Supplementary Information

Synthesis of selected plant metabolites of Icafolin-methyl via formation of a spirocyclic nitronate

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1. Materials and Methods

^{1}H NMR spectra were recorded at 600 MHz with a BRUKER Ascend-600 or a BRUKER UltraShield 600 Plus spectrometer at 323 K. ^{13}C NMR spectra were recorded at 151 MHz with a BRUKER Ascend-600 or a BRUKER UltraShield 600 Plus spectrometer. Multiplicities are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, sex = sextet, h = heptet, m = multiplet, br = broad. Chemical shift values of ^{1}H and ^{13}C NMR spectra are commonly reported in ppm relative to residual solvent signal as internal standard.

Column chromatography was performed using a TELEDYNE ISCO CombiFlash NextGen 300 flash column chromatography system applying TELEDYNE ISCO RediSep flash columns (normal phase) or TELEDYNE ISCO RediSep RP C18 flash columns (reverse phase), with the indicated solvent system.

Preparative supercritical fluid chromatography (SFC) was performed using a SEPIATEC SFC-250 benchtop system, with the indicated column and solvent system.

Analytical thin-layer chromatography was performed using precoated silica gel plates (MACHERY NAGEL) and the spots were visualized with UV light at 254 nm or alternatively by staining with permanganate solutions.

Specific Optical rotation values $[\alpha]^{T}_{D}$ were measured on a MCP 5100 by ANTON PAAR at a wavelength of 589 nm (D) and given temperature *T*.

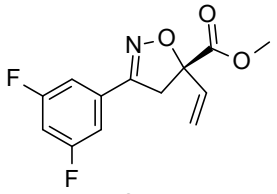
High-resolution mass spectrometry (HRMS) was measured with a SELECT SERIES Cyclic IMS mass spectrometry system by WATERS.

Differential scanning calorimetry (DSC) were measured on a DSC 1 calorimeter by METTLER TOLEDO.

Commercially available reagents, chromatography type or dry solvents were used as received or purified by standard techniques according to the literature.[S1] (5*S*)-3-(3,5-Difluorophenyl)-5-vinyl-4*H*-isoxazole-5-carboxylic acid[S2] and [*rac*-(3*R*,5*R*)-5-methoxycarbonyltetrahydrofuran-3-yl]ammonium chloride[S3] were synthesized according to literature-known procedures.

2. Chemical Syntheses

Methyl (5*S*)-3-(3,5-difluorophenyl)-5-vinyl-4*H*-isoxazole-5-carboxylate (SI-1)



SI-1

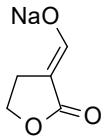
Thionyl chloride (2.16 mL, 29.7 mmol, 1.50 eq.) was added dropwise to a solution of (5*S*)-3-(3,5-difluorophenyl)-5-vinyl-4*H*-isoxazole-5-carboxylic acid (5.00 g, 19.7 mmol, 1.00 eq.) in MeOH (75.0 mL) at 0 °C. The resulting mixture was warmed up to ambient temperature and stirred for 16 h. Subsequently, the solvent was evaporated under reduced pressure and the residue was redissolved in a mixture of EtOAc (15.0 mL) and cyclohexane (15.0 mL). The solution was then filtered through a silica gel pad, which was washed with EtOAc/cyclohexane (1:1 *v/v*). The filtrated was concentrated under reduced pressure to give of the target methyl ester **SI-1** (4.98 g, 18.6 mmol, 95% yield) as a colorless oil which crystallizes upon storage.

^{1}H NMR (DMSO-d_6, 600 MHz): δ [ppm] 7.41 (3H, m, Ar*H*), 6.18 (1H, dd, C*H*, J = 17.2, 10.7 Hz), 5.48 (1H, d, CH_2, J = 17.2 Hz), 5.39 (1H, d, CH_2, J = 10.7 Hz), 3.97 (1H,d, CH_2, J = 17.7 Hz), 3.78 (3H, s, OCH_3), 3.70 (1H, d, CH_2, J = 17.7 Hz).

^{13}C NMR (DMSO-d_6, 151 MHz): δ [ppm] 170.11, 163.35, 163.26, 161.71, 161.62, 155.19, 155.17, 155.15, 134.79, 131.88, 131.81, 131.74, 117.10, 110.15, 110.12, 110.01, 109.97, 106.03, 105.85, 105.68, 88.87, 52.99, 42.70.

HRMS (ESI) calcd. for $C_{13}H_{11}NO_3F_2$ $[M+H]^+$: 268.0785; found: 268.0795.

Sodium (*E*)-(2-oxotetrahydrofuran-3-ylidene)methanolate (17)



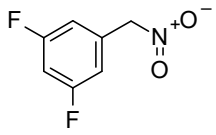
17

γ-Butyrolactone (50.0 g, 581 mmol, 1.00 eq.) and ethyl formate (43.0 g, 581 mol, 1.00 eq.) were dissolved in THF (750 mL). Sodium hydride (60 wt% in mineral oil, 25.6 g, 639 mmol, 1.10 eq.) was then added in 4 portions. Subsequently, EtOH (3.00 mL, 51.4 mmol, 8.85 mol%) was added in three equal portions within 3 h. The resulting suspension was stirred at ambient temperature for 16 h (reflux condenser is necessary as the reaction becomes exothermic). Obtained solids were then filtered off and washed twice with THF (50.0 mL). The filter cake was air dried to give the target compound **17** (72.7 g, 534 mmol, 92% yield) as a light-orange solid.

^{1}H NMR (D_2O, 600 MHz): δ [ppm] 8.44 (1H, s, C*H*), 4.33 (2H, t, CH_2, J = 8.0 Hz), 2.78 (2H, td, CH_2, J = 8.0, 1.9 Hz).

The analytical data are consistent with those reported in the literature.[S5]

3,5-Difluorophenylnitromethane (14)



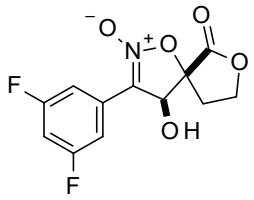
14

In 2 L Radley reactor, covered with aluminum foil, 3,5-difluorobenzyl bromide (172 g, 811 mmol, 1.00 eq.) and water (900 mL) were cooled under stirring to 5 °C. Then, silver nitrite (500 g, 3.24 mol, 4.00 eq.) were then added portion wise. The resulting suspension was stirred at 5 °C for 16 h. After HPLC showed complete conversion of the starting material, the mixture was warmed up to 20 °C and treated with MTBE (450 mL). The inorganic residues were filtered off and washed with MTBE (2x 350 mL). The phases were separated, and the organic phase was concentrated under vacuum on the rotary evaporator on the water bath at 30 °C. The residue was treated with *n*-heptane (1.00 L). The suspension was filtered. The filter cake was washed with *n*-heptane (300 mL) and air-dried to give 3,5-difluorophenylnitromethane (**14**) (97.1 g, 561 mmol, 68% yield) as a colorless solid.

^{1}H NMR (DMSO-d_6, 600 MHz): δ [ppm] 7.37 (1H, tt, Ar*H, J* = 9.4, 2.4 Hz), 7.34 – 7.27 (2H, m, Ar*H*), 5.79 (2H, s, CH_2).

The analytical data are consistent with those reported in the literature.[S3]

rac-(4*S*,5*R*)-3-(3,5-Difluorophenyl)-4-hydroxy-2-oxido-1,7-dioxa-2-azoniaspiro[4.4]non-2-en-6-one (19)



19

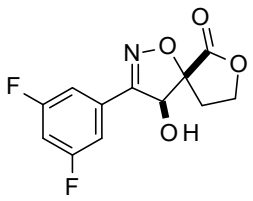
In a three necked 2 L-round bottom flask, a suspension of sodium (2-oxotetrahydrofuran-3-ylidene)methanolate (**17**) (88.4 g, 676 mmol, 1.30 eq.) in acetonitrile (1.00 L) was cooled to 3 °C. Then, a solution of bromine (33.3 mL, 650 mmol, 1.25 eq.) in acetonitrile (500 mL) was added via dropping funnel within 40 min at such rate, that the reaction temperature does not exceed 10 °C. Afterwards, a solution of 3,5-difluorophenylnitromethane (**14**) (90.0 g, 520 mmol, 1.00 eq.) in acetonitrile (300 ml) was added in one portion. To the resulting suspension triethylamine (79.7 mL, 572 mmol, 1.1 eq.) were added dropwise within 9 min, after which the reaction temperature reached 14 °C. The resulting suspension was stirred in the cooling bath for additional 10 min and then was let to warm up to 22 °C and stirred for 15 h. Subsequently, the mixture was concentrated in vacuo on the water bath at 40 °C. The residue was treated with water (600 mL) and chloroform (350 mL) and stirred for 90 min. The formed precipitate was filtered off, washed with chloroform (100 mL), water (150 mL) and once more with chloroform (150 mL). The filter cake was air dried for 12 h and the dried in vacuo at 30 °C for 24 h to give the target nitronate **19** (57.1 g, 200 mmol, 38% yield) as a colorless solid.

^{1}H NMR (DMSO-d_6, 600 MHz): δ [ppm] 7.68 – 7.60 (2H, m, Ar*H*), 7.42 (1H, tt, Ar*H*, *J* = 9.1, 2.4 Hz), 7.09 (1H, d, O*H*, *J* = 8.2 Hz), 5.98 (1H, d, C*H*OH, *J* = 8.0 Hz), 4.52 (1H, t, OC*H2*, *J* = 9.0 Hz), 4.37 (1H, ddd, OCH_2, *J* = 11.2, 9.3, 5.5 Hz), 2.74 (1H, dd, *J* = 12.7, 5.3 Hz), 2.65 (1H, ddd, CH_2, *J* = 12.7, 11.3, 8.9 Hz).

^{13}C NMR (DMSO-d_6, 151 MHz): δ [ppm] 169.88, 163.25, 163.16, 161.62, 161.53, 128.76, 114.00, 113.98, 109.24, 109.20, 109.09, 109.05, 105.44, 105.26, 105.09, 83.48, 78.02, 63.87, 39.52, 31.92.

HRMS (ESI) calcd. for $C_{12}H_8NO_4F_2$ $[M+H-H2O]^+$: 268.0421; found: 268.0418.

rac-(4*S*,5*R*)-3-(3,5-Difluorophenyl)-4-hydroxy-1,7-dioxa-2-azaspiro[4.4]non-2-en-6-one (22)



22

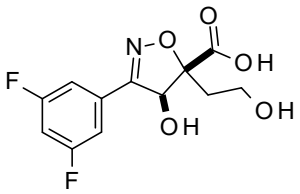
Nitronate **19** (55.4 g, 194 mmol, 1.00 eq.) was suspended in trimethyl phosphite (1.00 L). The mixture was heated under stirring at 105 °C. After complete dissolution of starting material has been achieved (approx. 13 h), the mixture was heated for additional 30 min and then concentrated under reduced pressure. The residue was treated with ice-cold water (500 mL) and 10% hydrochloric acid (50.0 mL). The resulting mixture was stirred for 65 min. The suspension was then filtered. The filter cake was washed with water (100 mL) and then suspended in chloroform (180 mL). After stirring the suspension was stirred for 20 min, it was filtered and the filter cake was washed with chloroform (2x 30.0 mL) and air-dried to give the target lactone **22** (44.2 g, 164 mmol, 83% yield) as a beige solid.

^{1}H NMR (DMSO-d_6, 600 MHz): δ [ppm] 7.44 (3H, m, Ar*H*), 6.86 (1H, d, O*H*, J = 8.0 Hz), 5.85 (1H, d, C*H*OH, J = 8.0 Hz), 4.51 (1H, ddd, OC*H2*, J = 9.4, 8.0, 1.7 Hz), 4.32 (1H, ddd, OCH_2, J = 10.5, 9.2, 6.0 Hz), 2.63 – 2.55 (2H, br m, CH_2).

^{13}C NMR (DMSO-d_6, 151 MHz): δ [ppm] 170.66, 163.31, 163.23, 161.68, 161.59, 156.14, 156.12, 156.10, 131.16, 131.09, 131.02, 110.33, 110.29, 110.19, 110.15, 106.09, 105.92, 105.75, 88.72, 81.19, 64.04, 32.47.

HRMS (ESI) calcd. for $C_{12}H_{10}NO_4F_2$ $[M+H]^+$: 270.0578; found: 270.0571.

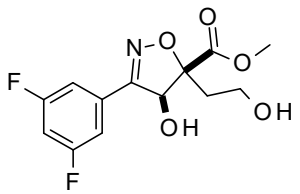
rac-(4*S*,5*R*)-3-(3,5-Difluorophenyl)-4-hydroxy-5-(2-hydroxyethyl)-4*H*-isoxazole-5-carboxylic acid (SI-2)



SI-2

A suspension of lactone **22** (44.1 g, 164 mmol, 1.00 eq.) in water (270 mL) and 20% aqueous NaOH solution (33.6 mL, 41.0 g, 205 mmol, 1.25 eq.) was stirred at rt for 4 h. The suspension was then treated with 20% hydrochloric acid (41.0 mL) and stirred for 28 min. The formed precipitate was filtered off, washed with water (100 mL) and air-dried for 48 h to give the corresponding carboxylic acid **SI-2** (46.4 g) as a light-grey solid which was used in the next step without any further purification.

Methyl *rac*-(4*S*,5*R*)-3-(3,5-Difluorophenyl)-4-hydroxy-5-(2-hydroxyethyl)-4*H*-isoxazole-5-carboxylate (23)



23

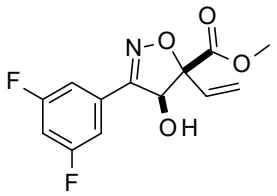
Carboxylic acid **SI-2** (15.0 g, 52.2 mmol, 1.00 eq.) was dissolved in a mixture of toluene (250 mL) and methanol (113 mL). The obtained solution was cooled to 4 °C and a solution of trimethylsilyldiazomethane (2.00 M in hexane, 49.6 mL, 99.2 mmol, 1.90 eq.) was added gradually over 20 min. After 2 h of stirring at temperatures in a range of 0 – 5 °C, complete conversion of starting material was observed by HPLC. The mixture was concentrated to dryness under reduced pressure at a bath temperature of 35 °C. The desired hydroxyester **23** (15.0 g, contained approx. 5% of lactone **22**, 47.0 mmol, 90% yield over two steps) as a colorless solid.

^{1}H NMR (DMSO-d_6, 600 MHz): δ [ppm] 7.39 (3H, m, Ar*H*), 6.68 (1H, d, O*H*, *J* = 7.8 Hz), 5.45 (1H, d, C*H*OH, *J* = 7.8 Hz), 4.59 (1H, t, O*H*, *J* = 5.0 Hz), 3.68 (3H, s, OCH_3), 3.46 (2H, m, OCH_2), 2.16 (1H, dt, CH_2, *J* = 14.2, 7.1 Hz), 1.87 (1H, ddd, CH_2, *J* = 14.2, 6.5, 5,5 Hz).

^{13}C NMR (DMSO-d_6, 151 MHz): δ [ppm] 168.15, 163.32, 163.23, 161.68, 161.60, 156.24, 156.21, 156.19, 131.73, 131.66, 131.59, 110.14, 110.10, 109.99, 109.96, 105.73, 105.56, 105.39, 91.62, 80.76, 56.16, 51.96, 37.30.

HRMS (ESI) calcd. for $C_{13}H_{14}NO_5F_2$ $[M+H]^+$: 302.0840; found: 302.0840.

Methyl (4*S*,5*R*)-3-(3,5-difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carboxylate (4a) and methyl (4*R*,5*S*)-3-(3,5-difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carboxylate (4c)



4a (4*S*, 5*R*)
4c (4*R*, 5*S*)

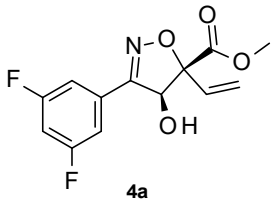
Hydroxyester **23** (12.0 g, 37.8 mmol, 1.00 eq.) and *ortho*-nitrophenyl-selenocyanate (10.7 g, 47.3 mmol, 1.25 eq.) were dissolved in 1,4-dioxane (240 mL) (solution A). Tri-*n*-butylphosphine (12.4 mL, 50.3 mmol, 1.33 eq.) were dissolved in 1,4-dioxane (120 mL) (solution B). The obtained solutions were passed through a 10 mL coil reactor at 23 °C (flow rates: 1.67 mL/min for solution A and 0.83 mL/min for solution B. The obtained mixture was collected, cooled down to 5 °C and treated with hydrogen peroxide (30% in H_2O, 11.6 mL, 114 mmol, 3.00 eq.). After stirring for 30 min at rt, the solution is cooled down again to 3 °C and then sodium sulfite solution (10% in H_2O, 300 mL) was added via a dropping funnel. After the addition was completed, the resulting emulsion was warmed up to ambient temperature and extracted with MTBE (1x 500 mL and 2x 250 mL). The combined organic phases were dried over sodium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography (cyclohexane/EtOAc) to give the target racemic mixture of olefins **4a** and **4c** (7.28 g, 25.7 mmol, 68% yield) as a light-yellow solid.

^{1}H NMR (CD_3CN, 600 MHz): δ [ppm] 7.39 (2H, m, Ar*H*), 7.09 (1H, tt, Ar*H*, *J* = 9.1, 2.4 Hz), 6.19 (1H, dd, C*H*, *J* = 17.1, 10.6 Hz), 5.48 (1H, dd, CH_2, *J* = 17.1, 0.9 Hz), 5.40 (1H, d, C*H*OH, *J* = 7.5 Hz), 5.32 (1H, dd, CH_2, *J* = 17.1, 0.9 Hz), 4.66 (1H, d, O*H*, J = 7.6 Hz), 3.81 (3H, s, OCH_3).

^{13}C NMR (CD_3CN, 151 MHz): δ [ppm] 167.75, 164.91, 164.82, 163.27, 163.18, 156.21, 156.18, 156.16, 133.47, 132.46, 132.39, 132.32, 117.35, 111.14, 111.10, 111.00, 110.96, 106.78, 106.61, 106.44, 94.27, 82.71, 53.31.

HRMS (ESI) calcd. for $C_{13}H_{12}NO_4F_2$ $[M+H]^+$: 284.0734; found: 284.0731.

Methyl (4*S*,5*R*)-3-(3,5-difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carboxylate (4a)



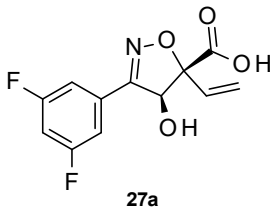
4a

Racemic resolution of olefins **4a** and **4c** (20.36 g, 71.9 mmol) was performed by SFC using a ChiralPak AZ-H column 5 µm, 250x30 mm, CO_2/MeOH = 4/1 isocratic, flow rate 100.0 mL/min). The desired (4*S*,5*R*)-enantiomer **4a** was collected as a light-yellow solid (7.87 g, 27.8 mmol).

