Journal of Organic Chemistry – Supporting Information

Formation of Spirocyclic Compounds from Heck Cyclizations Invoking Cyclic Enamides

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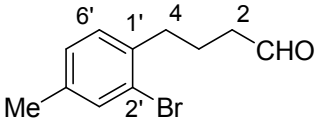
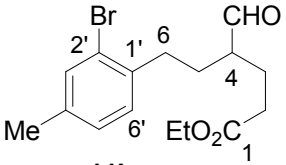
Experimental Section

^{1}H and ^{13}C NMR spectra were recorded at 295 K in $CDCl_3$ at 400 and 100 MHz, respectively. Chemical shifts are calibrated to the residual proton and carbon resonance of the solvent: $CDCl_3$ (δH 7.25, δC 77.0 ppm). Peak assignments were performed using DEPT and H-H COSY experiments. HRMS (FT-ICR): electron spray ionization (ESI). The theoretical HRMS values were calculated using software provided with the FT-ICR spectrometer. Analytical LC-MS: positive mode with fragmentor voltage of 40 eV, column: Nucleosil 100-5, C-18 HD, 5 μm, 70 × 3 mm Machery Nagel, eluent: NaCl solution (5 mM)/acetonitrile, gradient: 0-10-15-17-20 min with 20-80-80-99-99% acetonitrile, flow: 0.5 mL min^{-1}. Flash chromatography: silica gel 43-60 μm. Solvents were distilled prior to use; petroleum ether with a boiling range of 40–60 °C was used. Reactions were generally run under a nitrogen atmosphere.



9b

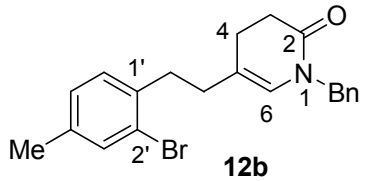
4-(2-Bromo-4-methylphenyl)butanal (9b). To a mixture of $Pd(OAc)_2$ (75.6 mg, 2 mol%), butenylalcohol (2.2 mL, 25.2 mmol), triethylbenzylammonium chloride (3.83 g, 16.8 mmol), and $NaHCO_3$ (2.8 g, 33.7 mmol) in DMF (40 mL) was added iodobromide[1] **8b** (5.0 g, 16.8 mmol), followed by stirring of the mixture at 40 °C for 24 h. After cooling, the mixture was treated with with aqueous NH_4Cl solution. This mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered, and concentrated in vacuo. Purification of the crude material by flash chromatography (ethyl acetate/hexane, 2:98 to1:19) furnished aldehyde **9b** (2.9 g, 72%) as colorless oil. R_f = 0.35 (ethyl acetate/hexane, -+1:19); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 9.77 (1 H, s, CH=O), 7.35 (1 H, s, 3'-H), 7.07 (1 H, 5'-H) and 7.03 (1 H, 6'-H) [2 d, J = 7.6 Hz], 2.73 (2 H, t, J = 7.4 Hz, 4-H), 2.47 (2 H, dt, J = 7.4, 1.3 Hz, 2-H), 2.28 (3 H, s, $ArCH_3$), 1.94 (2 H, quintet, J = 7.4 Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 202.2 (CH=O), 137.8 (C-1'), 137.3 (C-4'), 133.3 (CH), 130.1 (CH), 128.3 (CH), 124.1 (C-2'), 43.0 (C-3), 34.7 (C-2), 22.3 (C-3), 20.5 ($ArCH_3$).



11b

Ethyl 6-(2-bromo-4-methylphenyl)-4-formylhexanoate (11b). To a magnetically stirred solution of the aldehyde **9b** (2.1 g, 8.7 mmol) in C_6H_6 (10 mL) were added anhydrous K_2CO_3 (3.59 g, 26.1 mmol, 3 equiv) followed by pyrrolidine (1.4 mL, 17.4 mmol). The reaction mixture was stirred for 6 h at room temperature. Then the mixture was treated with saturated aqueous $NaHCO_3$ solution, extracted with diethyl ether (3 × 30 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to provide the crude enamine **10b**. To the crude enamine in CH_3CN (10 mL) at 5 °C were added molecular sieves (4 Å, 2 g) followed by ethyl acrylate (1.5 mL, 13.9 mmol). The resultant mixture was stirred for 2 h at room temperature, and then refluxed for 2 h. After cooling of the mixture to room temperature, AcOH (3 mL) in H_2O (12 mL) was added followed by refluxing of the mixture for 2 h. After cooling to ambient temperature, the mixture was treated with 3N HCl, and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Concentration of the filtrate and purification of the residue by flash chromatography (ethyl acetate/hexane, 3:97 to 1:8) furnished the aldehyde ester **11b** (2.1 g, 71% for two steps) as a colorless oil. R_f = 0.4 (ethyl acetate/hexane, 1:8); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 9.64 (1 H, s, CH=O), 7.34 (1 H, s, 3'-H), 7.07 (1 H, 5'-H) and 7.02 (1 H, 6'-H) [2 J = 7.9 Hz], 4.11 (2 H, q, J = 7.1 Hz, OCH_2CH_3), 2.80–2.60 (2 H, m, 6-H), 2.45–2.25 (3 H, m), 2.28 (3 H, s, $ArCH_3$), 2.10–1.65 (4 H, m), 1.24 (3 H, t, J = 7.1 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 203.8 (CH=O), 172.9 (OC=O), 138.0 (C-1'), 137.3 (C-4'), 133.3 (CH), 130.1 (CH), 128.4 (CH), 124.0 (C-2'), 60.5 (OCH_2CH_3), 50.6 (C-4), 33.0 (CH_2Ar), 31.5 (C-), 29.0 (C-5), 23.5 (C-3), 20.5 ($ArCH_3$), 14.2 (OCH_2CH_3).

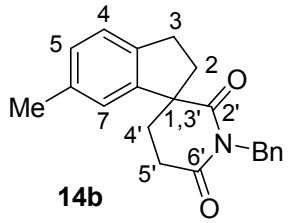
[1] (a) Bard, R. R.; Bunnett, J. F.; Traber, R. P. *J. Org. Chem.* **1979**, *44*, 4918-4924. (b) van Klink, G. P. M.; de Boer, H. J. R.; Schat, G.; Akkerman, O. S.; Bickelhaupt, F.; Spek, A. L. *Organometallics* **2002**, *21*, 2119-2135.



12b

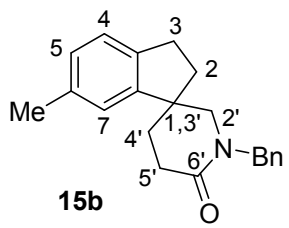
1-Benzyl-5-[2-(2-bromo-4-methylphenyl)ethyl]-3,4-dihydropyridin-2(1*H*)-one (12b). To a magnetically stirred solution of the aldehyde-ester **11b** (2.1 g, 6.1 mmol) in CH_2ClCH_2Cl (8 mL) at room temperature, were added sequentially benzyl amine (1.34 mL, 12.3 mmol) and AcOH (0.35 mL, 6.1 mmol) followed by refluxing of the mixture for 12 h. After cooling, the reaction mixture was treated with aqueous $NaHCO_3$ solution and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and filtered. Concentration of the filtrate followed by flash chromatography (ethyl acetate/hexane, 1:9 to 1:2) furnished the cyclic enamide **12b** (1.9 g, 82%) as brown viscous oil. R_f = 0.45 (ethyl acetate/hexane, 1:2); IR (neat): ν_{max}/cm^{-1} = 3030, 2924, 2838, 1667, 1606, 1491, 1439, 1408, 1270, 1211, 1040, 825, 703; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.40–7.23 (3 H, m, Ar-H), 7.36 (1 H, s, 3'-H), 7.22 (2 H, d, *J* = 7.6 Hz, Ar-H), 7.03 (1 H, 5'-H) and 7.01 (1 H, 6'-H) [2 d, *J* = 7.9 Hz], 5.78 (1 H, s, 6-H), 4.66 (2 H, s, NCH_2Ph), 2.79 (2 H, CH_2Ar) and 2.61 (2 H, CH_2C-5) [2 t, *J* = 7.9 Hz], 2.36 (2 H, 4-H) and 2.32 (2 H, 3-H) [2 d, *J* = 7.9 Hz], 2.31 (3 H, s, $ArCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 168.8 (NC=O), 137.7 (C-1'), 137.3 (2 C, C), 133.2 (C-3'), 130.0 (CH), 128.5 (2 C, CH), 128.2 (CH), 127.5 (2 C, CH), 127.3 (CH), 124.7 (C-6), 124.0 (C-2'), 119.0 (C-5), 48.8 (NCH_2Ph), 34.3 (CH_2Ar), 34.1 (CH_2C-5), 31.2 (C-3), 24.3 (C-4), 20.5 ($ArCH_3$); HRMS (ESI): calcd for $C_{21}H_{23}BrNO$ $[M + H]^+$ 384.0957, found 384.0957.

Palladium-catalyzed spiro cyclization of 5-(-bromophenyl)ethyl-substituted enamide 12b.
To a solution of the bromoenamide **12b** (230 mg, 0.6 mmol) in anhydrous DMF (3 mL), in an oven dried Schlenk tube fitted with a rubber septum, were added Ph_3P (31.5 mg, 20 mol%), Cs_2CO_3 (780 mg, 2.4 mmol) and $Pd(OAc)_2$ (13.4 mg, 10 mol%) at room temperature under nitrogen atmosphere. The magnetically stirred reaction mixture was heated in an oil bath at 120 °C for 3 days. The mixture was cooled to room temperature and washed with aqueous 3N HCl solution. After separation of the layers, the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the filtrate and purification of the crude material by flash chromatography (ethyl acetate/hexane, 1:9 to 1:4) furnished as first fraction the imide **14b** (32 mg, 17%) as brown viscous oil. Continuation of the elution with ethyl acetate/hexane (1:4 to 3:2) provided the amide **15b** (70 mg, 38%) as brown viscous oil. In this case the by-product **13b** was identified by LC-MS but could not be obtained pure due to coelution with an unidentified impurity.



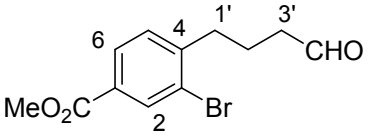
14b

1'-Benzyl-6-methyl-2,3-dihydro-2'*H*,6'*H*-spiro[indene-1,3'-piperidine]-2',6'-dione (14b): R_f = 0.8 (ethyl acetate/hexane, 4:1); IR (neat): ν_{max}/cm^{-1} = 3032, 2926, 2853, 1722, 1677, 1494, 1454, 1375, 1163, 820, 736, 701; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.43 (2 H, d, *J* = 7.6 Hz, Ar-H), 7.38–7.22 (3 H, m, Ar-H), 7.19 (1 H, 5-H) and 7.08 (1 H, 6-H) [2 d, *J* = 7.6 Hz], 6.74 (1 H, s, 7-H), 5.10 (1 H, d) and 5.06 (1 H, d) [*J* = 13.7 Hz, NCH_2Ph], 3.10–2.92 (2 H, m, 3-H), 2.94–2.70 (3 H, m), 2.28 (3 H, s, $ArCH_3$), 2.20 (1 H, ddd, *J* = 14.0, 8.4, 5.6 Hz, 5'-H), 2.10 (1 H, ddd, *J* = 12.7, 7.6, 5.1 Hz), 2.02 (1 H, ddd, *J* = 13.5, 7.1, 5.6 Hz, 5'-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 175.5 (C-2'), 172.2 (C-5'), 144.3 (C-7a), 140.7 (C-3a), 137.5 (C), 136.3 (C-6), 129.0 (CH), 128.9 (2 C, CH), 128.3 (2 C, CH), 127.4 (CH), 124.8 (CH), 123.8 (CH), 54.8 (C-(1,3')), 43.3 (NCH_2Ph), 36.6 (CH_2Ar), 30.0 (C-5'), 29.7 (C-2), 28.6 (C-4'), 21.2 ($ArCH_3$); HRMS (ESI): calcd for $C_{21}H_{22}NO_2$ $[M + H]^+$ 320.1645, found 320.1645.



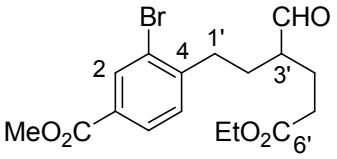
15b

1'-Benzyl-6-methyl-2,3-dihydro-6'*H*-spiro[indene-1,3'-piperidin]-6'-one (15b): R_f = 0.4 (ethyl acetate/hexane, 4:1); IR (neat): ν_{max}/cm^{-1} = 3029, 2926, 2857, 1642, 1493, 1453, 1417, 1356, 1237, 816, 701; ^1H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.38–7.18 (5 H, m, Ar-H), 7.06 (1 H, 5-H) and 6.98 (1 H, 4-H) [2 d, *J* = 7.6 Hz], 6.88 (1 H, s, 7-H), 4.78 (1 H, d) and 4.43 (1 H, d) [*J* = 14.2 Hz, NCH_2Ph], 3.23 (1 H, d, *J* = 12.2 Hz) and 3.04 (1 H, dd, *J* = 12.2, 2.0 Hz) [2'-H], 2.82 (1 H, ddd, *J* = 16.3, 8.7, 4.8 Hz), 2.78–2.52 (3 H, m), 2.28 (3 H, $ArCH_3$), 2.18 (1 H, ddd, *J* = 13.2, 9.7, 7.1 Hz), 2.00 (1 H, ddd, *J* = 13.0, 8.4, 5.1 Hz), 1.94–1.81 (1 H, m), 1.83–1.71 (1 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 169.5 (NC=O), 146.8 (C-7a), 140.3 (C-3a), 136.9 (C), 136.2 (C-6), 128.5 (2 C, CH), 128.4 (2 C, CH), 128.3 (CH), 127.4 (CH), 124.5 (CH), 123.3 (CH), 55.8 (C-2'), 50.2 (NCH_2Ph), 46.3 (C-(1,3')), 35.3 (C-3), 31.6 (C-5'), 29.5 (C-2), 29.0 (C-4'), 21.2 ($ArCH_3$); HRMS (ESI): calcd for $C_{21}H_{24}NO$ $[M + H]^+$ 306.1852, found 306.1853.



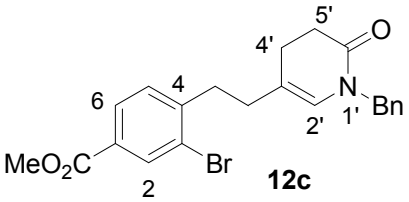
9c

Methyl 3-bromo-4-(4-oxobutyl)benzoate (9c). The reaction was performed as described for compound **9b**. Thus, to a mixture of $Pd(OAc)_2$ (76 mg, 2 mol%), butenylalcohol (2.2 mL, 25.6 mmol), triethylbenzylammonium chloride (3.9 g, 17 mmol) and $NaHCO_3$ (2.85 g, 34 mmol) in DMF (40 mL) was added iodobromide[2] **8c** (5.8 g, 17 mmol), followed by stirring at 40 °C for 24 h. Purification of the crude material by flash chromatography (ethyl acetate/hexane, 1:9 to 1:4) furnished the aldehyde **9c** (3.15 g, 65%) as colorless oil. R_f = 0.4 (ethyl acetate/hexane, 1:4); ^1H NMR (400 MHz, $CDCl_3$): δ[ppm] = 9.72 (1 H, s, CH=O), 8.12 (1 H, d, *J* = 1.8 Hz, 2-H), 7.82 (1 H, dd, *J* = 7.9, 1.8 Hz, 6-H), 7.21 (1 H, d, *J* = 7.9 Hz, 5-H), 3.83 (3 H, s, CO_2CH_3), 2.74 (2 H, t, *J* = 7.6 Hz, 1'-H), 2.44 (2 H, dt, *J* = 7.6, 1.3 Hz, 3'-H), 1.90 (2 H, quintet, *J* = 7.4 Hz, 2'-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 201.6 (CH=O), 165.6 (OC=O), 145.8 (C-4), 133.9 (C-2), 130.2 (C-6), 129.8 (C-1), 128.5 (C-5), 124.2 (C-3), 52.2 (CO_2CH_3), 42.9 (C-1'), 35.2 (C-3'), 21.8 (C-2').



11c

Methyl 3-bromo-4-(6-ethoxy-3-formyl-6-oxohexyl)benzoate (11c). The reaction was performed with aldehyde **9c** (1.0 g, 3.5 mmol), pyrrolidine (0.87 mL, 10.5 mmol) and ethyl acrylate (0.76 mL, 7 mmol) as described above (compound **11b**). Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:9 to 1:3) furnished the aldehyde ester **11c** (900 mg, 67% for two steps) as colorless oil. R_f = 0.45 (ethyl acetate/hexane, 1:3); ^1H NMR (400 MHz, $CDCl_3$): δ[ppm] = 9.65 (1 H, s, CH=O), 8.18 (1 H, d, *J* = 1.8 Hz, 2-H), 7.88 (1 H, dd, *J* = 7.9 Hz, 6-H), 7.27 (1 H, d, *J* = 7.9 Hz, 5-H), 4.11 (2 H, q, *J* = 7.1 Hz, OCH_2CH_3), 3.89 (3 H, s, CO_2CH_3), 2.90–2.62 (2 H, m, CH_2Ar), 2.45–2.25 (3 H, m), 2.13–1.65 (4 H, m), 1.23 (3 H, t, *J* = 7.1 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 203.4 (CH=O), 172.8 (C-6'), 165.6 (OC=O), 145.8 (C-4), 134.0 (C-2), 130.3 (C-6), 130.0 (C-1), 128.7 (C-5), 124.1 (C-3), 60.6 (OCH_2CH_3), 52.3 (CO_2CH_3), 50.5 (C-3'), 33.6 (CH_2Ar), 31.4 (C-5'), 28.4 (C-2'), 23.5 (C-4'), 14.2 (OCH_2CH_3).



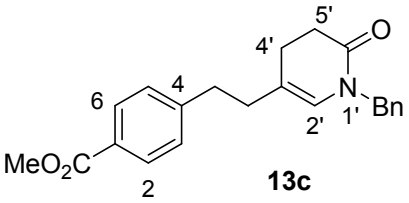
12c

Methyl 4-[2-(1-benzyl-6-oxo-1,4,5,6-tetrahydropyridin-3-yl)ethyl]-3-bromobenzoate (12c). As described for compound **12b**, the formyl ester **11c** (880 mg, 2.3 mmol) in CH_2ClCH_2Cl (5 mL) was reacted with benzylamine (0.76 mL, 6.9 mmol) and AcOH (0.2 mL, 3.5 mmol). Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:5 to 1:1) furnished the cyclic enamide **12c** (680 mg, 69%) as light brown viscous oil. R_f = 0.45 (ethyl acetate/hexane, 1:1); IR (neat): ν_{max}/cm^{-1} = 3030, 2949, 1723, 1667, 1602, 1496, 1435, 1409, 1285,

[2] Compound **1c**: Vu, C. B.; Corpuz, E. G.; Merry, T. J.; Pradeepan, S. G.; Bartlett, C.; Bohacek, R. S.; Botfield, M. C.; Eyermann, C. J.; Lynch, B. A.; MacNeil, I. A.; Ram, M. K.; van Schravendijk, M. R.; Violette, S.; Sawyer, T. K. *J. Med. Chem.* **1999**, *42*, 4088-4098.

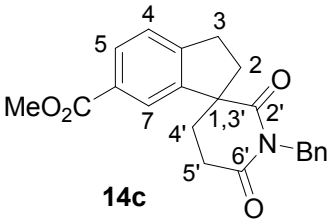
1257, 1212, 1112, 1040, 763, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 8.23 (1 H, d, *J* = 1.5 Hz, 2-H), 7.90 (1 H, dd, *J* = 7.9, 1.5 Hz, 6-H), 7.48–7.15 (6 H, m, Ar-H), 5.79 (1 H, s, 2'-H), 4.68 (2 H, s, NCH_2Ph), 3.98 (3 H, CO_2CH_3), 2.92 (2 H, CH_2Ar) and 2.65 (2 H, CH_2C-3') [2 t, *J* = 7.6 Hz], 2.40–2.25 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 168.7 (NC=O), 165.6 (OC=O), 145.7 (C-4), 137.1 (C), 133.9 (C-2), 130.2 (C-6), 129.8 (C-1), 128.5 (2 C, CH), 128.4 (C-5), 127.4 (2 C, CH), 127.3 (CH), 125.0 (C-2'), 124.1 (C-3), 118.2 (C-3'), 52.3 (CO_2CH_3), 48.8 (NCH_2Ph), 34.8 (CH_2Ar), 33.6 (CH_2C-3'), 31.1 (C-5'), 24.2 (C-4'); HRMS (ESI): calcd for $C_{22}H_{23}BrNO_3$ $[M + H]^+$ 428.0856, found 428.0855.

Palladium-catalyzed spiro cyclization of 5-(-bromophenyl)ethyl-substituted enamide 12c. The reaction was performed with the enamide **12c** (360 mg, 0.84 mmol) in anhydrous DMF (5 mL) with Ph_3P (44 mg, 20 mol%), Cs_2CO_3 (1.1 g, 3.3 mmol) and $Pd(OAc)_2$ (18.9 mg, 10 mol%). After loading of the reagents at room temperature, the mixture was heated to 120 °C, as described for compound **12b**. Purification of the crude product mixture by flash chromatography (ethyl acetate/hexane, 1:9 to 1:3) first furnished the imide **14c** (35 mg, 11%) as brown viscous oil. Further elution of the column using ethyl acetate/hexane (1:3 to 1:1) provided the debromoenamide **13c** (45 mg, 15%) as brown viscous oil. Continuation of the elution using ethyl acetate/hexane (1:3 to 7:3) gave the spirocylic amide **15c** (70 mg, 24%) as brown viscous oil.



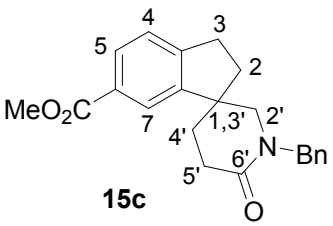
13c

Methyl 4-[2-(1-benzyl-6-oxo-1,4,5,6-tetrahydropyridin-3-yl)ethyl]benzoate (13c): R_f = 0.5 (ethyl acetate/hexane, 4:1); IR (neat): ν_{max}/cm^{-1} = 3030, 2950, 1719, 1665, 1610, 1496, 1435, 1414, 1280, 1110, 1020, 800, 763, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.84 (2 H, d, *J* = 8.1 Hz, 2-H and 6-H), 7.28–7.12 (3 H, m, Ar-H), 7.14–7.01 (4 H, m, Ar-H), 5.62 (1 H, s, 2'-H), 4.52 (2 H, s, NCH_2Ph), 3.83 (3 H, s, CO_2CH_3), 2.66 (2 H, CH_2Ar) and 2.48 (2 H, CH_2C-3') [2 t, *J* = 7.6 Hz], 2.25 (2 H, 4'-H) and 2.20 (2 H, 5'-H) [2 t, *J* = 7.9 Hz]; ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 168.7 (NC=O), 167.0 (OC=O), 146.7 (C-4), 137.1 (C), 129.7 (2 C, CH), 128.5 (2 C, CH), 128.3 (2 C, CH), 128.0 (C-1), 127.4 (2 C, CH), 127.3 (CH), 124.8 (C-2'), 118.5 (C-3'), 51.9 (CO_2CH_3), 48.8 (NCH_2Ph), 35.2 (CH_2Ar), 34.1 (CH_2C-3'), 31.1 (C-5'), 24.2 (C-4'); HRMS (ESI): calcd for $C_{22}H_{24}NO_3$ $[M + H]^+$ 350.1751, found 350.1751.



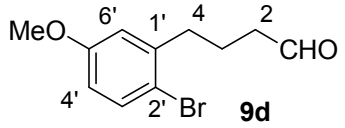
14c

Methyl 1'-benzyl-2',6'-dioxo-2,3-dihydrospiro[indene-1,3'-piperidine]-6-carboxylate (14c): R_f = 0.7 (ethyl acetate/hexane, 4:1); IR (neat): ν_{max}/cm^{-1} = 2951, 1720, 1676, 1435, 1293, 1233, 1165, 1107, 761, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.89 (1 H, dd, *J* = 7.9, 1.5 Hz, 5-H), 7.61 (1 H, d, *J* = 1.5 Hz, 4-H), 7.35–7.12 (6 H, m, Ar-H), 4.97 (1 H, d) and 4.93 (1 H, d) [*J* = 13.7 Hz, NCH_2Ph], 3.80 (3 H, CO_2CH_3), 3.13–2.90 (2 H, m, 3-H), 2.90–2.64 (2 H, m, 2-H), 2.59 (1 H, ddd, *J* = 15.2, 8.6, 6.8 Hz) and 2.23 (1 H, ddd, *J* = 13.9, 9.9, 5.6 Hz) [5'-H], 2.08 (1 H, ddd, *J* = 13.6, 7.9, 5.8 Hz) and 1.92 (1 H, dt, *J* = 13.6, 5.8 Hz) [4'-H]; ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 175.1 (C-2'), 171.8 (C-6'), 166.7 (OC=O), 149.5 (C-3a), 144.8 (C-7a), 137.3 (C), 129.9 (C-5), 129.1 (C-6), 128.8 (2 C, CH), 128.4 (2 C, CH), 127.4 (CH), 125.0 (CH), 124.5 (CH), 54.8 (C-(1,3')), 52.0 (CO_2CH_3), 43.4 (NCH_2Ph), 36.6 (CH_2Ar), 30.4 (C-5'), 30.0 (C-2), 28.8 (C-4'); HRMS (ESI): calcd for $C_{22}H_{21}NO_4Na$ $[M + Na]^+$ 386.1363, found 386.1362.



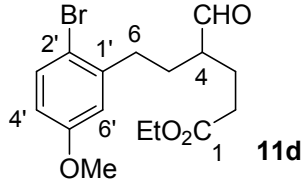
15c

Methyl 1'-benzyl-6'-oxo-2,3-dihydrospiro[indene-1,3'-piperidine]-6-carboxylate (15c): R_f = 0.3 (ethyl acetate/hexane, 4:1); IR (neat): ν_{max}/cm^{-1} = 2962, 1717, 1642, 1488, 1434, 1283, 1239, 1107, 762, 704; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.81 (1 H, dd, *J* = 7.9, 1.5 Hz, 5-H), 7.70 (1 H, d, *J* = 1.5 Hz, 7-H) 7.30–7.10 (6 H, m, Ar-H), 4.74 (1 H, d) and 4.32 (1 H, d) [*J* = 14.4 Hz, NCH_2Ph], 3.81 (3 H, s, CO_2CH_3), 3.21 (1 H, d, *J* = 12.1 Hz) and 2.95 (1 H, dd, *J* = 12.1, 2.0 Hz) [2'-H], 2.83 (1 H, ddd, *J* = 16.9, 8.6, 4.6 Hz), 2.77–2.45 (3 H, m), 2.19 (1 H, ddd, *J* = 13.1, 10.4, 7.3 Hz) and 1.99 (1 H, ddd, *J* = 12.9, 8.3, 4.5 Hz) [5'-H], 1.93–1.80 (1 H, m), 1.77–1.65 (1 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 169.2 (NC=O), 166.9 (OC=O), 149.1 (C-3a), 147.1 (C-7a), 136.8 (C), 129.3 (C-5), 128.9 (C-1), 128.5 (2 C, CH), 128.3 (2 C, CH), 127.4 (CH), 124.8 (CH), 123.8 (CH), 55.6 (C-2'), 52.0 (CO_2CH_3), 50.1 (NCH_2Ph), 46.4 (C-(1,3')), 34.7 (C-3), 31.8 (C-5'), 29.6 (C-2), 29.4 (C-4'); HRMS (ESI): calcd for $C_{22}H_{24}NO_3$ $[M + H]^+$ 350.1751, found 350.1750.



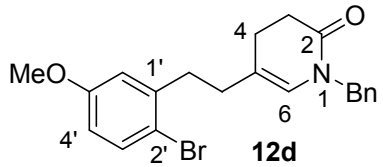
9d

4-(2-Bromo-5-methoxyphenyl)butanal (9d). The reaction was performed as described for compound **9b**. Thus, to a mixture of $Pd(OAc)_2$ (100 mg, 2 mol%), butenylalcohol (3.8 mL, 44.7 mmol), triethylbenzylammonium chloride (5.1 g, 22.3 mmol) and $NaHCO_3$ (3.2 g, 44.7 mmol) in DMF (50 mL) was added iodobromide[3] **8d** (7.0 g, 22.3 mmol), followed by stirring at 40 °C for 24 h. Purification of the crude material by flash chromatography (ethyl acetate/hexane, 1:19 to 1:9) furnished the aldehyde **9d** (4.1g, 71%) as colorless oil. R_f = 0.45 (ethyl acetate/hexane, 1:9); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 9.77 (1 H, s, CH=O), 7.40 (1 H, d, *J* = 8.7 Hz, 3'-H), 6.74 (1 H, d, *J* = 3.1 Hz, 6'-H), 6.63 (1 H, dd, *J* = 8.7, 3.1 Hz, 4'-H), 3.77 (3 H, s, OCH_3), 2.73 (2 H, t, *J* = 7.1 Hz, 4-H), 2.49 (2 H, dt, *J* = 7.1, 1.5 Hz, 2-H), 1.95 (2 H, quintet, *J* = 7.4 Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 202.1 (CH=O), 159.0 (C-5'), 141.5 (C-1'), 133.3 (C-3'), 116.1 (C-6'), 114.8 (C-2'), 113.4 (C-4'), 55.4 (OCH_3), 43.0 (C-4), 35.4 (C-2), 22.2 (C-3).



