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Conformationally restricted pyrrolidines by intramolecular [2+2] photocycloaddition reactions

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General information

All reactions, sensitive to air or moisture, were carried out in flame-dried glassware under positive pressure of argon using standard techniques.

For the photoreactions, the compounds were dissolved in the corresponding solvent, degassed by purging with Ar in an ultrasonicator for 15 minutes and irradiated in a Rayonet RPR 100 merry-go-round reactor, equipped with 16 Rayonet RPR-2537 Å lamps ($\lambda = 254$ nm). Unless otherwise stated, the reactions were stopped when the starting material was fully consumed according to thin layer chromatography (TLC) and gas chromatography (GC) analysis. The solvent was then removed and the residue was purified by column chromatography. Except as otherwise noted; only one reaction product could be determined. Typically, an immobile spot could be seen on TLC, which we tentatively attribute to polymeric side-products.

Flash chromatography was performed on silica gel 60 (Merck, 230-400 mesh) with the eluent mixtures given for the corresponding procedures.

TLC was performed on silica coated glass plates (silica gel 60 F₂₅₄). Compounds were detected by UV ($\lambda = 254$ nm), CAM (cerium ammonium molybdate solution) or KMnO₄.

All solvents for chromatography were distilled prior to use.

Analytical gas chromatography was performed at a HP 6890 Series GC (Agilent, achiral stationary phase: HP-5 column, polydimethyl/diphenyl-siloxane, 95/5) with a flame ionisation detector.

IR: JASCO IR-4100.

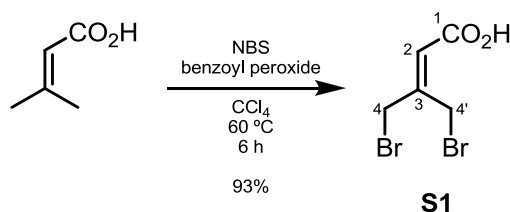
MS /HRMS: Finnigan MAT 8200.

¹H and ¹³C NMR: Bruker AV-250, AV-360 and AV-500 recorded at 300 K unless otherwise indicated. Chemical shifts are reported relative to the solvent [CHCl₃: δ (¹H) = 7.26 ppm, δ (¹³C) = 77.0 ppm, DMSO: δ (¹H) = 2.50 ppm, δ (¹³C) = 39.5 ppm] as reference. Apparent multiplets which occur as a result of accidental equality of coupling constants to those of magnetically non-equivalent protons are marked as virtual (virt.). The relative configuration of the products and the multiplicity of the ¹³C-NMR signals were determined by two-dimensional NMR spectra (COSY, NOESY, HSQC, HMBC).

Melting points were measured on a Büchi 510 and are not corrected.

Experimental procedures:

3,3-Bis(bromomethyl)acrylic acid (**S1**)^[1]



A solution of 3,3-dimethylacrylic acid (25.0 g, 0.25 mol, 1 eq) and N-bromo succinimide (NBS) (97.8 g, 0.55 mol, 2.2 eq) in CCl₄ (500 mL) was heated under reflux for three hours during which benzoyl peroxide (0.9 g) was added portion wise every 20 minutes. After six hours, the reaction mixture was allowed to cool to room temperature and the precipitated succinimide was removed by filtration. The solution was evaporated under reduced pressure to give the crude acid **S1** which was used in the next step.

R_f: 0.30 (pentane:EtOAc 1:1).

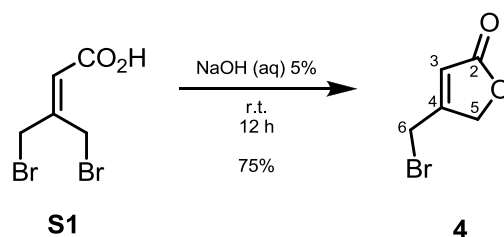
¹H NMR (360 MHz, CDCl₃): δ (ppm) 11.41 (s, 1 COOH), 6.10 (s, 1 H₂), 4.74 (s, 2 H₄), 4.22 (s, 2 H_{4'}).

¹³C NMR (91 MHz, CDCl₃): δ (ppm) 170.2 (C₁), 153.1 (C₃), 120.7 (C₂), 33.4 (C₄), 25.2 (C_{4'}).

The data obtained matched those reported in the literature.^[1]

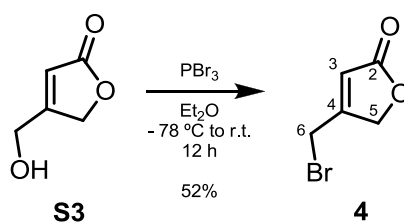
4-(Bromomethyl)furan-2(5H)-one (**4**):^[1]

Method A:



To 3,3-bis(bromomethyl)acrylic acid (**S1**) (40.0 g, 0.16 mol, 1 eq) was added at room temperature dropwise 5% NaOH (130 mL) over one hour, and the milky solution was stirred for twelve hours. The reaction mixture was extracted with CH₂Cl₂ (3 x 100 mL), and the combined extracts were washed with saturated NaHCO₃ (2 x 40 mL) and brine (2 x 100 mL) and dried over anhydrous Na₂SO₄. Concentration and purification of the residue by column chromatography (pentane:EtOAc 7:3) afforded the bromofuranone **4** as a clear yellow oil (21.1 g, 75%).

Method B:



To a solution of 4-(hydroxymethyl)furan-2(5H)-one (**S3**) (1.14 g, 10 mmol, 1 eq) in diethylether (20 ml) at -78 °C was added phosphorus tribromide (472 μ l, 5.0 mmol, 0.5 eq) in diethylether (2 ml). The mixture was warmed to room temperature and stirred for twelve hours. The reaction mixture was then poured onto ice water, diluted with diethylether and washed with brine. The combined organic phases were dried (MgSO_4), filtered and the solvent removed in vacuum to afford a light yellow oil (920 mg 52%).

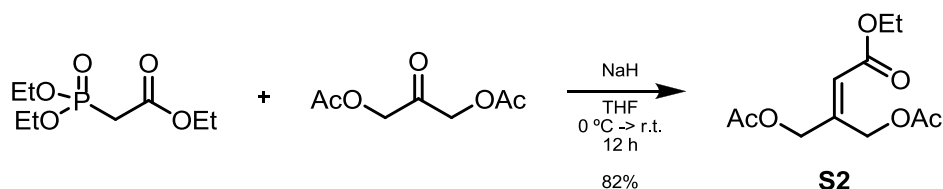
R_f : 0.32 (pentane:EtOAc 7:3).

$^1\text{H NMR}$ (360 MHz, CDCl_3): δ (ppm) 6.16 (s, 1 H_3), 4.96 (s, 2 H_5), 4.25 (s, 2 H_6).

$^{13}\text{C NMR}$ (91 MHz, CDCl_3): δ (ppm) 172.5 (C_2), 163.2 (C_4), 118.9 (C_3), 71.9 (C_5), 22.5 (C_6).

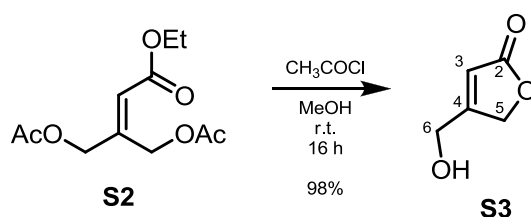
The data obtained matched those reported in the literature.^[1]

2-(2-Ethoxy-2-oxoethylidene)propane-1,3-diyl diacetate (**S2**)^[2]



To a suspension of NaH (12.1 g, 301 mmol, 1.05 eq) in THF (1.5 L) at 0 °C was added dropwise triethyl phosphonoacetate (57.5 ml, 287 mmol, 1 eq) and the mixture was stirred at 0 °C for one hour and then slowly warmed to room temperature. The resulting homogeneous yellow solution was cooled to 0 °C and 2-oxopropane-1,3-diyl diacetate (50 g, 287 mmol, 1 eq) was added slowly in one portion. The mixture was stirred at room temperature for twelve hours. Removal of the solvent in vacuum and purification by column chromatography afforded 2-(2-ethoxy-2-oxoethylidene)propane-1,3-diyl diacetate (**S2**) (57.7 g, 82%) as a colorless liquid.

4-(Hydroxymethyl)furan-2(5H)-one (**S3**)^[2]



To a solution of 2-(2-ethoxy-2-oxoethylidene)propane-1,3-diyl diacetate (**S2**) (34.9 g, 143 mmol, 1 eq) in methanol (160 ml) at room temperature was added dropwise acetyl chloride (11 ml, 143 mmol, 1 eq) and the mixture was stirred at room temperature for 16 hours. Dichloromethane was added and the combined organic phases were dried under vacuum to give 4-(hydroxymethyl)furan-2(5H)-one (**S3**) (15.8 g, 98%) as white crystals.

R_f: 0.20 (EtOAc).

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 1713 (vs, C=O), 1413 (m), 1149 (s), 1027 (m), 945 (m).

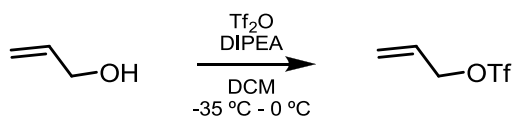
¹H NMR (360 MHz, CDCl₃): δ (ppm) 6.26-5.69 (m, 1 H₃), 4.88 (d, ⁴J = 1.7 Hz, 2 H₅), 4.62 (d, ⁴J = 3.7 Hz, 2 H₆).

¹³C NMR (91 MHz, CDCl₃): δ (ppm) 173.8 (C₂), 169.6 (C₄), 115.0 (C₃), 71.3 (C₅), 59.0 (C₆).

HRMS (ESI): Calculated for C₅H₇O₃⁺ [(M+H)]⁺ = 115.0390. Found = 115.0388.

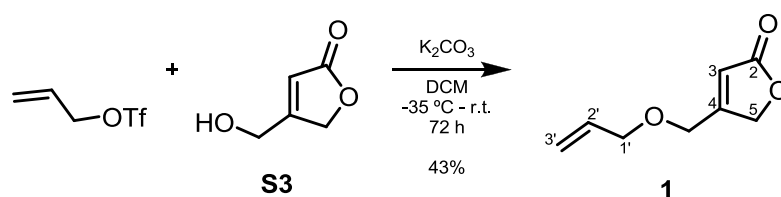
The data obtained matched those reported in the literature.^[2]

Preparation of allyltriflate:



Under argon, triflic anhydride (Tf₂O) (0.44 mL, 2.63 mmol, 5 eq) in dry CH₂Cl₂ (2 mL) was cooled to -35 °C. A solution of the alcohol (0.37 mL, 2.63 mmol, 5 eq) and *N,N*-Diisopropylethylamine (DIPEA) (0.46 mL, 2.63 mmol, 5 eq) in dry CH₂Cl₂ (2 mL) was added dropwise. After five minutes at -35 °C the solution was warmed to 0 °C for five minutes and the product used directly in the next step.

4-(Allyloxymethyl)furan-2(5H)-one (**1**)



4-(Hydroxymethyl)furan-2(5H)-one (**S3**) (60.0 mg, 0.52 mmol, 1 eq) and K_2CO_3 (432 mg, 3.12 mmol, 6 eq) were dissolved in dry CH_2Cl_2 (3 mL) and cooled to $-35\text{ }^\circ\text{C}$. A solution of allyl triflate (500 mg, 2.63 mmol, 5 eq) in dry CH_2Cl_2 (4 mL) was added slowly. The mixture was allowed to warm to room temperature and stirred for 72 hours. Evaporation to dryness and purification by column chromatography (pentane:EtOAc 1:1) afforded the expected product **1** (35.0 mg, 43%).

$R_f = 0.62$ (pentane:EtOAc 1:1).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2970 (s, C-H), 1760 (s, C=O), 1466 (s), 1406 (m), 1378 (m), 1340 (s), 1306 (s), 1160 (m), 1128 (m), 1106 (s), 982 (w), 816 (m).

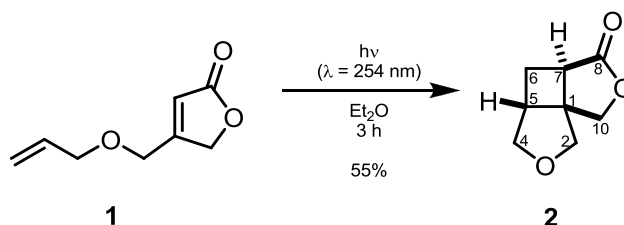
$^1\text{H NMR}$ (360 MHz, $CDCl_3$): δ (ppm) 6.08-6.01 (m, 1 H_3), 5.92 (ddt, $^3J = 17.1\text{ Hz}$, $^3J = 10.4\text{ Hz}$, $^3J = 5.7\text{ Hz}$, 1 H_2), 5.36-5.24 (m, 2 H_3'), 4.91-4.81 (m, 2 H_5), 4.44-4.34 (m, CH_2), 4.08 (dt, $^3J = 5.7\text{ Hz}$, $^4J = 1.4\text{ Hz}$, 2 H_1').

$^{13}\text{C NMR}$ (91 MHz, $CDCl_3$): δ (ppm) 173.3 (C_2), 166.4 (C_4), 133.5 (C_2'), 118.2 (C_3'), 116.0 (C_3), 72.2 (C_1'), 71.4 (C_5), 65.5 (CH_2).

MS (EI, 70 eV): m/z (%) = 154 (81) [M^+], 125 (30) [$(M-CH_2O)^+$], 98 (100) [$(M-C_2H_2O_2)^+$], 82 (15) [$(M-C_2H_2O_3)^+$], 79 (35).

HRMS (ESI): Calculated for $C_8H_{10}O_3^+ [(M)]^+ = 154.0630$. Found = 154.0628.

3,9-Dioxatricyclo[5.3.0.0^{1,5}]decan-8-one (**2**)



The compound was prepared from tetronate **1** (33.0 mg, 0.10 mmol) in 43 mL of Et_2O by irradiation for three hours (5 mM). Purification of the crude by column chromatography (pentane:EtOAc 1:1) afforded the photoproduct **2** as an oil (18.0 mg, 55%).

$R_f = 0.40$ (pentane:EtOAc 1:1).

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 2970 (s, C-H), 1755 (s, C=O), 1467 (w), 1375 (m), 1283 (w), 1170 (m), 1152 (m), 1130 (m), 1101 (m), 1054 (s), 950 (m), 904 (m), 817 (w).

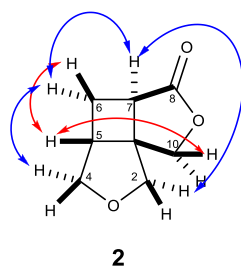
¹H NMR (500 MHz, CDCl₃): δ (ppm) 4.45 (d, ²J = 9.8 Hz, 1 H₁₀), 4.19 (d, ²J = 9.8 Hz, 1 H₁₀), 4.11 (d, ²J = 9.9 Hz, 1 H₂), 3.95 (d, ²J = 9.7 Hz, 1 H₄), 3.69 (dd, ²J = 9.7 Hz, ³J = 5.2 Hz, 1 H₄), 3.41 (d, ²J = 9.9 Hz, 1 H₂), 2.99 (dt, ³J = 8.0 Hz, ³J = 5.2 Hz, 1 H₅), 2.93 (ddd, ³J = 9.8 Hz, ³J = 3.9 Hz, ⁴J = 1.1 Hz, 1 H₇), 2.36-2.23 (m, 2 H₆).

¹³C NMR (91 MHz, CDCl₃): δ (ppm) 179.5 (C₈), 74.2 (C₄), 71.5 (C₂), 70.8 (C₁), 52.3 (C₁₀), 43.0 (C₅), 39.5 (C₇), 27.0 (C₆).

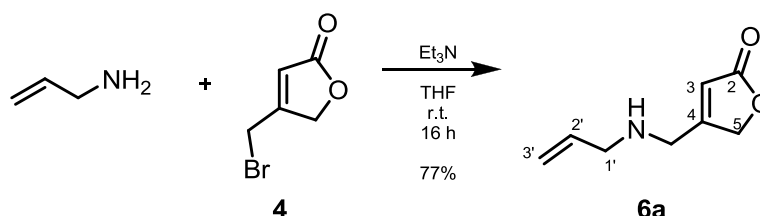
MS (EI, 70 eV): m/z (%) = 154 (55) [M⁺], 125 (30) [(M-CH₂O)⁺], 110 (4), [(M-CO₂)⁺], 98 (70) [(M-C₂H₂O₂)⁺], 82 (50) [(M-C₂H₂O₃)⁺], 79 (74), 41 (100).

HRMS (ESI): Calculated for C₈H₁₀O₃⁺ [(M)]⁺ = 154.0630. Found = 154.0631.

Important NOE contacts:



4-(Allylamino)methylfuran-2(5H)-one (6a**)**



To a solution of bromide **4** (600 mg, 3.41 mmol, 1 eq) in THF (20 mL) was added Et₃N (0.52 mL, 3.75 mmol, 1.1 eq) and finally allylamine (0.28 mL, 3.75 mmol, 1.1 eq). The resulting solution was stirred at room temperature for 16 hours. Water was added and the aqueous layer extracted with EtOAc, dried over Na₂SO₄ and filtered. The solvent was removed and the residue purified by column chromatography (pentane:EtOAc 1:3) to obtain amine **6a** as an orange oil (403 mg, 77%).

R_f: 0.12 (pentane:EtOAc 1:3).

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 1745 (vs, C=O), 1643 (w), 1416 (m), 1226 (m), 1168 (s), 1132 (m), 1024 (vs), 921 (m), 842 (w).

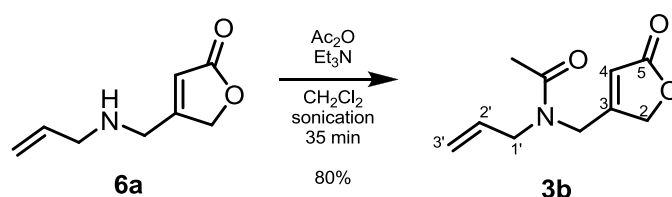
¹H NMR (360 MHz, CDCl₃): δ (ppm) 6.15-6.02 (m, 1 H₃), 5.80 (ddt, ³J = 16.7 Hz, ³J = 10.5 Hz, ³J = 6.3 Hz, 1 H₂), 5.34-5.22 (m, 2 H_{3'}), 4.81 (d, ⁴J = 1.7 Hz, 2 H₅), 3.49 (s, CH₂), 3.13 (d, ³J = 6.3 Hz, 2 H_{1'}).

¹³C NMR (91 MHz, CDCl₃): δ (ppm) 172.9 (C₂), 166.8 (C₄), 133.2 (C_{2'}), 119.8 (C_{3'}), 117.9 (C₃), 72.0 (C₅), 57.5, 51.8 (C_{1'}, CH₂).

MS (EI, 70 eV): *m/z* (%) = 154 [(M+H)⁺]

HRMS (ESI): Calculated for C₈H₁₂NO₂⁺ [(M+H)⁺] = 154.0863. Found = 154.0861.

N-allyl-N-((5-oxo-2,5-dihydrofuran-3-yl)methyl)acetamide (**3b**)



To the amine **6a** (153 mg, 1 mmol, 1 eq) in dry CH₂Cl₂ (10 mL) was added Et₃N (0.15 mL, 1.1 mmol, 1.1 eq) and the mixture was cooled to 0 °C. Ac₂O (0.11 mL, 1.1 mmol, 1.1 eq) was added slowly. The reaction was warmed to room temperature and sonicated for 30 minutes. 0.02 mL of Ac₂O was added and sonicated for further five minutes. The solution was diluted with CH₂Cl₂, washed with 0.2 M HCl, water and brine. The organic layer was dried over Na₂SO₄, filtered and evaporated to dryness. Column chromatography (pentane:EtOAc 1:1) afforded the acetyl protected product **3b** as a light orange oil (156 mg, 80%).

R_f: 0.19 (pentane:EtOAc 1:1).

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 1777 (vs, C=O), 1634 (w), 1470 (m), 1409 (s), 1359 (s), 1246 (m), 1169 (s), 1127 (m), 1025 (vs), 922 (m), 886 (w).

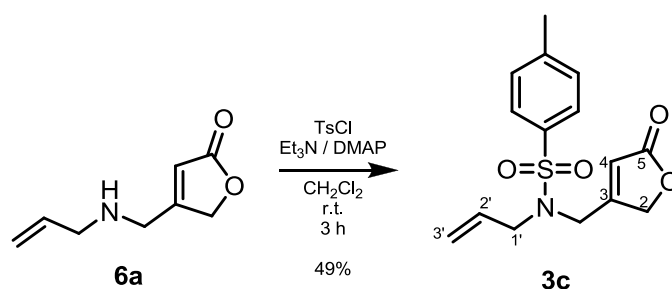
¹H NMR (360 MHz, CDCl₃): δ (ppm) 5.94-5.86 (m, 1 H₄), 5.78 (ddt, ³J = 17.0 Hz, ³J = 10.3 Hz, ³J = 5.1 Hz, 1 H₂), 5.32-5.15 (m, 2 H_{3'}), 4.79-4.76 (m, 2 H₂), 4.32 (s, CH₂), 3.94 (dd, ³J = 5.1 Hz, ⁴J = 3.6 Hz, 2 H_{1'}), 2.15 (s, CH₃).

¹³C NMR (91 MHz, CDCl₃): δ (ppm) 173.1 (C₅), 171.3 (COCH₃), 165.7 (C₃), 131.7 (C_{2'}), 117.9, 117.1 (C_{3'}, C₄), 72.2 (C₂), 51.4 (C_{1'}), 43.2 (CH₂), 21.0 (CH₃).

MS (EI, 70 eV): *m/z* (%) = 176 (35) [(M)⁺], 153 (55) [(M-Ac)⁺], 112 (63) [(M-C₅H₈O)⁺], 98 (34) [(M-C₅H₈NO)⁺], 56 (68) [(M-C₈H₁₂NO)⁺], 43 (100).

HRMS (ESI): Calculated for C₈H₁₂NO₂⁺ [(M-Ac + 2H)]⁺ = 154.0863. Found = 154.0865.

N-allyl-4-methyl-N-((5-oxo-2,5-dihydrofuran-3-yl)methyl)benzenesulfonamide (**3c**)



4-[(Allylamino)methyl]furan-2(5H)-one (**6a**) (90.0 mg, 0.59 mmol, 1 eq) was dissolved in CH_2Cl_2 (3 mL). Tosyl-Cl (123 mg, 0.65 mmol, 1.1 eq), Et_3N (0.25 mL, 1.76 mmol, 3 eq) and 4-DMAP (7.18 mg, 58.8 μmol , 0.1 eq) were added and the reaction mixture was stirred at room temperature for three hours. The solvent was evaporated and the residue purified by column chromatography to obtain N-allyl-4-methyl-N-[(5-oxo-2,5-dihydrofuran-3-yl)methyl]benzenesulfonamide (**3c**) (89.0 mg, 49%) as a dark brown oil.

R_f : 0.32 (heptane:EtOAc 1:1).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 1778 (vs, C=O), 1741 (s), 1559 (w), 1472 (m), 1338 (m), 1173 (s), 1147 (s).

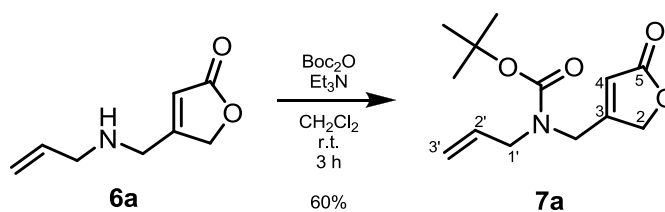
^1H NMR (500 MHz, CDCl_3): δ (ppm) 7.71 (virt. d, $J = 8.3$ Hz, 2 H_{Ph}), 7.35 (virt. dd, $J = 8.3$ Hz, $^4J = 0.7$ Hz, 2 H_{Ph}), 5.92-5.90 (m, 1 H_4), 5.61-5.56 (ddt, $^3J = 17.1$ Hz, $^3J = 9.8$ Hz, $^3J = 5.7$ Hz, 1 H_2), 5.21-5.14 (m, 2 $\text{H}_{3'}$), 4.82 (s, 2 H_2), 4.11 (s, CH_2), 3.80 (d, $^3J = 5.7$ Hz, 2 $\text{H}_{1'}$), 2.46 (s, CH_3).

^{13}C NMR (91 MHz, CDCl_3): δ (ppm) 172.9 (C_3), 165.1 (C_5), 144.3 (C_{ipso}), 135.8 (C_{ipso}), 135.8 (C_2), 131.8 (C_{Ph}), 127.2 (C_{Ph}), 120.8 (C_3), 118.2 (C_4), 72.0 (C_2), 51.6 ($\text{C}_{1'}$), 44.6 (CH_2), 21.6 (Me).

MS (EI, 70 eV): m/z (%) = 308 (100) [(M+H) $^+$].

HRMS (ESI): Calculated for $\text{C}_{15}\text{H}_{17}\text{NO}_4\text{S}^+$ [(M+H) $^+$] = 308.0957. Found = 308.0951

tert-Butyl allyl((5-oxo-2,5-dihydrofuran-3-yl)methyl)carbamate (**7a**)



To a solution of the amine **6a** (153 mg, 1 mmol, 1 eq) in dry CH_2Cl_2 (10 mL) was added Et_3N (0.15 mL, 1.1 mmol, 1.1 eq) and Boc_2O (240 mg, 1.1 mmol, 1.1 eq). The resulting solution was stirred at room temperature for three hours. After that time, the solvent was removed under reduced pressure

and the residue purified by column chromatography (pentane:EtOAc 3:7) to afford the boc-protected product **7a** as an orange oil (152 mg, 60%).

R_f: 0.75 (pentane:EtOAc 3:7).

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 2978 (s, C-H), 1779 (vs, C=O), 1748 (m), 1688 (w), 1455 (s), 1403 (m), 1366 (m), 1246 (m), 1162 (m), 1140 (m), 1118 (m), 1069 (s), 925 (m), 872 (w).

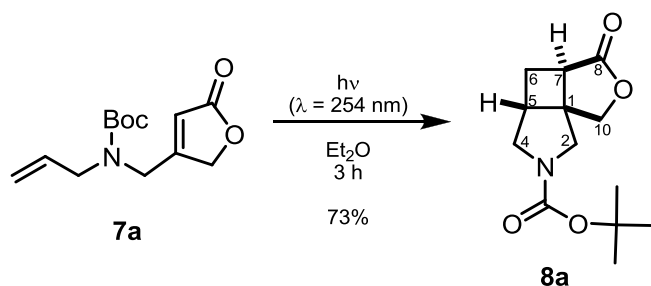
¹H NMR (250 MHz, CDCl₃): δ (ppm) 5.91-5.83 (m, 1 H₄), 5.73 (ddt, ³J = 16.4 Hz, ³J = 10.4 Hz, ³J = 5.9 Hz, 1 H₂), 5.21-5.01 (m, 2 H₃), 4.73 (d, ⁴J = 1.2 Hz, 2 H₂), 4.15 (s, CH₂), 3.91-3.76 (m, 2 H₁), 1.49 [s, 9 C(CH₃)₃].

¹³C NMR (91 MHz, CDCl₃): δ (ppm) 173.1 (C₅), 166.7 (COO^tBu), 155.3 (C₃), 133.0 (C₂), 117.6 (C₃), 116.6 (C₄), 81.0 [C(CH₃)₃], 71.9 (C₂), 50.3 (C₁), 44.2 (CH₂), 28.2 [C(CH₃)₃].

MS (EI, 70 eV): *m/z* (%) = 197 (36) [(M-C₄H₇)⁺], 153 (16) [(M-C₅H₉O)⁺], 112 (32) [(M-C₈H₁₄O₂)⁺], 57 (77) [(M-C₁₁H₁₈NO₂)⁺], 41 (100) [(M-C₃H₅)⁺].

HRMS (EI, 70 eV): Calculated for C₁₃H₁₉NO₄⁺ [(M)]⁺ = 253.1309. Found = 253.1304.

N-tert-butoxycarbonyl-3-aza-9-oxatricyclo[5.3.0.0^{1,5}]decan-8-one (**8a**)



The compound was prepared from tetronate **7a** (100 mg, 0.39 mmol) in 80 mL of Et₂O by irradiation for three hours (5 mM). Purification of the crude by column chromatography (pentane:EtOAc 1:1) afforded the photoproduct **8a** as a white solid (73.1 mg, 73%).

M.P.: (97-99) °C

R_f = 0.57 (pentane:EtOAc 1:1).

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 1755 (vs, C=O), 1692 (w), 1471 (m), 1397 (s), 1229 (m), 1161 (s), 1135 (m), 1011 (vs), 970 (m), 875 (m).

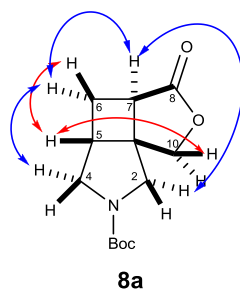
¹H NMR (500 MHz, CDCl₃): δ (ppm) 4.39 (d, ²J = 9.8 Hz, 1 H₁₀), 4.16 (d, ²J = 9.8 Hz, 1 H₁₀), 3.95-3.92 (br. s, 1 H₂), 3.73-3.58 (br. s, 1 H₄), 3.30 (dd, ²J = 11.8 Hz, ³J = 6.5 Hz, 1 H₄), 3.07 (d, ²J = 12.2 Hz, 1 H₂), 2.97-2.86 (m, 1 H₇, 1 H₅), 2.36 (ddd, ²J = 12.9 Hz, ³J = 8.5 Hz, ³J = 6.7 Hz, 1 H₆), 2.22 (ddd, ²J = 12.9 Hz, ³J = 8.5 Hz, ³J = 3.5 Hz, 1 H₆), 1.49 [s, 9 C(CH₃)₃].

^{13}C NMR (91 MHz, CDCl_3): δ (ppm) 179.3 (C_8), 155.0 ($\text{COO}t\text{Bu}$), 80.1 [$\text{C}(\text{CH}_3)_3$], 72.5 (C_{10}), 52.2 (C_4), 50.8 (C_2), 39.9 (C_7 , C_5), 28.4 [$\text{C}(\text{CH}_3)_3$], 27.6 (C_6). (C_1 not observed)

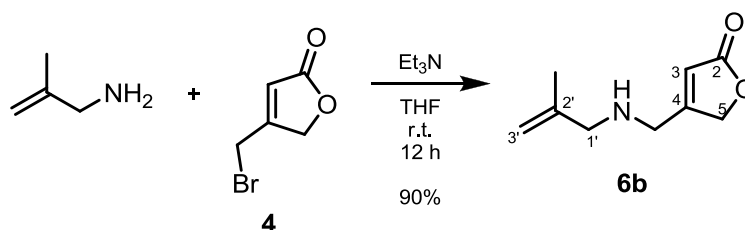
MS (EI, 70 eV): m/z (%) = 197 (31) [$(\text{M}-\text{C}_4\text{H}_7)^+$], 153 (26) [$(\text{M}-\text{C}_5\text{H}_9\text{O})^+$], 57 (100) [$(\text{M}-\text{C}_{11}\text{H}_{18}\text{NO}_2)^+$].

HRMS (ESI): Calculated for $\text{C}_{13}\text{H}_{20}\text{NO}_4^+$ [$(\text{M}+\text{H})^+$] = 254.1387. Found = 254.1390.

Important NOE contacts:

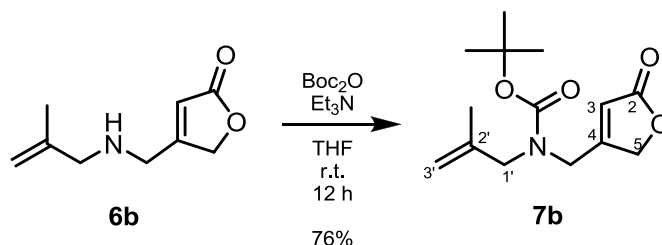


4-[(2-Methylallylamino)methyl]furan-2(5H)-one (6b)



To a solution of bromide **4** (397 mg, 2.26 mmol, 1 eq) in THF (15 mL) was added Et_3N (0.35 mL, 2.48 mmol, 1.1 eq) and finally methylallylamine (0.22 mL, 2.48 mmol, 1.1 eq). The resulting solution was stirred at room temperature for twelve hours. Water was added and the aqueous layer extracted with EtOAc , dried over Na_2SO_4 , filtered and evaporated to dryness to obtain the product as an oil (340 mg, 90%). This product (**6b**) was used for protection reactions without further purification.

***tert*-Butyl 2-methylallyl[(5-oxo-2,5-dihydrofuran-3-yl)methyl]carbamate (7b)**



To a solution of amine **6b** (333 mg, 1.99 mmol, 1 eq) in dry THF (10 mL) was added Et_3N (0.33 mL, 2.39 mmol, 1.2 eq) and Boc_2O (478 mg, 2.19 mmol, 1.1 eq). The resulting solution was stirred at room temperature for twelve hours. After that time, the solvent was removed under reduced pressure

and the residue purified by column chromatography (pentane:EtOAc 1:1) to afford the Boc-protected product **7b** as an orange oil (403 mg, 76%).

R_f: 0.77 (pentane:EtOAc 1:1).

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 2979 (w, C-H), 1779 (w), 1749 (m, C=O), 1693 (w), 1369 (m), 1242 (w), 1211 (w), 1161 (m), 1113 (s), 1063 (s), 1028 (m).

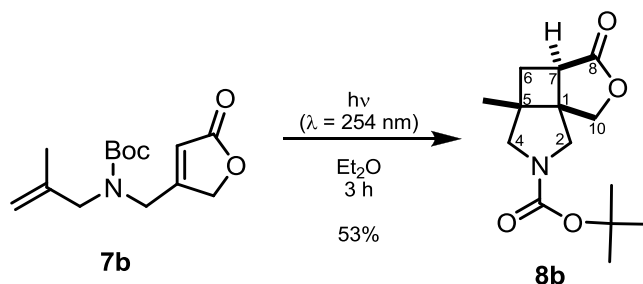
¹H NMR (500 MHz, CDCl₃): δ (ppm) 6.10-5.82 (m, 1 H_{3'}), 5.06-4.91 (m, 1 H₃), 4.89-4.78 (m, 1 H₃, 2 H₅), 4.34-4.07 (m, 2 H_{1'}), 3.97-3.67 (m, CH₂), 1.77 (s, CH₃), 1.73 [s, 9 C(CH₃)₃]. *Rotamers*

¹³C NMR (91 MHz, CDCl₃): δ (ppm) 173.3 (C₂), 167.7 (COO^tBu), 154.6 (C₄), 133.6 (C_{2'}), 117.8 (C_{3'}), 115.7 (C₃), 81.3 [C(CH₃)₃], 72.2 (C₅), 50.5 (C_{1'}), 43.9 (CH₂), 27.9 [C(CH₃)₃], 21.0 (CH₃).