Assignment of stereoisomers is based on X-Ray measurement (see below)

$\alpha_D^{20\,°C}$ = +7.731° (c = 1.00 g/100 mL, MeCN)

(4*S*,5*R*)-3-(3,5-Difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carboxylic acid (27a)



27a

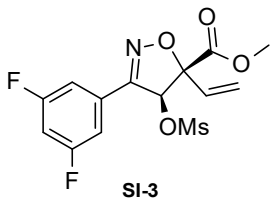
A suspension of methyl ester **4a** (1.80 g, 6.35 mmol, 1.00 eq.) was treated with an aqueous NaOH solution (2.00 M, 4.77 mL, 9.53 mmol, 1.50 eq.). After stirring for 4 h at ambient temperature, the reaction was terminated by the addition of aqueous HCl (20%, 4.00 mL). The resulting suspension was filtered. The filter cake was washed with water and dried. The filtrate was extracted with EtOAc (1x 25.0 mL, 1x 40.0 mL). The combined organic phases were washed with an aqueous NaCl solution (sat., 40.0 mL), dried over Na_2SO_4, filtrated and concentrated under reduced pressure. The residue was combined with the filter cake and dried under reduced pressure to obtain the desired carboxylic acid **27a** (1.72 g, 6.35 mmol, quant. yield) as a yellowish solid.

^{1}H NMR (DMSO-d_6, 600 MHz): δ [ppm] 7.41 (3H, m, Ar*H*), 6.86 (1H, br s, O*H*), 6.13 (1H, dd, C*H*, *J* = 17.1, 10.6 Hz), 5.39 (1H, s, C*H*OH), 5.35 (1H, dd, CH_2, *J* = 17.1, 1.2 Hz), 5.23 (1H, dd, CH_2, *J* = 17.1, 1.2 Hz).

^{13}C NMR (DMSO-d_6, 151 MHz): δ [ppm] 166.78, 162.77, 162.68, 161.13, 161.05, 154.82, 154.80, 154.78, 132.94, 130.96, 130.89, 130.82, 115.21, 109.56, 109.52, 109.41, 109.38, 105.27, 105.10, 104.93, 92.35, 80.09.

HRMS (ESI) calcd. for $C_{12}H_{10}NO_4F_2$ $[M+H]^+$: 270.0578; found: 270.0576.

Methyl (4*S*,5*R*)-3-(3,5-difluorophenyl)-4-methylsulfonyloxy-5-vinyl-4*H*-isoxazole-5-carboxylate (SI-3)

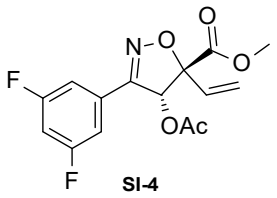


SI-3

A solution of methyl ester **4a** (2.00 g, 7.06 mmol, 1.00 eq.) and MsCl (0.77 mL, 9.89 mmol, 1.40 eq.) in CH_2Cl_2 (24.0 mL) was treated with Et_3N (1.38 mL, 9.89 mmol, 1.40 eq.) at 0 °C. The resulting

solution was warmed up to ambient temperature and stirred for 75 min. Subsequently, the mixture was quenched with H_2O (20.0 mL) and stirred for 5 min. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic extracts were washed with NaCl solution (aq. sat., 15.0 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the crude mesylate **SI-3** (2.83 g), which was used in the next step without purification.

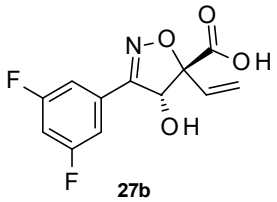
Methyl (4*R*,5*R*)-4-acetoxy-3-(3,5-difluorophenyl)-5-vinyl-4*H*-isoxazole-5-carboxylate (SI-4)



SI-4

Mesylate **SI-3** (2.83 g) and cesium acetate (2.95 g, 15.3 mmol, 2.20 eq.) were suspended in DMSO (14.0 ml) and the mixture was heated to 60 °C under stirring for 1.5 h. After complete conversion, the reaction mixture was cooled down to ambient temperature, poured into H_2O (35.0 mL) and extracted with Et_2O (2 x 20.0 mL). Combined organic phases were washed with H_2O (15.0 mL), dried over Na_2SO_4 and concentrated in vacuo to give the crude acetate **SI-4** (2.08 g) which was used directly in the next step.

(4*R*,5*R*)-3-(3,5-Difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carboxylic acid (27b)



27b

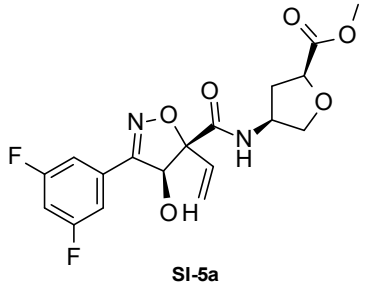
A solution of the crude acetate **SI-4** (2.08 g) in THF (17.0 mL) was treated with of aqueous NaOH solution (2.00 M, 7.31 mL, 14.6 mmol) and stirred at ambient temperature for 1 h. After complete conversion of the starting material, the mixture was treated with hydrochloric acid (2.00 M, 13.5 mL, 27.0 mmol). The resulting emulsion was diluted with H_2O and extracted with EtOAc (3 x 20.0 mL). The combined organic phases were dried over Na2SO4 and concentrated under reduced pressure. The obtained crude product was then purified via reverse-phase chromatography (0.10% aq. formic acid/MeCN) to give target carboxylic acid **27b** (1.50 g, 5.57 mmol, 79% yield over three steps) as a colorless solid.

^{1}H NMR (CD_3CN, 600 MHz): δ [ppm] 7.41 (2H, m, Ar*H*), 7.06 (1H, tt, Ar*H*, *J* = 9.1, 2.4 Hz), 6.12 (1H, dd, C*H*, *J* = 17.5, 11.0 Hz), 5.63 (1H, s, C*H*OH), 5.57 (1H, dd, C*H*, *J* = 17.5, 1.0 Hz), 5.50 (1H, dd, CH, *J* = 11.0, 1.0 Hz), 4.24 (1H, s, O*H*).

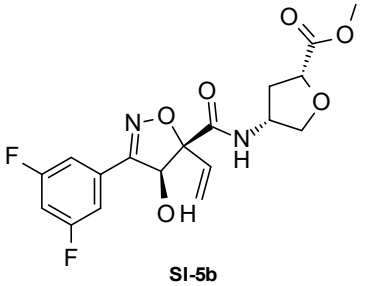
^{13}C NMR (DMSO-d_6, 151 MHz): δ [ppm] 170.78, 163.37, 163.28, 161.74, 161.65, 156.43, 156.41, 131.57, 131.50, 131.43, 130.29, 118.07, 110.19, 110.15, 110.05, 110.01, 105.89, 105.71, 105.54, 91.71, 79.15.

HRMS (ESI) calcd. for $C_{12}H_{10}NO_4F_2$ $[M+H]^+$: 270.0578; found: 270.0575.

Methyl (2*S*,4*S*)-4-[[(4*S*,5*R*)-3-(3,5-difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carbonyl]amino]tetrahydrofuran-2-carboxylate (SI-YYa) and methyl (2*R*,4*R*)-4-[[(4*S*,5*R*)-3-(3,5-difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carbonyl]amino]tetrahydrofuran-2-carboxylate(SI-XXB)



SI-5a

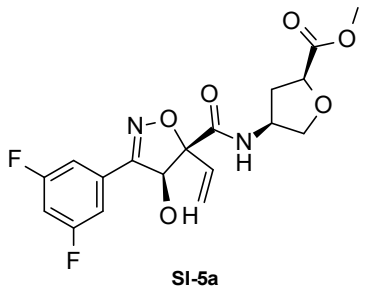


SI-5b

A suspension of carboxylic acid **27a** (1.70 g, 6.31 mmol, 1.00 eq.), [*rac*-(3*R*,5*R*)-5-methoxycarbonyltetrahydrofuran-3-yl]ammonium chloride (1.20 g, 6.63 mmol, 1.05 eq.) and HATU (2.52 g, 6.63 mmol, 1.05 eq.) in DMF (17.3 mL) was cooled to 0 °C and treated with *N,N*-diisopropylethylamine (2.27 mL, 13.2 mmol, 2.10 eq.). After 50 min, the reaction was terminated by the addition of H_2O (50.0 mL). The mixture was extracted with EtOAc (3x 60.0 mL). The combined organic phases were washed with an aqueous NaCl solution (sat., 40.0 mL), dried over Na_2SO_4, filtrated and concentrated under reduced pressure. The residue was purified by reverse-phase chromatography (0.10% aq. formic acid/MeCN) to obtain a mixture of the diastereomers (2.01 g, 5.07 mmol, 80%) as a colorless solid. The diastereomeric mixture was resolved by SFC using a ChiralPak IG column (5 µm, 250x30 mm, CO_2/MeOH = 3/1 isocratic, flow rate 100.0 mL/min). **SI-5a** (760 mg, 1.92 mmol, 30%) was collected as a yellowish oil, (2*R*,4*R*)-Ester **SI-5b** (735 mg, 1.85 mmol, 29%) as a colorless solid.

Assignment of stereoisomers is based on comparison of the corresponding 1H NMR spectra with ^{1}H NMR spectra of **SI-5c** and **SI-5d**, for which the configuration is determined based on X-Ray measurements.

Methyl (2*S*,4*S*)-4-[[(4*S*,5*R*)-3-(3,5-difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carbonyl]amino]tetrahydrofuran-2-carboxylate (SI-5a)



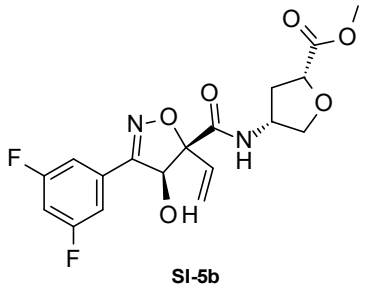
SI-5a

^{1}H NMR ($CDCl_3$, 600 MHz): δ [ppm] 7.51 (1H, d, Ar*H*, *J* = 8.0 Hz), 7.38 (2H, d, Ar*H*, *J* = 6.9 Hz), 6.88 (1H, dt, N*H*, *J* = 8.7, 2.3 Hz), 6.19 (1H, dd, C*H*, *J* = 17.1, 10.6 Hz), 5.52 (1H, dd, CH_2, *J* = 17.1, 2.0 Hz), 5.32 (2H, m, C*H*OH, CH_2), 4.57 (3H, m, 2xC*H*, O*H*), 3.99 (2H, m, OCH_2), 3.81 (3H, s, OCH_3), 2.55 (1H, m, CH_2), 2.10 (1H, dt, CH_2, *J* = 14.2, 2.1 Hz).

^{13}C NMR ($CDCl_3$, 151 MHz): δ [ppm] 173.64, 167.60, 164.07, 163.99, 162.42, 162.34, 155.83, 155.81, 155.79, 132.47, 131.08, 131.01, 130.94, 117.27, 110.56, 110.52, 110.42, 110.38, 106.28, 106.12, 105.95, 92.99, 83.03, 76.24, 74.76, 52.83, 50.09, 36.99.

HRMS (ESI) calcd. for $C_{18}H_{19}N_2O_6F_2$ $[M+H]^+$: 397.1211; found: 397.1211.

Methyl (2*R*,4*R*)-4-[[(4*S*,5*R*)-3-(3,5-difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carbonyl]amino]tetrahydrofuran-2-carboxylate (SI-5b)



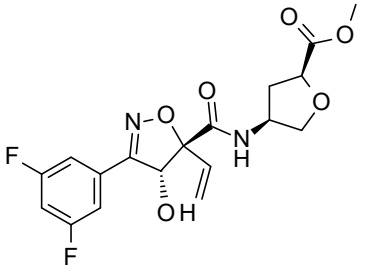
SI-5b

^{1}H NMR ($CDCl_3$, 600 MHz): δ [ppm] 7.52 (1H, d, Ar*H*, *J* = 8.0 Hz), 7.39 (2H, d, Ar*H*, *J* = 7.1 Hz), 6.88 (1H, dt, N*H*, *J* = 8.8, 2.3 Hz), 6.19 (1H, dd, C*H*, *J* = 17.1, 10.6 Hz), 5.53 (1H, dd, CH_2, *J* = 17.1, 2.1 Hz), 5.34 (1H, m, C*H*OH), 5.32 (1H, dd, CH_2, *J* = 17.1, 2.1 Hz), 4.60 (1H, m, C*H*), 4.55 (1H, dt, C*H*, *J* = 9.6, 2.8 Hz), 4.46 (d, 1H, O*H*, *J* = 5.6 Hz), 4.03 (2H, t, OCH_2, *J* = 2.8 Hz), 3.72 (3H, s, OCH_3), 2.52 (1H, m, CH_2), 2.14 (1H, dt, CH_2, *J* = 14.0, 2.4 Hz).

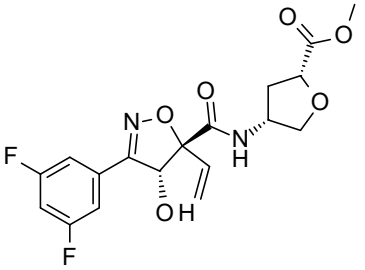
^{13}C NMR (CD_3CN, 151 MHz): δ [ppm] 173.67, 167.67, 164.08, 164.00, 162.43, 162.35, 155.77, 155.75, 155.72, 132.33, 131.10, 131.04, 130.97, 117.38, 110.53, 110.49, 110.39, 110.35, 106.28, 106.11, 105.94, 93.02, 83.10, 76.22, 74.26, 52.85, 50.19, 37.19.

HRMS (ESI) calcd. for $C_{18}H_{19}N_2O_6F_2$ $[M+H]^+$: 397.1211; found: 397.1210.

Methyl (2*R*,4*R*)-4-[[(4*R*,5*R*)-3-(3,5-difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carbonyl]amino]tetrahydrofuran-2-carboxylate (SI-5c) and methyl (2*S*,4*S*)-4-[[(4*R*,5*R*)-3-(3,5-difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carbonyl]amino]tetrahydrofuran-2-carboxylate (SI-5d)



SI-5c

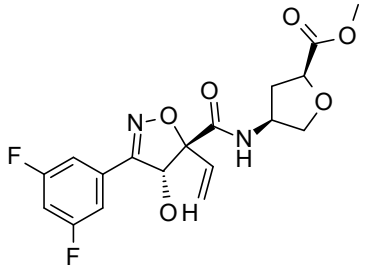


SI-5d

A suspension of carboxylic acid **27b** (1.14 g, 4.23 mmol, 1.00 eq.), [*rac*-(3*R*,5*R*)-5-methoxycarbonyltetrahydrofuran-3-yl]ammonium chloride (823 mg, 4.53 mmol, 1.07 eq.) and HATU (1.723 g, 4.53 mmol, 1.07 eq.) in DMF (11.4 mL) was cooled to 0 °C and treated with *N,N*-diisopropylethylamine (1.52 mL, 8.89 mmol, 2.10 eq.). After 60 minutes, the obtained solution was concentrated on rotary evaporator. The residue was purified by reverse-phase chromatography (0.10% aq. formic acid/MeCN) to obtain a mixture of the diastereomers (1.64 g, 4.14 mmol, 97%) as a colorless oil. The diastereomeric mixture was resolved by SFC using a Chiracel OX-H column (5 µm, 250x30 mm, CO_2/MeOH = 9/1 isocratic, flow rate 80.0 mL/min). (2*S*,4*S*)-Ester **5c** (650 mg, 1.64 mmol, 39%) was collected as a colorless oil, (2*R*,4*R*)-Ester **5d** (760 mg, 1.92 mmol, 43%) as a colorless oil.

Assignment of stereoisomers is based on X-Ray measurement (see below)

Methyl (2*S*,4*S*)-4-[[(4*S*,5*R*)-3-(3,5-difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carbonyl]amino]tetrahydrofuran-2-carboxylate (SI-5c)



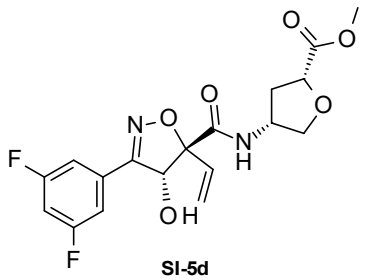
SI-5c

^{1}H NMR ($CDCl_3$, 600 MHz): δ [ppm] 7.61 (1H, d, Ar*H*, *J* = 8.2 Hz), 7.41 (2H, d, Ar*H*, *J* = 6.9 Hz), 6.89 (1H, ddt, N*H*, *J* = 8.4, 6.3, 2.4 Hz), 6.10 (1H, dd, CH, *J* = 17.5, 10.9 Hz), 5.64 (2H, m, CH_2), 5.34 (1H, m, C*H*OH), 5.51 (1H, dd, CH_2, *J* = 10.9, 2.0 Hz), 4.56 (2H, m, C*H*), 3.99 (1H, m, OCH_2), 3.88 (1H, m, OCH_2), 3.81 (3H, s, OCH_3), 3.51 (1H, m, O*H*), 2.55 (1H, m, CH_2), 2.08 (1H, m, CH_2).

^{13}C NMR (DMSO-d_6, 151 MHz): δ [ppm] 172.74, 169.32, 163.38, 163.29, 161.75, 161.66, 157.25, 157.22, 157.20, 131.39, 131.32, 131.25, 130.93, 118.15, 110.30, 110.26, 110.16, 110.12, 106.09, 105.92, 105.75, 92.75, 79.07, 75.32, 71.97, 51.79, 49.40, 34.85.

HRMS (ESI) calcd. for $C_{18}H_{19}N_2O_6F_2$ $[M+H]^+$: 397.1211; found: 397.1210.

Methyl (2*R*,4*R*)-4-[[(4R,5*R*)-3-(3,5-difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carbonyl]amino]tetrahydrofuran-2-carboxylate (SI-5d)



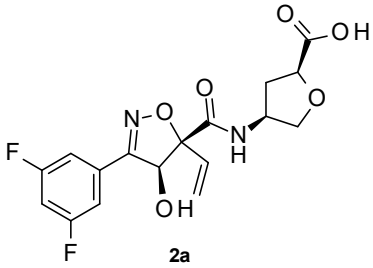
SI-5d

^{1}H NMR ($CDCl_3$, 600 MHz): δ [ppm] 7.66 (1H, d, Ar*H*, *J* = 8.4 Hz), 7.40 (2H, d, Ar*H*, *J* = 7.1 Hz), 6.88 (1H, tt, N*H*, *J* = 8.7, 2.4 Hz), 6.10 (1H, dd, C*H*, *J* = 17.5, 10.9 Hz), 5.65 (2H, m, CH_2), 5.34 (1H, m, C*H*OH), 5.52 (1H, dd, CH_2, *J* = 10.9, 2.0 Hz), 4.59 (1H, m, C*H*), 4.53 (1H, dd, C*H*, *J* = 9.4, 3.5 Hz), 4.02 (1H, dd, OCH_2, *J* = 9.5, 5.1 Hz), 3.94 (1H, dd, OCH_2, *J* = 9.5, 2.3 Hz), 3.79 (3H, s, OCH_3), 3.48 (1H, m, O*H*), 2.50 (1H, m, CH_2), 1.98 (1H, m, CH_2).

