Supplementary Information for

Double Cyclization of *O*-acylated hydroxyamides Generates 1,6-dioxa-3,9-diazaspiro[4.4]nonanes- a New Class of Oxy-oxazolidinones

Zohreh Nazarian* and Craig Forsyth

School of Chemistry, Monash University, Clayton VIC 3168, Australia

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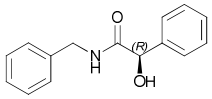
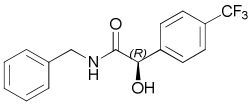
General remarks

All reactions were performed under N_2 unless otherwise stated. Melting points were measured on Reichert hot stage melting point apparatus. Optical Rotations were obtained at 20 °C using a 1 dm cell at a wavelength of 589 nm (sodium D line), quoted as: [α]ᴅ, concentration *c* (g/100 mL), solvent. The ^{1}H NMR spectra were recorded at 300 MHz, 400 MHz or at 600 MHz spectrometer and were reported in ppm relative to internal tetramethylsilane (TMS, δ 0.0) or with the solvent reference relative to TMS employed as the internal standard ($CDCl_3$, δ 7.26 ppm; C_6D_6, δ 7.16 ppm). ^{13}C NMR spectra were recorded at 75 MHz, 100 MHz or 150 MHz. Chemical shifts for carbon nuclear magnetic resonance (^{13}C NMR) spectra are reported in parts per million downfield relative to the centre line of the triplet of $CDCl_3$ at 77.0 ppm and/or C_6D_6 128.6 ppm. ^{19}F NMR spectra were determined at 377 MHz with trichlorofluoromethane as internal reference (δ 0.00 ppm). Accurate mass determinations were made on an Agilent G6220A LC-TOF system. All solvents were distilled from appropriate drying agents prior to use. Unless otherwise noted, commercially available chemicals were used as received.



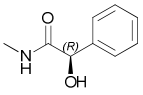
***(R)*-*N*-Benzyl-2-hydroxy-2-phenylacetamide (3a).**

To a solution of (*R*)-mandelic acid (5.00 mmol, 0.76 g), benzylamine (4.54 mmol, 0.5 mL) and *N*-hydroxysuccinimide (5.00 mmol, 0.58 g) in anhydrous THF (150 mL), was added DCC (5.00 mmol, 1.00 g). Subsequently, stirring at room temperature, overnight, the reaction mixture was diluted with Et_2O (200 ml) and washed with 2.5 % aqueous Na_2CO_3 (2 × 300 mL), 1 M aqueous HCl (2 × 300 mL) and water. The organic layer was dried over $MgSO_4$. Filtration and solvent removal in *vacuo* gave the crude product which was purified *via* flash chromatography on silica gel (35 % EtOAc/hexanes) to give **3a** (0.98 g, 90 %) as a white solid; m.p. 133-135[1] °C. The spectral data were in agreement with the literature values[2]. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42-7.17 (m, 10 H), 6.44 (br s, 1 H), 5.08 and 4.93 (2s, 1 H), 4.46-4.38 (m, 2 H), 3.66 (s, 1 H). **ESI-MS**. Calcd. for [$C_{15}H_{15}NO_2Na^+$] m/z = 264.09; found 264.1.



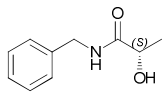
***(R)*-*N*-Benzyl-2-hydroxy-2-(4-(trifluoromethyl)phenyl)acetamide (3b).**

Following the procedure described for **3a**, using (*R*)-2-hydroxy-2-(4-(trifluoromethyl)phenyl) acetic acid (7.5 mmol, 1.65 g), benzylamine (6.8 mmol, 0.74 mL), *N*-hydroxysuccinimide (7.5 mmol, 0.86 g) and DCC (7.5 mmol, 1.5 g) in anhydrous THF (200 mL). Purification *via* flash chromatography on silica gel (35 % EtOAc/hexanes) gave **3b** (1.69 g, 73 %) as a white crystalline solid; m.p. 184-185 °C [lit[1] 185- 186] .The spectroscopy data were in agreement with literature values.[1]**H NMR** (400 MHz, $CDCl_3$) δ 7.63 (d, *J*= 8.0 Hz, 2 H), 7.56 (d, *J* = 8.0 Hz, 2 H), 7.32-7.29 (m, 3 H), 7.19 (d, *J* = 8.0 Hz, 2 H), 6.59 (br s, 1 H), 5.17 (s, 1 H), 4.49-4.40 (m, 2 H).



(*R*)-2-Hydroxy-*N*-methyl-2-phenylacetamide (3c).

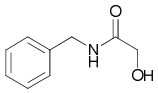
3c was prepared in two steps. First (*R*)-mandelic acid was (15 mmol, 2.28 g) converted into the corresponding α-hydroxy methyl ester *via* refluxing in MeOH (150 mmol, 6 mL) in the presence of catalytic amount of H_2SO_4. Then the resulting α-hydroxy methyl ester (12.78 mmol, 2.123 g) was used without further purification for next step to react with methyl amine (63.94 mmol, 5.5 mL) under reflux. After 24 hour, it was allowed to cool to room temperature. The volatiles were reduced under pressure and the crude was purified *via* flash chromatography (50 % EtOAc/hexanes) to give **3c** (2.029 g, 82 %); m.p. 101 °C [lit[3] 96-99 °C]. The spectral data were in agreement with the literature values. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41-7.31 (m, 5 H), δ 6.06 (br s, 1 H), 5.02 (s, 1 H), 3.61 (s, 1 H), 2.83 (d, *J* = 3.0 Hz, 3 H). **ESI-MS**: Calcd. for [$C_9H_{11}NNaO_2^+$] m/z =188.06; found 188.1.



***(S)*-*N*-Benzyl-2-hydroxypropanamide (3d).**

Ethyl (*S*) lactate (10 mmol, 1.14 mL) was placed in a flask containing benzylamine (10 mmol, 1.41 mL) and heated for 24 hours under reflux. Then, solution was allowed to cool to room temperature. The volatiles were removed under reduced pressure and the lactamide was purified *via* column chromatography on silica gel (50 % EtOAc/hexanes) to give **3d** as a colourless liquid (1.43 g, 80 %)[4]. The spectroscopy

data was in agreement with the literature values.[5] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34-7.23 (m, 5 H), 6.97 (br s, 1 H), 4.42 (d, *J* = 8.0 Hz, 2 H), 4.24 (q, *J* = 6.8 Hz, 1 H), 1.42 (d, *J* = 6.8 Hz, 3 H).



***N*-Benzyl-2-hydroxyacetamide (3e).**

To a stirring solution of glycolic acid (30 mmol, 2.28 g) were added benzylamine (30 mmol, 3.2 mL), EDCI.HCl (33 mmol, 6.3 g) and DMAP (9.0 mmol, 1.098 g) in CH_2Cl_2 at 0 °C. Subsequently stirring overnight at room temperature, the reaction mixture was washed with 1 M aqueous HCl and water and dried over $MgSO_4$. The crude product was purified by eluting through a short plug of silica (50 % EtOAc/hexanes) to give **3e** (4.2 g, 85 %) as a white solid; m.p. 98-99 °C [lit[6] 101-102 °C]. The spectral data were in agreement with the literature values. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27-7.19 (m, 5 H), 6.65 (br s, 1 H), 4.43 (d, *J* = 6.0 Hz, 2 H), 4.09 (s, 2 H). **ESI-MS** Calcd. for [$C_9H_{11}NNaO2^+$] m/z =188.06; found 188.0

General Procedure for Preparation of *N*-Boc-*N*-methyl α-amino acids

To a vigorously stirred solution of *N*-Boc-amino acid (15.8 mmol) and iodomethane (158 mmol, 22 g) in dry THF (60 mL) at 0 °C, NaH (60 % dispersion in mineral oil, 158 mmol, 6.34 g) was added slowly. Subsequently, reaction was removed from ice-bath and was allowed to stir at room temperature for 24 hours. Then, reaction was quenched with water (20 mL), EtOAc (16 mL) and evaporated in *vacuo*. The concentrate was diluted with water (330 mL) and washed with EtOAc (170 mL). The aqueous layer was acidified to pH ~ 3.5 with a solution of 5 % citric acid and extracted with EtOAc (500 mL). Then it was washed with brine and dried with $MgSO_4$ and evaporated in *vacuo* to give *N*-Boc-*N*-methyl amino acid as clear thick oil which was used without further purification[7].

(*S*)-2-((*tert*-Butoxycarbonyl)(methyl)amino) propanoic acid (4b).

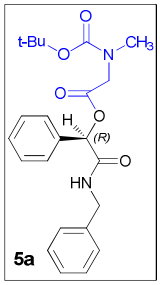
Following the general procedure, **4b** was obtained as an off white solid; m.p. 85-86 °C [lit[8] 89-91]. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.80-4.46 (br d, 1 H), 2.84 (br s, 3 H), 1.45-1.42 (m, 12 H). **HRMS** Calcd. for [$C_9H_{16}NO_4$] m/z =202.1079; found 202.1082.

(*S*)-2-((*tert*-Butoxycarbonyl)(methyl)amino)-3-methylbutanoic acid (4c).

Following the general procedure, **4c** was obtained as thick oil which was used without further purification[7]. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.31-3.98 (m, 1 H), 2.87 (s, 3 H), 2.27 (m, 1 H), 1.46 and 1.44 (2×s, 9 H), 1.02 (d, *J*= 6.6 Hz, 3 H), 0.91 (d, *J* = 6.7 Hz, 3 H). **ESI-MS**. Calcd. for $[C_{11}H_{21}NNaO_4^+]$ m/z =254.13 found 254.2.

(*S*)-2-((*tert*-Butoxycarbonyl)(methyl)amino)-3-phenylpropanoic (4d).

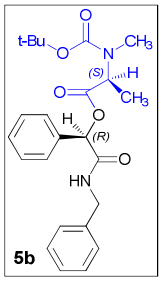
Following the general procedure, **4d** was obtained as thick oil which was used without further purification[8]. (Mixture of two rotamers) **^{1}H NMR** (300 MHz, $CDCl_3$) δ 10.99 (br s, 1 H),7.32-7.21 (m, 5 H), 4.91 (m, 1 H), 4.91and 4.63 (2×m, 1 H), 3.37-3.30 and 3.14-3.01 (2×m, 1 H), 2.11 and 2.11 (2×s, 3 H), 1.40 and 1.35 (2×s, 9 H).



(*R*)-2-(Benzylamino)-2-oxo-1-phenylethyl-2-((*tert*-butoxycarbonyl) (methyl)amino) acetate (5a).

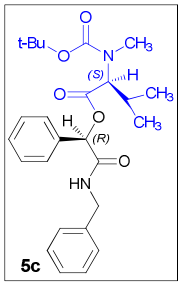
To a solution of **3a** (1.24 mmol, 0.3 g) in anhydrous CH_2Cl_2 at 0 °C were added commercially available *N*-Boc-sarcosine (1.24 mmol, 0.234 g) (**4a**), EDCI.HCl (1.98 mmol, 0.378 g) and DMAP (0.015 mmol, 0.124 g). To the resulting suspension, anhydrous Et_3N (1.61 mmol, 0.224 mL) was added dropwise while stirring vigorously. Then the mixture was warmed to room temperature and stirred for 7-8 hours. The mixture was diluted with CH_2Cl_2, washed with 1 M aqueous HCl and water and dried over $MgSO_4$. Filtration and solvent removal in *vacuo* gave a yellow oil which was purified *via* flash chromatography (20 % EtOAc/hexanes) to give **5a** (0.449 g, 88 %) as a white foam. (Mixture of two rotamers) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47–7.20 (m, 10 H), 6.15 (s, 1 H), 4.54–4.32 (m, 2 H), 4.15–3.82 (m, 2 H), 2.91 and 2.89 (2×s, 3 H), 1.37 and 1.30 (2×s, 9 H). (Mixture of two rotamers) **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.5, 168.3, 168, 156.8, 138.0, 135.2, 129.2, 128.9, 128.8, 128.7, 128.5, 127.7, 127.6, 127.5, 127.3, 127.3, 80.7 and 80.4, 76.0, 51.3 and 51.0, 43.2, 36.3 and 35.5, 28.2 and 28.1. **IR**ν_{max} 3301, 2975, 2929, 1754, 1663,

1536, 1453, 1389, 1366, 1239, 1144, 732, 696 cm^{-1}. **HRMS** Calcd. for $[C_{23}H_{28}N_2O_5Na]^+$ m/z = 435.1890; found 435.1891. **Specific rotation** $[\alpha]_D$ -51.8 (*c* 1.0, CH_2Cl_2)



(*S*)-(*R*)-2-(Benzylamino)-2-oxo-1-phenylethyl-2-((*tert*-butoxycarbonyl) (methyl)amino)propanoate (5b).

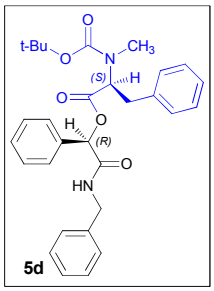
Following the procedure described for **5a**, **3a** (1.66 mmol, 0.4 g) was treated with *N*-Boc-*N*-methyl-alanine **4b** (1.66 mmol, 0.337 g). Purification of the crude product was accomplished *via* flash chromatography (20 % EtOAc/hexanes) to give **5b** (0.636 g, 90 %) as a colourless liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 (br s, 1 H), 7.47-7.23 (m, 10 H), 6.07 (s, 1 H), 4.56-4.36 (m, 2 H), 4.24 (br q, *J* = 14.4 Hz, 1 H), 2.92 (s, 3 H), 1.47 (d, *J* = 6.8 Hz, 3 H), 1.37 (s, 9 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.1, 168.6, 156.2, 138.2, 135.5, 128.8, 128.6, 128.5, 127.7, 127.3, 127.2, 80.7, 76.5, 56.3, 43.2, 33.4, 28.3, 14.6. **IR**ν_{max} 3299, 2975, 2930, 1745, 1663, 1541, 1479, 1391, 1366, 1150, 1541, 1479, 1391, 1366, 1150, 1089, 729, 695 cm^{-1}. **HRMS** Calcd. for $[C_{24}H_{30}N_2O_5Na]^+$ m/z = 449.2047; found 449.2051. **Specific rotation** $[\alpha]_D$ -62.9 (*c* 1.0, CH_2Cl_2).



(*S*)-(*R*)-2-(Benzylamino)-2-oxo-1-phenylethyl-2-((*tert*-butoxycarbonyl) (methyl)amino)-3-methylbutanoate (5c).

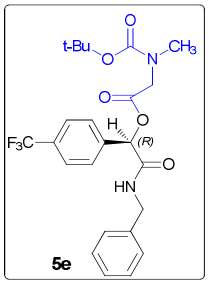
Following the procedure described for **5a**, **3a** (1.71 mmol, 0.414 g) was treated with *N*-Boc-*N*-methyl-valine **4c** (1.71 mmol, 0.397 g). Purification of the crude product was accomplished *via* flash chromatography (20 % EtOAc/hexanes) to give **5c** (0.69 g, 89 %) as a colourless liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49-7.23 (m, 10 H), 6.15 (s, 1 H), 4.57-4.34 (m, 2 H), 4.20 (d, *J* = 10.4 Hz, 1 H), 2.87 and 2.81 (2×s, 3 H), 2.21 (m, 1 H), 1.37 (s, 9 H), 0.89 (m, 6 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.3, 168.5,

156.9, 138.1, 135.6, 128.8, 128.5, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.3, 80.6, 75.5, 64.7 and 59.8, 43.3 and 43.2, 31.1, 28.3 and 28.2, 27.8, 19.9 and 19.1. **HRMS** Calcd. for $[C_{26}H_{34}N_2O_5Na^+]$ m/z = 477.2360; found 477.2368. **IR** ν_{max} 3308, 2966, 2929, 1724, 1664, 1690, 1533, 1453, 1389, 1366, 1304, 1255, 1142, 733, 695 cm^{-1}. **Specific rotation** $[\alpha]_D$ -54.7 (*c* 1.0, CH_2Cl_2).



(*S*)-(*R*)-2-(benzylamino)-2-oxo-1-phenylethyl-2-((*tert*-butoxycarbonyl) (methyl) amino)-3-phenylpropanoate (5d).

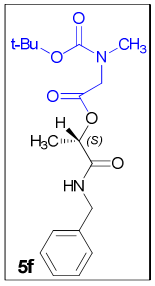
Following the procedure described for **5a**, **3a** (3.58 mmol, 0.862 g) was treated with *N*-Boc-*N*-methyl-phenylalanine **4d** (3.58 mmol, 1.00 g). Purification of the crude product was accomplished *via* flash chromatography (20 % EtOAc/hexanes) to give **5d** (1.56 g, 87 %) as a colourless liquid. (Mixture of two rotamers) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 (br s, 1 H), 7.38-7.13 (m, 15 H), 6.11 and 6.04 (2×s, 1 H), 4.50-4.36 (m, 2 H), 4.18 (m, 1 H), 3.36-3.21 (m, 2 H), 2.73 and 2.56 (2×s, 3 H), 1.33 and 1.28 (2×s, 9 H). (Mixture of two rotamers) **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.9, 168.6, 156.2, 138.2, 137.5, 135.4, 129.1, 128.7, 128.6, 128.4, 128.8, 127.2, 127.1, 126.8, 80.7, 76.8, 63.5 and 61.2, 43.1, 35.9, 35.2, 28.2. **HRMS** Calcd. for $[C_{30}H_{34}N_2O_5Na]^+$ m/z = 525.2360; found 525.2359. **IR** ν_{max} 3304, 2975, 2930, 1745, 1664, 1543, 1496, 1454, 1393, 1366, 1351, 1143, 737, 697 cm^{-1}. **Specific rotation** $[\alpha]_D$ -112.5 (*c* 1.0, CH_2Cl_2)



(*R*)-2-(Benzylamino)-2-oxo-1-(4-(trifluoromethyl)phenyl)ethyl-2-((*tert*-butoxycarbonyl)(methyl)amino)acetate (5e).

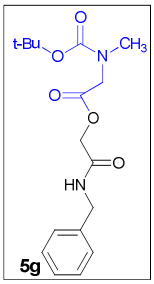
Following the procedure described for **5a**, **3b** (1.294 mmol, 0.4 g) was treated with **4a** (1.294 mmol, 0.244 g). Purification of the crude product was accomplished *via* flash chromatography (35 % EtOAc/hexanes) to

give **5e** (0.465 g, 75 %) as a colourless foam R_f (35 % EtOAc/hexanes) 0.37, (Mixture of two rotamers) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.0 Hz, 2 H), 7.57 (d, *J* = 8.0 Hz, 2 H), 7.27 (m, 5 H), 6.45 and 6.22 (2×s, 1 H), 4.56-4.34 (m, 2 H), 4.16-3.88 (m, 2 H), 2.95 and 2.91 (2×s, 3 H), 1.37 and 1.3 (2×s, 9 H). (Mixture of two rotamers) **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.2, 167.5, 156.8, 139.1, 137.8, 131.0 (q, $J_{C\text{-}F}$ = 61.8 Hz), 128.6, 127.8, 127.4, 127.0, 127.7, 81.0, 75.2, 51.5 and 49.5, 43.4, 36.5 and 35.6, 28.0.**^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.8. **HRMS** Calcd. for $[C_{24}C_{27}F_3N_2NaO_5]^+$ m/z = 503.1764; found 503.1770. **IR**ν_{max} 3301, 3032, 2978, 1760, 1667, 1540, 1419, 1391, 1324, 1241, 1148, 1126, 1067 cm^{-1}.



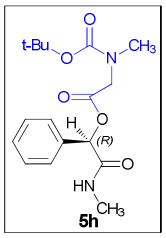
(*S*)-1-(Benzylamino)-1-oxopropan-2-yl 2-((*tert*-butoxycarbonyl) (methyl)amino) acetate (5f).

Following the procedure described for **5a**, **3d** (2.79 mmol, 0.5 g) was treated with **4a** (2.79 mmol, 0.52 g). Purification of the crude product was accomplished *via* flash chromatography (20 % EtOAc/hexanes) to give **5f** (0.976 g, 87 %) as a colourless liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38-7.22 (m, 5 H), 6.81 (br s, 1 H), 5.31-5.26 (m, 1 H), 4.50–4.44 (m, 2 H), 4.04-3.77 (m, 2 H), 2.93 and 2.88 (2×s, 3 H), 1.49 (d, *J* = 6.9 Hz, 3 H), 1.36 (s, 9 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.4 and 170.0, 168.9 and 168.7, 156.7 and 155.3, 138.2, 138.0, 128.7, 128.5, 127.8, 127.8, 127.6, 127.2, 80.6 and 80.3, 71.1 and 71.0, 51.3 and 51.0, 43.1 and 43.0, 36.3 and 35.5, 28.2, 18.0 and 17.8. **IR**ν_{max} 3312, 2977, 2934, 1755, 1663, 1537, 1452, 1389, 1366, 1240, 1178, 1146, 730, 697 cm^{-1}. **HRMS** Calcd. for $[C_{18}H_{26}N_2O_5Na]^+$ m/z = 373.1734; found 373.1735. **Specific rotation** $[\alpha]_D$ -14.2 (*c* 1.0, CH_2Cl_2)



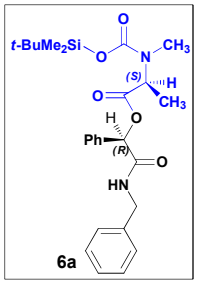
2-(Benzylamino)-2-oxoethyl 2-((*tert*-butoxycarbonyl)(methyl)amino) acetate (5g).

Following the procedure described for **5a**, **3e** (2.74 mmol, 0.452 g) was treated with **4a** (2.74 mmol, 0.517 g). Purification of the crude product was accomplished *via* flash chromatography (35 % EtOAc/hexanes) to give **5g** (0.644 g, 70 %) as a colourless liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31–7.25 (m, 5 H), 4.70 (ABq, *J* = 19.3 Hz, 2 H), 4.48 (d, *J* = 6.0 Hz, 2 H), 3.96 (ABq, *J* = 16.3 Hz, 2 H), 2.96 and 2.92 (2×s, 3 H), 1.36 (s, 9 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ169.0, 167.1, 156.7, 137.9, 128.76, 128.6, 127.7, 127.3, 80.8 and 80.5, 63.2 and 63.0, 51.2 and 50.8, 43.1 and 43.0, 36.4 and 35.5, 28.2. **IR**ν_{max} 3314, 2977, 2933, 1757, 1666, 1540, 1453, 1390, 1366, 1239, 1175, 1144, 732, 698 cm^{-1}. **HRMS** Calcd. for $[C_{17}H_{24}N_2O_5Na^+]$ m/z = 359.1577; found 359.1580.



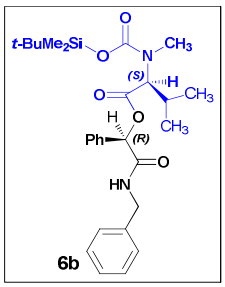
(*R*)-2-(Methylamino)-2-oxo-1-phenylethyl 2-((*tert*-butoxycarbonyl)(methyl) amino)acetate (5h).

Following the procedure described for **5a**, **3c** (10.5 mmol, 1.74 g) was treated with **4a** (10.5 mmol, 1.98 g). Purification of the crude product was accomplished *via* flash chromatography (35 % EtOAc/hexanes) to give **5h** (2.85 g, 81 %) as a colourless liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44-7.35 (m, 5 H), 7.09 (br s, 1 H), 6.14 (s, 1 H), 4.31-3.66 (m, 2 H), 2.96 (s, 3 H), 2.82 (d, *J* = 4.7 Hz, 3 H), 1.50 and 1.36 (2×s, 9 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.8, 168.3, 157.0, 135.4, 129.2, 128.9, 128.7, 127.5, 127.4, 81.0 and 80.6, 75.9, 51.5 and 51.2, 36.5, 28.4 and 28.2, 26.1. **IR**ν_{max} 3316, 2976, 2932, 1758, 1672, 1482, 1455, 1391, 1368, 1245, 1180, 1149 cm^{-1} **HRMS** Calcd. for $[C_{17}H_{24}N_2O_5Na]^+$ m/z = 359.1577; found 359.1581. **Specific rotation** $[\alpha]_D$ -4.88 (*c* 0.25, CH_2Cl_2)



(*S*)-(*R*)-2-(benzylamino)-2-oxo-1-phenylethyl 2-((((*tert*-butyldimethylsilyl)oxy)carbonyl)(methyl)amino)propanoate (**6a**).

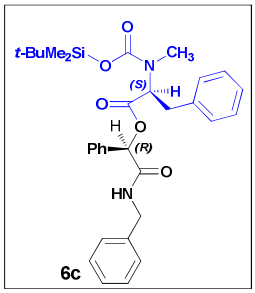
To a stirring solution of (*R*)- **5b** (0.387 mmol, 0.165 g) in dry CH_2Cl_2, Et_3N (0.387 mmol, 0.053 mL) was added dropwise at 0 °C *via* microsyringe through a septum, followed by TBSOTf (0.387 mmol, 0.102 mL) 5 min later. After stirring for 15 min, reaction mixture was warmed to room temperature and stirred overnight. Solvent removal in *vacuo* gave the crude product which was purified *via* flash chromatography on silica gel (20 % EtOAc/hexanes) to afford **6a** (0.118 g, 63 %) as a colourless viscous liquid R_f (20 % EtOAc/hexanes) 0.39. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.29-7.13 (m, 10 H), 6.03 and 6.0 (2×s, 1 H), 4.64 (q, *J* = 6.9 Hz, 1 H), 4.34 (m, 2 H), 2.7 (s, 3 H), 1.35 (d, *J* = 6.9 Hz, 3 H), 0.82 (s, 9 H), 0.11 (s, 3 H), 0.4 (s, 3 H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 170.2, 168.6, 156.9, 138.2, 135.3, 128.9, 127.7, 127.3, 127.1, 76.0, 54.8, 43.3, 31.6, 25.5, 17.6, 14.3, -4.8 **HRMS** Calcd. for [$C_{26}H_{36}N_2NaO_5Si^+$] m/z = 507.2286; found 507.2294. **IR**ν_{max} 3310, 2930, 2857, 1747, 1658, 1542, 1466, 1393, 1319, 1253, 1207, 1161, 1091, 838, 796, 697 cm^{-1}. **Specific rotation** $[\alpha]_D$ -75.2 (*c* 1.3, CH_2Cl_2).



(*S*)-(*R*)-2-(benzylamino)-2-oxo-1-phenylethy 2-((((*tert*-butyldimethylsilyloxy)carbonyl)(methyl)amino)-3-methylbutanoate (6b).

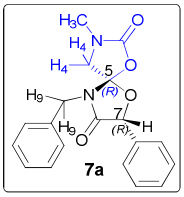
Following the procedure described for **6a**, *R*-**5c** (0.44 mmol, 0.2 g) was treated with TBSOTf (0.44 mmol, 0.116 mL) and Et_3N (0.44 mmol, 0.061 mL). **6b** was isolated *via* flash chromatography (0.148 g, 66 %) on silica gel (20 % EtOAc/hexanes) as a colourless viscous liquid. (Mixture of two rotamers) **^{1}H NMR** (400 MHz, C_6D_6) δ 7.54-7.01 (m, 10 H), 6.31 and 6.12 (2×s, 1 H), 4.56-4.51 and 4.39-4.31 (2×m, 2 H), 4.2 (d, *J* = 10.4 Hz, 1 H), 2.66 and 2.61 (2×s, 3 H), 2.11 (m, 1 H), 0.9 and 0.92 (2×s, 9 H), 0.67-0.78 (m, 6 H), 0.32

and 0.21(2×s, 6 H). **^{13}C NMR** (100 MHz, C_6D_6) δ 170.3, 167.7, 156.6, 139.1, 136.2, 128.5, 128.4, 128.3, 128.0, 127.9, 127.7, 127.4, 1267, 76.3, 65.3, 42.9, 32.3, 25.4, 19.6, 19.5, 17.5, -4.9, -4.9 **HRMS** Calcd. for [$C_{28}H_{40}N_2NaO_5Si^+$] m/z = 535.2599; found 535.2604. **IR** ν_{max} 3300, 2960, 1743, 1681, 1542, 1454, 1389, 1305, 1253, 1200, 1150, 1004, 827, 795, 696 cm^{-1}.



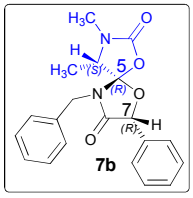
(*S*)-(*R*)-2-(benzylamino)-2-oxo-1-phenylethyl-2-((((*tert*-butyldimethylsilyl)oxy)carbonyl)(methyl) amino)-3-phenylpropanoate (6c).

Following the procedure described for **6a**, (*R*)-**5d** (0.398 mmol, 0.2 g) was treated with TBSOTf (0.398 mmol, 0.105 mL) and Et_3N (0.398 mmol, 0.055 mL). **6c** was isolated *via* flash chromatography (0.144 g, 65 %) on silica gel (20 % EtOAc/hexanes) as a colourless viscous liquid R_f (20 % EtOAc/hexanes) 0.55 (Mixture of two rotamers) **^{1}H NMR** (300 MHz, C_6D_6) δ 7.76 (br t, *J* = 5.7 Hz, 1 H), 7.35 (d, *J* = 7.5 Hz, 2 H), 7.04-6.79 (m, 13 H), 6.10 and 6.05 (2×s, 1 H), 4.25 (d, *J* = 5.7 Hz, 1 H), 4.07 (br d, *J* = 5.7 Hz,1 H), 3.79 (m, 1 H), 3.12 (m, 2 H), 2.65 and 2.17 (2×s, 3 H), 0.66 and 0.63 (2×s, 9 H), -0.02 (s, 3 H), -0.1 (s, 3 H). (Mixture of two rotamers) **^{13}C NMR** (75 MHz, C_6D_6) δ 170.0, 168.8 and 168.1, 156.1 and 155.3, 139.3 and 139.0, 138.1 and 137.9, 136.3 and 136.2, 129.5, 129.0, 128.9, 128.8, 128.8, 128.7, 128.1, 128.1, 128.0, 127.8, 127.7, 127.3, 127.03, 77.5 and 76.9, 63.7 and 61.8, 43.4, 36.3, 35.6 and 35.2, 26.0 and 25.8, 17.9 and 17.9, -4.4, -4.5. **HRMS** Calcd. for [$C_{32}H_{41}N_2O_5Si^+$] m/z = 561.2779; found 561.2786. **IR** ν_{max} 3315, 2930, 2919, 1745, 1654, 1542, 1454, 1394, 1349, 1252, 1209, 1146, 1029, 837, 794, 732, 695 cm^{-1}. **Specific rotation** $[\alpha]_D$ -94.2 (*c* 4.0, CH_2Cl_2).



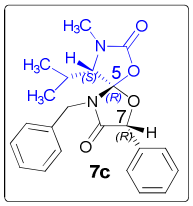
(5*R*,7*R*)-9-Benzyl-3-methyl-7-phenyl-1,6-dioxa-3,9-diazaspiro[4,4]nonane-2,8-dione (7a).

To a stirring solution of (*R*)-**5a** (0.463 mmol, 0.191 g) in dry CH_2Cl_2 at 0 °C was added Et_3N (1.15 mmol, 0.161 mL) *via* a microsyringe through a septum, followed by TBSOTf (1.15 mmol, 0.301 mL) 5 min later under. The reaction was held at 0 °C for about 15-20 min while stirring vigorously. Then, it was removed from ice bath and allowed to stir at room temperature for a further 13-14 hour. Subsequently, solvent removal in *vacuo*, gave the crude which was purified *via* flash chromatography, eluting with a solvent gradient of 20 % EtOAc/hexanes through 40 % EtOAc/hexanes to give **7a** as an off white solid m.p. 110-112 °C along with liquid diastereomer **8a (minor)** in 56 % combined yield (0.087 g) and 1: 1.2 dr ratio. **Major (7a) ^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44-7.25 (m, 10 H), 5.52 (s, 1 H), 5.10 (d, *J* = 15.6 Hz, 1 H), 4.09 (d, *J* = 15.7 Hz, 1 H), 3.58 (d, *J* = 11.1 Hz), 3.33 (d, *J* = 11.1 Hz, 1 H), 2.80 (s, 3 H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.4, 154.6, 135.4, 133.9, 129.3, 129.1, 129.0 , 128.4, 127.9, 126.5, 111.8, 78.4, 54.2, 43.8, 30.2. **HRMS** Calcd. for [$C_{19}H_{19}N_2O_4^+$] m/z = 339.1339; found 339.1343. **IR** ν_{max} 3033, 2928, 1769, 1731, 1413, 1396, 1365, 974 cm^{-1}. **Specific rotation** $[\alpha]_D$ -86 (*c* 0.73, CH_3OH). **Minor (8a) ^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55-7.26 (m, 10 H), 5.48 (s, 1 H), 5.04 (d, *J* = 15.5 Hz, 1 H), 4.09 (d, *J* = 15.5 Hz, 1 H), 3.56 (d, *J* = 11.0 Hz, 1 H), 3.23 (d, *J* = 11.0 Hz, 1 H), 2.78 (s, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.9, 154.7, 135.4, 134.4, 129.2, 129.2, 129.0, 128.7, 128.4, 126.6, 112.4, 79.7, 54.9, 43.9, 30.3. **HRMS** Calcd. for [$C_{19}H_{19}N_2O_4^+$] m/z = 339.1339; found 339.1345. **IR** ν_{max} 3032, 2929, 1768, 1728, 1413, 1398, 1364, 976 cm^{-1}. **Specific rotation** $[\alpha]_D$ +10.16(*c* 0.41, CH_2Cl_2)**.**



(4*S*,5*R*,7*R*)-9-Benzyl-3,4-dimethyl-7-phenyl-1,6-dioxa-3,9-diazaspiro[4,4]nonane-2,8-dione (7b).

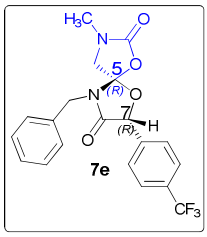
Following the procedure described for **7a**, (*R*)-**5b** (0.438 mmol, 0.187 g) was treated with TBSOTf (1.1 mmol, 0.290 mL) and Et_3N (1.1 mmol, 0.152 mL). The crude product was purified *via* flash chromatography, eluting with a solvent gradient of 20 % EtOAc/hexanes through 40 % EtOAc/hexanes to give **7b** as an off white solid; along with liquid diastereomer **8b (minor)** in 1: 1.1 dr ratio and in 55 % combined yield (0.087 g). **Major (7b) ^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45-7.23 (m, 10 H), 5.53 (s, 1 H), 5.10 (d, *J* = 16.0 Hz, 1 H), 4.13 (d, *J* = 16.0 Hz, 1 H), 3.56 (q, *J* = 6.6 Hz, 1 H), 2.76 (s, 3 H), 1.17 (d, *J* = 6.6 Hz, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.9, 154.3, 135.8, 133.9, 129.3, 129.1, 128.9, 128.2, 127.4, 126.8, 113.4, 77.9, 57.5, 43.8, 28.3, 12.4. **HRMS** Calcd. for [$C_{20}H_{20}N_2O_4Na^+$] m/z = 375.1315; found 375.1321. **IR** ν_{max} 3318 (br s, w), 2853 (w), 1774 (m), 1714 (s), 1431 (m), 1399 (m), 1322 (w), 1269 (m), 1112 (w), 1031 (w), 939 (w), 919 (w), 671 (w) cm^{-1}. **Specific rotation** $[\alpha]_D$ -25.9 (*c* 1.0, CH_2Cl_2). **Minor (8b) ^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 –7.27 (m, 10 H), 5.45 (s, 1 H), 5.01 (d, *J* = 15.8 Hz, 1 H), 4.16 (d, *J* = 15.8 Hz, 1 H), 3.45 (q, *J* = 6.5 Hz, 1 H), 2.74 (s, 3 H), 1.18 (d, *J* = 6.6 Hz, 3 H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.1, 154.3, 135.6, 134.4, 129.1, 129.1, 128.9, 128.4, 127.7, 126.5, 113.7, 79.7, 58.3, 43.8, 28.3, 12.2. **HRMS** Calcd. for [$C_{20}H_{20}N_2O_4Na^+$] m/z = 375.1315; found 375.1316. **IR** ν_{max} 3064, 3033, 2915, 1772, 1733, 1400, 1367, 1295, 1220, 1181, 970 cm^{-1}. **Specific rotation** $[\alpha]_D$ -8.1 (*c* 0.3, CH_2Cl_2)



(4*S*,5*R*,7*R*)-9-Benzyl-4-isopropyl-3-methyl-7-phenyl-1,6-dioxa-3,9-diazaspiro[4,4]nonane-2,8-dione (7c).

Following the procedure described for **7a**, (*R*)-**5c** (0.389 mmol, 0.177 g) was treated with TBSOTf (0.97 mmol, 0.256 mL) and Et_3N (0.97 mmol, 0.135 mL). The crude product was purified *via* flash column chromatography (20 % EtOAc/hexanes) to give **7c** as an off white solid; m.p. 153-155 °C together with liquid diastereomer **8c (minor)**. Two diastereomers were isolated in 52 % total yield (0.076 g) with 1: 1.4

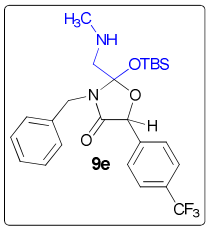
dr ratio. **Major (7c)** **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48-7.22 (m, 10 H), 5.54 (s, 1 H), 5.12 (d, *J* = 15.9 Hz, 1 H), 4.05 (d, *J* = 15.9 Hz, 1 H), 3.32 (d, *J* = 2.3 Hz, 1 H), 2.80 (s, 3 H), 2.09 (m, 1 H), 0.91 (d, *J* = 6.9 Hz, 3 H), 0.83 (d, *J* = 7.4 Hz, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.7, 154.5, 135.9, 133.6, 129.3, 128.9, 128.3, 127.6, 127.1, 113.8, 78.2, 66.3, 43.8, 30.7, 27.5, 19.8, 16.5 **HRMS** Calcd. for [$C_{22}H_{25}N_2O_4^+$] m/z = 381.1809; found 381.1814. **IR**ν_{max} 2966, 1766, 1723, 1413, 1400, 1322, 1261, 1198, 1173, 1146, 981, 937, 884, 843, 810, 771, 755 cm^{-1}. **Specific rotation** $[\alpha]_D$ -122.8 (*c* 1.0, CH_2Cl_2). (**Mixture of 7c and 8c**) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55-7.25 (m, 20 H) (mixture), 5.54 (s, 1 H) (minor), 5.43 (s, 1 H) (major), 5.12 (d, *J* = 15.9 Hz, 1 H) (major), 5.02 (d, *J* = 15.7 Hz, 1 H) (minor), 4.08 (d, *J* = 12.1 Hz, 1 H) (major), 4.04 (d, *J* = 12.2 Hz, 1 H) (minor), 3.32 (d, *J* = 2.3 Hz, 1 H) (minor), 3.22 (d, *J* = 3.1 Hz, 1 H) (major), 2.80 (s, 3 H) (major), 2.76 (s, 3 H) (minor), 2.10 – 2.04 (m, 2 H) (mixture), 0.97 (d, *J* = 7.0 Hz, 3 H) (minor), 0.93 (d, *J* = 7.3 Hz, 3 H) (major), 0.91 (d, *J* = 7.0 Hz, 3 H) (minor), 0.83 (d, *J* = 7.4 Hz, 3 H) (major). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.7 and 169.6, 155.0 and 154.7, 135.9, 135.6, 134.4, 133.6, 129.3, 129.0, 129.0, 128.9, 128.8, 128.4, 128.3, 128.0, 127.6, 127.1, 126.4, 114.4, 113.8, 79.5, 78.2, 66.8, 66.3, 43.8, 43.8, 30.7, 30.1, 27.7, 27.5, 19.8, 18.4, 17.0, 16.6.



