Asymmetric vinylogous Michael addition of 5-substituted-furan-2(3H)-ones to α,β-unsaturated-γ-lactam

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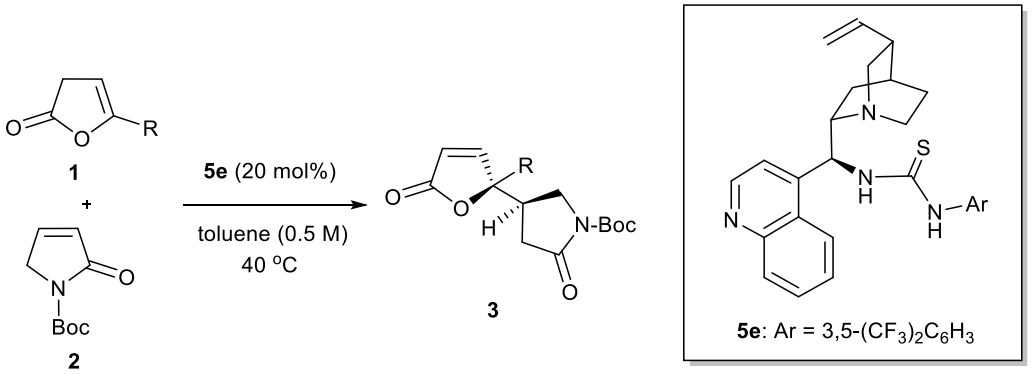
1. General information

Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification. NMR spectra were acquired on a Bruker Ultra Shield 700 instrument, running at 700 MHz for ^{1}H and 176 MHz for ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$: 7.26 ppm for ^{1}H NMR, 77.16 ppm for ^{13}C NMR). Mass spectra were recorded on a Bruker Maxis Impact spectrometer using electrospray (ES+) ionization (referenced to the mass of the charged species). Optical rotations were measured on a Perkin-Elmer 241 polarimeter and $[\alpha]_D$ values are given in deg•cm•g^{-1}•dm^{-1}; concentration c is listed in g•(100 mL)$^{-1}$ .Analytical thin layer chromatography (TLC) was performed using pre-coated aluminum-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation. The enantiomeric ratio (er) of the products was determined by chiral stationary phase UPC[2] (Daicel Chiralpak IB column). In order to find conditions for the separation of enantiomers, products **3** with low enantiomeric enrichment were prepared using equimolar amount of pseudoenantiomeric catalyst **5d** and **5e** (20 mol%) as catalyst of the reaction. Silica gel (Silica gel 60, 230-400 mesh, Fluka) was used for flash chromatography (FC). 5-Substituted-furane-2(3*H*)-ones **1**[1] and *N*-Boc-protected *α,β*-unsaturated-*γ*-lactam **2**[2] were synthetized according to literature procedures.

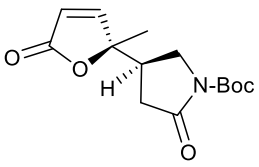
(1) A. Tsolomitis and C. *J.* Sandris, *Heterocycl. Chem.,* 1983, **20**, 1545-1548.

(2) S.J. Macdonald, G.A. Inglis, D. Bentley and M. D. Dowle, *Tetrahedron Lett.,* 2002, **43**, 5057-5060.

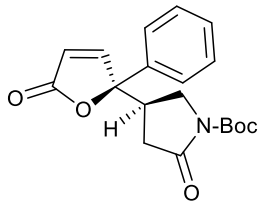
2. Asymmetric vinylogous Michael addition involving α,β-unsaturated-γ-lactam 2 as an acceptor - general procedure



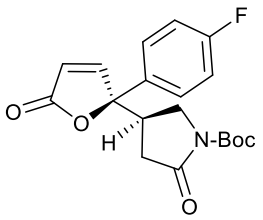
In an ordinary 4 mL glass vial, equipped with a magnetic stirring bar and a screw cap, catalyst **5e** (0.2 equiv, 0.01 mmol, 5.6 mg), 5-substituted-furane-2(3*H*)-one **1** (2.0 equiv, 0.1 mmol) and *N*-Boc-protected *α,β*-unsaturated-*γ*-lactam **2** (1.0 equiv, 0.05 mmol, 9.16 mg) were dissolved in toluene (0.1 mL) and stirred for 24-72 h at 40 °C using heating block. Crude product **3** was purified by the flash chromatography on silica gel.



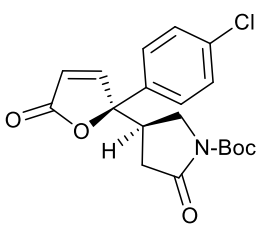
(*R*)-*tert*-Butyl 4-((*R*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3a). Following the general procedure, pure product **3a** was isolated after 72 h by FC on silica (hexane:ethyl acetate 2:1) in 80% yield (11.3 mg, >20:1 dr) as a white solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.35 (d, J = 5.7 Hz, 1H), 6.14 (d, J = 5.7 Hz, 1H), 3.88 (dd, J = 11.1, 8.4 Hz, 1H), 3.60 (dd, J = 11.1, 7.9 Hz, 1H), 2.75 – 2.67 (m, 1H), 2.44 (dd, J = 17.4, 8.9 Hz, 1H), 2.26 (dd, J = 17.4, 9.4 Hz, 1H), 1.52 (s, 3H), 1.51 (s, 9H).^{13}C NMR (176 MHz, $CDCl_3$) δ 171.5, 171.4, 157.7, 149.7, 122.3, 87.4, 83.7, 46.9, 37.4, 34.1, 28.1 (3C), 22.5. HRMS: calculated for [$C_{14}H_{19}NO_5$+Na^+]: 304.1161; found: 304.1156. $[\alpha]_D^{22}$ = 21.4° (c = 1.0, $CHCl_3$). The er was determined by UPC^2 using a chiral Chiralpack IB column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; τ_{minor} = 3.31 min, τ_{major} = 3.62 min, (97:3 er).



(*R*)-*tert*-Butyl 2-oxo-4-((*R*)-5-oxo-2-phenyl-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (3b). Following the modified general procedure (CH_2Cl_2 was used as a solvent), pure product **3b** was isolated after 72 h by FC on silica (hexane:ethyl acetate 2:1) in 89% yield (15.3 mg, >20:1 dr) as a white solid.^{1}H NMR (700 MHz, $CDCl_3$) δ 7.63 (d, J = 5.7 Hz, 1H), 7.45 – 7.33 (m, 5H), 6.16 (d, J = 5.6 Hz, 1H), 3.60 (dd, J = 11.3, 8.4 Hz, 1H), 3.53 (dd, J = 11.3, 8.4 Hz, 1H), 3.11 (dq, J = 9.8, 8.5 Hz, 1H), 2.43 (dd, J = 17.4, 8.8 Hz, 1H), 2.31 (dd, J = 17.4, 9.7 Hz, 1H), 1.47 (s, 9H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 171.3, 171.3, 157.2, 149.9, 136.7, 129.5 (2C), 129.1, 125.1 (2C), 121.3, 89.8, 83.6, 46.9, 38.6, 33.7, 28.1 (3C). HRMS: calculated for [$C_{19}H_{21}NO_5$+Na^+]: 366.1317; found: 366.1310. $[\alpha]_D^{22}$ = -64.4° (c = 1.0, $CHCl_3$). The er was determined by UPC^2 using a chiral Chiralpack IB column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; τ_{minor} = 3.75 min, τ_{major} = 4.33 min, (97:3 er).

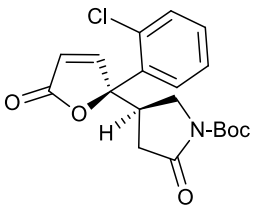


(*R*)-*tert*-Butyl 4-((*R*)-2-(4-fluorophenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3c). Following the modified general procedure (CH_2Cl_2 was used as a solvent), pure product **3c** was isolated after 72 h by FC on silica (hexane:ethyl acetate 2:1) in 99% yield (18.0 mg, >20:1 dr) as a white solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.61 (d, J = 5.6 Hz, 1H), 7.41 – 7.35 (m, 2H), 7.15 – 7.09 (m, 2H), 6.17 (d, J = 5.6 Hz, 1H), 3.60 – 3.50 (m, 2H), 3.12 – 3.04 (m, 1H), 2.43 (dd, J = 17.4, 8.8 Hz, 1H), 2.29 (dd, J = 17.4, 9.6 Hz, 1H), 1.48 (s, 9H).^{13}C NMR (176 MHz, $CDCl_3$) δ 171.1, 171.0, δ 162.9 (d, J_{C-F} = 249.3 Hz, 1C), 156.9, 149.8, 132.6 (d, J_{C-F} = 3.3 Hz, 1C), 127.0 (d, J_{C-F} = 8.3 Hz, 2C), 121.5, 116.5 (d, J_{C-F} = 22.0 Hz, 2C), 89.4, 83.6, 46.8, 38.6, 33.7, 28.1 (3C). HRMS: calculated for [$C_{19}H_{20}FNO_5$+Na^+]: 384.1223; found: 384.1232. $[\alpha]_D^{23}$ = -84.2° (c = 1.0, $CHCl_3$). The er was determined by UPC^2 using a chiral Chiralpack IB column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; τ_{minor} = 3,60 min, τ_{major} = 4.12 min, (96:4 er).

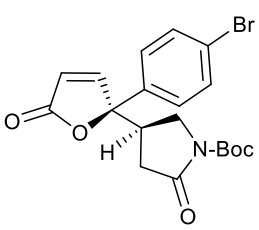


(*R*)-*tert*-Butyl 4-((*R*)-2-(4-chlorophenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3d). Following the general procedure, pure product **3d** was isolated after 24 h by FC on silica (hexane:ethyl acetate 2:1) in 95% yield (17.9 mg, >20:1 dr) as a light-yellow solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.59 (d, J = 5.7 Hz, 1H), 7.44 – 7.38 (m, 2H), 7.38 – 7.32 (m, 2H), 6.18 (d, J = 5.6 Hz, 1H), 3.60 – 3.50 (m, 2H), 3.07

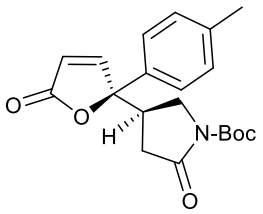
(dq, *J* = 9.7, 8.5 Hz, 1H), 2.43 (dd, *J* = 17.4, 8.8 Hz, 1H), 2.29 (dd, *J* = 17.4, 9.7 Hz, 1H), 1.48 (s, 9H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 171.0, 170.9, 156.7, 149.8, 135.3, 135.2, 129.7 (2C), 126.5 (2C), 121.6, 89.3, 83.7, 46.8, 38.5, 33.6, 28.1 (3C). HRMS: calculated for [$C_{19}H_{20}ClNO_5$+Na^+]: 400.0928; found: 400.0932. $[\alpha]_D^{23}$ = -72.4° (c = 1.0, $CHCl_3$). The er was determined by UPC^2 using a chiral Chiralpack IB column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; τ_{minor} = 3.94 min, τ_{major} = 4.48 min, (97:3 er).



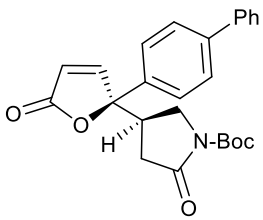
(*R*)-*tert*-Butyl 4-((*R*)-2-(2-chlorophenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3e). Following general procedure, pure product **3e** was isolated after 24 h by FC on silica (hexane:ethyl acetate 2:1) in 86% yield (16.3 mg, >20:1 dr) as a white solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.29 (d, *J* = 5.7 Hz, 1H), 7.76 – 7.66 (m, 1H), 7.49 – 7.40 (m, 1H), 7.38 – 7.32 (m, 2H), 6.16 (d, *J* = 5.7 Hz, 1H), 3.86 – 3.77 (m, 1H), 3.59 (dd, *J* = 10.9, 9.2 Hz, 1H), 3.39 (dd, *J* = 10.9, 8.7 Hz, 1H), 2.39 (dd, *J* = 17.2, 8.7 Hz, 1H), 2.28 (dd, *J* = 17.2, 10.6 Hz, 1H), 1.48 (s, 9H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 171.1, 170.6, 155.7, 150.1, 134.3, 131.7, 130.7, 130.1, 128.3, 128.0, 121.7, 89.4, 83.5, 47.0, 34.8, 33.2, 28.1 (3C). HRMS: calculated for [$C_{19}H_{20}ClNO_5$+Na^+]: 400.0928; found: 400.0926. $[\alpha]_D^{23}$ = -49.9° (c = 1.0, $CHCl_3$). The er was determined by UPC^2 using a chiral Chiralpack IB column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; τ_{minor} = 3.42 min, τ_{major} = 4.22 min, (72:28 er).



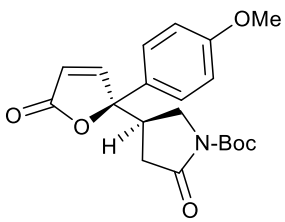
(*R*)-*tert*-Butyl 4-((*R*)-2-(4-bromophenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3f). Following general procedure, pure product **3f** was isolated after 24 h by FC on silica (hexane:ethyl acetate 2:1) in 97% yield (20.5 mg, >20:1 dr) as a white solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.59 (d, *J* = 5.6 Hz, 1H), 7.57 – 7.55 (m, 2H), 7.31 – 7.27 (m, 2H), 6.17 (d, *J* = 5.6 Hz, 1H), 3.59 – 3.51 (m, 2H), 3.07 (dq, *J* = 9.7, 8.5 Hz, 1H), 2.42 (dd, *J* = 17.4, 8.8 Hz, 1H), 2.29 (dd, *J* = 17.4, 9.7 Hz, 1H), 1.48 (s, 9H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 171.0, 170.9, 156.7, 149.8, 135.8, 132.7 (2C), 126.8 (2C), 123.4, 121.5, 89.3, 83.7, 46.8, 38.4, 33.6, 28.1 (3C). HRMS: calculated for [$C_{19}H_{20}BrNO_5$+Na^+]: 444.0423; found: 444.0425. $[\alpha]_D^{23}$ = -78.2° (c = 1.0, $CHCl_3$). The er was determined by UPC^2 using a chiral Chiralpack IB column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; τ_{minor} = 3.97 min, τ_{major} = 4.50 min, (97:3 er).



(*R*)-*tert*-Butyl 2-oxo-4-((*R*)-5-oxo-2-(*p*-tolyl)-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (**3g**)**.** Following general procedure, pure product **3g** was isolated after 24 h by FC on silica (hexane:ethyl acetate 2:1) in 94% yield (16.8 mg, >20:1 dr) as a white solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.61 (d, J = 5.7 Hz, 1H), 7.28 – 7.26 (m, 2H), 7.24 – 7.19 (m, 2H), 6.14 (d, J = 5.6 Hz, 1H), 3.61 – 3.51 (m, 2H), 3.09 (dq, J = 9.6, 8.4 Hz, 1H), 2.42 (dd, J = 17.4, 8.8 Hz, 1H), 2.35 (s, 3H), 2.30 (dd, J = 17.4, 9.7 Hz, 1H), 1.47 (s, 9H).^{13}C NMR (176 MHz, $CDCl_3$) δ 171.4, 157.3, 149.9, 139.1, 133.6, 130.1 (2C), 125.0 (2C), 121.1, 89.9, 83.5, 47.0, 38.5, 33.7, 28.1 (3C), 21.2. HRMS: calculated for $C_{20}H_{23}NO_5$+Na^+]: 380.1474; found: 380.1482. $[\alpha]_D^{23}$ = -62.8° (c = 1.0, $CHCl_3$). The er was determined by UPC^2 using a chiral Chiralpack IB column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; τ_{minor} = 3.70 min, τ_{major} = 4.28 min, (96:4 er).

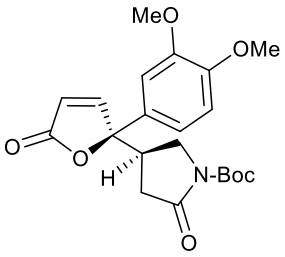


(*R*)-*tert*-Butyl 4-((*R*)-2-([1,1'-biphenyl]-4-yl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3h). Following general procedure, pure product **3h** was isolated after 24 h by FC on silica (hexane:ethyl acetate 2:1) in 98% yield (20.6 mg, >20:1 dr) as a transparent solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.66 (d, J = 5.6 Hz, 1H), 7.65 – 7.63 (m, 2H), 7.59 – 7.55 (m, 2H), 7.48 – 7.43 (m, 4H), 7.41 – 7.36 (m, 1H), 6.18 (d, J = 5.7 Hz, 1H), 3.67 – 3.57 (m, 2H), 3.16 (dq, J = 9.7, 8.5 Hz, 1H), 2.46 (dd, J = 17.4, 8.8 Hz, 1H), 2.34 (dd, J = 17.4, 9.7 Hz, 1H), 1.48 (s, 9H).^{13}C NMR (176 MHz, $CDCl_3$) δ 171.2 (2C), 157.1, 149.9, 142.1, 140.0, 135.5, 129.1 (2C), 128.1 (2C), 128.0, 127.2 (2C), 125.6 (2C), 121.4, 89.7, 83.6, 47.0, 38.5, 33.7, 28.1 (3C). HRMS: calculated for [$C_{25}H_{25}NO_5$+Na^+]: 442.1630; found: 442.1631. $[\alpha]_D^{23}$ = -118.6° (c = 1.0, $CHCl_3$). The er was determined by UPC^2 using a chiral Chiralpack IB column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; τ_{minor} = 4.51 min, τ_{major} = 5.14 min, (97:3 er).

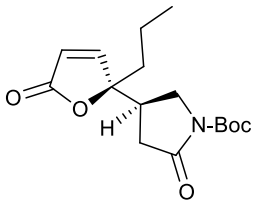


(*R*)-*tert*-Butyl 4-((*R*)-2-(4-methoxyphenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3i). Following general procedure, pure product **3i** was isolated after 24 h by FC on silica (hexane:ethyl acetate 2:1) in 91% yield (17.0 mg, >20:1 dr) as a white solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.60 (d, J = 5.6 Hz, 1H),

7.33 – 7.27 (m, 2H), 6.96 – 6.89 (m, 2H), 6.14 (d, *J* = 5.6 Hz, 1H), 3.81 (s, 3H), 3.62 – 3.53 (m, 2H), 3.07 (dq, *J* = 9.4, 8.4 Hz, 1H), 2.42 (dd, *J* = 17.5, 8.8 Hz, 1H), 2.30 (dd, *J* = 17.4, 9.5 Hz, 1H), 1.48 (s, 9H).^{13}C NMR (176 MHz, $CDCl_3$) δ 171.4 (2C), 160.1, 157.2, 149.9, 128.5, 126.4 (2C), 121.1, 114.8 (2C), 89.8, 83.5, 55.5, 47.0, 38.5, 33.8, 28.1 (3C). HRMS: calculated for [$C_{20}H_{23}NO_6$+Na^+]: 396.1423; found: 396.1421. $[\alpha]_D^{23}$ = -71.6° (c = 1.0, $CHCl_3$). The er was determined by UPC^2 using a chiral Chiralpack IB column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; τ_{minor} = 3.99 min, τ_{major} = 4.54 min, (97:3 er).

