Supporting information

Enantioselective Total Synthesis of the Highly Selective Sphingosine-1-Receptor VPC01091 by Heck Desymmetrization of a Non-Activated Cyclopentene-Fused Spiro-Pyrrolidinone

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1. General Informations

All of the Heck-Matsuda arylation reactions were performed in 4 mL screw-top vessels under an air atmosphere. Reaction temperatures different from room temperature are reported as the temperature of the heat transfer medium surrounding the vessel. Bottle grade solvents were used for Heck-Matsuda arylation reactions without any previous treatment (drying or distillation). Methanol refers to >99.8% and acetonitrile refers to >99.5%, both were purchased from synthesis. $Pd(TFA)_2$ (Palladium(II)trifluoroacetate) refers to >97% (Strem chemicals). Ligands **L_1, L_3, L_4 and L_5** were purchased from Sigma-Aldrich and used as received. Ligands **L_2, L_6** and **L_7** were prepared by procedure recently reported by our group.[1] DTBMP (2,6-ditertiarybutyl-4-methylpyridine)[2] and arenediazonium salts[3] were prepared by the literature procedures.

Normally, the general laboratory techniques were used. Moisture and air sensitive reactions were performed in oven-dried glassware fitted with air-tight rubber septum and under an inert (nitrogen) atmosphere. Standard syringe techniques were used to handle the reagents and solvents. Elevated temperatures were obtained by using a stirrer-hotplate and heating block.

Analytical thin layer chromatography was performed on Merck® TLC silica gel 60 F_{254} plates, 0.25mm thickness and eluted with ethylacetate/n-hexane mixtures. To visualize TLC, ultraviolet light (λ = 254nm), $KMnO_4$ and PMA (phosphomolybdic acid) solutions were used.

The crude products obtained were purified by flash column chromatography using Merck® Silica gel 60 (230-400 mesh), eluting with ethylacetate/n-hexane. Solvents used for chromatography were technical grade and were distilled before to use.

^{1}HNMR spectra were taken on Bruker® 250, 400, 500 and 600 MHz and ^{13}CNMR spectra at 100, 125 and 150 MHz instruments. At the methodology optimization stage, 1,3-bis(trifluoromethyl)-5-bromobenzene was used as an internal standard for the determination of chemical yields by ^{1}H NMR. The chemical shift values were recorded in parts per million (ppm) relative to the residual signals of the deuterated NMR solvents used as references ($CDCl_3$; ^{1}H: δ = 7.27 ppm, ^{13}C: δ = 77.26 ppm. $(CD_3)_2SO$; ^{1}H: δ = 2.50 ppm, ^{13}C: δ = 39.52 ppm). The multiplicities of the signals are denoted by s (singlet), d (doublet), t (triplet), q (quartet), sept (septate) bs (broad singlet), td (triplet of doublet), dt (doublet of triplet) dd (double doublet) and m (multiplet).

For determining enantiomeric ratios (*er*), compounds were analysed on Agilent technologies 1260 infinity instrument with an UV detector and Daicel Chiralpak® chiral columns as stationary phase. Isopropyl alcohol and n-hexane as an eluent stated with each product.

Optical rotations (α) were measured on a Perkin Elmer Model 341 polarimeter at 20 °C using a quartz glass cell (10 mm path length). Specific rotations $[\alpha]_D^{20}$ are given in [degcm^{3}g^{-1}dm^{-1}] and the concentration of the samples is expressed in [g/100 mL].

Exact ESI mass spectra were recorded on a Waters Xevo Q-TOF using electrospray ion source, positive mode, (ESI) and (TOF) analyzer. Mass calibration was carried out directly before the measurement of the sample using clusters of sodium formate. The major signals are quoted in m/z.

Melting points were determined on Thomas-Hoover Capillary Melting Point Apparatus, Model 6427-H10.

2. Substrates Synthesis

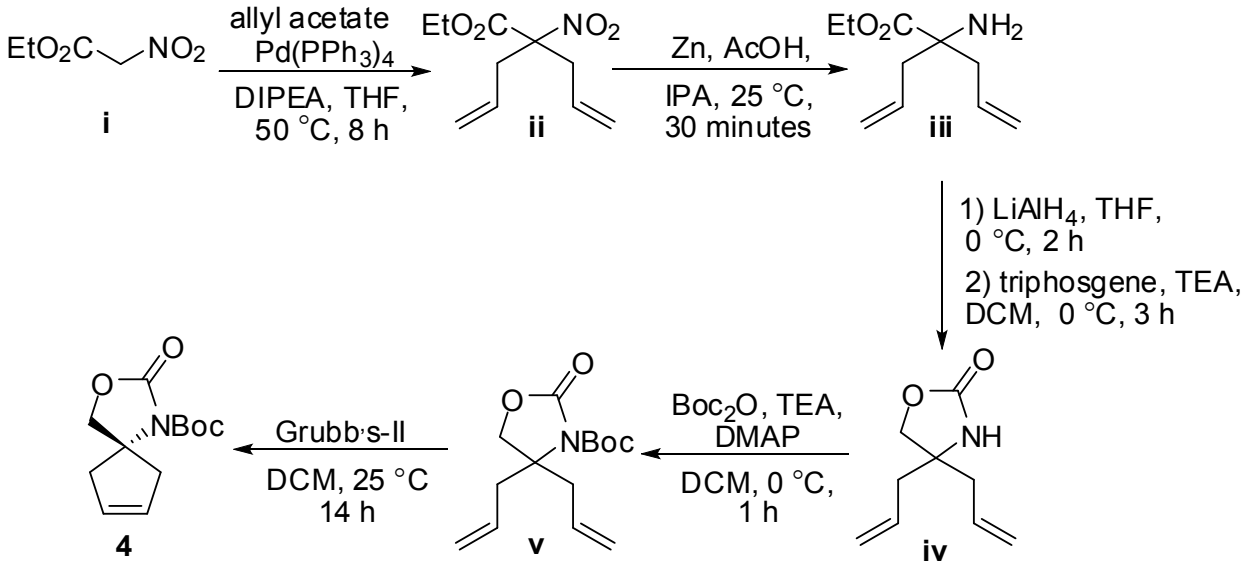
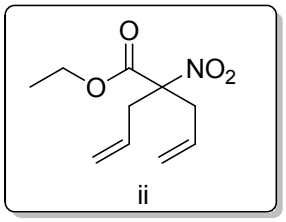


Figure 1. Substrate (**4**) Synthesis



ii

Ethyl-2,2-bis(allyl)-2-nitroacetate (ii)

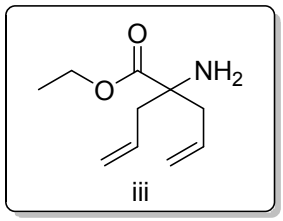
Experimental Procedure:[4]

To a solution of Ethyl-2-nitroacetate **(i)** (100 mol%, 15.03 mmol, 2.00 g, 1.67 mL) in dry THF (75 mL, 0.2 M) were added Allylacetate (210 mol%, 31.56 mmol, 3.4 mL) and $Pd(PPh_3)_4$ (10 mol%,1.50 mmol, 1.73 g). After stirring for 15 minutes, DIPEA (210 mol%, 31.56 mmol, 4.80 g, 5.50 mL) was added and the reaction mixture was stirred under N_2 atmosphere at 50 °C for 8 h. The progress of the reaction was checked by TLC using 2:8 ethylacetate/n-hexane. On completion of the reaction, the reaction mixture was filtered over celite-bed and washed with THF (2 × 100 mL). The filterate was concentrated at low pressure on rotary evaporator, the residue obtained was dissolved in DCM (75 mL) and washed with $NaHCO_3$ aq. solution (75 mL). The aq. layer was extracted with DCM (2 × 75 mL). The combined organic layers were dried on anhydrous Na_2SO_4 and concentrated at low pressure on rotary evaporator. The product obtained was purified by flash column chromatography using 2:98 ethylacetate/n-hexane (less polar eluent was used for column as the PPh_3 in the reaction mixture and the product have very similar R_f values.)

Compound **(ii)** was obtained as yellow oil; 96% yield (3.07 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 – 5.57 (m, 2 H), 5.22 – 5.17 (m, 4 H), 4.26 (q, J = 7.1 Hz, 2 H), 2.99 – 2.86 (m, 4 H), 1.28 (t, J = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 129.6, 121.6, 95.0, 63.0, 38.2, 14.1.



iii

Ethyl-2-allyl-2-aminopent-4-enoate (iii)

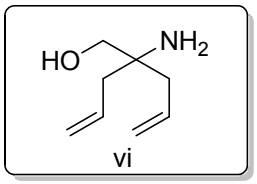
Experimental Procedure:[5]

To a solution of Ethyl-2,2-bis(allyl)-2-nitroacetate **(ii)** (100 mol%, 10.80 mmol, 2.30 g) in isopropanol (100 mL, 0.1 M) in a 250 mL 1 N round bottom flask, activated zinc (3,000 mol%, 324.03 mmol, 21.19 g) was added. Then AcOH (4000 mol%, 432.00 mmol, 24.7 mL) was added slowly (in 10 minutes) and the reaction mixture was stirred at 25 °C for 1 h. The progress of the reaction was checked by TLC. On completion of the reaction, the reaction mixture was filtered and washed with ethylacetate. The solvent and excess AcOH were removedat low pressure on rotary evaporator. The residue obtained was dissolved in EtOAc (100 mL) and washed with 100 mL $NaHCO_3$ aq. The aq. layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried on anhydrous Na_2SO_4 and concentrated at low pressure on rotary evaporator to a pure product.

Compound **(iii)** was obtained as Colourless oil; 92% yield (1.82 g).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.75 – 5.68 (m, 2 H), 5.17 – 5.14 (m, 4 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 2.58 (dd, *J* = 13.5, 6.5 Hz, 2 H), 2.29 (dd, *J* = 13.5, 8.3 Hz, 2 H), 1.29 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 175.1, 132.8, 119.8, 61.4, 60.7, 44.3, 14.6.



vi

2-Allyl-2-aminopent-4-en-1-ol (vi)

Experimental Procedure:[6]

An oven dried flask was purged with N_2, $LiAlH_4$ (200 mol%,16.36 mmol, 0.62 g) was taken in THF (40.00 mL THF), which was then cooled to 0 °C. The solution of the ester **(iii)** (100 mol%, 8.18 mmol, 1.5 g) in 20 mL dry THF was added dropwise (via syringe in 15 minutes) to the flask containing $LiAlH_4$ and stirred for 1 h at 0 °C. The progress of the reaction was checked by TLC using 1:1 ethylacetate/n-hexane. On completion of the reaction, the reaction mixture was diluted two fold with THF (by adding 40 mL THF) and quenched

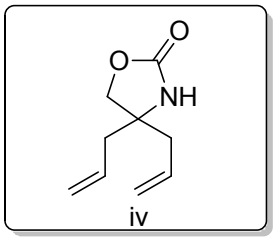
according to the Fieser procedure (by successive addition of water (0.4 mL/mmol $LiAlH_4$), 10% NaOH (0.4 mL/mmol $LiAlH_4$), and water (1.2 mL/mmol $LiAlH_4$) dropwise). The whole reaction mixture was dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography using 1:9 ethylacetate/n-hexane as an eluent.

Compound **(vi)** was obtained as a white solid; 89% yield (1.03g).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.87 – 5.79 (m, 2 H), 5.15 – 5.11 (m, 4 H), 3.35 (s, 2 H), 2.21 – 2.12 (m, 4 H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 133.7, 119.1, 68.4, 55.1, 42.1.

HRMS (ESI+) calculated for ($C_8H_{15}NO_+H^+$): 142.1232, found: 142.1238.



iv

4,4-Diallyloxazolidin-2-one (iv)

Experimental Procedure:[7]

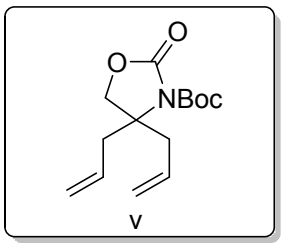
To a solution of 2-Allyl-2-aminopent-4-en-1-ol **(vi)** (100 mol%, 9.21 mmol, 1.30 g)in dry DCM (45 mL) at 0 °C was added triethylamine (200 mol%, 18.42 mmol, 2.57 mL). A solution of triphosgene (50 mol%, 4.61 mmol, 1.37 g) in dry DCM (45 mL) was added dropwise to the reaction mixture in 1 h. The reaction mixture was stirred further for 2 h at 0 °C. The progress of the reaction was checked by TLC by using 1:1 ethylacetate/n-hexane. On completion of the reaction, ether (70 mL) was added to the clear solution which resulted in appearance of white precipitate. The solids were filtered through a sintered glass crucible and washed with DCM. The filtrate was concentrated at low pressure on a rotary evaporator to nearly 15–20 mL. The resulting oil was loaded onto a small pad of silica gel (5 cm length) in a sintered glass crucible and washed slowly with ethylacetate. The filtrate was then concentrated on a rotatory evaporator to provide pure 4,4-Diallyloxazolidin-2-one **(iv)**.

Compound **(iv)** was obtained as light yellow oil; 96% yield (1.48 g).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.80 – 5.74 (m, 2 H), 5.24 – 5.18 (m, 4 H), 4.13 (s, 2 H), 2.38 (dd, J = 14.0, 7.1 Hz, 2 H), 2.32 (dd, J = 14.0, 7.7 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 159.5, 131.4, 120.8, 73.1, 59.9, 43.1.

HRMS (ESI+) calculated for ($C_9H_{13}NO_{2+}H^+$): 168.1024, found: 168.1022.



v

***tert*-Butyl-4,4-diallyl-2-oxooxazolidine-3-carboxylate (v)**

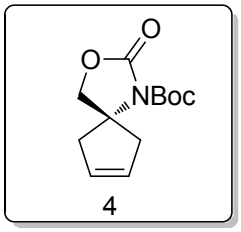
Experimental Procedure:[8]

To a solution of 4,4-Diallyloxazolidin-2-one **(iv)** (100 mol%, 7.18 mmol, 1.20 g) in DCM (75 mL, 0.1 M) were added triethylamine (250 mol%, 17.95 mmol, 2.50 mL), *4*-dimethylaminopyridine (50 mol%, 3.59 mmol, 0.44 g). $(Boc)_2O$ (300 mol%, 21.54 mmol, 4.70 g) dissolved in 35 mL DCM was added dropwise at 0 °C. After stirring for 5 minutes at 0 °C, the reaction mixture was warmed to room temperature, and stirred further for 1 h. The progress of the reaction was checked by TLC by using 2:8 ethylacetate/n-hexane. On completion of the reaction, the volatiles were removed at low pressure on rotary evaporator. The residue obtained was diluted with ethylacetate (100 mL). The organic layer was washed with 2 N HCl aq. solution (2 × 100 mL), saturated $NaHCO_3$ aqueous solution (2 × 100 mL), brine (2 × 100 mL). The organic layer was dried over anhydrous $MgSO_4$, concentrated under reduced pressure on rotary evaporator. The residue obtained was purified by flash column chromatography (using ethylacetate/n-hexane, 1:10 to 3:7).

Compound **(v)** was obtained as colourless oil; 93% yield (1.79 g).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.74 – 5.67 (m, 2 H), 5.24 – 5.18 (m, 4 H), 4.08 (s, 2 H), 2.88 (dd, J = 14.1, 7.3 Hz, 2 H), 2.34 (dd, J = 14.1, 7.4 Hz, 2 H), 1.56 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 152.9, 149.7, 130.9, 121.3, 84.1, 68.8, 63.7, 41.5, 28.2; **HRMS (ESI+)** calculated for ($C_{14}H_{21}NO_4 + H^+$): 268.1549, found: 268.1554.



4

***tert*-Butyl-2-oxo-3-oxa-1-azaspiro[4.4]non-7-ene-1-carboxylate (4)**

Experimental Procedure:[9]

tert-Butyl-4,4-diallyl-2-oxooxazolidine-3-carboxylate **(vi)** (100 mol%, 3.74 mmol, 1.00 g) was dissolved in 1200 mL DCM. To deoxygenate DCM, N_2 was bubbled through the solution

for 30 minutes. After that Grubb's-II catalyst (2.5 mol%, 0.18 mmol, 0.16 g) was added and stirred under N_2 at room temperature for overnight. The progress of the reaction was checked by TCL using 3:7 ethylacetate/n-hexane. On completion of the reaction, the solvent was evaporated at low pressure on rotary evaporator. The residue obtained was purified by flash column chromatography using 1:9 ethylacetate/n-hexane.

Compound **(4)** was obtained as off white solid; 93% yield (1.68 g).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.67 (s, 2 H), 4.17 (s, 2 H), 3.17 (d, *J* = 15.2 Hz, 2 H), 2.47 (d, *J* = 15.1 Hz, 2 H), 1.52 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 152.9, 149.6, 128.3, 84.3, 77.9, 67.0, 44.0, 28.3.

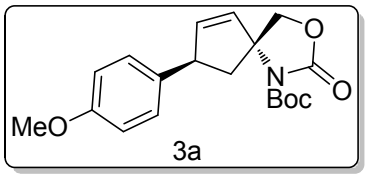
HRMS (ESI+) calculated for ($C_{12}H_{17}NO_4 + H^+$): 240.1236, found: 240.1227.

M.P.: 85 – 87 °C.

3. Synthesis and Characterization of Products

3.1 General procedure for the Heck-Matsuda arylation reactions using arenediazonium salts:

To a 4 mL screw-top vial containing a magnetic stir-bar was added $Pd(TFA)_2$ (5 mol%, 0.005 mmol, 0.00166 g), ligand (pyrazine-bisoxazoline, 7.5 mol%, 0.0075 mmol, 0.00248 g) and 0.25 mL of 2:8 acetonitrile/methanol (0.4 M). The resulting light orange colored solution was then stirred at 60 °C for 8 minutes to result in the formation of ligand-catalyst complex. After 8 minutes stirring at 60 °C, it was cooled to room temperature. Then the olefin **(4)** (100 mol%, 0.1 mmol, 0.0239 g), DTBMP (2,6-di-*tert*-butyl-4-methylpyridine) (100 mol%, 0.1 mmol, 0.0205 g) were added to it, followed by the addition of the appropriate arenediazonium salt **5a-5l** (120 mol%, 0.12 mmol). The progress of the reaction was monitored by TLC using 2:8 ethylacetate/n-hexane and stained by PMA (phosphomolybdic acid) solution. On complete consumption of the olefin shown by TLC, the reaction mixture was filtered through a short pad of silica gel in 24 mL plastic syringe and washed with 1:1 ethylacetate/n-hexane to remove the polar impurities. The resulting filtrate was concentrated at low pressure on rotary evaporator. The crude product obtained was purified by flash column chromatography using 1:9 ethylacetate/n-hexane as eluent to afford the Heck products with yield up to 93%. To determine the chemical yield by ^{1}HNMR, 1,3-bis(trifluoromethyl)-5-bromobenzene (1 eq, 0.0293 g, 17.2 µL for 0.1 mmol of substrate) was added to the crude reaction mixture as an internal standard and the olefinic protons signal was compared with the one proton signal of the internal standard.



3a

(5R,8R)-*tert*-Butyl-8-(4methoxyphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3a)

Compound **3a** was obtained as a colorless crystalline solid (30.4 mg, 0.088 mmol, 88% isolated yield); 92:8 dr (determined by NMR).

The enantiomeric ratio (*er*) determined by Agilent technologies 1260 infinity instrument in comparison to a racemic material using Daicel Chiralpak® IA-3 column (4.6 mm × 250 mm) at 25 °C, 1:99 isopropanol/n-hexane (1.0 mL/min) as mobile phase. (Major diastereomer: t_R =

28.72 min (major), 44.50 min (minor); minor diastereomer: t_R = 26.18 min (major), 32.67 min (minor)).

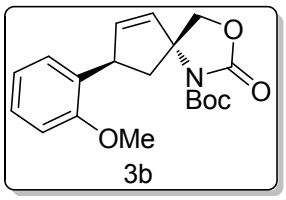
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.03 (d, *J* = 8.6 Hz, 2 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 6.07 (dd, *J* = 5.5, 2.3 Hz, 1 H), 5.80 (dd, *J* = 5.5, 2.3 Hz, 1 H), 4.27 – 4.23 (m, 1 H), 4.20 (d, *J* = 8.8 Hz, 1 H), 4.05 (d, *J* = 8.8 Hz, 1 H), 3.80 (s, 3 H), 2.97 (dd, *J* = 14.2, 9.2 Hz, 1 H), 1.90 (dd, *J* = 14.2, 4.2 Hz, 1 H), 1.55 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 158.7, 152.6, 149.5, 139.7, 136.3, 131.2, 128.2, 114.4, 84.2, 73.9, 73.8, 55.6, 49.8, 45.0, 28.3.

HRMS(ESI+) calculated for ($C_{19}H_{23}NO_5 + H^+$): 346.1654, found: 346.1644.

$[\alpha]_D^{20}$ (c 2.86, $CHCl_3$) = +184.2.

M.P.: 154 – 157 °C



3b

(5R,8R)-*tert*-Butyl-8-(2-methoxyphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3b)

Compound **3b** was obtained as a white solid (29.4 mg, 0.085 mmol, 85% isolated yield); 95:5 dr determined by NMR.

The enantiomeric ratio (*er*) determined by Agilent technologies 1260 infinity instrument in comparison to a racemic material using Daicel Chiralpak® IA-3 column (4.6 mm × 250 mm) at 25 °C, 1:99 isopropanol/n-hexane (1.0 mL/min) as mobile phase. (Major diastereomer: t_R = 30.33 min (major), 36.29 min (minor); minor diastereomer: t_R = 22.71 min (major), 25.67 min (minor)).

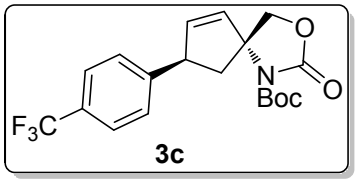
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (td, *J* = 8.1, 8.0, 1.7 Hz, 1 H), 6.96 (dd, *J* = 7.7, 1.6 Hz, 1 H), 6.94 – 6.87 (m, 2 H), 6.07 (dd, *J* = 5.6, 2.4 Hz, 1 H), 5.83 (dd, *J* = 5.5, 2.2 Hz, 1 H), 4.51 – 4.45 (m, 1 H), 4.12 (d, *J* = 8.8 Hz, 1 H), 3.96 (d, *J* = 8.8 Hz, 1 H), 3.84 (s, 3 H), 2.96 (dd, *J* = 14.1, 9.5 Hz, 1 H), 1.94 (dd, *J* = 14.1, 3.8 Hz, 1 H), 1.56 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.3, 152.8, 149.5, 138.3, 132.5, 131.8, 128.2, 127.0, 120.6, 110.7, 84.1, 73.8, 73.7, 55.4, 44.6, 43.1, 28.3.

HRMS (ESI+) calculated for ($C_{19}H_{23}NO_5 + H^+$): 346.1654, found: 346.1650.

$[\alpha]_D^{20}$ (c 2.90, $CHCl_3$) = +128.7.

M.P.: 70 – 73 °C.



(5R,8R)-*tert*-Butyl-2-oxo-8-(4-(trifluoromethyl)phenyl)-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3c)

Compound **3c** was obtained as a colorless crystalline solid (20.3 mg, 0.053 mmol, 53% isolated yield); 88:12 dr determined by NMR.

The enantiomeric ratio (*er*) was determined by Agilent technologies 1260 infinity instrument in comparison to a racemic material using Daicel Chiralpak® IC column (4.6 mm × 250 mm) at 25 °C, 10:90 isopropanol/n-hexane (1.0 mL/min) as mobile phase. (Major diastereomer: t_R = 35.08 min (major), 30.13 min (minor); minor diastereomer: t_R = 57.44 min (major), 38.71 min (minor)).

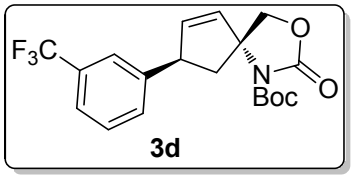
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.1 Hz, 2 H), 7.25 (d, *J* = 8.1 Hz, 2 H), 6.11 (dd, *J* = 5.5, 2.2 Hz, 1 H), 5.88 (dd, *J* = 5.5, 2.3 Hz, 1 H), 4.41 – 4.38 (m, 1 H), 4.24 (d, *J* = 8.9 Hz, 1 H), 4.05 (d, *J* = 8.9 Hz, 1 H), 3.05 (dd, *J* = 14.3, 9.2 Hz, 1 H), 1.90 (dd, *J* = 14.3, 4.6 Hz, 1 H), 1.57 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 152.3, 149.6, 148.3, 138.7, 132.1, 129.5 (q, *J* = 32.6 Hz), 127.7, 126.0 (q, *J* = 3.6 Hz), 124.4 (q, *J* = 269.6 Hz), 84.4, 73.7, 73.7, 50.5, 44.8, 28.3.

HRMS (ESI+) calculated for ($C_{19}H_{20}F_3NO_4 + H^+$): 384.1423, found: 384.1417.

$[\alpha]_D^{20}$ (c 1.05, $CHCl_3$) = +154.8.

M.P.: 139 – 143 °C.



(5R,8R)-*tert*-Butyl-2-oxo-8-(3-(trifluoromethyl)phenyl)-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3d)

Compound **3d** was obtained as a yellow sticky material (16.1 mg, 0.042 mmol, 42% isolated yield); 89:11 dr determined by NMR.

The enantiomeric ratio (*er*) determined by Agilent technologies 1260 infinity instrument in comparison to a racemic material using Daicel Chiralpak® IC column (4.6 mm × 250 mm) at 25 °C, 10:90 isopropanol/n-hexane (1.0 mL/min) as mobile phase. (Major diastereomer: t_R = 44.85

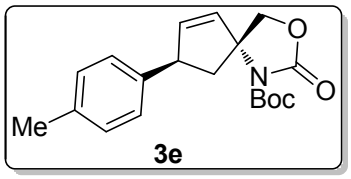
min (major), 35.94 min (minor); minor diastereomer: t_R = 40.46 min (major), min 51.32 (minor)).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.5 – 7.43 (m, 2 H), 7.36 – 7.30 (m, 2 H), 6.10 (dd, *J* = 5.5, 2.3 Hz, 1 H), 5.88 (dd, *J* = 5.5, 2.3 Hz, 1 H), 4.40 – 4.37 (m, 1 H), 4.24 (d, *J* = 8.9 Hz, 1 H), 4.05 (d, *J* = 8.9 Hz, 1 H), 3.04 (dd, *J* = 14.4, 9.2 Hz, 1 H), 1.90 (dd, *J* = 14.4, 4.7 Hz, 1 H), 1.55 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 152.3, 149.4, 145.2, 138.7, 132.2, 131.3 (q, *J* = 32.2 Hz), 130.7, 129.5, 124.2 (q, *J* = 272.3 Hz), 124.0 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 3.8 Hz), 84.3, 73.7, 73.6, 50.5, 44.8, 28.2.

HRMS (ESI+) calculated for ($C_{19}H_{20}F_3NO_4 + H^+$): 384.1423, found: 384.1414.

$[\alpha]_D^{20}$ (c 1.516, $CHCl_3$) = +188.0.



3e

(5R,8R)-*tert*-Butyl-2-oxo-8-(p-tolyl)-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3e)

Compound **3e** was obtained as a colorless crystallie solid (29.6 mg, 0.09 mmol, 90% isolated yield); 94:6 dr determined by NMR.

The enantiomeric ratio (*er*) determined by Agilent technologies 1260 infinity instrument in comparison to a racemic material using Daicel Chiralpak® IC column (4.6 mm × 250 mm) at 25 °C, 5:95 isopropanol/n-hexane (1.0 mL/min) as mobile phase. (Major diastereomer: t_R = 77.71 min (major), 84.38 min (minor); minor diastereomer: t_R = 99.28 min (major), 121.64 min (minor)).

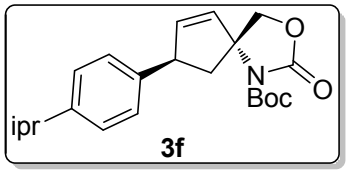
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 (d, *J* = 7.8 Hz, 2 H), 7.00 (d, *J* = 8.0 Hz, 2 H), 6.08 (dd, *J* = 5.5, 2.3 Hz, 1 H), 5.80 (dd, *J* = 5.5, 2.2 Hz, 1 H), 4.28 – 4.25 (m, 1 H), 4.20 (d, *J* = 8.8 Hz, 1 H), 4.05 (d, *J* = 8.8 Hz, 1 H), 2.99 (dd, *J* = 14.2, 9.2 Hz, 1 H), 2.34 (s, 3 H), 1.92 (dd, *J* = 14.2, 4.2 Hz, 1 H), 1.56 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 152.6, 149.5, 141.2, 139.5, 136.7, 131.2, 129.7, 127.1, 84.2, 73.9, 50.2, 44.9, 29.9, 28.3, 21.2.

HRMS (ESI+) calculated for ($C_{19}H_{23}NO_4 + H^+$): 330.1705, found: 330.1700.

$[\alpha]_D^{20}$ (c 1.459, $CHCl_3$) = +218.9.

M.P.: 115 – 118 °C.



(5R,8R)-*tert*-Butyl-8-(4-isopropylphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3f)

Compound **3f** was obtained as a white solid (30.7 mg, 0.0.86 mmol, 86% isolated yield); 95:5 dr determined by NMR.

The enantiomeric ratio (*er*) determined by Agilent technologies 1260 infinity instrument in comparison to a racemic material using Daicel Chiralpak® IA-3 column (4.6 mm × 250 mm) at 25 °C, 1:99 isopropanol/n-hexane (1.0 mL/min) as mobile phase. (Major diastereomer: t_R = 14.32 min (major), 16.30 min (minor); minor diastereomer: t_R = 34.92 min (major), 21.90 min (minor)).

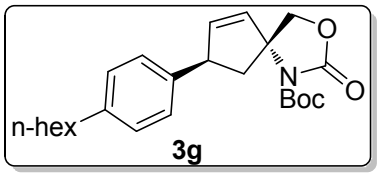
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.18 (d, *J* = 8.1 Hz, 2 H), 7.04 (d, *J* = 8.1 Hz, 2 H), 6.09 (dd, *J* = 5.5, 2.3 Hz, 1 H), 5.81 (dd, *J* = 5.5, 2.3 Hz, 1 H), 4.28 – 4.25 (m, 1 H), 4.21 (d, *J* = 8.8 Hz, 1 H), 4.07 (d, *J* = 8.8 Hz, 1 H), 2.98 (dd, *J* = 14.2, 9.3 Hz, 1 H), 2.89 (sept, *J* = 6.9 Hz, 1 H), 1.95 (dd, *J* = 14.3, 4.2 Hz, 1 H), 1.56 (s, *J* = 6.2 Hz, 9 H), 1.25 (d, *J* = 7.0 Hz, 6 H)

^{13}C NMR (150 MHz, $CDCl_3$): δ 152.6, 149.5, 147.6, 141.5, 139.5, 131.2, 127.2, 127.0, 84.1, 73.9, 73.8, 50.2, 44.8, 33.9, 28.2, 24.2.

HRMS (ESI+) calculated for ($C_{21}H_{27}NO_4 + H^+$): 358.2018, found: 358.2003.

$[\alpha]_D^{20}$ (c 1.91, $CHCl_3$) = +221.2.

M.P.: 97 – 99 °C.



(5R,8R)-*tert*-Butyl-8-(4-hexylphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3g)

Compound **3g** was obtained as a yellow sticky material (34.4 mg, 0.086 mmol, 86% isolated yield); 94:6 dr determined by NMR.

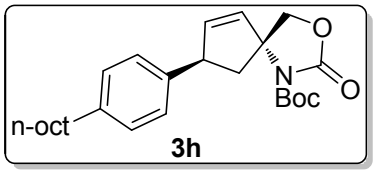
The enantiomeric ratio (*er*) determined by Agilent technologies 1260 infinity instrument in comparison to a racemic material using Daicel Chiralpak® IC column (4.6 mm × 250 mm) at 25 °C, 5:95 isopropanol/n-hexane (1.0 mL/min) as mobile phase. (Major diastereomer: t_R = 55.21 min (major), 60.17 min (minor); minor diastereomer: t_R = 84.65 min (major), 97.28 min (minor)).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 (d, *J* = 8.0 Hz, 2 H), 7.02 (d, *J* = 8.0 Hz, 2 H), 6.09 (dd, *J* = 5.5, 2.3 Hz, 1 H), 5.80 (dd, *J* = 5.5, 2.2 Hz, 1 H), 4.28 – 4.25 (m, 1 H), 4.21 (d, *J* = 8.8 Hz, 1 H), 4.06 (d, *J* = 8.8 Hz, 1 H), 2.98 (dd, *J* = 14.2, 9.2 Hz, 1 H), 2.58 (t, *J* = 8.0 Hz, 2 H), 1.94 (dd, *J* = 14.2, 4.2 Hz, 1 H), 1.63 – 1.58 (m, 2 H), 1.56 (s, 9 H), 1.35 – 1.27 (m, 6 H), 0.89 (t, *J* = 6.6 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 152.6, 149.6, 141.8, 141.4, 139.6, 131.2, 129.0, 127.4, 127.1, 84.2, 73.9, 50.3, 44.9, 35.8, 32.0, 31.7, 29.3, 28.3, 22.8, 14.3.

HRMS (ESI+) calculated for ($C_{24}H_{33}NO_4 + H^+$): 400.2472, found: 400.2488.

$[\alpha]_D^{20}$ (c 1.14, $CHCl_3$) = +88.1.



(5R,8R)-*tert*-Butyl-8-(4-octylphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3h)

Compound **3h** was obtained as a light brown solid (39.8 mg, 0.093 mmol, 93% isolated yield); 95:5 dr determined by NMR.

The enantiomeric ratio (*er*) determined by Agilent technologies 1260 infinity instrument in comparison to a racemic material using Daicel Chiralpak® IC column (4.6 mm × 250 mm) at 25 °C, 10:90 isopropanol/n-hexane (0.5 mL/min) as mobile phase. (Major diastereomer: t_R = 56.41 min (major), 59.54 min (minor); minor diastereomer: t_R = 73.95 min (major), 65.37 min (minor)).

