

*Supporting Information for*

**One-pot synthesis of 1-azaspiro frameworks initiated by photooxidation  
of simple furans**

Dimitris Kalaitzakis, Eirini Antonatou and Georgios Vassilikogiannakis\*

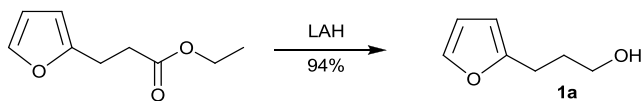
*Department of Chemistry, University of Crete, 71003 Iraklion, Crete, Greece. Fax: +30 2810 545166;*

*Tel: +30 2810 545074; E-mail: [vasil@chemistry.uoc.gr](mailto:vasil@chemistry.uoc.gr)*

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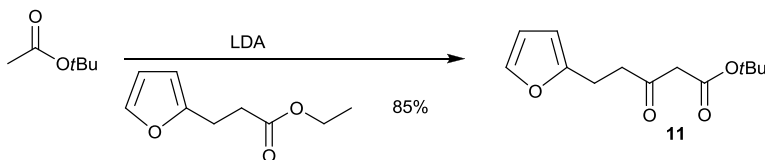
## Part A: Experimental procedures



### 3-(furan-2-yl)propan-1-ol (1a)

To a suspension of LAH (136 mg, 3.6 mmol) in anhydrous THF (10 mL) at 0 °C, ethyl 3-(furan-2-yl) propanoate (950  $\mu$ L, 5.9 mmol) was added and the solution was warmed to rt and stirred for 20 min. After completion of the reaction, as indicated by TLC analysis, a saturated aq. Rochelle salt solution (5 mL) was added and the mixture was extracted with Et<sub>2</sub>O (2  $\times$  10mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo* to afford the pure alcohol **1a**. Yield 94% (700 mg).

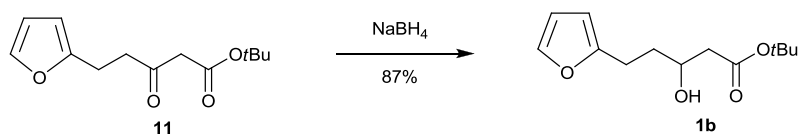
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.28 (d,  $J$  = 1.9 Hz, 1H), 6.26 (dd,  $J_1$  = 2.9 Hz,  $J_2$  = 1.9 Hz, 1H), 5.99 (d,  $J$  = 2.9 Hz, 1H), 3.64 (t,  $J$  = 6.4 Hz, 2H), 2.71 (t,  $J$  = 7.4 Hz, 2H), 2.49 (brs, 1H), 1.87 (m, 2H) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 155.5, 140.8, 110.0, 104.9, 61.7, 30.8, 24.2 ppm.



### tert-butyl 5-(furan-2-yl)-3-oxopentanoate (11)

To a solution of anhydrous diisopropylamine (490  $\mu$ L, 3.5 mmol) in anhydrous THF (4 mL) at 0 °C, a solution of *n*-BuLi (1.87 mL, 1.6 M in hexane, 3.0 mmol) was added. The solution was stirred for 15 min at the same temperature before it was cooled to -78 °C and a solution of *tert*-butyl acetate (415  $\mu$ L, 3.1 mmol) in anhydrous THF (2 mL) was added slowly. The solution was stirred for a further 75 min and the temperature was slowly raised to -50 °C. The reaction solution was then re-cooled to -78 °C and a solution of ethyl 3-(furan-2-yl) propanoate (237  $\mu$ L, 1.49 mmol) in anhydrous THF (2 mL) was added. The solution was warmed to -50 °C and stirred for a further 2 h. After completion of the reaction, as indicated by TLC analysis, the reaction was quenched with a saturated solution of aq. NH<sub>4</sub>Cl (8 mL). The mixture was extracted with EtOAc (2  $\times$  8 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The product was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 2:1). Yield 85% (302 mg).

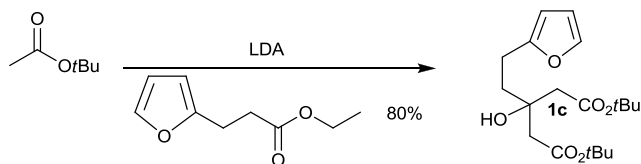
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 7.28 (d,  $J$  = 1.9 Hz, 1H), 6.26 (dd,  $J_1$  = 3.1 Hz,  $J_2$  = 1.9 Hz, 1H), 6.00 (d,  $J$  = 3.1 Hz, 1H), 3.36 (s, 2H), 2.89 (m, 4H), 1.46 (s, 9H) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 201.8, 166.2, 154.1, 141.1, 110.2, 105.3, 82.0, 50.6, 40.9, 27.9, 21.9 ppm.



### **tert-butyl 5-(furan-2-yl)-3-hydroxypentanoate (1b)**

To a solution of sodium borohydride (18 mg, 0.47 mmol) in anhydrous MeOH (2 mL) at 0 °C, *tert*-butyl 5-(furan-2-yl)-3-oxopentanoate **11** (300 mg, 1.26 mmol) was slowly added. The solution was stirred for 30 min at the same temperature. After completion of the reaction, as indicated by TLC analysis, the reaction was quenched with a saturated solution of aq. NH<sub>4</sub>Cl (4 mL) and the resulting mixture was extracted with Et<sub>2</sub>O (2 × 5 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The product was utilized without further purification. Yield 87% (438 mg).

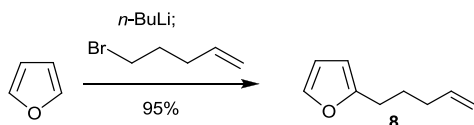
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 7.29 (d, *J* = 1.6 Hz, 1H), 6.27 (dd, *J*<sub>1</sub> = 3.0 Hz, *J*<sub>2</sub> = 1.6 Hz, 1H), 6.00 (d, *J* = 3.0 Hz, 1H), 3.98 (m, 1H), 2.90 (bs, 1H), 2.78 (m, 2H), 2.42 (dd, *J*<sub>1</sub> = 16.4 Hz, *J*<sub>2</sub> = 3.2 Hz, 1H), 2.35 (dd, *J*<sub>1</sub> = 16.4 Hz, *J*<sub>2</sub> = 8.8 Hz, 1H), 1.78 (m, 2H), 1.46 (s, 9H) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 172.4, 155.5, 140.9, 110.1, 105.0, 81.4, 67.2, 42.2, 34.6, 28.1 (3C), 24.0 ppm.



### **di-tert-butyl 3-(2-(furan-2-yl)ethyl)-3-hydroxypentanedioate (1c)**

To a solution of anhydrous diisopropylamine (1.32 mL, 9.5 mmol) in anhydrous THF (10 mL) at 0 °C was added a solution of *n*-BuLi (5.62 mL, 1.6 M in hexane, 9 mmol). The solution was stirred for 15 min at the same temperature before it was cooled to -78 °C and a solution of *tert*-butyl acetate (1.22 mL, 9.1 mmol) in anhydrous THF (5 mL) was slowly added. The reaction was stirred for a further 75 min and then the temperature was slowly raised to -50 °C. The reaction solution was re-cooled to -78 °C and a solution of ethyl 3-(furan-2-yl) propanoate (237 μL, 1.49 mmol) in anhydrous THF (2 mL) was added. The reaction mixture was warmed to -10 °C and stirred for a further 2 hours. After completion of the reaction, as indicated by TLC analysis, it was quenched with a saturated aq. solution of NH<sub>4</sub>Cl (8 mL) and extracted with EtOAc (2 × 8 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The product was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 2:1). Yield 80% (422 mg).

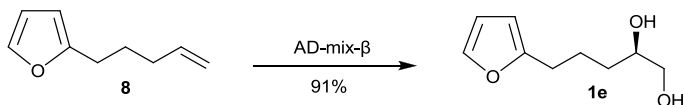
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 7.28 (d, *J* = 1.7 Hz, 1H), 6.26 (dd, *J*<sub>1</sub> = 3.1 Hz, *J*<sub>2</sub> = 1.7 Hz, 1H), 5.98 (d, *J* = 3.1 Hz, 1H), 2.78 (m, 2H), 2.62 (d, *J* = 15.2 Hz, 2H), 2.54 (d, *J* = 15.2 Hz, 2H), 1.95 (m, 2H), 1.46 (s, 18H) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 171.2 (2C), 155.8, 140.8, 110.1, 104.6, 81.4 (2C), 71.4, 43.9 (2C), 37.6, 28.1 (6C), 22.1 ppm.



### 2-(pent-4-enyl)furan (**8**)

To a solution of furan (972  $\mu$ L, 13.4 mmol) in anhydrous THF (7 mL) at 0 °C, *n*-BuLi (6.3 mL, 1.6 M in hexane, 10.1 mmol) was added dropwise. The solution was stirred for 30 min at the same temperature before the slow addition of a solution of 5-bromo-1-pentene (397  $\mu$ L, 3.36 mmol) in anhydrous THF (2 mL) also at 0 °C. The reaction was warmed to rt and stirred for a further 4 h. After completion of the reaction, a saturated aq. solution of NH<sub>4</sub>Cl (10 mL) was added and the mixture was extracted with Et<sub>2</sub>O (10 mL). The phases were separated and the organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The product was purified by flash column chromatography (silica gel, petroleum ether: EtOAc = 50:1  $\rightarrow$  20:1). Yield 95% (435 mg).

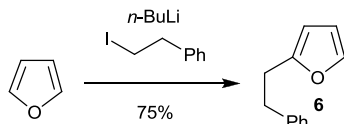
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.34 (d,  $J$  = 1.6 Hz, 1H), 6.32 (dd,  $J_1$  = 2.9 Hz,  $J_2$  = 1.6 Hz, 1H), 6.03 (d,  $J$  = 2.9 Hz, 1H), 5.90 (m, 1H), 5.09 (d,  $J$  = 17.2 Hz, 1H), 5.04 (d,  $J$  = 10.4 Hz, 1H), 2.70 (t,  $J$  = 7.5 Hz, 2H), 2.17 (q,  $J$  = 7.2 Hz, 2H), 1.81 (m, 2H) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 156.0, 140.7, 138.1, 114.8, 109.9, 104.7, 33.1, 27.3, 27.2 ppm.



### (*R*)-5-(furan-2-yl)pentane-1,2-diol (**1e**)

To a solution of 2-(pent-4-enyl)furan **8** (168 mg, 1.23 mmol) in H<sub>2</sub>O/*t*-BuOH (1/1.2 mL) AD-mix- $\beta$  (1.84 g) was added portionwise. The solution was stirred for 12 h at rt. After completion of the reaction, as indicated by TLC analysis, Na<sub>2</sub>SO<sub>3</sub> (2.77 g) was added and the mixture was further stirred for 1 h at rt. A saturated aq. solution of NH<sub>4</sub>Cl (4 mL) was then added to the reaction and the mixture was extracted with EtOAc (3  $\times$  4 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The product was purified by flash column chromatography (silica gel, petroleum ether: EtOAc = 1:1  $\rightarrow$  0:1 EtOAc). Yield 91% (191 mg).

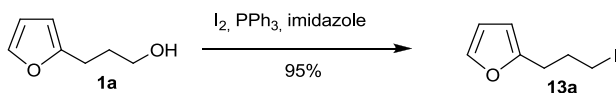
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.29 (d,  $J$  = 1.9 Hz, 1H), 6.27 (dd,  $J_1$  = 3.1 Hz,  $J_2$  = 1.9 Hz, 1H), 5.98 (d,  $J$  = 3.1 Hz, 1H), 3.72 (m, 1H), 3.64 (dd,  $J_1$  = 11.1 Hz,  $J_2$  = 3.0 Hz, 1H), 3.43 (dd,  $J_1$  = 11.1 Hz,  $J_2$  = 7.7 Hz, 1H), 2.65 (t,  $J$  = 7.5 Hz, 2H), 2.55 (m, 2H), 1.82 (m, 1H), 1.69 (m, 1H), 1.47 (m, 2H) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 155.7, 140.8, 110.1, 104.9, 72.0, 66.7, 32.4, 27.8, 24.1 ppm.



### 2-phenethylfuran (6)

To a solution of furan (543  $\mu$ L, 7.5 mmol) in anhydrous THF (7 mL) at 0 °C, *n*-BuLi (3.5 mL, 1.6 M in hexane, 5.6 mmol) was added dropwise. The solution was stirred for 30 min at the same temperature before the slow addition of a solution of the iodide (435  $\mu$ L, 1.87 mmol) in anhydrous THF (5 mL). The solution was warmed to rt and stirred for a further 2 h. After completion of the reaction, a saturated aq. solution of NH<sub>4</sub>Cl (10 mL) was added and the mixture was extracted with Et<sub>2</sub>O (10 mL). The phases were separated and the organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The product was purified by flash column chromatography (silica gel, petroleum ether). Yield 75% (242 mg).

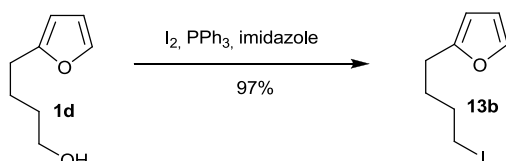
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.36 (s, 1H), 7.31 (d, *J* = 7.2 Hz, 2H), 7.23 (m, 3H), 6.32 (d, *J* = 2.7 Hz, 1H), 6.01 (d, *J* = 2.7 Hz, 1H), 2.99 (bs, 4H) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 155.4, 141.2, 140.8, 128.3 (3C), 126.0 (2C), 110.1, 105.1, 34.4, 29.9 ppm.



### 2-(3-iodopropyl)furan (13a)

To a solution of PPh<sub>3</sub> (440 mg, 1.7 mmol) and I<sub>2</sub> (427 mg, 1.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (7 mL), imidazole (191 mg, 2.8 mmol) was added and the solution was stirred for 10 min at rt. After slow addition of a solution 3-(furan-2-yl)propan-1-ol **1a** (139 mg, 1.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) the mixture was further stirred for 20 min, when completion of the reaction is indicated by TLC. The reaction was quenched with a saturated aq. solution of sodium thiosulfate (8 mL). The layers were separated and the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, petroleum ether: EtOAc = 10:1). Yield 95% (247 mg).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.31 (d, *J* = 1.8 Hz, 1H), 6.28 (dd, *J*<sub>1</sub> = 3.0 Hz, *J*<sub>2</sub> = 1.8 Hz, 1H), 6.05 (d, *J* = 3.0 Hz, 1H), 3.20 (t, *J* = 6.8 Hz, 2H), 2.76 (t, *J* = 7.1 Hz, 2H), 2.14 (m, 2H) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 154.0, 141.2, 110.2, 105.8, 31.7, 28.6, 5.8 ppm.



### 2-(4-iodobutyl)furan (**13b**)<sup>1</sup>

To a solution of  $PPh_3$  (440 mg, 1.7 mmol) and  $I_2$  (427 mg, 1.7 mmol) in  $CH_2Cl_2$  (7 mL) at rt, imidazole (191 mg, 2.8 mmol) was added and the solution was stirred for 10 min. After slow addition of a solution of 4-(furan-2-yl)butan-1-ol **1d**<sup>2</sup> (157 mg, 1.1 mmol) in  $CH_2Cl_2$  (1 mL) the mixture was stirred for a further 20 min, when completion of the reaction was indicated by TLC analysis. The reaction was quenched by a saturated aq. solution of sodium thiosulfate (8 mL). The layers were separated and the organic layer was dried over  $Na_2SO_4$ , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, petroleum ether: EtOAc = 10:1). Yield 97% (267 mg).

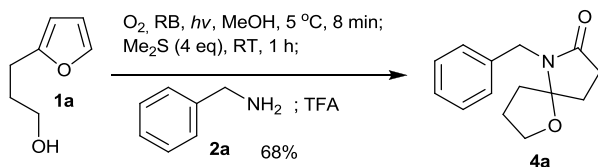
<sup>1</sup>H NMR (300 MHz,  $CDCl_3$ ):  $\delta$  = 7.30 (d,  $J$  = 1.5 Hz, 1H), 6.28 (dd,  $J_1$  = 3.0 Hz,  $J_2$  = 1.5 Hz, 1H), 6.00 (d,  $J$  = 3.0 Hz, 1H), 3.20 (t,  $J$  = 6.8 Hz, 2H), 2.66 (t,  $J$  = 7.2 Hz, 2H), 1.92 – 1.80 (m, 2H), 1.80 – 1.70 (m, 2H) ppm; <sup>13</sup>C NMR (300 MHz,  $CDCl_3$ ):  $\delta$  = 155.4, 140.9, 110.1, 105.0, 32.8, 28.9, 26.8, 6.4 ppm.

### General procedure for the preparation of spiroaminals 4a-h.

2-Substituted furans (1.0 mmol) were dissolved in methanol (6 mL) containing catalytic amounts of rose Bengal ( $10^{-4}$  M) as photosensitizer. The solutions were cooled with an ice bath. Oxygen was gently bubbled through the solution while it was irradiated with a xenon Variac Eimac Cermax 300 W lamp. The reaction was monitored by TLC. After completion of the reaction (usually 8 minutes), it was warmed to rt and  $Me_2S$  (292  $\mu$ L, 4.0 mmol) was added for the reduction of hydroperoxy group. After completion of the reduction (1.0 h), as indicated by TLC, the corresponding amine was added (0.9 mmol) and the mixture was stirred for 30 min at the same temperature. After the formation of the intermediate 2-pyrrolidinone (**B**), indicated by TLC, methanol was replaced with dichloromethane (4 mL), followed by addition of either TFA (0.2-0.5 mmol), or *p*-TsOH (0.2 mmol). After completion of the reaction (30 min), as indicated by TLC, the solution was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel, petroleum ether:EtOAc). In the case of compound **4g**, TFA (0.2 mmol) was used and before the concentration the mixture was neutralized by  $Et_3N$  (0.25 mmol).

<sup>1</sup> D. Kalaitzakis, T. Montagnon, E. Antonatou, N. Bardají, G. Vassilikogiannakis, *Chem. Eur. J.* 2013, **19**, 10119.

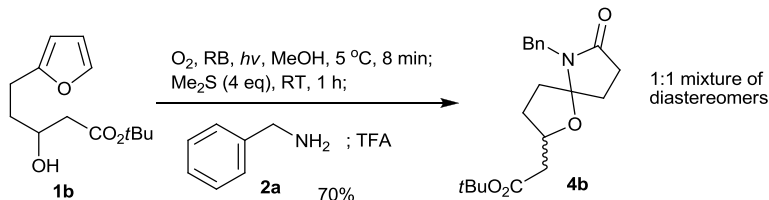
<sup>2</sup> D. Noutsias, I. Alexopoulou, T. Montagnon, G. Vassilikogiannakis, *Green Chem.* 2012, **14**, 601.



#### 6-benzyl-1-oxa-6-azaspiro[4.4]nonan-7-one (**4a**)

The reaction was accomplished according to the general experimental described above, utilizing 3-(furan-2-yl)propan-1-ol **1a** (126 mg, 1.0 mmol) and benzylamine (**2a**, 98  $\mu\text{L}$ , 0.9 mmol) followed by stirring at rt for 30 min. Finally, TFA (38  $\mu\text{L}$ , 0.5 mmol) was added and the solution in  $\text{CH}_2\text{Cl}_2$  (2 mL) was stirred for 30 min at rt. After concentration of the solution, the product was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 1:1). Yield 68% (141 mg).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.25 (m, 5H), 4.71 (d,  $J$  = 16.0 Hz, 1H), 4.16 (d,  $J$  = 16.0 Hz, 1H), 3.90 (m, 1H), 3.76 (m, 1H), 2.60 (m, 1H), 2.42 (ddd,  $J_1$  = 17.0 Hz,  $J_2$  = 9.2 Hz,  $J_3$  = 3.8 Hz, 1H), 2.22 – 1.72 (m, 6H) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 175.5, 138.4, 128.4 (2C), 127.0 (2C), 126.9, 100.8, 67.7, 42.7, 34.5, 33.9, 29.2, 25.5 ppm; HRMS (TOF ESI): calcd for  $\text{C}_{14}\text{H}_{18}\text{NO}_2$ : 232.1332 [ $\text{M} + \text{H}$ ] $^+$ ; found: 232.1324.

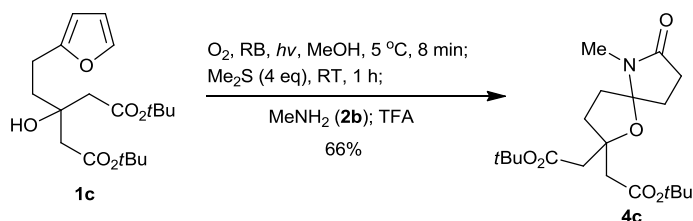


#### tert-butyl 2-(6-benzyl-7-oxo-1-oxa-6-azaspiro[4.4]nonan-2-yl)acetate (**4b**)

The reaction was accomplished according to the general experimental described above, utilizing *tert*-butyl 5-(furan-2-yl)-3-hydroxypentanoate **1b** (240 mg, 1.0 mmol) and benzylamine (**2a**, 98  $\mu\text{L}$ , 0.9 mmol) followed by stirring at rt for 30 min. Finally, TFA (38  $\mu\text{L}$ , 0.5 mmol) was added and the solution in  $\text{CH}_2\text{Cl}_2$  (2 mL) was stirred for 30 min at rt. After concentration of the solution, the product was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 3:1) to afford a 1:1 inseparable mixture of diastereomers. Yield 70% (217 mg).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.25 (m, 10H, for two diastereomers), 4.73 (d,  $J$  = 16.0 Hz, 1H, for one diastereomer), 4.72 (d,  $J$  = 16.0 Hz, 1H, for one diastereomer), 4.40 (m, 1H, for one diastereomer), 4.17 (m, 1H, for one diastereomer), 4.16 (d,  $J$  = 16.0 Hz, 1H, for one diastereomer), 4.14 (d,  $J$  = 16.0 Hz, 1H, for one diastereomer), 2.60 (m, 2H, for two diastereomers), 2.45 (m, 4H, for two diastereomers), 2.32 (dd,  $J_1$  = 15.1 Hz,  $J_2$  = 6.7 Hz, 1H, for one diastereomer), 2.27 (dd,  $J_1$  = 15.1 Hz,  $J_2$  = 6.7 Hz, 1H, for one diastereomer), 2.22 – 1.95 (m, 8H, for two diastereomers), 1.88 – 1.74 (m, 2H, for two diastereomers), 1.70 – 1.55 (m, 2H, for two diastereomers), 1.43 (s, 18H, for two diastereomers) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 175.9, 175.2, 170.0, 169.9, 138.4, 138.3, 128.4 (4C, for two diastereomers), 127.1 (2C, for two diastereomers), 127.0 (4C,

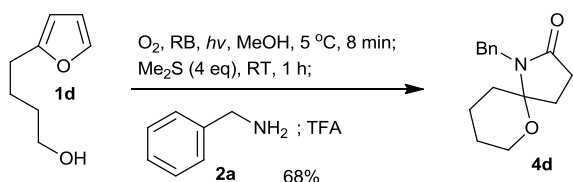
for two diastereomers), 101.0, 100.7, 80.8 (2C, for two diastereomers), 76.5, 74.4, 42.7, 42.5, 42.4, 41.1, 35.1, 34.8, 34.3, 33.8, 30.9, 30.6, 29.2, 29.1, 28.0 (6C, for two diastereomers) ppm; HRMS (TOF ESI): calcd for  $C_{20}H_{28}NO_4$ : 346.2013  $[M + H]^+$ ; found: 346.2014.



