Palladium-Catalyzed Annulation of Bromo-Anilines:A Route to Functionalized Indolines and Indoles

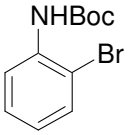
Praew Thansandote, David G. Hulcoop, Michael W. Langer and Mark Lautens*

General. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with chemical shifts using TMS or residual chloroform as internal standard. High-resolution mass spectra were obtained at 70 eV. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were freshly distilled under nitrogen from sodium benzophenone ketyl prior to use. Acetonitrile was distilled under nitrogen from CaH_2. Sealed tubes were 0.5 mL-2.0 mL tubes with sealable cap and Teflon septa provided by Biotage. All reactions were performed under nitrogen or argon.

General Procedure for Boc Protection

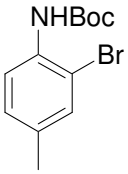
According to the procedure of Adapa.[1] The bromoaniline (1 equiv.) was stirred with Boc-anhydride (0.9 equiv.) and iodide (0.1 equiv.) at room temperature overnight. The reaction was then diluted with ether and washed with saturated sodium thiosulfate solution, and water. The solvent was removed *in vacuo* to provide the crude compound.

(2-Bromo-phenyl)-carbamic acid *tert*-butyl ester [7d]



Synthesized from 2-bromoaniline according to the general procedure. Purified by flash column chromatography (hexane:ethyl acetate, 12:1) yielding the title compound as a colorless oil (1.2 g, 41%); R_f = 0.65 (hexane:ethyl acetate, 2:1); δ_H (300 MHz, $CDCl_3$) 8.14 (1H, d, J = 8.4 Hz), 7.49 (1H, d, J = 7.2 Hz), 7.28 (1H, dd, J = 8.4, 7.2 Hz), 7.00 (1H, brs), 6.89 (1H, dd, J = 8.4, 7.2 Hz) 1.54 (9H, s); data identical to those previously reported.[2]

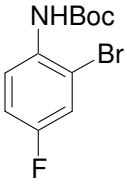
(2-Bromo-4-methyl-phenyl)-carbamic acid *tert*-butyl ester [7e]



Synthesized from 2-bromo-4-methylaniline according to the general procedure. Purified by flash column chromatography (hexane:ethyl acetate, 12:1) yielding the title compound as a colorless oil (2.3 g, 70%); R_f = 0.65 (hexane:ethyl acetate, 2:1); δ_H (300 MHz, $CDCl_3$) 7.98 (1H, d, J = 9.0 Hz), 7.32 (1H, s), 7.08 (1H, d, J = 9.0 Hz), 6.88 (1H, brs), 2.28 (3H, s), 1.54 (9H, s); data identical to those previously reported.[3]

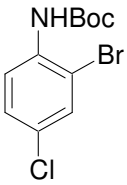
[1] Varala, R.; Nuvula, S.; Adapa, S.R. *J. Org. Chem.* **2006**, *71*, 8283.
[2] Cotter, J.; Hogan, A.M.L.; O'Shea, D.F. *Org. Lett.* **2007**, *9*, 1493.
[3] Zaitsev, V.G.; Dauglis, O. *J. Am. Chem. Soc.* **2005**, *127*, 4156.

(2-Bromo-4-fluoro-phenyl)-carbamic acid *tert*-butyl ester [7f]



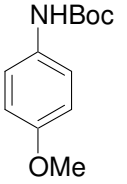
Synthesized from 2-bromo-4-fluoroaniline according to the general procedure. Purified by flash column chromatography (hexane:ethyl acetate, 12:1) yielding the title compound as a colorless oil (2.0 g, 66%); R_f = 0.68 (hexane:ethyl acetate, 2:1); δ_H (300 MHz, $CDCl_3$) 8.09 (1H, dd, *J* = 9.2, 5.8 Hz), 7.26 (1H, dd, *J* = 8.3, 2.8 Hz), 7.06-6.99 (1H, m), 6.85 (1H, brs), 1.53 (9H, s); data identical to those previously reported.[4]

(2-Bromo-4-chloro-phenyl)-carbamic acid *tert*-butyl ester [7g]



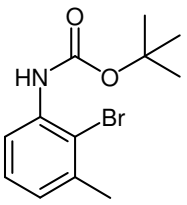
Synthesized from 2-bromo-4-chloroaniline according to the general procedure. Purified by flash column chromatography (hexane:ethyl acetate, 12:1) yielding the title compound as a colorless oil (1.2 g, 40%); R_f = 0.68 (hexane:ethyl acetate, 2:1); δ_H (300 MHz, $CDCl_3$) 8.10 (1H, d, *J* = 8.9 Hz), 7.5 (1H, d, *J* = 2,3 Hz), 7.25 (1H, dd, *J* = 8.9, 2.3 Hz), 6.95 (1H, brs), 1.53 (9H, s); data identical to those previously reported.[5]

(4-Methoxy-phenyl)-carbamic acid *tert*-butyl ester [precursor to 7h]



Synthesized from 4-methoxyaniline according to the general procedure. Purified by flash column chromatography (hexane:ethyl acetate, 7:1) yielding the title compound as a colorless oil (1.6 g, 87%); R_f = 0.50 (hexane:ethyl acetate, 2:1); δ_H (300 MHz, $CDCl_3$) 7.27-7.24 (2H, m), 6.85-6.81 (2H, m), 6.31 (1H, brs), 3.78 (3H, s), 1.51 (9H, s); data identical to those previously reported.[6]

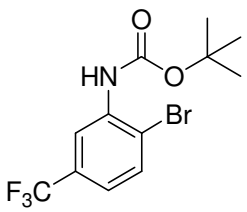
***tert*-butyl 2-bromo-3-methylphenylcarbamate [7i]**



Synthesized from 2-bromo-3-methylaniline according to the general procedure. Purified by flash column chromatography (hexane:ethyl acetate, 19:1) yielding the title compound as a light yellow oil (222 mg, 14%); R_f = 0.33 (hexane); δ_H (300 MHz, $CDCl_3$) 7.97 (1H, d, J = 8.4 Hz), 7.17 (1H, t, J = 7.6 Hz), 7.11 (1H, brs), 6.93-6.91 (1H, m), 2.40 (3H, s), 1.53 (9H, s); δ_C (100 MHz, $CDCl_3$) 152.7, 138.5, 136.6, 127.7, 125.0, 117.7, 115.5, 81.1, 28.5, 24.1; v_{max}/cm^{-1} ($CHCl_3$) 3414, 2978, 1736, 1517, 1158, 776; *m/z* (ESI) calcd. for $C_{12}H_{16}NO_2BrNa$ 308.0262: found 308.0256.

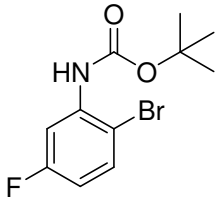
[4] Alberico, D.; Rudolph, A.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 775.
[5] Darnbrough, S.; Mervic, M.; Condon, S. M.; Burns, C. J. *Synth. Commun.* **2001**, *31*, 3273.
[6] Kessler, A.; Coleman, C.M.; Charoenying, P.; O'Shea, D.F. *J. Org. Chem.* **2004**, *69*, 7836.

***tert*-butyl 2-bromo-5-(trifluoromethyl)phenylcarbamate [7j]**



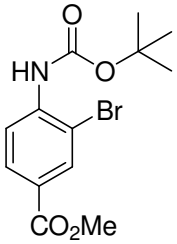
According to the procedure of Darnbrough.[5] To a solution of 2-bromo-5-(trifluoromethyl)aniline (1.0g, 4.17 mmol) in anhydrous THF (40 mL) was added Boc_2O (2.73 g, 12.50 mmol) followed by DMAP (51 mg, 0.417 mmol). The mixture was stirred at reflux for 3 hours, cooled to ambient temperature, and concentrated under reduced pressure to remove the solvent. The crude material was dissolved in methanol (40 mL) and potassium carbonate (1.73 g, 12.50 mmol) was added. The mixture was then refluxed for another 3 hours. After cooling to ambient temperature, the mixture was diluted with ether and extracted with water/brine (x3). The organic extracts were combined, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography with hexanes to give the title compound as a colorless oil (1.15 g, 81%). R_f = 0.54 (hexane:ethyl acetate, 10:1); δ_H (400 MHz, $CDCl_3$) 8.51 (1H, s), 7.62 (1H, d, J = 8.4 Hz), 7.14 (1H, dd, J = 8.4, 2.0 Hz), 7.10 (1H, brs), 1.55 (9H, s); data indentical to those previously reported.[5]

***tert*-butyl 2-bromo-5-fluorophenylcarbamate [7k]**



Synthesized according to the procedure of Darnbrough (above) using 2-bromo-5-fluoroaniline (1.0 g, 5.26 mmol). Purified by flash column chromatography (hexane:ethyl acetate, 19:1) yielding the title compound as a colourless oil (1.17 g, 76%); R_f = 0.74 (hexane:ethyl acetate, 9:1); δ_H (300 MHz, $CDCl_3$) 8.02 (1H, dd, J = 11.2, 2.8 Hz), 7.43 (1H, dd, J = 9.2, 6.0 Hz), 7.04 (1H, brs), 6.64 (ddd, J = 7.6, 2.8, 1.2 Hz), 1.54 (9H, s); δ_C (100 MHz, $CDCl_3$) 163.8, 161.4, 152.2, 137.9, 137.7, 133.0, 132.9, 110.9, 110.7, 107.7, 107.4, 106.2, 106.1, 81.8, 28.5; v_{max}/cm^{-1} ($CHCl_3$) 3411, 3105, 2979, 2932, 1735, 1607, 1522, 1153, 766; *m/z* (EI) calcd. for $C_{11}H_{13}NO_2BrF$ 289.0114: found 289.0108.

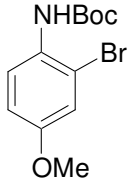
***tert*-butyl 4-(methoxycarbonyl)-2-bromophenylcarbamate [7l]**



Synthesized according to the procedure of Darnbrough (above) using methyl 4-amino-3-bromobenzoate (1.17 g, 5.07 mmol). Purified by flash column chromatography (hexane:ethyl acetate, 9:1) yielding the title compound as a white solid (204.4 mg, 12%); R_f = 0.29 (hexane:ethyl acetate, 9:1); δ_H (300 MHz, $CDCl_3$) 8.28 (1H, d, J = 8.6 Hz), 8.20 (1H, d, J = 2.0 Hz), 7.95 (1H, dd, J = 8.6,

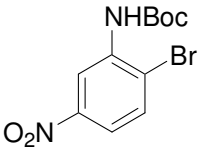
2.0 Hz), 7.22 (1H, brs), 3.90 (3H, s), 1.55 (9H, s); δ_C (100 MHz, $CDCl_3$) 165.6, 151.9, 140.4, 133.7, 129.9, 125.1, 118.5, 111.3, 81.8, 52.2, 28.2; ν_{max}/cm^{-1} ($CHCl_3$) 3408, 2977, 1724, 1523, 1153, 763; *m/z* (ESI) calcd. for $C_{13}H_{17}NO_4Br$ 330.0336: found 330.0335; m.p. = 108-109 °C.

(2-Bromo-4-methoxy-phenyl)-carbamic acid *tert*-butyl ester [7h]



According to the procedure of Muchowski.[7] *tert*-Butyl Lithium (6.5 mL of a 1.7M solution in pentane, 10.75 mmol) was added dropwise to a solution of (4-methoxy-phenyl)-carbamic acid *tert*-butyl ester (1g, 4.48 mmol) in THF (100 mL) at -78 °C. The reaction was then stirred at -20 °C for 1h. The reaction was cooled to -78 °C and 1,2-dibromoethane (0.94 mL, 2.07 g, 11.0 mmol) was then added dropwise and the reaction allowed to warm to room temperature overnight. The reaction was quenched with water (60 mL) and extracted with ether (3 × 60 mL), the combined organic layers were dried ($MgSO_4$), filtered and then the solvent removed *in vacuo*. The resulting oil was purified by flash column chromatography (hexane:ethyl acetate, 15:1) to yield the title compound as a colorless oil (0.19 g, 14%); R_f = 0.70 (hexane:ethyl acetate, 2:1); δ_H (300 MHz, $CDCl_3$) 7.94 (1H, d, J = 8.6 Hz), 7.07 (1H, d, J = 2.9 Hz), 6.85 (1H, dd, J = 8.6, 2.9 Hz), 6.72 (1H, brs), 3.77 (3H, s), 1.52 (9H, s); data indentical to those previously reported.[6]

(2-Bromo-5-nitro-phenyl)-carbamic acid *tert*-butyl ester [7m]

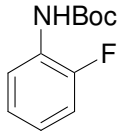


Acccording to the procedure of Ragnarsson.[8] Acetyl chloride (0.49 mL, 0.54 g, 6.91 mmol) was added dropwise to a stirred solution of 2-bromo-5-nitroaniline (1g, 4.61 mmol) and triethylamine (0.64 mL, 0.47 g, 4.61 mmol) in DCM (50 mL) at 0 °C. The reaction was then stirred at room temperature until complete by TLC (2h). The reaction was washed with 1M HCl (30 mL), saturated $NaHCO_3$ solution (30 mL) and water (30 mL) and then the organic layer dried ($MgSO_4$) and the solvent removed *in vacuo* to provide the crude amide product. This residue was dissolved in MeCN (20 mL) and DMAP (56.2 mg, 0.46 mmol) and Boc anhydride (1.26 g, 5.76 mmol) were added. The reaction was stirred at room temperature for 2h. Hydrazine hydrate (1.12 mL, 1.15 g, 23.0 mmol) was then added dropwise and the reaction stirred for a further 1.5h. The reaction was quenched with saturated NH_4Cl solution (20 mL) and extracted with ether (3 × 20 mL), the combined organic layers were dried ($MgSO_4$), filtered and then the solvent removed *in vacuo*. The resulting oil was purified by flash column chromatography (hexane:DCM, 4:1) to yield the

[7] Cho, S.; Gong, L.; Muchowski, J.M. *J. Org. Chem.* **1991**, *56*, 7288.
[8] Grehn, L.; Gunnarsson, K.; Ragnarsson, U. *J. Chem. Soc., Chem. Commun.* **1985**, 1317.

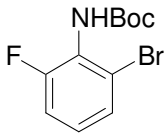
title compound as a yellow solid (0.43 g, 30%); R_f = 0.60 (hexane:DCM, 1:2); δ_H (300 MHz, $CDCl_3$) 9.11 (1H, s), 7.76 (1H, d, *J* = 8.7 Hz), 7.68 (1H, d, *J* = 8.7 Hz), 7.15 (1H, brs), 1.55 (9H, s); data identical to those previously reported.[5]

(2-Fluoro-phenyl)-carbamic acid *tert*-butyl ester [precursor to 7n]



Synthesized from 2-fluoroaniline according to the general procedure. Purified by flash column chromatography (hexane:ethyl acetate, 7:1) yielding the title compound as a colorless oil (1.6 g, 83%); R_f = 0.65 (hexane:ethyl acetate, 2:1); δ_H (300 MHz, $CDCl_3$) 8.08 (1H, t, *J* = 8.2 Hz), 7.12-6.93 (2H, m), 6.69 (1H, brs), 1.53 (9H, s); data identical to those previously reported.[9]

(2-Bromo-6-fluoro-phenyl)-carbamic acid tert-butyl ester [7n]



According to the procedure of Muchowski.[7] *tert*-Butyl Lithium (17.1 mL of a 1.7M solution in pentane, 10.1 mmol) was added dropwise to a solution of (2-fluoro-phenyl)-carbamic acid *tert*-butyl ester (1.5 g, 7.1 mmol) in THF (100 mL) at -78 ^oC. The reaction was then stirred at -20 ^oC for 1h. The reaction was cooled to -78 ^oC and 1,2-dibromoethane (1.54 mL, 3.36 g, 17.8 mmol) was then added dropwise and the reaction allowed to warm to room temperature overnight. The reaction was quenched with water (60 mL) and extracted with ether (3 × 60 mL), the combined organic layers were dried ($MgSO_4$), filtered and then the solvent removed *in vacuo*. The resulting oil was purified by flash column chromatography (hexane:ethyl acetate, 15:1) to yield the title compound as a white solid (0.99 g, 48%); R_f = 0.73 (hexane:ethyl acetate, 2:1);); δ_H (300 MHz, $CDCl_3$) 7.40-7.36 (1H, m), 7.11-7.07 (2H, m), 6.02 (1H, brs), 1.51 (9H, s); δ_C (75 MHz, $CDCl_3$) 160.0, 156.9, 156.6, 128.2, 122.4, 122.2, 115.9, 115.6, 114.2, 81.4, 28.3; v_{max}/cm^{-1} ($CHCl_3$) 2976, 2252, 1731, 1500; *m/z* (EI) calcd. for $C_{11}H_{13}NO_2BrF$ 289.0114: found 289.0111; mp = 68-70 ^oC (hexane:DCM, 4:1).

Annulation Reactions with *ortho*-Haloanilines

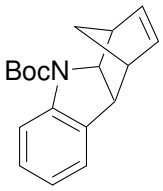
General Procedure

The substrate (0.2 mmol) was combined with $Pd(OAc)_2$ (4.9 mg, 0.02 mmol), $P^tBu_3HBF_4$ (11.6 mg, 0.04 mmol), Cs_2CO_3 (130.0 mg, 0.4 mmol) and the alkene (6 equiv.), toluene (2 mL) was

[9] Schlosser, M.; Gianneschi, A.; Leroux, F. *Eur. J. Org. Chem.* **2006**, *13*, 2956.

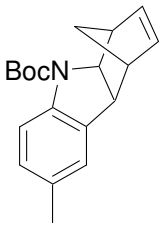
added, the reaction vessel flushed with nitrogen, sealed and then heated at 120 °C overnight. Once cooled, the reaction was diluted with DCM, then filtered through Celite™, washing with DCM. The solvent was removed *in vacuo* to provide the crude products.

Annulation Product 8d & 8o



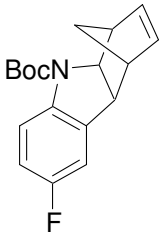
Synthesized from (2-bromo-phenyl)-carbamic acid *tert*-butyl according to the general procedure. Purified by flash column chromatography (hexane:ethyl acetate, 20:1) yielding the title compound as a clear oil (50.7 mg, 90%); R_f = 0.70 (hexane:ethyl acetate, 2:1); δ_H (300 MHz, $CDCl_3$) 7.84 (0.75H, brs), 7.40 (0.25H, brs), 7.17-7.11 (2H, m), 6.93 (1H, t, J = 7.0 Hz), 6.39-6.31 (1H, m), 6.12 (1H, brs), 4.21 (1H, brs), 3.37 (1H, d, J = 7.9 Hz), 3.22 (1H, brs), 2.91 (1H, s), 1.58 (9H, s), 1.40 (2H, s); δ_C (75 MHz, $CDCl_3$) 140.0, 135.7, 127.9, 124.0, 124.0, 122.4, 115.0, 48.6, 48.3, 47.8, 42.2, 28.7, 28.5; v_{max}/cm^{-1} ($CHCl_3$) 2976, 2252, 1694, 1601, 1481, 1389; *m/z* (EI) calcd. for $C_{18}H_{21}NO_2$ 283.1572: found 283.1570.

Annulation Product 8e



Synthesized from (2-bromo-4-methyl-phenyl)-carbamic acid *tert*-butyl ester according to the general procedure. Purified by flash column chromatography (hexane:ethyl acetate, 20:1) yielding the title compound as a white solid (58.6 mg, 94%); R_f = 0.80 (hexane:ethyl acetate, 2:1); δ_H (300 MHz, $CDCl_3$) 7.70 (0.75H, brs), 7.29 (0.25H, brs), 7.00-6.93 (2H, m), 6.31 (1H, s), 6.11 (1H, s), 4.27-4.19 (1H, m), 3.33 (1H, d, J = 8,0 Hz), 3.21 (0.75H, s), 2.89 (1H, s), 2.28 (3H, s), 1.57 (9H, s), 1.41 (2H, s); δ_C (75 MHz, $CDCl_3$) 153.0, 140.0, 135.7, 132.6, 131.8, 129.1, 128.4, 124.7, 114.7, 66.3, 48.6, 48.3, 47.7, 42.3, 28.7, 28.6, 28.5, 21.0,; v_{max}/cm^{-1} ($CHCl_3$) 2973, 2246, 1683, 1490m 1383; *m/z* (ESI+) calcd. for $C_{19}H_{24}NO_2$ 298.1801: found 298.1800.

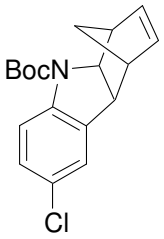
Annulation Product 8f



Synthesized from (2-bromo-4-fluoro-phenyl)-carbamic acid *tert*-butyl ester according to the general procedure. Purified by flash column chromatography (hexane:ethyl acetate, 20:1) yielding the title compound as a white solid (54.6 mg, 91%); R_f = 0.70 (hexane:ethyl acetate, 2:1); δ_H (300 MHz, $CDCl_3$) 7.77 (0.75H, brs), 7.33 (0.25H, brs), 6.83-6.81 (2H, m), 6.31 (1H, s), 6.11 (brs), 4.32-4.22 (1H,

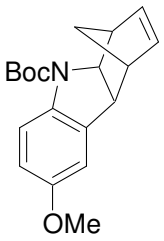
m), 3.34 (1H, J = 7.9 Hz), 3.22 (0.75H, s), 2.90 (1H, s), 1.57 (9H, s), 1.43 (2H, s); δ_C (75 MHz, $CDCl_3$) 161.8, 157.5, 152.8, 139.8, 135.8, 115.7, 115.6, 114.3, 114.0, 111.5, 80.8, 66.7, 48.5, 48.4, 47.7, 28.7, 28.5, 28.4; v_{max}/cm^{-1} ($CHCl_3$) 2976, 2252, 1684, 1485, 1388; *m/z* (EI) calcd. for $C_{18}H_{20}NO_2F$ 301.1478: found 301.1472; mp = 57-58 ^oC (hexane:ethyl acetate, 2:1).

Annulation Product 8g



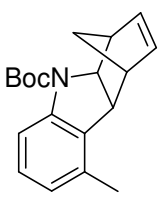
Synthesized from (2-bromo-4-chloro-phenyl)-carbamic acid *tert*-butyl ester using DavePhos according to the general procedure. Purified by flash column chromatography (hexane:ethyl acetate, 20:1) yielding the title compound (32.5 mg, 51%); R_f = 0.70 (hexane:ethyl acetate, 2:1); δ_H (300 MHz, $CDCl_3$) 7.77-7.75 (0.75H, m), 7.53-7.50 (0.25 H, m), 7.11-7.07 (2H, m), 6.33-6.30 (1H, m), 6.12 (1H, brs), 4.28-4.20 (1H, m), 3.34 (1H, d, J = 8.3 H), 3.22 (1H, brs), 2.91 (1H, s), 1.58 (9H, s), 0.98-0.85 (2H, m).); δ_C (100 MHz, $CDCl_3$) 152.5, 145.2, 139.8, 135.8, 133.8, 127.9, 127.3, 124.3, 115.9, 81.0, 66.7, 48.6, 48.3, 47.6, 42.3, 28.7; v_{max}/cm^{-1} ($CDCl_3$) 2974, 1698, 1479, 1379; *m/z* (EI+) calcd. for $C_{18}H_{20}ClNO_2$ 317.1183: found 317.1172.

Annulation Product 8h



Synthesized from (2-bromo-4-methoxy-phenyl)-carbamic acid *tert*-butyl ester according to the general procedure. Purified by flash column chromatography (hexane:ethyl acetate, 20:1) yielding the title compound as colorless needles (46.3 mg, 74%); R_f = 0.60 (hexane:ethyl acetate, 2:1); δ_H (300 MHz, $CDCl_3$) 7.75-7.72 (0.75H, m), 7.33-7.31 (0.25H, m), 6.70-6.67 (2H, m), 6.31 (1H, brs), 6.11 (1H, brs), 4.30-4.17 (1H, m), 3.77 (3H, s), 3.34 (1H, d, J = 8.3 Hz), 3.20 (0.75H, s), 2.91 (1H, s), 1.57 (9H, s), 1.41 (2H, s); δ_C (75 MHz, $CDCl_3$) 155.6, 139.9, 139.3, 135.8, 133.0, 115.5, 112.4, 110.6, 80.8, 66.5, 55.9, 48.5, 48.4, 47.9, 42.3, 28.8, 28.7; v_{max}/cm^{-1} ($CHCl_3$) 2976, 2252, 1682, 1488, 1390; *m/z* (ESI+) calcd. for $C_{19}H_{24}NO_3$ 314.1750: found 314.1738; mp = 96-98 ^oC (hexane).

