A Samarium(II)–Mediated, Stereoselective Cyclization for the Synthesis of Azaspirocycles

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Contents

General Experimental

All experiments were performed under an atmosphere of nitrogen, using anhydrous solvents, unless stated otherwise. Glassware for inert atmosphere reactions was oven-dried and cooled under a flow of nitrogen. THF was distilled from sodium/benzophenone, CH_2Cl_2 and diisoproylamine were distilled from CaH_2. DMPU was distilled from CaH_2 and stored under N_2. All other solvents and reagents were purchased from commercial sources and used as supplied.

^1H NMR and ^{13}C NMR were recorded on a Bruker 400, Bruker 500 or a 500 Varian spectrometer, with chemical shift values being reported in ppm relative to residual chloroform (δ_H = 7.27 or δ_C = 77.2) as internal standards unless otherwise stated. All coupling constants (*J*) are reported in Hertz (Hz).

Low-resolution mass spectra were recorded on a Fissions VG Trio 2000 quadrupole mass spectrometer or a Thermo LTQ FT spectrometer. Spectra were obtained using electron impact ionisation (EI) and chemical ionisation (CI) techniques, or positive and/or negative electrospray ionisation (ES). High-resolution mass spectra were recorded on a Thermo Finnigan MAT 95XP mass spectrometer.

Infra-red spectra were recorded using a JASCO FT/IR 410 spectrometer or using an ATI Mattson Genesis Series FTIR spectrometer as evaporated films or neat using sodium chloride windows.

Melting points were measured on a Sanyo Gallenkamp variable heater apparatus and are uncorrected.

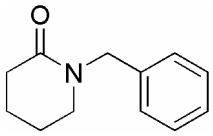
Column chromatography was carried out using Fischer Scientific 35 – 70 μ, 60A silica gel. Routine TLC analysis was carried out on aluminium sheets coated with Merck silica gel 60 F254, 0.2 mm thickness. Plates were viewed using a 254 mm ultraviolet lamp and dipped in aqueous potassium permanganate, p-anisaldehyde, Dragendorff's reagent or DNP.

Preparation of Samarium Iodide (SmI_2)

Samarium Iodide was prepared by a modification of the procedure of Imamoto and Ono.[1]

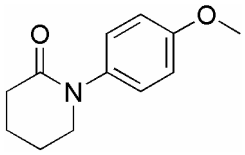
Samarium powder (2.00 g, 13.8 mmol, 1.2 eq) was added to an oven dried round bottomed flask, the flask sealed and flushed with N_2 for 20 min. THF (110 ml) was added and the resulting suspension bubbled with N_2 for 15 min. Finally, iodine (2.80 g, 10.8 mmol, 1 eq) was added and the flask flushed again with N_2 for 10 min. The flask was covered in aluminium foil and heated at 60 ºC for 18 hours. The approx 0.1 M solution was allowed to cool to room temperature and then used directly.

[1] Imamoto, T.; Ono, M. *Chem. Lett.* **1987**, 501.



1-Benzyl-piperidin-2-one[2]

To a suspension of NaH (0.73 g, 30.3 mmol, 1 eq) in THF (40 ml) at 0 °C was added a solution of δ-valerolactam (3.00 g, 30.3 mmol, 1 eq) in THF (40 ml) and the reaction mixture stirred for 30 min. The reaction was then warmed to room temperature and left to stir for a further 30 min until H_2 ceased to evolve. Benzyl bromide (3.60 ml, 30.3 mmol, 1 eq) was added dropwise and the reaction stirred for 18 hours. The reaction was quenched by the addition of H_2O (100 ml) and extracted with CH_2Cl_2 (3 × 80 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give 1-benzylpiperidin-2-one (4.07 g, 21.5 mmol, 71%) as a yellow oil; δ_H (500 MHz, $CDCl_3$) 1.80 (4H, m, CH_2CH_2), 2.49 (2H, t, *J* 6.5 Hz, CH_2C(O)), 3.22 (2H, t, *J* 6.0 Hz, CH_2N), 4.62 (2H, s, NCH_2Ph), 7.25 (5H, m, 5 × Ar-C*H*); δ_C (125 MHz, $CDCl_3$) 20.7 (*C*H_2), 22.5 (*C*H_2), 31.8 (*C*H_2), 46.6 (N*C*H_2), 49.3 (N*C*H_2Ph), 126.6 (Ar-*C*H), 127.4 (2 × Ar-*C*H), 127.9 (2 × Ar-*C*H), 136.7 (Ar-*C*), 169.0 (*C*(O)).



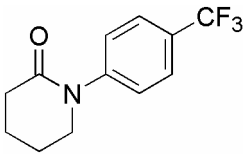
1-(4-Methoxy-phenyl)-piperidin-2-one[3]

To a solution of δ-valerolactam (2.85 g, 28.7 mmol, 1.2 eq) in DMF (30 ml) was added, CuI (0.91 g, 4.79 mmol, 0.2 eq), K_3PO_4 (10.2 g, 48.0 mmol, 2 eq), *N, N*'-dimethylethylenediamine (0.51 ml, 4.79 mmol, 0.2 eq) and 4-bromoanisole (3.00 ml, 24.0 mmol, 1 eq) and the reaction was heated to reflux at 110 °C for 18 hours. The reaction was quenched by filtering through a plug of Na_2SO_4 and washing with CH_2Cl_2 (3

[2] Diez, A.; Castells, J.; Forns, P.; Rubiralta, M. *Tetrahedron* **1994**, *50*, 6585.

[3] Wang, E, C.; Lin, H, J. *Heterocycles* **1998**, 48, 481.

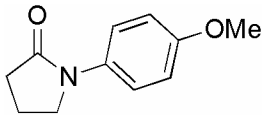
× 30 ml). The combined organic extracts were then washed with H_2O (4 × 40 ml) and dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. Purification by flash column chromatography on silica gel eluting with 70% EtOAc in petroleum ether (40-60) gave 1-(4-methoxy-phenyl)-piperidin-2-one (4.91 g, 21.6 mmol, 90%) as a yellow solid; ν_{max} (neat)/cm^{-1} 3435, 2945, 1651 (C(O)), 1511, 1411, 1243, 1164, 1032, 830, 641, 448 and 409; δ_H (500 MHz, $CDCl_3$) 1.93 (4H, m, C*H*$_2$C*H*$_2$), 2.56 (2H, t, *J* 6.2 Hz, C(O)C*H*$_2$), 3.60 (2H, t, *J* 5.7 Hz, NC*H*$_2$), 3.80 (3H, s, OC*H*$_3$), 6.91 (2H, d, *J* 8.8 Hz, 2 × Ar-C*H*), 7.15 (2H, d, *J* 8.8 Hz, 2 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 21.5 (*C*H_2), 23.6 (*C*H_2), 32.8 (C(O)*C*H_2), 52.0 (N*C*H_2), 55.5 (O*C*H_3), 114.5 (2 × Ar-*C*H), 127.4 (2 × Ar-*C*H), 136.3 (Ar-*C*N), 158.1 (Ar-*C*O) and 170.1 (*C*(O)); *m/z* (CI mode) 205 (M, 100), *m/z* (EI mode) 205 ((M), 70), 149 (50), 136 (45), 120 (15), 92 (10), 83 (100), 77 (5), 64 (5) and 55(3), (Found: (M), 205.1091. $C_{12}H_{15}O_2N$ requires *M*, 205.1097). mp (MeOH) 54-56 °C.



1-(4-Trifluoromethyl-phenyl)-piperidin-2-one

To a solution of δ-valerolactam (2.58 g, 26.1 mmol, 1.2 eq) in DMF (36 ml) was added, CuI (0.86 g, 4.35 mmol, 0.2 eq), K_3PO_4 (9.27 g, 43.5 mmol, 2 eq), *N, N*'-dimethylethylenediamine (0.46 ml, 4.35 mmol, 0.2 eq) and 4-bromoanisole (3.00 ml, 21.7 mmol, 1 eq) and the reaction was heated to reflux at 110 °C for 18 hours. Aqueous saturated NH_4Cl (15 ml) was then added and the aqueous layer was separated and extracted with EtOAc (3 × 50 ml). The combined organic extracts were then washed with H_2O (3 × 100 ml) and dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. Purification by flash column chromatography on silica gel eluting with 70% EtOAc in petroleum ether (40-60) gave 1-(4-trifluoromethyl-phenyl)-piperidin-2-one (3.58 g, 14.7 mmol, 68%) as a yellow solid; ν_{max} (neat)/cm^{-1} 2954, 2362, 1642 (C(O)), 1517, 1410, 1330, 1162, 1116, 1069, 838, 741, 700, 663, 603, 416 and 409; δ_H (500 MHz, $CDCl_3$) 1.89 (4H, m, C*H*$_2$C*H*$_2$), 2.52 (2H, t, *J* 6.0 Hz, C*H*$_2$C(O)), 3.60 (2H, t, *J* 6.0 Hz, NC*H*$_2$), 7.33 (2H, d, *J* 8.5 Hz, 2 × Ar-C*H*), 7.57 (2H, d, *J* 8.5 Hz, 2 × Ar-C*H*); δ_C

(100 MHz, $CDCl_3$) 21.4 (*C*H_2), 23.5 (*C*H_2), 32.9 (C(O)*C*H_2), 51.2 (N*C*H_2), 123.9 (*C*F_3, q, *J* 271 Hz), 126.1 (2 × Ar-*C*H), 126.2 (2 × Ar-*C*H), 128.5 (Ar-*C*CF_3, q, *J* 32 Hz), 146.4 (Ar-*C*N) and 170.1 (*C*(O)); *m/z* (CI mode) 244 (M + H, 100), *m/z* (EI mode) 242 ((M-H), 60), 224 (25), 215 (20), 186 (90), 174 (100), 145 (60), 118 (20), 95 (20), 75(25), 69 (35), 55 (65), 49 (30) and 42 (50), (Found: (M), 243.0861. $C_{12}H_{12}ONF_3$ requires *M*, 243.0866). mp (MeOH) 81-83 °C.

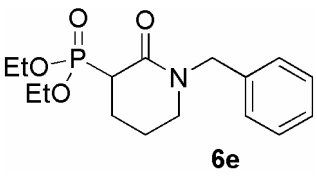


1-(4-Methoxy-phenyl)-pyrrolidin-2-one[3]

To a solution of pyrrolidin-2-one (8.00 ml, 104 mmol, 3 eq) in DMF (30 ml) was added, Cu powder (4.42 g, 69.6 mmol, 2 eq), K_3CO_3 (4.80 g, 34.8 mmol, 1 eq) and 1-iodo-4-methoxy-benzene (8.14 g, 34.8 mmol, 1 eq) and the reaction was heated to reflux at 150 °C for 18 hours. The reaction was quenched by filtering through a plug of silica and washing with CH_2Cl_2 (3 × 50 ml). Purification by flash column chromatography on silica gel eluting with 80% EtOAc in petroleum ether (40-60) gave 1-(4-methoxy-phenyl)-pyrrolidin-2-one (6.64 g, 34.7 mmol, 99%) as a yellow oil; ν_{max} (neat)/cm^{-1} 2952, 1883, 1682 (C(O)), 1514, 1400, 1253, 1126, 1032, 908, 756, and 665; δ_H (300 MHz, $CDCl_3$) 2.11 (2H, m, C*H*$_2$C*H*$_2$N), 2.56 (2H, t, *J* 7.8 Hz, C*H*$_2$), 3.77 (3H, s, OC*H*$_3$), 3.78 (2H, m, NC*H*$_2$), 6.88 (2H, d, *J* 9.0 Hz, 2 × Ar-C*H*), 7.47 (2H, d, *J* 9.0 Hz, 2 × Ar-C*H*); δ_C (75 MHz, $CDCl_3$) 18.0 (*C*H_2), 37.5 (*C*H_2), 49.2 (N*C*H_2), 55.5 (O*C*H_3), 114.0 (2 × Ar-*C*H), 122.2 (2 × Ar-*C*H), 132.7 (Ar-*C*N), 156.6 (Ar-*C*O), 173.9 (*C*(O)); *m/z* (CI mode) 192 (M + H, 100), 178 (30). *m/z* (EI mode) 191 (M, 40), 177 (10), 136 (100), 122 (35) and 68 (10). (Found: (M), 191.0936. $C_{11}H_{13}O_2N$ requires *M*, 191.0941).

[4]Klapars, A.; Jon, C.; Huang, X.; Buchwald, S.L. *J. Am. Chem. Soc* **2002**, 123, 7727.

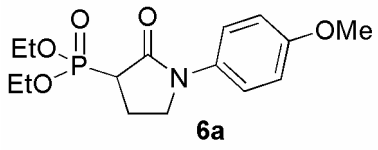
General Procedure A: Preparation of lactam phosphonates



6e

(1-Benzyl-2-oxo-piperidin-3-yl)-phosphonic acid diethyl ester 6e

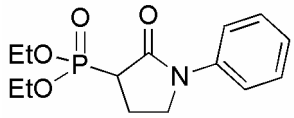
LDA was formed by the addition of *n*-BuLi (1.93 M in hexanes, 8.23 ml, 15.9 mmol, 2 eq) to a stirred solution at -78 °C of diisopropylamine (2.24 ml, 15.9 mmol, 2 eq) in THF (20 ml) and left for 1 hour. A solution of (1.50 g, 7.94 mmol, 1 eq) in THF (10 ml) was added and the reaction mixture stirred for 30 min, at which point it was raised to room temperature and diethylchlorophosphate (1.15 ml, 7.94 mmol, 1 eq) was added and stirred for 18 hours. The solution was acidified to pH 1 by the addition of 1M HCl and the aqueous layer was separated and extracted with CH_2Cl_2 (3 × 50 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. Purification by flash column chromatography on silica gel eluting with 60% EtOAc in petroleum ether (40-60) gave (1-benzyl-2-oxo-piperidin-3-yl)-phosphonic acid diethyl ester **6e** (1.42 g, 4.80 mmol, 60%) as a brown oil; ν_{max} (neat)/cm^{-1} 3469, 2982, 1625 (C(O)), 1493, 1451, 1355, 1286, 1247, 1165, 1026, 967, 752, 701 and 665; δ_H (500 MHz, $CDCl_3$) 1.40 (6H, m, 2 × CH_3), 1.77 (1H, m, 1H from C*H*$_2$$CH_2$N), 2.20 (3H, m, 1H from C*H*$_2$$CH_2$N and 2H from CHC*H*$_2$), 3.13 (1H, dt, *J* 26.7, 6.5 Hz, C*H*P), 3.30 (2H, m, NC*H*$_2$), 4.29 (4H, m, 2 × OC*H*$_2$), 4.57 (1H, d, *J* 14.8 Hz, 1H from NC*H*$_2$Ph), 4.79 (1H, d, *J* 14.8 Hz, 1H from NC*H*$_2$Ph), 7.34 (5H m, 5 × Ar-C*H*); δ_C (125 MHz, $CDCl_3$) 16.5 (2 × *C*H_3), 21.5 (*C*H_2), 23.3 (*C*H_2), 41.8 (*C*H, d, *J* 136 Hz), 47.2 (N*C*H_2), 50.3 (N*C*H_2Ph), 62.1 (O*C*H_2), 63.0 (O*C*H_2), 127.4 (Ar-*C*H), 127.9 (2 × Ar-*C*H), 128.6 (2 × Ar-*C*H), 136.9 (Ar-*C*N), 165.1 (*C*(O)); *m/z* (CI mode) 326 (*M*, 100) and 90 (30). *m/z* (EI mode) 326 (*M*, 5), 205 (5), 177 (9), 158 (80), 132 (40), 104 (20), 90 (100), 80 (12), 64 (30), 55 (30) and 50 (10). (Found: (*M*), 325.1445. $C_{16}H_{24}O_4NP$ requires *M*, 325.1437).



6a

1-(4-Methoxy-phenyl)-2-oxo-pyrrolidin-3-yl]-phosphonic acid diethyl ester 6a

As for general procedure A, a solution of LDA was prepared by the addition of *n*-BuLi (2.21 M in hexanes, 9.50 ml, 20.9 mmol, 2 eq) to a solution of diisopropylamine (3.00 ml, 20.9 mmol, 2 eq) in THF (40 ml), followed by the addition of 1-(4-methoxyphenyl)pyrrolin-2-one (2.00 g, 10.4 mmol, 1 eq) in THF (30 ml) and diethylchlorophosphate (1.50 ml, 10.4 mmol, 1 eq) in THF (6 ml), after purification by flash column chromatography on silica gel eluting with 5% MeOH in EtOAc gave 1-(4-methoxy-phenyl)-2-oxo-pyrrolidin-3-yl]-phosphonic acid diethyl ester **6a** (2.83 g, 8.65 mmol, 83%) as a yellow oil; ν_{max} (neat)/cm^{-1} 3467, 2984, 2050, 1686 (C(O)), 1513, 1443, 1323, 1296, 1181, 1121, 971, 832, 759, 665, 609, 559 and 430; δ_H (300 MHz, $CDCl_3$) 1.33 (6H, m, 2 × OCH_2CH_3), 2.47 (2H, m, $CHCH_2$), 3.14 (1H, m, CHP), 3.73 (1H, m, 1H from NCH_2), 3.78 (3H, s, OCH_3), 3.94 (1H, m, 1H from NCH_2), 4.20 (4H, m, 2 × OCH_2CH_3), 6.88 (2H, dd, *J* 9.0 and 2.3 Hz, 2 × Ar-CH), 7.46 (2H, dd, *J* 9.0 and 2.1 Hz, 2 × Ar-CH); δ_C (75 MHz, $CDCl_3$) 16.5 (2 × CH_3), 20.5 (CH_2), 42.4 (CH, d, *J* 141 Hz), 48.1 (CH_2), 55.5 (OCH_3), 62.5 (OCH_2), 63.3 (OCH_2), 114.1 (2 × Ar-CH), 122.2 (2 × Ar-CH), 132.2 (Ar-CN), 156.9 (Ar-CO), 168.3 (C(O)); *m/z* (CI mode) 328 (*M* + H, 100). *m/z* (EI mode) 327 (*M*, 100), 189 (20), 162 (20), 149 (35) and 136 (5). (Found: (*M*), 327.1227. $C_{15}H_{22}O_5NP$ requires *M*, 327.1230).

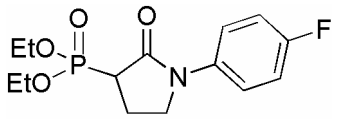


6b

(2-Oxo-1-phenyl-pyrrolidin-3-yl)-phosphonic acid diethyl ester 6b

As for general procedure A, a solution of LDA was prepared by the addition of *n*-BuLi (1.92 M in hexanes, 13.0 ml, 24.8 mmol, 2 eq) to a solution of diisopropylamine (3.52

ml, 24.8 mmol, 2 eq) in THF (40 ml), followed by the addition of 1-phenylpyrrolidin-2-one (2.00 g, 12.4 mmol, 1 eq) in THF (6 ml) and diethylchlorophosphate (1.80 ml, 12.4 mmol, 1 eq) in THF (6 ml) after purification by flash column chromatography on silica gel eluting with 2% MeOH in EtOAc gave (2-oxo-1-phenyl-pyrrolidin-3-yl)-phosphonic acid diethyl ester **6b** (3.30 g, 11.6 mmol, 93%) as a yellow oil; ν_{max} (neat)/cm^{-1} 3434, 3018, 1692 (C(O)), 1599, 1498, 1401, 1302, 1216, 1026, 973, 755 and 668; δ_H (500 MHz, $CDCl_3$) 1.35 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 1.38 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 2.51 (2H, m, CH_2CH_2N), 3.18 (1H, ddd, *J* 22.3, 9.9, 5.4 Hz, C*H*P), 3.84 (1H, m, 1H from NCH_2), 4.03 (1H, m, 1H from NCH_2), 4.25 (4H, m, 2 × OCH_2), 7.17 (1H, t, *J* 7.4 Hz, Ar-C*H*), 7.38 (2H, m, 2 × Ar-C*H*), 7.59 (2H, m, 2 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 16.4 (2 × CH_3), 20.4 (CH_2), 41.9 (*C*HP, d, *J* 142 Hz), 47.6 (NCH_2), 62.6 (OCH_2), 63.2 (OCH_2), 120.3 (2 × Ar-*C*H), 125.0 (Ar-*C*H), 128.9 (2 × Ar-*C*H), 138.9 (Ar-*C*N), 168.5 (*C*(O)); *m/z* (CI mode) 298 (*M* + H, 100). *m/z* (EI mode) 297 (*M*, 100), 269 (20), 240 (10), 160 (35), 132 (60), 119 (90), 105 (20), 77 (60), 55 (55) and 40 (45). (Found: (*M* + H), 298.1211. $C_{14}H_{21}O_4NP$ requires *M* + H, 298.1203).

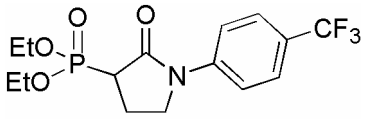


6c

[1-(4-Fluoro-phenyl)-2-oxo-pyrrolidin-3-yl]-phosphonic acid diethyl ester 6c

As for general procedure A, a solution of LDA was prepared by the addition of *n*-BuLi (2.21 M in hexanes, 10.1 ml, 22.3 mmol, 2 eq) to a solution of diisopropylamine (3.20 ml, 22.3 mmol, 2 eq) in THF (20 ml), followed by the addition of 1-(4-fluoro-phenyl)-pyrrolidin-2-one (1.75 g, 11.2 mmol, 1 eq) in THF (30 ml) and diethylchlorophosphate (1.60 ml, 11.2 mmol, 1 eq) in THF (6 ml) after purification by flash column chromatography on silica gel eluting with 5% MeOH in EtOAc gave [1-(4-fluoro-phenyl)-2-oxo-pyrrolidin-3-yl]-phosphonic acid diethyl ester **6c** (2.55 g, 8.10 mmol, 73%) as a yellow oil; ν_{max} (neat)/cm^{-1} 3435, 2097, 1640 (C(O)), 1510, 1217, 1025, 755, 665 and 441; δ_H (400 MHz, $CDCl_3$) 1.14 (3H, t, *J* 7.0 Hz, CH_3), 1.15 (3H, t, *J* 7.0 Hz, CH_3), 2.34 –2.37 (2H, m, CH_2CH_2N), 2.96 (1H, ddd, J_{HP} 22.2, *J* 5.4 and 10.0 Hz, C*H*P),

3.59 (1H, m, 1H from NCH_2), 3.80 (1H, m, 1H from NCH_2), 4.02 (4H, m, 2 × OCH_2), 6.86 (2H, m, 2 × Ar-CH), 7.34 (2H, m, 2 × Ar-CH); δ_C (100 MHz, $CDCl_3$) 16.4 (2 × OCH_2CH_3), 20.3 (CH_2), 42.2 (d, J_{CP} 143 Hz, CHP), 47.9 (NCH_2), 62.5 (OCH_2), 63.3 (OCH_2), 115.5 (Ar-C), 115.7 (2 × Ar-CH), 122.1 (2 × Ar-CH), 133.6 (d, J_{CF} 294 Hz, Ar-CF), 168.5 (C(O)); *m/z* (CI mode) 333 (40), 316 (*M* + H, 100) and 59 (30). *m/z* (EI mode) 315 (*M*, 100), 178 (20), 150 (25), 137 (35) 123 (35), 83 (100) and 49 (30). (Found: (*M* + H), 316.1110. $C_{14}H_{20}O_4NFP$ requires *M* + H, 316.1108)

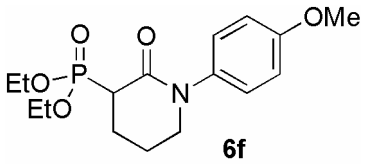


6d

[2-Oxo-1-(4-trifluoromethyl-phenyl)-pyrrolidin-3-yl]-phosphonic acid diethyl ester 6d

As for general procedure A, a solution of LDA was prepared by the addition of *n*-BuLi (2.50 M in hexanes, 7.50 ml, 17.5 mmol, 2 eq) to a solution of diisopropylamine (2.50 ml, 17.5 mmol, 2 eq) in THF (40 ml), followed by the addition of 1-(4-(trifluoromethyl)phenyl)prrolidin-2-one (2.00 g, 8.73 mmol, 1 eq) in THF (20 ml) and diethylchlorophosphate (1.30 ml, 8.73 mmol, 1 eq) in THF (5 ml) after purification by flash column chromatography on silica gel eluting with 2% MeOH in EtOAc gave [2-oxo-1-(4-trifluoromethyl-phenyl)-pyrrolidin-3-yl]-phosphonic acid diethyl ester **6d** (2.10 g, 5.75 mmol, 66%) as a yellow oil; ν_{max} (neat)/cm^{-1} 3431, 2984, 1701 (C(O)), 1615, 1522, 1390, 1323, 1228, 1166, 1120, 1022, 970 and 842; δ_H (500 MHz, $CDCl_3$) 1.33 (3H, t, *J* 6.9 Hz, OCH_2CH_3), 1.36 (3H, t, *J* 6.9 Hz, OCH_2CH_3), 2.52 (2H, m, $CHCH_2$), 3.19 (1H, ddd, *J* 22.5, 9.9, 5.2 Hz, CHP), 3.84 (1H, m, 1H from NCH_2), 4.04 (1H, q, *J* 8.2 Hz, 1H from NCH_2), 4.20 (4H, m, 2 × OCH_2), 7.61 (2H, d, *J* 8.8 Hz, 2 × Ar-CH), 7.75 (2H, d, *J* 8.8 Hz, 2 × Ar-CH); δ_C (125 MHz, $CDCl_3$) 16.4 (2 × CH_3), 20.2 (CH_2), 42.8 (*CH*, d, *J* 135 Hz), 47.3 (NCH_2), 62.6 (OCH_2), 63.2 (OCH_2), 119.5 (2 × Ar-CH), 123.6 (CF_3, q, *J* 271 Hz), 126.0 (2 × Ar-CH), 127.8 (Ar-CCF_3, q, *J* 32 Hz), 141.9 (Ar-CN), 169.0 (C(O)); *m/z* (CI mode) 366 (*M* + H, 100). *m/z* (EI mode) 366 (*M* + H, 20), 228 (20), 200 (25), 173

(25), 151 (40), 145 (100), 122 (70), 109 (60), 81 (60) and 54 (75). (Found: (*M*), 365.0990. $C_{15}H_{19}O_4NF_3P$ requires *M*, 365.0998).

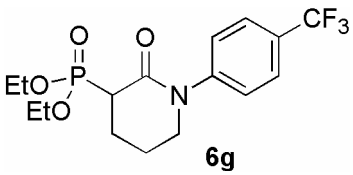


6f

[1-(4-Methoxy-phenyl)-2-oxo-piperidin-3-yl]-phosphonic acid diethyl ester 6f

LDA was formed by the addition of *n*-BuLi (2.32 M in hexanes, 3.50 ml, 8.20 mmol, 1.1 eq) to a stirred solution at -78 °C of diisopropylamine (1.20 ml, 8.20 mmol, 1.1 eq) in THF (20 ml) and left for 1 hour. A solution of 1-(4-methoxy-phenyl)-piperidin-2-one (1.31 g, 7.45 mmol, 1 eq) in THF (5 ml) was added and the reaction mixture stirred for another hour at which point it was raised to room temperature and a solution of diethylchlorophosphate (1.18 ml, 8.20 mmol, 1.1 eq) in DMPU (1.00 ml, 8.20 mmol, 1.1 eq) was added and stirred for 1 hour. A second solution of LDA was prepared by the addition of *n*-BuLi (2.32 M in hexanes, 7.10 ml, 16.4 mmol, 2.2 eq) to a stirred solution at -78 °C of diisopropylamine (2.30 ml, 16.4 mmol, 2.2 eq) in THF (20 ml), this was stirred for an hour before being added to the reaction which was stirred at -78 °C for 18 hours. The solution was acidified to pH 1 by the addition of 1M HCl and the aqueous layer was separated and extracted with EtOAc (3 × 50 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. Purification by flash column chromatography on silica gel eluting with 5% MeOH in EtOAc gave [1-(4-methoxy-phenyl)-2-oxo-piperidin-3-yl]-phosphonic acid diethyl ester **6f** (2.48 g, 7.27 mmol, 97%) as a brown oil; ν_{max} (neat)/cm^{-1} 3463, 2937, 1634 (C(O)), 1529, 1445, 1351, 1319, 1245, 1167, 1053, 969, 835, 758, 709 and 664; δ_H (400 MHz, $CDCl_3$) 1.34 (6H, apparent q, *J* 7.4 Hz, 2 × C*H*$_3$), 1.88 (2H, m, C*H*$_2$CH$_2$N), 2.27 (2H, m, CHC*H*$_2$), 3.14 (1H, dt, *J* 26.7, 6.7 Hz, C*H*P), 3.65 (2H, m, NC*H*$_2$), 3.79 (3H, s, OC*H*$_3$), 4.21 (4H, m, 2 × OC*H*$_2$), 6.91 (2H, d, *J* 8.8 Hz, 2 × Ar-*C*H), 7.16 (2H, d, *J* 9.1 Hz, 2 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 16.7 (*C*H$_2$), 18.1 (*C*H$_2$), 20.1 (2 × *C*H$_3$), 36.9 (C*H*P, d, *J* 137 Hz), 46.7 (NCH$_2$), 50.2 (OCH$_3$), 56.8 (OCH$_2$), 58.0 (OCH$_2$), 109.3 (2 × Ar-*C*H),

122.2 (2 × Ar-*C*H), 130.8 (Ar-*C*N), 153.1 (Ar-*C*O), 160.2 (*C*(O)); *m/z* (CI mode) 342 (M + H, 100), 129 (30) and 128 (60). *m/z* (EI mode) 342 (M + H, 15), 341 (30), 204 (35), 202 (20), 175 (30), 149 (100), 133 (20) and 120 (10). (Found: (M), 341.1403. $C_{16}H_{24}O_5NP$ requires *M*, 341.1387).



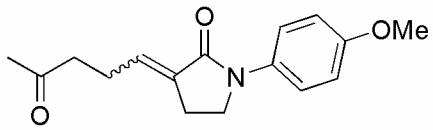
6g

[2-Oxo-1-(4-trifluoromethyl-phenyl)-piperidin-3-yl]-phosphonic acid diethyl ester 6g

LDA was formed by the addition of *n*-BuLi (2.32 M in hexanes, 5.50 ml, 12.7 mmol 1.1 eq) to a stirred solution at -78 °C of diisopropylamine (1.80 ml, 12.7 mmol, 1.1 eq) in THF (30 ml) and left for 1 hour. A solution of 1-(4-trifluoromethyl-phenyl)-piperidin-2-one (2.80 g, 11.5 mmol, 1 eq) in THF (10 ml) was added and the reaction mixture stirred for another hour at which point it was raised to room temperature and a solution of diethylchlorophosphate (1.83 ml, 12.7 mmol, 1.1 eq) in DMPU (1.50 ml, 12.7 mmol, 1.1 eq) was added and the reaction stirred for 1 hour. A second solution of LDA was prepared by the addition of *n*-BuLi (2.32 M in hexanes, 11.0 ml, 25.3 mmol, 2.2 eq) to a stirred solution at -78 °C of diisopropylamine (3.60 ml, 25.3 mmol, 2.2 eq) in THF (30 ml), this was stirred for an hour before being added to the reaction which was then stirred at -78 °C for 18 hours. The solution was acidified to pH 1 by the addition of 1M HCl and the aqueous layer was separated and extracted with EtOAc (3 × 70 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. Purification by flash column chromatography on silica gel eluting with 10% MeOH in EtOAc gave [2-oxo-1-(4-trifluoromethyl-phenyl)-piperidin-3-yl]-phosphonic acid diethyl ester **6g** (2.83 g, 7.46 mmol, 64%) as a brown solid; ν_{max} (neat)/cm^{-1} 3461, 2983, 2240, 1656 (C(O)), 1611, 1518, 1482, 1430, 1411, 1325, 1247, 1166, 1126, 1026, 968, 912, 842, 788 and 646; δ_H (300 MHz, $CDCl_3$) 1.28 (6H, apparent q, *J* 7.0 Hz, 2 × OCH_2CH_3), 1.68 (1H, m, 1H from CH_2), 2.22 (3H, m, 1H from CH_2 and 1H from $CHCH_2$), 3.10 (1H, dt, *J* 6.6, 26.8 Hz, C*H*P), 3.63 (2H, m, NCH_2), 4.14 (4H, m, 2 ×

OC*H*$_2$), 7.33 (2H, d, *J* 8.5 Hz, 2 × Ar-C*H*), 7.57 (2H, d, *J* 8.5 Hz, 2 × Ar-C*H*); δ_C (75 MHz, $CDCl_3$) 16.4 (2 × *C*H$_3$), 21.9 (*C*H$_2$), 23.2 (*C*H$_2$), 42.3 (*C*H, d, *J* 135 Hz), 51.2 (N*C*H$_2$), 62.1 (O*C*H$_2$), 63.2 (O*C*H$_2$), 123.6 (*C*F$_3$, q, *J* 271 Hz), 126.3 (2 × Ar-*C*H), 126.3 (2 × Ar-*C*H), 128.8 (Ar-*C*CF$_3$, q, *J* 32 Hz), 146.2 (Ar-*C*N), 165.6 (*C*(O)); *m/z* (CI mode) 380 (M + H, 100), and 165 (5). *m/z* (EI mode) 380 (M + H, 20), 241 (20), 214 (25), 187 (60), 165 (100), 145 (30), 137 (12), 109 (15), 91 (20), 81 (21) and 55 (65). (Found: (M + H), 380.1242. $C_{16}H_{22}O_4NF_3P$ requires *M* + *H*, 380.1233). mp (MeOH) 61-65 °C.

General Procedure B: Horner Wadsworth Emmons Procedure with K_2CO_3



4a

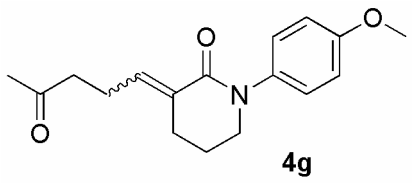
***E/Z* 1-(4-Methoxy-phenyl)-3-(4-oxo-pentylidene)-pyrrolidin-2-one 4a**

K_2CO_3 (0.65 g, 4.72 mmol, 1.1 eq) was added to a stirred solution of 18-crown-6 (2.29 g, 8.59 mmol, 2 eq) and 1-(4-methoxy-phenyl)-2-oxo-pyrrolidin-3-yl]-phosphonic acid diethyl ester **6a** (1.40 g, 4.29 mmol, 1 eq) in THF (60 ml) at room temperature and the resulting solution stirred for 2.5 hours. A solution of 4-oxopentanal (0.49 g, 5.15 mmol, 1.2 eq) in THF (50 ml) was then added and the reaction heated to 60 °C and stirred for 18 hours. Aqueous saturated NH_4Cl (50 ml) was then added and the aqueous layer was separated and extracted with EtOAc (3 × 70 ml). The combined organic extracts were then washed with H_2O (3 × 100 ml) and dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product *E/Z*-1-(4-Methoxy-phenyl)-3-(4-oxo-pentylidene)-pyrrolidin-2-one **4a** (1.17 g, 4.29 mmol, 86%, 1:1 E:Z ratio). Elution with 50% EtOAc in petroleum ether (40-60) gave (*E*)-1-(4-methoxy-phenyl)-3-(4-oxo-pentylidene)-pyrrolidin-2-one **4a** (590 mg, 2.16 mmol, 43%) as a yellow oil; ν_{max} (neat)/cm^{-1} 3325, 2920, 1710 (C(O)), 1660 (C(O)), 1513, 1443, 1397, 1358, 1286, 1250, 1180, 1038, 830 and 690; δ_H (400 MHz, $CDCl_3$) 2.18 (3H, s, C*H*$_3$), 2.45 (2H, q, *J* 7.3 Hz, CHC*H*$_2$), 2.65 (2H, t, *J* 7.2 Hz, C(O)C*H*$_2$), 2.85 (2H, m, C*H*$_2$CH$_2$N), 3.82 (3H, s, OC*H*$_3$), 3.85 (2H, t, *J* 7.1 Hz, NC*H*$_2$), 6.46 (1H, m, C*H*), 6.93 (2H, d, *J* 9.1 Hz, 2 × Ar-C*H*), 7.62 (2H, d, *J* 9.1 Hz, 2 × Ar-C*H*);

δ_C (100 MHz, $CDCl_3$) 21.4 (*C*H_2), 23.2 (*C*H_2), 29.9 (*C*H_3), 42.0 (C(O)*C*H_2), 45.7 (N*C*H_2), 55.4 (O*C*H_3), 113.9 (2 × Ar-*C*H), 121.4 (2 × Ar-*C*H), 131.8 (Ar-*C*), 133.1 (Ar-C), 133.2 (*C*H), 156.5 (Ar-*C*O), 167.0 (*C*(O)), 207.3 (*C*(O)); *m/z* (EI mode) 272 (*M* - H, 30), 229 (100), 201 (30), 134 (40), 120 (80), 107 (40), 91 (40), 82 (65), 77 (60), 65 (80) and 52 (70). (Found: (*M*), 273.1352. $C_{16}H_{19}O_3N$ requires *M*, 273.1359).

Further elution gave (*Z*)-1-(4-methoxy-phenyl)-3-(4-oxo-pentylidene)-pyrrolidin-2-one **4a** (0.490 mg, 1.79 mmol, 41%) as a yellow oil; ν_{max} (neat)/cm^{-1} 2955, 2915, 1704 (C(O)), 1677, 1654 (C(O)), 1517, 1407, 1363, 1322, 1248, 1208, 1172, 1030, 825 and 736; δ_H (400 MHz, $CDCl_3$) 2.17 (3H, s, C*H*$_3$), 2.62 (2H, t, *J* 7.1 Hz, C(O)C*H*$_2$), 2.79 (2H, m, CHC*H*$_2$), 3.04 (2H, m, C*H*$_2$CH$_2$N), 3.79 (2H, t, J 7.1 Hz, NC*H*$_2$), 3.81 (3H, s, OC*H*$_3$), 6.01 (1H, m, C*H*), 6.91 (2H, d, *J* 9.1 Hz, 2 × Ar-C*H*), 7.57 (2H, d, *J* 9.1 Hz, 2 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 22.7 (*C*H_2), 25.5 (*C*H_2), 29.7 (*C*H_3), 43.5 (C(O)*C*H_2), 45.8 (N*C*H_2), 55.5 (O*C*H_3), 113.9 (2 × Ar-*C*H), 121.4 (2 × Ar-*C*H), 131.0 (Ar-*C*), 132.9 (Ar-C), 135.9 (*C*H), 156.5 (Ar-*C*O), 167.2 (*C*(O)), 208.6 (*C*(O)); *m/z* (CI mode) 274 (*M* + H, 100). *m/z* (EI mode) 273 (*M*, 30), 230 (100), 136 (10), 121 (10), 86 (20) and 49 (30). (Found: (*M*), 273.1361. $C_{16}H_{19}O_3N$ requires *M*, 273.1359).

General Procedure C, Horner Wadsworth Emmons Procedure with KHMDS

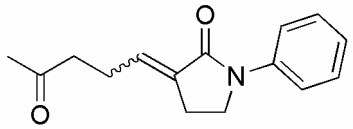


4g

(*Z*)-1-(4-Methoxy-phenyl)-3-(4-oxo-pentylidene)-piperidin-2-one 4g

KHMDS (0.5 M in toluene, 354 ml, 0.18 mmol, 1.1 eq) was added to a stirred solution of 18-crown-6 (213 mg, 0.80 mmol, 5 eq) and [1-(4-methoxy-phenyl)-2-oxo-piperidin-3-yl]-phosphonic acid diethyl ester **6f** (55 mg, 0.16 mmol, 1 eq) in THF (8 ml) at -78 °C and the resulting solution stirred for 30 min. 4-oxopentanal (21 mg, 0.21 mmol, 1.3 eq) was added in THF (2 ml) and the solution stirred for 18 hours allowing to warm to room temperature. Aqueous saturated NH_4Cl (15 ml) was then added and the aqueous layer

was separated and extracted with EtOAc (3 × 50 ml). The combined organic extracts were then washed with H_2O (3 × 100 ml) and dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. Purification by flash column chromatography on silica gel eluting with 50% EtOAc in petroleum ether (40-60) gave (*Z*)-1-(4-methoxy-phenyl)-3-(4-oxo-pentylidene)-piperidin-2-one **4g** (35 mg, 0.12 mmol, 76%) as a yellow oil; ν_{max} (neat)/cm^{-1} 3399, 2933, 1711 (C(O)), 1658 (C(O)), 1621, 1510, 1424, 1363, 1294, 1246, 1187, 1110, 1032, 829 and 863; δ_H (500 MHz, $CDCl_3$) 1.97 (2H, m, C*H*$_2$), 2.10 (3H, s, C*H*$_3$), 2.48 (2H, t, *J* 5.7 Hz, C*H*$_2$C(O)), 2.55 (2H, t, *J* 5.7 Hz, CC*H*$_2$), 2.79 (2H, q, *J* 7.2 Hz, CHC*H*$_2$), 3.61 (2H, t, *J* 6.0 Hz, NC*H*$_2$), 3.79 (3H, s, OC*H*$_3$), 5.88 (1H, m, C*H*), 6.91 (2H, d, *J* 8.8 Hz, 2 × Ar-C*H*), 7.16 (2H, d, *J* 8.8 Hz, 2 × Ar-C*H*). δ_C (125 MHz, $CDCl_3$) 23.9 (*C*H$_2$), 24.0 (*C*H$_2$), 29.7 (*C*H$_3$), 32.3 (*C*H$_2$), 43.6 (*C*H$_2$), 51.9 (NCH$_2$), 55.6 (OCH$_3$), 114.5 (2 × Ar-*C*H), 127.6 (2 × Ar-*C*H), 129.7 (Ar-*C*), 136.2 (*C*), 140.2 (*C*H), 158.1 (Ar-*C*O), 165.3 (*C*(O)), 208.9 (C(O)). *m/z* (ES^+ mode) 592 (30), 349 (30), 310 (20) and 288 ((*M* + H) 100%). (Found: (*M* + H), 288.1588. $C_{17}H_{22}O_3N$ requires *M* + H, 288.1564).



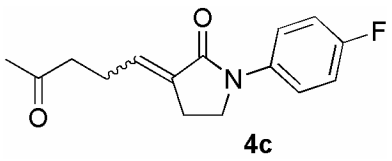
4b

***E/Z* 3-(4-Oxo-pentylidene)-1-phenyl-pyrrolidin-2-one 4b**

As for general procedure C, KHMDS (0.5 M in toluene, 9.50 ml, 4.77 mmol, 1.1 eq) was added to a solution of 18-crown-6 (5.73 g, 21.7 mmol, 5 eq) and (2-oxo-1-phenyl-pyrrolidin-3-yl)-phosphonic acid diethyl ester **6b** (1.24 g, 4.34 mmol, 1 eq) in THF (45 ml), followed by addition of 4-oxopentanal (570 mg, 5.65 mmol, 1.3 eq) in THF (60 ml) to give, after work-up gave *E/Z*-3-(4-oxo-pentylidene)-1-phenyl-pyrrolidin-2-one **4b** (663 mg, 2.73 mmol, 63%, 1:2, E:Z ratio). Elution with 50% EtOAc in petroleum ether (40-60) gave (*E*)-3-(4-oxo-pentylidene)-1-phenyl-pyrrolidin-2-one **4b** (221 mg, 0.90 mmol, 21%) as a yellow oil; ν_{max} (neat)/cm^{-1} 2915, 1706 (C(O)), 1688 (C(O)), 1656, 1597, 1497, 1458, 1393, 1304, 1162, 1097, 893, 757, 698 and 665; δ_H (400 MHz, $CDCl_3$) 2.17 (3H, s, C*H*$_3$), 2.44 (2H, q, *J* 7.2 Hz, CHC*H*$_2$), 2.64 (2H, m, C*H*$_2$CH$_2$N), 2.85 (2H, t, *J* 6.3 Hz,

C(O)C*H*$_2$), 3.87 (2H, t, *J* 6.8 Hz, NC*H*$_2$), 6.48 (1H, m, C*H*), 7.15 (1H, t, *J* 7.3 Hz, Ar-C*H*), 7.38 (2H, t, *J* 7.7 Hz, 2 × Ar-C*H*), 7.71 (2H, d, *J* 8.3 Hz, 2 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 21.4 (*C*H$_2$), 23.2 (*C*H$_2$), 30.1 (*C*H$_3$), 42.0 (C(O)*C*H$_2$), 45.4 (N*C*H$_2$), 119.7 (2 × Ar-*C*H), 124.6 (Ar-*C*H), 128.8 (2 × Ar-*C*H), 132.4 (Ar-*C*), 133.1 (*C*H), 139.7 (*C*), 167.3 (*C*(O)), 207.3 (*C*(O)); *m/z* (CI mode) 244 (*M* + H, 100), 200 (20), 116 (10), 91 (10), and 70 (10). (Found: (*M* + H), 244.1333. $C_{15}H_{18}O_2N$ requires *M* + H, 244.1332)

Further elution gave (*Z*)-3-(4-oxo-pentylidene)-1-phenyl-pyrrolidin-2-one (444 mg, 1.83 mmol, 42%) as yellow oil; δ_H (400 MHz, $CDCl_3$) 2.17 (3H, s, C*H*$_3$), 2.63 (2H, t, *J* 7.1 Hz, C(O)C*H*$_2$), 2.80 (2H, m, C*H*$_2$CH$_2$N), 3.06 (2H, m, CHC*H*$_2$), 3.82 (2H, t, *J* 6.8 Hz, NC*H*$_2$), 6.05 (1H, m, C*H*), 7.16 (1H, t, *J* 7.3 Hz, Ar-C*H*), 7.38 (2H, t, *J* 7.7 Hz, 2 × Ar-C*H*), 7.67 (2H, d, *J* 8.3 Hz, 2 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 21.4 (*C*H$_2$), 25.6 (*C*H$_2$), 29.7 (*C*H$_3$), 43.5 (C(O)*C*H$_2$), 45.5 (N*C*H$_2$), 119.7 (2 × Ar-*C*H), 124.6 (Ar-*C*H), 128.8 (2 × Ar-*C*H), 131.0 (Ar-*C*), 136.6 (*C*H), 139.7 (*C*), 167.5 (*C*(O)), 208.5 (*C*(O));



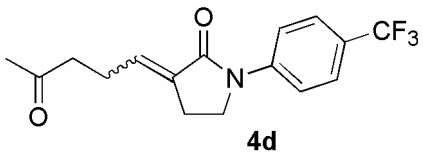
4c

***E/Z* 1-(4-Fluoro-phenyl)-3-[4-oxo-pentylidene]-pyrrolidin-2-one 4c**

As for general procedure C, KHMDS (0.5 M in toluene, 10.0 ml, 4.88 mmol, 1.1 eq) was added to a solution of 18-crown-6 (5.87 g, 22.2 mmol, 5 eq) and [1-(4-fluoro-phenyl)-2-oxo-pyrrolidin-3-yl]-phosphonic acid diethyl ester **6c** (1.40 g, 4.44 mmol, 1 eq) in THF (60 ml), followed by addition of 4-oxopentanal (680 mg, 5.77 mmol, 1.3 eq) in THF (50 ml) to give after work-up gave crude *E/Z*-1-(4-fluoro-phenyl)-3-[4-oxo-pentylidene]-pyrrolidin-2-one **4c** (0.49 g, 1.87 mmol, 42%, 1:2, E:Z ratio (77% on recovered starting material). Elution with 50% EtOAc in petroleum ether (40-60) gave (*E*)-1-(4-fluoro-phenyl)-3-[4-oxo-pentylidene]-pyrrolidin-2-one **4c** (165 mg, 0.63 mmol, 14%) as a yellow oil; ν_{max} (neat)/cm^{-1} 2916, 1715 (C(O)), 1656 (C(O)), 1510, 1427, 1400, 1359, 1314, 1229, 1160, 831 and 665; δ_H (400 MHz, $CDCl_3$) 2.16 (3H, s, C*H*$_3$), 2.46 (2H, q, *J* 7.3 Hz, CHC*H*$_2$), 2.66 (2H, t, *J* 7.2 Hz, C(O)C*H*$_2$), 2.87 (2H, m, C*H*$_2$CH$_2$N), 3.86 (2H, t,

J 7.3 Hz, NC*H*$_2$), 6.48 (1H, m, C*H*), 7.08 (2H, m, 2 × Ar-C*H*), 7.68 (2H, m, 2 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 21.4 (*C*H$_2$), 23.2 (*C*H$_2$), 30.1 (*C*H$_3$), 41.9 (C(O)*C*H$_2$), 45.6 (N*C*H$_2$), 115.5 (2 × Ar-*C*H), 121.3 (2 × Ar-*C*H), 132.5 (Ar-*C*), 132.8 (*C*H), 135.8 (*C*), 159.5 (d, J_{CF} 244.5 Hz, Ar-*C*F), 167.2 (*C*(O)), 207.3 (*C*(O)); *m/z* (CI mode) 262 (*M* + H, 100), 218 (20) and 85 (80). (Found: (*M* + H), 262.1238. $C_{15}H_{17}O_2NF$ requires *M* + H, 262.1238)

Further elution gave (*Z*)-1-(4-fluoro-phenyl)-3-[4-oxo-pentylidene]-pyrrolidin-2-one (321 mg, 1.23 mmol, 27%) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 2.17 (3H, s, C*H*$_3$), 2.63 (2H, t, *J* 7.1 Hz, C(O)C*H*$_2$), 2.81 (2H, m, CHC*H*$_2$), 3.04 (2H, m, C*H*$_2$CH$_2$N), 3.80 (2H, t, *J* 7.3 Hz, NC*H*$_2$), 6.05 (1H, m, C*H*), 7.07 (2H, m, 2 × Ar-C*H*), 7.64 (2H, m, 2 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 21.2 (*C*H$_3$), 25.4 (*C*H$_2$), 29.7 (*C*H$_2$), 43.4 (C(O)*C*H$_2$), 45.7 (N*C*H$_2$), 115.4 (2 × Ar-*C*H), 121.3 (2 × Ar-*C*H), 130.7 (Ar-*C*), 135.8 (*C*), 136.7 (*C*H), 159.5 (d, J_{CF} 244 Hz, Ar-*C*F), 167.3 (*C*(O)), 208.4 (*C*(O));



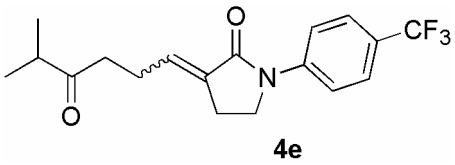
4d

***E/Z* 3-(4-Oxo-pentylidene)-1-(4-trifluoromethyl-phenyl)-pyrrolidin-2-one 4d**

As for general procedure B, K_2CO_3 (0.20 g, 1.43 mmol, 1.3 eq) was added to a solution of 18-crown-6 (0.87 g, 3.29 mmol, 3 eq) and [2-oxo-1-(4-trifluoromethyl-phenyl)-pyrrolidin-3-yl]-phosphonic acid diethyl ester **6d** (0.40 g, 1.10 mmol, 1 eq) in THF (20 ml), followed by addition of 4-oxopentanal (0.22 g, 2.20 mmol, 2 eq) in THF (20 ml).to give, after work up gave *E/Z*-3-(4-oxo-pentylidene)-1-(4-trifluoromethyl-phenyl)-pyrrolidin-2-one **4d** (0.24 g, 0.77 mmol, 69%, 1:2, E:Z ratio). Elution with 50% EtOAc in petroleum ether (40-60) gave (*E*)-3-(4-oxo-pentylidene)-1-(4-trifluoromethyl-phenyl)-pyrrolidin-2-one (7 mg, 0.22 mmol, 20%) as a yellow oil; ν_{max} (neat)/cm^{-1} 3408, 2916, 1711 (C(O)), 1667 (C(O)), 1616, 1521, 1430, 1395, 1326, 1228, 1197, 1165, 1118, 1076, 1014, 951, 844, 754 and 698; δ_H (400 MHz, $CDCl_3$) 2.11 (3H, s, C*H*$_3$), 2.39 (2H, q, *J* 7.5 Hz, C*H*$_2$CH), 2.59 (2H, t, *J* 7.1 Hz, C(O)C*H*$_2$), 2.83 (2H, m, C*H*$_2$CH$_2$N), 3.83 (2H, t, *J*

7.5 Hz, C*H*$_2$N), 6.46 (1H, m, C*H*), 7.56 (2H, d, *J* 8.8 Hz, 2 × Ar-C*H*), 7.80 (2H, d, *J* 8.8 hz, 2 × Ar-C*H*); δ_C (125 MHz, $CDCl_3$) 21.3 (*C*H$_2$), 23.2 (*C*H$_2$), 30.0 (*C*H$_3$), 41.8 (*C*H$_2$), 45.1 (N*C*H$_2$), 118.9 (2 × Ar-*C*H), 124.5 (C*C*F$_3$, q, *J* 271 Hz), 126.0 (2 × Ar-*C*H), 126.2 (Ar-*C*CF$_3$, q, *J* 32 Hz), 132.6 (*C*), 133.8 (*C*H), 142.7 (Ar-*C*N), 167.8 (*C*(O)), 207.1 (*C*(O)); *m/z* (CI mode) 312 (*M* + H , 100). *m/z* (EI mode) 311 (*M*, 60), 268 (80), 224 (10), 172 (10), 145 (10), 81 (10), 67 (100) and 43 (60). (Found: (*M* + H), 312.1209. $C_{16}H_{17}O_2NF_3$ requires *M* + H, 312.1206).

Further elution gave (*Z*)-3-(4-oxo-pentylidene)-1-(4-trifluoromethyl-phenyl)-pyrrolidin-2-one (17 mg, 0.54 mmol, 49%) as a yellow oil; ν_{max} (neat)/cm^{-1} 3406, 2904, 1711 (C(O)), 1686 (C(O)), 1657, 1615, 1521, 1476, 1428, 1391, 1326, 1196, 1164, 1184, 1071, 1014, 948, 896, 843, 755 and 665; δ_H (500 MHz, $CDCl_3$) 2.16 (3H, s, C*H*$_3$), 2.62 (2H, t, *J* 7.0 Hz, C(O)C*H*$_2$), 2.83 (2H, t, J 6.0 Hz, CC*H*$_2$), 3.04 (2H, q, *J* 7.2 Hz, C*H*$_2$CH), 3.83 (2H, t, *J* 7.0 Hz, NC*H*$_2$), 6.10 (1H, m, CH), 7.62 (2H, d, *J* 8.5 Hz, 2 × Ar-C*H*), 7.82 (2H, d, *J* 8.5 Hz, 2 × Ar-C*H*); δ_C (125 MHz, $CDCl_3$) 21.5 (*C*H$_2$), 25.3 (*C*H$_2$), 29.7 (*C*H$_3$), 43.2 (*C*H$_2$), 45.2 (N*C*H$_2$), 117.5 (2 × Ar-*C*H), 124.5 (C*C*F$_3$, q, *J* 271 Hz), 125.9 (2 × Ar-*C*H), 126.2 (Ar-*C*CF$_3$, q, *J* 32 Hz), 130.4 (*C*), 138.0 (*C*H), 142.7 (Ar-*C*N), 167.7 (*C*(O)), 208.2 (*C*(O)); *m/z* (CI mode) 312 (*M* + H , 100). *m/z* (EI mode) 310 (*M* – H, 30), 239 (30), 225 (20), 171 (40), 144 (50), 94 (20), 80 (40), 66 (100) and 48 (70). (Found: (*M*), 311.1137. $C_{16}H_{17}O_2NF_3$ requires *M*, 311.1128).