(5*R*,7*R*)-9-Benzyl-3-methyl-7-(4-(trifluoromethyl)phenyl)-1,6-dioxa-3,9diazaspiro[4,4]nonane-2,8-dione (7e).

Following the precedure described for **7a**, (*R*)-**5e** (0.373 mmol, 0.179 g) was reacted with Et_3N (0.858 mmol, 0.119 mL) and TBSOTf (0.858 mmol, 0.226 mL). Purification of the crude product was accomplished *via* flash chromatography eluting with a solvent gradient of 20 % EtOAc/hexanes through 50 % EtOAc/hexanes to give **7e** as a white solid compound together with diastereomer **8e** (**minor**) in 1:1.2 dr ratio and a combined yield of 35 % (0.053 g), in some cases spirocyclic compound **7e** was isolated as a single isomer along with mono cyclic orthoamide **9e** R_f (20 % EtOAc/hexanes) 0.78 in combined yield of (0.055 g, 30 %). **Major (7e)** **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.62 (q, *J* = 8.7 Hz, 4 H), 7.29-7.36 (m, 5 H), 5.46 (s, 1 H), 4.95 and 4.00 (ABq, *J* = 15.6 Hz, 2 H), 3.51 and 3.18 (ABq, *J* = 10.8 Hz, 2 H), 2.75 and 2.73 (2×s, 3 H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 169.0, 154.2, 138.0, 135.0, 129.1, 128.6, 128.2, 126.4, 125.8,

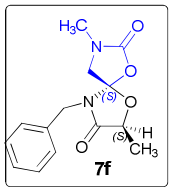
125.8, 112.3, 78.5, 54.6, 43.9, 30.2 **HRMS** Calcd. for $[C_{20}H_{17}F_3N_2NaO_4]^+$ m/z = 429.1033; found 429.1036. **IR**ν_{max} 2925, 2855, 1772, 1731, 1397, 1323, 1164, 1112, 1066, 973, 801, 703 cm^{-1}. **Minor** (**8e**) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (q, *J* = 8.4 Hz, 4 H), 7.27-7.15 (m, 5 H), 5.5 (s, 1 H), 5.00 and 4.00 (ABq, *J* = 15.6 Hz, 2 H), 3.53 and 3.27 (ABq, *J* = 10.4 Hz, 2 H), 2.74 (s, 3H).



9e

3-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-2-((methylamino)methyl)-5-(4-(trifluoromethyl)phenyl)oxazolidin-4-one (9e).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (ABq, *J* = 8.4 Hz, 2 H), 7.59 (ABq, *J* = 8.4 Hz, 2 H), 7.29-7.20 (m, 5 H), 5.39 (s, 1 H), 4.83 and 4.23 (ABq, *J* = 15.0 Hz, 2 H), 2.78 and 2.72 (ABq, *J* = 13.2 Hz, 2 H), 2.07 (s, 3 H), 0.90 and 0.89 (2×s, 9 H), 0.21 (s, 3 H), 0.16 (s, 3 H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 170.2 , 139.5, 136.9, 130.7 (q, $J_{C\text{-}F}$ = 62.5 Hz), 128.7, 128.3, 127.7, 127.3, 125.5, 125.5, 125.5, 125.4, 111.6, 77.5, 57.9, 43.9, 36.0, 25.6, -3.4 and -3.5 **HRMS** Calcd. for $[C_{25}H_{34}F_3N_2O_3Si]^+$ m/z = 495.2285; found 495.2288.

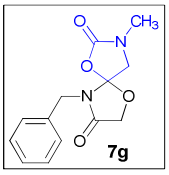


7f

(5*S*, 7*S*)-9-Benzyl-3,7-dimethyl-1,6-dioxa-3,9-diazaspiro[4,4]nonane-2,8-dione (7f).

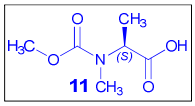
Following the procedure described for **7a**, (*S*)-**5f** (0.762 mmol, 0.267 g) was treated with TBSOTf (1.90 mmol 0.503 mL) and Et_3N (1.90 mmol, 0.264 mL). The crude product was purified *via* flash column chromatography eluting with a solvent gradient of 20 % EtOAc/hexanes through 50 % EtOAc/hexanes to give **7f** as an off white solid together with liquid diastereomer **8f (minor)**. Two diastereomers were isolated in 40 % total yield (0.084 g) with 1:1.3 dr ratio. Less polar isomer **7f** was isolated as an off white solid; m.p. 127-130 °C, R_f (50 % EtOAc/hexanes) 0.51 whereas more polar isomer **8f** was isolated as a mixture of both two diastereomers. **Major (7f) ^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40-7.24 (m, 5 H), 5.00 (d, *J* = 15.7 Hz, 1 H), 4.63 (q, *J* = 6.8 Hz, 1 H), 4.03 (d, *J* = 15.7 Hz, 1 H), 3.41 (d, *J* = 11.1 Hz, 1 H), 3.23 (d, *J* = 11.1 Hz, 1 H), 2.77 and 2.76 (2×s, 3 H), 1.51 (d, *J* = 6.8 Hz, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ

172.7, 154.7, 135.5, 129.0, 128.3, 127.8, 111.6, 73.5, 54.1, 43.5, 30.2, 17.1 **HRMS** Calcd. for [$C_{14}H_{16}N_2O_4Na^+$] m/z = 299.1002; found 299.1002. **IR** ν_{max} 3515, 2983, 2935, 1770, 1733, 1415, 1400, 1365, 1292, 969. **Specific rotation** $[\alpha]_D$ +60 (*c* 0.77, CH_2Cl_2). (**Mixture of 7f** & **8f**) **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.47–7.30 (m, 10 H) (mixture), 5.03 (d, *J* = 11.5 Hz, 1 H) (minor), 5.00 (d, *J* = 11.7 Hz, 1 H) (major), 4.63 (q, *J* = 6.9 Hz, 1 H) (minor), 4.56 (q, *J* = 7.2 Hz, 1 H) (major), 4.04 (d, *J* = 5.7 Hz, 1 H) (major), 4.02 (d, *J* = 5.6 Hz, 1 H) (minor), 3.45 (d, *J* = 4.8 Hz, 1 H) (major), 3.43 (d, *J* = 4.8 Hz, 1 H) (minor), 3.23 (d, *J* = 11.0 Hz, 1 H) (minor), 3.17 (d, *J* = 11.0 Hz, 1 H) (major), 2.77 (s, 3 H) (minor), 2.75 (s, 3 H) (major), 1.58 (d, *J* = 7.0 Hz, 3 H) (minor), 1.54 (d, *J* = 6.8 Hz, 3 H) (major). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 172.7, 172.6, 154.79, 154.7, 135.5, 135.6, 129.1, 129.0, 128.4, 128.4, 128.0, 127.9, 111.4, 112.2, 74.4, 73.4, 54.3, 54.1, 43.5, 30.2, 30.2, 18.4, 17.2. **HRMS** Calcd. for [$C_{14}H_{16}N_2O_4Na^+$] m/z=299.1002; found 299.1018.



9-Benzyl-3-methyl-1,6-dioxa-3,9-diazaspiro[4,4]nonane-2,8-dione (7g).

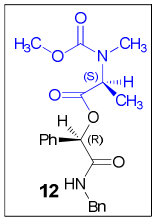
Following the procedure described for **7a**, **5g** (0.52 mmol, 0.178 g) was treated with TBSOTf (1.56 mmol, 0.41 mL), Et_3N (1.56 mmol, 0.21 mL). The crude product was purified *via* flash column chromatography, eluting with a solvent gradient of 20 % EtOAc/hexanes through 50 % EtOAc/hexanes to give trace amount of **7g** as an off white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5 H), 5.05 (d, *J* = 15.6 Hz, 1 H), 4.50 (ABq, *J* = 14.4 Hz, 1 H), 4.40 (ABq, *J* = 14.4 Hz, 1 H), 4.03 (d, *J* = 15.6 Hz, 1 H), 3.43 (ABq, *J* = 10.8 Hz, 1 H), 3.21 (ABq, *J* = 11.2 Hz, 1 H), 2.77 (s, 3 H). **HRMS** Calcd. for [$C_{13}H_{15}N_2O_4$]$^+$m/z = 263.1026; found 263.1147. The quantity of **7g** was insufficient for full characterization.



2-((Methoxycarbonyl)(methyl)amino)propanoic acid (11).

A round bottomed flask containing 6 mL NaOH (1 M) under an atmosphere of was charged with commercially available (*S*)-2-(Methylamino)propanoic acid **10** (2.91 mmol, 0.3 g) at r.t. This was stirred for 20-30 min and then the temperature was cooled to 3 °C. Then, Methyl chloroformate (5.76 mmol, 0.442 mL) was added dropwise. The mixture was stirred for 6 h at 3 °C. After that, the reaction was

warmed to 20 °C and then 1 M aqueous HCl (5-6 drops) was added dropwise until pH ~ 1 was obtained. Then, EtOAc was added (20-30 mL). The organic layer was washed with water and dried over $MgSO_4$ and evaporated in *vacuo* to yield **11** (0.254 g, 85 %) as an oil which was used without further purification.[9] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 10.87 (s, 1 H), 4.85–4.64 (m, 1 H), 3.67 (s, 3 H), 2.79 (br s, 3 H), 1.38 (d, *J* = 7.4 Hz, 3 H).

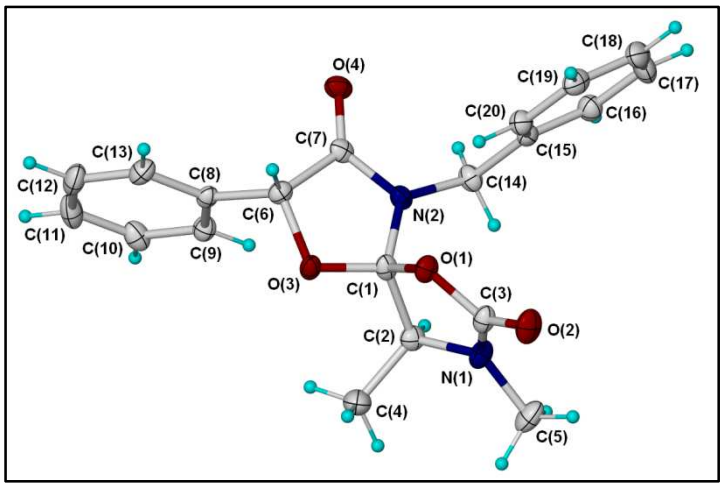


(*S*)-(*R*)-2-(Benzylamino)-2-oxo-1-phenylethyl 2-((methoxycarbonyl) (methyl)amino)propanoate (12)

Following the procedure described for the preparation of **5a**, **3a** (2.0 mmol, 0.483 g) was treated with **11** (2 mmol, 0.323 g) in the presence of EDCI.HCl (3.2 mmol, 0.611 g), DMAP (0.2 mmol, 0.024 g) and Et_3N (2.6 mmol, 0.361 g). Purification of the crude product was accomplished *via* flash chromatography (50 % EtOAc/hexanes) to afford **12** (0.691 g, 90 %) as a colourless liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42-7.23 (m, 10 H), 6.12 (s, 1 H), 4.55 (dd, *J* = 14.9, 6.2 Hz, 1 H), 4.42-4.35 (m, 2 H), 3.57 and 3.46 (2×s, 3 H), 2.92 (s, 3 H), 1.46 (d, *J* = 7.2 Hz, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.8, 168.2, 157.5, 138.2, 135.5, 128.9, 128.7, 128.5, 127.7, 127.4, 127.3, 76.3, 56.5, 52.9, 43.2, 32.5, 14.5. **IR** ν_{max} 3308 (br s, w), 1747 (m), 1683 (vs), 1557 (m), 1541 (m), 1455 (w), 1395 (w), 1206 (w), 1157 (w), 1091 (w), 698 (w) cm^{-1}. **HRMS** Calcd. for $[C_{21}H_{24}N_2NaO_5]^+$ m/z = 407.1577; found 407.1583. **Specific rotation** $[\alpha]_D$ -87 (*c* 0.4, CH_2Cl_2)

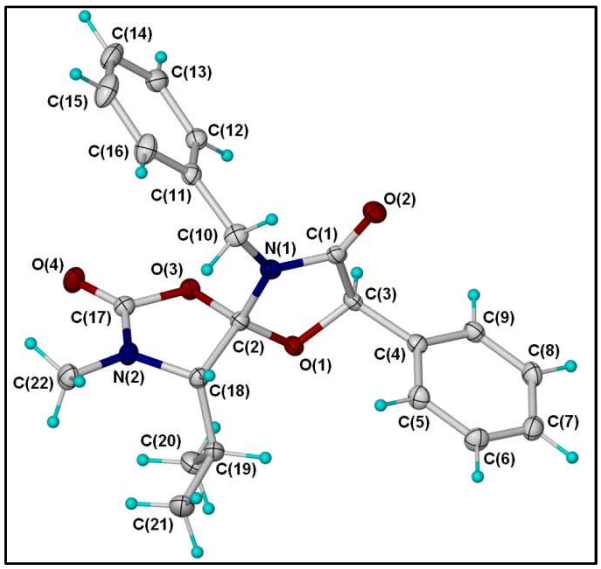
Crystallographic data for compounds 7b, 7c and 7f

X-ray Crystal analyses were performed on CrysAlisPro, Agilent Technologies, Version 1.171.35.15. Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm. CCDC **1477536**, **1477537**, **1477538** have been assigned to compound **7c**, **7e**, **7b** respectively. These data are available free of charge on the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk.



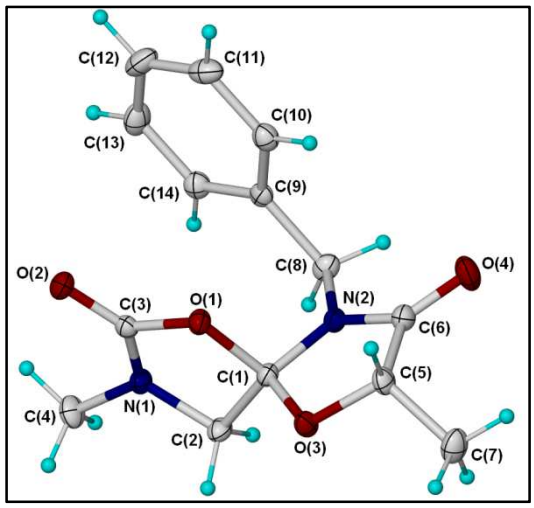
7b

Table S1. Crystal data and structure refinement for 7b.	
Empirical formula	$C_{20}H_{20}N_2O_4$
Formula weight	352.38
Temperature	123(2) K
Wavelength	1.54184 A
Crystal system, space group	Monoclinic, P 21
Unit cell dimensions	a = 10.1661(6) A alpha= 90 deg. b = 8.2577(4) A beta= 102.382(6) deg. c = 10.5397(6) A gamma= 90deg.
Volume	864.21(8) A^3
Z, Calculated density	2,1.354 Mg/m^3
Absorption coefficient	0.781 mm^-1
F(000)	372
Crystal size	0.25 x 0.25 x 0.25 mm
⊖ range for data collection	4.29 to 66.62 deg.
Limiting indices	-11<=h<=12, -9<=k<=8, -12<=l<=12
Reflections collected / unique	9089 / 2969 [R(int) = 0.0377]
Completeness to theta = 66.62	99.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.70733
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2969 / 1 / 238
Goodness-of-fit on F^2	1.083
Final R indices [I>2sigma(I)]	R1 = 0.0569, wR2 = 0.1498
R indices (all data)	R1 = 0.0585, wR2 = 0.1525
Absolute structure parameter	0.4(2)
Extinction coefficient	0.029(4)
Largest diff. peak and hole	0.317 and -0.245 e.A^-3
CCDC	**1477538**



7c

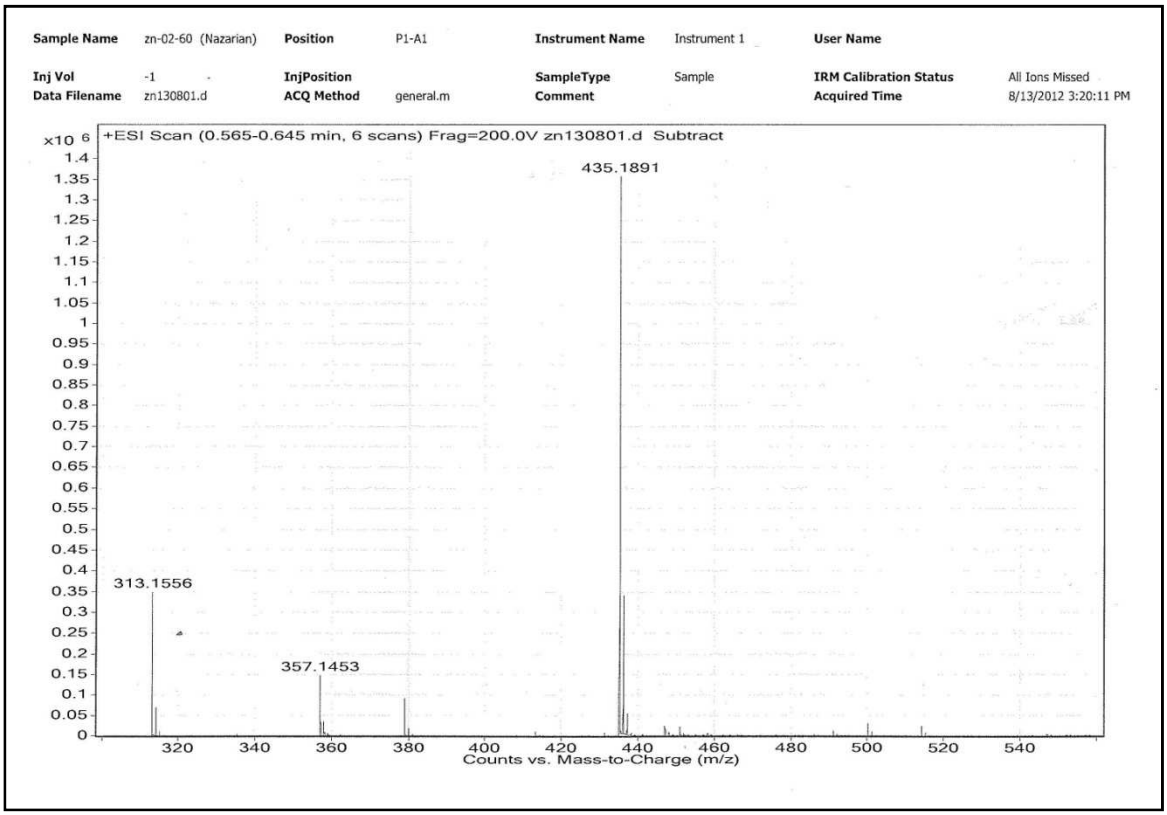
Table S2. Crystal data and structure refinement for 7c.	
Empirical formula	$C_{22}H_{24}N_2O_4$
Formula weight	380.43
Temperature	123(2) K
Wavelength	1.54184 A
Crystal system, space group	Orthorhombic, P 21 21 21
Unit cell dimensions	a = 9.0291(1) A alpha = 90 deg. b = 14.3287(3) A beta = 90 deg. c = 14.8824(3) A gamma = 90 deg.
Volume	1925.41(6) A^3
Z, Calculated density	4, 1.312 Mg/m^3
Absorption coefficient	0.739 mm^-1
F(000)	808
Crystal size	0.25 x 0.25 x 0.25 mm
Θ range for data collection	4.28 to 66.50 deg.
Limiting indices	-10<=h<=6, -16<=k<=17, -17<=l<=16
Reflections collected / unique	10532 / 3387 [R(int) = 0.0125]
Completeness to theta = 66.50	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.87487
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3387 / 0 / 255
Goodness-of-fit on F^2	1.052
Final R indices [I>2sigma(I)]	R1 = 0.0226, wR2 = 0.0589
R indices (all data)	R1 = 0.0231, wR2 = 0.0595
Absolute structure parameter	-0.05(12)
Extinction coefficient	0.0052(3)
Largest diff. peak and hole	0.154 and -0.147 e.A^-3
CCDC	**1477536**



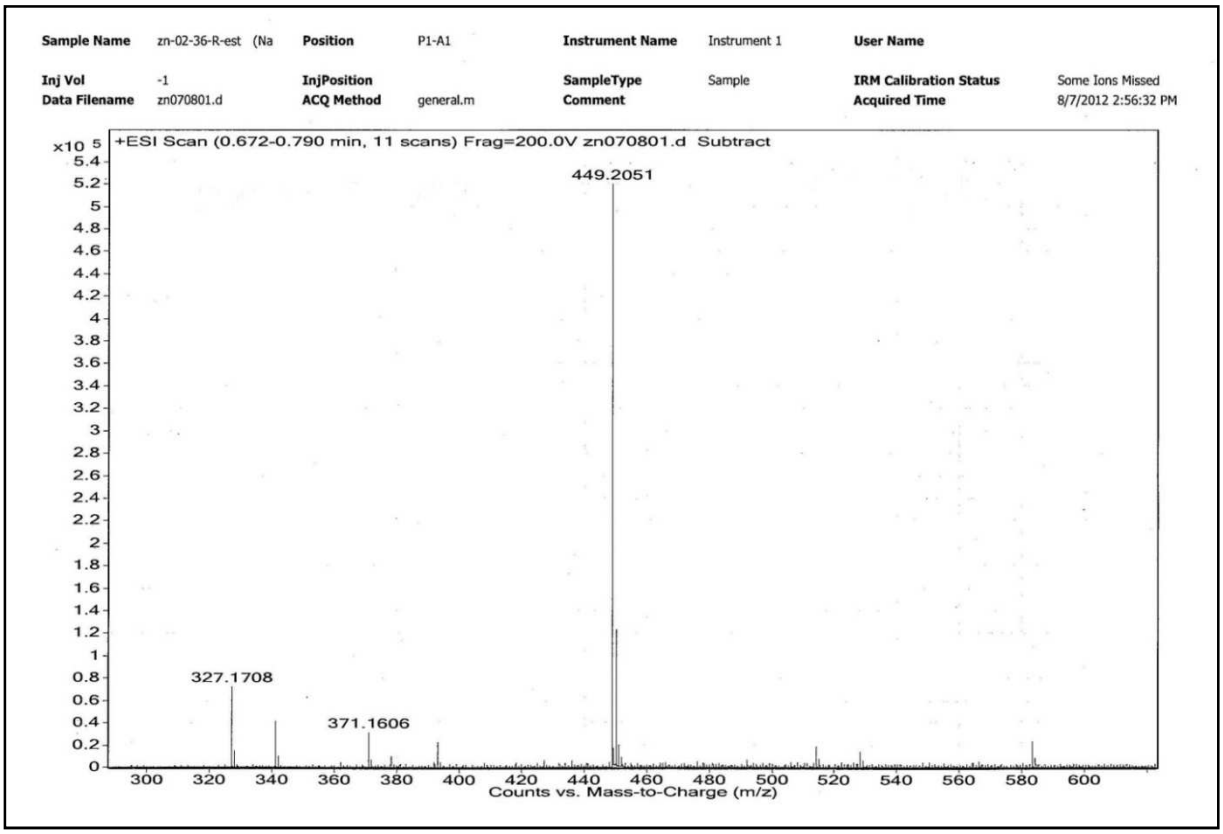
7f

Table S3. Crystal data and structure refinement for 7f.	
Empirical formula	$C_{14}H_{16}N_2O_4$
Formula weight	276.29
Temperature	123(2) K
Wavelength	1.54184 A
Crystal system, space group	Orthorhombic, P 21 21 21
Unit cell dimensions	a = 10.0012(12) A alpha = 90 deg. b = 10.3680(10) A beta = 90 deg. c = 12.5874(17) A gamma = 90 deg.
Volume	1305.2(3) A^3
Z, Calculated density	4, 1.406 Mg/m^3
Absorption coefficient	0.868 mm^-1
F(000)	584
Crystal size	0.20 x 0.20 x 0.20 mm
ϴ range for data collection	5.53 to 66.40 deg.
Limiting indices	-11<=h<=11, -11<=k<=12, -14<=l<=14
Reflections collected / unique	13825 / 2291 [R(int) = 0.0191]
Completeness to theta = 66.50	99.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.90240
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2291 / 0 / 183
Goodness-of-fit on F^2	1.091
Final R indices [I>2sigma(I)]	R1 = 0.0239, wR2 = 0.0619
R indices (all data)	R1 = 0.0242, wR2 = 0.0621
Absolute structure parameter	-0.16(15)
Largest diff. peak and hole	0.138 and -0.188 e.A^-3
CCDC	**1477537**

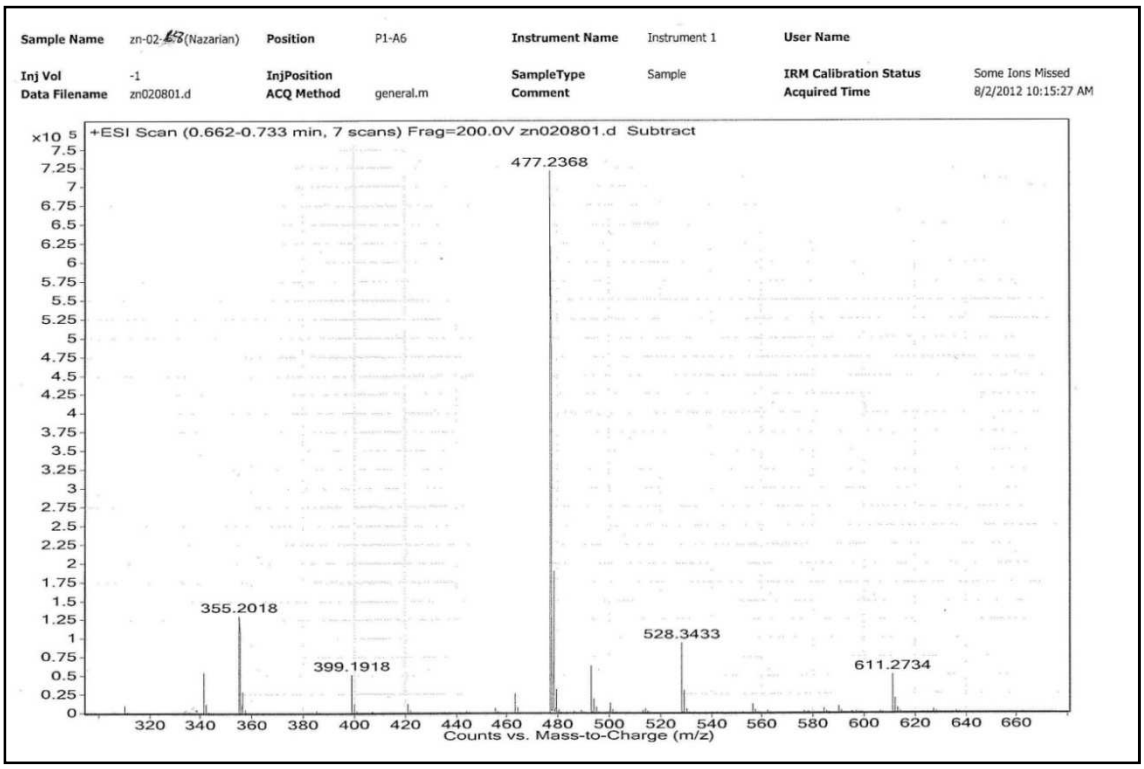
(*R*)-2-(Benzylamino)-2-oxo-1-phenylethyl-2-((*tert*-butoxycarbonyl)(methyl)amino)acetate (5a)



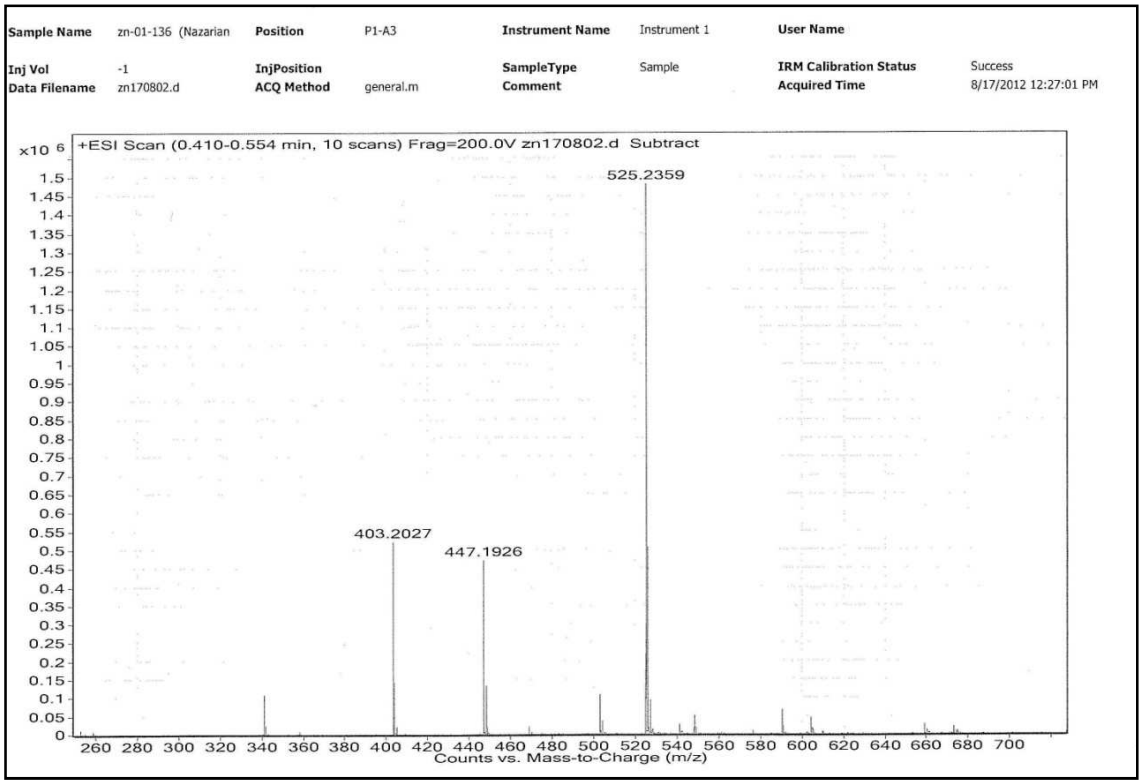
(*S*)-(*R*)-2-(Benzylamino)-2-oxo-1-phenylethyl-2-((*tert*-butoxycarbonyl)(methyl)amino) propanoate (5b)



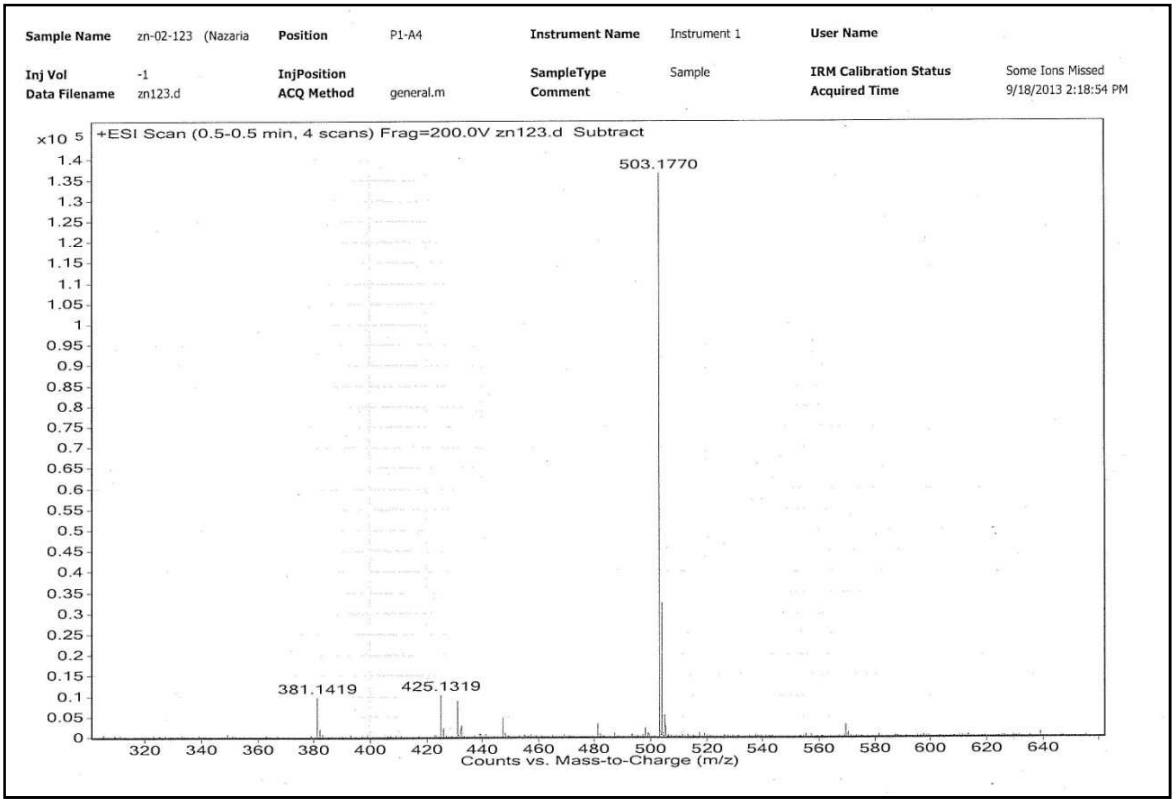
(*S*)-(*R*)-2-(Benzylamino)-2-oxo-1-phenylethyl-2-((*tert*-butoxycarbonyl)(methyl)amino)-3-methylbutanoate (5c)



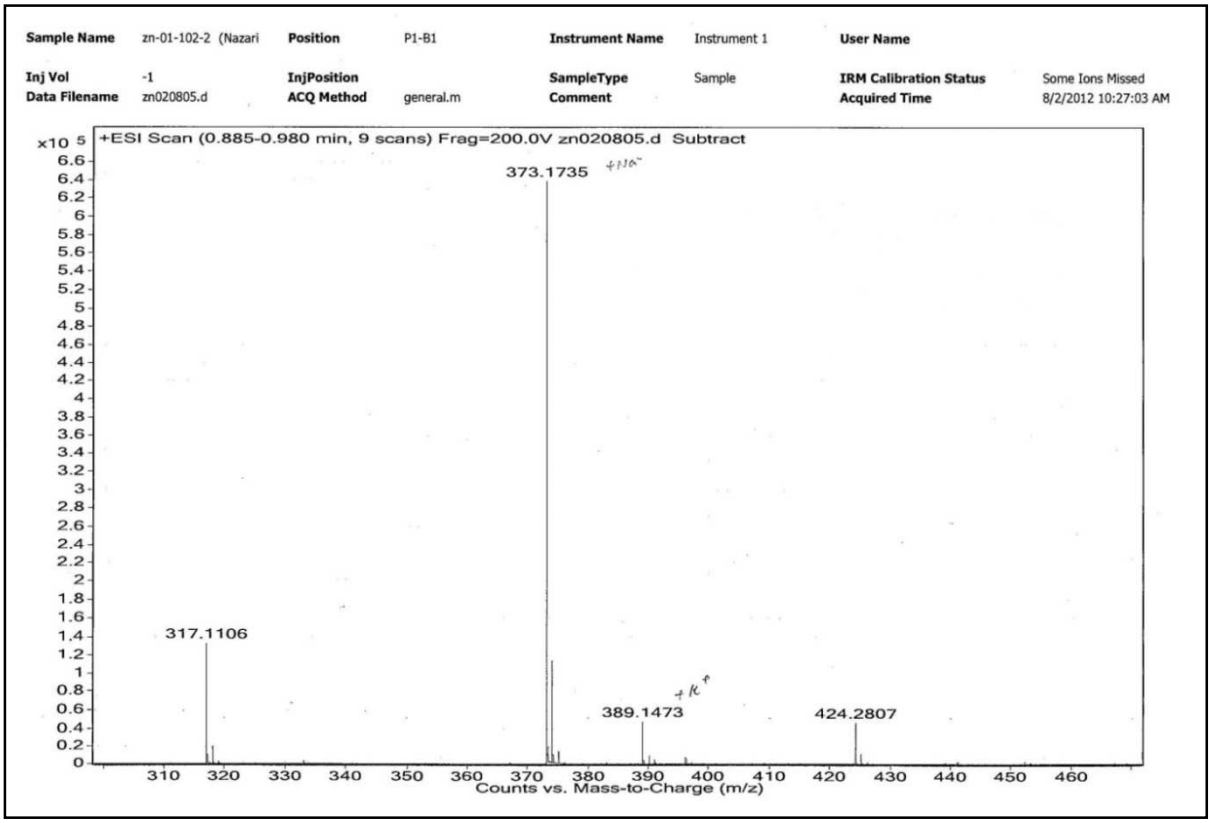
(*S*)-(*R*)-2-(benzylamino)-2-oxo-1-phenylethyl-2-((*tert*-butoxycarbonyl)(methyl)amino)-3-phenylpropanoate (5d)