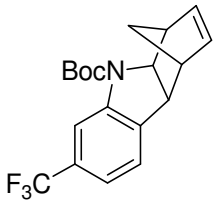
Annulation Product 8i



Synthesized from *tert*-butyl 2-bromo-3-methylphenylcarbamate according to the general procedure. Purified by flash column chromatography (hexane:ethyl acetate, 19:1) yielding the title compound as a clear oil (59.5 mg, 89%); R_f =

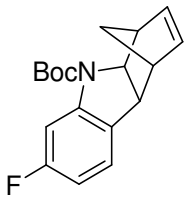
0.29 (hexane:ethyl acetate, 19:1); δ_H (400 MHz, $CDCl_3$) 7.70 (1H, brs), 7.06 (1H, t, J = 7.6 Hz), 6.74 (d, J = 7.6 Hz), 6.34 -6.33 (1H, m), 6.14 (1H, brs), 4.29-4.21 (1H, m), 3.35 (1H, d, J = 8.0 Hz), 3.24 (1H, brs), 3.03 (1H, brs), 2.32 (3H, s), 1.59 (9H, s), 1.43 (2H, brs); δ_C (100 MHz, $CDCl_3$) 140.1, 135.7, 128.1, 123.9, 112.5, 104.9, 66.3, 48.3, 47.3, 46.3, 42.4, 28.7, 18.6; v_{max}/cm^{-1} ($CHCl_3$) 2972, 1698, 1592, 1455, 1385, 1164, 733; *m/z* (ESI+) calcd. for $C_{19}H_{24}NO_2Na$ 320.1627: found 320.1621.

Annulation Product 8j



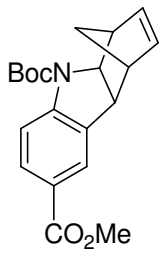
Synthesized from *tert*-butyl 2-bromo-5-(trifluoromethyl)phenylcarbamate according to the general procedure. Purified by flash column chromatography (hexane:ethyl acetate, 19:1) yielding the title compound as a clear oil (56.6 mg, 81%); R_f = 0.27 (hexane:ethyl acetate, 19:1); δ_H (400 MHz, $CDCl_3$) 8.13 (1H, brs), 7.20 (2H, brs), 6.34 (1H, brs), 6.14 (1H, brs), 4.34-4.26 (1H, m), 3.41 (1H, d, J = 8.0 Hz), 3.25 (1H, brs), 2.95 (1H, s), 1.51 (9H, s), 1.47-1.45 (1H, m), 1.39-1.37 (1H, m); δ_C (100 MHz, $CDCl_3$) 152.2, 139.7, 139.2, 135.6, 125.7, 124.0, 122.9, 119.3, 111.7, 81.1, 66.5, 48.4, 48.2, 47.6, 42.0, 28.4; v_{max}/cm^{-1} ($CHCl_3$) 2972, 1708, 1444, 1317, 1164, 1124; *m/z* (ESI+) calcd. for $C_{19}H_{20}NO_2F_3Na$ 374.1344: found 374.1338.

Annulation Product 8k



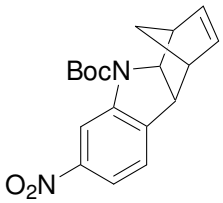
Synthesized from *tert*-butyl 2-bromo-5-fluorophenylcarbamate according to the general procedure. Purified by flash column chromatography (hexane:ethyl acetate, 19:1) yielding the title compound as a clear oil (53.1 mg, 88%); R_f = 0.27 (hexane:ethyl acetate, 19:1); δ_H (400 MHz, $CDCl_3$) 7.61-7.58 (1H, m), 7.02 (1H, t, J = 6.4 Hz), 6.61 (dt, J = 8.4, 2.4 Hz), 6.31 (1H, m), 6.11 (1H, brs), 4.32-4.21 (1H, m), 3.33 (1H, d, J = 8.0 Hz), 3.21 (1H, brs), 2.88 (1H, s), 1.58 (9H, s), 1.46-1.41 (2H, m); δ_C (100 MHz, $CDCl_3$) 139.9, 135.6, 124.5, 108.9, 108.7, 103.3, 103.0, 67.3, 48.6, 48.3, 47.2, 42.2, 28.6; v_{max}/cm^{-1} ($CHCl_3$) 2976, 1698, 1494, 1385, 1134, 863, 735; *m/z* (EI) calcd. for $C_{18}H_{20}NO_2F$ 301.1478: found 301.1491.

Annulation Product 8l



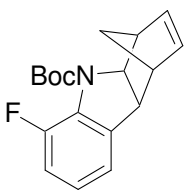
Synthesized from *tert*-butyl 4-(methoxycarbonyl)-2-bromophenylcarbamate according to the general procedure. Purified by flash column chromatography (hexane:ethyl acetate, 19:1) yielding the title compound as a clear oil (49.5 mg, 72%); R_f = 0.12 (hexane:ethyl acetate, 19:1); δ_H (400 MHz, $CDCl_3$) 7.87 (1H, m), 7.80 (1H, d, *J* = 0.8 Hz), 6.34 (1H, dd, *J* = 5.6, 2.8 Hz), 6.13 (1H, brs), 4.23 (1H, brs), 3.88 (3H, s), 3.39 (1H, d, *J* = 8.0 Hz), 3.25 (1H, brs), 2.97 (1H, brs), 1.59 (9H, s), 1.46-1.43 (1H, m), 1.38-1.36 (1H, m); δ_C (100 MHz, $CDCl_3$) 167.2, 152.4, 139.9, 135.8, 130.6, 125.7, 124.2, 114.3, 81.4, 67.0, 52.0, 48.7, 47.4, 42.2, 28.6; v_{max}/cm^{-1} ($CHCl_3$) 2973, 1718, 1705, 1379, 1269, 1163, 767; *m/z* (ESI+) calcd. for $C_{20}H_{24}NO_4$ 342.1700: found 342.1699; m.p. = 56-57 °C.

Annulation Product 8m



Synthesized from (2-bromo-5-nitro-phenyl)-carbamic acid *tert*-butyl ester according to the general procedure. Purified by flash column chromatography (hexane:ethyl acetate, 20:1) yielding the title compound as a yellow solid (48.8 mg, 8674%); R_f = 0.55 (hexane:ethyl acetate, 2:1); δ_H (300 MHz, $CDCl_3$) 8.66 (0.75H, brs), 8.29 (0.25H, brs), 7.83 (1H, dd, *J* = 8.2, 2.4 Hz), 7.22 (2H, d, *J* = 8.2 Hz), 6.37-6.34 (1H, m), 6.16 (1H, brs), 4.33 (1H, brs), 3.43 (1H, d, *J* = 7.7 Hz), 3.28 (1H brs), 2.98 (1H, s), 1.62 (9H, s), 1.48 (1H, d, *J* = 9.6 Hz), 1.36 (1H, d, *J* = 9.6 Hz); δ_C (75 MHz, $CDCl_3$) 152.1, 148.4, 139.8, 136.0, 124.1, 118.1, 110.0, 67.1, 61.1, 48.6, 48.4, 46.6, 42.2, 32.4, 28.5; v_{max}/cm^{-1} ($CHCl_3$) 2977, 2253, 1698, 1523, 1484, 1386, 1347; *m/z* (ESI+) calcd. for $C_{18}H_{21}N_2O_4$ 329.1495: found 329.1508; mp = 126-128 ^oC (hexane:ethyl acetate, 20:1).

Annulation Product 8n

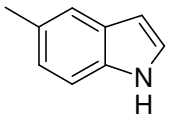


Synthesized from (2-bromo-6-fluoro-phenyl)-carbamic acid *tert*-butyl ester according to the general procedure. Purified by flash column chromatography (hexane:ethyl acetate, 20:1) yielding the title compound as a clear oil (54.9 mg, 91%); R_f = 0.70 (hexane:ethyl acetate, 2:1); δ_H (300 MHz, $CDCl_3$) 6.94-6.88 (3H, m), 6.29 (1H, dd, *J* = 5.6, 2.9 Hz), 6.15 (1H, dd, *J* = 5.6, 2.9 Hz), 4.25 (1H, d, *J* = 7.5 Hz), 3.48 (1H, d, *J* = 7.5 Hz), 3.21 (1H, s), 2.85 (1H, s), 1.55 (9H, s), 1.39 (1H, d, *J* = 9.2 Hz), 1.28 (1H, d, *J* = 9.2 Hz); δ_C (75 MHz, $CDCl_3$) 153.2, 152.1, 148.8, 139.2, 137.1, 137.0,

136.3, 132.2, 126.2, 124.4, 124.3, 119.7, 116.5, 116.2, 81.4, 67.8, 48.8, 48.5, 48.0, 42.2, 34.8, 31.8, 28.4; v_{max}/cm^{-1} ($CHCl_3$) 2989, 2252, 1690, 1483, 1371, 1344; *m/z* (EI) calcd. for $C_{18}H_{20}NFO_2$ 301.1478: found 301.1482.

Indole Formation

5-Methyl-1*H*-indole [9e]

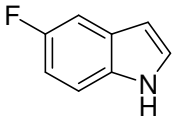


Procedure A: (2-Bromo-4-methyl-phenyl)-carbamic acid *tert*-butyl ester (50 mg, 0.17 mmol) was suspended in ethylene glycol (3 mL) and the mixture heated at 170 ^{o}C overnight. The reaction was quenched with water (10 mL) and the mixture extracted with ether (3 × 20 mL), the combined organic layers were dried ($MgSO_4$), filtered and then the solvent removed *in vacuo*. The resulting oil was purified by flash column chromatography (hexane:ethyl acetate 10:1) to yield the title compound as a white solid (17.8 mg, 81%).

Procedure B: (2-Bromo-4-methyl-phenyl)-carbamic acid *tert*-butyl ester (50 mg, 0.17 mmol) was suspended in xylenes (3 mL) and 1 pipette measure of silica added, the mixture heated at 170 ^{o}C overnight in a sealed tube. Once cooled, the reaction was diluted with DCM, then filtered through Celite^{TM}, washing with DCM. The solvent was removed *in vacuo* to provide the crude product. Purified by flash column chromatography (hexane:ethyl acetate 10:1) to yield the title compound as a white solid (17.3 mg, 79%).

R_f = 0.60 (hexane:ethyl acetate, 2:1); δ_H (300 MHz, $CDCl_3$) 8.02 (1H, brs), 7.43 (1H, s), 7.27 (1H, d, *J* = 8.1 Hz), 7.16 (1H, t, *J* = 3.1 Hz), 7.02 (1H, d, *J* = 8.1 Hz), 6.48-6.46 (1H, m); data identical to those previously reported.[10]

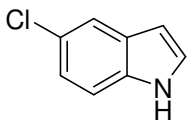
5-Fluoro-1*H*-indole [9f]



Synthesized according to Procedures A and B for **9a** except using annulation product **8f**. Purified by flash column chromatography (hexane:ethyl acetate, 9:1) yielding the title compound as a light brown oil (18.1 mg, 81% for Procedure A; 15.9 mg, 71% for Procedure B); R_f = 0.08 (hexane:ethyl acetate, 19:1); δ_H (300 MHz, $CDCl_3$) 8.14 (1H, brs), 7.30-7.27 (2H, m), 7.25-7.23 (1H, m), 6.94 (1H, dd, *J* = 9.2, 2.4 Hz), 6.52-6.51 (1H, m); data identical to those previously reported.[11]

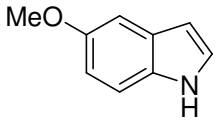
[10] Esaki, H.; Ito, N.; Sakai, S.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *Tetrahedron* **2006**, *62*, 10954.

5-chloro-1*H*-indole [9g]



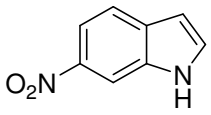
Synthesized according to Procedures A and B for **9a** except using annulation product **8g** on a 0.13-0.17 mmol scale. Purified by flash column chromatography (hexane:ethyl acetate, 5:1) yielding the title compound as light brown crystals (10.2 mg, 53% for Procedure A; 18.0 mg, 68% for Procedure B); R_f = 0.31 (hexane:ethyl acetate, 19:1); δ_H (400 MHz, $CDCl_3$) 8.17 (1H, brs), 7.61 (1H, d, *J* = 2.0 Hz), 7.30 (1H, d, *J* = 8.6 Hz), 7.23 (1H, t, *J* = 2.7 Hz), 7.15 (1H, dd, *J* = 8.5, 1.9 Hz), 6.51-6.49 (m, 1H); data identical to those previously reported.[12]

5-methoxy-1*H*-indole [9h]



Synthesized according to Procedures A and B for **9a** except using annulation product **8h** on a 0.10 mmol scale. Purified by flash column chromatography (hexane:ethyl acetate, 9:1) yielding the title compound as light brown crystals (7.5 mg, 53% for Procedure A; 13.7 mg, 97% for Procedure B); R_f = 0.13 (hexane:ethyl acetate, 9:1); δ_H (400 MHz, $CDCl_3$) 8.03 (1H, brs), 7.28 (1H, d, *J* = 8.8 Hz), 7.18 (1H, t, *J* = 2.8 Hz), 7.11 (1H, d, *J* = 2.3 Hz), 6.86 (1H, dd, *J* = 8.7, 2.4 Hz), 6.49-6.48 (m, 1H), 3.85 (s, 1H); data identical to those previously reported.[13]

6-nitro-1*H*-indole [9i]

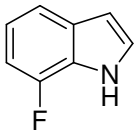


Synthesized according to Procedure A for **9a** except using annulation product **8i** on a 0.1 to 0.12 mmol scale. Purified by flash column chromatography (hexane:ethyl acetate, 5:1) yielding the title compound as yellow crystals (17.3 mg, 92% for Procedure A; 8.6 mg, 53% for Procedure B); R_f = 0.18 (hexane:ethyl acetate, 5:1); δ_H (400 MHz, $CDCl_3$) 8.60 (1H, brs), 8.39 (1H, d, *J* = 1.0 Hz), 8.04 (1H, dd, *J* = 8.7, 2.0 Hz), 7.69 (1H, d, *J* = 8.7 Hz), 7.51 (1H, t, *J* = 3.2 Hz), 6.68 (m, 1H); mp = 140-141 °C; data identical to those previously reported.[14]

---

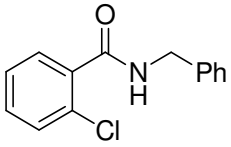
[11] Schlosser, M.; Ginanneschi, A.; Leroux, F. *Eur. J. Org. Chem.* **2006**, *13*, 2956.
[12] Trost, B.M.; McClory, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 2074.
[13] Coowar, D.; Bouissac, J.; Hanbali, M.; Paschaki, M.; Mohier, E.; Luu, B. *J. Med. Chem.* **2004**, *47*, 6270.
[14] Melhado, L.L.; Leonard, N.J. *J. Org. Chem.* **1983**, *48*, 5130.

7-fluoro-1*H*-indole [9j]



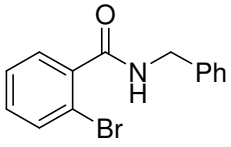
Synthesized according to Procedures A and B for **9a** except using annulation product **8j** on a 0.10-0.20 mmol scale. Purified by flash column chromatography (hexane:ethyl acetate, 9:1) yielding the title compound as yellow crystals (14 mg, 52% for Procedure A; 7.7 mg, 62% for Procedure B); R_f = 0.59 (hexane:ethyl acetate, 9:1); δ_H (400 MHz, $CDCl_3$) 8.30 (1H, brs), 7.40 (1H, d, *J* = 7.8 Hz), 7.23 (1H, t, *J* = 3.1 Hz), 7.02 (1H, ddd, *J* = 12.7, 8.2, 4.9 Hz), 6.90 (1H, dd, *J* = 10.6, 7.8 Hz), 6.59 (m, 1H); data identical to those previously reported.[15]

***N*-benzyl-2-chlorobenzamide [10a]**



To a solution of 0.80 mL o-chloro-benzoyl chloride (1.10 g, 6.31 mmol) in 40 mL DCM was added 1.50 mL triethylamine (1.09 g, 10.8 mmol) and 0.8 mL benzyl amine (785 mg, 7.32 mmol) dropwise at r.t. The reaction mixture was stirred overnight, quenched with a saturated NH_4Cl-solution and extracted three times with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography of the residue (hexane/EA=3:1) yielded 1.48 g (6.0 mmol, 95 %) as colorless crystalline solid. ^{1}H-NMR (400 MHz, 295 K, $CDCl_3$): δ = 7.67 (dd, *J* = 4.9 Hz, *J* = 2.1 Hz, 1H), 7.34 (m, 8H), 6.52 (s, 1H), 4.65 (d, *J* = 5.7 Hz, 2H); ^{13}C-NMR (100 MHz, 295 K, $CDCl_3$): δ = 166.6, 137.9, 131.6, 130.9, 130.5, 130.4, 129.0, 128.1, 127.9, 127.3, 44.5 ppm; MS (ESI): *m/z* (%): 246 ($[M+H]^+$, 100); HRMS (ESI): calc. for $[C_{14}H_{13}ClNO]^+$: 246.0680 ; found: 246.0687.

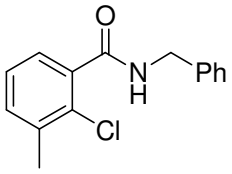
***N*-benzyl-2-bromobenzamide [Table 3]**



To a solution of 0.65 mL o-bromo-benzoyl chloride (1.10 g, 4.97 mmol) in 50 mL DCM was added 1.30 mL triethylamine (945 mg, 9.34 mmol) and 0.55 mL benzylamine (540 mg, 5.0 mmol) dropwise at r.t. The reaction mixture was stirred overnight, quenched with a saturated NH_4Cl-solution and extracted three times with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography of the residue (hexane/EA=3:1) yielded 1.34 g (4.61 mmol, 93 %) as colorless crystalline solid. Analytical data for $C_{14}H_{12}BrNO$ (290.16): in agreement with published literature. ^{1}H-NMR (400 MHz, 295 K, $CDCl_3$): δ = 7.57 (m, 2H), 7.37 (m, 4H), 7.28 (m, 3H), 6.26 (s, 1H), 4.65 (d, *J* = 5.7 Hz, 2H) ppm; MS (ESI): *m/z* (%): 290 ($[M+H]^+$, 100); HRMS (EI): calc. for $[C_{14}H_{13}BrNO]^+$: 290.0175; found: 290.0161.

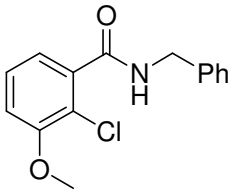
[15] Schlosser, M.; Ginanneschi, A.; Leroux, F. *Eur. J. Org. Chem.* **2006**, 2956.

***N*-benzyl-2-chloro-3-methylbenzamide [10b]**



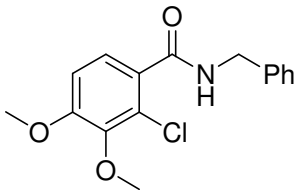
300 mg 2-chloro-3-methylbenzoic acid (1.76 mmol) was stirred in 1 mL oxalyl chloride (1.5 g, 11.8 mmol) overnight at r.t. The volatiles were removed and the residue redissolved in 10 mL DCM. 0.7 mL benzylamine (687 mg, 6.40 mmol) was added to the solution. The reaction mixture was stirred overnight, quenched with a saturated NH_4Cl-solution and extracted three times with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography of the residue (hexane/EA=2:1) yielded 441 mg (1.70 mmol, 96 %) as colorless solid. Analytical data for $C_{15}H_{14}ClNO$ (259.73): ^{1}H-NMR (400 MHz, 295 K, $CDCl_3$): δ = 7.29 (m, 4H), 7.20 (m, 3H), 7.10 (m, 1H), 6.29 (s, 1H), 4.55 (d, J = 5.7 Hz, 2H), 2.31 (s, 3H) ppm; ^{13}C-NMR (100 MHz, 295 K, $CDCl_3$): δ = 167.5, 138.0, 137.5, 136.3, 132.5, 129.0, 128.1, 127.8, 127.2, 126.8, 44.4, 20.7 ppm; MS (ESI): *m/z* (%): 260 ([M+H]$^+$, 100); HRMS (ESI): calc. for $[C_{15}H_{15}ClNO]^+$: 260.0836; found: 260.0842.

***N*-benzyl-2-chloro-3-methoxybenzamide [10c]**



2-chloro-3-methoxybenzoic acid (250 mg, 1.34 mmol) was stirred in 1 mL oxalyl chloride (1.5 g, 11.8 mmol) overnight at r.t. The volatiles were removed and the residue redissolved in 10 mL DCM. 0.7 mL benzylamine (687 mg, 6.40 mmol) was added to the solution. The reaction mixture was stirred overnight, quenched with a saturated NH_4Cl-solution and extracted three times with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography of the residue (hexane/EA=2:1) yielded 320 mg (1.16 mmol, 87%) as colorless solid. Analytical data for $C_{15}H_{14}ClNO_2$ (275.73); ^{1}H-NMR (400 MHz, 295 K, $CDCl_3$): δ = 7.29 (m, 6H), 7.18 (m, 1H), 6.96 (m, 1H), 6.41 (s, 1H), 4.63 (d, J = 5.7 Hz, 2H), 3.88 (s, 3H) ppm; ^{13}C-NMR (100 MHz, 295 K, $CDCl_3$): δ = 166.9, 155.5, 137.9, 137.2, 129.0, 129.0, 128.1, 127.9, 127.8, 121.4, 119.6, 113.6, 56.7, 44.4 ppm; MS (ESI): *m/z* (%): 276([M+H]$^+$, 100); HRMS (ESI): calc. for $[C_{15}H_{15}ClNO_2]^+$: 276.0785; found: 276.0789.

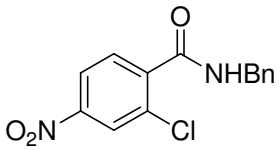
***N*-benzyl-2-chloro-3,4-dimethoxybenzamide [10d]**



2-chloro-3,4-dimethoxybenzoic acid (96 mg, 443 µmol) was stirred in 1 mL oxalyl chloride (1.5 g, 11.8 mmol) overnight at r.t. The volatiles were removed and the residue redissolved in 5 mL DCM. 0.5 mL benzylamine (491 mg, 4.58 mmol) was added to the solution. The reaction mixture was stirred overnight, quenched with a saturated NH^4Cl-solution and extracted three times with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography of the residue (hexane/EA=2:1) yielded 100 mg (327 µmol, 74 %) as colorless solid. Analytical data for $C_{16}H_{16}ClNO_3$ (305.76): ^{1}H-NMR (400 MHz, 295 K, $CDCl_3$): δ = 7.48 (d, J = 8.7

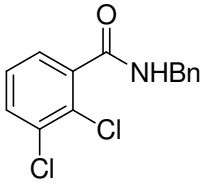
Hz, 1H), 7.32 (m, 5H), 6.84 (d, J = 8.7 Hz, 1H), 6.65 (s, 1H), 4.63 (d, J = 5.7 Hz, 2H), 3.88 (s, 3H), 3.83 (s, 3H) ppm; ^{13}C-NMR (100 MHz, 295 K, $CDCl_3$): δ = 166.2, 155.5, 145.7, 138.1, 128.9, 128.1, 128.0, 127.8, 126.0, 126.0, 110.7, 60.9, 56.4, 44.5 ppm; MS (ESI): *m/z* (%): 306 ([M+H]$^+$, 100); HRMS (ESI): calc. for $[C_{16}H_{17}ClNO_3]^+$: 306.0891; found: 306.0905.

_N_-benzyl-2-chloro-4-nitrobenzamide [10e]



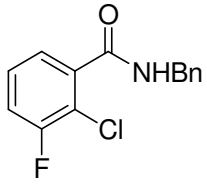
To a solution of 1.00 eq. of the benzoic acid (500 mg, 2.48 mmol) in DCM (0.12 M) was added 1.3 eq. of the coupling reagent (EDC or DCC) and 2.00 eq. triethylamine and stirred at r.t. for 10 mins. 1.50 eq. benzylamine was added and the reaction mixture stirred overnight at r.t. The reaction mixture was quenched with a saturated NH_4Cl-solution and extracted three times with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography of the residue (hexane/EA=3:1) 320 mg yielded 1.10 mmol (44 %) as yellow solid. Analytical data for $C_{14}H_{11}ClN_2O_3$ (290.70): ^{1}H-NMR (400 MHz, 295 K, $CDCl_3$): δ = 8.24 (m, 1H), 8.11 (m, 1H), 7.74 (m, 1H), 7.34 (m, 5H), 6.64 (s, 1H), 4.63 (d, J = 5.7 Hz, 2H) ppm; ^{13}C-NMR (100 MHz, 295 K, $CDCl_3$): δ = 164.8, 149.0, 141.0, 137.3, 132.2, 131.1, 129.1, 128.2, 128.1, 125.6, 122.2, 44.6 ppm; MS (ESI): *m/z* (%): 291 ([M+H]$^+$, 100); HRMS (ESI): calc. for $[C_{14}H_{12}ClN_2O_3]^+$: 291.0530; found: 291.0527.