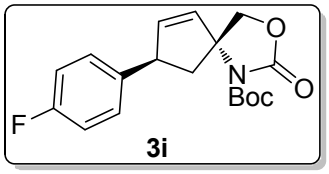
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.13 (d, *J* = 8.0 Hz, 2 H), 7.02 (d, *J* = 8.0 Hz, 2 H), 6.09 (dd, *J* = 5.5, 2.3 Hz, 1 H), 5.80 (dd, *J* = 5.5, 2.2 Hz, 1 H), 4.28 – 4.25 (m, 1 H), 4.21 (d, *J* = 8.8 Hz, 1 H), 4.06 (d, *J* = 8.8 Hz, 1 H), 2.98 (dd, *J* = 14.2, 9.3 Hz, 1 H), 2.58 (t, *J* = 7.8 Hz, 2 H), 1.94 (dd, *J* = 14.2, 4.2 Hz, 1 H), 1.66 – 1.59 (m, 2 H), 1.56 (s, 9 H), 1.34 – 1.25 (m, 10 H), 0.89 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 152.6, 149.5, 141.8, 141.4, 139.6, 131.2, 129.0, 127.1, 84.2, 73.9, 50.3, 44.8, 37.6, 35.8, 32.1, 31.7, 29.7, 29.6, 29.5, 28.3, 22.9, 14.3.

HRMS (ESI+) calculated for ($C_{26}H_{27}NO_4 + H^+$): 428.2801, found: 428.2807.

$[\alpha]_D^{20}$ (c 1.90, $CHCl_3$) = +145.0

M.P.: 55 – 57 °C.



(5R,8R)-*tert*-Butyl-8-(4-fluorophenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3i)

Compound **3i** was obtained as a yellow solid (28.3 mg, 0.085 mmol, 85% isolated yield); 89:11 dr determined by NMR.

The enantiomeric ratio (*er*) determined by Agilent technologies 1260 infinity instrument in comparison to a racemic material using Daicel Chiralpak® IA-3 column (4.6 mm × 250 mm) at 25 °C, 1:99 isopropanol/n-hexane (1.0 mL/min) as mobile phase. (Major diastereomer: t_R = 29.47 min (major), 44.57 min (minor); minor diastereomer: t_R = 26.95 min (major), 33.52 min (minor)).

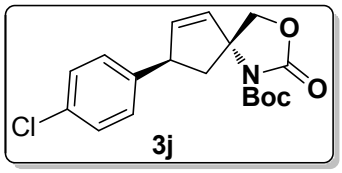
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.09 – 6.99 (m, 4 H), 6.08 (dd, *J* = 5.5, 2.2 Hz, 1 H), 5.83 (dd, *J* = 5.4, 2.2 Hz, 1 H), 4.31 – 4.29 (m, 1 H), 4.21 (d, *J* = 8.8 Hz, 1 H), 4.04 (d, *J* = 8.8 Hz, 1 H), 3.00 (dd, *J* = 14.2, 9.2 Hz, 1 H), 1.89 (dd, *J* = 14.3, 4.4 Hz, 1 H), 1.56 (s, *J* = 8.3 Hz, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.7 (d, *J* = 245.4 Hz), 152.2, 149.3, 139.7 (d, *J* = 2.9 Hz), 131.3, 128.5 (d, *J* = 7.9 Hz), 115.6 (d, *J* = 21.3 Hz), 114.2, 84.1, 73.6, 49.7, 44.8, 29.7, 28.1.

HRMS (ESI+) calculated for ($C_{18}H_{20}FNO_4 + H^+$): 334.1454, found: 334.1442.

$[\alpha]_D^{20}$ (c 0.99, $CHCl_3$) = +167.8.

M.P.: 68 – 71 °C.



(5R,8R)-*tert*-Butyl-8-(4-chlorophenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3j)

Compound **3j** was obtained as a white solid (29.0 mg, 0.083 mmol, 83% isolated yield); 90:10 dr determined by NMR.

The enantiomeric ratio (*er*) determined by Agilent technologies 1260 infinity instrument in comparison to a racemic material using Daicel Chiralpak® IB-3 column (4.6 mm × 250 mm) at 25 °C, 5:95 isopropanol/n-hexane (0.6 mL/min) as mobile phase. (Major diastereomer: t_R = 21.61 min (major), 24.48 min (minor); minor diastereomer: t_R = 26.82 min (major), 28.40 min (minor)).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (d, *J* = 8.4 Hz, 2 H), 7.07 (d, *J* = 8.4 Hz, 2 H), 6.10 (dd, *J* = 5.5, 2.2 Hz, 1 H), 5.86 (dd, *J* = 5.5, 2.2 Hz, 1 H), 4.32 – 4.30 (m, 1 H), 4.23 (d, *J* = 8.8 Hz, 1 H),

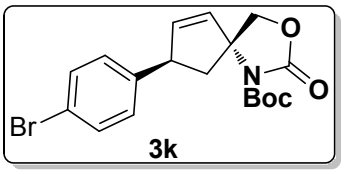
4.06 (d, *J* = 8.8 Hz, 1 H), 3.03 (dd, *J* = 14.3, 9.2 Hz, 1 H), 1.90 (dd, *J* = 14.3, 4.4 Hz, 1 H), 1.58 (s, *J* = 7.4 Hz, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 152.4, 149.5, 142.7, 139.0, 132.8, 131.8, 129.1, 128.6, 84.3, 73.7, 50.0, 44.8, 30.4, 28.2.

HRMS (ESI+) calculated for ($C_{18}H_{20}ClNO_4 + H^+$): 350.1159, found: 350.1146.

$[\alpha]_D^{20}$ (c 2.49, $CHCl_3$) = +237.1.

M.P.: 125 – 127 °C.



(5R,8R)-*tert*-Butyl-8-(4-bromophenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3k)

Compound **3k** was obtained as a light yellow solid (32.3 mg, 0.082 mmol, 82% isolated yield); 92:8dr determined by NMR.

The enantiomeric ratio (*er*) determined by Agilent technologies 1260 infinity instrument in comparison to a racemic material using Daicel Chiralpak® IC column (4.6 mm × 250 mm) at 25 °C, 10:90 isopropanol/n-hexane (1.0 mL/min) as mobile phase. (Major diastereomer: t_R = 65.73 min (major), 76.69 min (minor); minor diastereomer: t_R = 69.79 min (major), 61.58 min (minor)).

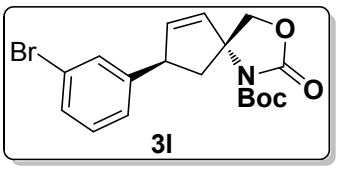
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.4 Hz, 2 H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.07 (dd, *J* = 5.5, 2.3 Hz, 1 H), 5.84 (dd, *J* = 5.5, 2.3 Hz, 1 H), 4.30 – 4.26 (m, 1 H), 4.21 (d, *J* = 8.8 Hz, 1 H), 4.04 (d, *J* = 8.8 Hz, 1 H), 3.01 (dd, *J* = 14.3, 9.2 Hz, 1 H), 1.88 (dd, *J* = 14.3, 4.5 Hz, 1 H), 1.55 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 152.4, 149.5, 143.3, 139.0, 132.1, 131.8, 129.0, 120.8, 84.3, 73.7, 50.1, 44.8, 44.0, 28.3.

HRMS (ESI+) calculated for ($C_{18}H_{20}BrNO_4 + H^+$): 394.0654, found: 394.0640.

$[\alpha]_D^{20}$ (c 0.77, $CHCl_3$) = +158.7.

M.P.: 136 – 139 °C.



(5R,8R)-*tert*-Butyl-8-(3-bromophenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3l)

Compound **3l** was obtained as a yellow sticky material (28.4 mg, 0.072 mmol, 72% isolated yield); >98:2 dr determined by NMR.

The enantiomeric ratio (*er*) determined by Agilent technologies 1260 infinity instrument in comparison to a racemic material using Daicel Chiralpak® IC column (4.6 mm × 250 mm) at 25 °C, 15:85 isopropanol/n-hexane (1.0 mL/min) as mobile phase. Major diastereomer: t_R = 42.79 min (major), 39.68 min (minor)).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39 – 7.05 (m, 4 H), 6.08 (dd, *J* = 5.5, 2.3 Hz, 1 H), 5.85 (dd, *J* = 5.5, 2.3 Hz, 1 H), 4.31 – 4.28 (m, 1 H), 4.23 (d, *J* = 8.9 Hz, 1 H), 4.06 (d, *J* = 8.9 Hz, 1 H), 3.01 (dd, *J* = 14.3, 9.2 Hz, 1 H), 1.90 (dd, *J* = 14.3, 4.6 Hz, 1 H), 1.56 (s, 9 H).

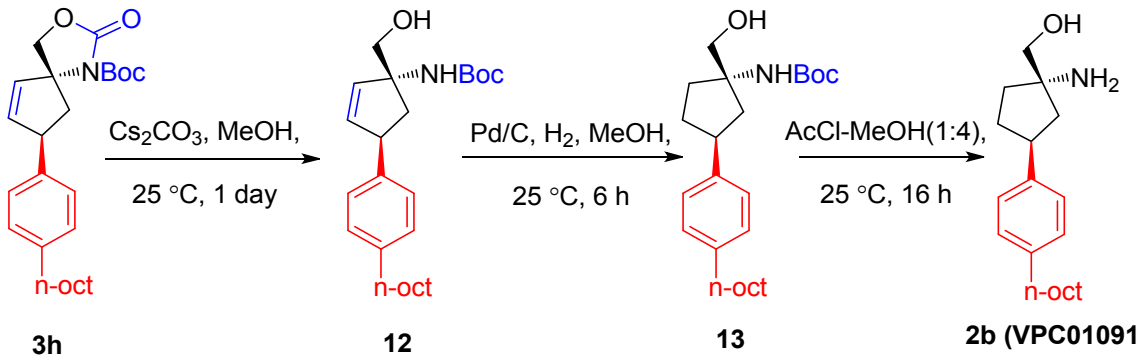
^{13}C NMR (150 MHz, $CDCl_3$): δ 152.4, 149.5, 146.6, 138.9, 132.0, 130.6, 130.4, 130.2, 126.0, 123.2, 84.4, 73.7, 50.4, 44.8, 29.9, 28.3.

HRMS (ESI+) calculated for ($C_{18}H_{20}BrNO_4 + H^+$): 394.0654, found: 394.0650.

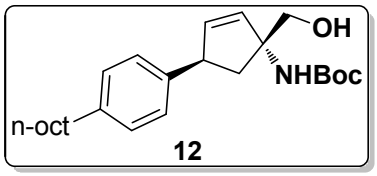
$[\alpha]_D^{20}$ (c 0.82, $CHCl_3$) = +146.3.

4. Application of the methodology for the Enantioselective Total Synthesis of the Highly Selective Sphingosine-1-Receptor, VPC01091

The Highly Selective Sphingosine-1-Receptor, VPC01091 was prepared by a short and concise way involving four steps starting from the spirosubstrate, 4 with the 62% overall yield



3h **12** **13** **2b (VPC01091)**



***tert*-Butyl-((1R,4R)-1-(hydroxymethyl)-4-(4-octylphenyl)cyclopent-2-en-1-yl)carbamate (12)**

Experimental procedure:[10]

To a solution of pyrolidinone **3h** (0.1 mmol, 0.0428 g) in 2 mL methanol was added Cs_2CO_3 (0.12 mmol, 0.0391 g) and stirred at 25 °C for 24 h. On completion, the reaction was quenched with H_2O and extracted with ethylacetate. The combined organic layers were washed with brine, dried on $MgSO_4$ and concentrated on rotary evaporator. The crude product was purified by flash column chromatography using 1:9 to 2:8 ethylacetate/n-hexane as an eluent.

Compound **12** was obtained as a white solid (32.9 mg, 0.082 mmol, 82% isolated yield).

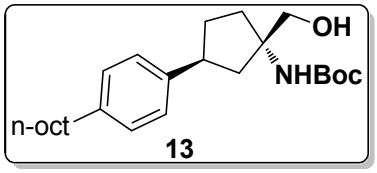
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.12 (d, *J* = 8.1 Hz, 2 H), 7.08 (d, *J* = 8.1 Hz, 2 H), 6.03 (dd, *J* = 5.6, 1.9 Hz, 1 H), 5.95 (dd, *J* = 5.5, 2.5 Hz, 1 H), 4.93 (s, 1 H), 4.16 – 4.13 (m, 1 H), 3.79 (s, 2 H), 2.59 – 2.56 (m, 3 H), 1.94 (dd, *J* = 14.0, 6.7 Hz, 1 H), 1.62 – 1.57 (m, 2 H), 1.47 (s, 9 H), 1.33 – 1.26 (m, 10 H), 0.89 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 156.2, 141.8, 141.4, 139.0, 133.0, 128.8, 127.3, 80.2, 70.5, 49.8, 49.7, 43.6, 35.8, 32.1, 31.8, 29.7, 29.6, 29.5, 28.6, 22.9, 14.3.

HRMS (ESI+) calculated for ($C_{25}H_{39}NO_3$ + H^+): 402.3008, found: 402.2998.

$[\alpha]_D^{20}$ (c 0.541, $CHCl_3$) = +90.2.

M.P.: 77 – 80 °C.



***tert*-Butyl-((1S,3S)-1-(hydroxymethyl)-3-(4-octylphenyl)cyclopentyl)carbamate (13)**

Experimental procedure:[11]

To a suspension of the *tert*-Butyl(1-(hydroxymethyl)-4-(4-octylphenyl)cyclopent-2-en-1-yl)carbamate **12** (0.0418 g, 0.1 mmol) in methanol (1 mL) was added Pd/C (5%, 0.0045 mmol, 0.011 g) and stirred at room temperature under H_2 atmosphere for 6 h. The progress of the reaction was checked by TLC using 3:7 ethylacetate/n-hexane. On completion of the reaction,

the reaction mixture was filtered through a short pad of silica gel and concentrated under reduced pressure on rotary evaporator to provide the pure product.

Compound **13** was obtained as a white solid (38.3 mg, 0.095 mmol, 95% isolated yield); 96:4 dr determined by HPLC.

The enantiomeric ratio (*er*) determined by Agilent technologies 1260 infinity instrument in comparison to a racemic material using Daicel Chiralpak® IA-3 column (4.6 mm × 250 mm) at 25 °C, 1:99 isopropanol/n-hexane (1.0 mL/min) as mobile phase. (Major diastereomer: t_R = 22.19 min (major), 19.32 min (minor); minor diastereomer: t_R = 24.78 min (major), 17.98 min (minor)).

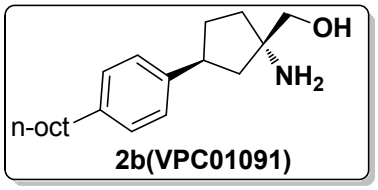
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (d, *J* = 8.1 Hz, 2 H), 7.11 (d, *J* = 8.1 Hz, 2 H), 4.87 (s, 1 H), 3.74 (dd, *J* = 34.7, 10.9 Hz, 2 H), 3.35 – 3.27 (m, 1 H), 2.57 (app. t, *J* = 7.7 Hz, 2 H), 2.32 (dd, *J* = 13.7, 7.4 Hz, 1 H), 2.20 – 2.07 (m, 2 H), 1.86 – 1.66 (m, 3 H), 1.63 – 1.57 (m, 2 H), 1.47 (s, *J* = 4.9 Hz, 9 H), 1.32 – 1.27 (m, 10 H), 0.89 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 156.5, 141.6, 141.1, 128.6, 127.0, 80.3, 70.3, 65.2, 43.9, 43.8, 36.6, 35.8, 33.2, 32.1, 31.8, 29.7, 29.6, 29.5, 28.6, 22.9, 14.4.

HRMS (ESI+) calculated for ($C_{25}H_{41}NO_3$ + H^+): 404.3165, found: 404.3184.

$[\alpha]_D^{20}$ (c 2.67, MeOH) = +16.09.

M.P.: 58 – 61 °C.



((1S,3S)-1-Amino-3-(4-octylphenyl)cyclopentyl)methanol Hydrochloride (2b, VPC01091)

Experimental procedure:[12]

Compound **13** (0.0436 g, 0.1 mmol) was dissolved in a carefully pre-mixed methanol and acetyl chloride (4:1, 5 ml), and stirred at 25 °C for 16 h. Upon completion of the reaction, the solvent was evaporated. The residue was dissolved in 10% NaOH aqueous solution and extracted with DCM. The combined organic layers were dried on Na_2SO_4, filtered and concentration on rotary evaporator into pure **2b** (VPC01091).

Compound **2b** (VPC01091) was obtained as a white solid (25.8 mg, 0.085 mmol, 85% isolated yield.

^{1}H NMR (400 MHz, DMSO): δ 7.14 (d, *J* = 8.2 Hz, 2 H), 7.10 (d, *J* = 8.2 Hz, 2 H), 3.53 – 3.46 (m, 2 H), 3.44 – 3.34 (m, 1 H), 2.54 – 2.50 (m, 2 H), 2.12 – 2.00 (m, 3 H), 1.78 – 1.46 (m, 5 H), 1.32 – 1.14 (m, 10 H), 0.85 (t, *J* = 6.83 Hz, 3 H).

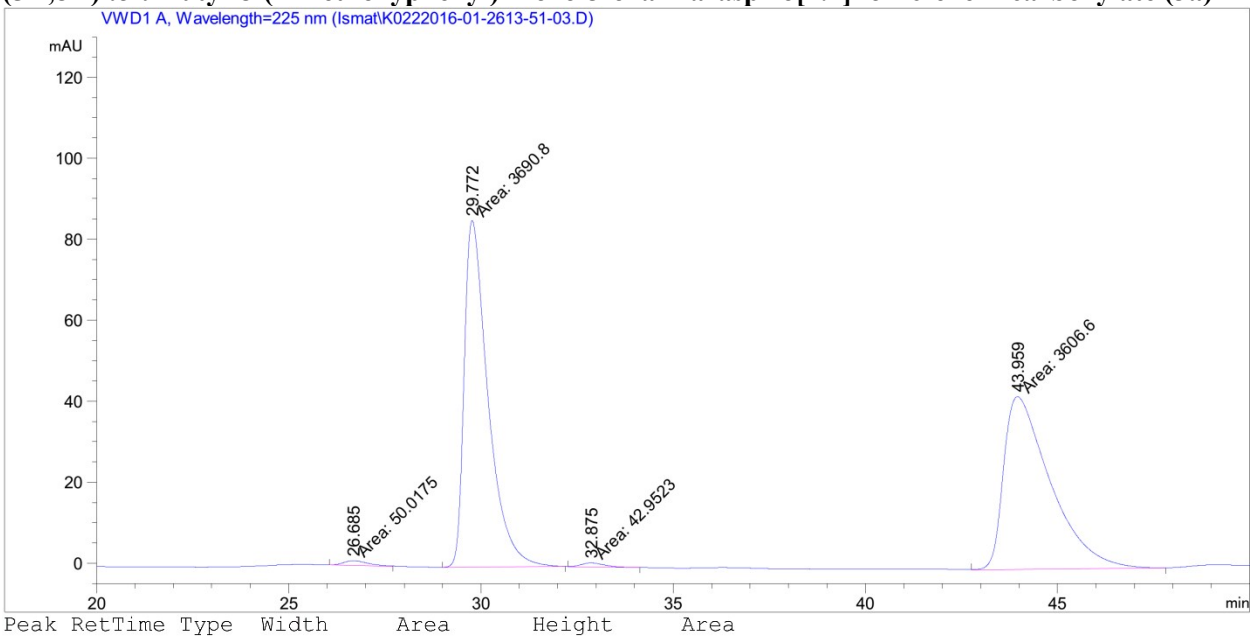
^{13}C NMR (100 MHz, DMSO): δ 140.9, 140.1, 128.2, 126.7, 65.6, 63.7, 42.8, 41.5, 34.7, 33.7, 33.0, 31.2, 31.0, 28.8, 28.7, 28.6, 22.0, 13.9.

HRMS (ESI+) calculated for ($C_{20}H_{33}NO_{+}H^{+}$): 304.2640, found: 304.2646.

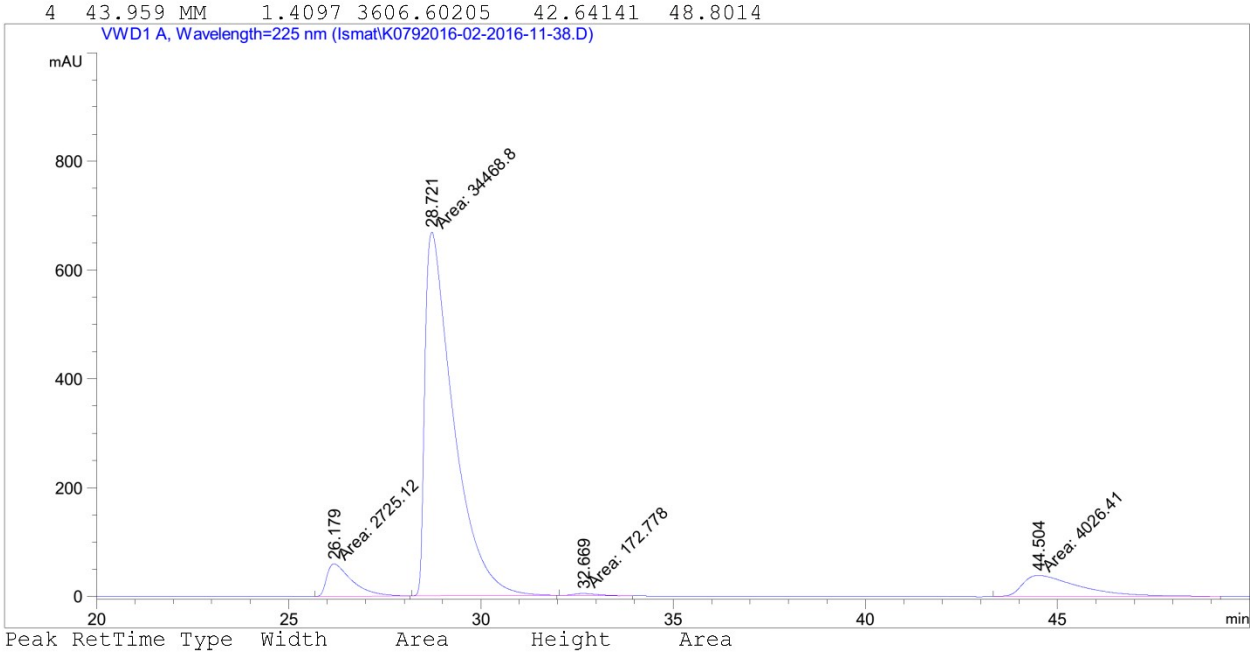
$[\alpha]_D^{20}$ (c 2.36, MeOH) = +2.

5. Chiral Chromatographic data:

(5R,8R)-*tert*-Butyl-8-(4-methoxyphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3a)

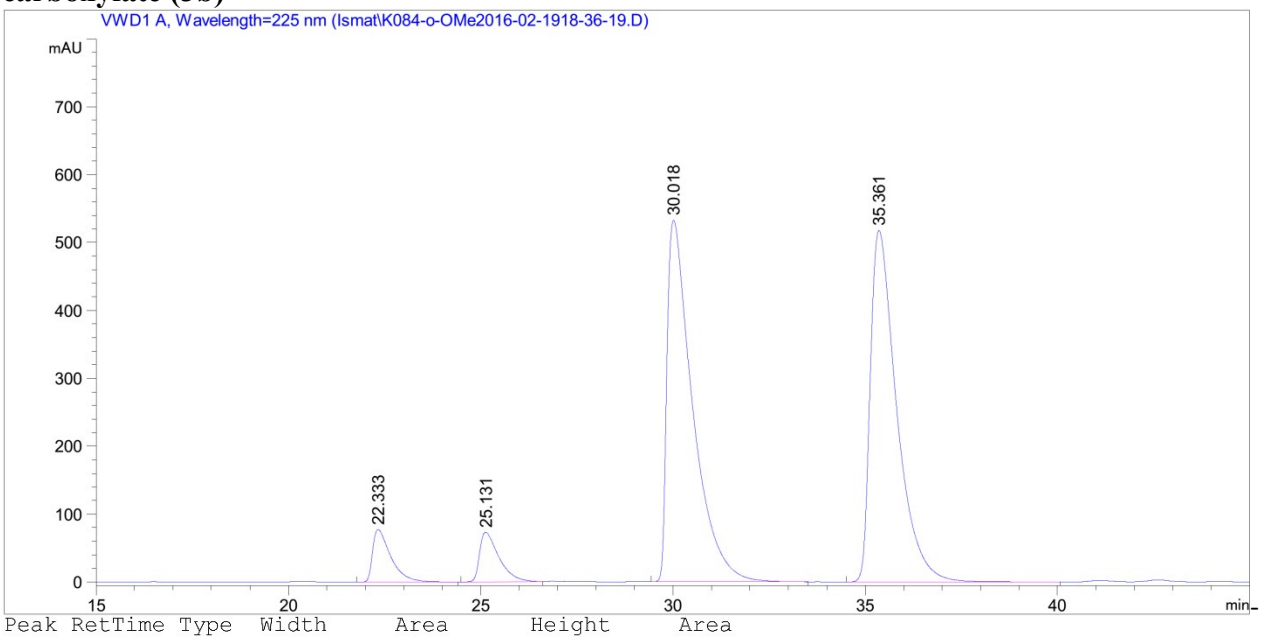


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.685	MM	0.7188	50.01747	1.15968	0.6768
2	29.772	MM	0.7185	3690.79907	85.61562	49.9406
3	32.875	MM	0.7121	42.95235	1.00525	0.5812
4	43.959	MM	1.4097	3606.60205	42.64141	48.8014

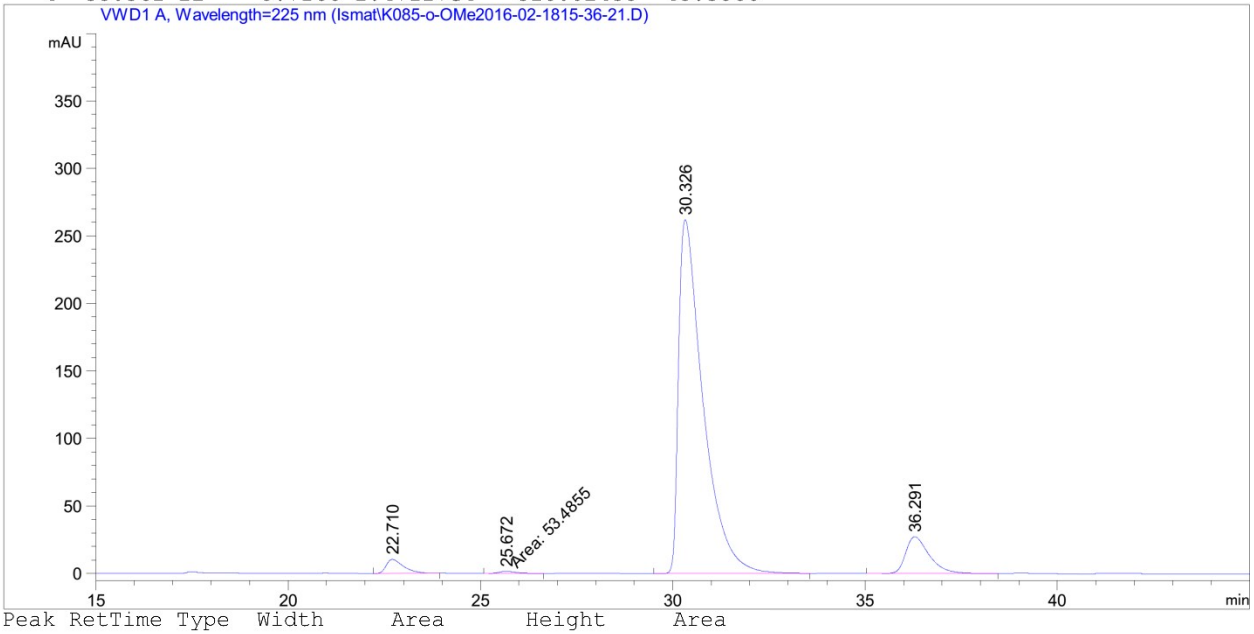


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.179	MM	0.7612	2725.11890	59.66516	6.5835
2	28.721	MM	0.8588	3.44688e4	668.92712	83.2718
3	32.669	MM	0.7578	172.77762	3.80008	0.4174
4	44.504	MM	1.7221	4026.40674	38.96862	9.7272

(5R,8R)-*tert*-Butyl-8-(2-methoxyphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3b)

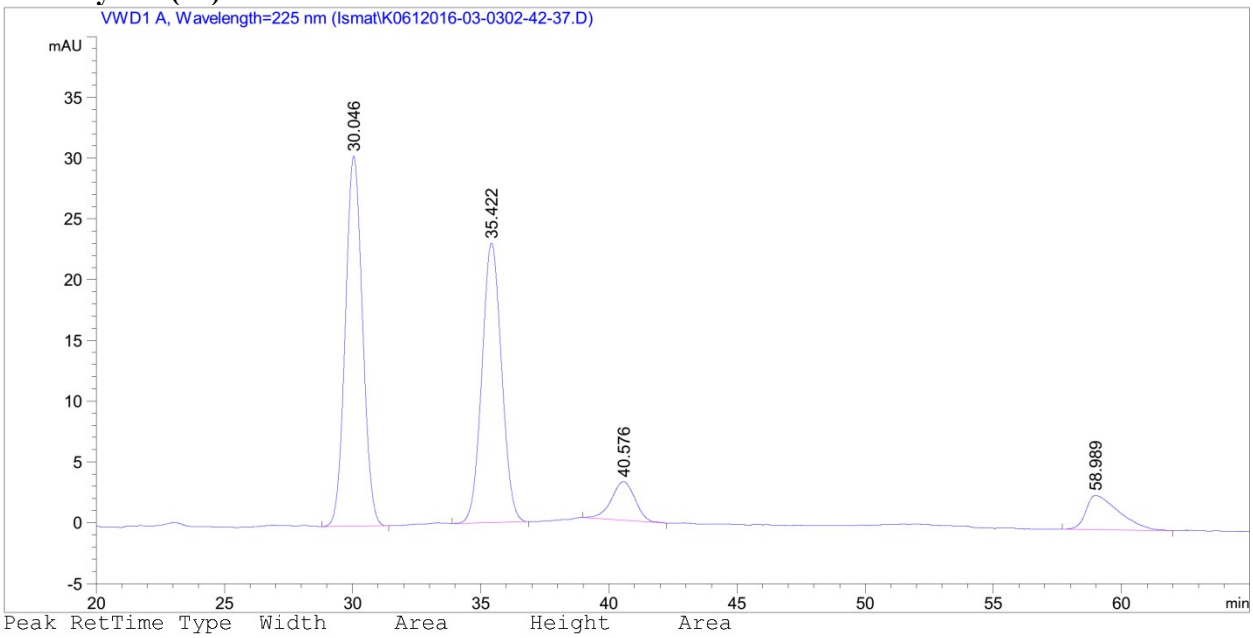


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.333	BB	0.4888	2562.11133	77.67301	4.7055
2	25.131	BB	0.5162	2545.46802	73.28597	4.6749
3	30.018	BB	0.6735	2.46291e4	532.63239	45.2330
4	35.361	BB	0.7166	2.47127e4	518.02435	45.3866

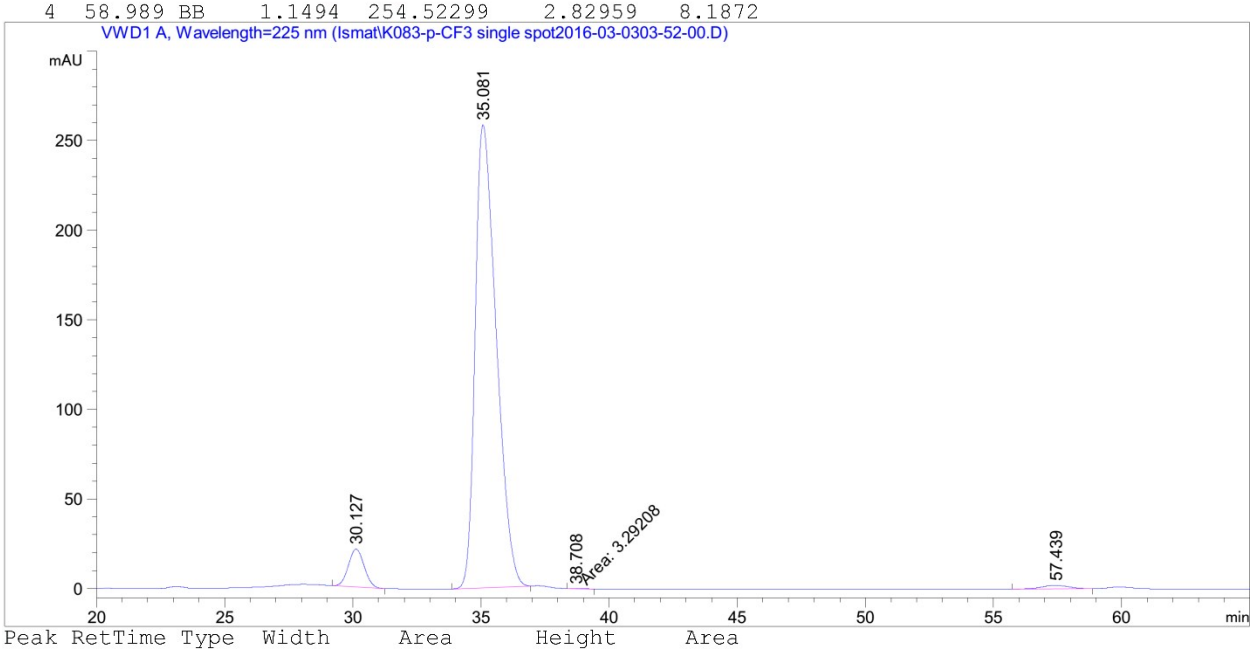


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.710	BB	0.4685	325.97748	10.40587	2.4839
2	25.672	MM	0.5522	53.48553	1.61419	0.4076
3	30.326	BB	0.6483	1.15779e4	262.10425	88.2221
4	36.291	BB	0.6466	1166.21606	27.28806	8.8864