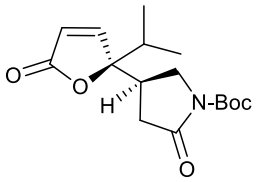


(*R*)-*tert*-Butyl 4-((*R*)-2-(3,4-dimethoxyphenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3j). Following general procedure, pure product **3j** was isolated after 24 h by FC on silica (hexane:ethyl acetate 2:1) in 98% yield (19.8 mg, >20:1 dr) as a light-yellow solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.61 (d, *J* = 5.7 Hz, 1H), 6.91 – 6.84 (m, 3H), 6.15 (d, *J* = 5.7 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.62 – 3.53 (m, 2H), 3.08 (dq, *J* = 9.4, 8.4 Hz, 1H), 2.42 (dd, *J* = 17.4, 8.8 Hz, 1H), 2.30 (dd, *J* = 17.5, 9.6 Hz, 1H), 1.48 (s, 9H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 171.3, 171.3, 157.2, 149.8, 149.8, 149.6, 129.0, 121.1, 117.7, 111.7, 108.3, 89.7, 83.5, 56.3, 56.2, 47.0, 38.7, 33.8, 28.1 (3C). HRMS: calculated for [$C_{21}H_{25}NO_7$+Na^+]: 426.1529; found: 426.1531. $[\alpha]_D^{23}$ = -88.5° (c = 1.0, $CHCl_3$). The er was determined by UPC^2 using a chiral Chiralpack IB column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; τ_{minor} = 3.96 min, τ_{major} = 4.41 min, (98:2 er).

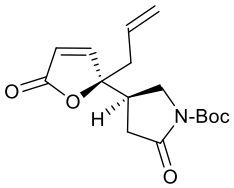


(*R*)-*tert*-Butyl 2-oxo-4-((*R*)-5-oxo-2-propyl-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (3k). Following general procedure, pure product **3k** was isolated after 96 h by FC on silica (hexane:ethyl acetate 2:1) in 45% yield (7.0 mg, >20:1 dr) as a white solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.27 (d, *J* = 5.7 Hz, 1H), 6.17 (d, *J* = 5.7 Hz, 1H), 3.86 (dd, *J* = 11.1, 8.4 Hz, 1H), 3.58 (dd, *J* = 11.1, 8.2 Hz, 1H), 2.80 – 2.72 (m, 1H), 2.40 (dd, *J* = 17.4, 8.8 Hz, 1H), 2.24 (dd, *J* = 17.3, 9.7 Hz, 1H), 1.85 (ddd, *J* = 14.1, 11.7, 4.7 Hz, 1H), 1.74 (ddd, *J* = 14.2, 11.7, 5.0 Hz, 1H), 1.51 (s, 9H), 1.32 – 1.26 (m, 1H), 1.23 – 1.17 (m, 1H), 0.93 (t, *J* = 7.4 Hz, 3H).^{13}C NMR (176 MHz, $CDCl_3$) δ 171.7, 171.5, 156.6, 149.7, 123.0, 90.0, 83.6, 46.8, 37.3, 36.5, 34.0, 28.1 (3C), 16.8, 14.1. HRMS: calculated for [$C_{16}H_{23}NO_5$+Na^+]: 332.1474; found: 332.1476. $[\alpha]_D^{22}$ = 7.3 (c = 1.0, $CHCl_3$). The er was determined by UPC^2 using a chiral

Chiralpack IB column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; τ_{minor} = 3.05 min, τ_{major} = 3.55 min, (98:2 er).

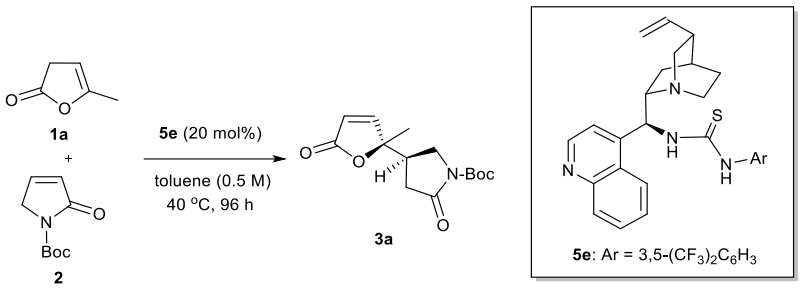


(*R*)-*tert*-Butyl 2-oxo-4-((*R*)-5-oxo-2-isopropyl-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (3l). Following general procedure, pure product **3l** was isolated after 96 h by FC on silica (hexane:ethyl acetate 2:1) in 43% yield (6.6 mg, >20:1 dr) as a yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.27 (d, *J* = 5.8 Hz, 1H), 6.22 (d, *J* = 5.8 Hz, 1H), 3.87 (dd, *J* = 10.9, 8.4 Hz, 1H), 3.61 (dd, *J* = 10.9, 8.8 Hz, 1H), 2.98 (dq, *J* = 10.3, 8.7 Hz, 1H), 2.32 (dd, *J* = 17.2, 8.7 Hz, 1H), 2.22 – 2.15 (m, 2H), 1.52 (s, 9H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H).^{13}C NMR (176 MHz, $CDCl_3$) δ 171.7, 171.5, 155.0, 149.8, 123.8, 92.4, 83.6, 46.7, 34.2, 33.9, 32.4, 28.2 (3C), 18.1, 16.7. HRMS: calculated for [$C_{16}H_{23}NO_5$+Na^+]: 332.1474; found: 332.1476. $[\alpha]_D^{22}$ = -6.3 (c = 1.0, $CHCl_3$). The er was determined by UPC^2 using a chiral Chiralpack IB column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; τ_{minor} = 3.18 min, τ_{major} = 3.81 min, (97:3 er).



(*R*)-*tert*-Butyl 2-oxo-4-((*R*)-5-oxo-2-allyl-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (3m). Following general procedure, pure product **3m** was isolated after 96 h by FC on silica (hexane:ethyl acetate 2:1) in 71% yield (11.0 mg, >20:1 dr) as a white solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.31 (d, *J* = 5.7 Hz, 1H), 6.19 (d, *J* = 5.7 Hz, 1H), 5.70 – 5.55 (m, 1H), 5.24 – 5.14 (m, 2H), 3.87 (dd, *J* = 11.1, 8.4 Hz, 1H), 3.60 (dd, *J* = 11.1, 8.2 Hz, 1H), 2.81 (dq, *J* = 9.8, 8.5 Hz, 1H), 2.56 (ddt, *J* = 12.5, 7.4, 1.2 Hz, 2H), 2.40 (dd, *J* = 17.4, 8.9 Hz, 1H), 2.24 (dd, *J* = 17.4, 9.8 Hz, 1H), 1.51 (s, 9H).^{13}C NMR (176 MHz, $CDCl_3$) δ 171.4, 171.3, 156.2, 149.7, 129.7, 123.4, 121.4, 89.2, 83.7, 46.7, 40.1, 35.7, 33.9, 28.1 (3C). HRMS: calculated for [$C_{16}H_{21}NO_5$+Na^+]: 330.1317; found: 330.1319. $[\alpha]_D^{22}$ = -3.6 (c = 1.0, $CHCl_3$). The er was determined by UPC^2 using a chiral Chiralpack IB column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; τ_{minor} = 3.27 min, τ_{major} = 3.62 min, (98:2 er).

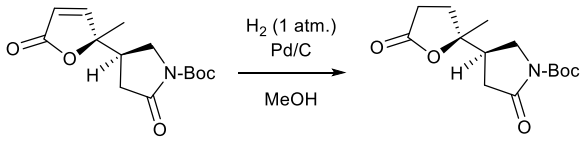
3. Synthesis of (*R*)-*tert*-butyl 4-((*R*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3a) on a 1 mmol scale



In an ordinary 12 mL glass vial, equipped with a magnetic stirring bar and a screw cap, catalyst **5e** (0.2 equiv, 0.2 mmol, 112 mg), 5-methylfuran-2(3*H*)-one **1a** (2.0 equiv, 2 mmol, 180 µl) and *N*-Boc-protected *α,β*-unsaturated-*γ*-lactam **2** (1.0 equiv, 1 mmol, 183.2 mg) were dissolved in toluene (2 mL) and stirred for 4 days at 40 °C using heating block. Pure product **3a** was isolated by FC on silica (hexane:ethyl acetate 2:1) in 91% yield (255.0 mg, >20:1 dr) as a white solid. Spectral data were in accordance with the data reported above. The er was determined by UPC[2] using a chiral Chiralpack IB column gradient from 100% CO_2 up to 40%; *i*-PrOH, 2.5 mL/min; τ_{minor} = 3.31 min, τ_{major} = 3.62 min, (97:3 er).

4. Transformations

Synthesis of (*R*)-*tert*-butyl 4-((*R*)-2-methyl-5-oxotetrahydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (6a)

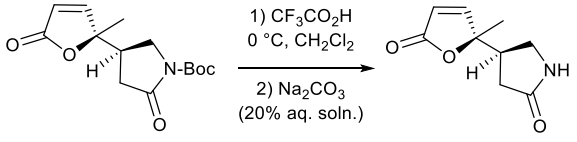


3a
97:3 er
20:1 er

6a
98% yield
20:1 dr

In a 25 mL round-bottomed flask equipped with a magnetic stirring bar and septum, (*R*)-*tert*-butyl 4-((*R*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate **3a** (1 equiv, 0.1 mmol, 28,13 mg) and Palladium on activated charcoal 10% (∼10 mg) were dissolved in MeOH (1.5 mL) and stirred for 24 h in H_2 atmosphere. Reaction mixture was filtered through celite, washed with MeOH and evaporated to give final product **6a** as a colorless oil in 98% yield (27.8 mg, >20:1 dr). **(*R*)-*tert*-butyl 4-((*R*)-2-methyl-5-oxotetrahydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (6a):** ^{1}H NMR (700 MHz, $CDCl_3$) δ 3.87 (dd, J = 11.1, 8.5 Hz, 1H), 3.58 (dd, J = 11.1, 8.3 Hz, 1H), 2.75 – 2.67 (m, 1H), 2.66 – 2.54 (m, 3H), 2.50 – 2.43 (m, 1H), 2.14 – 2.00 (m, 2H), 1.52 (s, 9H), 1.41 (s, 3H).^{13}C NMR (176 MHz, $CDCl_3$) δ 175.7, 172.2, 145.0, 85.2, 83.7, 47.2, 39.3, 34.1, 31.1, 28.6, 28.1 (3C), 24.2. HRMS: calculated for [$C_{14}H_{21}NO_5$+Na^+]: 306.1317; found: 306.1313. $[\alpha]_D^{22}$ = -15.5° (c = 1.0, $CHCl_3$).

Synthesis of (*R*)-4-((*R*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)pyrrolidin-2-one (7a)



3a
97:3 er
20:1 er

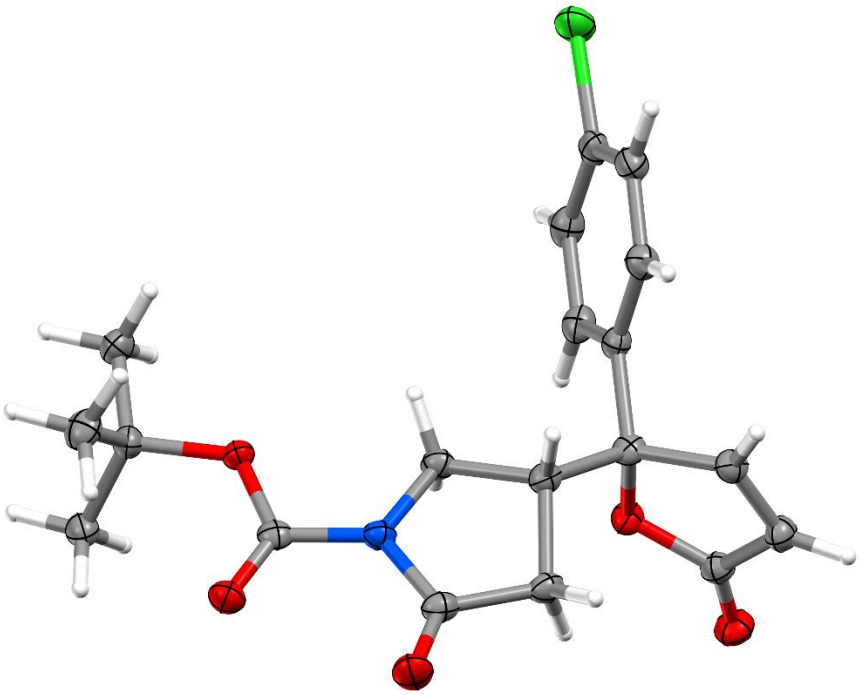
7a
78% yield
20:1 dr

In an ordinary 4 mL glass vial, equipped with a magnetic stirring bar and a screw cap, (*R*)-*tert*-butyl 4-((*R*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate **3a** (1 equiv, 0.04 mmol, 11.9 mg) was dissolved in CH_2Cl_2 (0.2 mL). Trifluoroacetic acid (10 equiv, 0.4 mmol, 30 μl) was added and the resulting mixture was stirred for 1 h at ambient temperature. Reaction mixture was cooled to 0 °C and carefully quenched with 20% solution of $Na_2CO_{3(aq)}$ (5 mL). Chloroform (10 ml) was added and organic phase was separated. Organic phase was washed with 20% solution of $Na_2CO_{3(aq)}$ (2x5 mL), brine (2x5 mL), dried over anhydrous $MgSO_4$ and evaporated to a give **7a** as yellowish oil in 79% yield (5.7 mg, >20:1 dr). **(*R*)-4-**

((*R*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)pyrrolidin-2-one (7a): ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.36 (d, J = 5.7 Hz, 1H), 6.15 (d, J = 5.7 Hz, 1H), 5.50 (s, 1H), 3.51 – 3.47 (m, 1H), 3.24 (dd, J = 9.8, 6.7 Hz, 1H), 2.95 – 2.90 (m, 1H), 2.33 (dd, J = 17.1, 9.4 Hz, 1H), 2.08 (dd, J = 17.1, 8.2 Hz, 1H), 1.52 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 175.8, 171.6, 157.7, 122.3, 88.1, 42.7, 41.4, 31.4, 22.7. HRMS: calculated for [$C_9H_{11}NO_3$+Na^+]: 204.0637; found: 204.0639. $[\alpha]_D^{22}$ = 15.1° (c = 1.0, $CHCl_3$).

5. Crystal and X ray data for 3d

The single-crystal X-ray diffraction study at a low temperature of 100 K revealed that compound **3d** ($C_{19}H_{20}ClNO_5$) crystallizes in the non-centrosymmetric monoclinic space group $P2_1$ (Z = 2) and the crystal structure consists of one crystallographically independent formula unit in the unit cell.



The molecular structure of the compound **3d** at 100 K, showing 50% probability displacement ellipsoids. Hydrogen atoms are drawn with an arbitrary radius.

Single crystal X-ray diffraction data were collected at 100 K by the ω-scan technique using a RIGAKU XtaLAB Synergy, Dualflex, Pilatus 300K diffractometer[3] with PhotonJet micro-focus X-ray Source Cu-Kα (λ = 1.54184 Å). Data collection, cell refinement, data reduction and absorption correction were performed using CrysAlis PRO software.[3] The crystal structure was solved by using direct methods with the SHELXT 2018/2 program.[4] Atomic scattering factors were taken from the International Tables for X-ray Crystallography. Positional parameters of non-H-atoms were refined by a full-matrix least-squares method on F^2 with anisotropic thermal parameters by using the SHELXL 2018/3 program.[5] All hydrogen atoms were found from the difference Fourier maps and for further calculations they were positioned geometrically in calculated positions (C–H = 0.95–1.00 Å) and constrained to ride on their parent atoms with isotropic displacement parameters set to 1.2-1.5 times the U_{eq} of the parent atom.

(*R*)-*tert*-Butyl 4-((*R*)-2-(4-chlorophenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3d): Formula $C_{19}H_{20}ClNO_5$, monoclinic, space group $P2_1$, Z = 2, unit cell constants a = 9.62610(9), b = 6.61723(11), c = 14.2237(2) Å, β = 98.0027(11)°, V = 897.20(2) Å^3. The integration of the data yielded a total of 21820 reflections with θ angles in the range of 4.64 to 66.58°, of which 3040 were independent (R_{int} = 1.92%), and 3038 were greater than 2σ(F^2). The final anisotropic full-matrix least-squares refinement on F^2 with 239 parameters converged at R_1 = 2.25% and wR_2 = 5.89% for all data. The largest peak in the final difference electron density synthesis was 0.172 e Å^{-3} and the largest hole was -0.175 e Å^{-3}. The goodness-of-fit was 1.054. The absolute configuration was determined from anomalous scattering, by calculating the x Flack parameter[6] of 0.020(6) using 1295 quotients.

CCDC 2013485 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

(3) Rigaku OD. CrysAlis PRO. Rigaku Oxford Diffraction Ltd, Yarnton, Oxfordshire, England, 2019.

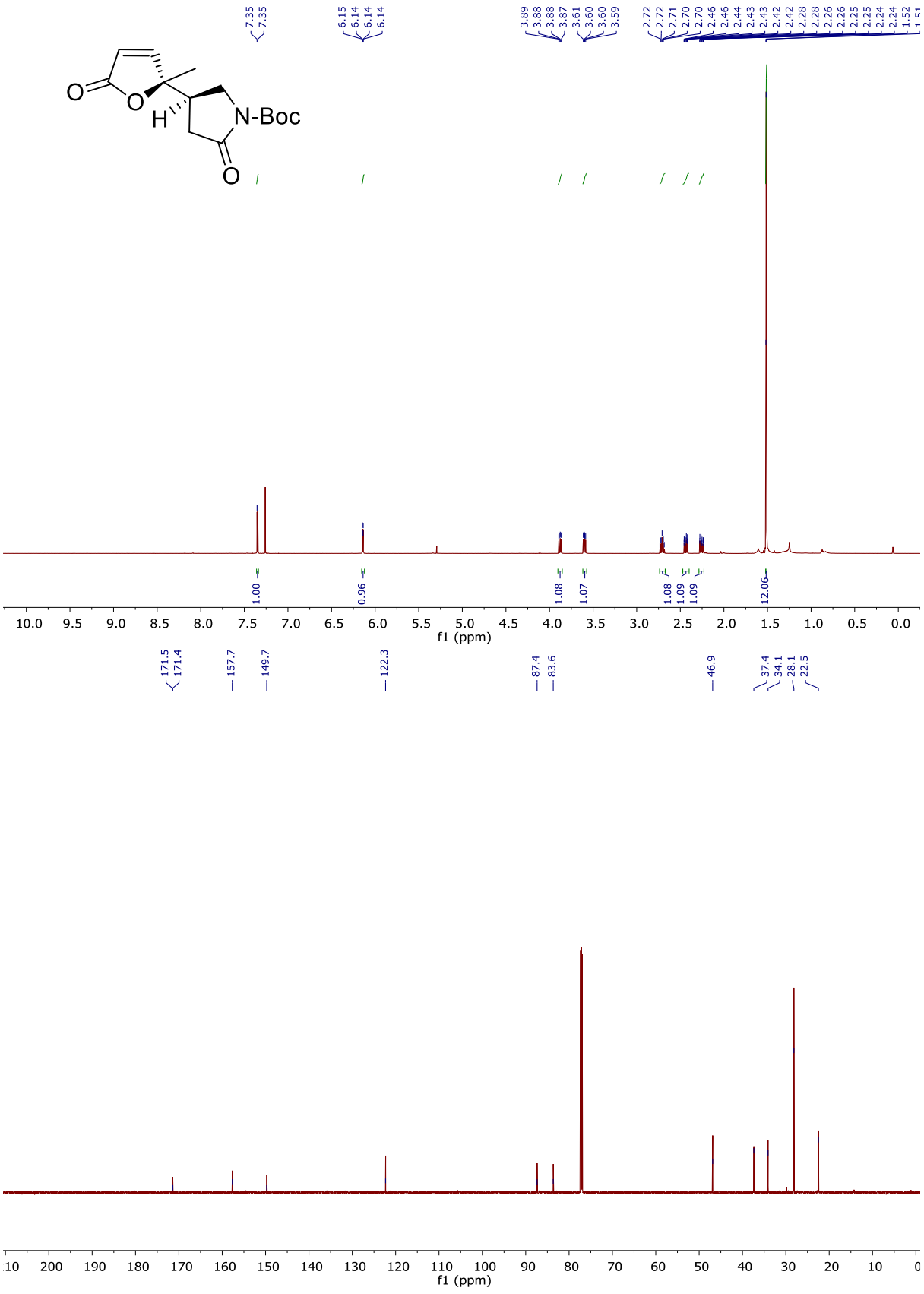
(4) G.M. Sheldrick, *Acta Cryst.* 2015, **A71**, 3-8.

