*Supporting information*

# Gold-silver catalyzed straightforward one pot synthesis of pyrano[3,4-*b*]pyrrol-7(1*H*)-ones.

*Pierre-Olivier Delaye, Julien Petrignet, Emilie Thiery and Jérôme Thibonnet**

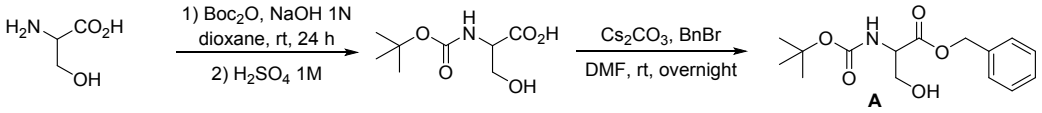
Laboratoire Infectiologie Santé Publique – Equipe de Recherche et Innovation en Chimie Médicinale, UMR-UFR INRA 1282, Faculté des Sciences et Techniques de Tours, Parc de Grandmont, 37200 Tours, France

Fax : (+33)-2-4736-7073 ; e-mail : jerome.thibonnet@univ-tours.fr

**Table of Contents**

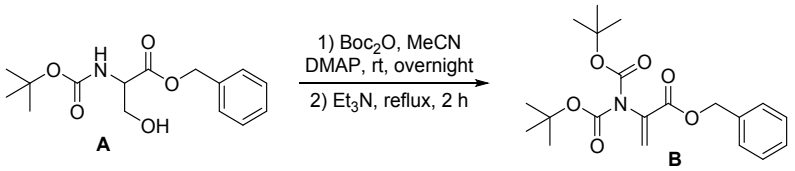
**1. Preparation of Benzyl 3,3-dibromo-2-(*tert*-butoxycarbonylamino)acrylate 1**

**1.1. Benzyl 2-(*tert*-butoxycarbonylamino)-3-hydroxypropanoate (A)**




Compound **A** was prepared from serine in two steps, according to literature.[1] Overall yield without any purification : 92%. $C_{15}H_{21}NO_5$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.43 (s, 9H), 2.39 (bs, 1H), 3.95 (ddd, $J$ = 3.6, 11.2, 27.3 Hz, 2H), 4.41 (bs, 1H), 5.20 (s, 2H), 5.53 (bs, 1H), 7.35 (m, 5H).

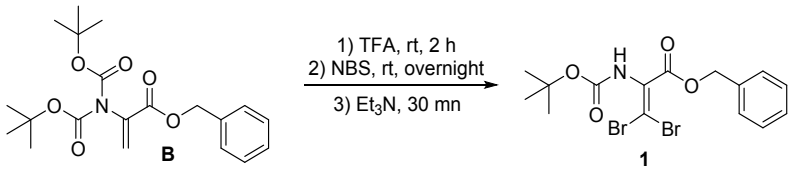
**1.2. Benzyl 2-(bis(*tert*-butoxycarbonyl)amino)acrylate (B)**




Compound **B** was prepared with a modified procedure from literature.[2] To a solution of **A** (12.27 g, 41.6 mmol) in $CH_3CN$ (30 mL) was added dropwise $Boc_2O$ (2.2 equiv., 91.52 mmol, 19.9 g) in solution in 10 mL of $CH_3CN$. DMAP (0.1 equiv., 4.16 mmol, 507 mg) was then added in one portion, and the reaction mixture stirred overnight at room temperature before $Et_3N$ was added (1 equiv., 41.6 mmol, 5.7 mL). The reaction was then refluxed for two hours. Cold reaction mixture was then diluted with 60 mL of $Et_2O$, washed with two times 50 mL of HCl 2M, two times 50 mL of aqueous saturated solution of $NaHCO_3$, and finally two times 50 mL of brine. Organic phase was dried over $MgSO_4$ and solvents were evaporated under vacuum. Crude product (12.27 g, 78%) was obtained as white solid and use directly in the next step without purification. $C_{20}H_{27}NO_6$; Rf (PE/$Et_2O$: 90/10) = 0.15; m.p.: 59–61 °C; IR (ATR): $\nu$ = 2991, 1791, 1717, 1278, 1255, 1152, 1089; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.41 (s, 18H), 5.24 (s, 2H), 5.67 (s, 1H), 6.39 (s, 1H), 7.31-7.38 (m, 5H).

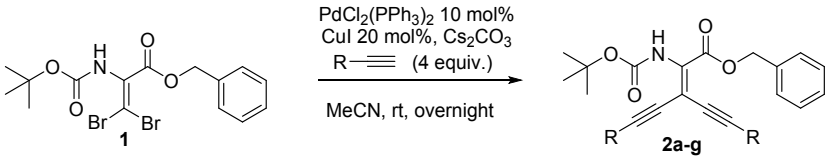
[1] (a) F. Corzana, J. H. Busto, G. Jiménez-Osés, J. L. Asensio, J. Jiménez-Barbero, J. M. Peregrina, A. Avenoza, *J. Am. Chem. Soc.,* 2006, **128**, 14640. (b) F. Friscourt, C. J. Fahrni, G.-J. Boons, *J. Am. Chem. Soc.,* 2012, **134**, 18809.
[2] P. M. T. Ferreira, H. L. S. Maia, L. S. Monteiro, J. Sacramento, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3697.

**1.3. Benzyl 3,3-dibromo-2-(*tert*-butoxycarbonylamino)acrylate 1**

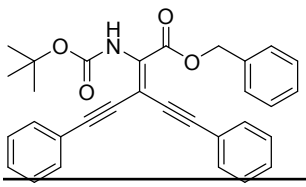



Compound **1** was prepared following literature[3] to yield the product after purification by flash chromatography on silica gel (PE/$Et_2O$: 80/20) as a white solid (76%). $C_{15}H_{17}Br_2NO_4$; Rf (PE/$Et_2O$: 80/20) = 0.33; m.p.: 97-99 °C; IR (ATR): $\nu$ = 3314, 2977, 2935, 1736, 1717, 1477, 1250, 1150; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.42 (s, 9H), 5.26 (s, 2H), 7.34-7.49 (m, 5H), 8.18 (bs, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 28.1 ($CH_3$), 68.3 ($CH_2$), 82.6 (Cq), 128.6 (CH), 128.8 (CH), 132.7 (Cq), 134.7 (Cq), 151.0 (Cq), 161.9 (Cq); HRMS (ESI) calcd. for $C_{15}H_{18}Br_2NO_4$ $[M+H]^+$: 433.95971; found: 433.96011.

**2. Synthetic procedures and analytical data of compounds 2**



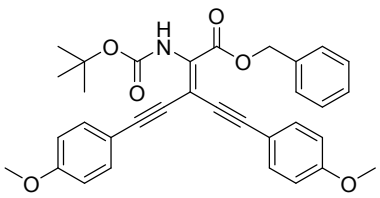

To a solution of **1** (3 mmol) in dry and degassed $CH_3CN$ (20 mL) were successively added $(PPh_3)_2$ $PdCl_2$ (10 mol%, 0.3 mmol, 210 mg), CuI (20 mol%, 0.6 mmol, 114 mg), alkyne (4 equiv., 12 mmol) and $Cs_2CO_3$ (1.4 equiv., 4.2 mmol, 1.36 g). The reaction mixture was stirred overnight at room temperature, and then filtrated on a pad of celite with EtOAc. Organic phase was washed with brine (20 mL) and water (20 mL), dried over $MgSO_4$ and solvents were evaporated under vacuum. The residues were purified by flash chromatography on silica gel to give compounds **2a-g**.



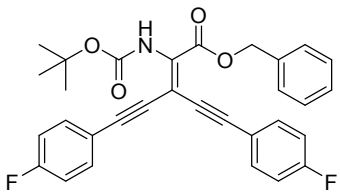
**Benzyl 2-(*tert*-butoxycarbonylamino)-5-phenyl-3-(phenylethynyl)pent-2-en-4-ynoate (2a).** Eluant : PE/$Et_2O$ 95/5→80/20, yield = 54%; $C_{31}H_{27}NO_4$; Rf (PE/$Et_2O$: 90/10) = 0.11; Orange solid ; m.p.: 111-113 °C; IR (ATR): $\nu$ = 3308,

[3] A. S. Abreu, N. O. Silva, P. M. T. Ferreira, M.-J. R. P. Queiroz, *Tetrahedron Lett.,* 2003, **44**, 3377.

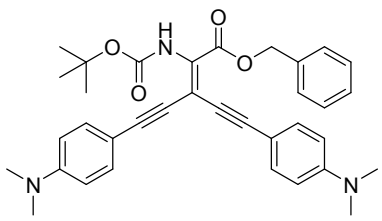
3035, 2974, 2199, 1728, 1692, 1150, 749, 686 ; $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.50 (s, 9H), 5.37 (s, 2H), 7.00 (bs, 1H), 7.28-7.54 (m, 15H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 28.2 ($CH_3$), 68.0 ($CH_2$), 82.3 (Cq), 82.8 (Cq), 83.4 (Cq), 93.0 (Cq), 98.5 (Cq), 122.0 (Cq), 122.7 (Cq), 128.3 (CH), 128.4 (CH), 128.59 (CH), 128.65 (CH), 129.4 (CH), 131.8 (CH), 131.9 (CH), 135.2 (Cq), 140.4 (Cq), 150.9 (Cq), 162.8 (Cq); HRMS (ESI) calcd. for $C_{31}H_{28}NO_4$ $[M+H]^+$: 478.20128; found: 478.20079.



**Benzyl 2-(*tert*-butoxycarbonylamino)-5-(4-methoxyphenyl)-3-((4-methoxyphenyl)ethynyl)pent-2-en-4-ynoate (2b).** Eluant: PE/AcOEt 80/20→70/30, yield = 66%; $C_{33}H_{31}NO_6$; Rf (PE/AcOEt: 80/20) = 0.17; Orange oil; IR (ATR): $\nu$ = 3390, 2976, 2934, 2837, 2195, 1725, 1508, 1246, 1146, 829; $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.47 (s, 9H), 3.78 (s, 3H), 3.79 (s, 3H), 5.33 (s, 2H), 6.78 (m, 2H), 6.86 (m, 2H), 6.95 (bs, 1H), 7.25-7.29 (m, 5H), 7.40-7.45 (m, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$) : $\delta$ = 28.1 ($CH_3$), 55.3 ($CH_3$), 55.4 ($CH_3$), 67.7 ($CH_2$), 81.5 (Cq), 82.42 (Cq), 82.44 (Cq), 93.3 (Cq), 98.7 (Cq), 113.9 (CH), 114.0 (Cq), 114.2 (CH), 114.8 (Cq), 128.3 (CH), 128.5 (CH), 133.2 (CH), 133.4 (CH), 135.3 (Cq) 138.9 (Cq), 151.1 (Cq), 159.9 (Cq), 160.4 (Cq), 163.0 (Cq); HRMS (ESI) calcd. for $C_{33}H_{32}NO_6$ $[M+H]^+$: 538.22241; found: 538.22271.

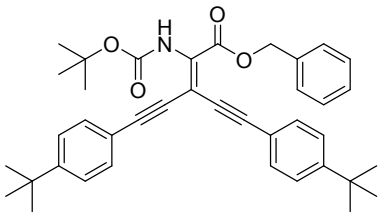


**Benzyl 2-(*tert*-butoxycarbonylamino)-5-(4-fluorophenyl)-3-((4–fluorophenyl)ethynyl)pent-2-en-4-ynoate (2c).** Eluant: PE/$Et_2O$ 90/10→80/20, yield = 44%; $C_{31}H_{25}F_2NO_4$; Rf (PE/AcOEt : 90/10) = 0.08; Pale yellow solid; m.p.: 163-165 °C; IR (ATR): ν = 3320, 2978, 2937, 2201, 1732, 1693, 1505, 1221, 1152, 838; $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.48 (s, 9H), 5.34 (s, 2H), 6.92-7.50 (m, 13H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 28.2 ($CH_3$), 68.0 ($CH_2$), 82.0 (Cq), 82.9 (Cq), 83.0 (Cq), 92.0 (Cq), 97.5 (Cq), 115.6 (d, $^{2}J_{C\text{-}F}$ = 22.1 Hz, CH), 116.0 (d, $^{2}J_{C\text{-}F}$ = 22.1 Hz, CH), 118.1 (d, $^{4}J_{C\text{-}F}$ = 3.6 Hz, Cq), 118.8 (d, $^{4}J_{C\text{-}F}$ = 3.5 Hz, Cq), 128.5 (CH), 128.6 (CH), 133.7 (d, $^{3}J_{C\text{-}F}$ = 8.4 Hz, CH), 133.9 (d, $^{3}J_{C\text{-}F}$ = 8.6 Hz, CH), 135.2 (CH), 140.5 (CH), 150.9 (CH), 162.7 (d, $^{1}J_{C\text{-}F}$ = 250.2 Hz, Cq), 162.8 (Cq), 163.2 (d, $^{1}J_{C\text{-}F}$ = 251.4 Hz, Cq); $^{19}$F NMR (282 MHz, $CDCl_3$): $\delta$ = -110.6, -109.4; HRMS (ESI) calcd. for $C_{31}H_{26}F_2NO_4$ $[M+H]^+$: 514.18244; found: 514.18275.

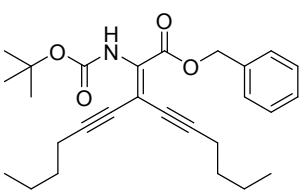


**Benzyl 2-(*tert*-butoxycarbonylamino)-5-(4 (dimethylamino)-phenyl)-3-((4-(dimethylamino)phenyl)ethynyl)pent-2-en-4-ynoate (2d).** Eluant: PE/AcOEt 70/30→50/50, yield = 66%; $C_{35}H_{37}N_3O_4$; Rf (PE/AcOEt: 70/30) = 0.43; orange solid; m.p.: 179-181 °C ; IR (ATR): ν = 3383, 2982, 2896, 2806, 2194, 1718, 1603, 1520, 1449, 1145; $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.47 (s, 9H), 2.95 (s, 6H), 2.97 (s, 6H), 6.56 (m, 2H), 6.62 (m, 2H), 6.85 (bs,

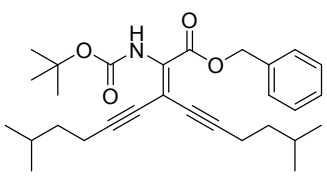
1H), 7.22-7.45 (m, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 28.2 ($CH_3$), 40.16 ($CH_3$), 40.21 ($CH_3$), 67.5 ($CH_2$), 81.6 (Cq), 82.0 (Cq), 82.3 (Cq), 95.0 (Cq), 100.3 (Cq), 108.4 (Cq), 109.6 (Cq), 111.6 (CH), 111.7 (Cq), 128.2 (CH), 128.47 (CH), 128.51 (CH), 133.0 (CH), 133.1 (CH), 135.5 (Cq), 136.7 (Cq), 150.3 (Cq), 150.7 (Cq), 151.5 (Cq), 163.3 (Cq); HRMS (ESI) calcd. for $C_{35}H_{38}N_3O_4$ $[M+H]^+$: 564.28568; found: 564.28603.



**Benzyl 2-(*tert*-butoxycarbonylamino)-5-(4-*tert*-butylphenyl)-3-((4-*tert*-butylphenyl)ethynyl)pent-2-en-4-ynoate (2e).** Eluant: PE/$Et_2O$ 80/20, yield = 62%; white solid; $C_{39}H_{43}NO_4$; Rf (PE/$Et_2O$: 80/20) = 0.34; m.p.: 151-153 °C; IR (ATR): $\nu$ = 3401, 2963, 2869, 2200, 1729, 1455, 1147, 833; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.31 (s, 9H), 1.32 (s, 9H), 1.48 (s, 9H), 5.34 (s, 2H), 6.94 (bs, 1H), 7.27-7.47 (m, 13H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 28.2 ($CH_3$), 31.2 ($CH_3$), 31.3 ($CH_3$), 34.9 (Cq), 35.0 (Cq), 67.9 (Cq), 81.9 (Cq), 82.6 (Cq), 82.9 (Cq), 93.3 (Cq), 98.7 (Cq), 119.0 (Cq), 119.8 (Cq), 125.3 (CH), 125.6 (CH), 128.3 (CH), 128.58 (CH), 128.63 (CH), 131.6 (CH), 131.7 (CH), 135.3 (Cq), 139.9 (Cq), 151.0 (Cq), 152.0 (Cq), 152.8 (Cq), 162.9 (Cq); HRMS (ESI) calcd. for $C_{39}H_{44}NO_4$ $[M+H]^+$: 590.32649; found: 590.32672.



**Benzyl 2-(*tert*-butoxycarbonylamino)-3-(hex-1-ynyl)non-2-en-4-ynoate (2f).** Eluant: PE/$Et_2O$ 90/10→80/20, yield = 69%; orange oil; $C_{27}H_{35}NO_4$; Rf (PE/$Et_2O$: 80/20) = 0.29; IR (ATR): $\nu$ = 3424, 2958, 2933, 2872, 2217, 1729, 1455, 1149, 733; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.87 (t, $J$ = 7.2 Hz, 3H), 0.93 (t, $J$ = 7.2 Hz, 3H), 1.31-1.60 (m, 17H), 2.20 (t, $J$ = 6.9Hz, 2H), 2.42 (t, $J$ = 7.0Hz, 2H), 5.28 (s, 2H), 6.73 (bs, 1H), 7.30-7.43 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 13.70 ($CH_3$), 13.73 ($CH_3$), 19.4 ($CH_2$), 19.5 ($CH_2$), 22.1 ($CH_2$), 28.2 ($CH_3$), 30.5 ($CH_2$), 30.6 ($CH_2$), 67.5 ($CH_2$), 74.8 (Cq), 82.2 (Cq), 94.6 (Cq), 100.2 (Cq), 128.3 (CH), 128.5 (CH), 128.6 (CH), 135.5 (Cq), 139.0 (Cq), 151.3 (Cq), 163.2 (Cq); HRMS (ESI) calcd. for $C_{27}H_{36}NO_4$ $[M+H]^+$: 438.26389; found: 438.26418.