(5R,8R)-*tert*-Butyl 2-oxo-8-(4-(trifluoromethyl)phenyl)-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3c)

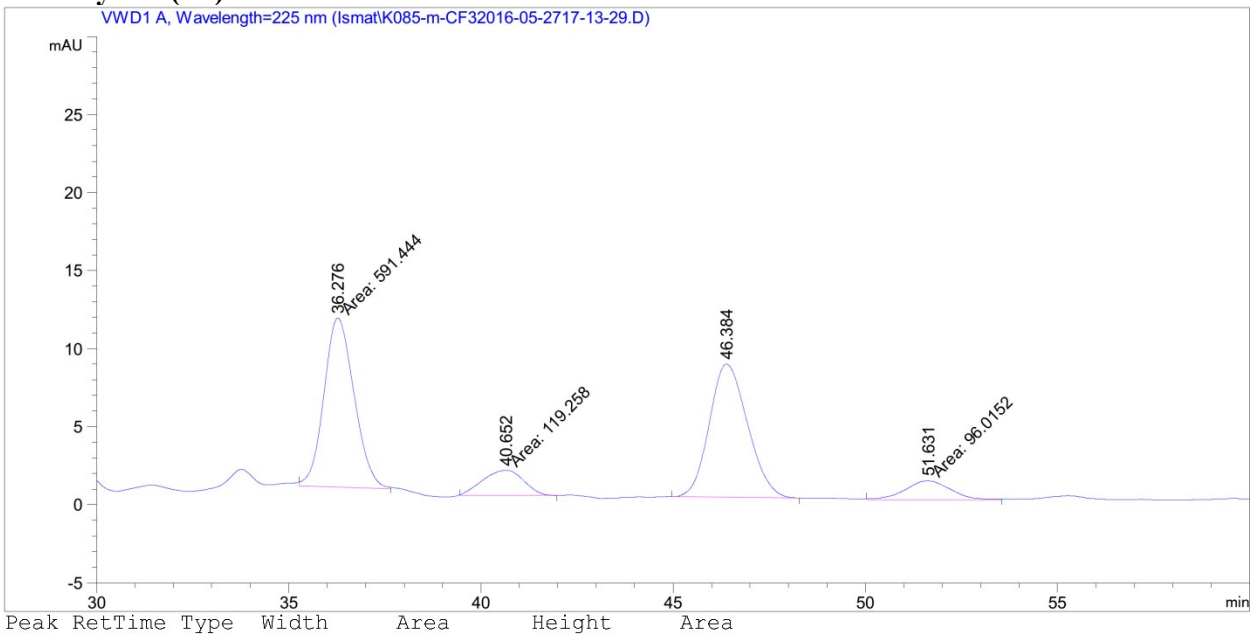


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.046	BB	0.7264	1421.28870	30.46033	45.7181
2	35.422	BB	0.8234	1229.21326	23.00314	39.5397
3	40.576	BB	0.8867	203.78325	3.17112	6.5550
4	58.989	BB	1.1494	254.52299	2.82959	8.1872

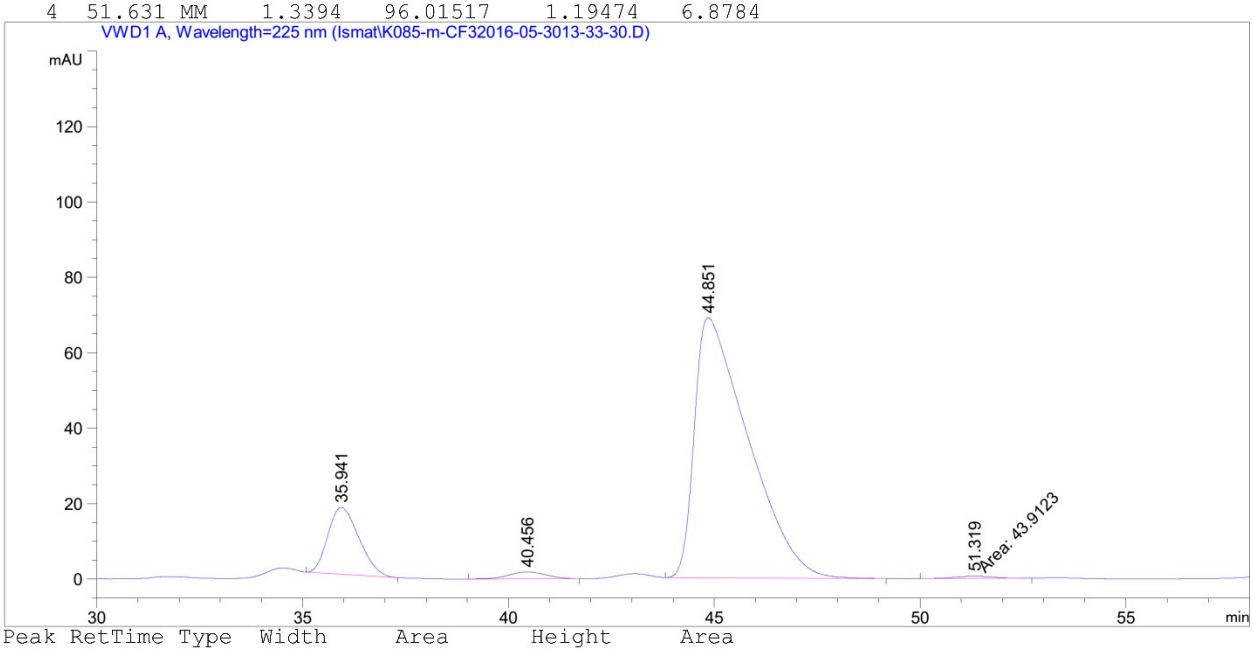


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.127	BB	0.6681	908.63080	21.19641	5.7534
2	35.081	BB	0.8825	1.47435e4	258.47415	93.3551
3	38.708	MM	0.4772	3.29208	1.14976e-1	0.0208
4	57.439	BB	0.8832	137.49384	1.83698	0.8706

(5R,8R)-*tert*-Butyl 2-oxo-8-(3-(trifluoromethyl)phenyl)-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3d)

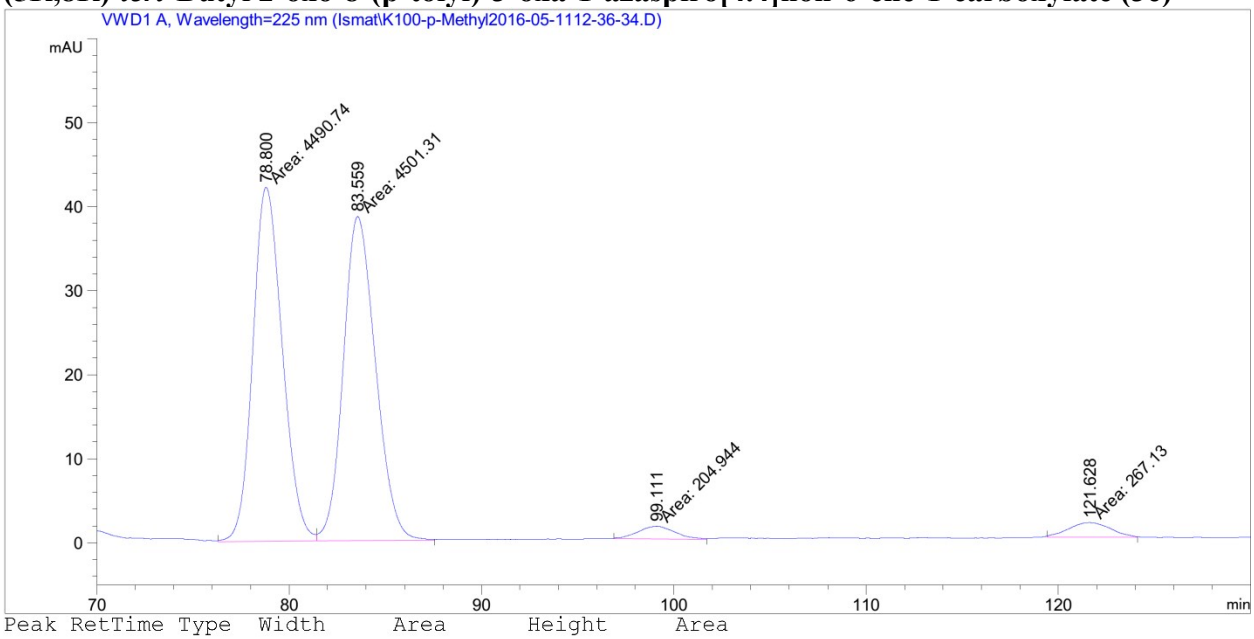


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	36.276	MM	0.9111	591.44379	10.81932	42.3705
2	40.652	MM	1.2317	119.25845	1.61375	8.5436
3	46.384	BB	1.0277	589.16901	8.53115	42.2075
4	51.631	MM	1.3394	96.01517	1.19474	6.8784

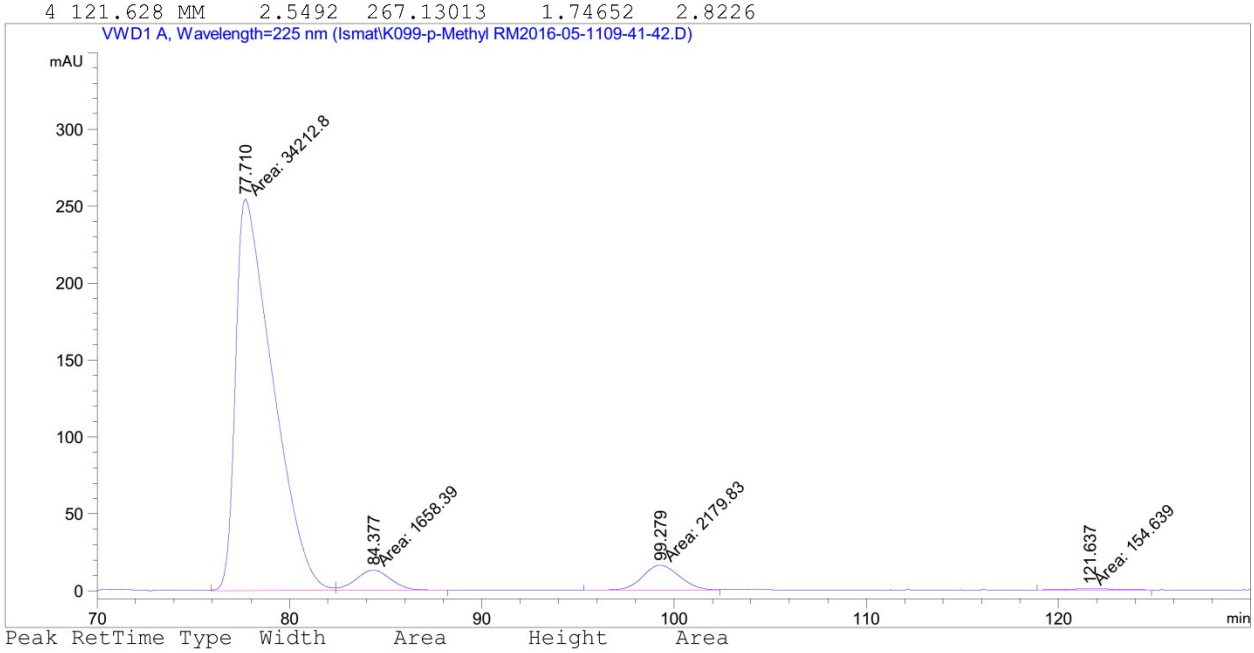


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.941	BB	0.8079	929.64380	17.72631	12.6636
2	40.456	BB	0.7497	113.74162	1.84136	1.5494
3	44.851	BB	1.2911	6253.78271	68.95488	85.1889
4	51.319	MM	1.1521	43.91227	6.35263e-1	0.5982

(5R,8R)-*tert*-Butyl 2-oxo-8-(p-tolyl)-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3e)

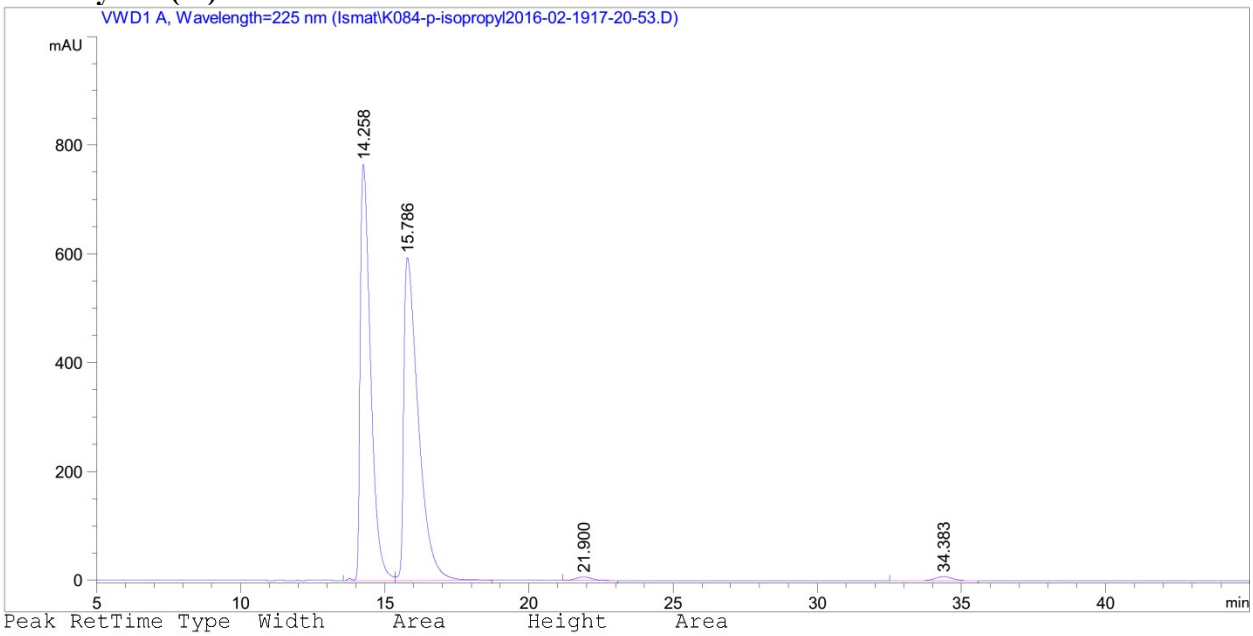


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	78.800	MF	1.7772	4490.73730	42.11440	47.4501
2	83.559	FM	1.9457	4501.30713	38.55714	47.5618
3	99.111	MM	2.2340	204.94353	1.52900	2.1655
4	121.628	MM	2.5492	267.13013	1.74652	2.8226

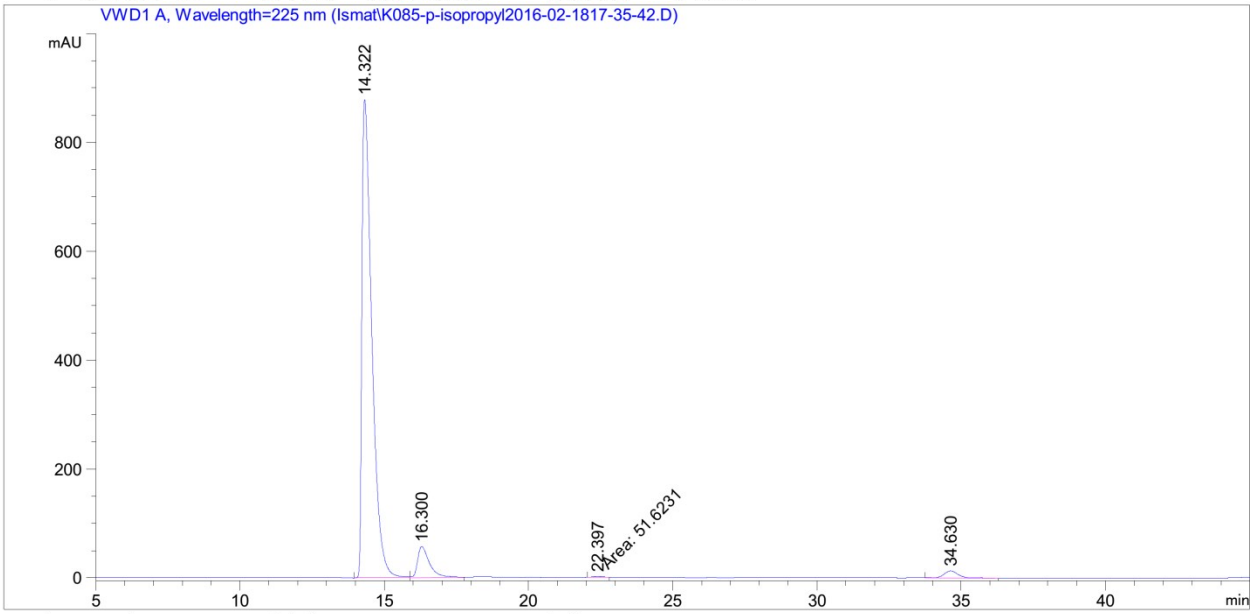


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	77.710	MF	2.2438	3.42128e4	254.13354	89.5490
2	84.377	FM	2.1066	1658.39148	13.12045	4.3407
3	99.279	MF	2.2376	2179.82642	16.23611	5.7055
4	121.637	MM	2.5639	154.63950	1.00522	0.4048

(5R,8R)-*tert*-Butyl 8-(4-isopropylphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3f)

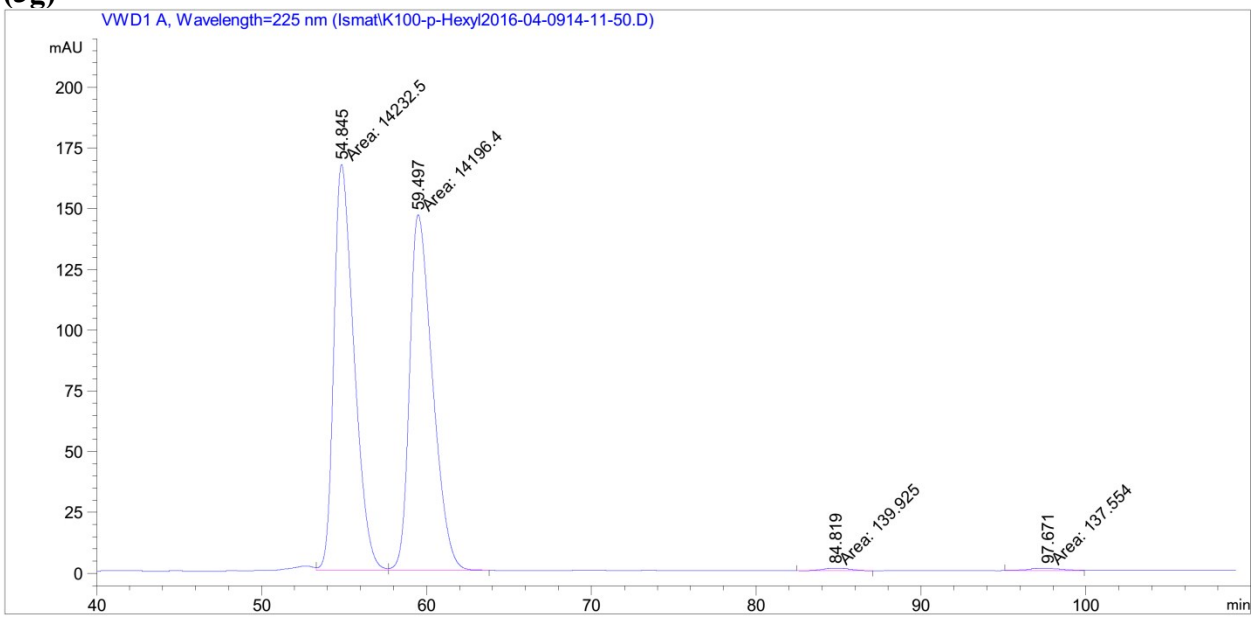


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.258	VV R	0.3849	1.91878e4	765.32233	47.3272
2	15.786	VB	0.5223	2.07771e4	593.73486	51.2472
3	21.900	BB	0.6132	244.77557	6.32857	0.6037
4	34.383	BB	0.6746	333.18182	7.56859	0.8218

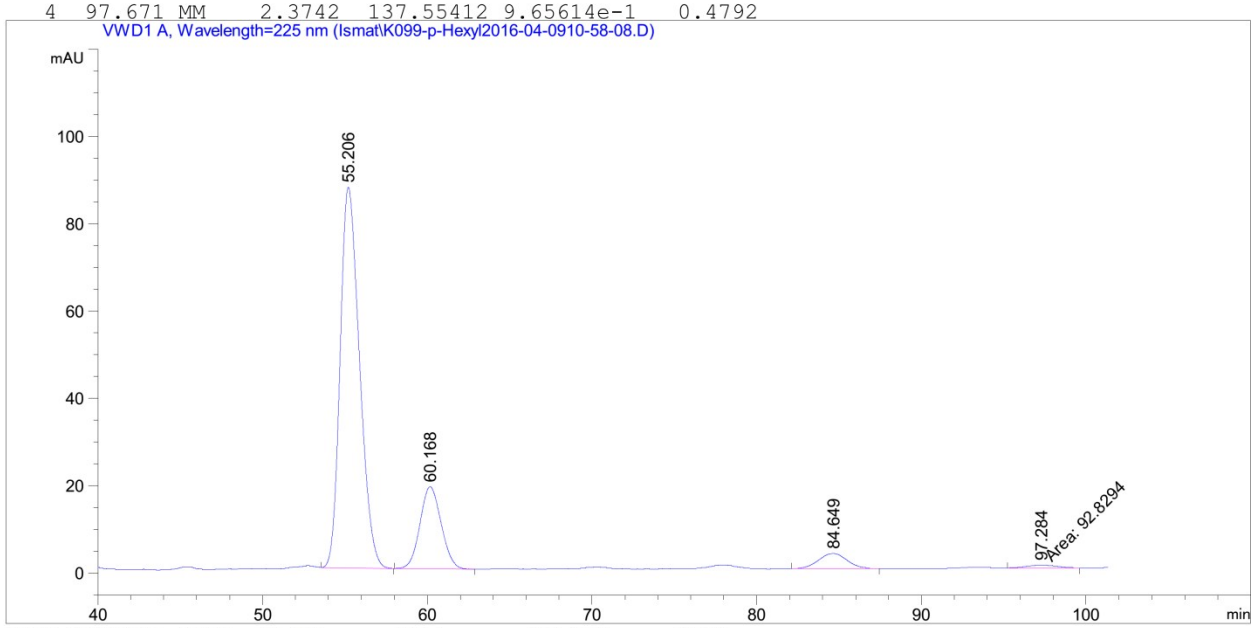


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.322	BV	0.3644	2.09785e4	878.99109	90.8771
2	16.300	VB	0.4224	1609.35339	56.83472	6.9716
3	22.397	MM	0.4247	51.62310	2.02596	0.2236
4	34.630	BB	0.5161	445.00763	13.20784	1.9277

(5R,8R)-*tert*-Butyl 8-(4-hexylphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3g)

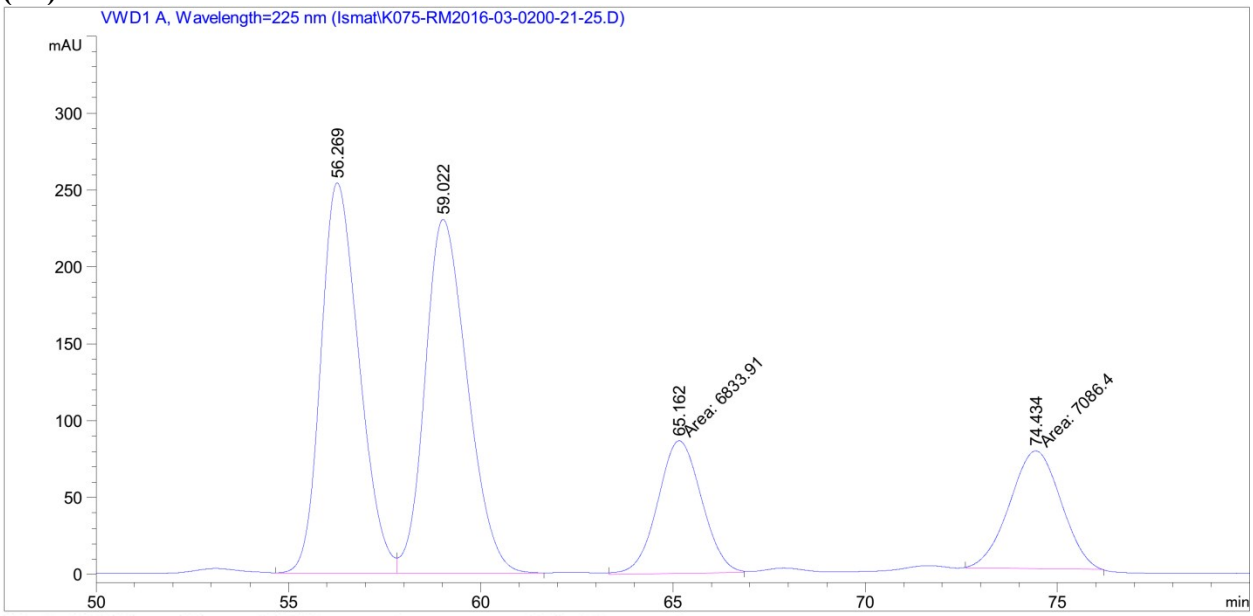


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	54.845	FM	1.4197	1.42325e4	167.08833	49.5795
2	59.497	FM	1.6163	1.41964e4	146.38824	49.4539
3	84.819	MM	2.0240	139.92500	1.15219	0.4874
4	97.671	MM	2.3742	137.55412	9.65614e-1	0.4792

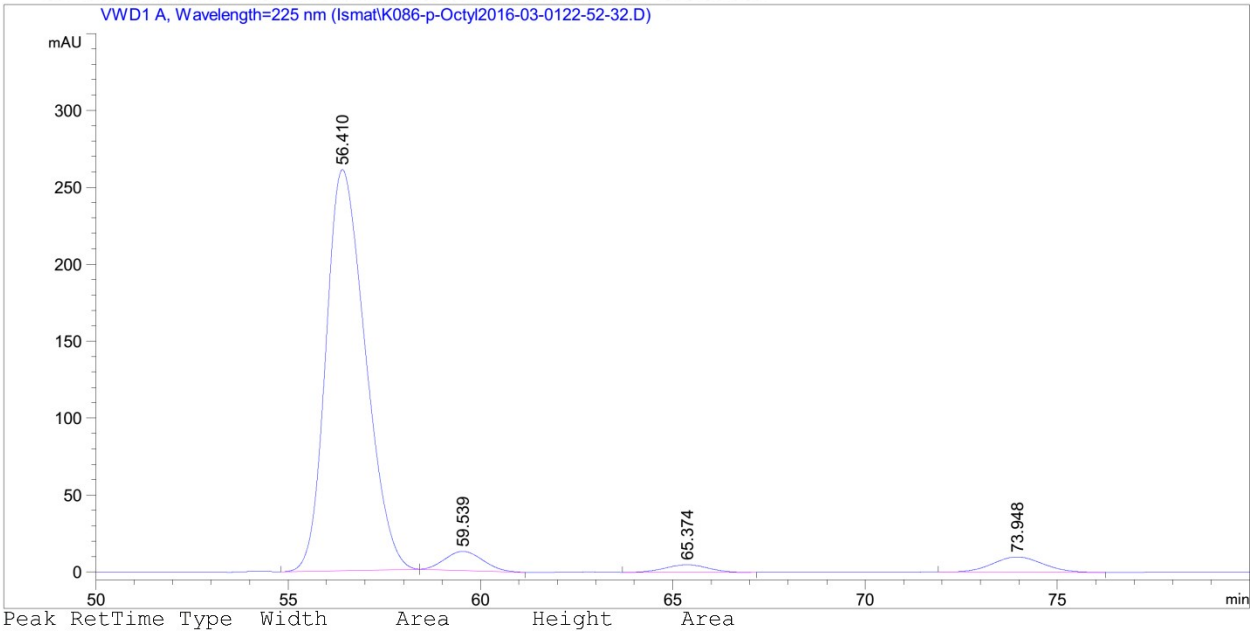


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	55.206	BB	1.2729	7123.82178	87.22224	76.4434
2	60.168	BB	1.3580	1680.14954	18.81181	18.0291
3	84.649	BB	1.5191	422.28012	3.49384	4.5313
4	97.284	MM	2.1525	92.82942	7.18764e-1	0.9961

(5R,8R)-*tert*-Butyl 8-(4-octylphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3h)

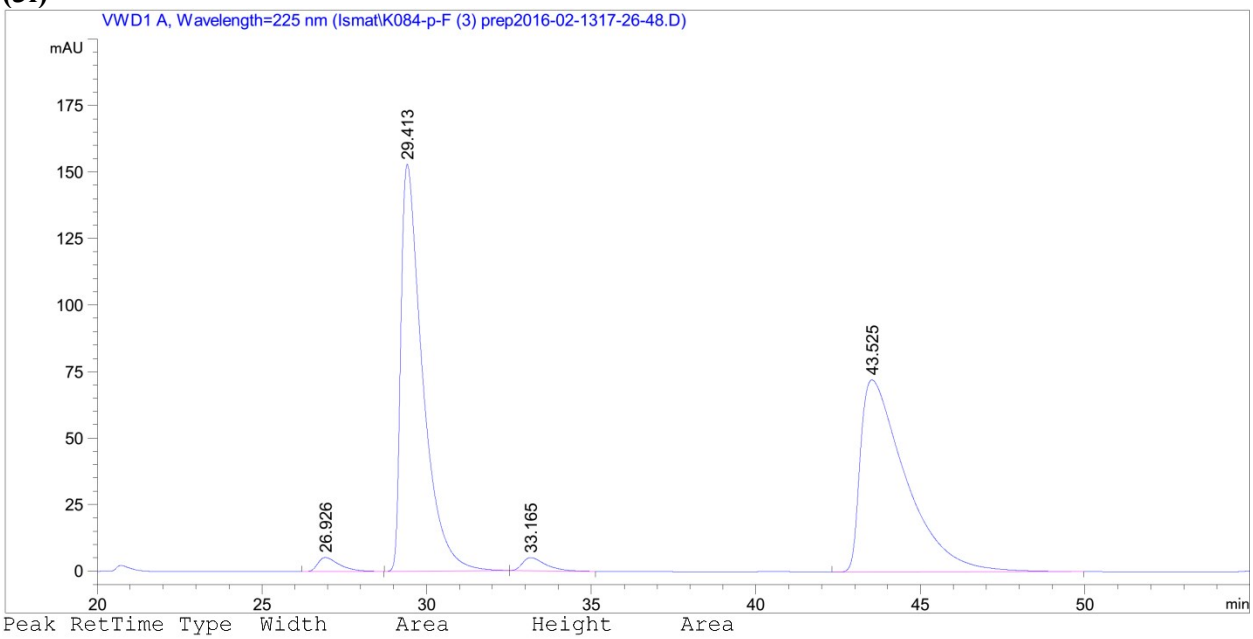


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	56.269	BV	1.0581	1.74710e4	253.47301	35.6929
2	59.022	VB	1.1789	1.75568e4	229.66644	35.8682
3	65.162	MM	1.3214	6833.90723	86.19666	13.9616
4	74.434	MM	1.5448	7086.40234	76.45336	14.4774

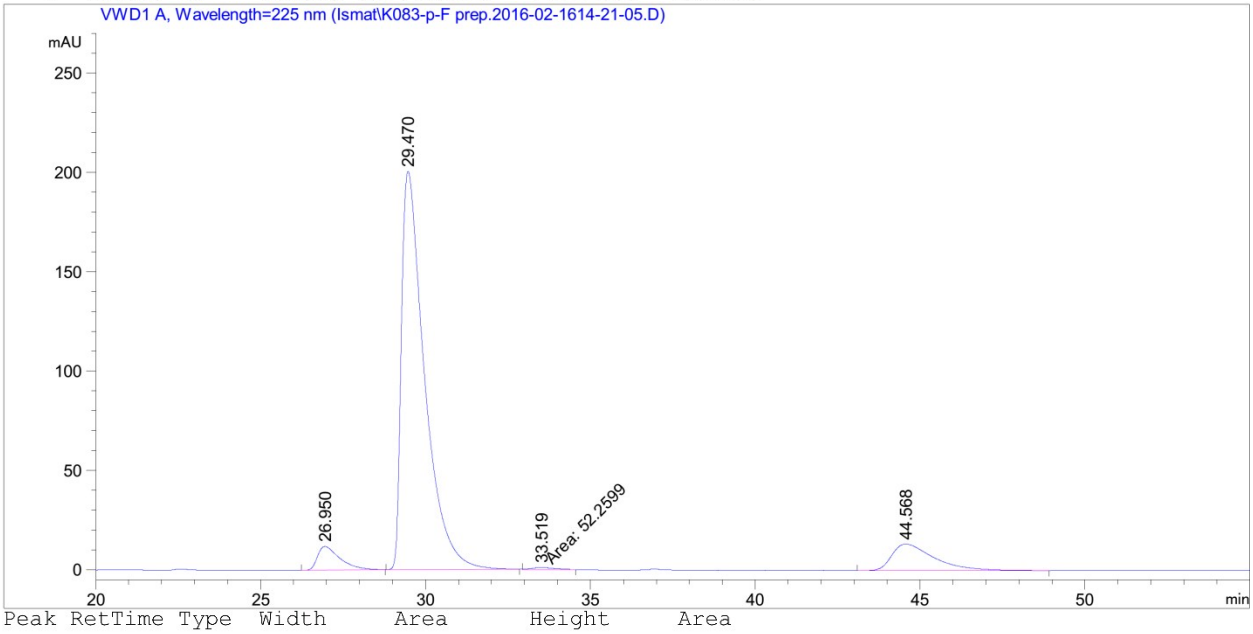


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	56.410	BB	1.1104	1.85215e4	260.53543	89.6831
2	59.539	BB	1.0444	839.86237	12.35047	4.0667
3	65.374	BB	1.0669	390.01590	4.94650	1.8885
4	73.948	BB	1.2216	900.78931	9.92767	4.3617