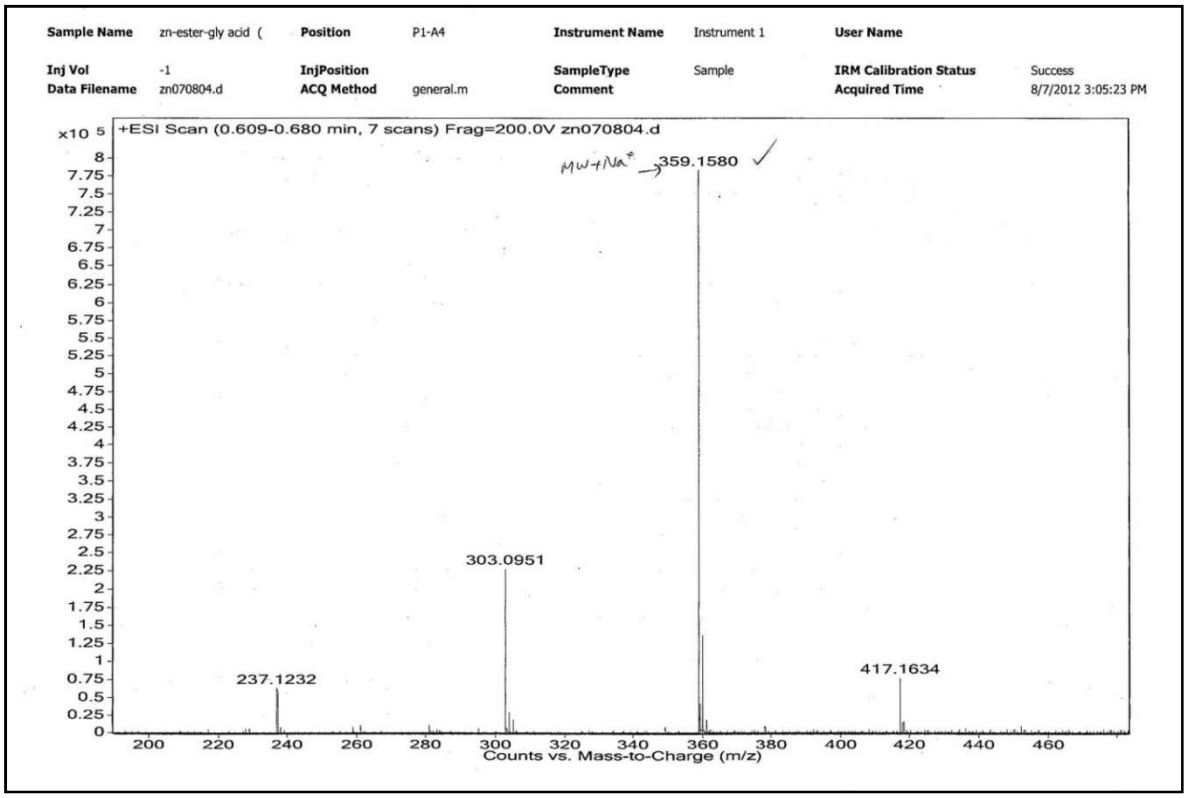
(*R*)-2-(Benzylamino)-2-oxo-1-(4-(trifluoromethyl)phenyl)ethyl-2-((*tert*-butoxycarbonyl) (methyl)amino)acetate (5e)



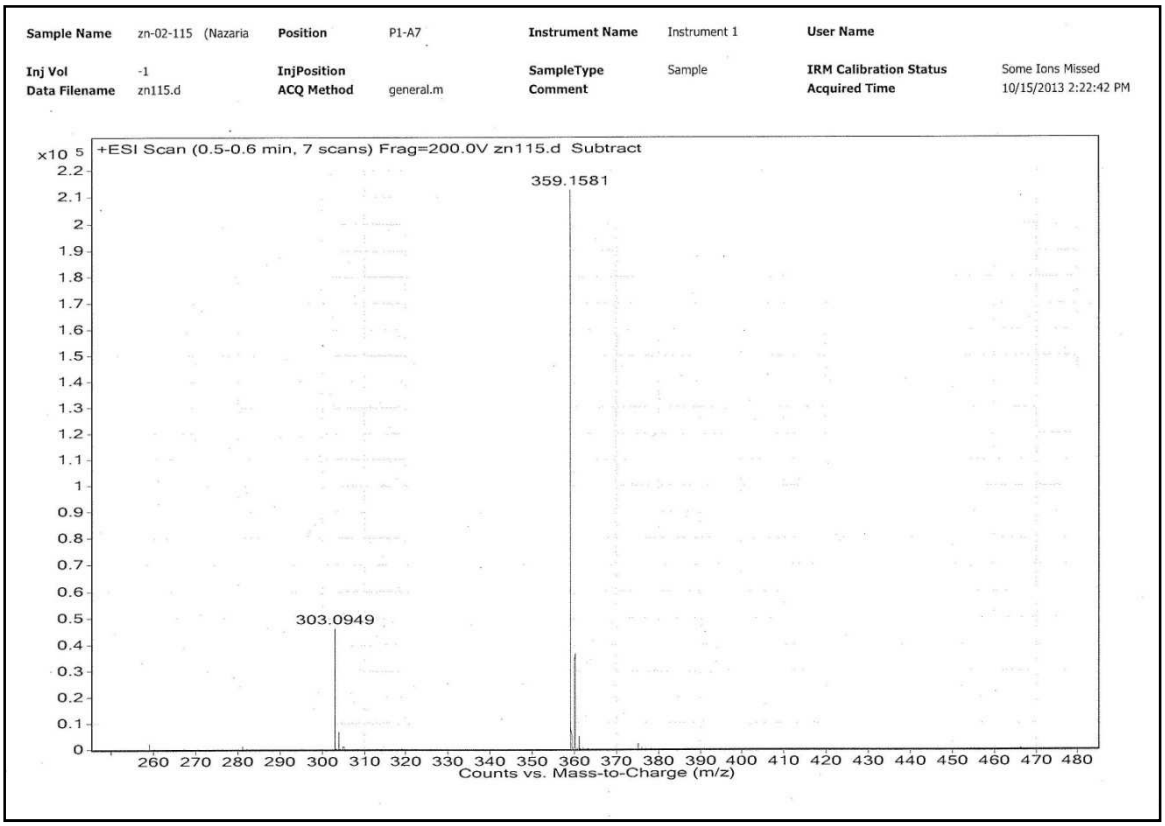
(*S*)-1-(Benzylamino)-1-oxopropan-2-yl 2-((*tert*-butoxycarbonyl)(methyl)amino) acetate (5f)



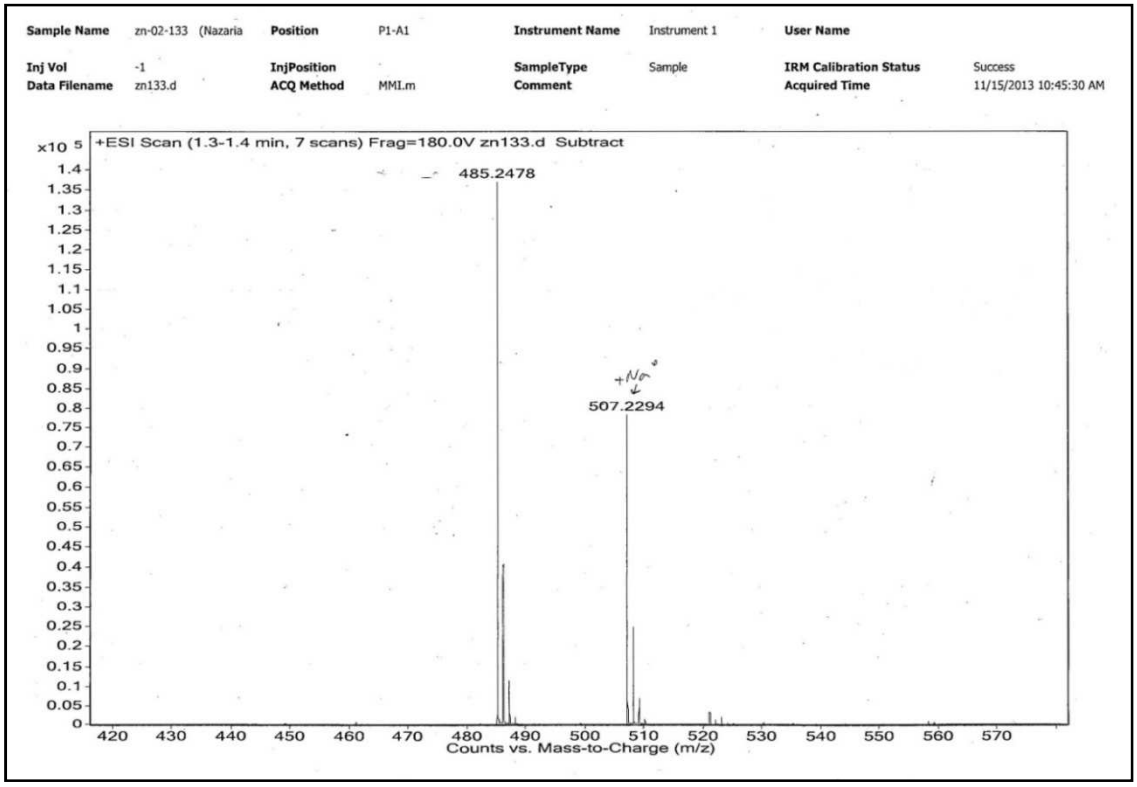
2-(Benzylamino)-2-oxoethyl 2-((*tert*-butoxycarbonyl)(methyl)amino) acetate (5g)



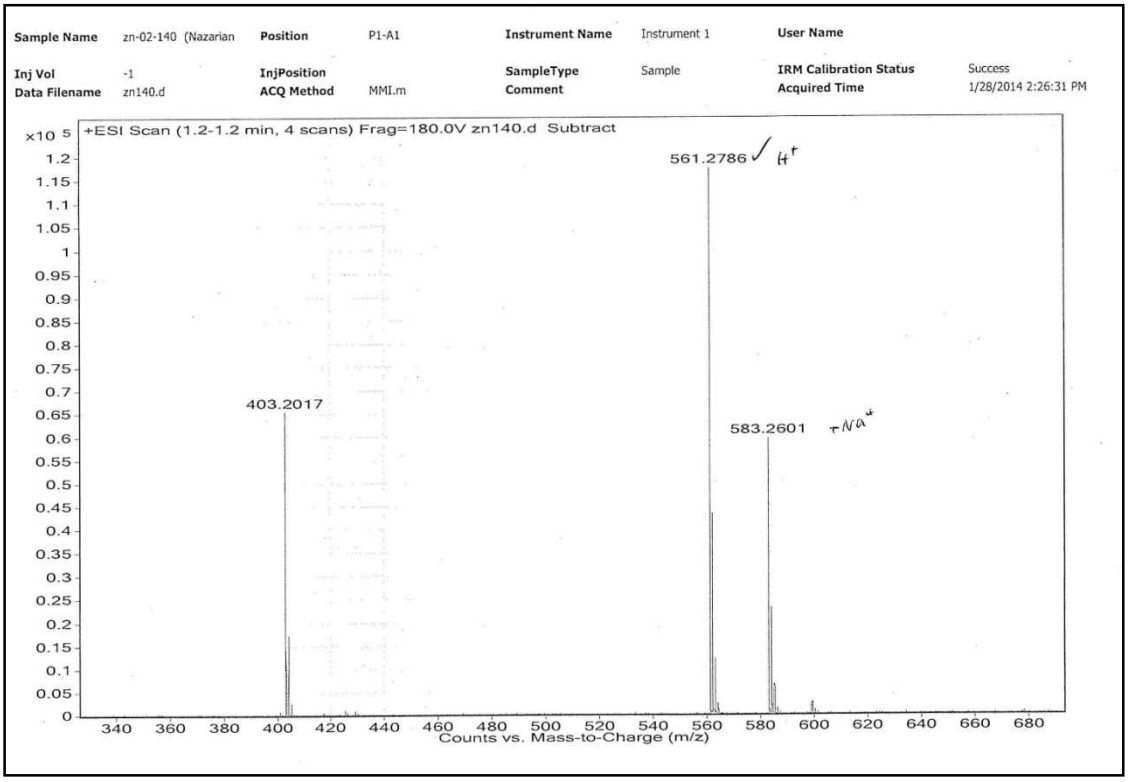
(*R*)-2-(Methylamino)-2-oxo-1-phenylethyl 2-((*tert*-butoxycarbonyl)(methyl) amino)acetate (5h)



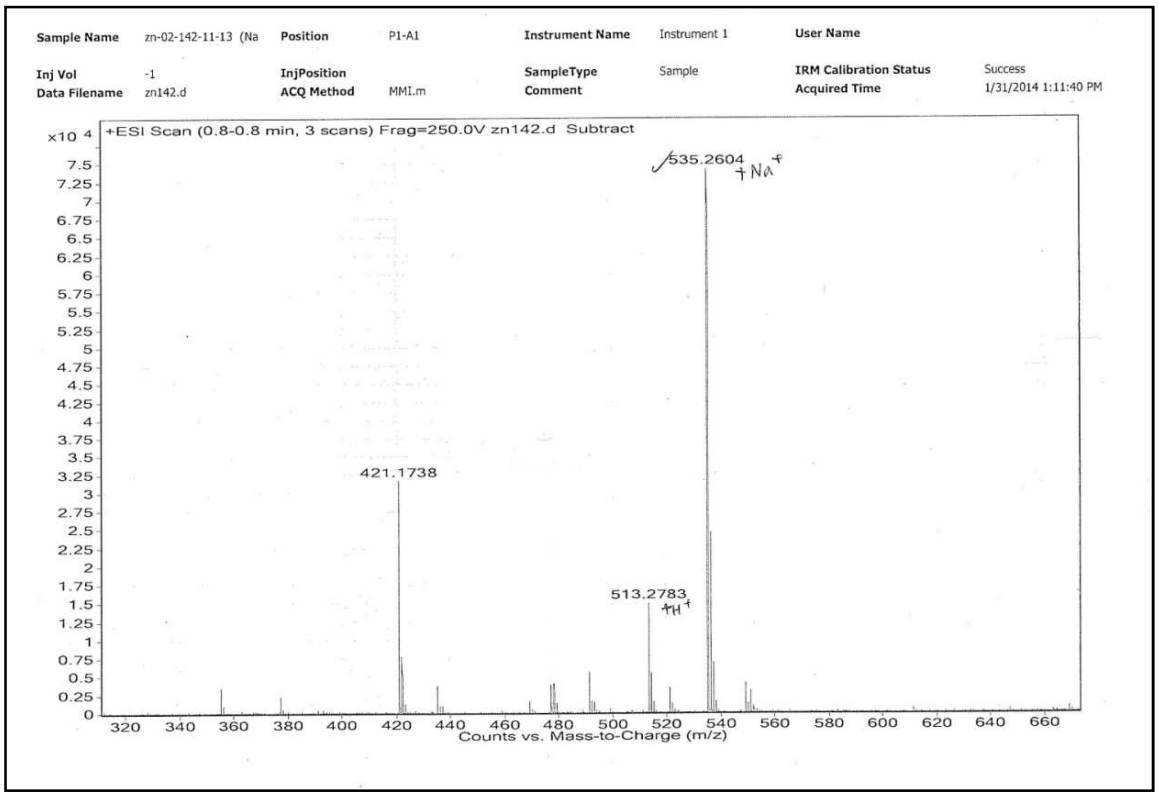
(*S*)-(*R*)-2-(benzylamino)-2-oxo-1-phenylethyl 2-((((*tert*-butyldimethylsilyl)oxy)carbonyl) (methyl)amino)propanoate (**6a**)



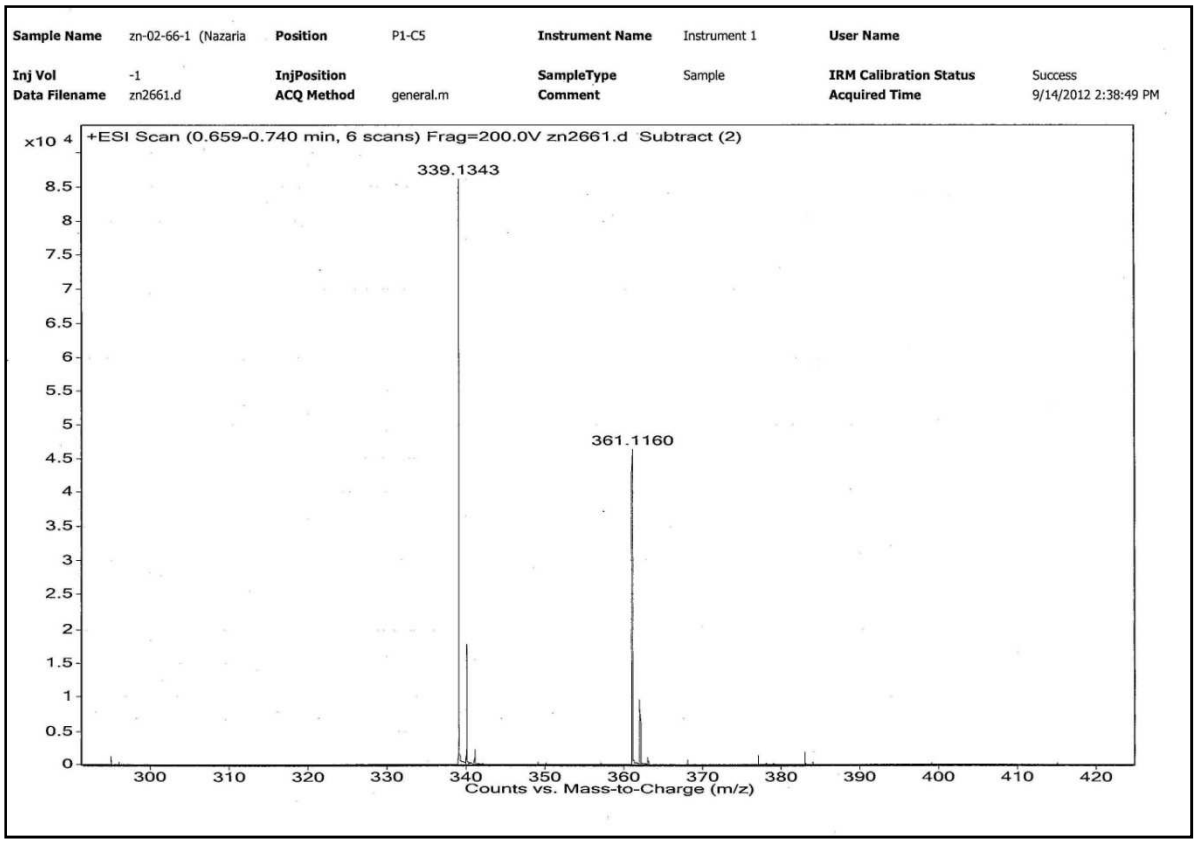
(*S*)-(*R*)-2-(benzylamino)-2-oxo-1-phenylethy 2-((((*tert*-butyldimethylsilyloxy)carbonyl) (methyl)amino)-3- methylbutanoate (**6b**)



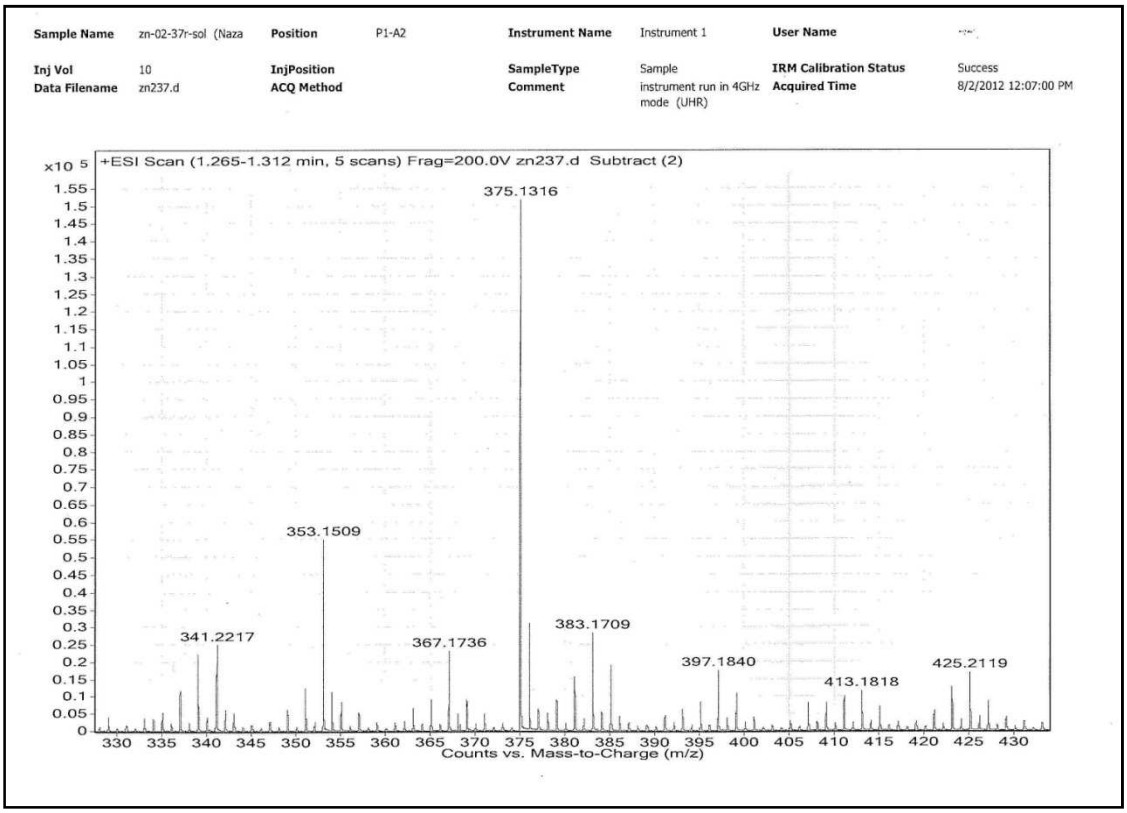
(*S*)-(*R*)-2-(benzylamino)-2-oxo-1-phenylethyl-2-((((*tert*-butyldimethylsilyl)oxy)carbonyl) (methyl)amino)-3-phenylpropanoate (6c)



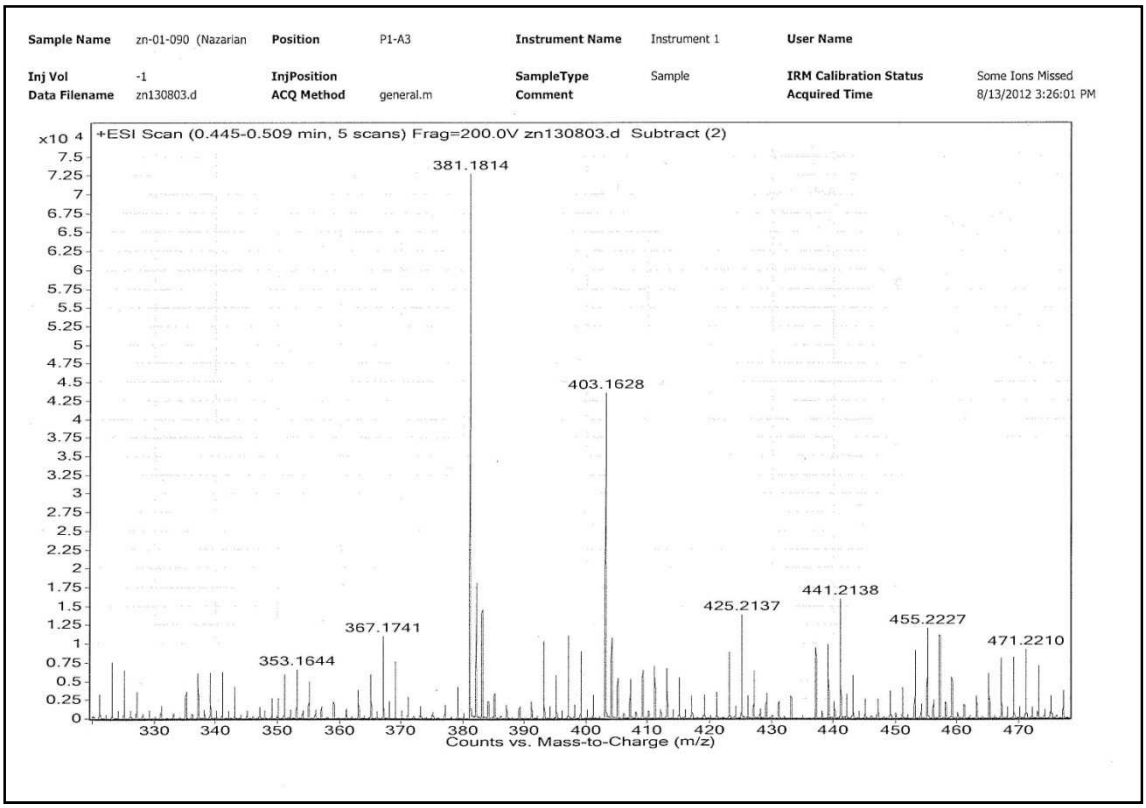
(5*R*,7*R*)-9-Benzyl-3-methyl-7-phenyl-1,6-dioxa-3,9-diazaspiro[4,4]nonane-2,8-dione (**7a**)



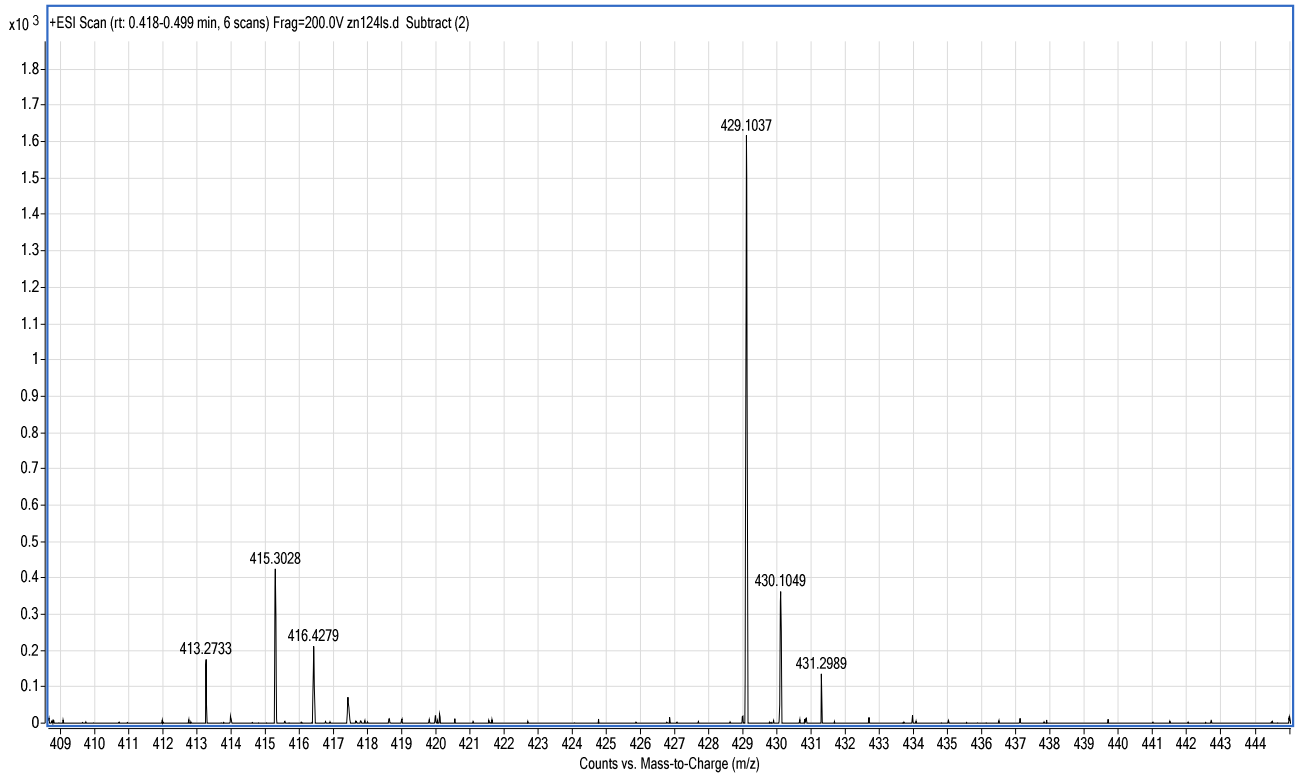
(4*S*,5*R*,7*R*)-9-Benzyl-3,4-dimethyl-7-phenyl-1,6-dioxa-3,9-diazaspiro[4,4] nonane-2,8-dione (7b)



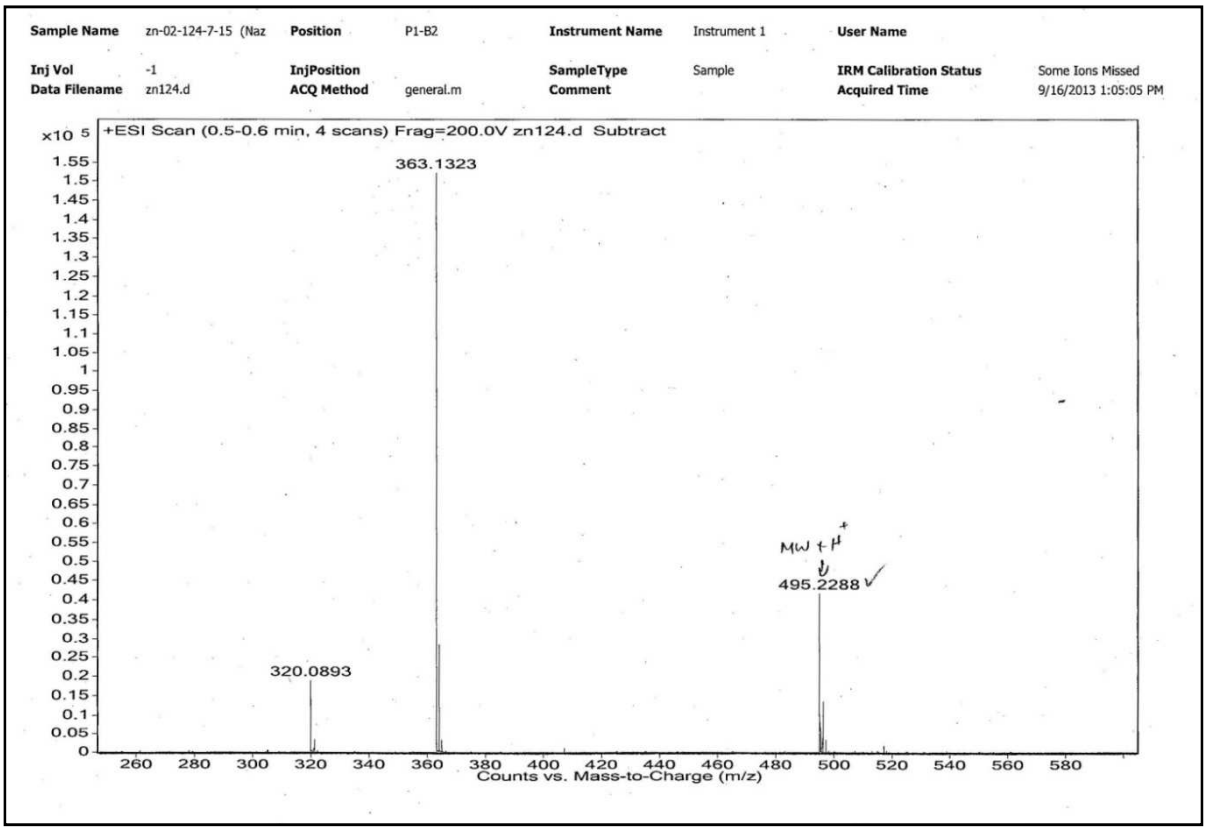
(4*S*,5*R*,7*R*)-9-Benzyl-4-isopropyl-3-methyl-7-phenyl-1,6-dioxa-3,9-diazaspiro[4,4]nonane-2,8-dione (**7c**)



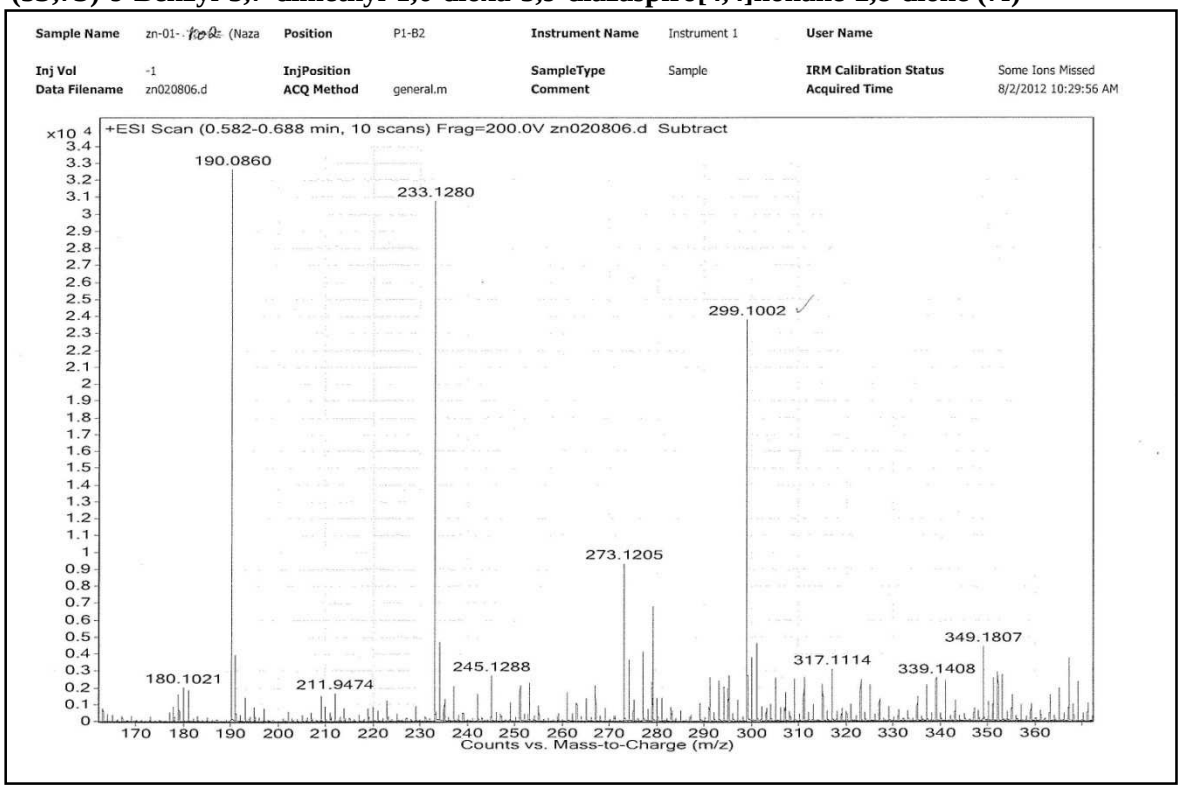
(5*R*,7*R*)-9-Benzyl-3-methyl-7-(4-(trifluoromethyl)phenyl)-1,6-dioxa-3,9diazaspiro[4,4]nonane-2,8-dione (7e)



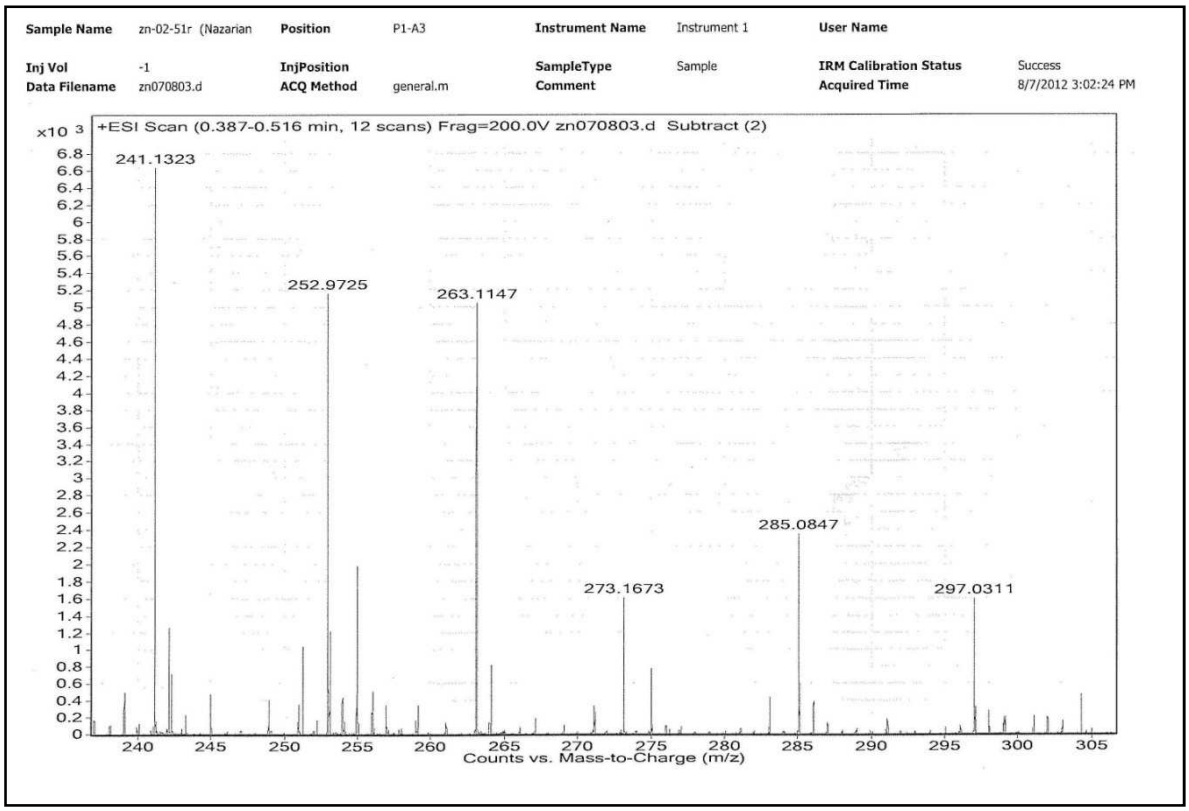
(5*R*,7*R*)-3-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-2-((methylamino)methyl)-5-(4-(trifluoromethyl) phenyl) oxazolidin-4-one (9e)