4e

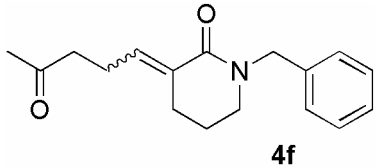
***E/Z* 3-(5-Methyl-4-oxo-hexylidene)-1-(4-trifluoromethyl-phenyl)-pyrrolidin-2-one 4e**

DBU (82 µl, 0.55 mmol, 1 eq) was added to a stirred solution of [2-oxo-1-(4-trifluoromethyl-phenyl)-pyrrolidin-3-yl]-phosphonic acid diethyl ester **6d** (0.20 g, 0.55 mmol, 1 eq) and LiCl (23 mg, 0.55 mmol, 1 eq) in CH_3CN (5 ml) at room temperature and the solution stirred for 10 min. 5-Methyl-4-oxohexanal (77 mg, 0.61 mmol, 1.1 eq) in CH_3CN (5 ml) was then added and the reaction left to stir for 18 hours at room

temperature followed by heating at reflux for 5 hours. The reaction was quenched with the addition of aqueous saturated solution of NH_4Cl (5 ml) and the aqueous layer separated and extracted with EtOAc (3 × 10 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. Purification by flash column chromatography on silica gel eluting with a solvent gradient of 50% EtOAc in petroleum ether (40-60) to give *E/Z*-3-(5-methyl-4-oxo-hexylidene)-1-(4-trifluoromethyl-phenyl)-pyrrolidin-2-one **4e** (12 mg, 0.35 mmol, 64%) as a white solid.

Characterisation as a mixture of double bond isomers;

ν_{max} (neat)/cm^{-1} 3400, 3019, 2925, 2853, 2360, 1701 (C(O)), 1664 (C(O)), 1615, 1521, 1466, 1443, 1389, 1323, 1216, 1166, 1120, 1068, 841 and 665; δ_H (400 MHz, $CDCl_3$) 1.03 (6H, d, *J* 3.3 Hz, 2 × C*H*$_3$), 1.04 (6H, d, *J* 3.3 Hz, 2 × C*H*$_3$), 2.40 (2H, q, *J* 7.2 Hz, C*H*$_2$CH), 2.57 (6H, m, 2 × C*H*C(O) and 2 × C(O)C*H*$_2$), 2.76 (2H, m, C*H*$_2$CH$_2$N), 2.84 (2H, m, CH$_2$CH$_2$N), 2.95 (2H, q, *J* 7.0 Hz, C*H*$_2$CH), 3.76 (2H, t, *J* 7.1 Hz, NC*H*$_2$), 3.83 (2H, t, *J* 7.1 Hz, NC*H*$_2$), 6.10 (1H, m, C*H*C), 6.46 (1H, m, C*H*C), 7.55 (2H, dd, *J* 8.7, 2.9 Hz, 2 × Ar-C*H*), 7.78 (2H, dd, *J* 17.8, 8.5 Hz, 2 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 18.2 (4 × *C*H$_3$), 21.3 (*C*H$_2$), 21.5 (*C*H$_2$), 23.4 (*C*H$_2$), 25.3 (*C*H$_2$), 38.5 (C(O)*C*H$_2$), 39.9 (C(O)*C*H$_2$), 40.7 (2 × C*C*H), 41.0 (2 × C(O)*C*H), 45.1 (N*C*H$_2$), 45.2 (N*C*H$_2$), 118.9 (4 × Ar-*C*H), 126.5 (4 × Ar-*C*H), 130.1 (2 × *C*), 132.4 (2 × Ar-*C*N), 134.1 (*C*HC), 138.5 (*C*HC), 165.0 (*C*(O)), 167.7 (*C*(O)), 213.2 (*C*(O)), 214.0 (*C*(O)); *m/z* (CI mode) 340 (*M* + H, 100). *m/z* (EI mode) 339 (*M*, 5), 268 (20), 172 (50), 145 (60), 109 (20), 84 (100), 67 (40) and 48 (30). (Found: (*M*), 339.1442. $C_{18}H_{20}O_2NF_3$ requires *M*, 339.1441).



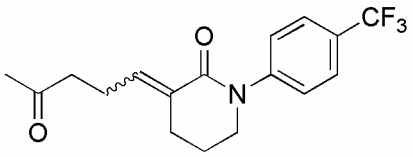
4f

***E/Z* 1-Benzyl-3-(4-oxo-pentylidene)-piperidin-2-one 4f**

As for general procedure B, K_2CO_3 (0.24 g, 1.69 mmol, 1.1 eq) was added to a solution of 18-crown-6 (0.45 g, 1.69 mmol, 1.1 eq) and (1-benzyl-2-oxo-piperidin-3-yl)-

phosphonic acid diethyl ester **6e** (0.50 g, 1.54 mmol, 1 eq) in THF (80 ml), followed by addition of 4-oxopentanal (0.19 g, 1.85 mmol, 1.2 eq) in THF (20 ml).to give, after work up and purification, *E/Z* 1-Benzyl-3-(4-oxo-pentylidene)-piperidin-2-one **4f** (0.117 g, 0.45 mmol, 27%, 6:1, E:Z (56% based on recovered starting material). Elution with 50% EtOAc in petroleum ether (40-60) gave (*E*)-1-benzyl-3-(4-oxo-pentylidene)-piperidin-2-one **4f** (93 mg, 0.34 mmol, 22%) as a yellow oil; ν_{max} (neat)/cm^{-1} 3416, 2930, 1713 (C(O)), 1659 (C(O)), 1611, 1491, 1452, 1353, 1261, 1201, 1164, 1076, 734 and 701; δ_H (100 MHz, $CDCl_3$) 1.75 (2H, m, C*H*$_2$CH$_2$N), 2.09 (3H, s, CH_3), 2.33 (2H, q, *J* 7.2 Hz, C*H*$_2$CH), 2.45 (2H, t, *J* 6.9 Hz, C*H*$_2$C(O)), 2.54 (2H, t, *J* 7.4 Hz, C*H*$_2$CH$_2$CH$_2$N), 3.20 (NC*H*$_2$), 4.57 (2H, s, NC*H*$_2$Ph), 6.73 (1H, m, C*H*), 7.22 (5H, m, 5 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 22.1 (*C*H$_2$), 22.6 (*C*H$_2$), 24.7 (*C*H$_3$), 30.1 (*C*H$_2$), 42.2 (*C*H$_2$), 47.2 (N*C*H$_2$), 50.9 (N*C*H$_2$Ph), 127.3 (Ar-*C*), 128.0 (2 × Ar-*C*H), 128.1 (2 × Ar-*C*H), 129.8 (Ar-*C*H), 136.7 (*C*H), 137.4 (*C*), 164.9 (*C*(O)), 207.6 (*C*(O)); *m/z* (CI mode) 272 (*M* + H, 100). *m/z* (EI mode) 272 (*M* + H, 2), 228 (5), 91 (100) and 65 (10). (Found: (*M*), 271.1563. $C_{17}H_{21}O_2N$ requires *M*, 271.1567).

Further elution gave (*Z*)-1-benzyl-3-(4-oxo-pentylidene)-piperidin-2-one **4f** (24 mg, 0.09 mmol, 7%) as a yellow oil; ν_{max} (neat)/cm^{-1} 3419, 2929, 1713 (C(O)), 1662 (C(O)), 1610, 1490, 1453, 1357, 1261, 1201, 1164, 1077, 736 and 701; δ_H (400 MHz, $CDCl_3$) 1.75 (2H, m, C*H*$_2$CH$_2$N), 2.09 (3H, s, C*H*$_3$), 2.35 (2H, m, C*H*$_2$CH$_2$CH$_2$N), 2.56 (2H, t, *J* 7.1 Hz, C*H*$_2$C(O)), 2.87 (2H, q, J 7.2 Hz, C*H*$_2$CH), 3.16 (2H, t, *J* 6.2 Hz, NC*H*$_2$), 4.55 (2H, s, NC*H*$_2$Ph), 5.73 (1H, m, C*H*), 7.23 (5H, m, 5 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 23.5 (*C*H$_2$), 24.0 (*C*H$_2$), 29.6 (*C*H$_3$), 32.4 (*C*H$_2$), 43.7 (*C*H$_2$), 47.4 (N*C*H$_2$), 49.9 (N*C*H$_2$Ph), 127.3 (Ar-*C*), 127.9 (2 × Ar-CH), 128.4 (2 × Ar-*C*H), 129.6 (Ar-*C*H), 137.4 (*C*H), 139.4 (*C*), 165.1 (*C*(O)), 208.9 (*C*(O)). *m/z* (CI mode) 272 (*M* + H, 100), 178 (10), 90 (20) and 84 (18). *m/z* (EI mode) 271 (*M*, 5), 227 (20), 90 (60), 64 (30) and 48 (85). (Found: (*M*), 271.1568. $C_{17}H_{21}O_2N$ requires *M*, 271.1567).

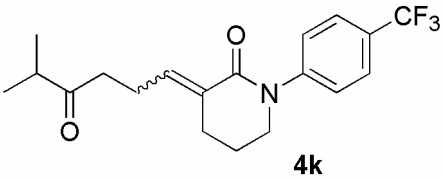


4h

***E/Z* 3-(4-Oxo-pentylidene)-1-(4-trifluoromethyl-phenyl)-piperidin-2-one 4h**

As for general procedure C, KHMDS (0.5 M in toluene, 5.80 ml, 2.90 mmol, 1.1 eq) was added to a solution of 18-crown-6 (3.50 g, 13.2 mmol, 5 eq) and (1.00 g, 2.64 mmol, 1 eq) in THF (40 ml), followed by addition of 4-oxopentanal (355 mg, 3.43 mmol, 1.3 eq) in THF (40 ml) to give after work-up and purification gave *E/Z* 3-(4-Oxo-pentylidene)-1-(4-trifluoromethyl-phenyl)-piperidin-2-one **4h** (328 mg, 1.00 mmol, 41%, 1:5, E:Z, (55% based on recovered starting material). Elution with 40% EtOAc in petroleum ether (40-60) gave (*E*)-3-(4-oxo-pentylidene)-1-(4-trifluoromethyl-phenyl)-piperidin-2-one **4h** (81 mg, 0.25 mmol, 9%) as a yellow oil; ν_{max} (neat)/cm^{-1} 3413, 292, 1716 (C(O)), 1666 (C(O)), 1612, 1518, 1409, 1356, 1164, 1121, 1067, 1017, 845, 732 and 665; δ_H (400 MHz, $CDCl_3$) 1.97 (2H, m, C*H*$_2$CH$_2$CH$_2$N), 2.10 (3H, s, C*H*$_3$), 2.34 (2H, q, *J* 7.3 Hz, C*H*$_2$CH), 2.58 (4H, m, C*H*$_2$C(O) and C*H*$_2$CH$_2$N), 3.67 (2H, m, NC*H*$_2$), 6.78 (1H, m, C*H*), 7.35 (2H, m, 2 × Ar-C*H*), 7.58 (2H, m, 2 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 22.2 (*C*H$_2$), 22.9 (*C*H$_2$), 24.7 (*C*H$_3$), 30.0 (*C*H$_2$), 41.9 (*C*H), 50.7 (N*C*H$_2$), 124.0 (C*C*F$_3$, q, *J* 281 Hz), 125.9 (4 × Ar-*C*H), 128.0 (Ar-CCF$_3$, q, *J* 32 Hz), 129.6 (Ar-*C*N), 138.6 (*C*H), 146.7 (*C*), 164.8 (*C*(O)), 207.4 (*C*(O)); *m/z* (CI mode) 326 (*M* + H, 100), 290 (10) and 118 (5). *m/z* (EI mode) 326 (*M* + H, 10), 254 (30), 218 (10), 174 (20), 145 (50) and 45 (20). (Found: (*M*), 325.1290. $C_{17}H_{18}O_2NF_3$ requires *M*, 325.1284).

Further elution gave (*Z*)-3-(4-oxo-pentylidene)-1-(4-trifluoromethyl-phenyl)-piperidin-2-one **4h** (278 mg, 0.86 mmol, 32%) as a yellow oil; δ_H (200 MHz, $CDCl_3$) 1.84-2.04 (2H, m, C*H*$_2$), 1.97 (3H, s, C*H*$_3$), 2.40-2.49 (4H, m, 2 × C*H*$_2$), 2.69 (2H, m, CHC*H*$_2$), 3.54 (2H, t, *J* 6.0 Hz, NC*H*$_2$), 5.80 (1H, m, C*H*), 7.27 (2H, d, *J* 8.2 Hz, 2 × Ar-C*H*), 7.50 (2H, d, *J* 8.3 Hz, 2 × Ar-C*H*); δ_C (125 MHz, $CDCl_3$) 23.7 (*C*H$_2$), 24.1 (*C*H$_2$), 29.7 (*C*H$_3$), 31.9 (*C*H$_2$), 43.4 (*C*H$_2$), 51.1 (N*C*H$_2$), 123.9 (C*C*F$_3$, q, *J* 272 Hz), 126.2 (2 × Ar-*C*H), 126.5 (2 × Ar-*C*H), 128.5 (Ar-*C*CF$_3$, q, *J* 32 Hz), 129.0 (*C*), 129.2 (Ar-*C*N), 141.5 (*C*H), 146.3 (Ar-*C*O), 165.2 (*C*(O)), 208.6 (*C*(O));



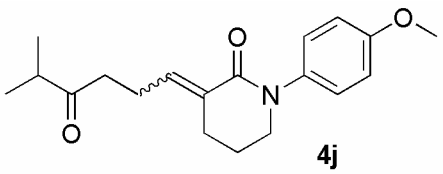
4k

***E/Z* 3-(5-Methyl-4-oxo-hexylidene)-1-(4-trifluoromethyl-phenyl)-piperidin-2-one 4k**

As for general procedure C, KHMDS (0.5 M in toluene, 5.80 ml, 2.90 mmol, 1.1 eq) was added to a solution of 18-crown-6 (3.48 g, 13.2 mmol, 5 eq) and [2-oxo-1-(4-trifluoromethyl-phenyl)-piperidin-3-yl]-phosphonic acid diethyl ester **6g** (1.00 g, 2.64 mmol, 1 eq) in THF (50 ml). Followed by addition of 5-methyl-4-oxohexanal (44 mg, 3.43 mmol, 1.3 eq) in THF (40 ml) to give after work-up gave *E/Z* 3-(5-methyl-4-oxo-hexylidene)-1-(4-trifluoromethyl-phenyl)-piperidin-2-one **4k** (518 mg, 1.47 mmol, 56%, 1:5, E:Z ratio). Elution with 50% EtOAc in petroleum ether (40-60) gave (*E*)-3-(5-Methyl-4-oxo-hexylidene)-1-(4-trifluoromethyl-phenyl)-piperidin-2-one **4k** (88 mg, 0.25 mmol, 9%) as a brown oil; ν_{max} (neat)/cm^{-1} 3511, 2969, 2245, 1709 (C(O)), 1625 (C(O)), 1518, 1449, 1423, 1408, 1325, 1165, 1122, 1068, 1018, 919, 836, 760 and 685; δ_H (500 MHz, $CDCl_3$) 1.11 (6H, d, *J* 6.8 Hz, 2 × C*H*$_3$), 2.05 (2H, m, CH_2), 2.45 (2H, q, *J* 7.5 Hz, CHC*H*$_2$), 2.61 (1H, m, C*H*(CH$_3$)), 2.67 (4H, m, 2H from C*H*$_2$C and 2H from C(O)C*H*$_2$), 3.74 (2H, t, *J* 6.0 Hz, NC*H*$_2$), 6.85 (1H, m, C*H*C), 7.43 (2H, d, *J* 8.2 Hz, 2 × Ar-C*H*), 7.63 (2H, d, *J* 8.2 Hz, 2 × Ar-C*H*); *m/z* (CI mode) 354 (*M* + H , 100) and 282 (10). *m/z* (EI mode) 353 (*M*, 5), 281 (40), 253 (10), 173 (10), 144 (30), 125 (10), 78 (20) and 48 (100). (Found: (*M*), 353.1595. $C_{19}H_{22}O_2NF_3$ requires *M*, 353.1597).

Further elution gave (*Z*)-3-(5-methyl-4-oxo-hexylidene)-1-(4-trifluoromethyl-phenyl)-piperidin-2-one **4k** (440 mg, 1.25 mmol, 45%) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 1.07 (6H, d, *J* 6.8 Hz, 2 × C*H*$_3$), 2.02 (2H, m, CH_2), 2.56-2.66 (5H, m, 2H from C(O)C*H*$_2$, 2H from CC*H*$_2$, 1H from C*H*), 2.84 (2H, q, *J* 7.0 Hz, CHC*H*$_2$), 3.69 (2H, t, J 6.0 Hz, NC*H*$_2$), 5.79 (1H, m, C*H*), 7.42 (2H, d, *J* 8.3 Hz, 2 × Ar-C*H*), 7.65 (2H, d, *J* 8.3 Hz, 2 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 18.3 (2 × *C*H$_3$), 23.4 (*C*H$_2$), 24.0 (*C*H$_2$), 31.9 (*C*H$_2$), 40.0 (*C*H$_2$), 40.1 (*C*H), 51.1 (N*C*H$_2$), 124.0 (*C*F$_3$, q, *J* 271 Hz), 126.1 (2 × Ar-

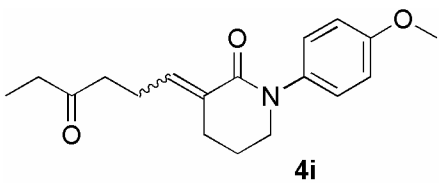
*C*H), 126.5 (2 × Ar-*C*H), 128.5 (Ar-*C*CF_3, q, *J* 32 Hz), 128.9 (Ar-*C*), 142.0 (*C*H), 146.4 (*C*), 165.2 (*C*(O)), 214.3 (*C*(O));



4j

***(Z)*-1-(4-Methoxy-phenyl)-3-(5-methyl-4-oxo-hexylidene)-piperidin-2-one 4j**

As for general procedure C, KHMDS (0.5 M in toluene, 6.00 ml, 2.98 mmol, 1.1 eq) was added to a solution of 18-crown-6 (3.60 g, 13.6 mmol, 5 eq) and [1-(4-methoxy-phenyl)-2-oxo-piperidin-3-yl]-phosphonic acid diethyl ester **6f** (924 mg, 2.71 mmol, 1 eq) in THF (50 ml), followed by addition of 5-methyl-4-oxohexanal (451 mg, 3.52 mmol, 1.3 eq) in THF (50 ml) to give after work-up and purification (*Z*)-1-(4-methoxy-phenyl)-3-(5-methyl-4-oxo-hexylidene)-piperidin-2-one **4j** (220 mg, 0.70 mmol, 26%) as a yellow oil; ν_{max} (neat)/cm^{-1} 2935, 2361, 1708 (C(O)), 1661 (C(O)), 1607, 1511, 1412, 1294, 1246, 1188, 1034, 827 and 665; δ_H (400 MHz, $CDCl_3$) 1.06 (6H, d, *J* 6.8 Hz, 2 × CH_3), 1.97 (2H, m, CH_2), 2.55-2.65 (5H, m, 2H from C(O)CH_2, 2H from CCH_2 and 1H from C*H*), 2.85 (2H, q, *J* 7.3 Hz, CHCH_2), 3.62 (2H, t, *J* 6.0 Hz, NCH_2), 3.80 (3H, s, OCH_3), 5.90 (1H, m, C*H*), 6.92 (2H, d, *J* 8.8 Hz, 2 × Ar-C*H*), 7.17 (2H, d, *J* 8.8 Hz, 2 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 18.3 (2 × *C*H_3), 23.9 (2 × *C*H_2), 32.3 (*C*H_2), 40.2 (*C*H_2), 40.5 (*C*H), 51.9 (N*C*H_2), 55.5 (O*C*H_3), 114.5 (2 × Ar-*C*H), 127.9 (2 × Ar-*C*H), 129.4 (*C*H), 136.2 (*C*), 140.7 (Ar-*C*N), 158.1 (Ar-*C*O), 165.4 (*C*(O)), 214.6 (*C*(O)); *m/z* (CI mode) 316 (*M* + H, 100). *m/z* (EI mode) 316 (*M* + H, 2), 134 (20), 120 (50), 92 (40), 77 (100), 71 (40), 66 (90) and 53 (50). (Found: (*M*), 315.1836. $C_{19}H_{25}O_3N$ requires *M*, 315.1829).

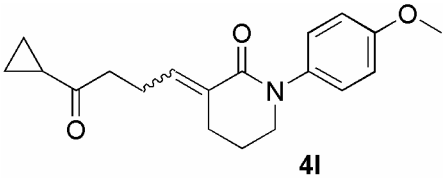


4i

***E/Z* 1-(4-Methoxy-phenyl)-3-(4-oxo-hexylidene)-piperidin-2-one 4i**

As for general procedure C, KHMDS (0.5 M in toluene, 9.00 ml, 4.50 mmol, 1.2 eq) was added to a solution of 18-crown-6 (4.95 g, 18.8 mmol, 5 eq) and [1-(4-methoxy-phenyl)-2-oxo-piperidin-3-yl]-phosphonic acid diethyl ester **6f** (1.28 g, 3.75 mmol, 1 eq) in THF (60 ml), followed by addition of 4-oxohexanal (855 mg, 7.50 mmol, 2 eq) in THF (60 ml) to give after work-up and purification gave *E/Z* 1-(4-Methoxy-phenyl)-3-(4-oxo-hexylidene)-piperidin-2-one **4i** (667 mg, 2.22 mmol, 59%, 1:3, E:Z ratio). Elution with 40% EtOAc in petroleum ether (40-60) gave (*E*)-1-(4-Methoxy-phenyl)-3-(4-oxo-hexylidene)-piperidin-2-one **4i** (152 mg, 0.51 mmol, 14%) as a yellow oil; ν_{max} (neat)/cm^{-1} 2937, 1711 (C(O)), 1659 (C(O)), 1621, 1506, 1446, 1424, 1374, 1294, 1245, 1187, 1112, 1032, 828, 774 and 674; δ_H (400 MHz, $CDCl_3$) 0.98 (3H, t, *J* 7.3 Hz, C*H*$_3$), 1.92 (2H, m, C*H*$_2$CH$_2$N), 2.37 (4H, m, 2H from C(O)C*H*$_2$CH$_3$ and C*H*$_2$CH), 2.54 (4H, m, 2H from C(O)C*H*$_2$ and 2H from C*H*$_2$CH$_2$CH$_2$N), 3.58 (2H, m, NC*H*$_2$), 3.72 (3H, s, OC*H*$_3$), 6.72 (1H, m, C*H*), 6.82 (2H, d, *J* 9.1 Hz, 2 × Ar-C*H*), 7.09 (2H, d, *J* 9.1 Hz, 2 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 7.80 (CH_3), 22.2 (CH_2), 23.1 (CH_2), 24.6 (CH_2), 36.0 (CH_2), 40.8 (CH_2), 51.5 (NCH_2), 55.4 (OCH_3), 114.3 (2 × Ar-CH), 127.2 (2 × Ar-CH), 129.9 (C), 136.7 (Ar-CN), 137.6 (CH), 157.9 (Ar-CO), 169.0 (C(O)), 209.6 (C(O)); *m/z* (ES+ mode) 360 (60), 324 (M + 23, 100), 302 (M + H, 70).

Further elution gave (*Z*)-1-(4-Methoxy-phenyl)-3-(4-oxo-hexylidene)-piperidin-2-one **4i** (515 mg, 1.71 mmol, 46%) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J* 7.4 Hz, C*H*$_3$), 1.84 (2H, m, C*H*$_2$CH$_2$N), 2.27 (2H, q, *J* 7.3 Hz, C(O)C*H*$_2$CH$_3$), 2.42 (4H, m, 2H from C*H*$_2$CH and 2H from C*H*$_2$CH$_2$CH$_2$N), 2.72 (2H, q, *J* 7.2 Hz, C(O)C*H*$_2$), 3.47 (2H, m, NC*H*$_2$), 3.65 (3H, s, OC*H*$_3$), 5.75 (1H, m, C*H*), 6.77 (2H, m, 2 × Ar-C*H*), 7.02 (2H, m, 2 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 7.76 (*C*H_3), 23.9 (*C*H_2), 24.1 (*C*H_2), 32.2 (*C*H_2), 35.5 (*C*H_2), 42.2 (*C*H_2), 51.8 (N*C*H_2), 55.4 (O*C*H_3), 114.4 (2 × Ar-*C*H), 127.6 (2 × Ar-*C*H), 129.5 (*C*), 136.2 (Ar-*C*N), 140.4 (*C*H), 158.0 (Ar-*C*O), 165.3 (*C*(O)), 211.4 (*C*(O));

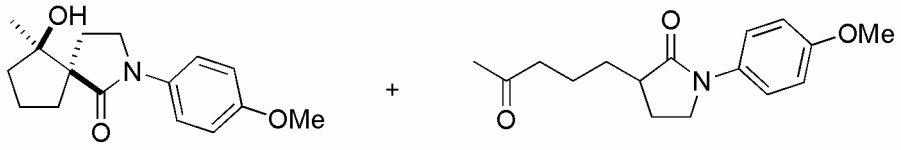


4l

(*Z*)-3-(4-Cyclopropyl-4-oxo-butylidene)-1-(4-methoxy-phenyl)-piperidin-2-one 4l

As for general procedure C, KHMDS (0.5 M in toluene, 1.60 ml, 0.80 mmol, 1.2 eq) was added to a solution of 18-crown-6 (0.88 g, 3.33 mmol, 5 eq) and [1-(4-Methoxy-phenyl)-2-oxo-piperidin-3-yl]-phosphonic acid diethyl ester **6f** (228 mg, 0.67 mmol, 1 eq) in THF (20 ml), followed by addition of 4-cyclopropyl-4-oxo-butyraldehyde (0.13 ml, 1.00 mmol, 1.5 eq) in THF (10 ml) to give after work-up and purification (*Z*)-3-(4-cyclopropyl-4-oxo-butylidene)-1-(4-methoxy-phenyl)-piperidin-2-one **4l** (135 mg, 0.43 mmol, 64%) as a yellow oil; ν_{max} (neat)/cm^{-1} 3434, 2929, 2858, 2361, 1647 (C(O)), 1646 (C(O)), 1510, 1459, 1349, 1295, 1243, 1182, 1153, 1107, 1033 and 827; δ_H (400 MHz, $CDCl_3$) 0.82 (2H, m, *c*-Pr-C*H*$_2$), 0.98 (2H, m, *c*-Pr-C*H*$_2$), 1.96 (3H, m, 1H from c-Pr-C*H*, 2H from C*H*$_2$CH$_2$N), 2.56 (2H, t, *J* 5.3 Hz, C*H*$_2$CH$_2$CH$_2$N), 2.73 (2H, t, *J* 7.2 Hz, C*H*$_2$C(O)), 2.91 (2H, q, *J* 7.1 Hz, C*H*$_2$CH), 3.62 (2H, m, NC*H*$_2$), 3.80 (3H, s, OC*H*$_3$), 5.91 (1H, t, *J* 7.6 Hz, C*H*C), 6.92 (2H, m, 2 × Ar-C*H*), 7.18 (2H, m, 2 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 10.6 (2 × *C*H$_2$), 20.2 (*C*HC(O)), 23.9 (*C*H$_2$), 24.2 (*C*H$_2$), 32.3 (*C*H$_2$), 43.3 (*C*H$_2$), 51.9 (N*C*H$_2$), 55.5 (O*C*H$_3$), 114.5 (2 × Ar-*C*H), 127.6 (2 × Ar-*C*H), 129.5 (*C*), 136.2 (Ar-*C*N), 140.6 (*C*HC), 158.0 (Ar-*C*O), 165.4 (*C*(O)), 210.8 (*C*(O)); *m/z* (CI mode) 314 (*M* + H, 100). *m/z* (EI mode) 314 (*M* + H, 80), 244 (50), 218 (20), 205 (20), 135 (30), 123 (45), 110 (40), 84 (40), 69 (100) and 58 (40). (Found: (*M*), 313.1680 $C_{19}H_{23}O_3N$ requires *M*, 313.1672).

General Procedure D: SmI_2-mediated cyclization of 5 membered subsrates



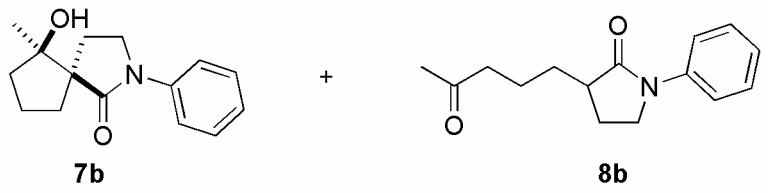
7a **8a**

***rac*-(5*R*, 6*R*)-6-Hydroxy-2-(4-methoxy-phenyl)-6-methyl-2-aza-spiro[4.4]nonan-1-one 7a and 1-(4-methoxy-phenyl)-3-(4-oxo-pentyl)-pyrrolidin-2-one 8a**

To a stirred solution of SmI_2 (0.1 M in THF, 7.30 ml, 0.73 mmol, 4 eq) at 0 °C, was added MeOH (0.74 ml, 18.3 mmol, 100 eq) at the reaction left to stir for 30 min. A solution of *E/Z* 1-(4-methoxy-phenyl)-3-(4-oxo-pentylidene)-pyrrolidin-2-one **4a** (50 mg, 0.18 mmol, 1 eq) in THF (2 ml) was added *via cannula* and the reaction left to stir for 18 hours. The reaction was quenched by opening to the air and the addition of aqueous saturated NaCl (25 ml). The aqueous layer was then separated and extracted with EtOAc (3 × 30 ml) and the combined organics dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. Purification by flash column chromatography on silica gel eluting with 50% EtOAc in petroleum ether (40-60) gave *rac*-6-hydroxy-2-(4-methoxy-phenyl)-6-methyl-2-aza-spiro[4.4]nonan-1-one **7a** (11.2 mg, 0.04 mmol, 18%) as a yellow oil; ν_{max} (neat)/cm^{-1} 3397 (OH), 2960, 1659 (C=O), 1510, 1443, 1392, 1297, 1249, 1180, 1038, 934, 830 and 665; δ_H (500 MHz, $CDCl_3$) 1.25 (3H, s, CH_3), 1.63 (3H, m, 1H from C*H*$_2$COH and 2H from C*H*$_2$C), 1.79 (1H, ddd, *J* 12.6, 7.4, 3.2 Hz, C*H*$_2$CH$_2$N), 1.91 (2H, m, C*H*$_2$CH$_2$C), 2.09 (1H, ddd, *J* 12.7, 8.5, 8.3 Hz, C*H*$_2$CH$_2$N), 2.30 (1H, m, 1H from C*H*$_2$COH), 3.66 (2H, m, NC*H*$_2$), 3.74 (3H, s, OC*H*$_3$), 4.92 (1H, s, O*H*), 6.84 (2H, m, 2 × Ar-C*H*), 7.43 (2H, m, 2 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 20.4 (*C*H$_2$), 22.7 (*C*H$_3$), 28.9 (*C*H$_2$), 33.9 (*C*H$_2$), 38.7 (*C*H$_2$), 45.9 (N*C*H$_2$), 55.5 (O*C*H$_3$), 56.8 (*C*), 82.6 (*C*OH), 114.1 (2 × Ar-*C*H), 121.9 (2 × Ar-*C*H), 132.1 (Ar-*C*N), 156.9 (Ar-*C*O), 177.7 (*C*(O)); *m/z* (CI mode) 276 (*M* + H, 100). *m/z* (EI mode) 276 (*M* + H, 40), 258 (30), 218 (10), 204 (100), 136 (70), 120 (30), 108 (30), 83 (30) and 58 (20). (Found: (*M*), 275.1519. $C_{16}H_{21}O_3N$ requires *M*, 275.1516).

Further elution with 50% EtOAc in petroleum ether (40-60) gave 1-(4-methoxy-phenyl)-3-(4-oxo-pentyl)-pyrrolidin-2-one **8a** (11.9 mg, 0.04 mmol, 20%); ν_{max} (neat)/cm^{-1} 3287, 2957, 2360, 1731, 1617 (C(O)), 1599 (C(O)), 1492, 1483, 1461, 1375, 1352, 1327, 1298, 1242, 1199, 1164, 1141, 1107, 1034, 982, 934, 906, 834, 754 and 659; δ_H (400 MHz, $CDCl_3$) 1.40 (1H, m, 1H from C*H*$_2$CH$_2$N), 1.61 (2H, m, CHC*H*$_2$), 1.82 (2H, m, C(O)CH$_2$C*H*$_2$), 2.09 (3H, s, CH_3), 2.27 (1H, m, 1H from C*H*$_2$CH$_2$N), 2.48 (3H, m, 1H from C*H*C(O) and C*H*$_2$C(O)), 3.68 (2H, m, NC*H*$_2$), 3.73 (3H, s, OC*H*$_3$), 6.83 (2H, d, *J* 9.1 Hz, 2 × Ar-C*H*), 7.43 (2H, d, *J* 9.3 Hz, 2 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 21.3 (*C*H$_2$), 24.7 (*C*H$_2$), 30.0 (*C*H$_3$), 30.7 (*C*H$_2$), 43.1 (*C*H$_2$), 43.5 (*C*H), 47.2 (NCH$_2$), 55.5 (OCH$_3$), 114.0 (2 × Ar-*C*H), 121.6 (2 × Ar-*C*H), 132.8 (Ar-*C*N), 156.5 (Ar-*C*O), 175.3

(*C*(O)), 208.7 (*C*(O)); *m/z* (CI mode) 276 (*M* + H, 100). *m/z* (EI mode) 276 (*M* + H, 70), 204 (30), 191 (100), 136 (25), 120 (20), 83 (60) and 49 (30). (Found: (*M*), 275.1525 $C_{16}H_{22}O_3N$ requires *M*, 275.1516).



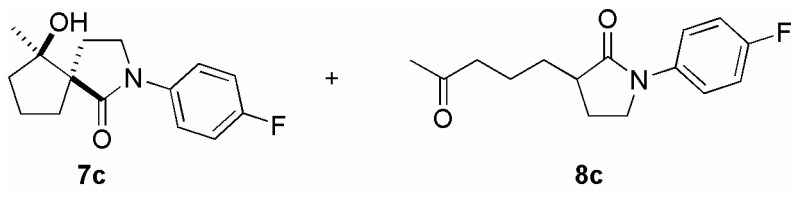
7b **8b**

***rac*-(5*R*, 6*R*)-6-Hydroxy-6-methyl-2-phenyl-2-aza-spiro[4.4]nonan-1-one 7b and 3-(4-oxo-pentyl)-1-phenyl-pyrrolidin-2-one 8b**

As for general procedure D, reaction of *E/Z* 3-(4-oxo-pentylidene)-1-phenyl-pyrrolidin-2-one **4b** (50 mg, 0.21 mmol, 1 eq) with SmI_2 (0.1 M in THF, 8.20 ml, 0.82 mmol, 4 eq) and MeOH (0.83 ml, 20.6 mmol, 100 eq), followed by purification by flash column chromatography on silica gel eluting with 40% EtOAc in petroleum ether (40-60) gave *rac*-(5*R*, 6*R*)-6-hydroxy-6-methyl-2-phenyl-2-aza-spiro[4.4]nonan-1-one **7b** (13.5 mg, 0.06 mmol, 24%) as a yellow oil; ν_{max} (neat)/cm^{-1} 3411 (OH), 2965, 2873, 1666 (C(O)), 1597, 1495, 1461, 1389, 1307, 1231, 1148, 1101, 934, 863, 760 and 691; δ_H (400 MHz, $CDCl_3$) 1.26 (3H, s, C*H*$_3$), 1.56 (1H, m, 1H from C*H*$_2$COH), 1.69 (2H, m, 1H from CH_2C and 1H from C*H*$_2$$CH_2$C), 1.80 (1H, m, 1H from C*H*$_2$$CH_2$N), 1.91 (2H, m, 1H from C*H*$_2$COH and 1H from C*H*$_2$$CH_2$C), 2.10 (1H, m, C*H*$_2$$CH_2$N), 2.30 (1H, m, C*H*$_2$C), 3.72 (2H, m, NC*H*$_2$), 4.56 (1H, s, O*H*), 7.10 (1H, m, Ar-C*H*), 7.32 (2H, m, 2 × Ar-C*H*), 7.56 (2H, m, 2 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 20.4 (*C*H_2), 22.7 (*C*H_3), 28.8 (*C*H_2), 33.9 (*C*H_2), 38.7 (*C*H_2), 45.5 (N*C*H_2), 56.9 (*C*OH), 82.6 (*C*), 120.2 (2 × Ar-*C*H), 125.1 (Ar-*C*H), 128.9 (2 × Ar-*C*H), 138.9 (Ar-*C*), 178.2 (*C*(O)); *m/z* (CI mode) 246 (*M* + H, 100). *m/z* (EI mode) 246 (*M* + H, 20), 174 (30), 160 (100), 106 (70), 77 (40), 55 (20) and 42 (40). (Found: (*M*), 245.1409. $C_{15}H_{19}O_2N$ requires *M*, 245.1410).

Further elution with 40% EtOAc in petroleum ether (40-60) gave 3-(4-oxo-pentyl)-1-phenyl-pyrrolidin-2-one **8b** (14.8 mg, 0.06 mmol, 27%); ν_{max} (neat)/cm^{-1} 3362, 3066, 2977, 2939, 2888, 2864, 1714 (C(O)), 1686 (C(O)), 1598, 1495, 1458, 1398, 1351, 1315,

1285, 1223, 1182, 1159, 1116, 1034, 888, 764, 698, 590 and 455; δ_H (500 MHz, $CDCl_3$) 1.48 (1H, m, 1H from C(O)$CH_2CH_2CH_2$), 1.70 (2H, m, C(O)CH_2CH_2), 1.84 (1H m, 1H from CH_2CH_2N), 1.93 (1H, m, 1H from C(O)$CH_2CH_2CH_2$), 2.16 (3H, s, CH_3), 2.35 (1H, m, 1H from CH_2CH_2N), 2.51 (2H, m, C(O)CH_2), 2.60 (1H, m, C*H*), 3.79 (2H, m, NCH_2), 7.14 (1H, t, *J* 7.4 Hz, Ar-C*H*), 7.37 (2H, t, *J* 8.0 Hz, 2 × Ar-C*H*), 7.66 (2H, d, *J* 7.9 Hz, 2 × Ar-C*H*); δ_C (125 MHz, $CDCl_3$) 21.3 (CH_2), 24.6 (CH_2), 30.0 (CH_3), 30.6 (CH_2), 43.3 (*C*H), 43.4 (CH_2), 46.7 (NCH_2), 119.8 (2 × Ar-*C*H), 124.4 (Ar-*C*H), 128.8 (2 × Ar-*C*H), 139.5 (Ar-*C*), 175.6 (*C*(O)), 208.6 (*C*(O)); *m/z* (CI mode) 246 (*M* + H, 100). *m/z* (EI mode) 246 (*M* + H, 20), 174 (30), 161 (100), 105 (20), 76 (10) and 54 (10). (Found: (*M*), 245.1407. $C_{15}H_{19}O_2N$ requires *M*, 245.1410).



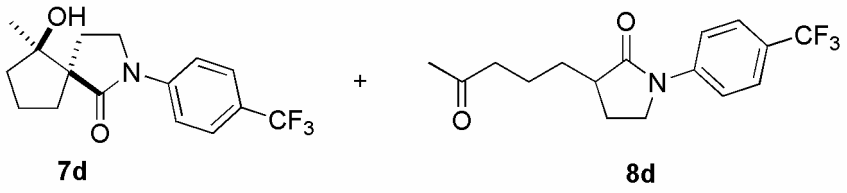
7c **8c**

***rac*-(5*R*, 6*R*)-2-(4-Fluoro-phenyl)-6-hydroxy-6-methyl-2-aza-spiro[4.4]nonan-1-one 7c and 1-(4-fluoro-phenyl)-3-(4-oxo-pentyl)-pyrrolidin-2-one 8c**

As for general procedure D, reaction of *E/Z*-1-(4-fluoro-phenyl)-3-[4-oxo-pentylidene]-pyrrolidin-2-one **4c** (30 mg, 0.12 mmol, 1 eq) with SmI_2 (0.1 M in THF, 4.60 ml, 0.46 mmol, 4 eq) and MeOH (0.46 ml, 2.76 mmol, 100 eq), followed by purification by flash column chromatography on silica gel eluting with 40% EtOAc in petroleum ether (40-60) gave *rac*-(5*R*, 6*R*)-2-(4-fluoro-phenyl)-6-hydroxy-6-methyl-2-aza-spiro[4.4]nonan-1-one **7c** (8.50 mg, 0.03 mmol, 26%) as a yellow oil; ν_{max} (neat)/cm^{-1} 3420 (OH), 2966, 2873, 1668 (C(O)), 1511, 1448, 1389, 1317, 1302, 1230, 1160, 1111, 1054, 934, 834 and 717; δ_H (500 MHz, $CDCl_3$) 1.25 (3H, s, CH_3), 1.59 (1H, m, 1H from CH_2COH), 1.68 (2H, m, CH_2C), 1.81 (1H, m, 1H form CH_2CH_2N), 1.91 (2H, m, CCH_2CH_2), 2.10 (1H, m, 1H from CH_2CH_2N), 2.29 (1H, m, 1H from CH_2C), 3.64 (1H, m, 1H form NCH_2), 3.73 (1H, m, 1H form NCH_2), 4.78 (1H, s, O*H*), 7.01 (2H, m, 2 × Ar-C*H*), 7.50 (2H, m, 2 × Ar-C*H*); δ_C (125 MHz, $CDCl_3$) 20.3 (CH_2), 22.7 (CH_3), 28.8 (CH_2), 33.9 (CH_2), 38.7 (CH_2), 45.8 (NCH_2), 56.8 (*C*OH), 82.6 (*C*), 115.6 (2 × Ar-*C*H), 121.9 (2 × Ar-*C*H), 135.0 (Ar-

C), 159.5 (Ar-*C*F, d, J_{CF} 250 Hz), 178.1 (*C*(O)); *m/z* (ES+ mode) 549 (60), 527 (50), 322 (50), 264 (*M* + H, 100).

Further elution with 40% EtOAc in petroleum ether (40-60) gave 1-(4-fluoro-phenyl)-3-(4-oxo-pentyl)-pyrrolidin-2-one **8c** (19.0 mg, 0.02 mmol, 58%) as a yellow oil; ν_{max} (neat)/cm^{-1} 2933, 1695 (C(O)), 1693 (C(O)), 1599, 1506, 1455, 1425, 1393, 1361, 1322, 1227, 1160, 1115, 1093, 890 and 834; δ_H (500 MHz, $CDCl_3$) 1.40 (1H, m, 1H from CH_2CH), 1.61 (2H, m, C(O)CH_2), 1.81 (2H, m, 1H from CH_2CH_2N and 1H from CH_2CH), 20.9 (3H, s, CH_3), 2.28 (1H, m, 1H from CH_2CH_2N), 2.44 (2H, td, *J* 7.3, 2.1 Hz, C(O)CH_2CH_2), 2.52 (1H, m, C*H*), 3.68 (2H, dt, *J* 8.6, 1.7 Hz, NCH_2), 6.99 (2H, d, *J* 8.3 Hz, 2 × Ar-C*H*), 7.50 (2H, dd, *J* 9.0, 4.8 Hz, 2 × Ar-C*H*); δ_C (125 MHz, $CDCl_3$) 21.1 (*C*H_2), 24.6 (*C*H_2), 30.1 (*C*H_3), 30.6 (*C*H_2), 43.1 (CH), 43.5 (*C*H_2), 47.0 (N*C*H_2), 115.5 (2 × Ar-*C*H), 121.5 (2 × Ar-*C*H), 135.6 (Ar-*C*N), 159.2 (Ar-*C*F), d, *J* 242 Hz), 175.5 (*C*(O)), 208.7 (*C*(O)); *m/z* (ES+ mode) 549 930), 322 (20), 286 (50), 264 (*M* + H, 100).



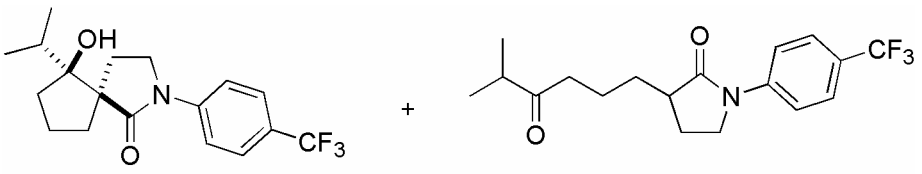
7d **8d**

***rac*-(5*R*, 6*R*)-6-Hydroxy-6-methyl-2-(4-trifluoromethyl-phenyl)-2-aza-spiro[4.4]nonan-1-one 7d and 3-(4-oxo-pentyl)-1-(4-trifluoromethyl-phenyl)-pyrrolidin-2-one 8d**

As for general procedure D, reaction of *E/Z*-3-(4-oxo-pentylidene)-1-(4-trifluoromethyl-phenyl)-pyrrolidin-2-one **4d** (31 mg, 0.10 mmol, 1 eq) with SmI_2 (0.1 M in THF, 4.00 ml, 0.40 mmol, 4 eq) and MeOH (0.40 ml, 9.90 mmol, 100 eq), followed by purification by flash column chromatography on silica gel eluting with 40% EtOAc in petroleum ether (40-60) gave *rac*-(5*R*, 6*R*)-6-hydroxy-6-methyl-2-(4-trifluoromethyl-phenyl)-2-aza-spiro[4.4]nonan-1-one **7d** (16 mg, 0.05 mmol, 54%) as a yellow oil; ν_{max} (neat)/cm^{-1} 3409 (OH), 2960, 1678 (C=O), 1614, 1521, 1429, 1393, 1305, 1230, 1194, 1165, 1121, 1069, 1014, 957, 841 and 666. δ_H (500 MHz, $CDCl_3$) 1.26 (3H, s, CH_3), 1.58 (1H, m, 1H

from C*H*$_2$C), 1.69 (2H, m, C*H*$_2$CH$_2$C), 1.85 (1H, m, 1H from C*H*$_2$CH$_2$N), 1.94 (2H, m, 1H from C*H*$_2$COH) and 1H from C*H*$_2$C), 2.13 (1H, m, 1H from C*H*$_2$CH$_2$N), 2.29 (1H, m, C*H*$_2$COH), 3.73 (2H, m, NC*H*$_2$), 4.54 (1H, s, O*H*), 7.57 (2H, d, *J* 8.6 Hz, 2 × Ar-C*H*), 7.72 (2H, d, *J* 8.6 Hz, 2 × Ar-C*H*); δ_C (125 MHz, $CDCl_3$) 20.3 (*C*H$_2$), 22.8 (*C*H$_3$), 28.6 (*C*H$_2$), 33.9 (*C*H$_2$), 38.7 (*C*H$_2$), 45.3 (N*C*H$_2$), 57.2 (*C*), 82.6 (*C*OH), 117.3 (*C*CF$_3$), 119.5 (2 × Ar-*C*H), 124.0 (*C*F$_3$, q, *J* 271 Hz), 126.0 (2 × Ar-*C*H), 141.9 (Ar-*C*N), 178.7 (*C*(O)); *m/z* (CI mode) 314 (*M* + H, 100) and 242 (10). *m/z* (EI mode) 314 (*M* + H, 10), 296 (15), 242 (100), 174 (15), 145 (15), 70 (20), 55 (50) and 43 (80). (Found: (*M* + H), 314.1358. $C_{16}H_{19}O_2NF_3$ requires *M* + H, 314.1362)

further elution gave 3-(4-oxo-pentyl)-1-(4-trifluoromethyl-phenyl)-pyrrolidin-2-one **8d** (6 mg, 0.02 mmol, 29%) as a yellow oil**;** ν_{max} (neat)/cm^{-1} 3368, 2946, 2833, 2523, 2043, 1654 (C(O)), 1648 (C(O)), 1449, 1420, 1115, 1027, 759, 665 and 452; δ_H (500 MHz, $CDCl_3$) 1.42 (1H, m, 1H from C*H*$_2$CH), 1.64 (2H, m, 1H from C*H*$_2$CH and 1H from C*H*$_2$CH$_2$CH), 1.84 (2H, m, 1H from C*H*$_2$CH$_2$CH and 1H from C*H*$_2$CH$_2$N), 2.09 (3H, s, C*H*$_3$), 2.32 (1H, m, C*H*$_2$CH$_2$N), 2.45 (2H, m, 1H from C*H*$_2$C(O) and 1H from C*H*), 2.56 (1H, m, C*H*$_2$C(O)), 3.74 (2H, dd, *J* 8.7, 5.2 Hz, NC*H*$_2$), 7.54 (2H, d, *J* 8.6 Hz, 2 × Ar-C*H*), 7.71 (2H, d, *J* 8.5 Hz, 2 × Ar-C*H*); δ_C (125 MHz, $CDCl_3$) 21.2 (*C*H$_2$), 24.5 (*C*H$_2$), 24.6 (*C*H$_2$), 30.1 (*C*H$_3$), 30.5 (*C*H$_2$), 43.4 (*C*H), 45.5 (N*C*H$_2$), 119.1 (2 × Ar-*C*H), 125.9 (2 × Ar-*C*H), 142.0 (Ar-*C*N), 176.3 (*C*(O)), 208.5 (*C*(O)), *C*CF$_3$ and *C*F$_3$ (not visible); *m/z* (CI mode) 314 (*M* + H, 100), 96 (20) and 79 (10). *m/z* (EI mode) 314 (*M*, 5), 256 (15), 242 (30), 229 (40), 145 (20), 83 (100), 69 (20) and 49 (40). (Found: (*M*), 313.1274. $C_{16}H_{18}O_2NF_3$ requires *M*, 313.1284);



7e **8e**

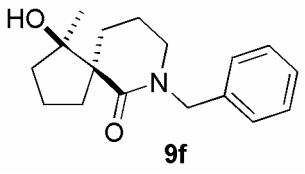
***rac*-(5*R*, 6*S*)-6-Hydroxy-6-isopropyl-2-(4-trifluoromethyl-phenyl)-2-aza-spiro[4.4]nonan-1-one 7e and 3-(5-methyl-4-oxo-hexyl)-1-(4-trifluoromethyl-phenyl)-pyrrolidin-2-one 8e**

As for general procedure D, reaction of *E/Z* 3-(5-methyl-4-oxo-hexylidene)-1-(4-trifluoromethyl-phenyl)-pyrrolidin-2-one **4e** (50 mg, 0.15 mmol, 1 eq) with SmI_2 (0.1 M in THF, 5.90 ml, 0.59 mmol, 4 eq) and MeOH (0.60 ml, 14.75 mmol, 100 eq), followed by purification by flash column chromatography on silica gel eluting with 20% EtOAc in petroleum ether (40-60) gave *rac*-(5*R*, 6*S*)-6-hydroxy-6-isopropyl-2-(4-trifluoromethyl-phenyl)-2-aza-spiro[4.4]nonan-1-one **7e** (19.6 mg, 0.06 mmol, 31%) as a yellow oil; ν_{max} (neat)/cm^{-1} 3401 (OH), 2967, 1674 (C=O), 1614, 1521, 1429, 1388, 1323, 1229, 1166, 1121, 1067, 1013, 841, 758, 665, 594 and 447; δ_H (400 MHz, $CDCl_3$) 0.79 (3H, d, *J* 6.8 Hz, *o*-Pr-C*H*$_3$), 0.95 (3H, d, *J* 6.6 Hz, *o*-Pr-C*H*$_3$), 1.54 (2H, m, CCH_2CH_2), 1.82 (3H, m, o-Pr-CH, 1H from CH_2CH_2N, 1H from C*H*$_2$COH), 2.01 (2H, m, CC*H*$_2$), 2.19 (1H, m, 1H from C*H*$_2$$CH_2N$), 2.34 (1H, m, 1H from C*H*$_2$COH), 3.82 (2H, m, NC*H*$_2$), 5.25 (1H, s, O*H*), 7.56 (2H, d, *J* 8.6 Hz, 2 × Ar-C*H*), 7.65 (2H, m, 2 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 17.1 (CH_3), 18.1 (*C*H_3), 20.1 (*C*H_2), 26.7 (*C*H_2), 33.3 (*C*H), 34.8 (*C*H_2), 37.9 (*C*H_2), 45.0 (N*C*H_2), 55.4 (*C*OH), 87.2 (*C*), 119.6 (2 × Ar-*C*H) 121.2 (C*C*F_3, q, *J* 338 Hz), 126.1 (2 × Ar-*C*H), 126.5 (Ar-CCF_3, q, *J* 32 Hz), 141.8 (Ar-*C*), 180.2 (*C*(O)); *m/z* (EI mode) 341 (*M*, 20), 297 (10), 256 (15), 242 (15), 174 (100), 144 (15), 68 (25) and 54 (20). (Found: (*M*), 341.1590. $C_{18}H_{22}O_2NF_3$ requires *M*, 341.1597).

Further elution with 20% EtOAc in petroleum ether (40-60) gave 3-(5-methyl-4-oxo-hexyl)-1-(4-trifluoromethyl-phenyl)-pyrrolidin-2-one **8e** (35 mg, 0.10 mmol, 69%) as a yellow oil; ν_{max} (neat)/cm^{-1} 3385, 2945, 1696 (C(O)), 1616 (C(O)), 1520, 1387, 1327, 1167, 1118, 1073, 1015, 892, 839 and 711; δ_H (300 MHz, $CDCl_3$) 1.02 (3H, d, *J* 0.9 Hz, C*H*$_3$), 1.04 (3H, d, *J* 1.1 Hz, C*H*$_3$), 1.40 (1H, m, C*H*$(CH_3)_2$), 1.62 (2H, m, C(O)CH_2C*H*$_2$), 1.83 (2H, m, C*H*$_2$$CH_2N$), 2.33 (1H, m, C*H*C(O)), 2.53 (4H, m, C*H*$_2$CH(O) and C(O)C*H*$_2$), 3.74 (2H, dd, *J* 8.7, 5.3 Hz, NC*H*$_2$), 7.54 (2H, d, *J* 8.7 Hz, 2 × Ar-C*H*), 7.71 (2H, d, *J* 8.7 Hz, 2 × Ar-C*H*); δ_C (75 MHz, $CDCl_3$) 17.3 (2 × *C*H_3), 20.1 (*C*H_2), 23.5 (*C*H_2), 29.7 (*C*H_2), 39.0 (*C*H_2), 39.9 (*C*H), 42.5 (*C*H), 45.5 (*C*H_2), 118.0 (2 × Ar-*C*H), 119.6 (*C*F_3, q, *J* 246 Hz), 124.9 (Ar-*C*CF_3, q, *J* 32 Hz), 124.9 (2 × Ar-*C*H), 141.4 (Ar-*C*N), 175.2 (*C*(O)), 213.4 (*C*(O)); *m/z* (CI mode) 342 (*M* + H, 100). *m/z* (EI mode) 341

(*M* + H, 15), 298 (15), 270 (20), 255 (20), 241 (40), 228 (75), 83 (100), 68 (30), 54 (70) and 48 (80). (Found: (*M*), 341.1604. $C_{18}H_{22}O_2NF_3$ requires *M*, 341.1597).

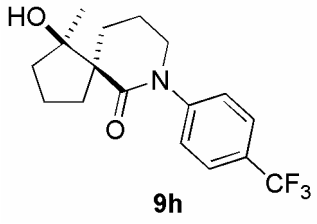
General Procedure E: SmI_2-mediated cyclization of 6-membered substrates



9f

***rac*-(1*R*, 5*R*)-7-Benzyl-1-hydroxy-1-methyl-7-aza-spiro[4.5]decan-6-one 9f**

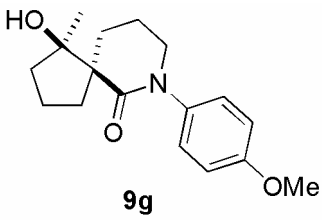
To a stirred solution of SmI_2 (0.1 M in THF, 13.6 ml, 1.36 mmol, 4 eq) at 0 °C, was added MeOH (0.34 ml, 10.2 mmol, 30 eq) at the reaction left to stir for 30 min. A solution of *E/Z* 1-Benzyl-3-(4-oxo-pentylidene)-piperidin-2-one **4f** (93 mg, 0.34 mmol, 1 eq) in THF (1.8 ml) was added *via cannula* and the reaction left to stir for 5 hours. The reaction was quenched by opening to the air and the addition of aqueous saturated NaCl (25 ml). The aqueous layer was then separated and extracted with EtOAc (3 × 30 ml) and the combined organics dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. Purification by flash column chromatography on silica gel eluting with 40% EtOAc in petroleum ether (40-60) gave *rac*-(1*R*, 5*R*)-7-Benzyl-1-hydroxy-1-methyl-7-aza-spiro[4.5]decan-6-one **9f** (16 mg, 0.06 mmol, 18%) as a yellow oil; ν_{max} (neat)/cm^{-1} 3450 (OH), 2924, 2853, 2339, 2097, 1641 (C(O)), 1511, 1460, 1397, 1285, 1245, 1179, 1119, 1028 and 850; δ_H (400 MHz, $CDCl_3$) 0.79 (2H, m, 2 × 1H from C*H*$_2$), 1.19 (£H, s, C*H*$_3$), 1.58- 1.92 (7H, m, 7 × 1H from C*H*$_2$), 2.35 (1H, m, 1H from C*H*$_2$), 3.17 (2H, m, NC*H*$_2$), 4.53 (2H, dd, *J* 70.1, 14.6 Hz, NC*H*$_2$Ph), 6.67 (1H, s, O*H*), 7.22 (5H, m, 5 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 19.6 (*C*H_2), 20.2 (*C*H_2), 23.0 (*C*H_3), 28.9 (*C*H_2), 35.3 (*C*H_2), 38.4 (*C*H_2), 47.7 (N*C*H_2), 50.7 (N*C*H_2Ph), 53.6 (*C*), 83.9 (*C*OH), 127.4 (Ar-*C*H), 127.8 (2 × Ar-*C*H), 128.7 (2 × Ar-*C*H), 136.9 (Ar-*C*), 176.1 (*C*(O)); *m/z* (CI mode) 274 (M + H, 60), 256 (40), 202 (35), 90 (50) and 82 (100). *m/z* (EI mode) 273 (M, 10), 255 (40), 227 (30), 202 (80), 189 (10), 91 (100) and 65 (10).



