

# **OBO Protected Pyruvates as Reagents for the Synthesis of Functionalized Heteroaromatic Compounds**

C. Henrique A. Esteves,<sup>a</sup> Maria Koyioni,<sup>a</sup> Kirsten E. Christensen,<sup>a</sup> Peter D. Smith<sup>b</sup> and Timothy J. Donohoe<sup>a\*</sup>

<sup>a</sup> *Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford, OX1 3TA, UK.*

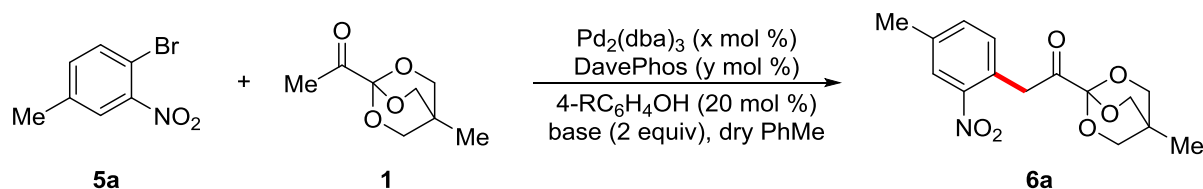
<sup>b</sup> *Early Chemical Development, Pharmaceutical Sciences, IMED Biotech Unit, AstraZeneca, Macclesfield, UK.*

*E-mail: timothy.donohoe@chem.ox.ac.uk*

<b>Table of Contents</b>		<b>Page</b>
S1	Screening of reaction conditions for the $\alpha$ -arylation of methyl OBO-ketone <b>1</b> with <i>o</i> -nitroaryl bromides <b>5</b>	S3
S2	General methods and materials	S3
S3	Experimental procedures and spectroscopic data	S5
S3.1	Synthesis of isoquinoline- and $\beta$ -carboline-3-carboxylates <b>4</b>	S5
S3.1.1	Arylated OBO-ketones <b>3</b>	S5
S3.1.2	$\alpha$ -Functionalisation of arylated OBO-ketone <b>3a</b>	S7
S3.1.3	$\alpha$ -Functionalisation of arylated OBO-ketone <b>3c</b>	S8
S3.1.4	Cyclisation to isoquinoline and $\beta$ -carboline-3-carboxylates <b>4</b>	S10
S3.2	Synthesis of indole-2-carboxylates <b>7</b>	S14
S3.2.1	Arylated OBO-ketones <b>6</b>	S14
S3.2.2	$\alpha$ -Functionalisation of arylated OBO-ketones <b>6</b>	S15
S3.2.3	Reductive cyclisation to indole-2-carboxylates <b>7</b>	S16
S3.3	Synthesis of pyrrole/furan-2-carboxylates <b>10-11</b> and <i>N</i> -substituted pyrrole-2-carboxylates <b>12-13</b>	S19
S3.3.1	1,4-Dicarbonyl scaffolds <b>9</b>	S19
S3.3.2	Cyclisation to pyrrole-2-carboxylates <b>10</b>	S21
S3.3.3	Cyclisation to furan-2-carboxylates <b>11</b>	S24
S3.3.4	Cyclisation to <i>N</i> -substituted pyrrole-2-carboxylates <b>12-13</b>	S26
S3.4	Synthesis of pyridine-2-carboxylates <b>16</b>	S29
S3.4.1	1,5-Dicarbonyl scaffolds <b>15</b>	S29
S3.4.2	Cyclisation to pyridine-2-carboxylates <b>16</b>	S32
S4	Single crystal X-ray diffraction for compounds <b>10c</b> , <b>11b</b> , <b>16a</b> and <b>17b</b>	S36
S5	References	S40
S6	$^1\text{H}$ and $^{13}\text{C}$ NMR spectra	S41

## S1 Screening of reaction conditions for the $\alpha$ -arylation of methyl OBO-ketone 1 with *o*-nitroaryl bromides 5

**Table S1:** Optimization for the coupling of 1-bromo-4-methyl-2-nitrobenzene (**5a**) with methyl-OBO-ketone **1**



entry	1/5a (equiv)	$\text{Pd}_2(\text{dba})_3$ (mol %)	DavePhos (mol %)	4- $\text{RC}_6\text{H}_4\text{OH}$ (R)	temp ( $^\circ\text{C}$ )	base	conversion (%)	yield (%)
1	1.1/1.0	1	4	OMe	50	$\text{K}_2\text{CO}_3$	37	28
2	1.1/1.0	1	4	OMe	50	<i>t</i> -BuONa	0	-
3	1.1/1.0	1	4	OMe	50	$\text{Cs}_2\text{CO}_3$	7	-
4	1.1/1.0	1	4	H	50	$\text{K}_2\text{CO}_3$	47	-
5	1.1/1.0	2	8	H	50	$\text{K}_2\text{CO}_3$	60	48
6	2.0/1.0	1	4	H	50	$\text{K}_2\text{CO}_3$	63	-
7	2.0/1.0	2	8	H	50	$\text{K}_2\text{CO}_3$	66	-
8	1.1/1.0	1	4	H	80	$\text{K}_2\text{CO}_3$	100	56
9	1.0/2.0	1	4	H	80	$\text{K}_2\text{CO}_3$	100	91
10 <sup>a</sup>	1.0/2.0	1	4	H	80	$\text{K}_2\text{CO}_3$	100	86

<sup>a</sup> Gram scale

## S2 General methods and materials

Solvents were dried over 4 Å molecular sieves or activated alumina columns. Dry ethanol used for OBO deprotection experiments was purified following a literature procedure.<sup>1</sup> All reagents were purchased from Sigma-Aldrich, Alfa Aesar, Acros Organics or Fluorochem and used without further purification. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) was purchased from Alfa Aesar. *t*-BuONa solution (2 M in THF) was purchased from Sigma-Aldrich (grade  $\text{ZrO}_2^\circ$ ). *p*-Toluenesulfonic acid was dried by heating *p*-toluenesulfonic acid monohydrate under vacuum at 100  $^\circ\text{C}$  for 4 h.  $\text{K}_2\text{CO}_3$  was dried by heating under vacuum at 400  $^\circ\text{C}$  for 30 min. All reactions requiring anhydrous conditions were carried out using flame-dried glassware. Flash column chromatography was performed using Merck Kieselgel 60 (0.040 – 0.063 mm) silica gel following the established literature method.<sup>2</sup> Thin layer chromatography was performed on Merck Kieselgel 60 F<sub>254</sub> 0.25 mm pre-coated aluminum-backed plates. Product spots were visualized under UV light ( $v_{\text{max}} = 254 \text{ nm}$ ) and/or by staining with vanillin, phosphomolybdic acid or  $\text{KMnO}_4$ . Melting points (mp) were obtained by using a Lecia VMTG heated-stage microscope with a Testo 720 thermometer and are uncorrected. Solvents used for recrystallization are indicated after the

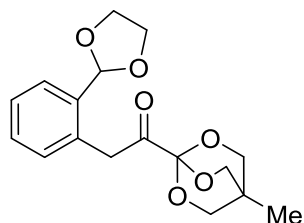
melting point.  $^1\text{H}$ ,  $^{13}\text{C}$  NMR and  $^{19}\text{F}$  NMR spectra were recorded on a Bruker AVII400 or AVIII400 instrument at 400, 101 and 376 MHz, respectively or on a Bruker AVIII500 at 500 and 126 MHz, for  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra, respectively.  $^{13}\text{C}$  NMR spectra were recorded with broadband proton decoupling. Chemical shifts,  $\delta$ , are reported relative to residual solvent peaks and quoted in parts per million (ppm) to the nearest 0.01 ppm for  $^1\text{H}$  and to the nearest 0.1 ppm for  $^{13}\text{C}$  and  $^{19}\text{F}$ . Coupling constants,  $J$ , are quoted to the nearest 0.1 Hz. Assignments were made based on DEPT, COSY, HSQC and HMBC experiments. Low temperature<sup>3</sup> single crystal X-ray diffraction data were collected using a (Rigaku) Oxford Diffraction SuperNova diffractometer. Raw frame data were reduced using CrysAlisPro and the structures were solved using 'Superflip'<sup>4</sup> before refinement with CRYSTALS<sup>5</sup> as per the SI (CIF). Full refinement details are given in the Supporting Information (CIF); Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1843229-32) and can be obtained via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif). High-resolution mass spectra were acquired using electrospray ionisation (ESI) as ionization source and were recorded on a Thermo Exactive orbitrap spectrometer equipped with a Waters Equity LC system. Infrared spectra (IR) were obtained either from evaporated films (indicated) or crystalline solids using a Bruker Tensor 27 spectrometer, equipped with a Pike Miracle Attenuated Total Reflectance (ATR) sampling accessory. Absorption is quoted in wavenumbers ( $\text{cm}^{-1}$ ) for the range 3500–600  $\text{cm}^{-1}$ . Compound names were generated by the software ChemDraw Professional 15.1. 1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethan-1-one (**1**),<sup>6</sup> 2-(2-bromophenyl)-1,3-dioxolane (**2a**),<sup>7</sup> 2-(2-bromo-4,5-dimethoxyphenyl)-1,3-dioxolane (**2b**),<sup>7</sup> 1-benzyl-3-bromo-2-(1,3-dioxolan-2-yl)-1*H*-indole (**2c**),<sup>8</sup> 1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-2-[4-(trifluoromethyl)-phenyl]ethan-1-one (**8a**),<sup>6</sup> 1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-2-(*p*-tolyl)-ethan-1-one (**8b**),<sup>6</sup> 2-(3-methoxyphenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-ethan-1-one (**8c**)<sup>6</sup> and 2-[4-(dimethylamino)phenyl]-1-(4-methyl-2,6,7-trioxabicyclo-[2.2.2]octan-1-yl)ethan-1-one (**8d**)<sup>6</sup> were prepared according to literature procedures.

## S3 Experimental procedures and spectroscopic data

### S3.1 Synthesis of isoquinoline- and $\beta$ -carboline-3-carboxylates 4

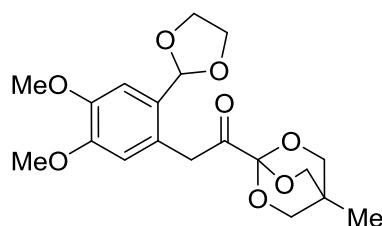
#### S3.1.1 Arylated OBO-ketones 3

##### 2-[2-(1,3-Dioxolan-2-yl)phenyl]-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethan-1-one (3a)



To a flame-dried Biotage<sup>®</sup> microwave vial capped with a rubber septum were added methyl-OBO-ketone **1**,<sup>6</sup> (100 mg, 0.581 mmol, 1.5 equiv), 2-(2-bromophenyl)-1,3-dioxolane (**2a**),<sup>7</sup> (89 mg, 0.39 mmol, 1.0 equiv), and Pd(dtbpf)Cl<sub>2</sub> (13 mg, 19  $\mu$ mol, 5 mol %). The rubber septum was then removed, and the reaction vessel was sealed with a microwave vial cap (Reseal<sup>™</sup> septum). THF (5.3 mL) and *t*-BuONa solution (490  $\mu$ L, 0.975 mmol, 2.5 equiv, 2 M in THF) were added *via* syringe. The vial was flushed with argon for 5 min and then heated at 70 °C for 24 h. The resulting mixture was filtered through a plug of silica using EtOAc as eluent and concentrated *in vacuo*. Purification by flash column chromatography (*n*-pentane/EtOAc, 65:35) gave the *title compound* **3a** (116 mg, 93%) as a brown solid. **mp**: 86–87 °C; **IR**:  $\nu_{\text{max}}$  (thin film) 2943, 2883, 1751, 1073, 1049, 993, 723 cm<sup>-1</sup>; **HRMS**: calculated for C<sub>17</sub>H<sub>21</sub>O<sub>6</sub>, 321.1333 [M+H]<sup>+</sup>, found *m/z* 321.1335,  $\Delta$  = 0.87 ppm; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.56–7.51 (1H, m, HC<sub>Ar</sub>), 7.33–7.24 (2H, m, 2  $\times$  HC<sub>Ar</sub>), 7.14–7.08 (1H, m, HC<sub>Ar</sub>), 5.80 (1H, s, CH(OR)<sub>2</sub>), 4.18 (2H, s, CH<sub>2</sub>C(O)), 4.10–3.90 (4H, m, (OCH<sub>2</sub>)<sub>2</sub>), 4.01 (6H, s, C(OCH<sub>2</sub>)<sub>3</sub>C), 0.83 (3H, s, CH<sub>3</sub>); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  195.4 (C(O)), 136.2 (C<sub>Ar</sub>), 132.3 (C<sub>Ar</sub>), 131.7 (HC<sub>Ar</sub>), 129.0 (HC<sub>Ar</sub>), 127.1 (HC<sub>Ar</sub>), 126.7 (HC<sub>Ar</sub>), 103.7 (CO<sub>3</sub>), 102.4 (CH(OR)<sub>2</sub>), 73.1 (C(OCH<sub>2</sub>)<sub>3</sub>C), 65.0 ((OCH<sub>2</sub>)<sub>2</sub>), 40.6 (CH<sub>2</sub>C(O)), 30.9 (C(OCH<sub>2</sub>)<sub>3</sub>CMe), 14.2 (CH<sub>3</sub>).

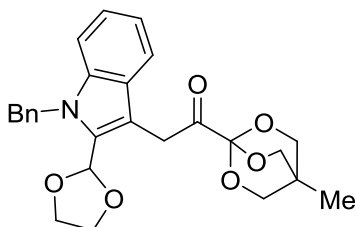
##### 2-[2-(1,3-Dioxolan-2-yl)-4,5-dimethoxyphenyl]-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethan-1-one (3b)



To a flame-dried Biotage<sup>®</sup> microwave vial capped with a rubber septum were added methyl-OBO ketone **1**<sup>6</sup> (103 mg, 0.598 mmol, 1.0 equiv), 2-(2-bromo-4,5-dimethoxyphenyl)-1,3-dioxolane (**2b**)<sup>7</sup> (191 mg, 0.661 mmol, 1.1 equiv) and Pd(dtbpf)Cl<sub>2</sub> (20 mg, 30  $\mu$ mol, 5 mol%). The rubber septum

was then removed, and the reaction vessel was sealed with a microwave vial cap (Reseal™ septum). THF (5.3 mL) and *t*-BuONa solution (750  $\mu$ L, 1.50 mmol, 2.5 equiv, 2 M in THF) were added *via* syringe. The vial was flushed with argon for 5 mins and then heated at 70 °C for 24 h. The resulting mixture was filtered through a plug of silica using EtOAc as eluent and concentrated *in vacuo*. Purification by flash column chromatography (*n*-pentane/EtOAc, 50:50) gave the *title compound* **3b** (205 mg, 90%) as a brown solid. **mp**: 100–103 °C; **IR**:  $\nu_{\text{max}}$  (thin film) 2939, 2883, 1751, 1518, 1268, 1121, 1075, 1034, 1004, 750  $\text{cm}^{-1}$ ; **HRMS**: calculated for  $\text{C}_{19}\text{H}_{25}\text{O}_8$ , 381.1544  $[\text{M}+\text{H}]^+$ , found  $m/z$  381.1542,  $\Delta = -0.58$  ppm.  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.01 (1H, s,  $\text{HC}_{\text{Ar}}$ ), 6.53 (1H, s,  $\text{HC}_{\text{Ar}}$ ), 5.63 (1H, s,  $\text{CH}(\text{OR})_2$ ), 4.03 (2H, s,  $\text{CH}_2\text{C}(\text{O})$ ), 4.00–3.83 (4H, m,  $(\text{OCH}_2)_2$ ), 3.92 (6H, s,  $\text{C}(\text{OCH}_2)_3\text{C}$ ), 3.79 (3H, s,  $\text{OCH}_3$ ), 3.74 (3H, s,  $\text{OCH}_3$ ), 0.74 (3H, s,  $\text{CCH}_3$ );  **$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  195.4 ( $\text{C}(\text{O})$ ), 148.7 ( $\text{C}_{\text{Ar}}$ ), 147.4 ( $\text{C}_{\text{Ar}}$ ), 128.1 ( $\text{C}_{\text{Ar}}$ ), 124.4 ( $\text{C}_{\text{Ar}}$ ), 114.2 ( $\text{HC}_{\text{Ar}}$ ), 109.5 ( $\text{HC}_{\text{Ar}}$ ), 103.4 ( $\text{CO}_3$ ), 101.7 ( $\text{CH}(\text{OR})_2$ ), 72.8 ( $\text{C}(\text{OCH}_2)_3\text{C}$ ), 64.7 ( $(\text{OCH}_2)_2$ ), 55.60 ( $\text{OCH}_3$ ), 55.59 ( $\text{OCH}_3$ ), 39.7 ( $\text{CH}_2\text{C}(\text{O})$ ), 30.5 ( $\text{C}(\text{OCH}_2)_3\text{CMe}$ ), 13.8 ( $\text{CCH}_3$ ).

**2-[1-Benzyl-2-(1,3-dioxolan-2-yl)-1H-indol-3-yl]-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]-octan-1-yl)ethan-1-one (3c)**

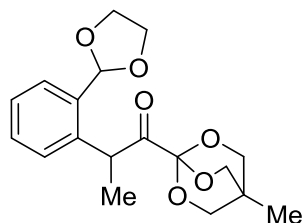


To a flame-dried Biotage® microwave vial capped with a rubber septum were added methyl-OBO-ketone **1**<sup>6</sup> (721 mg, 4.19 mmol, 1.5 equiv), 1-benzyl-3-bromo-2-(1,3-dioxolan-2-yl)-1H-indole (**2c**)<sup>8</sup> (1.00 g, 2.79 mmol, 1.0 equiv), and  $\text{Pd}(\text{dtbpf})\text{Cl}_2$  (46 mg, 70  $\mu\text{mol}$ , 2.5 mol %). The rubber septum was then removed, and the reaction vessel was sealed with a microwave vial cap (Reseal™ septum). THF (20.9 mL) and *t*-BuONa solution (2.8 mL, 7.0 mmol, 2.5 equiv, 2 M in THF) were added *via* syringe. The vial was flushed with argon for 5 min and then heated at 70 °C for 24 h. The resulting mixture was filtered through a plug of silica using EtOAc as eluent and concentrated *in vacuo*. Purification by flash column chromatography (*n*-pentane/EtOAc, 50:50) gave the *title compound* **3c** (1.05 g, 84%) as a brown solid. **mp**: 135–137 °C; **IR**:  $\nu_{\text{max}}$  (thin film) 3474, 2940, 2883, 1751, 1076, 735  $\text{cm}^{-1}$ ; **HRMS**: calculated for  $\text{C}_{26}\text{H}_{28}\text{NO}_6$ , 450.19111  $[\text{M}+\text{H}]^+$ , found  $m/z$  450.19093,  $\Delta = -0.4$  ppm;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.50 (1H, d,  $J = 7.9$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.28–7.02 (8H, m,  $8 \times \text{HC}_{\text{Ar}}$ ), 6.06 (1H, s,  $\text{CH}(\text{OR})_2$ ), 5.50 (2H, s,  $\text{PhCH}_2$ ), 4.32 (2H, s,  $\text{CH}_2\text{C}(\text{O})$ ), 4.05 (6H, s,  $\text{C}(\text{OCH}_2)_3\text{C}$ ), 4.02–3.88 (4H, m,  $(\text{OCH}_2)_2$ ), 0.87 (3H, s,  $\text{CCH}_3$ );  **$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  195.7 ( $\text{C}(\text{O})$ ), 138.4 ( $\text{C}_{\text{Ar}}$ ), 137.4 ( $\text{C}_{\text{Ar}}$ ), 131.7

(C<sub>Ar</sub>), 128.6 (HC<sub>Ar</sub>), 127.9 (C<sub>Ar</sub>), 127.1 (HC<sub>Ar</sub>), 126.2 (HC<sub>Ar</sub>), 122.9 (HC<sub>Ar</sub>), 119.7 (HC<sub>Ar</sub>), 119.4 (HC<sub>Ar</sub>), 110.0 (HC<sub>Ar</sub>), 107.9 (C<sub>Ar</sub>), 104.0 (CO<sub>3</sub>), 99.0 (CH(OR)<sub>2</sub>), 73.2 (C(OCH<sub>2</sub>)<sub>3</sub>C), 65.0 ((OCH<sub>2</sub>)<sub>2</sub>), 47.8 (PhCH<sub>2</sub>), 32.9 (CH<sub>2</sub>C(O)), 31.0 (C(OCH<sub>2</sub>)<sub>3</sub>CMe), 14.4 (CCH<sub>3</sub>).

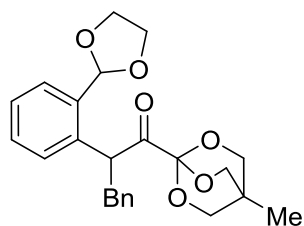
### S3.1.2 $\alpha$ -Functionalisation of arylated OBO-ketone **3a**

#### 2-[2-(1,3-Dioxolan-2-yl)phenyl]-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)propan-1-one (**S1**)



To a flame-dried Biotage<sup>®</sup> microwave vial capped with a rubber septum was added the arylated OBO-ketone **3a** (250 mg, 0.780 mmol, 1.0 equiv). The rubber septum was then removed, and the reaction vessel was sealed with a microwave vial cap (Reseal<sup>TM</sup> septum) and then dry THF (7.2 mL), *t*-BuONa solution (590  $\mu$ L, 1.20 mmol, 1.5 equiv, 2 M in THF) and MeI (53  $\mu$ L, 0.86 mmol, 1.1 equiv) were added sequentially *via* syringe. The vial was flushed with argon for 5 min and then heated at 70 °C for 3 h. The resulting mixture was filtered through a plug of silica using EtOAc as eluent, concentrated *in vacuo* and purified by flash column chromatography (*n*-pentane/EtOAc, 60:40) to give the *title compound* **S1** (175 mg, 67%) as brown solid. **mp**: 130–132 °C; **IR**:  $\nu_{\text{max}}$  (thin film) 2946, 2887, 2824, 1740, 1113, 1056, 1046, 930, 747 cm<sup>-1</sup>; **HRMS**: calculated for C<sub>18</sub>H<sub>23</sub>O<sub>6</sub>, 335.1489 [M+H]<sup>+</sup>, found *m/z* 335.1489,  $\Delta$  = 0.03 ppm; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.55 (1H, d, *J* = 7.4 Hz, HC<sub>Ar</sub>), 7.31–7.18 (3H, m, 3  $\times$  HC<sub>Ar</sub>), 6.22 (1H, s, CH(OR)<sub>2</sub>), 4.75 (1H, q, *J* = 6.9 Hz, CHCH<sub>3</sub>), 4.20–3.99 (4H, m, (OCH<sub>2</sub>)<sub>2</sub>), 3.88 (6H, s, C(OCH<sub>2</sub>)<sub>3</sub>C), 1.40 (3H, d, *J* = 6.9 Hz, CHCH<sub>3</sub>), 0.78 (3H, s, CCH<sub>3</sub>); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  198.9 (C(O)), 138.7 (C<sub>Ar</sub>), 135.2 (C<sub>Ar</sub>), 129.1 (HC<sub>Ar</sub>), 127.7 (HC<sub>Ar</sub>), 126.7 (HC<sub>Ar</sub>), 126.0 (HC<sub>Ar</sub>), 104.0 (CO<sub>3</sub>), 101.7 (CH(OR)<sub>2</sub>), 73.0 (C(OCH<sub>2</sub>)<sub>3</sub>C), 65.4 (OC<sub>a</sub>H<sub>2</sub>C<sub>b</sub>H<sub>2</sub>O), 65.1 (OC<sub>a</sub>H<sub>2</sub>C<sub>b</sub>H<sub>2</sub>O), 41.5 (CH<sub>3</sub>CH), 30.9 (C(OCH<sub>2</sub>)<sub>3</sub>CMe), 19.2 (CHCH<sub>3</sub>), 14.3 (CCH<sub>3</sub>).

#### 2-[2-(1,3-Dioxolan-2-yl)phenyl]-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-3-phenylpropan-1-one (**S2**)



To a flame-dried Biotage<sup>®</sup> microwave vial capped with a rubber septum was added the arylated OBO-ketone **3a** (100 mg, 0.312 mmol, 1.0 equiv). The rubber septum was then removed, and the reaction vessel was sealed with a microwave vial cap (Reseal<sup>TM</sup> septum) and then dry THF (2.9 mL), *t*-BuONa solution (235  $\mu$ L,

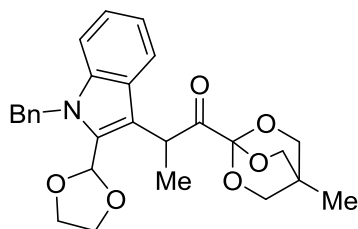
0.468 mmol, 1.5 equiv, 2 M in THF) and benzyl bromide (39  $\mu$ L, 0.33 mmol, 1.05 equiv) were added sequentially *via* syringe. The vial was flushed with argon for 5 min and then heated at 70 °C for 3 h. The resulting mixture was filtered through a plug of silica using EtOAc as eluent, concentrated *in vacuo* and purified by flash column chromatography (*n*-pentane/EtOAc, 50:50) to give the *title compound* **S2** (95 mg, 74%) as brown solid. **mp**: 170–173 °C; **IR**:  $\nu_{\text{max}}$  (thin film) 2980, 2884, 1748, 1072, 1062, 1029, 992, 943, 746, 726, 694  $\text{cm}^{-1}$ ; **HRMS**: calculated for  $\text{C}_{24}\text{H}_{27}\text{O}_6$ , 411.1802  $[\text{M}+\text{H}]^+$ , found  $m/z$  411.1802,  $\Delta = -0.10$  ppm;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.57 (1H, d,  $J = 7.5$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.34–7.11 (8H, m,  $8 \times \text{HC}_{\text{Ar}}$ ), 6.20 (1H, s,  $\text{CH}(\text{OR})_2$ ), 5.01 (1H, dd,  $J = 9.4, 5.0$  Hz,  $\text{CHC}(\text{O})$ ), 4.19–3.89 (4H, m,  $(\text{OCH}_2)_2$ ), 3.81 (6H, s,  $\text{C}(\text{OCH}_2)_3\text{C}$ ), 3.41 (1H, dd,  $J = 13.7, 9.3$  Hz,  $\text{PhCH}_a\text{H}_b$ ), 2.92 (1H, dd,  $J = 13.7, 5.0$  Hz,  $\text{PhCH}_a\text{H}_b$ ), 0.73 (3H, s,  $\text{CH}_3$ );  **$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  197.5 ( $\text{C}(\text{O})$ ), 139.8 ( $\text{C}_{\text{Ar}}$ ), 137.0 ( $\text{C}_{\text{Ar}}$ ), 135.7 ( $\text{C}_{\text{Ar}}$ ), 129.3 ( $\text{HC}_{\text{Ar}}$ ), 129.0 ( $\text{HC}_{\text{Ar}}$ ), 128.1 ( $\text{HC}_{\text{Ar}}$ ), 127.8 ( $\text{HC}_{\text{Ar}}$ ), 126.8 ( $\text{HC}_{\text{Ar}}$ ), 126.1 ( $\text{HC}_{\text{Ar}}$ ), 126.0 ( $\text{HC}_{\text{Ar}}$ ), 103.7 ( $\text{CO}_3$ ), 101.7 ( $\text{CH}(\text{OR})_2$ ), 72.9 ( $\text{C}(\text{OCH}_2)_3\text{C}$ ), 65.3 ( $\text{OC}_a\text{H}_2\text{C}_b\text{H}_2\text{O}$ ), 64.7 ( $\text{OC}_a\text{H}_2\text{C}_b\text{H}_2\text{O}$ ), 49.2 ( $\text{CHC}(\text{O})$ ), 39.5 ( $\text{CH}_2\text{Ph}$ ), 30.8 ( $\text{C}(\text{OCH}_2)_3\text{CMe}$ ), 14.1 ( $\text{CH}_3$ ).

### S3.1.3 $\alpha$ -Functionalisation of arylated OBO-ketone **3c**

**General procedure A:** To a flame-dried Biotage<sup>®</sup> microwave vial capped with a rubber septum were added the arylated OBO-ketone **3c** (1.0 equiv) and the appropriate electrophile (1.1 equiv). The rubber septum was then removed, and the reaction vessel was sealed with a microwave vial cap (Reseal<sup>TM</sup> septum) and dry DMF (0.2 M) was added. The mixture was stirred at 0 °C for 10 min, followed by the addition of NaH (60% in mineral oil) (1.2 equiv). The reaction was stirred for 15 min at 0 °C, after which the ice was removed from the cooling bath and the cold water was left to warm to rt over 2 h. The reaction was quenched with saturated aq  $\text{NH}_4\text{Cl}$  and extracted with DCM ( $\times 3$ ). The organic layers were combined and washed with water ( $\times 5$ ), dried over  $\text{MgSO}_4$ , filtered, concentrated *in vacuo* and purified by flash column chromatography to give the corresponding product **S3-S4**.



**2-[1-Benzyl-2-(1,3-dioxolan-2-yl)-1H-indol-3-yl]-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]-octan-1-yl)propan-1-one (S3)**

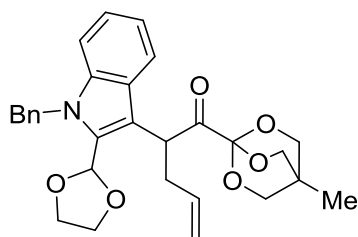


Arylated OBO-ketone **3c** (270 mg, 0.601 mmol, 1.0 equiv) and MeI (41  $\mu$ L, 0.66 mmol, 1.1 equiv) were subjected to **General procedure A** (chromatography eluent: DCM/MeOH, 99:1) to give the *title compound S3* (259 mg, 93%) as a white solid.

**mp:** 182–184 °C. **IR:**  $\nu_{\max}$  (thin film) 2935, 2880, 1740, 1075,

1031, 989, 908, 726  $\text{cm}^{-1}$ ; **HRMS:** calculated for  $\text{C}_{27}\text{H}_{30}\text{NO}_6$ , 464.20676  $[\text{M}+\text{H}]^+$ , found  $m/z$  464.20663,  $\Delta = -0.28$  ppm;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.73 (1H, d,  $J = 7.8$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.26–7.17 (3H, m,  $3 \times \text{HC}_{\text{Ar}}$ ), 7.12–7.01 (5H, m,  $5 \times \text{HC}_{\text{Ar}}$ ), 6.27 (1H, s,  $\text{CH}(\text{OR})_2$ ), 5.56 (1H, d,  $J = 17.0$  Hz,  $\text{PhCH}_a\text{H}_b$ ), 5.48 (1H, d,  $J = 17.0$  Hz,  $\text{PhCH}_a\text{H}_b$ ), 4.82 (1H, q,  $J = 7.1$  Hz,  $\text{CHCH}_3$ ), 4.12–3.95 (4H, m,  $(\text{OCH}_2)_2$ ), 3.86 (6H, s,  $\text{C}(\text{OCH}_2)_3\text{C}$ ), 1.63 (3H, d,  $J = 7.1$  Hz,  $\text{CHCH}_3$ ), 0.76 (3H, s,  $\text{CCH}_3$ );  **$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  197.9 ( $\text{C}(\text{O})$ ), 138.7 ( $\text{C}_{\text{Ar}}$ ), 137.6 ( $\text{C}_{\text{Ar}}$ ), 129.2 ( $\text{C}_{\text{Ar}}$ ), 128.3 ( $\text{HC}_{\text{Ar}}$ ), 126.7 ( $\text{HC}_{\text{Ar}}$ ), 126.1 ( $\text{C}_{\text{Ar}}$ ), 126.0 ( $\text{HC}_{\text{Ar}}$ ), 122.8 ( $\text{HC}_{\text{Ar}}$ ), 120.9 ( $\text{HC}_{\text{Ar}}$ ), 119.5 ( $\text{HC}_{\text{Ar}}$ ), 114.8 ( $\text{C}_{\text{Ar}}$ ), 110.1 ( $\text{HC}_{\text{Ar}}$ ), 104.0 ( $\text{CO}_3$ ), 98.4 ( $\text{CH}(\text{OR})_2$ ), 72.8 ( $\text{C}(\text{OCH}_2)_3\text{C}$ ), 64.94 ( $\text{OC}_a\text{H}_2\text{C}_b\text{H}_2\text{O}$ ), 64.86 ( $\text{OC}_a\text{H}_2\text{C}_b\text{H}_2\text{O}$ ), 47.9 ( $\text{PhCH}_2$ ), 37.8 ( $\text{CHC}(\text{O})$ ), 30.7 ( $\text{C}(\text{OCH}_2)_3\text{CMe}$ ), 16.8 ( $\text{CHCH}_3$ ), 14.2 ( $\text{CCH}_3$ ).

**2-[1-Benzyl-2-(1,3-dioxolan-2-yl)-1H-indol-3-yl]-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]-octan-1-yl)pent-4-en-1-one (S4)**



Arylated OBO-ketone **3c** (270 mg, 0.601 mmol, 1.0 equiv) and allyl bromide (57  $\mu$ L, 0.66 mmol, 1.1 equiv) were subjected to **General Procedure A** (chromatography eluent: DCM/MeOH, 99:1) to give the *title compound S4* (209 mg, 71%) as a white solid. **mp:** 177–180 °C; **IR:**  $\nu_{\max}$  (thin film) 2936, 2881, 1741,

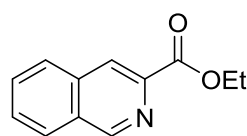
1496, 1344, 1077, 988, 953, 910, 730  $\text{cm}^{-1}$ ; **HRMS:** calculated for  $\text{C}_{29}\text{H}_{32}\text{NO}_6$ , 490.22241  $[\text{M}+\text{H}]^+$ , found  $m/z$  490.22208,  $\Delta = -0.69$  ppm;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.77–7.72 (1H, m,  $\text{HC}_{\text{Ar}}$ ), 7.26–7.16 (3H, m,  $3 \times \text{HC}_{\text{Ar}}$ ), 7.11–6.96 (5H, m,  $5 \times \text{HC}_{\text{Ar}}$ ), 6.25 (1H, s,  $\text{CH}(\text{OR})_2$ ), 5.80–5.66 (1H, m,  $\text{CH}_2=\text{CHCH}_2$ ), 5.55 (1H, d,  $J = 16.9$  Hz,  $\text{PhCH}_a\text{H}_b$ ), 5.49 (1H, d,  $J = 17.0$  Hz,  $\text{PhCH}_a\text{H}_b$ ), 5.05 (1H, dd,  $J = 17.1, 2.1$  Hz,  $\text{CH}_{\text{trans}}\text{H}_{\text{cis}}\text{CH}$ ), 4.97 (1H, dd,  $J = 10.2, 2.1$  Hz,  $\text{CH}_{\text{trans}}\text{H}_{\text{cis}}\text{CH}$ ), 4.74 (1H, t,  $J = 7.6$  Hz,  $\text{CHC}(\text{O})$ ), 4.10–3.95 (4H, m,  $(\text{OCH}_2)_2$ ), 3.87 (6H, s,  $\text{C}(\text{OCH}_2)_3\text{C}$ ), 3.10–3.00 (1H, m,  $\text{CHCH}_a\text{H}_b\text{CH}$ ), 2.80–2.70 (1H, m,  $\text{CHCH}_a\text{H}_b\text{CH}$ ), 0.76 (3H, s,  $\text{CCH}_3$ );  **$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  196.6 ( $\text{C}(\text{O})$ ), 138.7

(C<sub>Ar</sub>), 137.6 (C<sub>Ar</sub>), 135.9 (CH<sub>2</sub>=CHCH<sub>2</sub>), 130.0 (C<sub>Ar</sub>), 128.3 (HC<sub>Ar</sub>), 126.8 (HC<sub>Ar</sub>), 126.2 (C<sub>Ar</sub>), 126.0 (HC<sub>Ar</sub>), 122.8 (HC<sub>Ar</sub>), 121.0 (HC<sub>Ar</sub>), 119.7 (HC<sub>Ar</sub>), 116.5 (CH<sub>2</sub>=CHCH<sub>2</sub>), 112.6 (C<sub>Ar</sub>), 110.2 (HC<sub>Ar</sub>), 104.0 (CO<sub>3</sub>), 98.4 (CH(OR)<sub>2</sub>), 72.9 (C(OCH<sub>2</sub>)<sub>3</sub>C), 65.0 (OC<sub>a</sub>H<sub>2</sub>C<sub>b</sub>H<sub>2</sub>O), 64.9 (OC<sub>a</sub>H<sub>2</sub>C<sub>b</sub>H<sub>2</sub>O), 48.0 (PhCH<sub>2</sub>), 43.5 (CHC(O)), 34.8 (CH<sub>2</sub>=CHCH<sub>2</sub>), 30.8 (C(OCH<sub>2</sub>)<sub>3</sub>CMe), 14.3 (CCH<sub>3</sub>).

### S3.1.4 Cyclisation to isoquinoline- and $\beta$ -carboline-3-carboxylates 4

**General procedure B:** *Step 1:* To a Biotage<sup>®</sup> microwave vial NH<sub>4</sub>Cl (10 equiv), the appropriate acetal **3** or **S1-4** (1.0 equiv) and EtOH (0.1 M) were added. The reaction vessel was sealed with a microwave vial cap (Reseal<sup>TM</sup> septum) and the mixture stirred at 115 °C for 12 h. After cooling to rt, the crude material was concentrated *in vacuo*, passed through a short silica column using EtOAc as eluent and concentrated *in vacuo*. *Step 2:* The crude material was dissolved in dry EtOH (0.1 M) and transferred *via* syringe to a flamed-dried Biotage<sup>®</sup> microwave vial containing anhydrous *p*-toluenesulfonic acid (3.0 equiv) and stirred at 115 °C for 24 h for isoquinolines and for 36 h for  $\beta$ -carbolines. After cooling to rt, the reaction mixture was neutralised by the addition of solid NaHCO<sub>3</sub> (6.0 equiv) and concentrated *in vacuo*. The crude material was dissolved in DCM and washed with water. The organic phase was separated, and the aqueous layer was extracted with DCM ( $\times$  3). The organic layers were combined, dried over MgSO<sub>4</sub>, filtered, concentrated *in vacuo* and purified by flash column chromatography to give the corresponding isoquinoline **4**.

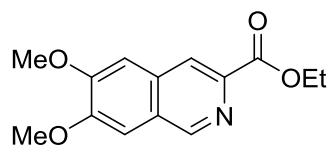
#### Ethyl isoquinoline-3-carboxylate (4a)



Arylated OBO-ketone **3a** (96 mg, 0.30 mmol, 1.0 equiv) was subjected to **General Procedure B** (chromatography eluent: *n*-pentane/EtOAc, 60:40) to give the *title compound 4a* (51 mg, 84%) as a light brown solid. **mp**: 43–45 °C (lit.<sup>9</sup> mp 45–45.5 °C); **IR**:  $\nu_{\text{max}}$  (thin film) 2975, 2880, 1710, 1280, 1150, 750 cm<sup>-1</sup>; **HRMS**: calculated for C<sub>12</sub>H<sub>12</sub>NO<sub>2</sub>, 202.08626 [M+H]<sup>+</sup>, found  $m/z$  202.08623,  $\Delta$  = –0.14 ppm; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.33 (1H, s, HC<sub>Ar</sub>(1)), 8.58 (1H, s, HC<sub>Ar</sub>(4)), 8.04 (1H, d,  $J$  = 7.8 Hz, HC<sub>Ar</sub>), 7.95 (1H, d,  $J$  = 7.9 Hz, HC<sub>Ar</sub>), 7.70–7.80 (2H, m, 2  $\times$  HC<sub>Ar</sub>), 4.52 (2H, q,  $J$  = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 1.47 (3H, t,  $J$  = 7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  165.9 (C(O)), 152.8 (HC<sub>Ar</sub>(1)), 141.9 (C<sub>Ar</sub>), 135.5 (C<sub>Ar</sub>), 131.2 (HC<sub>Ar</sub>), 130.0 (C<sub>Ar</sub>), 129.6 (HC<sub>Ar</sub>), 128.1 (HC<sub>Ar</sub>), 127.8 (HC<sub>Ar</sub>), 124.0 (HC<sub>Ar</sub>(4)), 62.0 (OCH<sub>2</sub>CH<sub>3</sub>), 14.6

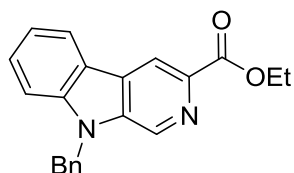
(OCH<sub>2</sub>CH<sub>3</sub>). Physical and spectroscopic data are consistent with those previously reported.<sup>9,10</sup>

#### ***Ethyl 6,7-dimethoxyisoquinoline-3-carboxylate (4b)***



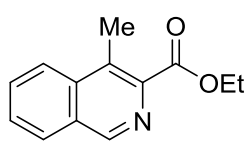
Arylated OBO-ketone **3b** (114 mg, 0.300 mmol, 1.0 equiv) was subjected to **General procedure B** (chromatography eluent: *n*-pentane/EtOAc, 30:70) to give the *title compound 4b* (63 mg, 80%) as a light brown solid. **mp**: 178–181 °C (lit.<sup>10</sup> mp 174–176 °C); **IR**:  $\nu_{\text{max}}$  (thin film) 3069, 2980, 2834, 1703, 1504, 1408, 1245, 1148, 1104, 1006, 861 cm<sup>-1</sup>; **HRMS**: calculated for C<sub>14</sub>H<sub>16</sub>NO<sub>4</sub>, 262.10738 [M+H]<sup>+</sup>, found *m/z* 262.10716,  $\Delta$  = –0.86 ppm; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.10 (1H, s, HC<sub>Ar</sub>(1)), 8.42 (1H, s, HC<sub>Ar</sub>(4)), 7.24 (1H, s, HC<sub>Ar</sub>), 7.16 (1H, s, HC<sub>Ar</sub>), 4.48 (2H, q, *J* = 7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 4.03 (3H, s, OCH<sub>3</sub>), 4.02 (3H, s, OCH<sub>3</sub>), 1.45 (3H, t, *J* = 7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  166.1 (C(O)), 153.5 (C<sub>Ar</sub>), 152.1 (C<sub>Ar</sub>), 150.0 (HC<sub>Ar</sub>(1)), 140.8 (C<sub>Ar</sub>), 132.2 (C<sub>Ar</sub>), 126.4 (C<sub>Ar</sub>), 122.7 (HC<sub>Ar</sub>(4)), 105.9 (HC<sub>Ar</sub>), 105.5 (HC<sub>Ar</sub>), 61.7 (OCH<sub>2</sub>CH<sub>3</sub>), 56.3 (OCH<sub>3</sub>), 56.3 (OCH<sub>3</sub>), 14.6 (OCH<sub>2</sub>CH<sub>3</sub>). Physical and spectroscopic data are consistent with those previously reported.<sup>10</sup>

#### ***Ethyl 9-benzyl-9H-pyrido[3,4-b]indole-3-carboxylate (4c)***



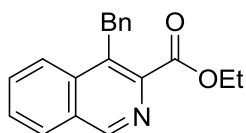
Arylated OBO-ketone **3c** (135 mg, 0.300 mmol, 1.0 equiv) was subjected to **General procedure B** (chromatography eluent: *n*-pentane/EtOAc, 60:40) to give the *title compound 4c* (88 mg, 89%) as a light brown solid. **mp**: 124–126 °C (lit.<sup>11</sup> mp 126–127 °C); **IR**:  $\nu_{\text{max}}$  (thin film) 3062, 3029, 2993, 1721, 1267, 1216, 1028, 749, 722 cm<sup>-1</sup>; **HRMS**: calculated for C<sub>21</sub>H<sub>19</sub>N<sub>2</sub>O<sub>2</sub>, 331.14410 [M+H]<sup>+</sup>, found *m/z* 331.14404,  $\Delta$  = –0.19 ppm; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.91–8.87 (2H, m, HC<sub>Ar</sub>(1) + HC<sub>Ar</sub>(4)), 8.22 (1H, d, *J* = 7.8 Hz, HC<sub>Ar</sub>), 7.59 (1H, ddd, *J* = 8.3, 7.2, 1.2 Hz, HC<sub>Ar</sub>), 7.48 (1H, d, *J* = 8.1 Hz, HC<sub>Ar</sub>), 7.36 (1H, ddd, *J* = 8.0, 7.1, 0.9 Hz, HC<sub>Ar</sub>), 7.29–7.21 (3H, m, 3 × HC<sub>Ar</sub>), 7.16–7.10 (2H, m, 2 × HC<sub>Ar</sub>), 5.59 (2H, s, PhCH<sub>2</sub>), 4.53 (2H, q, *J* = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 1.48 (3H, t, *J* = 7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  166.2 (C(O)), 141.8 (C<sub>Ar</sub>), 138.1 (C<sub>Ar</sub>), 138.0 (C<sub>Ar</sub>), 135.8 (C<sub>Ar</sub>), 132.1 (HC<sub>Ar</sub>(1)), 129.14 (HC<sub>Ar</sub>), 129.09 (HC<sub>Ar</sub>), 128.8 (C<sub>Ar</sub>), 128.1 (HC<sub>Ar</sub>), 126.6 (HC<sub>Ar</sub>), 122.2 (HC<sub>Ar</sub>), 121.6 (C<sub>Ar</sub>), 121.0 (HC<sub>Ar</sub>), 117.8 (HC<sub>Ar</sub>(4)), 110.2 (HC<sub>Ar</sub>), 61.7 (OCH<sub>2</sub>CH<sub>3</sub>), 47.3 (PhCH<sub>2</sub>), 14.6 (OCH<sub>2</sub>CH<sub>3</sub>). Physical and spectroscopic data are consistent with those previously reported.<sup>11,12</sup>

#### Ethyl 4-methylisoquinoline-3-carboxylate (**4d**)



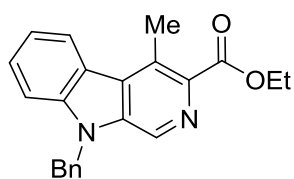
Arylated OBO-ketone **S1** (100 mg, 0.30 mmol, 1.0 equiv) was subjected to **General Procedure B** (chromatography eluent: *n*-pentane/EtOAc, 60:40) to give the *title compound* **4d** (45 mg, 70%) as a yellow oil. **IR**:  $\nu_{\max}$  (thin film) 2980, 1714, 1284, 1250, 1220, 1054, 768, 751  $\text{cm}^{-1}$ ; **HRMS**: calculated for  $\text{C}_{13}\text{H}_{14}\text{NO}_2$ , 216.10191  $[\text{M}+\text{H}]^+$ , found  $m/z$  216.10176,  $\Delta = -0.67$  ppm;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.15 (1H, s,  $\text{HC}(1)$ ), 8.13 (1H, d,  $J = 8.6$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.99 (1H, dd,  $J = 8.1, 1.2$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.79 (1H, ddd,  $J = 8.7, 6.8, 1.8$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.68 (1H, ddd,  $J = 8.0, 6.9, 1.1$  Hz,  $\text{HC}_{\text{Ar}}$ ), 4.51 (2H,  $J = 7.2$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 2.87 (3H, s,  $\text{ArCH}_3$ ), 1.46 (3H, t,  $J = 7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ );  **$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  167.6 ( $\text{C}(\text{O})$ ), 150.5 ( $\text{HC}_{\text{Ar}}(1)$ ), 141.7 ( $\text{C}_{\text{Ar}}$ ), 136.0 ( $\text{C}_{\text{Ar}}$ ), 131.0 ( $\text{HC}_{\text{Ar}}$ ), 130.0 ( $\text{C}_{\text{Ar}}$ ), 128.9 ( $\text{C}_{\text{Ar}}$ ), 128.5 ( $\text{HC}_{\text{Ar}}$ ), 128.2 ( $\text{HC}_{\text{Ar}}$ ), 124.3 ( $\text{HC}_{\text{Ar}}$ ), 61.8 ( $\text{OCH}_2\text{CH}_3$ ), 14.5 ( $\text{OCH}_2\text{CH}_3$ ), 14.4 ( $\text{ArCH}_3$ ).

#### Ethyl 4-benzylisoquinoline-3-carboxylate (**4e**)



Arylated OBO-ketone **S2** (123 mg, 0.300 mmol, 1.0 equiv) was subjected to **General procedure B** (chromatography eluent: *n*-pentane/EtOAc, 60:40) to give the *title compound* **4e** (62 mg, 71%) as an off-white solid. **mp**: 118–120  $^{\circ}\text{C}$ ; **IR**:  $\nu_{\max}$  (thin film) 3080, 3027, 2985, 1708, 1291, 1248, 1200, 1064, 789, 774, 693, 676  $\text{cm}^{-1}$ ; **HRMS**: calculated for  $\text{C}_{19}\text{H}_{18}\text{NO}_2$ , 292.13321  $[\text{M}+\text{H}]^+$ , found  $m/z$  292.13321,  $\Delta = 0.01$  ppm;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.25 (1H, s,  $\text{HC}_{\text{Ar}}(1)$ ), 8.98–8.10 (2H, m,  $2 \times \text{HC}_{\text{Ar}}$ ), 7.71–7.62 (2H, m,  $2 \times \text{HC}_{\text{Ar}}$ ), 7.25–7.11 (5H, m,  $5 \times \text{HC}_{\text{Ar}}$ ), 4.77 (2H, s,  $\text{PhCH}_2$ ), 4.46 (2H, q,  $J = 7.2$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 1.37 (3H, t,  $J = 7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ );  **$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  167.4 ( $\text{C}(\text{O})$ ), 151.5 ( $\text{C}(1)$ ), 142.9 ( $\text{C}_{\text{Ar}}$ ), 139.9 ( $\text{C}_{\text{Ar}}$ ), 135.8 ( $\text{C}_{\text{Ar}}$ ), 131.4 ( $\text{C}_{\text{Ar}}$ ), 131.3 ( $\text{HC}_{\text{Ar}}$ ), 129.4 ( $\text{C}_{\text{Ar}}$ ), 128.59 ( $\text{HC}_{\text{Ar}}$ ), 128.57 ( $\text{HC}_{\text{Ar}}$ ), 128.37 ( $\text{HC}_{\text{Ar}}$ ), 128.36 ( $\text{HC}_{\text{Ar}}$ ), 126.2 ( $\text{HC}_{\text{Ar}}$ ), 125.0 ( $\text{HC}_{\text{Ar}}$ ), 62.0 ( $\text{OCH}_2\text{CH}_3$ ), 33.8 ( $\text{PhCH}_2$ ), 14.4 ( $\text{OCH}_2\text{CH}_3$ ).

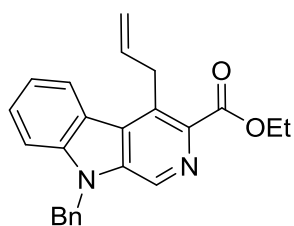
#### Ethyl 9-benzyl-4-methyl-9H-pyrido[3,4-b]indole-3-carboxylate (**4f**)



Arylated OBO-ketone **S3** (139 mg, 0.300 mmol, 1.0 equiv) was subjected to **General procedure B** (chromatography eluent: *n*-pentane/EtOAc, 60:40) to give the *title compound* **4f** (76 mg, 74%) as a light brown solid. **mp**: 116–118  $^{\circ}\text{C}$ ; **IR**:  $\nu_{\max}$  (thin film) 3031, 2979, 2933, 1709, 1368, 1332, 1273, 1220, 1075, 747, 730, 699  $\text{cm}^{-1}$ ; **HRMS**: calculated for  $\text{C}_{22}\text{H}_{21}\text{N}_2\text{O}_2$ , 345.15975  $[\text{M}+\text{H}]^+$ , found  $m/z$  345.15927,  $\Delta = -1.40$  ppm;  **$^1\text{H}$**

**NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.76 (1H, s,  $HC_{Ar}(1)$ ), 8.34 (1H, d,  $J = 7.8$  Hz,  $HC_{Ar}$ ), 7.59 (1H, ddd,  $J = 8.3, 7.2, 1.2$  Hz,  $HC_{Ar}$ ), 7.49 (1H, d,  $J = 8.1$  Hz,  $HC_{Ar}$ ), 7.36 (1H, ddd,  $J = 8.1, 7.2, 1.2$  Hz,  $HC_{Ar}$ ), 7.27–7.21 (3H, m,  $3 \times HC_{Ar}$ ), 7.13–7.08 (2H, m,  $2 \times HC_{Ar}$ ), 5.56 (2H, s,  $PhCH_2$ ), 4.51 (2H, q,  $J = 7.2$  Hz,  $OCH_2CH_3$ ), 3.15 (3H, s,  $ArCH_3$ ), 1.48 (3H, t,  $J = 7.1$  Hz,  $OCH_2CH_3$ ); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  167.3 ( $C(O)$ ), 141.5 ( $C_{Ar}$ ), 137.9 ( $C_{Ar}$ ), 137.0 ( $C_{Ar}$ ), 136.0 ( $C_{Ar}$ ), 131.4 ( $C_{Ar}$ ), 129.6 ( $HC_{Ar}(1)$ ), 129.1 ( $HC_{Ar}$ ), 129.0 ( $C_{Ar}$ ), 128.2 ( $HC_{Ar}$ ), 128.1 ( $HC_{Ar}$ ), 126.6 ( $HC_{Ar}$ ), 124.4 ( $HC_{Ar}$ ), 122.4 ( $C_{Ar}$ ), 120.8 ( $HC_{Ar}$ ), 110.0 ( $HC_{Ar}$ ), 61.5 ( $OCH_2CH_3$ ), 47.0 ( $PhCH_2$ ), 16.7 ( $ArCH_3$ ), 14.6 ( $OCH_2CH_3$ ).

**Ethyl 4-allyl-9-benzyl-9H-pyrido[3,4-b]indole-3-carboxylate (4g)**

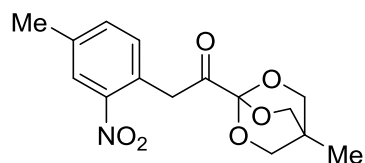


Arylated OBO-ketone **S4** (147 mg, 0.300 mmol, 1.0 equiv) was subjected to **General procedure B** (chromatography eluent: toluene/MeCN, 90:10) to give the *title compound 4g* (72 mg, 65%) as a light brown solid. **mp**: 82–85 °C; **IR**:  $\nu_{max}$  (thin film) 2980, 2928, 1712, 1453, 1388, 1368, 1334, 1272, 1236, 736 cm<sup>-1</sup>; **HRMS**: calculated for C<sub>24</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub>, 371.17540 [M+H]<sup>+</sup>, found  $m/z$  371, 17673,  $\Delta = 3.56$  ppm; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.83 (1H, s,  $HC_{Ar}(1)$ ), 8.30 (1H, d,  $J = 7.9$  Hz,  $HC_{Ar}$ ), 7.60 (1H, ddd,  $J = 8.4, 7.0, 1.4$  Hz,  $HC_{Ar}$ ), 7.52 (1H, d,  $J = 7.7$  Hz,  $HC_{Ar}$ ), 7.37 (1H, ddd,  $J = 8.1, 7.1, 1.1$  Hz,  $HC_{Ar}$ ), 7.29–7.23 (3H, m,  $3 \times HC_{Ar}$ ), 7.17–7.12 (2H, m,  $2 \times HC_{Ar}$ ), 6.30–6.18 (1H, m,  $CH_2=CH$ ), 5.61 (2H, s,  $PhCH_2$ ), 5.16–5.04 (2H, m,  $CH_2=CHCH_2$ ), 4.49 (2H, q,  $J = 7.1$  Hz,  $OCH_2CH_3$ ), 4.45–4.40 (2H, m,  $CH_2=CHCH_2$ ), 1.46 (3H, t,  $J = 7.2$  Hz,  $OCH_2CH_3$ ); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  167.0 ( $C(O)$ ), 141.8 ( $C_{Ar}$ ), 138.0 ( $C_{Ar}$ ), 137.4 ( $C_{Ar}$ ), 136.0 ( $C_{Ar}$ ), 135.0 ( $CH_2=CH$ ), 132.6 ( $C_{Ar}$ ), 130.2 ( $HC_{Ar}$ ), 129.1 ( $HC_{Ar}$ ), 128.5 ( $HC_{Ar}$ ), 128.2 ( $C_{Ar}$ ), 128.2 ( $HC_{Ar}$ ), 126.6 ( $HC_{Ar}$ ), 124.6 ( $HC_{Ar}$ ), 121.6 ( $C_{Ar}$ ), 121.0 ( $HC_{Ar}$ ), 116.5 ( $CH_2=CHCH_2$ ), 110.1 ( $HC_{Ar}$ ), 61.6 ( $OCH_2CH_3$ ), 47.1 ( $PhCH_2$ ), 33.5 ( $CH_2=CHCH_2$ ), 14.6 ( $OCH_2CH_3$ ). Compound **4g** was isolated as a mixture with a minor inseparable impurity.