11d

Ethyl 6-(2-bromo-5-methoxyphenyl)-4-formylhexanoate (11d). The reaction was performed with aldehyde **9d** (2.0 g, 7.8 mmol), pyrrolidine (1.3 mL, 15.5 mmol) and ethyl acrylate (1.35 mL, 12.4 mmol) as described above. Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:19 to 1:6) furnished the aldehyde ester **11d** (2.0 g, 72% for two steps) as colorless oil. R_f = 0.4 (ethyl acetate/hexane, 1:6); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 9.65 (1 H, s, CH=O), 7.39 (1 H, d, *J* = 8.7 Hz, 3'-H), 6.74 (1 H, d, *J* = 3.1 Hz, 6'-H), 6.62 (1 H, dd, *J* = 8.7, 3.1 Hz, Ar-H), 4.12 (2 H, q, *J* = 7.1 Hz, OCH_2CH_3), 3.76 (3 H, s, OCH_3), 2.79–2.60 (2 H, m, 6-H), 2.45–2.28 (3 H, m), 2.10–1.65 (4 H, m), 1.24 (3 H, t, *J* = 7.1 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 203.8 (CH=O), 172.9 (OC=O), 159.0 (C-5'), 141.5 (C-1'), 133.4 (C-3'), 116.0 (C-6'), 114.6 (C-2'), 113.5 (C-4'), 60.5 (OCH_2CH_3), 55.4 (OCH_3), 50.6 (C-4), 33.7 (CH_2Ar), 31.5 (C-2), 28.8 (C-5), 23.5 (C-3), 14.2 (OCH_2CH_3).



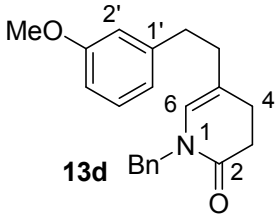
12d

1-Benzyl-5-[2-(2-bromo-5-methoxyphenyl)ethyl]-3,4-dihydropyridin-2(1*H*)-one (12d). As described for compound **12b**, the formyl ester **11d** (1.2 g, 3.36 mmol) in CH_2ClCH_2Cl (7 mL) was reacted with benzylamine (1.1 mL, 10.1 mmol) and AcOH (0.2 mL, 3.4 mmol). Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:9 to 2:3) furnished the cyclic enamide **12d** (1.1 g, 84%) as light brown viscous oil. R_f = 0.45 (ethyl acetate/hexane, 2:3); IR (neat): ν_{max}/cm^{-1} = 3033, 2936, 1667, 1595, 1572, 1472, 1410, 1278, 1241, 1212, 1054, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.38 (1 H, d, *J* = 8.7 Hz, 3'-H), 7.35–7.19 (3 H, m, Ar-H), 7.18 (2 H, d, *J* = 8.1 Hz, Ar-H), 6.68 (1 H, d, *J* = 3.1 Hz, 6'-H), 6.61 (1 H, dd, *J* = 8.7, 3.1 Hz, 4'-H), 5.77 (1 H, s, 6-H), 4.63 (2 H, s, NCH_2Ph), 3.73 (3 H, s, OCH_3), 2.75 (2 H, CH_2Ar) and 2.58 (2 H, CH_2C-5) [2 t, *J* = 7.6 Hz], 2.40–2.21 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 168.8 (NC=O), 158.9 (C-5'), 141.5 (C-1'), 137.2 (C), 133.3 (C-3'),

[3] (a) Kuwabe, S.-i.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202-12206. (b) Fürstner, A.; Kennedy, J. W. J. *Chem. Eur. J.* **2006**, *12*, 7398-7410.

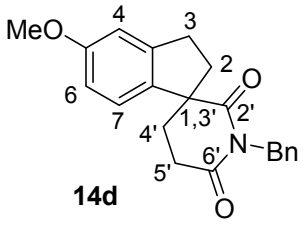
128.6 (2 C, CH), 127.5 (2 C, CH), 127.3 (CH), 124.7 (C-6), 118.9 (C-5), 116.1 (C-6'), 114.7 (C-2'), 113.2 (C-4'), 55.4 (OCH_3), 48.9 (NCH_2Ph), 35.0 (CH_2Ar), 34.0 (CH_2C-5), 31.2 (C-3), 24.2 (C-4); HRMS (ESI): calcd for $C_{21}H_{23}BrNO_2$ $[M + H]^+$ 400.0907, found 400.0905.

Palladium-catalyzed spiro cyclization of 5-(-bromophenyl)ethyl-substituted enamide 12d. The reaction was performed with the enamide **12d** (230 mg, 0.575 mmol) in anhydrous DMF (3 mL) with Ph_3P (30.0 mg, 20 mol%), Cs_2CO_3 (749 mg, 2.3 mmol) and $Pd(OAc)_2$ (12.9 mg, 10 mol%). After loading of the reagents at room temperature, the mixture was heated to 100 °C, as described for compound **12b**. Purification of the crude product mixture by flash chromatography (ethyl acetate/hexane, 1:9 to 1:3) first furnished the imide **14d** (17 mg, 9%) as brown viscous oil. Further elution of the column using ethyl acetate/hexane (1:3 to 2:3) as eluent furnished the debromoenamide **13d** (20 mg, 11%) as brown viscous oil. Continuation of the elution using ethyl acetate/hexane (2:3 to 3:2) as eluent furnished the spiro amide **15d** (81 mg, 44%) as brown viscous oil.



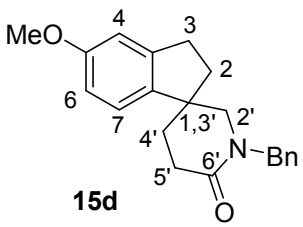
13d

1-Benzyl-5-[2-(3-methoxyphenyl)ethyl]-3,4-dihydropyridin-2(1*H*)-one (13d): R_f = 0.55 (ethyl acetate/hexane, 4:1); IR (neat): ν_{max}/cm^{-1} = 3030, 2934, 2835, 1667, 1602, 1584, 1492, 1454, 1260, 1212, 1153, 1050, 698; ^1H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.35–7.03 (6 H, m, Ar-H), 6.73–6.55 (3 H, m, Ar-H), 5.67 (1 H, s, 6-H), 4.55 (2 H, s, NCH_2Ph), 3.70 (3 H, s, OCH_3), 2.59 (2 H, CH_2Ar) and 2.49 (2 H, CH_2C-5) [2 t, *J* = 7.6 Hz], 2.22 (2 H, 4-H) and 2.20 (2 H, 3-H) [2 d, *J* = 7.9 Hz]; ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 168.8 (NC=O), 159.6 (C-3'), 142.9 (C-1'), 137.3 (C), 129.3 (CH), 128.6 (2 C, CH), 127.5 (2 C, CH), 127.3 (CH), 124.5 (C-6), 120.7 (C-6'), 119.2 (C-5), 114.1 (C-2'), 111.1 (C-4'), 55.1 (OCH_3), 48.8 (NCH_2Ph), 35.5 (CH_2Ar), 34.3 (CH_2C-5), 31.2 (C-3), 24.3 (C-4); HRMS (ESI): calcd for $C_{21}H_{24}NO_2$ $[M + H]^+$ 322.1802, found 322.1801.



14d

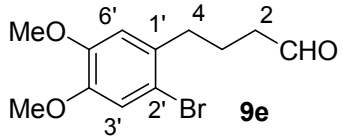
1'-Benzyl-5-methoxy-2,3-dihydro-2'*H*,6'*H*-spiro[indene-1,3'-piperidine]-2',6'-dione (14d): R_f = 0.75 (ethyl acetate/hexane, 4:1); IR (neat): ν_{max}/cm^{-1} = 3032, 2943, 2850, 1722, 1674, 1606, 1493, 1454, 1376, 1257, 1163, 1029, 816, 734, 701; ^1H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.29 (2 H, d, *J* = 7.6 Hz, Ar-H), 7.25–7.10 (3 H, m, Ar-H), 6.77 (1 H, d, *J* = 8.4 Hz, 7-H), 6.73 (1 H, d, *J* = 2.5 Hz, 4-H), 6.61 (1 H, dd, *J* = 8.4, 2.5 Hz, 6-H), 4.96 (1 H, d) and 4.91 (1 H, d) [*J* = 13.7 Hz, NCH_2Ph], 3.69 (3 H, s, OCH_3), 3.02–2.82 (2 H, m, 3-H), 2.82–2.55 (3 H, m), 2.09 (1 H, ddd, *J* = 14.0, 8.4, 5.6 Hz), 2.00 (1 H, ddd, *J* = 12.7, 7.6, 5.1 Hz), 1.88 (1 H, ddd, *J* = 13.5, 7.1, 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 175.6 (C-2'), 172.2 (C-6'), 159.9 (C-5), 145.5 (C-3a), 137.4 (C), 136.3 (C-7a), 128.8 (2 C, CH), 128.3 (2 C, CH), 127.3 (CH), 123.7 (C-7), 112.6 (C-4), 110.4 (C-6), 55.3 (OCH_3), 54.2 (C-(1,3')), 43.3 (NCH_2Ph), 36.8 (CH_2Ar), 30.3 (C-2), 30.1 (C-5'), 28.9 (C-4'); HRMS (ESI): calcd for $C_{21}H_{22}NO_3$ $[M + H]^+$ 336.1594, found 336.1594.



15d

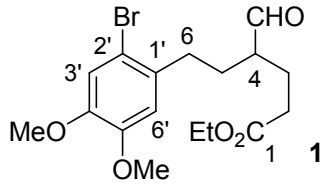
1'-Benzyl-5-methoxy-2,3-dihydro-6'*H*-spiro[indene-1,3'-piperidin]-6'-one (15d): R_f = 0.35 (ethyl acetate/hexane, 4:1); IR (neat): ν_{max}/cm^{-1} = 3038, 2926, 1639, 1492, 1453, 1356, 1248, 1031, 817, 701; ^1H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.30–7.10 (5 H, m, Ar-H), 6.92 (1 H, d, *J* = 8.3 Hz, 7-H), 6.66 (1 H, d, *J* = 2.5 Hz, 4-H), 6.63 (1 H, dd, *J* = 8.3, 2.5 Hz, 6-H), 4.77 (1 H, d) and 4.29 (1 H, d) [*J* = 14.4 Hz, NCH_2Ph], 3.69 (3 H, s, OCH_3), 3.13 (1 H, d, *J* = 12.4 Hz) and 2.96 (1 H, dd, *J* = 12.4, 2.0 Hz) [2'-H], 2.77 (1 H, ddd, *J* = 16.3, 8.7, 4.8

Hz), 2.70–2.45 (3 H, m), 2.10 (1 H, ddd, *J* = 13.2, 9.7, 7.1 Hz), 1.95 (1 H, ddd, *J* = 13.0, 8.4, 5.1 Hz), 1.88–1.76 (1 H, m), 1.75–1.62 (1 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 169.5 (NC=O), 159.5 (C-5), 145.0 (C-3a), 138.9 (C-7a), 137.0 (C), 128.5 (2 C, CH), 128.4 (2 C, CH), 127.4 (CH), 123.2 (C-7), 112.4 (C-4), 110.2 (C-6), 56.1 (C-2'), 55.4 (OCH_3), 50.3 (NCH_2Ph), 45.8 (C-(1,3')), 35.3 (C-3), 32.0 (C-5'), 29.7 (2 C, C-2 and C-4'); HRMS (ESI): calcd for $C_{21}H_{24}NO_2$ $[M + H]^+$ 322.1802, found 322.1802.



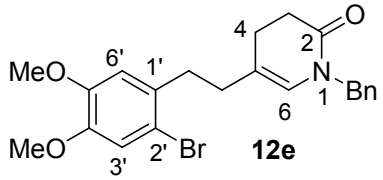
9e

4-(2-Bromo-4,5-dimethoxyphenyl)butanal (9e). The reaction was performed as described for the compound **9b**. Thus, to a mixture of $Pd(OAc)_2$ (65.4 mg, 2 mol%), butenylalcohol (1.87 mL, 21.8 mmol), triethylbenzylammonium chloride (3.32 g, 14.6 mmol) and $NaHCO_3$ (2.4 g, 29 mmol) in DMF (40 mL) was added iodobromide[4] **8e** (5.0 g, 14.6 mmol), followed by stirring at 40 °C for 24 h. Purification of the crude material by flash chromatography (ethyl acetate/hexane, 1:9 to 1:3) furnished the aldehyde **9e** (3.2 g, 76%) as colorless oil. R_f = 0.4 (ethyl acetate/hexane, 1:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 9.77 (1 H, s, CH=O), 6.98 (1 H, s, 3'-H), 6.69 (1 H, s, 6'-H), 3.84 (3 H, s) and 3.83 (3 H, s) [2 OCH_3], 2.69 (2 H, t, *J* = 7.1 Hz, 4-H), 2.48 (2 H, dt, *J* = 7.1, 1.5 Hz, 2-H), 1.93 (2 H, quintet, *J* = 7.4 Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 202.2 (CH=O), 148.4 (C-5'), 148.0 (C-4'), 132.5 (C-1'), 115.6 (C-3'), 114.0 (C-2'), 113.0 (C-6'), 56.1, 56.0 (2 OCH_3), 43.0 (C-4), 34.8 (C-2), 22.6 (C-3).



11e

Ethyl 6-(2-bromo-4,5-dimethoxyphenyl)-4-formylhexanoate (11e). The reaction was performed with aldehyde **9e** (3.0 g, 10.4 mmol), pyrrolidine (1.7 mL, 20.9 mmol) and ethyl acrylate (1.8 mL, 16.6 mmol) as described above. Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:9 to 1:3) furnished the aldehyde ester **11e** (3.0 g, 74% for two steps) as colorless oil. R_f = 0.35 (ethyl acetate/hexane, 1:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 9.64 (1 H, s, CH=O), 6.97 (1 H, s, 3'-H), 6.69 (1 H, s, 6'-H), 3.84 (3 H, s) and 3.83 (3 H, s) [2 OCH_3], 4.11 (2 H, q, *J* = 7.1 Hz, OCH_2CH_3), 2.80–2.55 (2 H, m, 6-H), 2.45–2.24 (3 H, m), 2.10–1.63 (4 H, m), 1.23 (3 H, t, *J* = 7.1 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 203.8 (CH=O), 172.9 (OC=O), 148.4 (C-5'), 148.1 (C-4'), 132.4 (C-1'), 115.6 (C-6'), 113.8 (C-2'), 113.0 (C-3'), 60.5 (OCH_2CH_3), 56.1, 56.0 (2 OCH_3), 50.5 (C-4), 33.2 (CH_2Ar), 31.5 (C-2), 29.1 (C-5), 23.6 (C-3), 14.2 (OCH_2CH_3).

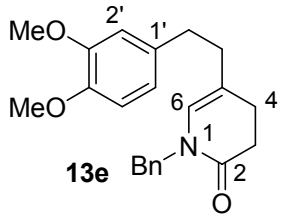


12e

1-Benzyl-5-[2-(2-bromo-4,5-dimethoxyphenyl)ethyl]-3,4-dihydropyridin-2(1*H*)-one (12e). As described for compound **12b**, the formyl ester **11e** (3.0 g, 9 mmol) in CH_2ClCH_2Cl (10 mL) was reacted with benzylamine (1.97 mL, 18.1 mmol) and AcOH (0.5 mL, 9 mmol). Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:5 to 1:1) as eluent furnished the cyclic enamide **12e** (2.5 g, 75%) as light brown viscous oil. R_f = 0.45 (ethyl acetate/hexane, 1:1); IR (neat): ν_{max}/cm^{-1} = 2932, 2839, 1666, 1603, 1508, 1439, 1408, 1381, 1256, 1217, 1163, 1031, 734, 704; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.40–7.23 (3 H, m, Ar-H), 7.22 (2 H, d, *J* = 8.1 Hz, Ar-H), 7.00 (1 H, s, 3'-H) and 6.66 (1 H, s, 6'-H), 5.80 (1 H, s, 6-H), 4.67 (2 H, s, NCH_2Ph), 3.87 (3 H, s) and 3.83 (3 H, s) [2 OCH_3], 2.76 (2 H, CH_2Ar) and 2.62 (2 H, CH_2C-5) [2 t, *J* = 7.9 Hz], 2.37 (2 H, 4-H) and 2.30 (2 H, 3-H) [2 t, *J* = 7.9 Hz]; ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 168.8 (NC=O), 148.3 (C-5'), 147.9 (C-4'), 137.2 (C), 132.5 (C-1'), 128.5 (2 C, CH), 127.4 (2 C, CH), 127.3 (CH), 124.7 (C-6), 118.9 (C-5), 115.5 (C-6'), 113.9 (C-2'), 112.8 (C-3'), 56.1, 56.0 (2 OCH_3), 48.8 (NCH_2Ph), 34.4 (CH_2Ar), 34.3 (CH_2C-5), 31.2 (C-3), 24.3 (C-4); HRMS (ESI): calcd for $C_{22}H_{25}BrNO_3$ $[M + H]^+$ 430.1012, found 430.1013.

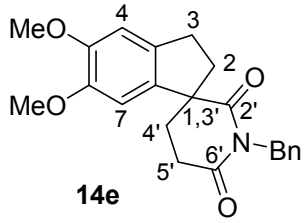
[4] Orito, K.; Hatakeyama, T.; Takeo, M.; Suginome, H. *Synthesis* **1995**, 1273-1277.

Palladium-catalyzed spiro cyclization of 5-(-bromophenyl)ethyl-substituted enamide 12e. The reaction was performed with the enamide **12e** (300 mg, 0.7 mmol) in anhydrous DMF (4 mL) with Ph_3P (36.5 mg, 20 mol%), Cs_2CO_3 (909 mg, 3.3 mmol) and $Pd(OAc)_2$ (15.6 mg, 10 mol%). After loading of the reagents at room temperature, the mixture was heated to 120 °C, as described for compound **12b**. Purification of the crude product mixture by flash chromatography (ethyl acetate/hexane, 1:5 to 2:3) first furnished the imide **14e** (40 mg, 16%) as brown viscous oil. Further elution of the column using ethyl acetate/hexane (2:3 to 1:1) as eluent furnished the debromoenamide **13e** (20 mg, 8%) as brown viscous oil. Continuation of the elution with ethyl acetate-hexane (1:1 to 7:3) as eluent furnished the spiro amide **15e** (110 mg, 45%) as brown viscous oil.



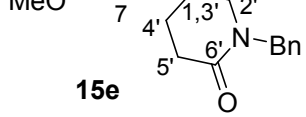
13e

1-Benzyl-5-[2-(3,4-dimethoxyphenyl)ethyl]-3,4-dihydropyridin-2(1*H*)-one (13e): R_f = 0.45 (ethyl acetate/hexane, 4:1); IR (neat): ν_{max}/cm^{-1} = 2932, 2834, 1665, 1603, 1508, 1439, 1408, 1381, 1256, 1217, 1163, 1031, 734, 704; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.37–7.24 (3 H, m, Ar-H), 7.18 (2 H, d, *J* = 8.1 Hz, Ar-H), 6.76 (1 H, 6'-H) and 6.66 (1 H, 5'-H) [2 d, *J* = 7.9 Hz], 6.65 (1 H, s, 2'-H), 5.75 (1 H, s, 6-H), 4.64 (2 H, s, NCH_2Ph), 3.86 (3 H, s) and 3.84 (3 H, s) [2 OCH_3], 2.64 (2 H, CH_2Ar) and 2.58 (2 H, CH_2C-5) [2 t, *J* = 7.9 Hz], 2.30 (4 H, t, *J* = 7.9 Hz, 4-H, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 168.8 (NC=O), 148.8 (C-3'), 147.3 (C-4'), 137.3 (C), 133.9 (C-1'), 128.6 (2 C, CH), 127.4 (2 C, CH), 127.3 (CH), 124.5 (C-6), 120.2 (C-6'), 119.3 (C-5), 111.6 (C-2'), 111.2 (C-5'), 55.9, 55.8 (2 OCH_3], 48.8 (NCH_2Ph), 35.8 (CH_2Ar), 33.9 (CH_2C-5), 31.2 (C-3), 24.3 (C-4); HRMS (ESI): calcd for $C_{22}H_{26}NO_3$ $[M + H]^+$ 352.1907, found 352.1907.



14e

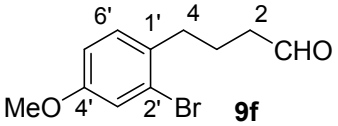
1'-Benzyl-5,6-dimethoxy-2,3-dihydro-2'*H*,6'*H*-spiro[indene-1,3'-piperidine]-2',6'-dione (14e): R_f = 0.6 (ethyl acetate/hexane,4:1); IR (neat): ν_{max}/cm^{-1} = 3032, 2938, 2855, 1722, 1675, 1605, 1505, 1454, 1376, 1212, 1162, 1035, 856, 734, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.31 (2 H, d, *J* = 7.6 Hz, Ar-H), 7.23–7.13 (3 H, m, Ar-H), 6.69 (1 H, s, 7-H), 6.24 (1 H, s, 4-H), 4.94 (1 H, d) and 4.91 (1 H, d) [*J* = 14.2 Hz, NCH_2Ph], 3.75 (3 H, s) and 3.53 (3 H, s) [2 OCH_3], 2.93–2.79 (2 H, m, 3-H), 2.79–2.55 (3 H, m), 2.07 (1 H, ddd, *J* = 14.0, 8.4, 5.6 Hz), 1.98 (1 H, ddd, *J* = 12.7, 7.6, 5.1 Hz), 1.89 (1 H, ddd, *J* = 13.5, 7.1, 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 175.6 (C-2'), 172.1 (C-5'), 149.4 (C-6), 148.2 (C-5), 137.5 (C), 135.8 (C-7a), 135.6 (C-3a), 129.1 (2 C, CH), 128.3 (2 C, CH), 127.4 (CH), 108.0 (C-4), 106.1 (C-7), 55.9 (2 OCH_3), 55.0 (C-(1,3')), 43.2 (NCH_2Ph), 36.8 (CH_2Ar), 30.2 (C-2), 30.1 (C-5'), 28.9 (C-4'); HRMS (ESI): calcd for $C_{22}H_{24}NO_4$ $[M + H]^+$ 366.1700, found 366.1699.



15e

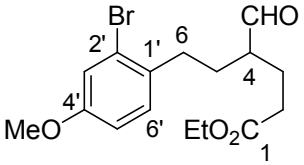
1'-Benzyl-5,6-dimethoxy-2,3-dihydro-6'*H*-spiro[indene-1,3'-piperidin]-6'-one (15e): R_f = 0.3 (ethyl acetate/hexane, 4:1); IR (neat): ν_{max}/cm^{-1} = 2933, 2854, 1638, 1500, 1453, 1299, 1267, 1216, 1119, 1027, 857, 820, 722, 698; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.28–7.15 (5 H, m, Ar-H), 6.65 (1 H, s, 7-H), 6.51 (1 H, s, 4-H), 4.67 (1 H, d) and 4.39 (1 H, d) [*J* = 14.4 Hz, NCH_2Ph], 3.76 (3 H, s) and 3.72 (3 H, s) [2 OCH_3], 3.17 (1 H, d, *J* = 12.4 Hz) and 2.97 (1 H, dd, *J* = 12.4, 2.0 Hz) [3-H], 2.75 (1 H, ddd, *J* = 16.3, 8.7, 4.8 Hz), 2.68–2.48 (3 H, m), 2.11 (1 H, ddd, *J* = 13.2, 9.7, 7.1 Hz), 1.96 (1 H, ddd, *J* = 13.0, 8.4, 5.1 Hz), 1.89–1.76 (1 H, m), 1.76–1.65 (1 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 169.4 (NC=O), 149.9 (C-6), 148.2 (C-5), 138.3 (C-7a), 137.0 (C), 135.0 (C-3a), 128.5 (4 C, CH), 127.4 (CH), 107.8 (C-4), 105.9 (C-7), 56.1 (OCH_3), 55.9 (2 C, OCH_3 and C-2'), 50.3

(NCH_2Ph), 46.6 (C-(1,3')), 35.5 (C-3), 32.0 (C-5'), 29.6 (C-2), 29.4 (C-4'); HRMS (ESI): calcd for $C_{22}H_{26}NO_3$ [M + H]$^+$ 352.1907, found 352.1907.



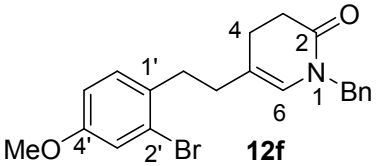
9f

4-(2-Bromo-4-methoxyphenyl)butanal (9f). The reaction was performed as described for the compound **9b** with $Pd(OAc)_2$ (57 mg, 2 mol%), butenylalcohol (1.6 mL, 19.2 mmol), triethylbenzylammonium chloride (2.9 g, 12.8 mmol) and $NaHCO_3$ (2.1 g, 25.5 mmol) in DMF (25 mL) was added iodobromide[4] **8f** (4.0 g, 12.8 mmol). Purification of the crude material by flash chromatography (ethyl acetate/hexane, 1:19 to 1:9) furnished the aldehyde **9f** (2.3 g, 71%) as colorless oil. R_f = 0.45 (ethyl acetate/hexane, 1:9); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 9.76 (1 H, s, CH=O), 7.09 (1 H, d, *J* = 8.4 Hz, 6'-H), 7.08 (1 H, d, *J* = 2.6 Hz, 3'-H), 6.79 (1 H, dd, *J* = 8.4, 2.6 Hz, 5'-H), 3.76 (3 H, s, OCH_3), 2.70 (2 H, t, *J* = 7.4 Hz, 4-H), 2.46 (2 H, dt, *J* = 7.4, 1.5 Hz, 2-H), 1.95 (2 H, quintet, *J* = 7.4 Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 202.2 (CH=O), 158.5 (C-4'), 132.4 (C-1'), 130.7 (C-6'), 124.4 (C-2'), 117.9 (C-5'), 113.6 (C-3'), 55.5 (OCH_3), 43.0 (C-4), 34.2 (C-2), 22.5 (C-3).



11f

Ethyl 6-(2-bromo-4-methoxyphenyl)-4-formylhexanoate (11f). The reaction was performed with aldehyde **9f** (2.0 g, 7.8 mmol), pyrrolidine (1.3 mL, 15.5 mmol), K_2CO_3 (3.0 g, 23.35 mmol) and ethyl acrylate (1.35 mL, 12.4 mmol) as described above. Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:19 to 1:6) furnished the aldehyde ester **11f** (2.0 g, 72% for two steps) as colorless oil. R_f = 0.4 (ethyl acetate/hexane, 1:6); ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 9.64 (1 H, s, CH=O), 7.09 (1 H, d, *J* = 8.4 Hz, 6'-H), 7.08 (1 H, d, *J* = 2.5 Hz, 3'-H), 6.79 (1 H, dd, *J* = 8.4, 2.5 Hz, 5'-H), 4.11 (2 H, q, *J* = 7.1 Hz, OCH_2CH_3), 3.76 (3 H, s, OCH_3), 2.77–2.57 (2 H, m, 6-H), 2.45–2.25 (3 H, m), 2.12–1.62 (4 H, m), 1.24 (3 H, t, *J* = 7.1 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 203.8 (CH=O), 172.9 (OC=O), 158.6 (C-4'), 132.4 (C-1'), 130.7 (C-6'), 124.3 (C-2'), 118.0 (C-5'), 113.7 (C-3'), 60.5 (OCH_2CH_3), 55.5 (OCH_3), 50.6 (C-4), 32.6 (CH_2Ar), 31.5 (C-2), 29.1 (C-5), 23.6 (C-3), 14.2 (OCH_2CH_3).

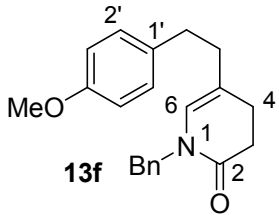


12f

1-Benzyl-5-[2-(2-bromo-4-methoxyphenyl)ethyl]-3,4-dihydropyridin-2(1*H*)-one (12f). As described for compound **12b**, the formyl ester **11f** (2.0 g, 5.6 mmol) in CH_2ClCH_2Cl (8 mL) was reacted with benzylamine (1.2 mL, 11.2 mmol) and AcOH (0.32 mL, 5.6 mmol). Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:9 to 2:3) as eluent furnished the cyclic enamide **12f** (1.8 g, 80%) as light brown viscous oil. R_f = 0.4 (ethyl acetate/hexane, 2:3); IR (neat): ν_{max}/cm^{-1} = 2933, 1665, 1604, 1566, 1493, 1439, 1408, 1281, 1241, 1211, 1029, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.35–7.17 (3 H, m, Ar-H), 7.14 (2 H, d, *J* = 8.1 Hz, Ar-H), 7.02 (1 H, d, *J* = 2.5 Hz, 3'-H), 6.98 (1 H, d, *J* = 8.7 Hz, 6'-H), 6.70 (1 H, dd, *J* = 8.7, 2.5 Hz, 5'-H), 5.70 (1 H, s, 6-H), 4.59 (2 H, s, NCH_2Ph), 3.72 (3 H, s, OCH_3), 2.70 (2 H, CH_2Ar) and 2.53 (2 H, CH_2C-5) [2 t, *J* = 7.6 Hz], 2.27 (2 H, 4-H) and 2.22 (2 H, 3-H) [2 t, *J* = 7.9 Hz]; ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 168.8 (NC=O), 158.4 (C-4'), 137.3 (C), 132.4 (C-1'), 130.6 (C-6'), 128.5 (2 C, CH), 127.4 (2 C, CH), 127.3 (CH), 124.7 (C-6), 124.3 (C-2'), 119.0 (C-5), 117.9 (C-5'), 113.5 (C-3'), 55.4 (OCH_3), 48.8 (NCH_2Ph), 34.2 (CH_2Ar), 33.8 (CH_2C-5), 31.2 (C-3), 24.2 (C-4); HRMS (ESI): calcd for $C_{21}H_{23}BrNO_2$ [M + H]$^+$ 400.0907, found 400.0906.