#### ***tert*-butyl 2,2'-(6-methyl-7-oxo-1-oxa-6-azaspiro[4.4]nonane-2,2-diyl)diacetate (**4c**)**

The reaction was accomplished according to the general experimental described above, utilizing di-*tert*-butyl 3-(2-(furan-2-yl)ethyl)-3-hydroxypentanedioate **1c** (354 mg, 1.0 mmol) and methylamine (**2b**, 70  $\mu$ L, 40% w/v in  $H_2O$ , 0.9 mmol) followed by stirring at rt for 30 min. Finally, TFA (38  $\mu$ L, 0.5 mmol) was added and the solution in  $CH_2Cl_2$  (2 mL) was stirred for 30 min at rt. After concentration of the solution, the product was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 2:1). Yield 66% (211 mg).

$^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  = 2.91 (d,  $J$  = 15.4 Hz, 1H), 2.77 (s, 3H), 2.73 (d,  $J$  = 15.0 Hz, 1H), 2.63 (d,  $J$  = 15.0 Hz, 1H), 2.61 (d,  $J$  = 15.4 Hz, 1H), 2.49 (m, 1H), 2.32 – 2.03 (m, 7H), 1.45 (s, 9H), 1.44, (s, 9H) ppm;  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  = 174.7, 169.7, 169.6, 101.0, 81.9, 80.9, 80.8, 44.3, 44.0, 36.0, 34.2, 33.5, 29.3, 28.1 (6C), 24.3 ppm; HRMS (TOF ESI): calcd for  $C_{20}H_{33}NNaO_6$ : 406.2206  $[M + Na]^+$ ; found: 406.2201.



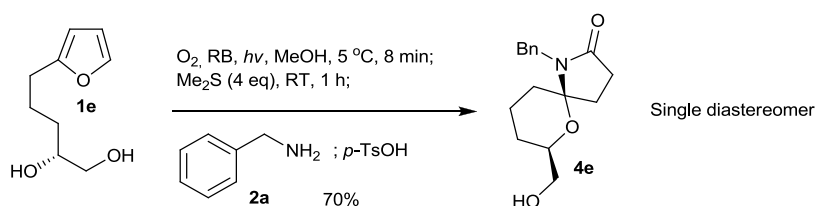
#### **1-benzyl-6-oxa-1-azaspiro[4.5]decan-2-one (**4d**)**

The reaction was accomplished according to the general experimental described above, utilizing 4-(furan-2-yl)butan-1-ol **1d** (140 mg, 1.0 mmol) and benzylamine (**2a**, 98  $\mu$ L, 0.9 mmol) followed by stirring at rt for 30 min. Finally, TFA (38  $\mu$ L, 0.5 mmol) was added and the solution in  $CH_2Cl_2$  (2 mL) was stirred for 30 min at rt. After concentration of the solution, the product was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 5:1). Yield 68% (150 mg).

$^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  = 7.27 – 7.18 (m, 5H), 4.79 (d,  $J$  = 15.9 Hz, 1H), 4.20 (d,  $J$  = 15.9 Hz, 1H), 3.87 (m, 1H), 3.65 (m, 1H), 2.60 – 2.32 (m, 3H), 1.87 (dt,  $J_1$  = 12.8 Hz,  $J_2$  = 9.0 Hz, 1H), 1.71 – 1.36 (m, 6H) ppm;  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$  = 175.8,



139.0, 128.3 (2C), 127.2 (2C), 126.8, 93.1, 64.2, 42.7, 34.7, 28.6, 26.8, 25.1, 20.3 ppm;  
HRMS (TOF ESI): calcd for C<sub>15</sub>H<sub>20</sub>NO<sub>2</sub>: 246.1489 [M + H]<sup>+</sup>; found: 246.1488.

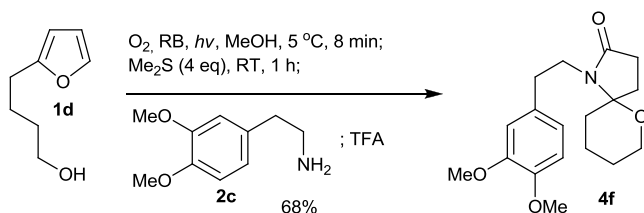
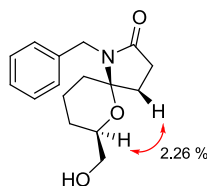


### (5*R*,7*R*)-1-benzyl-7-(hydroxymethyl)-6-oxa-1-azaspiro[4.5]decan-2-one (**4e**)

The reaction was accomplished according to the general experimental described above, utilizing (*R*)-5-(furan-2-yl)pentane-1,2-diol **1e** (170 mg, 1.0 mmol) and benzylamine (**2a**, 98 μL, 0.9 mmol) followed by stirring at rt for 30 min. Finally, *p*-TsOH (38 mg, 0.2 mmol) was added and the solution in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was stirred for 30 min at rt. After concentration of the solution, the residue was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 1:1). Yield 70% (173 mg).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 7.30 – 7.21 (m, 5H), 4.57 (d, *J* = 15.7 Hz, 1H), 4.45 (d, *J* = 15.7 Hz, 1H), 3.66 (m, 1H), 3.51 (dd, *J*<sub>1</sub> = 11.4 Hz, *J*<sub>2</sub> = 2.5 Hz, 1H), 3.39 (dd, *J*<sub>1</sub> = 11.4 Hz, *J*<sub>2</sub> = 6.0 Hz, 1H), 2.57 (m, 1H), 2.45 (m, 1H), 2.34 (brt, *J* = 10.0 Hz, 1H), 1.95 (bs, 1H), 1.89 (m, 1H), 1.80 (m, 1H), 1.71 (m, 1H), 1.62 (qt, *J*<sub>1</sub> = 13.2 Hz, *J*<sub>2</sub> = 3.3 Hz, 1H), 1.44 (m, 2H), 1.25 (m, 1H) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 175.7, 139.0, 128.3 (2C), 127.4 (2C), 126.9, 93.8, 74.0, 65.8, 42.6, 33.6, 28.6, 27.5, 26.0, 19.7 ppm; HRMS (TOF ESI): calcd for C<sub>16</sub>H<sub>21</sub>NNaO<sub>3</sub>: 298.1414 [M + Na]<sup>+</sup>; found: 298.1410.

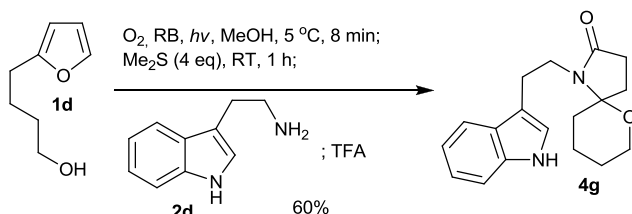
NOE



### 1-(3,4-dimethoxyphenethyl)-6-oxa-1-azaspiro[4.5]decan-2-one (**4f**)

The reaction was accomplished according to the general experimental described above, utilizing 4-(furan-2-yl)butan-1-ol **1d** (140 mg, 1.0 mmol) and 3,4-dimethoxyphenethylamine (**2c**, 163 mg, 0.9 mmol) followed by stirring at rt for 30 min. Finally, TFA (38 μL, 0.5 mmol) was added and the solution in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was stirred for 30 min at rt. After concentration of the solution, the product was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 2:1). Yield 68% (195 mg).

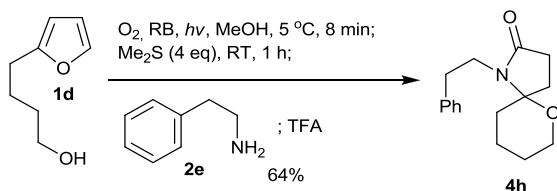
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 6.78 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.65 (m, 1H), 3.43 (m, 2H), 2.94 – 2.73 (m, 2H), 2.48 (m, 1H), 2.31 (m, 2H), 1.90 – 1.74 (m, 4H), 1.69 – 1.43 (m, 4H) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 175.3, 148.9, 147.5, 132.2, 120.7, 112.2, 111.3, 93.0, 64.1, 55.9 (2C), 41.5, 35.2, 33.7, 28.7, 26.9, 25.0, 20.4 ppm; HRMS (TOF ESI): calcd for  $\text{C}_{18}\text{H}_{25}\text{NNaO}_4$ : 342.1676  $[\text{M} + \text{Na}]^+$ ; found: 342.1674.



### 11b-(4-hydroxybutyl)-5,6,11,11b-tetrahydro-1H-indolizino[8,7-b]indol-3(2H)-one (**4g**)

The reaction was accomplished according to the general experimental described above, utilizing 4-(furan-2-yl)butan-1-ol **1d** (140 mg, 1.0 mmol) and tryptamine (**2d**, 144 mg, 0.9 mmol) followed by stirring at rt for 30 min. Finally, TFA (15  $\mu\text{L}$ , 0.2 mmol) was added and the solution in  $\text{CH}_2\text{Cl}_2$  (2 mL) was stirred for 30 min at rt. After neutralization with  $\text{Et}_3\text{N}$  (35  $\mu\text{L}$ , 0.25 mmol), the solution was concentrated and the product was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 1:1). Yield 60% (160 mg).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.14 (brs, 1H), 7.71 (d,  $J$  = 7.8 Hz, 1H), 7.35 (d,  $J$  = 8.0 Hz, 1H), 7.18 (dd,  $J_1$  = 8.0 Hz,  $J_2$  = 7.2 Hz, 1H), 7.12 (dd,  $J_1$  = 7.8 Hz,  $J_2$  = 7.2 Hz, 1H), 7.06 (s, 1H), 3.90 (m, 1H), 3.66 (td,  $J_1$  = 11.5 Hz,  $J_2$  = 3.7 Hz, 1H), 3.54 (dd,  $J_1$  = 8.7 Hz,  $J_2$  = 7.8 Hz, 2H), 3.12 (m, 1H), 3.02 (m, 1H), 2.51 (ddd,  $J_1$  = 17.3 Hz,  $J_2$  = 9.9 Hz,  $J_3$  = 7.3 Hz, 1H), 2.35 (m, 2H), 1.88 (m, 3H), 1.65 – 1.50 (m, 4H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 175.3, 136.2, 127.5, 121.9, 121.8, 119.2, 118.9, 113.7, 111.1, 93.1, 64.1, 40.4, 33.7, 28.8, 27.0, 25.3, 25.1, 20.4 ppm; HRMS (TOF ESI): calcd for  $\text{C}_{18}\text{H}_{22}\text{N}_2\text{NaO}_2$ : 321.1573  $[\text{M} + \text{Na}]^+$ ; found: 321.1576.



### 1-phenethyl-6-oxa-1-azaspiro[4.5]decan-2-one (**4h**)

The reaction was accomplished according to the general experimental described above, utilizing 4-(furan-2-yl)butan-1-ol **1d** (140 mg, 1.0 mmol) and phenethylamine (**2e**, 109 mg, 0.9 mmol) followed by stirring at rt for 30 min. Finally, TFA (38  $\mu\text{L}$ , 0.5 mmol) was added and the solution in  $\text{CH}_2\text{Cl}_2$  (2 mL) was stirred for 30 min at rt. After concentration

of the solution, the product was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 2:1). Yield 64% (149 mg).

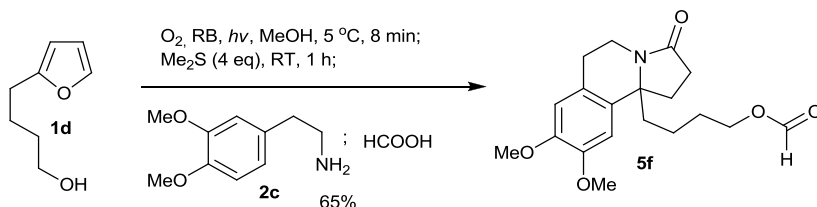
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.41 – 7.20 (m, 5H), 3.87 (m, 1H), 3.64 (m, 1H), 3.45 (m, 2H), 3.00 – 2.83 (m, 2H), 2.46 (m, 1H), 2.32 (m, 2H), 1.90 – 1.74 (m, 3H), 1.69 – 1.43 (m, 4H) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 175.2, 139.6, 128.9 (2C), 128.4 (2C), 126.2, 93.0, 64.1, 41.3, 35.6, 33.7, 28.7, 26.9, 25.1, 20.4 ppm; HRMS (TOF ESI): calcd for  $\text{C}_{16}\text{H}_{22}\text{NO}_2$ : 260.1645  $[\text{M} + \text{H}]^+$ ; found: 260.1642.

### General procedure for the preparation of fused bicyclic lactams **5f**, **5g** and **5h**.

Furan **1d** (1.0 mmol) was dissolved in methanol (6 mL) containing catalytic amounts of rose Bengal ( $10^{-4}$  M) as photosensitizer. The solutions were cooled with an ice bath. Oxygen was gently bubbled through the solutions while they were irradiated with a xenon Variac Eimac Cermax 300 W lamp. After completion of the reaction (usually 8 min) as indicated by TLC, it was warmed to rt and  $\text{Me}_2\text{S}$  (292  $\mu\text{L}$ , 4.0 mmol) was added for the reduction of hydroperoxy group (usually 1 h). This was followed by the addition of the corresponding amine (0.9 mmol) and stirring for 30 min at the same temperature in order to form the intermediate 2-pyrrolidinone (**B**, Scheme 1). Methanol was then replaced by either dichloromethane (4 mL) followed by addition of *p*-TsOH, or HCOOH as solvent.

In the case of compound **5h**, after the formation of the intermediate 2-pyrrolidinone of type **B** a solution of HCl (0.1 N) was added followed by extraction with  $\text{CH}_2\text{Cl}_2$ , separation of the layers, drying of the combined organic layers with  $\text{Na}_2\text{SO}_4$  and concentration *in vacuo*. Afterwards,  $\text{TiCl}_4$  was added in dry  $\text{CH}_2\text{Cl}_2$ .

After completion of the final acid-catalyzed step of these sequences, as indicated by TLC, the mixture was concentrated *in vacuo* (when *p*-TsOH, or HCOOH were used), or quenched by a saturated aq. solution of  $\text{Na}_2\text{CO}_3$  (when  $\text{TiCl}_4$  was used). After separation of the phases, the aqueous phase was twice re-extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic phases were dried with  $\text{Na}_2\text{SO}_4$ , filtered, and the solvent was removed under reduced pressure. The residues were purified by flash column chromatography (silica gel, petroleum ether:EtOAc).

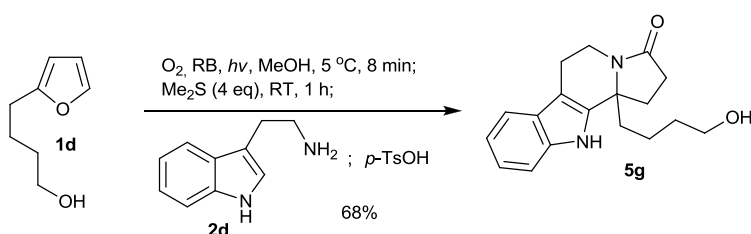


### 4-(8,9-dimethoxy-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-10b-yl)butyl formate (**5f**)

The reaction was accomplished according to the general experimental described above, utilizing 4-(furan-2-yl)butan-1-ol **1d** (140 mg, 1.0 mmol) and 3,4-

dimethoxyphenethylamine (**2c**, 163 mg, 0.9 mmol), followed by stirring at rt for 30 min. Finally, methanol was replaced by HCOOH (2 mL) and the solution was refluxed for 2 h. After concentration of the solution, the product was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 1:1). Yield 65% (203 mg).

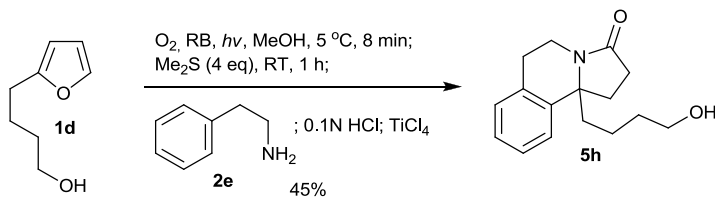
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 8.03 (s, 1H), 6.56 (s, 1H), 6.54 (s, 1H), 4.32 (ddd, *J*<sub>1</sub> = 13.0 Hz, *J*<sub>2</sub> = 6.5 Hz, *J*<sub>3</sub> = 1.6 Hz, 1H), 4.14 (t, *J* = 6.3 Hz), 3.86 (s, 3H), 3.84 (s, 3H), 3.06 (td, *J*<sub>1</sub> = 12.2 Hz, *J*<sub>2</sub> = 5.0 Hz, 1H), 2.89 (ddd, *J*<sub>1</sub> = 15.7 Hz, *J*<sub>2</sub> = 12.2 Hz, *J*<sub>3</sub> = 6.5 Hz, 1H), 2.61 (m, 2H), 2.41 (m, 2H), 2.15 (m, 1H), 1.86 (m, 2H), 1.64 (m, 2H), 1.51 – 1.25 (m, 2H) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 173.2, 161.0, 148.0, 147.9, 134.6, 124.6, 111.6, 108.0, 63.6, 63.3, 56.2, 55.9, 41.5, 34.6, 32.1, 31.2, 28.6, 27.7, 20.6 ppm; HRMS (TOF ESI): calcd for C<sub>38</sub>H<sub>51</sub>N<sub>2</sub>O<sub>10</sub>: 695.3544 [2M + H]<sup>+</sup>; found: 695.3537.



### **11b-(4-hydroxybutyl)-5,6,11,11b-tetrahydro-1H-indolizino[8,7-b]indol-3(2H)-one (5g)**

The reaction was accomplished according to the general experimental described above, utilizing 4-(furan-2-yl)butan-1-ol **1d** (140 mg, 1.0 mmol) and tryptamine (**2d**, 144 mg, 0.9 mmol), followed by stirring at rt for 30 min. Finally, *p*-TsOH (76 mg, 0.4 mmol) was added in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and the mixture was stirred for 30 min at rt. After concentration of the solution, the residue was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 1:1). Yield 68% (182 mg).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 8.70 (s, 1H), 7.46 (d, *J* = 7.4 Hz, 1H), 7.33 (d, *J* = 7.4 Hz, 1H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 4.47 (dd, *J*<sub>1</sub> = 12.8 Hz, *J*<sub>2</sub> = 6.2 Hz, 1H), 3.62 (m, 2H), 3.13 (td, *J*<sub>1</sub> = 12.8 Hz, *J*<sub>2</sub> = 5.0 Hz, 1H), 2.84 (ddd, *J*<sub>1</sub> = 15.3 Hz, *J*<sub>2</sub> = 11.5 Hz, *J*<sub>3</sub> = 6.2 Hz, 1H), 2.76 (dd, *J*<sub>1</sub> = 15.3 Hz, *J*<sub>2</sub> = 5.0 Hz, 1H), 2.64 (m, 2H), 2.39 (m, 2H), 2.16 (q, *J* = 10.3 Hz, 1H), 2.02 – 1.86 (m, 2H), 1.49 (m, 4H) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 173.8, 137.3, 136.1, 126.6, 122.0, 119.7, 118.4, 111.0, 106.8, 62.7, 62.2, 39.6, 35.7, 32.6, 31.1, 30.4, 21.0, 20.7 ppm; HRMS (TOF ESI): calcd for C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>NaO<sub>2</sub>: 321.1573 [M + Na]<sup>+</sup>; found: 321.1575.



### 10b-(4-hydroxybutyl)-1,2,5,6-tetrahydropyrrolo[2,1-a]isoquinolin-3(10bH)-one (5h)

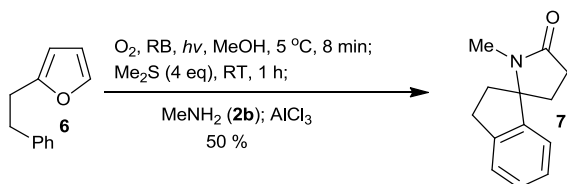
The reaction was accomplished according to the general experimental described above, utilizing 4-(furan-2-yl)butan-1-ol **1d** (140 mg, 1.0 mmol) and phenethylamine (**2e**, 109 mg, 0.9 mmol), followed by stirring at rt for 30 min. After concentration of the solution, HCl (0.1 N, 5 mL) was added followed by extraction with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 5$  mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and the solvent was removed *in vacuo*. The residue was then dissolved in dry  $\text{CH}_2\text{Cl}_2$  (4 mL) and cooled to -10 °C. Addition of  $\text{TiCl}_4$  (330  $\mu\text{L}$ , 3.0 mmol) followed and the reaction was warmed to rt and stirred for 12 h. After completion of the reaction, a saturated aq. solution of  $\text{Na}_2\text{CO}_3$  (4 mL) was added. After separation of the layers, the aqueous phase was re-extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 5$  mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and the solvent was removed *in vacuo*. The product was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 1:1). Yield 45% (105 mg).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.23 – 7.08 (m, 4H), 4.31 (m, 1H), 3.62 (t,  $J$  = 6.2 Hz, 2H), 3.12 (td,  $J_1$  = 12.0 Hz,  $J_2$  = 4.3 Hz, 1H), 2.97 (ddd,  $J_1$  = 16.0 Hz,  $J_2$  = 12.0 Hz,  $J_3$  = 6.4 Hz, 1H), 2.77 (dd,  $J_1$  = 16.0 Hz,  $J_2$  = 4.3 Hz, 1H), 2.62 (m, 1H), 2.52 – 2.37 (m, 2H), 2.18 (m, 1H), 1.92 – 1.80 (m, 3H), 1.58 – 1.25 (m, 4H) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 173.3, 142.9, 132.4, 129.2, 126.7 (2C), 125.0, 64.1, 62.4, 41.9, 34.6, 32.7, 32.0, 31.3, 28.1, 20.5 ppm; HRMS (TOF ESI): calcd for  $\text{C}_{16}\text{H}_{22}\text{NO}_2$ : 260.1645 [ $\text{M} + \text{H}$ ] $^+$ ; found: 260.1646.