## S3.2 Synthesis of indole-2-carboxylates 7

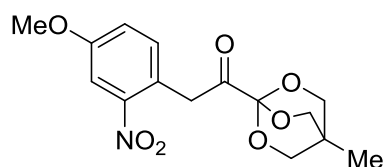
### S3.2.1 Arylated OBO-ketones 6

#### 2-(4-Methyl-2-nitrophenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethan-1-one (6a)



To a flame-dried Biotage<sup>®</sup> microwave vial capped with a rubber septum were added methyl-OBO ketone **1**<sup>6</sup> (861 mg, 5.00 mmol, 1.0 equiv), 1-bromo-4-methyl-2-nitrobenzene (**5a**) (2.16 g, 10.0 mmol, 2.0 equiv), Pd<sub>2</sub>(dba)<sub>3</sub> (46 mg, 50 μmol, 1 mol %), DavePhos (79 mg, 0.20 mmol, 4 mol %), K<sub>2</sub>CO<sub>3</sub> (1.38 g, 10.0 mmol, 2.0 equiv) and phenol (94 mg, 1.00 mmol, 20 mol %). The rubber septum was then removed, and the reaction vessel was sealed with a microwave vial cap (Reseal<sup>TM</sup> septum). Dry toluene (2.0 mL, 2.5 M) was added *via* syringe. The vial was flushed with argon for 5 min and heated at 80 °C for 24 h. The resulting mixture was filtered through a plug of silica using EtOAc as eluent and concentrated *in vacuo* and purified by flash column chromatography (*n*-pentane/EtOAc, 80:20) to give the *title compound* **6a** (1.32 g, 86%) as a yellow solid. **mp**: 175–177 °C; **IR**:  $\nu_{\text{max}}$  (thin film) 2933, 2879, 1723, 1613, 1521, 1350, 1076, 1032, 999, 909, 817, 739 cm<sup>-1</sup>; **HRMS**: calculated for C<sub>15</sub>H<sub>18</sub>NO<sub>6</sub>, 308.11286 [M+H]<sup>+</sup>, found *m/z* 308.11267,  $\Delta$  = -0.63 ppm; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.89 (1H, s, C<sub>Ar</sub>C<sub>Ar</sub>(H)C<sub>Ar</sub>), 7.35 (1H, d, *J* = 7.8 Hz, HC<sub>Ar</sub>), 7.12 (1H, d, *J* = 7.7 Hz, HC<sub>Ar</sub>), 4.36 (2H, s, CH<sub>2</sub>C(O)), 4.03 (6H, s, C(OCH<sub>2</sub>)<sub>3</sub>C), 2.40 (3H, s, ArCH<sub>3</sub>), 0.87 (3H, s, CCH<sub>3</sub>); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  194.0 (C(O)), 148.9 (O<sub>2</sub>NC<sub>Ar</sub>), 139.0 (C<sub>Ar</sub>), 134.3 (HC<sub>Ar</sub>), 133.3 (HC<sub>Ar</sub>), 126.2 (C<sub>Ar</sub>), 125.6 (C<sub>Ar</sub>C<sub>Ar</sub>(H)C<sub>Ar</sub>), 103.7 (CO<sub>3</sub>), 73.3 (C(OCH<sub>2</sub>)<sub>3</sub>C), 42.0 (CH<sub>2</sub>C(O)), 31.0 (C(OCH<sub>2</sub>)<sub>3</sub>CMe), 20.9 (ArCH<sub>3</sub>), 14.3 (CCH<sub>3</sub>).

#### 2-(4-Methoxy-2-nitrophenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethan-1-one (6b)



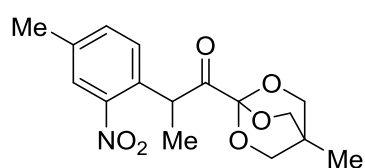
To a flame-dried Biotage<sup>®</sup> microwave vial capped with a rubber septum were added methyl-OBO ketone **1**<sup>6</sup> (431 mg, 2.50 mmol, 1.0 equiv), 1-bromo-4-methoxy-2-nitrobenzene (**5b**) (1.16 g, 5.00 mmol, 2.0 equiv), Pd<sub>2</sub>(dba)<sub>3</sub> (23 mg, 25 μmol, 1 mol %), DavePhos (40 mg, 0.10 mmol, 4 mol %), K<sub>2</sub>CO<sub>3</sub> (691 mg, 5.00 mmol, 2.0 equiv) and phenol (47 mg, 0.50 mmol, 20 mol %). The rubber septum was then removed, and the reaction vessel was sealed with a microwave vial cap (Reseal<sup>TM</sup> septum). Dry toluene (2.0

mL, 1.25 M) was added *via* syringe. The vial was flushed with argon for 5 min and heated at 80 °C for 24 h. The resulting mixture was filtered through a plug of silica using EtOAc as eluent, concentrated *in vacuo* and purified by flash column chromatography (*n*-pentane/EtOAc, 60:40) to give the *title compound* **6b** (727 mg, 90%) as yellow solid. **mp**: 152–154 °C; **IR**:  $\nu_{\max}$  (thin film) 2940, 2883, 1753, 1528, 1347, 1247, 1075, 1047, 1033, 993, 729  $\text{cm}^{-1}$ ; **HRMS**: calculated for  $\text{C}_{15}\text{H}_{18}\text{NO}_7$ , 324.10778  $[\text{M}+\text{H}]^+$ , found  $m/z$  324.10785,  $\Delta = 0.22$  ppm;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.60 (1H, d,  $J = 2.7$  Hz,  $\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}(\text{H})\text{C}_{\text{Ar}}$ ), 7.13 (1H, d,  $J = 8.6$  Hz,  $\text{CH}_2\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}(\text{H})\text{C}_{\text{Ar}}(\text{H})$ ), 7.08 (1H, dd,  $J = 8.5, 2.6$  Hz,  $\text{CH}_2\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}(\text{H})\text{C}_{\text{Ar}}(\text{H})$ ), 4.33 (2H, s,  $\text{CH}_2\text{C}(\text{O})$ ), 4.02 (6H, s,  $\text{C}(\text{OCH}_2)_3\text{C}$ ), 3.83 (3H, s,  $\text{OCH}_3$ ), 0.86 (3H, s,  $\text{CCH}_3$ );  **$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  194.2 ( $\text{C}(\text{O})$ ), 159.3 ( $\text{C}_{\text{Ar}}$ ), 149.6 ( $\text{C}_{\text{Ar}}$ ), 134.2 ( $\text{CH}_2\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}(\text{H})\text{C}_{\text{Ar}}(\text{H})$ ), 121.1 ( $\text{C}_{\text{Ar}}$ ), 120.0 ( $\text{CH}_2\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}(\text{H})\text{C}_{\text{Ar}}(\text{H})$ ), 110.0 ( $\text{C}_{\text{Ar}}\text{C}_{\text{Ar}}(\text{H})\text{C}_{\text{Ar}}$ ), 103.7 ( $\text{CO}_3$ ), 73.2 ( $\text{C}(\text{OCH}_2)_3\text{C}$ ), 55.9 ( $\text{OCH}_3$ ), 41.7 ( $\text{CH}_2\text{C}(\text{O})$ ), 31.0 ( $\text{C}(\text{OCH}_2)_3\text{CMe}$ ), 14.2 ( $\text{CCH}_3$ ).

### S3.2.2 $\alpha$ -Functionalisation of arylated OBO-ketones **6**

**General procedure C:** To a flame-dried Biotage<sup>®</sup> microwave vial capped with a rubber septum were added the appropriate arylated OBO-ketone **6a,b** (1.0 equiv) and electrophile (1.1 equiv). The rubber septum was then removed, and the reaction vessel was sealed with a microwave vial cap (Reseal<sup>TM</sup> septum) and dry DMF (0.2 M) was added. The mixture was stirred at 0 °C for 10 min, followed by the addition of NaH (60% in mineral oil) (1.2 equiv). The reaction was stirred for 15 min at 0 °C, after which the ice was removed from the cooling bath and the cold water was left to warm to rt over 2 h. The reaction was quenched with saturated aq  $\text{NH}_4\text{Cl}$  and extracted with DCM ( $\times 3$ ). The organic layers were combined and washed with water ( $\times 5$ ), dried over  $\text{MgSO}_4$ , filtered, concentrated *in vacuo* and purified by flash column chromatography to give the corresponding product **S5-S6**.

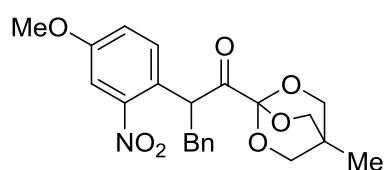
#### 2-(4-Methyl-2-nitrophenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)propan-1-one (**S5**)



Arylated OBO-ketone **6a** (184 mg, 0.599 mmol, 1.0 equiv) and MeI (41  $\mu\text{L}$ , 0.66 mmol, 1.1 equiv) were subjected to **General procedure C** (chromatography eluent: *n*-pentane/EtOAc, 80:20) to give the *title compound* **S5** (184 mg, 95%) as a yellow solid. **mp**: 126–128 °C; **IR**:  $\nu_{\max}$  (thin film) 2937, 2882, 1748, 1527, 1354, 1032, 988, 946, 748  $\text{cm}^{-1}$ ; **HRMS**: calculated

for  $C_{16}H_{20}NO_6$ , 322.12851  $[M+H]^+$ , found  $m/z$  322.12845,  $\Delta = -0.20$  ppm;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.54 (1H, s,  $C_{Ar}C_{Ar}(H)C_{Ar}$ ), 7.28 (1H, d,  $J = 8.2$  Hz,  $HC_{Ar}$ ), 7.20 (1H, d,  $J = 8.0$  Hz,  $HC_{Ar}$ ), 4.89 (1H, q,  $J = 6.9$  Hz,  $CHC(O)$ ), 3.81 (6H, s,  $C(OCH_2)_3C$ ), 2.36 (3H, s,  $ArCH_3$ ), 1.44 (3H, d,  $J = 6.8$  Hz,  $CHCH_3$ ), 0.75 (3H, s,  $CCH_3$ );  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  197.5 ( $C(O)$ ), 149.8 ( $C_{Ar}$ ), 138.0 ( $C_{Ar}$ ), 133.4 ( $HC_{Ar}$ ), 130.8 ( $C_{Ar}$ ), 129.2 ( $HC_{Ar}$ ), 124.6 ( $C_{Ar}C_{Ar}(H)C_{Ar}$ ), 103.8 ( $CO_3$ ), 73.0 ( $C(OCH_2)_3C$ ), 40.4 ( $CHC(O)$ ), 30.9 ( $C(OCH_2)_3CMe$ ), 20.8 ( $ArCH_3$ ), 17.3 ( $CHCH_3$ ), 14.1 ( $CCH_3$ ).

**2-(4-Methoxy-2-nitrophenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-3-phenylpropan-1-one (S6)**



Arylated OBO-ketone **6b** (194 mg, 0.600 mmol, 1.0 equiv) and benzyl bromide (78  $\mu$ L, 0.66 mmol, 1.1 equiv) were subjected to **General procedure C** (chromatography eluent: *n*-pentane/EtOAc, 60:40) to give the *title compound S6* (235 mg, 95%) as a yellow solid. **mp**: 123–125 °C; **IR**:  $\nu_{max}$  (thin film) 2937, 2883, 1747, 1529, 1356, 1251, 1030, 1001, 910, 729, 699  $cm^{-1}$ ; **HRMS**: calculated for  $C_{22}H_{24}NO_7$ , 414.15473  $[M+H]^+$ , found  $m/z$  414.15479,  $\Delta = 0.14$  ppm  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.33 (1H, d,  $J = 8.7$  Hz,  $MeOC_{Ar}C_{Ar}(H)C_{Ar}(H)$ ), 7.23 (1H, d,  $J = 3.4$  Hz,  $C_{Ar}C_{Ar}(H)C_{Ar}$ ), 7.20–7.09 (5H, m,  $5 \times HC_{Ar}$ ), 7.04 (1H, dd,  $J = 8.8$ , 3.4 Hz,  $MeOC_{Ar}C_{Ar}(H)C_{Ar}(H)$ ), 5.22 (1H, dd,  $J = 8.1$ , 6.7 Hz,  $CHC(O)$ ), 3.784 (3H, s,  $OCH_3$ ), 3.777 (6H, s,  $C(OCH_2)_3C$ ), 3.41 (1H, dd,  $J = 13.9$ , 8.3 Hz,  $PhCH_aH_b$ ), 3.03 (1H, dd,  $J = 13.9$ , 6.7 Hz,  $PhCH_aH_b$ ), 0.72 (3H, s,  $CCH_3$ );  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  196.3 ( $C(O)$ ), 158.5 ( $C_{Ar}$ ), 150.7 ( $C_{Ar}$ ), 138.3 ( $C_{Ar}$ ), 130.4 ( $MeOC_{Ar}C_{Ar}(H)C_{Ar}(H)$ ), 129.2 ( $HC_{Ar}$ ), 128.1 ( $HC_{Ar}$ ), 126.2 ( $HC_{Ar}$ ), 123.5 ( $C_{Ar}$ ), 118.7 ( $MeOC_{Ar}C_{Ar}(H)C_{Ar}(H)$ ), 109.5 ( $C_{Ar}C_{Ar}(H)C_{Ar}$ ), 103.6 ( $CO_3$ ), 72.9 ( $C(OCH_2)_3C$ ), 55.7 ( $OCH_3$ ), 46.8 ( $CHC(O)$ ), 37.8 ( $CHCH_2$ ), 30.7 ( $C(OCH_2)_3CMe$ ), 14.0 ( $CCH_3$ ).

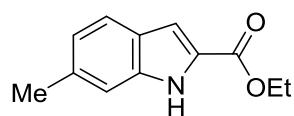
### S3.2.3 Reductive cyclisation to indole-2-carboxylates 7

**General procedure D: Step 1:** To a Biotage<sup>®</sup> microwave vial were added an aqueous solution of  $TiCl_3$  (16.5 equiv), a 6.6 M aqueous solution of  $NH_4OAc$  (100 equiv) and EtOH (0.2 M). The vial was capped with a rubber septum and purged with argon for 5 min. A solution of the indicated arylated OBO-ketone **6** or **S5-6** (1.0 equiv) dissolved in EtOH (0.07 M) was added dropwise and stirred at rt for 1 h. The mixture was extracted with DCM ( $\times 3$ ), dried over  $MgSO_4$  and concentrated *in vacuo*. **Step 2:** The crude material was dissolved in



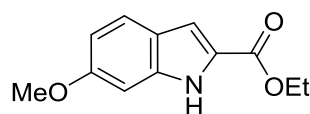
dry EtOH (0.1 M) and added *via* syringe to a flame-dried Biotage<sup>®</sup> microwave vial containing anhydrous *p*-toluenesulfonic acid (3.0 equiv) and stirred at 115 °C for 16 h. After cooling to rt, the reaction was neutralized by the addition of solid NaHCO<sub>3</sub> (6.0 equiv) and concentrated *in vacuo*. The crude material was dissolved in DCM and washed with water. The organic layer was separated, and the aqueous layer was extracted with DCM (× 3). The organic layers were combined, dried over MgSO<sub>4</sub>, filtered, concentrated *in vacuo* and purified by flash column chromatography to give the corresponding indole **7**.

#### ***Ethyl 6-methyl-1H-indole-2-carboxylate (7a)***



Arylated OBO-ketone **6a** (92 mg, 0.30 mmol, 1.0 equiv) was subjected to **General procedure D** (chromatography eluent: *n*-pentane/EtOAc, 90:10) to give the *title compound 7a* (57 mg, 93%) as a white solid. **mp**: 122–123 °C (lit.<sup>13</sup> mp 122–125 °C); **IR**:  $\nu_{\text{max}}$  (thin film) 3308, 1684, 1522, 1327, 1250, 1206, 1021, 824, 773, 745 cm<sup>-1</sup>; **HRMS**: calculated for C<sub>12</sub>H<sub>14</sub>NO<sub>2</sub>, 204.10191 [M+H]<sup>+</sup>, found  $m/z$  204.10211,  $\Delta$  = 1.01 ppm; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.94 (1H, s, NH), 7.57 (1H, d,  $J$  = 8.2 Hz, HC<sub>Ar</sub>), 7.22–7.18 (2H, m, 2 × HC<sub>Ar</sub>), 7.00 (1H, dd,  $J$  = 8.2, 1.5 Hz, HC<sub>Ar</sub>), 4.42 (2H, q,  $J$  = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 2.48 (3H, s, ArCH<sub>3</sub>), 1.42 (3H, t,  $J$  = 7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  162.3 (C(O)), 137.5 (C<sub>Ar</sub>), 135.7 (C<sub>Ar</sub>), 127.0 (C<sub>Ar</sub>), 125.5 (C<sub>Ar</sub>), 123.0 (HC<sub>Ar</sub>), 122.3 (HC<sub>Ar</sub>), 111.6 (HC<sub>Ar</sub>), 108.8 (HC<sub>Ar</sub>), 61.1 (OCH<sub>2</sub>CH<sub>3</sub>), 22.1 (ArCH<sub>3</sub>), 14.6 (OCH<sub>2</sub>CH<sub>3</sub>). Physical and spectroscopic data are consistent with those previously reported.<sup>13,14</sup>

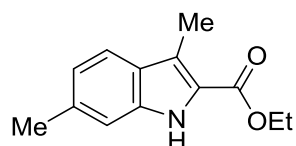
#### ***Ethyl 6-methoxy-1H-indole-2-carboxylate (7b)***



Arylated OBO-ketone **6b** (97 mg, 0.30 mmol, 1.0 equiv) was subjected to **General procedure D** (chromatography eluent: *n*-pentane/EtOAc, 85:15) to give the *title compound 7b* (56 mg, 85%) as a white solid. **mp**: 133–135 °C (lit.<sup>15</sup> mp 131–133 °C); **IR**:  $\nu_{\text{max}}$  (thin film) 3317, 1677, 1626, 1253, 1196, 1023, 822, 767, 735 cm<sup>-1</sup>; **HRMS**: calculated for C<sub>12</sub>H<sub>14</sub>NO<sub>3</sub>, 220.09682 [M+H]<sup>+</sup>, found  $m/z$  220.09700,  $\Delta$  = 0.82 ppm; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.22 (1H, s, NH), 7.55 (1H, d,  $J$  = 8.6 Hz, HC<sub>Ar</sub>), 7.18 (1H, d,  $J$  = 2.3 Hz, HC<sub>Ar</sub>), 6.86–6.81 (2H, m, 2 × HC<sub>Ar</sub>), 4.42 (2H, q,  $J$  = 7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 3.85 (3H, s, OCH<sub>3</sub>), 1.42 (3H, t,  $J$  = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  162.3 (C(O)), 158.9 (C<sub>Ar</sub>), 138.2 (C<sub>Ar</sub>), 126.5 (C<sub>Ar</sub>), 123.4 (HC<sub>Ar</sub>), 121.9 (C<sub>Ar</sub>), 112.4 (HC<sub>Ar</sub>), 109.1 (HC<sub>Ar</sub>), 93.8 (HC<sub>Ar</sub>), 60.9

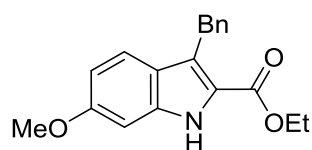
(OCH<sub>2</sub>CH<sub>3</sub>), 55.5 (OCH<sub>3</sub>), 14.5 (OCH<sub>2</sub>CH<sub>3</sub>). Physical and spectroscopic data are consistent with those previously reported.<sup>15</sup>

**Ethyl 3,6-dimethyl-1H-indole-2-carboxylate (7c)**



Arylated OBO-ketone **S5** (96 mg, 0.30 mmol, 1.0 equiv) was subjected to **General procedure D** (chromatography eluent: CHCl<sub>3</sub>) to give the *title compound 7c* (48 mg, 74%) as a white solid. **mp**: 129–131 °C; **IR**:  $\nu_{\text{max}}$  (thin film) 3315, 2975, 1676, 1327, 1266, 797, 776 cm<sup>-1</sup>; **HRMS**: calculated for C<sub>13</sub>H<sub>16</sub>NO<sub>2</sub>, 218.11756 [M+H]<sup>+</sup>, found  $m/z$  218.11769,  $\Delta$  = 0.62 ppm. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.56 (1H, s, NH), 7.54 (1H, d,  $J$  = 8.1 Hz, HC<sub>Ar</sub>), 7.14 (1H, s, HC<sub>Ar</sub>), 6.98 (1H, dd,  $J$  = 8.3, 1.5 Hz, HC<sub>Ar</sub>), 4.41 (2H, q,  $J$  = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 2.59 (3H, s, ArCH<sub>3</sub>), 2.47 (3H, s, C<sub>Ar</sub>(3)CH<sub>3</sub>), 1.43 (3H, t,  $J$  = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>); **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  162.9 (C(O)), 136.4 (C<sub>Ar</sub>), 135.9 (C<sub>Ar</sub>), 126.7 (C<sub>Ar</sub>), 123.0 (C<sub>Ar</sub>), 122.1 (HC<sub>Ar</sub>), 120.5 (HC<sub>Ar</sub>), 120.4 (C<sub>Ar</sub>), 111.4 (HC<sub>Ar</sub>), 60.7 (OCH<sub>2</sub>CH<sub>3</sub>), 22.1 (ArCH<sub>3</sub>), 14.6 (OCH<sub>2</sub>CH<sub>3</sub>), 10.1 (C<sub>Ar</sub>(3)CH<sub>3</sub>).

**Ethyl 3-benzyl-6-methoxy-1H-indole-2-carboxylate (7d)**



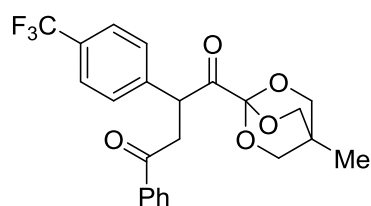
Arylated OBO-ketone **S6** (124 mg, 0.300 mmol, 1.0 equiv) was subjected to **General procedure D** (chromatography eluent: *n*-pentane/EtOAc, 90:10) to give the *title compound 7d* (80 mg, 86%) as a white solid. **mp**: 142–145 °C; **IR**:  $\nu_{\text{max}}$  (thin film) 3330, 2980, 2835, 1672, 1247, 1027, 950, 669 cm<sup>-1</sup>; **HRMS**: calculated for C<sub>19</sub>H<sub>20</sub>NO<sub>3</sub>, 310.14377 [M+H]<sup>+</sup>, found  $m/z$  310.14377,  $\Delta$  = 0.00 ppm; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.89 (1H, s, NH), 7.48 (1H, d,  $J$  = 8.7 Hz, HC<sub>Ar</sub>), 7.31–7.21 (4H, m, 4  $\times$  HC<sub>Ar</sub>), 7.19–7.13 (1H, m, HC<sub>Ar</sub>), 6.82–6.75 (2H, m, 2  $\times$  HC<sub>Ar</sub>), 4.49 (2H, s, PhCH<sub>2</sub>), 4.41 (2H, q,  $J$  = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 3.84 (3H, s, OCH<sub>3</sub>), 1.38 (3H, t,  $J$  = 7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  162.5 (C(O)), 159.1 (C<sub>Ar</sub>), 141.1 (C<sub>Ar</sub>), 137.1 (C<sub>Ar</sub>), 128.4 (HC<sub>Ar</sub>), 128.3 (HC<sub>Ar</sub>), 125.8 (HC<sub>Ar</sub>), 123.1 (C<sub>Ar</sub>), 122.6 (C<sub>Ar</sub>), 122.6 (C<sub>Ar</sub>), 122.1 (HC<sub>Ar</sub>), 111.7 (HC<sub>Ar</sub>), 93.6 (HC<sub>Ar</sub>), 60.7 (OCH<sub>2</sub>CH<sub>3</sub>), 55.5 (OCH<sub>3</sub>), 30.7 (PhCH<sub>2</sub>), 14.5 (OCH<sub>2</sub>CH<sub>3</sub>).

### S3.3 Synthesis of pyrrole/furan-2-carboxylates 10/11 and N-substituted pyrrole-2-carboxylates 12-13

#### S3.3.1 1,4-Dicarbonyl scaffolds 9

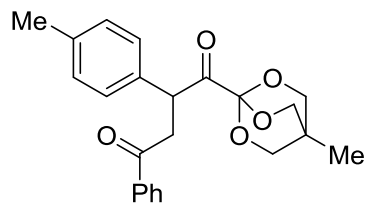
**General procedure E:** To a stirred solution of the appropriate arylated OBO-ketone **8** (1.0 equiv) in THF (0.06 M) at rt or at 66 °C was added in one portion a *t*-BuONa solution (1.2 equiv, 2 M in THF). After stirring for 30 mins, a solution of bromoacetophenone (1.2 equiv) in THF (0.08 M) was added dropwise *via* syringe (rate 10 mL/h). The reaction mixture was then stirred for 1 h and quenched with saturated aq NH<sub>4</sub>Cl. The aqueous phase was extracted with DCM (x 4) and the organic extracts were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated *in vacuo* and purified by flash column chromatography to give the corresponding product **9**.

#### *1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-4-phenyl-2-[4-(trifluoromethyl)phenyl]-butane-1,4-dione (9a)*



Arylated OBO-ketone **8a**<sup>6</sup> (32 mg, 0.10 mmol, 1.0 equiv) in THF (1.5 mL), *t*-BuONa solution (60  $\mu$ L, 0.12 mmol, 1.2 equiv, 2 M in THF) and BrCH<sub>2</sub>COPh (24 mg, 0.12 mmol, 1.2 equiv) in THF (1.5 mL) were subjected to **General procedure E** (rt) (chromatography eluent: *n*-pentane/acetone, 80:20) to give the *title compound 9a* (43 mg, 99%) as colorless needles. **mp**: 149–151 °C (*c*-hexane/EtOH); **IR**:  $\nu_{\text{max}}$  3062, 2924, 2902, 2849, 1752, 1685, 1616, 1595, 1582, 1471, 1450, 1426, 1415, 1400, 1353, 1330, 1299, 1265, 1214, 1193, 1152, 1115, 1069, 1049, 1033, 1004, 980, 961, 948, 919, 899, 859, 830, 777, 756, 741, 729, 718, 690, 657, 628 cm<sup>-1</sup>; **HRMS**: calculated for C<sub>23</sub>H<sub>22</sub>F<sub>3</sub>O<sub>5</sub>, 435.14138 [M+H]<sup>+</sup>, found  $m/z$  435.14110,  $\Delta$  = -0.62 ppm; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.93 (2H, d,  $J$  = 7.4 Hz, HC<sub>Ar</sub>), 7.59–7.49 (3H, m, HC<sub>Ar</sub>), 7.48–7.36 (4H, m, HC<sub>Ar</sub>), 5.07 (1H, dd,  $J$  = 8.5, 5.7 Hz, C<sub>Ar</sub>CHC(O)), 3.95 (6H, s, C(OCH<sub>2</sub>)<sub>3</sub>C), 3.86 (1H, dd,  $J$  = 18.1, 8.5 Hz, C(O)CH<sub>a</sub>H<sub>b</sub>C), 3.36 (1H, dd,  $J$  = 18.1, 5.7 Hz, C(O)CH<sub>a</sub>H<sub>b</sub>C), 0.81 (3H, s, CH<sub>3</sub>); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  197.1 (C(O)), 196.7 (C(O)), 141.8 (q,  $^5J_{\text{CF}}$  = 1.7 Hz, C<sub>Ar</sub>), 136.4 (C<sub>Ar</sub>), 133.6 (HC<sub>Ar</sub>), 129.6 (q,  $^2J_{\text{CF}}$  = 32.4 Hz, F<sub>3</sub>CC<sub>Ar</sub>), 129.2 (HC<sub>Ar</sub>), 128.8 (HC<sub>Ar</sub>), 128.3 (HC<sub>Ar</sub>), 125.7 (q,  $^3J_{\text{CF}}$  = 3.9 Hz, HC<sub>Ar</sub>), 124.4 (q,  $^1J_{\text{CF}}$  = 272.2 Hz, CF<sub>3</sub>), 104.3 (CO<sub>3</sub>), 73.3 (C(OCH<sub>2</sub>)<sub>3</sub>C), 47.3 (C<sub>Ar</sub>CHC(O)), 42.9 (C(O)CH<sub>a</sub>H<sub>b</sub>C), 31.1 (C(OCH<sub>2</sub>)<sub>3</sub>CMe), 14.4 (CCH<sub>3</sub>). **<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>)  $\delta$  -62.5 (3F, s, CF<sub>3</sub>).

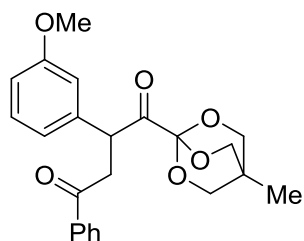
**1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-4-phenyl-2-(p-tolyl)butane-1,4-dione (9b)**



Arylated OBO-ketone **8b**<sup>6</sup> (394 mg, 1.50 mmol, 1.0 equiv) in THF (25 mL), *t*-BuONa solution (900  $\mu$ L, 1.80 mmol, 1.2 equiv, 2 M in THF) and BrCH<sub>2</sub>COPh (358 mg, 1.80 mmol, 1.2 equiv) in THF (23 mL) were subjected to **General procedure E** (66 °C) (chromatography eluent: *n*-pentane/acetone, 80:20)

to give the *title compound 9b* (520 mg, 91%) as colorless needles. **mp** 141–143 °C (*c*-hexane/EtOH); **IR**:  $\nu_{\text{max}}$  2940, 2881, 1734, 1678, 1594, 1578, 1509, 1470, 1449, 1414, 1397, 1342, 1266, 1252, 1207, 1195, 1176, 1092, 1071, 1032, 1013, 993, 955, 921, 890, 849, 818, 765, 753, 736, 722, 689, 649, 633, 610 cm<sup>-1</sup>; **HRMS**: calculated for C<sub>23</sub>H<sub>25</sub>O<sub>5</sub>, 381.16965 [M+H]<sup>+</sup>, found  $m/z$  381.17001,  $\Delta$  = 0.95 ppm; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.94 (2H, d,  $J$  = 7.2 Hz, HC<sub>Ar</sub>), 7.52 (1H, dd,  $J$  = 7.4, 7.4 Hz, HC<sub>Ar</sub>), 7.41 (2H, dd,  $J$  = 7.7, 7.7 Hz, HC<sub>Ar</sub>), 7.17 (2H, d,  $J$  = 8.1 Hz, HC<sub>Ar</sub>), 7.10 (2H, d,  $J$  = 8.0 Hz, HC<sub>Ar</sub>), 4.96 (1H, dd,  $J$  = 9.1, 5.1 Hz, C<sub>Ar</sub>CHC(O)), 3.95 (6H, s, C(OCH<sub>2</sub>)<sub>3</sub>C), 3.87 (1H, dd,  $J$  = 18.1, 9.1 Hz, C(O)CH<sub>a</sub>H<sub>b</sub>C), 3.31 (1H, dd,  $J$  = 18.1, 5.1 Hz, C(O)CH<sub>a</sub>H<sub>b</sub>C), 2.31 (3H, s, H<sub>3</sub>CC<sub>Ar</sub>), 0.81 (3H, s, CCH<sub>3</sub>); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  197.9 (C(O)), 197.4 (C(O)), 136.9 (C<sub>Ar</sub>), 136.6 (C<sub>Ar</sub>), 134.5 (C<sub>Ar</sub>), 133.3 (HC<sub>Ar</sub>), 129.5 (HC<sub>Ar</sub>), 128.7 (2  $\times$  HC<sub>Ar</sub>), 128.4 (HC<sub>Ar</sub>), 104.3 (CO<sub>3</sub>), 73.2 (C(OCH<sub>2</sub>)<sub>3</sub>C), 47.0 (C<sub>Ar</sub>CHC(O)), 43.4 (C(O)CH<sub>a</sub>H<sub>b</sub>C), 31.1 (C(OCH<sub>2</sub>)<sub>3</sub>CMe), 21.3 (H<sub>3</sub>CC<sub>Ar</sub>), 14.5 (CCH<sub>3</sub>). Spectroscopic data consistent with those previously reported.<sup>6</sup>

**2-(3-Methoxyphenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-4-phenylbutane-1,4-dione (9c)**

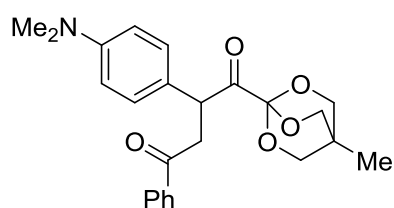


Arylated OBO-ketone **8c**<sup>3</sup> (278 mg, 1.00 mmol, 1.0 equiv) in THF (17 mL), *t*-BuONa solution (600  $\mu$ L, 1.20 mmol, 1.2 equiv, 2 M in THF) and BrCH<sub>2</sub>COPh (239 mg, 1.20 mmol, 1.2 equiv) in THF (15 mL) were subjected to **General procedure E** (66 °C) (chromatography eluent: *n*-pentane/acetone, 80:20) to give the *title compound 9c* (365 mg, 92%) as colorless needles. **mp**: 63–65 °C (*c*-hexane/EtOH); **IR**:  $\nu_{\text{max}}$

2880, 2841, 1742, 1684, 1608, 1597, 1583, 1485, 1470, 1448, 1397, 1353, 1297, 1255, 1234, 1195, 1143, 1100, 1069, 1044, 1033, 995, 950, 905, 864, 827, 778, 760, 734, 694, 660, 625 cm<sup>-1</sup>; **HRMS**: calculated for C<sub>23</sub>H<sub>24</sub>O<sub>6</sub><sup>23</sup>Na, 419.14651 [M+Na]<sup>+</sup>, found  $m/z$  419.14602,  $\Delta$  = -1.16 ppm; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.94 (2H, dd,  $J$  = 8.4, 1.3 Hz, HC<sub>Ar</sub>), 7.53 (1H, dd,  $J$  = 7.4, 7.4 Hz, HC<sub>Ar</sub>), 7.41 (2H, dd,  $J$  = 7.6, 7.6 Hz, HC<sub>Ar</sub>), 7.21 (1H, dd,  $J$  = 7.9, 7.9 Hz,

$HC_{Ar}$ ), 6.87 (1H, d,  $J = 7.7$  Hz,  $HC_{Ar}$ ), 6.85–6.81 (1H, m,  $HC_{Ar}$ ), 6.77 (1H, ddd,  $J = 8.2, 2.6, 0.8$  Hz,  $HC_{Ar}$ ), 4.96 (1H, dd,  $J = 9.3, 4.9$  Hz,  $C_{Ar}CHC(O)$ ), 3.96 (6H, s,  $C(OCH_2)_3C$ ), 3.89 (1H, dd,  $J = 18.1, 9.3$  Hz,  $C(O)CH_aH_bC$ ), 3.78 (3H, s,  $OCH_3$ ), 3.32 (1H, dd,  $J = 18.1, 4.9$  Hz,  $C(O)CH_aH_bC$ ), 0.81 (3H, s,  $CH_3$ );  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  197.6 ( $C(O)$ ), 197.3 ( $C(O)$ ), 159.8 ( $C_{Ar}$ ), 139.1 ( $C_{Ar}$ ), 136.5 ( $C_{Ar}$ ), 133.4 ( $HC_{Ar}$ ), 129.7 ( $HC_{Ar}$ ), 128.7 ( $HC_{Ar}$ ), 128.4 ( $HC_{Ar}$ ), 121.2 ( $HC_{Ar}$ ), 114.4 ( $HC_{Ar}$ ), 112.9 ( $HC_{Ar}$ ), 104.3 ( $CO_3$ ), 73.2 ( $C(OCH_2)_3C$ ), 55.4 ( $OCH_3$ ), 47.4 ( $C_{Ar}CHC(O)$ ), 43.4 ( $C(O)CH_aH_bC$ ), 31.1 ( $C(OCH_2)_3CMe$ ), 14.4 ( $CCH_3$ ).

**2-[4-(Dimethylamino)phenyl]-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-4-phenylbutane-1,4-dione (9d)**



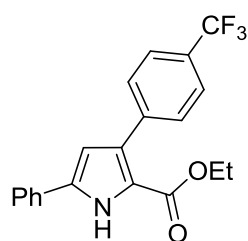
Arylated OBO-ketone **8d**<sup>6</sup> (291 mg, 1.00 mmol, 1.0 equiv) in THF (17 mL), *t*-BuONa solution (600  $\mu$ L, 1.20 mmol, 1.2 equiv, 2 M in THF) and  $BrCH_2COPh$  (239 mg, 1.20 mmol, 1.2 equiv) in THF (15 mL) were subjected to **General procedure E** (rt). Flash column chromatography (*n*-pentane/acetone, 80:20) gave unreacted starting material **8d** (41 mg, 14%). Further elution (*n*-pentane/acetone, 80:20) gave the *title compound* **9d** (274 mg, 67%) as colorless needles. **mp**: 203–205 °C (*c*-hexane/EtOH); **IR**:  $\nu_{max}$  2958, 2883, 2804, 1732, 1685, 1611, 1597, 1581, 1519, 1473, 1449, 1399, 1350, 1327, 1294, 1229, 1193, 1179, 1166, 1096, 1062, 1043, 1033, 986, 950, 929, 866, 815, 780, 754, 730, 718, 690, 651, 634, 607  $cm^{-1}$ ; **HRMS**: calculated for  $C_{24}H_{28}NO_5$ , 410.19620  $[M+H]^+$ , found  $m/z$  410.19542,  $\Delta = -1.86$  ppm;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.94 (2H, d,  $J = 7.2$  Hz,  $HC_{Ar}$ ), 7.51 (1H, dd,  $J = 7.4, 7.4$  Hz,  $HC_{Ar}$ ), 7.40 (2H, dd,  $J = 7.6, 7.6$  Hz,  $HC_{Ar}$ ), 7.14 (2H, d,  $J = 8.8$  Hz,  $HC_{Ar}$ ), 6.66 (2H, d,  $J = 8.8$  Hz,  $HC_{Ar}$ ), 4.89 (1H, dd,  $J = 9.2, 5.0$  Hz,  $C_{Ar}CHC(O)$ ), 3.95 (6H, s,  $C(OCH_2)_3C$ ), 3.86 (1H, dd,  $J = 18.1, 9.2$  Hz,  $C(O)CH_aH_bC$ ), 3.29 (1H, dd,  $J = 18.1, 5.0$  Hz,  $C(O)CH_aH_bC$ ), 2.92 (6H, s,  $N(CH_3)_2$ ), 0.80 (3H, s,  $CH_3$ );  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  198.0 ( $C(O)$ ), 197.7 ( $C(O)$ ), 149.8 ( $C_{Ar}$ ), 136.7 ( $C_{Ar}$ ), 133.2 ( $HC_{Ar}$ ), 129.5 ( $HC_{Ar}$ ), 128.6 ( $HC_{Ar}$ ), 128.4 ( $HC_{Ar}$ ), 124.9 ( $C_{Ar}$ ), 112.8 ( $HC_{Ar}$ ), 104.3 ( $CO_3$ ), 73.2 ( $C(OCH_2)_3C$ ), 46.4 ( $C_{Ar}CHC(O)$ ), 43.4 ( $C(O)CH_aH_bC$ ), 40.7 ( $N(CH_3)_2$ ), 31.0 ( $C(OCH_2)_3CMe$ ), 14.5 ( $CCH_3$ ).

### S3.3.2 Cyclisation to pyrrole-2-carboxylates 10

**General procedure F: Step 1:** A mixture of the appropriate dicarbonyl precursor **9** (0.10 mmol, 1.0 equiv) and  $NH_4OAc$  (77 mg, 1.0 mmol, 10 equiv) in AcOH (3 mL) was heated at

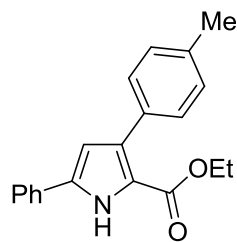
100 °C for 20 mins. The reaction mixture was cooled to rt and then poured onto crushed ice and neutralized by careful addition of solid K<sub>2</sub>CO<sub>3</sub>. The aqueous phase was extracted with DCM (3 × 50 mL) and the combined organic extracts were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated *in vacuo*. *Step 2*: The crude residue was dissolved in EtOH (3 mL) and transferred to a round bottom flask. Dried and finely powdered K<sub>2</sub>CO<sub>3</sub> (28 mg, 0.20 mmol, 2.0 equiv) was then added to the solution and the mixture was heated under reflux for 2 h. The reaction mixture was cooled to rt, the solvent was evaporated *in vacuo*, and the residue was partitioned in DCM/water. The organic layer was collected, and the aqueous phase was extracted with DCM (3 × 50 mL). The combined organic extracts were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness to give the corresponding pyrrole **10**.

**Ethyl 5-phenyl-3-[4-(trifluoromethyl)phenyl]-1H-pyrrole-2-carboxylate (10a)**



1,4-Dicarbonyl compound **9a** (43 mg, 0.10 mmol, 1.0 equiv) was subjected to **General procedure F** to give the *title compound 10a* (33 mg, 90%) as colourless needles. **mp**: 170–171.5 °C (*c*-hexane); **IR**:  $\nu_{\text{max}}$  3321, 1650, 1616, 1533, 1504, 1462, 1445, 1413, 1387, 1365, 1324, 1288, 1266, 1203, 1160, 1137, 1103, 1063, 1022, 990, 907, 874, 852, 839, 816, 773, 759, 747, 716, 688, 675, 662, 618 cm<sup>-1</sup>; **HRMS**: calculated for C<sub>20</sub>H<sub>17</sub>F<sub>3</sub>NO<sub>2</sub>, 360.12059 [M+H]<sup>+</sup>, found *m/z* 360.12054,  $\Delta$  = −0.13 ppm; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.38 (1H, br s, NH), 7.71 (2H, d, *J* = 8.2 Hz, HC<sub>Ar</sub>), 7.66–7.56 (4H, m, HC<sub>Ar</sub>), 7.45 (2H, dd, *J* = 7.6, 7.6 Hz, HC<sub>Ar</sub>), 7.35 (1H, dd, *J* = 7.4, 7.4 Hz, HC<sub>Ar</sub>), 6.63 (1H, d, *J* = 3.0 Hz, HC<sub>pyrrole</sub>), 4.30 (2H, q, *J* = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 1.27 (3H, t, *J* = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  161.0 (C(O)), 139.0 (C<sub>Ar</sub>), 135.8 (C<sub>Ar</sub>), 132.1 (C<sub>Ar</sub>), 131.0 (C<sub>Ar</sub>), 130.0 (HC<sub>Ar</sub>), 129.4 (HC<sub>Ar</sub>), 129.3 (q, <sup>2</sup>*J*<sub>CF</sub> = 32.6 Hz, F<sub>3</sub>CC<sub>Ar</sub>), 128.4 (HC<sub>Ar</sub>), 125.0 (HC<sub>Ar</sub>), 124.8 (q, <sup>3</sup>*J*<sub>CF</sub> = 3.8 Hz, HC<sub>Ar</sub>), 124.6 (q, <sup>1</sup>*J*<sub>CF</sub> = 271.8 Hz, CF<sub>3</sub>), 119.1 (C<sub>Ar</sub>), 110.0 (HC<sub>pyrrole</sub>), 60.8 (OCH<sub>2</sub>CH<sub>3</sub>), 14.5 (OCH<sub>2</sub>CH<sub>3</sub>); **<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>)  $\delta$  −62.4 (3F, s, CF<sub>3</sub>).

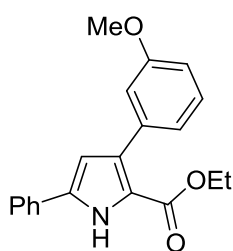
**Ethyl 5-phenyl-3-(p-tolyl)-1H-pyrrole-2-carboxylate (10b)**



1,4-Dicarbonyl compound **9b** (38 mg, 0.10 mmol, 1.0 equiv) was subjected to **General procedure F** to give the *title compound 10b* (24 mg, 78%) as colourless needles. **mp**: 171–173 °C (*c*-hexane) (lit.<sup>16</sup> mp 166.2–167 °C); **IR**:  $\nu_{\text{max}}$  3313, 2978, 2917, 2860, 1654, 1607, 1529, 1499, 1474, 1460, 1443, 1408, 1385, 1363, 1320, 1307, 1291, 1266, 1212, 1200, 1184, 1159, 1131, 1110, 1079, 1026, 988, 966, 945, 908, 873, 841, 827, 809,

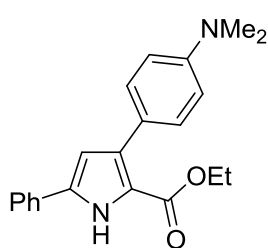
771, 758, 728, 708, 689, 675, 664, 638, 617  $\text{cm}^{-1}$ ; **HRMS**: calculated for  $\text{C}_{20}\text{H}_{20}\text{NO}_2$ , 306.14886  $[\text{M}+\text{H}]^+$ , found  $m/z$  306.14901,  $\Delta = 0.52$  ppm;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.30 (1H, br s, NH), 7.60 (2H, d,  $J = 7.3$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.51 (2H, d,  $J = 8.1$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.43 (2H, dd,  $J = 7.7, 7.7$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.33 (1H, dd,  $J = 7.4, 7.4$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.20 (2H, d,  $J = 7.9$  Hz,  $\text{HC}_{\text{Ar}}$ ), 6.62 (1H, d,  $J = 3.1$  Hz,  $\text{HC}_{\text{pyrrole}}$ ), 4.29 (2H, q,  $J = 7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 2.40 (3H, s,  $\text{ArCH}_3$ ), 1.29 (3H, t,  $J = 7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ );  **$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  161.4 ( $\text{C}(\text{O})$ ), 137.0 ( $\text{C}_{\text{Ar}}$ ), 135.5 ( $\text{C}_{\text{Ar}}$ ), 133.7 ( $\text{C}_{\text{Ar}}$ ), 132.2 ( $\text{C}_{\text{Ar}}$ ), 131.3 ( $\text{C}_{\text{Ar}}$ ), 129.6 ( $\text{HC}_{\text{Ar}}$ ), 129.3 ( $\text{HC}_{\text{Ar}}$ ), 128.6 ( $\text{HC}_{\text{Ar}}$ ), 128.1 ( $\text{HC}_{\text{Ar}}$ ), 124.9 ( $\text{HC}_{\text{Ar}}$ ), 118.7 ( $\text{C}_{\text{Ar}}$ ), 110.1 ( $\text{HC}_{\text{pyrrole}}$ ), 60.6 ( $\text{OCH}_2\text{CH}_3$ ), 21.5 ( $\text{ArCH}_3$ ), 14.5 ( $\text{OCH}_2\text{CH}_3$ ). Physical and spectroscopic data are consistent with those previously reported.<sup>16</sup>

### **Ethyl 3-(3-methoxyphenyl)-5-phenyl-1H-pyrrole-2-carboxylate (10c)**



1,4-Dicarbonyl compound **9c** (40 mg, 0.10 mmol, 1.0 equiv) was subjected to **General procedure F** to give the *title compound 10c* (32 mg, 100%) as colourless plates. **mp**: 119–121 °C (*c*-hexane); **IR**:  $\nu_{\text{max}}$  3305, 3008, 2961, 2936, 2834, 1659, 1610, 1577, 1519, 1486, 1470, 1453, 1435, 1387, 1365, 1315, 1288, 1267, 1207, 1174, 1129, 1081, 1049, 1021, 995, 970, 917, 877, 849, 825, 817, 783, 770, 725, 695, 658, 616  $\text{cm}^{-1}$ ; **HRMS**: calculated for  $\text{C}_{20}\text{H}_{20}\text{NO}_3$ , 322.14377  $[\text{M}+\text{H}]^+$ , found  $m/z$  322.14386,  $\Delta = 0.28$  ppm;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.34 (1H, br s, NH), 7.60 (2H, d,  $J = 7.1$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.44 (2H, dd,  $J = 7.6, 7.6$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.38–7.27 (2H, m,  $\text{HC}_{\text{Ar}}$ ), 7.22–7.15 (2H, m,  $\text{HC}_{\text{Ar}}$ ), 6.88 (1H, ddd,  $J = 8.2, 2.6, 1.1$  Hz,  $\text{HC}_{\text{Ar}}$ ), 6.64 (1H, d,  $J = 3.1$  Hz,  $\text{HC}_{\text{pyrrole}}$ ), 4.29 (2H, q,  $J = 7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 3.86 (3H, s,  $\text{OCH}_3$ ), 1.28 (3H, t,  $J = 7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ );  **$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  161.4 ( $\text{C}(\text{O})$ ), 159.3 ( $\text{C}_{\text{Ar}}$ ), 136.6 ( $\text{C}_{\text{Ar}}$ ), 135.5 ( $\text{C}_{\text{Ar}}$ ), 133.4 ( $\text{C}_{\text{Ar}}$ ), 131.2 ( $\text{C}_{\text{Ar}}$ ), 129.3 ( $\text{HC}_{\text{Ar}}$ ), 128.8 ( $\text{HC}_{\text{Ar}}$ ), 128.2 ( $\text{HC}_{\text{Ar}}$ ), 125.0 ( $\text{HC}_{\text{Ar}}$ ), 122.3 ( $\text{HC}_{\text{Ar}}$ ), 118.9 ( $\text{C}_{\text{Ar}}$ ), 115.4 ( $\text{HC}_{\text{Ar}}$ ), 113.0 ( $\text{HC}_{\text{Ar}}$ ), 110.2 ( $\text{HC}_{\text{pyrrole}}$ ), 60.7 ( $\text{OCH}_2\text{CH}_3$ ), 55.5 ( $\text{OCH}_3$ ), 14.5 ( $\text{OCH}_2\text{CH}_3$ ).

### **Ethyl 3-[4-(dimethylamino)phenyl]-5-phenyl-1H-pyrrole-2-carboxylate (10d)**



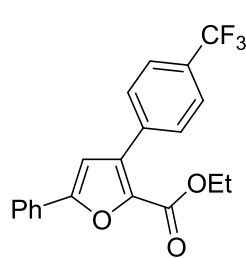
1,4-Dicarbonyl compound **9d** (41 mg, 0.10 mmol, 1.0 equiv) was subjected to **General procedure F**. Purification by flash column chromatography (DCM) gave the *title compound 10d* (29 mg, 86%) as colourless needles. **mp**: 141–143 °C (*c*-hexane) [lit.<sup>17</sup> mp 135–137 °C (EtOH)]; **IR**:  $\nu_{\text{max}}$  3333, 3069, 2888, 2799, 1659, 1611, 1556, 1531, 1502, 1477, 1443, 1387, 1351, 1289, 1262, 1197, 1164, 1135, 1124, 1076, 1061, 1028, 985,

945, 907, 878, 809, 773, 755, 732, 686, 642, 614  $\text{cm}^{-1}$ ; **HRMS**: calculated for  $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_2$ , 335.17540  $[\text{M}+\text{H}]^+$ , found  $m/z$  335.17532,  $\Delta = -0.24$  ppm;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  9.40 (1H, br s, NH), 7.64 (2H, d,  $J = 7.3$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.52 (2H, d,  $J = 8.8$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.44 (2H, dd,  $J = 7.7, 7.7$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.33 (1H, dd,  $J = 7.4, 7.4$  Hz,  $\text{HC}_{\text{Ar}}$ ), 6.76 (2H, d,  $J = 8.8$  Hz,  $\text{HC}_{\text{Ar}}$ ), 6.63 (1H, d,  $J = 3.1$  Hz,  $\text{HC}_{\text{pyrrole}}$ ), 4.30 (2H, q,  $J = 7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 2.99 (6H, s,  $\text{N}(\text{CH}_3)_2$ ), 1.32 (3H, t,  $J = 7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ );  **$^{13}\text{C}$  NMR** (101 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  161.6 ( $\text{C}(\text{O})$ ), 150.5 ( $\text{C}_{\text{Ar}}$ ), 135.6 ( $\text{C}_{\text{Ar}}$ ), 134.3 ( $\text{C}_{\text{Ar}}$ ), 131.8 ( $\text{C}_{\text{Ar}}$ ), 130.7 ( $\text{HC}_{\text{Ar}}$ ), 129.6 ( $\text{HC}_{\text{Ar}}$ ), 128.3 ( $\text{HC}_{\text{Ar}}$ ), 125.2 ( $\text{HC}_{\text{Ar}}$ ), 123.3 ( $\text{C}_{\text{Ar}}$ ), 118.6 ( $\text{C}_{\text{Ar}}$ ), 112.2 ( $\text{HC}_{\text{Ar}}$ ), 109.9 ( $\text{HC}_{\text{pyrrole}}$ ), 60.8 ( $\text{OCH}_2\text{CH}_3$ ), 40.9 ( $\text{N}(\text{CH}_3)_2$ ), 14.8 ( $\text{OCH}_2\text{CH}_3$ ). Physical and spectroscopic data are consistent with those previously reported.<sup>17</sup>

### S3.3.3 Cyclisation to furan-2-carboxylates 11

**General procedure G: Step 1:** In a Biotage<sup>®</sup> microwave vial, a mixture of the appropriate 1,4-dicarbonyl scaffold **9** (0.10 mmol, 1.0 equiv) and *p*-toluenesulfonic acid monohydrate (190 mg, 1.00 mmol, 10 equiv) in EtOH (3 mL) was heated at 115 °C for 24 h. The reaction mixture was cooled to rt, diluted with DCM and washed with saturated aq  $\text{NaHCO}_3$ . The aqueous phase was extracted with DCM ( $3 \times 50$  mL) and the combined organic extracts were dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography to afford the desired furans **11**.