_N_-benzyl-2,3-dichlorobenzamide [10f]



To a solution the benzoic acid (300 mg, 1.57 mmol) in DCM (0.12 M) was added 1.3 eq. of the coupling reagent (EDC or DCC) and 2.00 eq. triethylamine and stirred at r.t. for 10 mins. 1.50 eq. benzylamine was added and the reaction mixture stirred overnight at r.t. The reaction mixture was quenched with a saturated NH_4Cl-solution and extracted three times with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated. Flash-chromatography (hexane/EA=3:1) yielded 193 mg (689 mmol, 44 %) as colorless solid. Analytical data for $C_{14}H_{11}C_{l2}NO$ (280.15): ^{1}H-NMR (400 MHz, 295 K, $CDCl_3$): δ = 7.53 (dd, J = 1.6 Hz, J = 8.0 Hz, 1H), 7.53 (dd, J = 1.6 Hz, J = 7.7 Hz, 1H), 7.30 (m, 6H), 6.24 (s, 1H), 4.67 (d, J = 5.7 Hz, 2H) ppm; ^{13}C-NMR (100 MHz, 295 K, $CDCl_3$): δ = 166.2, 137.9, 137.6, 134.1, 132.1, 129.5, 129.0, 128.1, 128.0, 127.9, 127.8, 44.5 ppm; MS (ESI): *m/z* (%): 280 ([M+H]$^+$, 100); HRMS (ESI): calc. for $[C_{14}H_{12}Cl_2NO]^+$: 280.0290; found: 280.0281.

_N_-benzyl-2-chloro-3-fluorobenzamide [10g]



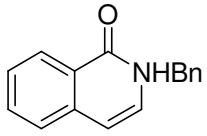
Starting from 300 mg (1.72 mmol) of the corresponding carboxylic acid. Flash-chromatography (hexane/EA=3:1) yielded 206 mg (781 µmol, 45 %) as colorless solid. To a solution of 1.00 eq. of the benzoic acid in DCM (0.12 M) was added 1.3 eq. of the coupling reagent (EDC or DCC) and 2.00 eq. triethylamine and stirred at r.t. for 10 mins. 1.50 eq. benzylamine was added and the reaction mixture stirred overnight at r.t. The reaction mixture was quenched with a saturated NH_4Cl-solution and extracted three times with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography of the residue yielded the benzamides as colorless solids. Analytical data for $C_{14}H_{11}ClFNO$ (263.69): ^{1}H-NMR (400 MHz, 295 K, $CDCl_3$): δ = 7.46 (m, 1H), 7.37 (m, 4H), 7.30 (m, 2H), 7.22 (m, 1H), 6.39 (s, 1H), 4.67 (d, J = 5.7 Hz, 2H) ppm; ^{13}C-NMR (100 MHz, 295 K, $CDCl_3$): δ = 159.7, 137.7, 137.4, 129.1, 128.4, 128.3, 128.1, 128.0, 125.3, 125.3, 118.4, 118.2, 105.0, 44.5 ppm; ^{19}F-NMR (282 MHz, 295 K, $CDCl_3$): δ = -113.3 (dd, J = 5.6 Hz, J = 8.6 Hz) ppm; MS (ESI): *m/z* (%): 264 ([M+H]$^+$, 100); HRMS (ESI): calc. for $[C_{14}H_{12}ClFNO]^+$: 264.0585; found: 264.0581.

Annulation Reactions with *ortho*-Halobenzamides

General Procedure

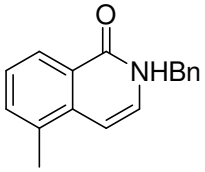
The substrate (0.2 mmol) was combined with $Pd(OAc)_2$ (4.9 mg, 0.02 mmol), $P^tBu_3HBF_4$ (11.6 mg, 0.04 mmol), Cs_2CO_3 (130.0 mg, 0.4 mmol) and the alkene (1 mL, 5 equiv.) in a sealed tube. After toluene (4 mL) was added, the reaction vessel was flushed with nitrogen and the tube was sealed. After the reaction mixture was stirred for 5 minutes at room temperature, the reaction was heated at 130 ^{o}C overnight. Once cooled, the reaction was diluted with DCM, then filtered through Celite^{TM}, washing with DCM. The solvent was removed *in vacuo* to provide the crude products, which were purified by flash column chromatography.

2-benzylisoquinolin-1(2H)-one [11a]



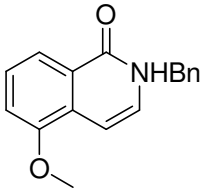
Synthesized from the general procedure using flash chromatography in hexane/EA=3:1 to give the title compound in 55% yield. Analytical data for $C_{16}H_{13}NO$ (235.28): in agreement with published literature; ^{1}H-NMR (400 MHz, 295 K, $CDCl_3$): δ = 8.46 (d, J = 7.5 Hz, 1H), 7.63 (m, 1H), 7.48 (m, 2H), 7.31 (m, 5H), 7.08 (d, J = 7.4 Hz, 1H), 6.48 (d, J = 7.4 Hz, 1H), 5.21 (s, 2H) ppm; MS (ESI): *m/z* (%): 236 ([M+H]$^+$, 100); HRMS (ESI): calc. for $[C_{16}H_{14}NO]^+$: 236.1069; found: 236.1080.

2-benzyl-5-methylisoquinolin-1(2H)-one [11b]



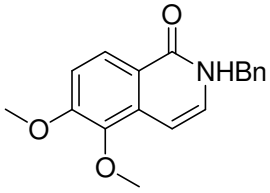
Synthesized from the general procedure using flashchromatography in hexane/EA=4:1 to give the title compound in 86% yield. Analytical data for $C_{17}H_{15}NO$ (249.31): ^{1}H-NMR (400 MHz, 295 K, $CDCl_3$): δ = 8.35 (d, J = 8.1 Hz, 1H), 7.46 (d, J = 6.8 Hz, 1H), 7.37 (m, 1H), 7.30 (m, 5H), 7.10 (d, J = 7.6 Hz, 1H), 6.59 (dd, J = 0.6 Hz, J = 7.6 Hz, 1H), 5.22 (s, 2H), 2.50 (s, 3H) ppm. ^{13}C-NMR (100 MHz, 295 K, $CDCl_3$): δ = 162.7, 137.2, 136.2, 133.4, 133.2, 131.2, 129.0, 128.2, 128.0, 126.8, 126.7, 126.3, 103.3, 51.9, 19.1 ppm; MS (EI): *m/z* (%):249 ([M]$^+$, 100); HRMS (EI): calc. for $[C_{17}H_{15}NO]^+$: 249.1154; found: 249.1157.

2-benzyl-5-methoxyisoquinolin-1(2H)-one [11c]



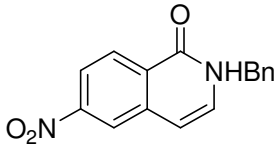
Synthesized from the general procedure using flash chromatography in hexane/EA=5:1 to give the title compound in 43% yield. Analytical data for $C_{17}H_{15}NO_2$ (265.31): ^{1}H-NMR (400 MHz, 295 K, $CDCl_3$): δ = 8.06 (d, J = 8.1 Hz, 1H), 7.41 (m, 1H), 7.30 (m, 4H), 7.30 (m, 5H), 7.06 (m, 2H), 6.85 (d, J = 7.8 Hz, 1H), 5.22 (s, 2H), 3.92 (s, 3H) ppm; ^{13}C-NMR (100 MHz, 295 K, $CDCl_3$): δ = 162.2, 154.7, 137.1, 130.8, 129.0, 128.3, 128.1, 128.0, 127.6, 127.4, 119.9, 111.6, 101.0, 56.0, 52.0 ppm; MS (EI): *m/z* (%): 265 ([M]$^+$, 100); HRMS (EI): calc. for $[C_{17}H_{15}NO_2]^+$: 265.1103; found: 265.1108.

2-benzyl-5,6-dimethoxyisoquinolin-1(2H)-one [11d]



Synthesized according to the general procedure using flashchromatography in hexane/EA=4:1 to give the title compound in 30% yield. Analytical data for $C_{18}H_{17}NO_3$ (295.33): ^{1}H-NMR (400 MHz, 295 K, $CDCl_3$): δ = 8.16 (d, J = 8.9 Hz, 1H), 7.27 (m, 3H), 7.22 (m, 3H), 7.07 (d, J = 9.0 Hz, 1H), 6.98 (d, J = 7.6 Hz, 1H), 6.68 (d, J = 7.6 Hz, 1H),5.12 (s, 2H), 3.91 (s, 3H), 3.82 (s, 3H) ppm; ^{13}C-NMR (100 MHz, 295 K, $CDCl_3$): δ = 162.1, 154.8, 137.3 132.5, 131.8, 129.0, 128.1, 128.0, 125.2, 120.9, 112.6, 100.8, 61.4, 56.3, 51.7 ppm; MS (ESI): *m/z* (%): 296 ([M+H]$^+$, 100); HRMS (ESI): calc. for $[C_{18}H_{18}NO_3]^+$: 296.1281; found: 296.1285.

2-benzyl-6-nitroisoquinolin-1(2H)-one [11e]

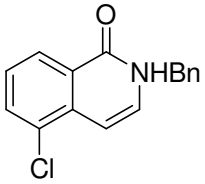


Synthesized according to the general procedure to yield traces of the title compound whose identity was confirmed by HRMS. Analytical data for $C_{16}H_{12}N_2O_3$ (280.28): **MS** (ESI): *m/z* (%): 281 ([M+H]$^+$, 100); **HRMS** (ESI): calc. for $[C_{16}H_{13}NO_3]^+$: 281.0920; found: 281.0907.

General procedure for Annulation Reactions with Electron-Deficient ortho-Chlorobenzamides

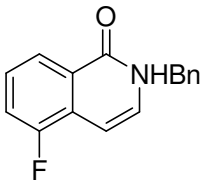
$Pd(OAc)_2$ (4.5 mg, 19.9 μmol), PPh_3 (11.3 mg, 43 μmol), 0.2 mmol substrate and 131 mg Cs_2CO_3 (0.4 mmol) were added to a sealed tube and purged with nitrogen. Toluene (4 mL) and norbornadiene (1 mL, 0.98 mmol) were added and the reaction mixture stirred for 5 minutes at room temperature. The sealed tube was then put into a preheated oil bath at 130°C and stirred overnight. The reaction mixture was cooled to room temperature and filtrated over a plug of Celite™ and washed with 40 mL of DCM. The volatiles were removed and the residue purified by flash-chromatography over silica (hexane/EA).

2-benzyl-5-chloroisoquinolin-1(2H)-one [11f]



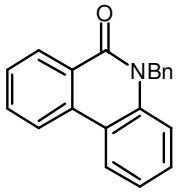
Synthesized according to the general procedure using flash chromatography in hexane/EA=3:1 to give the title compound in 35% yield. Analytical data for $C_{16}H_{12}ClNO$ (269.73): ^{1}H-NMR (400 MHz, 295 K, $CDCl_3$): δ = 8.39 (d, J = 8.1 Hz, 1H), 7.68 (d, J = 7.7 Hz, 1H), 7.38 (m, 1H), 7.32 (m, 4H), 7.18 (d, J = 7.6 Hz, 1H), 6.85 (d, J = 7.7 Hz, 1H), 5.22 (s, 2H) ppm; ^{13}C-NMR (100 MHz, 295 K, $CDCl_3$): δ = 161.8, 136.7, 135.1, 132.7, 132.6, 130.6, 129.1, 128.2, 127.2, 127.2, 102.7, 52.1 ppm.; MS (EI): *m/z* (%): 269 ([M]$^+$, 100); HRMS (EI): calc. for $[C_{16}H_{12}ClNO]^+$: 269.0607; found: 269.0602.

2-benzyl-5-fluoroisoquinolin-1(2H)-one [11g]



Synthesized according to the general procedure using flash chromatography in hexane/EA=3:1 to give the title compound in 44% yield. Analytical data for $C_{16}H_{12}FNO$ (253.27): ^{1}H-NMR (400 MHz, 295 K, $CDCl_3$): δ = 8.24 (d, J = 8.0 Hz, 1H), 7.42 (m, 1H), 7.33 (m, 5H), 7.13 (d, J = 7.5 Hz, 1H,), 6.70 (d, J = 7.5 Hz, 1H), 5.22 (s, 2H) ppm; ^{13}C-NMR (100 MHz, 295 K, $CDCl_3$): δ = 161.5, 161.5, 159.0, 156.5, 136.8, 132.1, 129.1, 128.2, 128.2, 127.3, 127.3, 124.0, 123.9, 117.4, 117.2, 99.2, 99.1, 52.1 ppm; ^{19}F-NMR (282 MHz, 295 K, $CDCl_3$): δ = -122.9 (q, J = 5.3 Hz) ppm; MS (EI): *m/z* (%): 253 ([M]$^+$, 100); HRMS (EI): calc. for $[C_{16}H_{12}FNO]^+$: 253.0903; found: 253.0905.

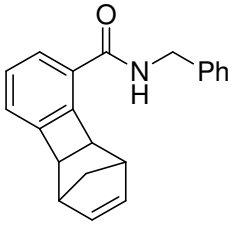
Annulation Byproduct 13



Synthesized according to the general procedure with **10a** and isolated as a byproduct. ^{1}H-NMR (400 MHz, 295 K, $CDCl_3$): δ = 8.63 (1H, dd, J = 8.6, 1.5),

8.33-8.29 (2H, m), 7.84-7.78 (1H, m), 7.65-7.61 (1H, m), 7.42-7.38 (1H, m), 7.32-7.23 (m, 7H), 5.68 (2H, brs) ppm. Data identical to those previously reported.[16]

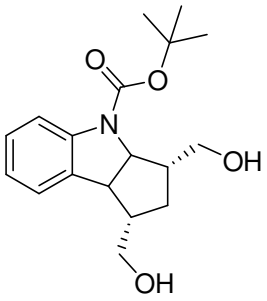
Annulation Byproduct 14



Synthesized according to the general procedure with **10a** and isolated as a byproduct. Analytical data for $C_{21}H_{19}NO$ (301.38): ^{1}H-NMR (400 MHz, 295 K, $CDCl_3$): δ = 7.79 (1H, d, J = 7.8 Hz), 7.37-7.36 (3H, m), 7.33-7.29 (3H, m), 7.19-7.15 (1H, m), 6.38 (1H, brs), 6.24 (1H, dd, J = 5.4, 2.8 Hz), 6.16 (1H, dd, J = 5.4, 3.2 Hz), 4.68 (2H, dq, J = 14.9, 5.9 Hz), 3.23 (2H, dd, J = 18.8, 3.9 Hz), 2.80 (2H, dd, J = 18.3, 1.7 Hz), 1.32 (1H, d, J = 9.3 Hz), 0.85 (1H, d, J = 9.3 Hz) ppm; ^{13}C-NMR (100 MHz, 295 K, $CDCl_3$): δ = 146.5, 137.2, 136.4, 129.0, 128.4, 127.9, 127.8, 126.8, 125.0, 102.7, 52.1, 48.1, 44.1, 41.8, 41.7, 41.3 ppm; **MS** (ESI): *m/z* (%): 302 ([M+H]$^+$, 100); **HRMS** (ESI): calc. for $[C_{21}H_{20}NO]^+$: 302.1545; found: 302.1539.

Post-Modifications

Tricyclic Indoline [15]

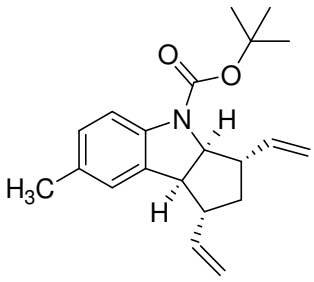


According to the procedure of Cremer.[17] A solution of 50 mg (0.17 mmol) of **8d** in 3 mL of dichloromethane was cooled to -78 "C. Pure oxygen was bubbled through the solution for 15 min. Ozone was bubbled through the solution until the reaction turned blue to indicate completion. Dry argon was bubbled through the solution for 5 min, and the solution warmed to -35 "C. Then 10.3 mg (0.27 mmol) of solid NaBH, was added. The mixture was stirred at room temperature for 12 h. The solution was cooled in an ice bath, quenched by addition of H_2O, and stirred at room temperature for 4 h. The solution was evaporated to near dryness and the resulting residue extracted with ethyl acetate and water. The combined organic extracts were concentrated under reduced pressure. The crude residue was purified by flash chromatography (ethyl acetate) to yield **15** as clear oil (48.2 mg, 44%); R_f = 0.23 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.44 (1H, d, J = 6.6 Hz), 7.29 (1H, m), 7.18 (1H, t, J = 7.6 Hz), 7.00 (1H, t, J = 7.6 Hz), 4.49 (2H, dd, J = 9.9 Hz, 7.1 Hz), 3.85-3.78 (1H, m), 3.66-3.60 (2H, m), 2.28-2.14 (2H, m), 1.90-1.79 (2H, m), 1.60 (9H, s), 1.28-1.24 (2H, m); δ_C (100 MHz, $CDCl_3$) 135.7, 127.8, 124.8, 123.5, 122.9, 116.3, 68.9, 66.2, 65.3, 50.7, 48.9, 48.7, 32.2, 28.6, 28.6, 14.4; ν_{max}/cm^{-1} ($CHCl_3$) 2951, 2930, 2868, 1730, 1711, 1601, 1579, 1487, 1461, 1377,

[16] Furuta, T.; Kitamura, Y.; Hashimoto, A.; Fujii, S.; Tanaka, K.; Kan, T. Org. Lett. **2007**, *9*, 183.
[17] Sommese, A.G.; Cremer, S.E. *Organometallics* **1990**, *9*, 1784.

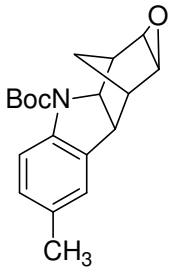
1368, 1314, 1289, 1269, 1164, 1144, 1071, 749; *m/z* (ESI+) calcd. for $C_{18}H_{26}NO_4$ 320.1857: found 320.1856.

Tricyclic Indoline [16]



According to the procedure of Cha.[18] Ethylene was bubbled gently through a solution of annulation product **8e** (59.5 mg, 0.2 mmol) in dichloromethane (40 mL) for 10 minutes. Grubbs II Catalyst (17 mg, 0.02 mmol) was then added and the reaction was stirred at room temperature under ethylene (1 atm) until TLC showed consumption of the starting material (approximately 4 hours). The reaction mixture was filtered over Celite using dichloromethane to wash the Celite pad and then the combined filtrates were concentrated under reduced pressure. The crude residue was purified by flash column chromatography (hexane:ethyl acetate, 19:1) yielding **16** as a clear oil (33.0 mg, 55%); R_f = 0.32 (hexane:ethyl acetate, 19:1); δ_H (400 MHz, $CDCl_3$) 7.70 (1H, brs), 7.00-6.98 (2H, m), 5.97 (2H, ddd, *J* = 16.8 Hz, 10.2 Hz, 8.0 Hz), 5.19-4.99 (4H, m), 4.50-4.41 (1H, m), 3.52 (1H, t, *J* = 8.0 Hz), 2.63-2.53 (2H, m), 2.29 (3H, s), 1.90-1.84 (1H, m), 1.58 (1H, m), 1.53 (9H, s); δ_C (100 MHz, $CDCl_3$) 141.7, 141.4, 132.4, 128.6, 128.4, 127.5, 124.3, 121.1, 115.7, 114.7, 114.2, 81.1, 69.9, 61.3, 52.4, 51.4, 50.4, 46.5, 39.2, 33.2, 32.3, 28.7, 28.6, 21.1, 20.6, 15.5, 14.7; ν_{max}/cm^{-1} ($CHCl_3$) 2977, 1699, 1490, 1386, 1151, 909, 735; *m/z* (ESI+) calcd. for $C_{21}H_{27}NO_2Na$ 348.1940: found 348.1934.

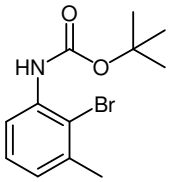
Tetracyclic Indole Derivative [17]



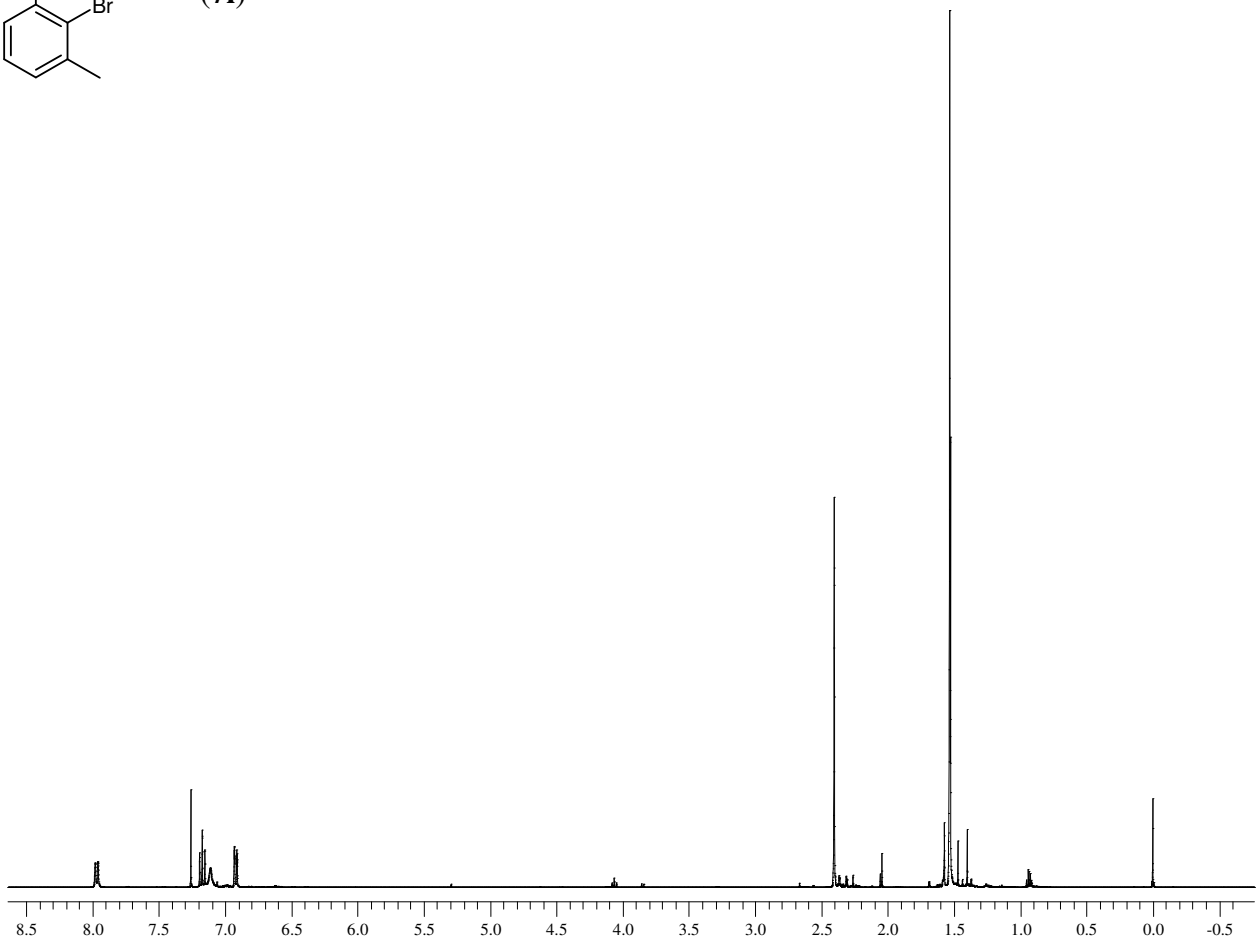
A solution of annulation product **8e** (50 mg, 0.17 mmol), MCPBA (50 mg, 0.22 mmol), and sodium carbonate (36 mg, 0.34 mmol) dissolved in dichloromethane (3 mL) was stirred at room temperature for 12 hours. The mixture was then thoroughly washed with sodium thiosulfate and extracted with dichloromethane (x3). The organic extracts were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (hexane:ethyl acetate, 9:1) yielding **17** as a light yellow oil (32.0 mg, 60%); R_f = 0.14 (hexane:ethyl acetate, 9:1); δ_H (400 MHz, $CDCl_3$) 7.70 (1H, d, *J* = 7.2 Hz), 6.95 (1H, d, *J* = 6.0 Hz), 6.90 (1H, s), 4.25-4.11 (1H, m), 3.37 (1H, d, *J* = 8.0 Hz), 3.28 (1H, d, *J* = 3.2 Hz), 3.23-3.16 (1H, m), 3.01-2.91 (1H, m), 2.59 (1H, s), 2.28 (3H, s), 1.57 (9H, s), 1.18 (1H, d, *J* = 10.8 Hz), 0.90-0.85 (1H, m); δ_C (100 MHz, $CDCl_3$) 132.2, 128.7, 124.8, 114.6, 80.8, 64.4, 51.8, 49.9,

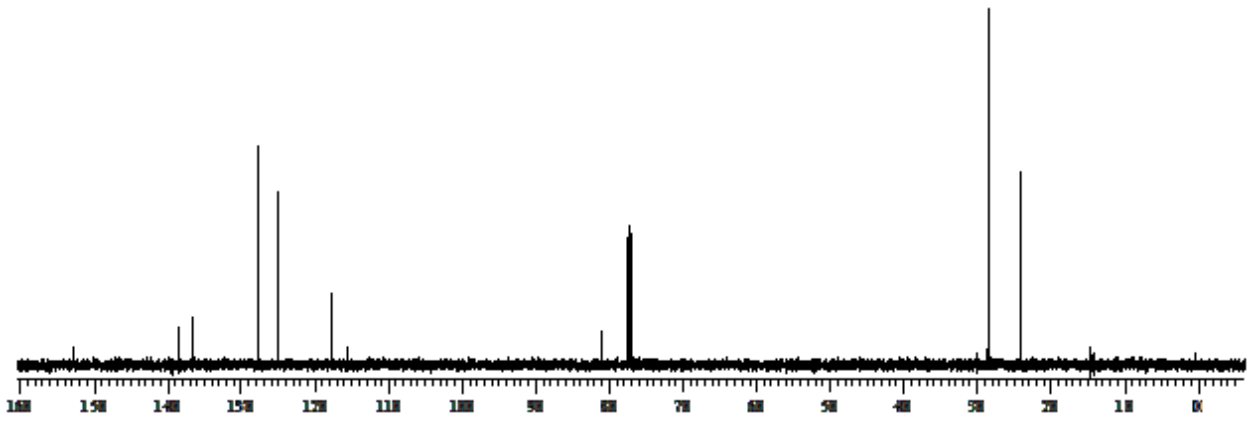
[18] Lysenko, I.L.; Lee, H.G.; Cha, J.K. *Org. Lett.* **2006**, *8*, 2671.