(5) G.M. Sheldrick, *Acta Cryst.* 2015, **C71**, 3-8.

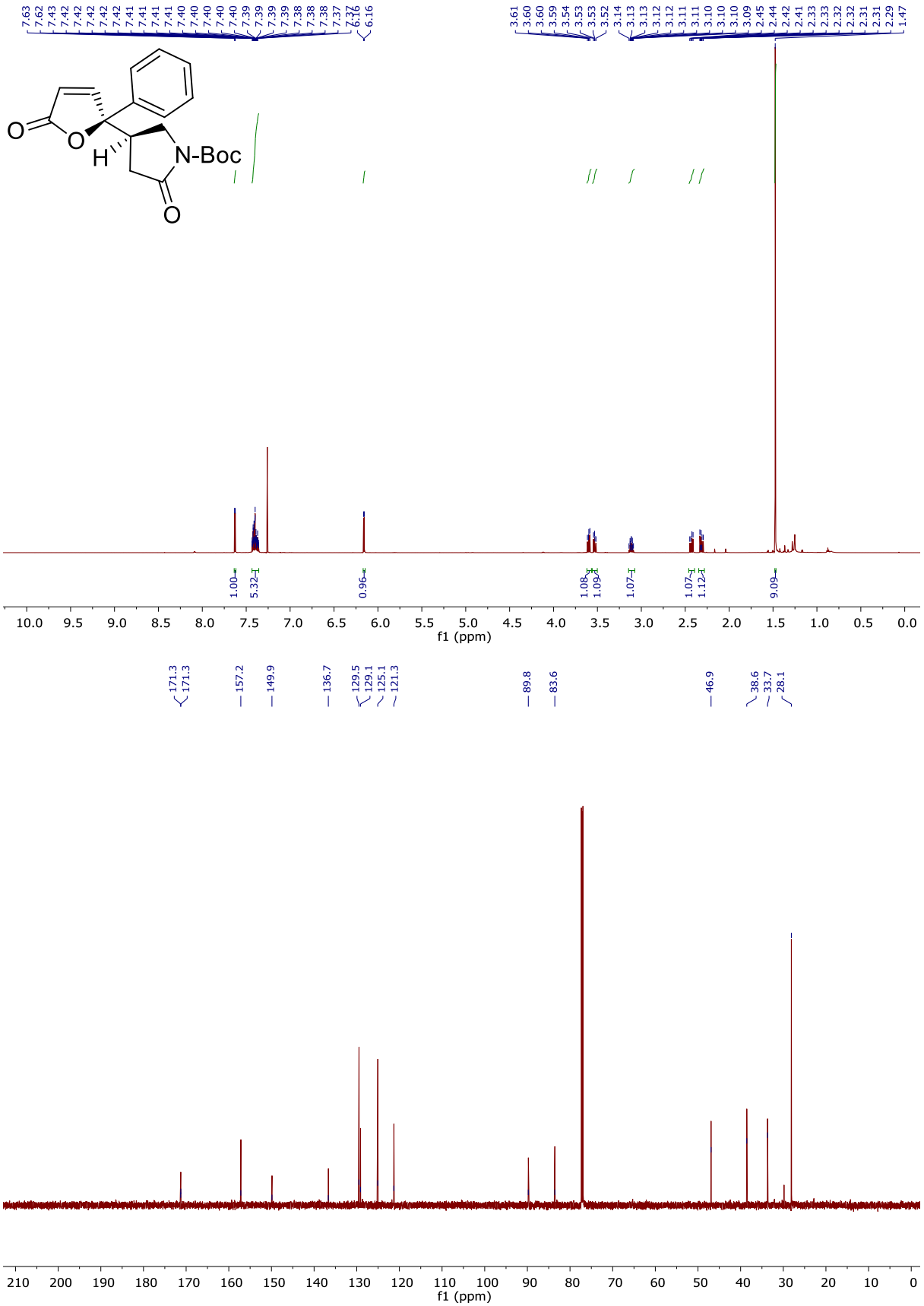
(6) S. Parsons, H.D. Flack and T. Wagner *Acta Cryst.* 2013, **B69**, 249-259.

6. NMR data

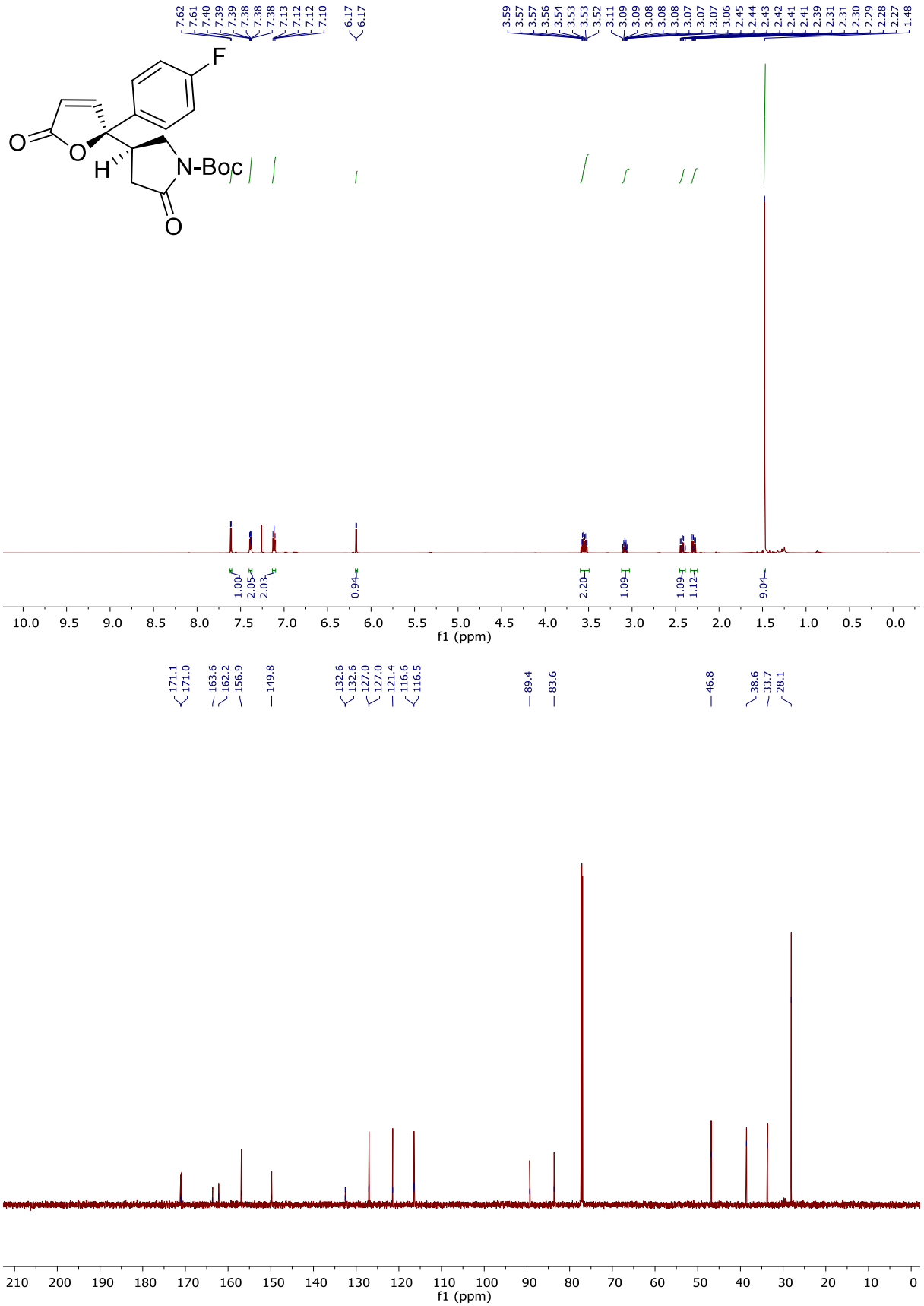
(*R*)-*tert*-Butyl 4-((*R*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3a)



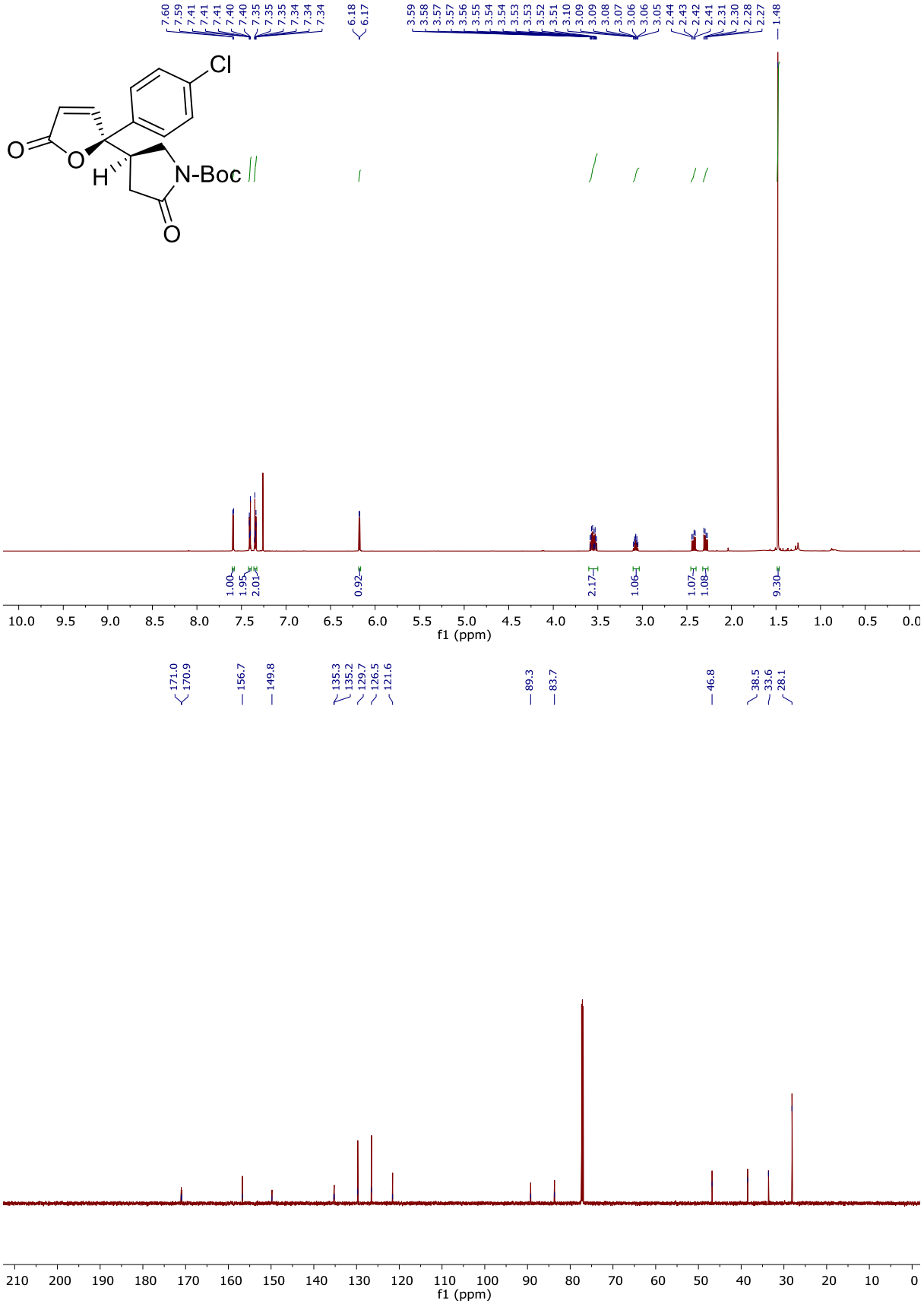
(*R*)-*tert*-Butyl 2-oxo-4-((*R*)-5-oxo-2-phenyl-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (3b)



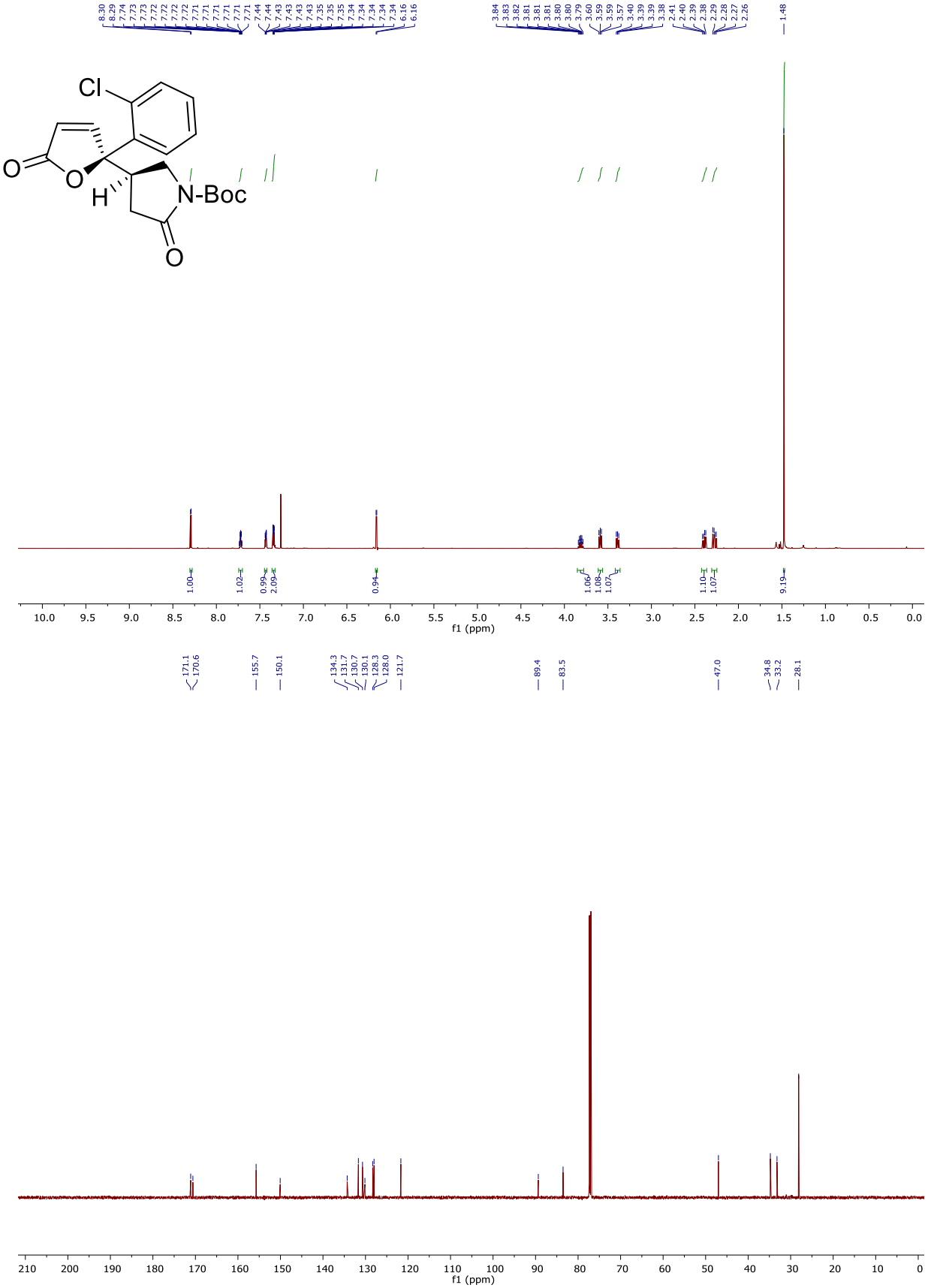
(*R*)-*tert*-Butyl 4-((*R*)-2-(4-fluorophenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3c)



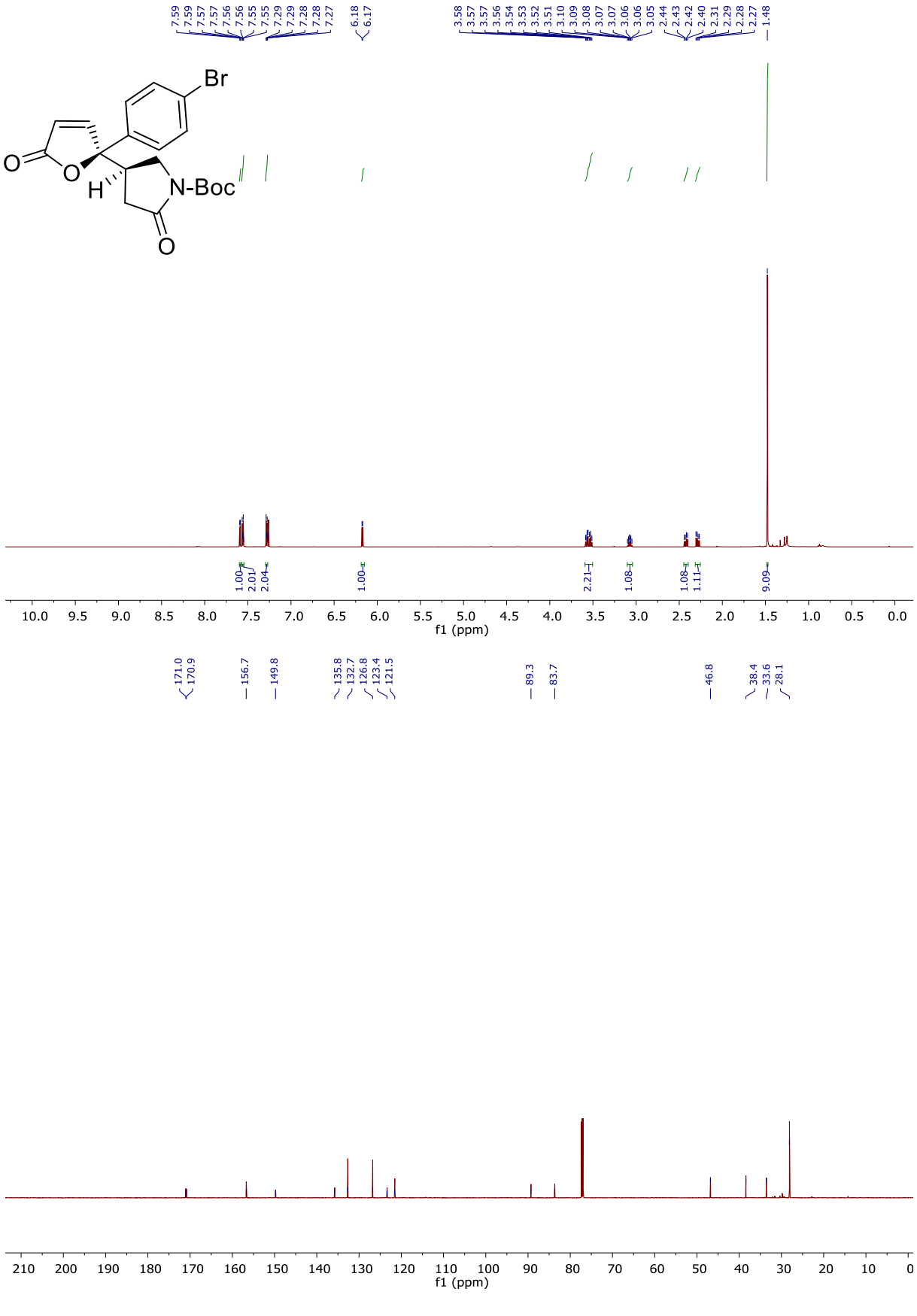
(*R*)-*tert*-Butyl 4-((*R*)-2-(4-chlorophenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3d)