#### *Ethyl 5-phenyl-3-[4-(trifluoromethyl)phenyl]furan-2-carboxylate (11a)*

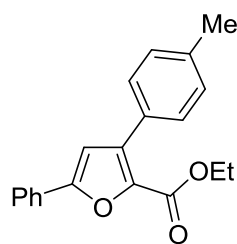


1,4-Dicarbonyl compound **9a** (43 mg, 0.10 mmol, 1.0 equiv) was subjected to **General procedure G** (chromatography eluent: *n*-pentane/ $\text{Et}_2\text{O}$ , 95:5) to give the *title compound 11a* (25 mg, 68%) as colourless plates. **mp**: 124–125 °C (*n*-pentane/ $\text{Et}_2\text{O}$  at –20 °C); **IR**:  $\nu_{\text{max}}$  3073, 3001, 2976, 2940, 2909, 1713, 1638, 1620, 1578, 1543, 1509, 1476, 1448, 1418, 1402, 1388, 1360, 1321, 1294, 1267, 1183, 1166, 1120, 1107, 1068, 1021, 984, 959, 933, 921, 857, 846, 819, 773, 746, 693, 678, 659, 631, 618  $\text{cm}^{-1}$ ; **HRMS**: calculated for  $\text{C}_{20}\text{H}_{15}\text{F}_3\text{O}_3$ <sup>23</sup>Na, 383.08655  $[\text{M}+\text{Na}]^+$ , found  $m/z$  383.08646,  $\Delta = -0.24$  ppm;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.83 (2H, d,  $J = 7.2$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.74 (2H, d,  $J = 8.3$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.68 (2H, d,  $J = 8.3$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.46 (2H, dd,  $J = 7.4, 7.4$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.39 (1H, dd,  $J = 7.3, 7.3$  Hz,  $\text{HC}_{\text{Ar}}$ ), 6.85 (1H, s,  $\text{HC}_{\text{furan}}$ ), 4.34 (2H, q,  $J = 7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 1.32 (3H, t,  $J = 7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ );  **$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  159.2 ( $\text{C}(\text{O})$ ), 156.4 ( $\text{C}_{\text{Ar}}$ ), 138.7 ( $\text{C}_{\text{Ar}}$ ),



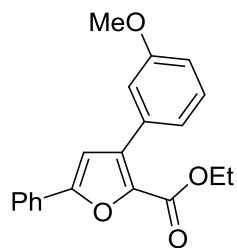
136.1 ( $C_{Ar}$ ), 135.2 ( $C_{Ar}$ ), 130.5 (q,  $^2J_{CF}$  = 32.5 Hz,  $F_3CC_{Ar}$ ), 129.9 ( $HC_{Ar}$ ), 129.5 ( $HC_{Ar}$ ), 129.3 ( $C_{Ar}$ ), 129.1 ( $HC_{Ar}$ ), 125.2 ( $HC_{Ar}$ ), 125.1 (q,  $^3J_{CF}$  = 3.8 Hz,  $HC_{Ar}$ ), 124.3 (q,  $^1J_{CF}$  = 272.0 Hz,  $CF_3$ ), 109.2 ( $HC_{furan}$ ), 61.2 ( $OCH_2CH_3$ ), 14.4 ( $OCH_2CH_3$ );  $^{19}F$  NMR (376 MHz,  $CDCl_3$ )  $\delta$  -62.6 (3F, s,  $CF_3$ ).

#### ***Ethyl 5-phenyl-3-(p-tolyl)furan-2-carboxylate (11b)***



1,4-Dicarbonyl compound **9b** (38 mg, 0.10 mmol, 1.0 equiv) was subjected to **General procedure G** (chromatography eluent: *n*-pentane/ $Et_2O$ , 95:5) to give the *title compound 11b* (28 mg, 94%) as colourless plates. **mp**: 112–113 °C (*n*-pentane at -20 °C); **IR**:  $\nu_{max}$  2997, 2974, 2907, 1705, 1614, 1589, 1576, 1541, 1505, 1476, 1446, 1414, 1400, 1387, 1376, 1357, 1317, 1289, 1266, 1226, 1177, 1157, 1125, 1109, 1074, 1063, 1024, 1000, 982, 951, 932, 920, 874, 843, 811, 772, 721, 693, 660, 634, 619  $cm^{-1}$ ; **HRMS**: calculated for  $C_{20}H_{19}O_3$ , 307.13287  $[M+H]^+$ , found  $m/z$  307.13300,  $\Delta$  = 0.41 ppm;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.82 (2H, d,  $J$  = 7.2 Hz,  $HC_{Ar}$ ), 7.53 (2H, d,  $J$  = 8.1 Hz,  $HC_{Ar}$ ), 7.44 (2H, dd,  $J$  = 7.4, 7.4 Hz,  $HC_{Ar}$ ), 7.37 (1H, dd,  $J$  = 7.4, 7.4 Hz,  $HC_{Ar}$ ), 7.23 (2H, d,  $J$  = 8.2 Hz,  $HC_{Ar}$ ), 6.84 (1H, s,  $HC_{furan}$ ), 4.34 (2H, q,  $J$  = 7.1 Hz,  $OCH_2CH_3$ ), 2.40 (3H, s,  $ArCH_3$ ), 1.33 (3H, t,  $J$  = 7.1 Hz,  $OCH_2CH_3$ );  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  159.5 ( $C(O)$ ), 155.9 ( $C_{Ar}$ ), 138.4 ( $C_{Ar}$ ), 138.2 ( $C_{Ar}$ ), 136.7 ( $C_{Ar}$ ), 129.6 ( $C_{Ar}$ ), 129.4 ( $HC_{Ar}$ ), 129.3 ( $C_{Ar}$ ), 129.2 ( $HC_{Ar}$ ), 129.0 ( $HC_{Ar}$ ), 128.9 ( $HC_{Ar}$ ), 125.1 ( $HC_{Ar}$ ), 109.6 ( $HC_{furan}$ ), 60.9 ( $OCH_2CH_3$ ), 21.5 ( $ArCH_3$ ), 14.5 ( $OCH_2CH_3$ ).

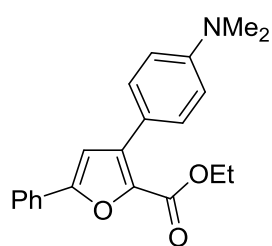
#### ***Ethyl 3-(3-methoxyphenyl)-5-phenylfuran-2-carboxylate (11c)***



1,4-Dicarbonyl compound **9c** (40 mg, 0.10 mmol, 1.0 equiv) was subjected to **General procedure G** (chromatography eluent: *n*-pentane/ $Et_2O$ , 95:5) to give the *title compound 11c* (27 mg, 85%) as colourless needles. **mp**: 102–104 °C (*n*-pentane/ $Et_2O$  at -20 °C); **IR**:  $\nu_{max}$  3083, 2998, 2937, 2837, 1702, 1607, 1593, 1577, 1540, 1481, 1450, 1429, 1397, 1357, 1313, 1265, 1248, 1200, 1168, 1110, 1089, 1066, 1052, 1024, 1001, 932, 878, 831, 812, 783, 770, 704, 692, 661, 617  $cm^{-1}$ ; **HRMS**: calculated for  $C_{20}H_{19}O_4$ , 323.12779  $[M+H]^+$ , found  $m/z$  323.12790,  $\Delta$  = 0.35 ppm;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.82 (2H, d,  $J$  = 7.1 Hz,  $HC_{Ar}$ ), 7.45 (2H, dd,  $J$  = 7.4, 7.4 Hz,  $HC_{Ar}$ ), 7.41–7.30 (2H, m,  $HC_{Ar}$ ), 7.23–7.14 (2H, m,  $HC_{Ar}$ ), 6.93 (1H, ddd,  $J$  = 8.3, 2.6, 1.1 Hz,  $HC_{Ar}$ ), 6.85 (1H, s,  $HC_{furan}$ ), 4.34 (2H, q,  $J$  = 7.1 Hz,  $OCH_2CH_3$ ), 3.86 (3H, s,  $OCH_3$ ), 1.32 (3H, t,  $J$  = 7.1 Hz,

OCH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 159.4 (C(O) and MeOC<sub>Ar</sub>), 156.0 (C<sub>Ar</sub>), 138.5 (C<sub>Ar</sub>), 136.4 (C<sub>Ar</sub>), 133.6 (C<sub>Ar</sub>), 129.6 (C<sub>Ar</sub>), 129.3 (HC<sub>Ar</sub>), 129.2 (HC<sub>Ar</sub>), 129.1 (HC<sub>Ar</sub>), 125.1 (HC<sub>Ar</sub>), 122.0 (HC<sub>Ar</sub>), 115.3 (HC<sub>Ar</sub>), 114.1 (HC<sub>Ar</sub>), 109.6 (HC<sub>furan</sub>), 61.0 (OCH<sub>2</sub>CH<sub>3</sub>), 55.5 (OCH<sub>3</sub>), 14.5 (OCH<sub>2</sub>CH<sub>3</sub>).

#### **Ethyl 3-[4-(dimethylamino)phenyl]-5-phenylfuran-2-carboxylate (11d)**



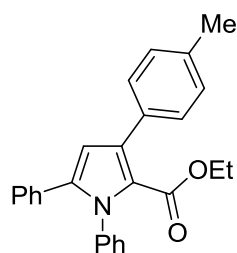
1,4-Dicarbonyl compound **9d** (41 mg, 0.10 mmol, 1.0 equiv) was subjected to **General procedure G** (chromatography eluent: *n*-pentane/Et<sub>2</sub>O, 80:20) to give the *title compound 11d* (33 mg, 97%) as pale-yellow needles. **mp**: 115–117 °C (*c*-hexane); **IR**:  $\nu_{\max}$  2979, 2934, 2903, 2803, 1699, 1611, 1543, 1509, 1478, 1446, 1403, 1385, 1353, 1319, 1295, 1283, 1267, 1222, 1197, 1175, 1157, 1132, 1110, 1074, 1061, 1024, 980, 945, 931, 920, 877, 838, 826, 812, 774, 729, 694, 659, 629, 614 cm<sup>-1</sup>; **HRMS**: calculated for C<sub>21</sub>H<sub>22</sub>NO<sub>3</sub>, 336.15942 [M+H]<sup>+</sup>, found *m/z* 336.15924, Δ = −0.53 ppm; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.82 (2H, d, *J* = 7.2 Hz, HC<sub>Ar</sub>), 7.60 (2H, d, *J* = 8.9 Hz, HC<sub>Ar</sub>), 7.44 (2H, dd, *J* = 7.5, 7.5 Hz, HC<sub>Ar</sub>), 7.35 (1H, dd, *J* = 7.4, 7.4 Hz, HC<sub>Ar</sub>), 6.85 (1H, s, HC<sub>furan</sub>), 6.77 (2H, d, *J* = 8.8 Hz, HC<sub>Ar</sub>), 4.36 (2H, q, *J* = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 3.01 (6H, s, N(CH<sub>3</sub>)<sub>2</sub>), 1.37 (3H, t, *J* = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 159.8 (C(O)), 155.7 (C<sub>Ar</sub>), 150.7 (C<sub>Ar</sub>), 137.5 (C<sub>Ar</sub>), 137.2 (C<sub>Ar</sub>), 130.5 (HC<sub>Ar</sub>), 129.8 (C<sub>Ar</sub>), 129.04 (HC<sub>Ar</sub>), 128.98 (HC<sub>Ar</sub>), 125.1 (HC<sub>Ar</sub>), 119.7 (C<sub>Ar</sub>), 111.9 (HC<sub>Ar</sub>), 109.4 (HC<sub>furan</sub>), 60.8 (OCH<sub>2</sub>CH<sub>3</sub>), 40.7 (N(CH<sub>3</sub>)<sub>2</sub>), 14.6 (OCH<sub>2</sub>CH<sub>3</sub>).

#### **S3.3.4 Cyclisation to *N*-substituted pyrrole-2-carboxylates 12-13**

**General procedure H: Step 1:** In a Biotage<sup>®</sup> microwave vial sealed with a microwave vial cap (Reseal<sup>TM</sup> septum), a mixture of 1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-4-phenyl-2-(*p*-tolyl)butane-1,4-dione (**9b**) (38.0 mg, 0.10 mmol, 1.0 equiv) and the appropriate amine (0.12 mmol, 1.2 equiv) in AcOH (3 mL) was heated at 120 °C for 15 h. The reaction mixture was then cooled to rt, poured onto crushed ice and neutralized by careful addition of solid K<sub>2</sub>CO<sub>3</sub>. The aqueous phase was extracted with DCM (3 × 50 mL) and the combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated *in vacuo*. **Step 2:** The crude residue was dissolved in EtOH (3 mL) and transferred to a Biotage<sup>®</sup> microwave vial. Dried and finely powdered K<sub>2</sub>CO<sub>3</sub> (55 mg, 0.40 mmol, 4.0 equiv) was added and the vial was sealed with a microwave vial cap (Reseal<sup>TM</sup> septum). The mixture was heated at 120 °C for 15 h.

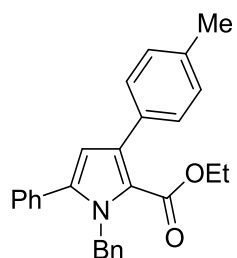
The temperature was then increased to 140 °C and the reaction was heated for additional 5 h (CAUTION: high pressure - protected with blast shield). The reaction mixture was then cooled to rt, the solvent was evaporated *in vacuo* and the residue was partitioned in DCM/water. The organic layer was collected, and the aqueous layer was extracted with DCM (3 × 50 mL). The combined organic extracts were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. Purification by column chromatography gave the corresponding pyrroles **12-13**.

**Ethyl 1,5-diphenyl-3-(p-tolyl)-1H-pyrrole-2-carboxylate (12)**



Aniline (11 μL, 0.12 mmol, 1.2 equiv) was subjected to **General procedure H** (chromatography eluent: *n*-pentane/Et<sub>2</sub>O, 95:5) to give the *title compound 12* (28 mg, 73%) as colourless needles. **mp**: 136–137 °C (*n*-pentane/Et<sub>2</sub>O at –20 °C); **IR**:  $\nu_{\text{max}}$  3057, 2978, 1699, 1598, 1552, 1522, 1496, 1462, 1450, 1421, 1403, 1370, 1338, 1315, 1295, 1281, 1206, 1195, 1128, 1110, 1089, 1030, 1015, 981, 966, 950, 923, 867, 844, 832, 813, 784, 765, 697, 670 cm<sup>-1</sup>; **HRMS**: calculated for C<sub>26</sub>H<sub>23</sub>NO<sub>2</sub><sup>23</sup>Na, 404.16210 [M+Na]<sup>+</sup>, found *m/z* 404.16229,  $\Delta$  = 0.48 ppm; **<sup>1</sup>H NMR** (400 MHz, acetone-*d*<sub>6</sub>)  $\delta$  7.47 (2H, d, *J* = 8.1 Hz, HC<sub>Ar</sub>), 7.40–7.35 (3H, m, HC<sub>Ar</sub>), 7.29–7.24 (2H, m, HC<sub>Ar</sub>), 7.23–7.15 (7H, m, HC<sub>Ar</sub>), 6.53 (1H, s, HC<sub>pyrrole</sub>), 3.91 (2H, q, *J* = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 2.36 (3H, s, ArCH<sub>3</sub>), 0.86 (3H, t, *J* = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>); **<sup>13</sup>C NMR** (101 MHz, acetone-*d*<sub>6</sub>)  $\delta$  161.9 (C(O)), 140.7 (C<sub>Ar</sub>), 139.8 (C<sub>Ar</sub>), 137.1 (C<sub>Ar</sub>), 133.8 (C<sub>Ar</sub>), 133.2 (C<sub>Ar</sub>), 133.1 (C<sub>Ar</sub>), 130.1 (HC<sub>Ar</sub>), 129.9 (HC<sub>Ar</sub>), 129.6 (HC<sub>Ar</sub>), 129.4 (HC<sub>Ar</sub>), 129.3 (HC<sub>Ar</sub>), 129.0 (HC<sub>Ar</sub>), 128.8 (HC<sub>Ar</sub>), 128.3 (HC<sub>Ar</sub>), 123.3 (C<sub>Ar</sub>), 112.4 (HC<sub>pyrrole</sub>), 60.5 (OCH<sub>2</sub>CH<sub>3</sub>), 21.3 (ArCH<sub>3</sub>), 14.0 (OCH<sub>2</sub>CH<sub>3</sub>).

**Ethyl 1-benzyl-5-phenyl-3-(p-tolyl)-1H-pyrrole-2-carboxylate (13)**



Benzylamine (8.5 μL, 0.12 mmol, 1.2 equiv) was subjected to **General procedure H** (chromatography eluent: *n*-pentane/Et<sub>2</sub>O, 95:5) to give the *title compound 13* (26 mg, 66%) as colourless plates. **mp**: 106–107 °C (*n*-pentane/Et<sub>2</sub>O at –20 °C); **IR**:  $\nu_{\text{max}}$  3027, 2982, 2936, 1681, 1604, 1586, 1554, 1525, 1494, 1478, 1452, 1438, 1419, 1399, 1361, 1345, 1308, 1274, 1244, 1204, 1190, 1158, 1128, 1109, 1076, 1059, 1027, 1002, 977, 923, 898, 873, 839, 818, 772, 764, 729, 696 cm<sup>-1</sup>; **HRMS**: calculated for C<sub>27</sub>H<sub>25</sub>NO<sub>2</sub><sup>23</sup>Na, 418.17775 [M+Na]<sup>+</sup>, found *m/z* 418.17786,  $\Delta$  = 0.25 ppm; **<sup>1</sup>H NMR** (400 MHz, acetone-*d*<sub>6</sub>)  $\delta$  7.48–7.39 (5H, m, HC<sub>Ar</sub>), 7.35 (2H, d, *J* = 8.1 Hz, HC<sub>Ar</sub>), 7.24 (2H, dd, *J* = 7.3, 7.3 Hz, HC<sub>Ar</sub>), 7.21–

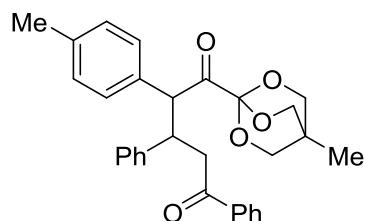
7.14 (3H, m,  $HC_{Ar}$ ), 6.90 (2H, d,  $J = 7.1$  Hz,  $HC_{Ar}$ ), 6.35 (1H, s,  $HC_{pyrrole}$ ), 5.66 (2H, s,  $PhCH_2N$ ), 4.00 (2H, q,  $J = 7.1$  Hz,  $OCH_2CH_3$ ), 2.35 (3H, s,  $ArCH_3$ ), 0.97 (3H, t,  $J = 7.1$  Hz,  $OCH_2CH_3$ );  $^{13}C$  NMR (101 MHz, acetone- $d_6$ )  $\delta$  162.4 ( $C(O)$ ), 141.3 ( $C_{Ar}$ ), 140.5 ( $C_{Ar}$ ), 136.9 ( $C_{Ar}$ ), 134.6 ( $C_{Ar}$ ), 134.5 ( $C_{Ar}$ ), 133.1 ( $C_{Ar}$ ), 130.4 ( $HC_{Ar}$ ), 130.2 ( $HC_{Ar}$ ), 129.6 ( $HC_{Ar}$ ), 129.3 ( $HC_{Ar}$ ), 129.3 ( $HC_{Ar}$ ), 129.1 ( $HC_{Ar}$ ), 127.8 ( $HC_{Ar}$ ), 126.7 ( $HC_{Ar}$ ), 120.9 ( $C_{Ar}$ ), 112.7 ( $HC_{pyrrole}$ ), 60.4 ( $OCH_2CH_3$ ), 50.1 ( $PhCH_2N$ ), 21.3 ( $ArCH_3$ ), 14.2 ( $OCH_2CH_3$ ).

### S3.4 Synthesis of pyridine-2-carboxylates 16

#### S3.4.1 1,5-Dicarbonyl scaffolds 15

**General procedure I:** To a stirred mixture of the appropriate arylated OBO-ketone **8** (0.50 mmol, 1.0 equiv), KOH (34 mg, 0.60 mmol, 1.2 equiv) and EtOH (7.5 mL), the appropriate  $\alpha,\beta$ -unsaturated ketone **14** (0.55 mmol, 1.1 equiv) was added in one portion and the mixture was stirred at rt. After complete consumption of the starting material (2 h, by TLC), the reaction was quenched with saturated aq  $\text{NH}_4\text{Cl}$  and extracted with DCM ( $3 \times 80$  mL). The combined organic extracts were then dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography to give the corresponding product **15**.

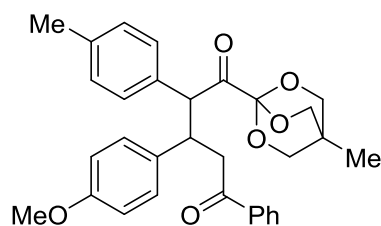
#### 1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-3,5-diphenyl-2-(p-tolyl)pentane-1,5-dione (**15a**)



Arylated OBO-ketone **8b**<sup>6</sup> (131 mg, 0.499 mmol, 1.0 equiv) and *trans*-chalcone (**14a**) (115 mg, 0.552 mmol, 1.1 equiv) were subjected to **General procedure I** (chromatography eluent: *n*-pentane/acetone, 80:20) to give the *title compound* **15a** (217 mg, 92%) as colourless needles. **mp**: 227–229 °C

(*c*-hexane/EtOH); **IR**:  $\nu_{\text{max}}$  3031, 2961, 2934, 2891, 1742, 1682, 1598, 1581, 1513, 1494, 1470, 1450, 1401, 1352, 1304, 1244, 1193, 1073, 1060, 1047, 1031, 1003, 987, 953, 928, 907, 880, 861, 834, 805, 788, 778, 763, 750, 716, 697, 689, 610  $\text{cm}^{-1}$ ; **HRMS**: calculated for  $\text{C}_{30}\text{H}_{31}\text{O}_5$ , 471.21660  $[\text{M}+\text{H}]^+$ , found  $m/z$  471.21585,  $\Delta = -1.59$  ppm; **<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.62 (2H, d,  $J = 7.1$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.45 (1H, dd,  $J = 7.4, 7.4$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.32 (2H, dd,  $J = 7.7, 7.7$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.29–7.23 (4H, m,  $\text{HC}_{\text{Ar}}$ ), 7.18 (2H, dd,  $J = 7.5, 7.5$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.13–7.04 (3H, m,  $\text{HC}_{\text{Ar}}$ ), 4.75 (1H, d,  $J = 10.8$  Hz,  $\text{ArCHC}(\text{O})$ ), 4.13 (1H, ddd,  $J = 10.4, 10.4, 3.9$  Hz,  $\text{PhCH}$ ), 3.80 (6H, s,  $\text{C}(\text{OCH}_2)_3\text{C}$ ), 3.10 (1H, dd,  $J = 16.2, 10.0$  Hz,  $\text{C}(\text{O})\text{CH}_a\text{H}_b\text{C}$ ), 3.00 (1H, dd,  $J = 16.2, 4.0$  Hz,  $\text{C}(\text{O})\text{CH}_a\text{H}_b\text{C}$ ), 2.31 (3H, s,  $\text{ArCH}_3$ ), 0.74 (3H, s,  $\text{CH}_3$ ); **<sup>13</sup>C NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  198.9 ( $\text{C}(\text{O})$ ), 196.8 ( $\text{C}(\text{O})$ ), 141.9 ( $\text{C}_{\text{Ar}}$ ), 137.4 ( $\text{C}_{\text{Ar}}$ ), 137.3 ( $\text{C}_{\text{Ar}}$ ), 133.3 ( $\text{C}_{\text{Ar}}$ ), 132.8 ( $\text{HC}_{\text{Ar}}$ ), 129.6 ( $\text{HC}_{\text{Ar}}$ ), 129.5 ( $\text{HC}_{\text{Ar}}$ ), 128.8 ( $\text{HC}_{\text{Ar}}$ ), 128.5 ( $\text{HC}_{\text{Ar}}$ ), 128.2 ( $\text{HC}_{\text{Ar}}$ ), 128.1 ( $\text{HC}_{\text{Ar}}$ ), 126.7 ( $\text{HC}_{\text{Ar}}$ ), 103.9 ( $\text{CO}_3$ ), 73.0 ( $\text{C}(\text{OCH}_2)_3\text{C}$ ), 57.0 ( $\text{ArCHC}(\text{O})$ ), 44.6 ( $\text{PhCH}$ ), 42.9 ( $\text{C}(\text{O})\text{CH}_a\text{H}_b\text{C}$ ), 31.0 ( $\text{C}(\text{OCH}_2)_3\text{CMe}$ ), 21.3 ( $\text{ArCH}_3$ ), 14.4 ( $\text{CH}_3$ ).

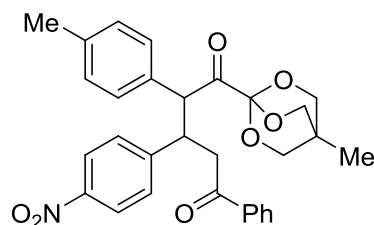
**3-(4-Methoxyphenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-5-phenyl-2-(p-tolyl)pentane-1,5-dione (15b)**



Arylated OBO-ketone **8b**<sup>6</sup> (131 mg, 0.499 mmol, 1.0 equiv) and 4-methoxychalcone (**14b**) (131 mg, 0.550 mmol, 1.1 equiv) were subjected to **General procedure I** (chromatography eluent: *n*-pentane/acetone, 80:20) to give the *title compound* **15b** (215 mg, 86%) as colourless needles.

**mp**: 218.5–220 °C (*c*-hexane/EtOH); **IR**:  $\nu_{\max}$  2936, 2883, 2834, 1742, 1680, 1612, 1597, 1581, 1512, 1449, 1399, 1347, 1303, 1286, 1247, 1179, 1110, 1076, 1032, 1001, 992, 928, 880, 861, 827, 796, 751, 735, 709, 691  $\text{cm}^{-1}$ ; **HRMS**: calculated for  $\text{C}_{31}\text{H}_{32}\text{O}_6^{23}\text{Na}$ , 523.20911  $[\text{M}+\text{Na}]^+$ , found  $m/z$  523.20917,  $\Delta = 0.11$  ppm; **<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.62 (2H, d,  $J = 7.1$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.45 (1H, dd,  $J = 7.4, 7.4$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.32 (2H, dd,  $J = 7.7, 7.7$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.26 (2H, d,  $J = 8.1$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.15 (2H, d,  $J = 8.7$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.10 (2H, d,  $J = 7.9$  Hz,  $\text{HC}_{\text{Ar}}$ ), 6.72 (2H, d,  $J = 8.7$  Hz,  $\text{HC}_{\text{Ar}}$ ), 4.69 (1H, d,  $J = 10.8$  Hz,  $\text{ArCHC}(\text{O})$ ), 4.07 (1H, ddd,  $J = 10.4, 10.4, 4.0$  Hz,  $4\text{-MeOC}_6\text{H}_4\text{CH}$ ), 3.80 (6H, s,  $\text{C}(\text{OCH}_2)_3\text{C}$ ), 3.72 (3H, s,  $\text{OCH}_3$ ), 3.04 (1H, dd,  $J = 16.0, 10.0$  Hz,  $\text{C}(\text{O})\text{CH}_a\text{H}_b\text{C}$ ), 2.96 (1H, dd,  $J = 16.1, 4.1$  Hz,  $\text{C}(\text{O})\text{CH}_a\text{H}_b\text{C}$ ), 2.31 (3H, s,  $\text{ArCH}_3$ ), 0.74 (3H, s,  $\text{CH}_3$ ); **<sup>13</sup>C NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  199.1 ( $\text{C}(\text{O})$ ), 196.9 ( $\text{C}(\text{O})$ ), 158.2 ( $\text{C}_{\text{Ar}}$ ), 137.4 ( $\text{C}_{\text{Ar}}$ ), 137.3 ( $\text{C}_{\text{Ar}}$ ), 134.0 ( $\text{C}_{\text{Ar}}$ ), 133.5 ( $\text{C}_{\text{Ar}}$ ), 132.8 ( $\text{HC}_{\text{Ar}}$ ), 129.7 ( $\text{HC}_{\text{Ar}}$ ), 129.6 ( $\text{HC}_{\text{Ar}}$ ), 129.5 ( $\text{HC}_{\text{Ar}}$ ), 128.5 ( $\text{HC}_{\text{Ar}}$ ), 128.1 ( $\text{HC}_{\text{Ar}}$ ), 113.6 ( $\text{HC}_{\text{Ar}}$ ), 103.9 ( $\text{CO}_3$ ), 73.0 ( $\text{C}(\text{OCH}_2)_3\text{C}$ ), 57.2 ( $\text{ArCHC}(\text{O})$ ), 55.3 ( $\text{OCH}_3$ ), 44.0 ( $4\text{-MeOC}_6\text{H}_4\text{CH}$ ), 43.1 ( $\text{C}(\text{O})\text{CH}_a\text{H}_b\text{C}$ ), 31.0 ( $\text{C}(\text{OCH}_2)_3\text{CMe}$ ), 21.3 ( $\text{ArCH}_3$ ), 14.4 ( $\text{CCH}_3$ ).

**1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-3-(4-nitrophenyl)-5-phenyl-2-(p-tolyl)pentane-1,5-dione (15c)**

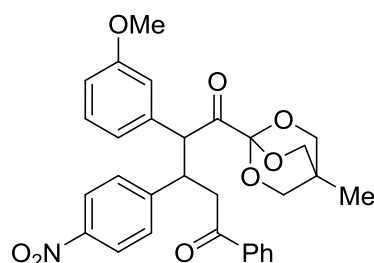


Arylated OBO-ketone **8b**<sup>6</sup> (131 mg, 0.499 mmol, 1.0 equiv) and 4-nitrochalcone (**14c**) (139 mg, 0.549 mmol, 1.1 equiv) were subjected to **General procedure I** (chromatography eluent: *n*-pentane/acetone, 80:20) to give the *title compound* **15c** (250 mg, 97%) as pale-yellow needles. **mp**: 273–275 °C

(*c*-hexane/EtOH); **IR**:  $\nu_{\max}$  3032, 2941, 2876, 1737, 1682, 1597, 1581, 1517, 1491, 1468, 1449, 1412, 1398, 1345, 1243, 1193, 1109, 1070, 1043, 1030, 1000, 950, 927, 881, 868, 855, 849, 832, 807, 789, 779, 757, 720, 691, 654, 632  $\text{cm}^{-1}$ ; **HRMS**: calculated for  $\text{C}_{30}\text{H}_{29}\text{NO}_7^{23}\text{Na}$ , 538.18362  $[\text{M}+\text{Na}]^+$ , found  $m/z$  538.18359,  $\Delta = -0.06$  ppm; **<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.06 (2H, d,  $J = 8.7$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.63 (2H, d,  $J = 7.3$  Hz,  $\text{HC}_{\text{Ar}}$ ), 7.53–7.44

(3H, m,  $HC_{Ar}$ ), 7.34 (2H, dd,  $J = 7.7, 7.7$  Hz,  $HC_{Ar}$ ), 7.26 (2H, d,  $J = 8.0$  Hz,  $HC_{Ar}$ ), 7.13 (2H, d,  $J = 7.9$  Hz,  $HC_{Ar}$ ), 4.73 (1H, d,  $J = 11.2$  Hz,  $ArCHC(O)$ ), 4.23 (1H, ddd,  $J = 10.7, 10.7, 3.5$  Hz,  $4-O_2NC_6H_4CH$ ), 3.79 (6H, s,  $C(OCH_2)_3C$ ), 3.15 (1H, dd,  $J = 16.9, 10.3$  Hz,  $C(O)CH_aH_bC$ ), 3.02 (1H, dd,  $J = 16.8, 3.5$  Hz,  $C(O)CH_aH_bC$ ), 2.32 (3H, s,  $ArCH_3$ ), 0.75 (3H, s,  $CCH_3$ );  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  197.9 ( $C(O)$ ), 196.4 ( $C(O)$ ), 150.1 ( $C_{Ar}$ ), 146.8 ( $C_{Ar}$ ), 137.9 ( $C_{Ar}$ ), 136.8 ( $C_{Ar}$ ), 133.3 ( $C_{Ar}$ ), 132.5 ( $HC_{Ar}$ ), 129.9 ( $HC_{Ar}$ ), 129.8 ( $HC_{Ar}$ ), 129.4 ( $HC_{Ar}$ ), 128.7 ( $HC_{Ar}$ ), 128.0 ( $HC_{Ar}$ ), 123.5 ( $HC_{Ar}$ ), 103.8 ( $CO_3$ ), 73.1 ( $C(OCH_2)_3C$ ), 56.7 ( $ArCHC(O)$ ), 44.5 ( $4-O_2NC_6H_4CH$ ), 42.4 ( $C(O)CH_aH_bC$ ), 31.0 ( $C(OCH_2)_3CMe$ ), 21.4 ( $ArCH_3$ ), 14.3 ( $CCH_3$ ).

**2-(3-Methoxyphenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-3-(4-nitrophenyl)-5-phenylpentane-1,5-dione (15d)**

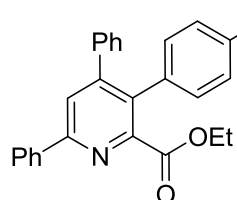


Arylated OBO-ketone **8c** (138 mg, 0.496 mmol, 1.0 equiv) and 4-nitrochalcone (**14c**) (139 mg, 0.549 mmol, 1.1 equiv) were subjected to **General procedure I** (chromatography eluent: *n*-pentane/acetone, 80:20) to give the *title compound* **15d** (249 mg, 94%) as pale-yellow plates. **mp**: 222–224 °C (*c*-hexane); **IR**:  $\nu_{max}$  3069, 2934, 2883, 1742, 1731, 1682, 1606, 1581, 1518, 1487, 1471, 1449, 1433, 1400, 1344, 1320, 1294, 1259, 1244, 1185, 1147, 1108, 1076, 1044, 1027, 1002, 988, 957, 928, 902, 890, 870, 853, 826, 798, 777, 754, 713, 692, 670, 658, 633, 611  $cm^{-1}$ ; **HRMS**: calculated for  $C_{30}H_{29}NO_8^{23}Na$ , 554.17854  $[M+Na]^+$ , found  $m/z$  554.17914,  $\Delta = 1.08$  ppm;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.07 (2H, d,  $J = 8.8$  Hz,  $HC_{Ar}$ ), 7.64 (2H, d,  $J = 7.2$  Hz,  $HC_{Ar}$ ), 7.51–7.45 (3H, m,  $HC_{Ar}$ ), 7.34 (2H, dd,  $J = 7.7, 7.7$  Hz,  $HC_{Ar}$ ), 7.25 (1H, dd,  $J = 7.9, 7.9$  Hz,  $HC_{Ar}$ ), 6.98 (1H, d,  $J = 7.7$  Hz,  $HC_{Ar}$ ), 6.94–6.90 (1H, m,  $HC_{Ar}$ ), 6.81 (1H, dd,  $J = 8.2, 2.1$  Hz,  $HC_{Ar}$ ), 4.75 (1H, d,  $J = 11.3$  Hz,  $ArCHC(O)$ ), 4.24 (1H, ddd,  $J = 10.7, 10.7, 3.5$  Hz,  $4-O_2NC_6H_4CH$ ), 3.80 (6H, s,  $C(OCH_2)_3C$ ), 3.79 (3H, s,  $OCH_3$ ), 3.17 (1H, dd,  $J = 16.9, 10.3$  Hz,  $C(O)CH_aH_bC$ ), 3.03 (1H, dd,  $J = 16.9, 3.6$  Hz,  $C(O)CH_aH_bC$ ), 0.75 (3H, s,  $CH_3$ );  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  197.8 ( $C(O)$ ), 196.2 ( $C(O)$ ), 160.1 ( $C_{Ar}$ ), 150.0 ( $C_{Ar}$ ), 146.8 ( $C_{Ar}$ ), 137.1 ( $C_{Ar}$ ), 136.8 ( $C_{Ar}$ ), 133.3 ( $HC_{Ar}$ ), 130.0 ( $HC_{Ar}$ ), 129.9 ( $HC_{Ar}$ ), 128.7 ( $HC_{Ar}$ ), 128.0 ( $HC_{Ar}$ ), 123.5 ( $HC_{Ar}$ ), 122.0 ( $HC_{Ar}$ ), 114.9 ( $HC_{Ar}$ ), 113.7 ( $HC_{Ar}$ ), 103.8 ( $CO_3$ ), 73.1 ( $C(OCH_2)_3C$ ), 57.0 ( $ArCHC(O)$ ), 55.5 ( $OCH_3$ ), 44.5 ( $4-O_2NC_6H_4CH$ ), 42.4 ( $C(O)CH_aH_bC$ ), 31.0 ( $C(OCH_2)_3CMe$ ), 14.3 ( $CH_3$ ).

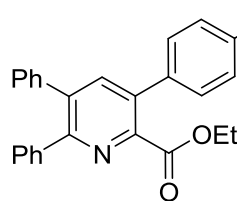
### S3.4.2 Cyclisation to pyridine-2-carboxylates **16**

**General procedure J:** *Step 1:* In a Biotage<sup>®</sup> microwave vial sealed with a microwave vial cap (Reseal<sup>™</sup> septum), a mixture of the appropriate 1,5-dicarbonyl compound **15** (0.10 mmol, 1.0 equiv), hydroxylamine hydrochloride (21 mg, 0.30 mmol, 3.0 equiv), *p*-toluenesulfonic acid monohydrate (190 mg, 1.00 mmol, 10 equiv) and EtOH (3 mL) was heated at 115 °C for 16 h. The reaction mixture was cooled to rt, diluted with DCM (30 mL) and washed with saturated aq NaHCO<sub>3</sub> (50 mL). The aqueous layer was extracted with DCM (4 x 30 mL) and the organic extracts were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated *in vacuo* and purified by flash column chromatography to give the corresponding pyridine-2-carboxylate **16**.

#### *Ethyl 4,6-diphenyl-3-(p-tolyl)picolinate (16a)*



1,5-Dicarbonyl compound **15a** (47 mg, 0.10 mmol, 1.0 equiv) subjected to **General procedure J** (chromatography eluent: *n*-pentane/Et<sub>2</sub>O, 90:10) to give the *title compound* **16a** (33 mg, 84%) as colourless prisms. **mp**: 138–139 °C (*c*-hexane); **IR**:  $\nu_{\max}$  3037, 2976, 2927, 1736, 1586, 1576, 1536, 1516, 1495, 1465, 1453, 1428, 1395, 1366, 1350, 1319, 1287, 1240, 1191, 1112, 1103, 1094, 1071, 1026, 1003, 976, 927, 891, 863, 840, 824, 800, 777, 762, 744, 721, 705, 696, 678, 668, 637, 617 cm<sup>-1</sup>; **HRMS**: calculated for C<sub>27</sub>H<sub>24</sub>NO<sub>2</sub>, 394.18016 [M+H]<sup>+</sup>, found *m/z* 394.18027,  $\Delta$  = 0.28 ppm; **<sup>1</sup>H NMR** (400 MHz, acetone-*d*<sub>6</sub>)  $\delta$  8.26–8.22 (2H, m, HC<sub>Ar</sub>), 8.03 (1H, s, HC<sub>pyridine</sub>), 7.57–7.43 (3H, m, HC<sub>Ar</sub>), 7.33–7.22 (5H, m, HC<sub>Ar</sub>), 7.09 (2H, d, *J* = 7.9 Hz, HC<sub>Ar</sub>), 7.04 (2H, d, *J* = 8.2 Hz, HC<sub>Ar</sub>), 4.09 (2H, q, *J* = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 2.29 (3H, s, ArCH<sub>3</sub>), 1.00 (3H, t, *J* = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  168.0 (C(O)), 156.1 (C<sub>Ar</sub>), 151.9 (C<sub>Ar</sub>), 150.7 (C<sub>Ar</sub>), 138.8 (C<sub>Ar</sub>), 138.5 (C<sub>Ar</sub>), 137.4 (C<sub>Ar</sub>), 133.3 (C<sub>Ar</sub>), 132.7 (C<sub>Ar</sub>), 130.0 (HC<sub>Ar</sub>), 129.5 (HC<sub>Ar</sub>), 129.5 (HC<sub>Ar</sub>), 128.9 (HC<sub>Ar</sub>), 128.9 (HC<sub>Ar</sub>), 128.3 (HC<sub>Ar</sub>), 128.0 (HC<sub>Ar</sub>), 127.4 (HC<sub>Ar</sub>), 122.8 (HC<sub>pyridine</sub>), 61.6 (OCH<sub>2</sub>CH<sub>3</sub>), 21.4 (ArCH<sub>3</sub>), 13.9 (OCH<sub>2</sub>CH<sub>3</sub>).

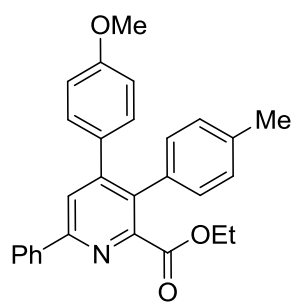


Further elution (*n*-pentane/Et<sub>2</sub>O, 90:10) gave ethyl 5,6-diphenyl-3-(*p*-tolyl)picolinate (**17a**) (4.8 mg, 12%) as colourless plates. **mp**: 142–145 °C (*c*-hexane); **IR**:  $\nu_{\max}$  3055, 3030, 2980, 2921, 1734, 1578, 1518, 1495, 1448, 1426, 1398, 1365, 1319, 1269, 1244, 1205, 1128, 1067, 1021, 1008, 912, 866, 822, 789, 766, 700 cm<sup>-1</sup>; **HRMS**: calculated for C<sub>27</sub>H<sub>23</sub>NO<sub>2</sub><sup>23</sup>Na, 416.16210 [M+Na]<sup>+</sup>, found *m/z* 416.16275,  $\Delta$  = 1.57 ppm; **<sup>1</sup>H NMR** (400



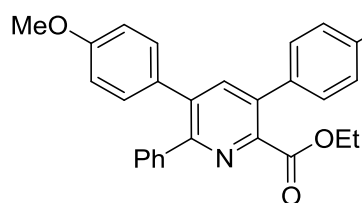
MHz, acetone- $d_6$ )  $\delta$  7.78 (1H, s,  $HC_{\text{pyridine}}$ ), 7.48–7.39 (2H, m,  $HC_{\text{Ar}}$ ), 7.35 (2H, d,  $J = 7.9$  Hz,  $HC_{\text{Ar}}$ ), 7.31–7.18 (10H, m,  $HC_{\text{Ar}}$ ), 4.25 (2H, q,  $J = 7.1$  Hz,  $OCH_2CH_3$ ), 2.41 (3H, s,  $ArCH_3$ ), 1.14 (3H, t,  $J = 7.1$  Hz,  $OCH_2CH_3$ );  $^{13}\text{C}$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  167.6 ( $C(O)$ ), 155.7 ( $C_{\text{Ar}}$ ), 148.2 ( $C_{\text{Ar}}$ ), 140.7 ( $HC_{\text{pyridine}}$ ), 139.4 ( $C_{\text{Ar}}$ ), 139.3 ( $C_{\text{Ar}}$ ), 138.2 ( $C_{\text{Ar}}$ ), 137. ( $C_{\text{Ar}}$ ), 135.2 ( $C_{\text{Ar}}$ ), 135.1 ( $C_{\text{Ar}}$ ), 130.4 ( $HC_{\text{Ar}}$ ), 129.7 ( $HC_{\text{Ar}}$ ), 129.5 ( $HC_{\text{Ar}}$ ), 128.7 ( $HC_{\text{Ar}}$ ), 128.5 ( $HC_{\text{Ar}}$ ), 128.3 ( $HC_{\text{Ar}}$ ), 128.1 ( $HC_{\text{Ar}}$ ), 127.9 ( $HC_{\text{Ar}}$ ), 61.8 ( $OCH_2CH_3$ ), 21.5 ( $ArCH_3$ ), 14.0 ( $OCH_2CH_3$ ).

**Ethyl 4-(4-methoxyphenyl)-6-phenyl-3-(p-tolyl)picolinate (16b)**



1,5-Dicarbonyl compound **15b** (50 mg, 0.10 mmol, 1.0 equiv) was subjected to **General procedure J** (chromatography eluent: *n*-pentane/ $Et_2O$ , 90:10) gave the *title compound* **16b** (25 mg, 59%) as colourless plates. **mp**: 142–144 °C (*c*-hexane); **IR**:  $\nu_{\text{max}}$  3036, 2979, 2958, 2837, 1729, 1608, 1578, 1535, 1513, 1495, 1465, 1451, 1433, 1413, 1397, 1376, 1367, 1346, 1301, 1286, 1250, 1204, 1185,

1178, 1152, 1113, 1103, 1072, 1029, 1016, 967, 942, 924, 912, 895, 865, 851, 835, 820, 805, 789, 773, 738, 720, 696, 671, 643, 625  $\text{cm}^{-1}$ ; **HRMS**: calculated for  $C_{28}H_{26}NO_3$ , 424.19072  $[M+H]^+$ , found  $m/z$  424.19043,  $\Delta = -0.68$  ppm;  $^1\text{H}$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.11 (2H, d,  $J = 7.0$  Hz,  $HC_{\text{Ar}}$ ), 7.84 (1H, s,  $HC_{\text{pyridine}}$ ), 7.60–7.39 (3H, m,  $HC_{\text{Ar}}$ ), 7.14–6.99 (6H, m,  $HC_{\text{Ar}}$ ), 6.80 (2H, d,  $J = 8.8$  Hz,  $HC_{\text{Ar}}$ ), 4.16 (2H, q,  $J = 7.1$  Hz,  $OCH_2CH_3$ ), 3.81 (3H, s,  $OCH_3$ ), 2.35 (3H, s,  $ArCH_3$ ), 1.04 (3H, t,  $J = 7.1$  Hz,  $OCH_2CH_3$ );  $^{13}\text{C}$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  168.1 ( $C(O)$ ), 159.5 ( $C_{\text{Ar}}$ ), 156.2 ( $C_{\text{Ar}}$ ), 152.0 ( $C_{\text{Ar}}$ ), 150.3 ( $C_{\text{Ar}}$ ), 138.7 ( $C_{\text{Ar}}$ ), 137.4 ( $C_{\text{Ar}}$ ), 133.6 ( $C_{\text{Ar}}$ ), 132.5 ( $C_{\text{Ar}}$ ), 131.1 ( $C_{\text{Ar}}$ ), 130.8 ( $HC_{\text{Ar}}$ ), 130.1 ( $HC_{\text{Ar}}$ ), 129.4 ( $HC_{\text{Ar}}$ ), 129.0 ( $HC_{\text{Ar}}$ ), 128.9 ( $HC_{\text{Ar}}$ ), 127.4 ( $HC_{\text{Ar}}$ ), 122.8 ( $HC_{\text{pyridine}}$ ), 113.8 ( $HC_{\text{Ar}}$ ), 61.6 ( $OCH_2CH_3$ ), 55.4 ( $OCH_3$ ), 21.5 ( $ArCH_3$ ), 13.9 ( $OCH_2CH_3$ ).

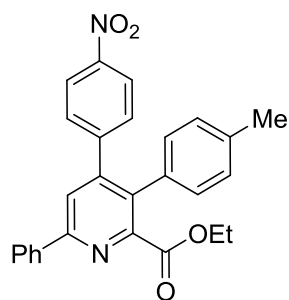


Further elution (*n*-pentane/ $Et_2O$ , 90:10) gave ethyl 5-(4-methoxyphenyl)-6-phenyl-3-(*p*-tolyl)picolinate (**17b**) (13 mg, 30%) as colourless needles. **mp**: 193–194 °C (*c*-hexane); **IR**:  $\nu_{\text{max}}$  3020, 2983, 2924, 2844, 1723, 1606,

1578, 1510, 1468, 1448, 1426, 1393, 1362, 1318, 1310, 1293, 1269, 1247, 1221, 1203, 1178, 1138, 1112, 1078, 1066, 1032, 1016, 1001, 974, 948, 920, 912, 869, 842, 822, 788, 758, 734, 724, 703, 695, 675, 636  $\text{cm}^{-1}$ ; **HRMS**: calculated for  $C_{28}H_{25}NO_3^{23}\text{Na}$ , 446.17266  $[M+Na]^+$ , found  $m/z$  446.17310,  $\Delta = 0.97$  ppm;  $^1\text{H}$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.75 (1H, s,  $HC_{\text{pyridine}}$ ),

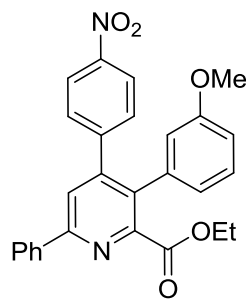
7.45–7.43 (2H, m,  $HC_{Ar}$ ), 7.34 (2H, d,  $J = 8.1$  Hz,  $HC_{Ar}$ ), 7.29–7.22 (5H, m,  $HC_{Ar}$ ), 7.13 (2H, d,  $J = 8.7$  Hz,  $HC_{Ar}$ ), 6.82 (2H, d,  $J = 8.8$  Hz,  $HC_{Ar}$ ), 4.24 (2H, q,  $J = 7.1$  Hz,  $OCH_2CH_3$ ), 3.80 (3H, s,  $OCH_3$ ), 2.41 (3H, s,  $ArCH_3$ ), 1.13 (3H, t,  $J = 7.1$  Hz,  $OCH_2CH_3$ );  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  167.6 ( $C(O)$ ), 159.4 ( $C_{Ar}$ ), 155.6 ( $C_{Ar}$ ), 147.7 ( $C_{Ar}$ ), 140.6 ( $HC_{pyridine}$ ), 139.5 ( $C_{Ar}$ ), 138.1 ( $C_{Ar}$ ), 137.3 ( $C_{Ar}$ ), 135.3 ( $C_{Ar}$ ), 135.2 ( $C_{Ar}$ ), 131.5 ( $C_{Ar}$ ), 130.8 ( $HC_{Ar}$ ), 130.3 ( $HC_{Ar}$ ), 129.4 ( $HC_{Ar}$ ), 128.5 ( $HC_{Ar}$ ), 128.19 ( $HC_{Ar}$ ), 128.16 ( $HC_{Ar}$ ), 114.1 ( $HC_{Ar}$ ), 61.8 ( $OCH_2CH_3$ ), 55.5 ( $OCH_3$ ), 21.4 ( $ArCH_3$ ), 14.0 ( $OCH_2CH_3$ ).

#### ***Ethyl 4-(4-nitrophenyl)-6-phenyl-3-(p-tolyl)picolinate (16c)***



1,5-Dicarbonyl compound **15c** (52 mg, 0.10 mmol, 1.0 equiv) was subjected to **General procedure J** (chromatography eluent: *n*-pentane/DCM, 20:80 to 0:100) to give the *title compound* **16c** (38 mg, 87%) as colourless plates. **mp**: 205–206 °C (*c*-hexane/EtOH); **IR**:  $\nu_{max}$  3108, 3081, 2991, 2909, 1740, 1600, 1585, 1640, 1509, 1474, 1454, 1428, 1378, 1363, 1344, 1312, 1285, 1191, 1157, 1108, 1069, 1022, 963, 924, 898, 869, 852, 830, 805, 791, 783, 770, 753, 722, 692, 663, 642, 619  $cm^{-1}$ ; **HRMS**: calculated for  $C_{27}H_{23}N_2O_4$ , 439.16523  $[M+H]^+$ , found  $m/z$  439.16510,  $\Delta = -0.3$  ppm;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.14–8.00 (4H, m,  $HC_{Ar}$ ), 7.82 (1H, s,  $HC_{pyridine}$ ), 7.54–7.41 (3H, m,  $HC_{Ar}$ ), 7.31 (2H, d,  $J = 8.7$  Hz,  $HC_{Ar}$ ), 7.06 (2H, d,  $J = 7.9$  Hz,  $HC_{Ar}$ ), 6.99 (2H, d,  $J = 8.0$  Hz,  $HC_{Ar}$ ), 4.16 (2H, q,  $J = 7.1$  Hz,  $OCH_2CH_3$ ), 2.33 (3H, s,  $ArCH_3$ ), 1.03 (3H, t,  $J = 7.1$  Hz,  $OCH_2CH_3$ );  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  167.4 ( $C(O)$ ), 156.5 ( $C_{Ar}$ ), 152.2 ( $C_{Ar}$ ), 148.4 ( $C_{Ar}$ ), 147.5 ( $C_{Ar}$ ), 145.5 ( $C_{Ar}$ ), 138.1 ( $C_{Ar}$ ), 138.0 ( $C_{Ar}$ ), 132.5 ( $C_{Ar}$ ), 132.4 ( $C_{Ar}$ ), 130.4 ( $HC_{Ar}$ ), 129.9 (2  $\times$   $HC_{Ar}$ ), 129.2 ( $HC_{Ar}$ ), 129.1 ( $HC_{Ar}$ ), 127.4 ( $HC_{Ar}$ ), 123.6 ( $HC_{Ar}$ ), 122.1 ( $HC_{pyridine}$ ), 61.8 ( $OCH_2CH_3$ ), 21.4 ( $ArCH_3$ ), 13.9 ( $OCH_2CH_3$ ).

#### ***Ethyl 3-(3-methoxyphenyl)-4-(4-nitrophenyl)-6-phenylpicolinate (16d)***

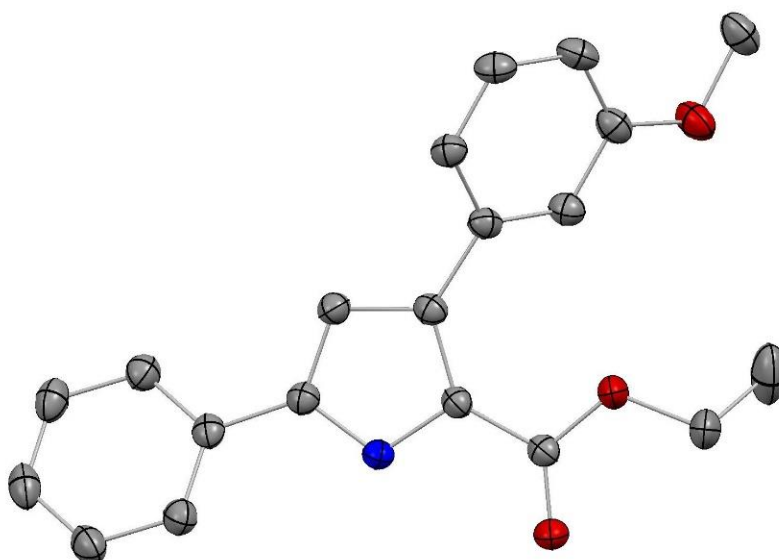


1,5-Dicarbonyl compound **15d** (53 mg, 0.10 mmol, 1.0 equiv) was subjected to **General procedure J** (chromatography eluent: DCM) to give the *title compound* **16d** (37 mg, 83%) as colourless needles. **mp**: 170–171 °C (*c*-hexane); **IR**:  $\nu_{max}$  3106, 3080, 2995, 2933, 2833, 1736, 1588, 1537, 1514, 1495, 1462, 1435, 1418, 1398, 1366, 1346, 1321, 1302, 1287, 1270, 1224, 1192, 1181, 1106, 1093, 1069, 1046, 1030, 1014, 976, 934, 908, 872, 856, 831, 792, 772, 755, 748, 703, 666, 633, 619  $cm^{-1}$ ; **HRMS**: calculated for  $C_{27}H_{22}N_2O_5^{23}Na$ , 477.14209  $[M+Na]^+$ , found  $m/z$  477.14212,  $\Delta = 0.06$  ppm;

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 8.13 (2H, d, *J* = 8.8 Hz, HC<sub>Ar</sub>), 8.10 (2H, dd, *J* = 8.1, 1.5 Hz, HC<sub>Ar</sub>), 7.83 (1H, s, HC<sub>pyridine</sub>), 7.54–7.41 (3H, m, HC<sub>Ar</sub>), 7.34 (2H, d, *J* = 8.7 Hz, HC<sub>Ar</sub>), 7.17 (1H, dd, *J* = 7.9, 7.9 Hz, HC<sub>Ar</sub>), 6.82 (1H, dd, *J* = 8.1, 2.2 Hz, HC<sub>Ar</sub>), 6.71–6.65 (2H, m, HC<sub>Ar</sub>), 4.17 (2H, q, *J* = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 3.69 (3H, s, ArCH<sub>3</sub>), 1.03 (3H, t, *J* = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 167.4 (C(O)), 159.6 (C<sub>Ar</sub>), 156.8 (C<sub>Ar</sub>), 152.1 (C<sub>Ar</sub>), 148.4 (C<sub>Ar</sub>), 147.6 (C<sub>Ar</sub>), 145.4 (C<sub>Ar</sub>), 137.9 (C<sub>Ar</sub>), 136.8 (C<sub>Ar</sub>), 132.3 (C<sub>Ar</sub>), 130.4 (HC<sub>Ar</sub>), 130.0 (HC<sub>Ar</sub>), 129.6 (HC<sub>Ar</sub>), 129.1 (HC<sub>Ar</sub>), 127.4 (HC<sub>Ar</sub>), 123.6 (HC<sub>Ar</sub>), 122.6 (HC<sub>Ar</sub>), 122.1 (HC<sub>pyridine</sub>), 115.8 (HC<sub>Ar</sub>), 113.8 (HC<sub>Ar</sub>), 61.9 (OCH<sub>2</sub>CH<sub>3</sub>), 55.4 (OCH<sub>3</sub>), 13.9 (OCH<sub>2</sub>CH<sub>3</sub>).