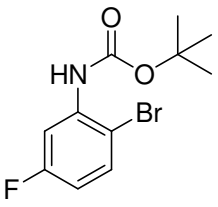
47.1, 46.2, 44.5, 43.6, 42.7; ν_{max}/cm^{-1} ($CHCl_3$) 2970, 1698, 1494, 1385, 1145, 848; *m/z* (EI) calcd. for $C_{19}H_{23}NO_3$ 313.1678: found 313.1690.



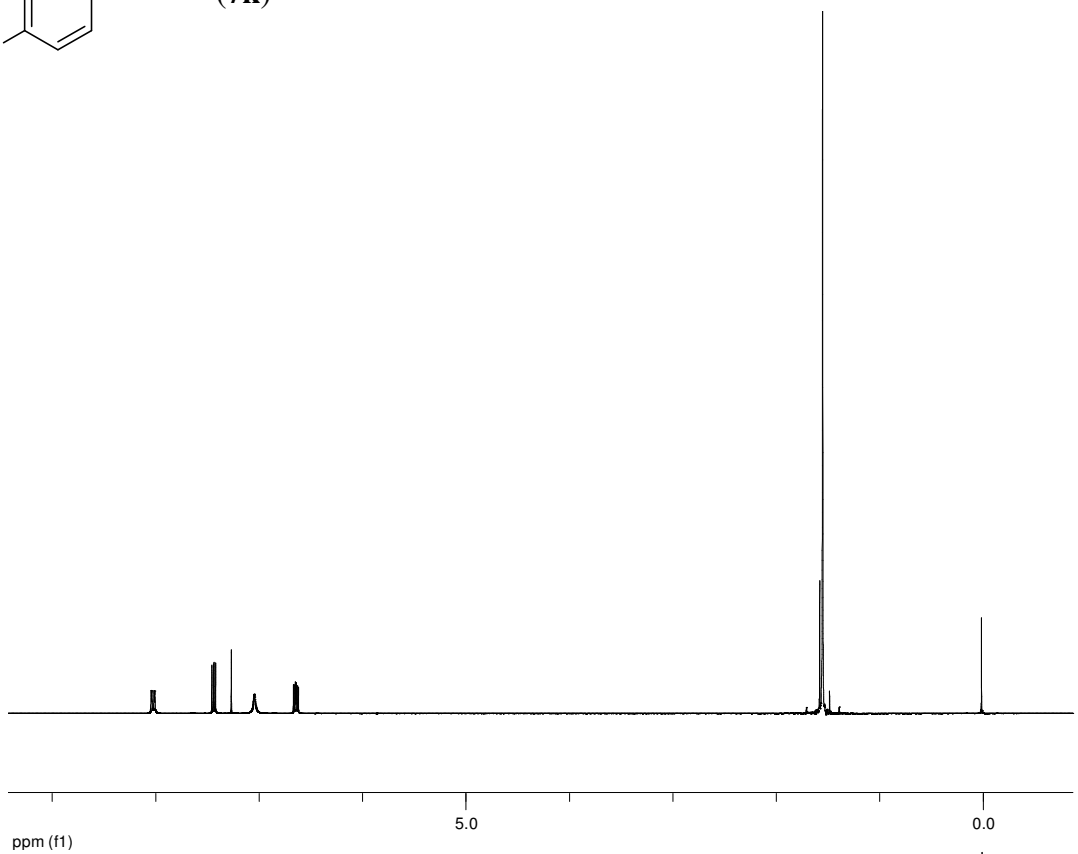
(**7i**)

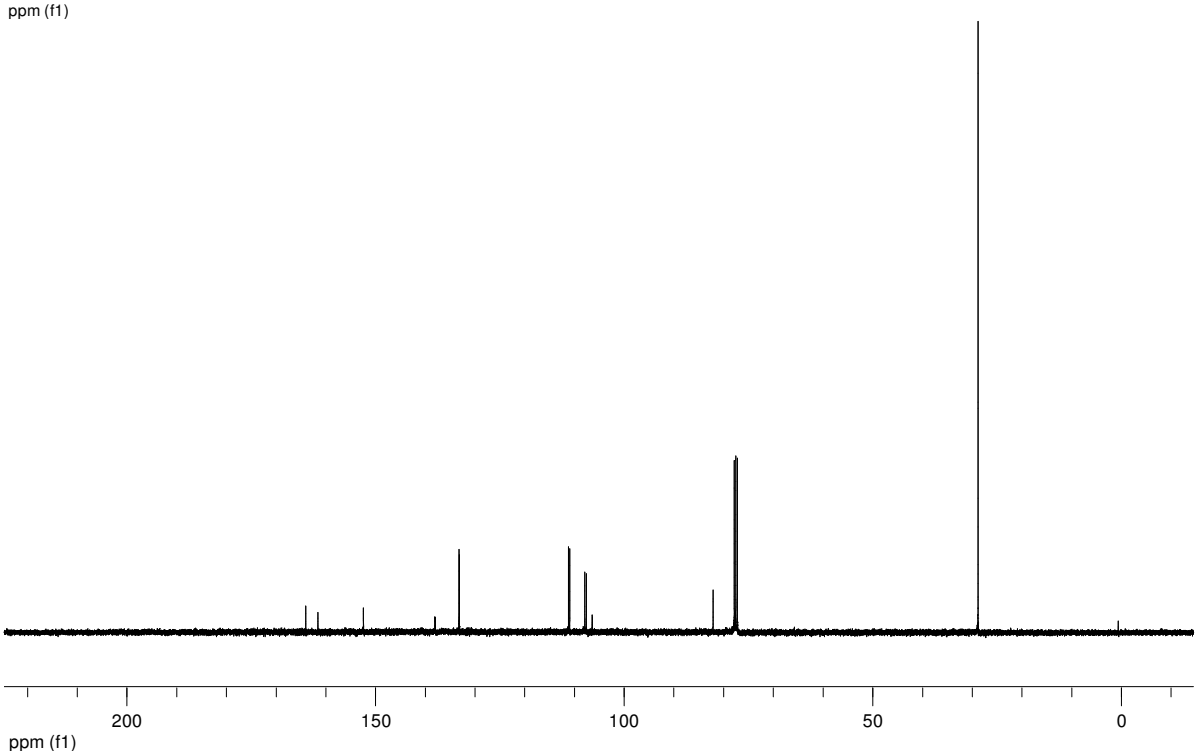


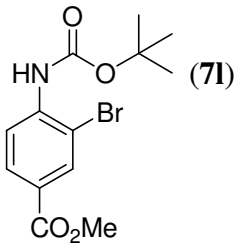




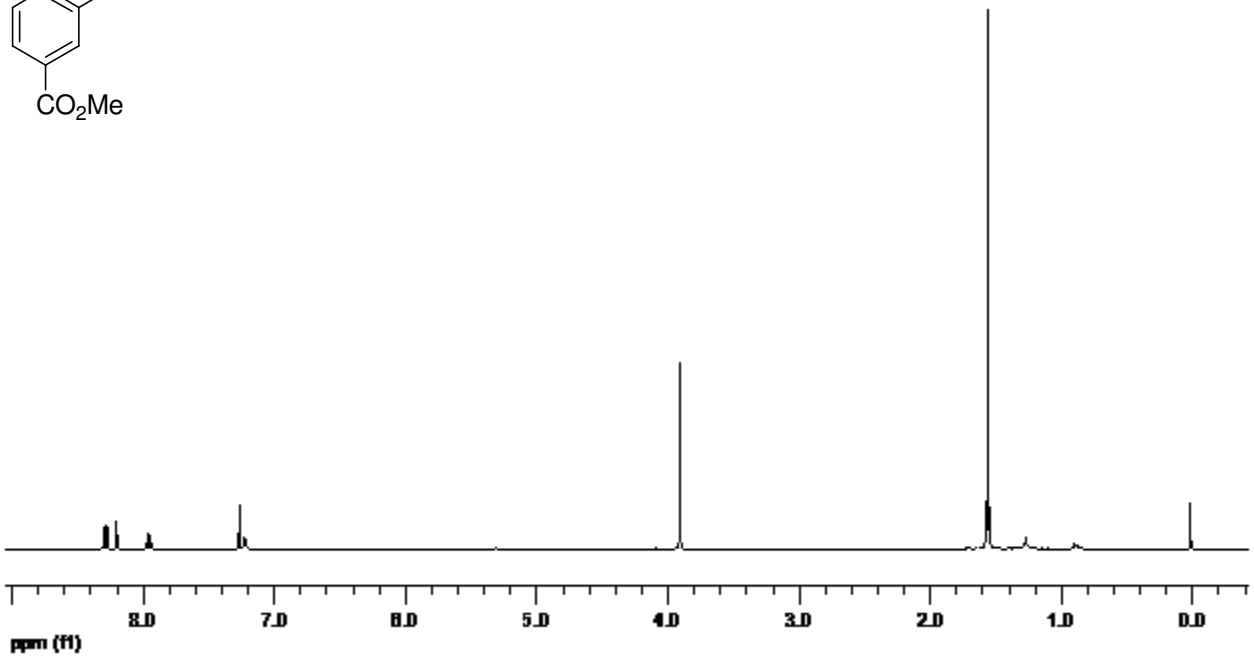
(**7k**)

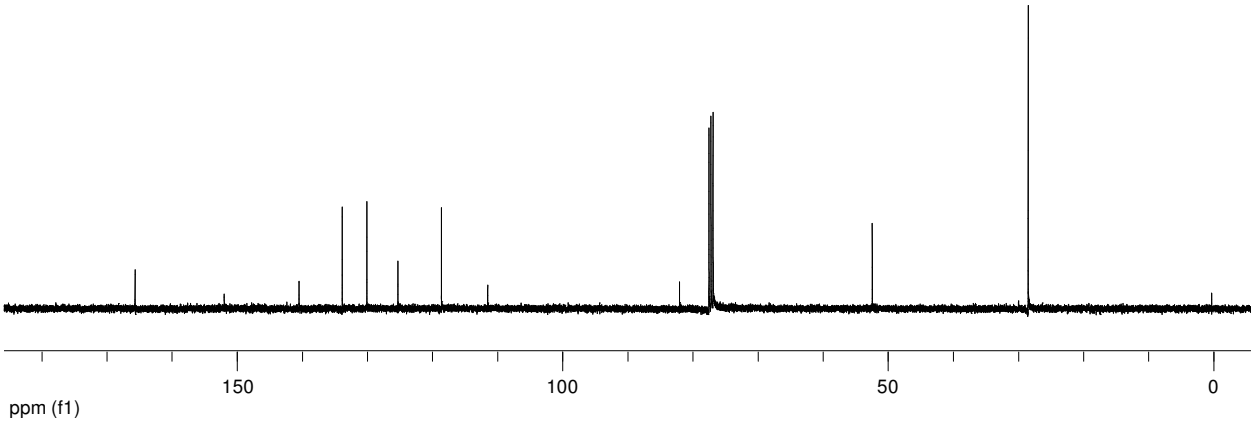


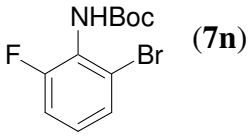




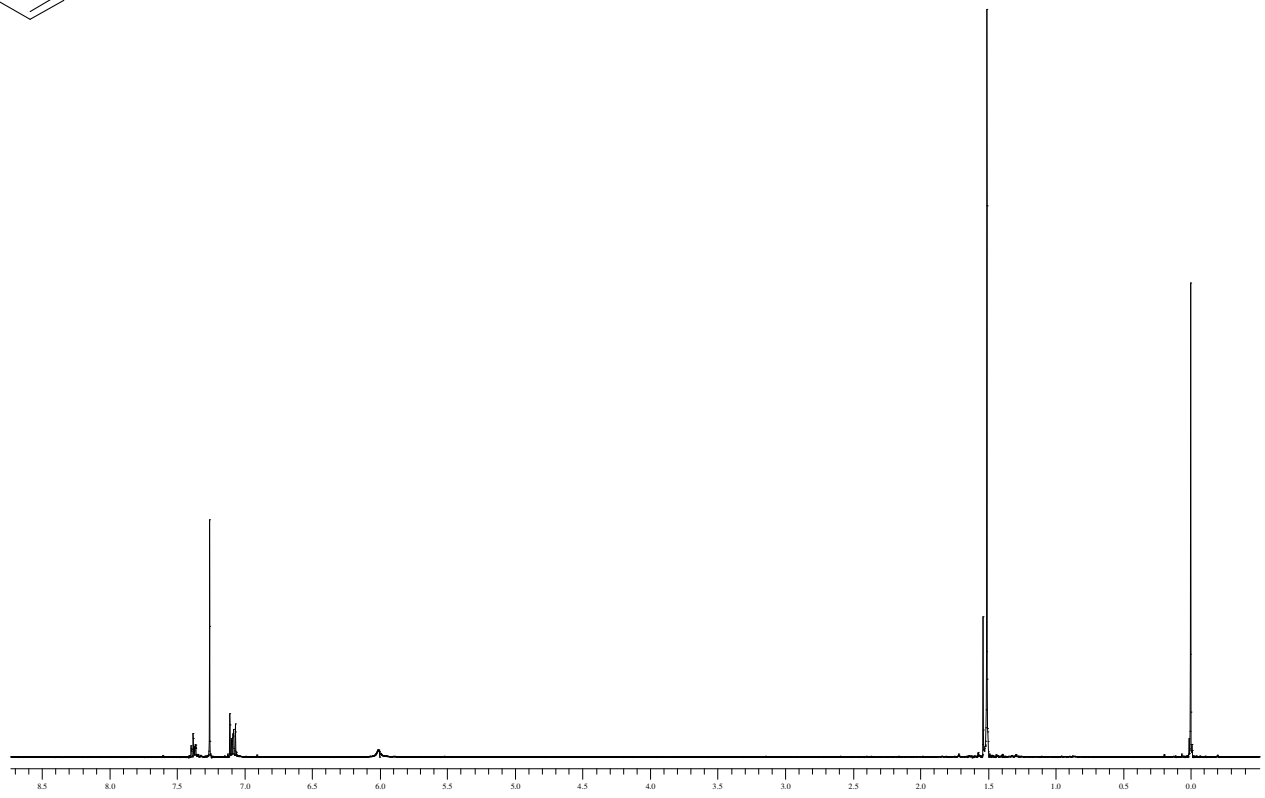
(**7l**)

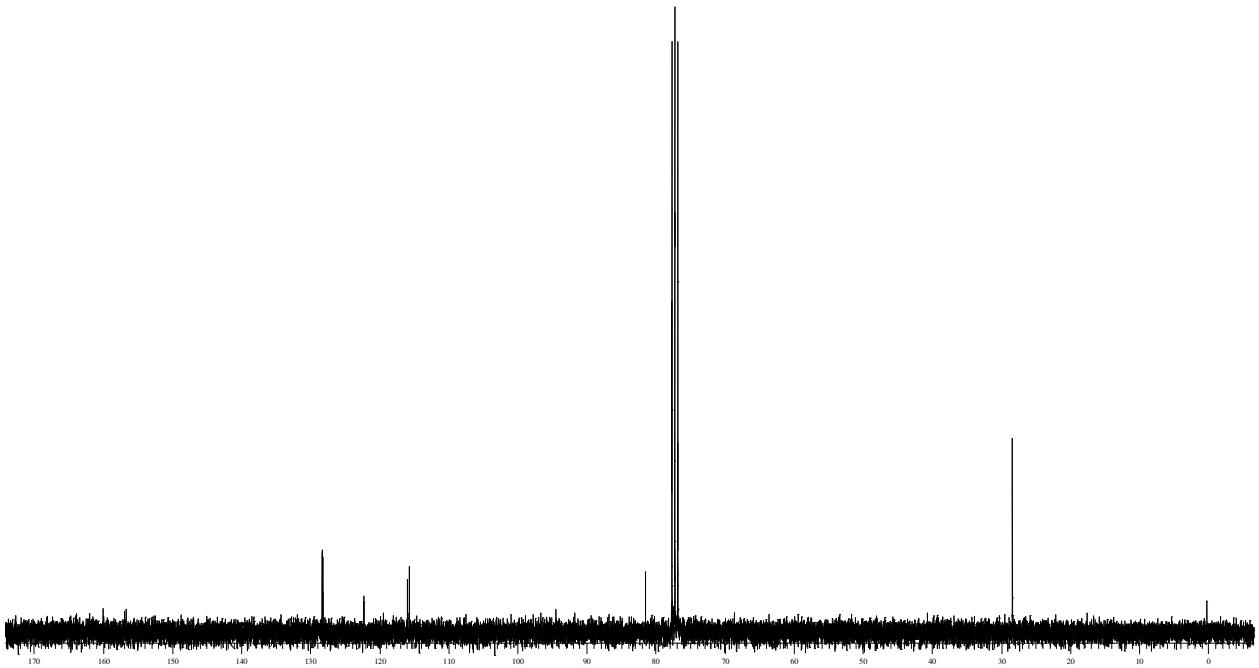


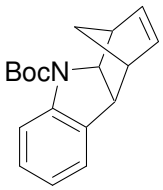




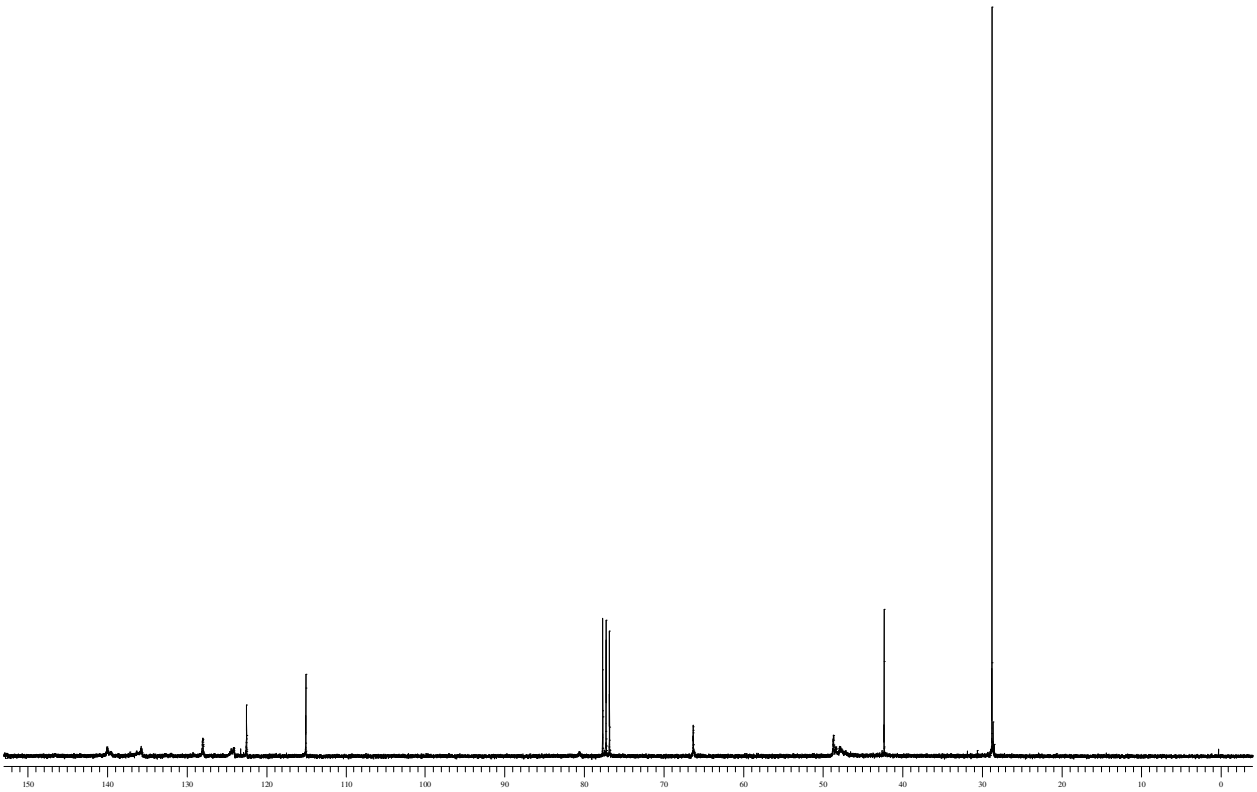
(**7n**)

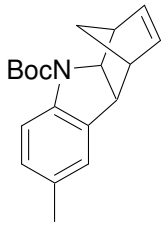




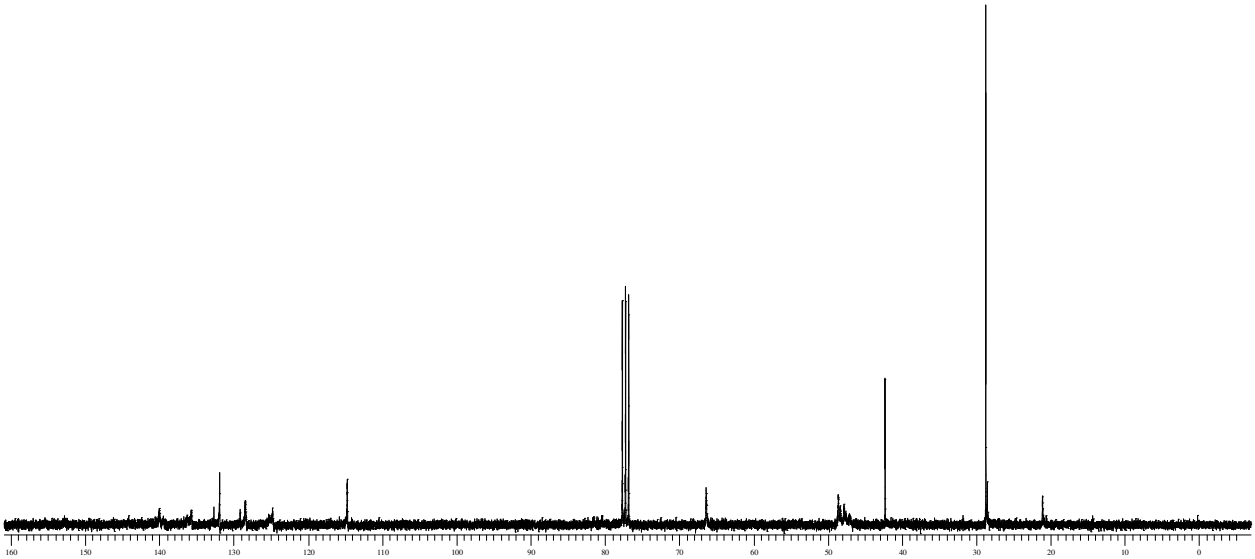


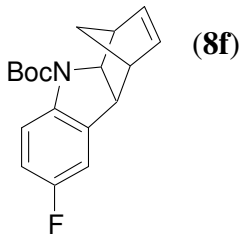
(**8d and 8o**)