### General procedure for the preparation of 1-azaspirocycles 7, 9, 10 and 12.

2-Substituted furans **6**, **8** or **11** (1.0 mmol) were dissolved in methanol (6 mL) containing catalytic amounts of rose Bengal ( $10^{-4}$  M) as photosensitizer. The solutions were cooled with an ice bath. Oxygen was gently bubbled through the solutions while they were irradiated with a xenon Variac Eimac Cermac 300 W lamp. After completion of the reaction (usually 8 min) the reaction was warmed to rt and  $\text{Me}_2\text{S}$  (292  $\mu\text{L}$ , 4.0 mmol) was added for the reduction of hydroperoxy group (usually 1.0 h), as indicated by TLC. Methylamine, or benzylamine, was then added (0.9 mmol) and the solution was stirred for 30 min at rt. After complete formation of the intermediate 2-pyrrolidinone (**B**), as indicated by TLC, methanol was replaced by either dichloromethane (4 mL) followed by addition of a Lewis acid ( $\text{AlCl}_3$ ,  $\text{SnCl}_2$ , or  $\text{FeCl}_3$ ), or by HCOOH as solvent. After completion of the reaction, indicated by TLC, the mixture was concentrated (when HCOOH was used), or quenched by an aq. saturated solution of  $\text{Na}_2\text{CO}_3$  (when  $\text{AlCl}_3$ ,  $\text{SnCl}_2$  or  $\text{FeCl}_3$  were used). After separation of the organic phase, the aqueous phase was extracted twice with  $\text{CH}_2\text{Cl}_2$  (5 mL). The combined organic phases were dried with

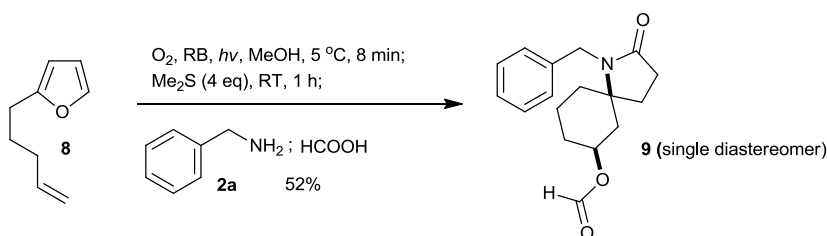
Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The residues were purified by flash column chromatography (silica gel, petroleum ether:EtOAc).



### 1'-methyl-2,3-dihydrospiro[indene-1,2'-pyrrolidin]-5'-one (**7**)<sup>3</sup>

The reaction was accomplished according to the general experimental described above, utilizing 2-phenethyl furan **6** (172 mg, 1.0 mmol) and methylamine (**2b**, 70 μL, 40% w/v in H<sub>2</sub>O, 0.9 mmol), followed by stirring at rt for 30 min. Finally, AlCl<sub>3</sub> (400 mg, 3.0 mmol) was added at 0 °C and the solution in dry CH<sub>2</sub>Cl<sub>2</sub> (4 mL) was stirred for 12 h at rt. After completion of the reaction, a saturated aq. solution of Na<sub>2</sub>CO<sub>3</sub> (4 mL) was added and after separation of the layers, the aqueous phase was re-extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 5 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent was removed *in vacuo*. The product was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 2:1). Yield 50% (104 mg).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 7.27 (m, 3H), 7.09 (m, 1H), 2.96 (m, 2H), 2.60 (s, 3H), 2.54 (dd, *J*<sub>1</sub> = 9.2 Hz, *J*<sub>2</sub> = 6.2 Hz, 2H), 2.24 (m, 2H), 2.09 (m, 2H) ppm; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 174.9, 144.3, 142.7, 128.4, 127.3, 125.1, 122.8, 74.3, 35.0, 33.9, 30.2, 29.4, 25.4 ppm; HRMS (TOF ESI): calcd for C<sub>13</sub>H<sub>15</sub>NNaO: 224.1046 [M + Na]<sup>+</sup>; found: 224.1055.



### 1-benzyl-2-oxo-1-azaspiro[4.5]decan-7-yl formate (**9**)

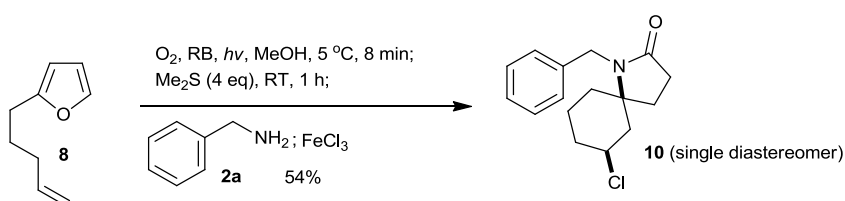
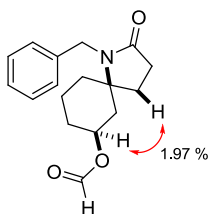
The reaction was accomplished according to the general experimental described above, utilizing 2-(pent-4-enyl)furan **8** (136 mg, 1.0 mmol) and benzylamine (**2a**, 98 μL, 0.9 mmol) followed by stirring at rt for 30 min. Finally, methanol was replaced with HCOOH (2 mL) and the mixture was refluxed for 12 h. After concentration of the solution, the residue was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 2:1). Yield 52% (134 mg).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 7.95 (s, 1H), 7.30 – 7.23 (m, 5H), 4.90 (m, 1H), 4.48 (d, *J* = 15.6 Hz, 1H), 4.40 (d, *J* = 15.6 Hz, 1H), 2.50 (m, 2H), 2.03 – 1.92 (m, 3H), 1.76 (m,

<sup>3</sup> P. D. Bailey, K. M. Morgan, D. I. Smith, J. M. Vernon, *Tetrahedron* 2003, **59**, 3369.

3H), 1.59 (t,  $J = 11.8$  Hz, 1H), 1.48 – 1.36 (m, 2H), 1.20 (m, 1H) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 174.8, 160.3, 138.6, 128.5$  (2C), 127.2 (2C), 127.1, 69.9, 64.4, 42.7, 40.4, 34.1, 30.6, 29.8, 29.1, 19.7 ppm; HRMS (TOF ESI): calcd for  $\text{C}_{17}\text{H}_{21}\text{NNaO}_3$ : 310.1414  $[\text{M} + \text{Na}]^+$ ; found: 310.1415.

NOE

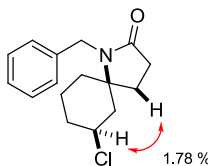


### 1-benzyl-7-chloro-1-azaspiro[4.5]decan-2-one (10)

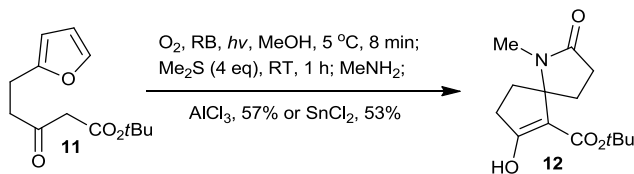
The reaction was accomplished according to the general experimental described above, utilizing 2-(pent-4-enyl)furan **8** (136 mg, 1.0 mmol) and benzylamine (**2a**, 98  $\mu\text{L}$ , 0.9 mmol) followed by stirring at rt for 30 min. Finally,  $\text{FeCl}_3$  (324 mg, 2.0 mmol) was added at 0 °C and the solution in dry  $\text{CH}_2\text{Cl}_2$  (4 mL) was stirred for 12 h at rt. After completion of the reaction, a saturated aq. solution of  $\text{Na}_2\text{CO}_3$  (4 mL) was added and after separation of the layers, the aqueous phase was re-extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 5$  mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and the solvent was removed *in vacuo*. The product was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 2:1). Yield 54% (134 mg).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.27$  (m, 5H), 4.57 (d,  $J = 15.8$  Hz, 1H), 4.33 (d,  $J = 15.8$  Hz, 1H), 3.87 (m, 1H), 2.49 (t,  $J = 8.2$  Hz, 2H), 2.17 (m, 1H), 1.96 – 1.86 (m, 3H), 1.81 (t,  $J = 12.2$  Hz, 1H), 1.75 (m, 1H), 1.39 (m, 4H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta = 174.7, 138.5, 128.5$  (2C), 127.2 (2C), 127.1, 64.8, 55.5, 45.3, 42.7, 35.9, 34.1, 29.6, 29.0, 21.6 ppm; HRMS (TOF ESI): calcd for  $\text{C}_{16}\text{H}_{20}\text{ClNNaO}$ : 300.1131  $[\text{M} + \text{Na}]^+$ ; found: 300.1127.

NOE







### ***tert*-butyl 7-hydroxy-1-methyl-2-oxo-1-azaspiro[4.4]non-6-ene-6-carboxylate (**12**)**

The reaction was accomplished according to the general experimental described above, utilizing *tert*-butyl 5-(furan-2-yl)-3-oxopentanoate **11** (238 mg, 1.0 mmol) and methylamine (**2b**, 70  $\mu$ L, 40% w/v in H<sub>2</sub>O, 0.9 mmol), followed by stirring at rt for 30 min. Finally, AlCl<sub>3</sub> (266 mg, 2.0 mmol) was added at 0 °C and the solution in dry CH<sub>2</sub>Cl<sub>2</sub> (4 mL) was stirred for 1 h. After completion of the reaction, a saturated aq. solution of Na<sub>2</sub>CO<sub>3</sub> (4 mL) was added and after separation of the layers, the aqueous phase was re-extracted with CH<sub>2</sub>Cl<sub>2</sub> (2  $\times$  5 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent was removed *in vacuo*. The product was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 2:1). Yield 57% (137 mg).

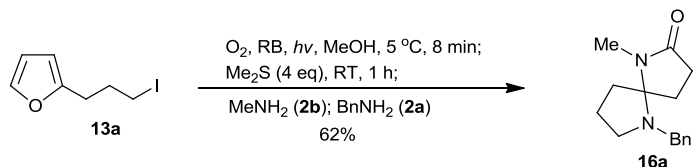
Alternatively, SnCl<sub>2</sub> (665 mg, 3.5 mmol) could be added, instead of AlCl<sub>3</sub>, at rt and the solution in dry CH<sub>2</sub>Cl<sub>2</sub> (4 mL) was stirred for 5 h. After completion of the reaction, water (4 mL) was added and after separation of the layers, the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed *in vacuo*. Yield 53% (127 mg).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 11.11 (s, 1H), 2.60 (s, 3H), 2.54 (m, 2H), 2.44 (m, 2H), 2.29 (ddd,  $J_1$  = 13.0 Hz,  $J_2$  = 10.4 Hz,  $J_3$  = 7.4 Hz, 1H), 2.03 – 1.91 (m, 3H), 1.46 (s, 9H) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 177.8, 174.0, 168.7, 103.7, 82.2, 71.9, 33.0, 32.3, 30.1, 29.9, 28.3 (3C), 24.9 ppm; HRMS (TOF ESI): calcd for C<sub>14</sub>H<sub>21</sub>NNaO<sub>4</sub>: 290.1363 [M + Na]<sup>+</sup>; found: 290.1368.

### **General procedure for the preparation of 1,6-diazaspirocycles 16a and 16b**

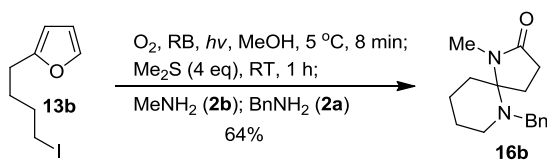
2-Substituted furans **13a** or **13b** (1.0 mmol) were dissolved in methanol (6 mL) containing catalytic amounts of rose Bengal (10<sup>-4</sup> M) as photosensitizer. The solutions were cooled with an ice bath. Oxygen was gently bubbled through the solutions while they were irradiated with a xenon Variac Eimac Cermax 300 W lamp. After completion of the reaction (usually 8 min) it was warmed to rt and Me<sub>2</sub>S (292  $\mu$ L, 4.0 mmol) was added followed by stirring for 1h. Methylamine was then added (1.0 mmol) and the mixture was stirred for 30 min at rt. After the formation of the intermediate 2-pyrrolidinone (**B**), methanol was replaced by chloroform (4 mL) followed by addition of benzylamine (1.5 mmol) and the solution was stirred under reflux for 8 h. The reaction solution was concentrated under reduced pressure and the residues were purified by flash column chromatography (silica gel, petroleum ether:EtOAc).





### 6-benzyl-1-methyl-1,6-diazaspiro[4.4]nonan-2-one (**16a**)

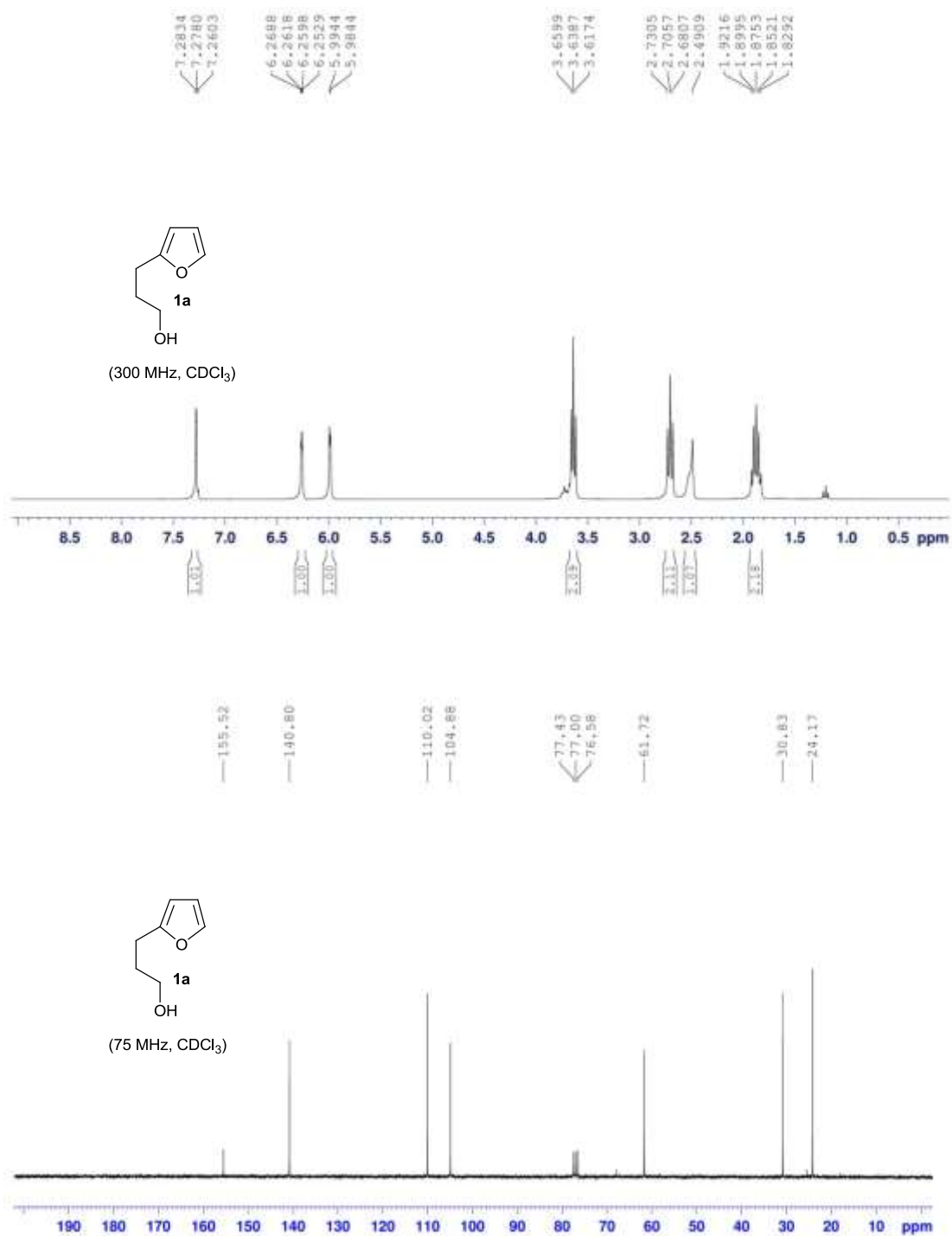
The reaction was accomplished according to the general experimental described above, utilizing 2-(3-iodopropyl)furan **13a** (236 mg, 1.0 mmol) and methylamine (**2b**, 78  $\mu\text{L}$ , 40% w/v in  $\text{H}_2\text{O}$ , 1.0 mmol) followed by stirring at rt for 30 min. Finally, methanol was replaced by  $\text{CHCl}_3$  (4 mL), benzylamine (**2a**, 142  $\mu\text{L}$ , 1.3 mmol) was added and the solution was refluxed for 8 h. After concentration, the residue was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 2:1). Yield 62% (151 mg).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.31 – 7.22 (m, 5H), 3.62 (d,  $J$  = 13.3 Hz, 1H), 3.35 (d,  $J$  = 13.3 Hz, 1H), 2.94 (m, 1H), 2.83 (s, 3H), 2.52 – 2.40 (m, 3H), 2.21 (m, 1H), 2.13 (m, 1H), 1.87 – 1.78 (m, 4H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 174.2, 139.1, 128.3 (2C), 128.0 (2C), 126.9, 86.1, 51.1, 49.2, 35.3, 29.9, 26.2, 24.8, 20.1 ppm; HRMS (TOF ESI): calcd for  $\text{C}_{15}\text{H}_{20}\text{N}_2\text{NaO}$ : 267.1474 [ $\text{M} + \text{Na}$ ] $^+$ ; found: 267.1484.

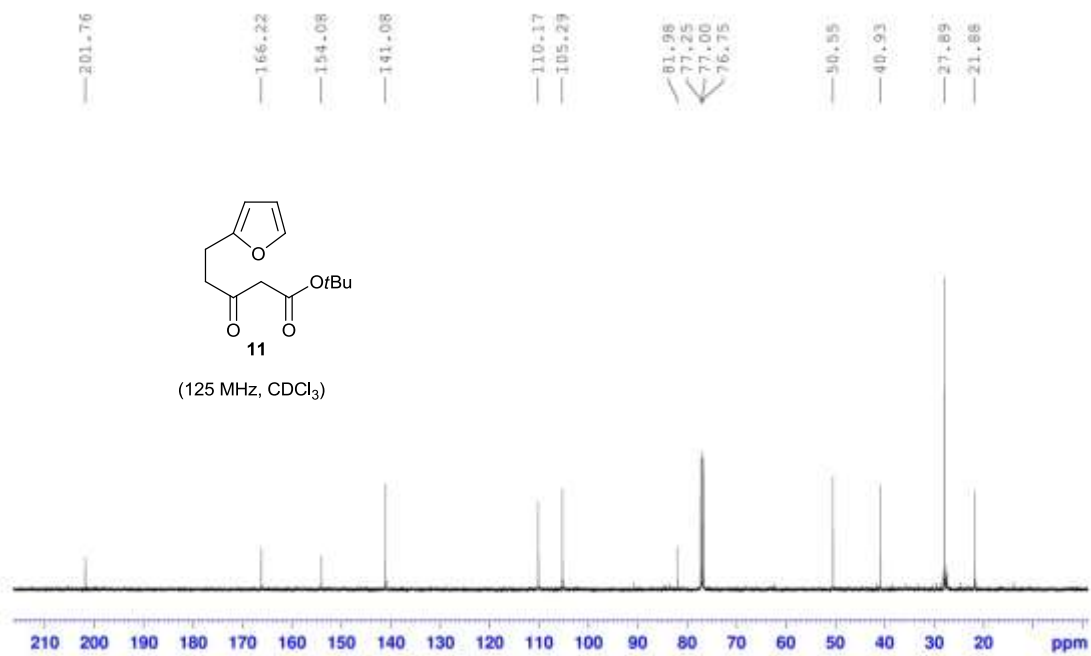
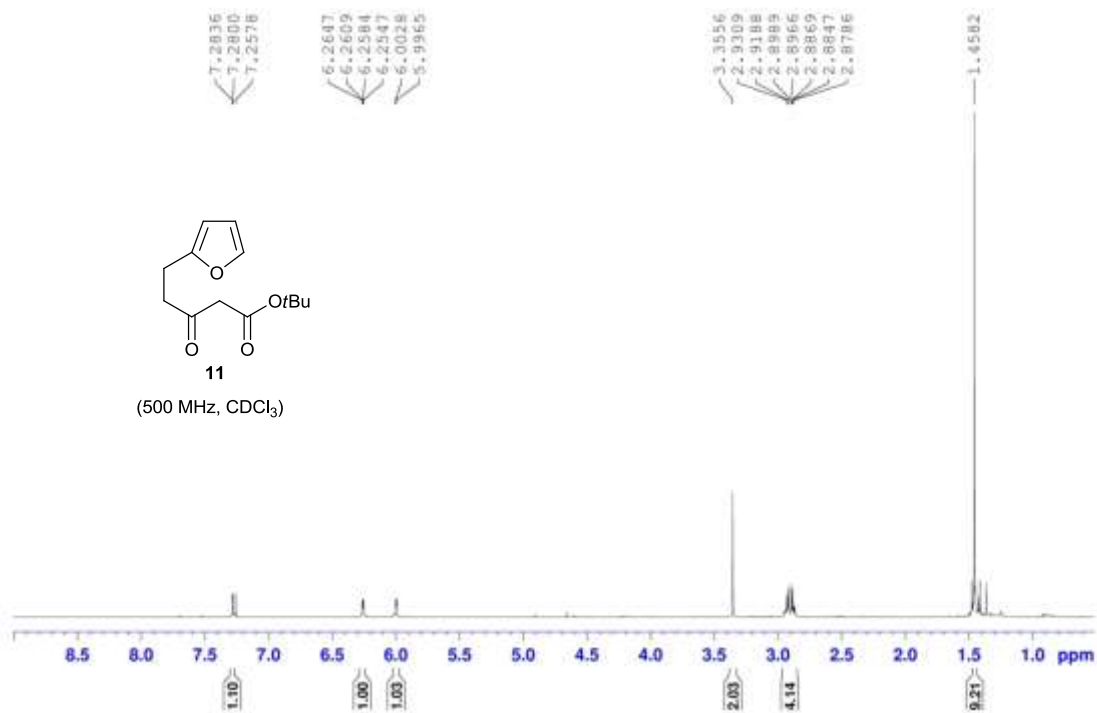