MS (EI, 70 eV): m/z (%) = 267 (3) [(M)⁺], 211 (55) [(M-C₅H₇)⁺], 194 (15), 167 (25) [(M-C₅H₉O₂)⁺], 112 (45), 96 (20), 57 (100), 55 (35), 41 (45) [(M-C₁₁H₁₆NO₄)⁺].

HRMS (EI, 70 eV): Calculated for C₁₄H₂₁NO₄ = 267.1465. Found = 267.1464.

N-tert-butoxycarbonyl-5-methyl-3-aza-9-oxatricyclo[5.3.0.0^{1,5}]decan-8-one (8b)



The compound was prepared from tetronate **7b** (60.0 mg, 0.22 mmol) in 45 mL of Et₂O by irradiation for three hours (5 mM). Purification of the crude by column chromatography (pentane:EtOAc 1:1) afforded the photoproduct **8b** as a white solid (31.8 mg, 53%).

M.P.: 123 °C

R_f: 0.57 (pentane:EtOAc 1:1).

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 2971 (w, C-H), 1755 (s, C=O), 1697 (s), 1389 (s), 1363 (m), 1241 (s), 1138 (s), 1013 (s), 878 (m).

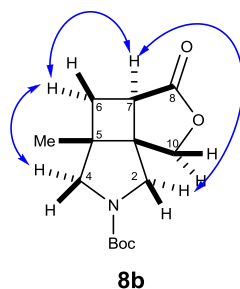
¹H NMR (500 MHz, CDCl₃): δ (ppm) 4.40 (d, ²J = 10.2 Hz, 1 H₁₀), 4.09 (d, ²J = 10.2 Hz, 1 H₁₀), 4.02-3.90 (m, 1 H₄), 3.82-3.64 (m, 1 H₂), 3.06 (d, ²J = 12.1 Hz, 1 H₄), 2.89 (d, ²J = 11.6 Hz, 1 H₂), 2.86 (dd, ³J = 10.2 Hz, ³J = 3.6 Hz, 1 H₇), 2.42 (dd, ²J = 12.9 Hz, ³J = 10.2 Hz, 1 H₆), 1.99 (dd, ²J = 12.9 Hz, ³J = 3.6 Hz, 1 H₆), 1.50 [s, 9 C(CH₃)₃], 1.27 (s, CH₃).

^{13}C NMR (91 MHz, CDCl_3): δ (ppm) 179.6 (C_8), 154.8 (COO^tBu), 80.2 [$\text{C}(\text{CH}_3)_3$], 68.4 (C_{10}), 59.0 (C_4), 51.3 (C_2), 44.8 (C_5), 42.1 (C_1), 38.1 (C_7), 34.2 (C_6), 28.4 [$\text{C}(\text{CH}_3)_3$], 19.2 (CH_3).

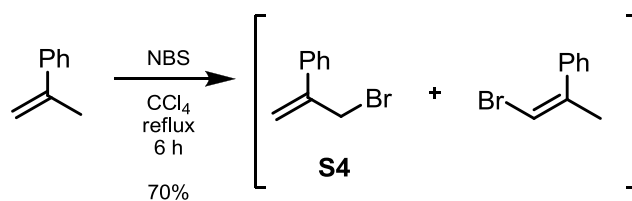
MS (EI, 70 eV): m/z (%) = 212 (40) [$(\text{M}-\text{C}_4\text{H}_7)^+$], 167 (15) [$(\text{M}-\text{C}_5\text{H}_9\text{O})^+$], 57 (100) [$(\text{M}-\text{C}_{11}\text{H}_{18}\text{NO}_2)^+$], 41 (23).

HRMS (EI, 70 eV): Calculated for $\text{C}_{14}\text{H}_{21}\text{NO}_4$ = 267.1465. Found = 267.1467.

Important NOE contacts:

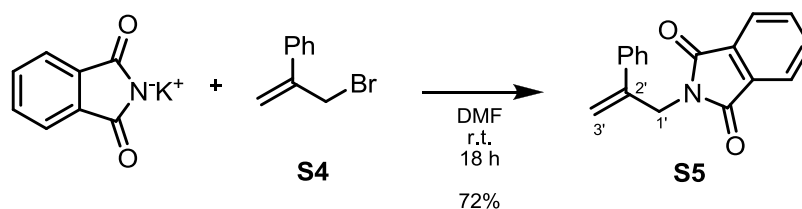


(3-Bromoprop-1-en-2-yl)benzene (S4)^[3]



A mixture of α -methylstyrene (3.00 g, 25.4 mmol, 1 eq) and NBS (5.42 g, 30.5 mmol, 1.2 eq) were suspended in CCl_4 (60 mL) and heated under reflux for six hours. After that time, the mixture was cooled and the precipitated succinimide was separated by filtration and the solvent and the excess of α -methylstyrene removed under reduced pressure. Of the 4.21 g of the clear yellow oil obtained, GC-MS analysis indicated a ca. 3:1 ratio of product to 1-bromo-2-phenyl-1-propene. This product (**S4**) was used without further purification (3.50 g, 70%).

2-(2-Phenylallyl)isoindoline-1,3-dione (S5)^[4]



Potassium phthalimide (2.58 g, 13.9 mmol, 1.1 eq) was added to a solution of **S4** (2.5 g, 12.7 mmol, 1 eq) in DMF (35 mL) at room temperature. The resulting mixture was stirred for 18 hours, after which

time a dark brown colour was formed and a white precipitate observed. Dichloromethane (30 mL) was added and the mixture poured onto water (100 mL). The aqueous phase was separated and extracted with dichloromethane (3x). The combined organic extract was then washed with NaOH aq (0.2 M) and dried with anhydrous sodium sulfate. The dichloromethane was removed in vacuo and the residue purified by column chromatography (pentane:EtOAc 7:3) to afford the protected product **S5** as white needles (2.39 g, 72%).

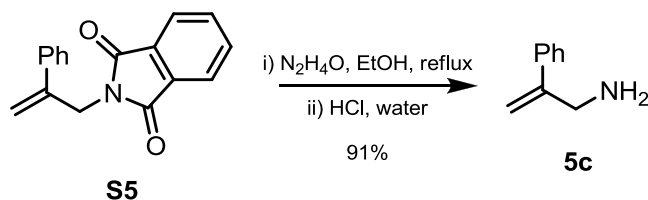
M.P.: 117 °C (*lit.* 118-119 °C).^[4]

¹H NMR (360 MHz, CDCl₃): δ (ppm) 7.78 (dd, ³J = 5.4 Hz, ⁴J = 3.1 Hz, 2 H_{PhH}), 7.63 (dd, ³J = 5.4 Hz, ⁴J = 3.1 Hz, 2 H_{PhH}), 7.31-7.13 (m, 5 H_{Ph}), 6.53 (d, ²J = 16 Hz, 1 H_{3'}), 6.19 (dt, ²J = 16 Hz, ⁴J = 6.5 Hz, 1 H_{3'}), 4.37 (d, ⁴J = 6.5 Hz, 2 H_{1'})

¹³C NMR (91 MHz, CDCl₃): δ (ppm) 176.9 (C=O), 136.2 (C_{2'}), 133.9 (C_{m-Ph}), 133.7 (C_{i-Ph}), 132.2 (C_{i-Ph}), 128.5 (C_{m-Ph}), 127.8 (C_{p-Ph}), 126.5 (C_{o-Ph}), 122.9 (C_{3'}), 39.7 (C_{1'}).

The data obtained matched those reported in the literature.^[4]

2-Phenylprop-2-en-1-amine (**5c**)^[4]

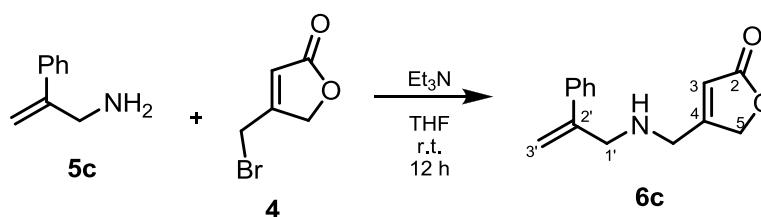


Hydrazine hydrate (1.64 mL, 33.8 mmol, 5 eq) was added to a suspension of **S5** (1.78 g, 6.77 mmol, 1 eq) in ethanol (120 mL). The resulting mixture was heated under reflux for one hour. Then HCl aq. (2.0 M) (12 mL) was added and the reaction heated for a further one hour. The reaction mixture was then cooled to 4 °C and the phthalyl hydrazide removed by filtration. The ethanol was removed in vacuum and the solid residue was redissolved in 20 mL NaOH aq. (2.0 M). The solution was extracted with diethyl ether (5x) and the organic extract was dried (Na₂SO₄), filtered and the solvent removed to give the product **5c** as a colourless oil (819 mg, 91%).

¹H NMR (360 MHz, CDCl₃): δ (ppm) 7.31-7.13 (m, 5 H_{Ph}), 6.43 (br. d, ²J = 16 Hz, 1 H_{3'}), 6.23 (dt, ²J = 16 Hz, ⁴J = 6.0 Hz, 1 H_{3'}), 3.52 (d, ⁴J = 6.0 Hz, 2 H_{1'}), 1.47 (br. s, 2 NH)

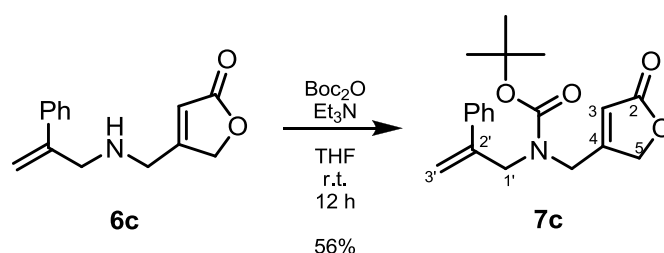
The data obtained matched those reported in the literature.^[4]

4-[(2-Phenylallyl)amino]methylfuran-2(5H)-one (**6c**)



To a solution of bromide **4** (313 mg, 1.76 mmol, 1 eq) in THF (20 mL) was added triethylamine (0.37 mL, 2.64 mmol, 1.5 eq) and finally phenylallylamine (235 mg, 1.76 mmol, 1 eq). The resulting solution was stirred at room temperature for twelve hours. Water was added and the aqueous layer extracted with EtOAc, dried over Na₂SO₄, filtered and evaporated to dryness. This product (**6c**) was used for protection reactions without further purification.

tert-Butyl 2-phenylallyl[(5-oxo-2,5-dihydrofuran-3-yl)methyl]carbamate (**7c**)



To a solution of the amine **6c** (200 mg, 0.873 mmol, 1 eq) in dry THF (10 mL) was added triethylamine (0.18 mL, 1.31 mmol, 1.5 eq) and Boc₂O (210 mg, 0.96 mmol, 1.1 eq). The resulting solution was stirred at room temperature for twelve hours. After that time, the solvent was removed under reduced pressure and the residue purified by column chromatography (pentane:EtOAc 3:7) to afford the Boc-protected product **7c** as an orange oil (160 mg, 56%).

*R*_f: 0.55 (pentane:EtOAc 3:7).

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 2976 (m, C-H), 2830 (w, C-H), 1778 (s, C=O), 1747 (s, C=O), 1688 (s), 1644 (m, C=C), 1365 (m), 1242 (m), 1160 (s), 781 (m), 700 (m).

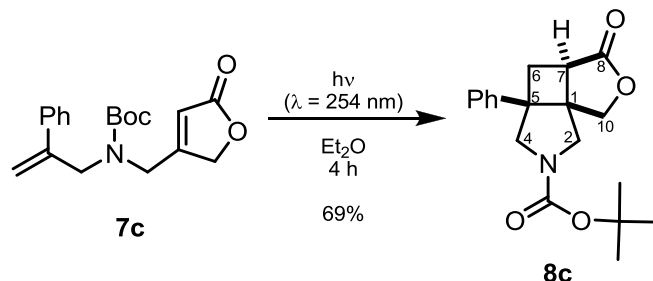
¹H NMR (500 MHz, DMSO-*d*₆): δ (ppm) 7.48-7.41 (m, 2 H_{Ph}), 7.41-7.25 (m, 3 H_{Ph}), 5.86-5.77 (m, 1 H₃), 5.55-5.43 (m, 1 H_{3'}), 5.25-5.15 (m, 1 H_{3'}), 4.60-4.45 (m, 2 H₅), 4.40-4.30 (m, 2 H_{1'}), 4.20-4.06 (m, 2 CH₂), 1.39 [s, 9 C(CH₃)₃]. **Rotamers**

¹³C NMR (91 MHz, DMSO-*d*₆): δ (ppm) 173.5 (C₂), 166.7 (COO^{*t*}Bu), 133.9 (C_{Ph}), 131.7 (C_{Ph}), 129.0 (C_{ipso}), 126.8 (C_{Ph}), 117.7 (C₃), 116.0 (C_{3'}), 81.2 [C(CH₃)₃], 71.8 (C₅), 51.3 (C_{1'}), 43.7 (CH₂), 28.6 [C(CH₃)₃]. C_{2'} and C₄ not shown

MS (EI, 70 eV): *m/z* (%): 330 (15) [(M+H)⁺], 274 (100) [(M-C₄H₈)⁺].

HRMS (EI, 70 eV): Calculated for $C_{19}H_{24}NO_4$ $[(M+H)^+]$ = 330.1705. Found = 330.1701.

N-tert-butoxycarbonyl-5-phenyl-3-aza-9-oxatricyclo[5.3.0.0^{1,5}]decan-8-one (8c)



The compound was prepared from tetronate **7c** (100 mg, 0.30 mmol) in 61 mL of Et_2O by irradiation for four hours (5 mM). Purification of the crude by column chromatography (pentane:EtOAc 1:1) afforded the photoproduct **8b** as a white solid (69.1 mg, 69%).

M.P.: 65 °C

R_f: 0.49 (pentane:EtOAc 1:1).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2976 (w, C-H), 2930 (w), 1778 (s, C=O), 1747 (vs), 1688 (vs), 1365 (m), 1242 (s), 1160 (vs), 781 (s, arom), 700 (s, arom).

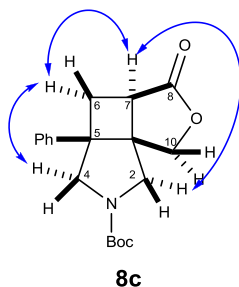
¹H NMR (500 MHz, CDCl_3): δ (ppm) 7.43-7.39 (m, 3 H_{Ph}), 7.19-7.13 (m, 2 H_{Ph}), 4.19 (d, $^2J = 10.1$ Hz, 1 H_{10}), 4.07 (d, $^2J = 10.1$ Hz, 1 H_{10}), 4.11-3.97 (m, 1 H_4), 3.82-3.64 (m, 1 H_2), 3.52 (d, $^2J = 12.1$ Hz, 1 H_4), 3.33 (d, $^2J = 11.9$ Hz, 1 H_2), 3.01 (dd, $^3J = 9.9$ Hz, $^3J = 4.6$ Hz, 1 H_7), 2.93 (dd, $^2J = 12.9$ Hz, $^3J = 4.6$ Hz, 1 H_6), 2.64 (dd, $^2J = 12.9$ Hz, $^3J = 9.9$ Hz, 1 H_6), 1.50 [s, 9 $\text{C}(\text{CH}_3)_3$].

¹³C NMR (91 MHz, CDCl_3): δ (ppm) 178.5 (C_8), 130.3 (C_{Ph}), 129.1 (C_{Ph}), 127.4 (C_{ipso}), 126.7 (C_{Ph}), 80.5 [$\text{C}(\text{CH}_3)_3$], 68.6 (C_{10}), 59.1 (C_4), 51.7 (C_2), 38.1 (C_5), 35.5 (C_7), 33.4 (C_1), 29.7 (C_6), 28.5 [$\text{C}(\text{CH}_3)_3$].

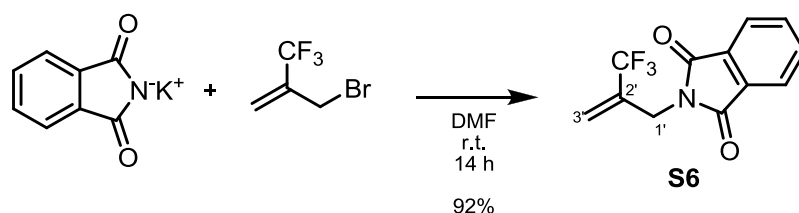
MS (EI, 70 eV): m/z (%): 352 (100) $[(M+\text{Na})^+]$, 330 (13) $[(M+H)^+]$, 274 (74) $[(M-\text{C}_4\text{H}_8)^+]$.

HRMS (EI, 70 eV): Calculated for $C_{19}H_{24}NO_4$ $[(M+H)^+]$ = 330.1705. Found = 330.1701.

Important NOE contacts:



2-(2-Trifluoromethyl-allyl)isoindoline-1,3-dione (S6)



Potassium phthalimide (1.47 g, 7.94 mmol, 1.5 eq) was added to a solution of 2-(bromomethyl)-3,3,3-trifluoroprop-1-ene (1.00 g, 5.29 mmol, 1 eq) in DMF (12 mL) at room temperature. The resulting mixture was stirred for 14 hours, after which time a dark brown colour was formed and a white precipitate observed. Dichloromethane (12 mL) was added and the mixture poured onto water (12 mL). The aqueous phase was separated and extracted with dichloromethane (3x). The combined organic extract was then washed with NaOH aq (0.2 M) and dried with anhydrous sodium sulfate. The dichloromethane was removed in vacuo and the residue purified by column chromatography (hexane:EtOAc 1:1) to afford the protected product **S6** as white solid (1.24 g, 92%).

M.P.: (83-85) °C.

R_f: 0.53 (Hexane:EtOAc 1:1).

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 3099 (w), 2922 (s, C-H), 1754 (vs, C=O), 1636 (m, C=C), 1321 (m, C-F), 1109 (s), 733 (s, Pht), 712 (s, Pht).

¹H NMR (360 MHz, CDCl₃): δ (ppm) 7.89 (dd, ³J = 5.4 Hz, ⁴J = 2.7 Hz, 2 H_{Pht}), 7.78 (dd, ³J = 5.4 Hz, ⁴J = 2.7 Hz, 2 H_{Pht}), 5.88 (br. s, 1 H_{3'}), 5.56 (br. s, 1 H_{3'}), 4.48 (s, 2 H_{1'}).

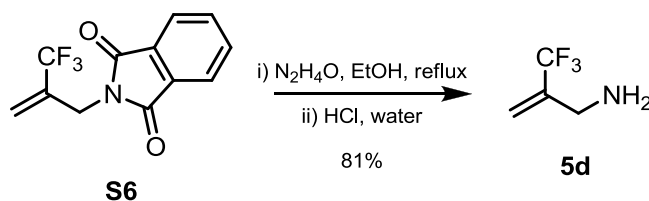
¹³C NMR (91 MHz, CDCl₃): δ (ppm) 167.3 (C=O), 134.4 (C_{m-pht}), 133.2-132.8 (m, C_{2'}), 131.8 (C_{i-pht}), 123.6 (C_{p-pht}), 121.1-121.0 (m, C_{3'}), 36.4 (C_{1'}).

¹⁹F NMR (235 MHz, CDCl₃): δ (ppm) -67.9.

MS (EI, 70 eV): *m/z* (%) = 255 (100) [(M)⁺], 235 (75) [(M-HF)⁺], 186 (39) [(M-CF₃)⁺], 160 (62), 104 (51), 76 (48).

HRMS (EI, 70 eV): Calculated for C₁₂H₉F₃NO₂ [(M+H)⁺] = 256.0585. Found = 256.0581.

2-Trifluoromethyl-prop-2-en-1-amine (5d)



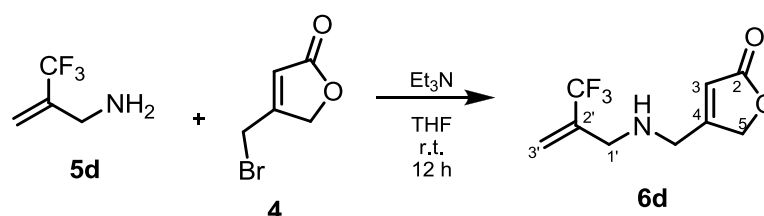
Hydrazine hydrate (1.35 mL, 27.9 mmol, 5 eq) was added to a suspension of **S6** (1.42 g, 5.59 mmol, 1 eq) in ethanol (25 mL). The resulting mixture was heated under reflux for one hour. Then HCl aq. (2.0 M) (17.0 mL) was added and the reaction heated for a further one hour. The reaction mixture was then cooled to 4 °C and the phthalyl hydrazide removed by filtration. The ethanol was removed in vacuo and the solid residue was redissolved in 20 mL NaOH aq. (2.0 M). The solution was extracted with diethyl ether (5x) and the organic extract was dried (Na₂SO₄), filtered and the solvent removed to give product **5d** as a colourless oil (569 mg, 81%).

¹H NMR (250 MHz, CDCl₃): δ (ppm) 6.10 (br. s, 1 H_{3'}), 5.85 (br. s, 1 H_{3'}), 3.80 (br. s, 2 H_{1'}).

¹⁹F NMR (235 MHz, CDCl₃): δ (ppm) -67.8.

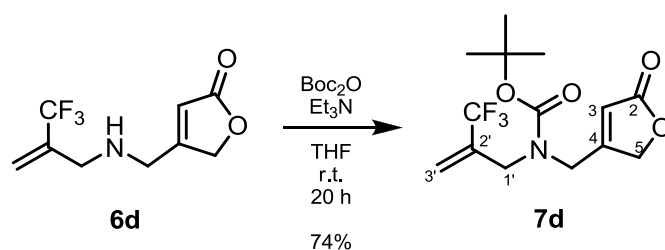
MS (EI, 70 eV): *m/z* (%) = 126 (100) [(M+H)⁺].

4-[(2-Trifluoromethyl-allylamino)methyl]furan-2(5H)-one (**6d**)



To a solution of bromide **4** (1.06 g, 6.00 mmol, 1 eq) in THF (35 mL) was added triethylamine (3.35 mL, 24.0 mmol, 4 eq) and finally trifluoromethyl-allylamine (970 mg, 6.19 mmol, 1 eq). The resulting solution was stirred at room temperature for twelve hours. Water was added and the aqueous layer extracted with EtOAc, dried over Na₂SO₄, filtered and evaporated to dryness. This product (**6d**) was used for protection reactions without further purification.

tert-Butyl 2-trifluoromethyl-allyl[(5-oxo-2,5-dihydrofuran-3-yl)methyl]carbamate (**7d**)



To a solution of amine **6d** (55.0 mg, 0.25 mmol, 1 eq) in dry THF (1 mL) was added triethylamine (40.0 μL, 0.28 mmol, 1.1 eq) and Boc₂O (60.0 mg, 0.28 mmol, 1.1 eq). The resulting solution was stirred at room temperature for 20 hours. After that time, the solvent was removed under reduced

pressure and the residue purified by column chromatography (pentane:EtOAc 1:1) to afford the Boc-protected product **7d** as a colourless oil (59.1 mg, 74%).

R_f: 0.41 (pentane:EtOAc 1:1).

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 1740 (s, C=O), 1669 (s, C=O), 1665 (w, C=C), 1321 (m, C-F), 893 (w, C=C).

¹H NMR (500 MHz, CDCl₃): δ (ppm) 5.93 (s, 1 H₃), 5.87 (br. s, 1 H_{3'}), 5.44 (br. s, 1 H_{3''}), 4.78 (s, 2 H₅), 4.21 (br. s, 1 H_{1'}), 4.03 (br. s, CH₂). *Rotamers*

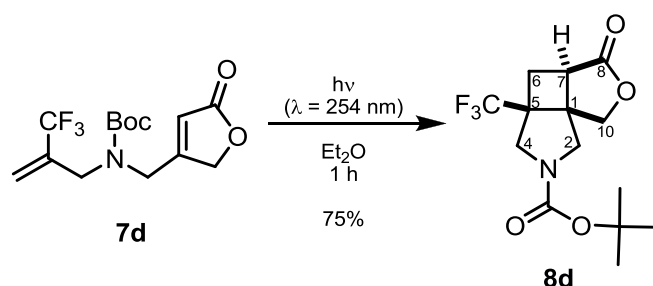
¹⁹F NMR (235 MHz, CDCl₃): δ (ppm) -67.7.

¹³C NMR (91 MHz, CDCl₃): δ (ppm) 165.5 (C₂), 158.1 (C₄), 146.8 (COO^tBu), 119.8 (C₃), 117.2 (C_{3'}), 81.9 [C(CH₃)₃], 71.9 (C₅), 46.6 (CH₂), 44.3 (C_{1'}), 28.1 [C(CH₃)₃].

MS (EI, 70 eV): m/z (%) = 265 (15) [(M-C₄H₈)⁺], 221 (13) [(M-C₃H₈O₂)⁺], 57 (100), 41 (8).

HRMS (EI, 70 eV): Calculated for C₁₄H₂₂F₃N₂O₄ [(M+NH₄⁺)] = 339.1532. Found = 339.1529.

N-tert-butoxycarbonyl-5-trifluoromethyl-3-aza-9-oxatricyclo[5.3.0.0^{1,5}]decan-8-one (8d)



The compound was prepared from tetronate **7d** (64.0 mg, 0.20 mmol) in 40 mL of Et₂O by irradiation for one hour (5 mM). Purification of the crude by column chromatography (pentane:EtOAc 1:1) afforded the photoproduct **8d** as a white solid (49.9 mg, 75%).

M.P.: (124-126) °C

R_f: 0.47 (pentane:EtOAc 1:1).

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 3971 (w, C-H), 1763 (s, C=O), 1666 (s, C=O), 1321 (m, C-F).

¹H NMR (500 MHz, CDCl₃): δ (ppm) 4.64 (d, ²J = 11.1 Hz, 1 H₁₀), 4.14 (d, ²J = 10.2 Hz, 1 H₁₀), 4.02-3.92 (br. s, 1 H₄), 3.89-3.80 (br. s, 1 H₂), 3.46 (d, ²J = 11.9 Hz, 1 H₂), 3.16 (d, ²J = 12.1 Hz, 1 H₄), 2.96 (dd, ³J = 10.3 Hz, ³J = 4.4 Hz, 1 H₇), 2.61 (ddd, ²J = 13.1 Hz, ³J = 4.4 Hz, ⁴J_(F) = 1.0 Hz, 1 H₆), 2.46 (dd, ²J = 13.1 Hz, ³J = 10.3 Hz, 1 H₆), 1.50 [s, 9 C(CH₃)₃].

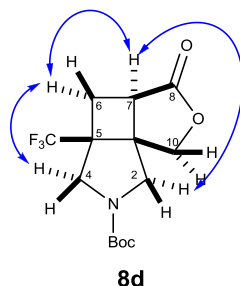
¹⁹F NMR (235 MHz, CDCl₃): δ (ppm) -72.3.

^{13}C NMR (151 MHz, CDCl_3): δ (ppm) 176.0 (C_8), 153.6 (COO^tBu), 123.9 (q, $^1J_{\text{F}} = 278.4$ Hz, CF_3), 80.2 [$\text{C}(\text{CH}_3)_3$], 66.9 (C_{10}), 51.5 (C_4), 51.1 (C_2), 37.0 (C_7), 27.3 [$\text{C}(\text{CH}_3)_3$], 27.2 (C_6).

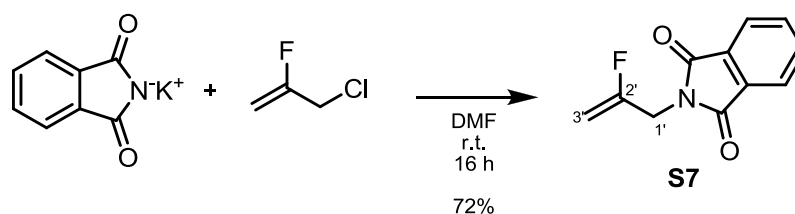
MS (EI, 70 eV): m/z (%) = 321 (13) [$(\text{M})^+$], 266 (15) [$(\text{M}-\text{C}_4\text{H}_7)^+$], 248 (25), 57 (100), 41 (11).

HRMS (EI, 70 eV): Calculated for $\text{C}_{14}\text{H}_{22}\text{F}_3\text{N}_2\text{O}_4$ [$(\text{M}+\text{H})^+$] = 322.1266. Found = 322.1262.

Important NOE contacts:



2-(2-Fluoroallyl)isoindoline-1,3-dione (S7)^[5]



Potassium phthalimide (11.7 g, 63.0 mmol, 1.5 eq) was added to a solution of 3-chloro-2-fluoroprop-1-ene (3.97 g, 42.0 mmol, 1 eq) in DMF (92 mL) at room temperature. The resulting mixture was stirred for 16 hours. Dichloromethane (50 mL) was added and the mixture poured onto water (50 mL). The aqueous phase was separated and extracted with dichloromethane (3x). The combined organic extract was then washed with NaOH aq (0.2 M) and dried with anhydrous sodium sulfate. The dichloromethane was removed in vacuo and the residue purified by column chromatography (heptane:EtOAc 1:1) to afford the protected product **S7** as white solid (6.20 g, 72%).

M.P.: (79-80) °C.

R_f: 0.37 (heptane:EtOAc 1:1).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 1772 (vs, C=O), 1719 (s), 1678 (s, C=C), 1612 (w), 1254 (m), 845 (s, C=C), 731 (s, Pht).

^1H NMR (250 MHz, CDCl_3): δ (ppm) 7.89 (dd, $^3J = 5.4$ Hz, $^4J = 3.0$ Hz, 2 H_{Pht}), 7.75 (dd, $^3J = 5.4$ Hz, $^4J = 3.0$ Hz, 2 H_{Pht}), 4.76 (dd, $^3J_{\text{F}} = 16.1$ Hz, $^2J = 3.4$ Hz, 1 $\text{H}_{3'}$), 4.56 (dd, $^3J_{\text{F}} = 47.5$ Hz, $^2J = 3.5$ Hz, 1 $\text{H}_{3'}$), 4.41 (d, $^3J_{\text{F}} = 12.1$ Hz, 2 $\text{H}_{1'}$).

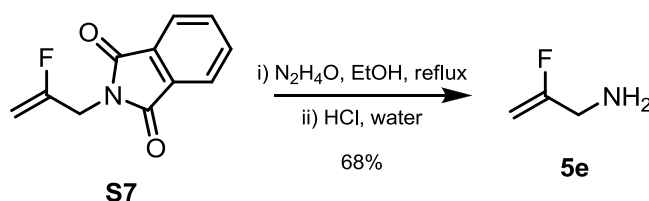
^{19}F NMR (235 MHz, CDCl_3): δ (ppm) -103.6 (ddt, $^3J = 48.8$ Hz, $^3J = 16.8$ Hz, $^3J = 11.5$ Hz).

^{13}C NMR (91 MHz, CDCl_3): δ (ppm) 164.3 (C=O), 159.1 (d, $^1J_{\text{F}} = 260$ Hz, $\text{C}_{2'}$), 134.2 ($\text{C}_{m\text{-pht}}$), 131.9 ($\text{C}_{i\text{-pht}}$), 123.6 ($\text{C}_{p\text{-pht}}$), 93.0 (d, $^2J_{\text{F}} = 17.3$ Hz, $\text{C}_{3'}$), 37.9 (d, $^2J_{\text{F}} = 35.5$ Hz, $\text{C}_{1'}$).

MS (EI, 70 eV): m/z (%) = 205 (95) [(M) $^+$], 185 (100) [(M-HF) $^+$], 157 (20), 130 (11), 104 (32), 76 (42).

HRMS (EI, 70 eV): Calculated for $\text{C}_{11}\text{H}_9\text{FNO}_2$ [(M+H) $^+$] = 206.0617. Found = 206.0612.

2-Fluoroprop-2-en-1-amine (5e)^[6]



Hydrazine hydrate (2.39 mL, 48.7 mmol, 2 eq) was added to a suspension of **S7** (5.00 g, 24.4 mmol, 1 eq) in ethanol (120 mL). The resulting mixture was heated under reflux for one hour. Then HCl aq. (2.0 M) (73 mL) was added and the reaction heated for a further one hour. The reaction mixture was then cooled to 4 °C and the phthalyl hydrazide removed by filtration. The ethanol was removed in vacuo and the solid residue was redissolved in 100 mL NaOH aq. (2.0 M). The solution was extracted with diethyl ether (5x) and the organic extract was dried (Na_2SO_4), filtered and the solvent removed to give product **5e** as a colourless oil (1.23 g, 68%).

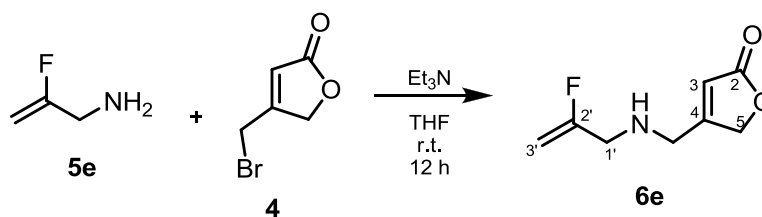
^1H NMR (250 MHz, CDCl_3): δ (ppm) 4.61 (dd, $^3J_{\text{F}} = 16.6$ Hz, $^2J = 4.0$ Hz, 1 $\text{H}_{3'}$), 4.51 (dd, $^3J_{\text{F}} = 48.5$ Hz, $^2J = 4.0$ Hz, 1 $\text{H}_{3'}$), 3.33 (d, $^3J_{\text{F}} = 16.0$ Hz, 2 $\text{H}_{1'}$).

^{19}F NMR (235 MHz, CDCl_3): δ (ppm) -104.1 (ddt, $^3J = 48.1$ Hz, $^3J = 19.1$ Hz, $^3J = 11.4$ Hz).