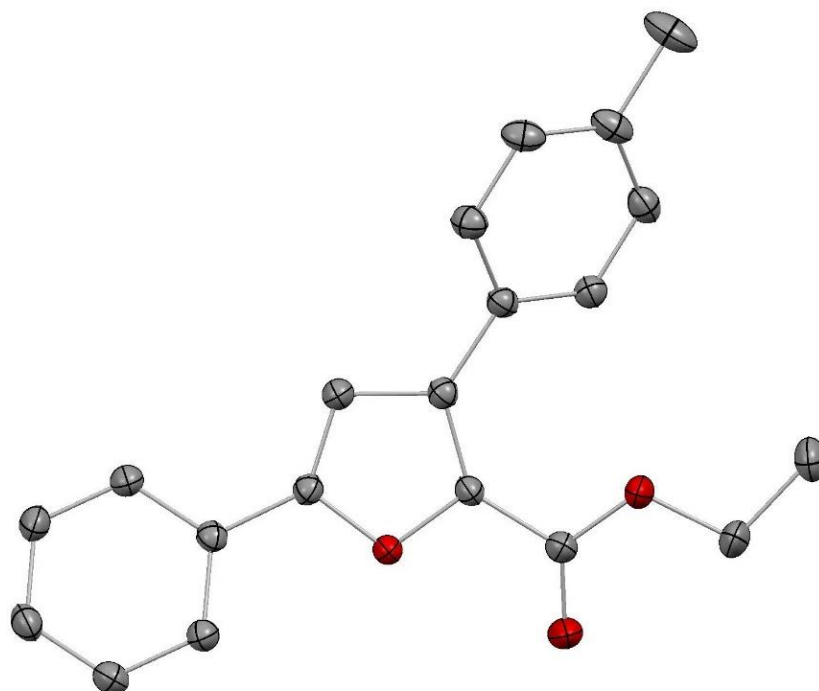
**S4**      **Single crystal X-ray diffraction for compounds 10c, 11b, 16a and 17b**

Single Crystal Data for **10c**:     $\text{C}_{20}\text{H}_{19}\text{NO}_3$   
Mr = 321.38  
150 K  
Monoclinic                       $P2_1/c$   
 $a = 11.0495(2) \text{ \AA}$ ,  $b = 7.3658(2) \text{ \AA}$ ,  $c = 20.3211(5) \text{ \AA}$   
 $\beta = 102.670(2)^\circ$   
 $V = 1613.63(7) \text{ \AA}^3$   
Data/restraints/parameters – 3337/0/217  
 $R_{\text{int}} = 0.033$   
Final  $R1 = 0.0438$ ,  $wR2 = 0.1154$  ( $I > 2\sigma(I)$ )



**Figure S1.** X-ray crystal structure (ellipsoid representation, probability level of 50%) for ethyl 3-(3-methoxyphenyl)-5-phenyl-1*H*-pyrrole-2-carboxylate (**10c**). H atoms are omitted for clarity.

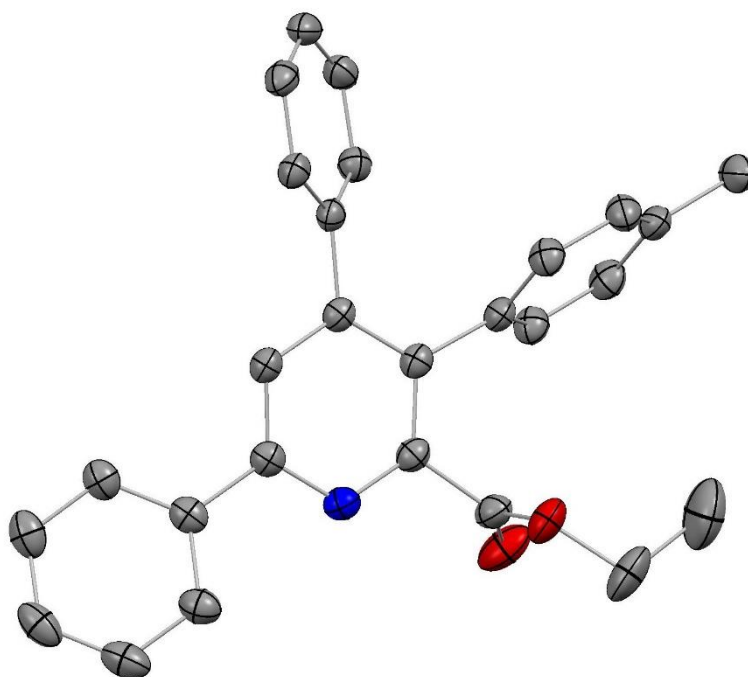
Single Crystal Data for **11b**: C<sub>20</sub>H<sub>18</sub>O<sub>3</sub>  
 Mr = 306.36  
 150 K  
 Triclinic *P*-1  
 $a = 8.2046(5) \text{ \AA}$ ,  $b = 9.7927(6) \text{ \AA}$ ,  $c = 10.6455(6) \text{ \AA}$   
 $\alpha = 107.704(5)^\circ$ ,  $\beta = 93.556(5)^\circ$ ,  $\gamma = 103.034(5)^\circ$   
 $V = 785.92(9) \text{ \AA}^3$   
 Data/restraints/parameters – 3229/0/208  
 Rint = 0.024  
 Final R1 = 0.0383, wR2 = 0.0983 (I>2 $\sigma$ (I))



**Figure S2.** X-ray crystal structure (ellipsoid representation, probability level of 50%) for ethyl 5-phenyl-3-(*p*-tolyl)furan-2-carboxylate (**11b**). H atoms are omitted for clarity.

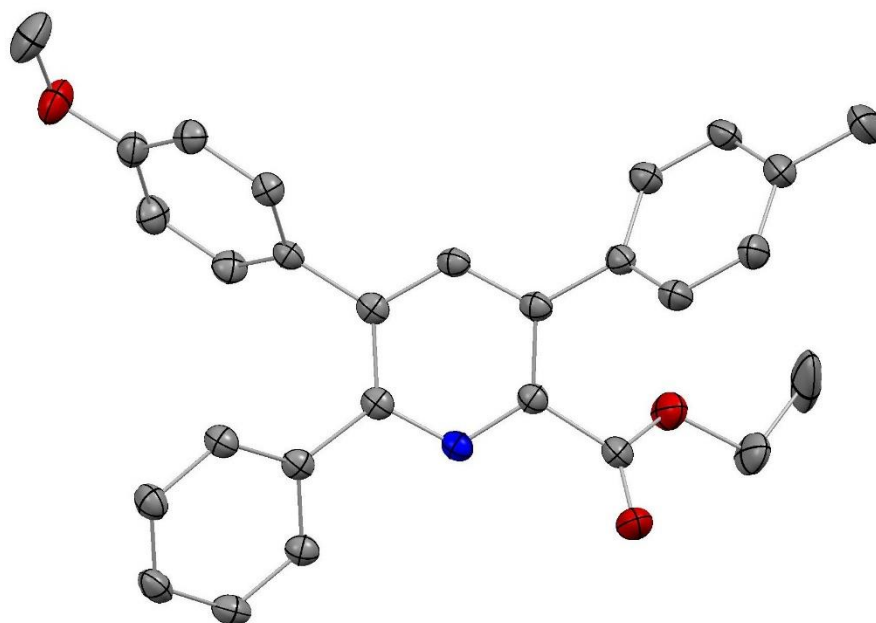
The single crystal data of a similar compound, ethyl 3,5-diphenylfuran-2-carboxylate, have been reported previously.<sup>18</sup>

Single Crystal Data for **16a**:  $C_{27}H_{23}NO_2$   
 Mr = 393.49  
 150 K  
 Monoclinic  $P2_1/c$   
 $a = 10.2055(2) \text{ \AA}$ ,  $b = 20.3705(4) \text{ \AA}$ ,  $c = 10.6093(2) \text{ \AA}$   
 $\beta = 105.618(2)$   
 $V = 2124.15(7) \text{ \AA}^3$   
 Data/restraints/parameters – 4408/4/288  
 $R_{int} = 0.020$   
 Final  $R1 = 0.0371$ ,  $wR2 = 0.0930$  ( $I > 2\sigma(I)$ )



**Figure S3.** X-ray crystal structure (ellipsoid representation, probability level of 50%) for 4,6-diphenyl-3-(*p*-tolyl)picolinate (**16a**). H atoms and minor disordered component are omitted for clarity.

Single Crystal Data for **17b**:  $\text{C}_{28}\text{H}_{25}\text{NO}_3$   
 Mr = 423.51  
 150 K  
 Monoclinic  $P2_1/c$   
 $a = 17.4949(5) \text{ \AA}$ ,  $b = 9.0087(3) \text{ \AA}$ ,  $c = 28.6456(9) \text{ \AA}$   
 $\beta = 99.604(3)^\circ$   
 $V = 4451.5(2) \text{ \AA}^3$   
 Data/restraints/parameters – 8037/4/596  
 Rint = 0.050  
 Final R1 = 0.0394, wR2 = 0.0892 ( $I > 2\sigma(I)$ )



**Figure S4.** X-ray crystal structure (ellipsoid representation, probability level of 50%) for ethyl 5-(4-methoxyphenyl)-6-phenyl-3-(*p*-tolyl)picolinate (**17b**). H atoms and minor disordered component are omitted for clarity.

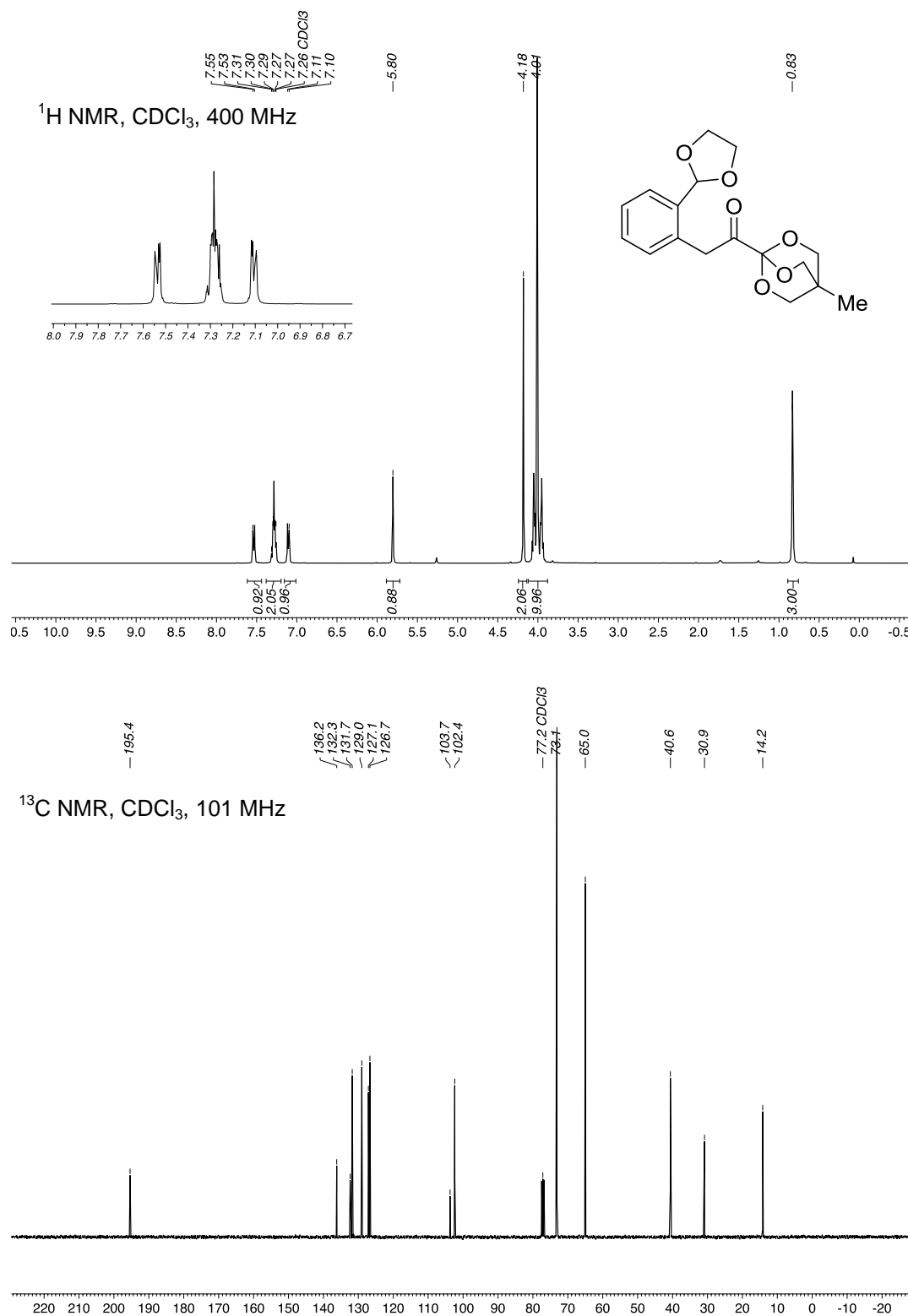
## S5      References

- (1) Smith, E. L. *J. Chem. Soc.* **1927**, 1284-1288.
- (2) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.
- (3) Cosier J.; Glazer, A. M. *J. Appl. Cryst.* **1986**, *19*, 105-107.
- (4) Palatinus L.; Chapuis, G. *J. Appl. Cryst.* **2007**, *40*, 786-790.
- (5) (a) Parois, P.; Cooper, R. I.; Thompson, A. L. *Chem. Cent. J.* **2015**, 9:30. (b) Cooper, R. I.; Thompson, A. L.; Watkin, D. J. *J. Appl. Cryst.* **2010**, *43*, 1100-1107.
- (6) Esteves, C. H. A.; Hall, C. J. J.; Smith, P. D.; Donohoe, T. J. *Org. Lett.* **2017**, *19*, 5248-5251.
- (7) Donohoe, T. J.; Pilgrim, B. S.; Jones, G. R.; Bassuto, J. A. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 11605-11608.
- (8) Esteves, C. H. A.; Smith, P. D.; Donohoe, T. J. *J. Org. Chem.* **2017**, *82*, 4435-4443.
- (9) Kikugawa, Y.; Kuramoto, M.; Saito, I.; Yamada, S.-I. *Chem. Pharm. Bull.* **1973**, *21*, 1927-1937.
- (10) Meziane, M. A. A. A.; Bazureau, J. P. *Molecules* **2002**, *7*, 252-263.
- (11) Cao, R.; Chen, Q.; Hou, X.; Chen, H.; Guan, H.; Ma, Y.; Peng, W.; Xu, A. *Bioorg. Med. Chem.* **2004**, *12*, 4613-4623.
- (12) Chen, Y.-F.; Lin, Y.-C.; Chen, J.-P.; Chan, H.-C.; Hsu, M.-H.; Lin, H.-Y.; Kuo, S.-C.; Huang, L.-J. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3873-3877.
- (13) Zhu, Z.; Yuan, J.; Zhou, Y.; Qin, Y.; Xu, J.; Peng, Y. *Eur. J. Org. Chem.* **2014**, 511-514.
- (14) Clagg, K.; Hou, H.; Weinstein, A. B.; Russell, D.; Stahl, S. S.; Koenig, S. G. *Org. Lett.* **2016**, *18*, 3586-3589.
- (15) McNulty, J.; Keskar, K. *Eur. J. Org. Chem.* **2011**, 6902-6908.
- (16) Teng, Q.-h.; Xu, Y.-l.; Liang, Y.; Wang, H.-s.; Wang, Y.-c.; Pan, Y.-m. *Adv. Synth. Catal.* **2016**, *358*, 1897-1902.
- (17) Killoran, J.; Gallagher, J. F.; Murphy, P. V.; O'Shea, D. F. *New J. Chem.* **2005**, *29*, 1258-1265.
- (18) Zhao, L.-B.; Guan, Z.-H.; Han, Y.; Xie, Y.-X.; He, S.; Liang, Y.-M. *J. Org. Chem.* **2007**, *72*, 10276-10278.

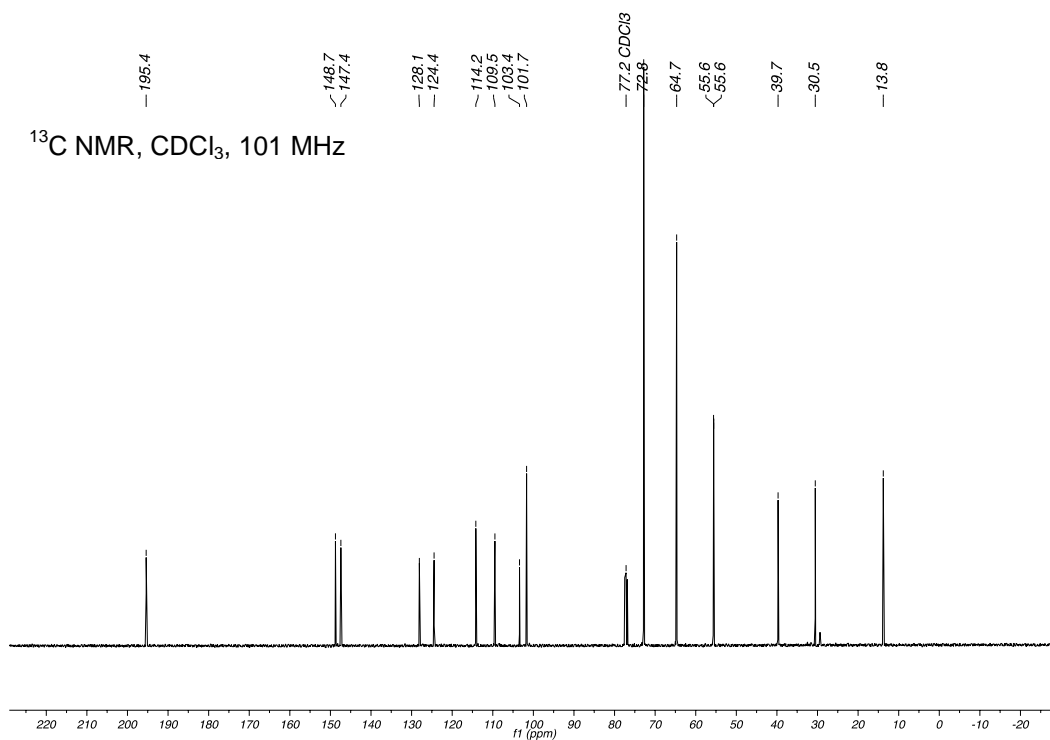
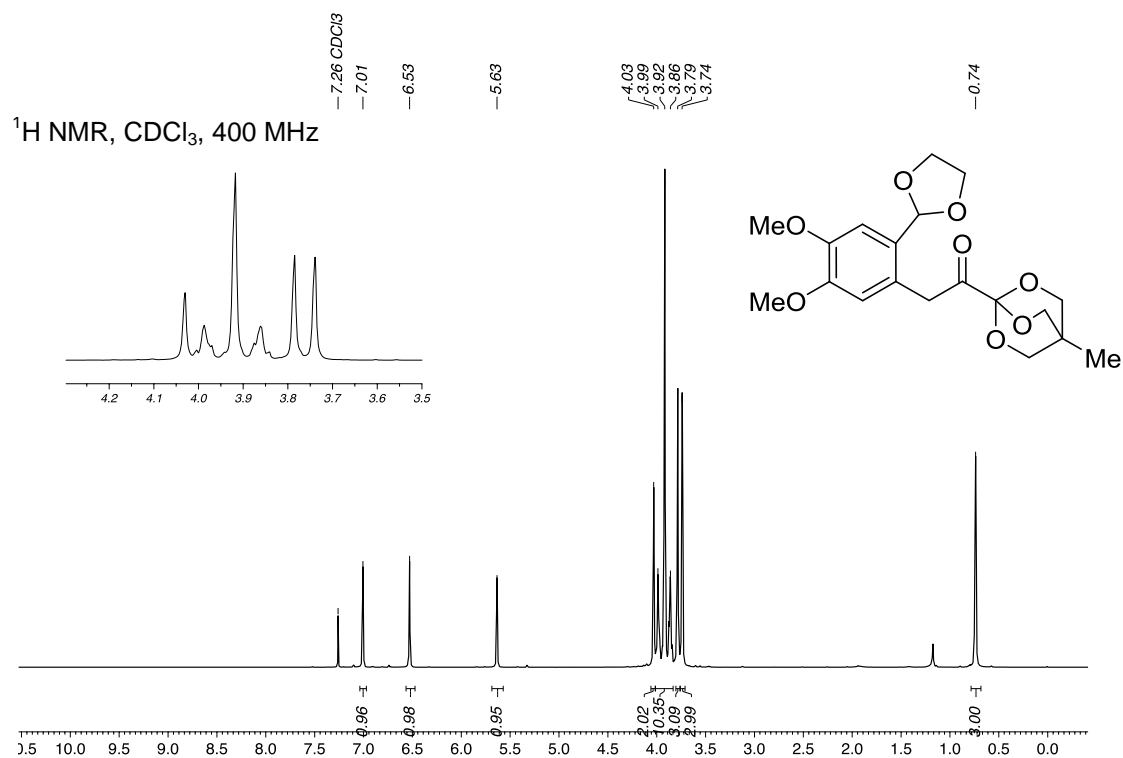


# S6 <sup>1</sup>H and <sup>13</sup>C NMR spectra

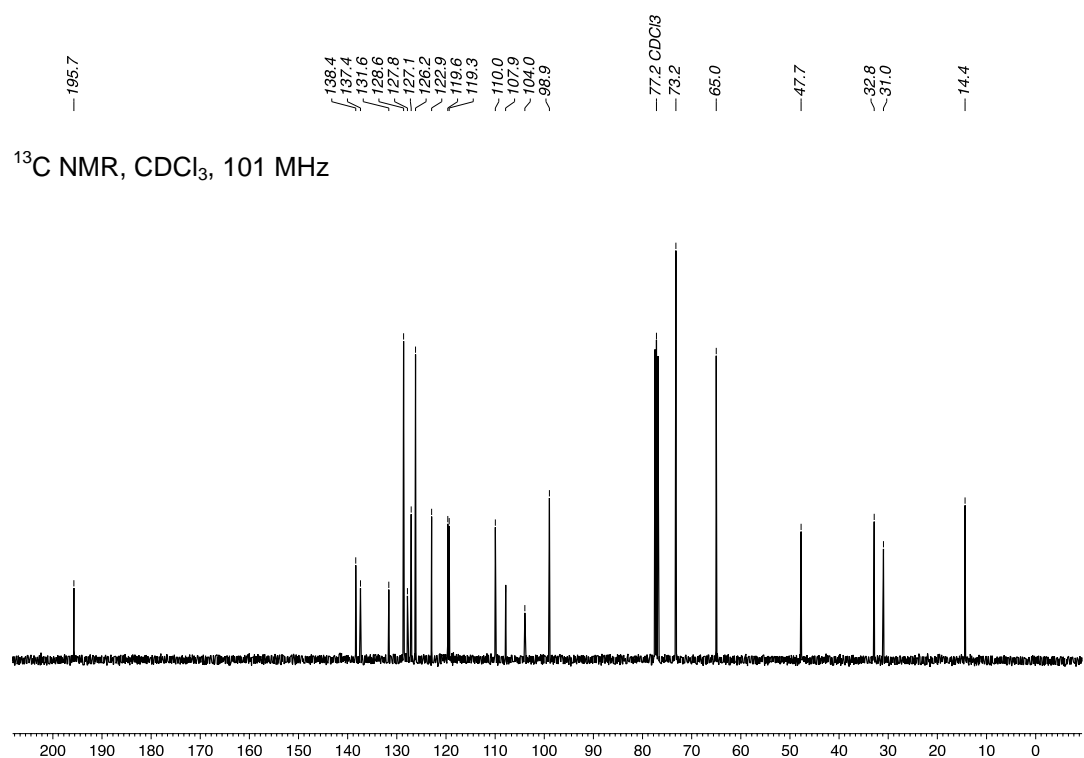
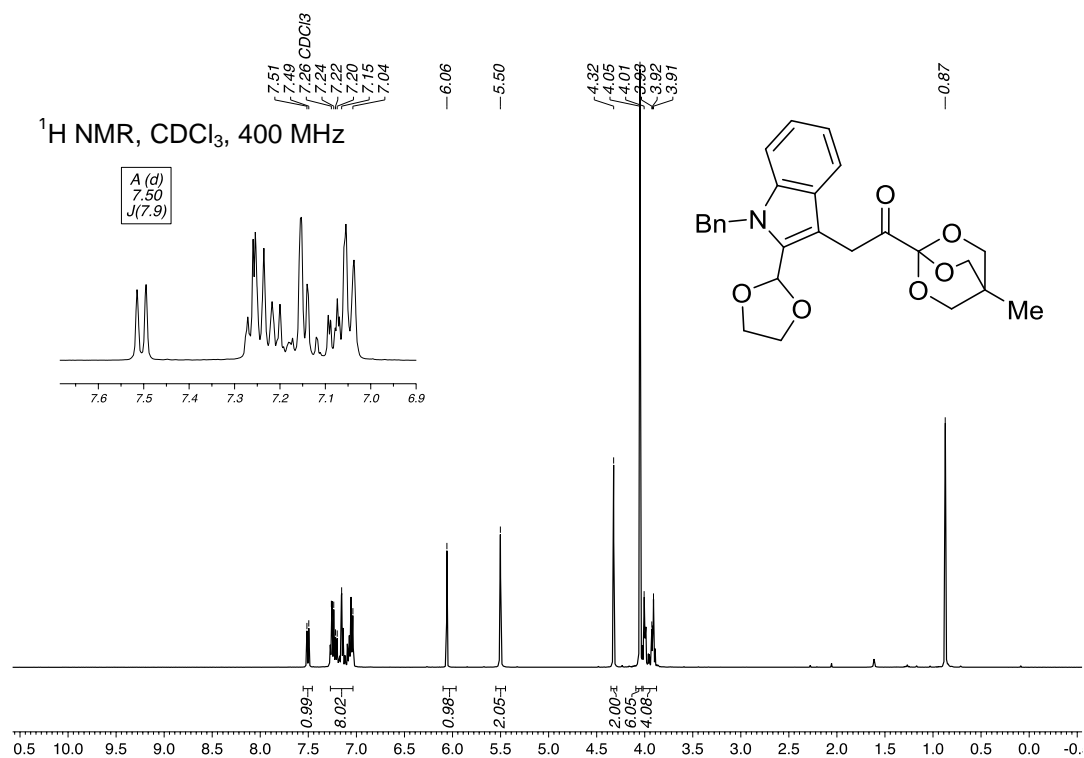
## 2-[2-(1,3-Dioxolan-2-yl)phenyl]-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethan-1-one (3a)



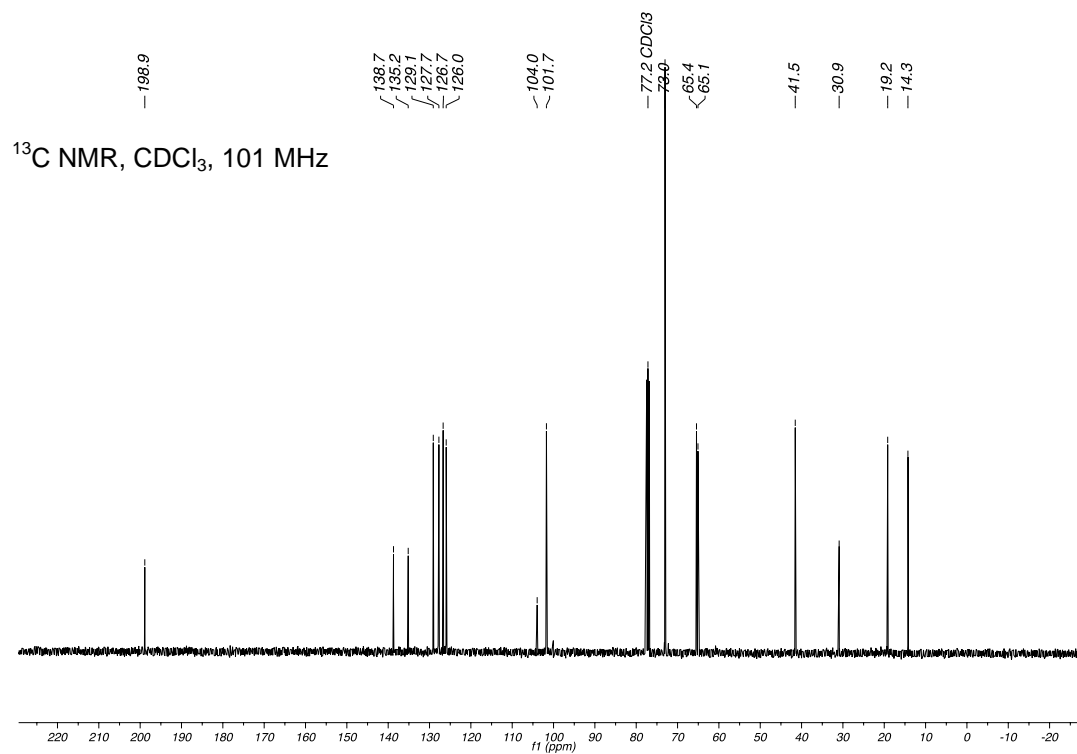
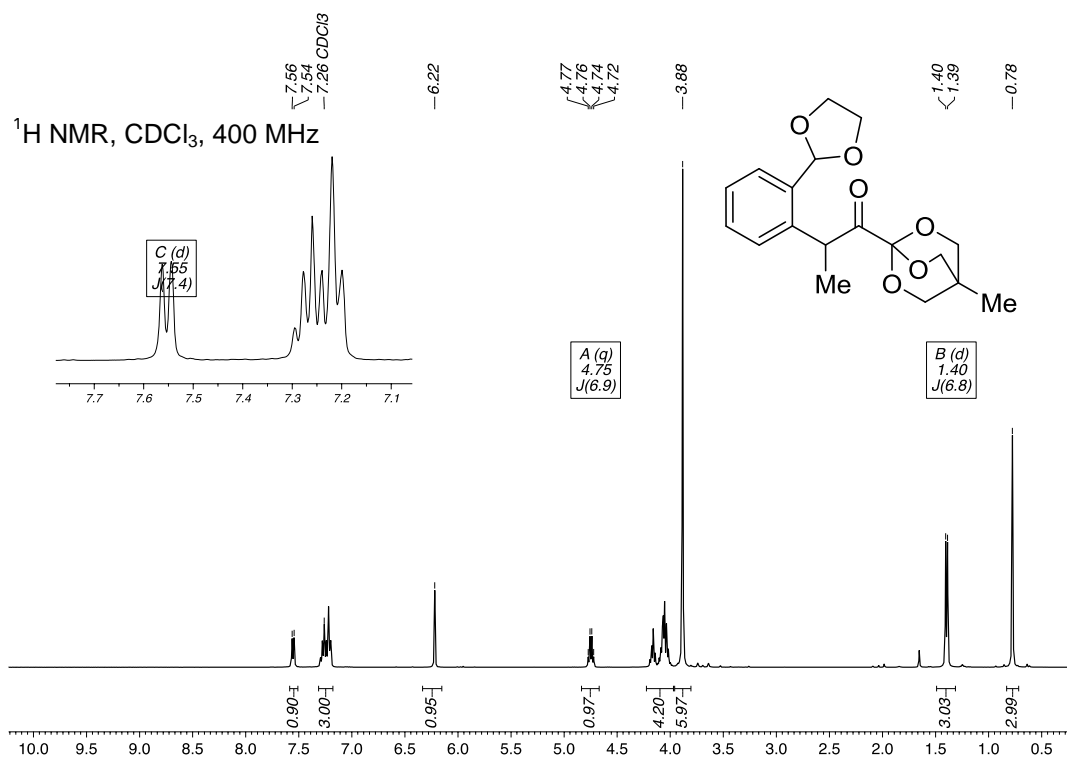
**2-[2-(1,3-Dioxolan-2-yl)-4,5-dimethoxyphenyl]-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]-octan-1-yl)ethan-1-one (3b)**



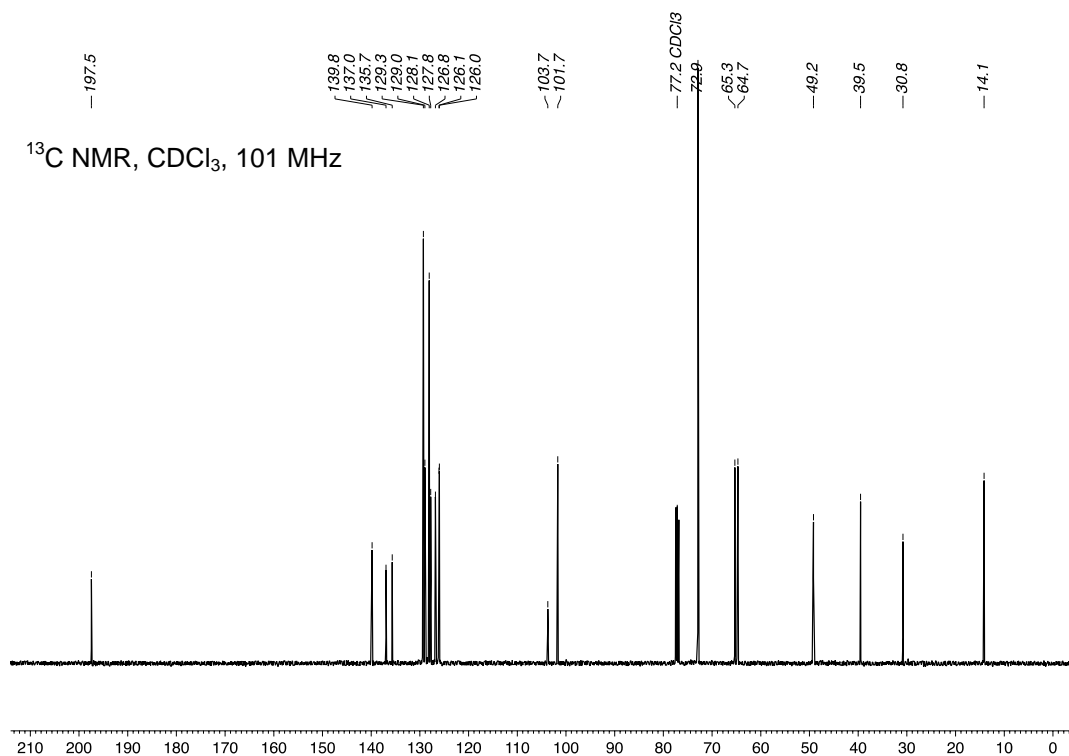
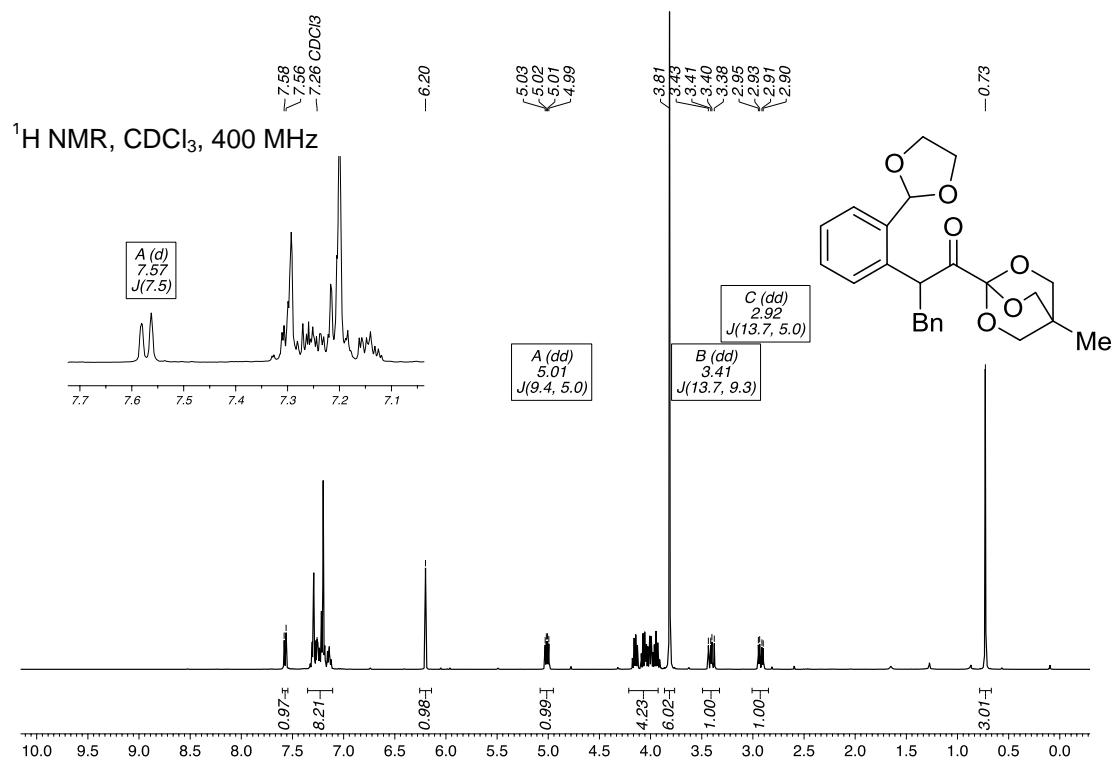
**2-[1-Benzyl-2-(1,3-dioxolan-2-yl)-1*H*-indol-3-yl]-1-(4-methyl-2,6,7-trioxabicyclo-[2.2.2]-octan-1-yl)ethan-1-one (3c)**



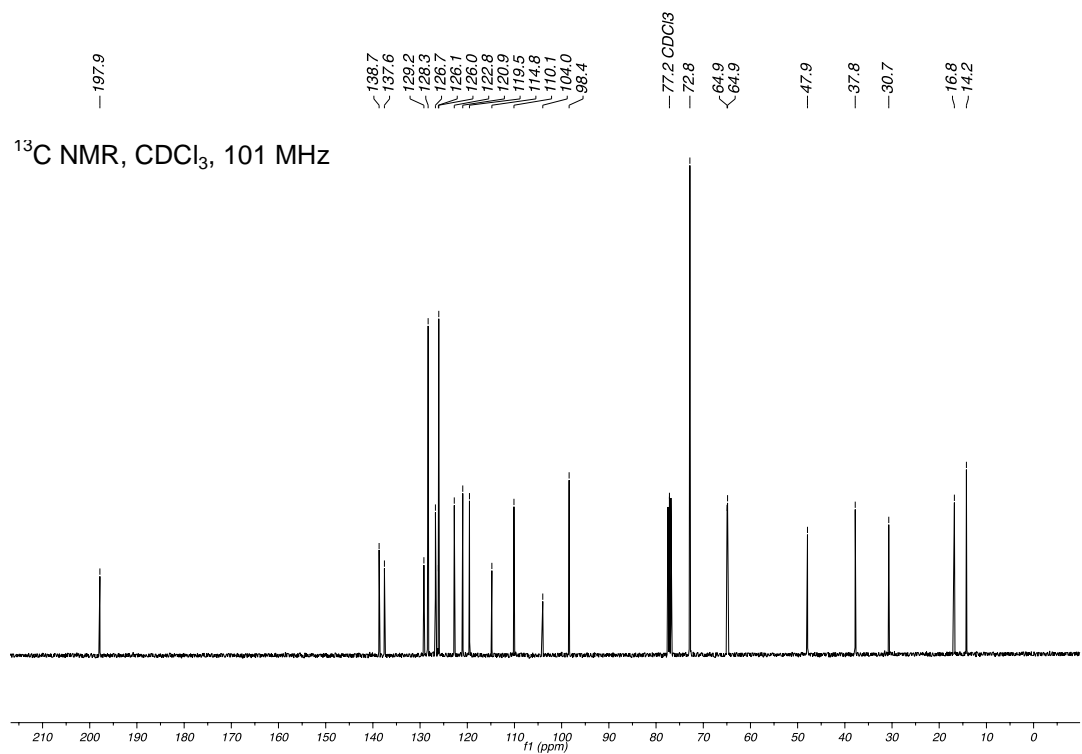
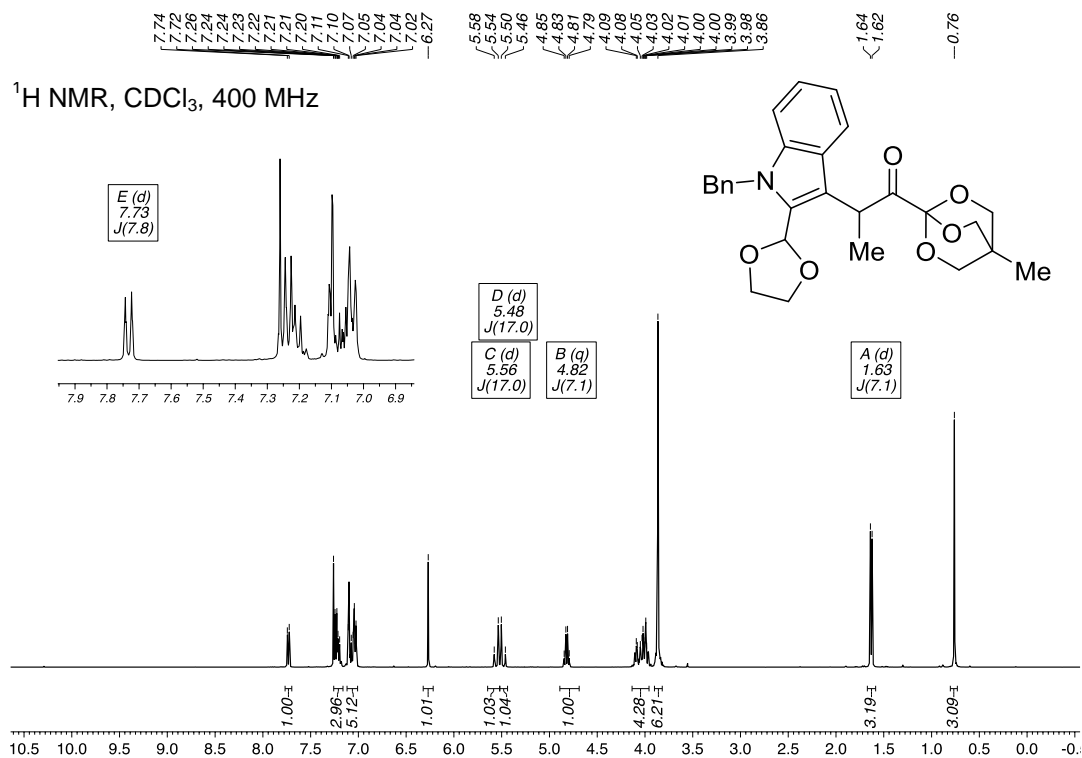
**2-[2-(1,3-Dioxolan-2-yl)phenyl]-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)propan-1-one (S1)**



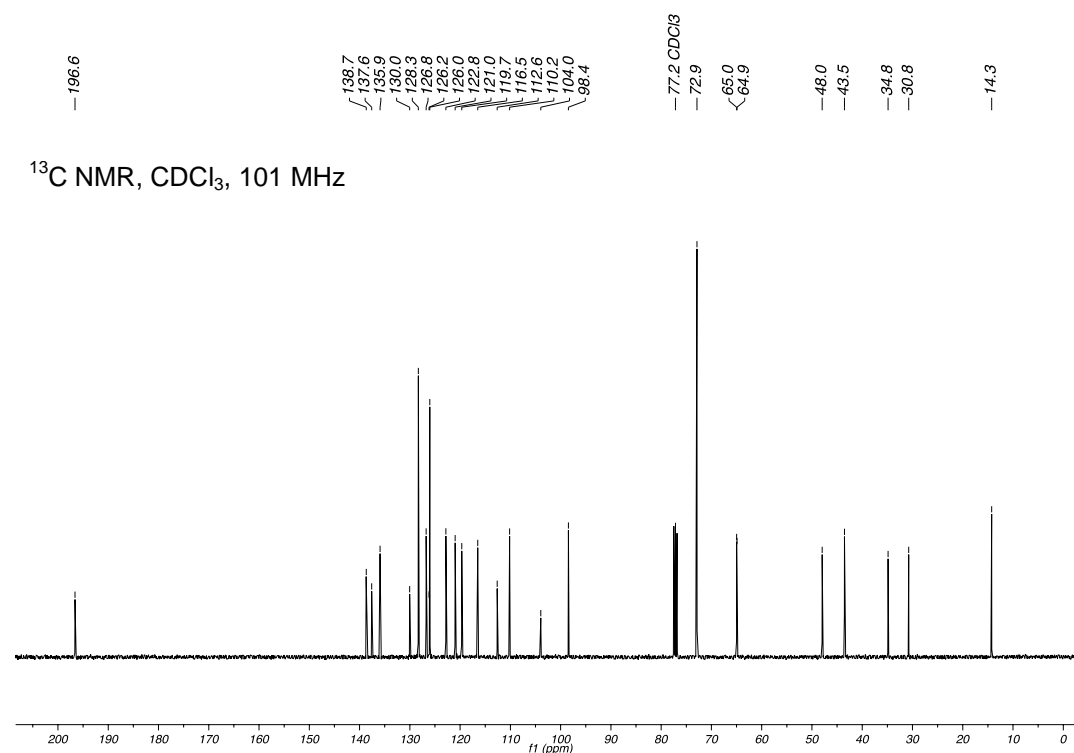
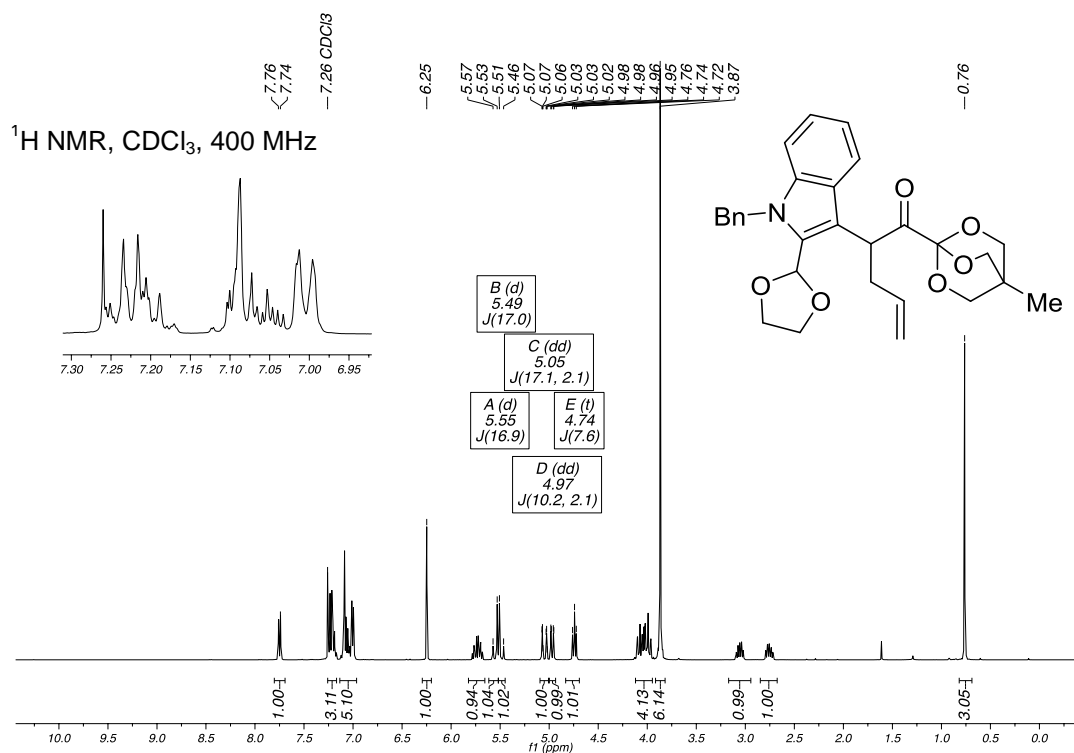
**2-[2-(1,3-Dioxolan-2-yl)phenyl]-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-3-phenylpropan-1-one (S2)**



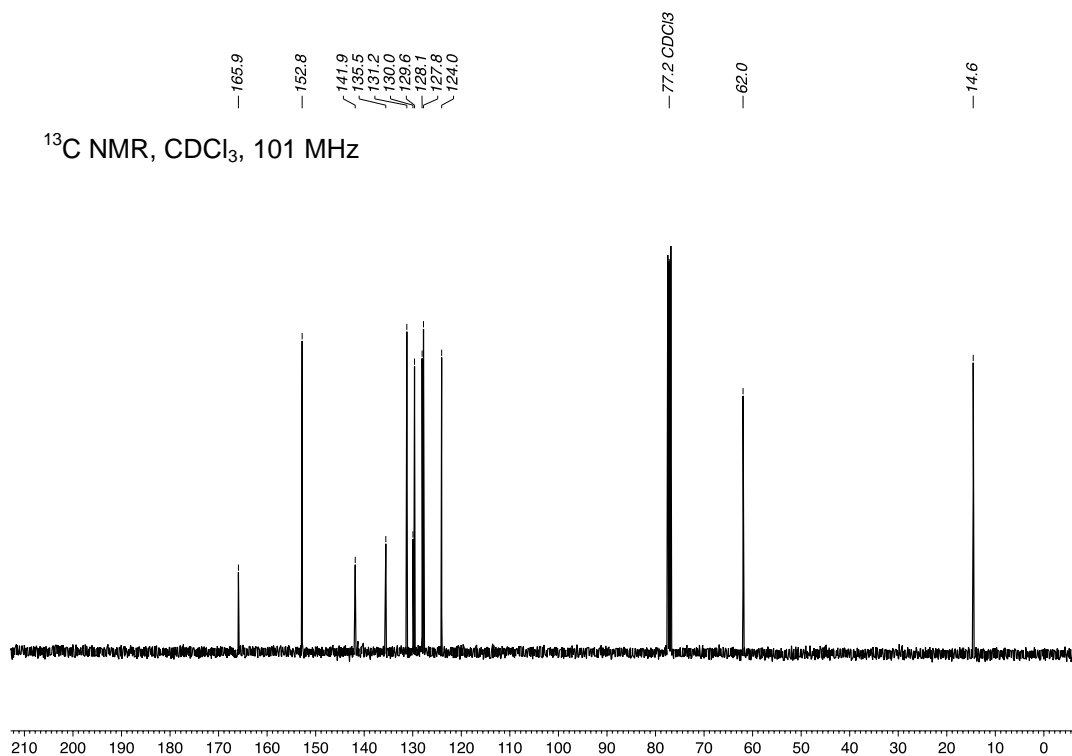
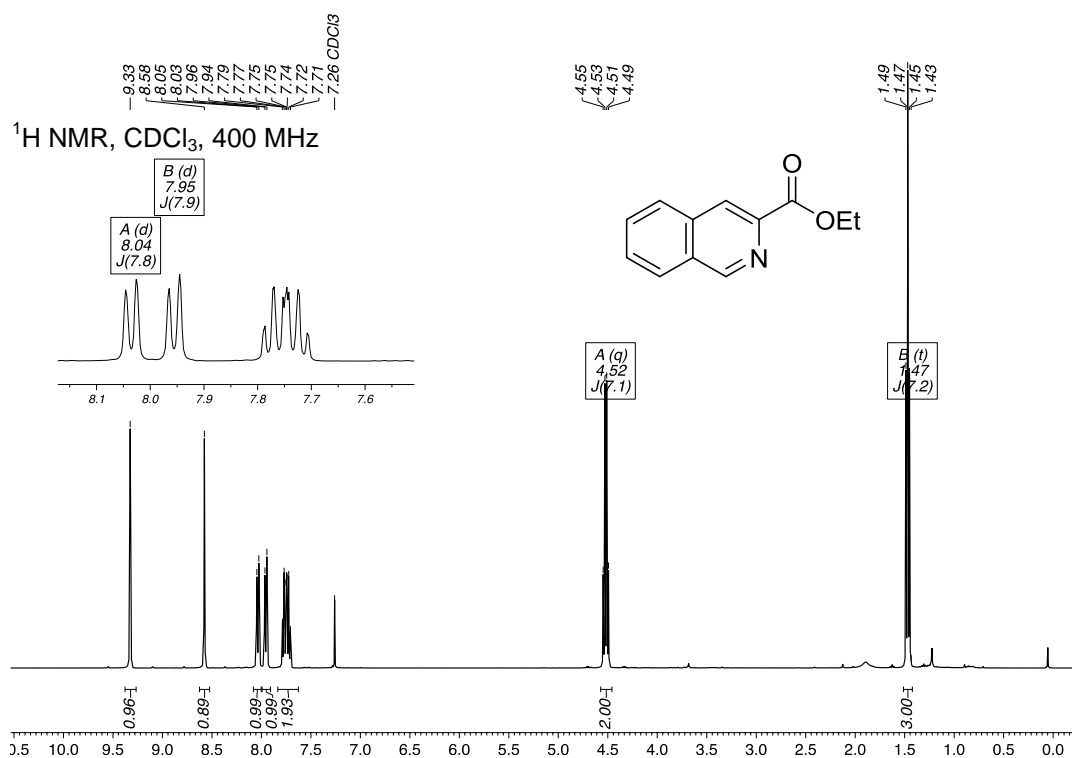
**2-[1-Benzyl-2-(1,3-dioxolan-2-yl)-1*H*-indol-3-yl]-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]-octan-1-yl)propan-1-one (S3)**



**2-[1-Benzyl-2-(1,3-dioxolan-2-yl)-1*H*-indol-3-yl]-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]-octan-1-yl)pent-4-en-1-one (S4)**