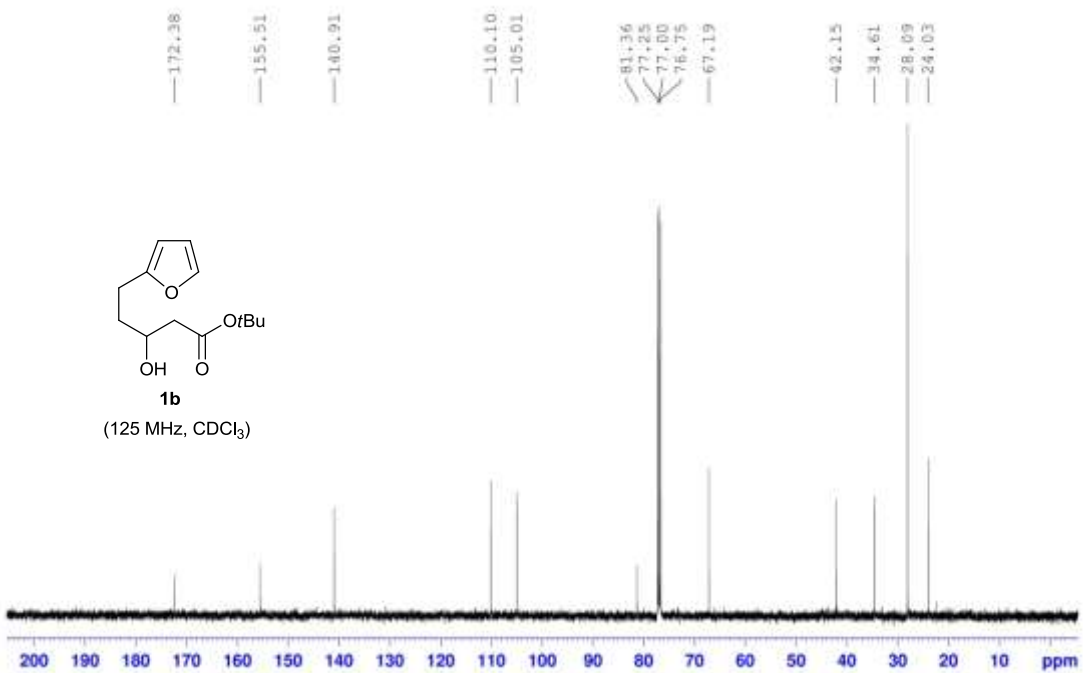
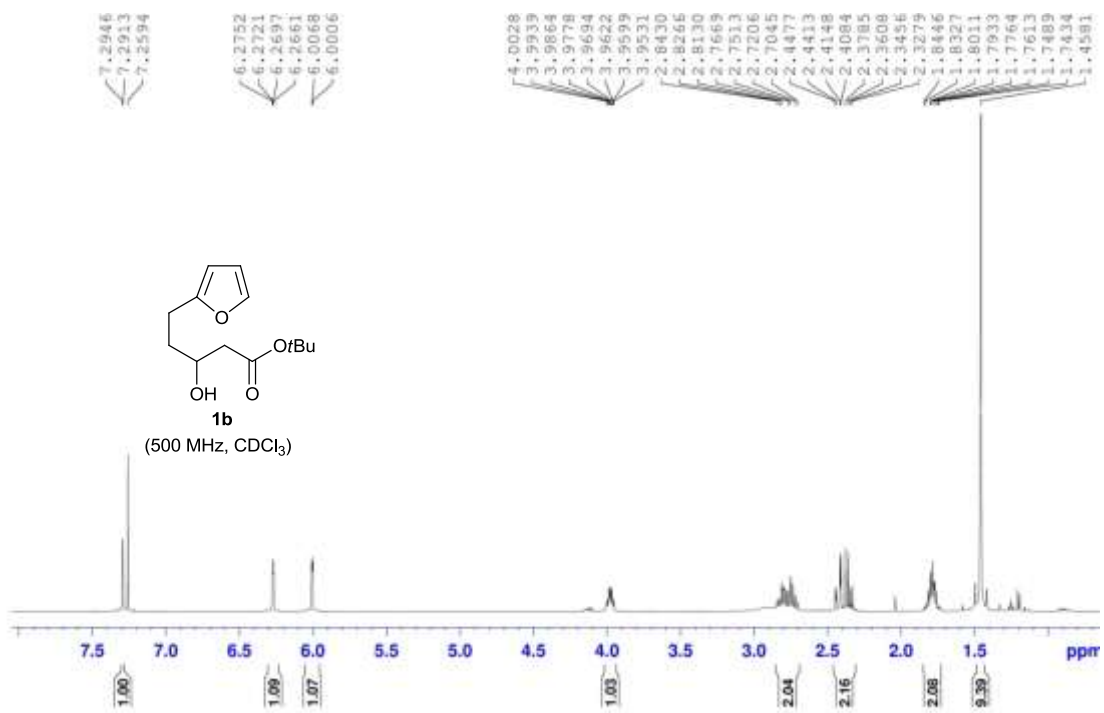
### 6-benzyl-1-methyl-1,6-diazaspiro[4.5]decan-2-one (**16b**)

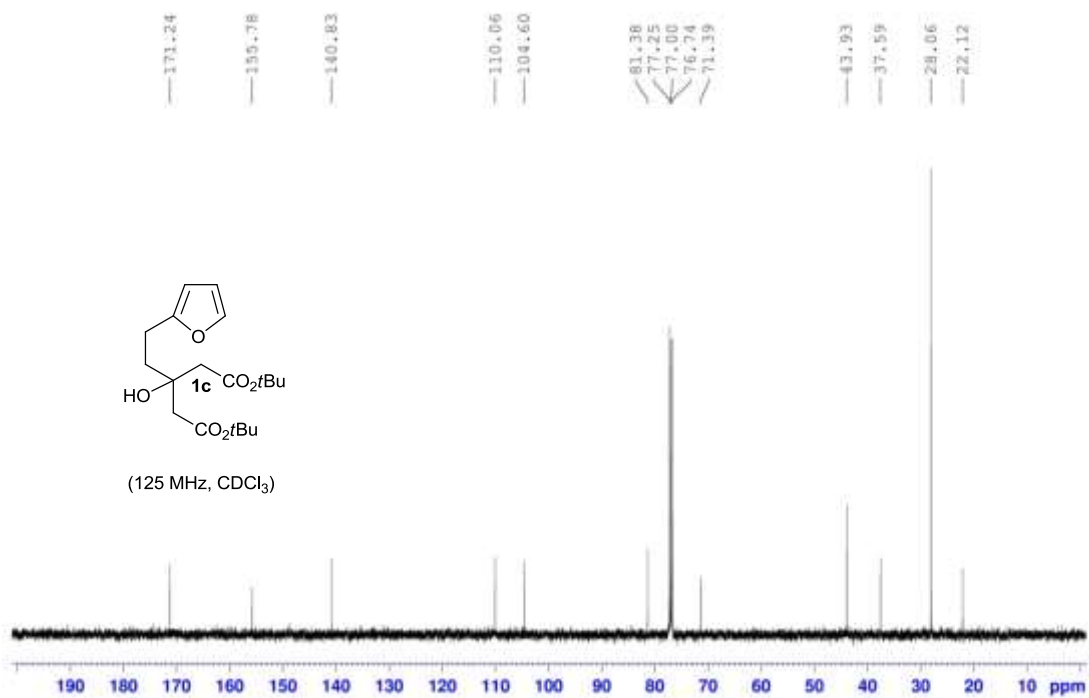
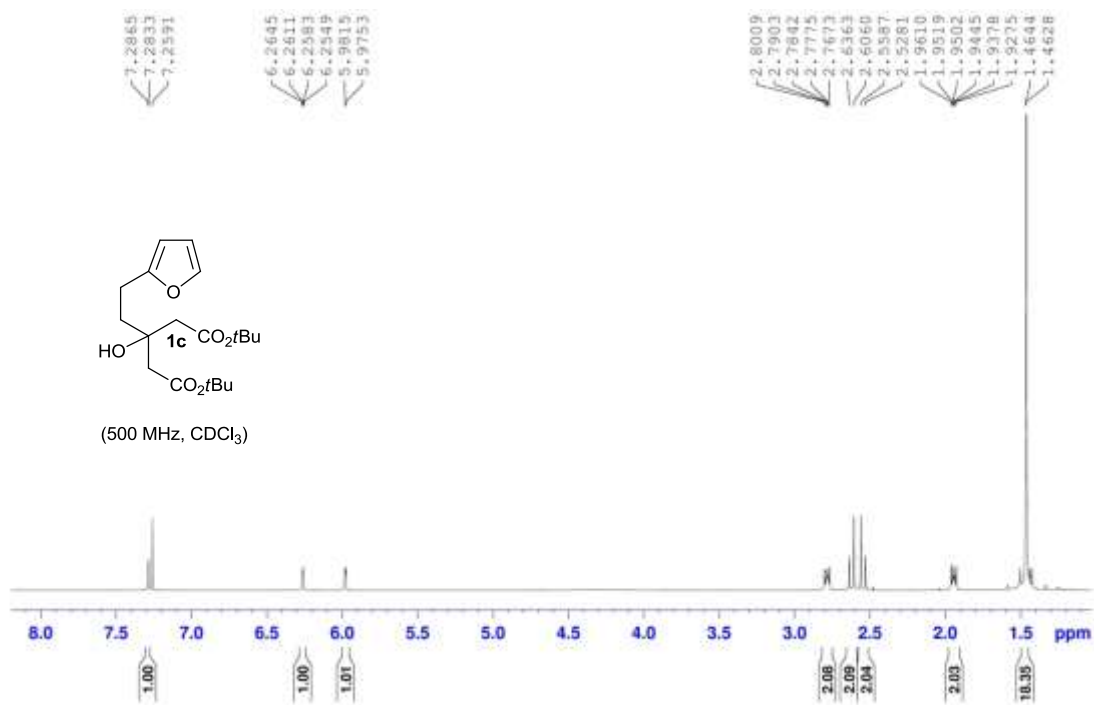
The reaction was accomplished according to the general experimental described above, utilizing 2-(4-iodopropyl)furan **13b** (250 mg, 1.0 mmol) and methylamine (**2b**, 78  $\mu\text{L}$ , 40% w/v in  $\text{H}_2\text{O}$ , 1.0 mmol) followed by stirring at rt for 30 min. Finally, methanol was replaced by  $\text{CHCl}_3$  (4 mL), benzylamine (**2a**, 142  $\mu\text{L}$ , 1.3 mmol) was added and the solution was refluxed for 8 h. After concentration, the residue was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 2:1). Yield 64% (165 mg).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.30 – 7.22 (m, 5H), 3.70 (d,  $J$  = 13.7 Hz, 1H), 2.90 (d,  $J$  = 13.7 Hz, 1H), 2.84 (s, 3H), 2.73 (brd,  $J$  = 12.5 Hz, 1H), 2.43 (t,  $J$  = 8.2 Hz, 2H), 2.16 (m, 2H), 2.13 (m, 1H), 1.91 – 1.78 (m, 3H), 1.54 – 1.42 (m, 4H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 174.3, 139.0, 128.4 (2C), 128.1 (2C), 126.8, 81.0, 52.4, 47.7, 35.4, 29.8, 25.5, 24.8, 21.7, 20.5 ppm; HRMS (TOF ESI): calcd for  $\text{C}_{16}\text{H}_{23}\text{N}_2\text{O}$ : 259.1810 [ $\text{M} + \text{H}$ ] $^+$ ; found: 259.1805.

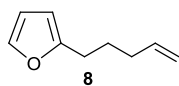
### Part B: Copies of $^1\text{H-NMR}$ $^{13}\text{C-NMR}$ and NOE spectra



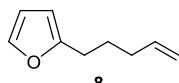
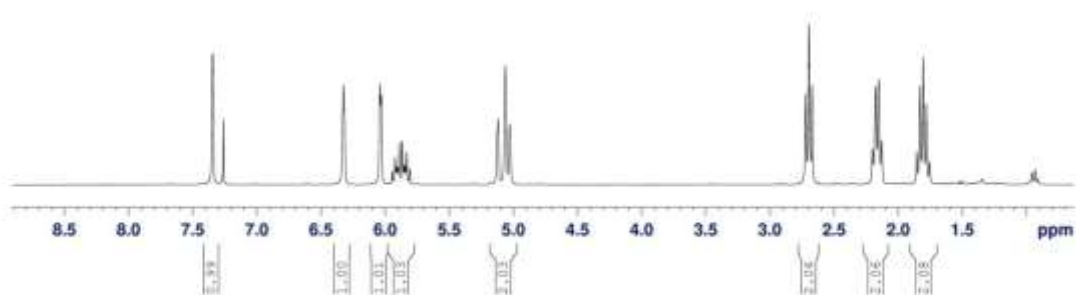




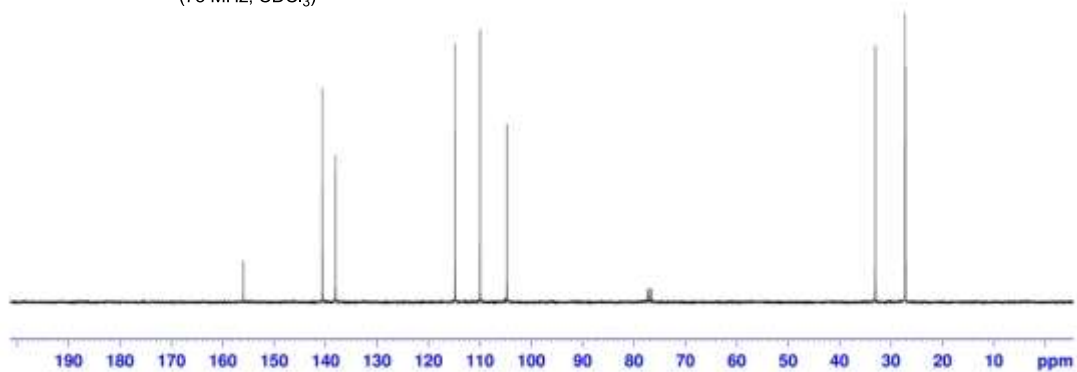


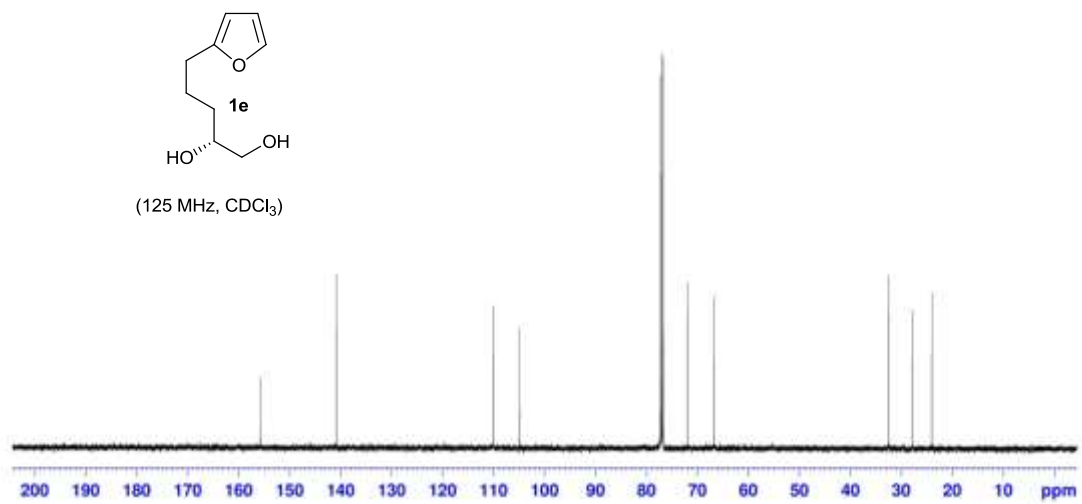
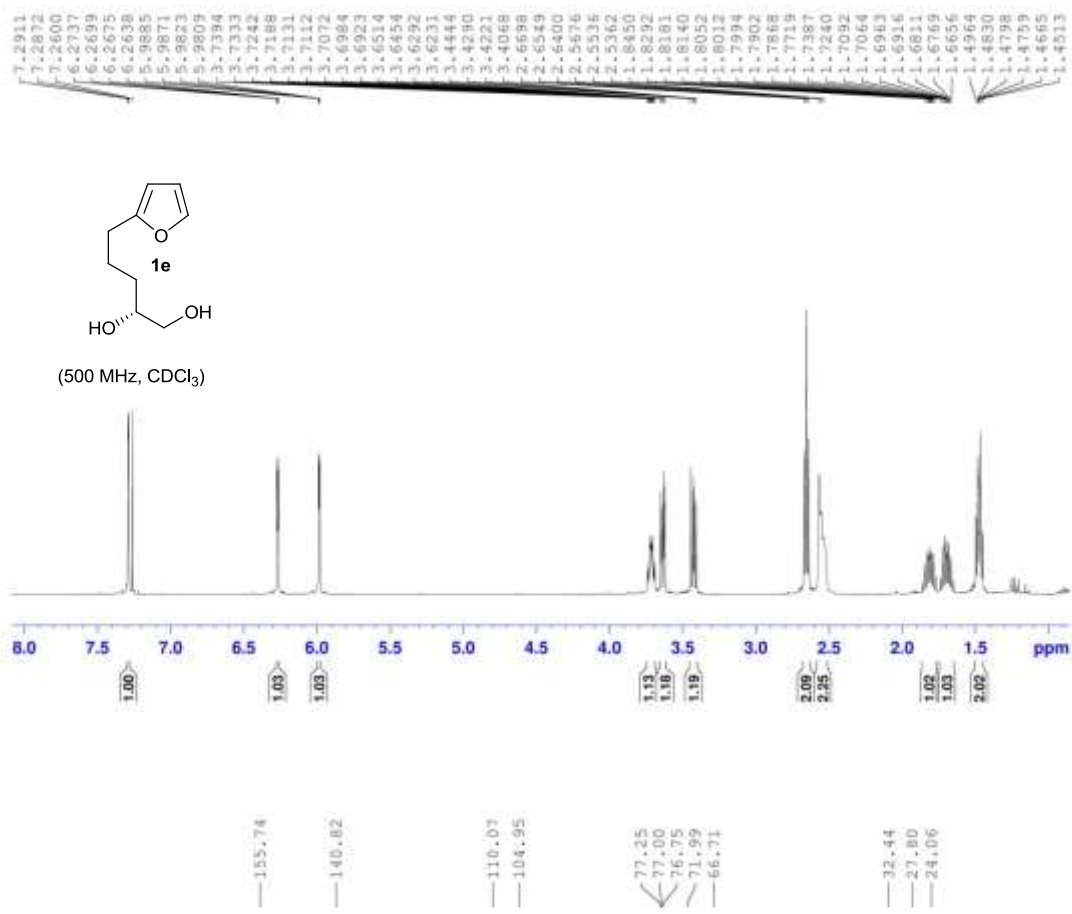


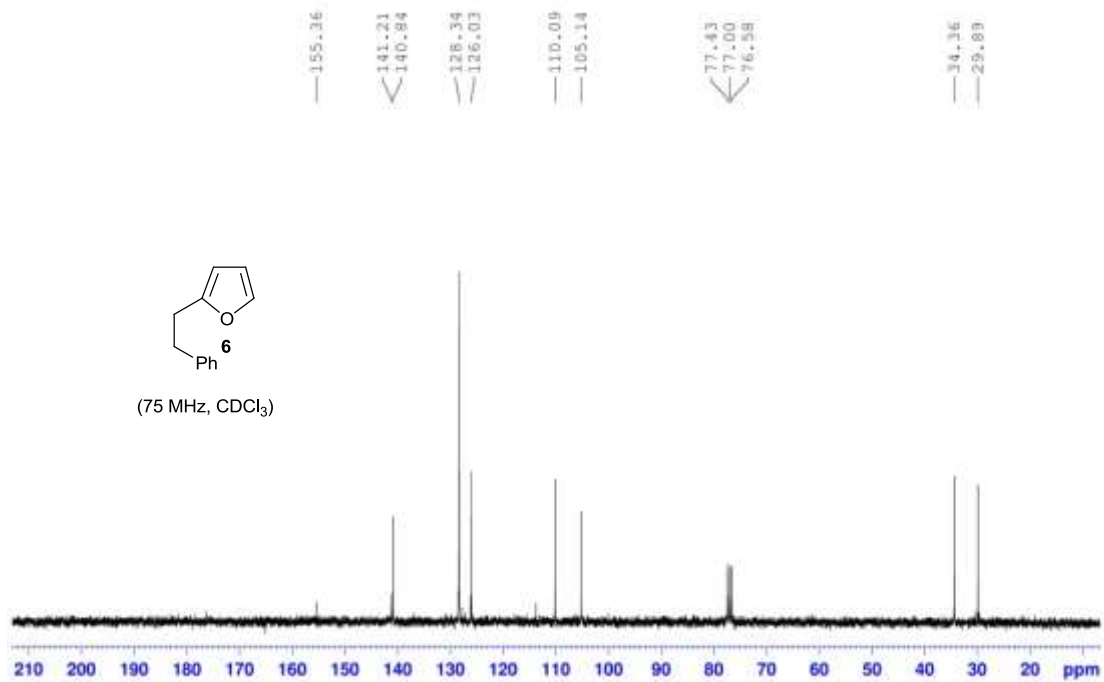
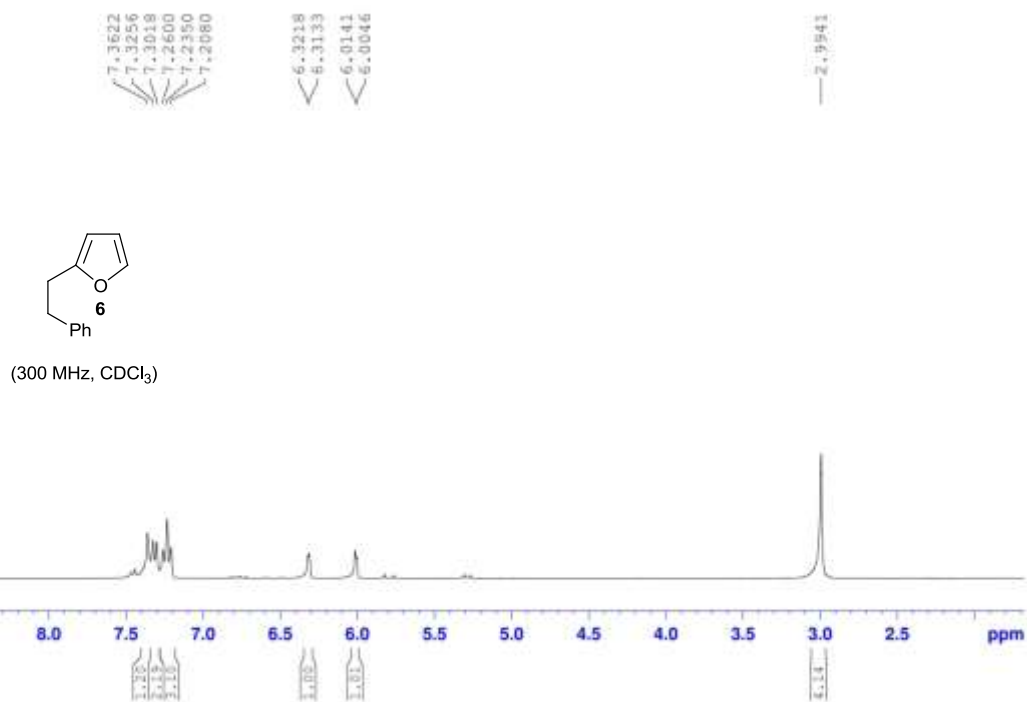
(300 MHz, CDCl<sub>3</sub>)



