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Organocatalytic Enantioselective Synthesis of 2,3-Dihydropyridazines

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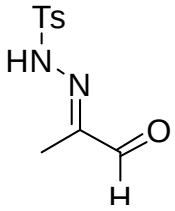
General Methods.[1] NMR spectra were acquired on a Bruker 300 spectrometer, running at 300 and 75 MHz for ^{1}H and ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, 77.0 ppm for ^{13}C NMR). The following abbreviations are used to indicate the multiplicity in ^{1}H NMR spectra: s, singlet; d, doublet; t, triplet; m, multiplet; bs, broad signal. ^{13}C NMR spectra were acquired on a broad band decoupled mode. IR spectra were measured in a Jasco FT/IR 4100 and only characteristic bands are given. Mass spectra (MS) were recorded on an Agilent 7890A gas chromatograph coupled to an Agilent 5975 mass spectrometer (EI). High resolution mass spectra (HRMS) were recorded on a micromass GCT spectrometer using chemical ionization (CI). X-ray data collections were performed in a Oxford Diffraction Xcalibur 2 diffractometer equipped with a Sapphire 2 CCD area detector, and a MoKα sealed-tube source with graphite monochromator (λ = 0.71073Å, 0.5mm collimator). The sample was kept at 100(1)K with a Oxford Cryosystems Cryostream 700 cooler. Analytical thin layer chromatography (TLC) was performed using pre-coated aluminium-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or *p*-anisaldehyde dip.[2] Melting points (M.p.) were measured in a Büchi B-540 apparatus and are uncorrected. Optical rotations were measured on a Jasco P-2000 polarimeter. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC in a Waters 2695 chromatograph with a Waters 2998 photodiode array detector (Daicel Chiralpak IC and AD-H columns).

Materials. Analytical grade solvents and commercially available reagents were used without further purification. For flash chromatography (FC) silica gel (Silica gel 60, 230-400 mesh, Merck) was employed.

[1] SGIker technical support (MEC, GV/EJ and European Social Fund) is gratefully acknowledged (NMR, HRMS and X-ray analysis).
[2] E. Stahl, *Thin Layer Chromatography*, Springer-Verlag, Berlin, **1969**.

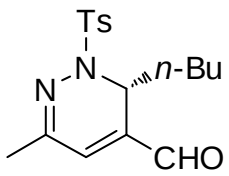
Experimental Procedures and Characterizations

General Procedure for the Preparation of the hydrazone 2.



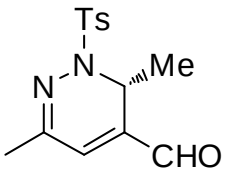
(*E*)-4-methyl-*N'*-(1-oxopropan-2-ylidene)benzenesulfonohydrazide (2). To a suspension of *p*-toluenesulfonyl hydrazide (5.0 g, 26.8 mmol) in ether (15 mL), a 40% methyl glyoxal solution in water (5.5 mL, 32.2 mmol) was added, followed by the addition of Na_2SO_4 anhydre. The reaction mixture was vigorously stirred at room temperature for 18 h. Solids were removed by filtration and washed with ether. The filtrates were concentrated *in vacuo*. The crude was purified by FC (n-hexane/EtOAc gradient from 19:1 to 7:3) yielding the corresponding hydrazone **2** (955 mg, 3.97 mmol) in 15%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.33 (s, 1H), 9.08 (s, 1H), 7.87 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 2.44 (s, 3H), 1.87 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.4, 150.8, 145.1, 134.5, 129.9, 128.0, 21.6, 8.3. IR: 3220.5, 1696.1, 1338.4, 1166.7 cm^{-1}. MS (EI) m/z (%): 214 (2), 197 (3), 184 (4), 155 (25), 139 (100), 123 (40), 108 (4), 91 (56), 77 (14), 65 (15), 51 (3). M.p. (*n*-hexane/EtOAc): 123-125 ºC.

General Procedure for the Preparation of 2,3-Dihydropyridazines 4. An ordinary vial equipped with a magnetic stirring bar was charged with catalyst **3b** (0.06 mmol, 20 mol%), PhCOOH (0.30 mmol) and toluene (6 mL). Then, the α,β-unsatured aldehyde **1** (0.30 mmol) was added and the mixture was stirred for 10 minutes prior to the addition of hydrazone **2** (0.60 mmol). The stirring was maintained at room temperature until the reaction was complete (3-6 days). The reaction mixture was washed twice with a saturated solution of $NaHCO_3$, dried over Na_2SO_4 and concentrated *in vacuo*. The crude was charged onto silica gel and subjected to FC. The racemic standards for HPLC separation conditions were prepared using a mixture of (*R*) and (*S*) catalyst **3b** (0.06 mmol, 20 mol%).

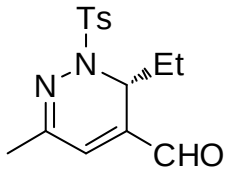


(*R*)-3-butyl-6-methyl-2-(*p*-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (4a). Following the general procedure **4a** (84 mg, 0.25 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) in 84% yield starting from aldehyde **1a** (41 µL, 0.30 mmol) and hydrazone **2** (144 mg, 0.60 mmol) in the presence of **3b** (36 mg, 0.06 mmol), PhCOOH (34 mg, 0.30 mmol) and using toluene (6 mL) as solvent. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.3 Hz, 2H), 6.37 (s, 1H), 5.45 (t, *J* = 6.4 Hz, 1H), 2.40 (s, 3H), 2.16 (s, 3H), 1.44–1.32 (m, 2H), 1.29-1.09 (m, 3H), 1.08–0.97 (m, 1H), 0.78 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.1, 148.2, 144.0, 138.0, 136.3, 130.6, 129.5, 127.7, 49.3, 32.8, 26.0, 22.3, 21.6, 21.2, 13.8. IR: 1680.7, 1597.7, 1356.7, 1165.8 cm^{-1}. MS (EI) m/z (%): 334 (M^+, 20), 320 (2), 291 (7), 179 (100), 137.1 (76), 122 (8), 108 (14), 91 (25), 77 (12), 53 (6).

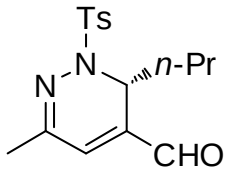
HRMS: Calculated for $[C_{17}H_{23}N_2O_3S]^+$: 335.1429 $[(M+H)^+]$; found: 335.1443. The ee was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 12.64 min, τ_{minor} = 16.44 min (97% ee). $[\alpha]_D^{rt}$: -428.3 (*c* = 1.0, CH_2Cl_2).



(*R*)-3-methyl-6-methyl-2-(*p*-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (4b). Following the general procedure **4b** (80 mg, 0.27 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) in 91% yield starting from aldehyde **1b** (29 µL, 0.30 mmol) and hydrazone **2** (144 mg, 0.60 mmol) in the presence of **3b** (36 mg, 0.06 mmol), PhCOOH (34 mg, 0.30 mmol) and using toluene (6 mL) as solvent. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.40 (s, 1H), 5.45 (q, *J* = 6.5 Hz, 1H), 2.41 (s, 3H), 2.18 (s, 3H), 0.97 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.7, 147.4, 144.2, 140.0, 136.4, 130.4, 129.6, 128.0, 45.4, 21.6, 21.2, 17.2. IR: 1679.7, 1596.8, 1354.8, 1165.8 cm^{-1}. MS (EI) m/z (%): 292 (M+, 20), 207 (3), 155 (2), 137 (100), 122 (2), 109 (16), 91 (14), 77 (7), 65 (9), 53 (5). HRMS: Calculated for $[C_{14}H_{17}N_2O_3S]^+$: 293.0960 $[(M+H)^+]$; found: 293.0972. The ee was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 18.16 min, τ_{minor} = 23.38 min (89% ee). $[\alpha]_D^{rt}$: -274.7 (*c* = 1.0, CH_2Cl_2).

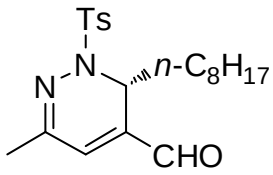


(*R*)-3-ethyl-6-methyl-2-(*p*-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (4c). Following the general procedure **4c** (68 mg, 0.22 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) in 74% yield starting from aldehyde **1c** (32 µL, 0.30 mmol) and hydrazone **2** (144 mg, 0.60 mmol) in the presence of **3b** (36 mg, 0.06 mmol), PhCOOH (34 mg, 0.30 mmol) and using toluene (6 mL) as solvent. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.56 (s, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.3 Hz, 2H), 6.40 (s, 1H), 5.42 (t, *J* = 6.4 Hz, 1H), 2.40 (s, 3H), 2.15 (s, 3H), 1.58–1.37 (m, 2H), 0.74 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.2, 147.9, 144.0, 137.6, 136.2, 130.8, 129.5, 127.7, 50.3, 26.3, 21.6, 21.1, 8.6. IR: 1680.7, 1597.6, 1357.6, 1166.7 cm^{-1}. MS (EI) m/z (%): 306 (M+, 16), 207 (2), 151 (100), 136 (5), 123 (9), 106 (12), 91 (21), 78 (11), 65 (13), 51 (5). HRMS: Calculated for $[C_{15}H_{19}N_2O_3S]^+$: 307.1116 $[(M+H)^+]$; found: 307.1103. The ee was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 14.76 min, τ_{minor} = 21.22 min (96% ee). $[\alpha]_D^{rt}$: -391.7 (*c* = 1.0, CH_2Cl_2).

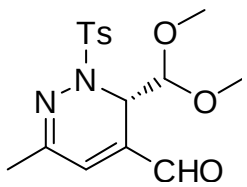


(*R*)-6-methyl-3-propyl-2-(*p*-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (4d). Following the general procedure **4d** (69 mg, 0.22 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) in 72% yield starting from

aldehyde **1d** (36 µL, 0.30 mmol) and hydrazone **2** (144 mg, 0.60 mmol) in the presence of **3b** (36 mg, 0.06 mmol), PhCOOH (34 mg, 0.30 mmol) and using toluene (6 mL) as solvent. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 6.37 (s, 1H), 5.46 (t, *J* = 6.4 Hz, 1H), 2.40 (s, 3H), 2.16 (s, 3H), 1.44–1.36 (m, 2H), 1.34-1.19 (m, 1H), 1.19-1.01 (m, 1H), 0.80 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.1, 148.2, 144.0, 138.0, 136.2, 130.6, 129.5, 127.7, 49.1, 35.3, 21.6, 21.2, 17.3, 13.7. IR: 1681.6, 1597.5, 1355.7, 1167.7 cm^{-1}. MS (EI) m/z (%): 320 (M+, 21), 291 (6), 207 (8), 165 (100), 151 (3), 137 (25), 122 (11), 108 (14), 91 (26), 65 (14), 51 (6). HRMS: Calculated for $[C_{16}H_{21}N_2O_3S]^+$: 321.1273 $[(M+H)^+]$; found: 321.1286. The ee was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 12.87 min, τ_{minor} = 17.57 min (96% ee). $[\alpha]_D^{rt}$: -359.5 (*c* = 1.0, CH_2Cl_2).

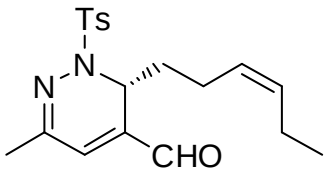


(*R*)-6-methyl-3-octyl-2-(*p*-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (4e). Following the general procedure **4e** (74 mg, 0.19 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) in 63% yield starting from aldehyde **1e** (60 µL, 0.30 mmol) and hydrazone **2** (144 mg, 0.60 mmol) in the presence of **3b** (36 mg, 0.06 mmol), PhCOOH (34 mg, 0.30 mmol) and using toluene (6 mL) as solvent. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.56 (s, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.3 Hz, 2H), 6.37 (s, 1H), 5.44 (t, *J* = 6.4 Hz, 1H), 2.40 (s, 3H), 2.16 (s, 3H), 1.48–1.07 (m, 14H), 0.86 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.1, 148.2, 144.0, 138.0, 136.3, 130.6, 129.5, 127.7, 49.3, 33.1, 31.8, 29.3, 29.3, 29.2, 23.9, 22.6, 21.6, 21.2, 14.1. IR: 1681.6, 1596.5, 1358.6, 1167.7 cm^{-1}. MS (EI) m/z (%): 390 (M+, 14), 291 (7), 235 (100), 207 (12), 137 (45), 109 (10), 91 (15), 65 (6). HRMS: Calculated for $[C_{21}H_{31}N_2O_3S]^+$: 391.2055 $[(M+H)^+]$; found: 391.2056. The ee was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 9.22 min, τ_{minor} = 10.83 min (97% ee). $[\alpha]_D^{rt}$: -274.0 (*c* = 1.0, CH_2Cl_2).

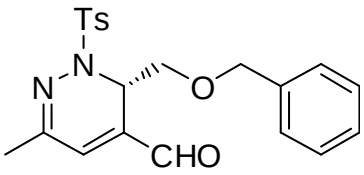


(*S*)-3-dimethoxymethyl-6-methyl-2-(*p*-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (4f). Following the general procedure **4f** (64 mg, 0.18 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) in 61% yield starting from aldehyde **1f** (38 µL, 0.30 mmol) and hydrazone **2** (144 mg, 0.60 mmol) in the presence of **3b** (36 mg, 0.06 mmol), PhCOOH (34 mg, 0.30 mmol) and using toluene (6 mL) as solvent. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (s, 1H), 7.80 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.3 Hz, 2H), 6.48 (s, 1H), 5.59 (d, *J* = 5.0 Hz, 1H), 4.15 (d, *J* = 5.0 Hz, 1H), 3.31 (s, 3H), 3.25 (s, 3H), 2.40 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.7, 147.9, 144.1, 136.0, 133.4, 130.5, 129.4, 127.9, 104.0, 56.0, 55.1, 49.1, 21.6, 21.2. IR: 1685.5, 1353.8, 1168.7, 1119.5 cm^{-1}. MS (EI) m/z (%): 278 (14), 214 (6), 185 (9), 171 (4), 155 (8), 139 (2), 123 (100), 106 (6), 91 (31), 79 (5), 65 (16), 51 (4). HRMS: Calculated for

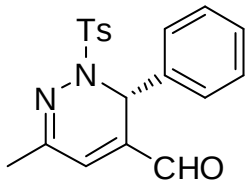
$[C_{16}H_{21}N_2O_5S]^+$: 353.1171 $[(M+H)^+]$; found: 353.1176. The ee was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 17.42 min, τ_{minor} = 21.97 min (97% ee). $[\alpha]_D^{rt}$: -545.1 (*c* = 1.0, CH_2Cl_2).



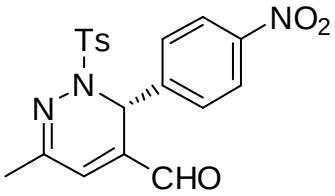
(*R*,*Z*)-3-(hex-3-en-1-yl)-6-methyl-2-(*p*-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (4g). Following the general procedure **4g** (74 mg, 0.21 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) in 68% yield starting from aldehyde **1g** (45 µL, 0.30 mmol) and hydrazone **2** (144 mg, 0.60 mmol) in the presence of **3b** (36 mg, 0.06 mmol), PhCOOH (34 mg, 0.30 mmol) and using toluene (6 mL) as solvent. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.3 Hz, 2H), 6.39 (s, 1H), 5.48 (t, *J* = 6.4 Hz, 1H), 5.37–5.26 (m, 1H), 5.19–5.07 (m, 1H), 2.40 (s, 3H), 2.17 (s, 3H), 2.03–1.79 (m, 4H), 1.49-1.39 (m, 2H), 0.91 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0, 148.4, 144.1, 137.8, 136.2, 132.8, 130.6, 129.5, 127.7, 127.1, 49.1, 33.2, 22.0, 21.6, 21.2, 20.5, 14.2. IR: 1681.6, 1595.8, 1353.6, 1166.7 cm^{-1}. MS (EI) m/z (%): 360 (M+, 2), 291 (100), 226 (1), 205 (92), 155 (3), 135 (52), 106 (46), 91 (25), 65 (13). HRMS: Calculated for $[C_{19}H_{25}N_2O_3S]^+$: 361.1586 $[(M+H)^+]$; found: 361.1601. The ee was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (93:7)]; flow rate 1.0 mL/min; τ_{major} = 16.54 min, τ_{minor} = 21.86 min (97% ee). $[\alpha]_D^{rt}$: -236.3 (*c* = 1.0, CH_2Cl_2).



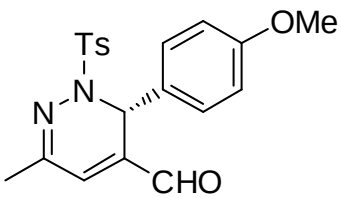
(*S*)-3-[(benzyloxy)methyl]-6-methyl-2-(*p*-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (4h). Following the general procedure **4h** (82 mg, 0.21mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) in 69% yield starting from aldehyde **1h** (53 mg, 0.30 mmol) and hydrazone **2** (144 mg, 0.60 mmol) in the presence of **3b** (36 mg, 0.06 mmol), PhCOOH (34 mg, 0.30 mmol) and using toluene (6 mL) as solvent. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.40-7.17 (m, 5H), 7.14-7.07 (m, 2H), 6.47 (s, 1H), 5.63 (t, *J* = 4.4 Hz, 1H), 4.33–4.18 (m, 2H), 3.48–3.31 (m, 2H), 2.37 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.8, 147.0, 144.1, 137.6, 136.2, 135.3, 132.1, 129.4, 128.2, 128.0, 127.5, 127.3, 73.0, 69.9, 48.8, 21.6, 21.1. IR: 1679.7, 1595.8, 1353.8, 1165.8, 1090.6 cm^{-1}. MS (EI) m/z (%): 398 (M+, 2), 355 (4), 281 (4), 241 (5), 207 (18), 171 (4), 121 (4), 107 (63), 91 (100), 77 (90), 65 (14), 51 (25). HRMS: Calculated for $[C_{21}H_{23}N_2O_4S]^+$: 399.1379 $[(M+H)^+]$; found: 399.1375. The ee was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 73.07 min, τ_{minor} = 62.73 min (96% ee). $[\alpha]_D^{rt}$: -103.8 (*c* = 1.0, CH_2Cl_2).



(*R*)-6-methyl-3-phenyl-2-(*p*-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (4i). Following the general procedure **4i** (52 mg, 0.15 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) in 49% yield starting from aldehyde **1i** (76 µL, 0.60 mmol) and hydrazone **2** (72 mg, 0.30 mmol) in the presence of **3b** (36 mg, 0.06 mmol), PhCOOH (34 mg, 0.30 mmol) and using toluene (6 mL) as solvent. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.23–7.14 (m, 1H), 7.14–7.08 (m, 4H), 7.03 (d, *J* = 8.2 Hz, 2H), 6.51 (s, 1H), 6.43 (s, 1H), 2.33 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.7, 145.7, 143.7, 138.3, 137.9, 135.6, 129.9, 128.9, 128.7, 128.5, 127.9, 127.3, 52.8, 21.5, 21.2. IR: 1688.4, 1599.7, 1359.6, 1168.7 cm^{-1}. MS (EI) m/z (%): 354 (M+, 100), 327 (2), 281 (3), 226 (1), 199 (53), 171 (60), 155 (30), 144 (11), 115 (24), 91 (32), 65 (16). HRMS: Calculated for $[C_{19}H_{19}N_2O_3S]^+$: 355.1116 [$(M+H)^+$]; found: 355.1117. The ee was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 84.87 min, τ_{minor} = 45.38 min (89% ee). $[\alpha]_D^{rt}$: -33.3 (*c* = 1.0, CH_2Cl_2).

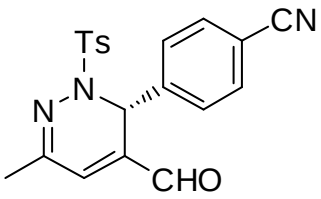


(*R*)-6-methyl-3-(4-nitrophenyl)-2-(*p*-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (4j). Following the general procedure **4j** (62 mg, 0.16 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) in 52% yield starting from aldehyde **1j** (108 mg, 0.60 mmol) and hydrazone **2** (72 mg, 0.30 mmol) in the presence of **3b** (36 mg, 0.06 mmol), PhCOOH (34 mg, 0.30 mmol) and using toluene (6 mL) as solvent. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.95 (d, *J* = 8.1 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.1 Hz, 2H), 6.57 (s, 1H), 6.54 (s, 1H), 2.36 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.5, 147.8, 146.0, 144.7, 144.6, 137.2, 135.3, 130.6, 129.3, 128.0, 127.8, 123.7, 51.2, 21.5, 21.2. IR: 1681.6, 1597.7, 1521.6, 1346.1, 1303.6, 1166.7 cm^{-1}. MS (EI) m/z (%): 399 (M+, 100), 327 (2), 281 (14), 253 (9), 241 (70), 227 (77), 198 (66), 171 (60), 169 (37), 139 (16), 115 (21), 91 (69), 65 (21). HRMS: Calculated for $[C_{19}H_{18}N_3O_5S]^+$: 400.0967 [$(M+H)^+$]; found: 400.0984. The ee was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 103.45 min, τ_{minor} = 60.82 min (95% ee). $[\alpha]_D^{rt}$: -96.7 (*c* = 1.0, CH_2Cl_2).

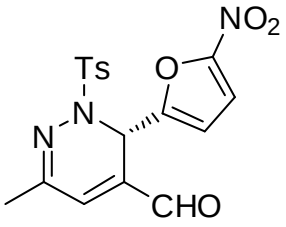


(*R*)-3-(4-methoxyphenyl)-6-methyl-2-(*p*-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (4k). Following the general procedure **4k** (69 mg, 0.18 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 7:3) in 60% yield starting from aldehyde **1k** (98 mg, 0.60 mmol) and hydrazone **2** (72 mg, 0.30 mmol) in the presence of **3b** (36 mg, 0.06 mmol), PhCOOH (34 mg, 0.30 mmol) and using toluene (6 mL) as solvent. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.53 (s, 1H), 7.41 (d, *J* = 8.3

Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 4H), 6.61 (d, *J* = 8.7 Hz, 2H), 6.51 (s, 1H), 6.34 (s, 1H), 3.74 (s, 3H), 2.33 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.8, 160.0, 145.5, 143.5, 138.5, 135.7, 130.2, 129.6, 128.8, 128.8, 127.9, 113.7, 55.3, 52.4, 21.5, 21.2. IR: 1682.6, 1608.3, 1354.8, 1168.7, 1085.7 cm^{-1}. MS (EI) m/z (%): 384 (M+, 100), 327 (2), 281 (6), 253 (5), 229 (50), 201 (44), 171 (15), 169 (37), 128 (11), 91 (35), 65 (14). HRMS: Calculated for $[C_{20}H_{21}N_2O_4S]^+$: 385.1222 $[(M+H)^+]$; found: 385.1237. The ee was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 133.94 min, τ_{minor} = 77.78 min (85% ee). $[\alpha]_D^{rt}$: +21.4 (*c* = 1.0, CH_2Cl_2).