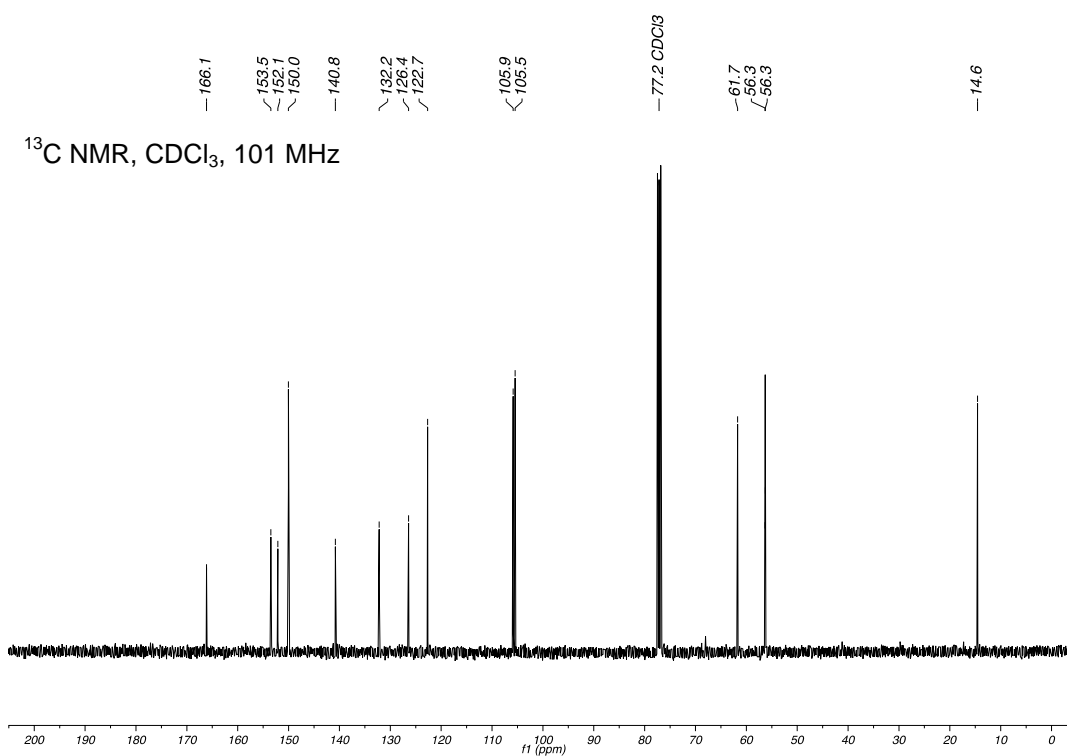
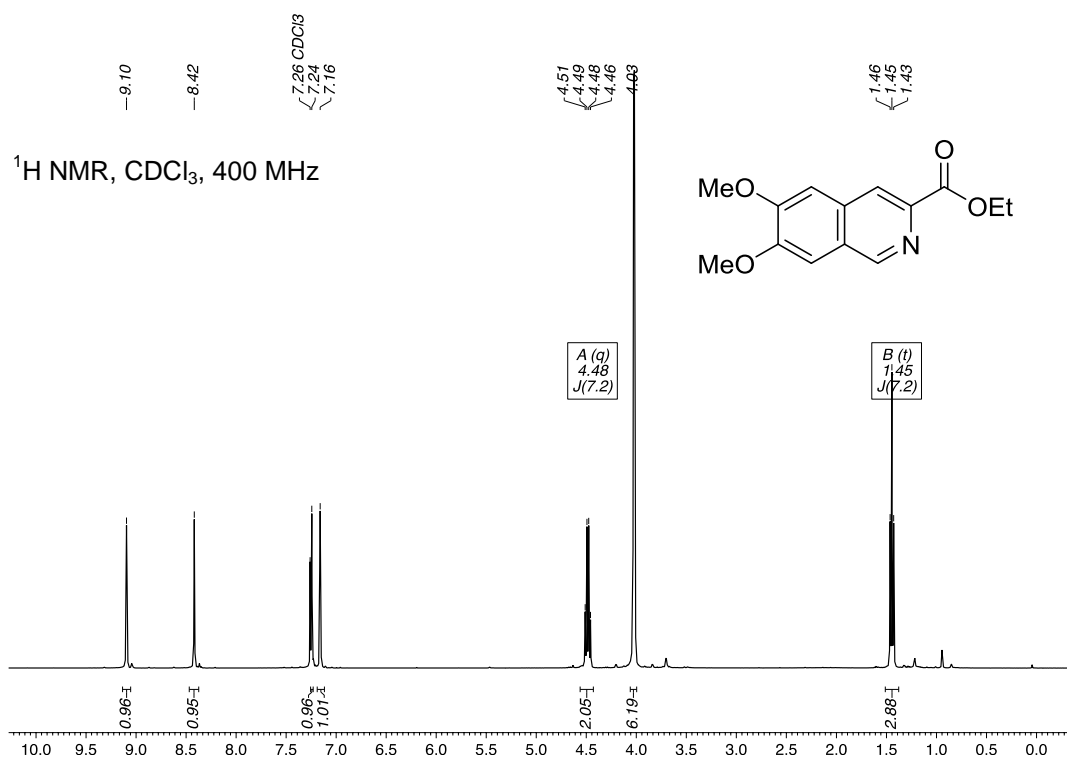


# Ethyl isoquinoline-3-carboxylate (4a)

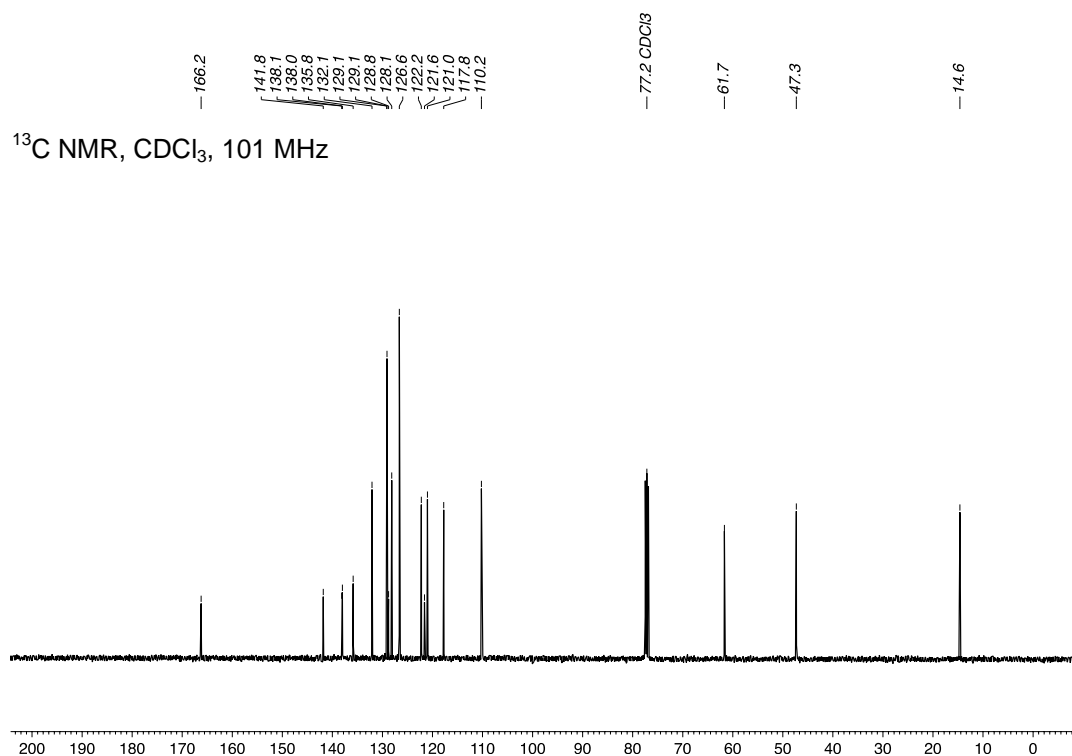




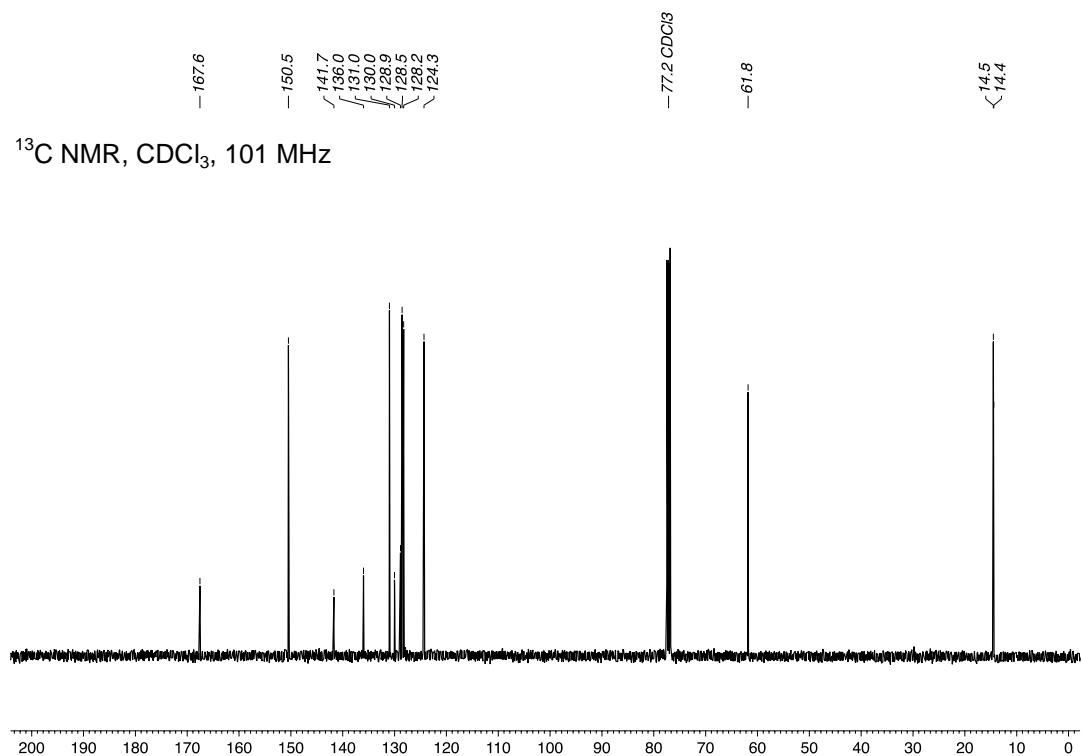
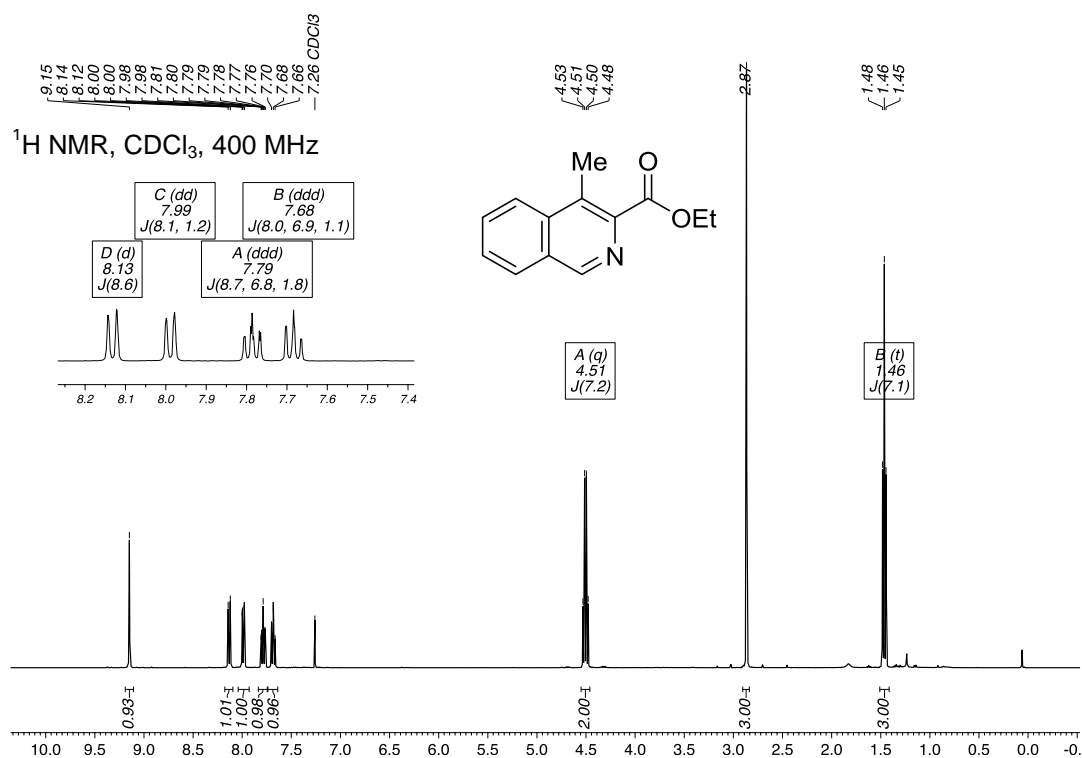
# **Ethyl 6,7-dimethoxyisoquinoline-3-carboxylate (4b)**



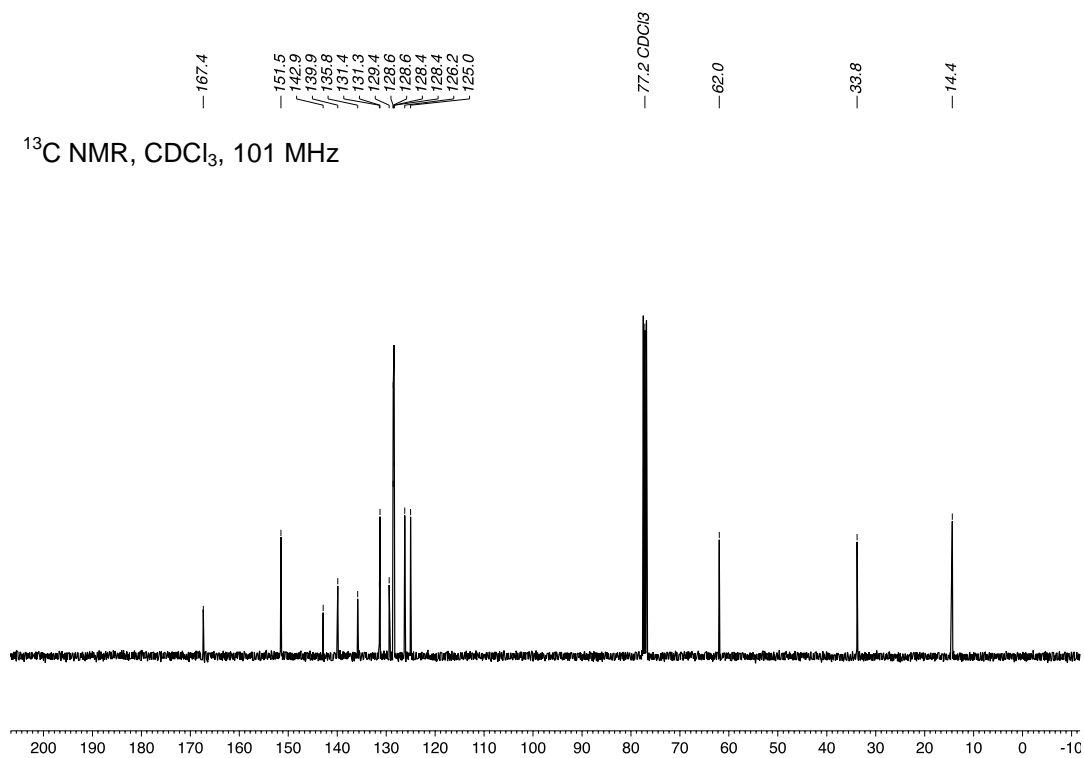
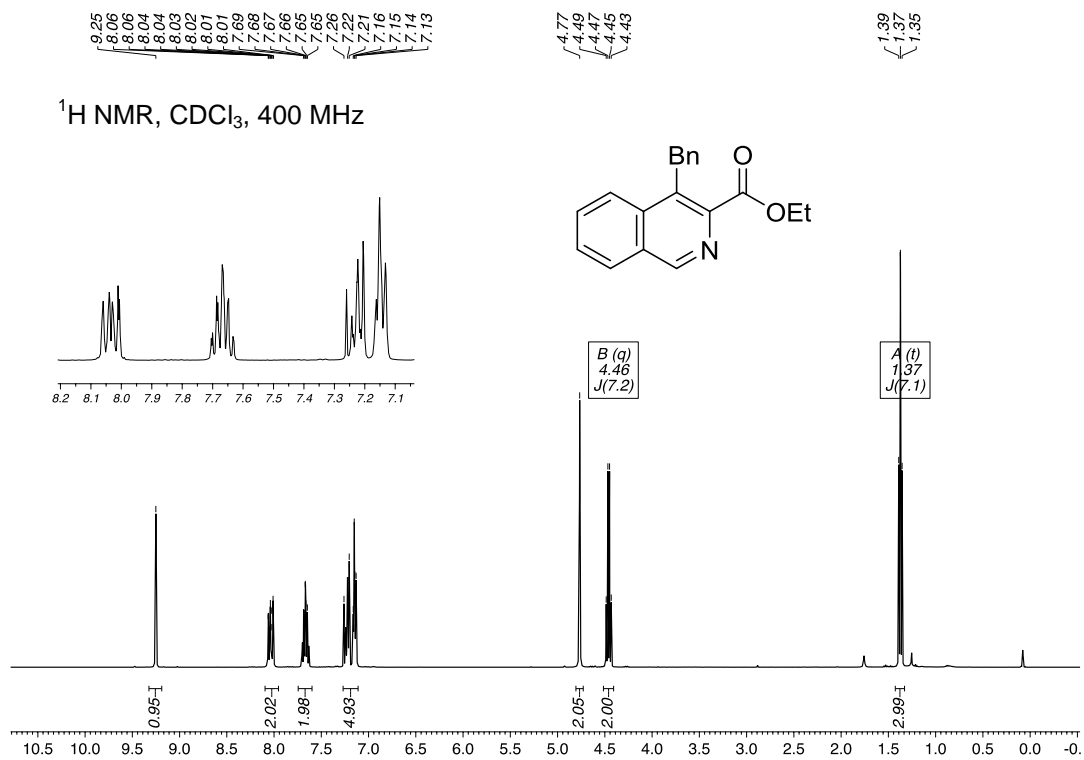
**Ethyl 9-benzyl-9H-pyrido[3,4-b]indole-3-carboxylate (4c)**



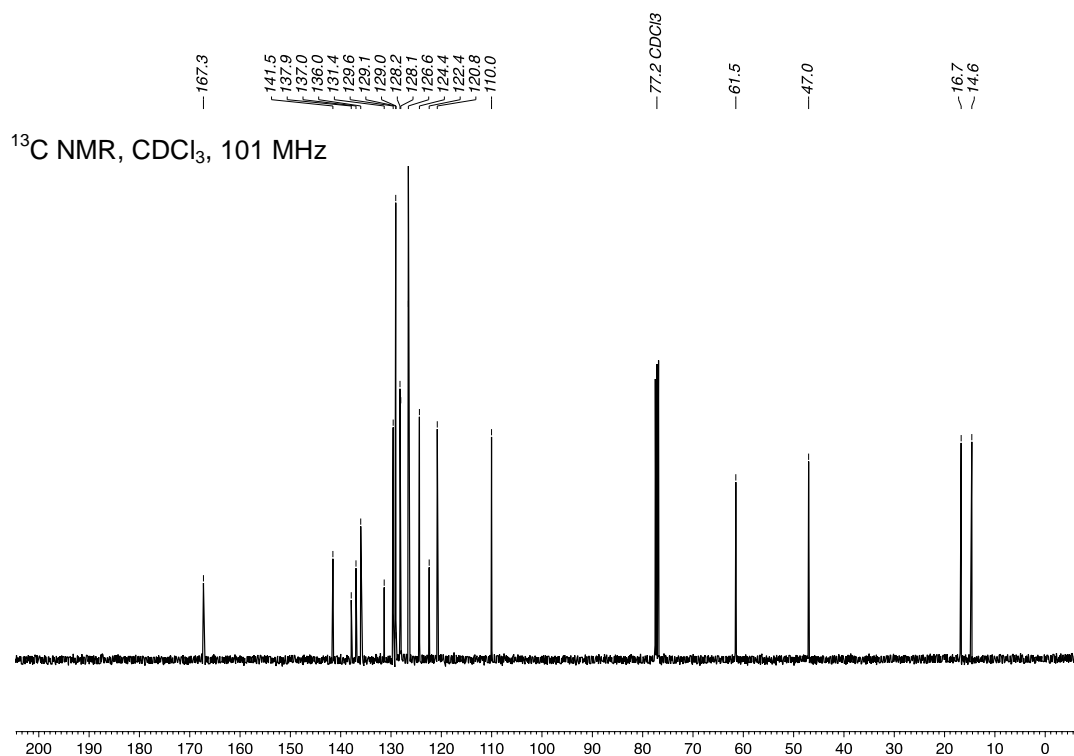
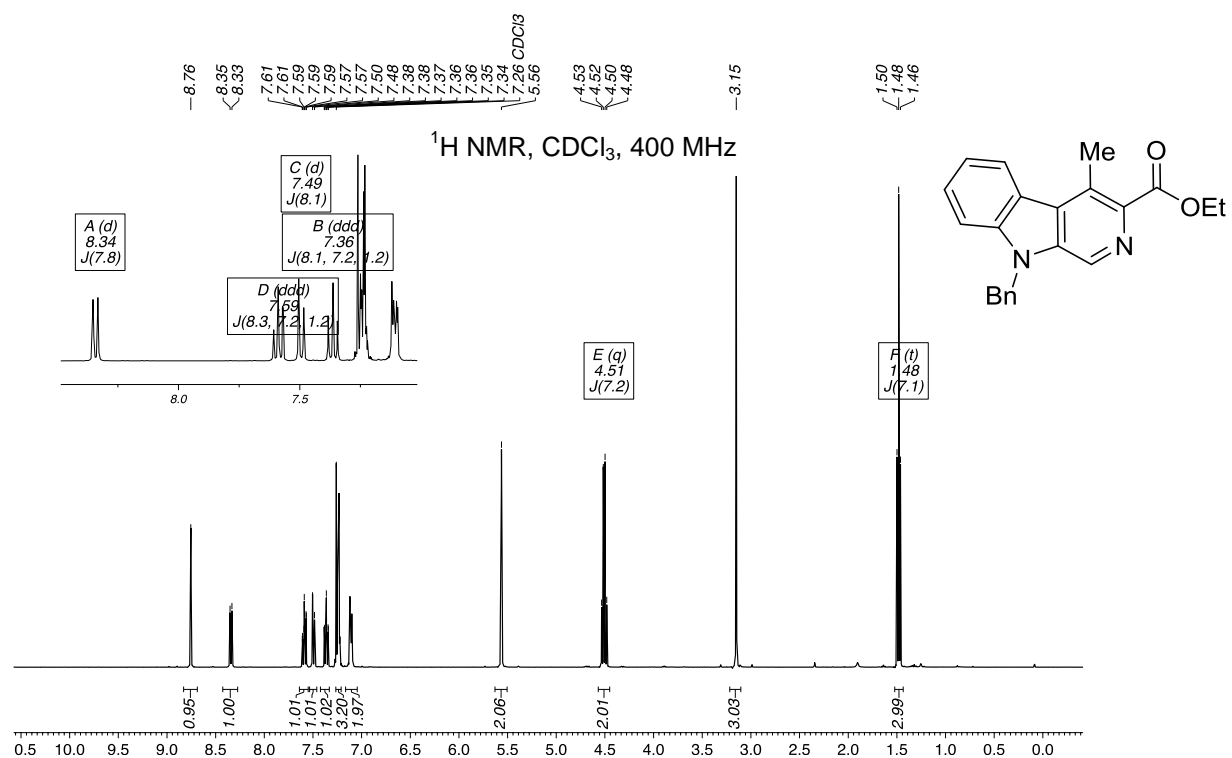
# Ethyl 4-methylisoquinoline-3-carboxylate (4d)



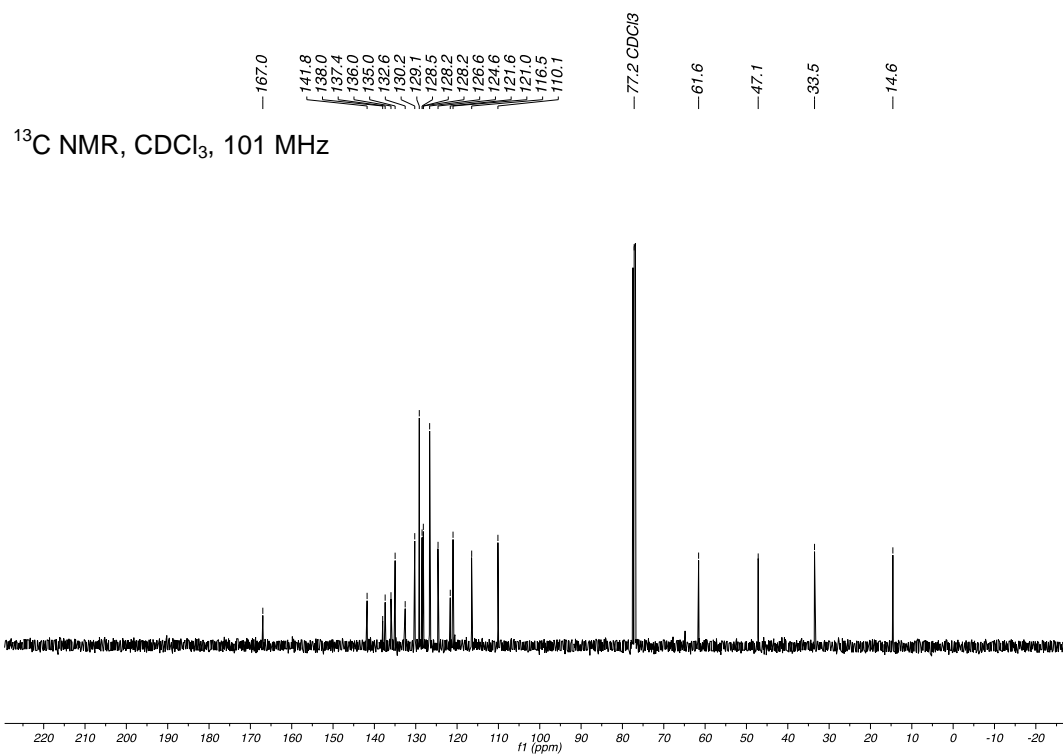
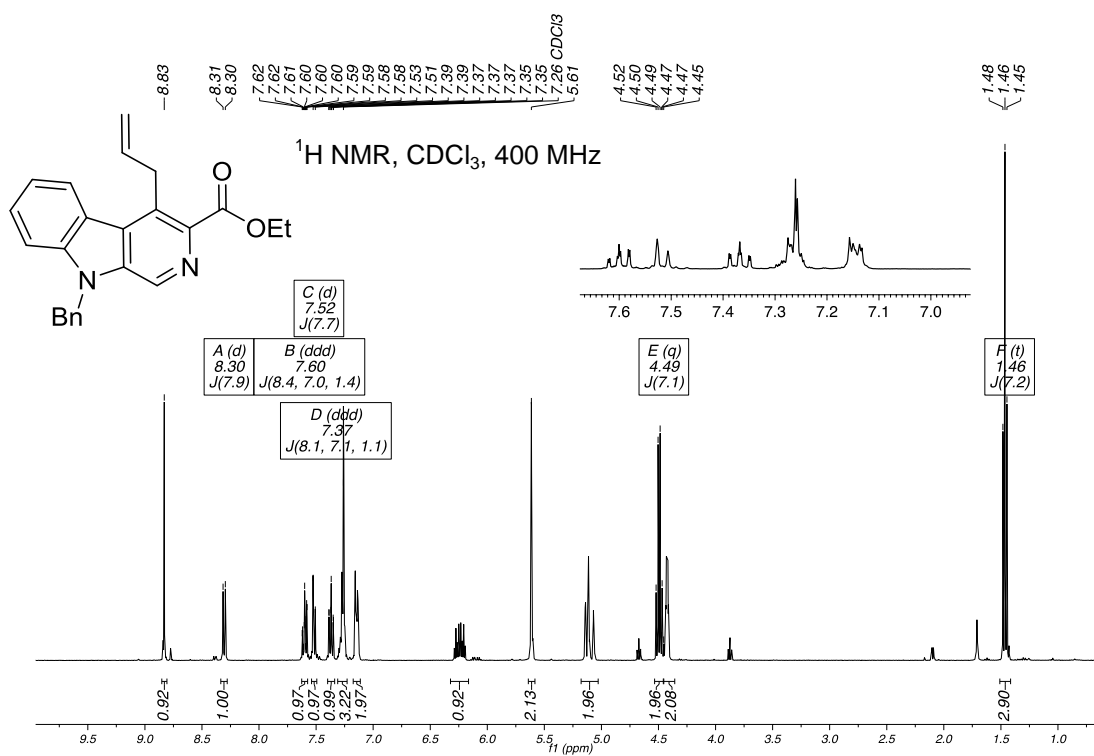
# **Ethyl 4-benzylisoquinoline-3-carboxylate (4e)**



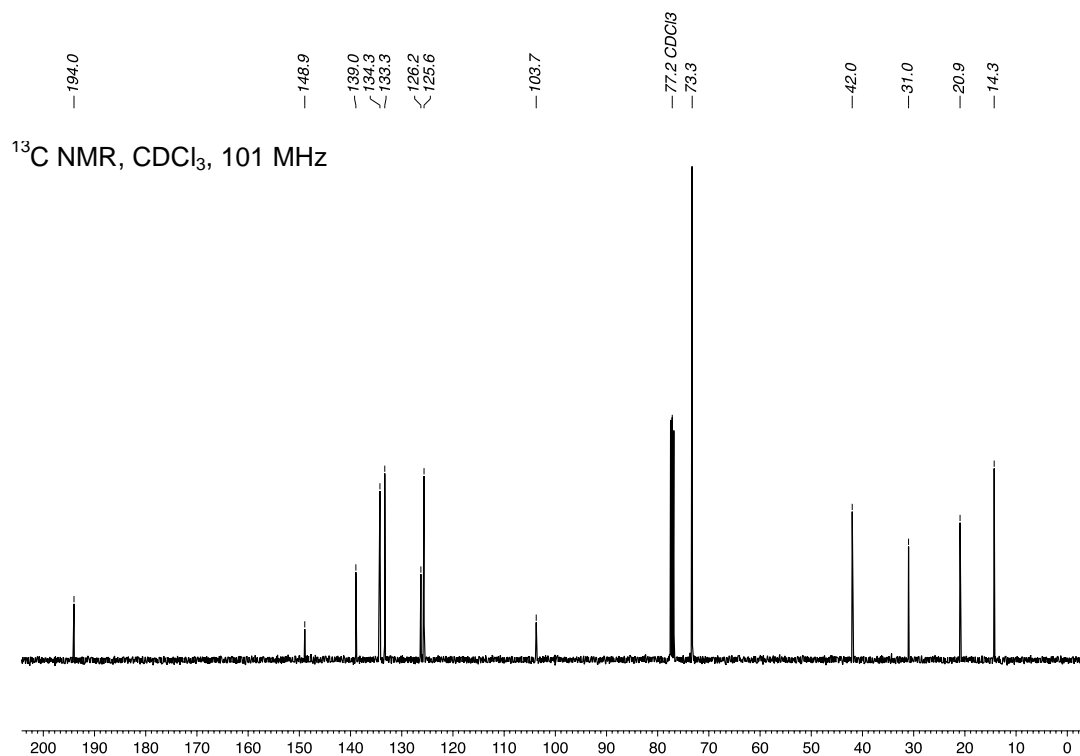
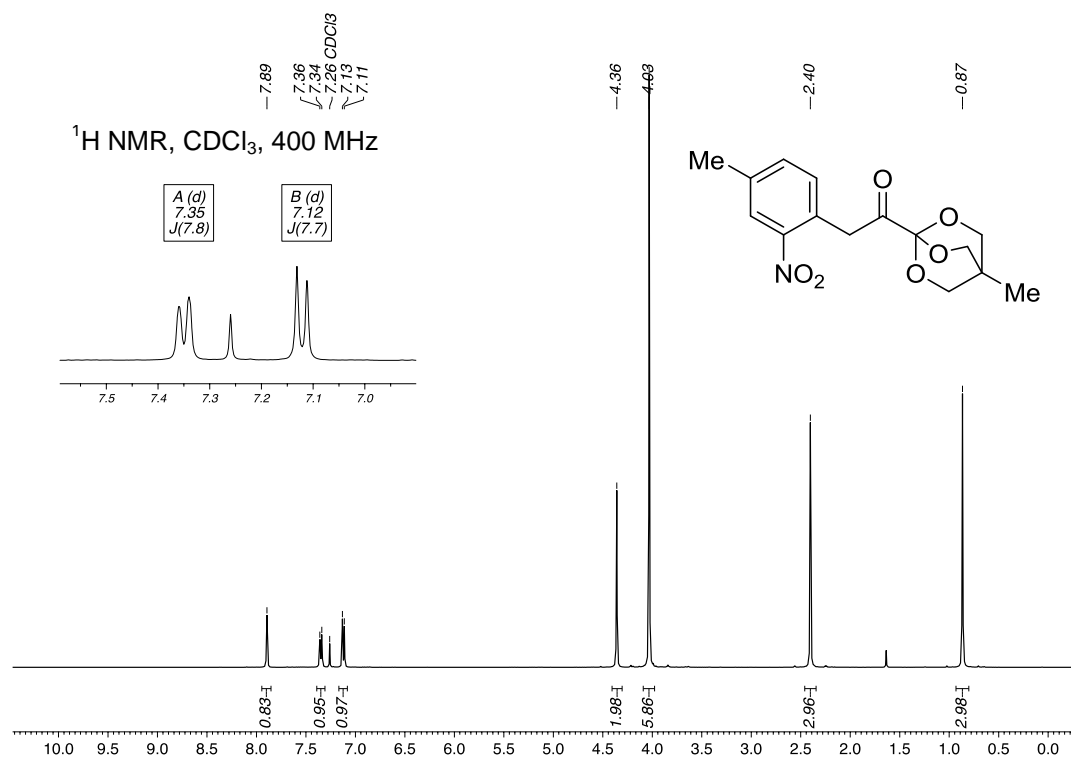
**Ethyl 9-benzyl-4-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (4f)**



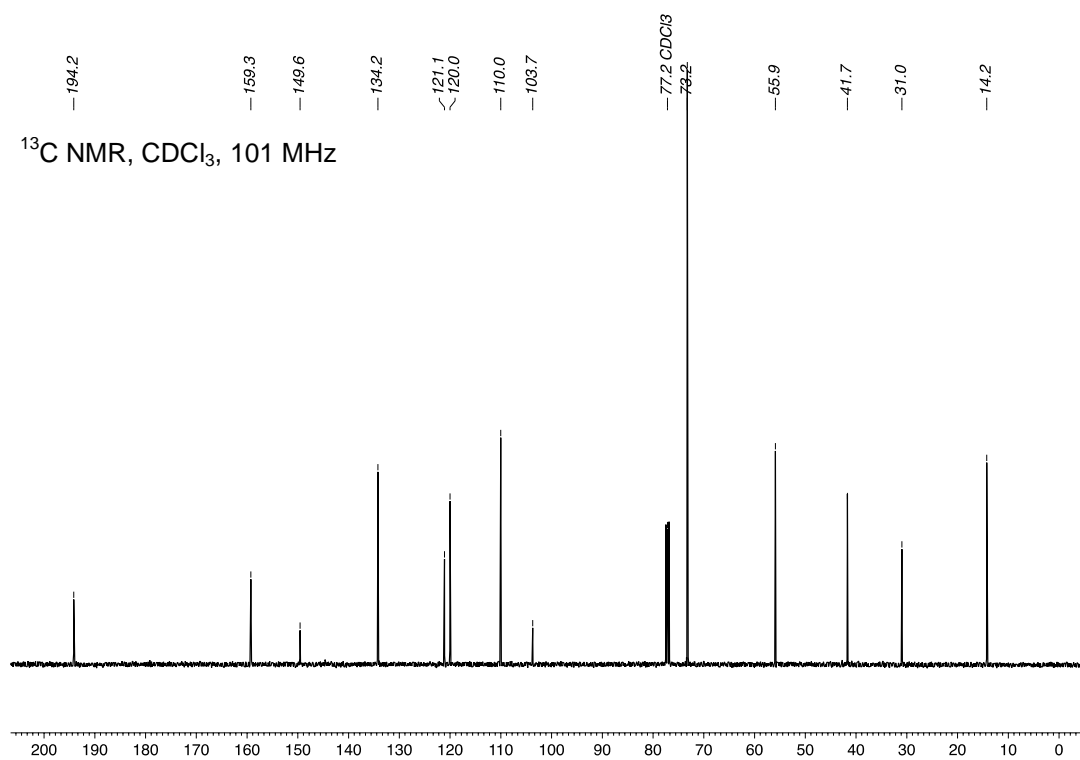
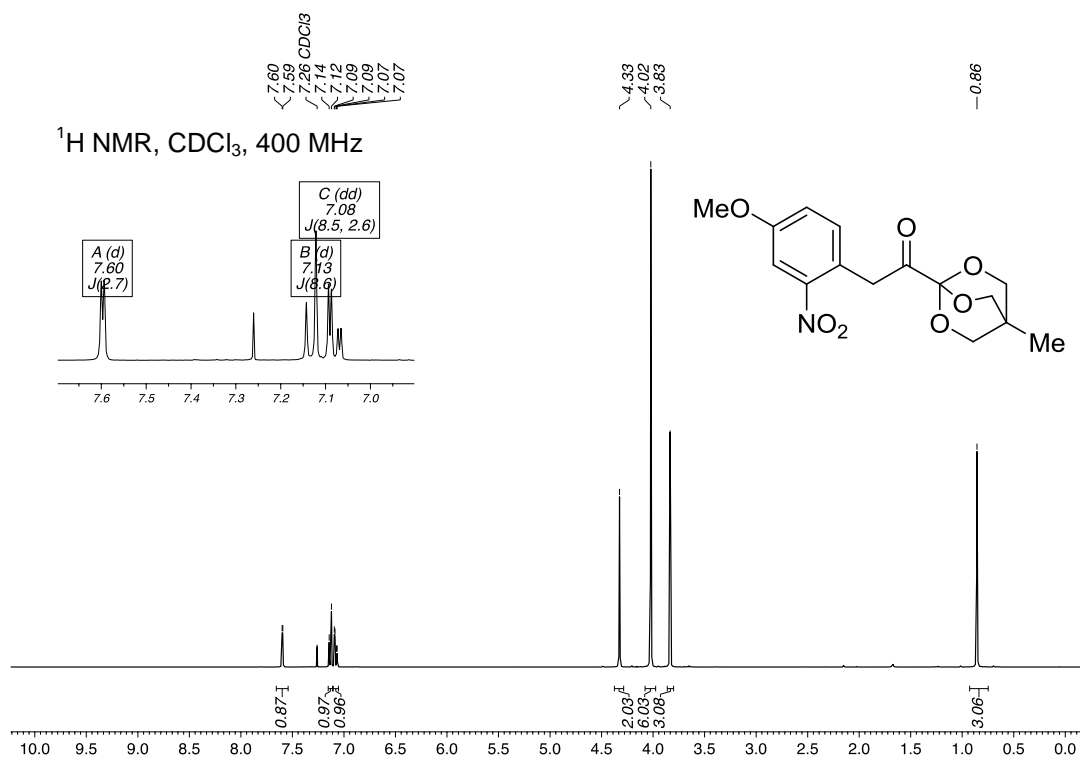
**Ethyl 4-allyl-9-benzyl-9H-pyrido[3,4-*b*]indole-3-carboxylate (4g)**



**2-(4-Methyl-2-nitrophenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-ethan-1-one (6a)**

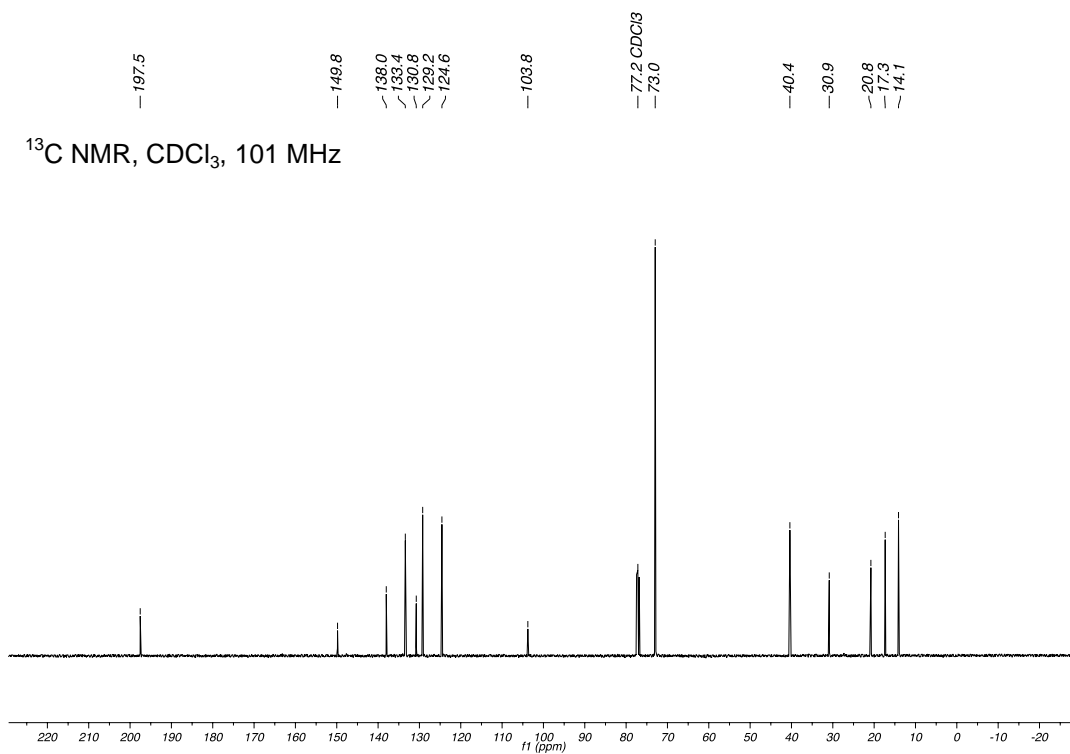
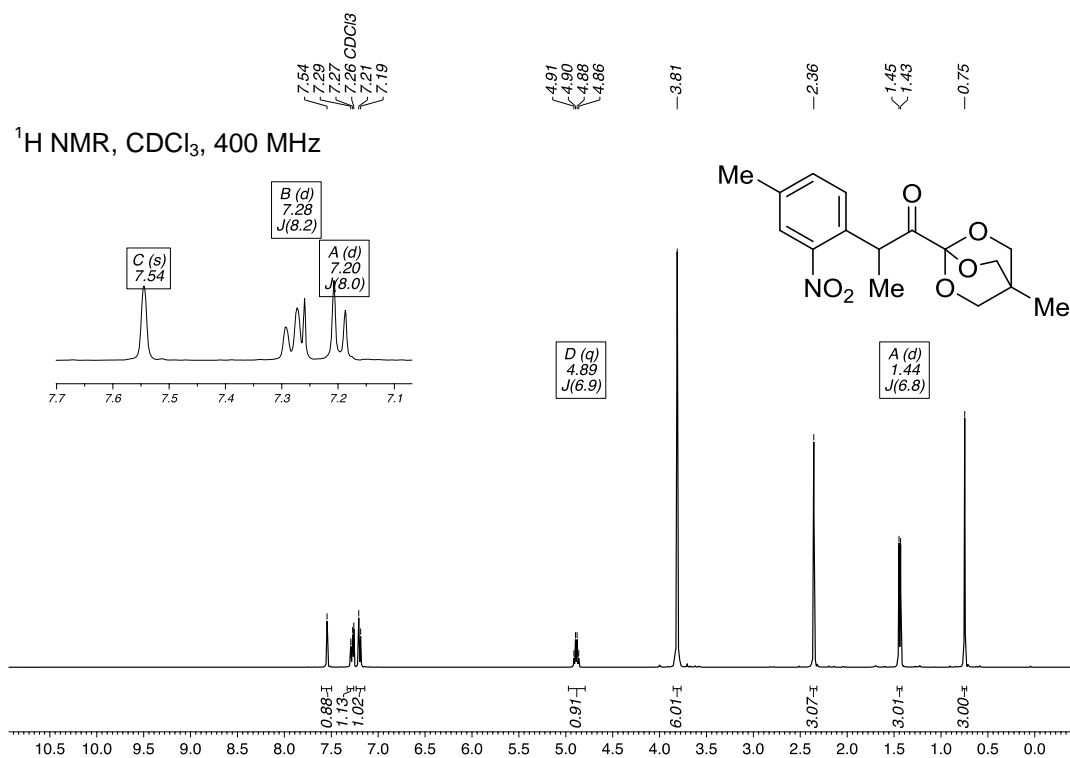


**2-(4-Methoxy-2-nitrophenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethan-1-one (6b)**

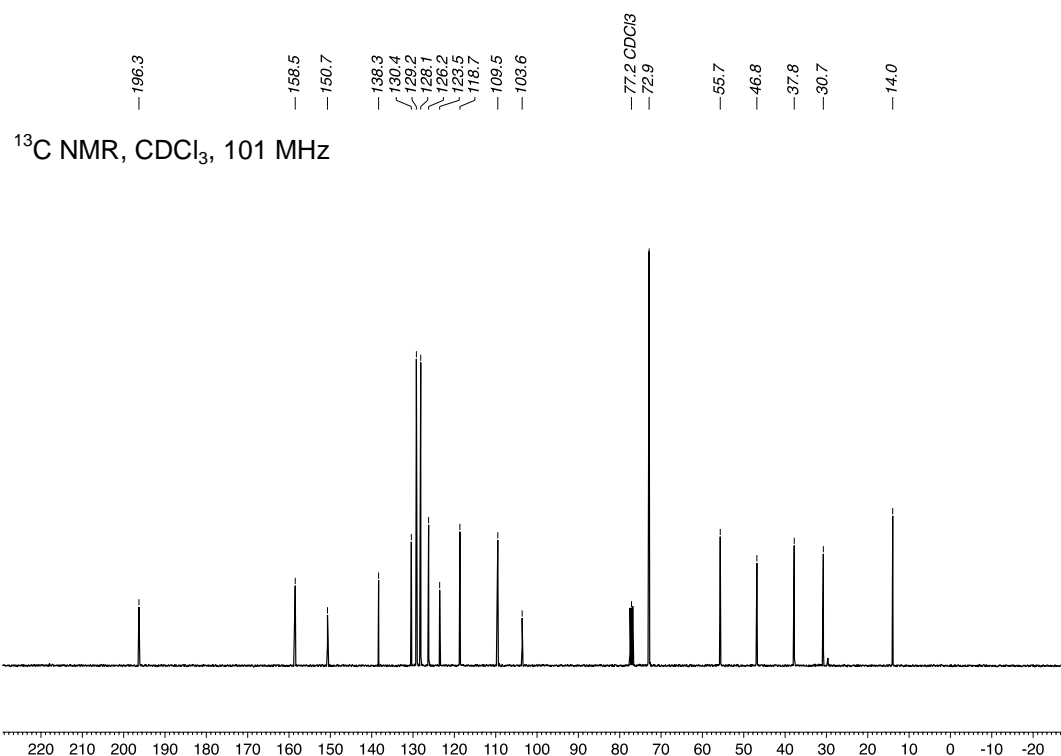
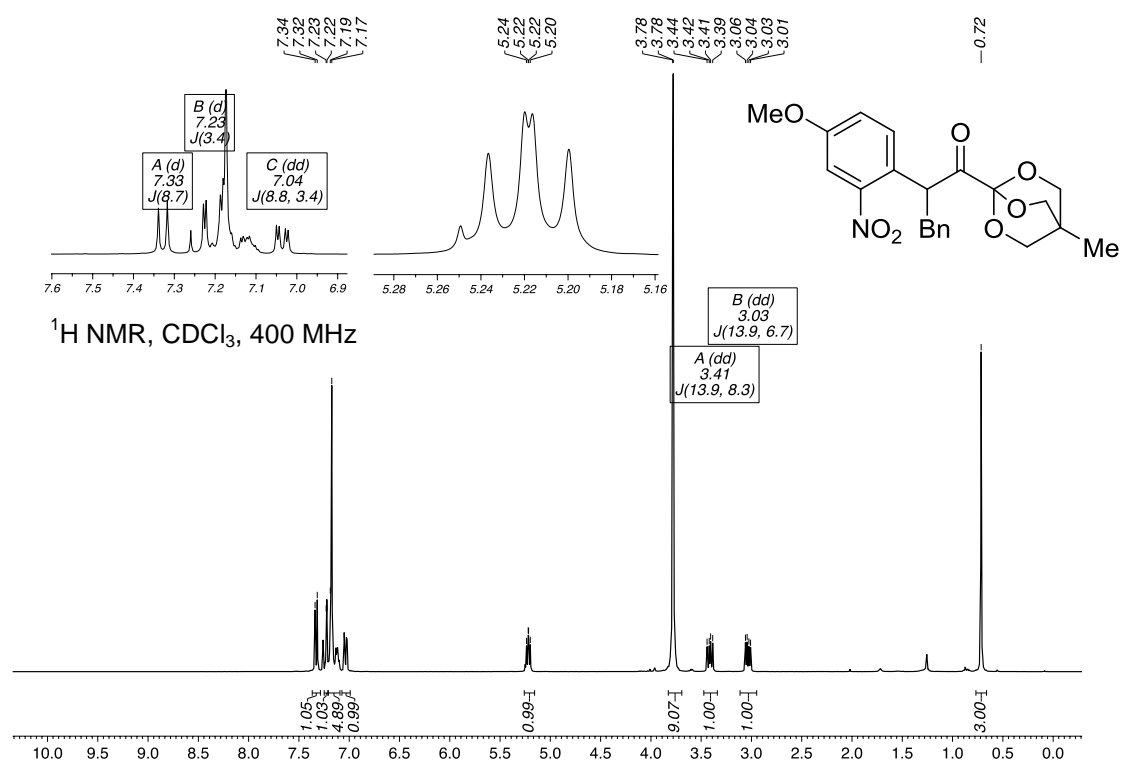




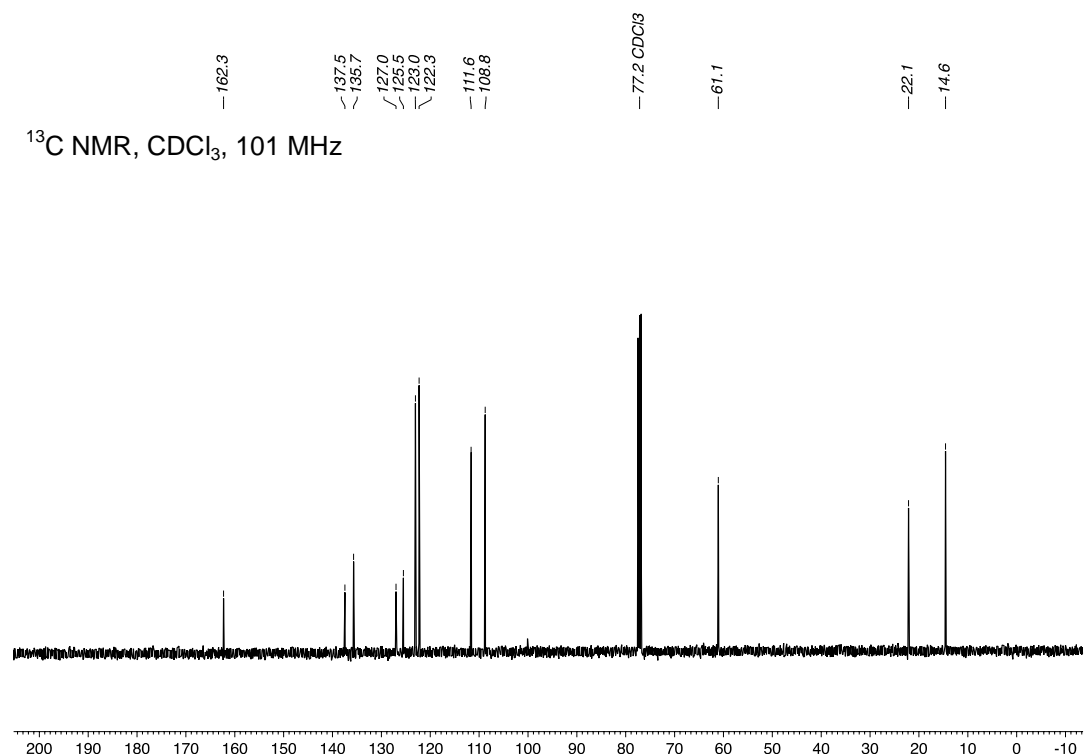
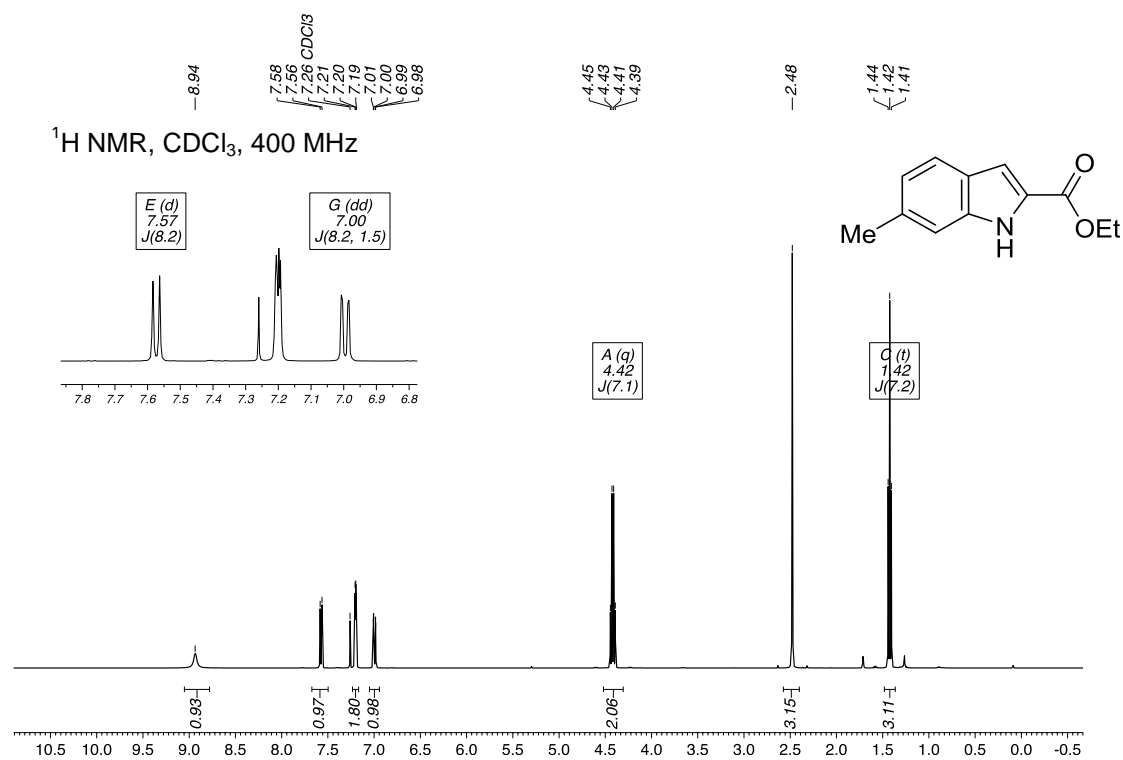
**2-(4-Methyl-2-nitrophenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)propan-1-one (S5)**