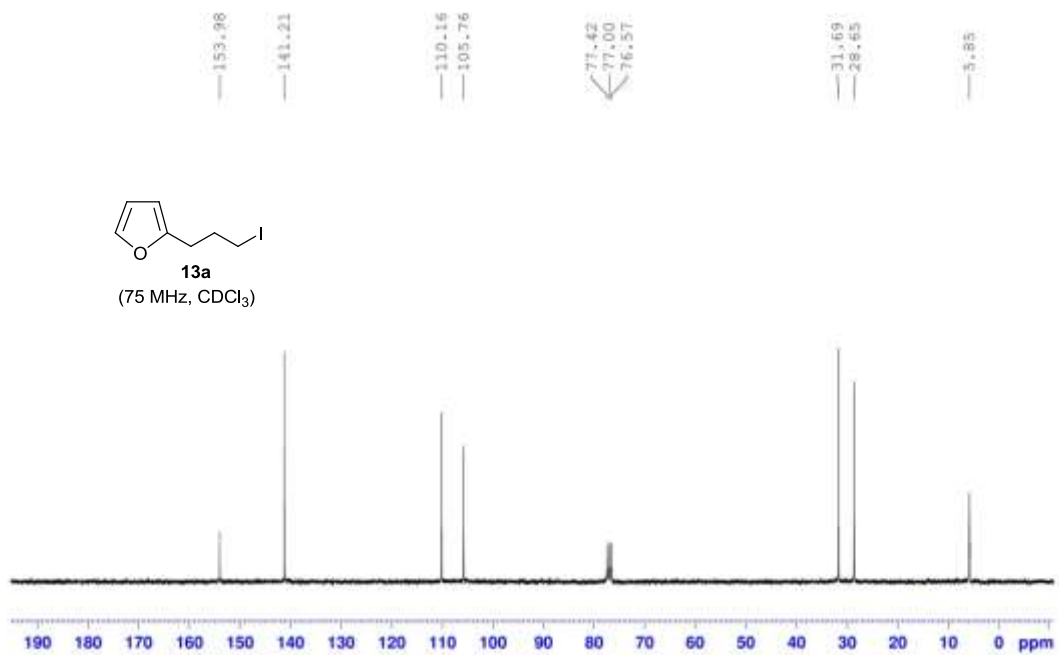
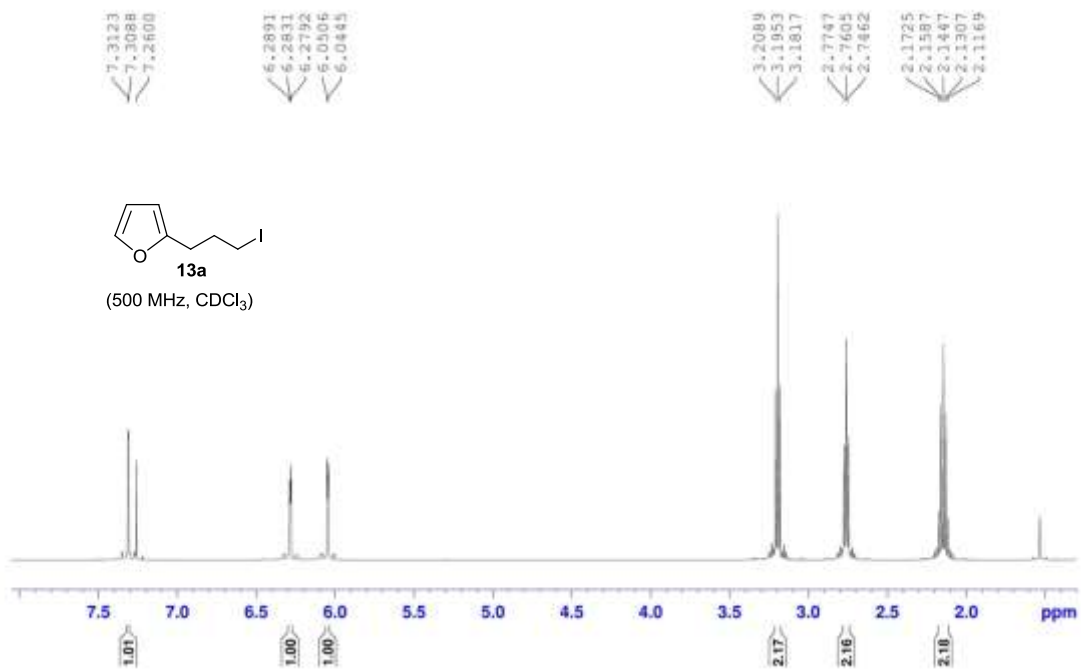
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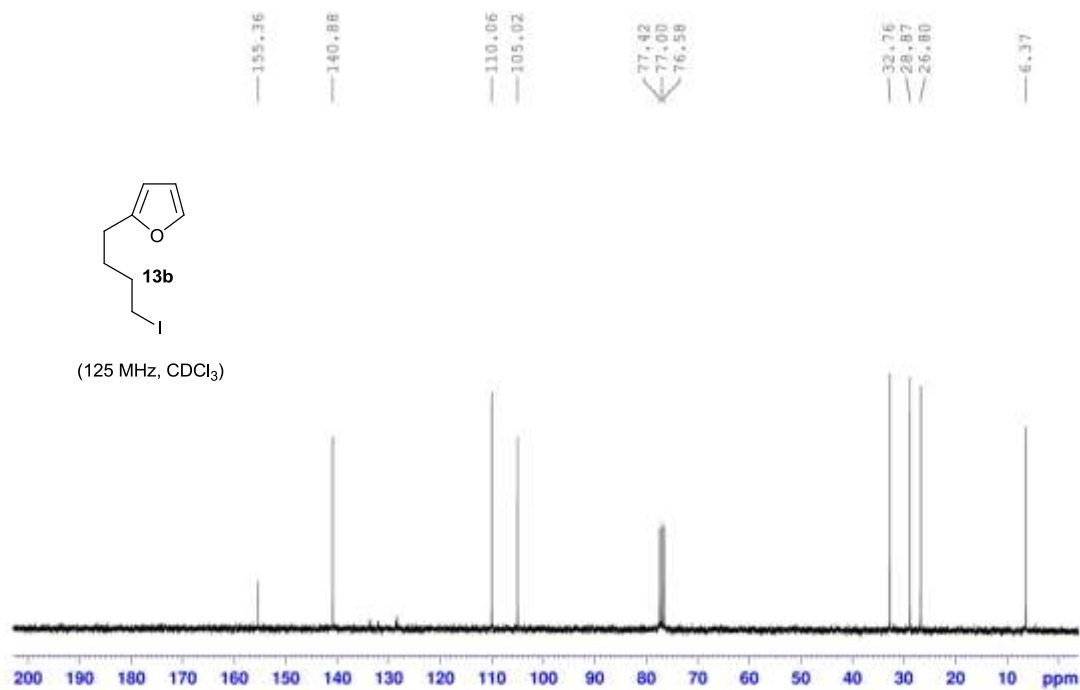
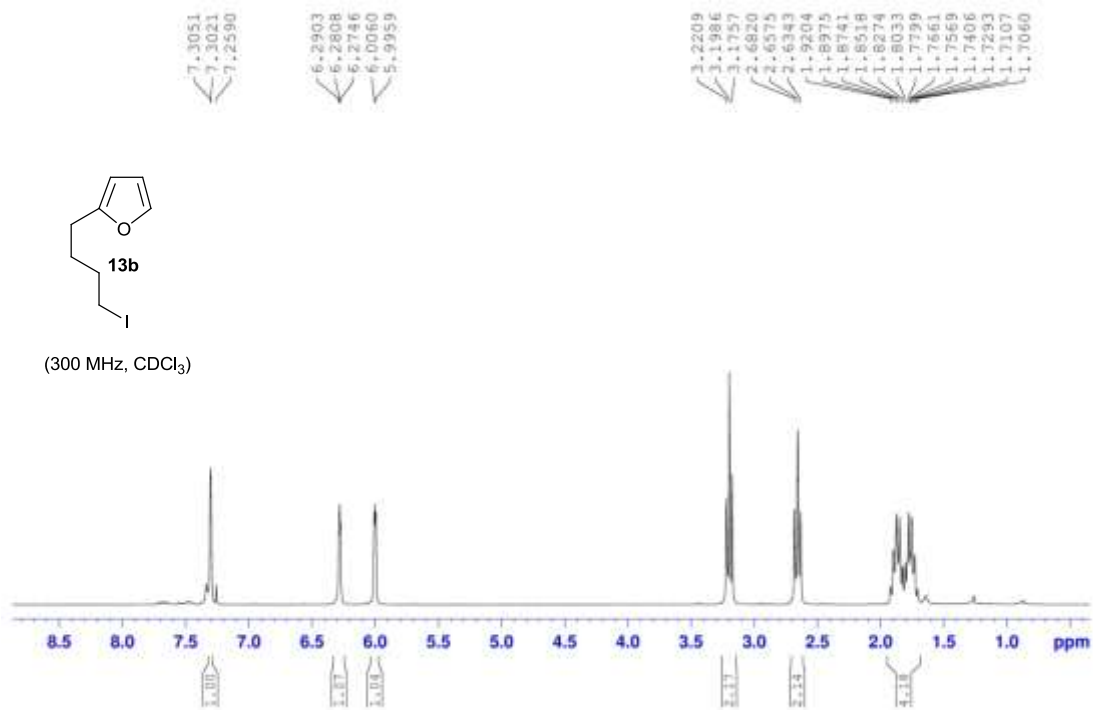


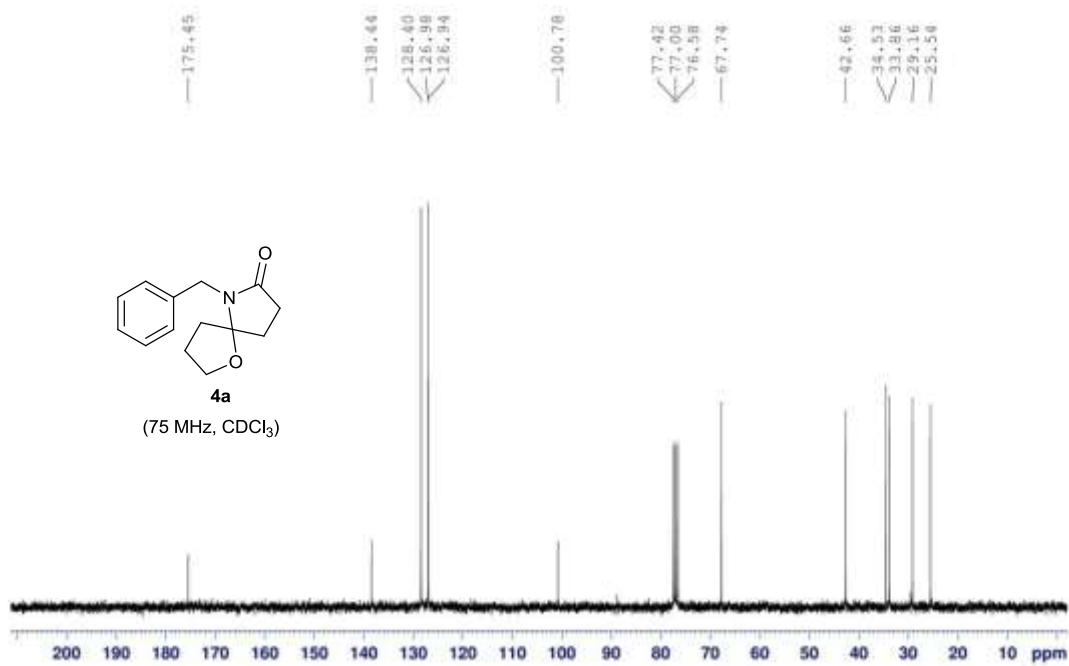
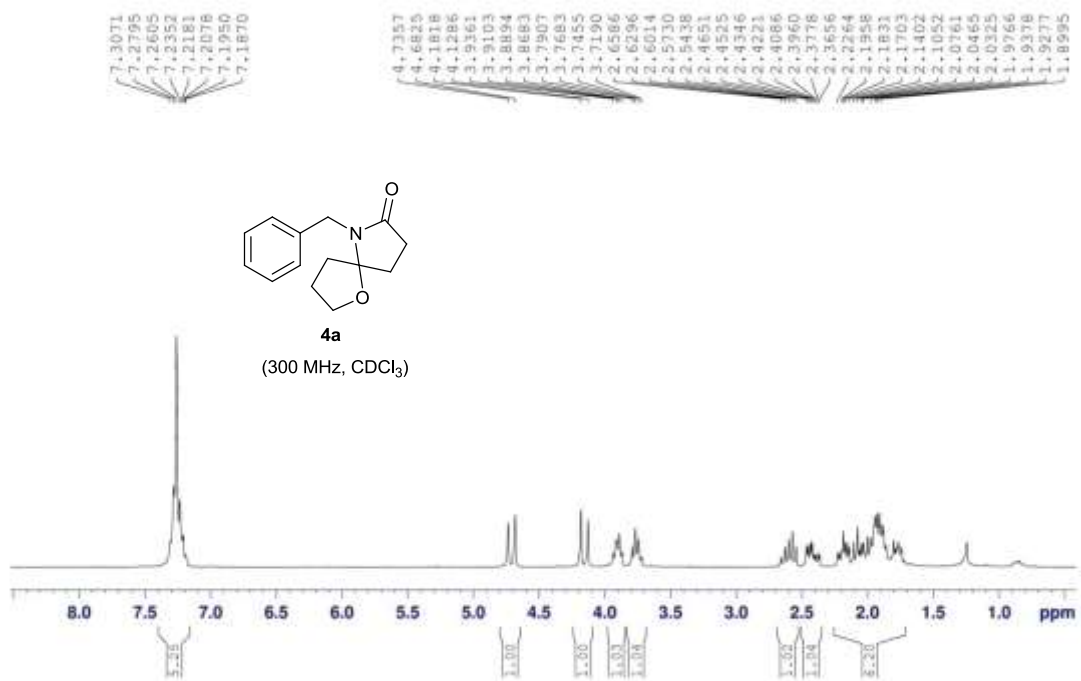


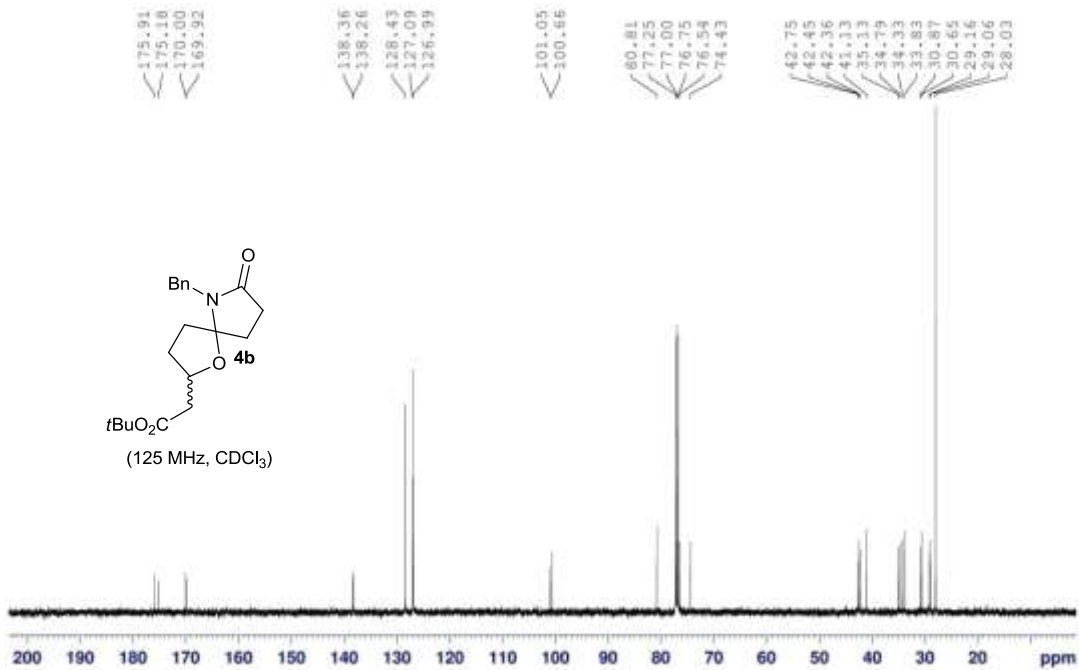
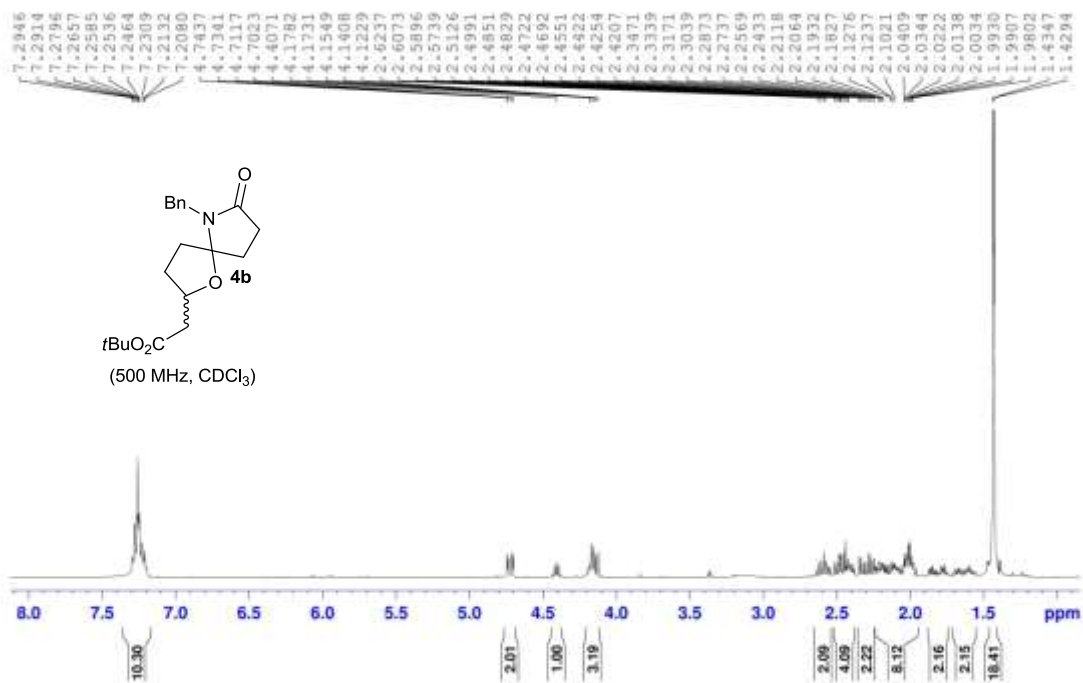


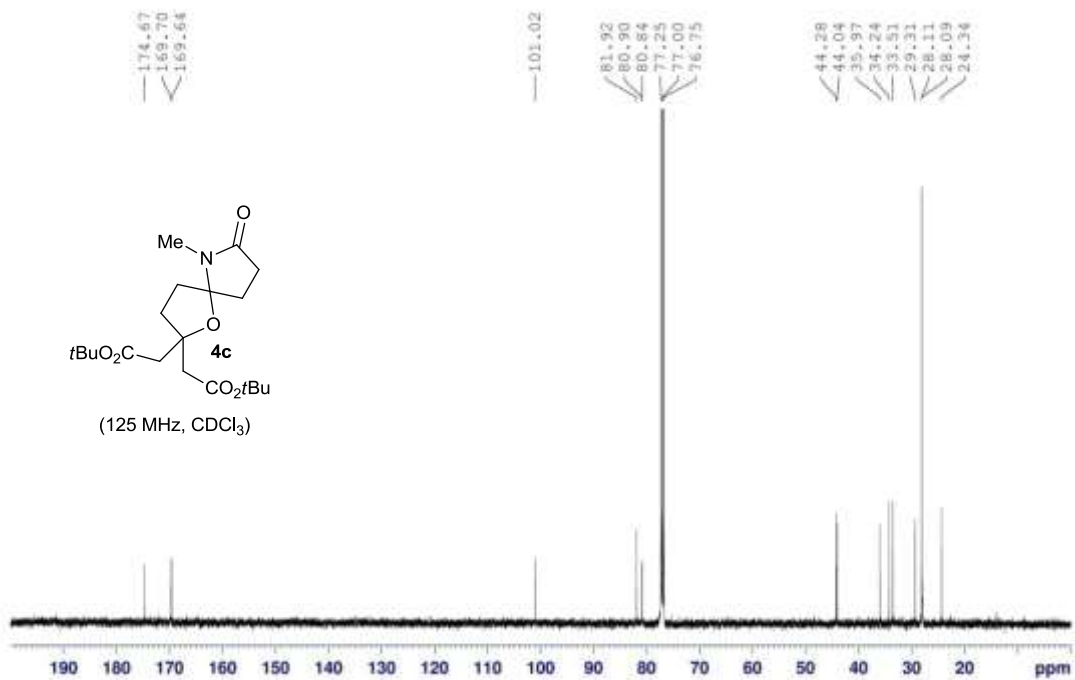
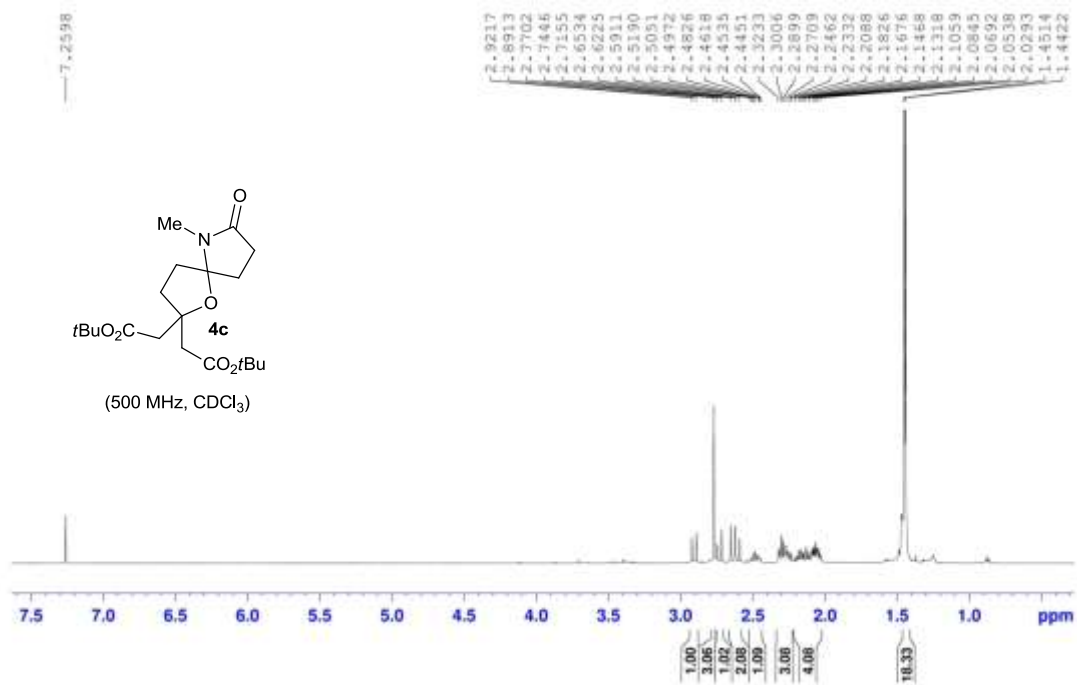