9h

***rac*-(1*R*, 5*R*)-1-Hydroxy-1-methyl-7-(4-trifluoromethyl-phenyl)-7-aza-spiro[4.5]decan-6-one 9h**

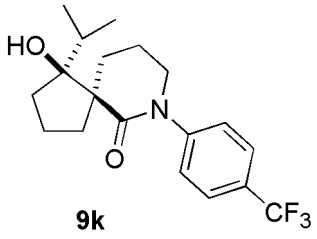
As for general procedure E, treatment of *E/Z*-3-(4-oxo-pentylidene)-1-(4-trifluoromethyl-phenyl)-piperidin-2-one **4h** (200 mg, 0.62 mmol, 1 eq) with SmI_2 (0.1 M in THF, 24.6 ml, 2.46 mmol, 4 eq) and MeOH (0.75 ml, 18.6 mmol, 30 eq), followed by purification by flash column chromatography on silica gel eluting with 40% EtOAc in petroleum ether (40-60) gave *rac*-(1*R*, 5*R*)-1-hydroxy-1-methyl-7-(4-trifluoromethyl-phenyl)-7-aza-spiro[4.5]decan-6-one **9h** (201 mg, 0.54 mmol, 87%); ν_{max} (neat)/cm^{-1} 3325 (OH), 2961, 1624 (C(O)), 1603, 1484, 1408, 1304, 1165, 1124, 1067, 933, 907, 846, 756 and 664; δ_H (500 MHz, $CDCl_3$) 1.36 (3H, s, C*H*$_3$), 1.70-1.77 (3H, m, 3 × 1H from C*H*$_2$), 1.89-1.93 (3H, m, 3 × 1H from C*H*$_2$), 2.00-2.11 (3H, m, 2 H from C*H*$_2$CH$_2$N and 1H from C*H*$_2$), 2.45 (1H, m, 1H from C*H*$_2$), 3.63 (1H, m, 1H from NC*H*$_2$), 3.75 (1H, m, 1H from NC*H*$_2$), 6.02 (1H, s, O*H*), 7.34 (2H, d, *J* 8.5 Hz, 2 × Ar-C*H*), 7.69 (2H, d, *J* 8.2 Hz, 2 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 20.2 (*C*H$_2$), 20.3 (*C*H$_2$), 23.1 (*C*H$_3$), 29.1 (*C*H$_2$), 35.6 (*C*H$_2$), 38.7 (*C*H$_2$), 51.7 (N*C*H$_2$), 54.2 (C), 84.0 (*C*OH), 123.8 (*C*F$_3$, q, *J* 272 Hz), 126.3 (2 × Ar-*C*H), 126.4 (2 × Ar-*C*H), 129.5 (Ar-*C*CF$_3$, q, *J* 32 Hz), 146.3 (Ar-*C*) and 176.9 (*C*(O)); *m/z* (CI mode) 328 (*M* + H, 100), 310 (15) and 256 (5). *m/z* (EI mode) 327 (*M*, 3), 256 (30), 186 (15), 174 (100), 145 (60), 69 (20) and 43 (40). (Found: (*M*), 327.1442. $C_{17}H_{20}O_2NF_3$ requires *M*, 327.1441).



9g

***rac*-(1*R*, 5*R*)-1-Hydroxy-7-(4-methoxy-phenyl)-1-methyl-7-aza-spiro[4.5]decan-6-one 9g**

As for general procedure E, treatment of *E/Z*-1-(4-methoxy-phenyl)-3-(4-oxo-pentylidene)-piperidin-2-one **4g** (200 mg, 0.70 mmol, 1 eq) with SmI_2 (0.1 M in THF, 28.0 ml, 2.80 mmol, 4 eq) and MeOH (0.85 ml, 21.0 mmol, 30 eq), followed by purification by flash column chromatography on silica gel eluting with 60% EtOAc in petroleum ether (40-60) *rac*-(1*R*, 5*R*)-1-hydroxy-7-(4-methoxy-phenyl)-1-methyl-7-aza-spiro[4.5]decan-6-one **9g** (159 mg, 0.55 mmol, 79%) as a yellow oil; ν_{max} (neat)/cm^{-1} 3293 (OH), 2957, 1617 (C(O)), 1599, 1480, 1463, 1411, 1351, 1327, 1298, 1243, 1164, 1141, 1035, 934, 906, 833, 754 and 665; δ_H (125 MHz, $CDCl_3$) 1.34 (3H, s, C*H*$_3$), 1.69 (3H, m, 1H from C*H*$_2$ and 2H from C*H*$_2$), 1.96 (6H, m, 3 × C*H*$_2$), 2.43 (1H, m, 1H from C*H*$_2$CH$_2$N), 3.56 (1H, m 1H from NC*H*$_2$), 3.65 (1H, m, NC*H*$_2$), 3.80 (3H, s, OC*H*$_3$), 6.92 (2H, m, 2 × Ar-C*H*), 7.12 (2H, m, 2 × Ar-C*H*); δ_C (125 MHz, $CDCl_3$) 20.2 (2 × *C*H$_2$), 22.9 (*C*H$_3$), 29.1 (*C*H$_2$), 35.4 (*C*H$_2$), 38.5 (*C*H$_2$), 52.3 (*C*), 53.4 (N*C*H$_2$), 55.5 (O*C*H$_3$), 84.0 (*C*OH), 114.6 (2 × Ar-*C*H), 127.5 (2 × Ar-*C*H), 135.9 (Ar-*C*), 158.5 (Ar-*C*) and 176.8 (*C*(O)); *m/z* (CI mode) 290 (*M* + H, 100), 272 (10), 218 (5) and 136 (4). *m/z* (EI mode) 289 (*M*, 10), 218 (100), 205 (10), 149 (30), 136 (70), 120 (35), 84 (55) and 49 (80). (Found: (*M*), 289.1683. $C_{17}H_{23}O_3N$ requires *M*, 289.1672).

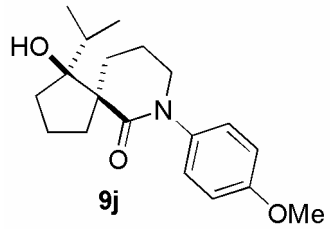


9k

***rac*-(1*S*, 5*R*)-1-Hydroxy-1-isopropyl-7-(4-trifluoromethyl-phenyl)-7-aza-spiro[4.5]decan-6-one 9k**

As for general procedure E, treatment of *E/Z*-3-(5-methyl-4-oxo-hexylidene)-1-(4-trifluoromethyl-phenyl)-piperidin-2-one **4k** (100 mg, 0.28 mmol, 1 eq) with SmI_2 (0.1 M in THF, 12 ml, 1.19 mmol, 4 eq) and MeOH (0.34 ml, 8.40 mmol, 30 eq), followed by

purification by flash column chromatography on silica gel eluting with 40% EtOAc in petroleum ether (40-60) *rac*-(1*S*, 5*R*)-1-hydroxy-1-isopropyl-7-(4-trifluoromethyl-phenyl)-7-aza-spiro[4.5]decan-6-one **9k** (79 mg, 0.22 mmol, 79%) as a white solid; ν_{max} (neat)/cm^{-1} 3307 (OH), 2964, 1624 (C(O)), 1602, 1408, 1350, 1194, 1165, 1126, 1068, 1017, 982, 917, 844, 756 and 664; δ_H (100 MHz, $CDCl_3$) 0.93 (3H, d, *J* 7.0 Hz, C*H*$_3$), 1.00 (3H, d, *J* 6.9 Hz, C*H*$_3$), 1.68 (3H, m, 1H from CCH$_2$C*H*$_2$ and CC*H*$_2$), 1.99 (7H, m, C*H*(CH$_3$)$_2$, C*H*$_2$C*H*$_2$COH, CC*H*$_2$ and C*H*$_2$COH), 2.48 (1H, m, 1H from CCH$_2$C*H*$_2$), 3.61 (1H, m, 1H from NC*H*$_2$), 3.76 (1H, m, 1H from NC*H*$_2$), 6.50 (1H, s, O*H*), 7.33 (2H, d, *J* 8.2 Hz, 2 × Ar-C*H*), 7.67 (2H, d, *J* 8.2 Hz, 2 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 17.6 (*C*H$_3$), 18.1 (*C*H$_3$), 19.8 (*C*H$_2$), 20.2 (*C*H$_2$), 27.6 (*C*H$_2$), 33.2 (*C*H), 36.9 (*C*H$_2$), 37.4 (*C*H$_2$), 51.9 (N*C*H$_2$), 52.5 (*C*), 88.9 (*C*OH), 123.7 (*C*F$_3$, q, *J* 272 Hz)126.5 (2 × Ar-*C*H), 126.7 (2 × Ar-*C*H), 129.3 (Ar-*C*CF$_3$, q, *J* 32 Hz), 146.2 (Ar-*C*N), 177.7 (*C*(O)); *m/z* (CI mode) 356 (*M* + H, 100), 338 (10), 312 (8) and 255 (3). *m/z* (EI mode) 356 (*M* + H, 10), 338 (8), 312 (30), 256 (80), 243 (20), 228 (10), 200 (20), 187 (15), 174 (65), 145 (100), 123 (50), 117 (25), 107 (30), 95 (70), 91 (50), 79 (50), 69 (55) and 55 (40).(Found: (*M*), 355.1759. $C_{19}H_{24}O_2NF_3$ requires *M*, 355.1754). mp (MeOH) 132 °C.

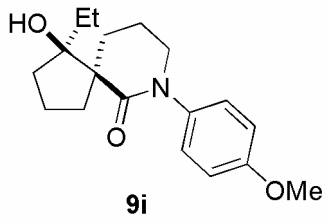


9j

***rac*-(1*S*, 5*R*)-1-Hydroxy-1-isopropyl-7-(4-methoxy-phenyl)-7-aza-spiro[4.5]decan-6-one 9j**

As for general procedure E, treatment of *E/Z*-1-(4-methoxy-phenyl)-3-(5-methyl-4-oxo-hexylidene)-piperidin-2-one **4j** (110 mg, 0.35 mmol, 1 eq) with SmI_2 (0.1 M in THF, 14.0 ml, 1.40 mmol, 4 eq) and MeOH (0.42 ml, 10.5 mmol, 30 eq), followed by purification by flash column chromatography on silica gel eluting with 50% EtOAc in petroleum ether (40-60) *rac*-(1*S*, 5*R*)-1-hydroxy-1-isopropyl-7-(4-methoxy-phenyl)-7-aza-spiro[4.5]decan-6-one **9j** (76 mg, 0.24 mmol, 68%); ν_{max} (neat)/cm^{-1} 3278 (OH), 2961,

2873, 2838, 1618 (C(O)), 1600, 1484, 1466, 1447, 1382, 1353, 1327, 1300, 1244, 1197, 1160, 1133, 1106, 1072, 1034, 1014, 982, 917, 833, 753 and 662; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, d, *J* 6.8 Hz, C*H*$_3$), 0.92 (3H, d, *J* 6.6 Hz, C*H*$_3$), 1.54 (3H, m, 1H from C*H*$_2$, 1H from C*H*$_2$, 1H from C*H*$_2$), 1.87 (7H, m, C*H*$_2$CH$_2$N, C*H*, 1H from C*H*$_2$, 1H from C*H*$_2$, 1H from C*H*$_2$, 1H from C*H*$_2$), 2.39 (1H, m, 1H from C*H*$_2$), 3.48 (1H, m, 1H from NC*H*$_2$), 3.61 (1H, m, 1H from NC*H*$_2$), 3.72 (3H, s, OC*H*$_3$), 6.85 (2H, m, 2 × Ar-C*H*), 7.01 (2H, m, 2 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 17.5 (*C*H$_3$), 18.1 (*C*H$_2$), 19.8 (*C*H$_2$), 20.2 (*C*H$_2$), 27.6 (*C*H$_2$), 33.2 (*C*H), 36.7 (*C*H$_2$), 37.4 (*C*H$_2$), 52.6 (N*C*H$_2$), 55.5 (O*C*H$_3$), 60.4 (*C*), 88.8 (*C*OH), 114.7 (2 × Ar-*C*H), 127.3 (2 × Ar-*C*H), 135.9 (Ar-*C*N), 158.5 (Ar-*C*O), 177.7 (*C*(O)); *m/z* (CI mode) 318 (*M* + H, 100), 300 (10), 274 (15), 218 (30) and 136 (15). *m/z* (EI mode) 317 (*M*, 20), 274 (20), 218 (100), 205 (10) and 136 (30). (Found: (*M* + H), 318.2068. $C_{19}H_{28}O_3N$ requires *M* + H, 318.2064).

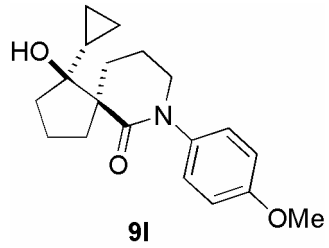


9i

***rac*-(1*R*, 5*R*)-1-Ethyl-1-hydroxy-7-(4-methoxy-phenyl)-7-aza-spiro[4,5]decan-6-one 9i**

As for general procedure E, treatment of *E/Z* 1-(4-methoxy-phenyl)-3-(4-oxo-hexylidene)-piperidin-2-one **4i** (100 mg, 0.33 mmol, 1 eq) with SmI_2 (0.1 M in THF, 13.3 ml, 1.33 mmol, 4 eq) and MeOH (0.40 ml, 9.96 mmol, 30 eq), followed by purification by flash column chromatography on silica gel eluting with 60% EtOAc in petroleum ether (40-60) gave *rac*-(1*R*, 5*R*)-1-ethyl-1-hydroxy-7-(4-methoxy-phenyl)-7-aza-spiro[4,5]decan-6-one **9i** (95 mg, 0.29 mmol, 88%) as a yellow oil; ν_{max} (neat)/cm^{-1} 3283 (OH), 2957, 1617 (C(O)), 1511, 1452, 1414, 1352, 1328, 1299, 1243, 1196, 1160, 1135, 1106, 1039, 977, 958, 913, 833, 816, 753,. 660, 578 and 440; δ_H (400 MHz, $CDCl_3$) 0.92 (3H, t, *J* 7.5 Hz, CH_3), 1.59 (5H, m, 2H from C*H*$_2$CH$_3$ and 1H from C*H*$_2$ and 1H from C*H*$_2$ and 1H from C*H*$_2$), 1.74 (2H, m, 1H from C*H*$_2$ and 1H from C*H*$_2$), 1.86 (2H, m, 1H from C*H*$_2$CH$_2$N and 1H from C*H*$_2$), 1.96 (2H, m, C*H*$_2$), 2.37 (1H, m, 1H from

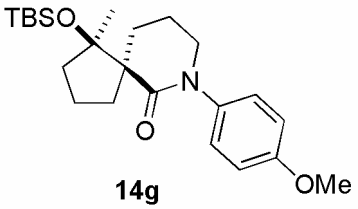
C*H*$_2$CH$_2$N), 3.53 (2H, m, NC*H*$_2$), 3.71 (3H, s, OC*H*$_3$), 6.84 (2H, d, *J* 9.1 Hz, 2 × Ar-C*H*), 7.02 (2H, d, *J* 8.8 Hz, 2 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 8.76 (*C*H$_3$), 19.9 (*C*H$_2$), 20.2 (*C*H$_2$), 28.4 (*C*H$_2$), 29.4 (*C*H$_2$), 36.1 (*C*H$_2$), 37.6 (*C*H$_2$), 52.4 (N*C*H$_2$), 52.7 (*C*), 55.5 (O*C*H$_3$), 86.8 (*C*OH), 114.7 (2 × Ar-*C*H), 127.5 (2 × Ar-*C*H), 135.9 (Ar-*C*N), 158.5 (Ar-*C*O), 177.3 (*C*(O)); *m/z* (ES mode) 467 (30), 326 (M + 23, 100), 304 (M + H, 10).



9l

rac-(1_R_, 5_R_)-1-Cyclopropyl-1-hydroxy-7-(4-methoxy-phenyl)-7-aza-spiro[4.5]decan-6-one 9l

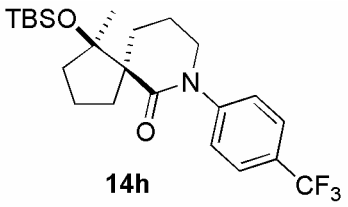
As for general procedure E, treatment of *E/Z* 3-(4-Cyclopropyl-4-oxo-butylidene)-1-(4-methoxy-phenyl)-piperidin-2-one **4l** (35 mg, 0.11 mmol, 1 eq) with SmI_2 (0.1 M in THF, 4.45 ml, 0.45 mmol, 4 eq) and MeOH (0.14 ml, 3.36 mmol, 30 eq), followed by purification by flash column chromatography on silica gel eluting with 40% EtOAc in petroleum ether (40-60) gave *rac*-(1*R*, 5*R*)-1-cyclopropyl-1-hydroxy-7-(4-methoxy-phenyl)-7-aza-spiro[4.5]decan-6-one **9l** (29 mg, 0.09 mmol, 82%) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 0.29 (2H, m, *c*-Pr-C*H*$_2$), 0.57 (1H, m, *c*-Pr-C*H*), 0.86 (2H, m, *c*-Pr-C*H*$_2$), 1.66 (4H, m, 2 × C*H*$_2$), 1.91 (4H, m, 2H from C*H*$_2$CH$_2$N and 2H from C*H*$_2$), 2.09 (1H, m, 1H from C*H*$_2$), 2.38 (1H, m, 1H form C*H*$_2$), 3.54 (2H, m, NC*H*$_2$), 3.74 (3H, s, OC*H*$_3$), 6.32 (1H, s, O*H*), 6.86 (2H, m, 2 × Ar-C*H*), 7.03 (2H, m, 2 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) -1.36 (*c*-Pr-*C*H$_2$), 0.00 (*c*-Pr-*C*H$_2$), 13.9 (*C*H), 19.5 (*C*H$_2$), 19.8 (*C*H$_2$), 28.3 (*C*H$_2$), 35.6 (*C*H$_2$), 36.5 (*C*H$_2$), 52.0 (N*C*H$_2$), 53.4 (*C*), 54.9 (O*C*H$_3$), 83.6 (*C*OH), 114.1 (2 × Ar-*C*H), 126.9 (2 × Ar-*C*H), 135.5 (Ar-*C*N), 157.9 (Ar-*C*O), 176.6 (*C*(O));



14g

rac-(1_R_, 5_R_)-1-(_tert_-Butyl-dimethyl-silanyloxy)-7-(4-methoxy-phenyl)-1-methyl-7-aza-spiro[4.5]decan-6-one 14g

To a stirred solution of *rac*-(1*R*, 5*R*)-1-hydroxy-7-(4-methoxy-phenyl)-1-methyl-7-aza-spiro[4.5]decan-6-one **9g** (0.06 g, 0.17 mmol, 1 eq) in DMF (4 ml) at 0 °C was added, 2,6-lutidine (0.21 ml, 1.07 mmol, 10 eq) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.24 ml, 1.04 mmol, 6 eq) and warmed to room temperature and left to stir for 2 hours. The reaction was quenched with the addition of aqueous saturated solution of $NaHCO_3$ (5 ml) and the aqueous layer separated and extracted with EtOAc (3 × 10 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. Purification by flash column chromatography on silica gel eluting with a solvent gradient of 20% EtOAc in petroleum ether (40-60) to give *rac*-(1*R*, 5*R*)-1-(*tert*-butyl-dimethyl-silanyloxy)-7-(4-methoxy-phenyl)-1-methyl-7-aza-spiro[4.5]decan-6-one **14g** (79 mg, 0.17 mmol, 97%) as a yellow oil; ν_{max} (neat)/cm^{-1} 2932, 1649 (C(O)), 1510, 1462, 1427, 1349, 1322, 1245, 1183, 1162, 1143, 1105, 1037, 1020, 834, 773 and 662.; δ_H (400 MHz, $CDCl_3$) 0.09 (3H, s, SiCH_3), 0.14 (3H, s, SiCH_3), 0.91 (9H, s, 3 × CCH_3), 1.28 – 1.36 (1H, m, 1H from CCH_2), 1.30 (3H, s, CH_3), 1.44 – 1.58 (1H, m, 1H from CCH_2CH_2), 1.66 – 1.75 (2H, m, 1H from CH_2CH_2N, and 1H from CH_2CO), 1.77 - 1.82 (1H, m, 1H from C$H_2CH_2CH_2$N), 1.87 – 1.99 (1H, m, CCH_2CH_2), 2.03 - 2.09 (1H, m, C$H_2CH_2CH_2$N), 2.16 (1H, dq, *J* 10.4, 3.8 Hz, 1H from CCH_2), 2.41 - 2.52 (1H, m, 1H from CH_2CH_2N), 2.62 (1H, apparent q, *J* 10.4 Hz, 1H from CH_2CO), 3.54 - 3.65 (2H, m, CH_2N), 3.78 (3H, s, OCH_3), 6.89 (2H, dd, *J* 9.1, 2.3 Hz, 2 × Ar-C*H*), 7.19 (2H, dd, *J* 9.1, 2.3 Hz, 2 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 0.00 (2 × SiCH_3), 20.2 (CH_2), 21.5 (2 × CH_2), 22.5 (Si*C*), 28.2 (3 × SiCCH_3), 31.8 (CH_3), 37.5 (CH_2), 42.5 (CH_2), 54.3 (NCH_2), 57.4 (*C*), 57.6 (OCH_3), 87.3 (*C*OSi), 116.3 (2 × Ar-*C*H), 129.8 (2 × Ar-*C*H), 139.4 (Ar-*C*N), 159.8 (Ar-*C*O), 176.9 (*C*(O)); *m/z* (ES^+ mode) 824 (30), 404 (*M* + H, 100). (Found: (*M* + H), 404.2623. $C_{23}H_{38}O_3NSi$ requires *M* + H, 404.2615).

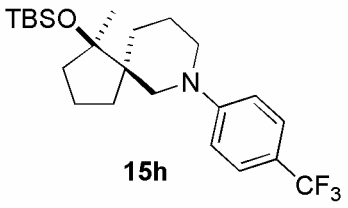


14h

***rac*-(1*R*, 5*R*)-1-(*tert*-Butyldimethylsilyloxy)-1-methyl-7-(4-trifluoromethyl-phenyl)-7-aza-spiro[4.5]decan-6-one 14h**

To a stirred solution of *rac*-(1*R*, 5*R*)-1-hydroxy-1-methyl-7-(4-trifluoromethyl-phenyl)-7-aza-spiro[4.5]decan-6-one **9h** (27 mg, 0.08 mmol, 1 eq) in DMF (2 ml) at 0 °C was added, 2,6-lutidine (97 µl, 0.83 mmol, 10 eq) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.13 ml, 0.49 mmol, 6 eq) and warmed to room temperature and left to stir for 2 hours. The reaction was quenched with the addition of aqueous saturated solution of $NaHCO_3$ (5 ml) and the aqueous layer separated and extracted with EtOAc (3 × 10 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. Purification by flash column chromatography on silica gel eluting with a solvent gradient of 30% EtOAc in petroleum ether (40-60) to give *rac*-(1*R*, 5*R*)-1-(*tert*-butyldimethylsilyloxy)-1-methyl-7-(4-trifluoromethyl-phenyl)-7-aza-spiro[4.5]decan-6-one **14h** (36 mg, 0.08 mmol, 100%) as a yellow oil; ν_{max} (neat)/cm^{-1} 2933, 2858, 1652 (C(O)), 1612, 1518, 1472, 1423, 1408, 1374, 1349, 1322, 1294, 1257, 1181, 1164, 1125, 1068, 1036, 1019, 958, 835, 774 and 734; δ_H (400 MHz, $CDCl_3$) 0.01 (3H, s, SiC*H*$_3$), 0.05 (3H, s, SiC*H*$_3$), 0.78 (9H, s, 3 × CC*H*$_3$), 1.23 (3H, s, C*H*$_3$), 1.26 (1H, m, 1H from C*H*$_2$), 1.45 (1H, m, 1H from C*H*$_2$), 1.65 (3H, m, 1H from C*H*$_2$CH$_2$N and 2H from C*H*$_2$), 1.84 (1H, dq, *J* 10.9, 5.9 Hz, 1H from C*H*$_2$), 2.04 (2H, m, 2 × 1H from C*H*$_2$), 2.39 (1H, m, 1H from C*H*$_2$CH$_2$N), 2.51 (1H, apparent q, *J* 10.9 Hz, 1H from C*H*$_2$), 3.52 (1H, m, 1H from NC*H*$_2$), 3.61 (1H, dt, *J* 11.0, 5.5 Hz, 1H from NC*H*$_2$), 7.36 (2H, d, *J* 8.3 Hz, 2 × Ar-C*H*), 7.52 (2H, d, *J* 8.3 Hz, 2 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 0.27 (2 × Si*C*H$_3$), 20.2 (*C*H$_2$), 21.5 (*C*H$_2$), 22.6 (Si*C*), 28.0 (3 × C*C*H$_3$), 28.1 (*C*H$_3$), 32.3 (*C*H$_2$), 37.5 (*C*H$_2$), 42.5 (*C*H$_2$), 53.6 (N*C*H$_2$), 57.8 (*C*), 87.6 (*C*OSi), 126.3 (Ar-C*C*F$_3$, q, *J* 271 Hz), 127.9 (2 × Ar-*C*H), 128.6 (2 × Ar-*C*H), 129.9 (Ar-*C*CF$_3$, q, *J* 32 Hz), 149.4 (Ar-*C*), 177.2 (*C*(O)); *m/z* (CI mode) 442 (*M* + H, 400), 383 (60), 310 (100), 256 (30), 186 (10),

90 (20), 73 (50) and 57 (25). *m/z* (EI mode) 442 (*M* + H, 5), 384 (100), 310 (40), 256 (30), 186 (20), 174 (25), 161 (30), 145 (25), 74 (50) and 48 (55). (Found: (*M*), 441.2313. $C_{23}H_{34}O_2NF_3Si$ requires *M*, 441.2305)

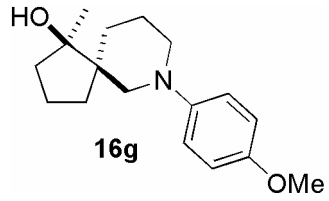


15h

***rac*-(1*R*, 5*S*)-1-(*tert*-Butyl-dimethyl-silanyloxy)-1-methyl-7-(4-trifluoromethyl-phenyl)-7-aza-spiro[4.5]decane 15h**

To a stirred solution of *rac*-(1*R*, 5*R*)-1-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl-7-(4-trifluoromethyl-phenyl)-7-aza-spiro[4.5]decan-6-one **14h** (30 mg, 0.068 mmol, 1 eq) in THF (5 ml), was added BH_3·THF (1.0 M, 0.85 ml, 0.82 mmol, 12 eq) solution dropwise and the reaction heated to 60 °C and stirred for 18 hours. The reaction was quenched by the addition of 1M NaOH (2 ml) and the aqueous layer separated and extracted with EtOAc (3 × 10 ml). The combined organics were dried ($NaSO_4$) and concentrated *in vacuo* to give crude product. Purification by flash column chromatography on silica gel eluting with 5% EtOAc in petroleum ether (40-60) gave *rac*-(1*R*, 5*S*)-1-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl-7-(4-trifluoromethyl-phenyl)-7-aza-spiro[4.5]decane **15h** (22 mg, 0.05 mmol, 74%); ν_{max} (neat)/cm^{-1} 2954, 2857, 1615, 1572, 1462, 1382, 1325, 1248, 1195, 1162, 1113, 1071, 1021, 955, 873, 833, 773 and 650; δ_H (500 MHz, $CDCl_3$) 0.10 (6H, s, 2 × SiCH_3), 0.90 (9H, s, 3 × CCH_3), 1.25 (3H, s, CH_3), 1.40 (2H, m, 1H from CCH_2 and 1H from CCH_2CH_2), 1.58 (2H, m, 1H from CCH_2 and 1H from CCH_2CH), 1.75 (4H, m, 2H from CH_2COSi and 1H from CH_2CH_2N and 1H from CCH_2), 1.88 (2H, m, 1H from CH_2CH_2N and 1H from CCH_2), 2.67 (1H, d, *J* 8.5 Hz, 1H from CCH_2N), 2.83 (1H, d, *J* 12.8 Hz, 1H from CCH_2N), 3.70 (2H, dd, *J* 31.0, 12.1 Hz, NCH_2), 6.95 (2H, m, 2 × Ar-C*H*), 7.46 (2H, d, *J* 7.9 Hz, 2 × Ar-C*H*); δ_C (125 MHz, $CDCl_3$) -0.40 (SiCH_3), -0.01 (SiCH_3), 20.4 (2 × CH_2), 21.2 (CH_2), 24.5 (CH_3), 25.2 (Si*C*), 28.0 (3 × CCH_3), 31.8 (CH_2), 33.5 (CH_2), 40.8 (2 × NCH_2), 51.1 (*C*), 86.7 (*C*OSi), 128.5 (4 × Ar-

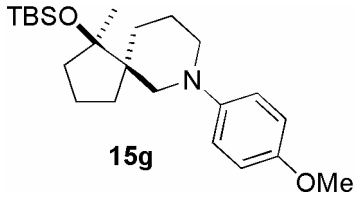
*C*H); *m/z* (ES+ mode) 440 (20), 428 (*M* + H, 100), 401 (5), 327 (20), 301 (10) and 117 (10).



16g

***rac*-(1*R*, 5*S*)-7-(4-Methoxy-phenyl)-1-methyl-7-aza-spiro[4.5]decan-1-ol 16g**

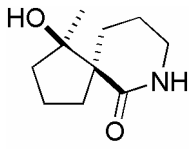
To a stirred solution of *rac*-(1*R*, 5*R*)-1-hydroxy-7-(4-methoxy-phenyl)-1-methyl-7-aza-spiro[4.5]decan-6-one **9g** (25 mg, 0.087 mmol, 1 eq) in THF (2 ml), was added BH_3•THF (1.0 M, 1.04 ml, 1.04 mmol, 12 eq) solution dropwise and the reaction heated to 60 °C and stirred for 18 hours. The reaction was quenched by the addition of 1M NaOH (2 ml) and the aqueous layer separated and extracted with EtOAc (3 × 10 ml). The combined organics were dried ($NaSO_4$) and concentrated *in vacuo* to give crude product. Purification by flash column chromatography on silica gel eluting with 20% EtOAc in petroleum ether (40-60) gave *rac*-(1*R*, 5*S*)-7-(4-methoxy-phenyl)-1-methyl-7-aza-spiro[4.5]decan-1-ol **16g** (24 mg, 0.087 mmol, 100%) as a yellow oil; ν_{max} (neat)/cm^{-1} 3401 (OH), 2938, 1713, 1666, 1511, 1443, 1372, 1245, 1180, 1122, 1036, 943, 826, 728 and 665; δ_H (500 MHz, $CDCl_3$) 1.19 (3H, s, CH_3), 1.37- 1.79 (8H, m, 4 × C*H*$_2$), 1.95 - 2.04 (2H, m, C*H*$_2$CH_2N) 2.55 (1H, m, 1H from CC*H*$_2$N), 2.69 (1H, m, 1H from CH_2-C*H*$_2$N), 3.12 (1H, m, 1H from CH_2C*H*$_2$N), 3.39 (1H, m, 1H from CC*H*$_2$N), 3.69 (3H, s, OC*H*$_3$), 6.78 (2H, d, *J* 8.8 Hz, 2 × Ar-C*H*), 6.95 (2H, m, 2 × Ar-C*H*); δ_C (125 MHz, $CDCl_3$) 14.2 (*C*H_2), 18.5 (*C*H_3), 22.7 (*C*H_2), 24.8 (*C*H_2), 30.9 (*C*H_2), 35.7 (*C*H_2), 41.7 (N*C*H_2), 55.5 (O*C*H_3), 60.4 (*C*), 62.6 (N*C*H_2), 81.9 (*C*OH), 114.4 (2 × Ar-*C*H), 114.9 (2 × Ar-*C*H), 121.2 (Ar-*C*N), 123.8 (Ar-*C*O); *m/z* (CI mode) 276 (*M* + H, 100), 258 (5), 149 (10) and 135 (3). *m/z* (EI mode) 275 (*M*, 5), 150 (80), 135 (100), 120 (25) and 107 (10). (Found: (*M*), 275.1886. $C_{17}H_{25}O_2N$ requires *M*, 275.1880).



15g

***rac*-(1*R*, 5*S*)-1-(*tert*-Butyldimethylsilyloxy)-7-(4-methoxy-phenyl)-1-methyl-7-aza-spiro[4.5]decane 15g**

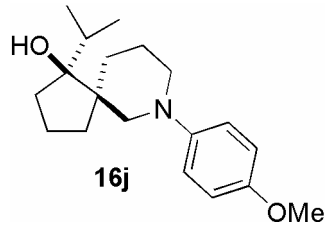
To a stirred solution of *rac*-(1*R*, 5*R*)-1-(*tert*-butyl-dimethyl-silanyloxy)-7-(4-methoxy-phenyl)-1-methyl-7-aza-spiro[4.5]decan-6-one **14g** (43 mg, 0.11 mmol, 1 eq) in THF (5 ml), was added BH_3•THF (1.0 M, 1.31 ml, 1.31 mmol, 12 eq) solution dropwise and the reaction heated to 60 °C and stirred for 18 hours. The reaction was quenched by the addition of 1M NaOH (2 ml) and the aqueous layer separated and extracted with EtOAc (3 × 10 ml). The combined organics were dried ($NaSO_4$) and concentrated *in vacuo* to give crude product. Purification by flash column chromatography on silica gel eluting with 5% EtOAc in petroleum ether (40-60) gave *rac*-(1*R*, 5*S*)-1-(*tert*-butyldimethylsilyloxy)-7-(4-methoxy-phenyl)-1-methyl-7-aza-spiro[4.5]decane **15g** (38 mg, 0.08 mmol, 76%) as a yellow oil; ν_{max} (neat)/cm^{-1} 2952, 2361, 2055, 1741, 1559, 1462, 1442, 1377, 1359, 1330, 1286, 1246, 1187, 1129, 1040, 1005, 988, 954, 874, 833 and 772; δ_H (500 MHz, $CDCl_3$) 0.00 (3H, s, $SiCH_3$), 0.01 (3H, s, $SiCH_3$), 0.81 (9H, s, 3 × CCH_3), 1.13 (3H, s, C*H*$_3$), 1.16 – 1.25 (2H, m, CH_2), 1.44 – 1.51 (1H, m, 1H from CH_2), 1.53 – 1.69 (5H, m, CH_2, 1H from CH_2, 1H from CH_2, 1H from CH_2), 1.75 – 1.77 (1H, m, 1H from CH_2), 1.90 (1H, m, 1H from CH_2), 2.35 (1H, m, 1H from CH_2CH_2N), 2.47 (1H, m, 1H from CCH_2N), 3.28 (1H, d, *J* 11.7 Hz, 1H from CCH_2N), 3.35 (1H, d, *J* 11.0 Hz, 1H from CH_2CH_2N), 3.68 (3H, s, OCH_3), 6.73 (2H, m, 2 × Ar-C*H*), 6.78 (2H, m, 2 × Ar-C*H*); δ_C (125 MHz, $CDCl_3$) -0.40 ($SiCH_3$), -0.00 ($SiCH_3$), 20.4 (Si*C*), 21.3 (CH_2), 25.1 (CH_3), 25.2 (CH_2), 28.0 (3 × $SiCCH_3$), 31.9 (CH_2), 33.8 (CH_2), 40.9 (CH_2), 50.9 (*C*), 53.2 (NCH_2), 57.7 (OCH_3), 59.7 (NCH_2), 86.7 (*C*OSi), 116.4 (2 × Ar*C*H), 120.6 (2 × Ar-*C*H), 149.8 (Ar-*C*N), 155.2 (Ar-*C*O); *m/z* (ES^+ mode) 390 (*M* + H, 100) and 284 (10). (Found: (*M* + H), 390.2830. $C_{23}H_{40}O_2NSi$ requires *M*, 390.2823).



17g

***rac*-(1*R*, 5*S*)-1-Hydroxy-1-methyl-7-aza-spiro[4.5]decan-6-one 17g**

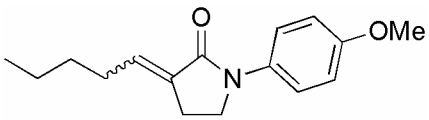
To a solution of *rac*-(1*R*, 5*R*)-1-hydroxy-7-(4-methoxy-phenyl)-1-methyl-7-aza-spiro[4.5]decan-6-one **9g** (50 mg, 0.18 mmol, 1 eq) in CH_3CN (90 ml) and H_2O (10 ml), was added $NaClO_4$ (22 mg, 1.73 mmol, 26 eq). The electrolysis was carried out at room temperature in a divided glass cell equipped with two platium electrodes. The potential was maintained at a constant valve of 1.6 V for 37 hours. The two compartments of the glass cell were separated by a porous glass disk. The working electrode was a Pt plate (2 cm^2). The reference electrode was a Ag/AgCl electrode to which the potential is referred. These two electrodes were placed in the aniodic compartment of the cell. The counter electrode was a Pt grid and was placed in the cathiodic compartment filled with the same solution. The potentiostat galvanostat was included in the circuit. The organic solution was then concentrated and the aqueous layer separated and extracted with EtOAc (3 × 50 ml). The combined organics were dried ($NaSO_4$) and concentrated *in vacuo* to give crude product. Purification by flash column chromatography on silica gel eluting with EtOAc gave *rac*-(*R*)-1-Hydroxy-1-methyl-7-aza-spiro[4.5]decan-6-one **17g** (22 mg, 0.12 mmol, 67%, 98% based on recovered starting material) as a clear oil; ν_{max} (neat)/cm^{-1} 3275 (OH), 2958, 1632 (C(O)), 1489, 1465, 1456, 1452, 1394, 1373, 1355, 1331, 1301, 1281, 1232, 1206, 1174, 1139, 1109, 1068, 1016, 971, 935. 907 and 867; δ_H (500 MHz, $CDCl_3$) 1.22 (3H, s, C*H*$_3$), 1.48 (1H, m, 1H from CC*H*$_2$), 1.62 (3H, m, 1H from C*H*$_2$CH$_2$COH and 1H from C*H*$_2$CH$_2$CH$_2$N and 1H from CC*H*$_2$), 1.76 (4H, m, 2H from C*H*$_2$CH$_2$N and 1H from C*H*$_2$CCOH and 1H from C*H*$_2$CH$_2$CH$_2$N), 1.91 (1H, m, 1H from C*H*$_2$CH$_2$COH), 2.31 (1H, m, 1H from C*H*$_2$CCOH), 3.25 (2H, m, NC*H*$_2$), 5.97 (1H, s, O*H*), 6.32 (1H, s, N*H*); δ_C (125 MHz, $CDCl_3$) 19.6 (*C*H$_2$), 20.2 (*C*H$_2$), 22.8 (*C*H$_3$), 28.5 (*C*H$_2$), 35.3 (*C*H$_2$), 38.3 (*C*H$_2$), 42.4 (N*C*H$_2$), 53.2 (*C*), 83.8 (*C*OH), 178.5 (C(O)); *m/z* (CI mode) 184 (*M* + H, 100), 166 (30) and 112 (80). *m/z* (EI mode) 183 (*M*, 5), 166 (20), 112 (100) and 49 (20). (Found: (*M* + H), 184.1337. $C_{10}H_{18}O_2N$ requires *M* + H, 184.1332).



16j

***rac*-(1*S*, 5*S*)-1-Isopropyl-7-(4-methoxy-phenyl)-7-aza-spiro[4.5]decan-1-ol 16j**

To a stirred solution of (*Z*)-1-(4-methoxy-phenyl)-3-(5-methyl-4-oxo-hexylidene)-piperidin-2-one **4j** (40 mg, 0.13 mmol, 1 eq) in THF (3 ml), was added BH_3•THF (1.0 M, 1.50 ml, 1.51 mmol, 12 eq) solution dropwise and the reaction heated to 60 °C and stirred for 18 hours. The reaction was quenched by the addition of 1M NaOH (2 ml) and the aqueous layer separated and extracted with EtOAc (3 × 10 ml). The combined organics were dried ($NaSO_4$) and concentrated *in vacuo* to give crude product. Purification by flash column chromatography on silica gel eluting with 20% EtOAc in petroleum ether (40-60) gave *rac*-(1*S*, 5*S*)-1-isopropyl-7-(4-methoxy-phenyl)-7-aza-spiro[4.5]decan-1-ol **16j** (38 mg, 0.125 mmol, 95%) as a yellow oil; ν_{max} (neat)/cm^{-1} 3583 (OH), 2946, 2361, 1510, 1464, 1381, 1290, 1242, 1182, 1122, 1039, 947, 885, 826 and 665; δ_H (400 MHz, $CDCl_3$)0.89 (3H, d, *J* 6.8 Hz, CHC*H*$_3$), 0.97 (3H, d, *J* 6.6 Hz, CHC*H*$_3$), 1.25 (2H, m, C*H*$_2$), 1.48 (1H, m, C*H*), 1.82 (8H, m, 4 × C*H*$_2$), 2.95 (4H, m, 2 × NC*H*$_2$), 3.69 (3H, s, OC*H*$_3$), 6.76 (2H, d, *J* 8.6 Hz, 2 × Ar-C*H*), 6.97 (2H, m, 2 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 18.2 (*C*H$_2$), 19.2 (*C*H$_3$), 19.9 (*C*H$_3$), 23.2 (2 × *C*H$_2$), 29.7 (*C*H$_2$), 33.9 (*C*H), 36.7 (*C*H$_2$), 37.2 (NCH$_2$), 47.8 (NCH$_2$), 55.6 (OCH$_3$), 62.0 (C), 88.3 (*C*OH), 114.4 (4 × Ar-*C*H), 120.2 (Ar-*C*N), 143.9 (Ar-*C*O); *m/z* (ES^+ mode) 326 ((*M* + Na) 30), 304 ((M + H) 100), 289 (10), 243 (10). (Found: (*M* + H), 304.2266. $C_{19}H_{30}O_2N$ requires *M* + H, 304.2271).

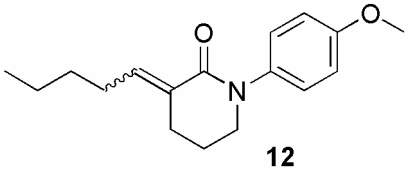


11

***E/Z* 1-(4-Methoxy-phenyl)-3-pentylidene-pyrrolidin-2-one 11**

As for general procedure B, K_2CO_3 (0.83 g, 6.02 mmol, 1.1 eq) was added to a solution of 18-crown-6 (2.89 g, 10.9 mmol, 2 eq) and 1-(4-methoxy-phenyl)-2-oxo-pyrrolidin-3-yl]-phosphonic acid diethyl ester **6a** (1.79 g, 5.47 mmol, 1 eq) in THF (40 ml), followed by addition of valeraldehyde (0.75 ml, 7.11 mmol, 1.3 eq) in THF (20 ml).to give, after work up and purification by flash column chromatography on silica gel eluting with 20% EtOAc in petroleum ether (40-60) gave (*E*)-1-(4-methoxy-phenyl)-3-pentylidene-pyrrolidin-2-one **11** (0.24 g, 1.1 mmol, 21%) as a yellow oil; ν_{max} (neat)/cm^{-1} 2956, 1881, 1685 (C(O)), 1513, 1486, 1465, 1443, 1396, 1321, 1293, 1252, 1182, 1122, 1080, 1032, 829, 752, 667 and 591; δ_H (400 MHz, $CDCl_3$) 0.85 (3H, t, *J* 7.2 Hz, C*H*$_3$), 1.37 (4H, m, C*H*$_2$C*H*$_2$CH$_3$), 2.11 (2H, q, *J* 7.4 Hz, C*H*$_2$CH), 2.71 (2H, m, C*H*$_2$CH$_2$N), 3.74 (5H, m, 3H form OC*H*$_3$ and 2H form C*H*$_2$N), 6.50 (1H, m, C*H*), 6.84 (2H, d, *J* 9.1 Hz, 2 × Ar-C*H*), 7.55 (2H, d, *J* 9.5 Hz, 2 × Ar-C*H*); δ_C (75 MHz, $CDCl_3$) 13.9 (*C*H$_3$), 21.5 (*C*H$_2$), 22.5 (*C*H$_2$), 25.8 (*C*H$_2$), 30.6 (*C*H$_2$), 45.7 (*C*H$_2$N), 55.5 (O*C*H$_3$), 114.0 (2 × Ar-*C*H), 121.3 (2 × Ar-*C*H), 131.7 (Ar-*C*N), 134.7 (*C*H), 138.7 (*C*), 156.5 (Ar-*C*O), 167.4 (*C*(O)); *m/z* (CI mode) 260 (*M* + H, 100). *m/z* (EI mode) 259 (*M*, 100), 230 (60) and 202 (20). (Found: (*M* + H), 260.1650. $C_{16}H_{22}O_2N$ requires *M* + H, 260.1645).

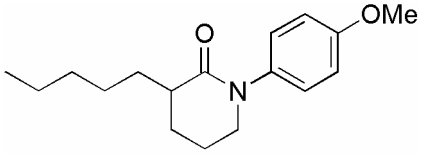
Further elution gave (*Z*)-1-(4-methoxy-phenyl)-3-pentylidene-pyrrolidin-2-one **11** (0.59 g, 2.3 mmol, 42%) as a yellow oil. δ_H (400 MHz, $CDCl_3$) 0.82 (3H, t, *J* 7.1 Hz, CH_3), 1.30 (4H, m, 4H from C*H*$_2$C*H*$_2$CH$_3$), 2.69 (4H, m, 2H from C*H*$_2$CH and 2H from C*H*$_2$CH$_2$N), 3.69 (2H, t, *J* 7.0 Hz, C*H*$_2$N), 3.70 (3H, s, OC*H*$_3$), 5.86 (1H, m, C*H*), 6.79 (2H, d, *J* 6.9 Hz, 2 × Ar-C*H*), 7.49 (2H, d, *J* 9.3 Hz, 2 × Ar-C*H*); δ_C (75 MHz, $CDCl_3$) 13.9 (*C*H$_3$), 21.5 (*C*H$_2$), 22.5 (*C*H$_2$), 25.8 (*C*H$_2$), 30.6 (*C*H$_2$), 45.7 (*C*H$_2$N), 55.5 (O*C*H$_3$), 114.0 (2 × Ar-*C*H), 121.3 (2 × Ar-*C*H), 131.7 (Ar-*C*N), 134.7 (*C*H), 138.7 (*C*), 156.5 (Ar-*C*O), 167.4 (*C*(O));



12

***E/Z* 1-(4-Methoxy-phenyl)-3-pentylidene-piperidin-2-one 12**

As for general procedure C, KHMDS (0.5 M in toluene, 2.17 ml, 1.09 mmol, 1.2 eq) was added to a solution of 18-crown-6 (1.19 g, 4.53 mmol, 5 eq) and [1-(4-methoxy-phenyl)-2-oxo-piperidin-3-yl]-phosphonic acid diethyl ester **6f** (0.31 g, 0.91 mmol, 1 eq) in THF (50 ml), followed by addition of valeraldehyde (0.14 ml, 1.36 mmol, 1.5 eq) in THF (10 ml) to give after work-up and purification by flash column chromatography on silica gel eluting with 40% EtOAc in petroleum ether (40-60) gave (*Z*)-1-(4-methoxy-phenyl)-3-pentylidene-piperidin-2-one **12** (157 mg, 0.58 mmol, 63%) as a yellow oil; ν_{max} (neat)/cm^{-1} 3429 (OH), 2955, 1724, 1660 (C(O)), 1606, 1511, 1452, 1426, 1376, 1295, 1246, 1188, 1123, 1035, 827 and 757; *m/z* (CI mode) 274 (*M* + H, 100), 244 (50) and 215 (10); δ_H (400 MHz, $CDCl_3$) 0.84 (3H, m, C*H*$_3$), 1.29 (4H, m, 2H from C*H*$_2$CH$_3$ and C*H*$_2$CH$_2$CH$_3$), 1.92 (2H, m, C*H*$_2$CH$_2$N), 2.50 (2H, m, CC*H*$_2$), 2.58 (2H, q, *J* 7.2 Hz, C*H*$_2$CH), 3.54 (2H, m, NC*H*$_2$), 3.73 (3H, s, OC*H*$_3$), 5.76 (1H, m, C*H*), 6.84 (2H, m, 2 × Ar-C*H*), 7.11 (2H, m, 2 × Ar-C*H*); δ_C (75 MHz, $CDCl_3$) 14.2 (*C*H$_3$), 22.6 (*C*H$_2$), 24.1 (*C*H$_2$), 29.3 (*C*H$_2$), 31.9 (*C*H$_2$), 32.4 (*C*H$_2$), 51.9 (N*C*H$_2$), 55.5 (O*C*H$_3$), 114.4 (2 × Ar-*C*H), 127.6 (2 × Ar-*C*H), 128.3 (Ar-*C*N), 136.4 (*C*), 143.1 (*C*H), 158.0 (Ar-*C*O), 165.7 (*C*(O)); *m/z* (EI mode) 273 (*M*, 80), 244 (100), 216 (10) and 135 (10). (Found: (*M* + H), 274.1808. $C_{17}H_{24}O_2N$ requires *M* + H, 274.1802).

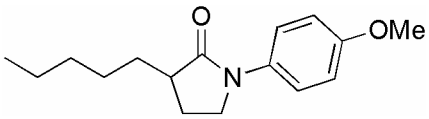


13

1-(4-Methoxyphenyl)-3-pentylpiperidin-2-one 13

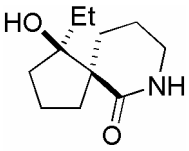
As for general procedure E, treatment of *E/Z* 1-(4-Methoxy-phenyl)-3-pentylidene-piperidin-2-one **12** (90 mg, 0.33 mmol, 1 eq) with SmI_2 (0.1 M in THF, 13.2. ml, 1.32 mmol, 4 eq) and MeOH (0.40 ml, 9.87 mmol, 30 eq), followed by purification by flash column chromatography on silica gel eluting with 60% EtOAc in petroleum ether (40-60) gave 1-(4-Methoxyphenyl)-3-pentylpiperidin-2-one **13** (77 mg, 0.28 mmol, 85%) as a clear oil; ν_{max} (neat)/cm^{-1} 3453, 2935, 1731 (C(O)), 1495, 1454, 1370, 1275, 1161, 1100,

1028, 913, 737 and 698; δ_H (500 MHz, $CDCl_3$) 0.81 (3H, t, *J* 6.9 Hz, C*H*$_3$), 1.28 (5H, m, 2H from C*H*$_2$CH$_3$, 1H from CH, 2H from C*H*$_2$), 1.52 (3H, m, 1H from C*H*$_2$ and 2H from C*H*$_2$), 1.90 (4H, m, 2H from C*H*$_2$CH$_2$N and 2H from C*H*$_2$), 2.35 (1H, m, 1H from C*H*$_2$), 3.52 (2H, m, NC*H*$_2$), 3.74 (3H, s, OC*H*$_3$), 6.82 (2H, d, *J* 8.8 Hz, 2 × Ar-C*H*), 7.06 (2H, d, *J* 9.0 Hz, 2 × Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*H$_3$), 22.2 (*C*H$_2$), 22.6 (*C*H$_2$), 26.5 (*C*H$_2$), 26.8 (*C*H$_2$), 31.9 (*C*H$_2$), 31.9 (*C*H$_2$), 41.9 (*C*H), 51.9 (N*C*H$_2$), 55.5 (O*C*H$_3$), 114.3 (2 × Ar-*C*H), 127.4 (2 × Ar-*C*H), 136.6 (Ar-*C*), 157.9 (Ar-*C*O), 173.2 (*C*(O)); *m/z* (CI mode) 276 (*M* + H, 100) and 204 (20). *m/z* (EI mode) 275 (*M*, 10), 204 (100), 136 (15), 83 (15) and 55 (10). (Found: (*M*), 275.1870. $C_{17}H_{25}O_2N$ requires *M*, 275.1880).



1-(4-Methoxy-phenyl)-3-pentyl-pyrrolidin-2-one

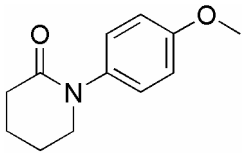
As for general procedure E, treatment of *E/Z* 1-(4-Methoxy-phenyl)-3-pentylidene-pyrrolidin-2-one **11** (40 mg, 0.16 mmol, 1 eq) with SmI_2 (0.1 M in THF, 6.20. ml, 0.62 mmol, 4 eq) and MeOH (0.19 ml, 4.65 mmol, 30 eq), followed by purification by flash column chromatography on silica gel eluting with 60% EtOAc in petroleum ether (40-60) gave 1-(4-Methoxy-phenyl)-3-pentyl-pyrrolidin-2-one (32 mg, 0.13 mmol, 80%) as a yellow oil; ν_{max} (neat)/cm^{-1} 3435, 2923, 1678 (C(O)), 1513, 1465, 1398, 1322, 1288, 1249, 1225, 1180, 1120, 1100, 1032, 825, 755 and 665; δ_H (300 MHz, $CDCl_3$) 0.82 (3H, m, C*H*$_3$), 1.31 (7H, m, 2H from C*H*$_2$CH$_3$, 2H from 2 × C*H*$_2$ and 1H from C*H*$_2$), 1.72 (1H, m, 1H from C*H*$_2$CH$_2$N), 1.88 (1H, m, 1H from C*H*$_2$), 2.25 (1H, m, 1H from C*H*$_2$CH$_2$N), 2.49 (1H, m, C*H*), 3.67 (2H, m, NC*H*$_2$), 3.73 (3H, s, OC*H*$_3$), 6.83 (2H, d, *J* 9.0 Hz, 2 × Ar-C*H*), 7.45 (2H, d, *J* 9.0 Hz, 2 × Ar-C*H*); δ_C (75 MHz, $CDCl_3$) 14.1 (*C*H$_3$), 22.6 (*C*H$_2$), 24.9 (*C*H$_2$), 26.9 (*C*H$_2$), 31.3 (*C*H$_2$), 31.8 (*C*H$_2$), 43.3 (*C*H), 47.2 (N*C*H$_2$), 55.5 (O*C*H$_3$), 114.0 (2 × Ar-*C*H), 121.4 (2 × Ar-*C*H), 132.9 (Ar-*C*N), 156.4 (Ar-*C*O), 175.8 (*C*(O)), *m/z* (CI mode) 261 (*M*, 100), 203 (20), 190 (70), 135 (20) and 82 (40). *m/z* (EI mode) 261 (*M*, 90), 204 (30), 191 (100), 136 (20) and 83 (20). (Found: (*M*), 261.1722. $C_{16}H_{23}O_2N$ requires *M*, 261.1729).