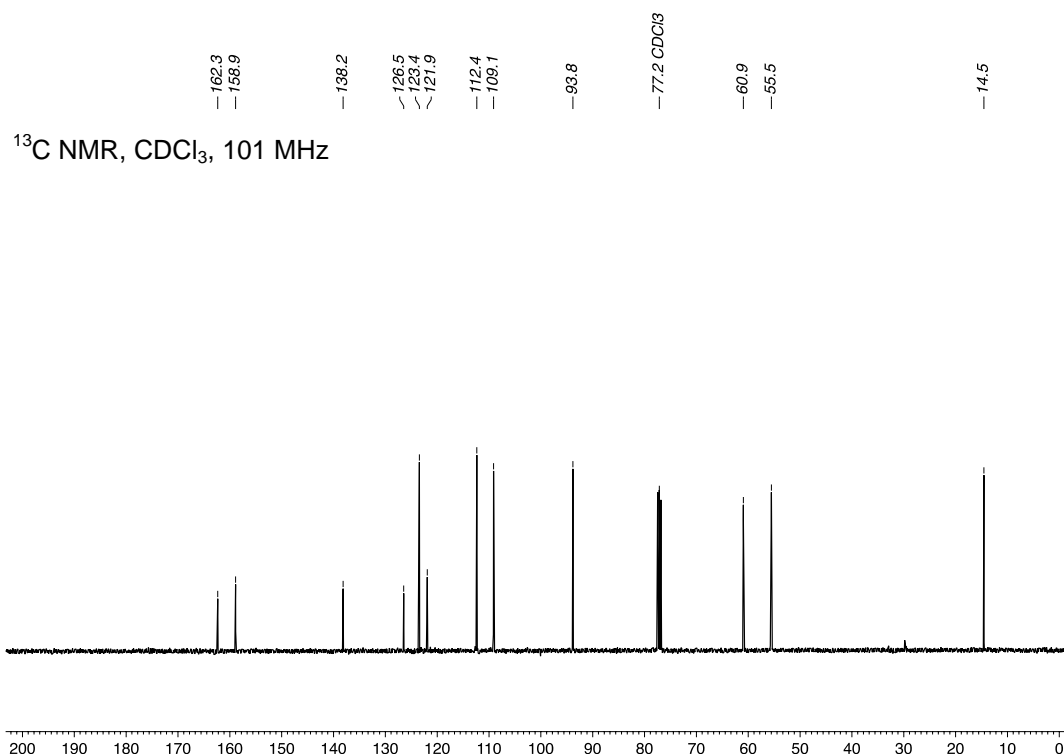
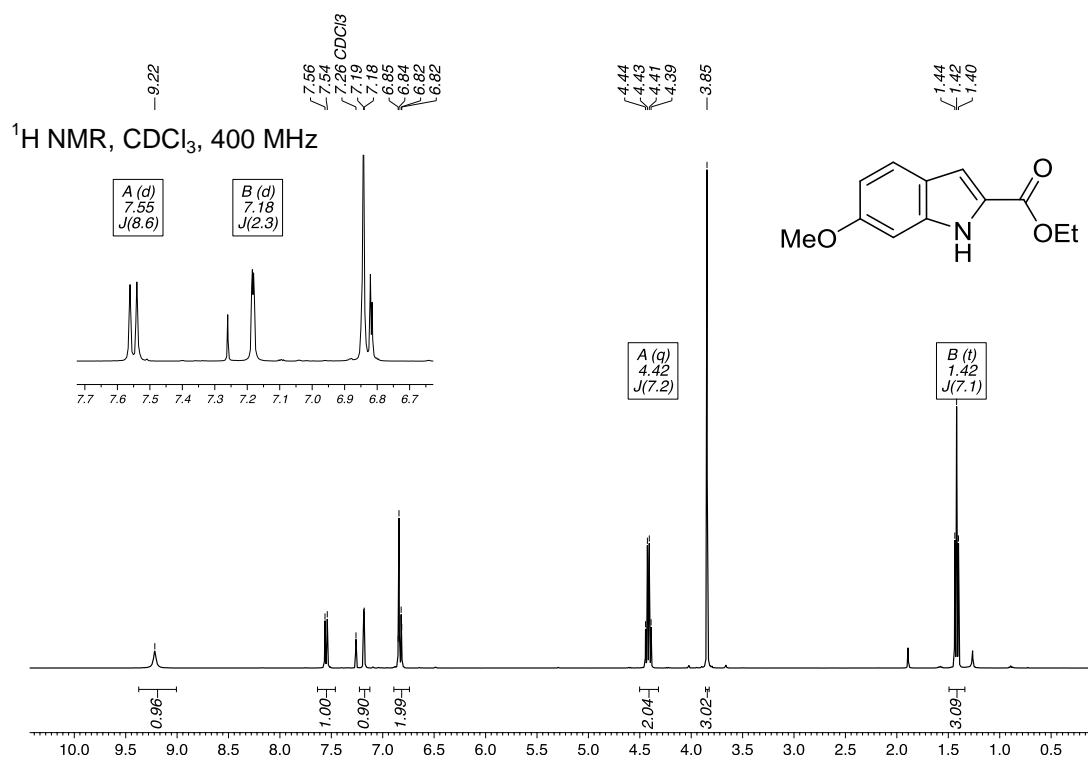
**2-(4-Methoxy-2-nitrophenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-3-phenylpropan-1-one (S6)**



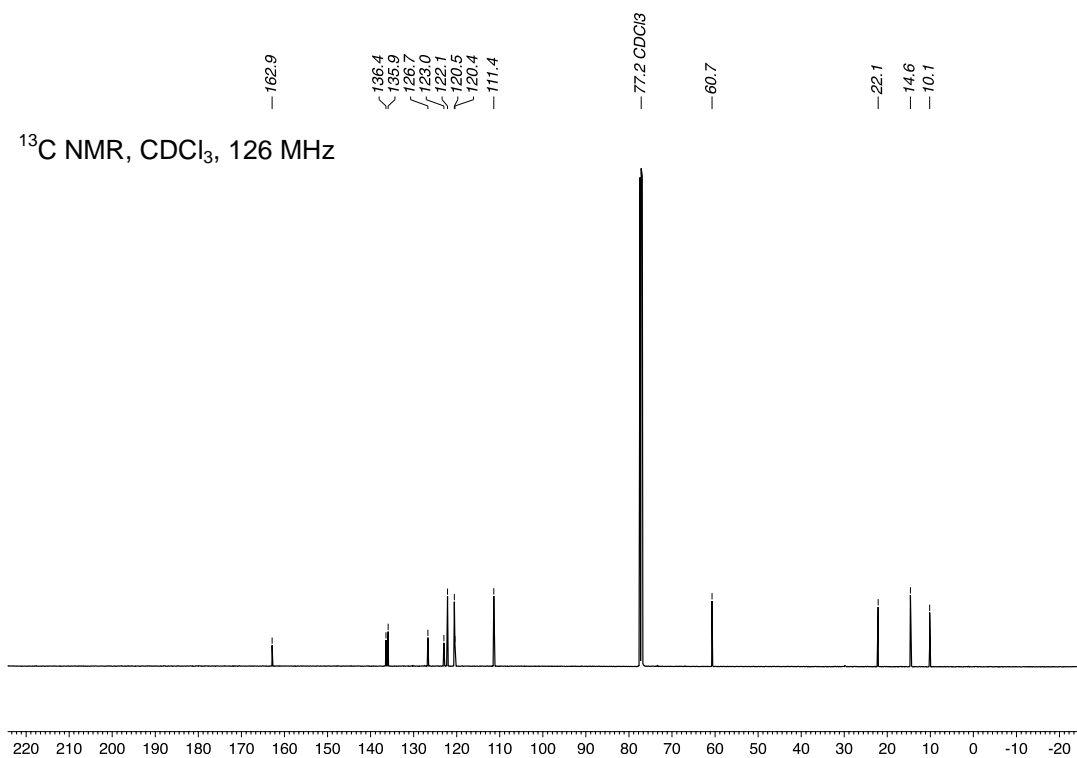
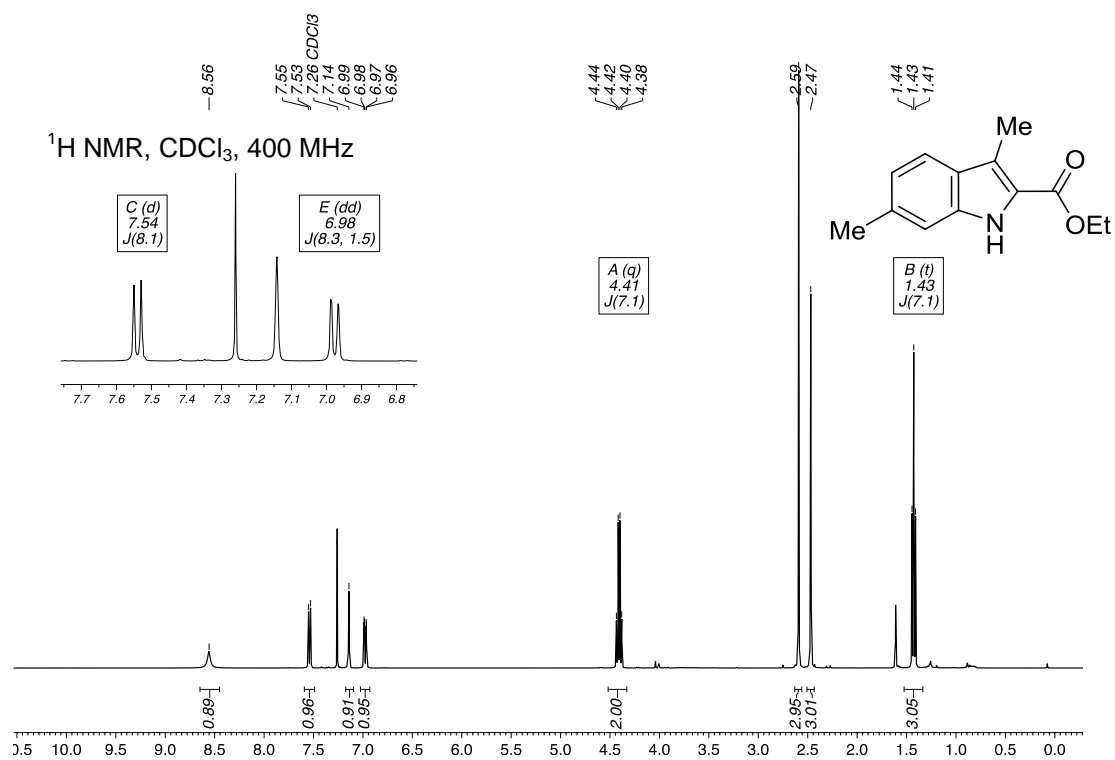
# **Ethyl 6-methyl-1*H*-indole-2-carboxylate (7a)**



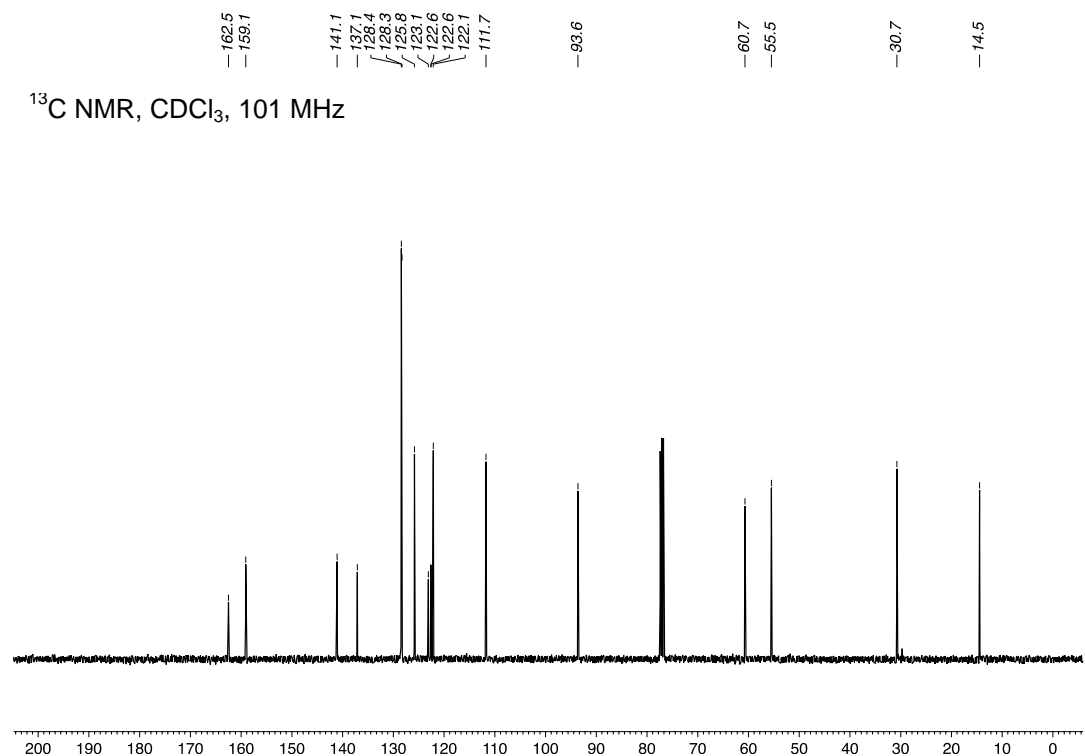
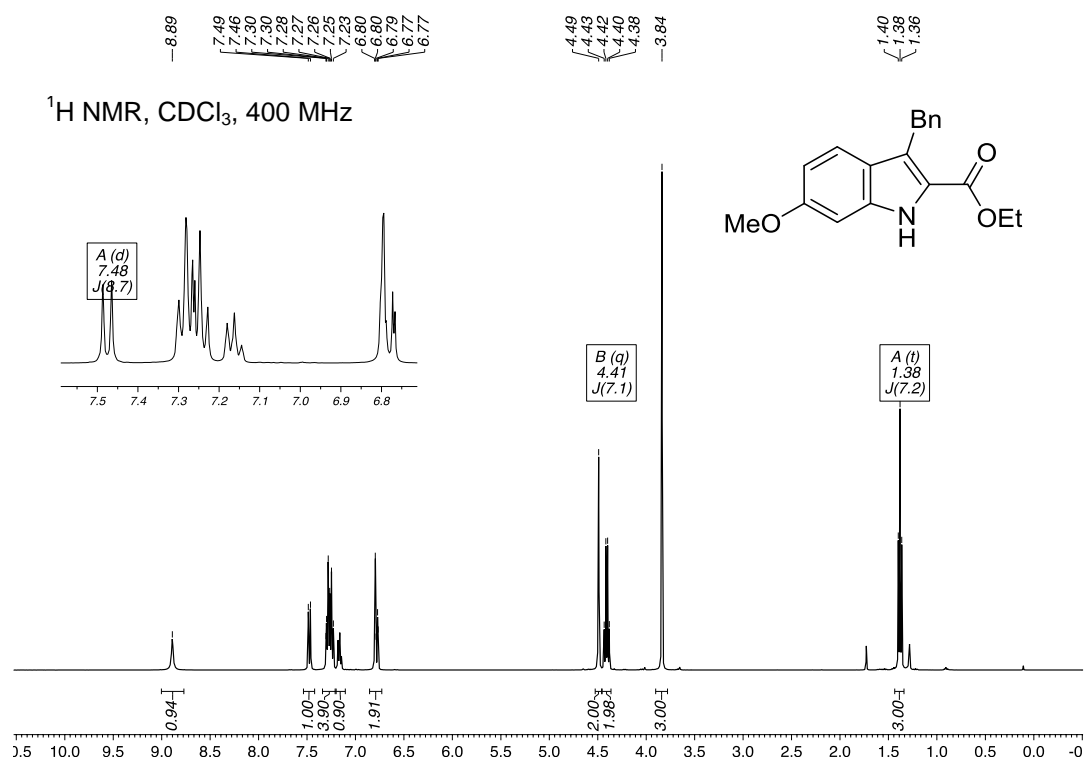
# **Ethyl 6-methoxy-1*H*-indole-2-carboxylate (7b)**



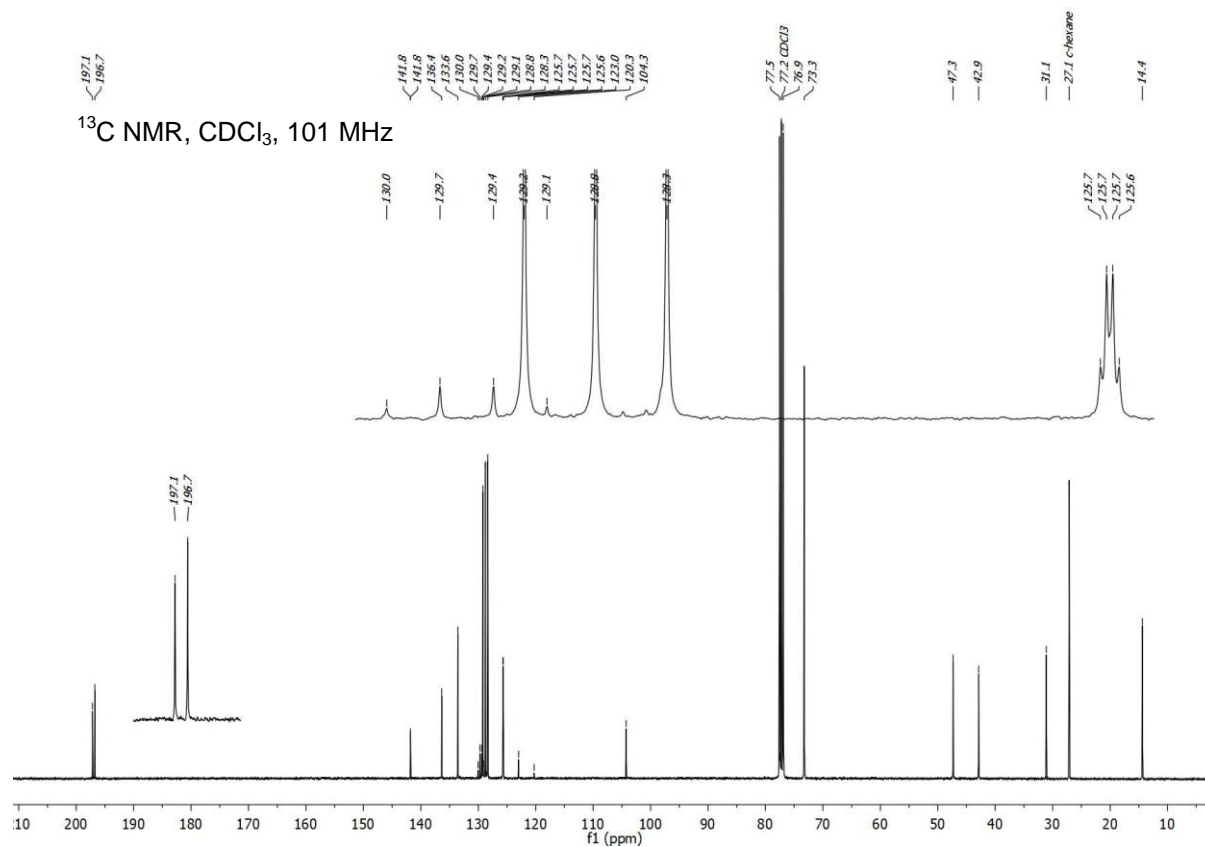
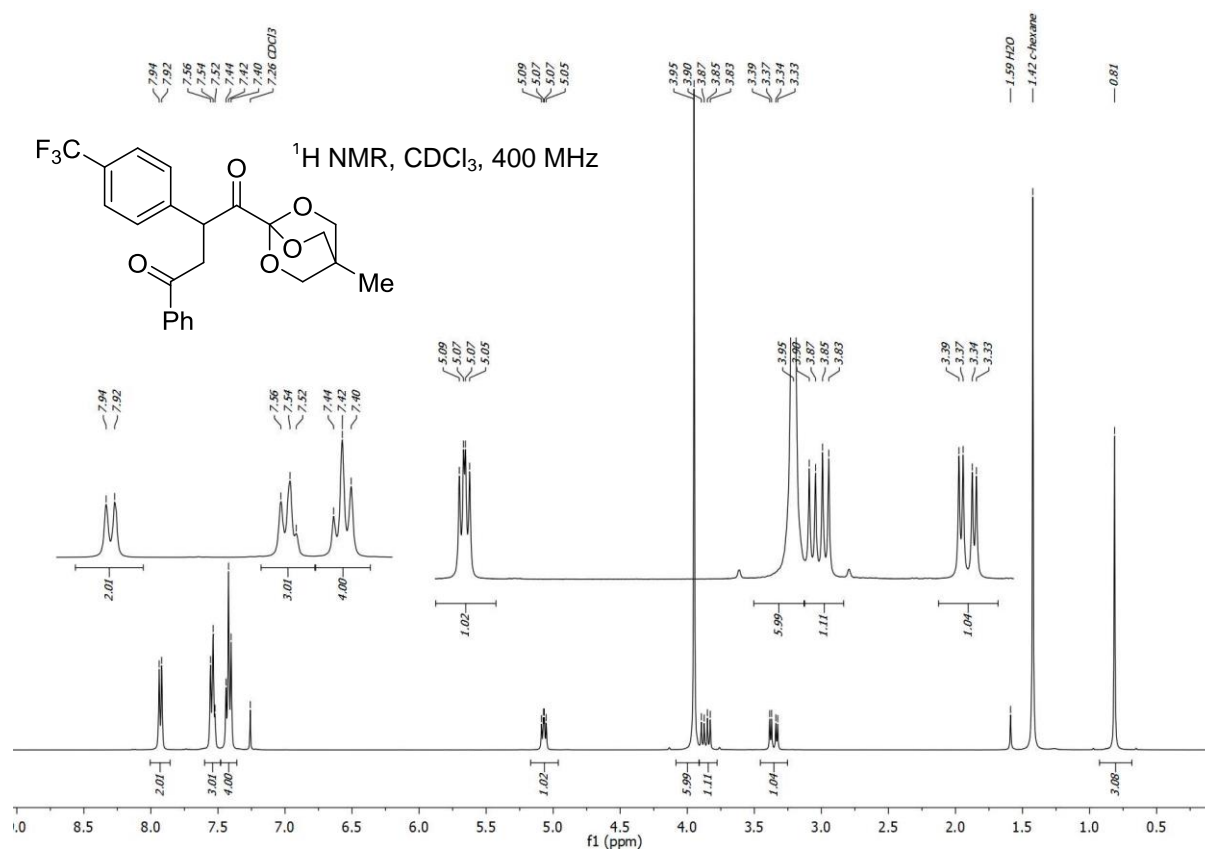
**Ethyl 3,6-dimethyl-1*H*-indole-2-carboxylate (7c)**



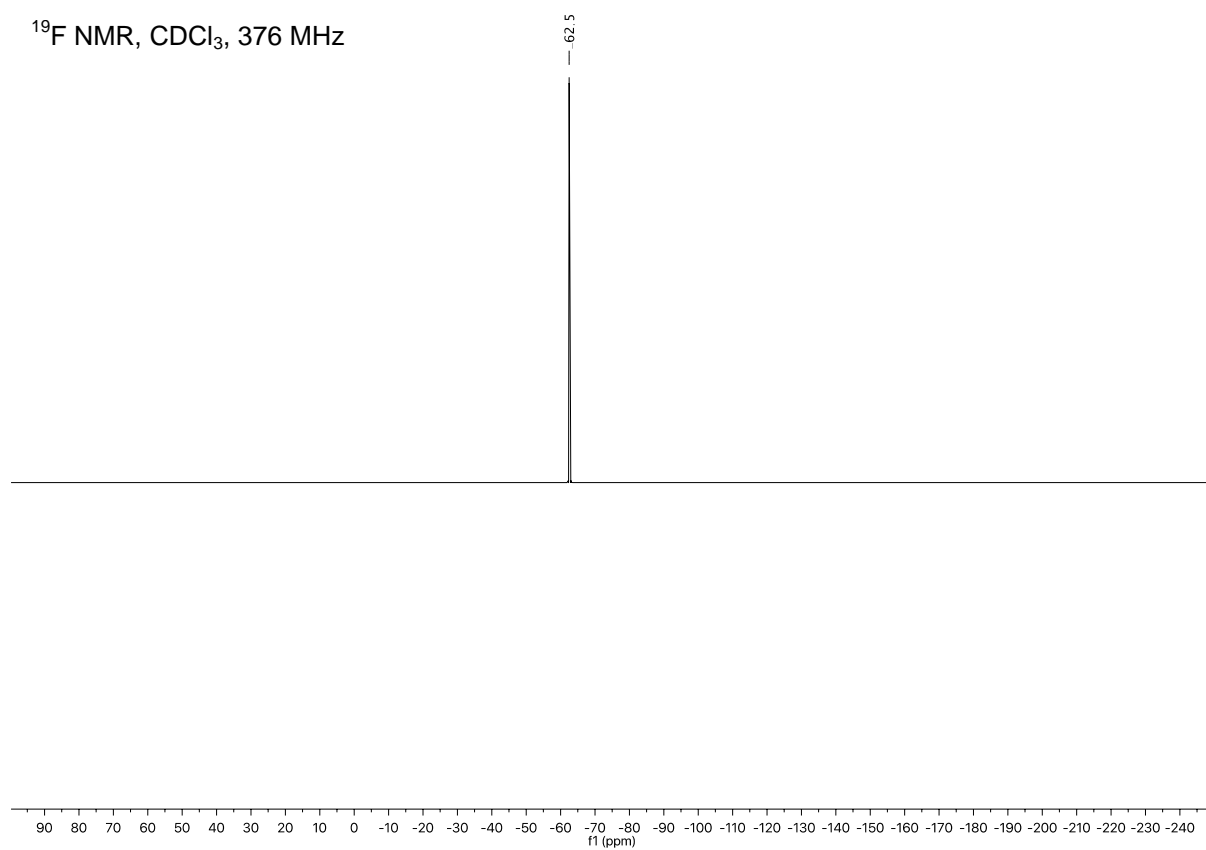
**Ethyl 3-benzyl-6-methoxy-1*H*-indole-2-carboxylate (7d)**



**1-[4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl]-4-phenyl-2-[4-(trifluoromethyl)-phenyl]butane-1,4-dione (9a)**

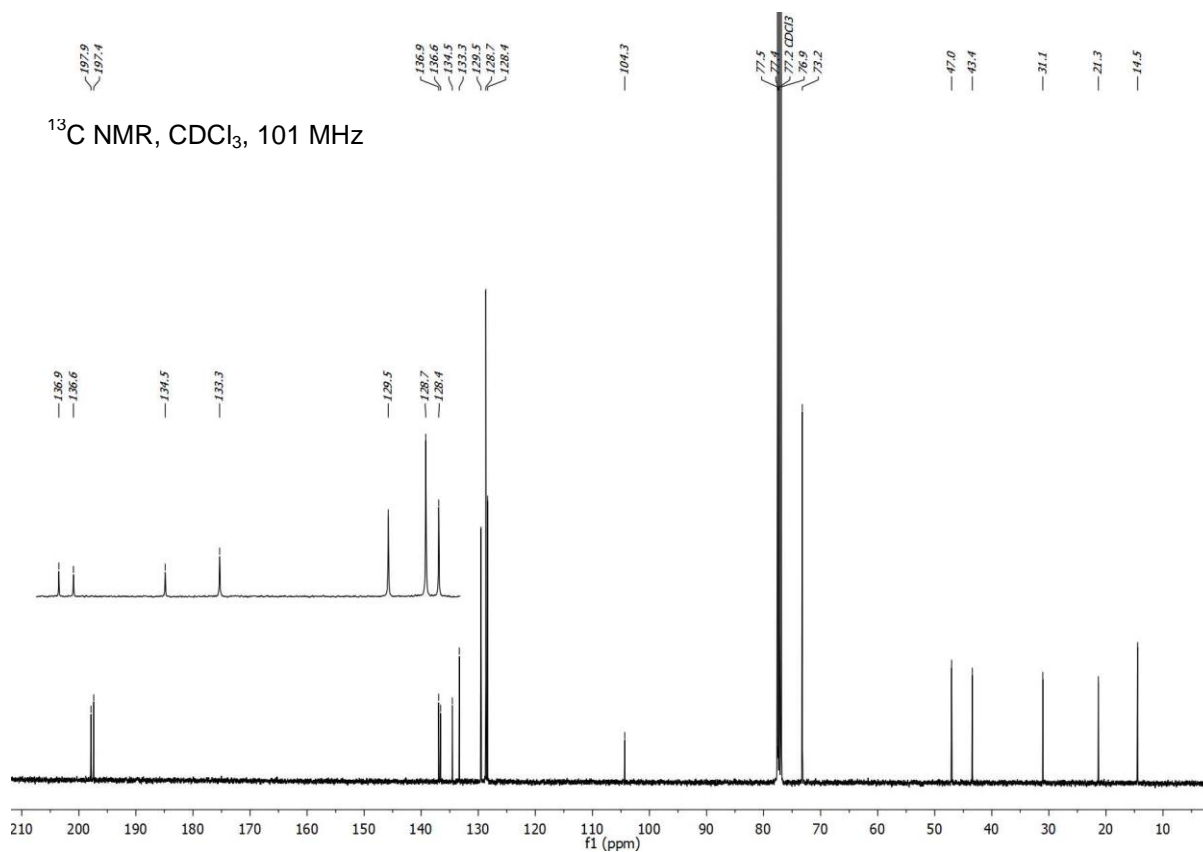
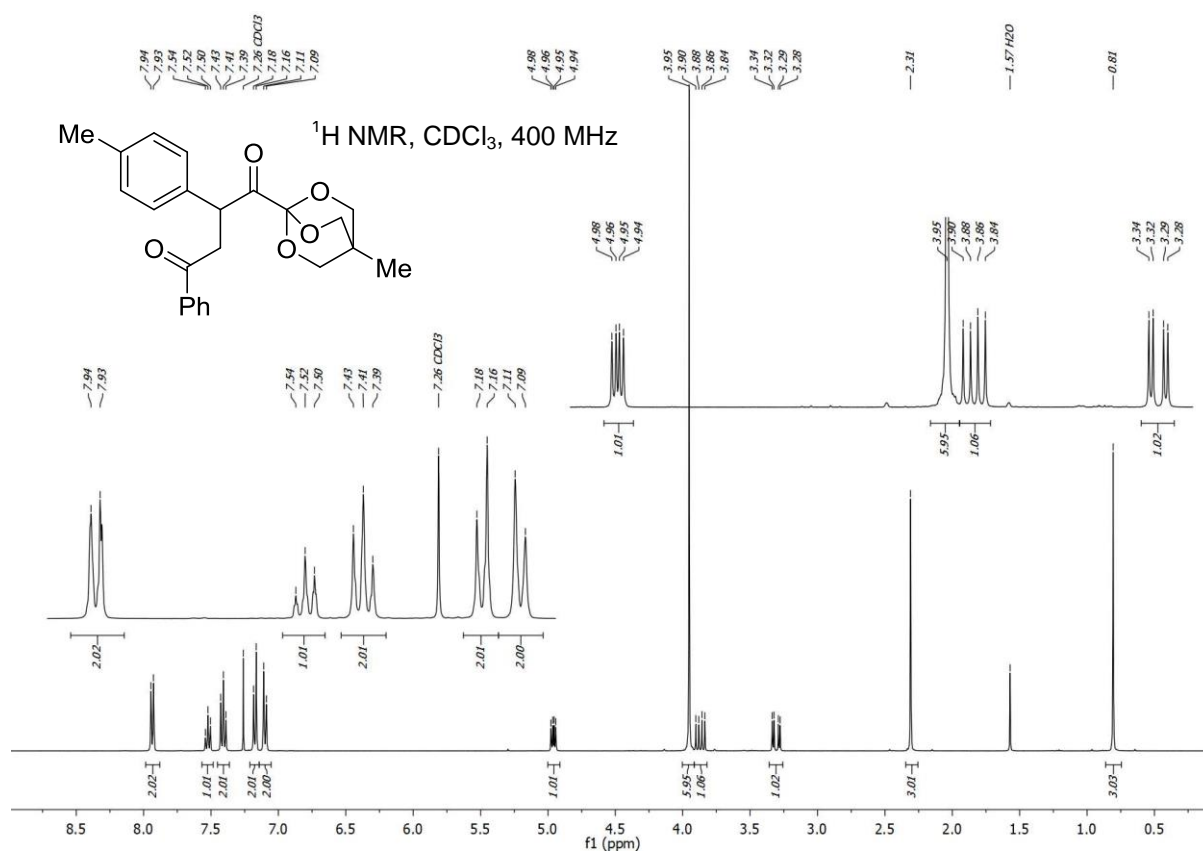


$^{19}\text{F}$  NMR,  $\text{CDCl}_3$ , 376 MHz

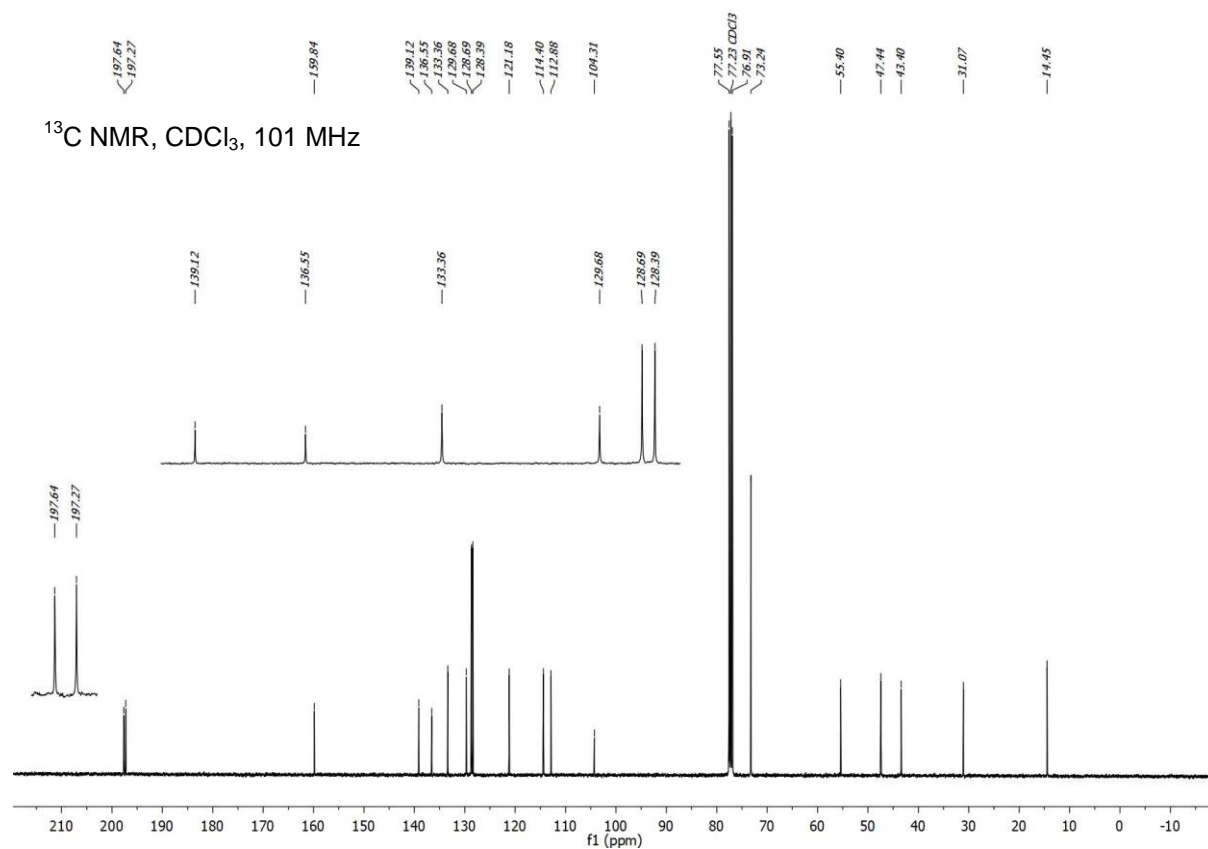
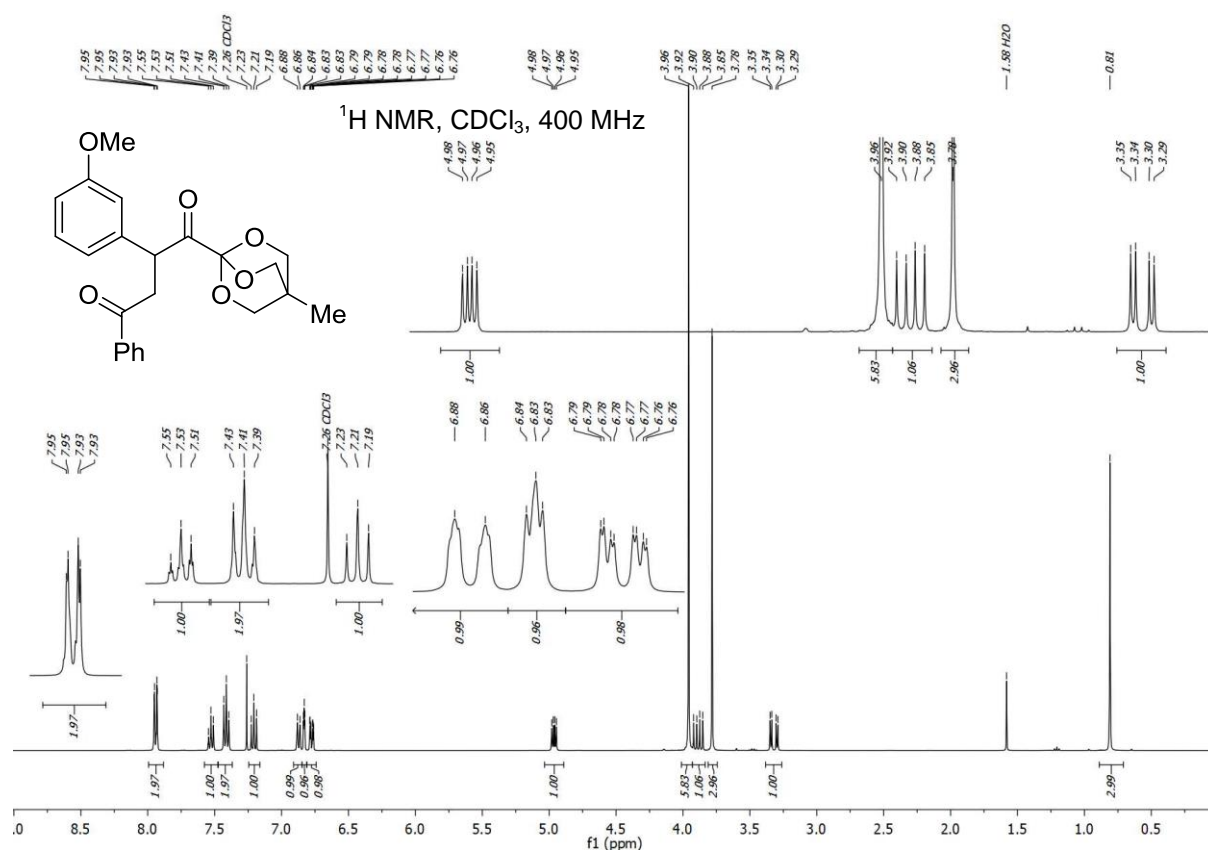




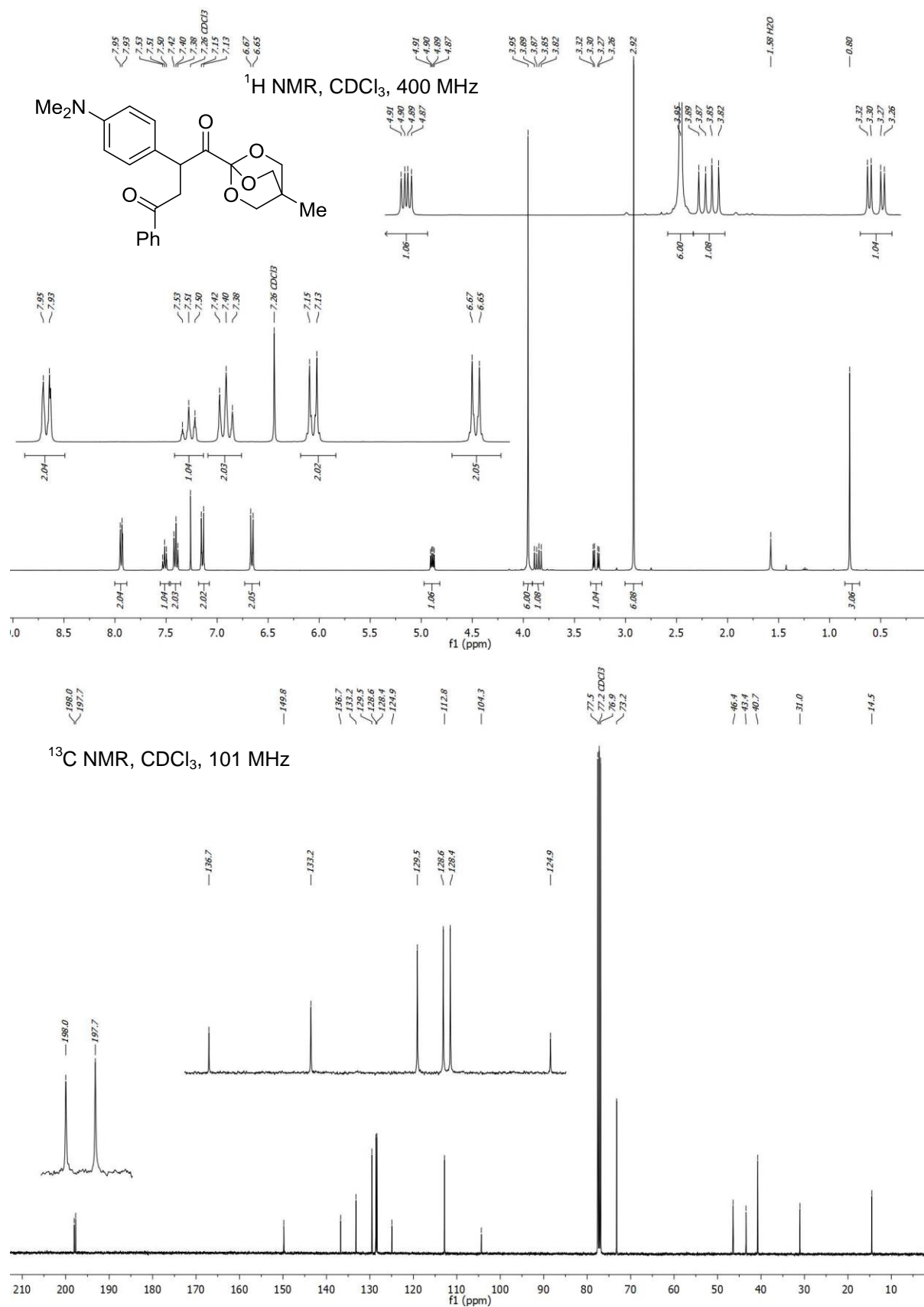
**1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-4-phenyl-2-(*p*-tolyl)butane-1,4-dione**  
**(9b)**



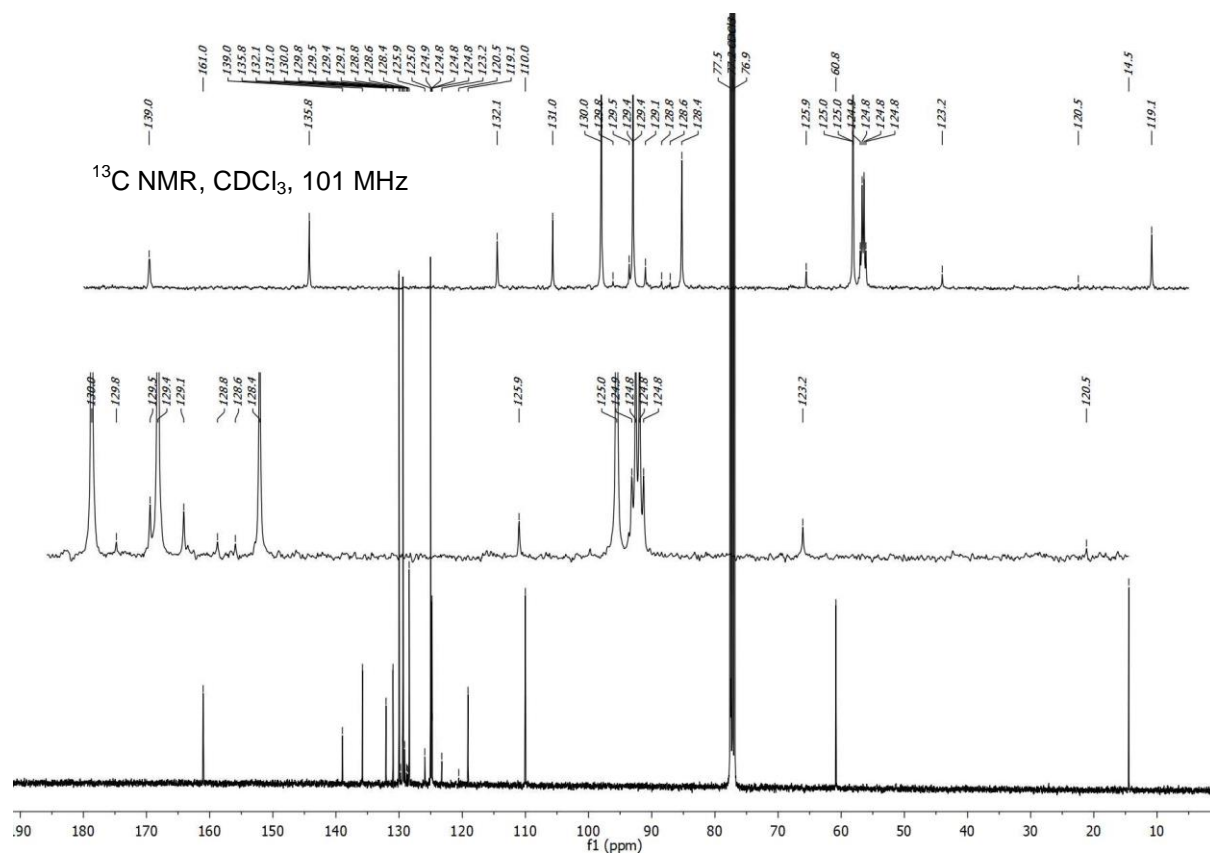
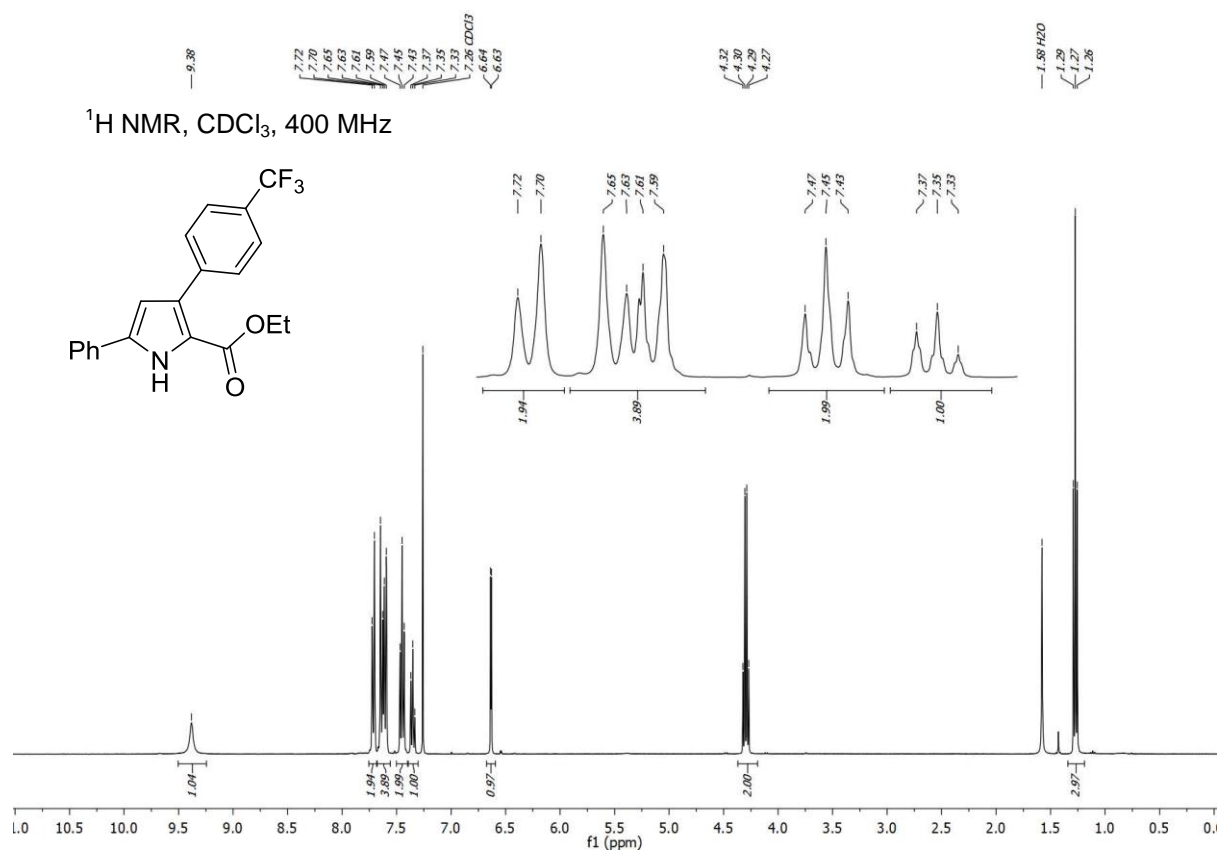
**2-(3-Methoxyphenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-4-phenylbutane-1,4-dione (9c)**

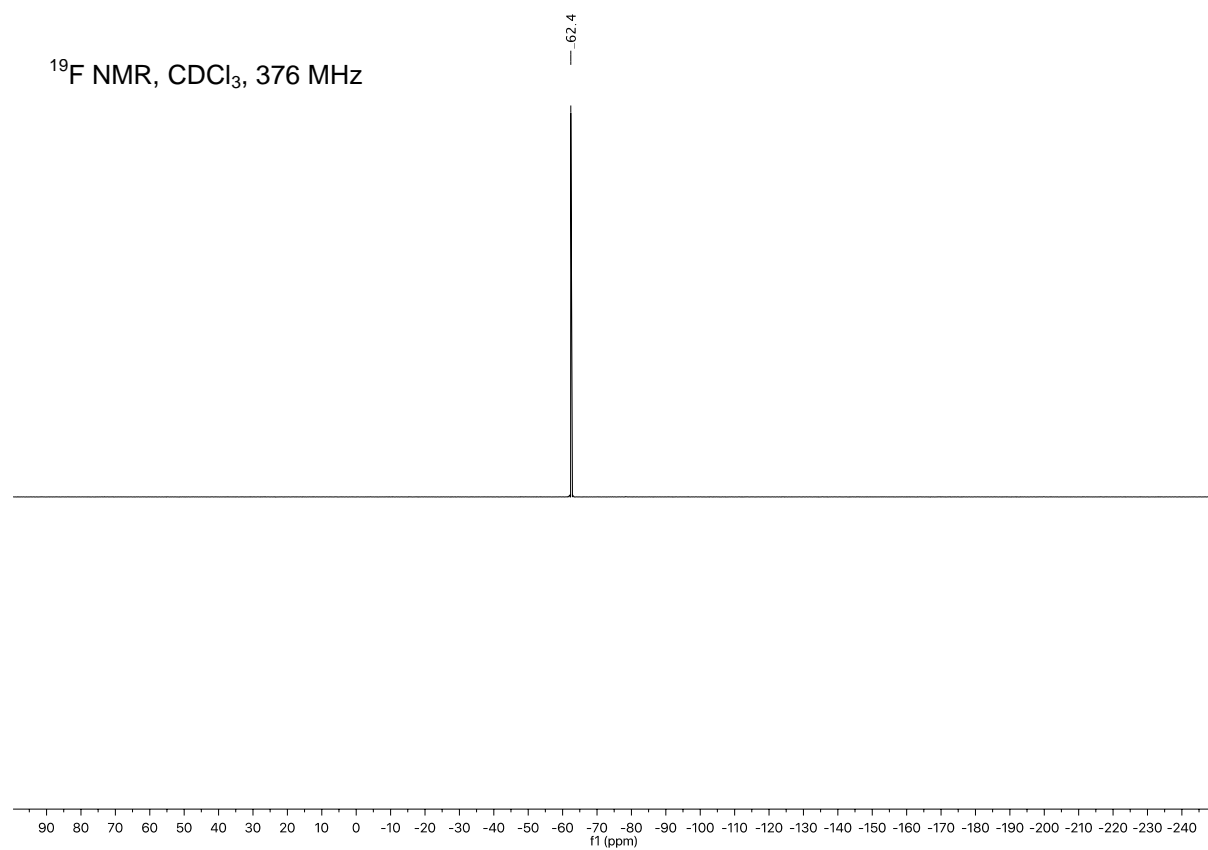


**2-[4-(Dimethylamino)phenyl]-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-4-phenylbutane-1,4-dione (9d)**

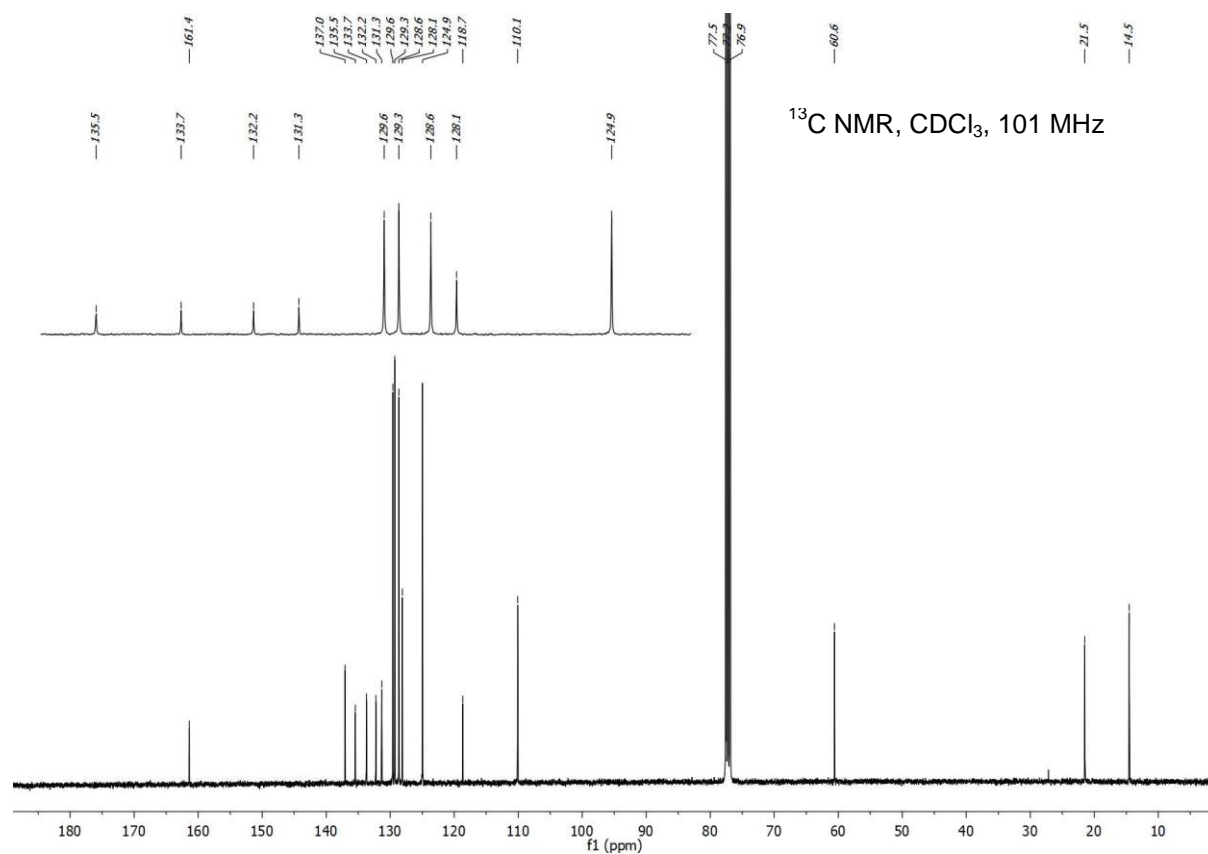
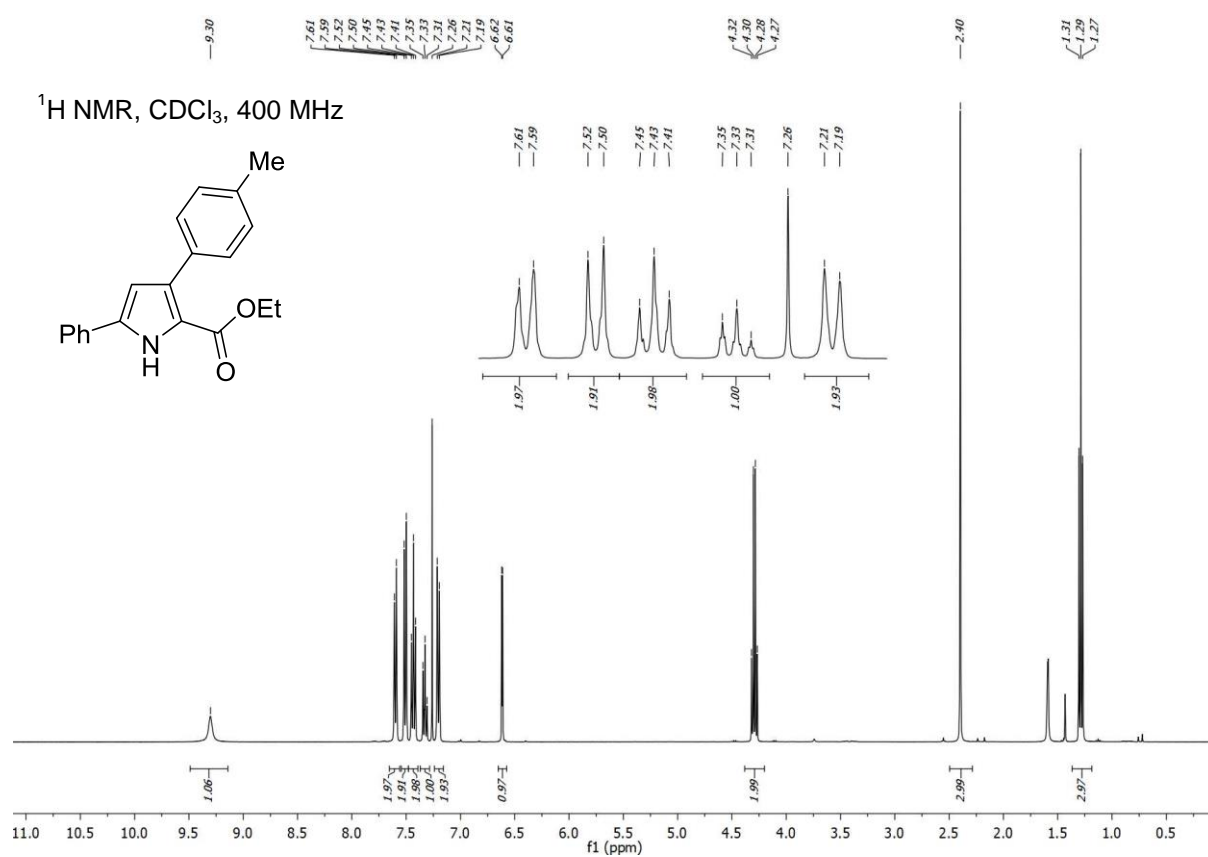