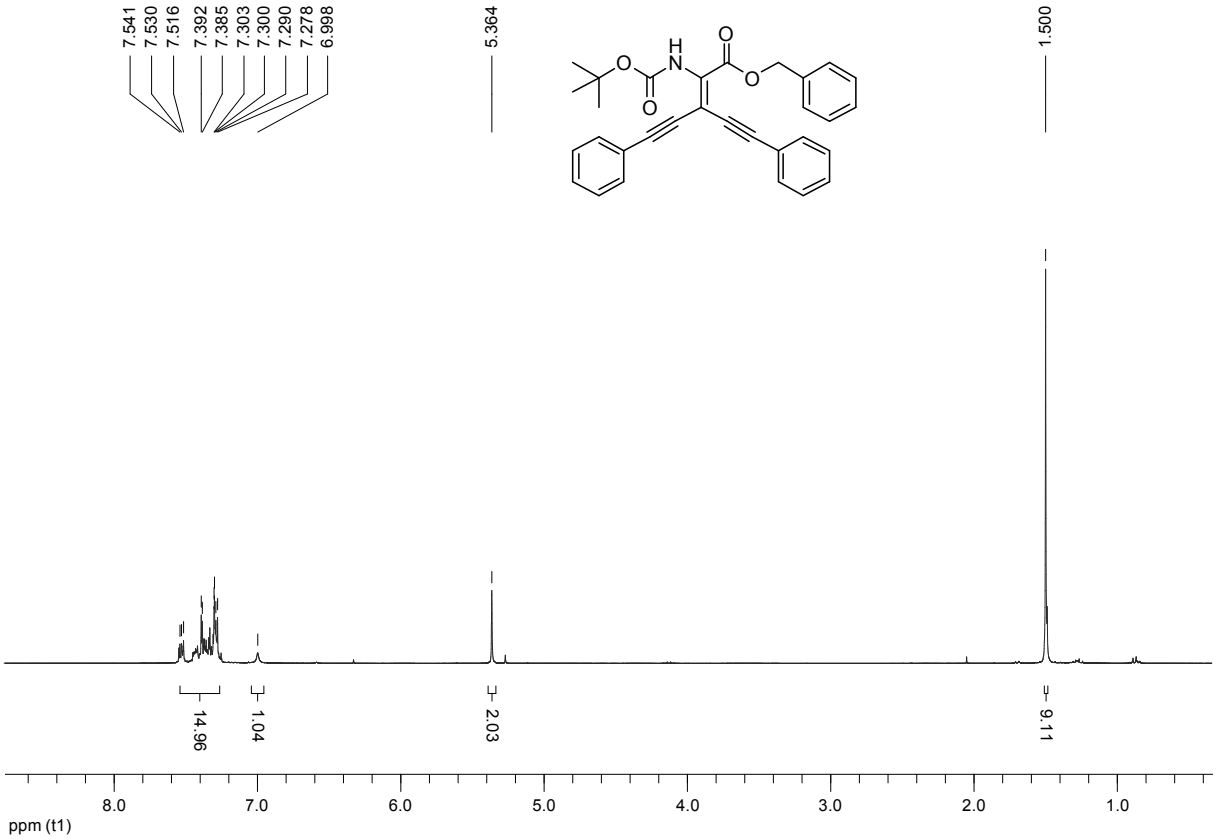


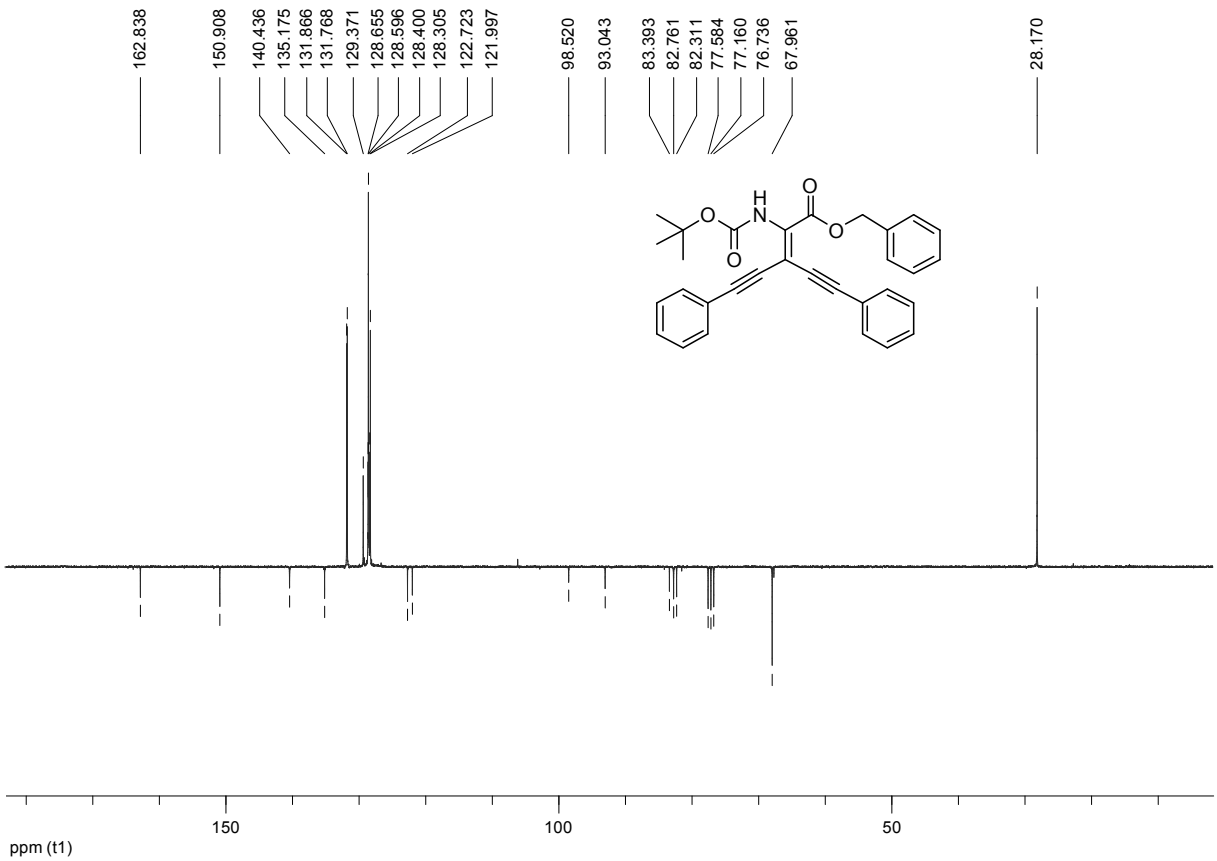
**Benzyl 2-(*tert*-butoxycarbonylamino)-8-methyl-3-(5-methylhex-1-ynyl)non-2-en-4-ynoate (2g).** Eluant: PE/$Et_2O$ 90/10, yield = 53%; Rf (PE/$Et_2O$: 90/10) = 0.16; orange oil; $C_{29}H_{39}NO_4$; IR (ATR): $\nu$ = 3397, 2955, 2933, 2869, 2218, 1732, 1455, 1149; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.85 (d, $J$ = 6.6 Hz, 3H), 0.92 (d, $J$ = 6.6 Hz, 3H), 1.33 (q, $J$ = 6.9 Hz, 2H), 1.43-1.50 (m, 11H), 1.55-1.77 (m, 2H), 2.20 (t, $J$ = 7.5 Hz, 2H), 2.42 (t, $J$ = 7.2 Hz, 2H), 5.28 (s, 2H), 6.72 (bs, 1H), 7.30-7.43 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 17.7 ($CH_2$), 17.9 ($CH_2$), 22.3 ($CH_3$), 27.39 (CH), 27.41 (CH), 28.2 ($CH_3$), 37.3 ($CH_2$), 37.4 ($CH_2$), 67.5 ($CH_2$), 74.7 (Cq), 74.8 (Cq), 82.1 (Cq), 94.6 (Cq), 100.2 (Cq), 128.3 (CH), 128.48 (CH),

128.55 (CH), 135.5 (Cq), 139.0 (Cq), 151.3 (Cq), 163.1 (Cq); HRMS (ESI) calcd. for $C_{29}H_{40}NO_4$ $[M+H]^+$: 466.29519; found: 466.29521.

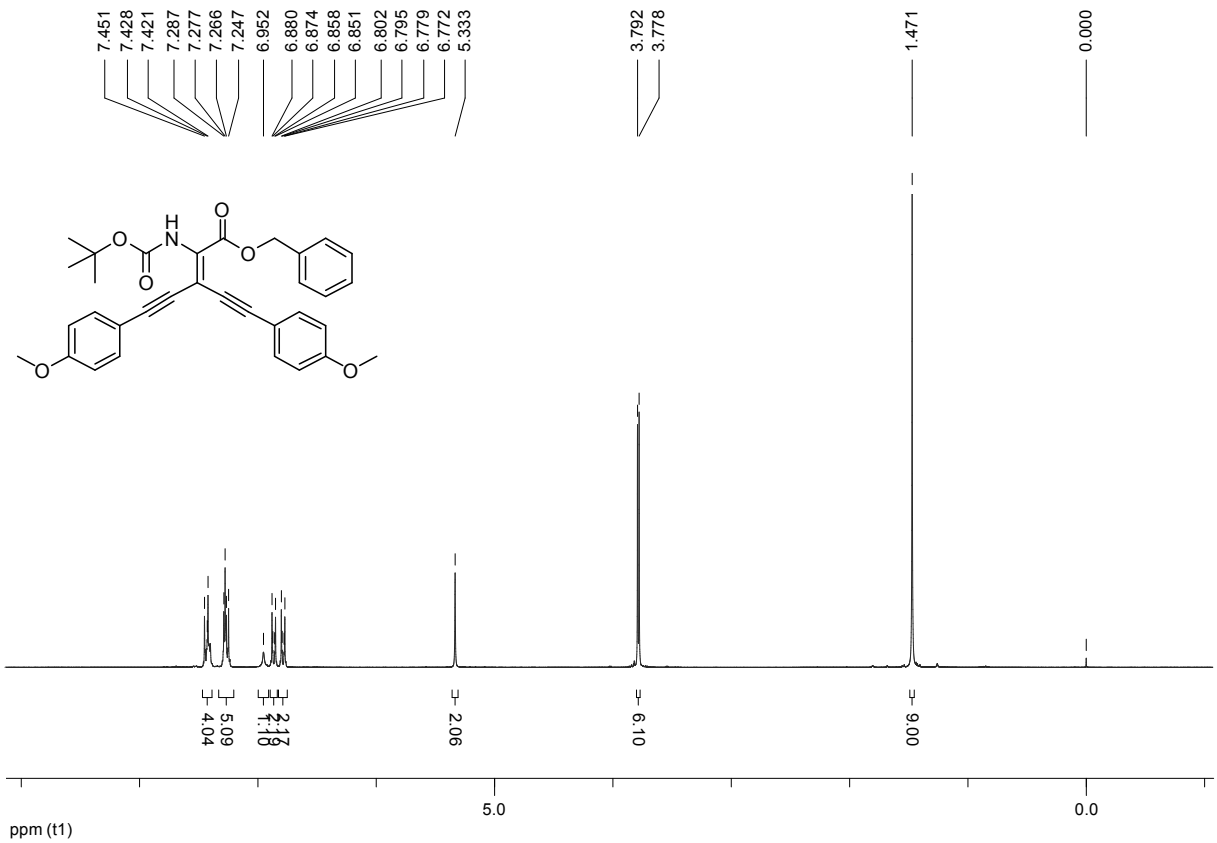
**3.$^1$H NMR and $^{13}$C NMR spectra of compounds 2, 3 and 4.**

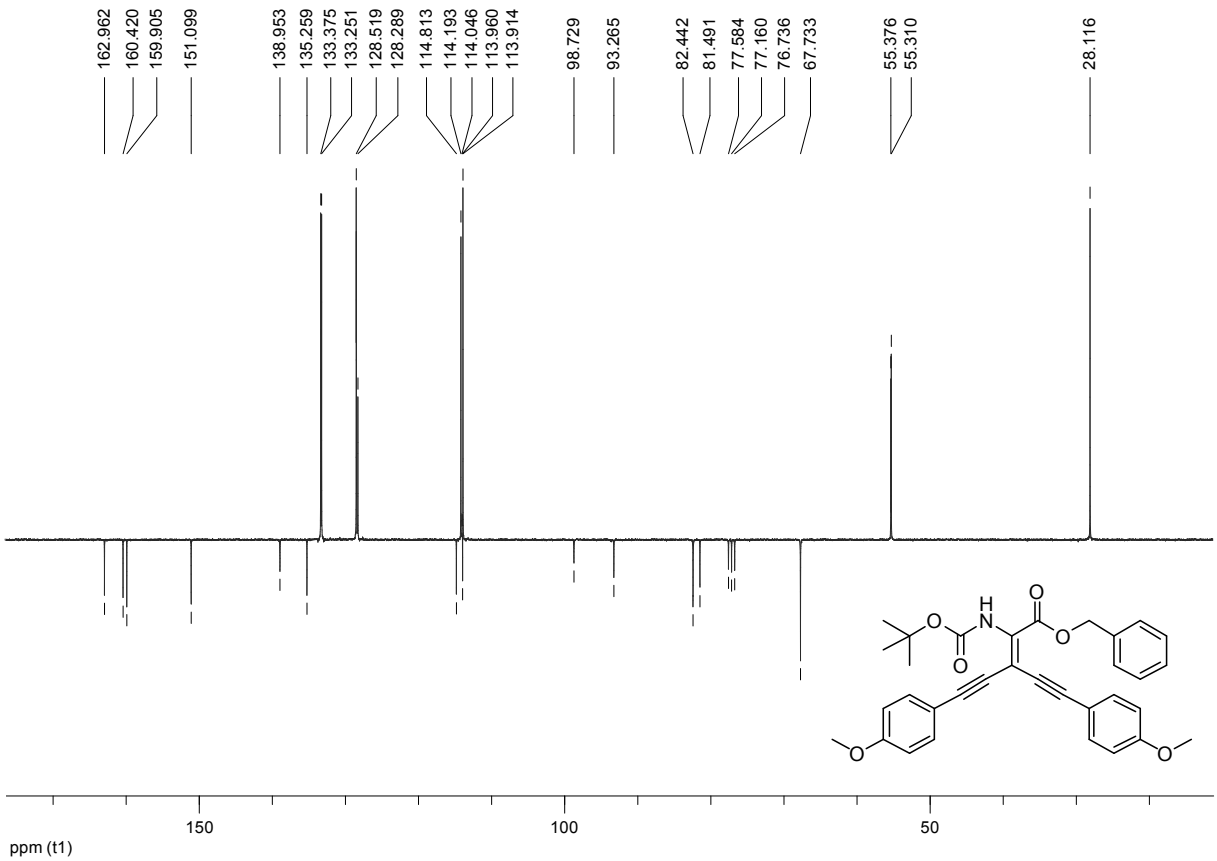
**Benzyl 2-(*tert*-butoxycarbonylamino)-5-phenyl-3-(phenylethynyl)pent-2-en-4-ynoate (2a)**