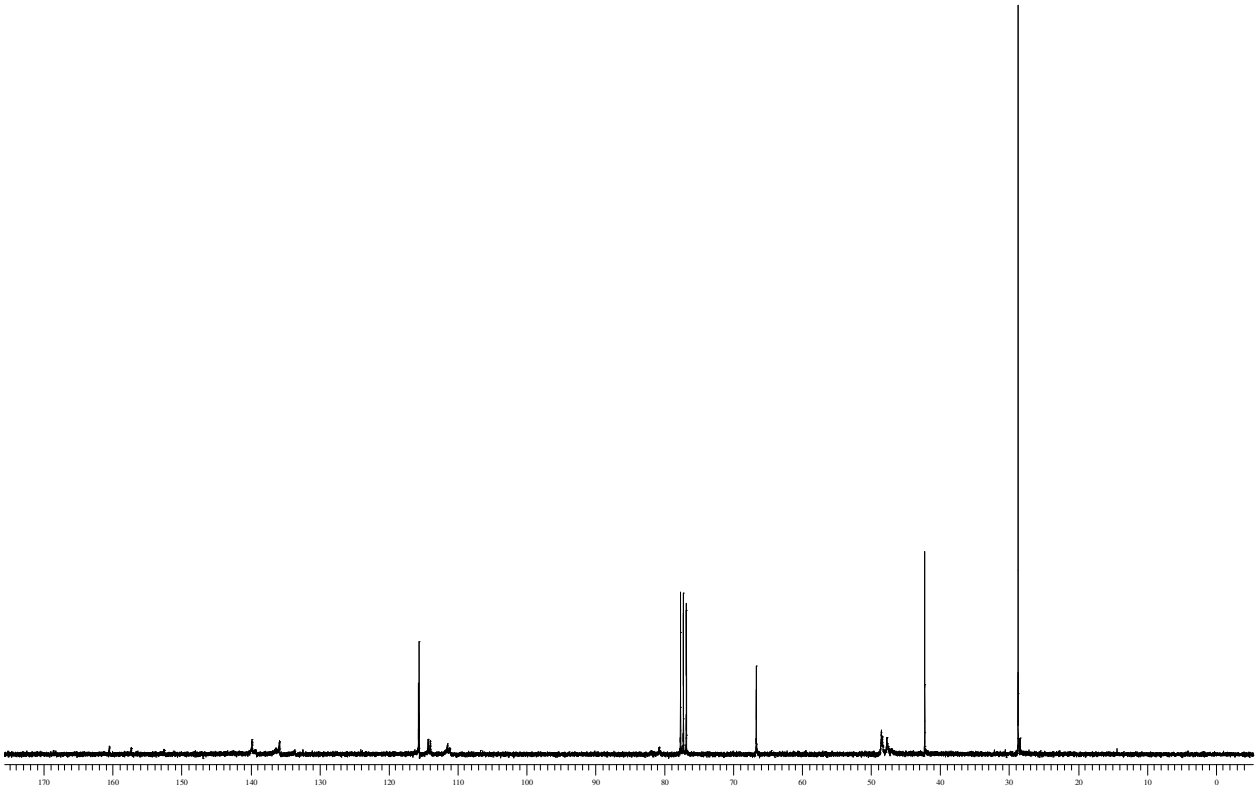


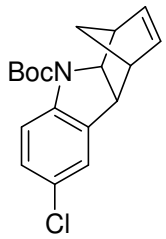
(**8e**)



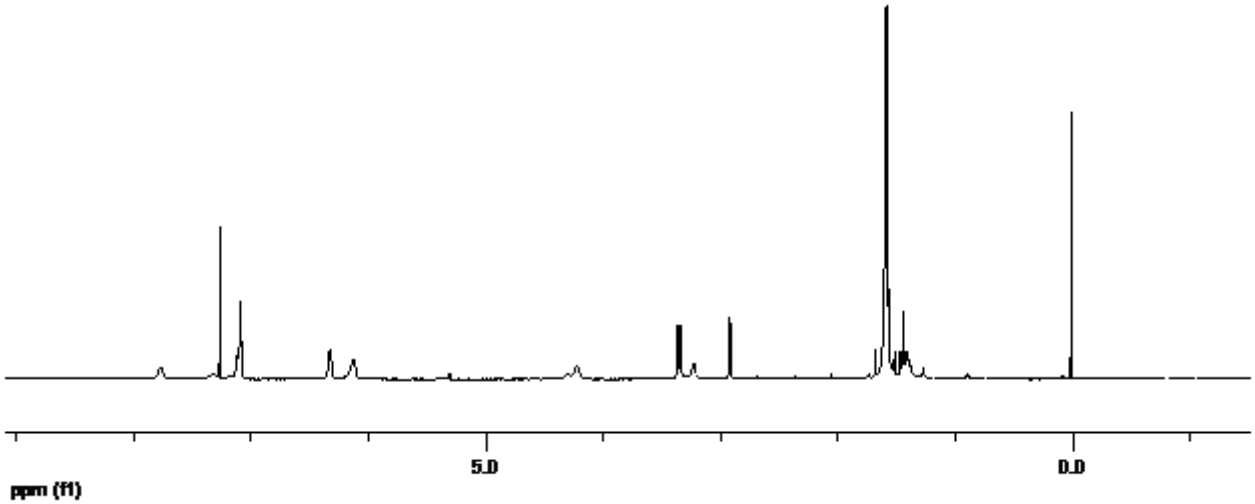


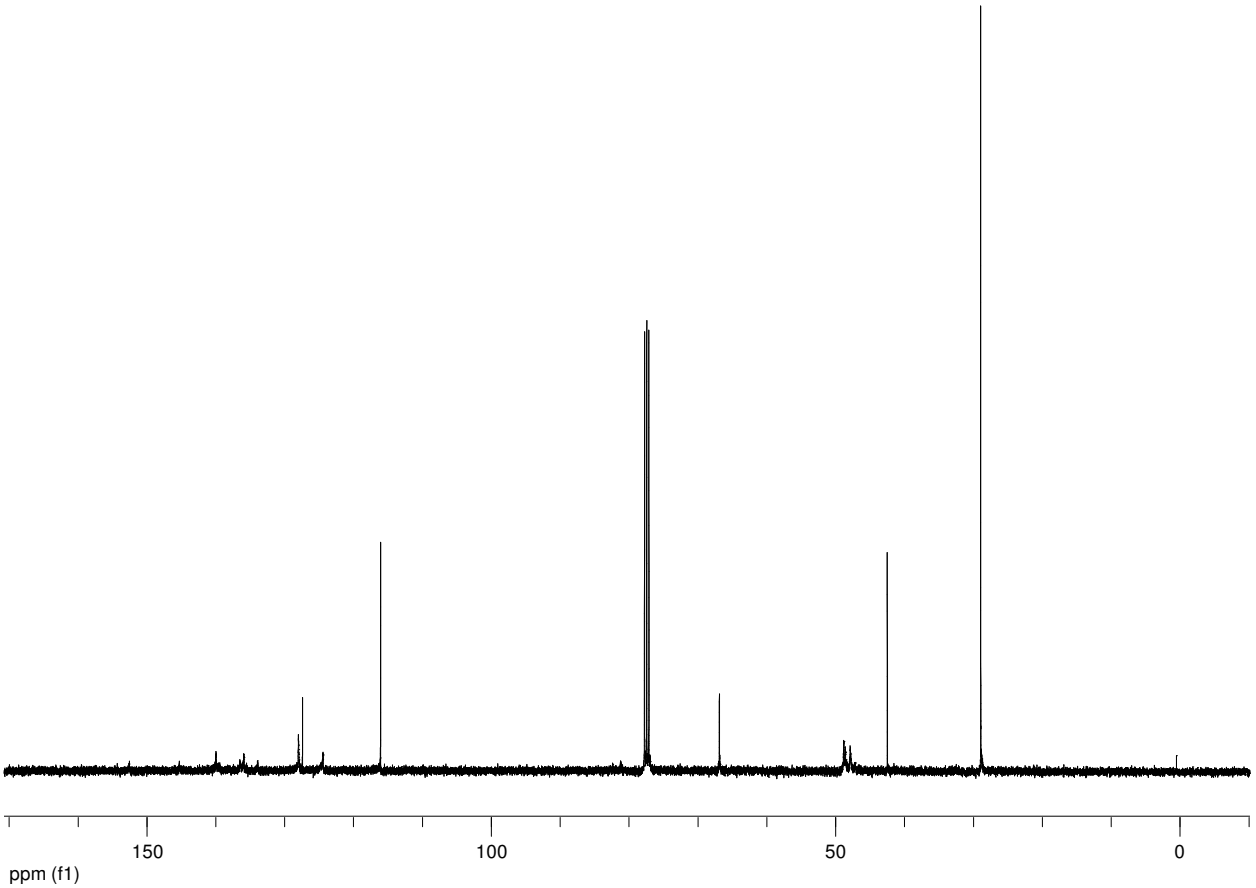
(**8f**)

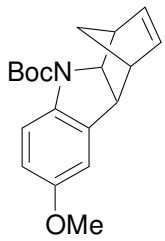




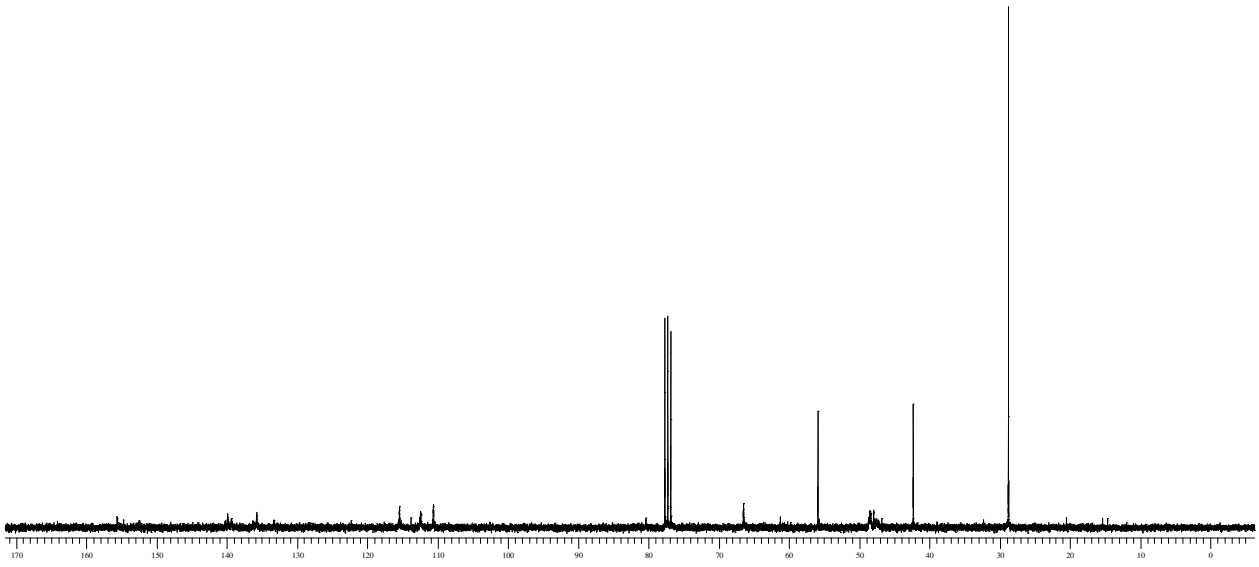
(**8g**)

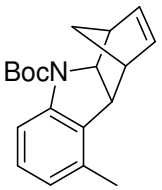




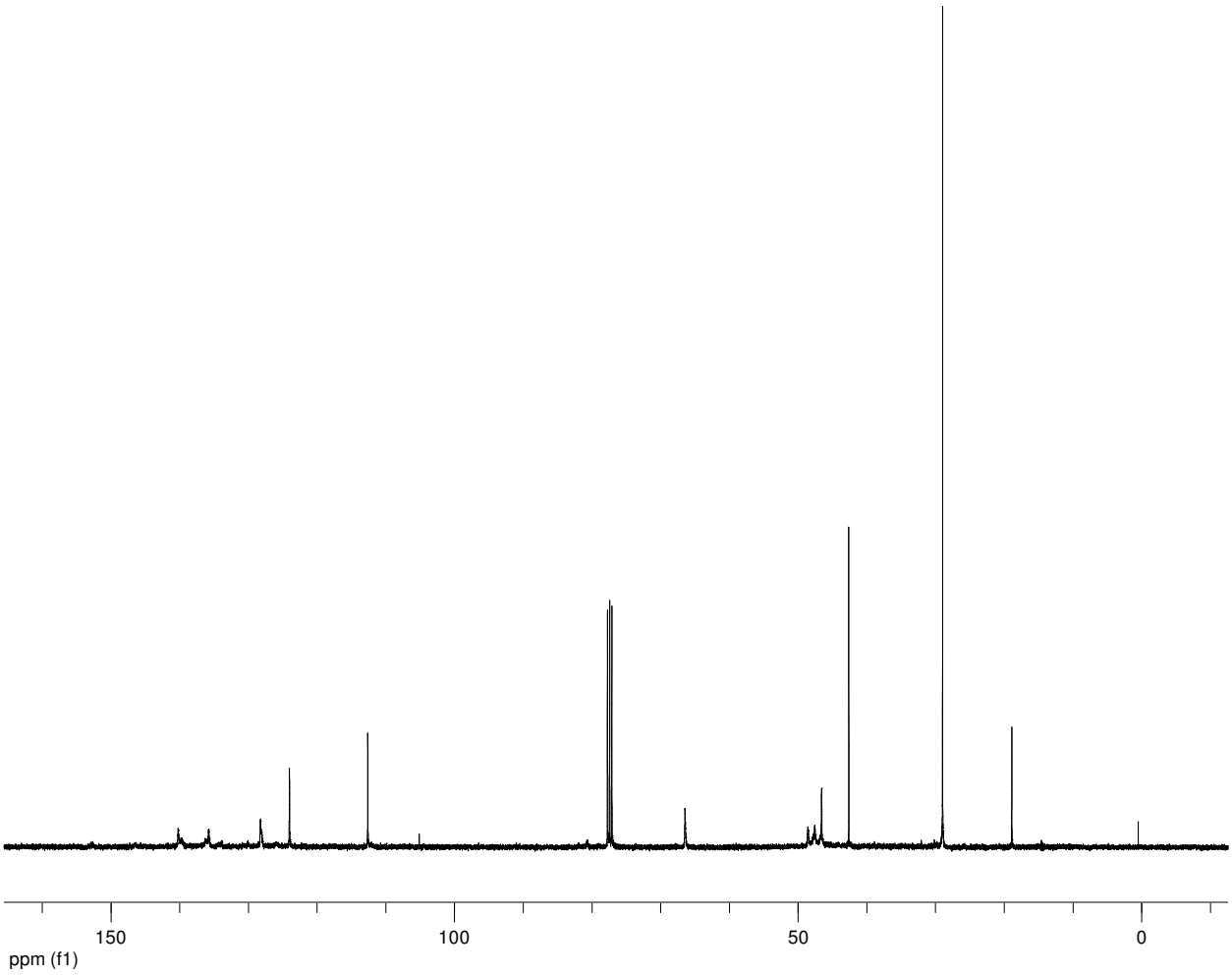


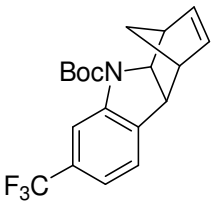
(**8h**)



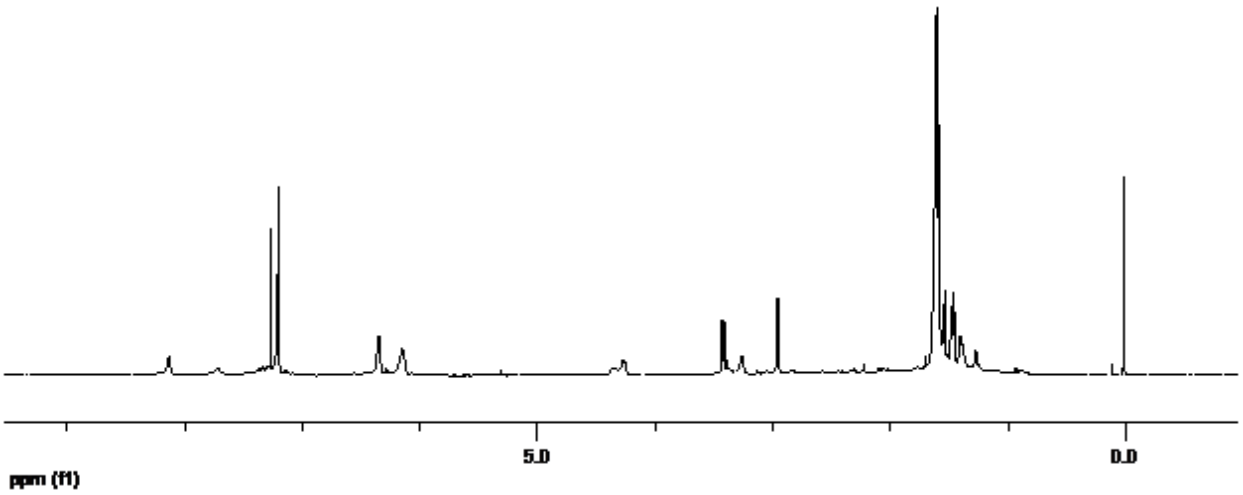


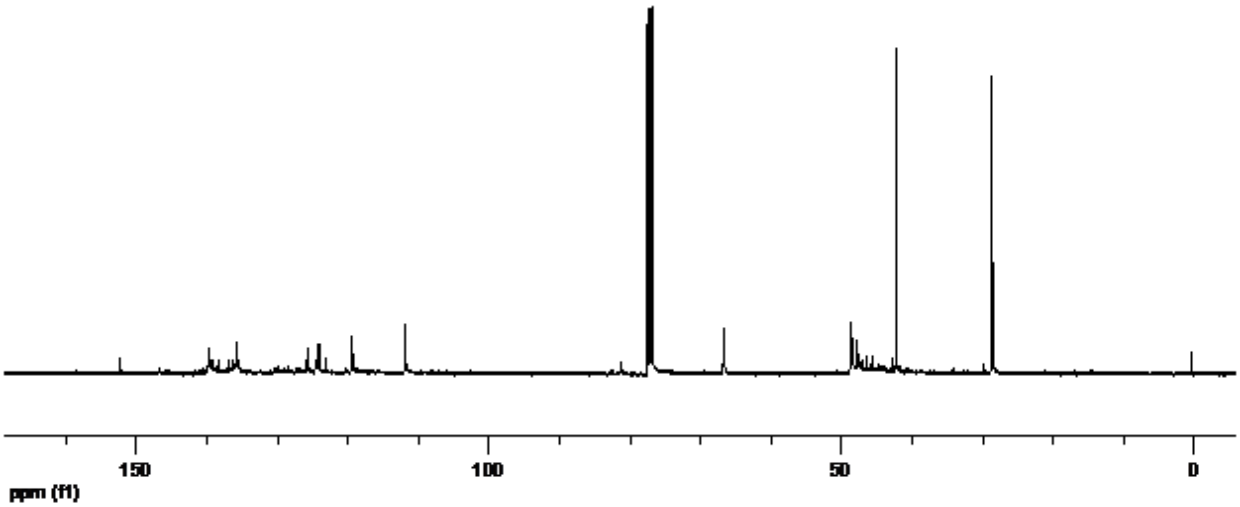
(**8i**)



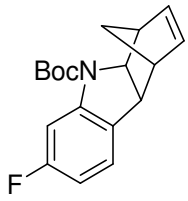


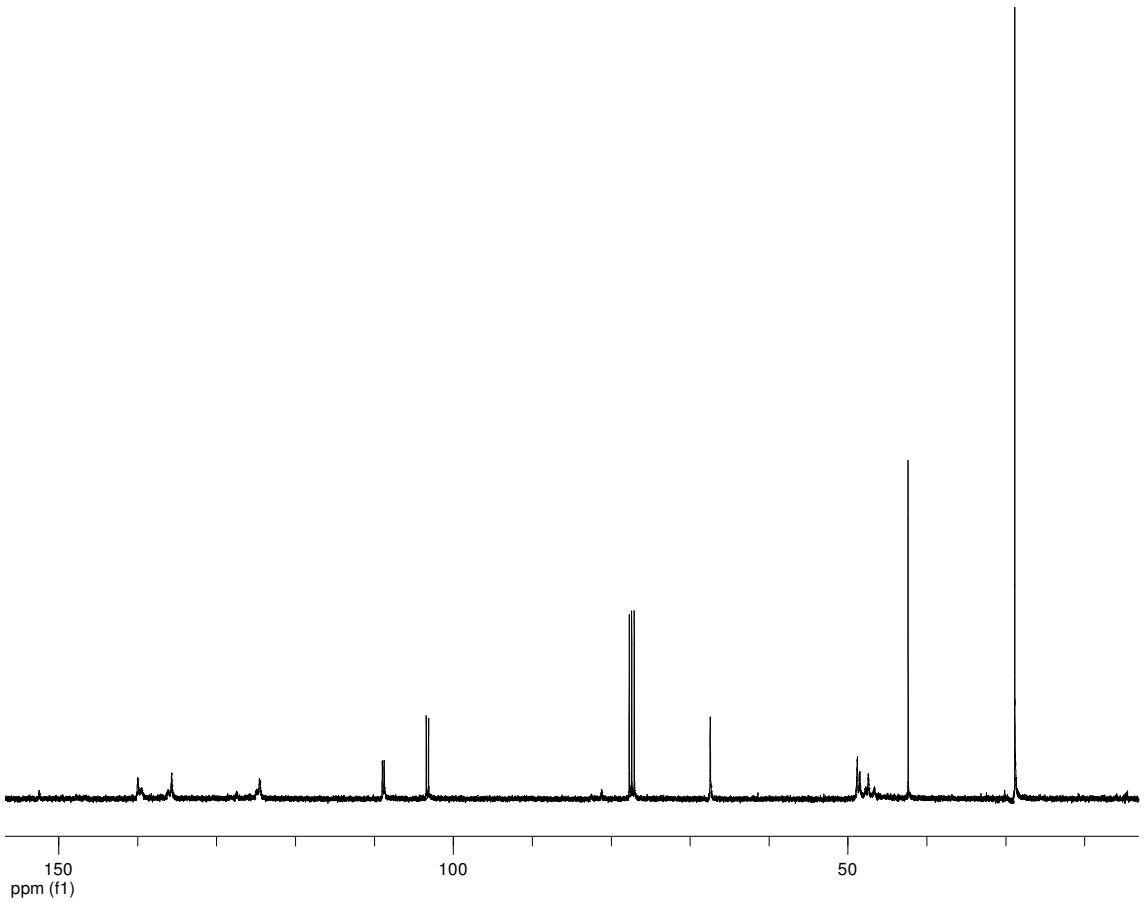
(**8j**)



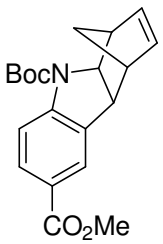


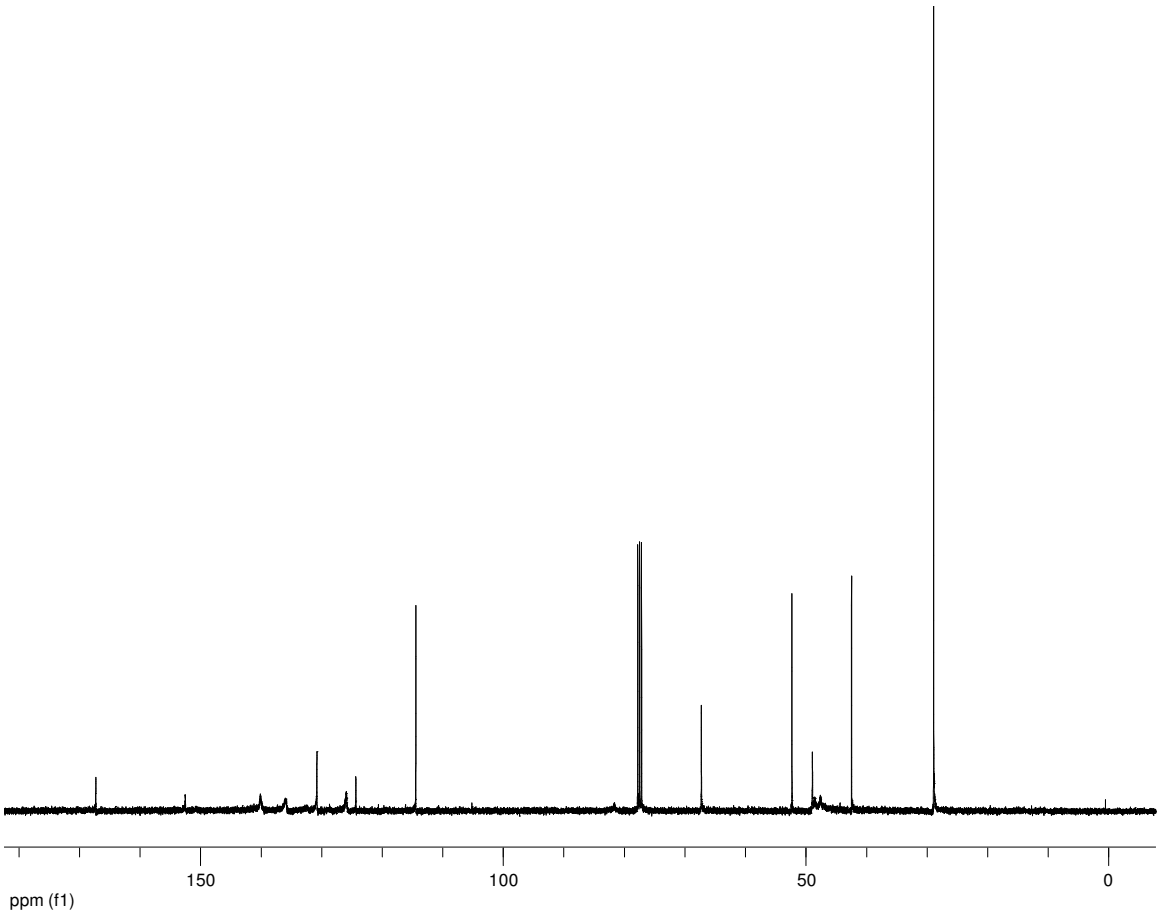
(**8k**)