**Ethyl 5-phenyl-3-[4-(trifluoromethyl)phenyl]-1H-pyrrole-2-carboxylate (10a)**

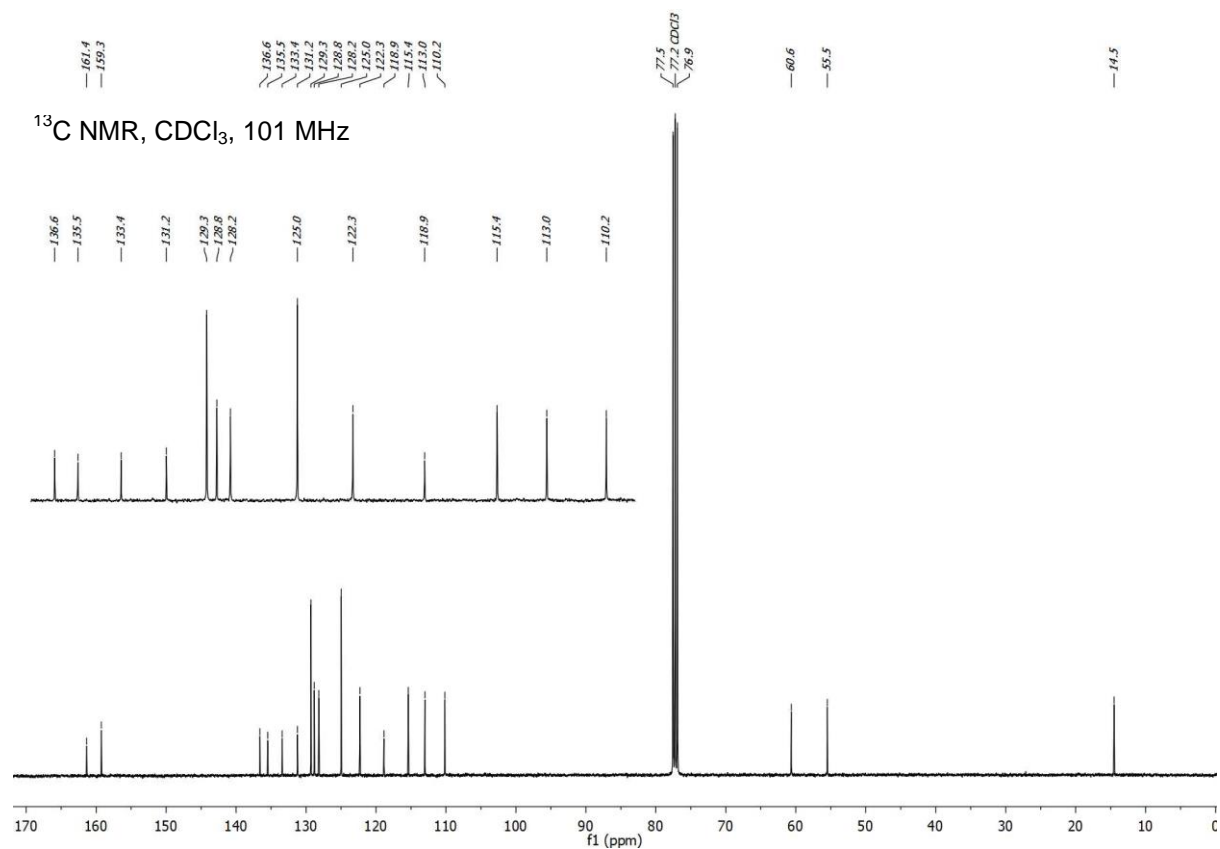
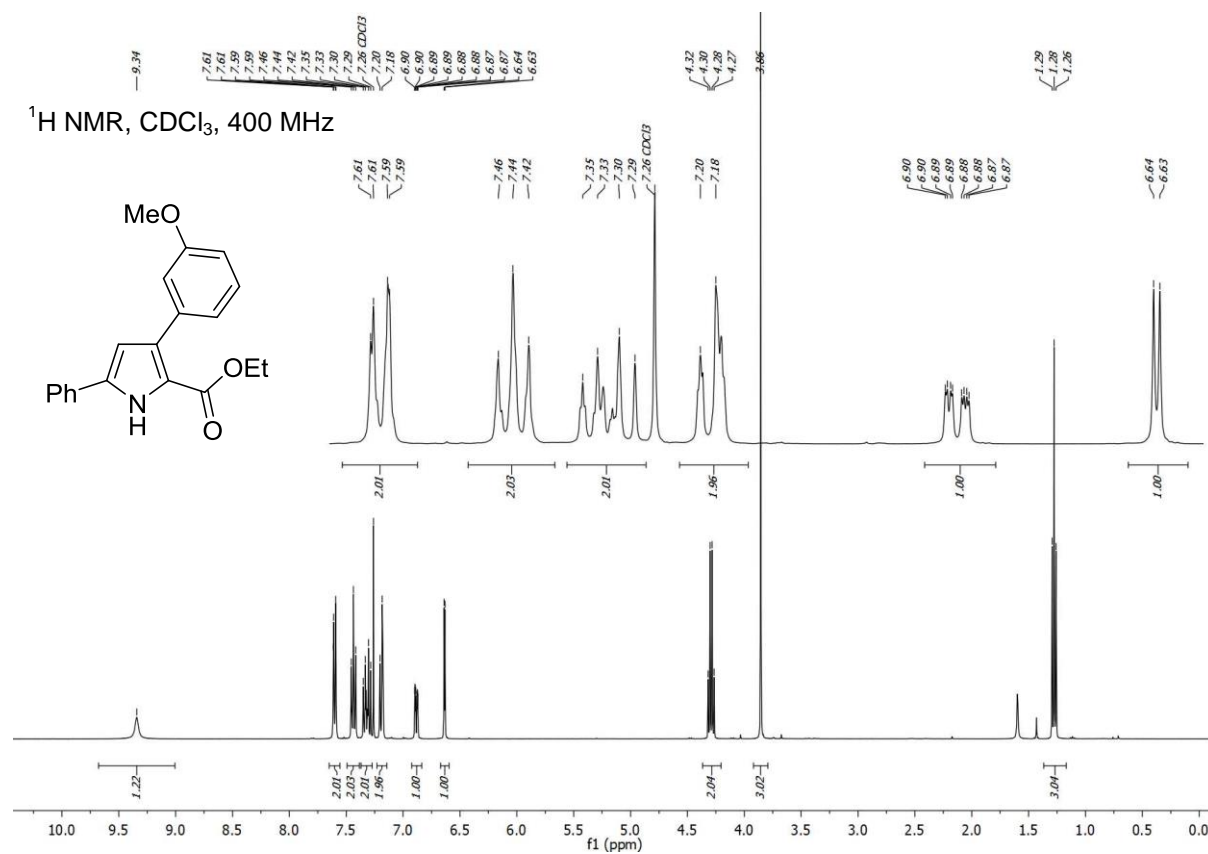




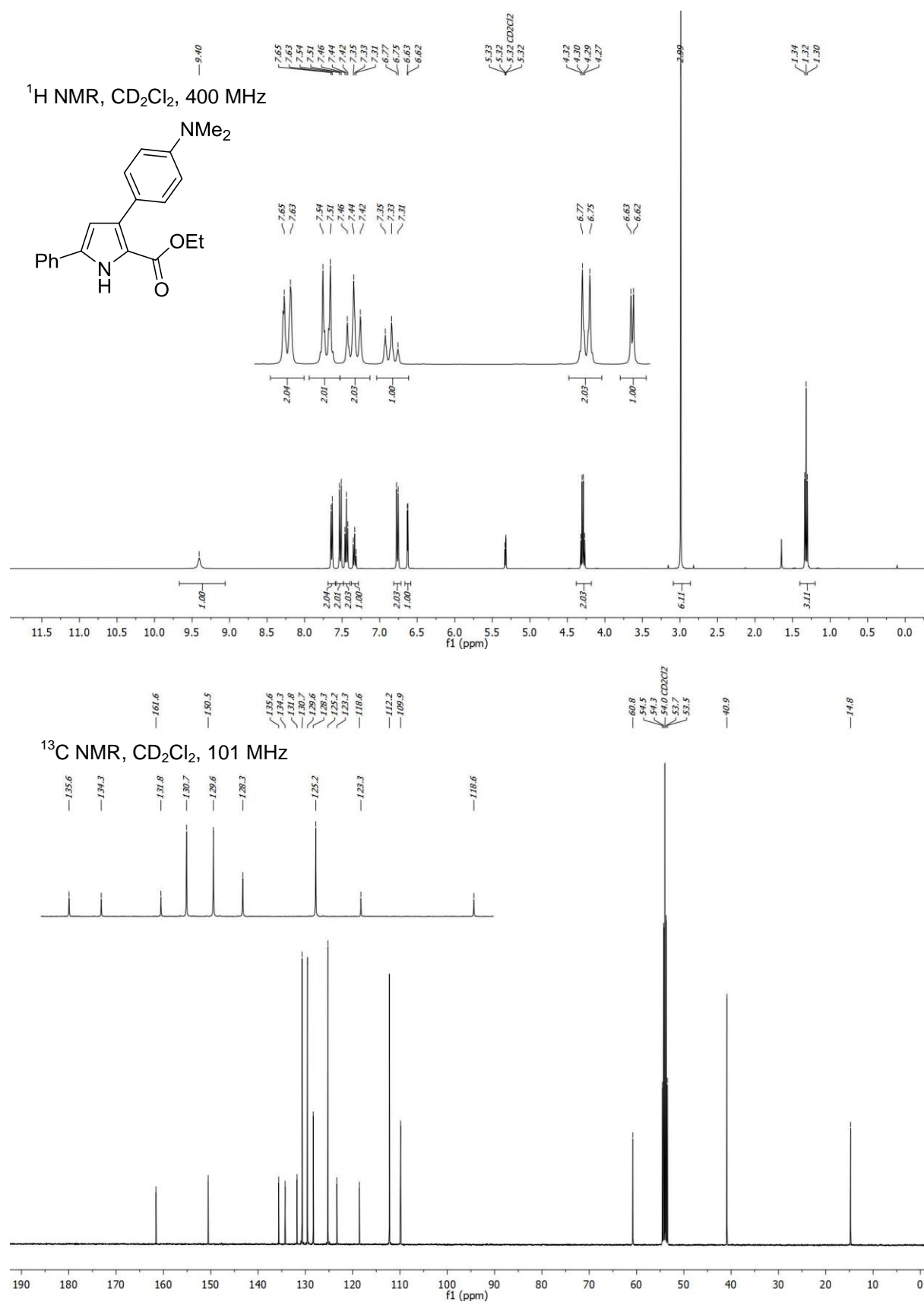
**Ethyl 5-phenyl-3-(*p*-tolyl)-1*H*-pyrrole-2-carboxylate (10b)**



**Ethyl 3-(3-methoxyphenyl)-5-phenyl-1H-pyrrole-2-carboxylate (10c)**

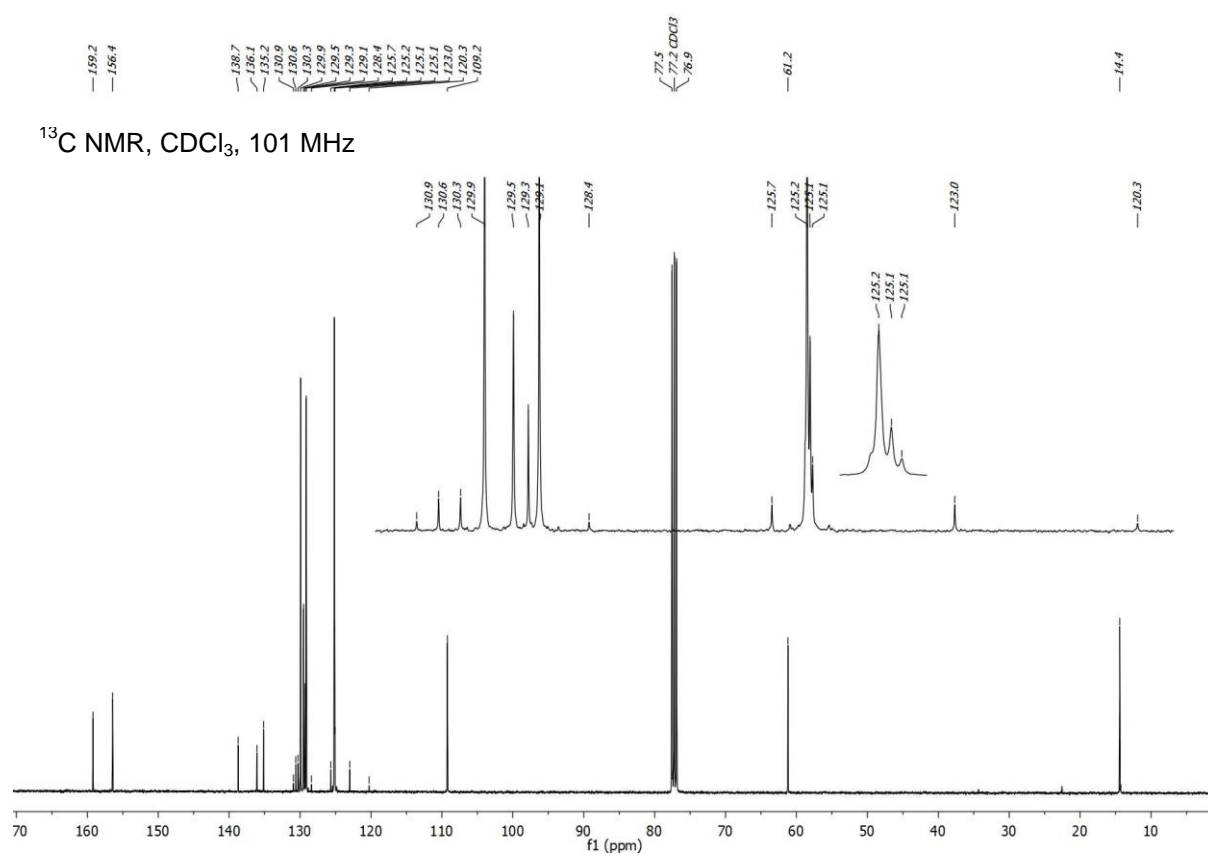
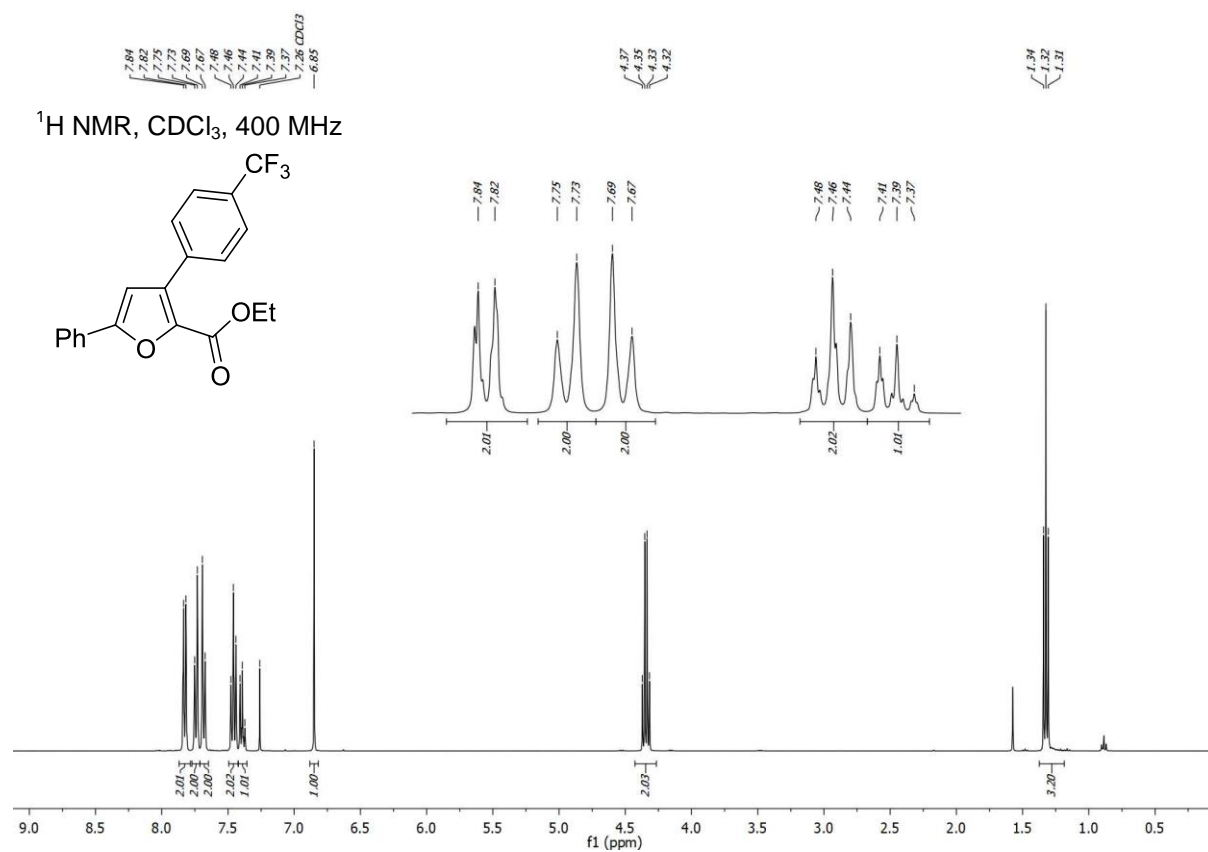


**Ethyl 3-[4-(dimethylamino)phenyl]-5-phenyl-1*H*-pyrrole-2-carboxylate (10d)**

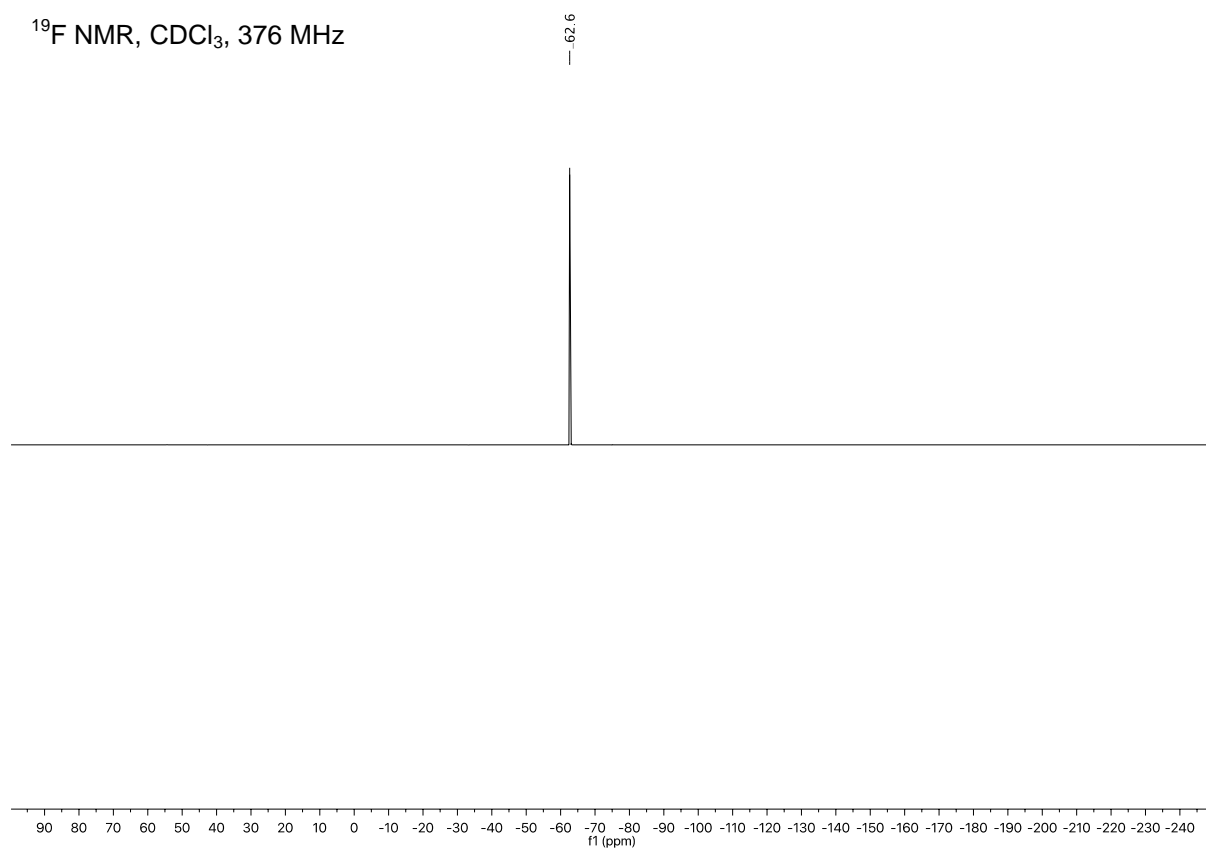




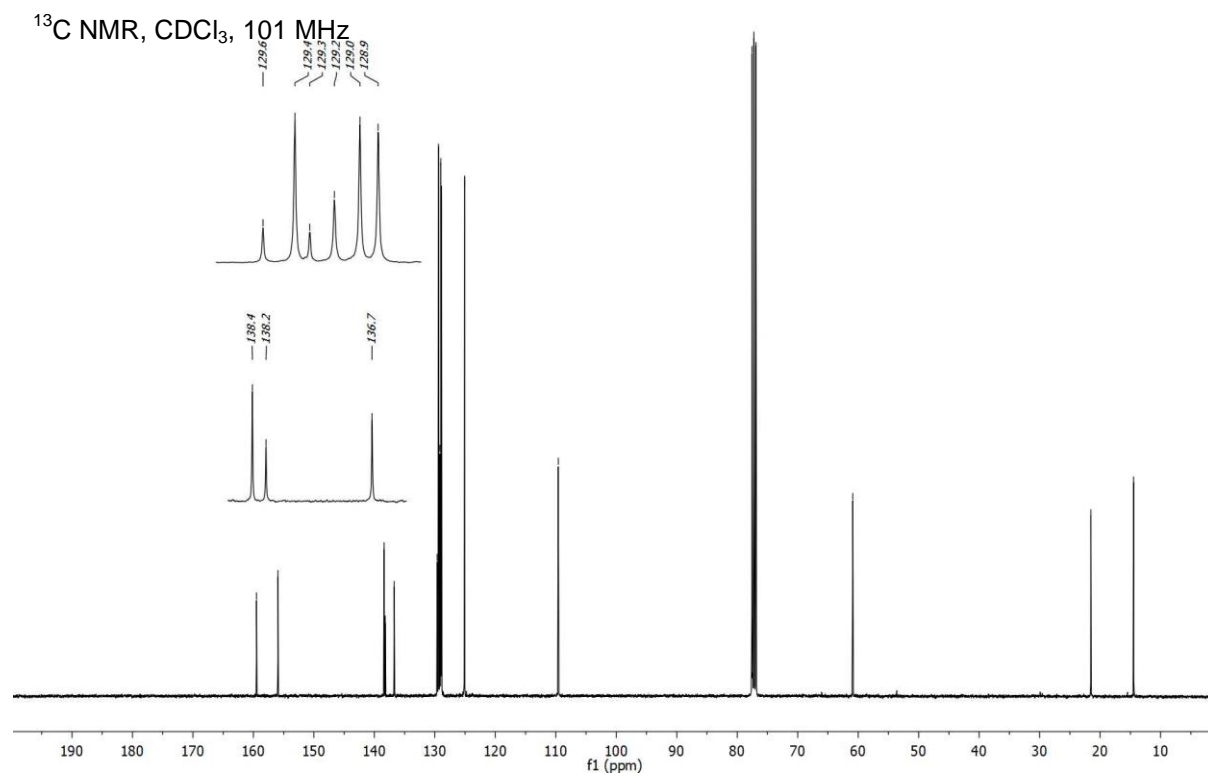
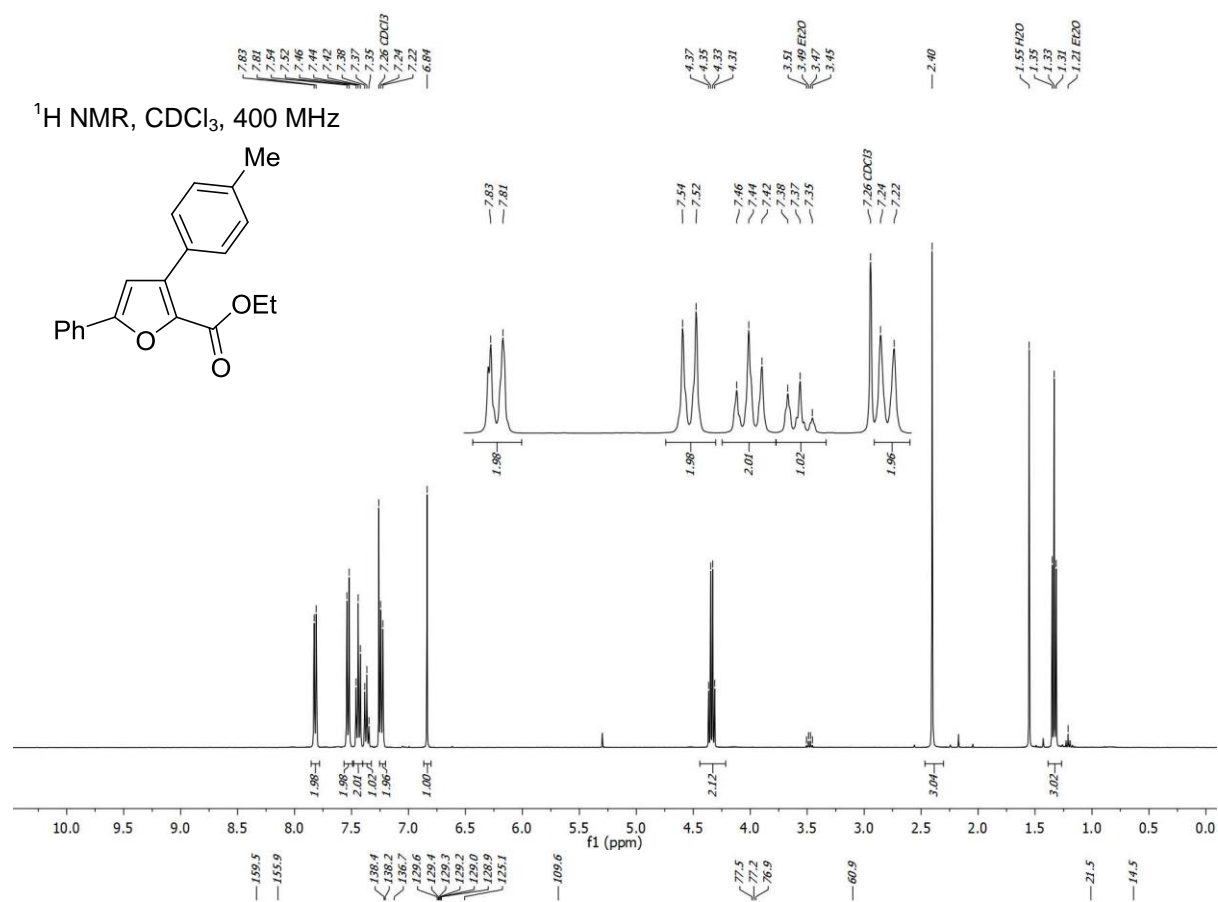
# **Ethyl 5-phenyl-3-[4-(trifluoromethyl)phenyl]furan-2-carboxylate (11a)**



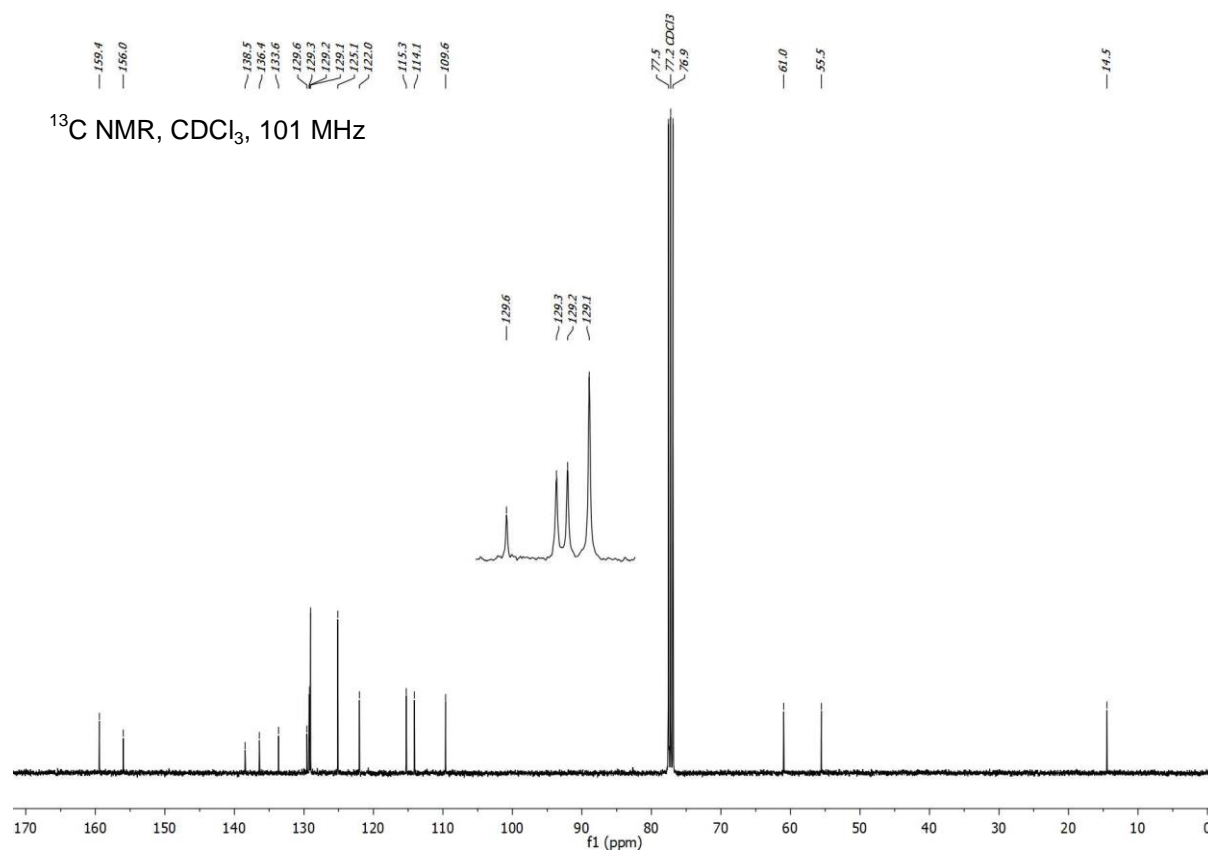
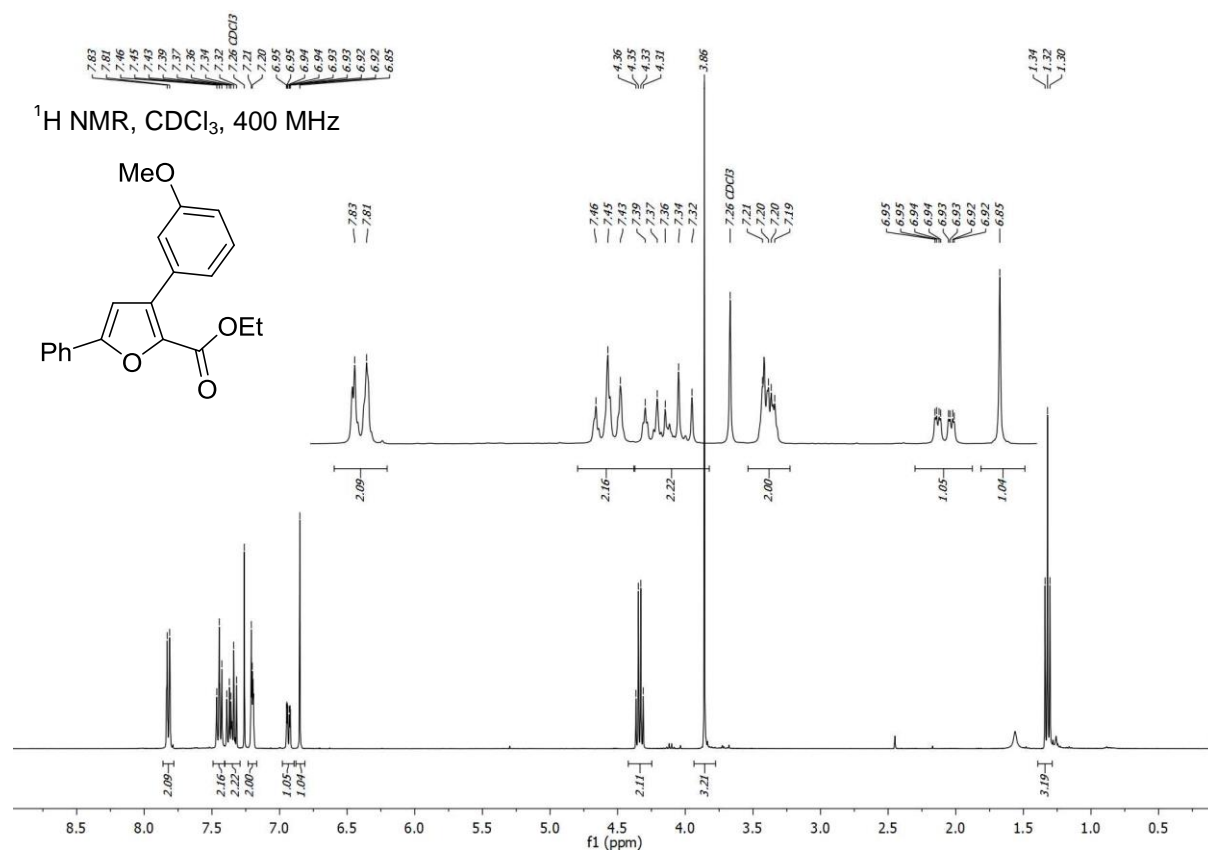
$^{19}\text{F}$  NMR,  $\text{CDCl}_3$ , 376 MHz



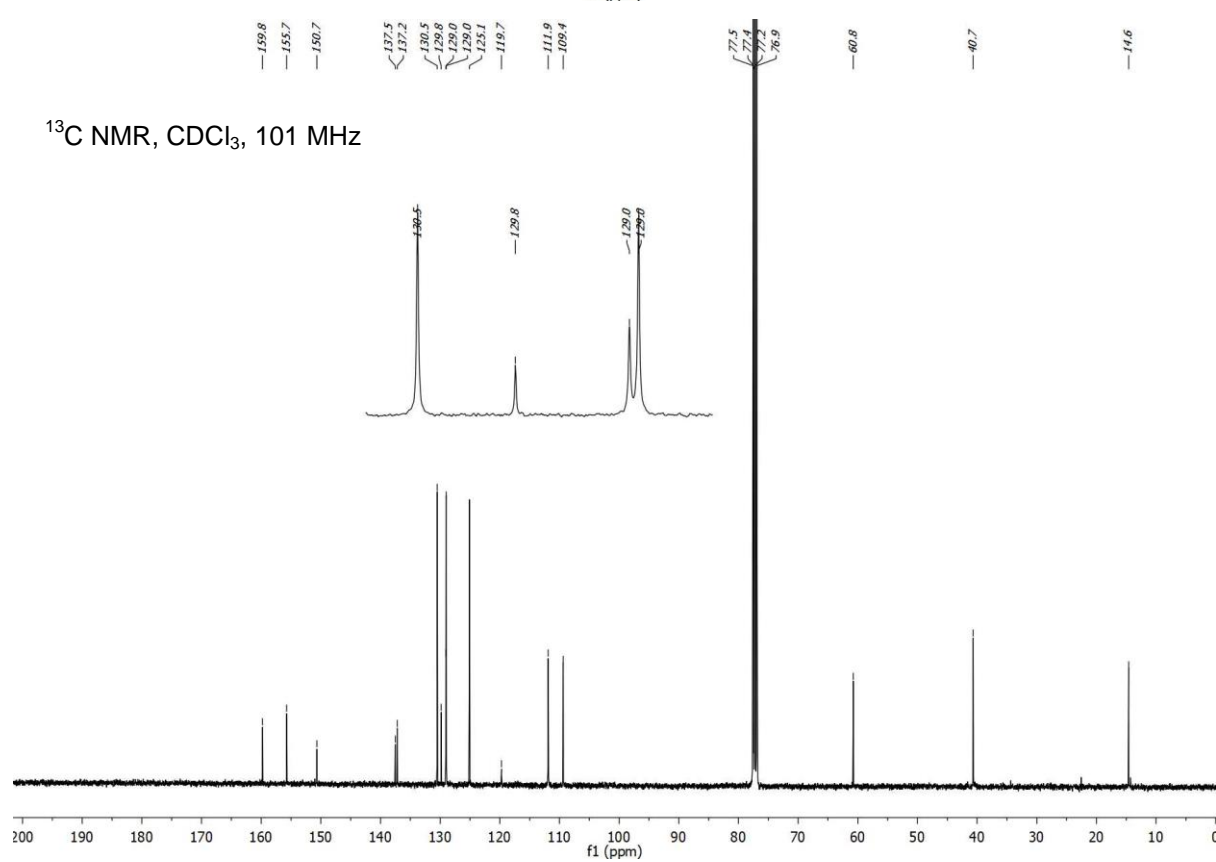
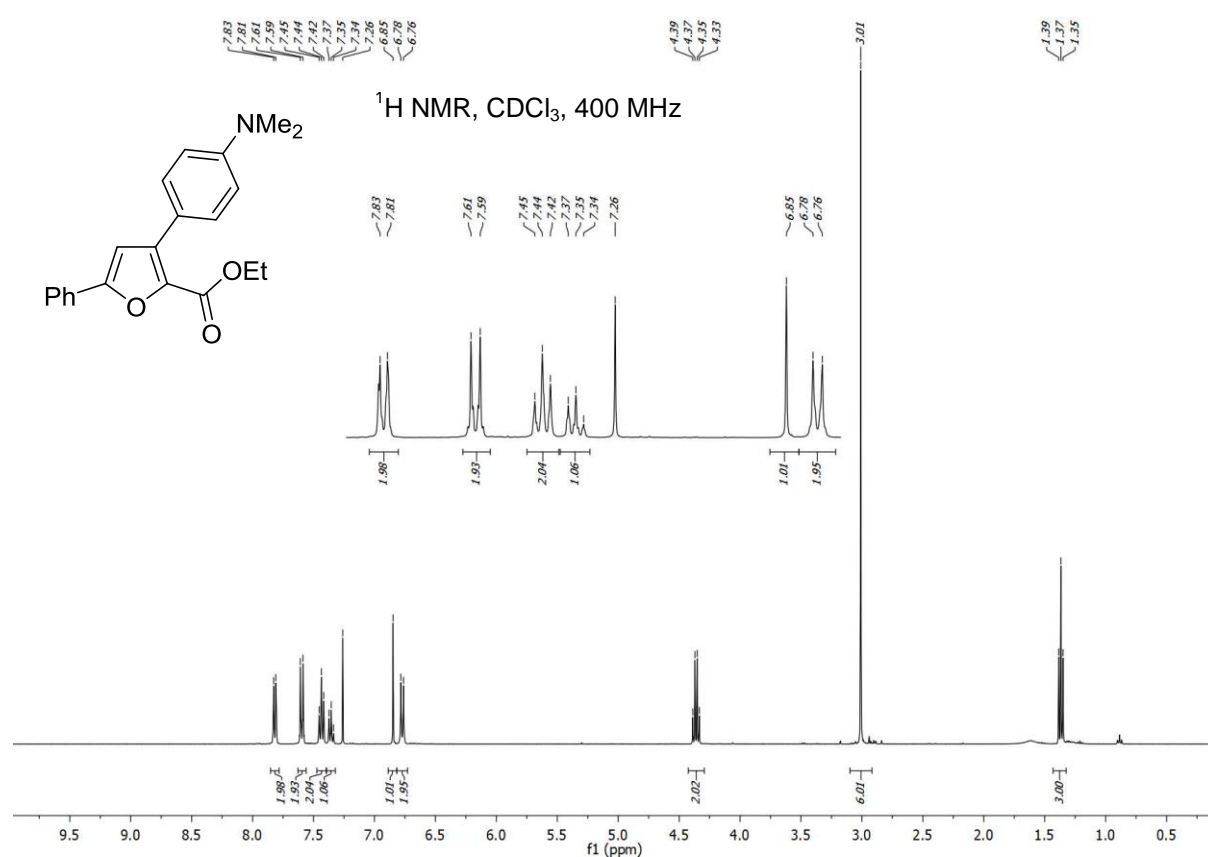
# **Ethyl 5-phenyl-3-(*p*-tolyl)furan-2-carboxylate (11b)**



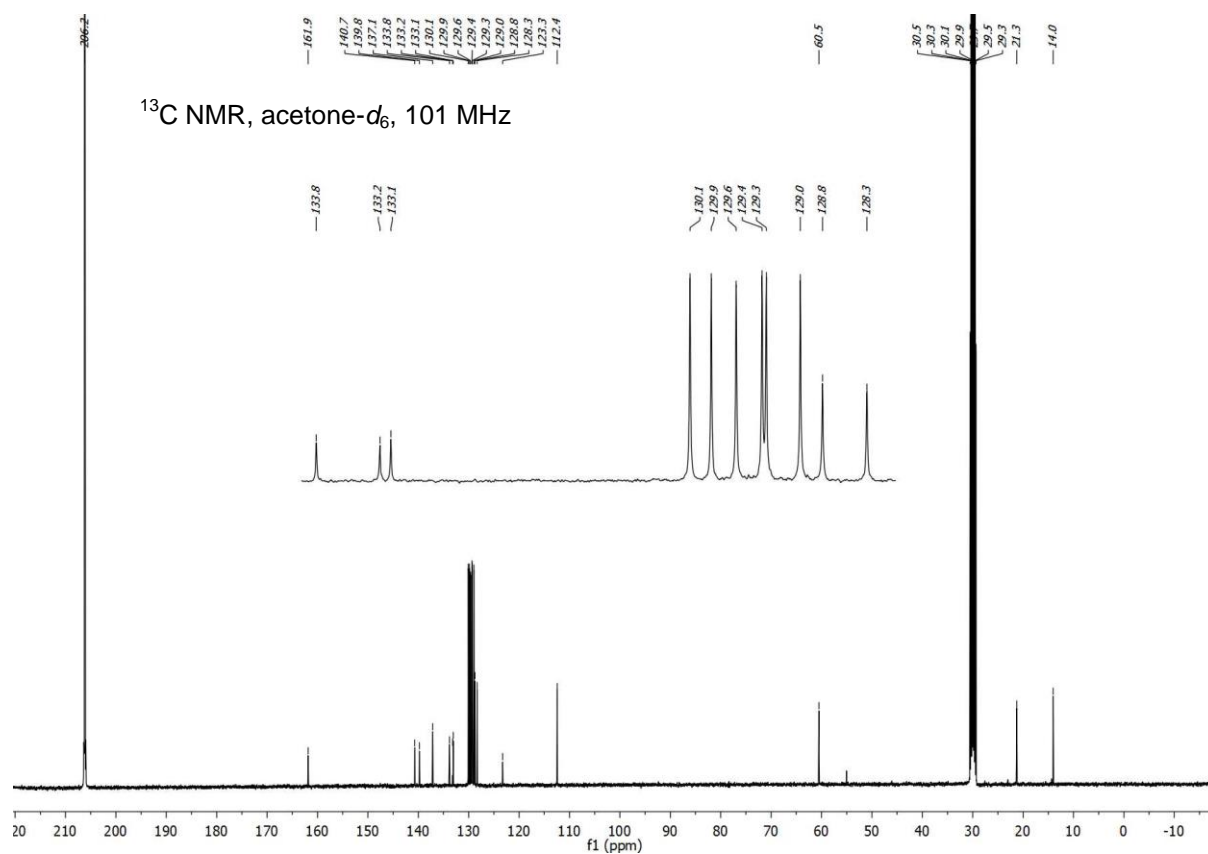
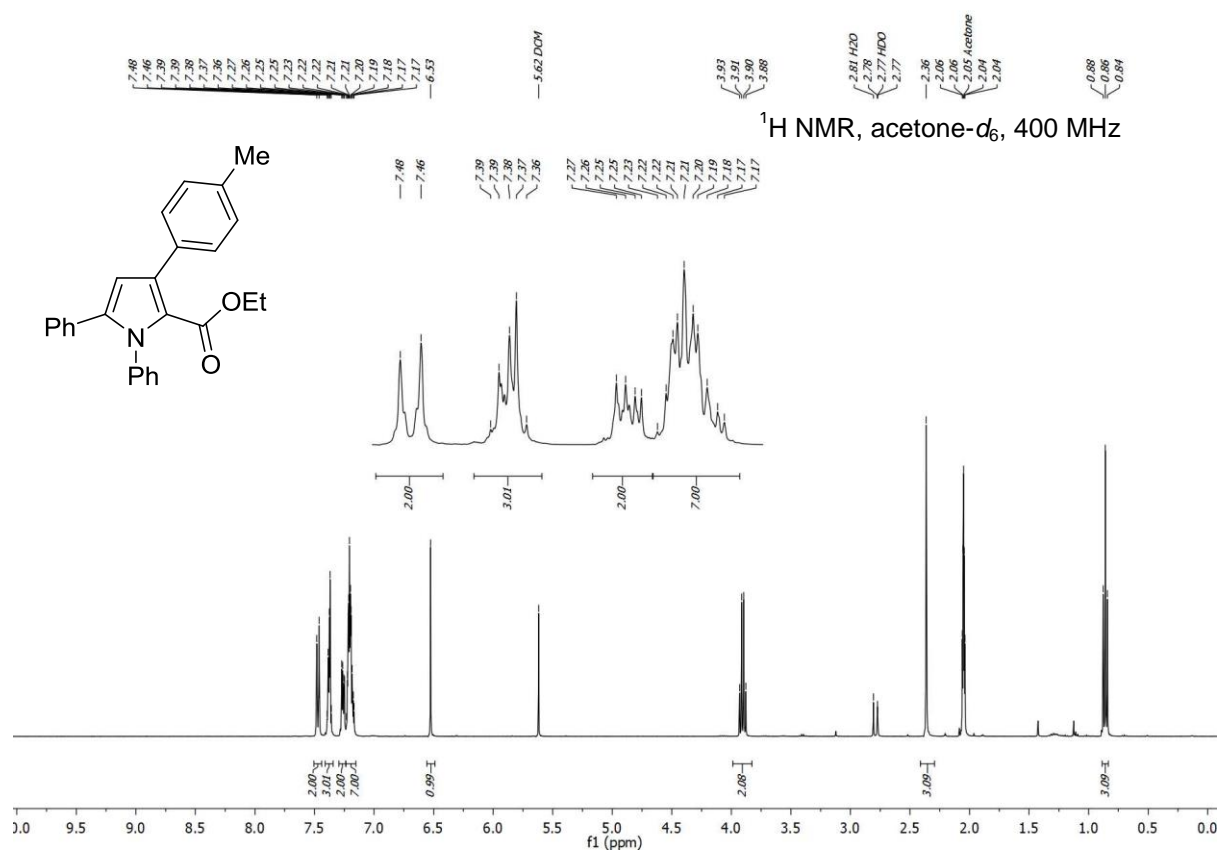
**Ethyl 3-(3-methoxyphenyl)-5-phenylfuran-2-carboxylate (11c)**



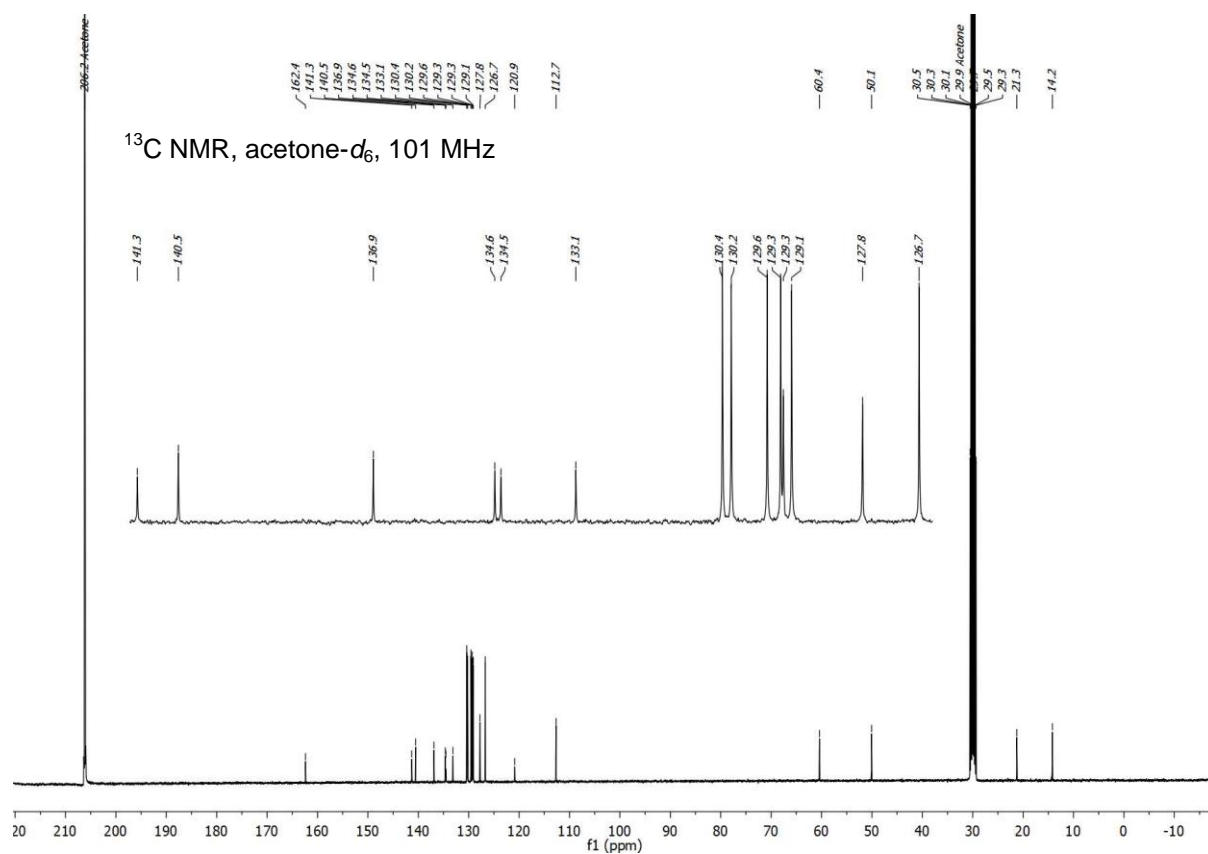
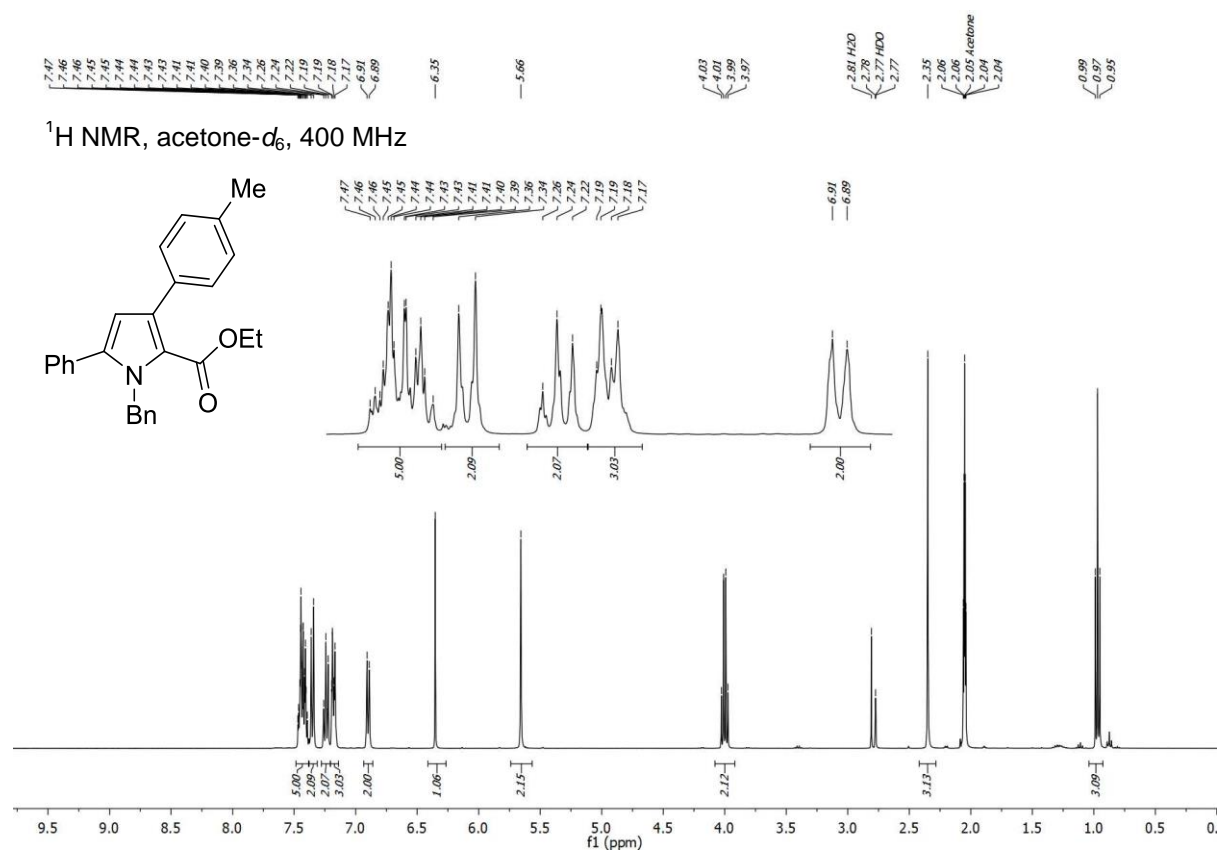
**Ethyl 3-[4-(dimethylamino)phenyl]-5-phenylfuran-2-carboxylate (11d)**