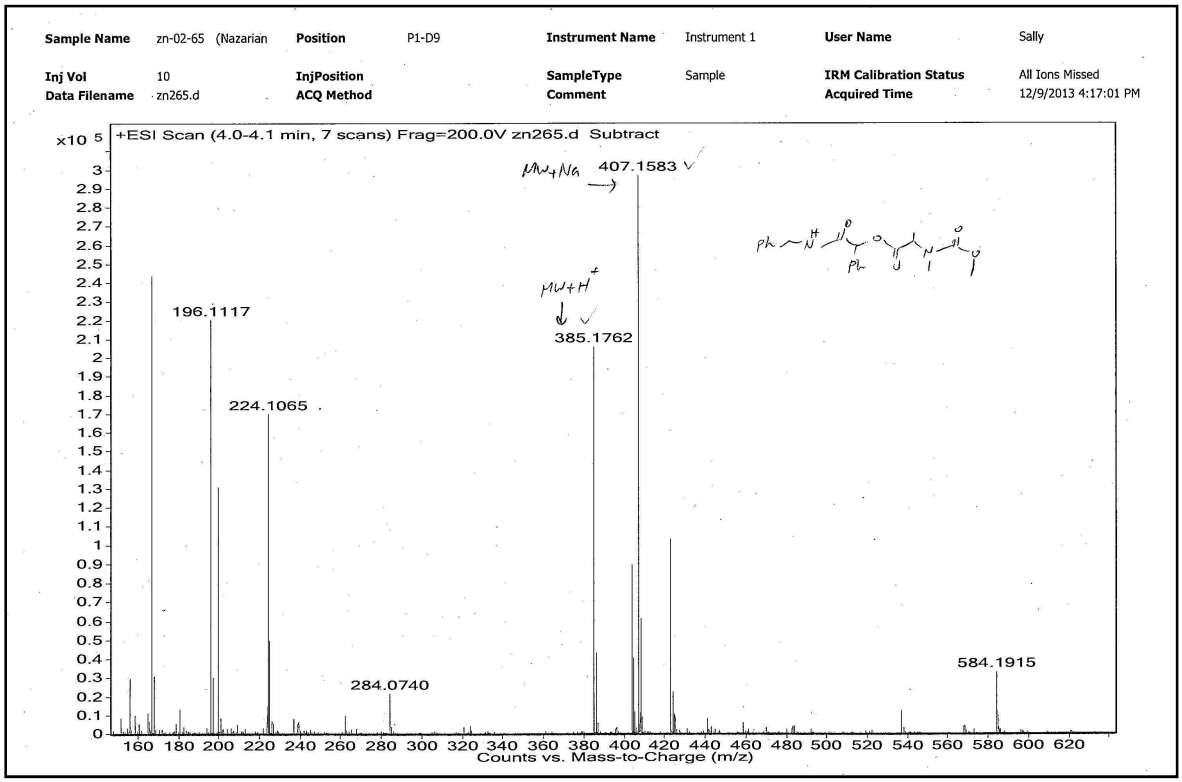
(5*S*,7*S*)-9-Benzyl-3,7-dimethyl-1,6-dioxa-3,9-diazaspiro[4,4]nonane-2,8-dione (7f)



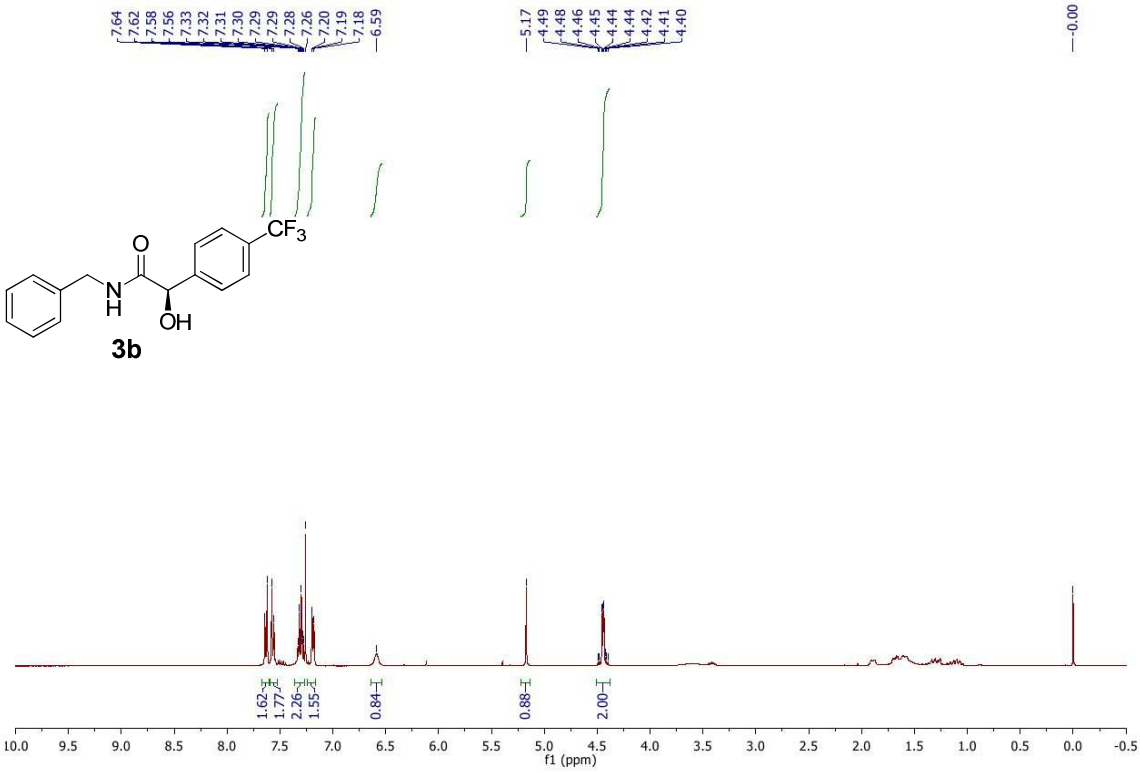
9-Benzyl-3-methyl-1,6-dioxa-3,9-diazaspiro[4,4]nonane-2,8-dione (**7g**)



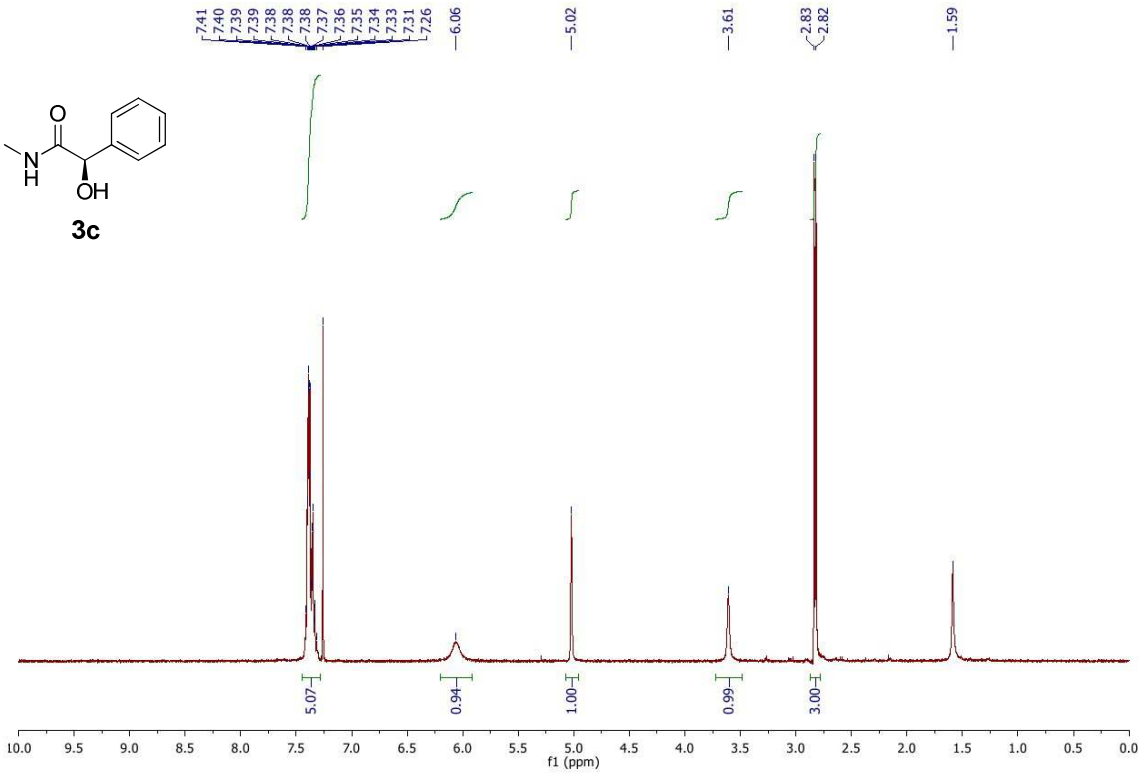
(*R*)-2-(Benzylamino)-2-oxo-1-phenylethyl 2-((methoxy carbonyl) (methyl)amino)propanoate (12)