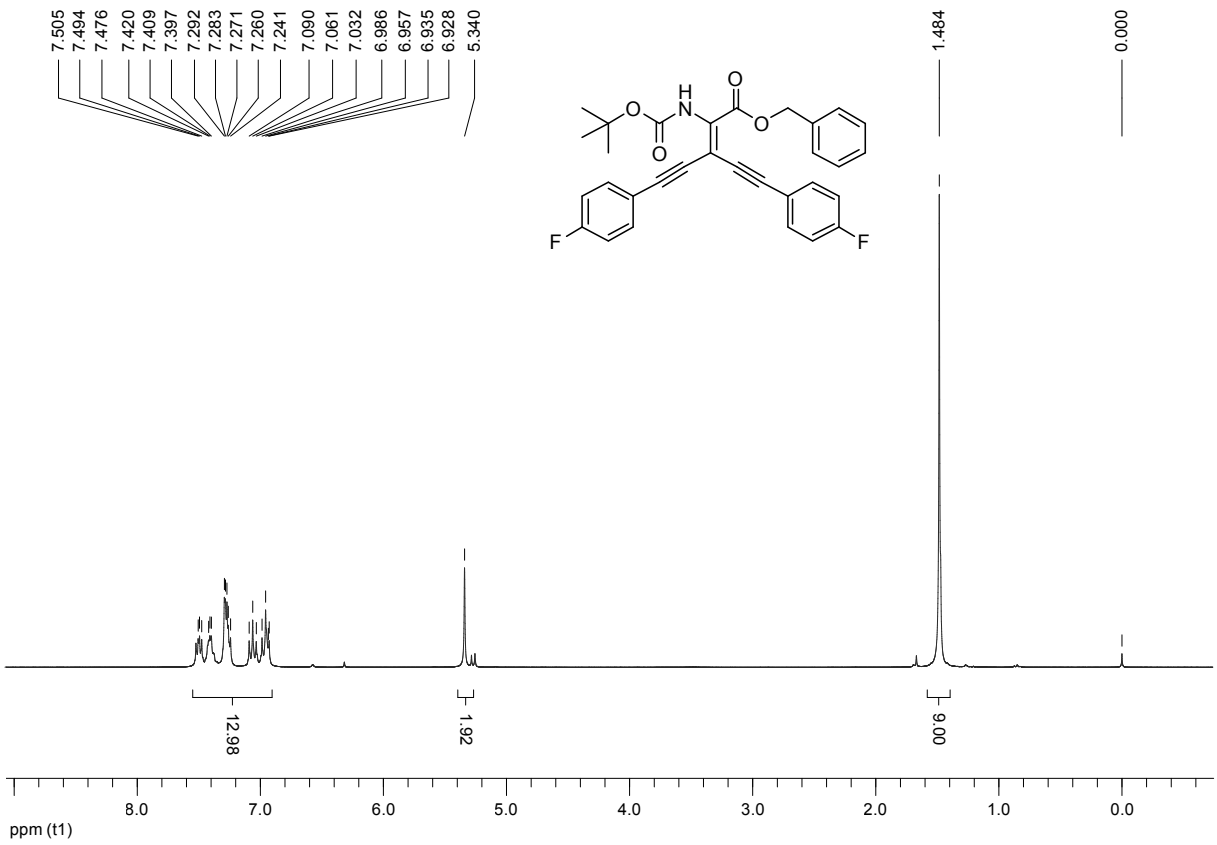


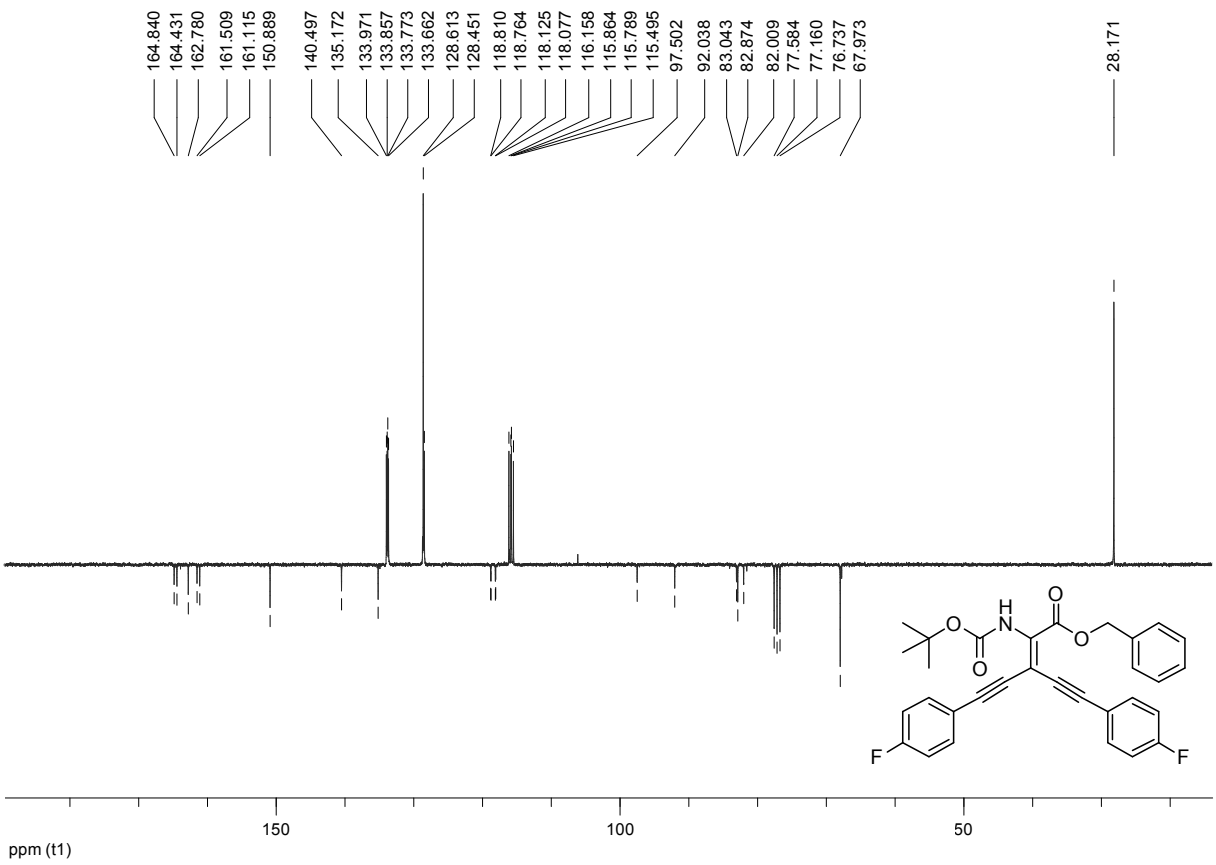

**Benzyl 2-(*tert*-butoxycarbonylamino)-5-(4-methoxyphenyl)-3-((4-methoxyphenyl )ethynyl)pent-2-en-4-ynoate (2b)**

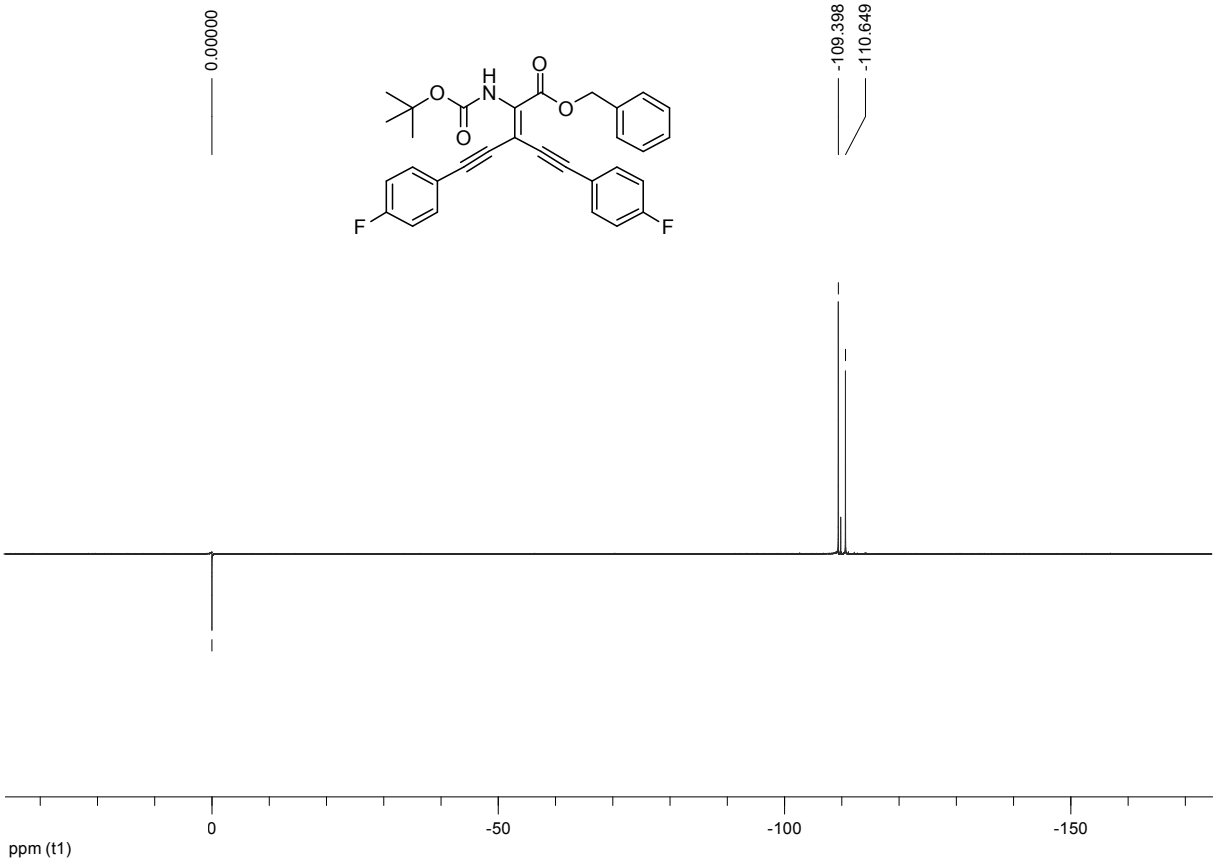




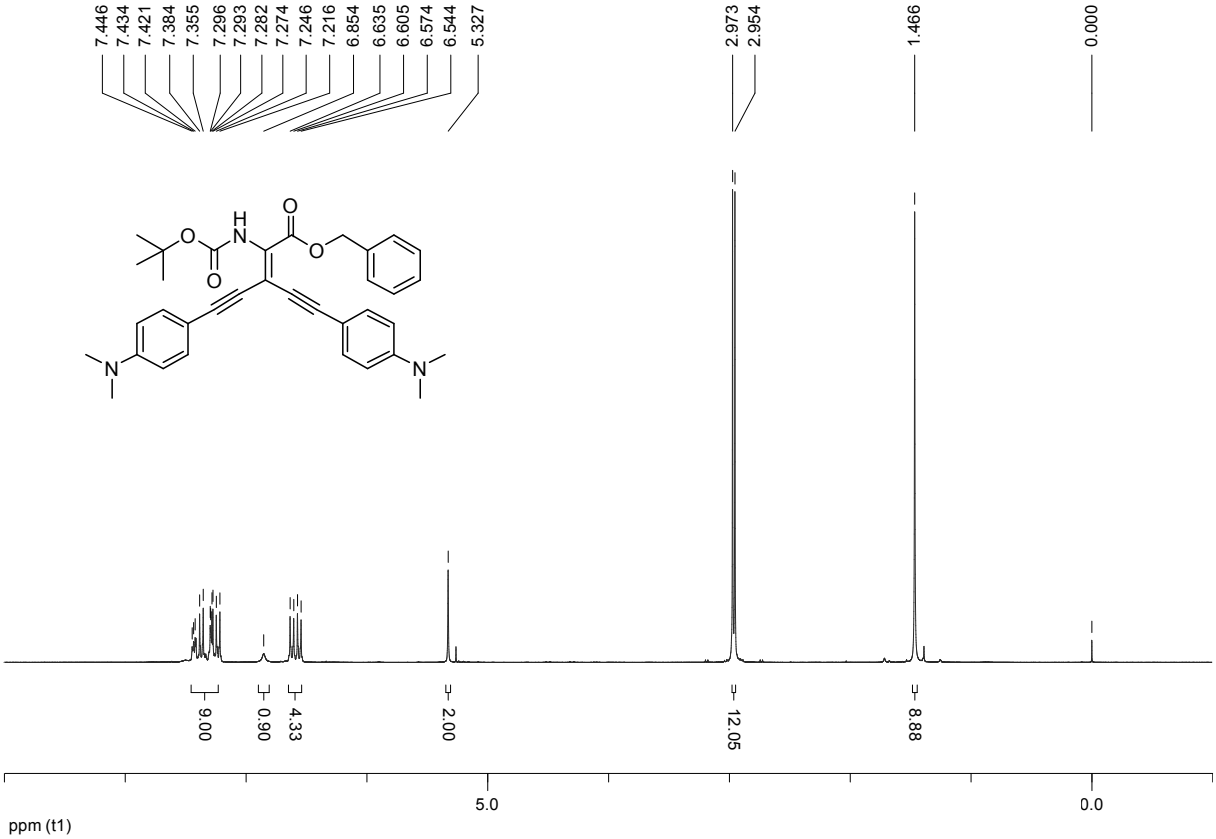

**Benzyl 2-(*tert*-butoxycarbonylamino)-5-(4-fluorophenyl)-3-((4–fluorophenyl)ethynyl)pent-2-en-4-ynoate (2c)**

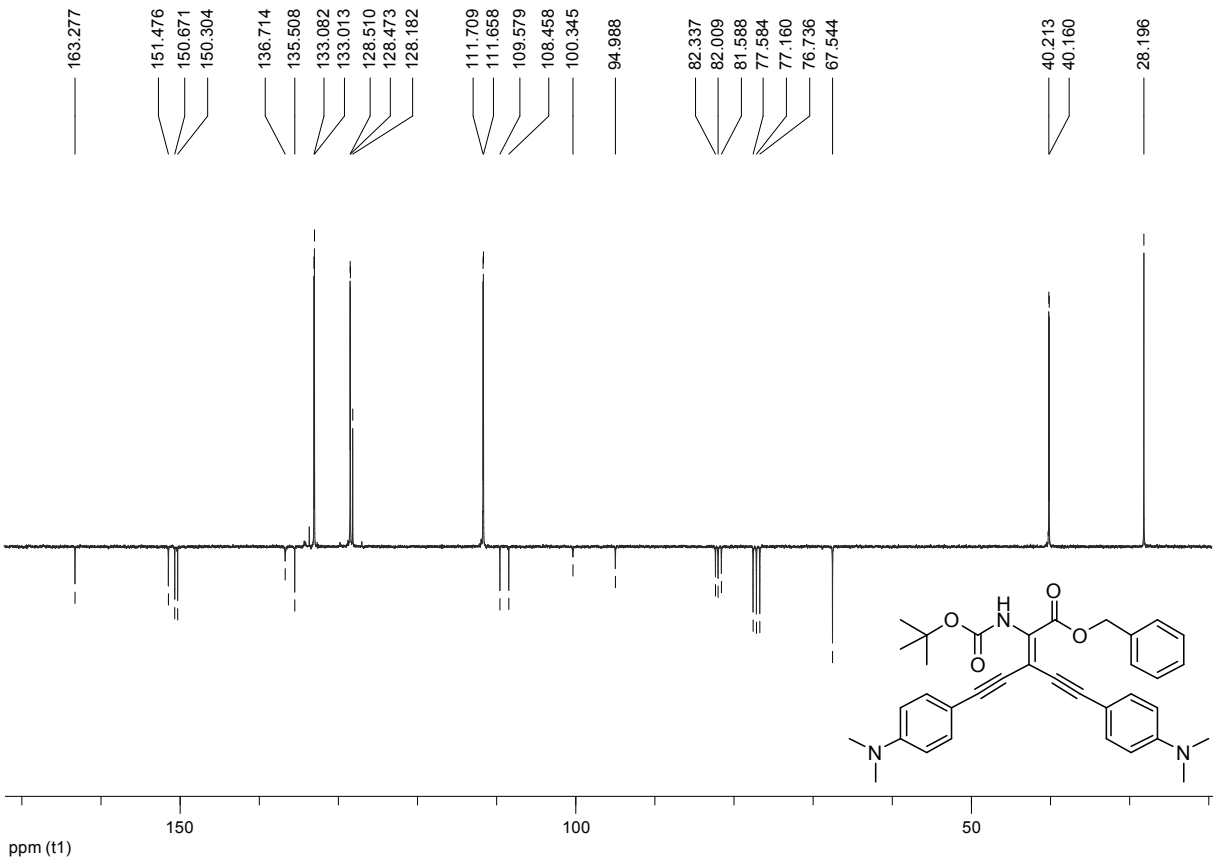



164.840
164.431
162.780
161.509
161.115
150.889
140.497
135.172
133.971
133.857
133.773
133.662
128.613
128.451
118.810
118.764
118.125
118.077
116.158
115.864
115.789
115.495
97.502
92.038
83.043
82.874
82.009
77.584
77.160
76.737
67.973
28.171
150
100
50
ppm (t1)

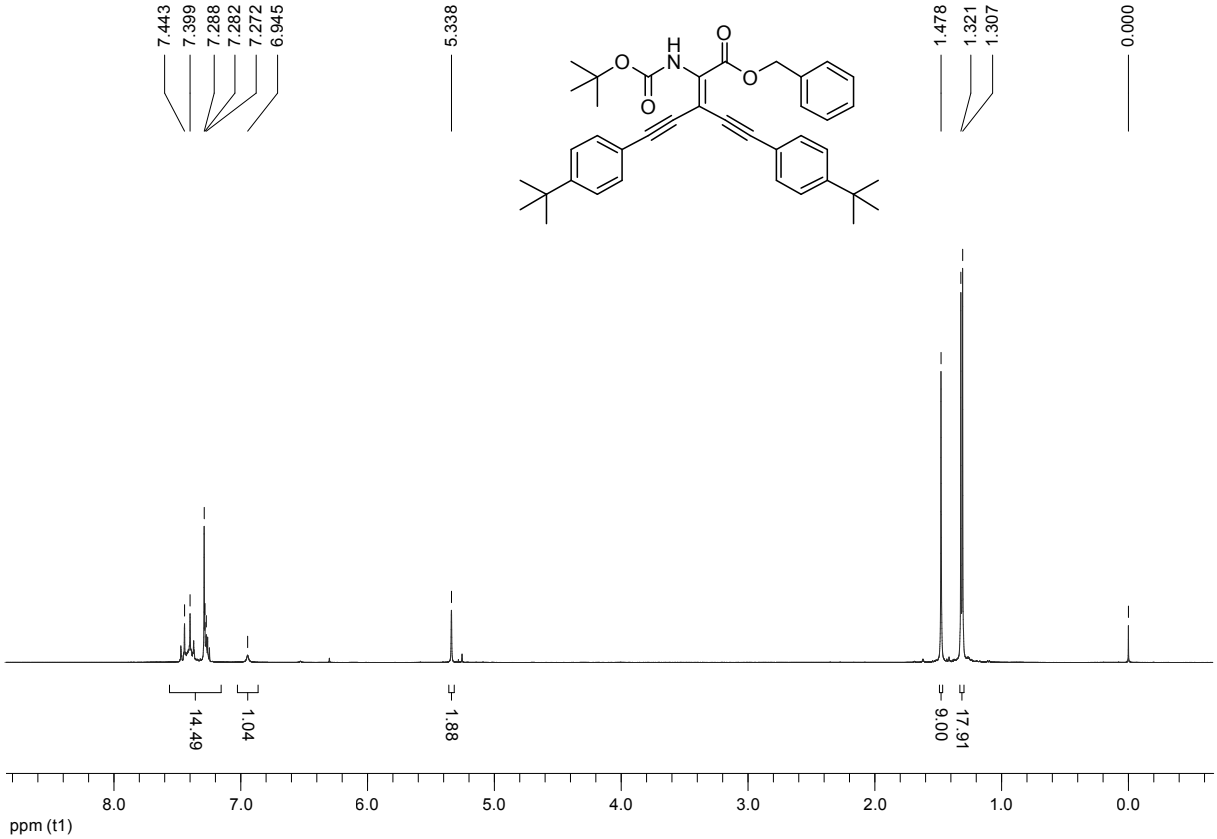

0.00000
-109.398
-110.649
0
-50
-100
-150
ppm (t1)