(5R,8R)-*tert*-Butyl 8-(4-fluorophenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3i)

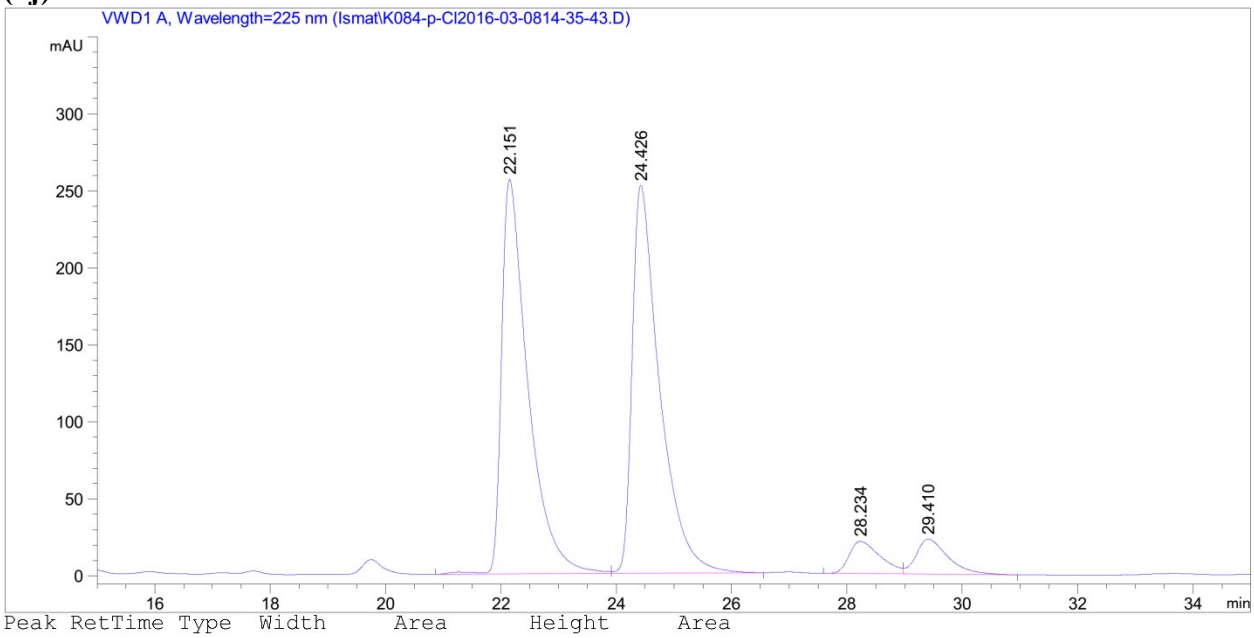


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.926	BB	0.6677	242.53445	5.31139	1.6847
2	29.413	BB	0.6756	6992.71191	152.90343	48.5733
3	33.165	BB	0.6998	234.66388	4.91657	1.6300
4	43.525	BB	1.4028	6926.29248	72.22559	48.1119

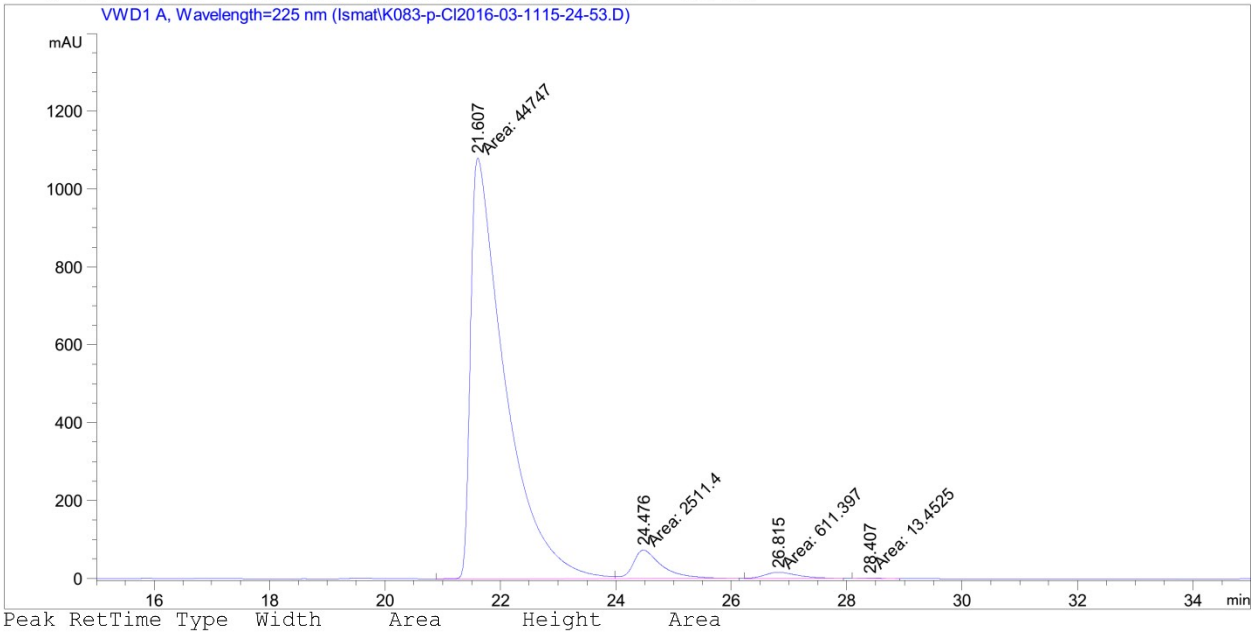


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.950	BB	0.6984	562.67645	11.88321	4.8566
2	29.470	BB	0.7219	9776.78516	200.50653	84.3860
3	33.519	MM	0.8284	52.25993	1.05148	0.4511
4	44.568	BB	1.2730	1194.06262	13.36921	10.3063

(5R,8R)-*tert*-Butyl 8-(4-chlorophenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3j)

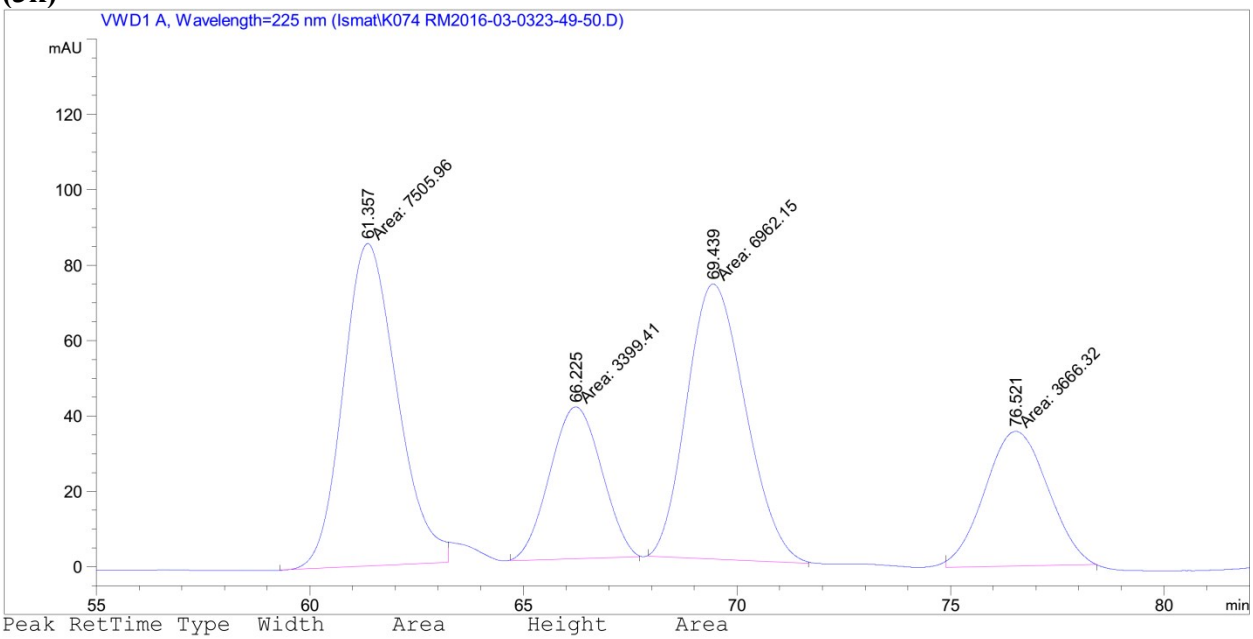


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.151	VV R	0.4660	8145.19629	256.11673	44.9268
2	24.426	VB	0.4813	8316.16797	251.78970	45.8699
3	28.234	BV	0.5668	790.81891	21.02683	4.3620
4	29.410	VB	0.5709	877.73016	22.86403	4.8413

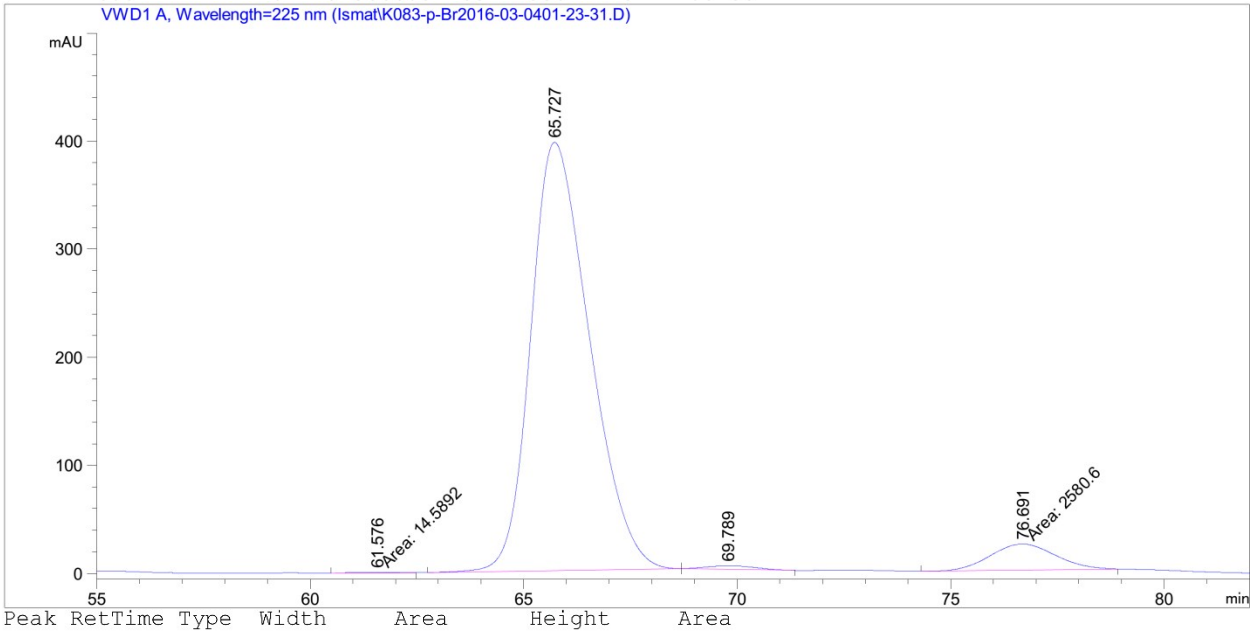


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.607	MF	0.6900	4.47470e4	1080.91772	93.4502
2	24.476	FM	0.5731	2511.39722	73.03512	5.2448
3	26.815	MM	0.6535	611.39691	15.59295	1.2768
4	28.407	MM	0.4491	13.45247	4.99183e-1	0.0281

(5R,8R)-*tert*-Butyl 8-(4-bromophenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3k)

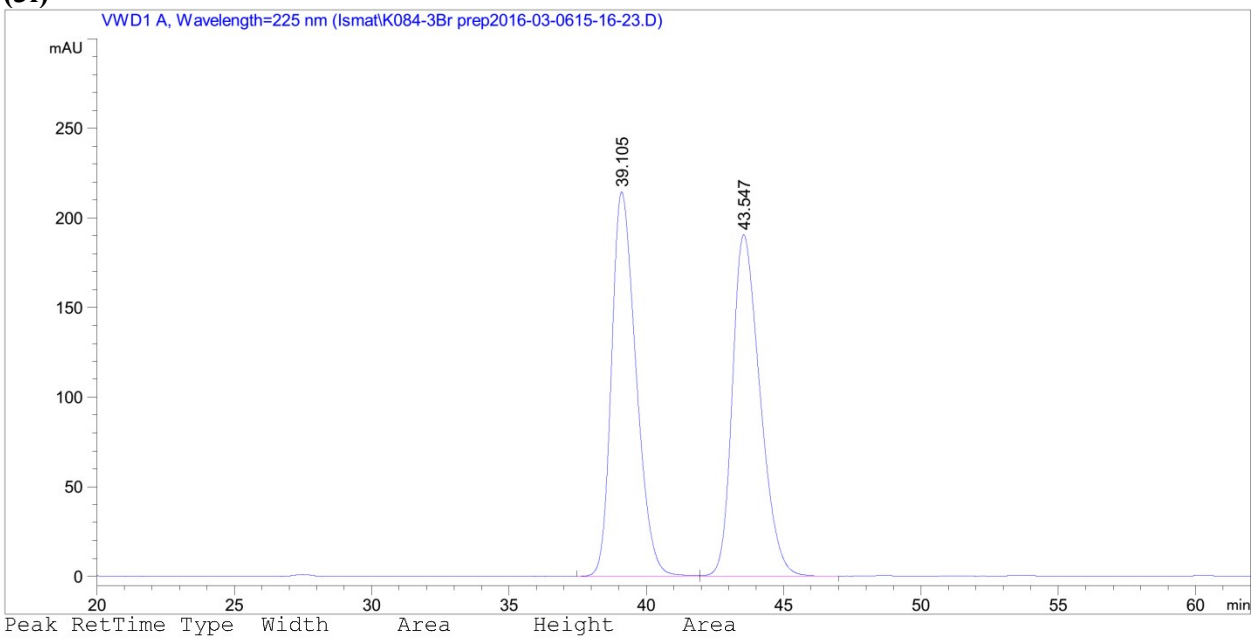


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	61.357	MF	1.4634	7505.96436	85.48797	34.8566
2	66.225	MM	1.4060	3399.41333	40.29789	15.7864
3	69.439	MM	1.5891	6962.15186	73.01846	32.3312
4	76.521	MM	1.7110	3666.31763	35.71218	17.0258

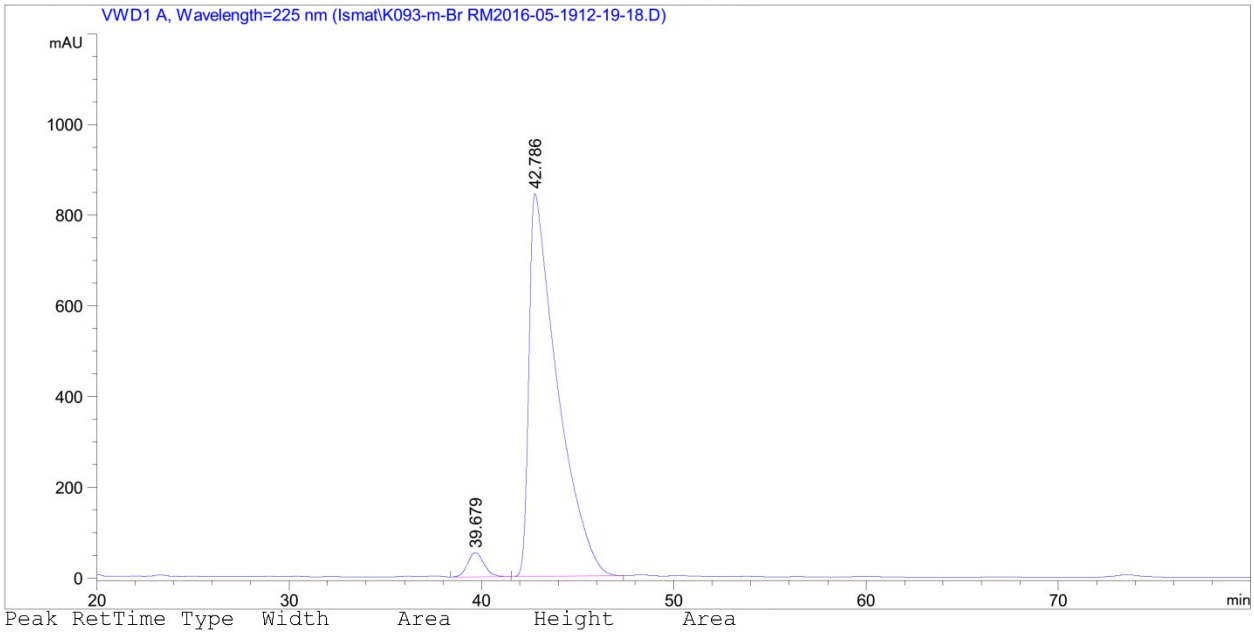


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	61.576	MM	1.0746	14.58915	2.26271e-1	0.0358
2	65.727	BB	1.4510	3.78964e4	396.15619	93.0031
3	69.789	BB	0.9676	255.84627	3.22836	0.6279
4	76.691	MM	1.7821	2580.60254	24.13498	6.3332

(5R,8R)-*tert*-Butyl 8-(3-bromophenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3l)

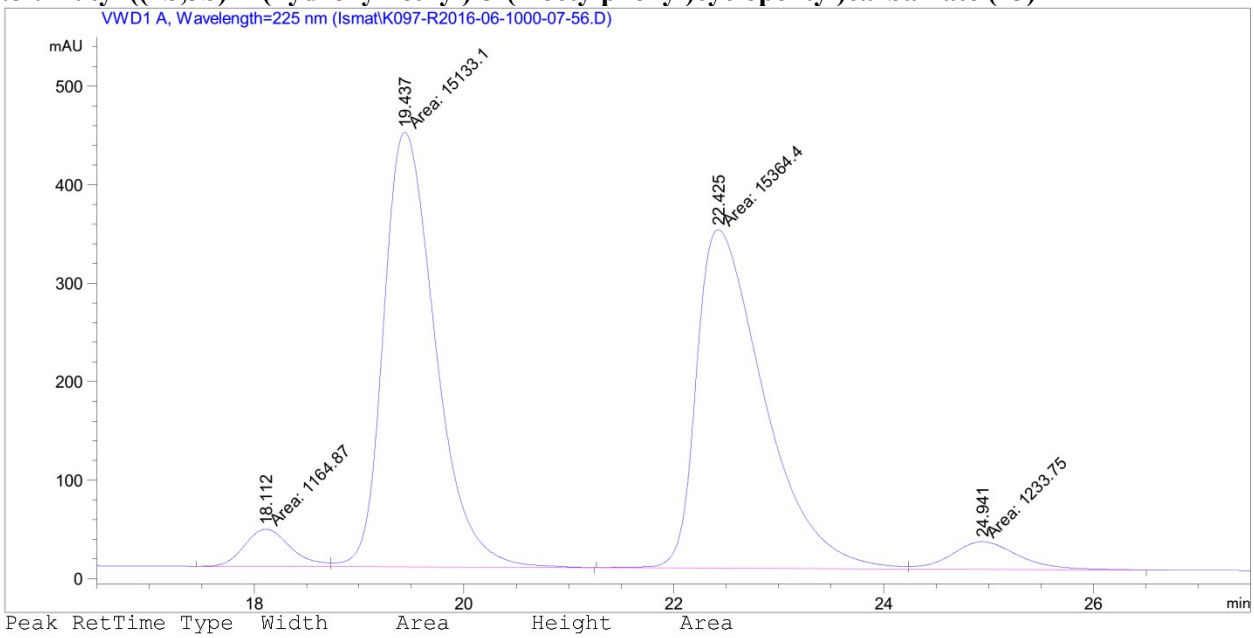


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	39.105	BB	0.9525	1.32549e4	214.32611	49.9566
2	43.547	BB	1.0688	1.32779e4	190.35992	50.0434

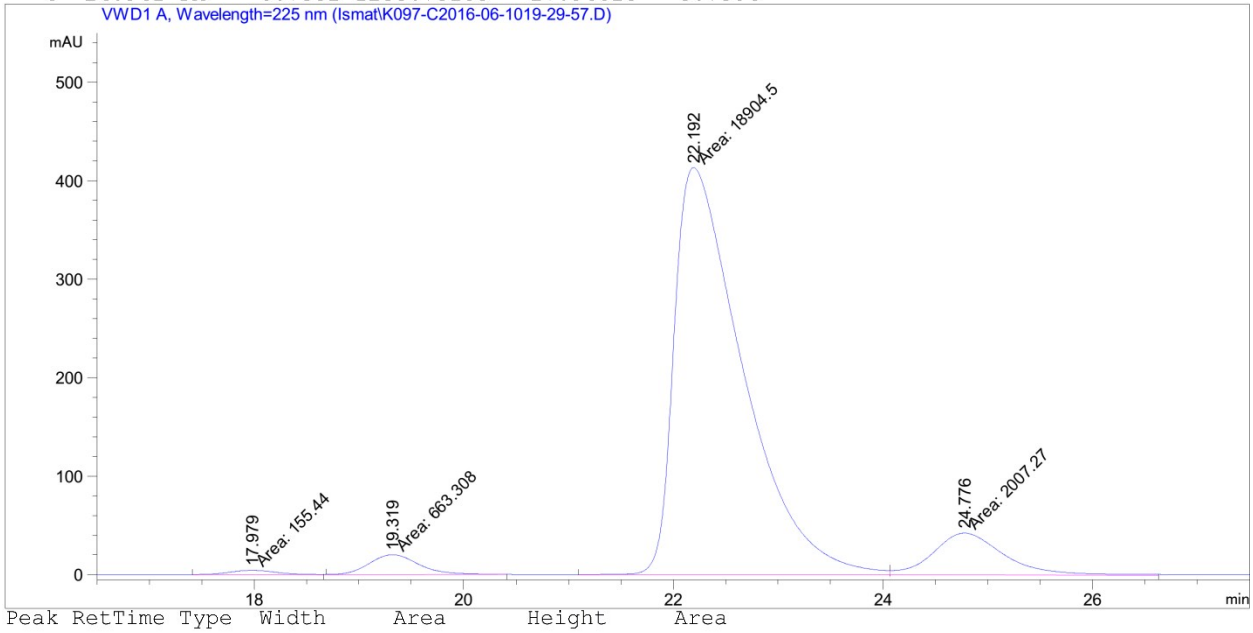


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	39.679	BB	0.9178	3176.57080	53.26220	3.5420
2	42.786	BB	1.4199	8.65068e4	843.91589	96.4580

***tert*-Butyl ((1S,3S)-1-(hydroxymethyl)-3-(4-octylphenyl)cyclopentyl)carbamate (13)**



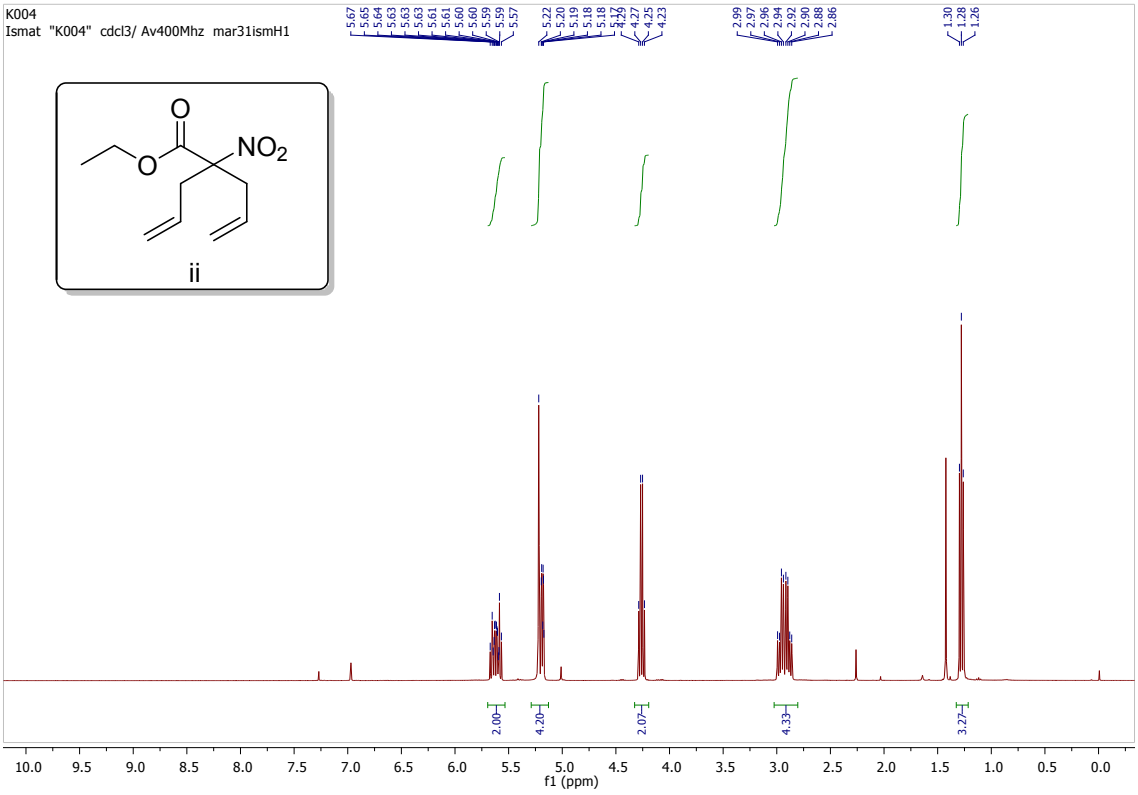
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.112	MF	0.5116	1164.86890	37.95044	3.5411
2	19.437	FM	0.5712	1.51331e4	441.55057	46.0027
3	22.425	MF	0.7451	1.53644e4	343.67081	46.7058
4	24.941	FM	0.7352	1233.75183	27.96825	3.7504

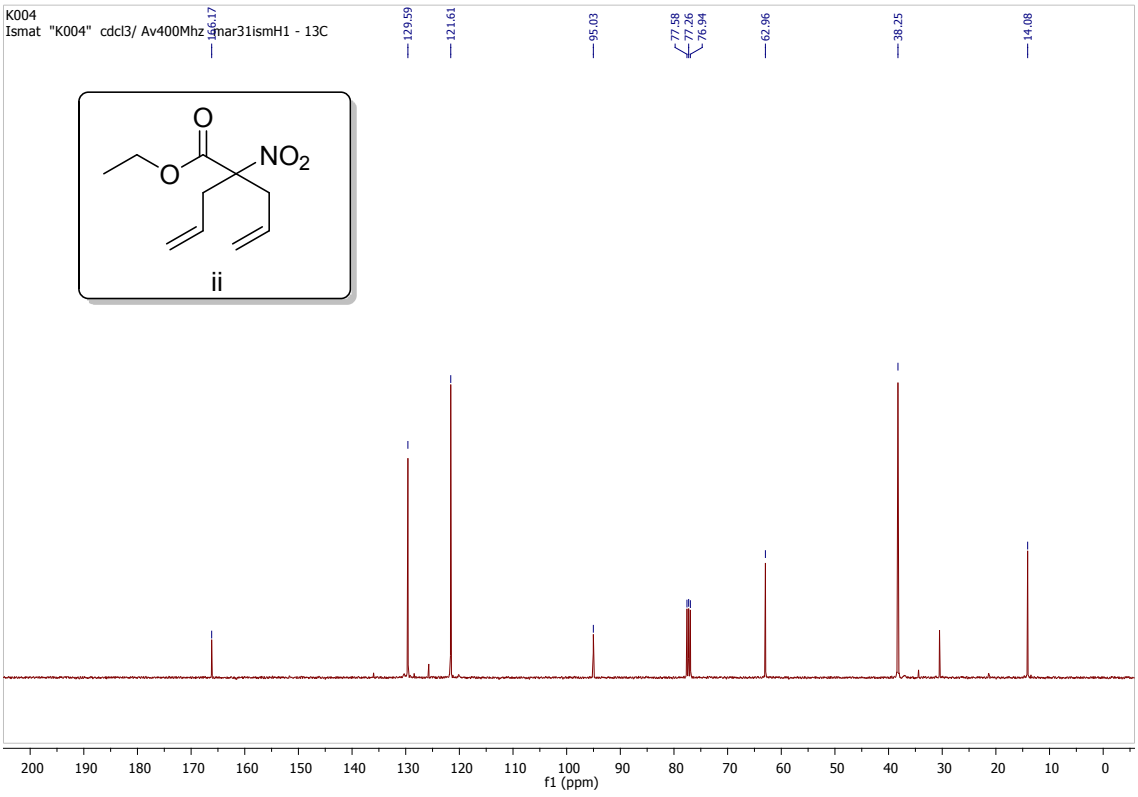


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.979	MF	0.5602	155.44002	4.62465	0.7153
2	19.319	MM	0.5492	663.30786	20.12846	3.0524
3	22.192	MF	0.7619	1.89045e4	413.54556	86.9952
4	24.776	MF	0.7867	2007.26733	42.52733	9.2371

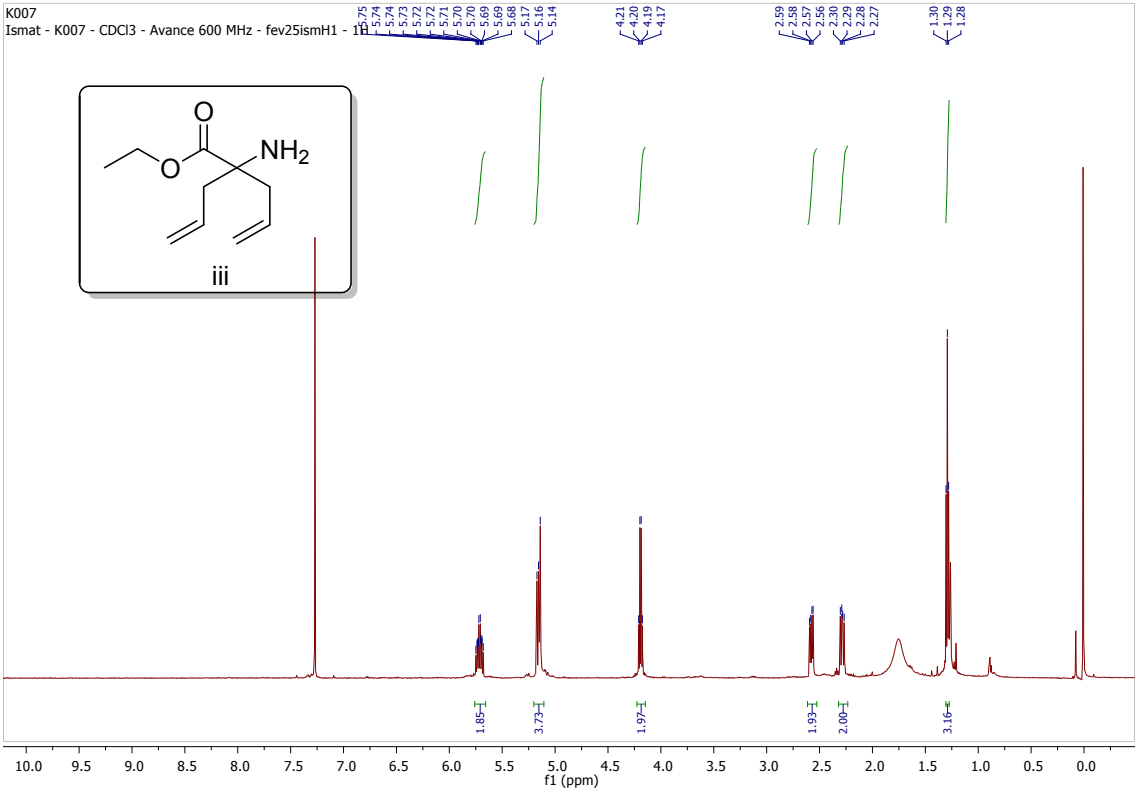
6. NMR Spectra

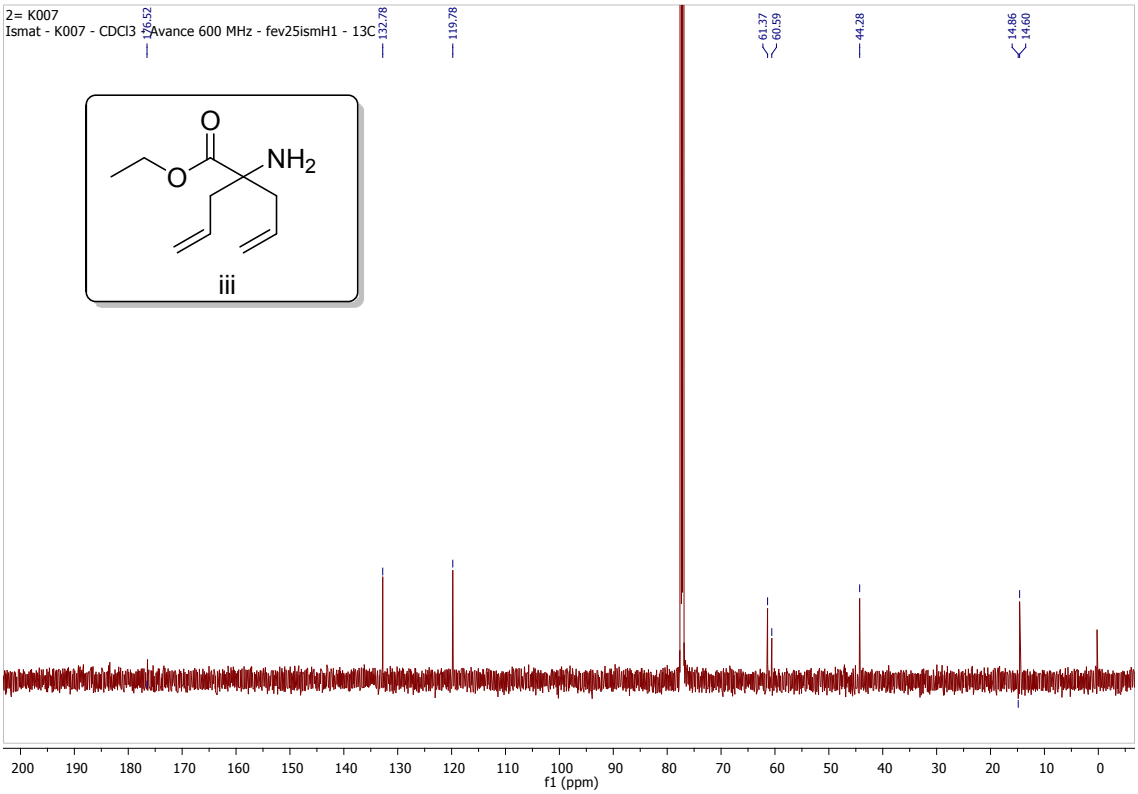
Ethyl-2,2-bis(allyl)-2-nitroacetate (ii)