^{13}C NMR (91 MHz, CDCl_3): δ (ppm) 157.8 (d, $^1J_{\text{F}} = 254$ Hz, $\text{C}_{2'}$), 97.4 (d, $^2J_{\text{F}} = 16$ Hz, $\text{C}_{3'}$), 40.3 (d, $^2J_{\text{F}} = 33$ Hz, $\text{C}_{1'}$).

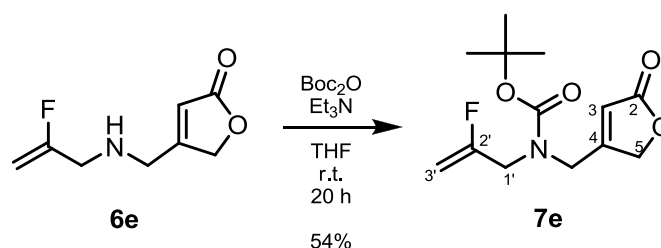
The data obtained matched those reported in the literature.^[6]

4-[(2-Fluoroallylamino)methyl]furan-2(5H)-one (6e)



To a solution of bromide **4** (100 mg, 0.21 mmol, 1 eq) in THF (2 mL) was added triethylamine (60 μ L, 0.43 mmol, 2 eq) and finally fluoroallylamine (**5e**) (16.0 mg, 0.21 mmol, 1 eq). The resulting solution was stirred at room temperature for twelve hours. Water was added and the aqueous layer extracted with EtOAc, dried over Na₂SO₄, filtered and evaporated to dryness. This product (**6e**) was used for protection reactions without further purification.

tert-Butyl 2-fluoroallyl[(5-oxo-2,5-dihydrofuran-3-yl)methyl]carbamate (7e)



To a solution of amine **6e** (68.0 mg, 0.40 mmol, 1 eq) in dry THF (2 mL) was added triethylamine (60 μ L, 0.44 mmol, 1.1 eq) and Boc₂O (95.0 mg, 0.44 mmol, 1.1 eq). The resulting solution was stirred at room temperature for 20 hours. After that time, the solvent was removed under reduced pressure and the residue purified by column chromatography (pentane:EtOAc 1:1) to afford the Boc-protected product **7e** as a yellow oil (58.0 mg, 54%).

R_f: 0.39 (pentane:EtOAc 1:1).

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 2974 (m, C-H), 1740 (vs, C=O), 1699 (s), 1665 (w) 1651 (w), 1308 (m), 1120 (s), 1101 (s) 881 (m).

¹H NMR (500 MHz, DMSO-d₆): δ (ppm) 5.94 (br. s, 1 H₃), 4.84 (br. s, 2 H₅), 4.76 (dd, ³J_F = 17.1 Hz, ²J = 3.2 Hz, 1 H_{3'}), 4.47 (dd, ³J_F = 50.0 Hz, ²J = 3.2 Hz, 1 H_{3'}), 4.23 (br. s, CH₂), 3.99 (br. d, ³J_F = 10.5 Hz, 2 H_{1'}), 1.40 [s, 9 C(CH₃)₃].

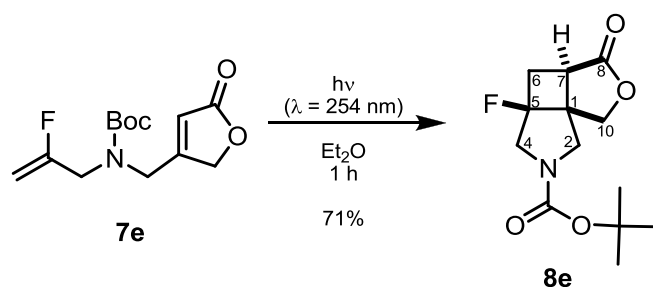
¹⁹F NMR (235 MHz, DMSO-d₆): δ (ppm) -109.1 (ddt, ³J = 50.0 Hz, ³J = 17.1 Hz, ³J = 10.5 Hz).

¹³C NMR (91 MHz, DMSO-d₆): δ (ppm) 173.6 (C₂), 169.3 (C₄), 169.1 (COO^tBu), 115.1 (C₃), 93.4 (d, ²J_F = 16.2 Hz, C_{3'}), 80.6 [C(CH₃)₃], 72.1 (C₅), 47.4 (d, ²J_F = 26.1 Hz, C_{1'}), 45.2 (CH₂), 28.2 [C(CH₃)₃].

MS (EI, 70 eV): m/z (%) = 272 (21) [(M+H)⁺], 216 (100) [(M-C₄H₈)⁺], 172 (10).

HRMS (EI, 70 eV): Calculated for C₁₃H₁₉FNO₄ [(M+H)⁺] = 272.1298. Found = 272.1294

N-tert-butoxycarbonyl-5-fluoromethyl-3-aza-9-oxatricyclo[5.3.0.0^{1,5}]decan-8-one (8e)



The compound was prepared from tetronate **7e** (52.0 mg, 0.19 mmol) in 40 mL of Et₂O by irradiation for one hour (5 mM). Purification of the crude by column chromatography (pentane:EtOAc 1:1) afforded the photoproduct **8e** as a colourless oil (36.7 mg, 71%).

R_f: 0.43 (pentane:EtOAc 1:1).

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 2968 (w), 1764 (m, C=O), 1692 (s, C=O), 1411 (s), 1171 (s), 876 (w).

¹H NMR (500 MHz, CDCl₃): δ (ppm) 4.76 (d, ²J = 10.5 Hz, 1 H₁₀), 4.19 (d, ²J = 10.5 Hz, 1 H₁₀), 3.97-3.87 (br. m, 1 H₄, 1 H₂), 3.52 (ddd, ³J_F = 21.6 Hz, ²J = 12.4 Hz, ⁴J = 1.2 Hz, 1 H₄), 3.28 (d, ²J = 12.1 Hz, 1 H₂), 2.87-2.81 (m, 1 H₆), 2.75-2.70 (m, 1 H₇), 2.61 (dddd, ³J_F = 18.7 Hz, ²J = 13.1 Hz, ³J = 5.7 Hz, ⁴J = 1.2 Hz, 1 H₆), 1.50 [s, 9 C(CH₃)₃].

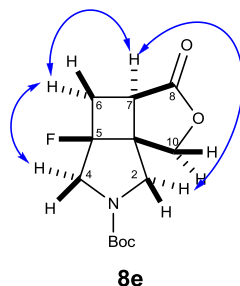
¹⁹F NMR (235 MHz, DMSO-d₆): δ (ppm) -106.3.

¹³C NMR (91 MHz, DMSO-d₆): δ (ppm) 177.0 (C₈), 154.1 (COO^tBu), 144.1 (m, C₅), 80.2 [C(CH₃)₃], 66.5 (C₁₀), 56.2 (m, C₄), 51.3 (m, C₂), 35.2 (d, ²J_F = 27.5 Hz, C₆), 34.4 (d, ³J_F = 9.1 Hz, C₇), 28.4 [C(CH₃)₃].

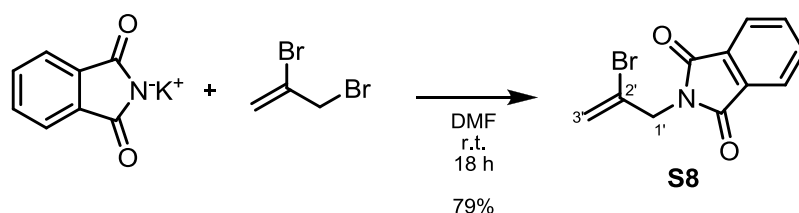
MS (EI, 70 eV): m/z (%) = 272 (100) [(M+H)⁺], 216 (51) [(M-C₄H₈)⁺].

HRMS (EI, 70 eV): Calculated for C₁₃H₁₉FNO₄ [(M+H)⁺] = 272.1298. Found = 272.1293

Important NOE contacts:



2-(2-Bromoallyl)isoindoline-1,3-dione (**S8**)^[7]



Potassium phthalimide (5.56 g, 30.0 mmol, 1.2 eq) was added to a solution of 2,3-dibromoprop-1-ene (5.00 g, 25.0 mmol, 1 eq) in DMF (55 mL) at room temperature. The resulting mixture was stirred for 18 hours, after which time a dark brown colour was formed and a white precipitate observed. Dichloromethane (50 mL) was added and the mixture poured onto water (50 mL). The aqueous phase was separated and extracted with dichloromethane (3x). The combined organic extract was then washed with NaOH aq (0.2 M) and dried with anhydrous sodium sulfate. The dichloromethane was removed in vacuo and the residue purified by column chromatography (pentane:EtOAc 1:1) to afford the protected product **S8** as white solid (5.30 g, 79%).

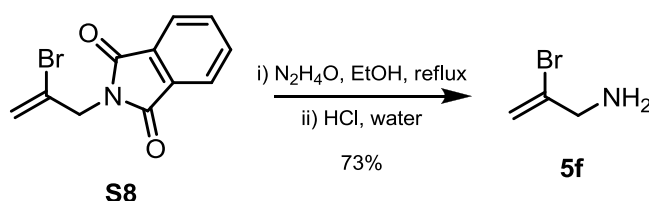
R_f: 0.65 (pentane:EtOAc 1:1).

¹H NMR (250 MHz, CDCl₃): δ (ppm) 7.91 (dd, ³J = 5.1 Hz, ⁴J = 3.3 Hz, 2 H_{PhH}), 7.75 (dd, ³J = 5.1 Hz, ⁴J = 3.3 Hz, 2 H_{PhH}), 5.86-5.84 (m, 1 H_{3'}), 5.64-5.62 (m, 1 H_{3'}), 4.55 (t, ³J = 1.1 Hz, 2 H_{1'}).

MS (EI, 70 eV): *m/z* (%) = 264 and 266.

The data obtained matched those reported in the literature.^[7]

2-Bromoprop-2-en-1-amine (**5f**)^[8]



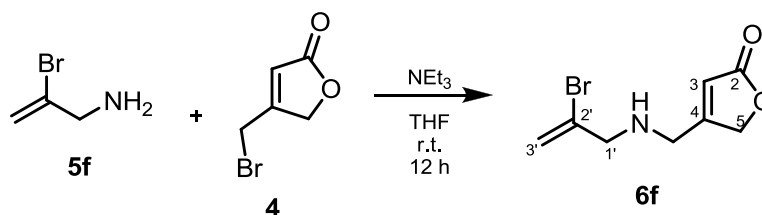
Hydrazine hydrate (0.21 mL, 4.14 mmol, 2 eq) was added to a suspension of **S8** (550 mg, 2.07 mmol, 1 eq) in ethanol (7.0 mL). The resulting mixture was heated under reflux for one hour. Then HCl aq. (2.0 M) (6.0 mL) was added and the reaction heated for a further one hour. The reaction mixture was then cooled to 4 °C and the phthalyl hydrazide removed by filtration. The ethanol was removed in vacuo and the solid residue was redissolved in 10 mL NaOH aq. (2.0 M). The solution was extracted with diethyl ether (5x) and the organic extract was dried (Na₂SO₄), filtered and the solvent removed to give product **5f** as a colourless oil (518 mg, 73%).

$^1\text{H NMR}$ (250 MHz, CDCl_3): δ (ppm) 5.78 (br. s, 1 H_3), 5.47 (br. s, 1 H_3), 3.47 (t, $^3J = 1.0$ Hz, 2 H_1).

MS (EI, 70 eV): m/z (%) = 136 and 138.

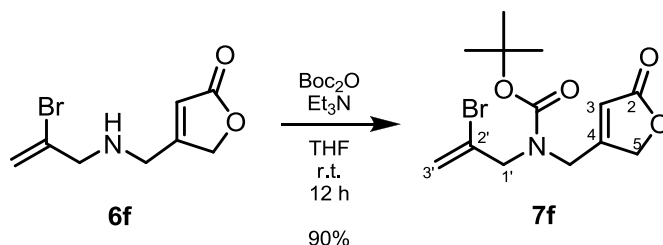
The data obtained matched those reported in the literature.^[8]

4-[(2-Bromoallyl)amino]methylfuran-2(5H)-one (**6f**)



To a solution of bromide **4** (150 mg, 0.85 mmol, 1 eq) in THF (5 mL) was added triethylamine (153 μL , 1.1 mmol, 1.3 eq) and finally 2-bromoprop-2-en-1-amine (115 mg, 0.85 mmol, 1 eq). The resulting solution was stirred at room temperature for twelve hours. Water was added and the aqueous layer extracted with EtOAc, dried over Na_2SO_4 , filtered and evaporated to dryness. This product (**6f**) was used for protection reactions without further purification.

tert-Butyl 2-bromoallyl[(5-oxo-2,5-dihydrofuran-3-yl)methyl]carbamate (**7f**)



To a solution of amine **6f** (130 mg, 0.56 mmol, 1 eq) in dry THF (2 mL) was added triethylamine (155 μL , 1.12 mmol, 2 eq) and Boc_2O (122 mg, 0.56 mmol, 1.1 eq). The resulting solution was stirred at room temperature for twelve hours. After that time, the solvent was removed under reduced pressure and the residue purified by column chromatography (pentane:EtOAc 1:1) to afford the Boc-protected product **7f** as an oil (167 mg, 90%).

R_f : 0.51 (pentane:EtOAc 1:1).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2974 (m, C-H), 1764 (s, C=O), 1692 (vs, C=O), 1335 (m), 1150 (s), 1011 (vs).

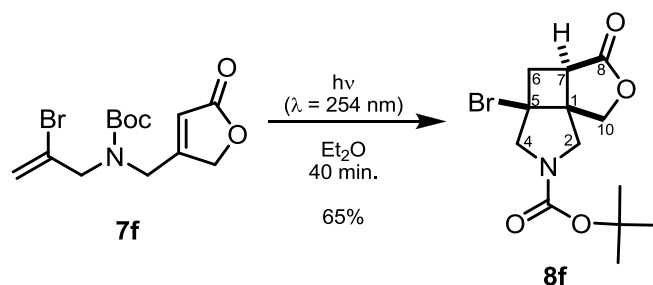
$^1\text{H NMR}$ (500 MHz, CDCl_3): δ (ppm) 5.93 (s, 1 H_3), 5.79 (br. s, 1 H_3), 5.44 (br. s, 1 H_3), 4.80 (s, 2 H_5), 4.25 (br. s, 2 H_1), 4.08 (br. s, CH_2), 1.49 [s, 9 $\text{C}(\text{CH}_3)_3$]. *Rotamers*

¹³C NMR (91 MHz, CDCl₃): δ (ppm) 173.1 (C₂), 160.1 (C₄), 155.0 (COO*t*Bu), 128.9 (CH₂), 119.4 (C₃), 116.9 (C₃), 81.8 [C(CH₃)₃], 72.0 (C₅), 55.2 (CH₂), 44.3 (C₁), 26.4 [C(CH₃)₃]. *Rotamers*

MS (EI, 70 eV): *m/z* (%) = 275, 277 (5) [(M-C₄H₈)⁺], 196 (100) [(M-C₄H₈Br)⁺], 152 (23) [(M-C₅H₈BrO)⁺], 12 (41), 57 (90), 41 (12).

HRMS (EI, 70 eV): Calculated for C₁₃H₁₈BrNO₄ = 331.0419 and 333.0399. Found = 331.0416 and 333.0408.

N-tert-butoxycarbonyl-5-bromomethyl-3-aza-9-oxatricyclo[5.3.0.0^{1,5}]decan-8-one (8f)



The compound was prepared from tetronate **7f** (120 mg, 0.36 mmol) in 72 mL of Et₂O by irradiation for 40 minutes (5 mM). Purification of the crude by column chromatography (pentane:EtOAc 1:1) afforded the photoproduct **8f** as a white solid (77.8 mg, 65%).

M.P.: 134 °C

R_f: 0.29 (pentane:EtOAc 1:1).

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 2978 (w, C-H), 1780 (s, C=O), 1743 (vs), 1689 (s, C=O), 1367 (m), 1251 (m), 1160 (s), 879 (s).

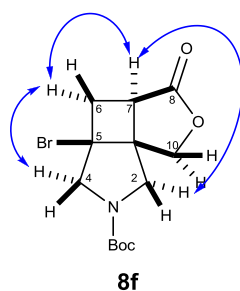
¹H NMR (500 MHz, CDCl₃): δ (ppm) 4.75 (d, ²*J* = 10.5 Hz, 1 H₁₀), 4.29 (d, ²*J* = 10.5 Hz, 1 H₁₀), 4.26-4.25 (br. s, 1 H₄), 4.02-3.97 (br. s, 1 H₂), 3.60 (d, ²*J* = 12.3 Hz, 1 H₄), 3.16 (d, ²*J* = 12.2 Hz, 1 H₂), 3.01-2.96 (m, 1 H₇, 1 H₆), 2.80 (dd, ²*J* = 9.8 Hz, ³*J* = 1.1 Hz, 1 H₆), 1.49 [s, 9 C(CH₃)₃]. *Rotamers*

¹³C NMR (91 MHz, CDCl₃): δ (ppm) 177.4 (C₈), 154.0 (COO*t*Bu), 110.1 (C₅), 81.1 [C(CH₃)₃], 70.6 (C₁₀), 61.6 (C₄), 50.5 (C₂), 40.0 (C₆), 38.7 (C₄), 28.3 [C(CH₃)₃]. *Rotamers*

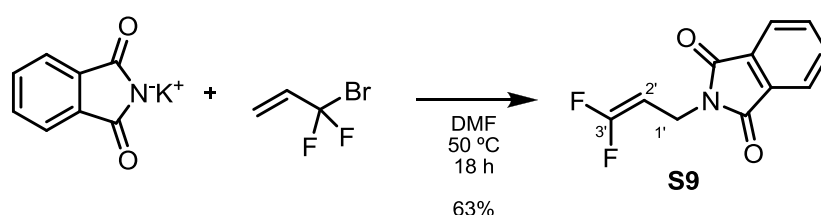
MS (EI, 70 eV): *m/z* (%) = 276 and 278 (100) [(M-C₄H₈)⁺].

HRMS (EI, 70 eV): Calculated for C₁₃H₁₉BrNO₄ = 332.0497 and 334.0477. Found = 332.0492 and 334.0472.

Important NOE contacts:



2-(3,3-Difluoroallyl)isoindoline-1,3-dione (S9)



Potassium phthalimide (1.18 g, 6.37 mmol, 1.3 eq) was added to a solution of 3-bromo-3,3-difluoroprop-1-ene (772 mg, 4.92 mmol, 1 eq) in DMF (10 mL) at room temperature in a sealed tube. The resulting mixture was stirred for 18 hours at 50 °C. The mixture was poured onto water (10 mL), the aqueous phase was separated and extracted with ethyl acetate (3x). The combined organic extract was dried with anhydrous sodium sulfate, the solvent removed in vacuo and the residue purified by column chromatography (pentane:EtOAc 1:1) to afford the protected product **S9** as white solid (684 mg, 63%).

M.P.: 83 °C

R_f: 0.46 (pentane:EtOAc 1:1).

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 3099 (w, C-H), 1773 (s, C=O), 1706 (vs), 1634 (s), 1321 (m), 898 (C=C), 733 (Ph).

¹H NMR (250 MHz, CDCl₃): δ (ppm) 7.85 (dd, ³J = 4.4 Hz, ⁴J = 3.0 Hz, 2 H_{Ph}), 7.75 (dd, ³J = 2.4 Hz, ⁴J = 3.0 Hz, 2 H_{Ph}), 4.49 (dddd, ³J_F = 23.7 Hz, ³J_F = 15.6 Hz, ³J = 7.8 Hz, ³J = 1.5 Hz, 1 H_{2'}), 4.30 (dd, ³J = 7.9 Hz, ³J = 1.5 Hz, 2 H_{1'}).

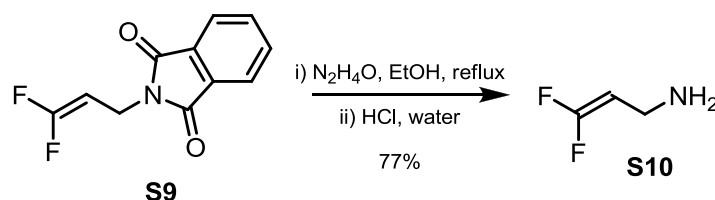
¹⁹F NMR (235 MHz, CDCl₃): δ (ppm) -85.0, -85.3.

¹³C NMR (91 MHz, CDCl₃): δ (ppm) 164.3 (C=O), 158.3 (t, ¹J_F = 249.2 Hz, C_{3'}), 134.3 (C_{m-Ph}), 132.1 (C_{i-Ph}), 123.4 (C_{p-Ph}), 74.5 (d, ²J_F = 25.6 Hz, ²J_F = 18.7 Hz, C_{2'}), 37.9 (d, ³J_F = 8.1 Hz, C_{1'}).

MS (EI, 70 eV): *m/z* (%) = 223 (100) [(M)⁺], 1945 (19) [(M-COH)⁺], 172 (23) [(M-CF₂H)⁺], 104 (25).

HRMS (EI, 70 eV): Calculated for C₁₁H₈F₂NO₂ [(M+H)⁺] = 224.0523. Found = 224.0518.

3,3-Difluoroprop-2-en-1-amine (S10)

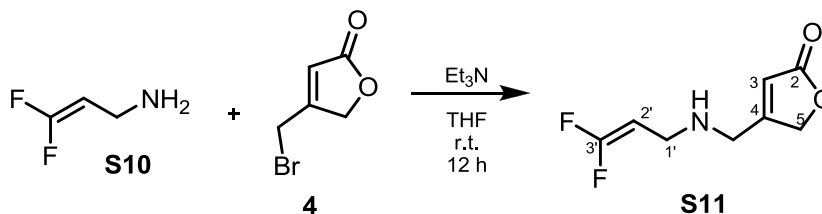


Hydrazine hydrate (1.23 mL, 25.4 mmol, 5 eq) was added to a suspension of **S9** (1.13 g, 5.08 mmol, 1 eq) in ethanol (15 mL). The resulting mixture was heated under reflux for one hour. Then HCl aq. (2.0 M) (20 mL) was added and the reaction heated for a further one hour. The reaction mixture was then cooled to 4 °C and the phthalyl hydrazide removed by filtration. The ethanol was removed in vacuo and the solid residue was redissolved in 20 mL NaOH aq. (2.0 M). The solution was extracted with diethyl ether (5x) and the organic extract was dried (Na₂SO₄), filtered and the solvent removed to give product **S10** as a colourless oil (512 mg, 77%).

¹H NMR (250 MHz, D₂O): δ (ppm) 4.49-4.47 (m, 1 H₂), 4.31-4.29 (m, 2 H₁).

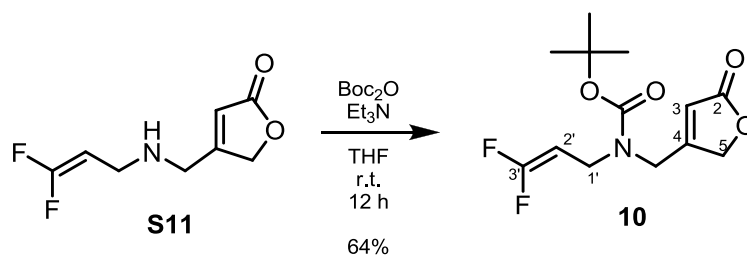
¹⁹F NMR (235 MHz, D₂O): δ (ppm) -81.2, -83.9.

4-[(3,3-Difluoroallylamino)methyl]furan-2(5H)-one (S11)



To a solution of bromide **4** (956 mg, 5.4 mmol, 1 eq) in THF (30 mL) was added triethylamine (3.0 mL, 21.6 mmol, 4 eq) and finally **S10** (600 mg, 5.4 mmol, 1 eq). The resulting solution was stirred at room temperature for twelve hours. Water was added and the aqueous layer extracted with EtOAc, dried over Na₂SO₄, filtered and evaporated to dryness. This product (**S11**) was used for protection reactions without further purification.

tert-Butyl 3,3-difluoroallyl[(5-oxo-2,5-dihydrofuran-3-yl)methyl]carbamate (10)



To a solution of amine **S11** (106 mg, 0.56 mmol, 1 eq) in dry THF (1.5 mL) was added triethylamine (85.7 μL , 0.62 mmol, 1.1 eq) and Boc_2O (135 mg, 0.62 mmol, 1.1 eq). The resulting solution was stirred at room temperature for twelve hours. After that time, the solvent was removed under reduced pressure and the residue purified by column chromatography (pentane:EtOAc 1:1) to afford the Boc-protected product **10** as a yellow oil (103 mg, 64%).

R_f: 0.63 (pentane:EtOAc 1:1).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 2884 (w, C-H), 1769 (vs, C=O), 1696 (w), 1444 (m), 1167 (m), 1134 (m), 876 (w).

¹H NMR (360 MHz, CDCl_3): δ (ppm) 5.94 (dd, $^4J = 3.4$ Hz, $^4J = 1.4$ Hz, 1 H₃), 4.78 (d, $^4J = 1.4$ Hz, 2 H₅), 4.36 (br. s, 1 H₂), 4.18 (br. s, 2 H_{1'}), 3.84 (br. s, CH₂), 1.47 [s, 9 C(CH₃)₃].

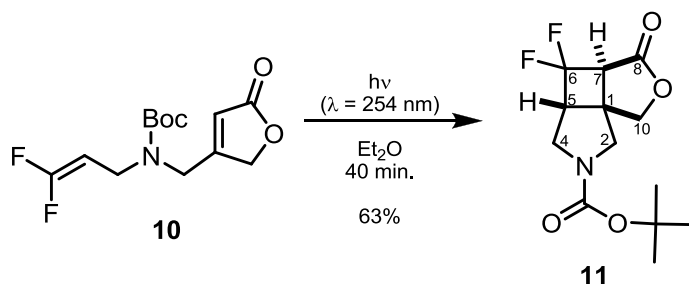
¹⁹F NMR (235 MHz, CDCl_3): δ (ppm) -85.4, -87.5.

¹³C NMR (91 MHz, CDCl_3): δ (ppm) 171.1 (C₂), 166.1 (C₄), 146.8 (COO^tBu), 130.2 (m, C_{3'}), 117.0 (C₃), 85.2 (C₅), 81.5 [C(CH₃)₃], 75.1 (m, C_{2'}), 44.5 (CH₂), 40.9 (m, C_{1'}), 27.4 [C(CH₃)₃].

MS (EI, 70 eV): m/z (%): 289 (2) [(M)⁺], 233 (34) [(M-C₄O₈)⁺], 189 (39) [(M-C₅H₈O₂)⁺], 112 (50), 88 (57), 57 (100).

RMS (EI, 70 eV): Calculated for C₁₃H₁₇F₂NO₄ [(M)⁺] = 289.1126. Found = 289.1130.

N-tert-butoxycarbonyl-6,6-difluoromethyl-3-aza-9-oxatricyclo[5.3.0.0^{1,5}]decan-8-one (11)



The compound was prepared from tetronate **10** (59.0 mg, 0.20 mmol) in 40 mL of Et₂O by irradiation for 40 minutes (5 mM). Purification of the crude by column chromatography (pentane:EtOAc 1:1) afforded the photoproduct **8f** as a white solid (37.2 mg, 63%).

M.P.: 117 °C

R_f: 0.41 (pentane:EtOAc 1:1).

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 2968 (w, C-H), 2913 (w), 1764 (s, C=O), 1692 (s), 1411 (m), 1381 (s), 1169 (s), 1025 (m), 876 (w).

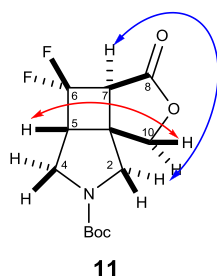
¹H NMR (500 MHz, CDCl₃): δ (ppm) 4.57 (d, ²J = 10.2 Hz, 1 H₁₀), 4.32 (d, ²J = 10.2 Hz, 1 H₁₀), 4.14-4.12 (br. s, 1 H₄), 4.07-3.99 (br. s, 1 H₂), 3.56 (ddd, ³J_F = 10.7 Hz, ³J_F = 4.2 Hz, ⁴J = 1.3 Hz, 1 H₇), 3.40 (br. s, 1 H₄), 3.34 (ddt, ³J_F = 9.2 Hz, ³J_F = 7.9 Hz, ³J = 5.3 Hz, 1 H₅), 3.19 (d, ²J = 12.3 Hz, 1 H₂), 1.48 [s, 9 C(CH₃)₃]. *Rotamers*

¹³C NMR (91 MHz, CDCl₃): δ (ppm) 169.4 (dd, ³J_F = 6.3 Hz, ³J_F = 2.2 Hz, C₈), 154.1 (COO^tBu), 114.2 (t, ¹J_F = 290.5 Hz, C₆), 80.8 [C(CH₃)₃], 72.1 (C₁₀), 56.3 (m, C₅), 51.3 (m, C₇), 49.9 (C₂), 45.3 (m, C₄), 28.4 [C(CH₃)₃].

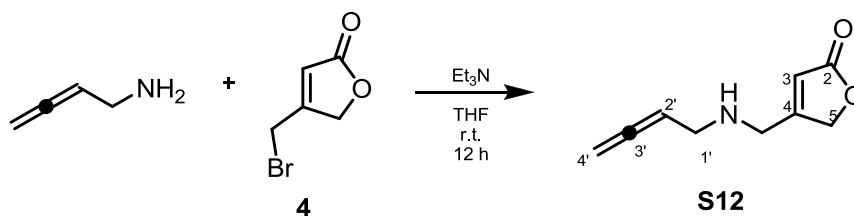
MS (EI, 70 eV): *m/z* (%) = 290 (49) [(M+H)⁺], 234 (62) [(M-C₄H₉)⁺], 98 (100), 85 (71).

HRMS (EI, 70 eV): Calculated for C₁₃H₁₈F₂NO₄ [(M)⁺] = 290.1204. Found = 290.1199.

Important NOE contacts:



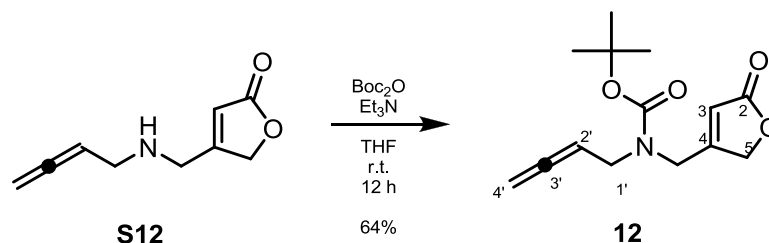
4-[(Buta-2,3-dienylamino)methyl]-furan-2(5H)-one (S12)



To a solution of bromide **4** (503 mg, 2.84 mmol, 1 eq) in THF (4 mL) was added triethylamine (1.6 mL, 11.4 mmol, 4 eq) and finally buta-2,3-dien-1-amine (300 mg, 2.84 mmol, 1 eq). The resulting solution was stirred at room temperature for twelve hours. Water was added and the aqueous layer

extracted with EtOAc, dried over Na₂SO₄ and filtered. The solvent was removed and the crude product **S12** was used in the next reaction.

tert-Butyl buta-2,3-dienyl[(2-oxo-2,5-dihydrofuran-3-yl)methyl]carbamate (12)



To a solution of the amine **S12** (186 mg, 1.13 mmol, 1 eq) in dry THF (3 mL) was added triethylamine (173 μL , 1.24 mmol, 1.1 eq) and Boc₂O (270 mg, 1.24 mmol, 1.1 eq). The resulting solution was stirred at room temperature for twelve hours. After that time, the solvent was removed under reduced pressure and the residue purified by column chromatography (pentane:EtOAc 1:1) to afford the boc-protected product **12** as a light-orange oil (191 mg, 64%).

R_f: 0.41 (pentane:EtOAc 1:1).

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 2976 (s, C-H), 1956 (w, C=C=C), 1778 (vs, C=O), 1746 (s), 1687 (s), 1455 (m), 1365 (m), 1241 (m), 1160 (s).

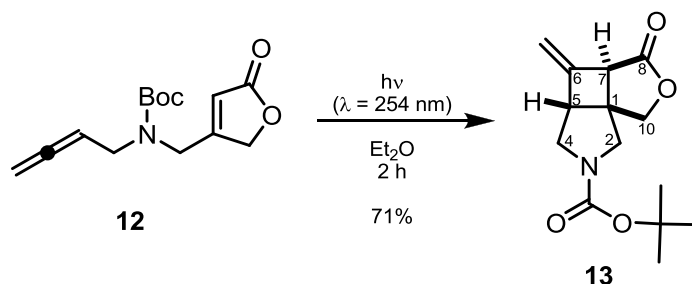
¹H NMR (500 MHz, CDCl₃): δ (ppm) 5.92 (t, ⁴J = 1.6 Hz, 1 H₃), 5.14 (dt, ⁴J = 6.5 Hz, ³J = 13.5 Hz, 1 H₂), 4.83-4.80 (m, 2 H₄, 2 H₅), 4.24 (br. s, CH₂), 3.66 (br. s, 2 H₁), 1.47 [s, 9 C(CH₃)₃].

¹³C NMR (91 MHz, CDCl₃): δ (ppm) 208.8 (C₃), 173.2 (C₂), 167.5 (COO^tBu), 116.2 (C₃), 86.8 (C₂), 80.7 [C(CH₃)₃], 78.8 (C₅), 72.2 (C₄), 46.7 (C₁), 44.2 (CH₂), 28.2 [C(CH₃)₃].

MS (EI, 70 eV): m/z (%) = 265 (29) [(M+H)⁺], 210 (100) [(M-C₄H₉)⁺].

HRMS (EI, 70 eV): Calculated for C₁₄H₂₃N₂O₄ [(M+NH₄)⁺] = 283.1658. Found = 283.1656.

N-tert-butoxycarbonyl-6-methylene-3-aza-9-oxatricyclo[5.3.0.0^{1,5}]decan-8-one (13)



The compound was prepared from tetronate **12** (65.0 mg, 0.25 mmol) in 49 mL of Et₂O by irradiation for two hours (5 mM). Purification of the crude by column chromatography (pentane:EtOAc 1:1) afforded the photoproduct **13** as a colorless oil (46.2 mg, 71%).

R_f = 0.61 (pentane:EtOAc 1:1).