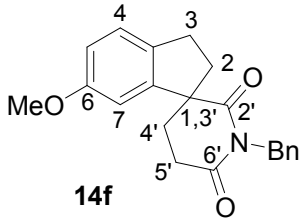
Palladium-catalyzed spiro cyclization of 5-(-bromophenyl)ethyl-substituted enamide 12f. The reaction was performed with the enamide **12f** (150 mg, 0.37 mmol) in anhydrous DMF (3 mL) with Ph_3P (19.6 mg, 20 mol%), Cs_2CO_3 (488 mg, 1.5 mmol) and $Pd(OAc)_2$ (8.4 mg, 10 mol%). After loading of the reagents at room temperature, the mixture was heated to 120 °C, as described for compound **12b**. Purification of the crude product mixture by flash chromatography (ethyl acetate/hexane, 1:9 to 1:3) first furnished the imide **14f** (20 mg, 16%) as brown viscous oil. Further elution of the column using ethyl acetate/hexane (1:3 to 2:3) as eluent furnished the

debromoenamide **13f** (23 mg, 19%) as brown viscous oil. Continuation of the elution with ethyl acetate-hexane (2:3 to 3:2) as eluent furnished the spiro amide **15f** (50 mg, 45%) as brown viscous oil.



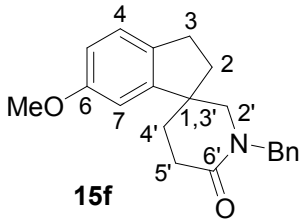
13f

1-Benzyl-5-[2-(4-methoxyphenyl)ethyl]-3,4-dihydropyridin-2(1*H*)-one (13f). R_f = 0.55 (ethyl acetate/hexane, 4:1); IR (neat): ν_{max}/cm^{-1} = 2926, 2835, 1666, 1602, 1512, 1495, 1409, 1245, 1212, 1178, 1032, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.38–7.18 (3 H, m, Ar-H), 7.16 (2 H, d, *J* = 7.9 Hz, Ar-H), 7.02 (2 H, 2',6'-H) and 6.78 (2 H, 3',5'-H) [2 d, *J* = 8.6 Hz], 5.71 (1 H, s, 6-H), 4.61 (2 H, s, NCH_2Ph), 3.77 (3 H, s, OCH_3), 2.62 (2 H, CH_2Ar) and 2.55 (2 H, CH_2C-5) [2 t, *J* = 7.6 Hz], 2.26 (4 H, t, *J* = 7.6 Hz, 4-H, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 168.9 (NC=O), 157.8 (C-4'), 137.3 (C), 133.3 (C-1'), 129.2 (2 C, CH), 128.6 (2 C, CH), 127.5 (2 C, CH), 127.3 (CH), 124.5 (C-6), 119.3 (C-5), 113.7 (2 C, CH), 55.2 (OCH_3), 48.8 (NCH_2Ph), 35.8 (CH_2Ar), 33.3 (*C*H_2C-5), 31.2 (C-3), 24.3 (C-4); HRMS (ESI): calcd for $C_{21}H_{24}NO_2$ $[M + H]^+$ 322.1802, found 322.1802.



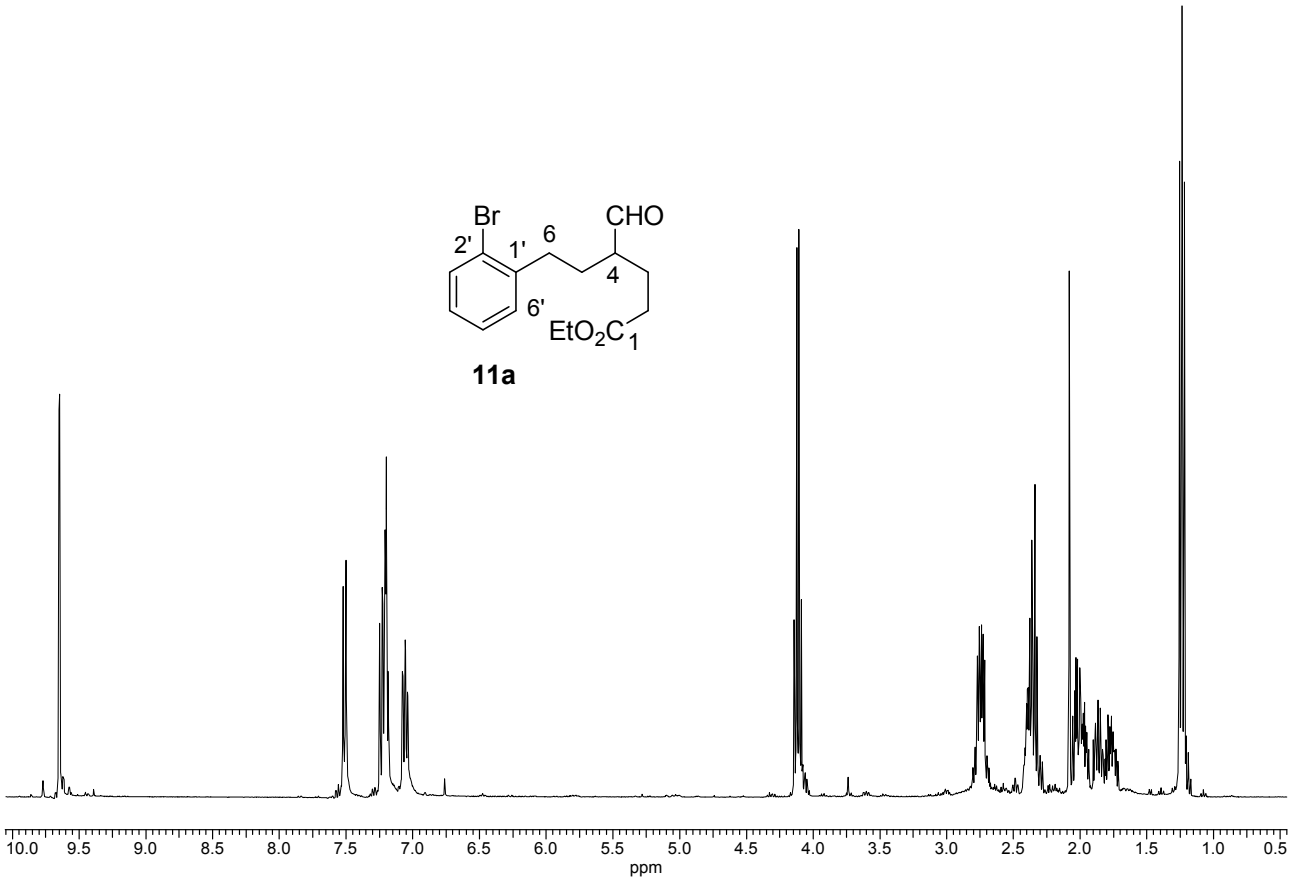
14f

1'-Benzyl-6-methoxy-2,3-dihydro-2'H,6'H-spiro[indene-1,3'-piperidine]-2',6'-dione (14f). R_f = 0.75 (ethyl acetate/hexane, 4:1); IR (neat): ν_{max}/cm^{-1} = 2938, 2850, 1722, 1676, 1608, 1495, 1454, 1353, 1290, 1163, 1031, 700; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.41 (2 H, d, *J* = 7.6 Hz, Ar-H), 7.35-7.20 (3 H, m, Ar-H), 7.18 (1 H, d, *J* = 8.3 Hz, 4-H), 6.80 (1 H, dd, *J* = 8.3, 2.5 Hz, 5-H), 6.45 (1 H, d, *J* = 2.5 Hz, 7-H), 5.06 (1 H, d) and 5.03 (1 H, d) [*J* = 13.7 Hz, NCH_2Ph], 3.66 (3 H, s, OCH_3), 3.08–2.62 (5 H, m), 2.20 (1 H, ddd, *J* = 13.6, 8.3, 5.6 Hz), 2.10 (1 H, ddd, *J* = 12.6, 7.3, 5.1 Hz), 2.00 (1 H, ddd, *J* = 13.4, 7.1, 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 175.3 (C-2'), 172.1 (C-6'), 158.8 (C-6), 145.6 (C-7a), 137.5 (C), 135.6 (C-3a), 129.0 (2 C, CH), 128.4 (2 C, CH), 127.4 (CH), 125.7 (C-4), 114.2 (C-5), 108.6 (C-7), 55.4 (OCH_3), 55.1 (C-(1,3')), 43.3 (NCH_2Ph), 37.0 (CH_2Ar), 30.1 (C-2), 29.3 (C-5'), 28.6 (C-4'); HRMS (ESI): calcd for $C_{21}H_{22}NO_3$ $[M + H]^+$ 336.1594, found 336.1595.

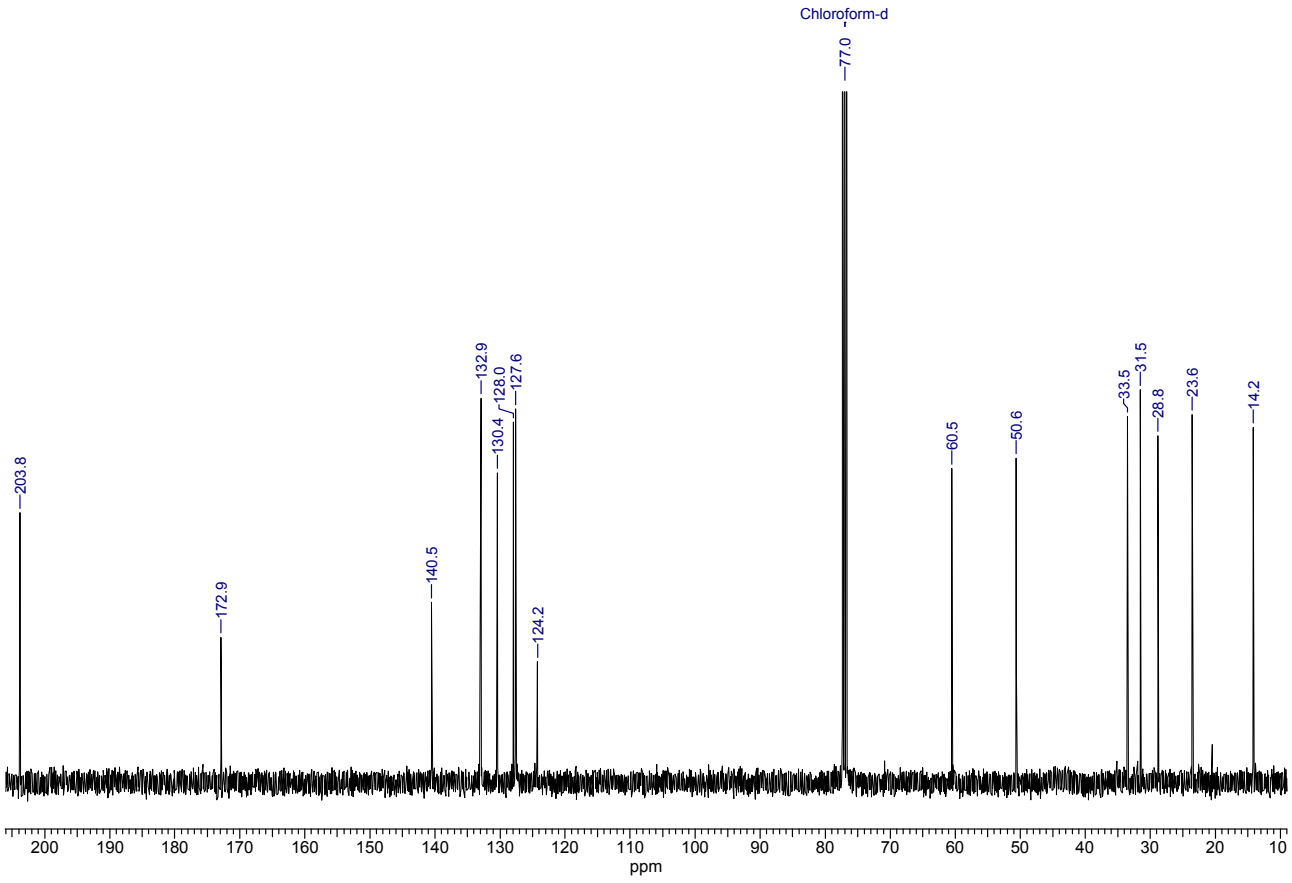


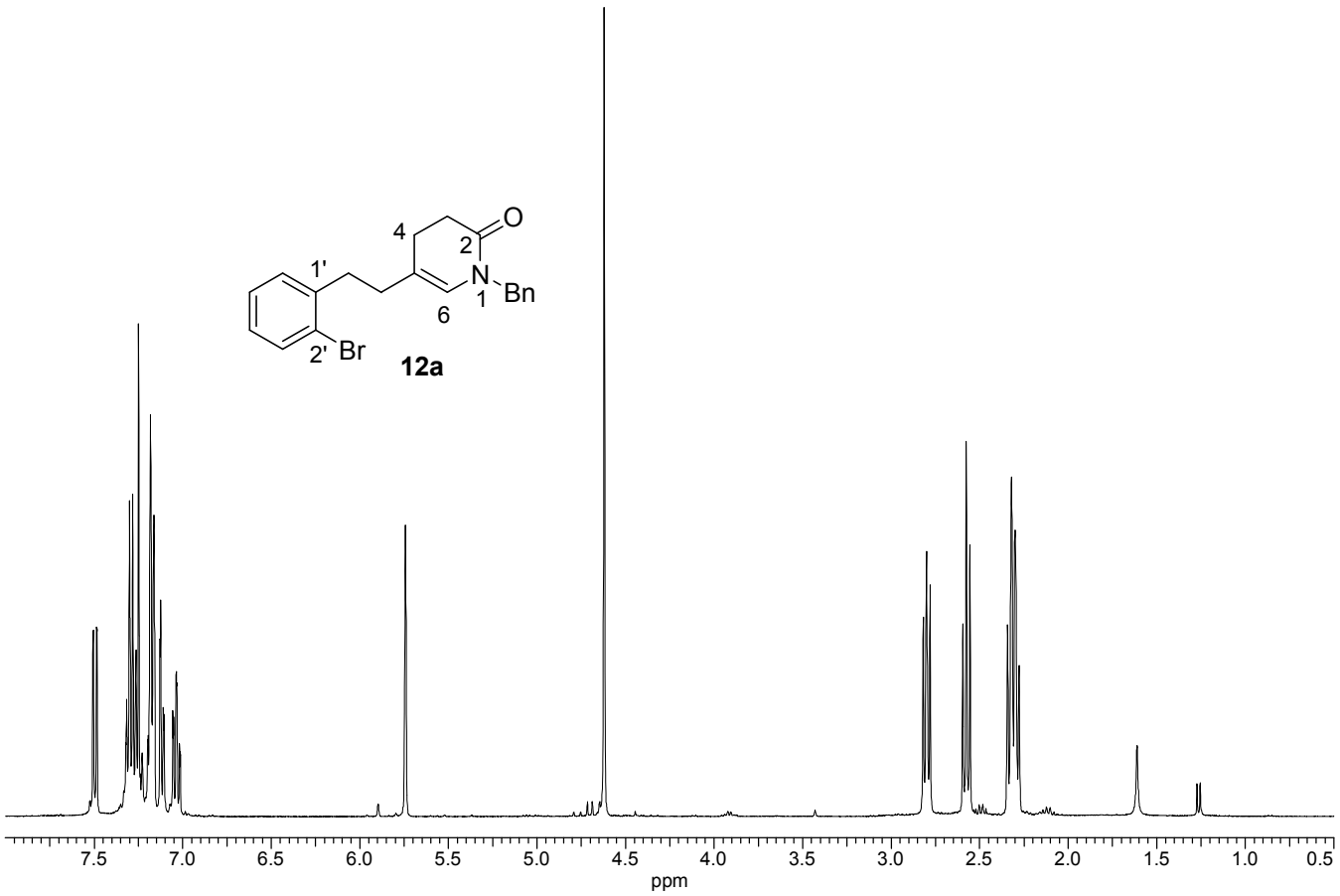
15f

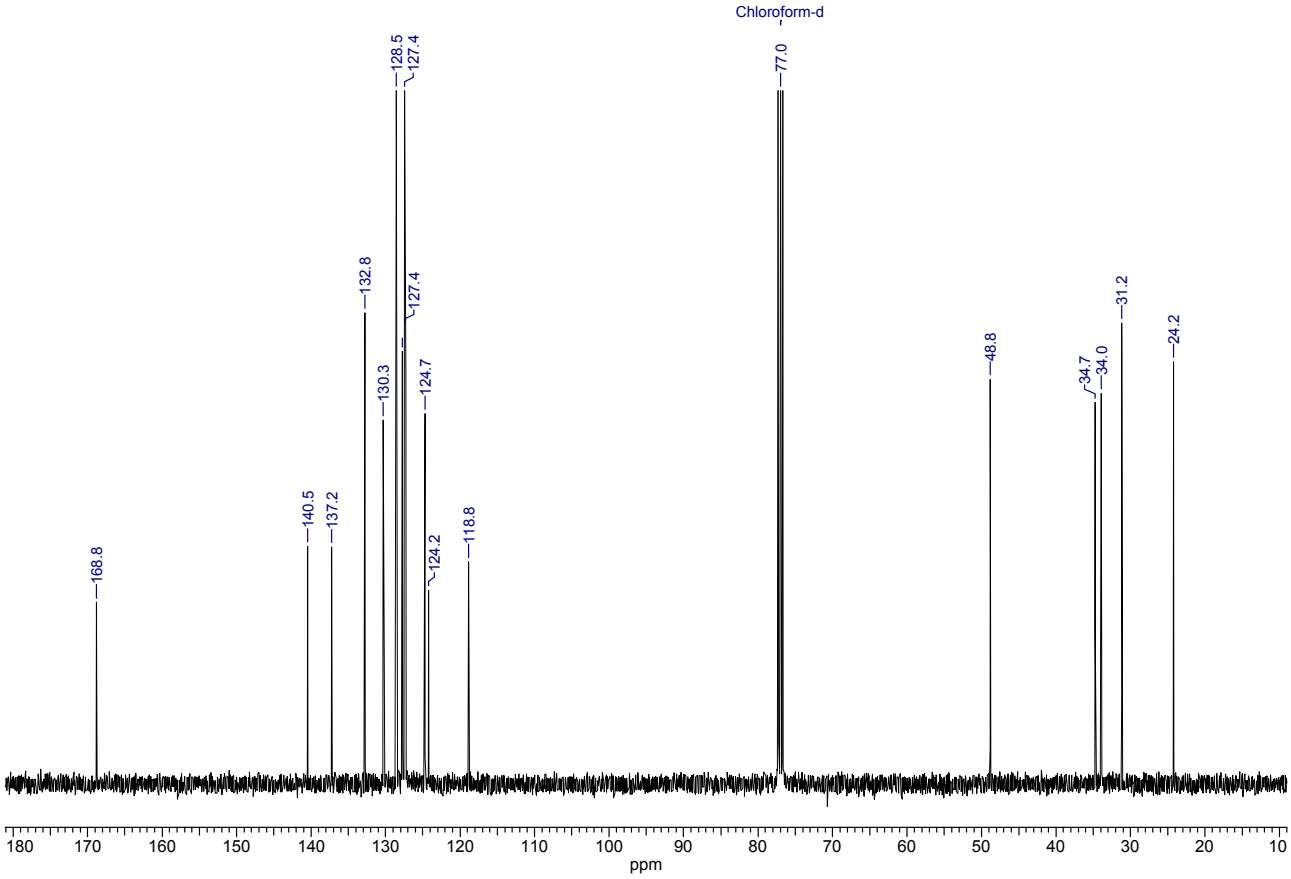
1'-Benzyl-6-methoxy-2,3-dihydro-6'H-spiro[indene-1,3'-piperidin]-6'-one (15f). R_f = 0.35 (ethyl acetate/hexane, 4:1); IR (neat): ν_{max}/cm^{-1} = 3029, 2934, 2853, 1641, 1494, 1454, 1357, 1286, 1220, 1033, 910, 819, 731, 701; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.30–7.10 (5 H, m, Ar-H), 7.00 (1 H, d, *J* = 8.1 Hz, 4-H), 6.66 (1 H, dd, *J* = 8.1, 2.3 Hz, 5-H), 6.55 (1 H, d, *J* = 2.5 Hz, 7-H), 4.72 (1 H, d) and 4.32 (1 H, d) [*J* = 14.4 Hz, NCH_2Ph], 3.66 (3 H, s, OCH_3), 3.16 (1 H, d, *J* = 12.4 Hz) and 2.96 (1 H, dd, *J* = 12.1, 2.0 Hz) [2'-H], 2.72 (1 H, ddd, *J* = 15.7, 8.6, 4.6 Hz), 2.65–2.47 (3 H, m), 2.10 (1 H, ddd, *J* = 13.2, 9.7, 7.1 Hz), 1.95 (1 H, ddd, *J* = 12.7, 8.6, 4.6 Hz), 1.89–1.76 (1 H, m), 1.76–1.63 (1 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 169.4 (NC=O), 158.9 (C-6), 148.3 (C-7a), 137.0 (C), 135.2 (C-3a), 128.5 (2 C, CH), 128.4 (2 C, CH), 127.4 (CH), 125.3 (C-4), 113.1 (C-5), 108.5 (C-7), 55.7 (NCH_2Ph), 55.4 (OCH_3), 50.2 (C-2'), 46.6 (C-(1,3')), 35.6 (C-3), 31.7 (C-5'), 29.5 (C-2) 28.6 (C-4'); HRMS (ESI): calcd for $C_{21}H_{24}NO_2$ $[M + H]^+$ 322.1802, found 322.1801.