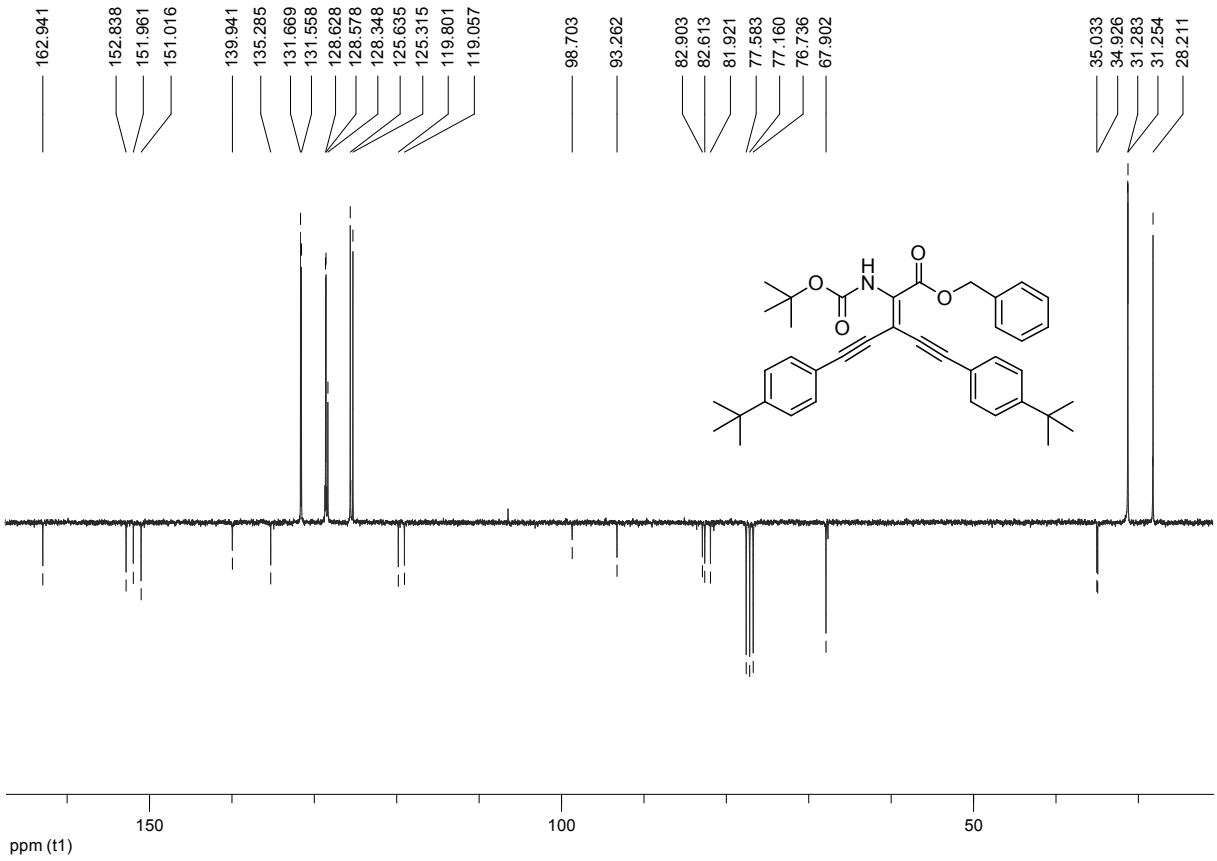
**Benzyl 2-(*tert*-butoxycarbonylamino)-5-(4-(dimethylamino)phenyl)-3-((4-(dimethylamino)phenyl)ethynyl)pent-2-en-4-ynoate (2d)**



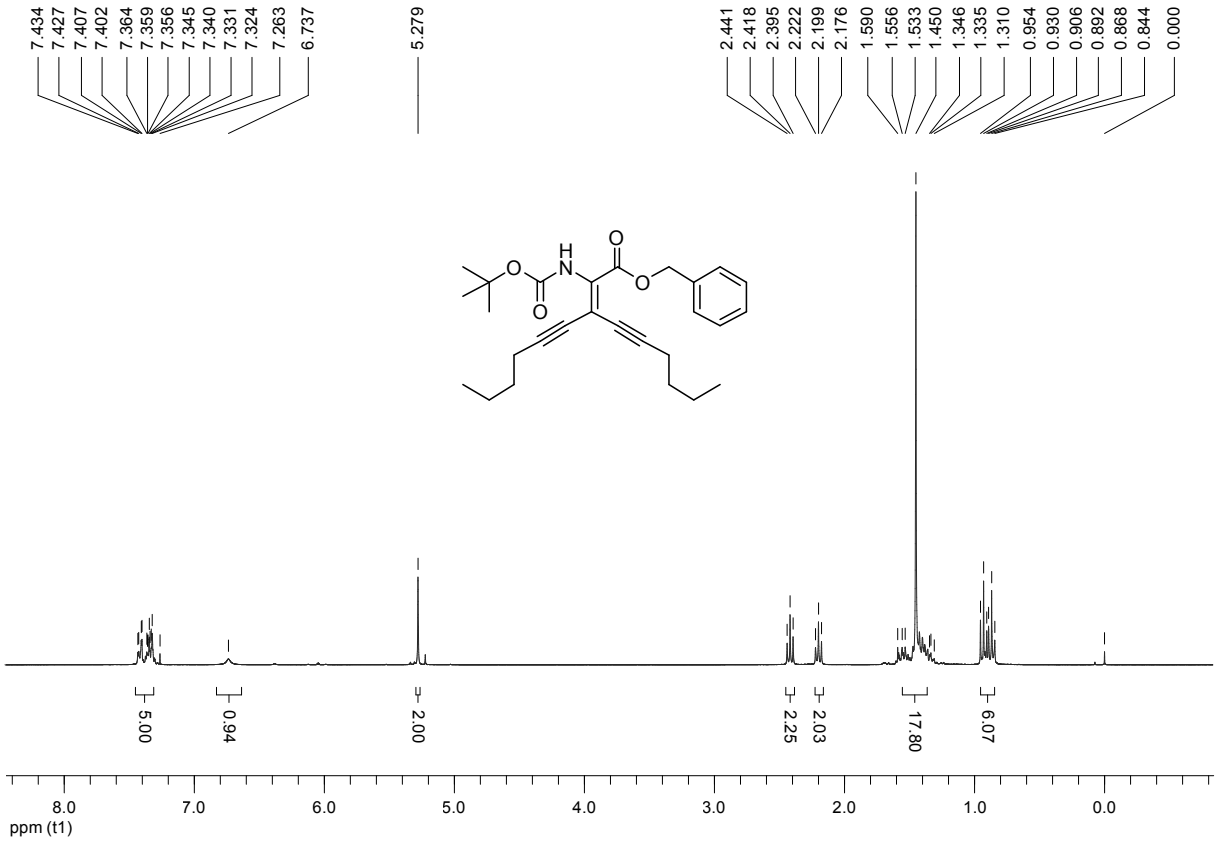



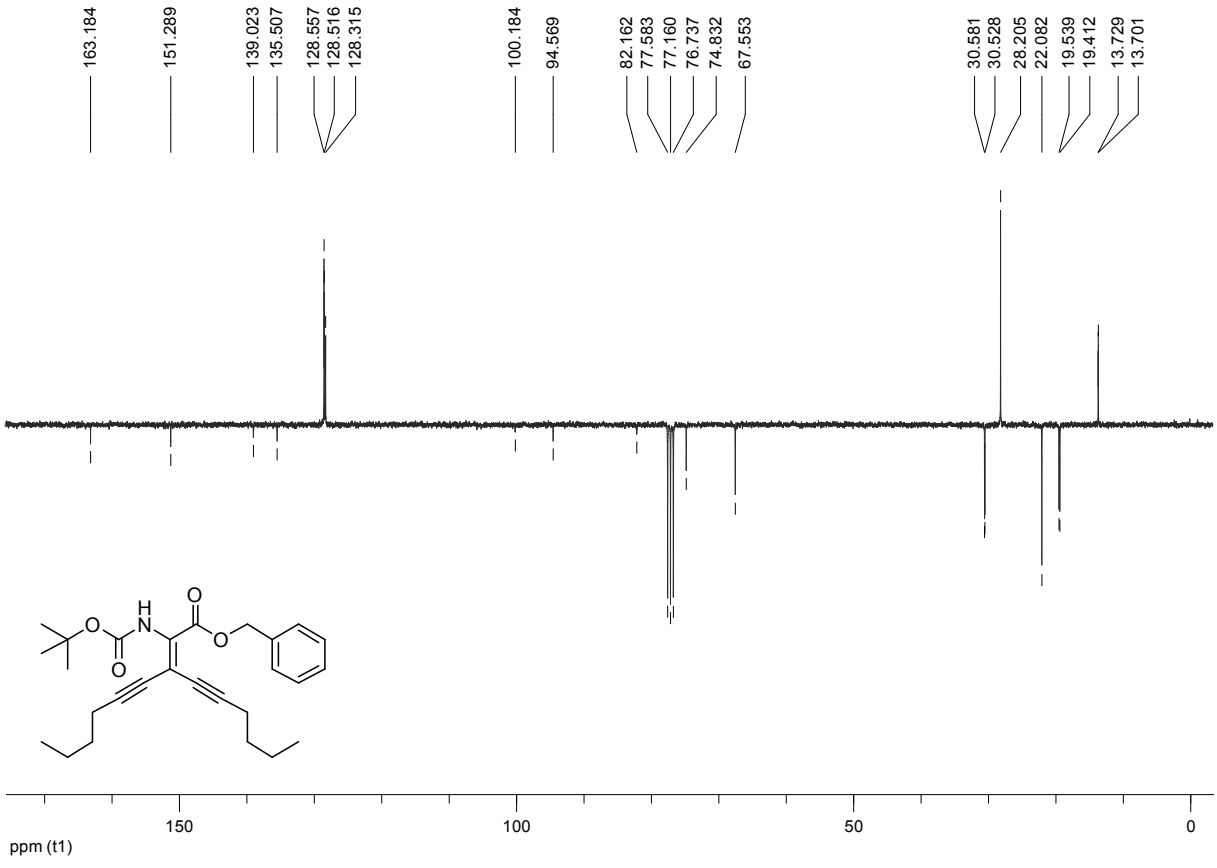
**Benzyl 2-(*tert*-butoxycarbonylamino)-5-(4-*tert*-butylphenyl)-3-((4-*tert*-butylphenyl)ethynyl)pent-2-en-4-ynoate (2e)**



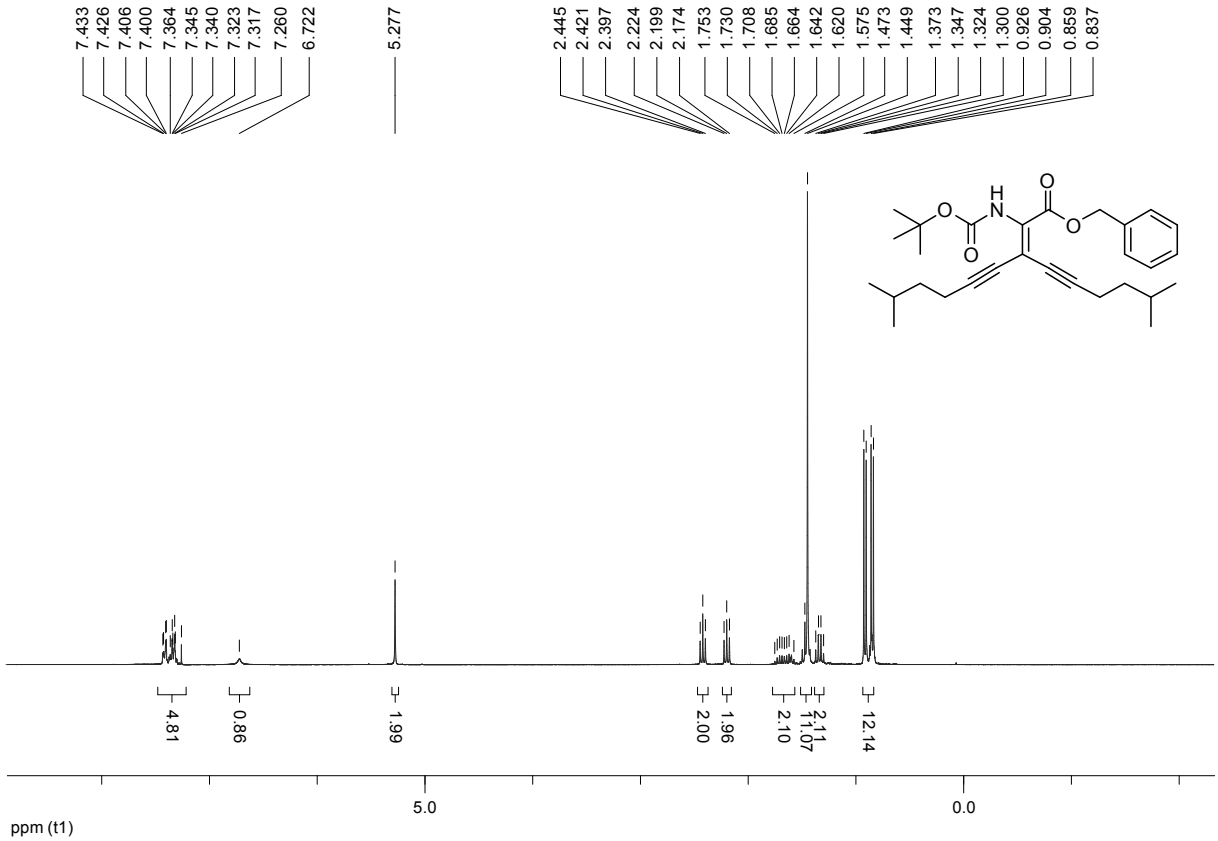



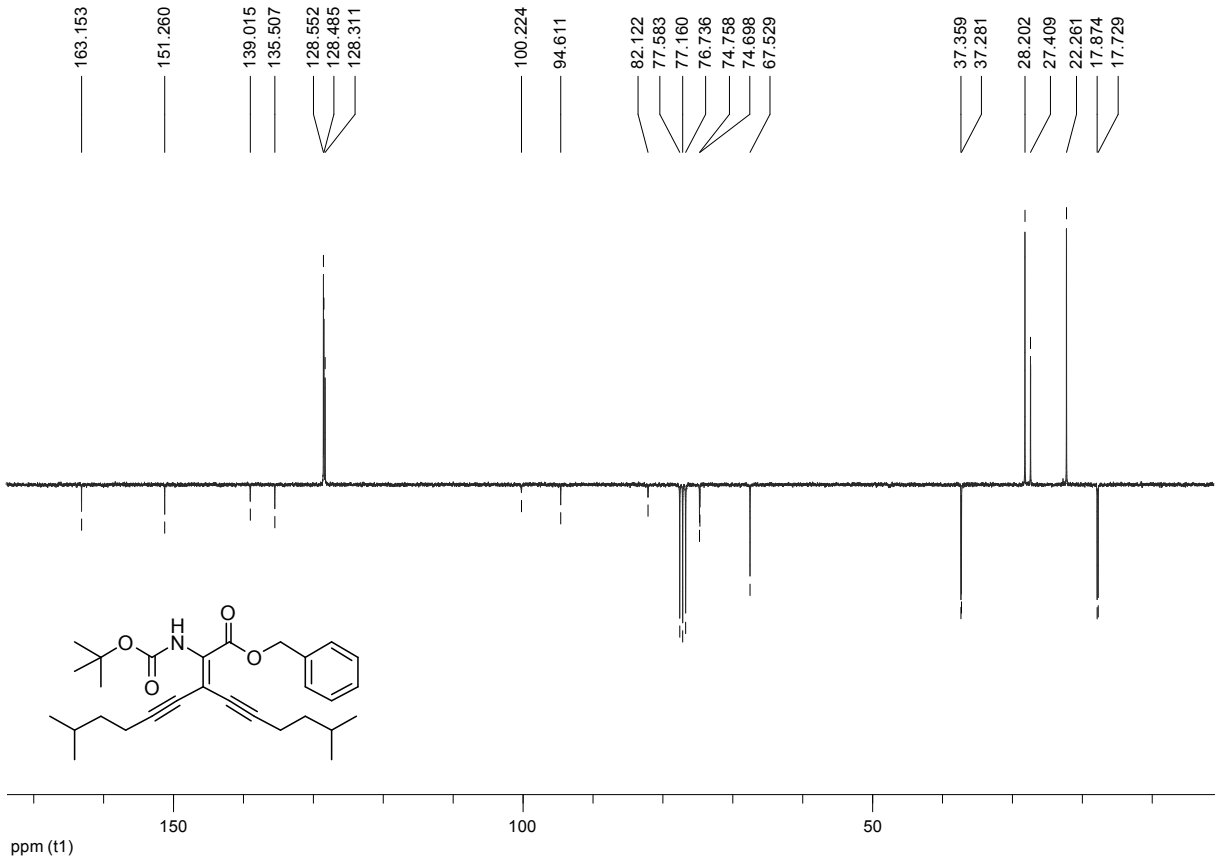
**Benzyl 2-(*tert*-butoxycarbonylamino)-3-(hex-1-ynyl)non-2-en-4-ynoate (2f)**