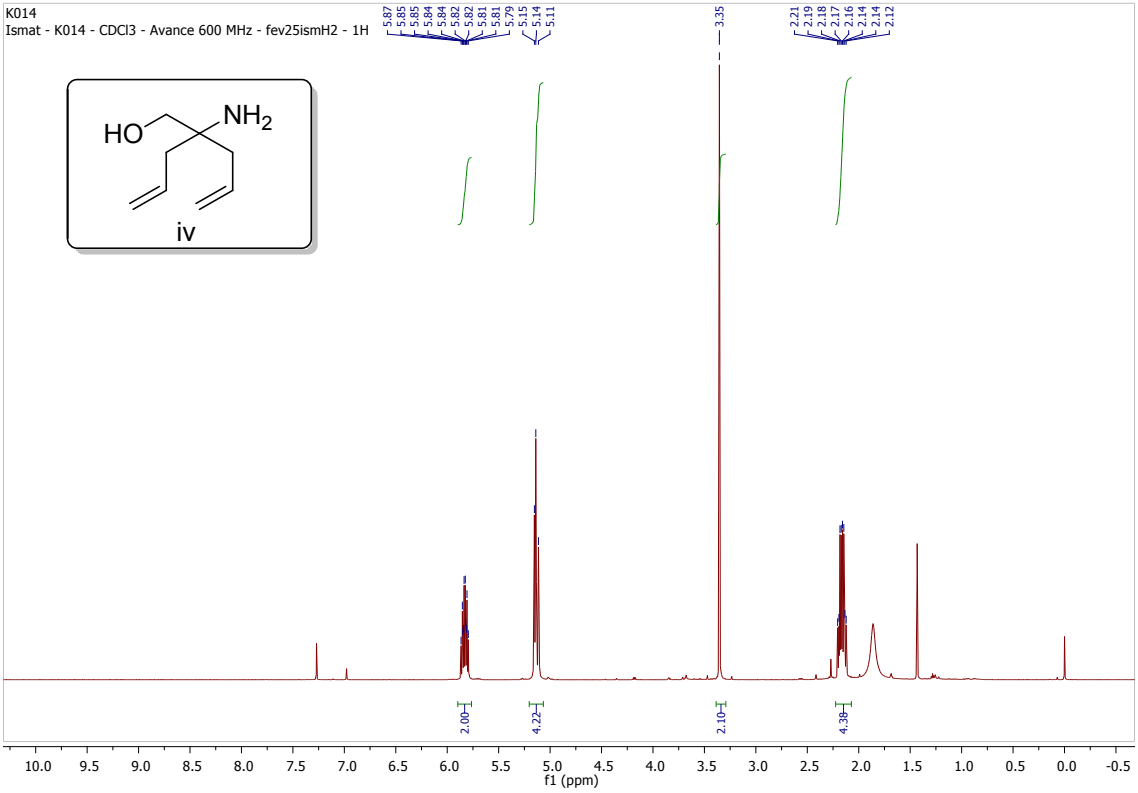


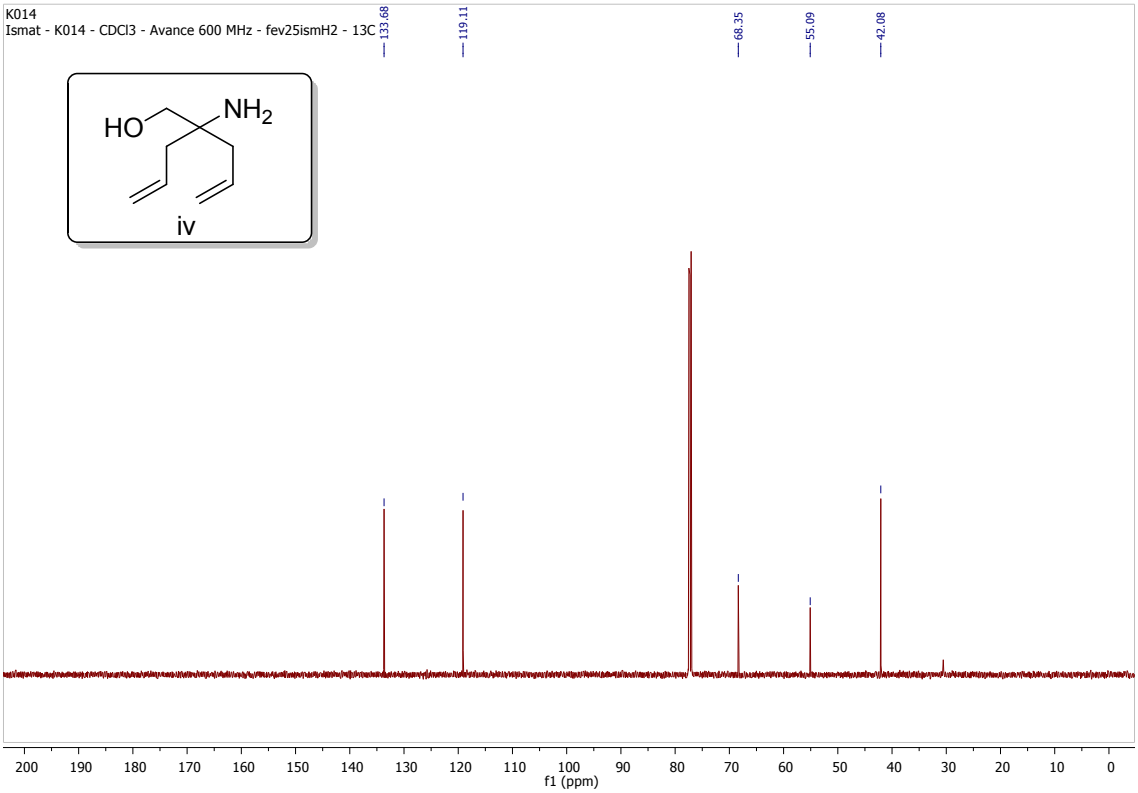
Ethyl-2-allyl-2-aminopent-4-enoate (iii)



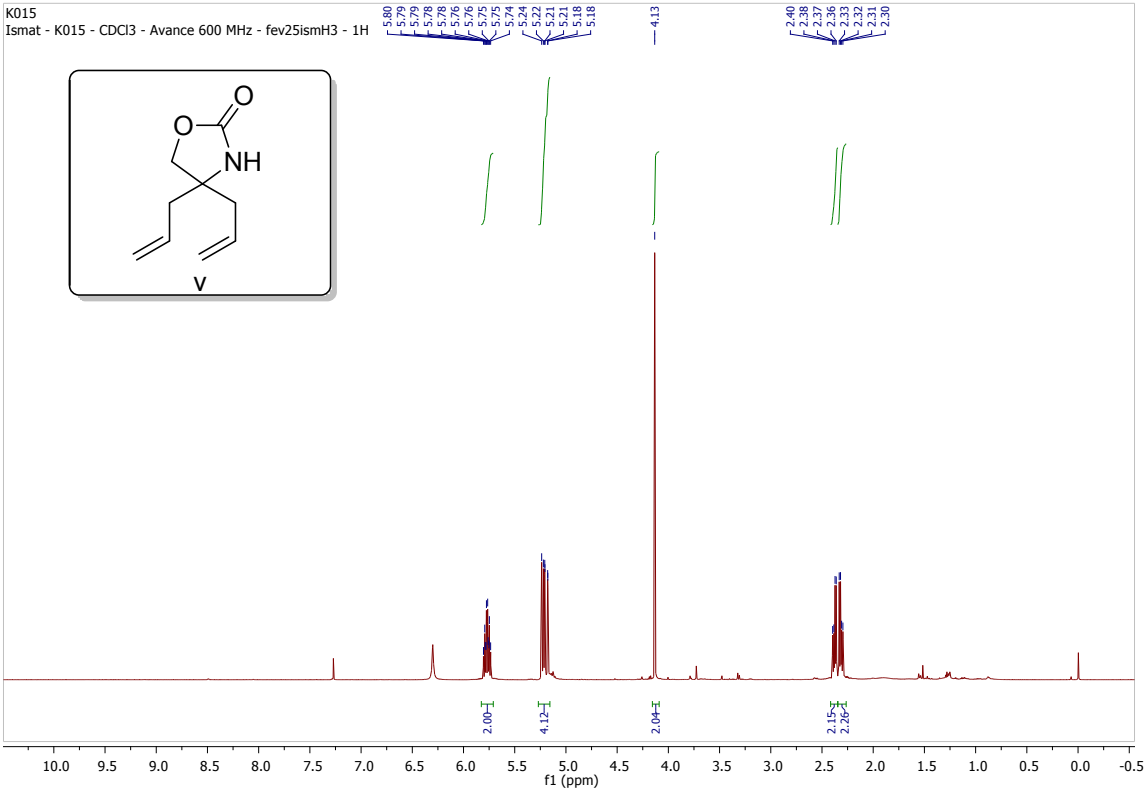


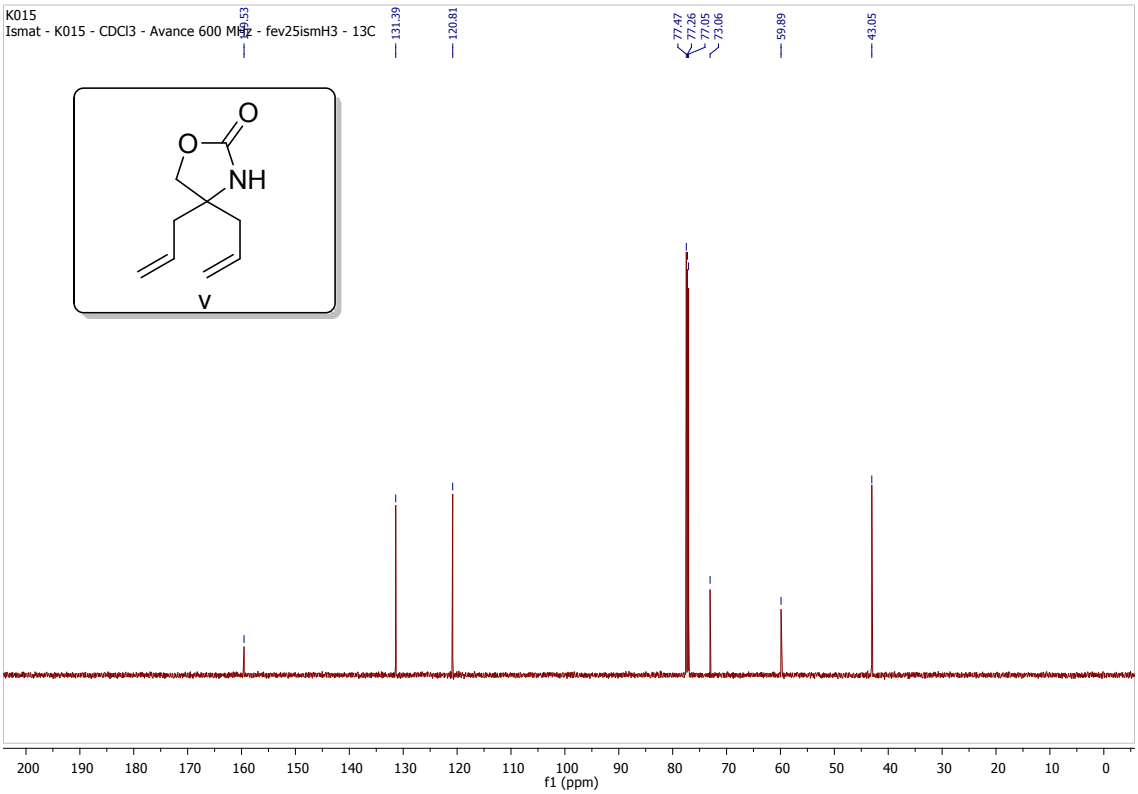
2-Allyl-2-aminopent-4-en-1-ol (iv)



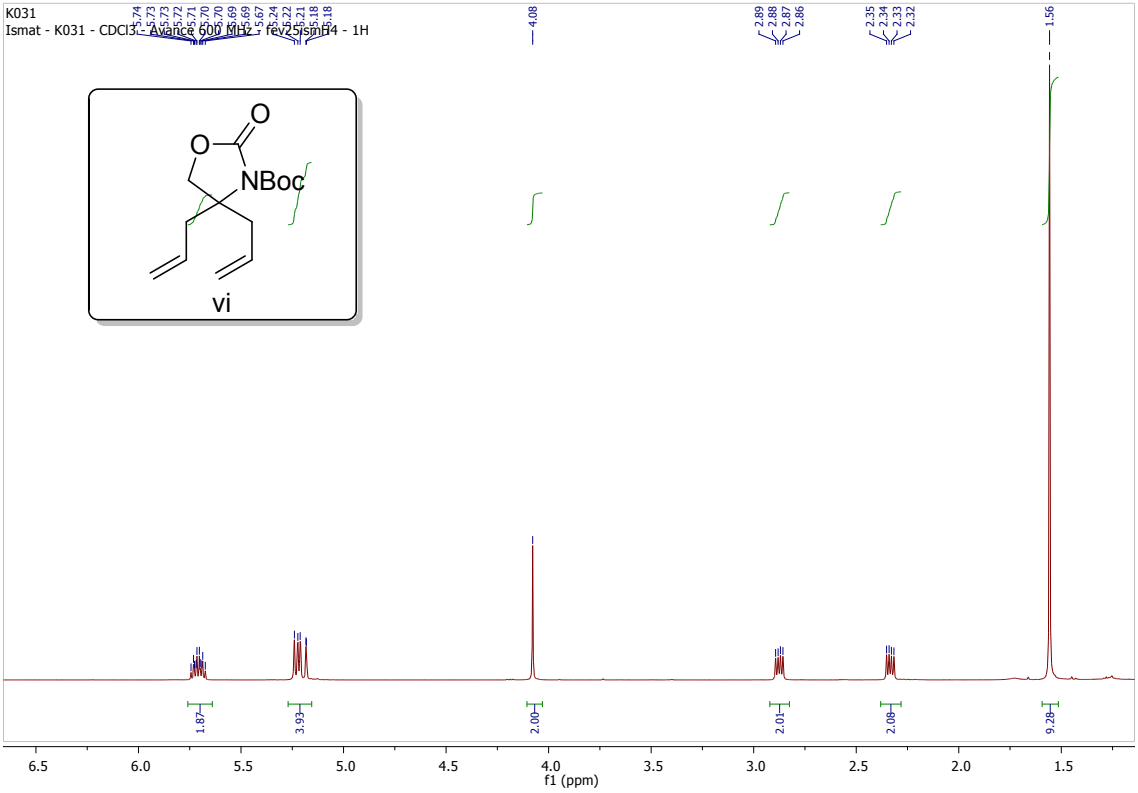


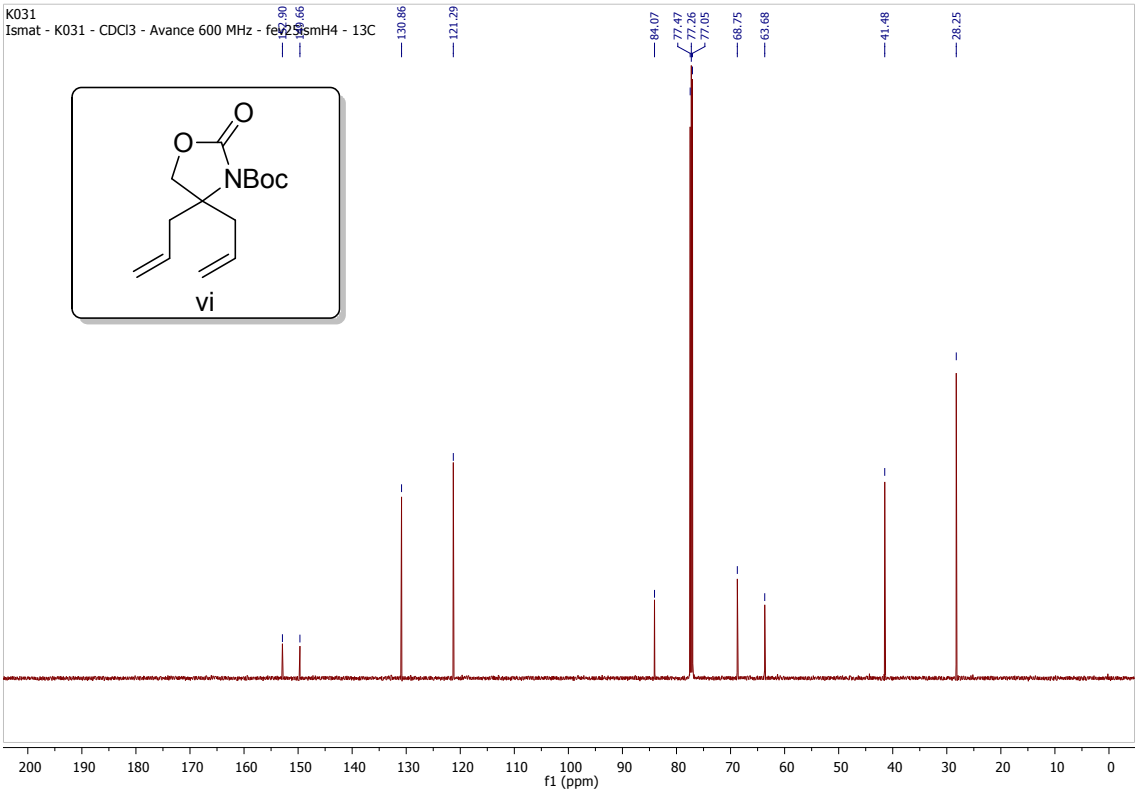
4,4-Diallyloxazolidin-2-one (v)



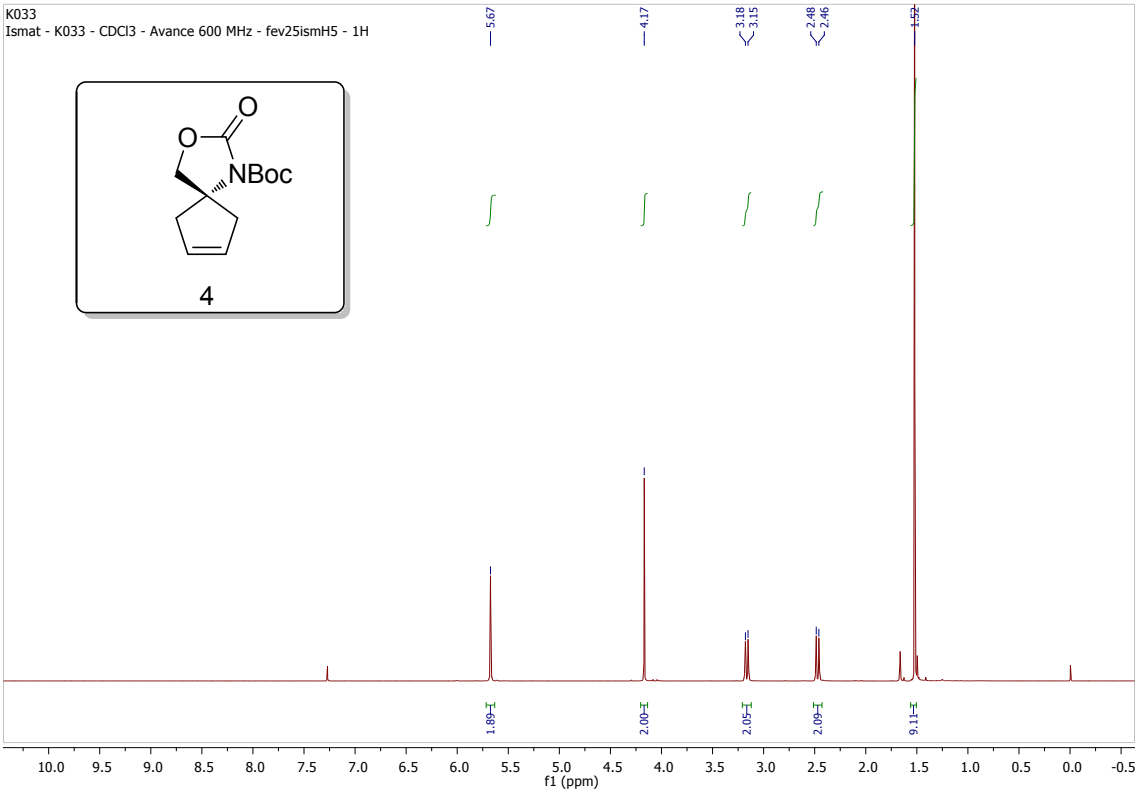


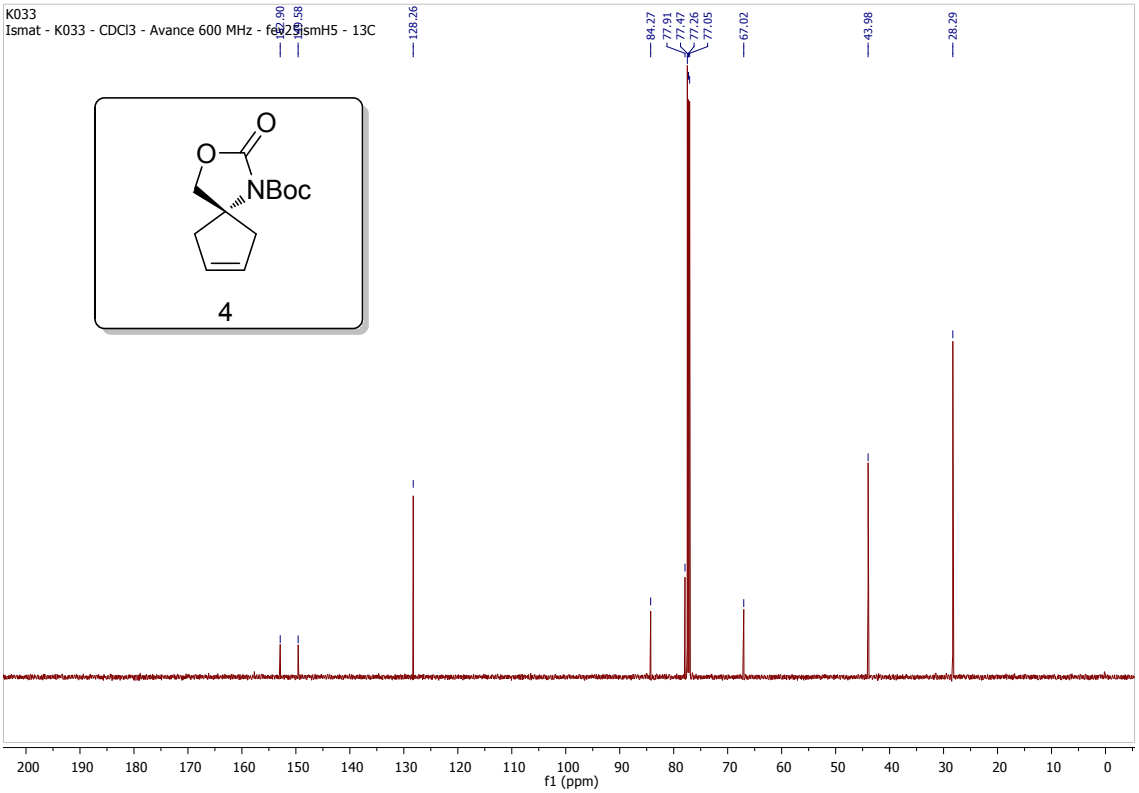
tert-Butyl-4,4-diallyl-2-oxooxazolidine-3-carboxylate (vi)



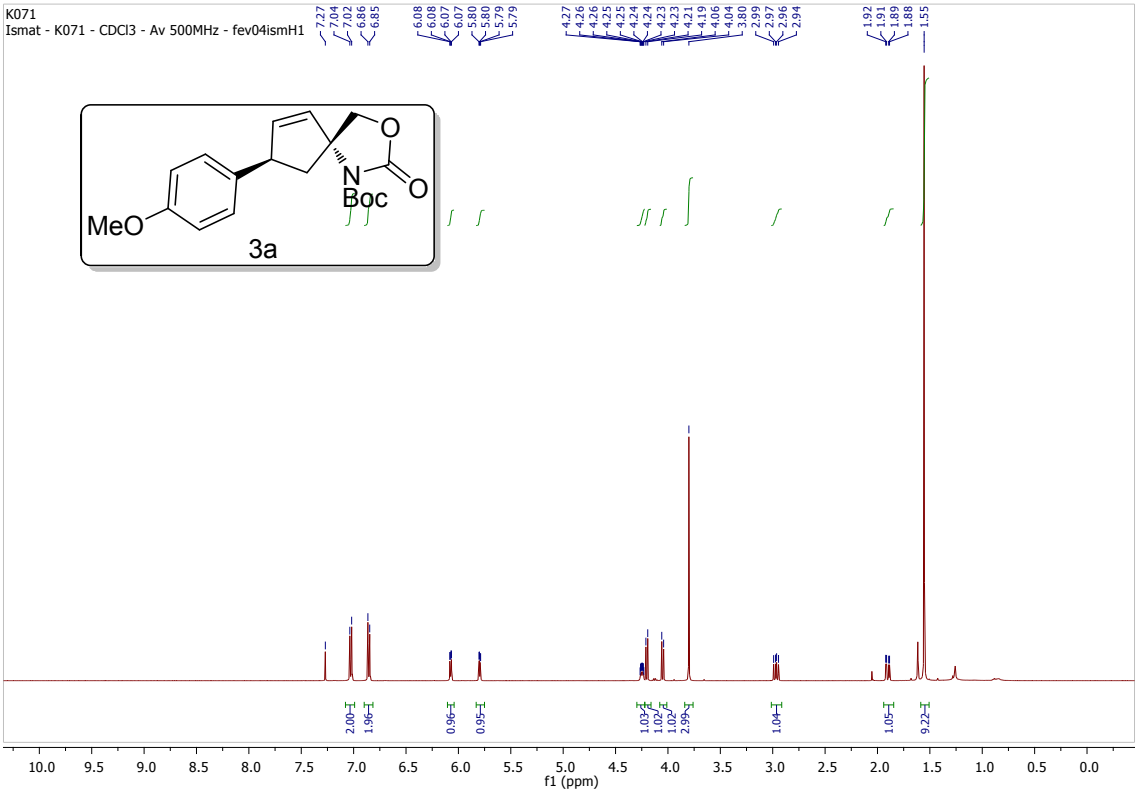


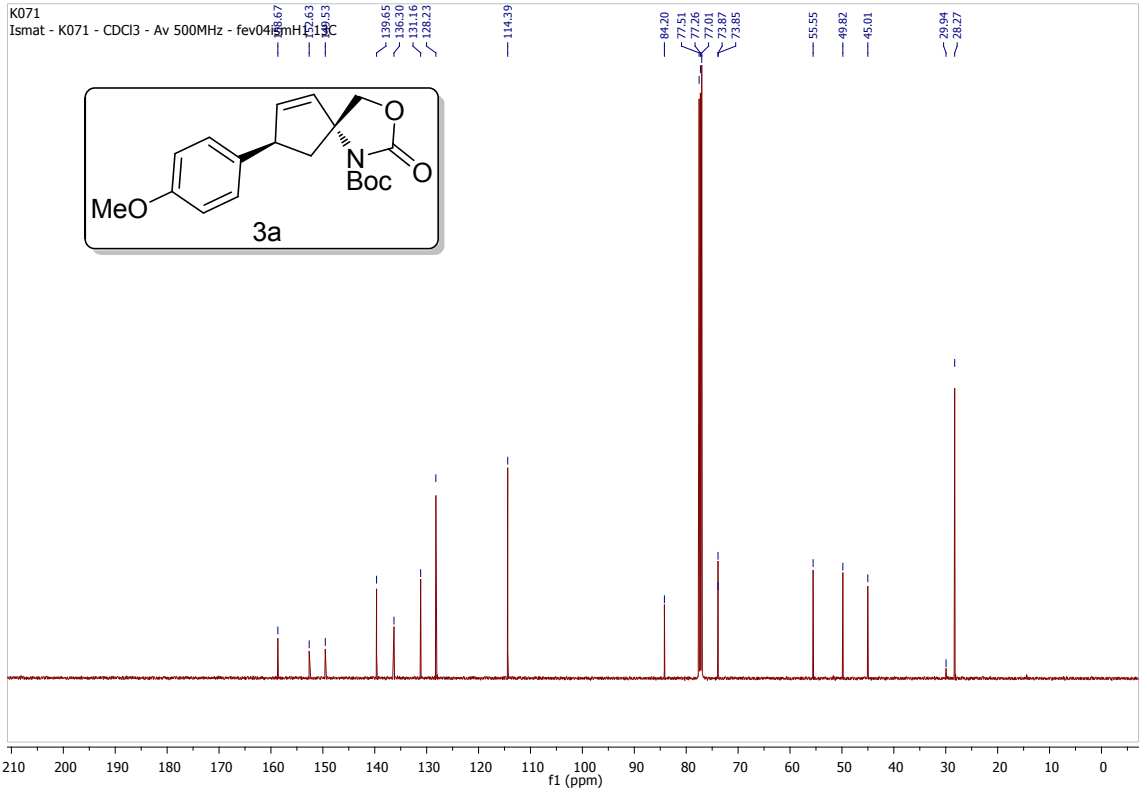
tert-Butyl-2-oxo-3-oxa-1-azaspiro[4.4]non-7-ene-1-carboxylate (4)



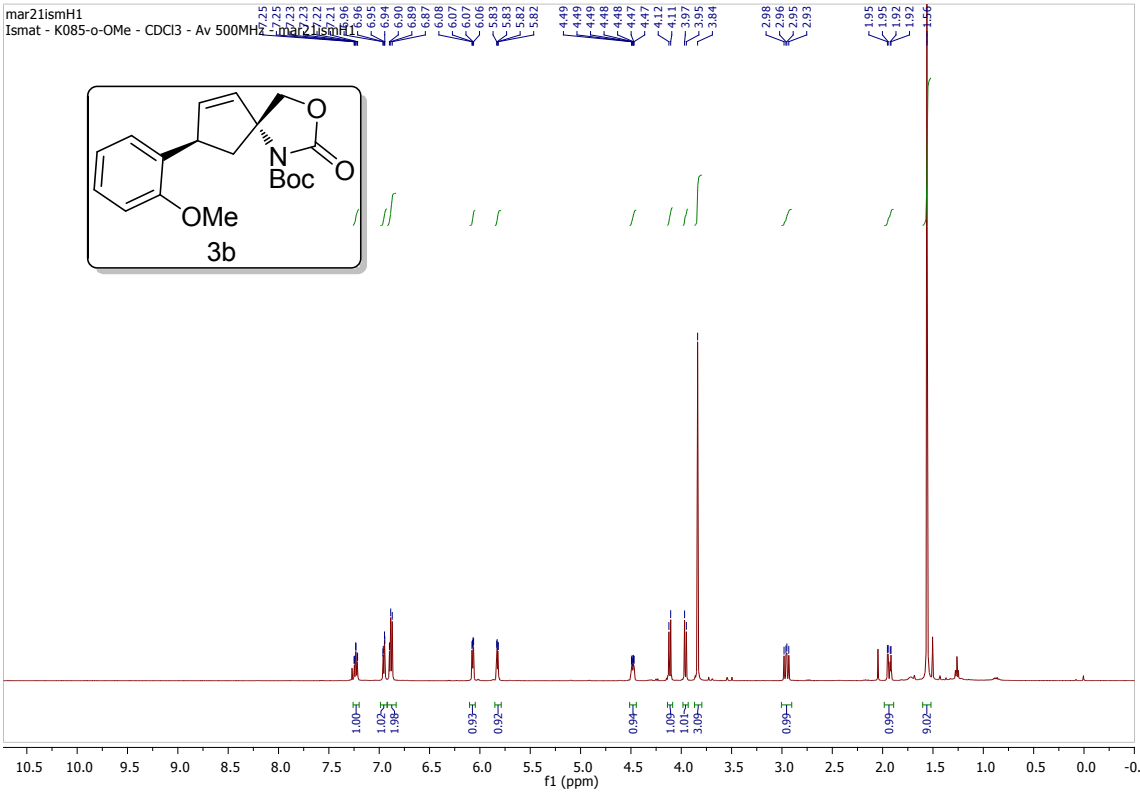


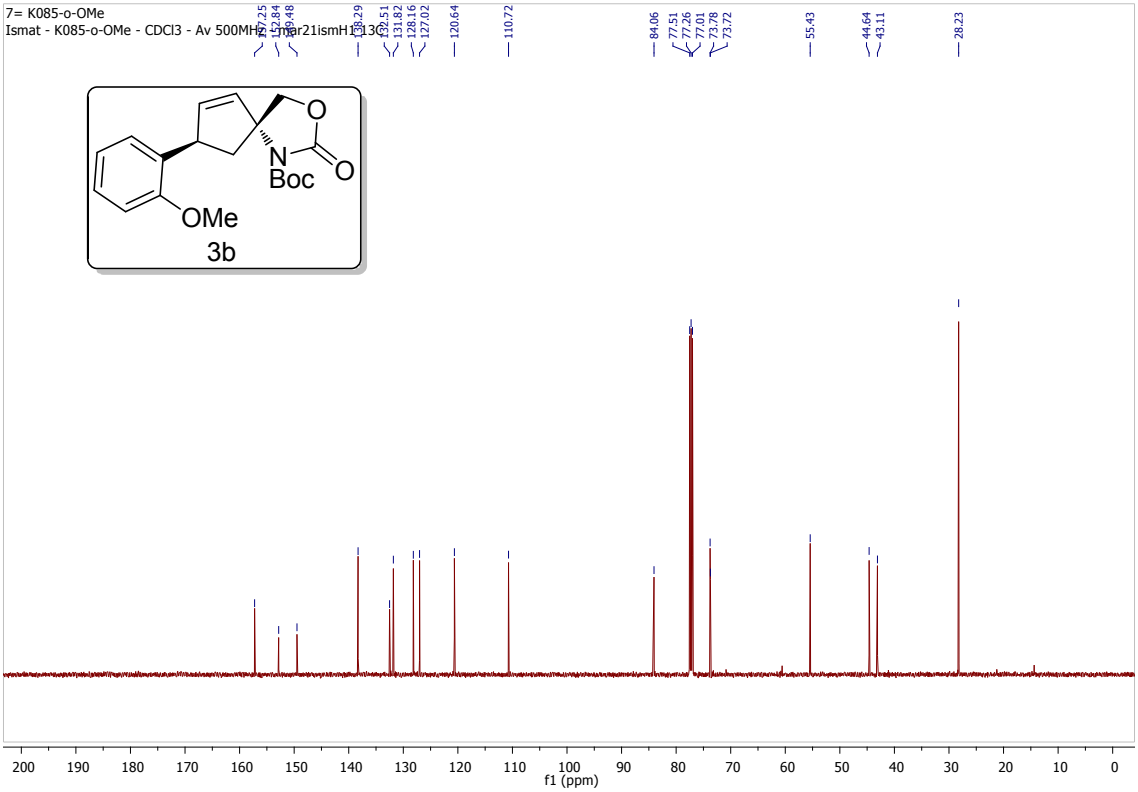
(5R,8R)-*tert*-Butyl 8-(4-methoxyphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3a)