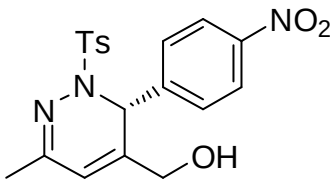


(*R*)-3-(4-cyanophenyl)-6-methyl-2-(*p*-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (4l). Following the general procedure **4l** (82 mg, 0.22 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 1:1) in 72% yield starting from aldehyde **1l** (94 mg, 0.60 mmol) and hydrazone **2** (72 mg, 0.30 mmol) in the presence of **3b** (36 mg, 0.06 mmol), PhCOOH (34 mg, 0.30 mmol) and using toluene (6 mL) as solvent. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4, 2H), 7.11 (d, *J* = 8.3 Hz, 2H), 6.55 (s, 1H), 6.48 (s, 1H), 2.38 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.5, 145.9, 144.4, 142.8, 137.2, 135.3, 132.3, 130.5, 129.2, 127.8, 127.8, 118.2, 112.4, 52.2, 21.6, 21.2. IR: 2228.3, 1677.8, 1595.8, 1357.6, 1165.8 cm^{-1}. MS (EI) m/z (%): 379 (M+, 100), 281 (2), 224 (59), 196 (59), 155 (20), 127 (16), 91 (55), 65 (19). HRMS: Calculated for $[C_{20}H_{18}N_3O_3S]^+$: 380.1069 $[(M+H)^+]$; found: 380.1063. The ee was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 148.17 min, τ_{minor} = 81.53 min (94% ee). $[\alpha]_D^{rt}$: -48.3 (*c* = 1.0, CH_2Cl_2).



(*S*)-6-methyl-3-(5-nitrofuran-2-yl)-2-(*p*-toluenesulfonyl)-2,3-dihydropyridazine-4-carbaldehyde (4m). Following the general procedure **4m** (64 mg, 0.16 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 19:1 to 1:1) in 55% yield starting from aldehyde **1m** (94 mg, 0.60 mmol) and hydrazone **2** (72 mg, 0.30 mmol) in the presence of **3b** (36 mg, 0.06 mmol), PhCOOH (34 mg, 0.30 mmol) and using toluene (6 mL) as solvent. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.61 (s, 1H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 7.00 (d, *J* = 3.6 Hz, 1H), 6.70 (s, 1H), 6.50-6.46 (m, 2H), 2.34 (s, 3H), 2.29 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 188.6, 151.7, 151.6, 146.6, 144.7, 134.4, 134.0, 131.8, 129.1, 127.9, 112.4, 111.3, 45.2, 21.5, 21.2. IR: 1681.6, 1532.2, 1501.3, 1348.0, 1310.4, 1161.9 cm^{-1}. MS (EI) m/z (%): 389 (M+, 100), 234 (30), 188 (56), 155 (19), 132 (39), 91 (76), 65 (18). HRMS: Calculated for $[C_{17}H_{16}N_3O_6S]^+$: 390.0760 $[(M+H)^+]$; found: 390.0757. The ee was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 76.54 min, τ_{minor} = 59.32 min (90% ee). $[\alpha]_D^{rt}$: +19.9 (*c* = 1.0, CH_2Cl_2).

Determination of the absolute configuration.



(*R*)-[6-methyl-3-(4-nitrophenyl)-2-(*p*-toluenesulfonyl)-2,3-dihydropyridazin-4-yl]methanol (5j). To a solution of the dihydropyridazine **4j** (42 mg, 0.10 mmol) in methanol (3 mL), $NaBH_4$ (~50 mg) was added at 0 ºC. The reaction mixture was stirred at this temperature for 20 minutes prior to the addition of a saturated solution of aqueous NH_4Cl (3 mL) and CH_2Cl_2 (5 mL) and then stirred at room temperature 30 minutes more. The mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the collected organic fractions were dried over Na_2SO_4, filtered and the solvents were removed under reduced pressure. The crude was purified by FC (n-hexane/EtOAc 1:1) yielding the corresponding alcohol **5j** (32 mg, 0.08 mmol) in 76%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.7 Hz, 2H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.7 Hz, 2H), 7.01 (d, *J* = 8.3 Hz, 2H), 6.04 (s, 1H), 5.93 (s, 1H), 4.19–4.01 (m, 2H), 2.32 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 147.9, 144.2, 143.9, 143.6, 135.6, 128.9, 128.5, 127.6, 123.6, 114.0, 62.1, 55.0, 21.7, 21.4. IR: 3418.2, 1596.8, 1520.6, 1343.2, 1304.5, 1161.9 cm^{-1}. MS (EI) m/z (%): 401 (M^+, 2), 385 (49), 355 (12), 281 (11), 253 (20), 230 (72), 207 (90), 184 (100), 171 (19), 139 (22), 115 (19), 91 (91), 65 (22). HRMS: Calculated for $[C_{19}H_{20}N_3O_5S]^+$: 402.1124[$(M+H)^+$]; found: 402.1139. M.p. (*n*-hexane/EtOAc): 188-190 ºC. The ee was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 70.74 min, τ_{minor} = 112.60 min (93 % ee). $[\alpha]_D^{rt}$: -47.5 (*c* = 1.0, CH_2Cl_2).

The absolute configuration of the dihydropyrazidine **5j** was determined by single-crystal X-ray analysis. The same stereochemistry was assumed for assigning the configuration of the rest of the compounds.

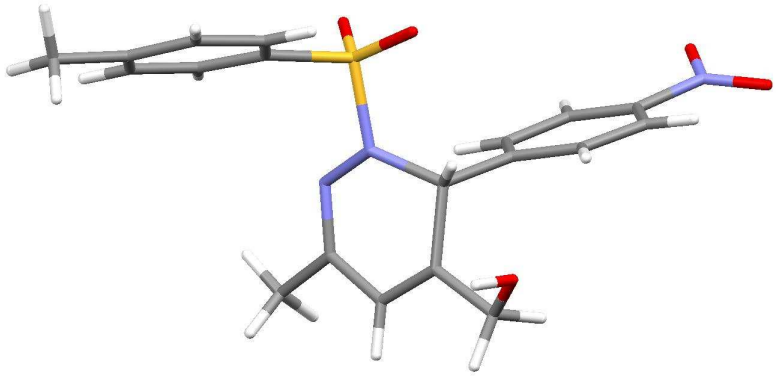


Figure S1: X-ray determined crystal structure.

NMR spectra of compound 2

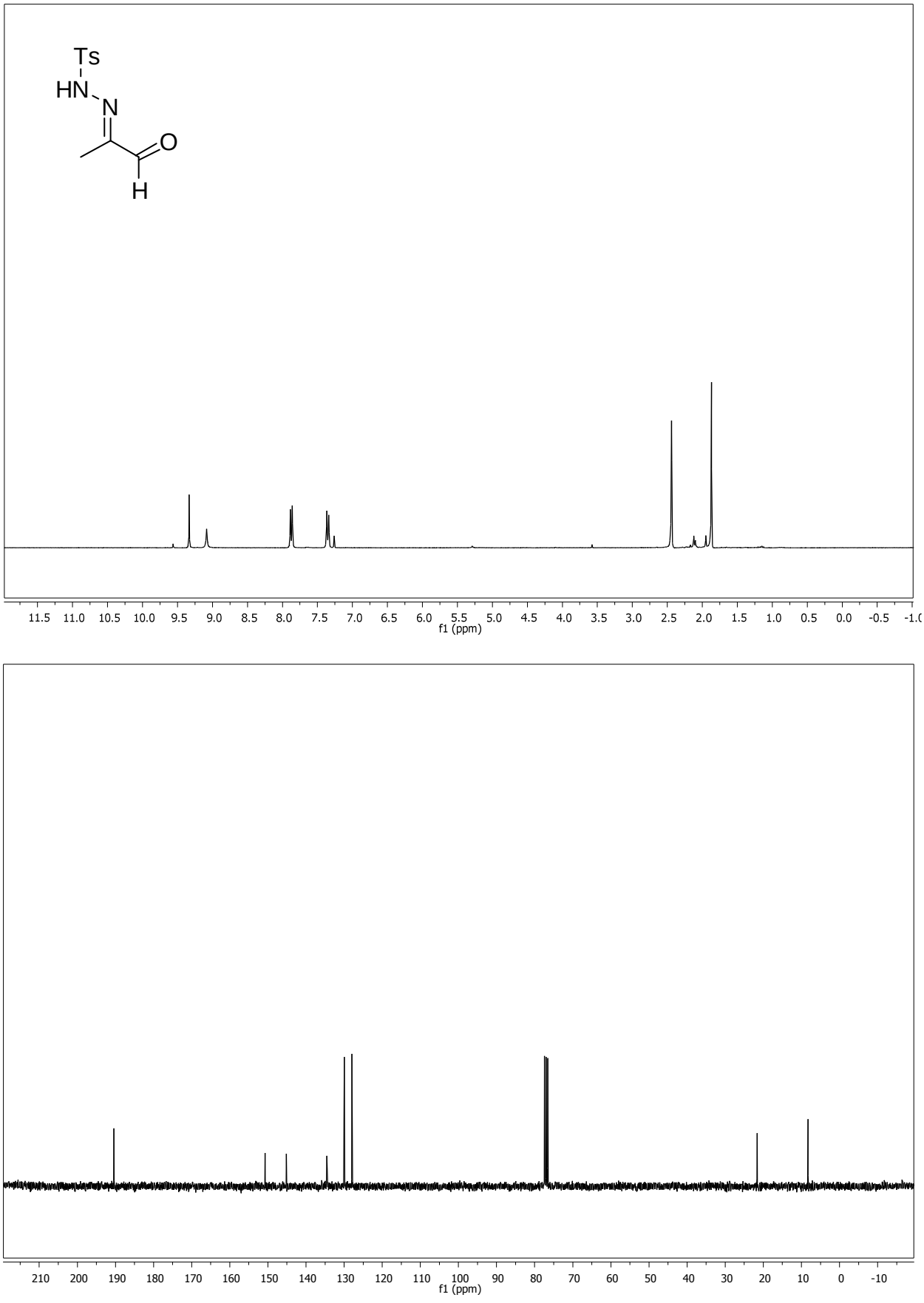


Figure S2: NMR spectra of compound **2**.

NMR spectra of compounds 4a-q

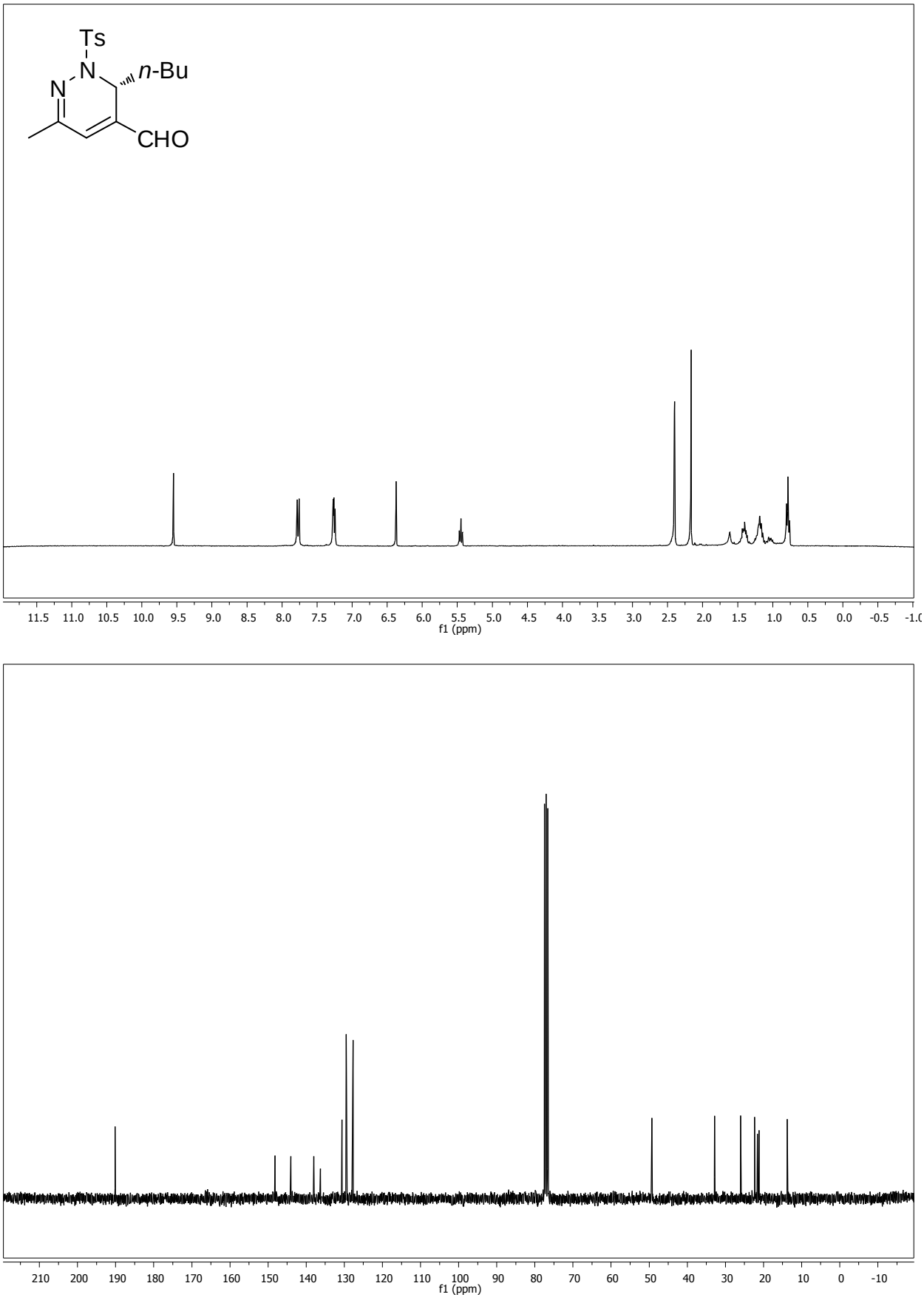
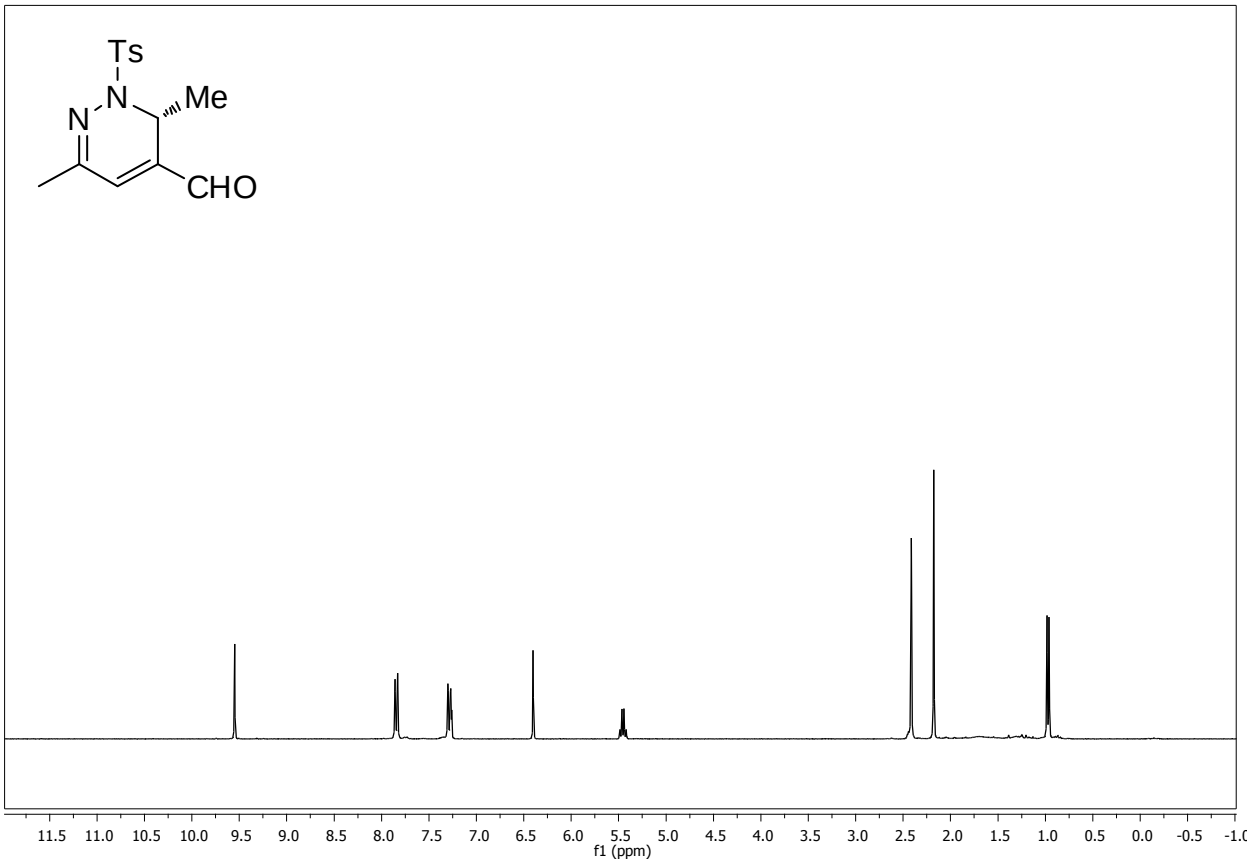


Figure S3: NMR spectra of compound **4a**.



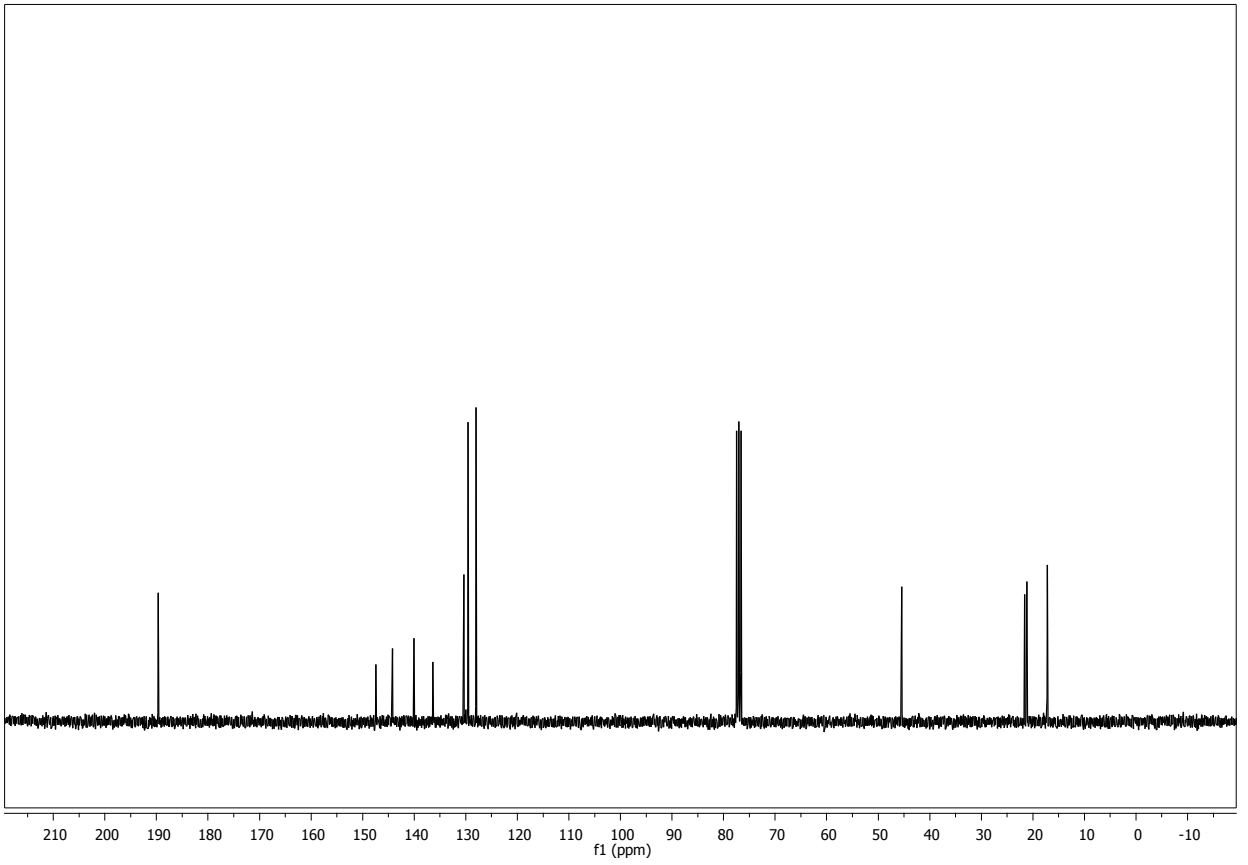


Figure S4: NMR spectra of compound **4b**.