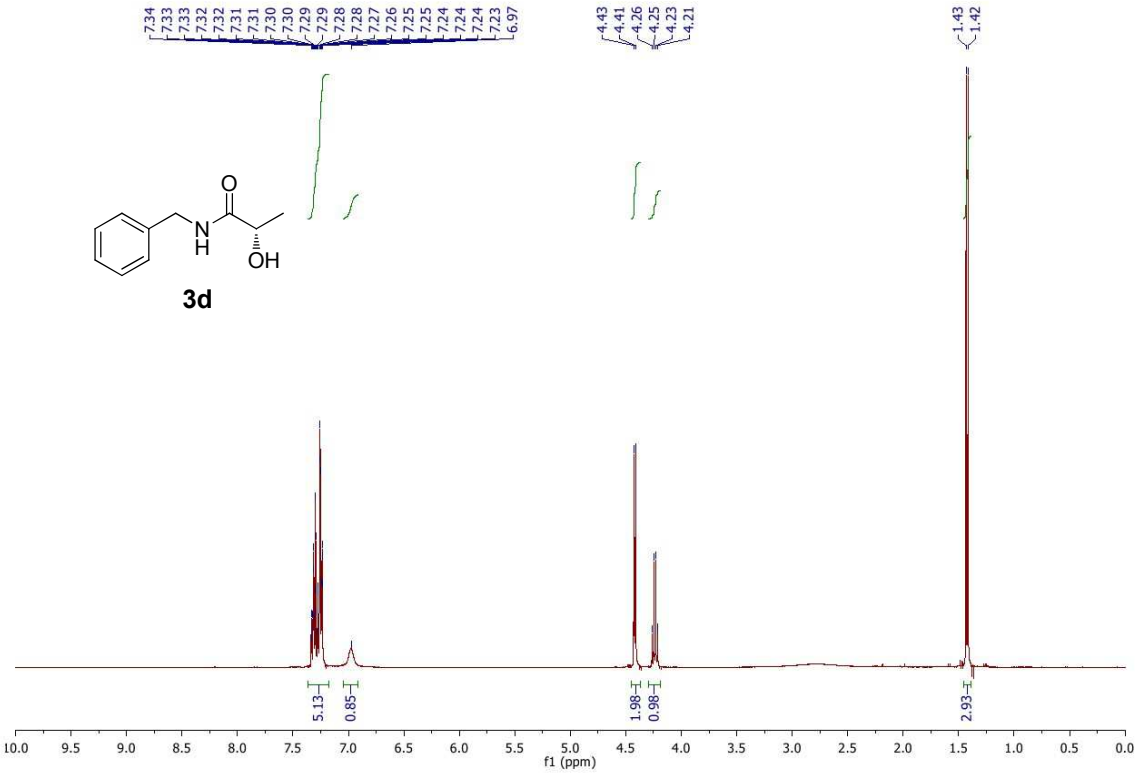
3b ^{1}H NMR/ $CDCl_3$/400 MHz



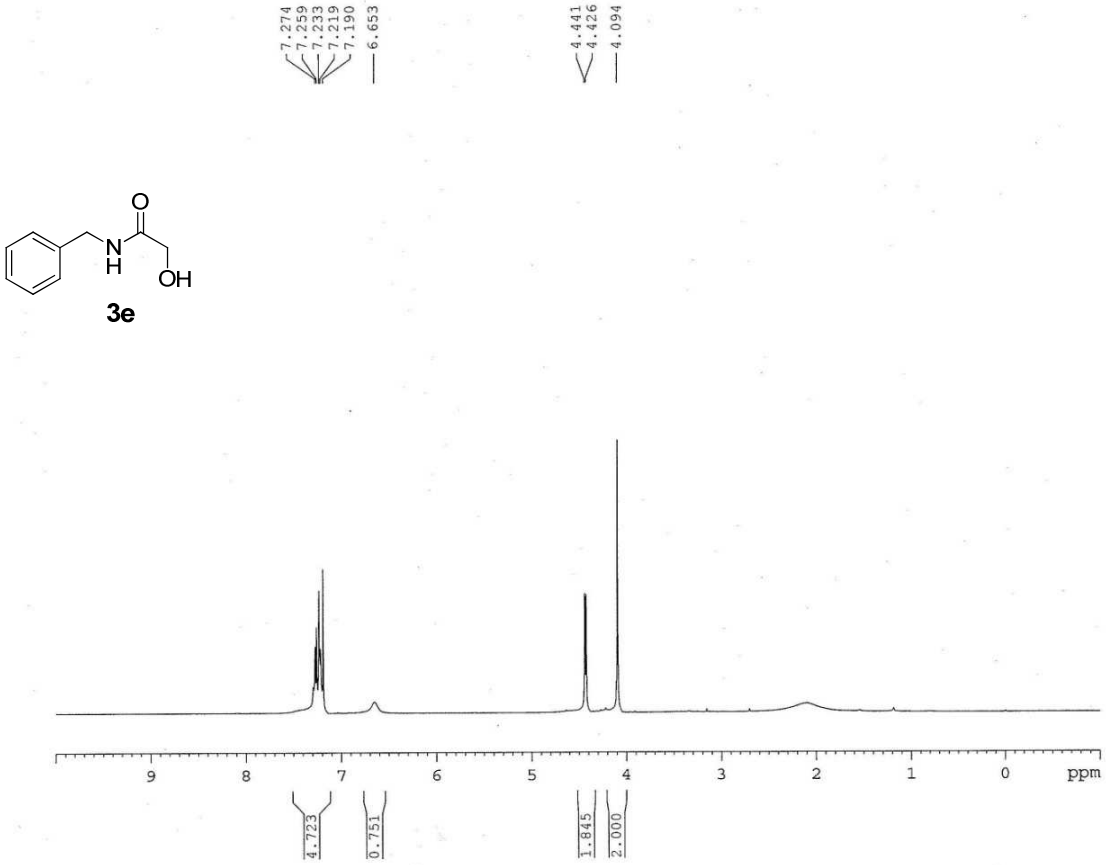
3c ^{1}H NMR/ $CDCl_3$/300 MHz



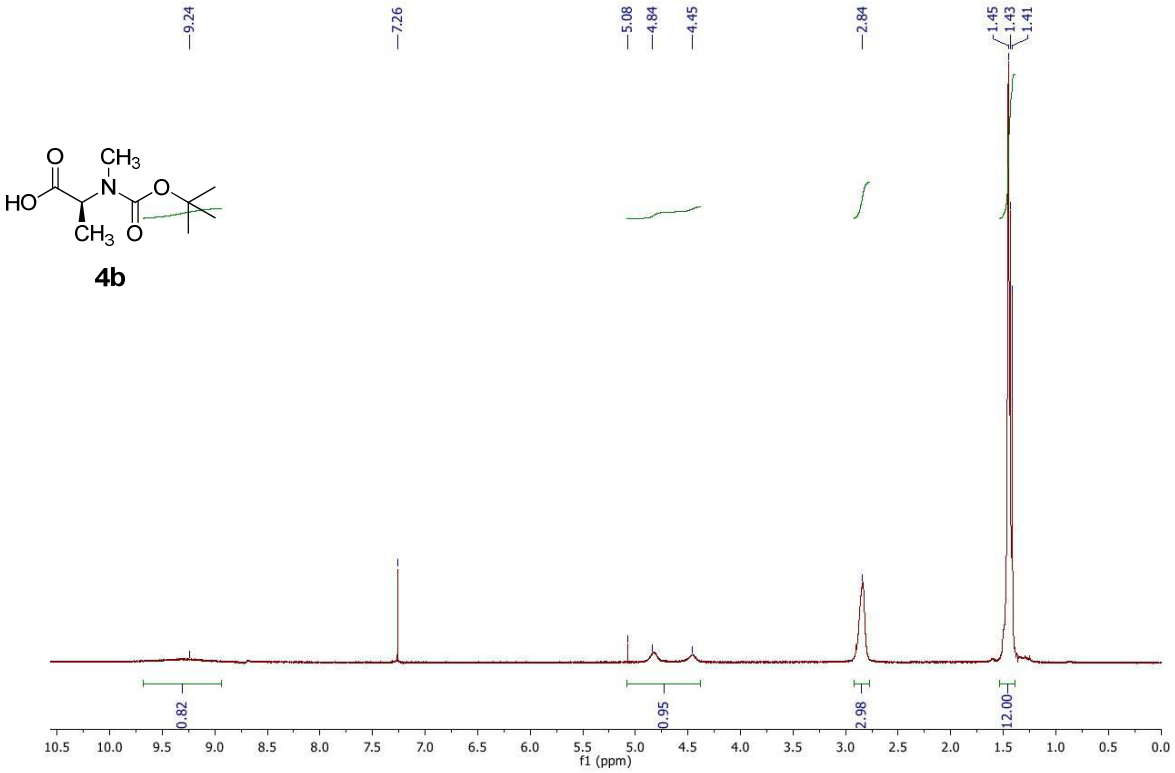
3d ^{1}H NMR/ $CDCl_3$/ 400 MHz



3e ^{1}H NMR/ $CDCl_3$/ 400 MHz

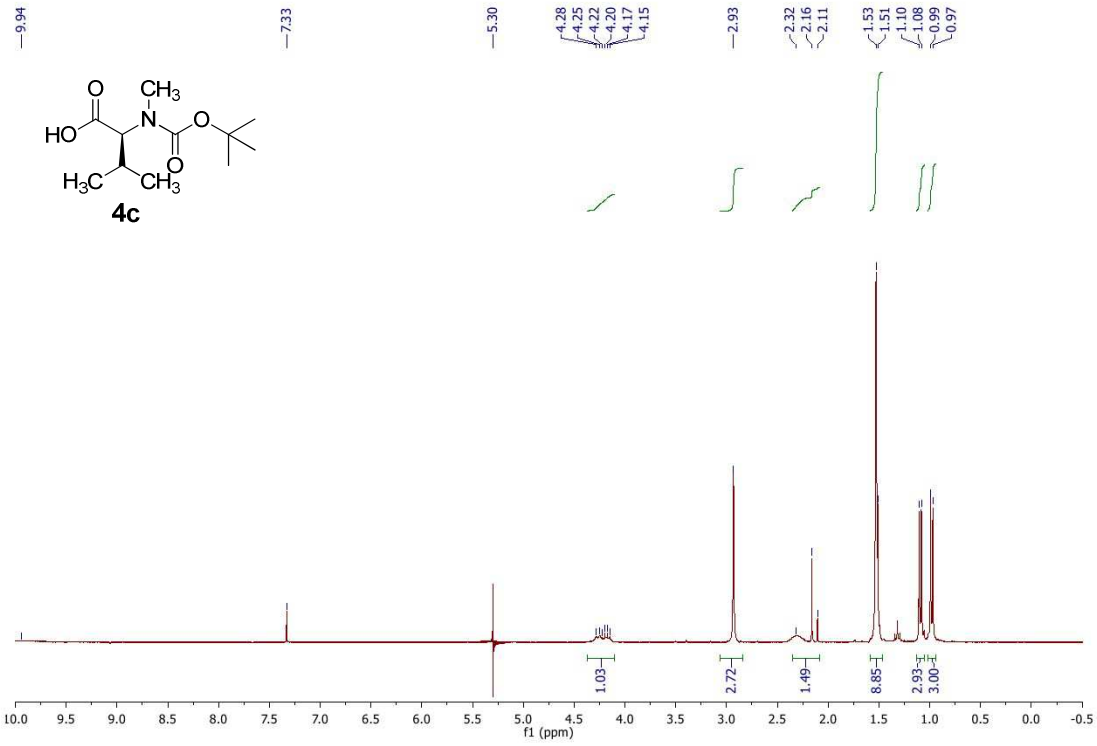


4b ^{1}H NMR/ $CDCl_3$/ 400 MHz



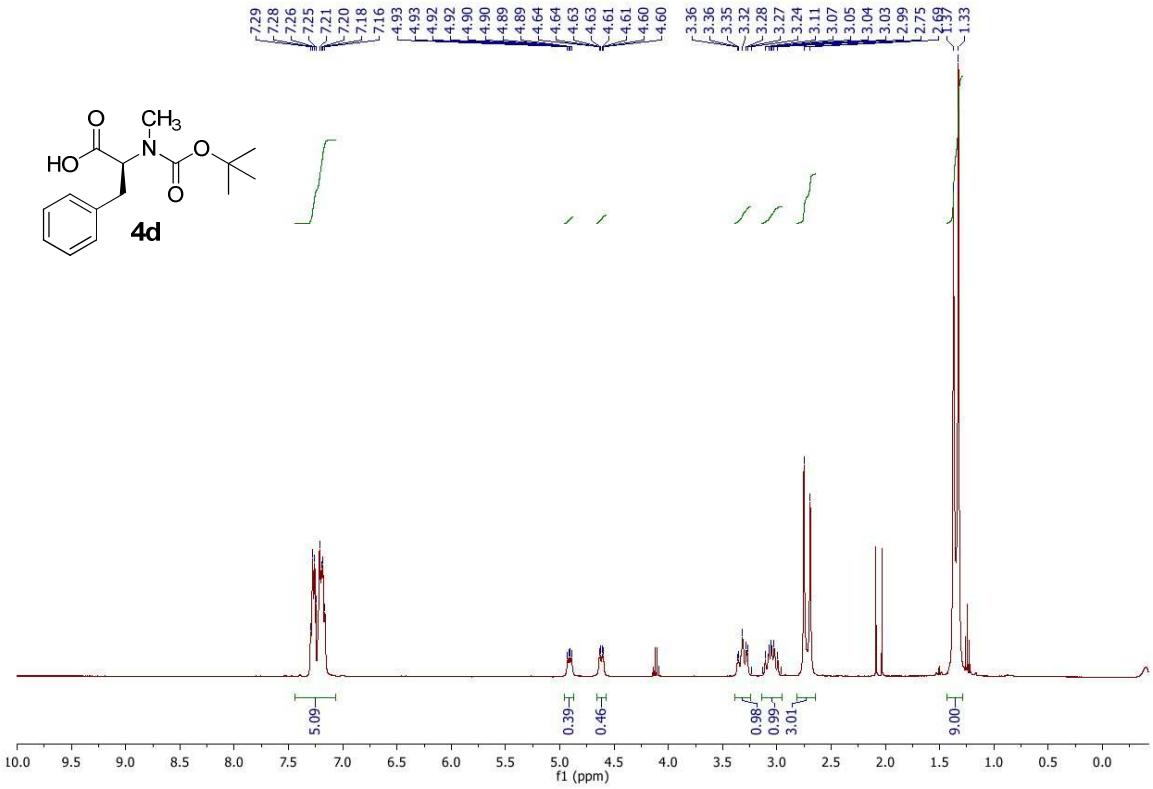
4b

4c ^{1}H NMR/ $CDCl_3$/300 MHz

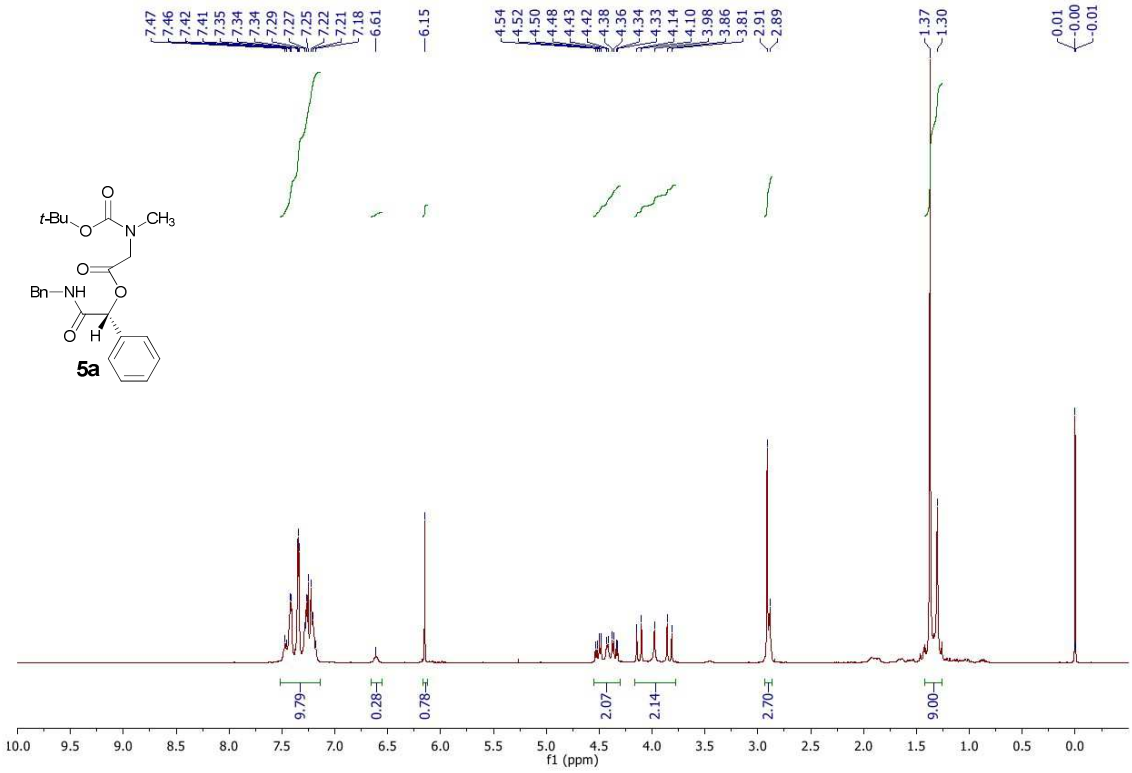


4c

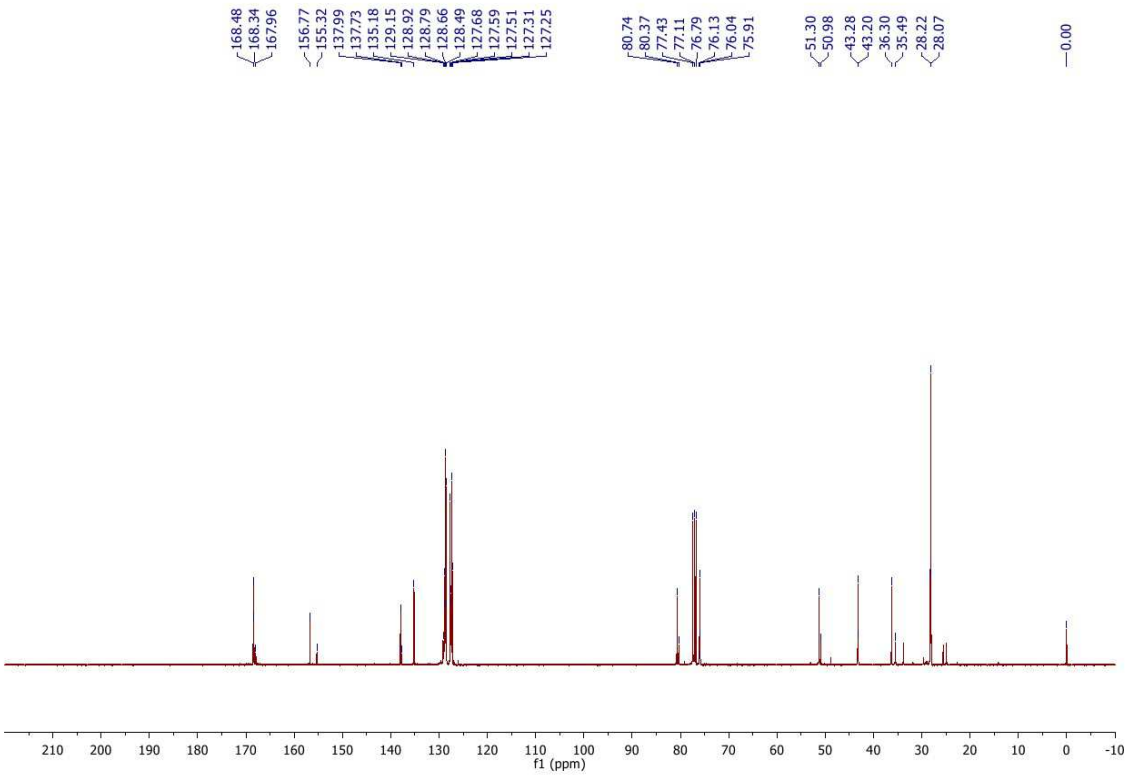
4d ^{1}H NMR/ $CDCl_3$/ 400 MHz



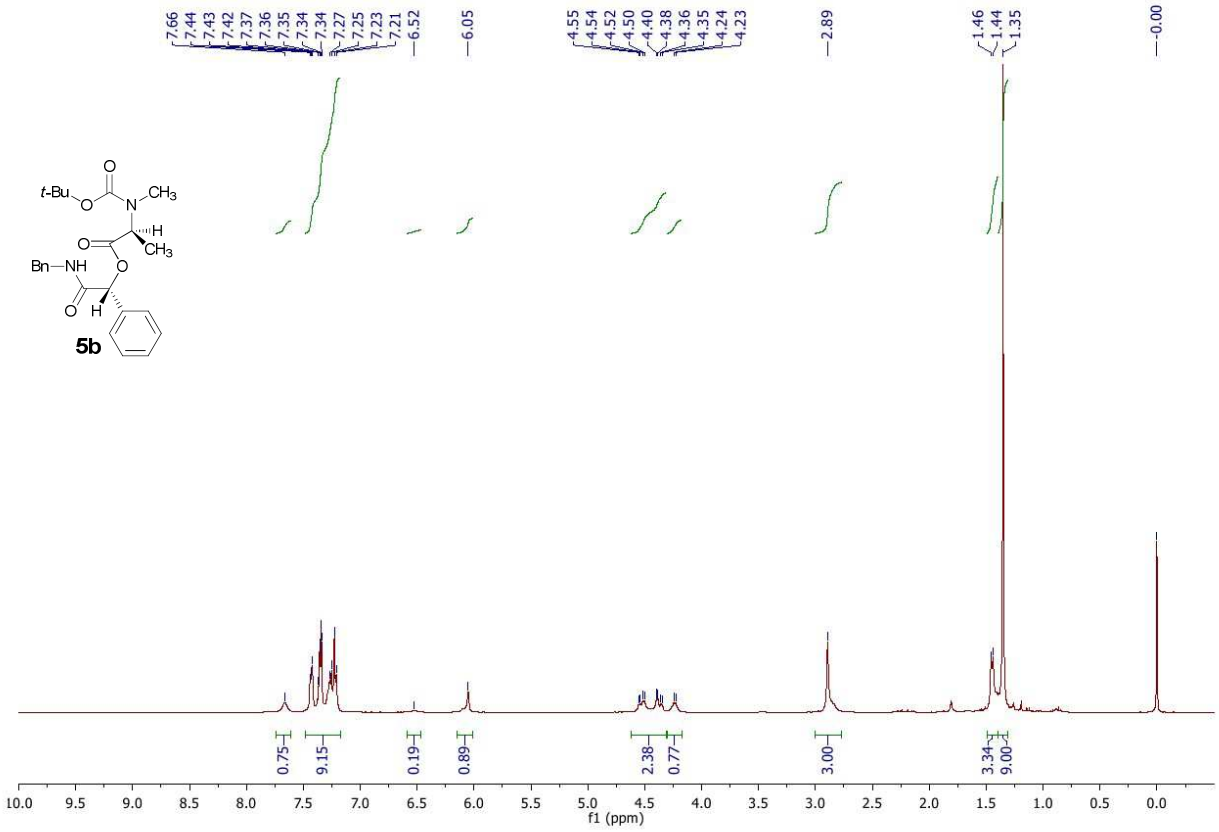
5a (*R*) ^{1}H NMR/ $CDCl_3$/ 400 MHz

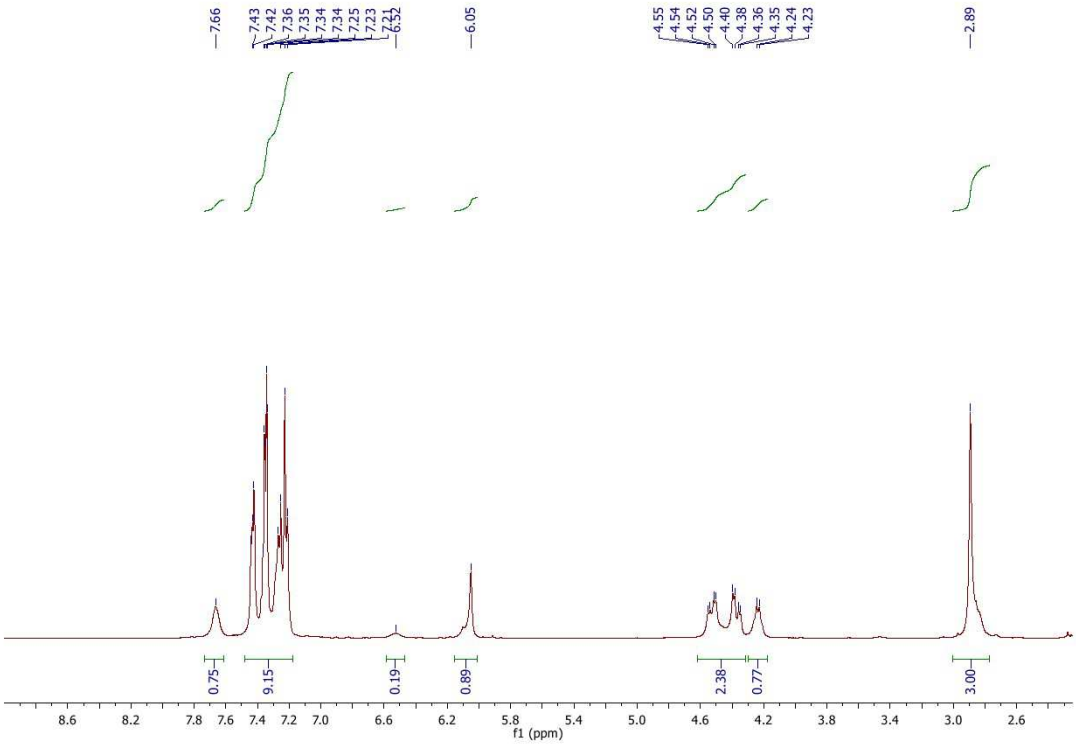


5a (*R*) ^{13}C NMR/ $CDCl_3$/ 101 MHz

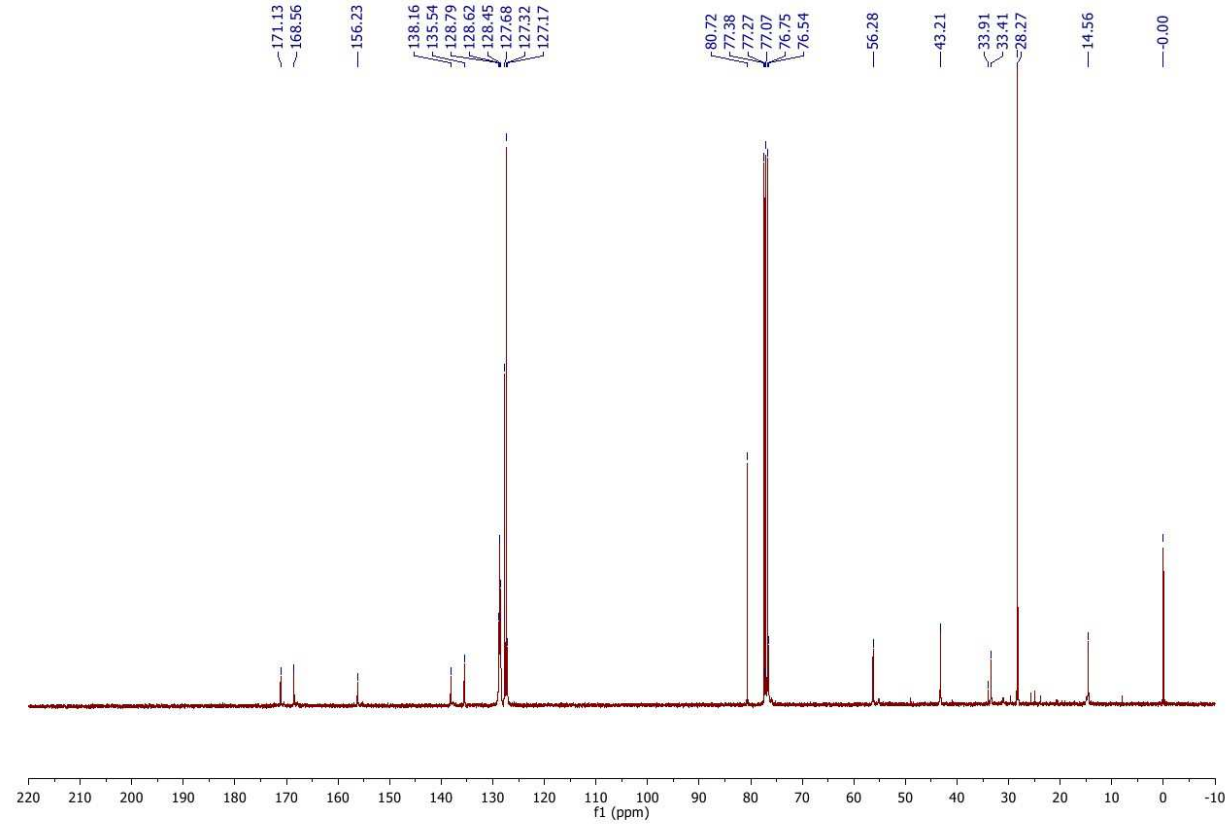


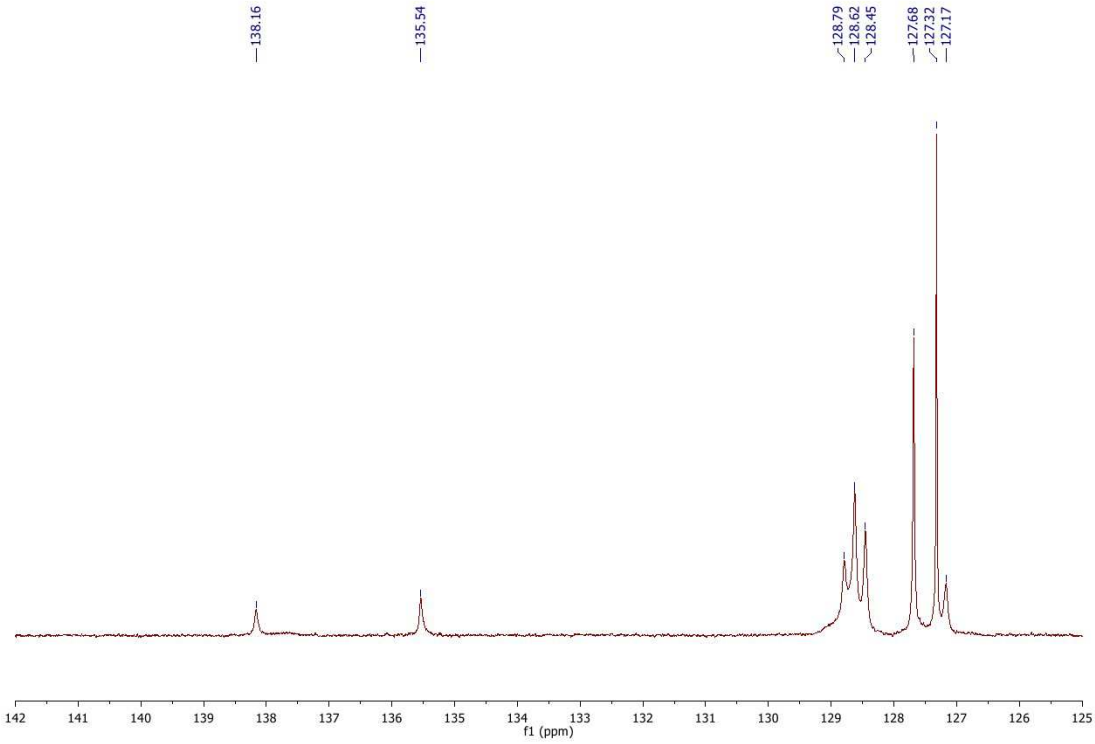
5b (*R*) ^{1}H NMR/ $CDCl_3$/ 400 MHz



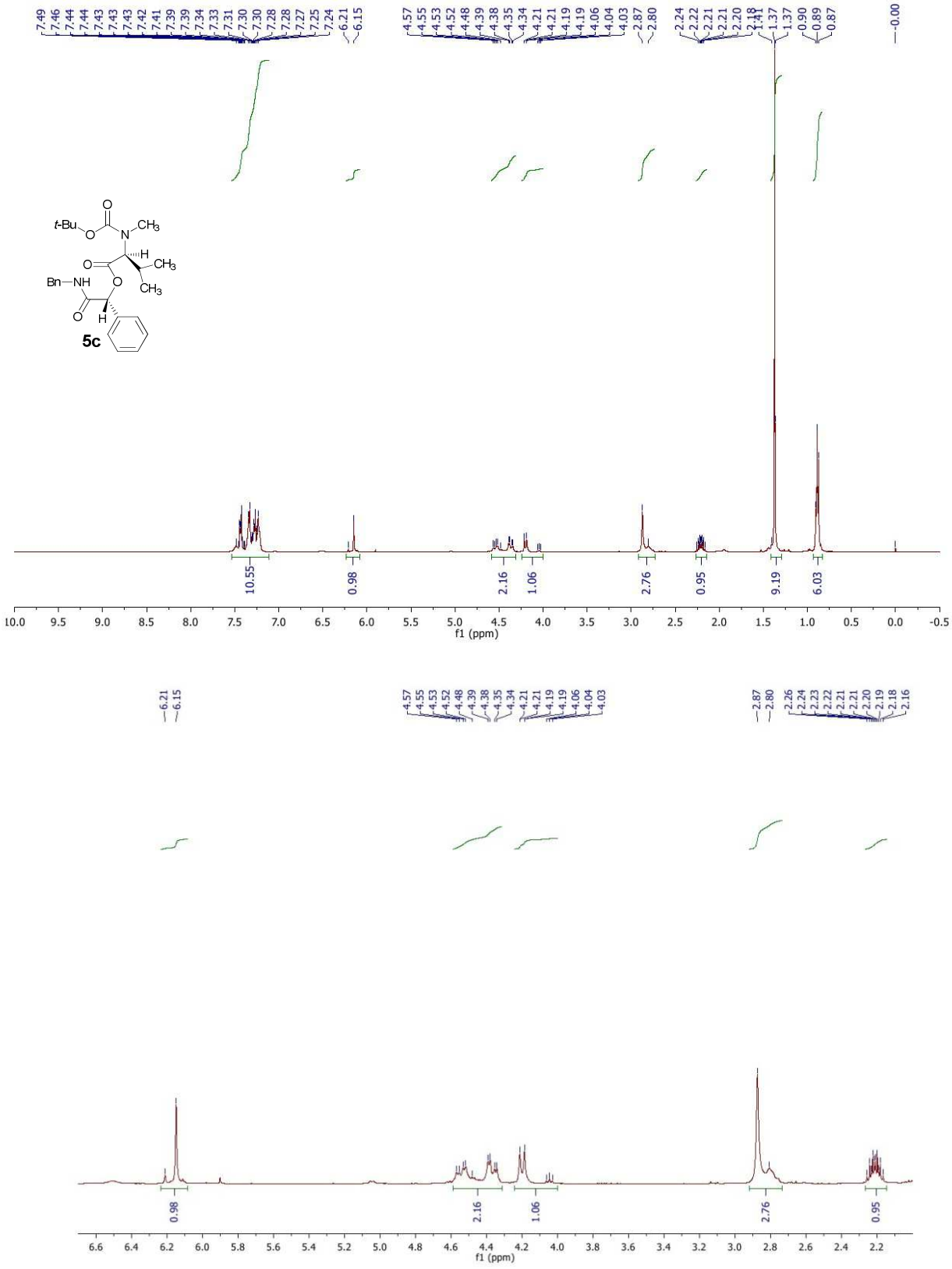


5b (*R*) ^{13}C NMR/ $CDCl_3$/ 101 MHz

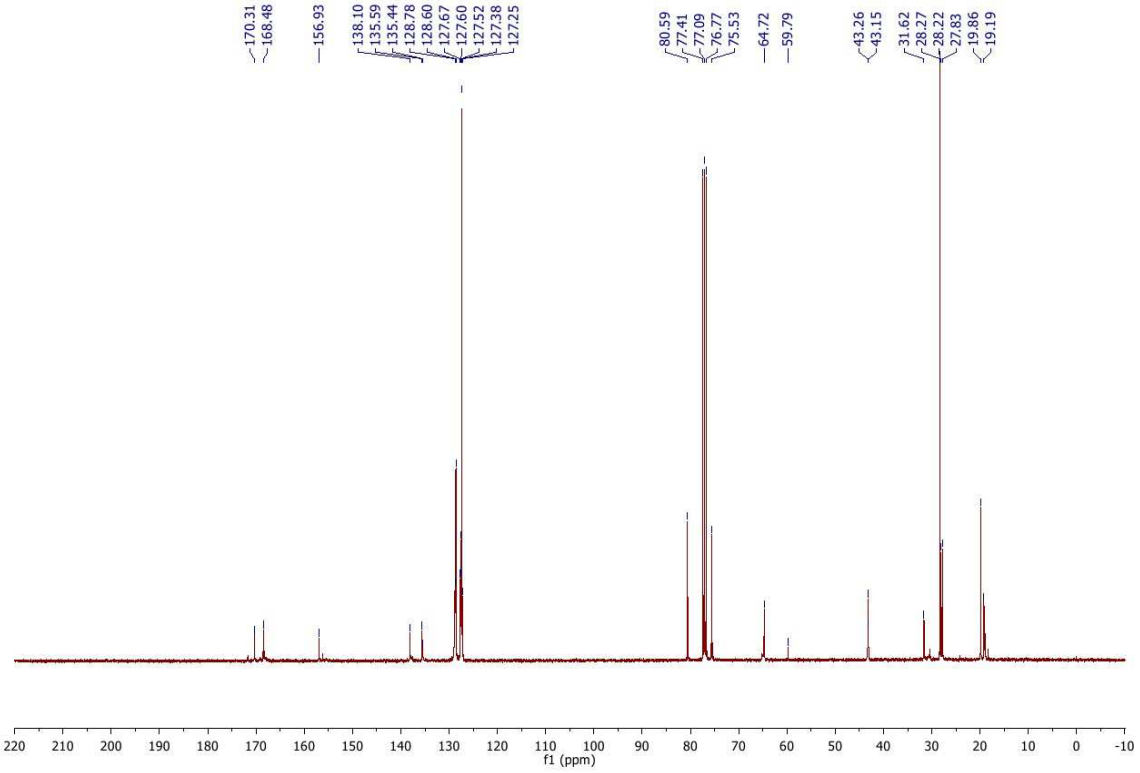


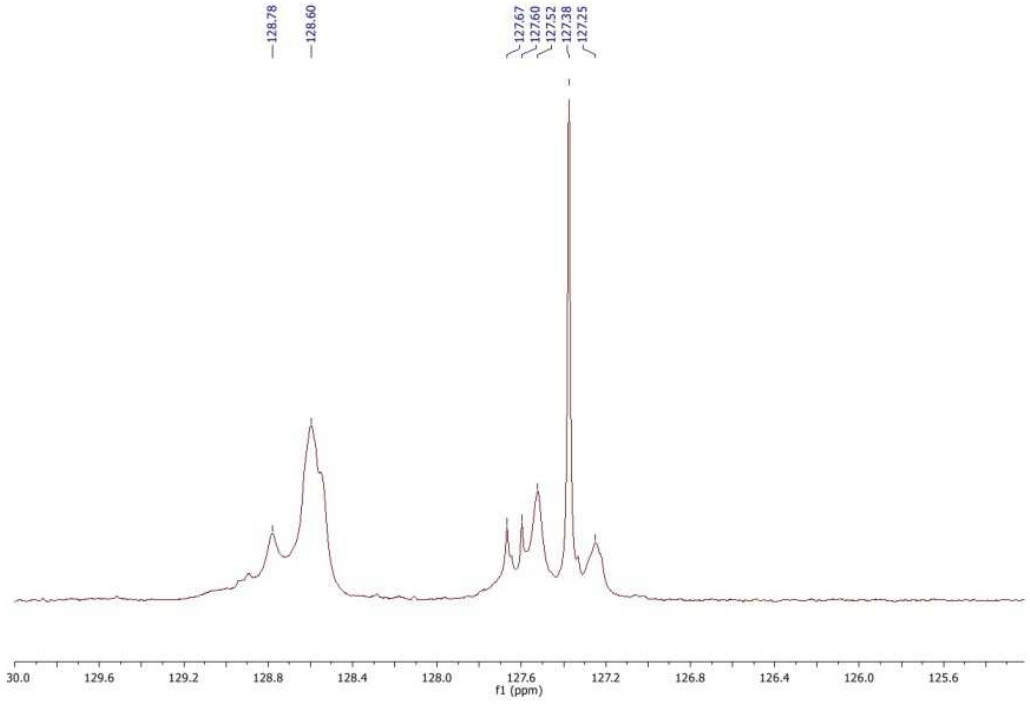


5c (*R*) ^{1}H NMR/ $CDCl_3$/ 400 MHz

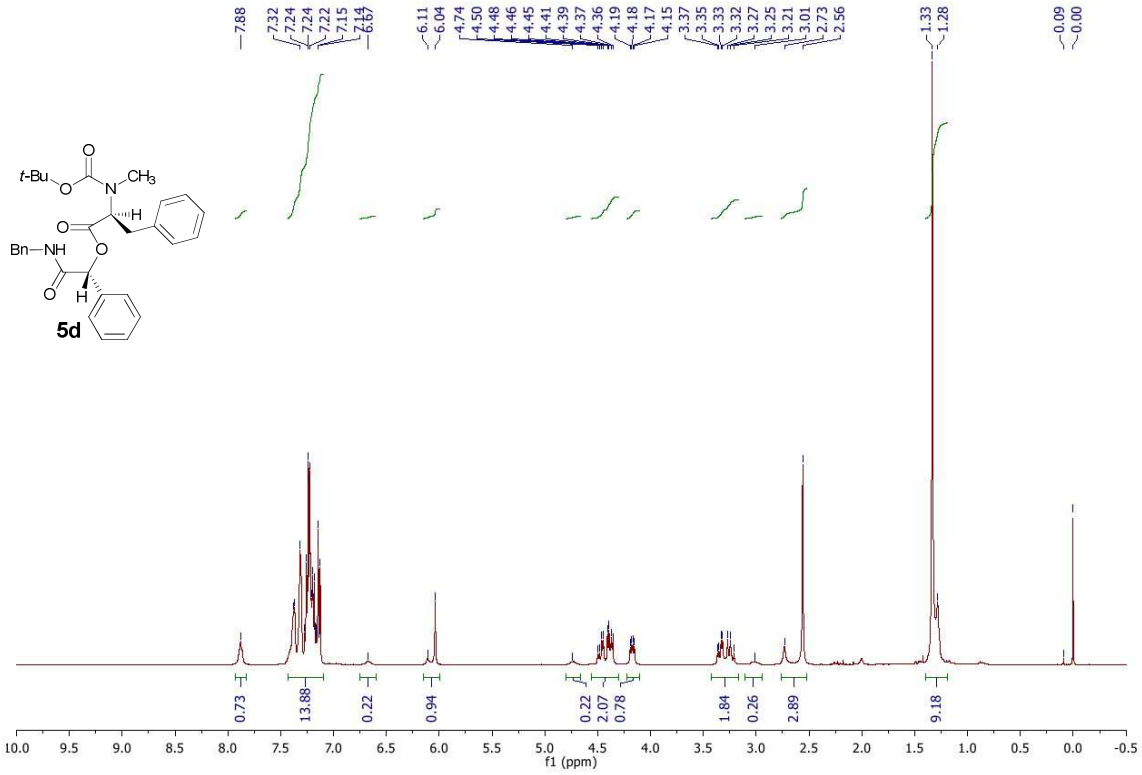


5c (*R*) ^{13}C NMR/ $CDCl_3$/ 101 MHz

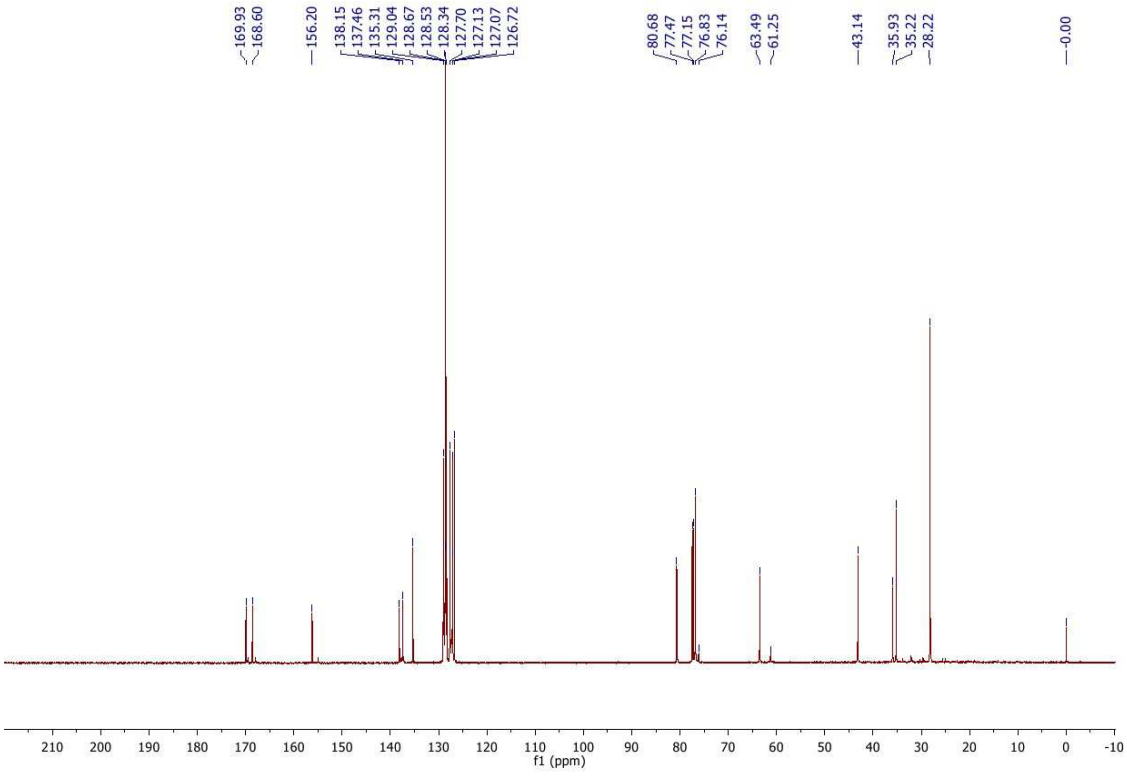




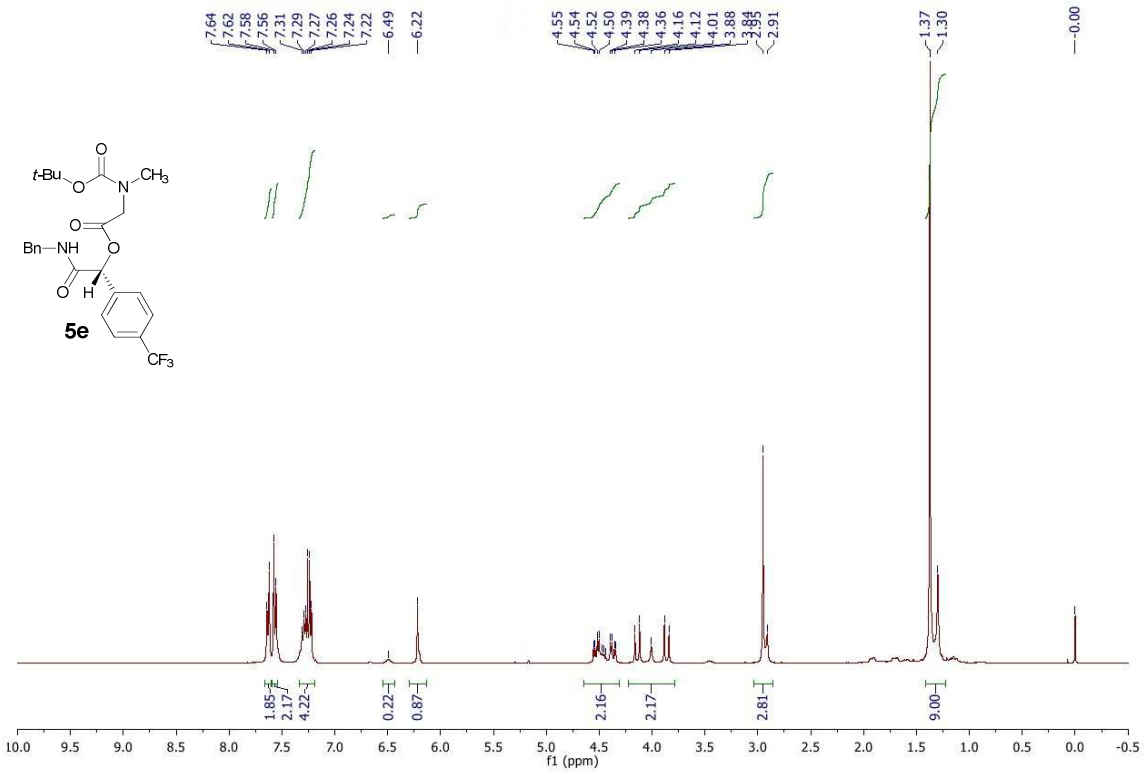
5d (*R*) ^{1}H NMR/ $CDCl_3$/ 400 MHz



5d (*R*) ^{13}C NMR/ $CDCl_3$/ 101 MHz

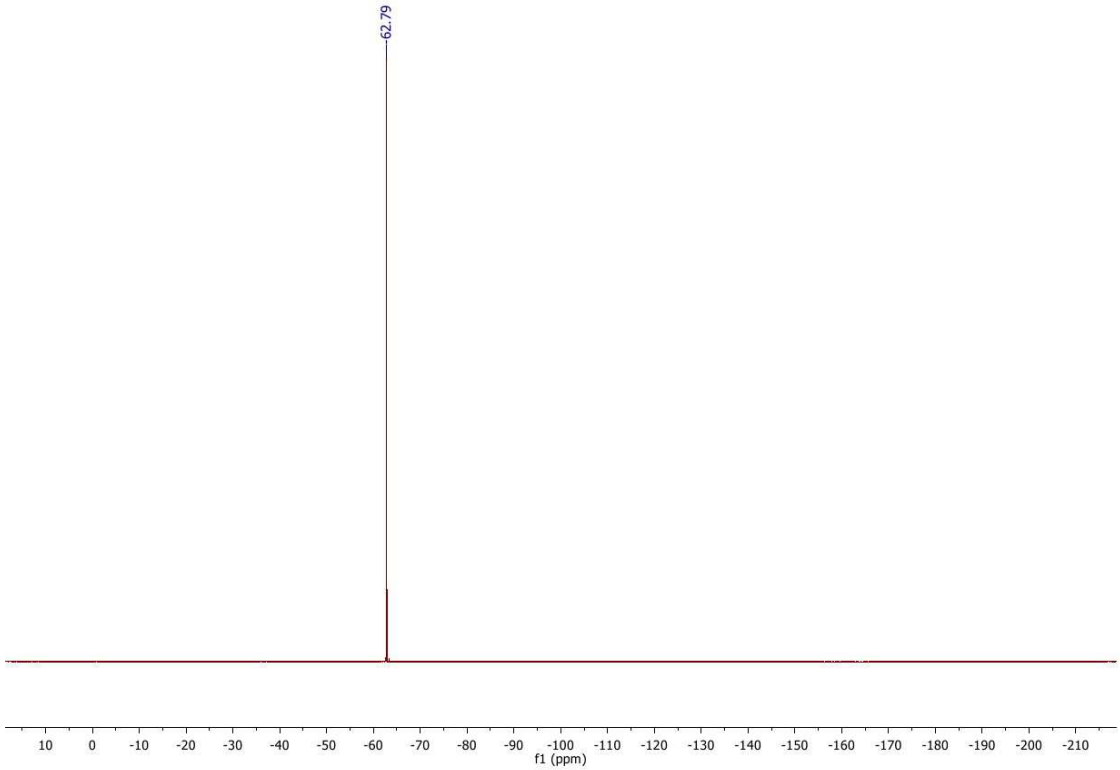


5e (*R*) ^{1}H NMR/ $CDCl_3$/ 400 MHz

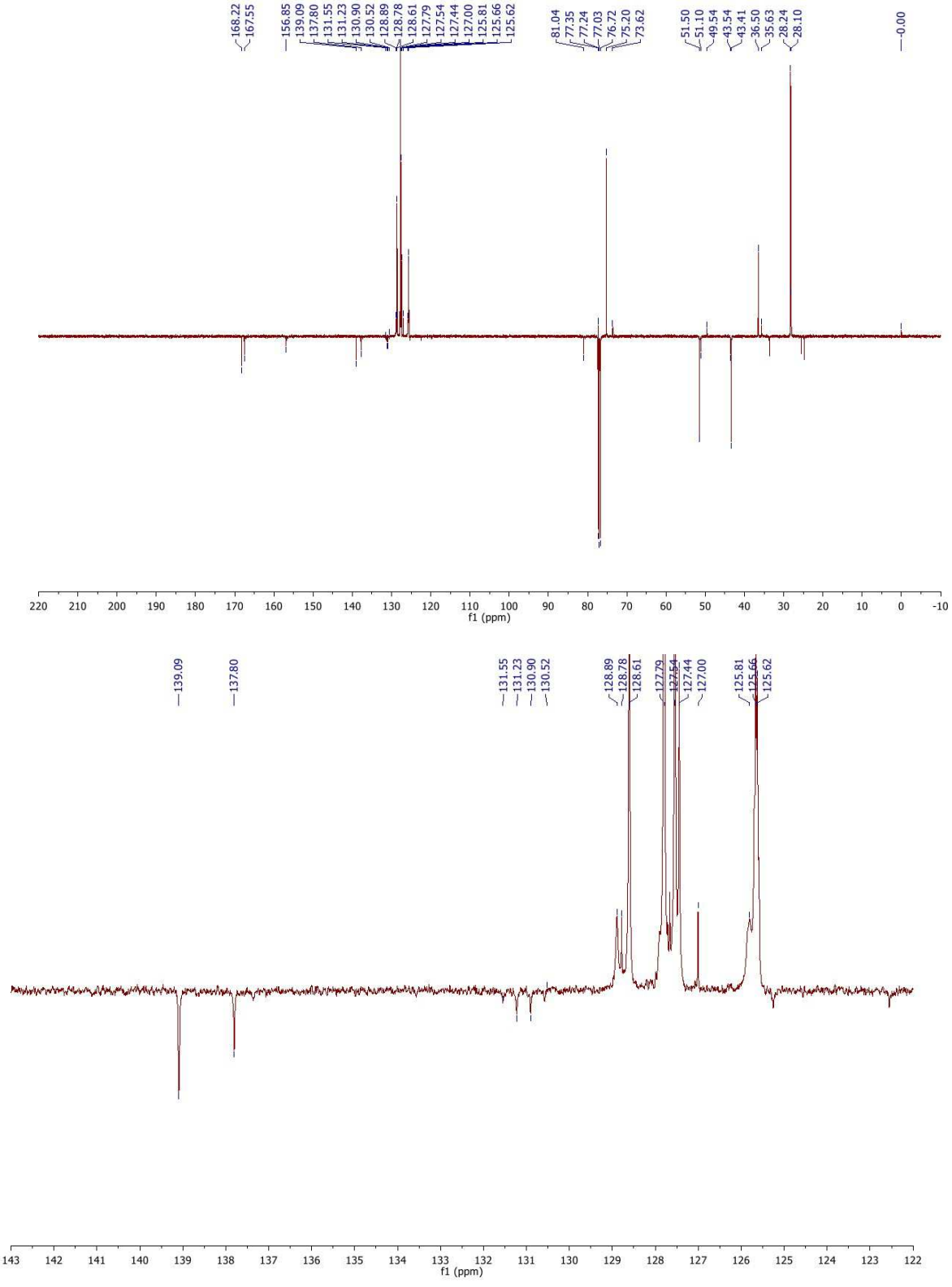


(suppressed DCM peak)