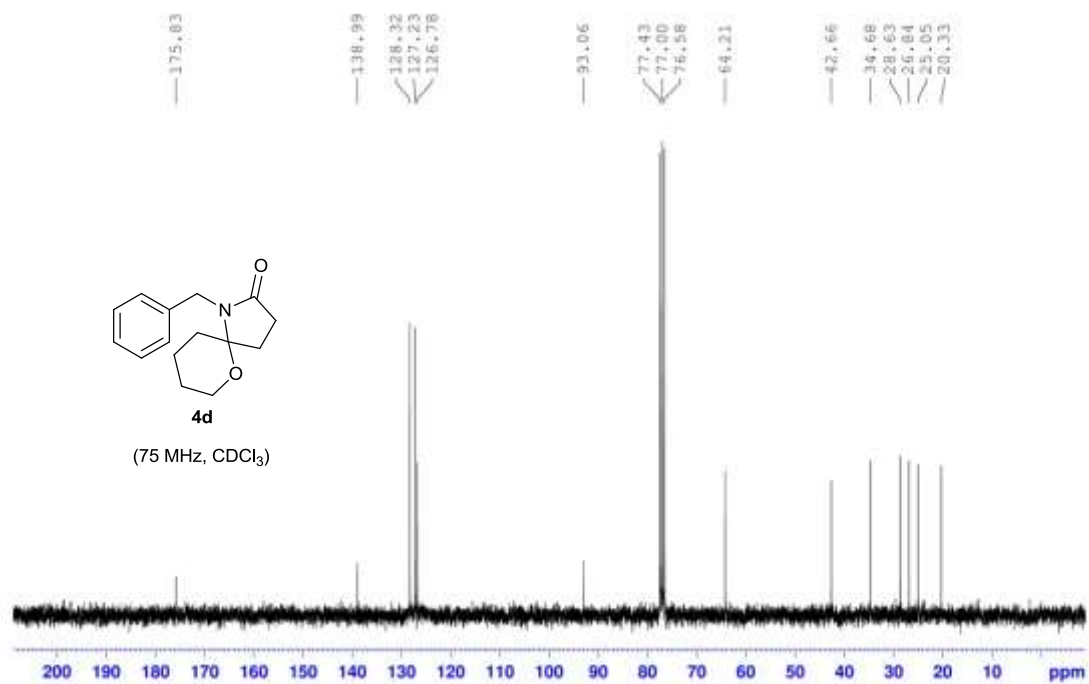
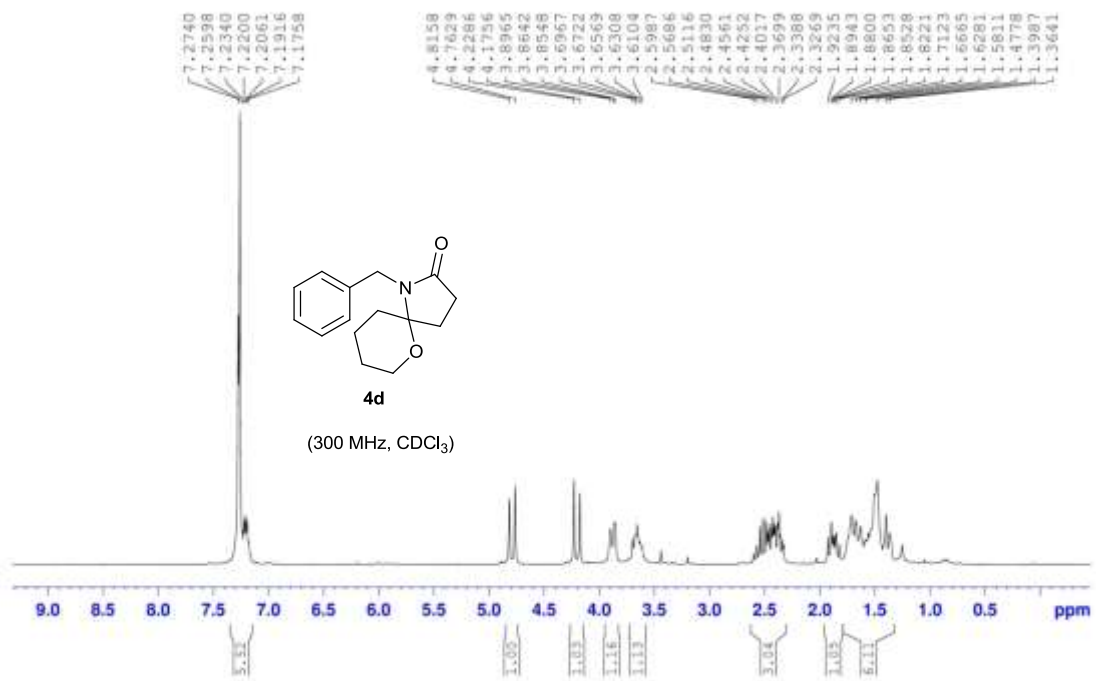


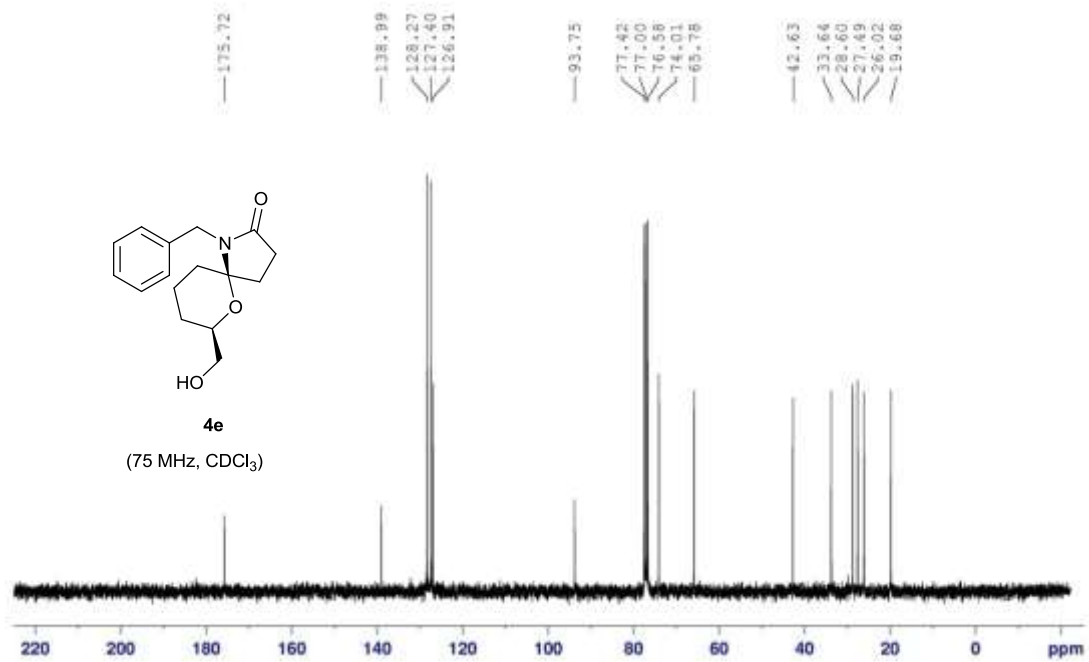
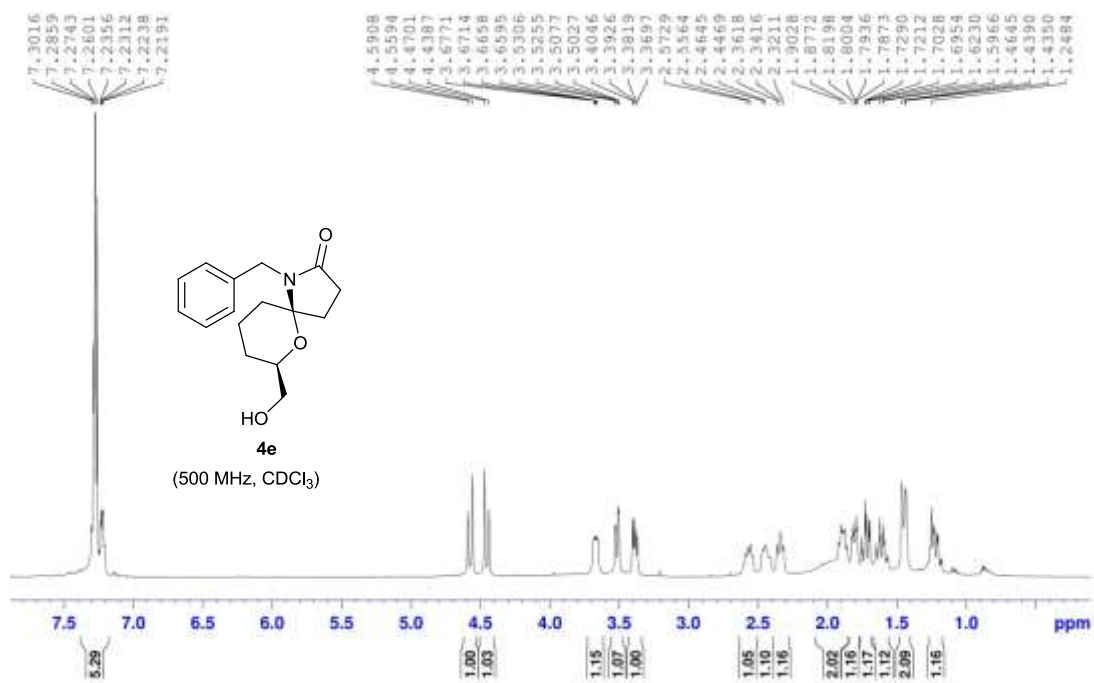






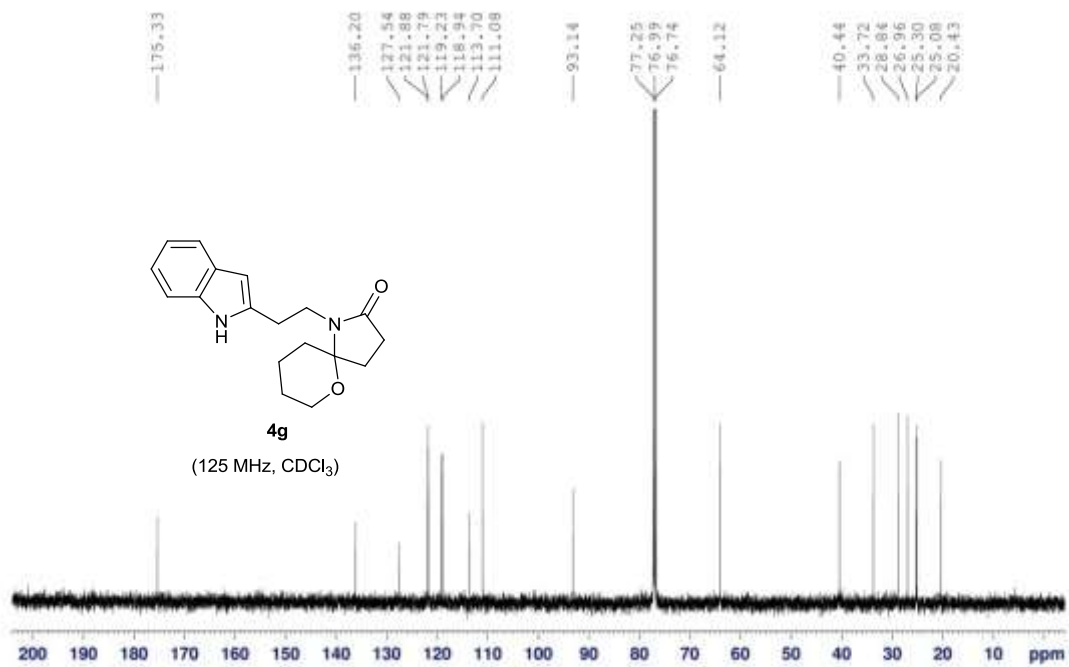
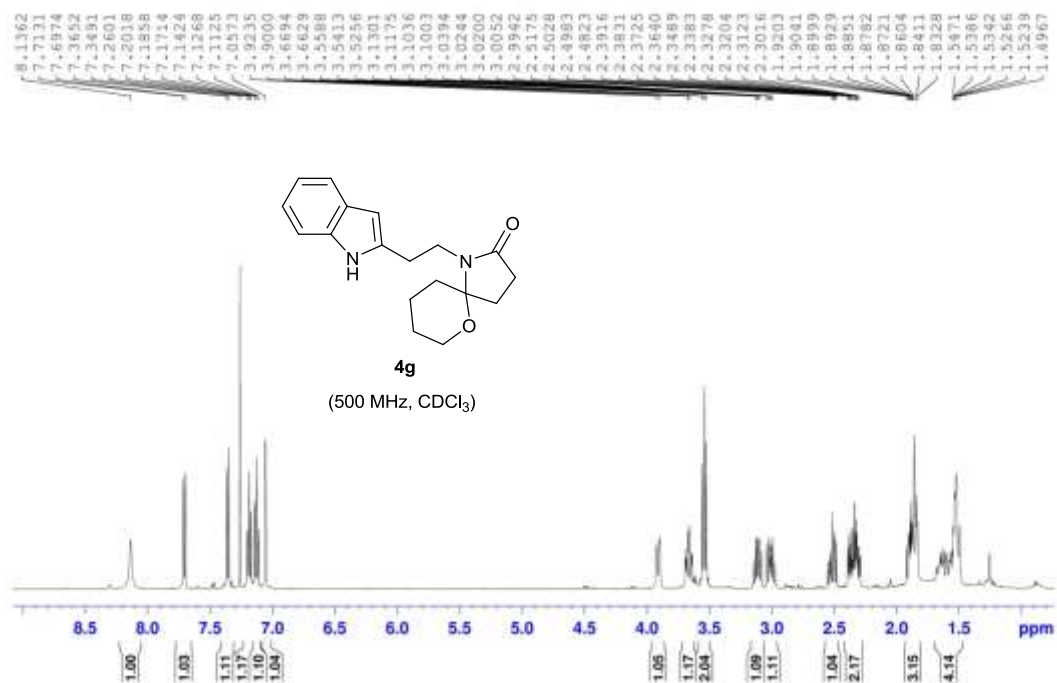


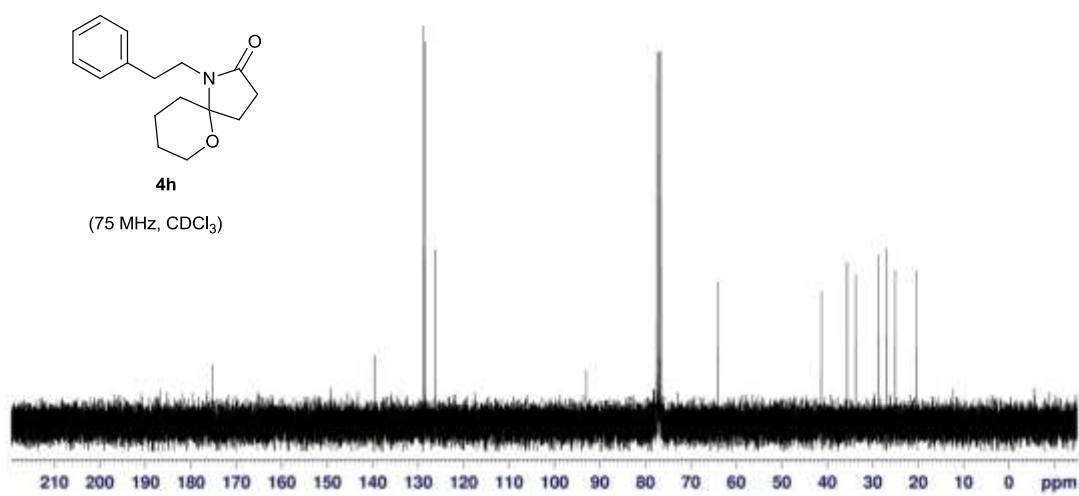
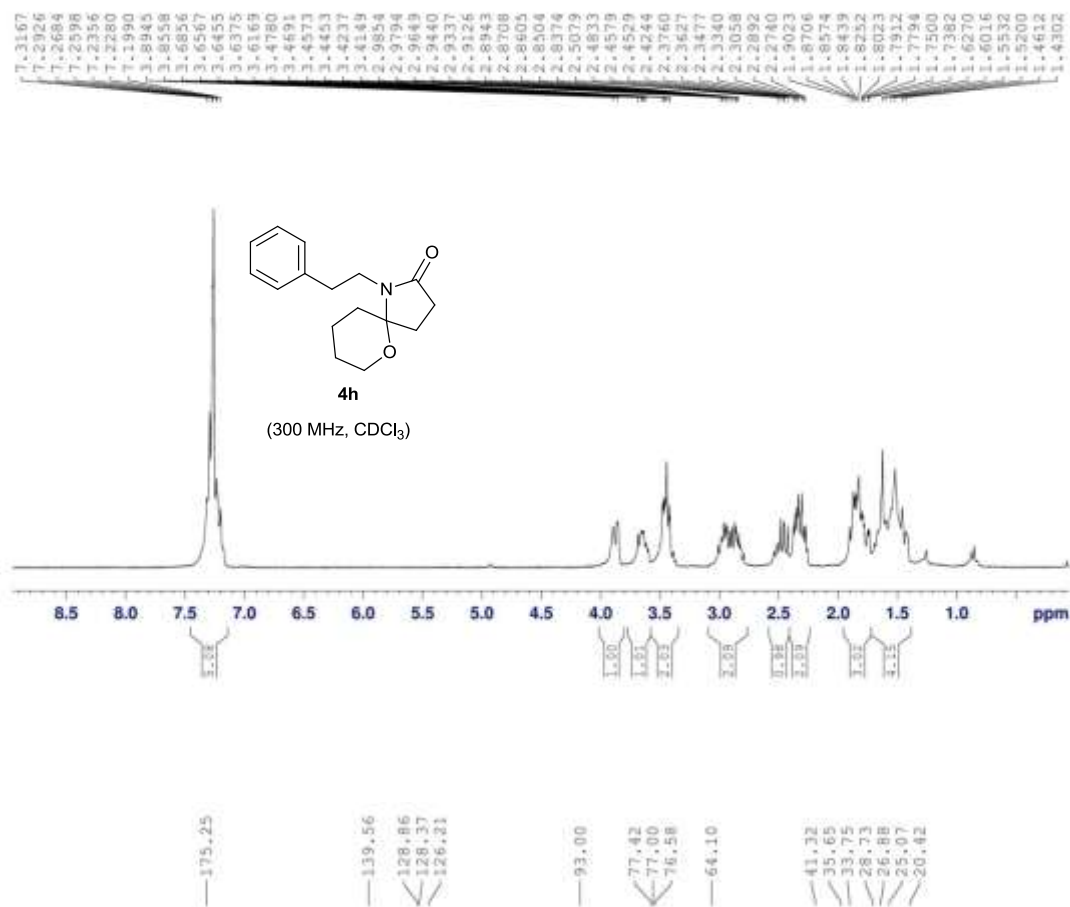


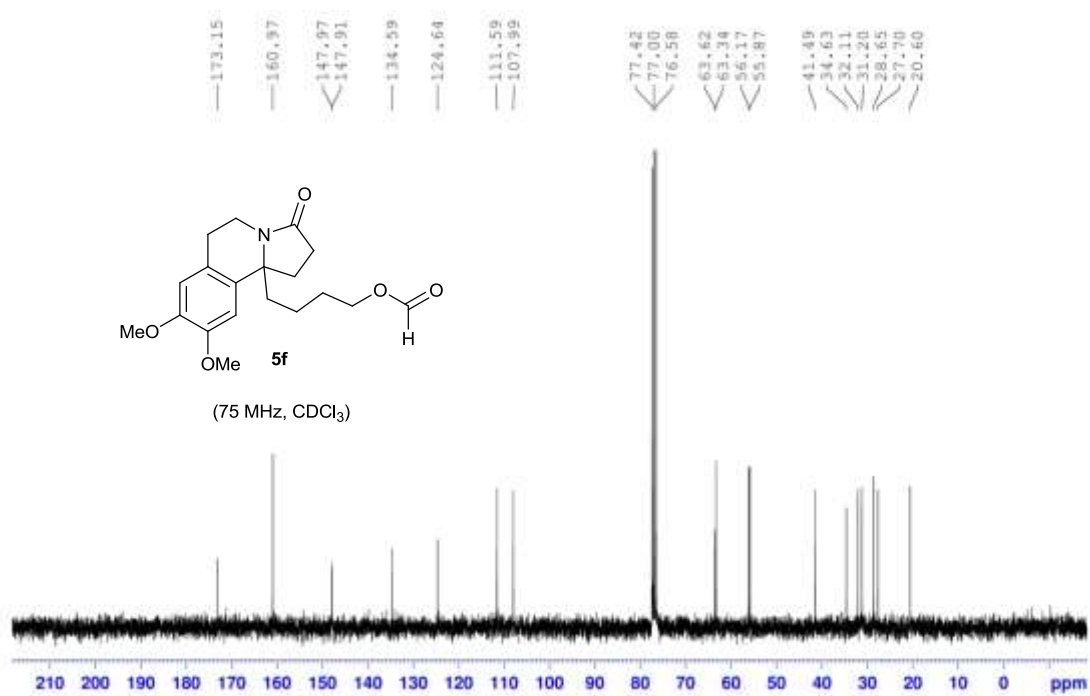
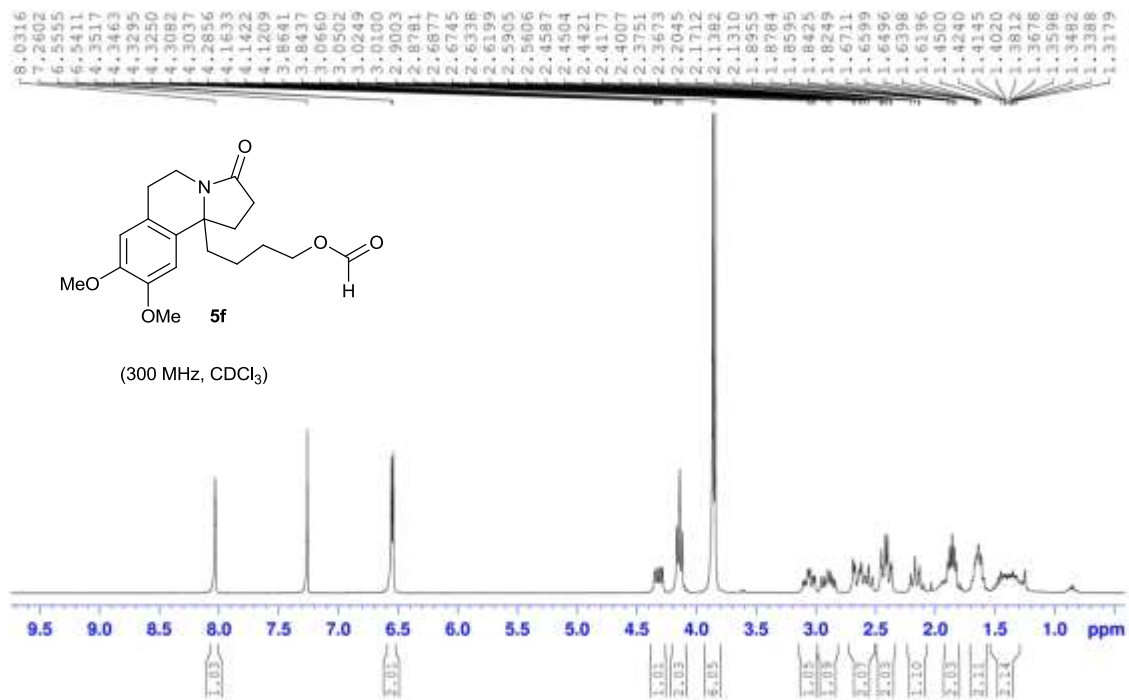