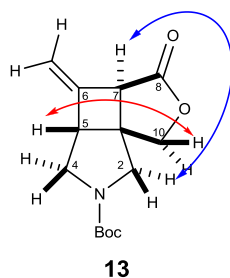
IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 2979 (s, C-H), 1770 (vs, C=O), 1687 (s), 1636 (m), 1441 (w), 1363 (s), 1241 (m), 1160 (s).

¹H NMR (500 MHz, CDCl₃): δ (ppm) 5.30 (d, ² J = 5.2 Hz, 1 H_{6'}), 5.15 (d, ² J = 5.2 Hz, 1 H_{6''}), 4.52 (d, ² J = 9.9 Hz, 1 H₁₀), 4.27 (d, ² J = 9.9 Hz, 1 H₁₀), 3.9 (br. s, 1 H₂), 3.78 (br. s, 1 H₄), 3.55-3.52 (m, 1 H₄), 3.45-3.37 (m, 1 H₇, 1 H₅), 2.97-2.86 (m, 1 H₇, 1 H₅), 3.14 (d, ² J = 12.3 Hz, 1 H₂), 1.47 [s, 9 C(CH₃)₃].

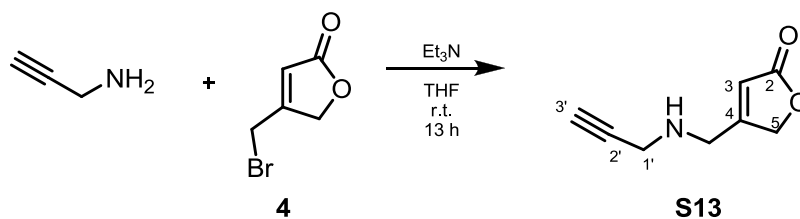
MS (EI, 70 eV): m/z (%) = 266 (100) [(M+H)⁺], 210 (50) [(M-C₄H₈)⁺].

HRMS (ESI): Calculated for C₁₄H₁₉NO₄⁺ [(M)⁺] = 265.1314. Found = 265.1313.

Important NOE contacts:

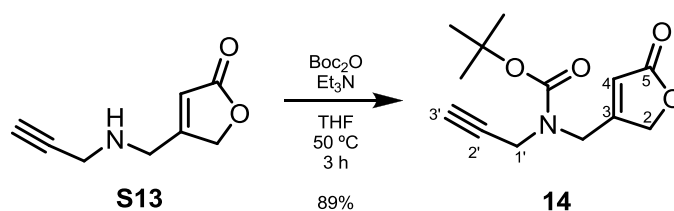


4-[(Prop-2-ynylamino)methyl]-furan-2(5H)-one (**S13**)



To a solution of bromide **4** (600 mg, 3.41 mmol, 1 eq) in THF (20 mL) was added triethylamine (0.52 mL, 3.75 mmol, 1.1 eq) and finally propargylamine (0.28 mL, 3.75 mmol, 1.1 eq). The resulting solution was stirred at room temperature for 13 hours. Water was added and the aqueous layer extracted with EtOAc, dried over Na₂SO₄ and filtered. The solvent was removed and the crude product (**S13**) used for the next reaction.

***tert*-Butyl (5-oxo-2,5-dihydrofuran-3-yl)methyl(prop-2-ynyl)carbamate (**14**)**



To a solution of the amine **S13** (220 mg, 1.46 mmol, 1 eq) in dry THF (4 mL) was added triethylamine (0.22 mL, 1.6 mmol, 1.1 eq) and Boc₂O (349 mg, 1.6 mmol, 1.1 eq). The resulting solution was stirred at 50 °C for three hours. After that time, the solvent was removed under reduced pressure and the residue purified by column chromatography (pentane:EtOAc 1:1) to afford the boc-protected product **14** as an light orange solid (315 mg, 89%).

M.P.: 75 °C

R_f: 0.49 (pentane:EtOAc 1:1).

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 3258 (m, C≡C), 2119 (w, C≡C), 1725 (vs, C=O), 1687 (vs, C=O), 1352 (w), 1247 (m), 1118 (s), 1023 (s).

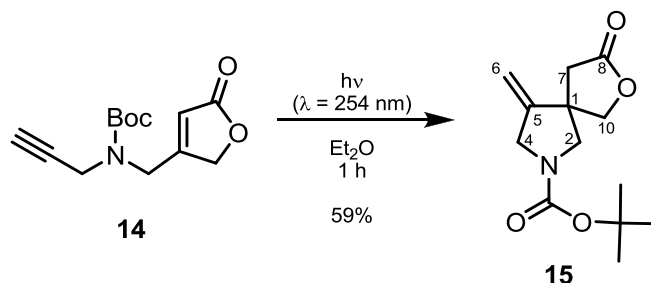
¹H NMR (500 MHz, CDCl₃): δ (ppm) 5.99-5.98 (m, 1 H₄), 4.81 (d, ⁴J = 1.2 Hz, 2 H₂), 4.15 (br. s, CH₂), 4.15-4.05 (br. s, 2 H₁), 2.28 (t, ⁴J = 2.5 Hz, 1 H₃), 1.49 [s, 9 C(CH₃)₃]. *Rotamers*

¹³C NMR (91 MHz, CDCl₃): δ (ppm) 173.1 (C₅), 166.0 (COO^tBu), 152.3 (C₃), 151.1 (C₂), 117.2 (C₄), 81.0 [C(CH₃)₃], 73.2 (C₂), 72.0 (C₃), 44.5 (CH₂), 37.4 (C₁), 28.3 [C(CH₃)₃].

MS (EI, 70 eV): m/z (%) = 274 (100) [(M+Na)⁺].

HRMS (EI, 70 eV): Calculated for C₁₃H₂₁N₂O₄ [(M + NH₄)⁺] = 269.1501. Found = 269.1495.

***tert*-Butyl 9-methylene-3-oxo-2-oxa-7-azaspiro[4.4]nonane-7-carboxylate (**15**)**



The compound was prepared from tetronate **14** (54.0 mg, 0.21 mmol) in 43 mL of Et₂O by irradiation for one hour (5 mM). Purification of the crude by column chromatography (pentane:EtOAc 1:1) afforded the photoproduct **15** as a colourless oil (31.9 mg, 59%).

R_f = 0.28 (pentane:EtOAc 1:1).

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 2981 (s, C-H), 1773 (vs, C=O), 1686 (s, C=O), 1435 (m), 1363 (m), 1239 (w), 1160 (s).

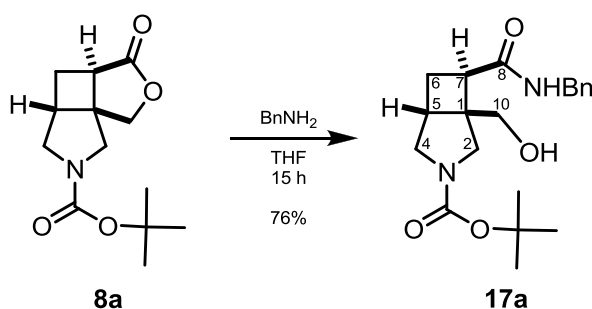
¹H NMR (500 MHz, CDCl₃): δ (ppm) 5.18 (br. s, 1 H₆), 5.12 (br. s, 1 H₆), 4.26-4.24 (m, 2 H₁₀), 4.11 (br. s, 2 H₂), 3.62 (br. s, 1 H₄), 3.47 (br. s, 1 H₄), 2.71 (br. s, 1 H₇), 2.60 (br. s, 1 H₇), 1.48 [s, 9 C(CH₃)₃].

¹³C NMR (91 MHz, CDCl₃): δ (ppm) 171.9 (C₈), 154.2 (COO^tBu), 148.1 (C₅), 107.3 (C₆), 80.3 [C(CH₃)₃], 76.1 (C₁₀), 70.7 (C₁), 55.9 (C₄), 50.0 (C₂), 38.6 (C₇), 28.3 [C(CH₃)₃].

MS (EI, 70 eV): m/z (%) = 255 (100) [(M+H)⁺], 199 (27) [(M-C₄H₈)⁺].

HRMS (ESI): Calculated for C₁₃H₂₀NO₄⁺ = 254.1387. Found = 254.1390.

***tert*-Butyl-7-(benzylcarbamoyl)-1-(hydroxymethyl)-3-azabicyclo[3.2.0]heptane-3-carboxylate (17a)**



To a solution of the *N*-Boc derivative **8a** (34.0 mg, 0.13 mmol, 1 eq) in THF (2 mL) under argon, was added benzyl amine (30.0 μ L, 0.27 mmol, 2 eq) and the mixture was stirred at room temperature for 15 hours. Evaporation to dryness and purification by column chromatography (pentane:EtOAc 3:7) afforded the desired product **17a** as a white solid (36.7 mg, 76%).

M.P.: (117-119) °C

R_f = 0.34 (pentane:EtOAc 3:7).

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 3485 (s, C-OH), 3298 (s, NH), 3024 (m), 1676 (vs, NH-C=O), 1645 (w), 1414 (m), 1365 (m), 1254 (s), 1174 (s), 732 (s), 697 (s).

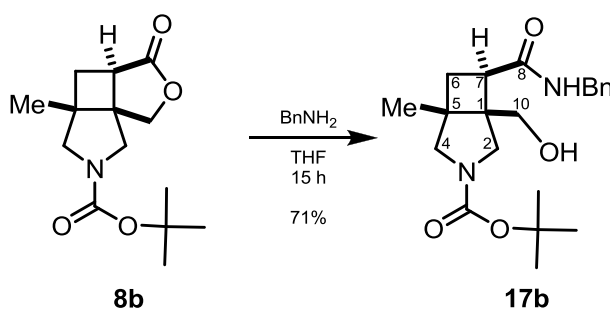
¹H NMR (500 MHz, DMSO-*d*₆): δ (ppm) 8.28 (br. s., 1 NH), 7.34-7.28 (m, 2 H_{Ph}), 7.27-7.18 (m, 3 H_{Ph}), 4.64 (t, ³*J* = 5.3 Hz, 1 OH), 4.28 (dd, ²*J* = 15.1 Hz, ³*J* = 5.9 Hz, 1 H₁₁), 4.22 (dd, ²*J* = 15.1 Hz, ³*J* = 5.9 Hz, 1 H₁₁), 3.64-3.51 (br. s, 1 H₂), 3.48 (dd, ²*J* = 11.0 Hz, ³*J* = 4.6 Hz, 1 H₁₀), 3.45-3.43 (m, 1 H₁₀), 3.41 (dd, ²*J* = 11.4 Hz, ³*J* = 1.8 Hz, 1 H₄), 3.28-3.21 (br. s, 1 H₄), 3.20-3.11 (br. s, 1 H₂), 2.90 (t, ³*J* = 8.2 Hz, 1 H₇), 2.53-2.49 (m, 1 H₅), 2.47-2.42 (m, 1 H₆), 1.58 (dd, ²*J* = 11.3 Hz, ³*J* = 2.6 Hz, 1 H₆), 1.42 [s, 9 C(CH₃)₃].

^{13}C NMR (91 MHz, DMSO- d_6): δ (ppm) 171.3 (C_8), 154.7 (COO^tBu), 140.1 (C_{ipso}), 128.7 (C_{Ph}), 127.8 (C_{Ph}), 127.2 (C_{Ph}), 78.8 [$\text{C}(\text{CH}_3)_3$], 61.4 (C_{10}), 53.3 (C_2), 52.8 (C_4), 43.4 (C_7), 42.7 (C_{11}), 40.6 (C_5), 28.6 [$\text{C}(\text{CH}_3)_3$], 24.3 (C_6). (C_1 not observed)

MS (EI, 70 eV): m/z (%) = 361 (11) [$(\text{M}+\text{H})^+$], 306 (100) [$(\text{M}-\text{C}_4\text{H}_8)^+$].

HRMS (ESI): Calculated for $\text{C}_{20}\text{H}_{29}\text{N}_2\text{O}_4^+$ [$(\text{M}+\text{H})^+$] = 361.2122. Found = 361.2122.

***tert*-Butyl-7-(benzylcarbamoyl)-1-(hydroxymethyl)-5-methyl-3-azabicyclo[3.2.0]heptane-3-carboxylate (17b)**



To a solution of the *N*-Boc derivative **8b** (500 mg, 1.87 mmol, 1 eq) in THF (24 mL) under argon, was added benzylamine (409 μL , 3.74 mmol, 2 eq) and the mixture stirred at room temperature for 15 hours. Evaporation to dryness and purification by column chromatography (pentane:EtOAc 3:7) afforded the desired product **17b** as a light-yellow solid (367 mg, 71%).

M.P.: 135 $^\circ\text{C}$

R_f = 0.44 (pentane:EtOAc 3:7).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3481 (s, C-OH), 3298 (s, NH), 1673 (vs, NH-C=O), 1645 (w), 1417 (m), 1255 (s), 1174 (m), 737 (s), 699 (s).

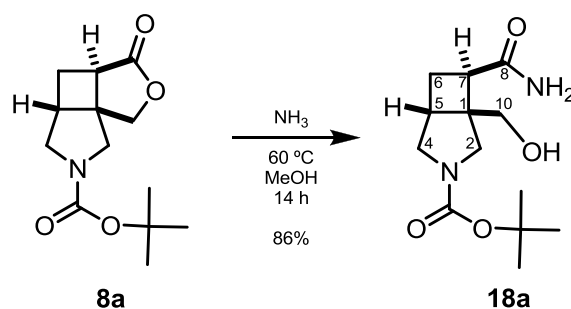
^1H NMR (500 MHz, DMSO- d_6): δ (ppm) 8.28 (br. s, 1 NH), 7.32-7.29 (m, 2 H_{Ph}), 7.27-7.26 (m, 2 H_{Ph}), 7.24-7.21 (m, 1 H_{Ph}), 4.53 (t, $^3J = 4.5$ Hz, 1 OH), 4.28 (dd, $^2J = 15.0$ Hz, $^3J = 5.8$ Hz, 1 H_{11}), 4.23 (dd, $^2J = 15.0$ Hz, $^3J = 5.8$ Hz, 1 H_{11}), 3.70-3.61 (br. s, 1 H_2), 3.53-3.47 (m, 2 H_{10} , 1 H_4), 3.33-3.24 (br. s, 1 H_4), 2.90-2.83 (br. s, 1 H_2), 2.76 (dd, $^3J = 9.1$ Hz, $^3J = 7.5$ Hz, 1 H_7), 2.11 (dd, $^2J = 11.7$ Hz, $^3J = 7.5$ Hz, 1 H_6), 1.74 (virt t., $^2J = ^3J = 10.1$ Hz, 1 H_6), 1.42 [s, 9 $\text{C}(\text{CH}_3)_3$], 1.11 (s, CH_3).

^{13}C NMR (91 MHz, DMSO- d_6): δ (ppm) 172.2 (C_8), 154.8 (COO^tBu), 140.1 (C_{ipso}), 128.7 (C_{Ph}), 127.9 (C_{Ph}), 127.2 (C_{Ph}), 78.8 [$\text{C}(\text{CH}_3)_3$], 60.1-60.0 (C_{10}), 59.5 (C_1), 56.1-55.9 (C_2), 53.3-52.6 (C_4), 43.8 (C_{11}), 42.8 (C_5), 42.5 (C_7), 31.3 (C_6), 28.7 [$\text{C}(\text{CH}_3)_3$], 19.9 (CH_3). *Rotamers*

MS (EI, 70 eV): m/z (%) = 375 (27) [$(\text{M}+\text{H})^+$], 320 (100) [$(\text{M}-\text{C}_4\text{H}_9)^+$].

HRMS (ESI): Calculated for $\text{C}_{21}\text{H}_{30}\text{N}_2\text{O}_4^+$ [$(\text{M})^+$] = 374.2206. Found = 374.2211.

tert-Butyl 7-carbamoyl-1-(hydroxymethyl)-3-azabicyclo[3.2.0]heptane-3-carboxylate (18a)



The *N*-Boc derivative **8a** (150 mg, 0.59 mmol, 1 eq) was combined with ammonia (7.0 M in methanol) (5.0 mL) to give a clear solution. The reaction mixture was stirred at 60 °C for twelve hours and then concentrated in vacuo to give the desired product **18a** as a colorless oil (136 mg, 86%).

IR (ATR): $\tilde{\nu}$ (cm⁻¹) = 3405 (s), 3172 (s, NH-C=O), 1688 (s, C=O), 1657 (s, NH-C=O), 1477 (m), 1367 (m), 1257 (m), 1159 (m), 1148 (m).

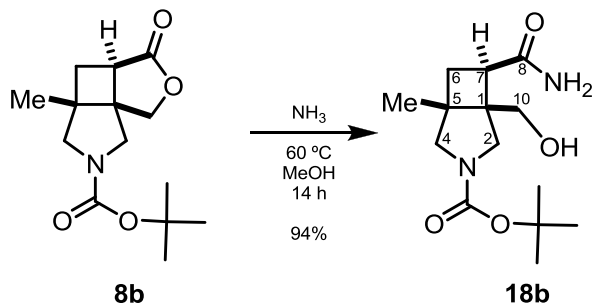
¹H NMR (500 MHz, DMSO-*d*₆): δ (ppm) 6.54 (br. s, 2 NH), 4.21 (br. s, 1 OH), 3.59-3.51 (m, 2 H₁₀, 1 H₂), 3.42 (dd, ²*J* = 11.6 Hz, ³*J* = 2.1 Hz, 1 H₄), 3.27 (dd, ²*J* = 11.6 Hz, ³*J* = 7.4 Hz, 1 H₄), 3.19 (d, ²*J* = 11.4 Hz, 1 H₂), 2.86 (t, ³*J* = 8.4 Hz, 1 H₇), 2.54-2.50 (m, 1 H₅), 2.41-2.37 (m, 1 H₆), 1.61 (ddd, ²*J* = 11.8 Hz, ³*J* = 8.4 Hz, ³*J* = 3.8 Hz, 1 H₆), 1.43 [s, 9 C(CH₃)₃].

¹³C NMR (91 MHz, DMSO-*d*₆): δ (ppm) 174.0 (C₈), 154.8 (COO^tBu), 79.0 [C(CH₃)₃], 61.2 (C₁₀), 55.3-54.7 (C₂), 53.3 (C₁), 52.4 (C₄), 43.3 (C₇), 37.8-36.9 (C₅), 28.6 [C(CH₃)₃], 24.3 (C₆).

MS (EI, 70 eV): *m/z* (%) = 270 (10) [(M)⁺], 215 (100) [(M-C₄H₈)⁺].

HRMS (ESI): Calculated for C₁₃H₂₂N₂O₄⁺ [(M)⁺] = 270.1580. Found = 270.1581.

tert-Butyl-6-carbamoyl-5-(hydroxymethyl)-1-methyl-3-azabicyclo[3.2.0]heptane-3-carboxylate (18b)



The *N*-Boc derivative **8b** (221 mg, 0.83 mmol, 1 eq) was combined with ammonia (7.0 M in methanol) (10 mL) to give a clear solution. The reaction mixture was stirred at 60 °C for twelve hours and then concentrated in vacuo to give the desired product **18b** as a colorless oil (220 mg, 94%).

IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3415 (s), 3161 (s, NH-C=O), 1678 (s, C=O), 1644 (s, NH-C=O), 1367 (m), 1257 (m), 1159 (m), 1148 (m).

^1H NMR (500 MHz, DMSO- d_6): δ (ppm) 6.58 (br. s, 2 NH), 4.08 (br. s, 1 OH), 3.64-3.61 (m, 1 H₂, 1 H₁₀), 3.57-3.51 (m, 1 H₁₀, 1 H₄), 3.28 (d, $^2J = 11.6$ Hz, 1 H₄), 2.90 (dd, $^3J = 11.3$ Hz, $^4J = 1.0$ Hz, 1 H₂), 2.74 (dd, $^3J = 9.2$ Hz, $^3J = 7.7$ Hz, 1 H₇), 2.07 (ddd, $^2J = 11.8$ Hz, $^3J = 7.7$ Hz, $^4J = 1.0$ Hz, 1 H₆), 1.79 (dd, $^2J = 11.8$ Hz, $^3J = 9.2$ Hz, 1 H₆), 1.43 [s, 9 C(CH₃)₃], 1.11 (s, CH₃).

^{13}C NMR (91 MHz, DMSO- d_6): δ (ppm) 174.2 (C₈), 154.8 (COO^tBu), 78.8 [C(CH₃)₃], 60.1-60.0 (C₁₀), 59.5 (C₁), 56.0-55.4 (C₂), 53.8-52.2 (C₄), 43.7-42.7 (C₇), 42.0 (C₅), 31.3 (C₆), 28.7 [C(CH₃)₃], 20.0 (CH₃). *Rotamers*

MS (EI, 70 eV): m/z (%) = 285 (5) [(M+H)⁺], 229 (100) [(M-C₄H₈)⁺].

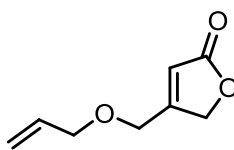
HRMS (ESI): Calculated for C₁₄H₂₄N₂O₄⁺ [(M)]⁺ = 284.1744. Found = 284.1746.

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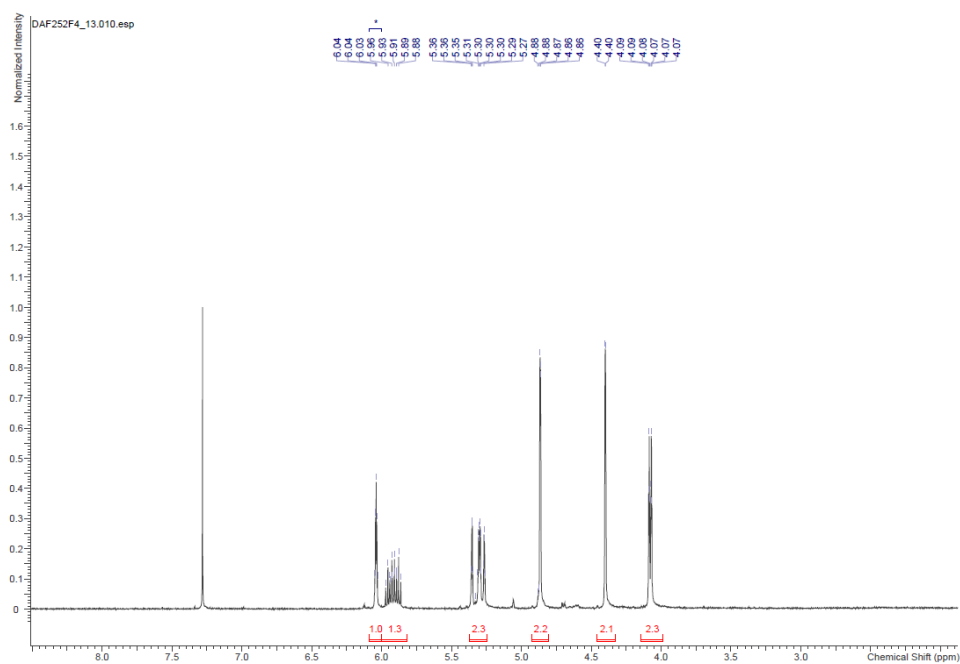
NMR spectra of new compounds:

4-(Allyloxymethyl)furan-2(5H)-one (1)

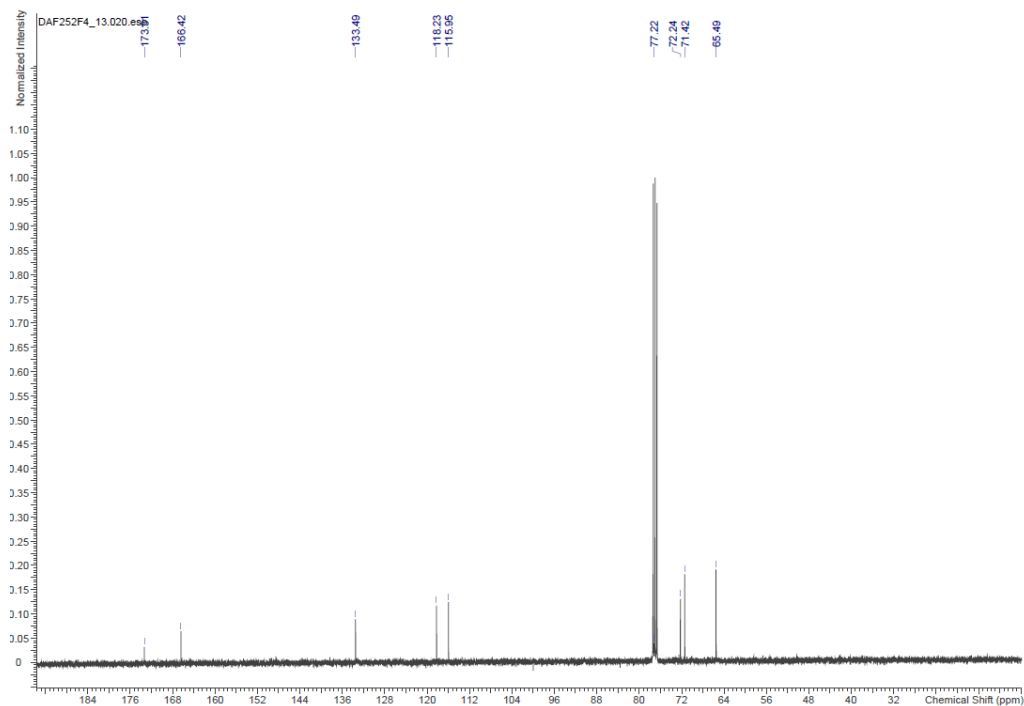


1

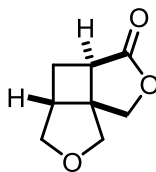
¹H NMR (300 K, CDCl₃):



¹³C NMR (300 K, CDCl₃)

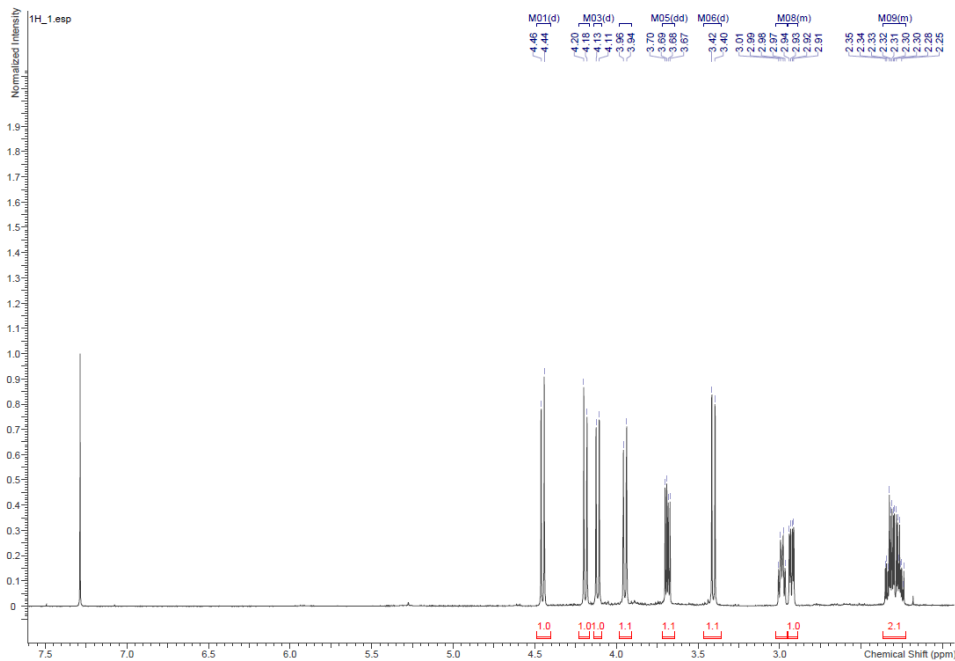


3,9-Dioxatricyclo[5.3.0.0^{1,5}]decan-8-one (2)

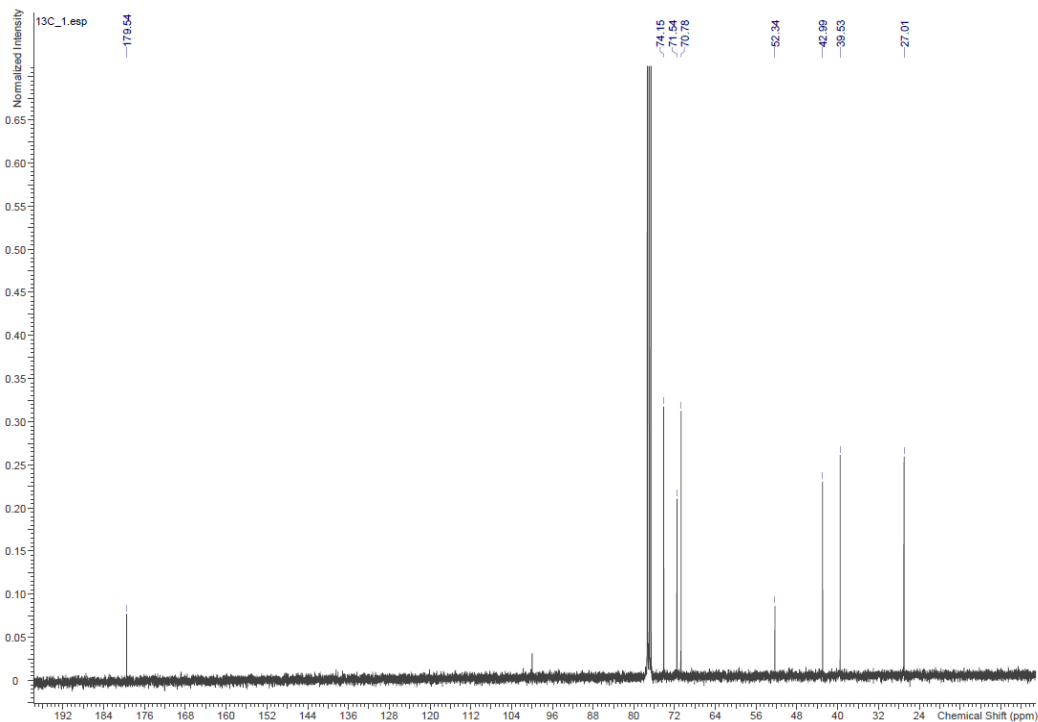


2

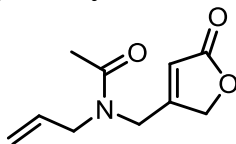
¹H NMR (300 K, CDCl₃):



¹³C NMR (300 K, CDCl₃)

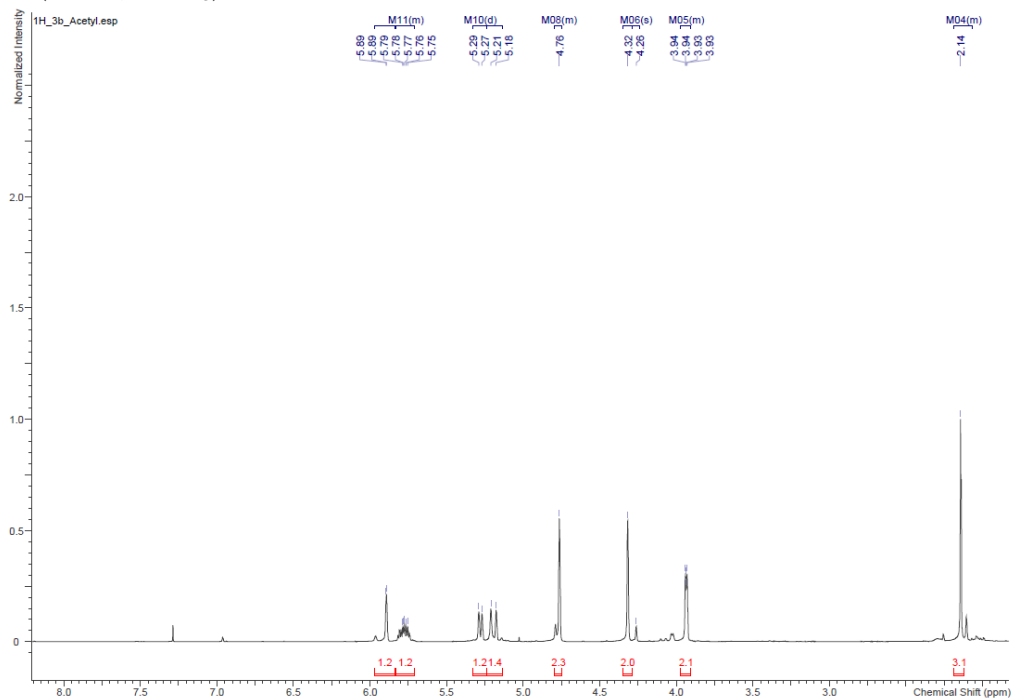


N-allyl-N-((5-oxo-2,5-dihydrofuran-3-yl)methyl)acetamide (**3b**)

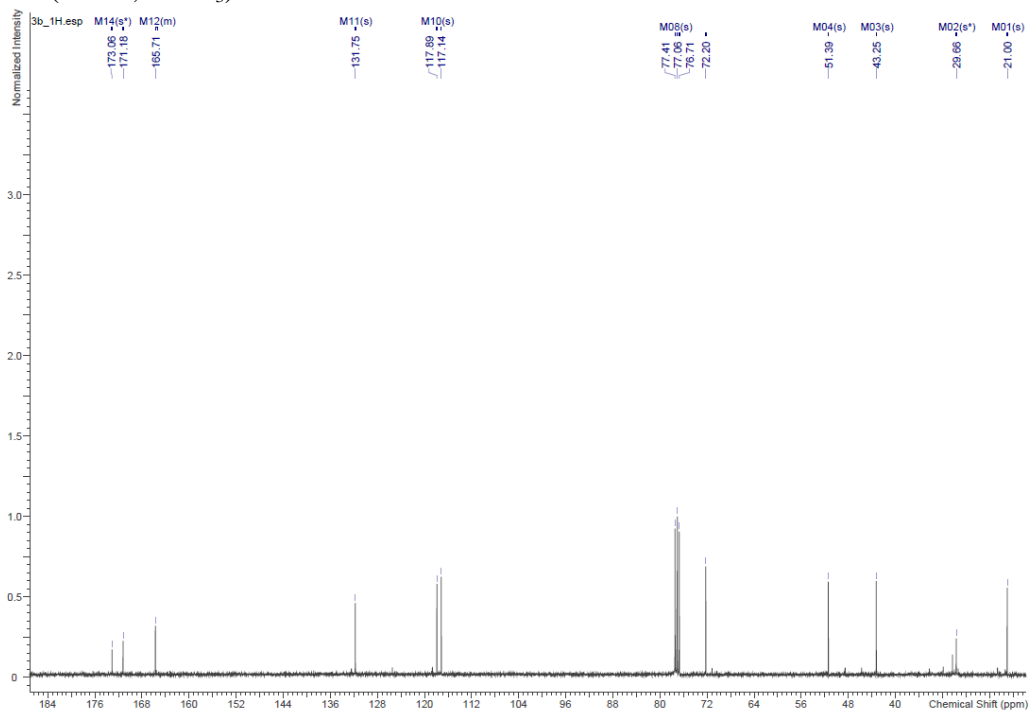


3b

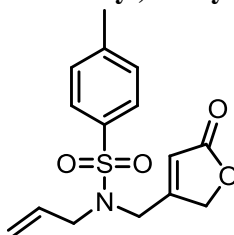
¹H NMR (300 K, CDCl₃):