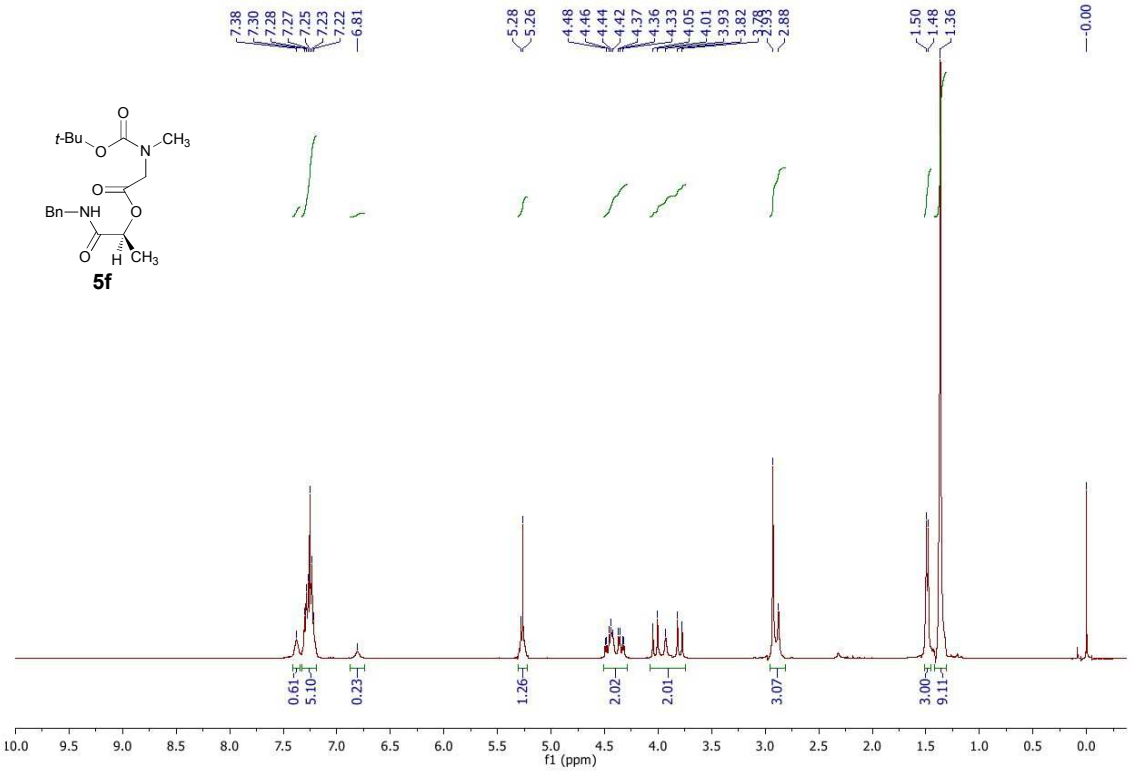
5e (*R*) ^{19}F NMR/ $CDCl_3$/ 377 MHz



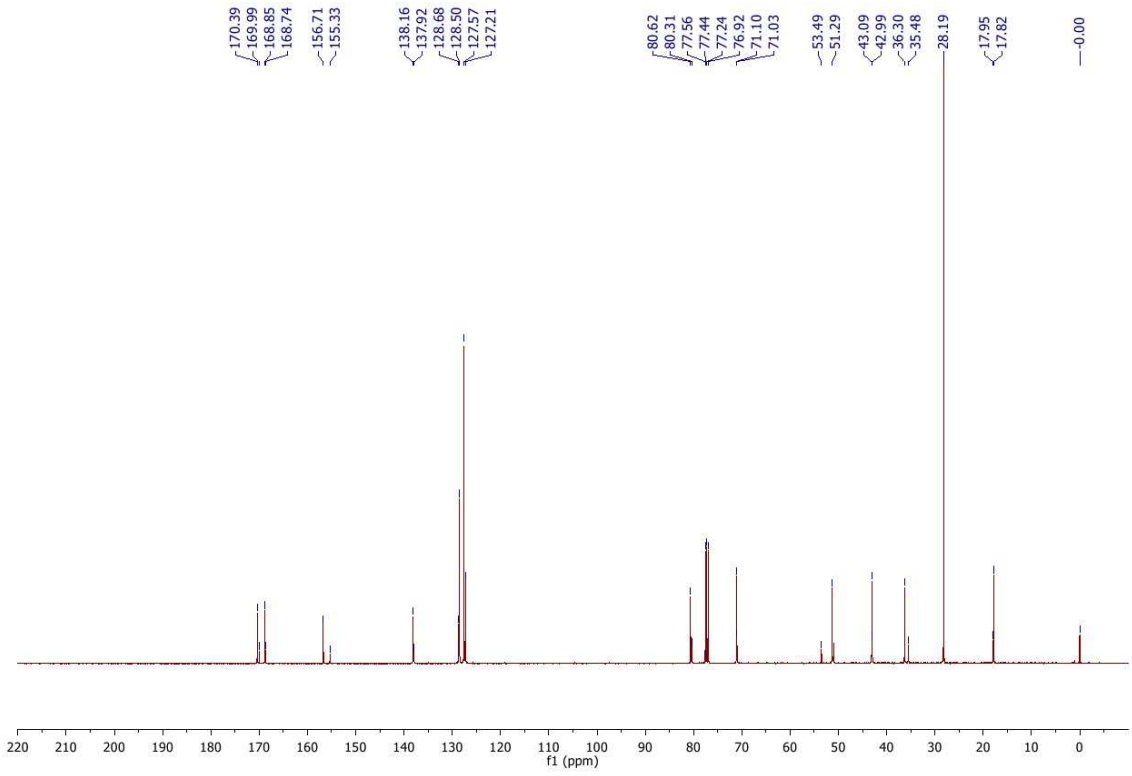
5e (*R*) ^{13}C NMR/ $CDCl_3$/ 101 MHz



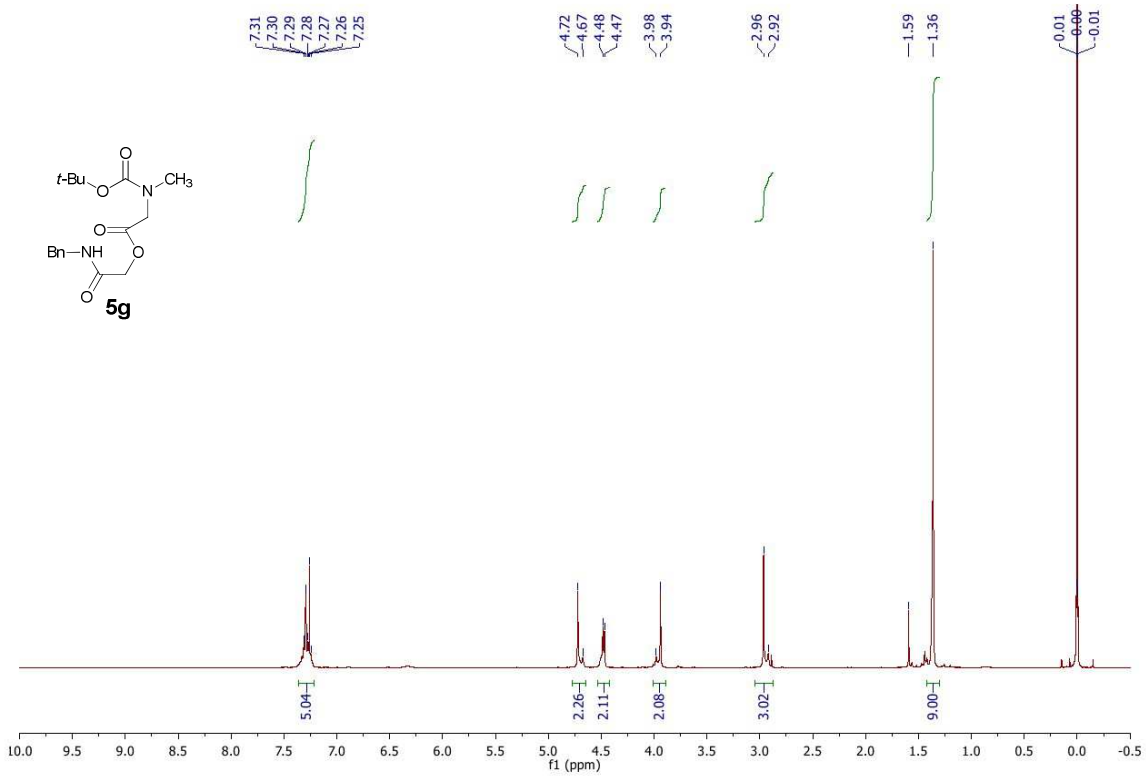
5f (*S*) ^{1}H NMR/ $CDCl_3$/ 400 MHz



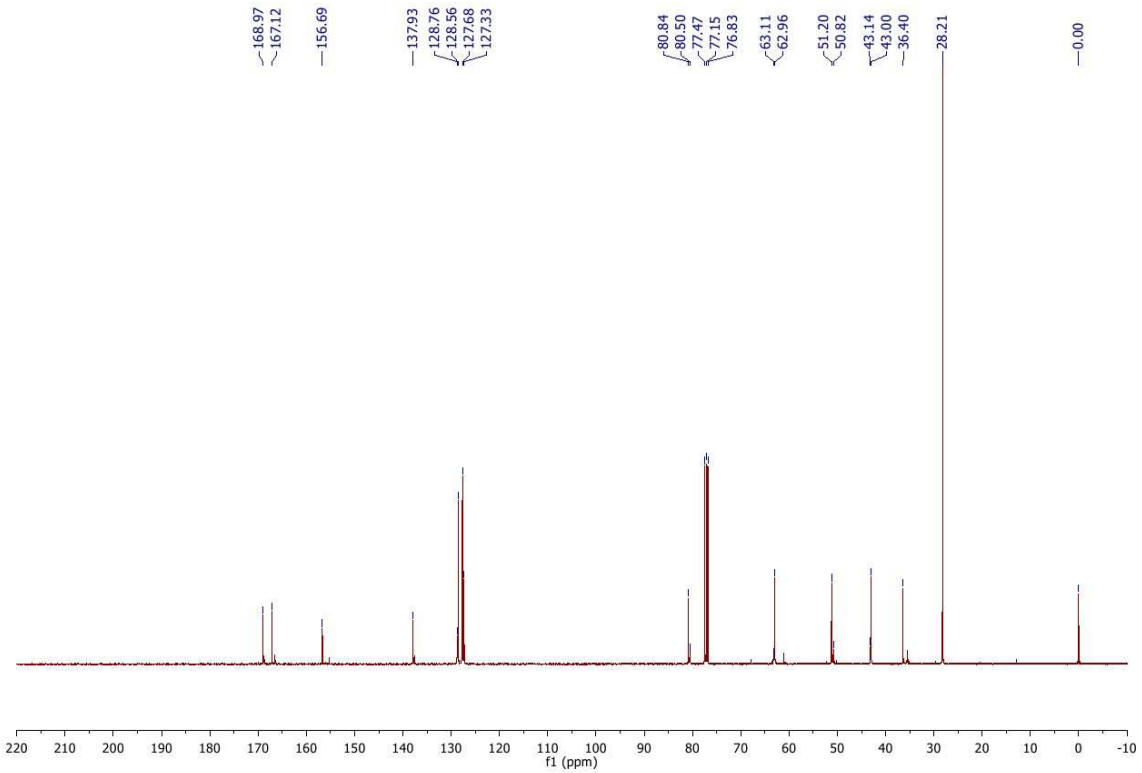
5f (*S*) ^{13}C NMR/$CDCl_3$/101 MHz



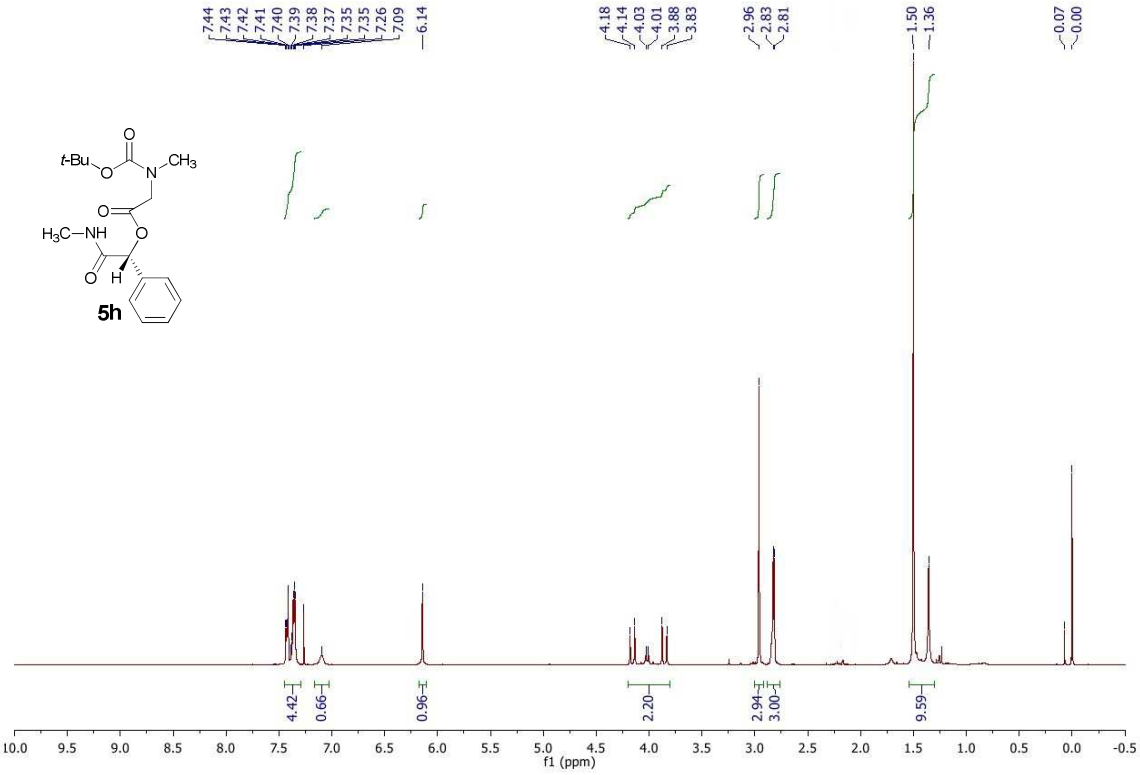
5g ^{1}H NMR/ $CDCl_3$/ 400 MHz



5g ^{13}C NMR/$CDCl_3$/101 MHz

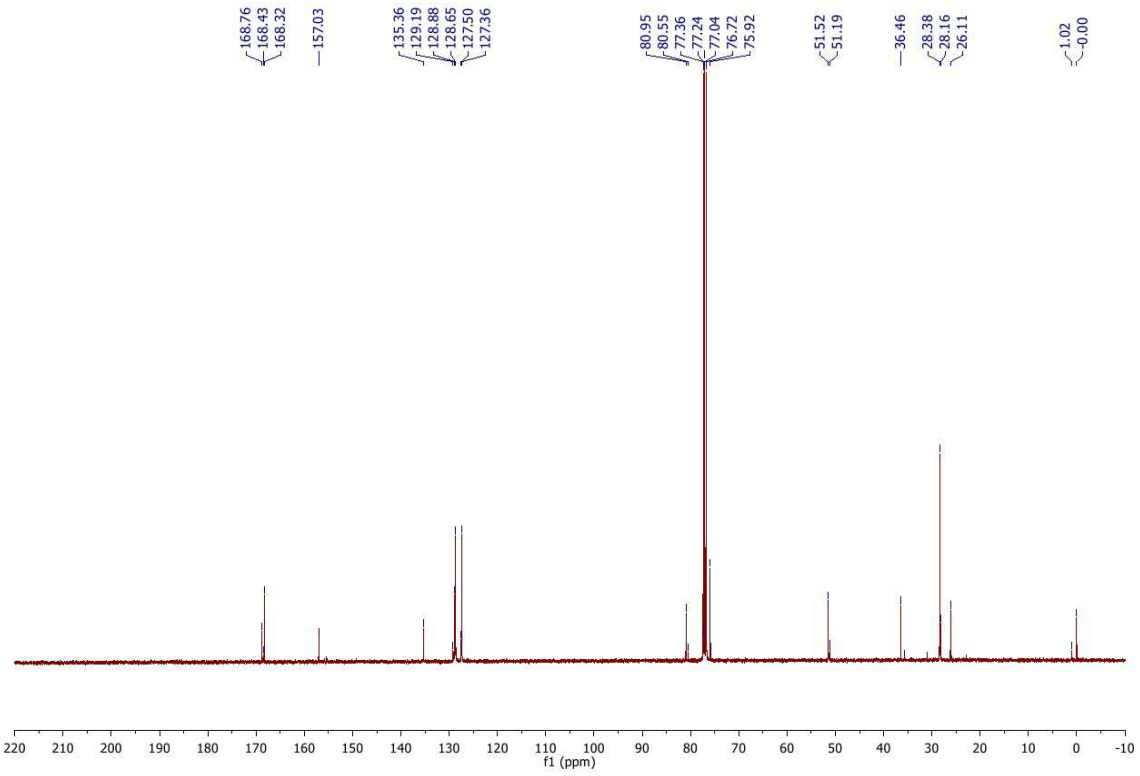


5h (*R*) ^{1}H NMR/ $CDCl_3$/ 400 MHz

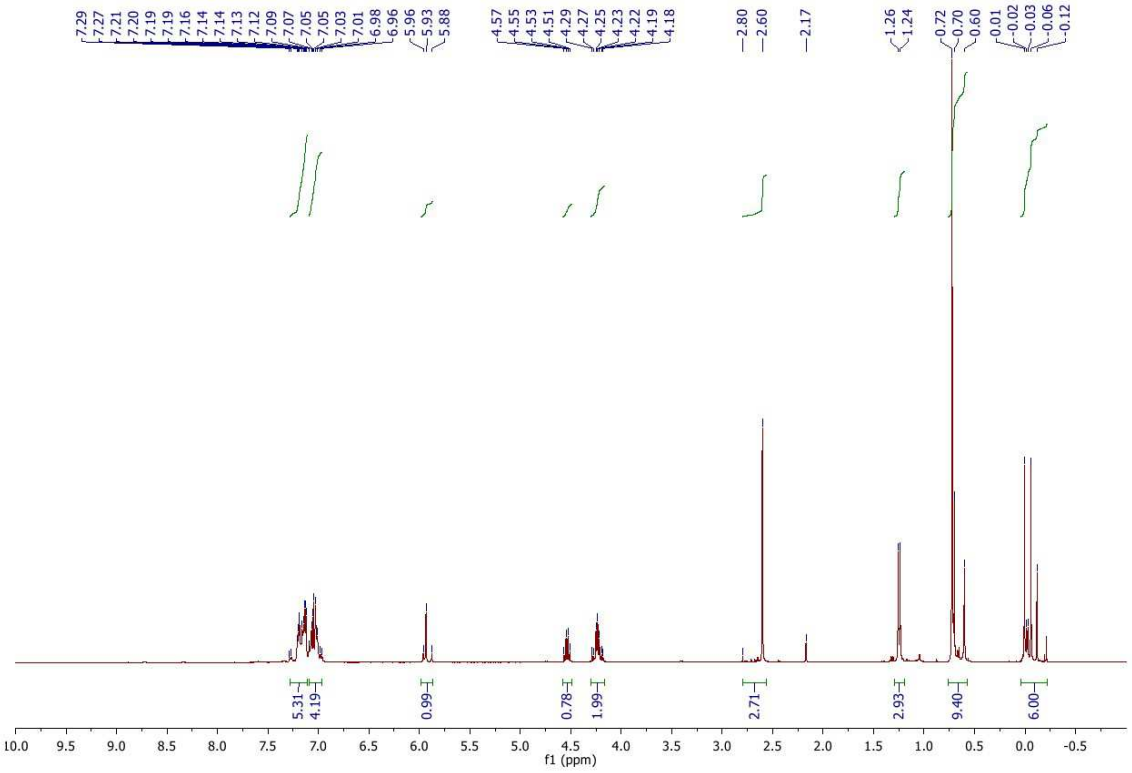


(suppressed acetone peak)

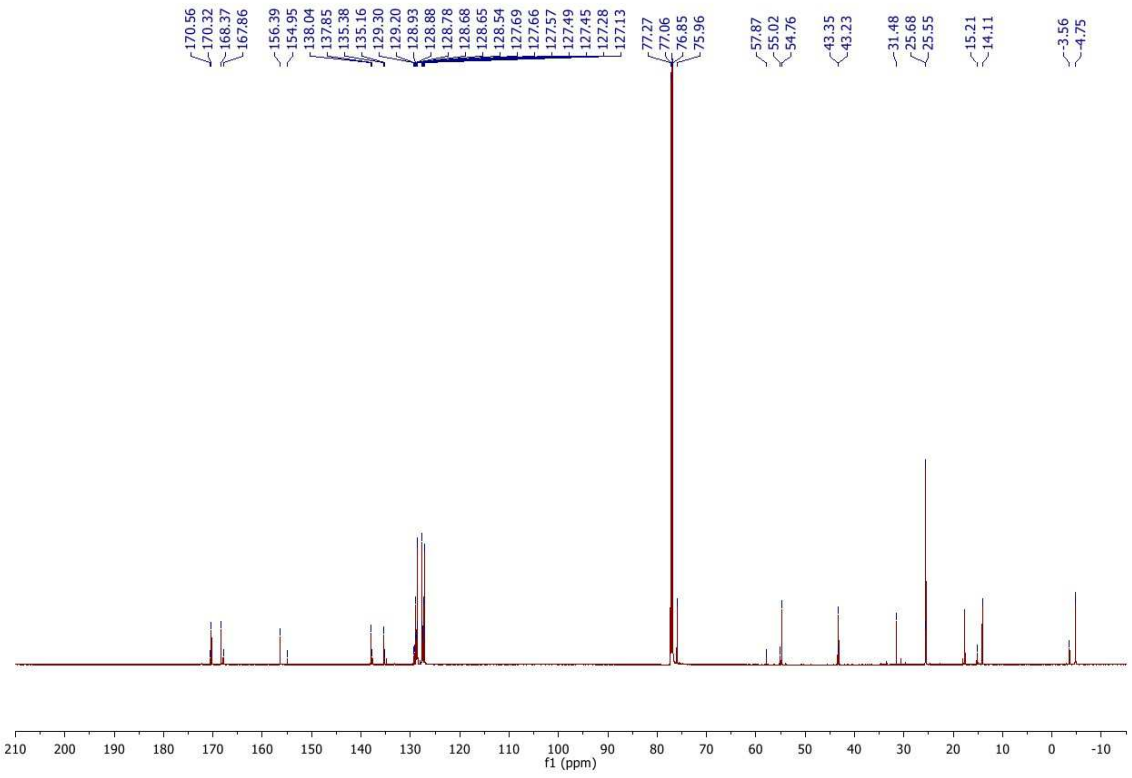
5h (*R*) ^{13}C NMR/ $CDCl_3$/ 101 MHz



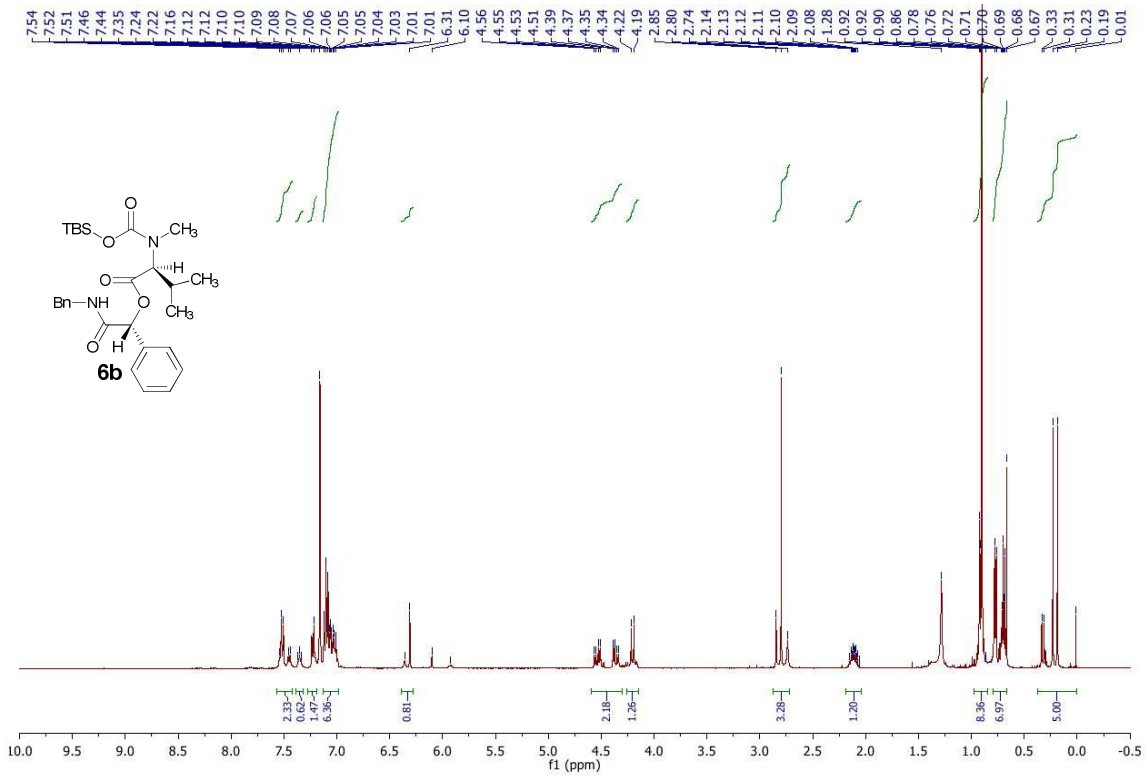
6a ^{1}H NMR/ $CDCl_3$/ 400 MHz



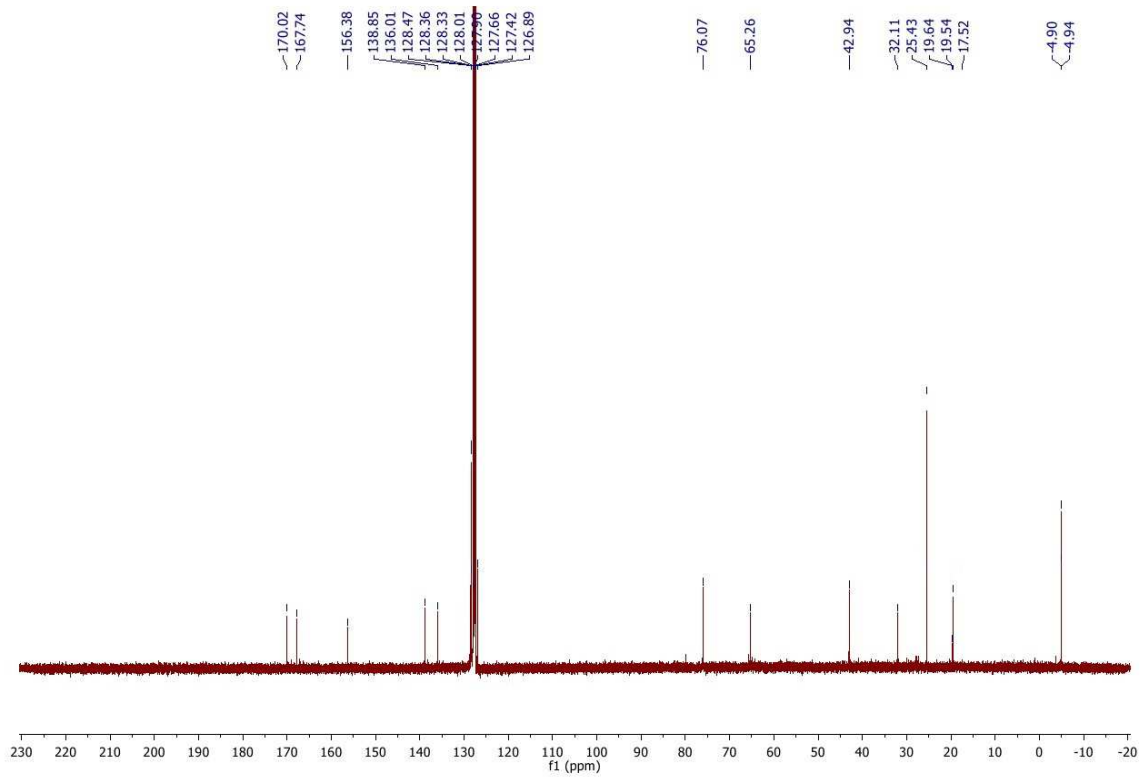
6a ^{13}C NMR/ $CDCl_3$/ 151 MHz



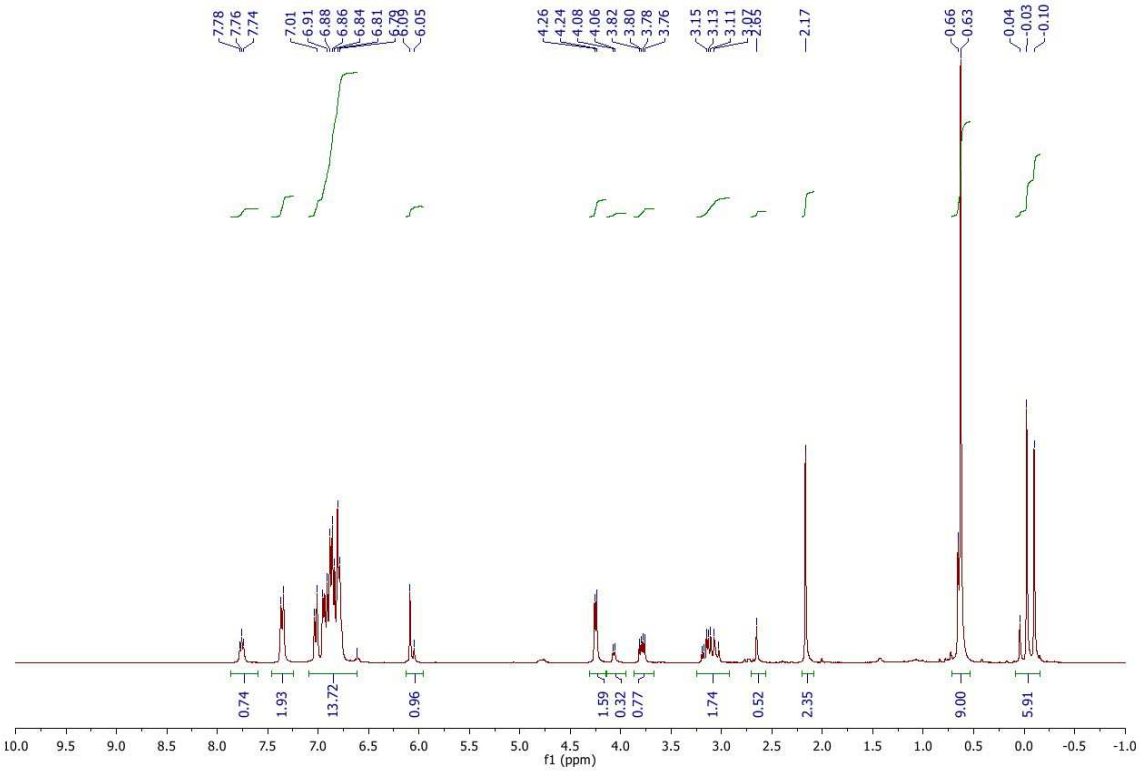
6b ^{1}H NMR/ C_6D_6/ 400 MHz



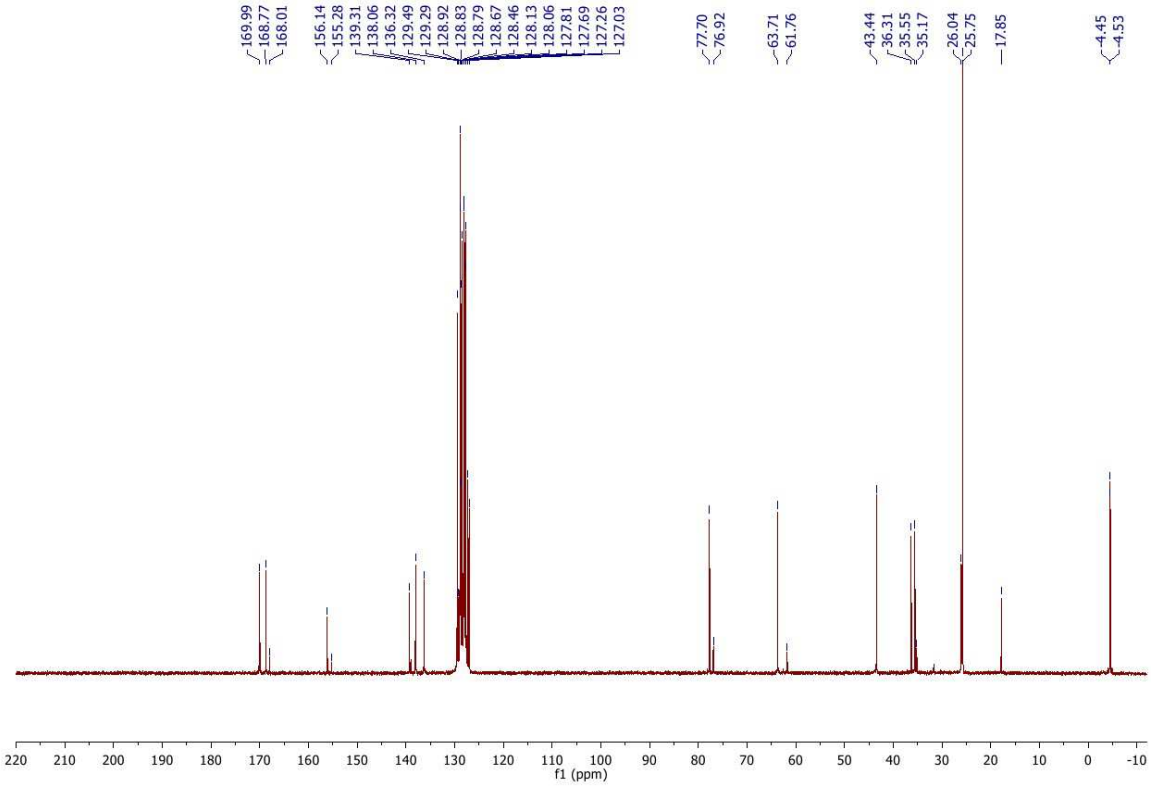
6b ^{13}C NMR/ C_6D_6/ 101 MHz



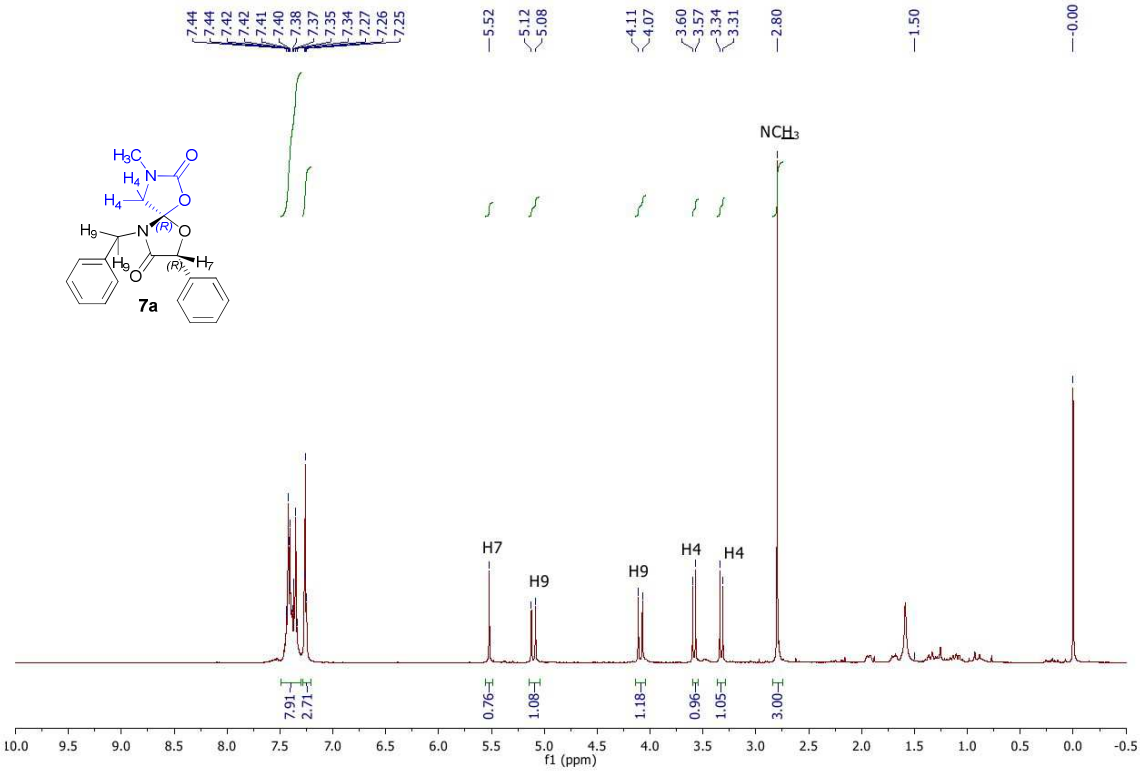
6c ^{1}H NMR/ C_6D_6/ 300 MHz



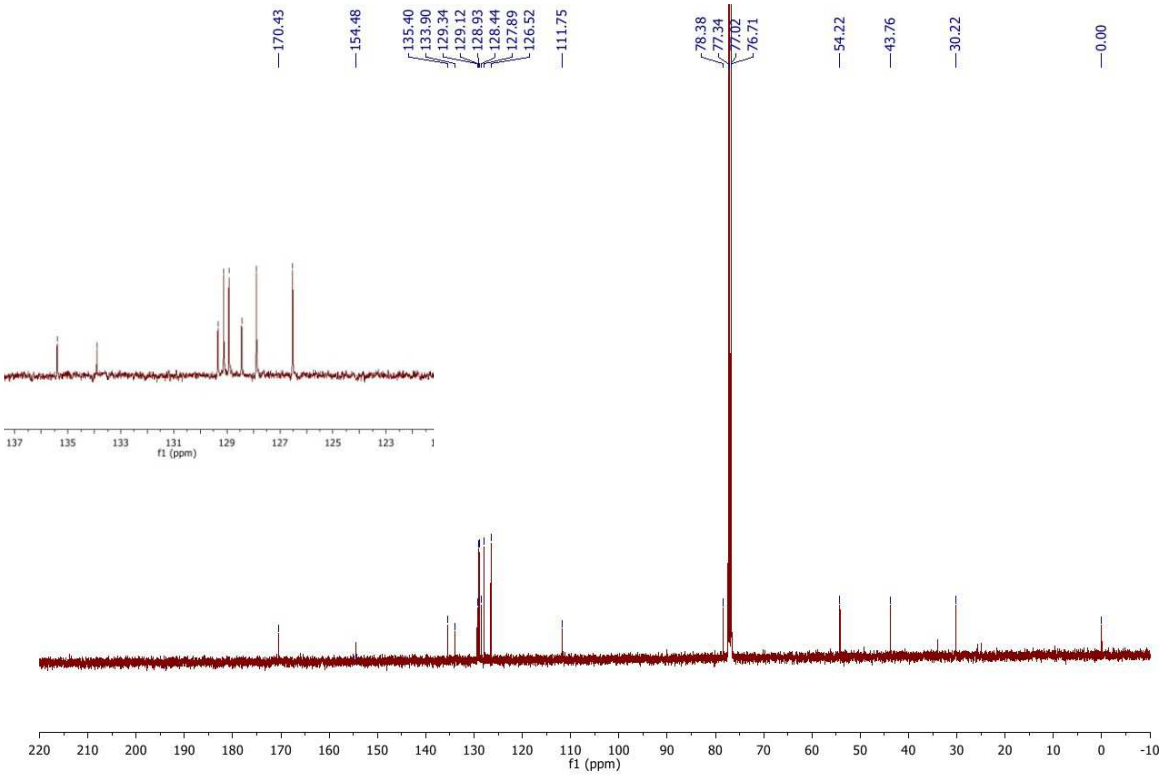
6c ^{13}C NMR/ C_6D_6/ 75 MHz



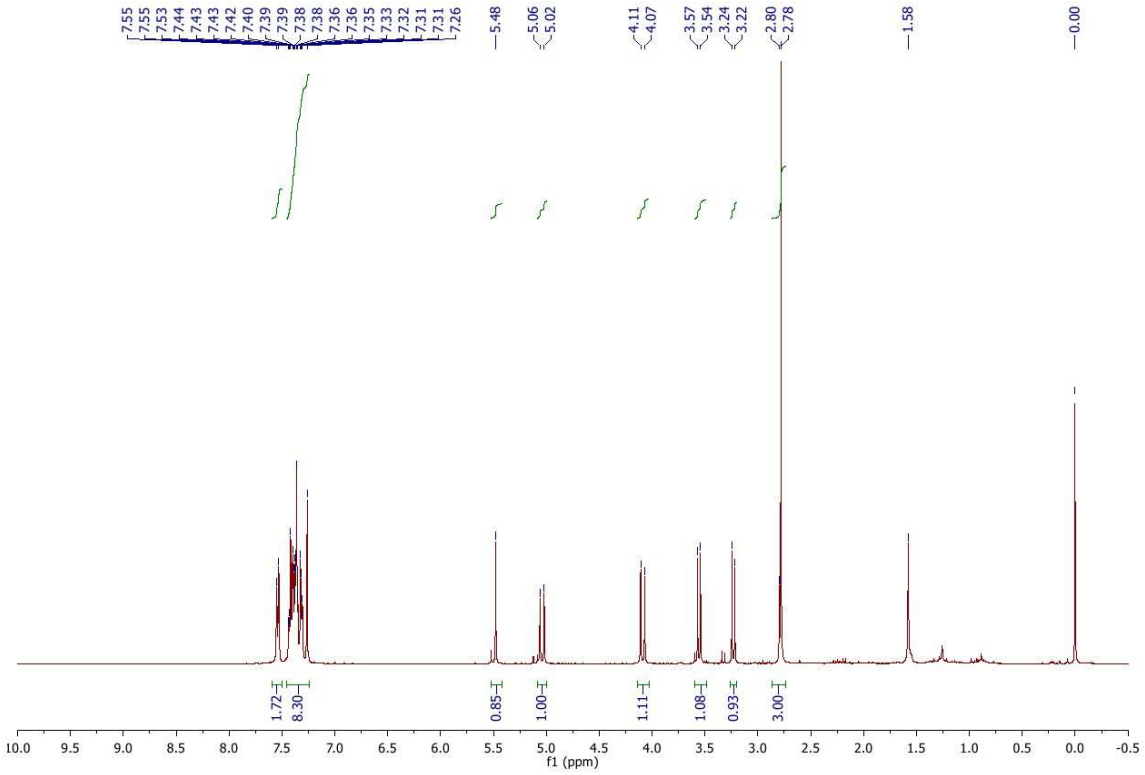
major isomer (**7a**) ^{1}H NMR/ $CDCl_3$/ 400 MHz



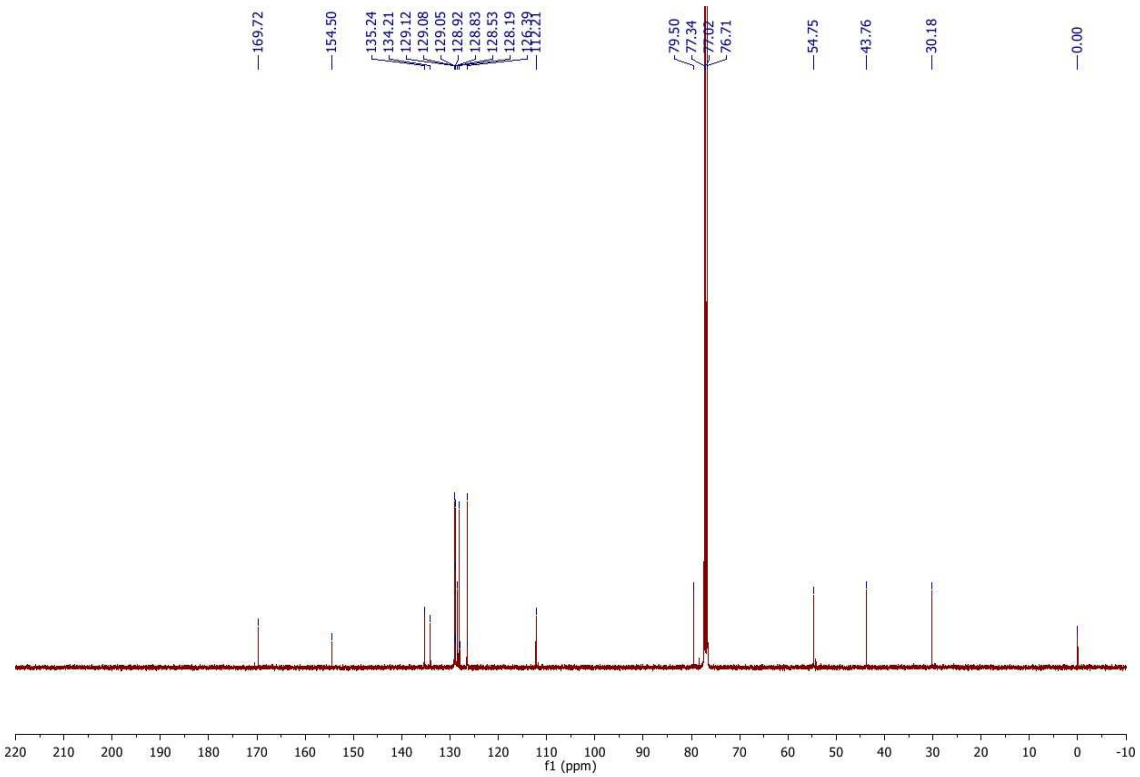
major isomer (**7a**) ^{13}C NMR/ $CDCl_3$/ 101 MHz



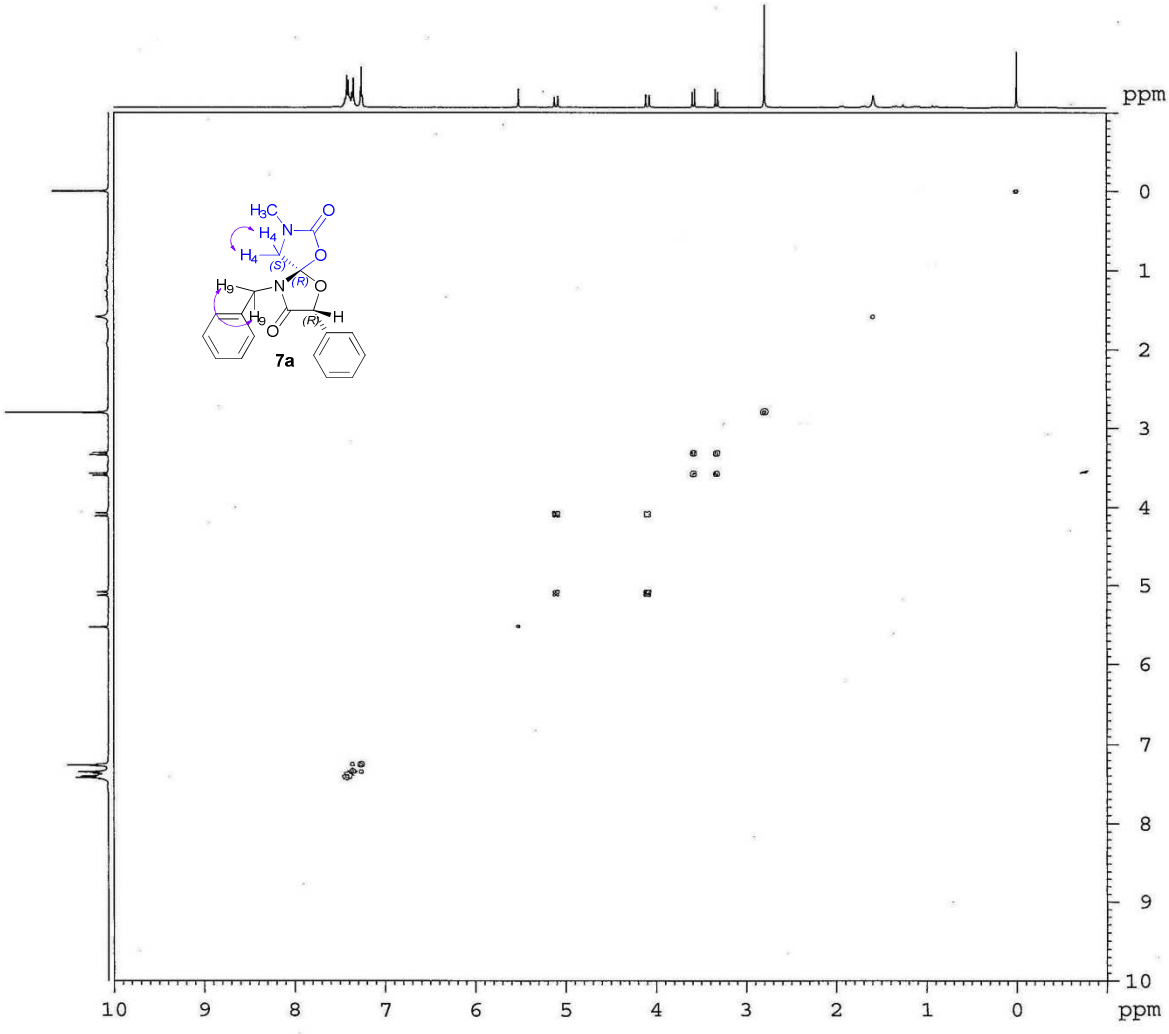
minor isomer (**8a**) ^{1}H NMR/ $CDCl_3$/ 400 MHz