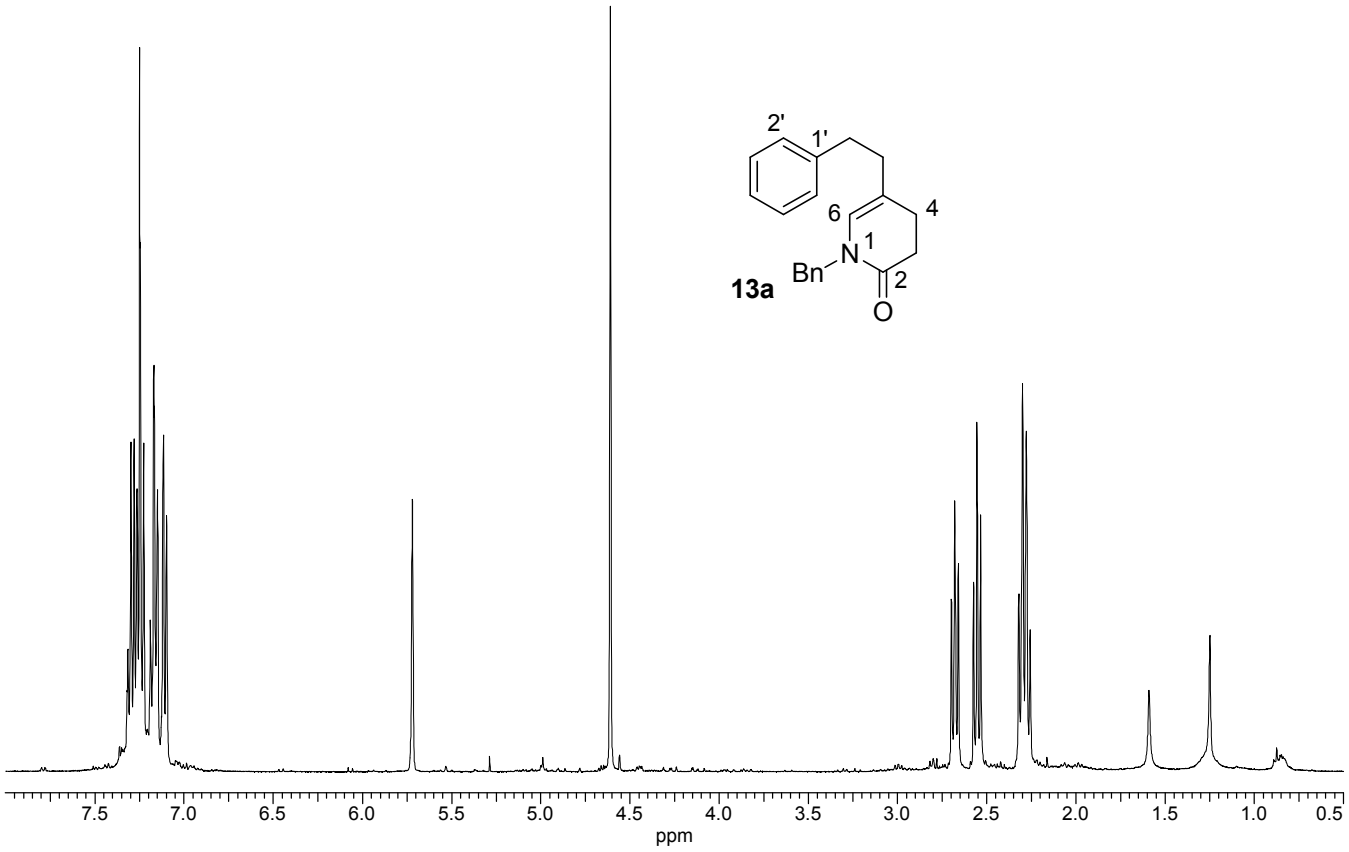

Br
CHO
2'
1'
6
4
6'
EtO2C
1

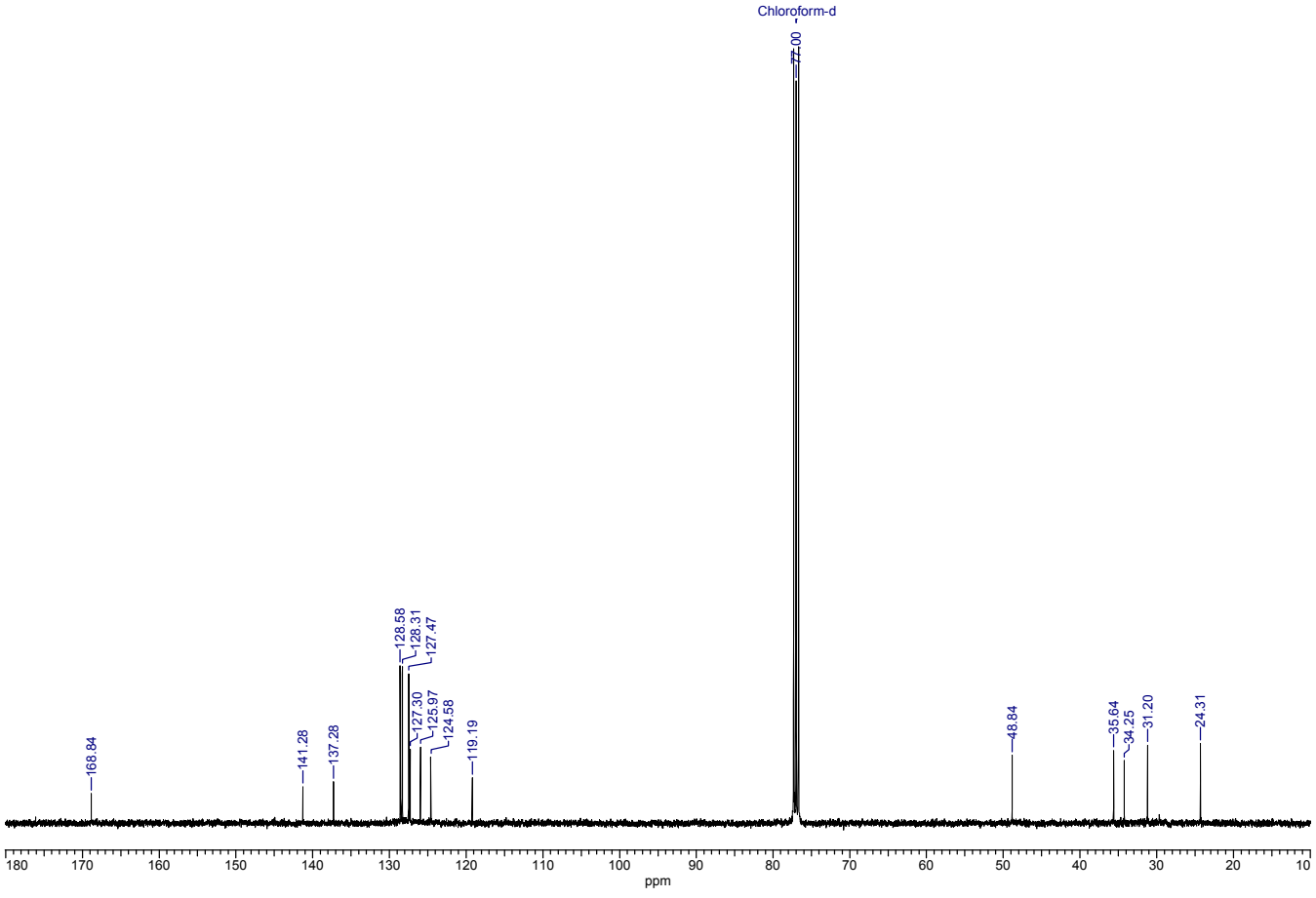
11a

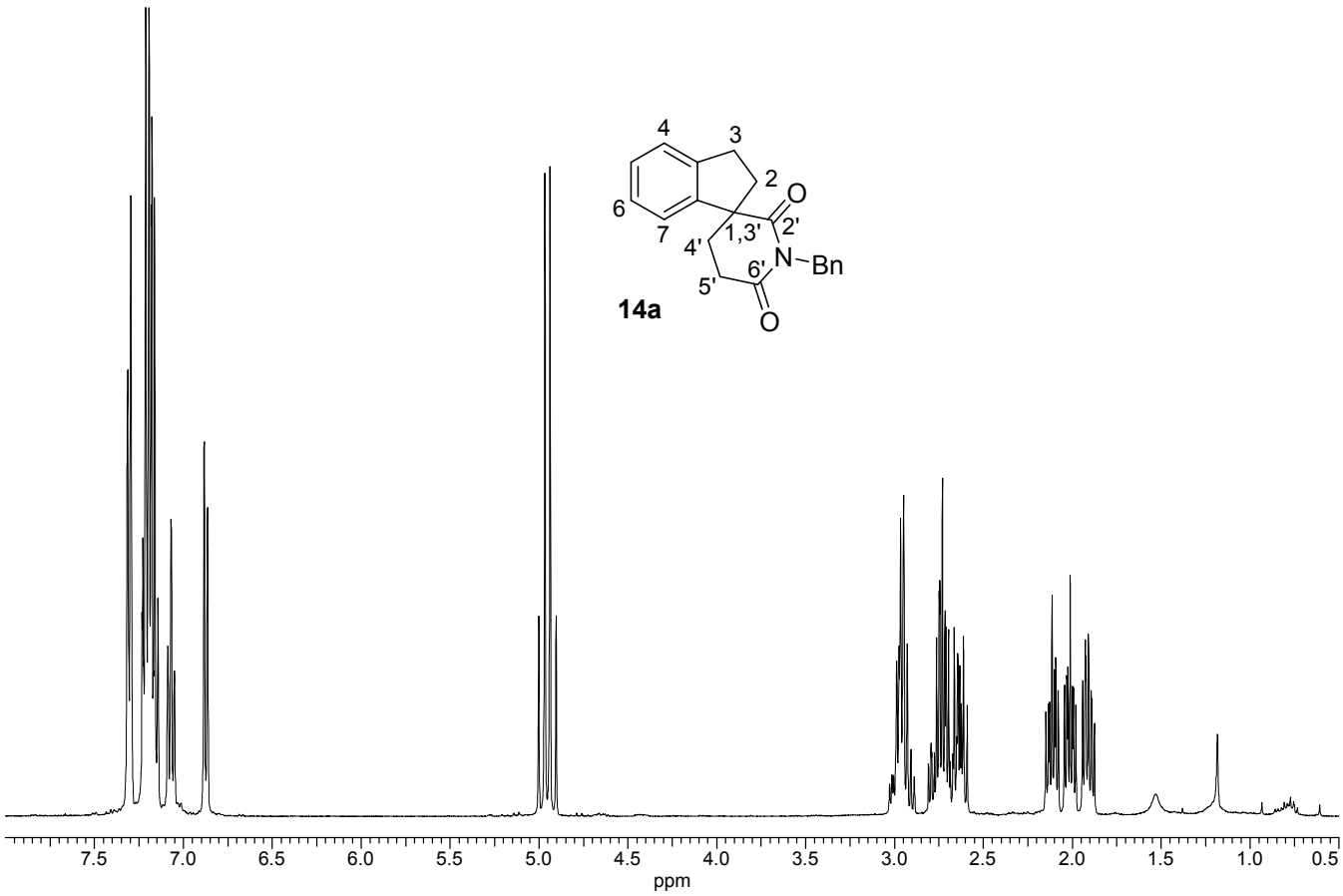

Chloroform-d
77.0
203.8
172.9
140.5
132.9
130.4
128.0
127.6
124.2
60.5
50.6
33.5
31.5
28.8
23.6
14.2

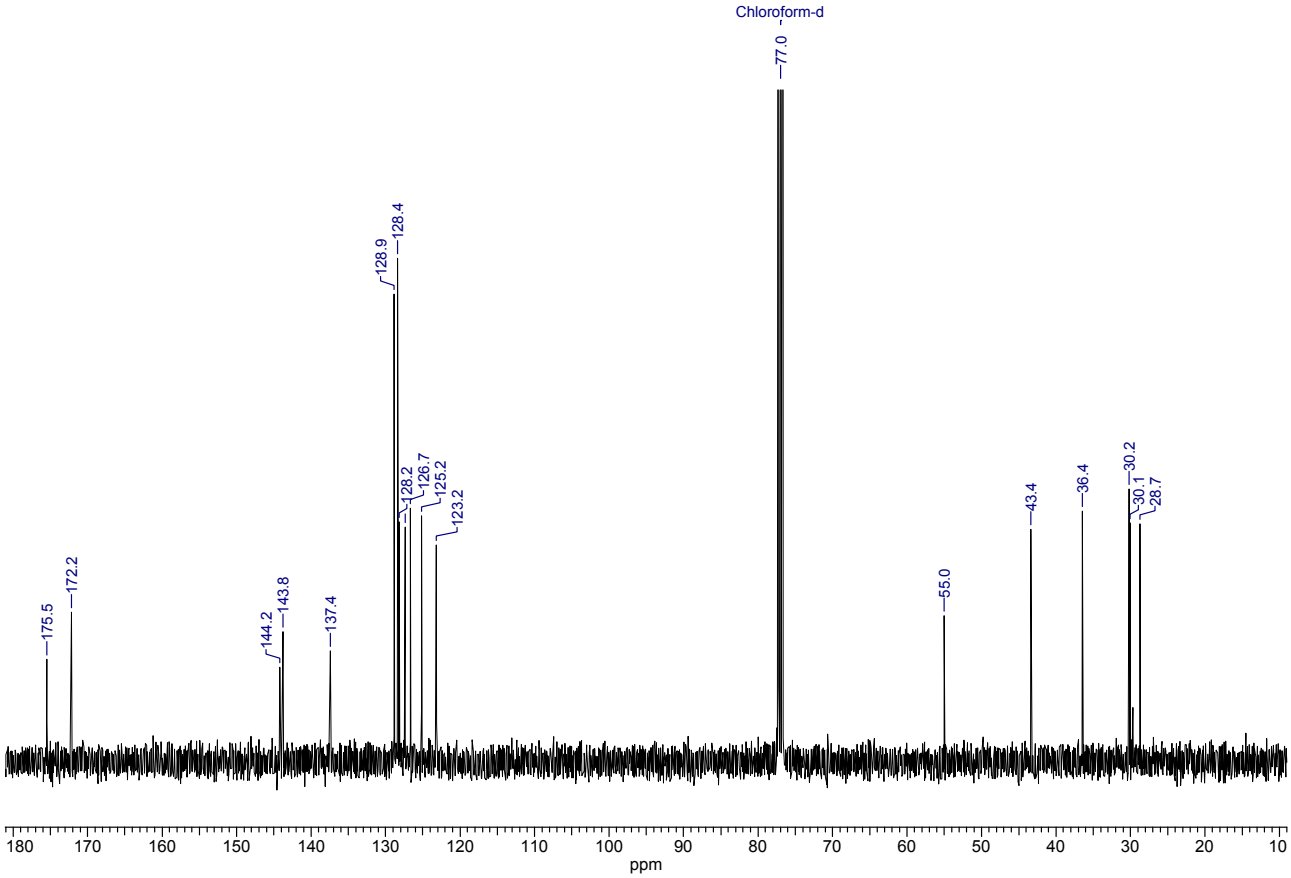

4
O
2
1'
N
Bn
1
6
2' Br
12a
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

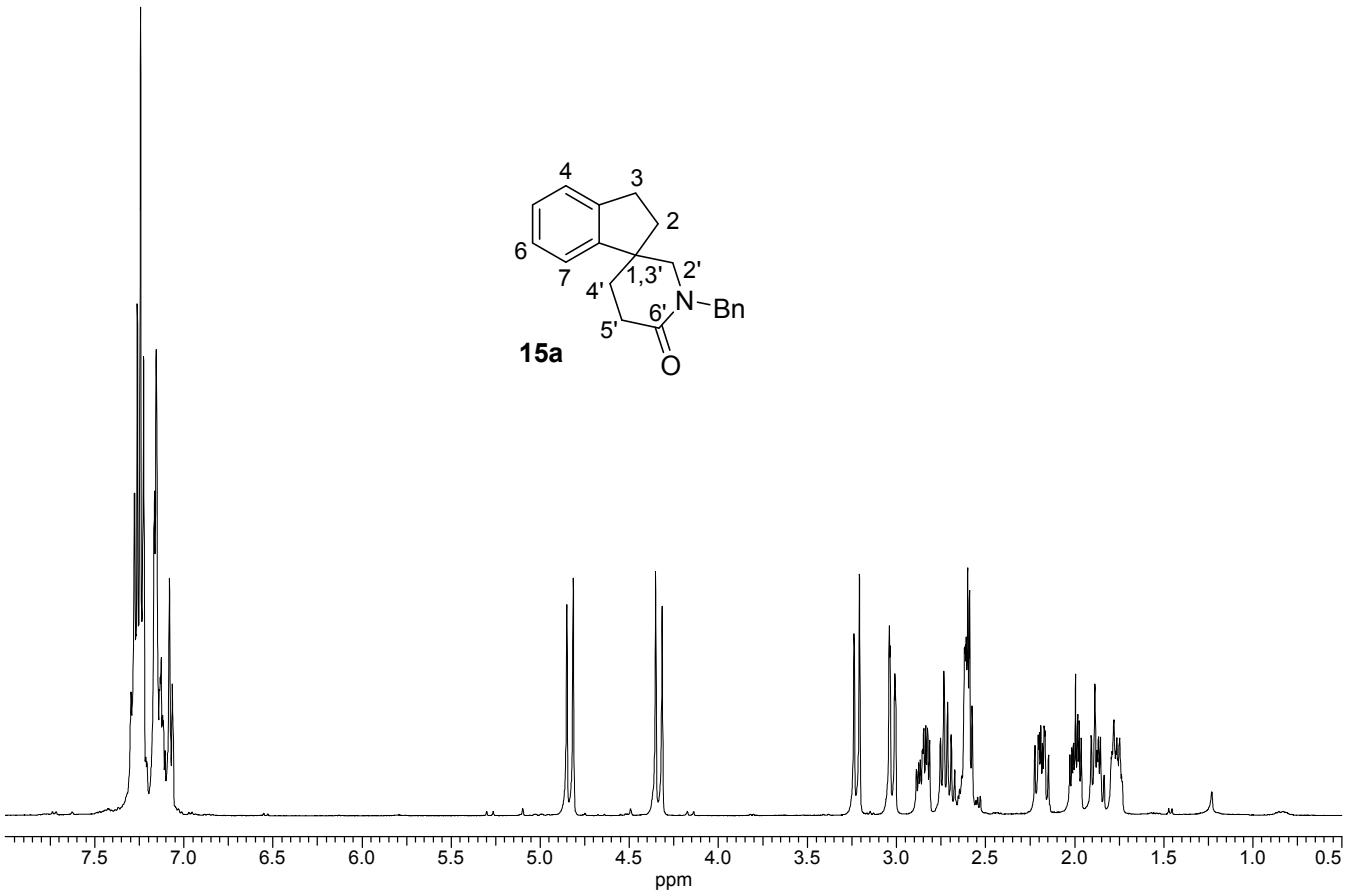

Chloroform-d
128.5
127.4
77.0
132.8
127.4
130.3
124.7
48.8
34.7
34.0
31.2
24.2
140.5
137.2
124.2
118.8
168.8
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

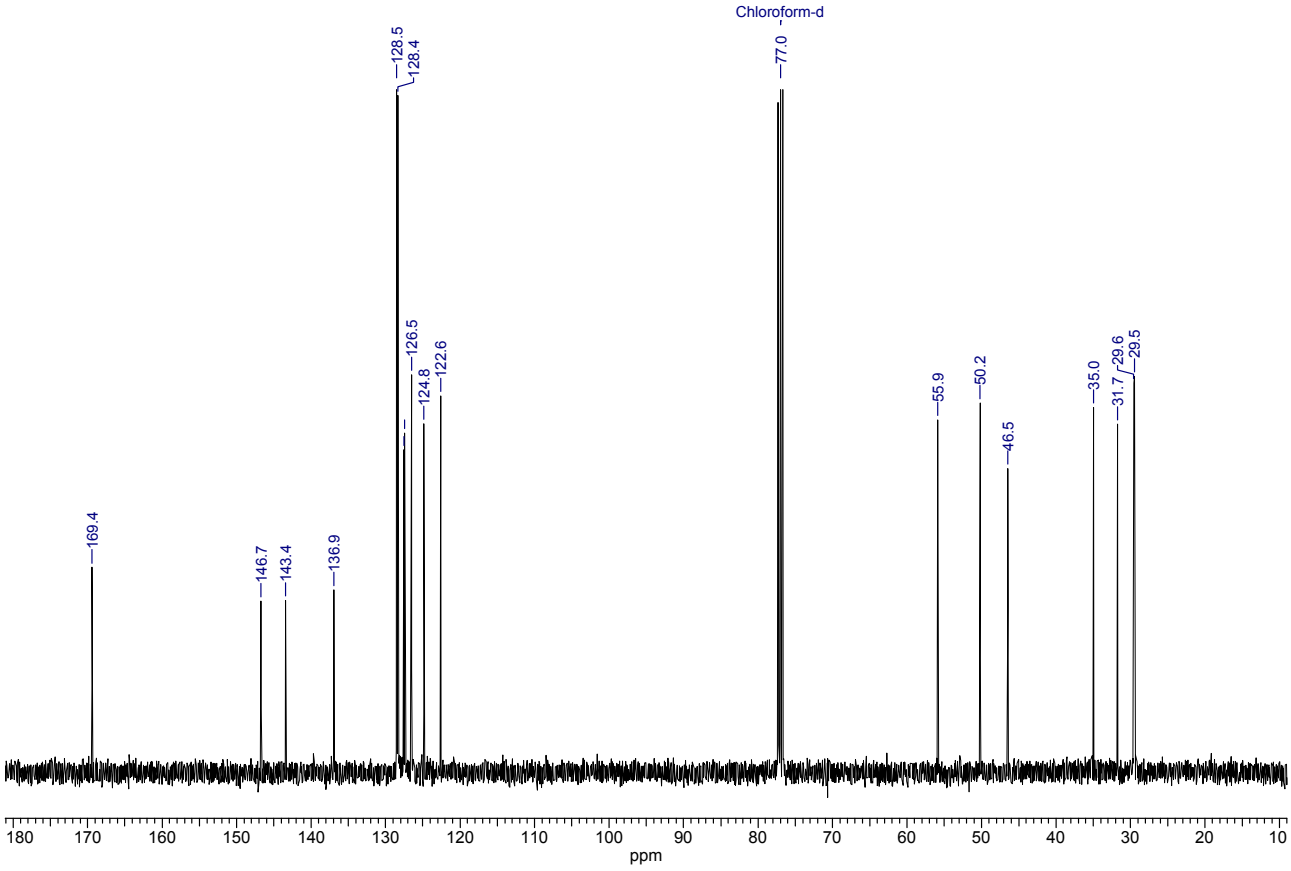

2'
1'
6
4
1
N
Bn
2
O
13a
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

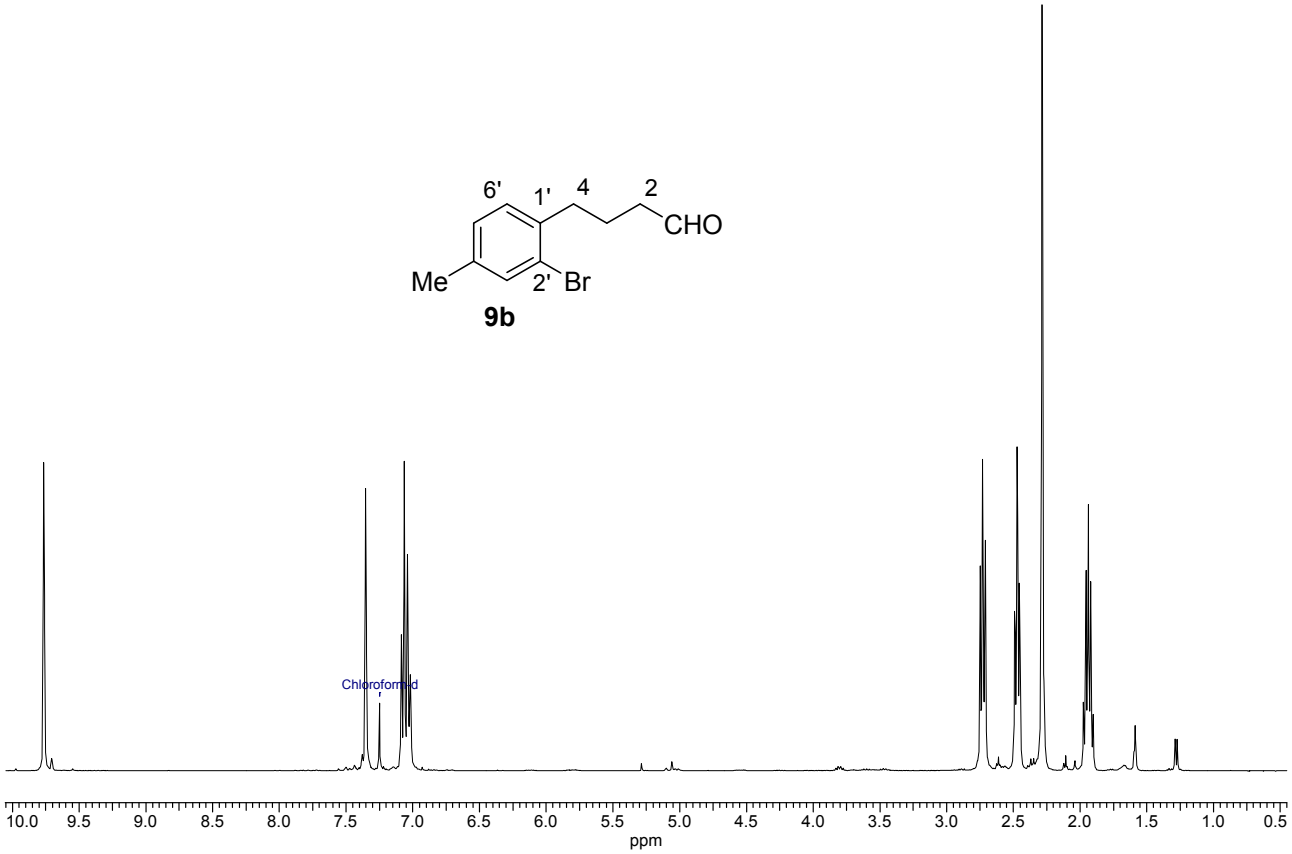

Chloroform-d
77.00
168.84
141.28
137.28
128.58
128.31
127.47
127.30
125.97
124.58
119.19
48.84
35.64
34.25
31.20
24.31
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


4
3
2
O
6
2'
7
1,3'
4'
N
Bn
6'
5'
O
14a
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
ppm

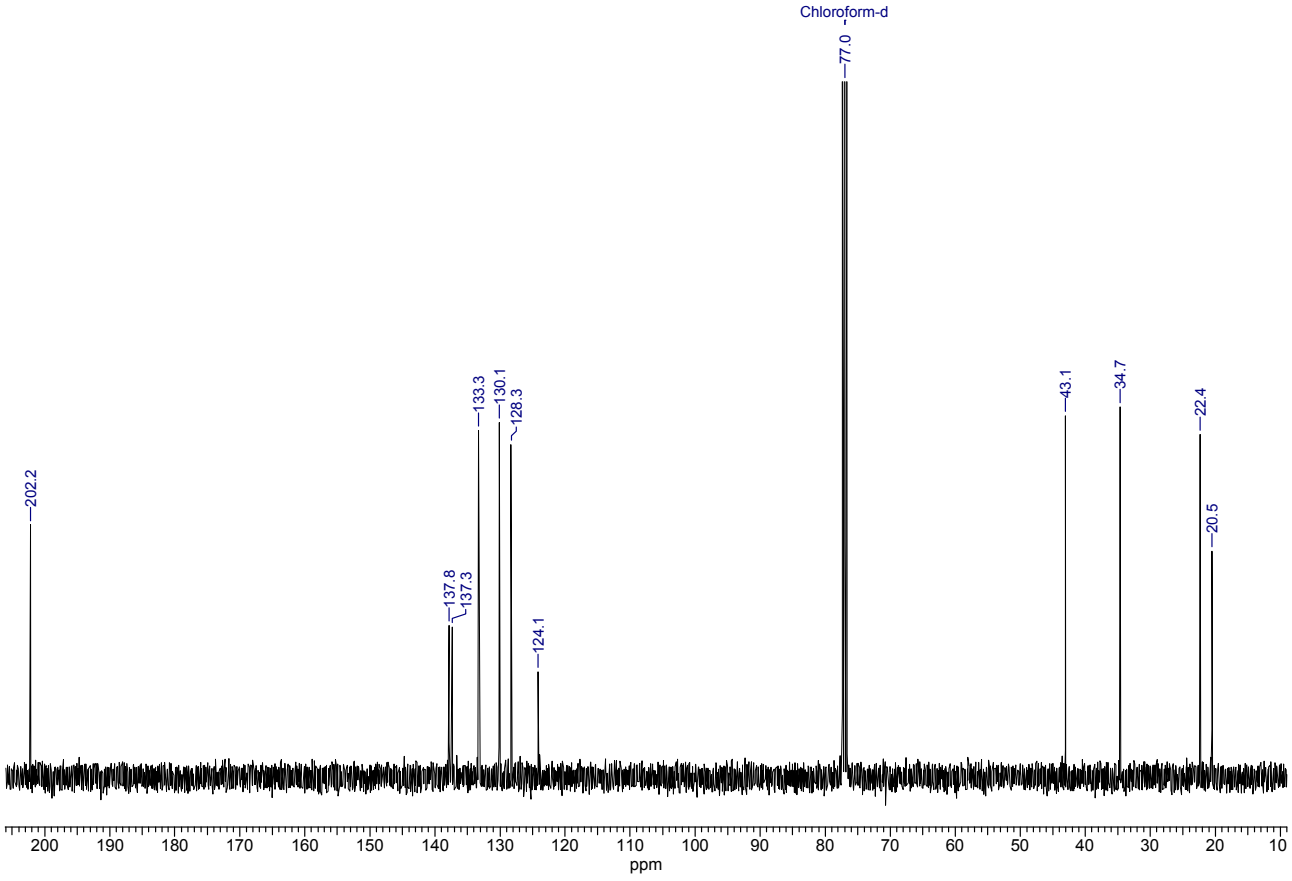

Chloroform-d
77.0
128.9
128.4
128.2
126.7
125.2
123.2
175.5
172.2
144.2
143.8
137.4
55.0
43.4
36.4
30.2
30.1
28.7
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

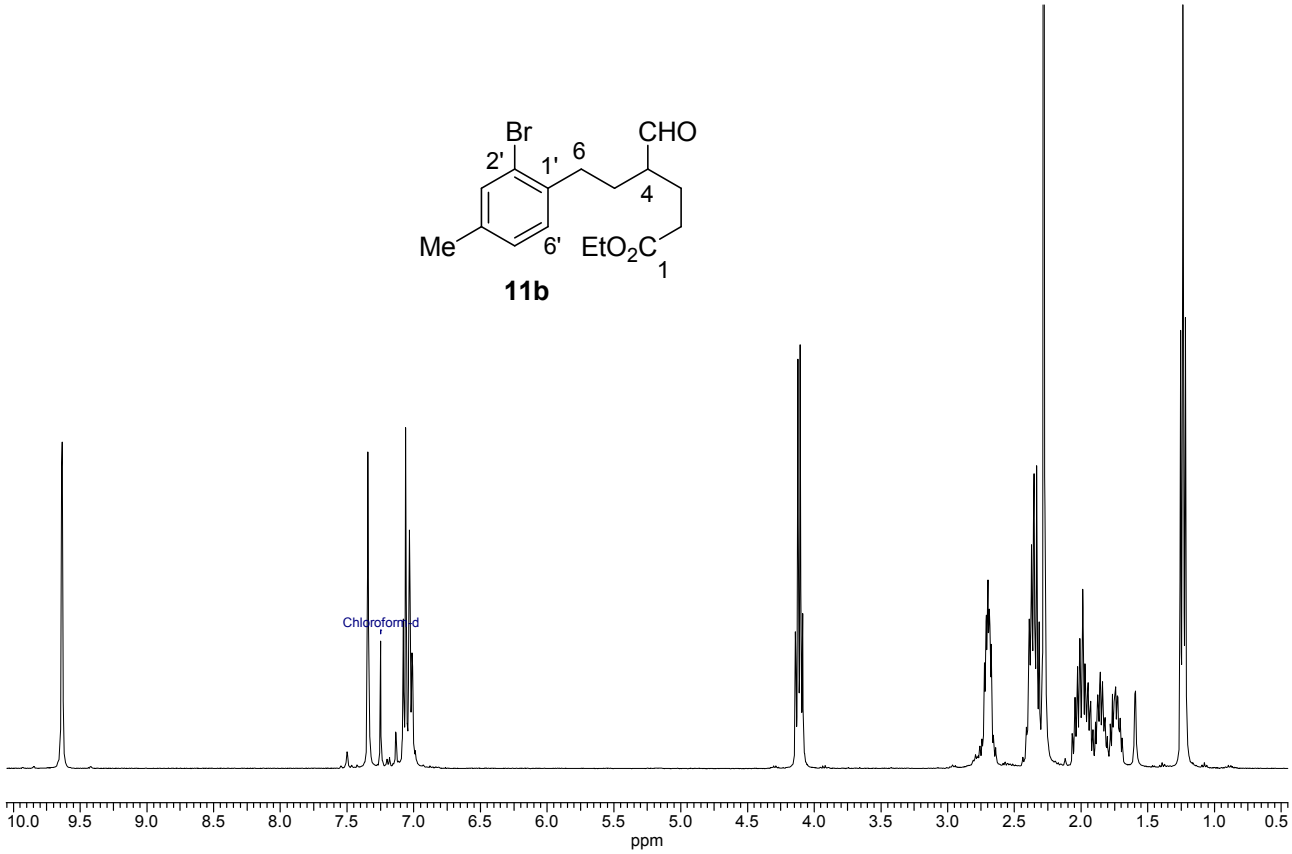

4
3
2
6
7
1,3'
2'
4'
N
Bn
6'
5'
O
15a
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


Chloroform-d
128.5
128.4
77.0
126.5
124.8
122.6
55.9
50.2
46.5
35.0
31.7
29.6
29.5
169.4
146.7
143.4
136.9
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