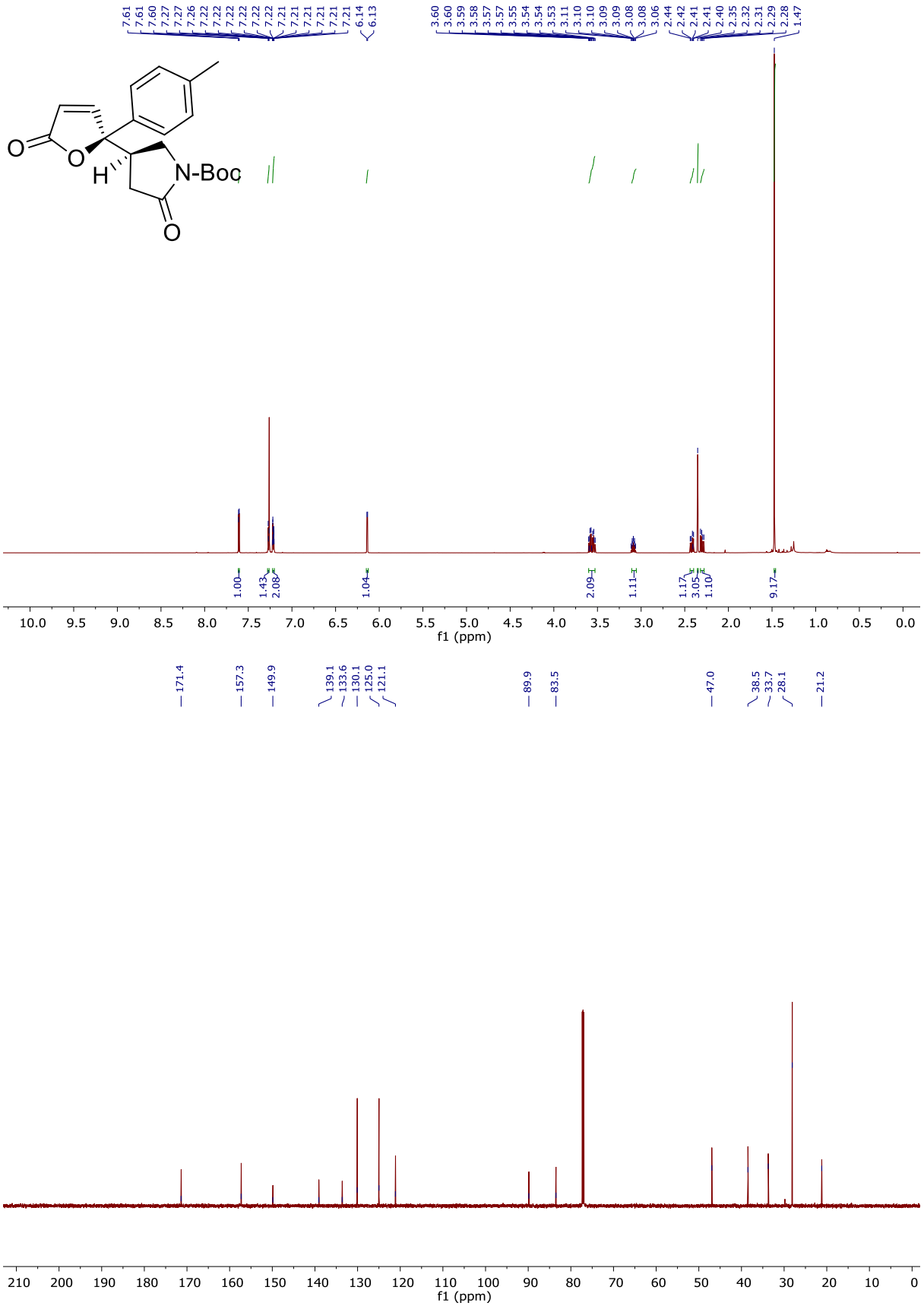
(*R*)-*tert*-Butyl 4-((*R*)-2-(2-chlorophenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3e)



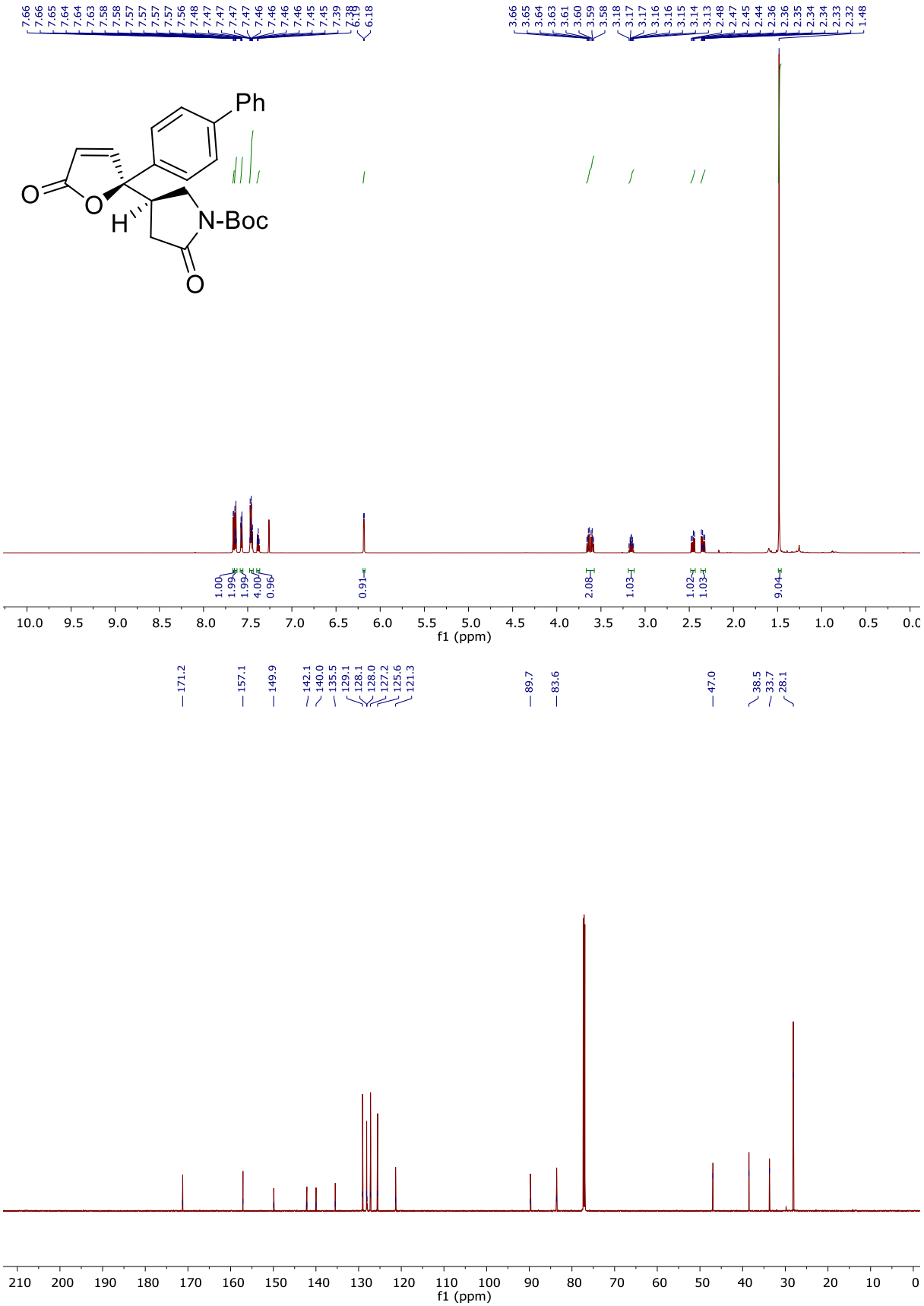
(*R*)-*tert*-Butyl 4-((*R*)-2-(4-bromophenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3f)



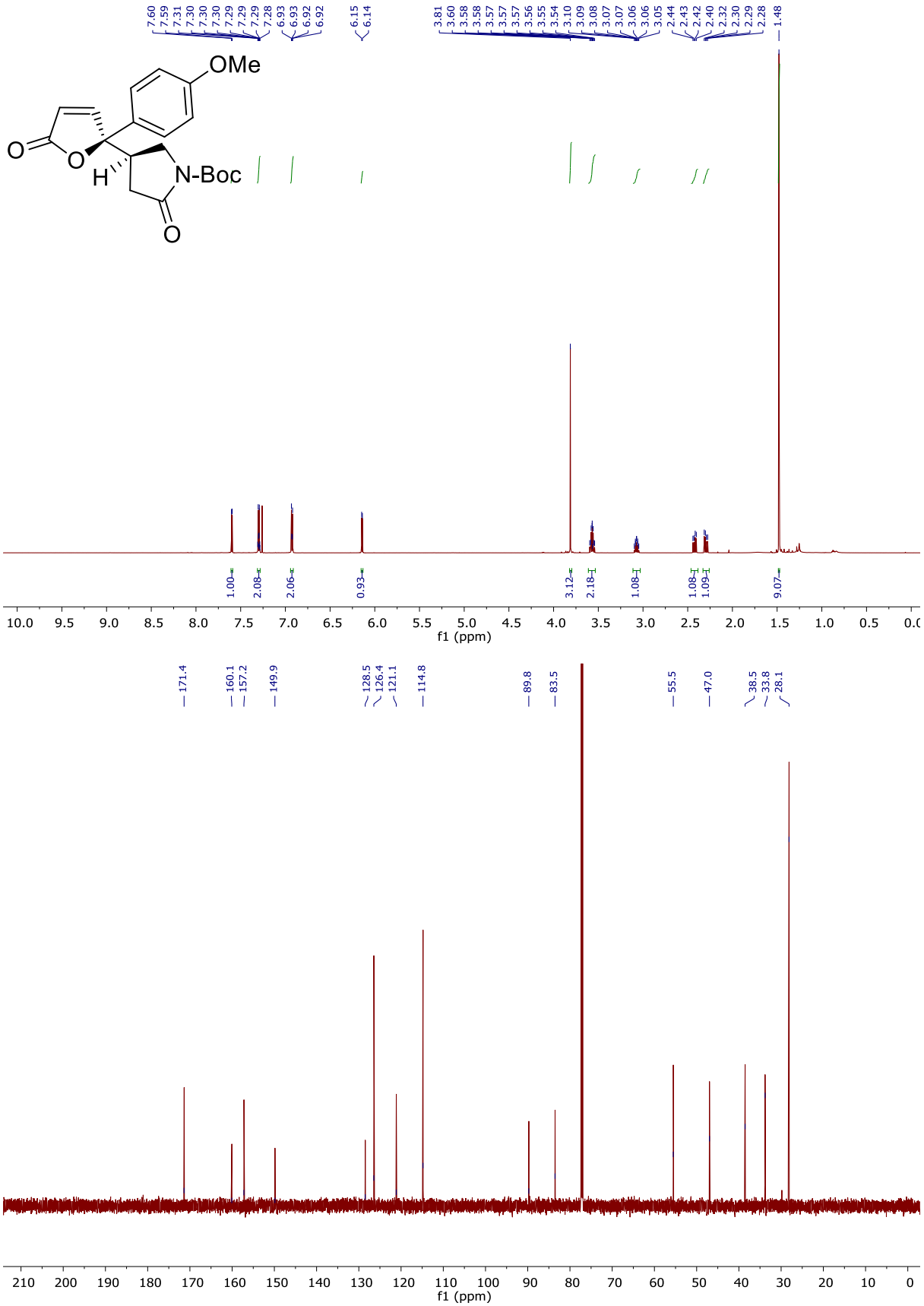
(*R*)-*tert*-Butyl 2-oxo-4-((*R*)-5-oxo-2-(*p*-tolyl)-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (3g)



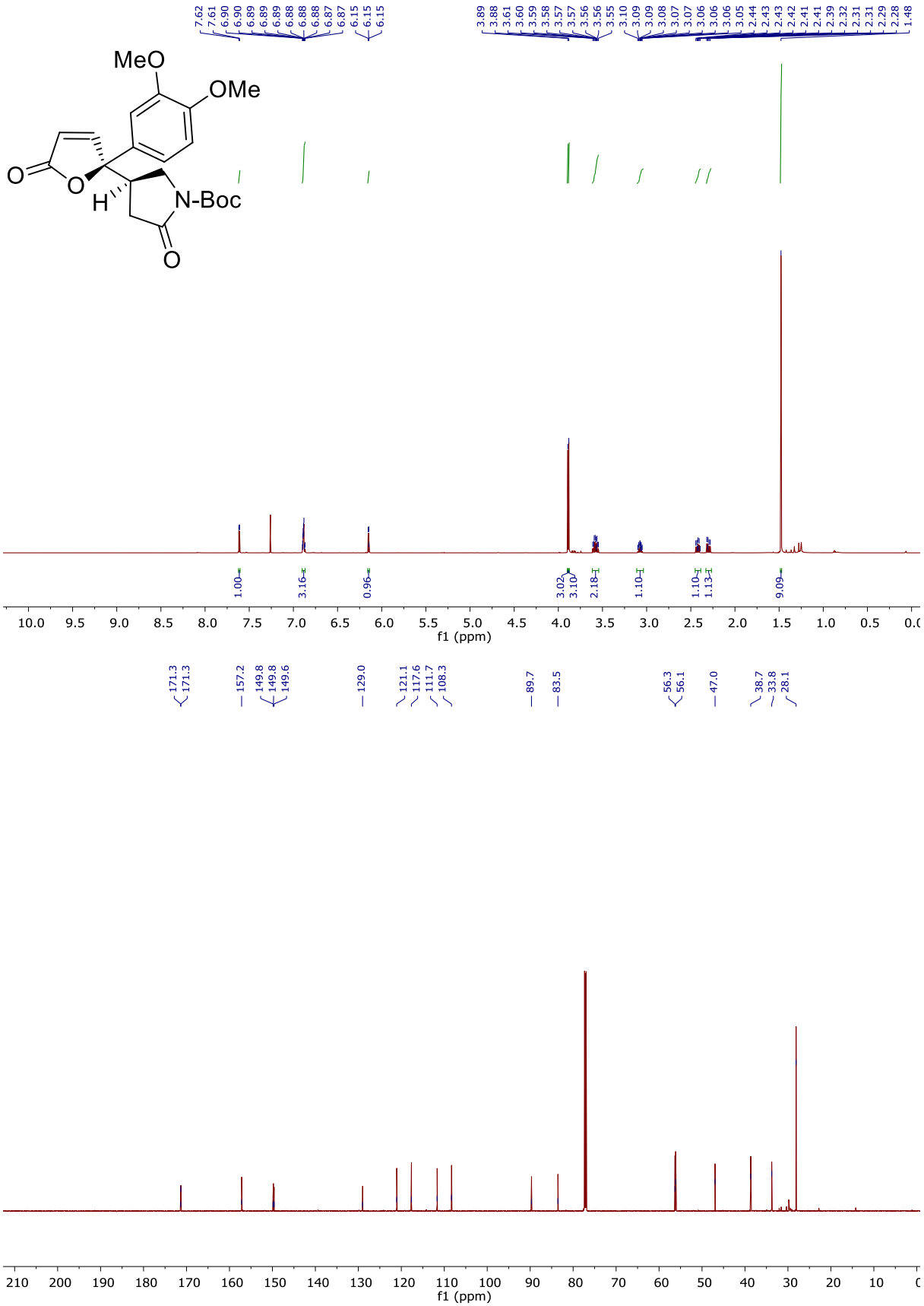
(*R*)-*tert*-Butyl 4-((*R*)-2-([1,1'-biphenyl]-4-yl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3h)



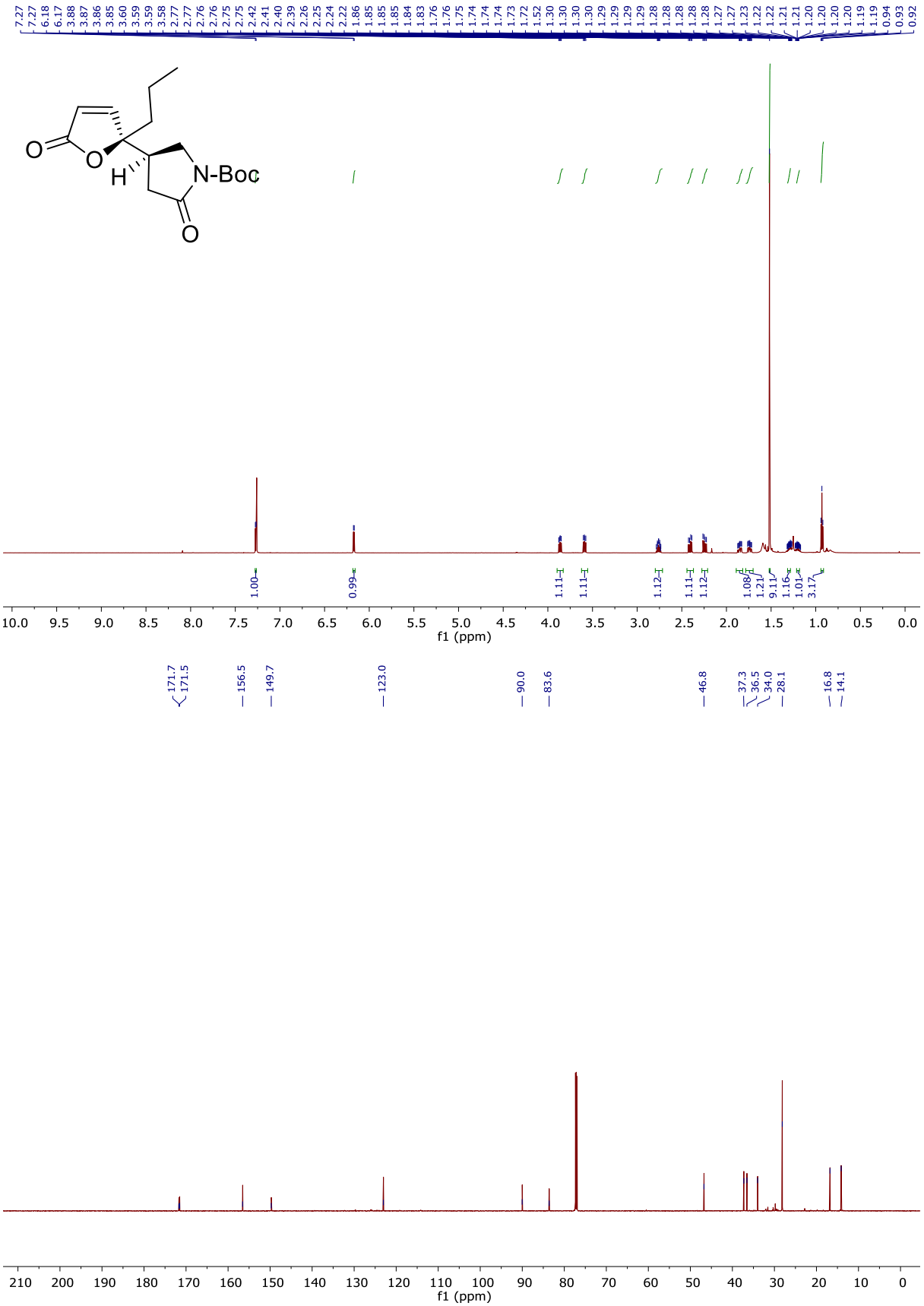
(*R*)-*tert*-Butyl 4-((*R*)-2-(4-methoxyphenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3i)