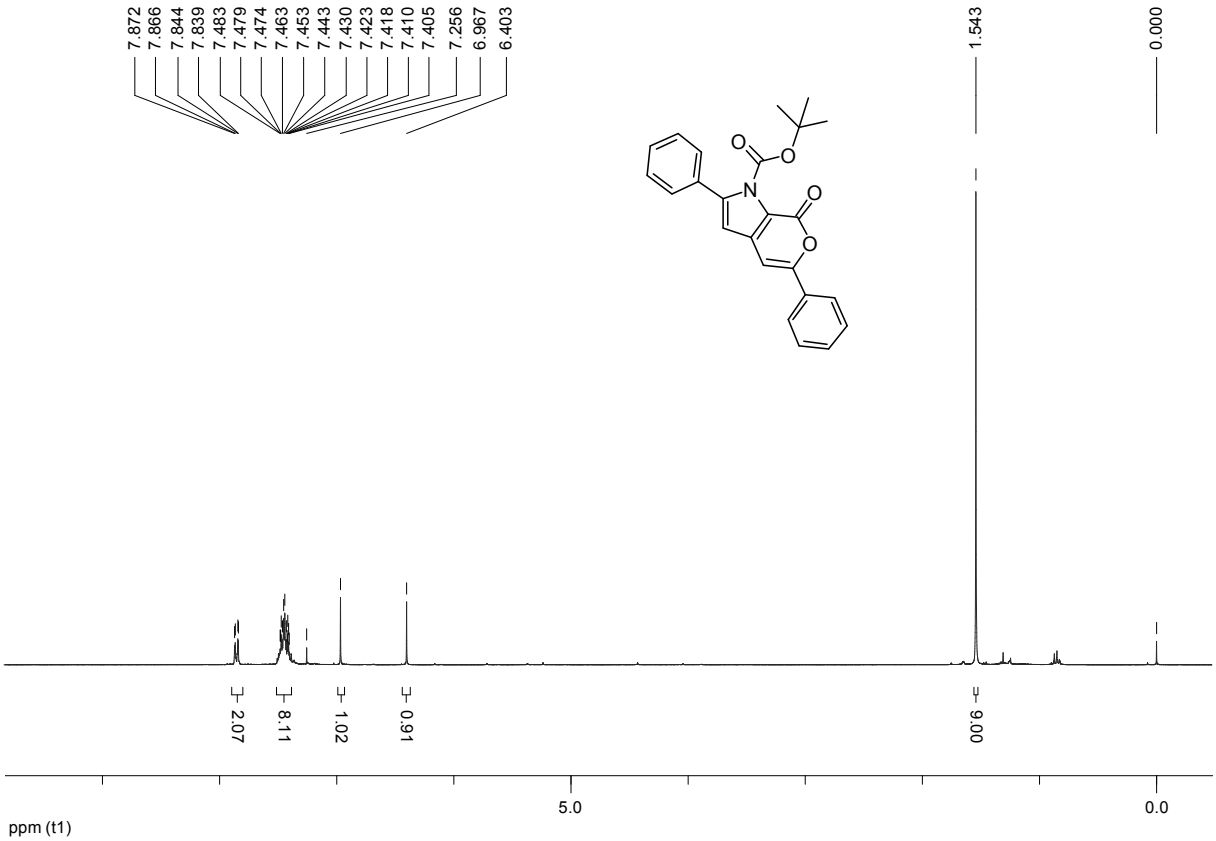



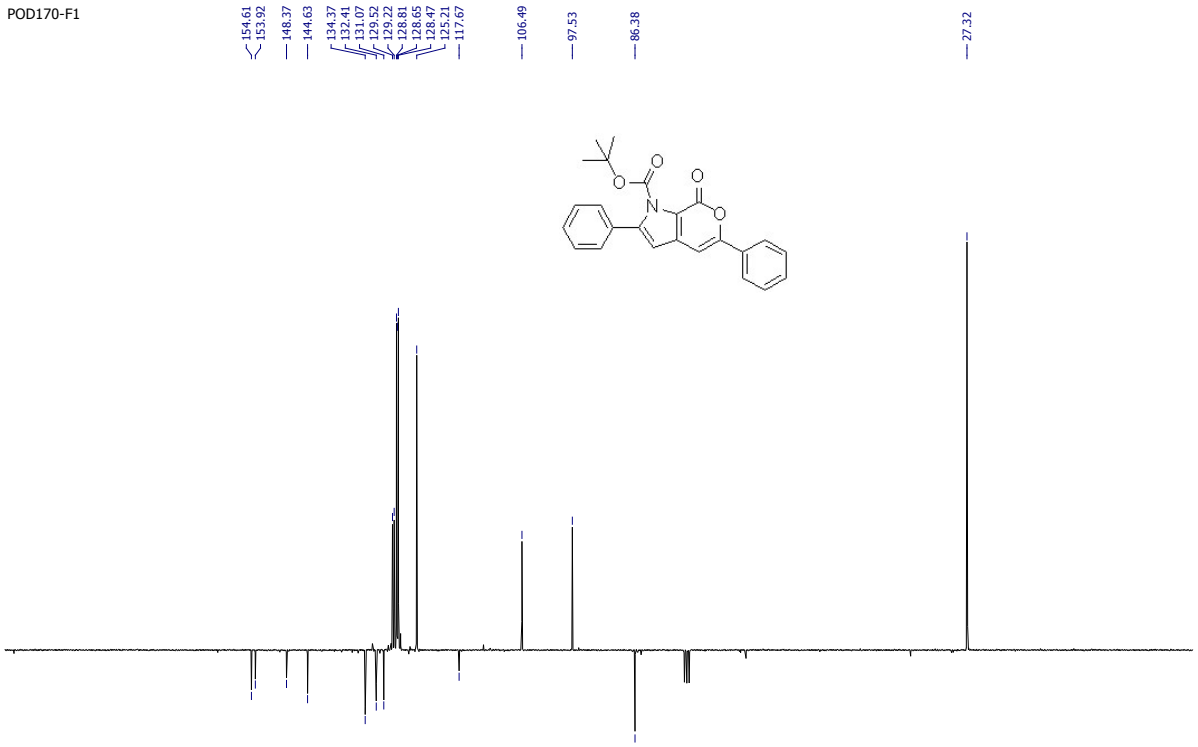
**Benzyl 2-(*tert*-butoxycarbonylamino)-8-methyl-3-(5-methylhex-1-ynyl)non-2-en-4-ynoate (2g)**

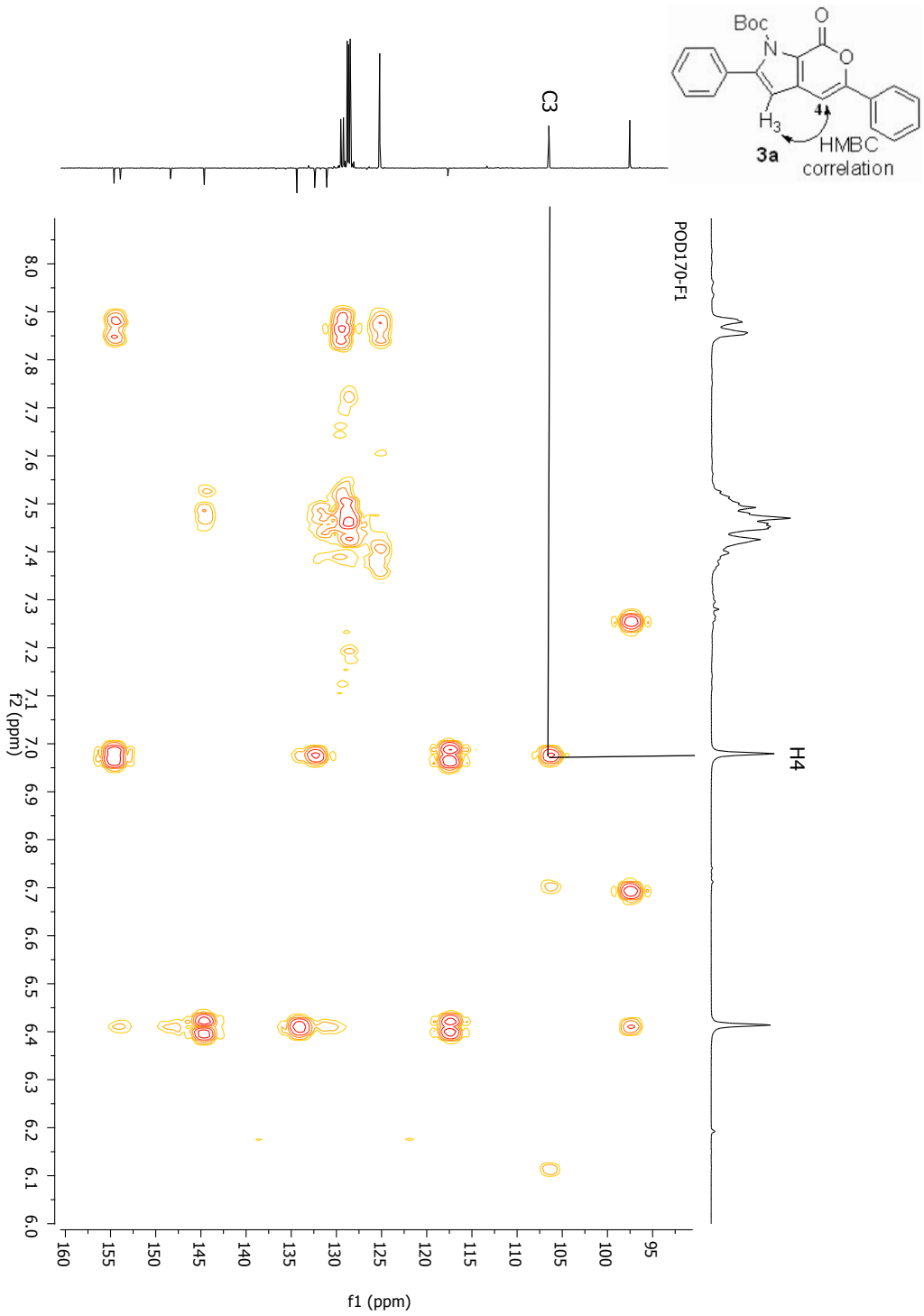


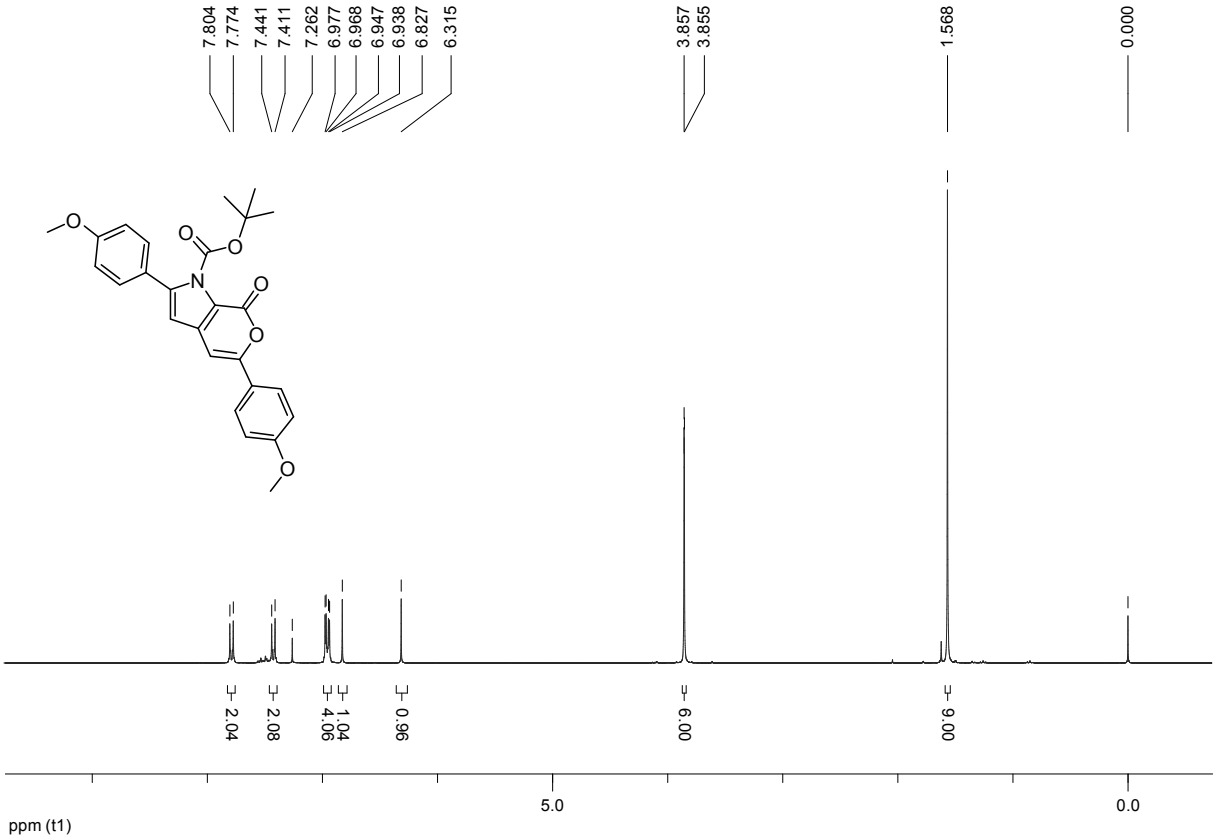
***tert*-Butyl 7-oxo-2,5-diphenylpyrano[3,4-*b*]pyrrole-1(7*H*)-carboxylate (3a)**

