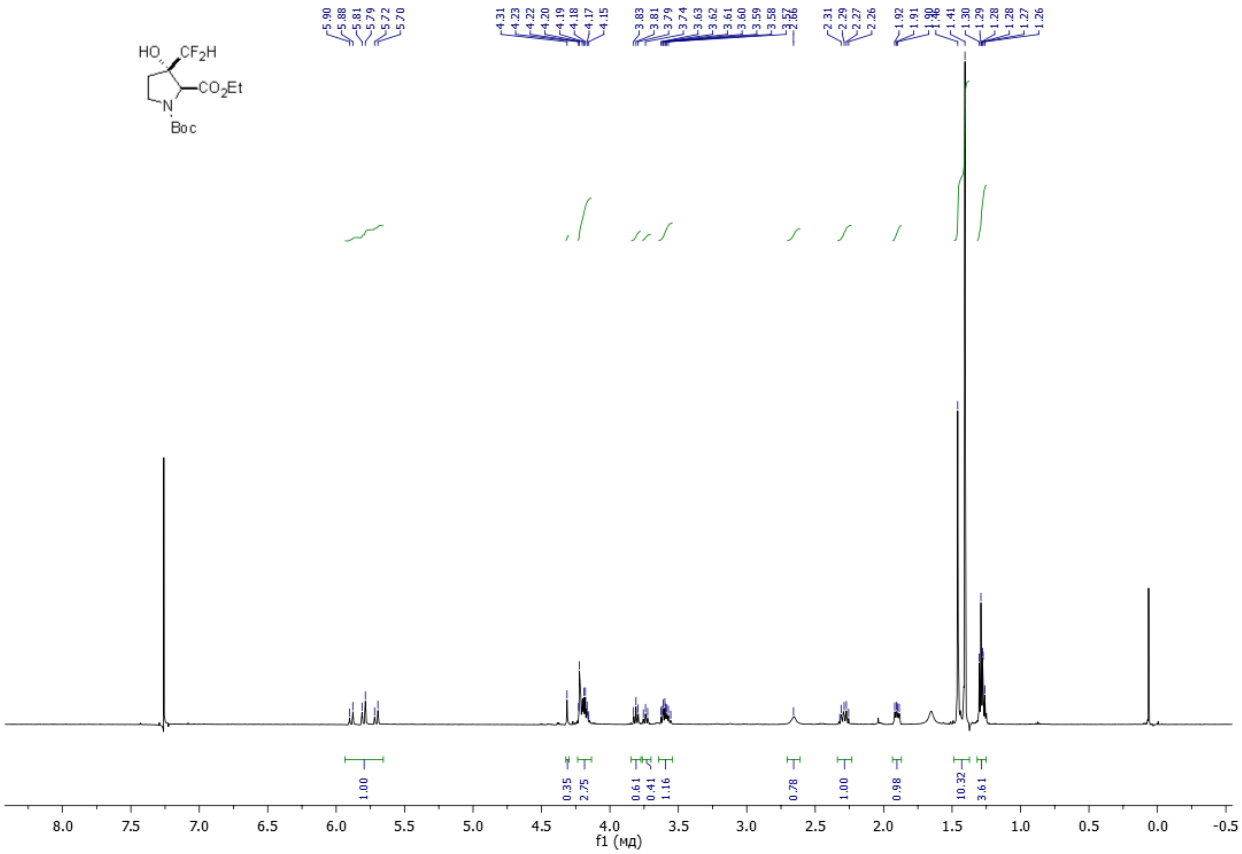
^{13}C NMR, compound ***trans*-17e**



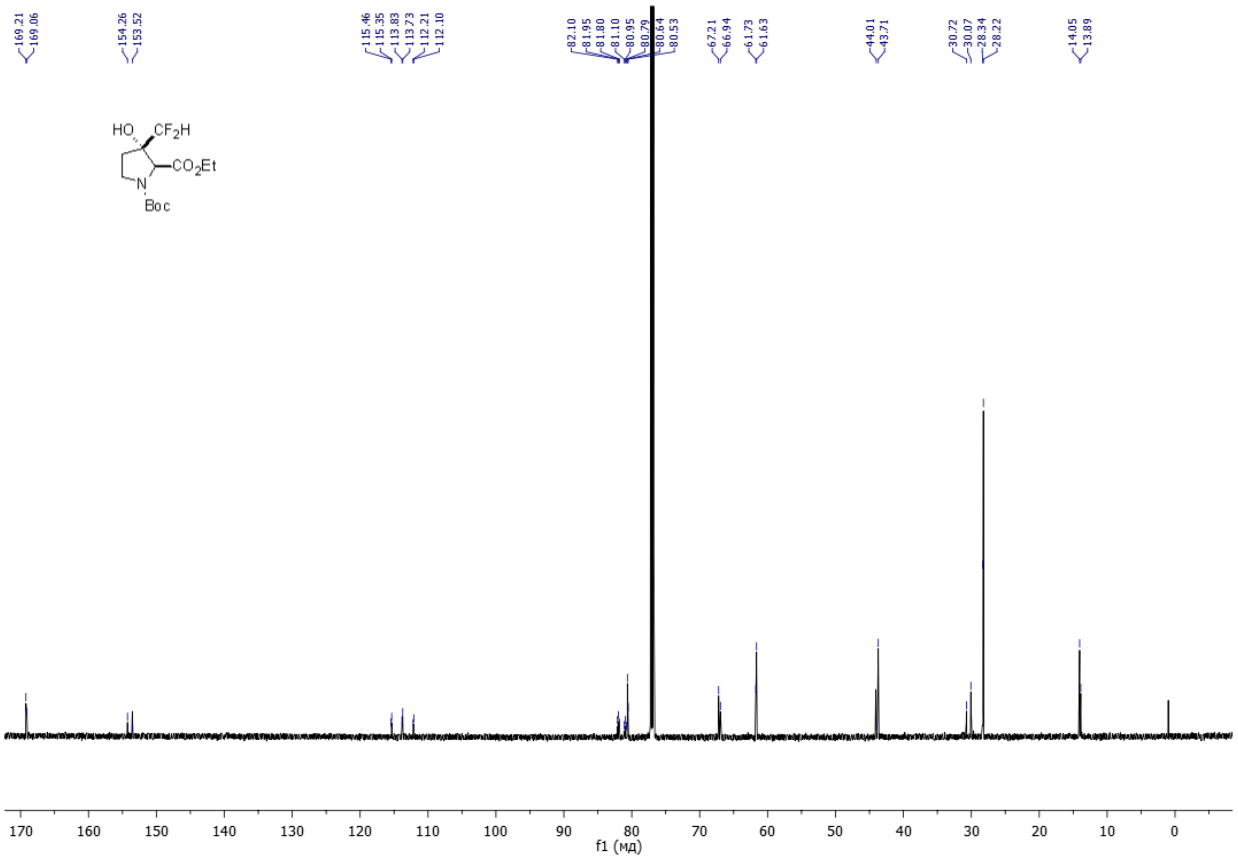