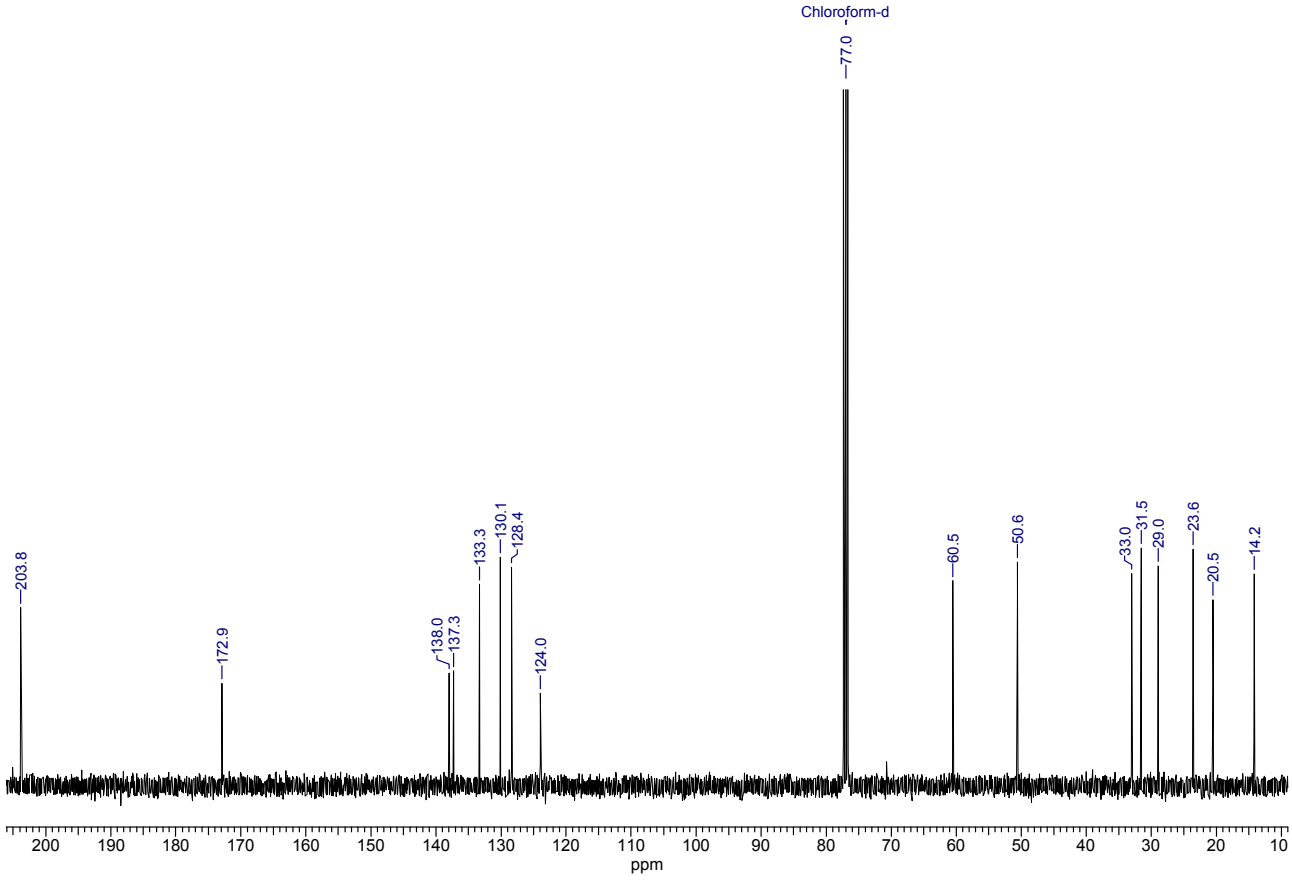

6'
1'
4
2
CHO
Me
2'
Br
Chloroform-d
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm

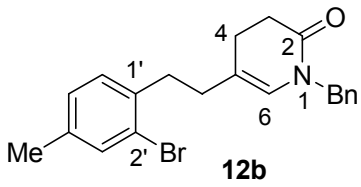
9b


Chloroform-d
77.0
202.2
137.8
137.3
133.3
130.1
128.3
124.1
43.1
34.7
22.4
20.5
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm


Br
CHO
2'
1'
6
4
Me
6'
EtO2C
1
Chloroform-d
10.0 9.5 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
ppm

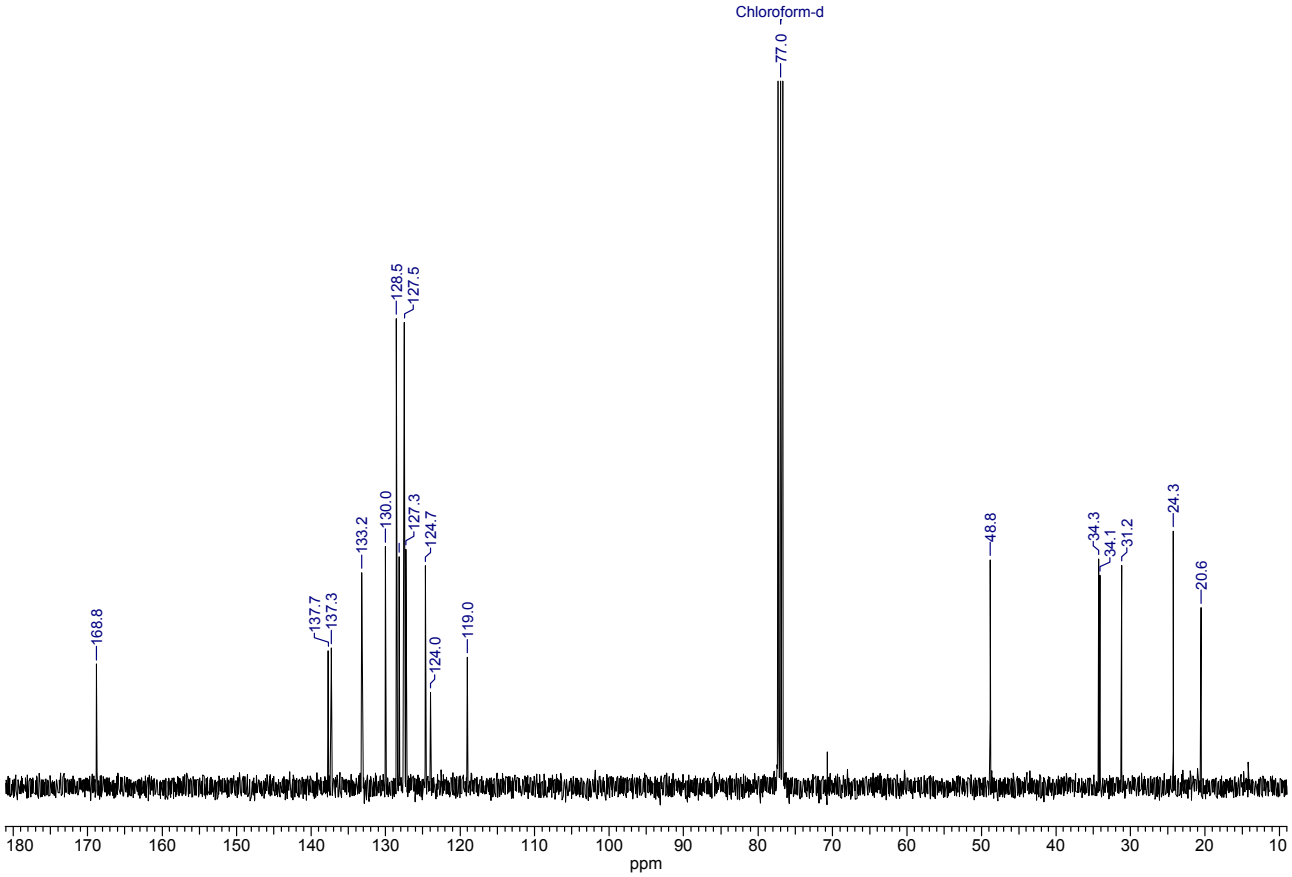
11b

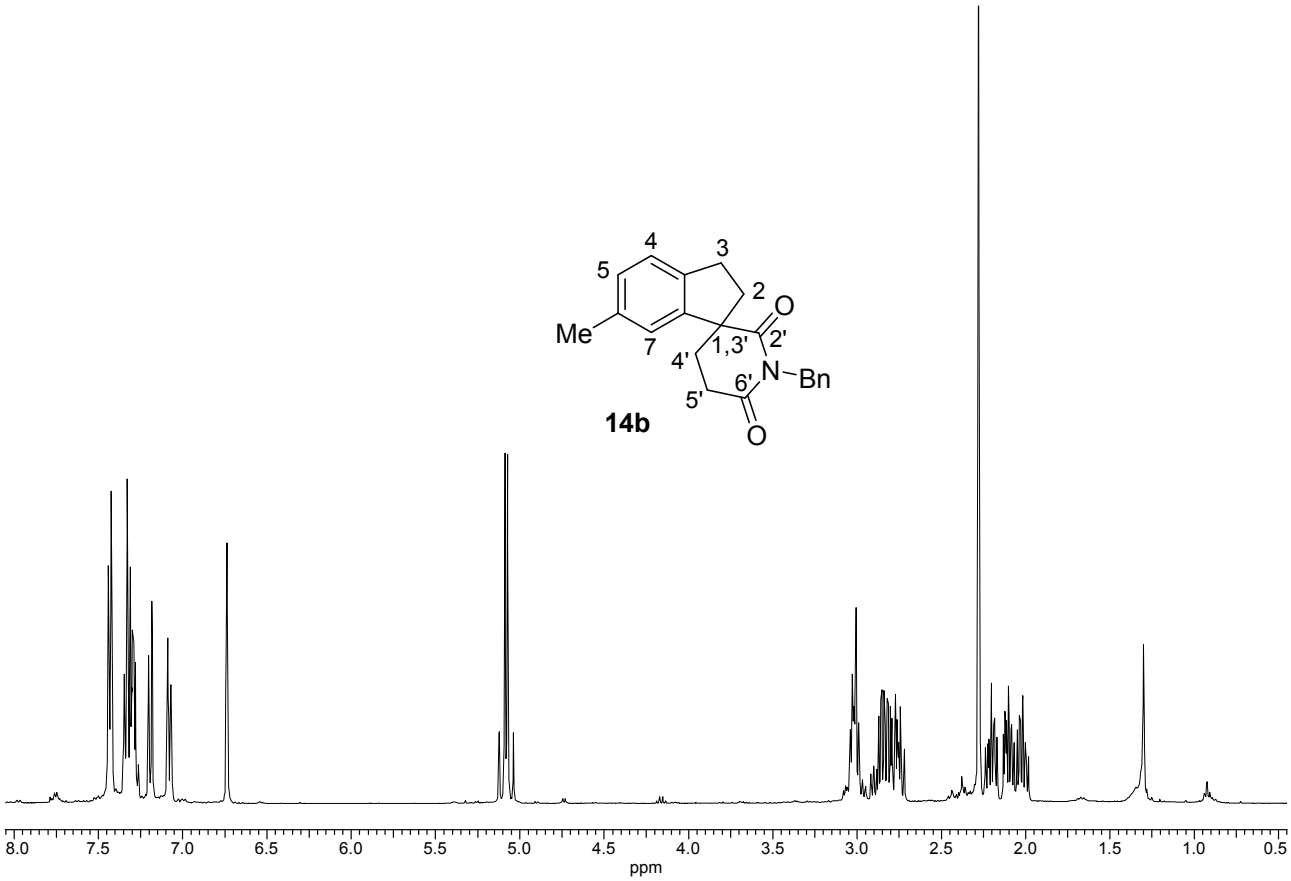

Chloroform-d
77.0
203.8
172.9
138.0
137.3
133.3
130.1
128.4
124.0
60.5
50.6
33.0
31.5
29.0
23.6
20.5
14.2
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

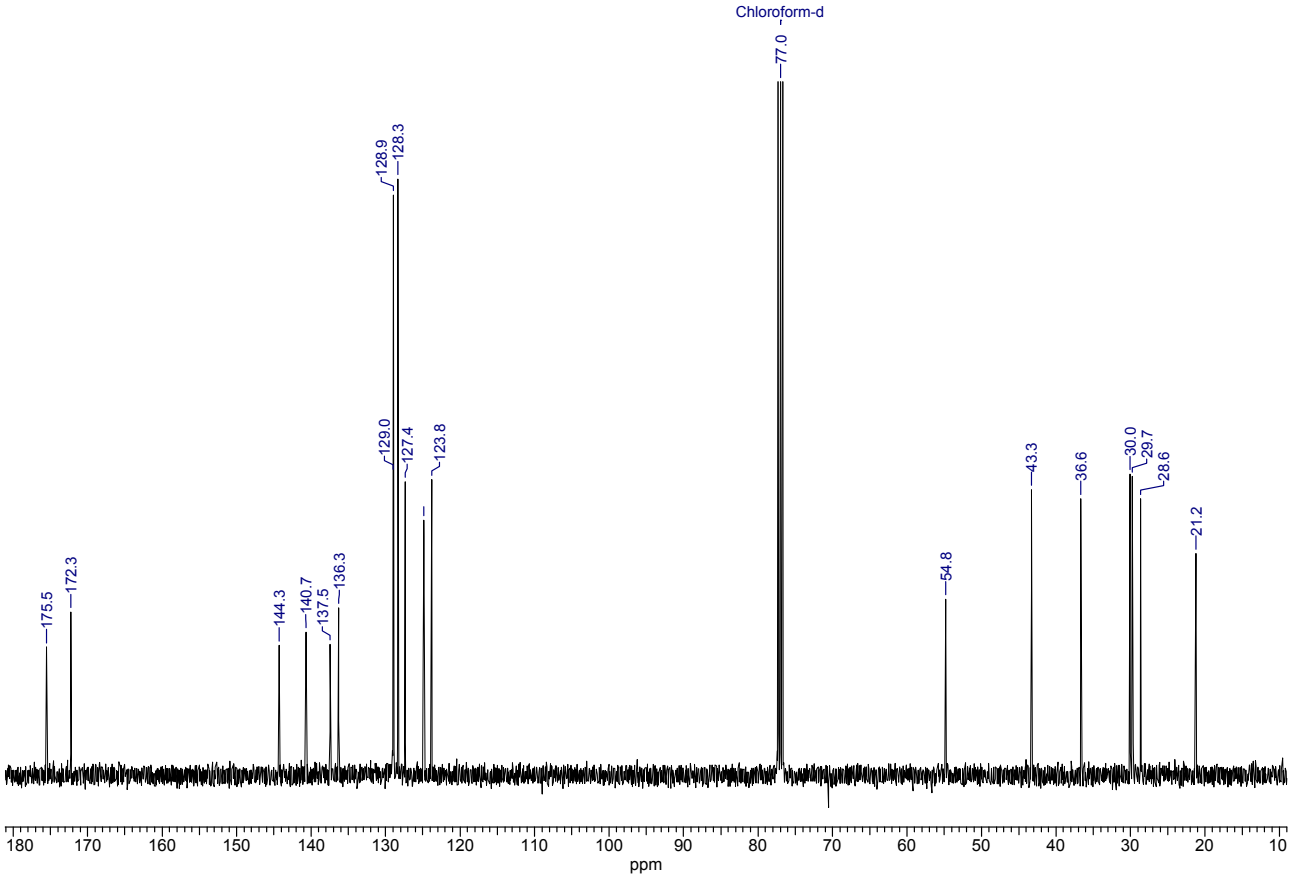

4
2
O
1'
N
Bn
1
6
Me
2'
Br

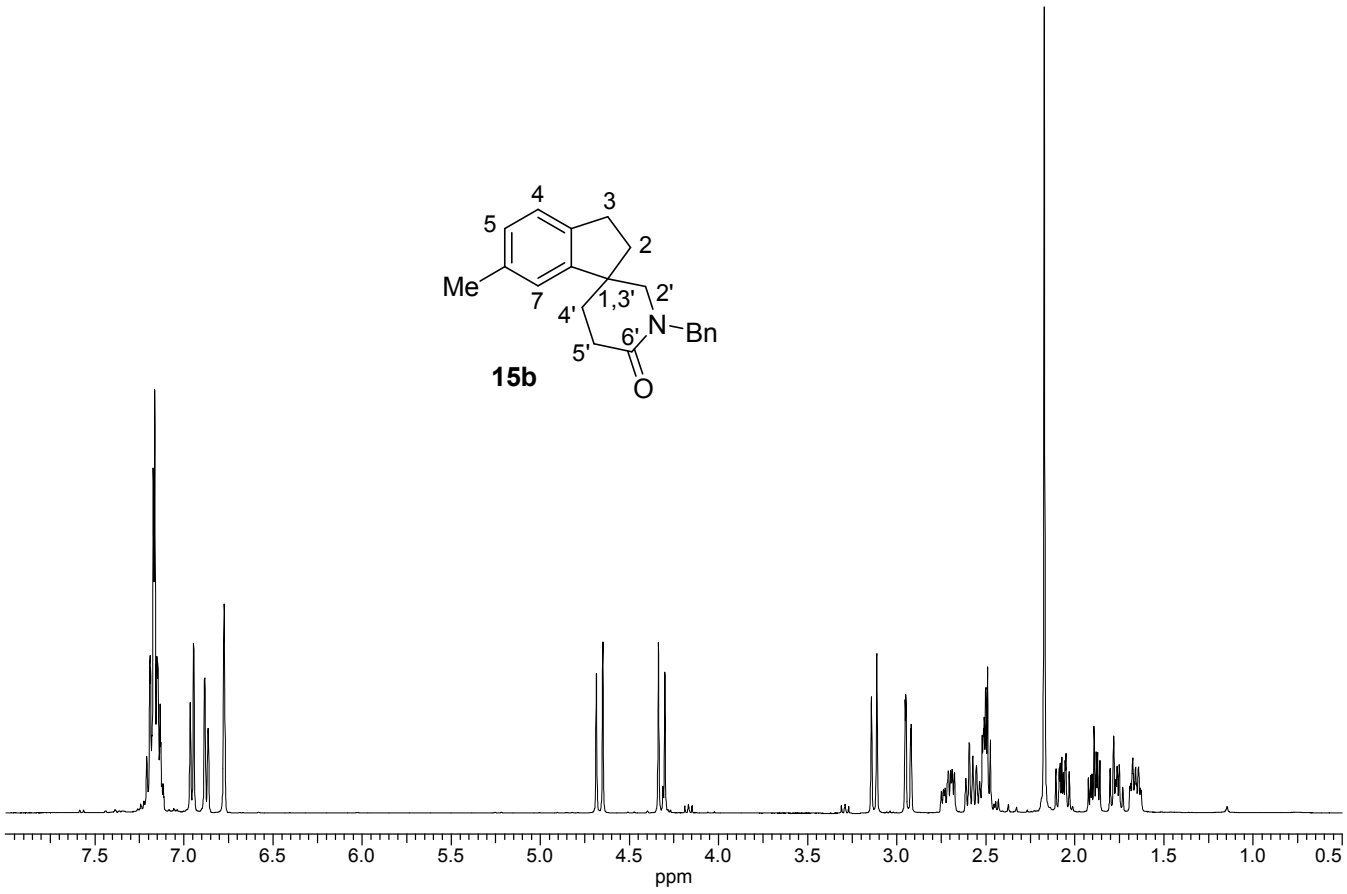
12b

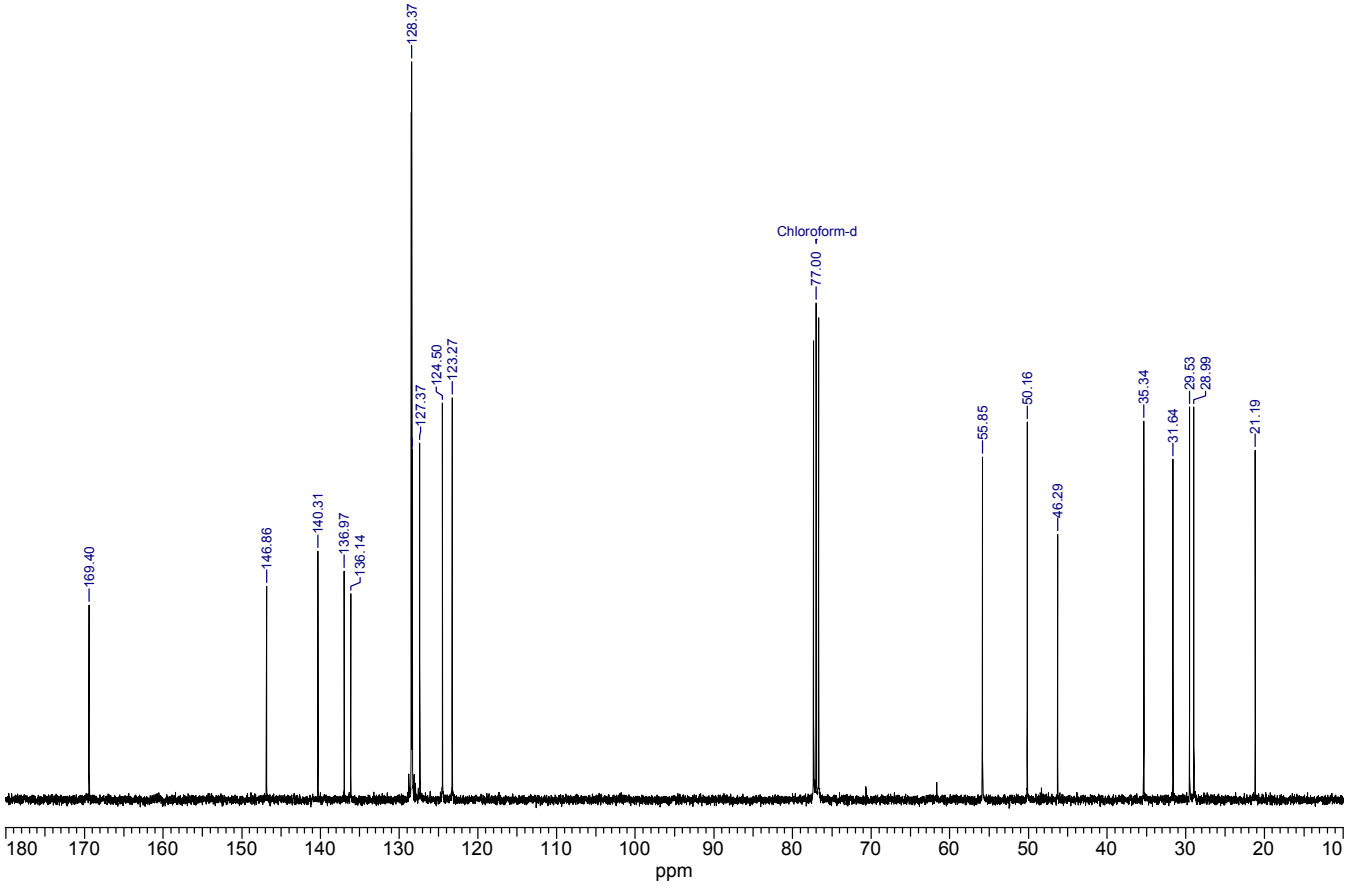
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

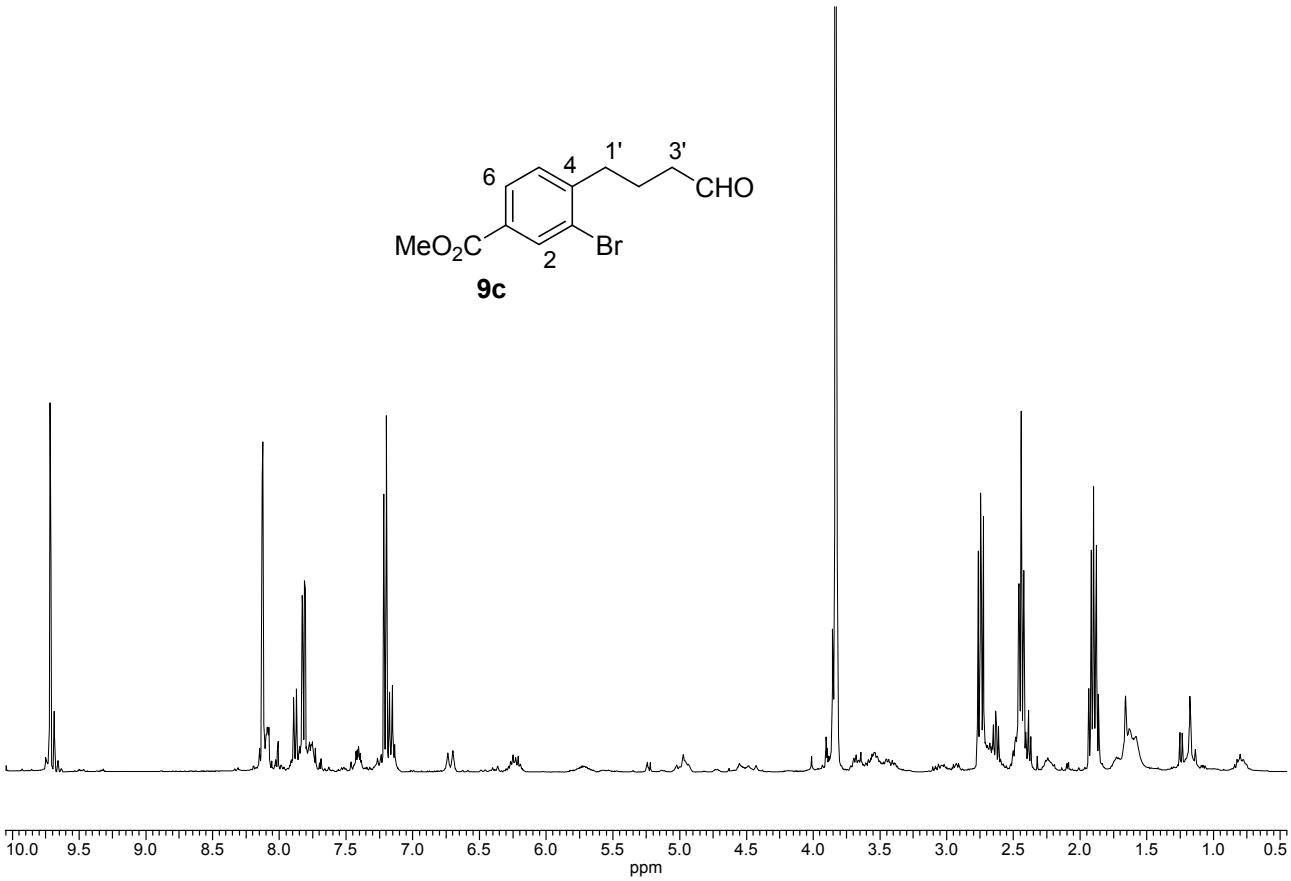

Chloroform-d
77.0
168.8
137.7
137.3
133.2
130.0
128.5
127.5
127.3
124.7
124.0
119.0
48.8
34.3
34.1
31.2
24.3
20.6
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

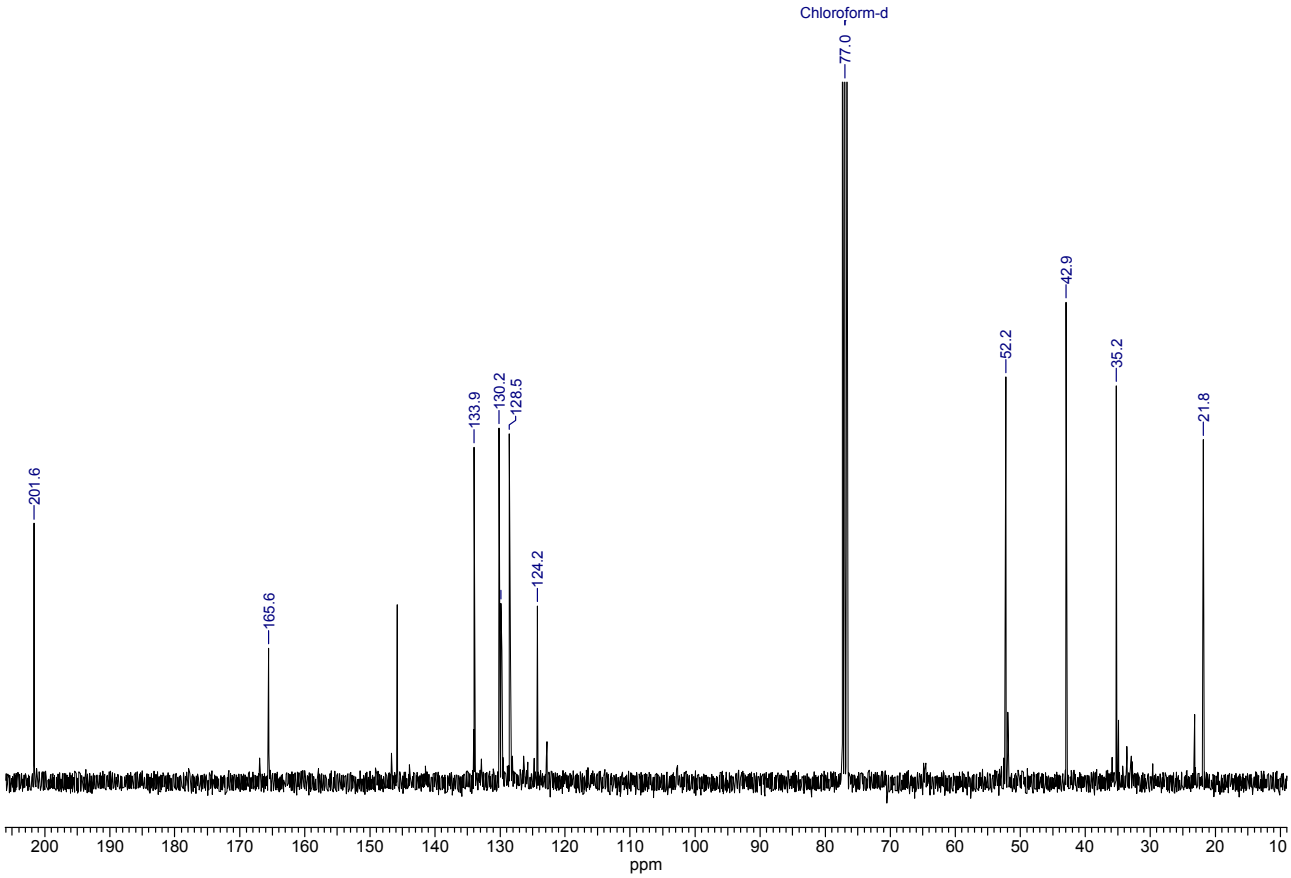

4
3
5
2
O
Me
7
1,3'
2'
4'
6'
N
Bn
5'
O
14b
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