^{13}C NMR (DMSO-d_6, 151 MHz): δ [ppm] 172.67, 169.40, 163.38, 163.29, 161.75, 161.66, 157.22, 157.20, 157.18, 131.41, 131.34, 131.27, 130.91, 118.26, 110.28, 110.24, 110.13, 110.09, 106.08, 105.91, 105.74, 92.77, 79.07, 75.32, 71.89, 51.71, 49.50, 34.73.

HRMS (ESI) calcd. for $C_{18}H_{19}N_2O_6F_2$ $[M+H]^+$: 397.1211; found: 397.1210.

(2*S*,4*S*)-4-[[(4*S*,5*R*)-3-(3,5-Difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carbonyl]amino]tetrahydrofuran-2-carboxylic acid (2a)



2a

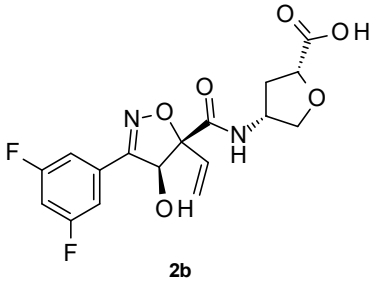
A suspension of methyl ester **SI-5a** (760 mg, 1.91 mmol, 1.00 eq.) in a mixture of EtOH (2.00 mL) and H_2O (4.00 mL) was treated with an aqueous NaOH solution (2.00 M, 1.27 mL, 2.53 mmol, 1.3 eq.). After 70 min at rt, the reaction mixture was diluted with H_2O (10.0 mL) and EtOAc (30.0 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (1x 30.0 mL, 1x 20.0 mL). The combined organic phases were washed with an aqueous NaCl solution (sat., 30.0 mL), dried over Na_2SO_4 and concentrated. The desired carboxylic acid **2a** (627 mg, 99%) was obtained a colorless solid.

^{1}H NMR (DMSO-d_6, 600 MHz): δ [ppm] 12.75 (1H, s, COO*H*), 7.97 (1H, d, N*H*, *J* = 7.7 Hz), 7.42 (3H, m, Ar*H*), 6.75 (1H, d, O*H*, *J* = 8.0 Hz), 6.18 (1H, dd, C*H*, *J* = 17.2, 10.6 Hz), 5.32 (1H, s, C*H*OH), 5.25 (1H, dd, CH_2, *J* = 17.2, 1.3 Hz), 5.19 (1H, dd, CH_2, *J* = 10.7, 1.3 Hz), 4.37 (2H, m, CH), 3.88 (1H, dd, CH_2, J = 8.6, 6.3 Hz), 3.65 (1H, dd, CH_2, *J* = 8.6, 5.5 Hz), 2.46 (1H, m, 1H, CH_2), 2.02 (1H, dt, CH_2, *J* = 12.6, 6.1 Hz).

^{13}C NMR (DMSO-d_6, 151 MHz): δ [ppm] 173.39, 165.15, 162.78, 162.69, 161.15, 161.05, 155.42, 155.39, 155.37, 133.09, 130.81, 130.74, 130.67, 114.61, 109.63, 109.60, 109.49, 109.45, 105.48, 1ß5.31, 105.13, 92.48, 80.20, 74.77, 71.19, 48.67, 34.23.

HRMS (ESI) calcd. for $C_{17}H_{17}N_2O_6F_2$ $[M+H]^+$: 383.1055; found: 383.1051.

(2*R*,4*R*)-4-[[(4*S*,5*R*)-3-(3,5-Difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carbonyl]amino]tetrahydrofuran-2-carboxylic acid (2b)



2b

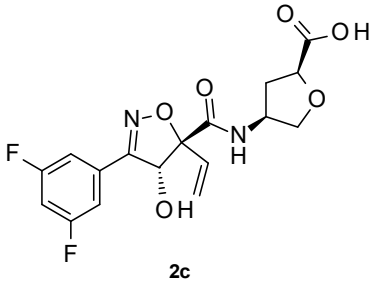
A suspension of methyl ester **SI-5b** (720 mg, 1.81 mmol, 1.00 eq.) in a mixture of EtOH (2.50 mL) and H_2O (4.00 mL) was treated with an aqueous NaOH solution (2.00 M, 1.18 mL, 2.36 mmol, 1.3 eq.). After 50 min at rt, the reaction mixture was treated with hydrochloric acid (1.00 M, 4.00 mL) and diluted with H_2O (10 mL) and EtOAc (30 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (2x 30 mL). The combined organic phases were washed with an aqueous NaCl solution (sat., 30.0 mL), dried over Na_2SO_4 and concentrated. The desired carboxylic acid **2b** (655 mg, 91% yield) was obtained a colorless solid.

^{1}H NMR (DMSO-d_6, 600 MHz): δ [ppm] 12.71 (1H, s, COO*H*), 7.95 (1H, d, N*H*, *J* = 7.5 Hz), 7.42 (3H, m, Ar*H*), 6.74 (1H, d, O*H*, *J* = 8.0 Hz), 6.18 (1H, dd, C*H*, *J* = 17.2, 10.6 Hz), 5.32 (1H, d, C*H*OH, *J* = 6.4 Hz), 5.32 (1H, dd, CH_2, *J* = 17.2, 1.3 Hz), 5.32 (1H, dd, CH_2, *J* = 10.6, 1.3 Hz), 4.36 (2H, m, C*H*), 3.89 (1H, dd, CH_2, *J* = 8.6, 6.3 Hz), 3.67 (1H, dd, CH_2, *J* = 8.6, 5.8 Hz), 2.48 (1H, m, CH_2), 1.98 (1H, dt, CH_2, *J* =12.7, 6.1 Hz).

^{13}C NMR (DMSO-d_6, 151 MHz): δ [ppm] 173.33, 165.19, 162.78, 162.69, 161.14, 161.06, 155.38, 155.36, 155.34, 133.15, 130.82, 130.75, 114.58, 109.63, 109.59, 109.49, 109.45, 105.47, 1ß5.30, 105.13, 92.49, 80.23, 74.81, 71.47, 48.64, 34.49.

HRMS (ESI) calcd. for $C_{17}H_{17}N_2O_6F_2$ $[M+H]^+$: 383.1055; found: 383.1055

(2S,4*S*)-4-[[(4*R*,5*R*)-3-(3,5-Difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carbonyl]amino]tetrahydrofuran-2-carboxylic acid (2c)



2c

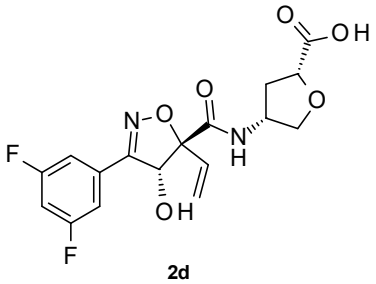
Methyl Ester **SI-5c** (760 mg, 1.91 mmol) was dissolved in 5.2 ml of tetrahydrofuran. Water (2.6 ml) and lithium hydroxide (55.1 mg, 2.30 mmol, 1.2 eq.) were then added. The mixture was stirred at room temperature for 20 minutes until complete conversion of starting material was achieved. Resulting solution was treated with hydrochloric acid (1.00 M, 3.50 mL) and the extracted with ethyl acetate (3 x 15 ml). Combined organic phases were washed with 10 ml brine, dried over sodium sulphate and the concentrated in vacuo to give desired carboxylic acid **2c** as a colorless solid (637 mg, 86% yield).

^{1}H NMR (DMSO-d_6, 600 MHz): δ [ppm] 12.72 (1H, s, COO*H*), 8.23 (1H, d, N*H*, *J* = 7.5 Hz), 7.43 (3H, m, Ar*H*), 6.51 (1H, d, O*H*, *J* = 8.4 Hz), 6.04 (1H, dd, C*H*, *J* = 17.4, 11.0 Hz), 5.61 (1H, m, C*H*OH), 5.40 (2H, m, CH_2,), 4.32 (2H, m, CH), 3.81(1H, dd, CH_2, J = 8.6, 6.3 Hz), 3.57 (1H, m, CH_2), 2.44 (1H, m, CH_2), 1.97 (1H, dt, CH_2, *J* =12.7, 5.7 Hz).

^{13}C NMR (DMSO-d_6, 151 MHz): δ [ppm] 173.34, 168.62, 162.78, 162.69, 161.14, 161.05, 156.63, 156.61, 156.59, 130.81, 130.74, 130.67, 130.26, 130.24, 117.63. 109.69, 109.65, 109.54, 109.51, 105.47, 105.30, 105.13, 92.13, 92.11, 78.46, 78.34, 74.73, 71.47, 48.82, 34.46, 34.44.

HRMS (ESI) calcd. for $C_{17}H_{17}N_2O_6F_2$ $[M+H]^+$: 383.1055; found: 383.1051.

(2*R*,4*R*)-4-[[(4*R*,5*R*)-3-(3,5-Difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carbonyl]amino]tetrahydrofuran-2-carboxylic acid (2d)



2d

Methyl Ester **SI-5d** (650 mg, 1.64 mmol) was dissolved in 5.0 ml of tetrahydrofuran. Water (2.5 ml) and lithium hydroxide (47.1 mg, 1.96 mmol, 1.2 eq.) were then added. The mixture was stirred at room temperature for 20 minutes until complete conversion of starting material was achieved. Resulting solution was treated with hydrochloric acid (1.00 M, 3.00 mL) and the extracted with ethyl acetate (3 x 15 ml). Combined organic phases were washed with 8 ml brine, dried over sodium sulphate and the concentrated in vacuo to give desired carboxylic acid **2d** as a colorless solid (603 mg, 96% yield).

^{1}H NMR (DMSO-d_6, 600 MHz): δ [ppm] 12.70 (1H, s, COO*H*), 8.29 (1H, d, N*H*, *J* = 7.7 Hz), 7.43 (3H, m, Ar*H*), 6.51 (1H, d, O*H*, *J* = 8.4 Hz), 6.05 (1H, dd, C*H*, *J* = 17.4, 11.0 Hz), 5.61 (1H, m, C*H*OH), 5.40 (2H, m, CH_2,), 4.30 (2H, m, CH), 3.88 (1H, dd, CH_2, J = 8.5, 6.3 Hz), 3.62 (1H, m, CH_2), 2.39 (1H, dt, CH_2, J = 12.8, 8.2 Hz), 1.92 (1H, dt, CH_2, *J* =12.7, 6.2 Hz).

^{13}C NMR (DMSO-d_6, 151 MHz): δ [ppm] 173.22, 168.71, 162.77, 162.68, 161.14, 161.05, 156.61, 156.58, 1. 130.32, 117.63, 109.68, 109.64, 109.53, 109.50, 105.46, 105.28, 105.11, 92.14, 92.12, 78.47, 74.78, 71.40, 48.87, 34.12.

HRMS (ESI) calcd. for $C_{17}H_{17}N_2O_6F_2$ $[M+H]^+$: 383.1055; found: 383.1048.

3. X-ray crystal structure analysis

(2*R*,4*R*)-4-[[(4*R*,5*R*)-3-(3,5-Difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carbonyl]amino]tetrahydrofuran-2-carboxylic acid (2d)

Fig. 4: Configuration of C13

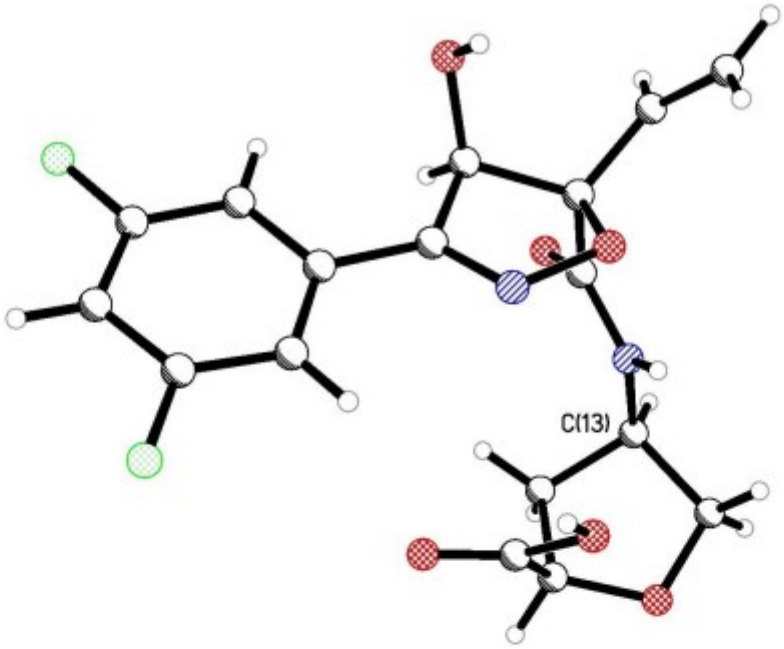
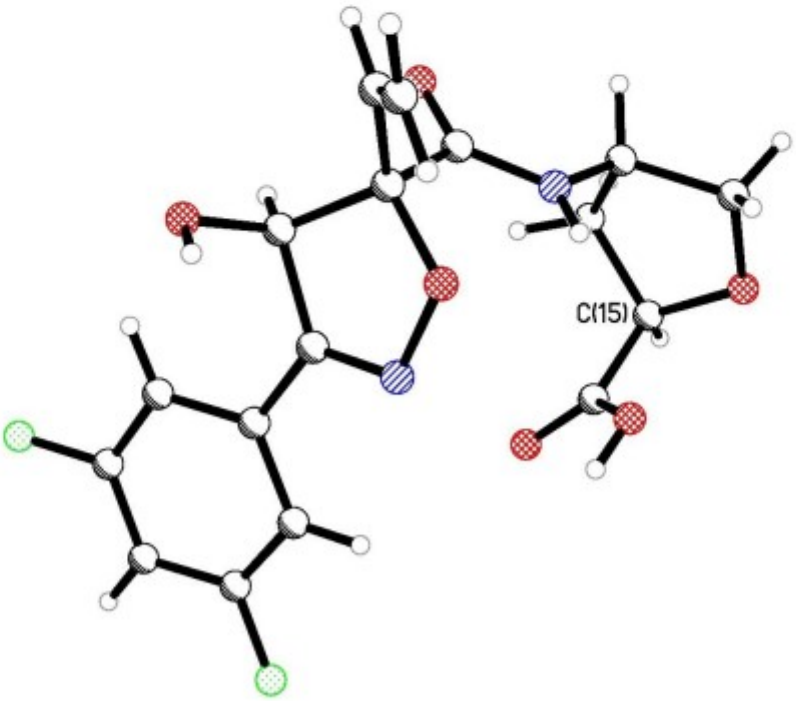


Fig. 5: Configuration of C15

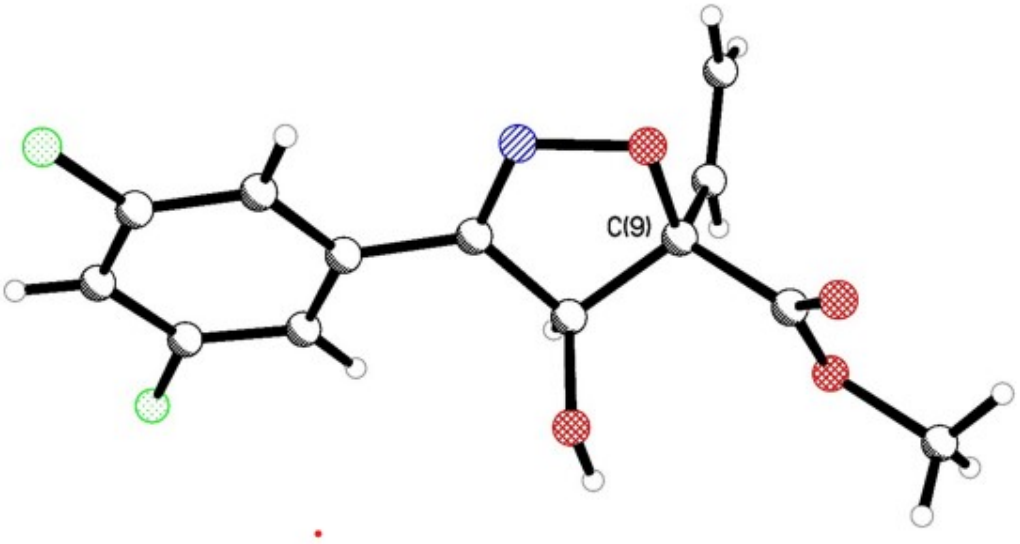


Experimental

Diffractometer:	Bruker AXS X8 Prospector, QS-Nr. 02506
Detector:	Photon II-CCD area detector
Radiation:	Cu K_α (1,54056 Å)
Tube:	IμS-microsource
Monochromator:	mirror
Low temperature device:	Cryostream 700
Measurement temperature:	110K
Measurement method:	omega and phi scans
Data collection and reduction software:	APEX 3, v2019.1.0 (Bruker AXS, 2019)
Absorption correction:	Multi-scan (SADABS)
Structure solution and refinement software:	SHELXT-2018/3 (Bruker AXS, 2018)
Visualization software:	XP (Bruker AXS, 2018)

Methyl (4*S*,5*R*)-3-(3,5-difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carboxylate (4a)