¹³C NMR (300 K, CDCl₃)

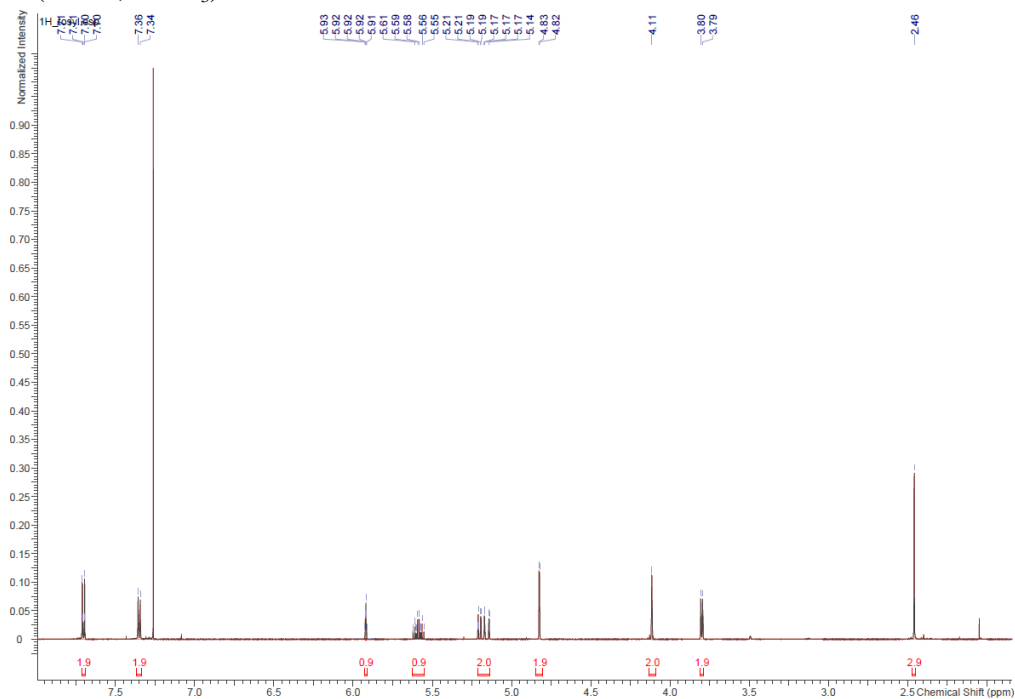


N-allyl-4-methyl-N-((5-oxo-2,5-dihydrofuran-3-yl)methyl)benzenesulfonamide (3c)

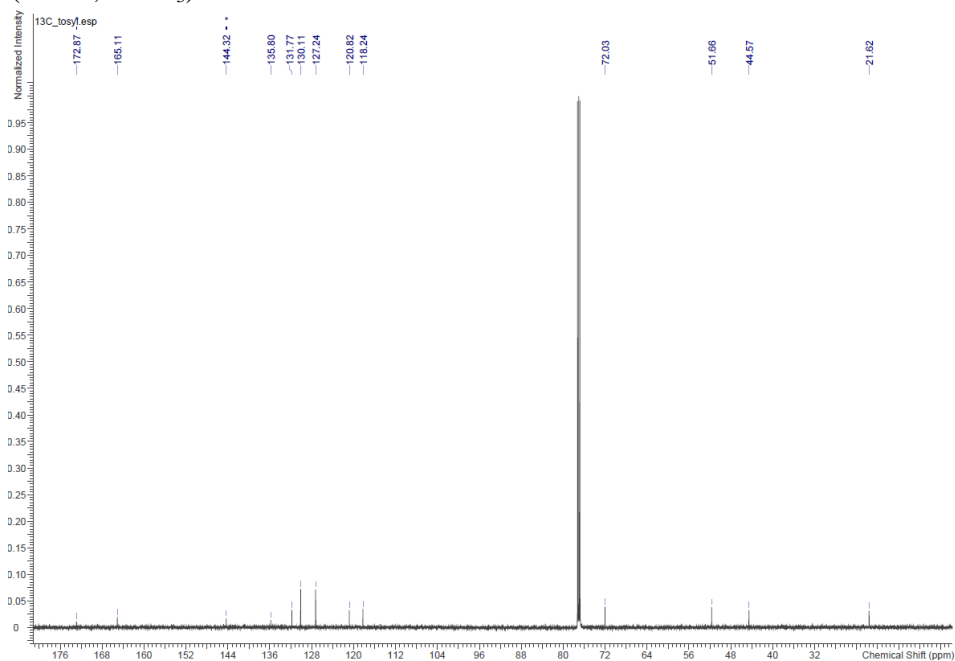


3c

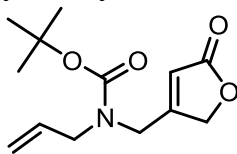
¹H NMR (300 K, CDCl₃):



¹³C NMR (300 K, CDCl₃):

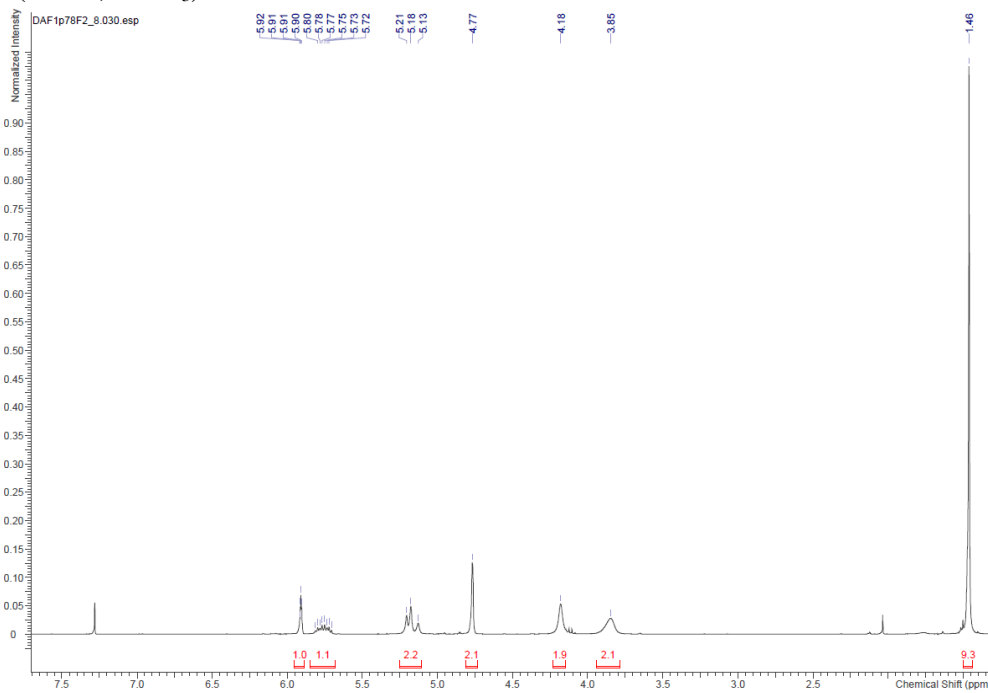


***tert*-Butyl allyl((5-oxo-2,5-dihydrofuran-3-yl)methyl)carbamate (7a)**

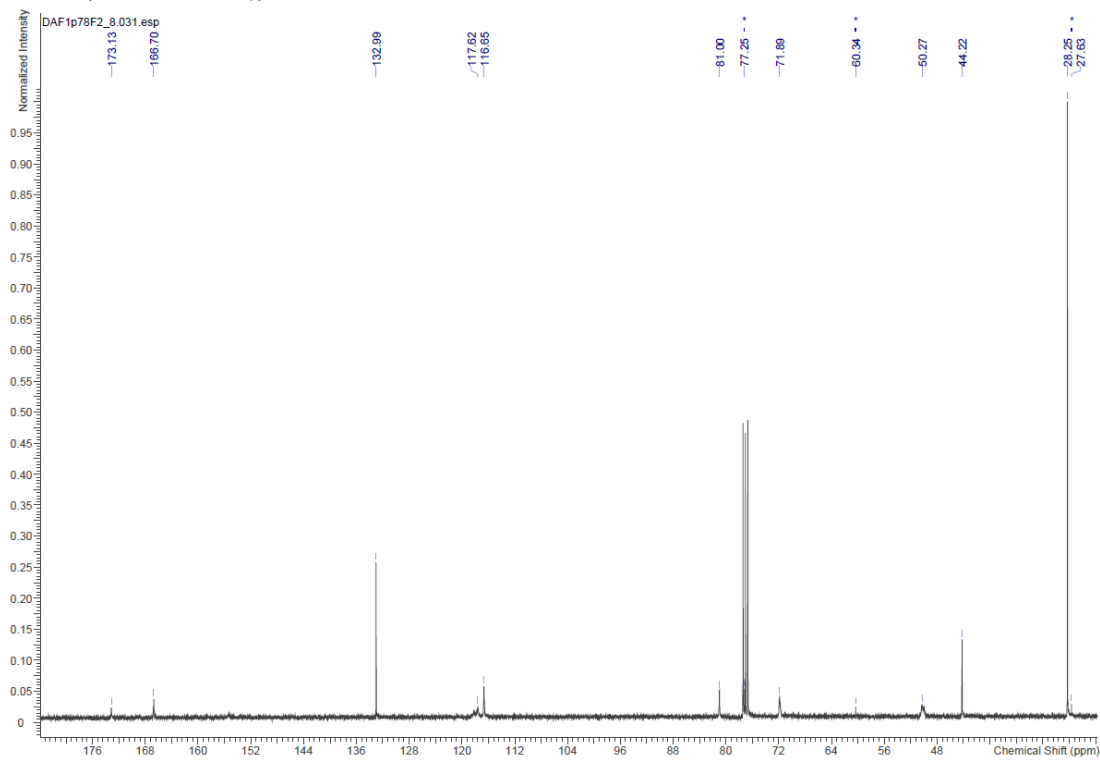


7a

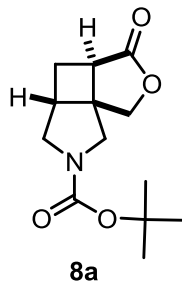
¹H NMR (300 K, CDCl₃):



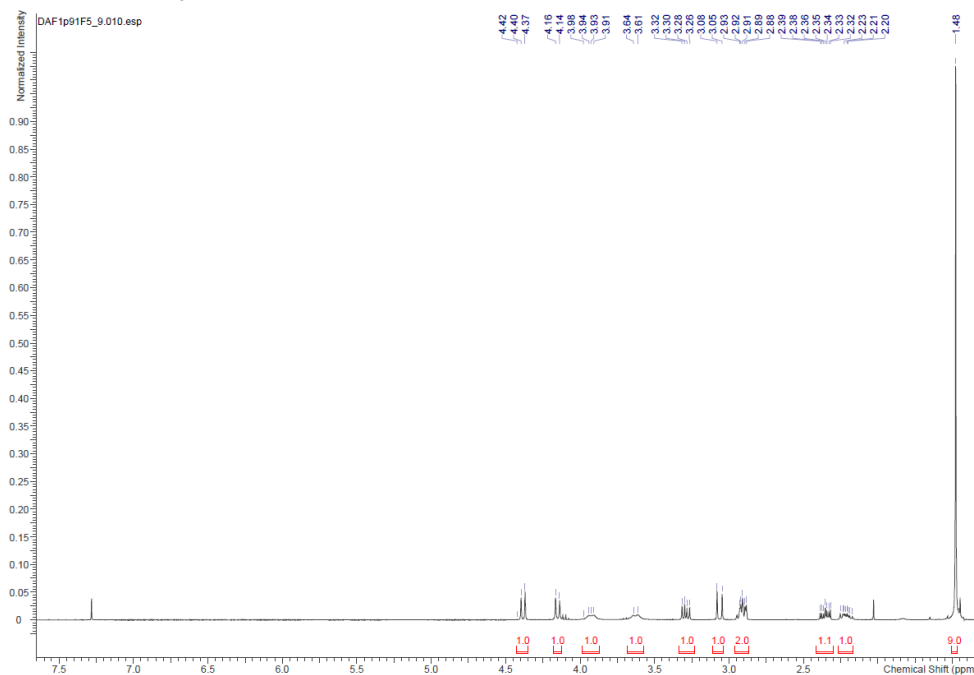
¹³C NMR (300 K, CDCl₃)



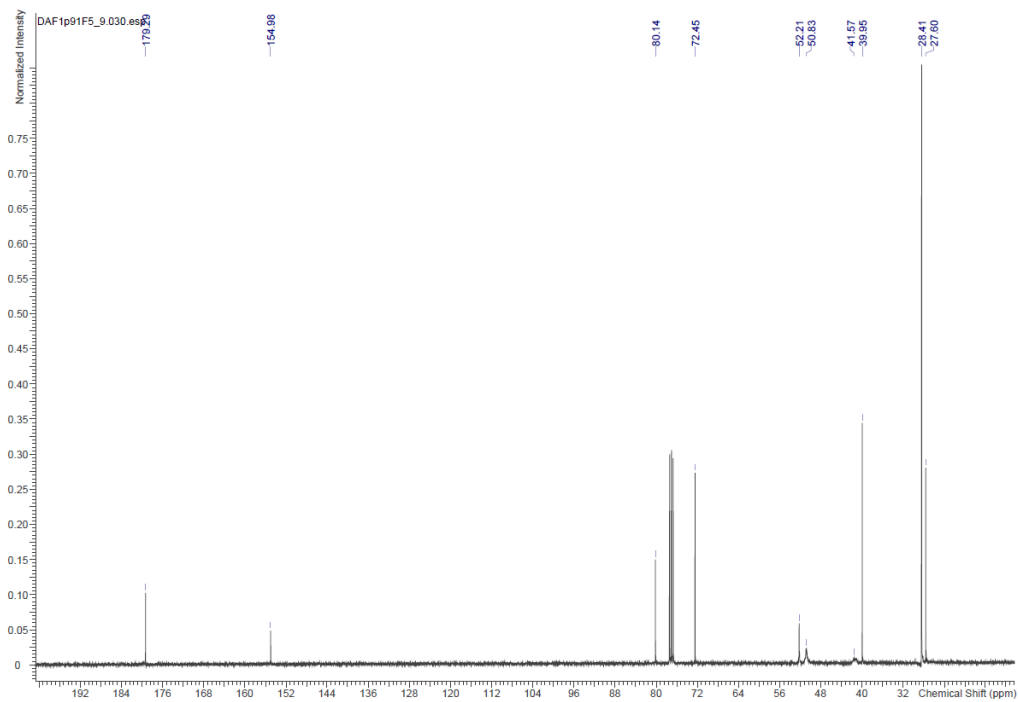
N-tert-butoxycarbonyl-3-aza-9-oxatricyclo[5.3.0.0^{1,5}]decan-8-one (8a)



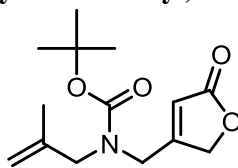
¹H NMR (300 K, CDCl₃):



¹³C NMR (300 K, CDCl₃):

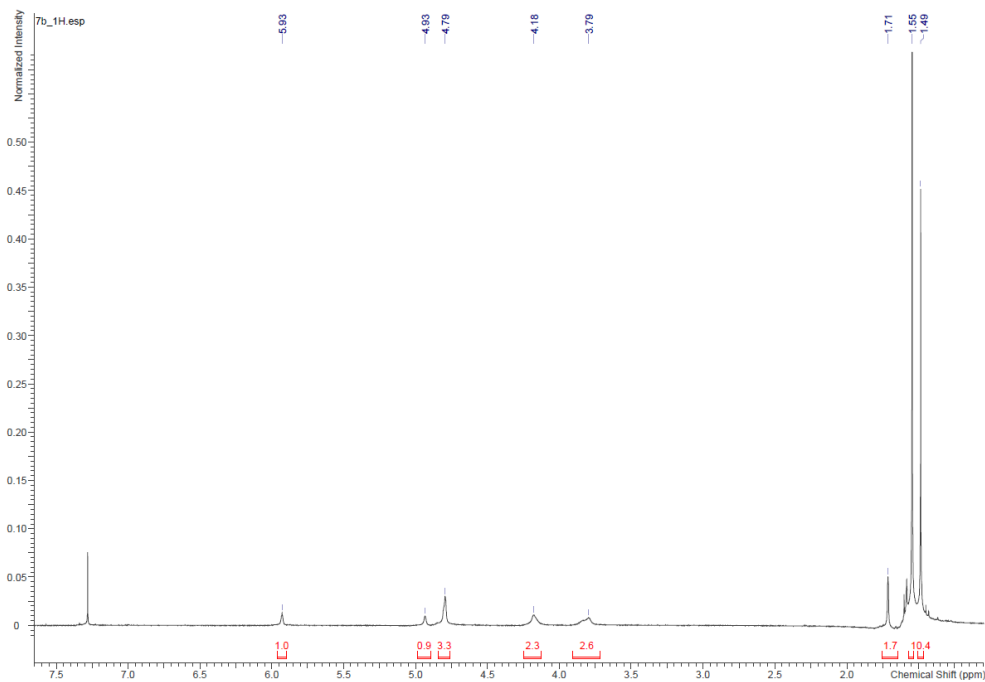


***tert*-Butyl 2-methylallyl[(5-oxo-2,5-dihydrofuran-3-yl)methyl]carbamate (7b)**

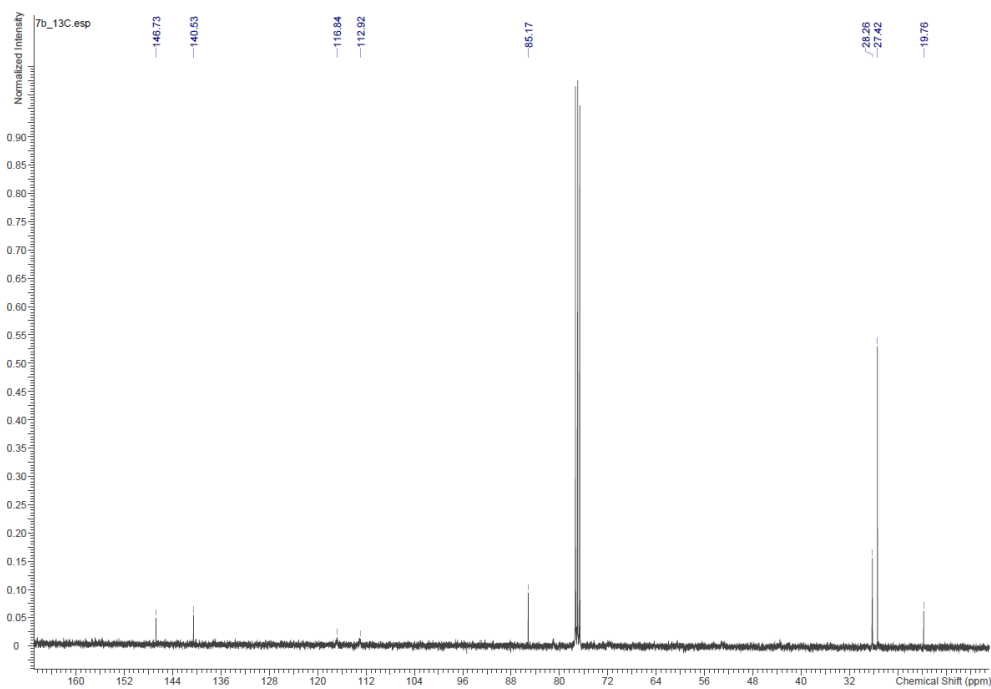


7b

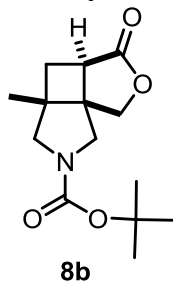
¹H NMR (300 K, CDCl₃):



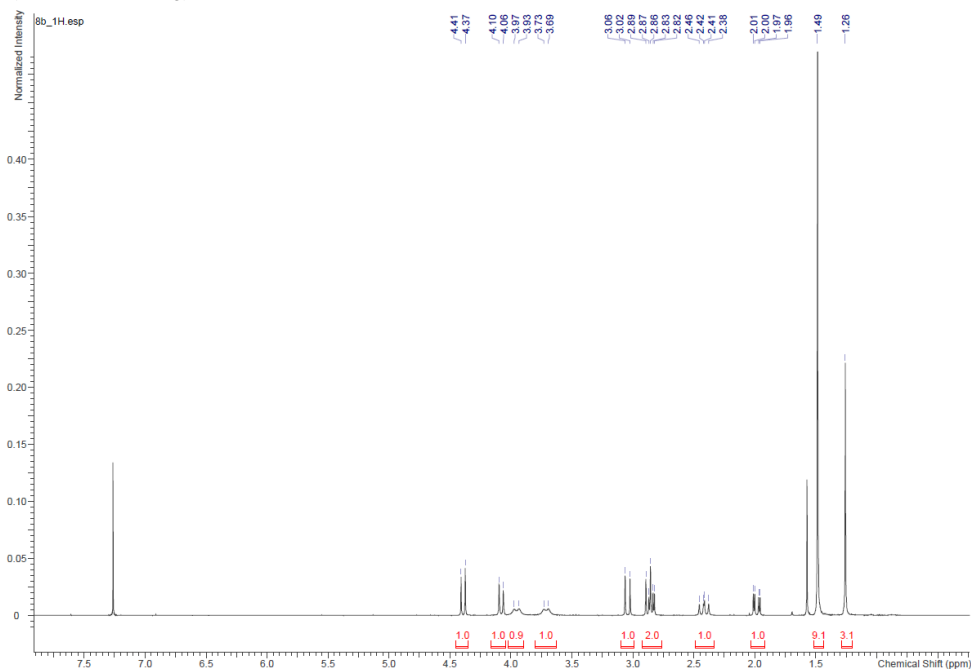
¹³C NMR (300 K, CDCl₃):



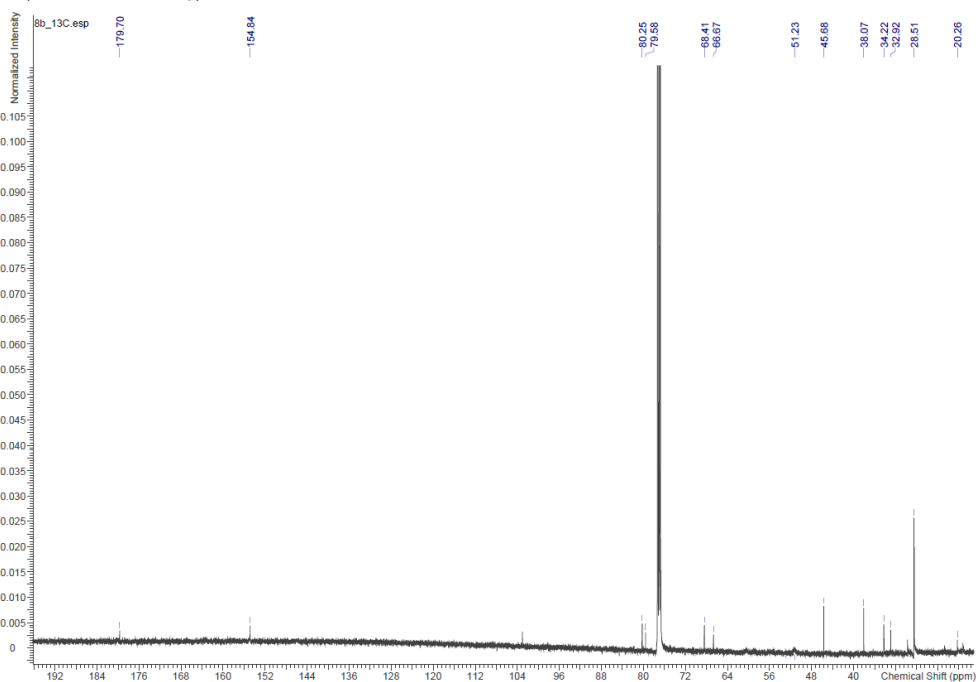
N-tert-butoxycarbonyl-5-methyl-3-aza-9-oxatricyclo[5.3.0.0^{1,5}]decan-8-one (8b)



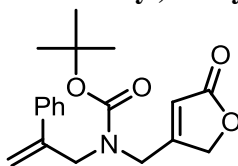
¹H NMR (300 K, CDCl₃):



¹³C NMR (300 K, CDCl₃):

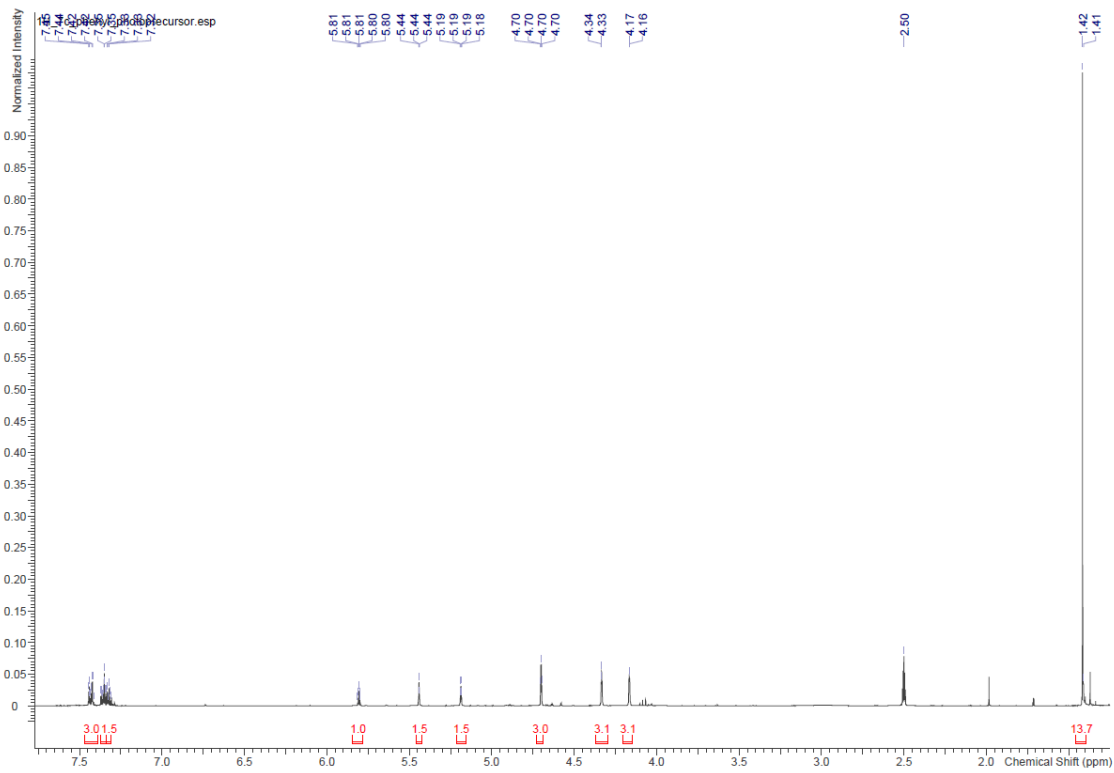


***tert*-Butyl 2-phenylallyl[(5-oxo-2,5-dihydrofuran-3-yl)methyl]carbamate (7c)**

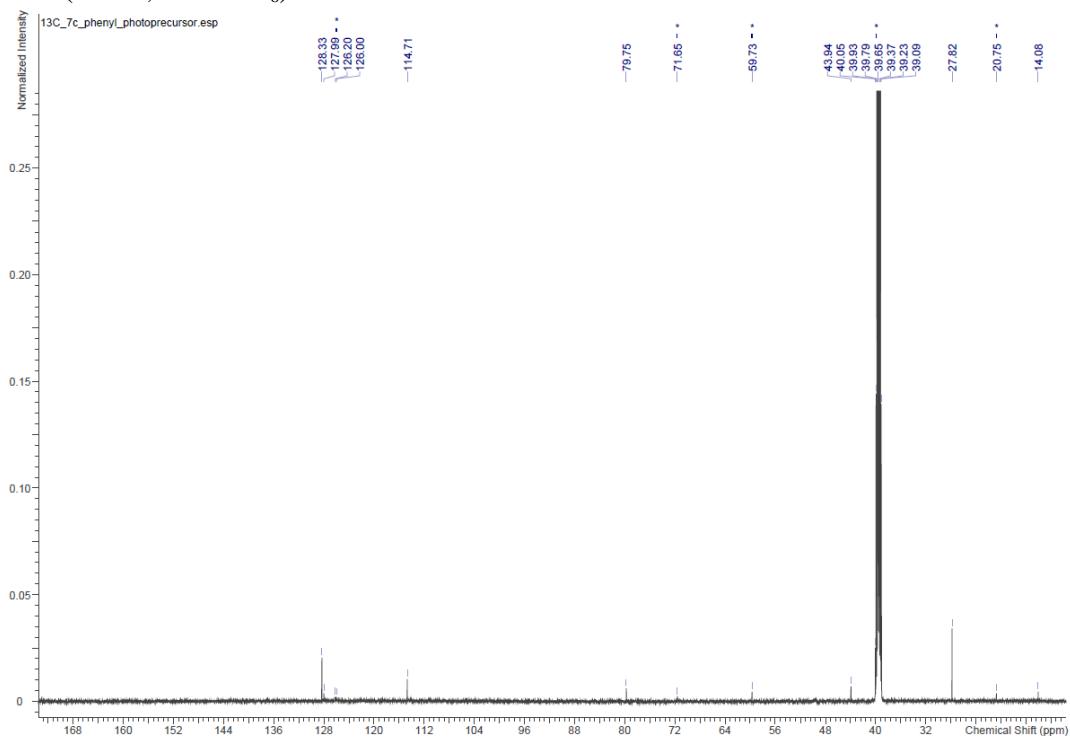


7c

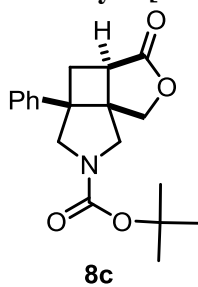
^1H NMR (300 K, DMSO- d_6):



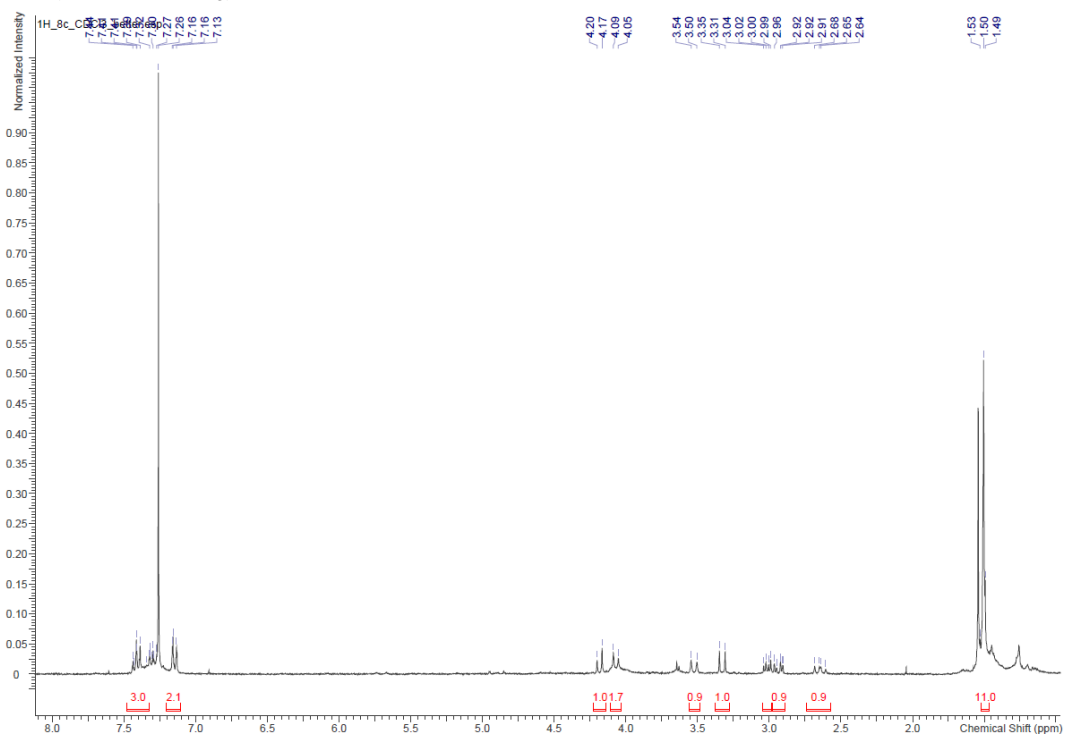
^{13}C NMR (300 K, DMSO- d_6):