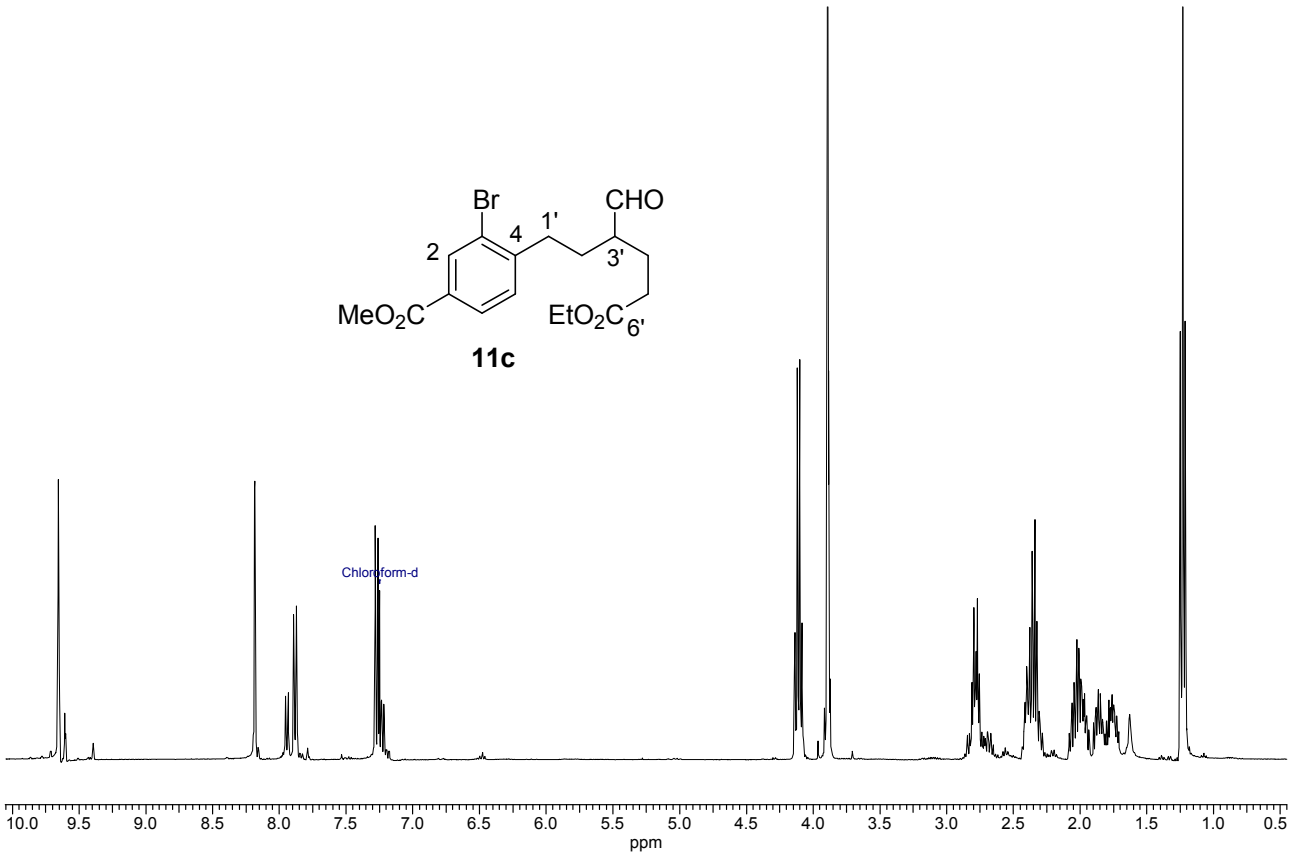

Chloroform-d
77.0
128.9
128.3
129.0
127.4
123.8
175.5
172.3
144.3
140.7
137.5
136.3
54.8
43.3
36.6
30.0
29.7
28.6
21.2
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


4
3
5
2
Me
7
1,3'
2'
4'
N
Bn
6'
5'
O
15b
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
ppm

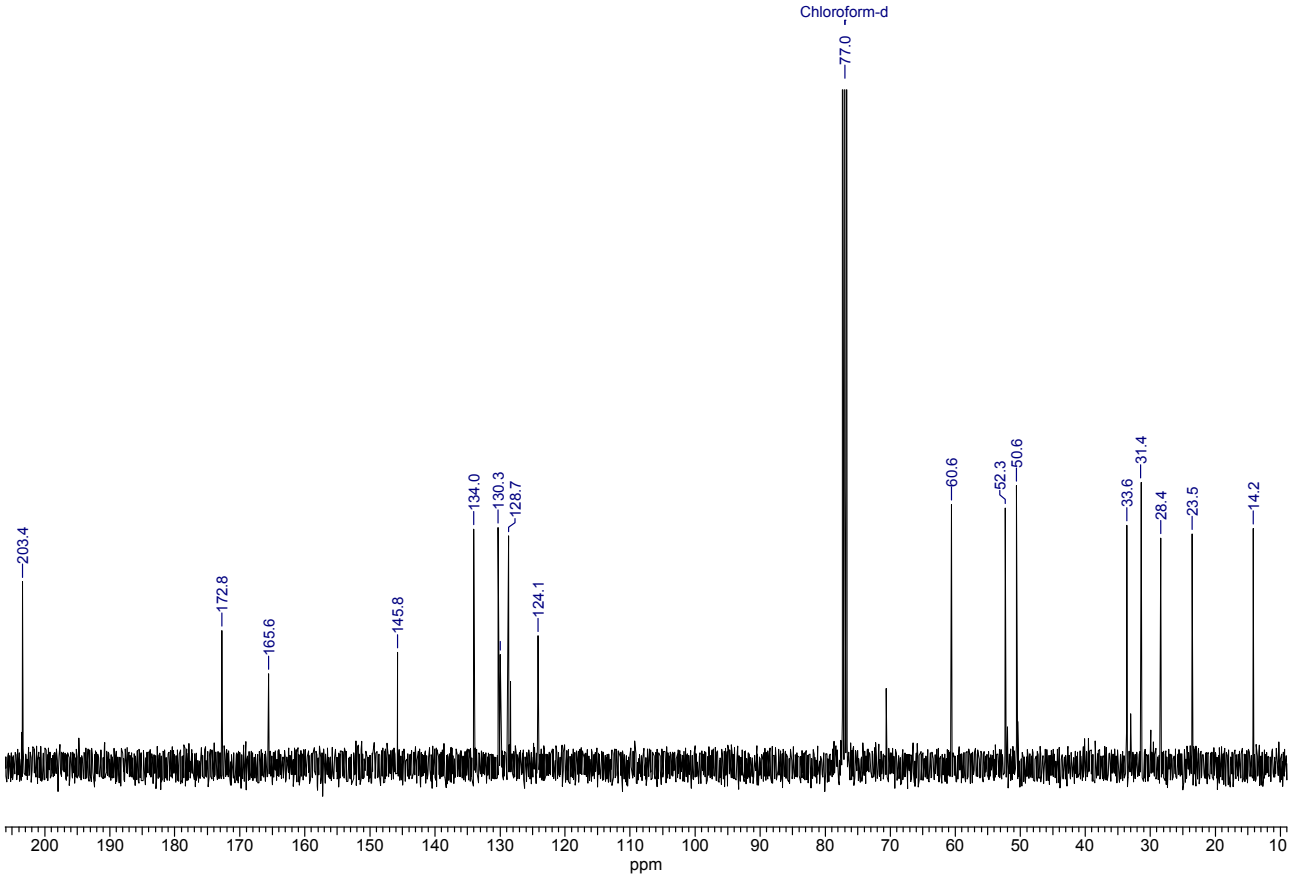

128.37
Chloroform-d
77.00
127.37
124.50
123.27
55.85
50.16
35.34
29.53
28.99
31.64
21.19
169.40
146.86
140.31
136.97
136.14
46.29
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

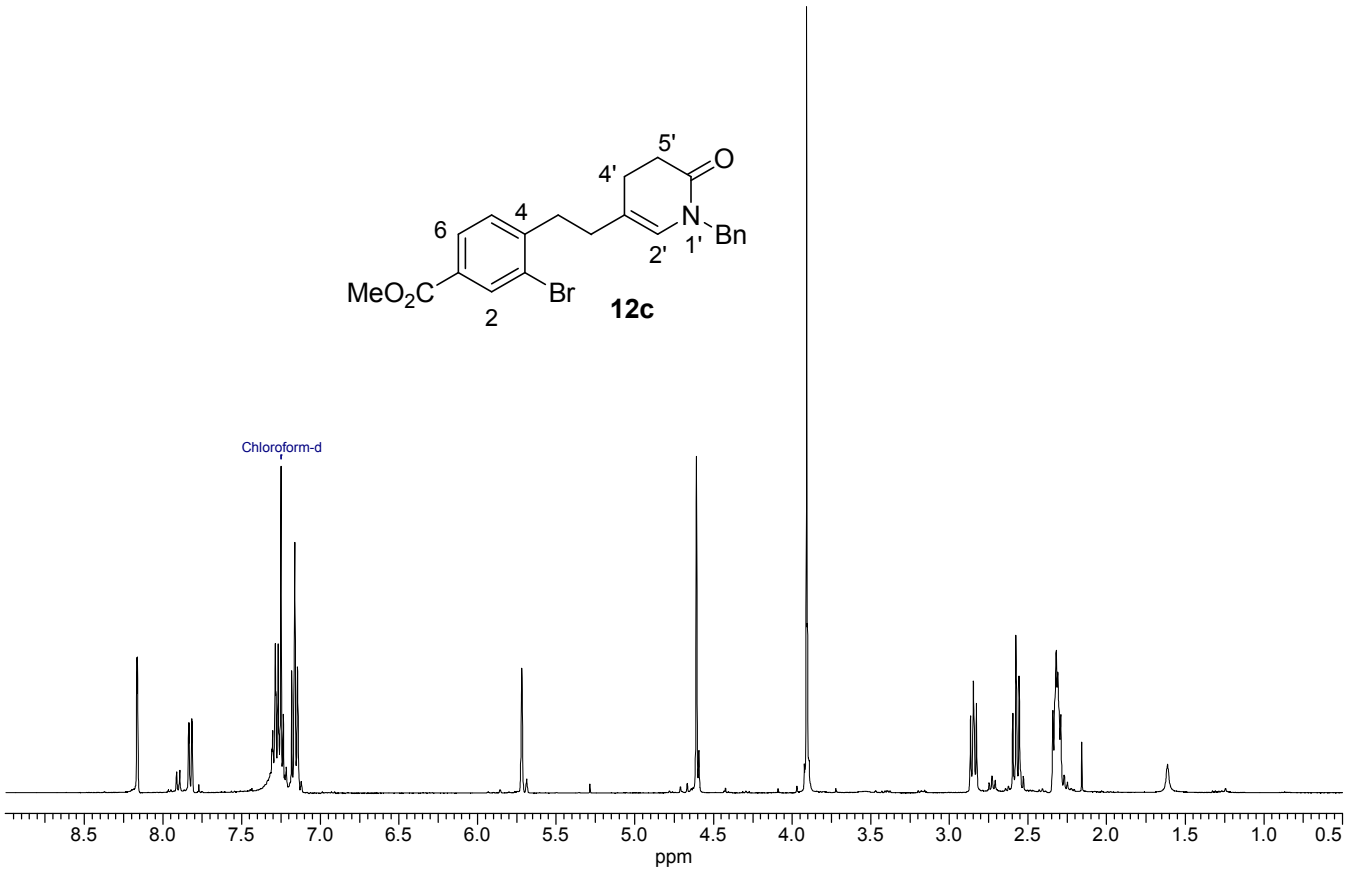

6
4
1'
3'
CHO
MeO2C
2
Br
9c
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm

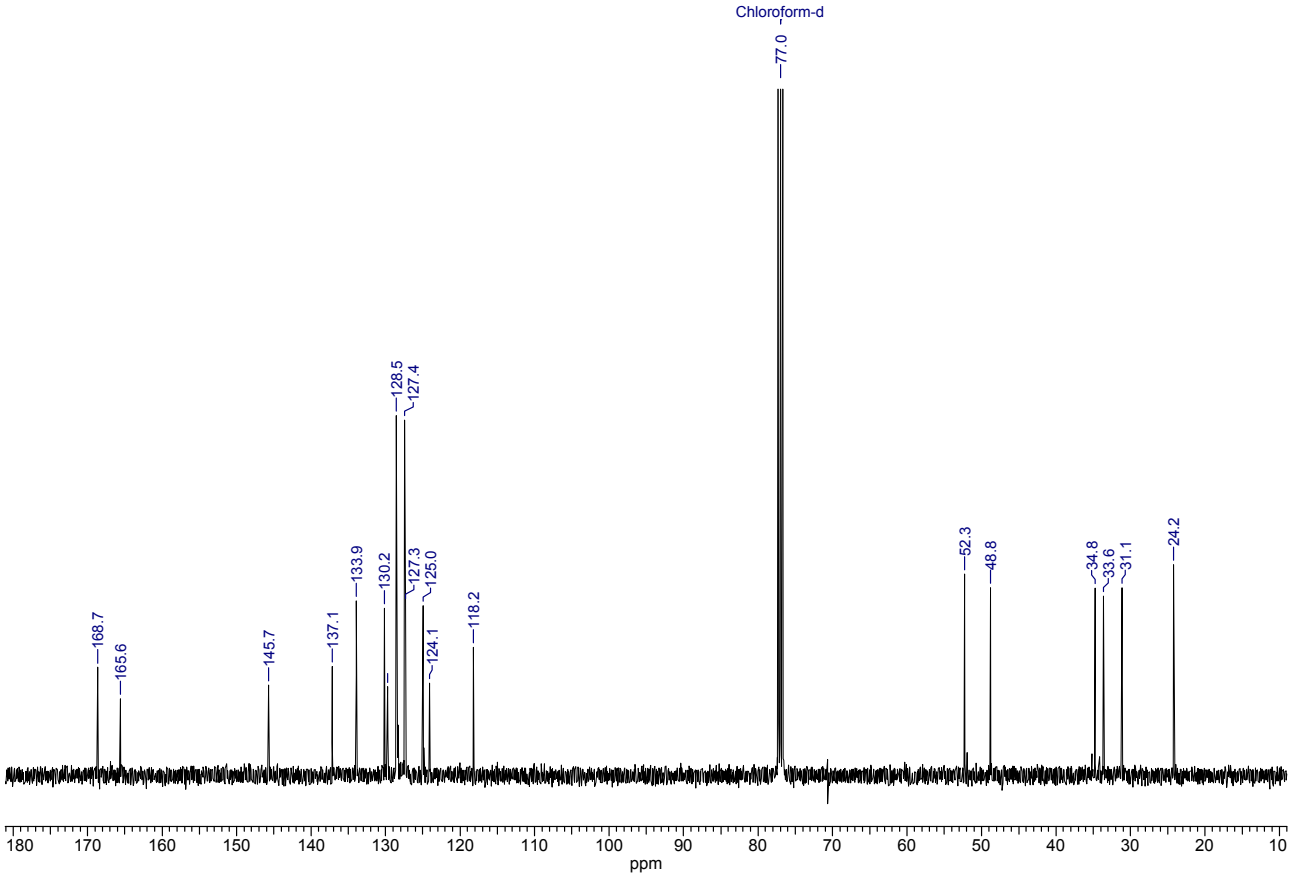

Chloroform-d
77.0
201.6
165.6
133.9
130.2
128.5
124.2
52.2
42.9
35.2
21.8
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

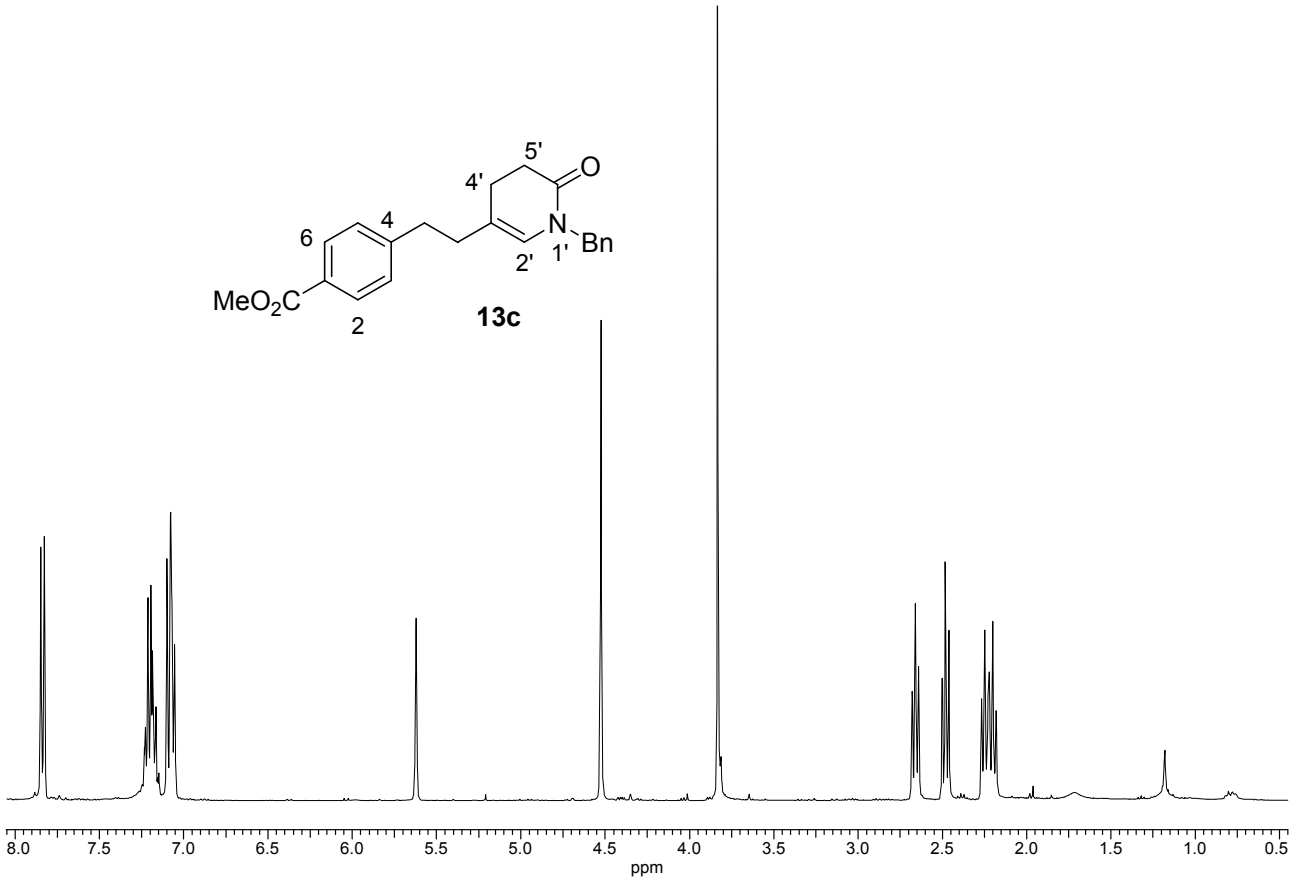

Br
CHO
1'
4
2
3'
MeO2C
EtO2C
6'
Chloroform-d
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm

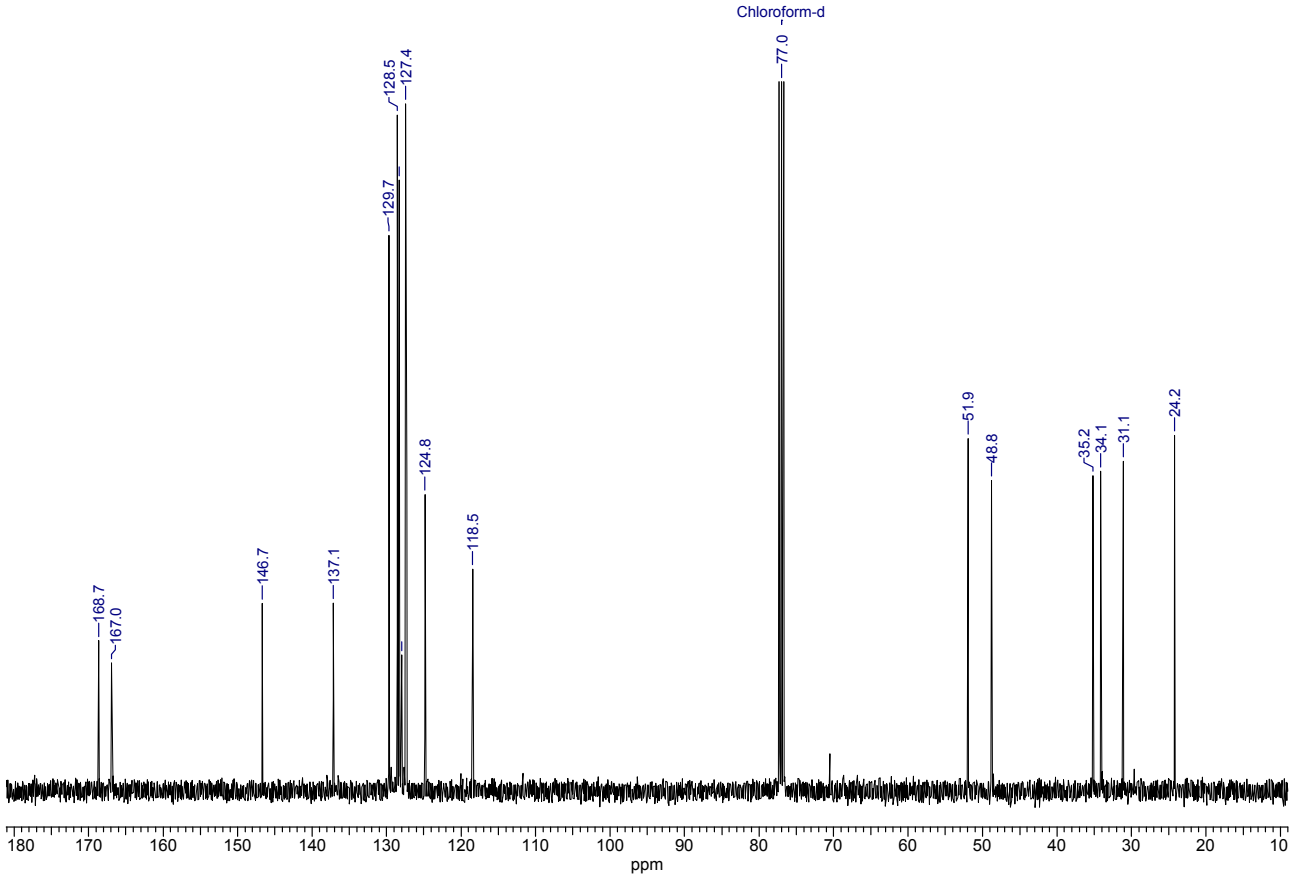
11c

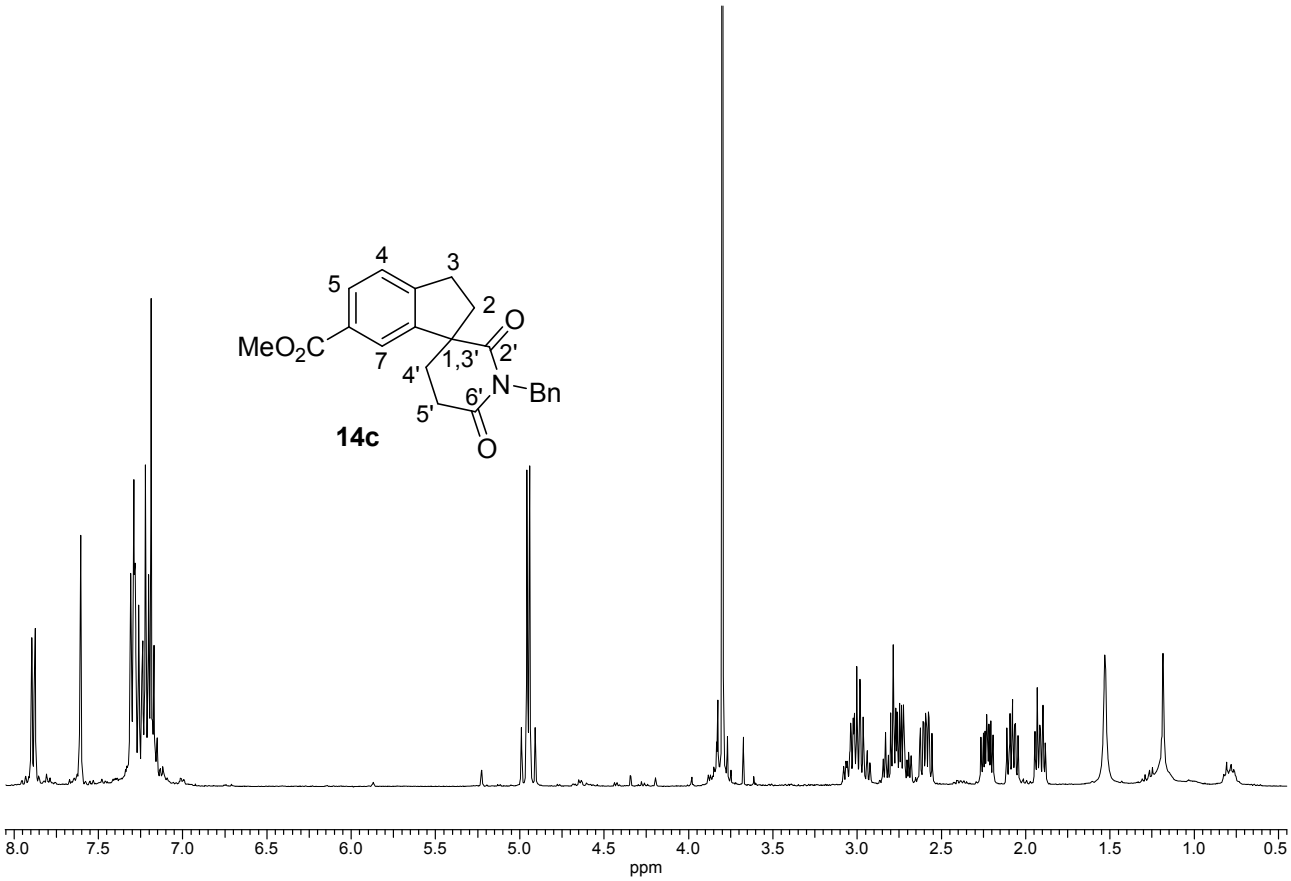

Chloroform-d
77.0
203.4
172.8
165.6
145.8
134.0
130.3
128.7
124.1
60.6
52.3
50.6
33.6
31.4
28.4
23.5
14.2
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

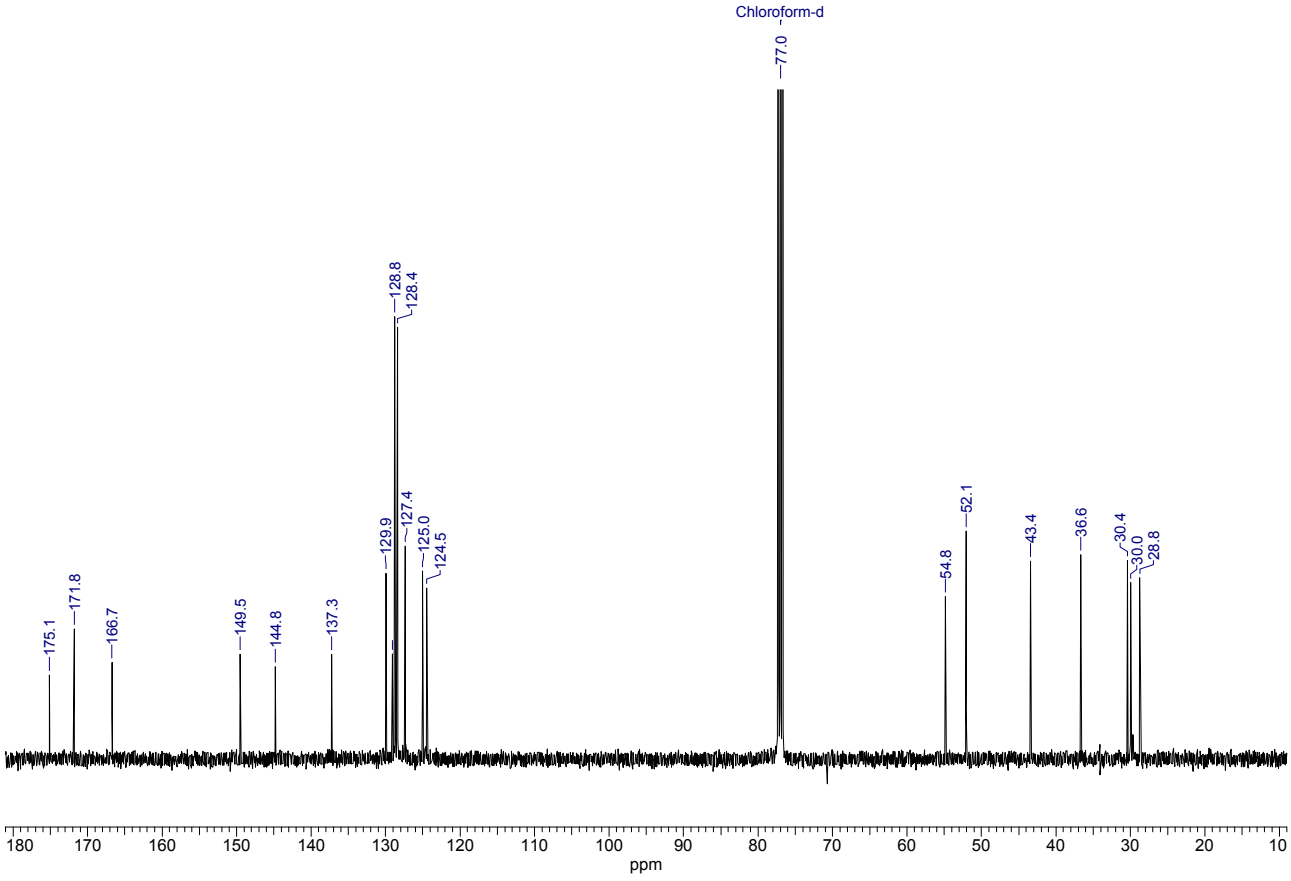

5'
4'
O
4
N
Bn
6
1'
2'
MeO2C
Br
2
12c
Chloroform-d
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