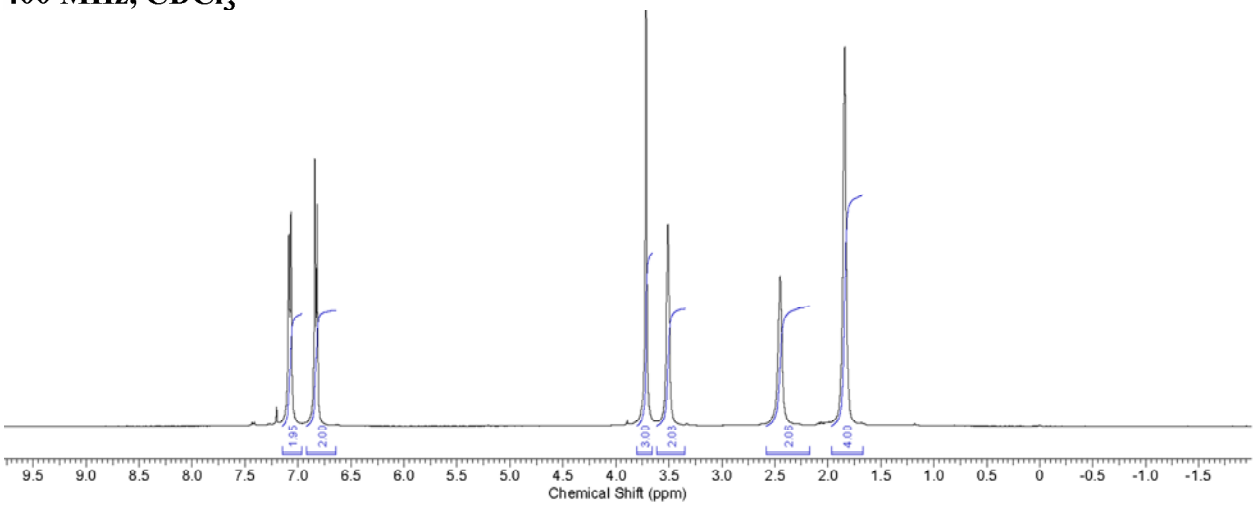
17i

***rac*-(1*R*, 5*S*)-1-Ethyl-1-hydroxy-7-aza-spiro[4,5]decan-6-one 17i**

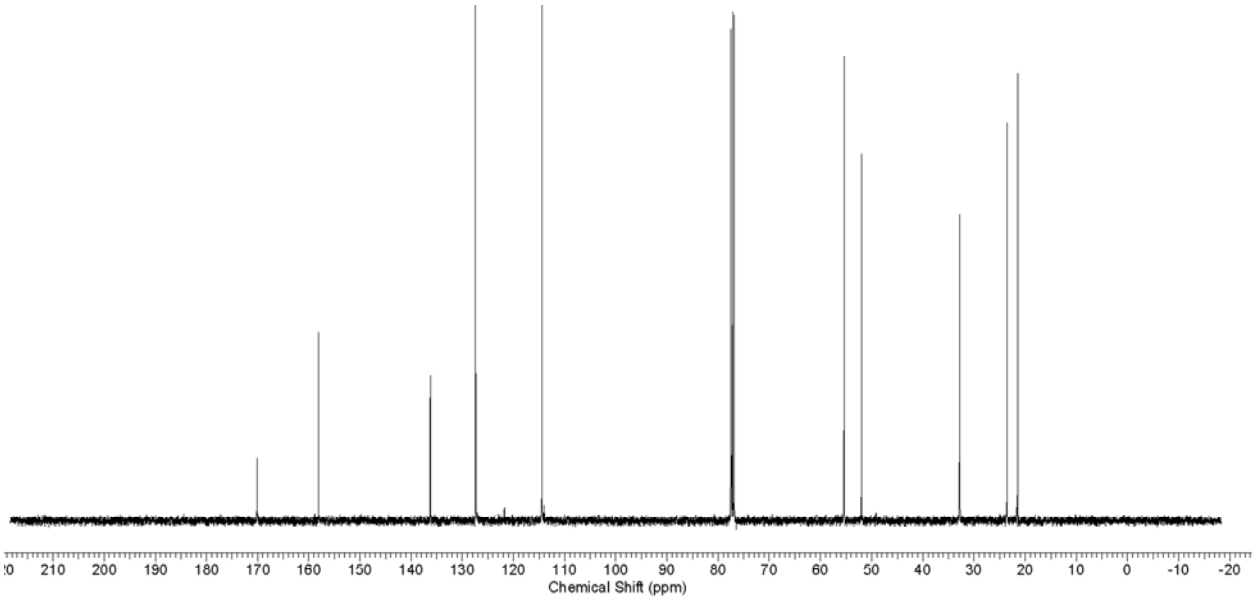
To a solution of *rac*-(1*R*, 5*R*)-1-ethyl-1-hydroxy-7-(4-methoxy-phenyl)-7-aza-spiro[4,5]decan-6-one **9i** (50 mg, 0.17 mmol, 1 eq) in CH_3CN (90 ml) and H_2O (10 ml), was added $NaClO_4$ (21 mg, 1.65 mmol, 10 eq). The electrolysis was carried out at room temperature in a divided glass cell equipped with two platium electrodes. The potential was maintained at a constant valve of 1.7 V for 37 hours. The two compartments of the glass cell were seperated by a porous glass disk. The working electrode was a Pt plate (2 cm^2). The reference electrode was a Ag/AgCl electrode to which the potential is referred. These two electrodes were placed in the aniodic compartment of the cell. The counter electrode was a Pt grid and was placed in the cathiodic compartment filled with the same solution. The potentiostat galvanostat was included in the circuit. The organic solution was then concentrated *in vacuo* and the aqueous layer separated and extracted with EtOAc (3 × 50 ml). The combined organics were dried ($NaSO_4$) and concentrated *in vacuo* to give crude product. Purification by flash column chromatography on silica gel eluting with EtOAc gave *rac*-(1*R*, 5*S*)-1-ethyl-1-hydroxy-7-aza-spiro[4,5]decan-6-one **17i** (22 mg, 0.12 mmol, 73%, 98% based on recovered starting material) as a clear oil; ν_{max} (neat)/cm^{-1} 3280, 2955, 1635 (C(O)), 1490, 1452, 1401, 1355, 1331, 1301, 1280, 1232, 1205, 1133, 1110, 1028, 998, 974, 954, 915, 874, 795 and 658; δ_H (500 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.5 Hz, C*H*$_3$), 1.42 -1.95 (11H, 5 × C*H*$_2$ and 1H from C*H*$_2$), 2.30 (1H, m, 1H from C*H*$_2$), 3.24 (2H, m, NC*H*$_2$), 6.45 (1H, s, O*H*), 6.60 (1H, s, N*H*); δ_C (75 MHz, $CDCl_3$) 19.6 (*C*H_2), 19.9 (*C*H_3), 27.9 (*C*H_2), 29.3 (*C*H_2), 35.8 (*C*H_2), 37.1 (*C*H_2), 42.4 (N*C*H_2), 51.9 (*C*), 86.6 (*C*OH), 179.3 (*C*(O)); *m/z* (CI mode) 198 (*M* + H, 100), 180 (50) and 111 (10). *m/z* (EI mode) 197 (*M*, 10), 180 (10), 112 (100) and 84 (40).