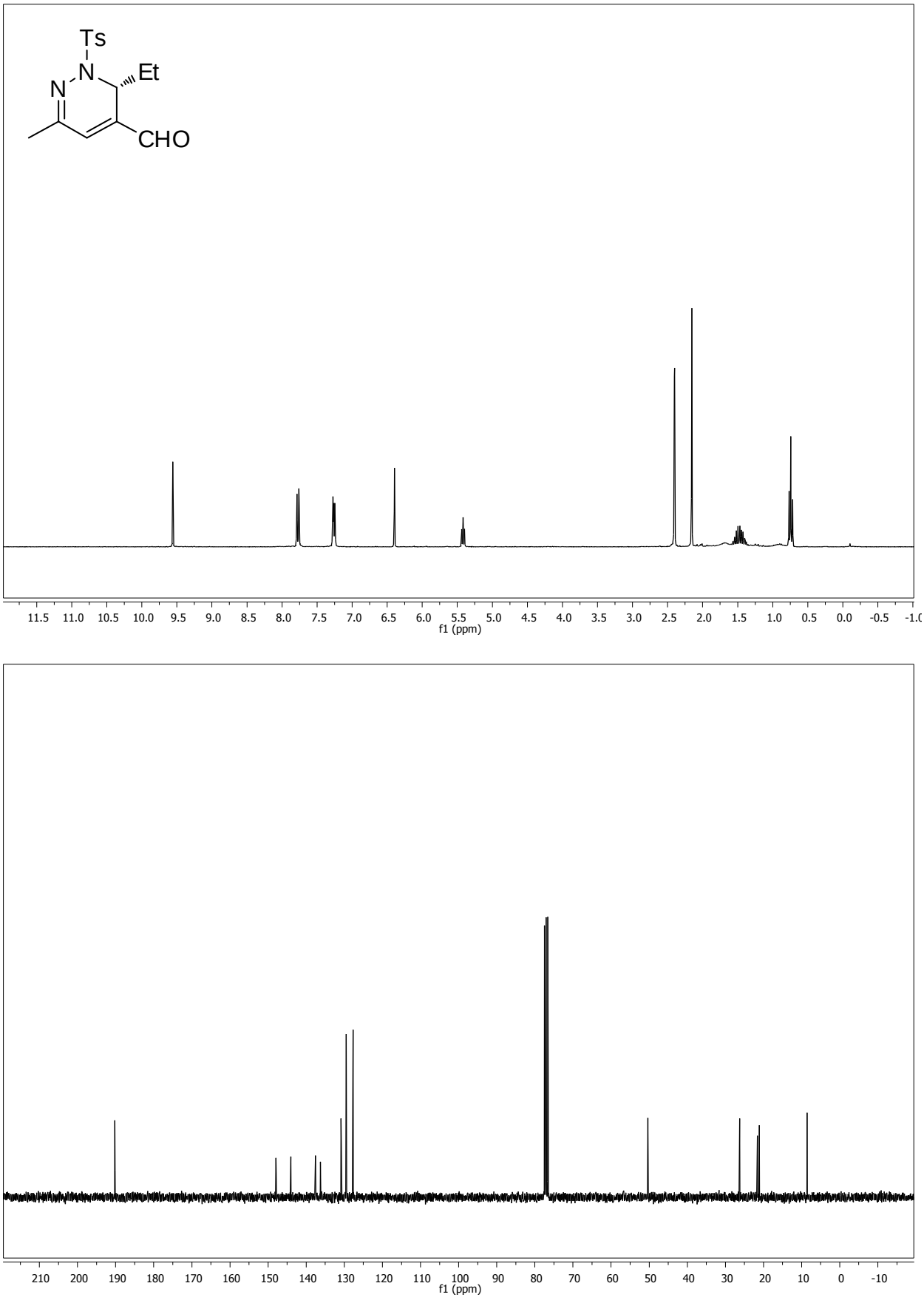


Figure S5: NMR spectra of compound **4c**.

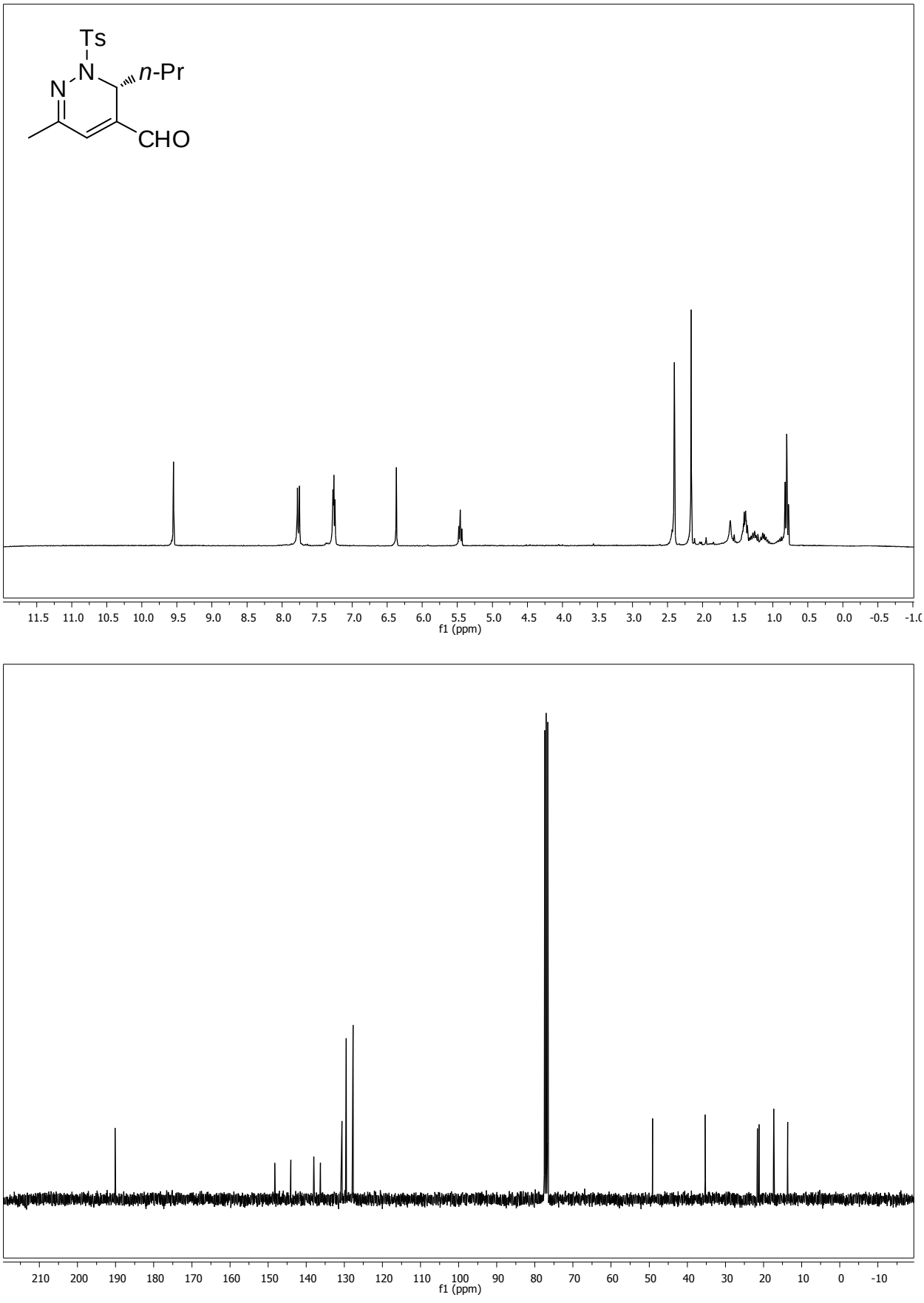


Figure S6: NMR spectra of compound **4d**.

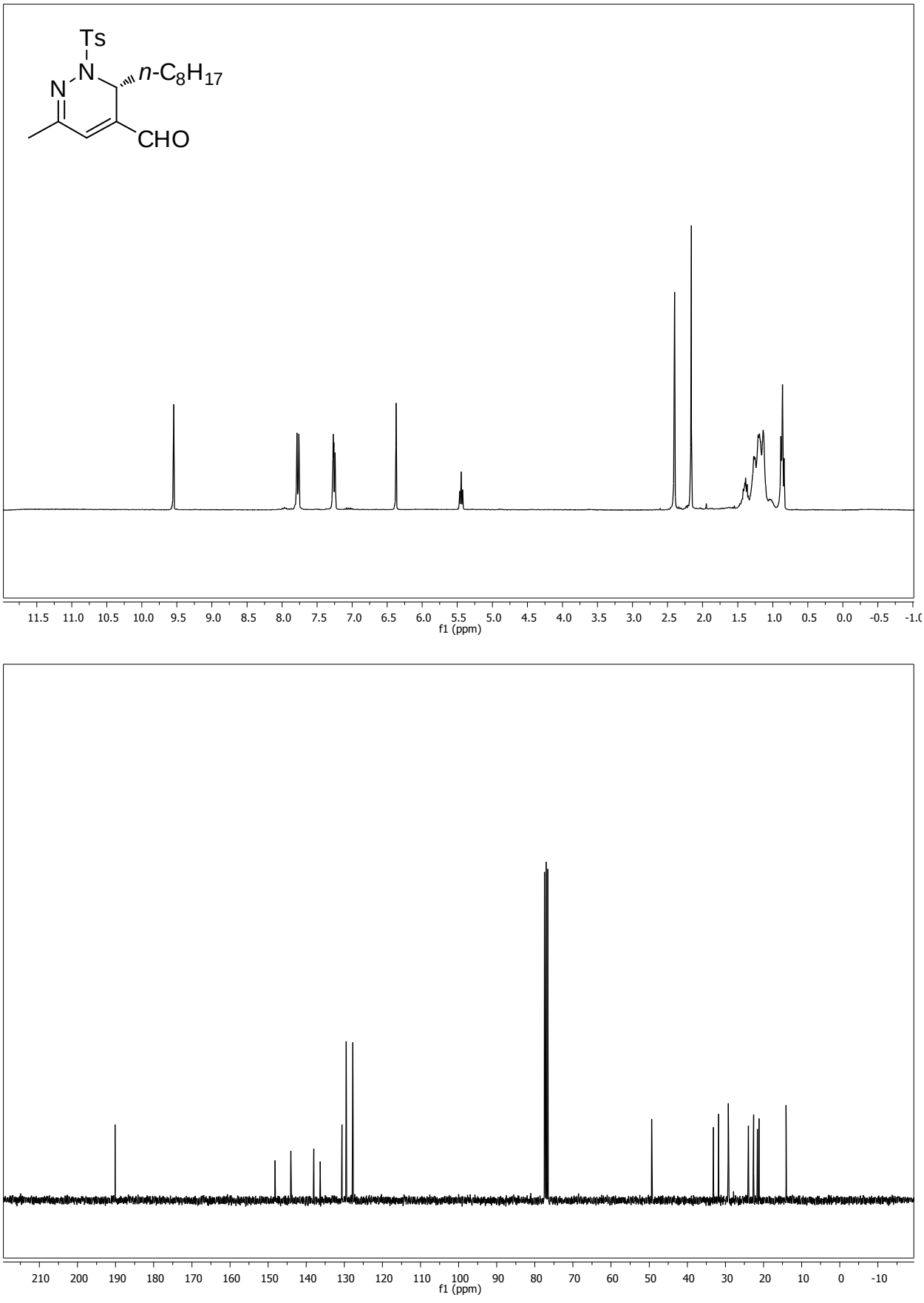


Figure S7: NMR spectra of compound **4e**.

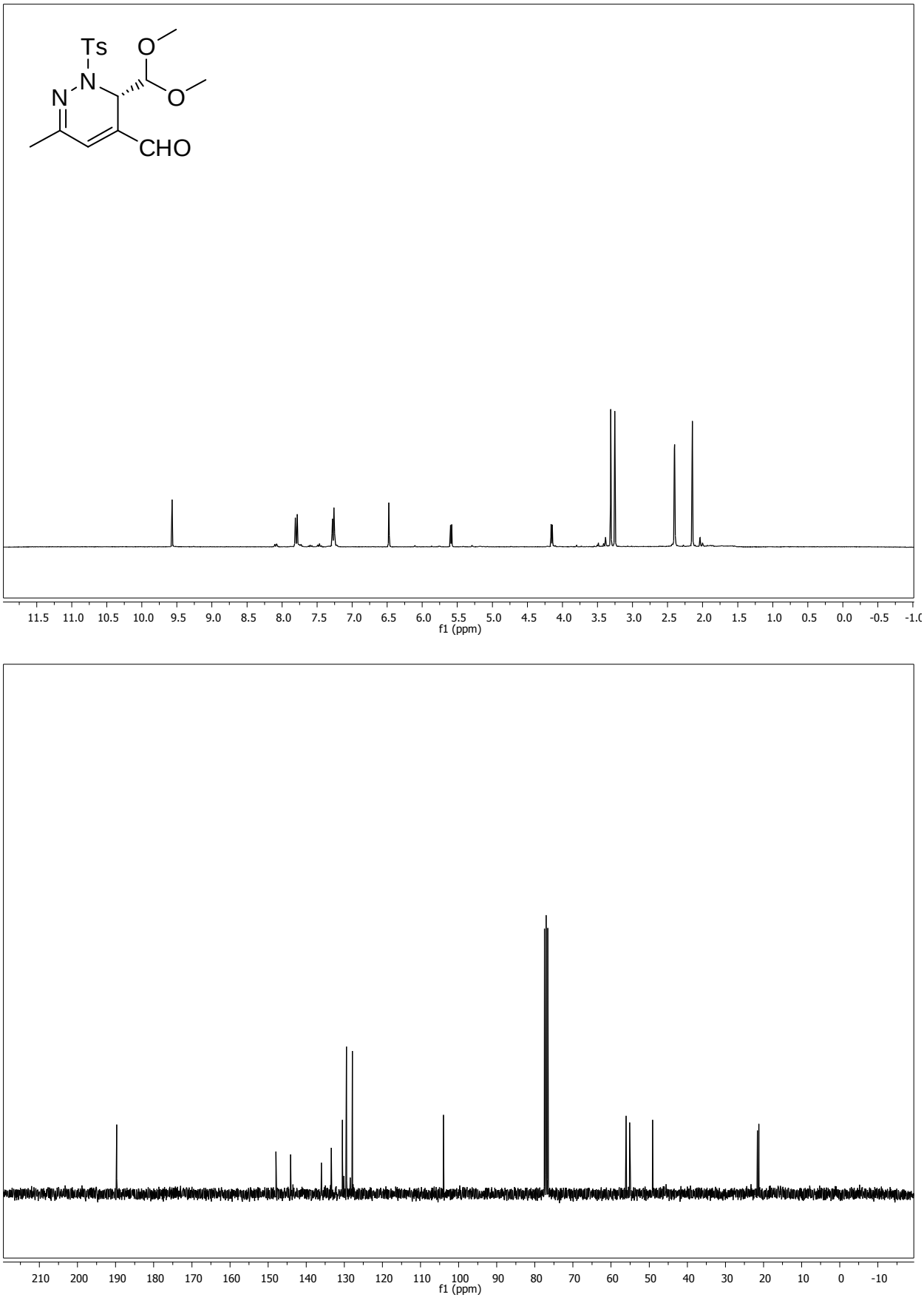
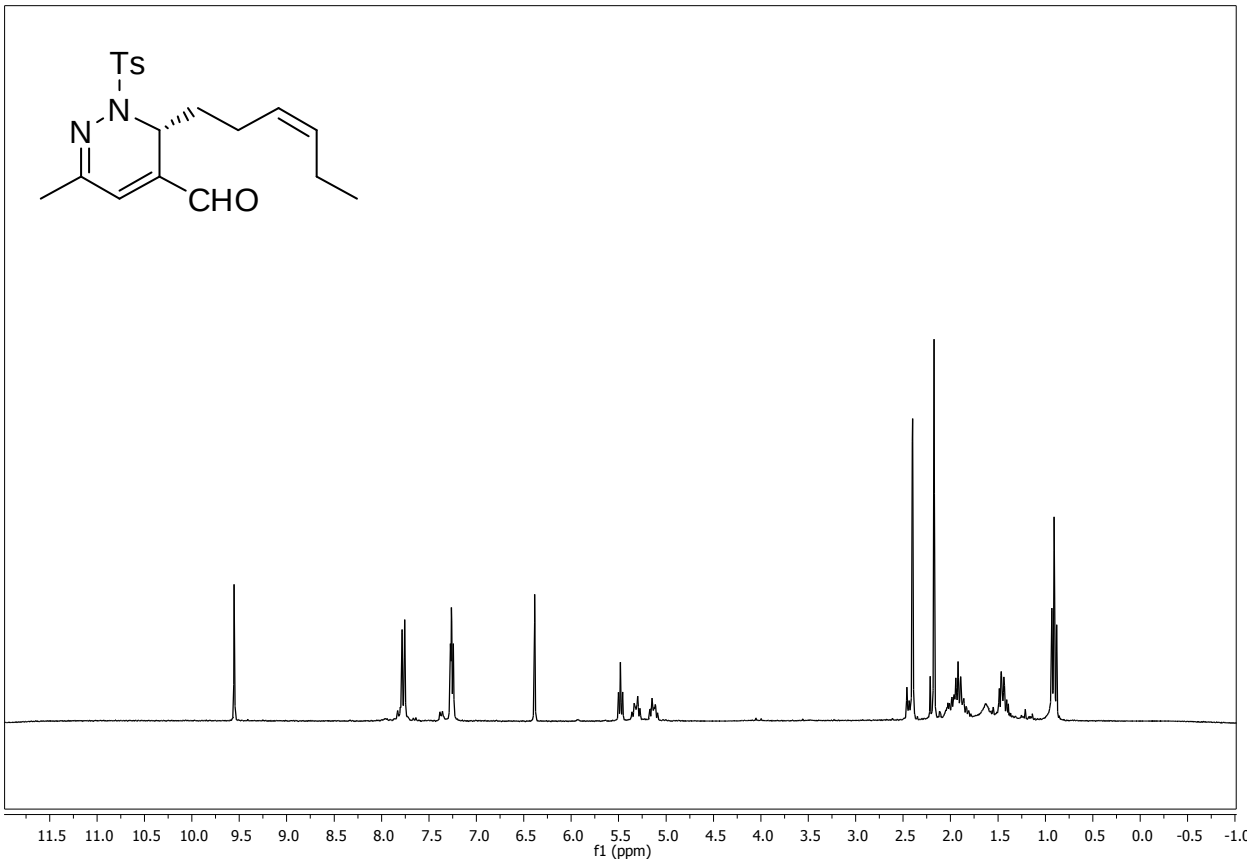


Figure S8: NMR spectra of compound **4f**.



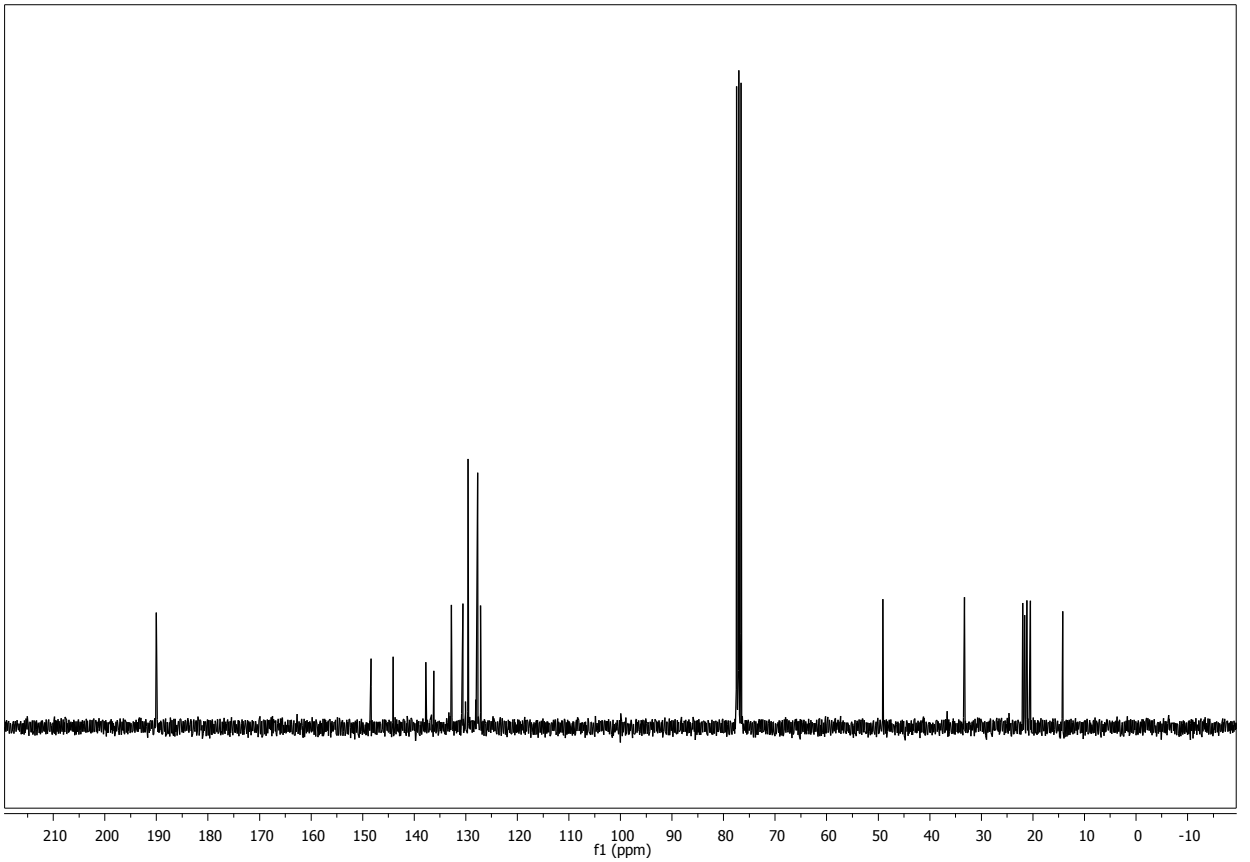
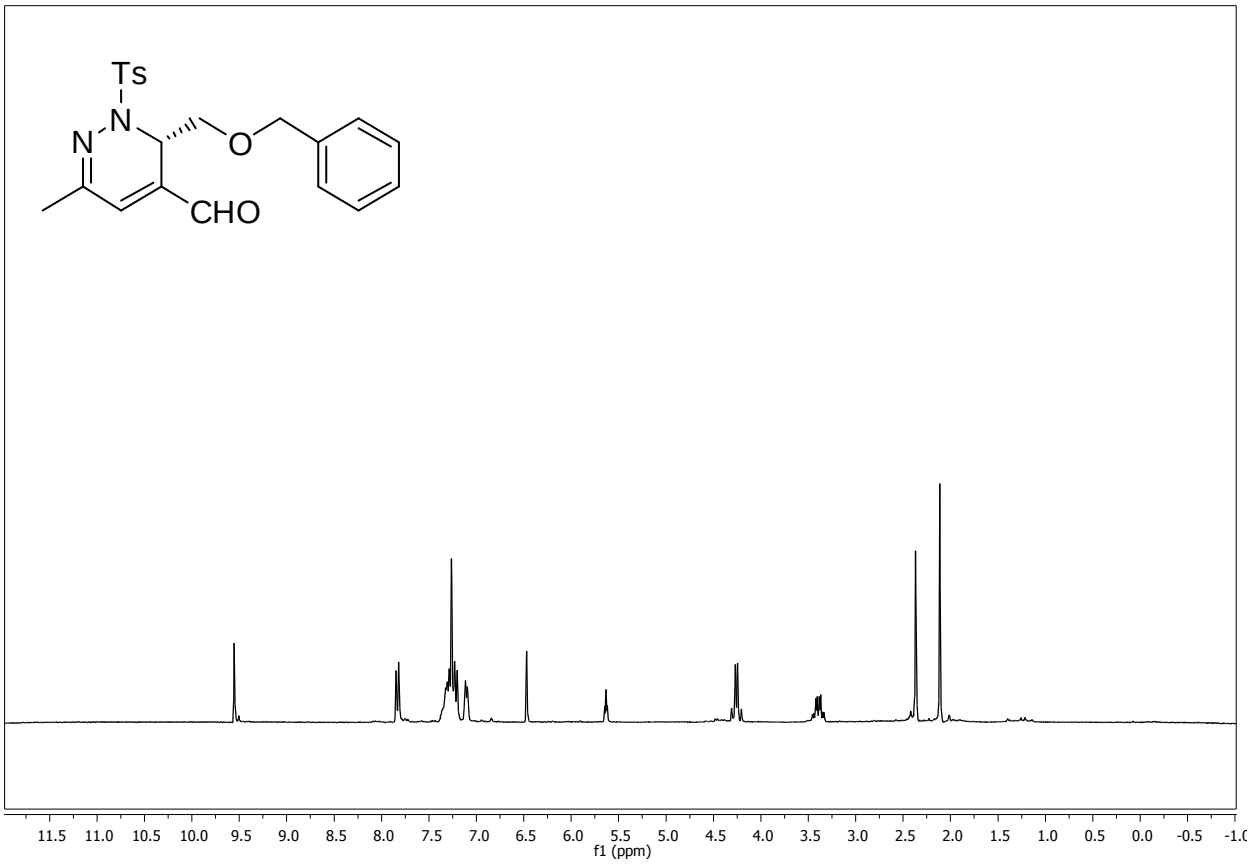


Figure S9: NMR spectra of compound **4g**.