^{19}F NMR, compound ***trans*-17e**



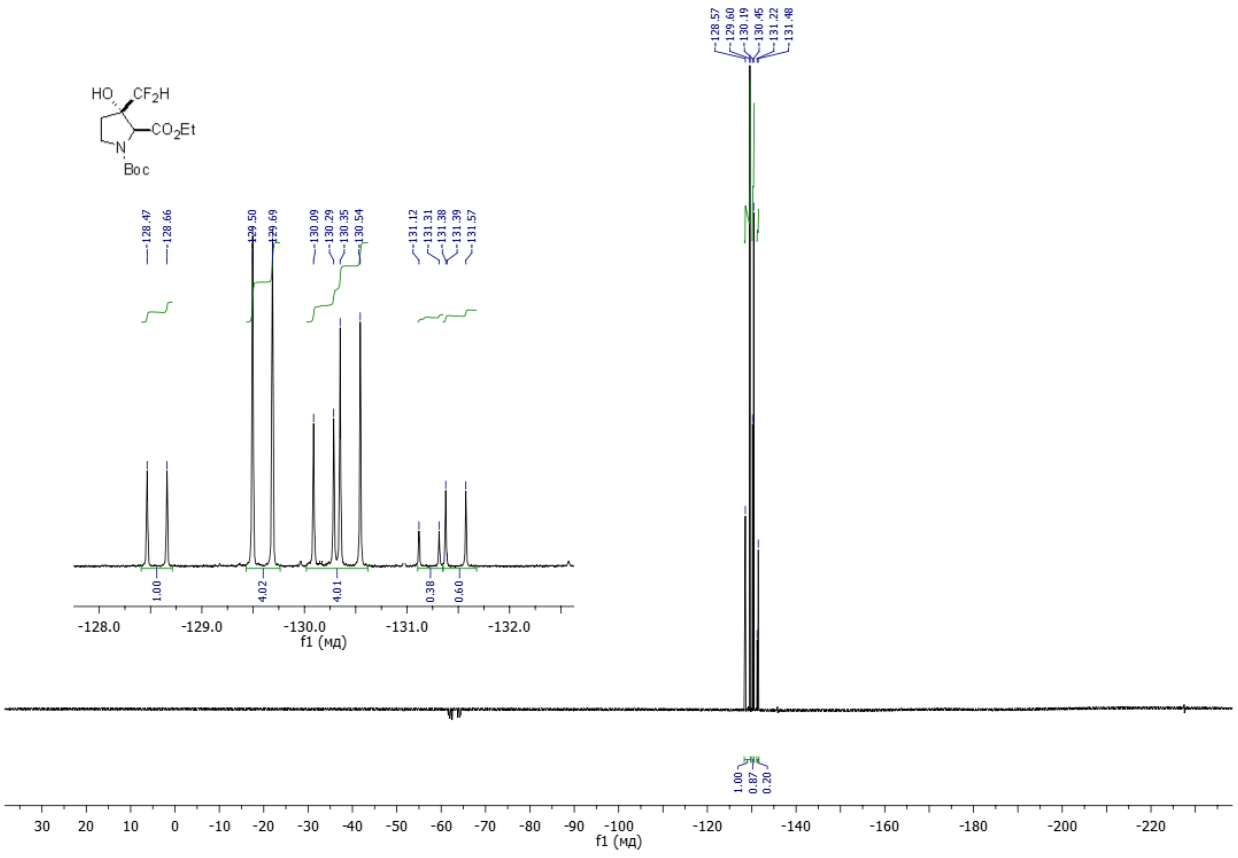
^{1}H NMR, compound ***trans*-17c**