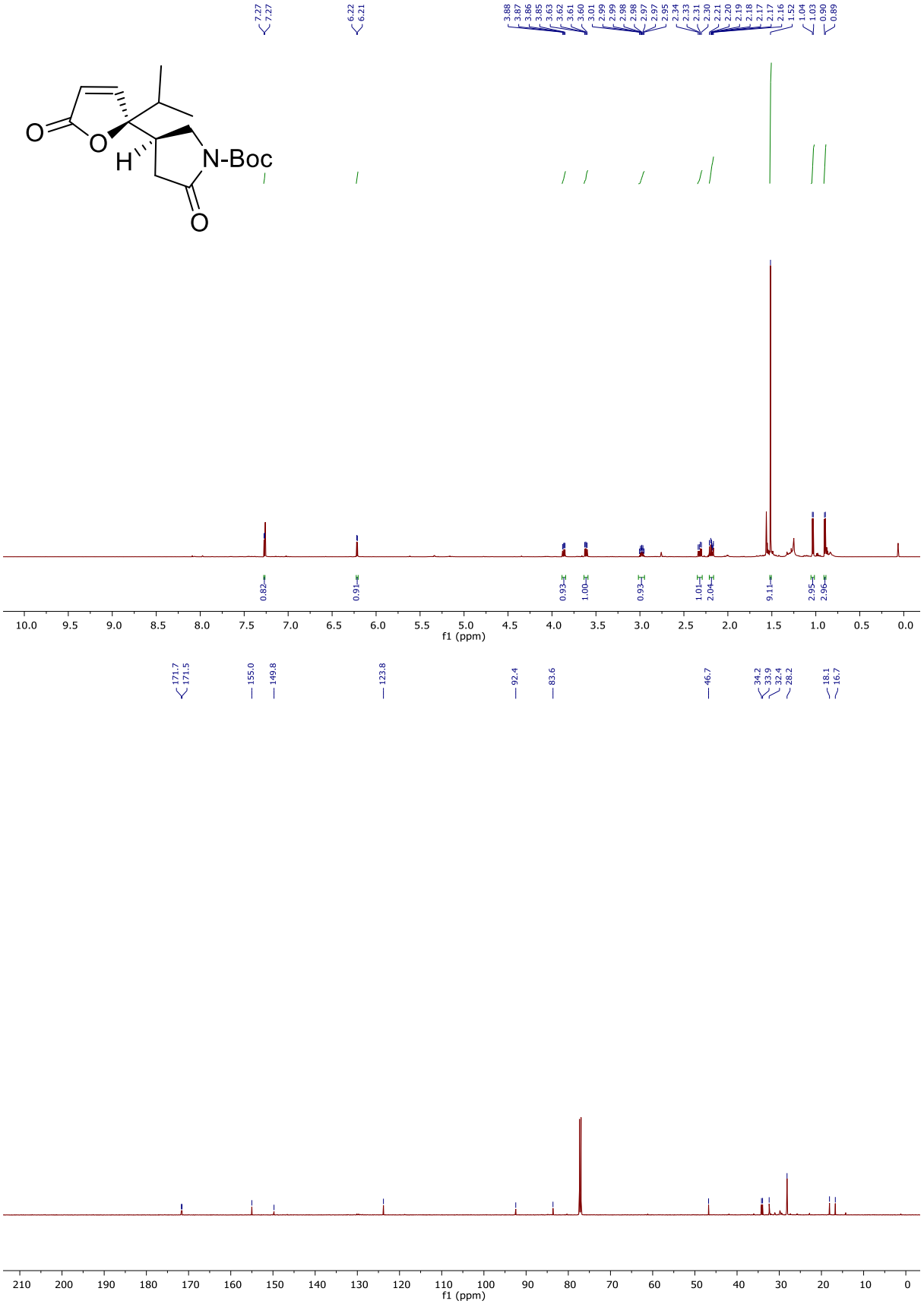
(*R*)-*tert*-Butyl 4-((*R*)-2-(3,4-dimethoxyphenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3j)



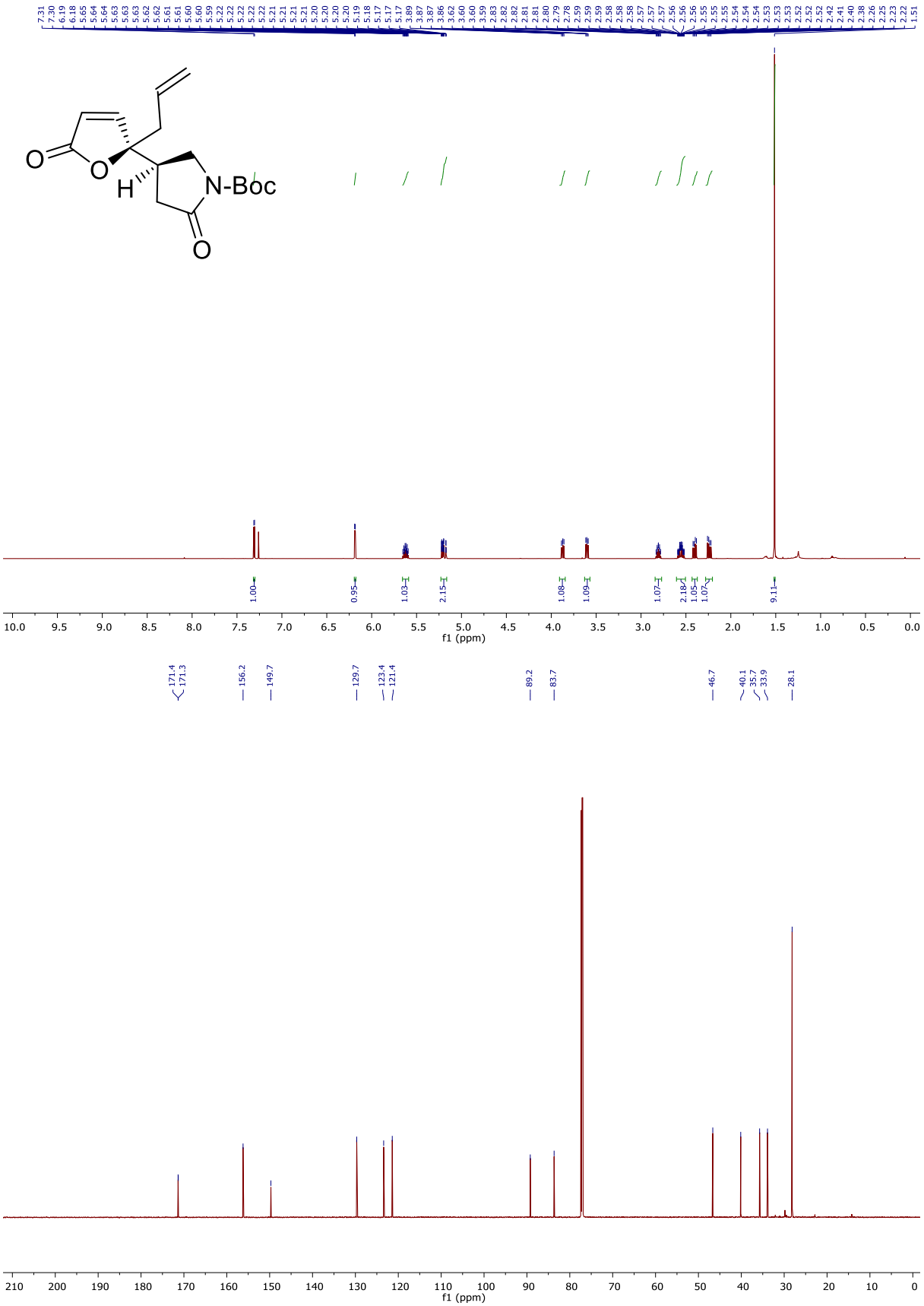
(*R*)-*tert*-Butyl 2-oxo-4-((*R*)-5-oxo-2-propyl-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (3k)



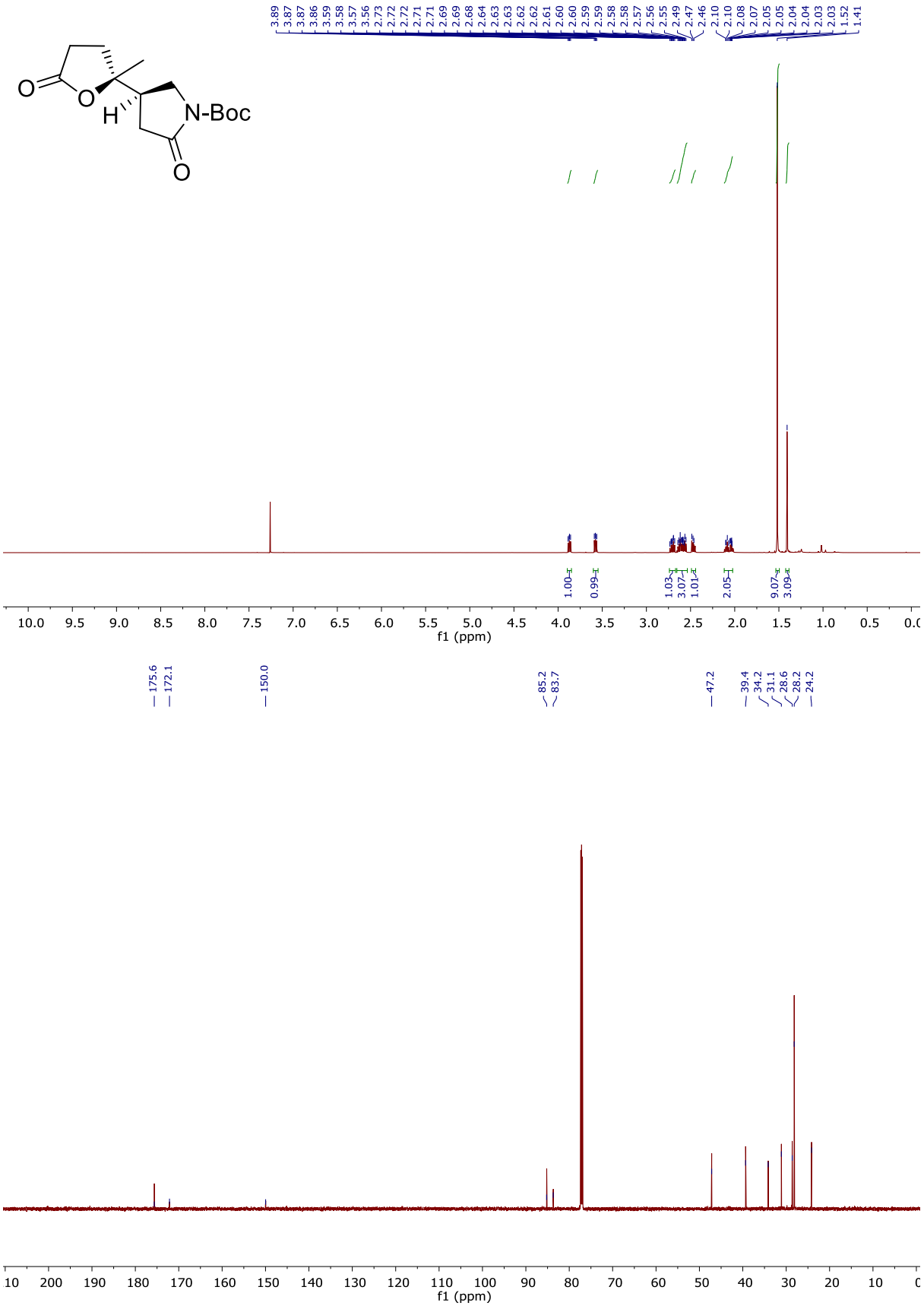
(*R*)-*tert*-Butyl 2-oxo-4-((*R*)-5-oxo-2-isopropyl-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (3l)



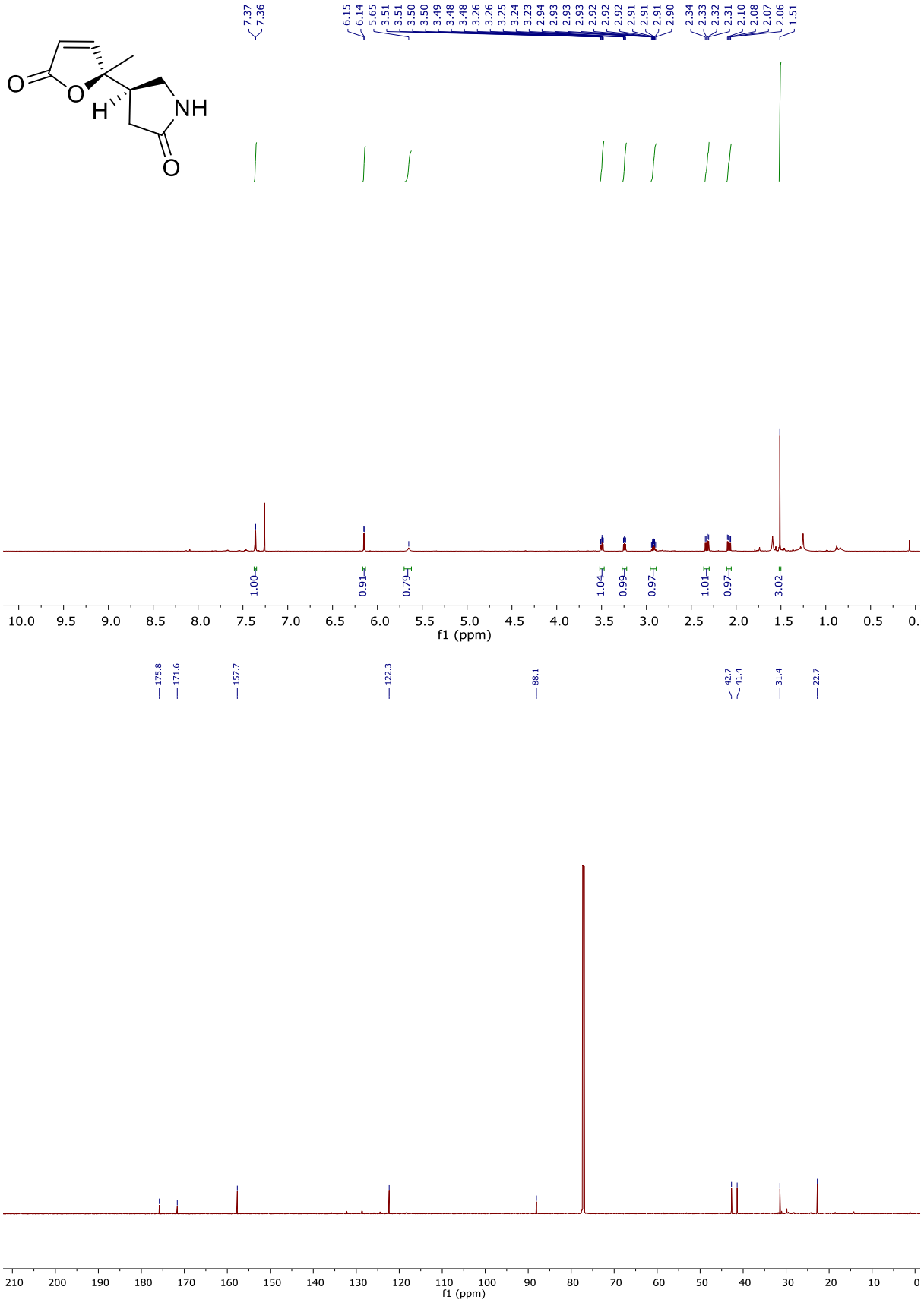
(*R*)-*tert*-Butyl 2-oxo-4-((*R*)-5-oxo-2-allyl-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (3m)



(*R*)-*tert*-Butyl 4-((*R*)-2-methyl-5-oxotetrahydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (6a)

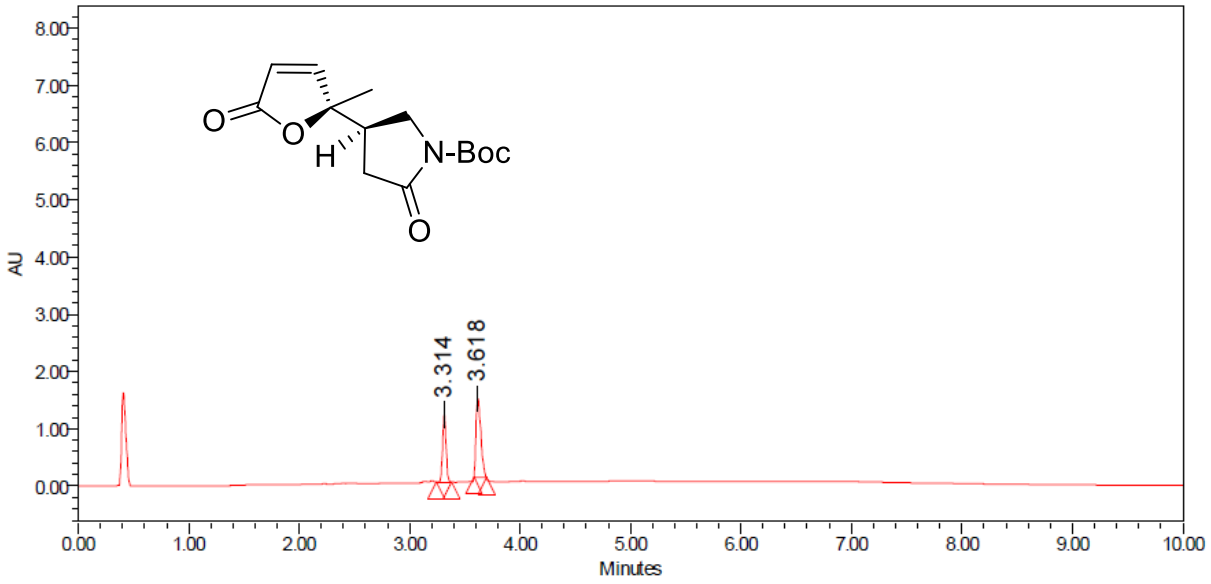


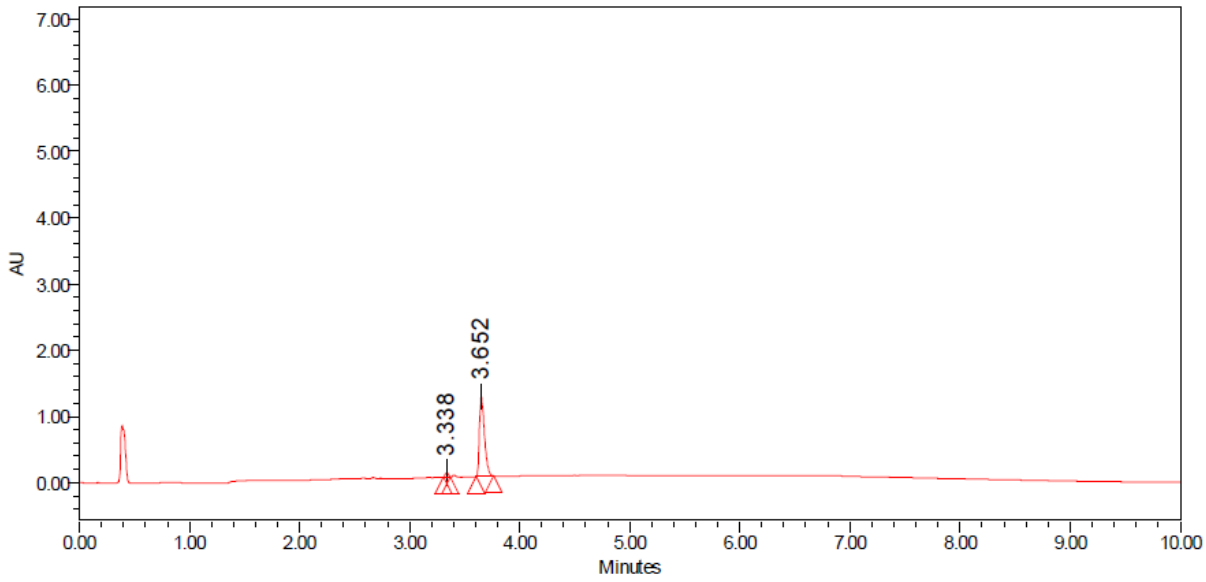
(*R*)-4-((*R*)-2-Methyl-5-oxo-2,5-dihydrofuran-2-yl)pyrrolidin-2-one (7a)