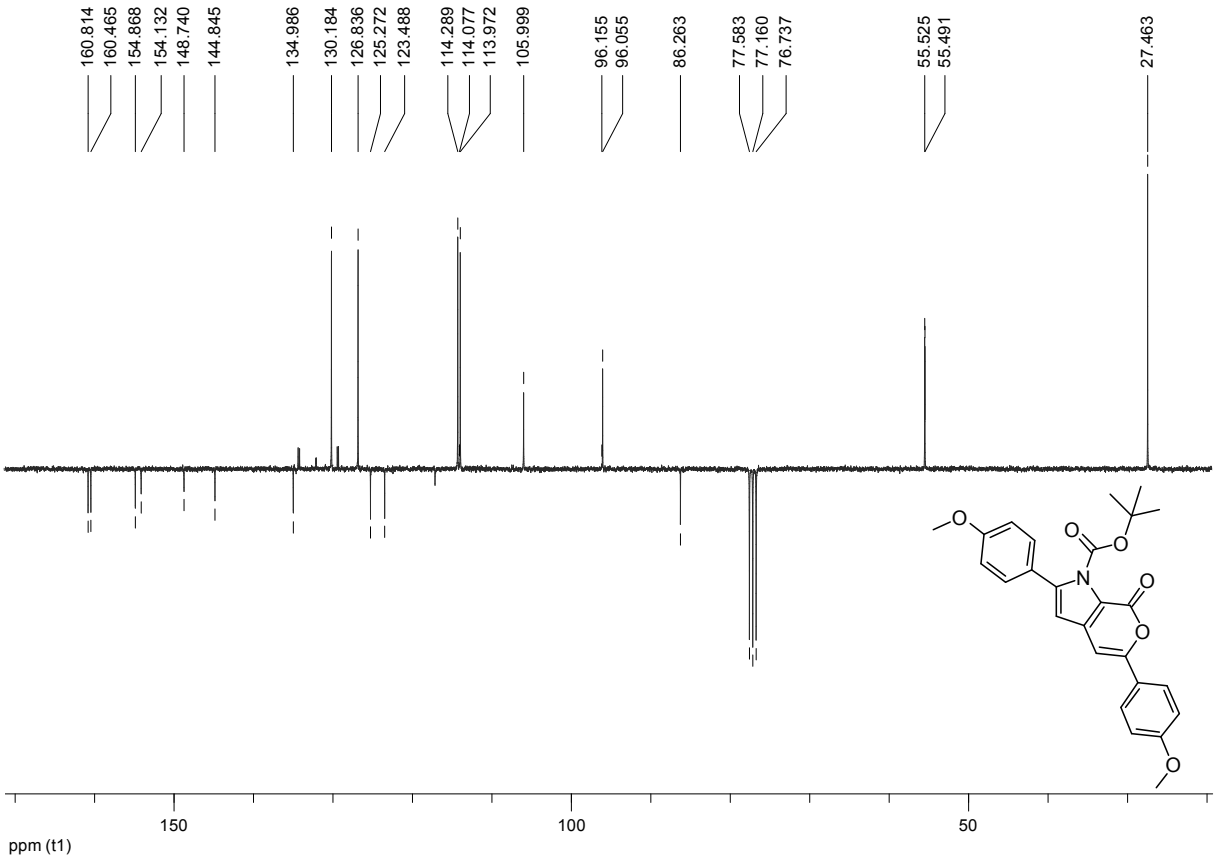


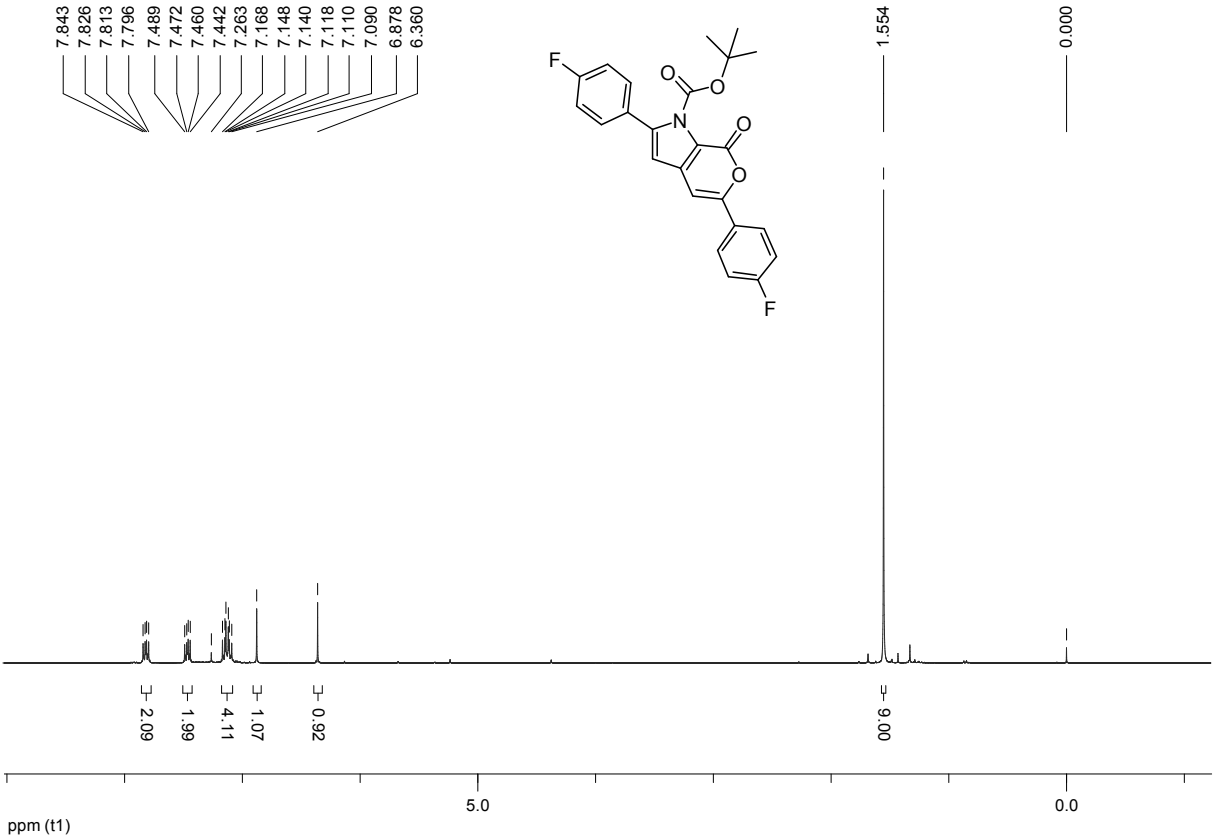


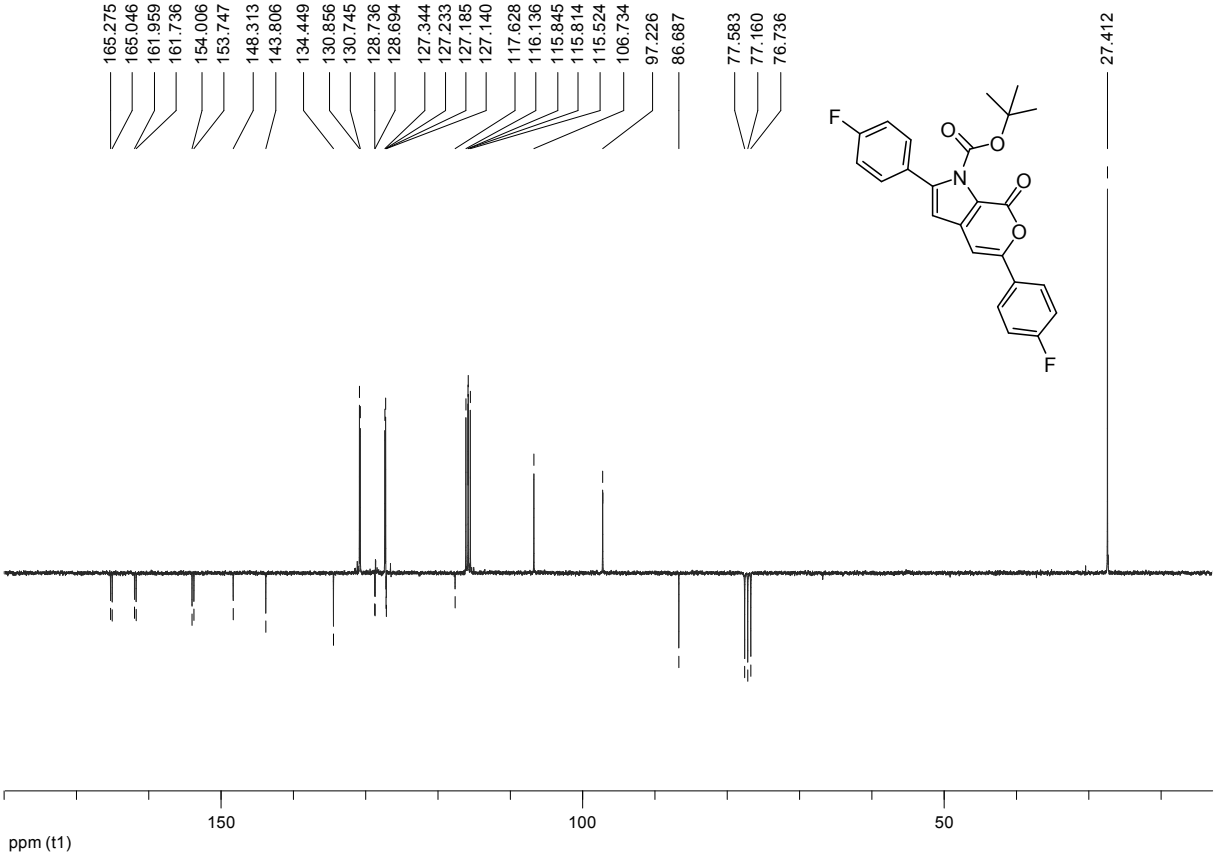

***tert*-Butyl 2,5-bis(4-methoxyphenyl)-7-oxopyrano[3,4-*b*]pyrrole-1(7*H*)-carboxylate (3b)**

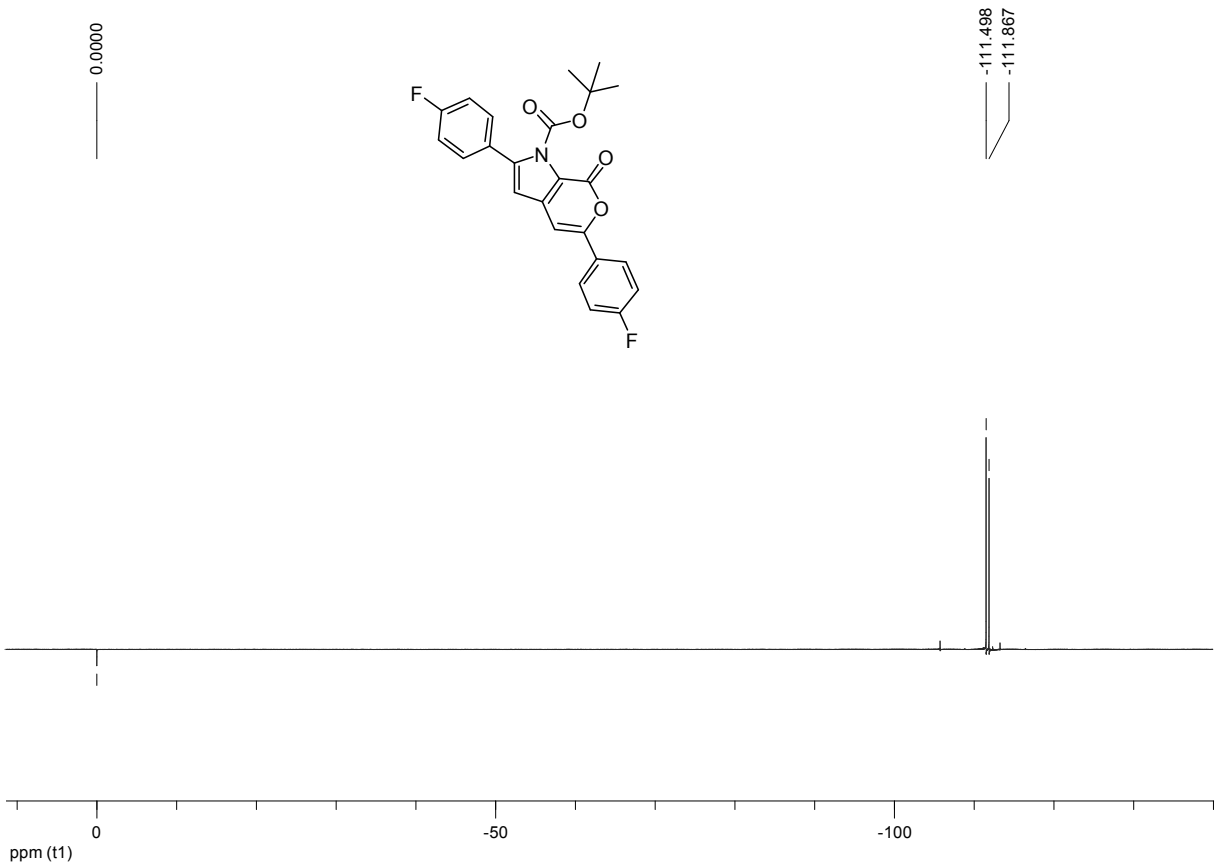


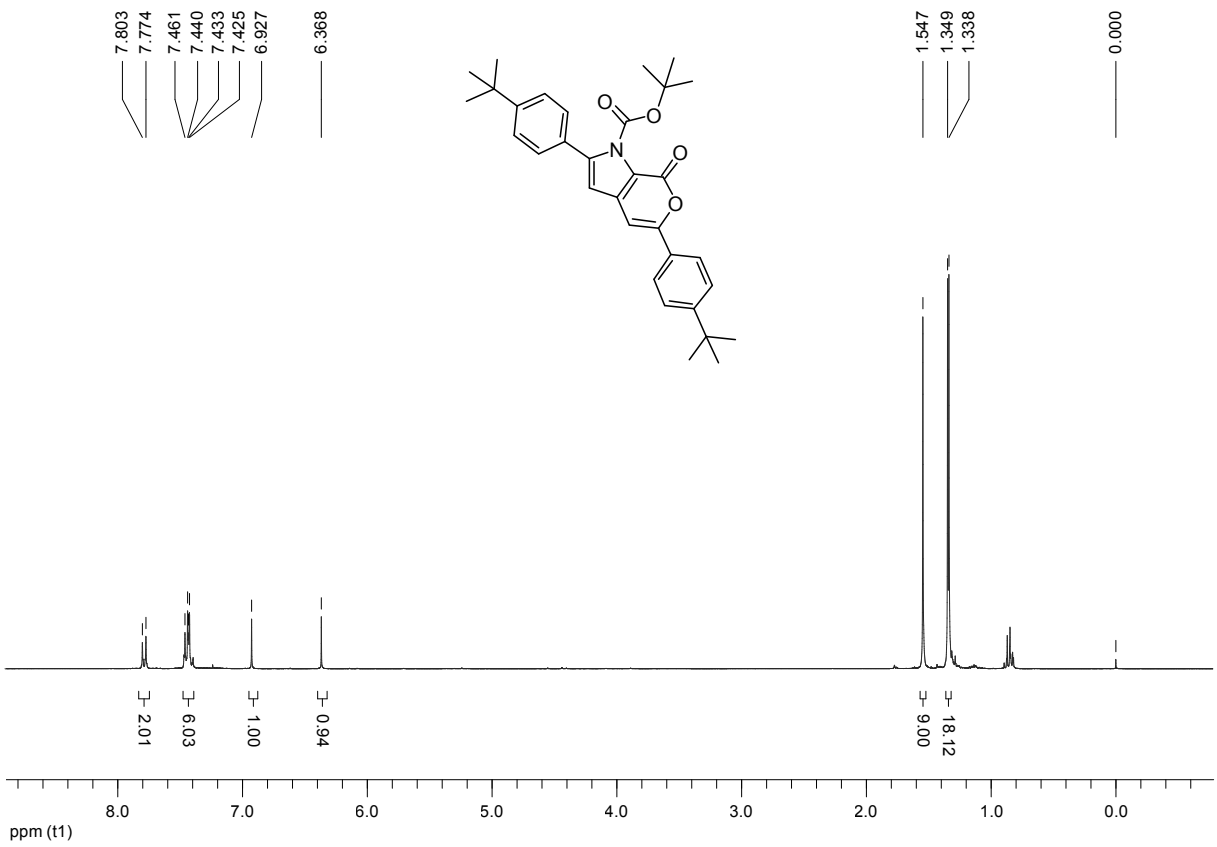

***tert*-Butyl 2,5-bis(4-fluorophenyl)-7-oxopyrano[3,4-*b*]pyrrole-1(7*H*)-carboxylate (3c)**

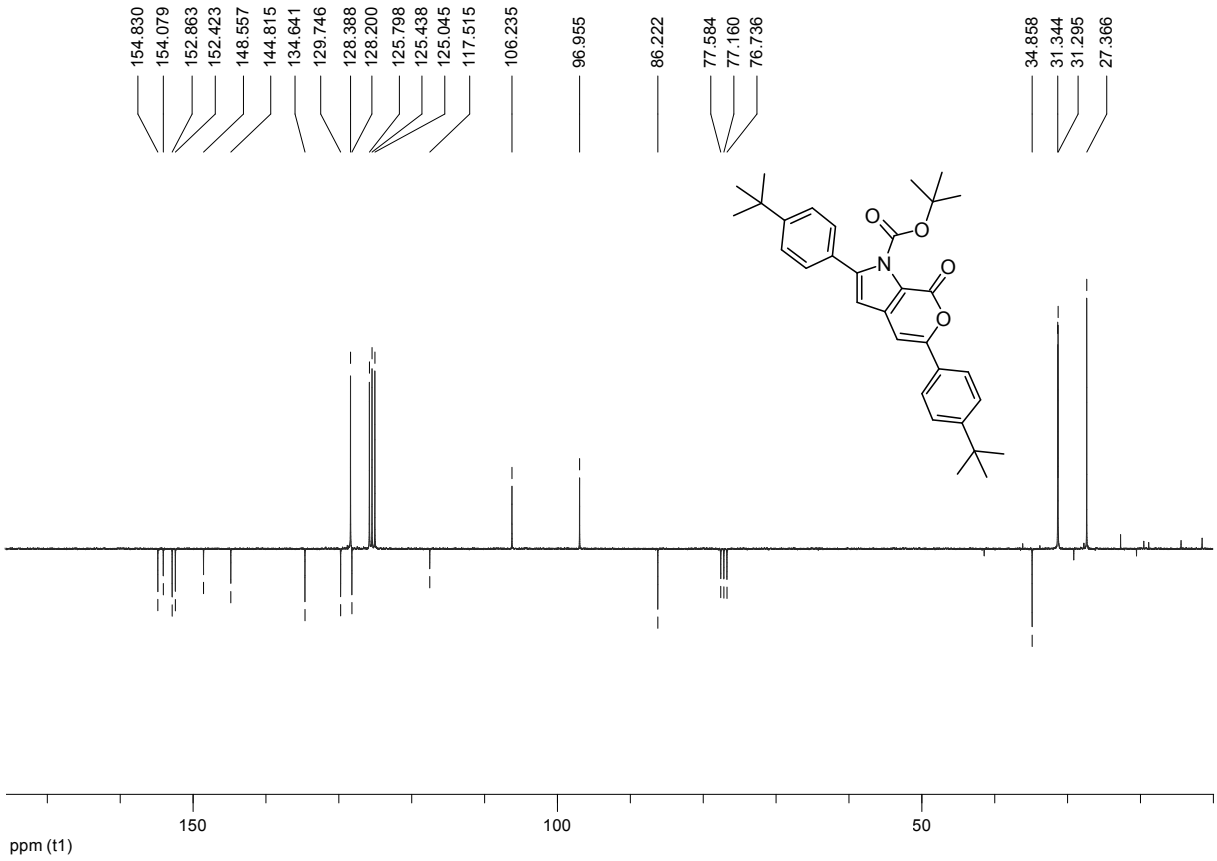

7.843
7.826
7.813
7.796
7.489
7.472
7.460
7.442
7.263
7.168
7.148
7.140
7.118
7.110
7.090
6.878
6.360
1.554
0.000
F
O
O
N
O
O
F
2.09
1.99
4.11
1.07
0.92
9.00
5.0
0.0
ppm (t1)


165.275
165.046
161.959
161.736
154.006
153.747
148.313
143.806
134.449
130.856
130.745
128.736
128.694
127.344
127.233
127.185
127.140
117.628
116.136
115.845
115.814
115.524
106.734
97.226
86.687
77.583
77.160
76.736
27.412
F
O
O
N
O
O
F
150
100
50
ppm (t1)

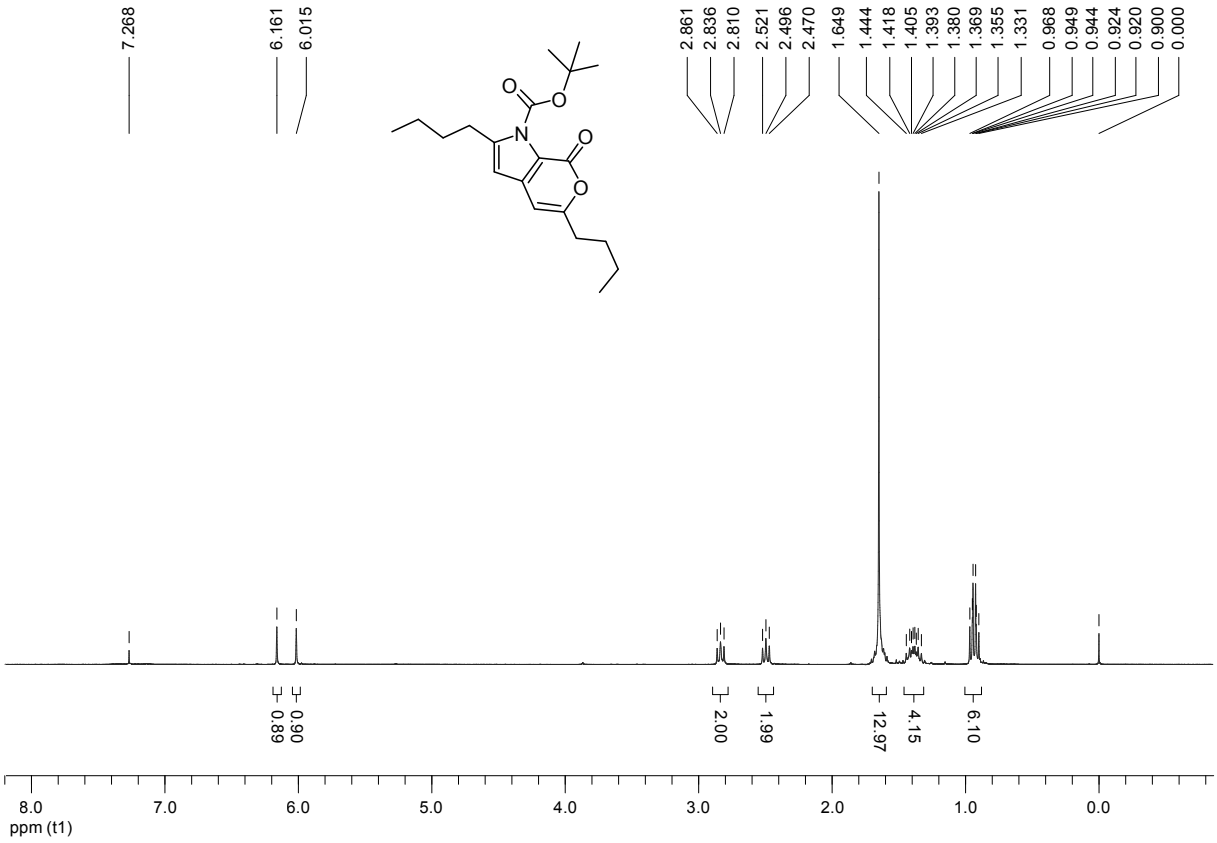

0.0000
-111.498
-111.867
F
O
O
N
O
O
F
0
-50
-100
ppm (t1)