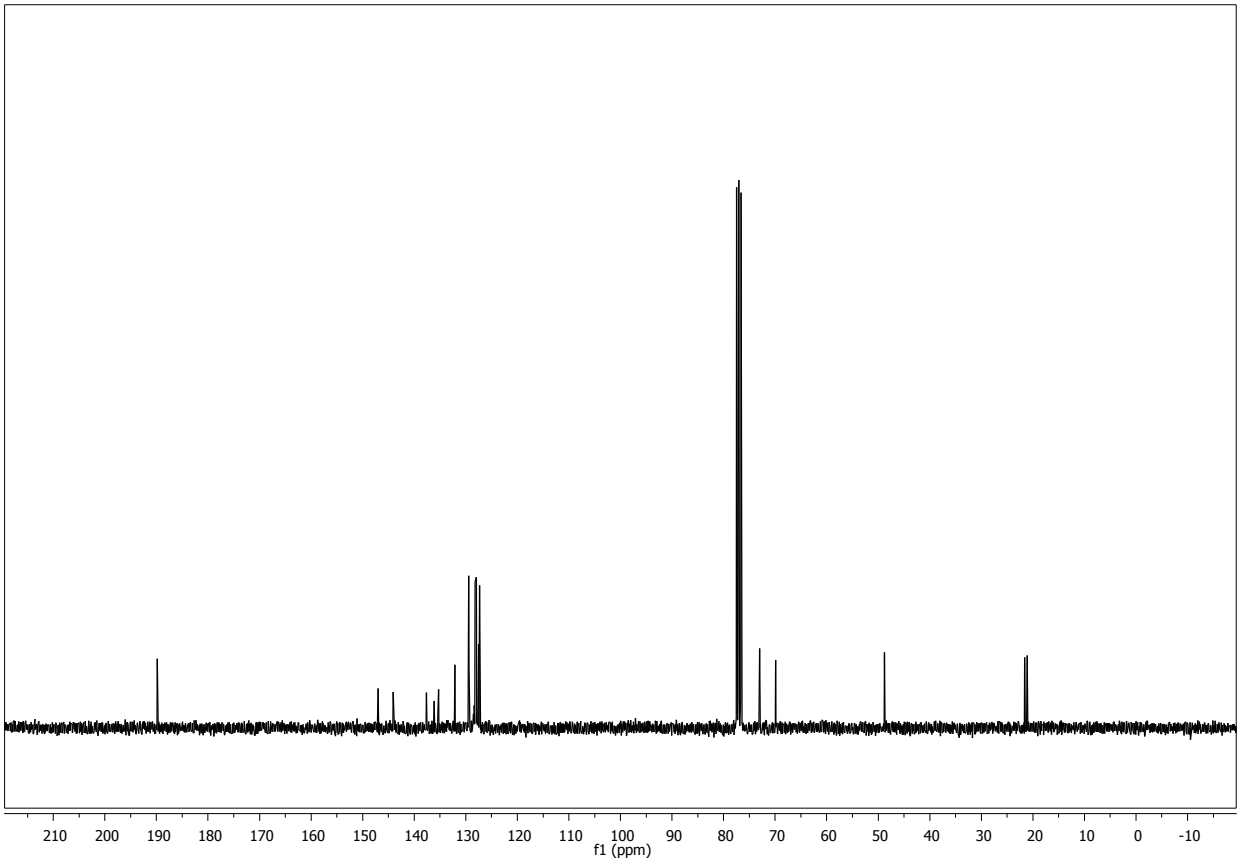


Figure S10: NMR spectra of compound **4h**.

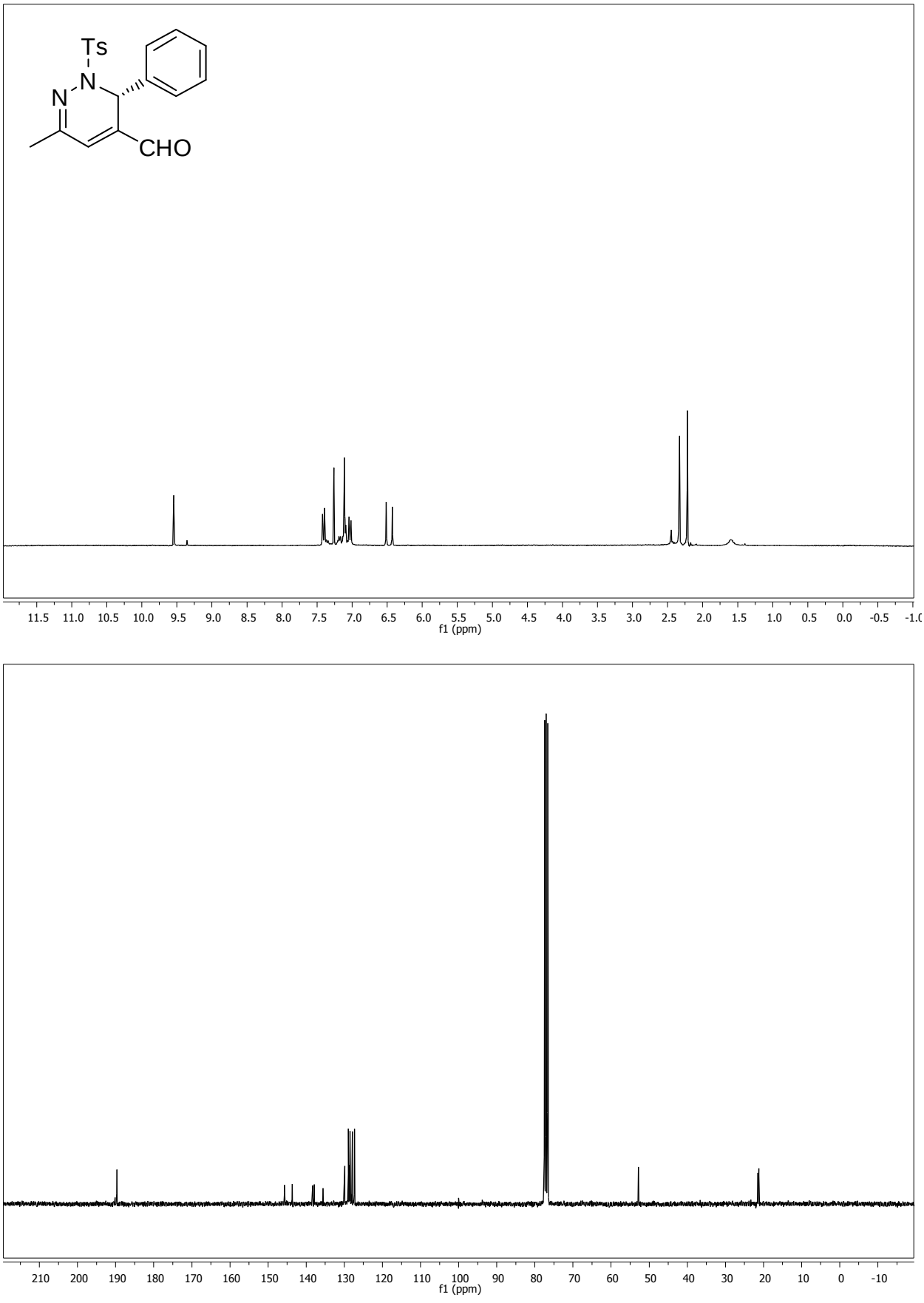
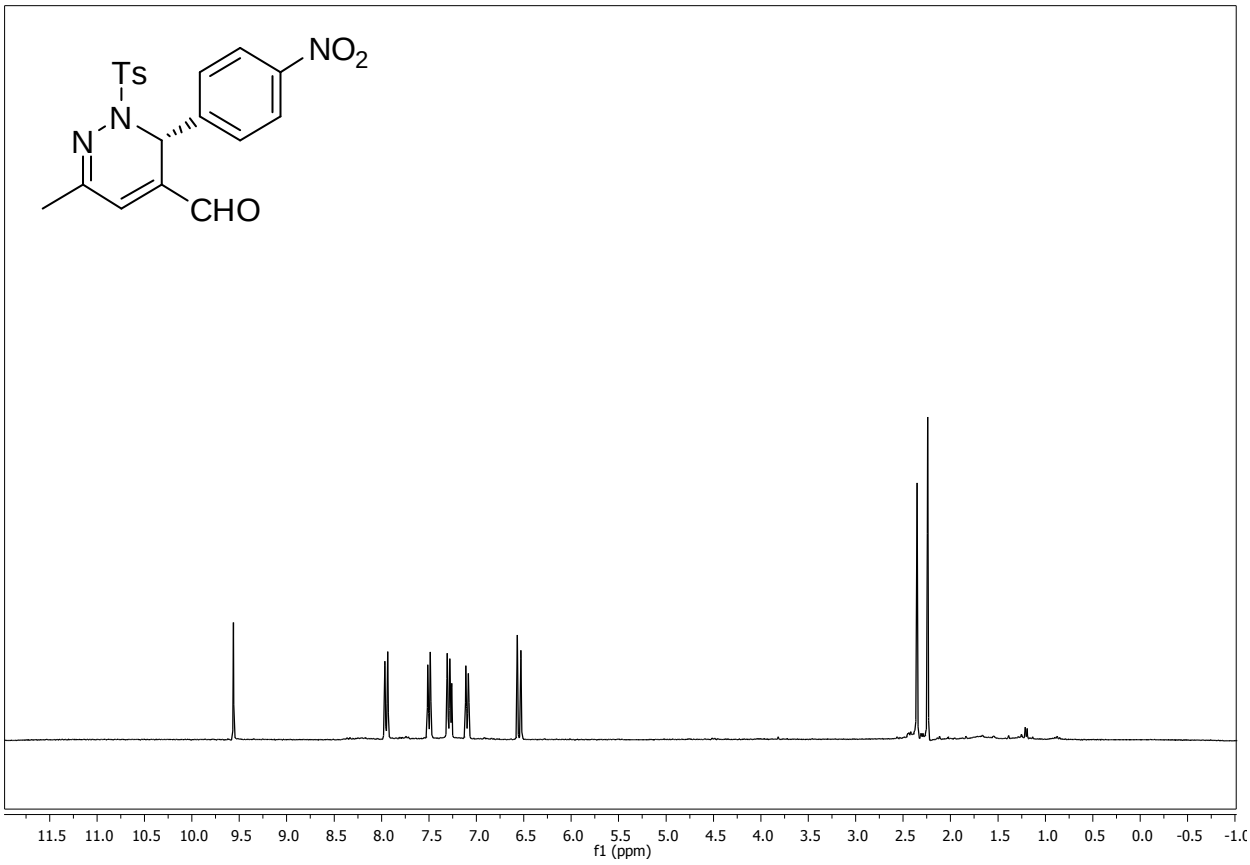


Figure S11: NMR spectra of compound **4i**.



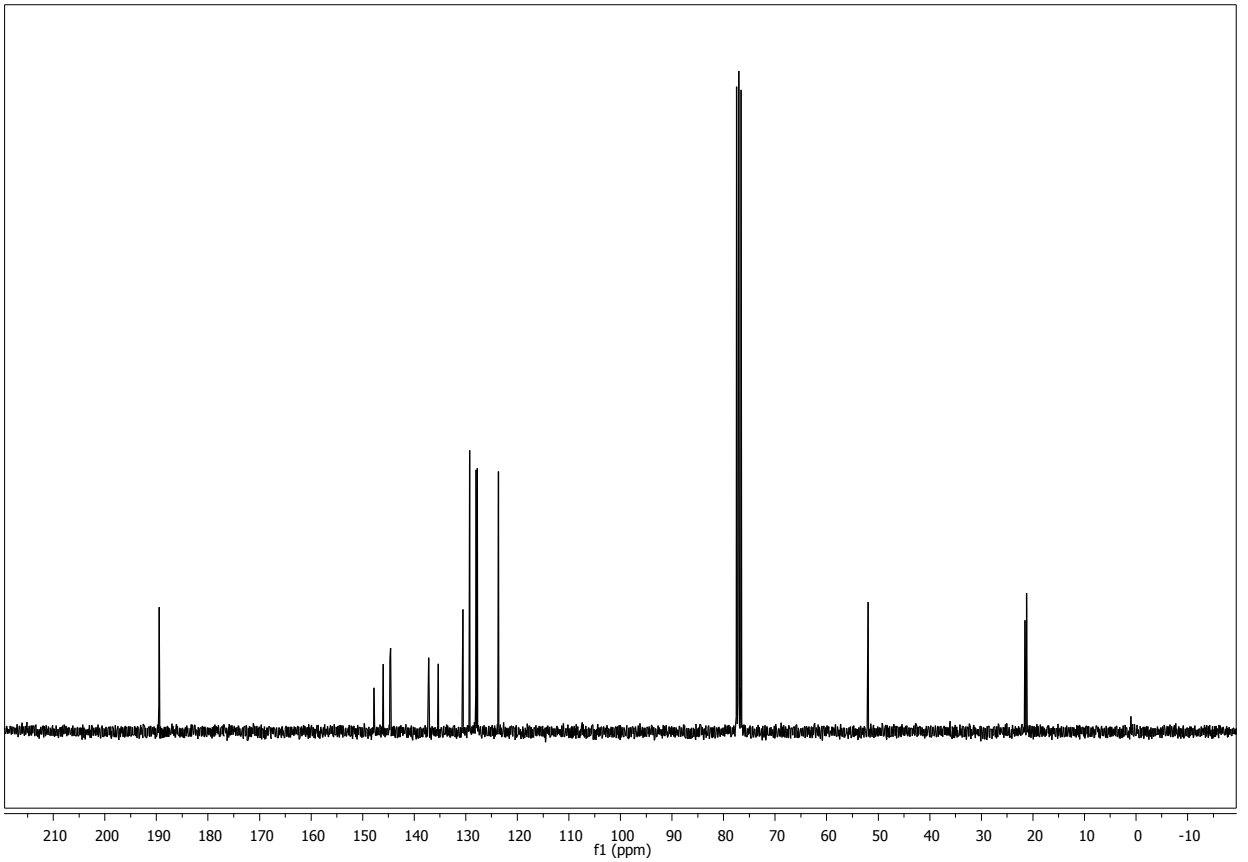
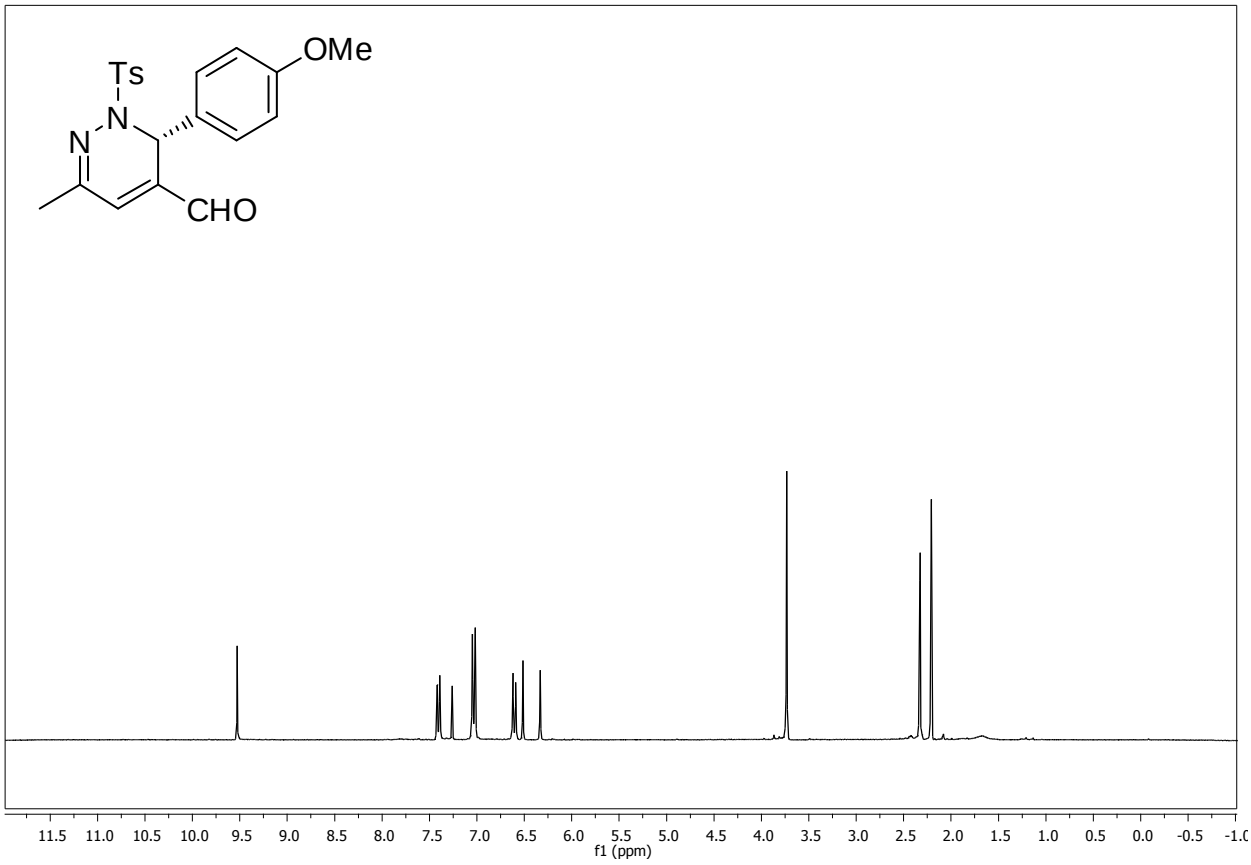


Figure S12: NMR spectra of compound **4j**.



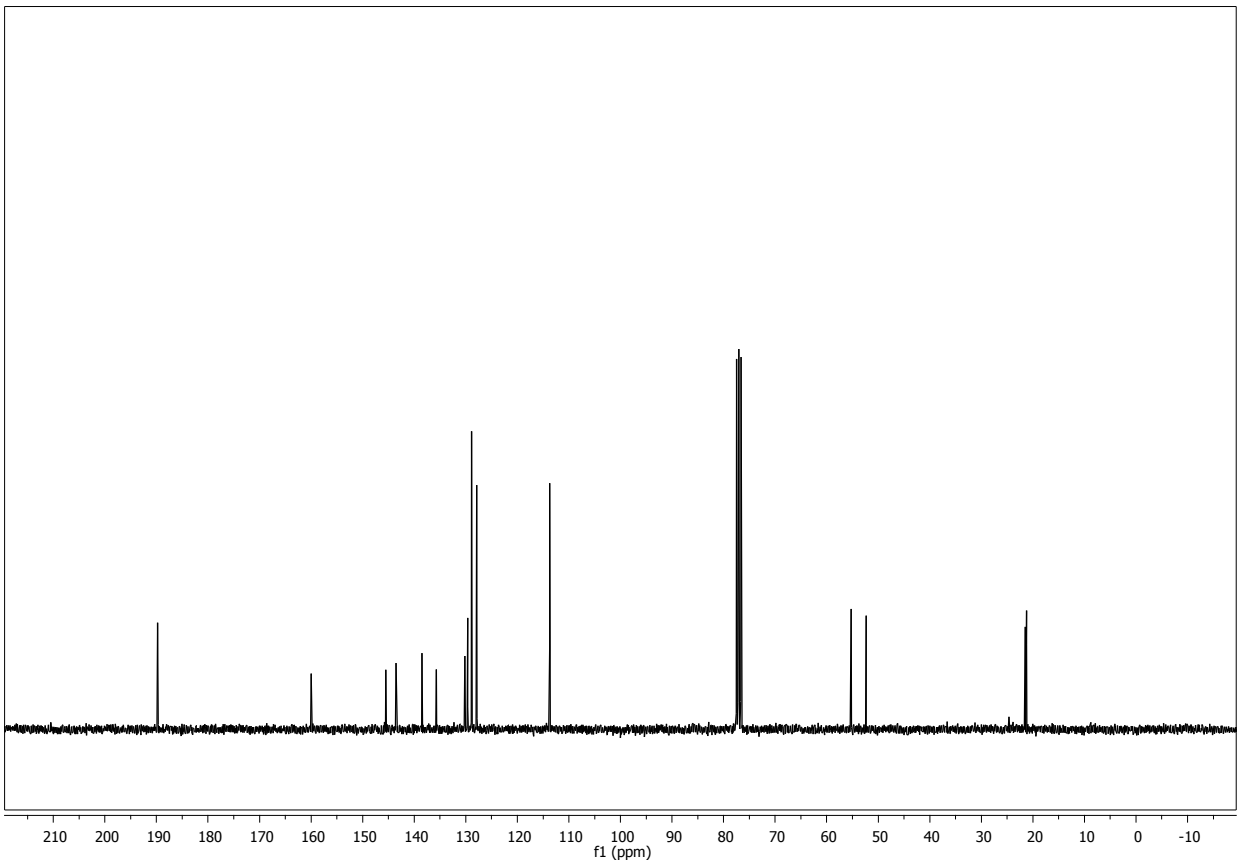
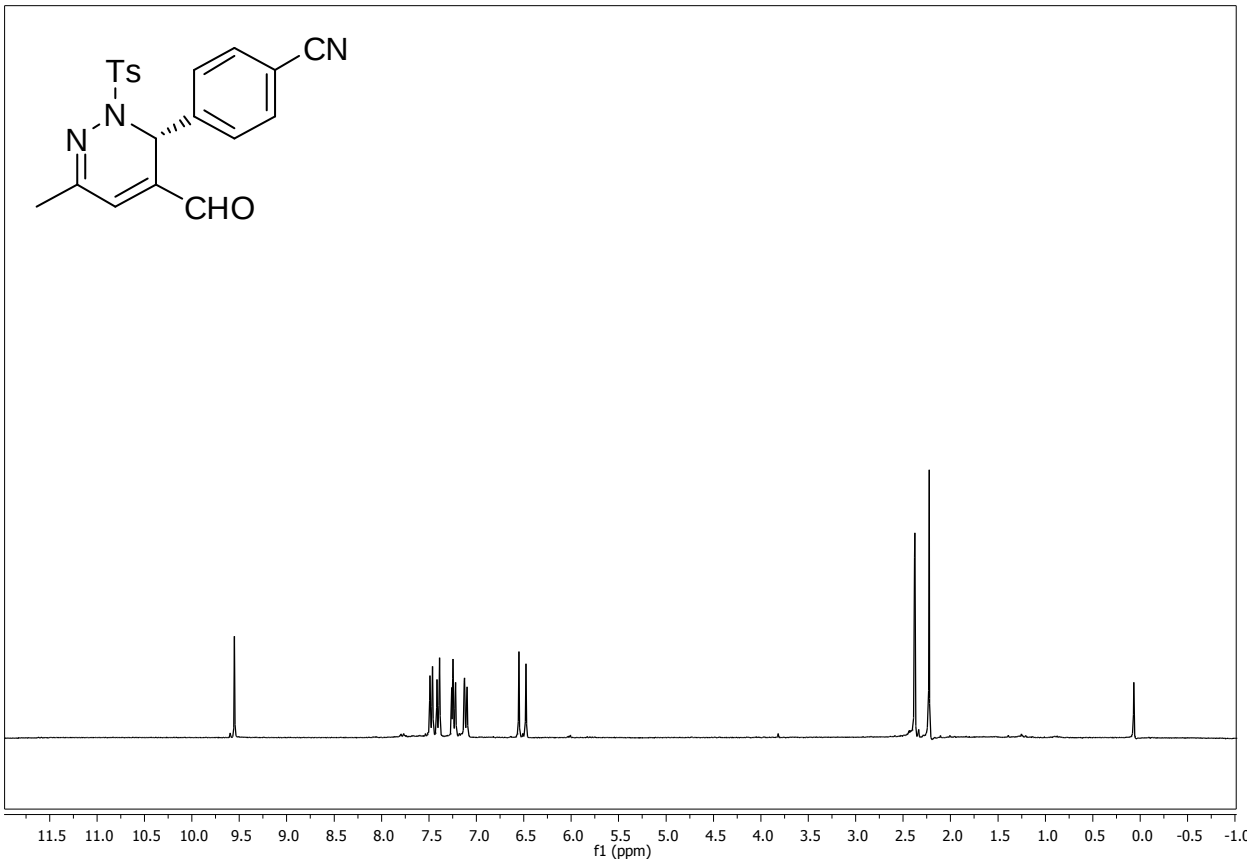


Figure S13: NMR spectra of compound **4k**.