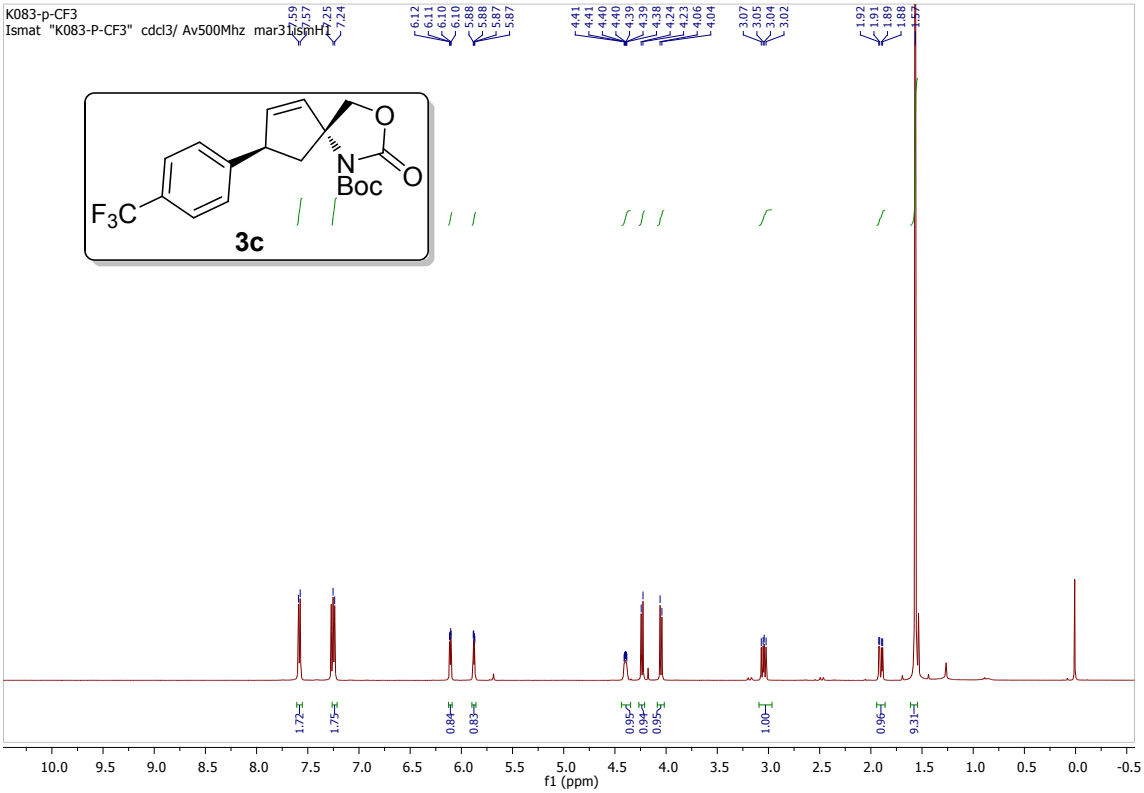


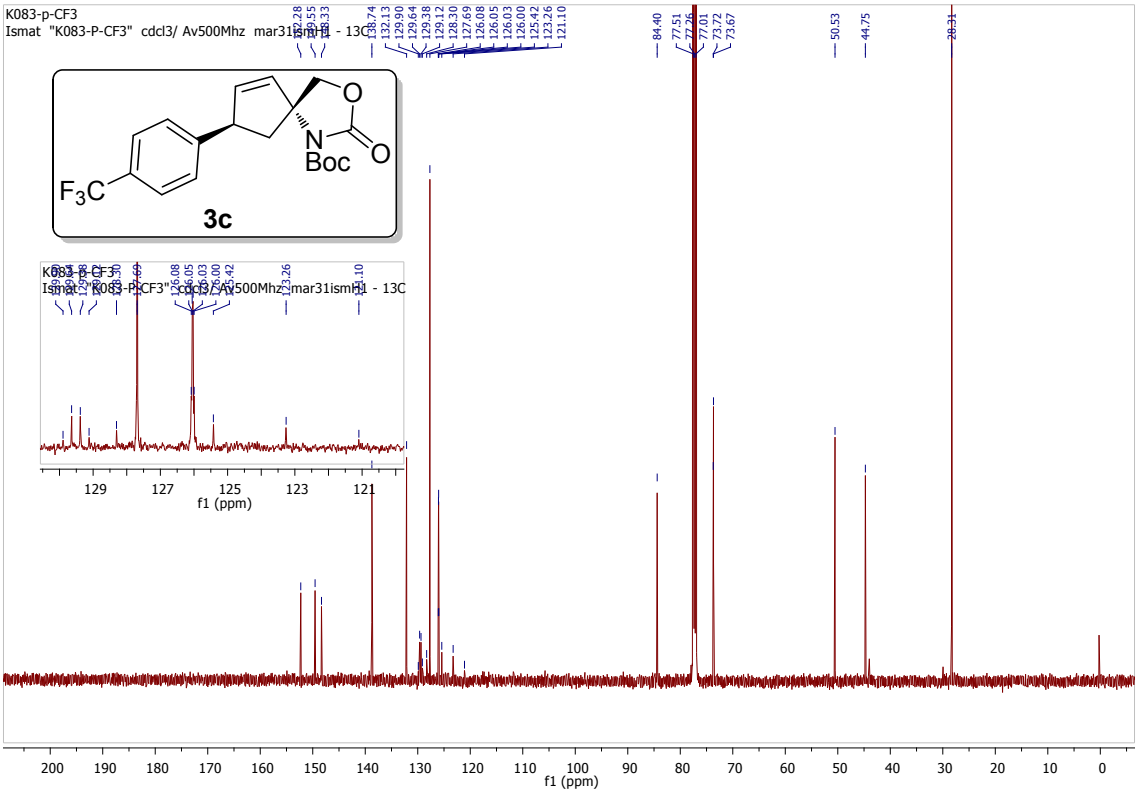
(5R,8R)-*tert*-Butyl 8-(2-methoxyphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3b)



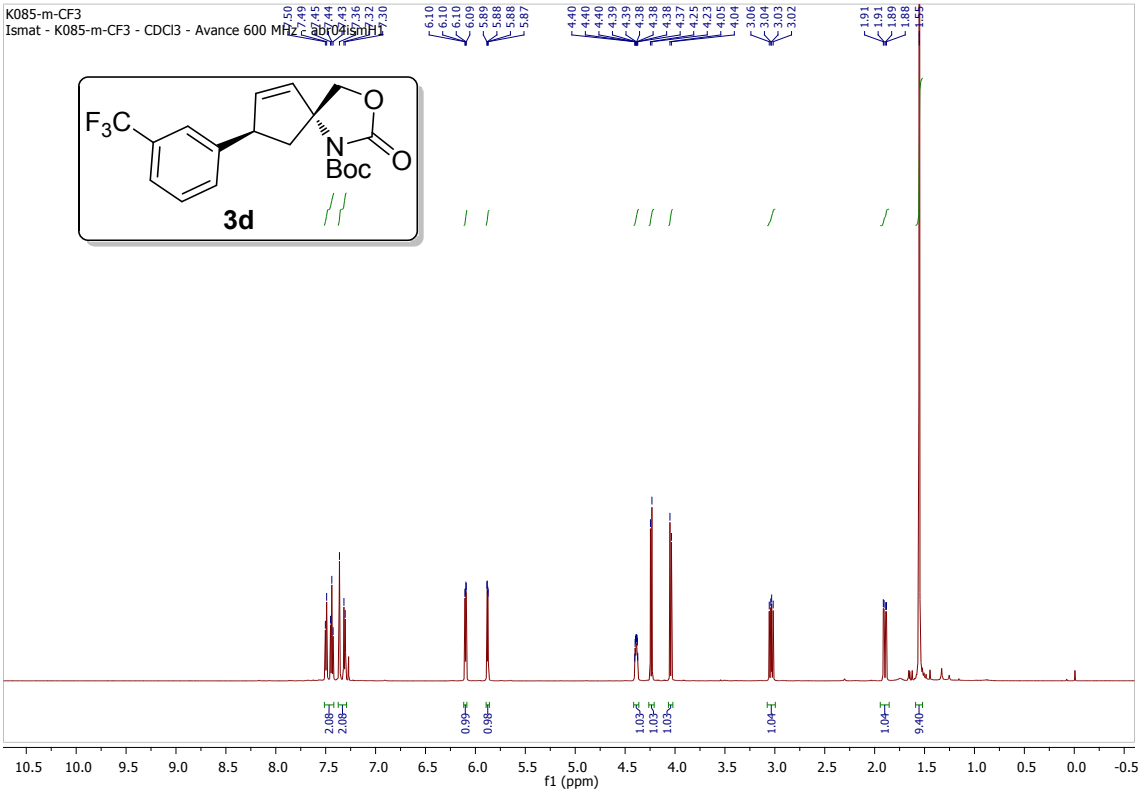


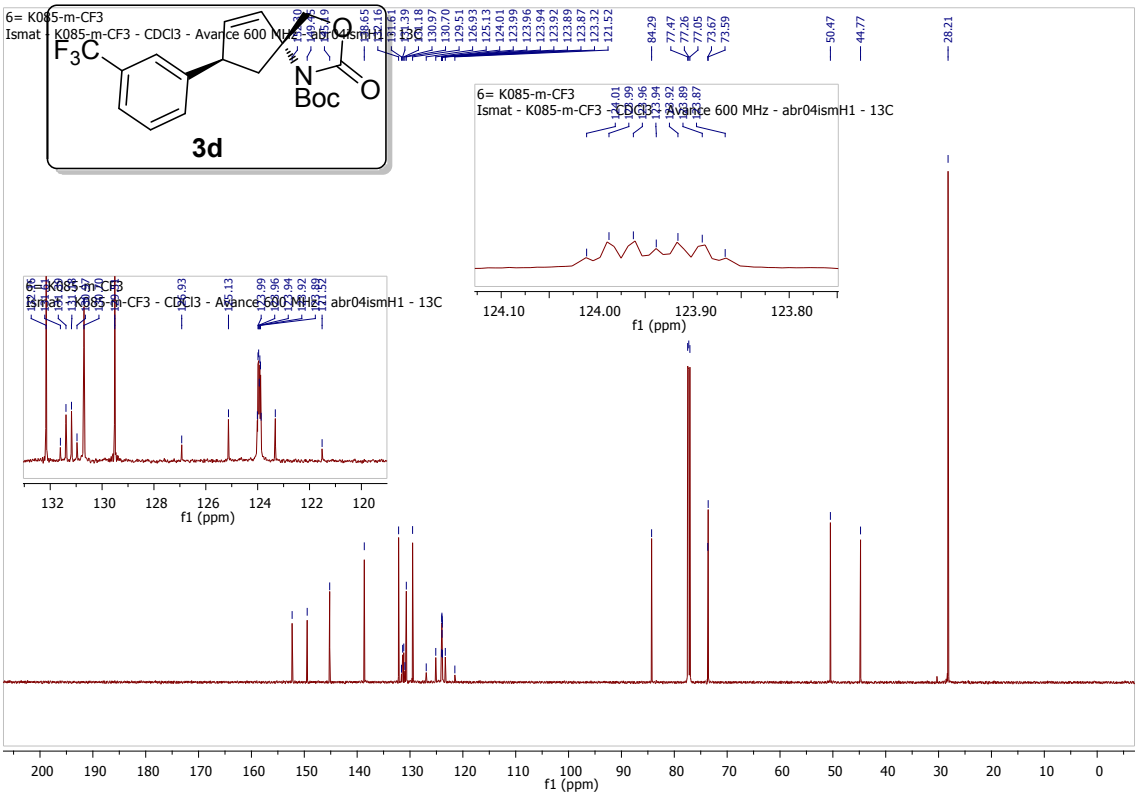
(5R,8R)-*tert*-Butyl 2-oxo-8-(4-(trifluoromethyl)phenyl)-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3c)



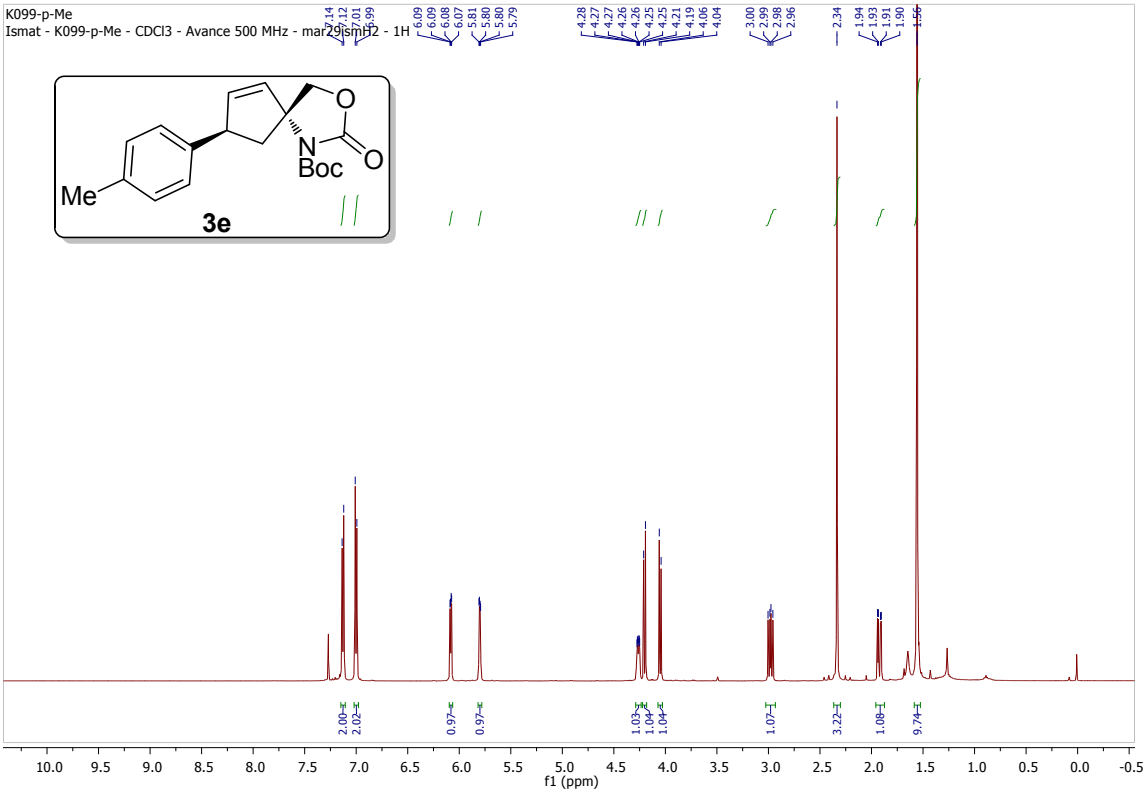


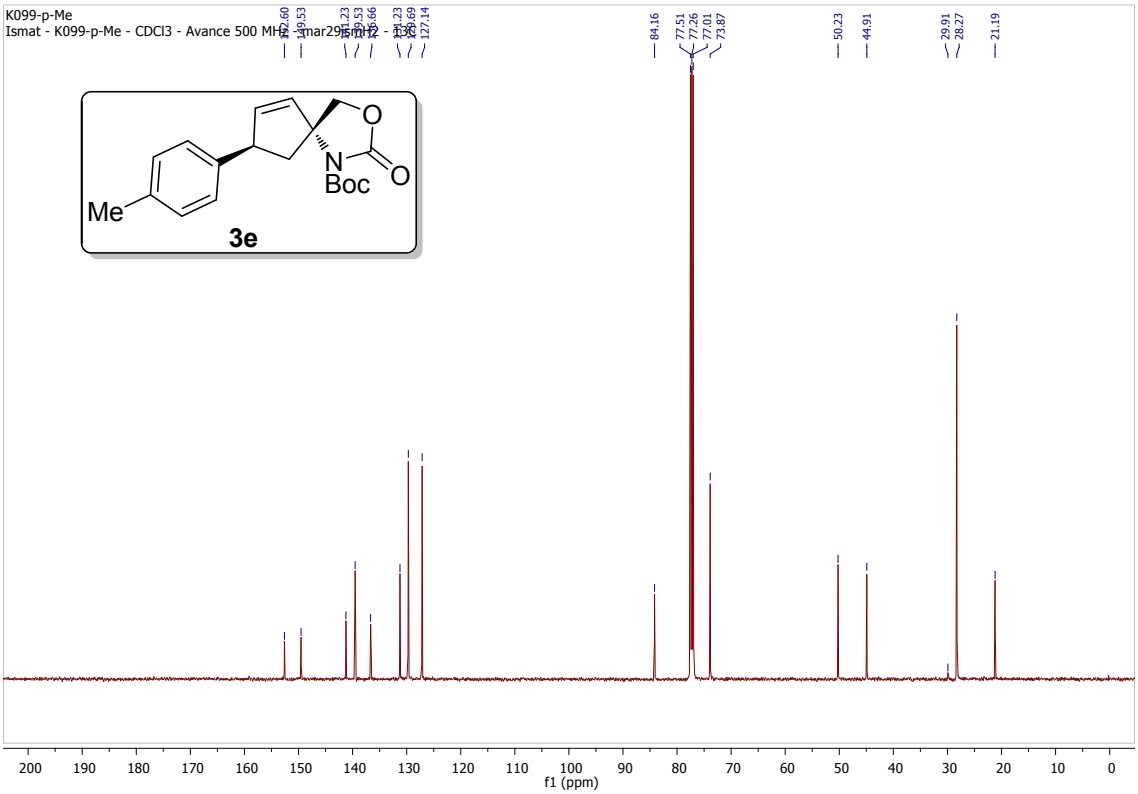
(5R,8R)-*tert*-Butyl 2-oxo-8-(3-(trifluoromethyl)phenyl)-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3d)



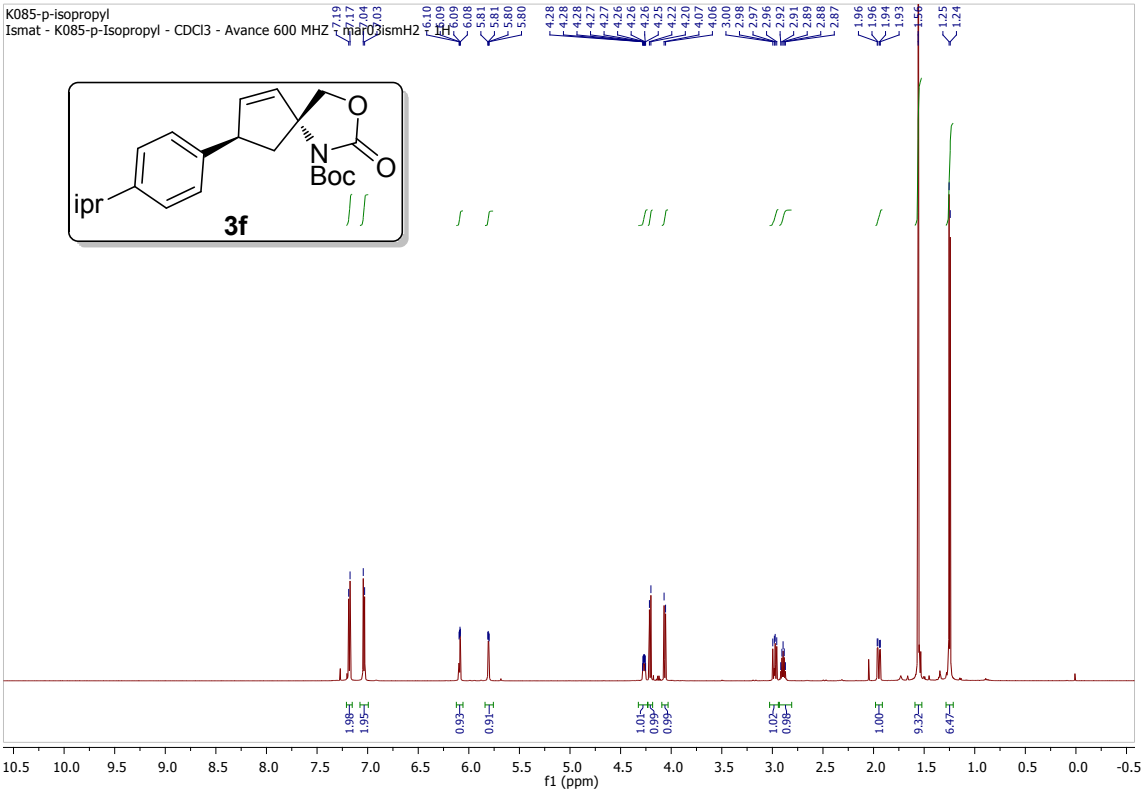


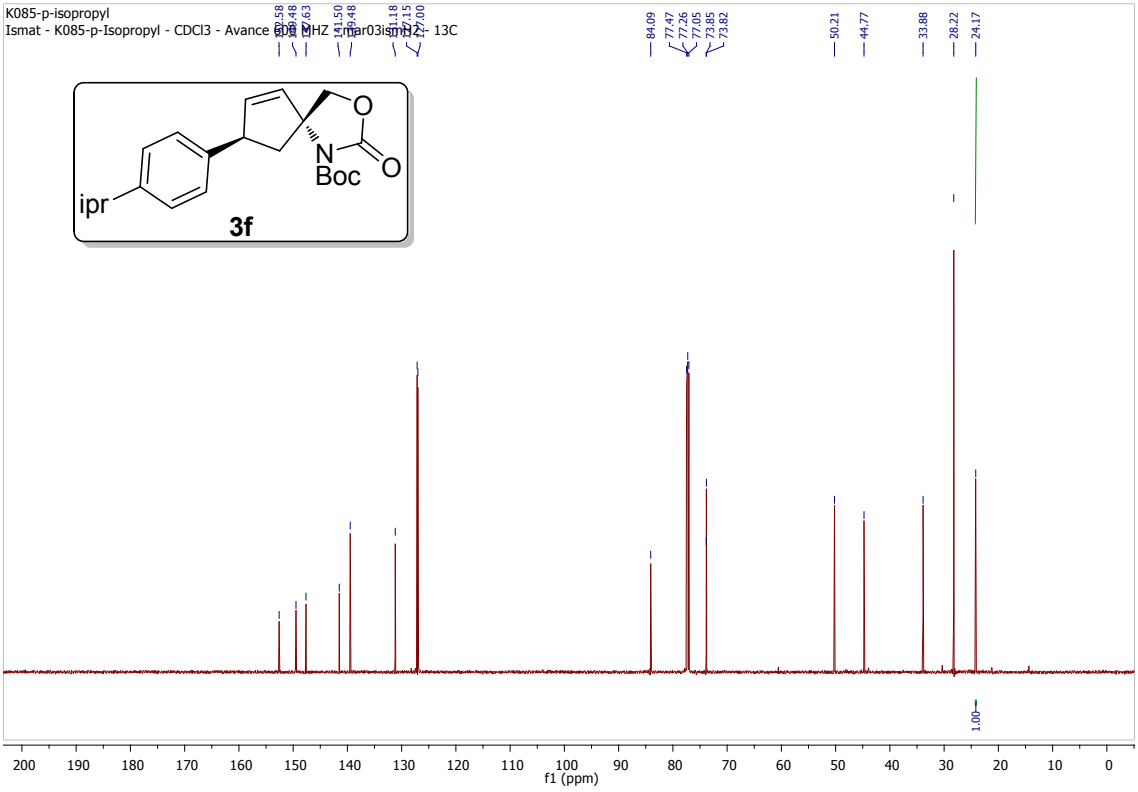
(5R,8R)-*tert*-Butyl 2-oxo-8-(p-tolyl)-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3e)



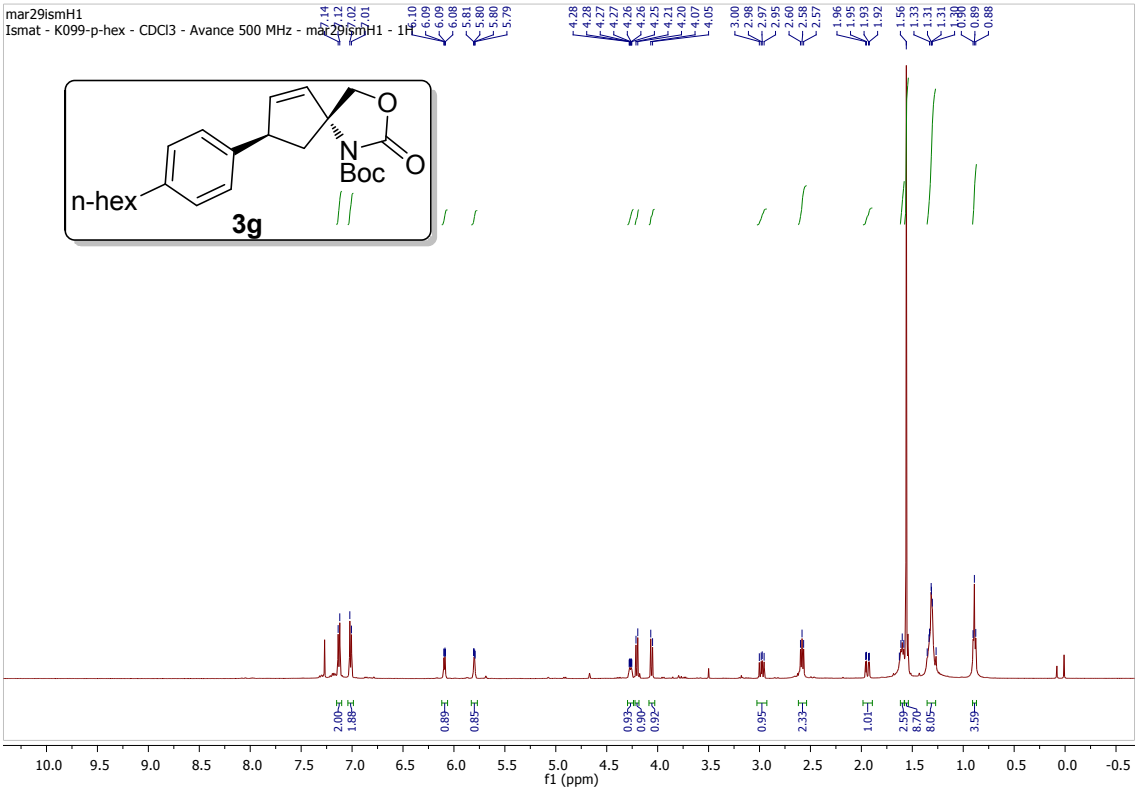


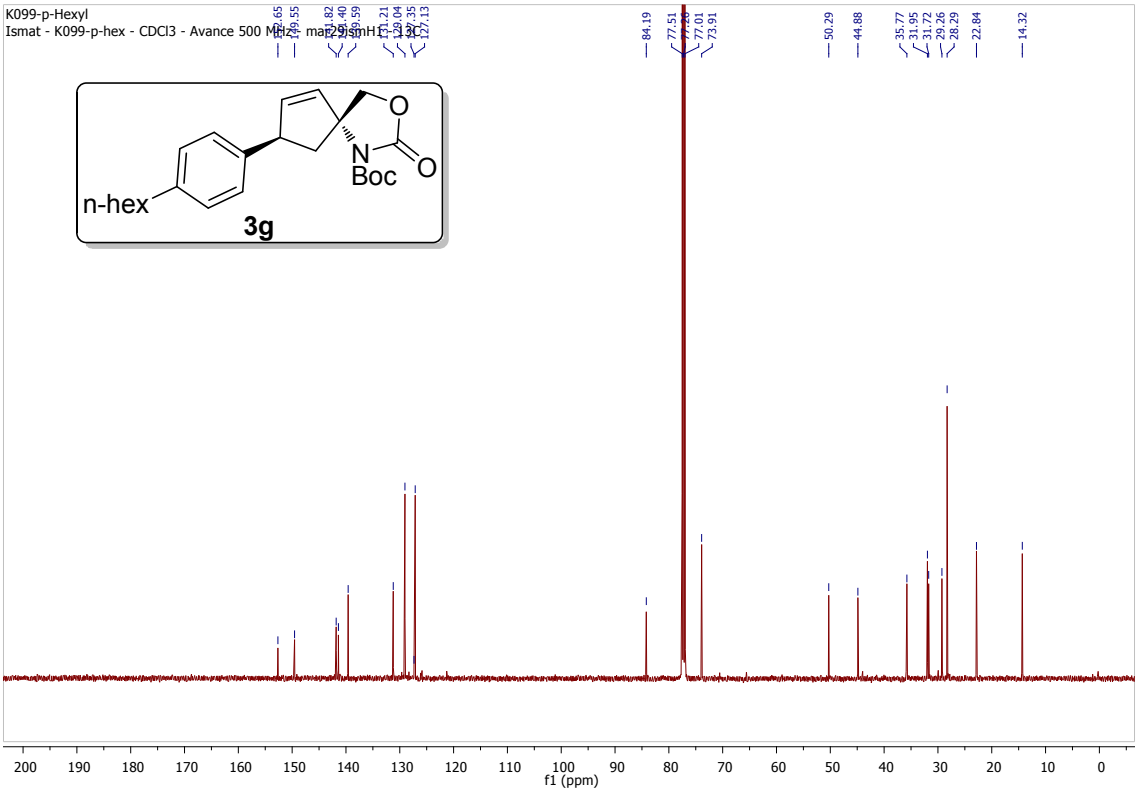
(5R,8R)-*tert*-Butyl 8-(4-isopropylphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3f)



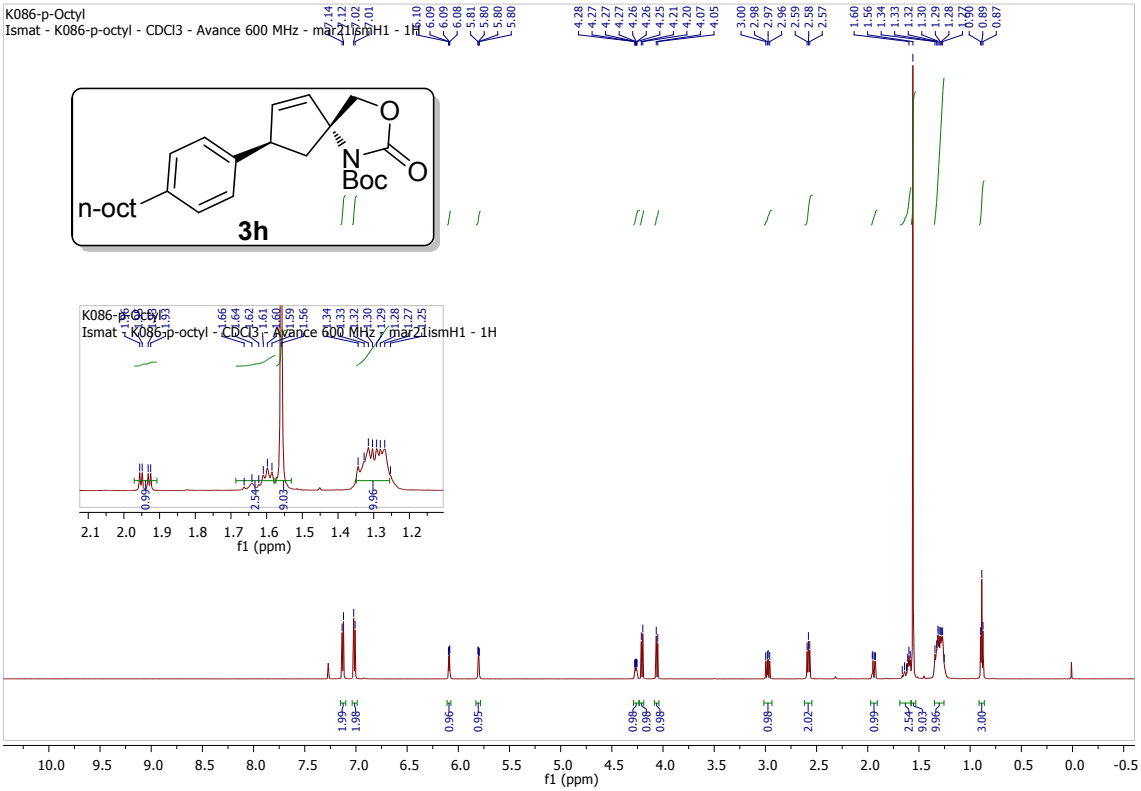


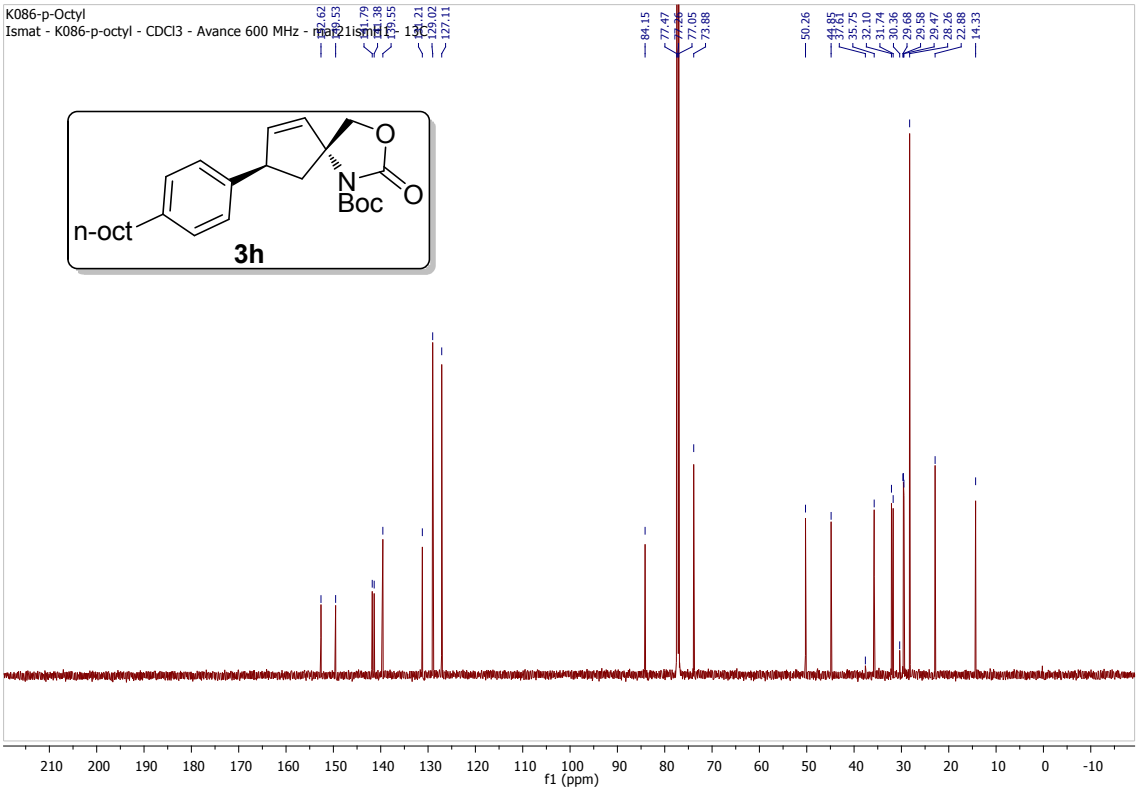
(5R,8R)-*tert*-Butyl 8-(4-hexylphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3g)