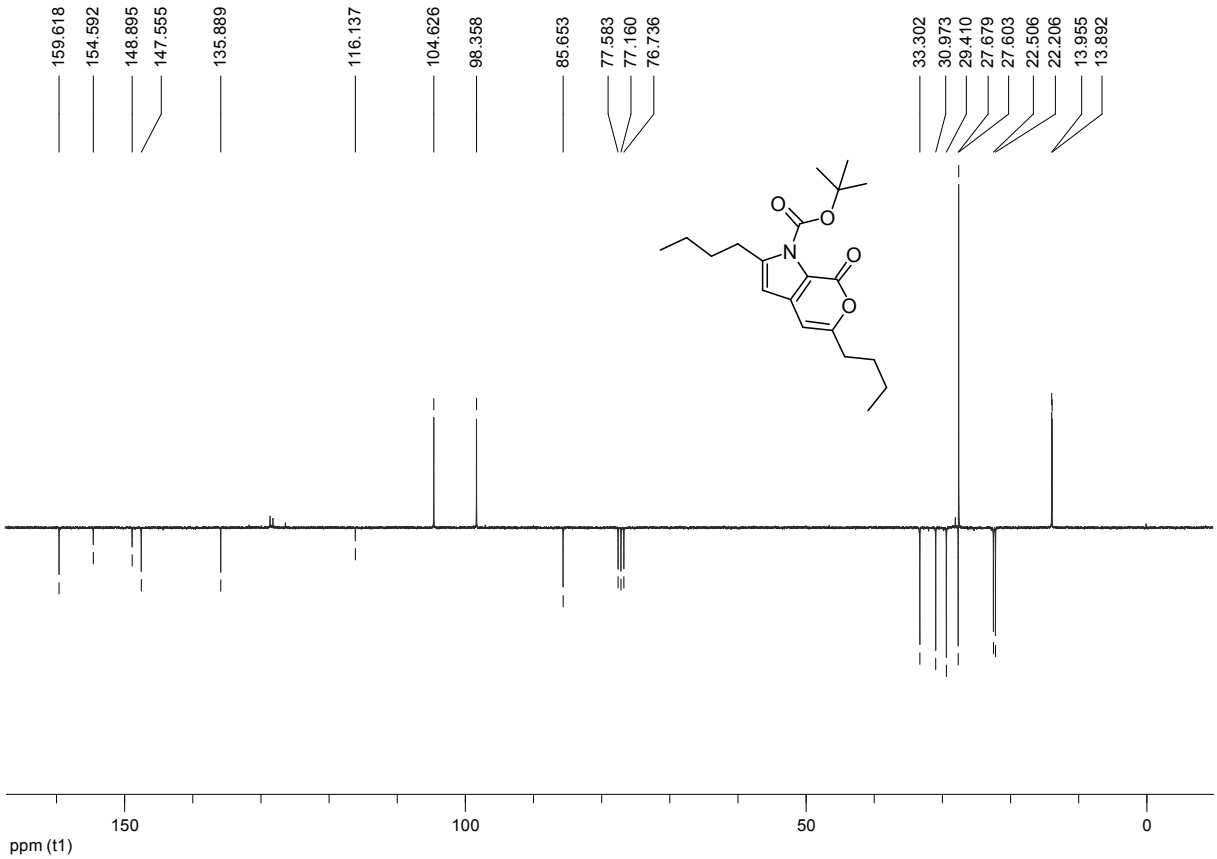
***tert*-Butyl 2,5-bis(4-*tert*-butylphenyl)-7-oxopyrano[3,4-*b*]pyrrole-1(7*H*)-carboxylate (3e)**



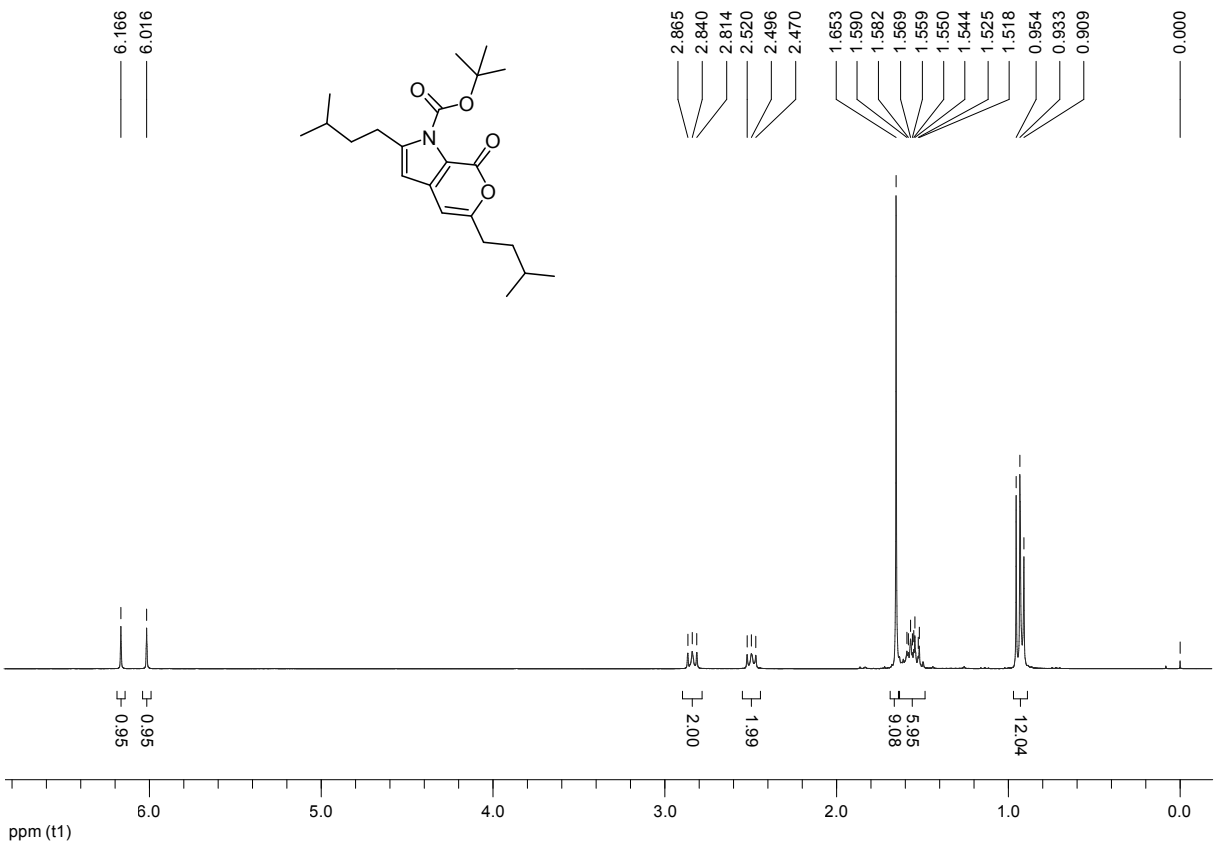



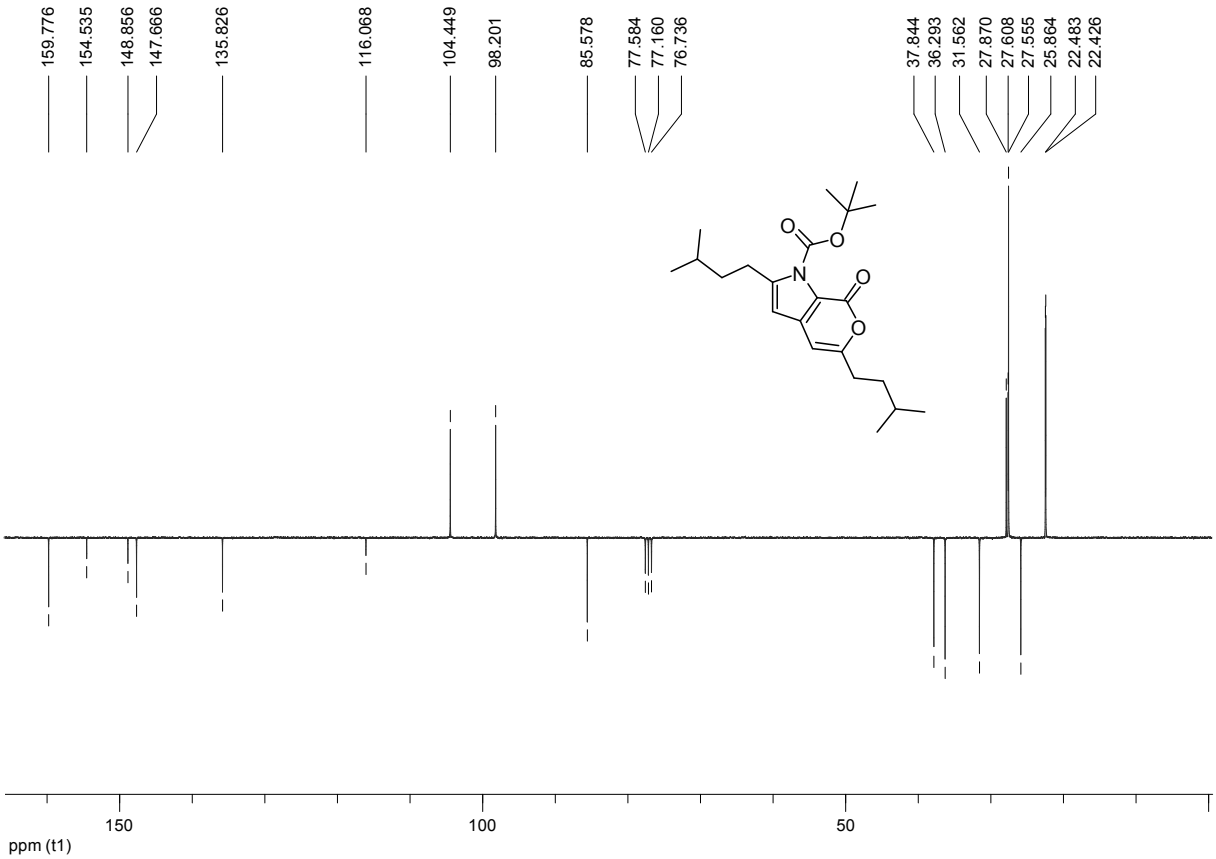
**_tert_-Butyl 2,5-dibutyl-7-oxopyrano[3,4-_b_]pyrrole-1(7_H_)-carboxylate (3f)**



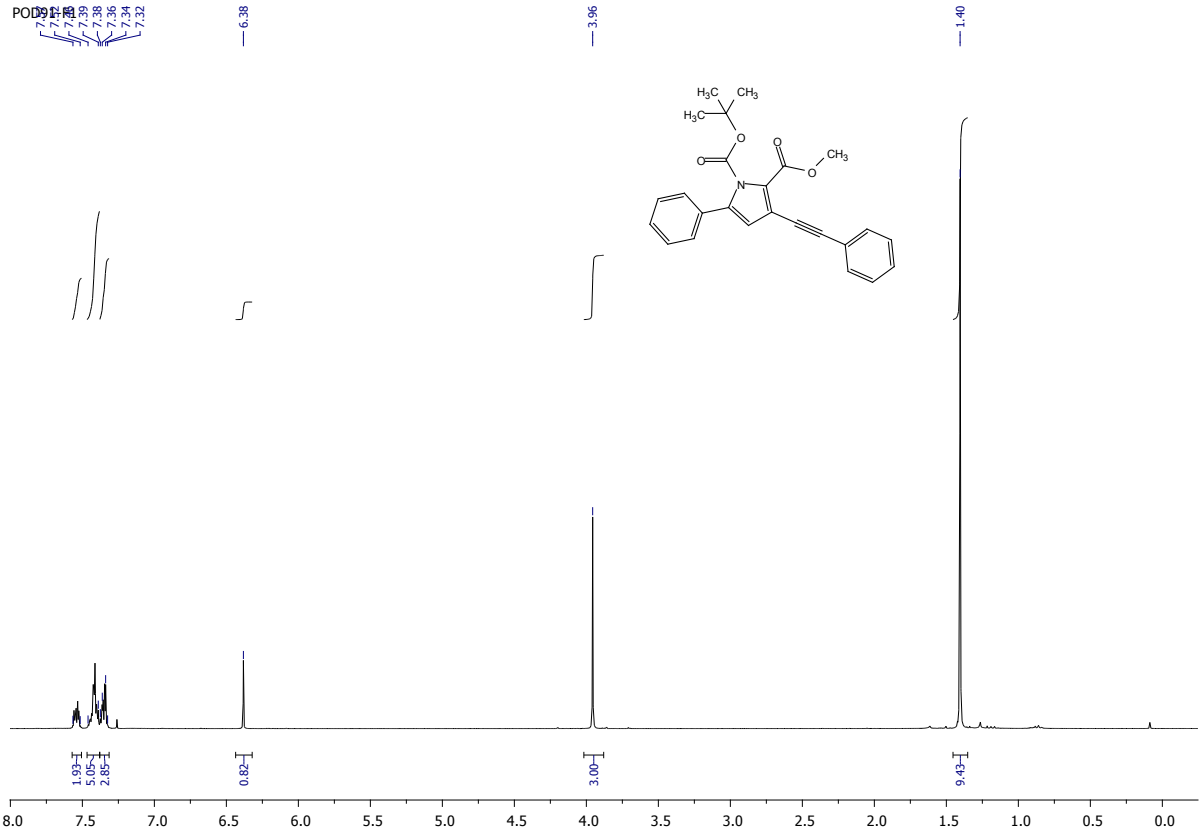



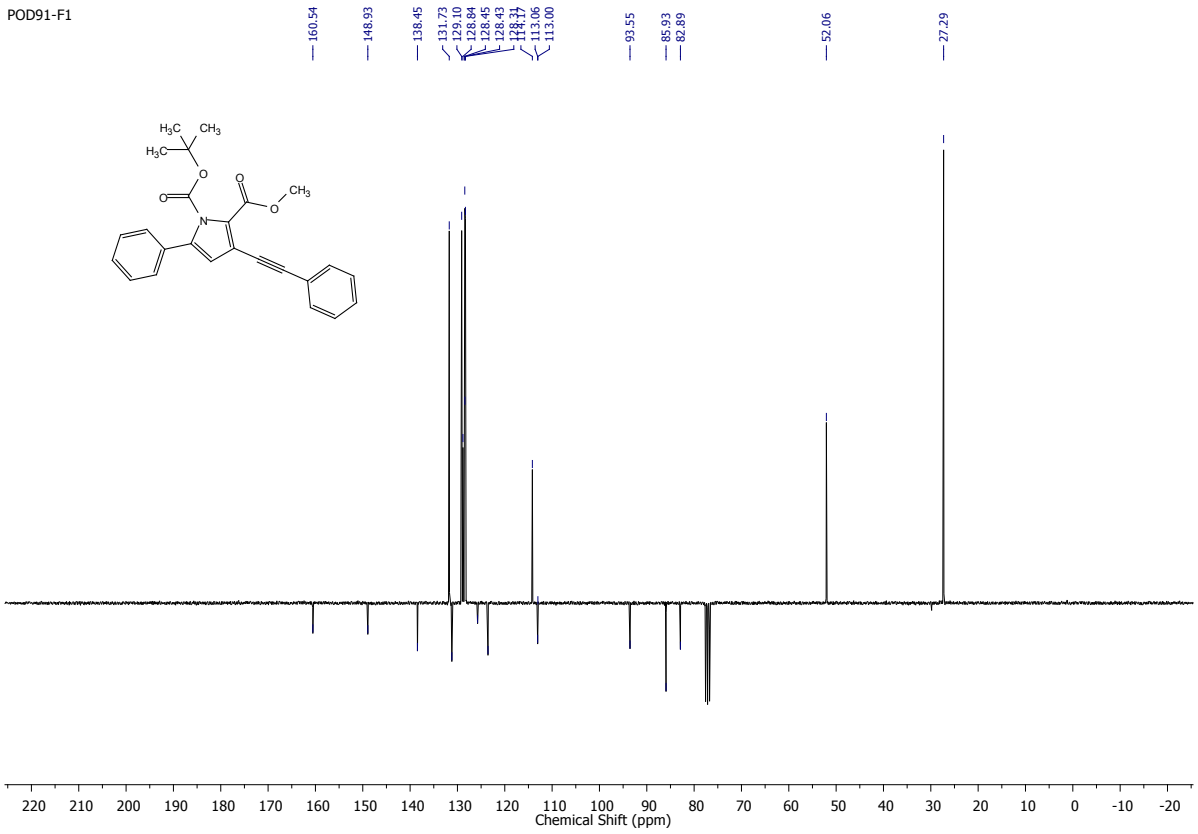
**_tert_-Butyl 2,5-diisopentyl-7-oxopyrano[3,4-_b_]pyrrole-1(7_H_)-carboxylate (3g)**