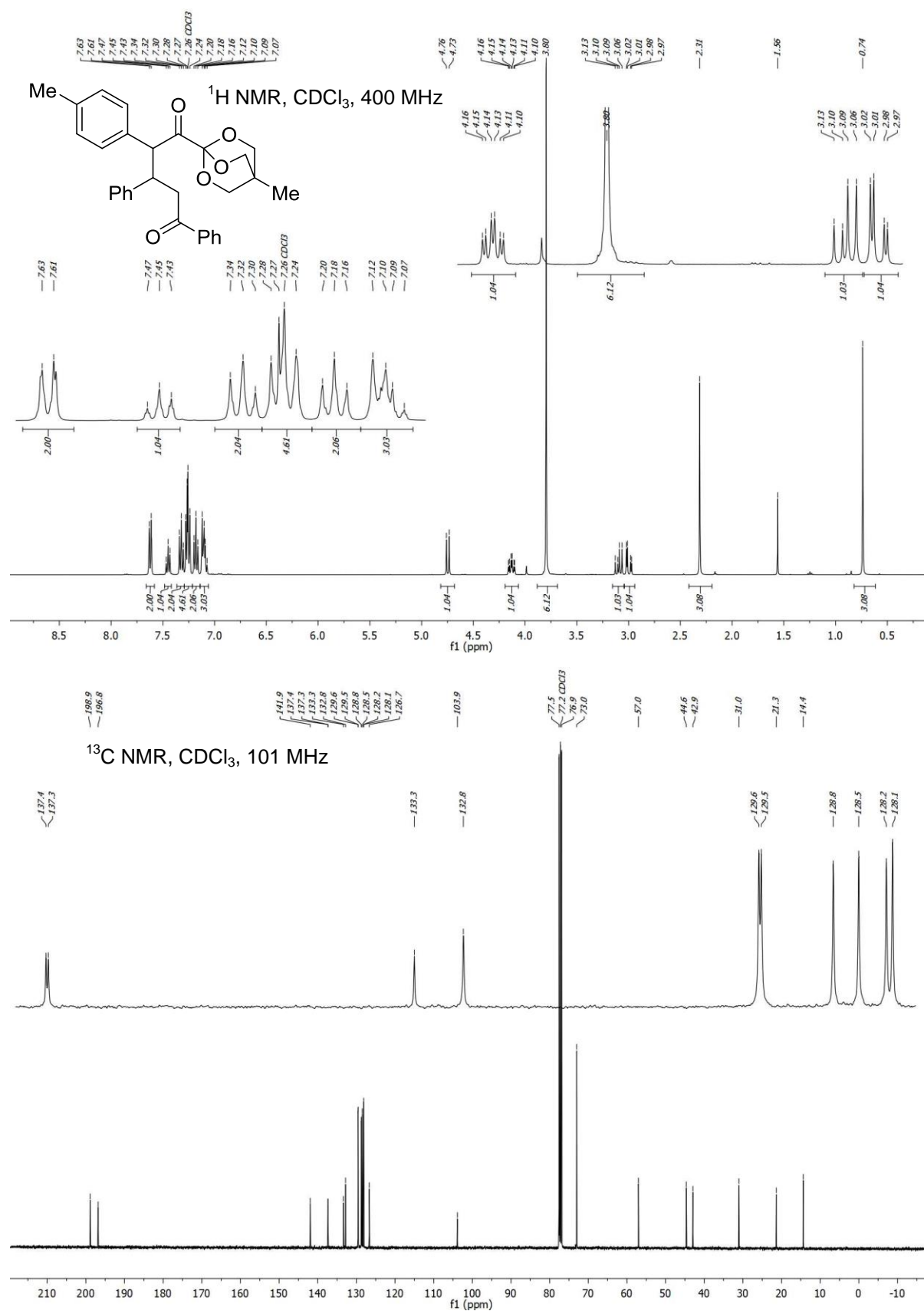
# **Ethyl 1,5-diphenyl-3-(*p*-tolyl)-1*H*-pyrrole-2-carboxylate (12)**



# **Ethyl 1-benzyl-5-phenyl-3-(*p*-tolyl)-1*H*-pyrrole-2-carboxylate (13)**

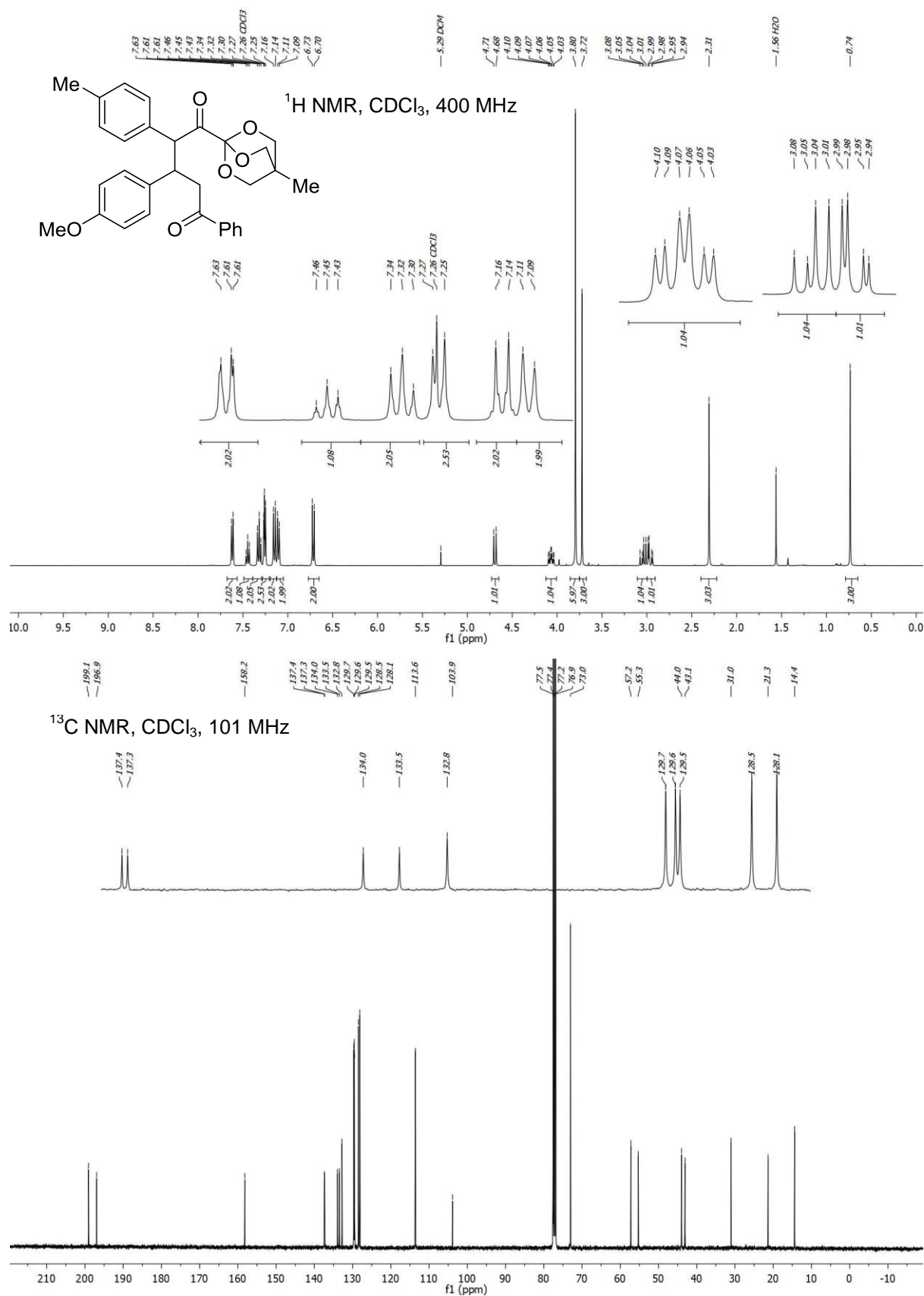


**1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-3,5-diphenyl-2-(*p*-tolyl)pentane-1,5-dione (15a)**

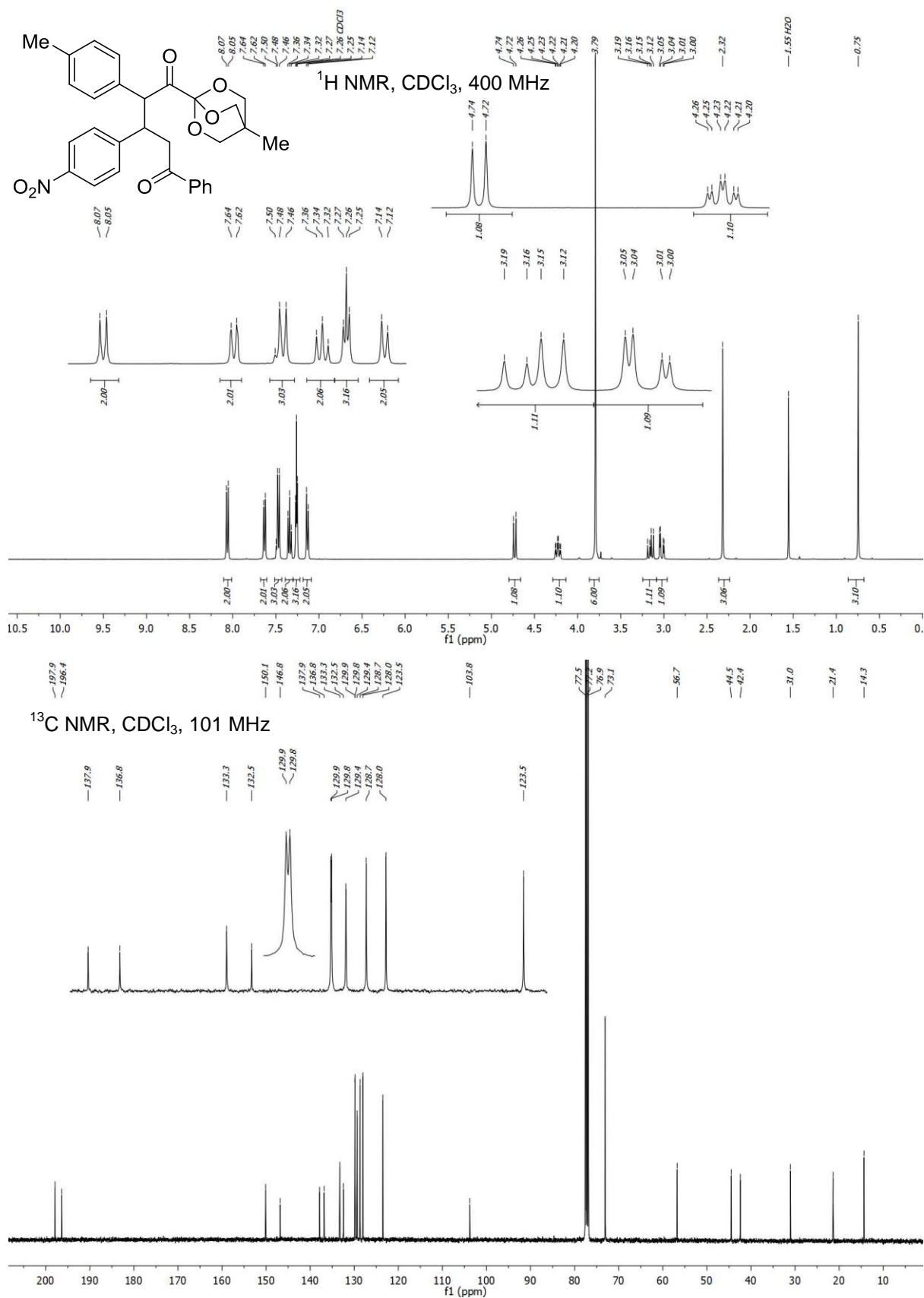




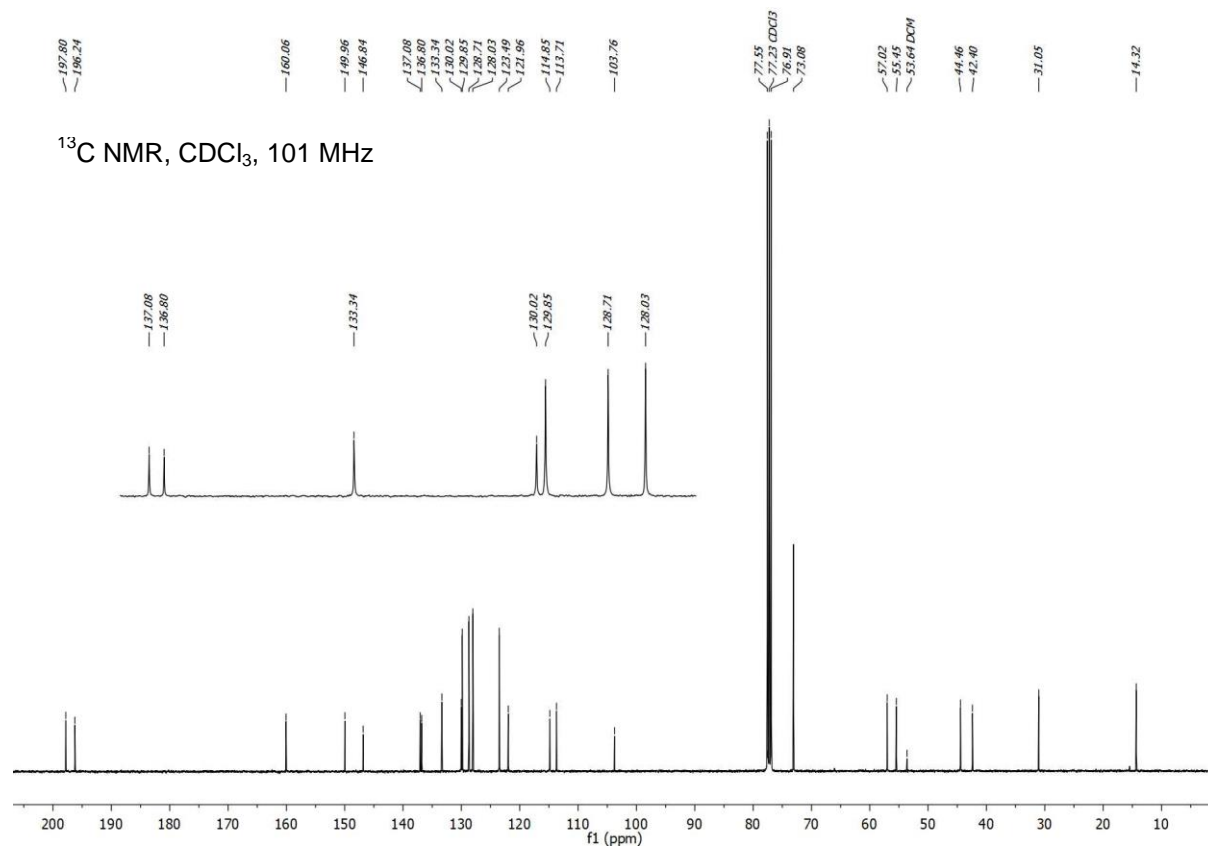
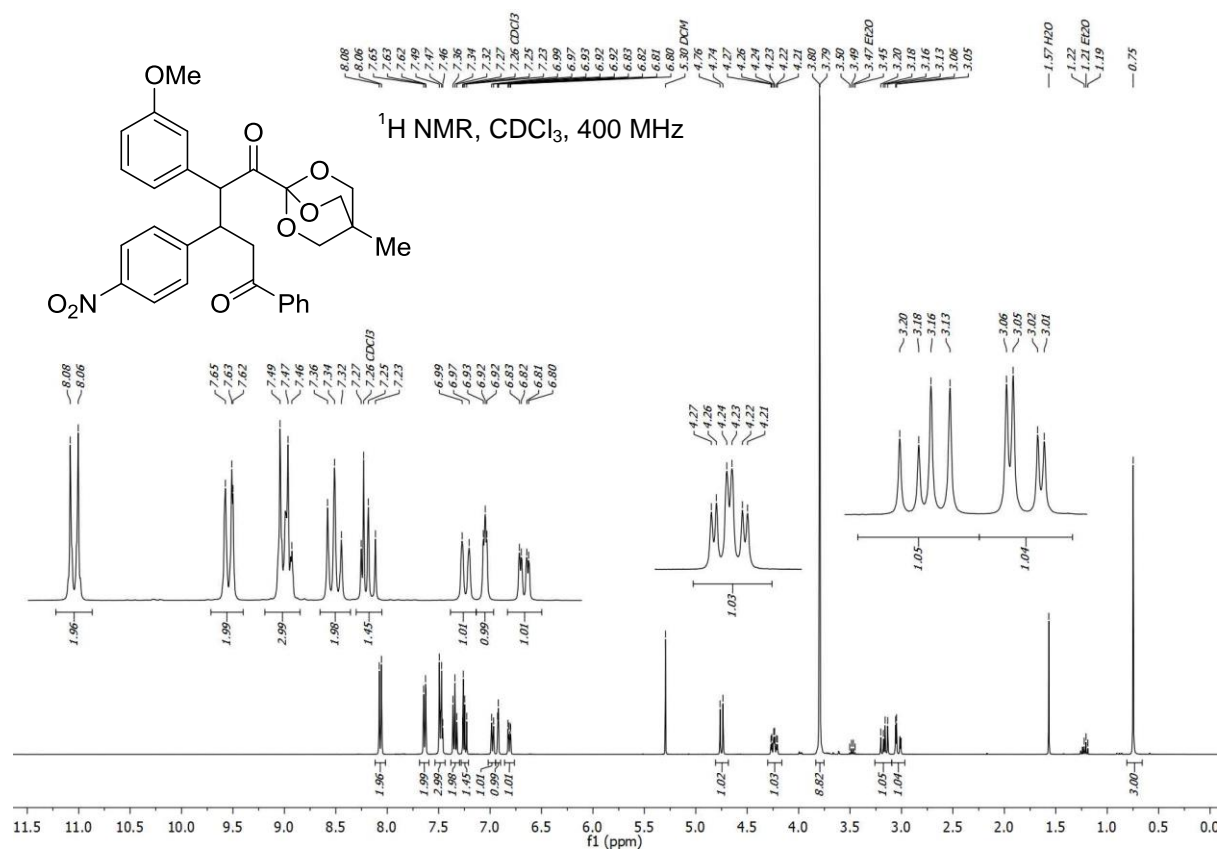
**3-(4-Methoxyphenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-5-phenyl-2-(*p*-tolyl)pentane-1,5-dione (15b)**



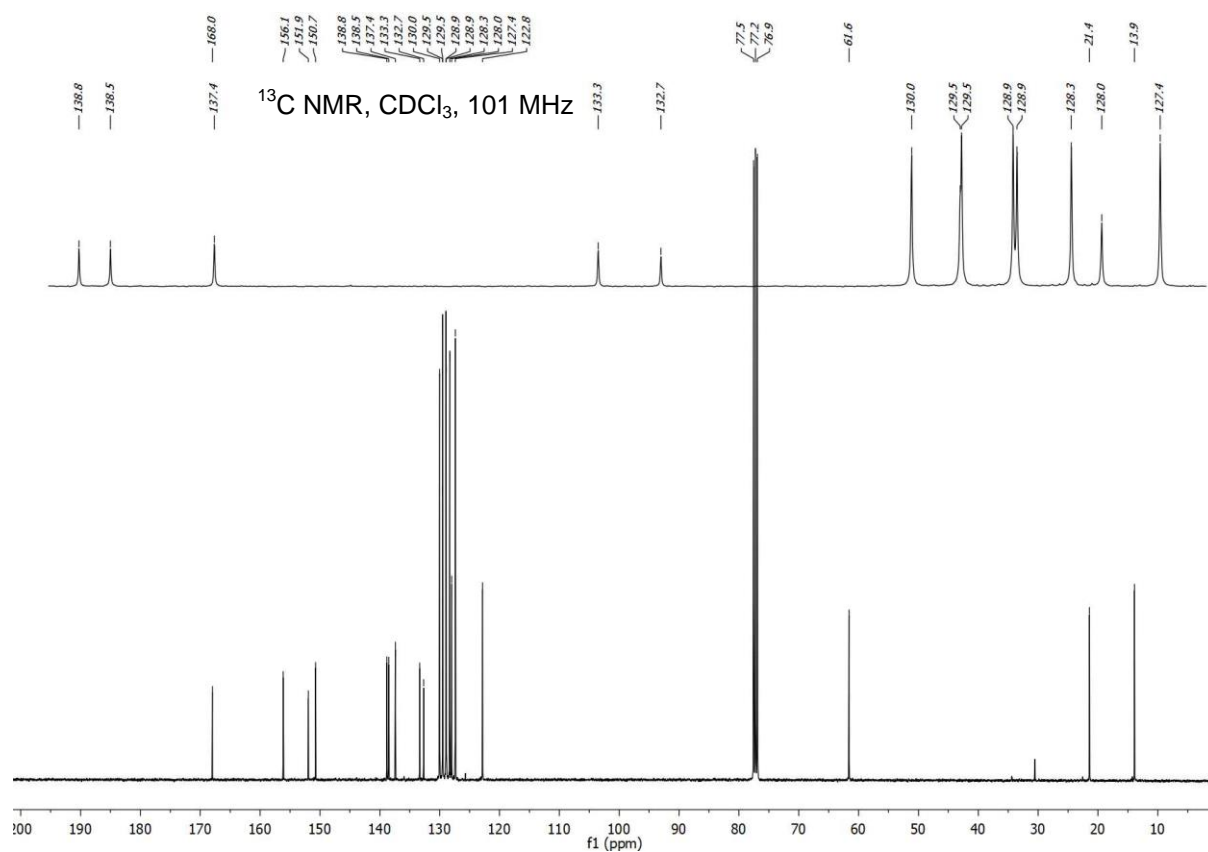
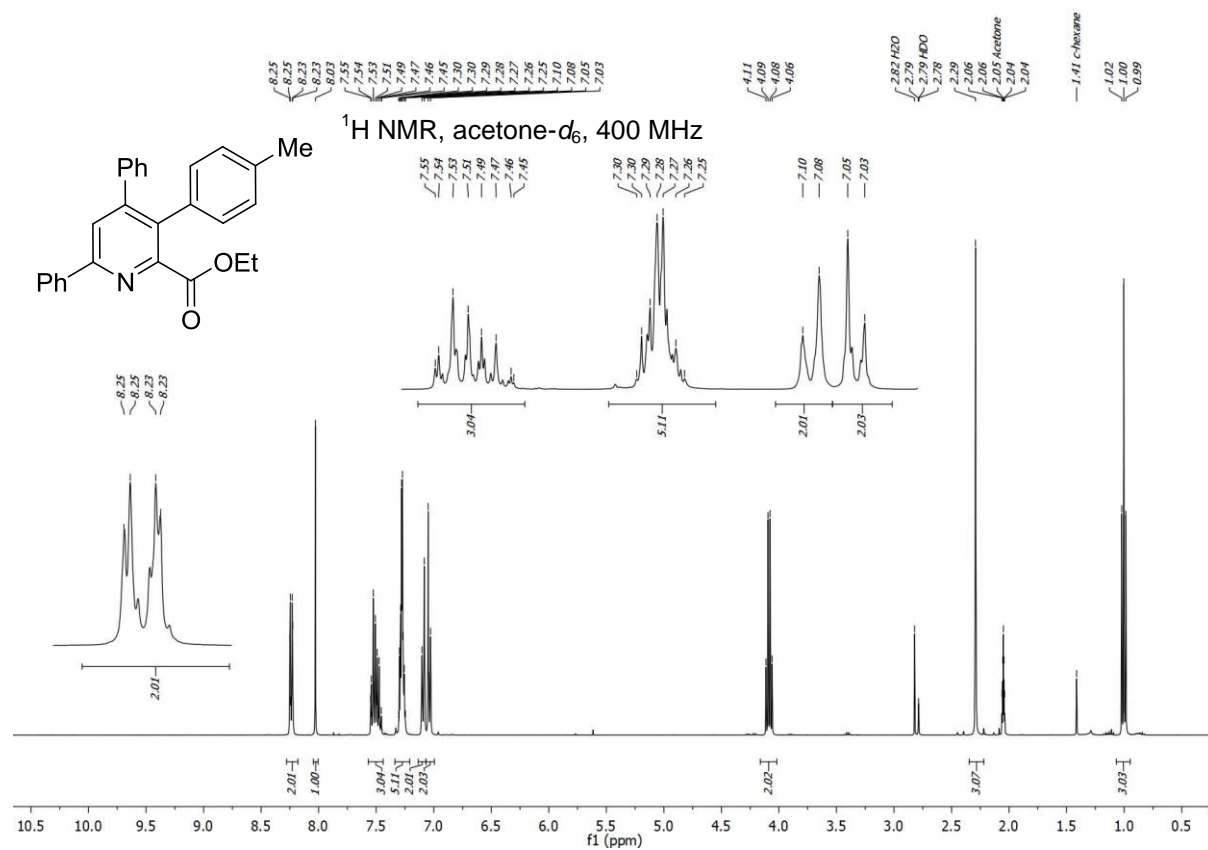
**1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-3-(4-nitrophenyl)-5-phenyl-2-(*p*-tolyl)pentane-1,5-dione (15c)**



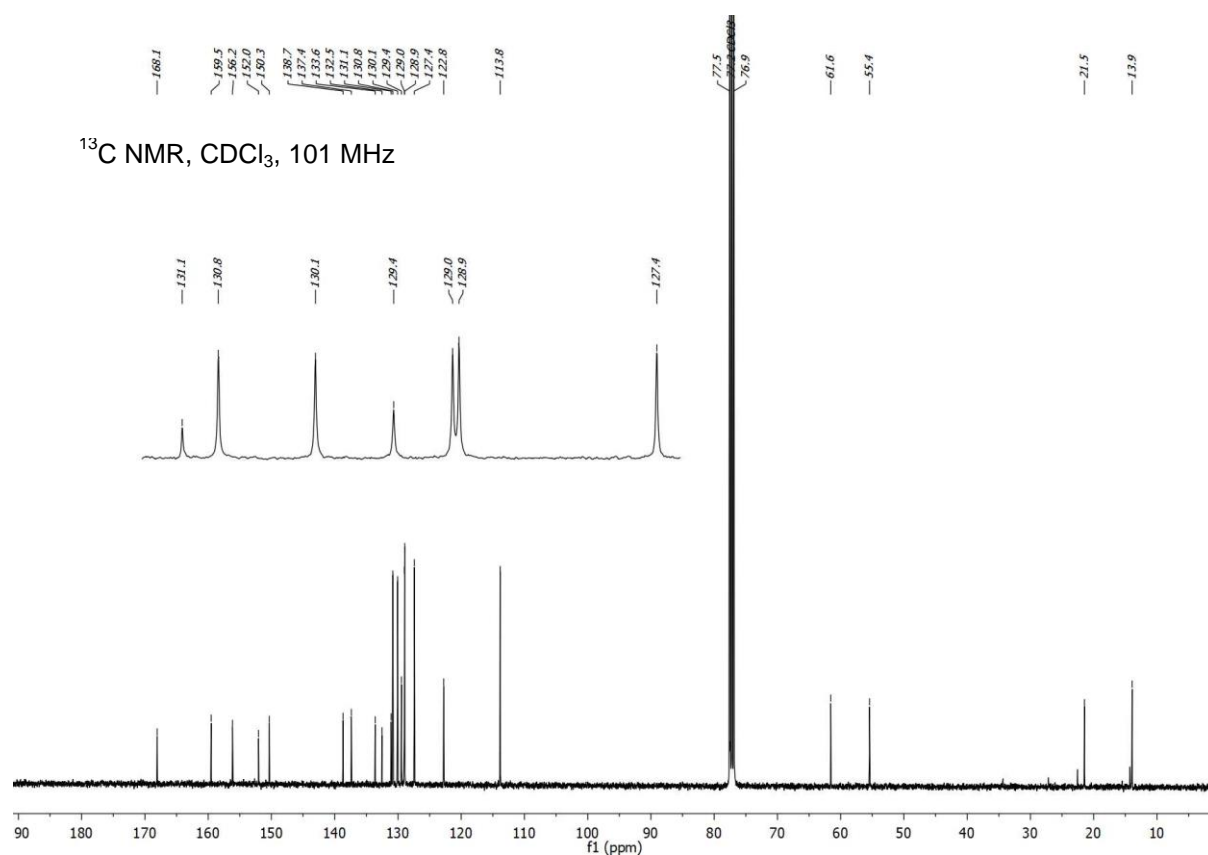
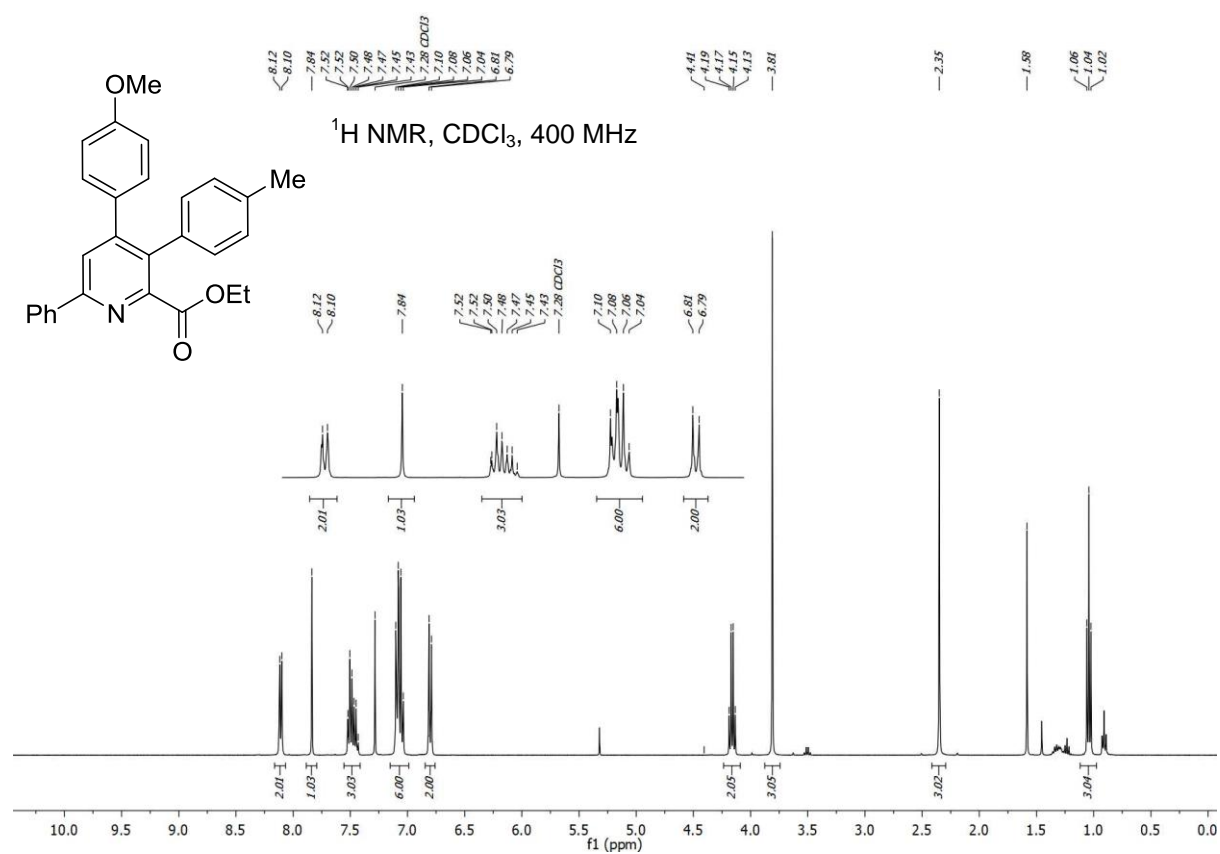
**2-(3-Methoxyphenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-3-(4-nitrophenyl)-5-phenylpentane-1,5-dione (15d)**



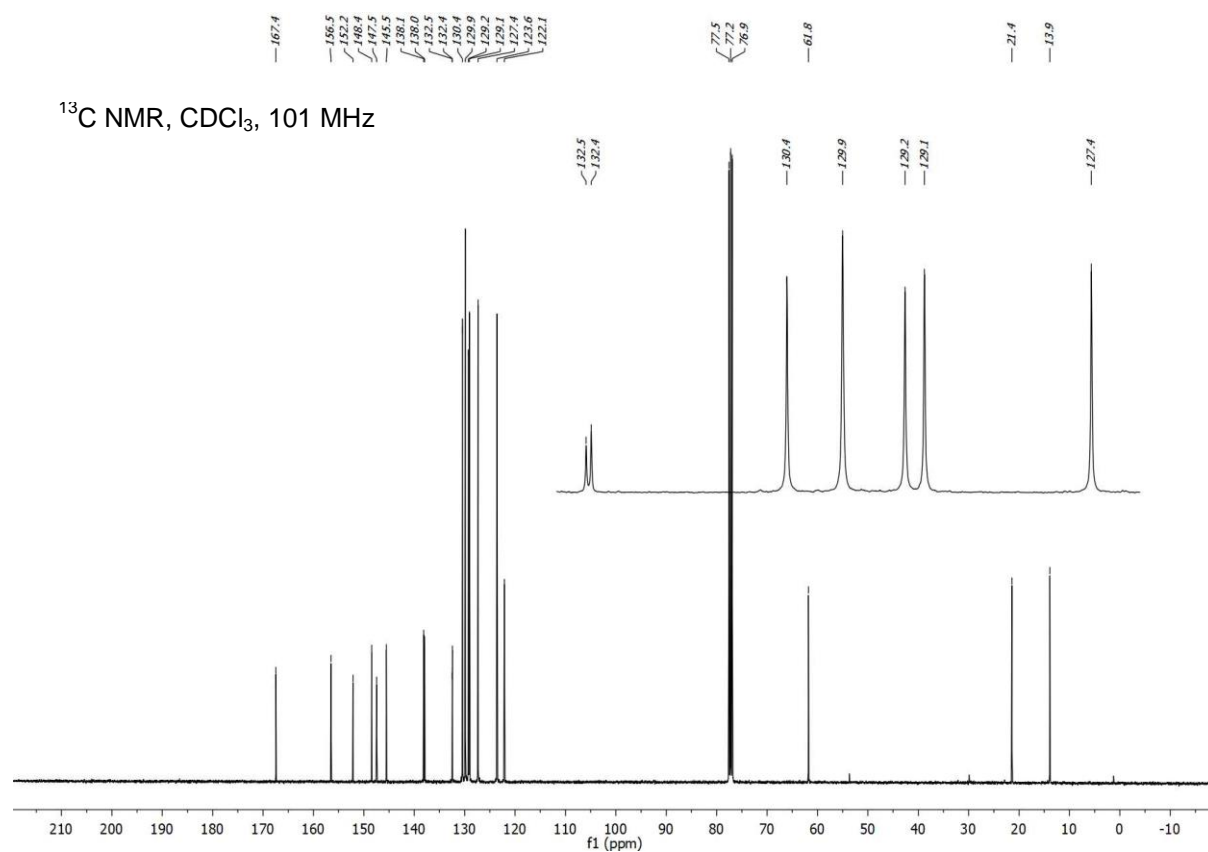
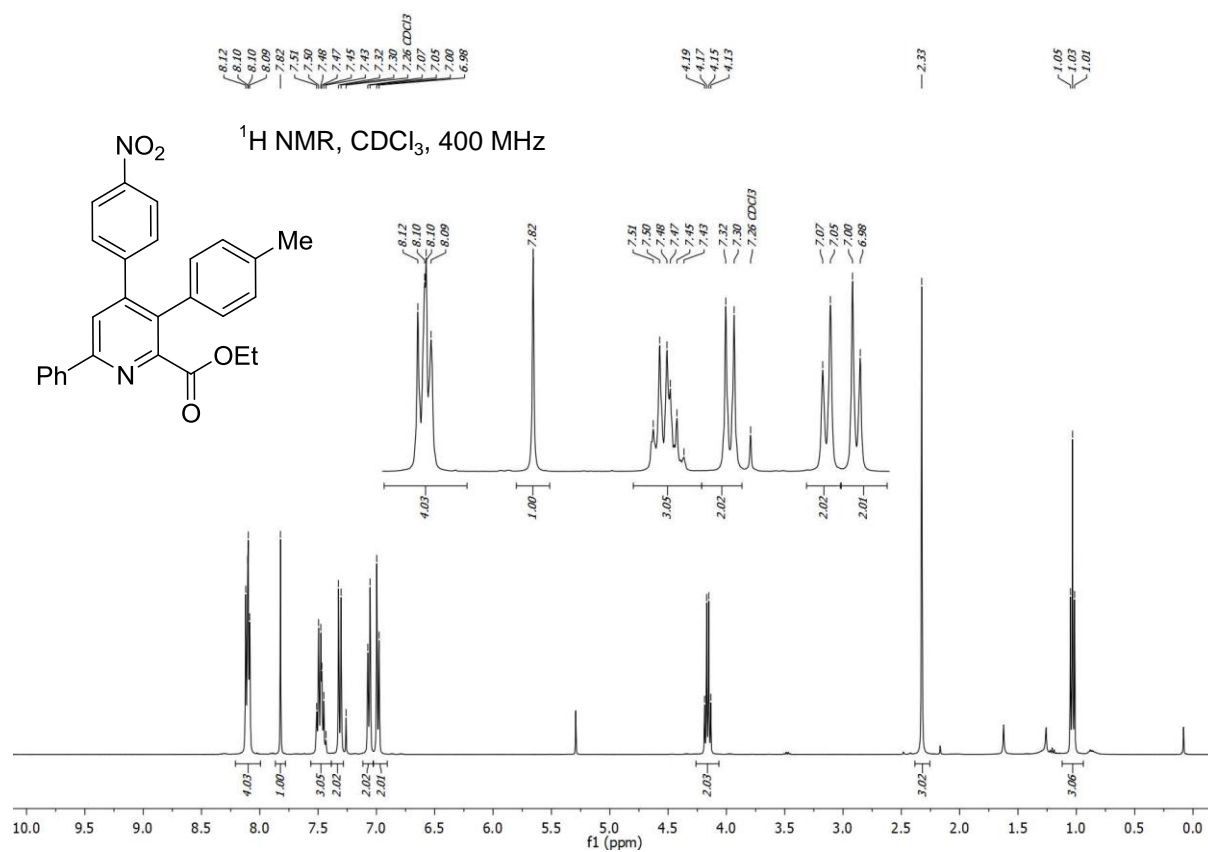
# **Ethyl 4,6-diphenyl-3-(*p*-tolyl)picolinate (16a)**



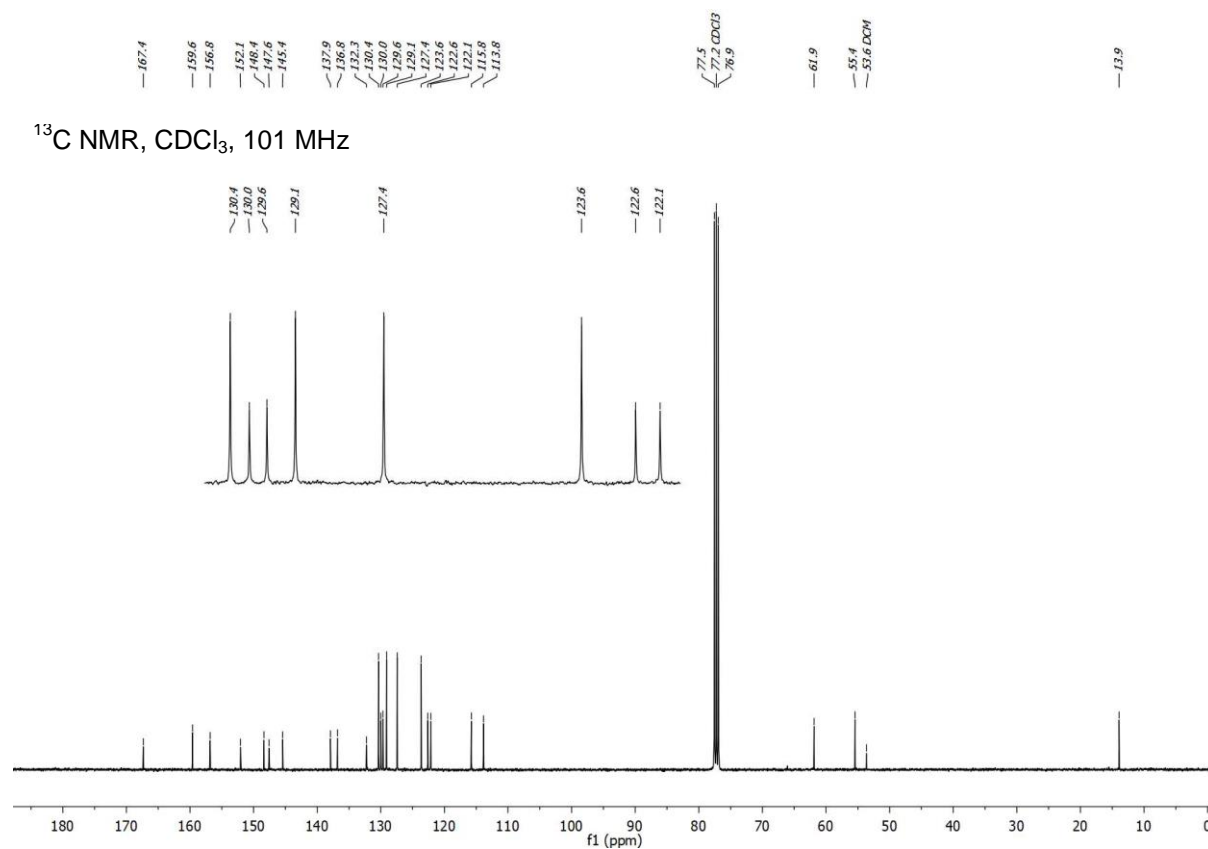
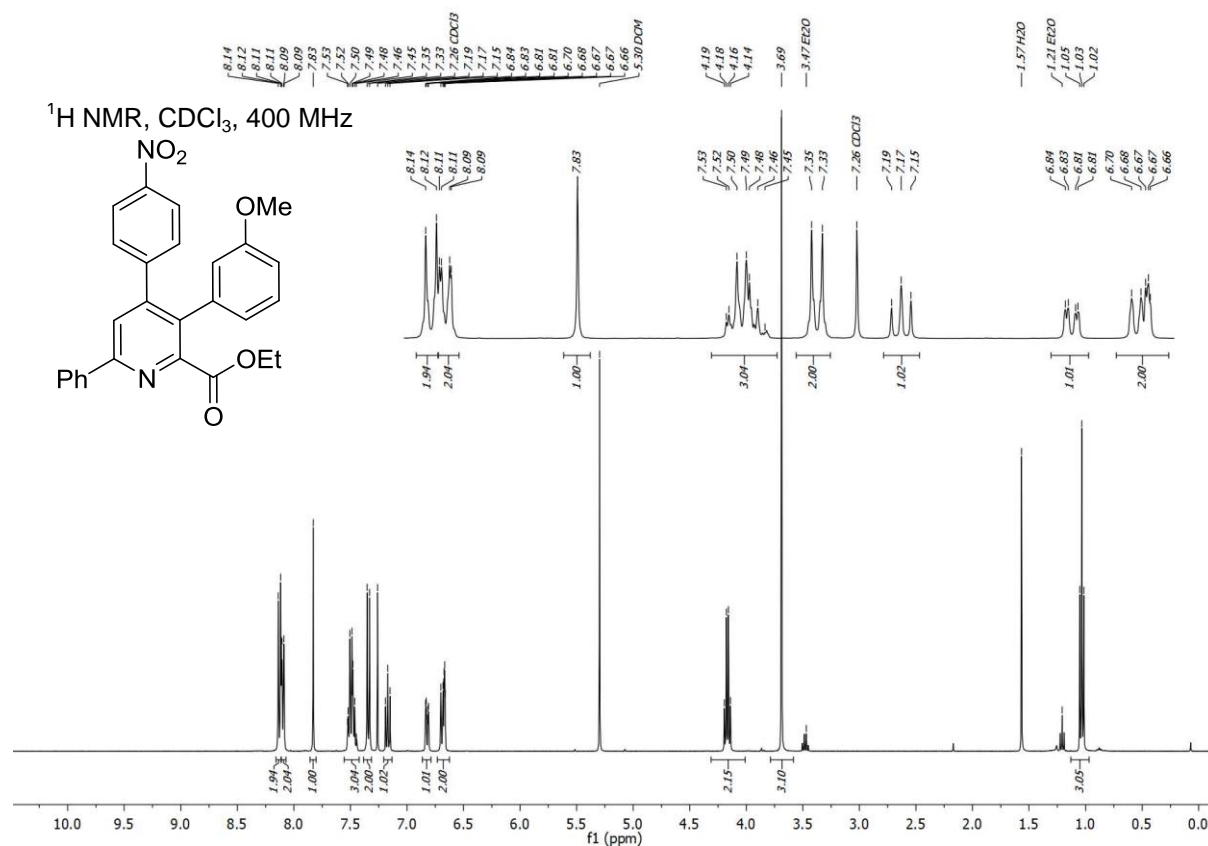
# **Ethyl 4-(4-methoxyphenyl)-6-phenyl-3-(*p*-tolyl)picolinate (16b)**



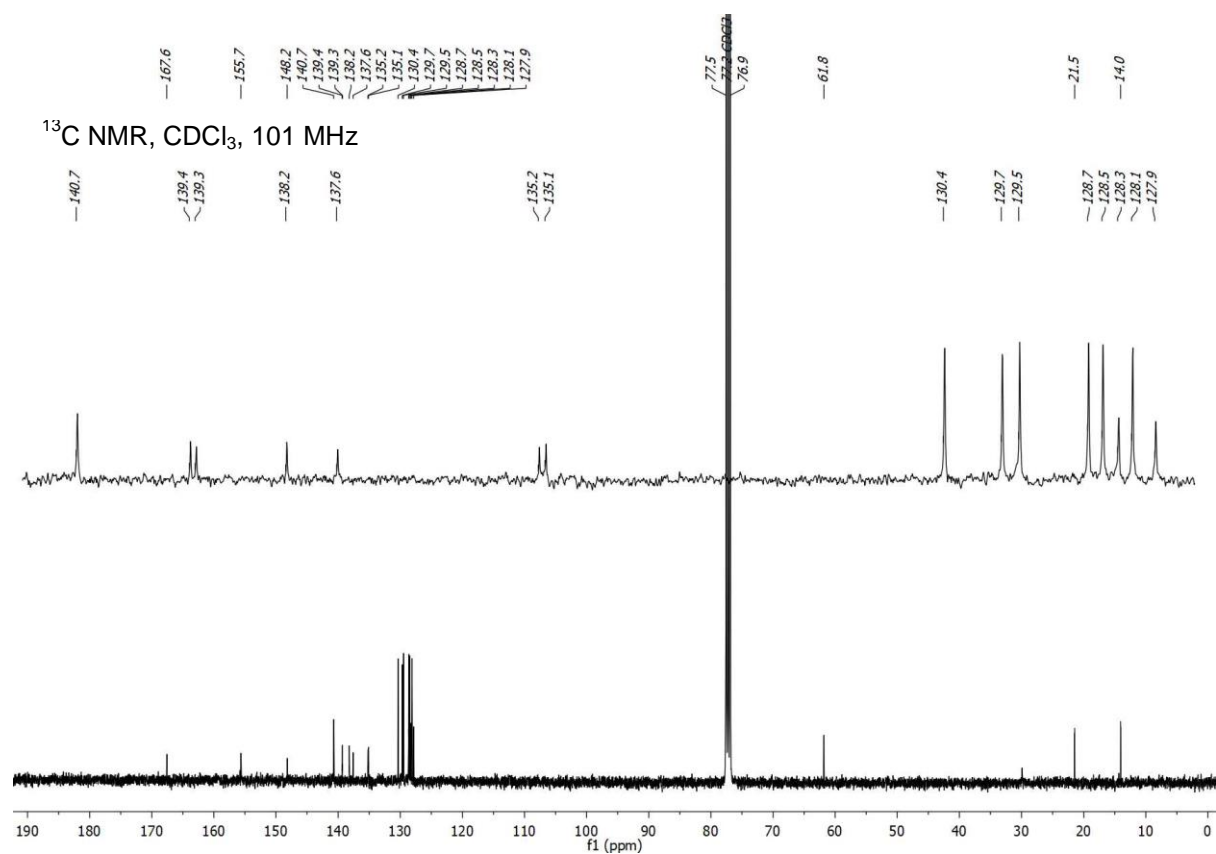
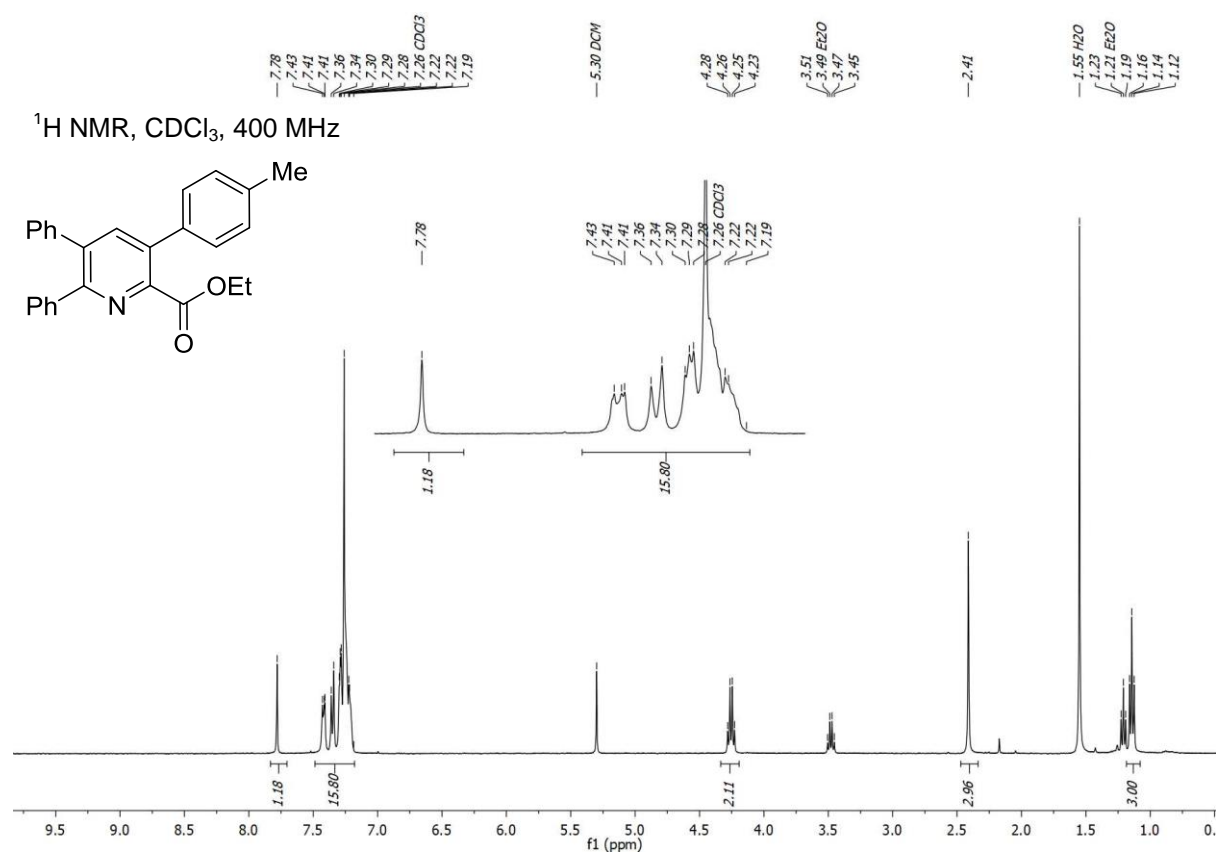
# **Ethyl 4-(4-nitrophenyl)-6-phenyl-3-(*p*-tolyl)picolinate (16c)**



# **Ethyl 3-(3-methoxyphenyl)-4-(4-nitrophenyl)-6-phenylpicolinate (16d)**



# **Ethyl 5,6-diphenyl-3-(*p*-tolyl)picolinate (17a)**





**Ethyl 5-(4-methoxyphenyl)-6-phenyl-3-(*p*-tolyl)picolinate (17b)**