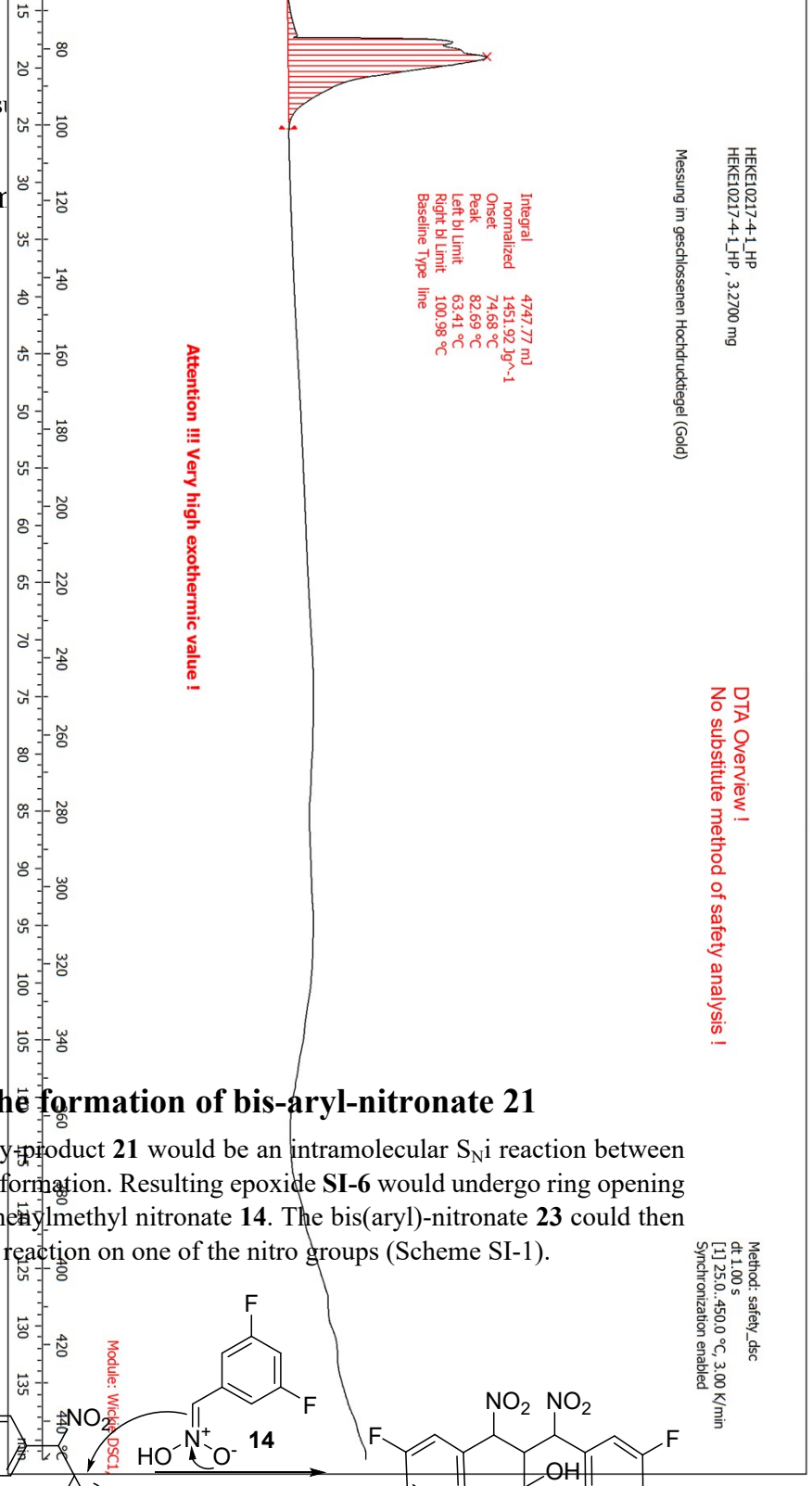
Fig. 3: Configuration of C9



Experimental

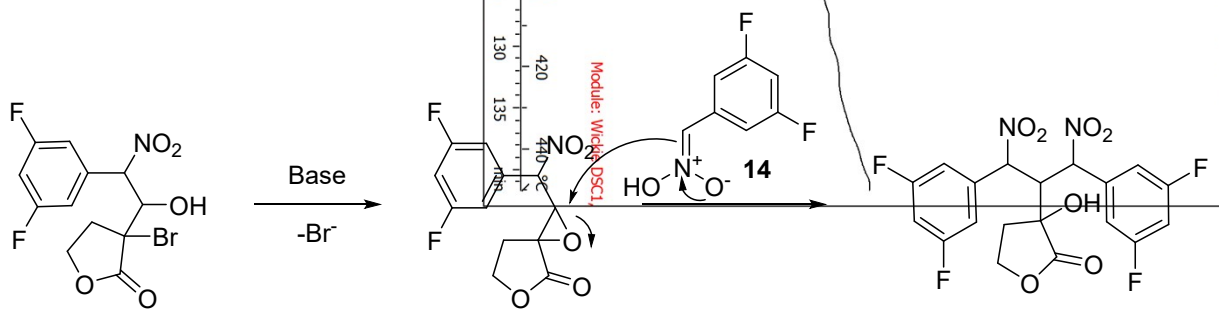
Diffractometer:	Bruker AXS X8 Prospector, QS-Nr. 02506
Detector:	Photon II-CCD area detector
Radiation:	Cu K_α (1,54056 Å)
Tube:	IμS-microsource
Monochromator:	mirror
Low temperature device:	Cryostream 700
Measurement temperature:	110K
Measurement method:	omega and phi scans
Data collection and reduction software:	APEX 3, v2019.1.0 (Bruker AXS, 2019)
Absorption correction:	Multi-scan (SADABS)
Structure solution and refinement software:	SHELXT-2018/3 (Bruker AXS, 2018)
Visualization software:	XP (Bruker AXS, 2018)

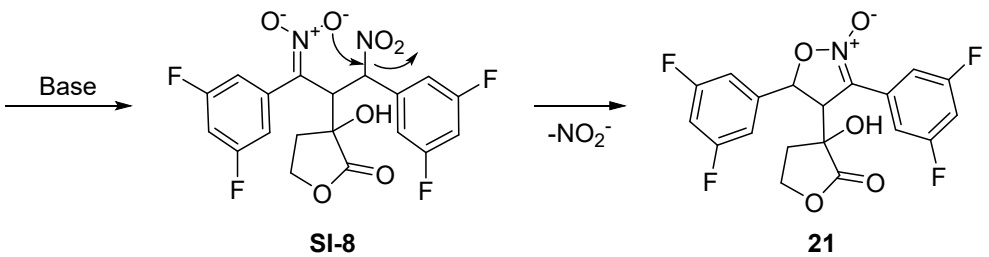
4. DSC measurement of bis(m



5. Proposed mechanism for the formation of bis-aryl-nitronate 21

A plausible route for the formation of by-product **21** would be an intramolecular S_Ni reaction between alcohol and bromide leading to epoxide formation. Resulting epoxide **SI-6** would undergo ring opening via nucleophilic attack of 3,5-difluorophenylmethyl nitronate **14**. The bis(aryl)-nitronate **23** could then be formed via second intramolecular S_N reaction on one of the nitro groups (Scheme SI-1).





Scheme SI-1 Proposed mechanism for the formation of bis-aryl-nitronate **21**.

6. References

[S1] J. Leonard, B. Lygo and G. Procter, *Praxis der organischen Chemie: Ein Handbuch*, Wiley-VCH, Weinheim, 1996.

[S2] a) D. Cibu and A. Lishchynskyi, WIPO Pat., WO2024141382A1, 2024; b) A. Lishchynskyi, S. Pazenok, M. J. Ford, F. Memmel, A. Rembiak and W. A. Moradi, WIPO Pat., WO2024038036, 2024.

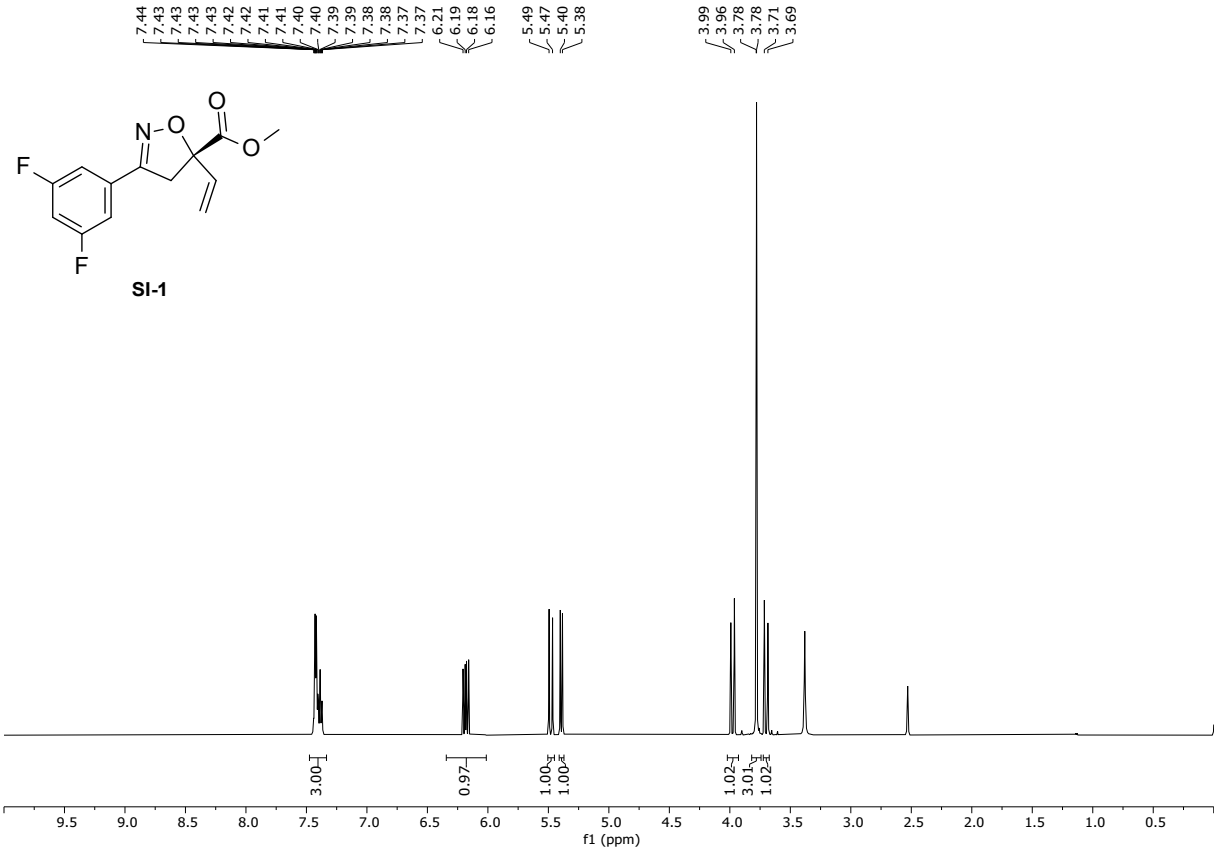
[S3] D. Brohm, A. Rembiak and W. A. Moradi, WIPO Pat., WO2023161204A1, 2023.

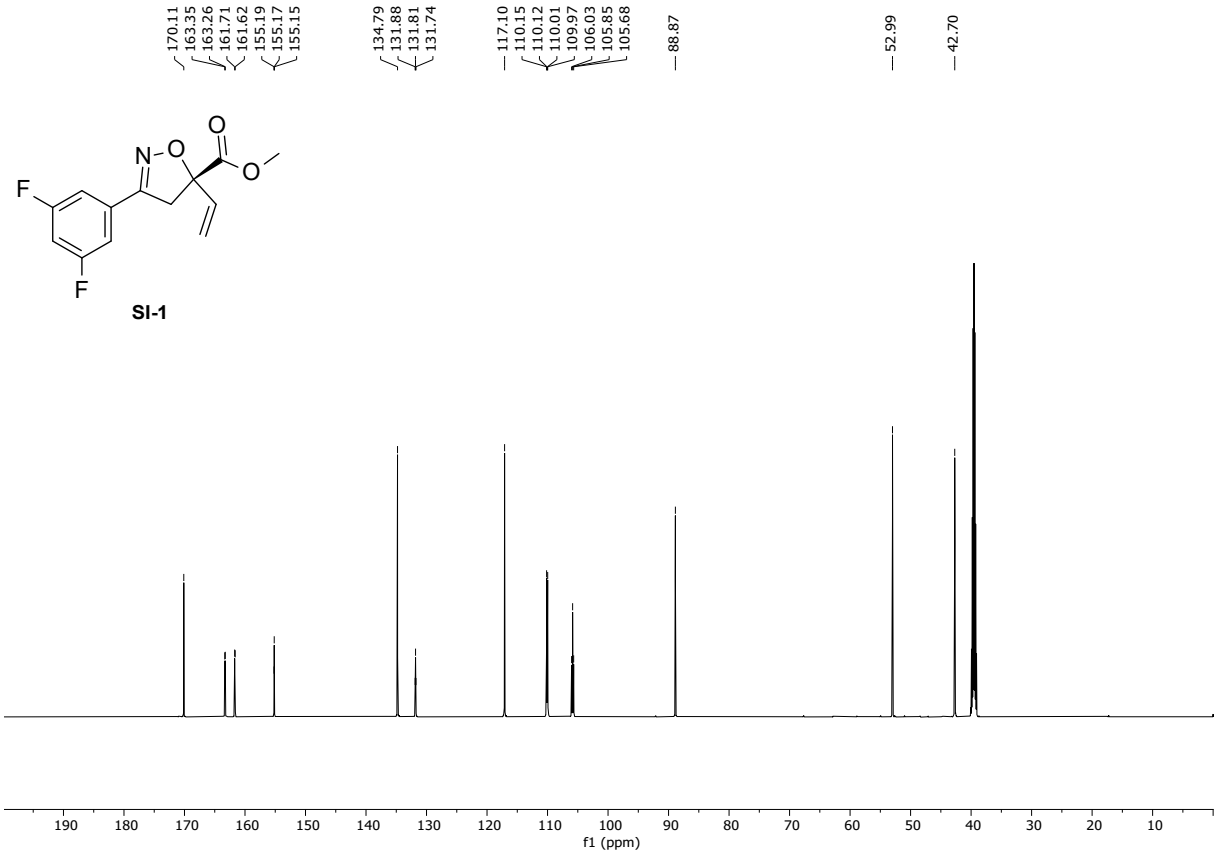
[S4] M. Capuzzi, A. Gambacorta, T. Gasperi, A. M. Loreto, A. P. Tardella, *Eur. J. Org. Chem.,* 2006, **22,** 5076-5082.

[S5] S. V. Tsukanov, M. D. Johnson, S. A. May, S. P. Kolis, M. H. Yates, J. N. Johnston, *Org. Process Res. Dev.*, 2018, **22**, 971-977.

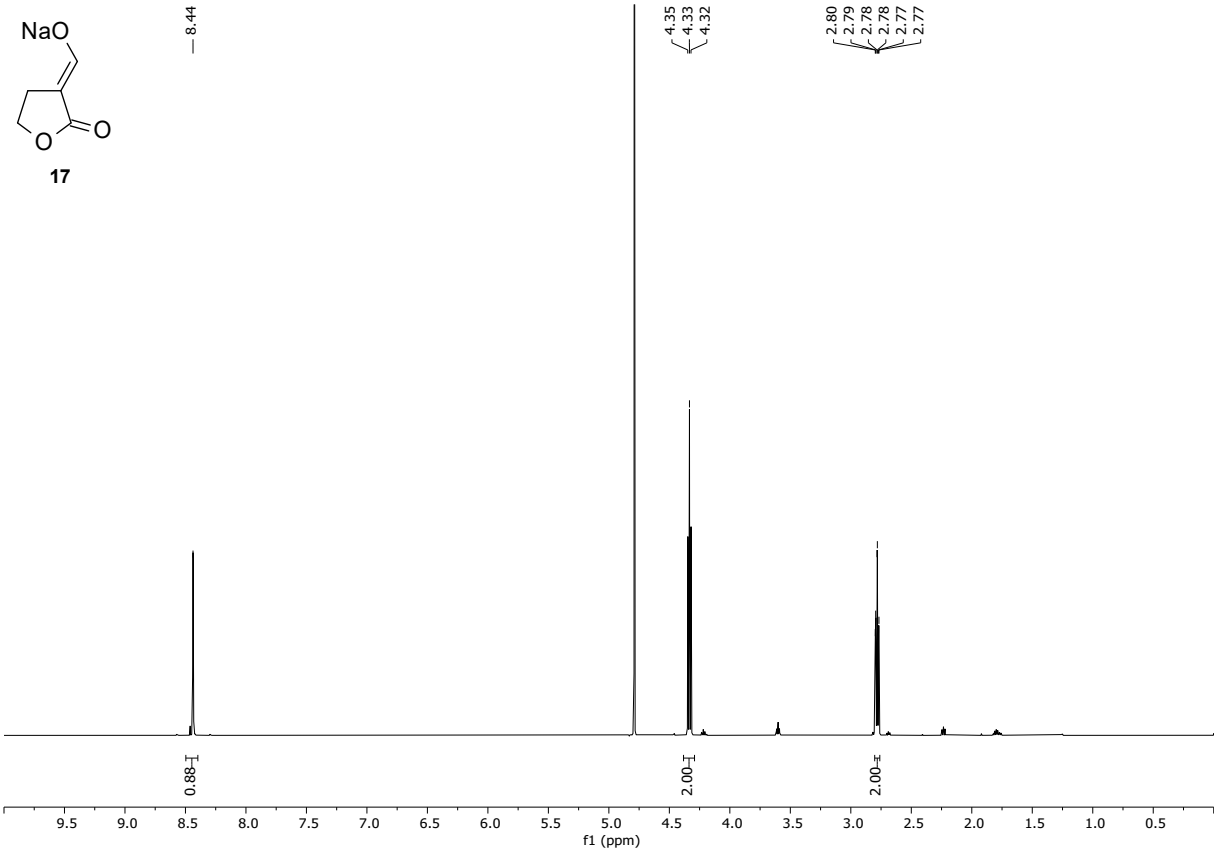
7. Attachments: NMR Spectra

Methyl (5*S*)-3-(3,5-difluorophenyl)-5-vinyl-4*H*-isoxazole-5-carboxylate (SI-1)