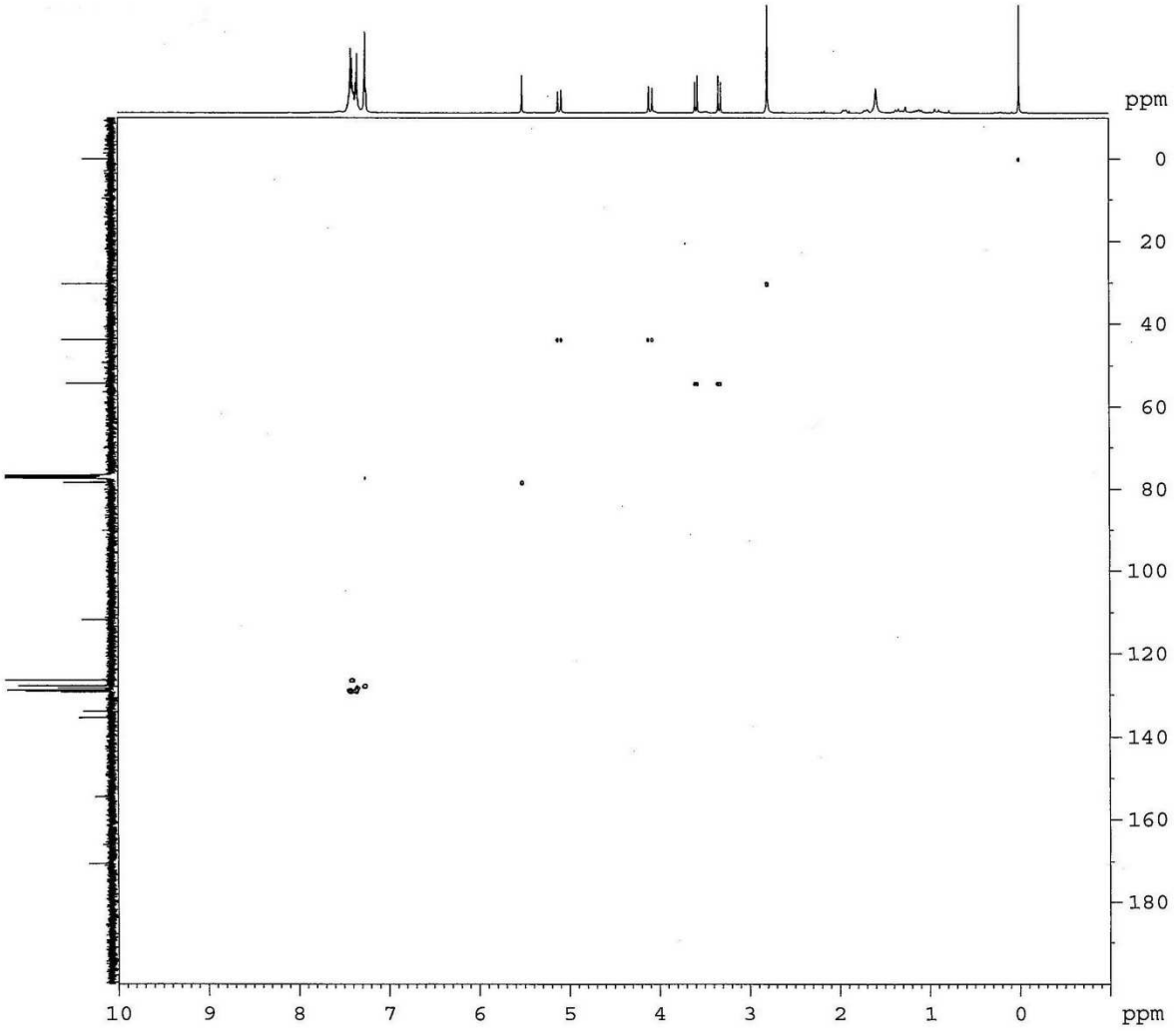
minor isomer (**8a**) ^{13}C NMR/$CDCl_3$/ 101 MHz



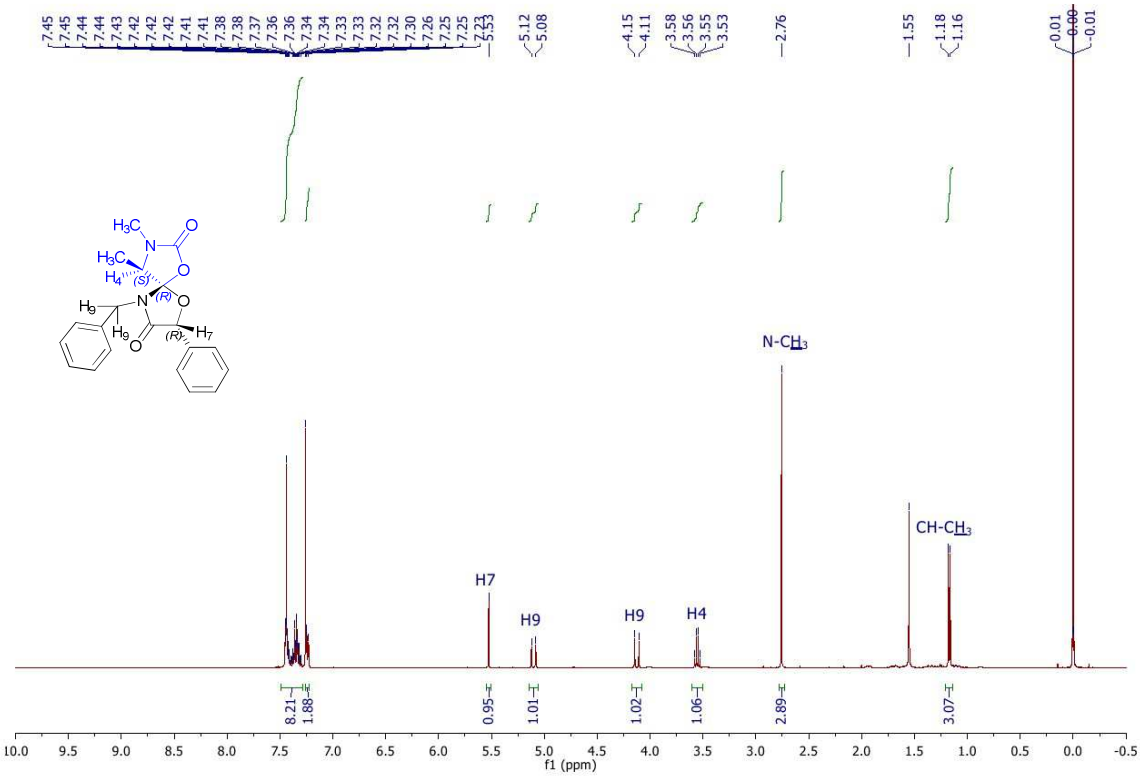
COSY Correlation



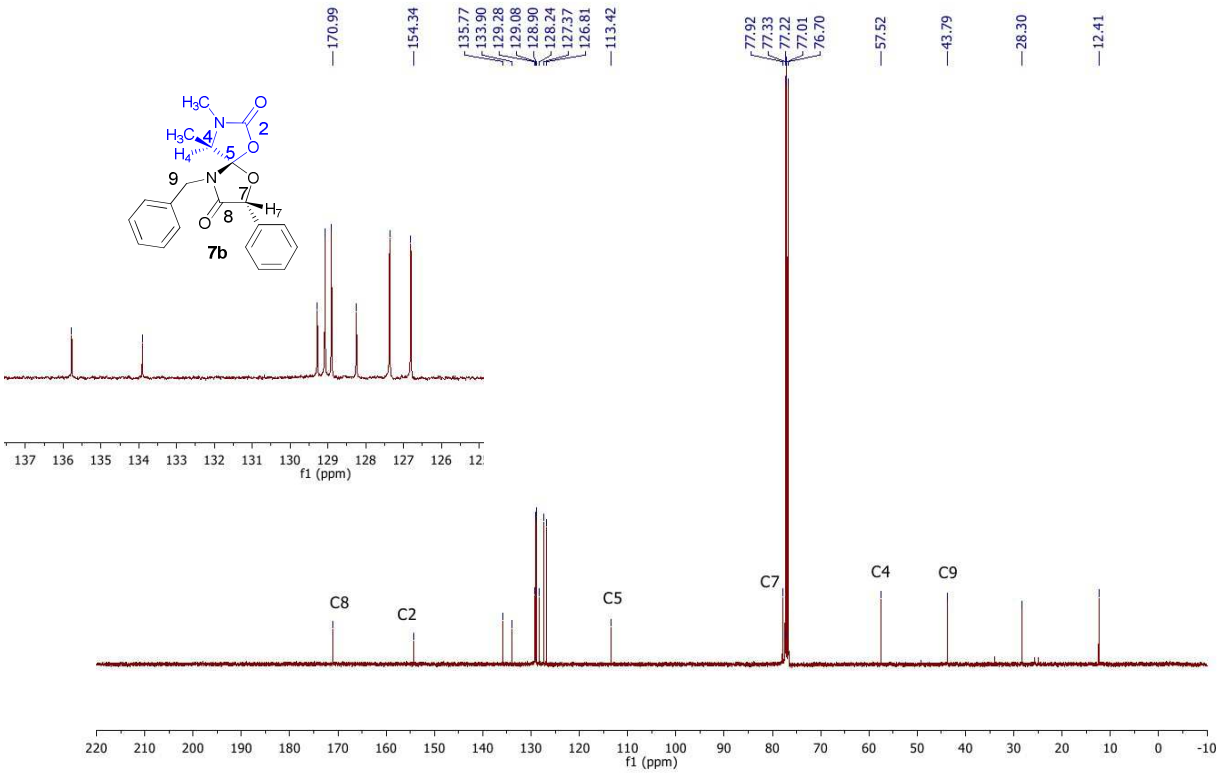
(7a) HSQC Correlation



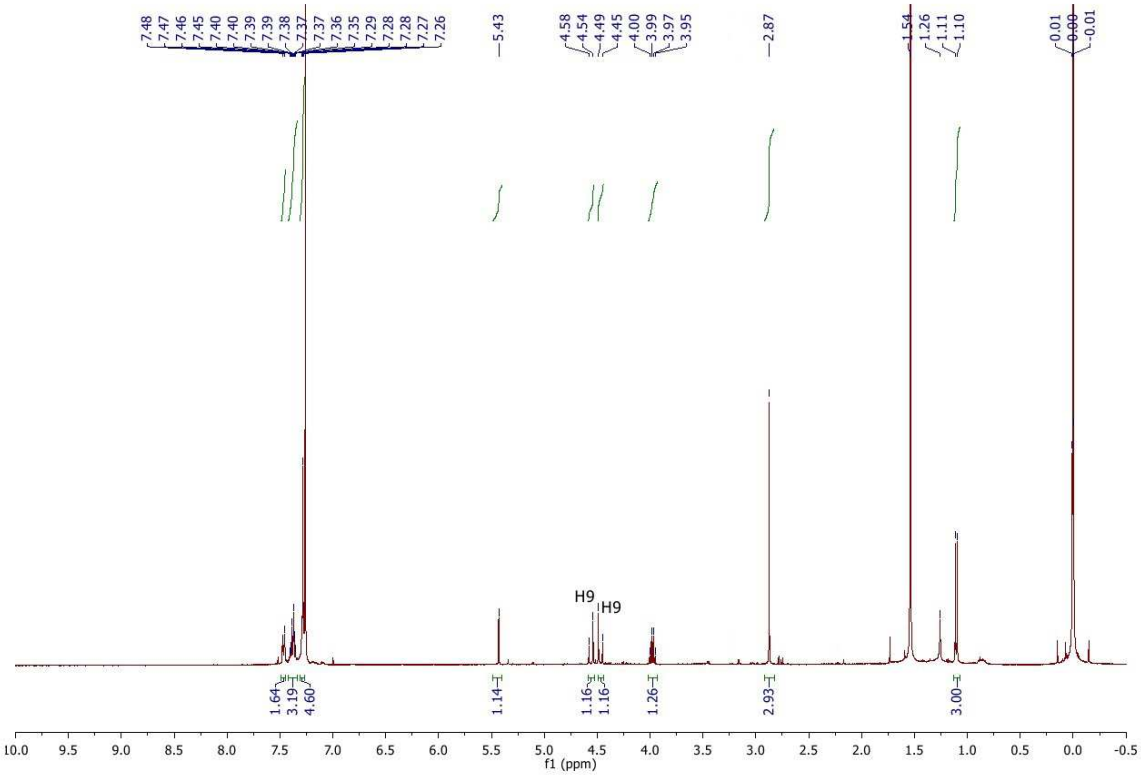
major isomer (**7b**) ^{1}H NMR/ $CDCl_3$/ 400 MHz



major isomer (**7b**) ^{13}C NMR / $CDCl_3$/ 101 MHz

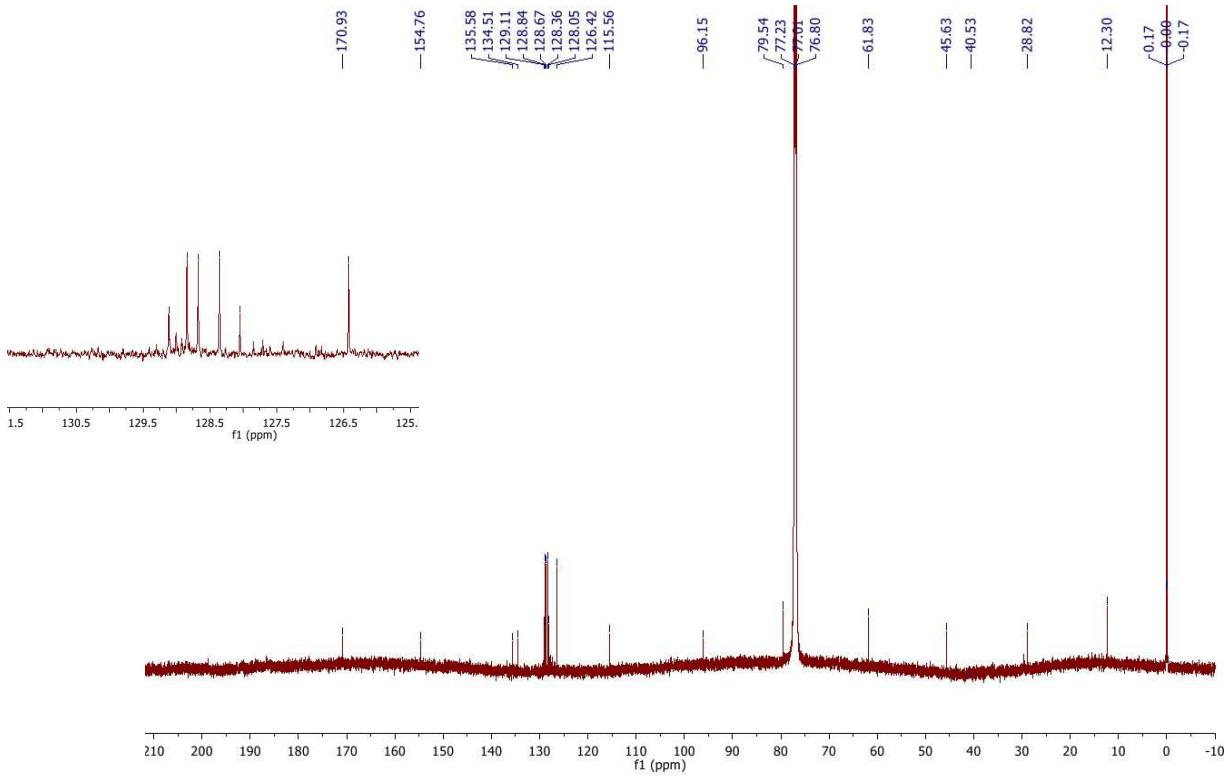


minor isomer (**8b**) ^{1}H NMR/ $CDCl_3$/ 400 MHz

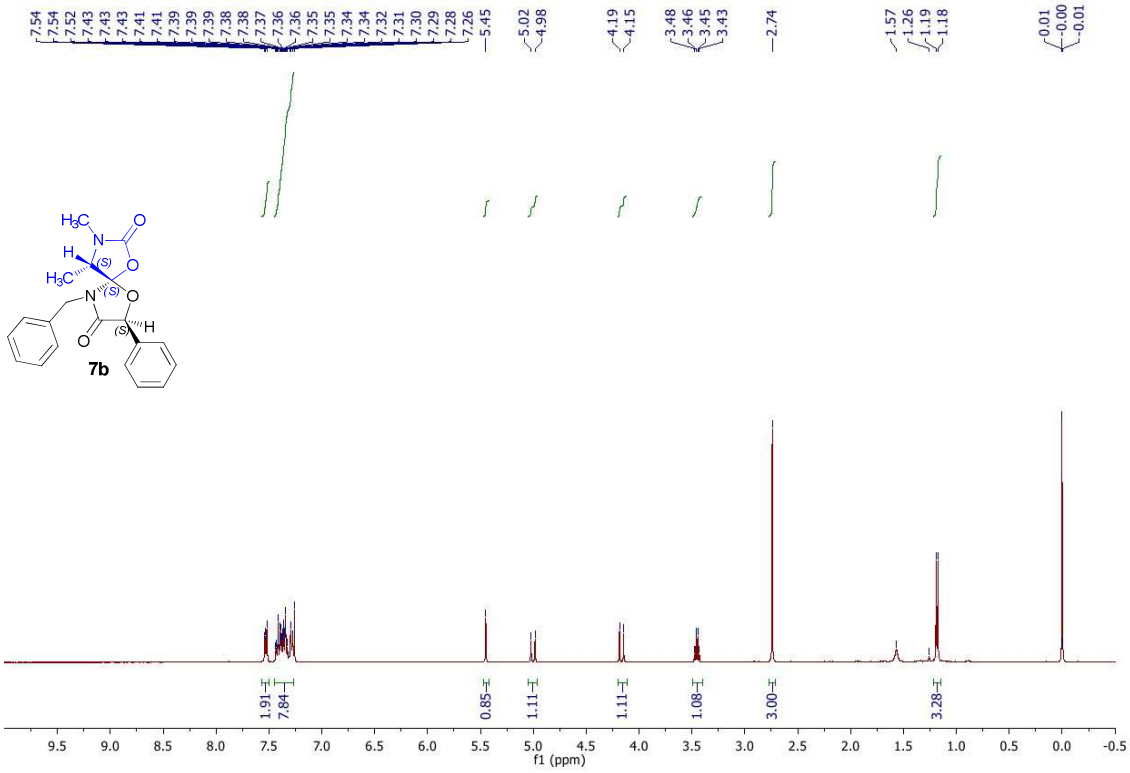


(suppressed acetone peak)

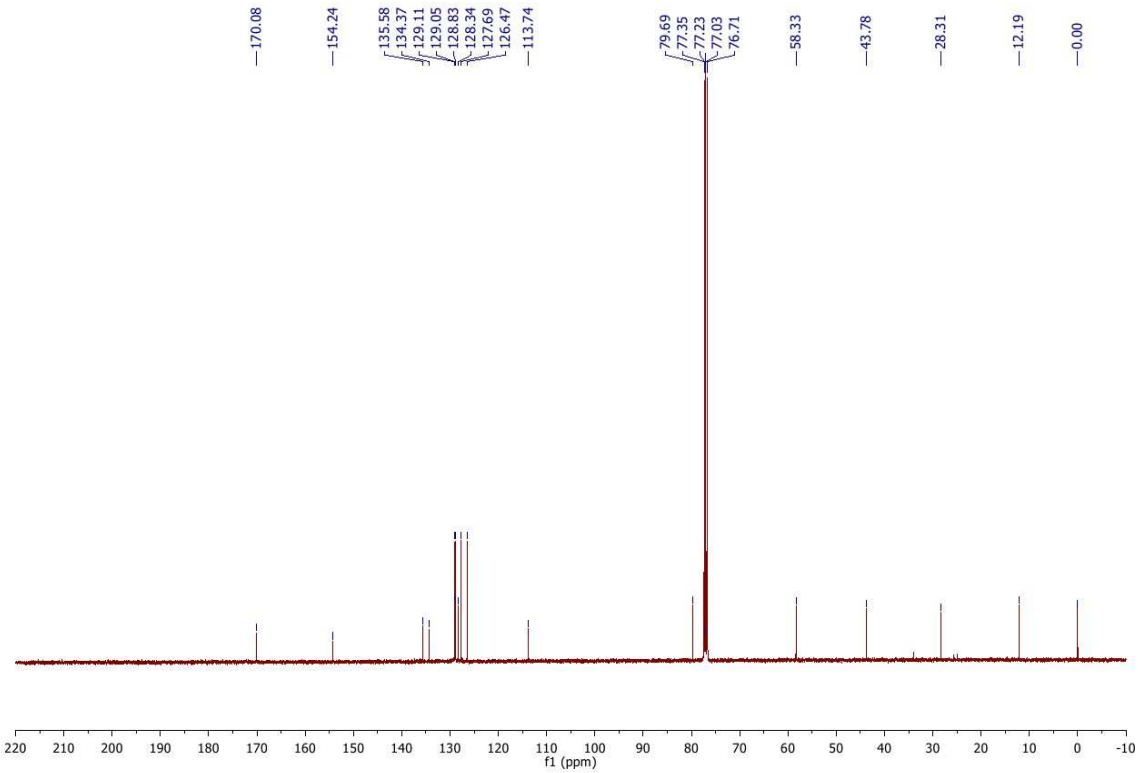
minor isomer (**8b**) ^{13}C NMR/ $CDCl_3$/ 151 MHz



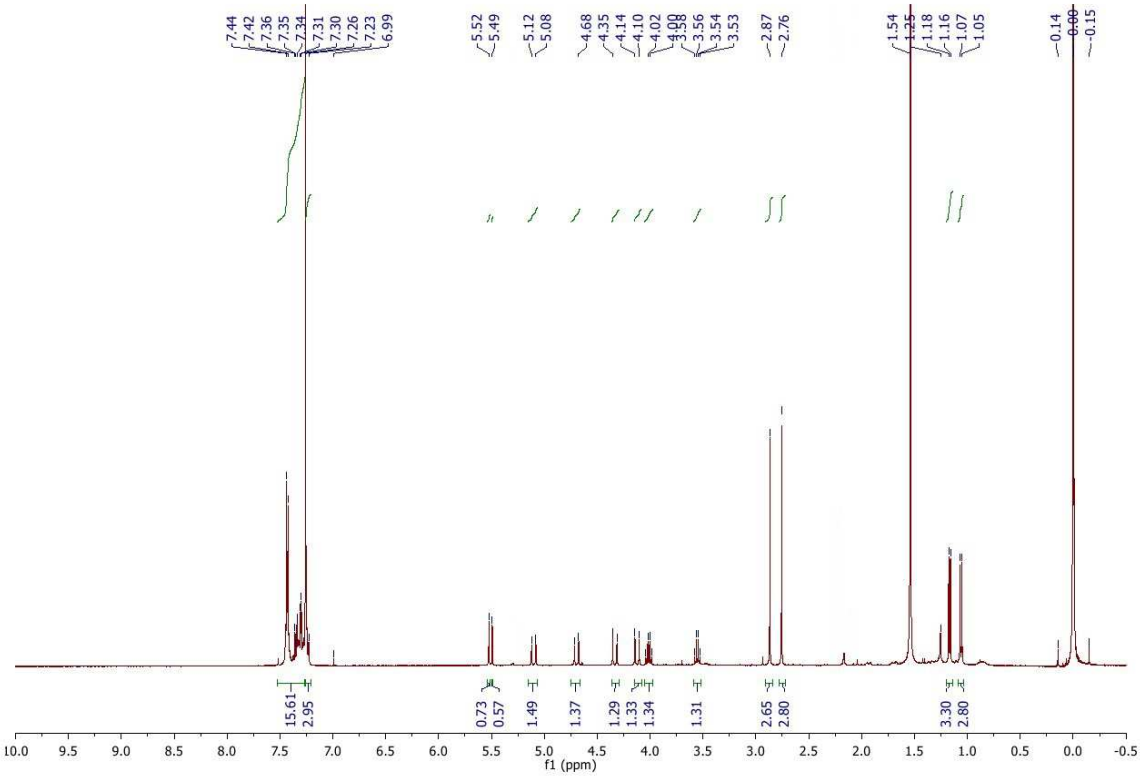
major isomer (**7b**) ^{1}H NMR/ $CDCl_3$/ 400 MHz



major isomer (**7b**) ^{13}C NMR/ $CDCl_3$/ 101 MHz

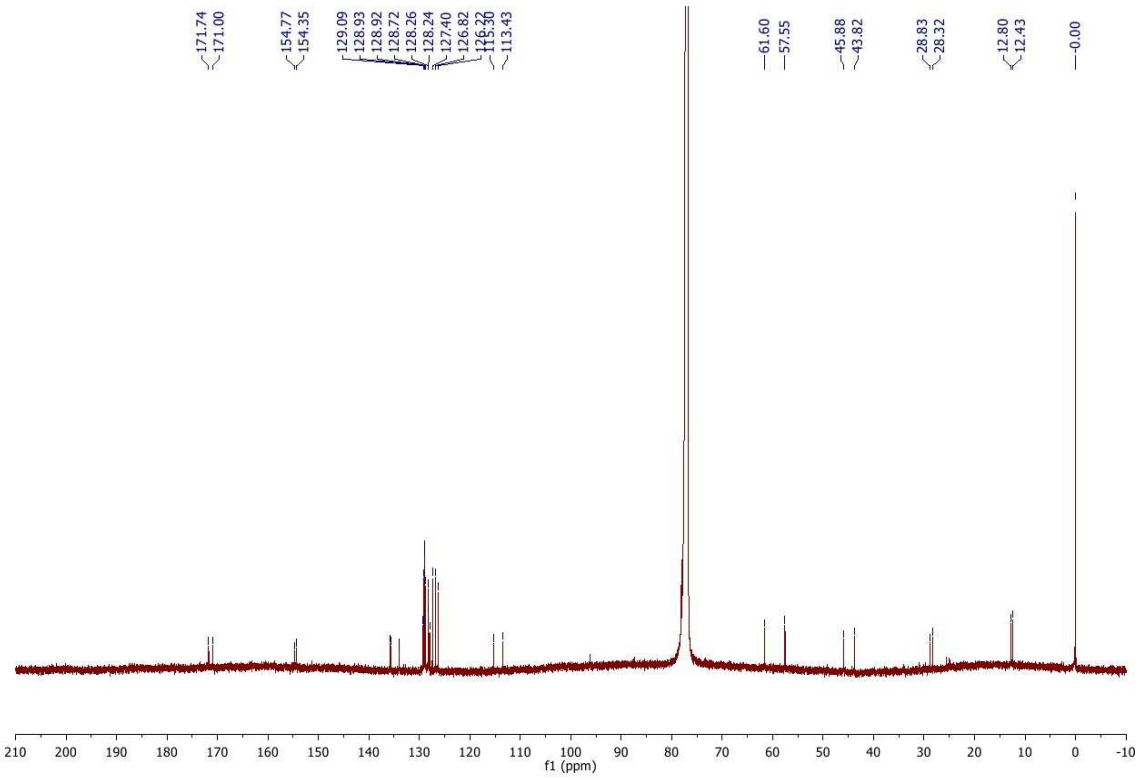


mixture of **(7b)** and **(8b)** ^{1}H NMR/ $CDCl_3$/ 400 MHz

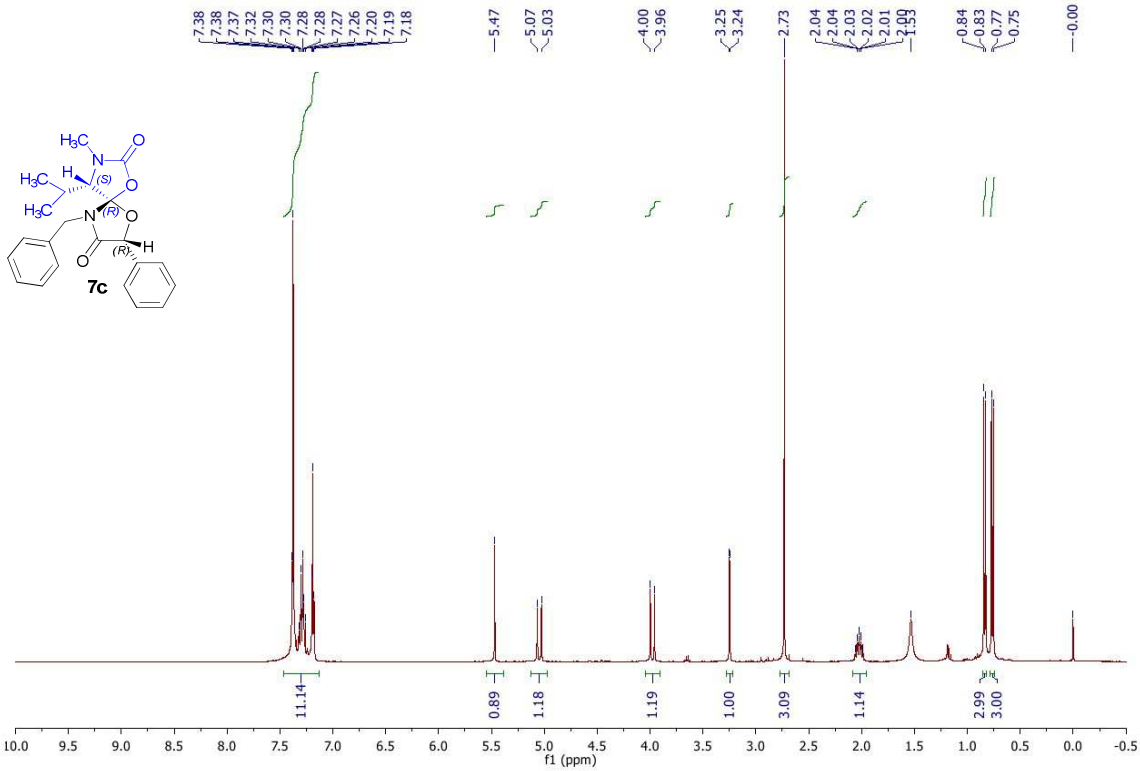


(suppressed acetone and DCM peak)

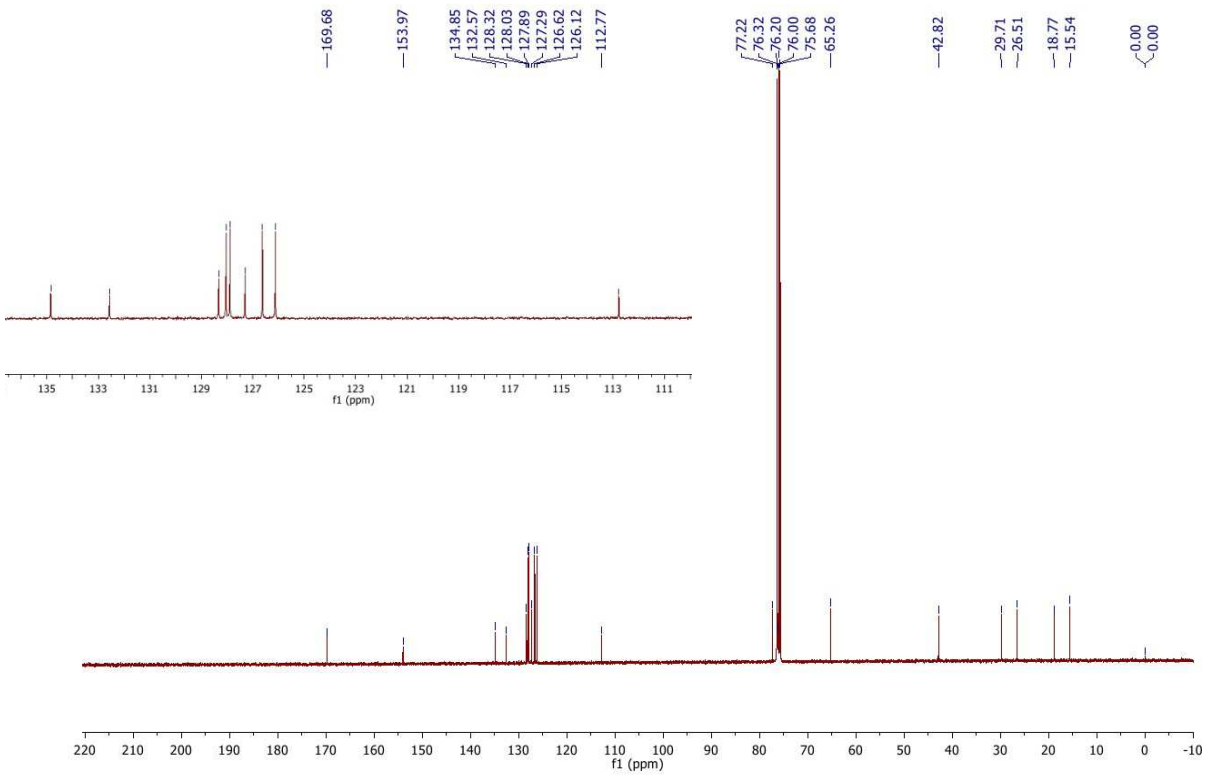
mixture of (**7b**) and (**8b**) ^{13}C NMR/ $CDCl_3$/ 150 MHz



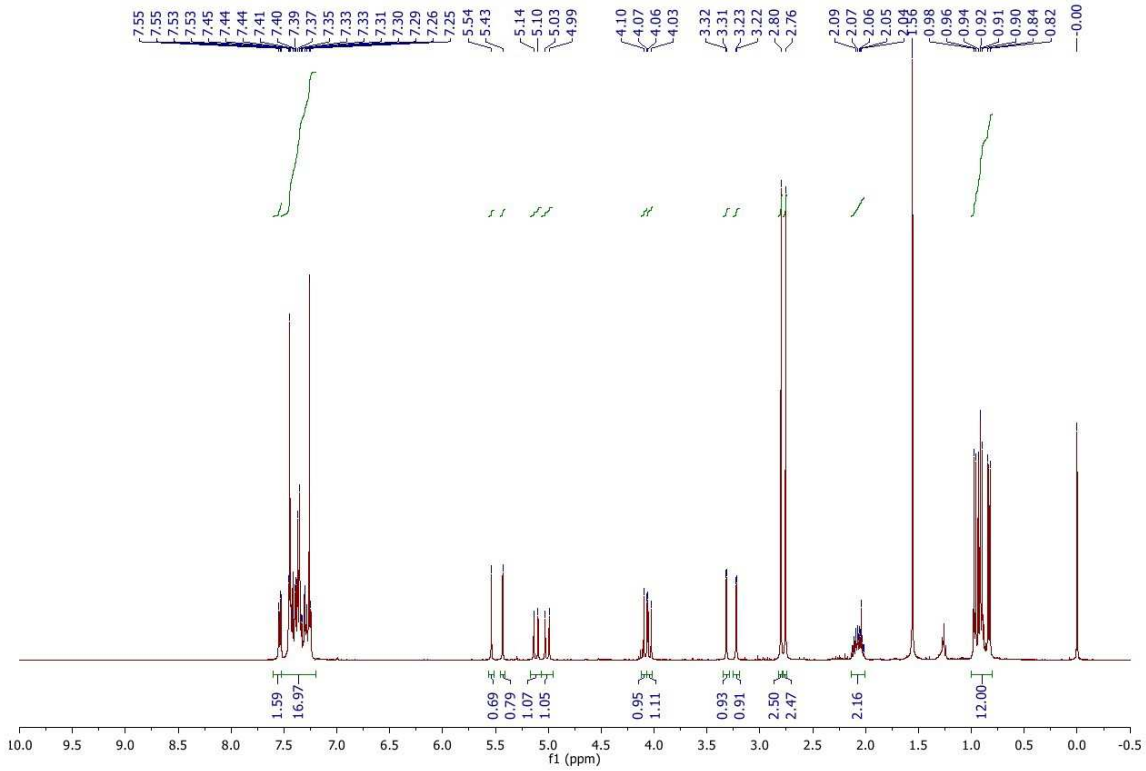
major isomer (**7c**) ^{1}HNMR/ $CDCl_3$/ 400 MHz



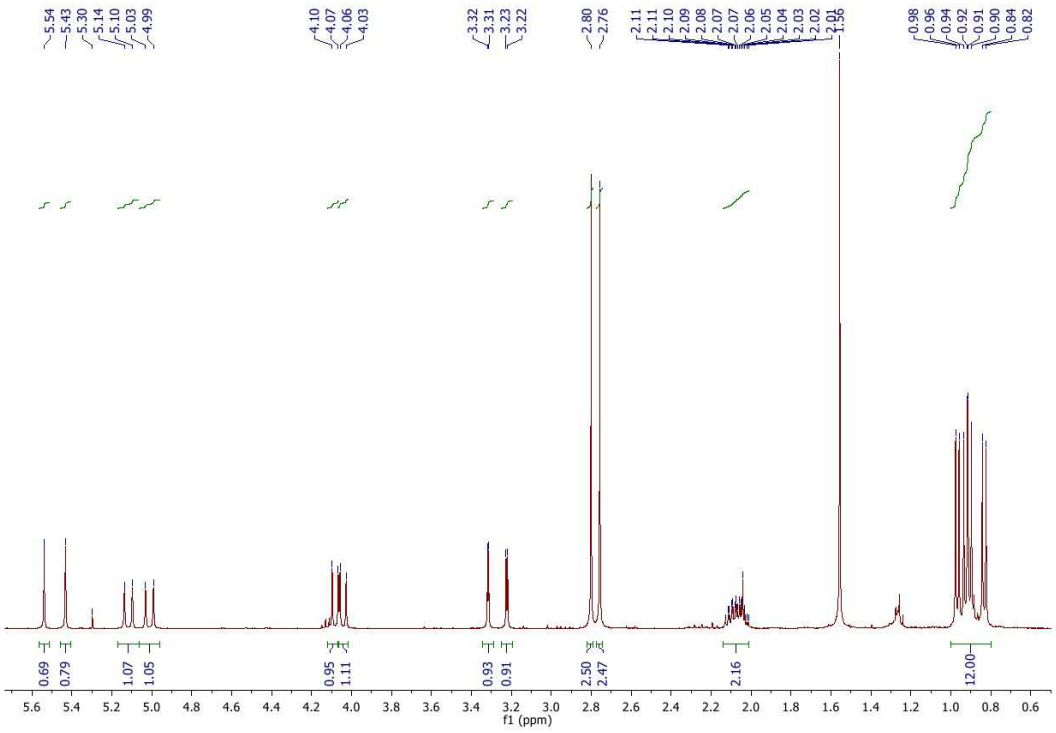
major isomer (**7c**) ^{13}C NMR/ $CDCl_3$/ 101 MHz