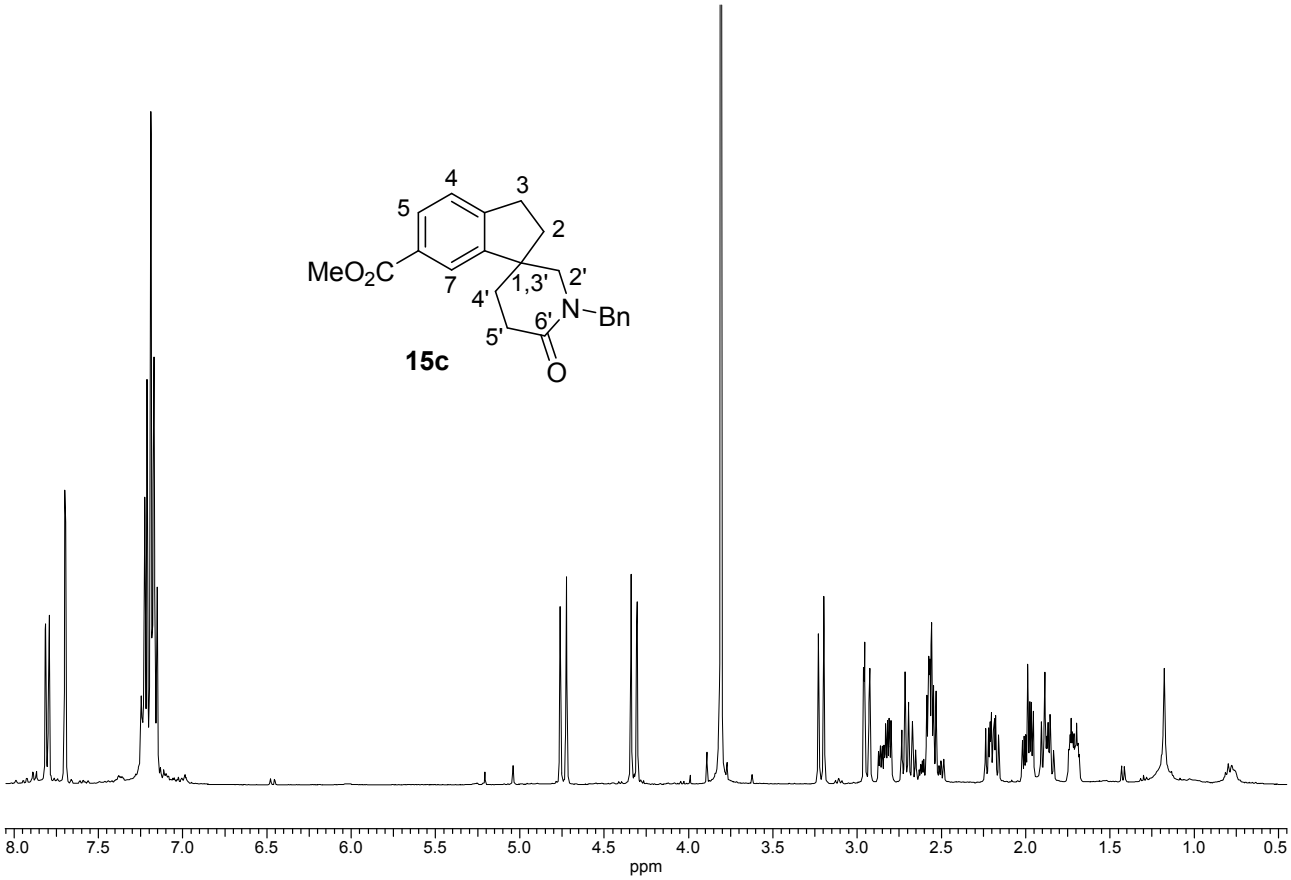

Chloroform-d
77.0
168.7
165.6
145.7
137.1
133.9
130.2
128.5
127.4
127.3
125.0
124.1
118.2
52.3
48.8
34.8
33.6
31.1
24.2
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

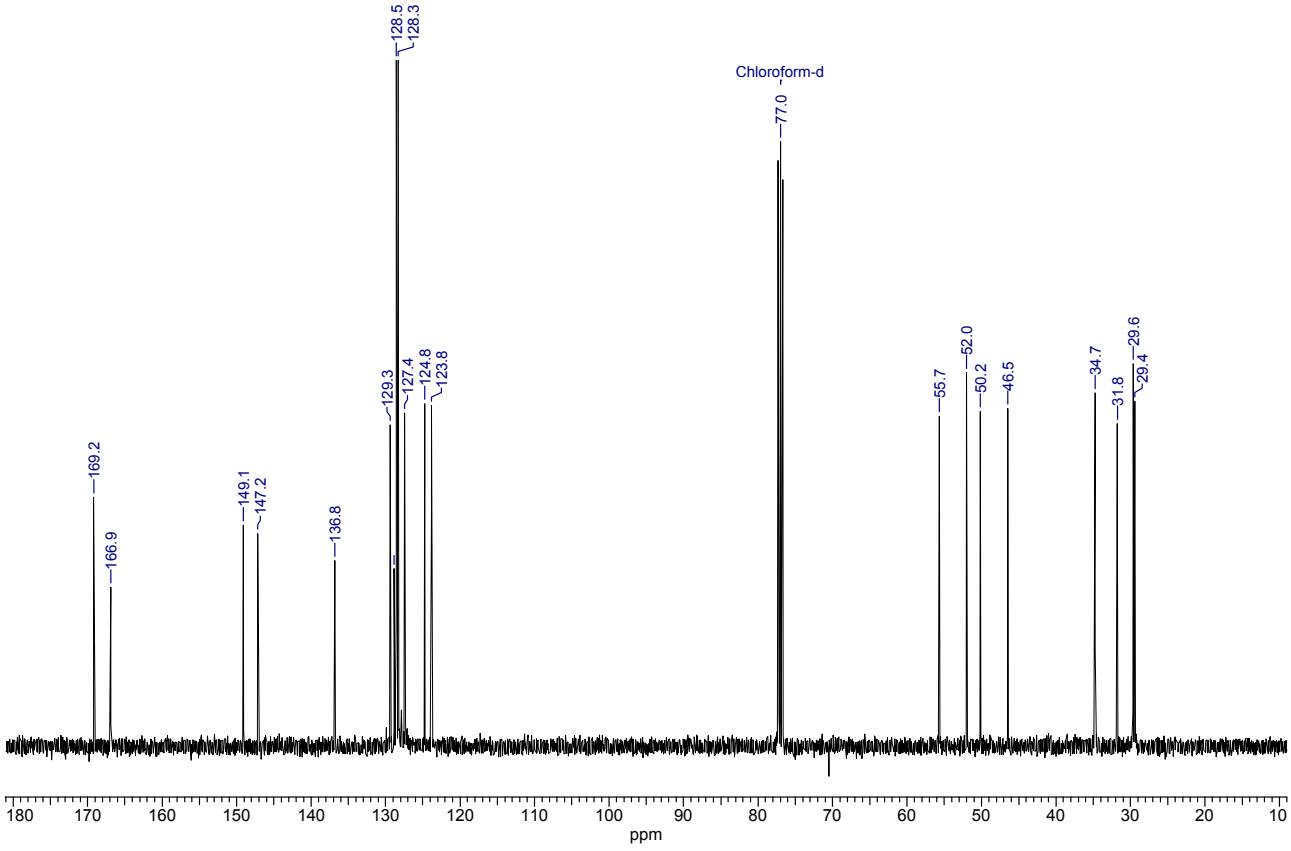

5'
4'
O
4
6
N
Bn
1'
2'
MeO2C
2
13c
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

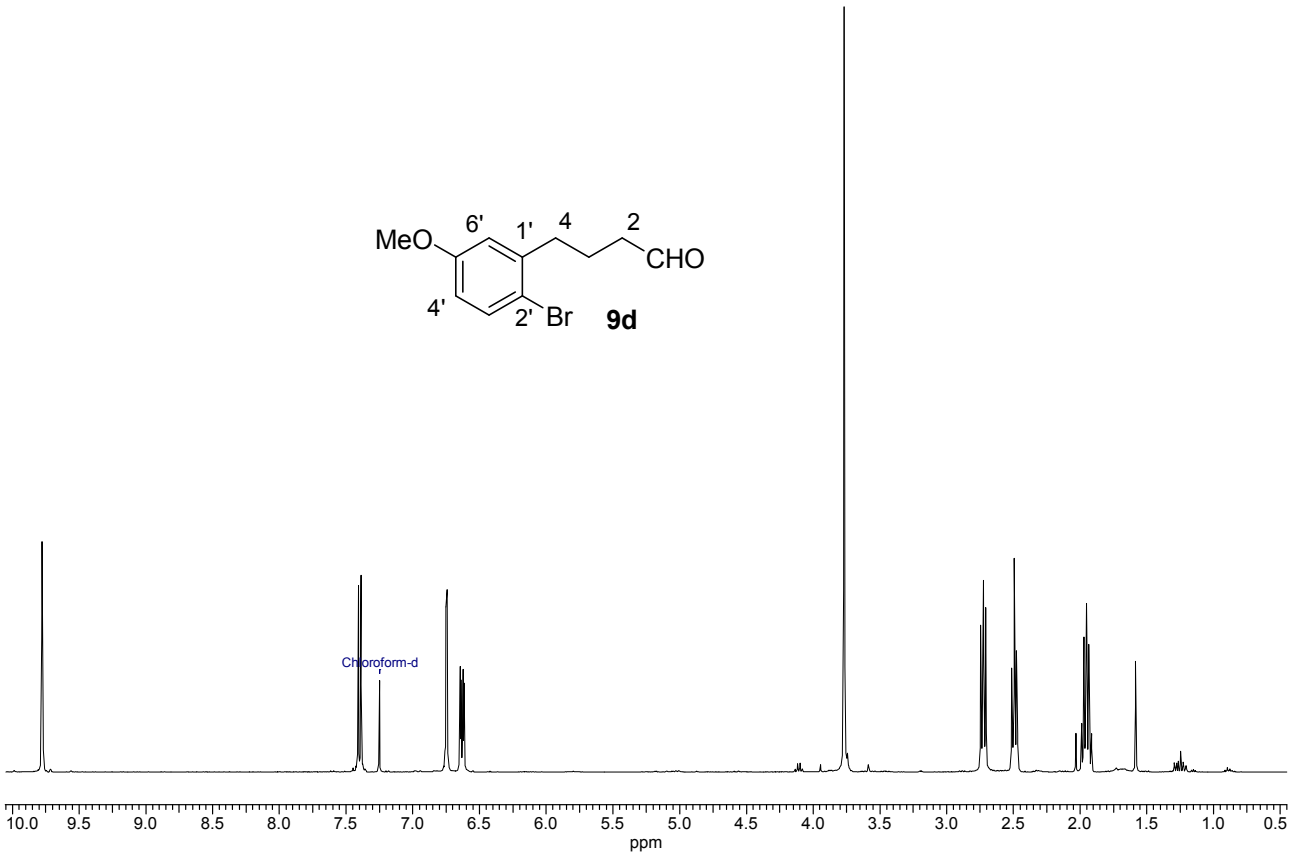

Chloroform-d
77.0
128.5
127.4
129.7
124.8
118.5
146.7
137.1
168.7
167.0
51.9
48.8
35.2
34.1
31.1
24.2
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

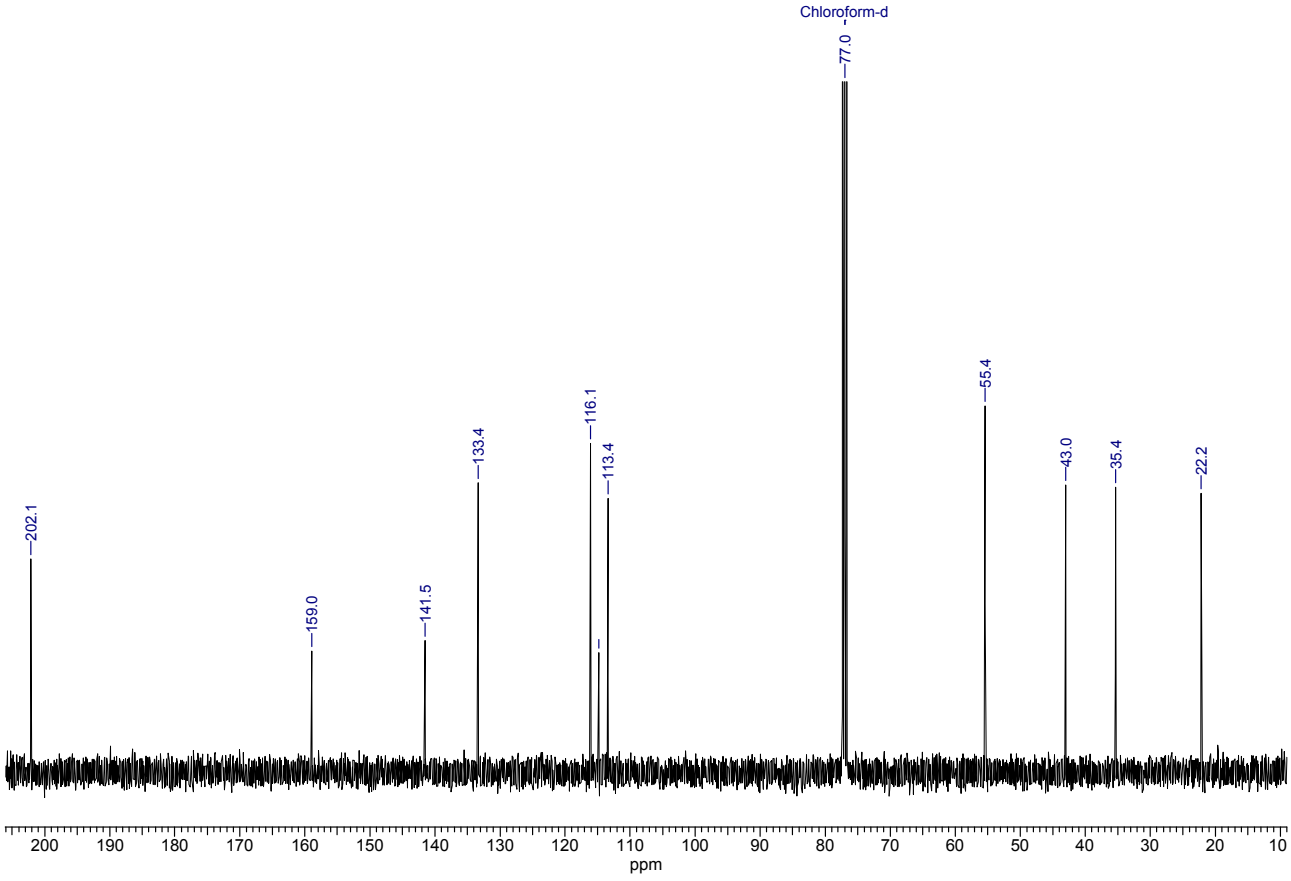

4
3
5
2
O
MeO2C
7
1,3'
2'
4'
N–Bn
6'
5'
O
14c
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

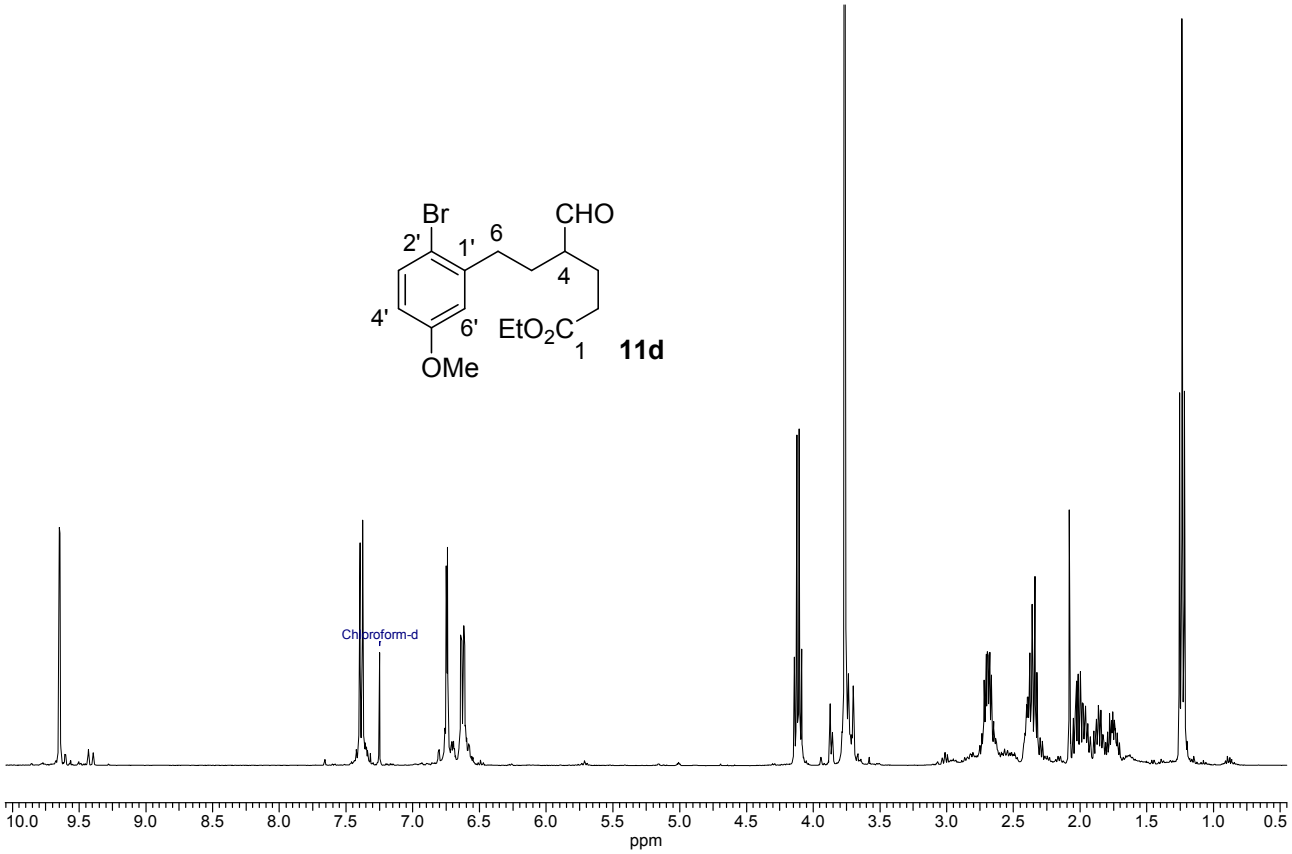

Chloroform-d
77.0
128.8
128.4
129.9
127.4
125.0
124.5
175.1
171.8
166.7
149.5
144.8
137.3
54.8
52.1
43.4
36.6
30.4
30.0
28.8
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

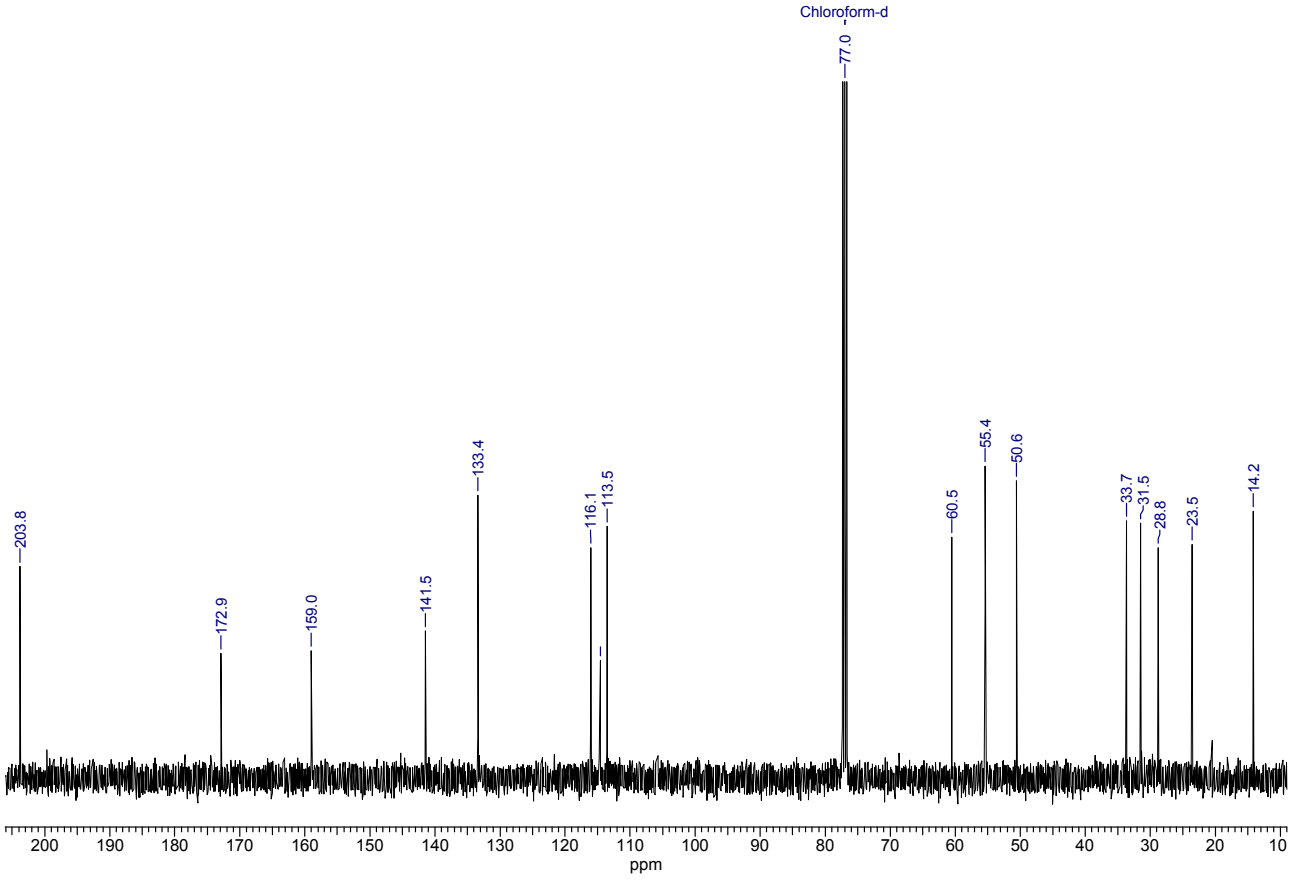

4
3
5
2
MeO2C
7
1,3'
2'
4'
N
Bn
6'
5'
O
15c
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

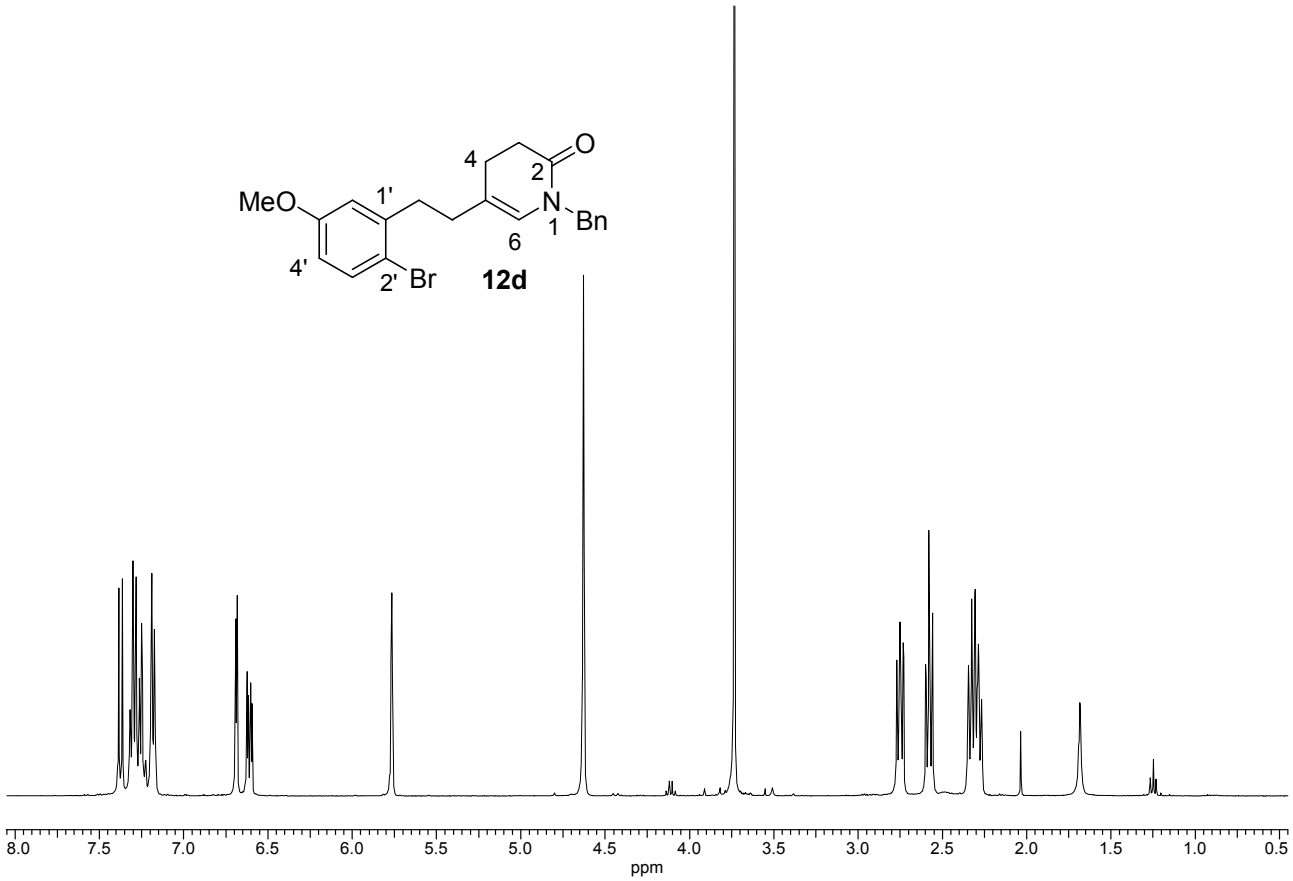

128.5
128.3
Chloroform-d
77.0
169.2
166.9
149.1
147.2
136.8
129.3
127.4
124.8
123.8
55.7
52.0
50.2
46.5
34.7
31.8
29.6
29.4
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