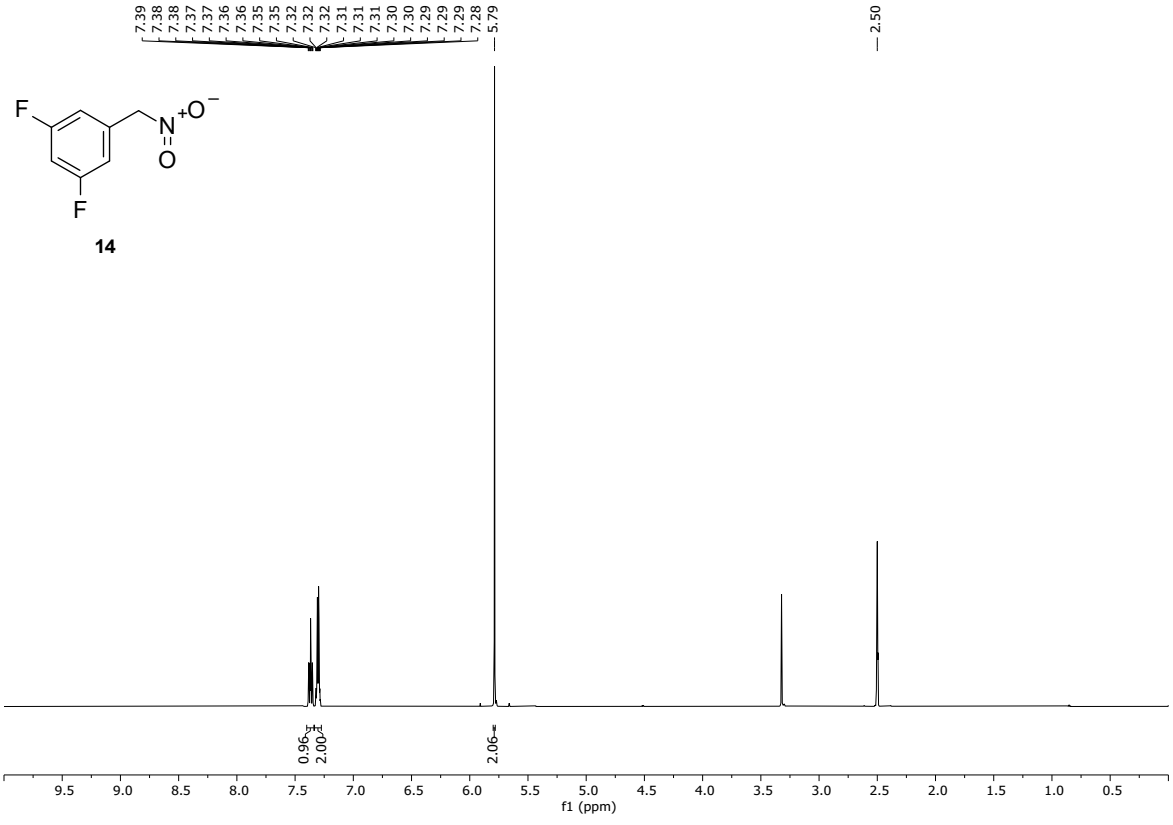




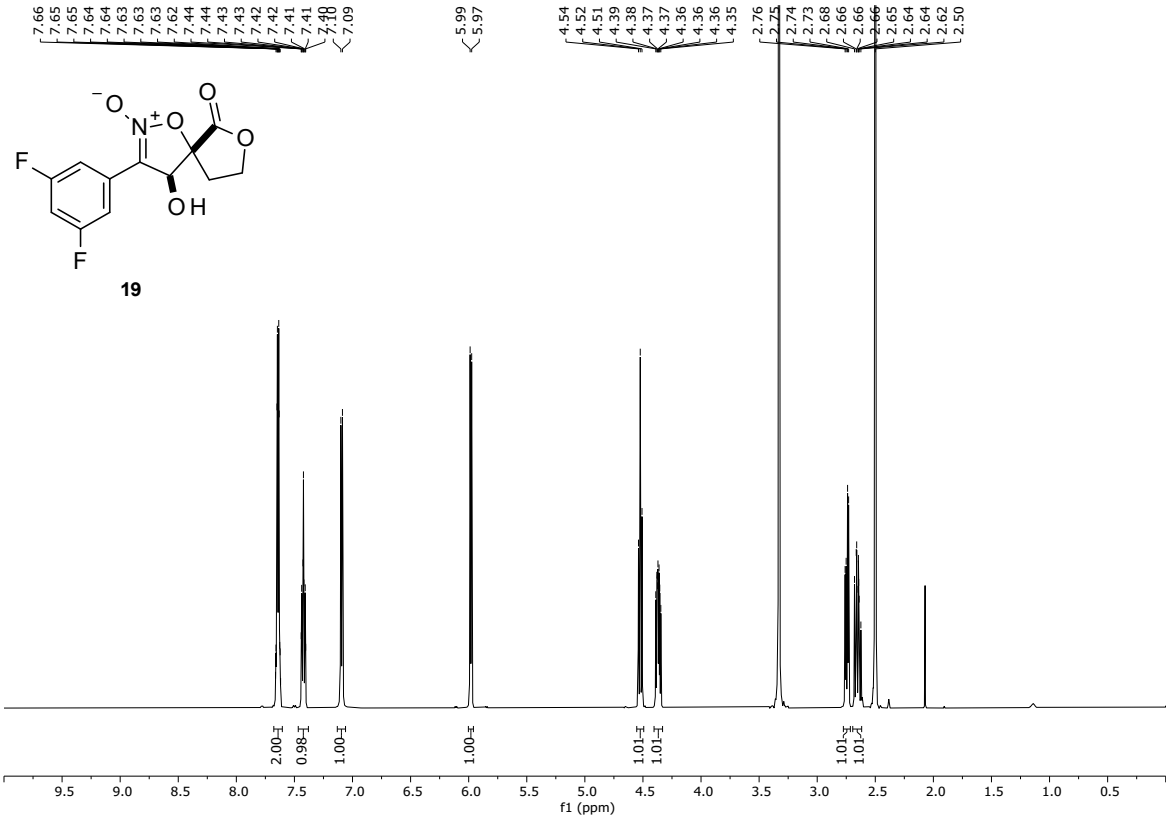
Sodium (*E*)-(2-oxotetrahydrofuran-3-ylidene)methanolate (17)

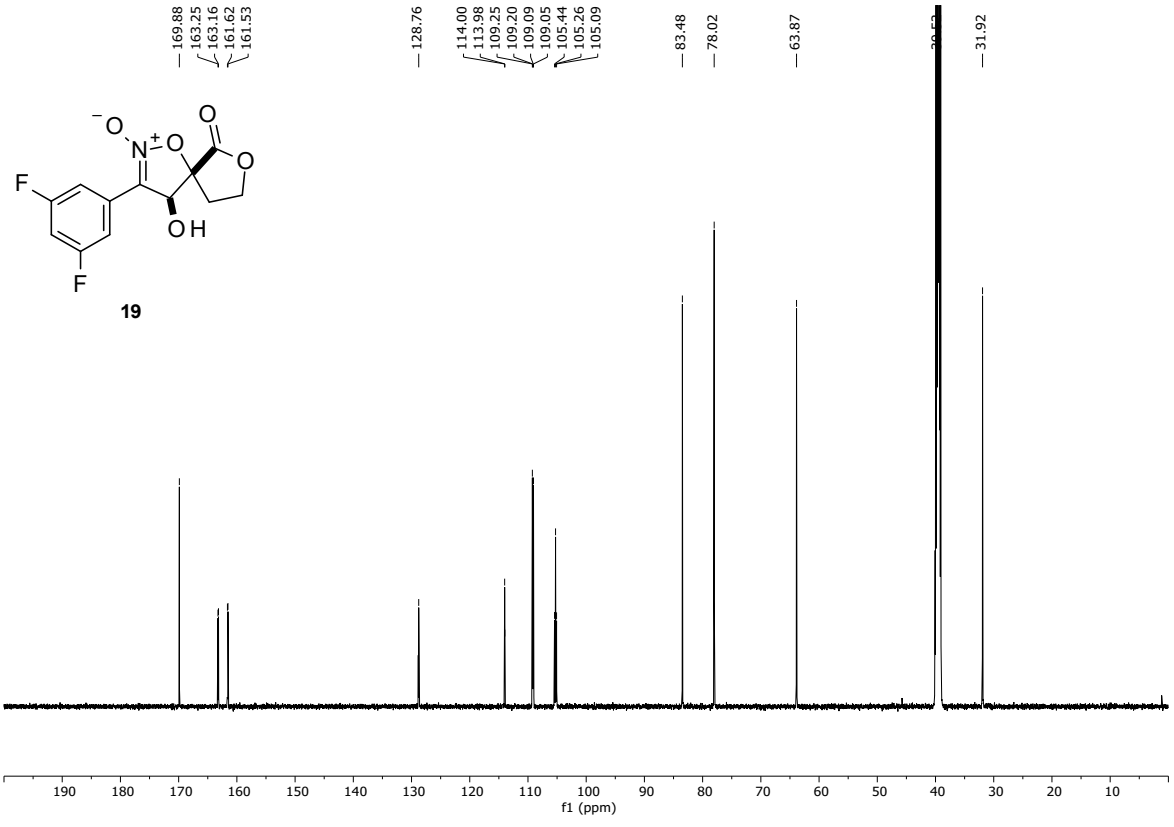


3,5-Difluorophenylnitromethane (14)

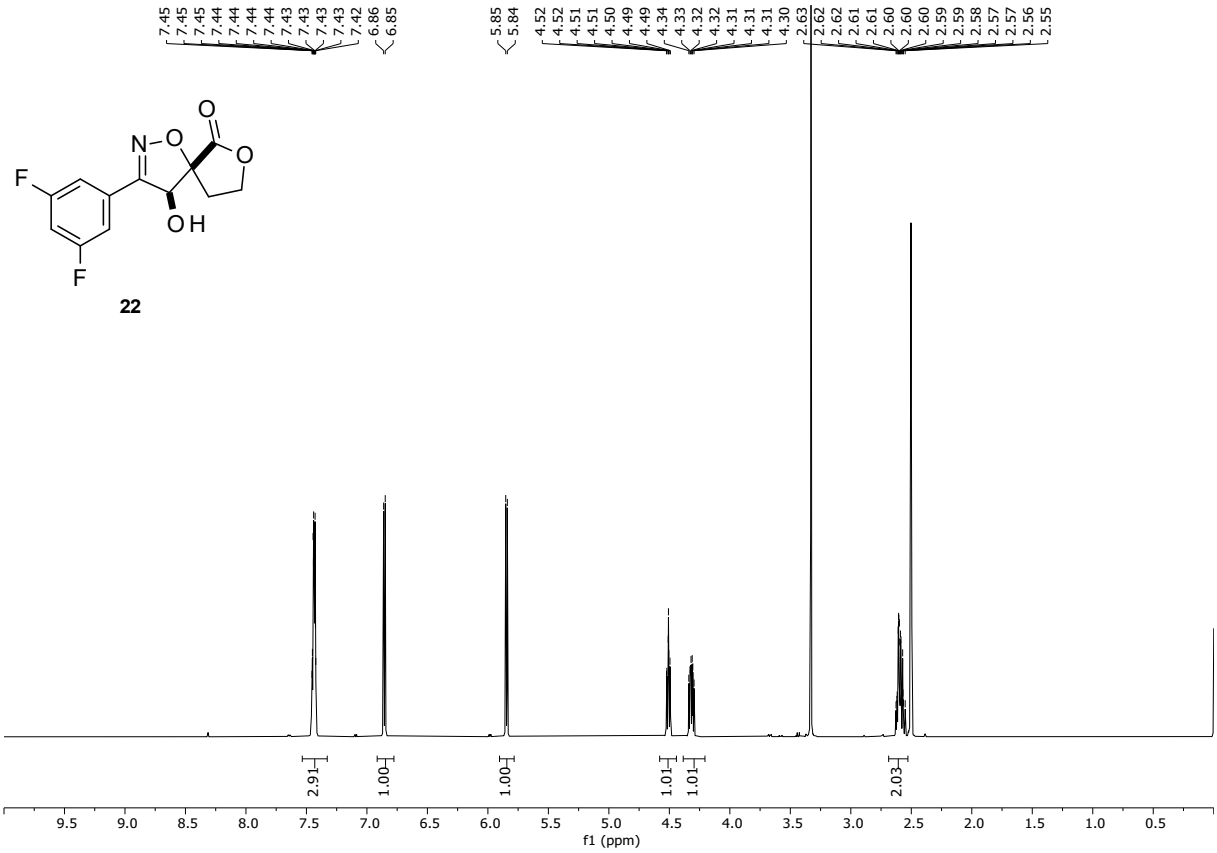


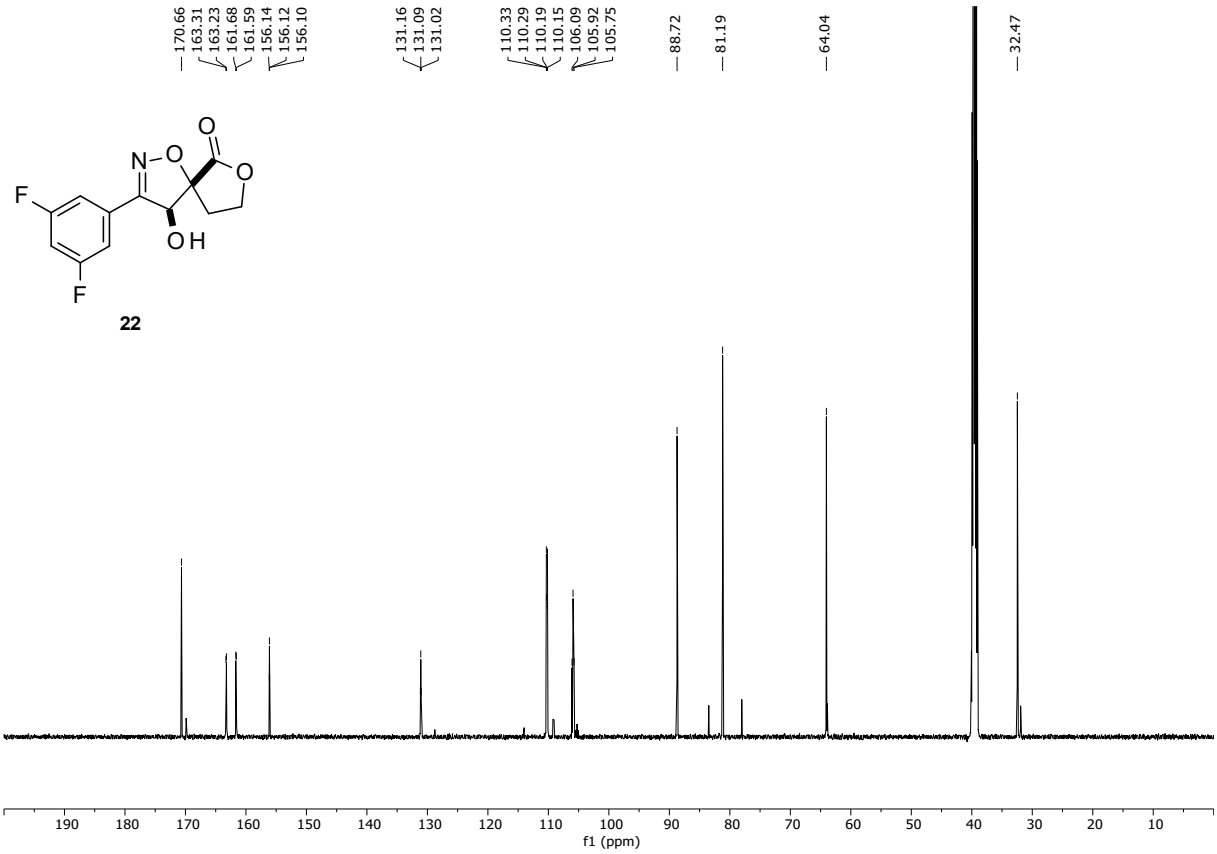
rac-(4_S_,5_R_)-3-(3,5-Difluorophenyl)-4-hydroxy-2-oxido-1,7-dioxa-2-azoniaspiro[4.4]non-2-en-6-one (19)



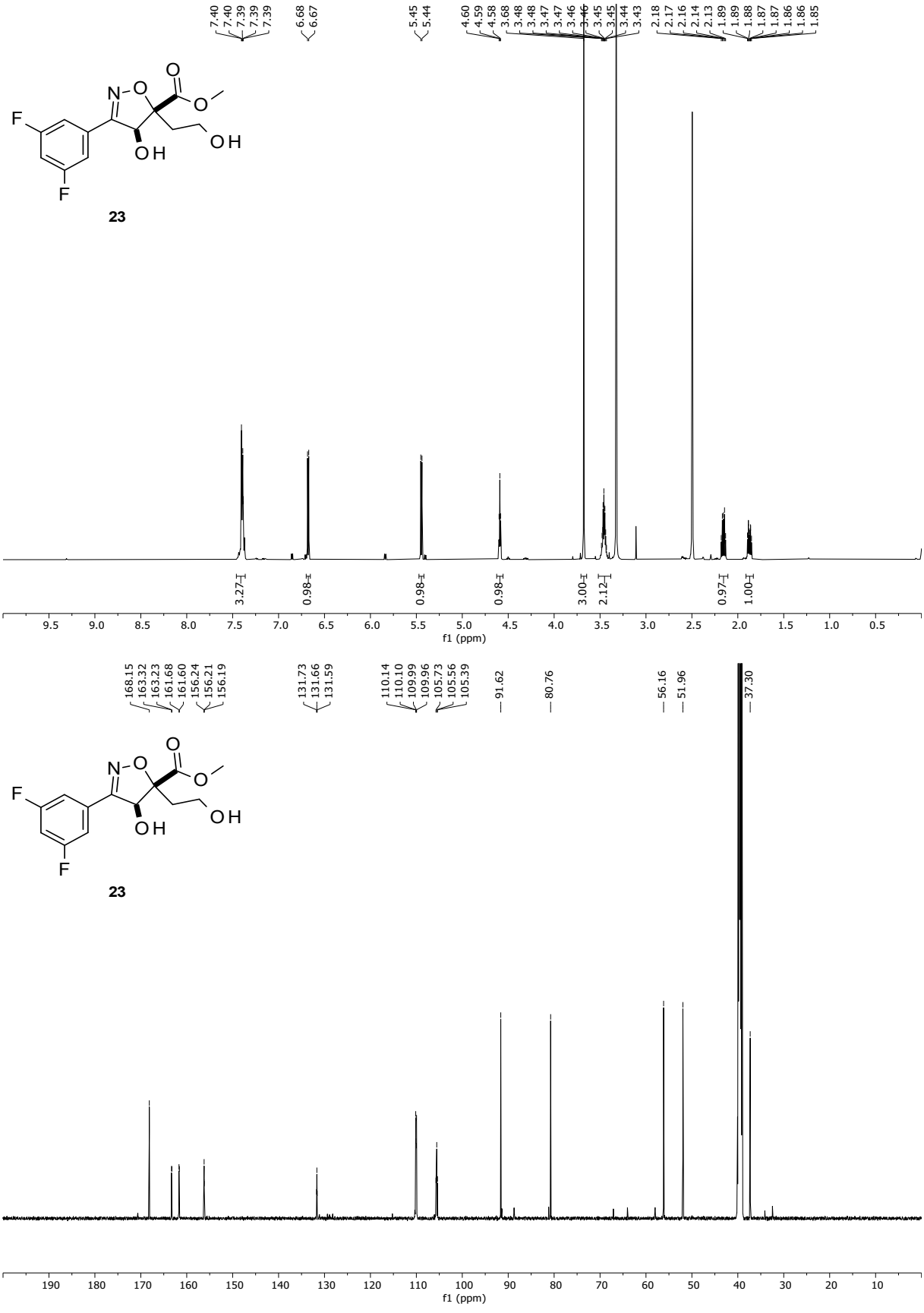


rac-(4_S_,5_R_)-3-(3,5-Difluorophenyl)-4-hydroxy-1,7-dioxa-2-azaspiro[4.4]non-2-en-6-one (22)