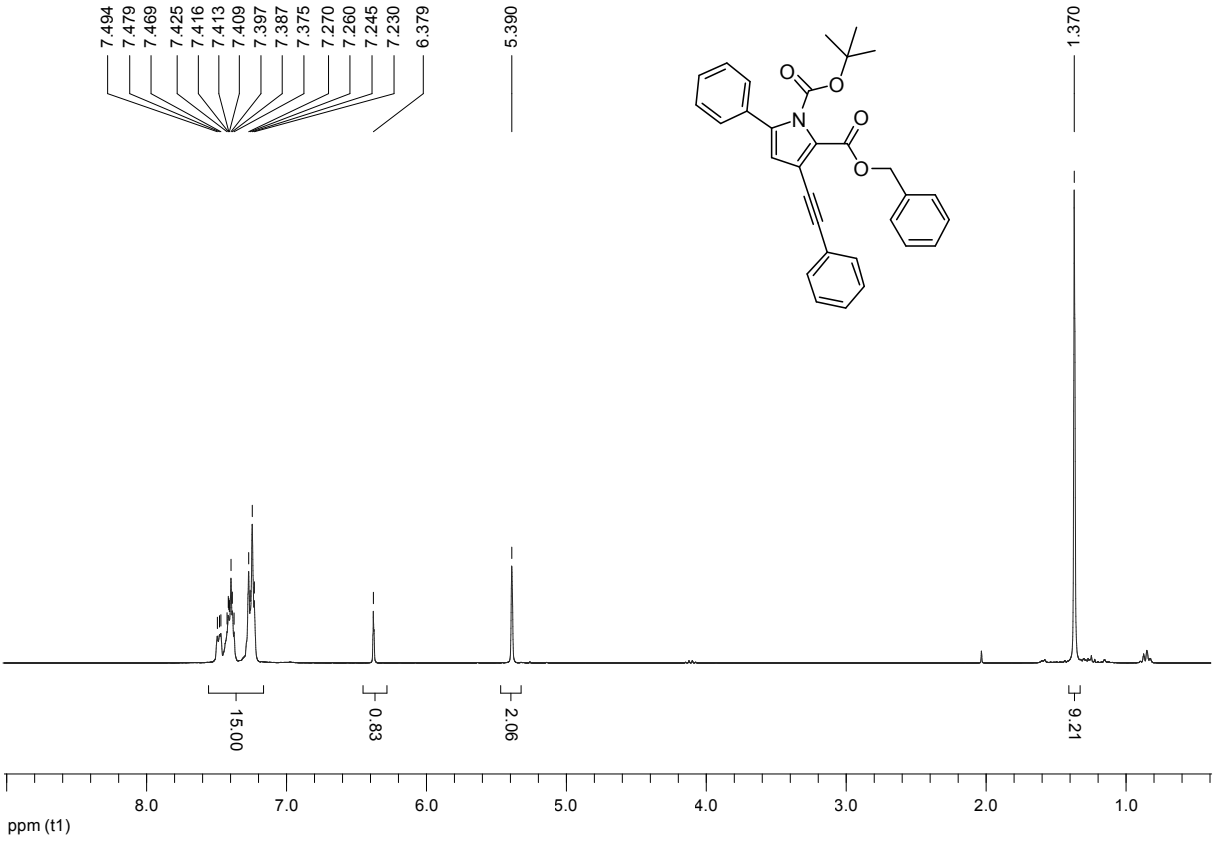



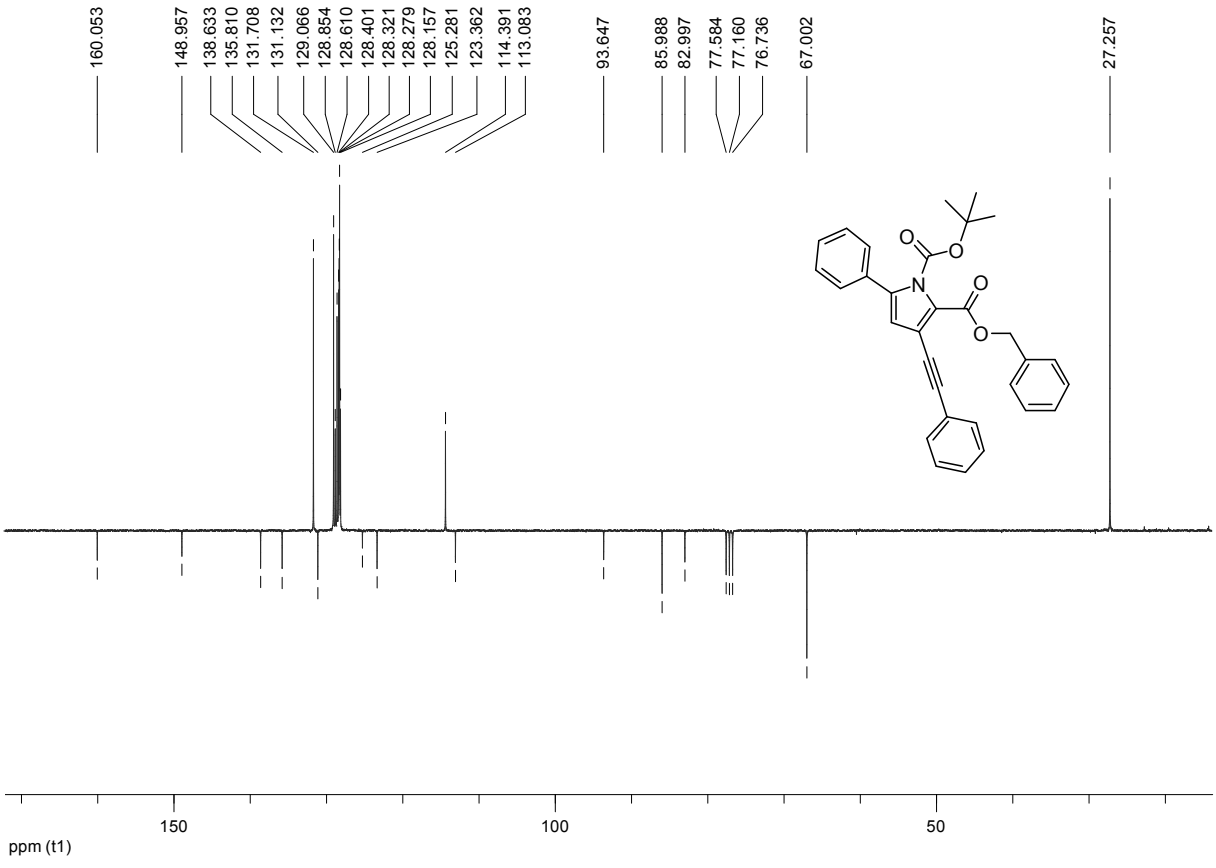
**1-(*tert*-Butyl) 2-methyl 5-phenyl-3-(phenylethynyl)-1*H*-pyrrole-1,2-dicarboxylate (4'a)**



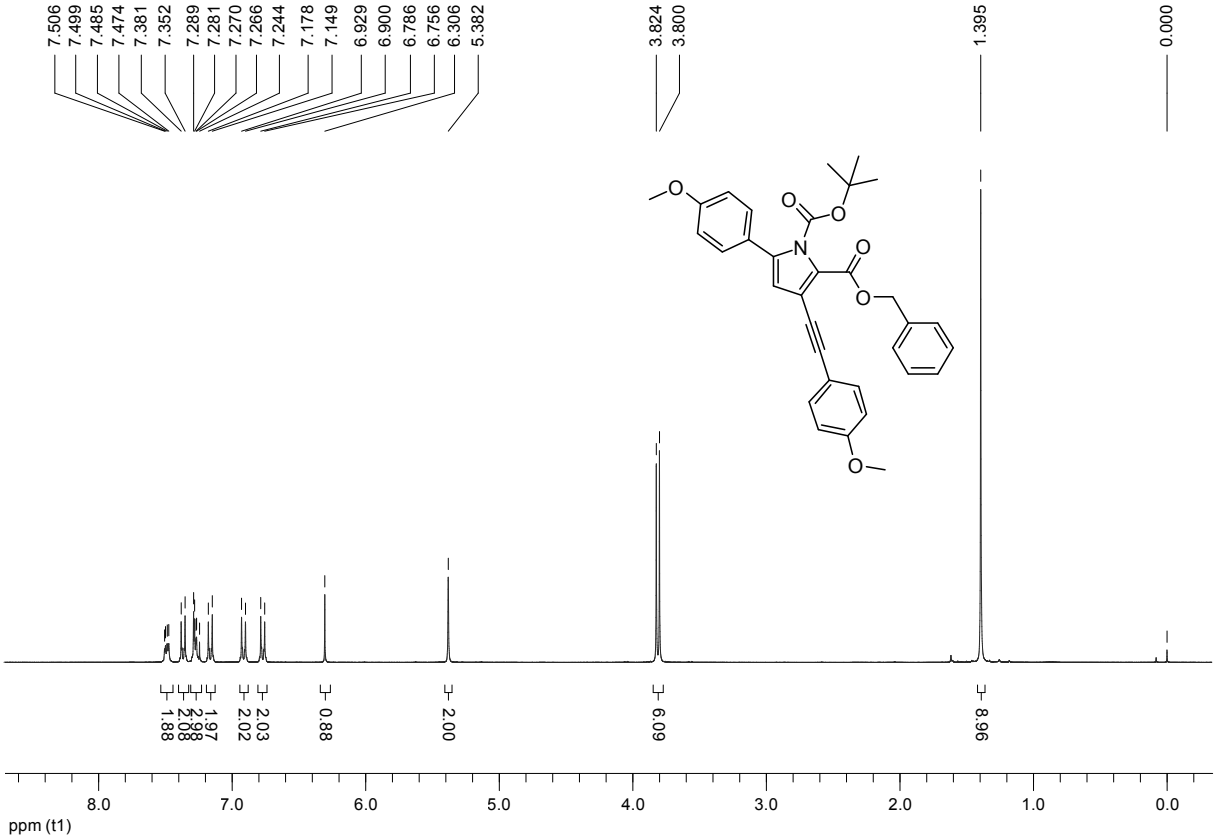



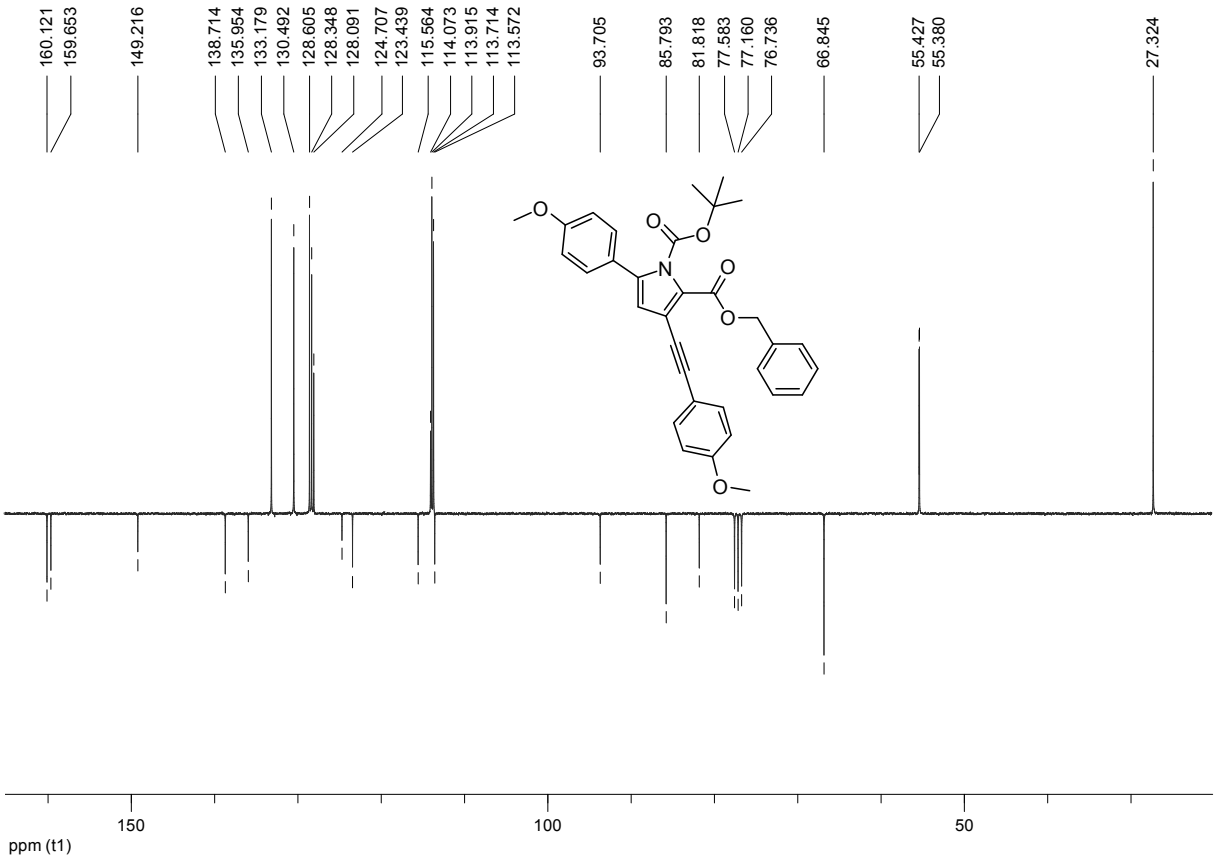

**2-Benzyl 1-*tert*-butyl 5-phenyl-3-(phenylethynyl)-1*H*-pyrrole-1,2-dicarboxylate (4a)**


7.494
7.479
7.469
7.425
7.416
7.413
7.409
7.397
7.387
7.375
7.270
7.260
7.245
7.230
6.379
5.390
1.370
1.00
0.83
2.06
9.21
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

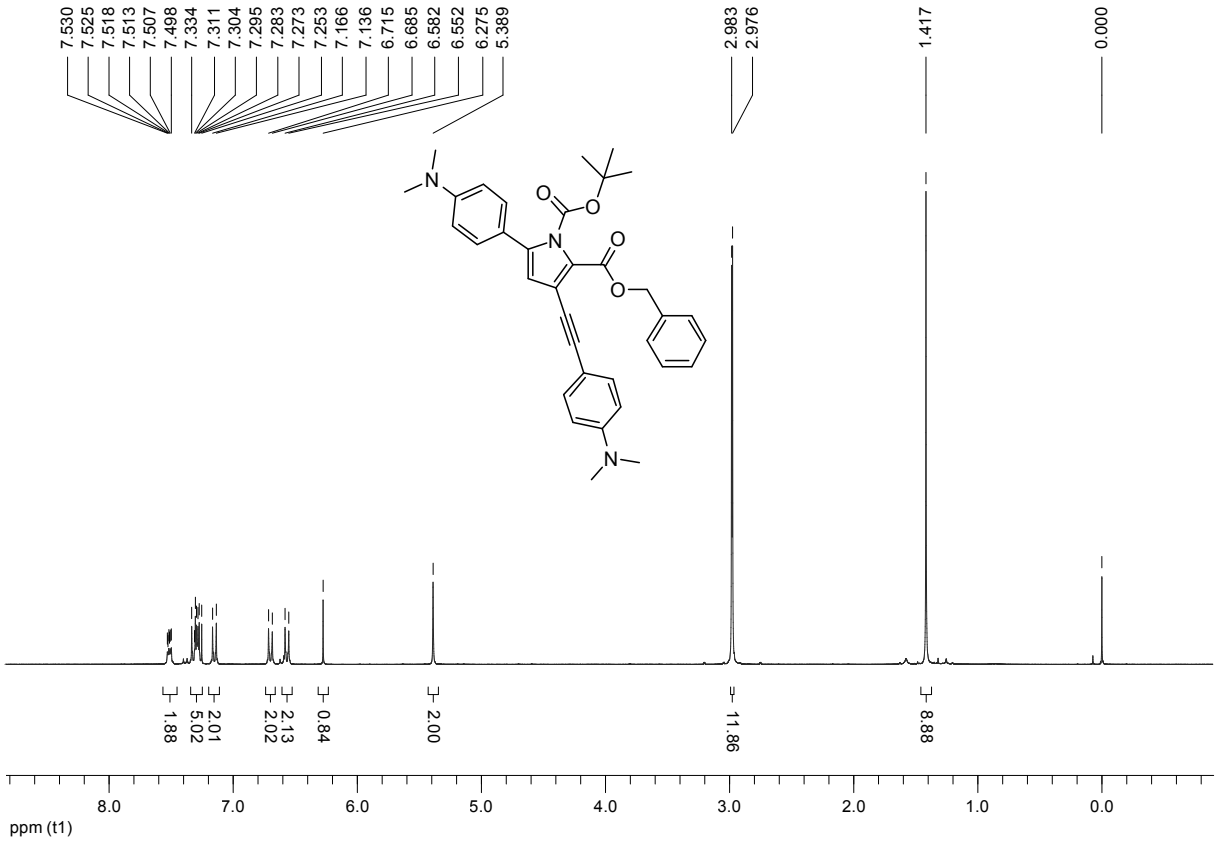

160.053
148.957
138.633
135.810
131.708
131.132
129.066
128.854
128.610
128.401
128.321
128.279
128.157
125.281
123.362
114.391
113.083
93.647
85.988
82.997
77.584
77.160
76.736
67.002
27.257
150
100
50
ppm (t1)

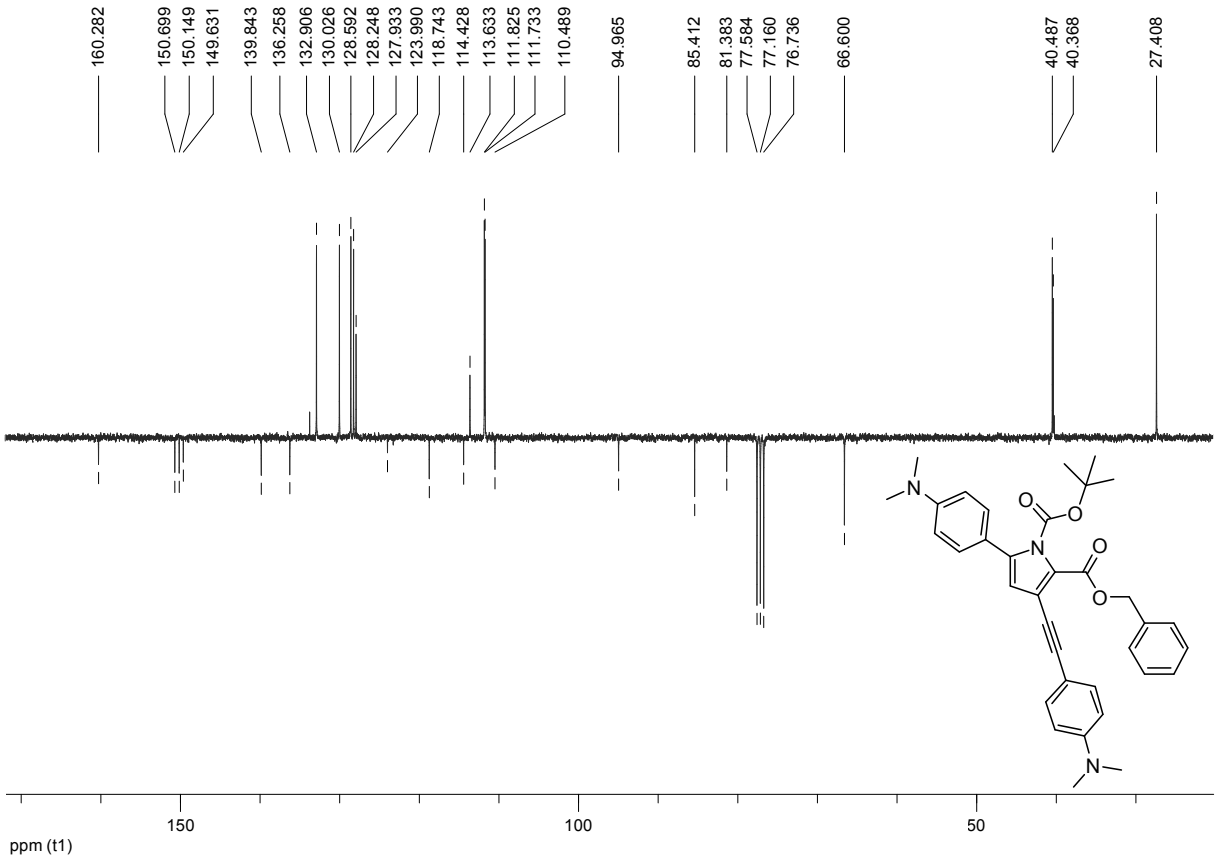
**2-Benzyl 1-*tert*-butyl 5-(4-methoxyphenyl)-3-((4-methoxyphenyl)ethynyl)-1*H*-pyrrole-1,2-dicarboxylate (4b)**



**2-Benzyl 1-*tert*-butyl 5-(4-(dimethylamino)phenyl)-3-((4-(dimethylamino)phenyl) ethynyl)-1*H*-pyrrole-1,2-dicarboxylate (4d)**



**2-Benzyl 1-*tert*-butyl 5-butyl-3-(hex-1-ynyl)-1*H*-pyrrole-1,2-dicarboxylate (4f)**