7. UPC^2 traces

(*R*)-*tert*-Butyl 4-((*R*)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3a)

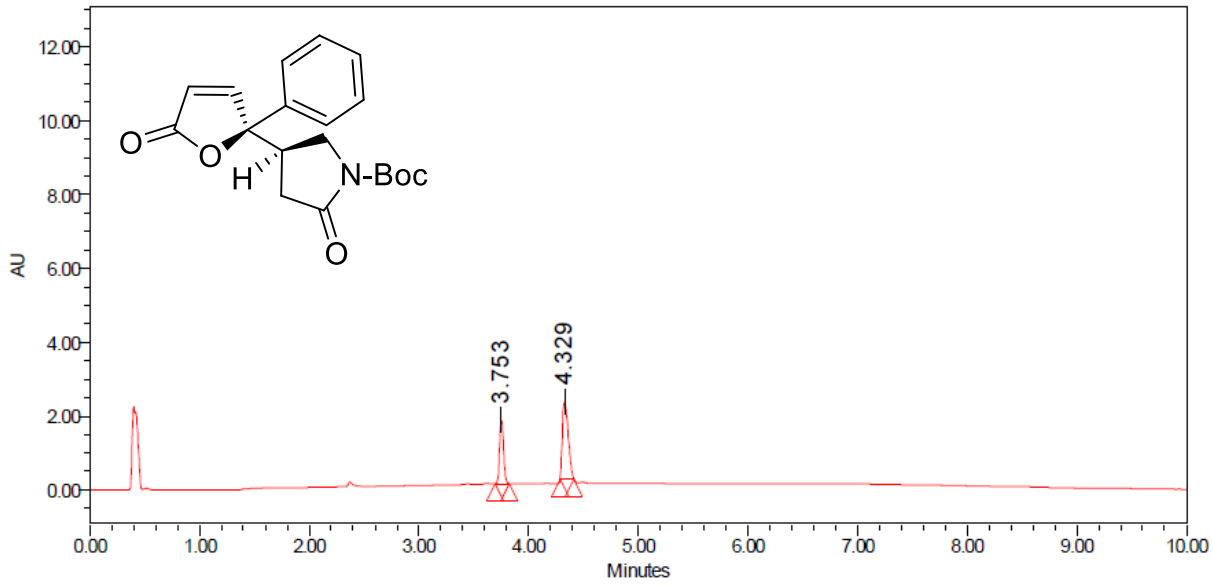


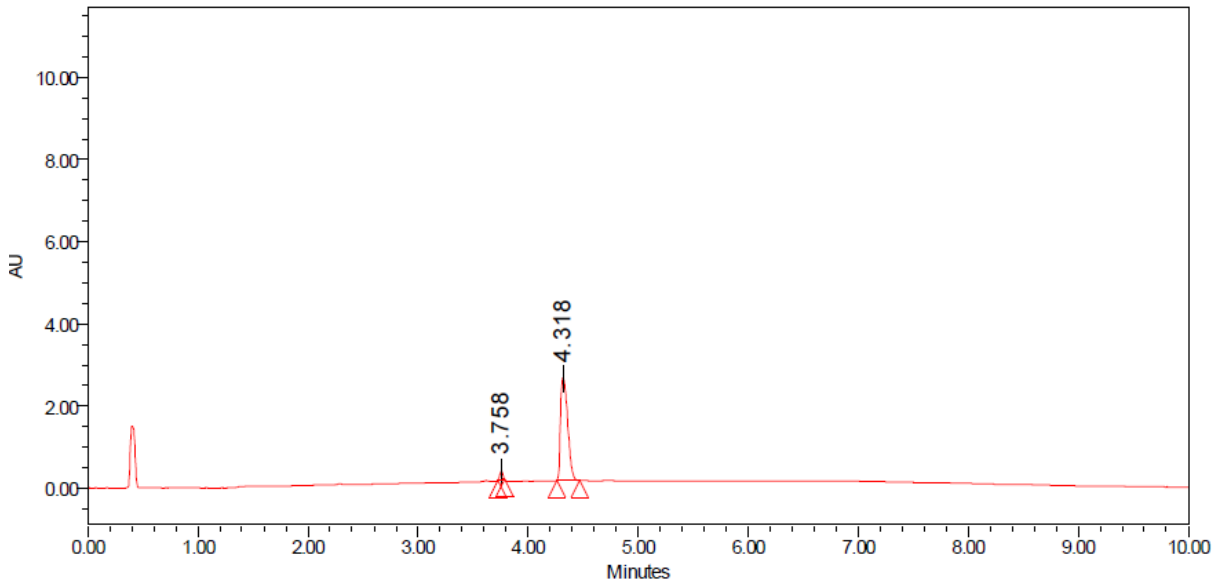


Peak Results

	RT	% Area
1	3.338	3.06
2	3.652	96.94

(*R*)-*tert*-Butyl 2-oxo-4-((*R*)-5-oxo-2-phenyl-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (3b)

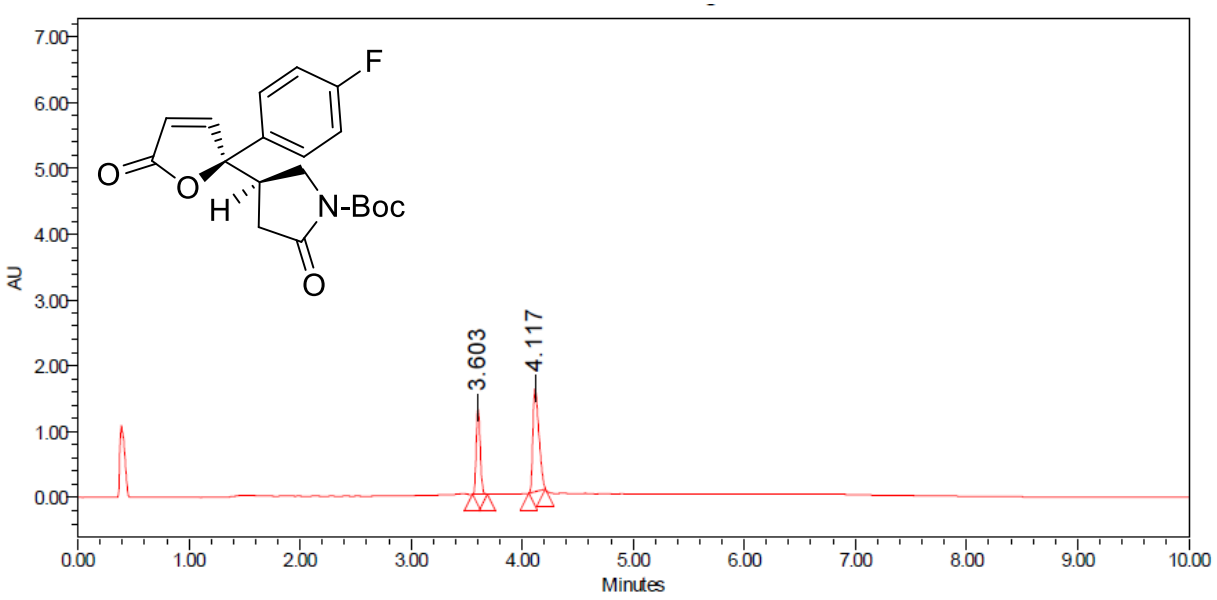


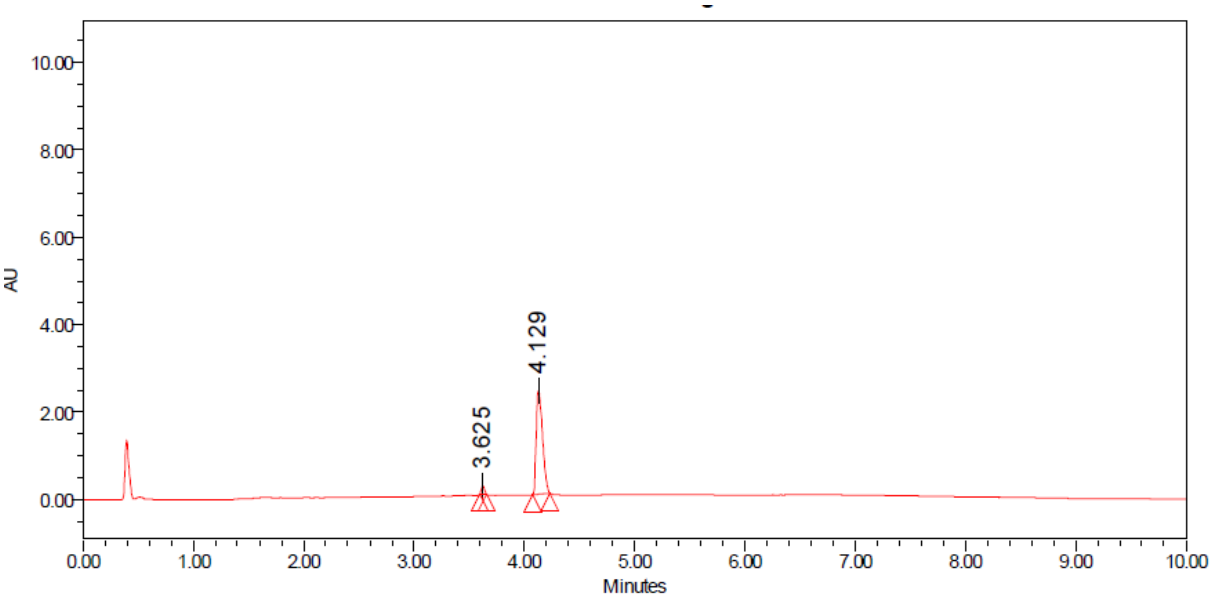


Peak Results

	RT	% Area
1	3.758	3.41
2	4.318	96.59

(*R*)-*tert*-Butyl 4-((*R*)-2-(4-fluorophenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3c)

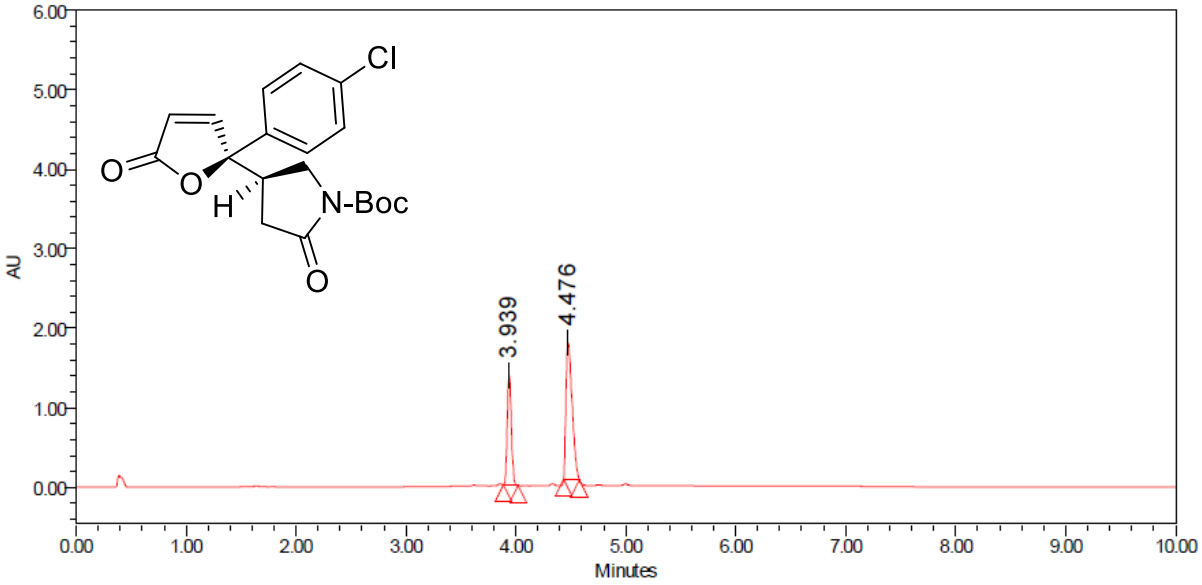


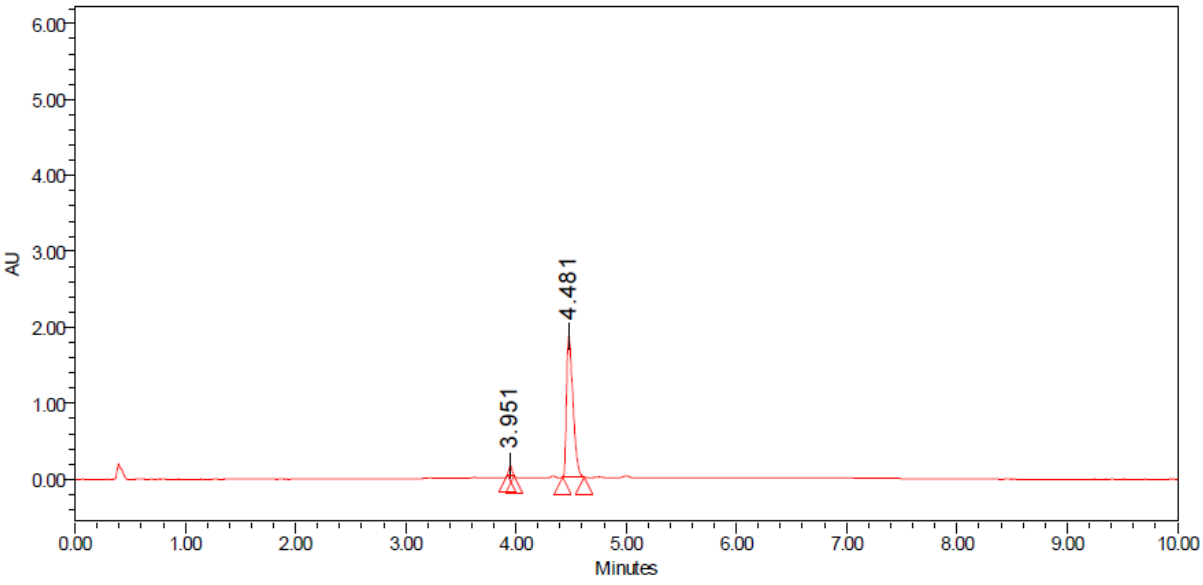


Peak Results

	RT	% Area
1	3.625	3.66
2	4.129	96.34

(*R*)-*tert*-Butyl 4-((*R*)-2-(4-chlorophenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3d)

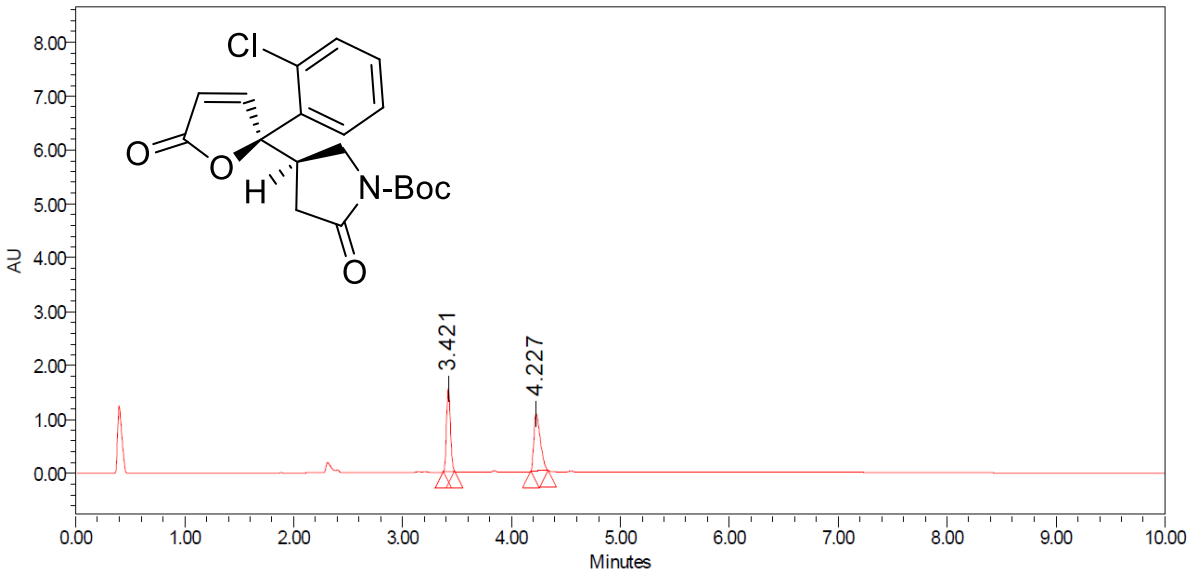


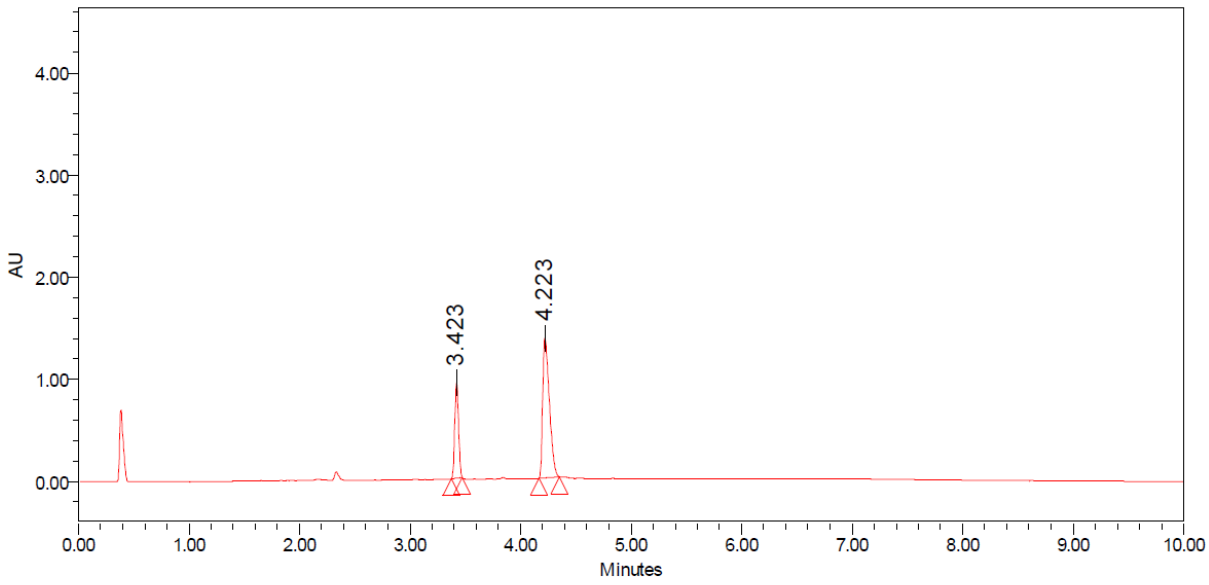


Peak Results

	RT	% Area
1	3.951	3.26
2	4.481	96.74

(*R*)-*tert*-Butyl 4-((*R*)-2-(2-chlorophenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3e)