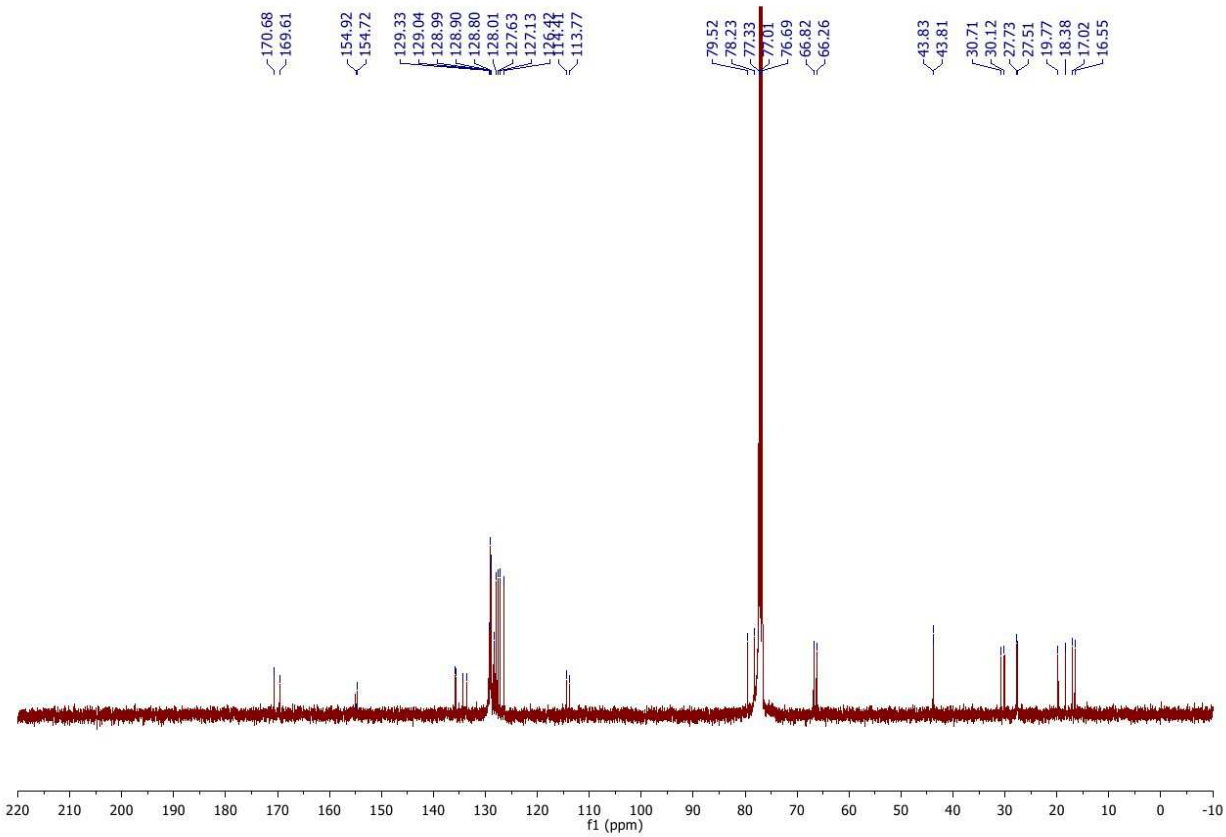
mixture of (**7c**) and (**8c**) ^{1}HNMR/ $CDCl_3$/ 400 MHz

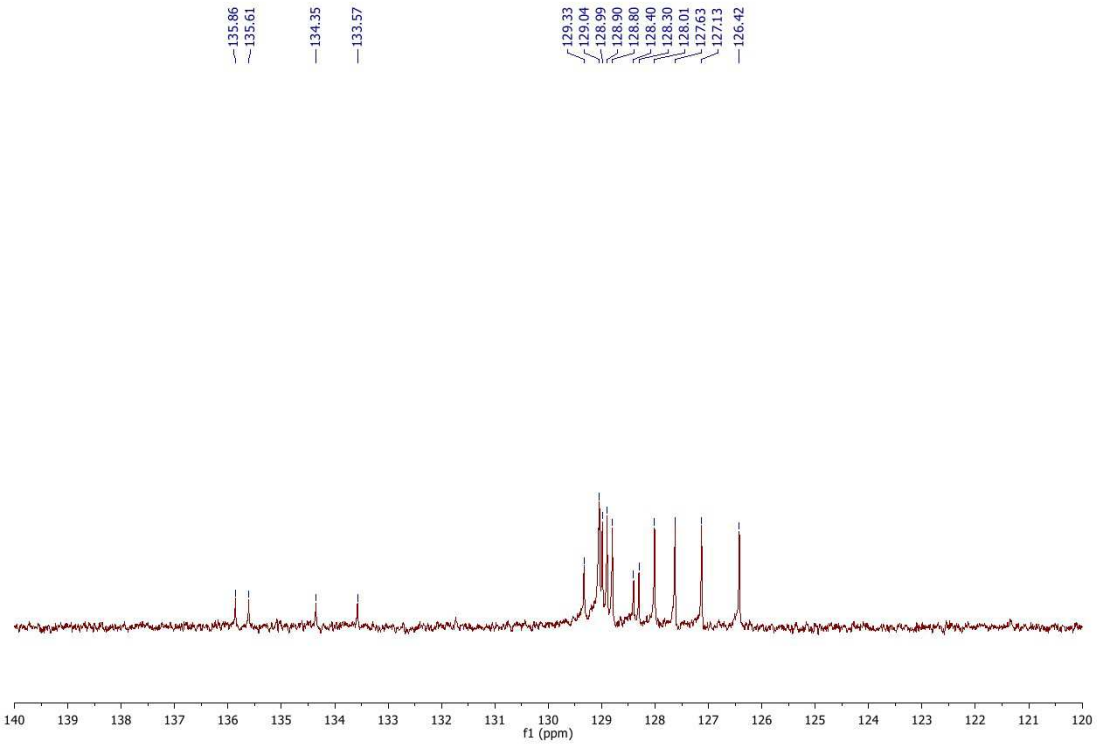


(suppressed DCM peak)

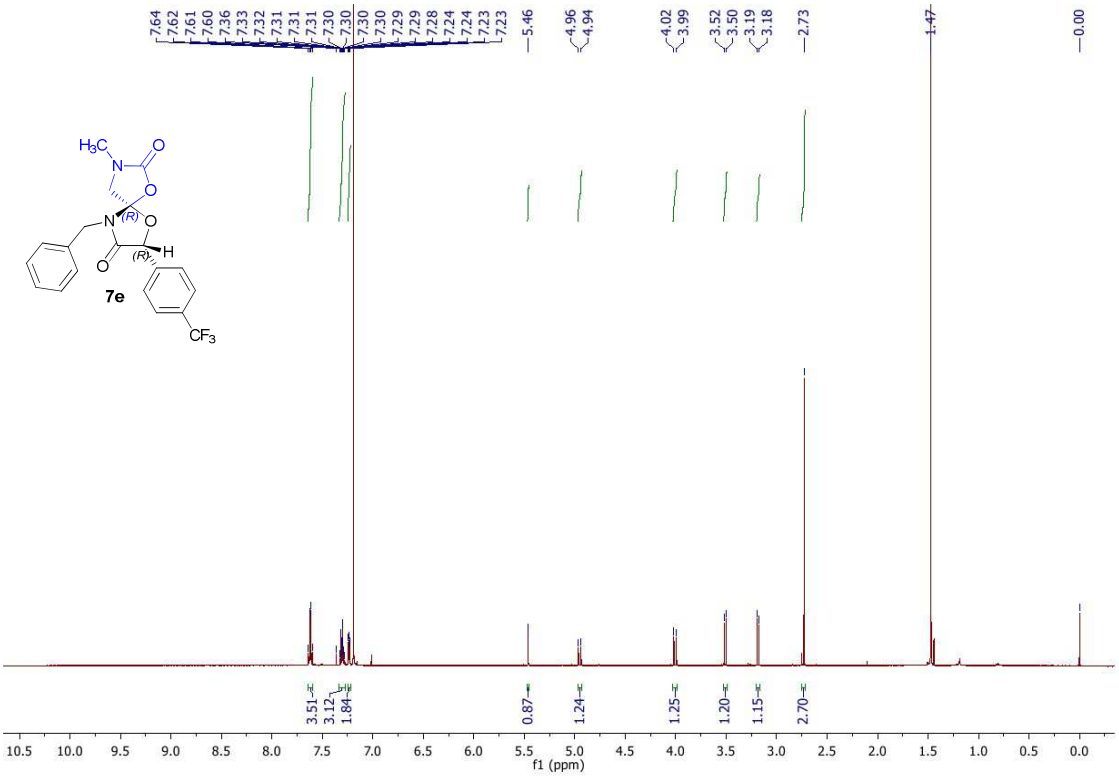


mixture of (**7c**) and (**8c**) ^{13}C NMR/ $CDCl_3$/ 101 MHz

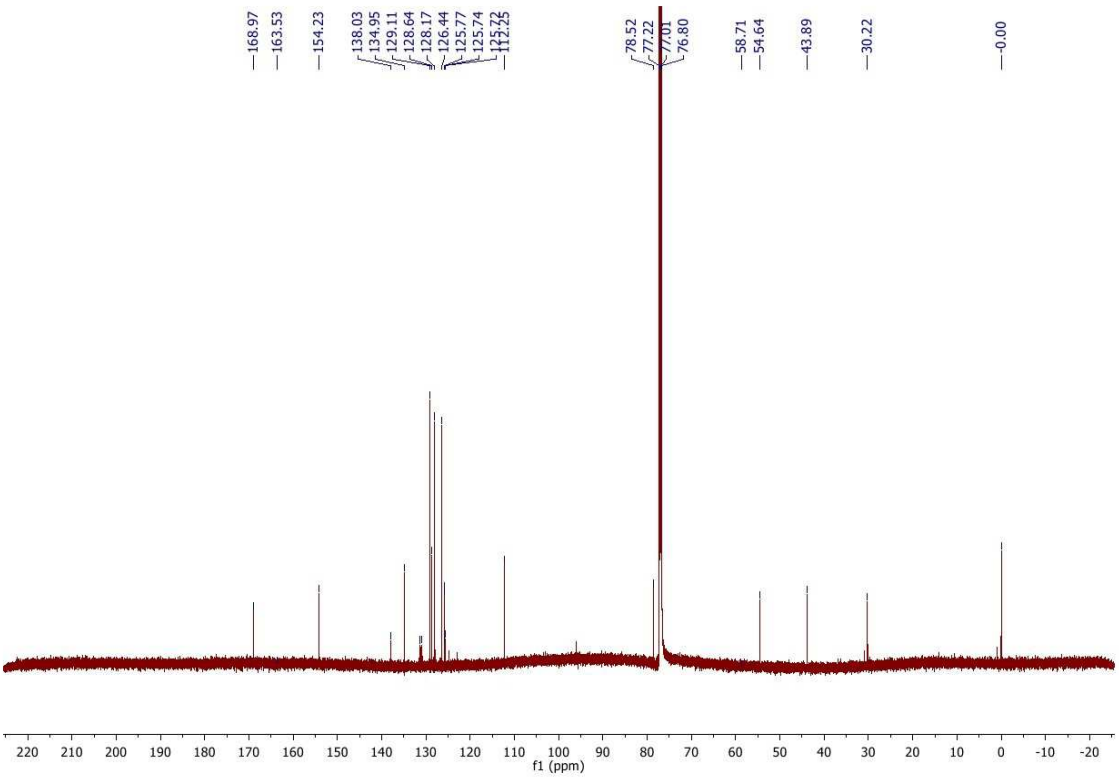




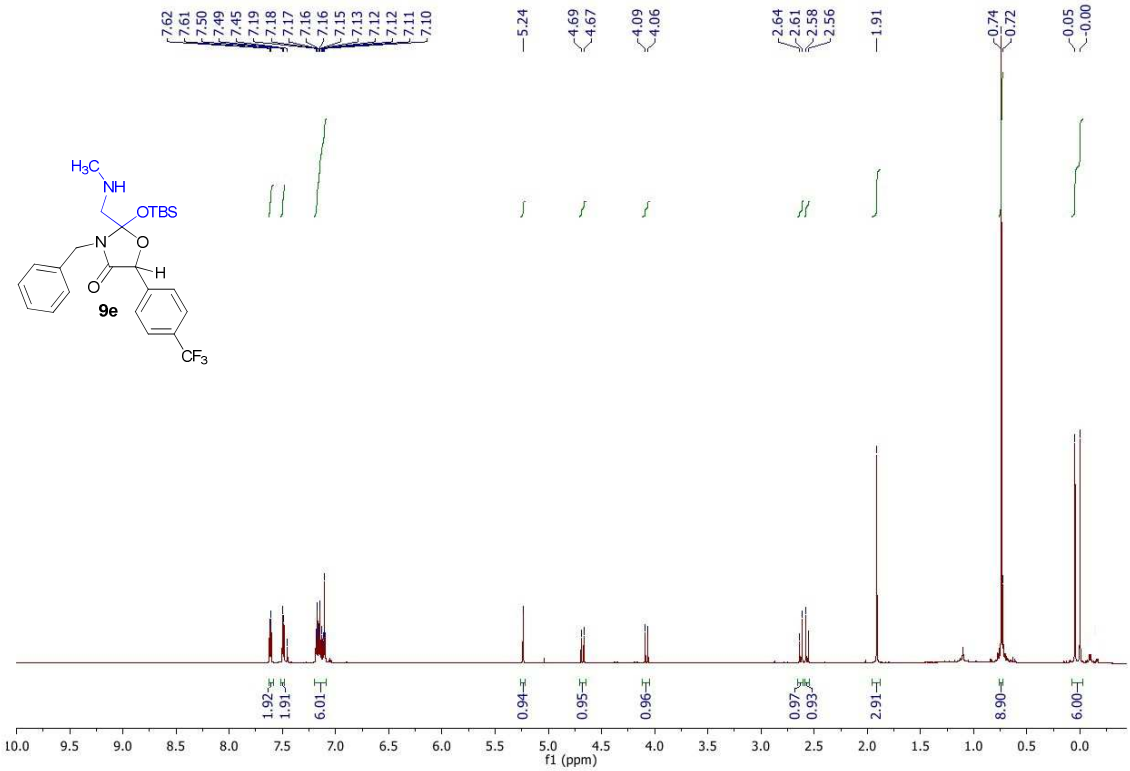
(**7e**) ^{1}H NMR/ $CDCl_3$/ 600 MHz



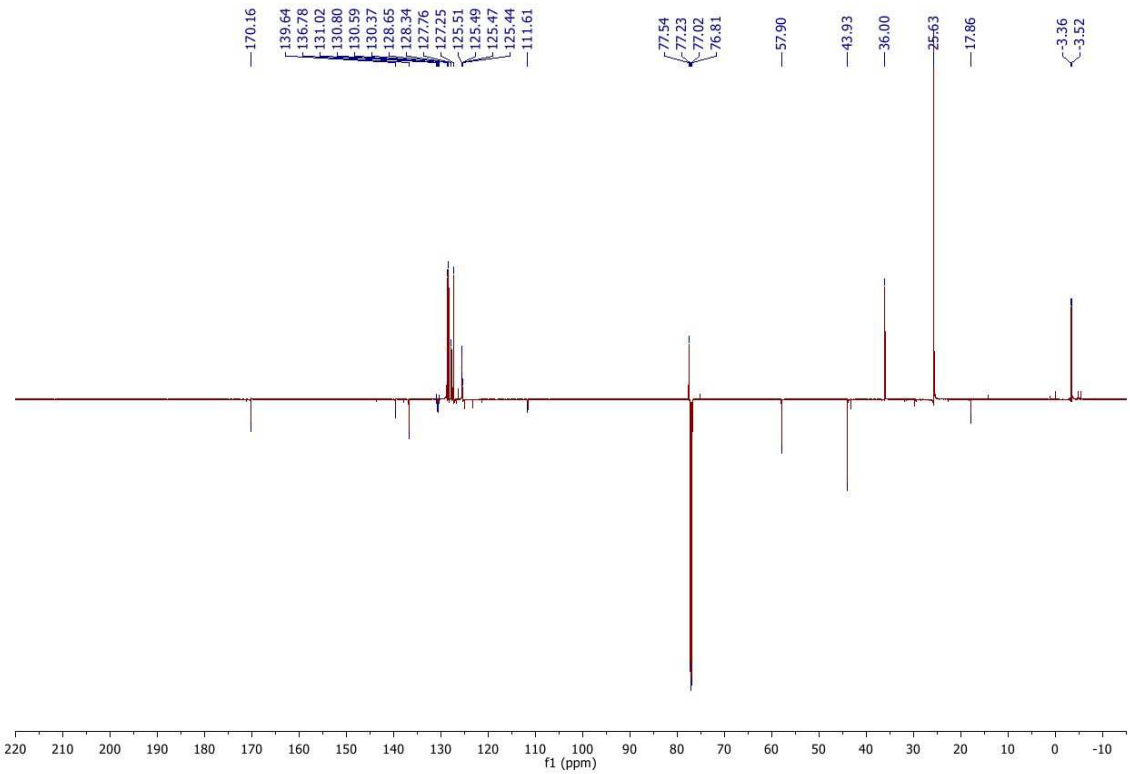
(**7e**) ^{13}C NMR/ $CDCl_3$/ 150 MHz



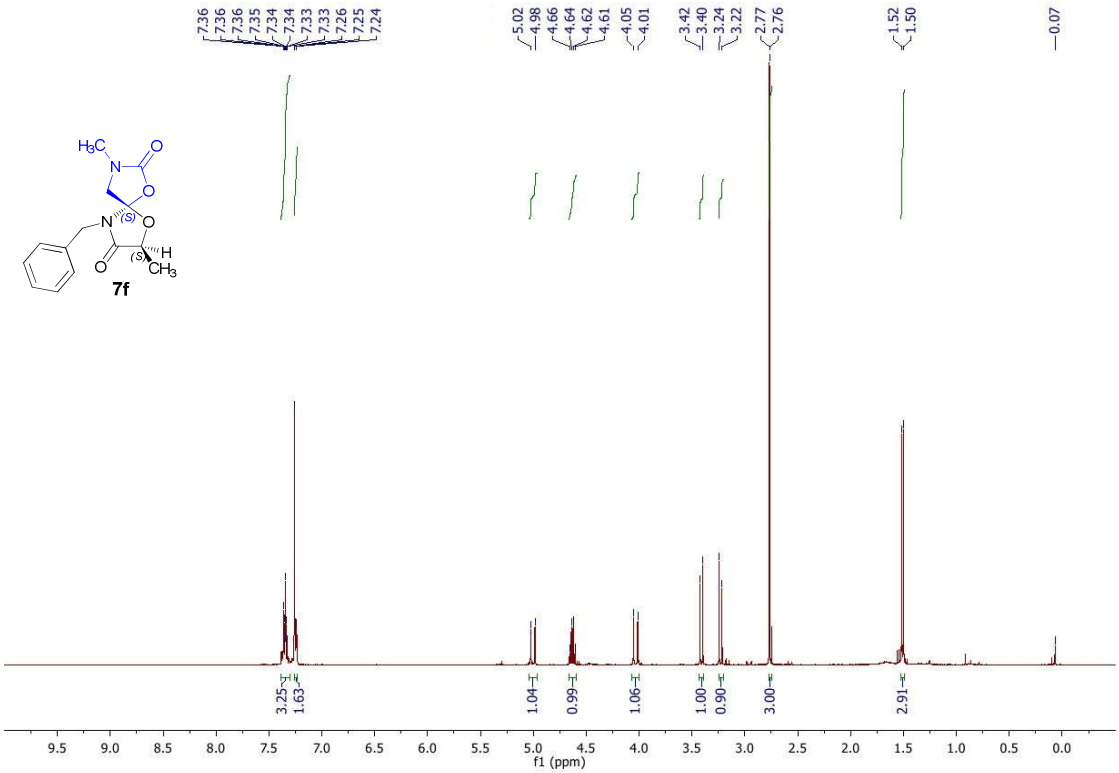
(**9e**) ^{1}H NMR/ $CDCl_3$/ 600 MHz



(**9e**) ^{13}C NMR/$CDCl_3$/ 151 MHz



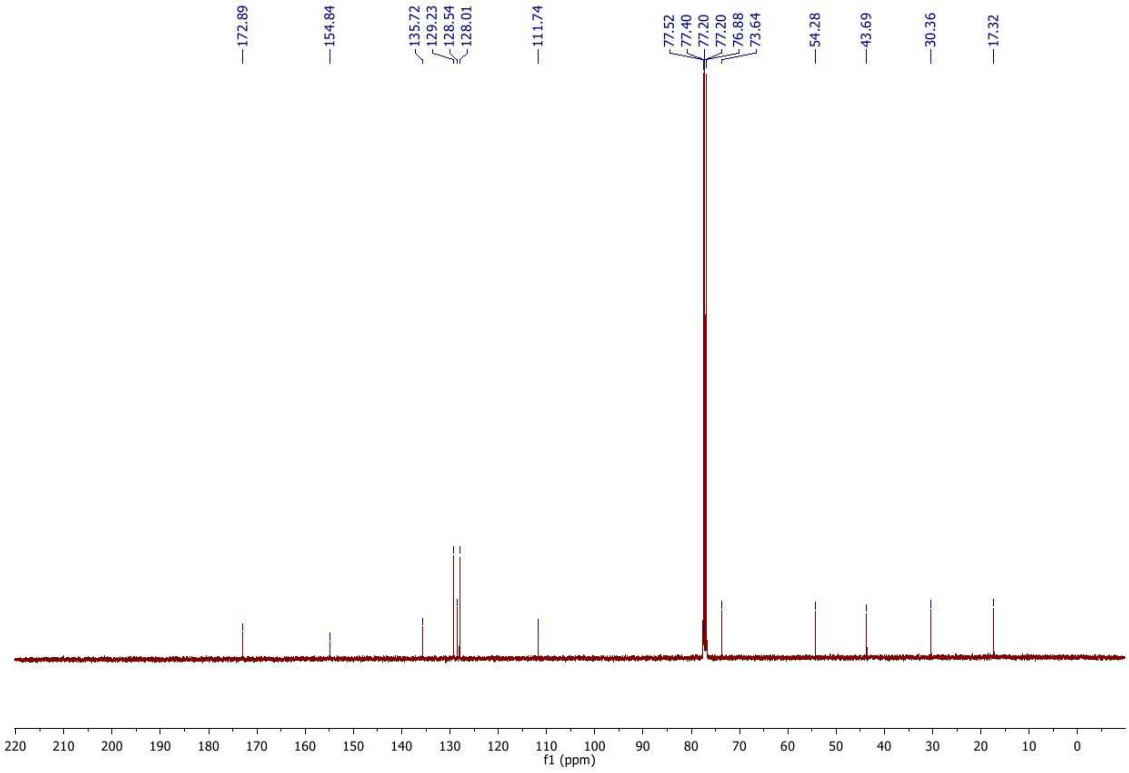
major isomer (**7f**) ^{1}H NMR/ $CDCl_3$/ 400 MHz



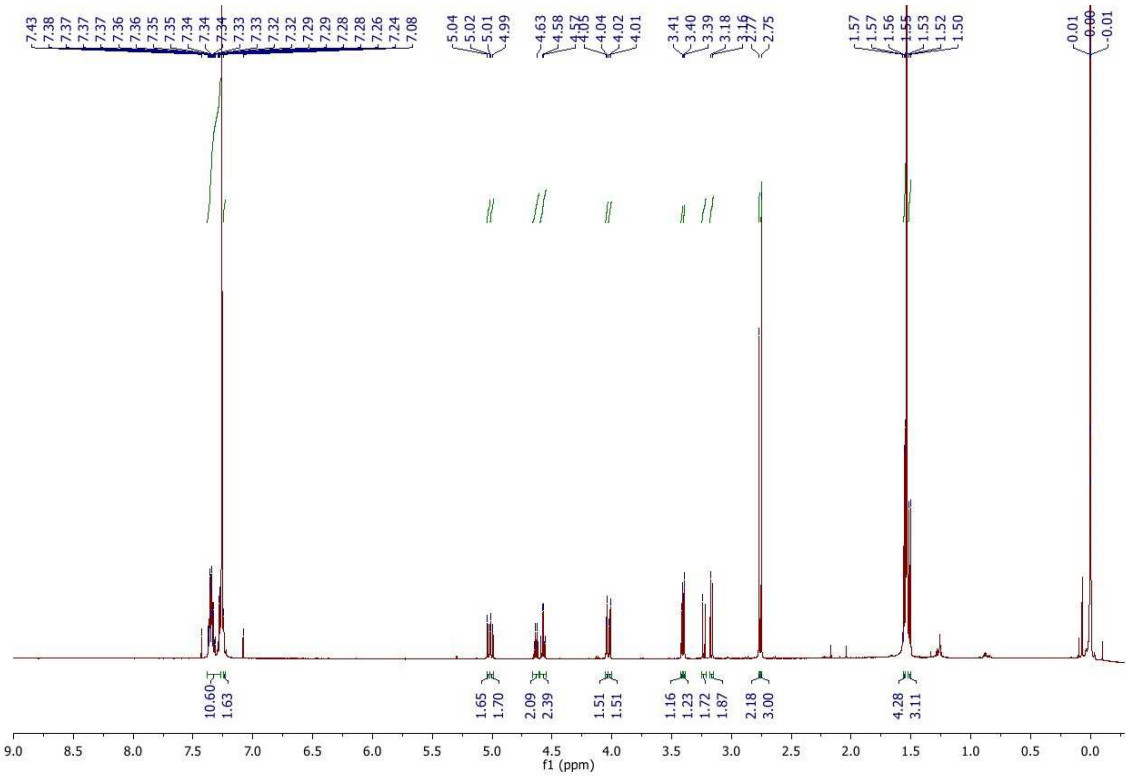
7f

(suppressed DCM peak)

major isomer (**7f**) ^{13}C NMR/ $CDCl_3$/ 101 MHz

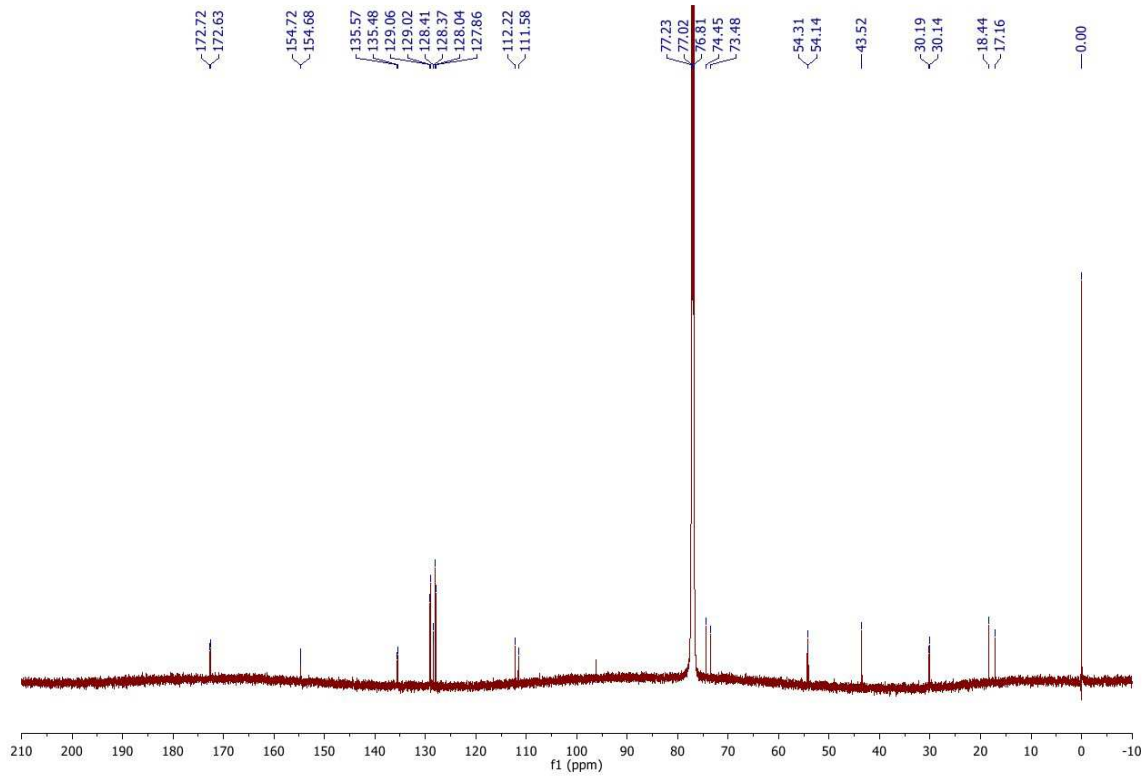


mixture (**7f**) and (**8f**) ^{1}H NMR/ $CDCl_3$/ 600 MHz

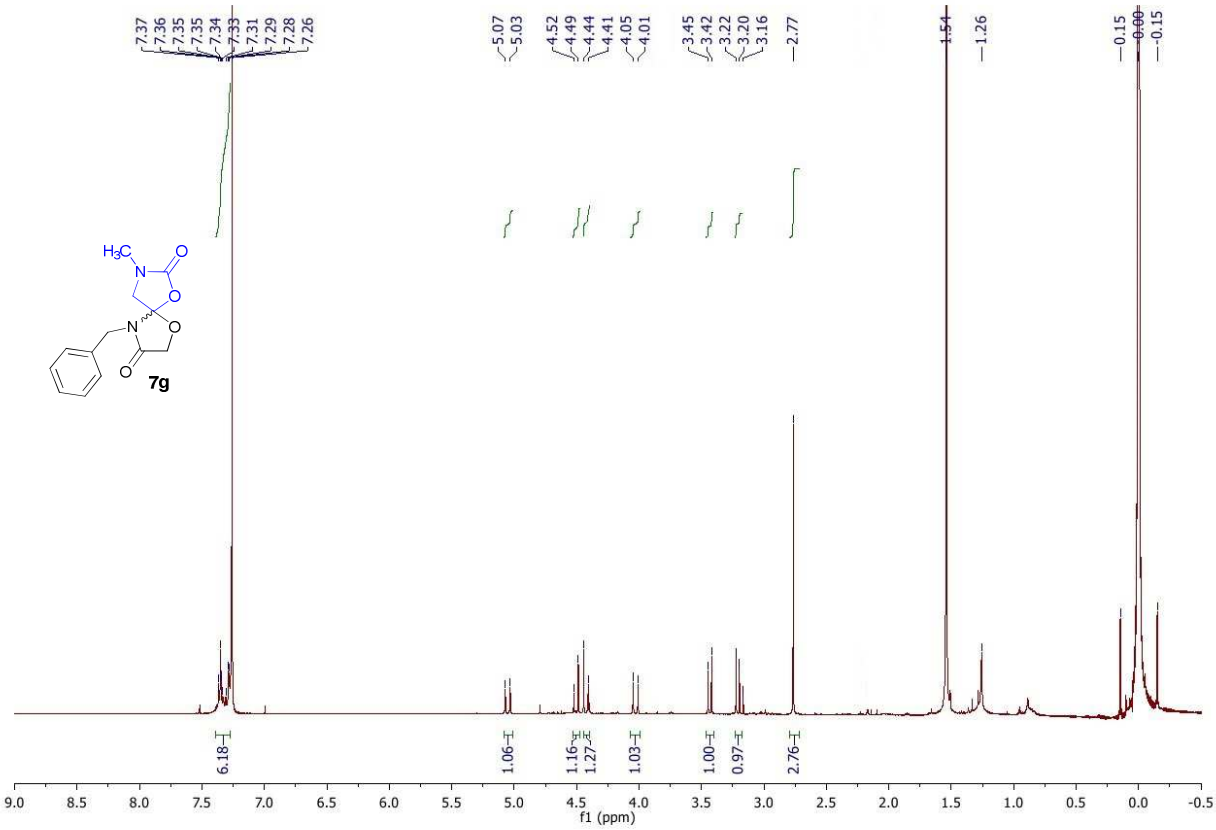


(suppressed DCM peak)

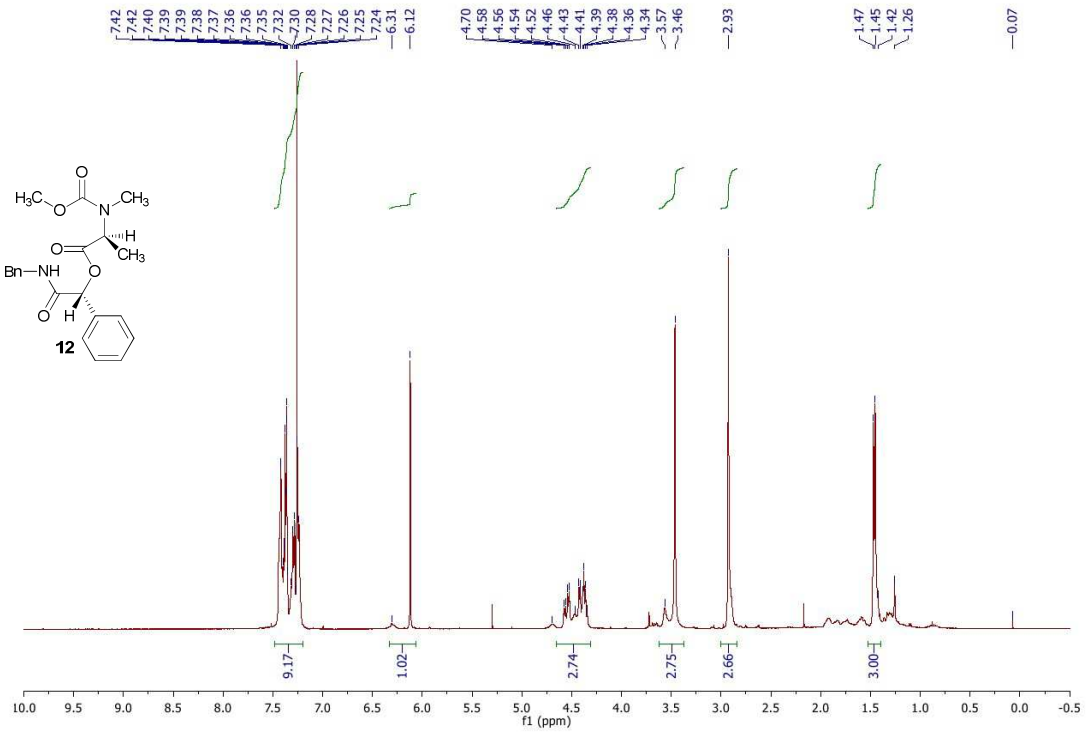
mixture (**7f**) and (**8f**) ^{13}C NMR/ $CDCl_3$/ 150 MHz



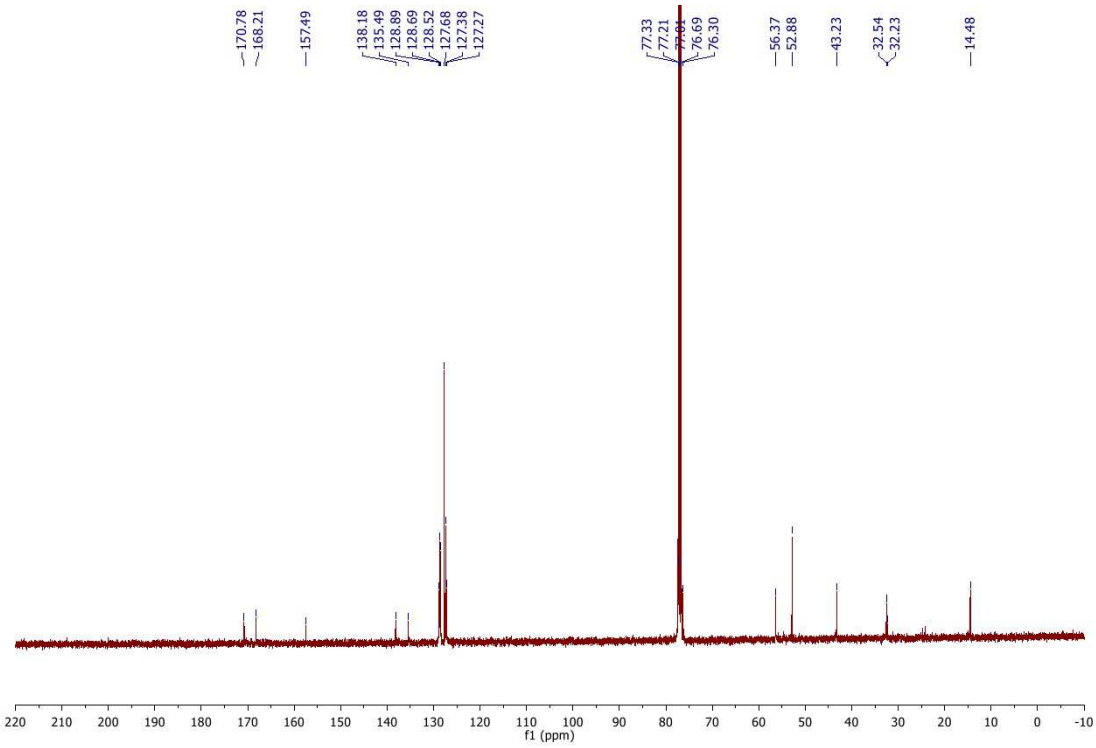
Trace (**7g**) ^{1}H NMR/ $CDCl_3$/ 400 MHz



^{1}H NMR/ $CDCl_3$/ 400 MHz



^{13}C NMR/ $CDCl_3$/ 101 MHz



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