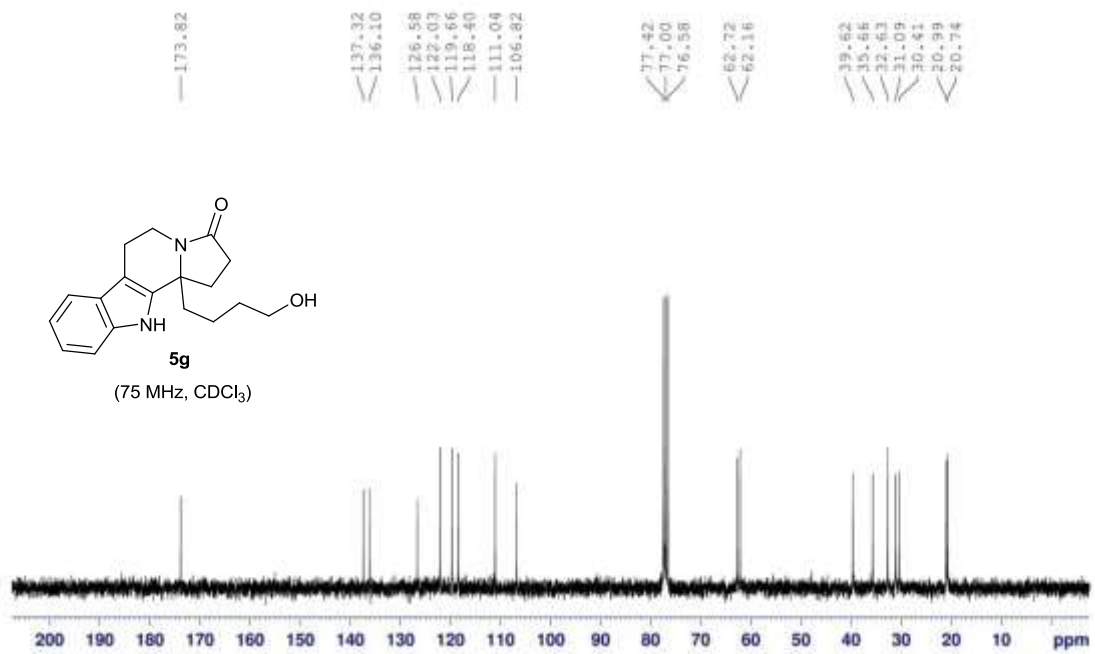
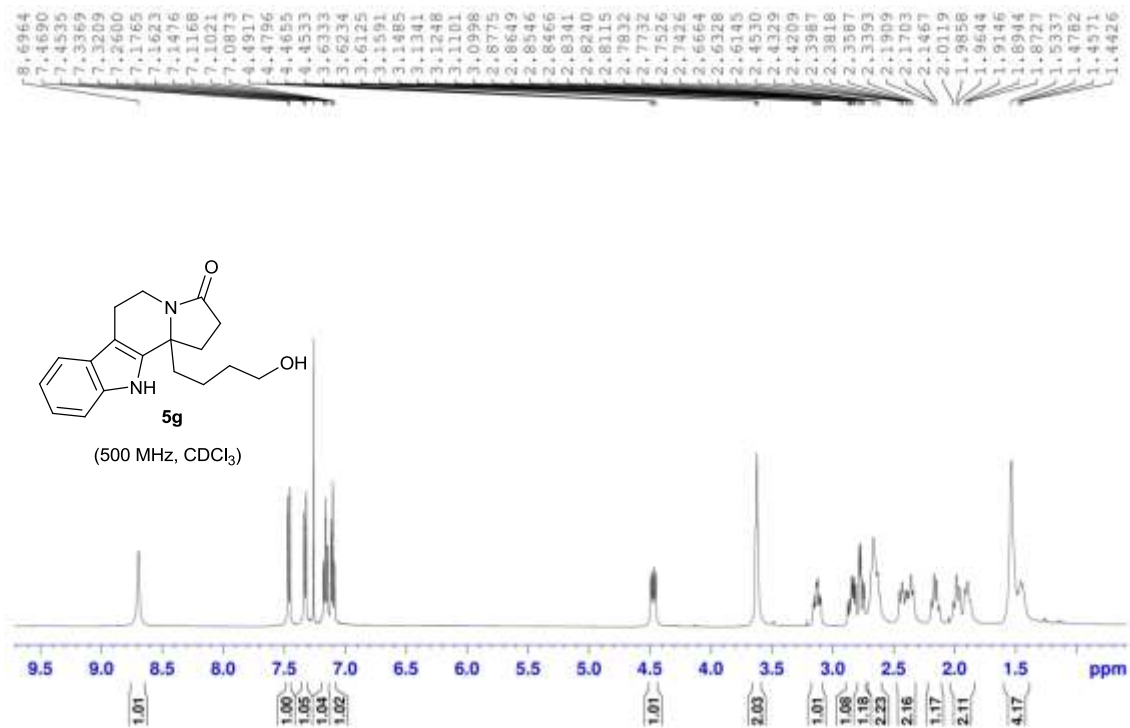


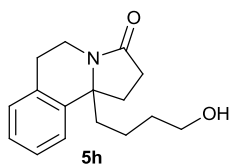




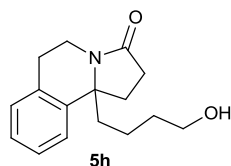
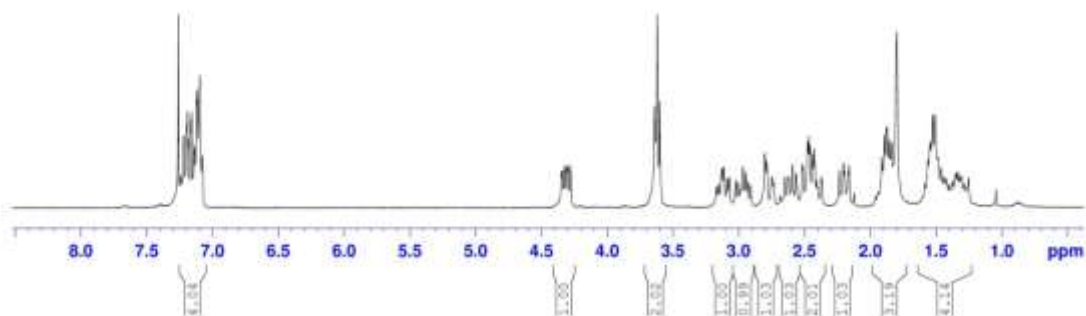




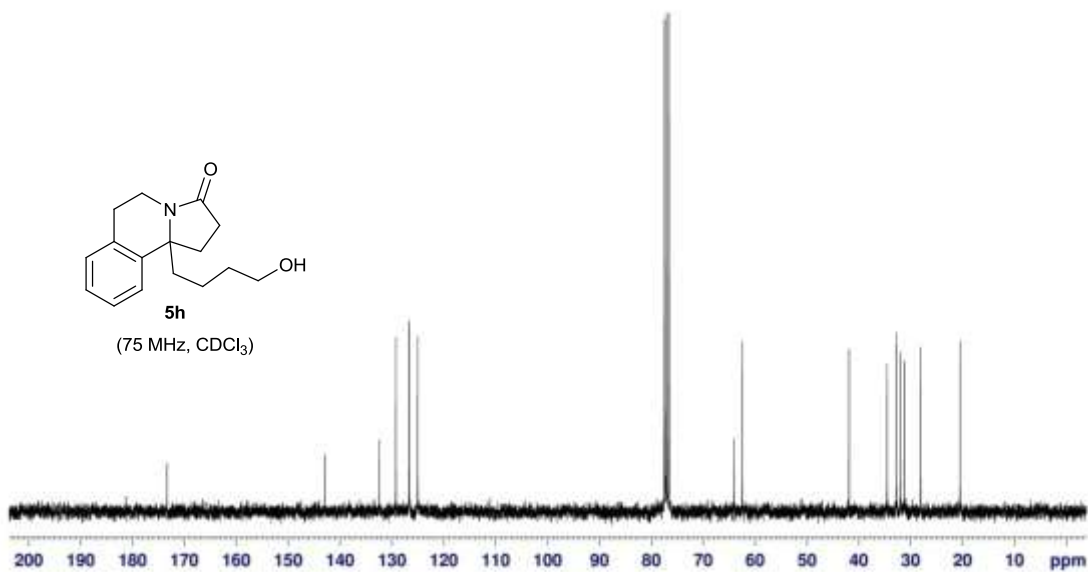


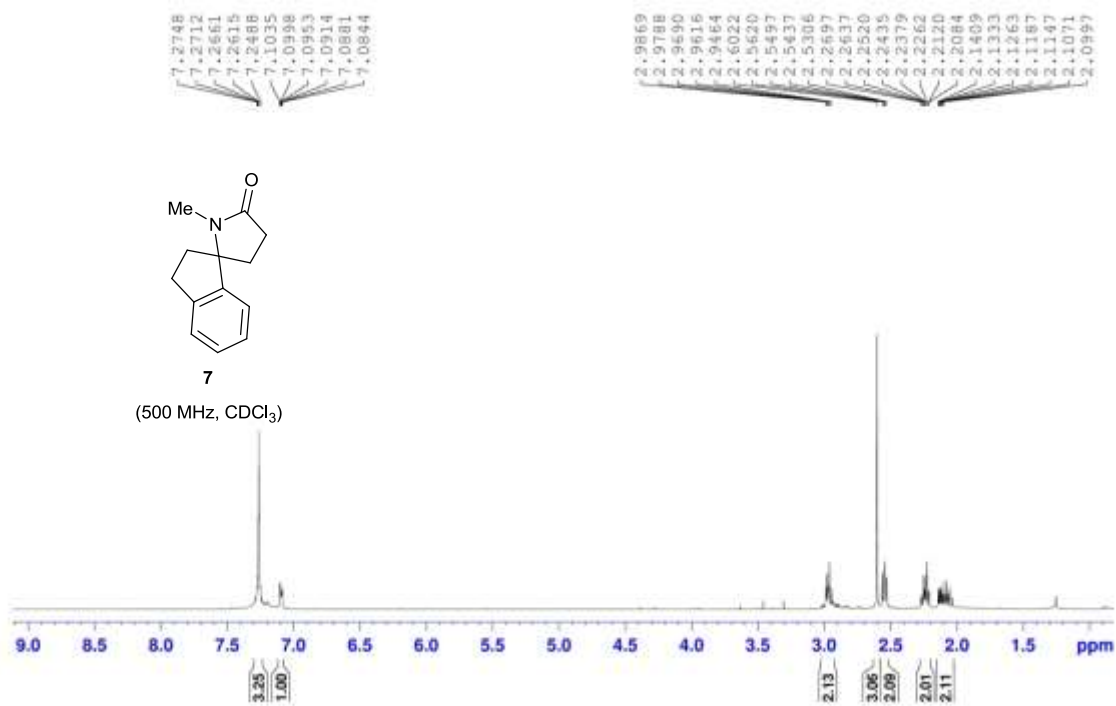


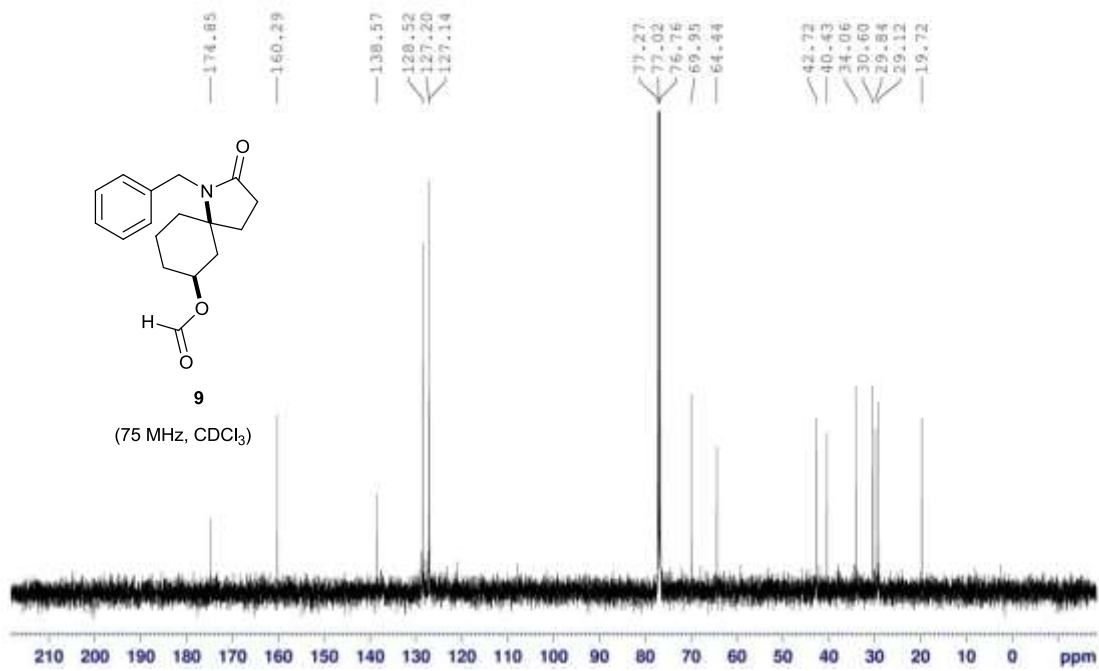
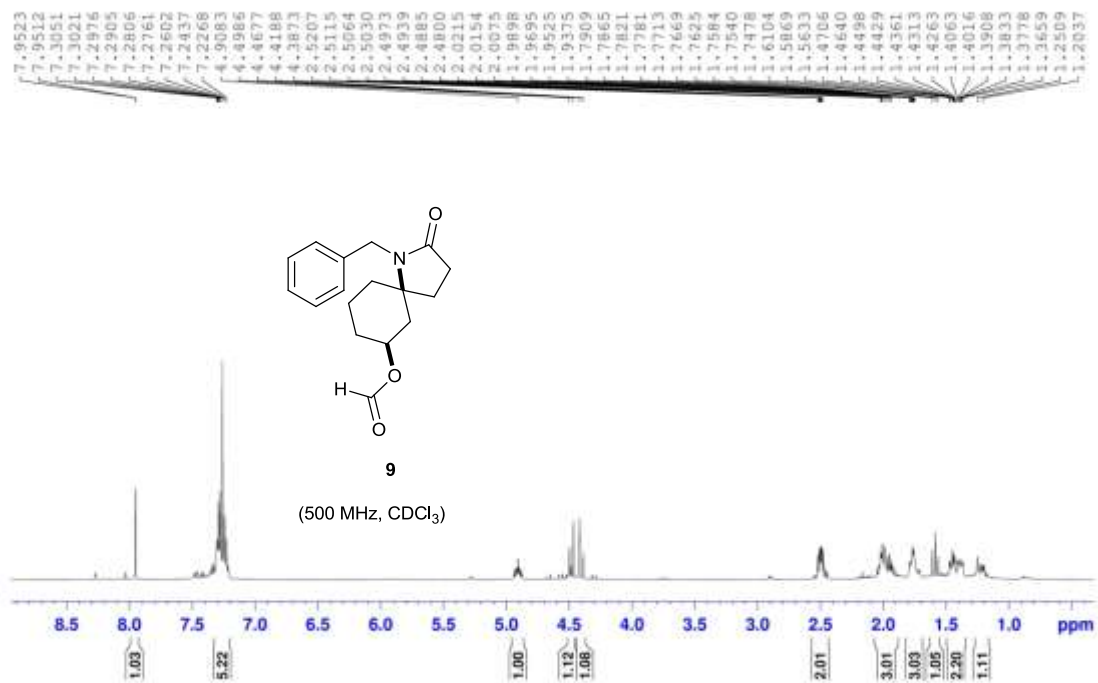
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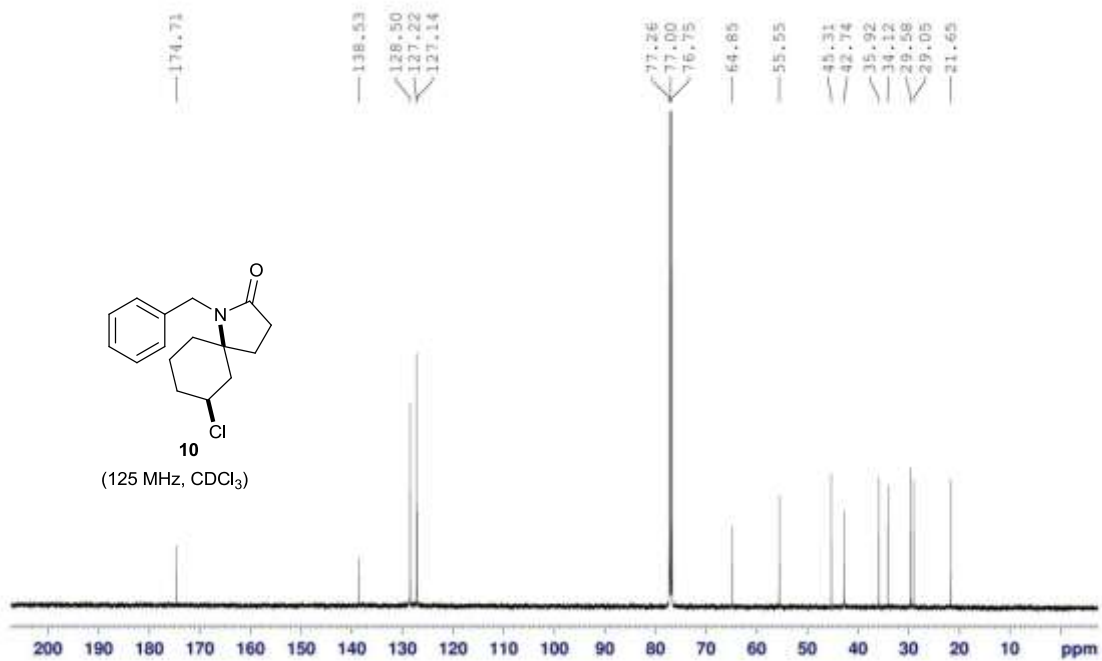
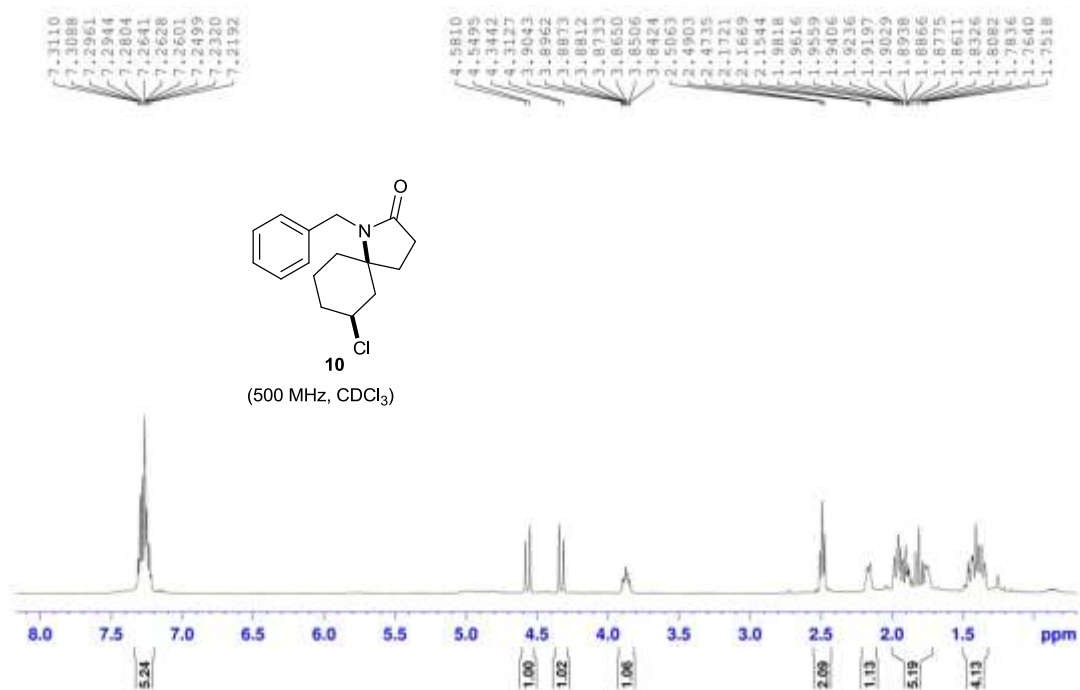


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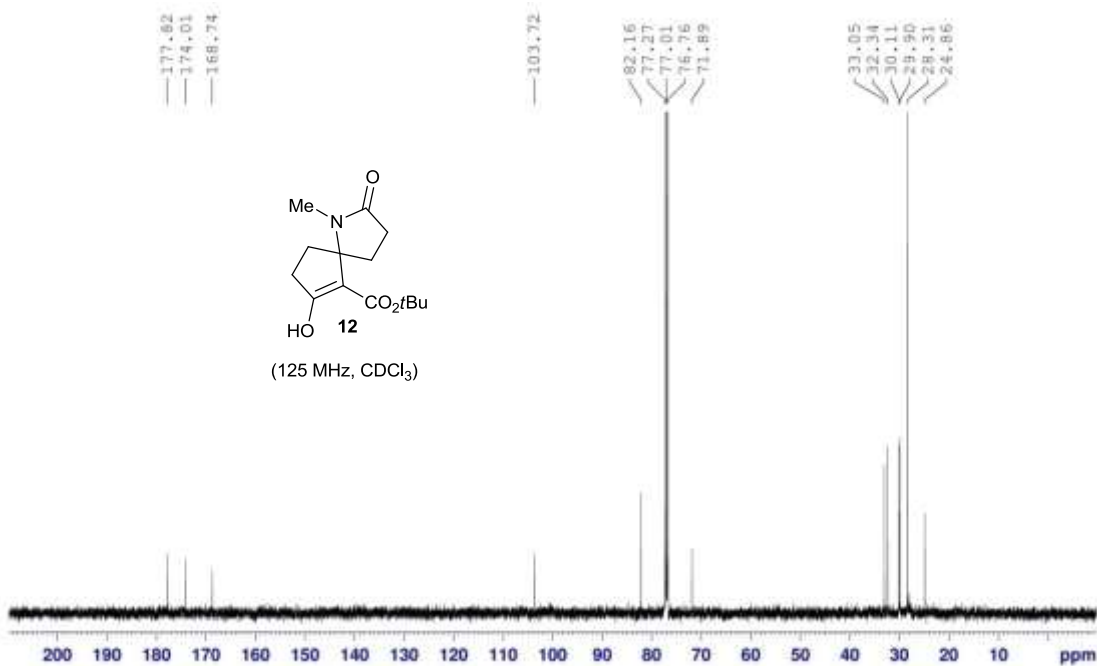
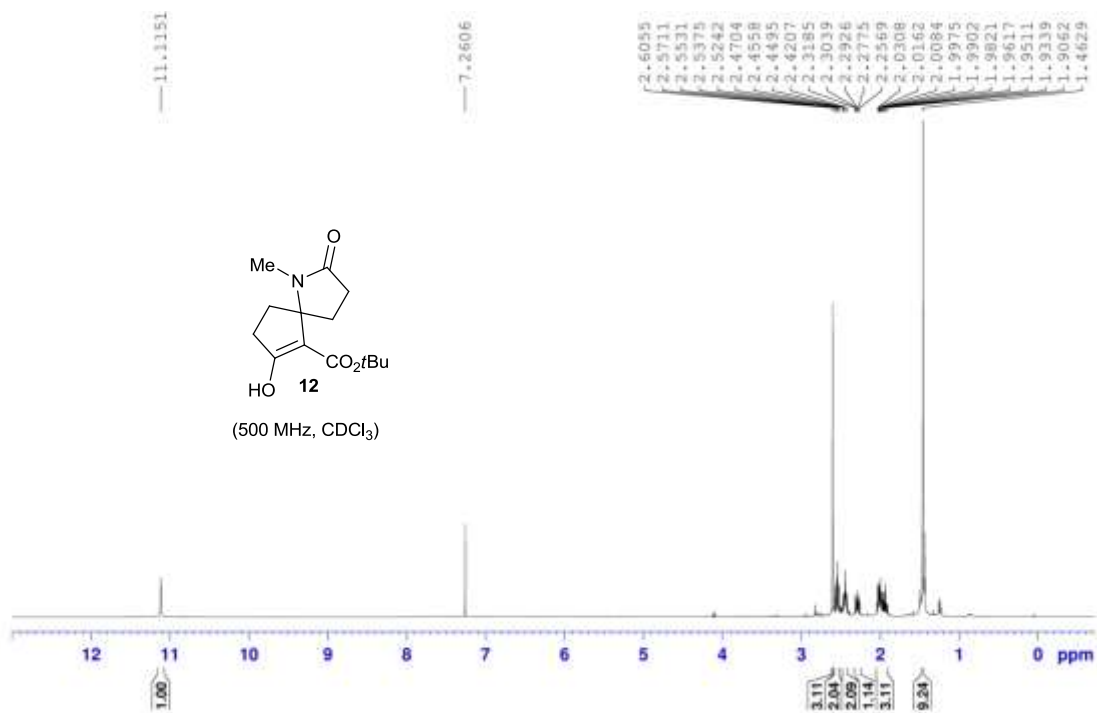