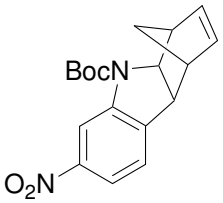




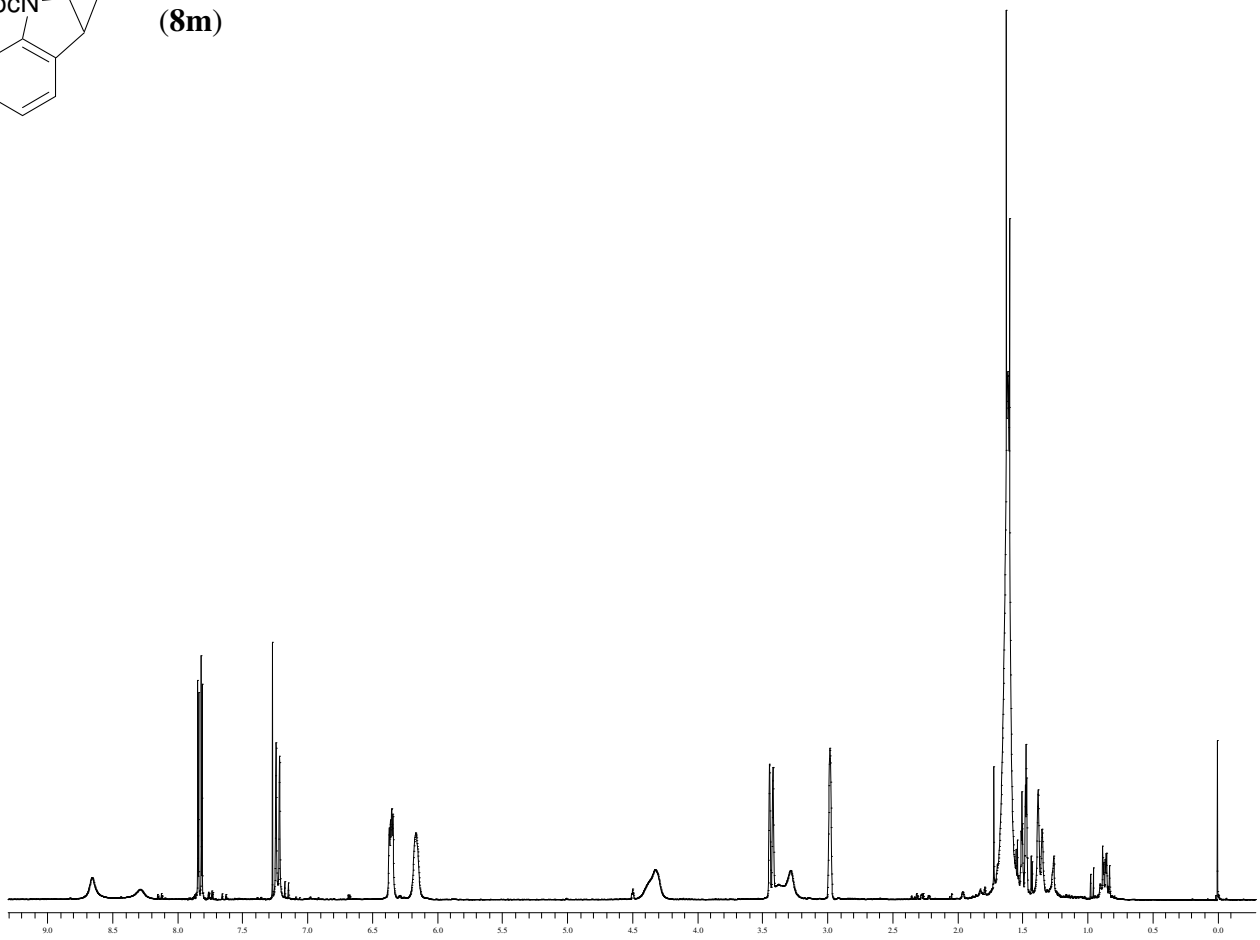
(**8l**)

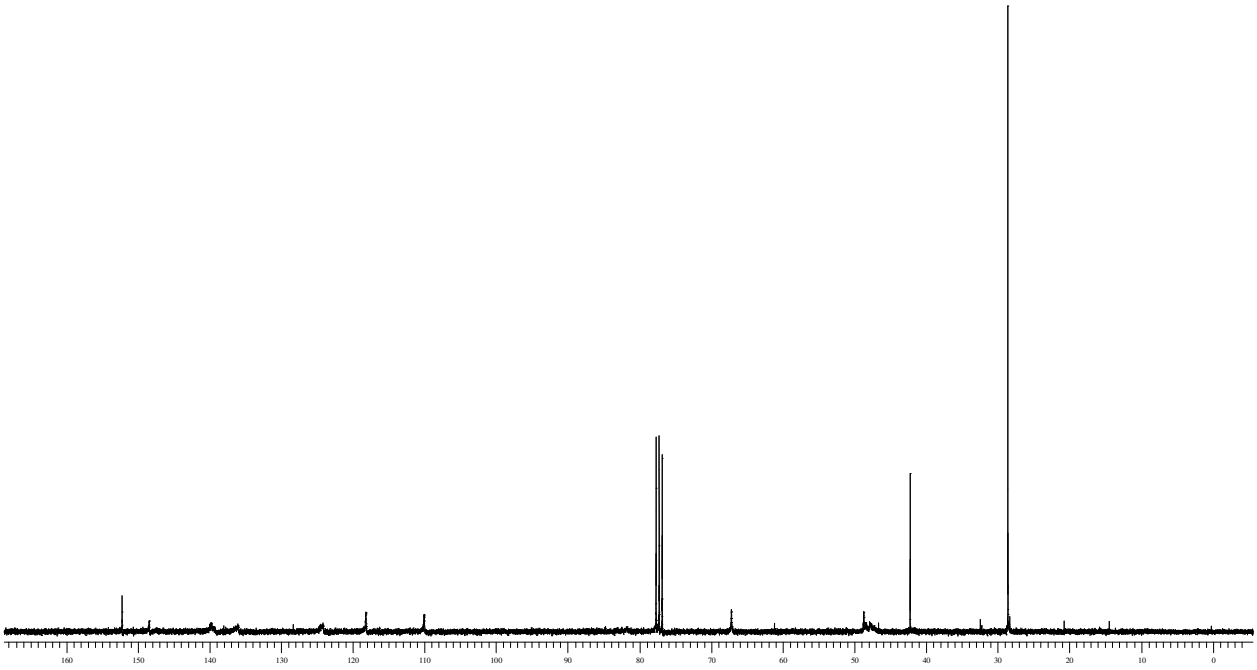


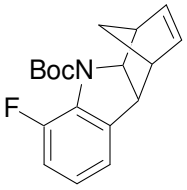




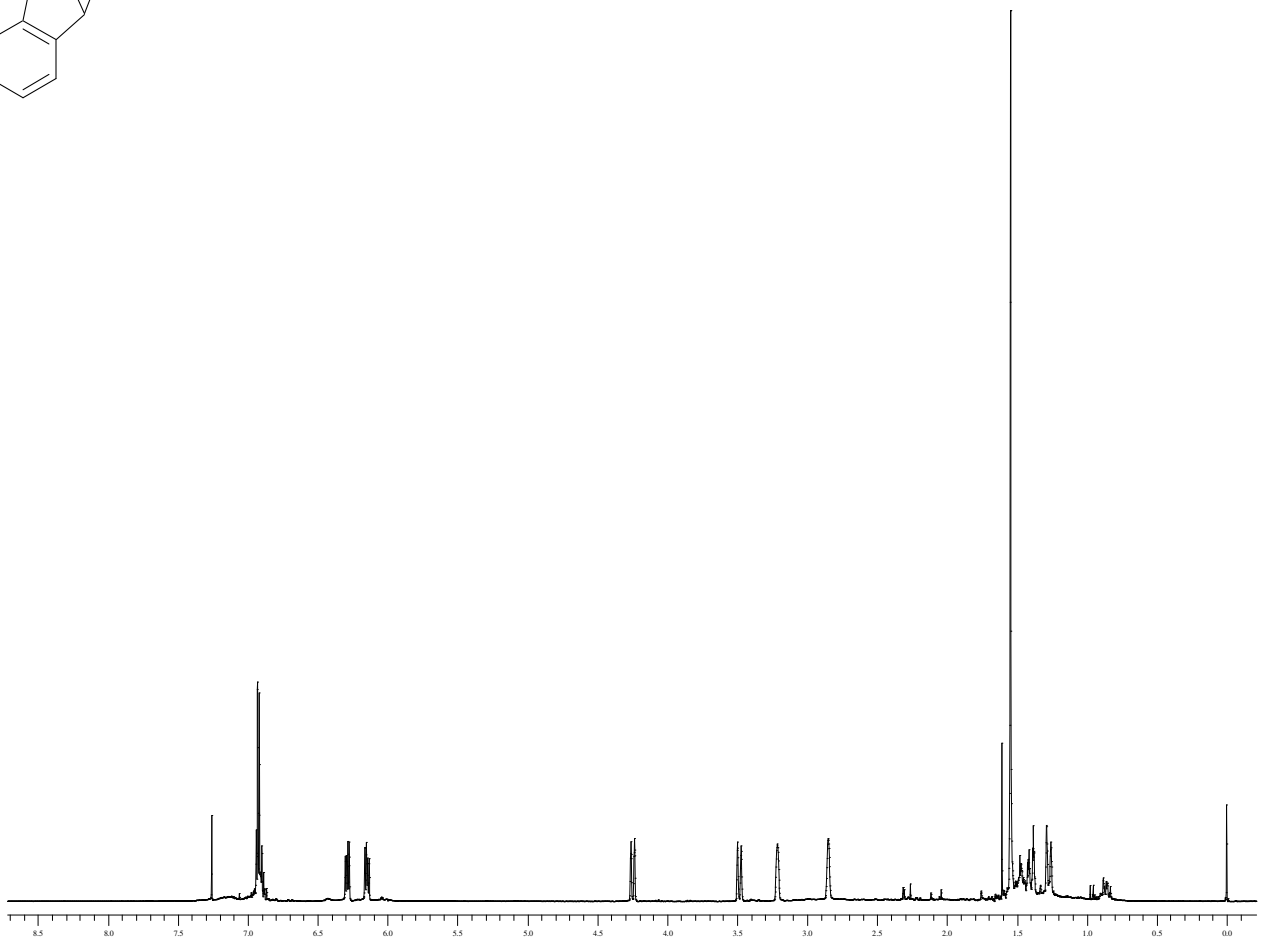
(**8m**)

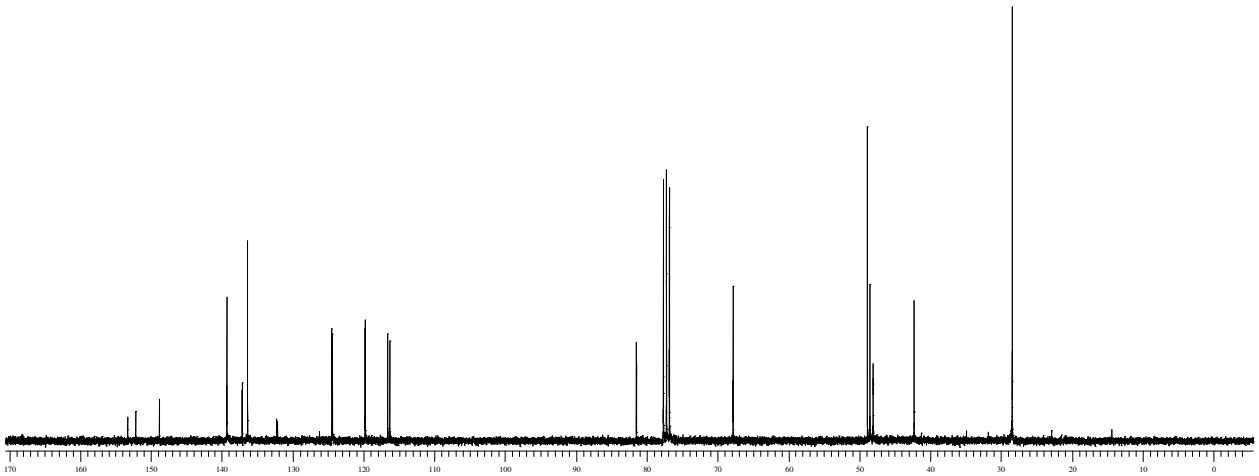


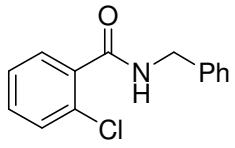




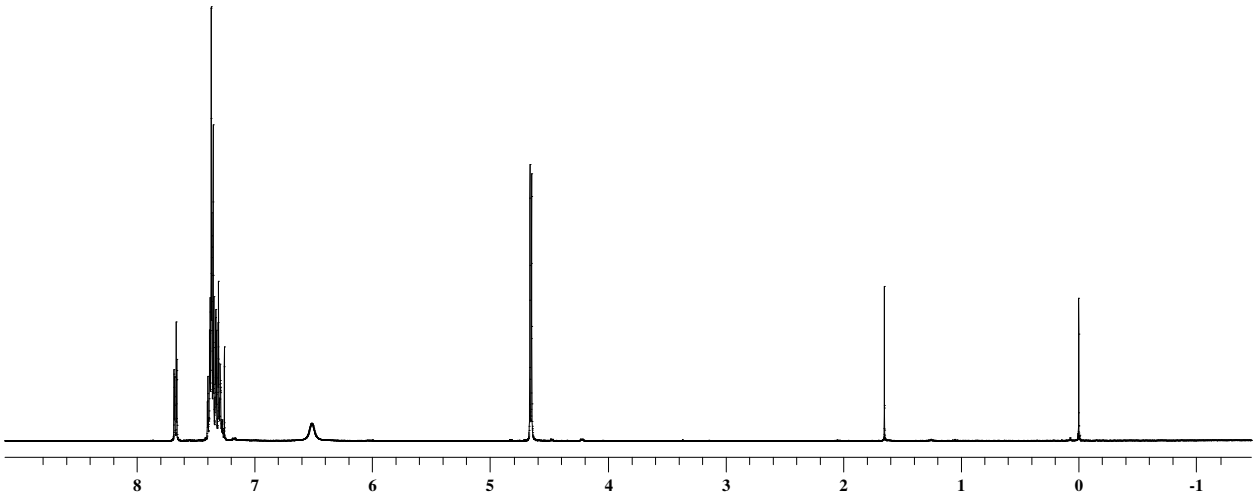
(**8n**)

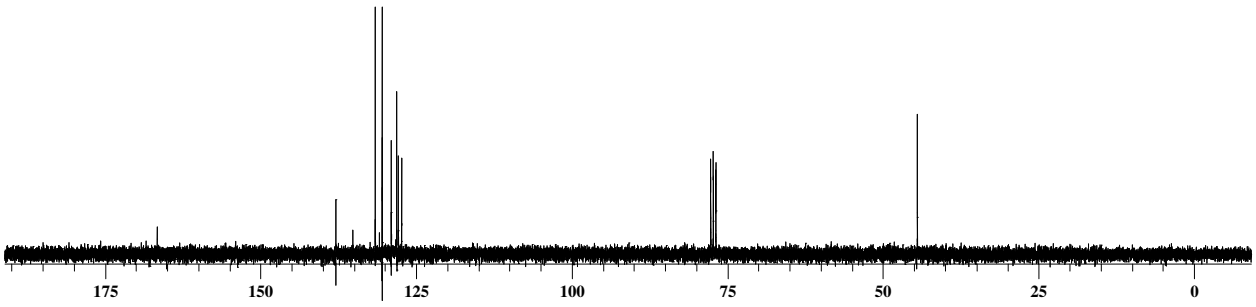


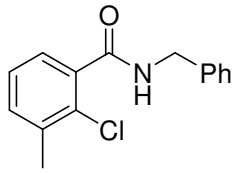




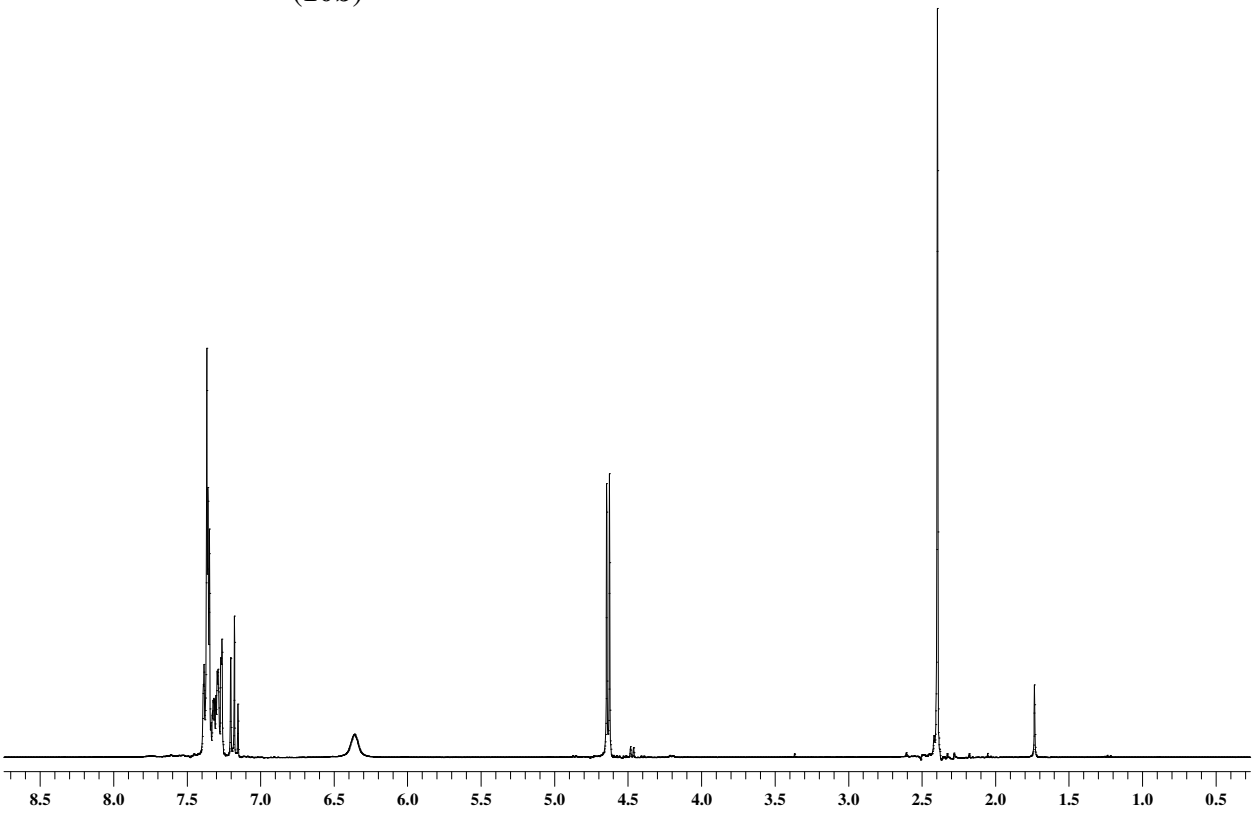
(**10a**)

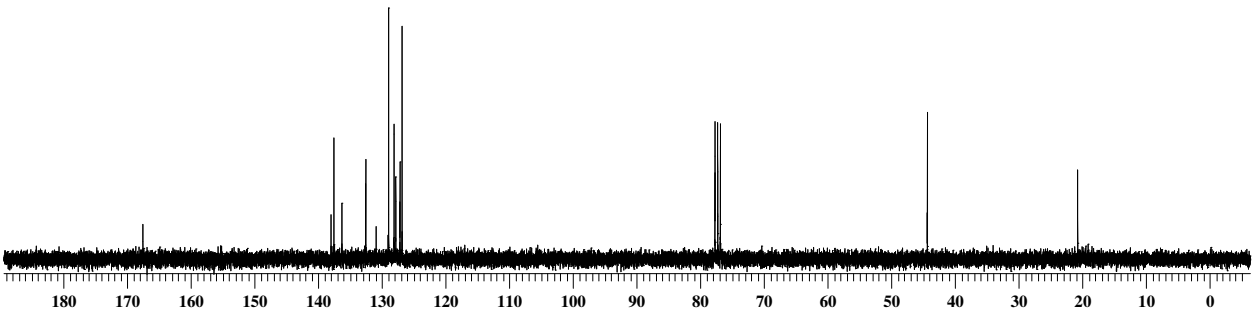


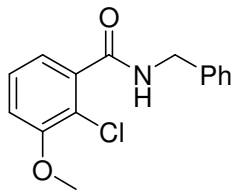



O
N
H
Ph
Cl

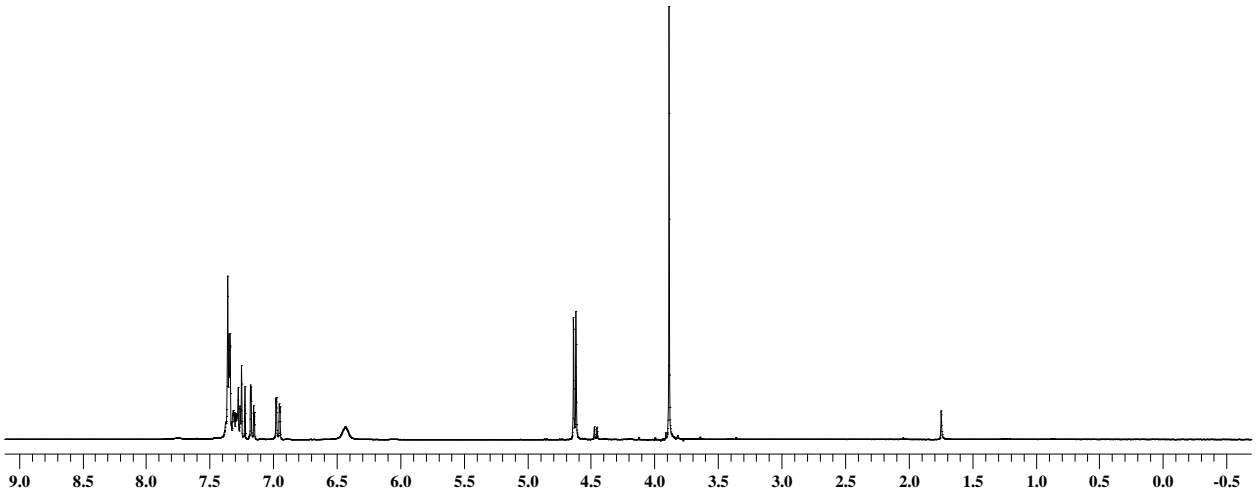
(**10b**)

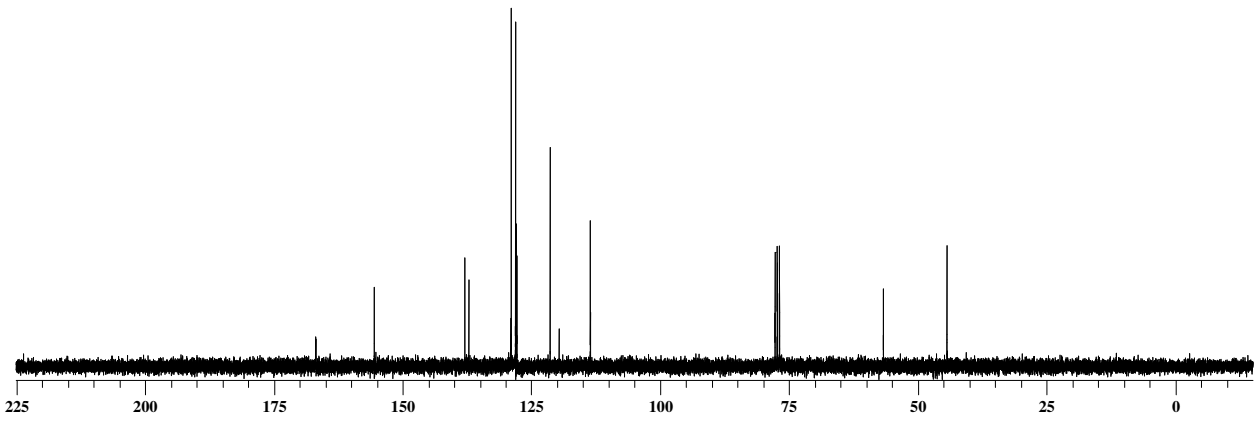

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

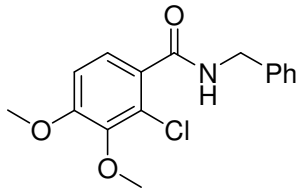

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


O
N
H
Ph
Cl
O

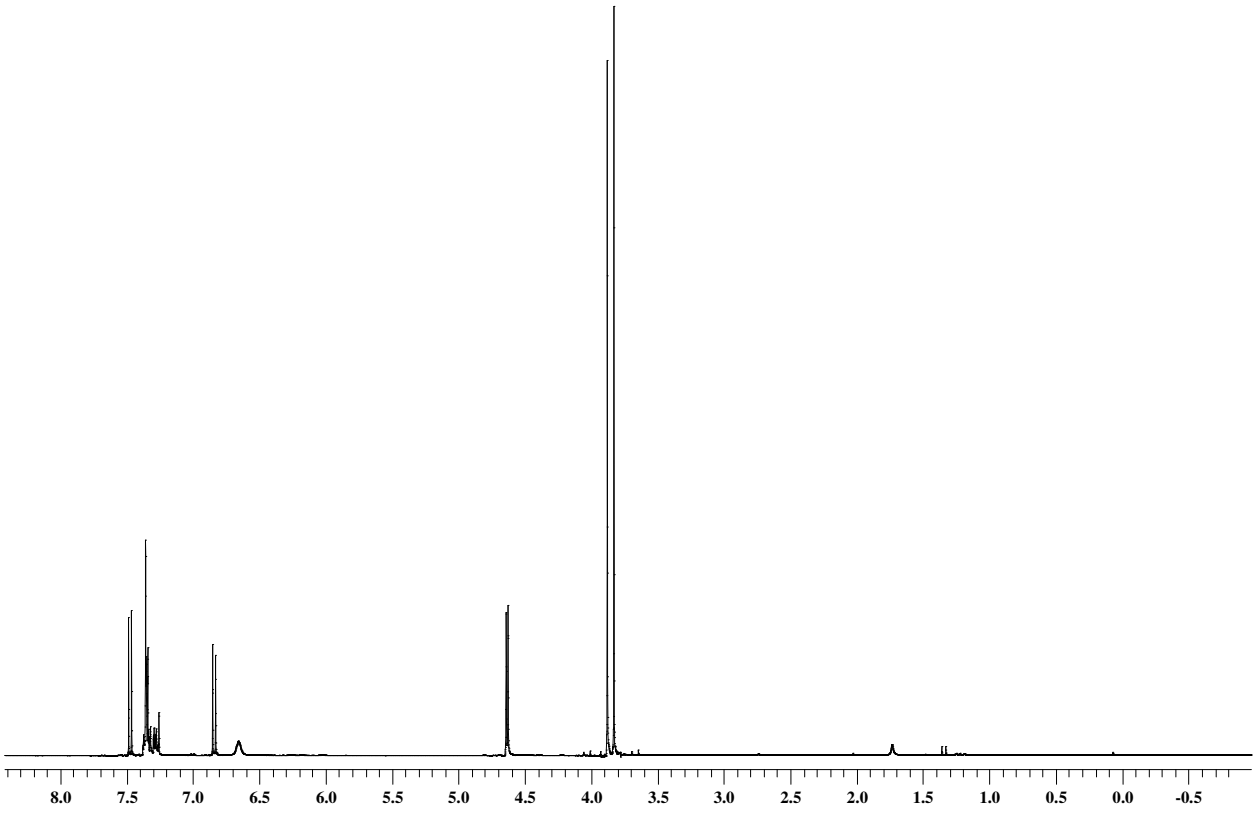
(**10c**)