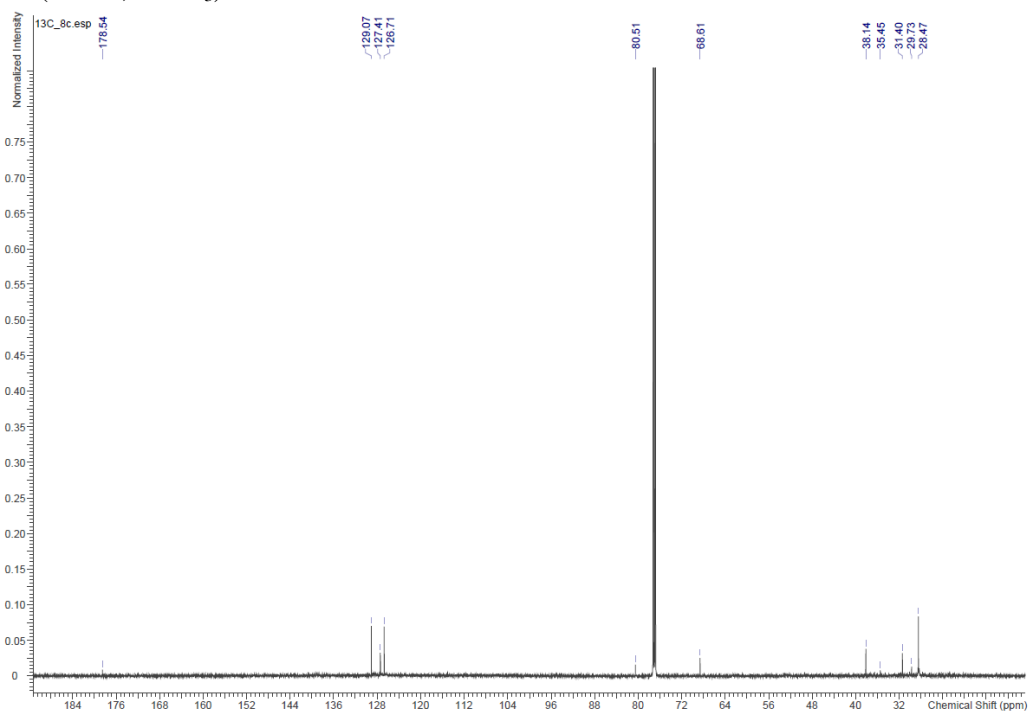
N-tert-butoxycarbonyl-5-phenyl-3-aza-9-oxatricyclo[5.3.0.0^{1,5}]decan-8-one (8c)



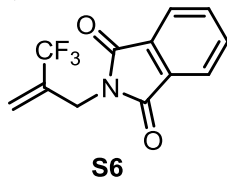
¹H NMR (300 K, CDCl₃):



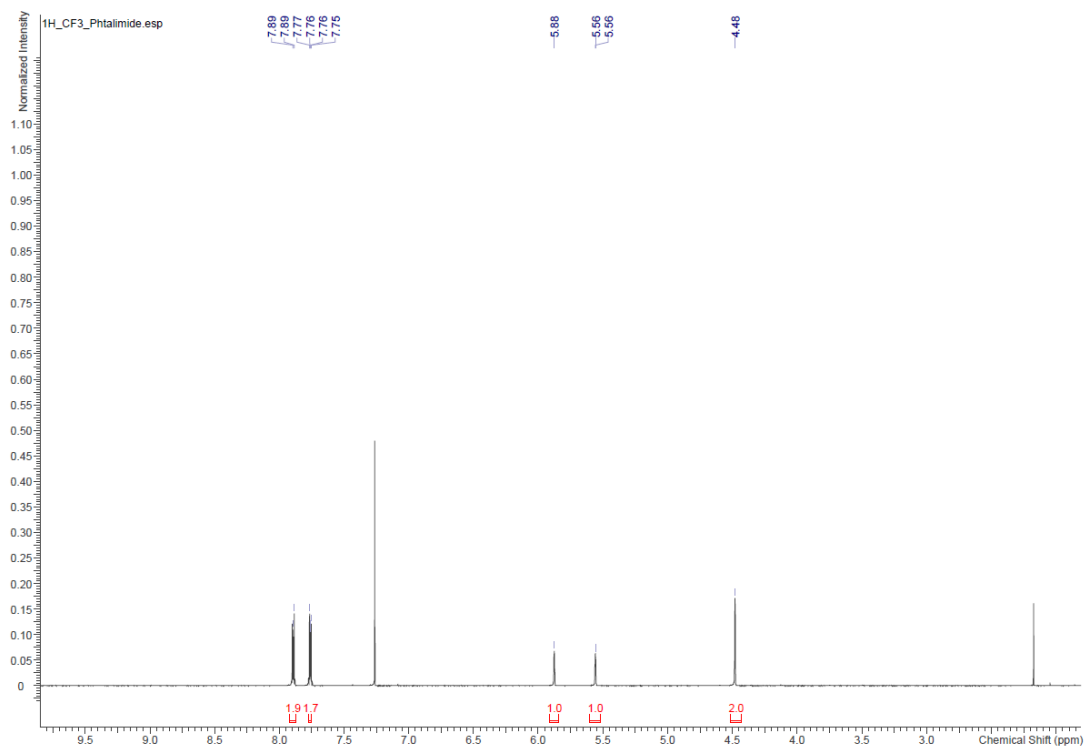
¹³C NMR (300 K, CDCl₃)



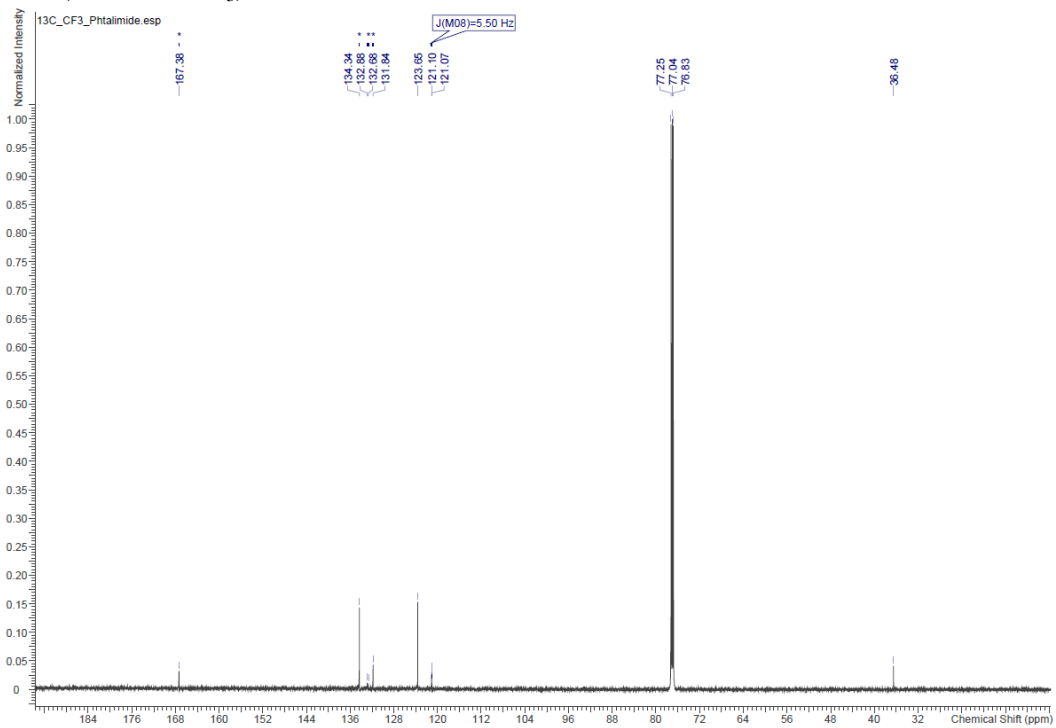
2-(2-Trifluoromethyl-allyl)isoindoline-1,3-dione (S6)



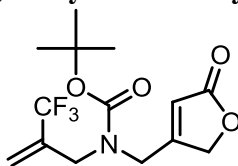
¹H NMR (300 K, CDCl₃):



¹³C NMR (300 K, CDCl₃)

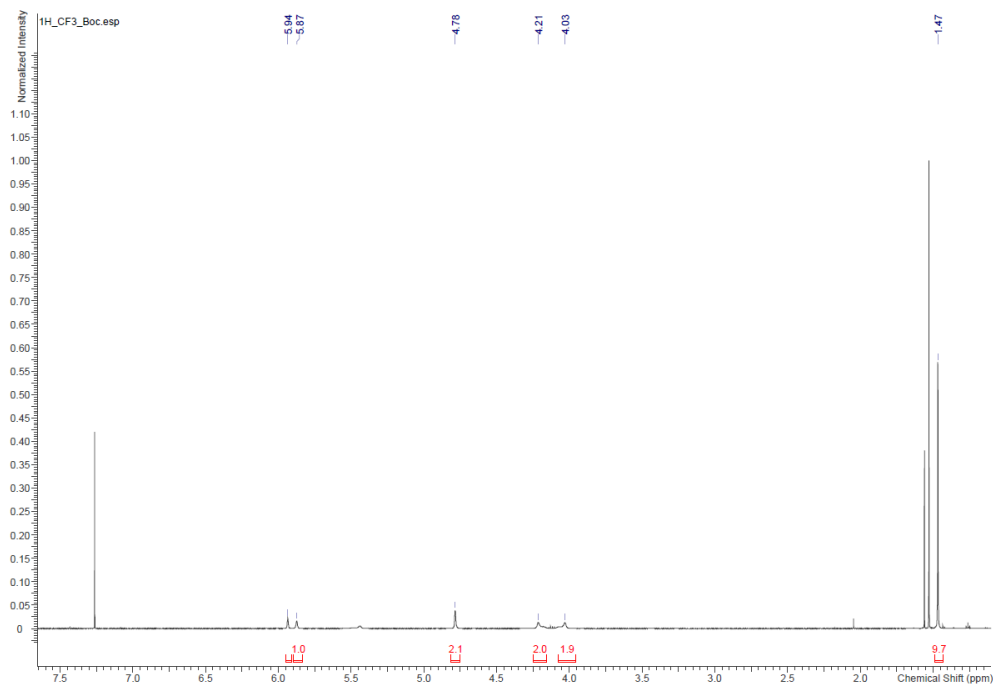


***tert*-Butyl 2-trifluoromethyl-allyl[(5-oxo-2,5-dihydrofuran-3-yl)methyl]carbamate (7d)**

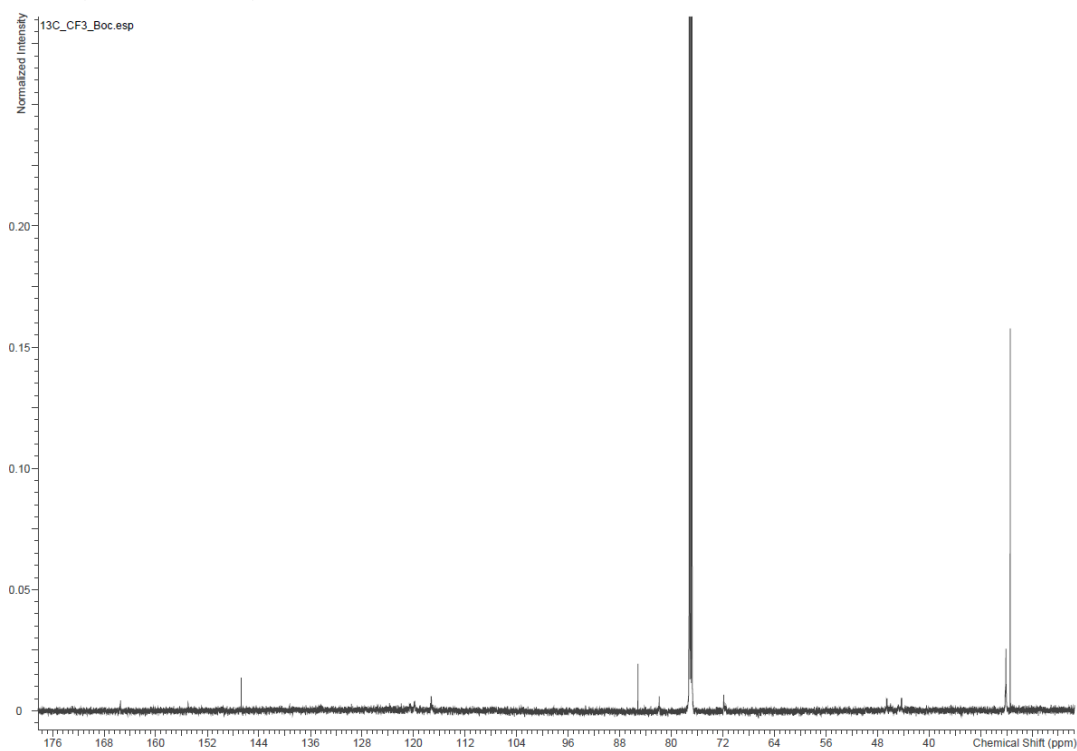


7d

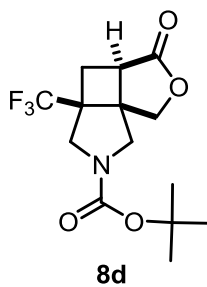
¹H NMR (300 K, CDCl₃):



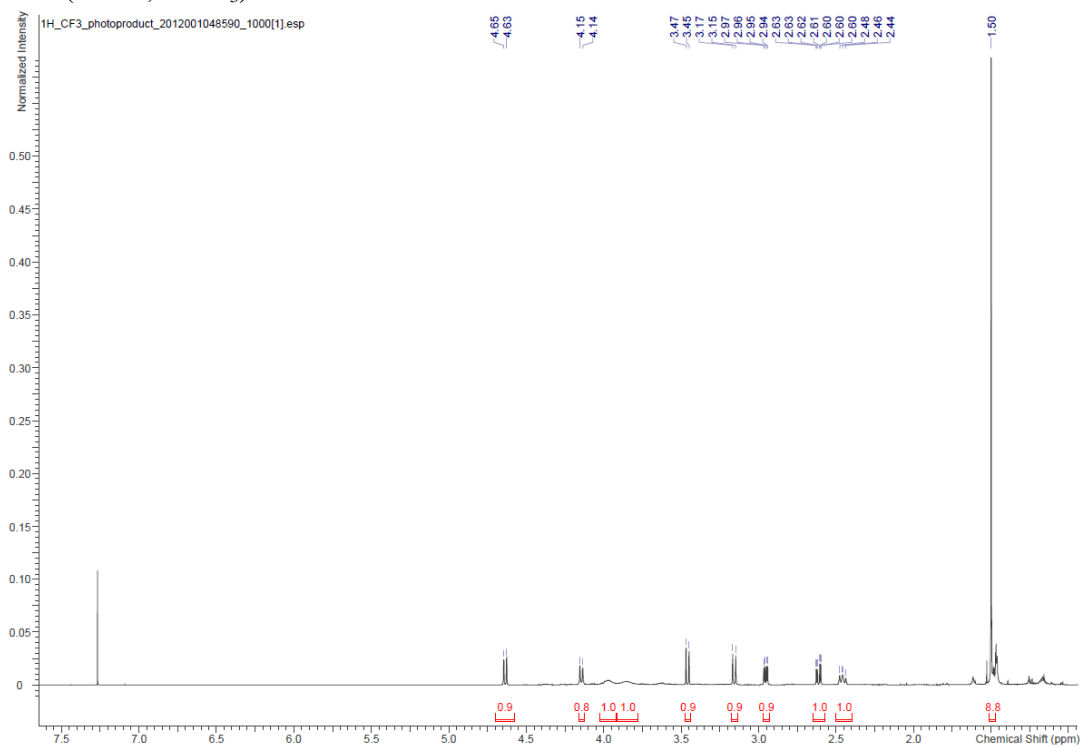
¹³C NMR (300 K, CDCl₃)



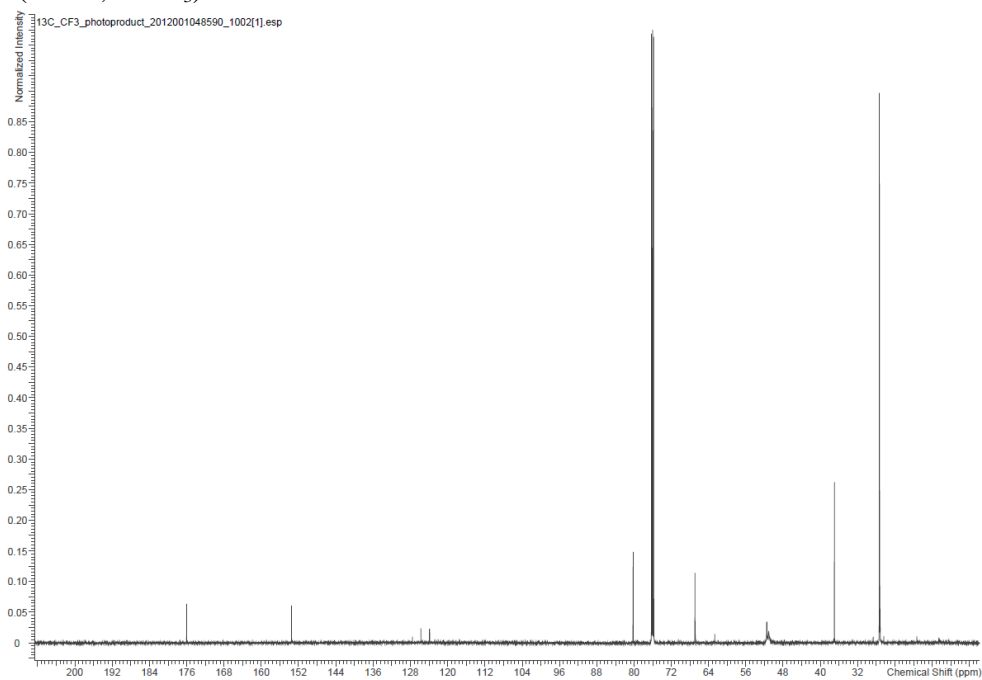
N-tert-butoxycarbonyl-5-trifluoromethyl-3-aza-9-oxatricyclo[5.3.0.0^{1,5}]decan-8-one (8d)



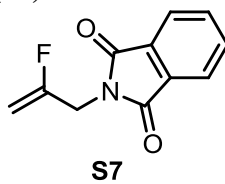
¹H NMR (300 K, CDCl₃):



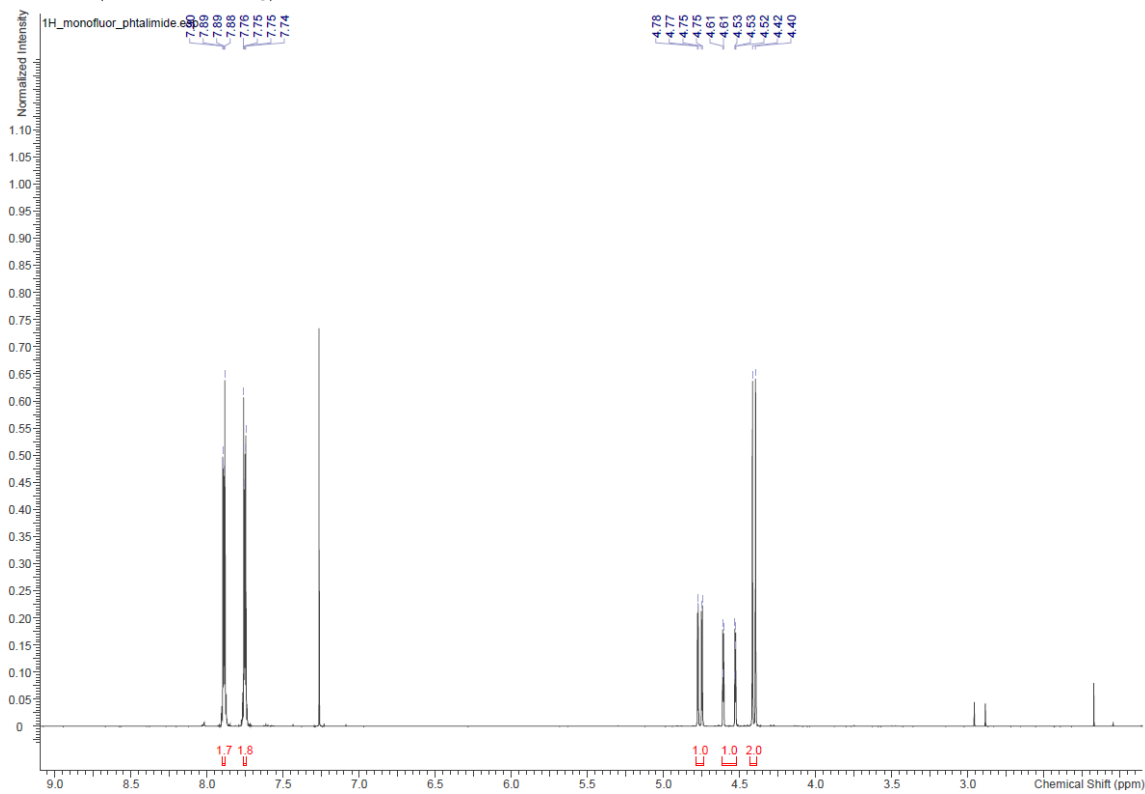
¹³C NMR (300 K, CDCl₃)



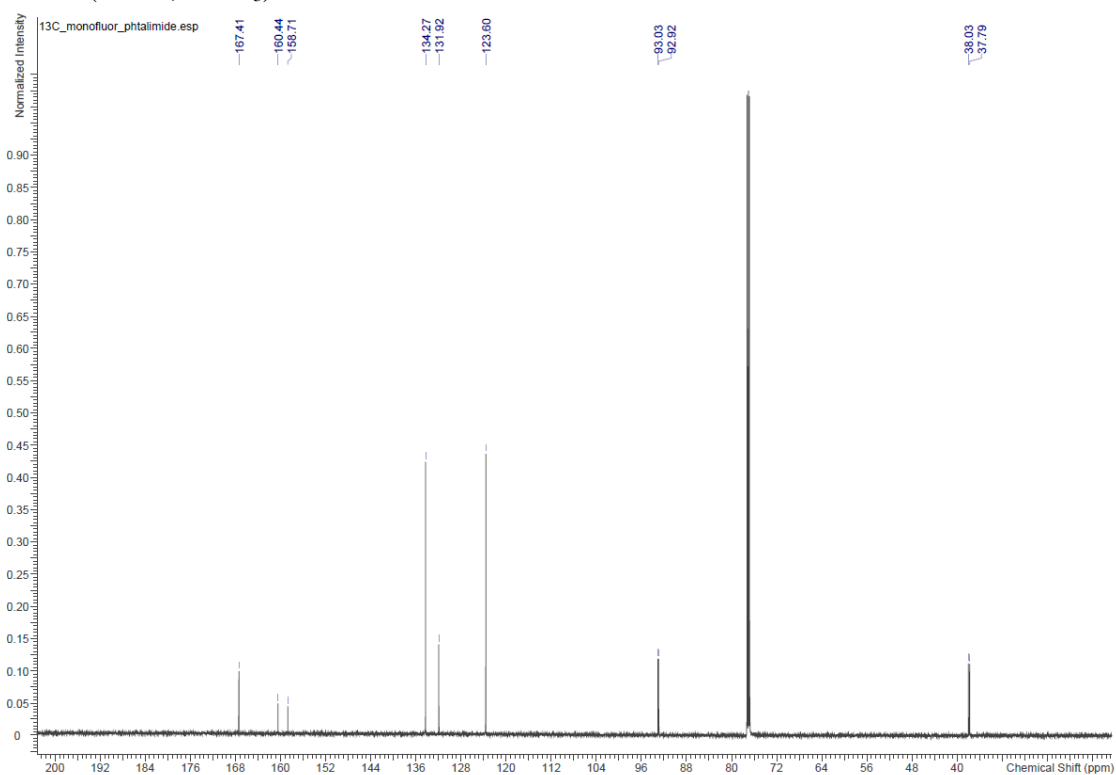
2-(2-Fluoroallyl)isoindoline-1,3-dione (S7)



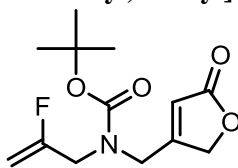
^1H NMR (300 K, CDCl_3):



^{13}C NMR (300 K, CDCl_3)

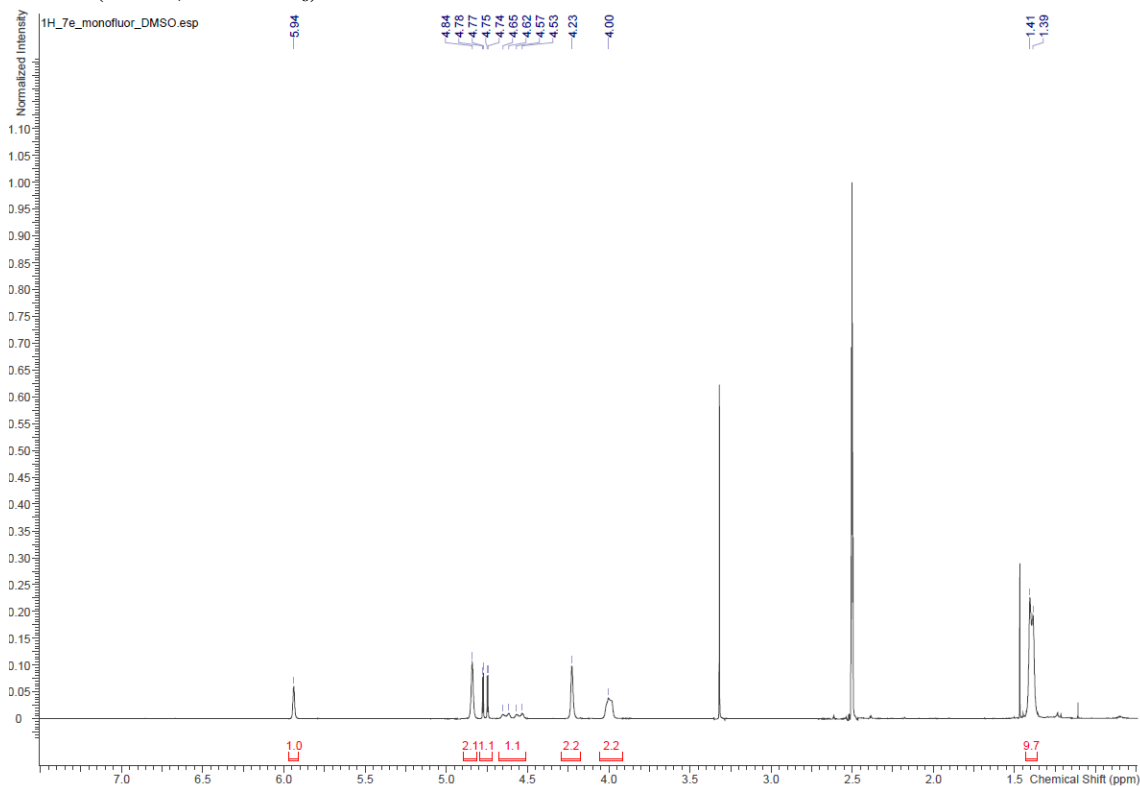


***tert*-Butyl 2-fluoroallyl[(5-oxo-2,5-dihydrofuran-3-yl)methyl]carbamate (7e)**

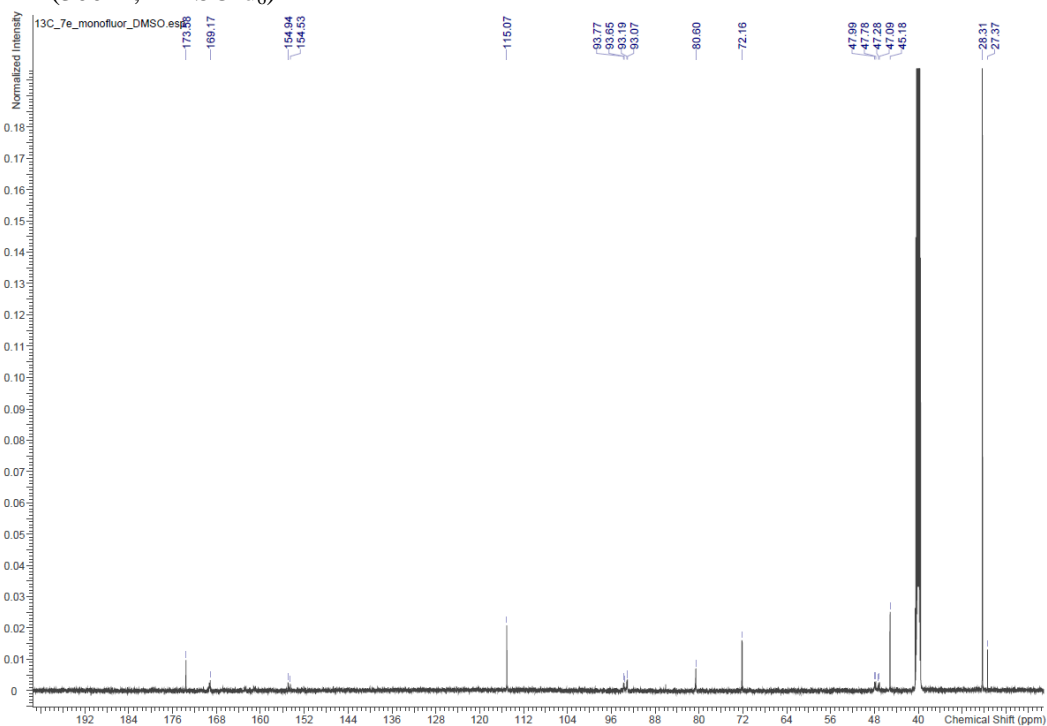


7e

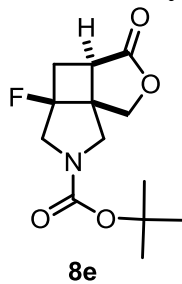
¹H NMR (300 K, DMSO-d₆):



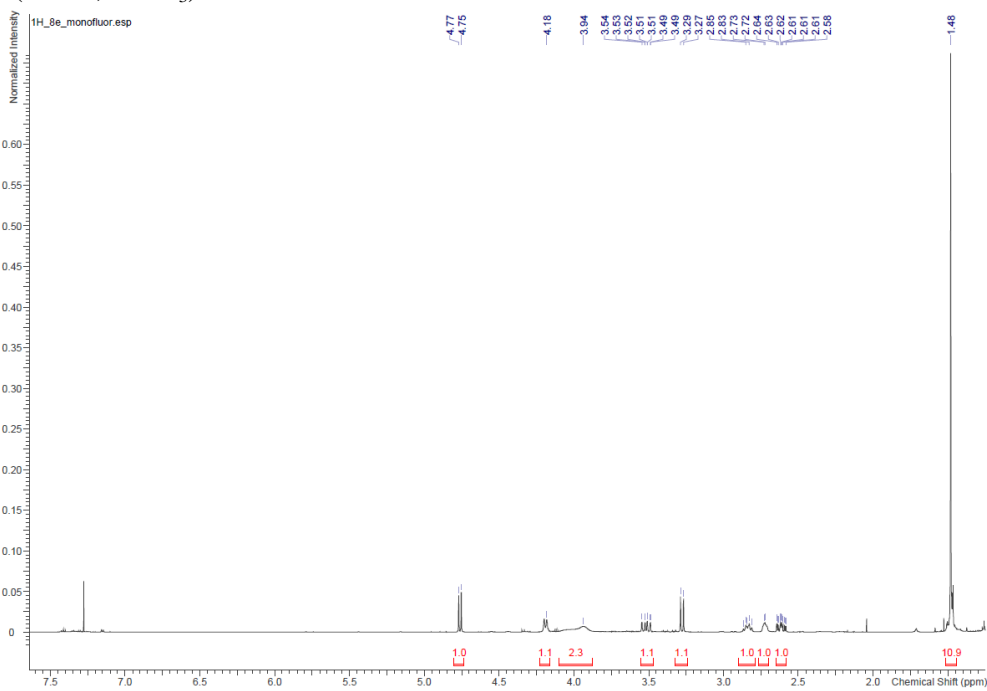
¹³C NMR (300 K, DMSO-d₆):



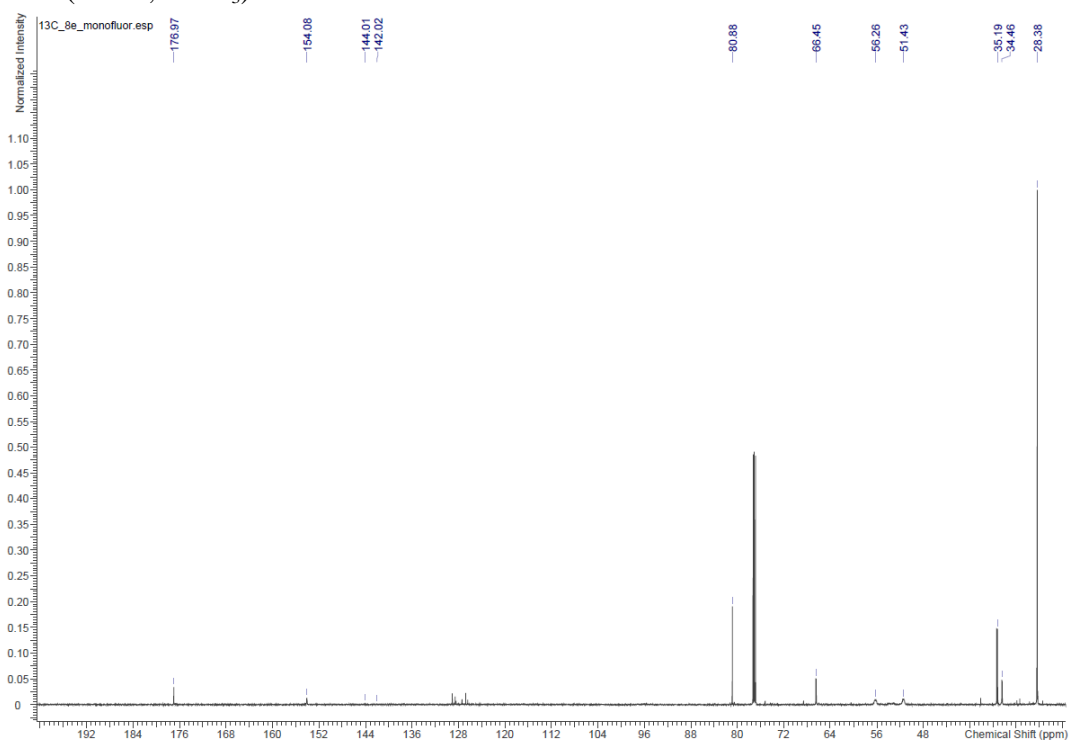
N-tert-butoxycarbonyl-5-fluoromethyl-3-aza-9-oxatricyclo[5.3.0.0^{1,5}]decan-8-one (8e)