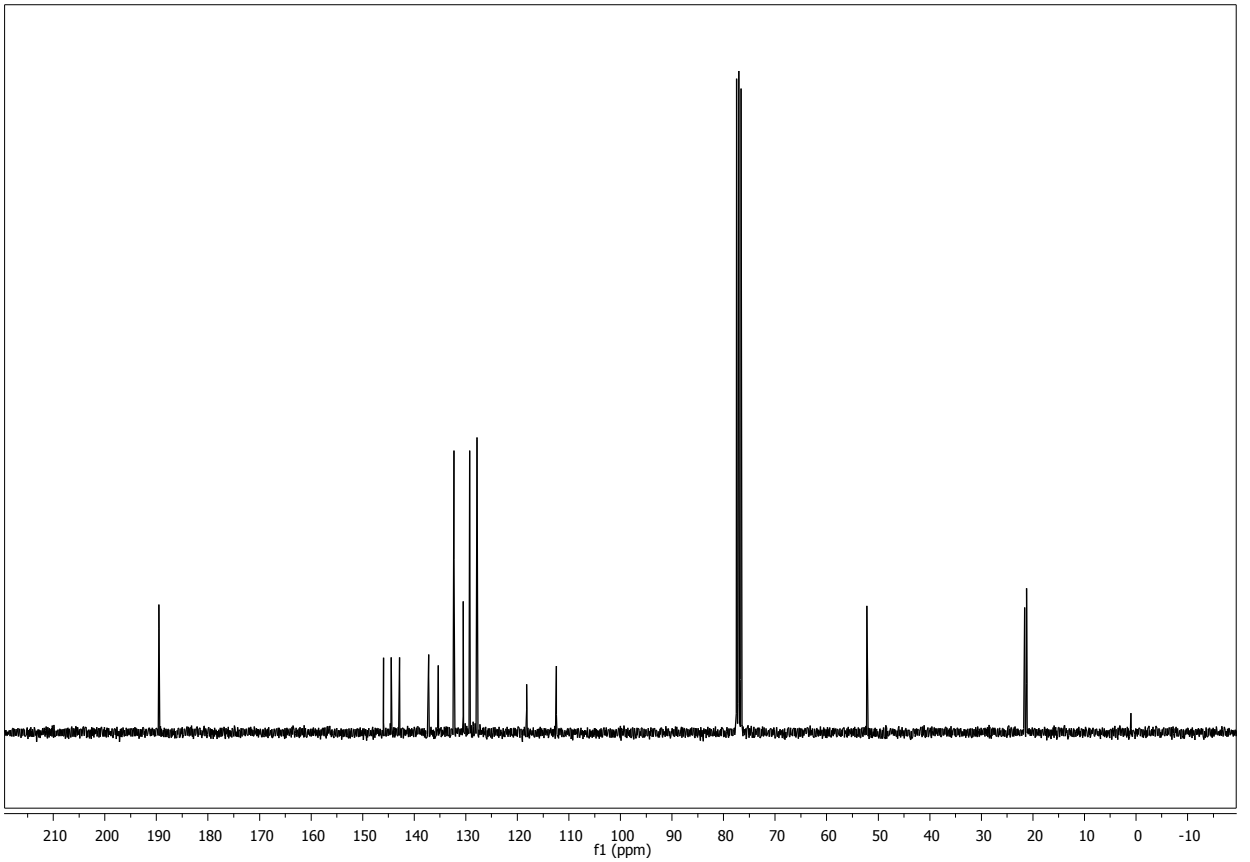
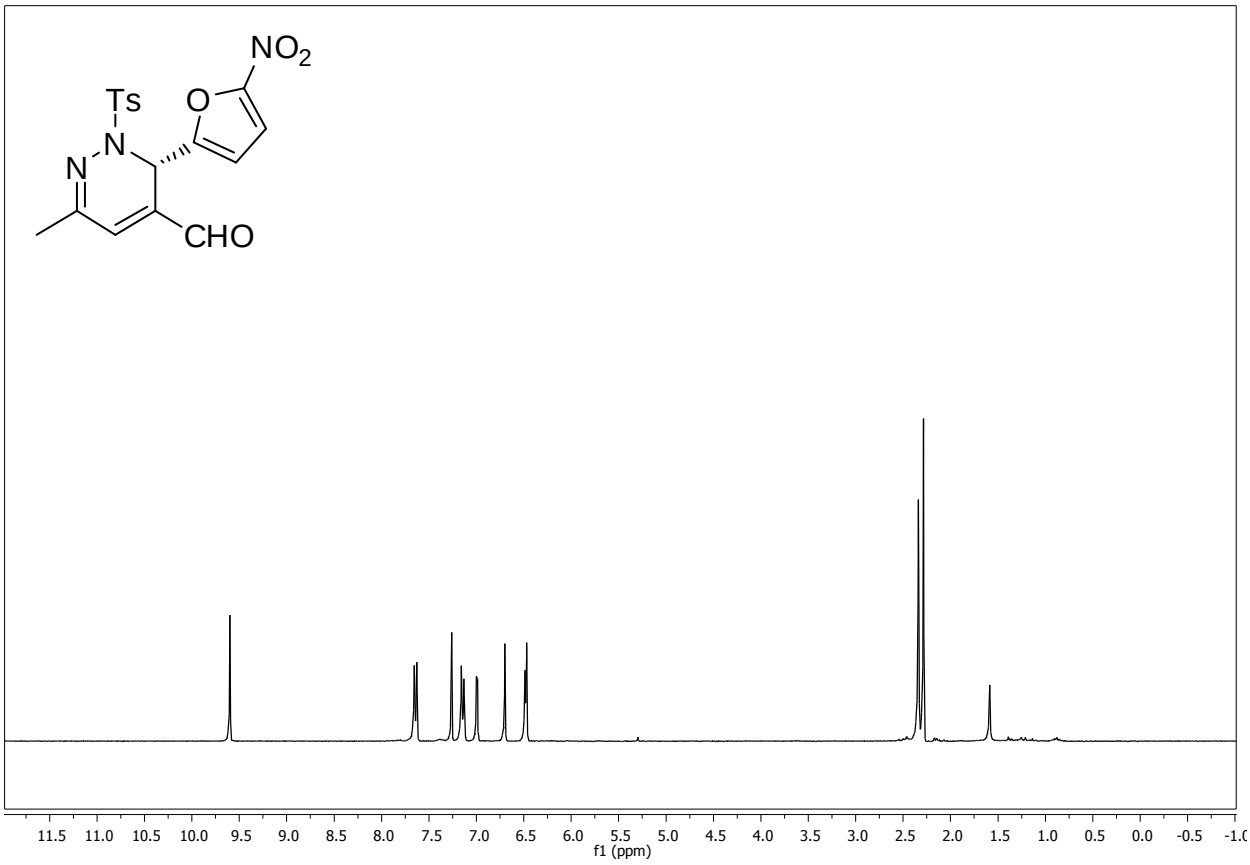


Figure S14: NMR spectra of compound **4l**.



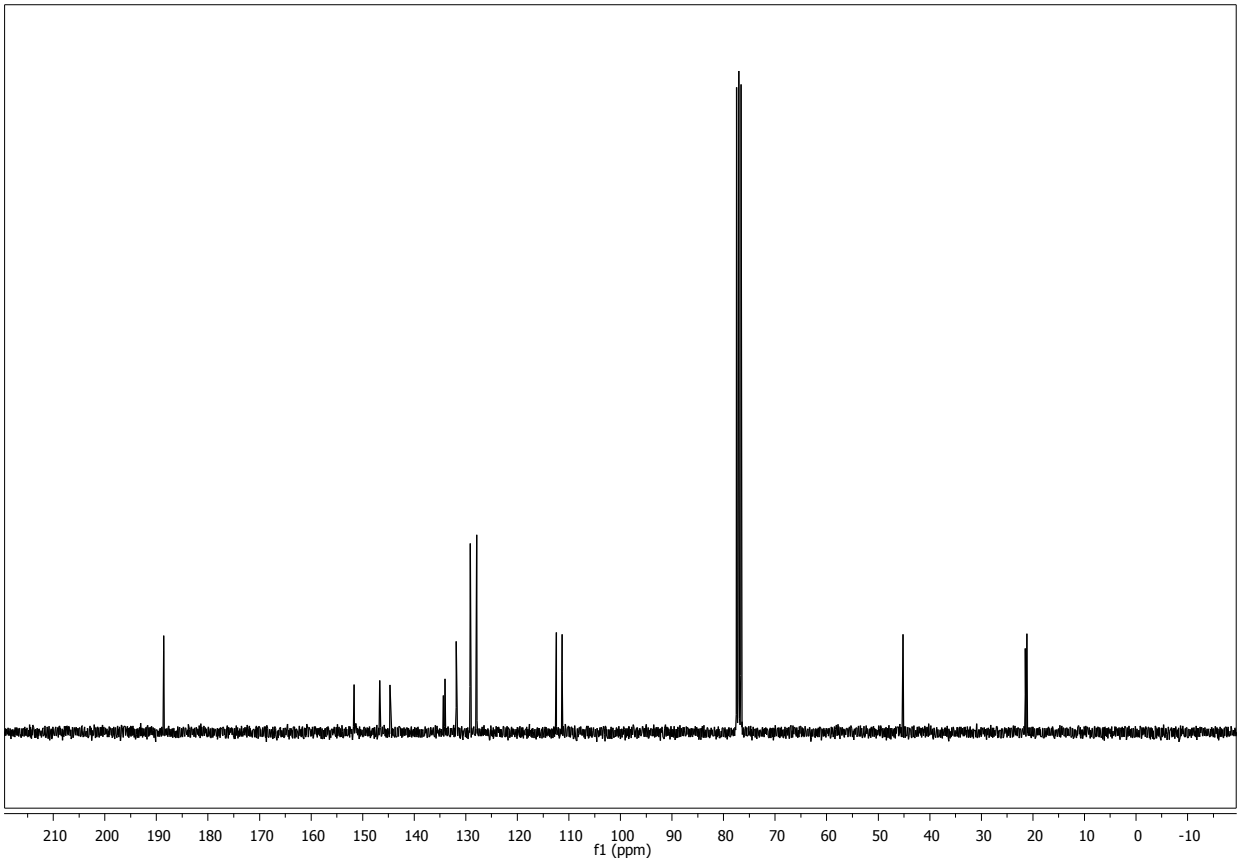


Figure S15: NMR spectra of compound **4m**.

NMR spectra of compounds 5j

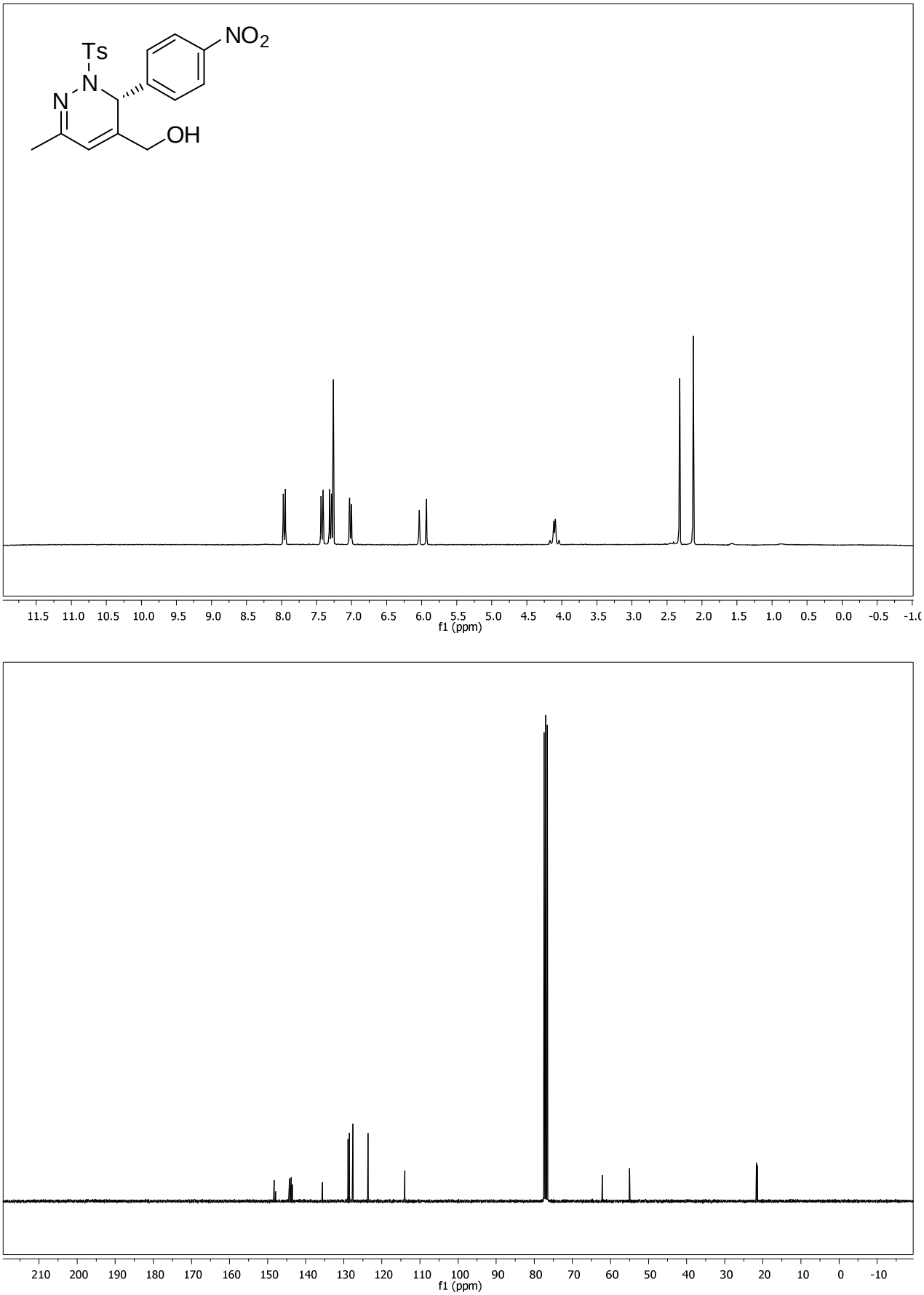
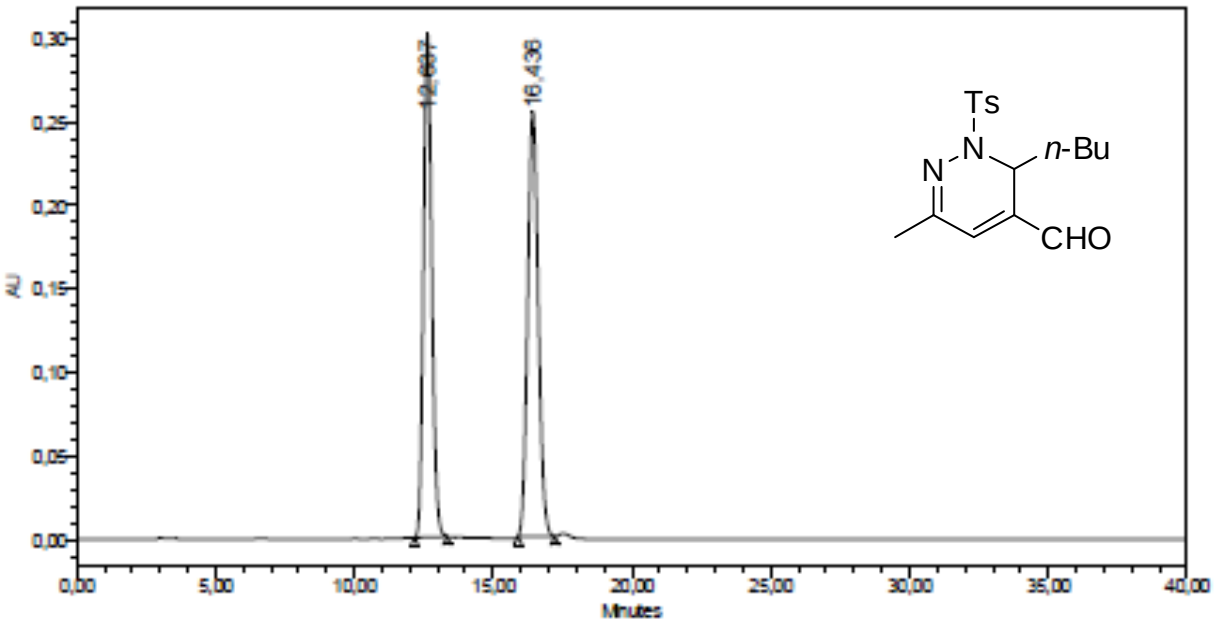
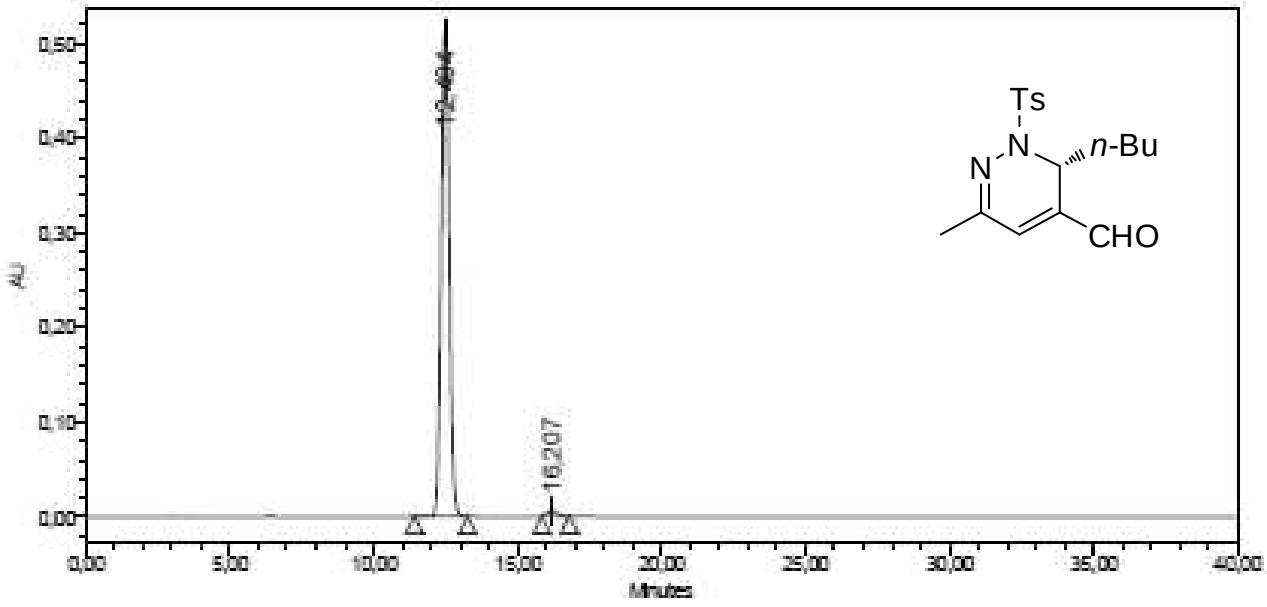


Figure S16: NMR spectra of compound **5j**.