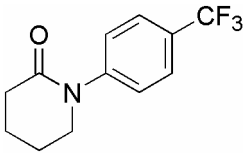


400 MHz, $CDCl_3$

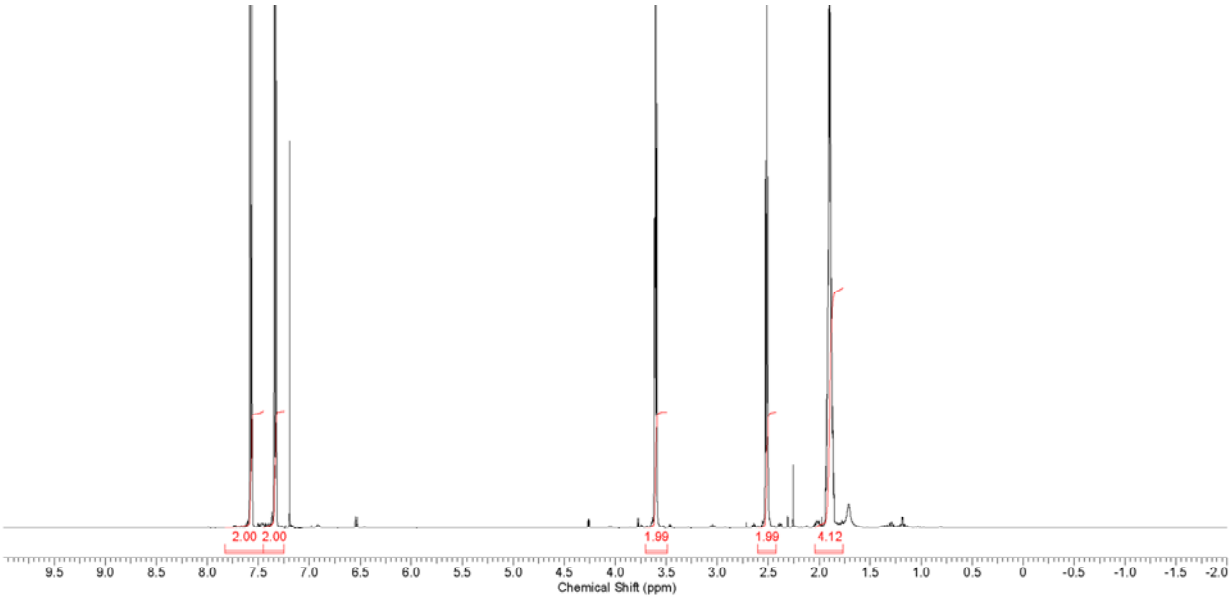


100 MHz, $CDCl_3$

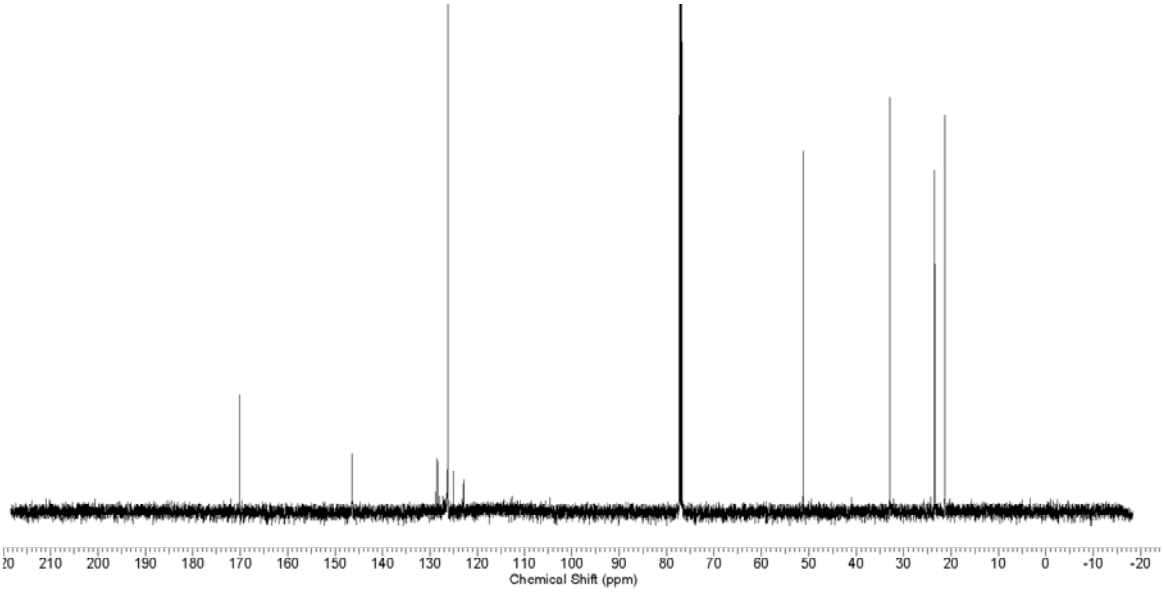


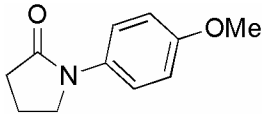


500 MHz, $CDCl_3$

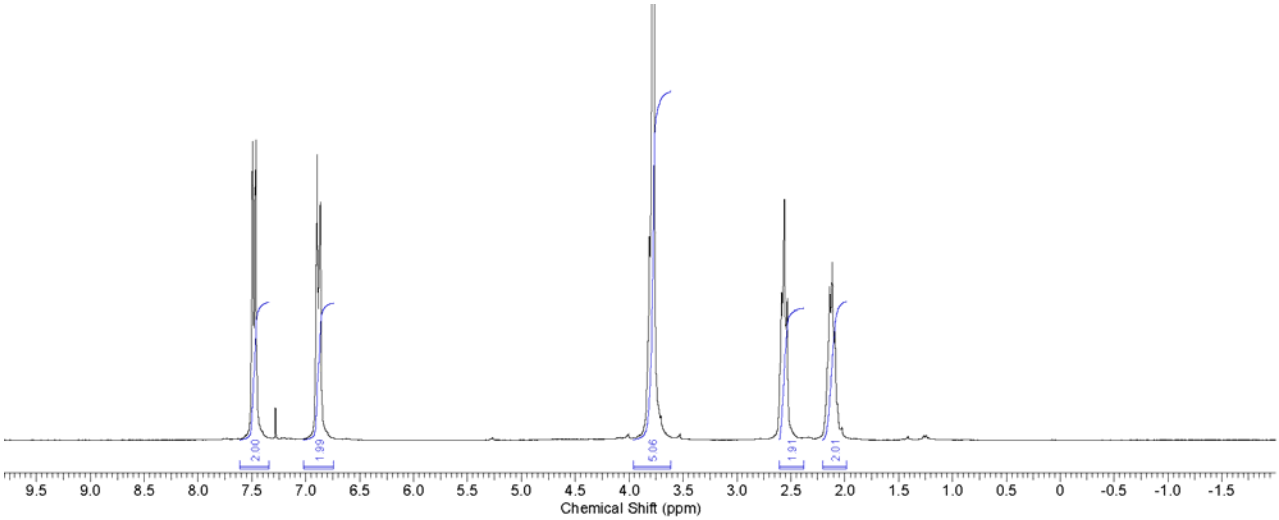


125 MHz, $CDCl_3$

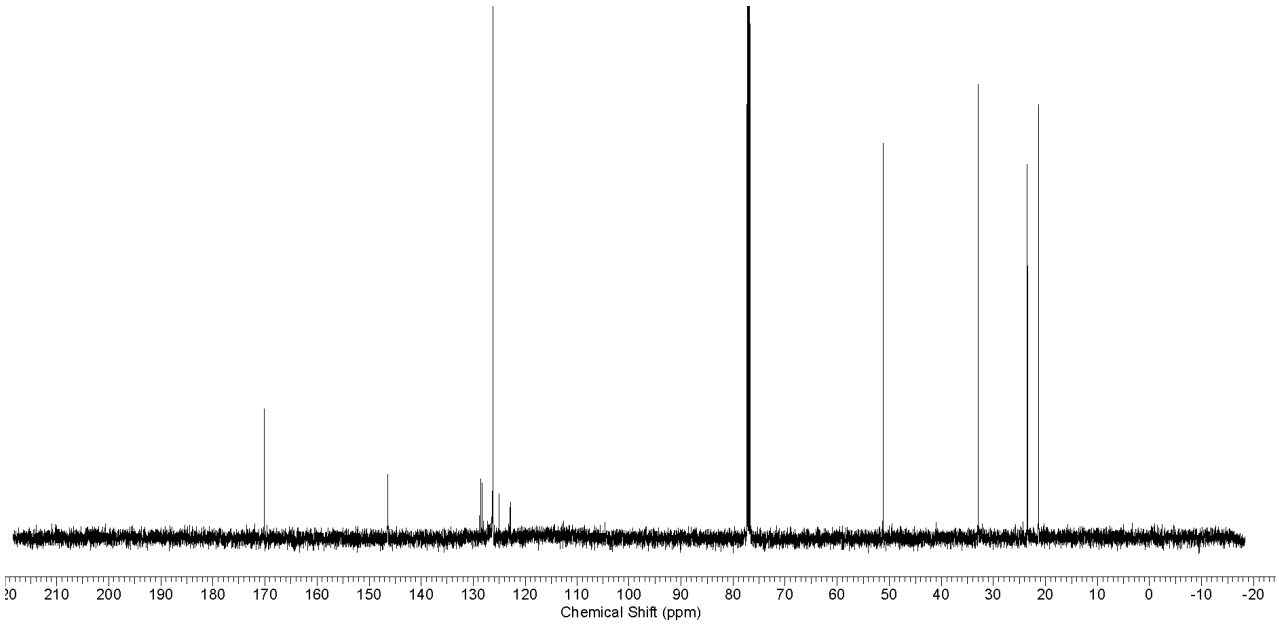


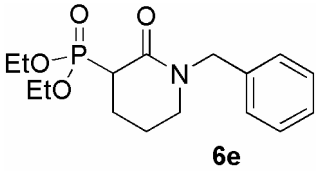


300 MHz, $CDCl_3$



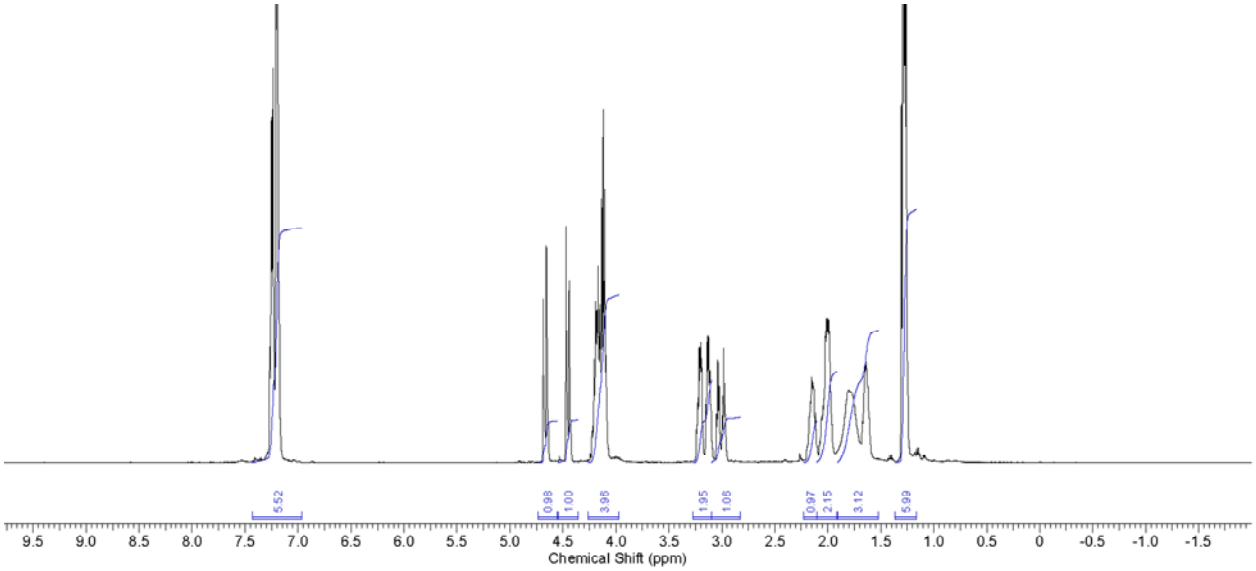
100 MHz, $CDCl_3$



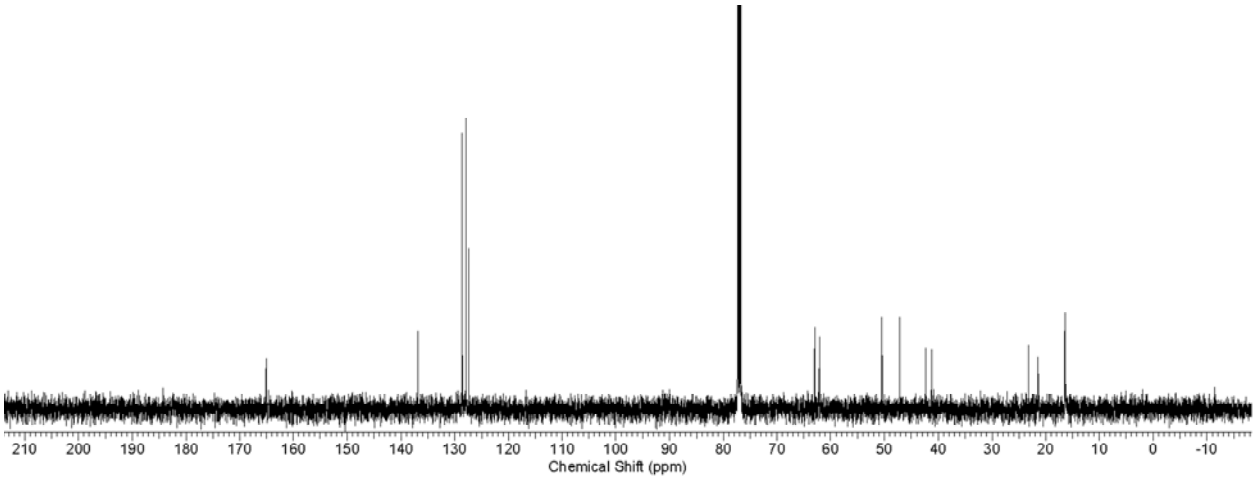


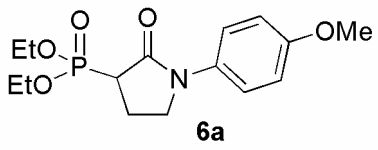
6e

500 MHz, $CDCl_3$



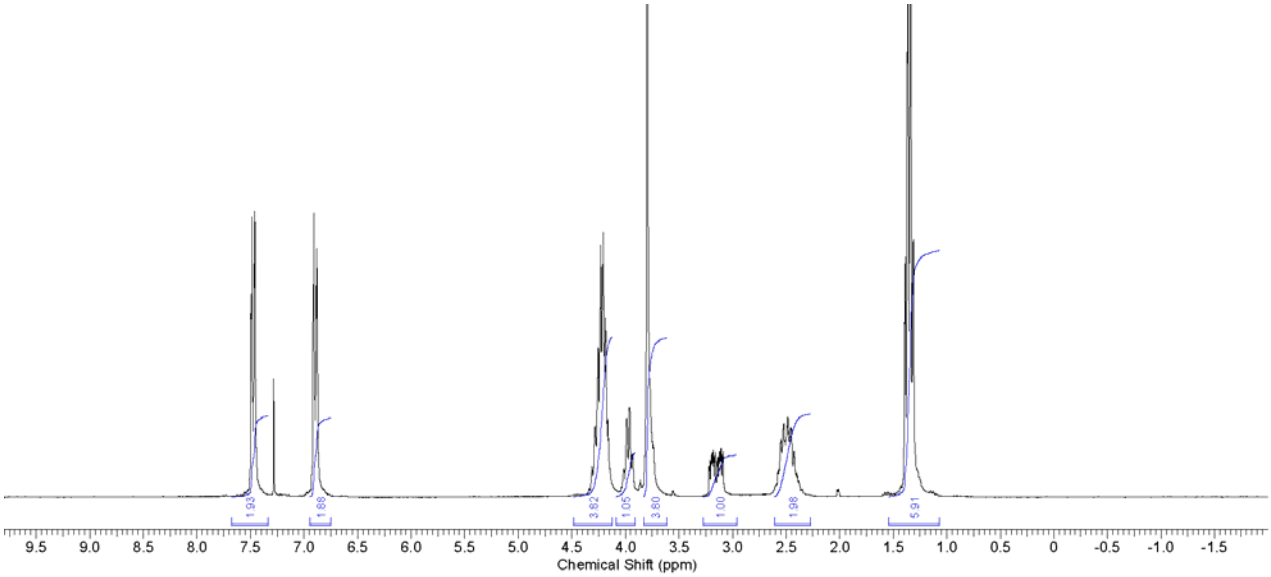
125 MHz, $CDCl_3$



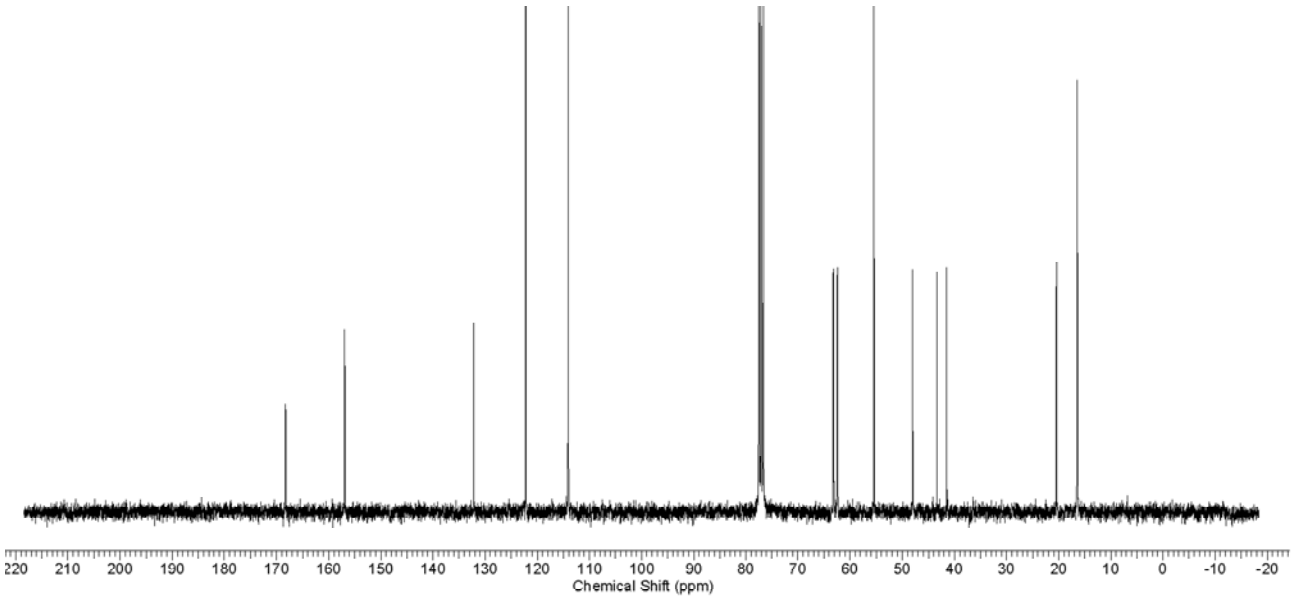


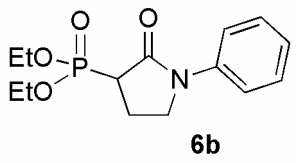
6a

300 MHz, $CDCl_3$



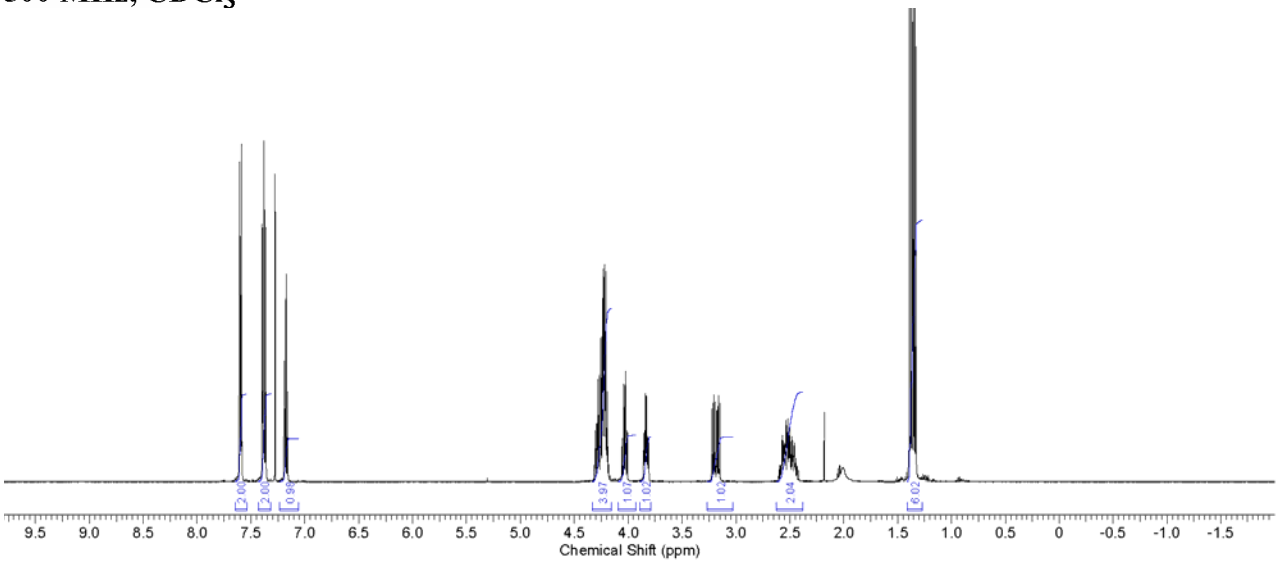
75 MHz, $CDCl_3$



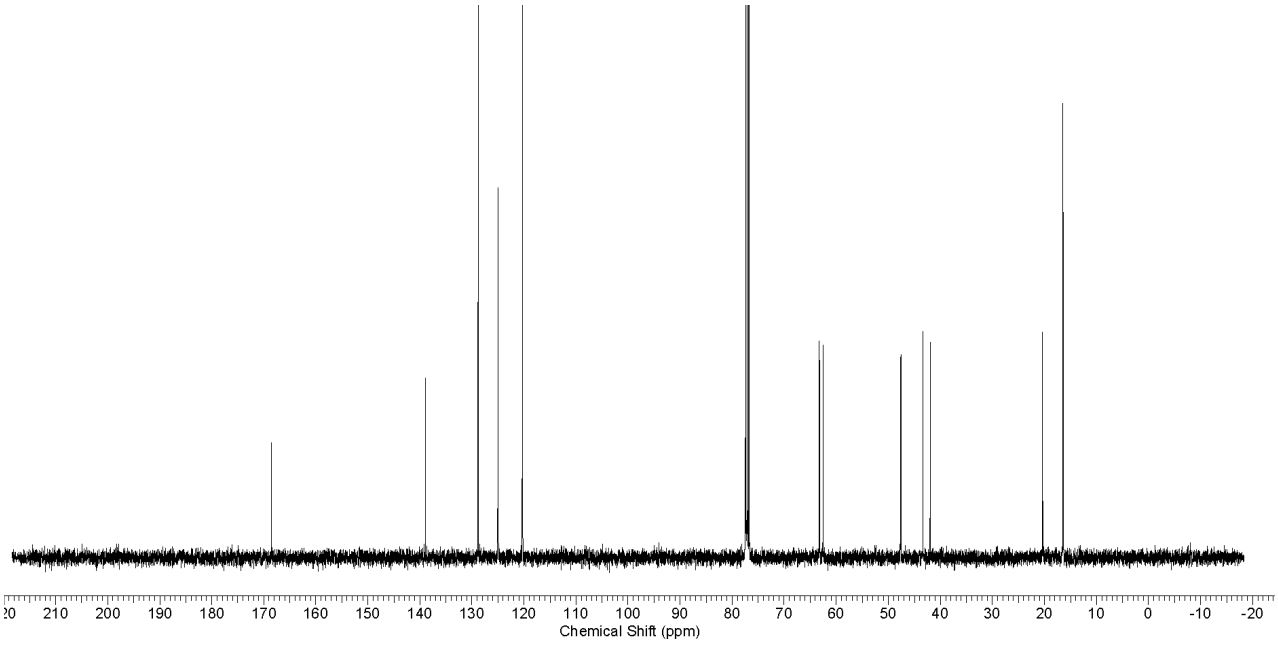


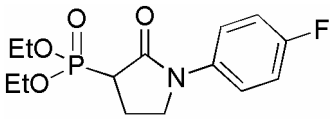
6b

500 MHz, $CDCl_3$



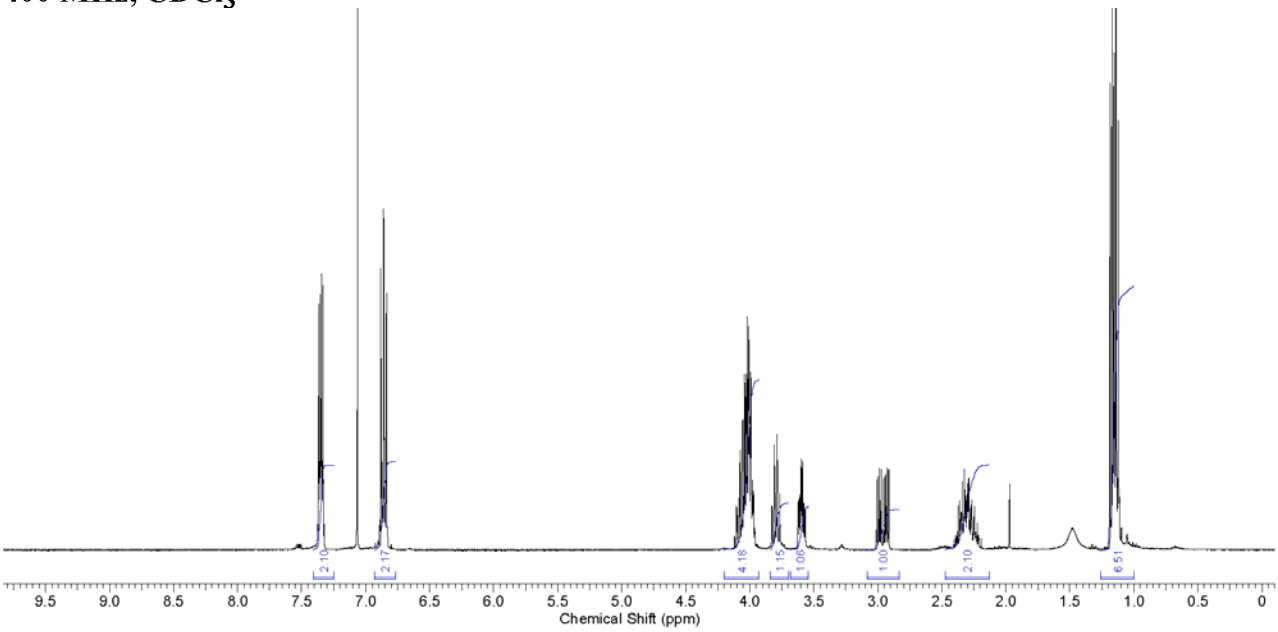
100 MHz, $CDCl_3$



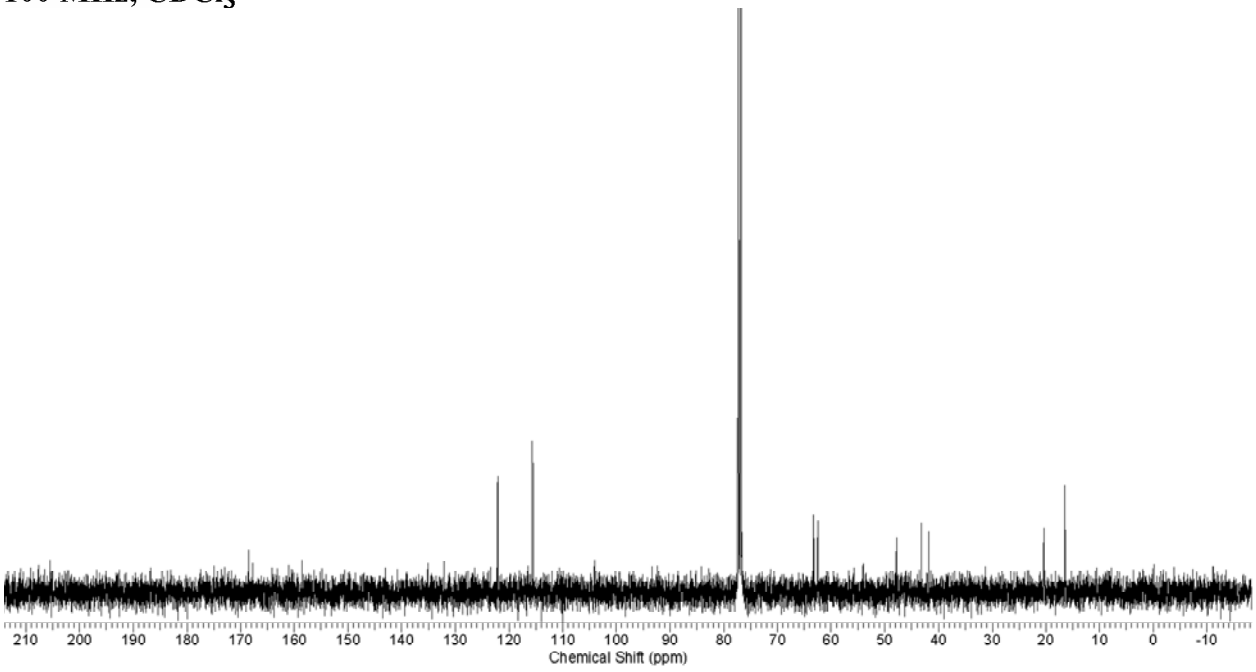


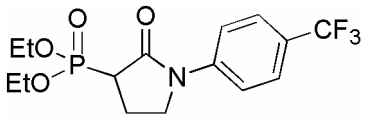
6c

400 MHz, $CDCl_3$



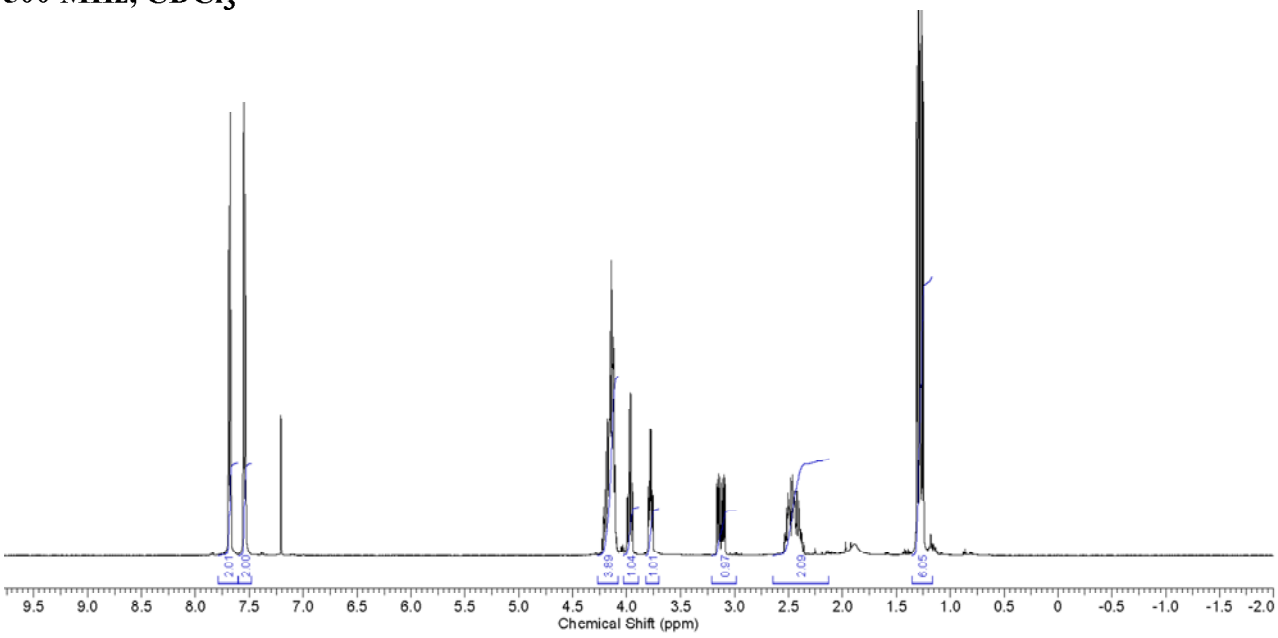
100 MHz, $CDCl_3$



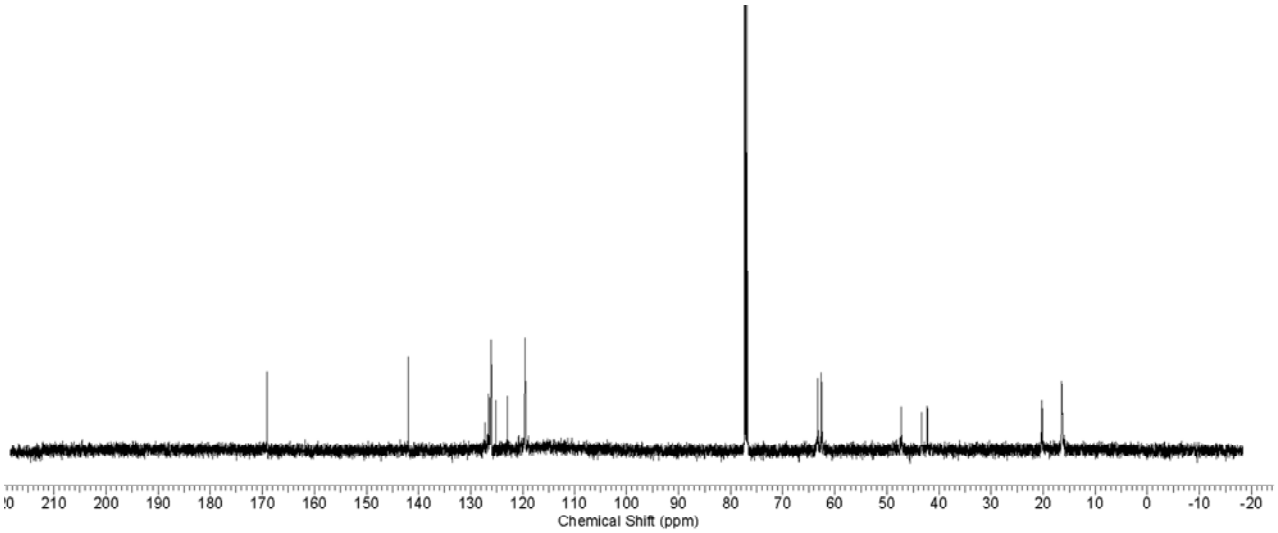


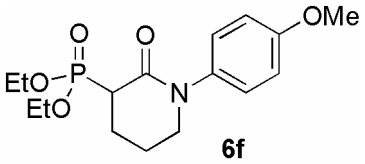
6d

500 MHz, $CDCl_3$



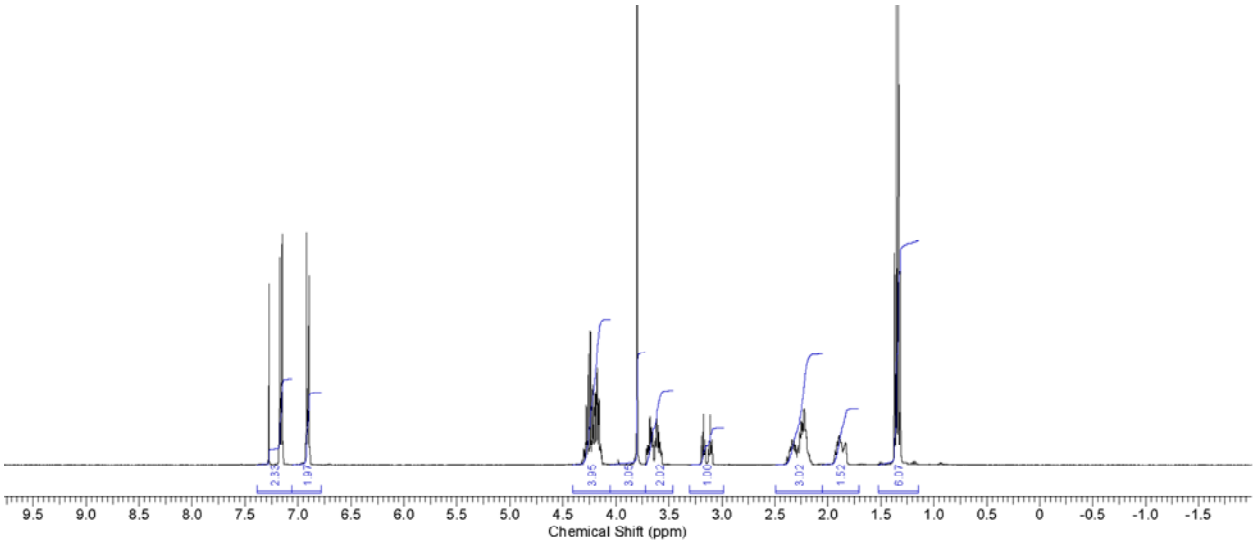
125 MHz, $CDCl_3$



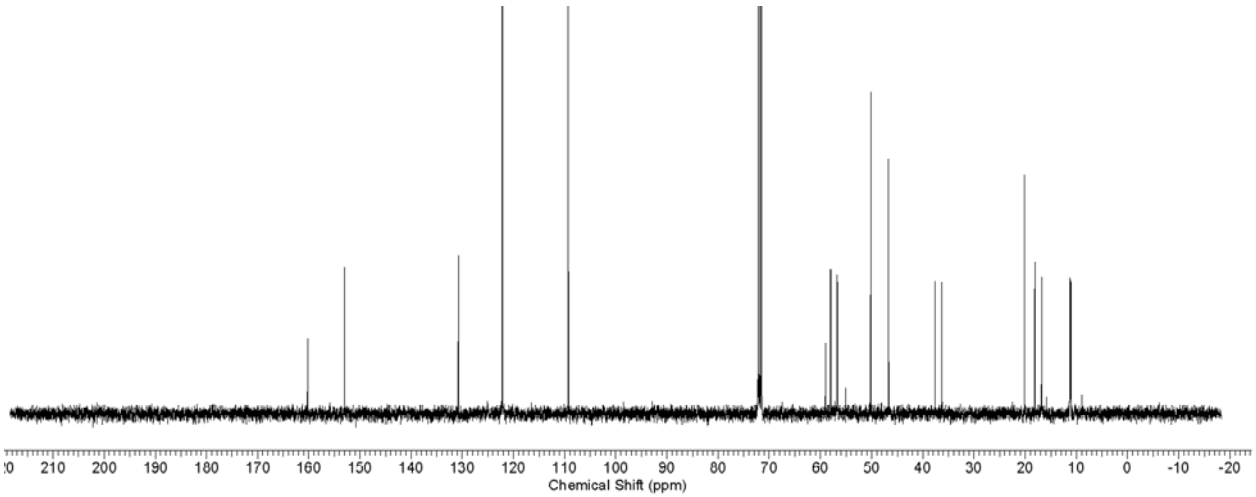


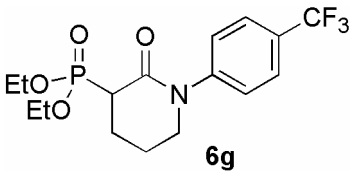
6f

400 MHz, $CDCl_3$



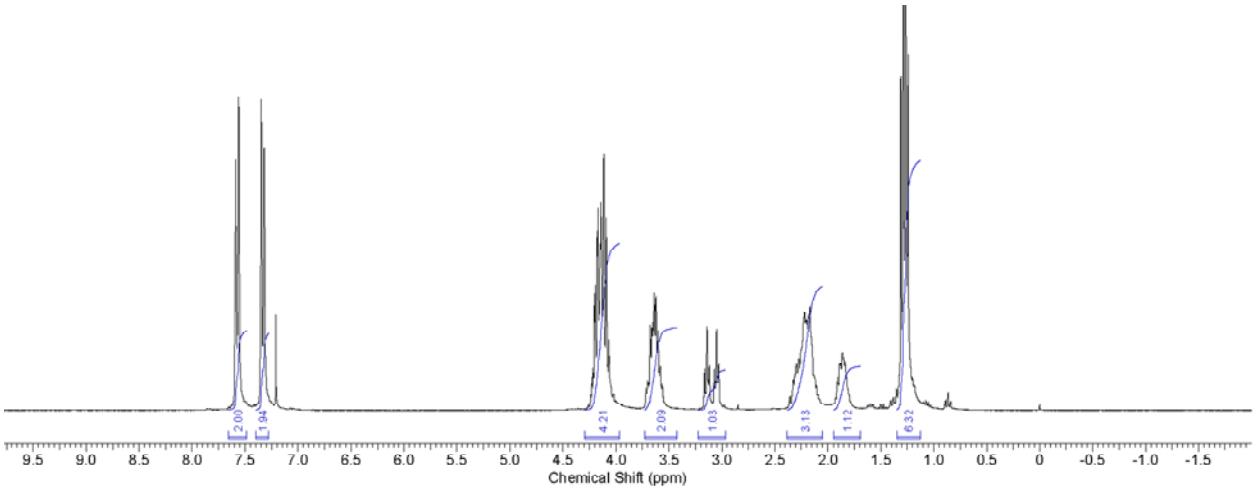
100 MHz, $CDCl_3$



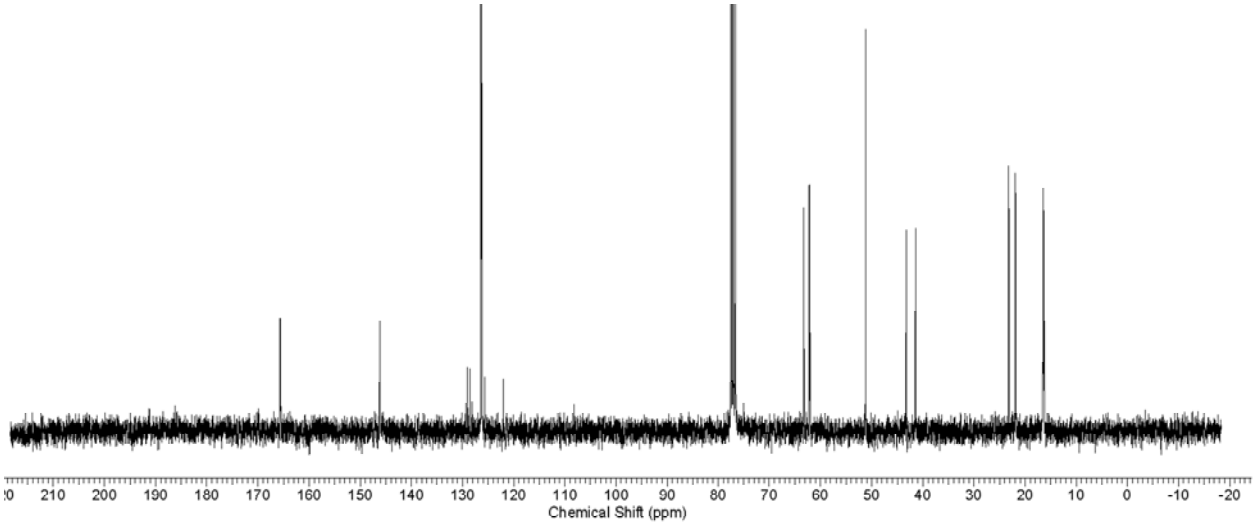


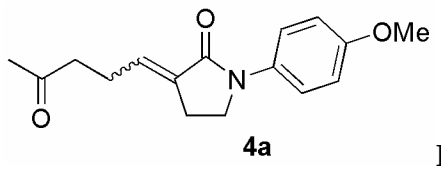
6g

300 MHz, $CDCl_3$



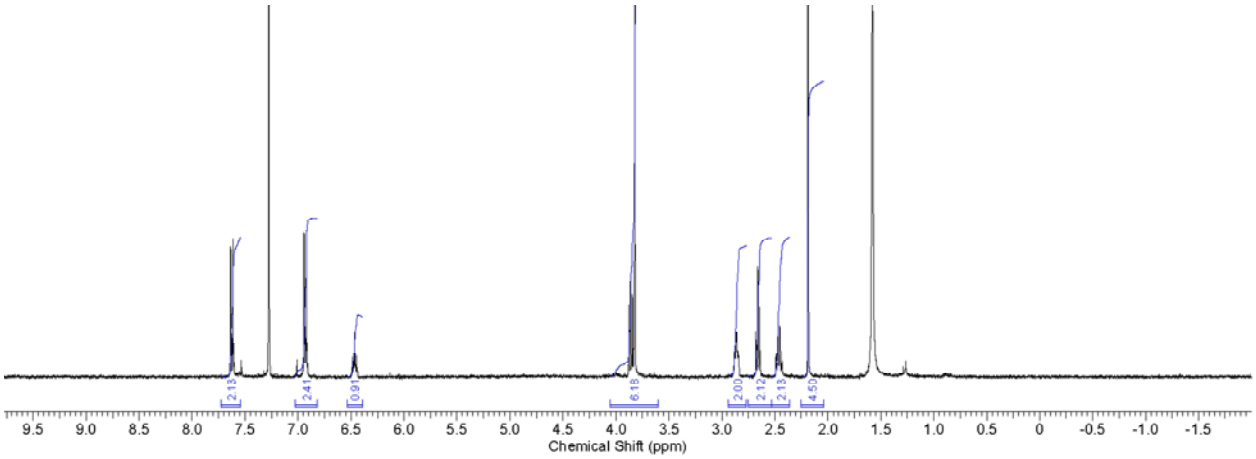
75 MHz, $CDCl_3$



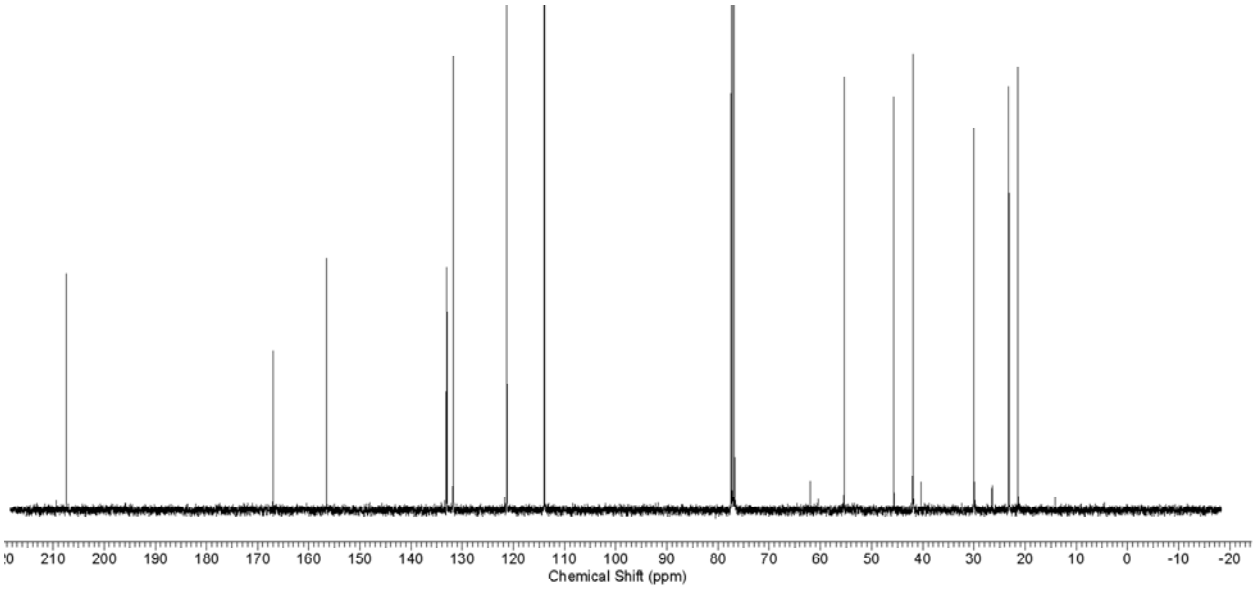


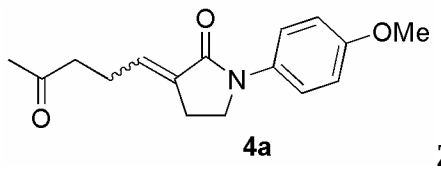
4a **E isomer**

400 MHz, $CDCl_3$



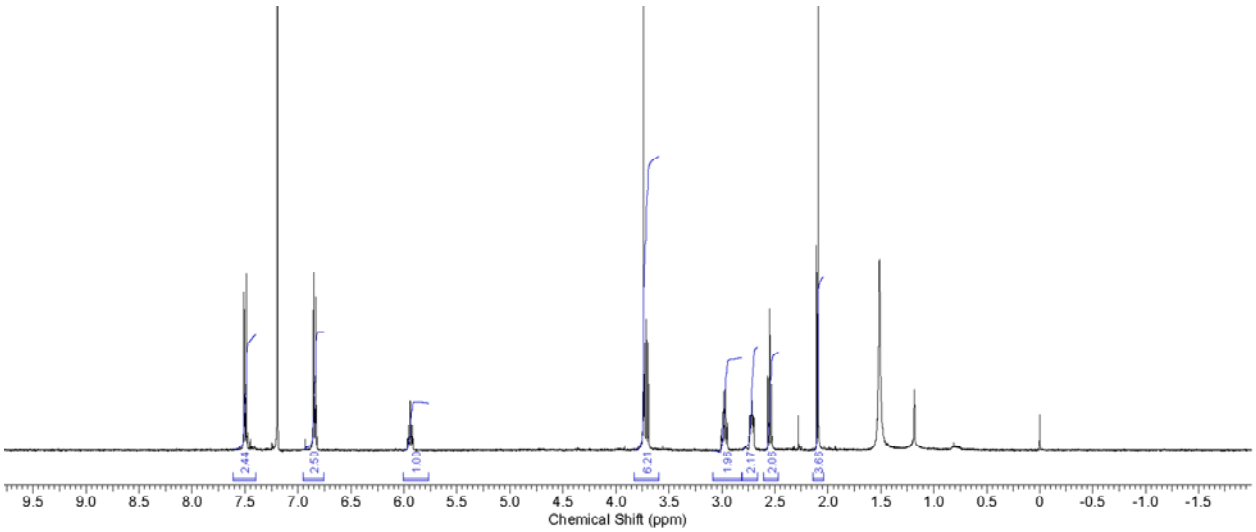
100 MHz, $CDCl_3$



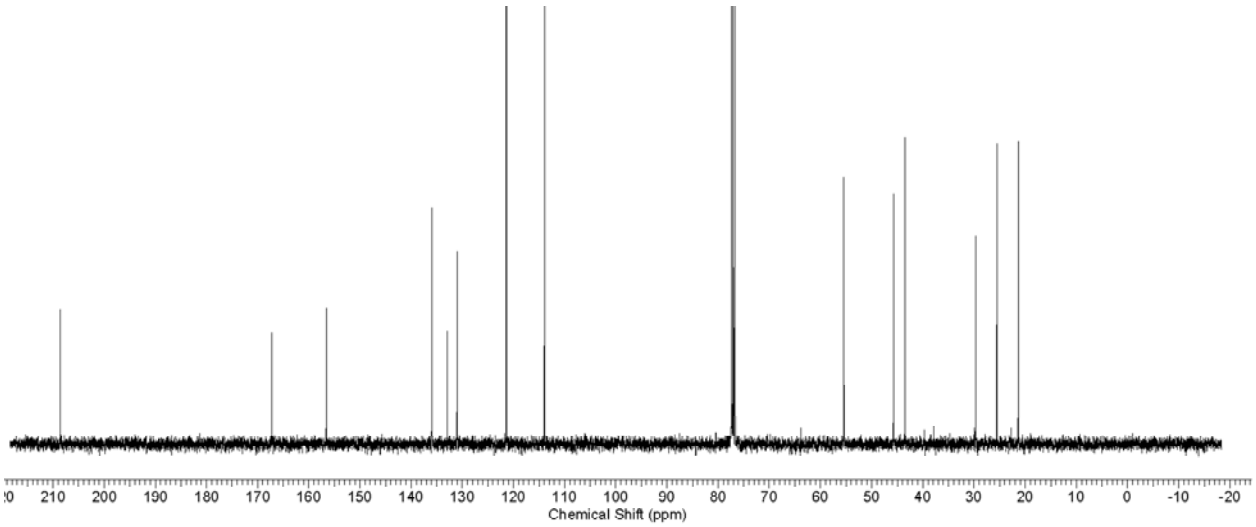


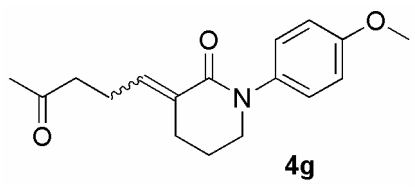
4a **Z isomer**

400 MHz, $CDCl_3$



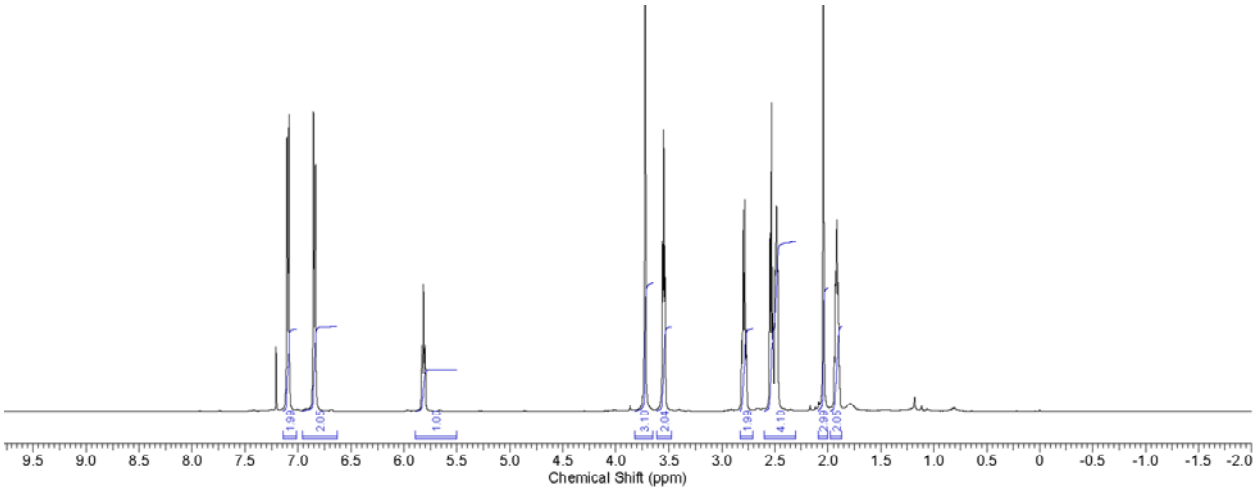
100 MHz, $CDCl_3$



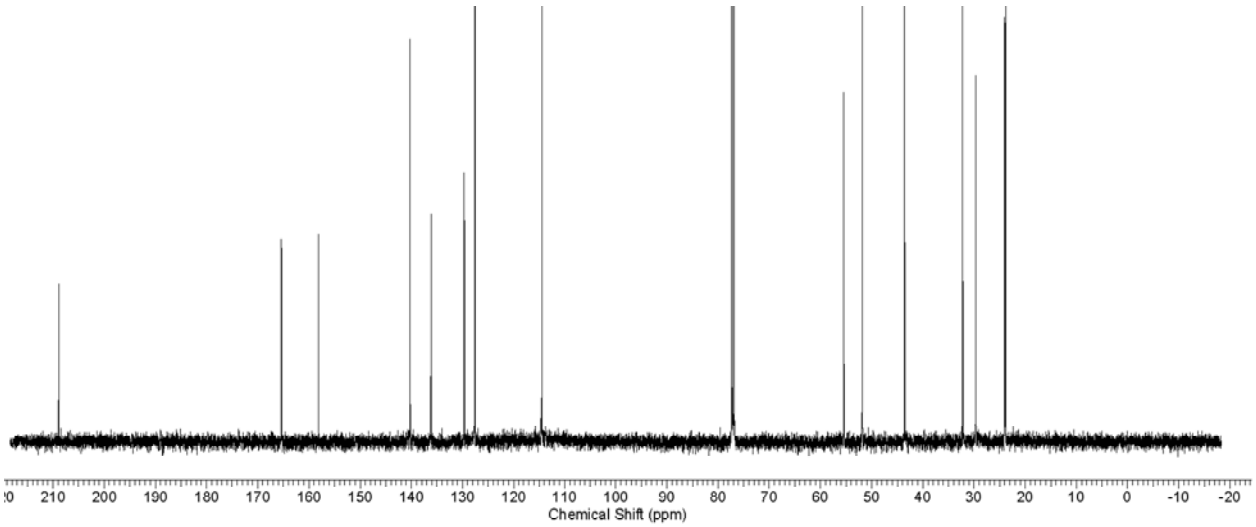


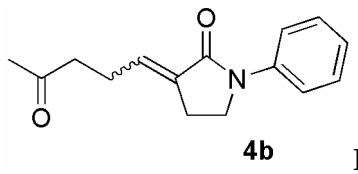
4g **Z isomer**

500 MHz, $CDCl_3$



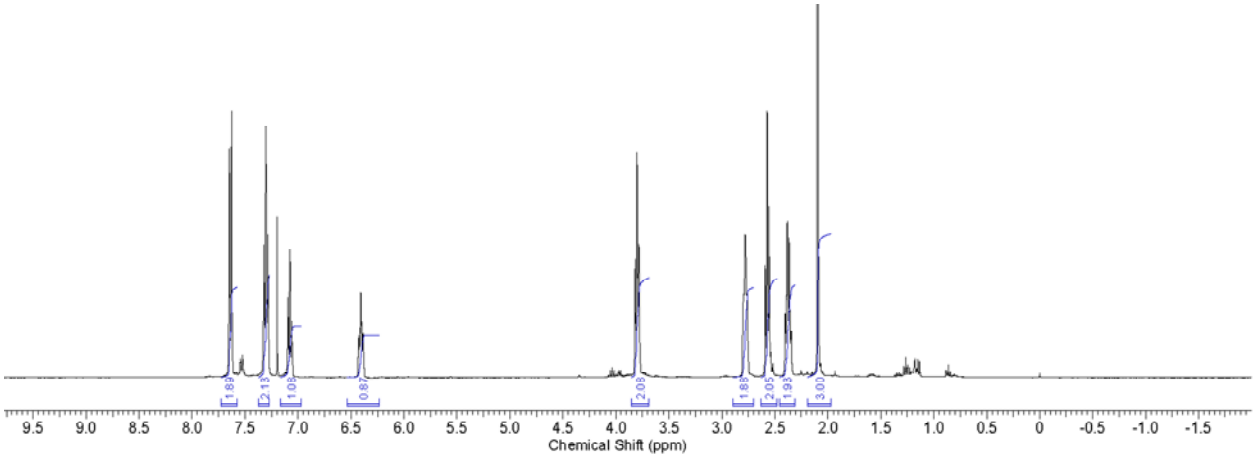
125 MHz, $CDCl_3$



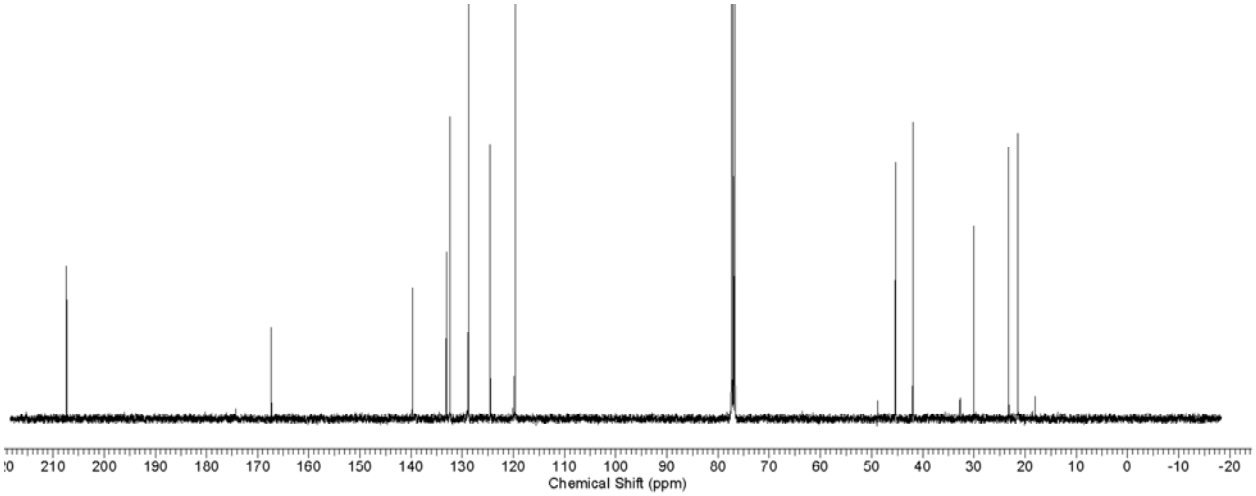


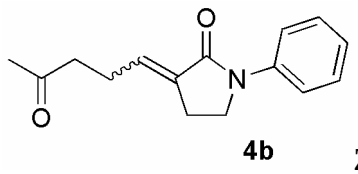
4b **E isomer**

400 MHz, $CDCl_3$



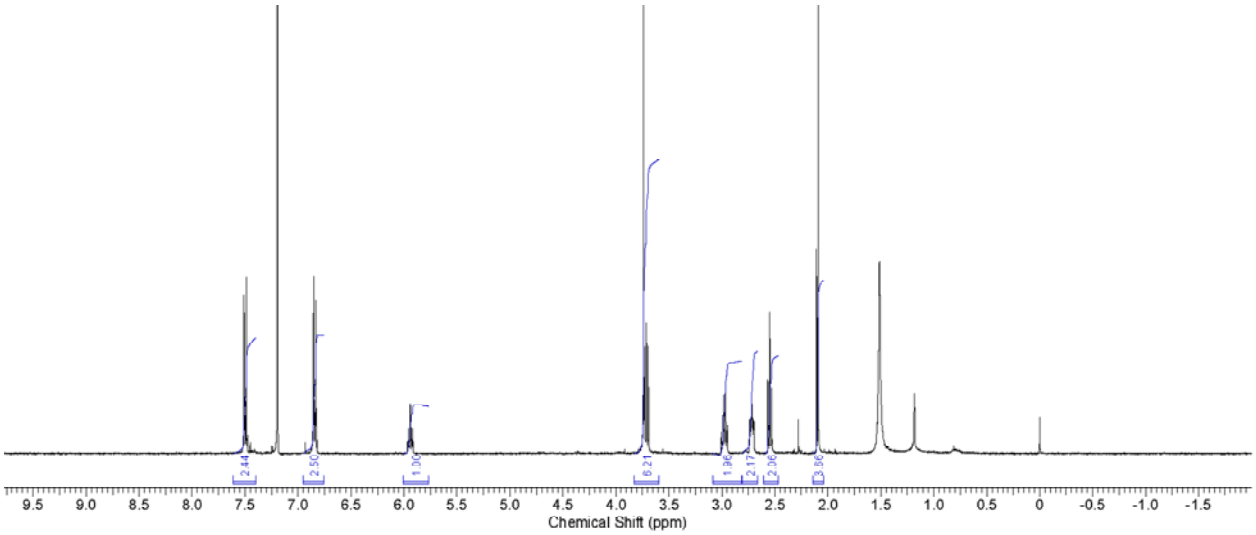
100 MHz, $CDCl_3$



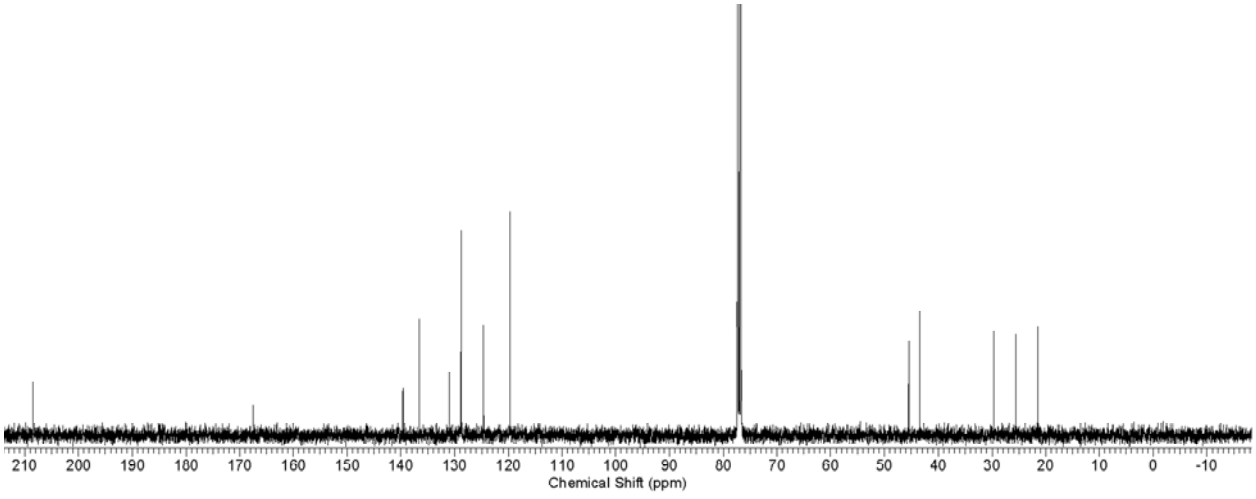


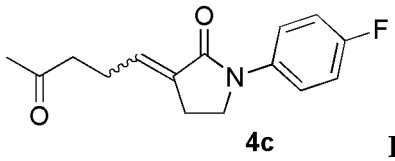
4b **Z isomer**

400 MHz, $CDCl_3$



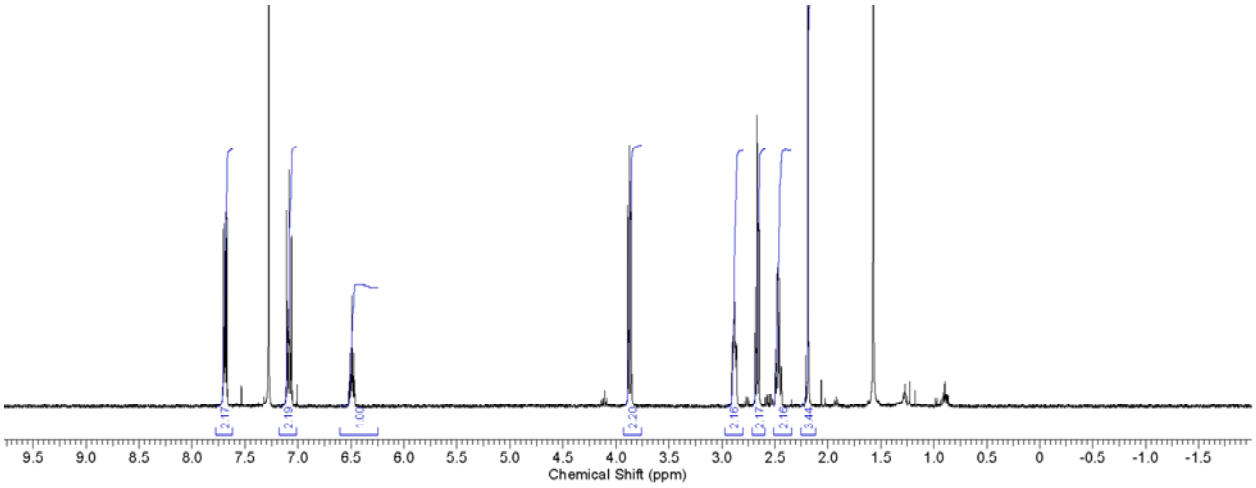
100 MHz, $CDCl_3$



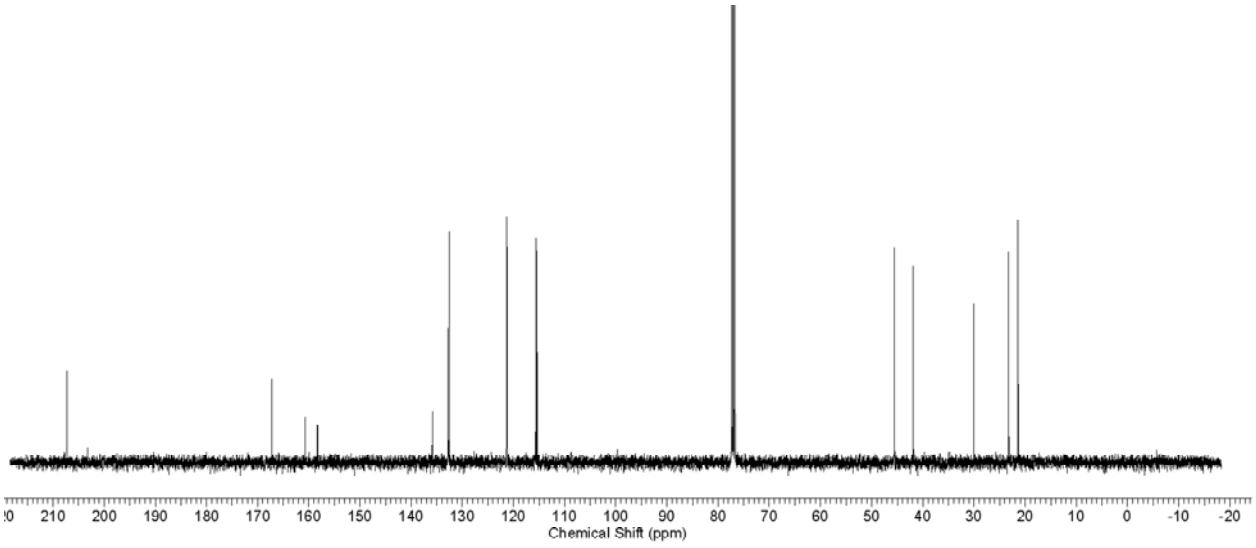