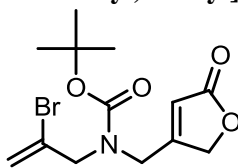
¹H NMR (300 K, CDCl₃):



¹³C NMR (300 K, CDCl₃):

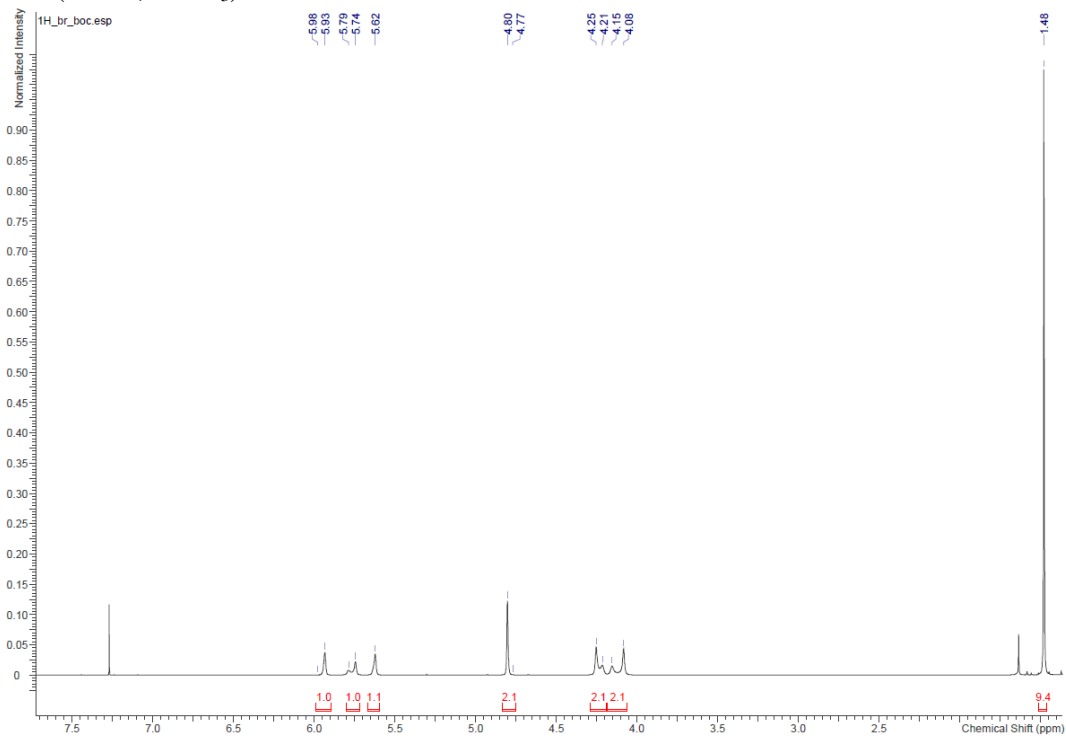


***tert*-Butyl 2-bromoallyl[(5-oxo-2,5-dihydrofuran-3-yl)methyl]carbamate (7f)**

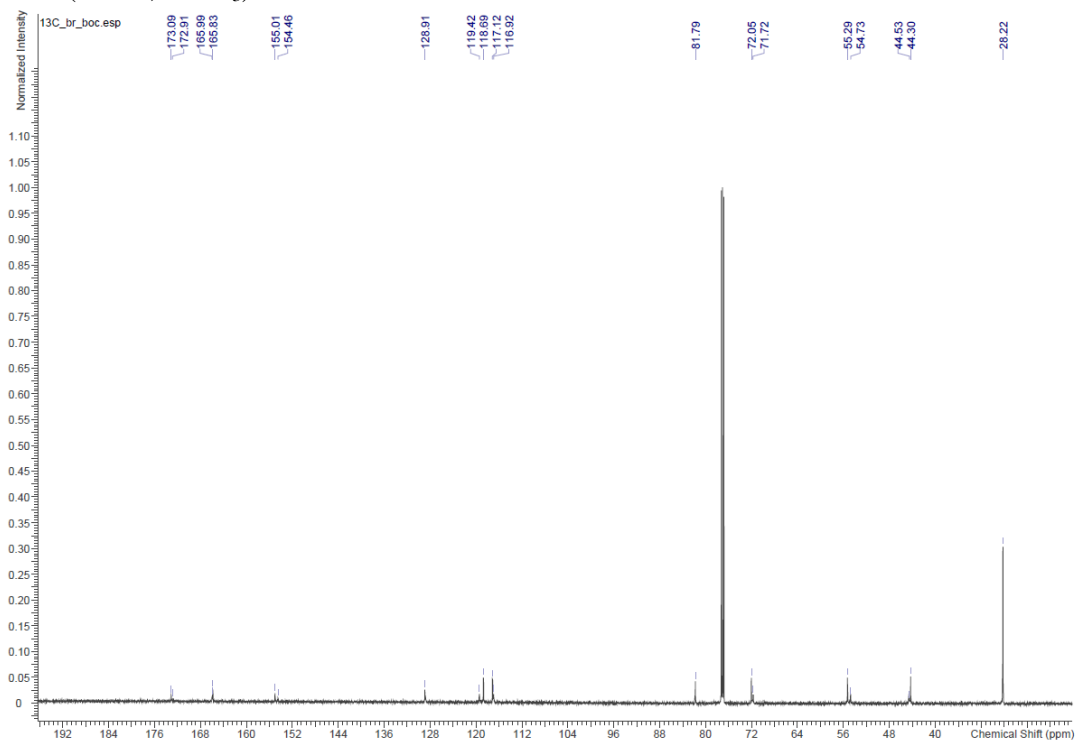


7f

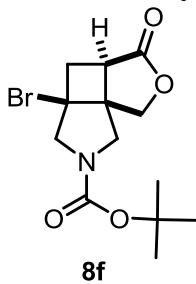
¹H NMR (300 K, CDCl₃):



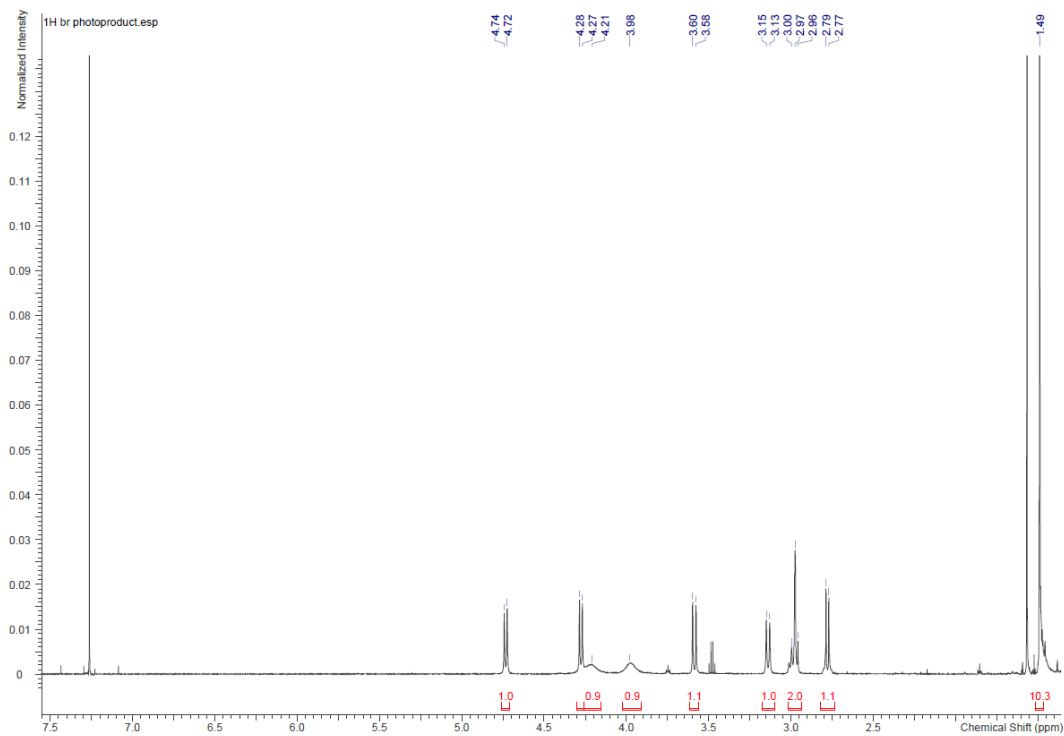
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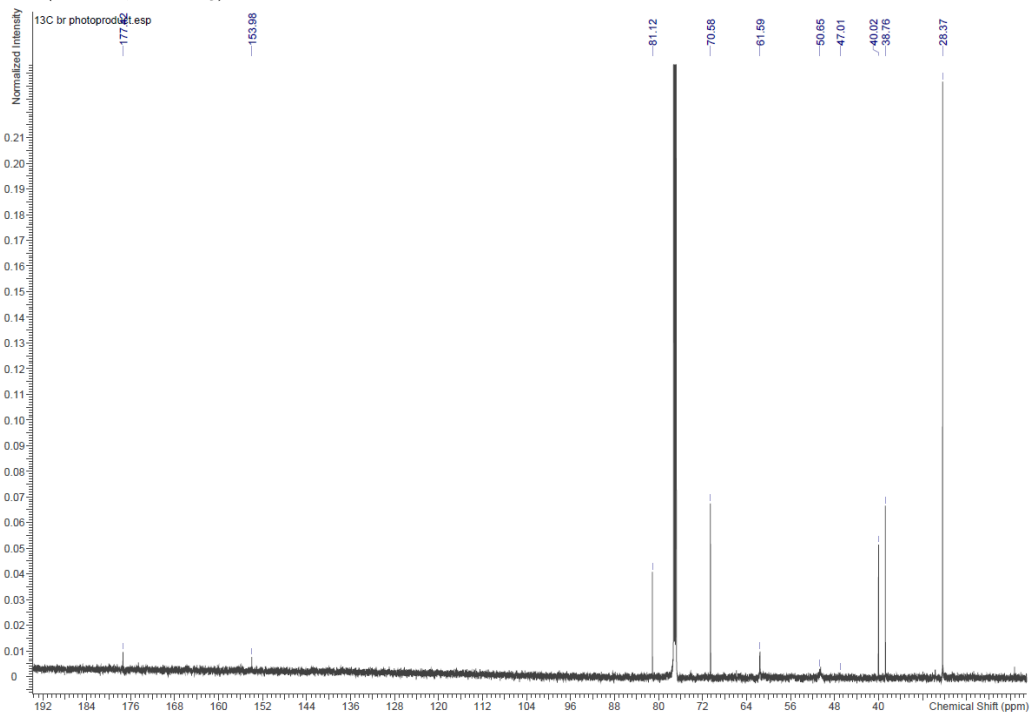
N-tert-butoxycarbonyl-5-bromomethyl-3-aza-9-oxatricyclo[5.3.0.0^{1,5}]decan-8-one (8f)



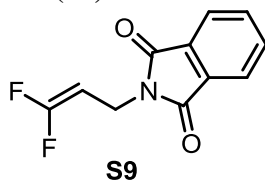
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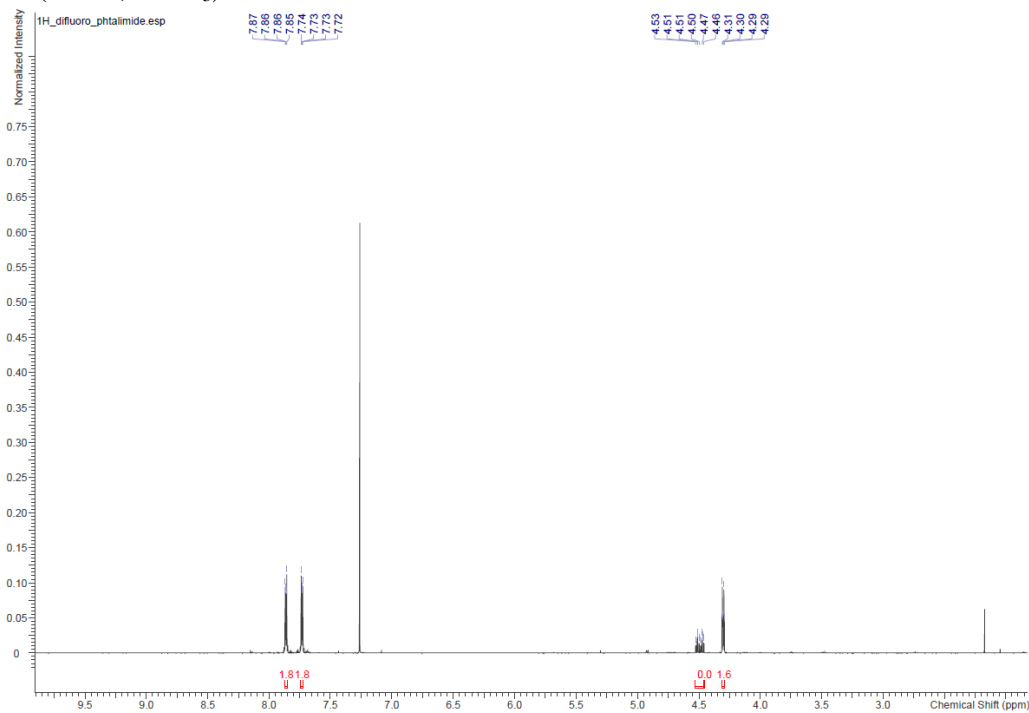
¹³C NMR (300 K, CDCl₃)



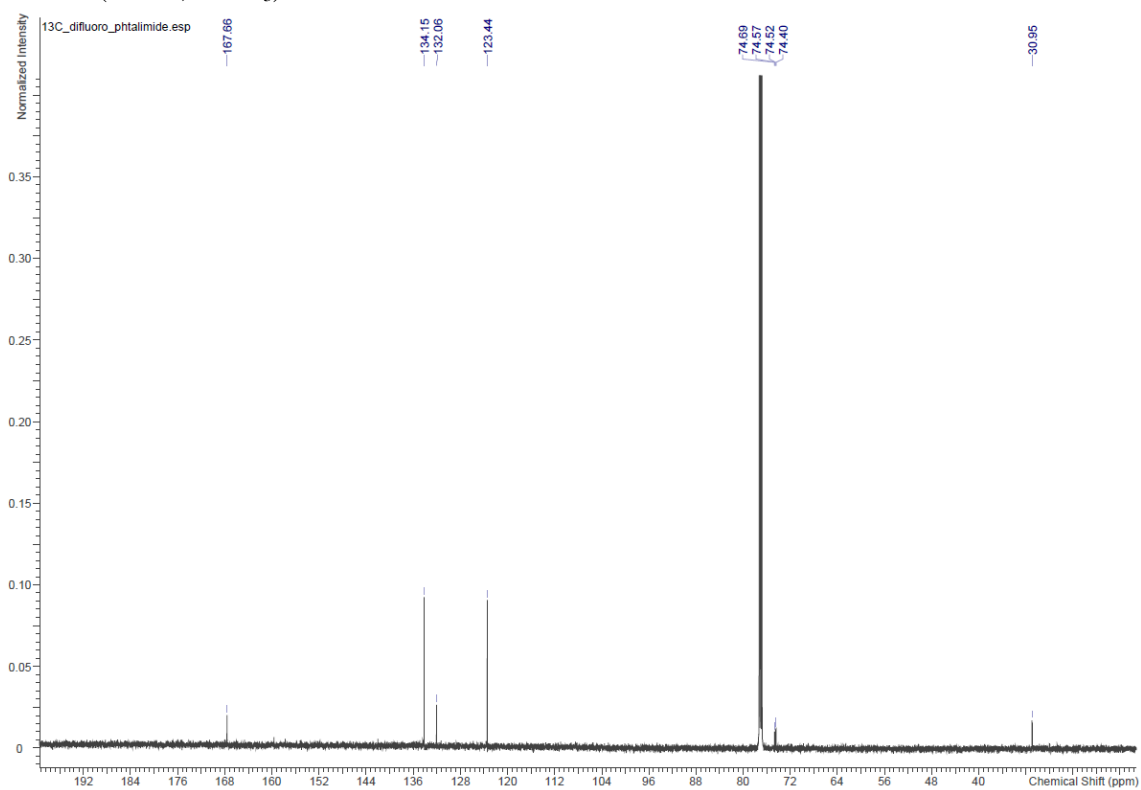
2-(3,3-Difluoroallyl)isoindoline-1,3-dione (S9)



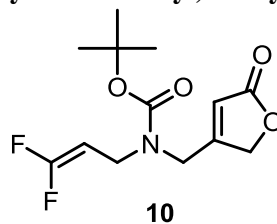
¹H NMR (300 K, CDCl₃):



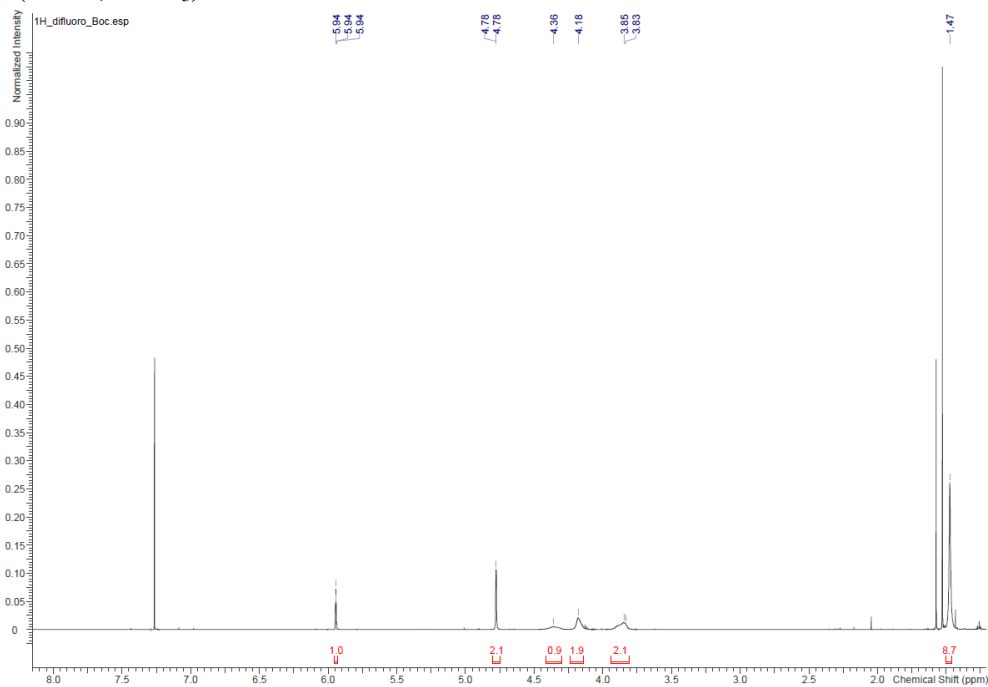
¹³C NMR (300 K, CDCl₃)



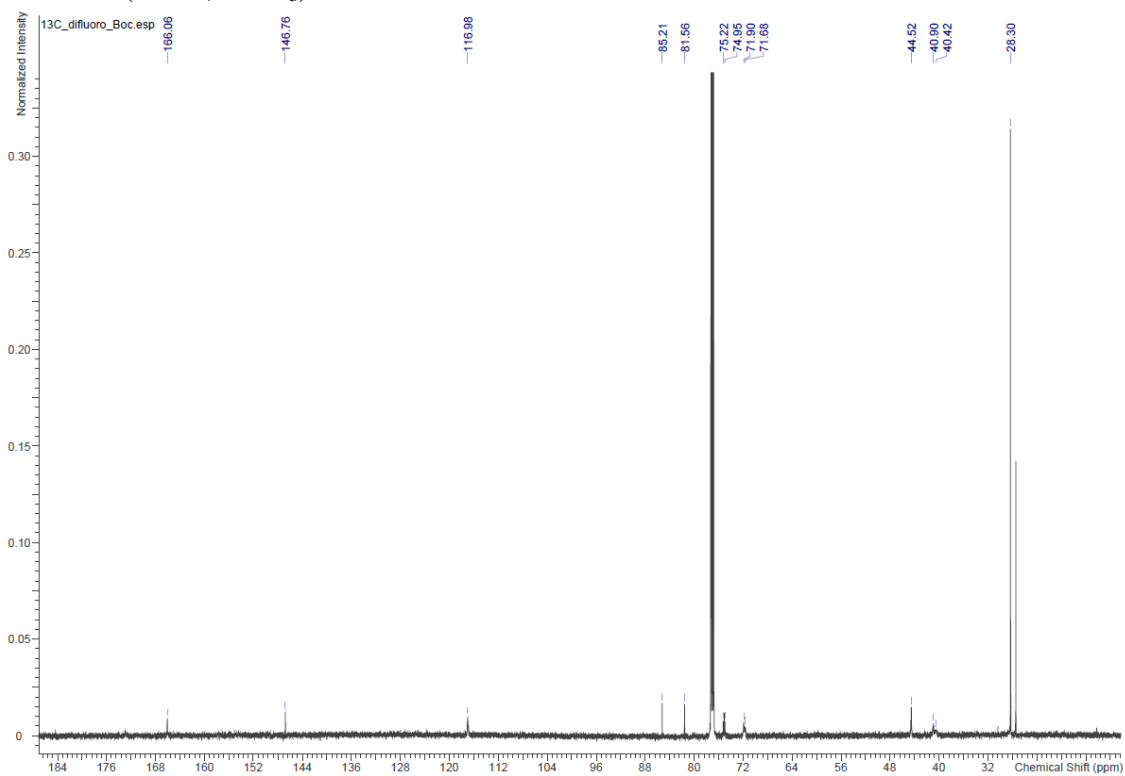
***tert*-Butyl 3,3-difluoroallyl[(5-oxo-2,5-dihydrofuran-3-yl)methyl]carbamate (10)**



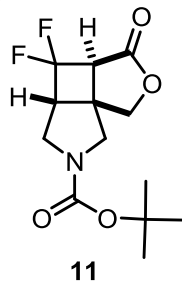
¹H NMR (300 K, CDCl₃):



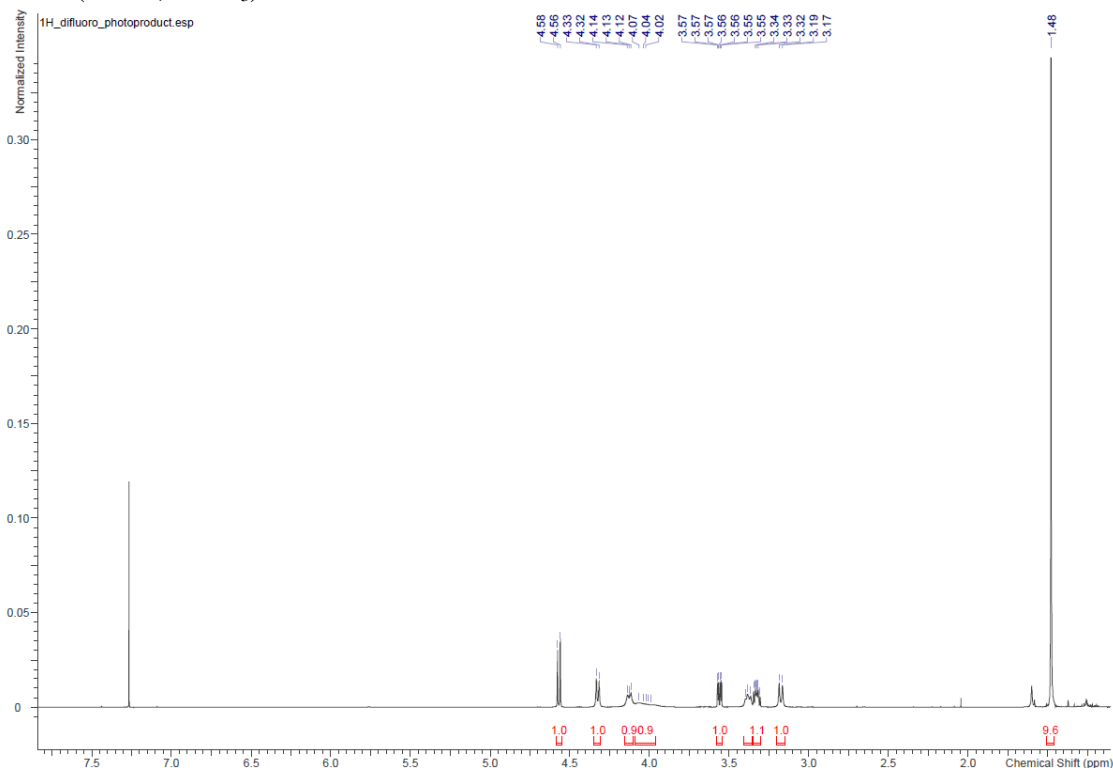
¹³C NMR (300 K, CDCl₃)



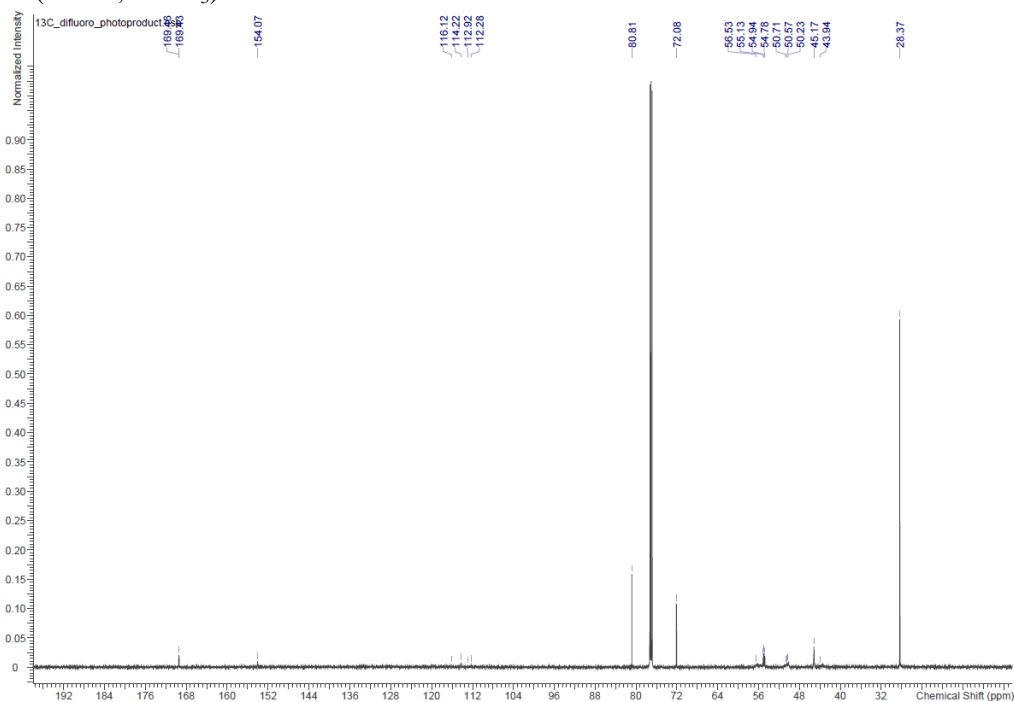
N-tert-butoxycarbonyl-6,6-difluoromethyl-3-aza-9-oxatricyclo[5.3.0.0^{1,5}]decan-8-one (11)



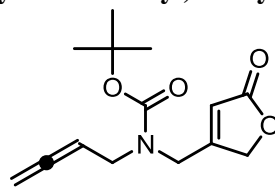
¹H NMR (300 K, CDCl₃):



¹³C NMR (300 K, CDCl₃):

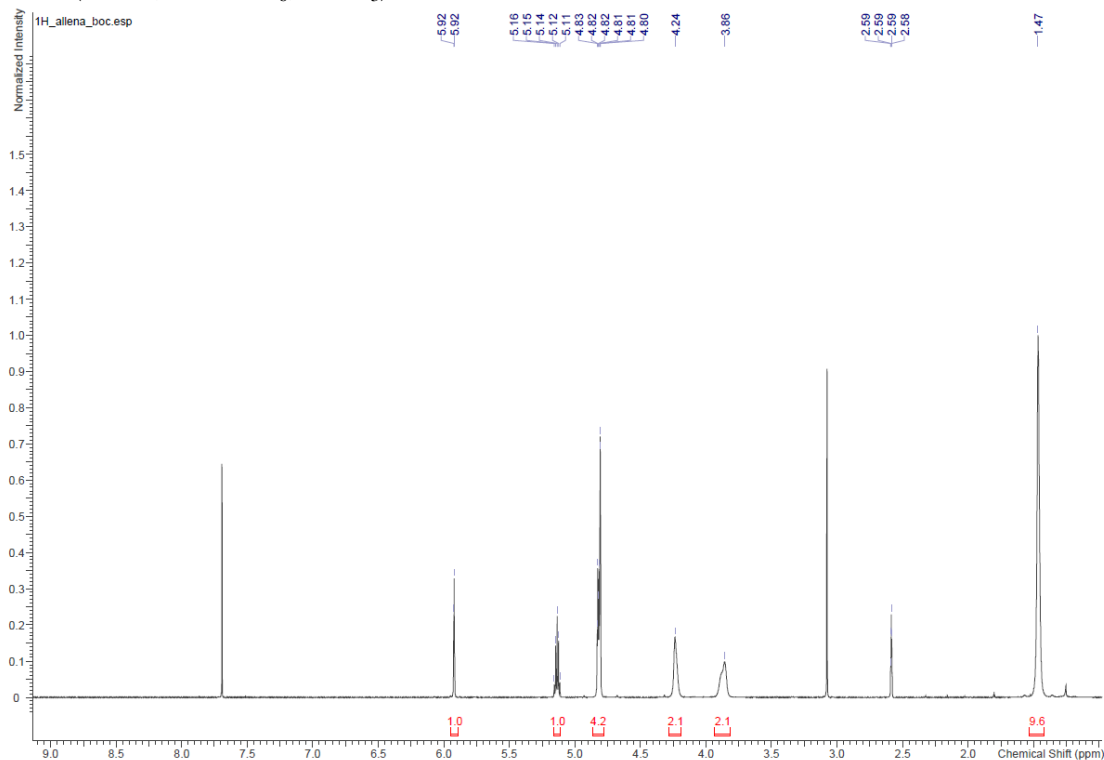


***tert*-Butyl buta-2,3-dienyl((2-oxo-2,5-dihydrofuran-3-yl)methyl)carbamate (12)**

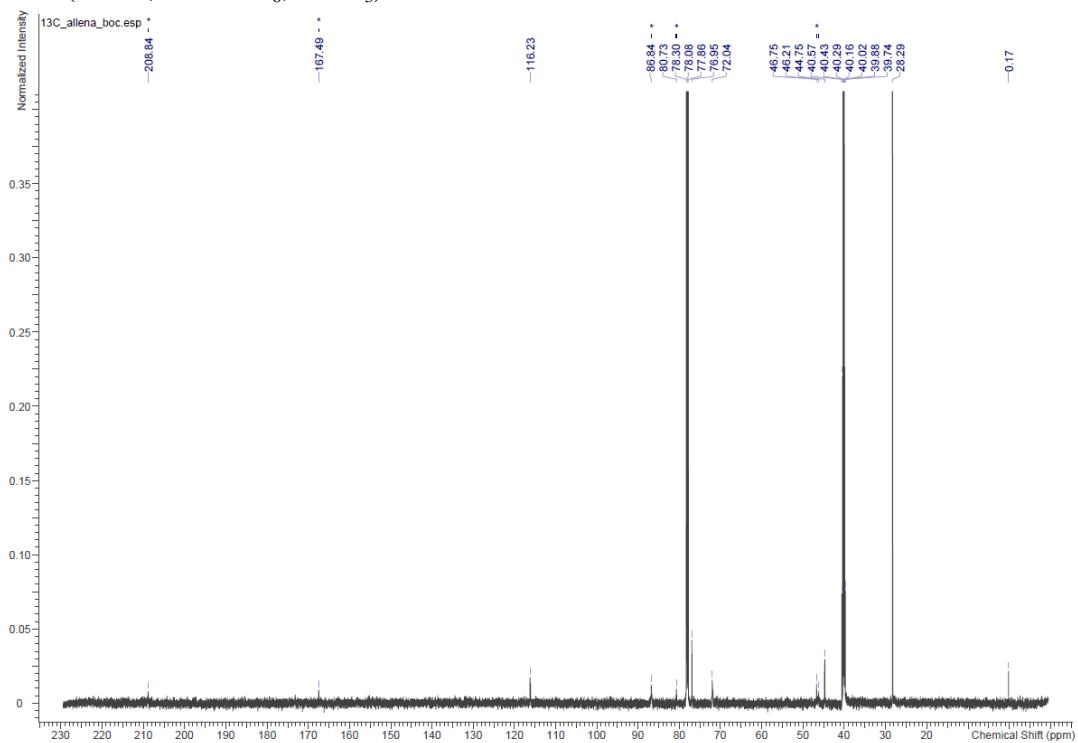


12

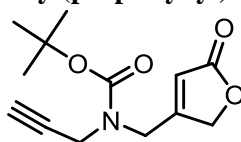
¹H NMR (300 K, DMSO-d₆, CDCl₃):



¹³C NMR (300 K, DMSO-d₆, CDCl₃):