HPLC chromatograms of racemic and enantioenriched compounds 4a-m



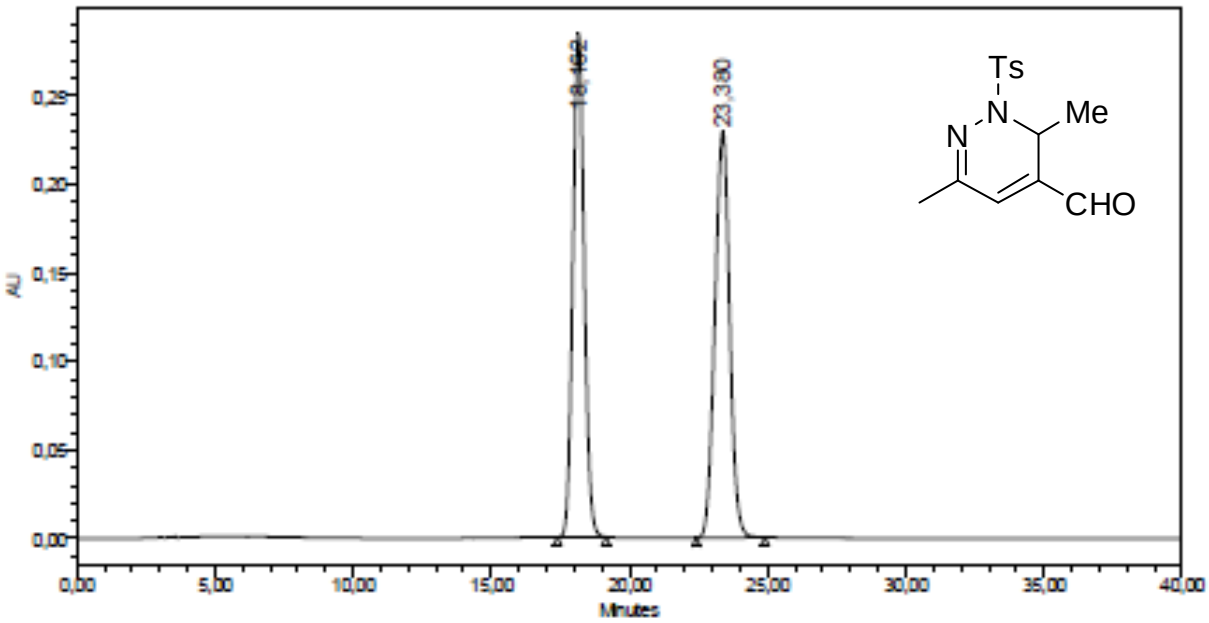
	RT	% Area
1	12,637	48,10
2	16,436	51,90



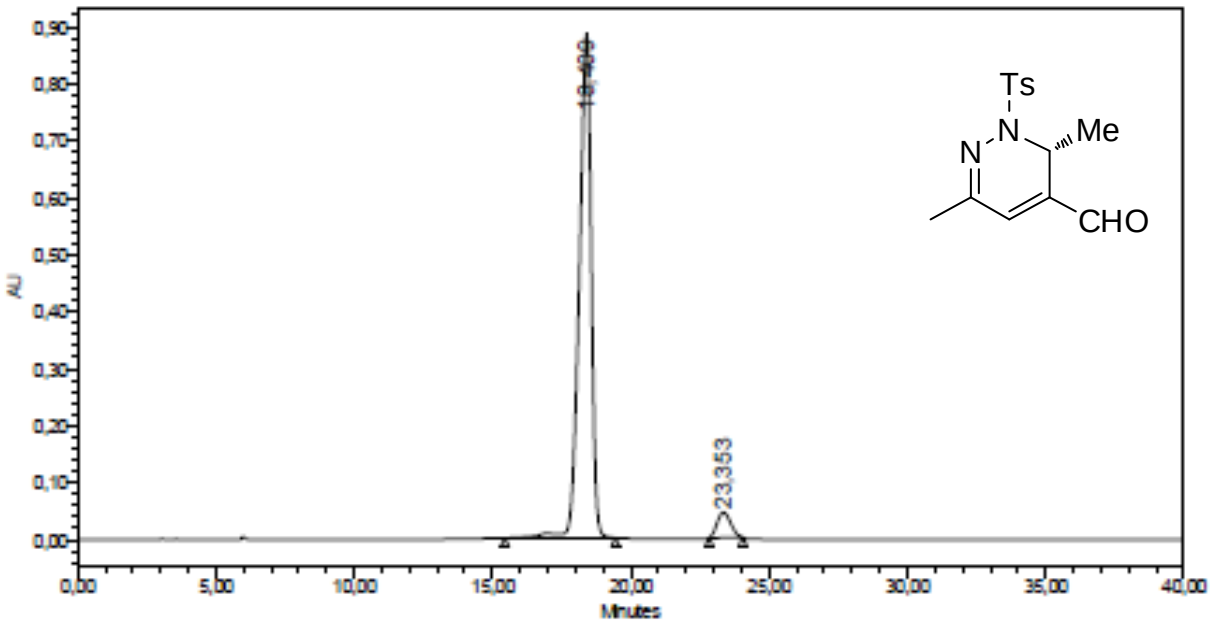
Peak Results

	RT	Area (µV*sec)	Height (µV)	% Area
1	12,494	9125710	511982	98,47
2	16,207	141561	6492	1,53

Figure S17: HPLC chromatogram of compound **4a**.

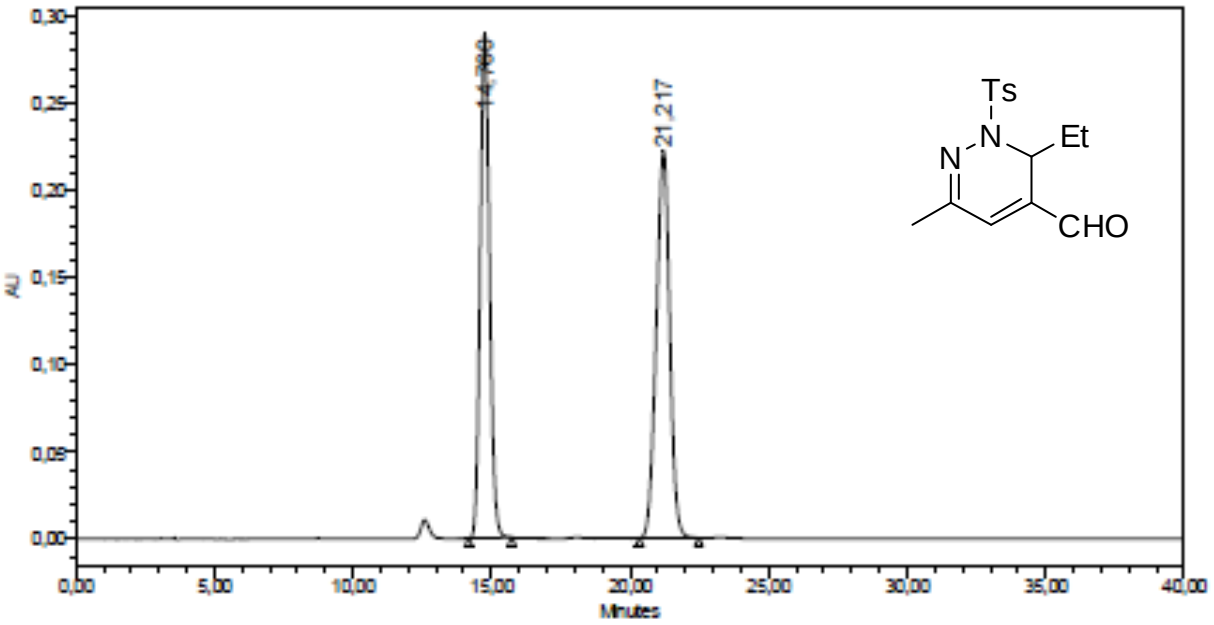


	RT	% Area
1	18,162	48,73
2	23,380	51,27

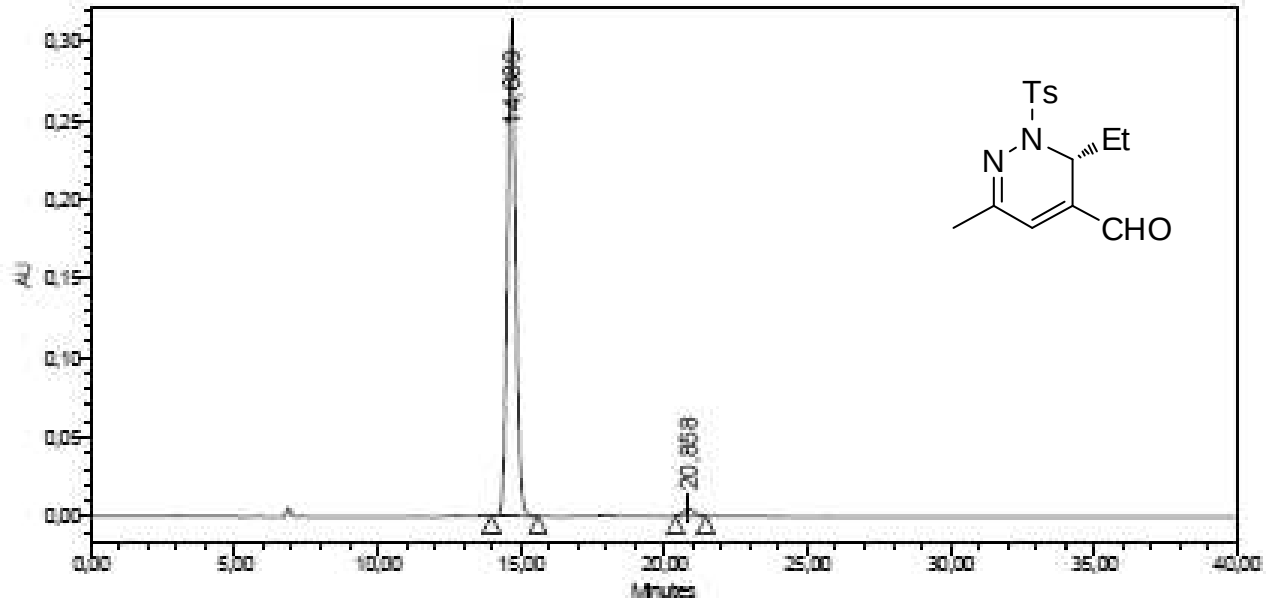


	RT	% Area
1	18,409	94,60
2	23,353	5,40

Figure S18: HPLC chromatogram of compound **4b**.



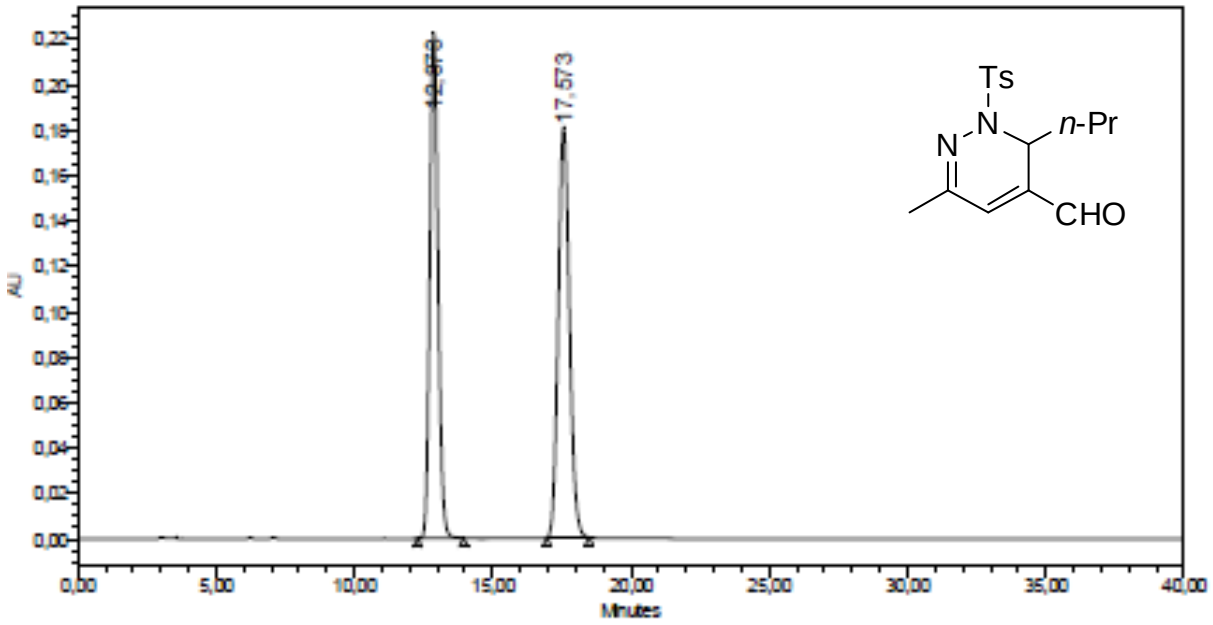
	RT	% Area
1	14,760	47,58
2	21,217	52,42



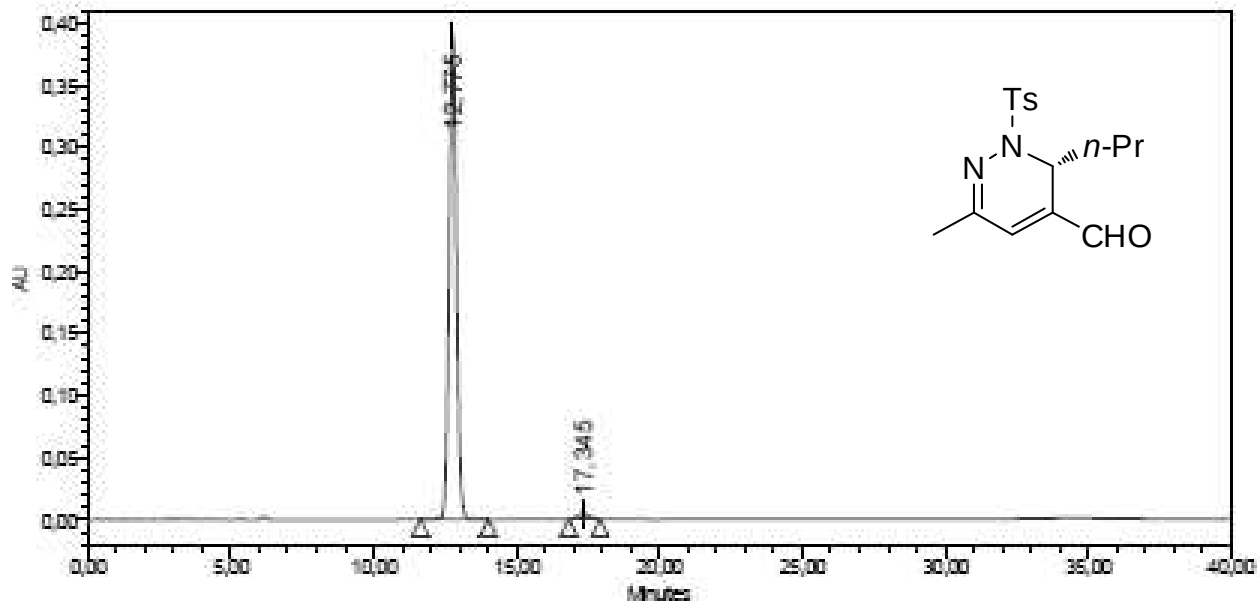
Peak Results

	RT	Area (µV*sec)	Height (µV)	% Area
1	14,689	6210686	306119	97,99
2	20,858	127216	4602	2,01

Figure S19: HPLC chromatogram of compound **4c**.



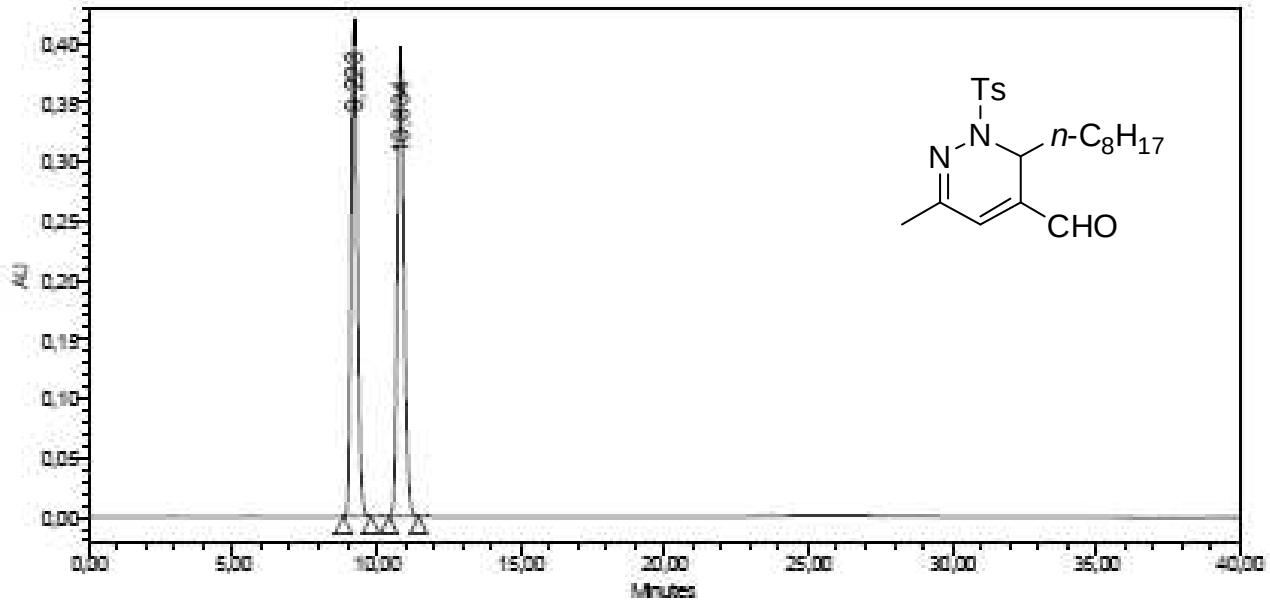
	RT	% Area
1	12,873	47,56
2	17,573	52,44



Peak Results

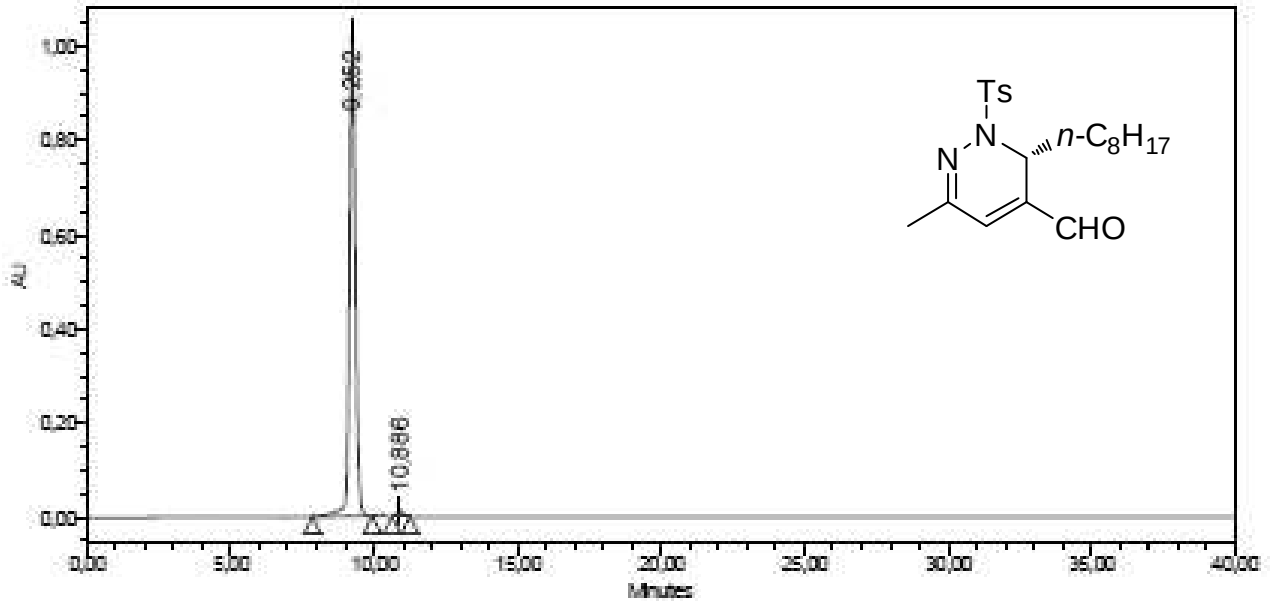
	RT	Area (µV*sec)	Height (µV)	% Area
1	12,775	6985021	390070	98,14
2	17,345	132116	5193	1,86

Figure S20: HPLC chromatogram of compound **4d**.