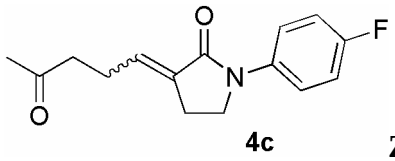
4c **E isomer**

400 MHz, $CDCl_3$



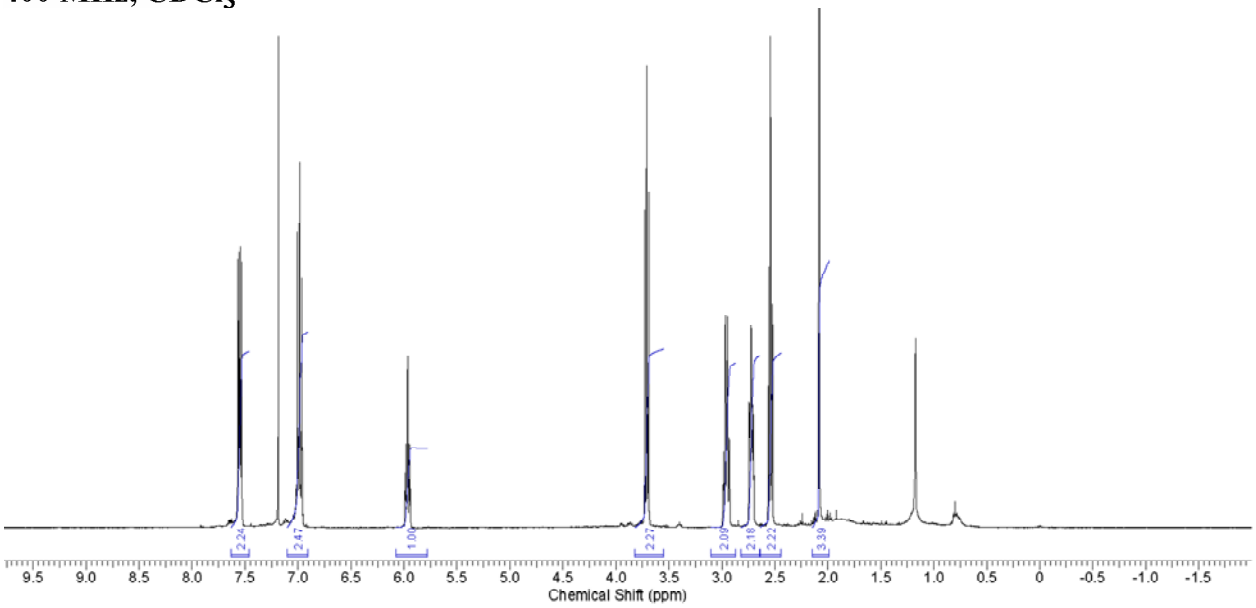
100 MHz, $CDCl_3$



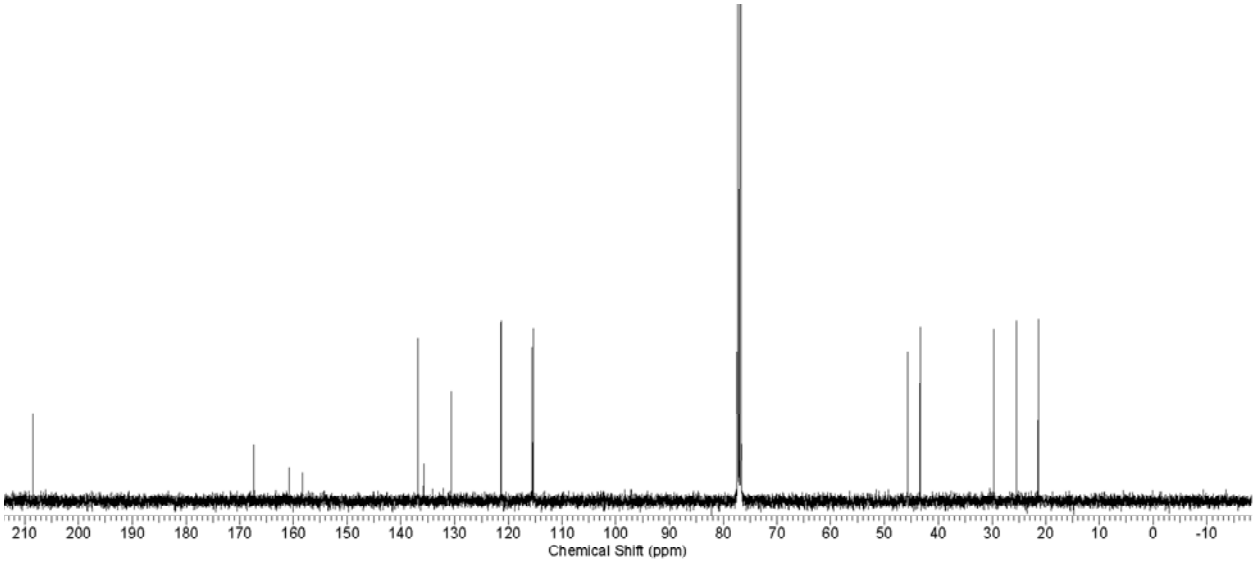


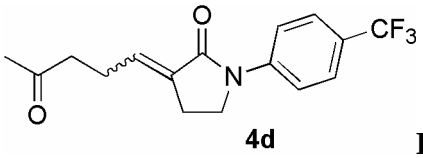
4c **Z isomer**

400 MHz, $CDCl_3$



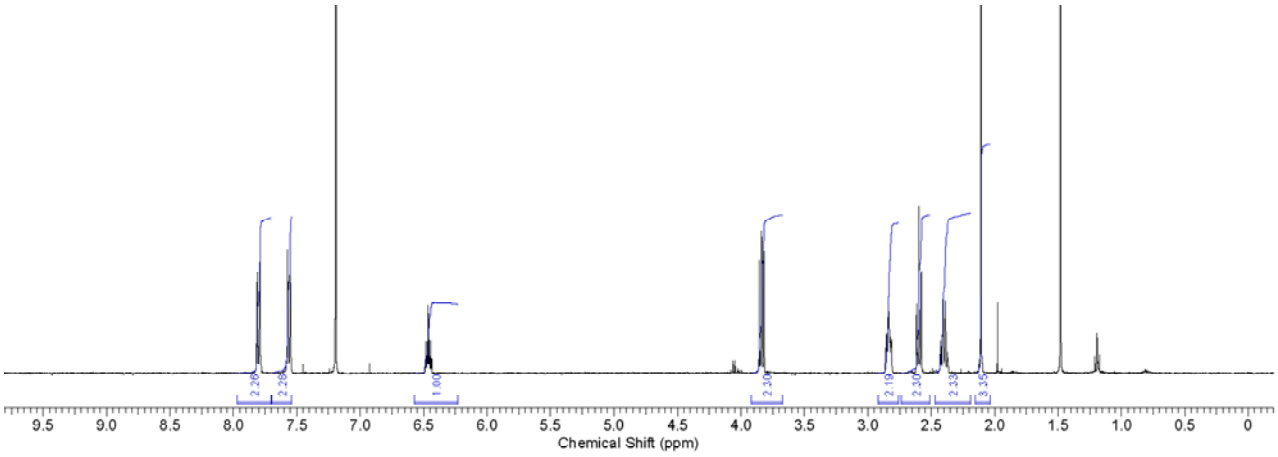
100 MHz, $CDCl_3$



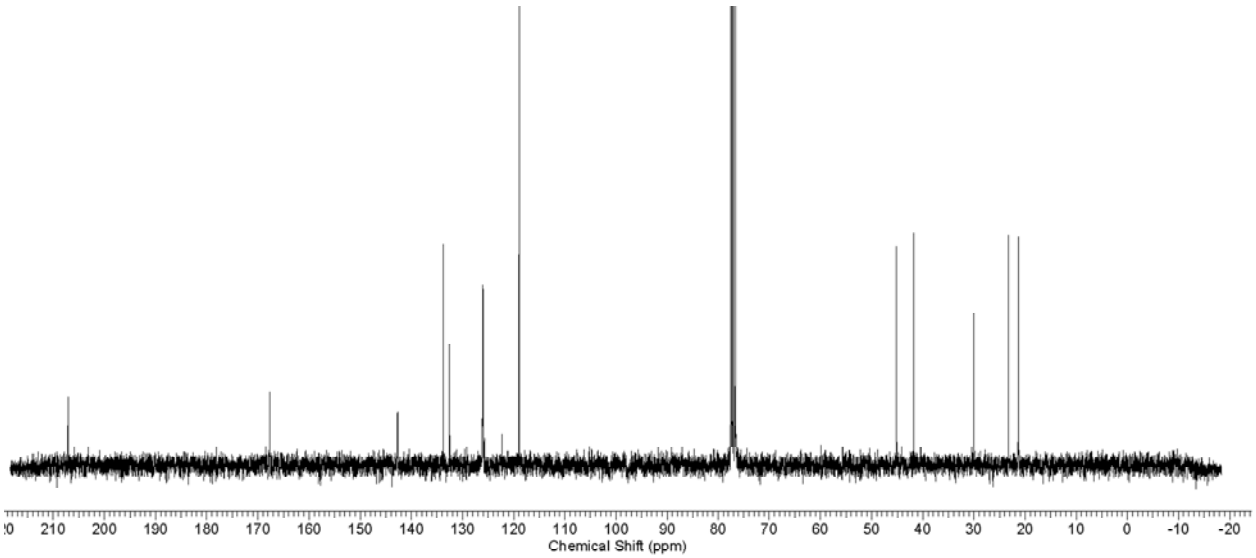


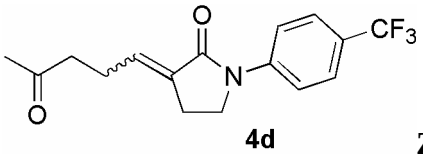
4d **E isomer**

400 MHz, $CDCl_3$



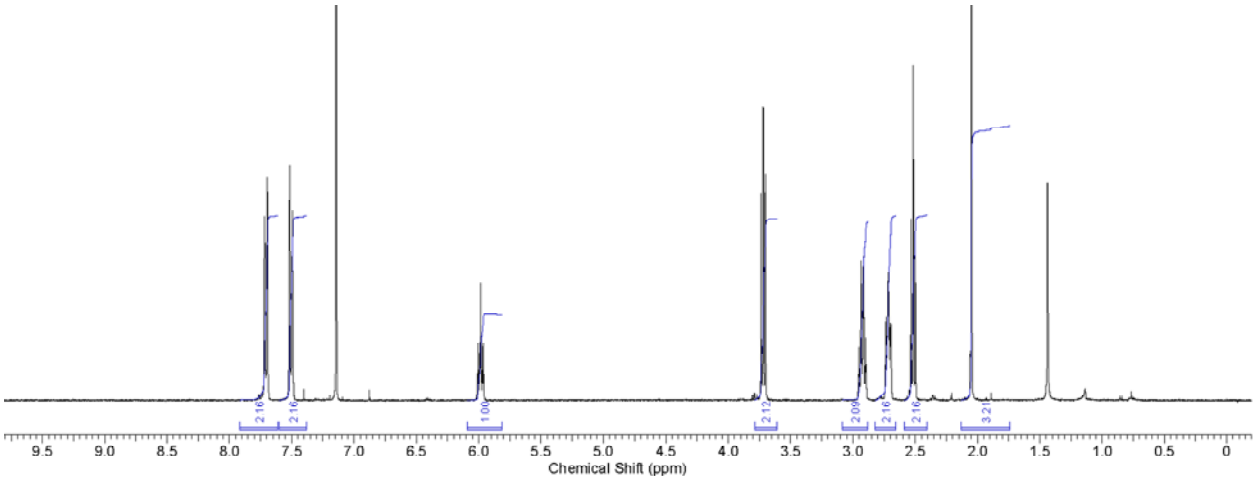
100 MHz, $CDCl_3$



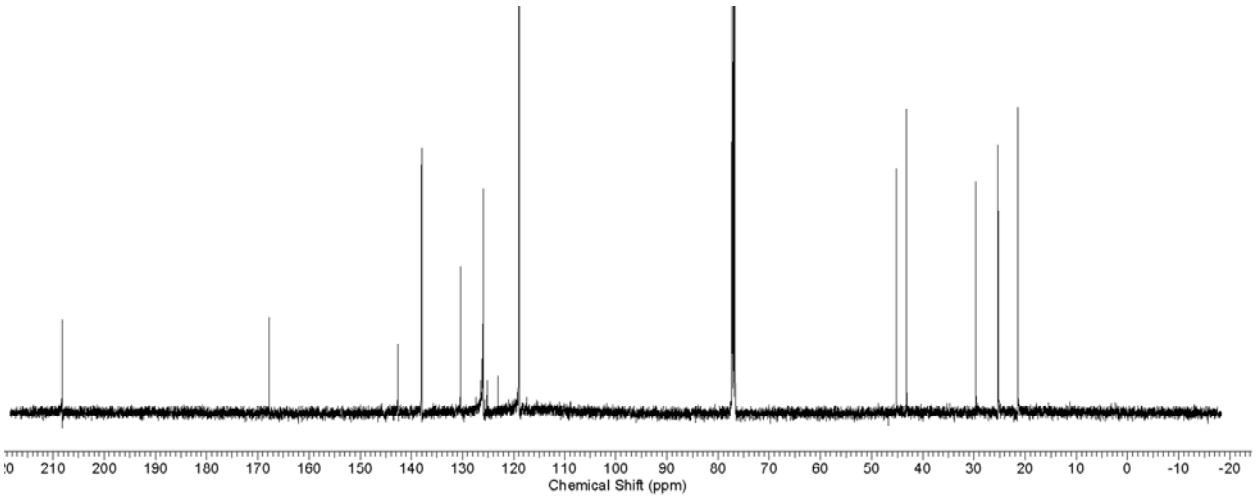


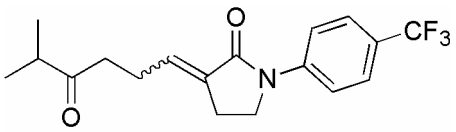
4d **Z isomer**

400 MHz, $CDCl_3$



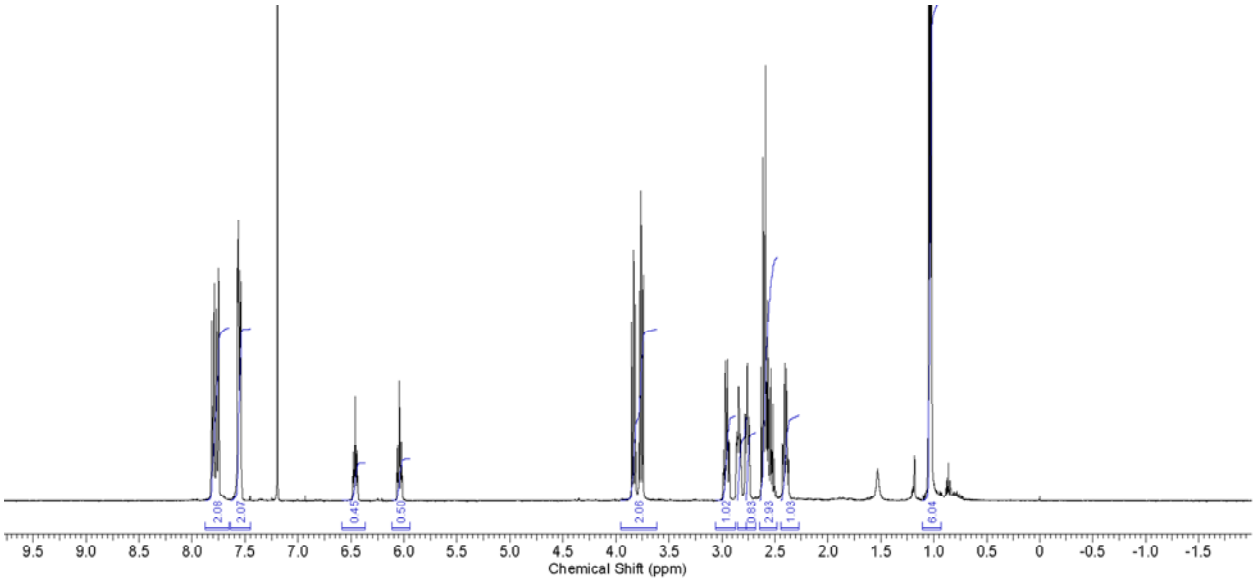
100 MHz, $CDCl_3$



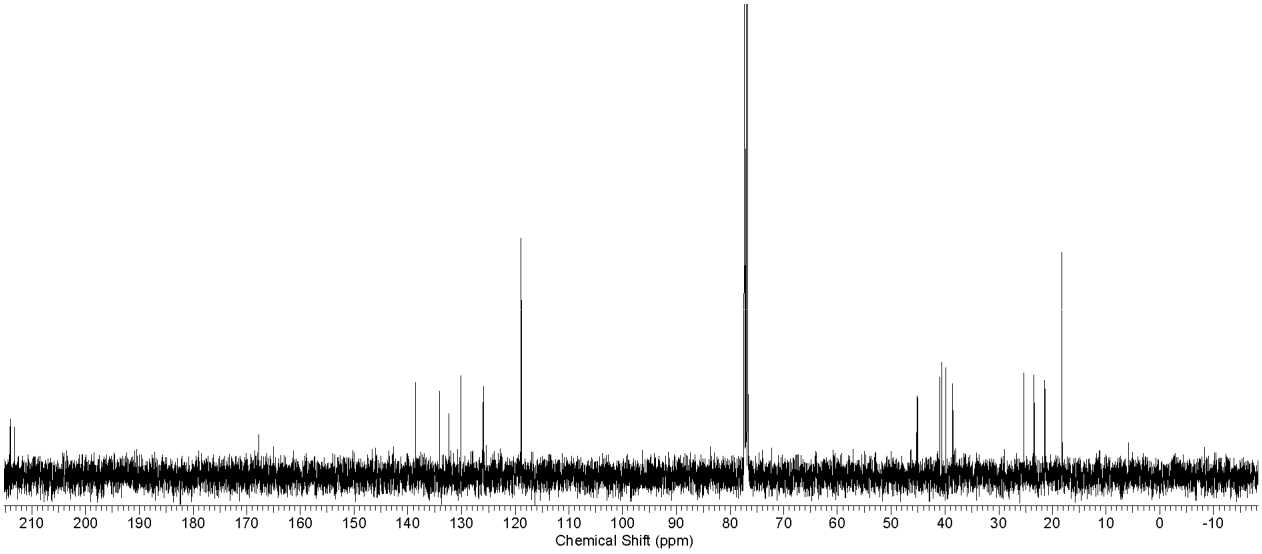


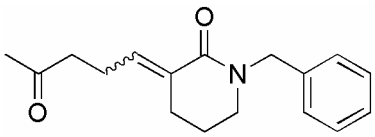
4e **mixture of diasteroisomers**

400 MHz, $CDCl_3$



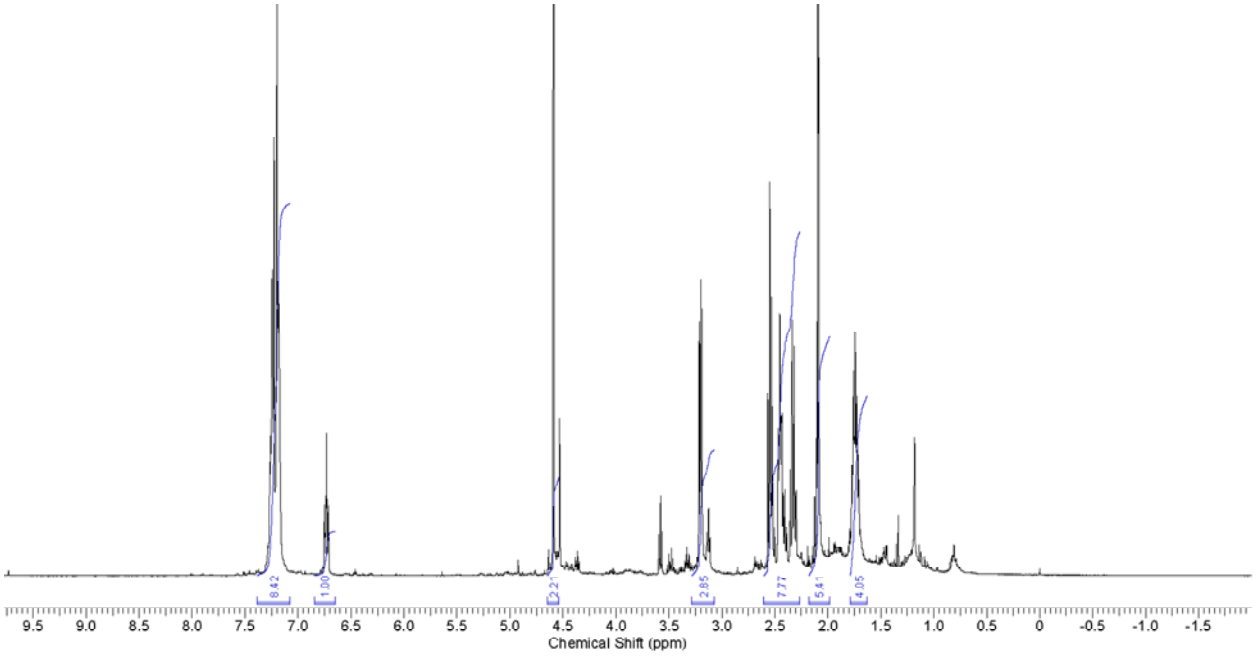
100 MHz, $CDCl_3$



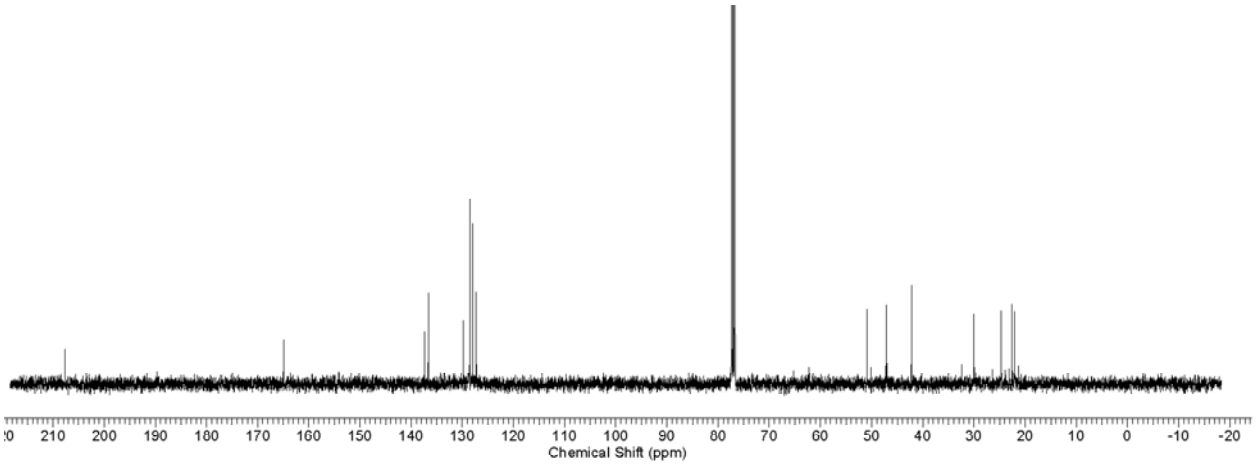


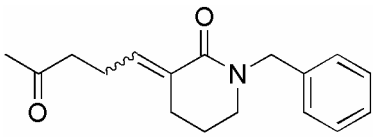
4f **E isomer**

400 MHz, $CDCl_3$



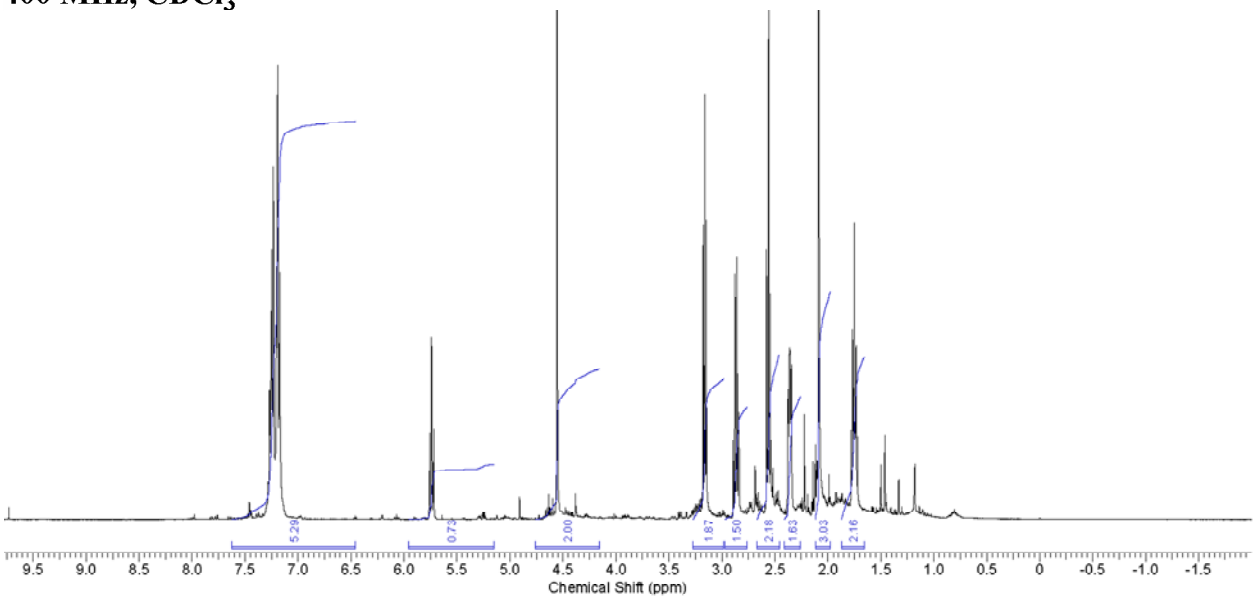
100 MHz, $CDCl_3$



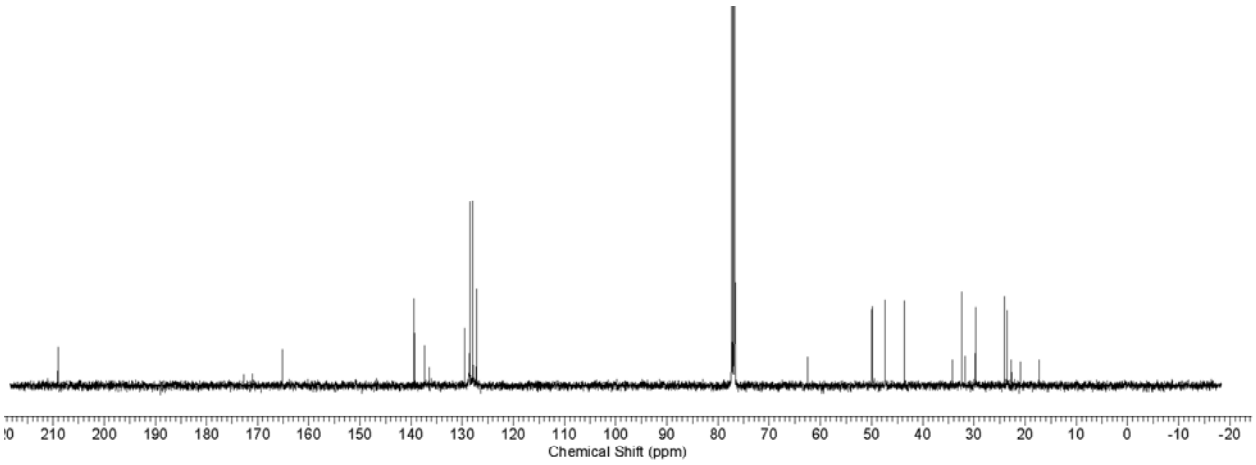


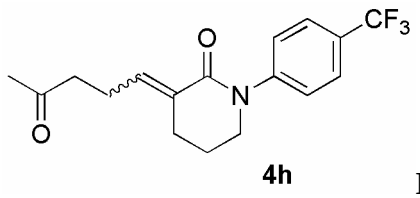
4f **Z isomer**

400 MHz, $CDCl_3$



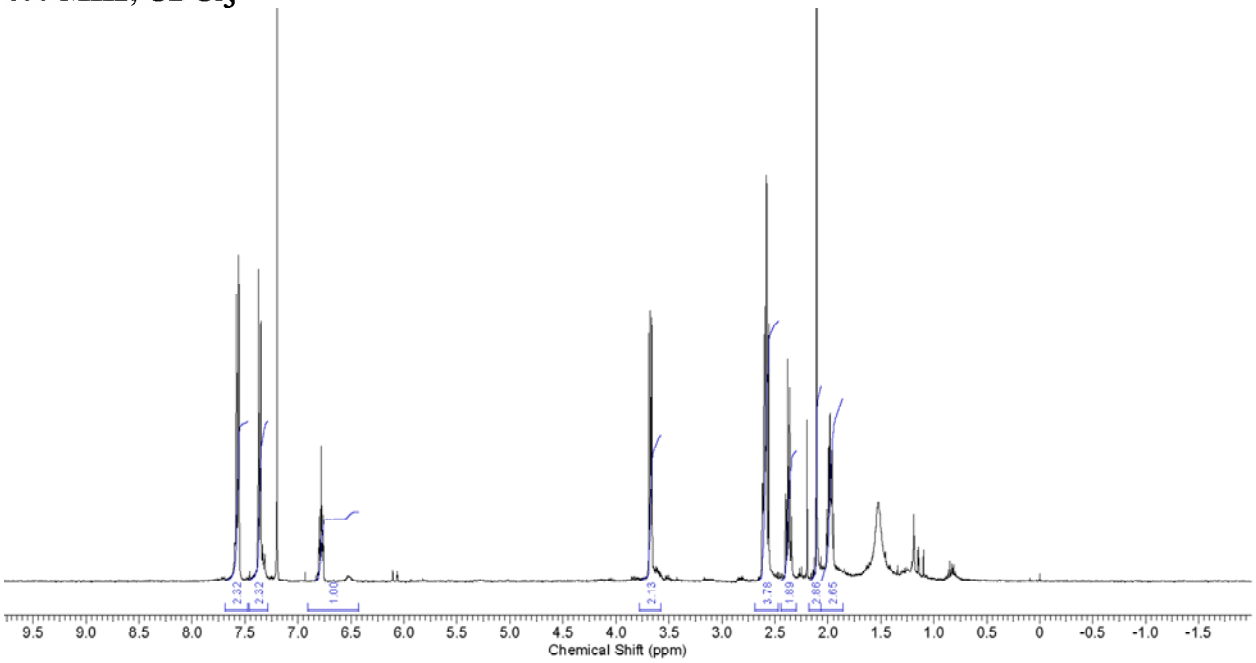
100 MHz, $CDCl_3$



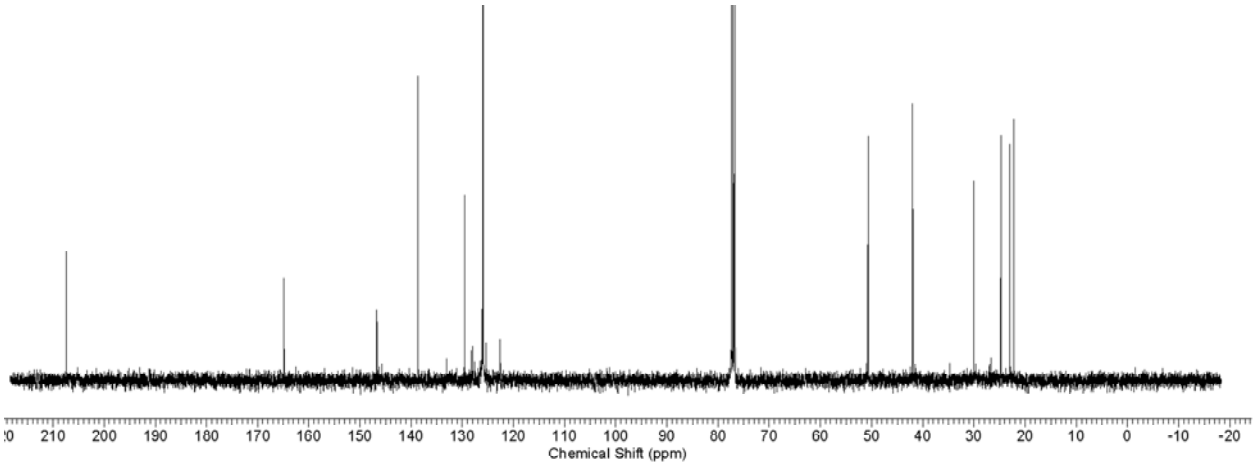


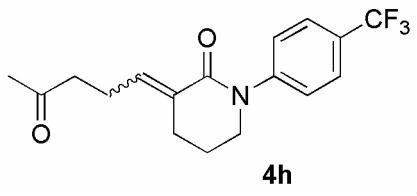
4h **E isomer**

400 MHz, $CDCl_3$



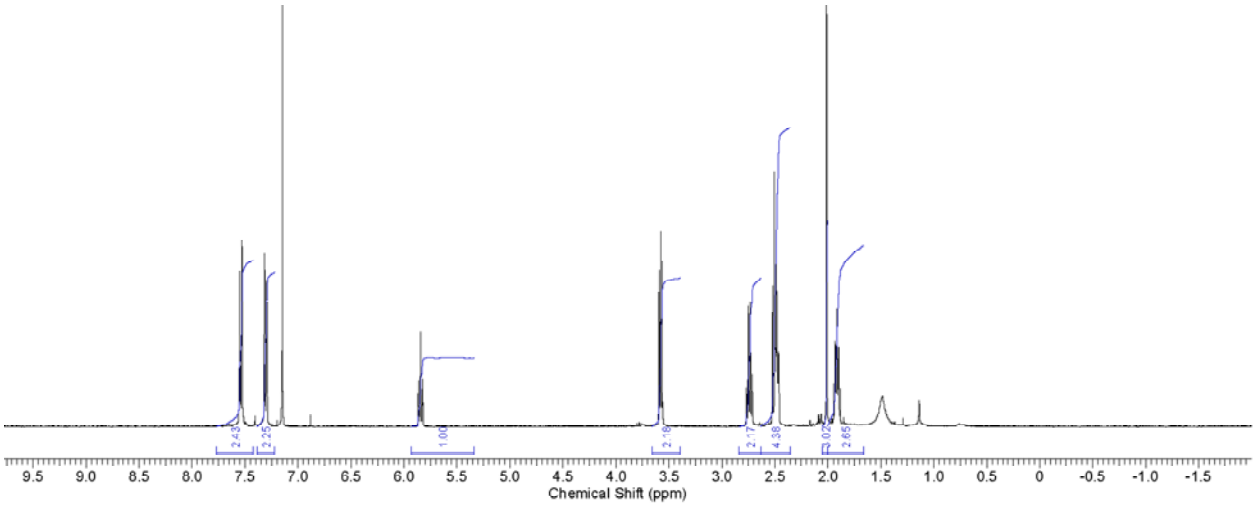
100 MHz, $CDCl_3$



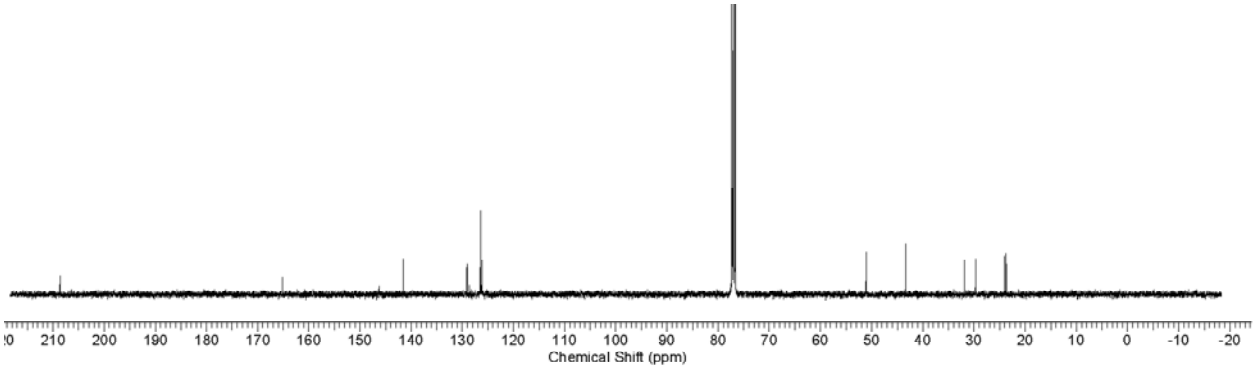


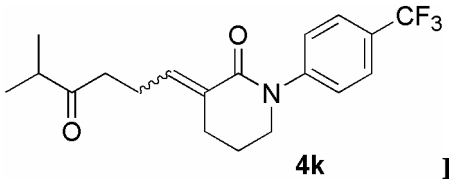
4h **Z isomer**

400 MHz, $CDCl_3$



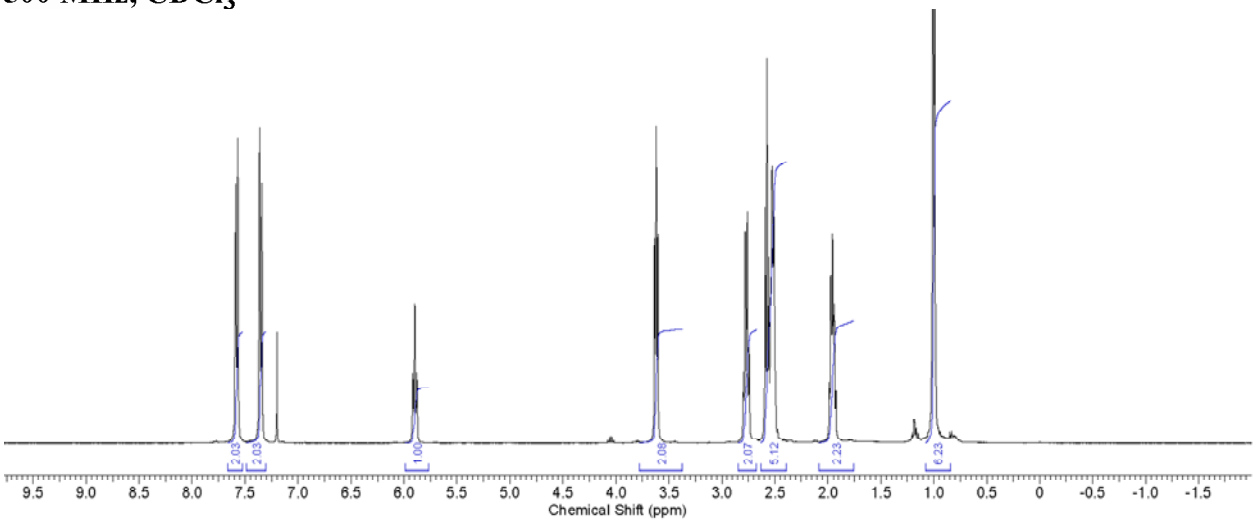
100 MHz, $CDCl_3$



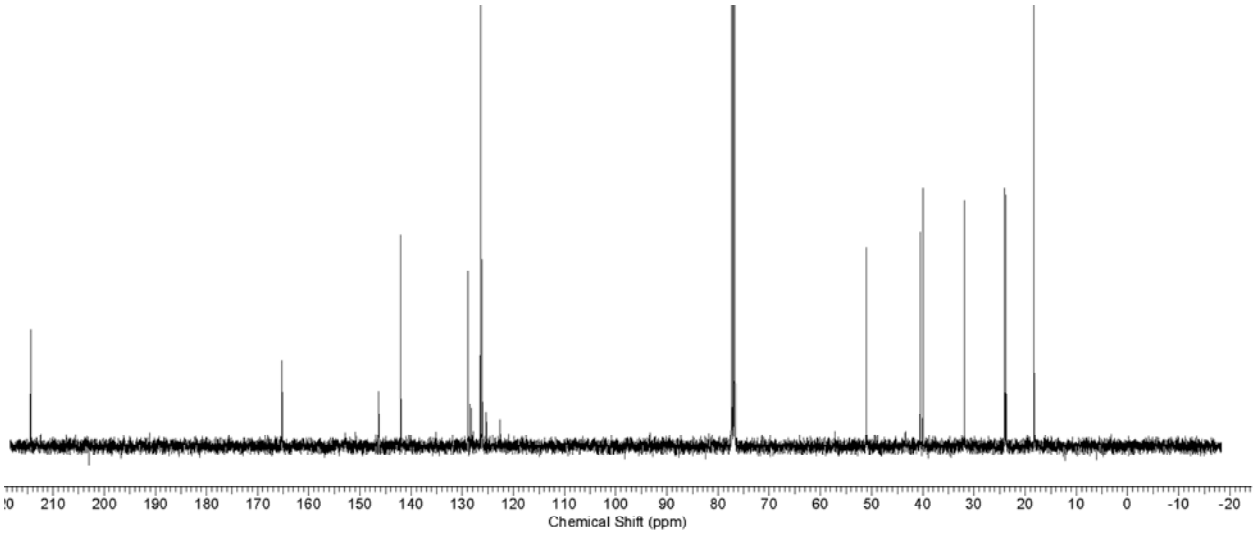


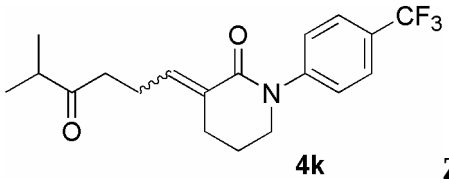
4k **E isomer**

500 MHz, $CDCl_3$



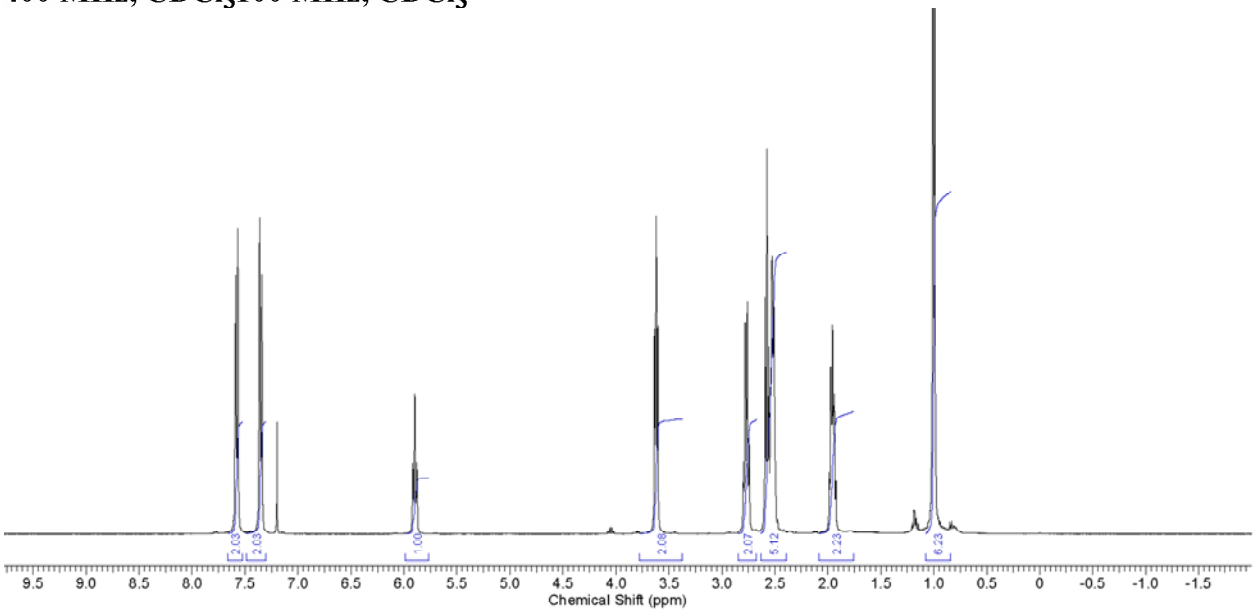
125 MHz, $CDCl_3$

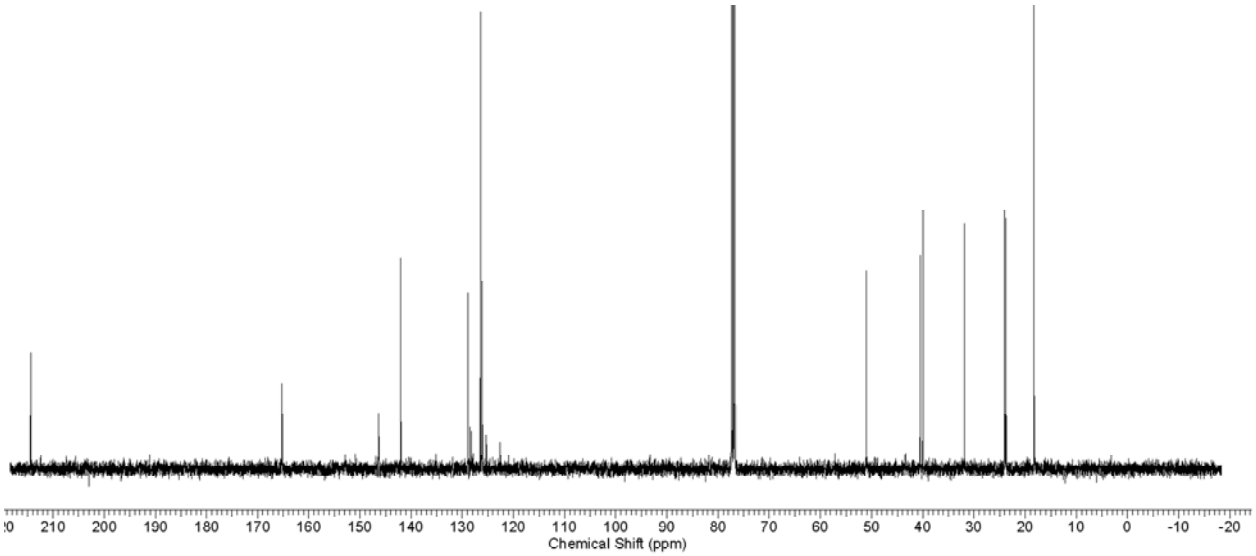


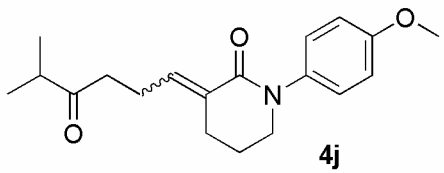


4k **Z isomer**

400 MHz, $CDCl_3$100 MHz, $CDCl_3$

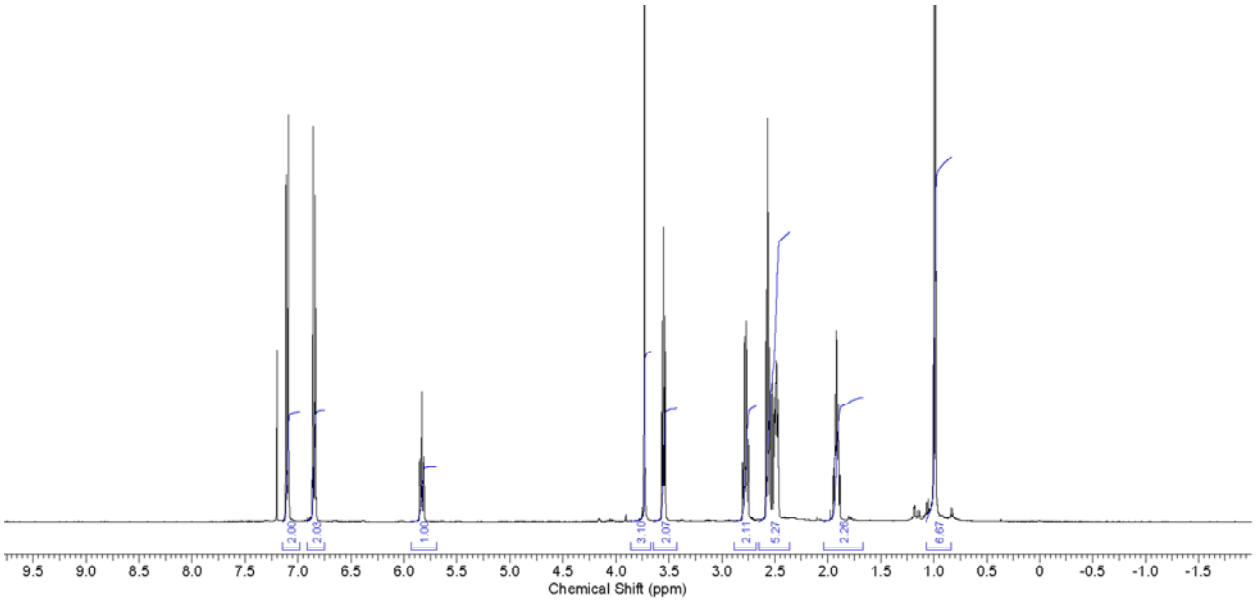




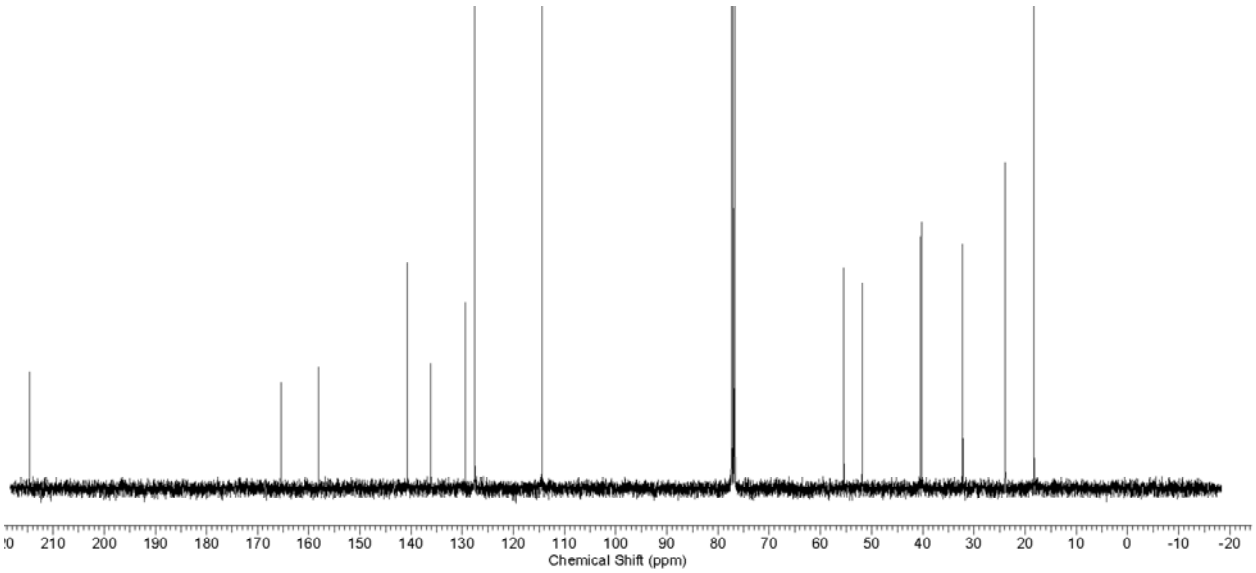


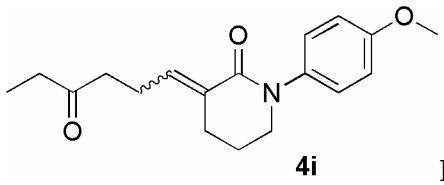
4j **Z isomer**

400 MHz, $CDCl_3$



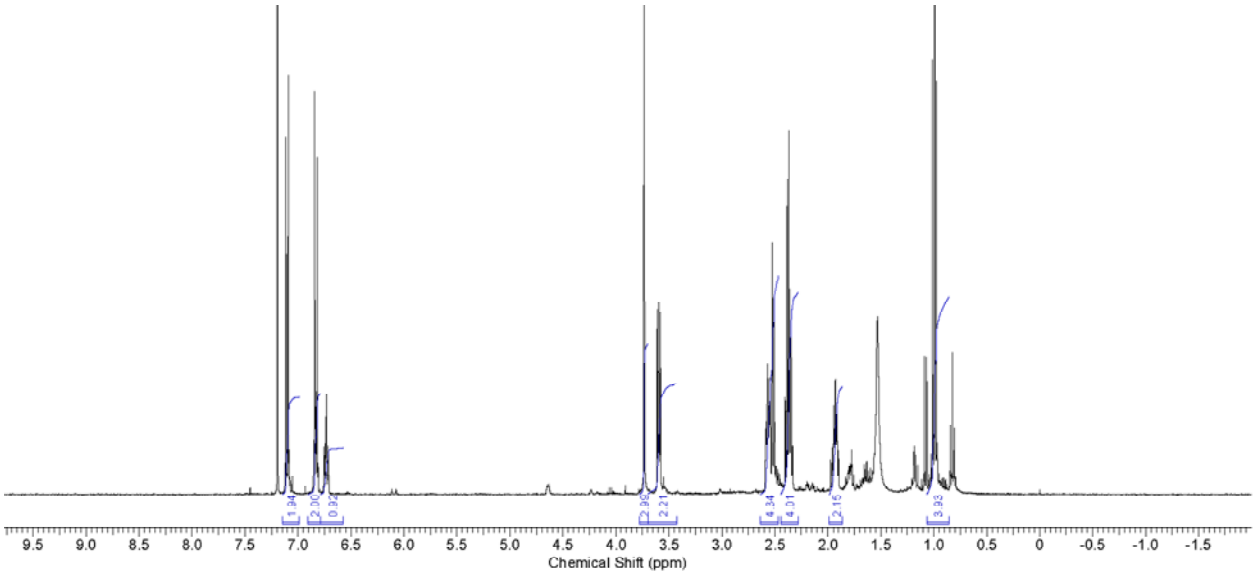
100 MHz, $CDCl_3$



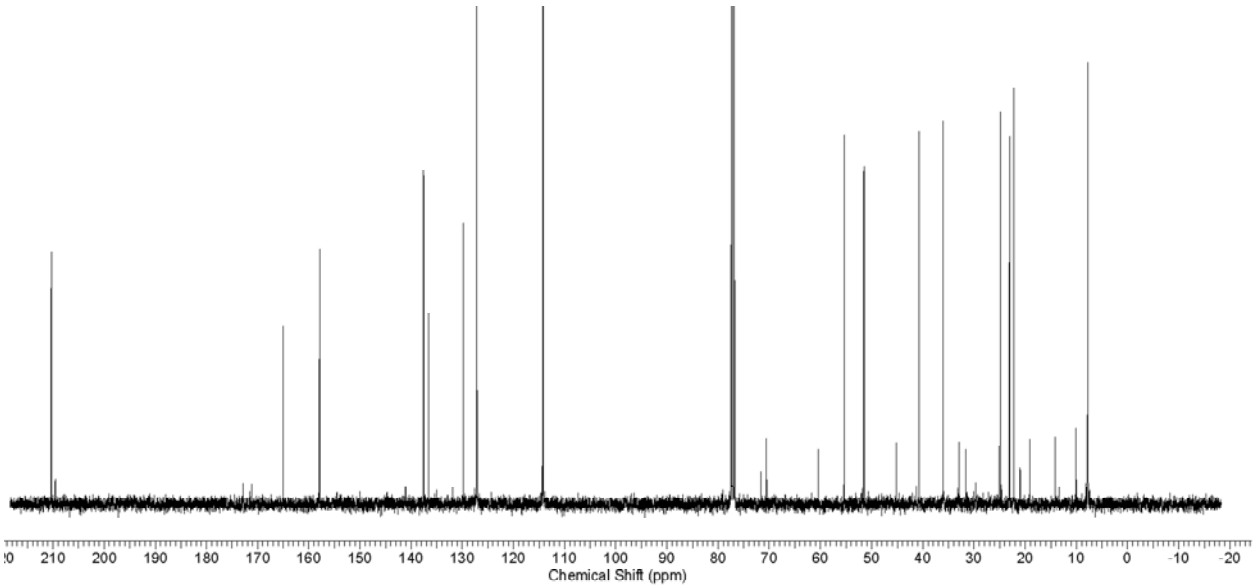


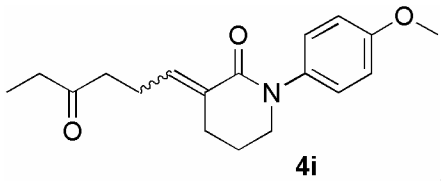
4i **E isomer**

400 MHz, $CDCl_3$



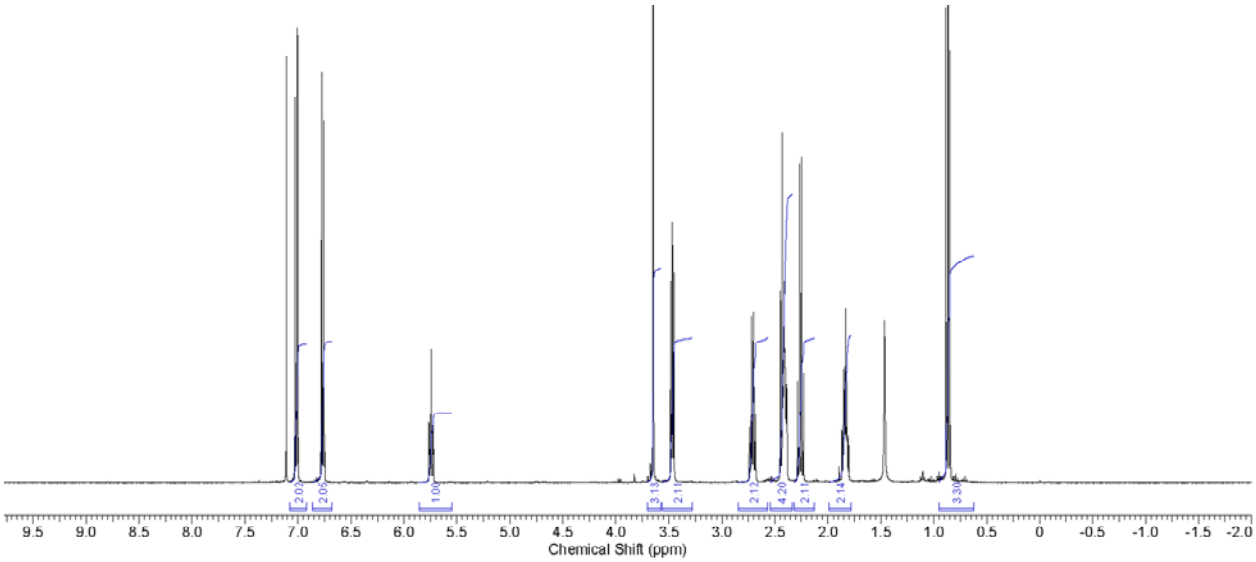
100 MHz, $CDCl_3$



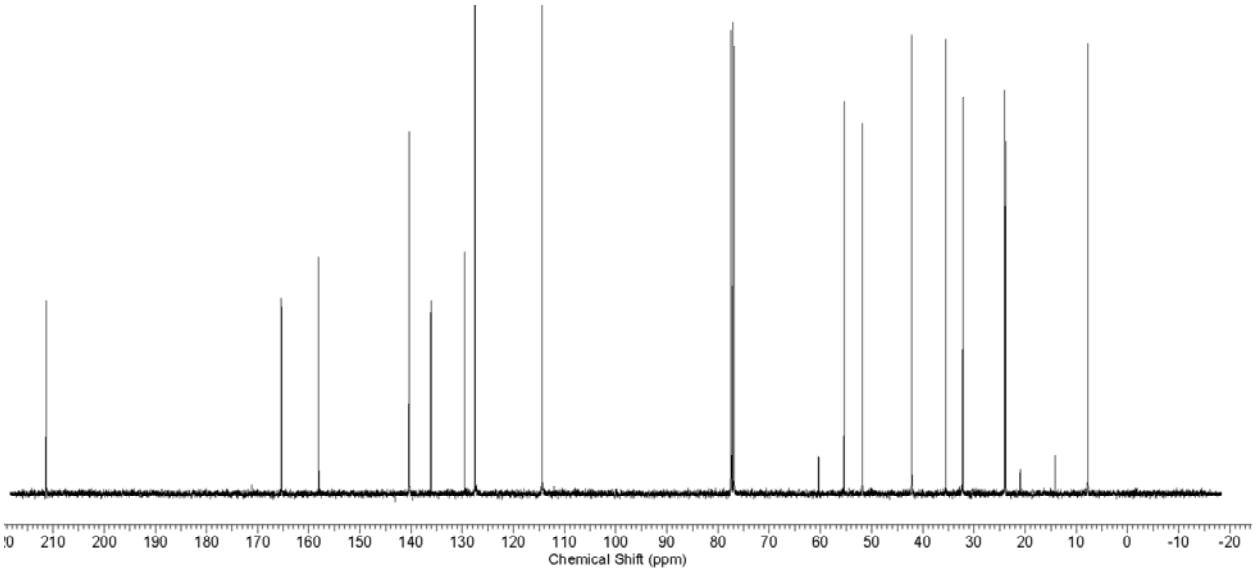


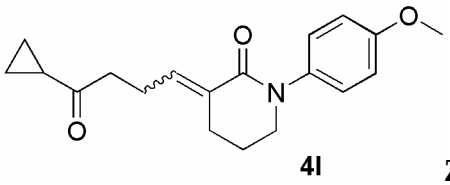
4i **Z isomer**

400 MHz, $CDCl_3$



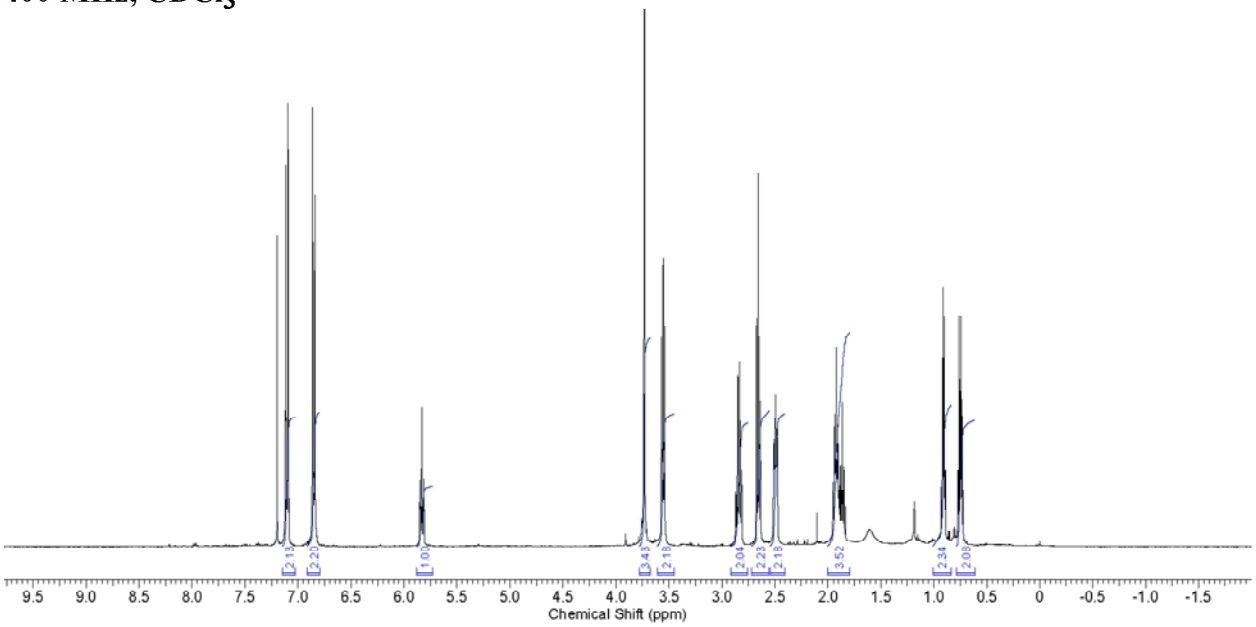
100 MHz, $CDCl_3$



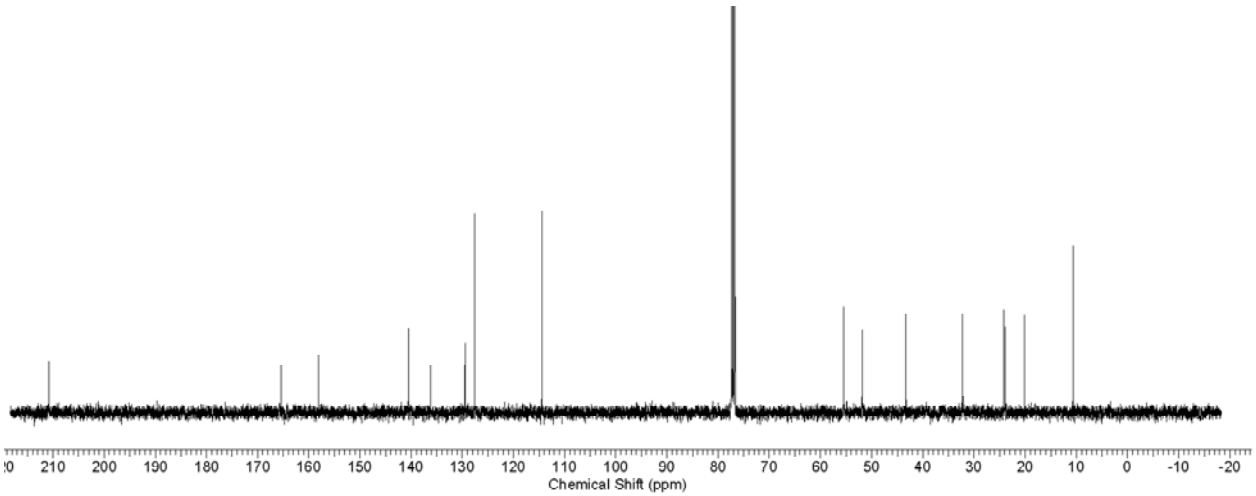