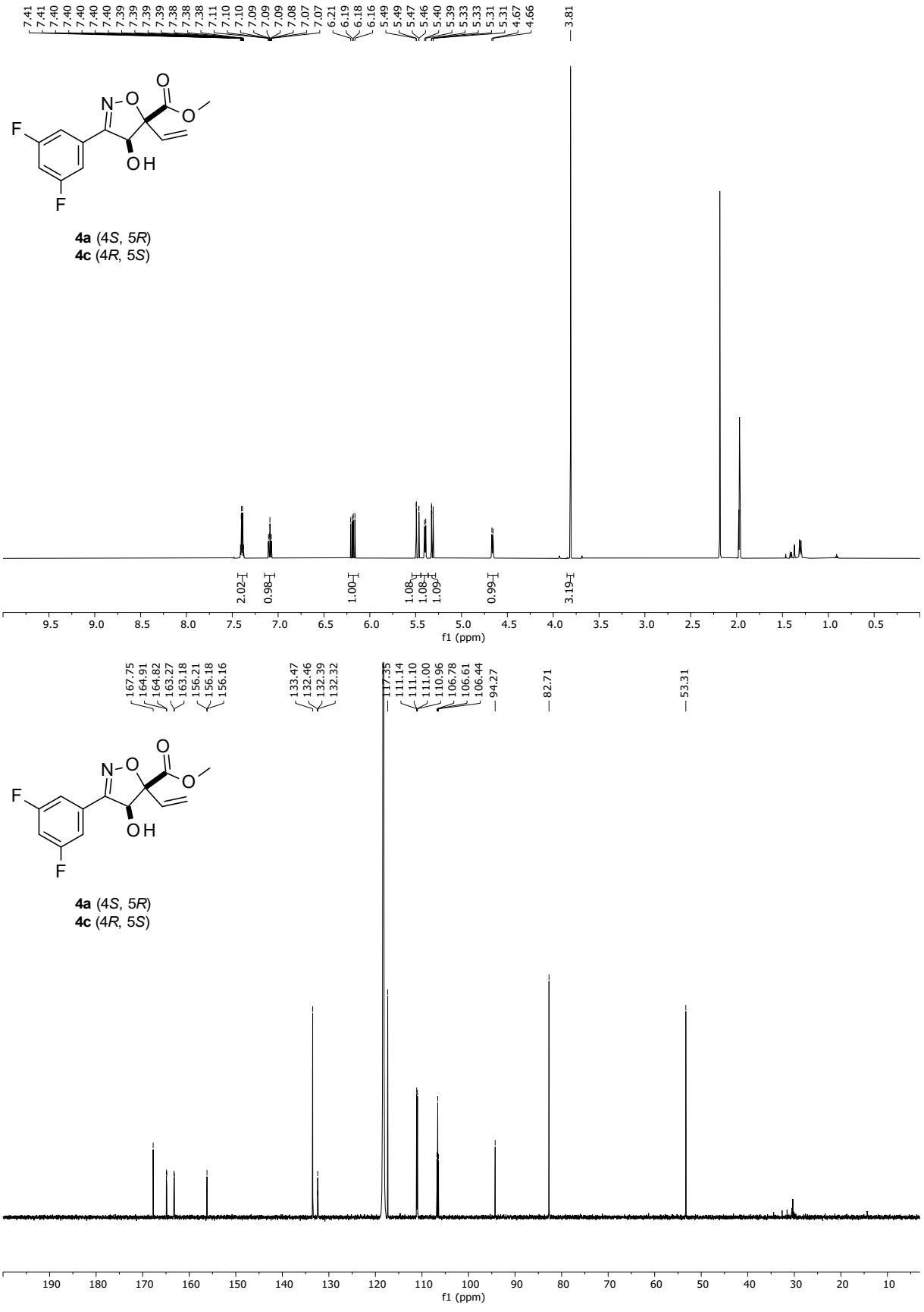




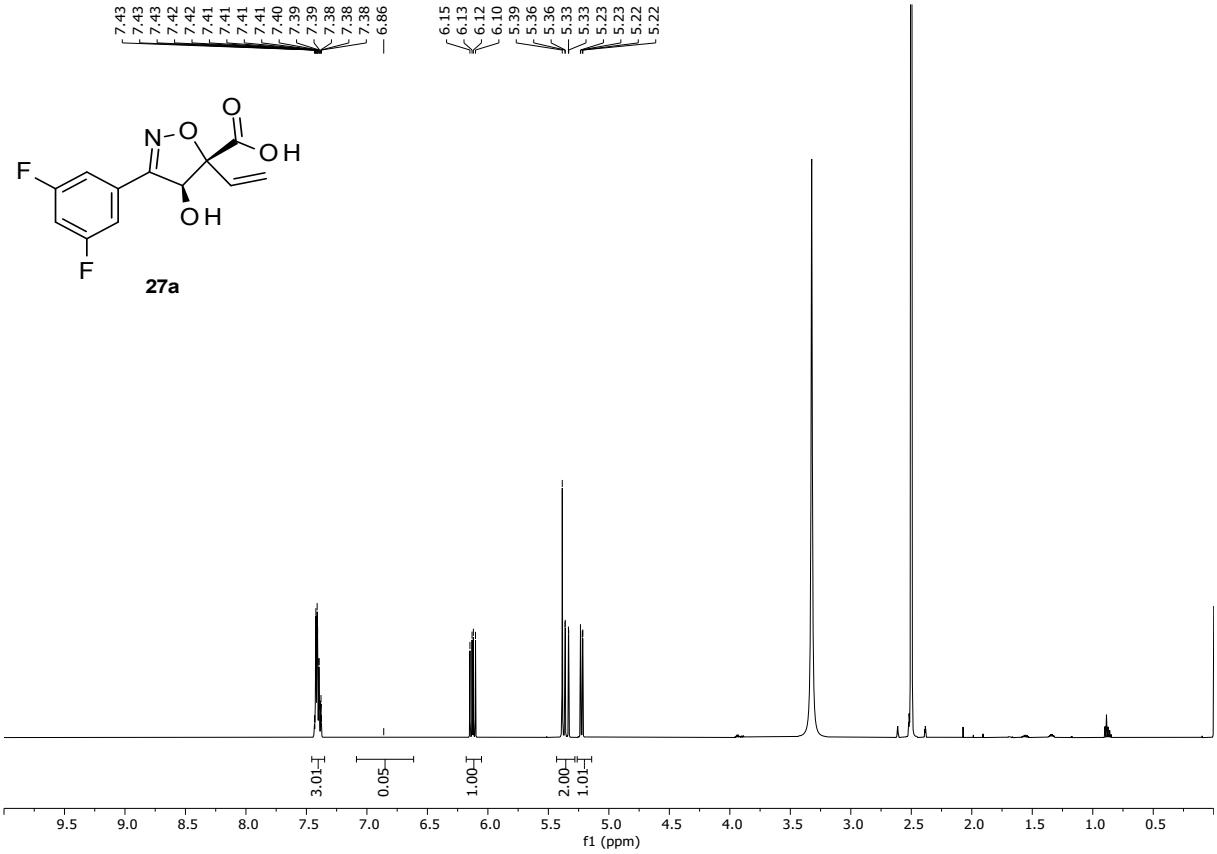
Methyl *rac*-(4*S*,5*R*)-3-(3,5-Difluorophenyl)-4-hydroxy-5-(2-hydroxyethyl)-4*H*-isoxazole-5-carboxylate (23)

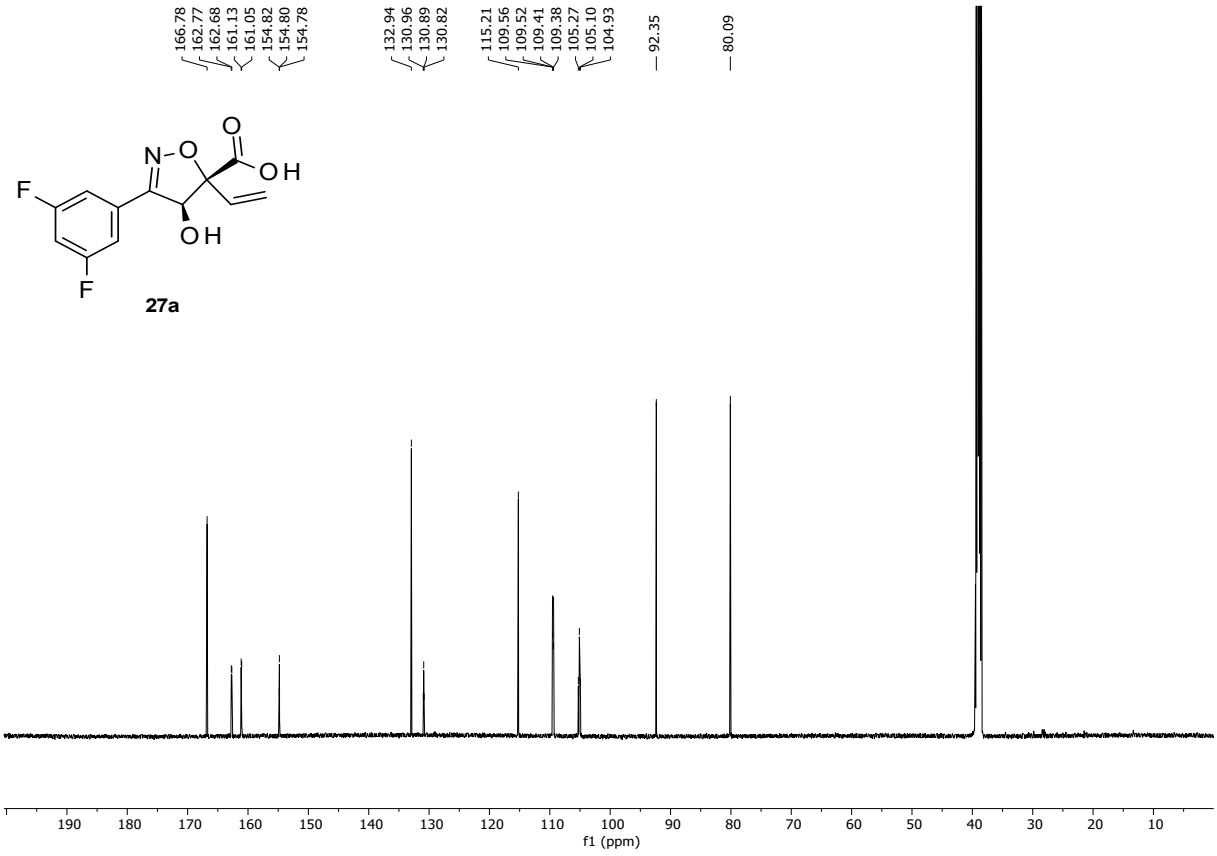


Methyl (4*S*,5*R*)-3-(3,5-difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carboxylate (4a) and methyl (4*R*,5*S*)-3-(3,5-difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carboxylate (4c)

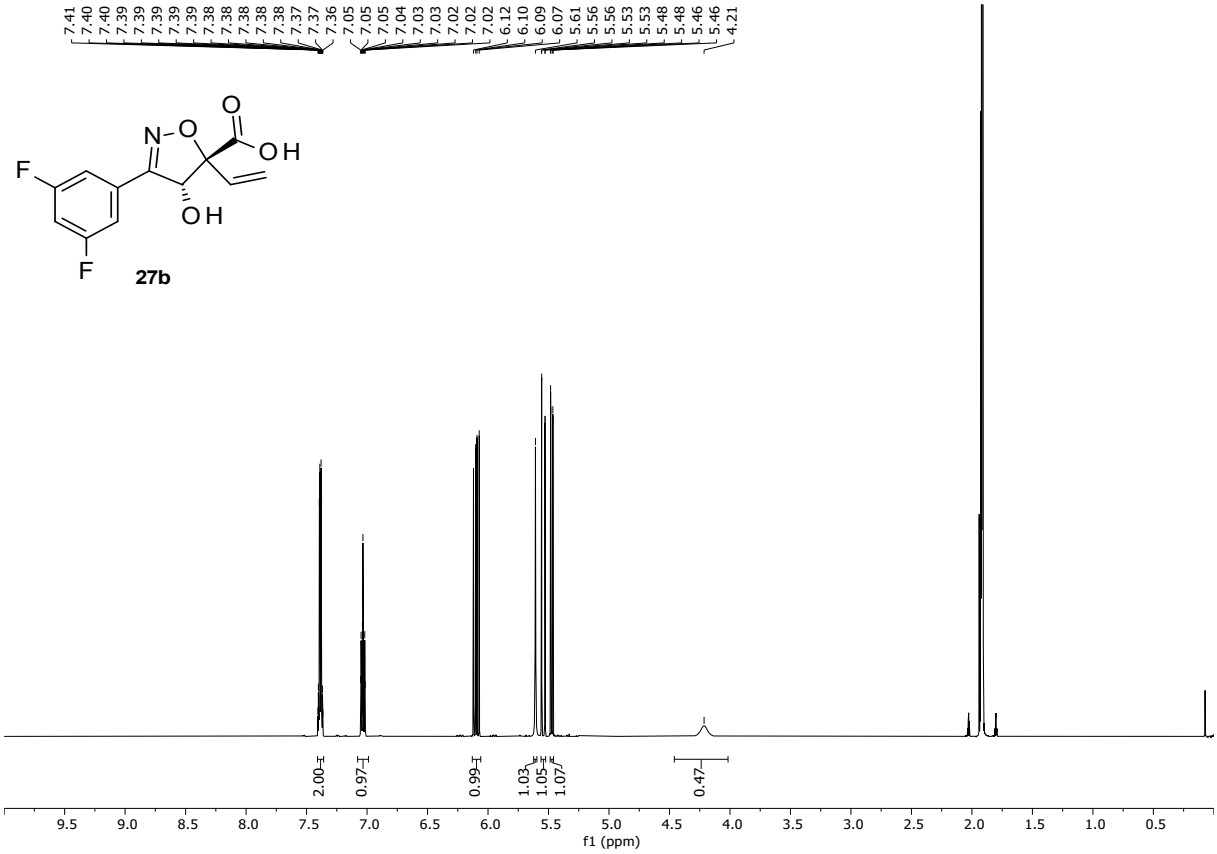


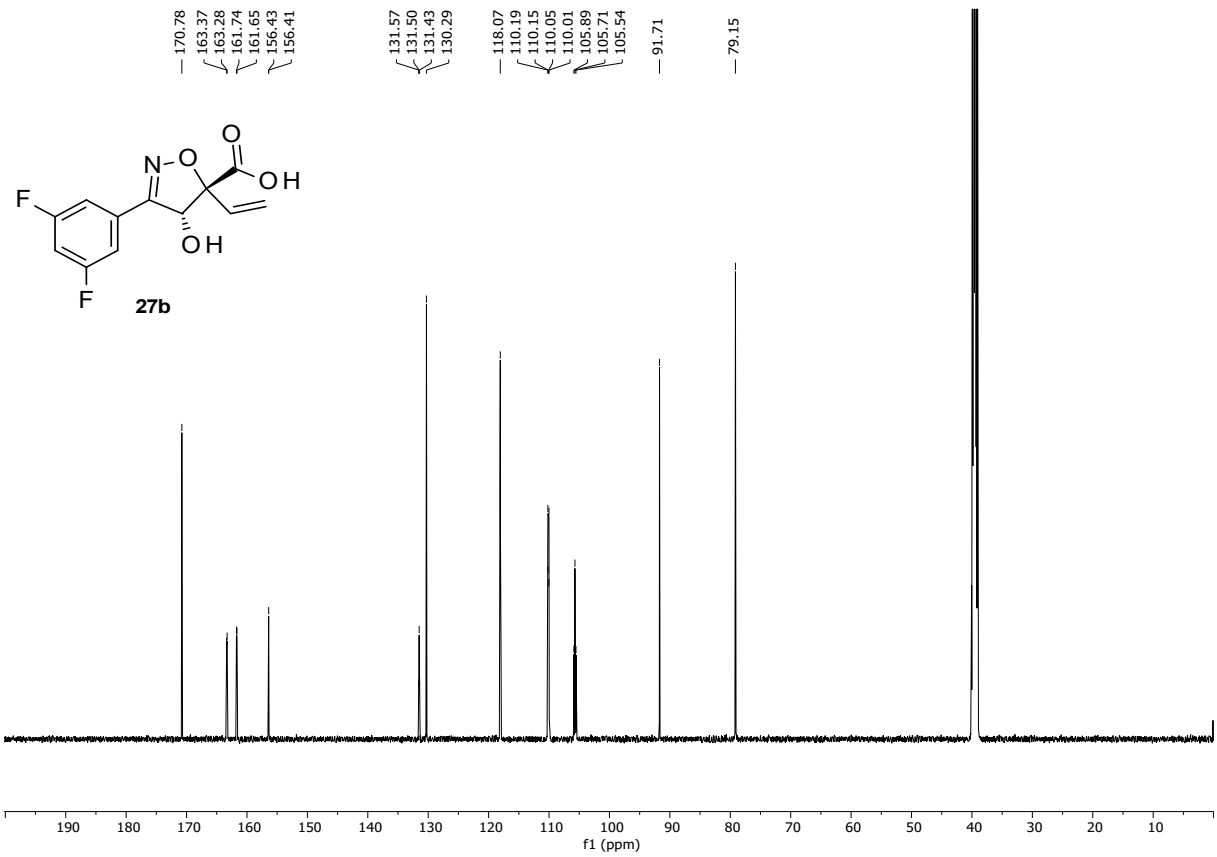
(4*S*,5*R*)-3-(3,5-Difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carboxylic acid (27a)