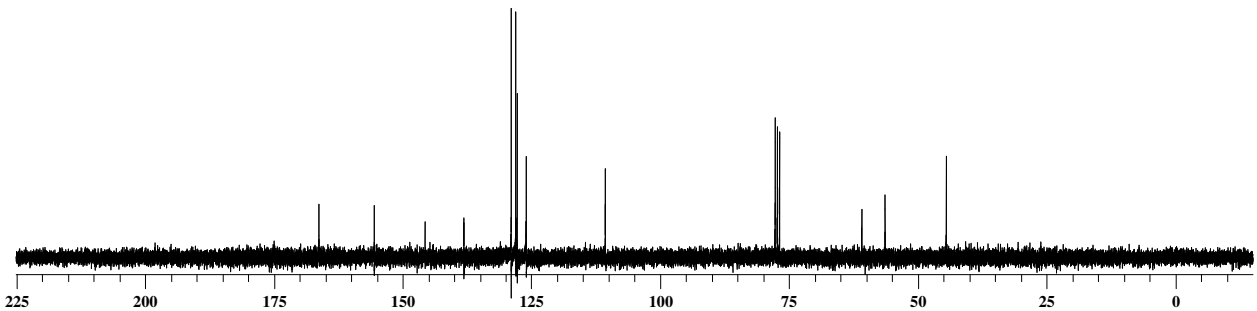

9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

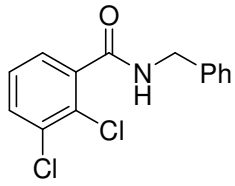

225
200
175
150
125
100
75
50
25
0


O
N
H
Ph
Cl
O
O

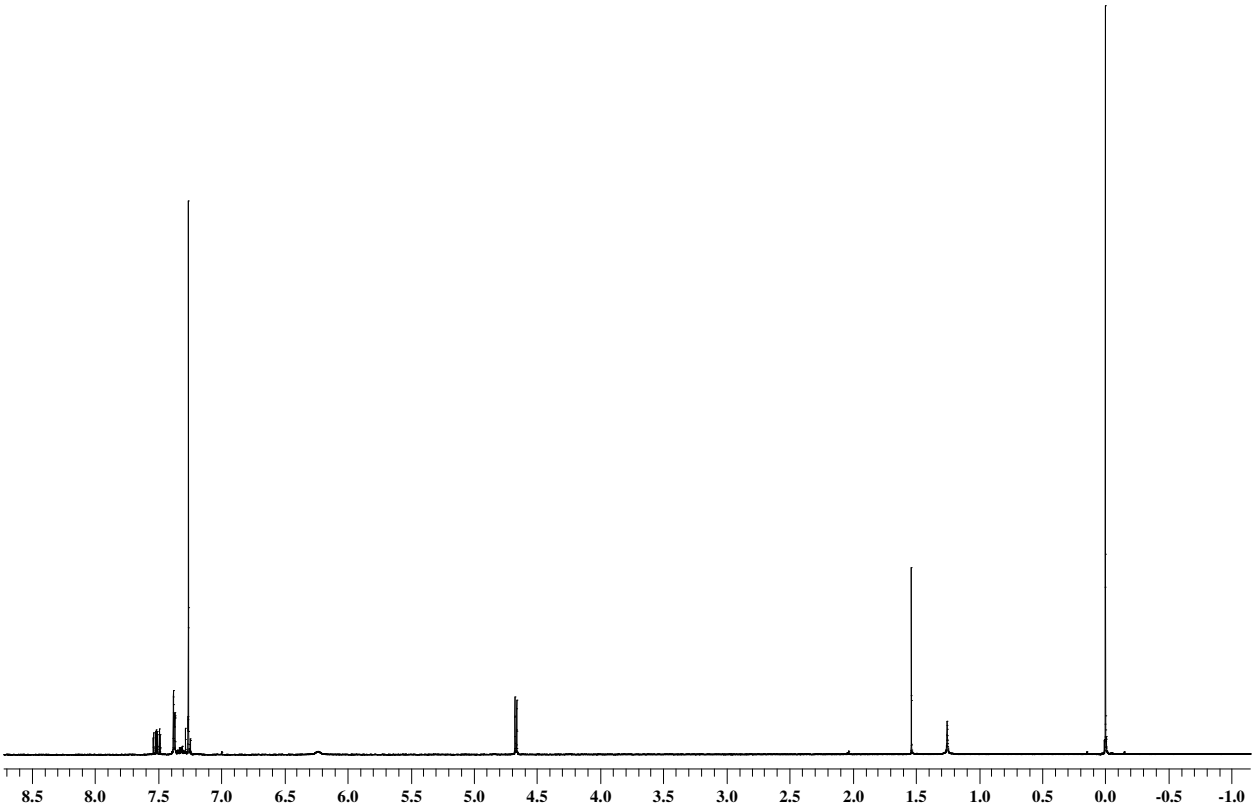
(**10d**)

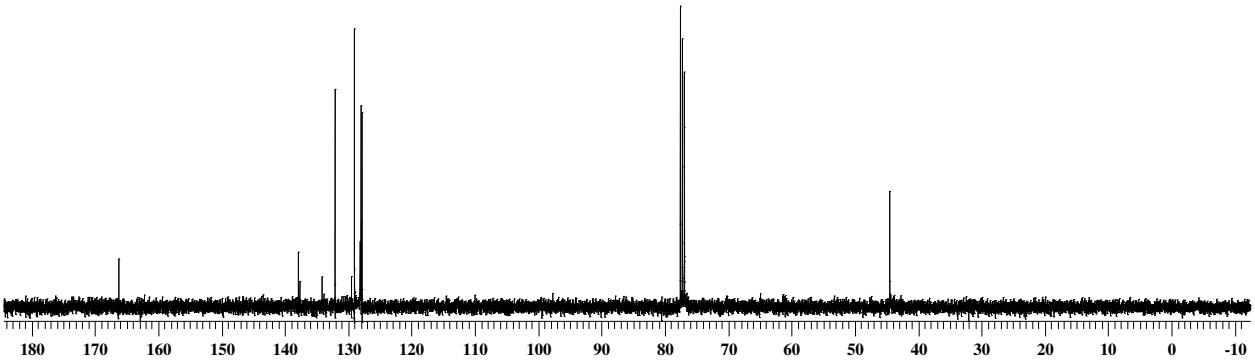

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

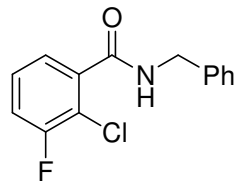

225
200
175
150
125
100
75
50
25
0


O
N
H
Ph
Cl
Cl

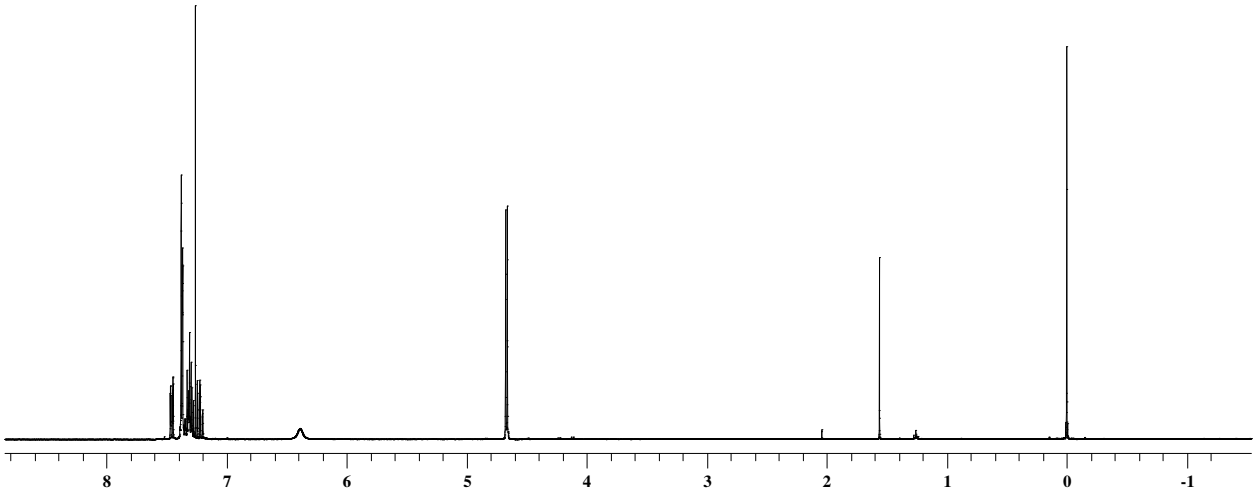
(**10f**)

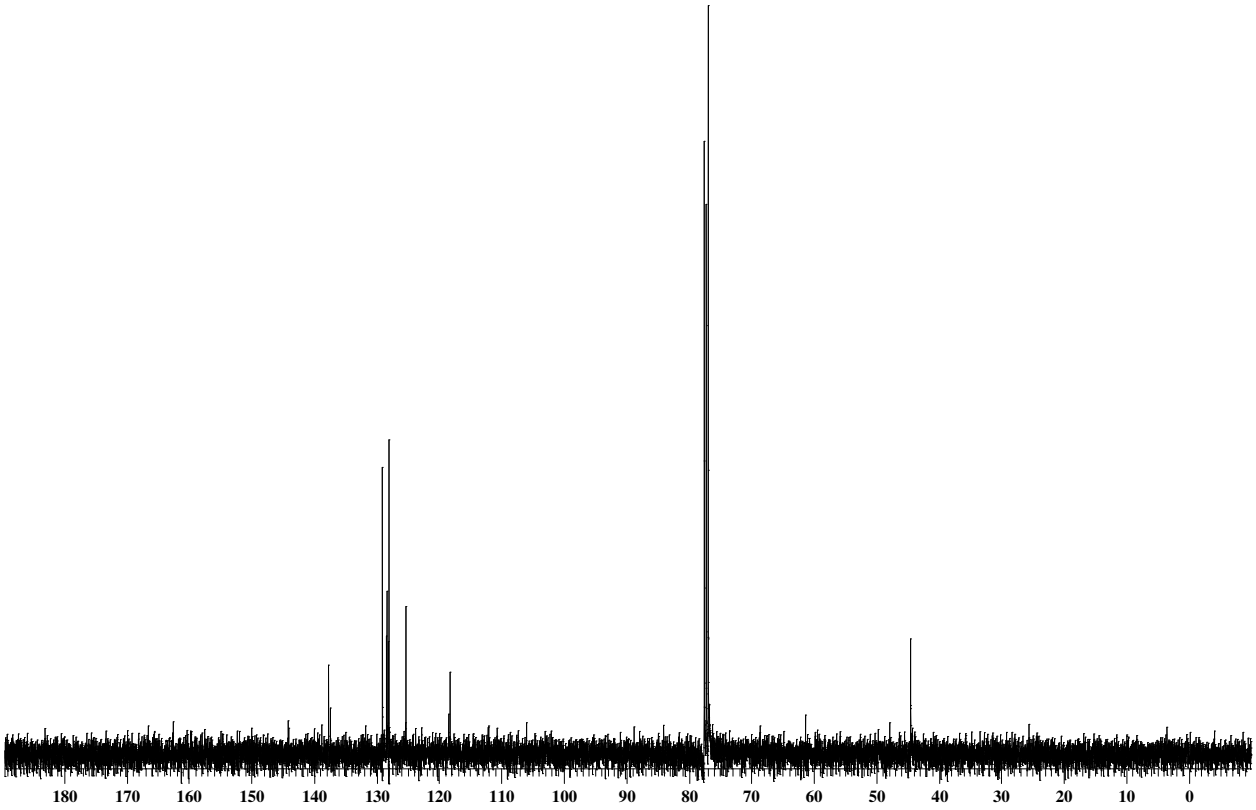

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0

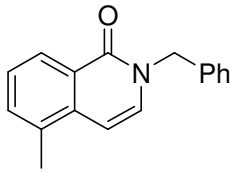

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


O
N
H
Ph
Cl
F

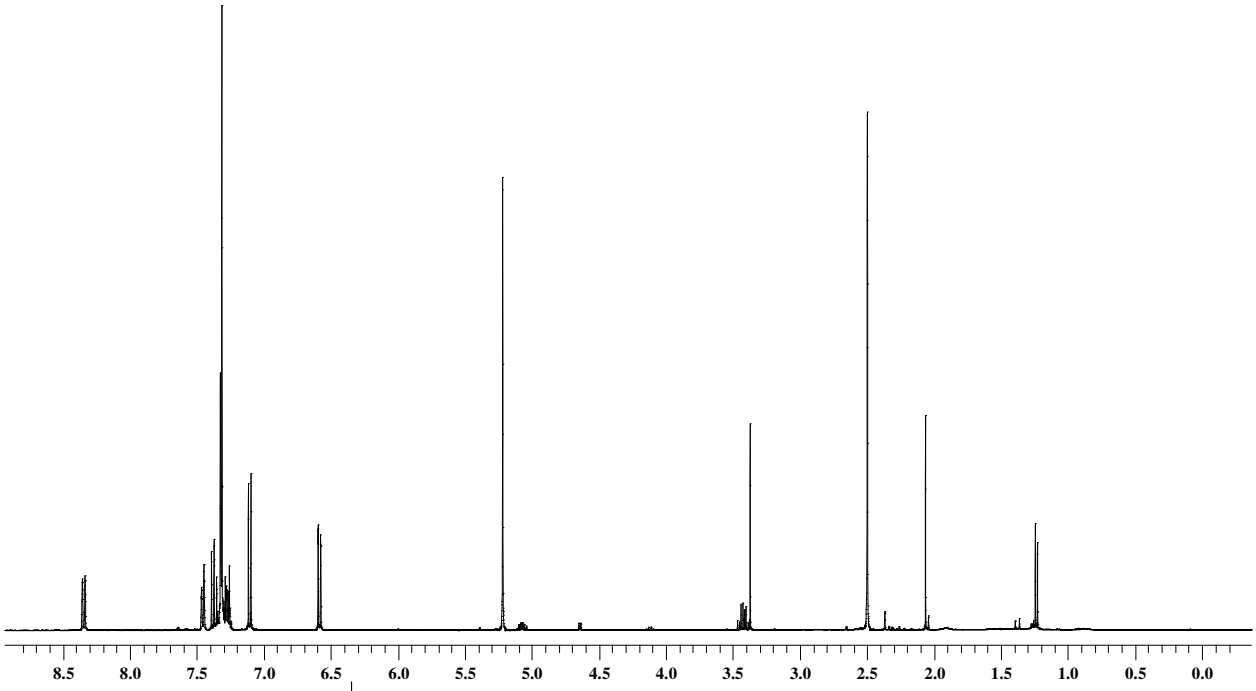
(**10g**)

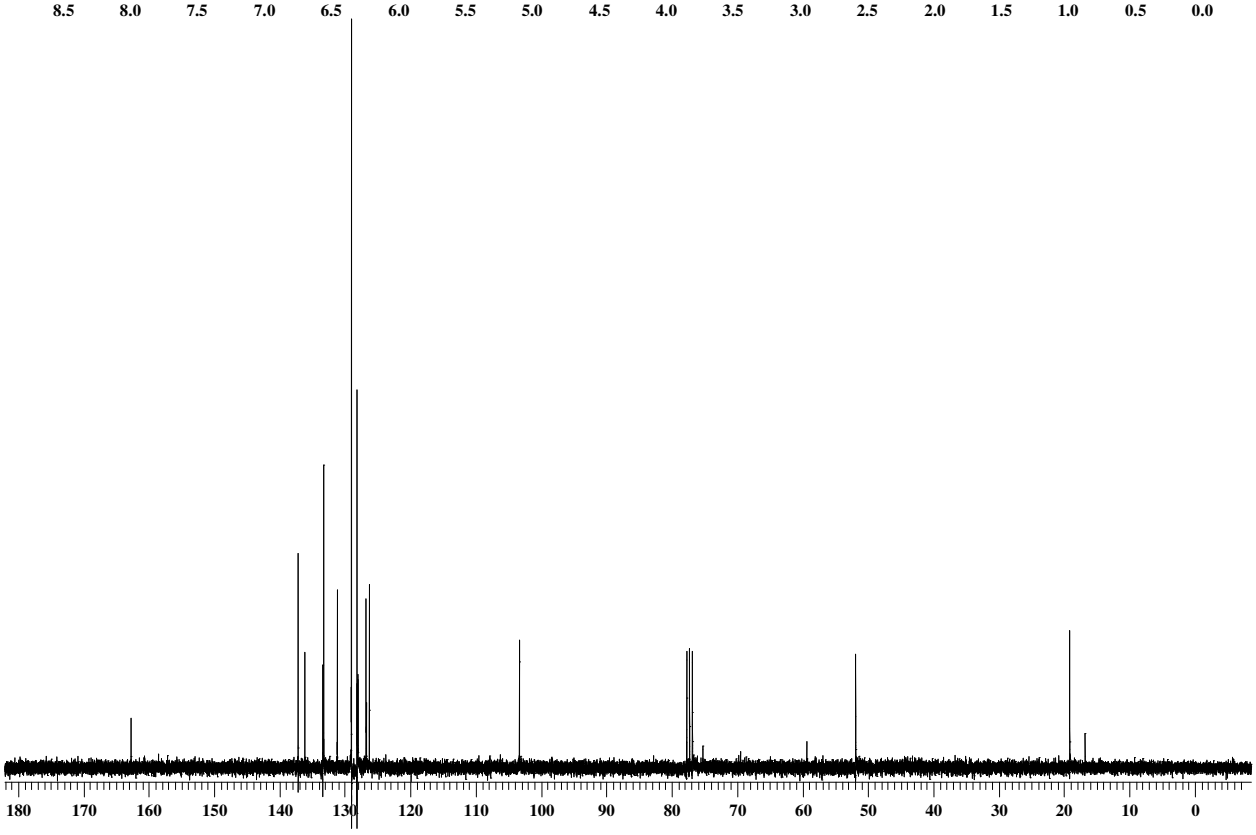

8
7
6
5
4
3
2
1
0
-1

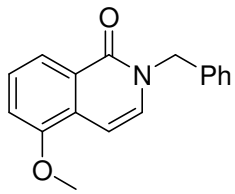

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


O
N
Ph

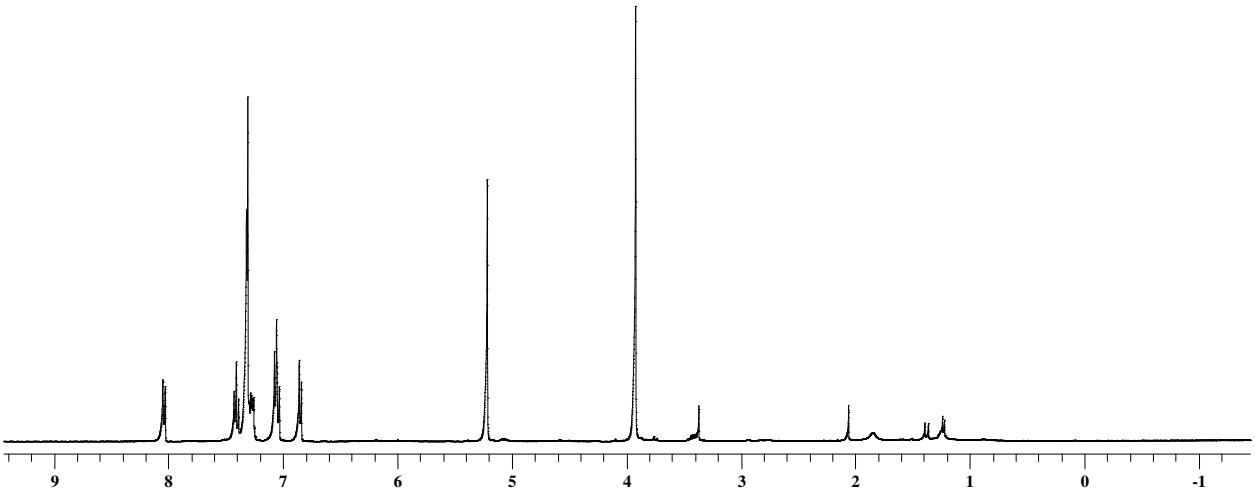
(**11b**)

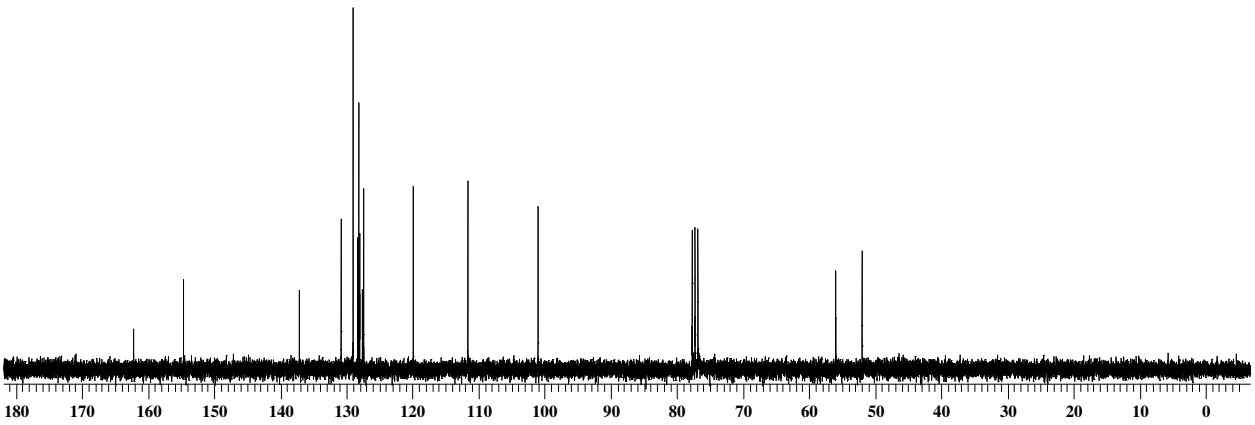

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

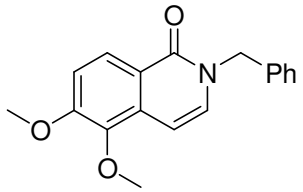

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


O
N
Ph
O

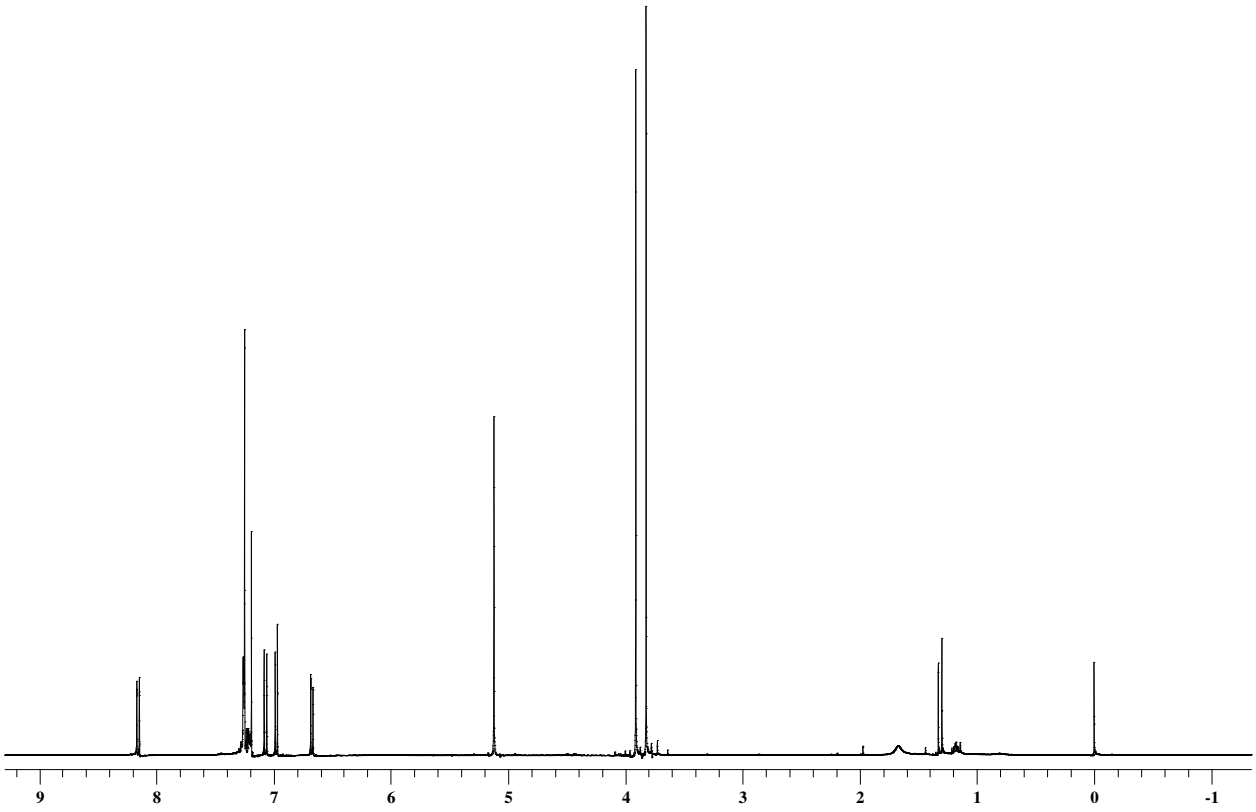
(**11c**)