Peak Results

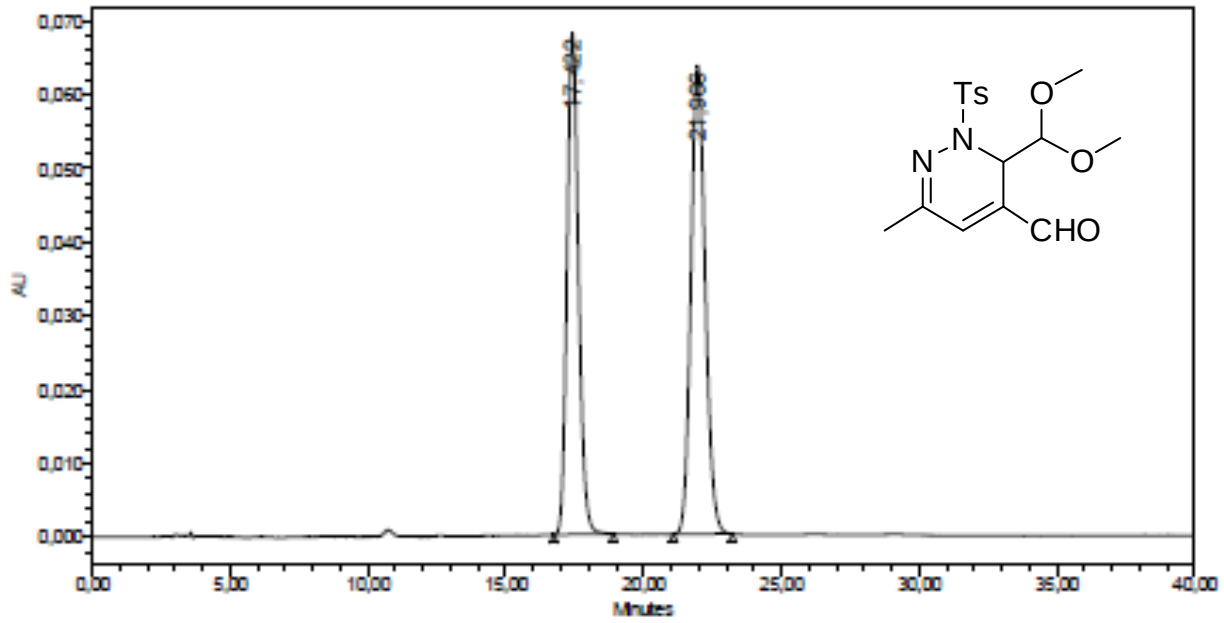
	RT	Area (µV*sec)	Height (µV)	% Area
1	9,223	5590066	409159	46,85
2	10,834	6340806	385133	53,15



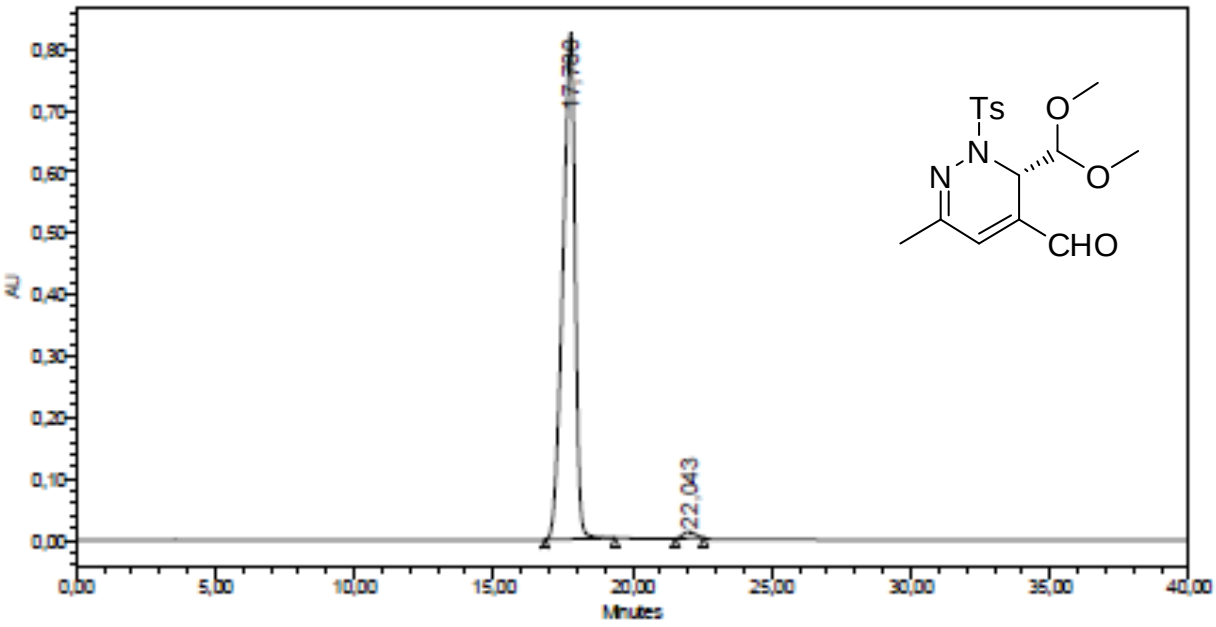
Peak Results

	RT	Area (µV*sec)	Height (µV)	% Area
1	9,252	14916286	1029915	98,53
2	10,886	223182	14047	1,47

Figure S21: HPLC chromatogram of compound **4e**.

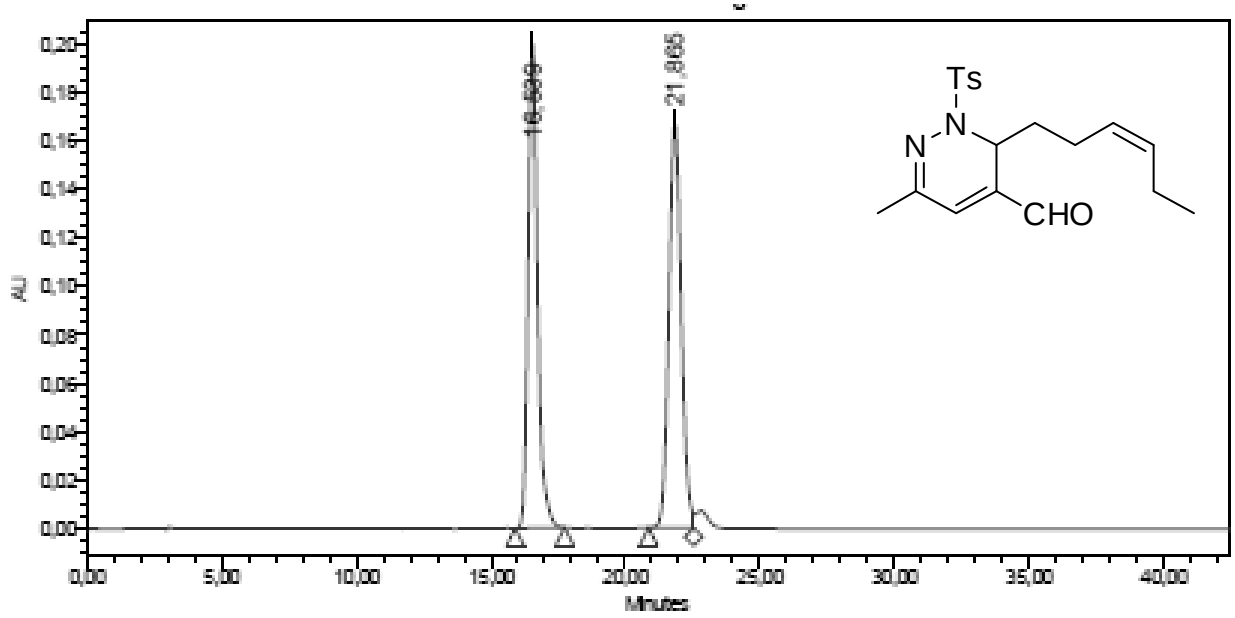


	RT	% Area
1	17,422	46,21
2	21,966	53,79



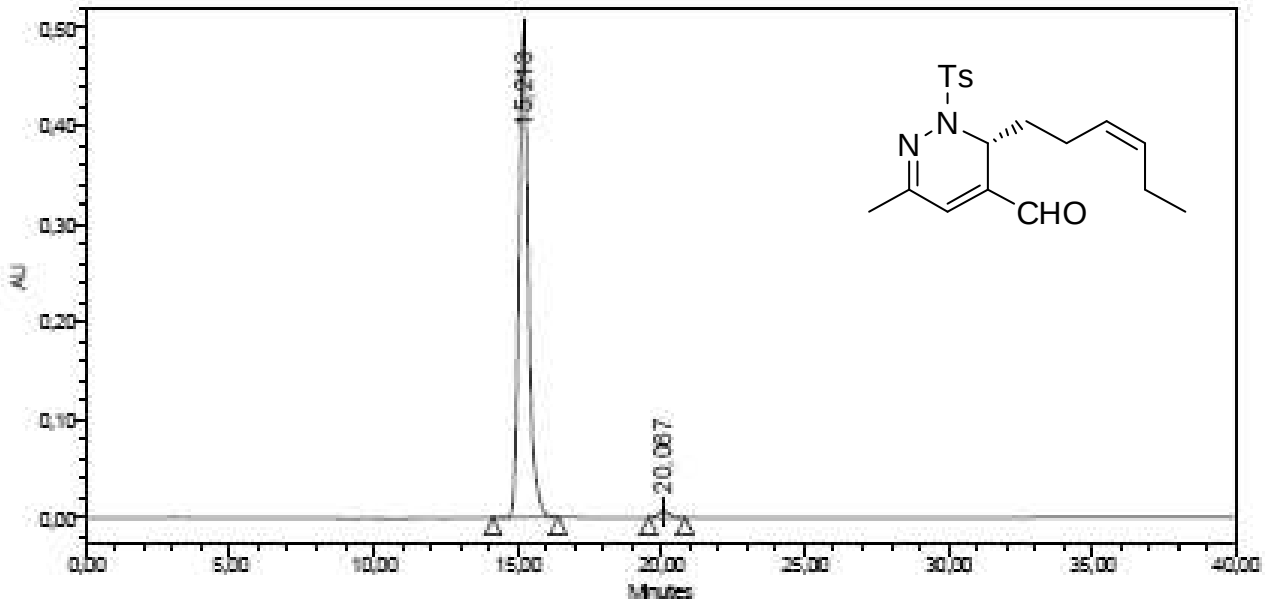
	RT	% Area
1	17,760	98,68
2	22,043	1,32

Figure S22: HPLC chromatogram of compound **4f**.



Peak Results

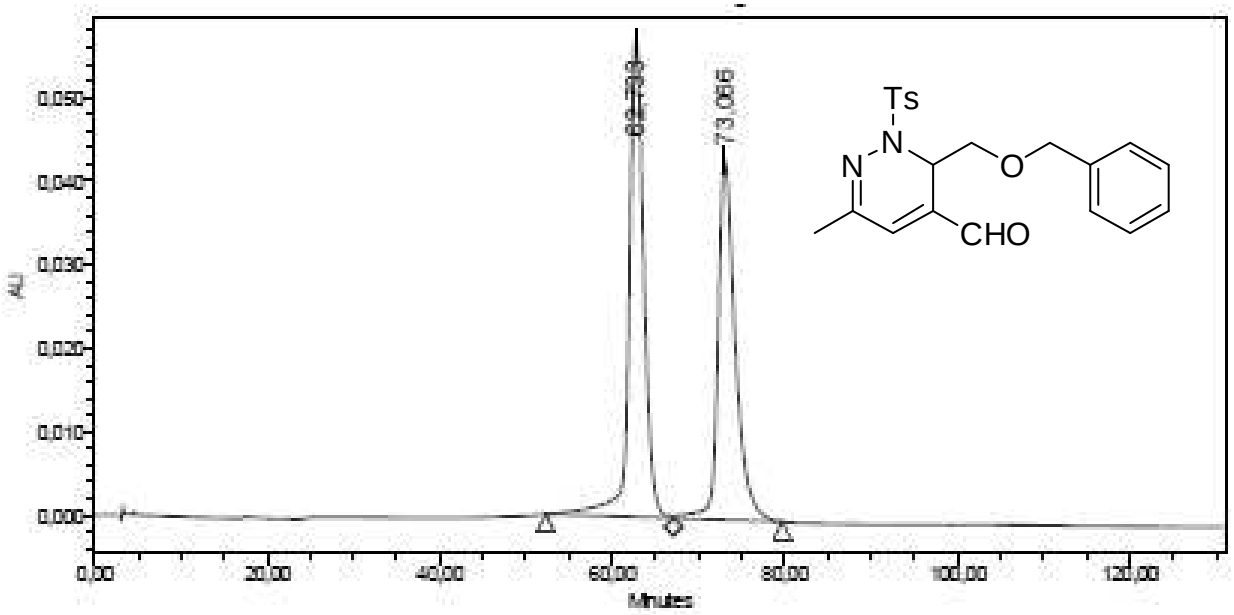
	RT	Area (µV*sec)	Height (µV)	% Area
1	16,539	4918822	199211	47,98
2	21,865	5332360	166028	52,02



Peak Results

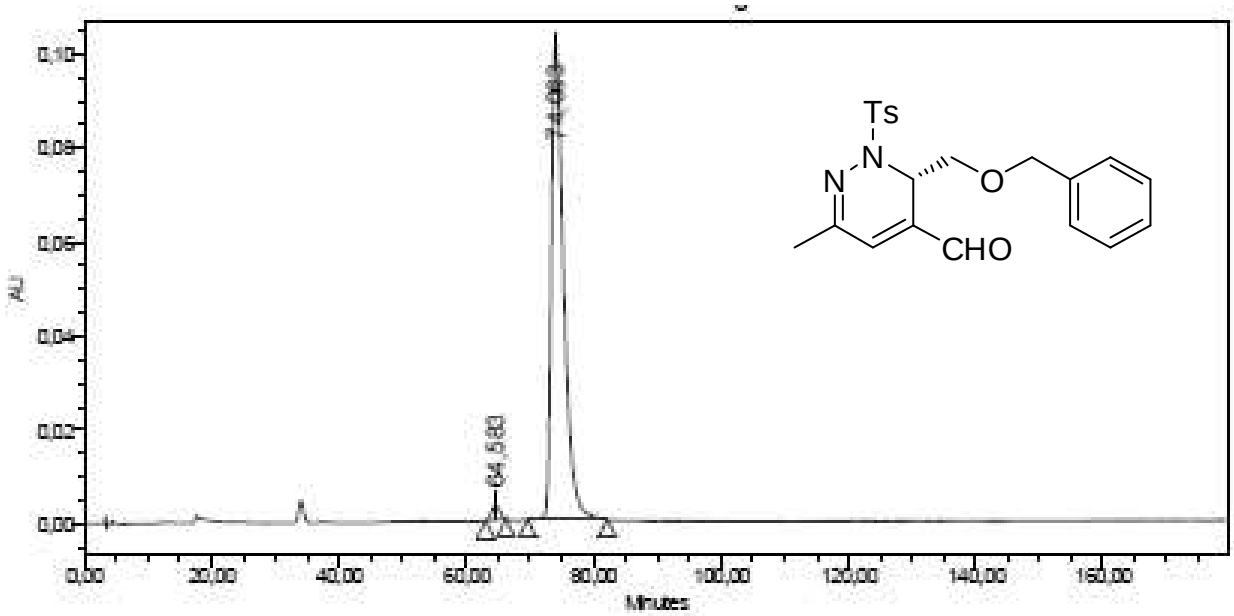
	RT	Area (µV*sec)	Height (µV)	% Area
1	15,213	11527226	496138	98,33
2	20,067	195417	6967	1,67

Figure S23: HPLC chromatogram of compound **4g**.



Peak Results

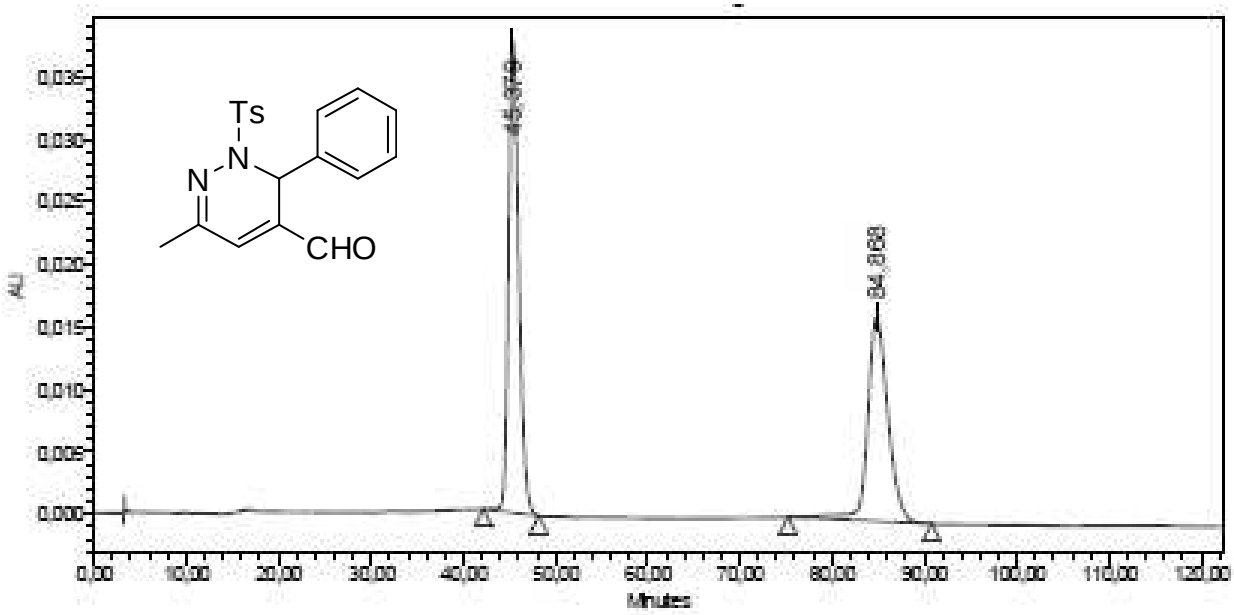
	RT	Area (µV*sec)	Height (µV)	% Area
1	62,733	6536415	56978	51,87
2	73,066	6064059	42937	48,13



Peak Results

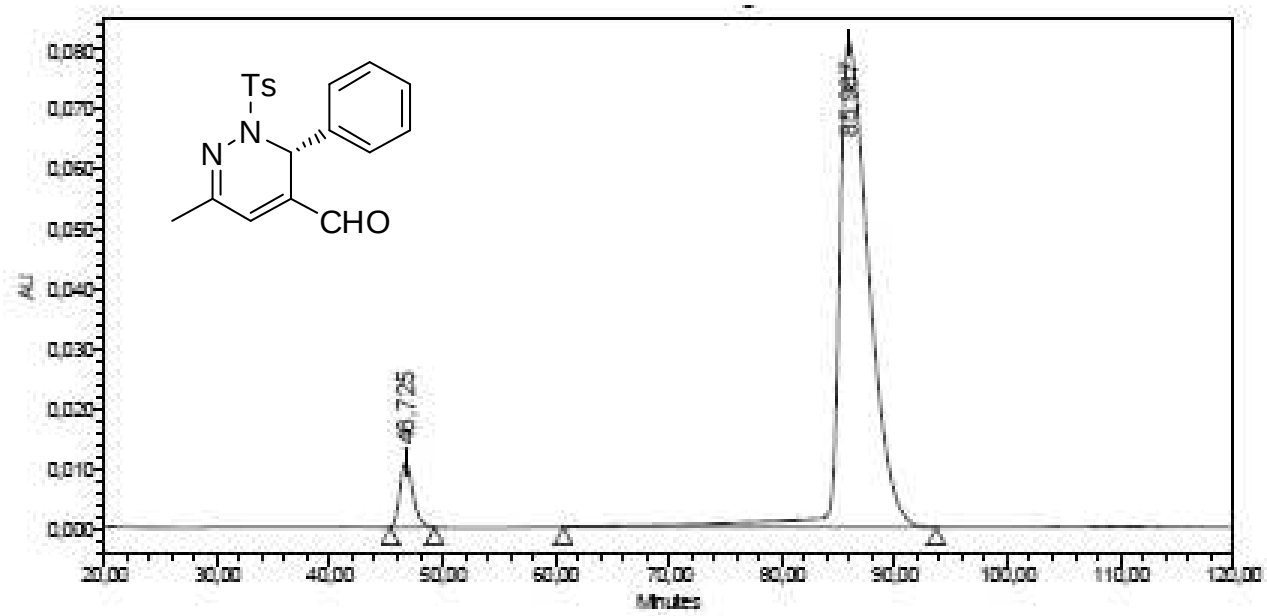
	RT	Area (µV*sec)	Height (µV)	% Area
1	64,583	279449	3123	1,99
2	74,063	13781619	100947	98,01

Figure S24: HPLC chromatogram of compound **4h**.



Peak Results

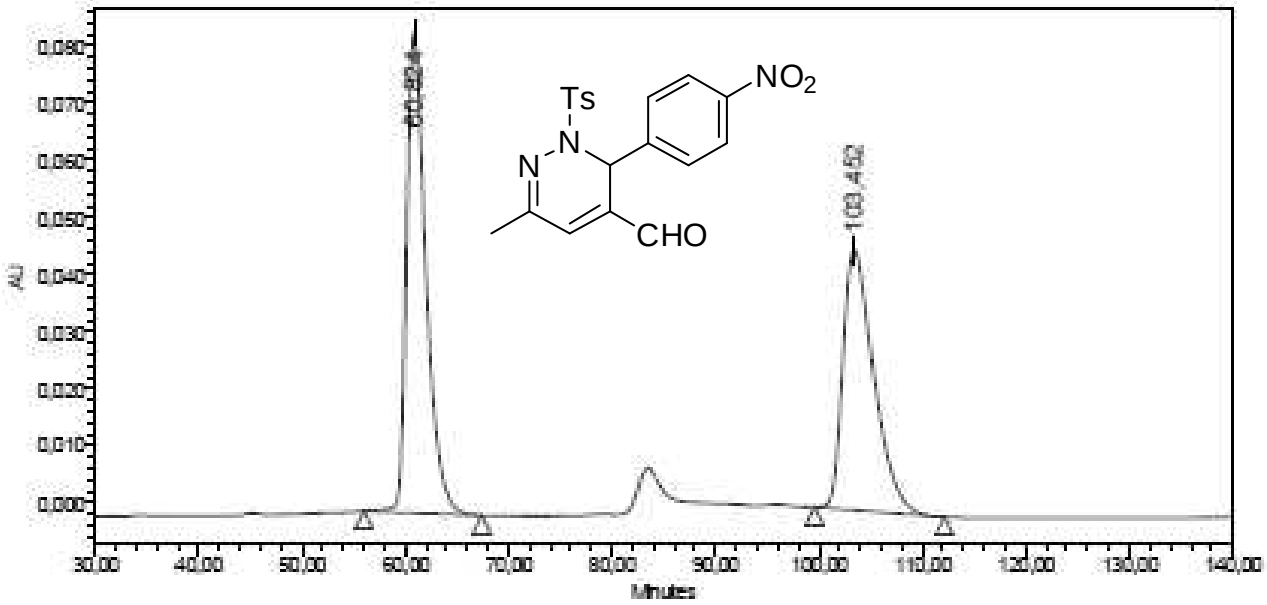
	RT	Area (µV*sec)	Height (µV)	% Area
1	45,379	2931694	37732	53,97
2	84,868	2499990	16318	46,03



Peak Results

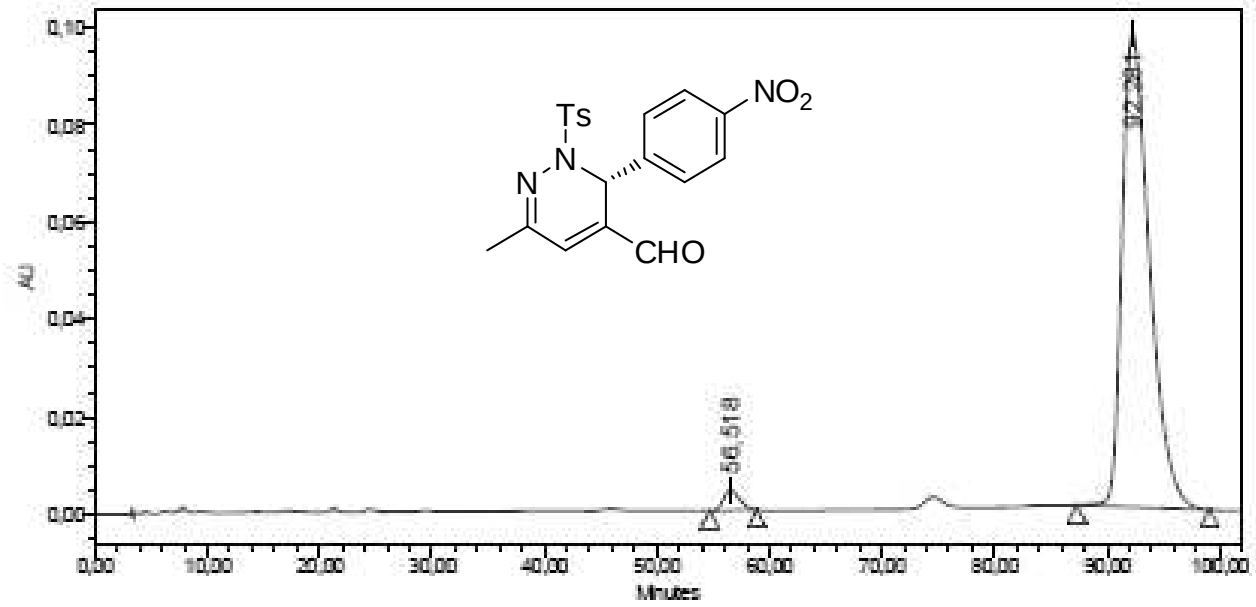
	RT	Area (µV*sec)	Height (µV)	% Area
1	46,725	871714	10851	5,44
2	85,987	15156654	81084	94,56

Figure S25: HPLC chromatogram of compound **4i**.