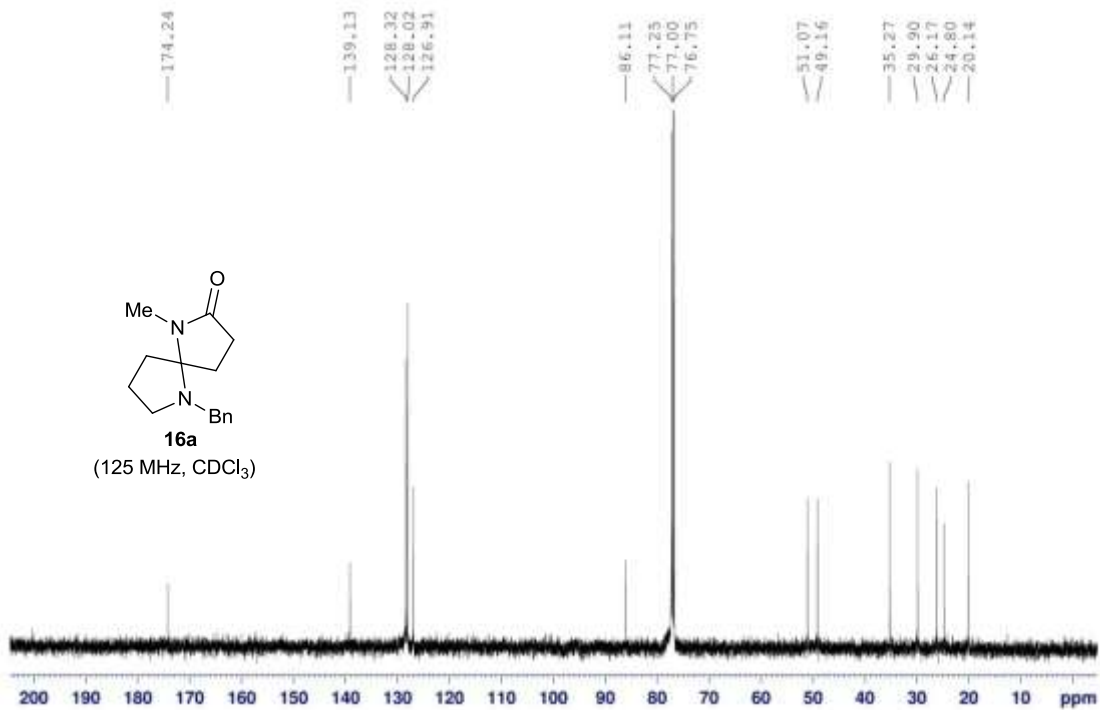
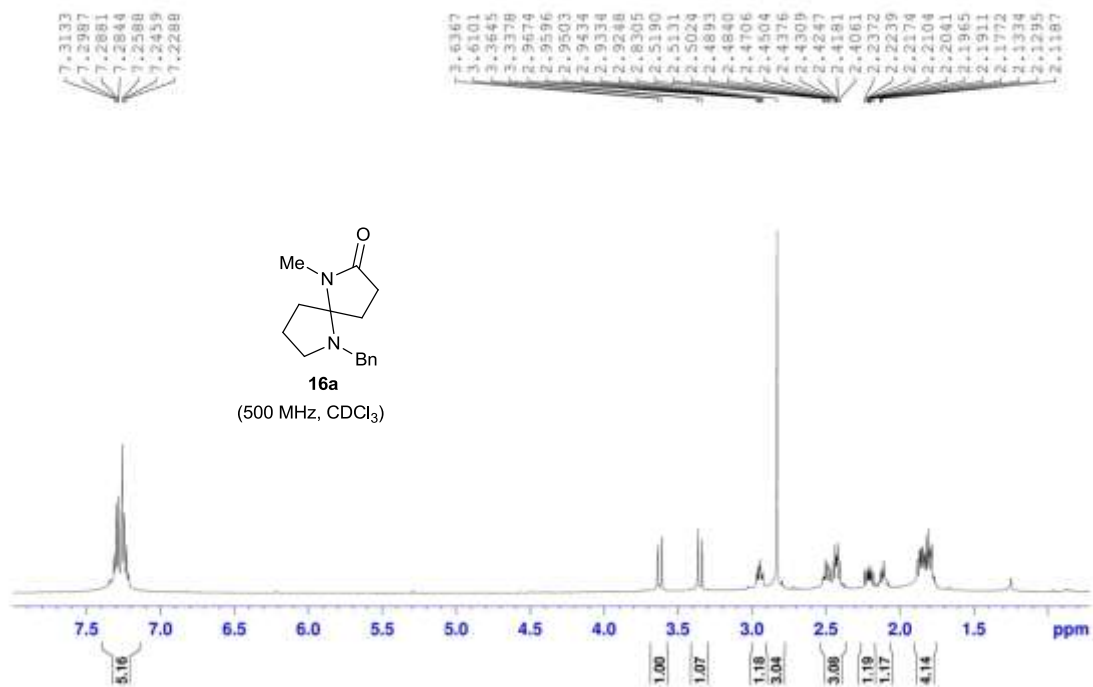


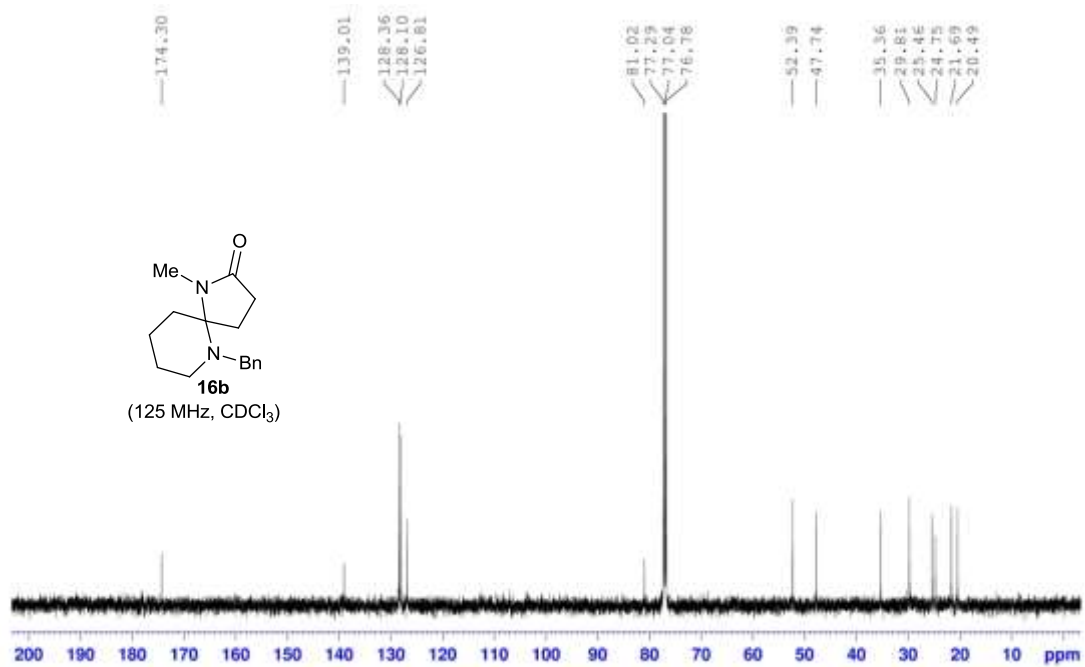
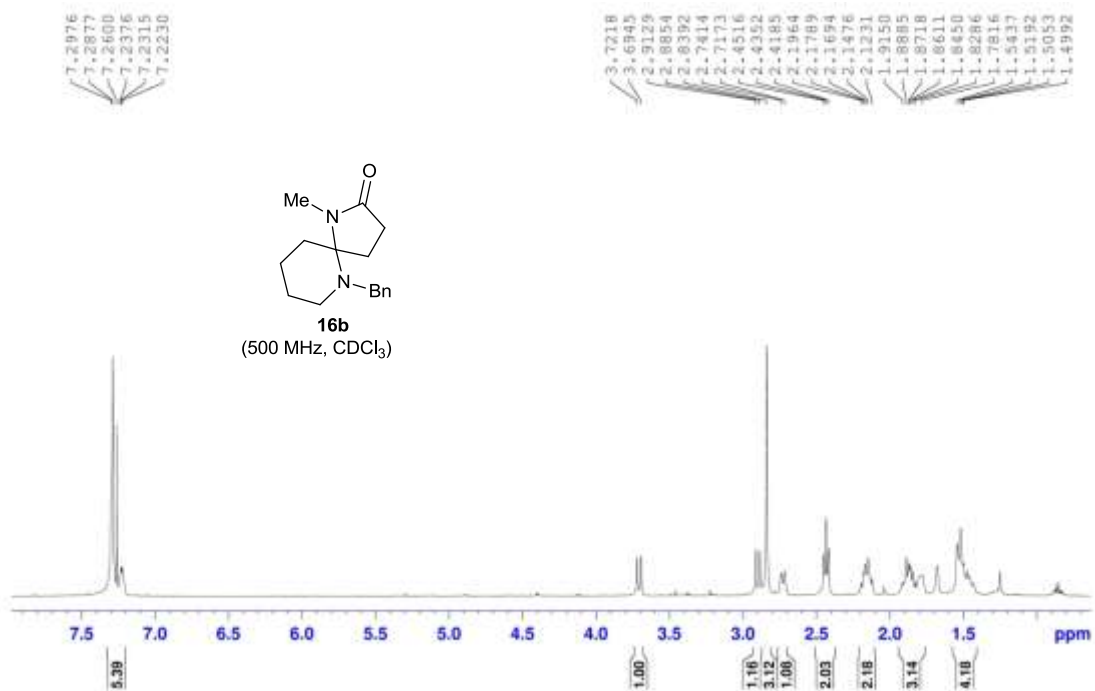




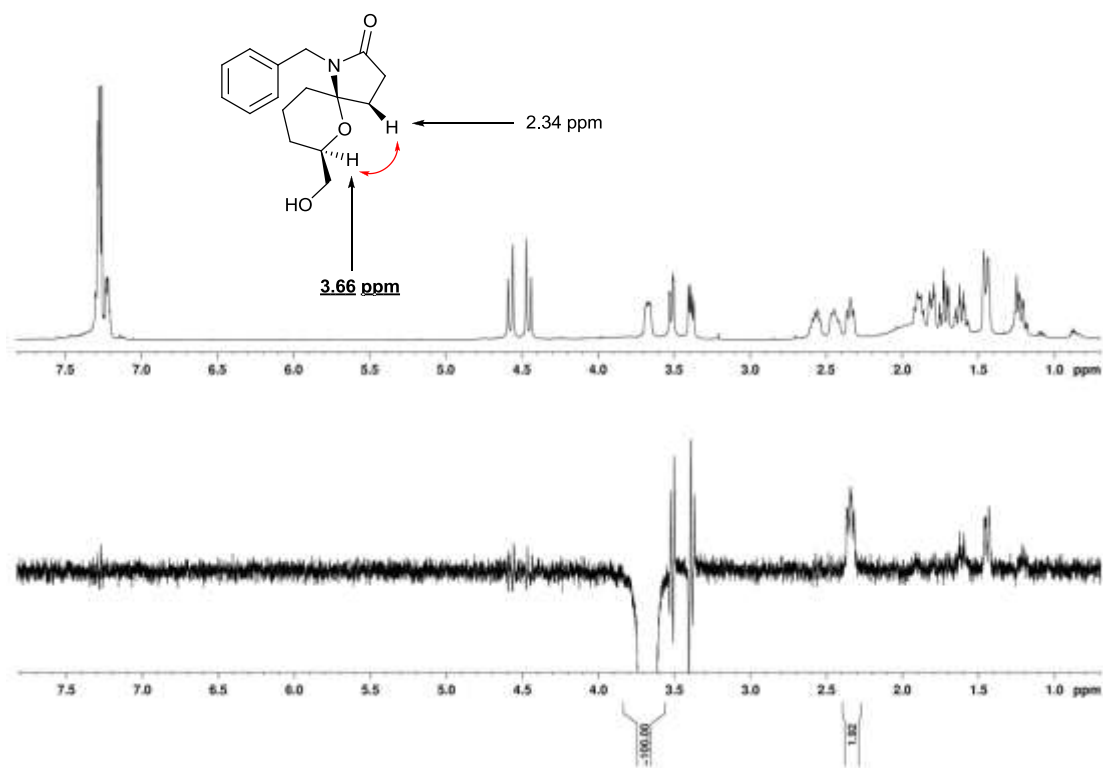




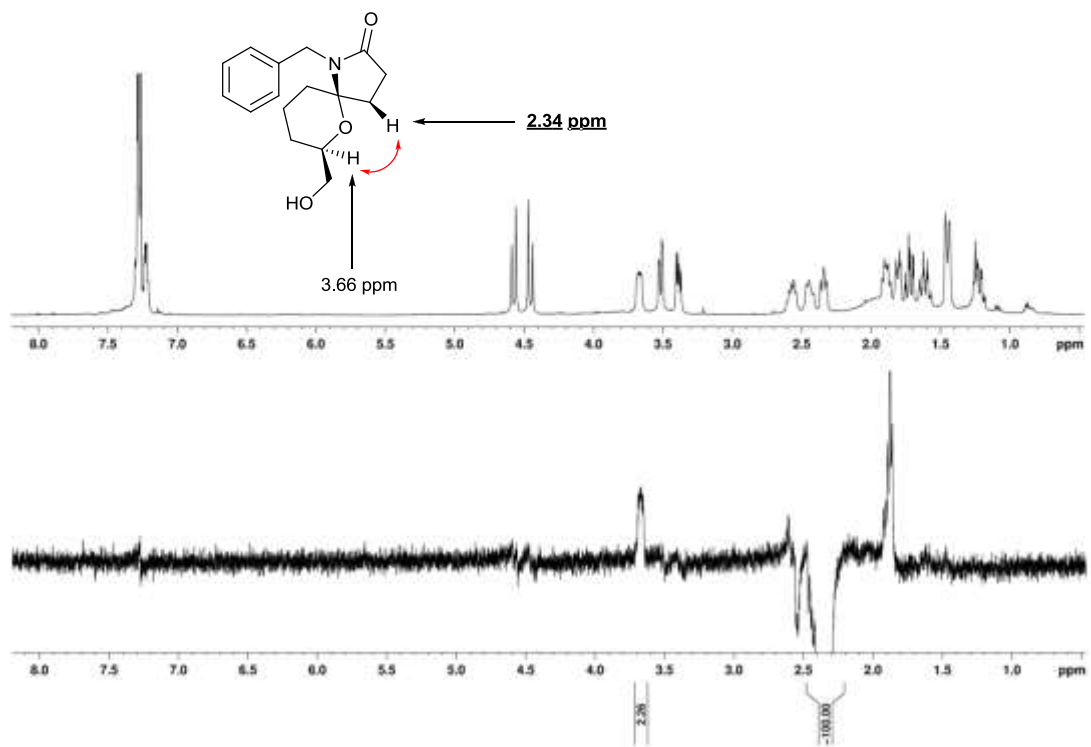




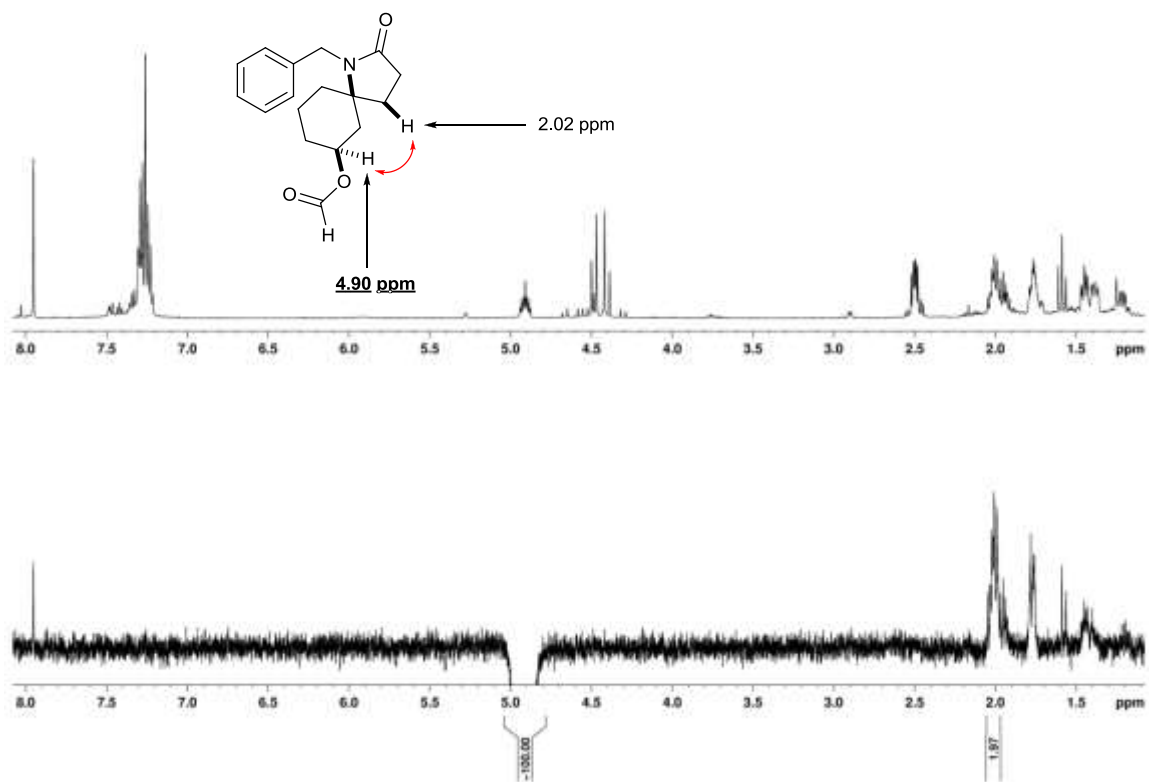
NOE experiment of compound **4e** at 3.66 ppm



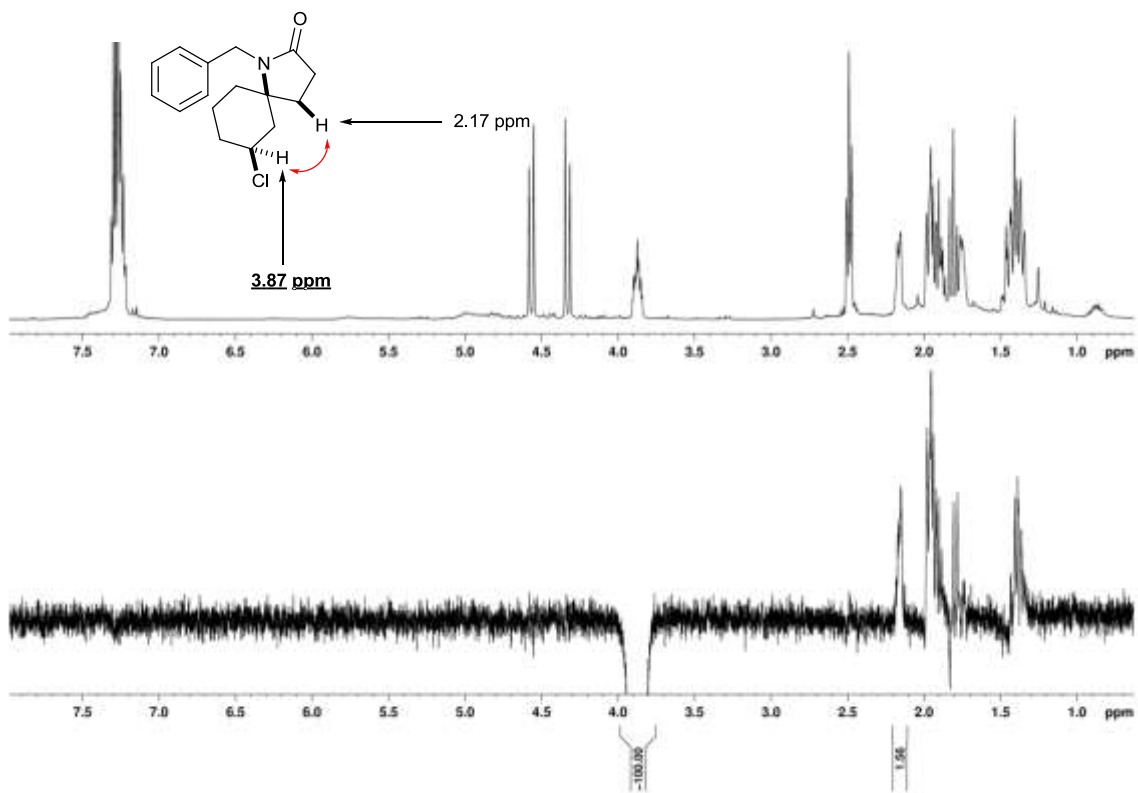
NOE experiment of compound **4e** at 2.34 ppm



NOE experiment of compound **9** at 4.90 ppm



NOE experiment of compound **10** at 3.87 ppm



NOE experiment of compound **10** at 2.17 ppm