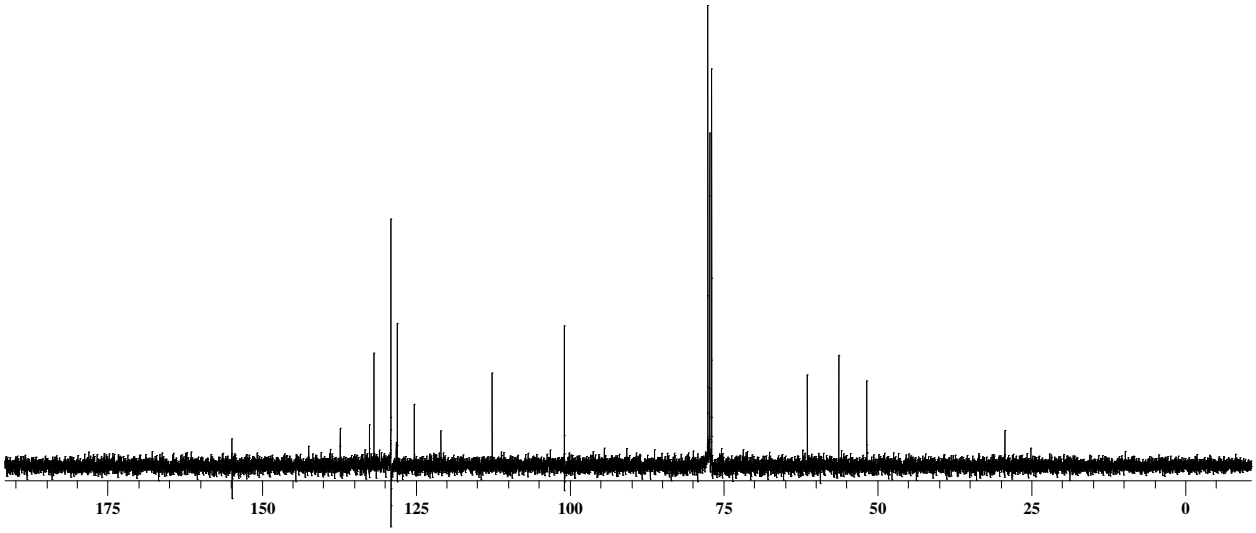

9
8
7
6
5
4
3
2
1
0
-1

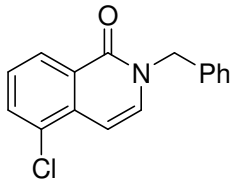

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0



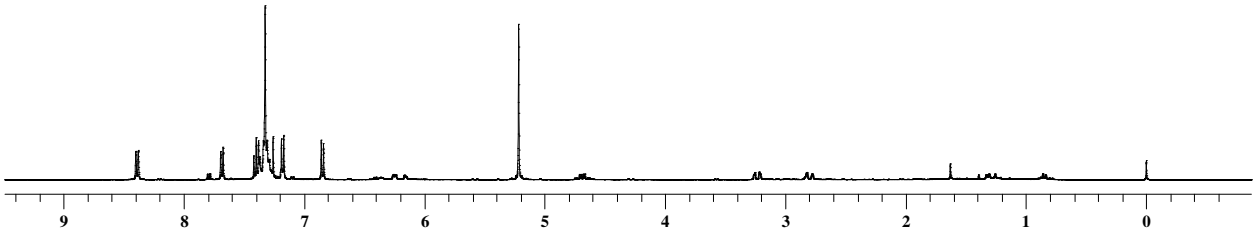
(**11d**)

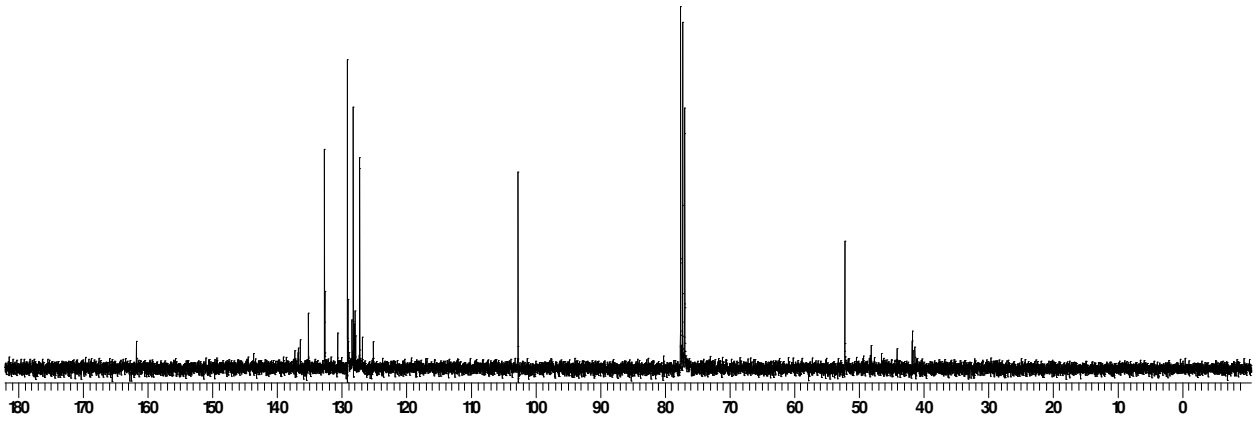


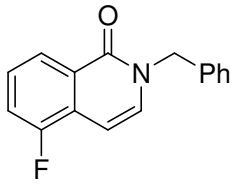



O
N
Ph
Cl

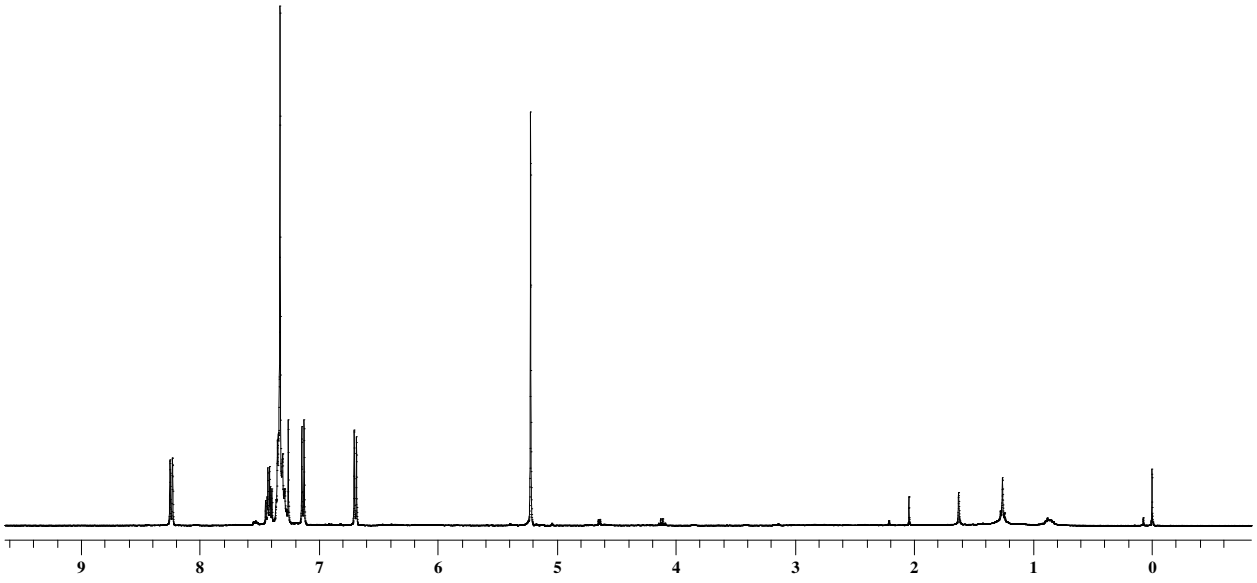
(11f)

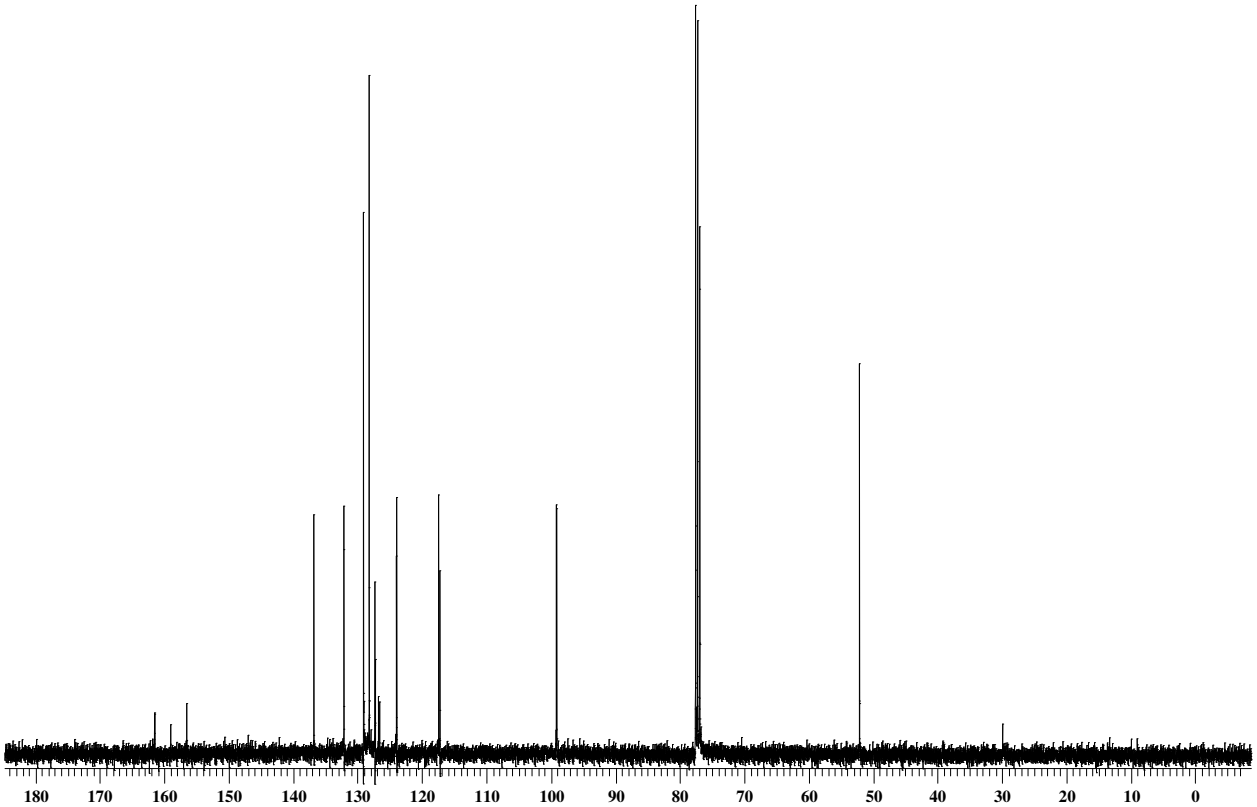

9
8
7
6
5
4
3
2
1
0

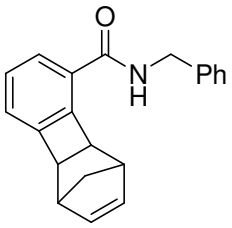

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


O
N
Ph
F

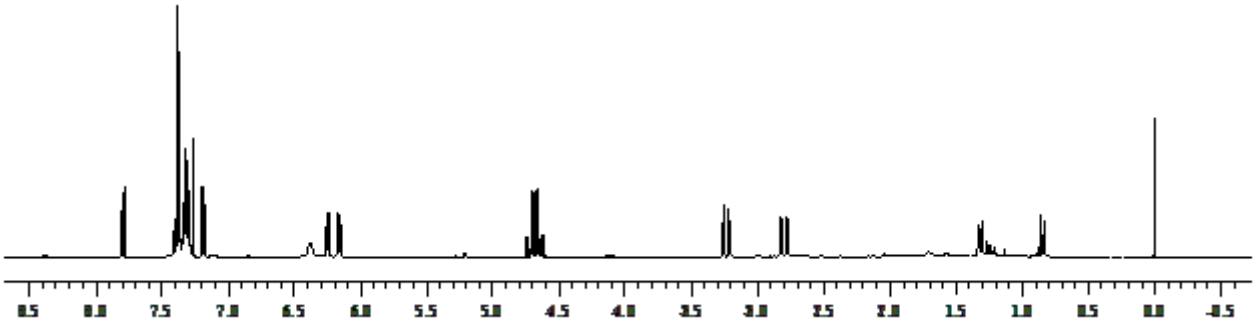
(**11g**)

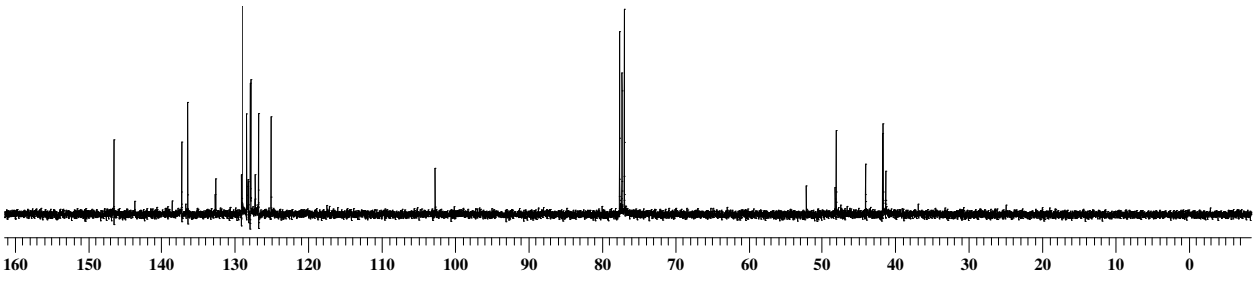

9
8
7
6
5
4
3
2
1
0

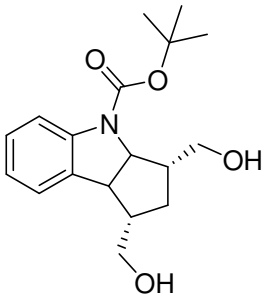

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


O
N
H
Ph

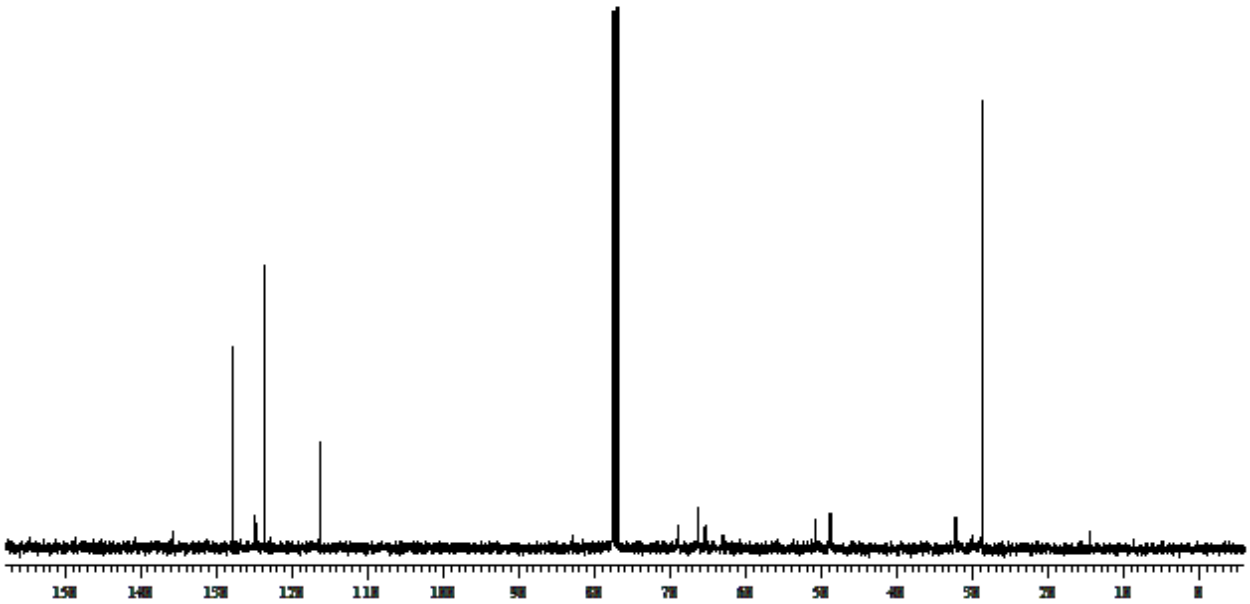
(14)


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

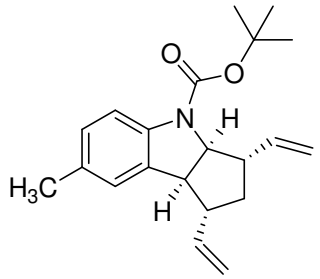

160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

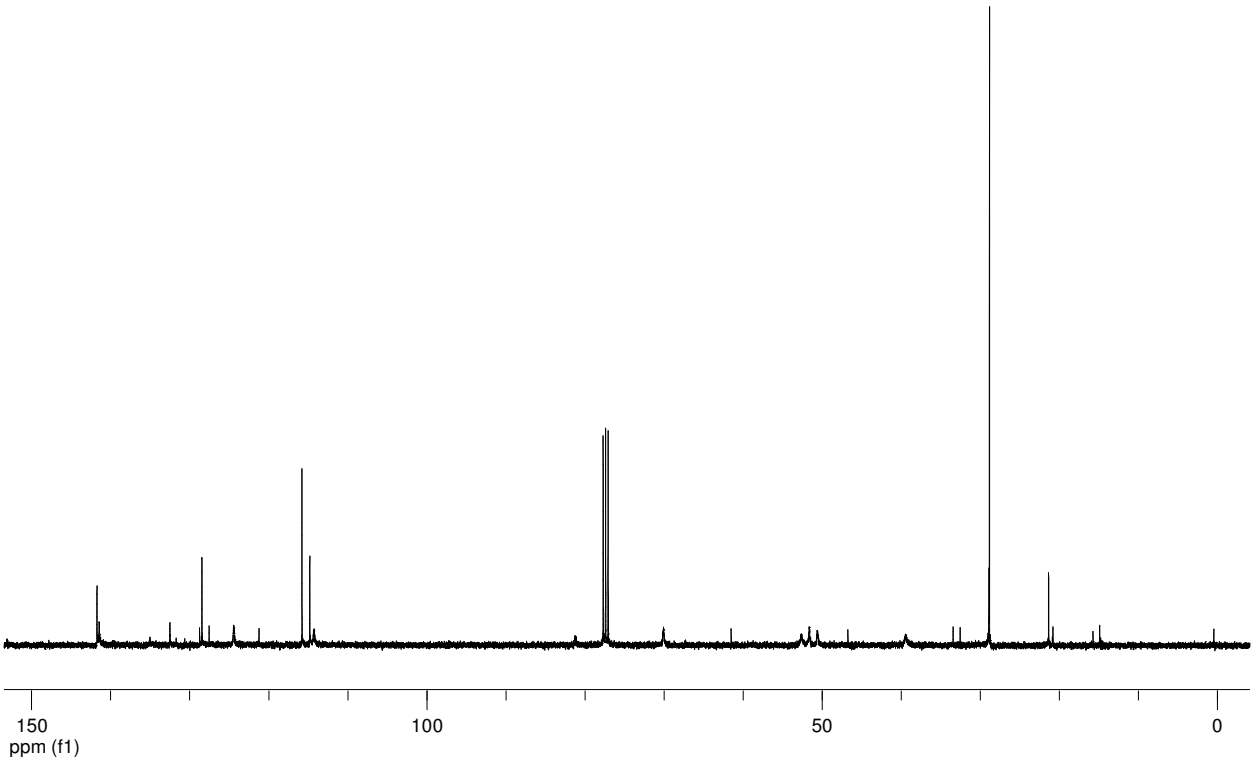


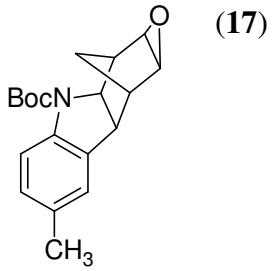
(**15**)



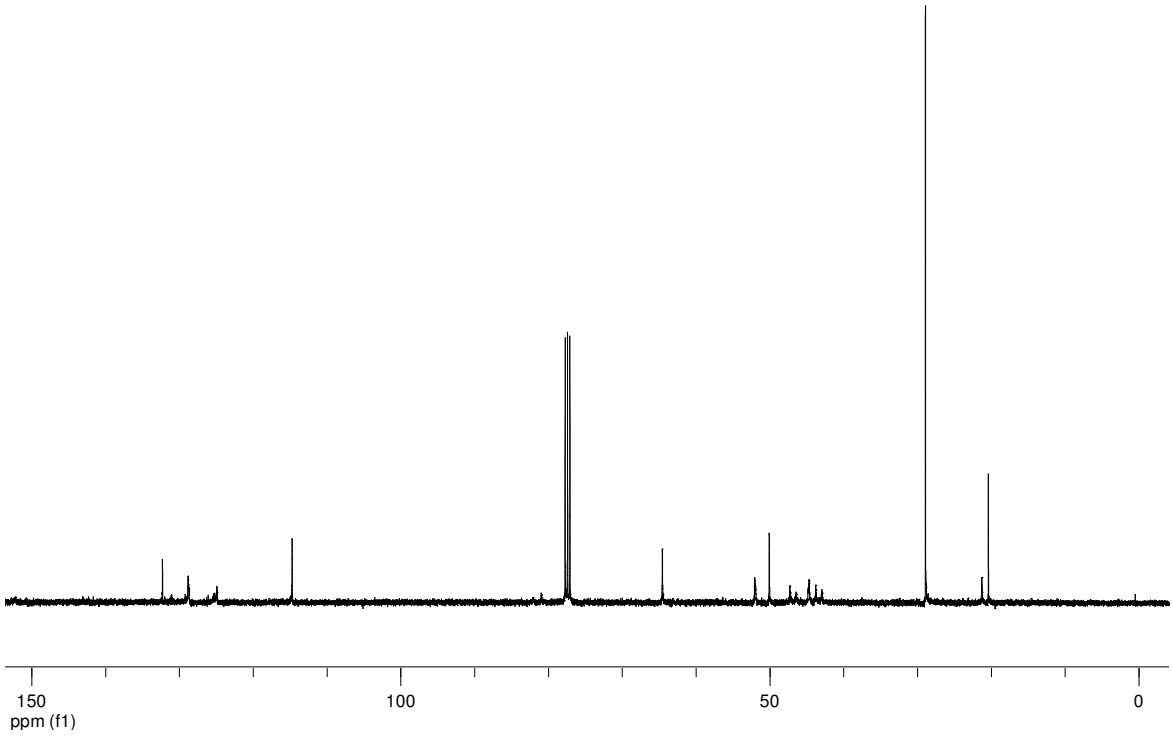
(**16**)







(**17**)



X-ray crystallographic picture of **8h**