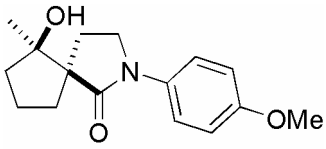
4l **Z isomer**

400 MHz, $CDCl_3$



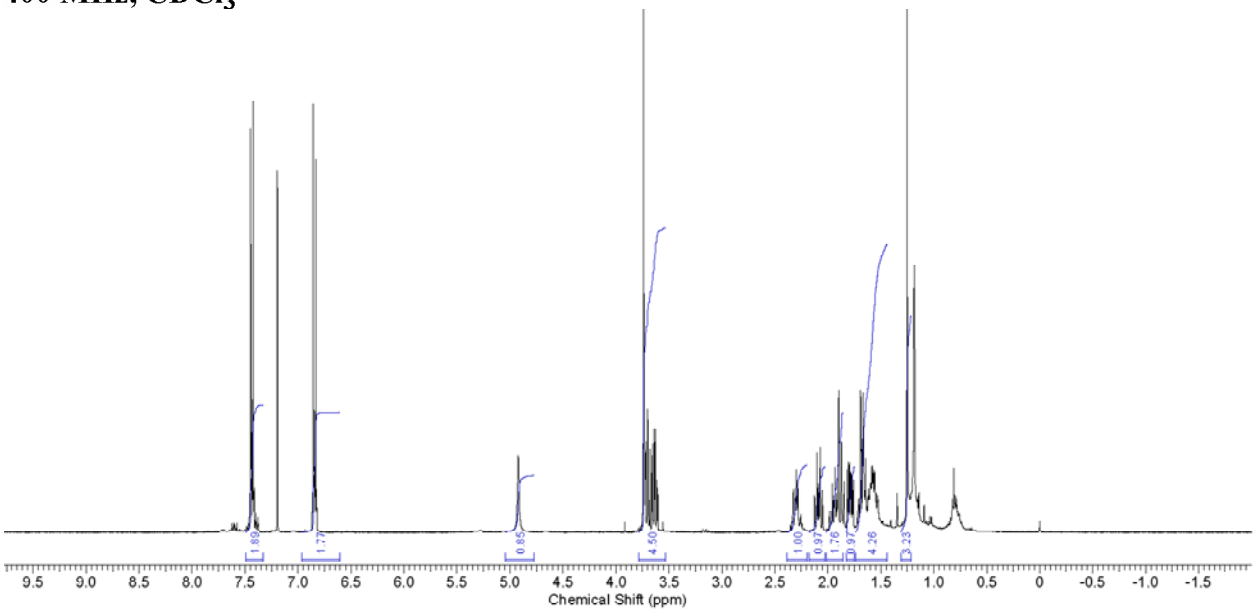
100 MHz, $CDCl_3$



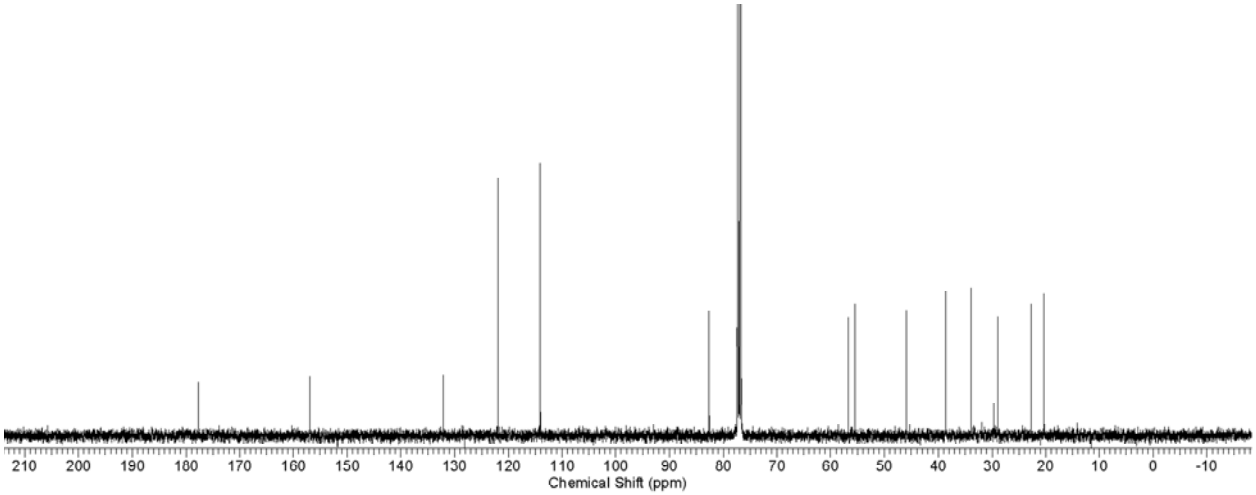


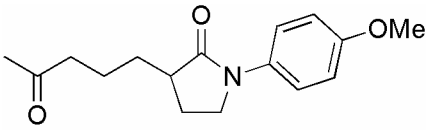
7a

400 MHz, $CDCl_3$



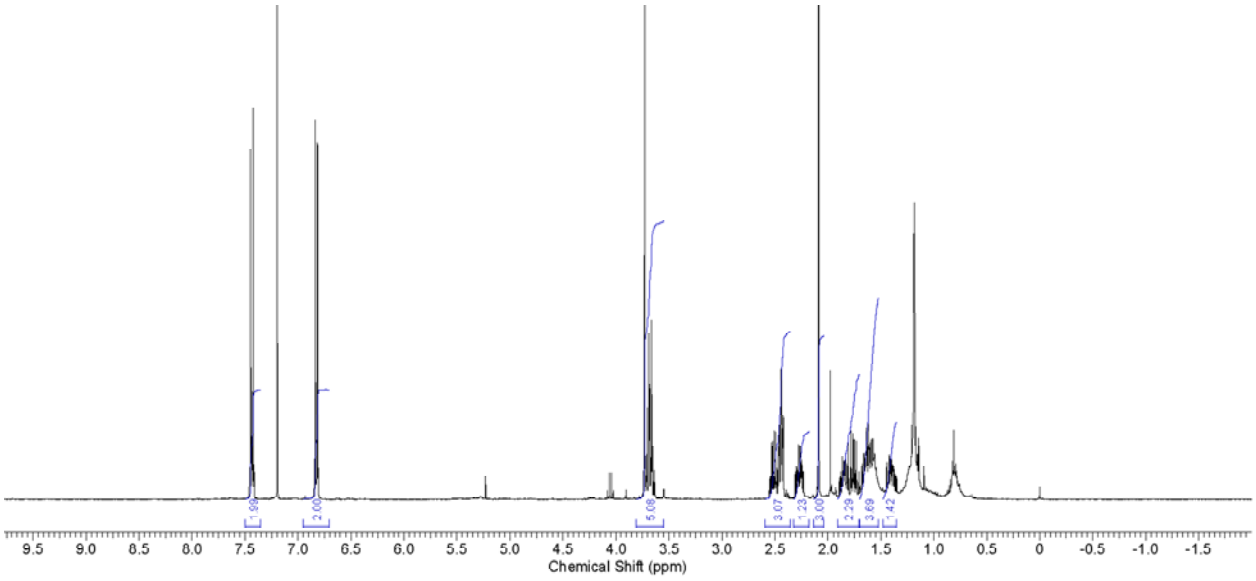
100 MHz, $CDCl_3$



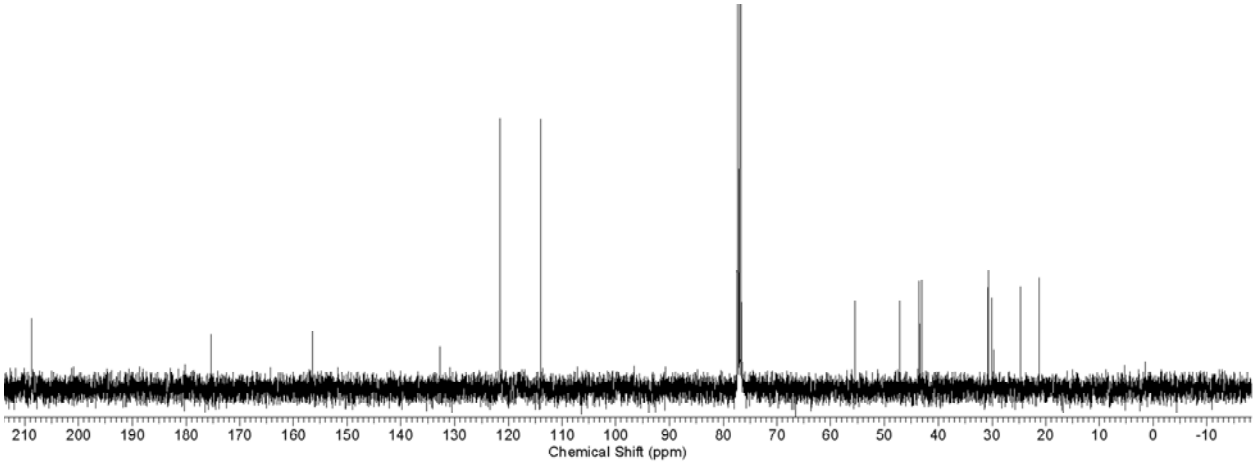


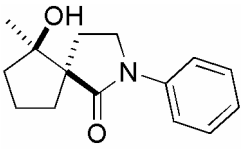
8a

400 MHz, $CDCl_3$



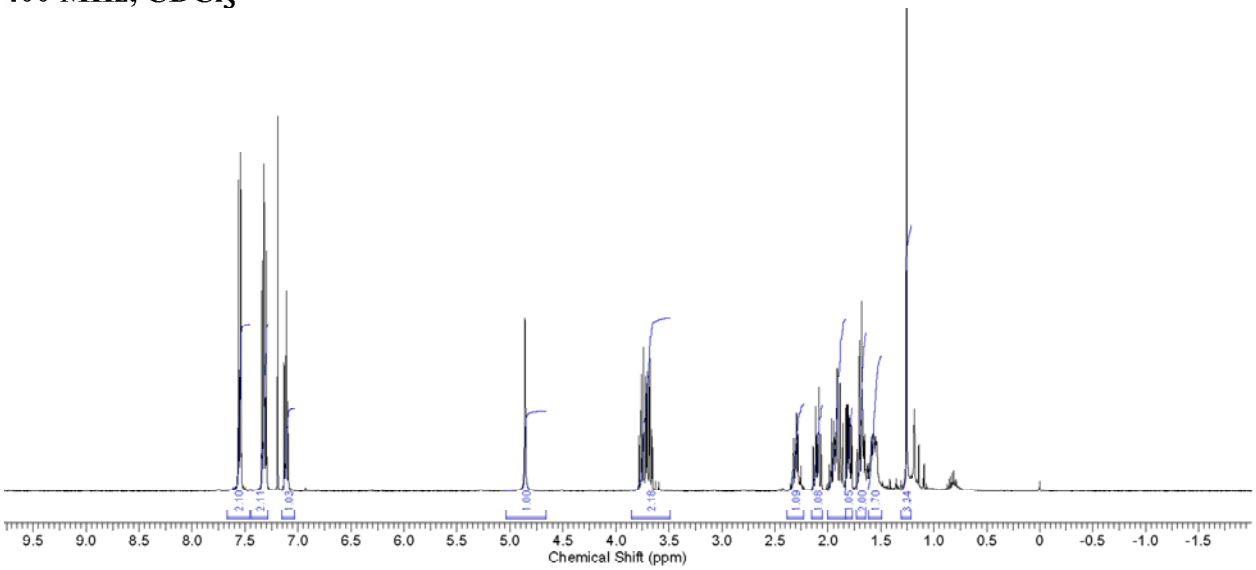
100 MHz, $CDCl_3$



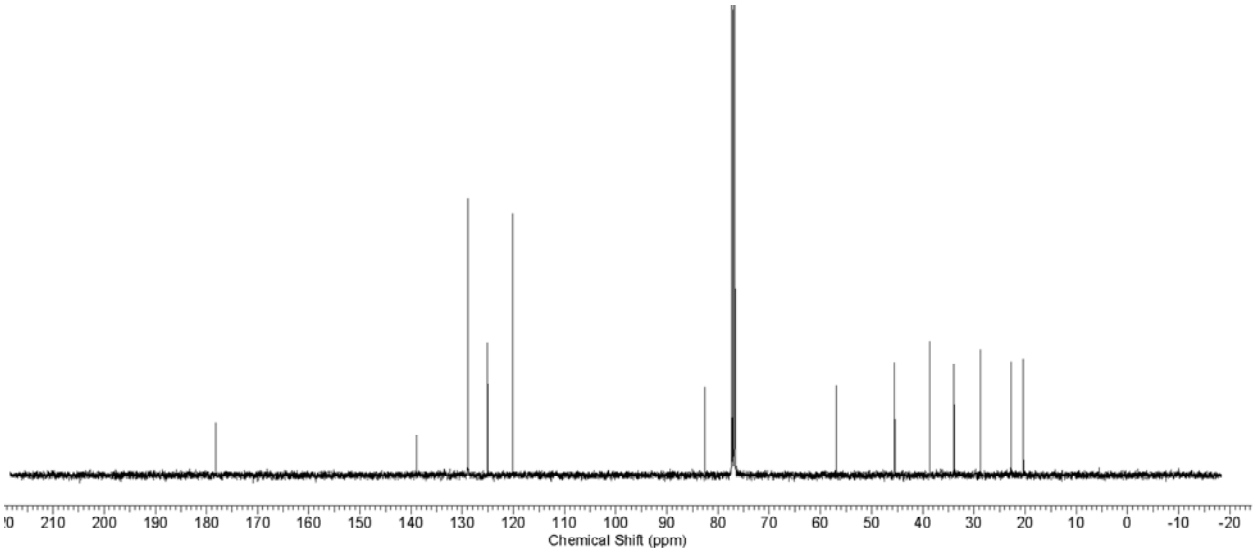


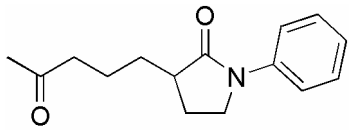
7b

400 MHz, $CDCl_3$



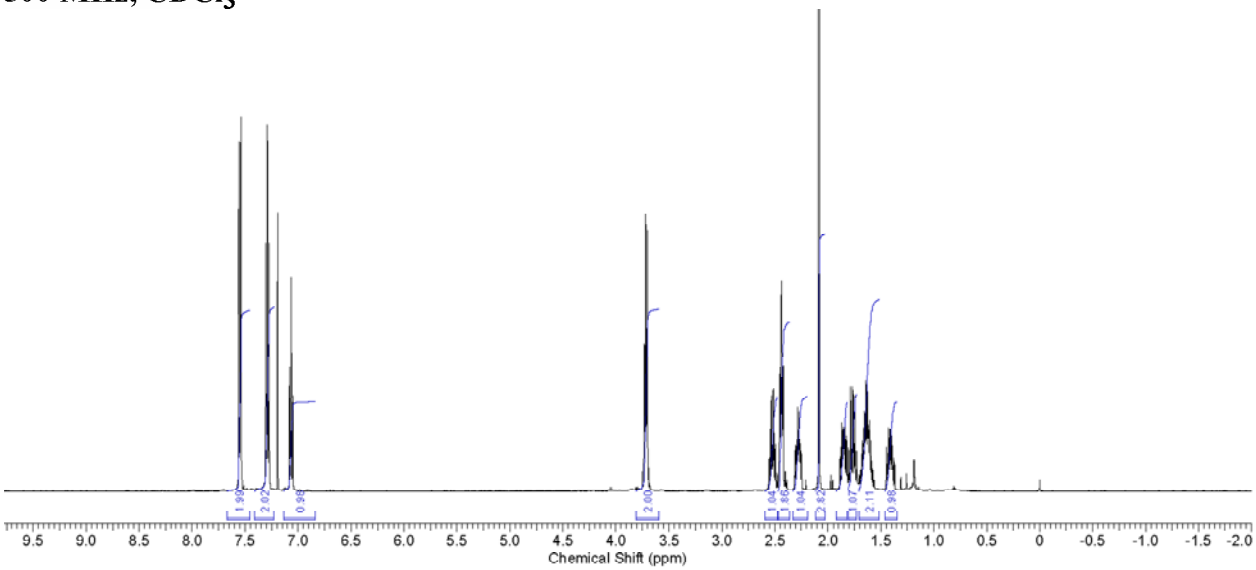
100 MHz, $CDCl_3$



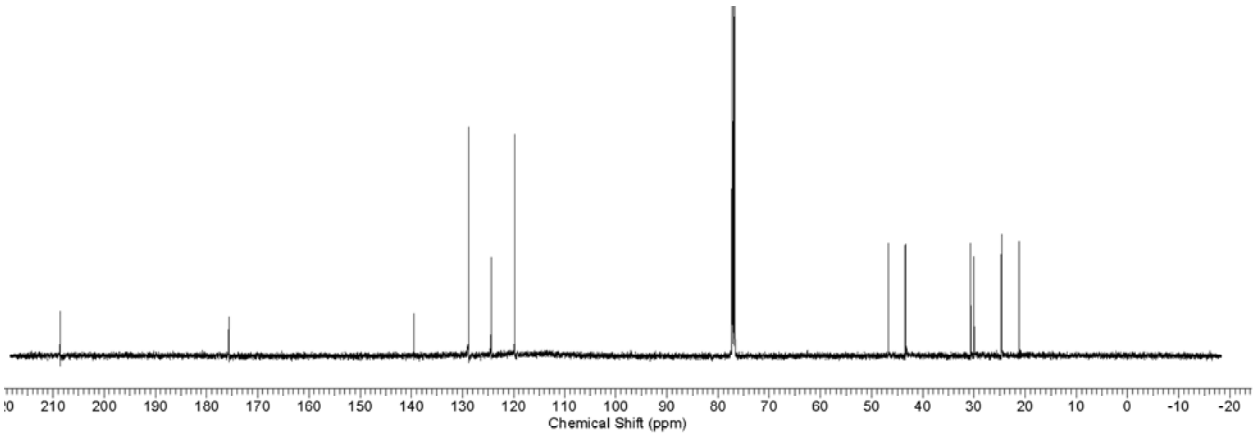


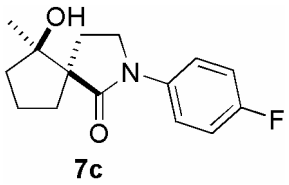
8b

500 MHz, $CDCl_3$



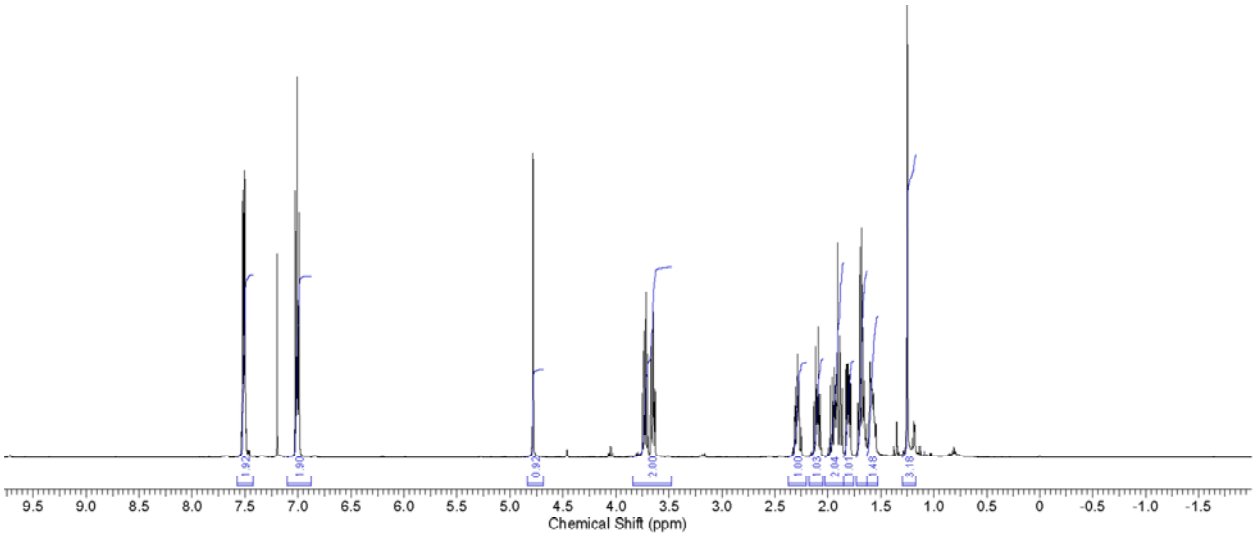
125 MHz, $CDCl_3$



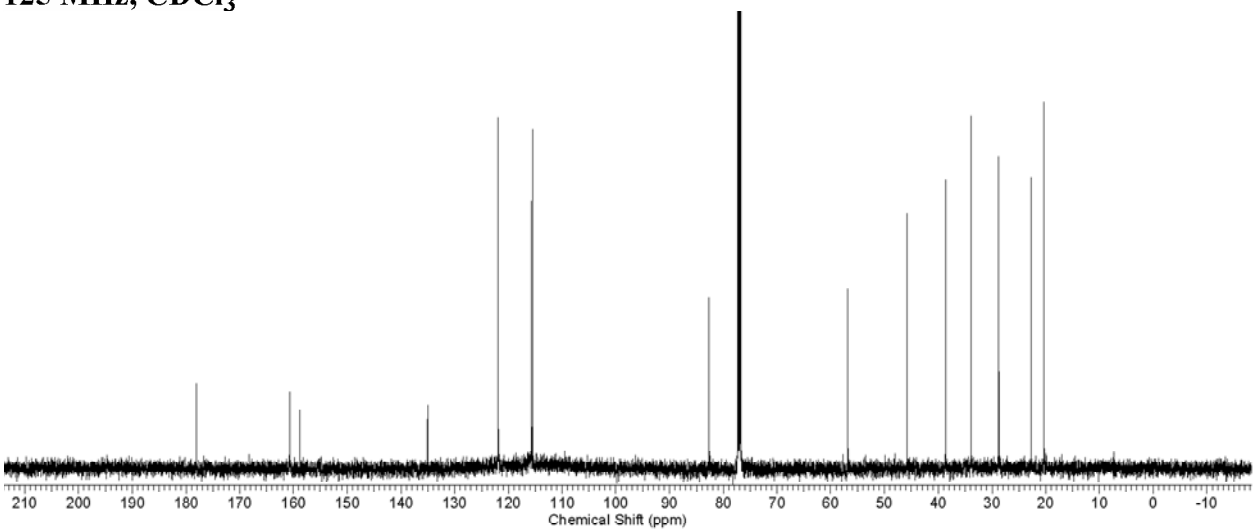


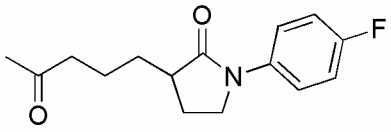
7c

500 MHz, $CDCl_3$



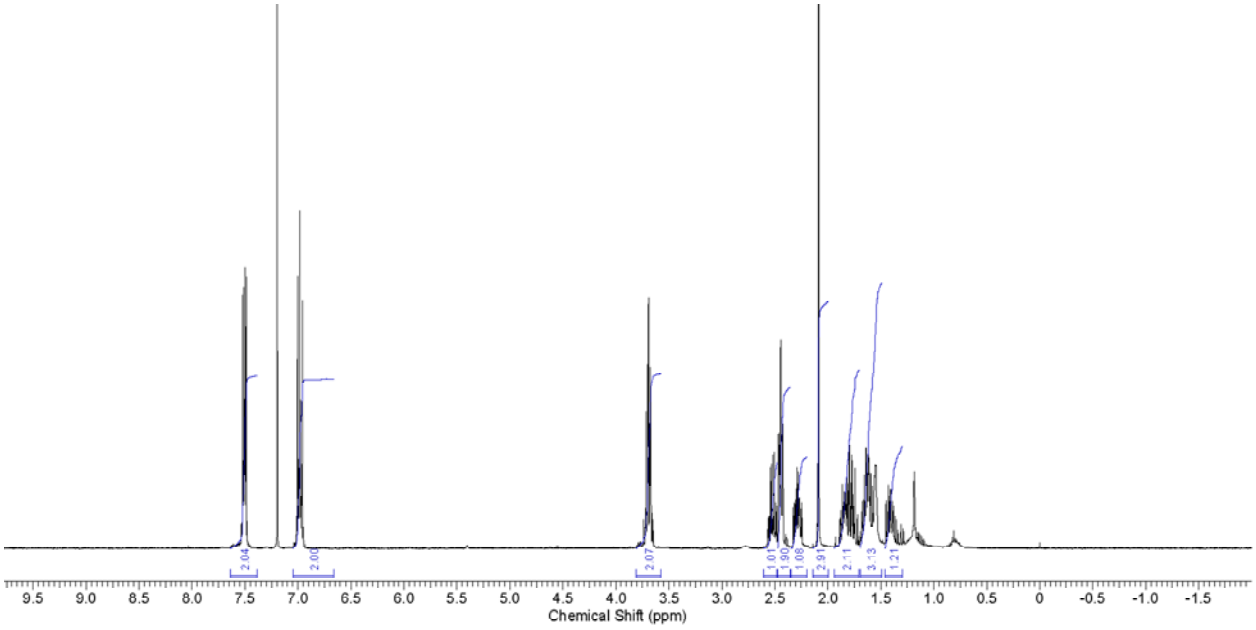
125 MHz, $CDCl_3$



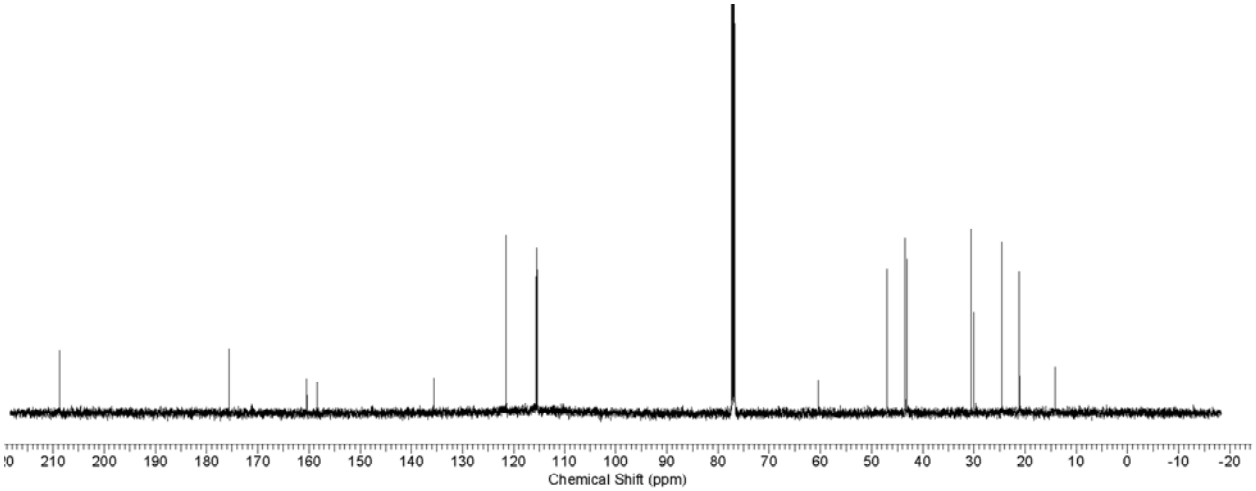


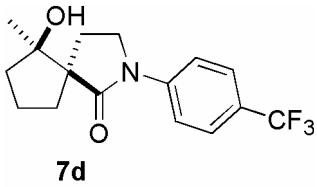
8c

400 MHz, $CDCl_3$



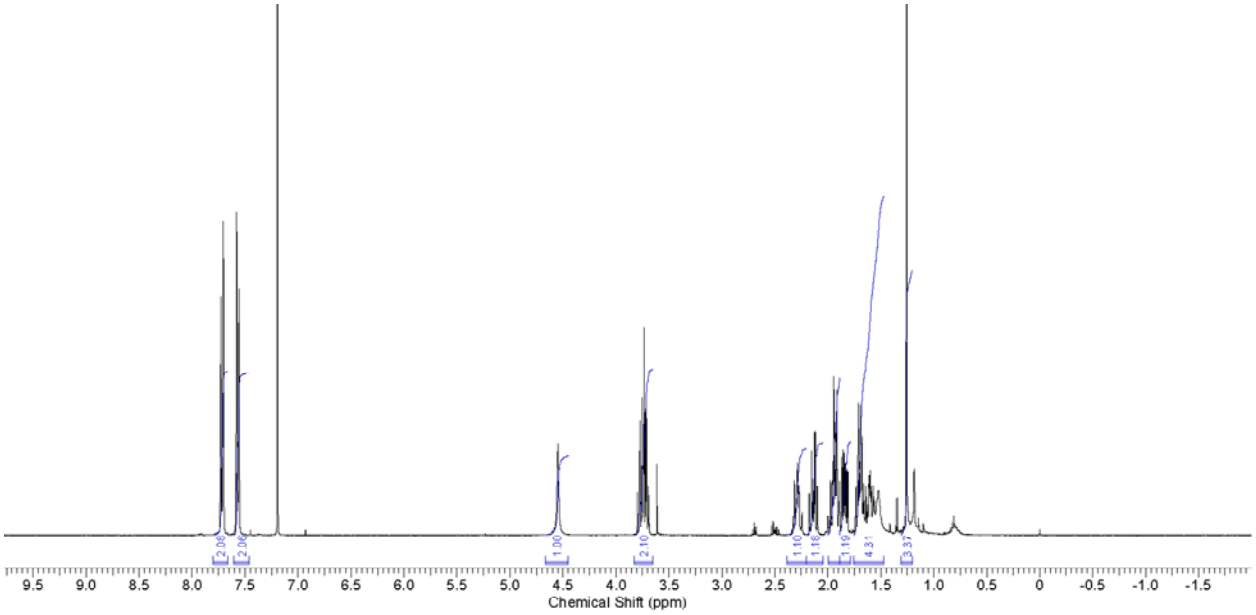
125 MHz, $CDCl_3$



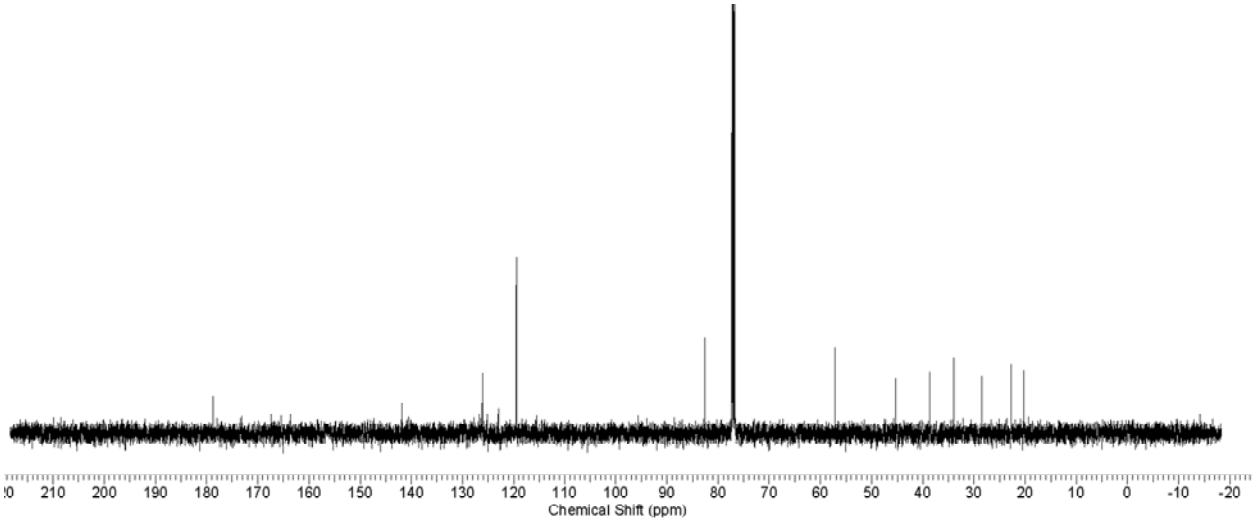


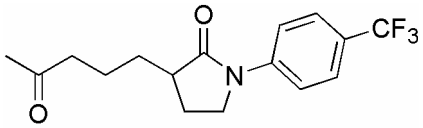
7d

400 MHz, $CDCl_3$



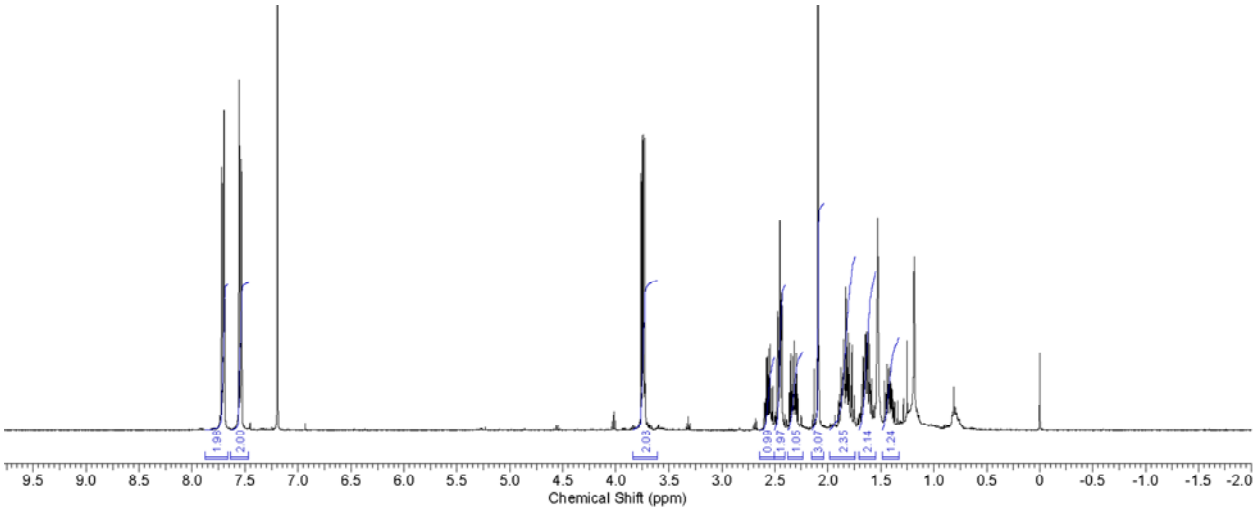
125 MHz, $CDCl_3$



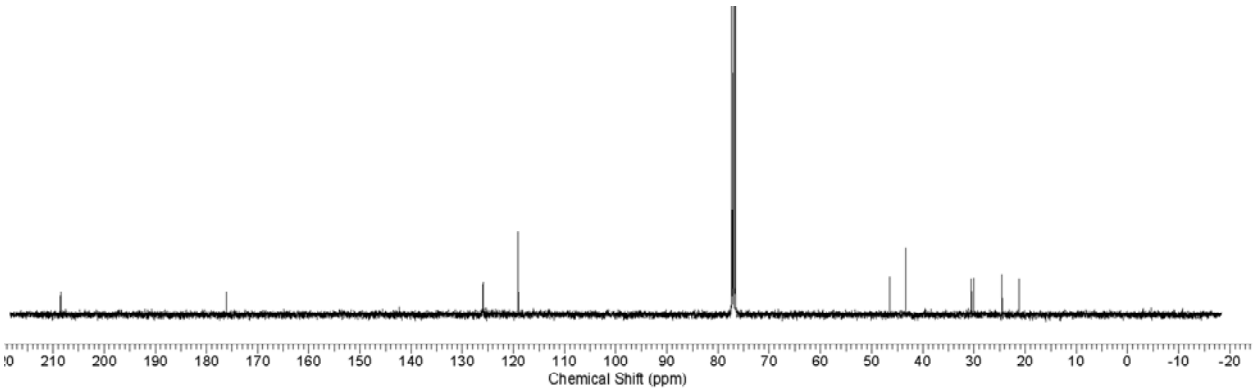


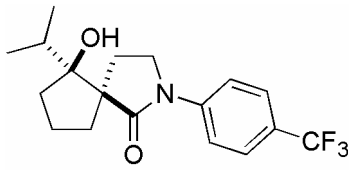
8d

400 MHz, $CDCl_3$



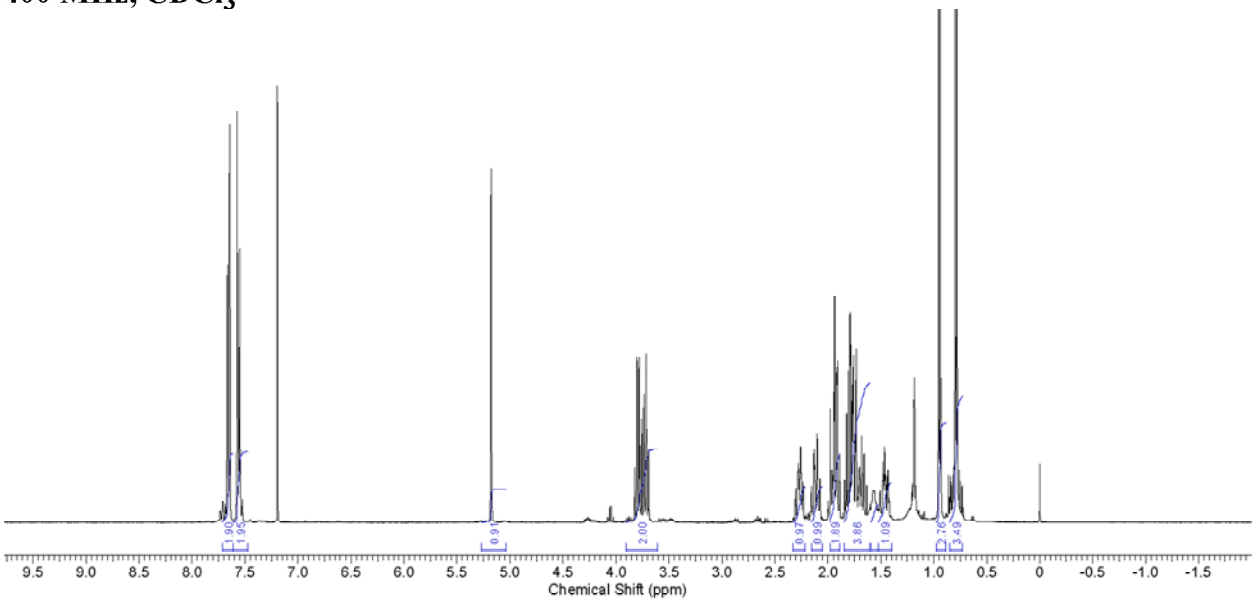
100 MHz, $CDCl_3$



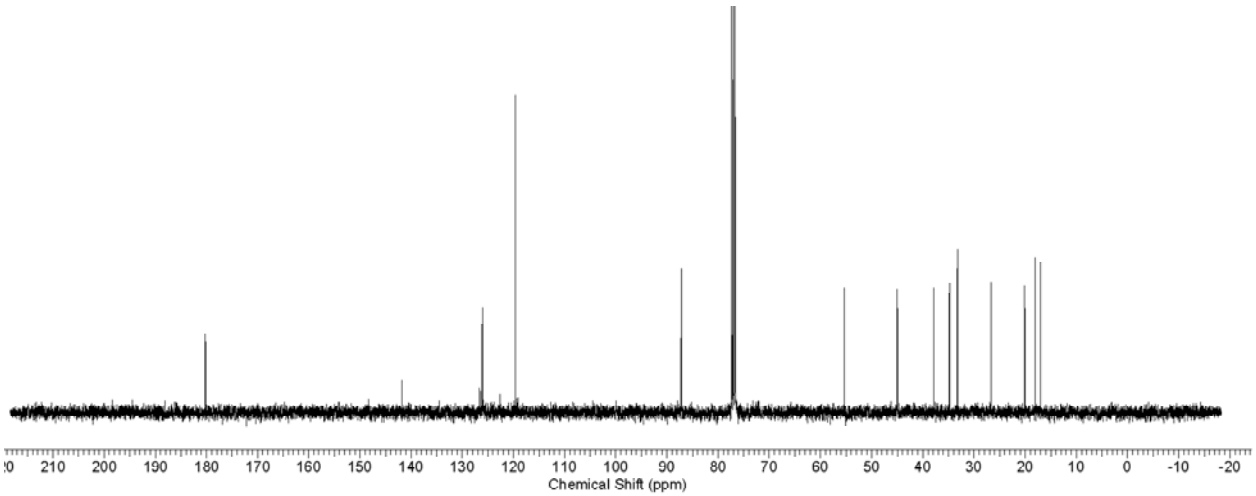


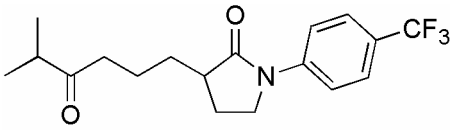
7e

400 MHz, $CDCl_3$



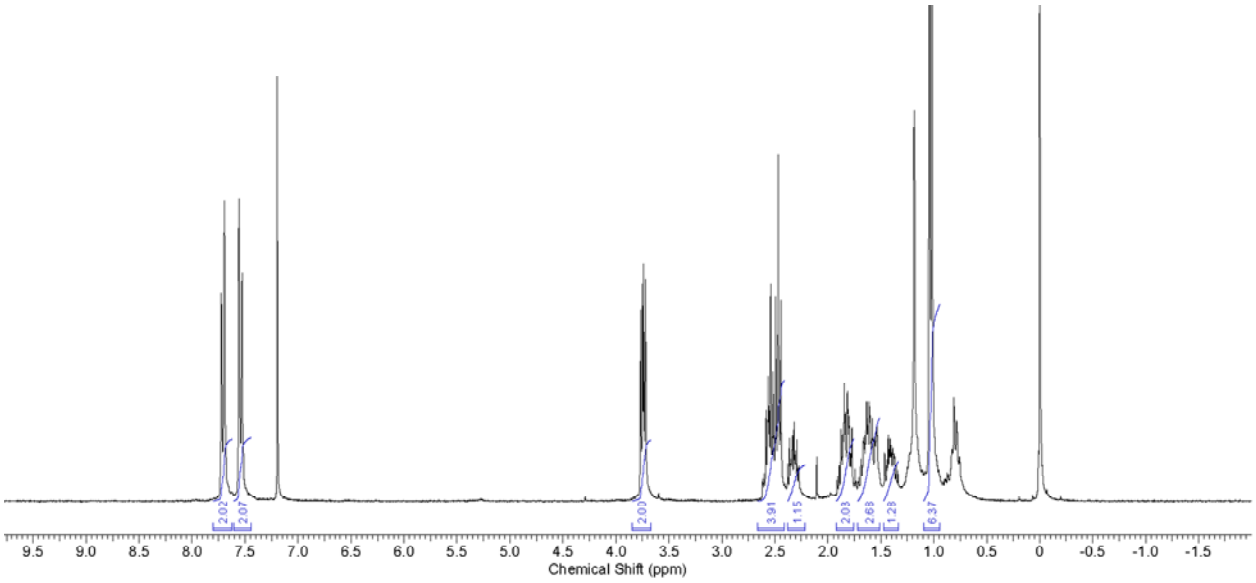
100 MHz, $CDCl_3$



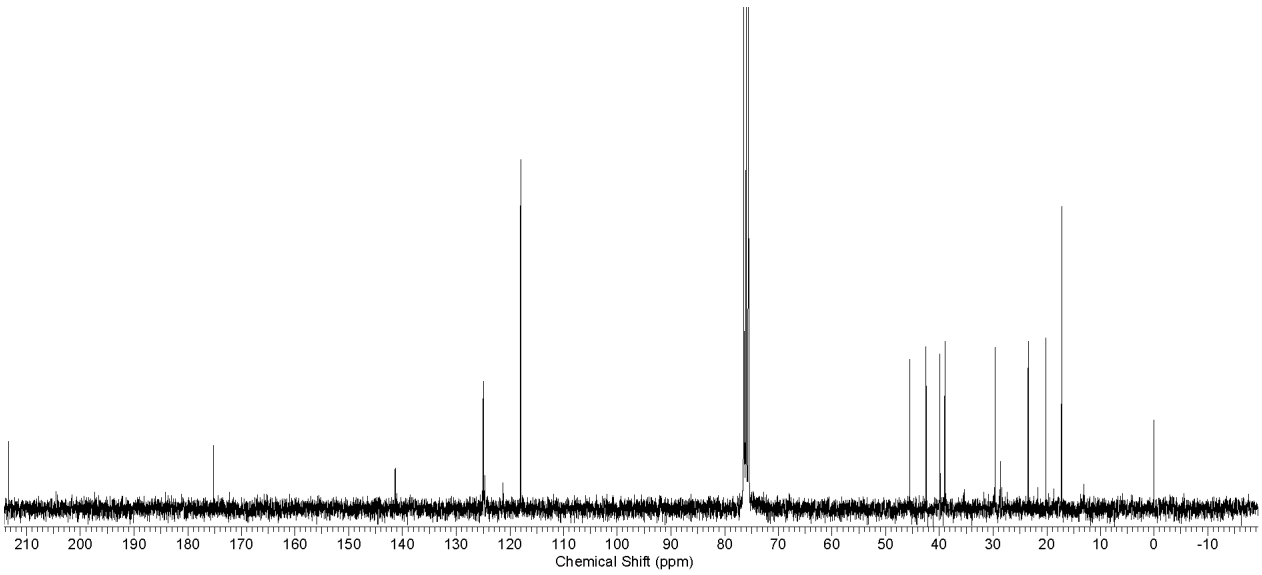


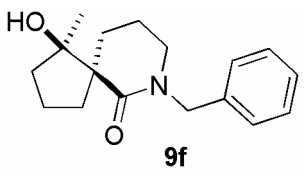
8e

300 MHz, $CDCl_3$



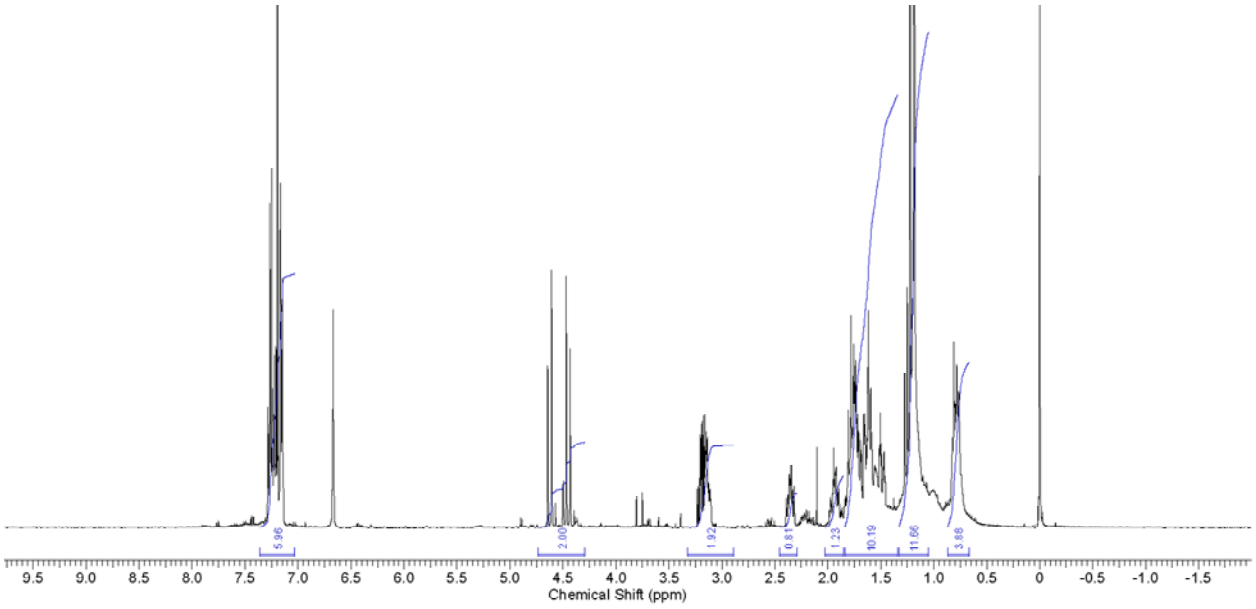
100 MHz, $CDCl_3$



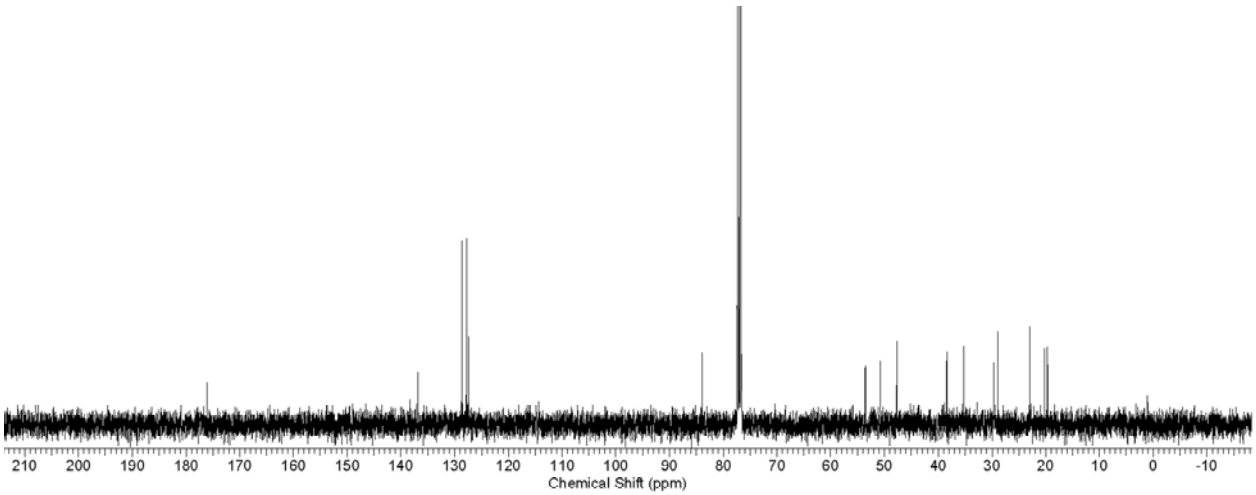


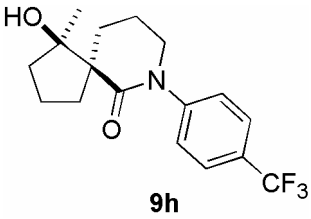
9f

400 MHz, $CDCl_3$



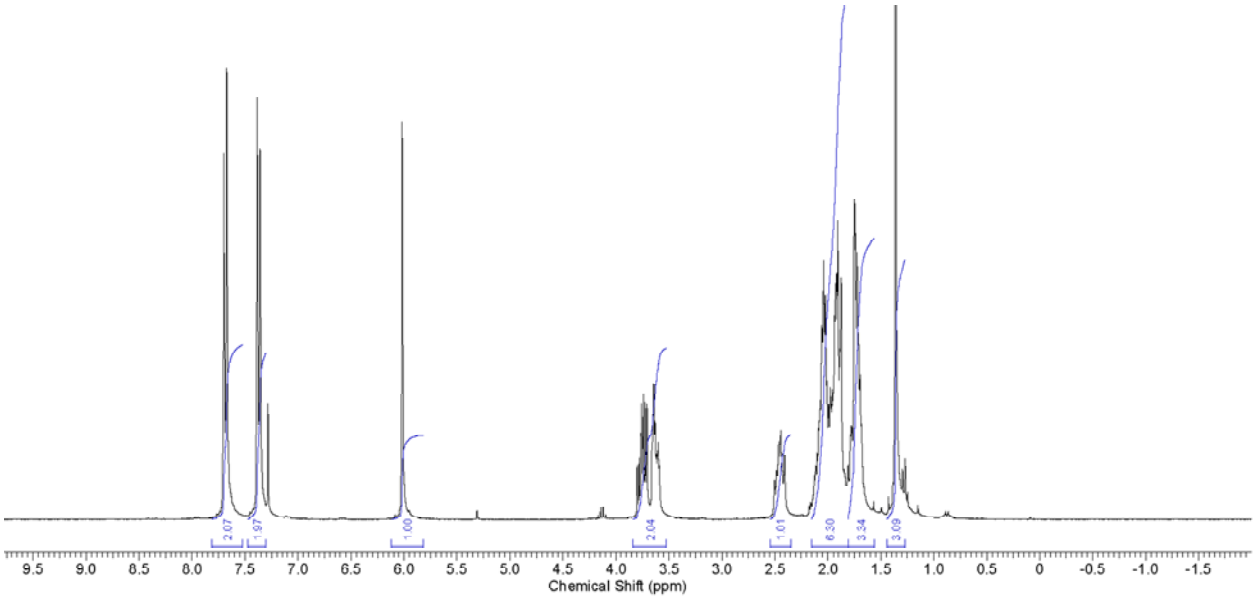
100 MHz, $CDCl_3$



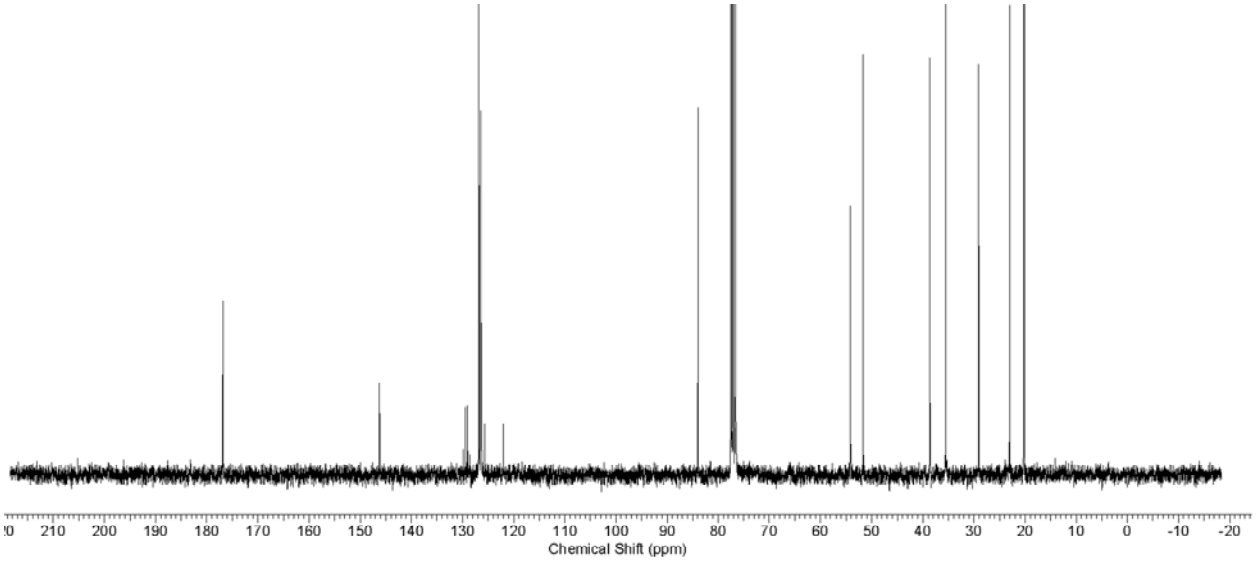


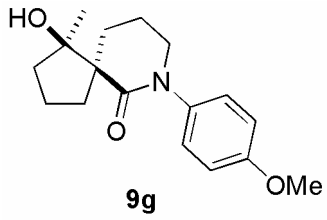
9h

300 MHz, $CDCl_3$



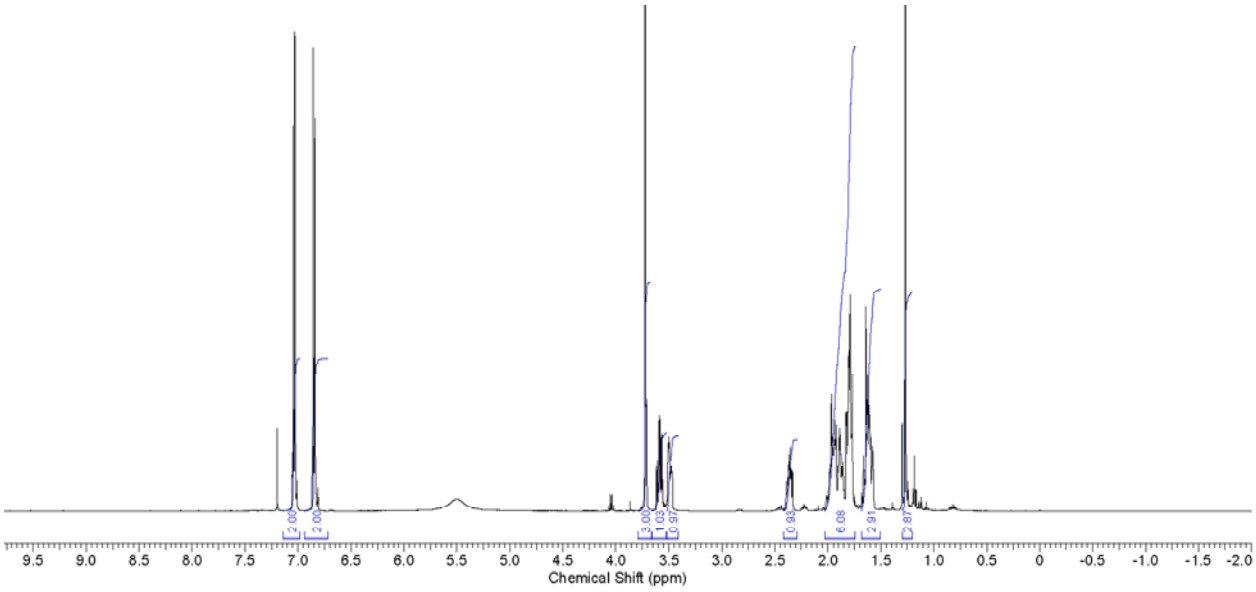
75 MHz, $CDCl_3$



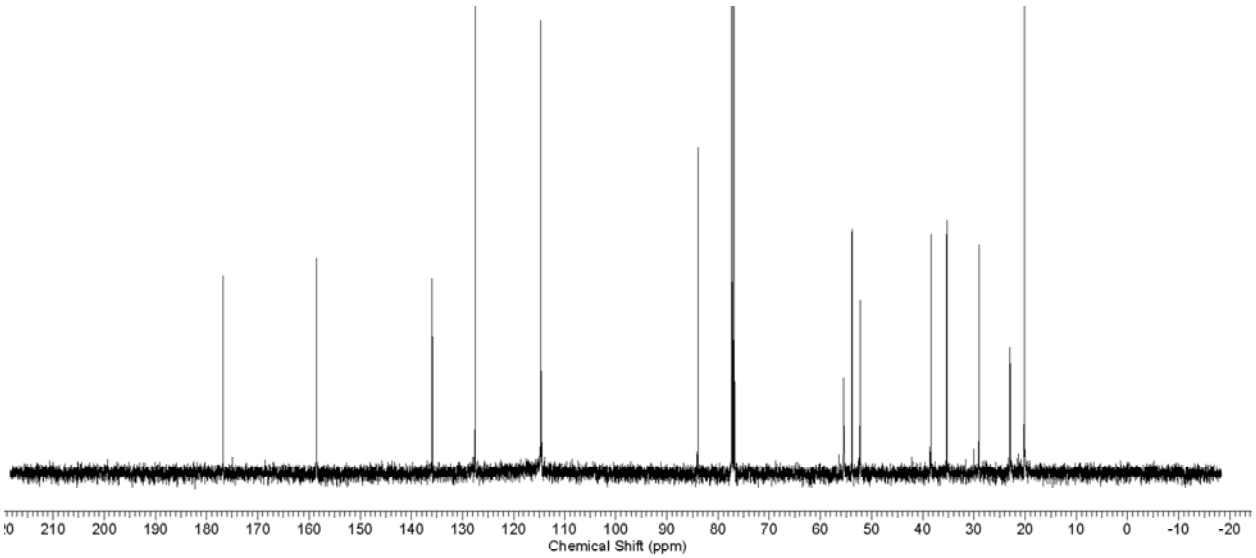


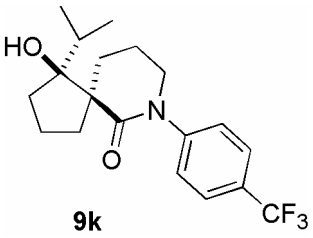
9g

500 MHz, $CDCl_3$



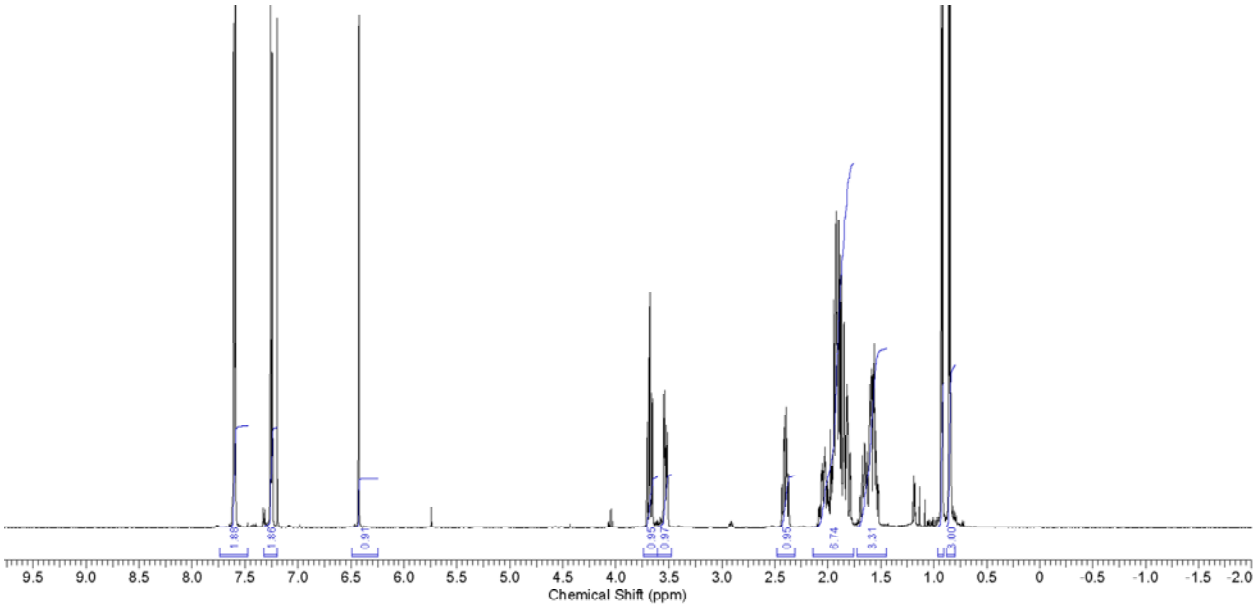
125 MHz, $CDCl_3$



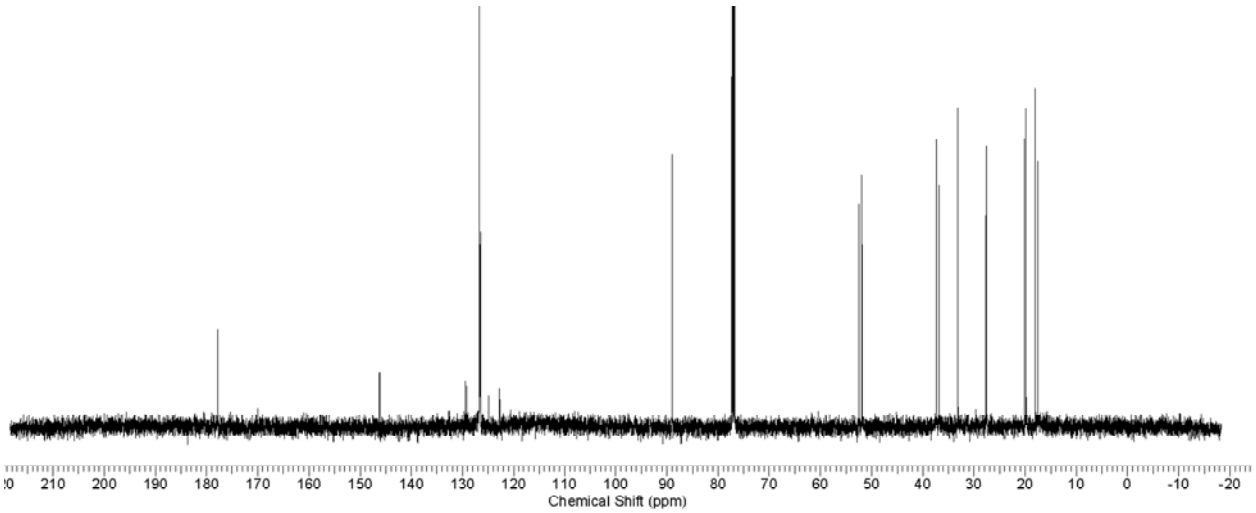


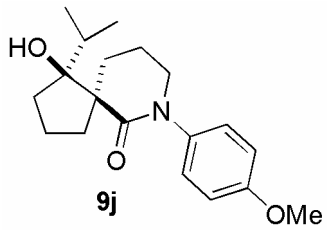
9k

500 MHz, $CDCl_3$



125 MHz, $CDCl_3$

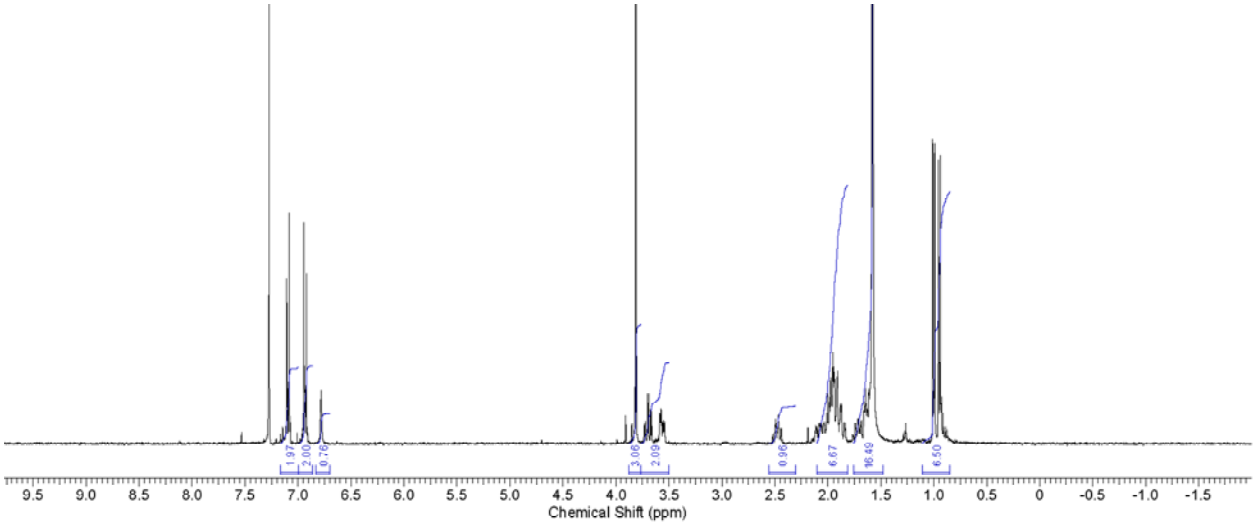




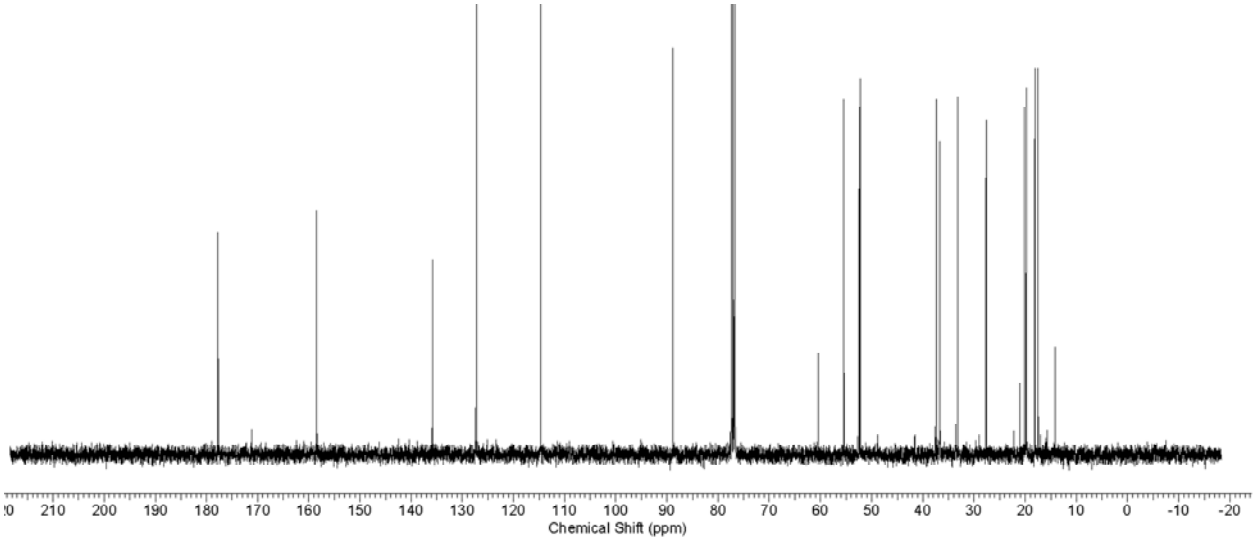
9j

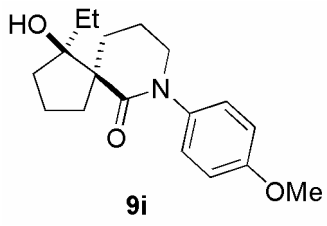
]