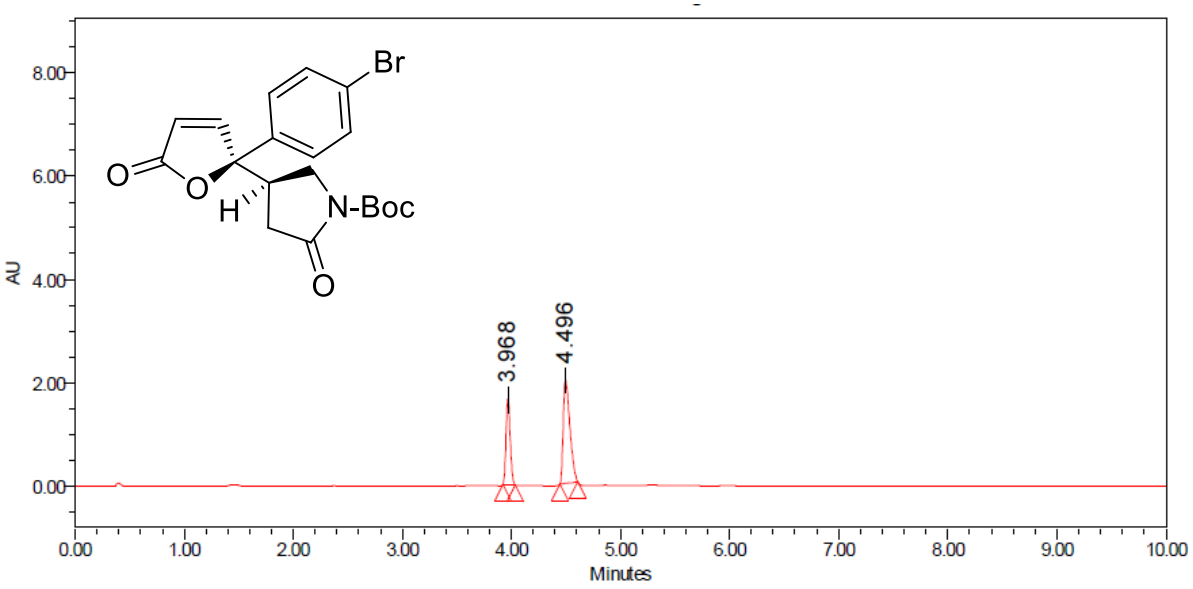


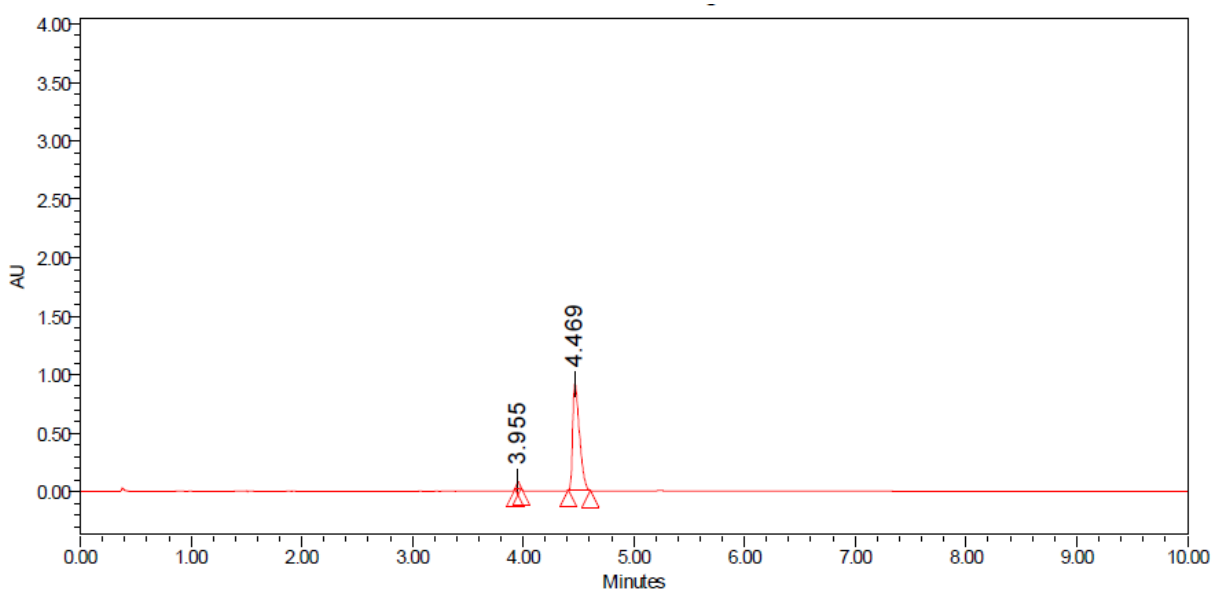


Peak Results

	RT	% Area
1	3.423	28.03
2	4.223	71.97

(*R*)-*tert*-Butyl 4-((*R*)-2-(4-bromophenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3f)

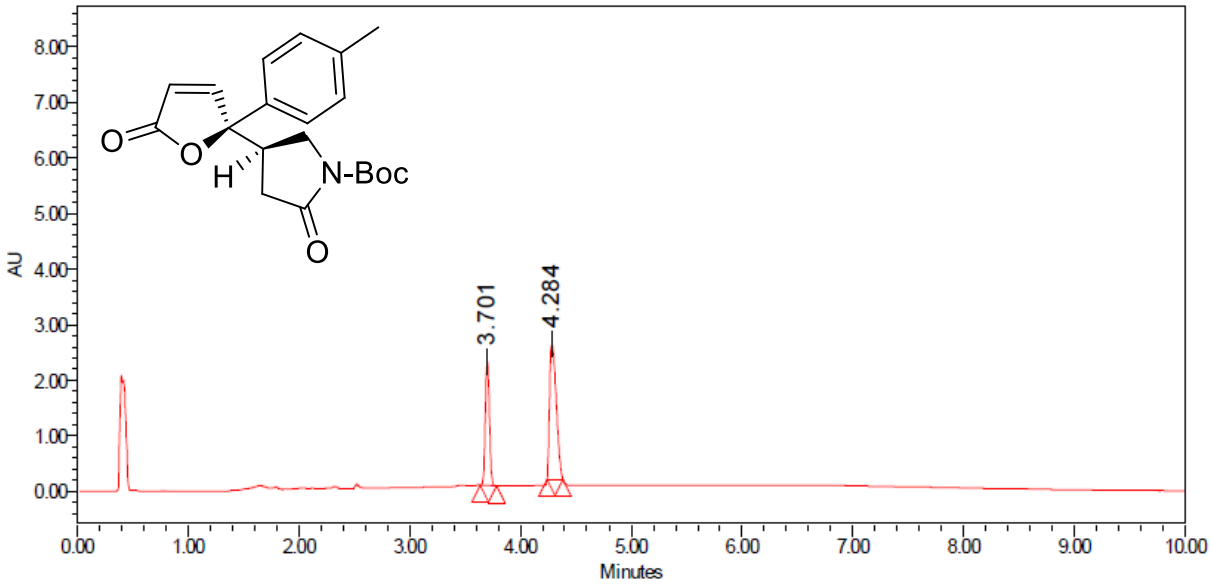


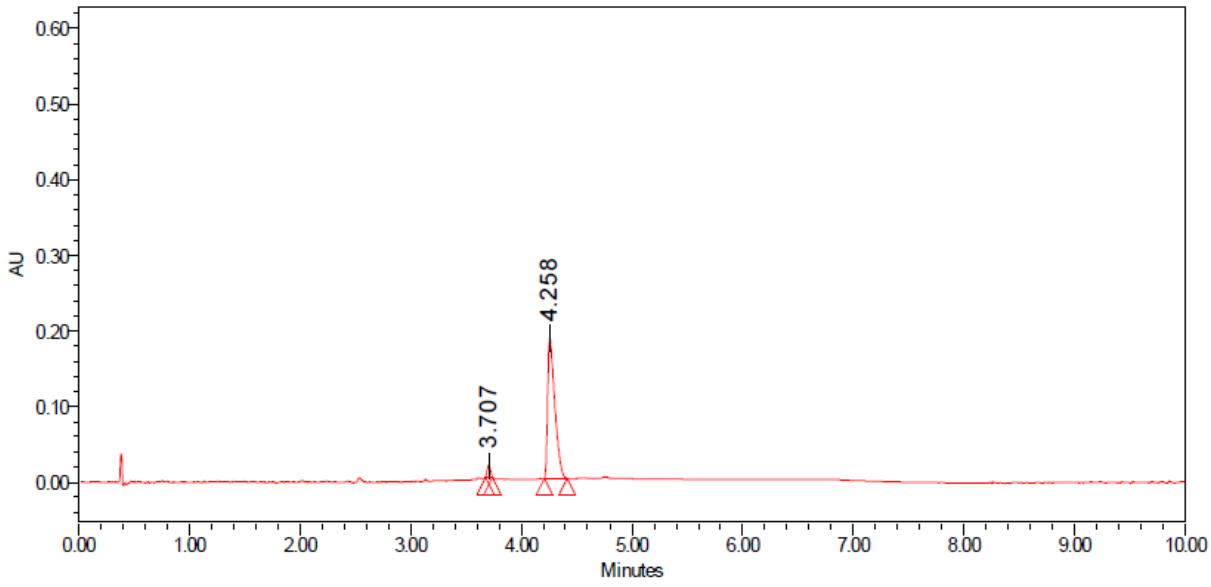


Peak Results

	RT	% Area
1	3.955	2.90
2	4.469	97.10

(*R*)-*tert*-Butyl 2-oxo-4-((*R*)-5-oxo-2-(*p*-tolyl)-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (3g)

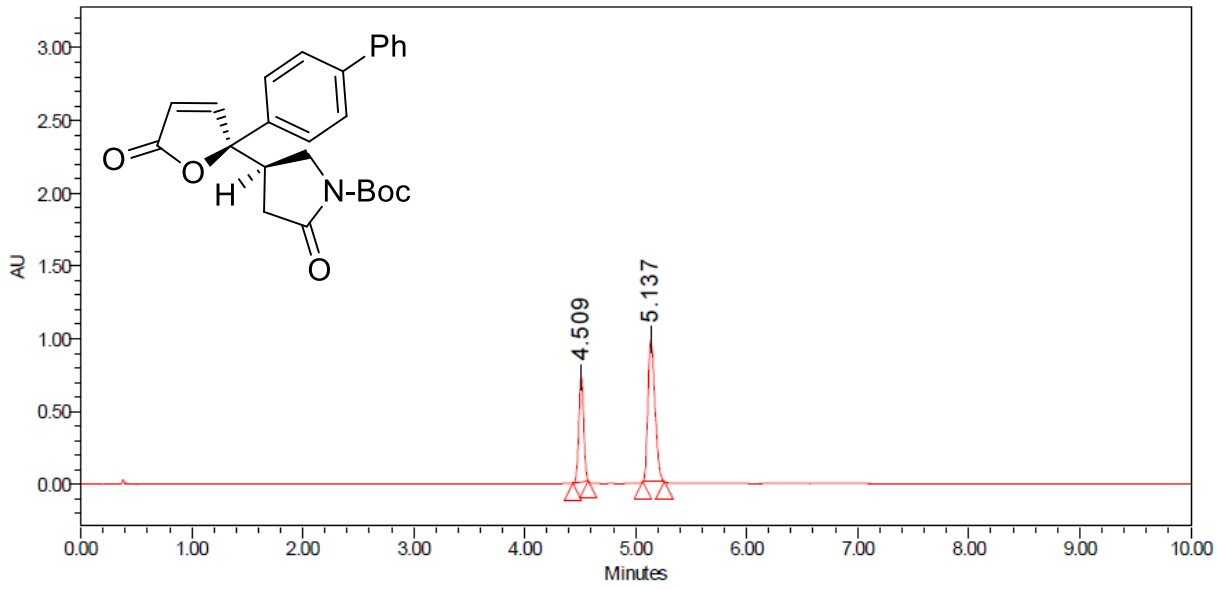


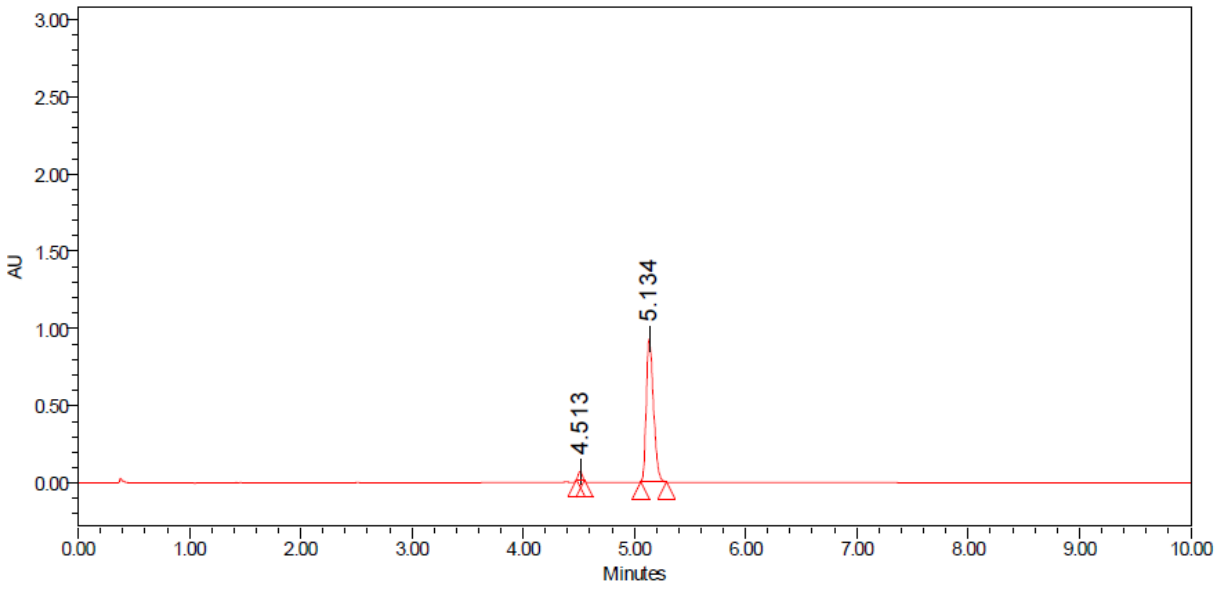


Peak Results

	RT	% Area
1	3.707	3.61
2	4.258	96.39

(*R*)-*tert*-Butyl 4-((*R*)-2-([1,1'-biphenyl]-4-yl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3h)

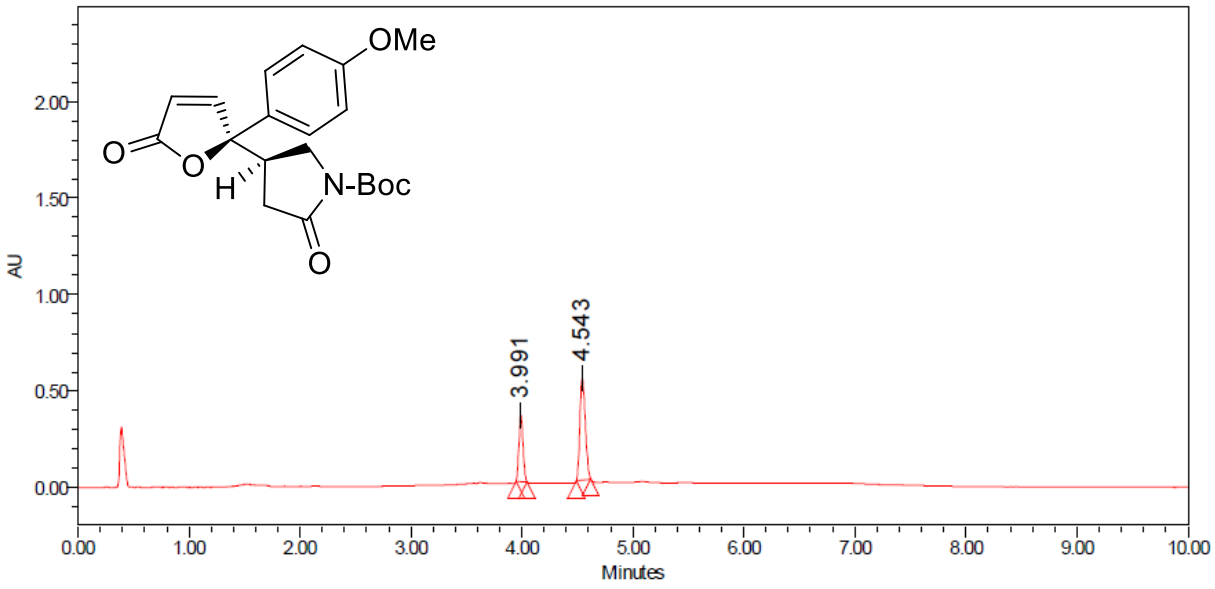


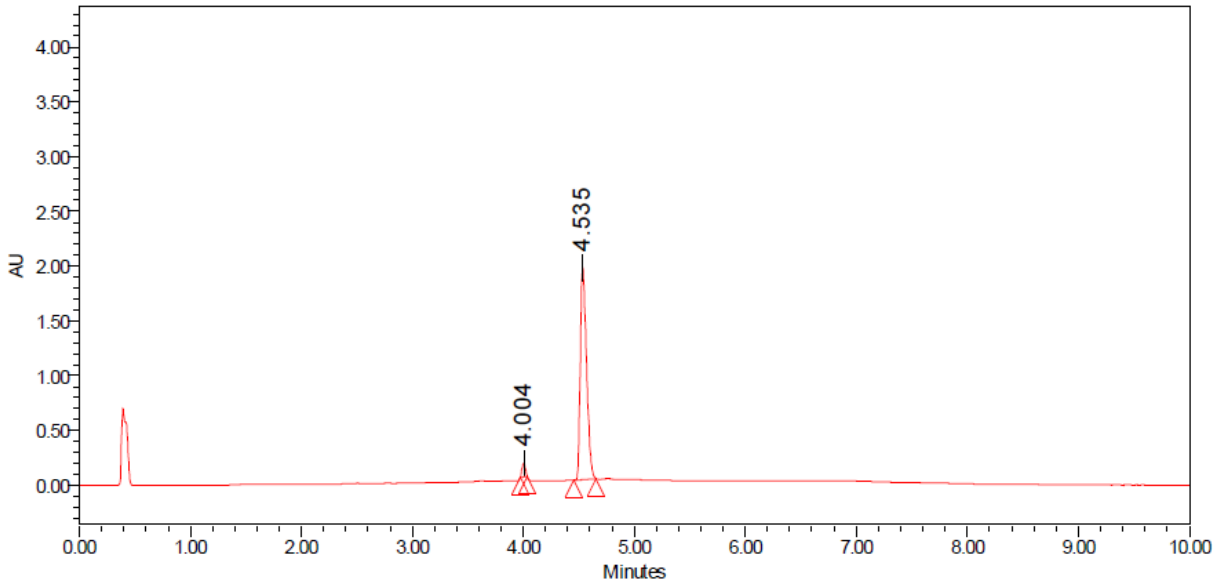


Peak Results

	RT	% Area
1	4.513	2.96
2	5.134	97.04

(*R*)-*tert*-Butyl 4-((*R*)-2-(4-methoxyphenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3i)