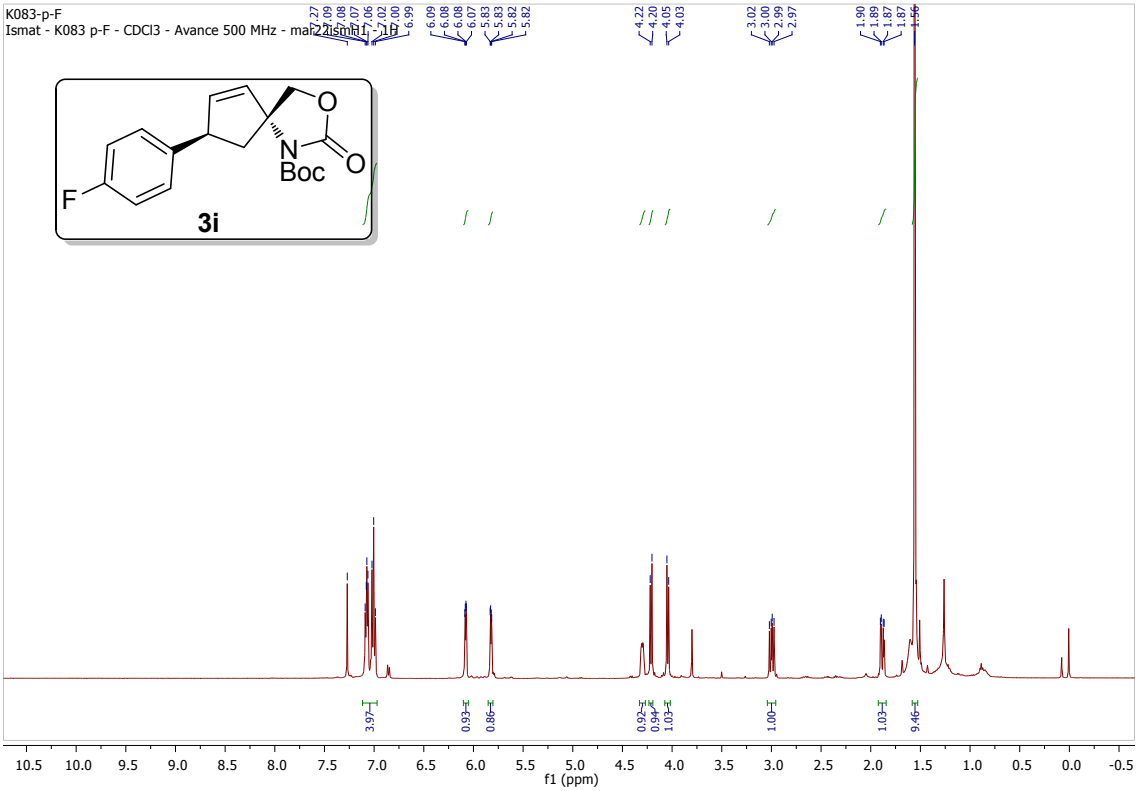


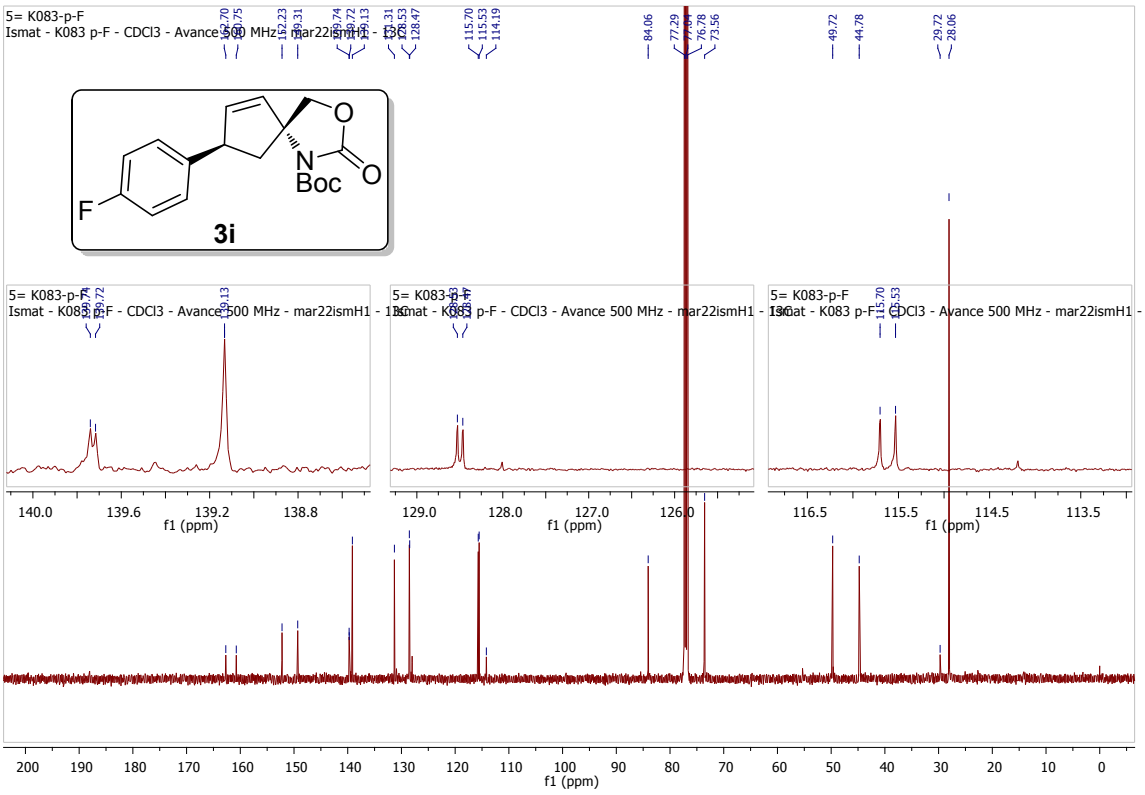
(5R,8R)-*tert*-Butyl 8-(4-octylphenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate(3h)



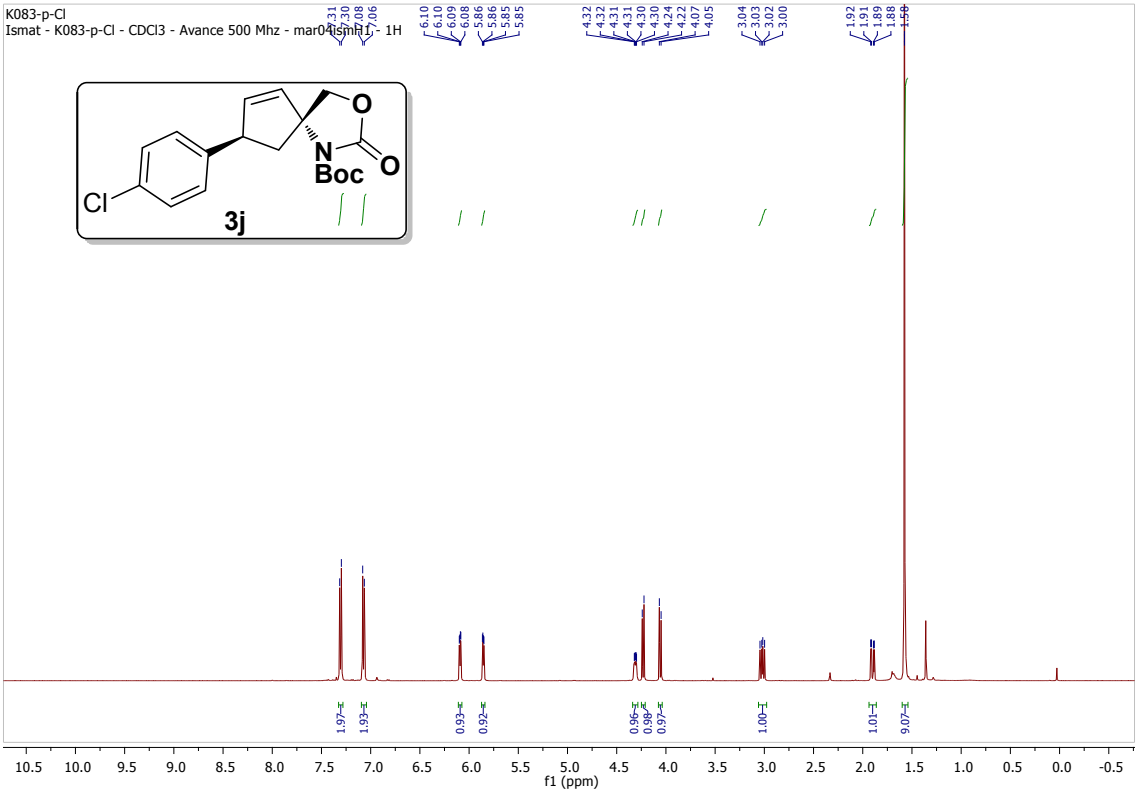


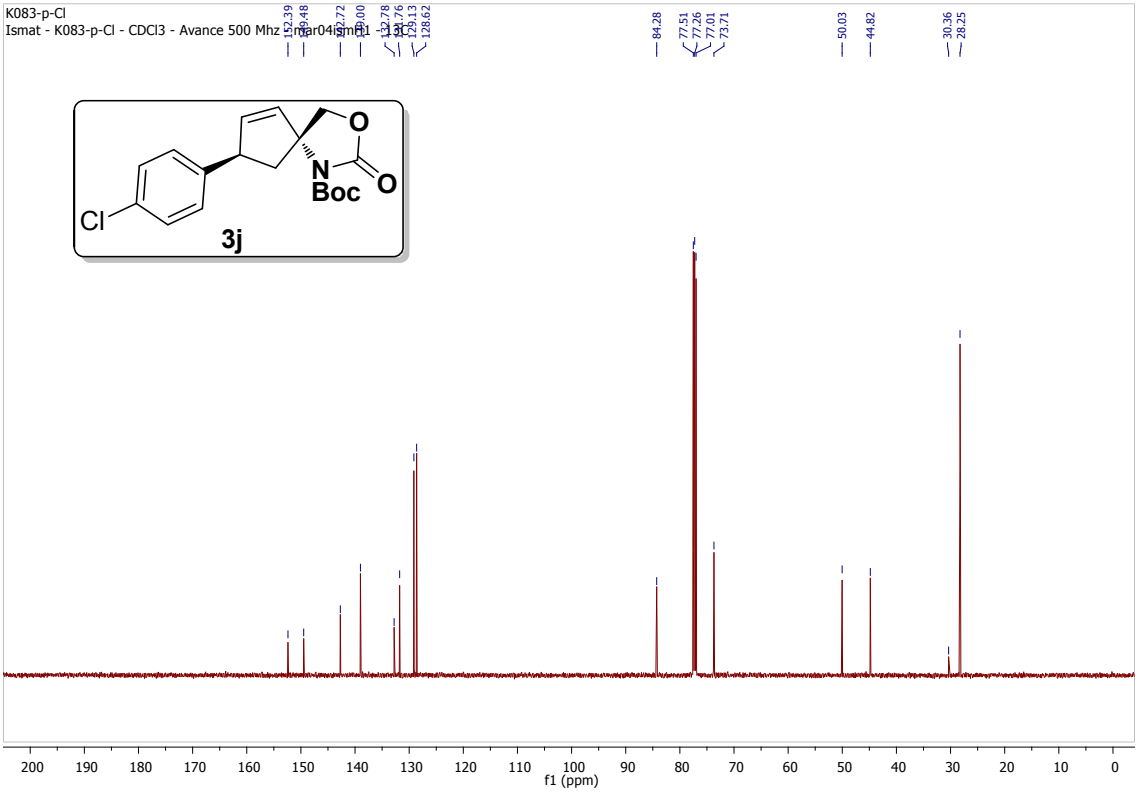
(5R,8R)-*tert*-Butyl 8-(4-fluorophenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3i)



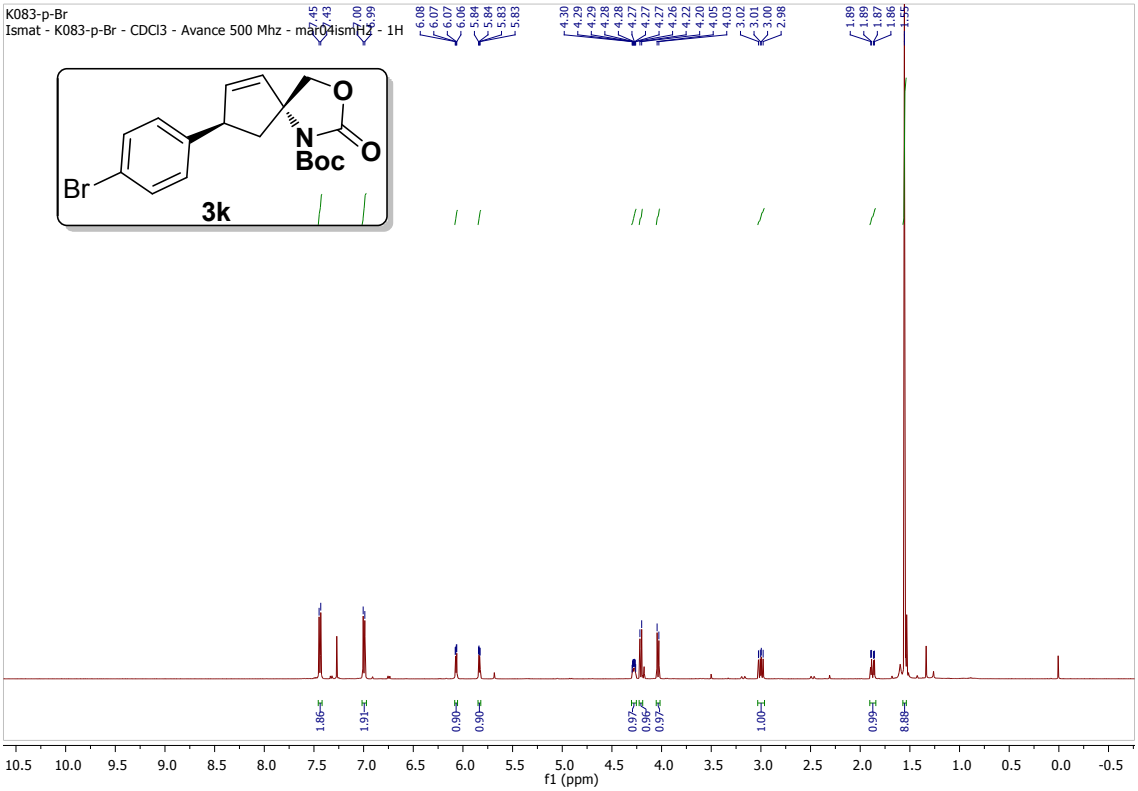


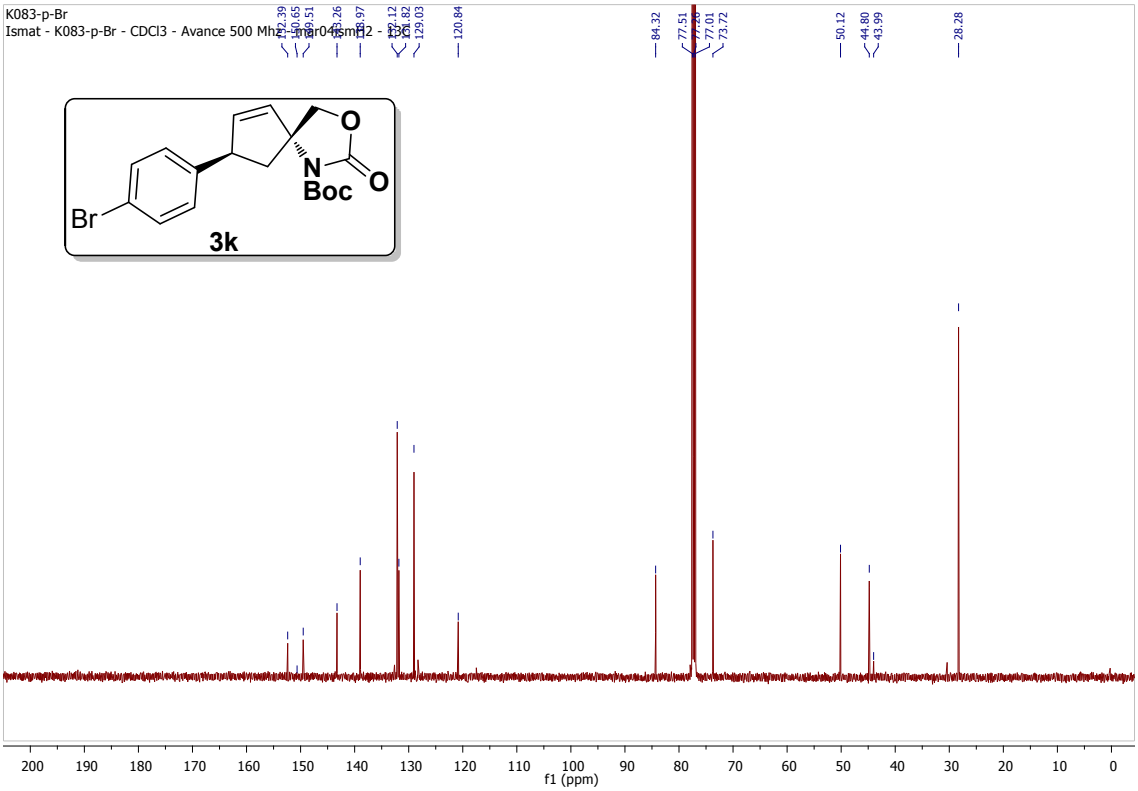
(5R,8R)-*tert*-Butyl 8-(4-chlorophenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3j)



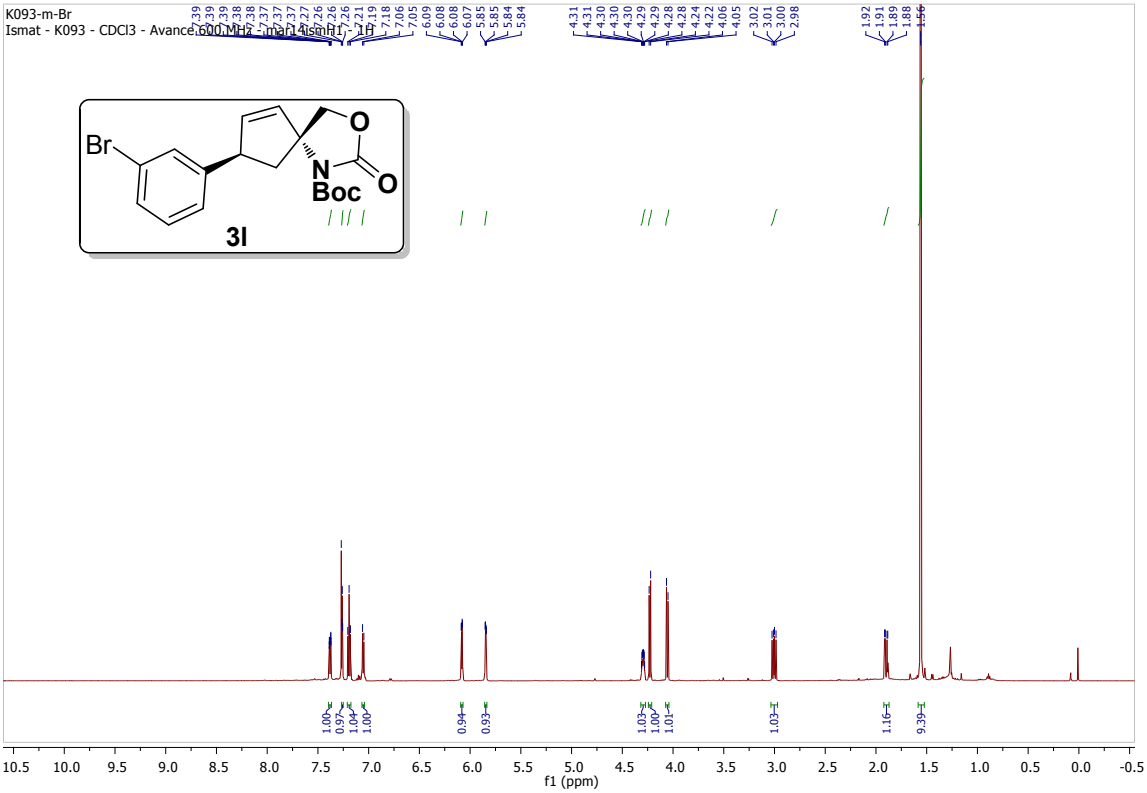


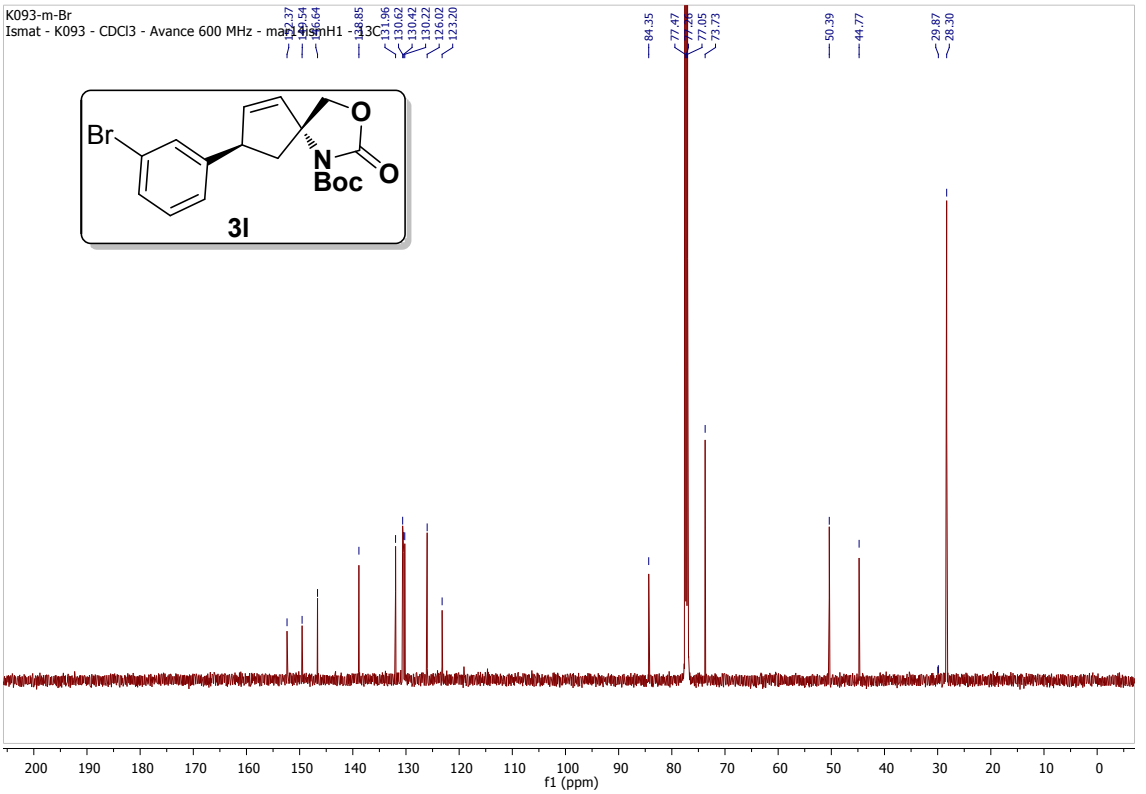
(5R,8R)-*tert*-Butyl 8-(4-bromophenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3k)



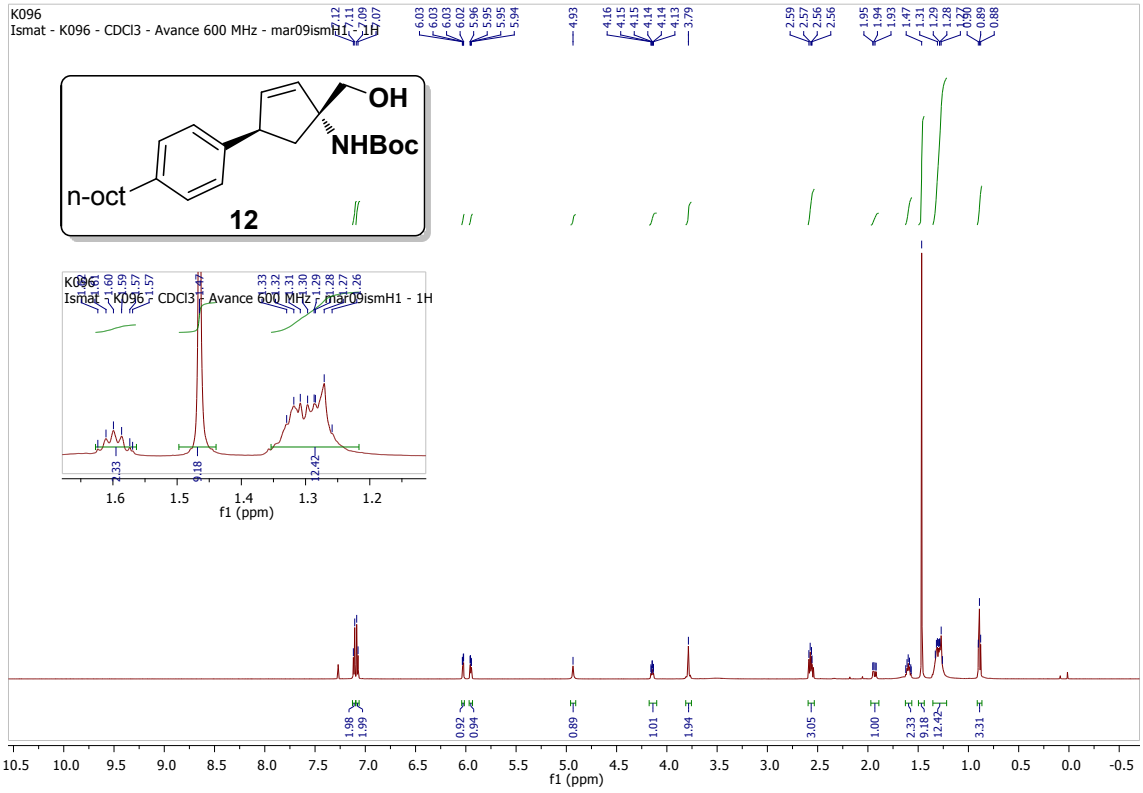


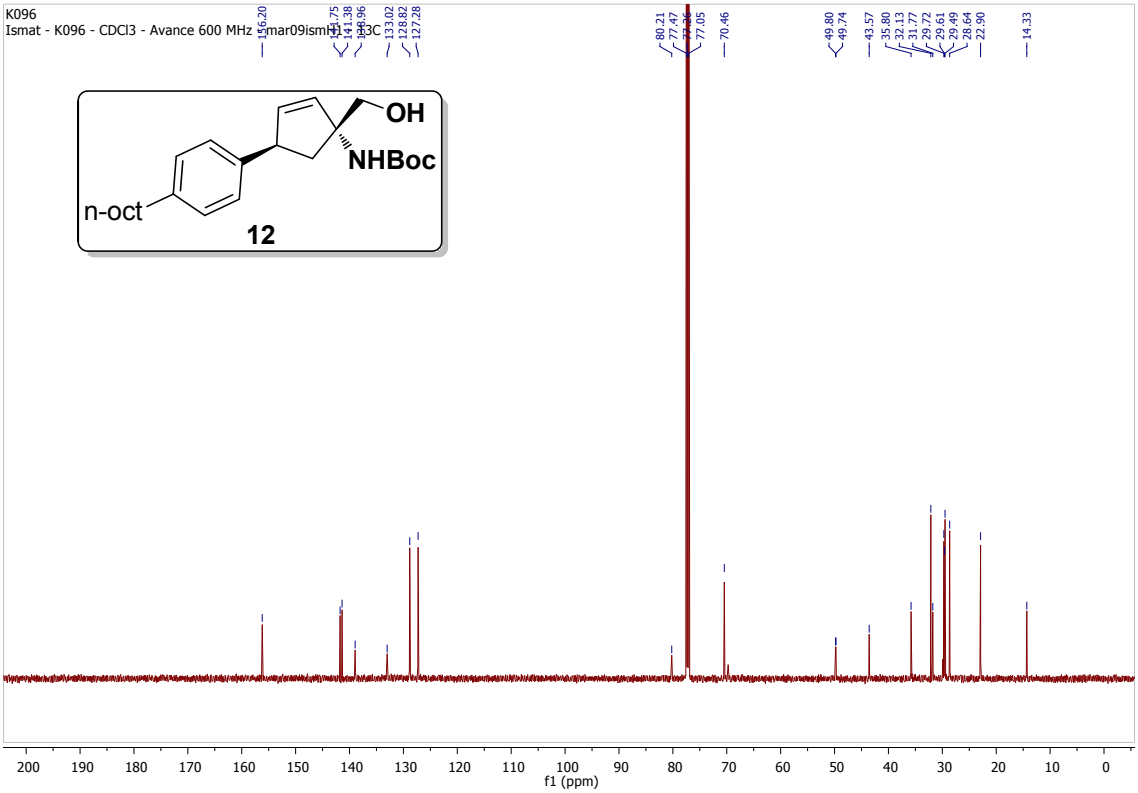
(5R,8R)-*tert*-Butyl 8-(3-bromophenyl)-2-oxo-3-oxa-1-azaspiro[4.4]non-6-ene-1-carboxylate (3l)