Peak Results

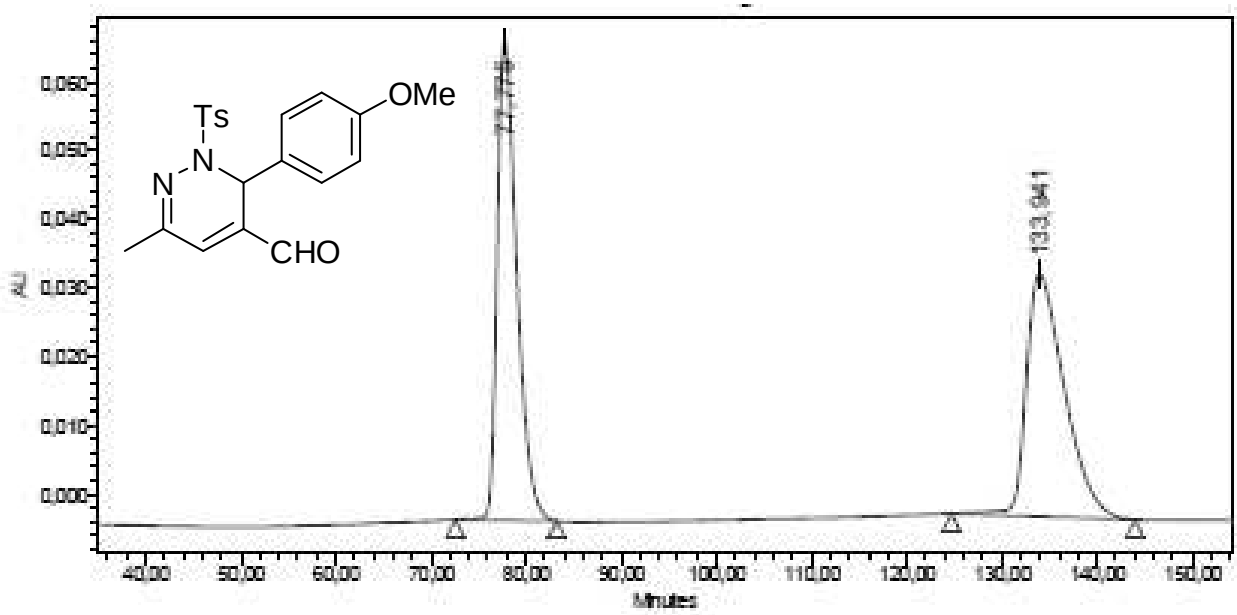
	RT	Area (µV*sec)	Height (µV)	% Area
1	60,824	10798393	84208	53,41
2	109,452	9418293	45714	46,59



Peak Results

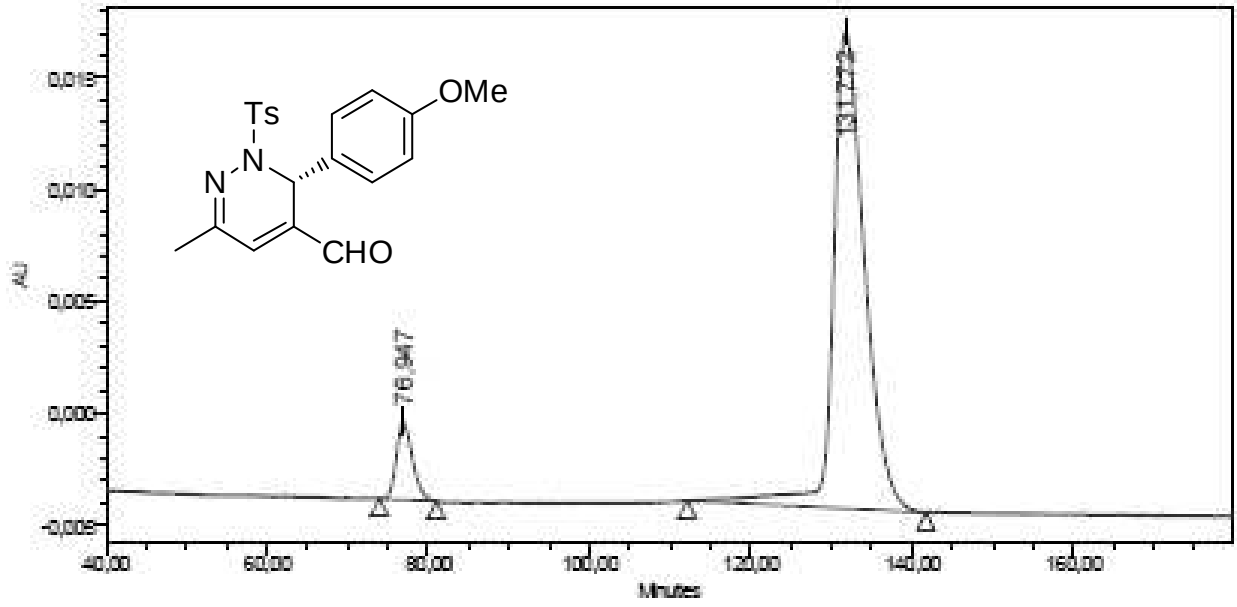
	RT	Area (µV*sec)	Height (µV)	% Area
1	56,518	413213	4115	2,43
2	92,281	16622552	97124	97,57

Figure S26: HPLC chromatogram of compound **4j**.



Peak Results

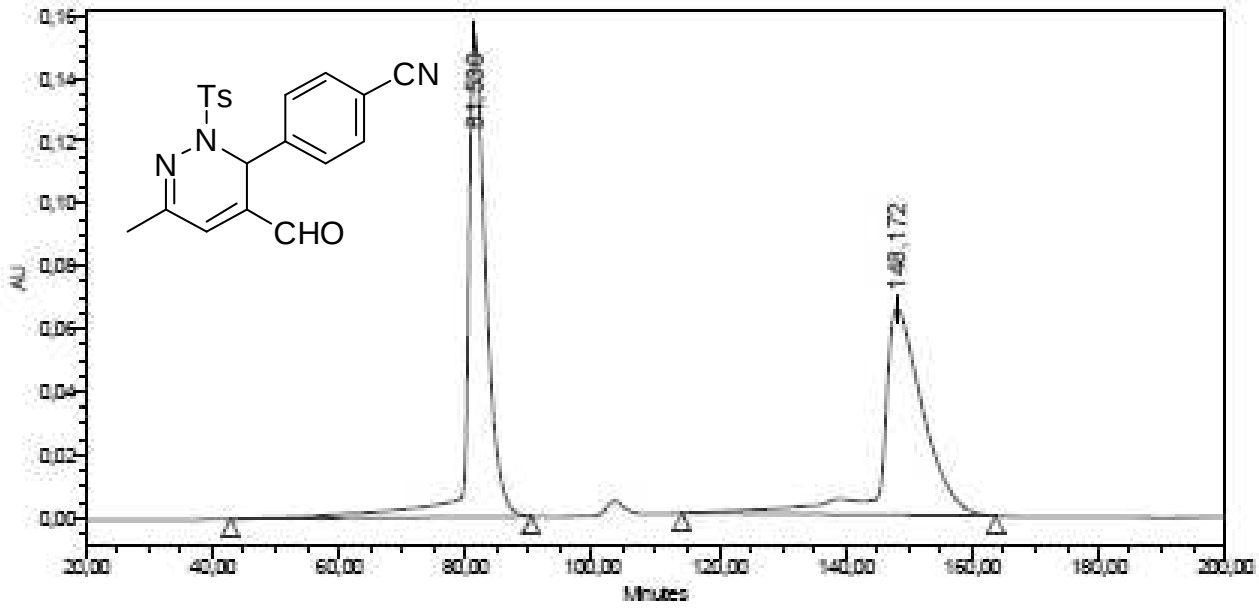
	RT	Area (µV*sec)	Height (µV)	% Area
1	77,775	10037121	69714	50,75
2	133,941	9742171	35150	49,25



Peak Results

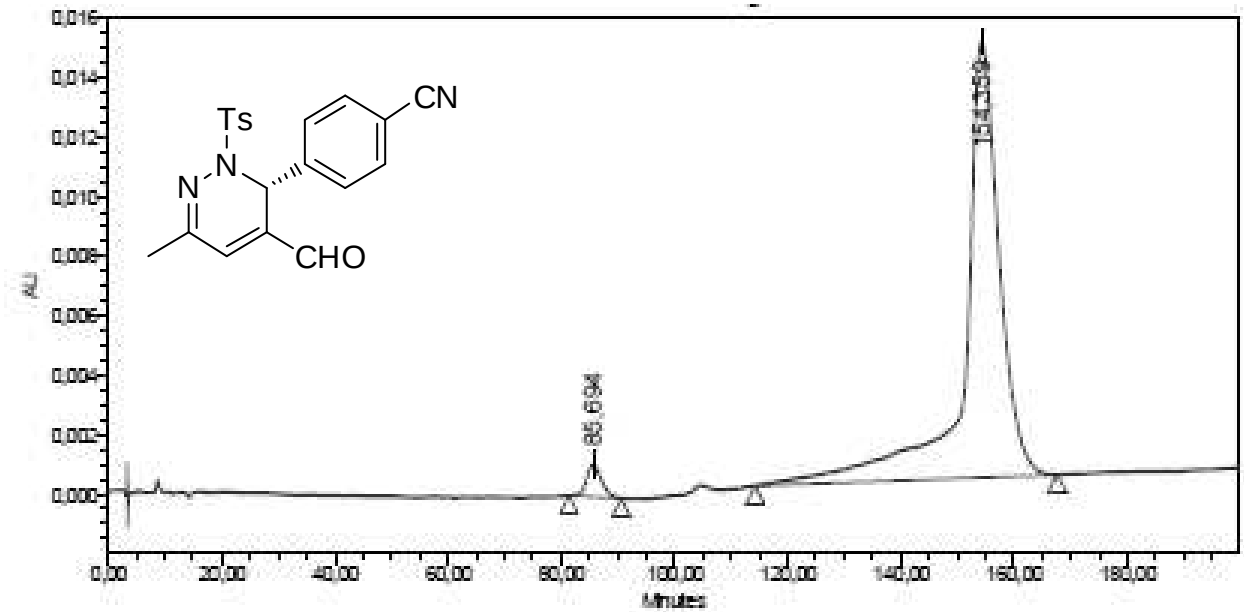
	RT	Area (µV*sec)	Height (µV)	% Area
1	76,947	483294	3472	7,71
2	131,772	5786828	21312	92,29

Figure S27: HPLC chromatogram of compound **4k**.



Peak Results

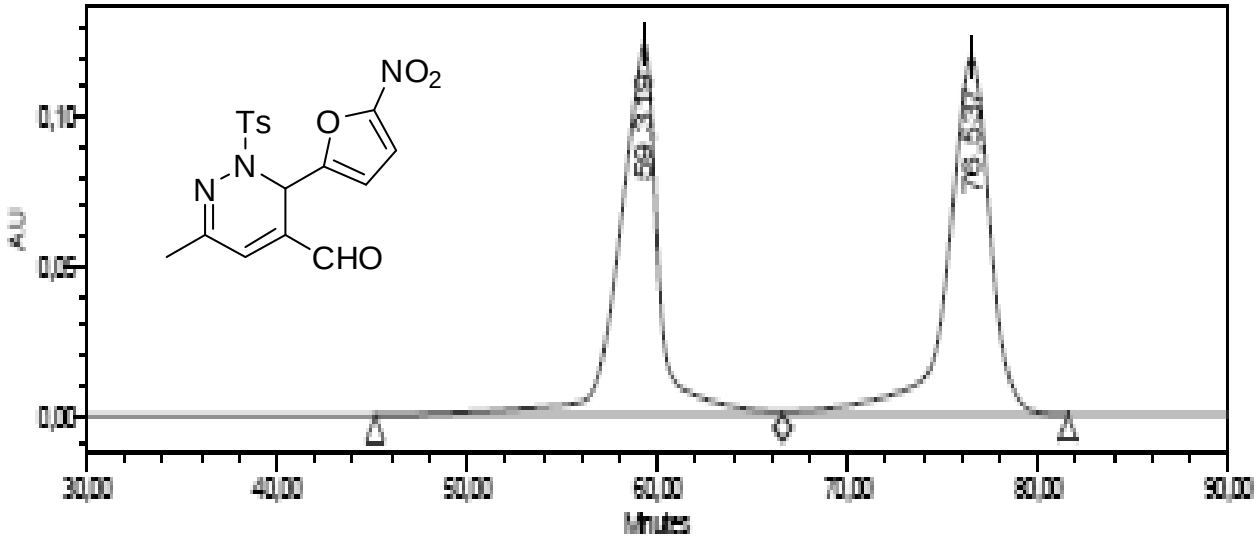
	RT	Area (µV*sec)	Height (µV)	% Area
1	81,530	31497400	153658	51,61
2	148,172	29532294	65695	48,39



Peak Results

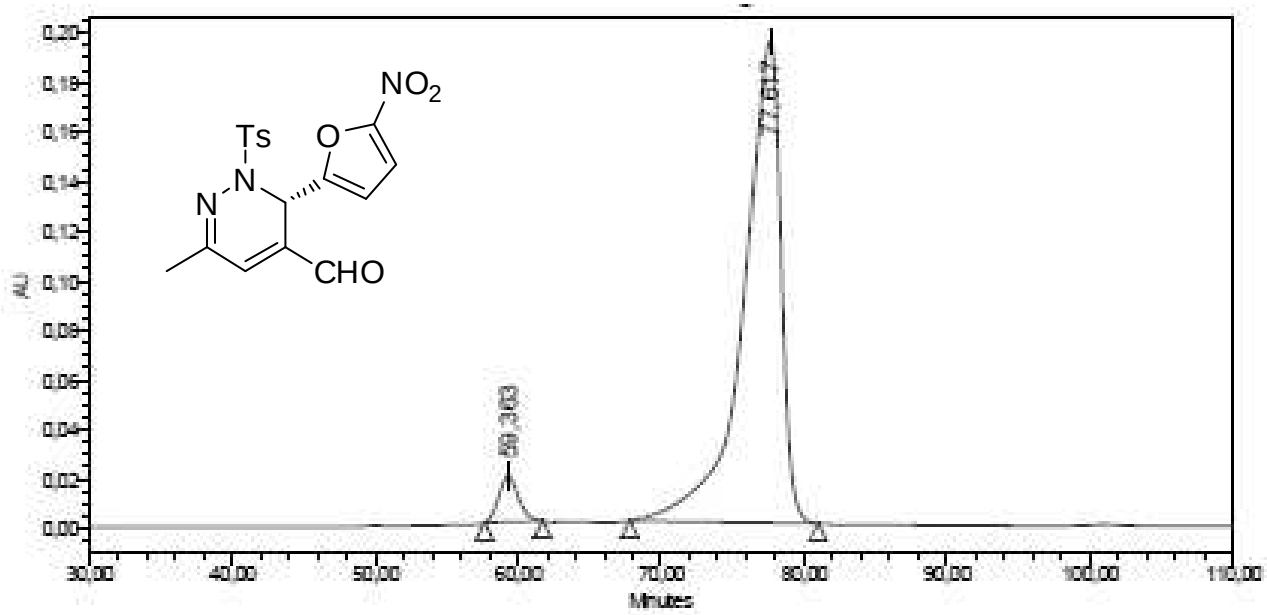
	RT	Area (µV*sec)	Height (µV)	% Area
1	85,694	200070	1099	3,03
2	154,359	6408068	14668	96,97

Figure S28: HPLC chromatogram of compound **4l**.



Peak Results

	Name	RT	Area	Height	% Area
1		59,319	17865546	134727	48,58
2		76,537	18910561	119868	51,42

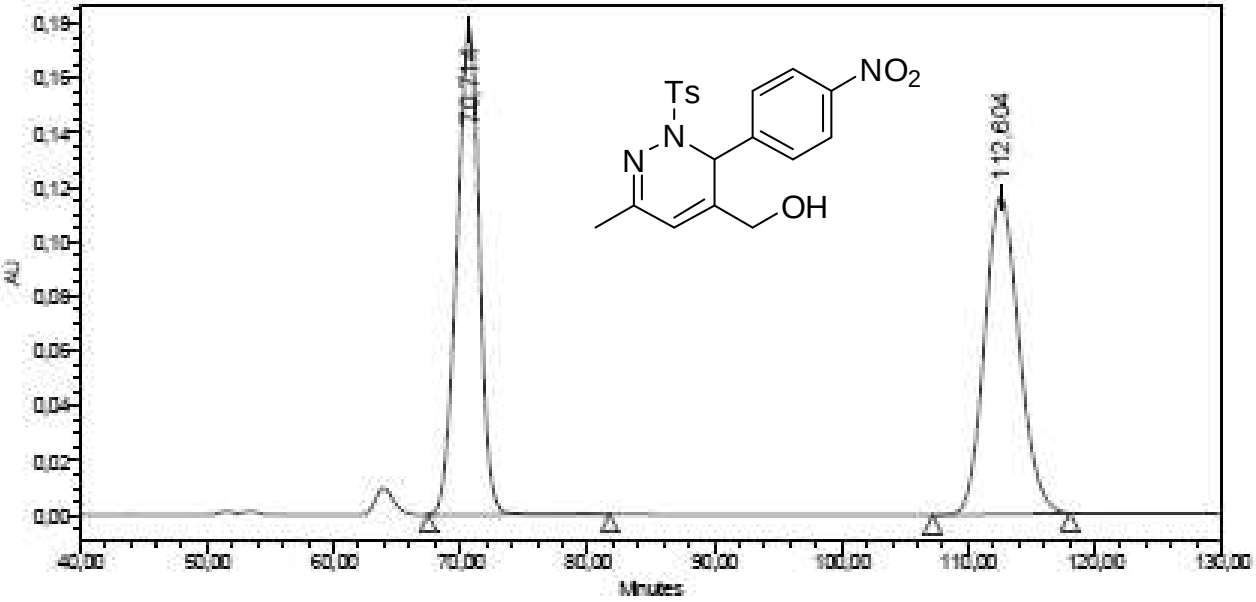


Peak Results

	RT	Area (µV*sec)	Height (µV)	% Area
1	59,363	1780838	18398	4,84
2	77,617	34985419	194310	95,16

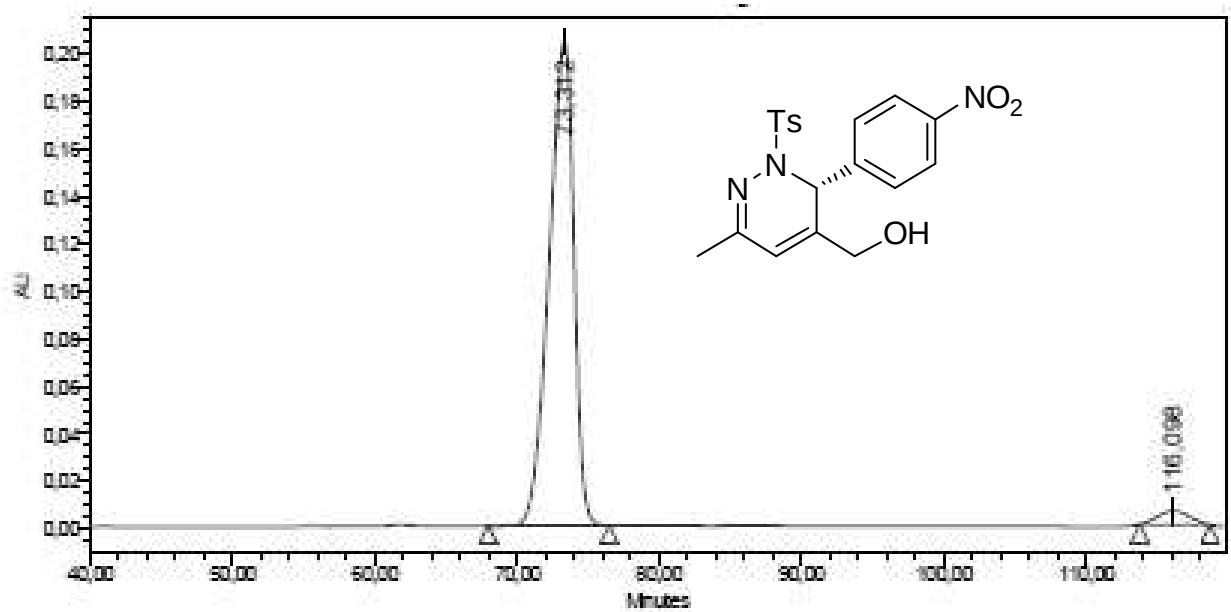
Figure S29: HPLC chromatogram of compound **4m**.

HPLC chromatograms of racemic and enantioenriched compound 5j



Peak Results

	RT	Area (µV*sec)	Height (µV)	% Area
1	70,714	21380065	177578	49,21
2	112,604	22066200	115829	50,79



Peak Results

	RT	Area (µV*sec)	Height (µV)	% Area
1	73,312	24767209	204086	96,47
2	116,098	907253	5822	3,53

Figure S30: HPLC chromatogram of compound **5j**.