400 MHz, $CDCl_3$



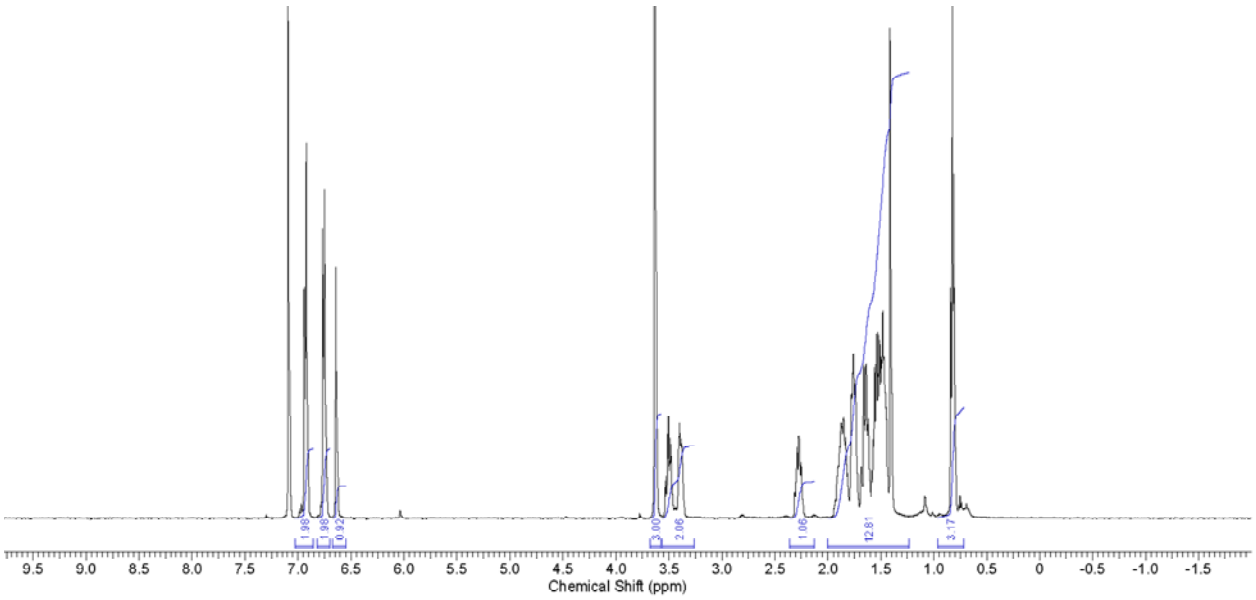
100 MHz, $CDCl_3$



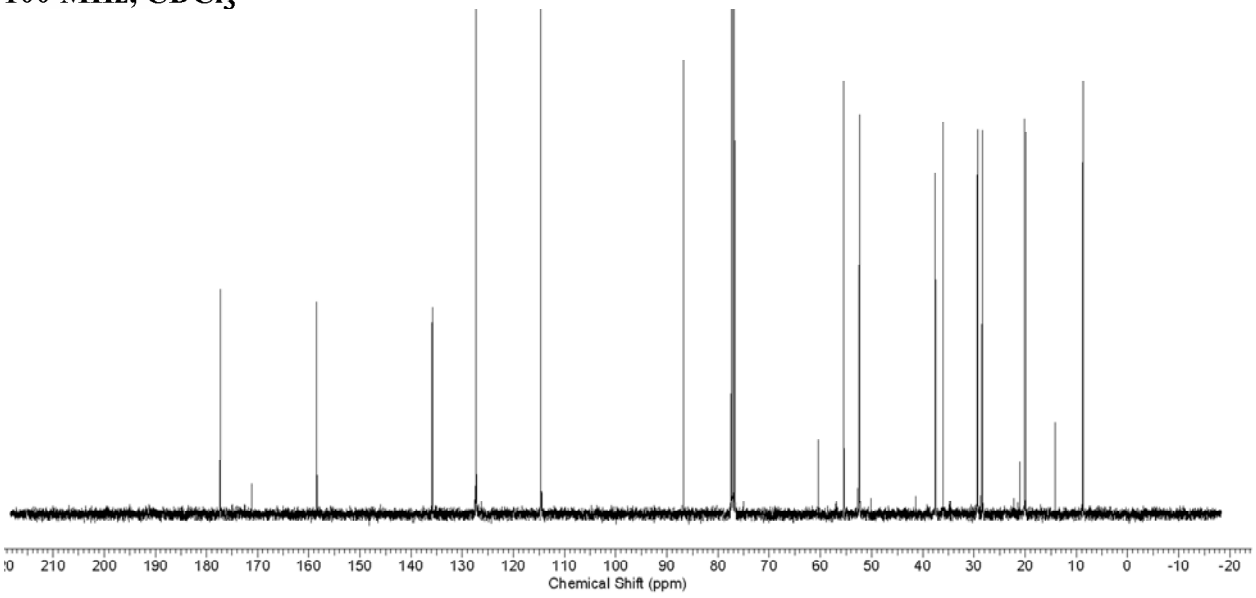


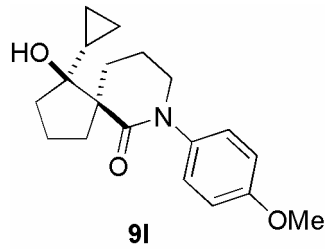
9i

500 MHz, $CDCl_3$



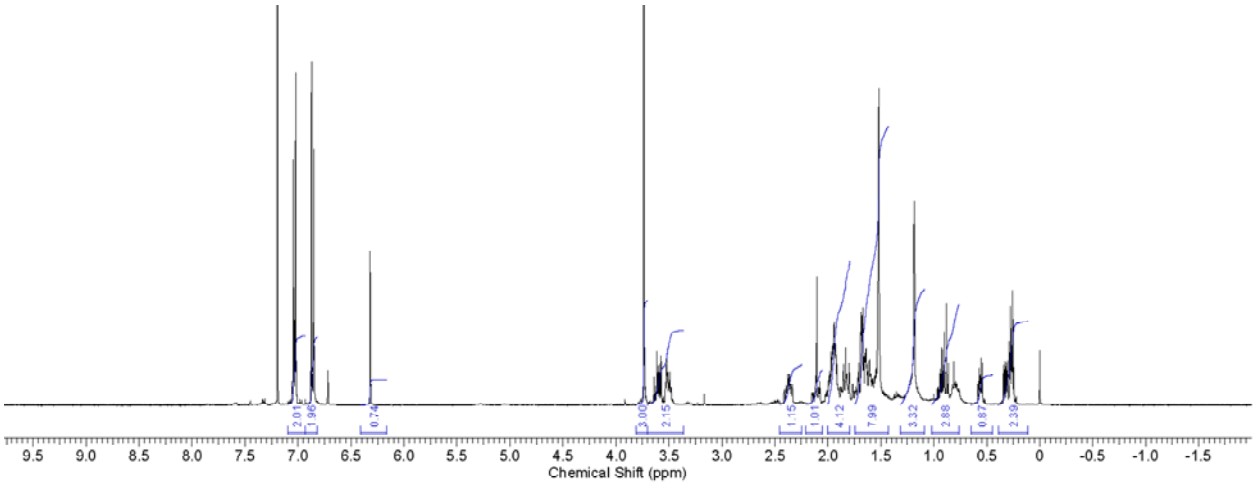
100 MHz, $CDCl_3$



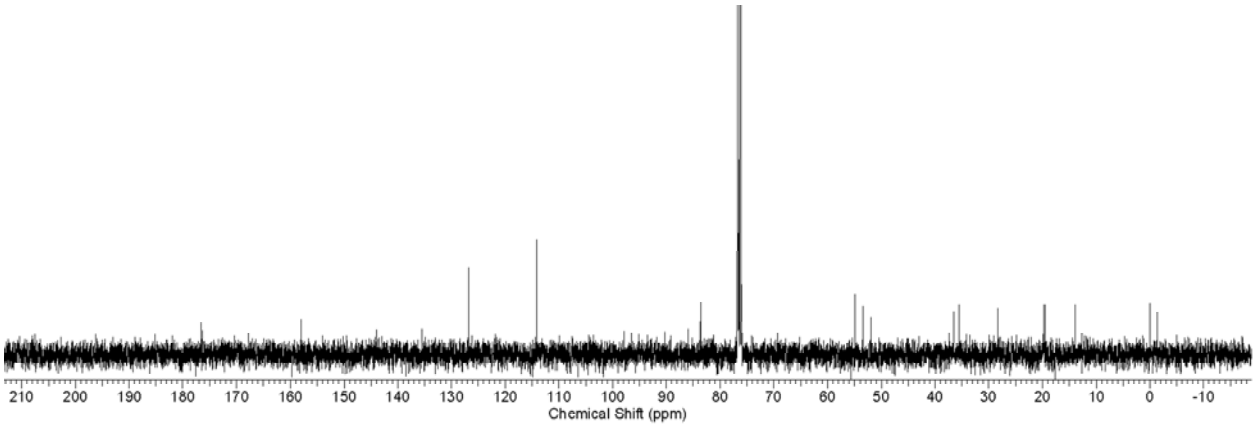


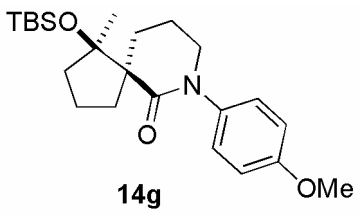
9l

400 MHz, $CDCl_3$



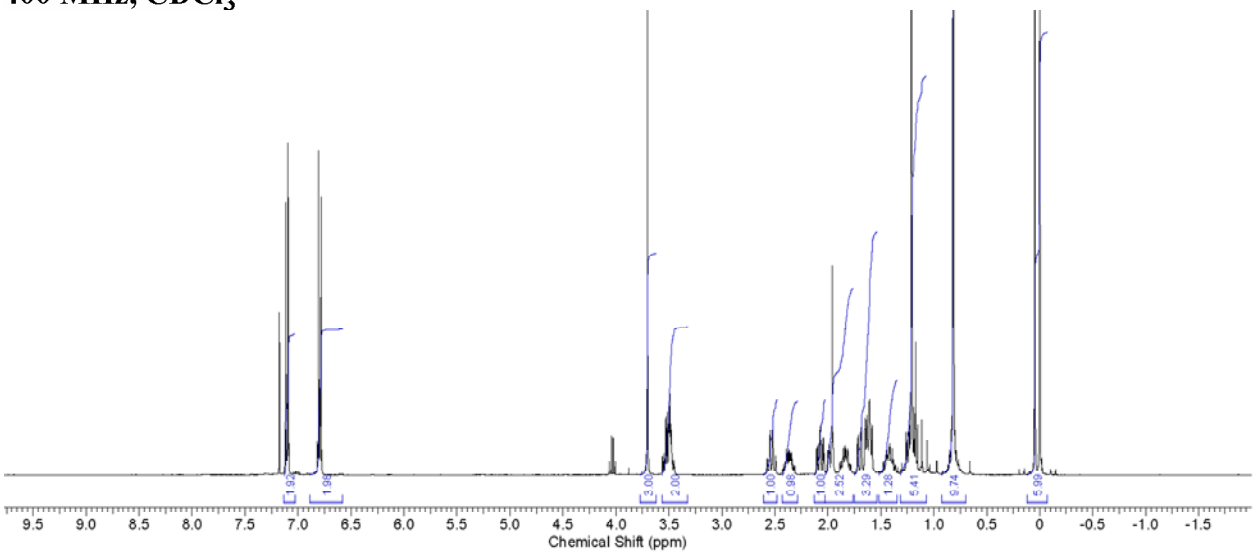
100 MHz, $CDCl_3$



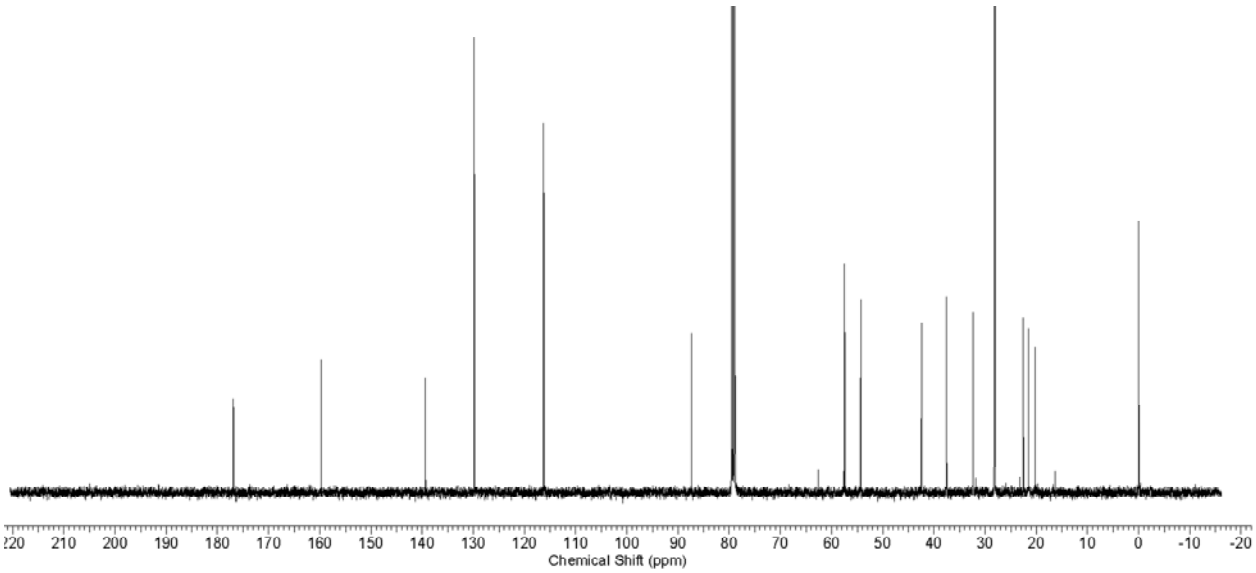


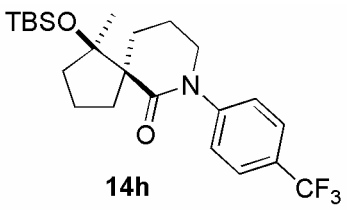
14g

400 MHz, $CDCl_3$



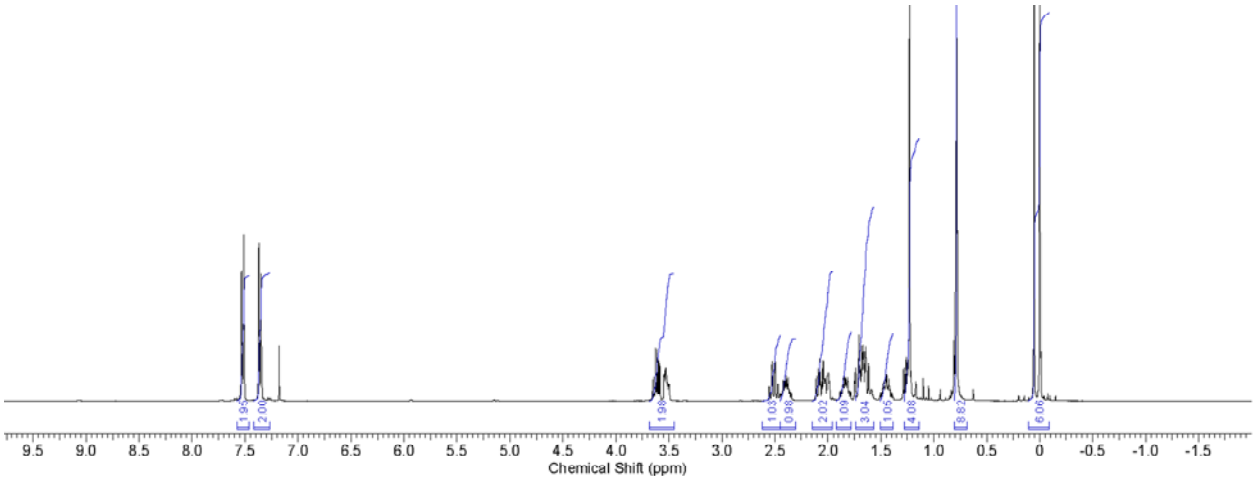
100 MHz, $CDCl_3$



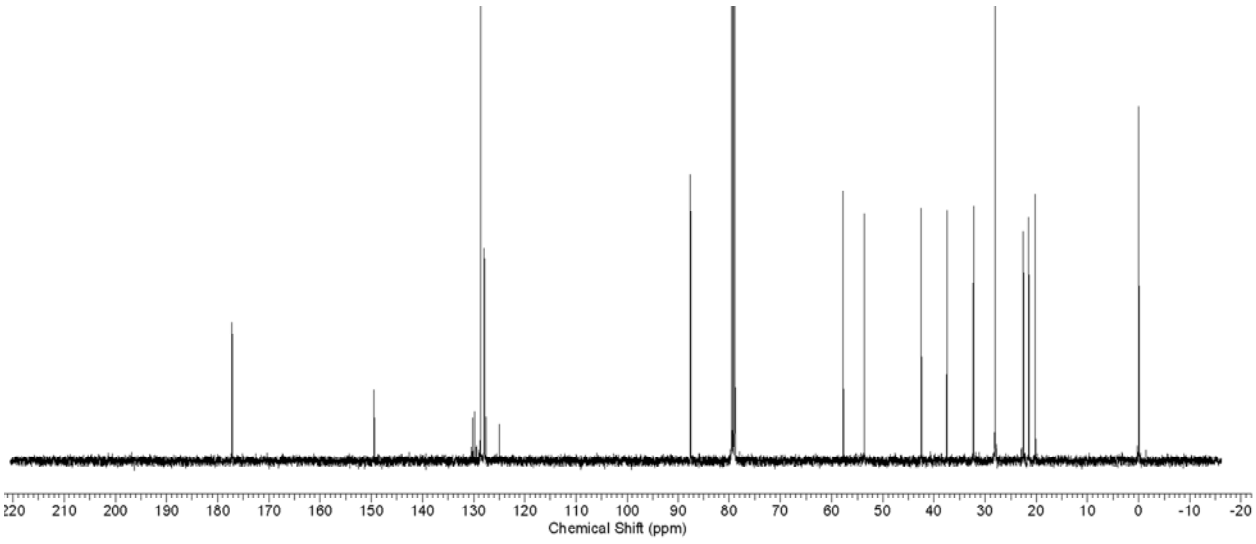


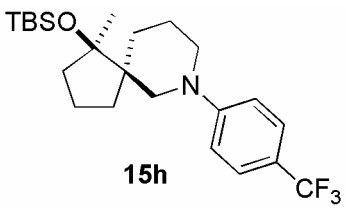
14h

400 MHz, $CDCl_3$



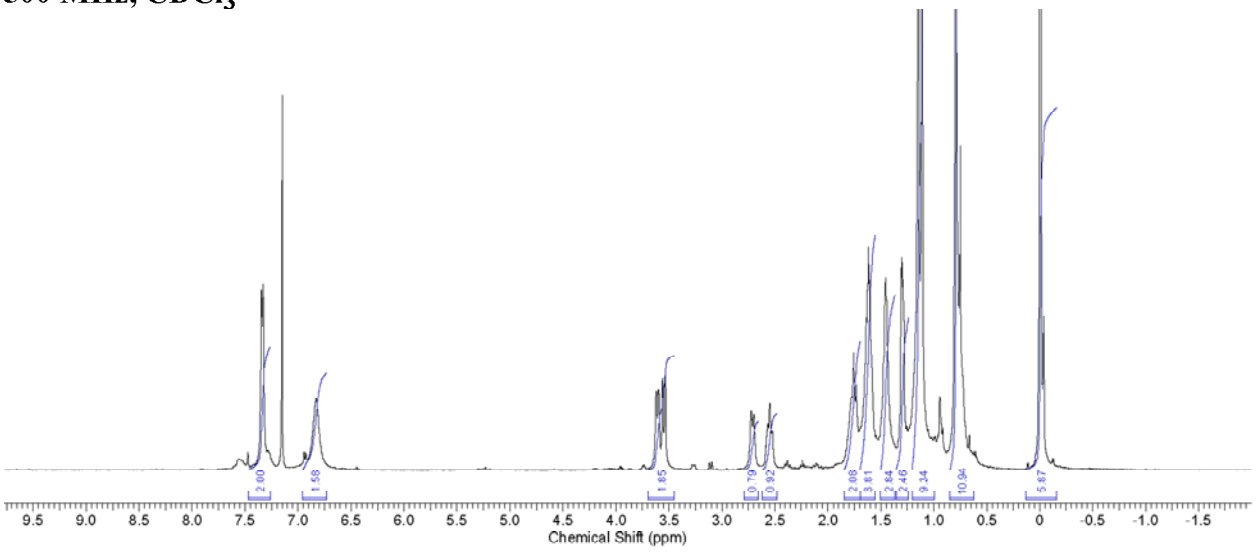
100 MHz, $CDCl_3$



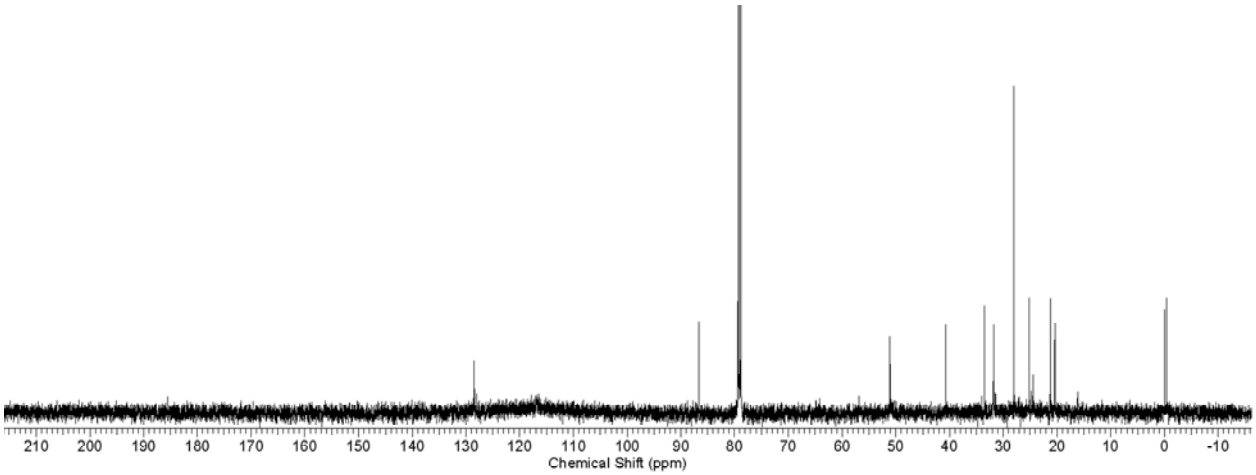


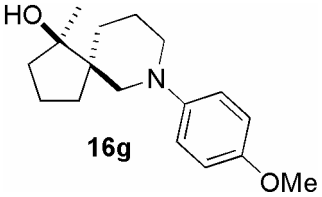
15h

500 MHz, $CDCl_3$



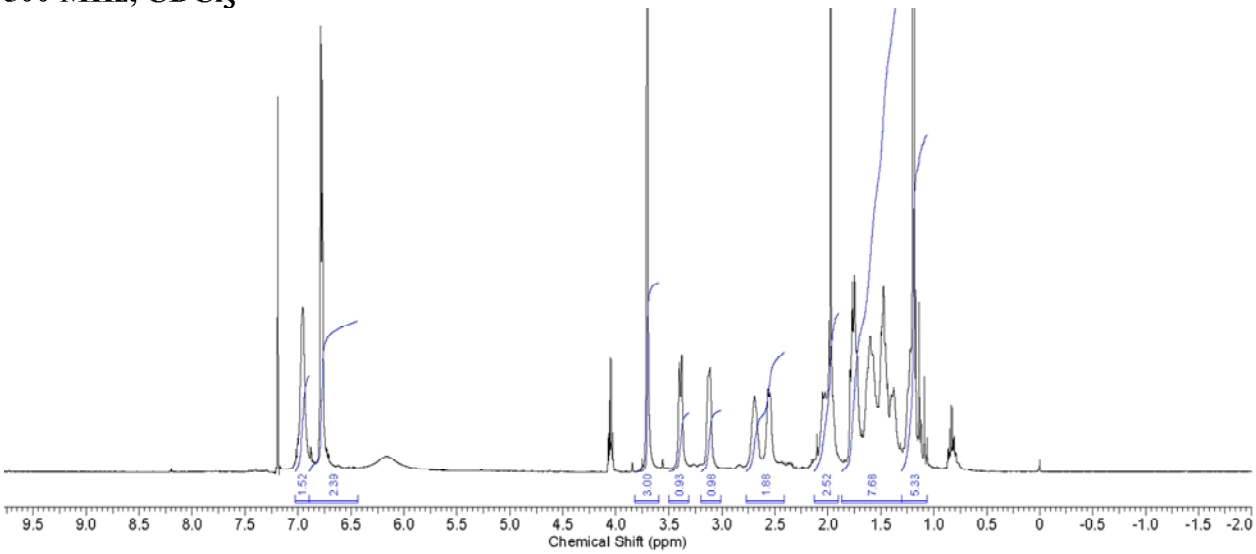
125 MHz, $CDCl_3$



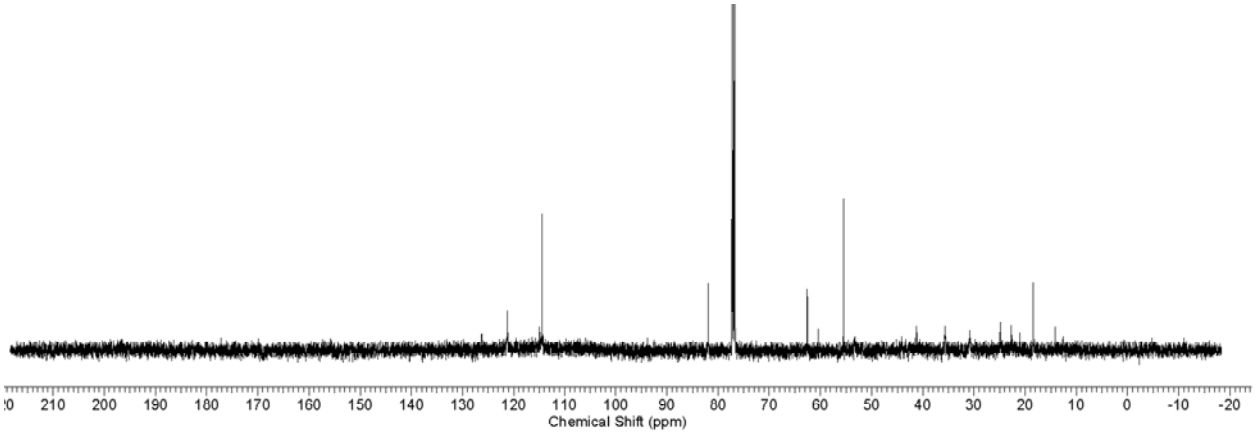


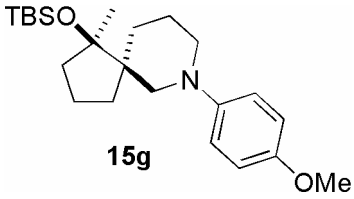
16g

500 MHz, $CDCl_3$



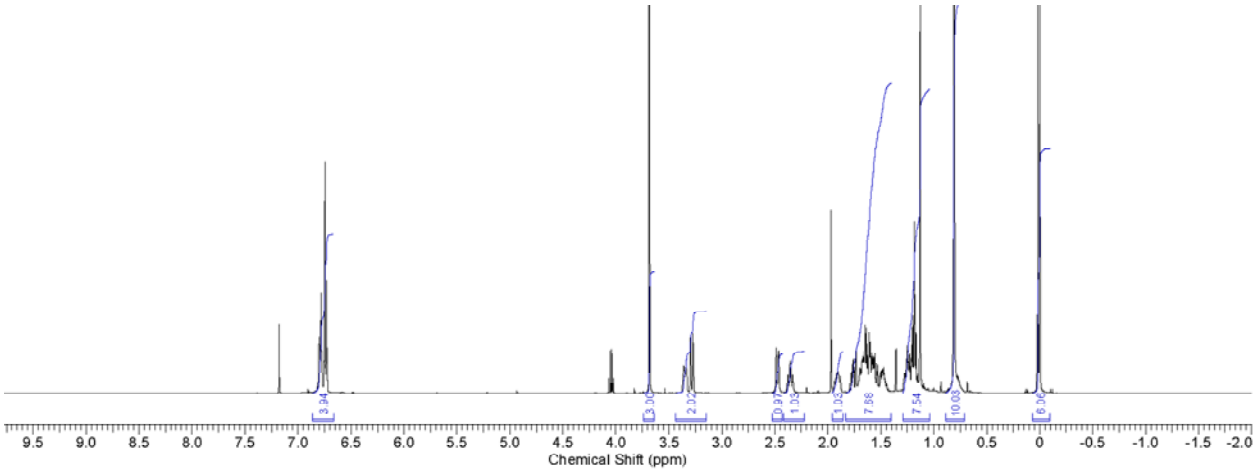
125 MHz, $CDCl_3$



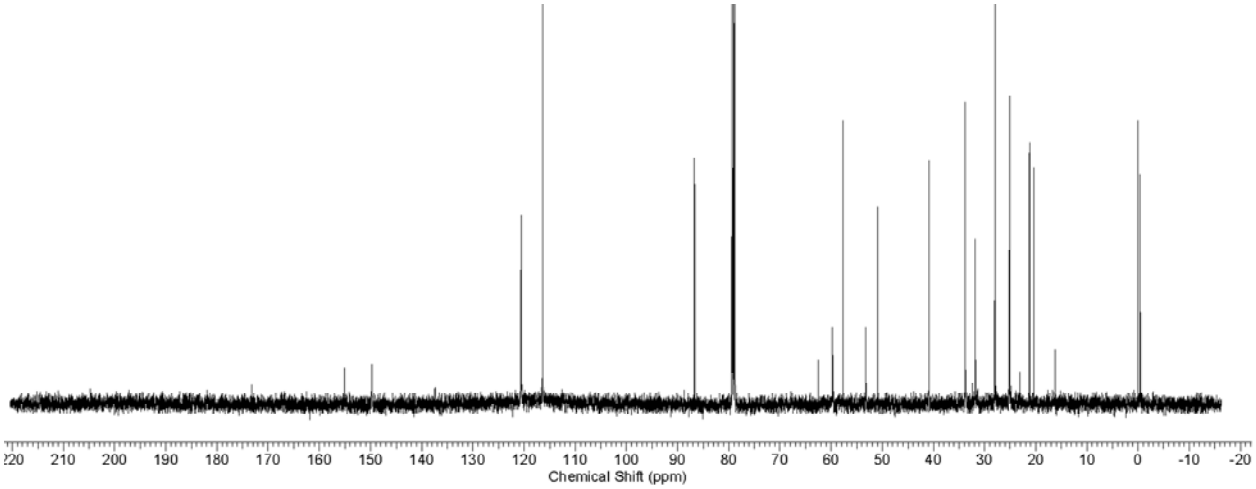


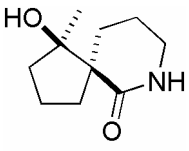
15g

500 MHz, $CDCl_3$



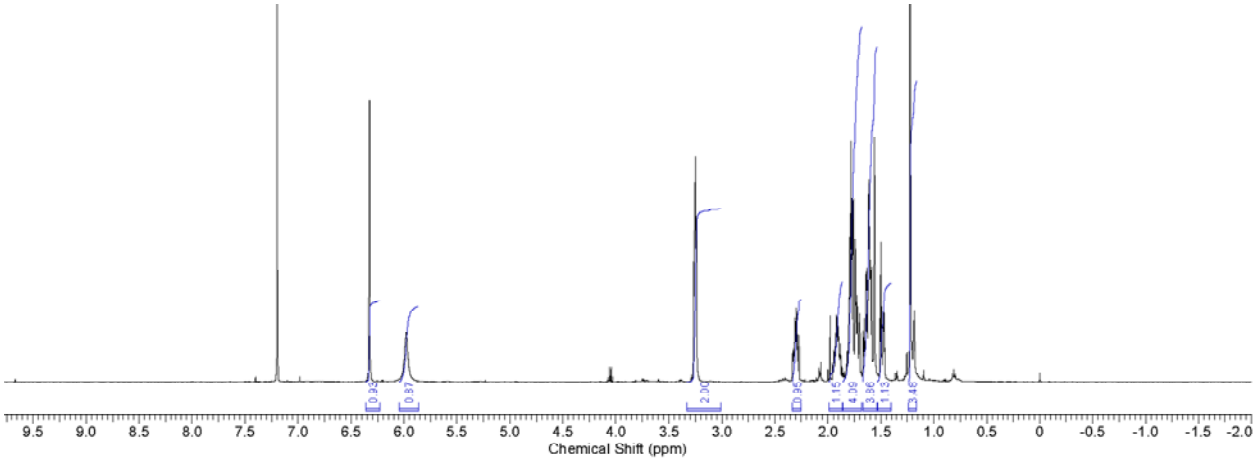
125 MHz, $CDCl_3$



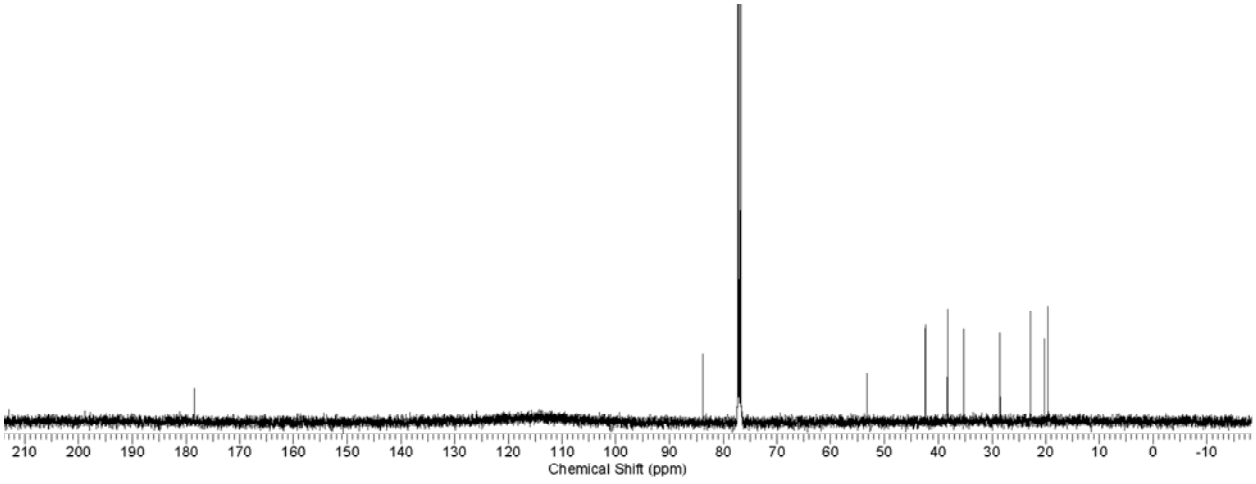


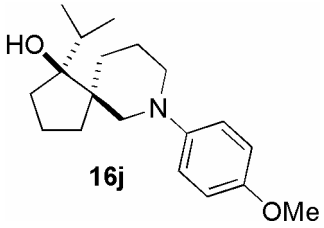
17g

400 MHz, $CDCl_3$



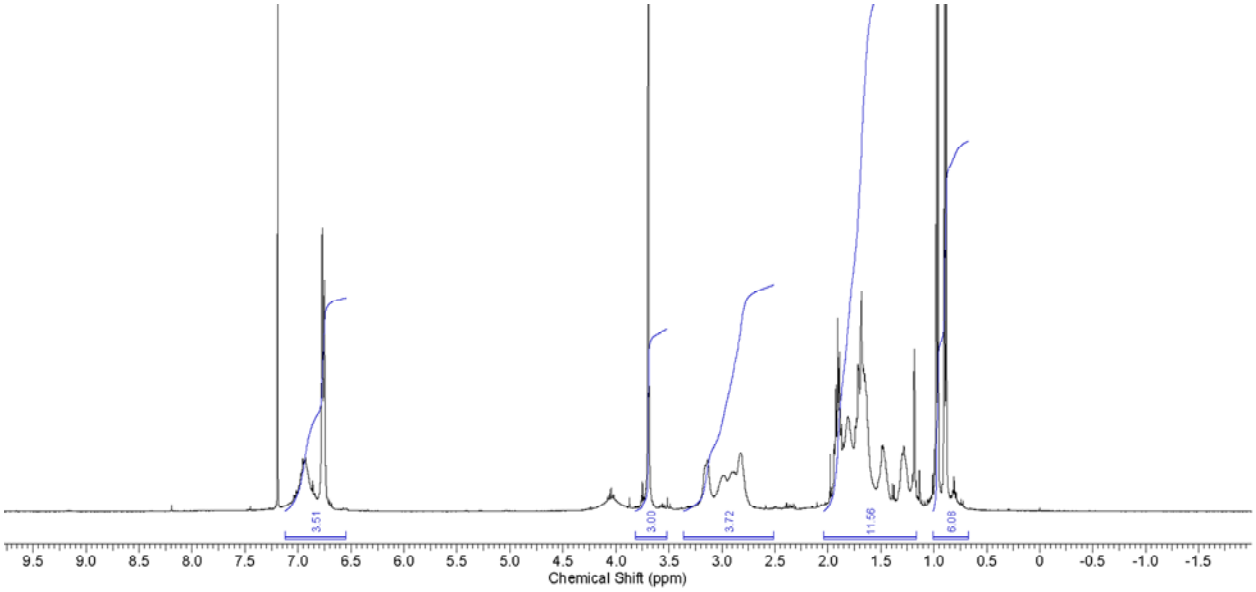
100 MHz, $CDCl_3$



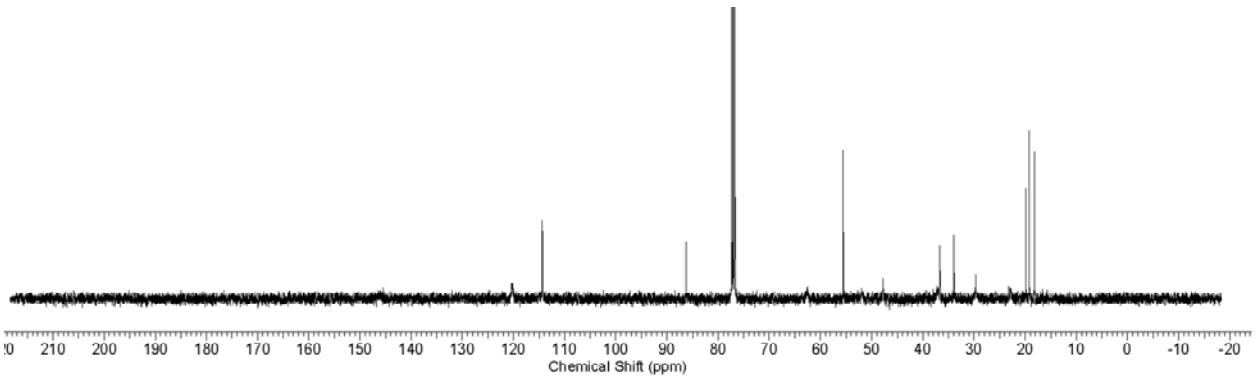


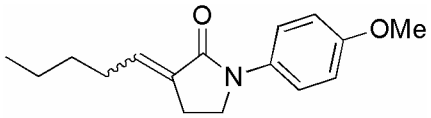
16j

400 MHz, $CDCl_3$



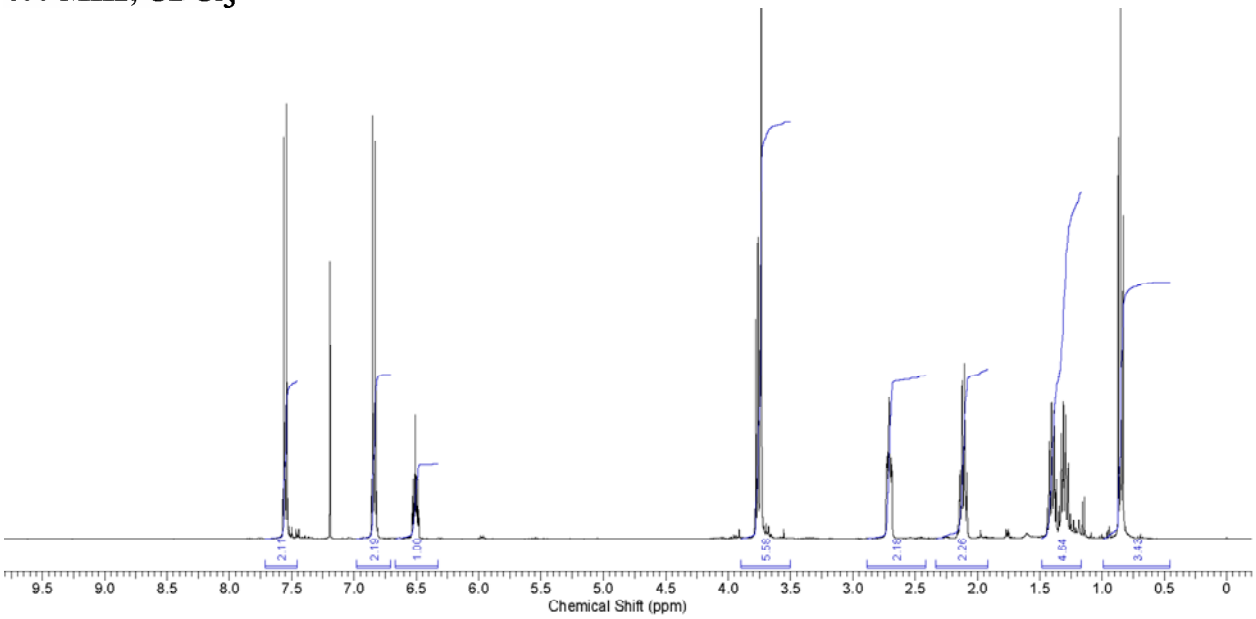
100 MHz, $CDCl_3$



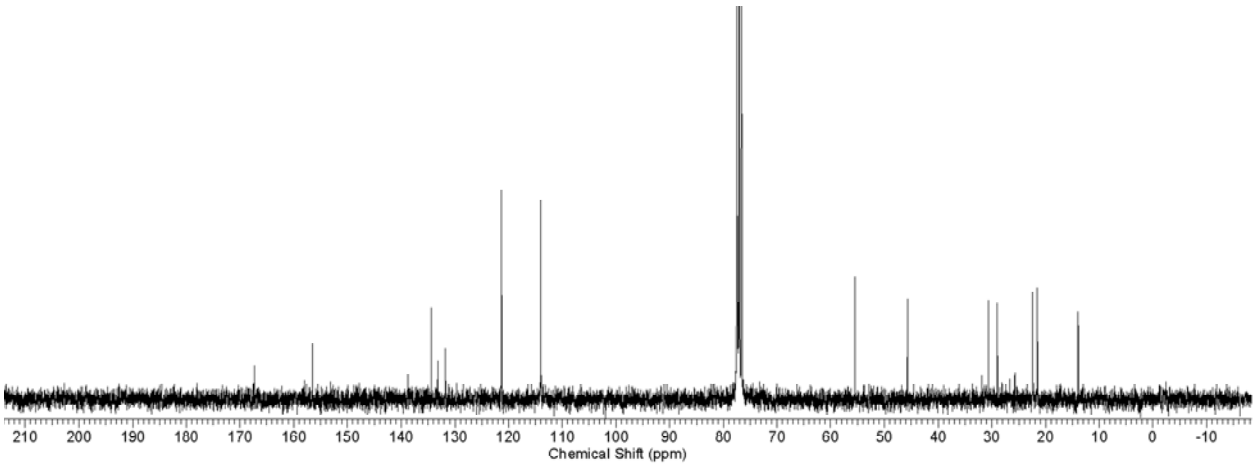


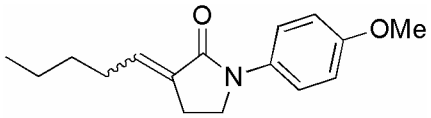
11 **E isomer**

400 MHz, $CDCl_3$



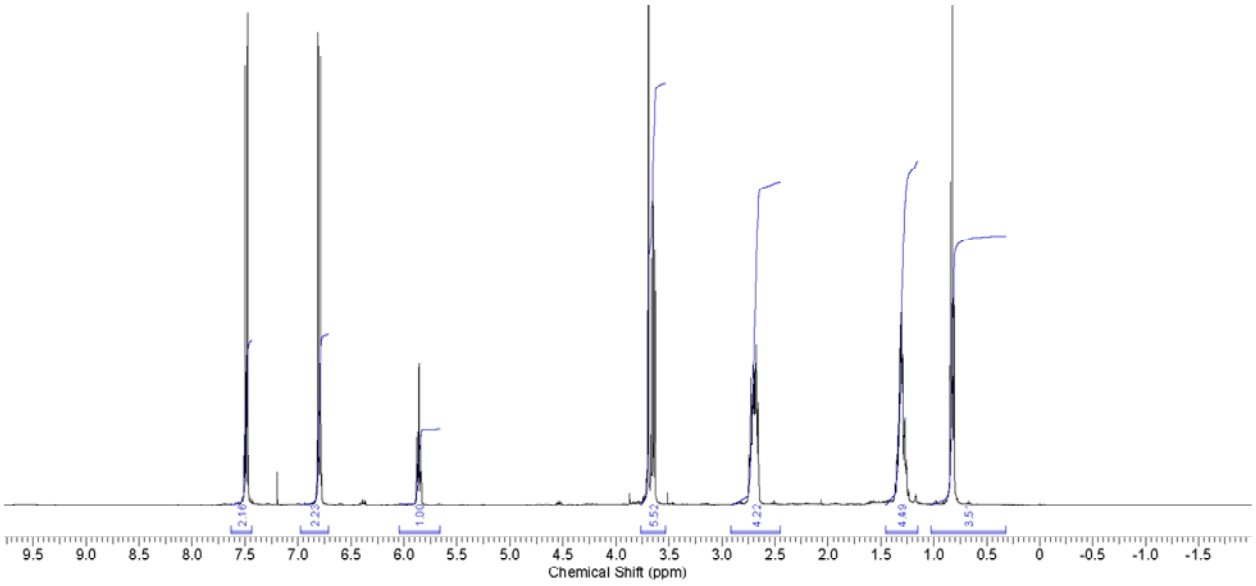
75 MHz, $CDCl_3$



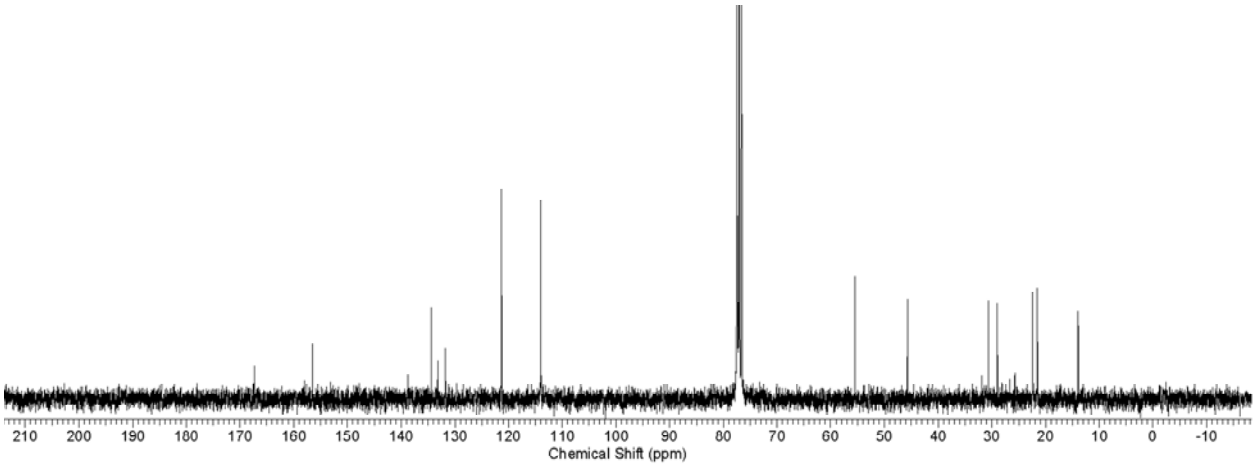


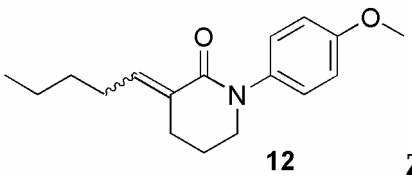
11 **Z isomer**

400 MHz, $CDCl_3$



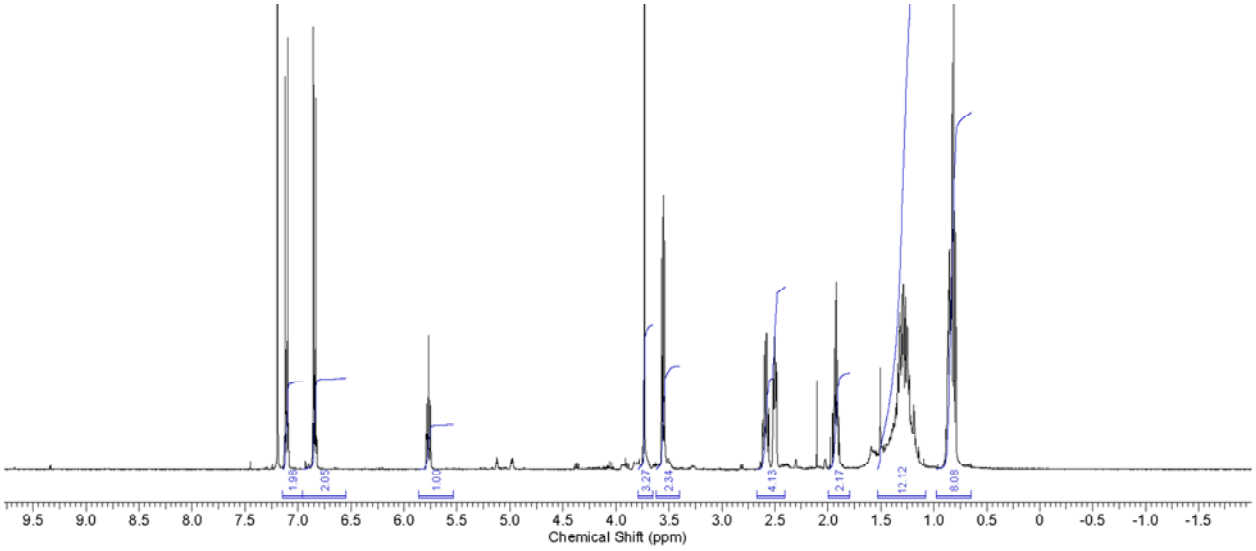
75 MHz, $CDCl_3$



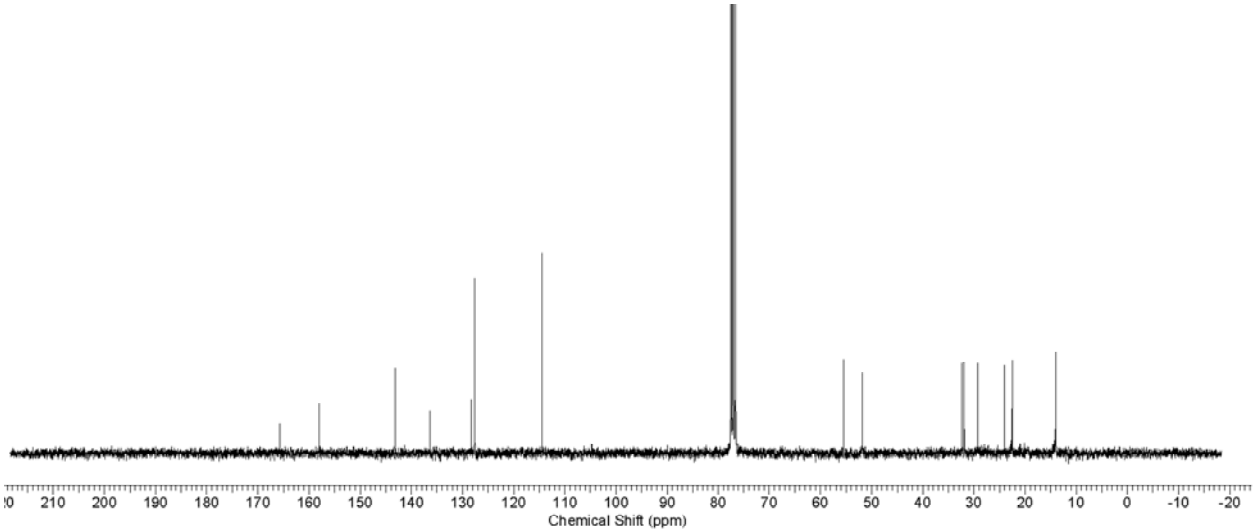


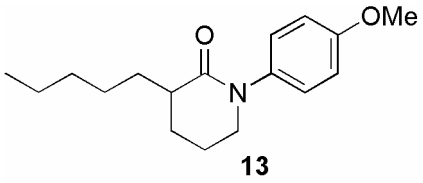
12 **Z isomer**

400 MHz, $CDCl_3$



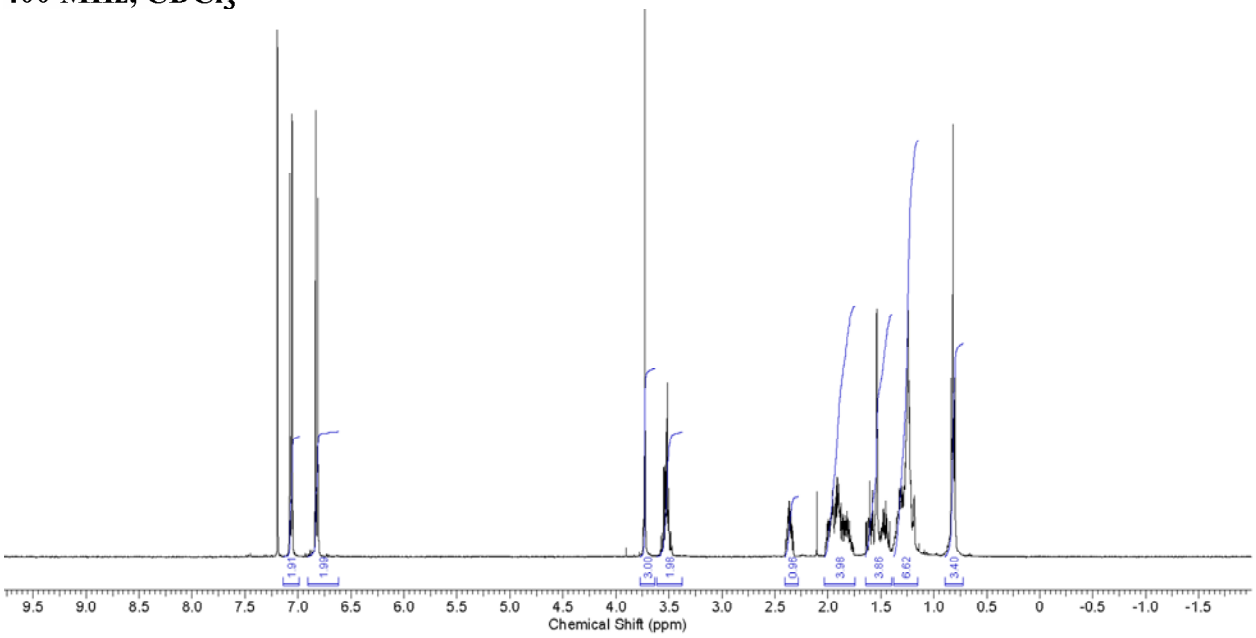
75 MHz, $CDCl_3$



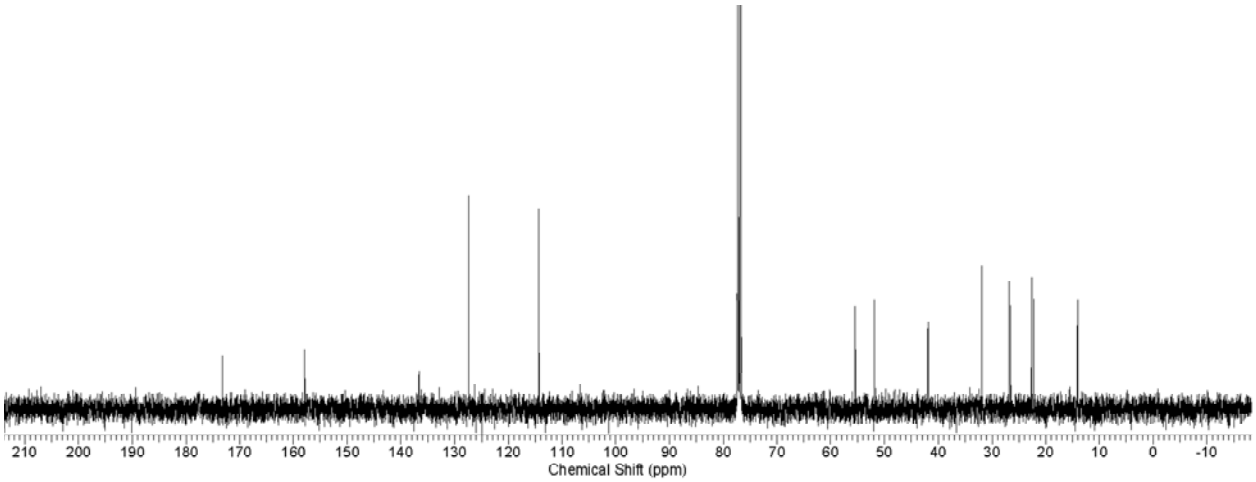


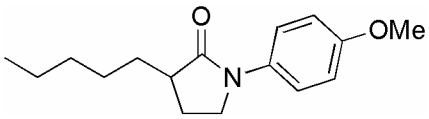
13

400 MHz, $CDCl_3$

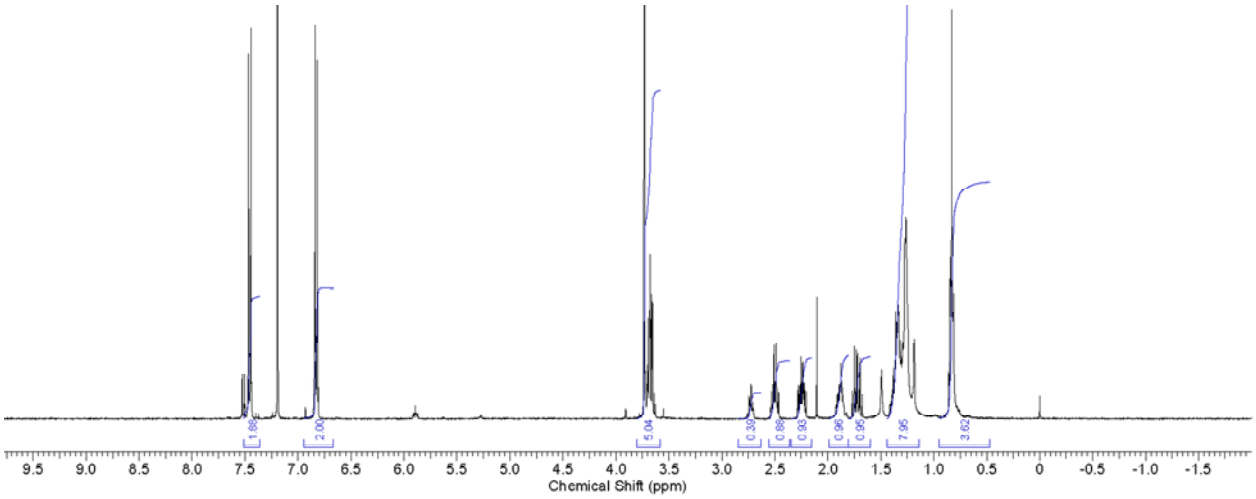


100 MHz, $CDCl_3$

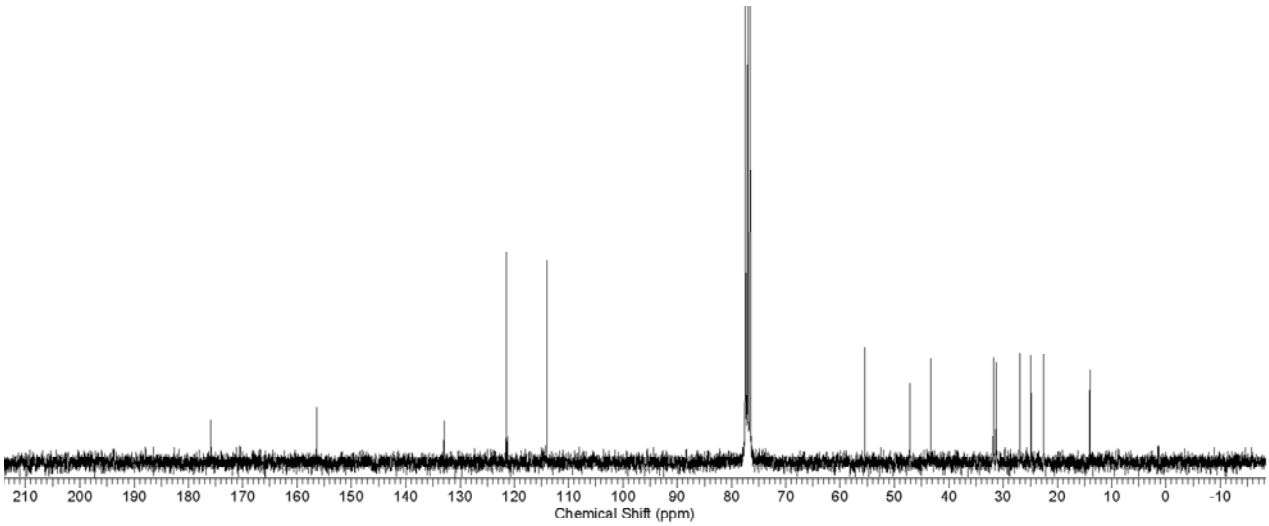


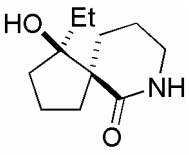


400 MHz, $CDCl_3$



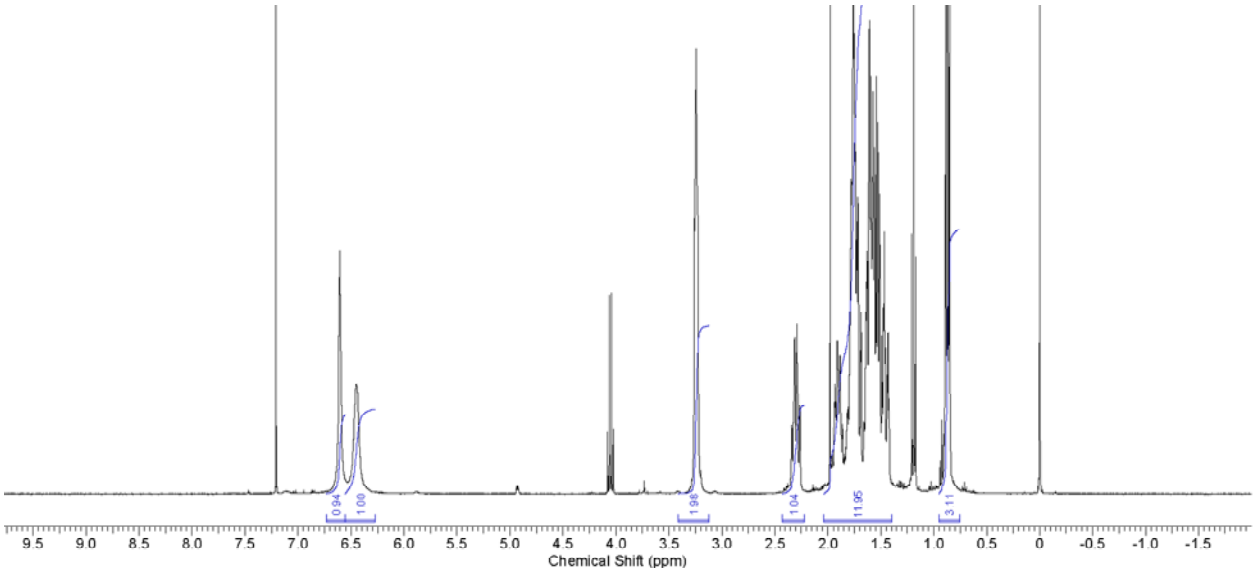
100 MHz, $CDCl_3$



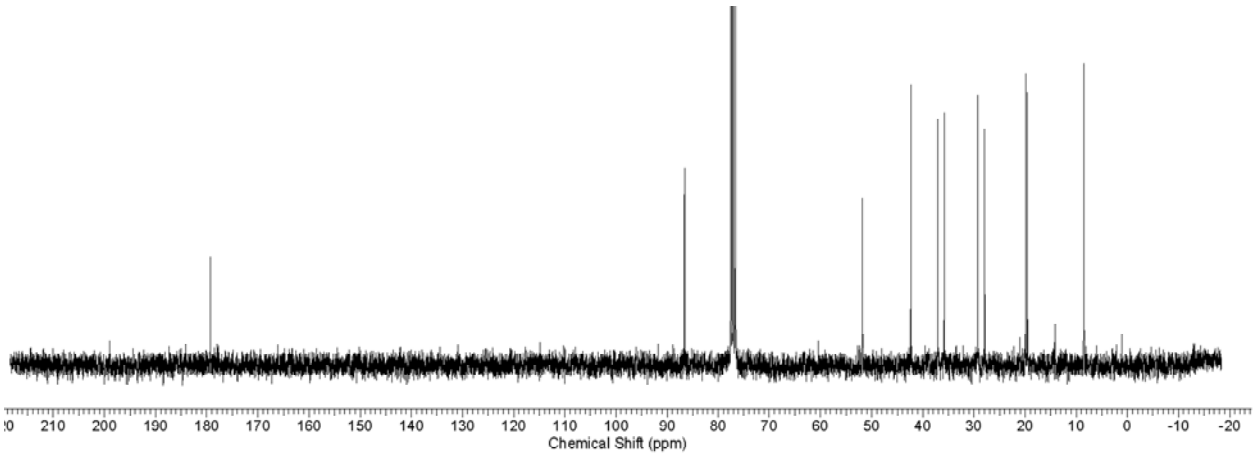


17i

400 MHz, $CDCl_3$

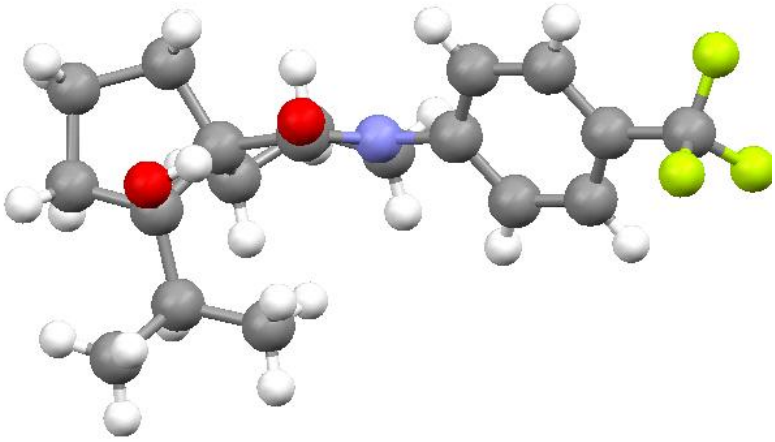


100 MHz, $CDCl_3$



X ray crystal of structure 9k

CCDC 694542



X ray crystal of structure 7d

CCDC 694541