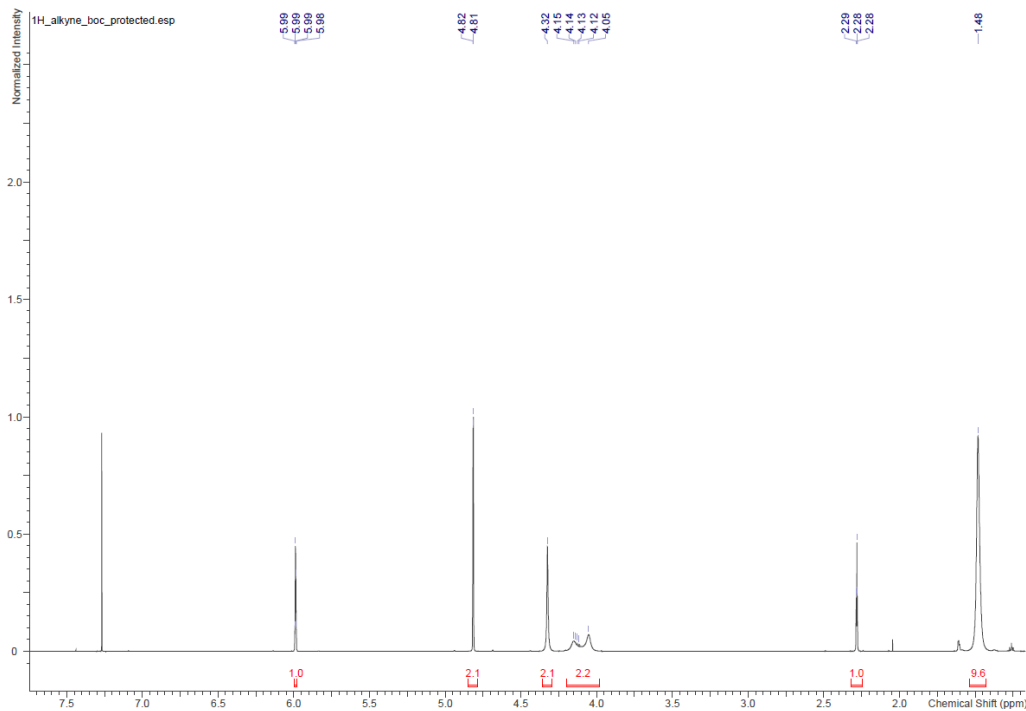


***tert*-Butyl (5-oxo-2,5-dihydrofuran-3-yl)methyl(prop-2-ynyl)carbamate (14)**

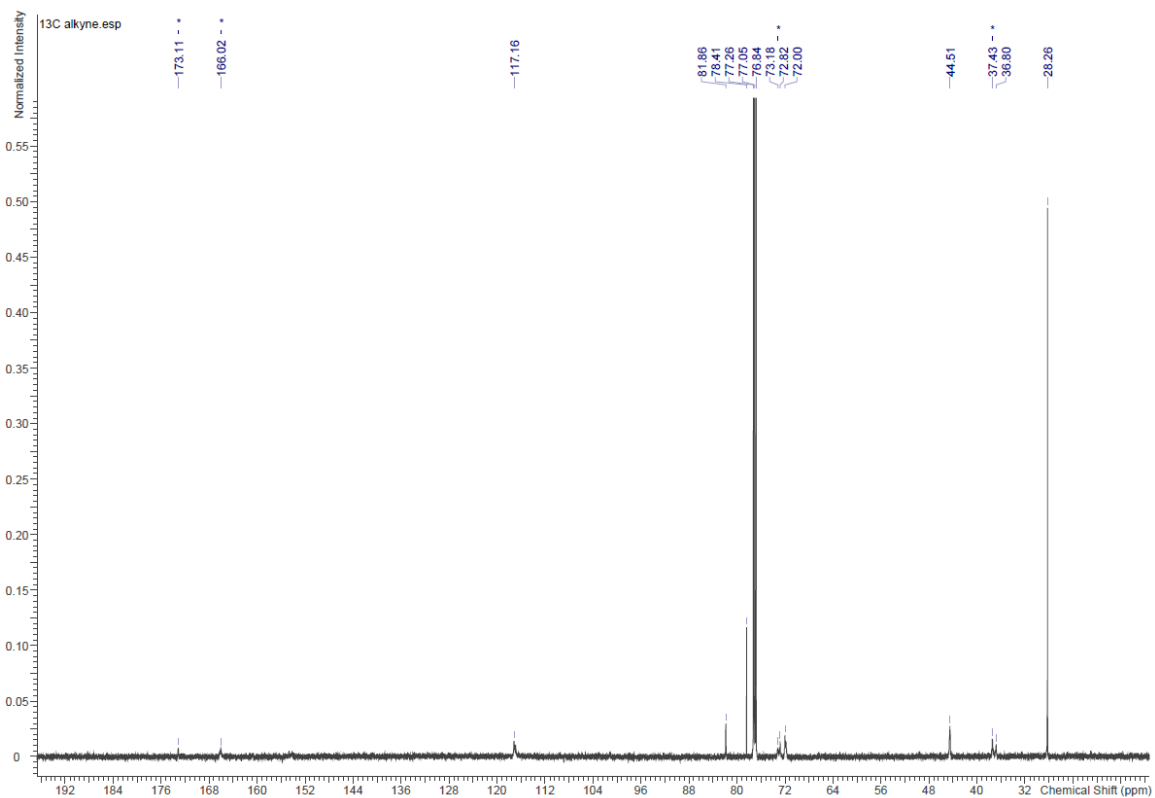


14

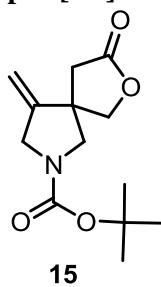
¹H NMR (300 K, CDCl₃):



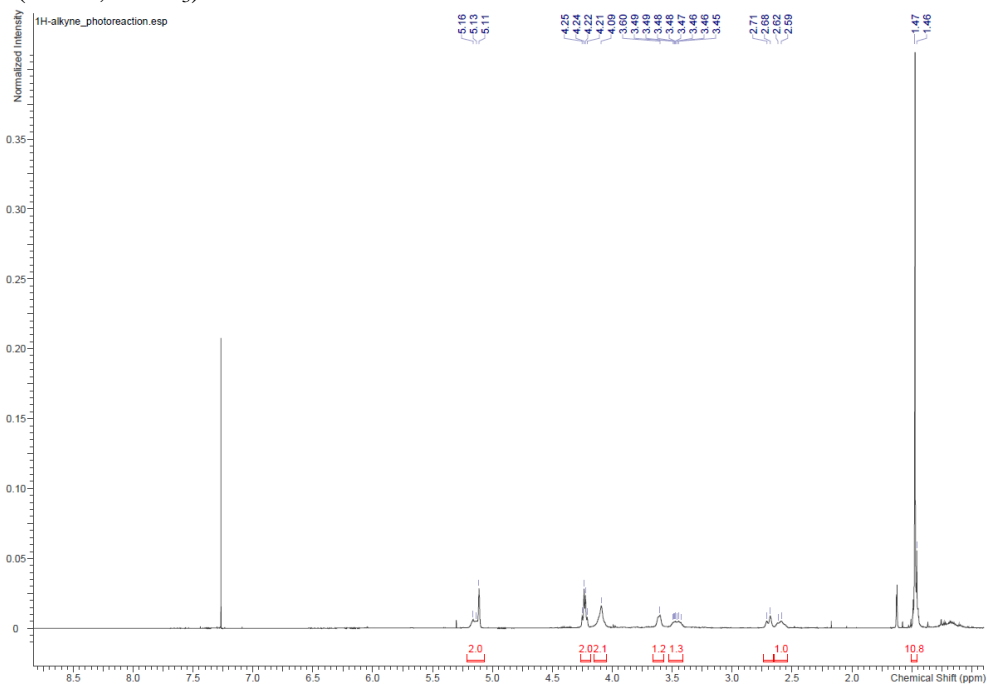
¹³C NMR (300 K, CDCl₃)



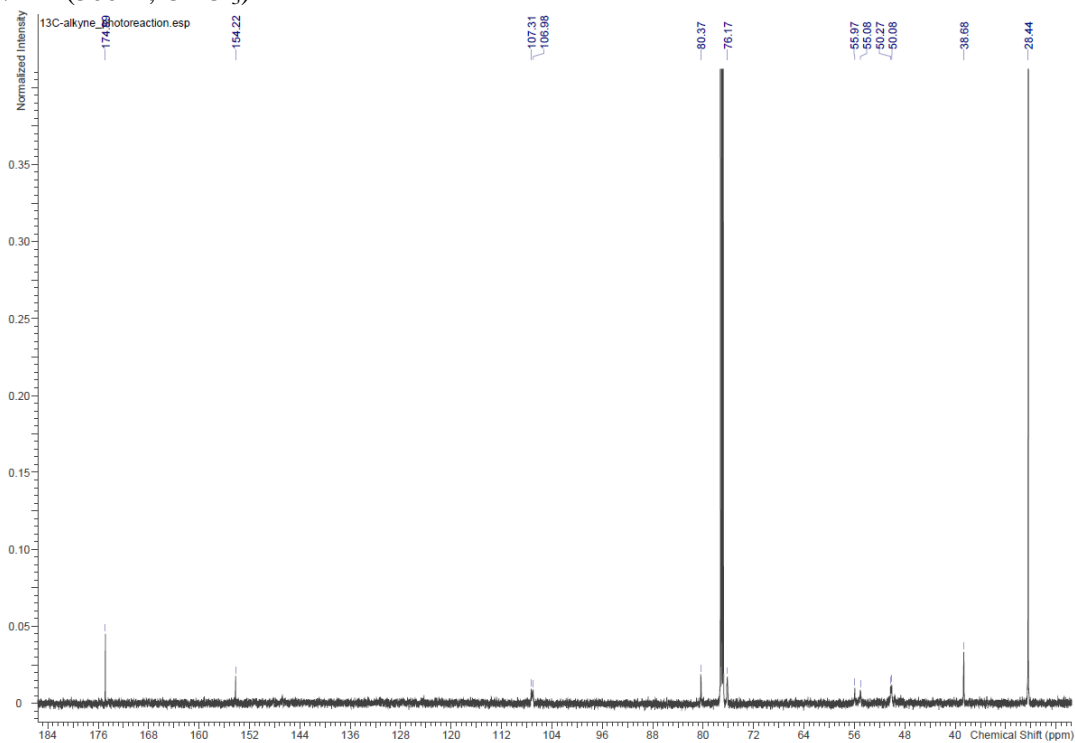
***tert*-Butyl 9-methylene-3-oxo-2-oxa-7-azaspiro[4.4]nonane-7-carboxylate (15)**



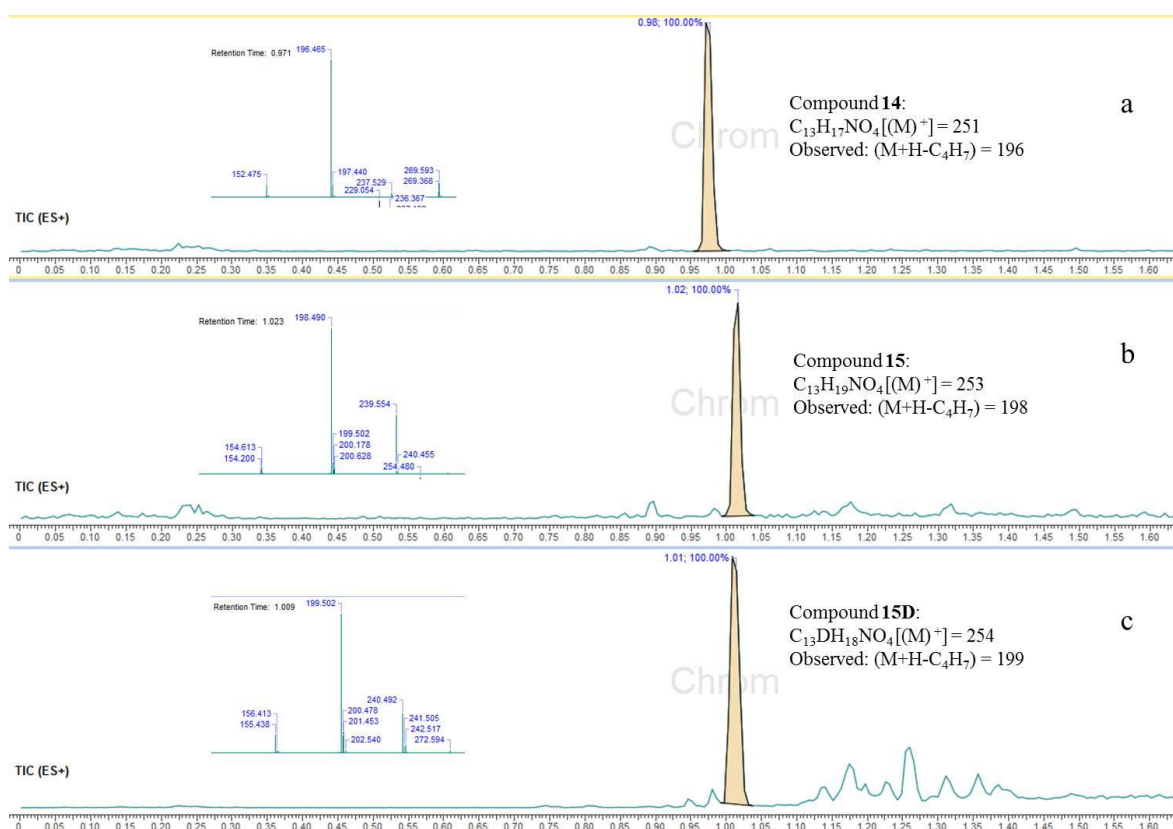
¹H NMR (300 K, CDCl₃):



¹³C NMR (300 K, CDCl₃):

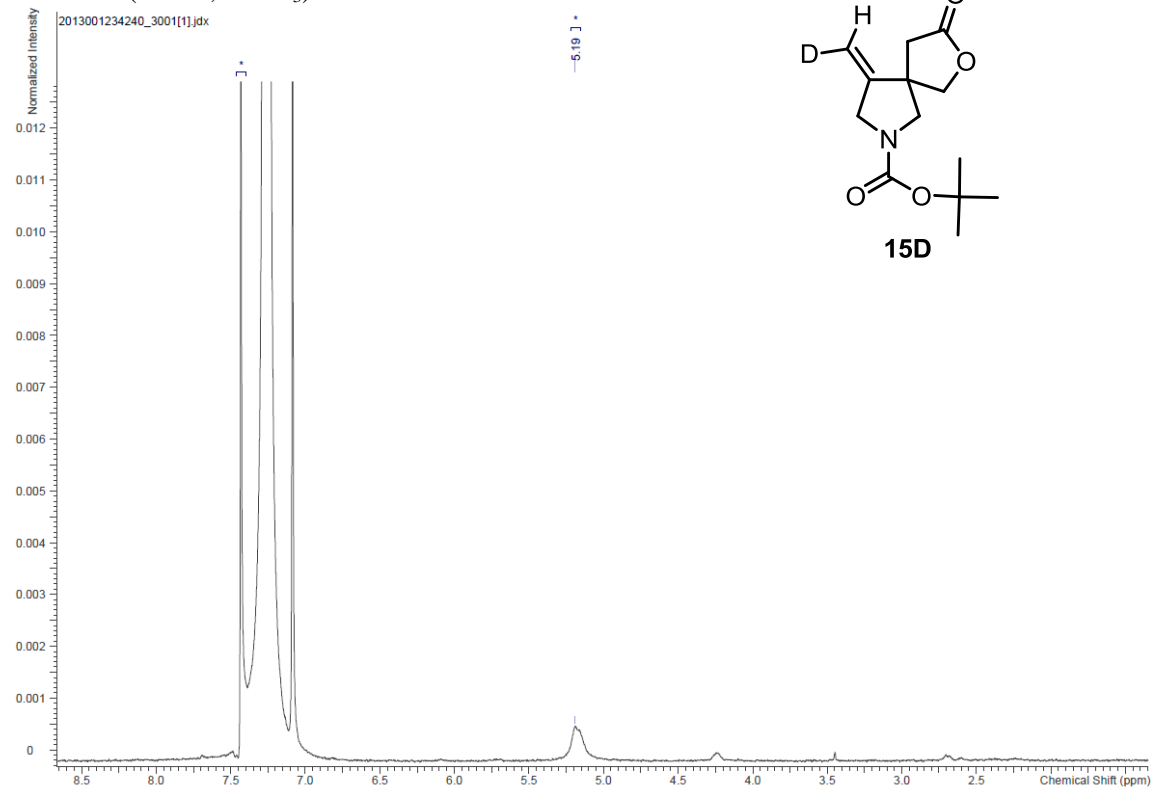


LC-MS comparison for compounds **14** (a), **15** (b) and **15D** (c)

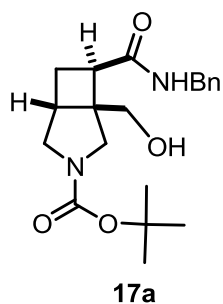


***tert*-Butyl -9-(deuteriomethylene)-2-oxo-3-oxa-7-azaspiro[4.4]nonane-7-carboxylate (**15D**)**

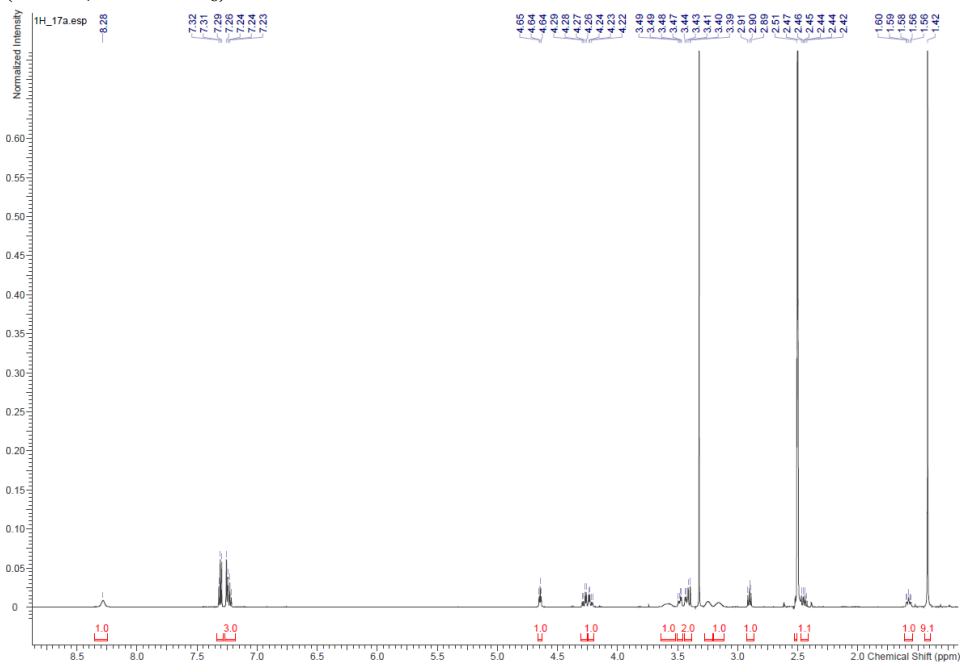
2H NMR (300 K, $CDCl_3$):



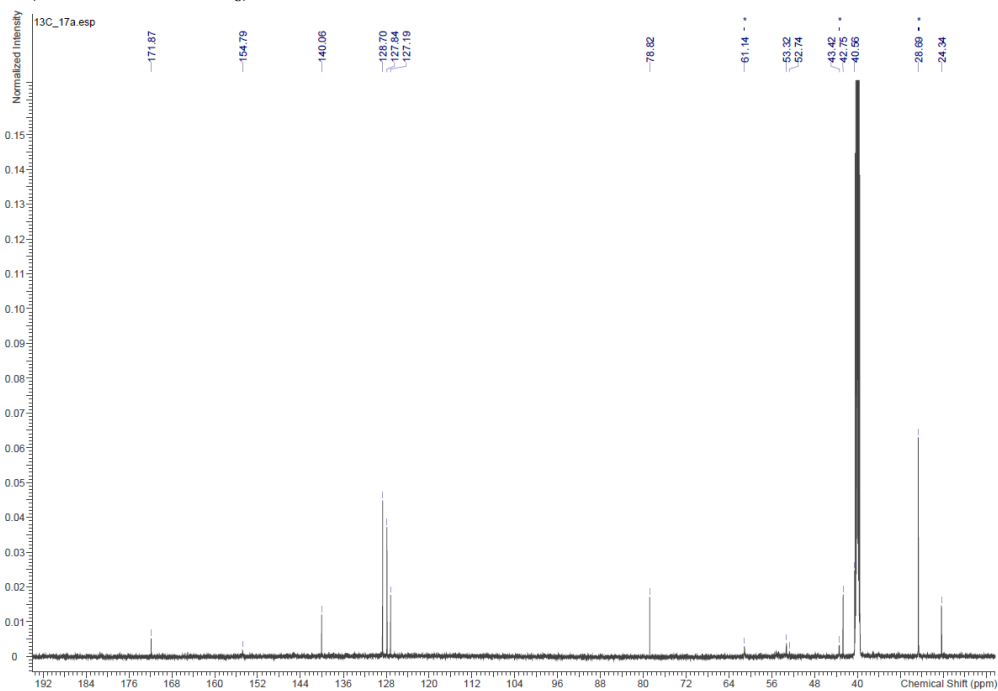
***tert*-Butyl-7-(benzylcarbamoyl)-1-(hydroxymethyl)-3-azabicyclo[3.2.0]heptane-3-carboxylate (17a)**



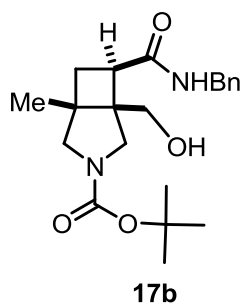
¹H NMR (300 K, DMSO-d₆):



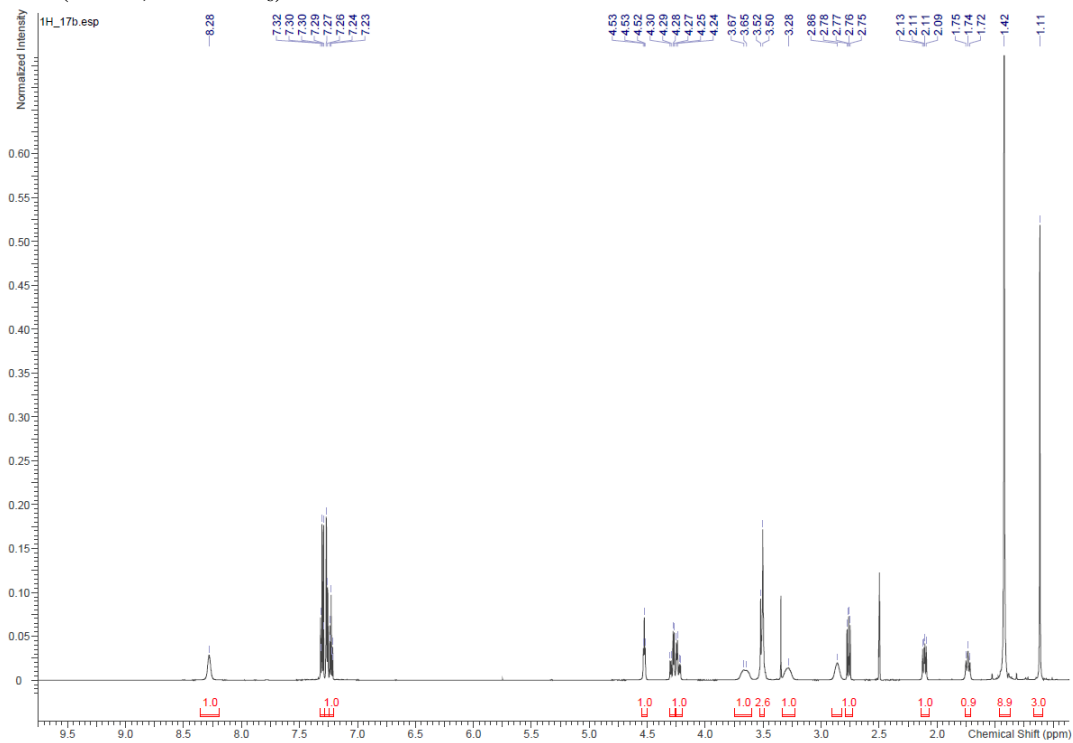
¹³C NMR (300 K, DMSO-d₆):



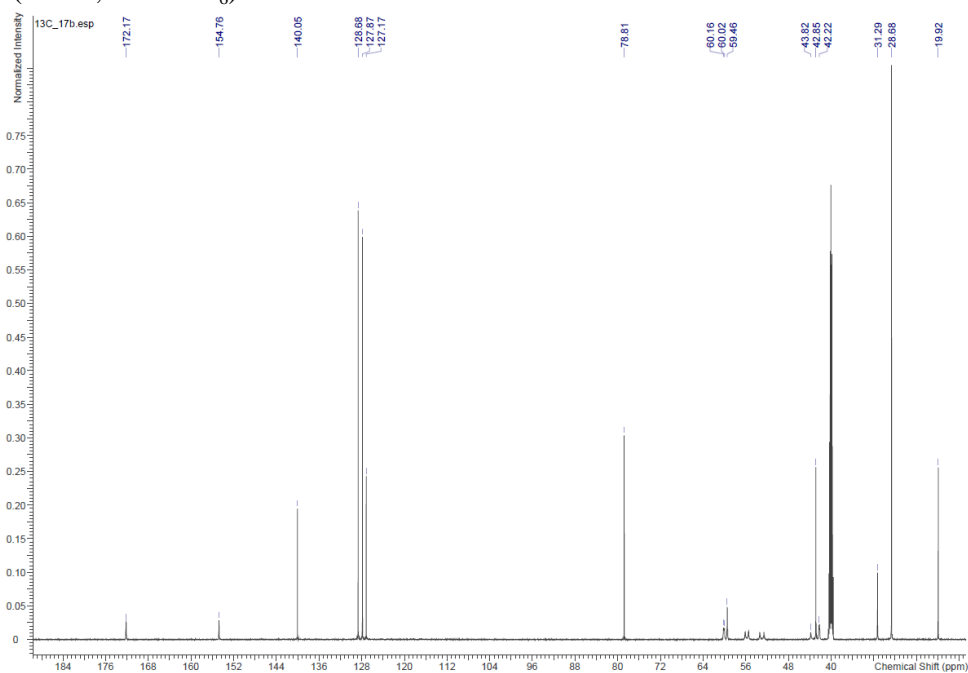
***tert*-Butyl-7-(benzylcarbamoyl)-1-(hydroxymethyl)-5-methyl-3-azabicyclo[3.2.0]heptane-3-carboxylate (17b)**



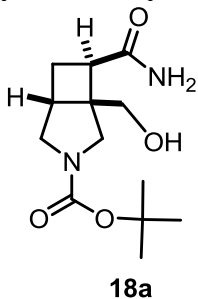
¹H NMR (300 K, DMSO-d₆):



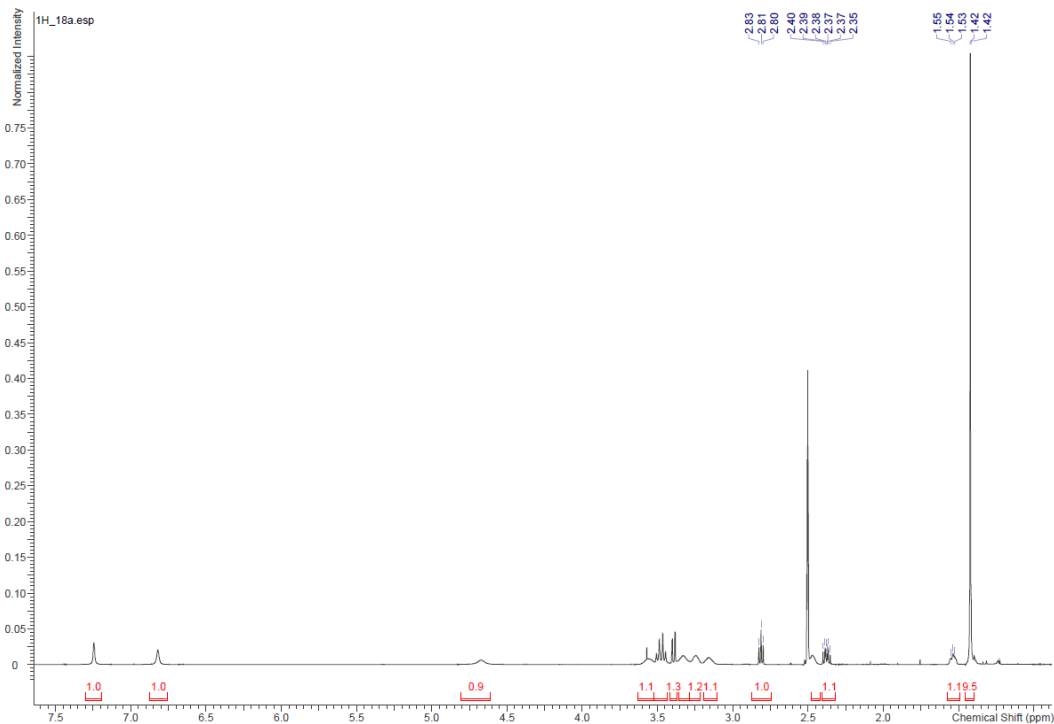
¹³C NMR (300 K, DMSO-d₆):



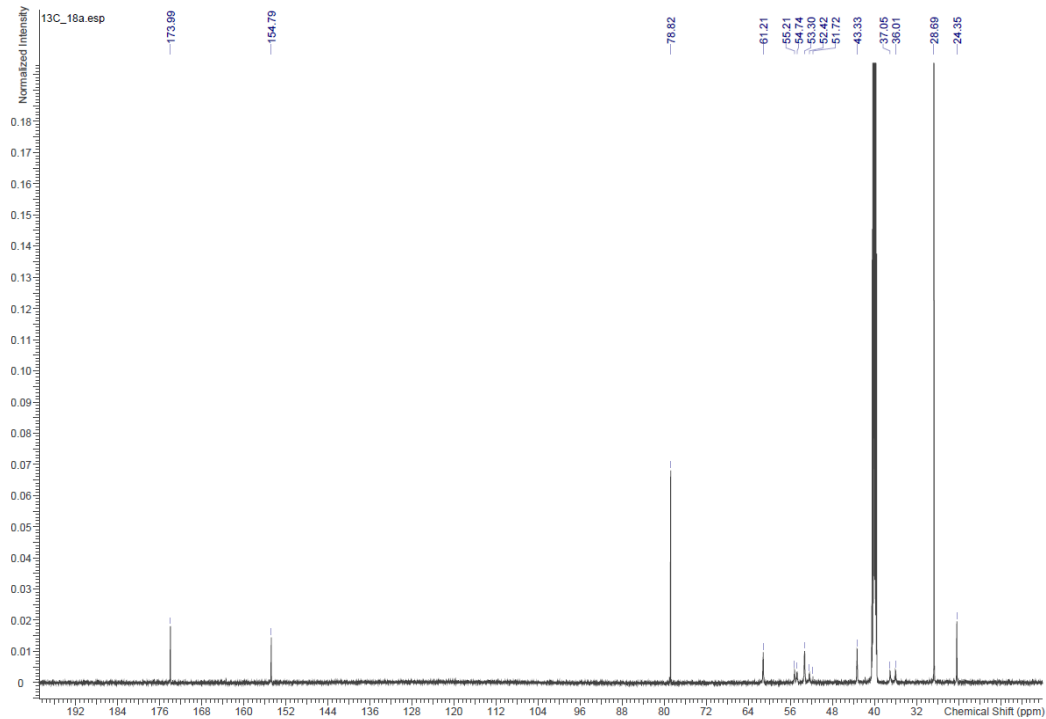
tert-Butyl 7-carbamoyl-1-(hydroxymethyl)-3-azabicyclo[3.2.0]heptane-3-carboxylate (18a)



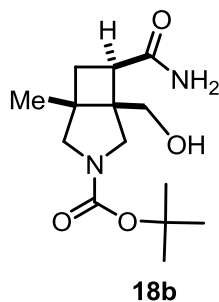
¹H NMR (323 K, DMSO-d₆):



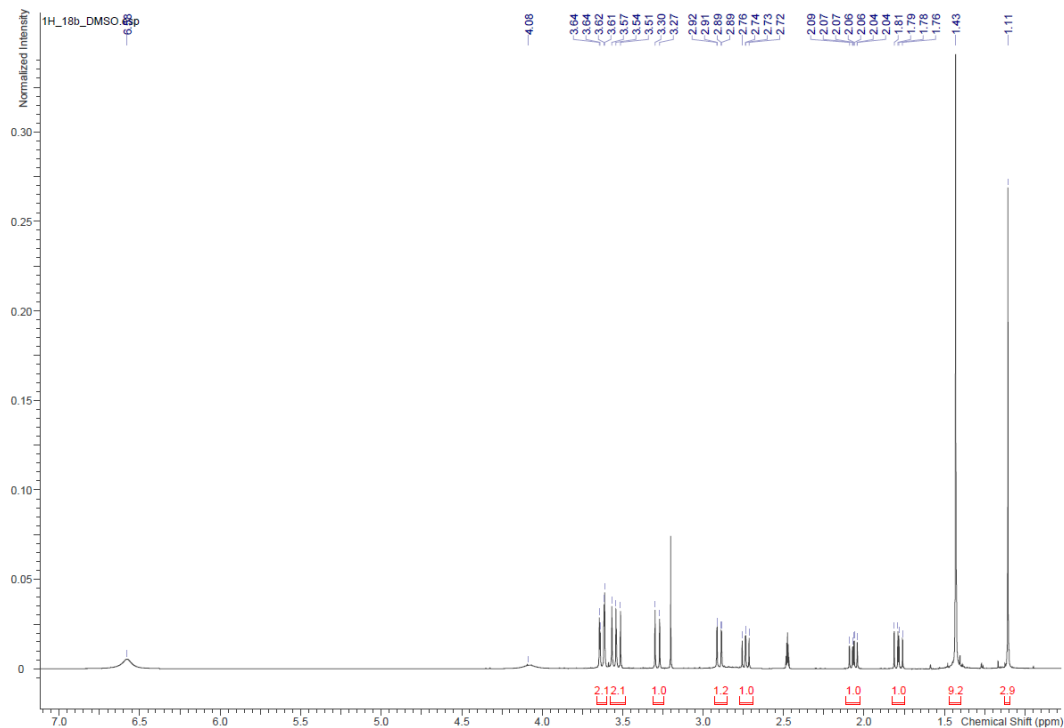
¹³C NMR (323 K, DMSO-d₆)



tert-Butyl-6-carbamoyl-5-(hydroxymethyl)-1-methyl-3-azabicyclo[3.2.0]heptane-3-carboxylate (18b)



¹H NMR (323 K, DMSO-d₆):



¹³C NMR (323 K, DMSO-d₆):