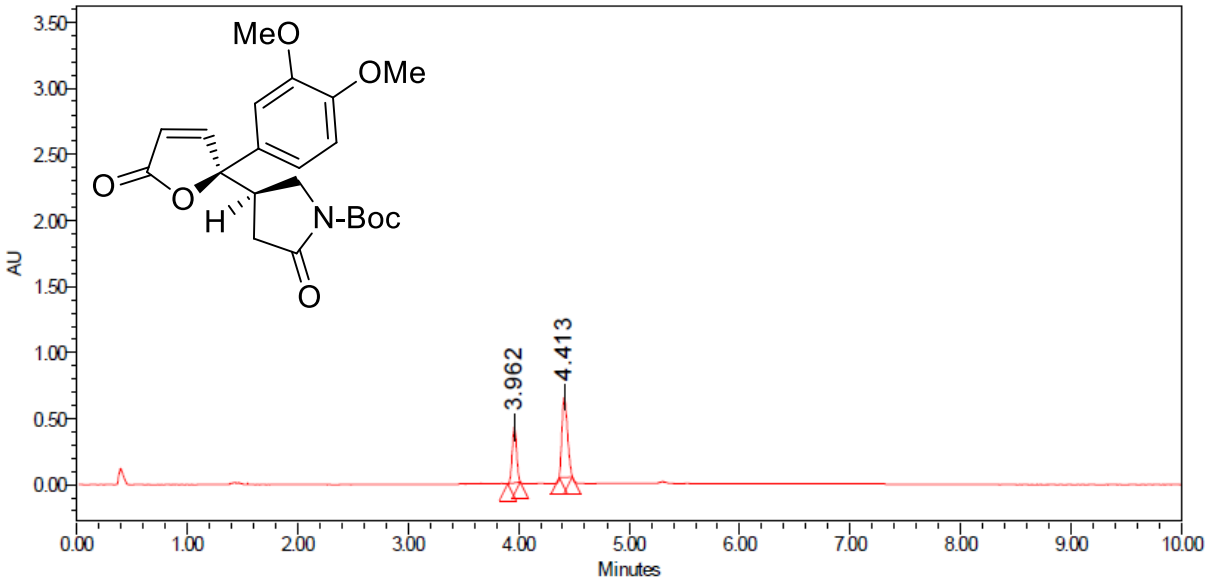


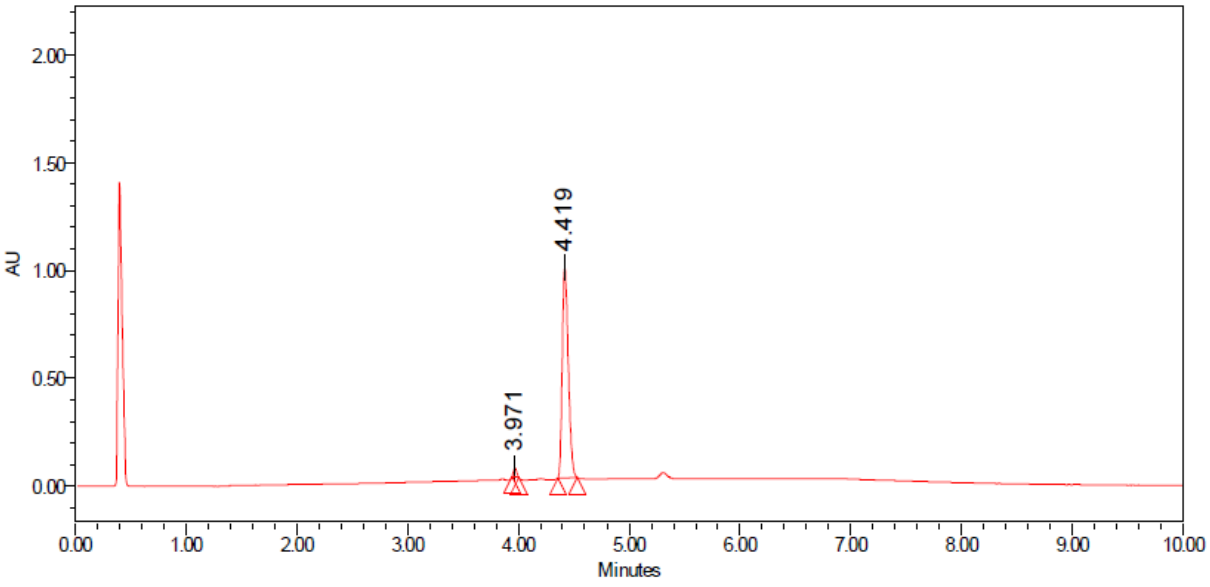


Peak Results

	RT	% Area
1	4.004	3.35
2	4.535	96.65

(*R*)-*tert*-Butyl 4-((*R*)-2-(3,4-dimethoxyphenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3j)

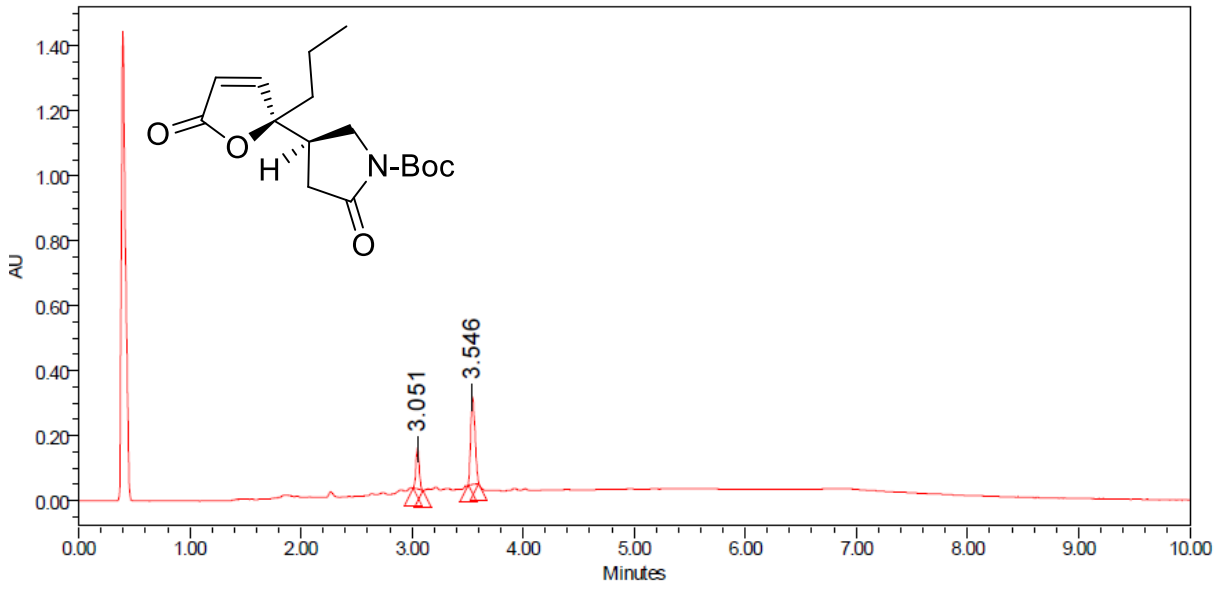


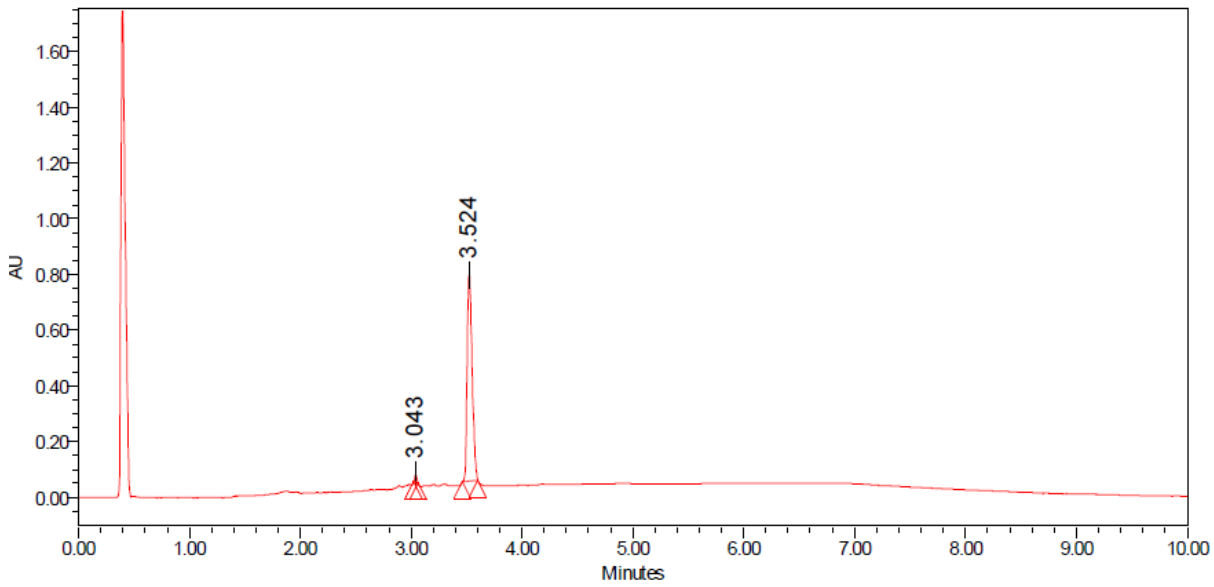


Peak Results

	RT	% Area
1	3.971	2.09
2	4.419	97.91

(*R*)-*tert*-Butyl 2-oxo-4-((*R*)-5-oxo-2-propyl-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (3k)

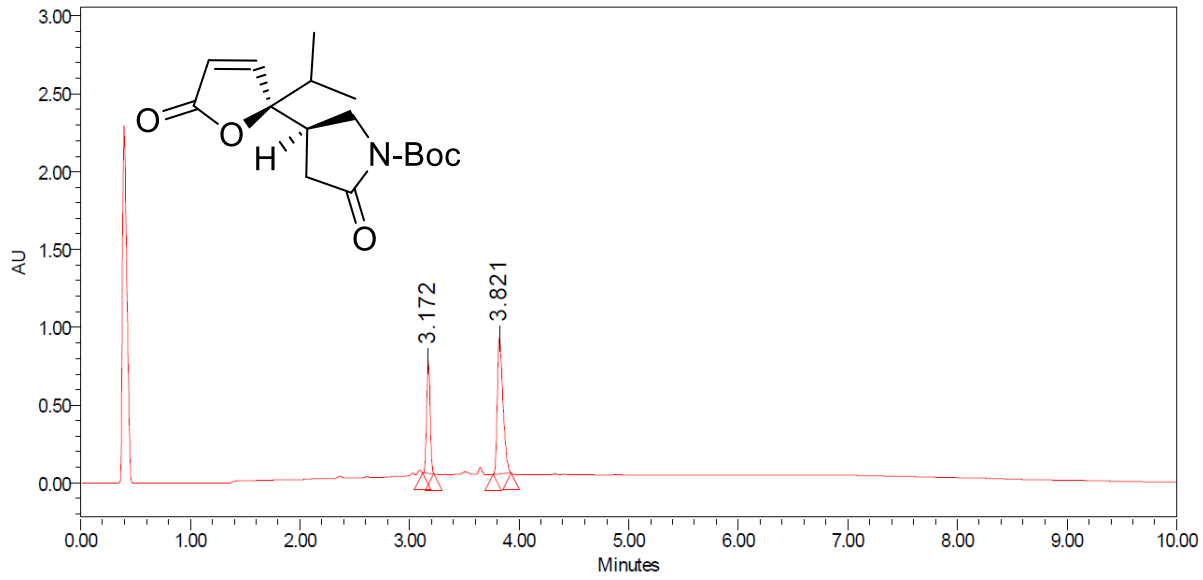


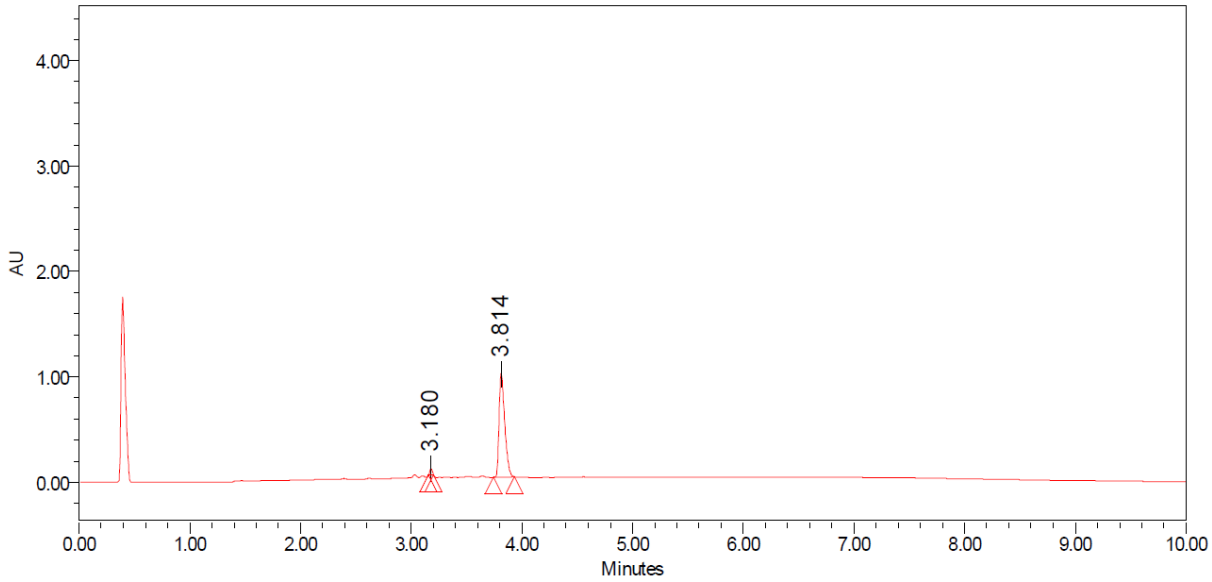


Peak Results

	RT	% Area
1	3.043	1.54
2	3.524	98.46

(*R*)-*tert*-Butyl 2-oxo-4-((*R*)-5-oxo-2-isopropyl-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (3l)

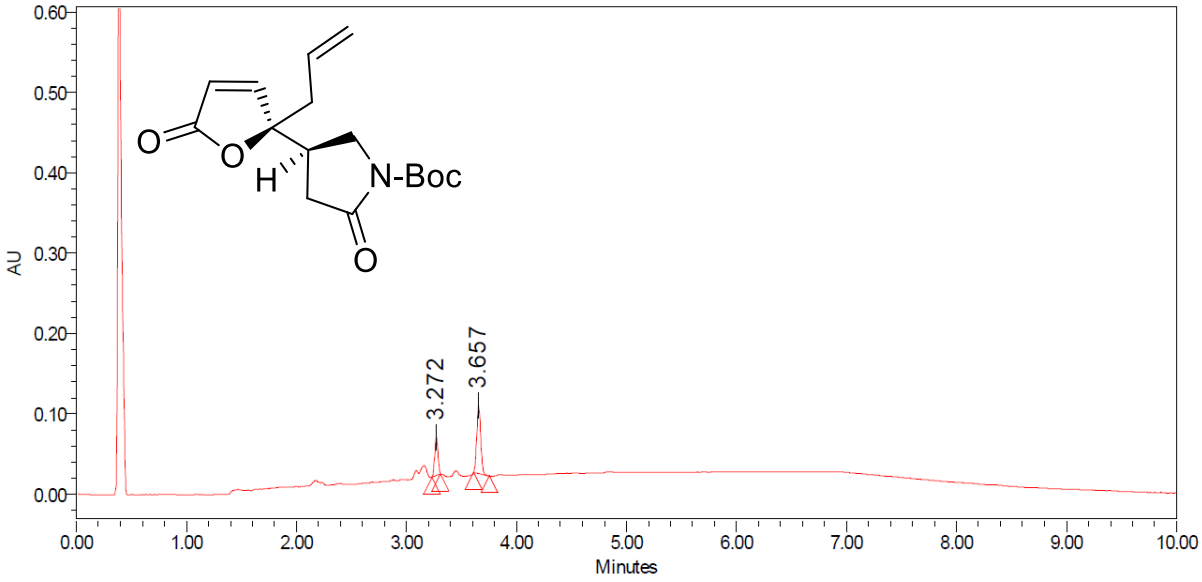


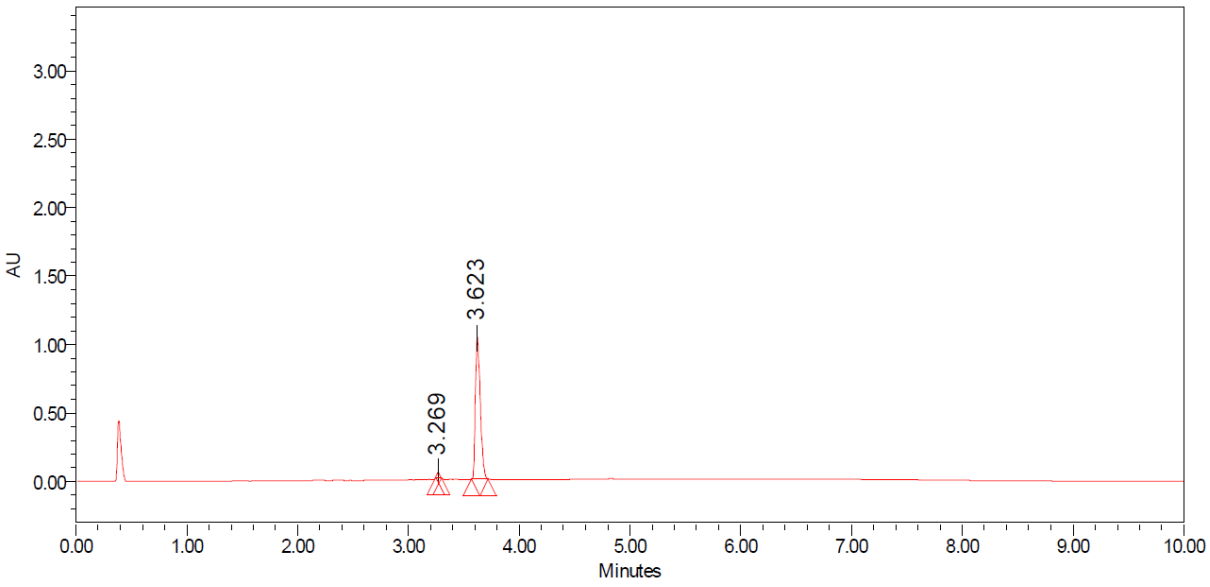


Peak Results

	RT	% Area
1	3.180	2.60
2	3.814	97.40

(*R*)-*tert*-Butyl 2-oxo-4-((*R*)-5-oxo-2-allyl-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (3m)





Peak Results

	RT	% Area
1	3.269	2.12
2	3.623	97.88