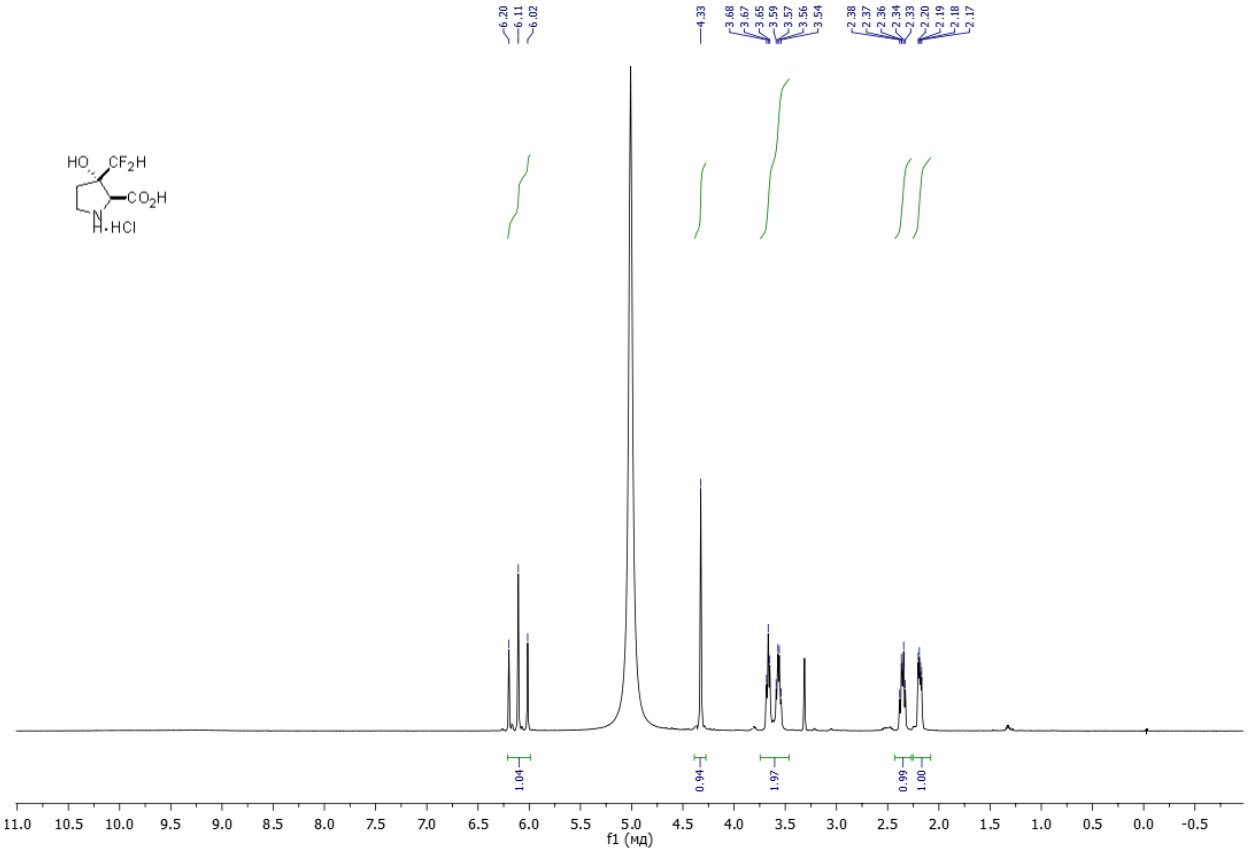
^{13}C NMR, compound ***trans*-17c**



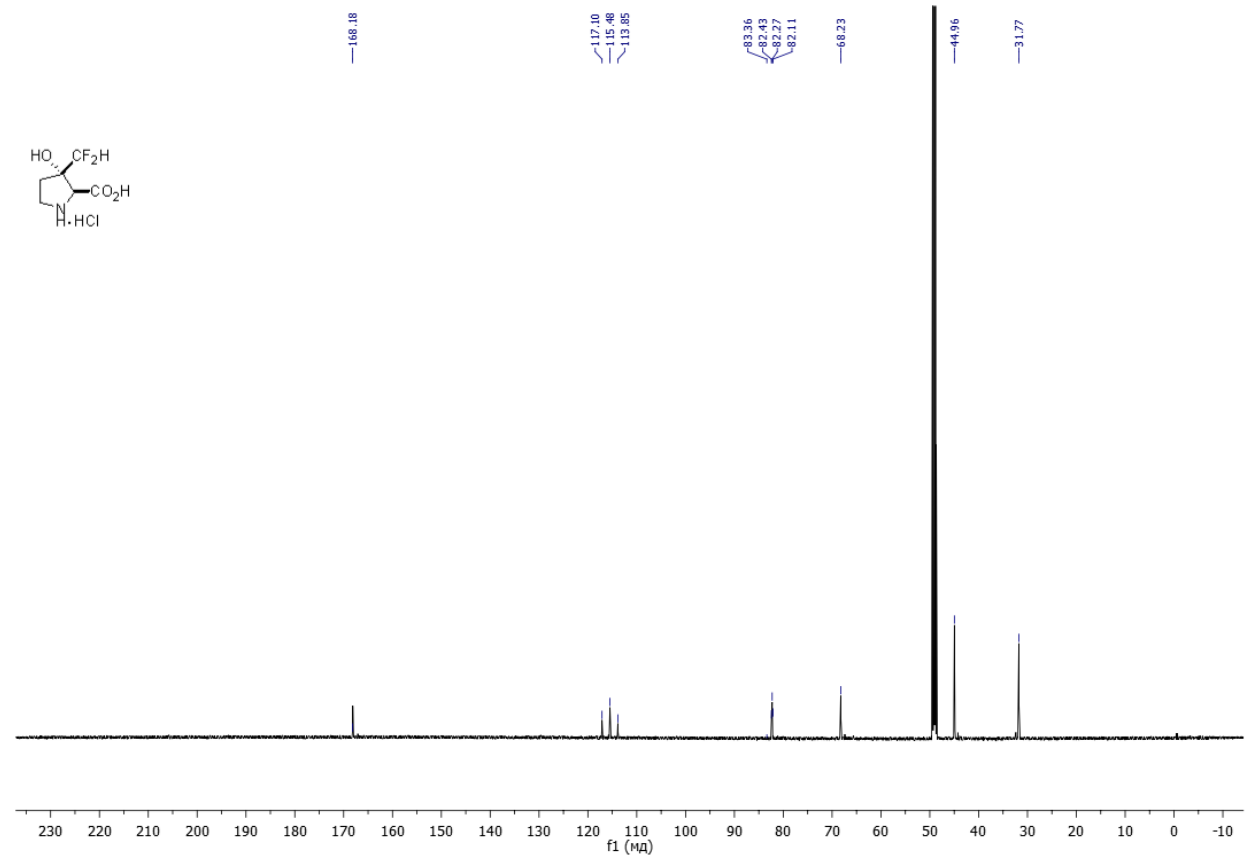
^{19}F NMR, compound ***trans*-17c**



^{1}H NMR, compound ***trans*-16c**



^{13}C NMR, compound ***trans*-16c**



^{19}F NMR, compound ***trans*-16c**