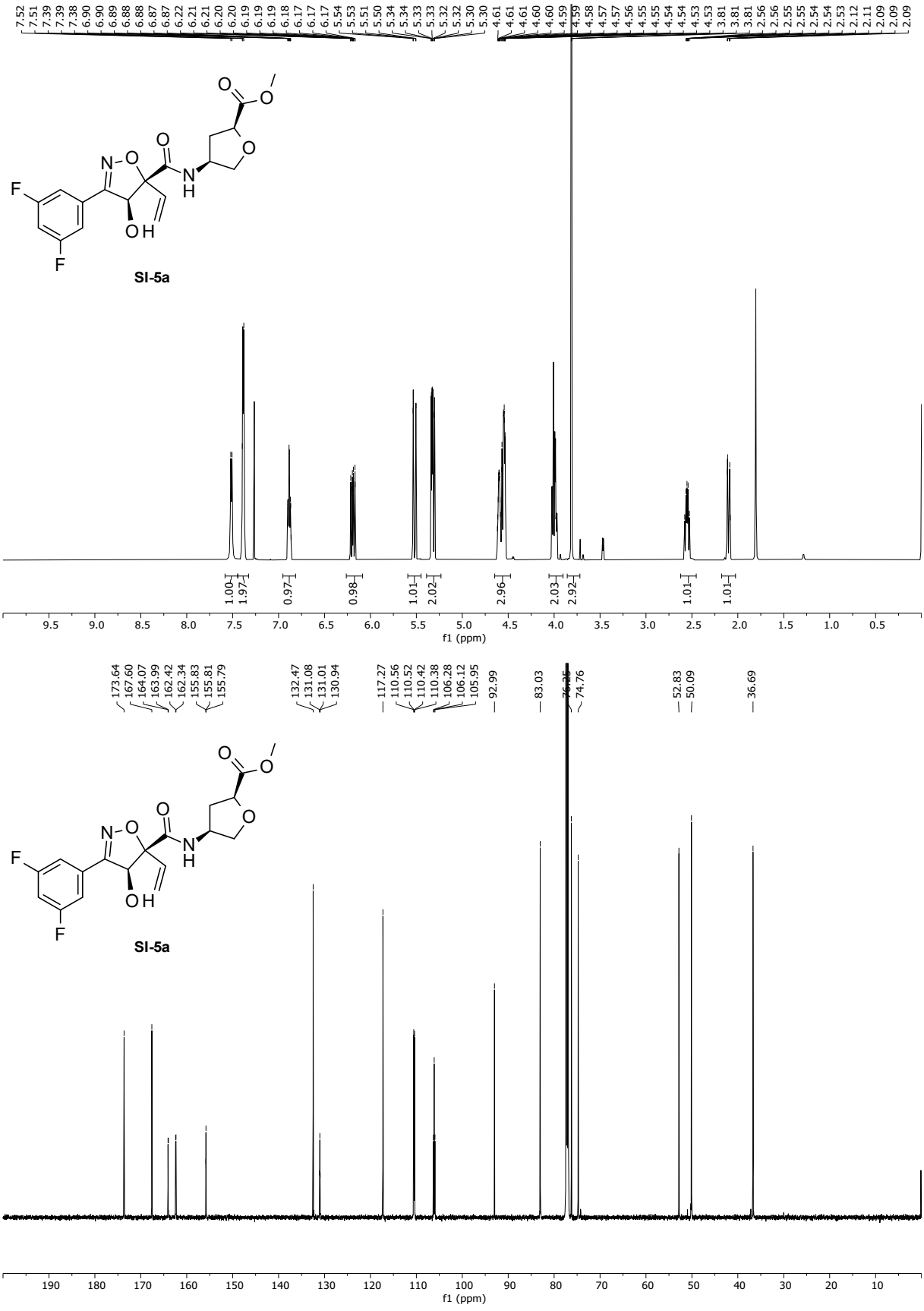


(4*R*,5*R*)-3-(3,5-difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carboxylic acid (27b)

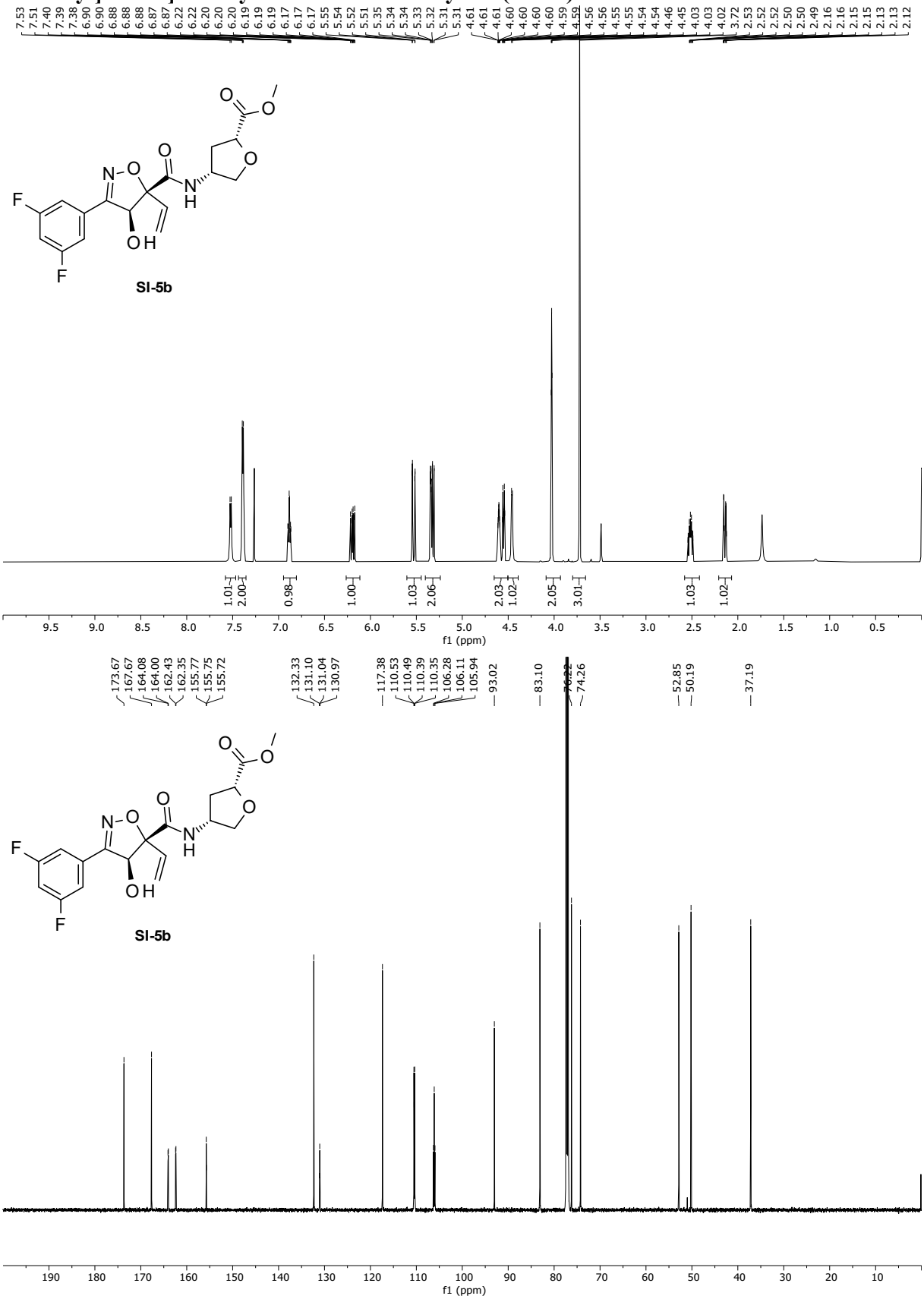




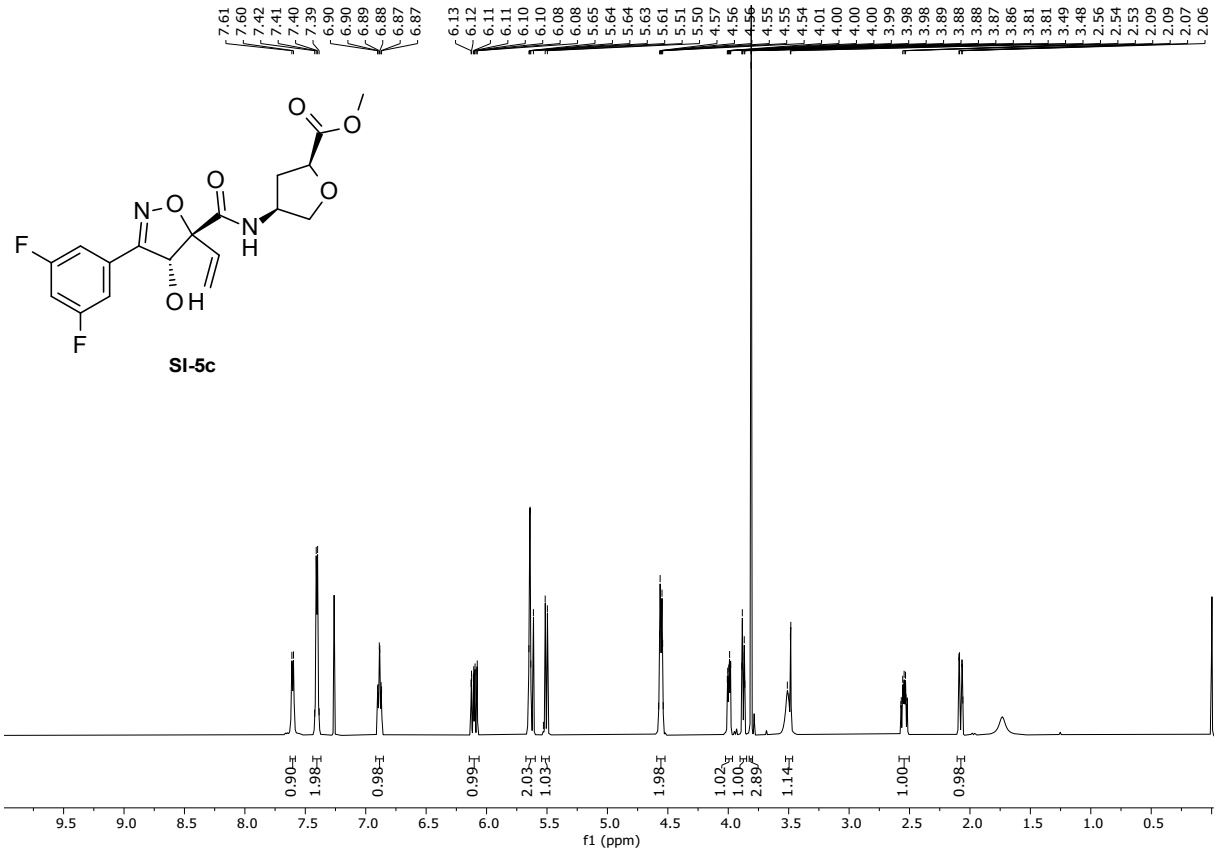
Methyl (2*S*,4*S*)-4-[[(4*S*,5*R*)-3-(3,5-difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carbonyl]amino]tetrahydrofuran-2-carboxylate (SI-5a)

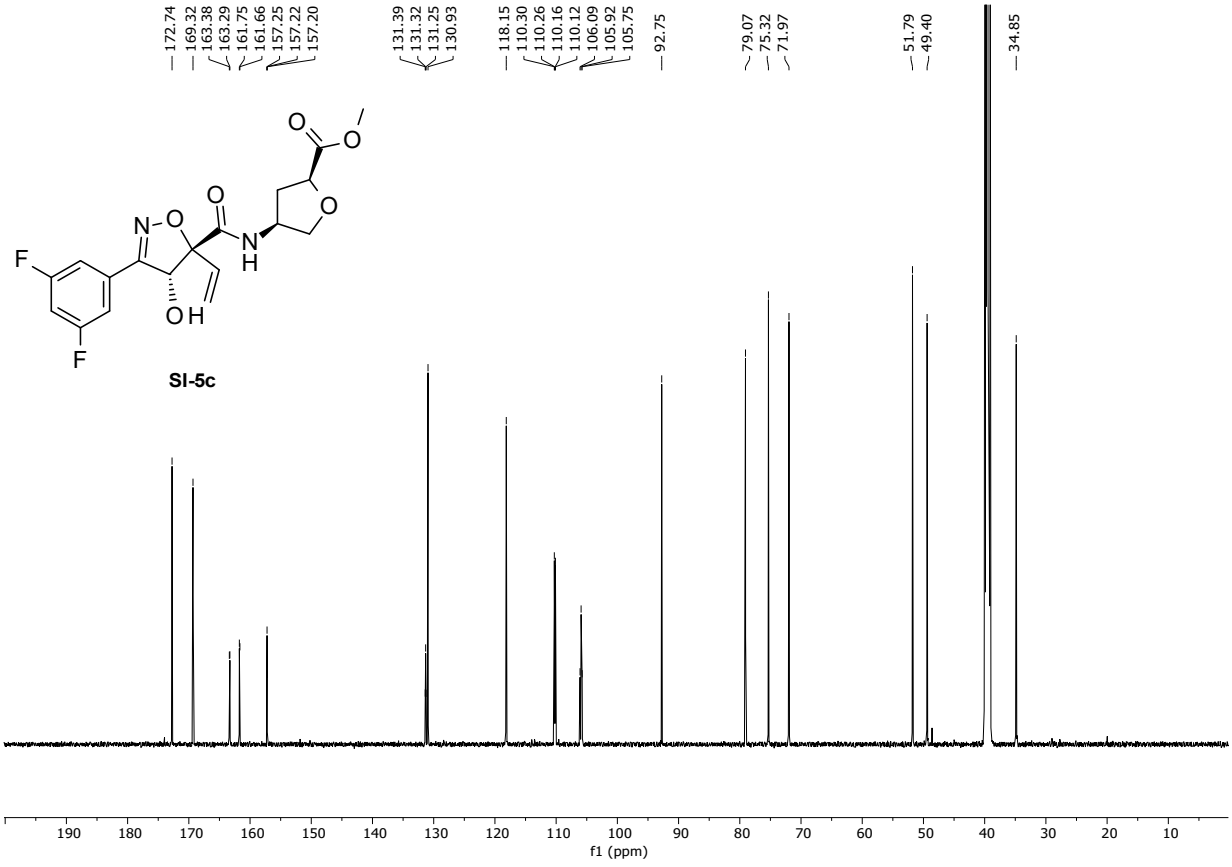


Methyl (2*R*,4*R*)-4-[[(4*S*,5*R*)-3-(3,5-difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carbonyl]amino]tetrahydrofuran-2-carboxylate (SI-5b)

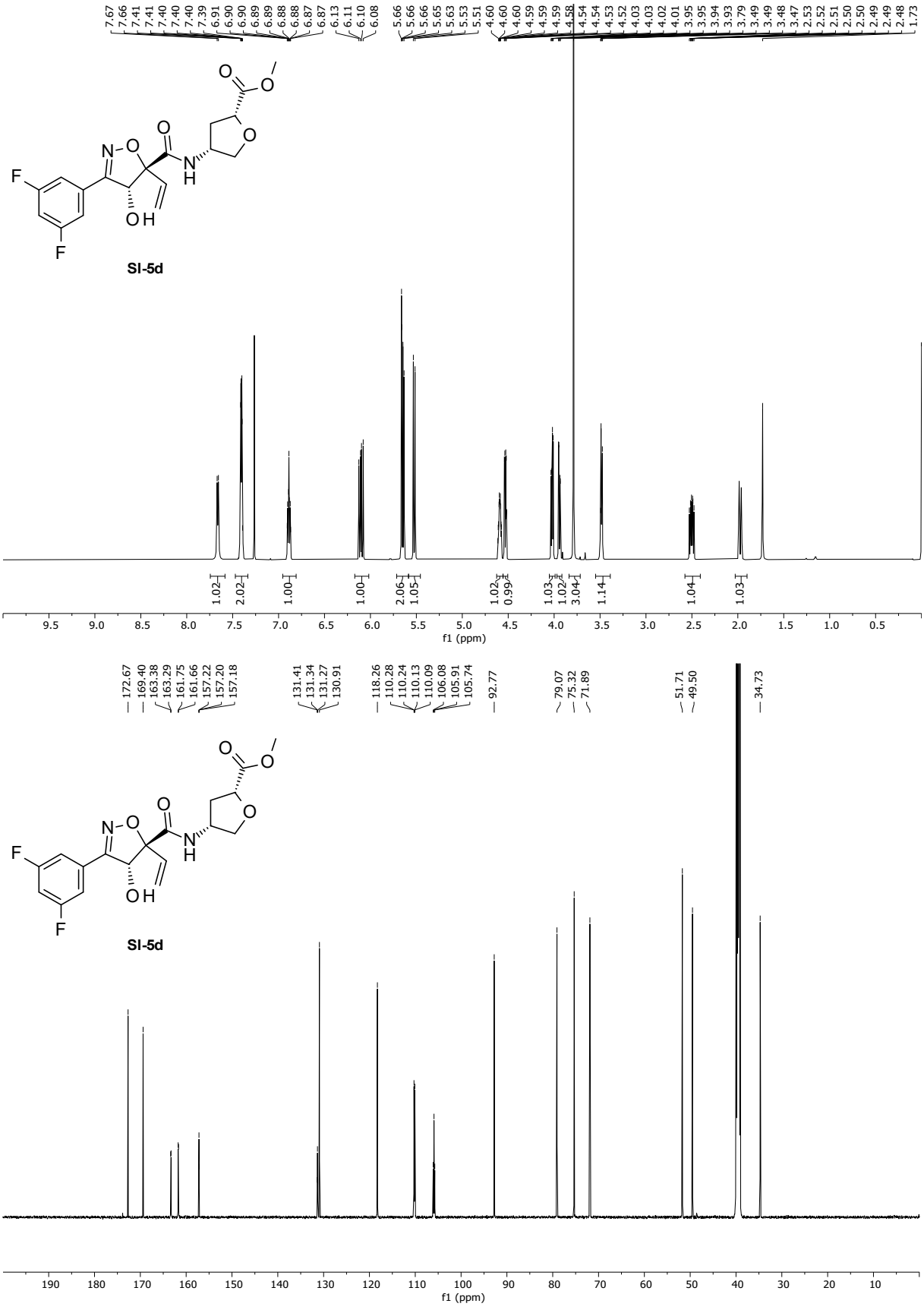


Methyl (2S,4S)-4-[[(4*S*,5*R*)-3-(3,5-difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carbonyl]amino]tetrahydrofuran-2-carboxylate (SI-5c)