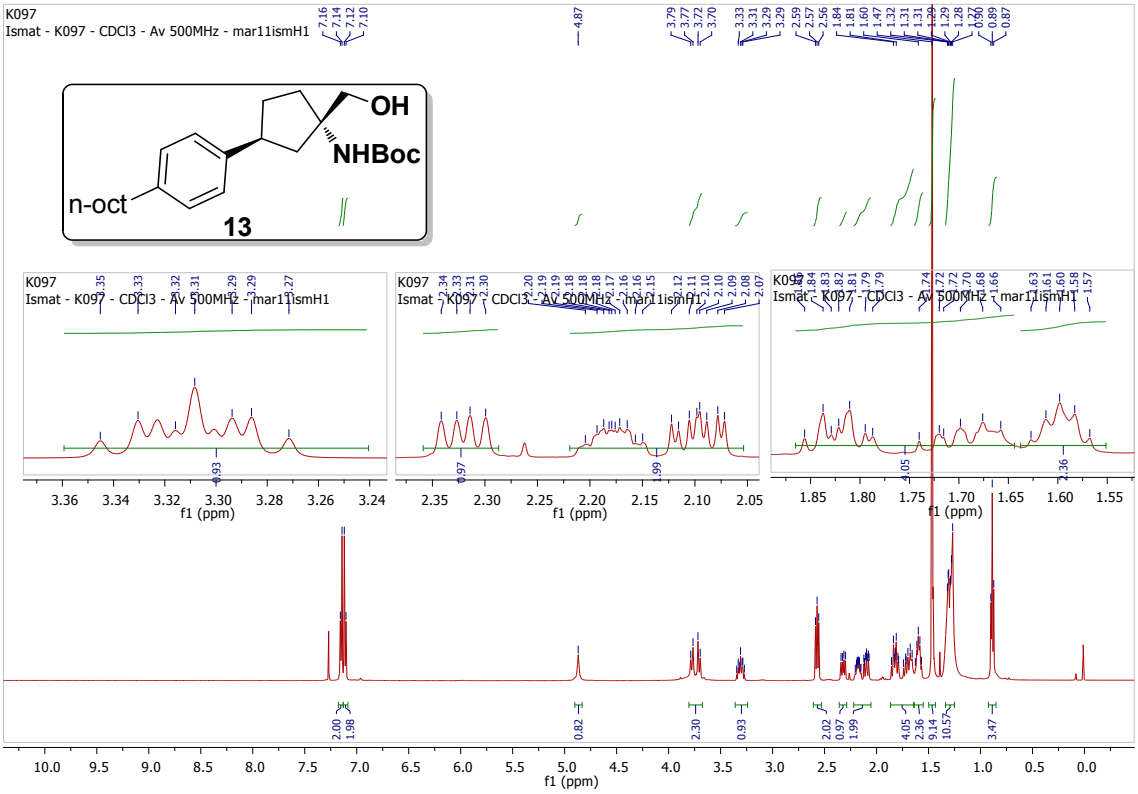


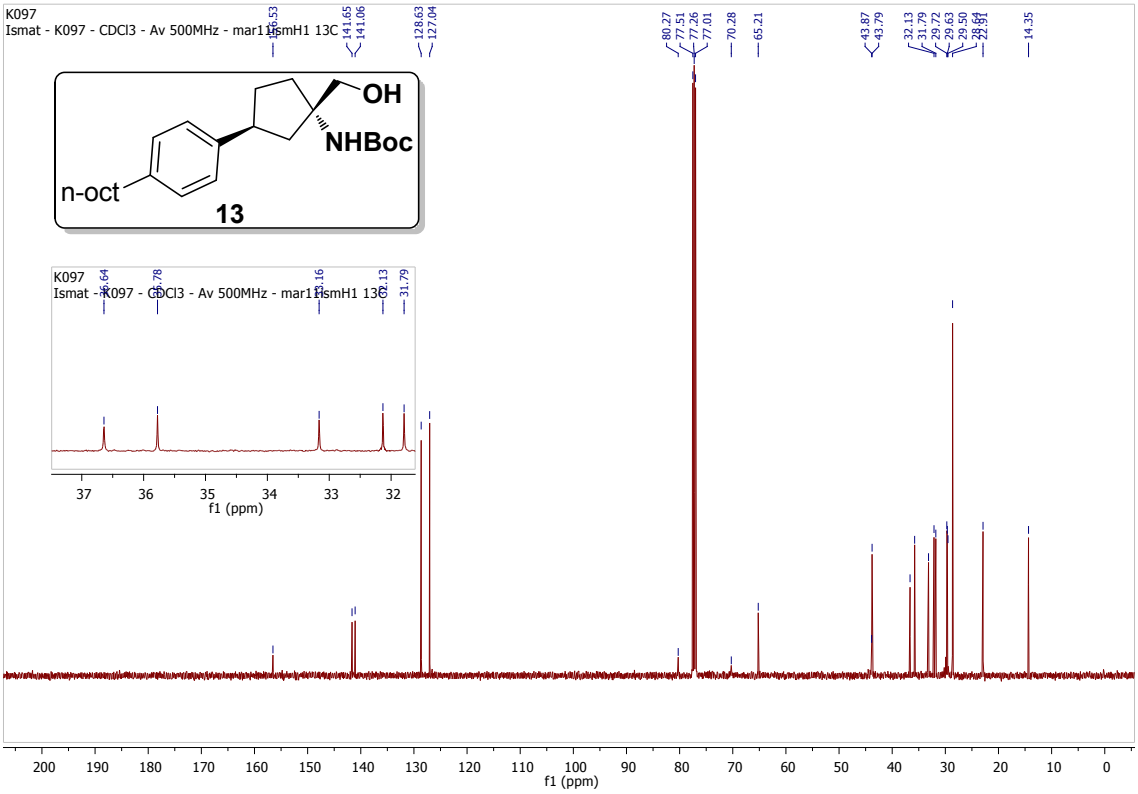
tert-Butyl ((1R,4R)-1-(hydroxymethyl)-4-(4-octylphenyl)cyclopent-2-en-1-yl)carbamate (12)



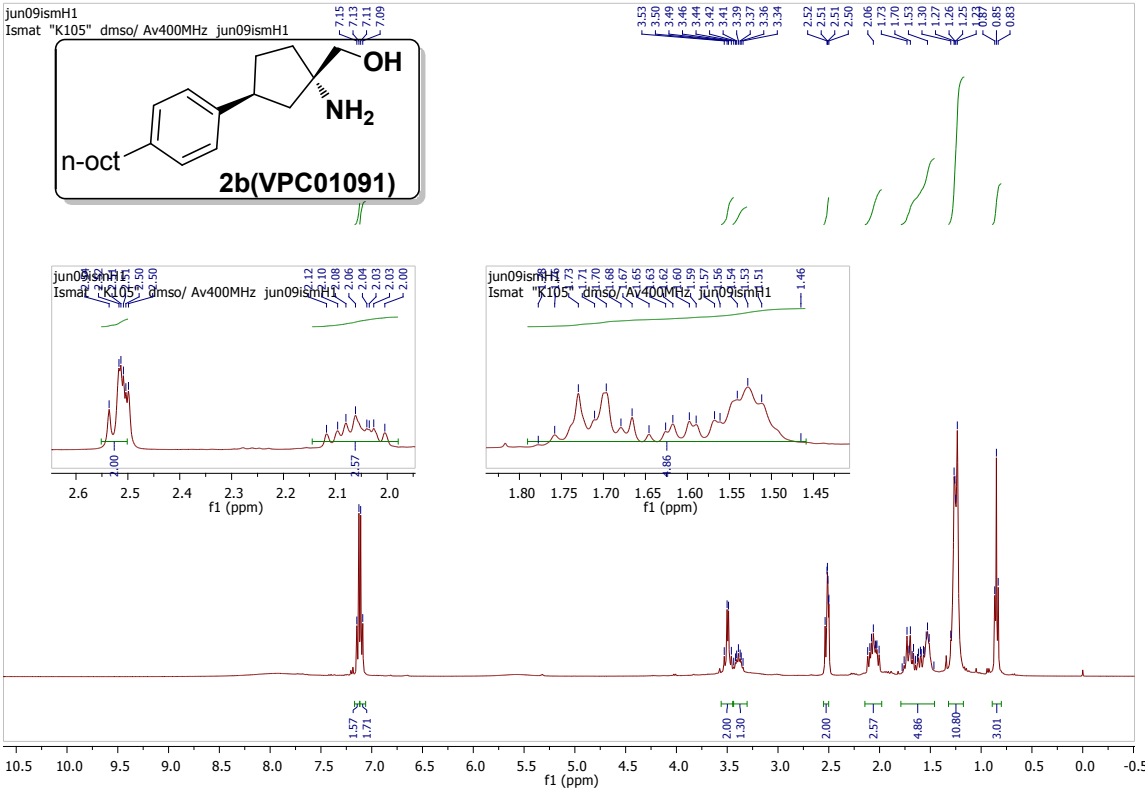


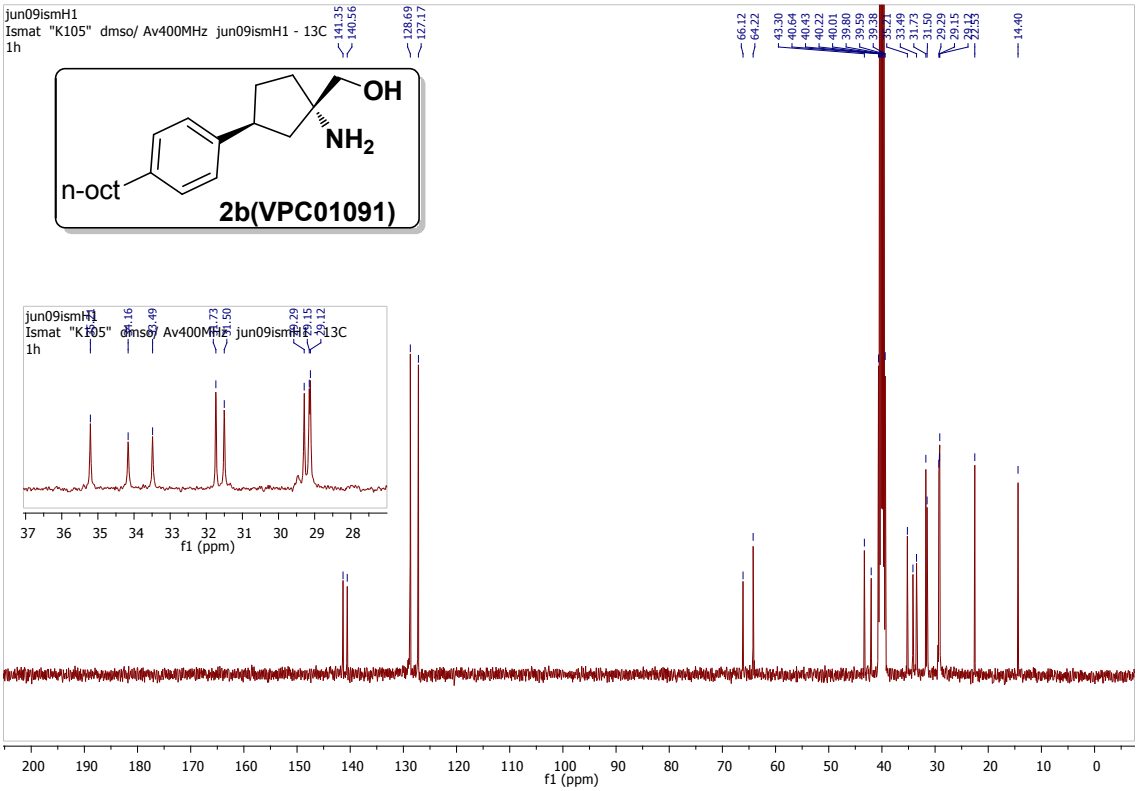
tert-Butyl ((1S,3S)-1-(hydroxymethyl)-3-(4-octylphenyl)cyclopentyl)carbamate (13)





((1S,3S)-1-Amino-3-(4-octylphenyl)cyclopentyl)methanol Hydrochloride (2b, VPC01091)





7. Assignment of the Relative Stereochemistry for the Heck Adducts.

7.1. Relative stereochemistry assignment by ^{1}H-^{1}H NOESY experiment

The relative stereochemistry of the major isomer of Heck adduct **3a** was determined by 2D ^{1}H-^{1}H NOESY, (**Figure 2**), on the basis of the presence of the key cross signals of H^1 with H^4 and H^6 ,but no cross signal with H^3. Similarly, the presence of the key cross signal of H^2 with H^3 , but no cross signals with H^4 and H^6.

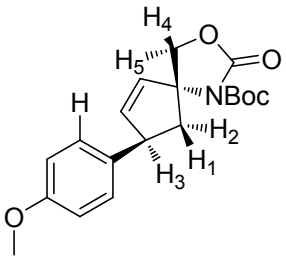
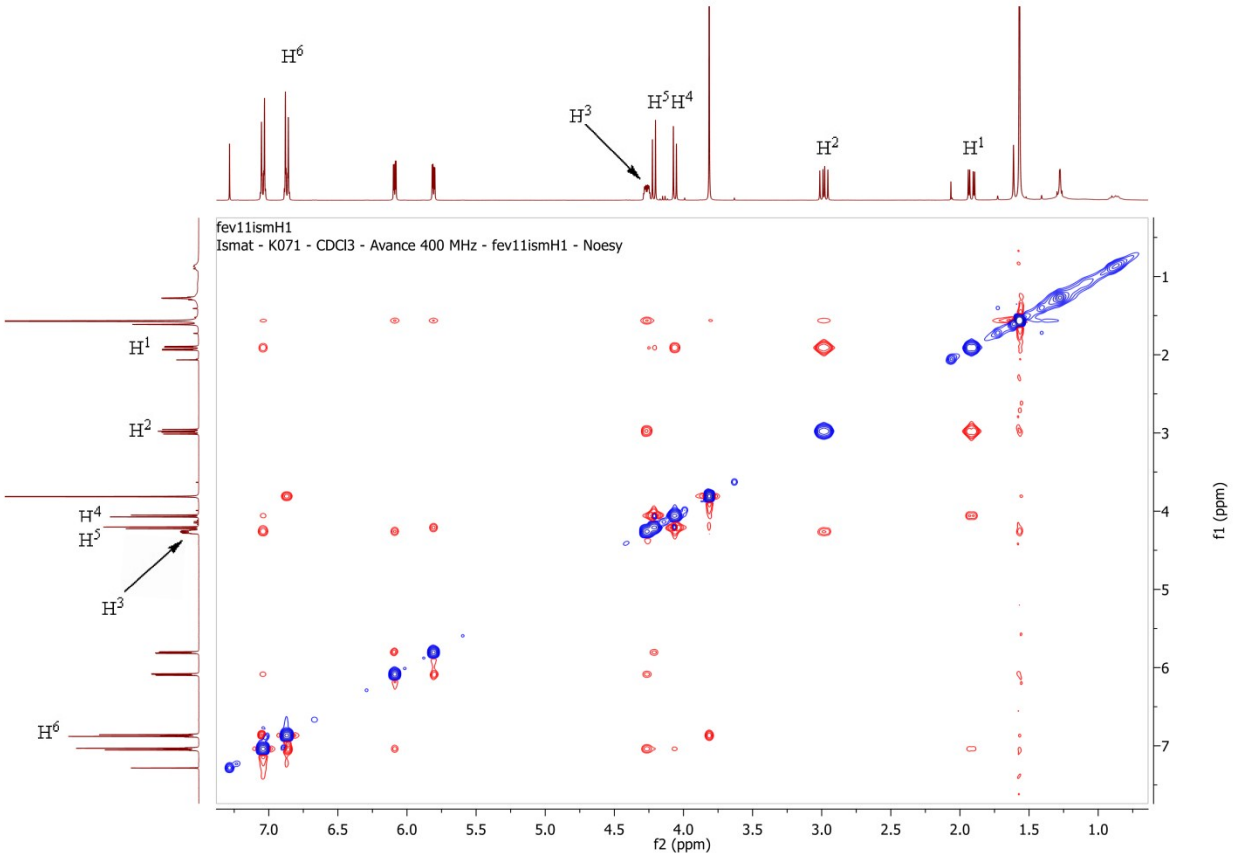
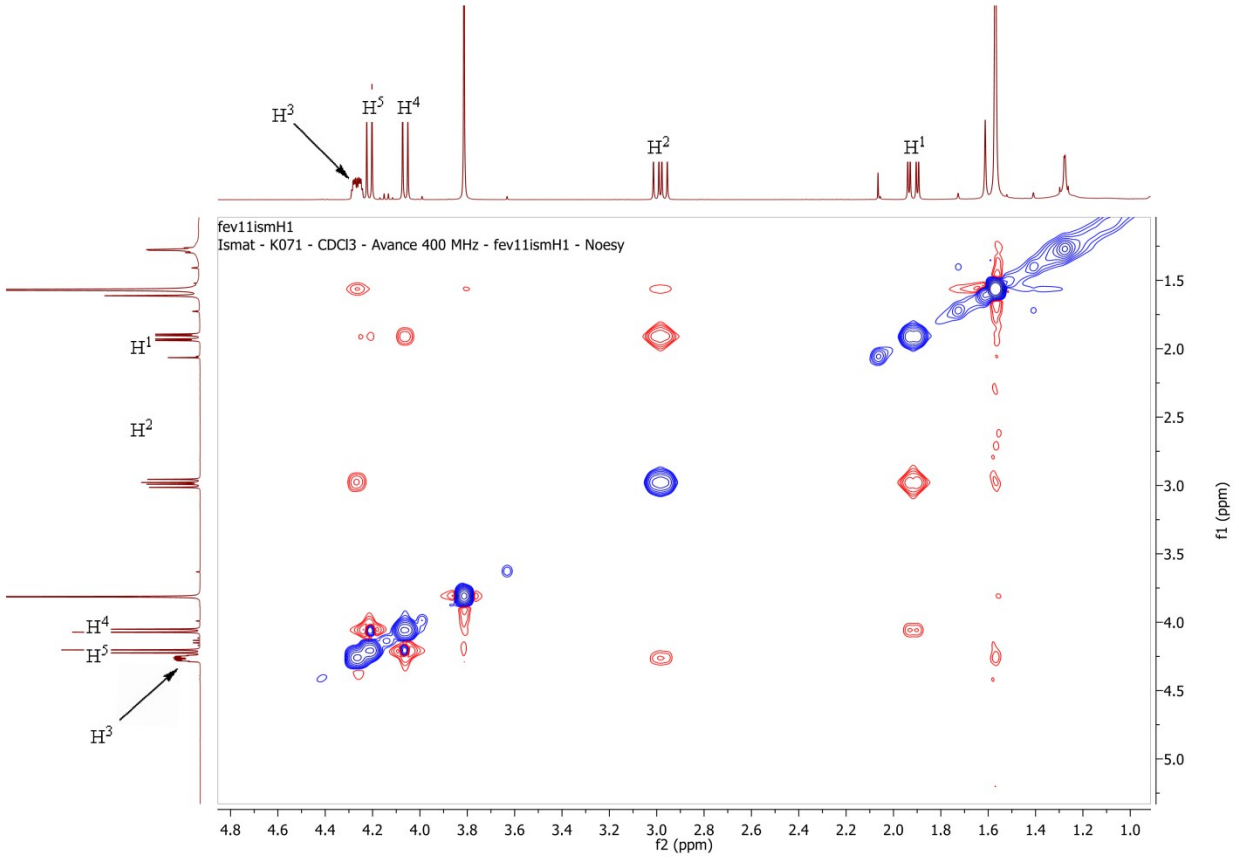


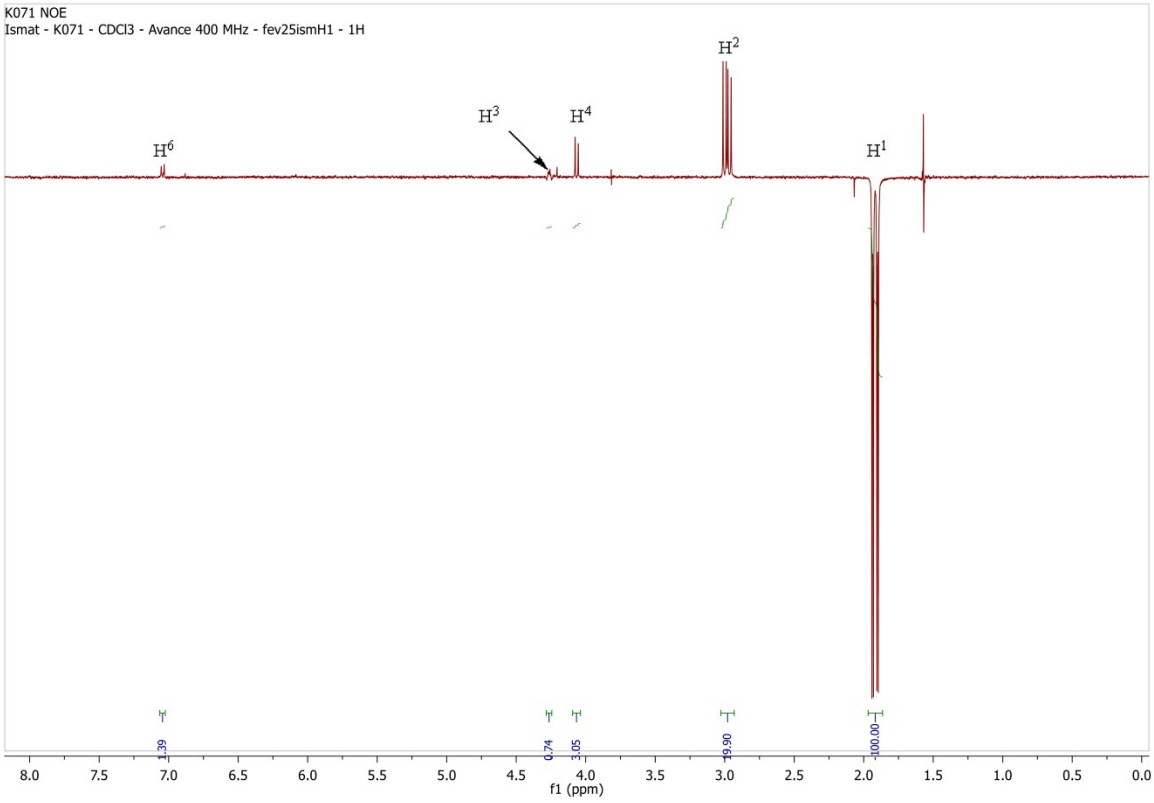
Figure 2. 2D ^{1}H-^{1}H NOESY and stereochemical assignment for the Heck product **3a**.

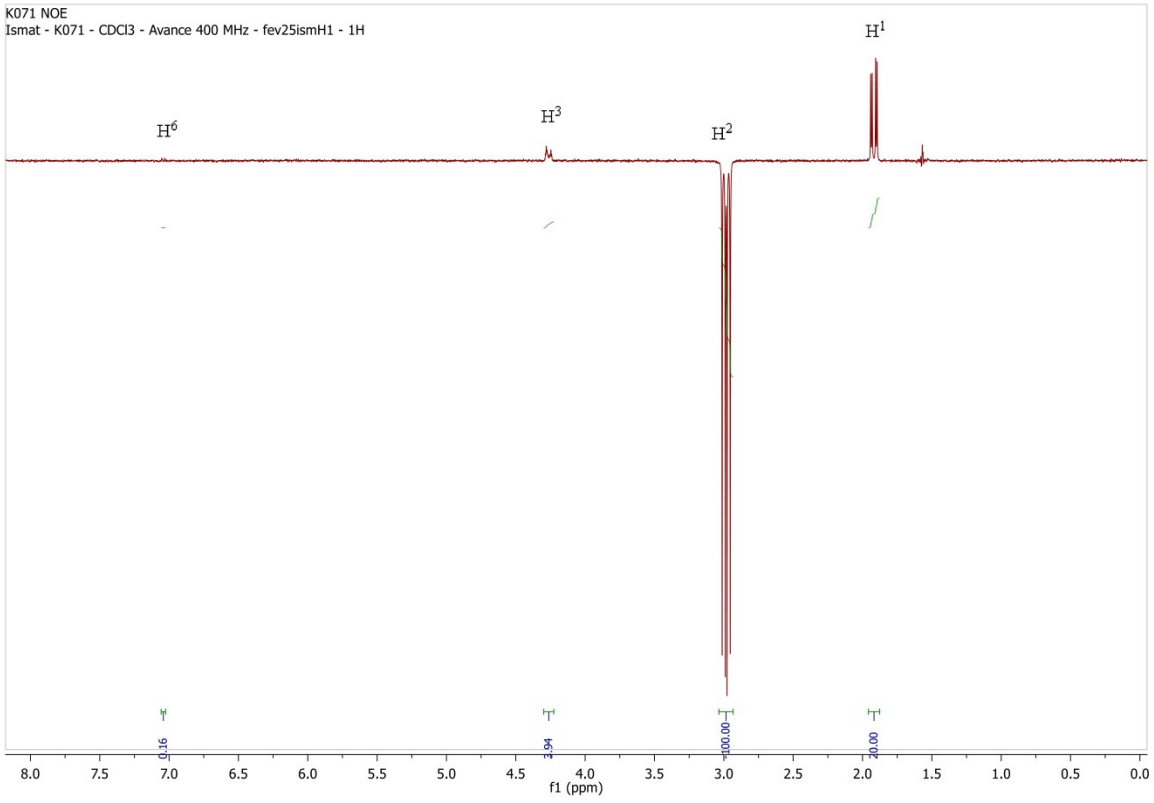




7.2. NOE increments and stereochemical assignment for the Heck product 3a.

The H^1 (which is syn to aromatic ring) is shielded by aromatic ring and is observed in ^1H NMR spectrum at 1.9 ppm as a doublet of doublet with coupling constants of 14.2 and 4.2 Hz while the H^2 (which is trans to aromatic ring) appears at 3.0 ppm as a doublet of doublet with coupling constant of 14.2 and 9.2 Hz. In order to confirm the relative position of aromatic ring, we performed NOE (Nuclear Overhauser Effect) experiments with the Heck adduct **3a** by irradiating the methylene hydrogens (H^1 and H^2). Irradiating the H^1, induced an NOE increment 1.4% in H^6, 0.7% in H^3 and 3.1% in H^4, indicating the greater proximity between H^1 and H^4. Similarly irradiating the H^2, induced no NOE in H^4, 0.2% in H^6 and 3.9% in H^3 indicating the greater proximity between H^1 and H^3. The NOE increments, confirmed the relative stereochemistry of the Heck adduct deduced from 2D ^1H-^1H NOESY, (**Figure 3)**, which was further confirmed by the X-rays crystallographic data for **3a** given in **Figure 4**.


K071 NOE
Ismat - K071 - CDCl3 - Avance 400 MHz - fev25ismH1 - 1H
H6
H3
H4
H2
H1
1.39
0.74
3.05
19.90
100.00
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


K071 NOE
Ismat - K071 - CDCl3 - Avance 400 MHz - fev25ismH1 - 1H
H6
H3
H2
H1
0.16
3.94
100.00
20.00
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

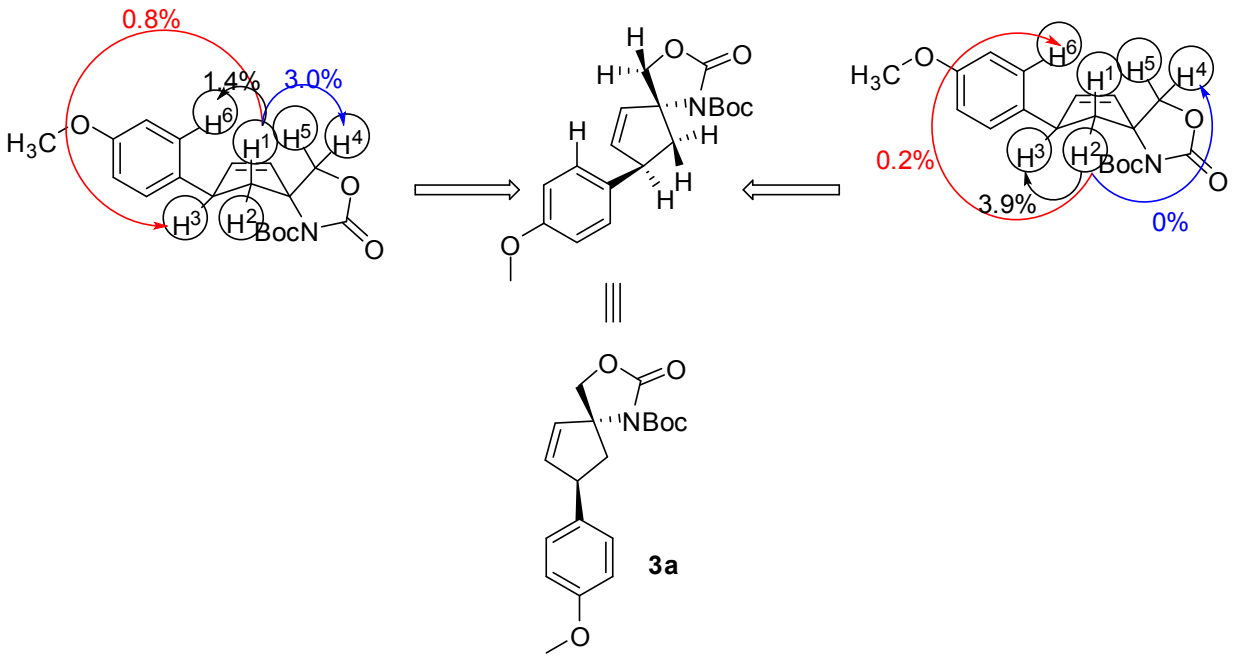
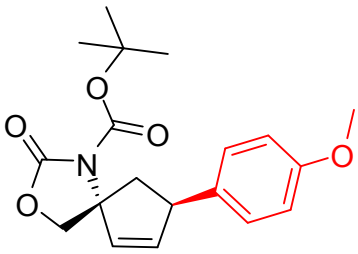


Figure 3. NOE increments and stereochemical assignment and for the Heck product **3a.**

8. Absolute Configuration of Heck product 3a

The absolute stereochemistry of the Heck product, **3a** was attributed by X-ray crystallographic analysis while all the other Heck products were attributed in analogy.



(5*R*,8*R*)-**3a**

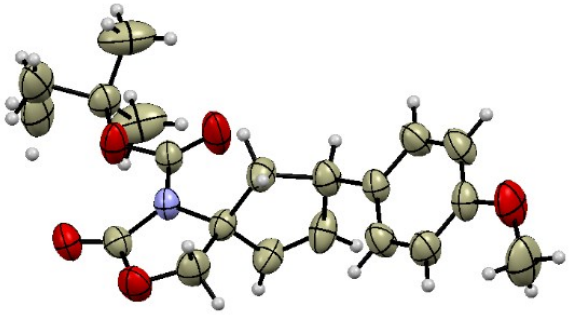


Figure 3. ORTEP illustration of compound **3a** (Thermal ellipsoids are shown with 50% probability)

8.1. X-rays Crystallographic Data for Compound 3a

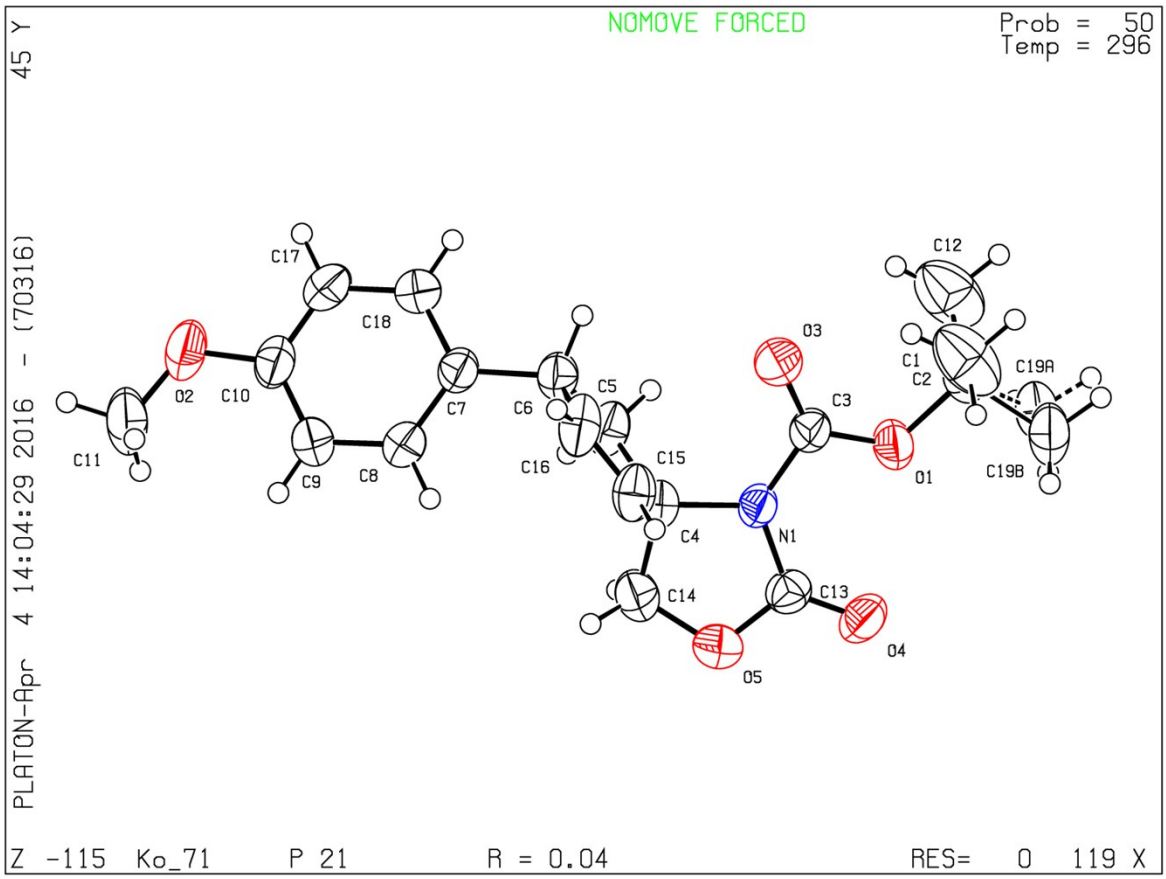
Data sets for the Heck product **3a** were collected with a Bruker APEX CCD detector diffractometer. Programs used: data collection, *APEX2* (Bruker, 2010); cell refinement: *SAINT* (Bruker, 2010); data reduction: *SAINT* (Bruker, 2010); program(s) used to solve structure: *SHELXS97*[13] (Sheldrick, 2008); program(s) used to refine structure: *SHELXL2014*/7[13]

(Sheldrick, 2014); and graphics, Mercury 3.5.1 (Build RC5, 2014). Thermals ellipsoids are shown with 50% probability, *R*-values are given for observed reflections, and wR^2 values are given for all reflections. Single-crystals were obtained from ethanol. The enantiomeric ratio was 99:1 (determined as stated for compound **3a**). Crystallographic data for structure **3a** in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication **number CCDC 1497742**

Compound-**3a**: CCDC 1497742

Formula: $C_{19}\ H_{23}\ N_1\ O_5$

Unit Cell Parameters: a 12.0073(4) b 5.9225(2) c 13.6415(4) P21



Crystal data

$C_{19}H_{23}NO_5$	$V = 913.97\ (5)$ Å^3
$M_r = 345.38$	$Z = 2$

Monoclinic, $P2_1$	Cu $K\alpha$ radiation
a = 12.0073 (4) Å	μ = 0.75 mm^{-1}
b = 5.9225 (2) Å	T = 296 K
c = 13.6415 (4) Å	0.32 × 0.32 × 0.13 mm
β = 109.584 (1)°	

Data collection

Bruker APEX CCD detector diffractometer	3241 independent reflections
Absorption correction: multi-scan *SADABS* (Bruker, 2010)	3228 reflections with $I > 2\sigma(I)$
T_{min} = 0.673, T_{max} = 0.753	R_{int} = 0.028
30012 measured reflections	θ_{max} = 68.1°

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.040	H-atom parameters constrained
$wR(F^2)$ = 0.098	$\Delta\rho_{max}$ = 0.25 e Å^{-3}
S = 1.09	$\Delta\rho_{min}$ = −0.24 e Å^{-3}
3241 reflections	Absolute structure: Flack x determined using 1404 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
242 parameters	Absolute structure parameter: 0.03 (2)
1 restraint	

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