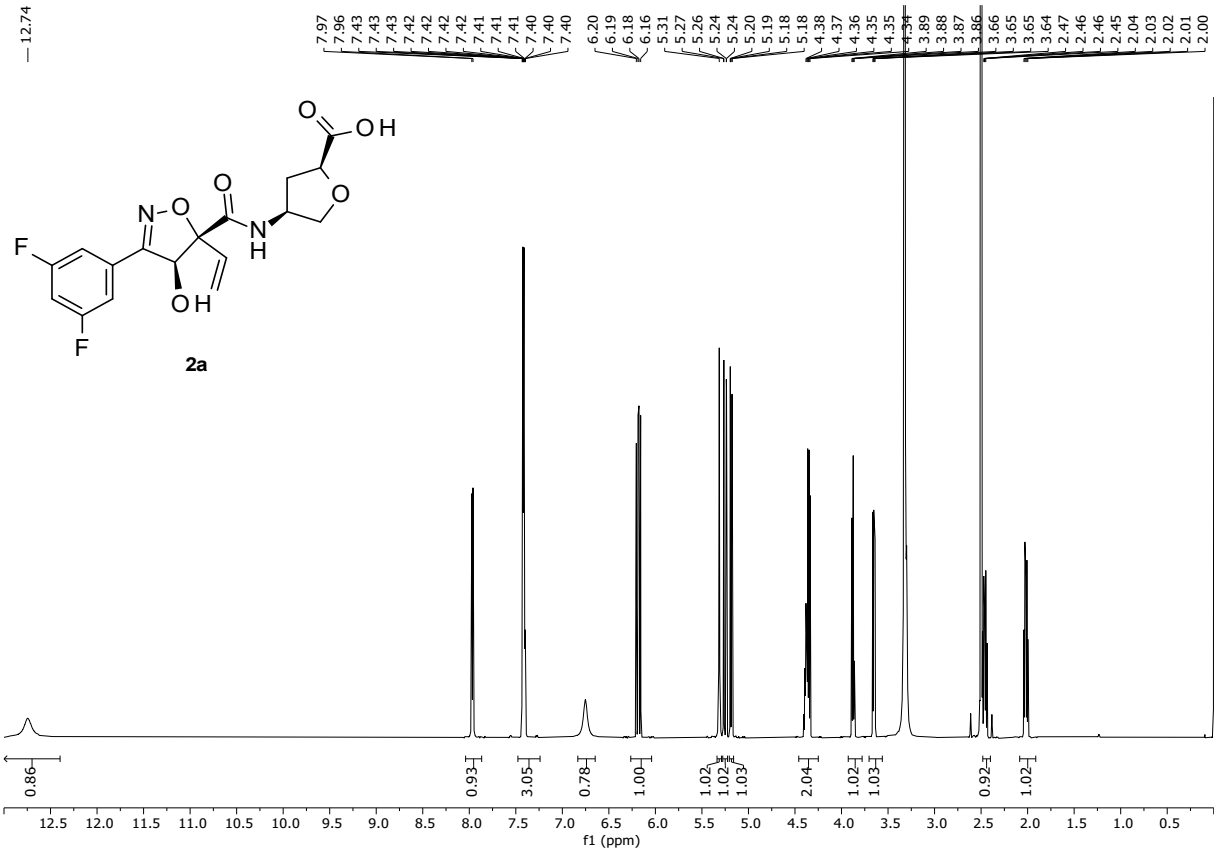


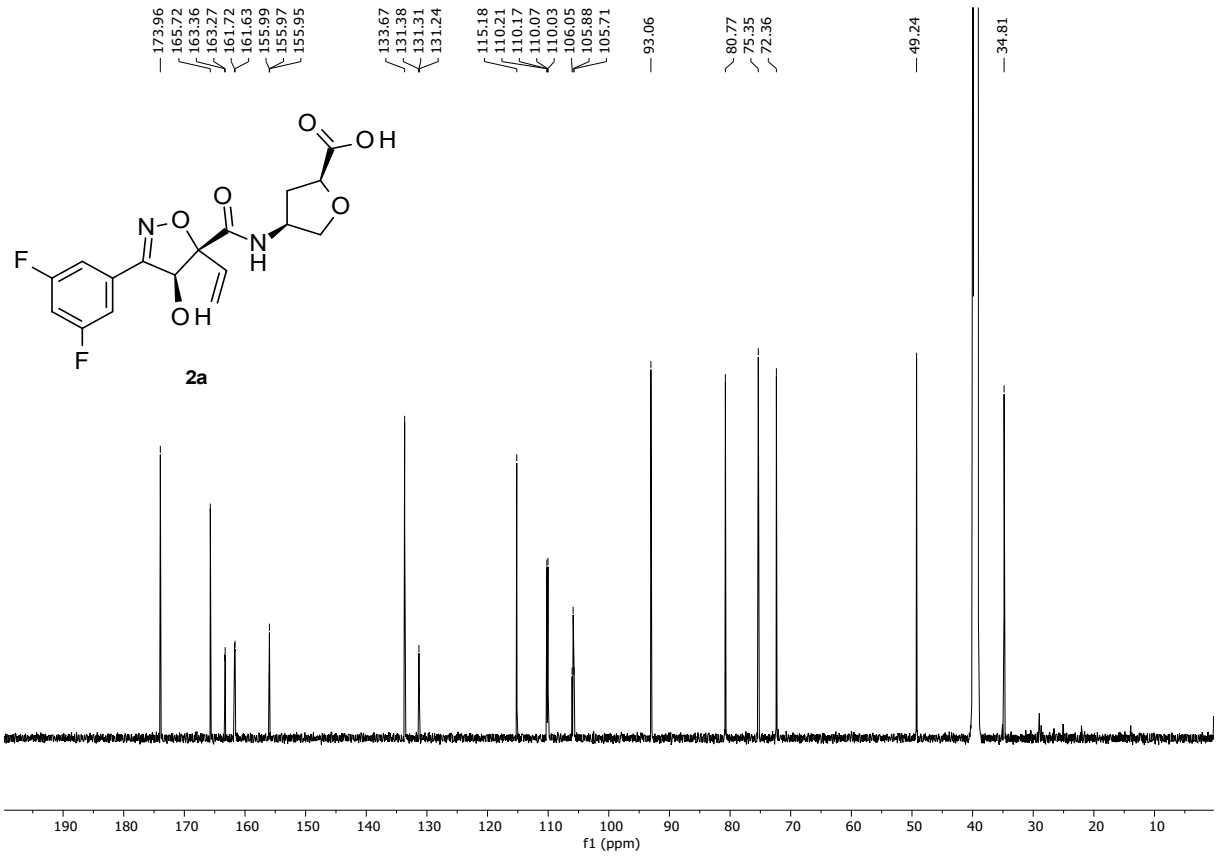


Methyl (2*R*,4*R*)-4-[[(4R,5*R*)-3-(3,5-difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carbonyl]amino]tetrahydrofuran-2-carboxylate (SI-5d)

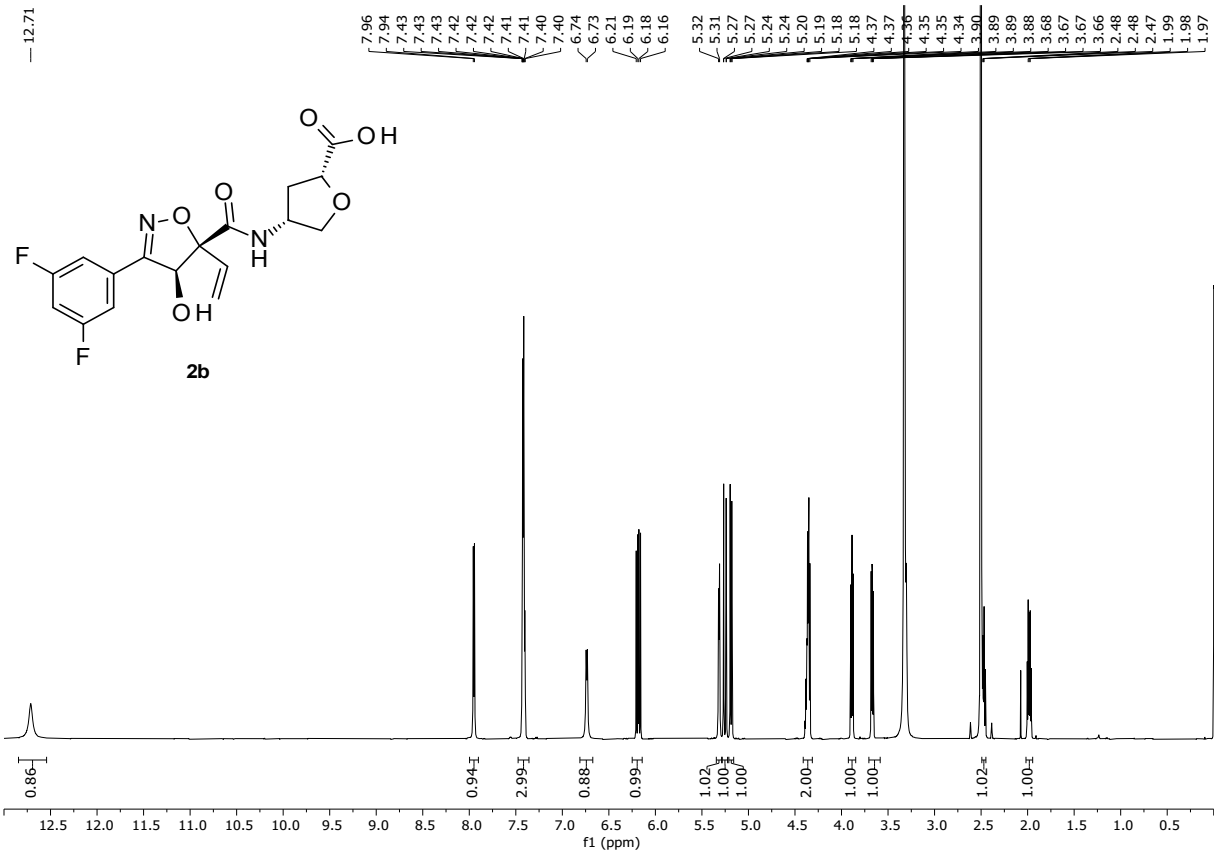


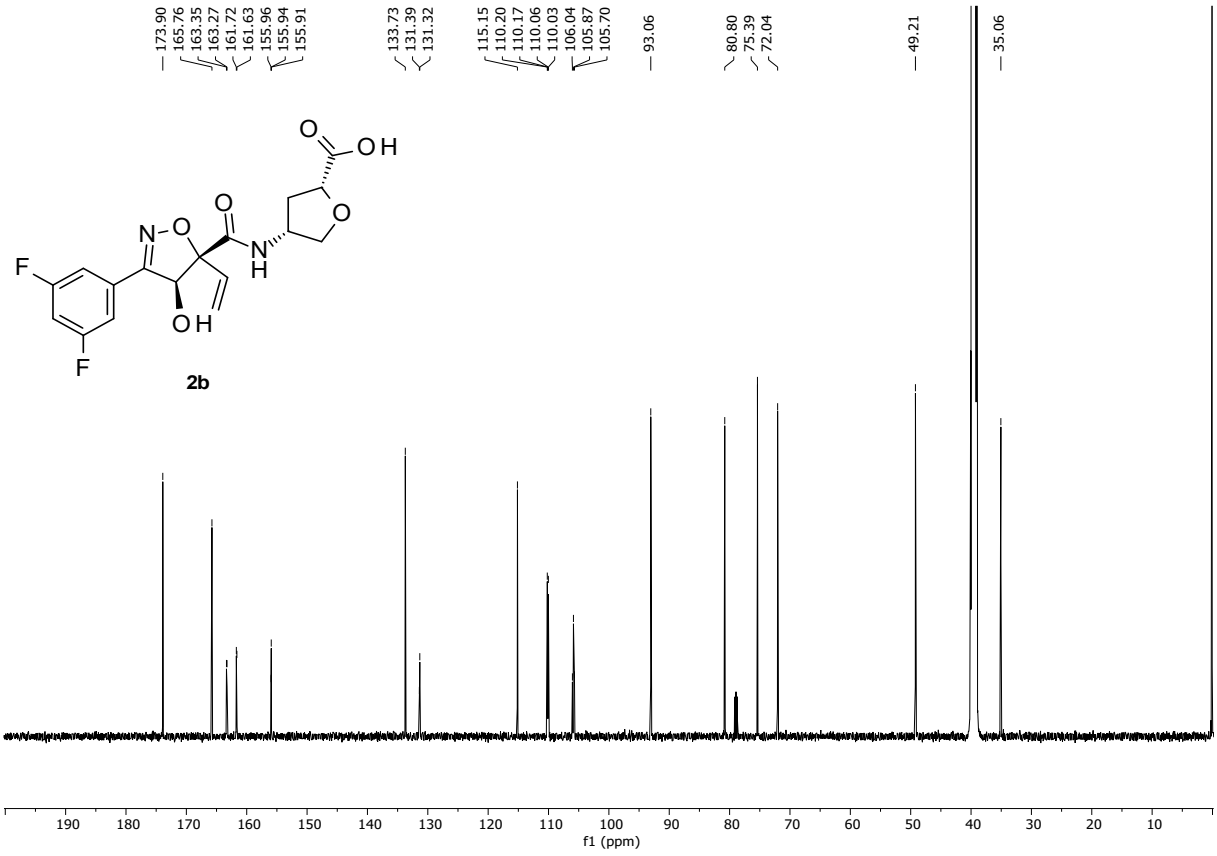
(2*S*,4*S*)-4-[[(4*S*,5*R*)-3-(3,5-Difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carbonyl]amino]tetrahydrofuran-2-carboxylic acid (2a)



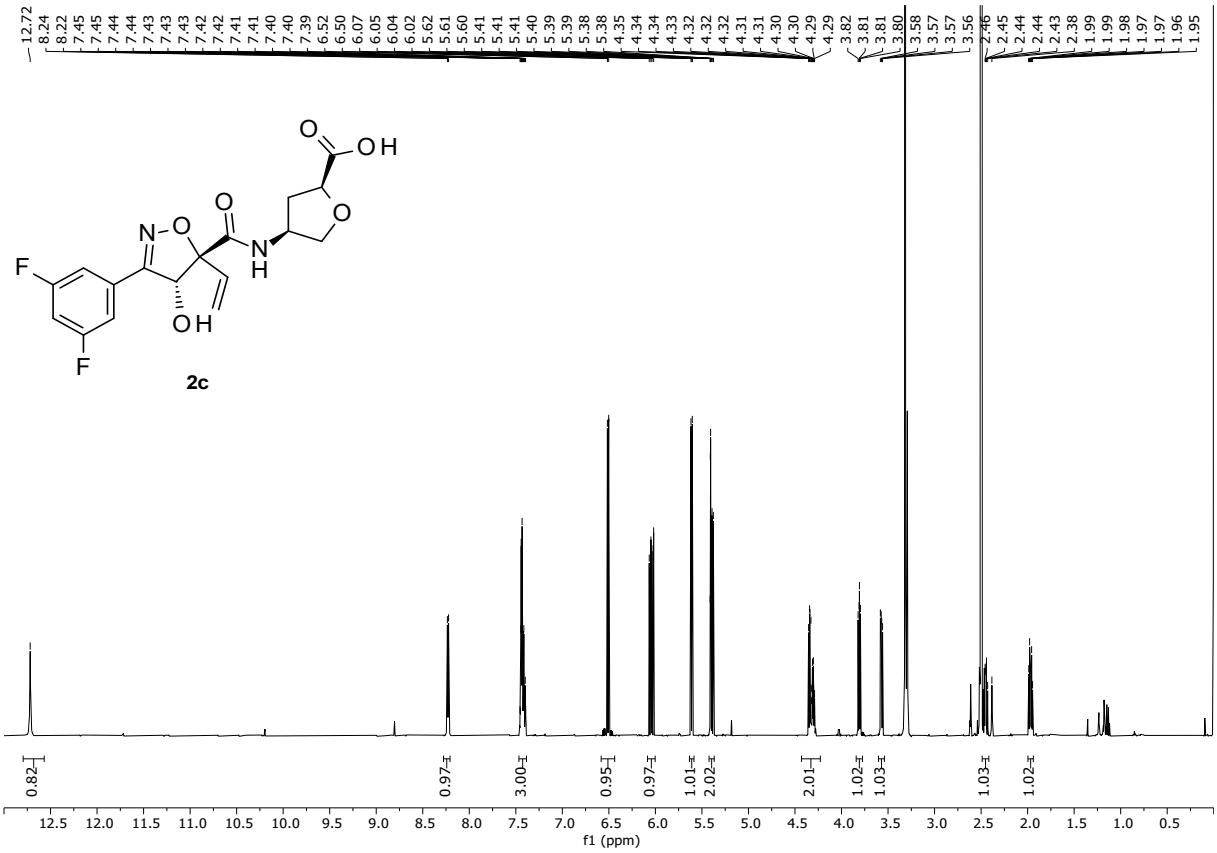


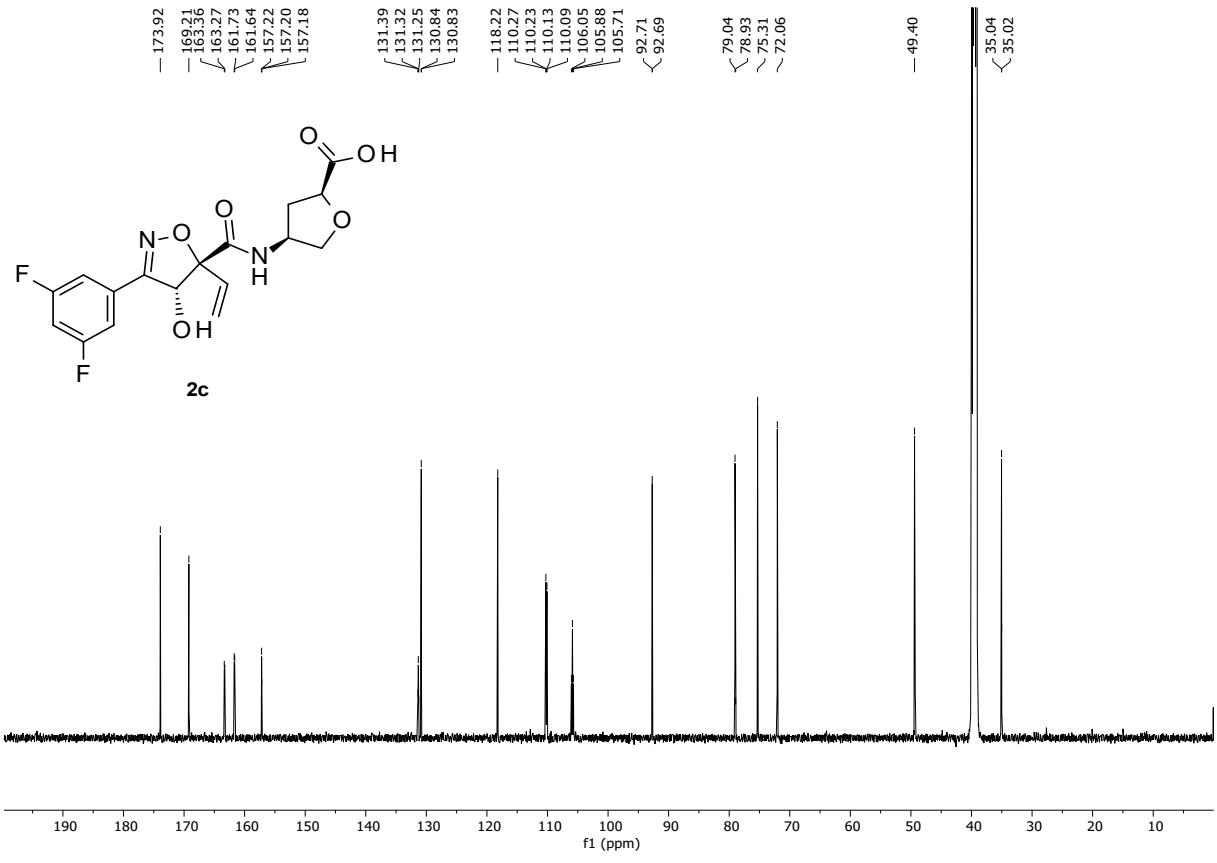
(2*R*,4*R*)-4-[[(4*S*,5*R*)-3-(3,5-Difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carbonyl]amino]tetrahydrofuran-2-carboxylic acid (2b)





(2S,4S)-4-[[(4R,5*R*)-3-(3,5-Difluorophenyl)-4-hydroxy-5-vinyl-4*H*-isoxazole-5-carbonyl]amino]tetrahydrofuran-2-carboxylic acid (2c)





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