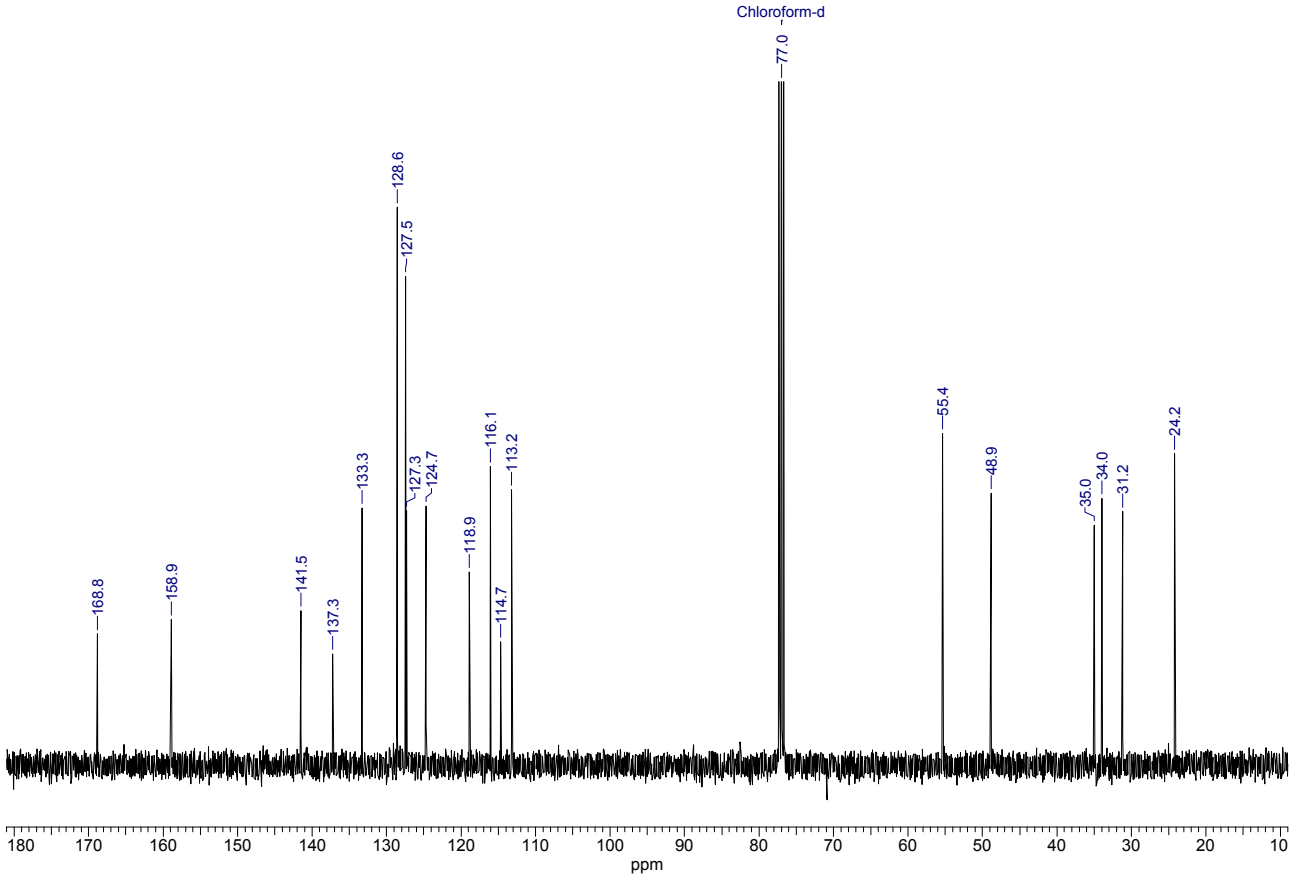

MeO
6'
1'
4
2
CHO
4'
2'
Br
9d
Chloroform-d
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm

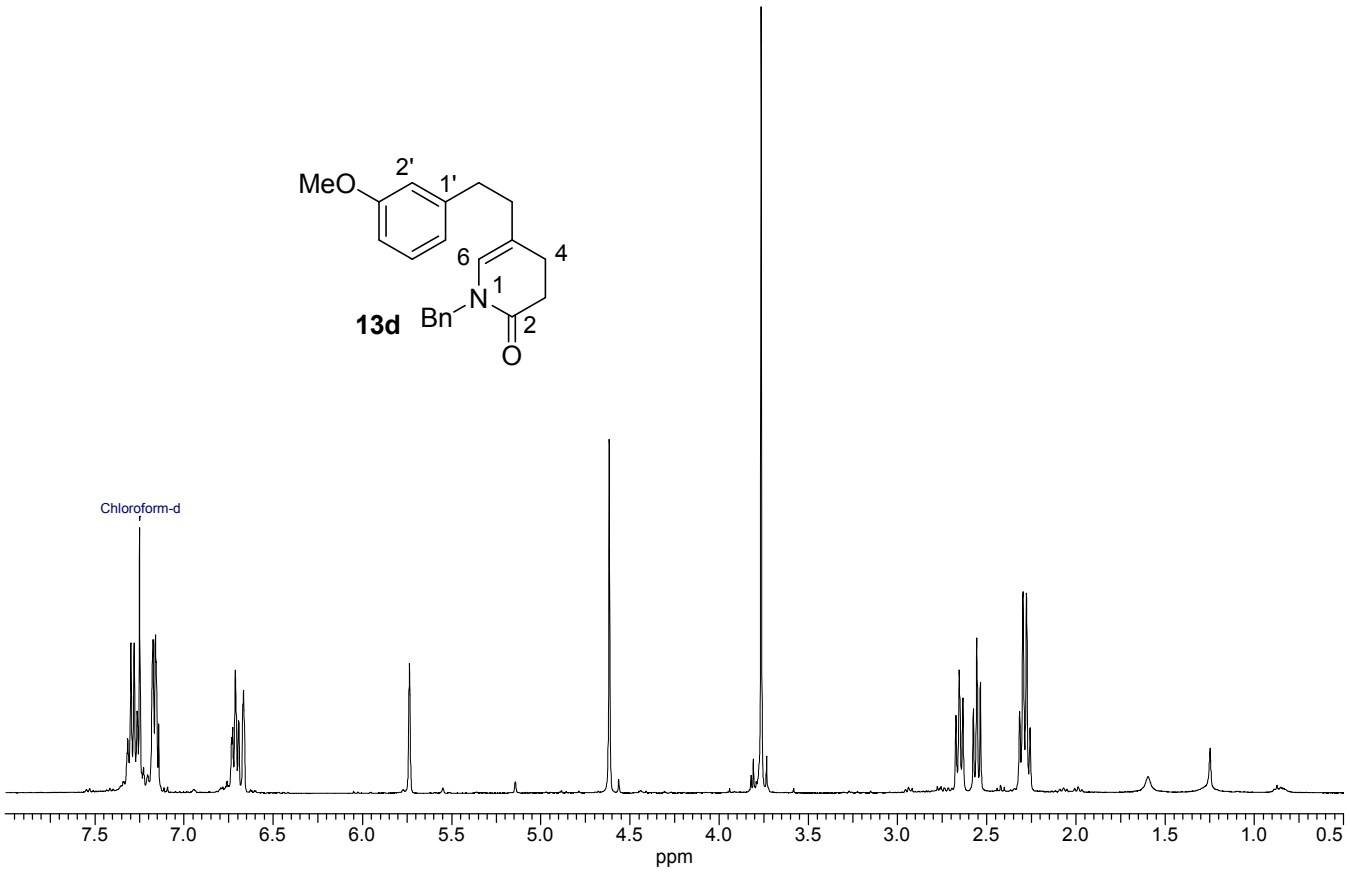

Chloroform-d
77.0
202.1
159.0
141.5
133.4
116.1
113.4
55.4
43.0
35.4
22.2
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

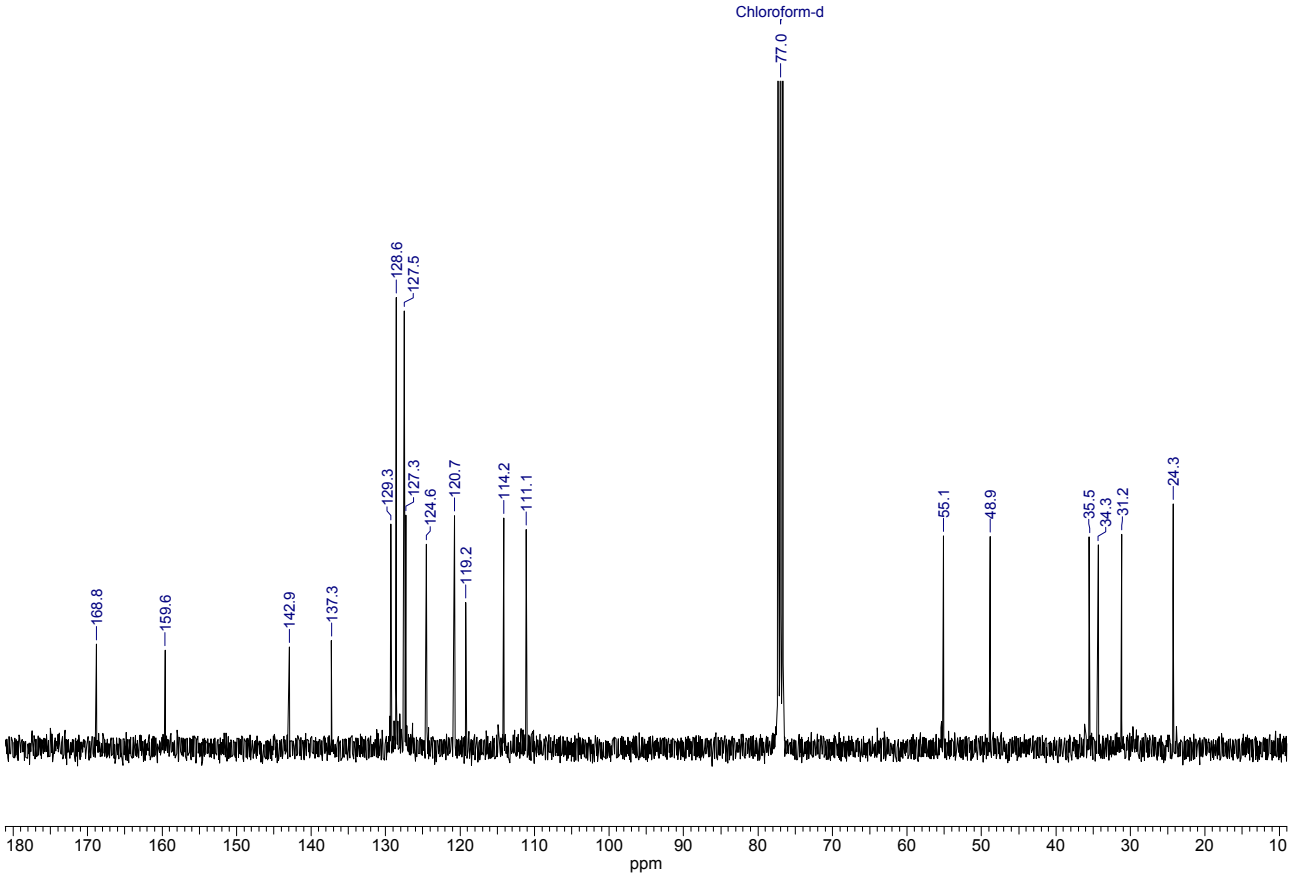

Br
CHO
2'
1'
6
4
4'
6'
EtO2C
1
OMe
11d
Chloroform-d
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm

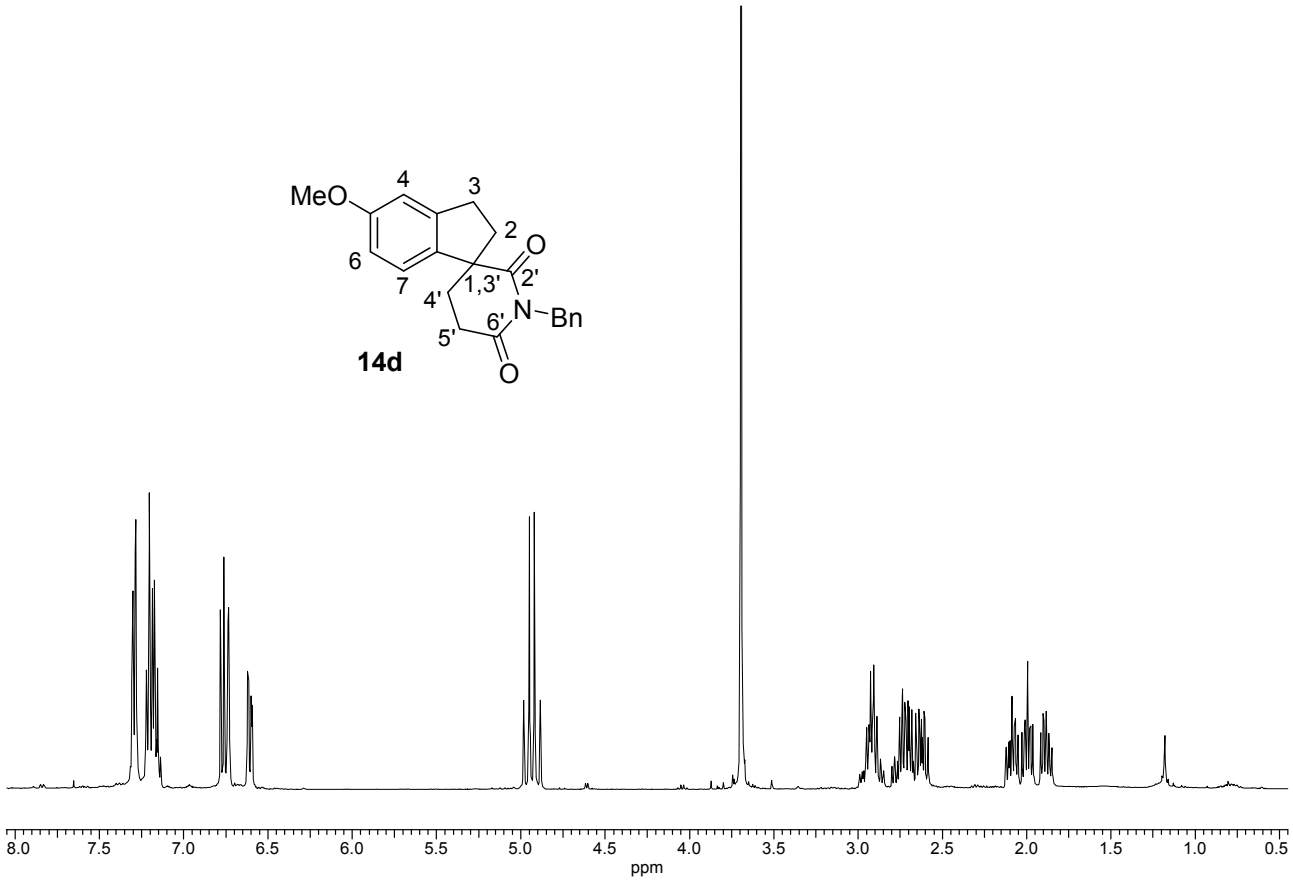

Chloroform-d
77.0
203.8
172.9
159.0
141.5
133.4
116.1
113.5
60.5
55.4
50.6
33.7
31.5
28.8
23.5
14.2
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

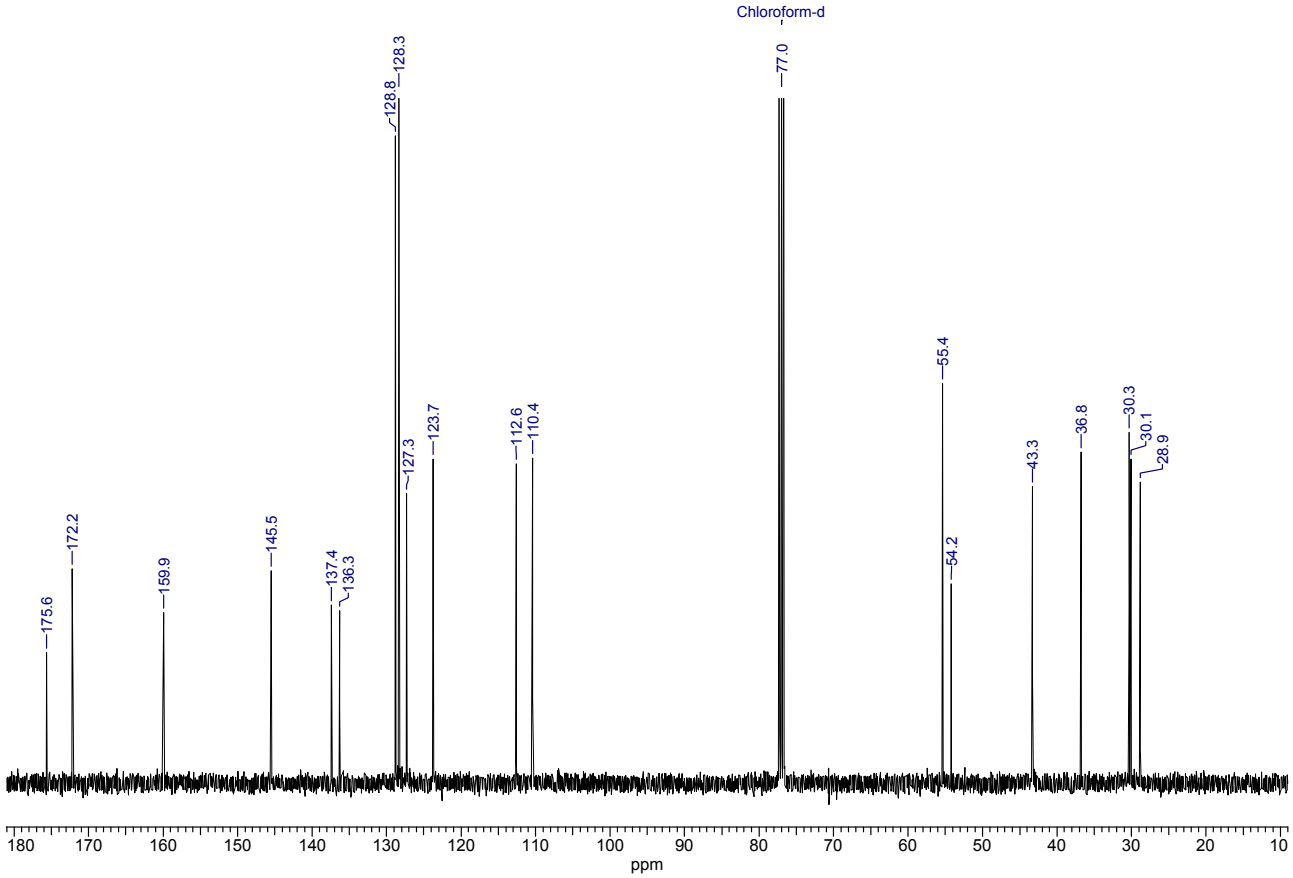

MeO
1'
4'
2' Br
4
2
O
N
1
Bn
6
12d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

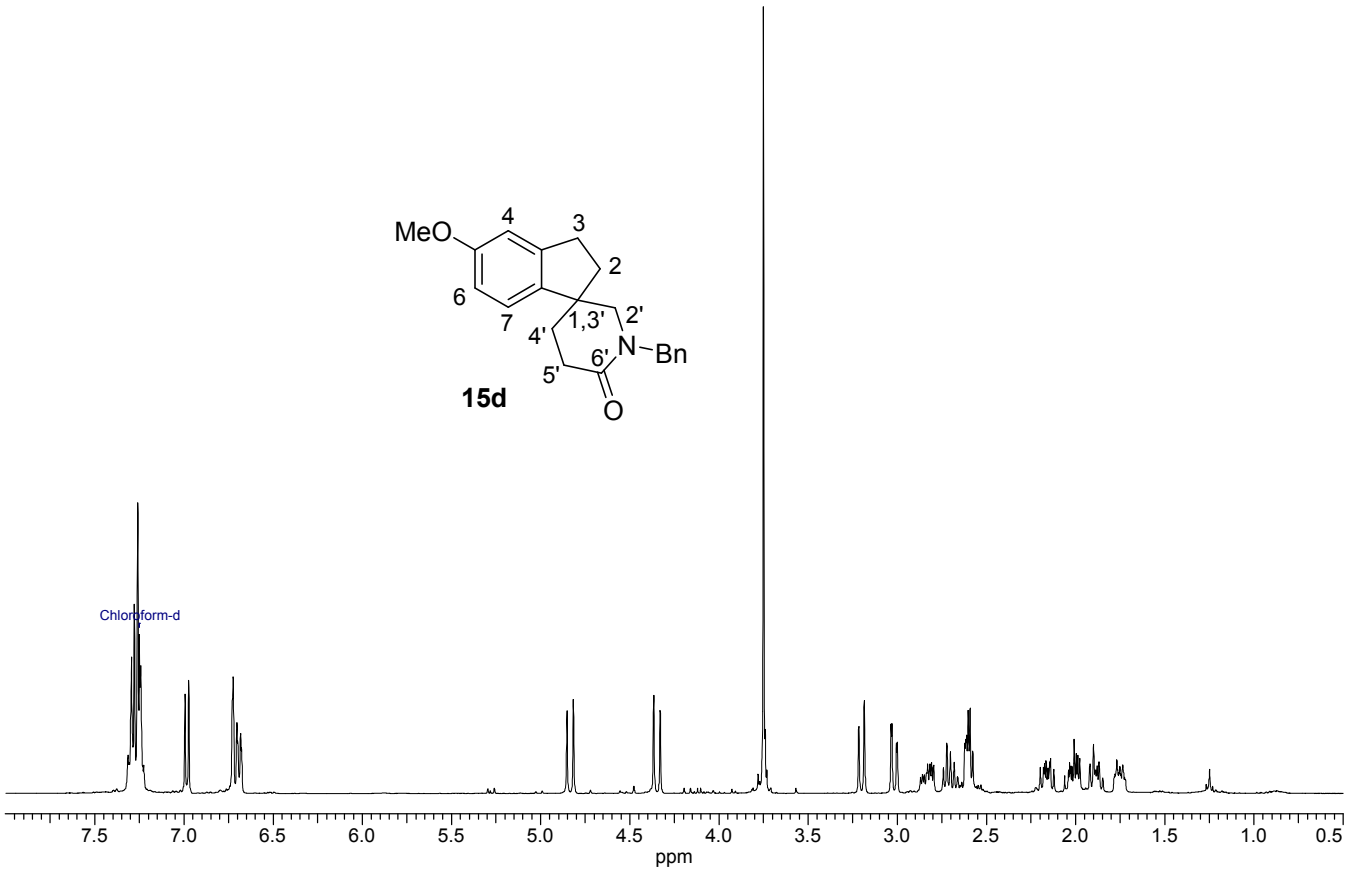

Chloroform-d
77.0
168.8
158.9
141.5
137.3
133.3
128.6
127.5
127.3
124.7
118.9
116.1
114.7
113.2
55.4
48.9
35.0
34.0
31.2
24.2
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

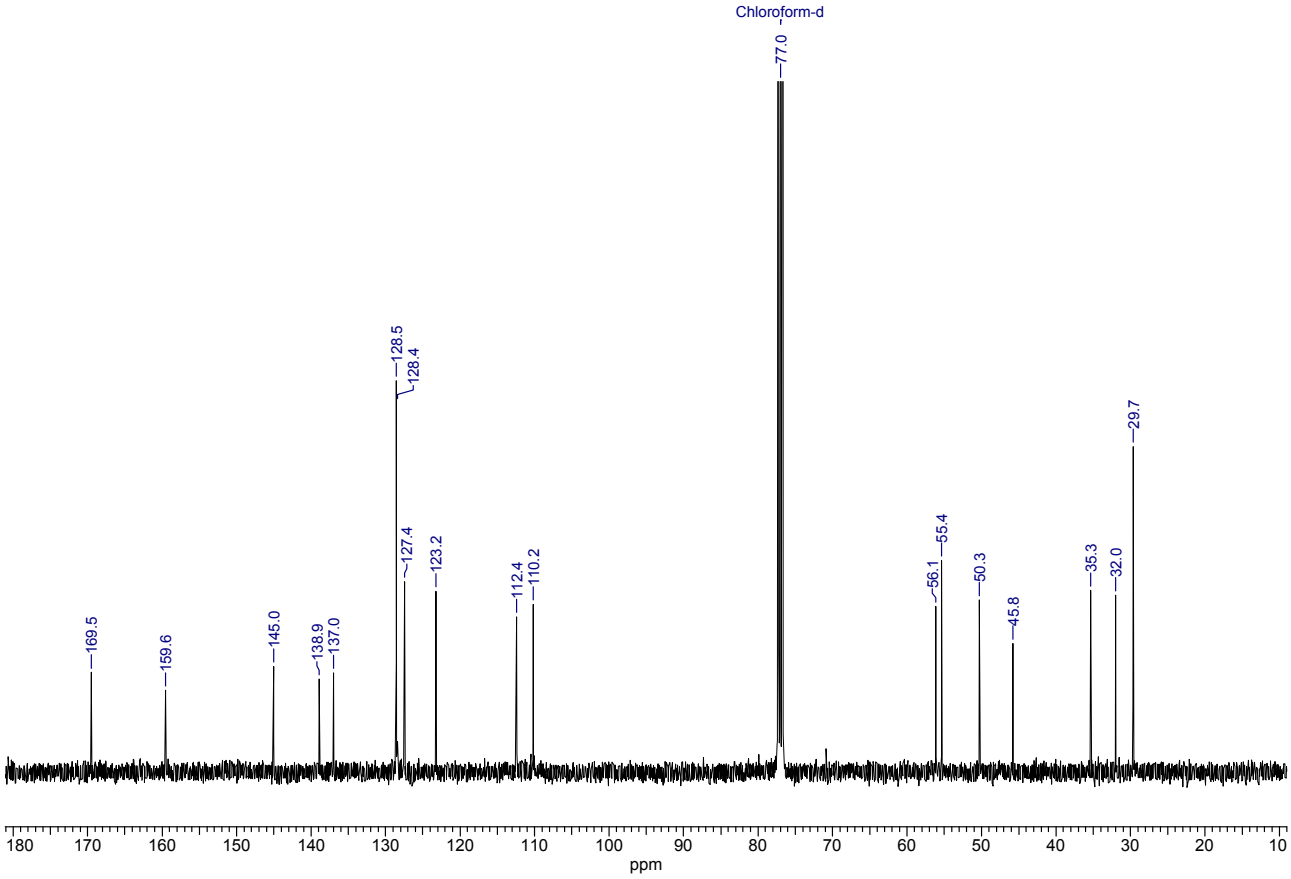

MeO
2'
1'
6
4
N
1
Bn
2
O
13d
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

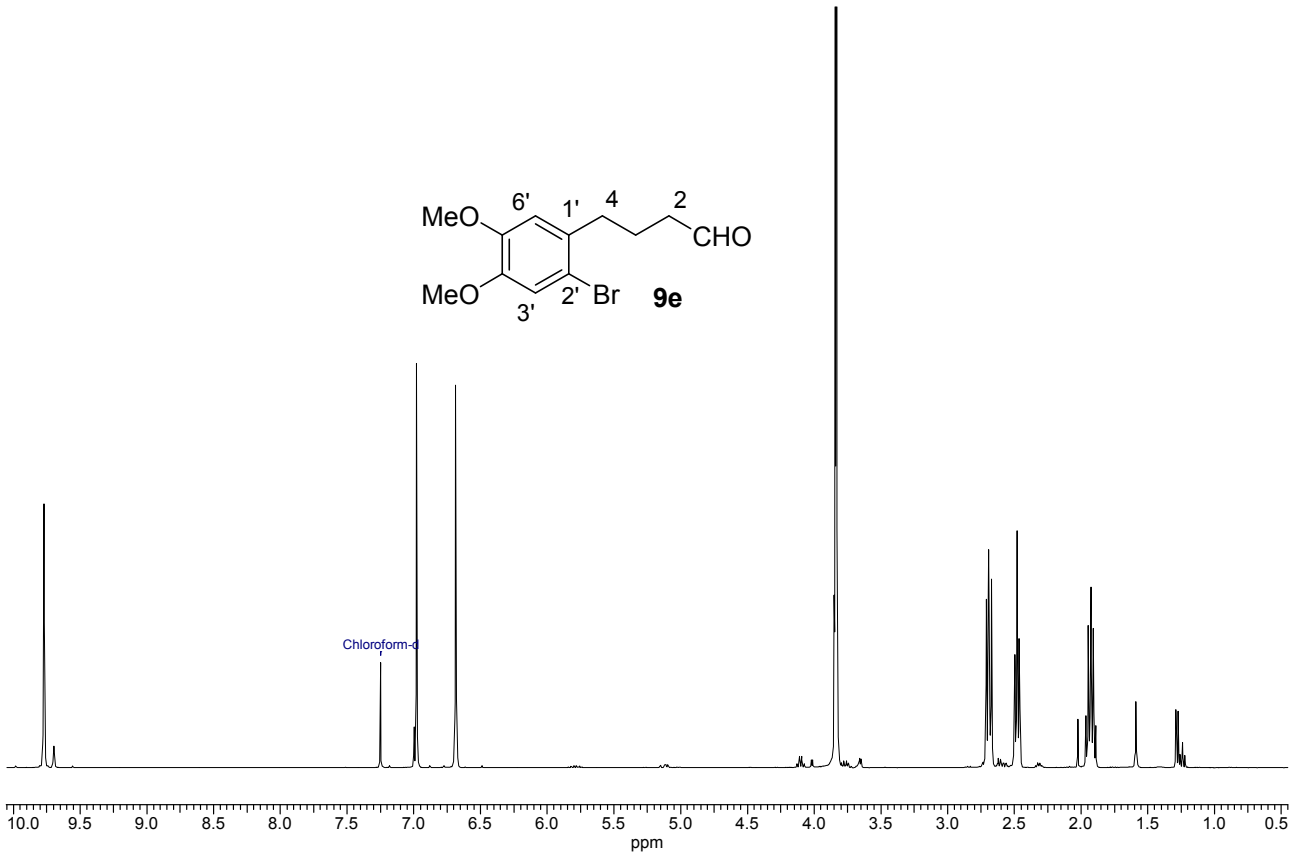

Chloroform-d
77.0
128.6
127.5
129.3
127.3
124.6
120.7
119.2
114.2
111.1
168.8
159.6
142.9
137.3
55.1
48.9
35.5
34.3
31.2
24.3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

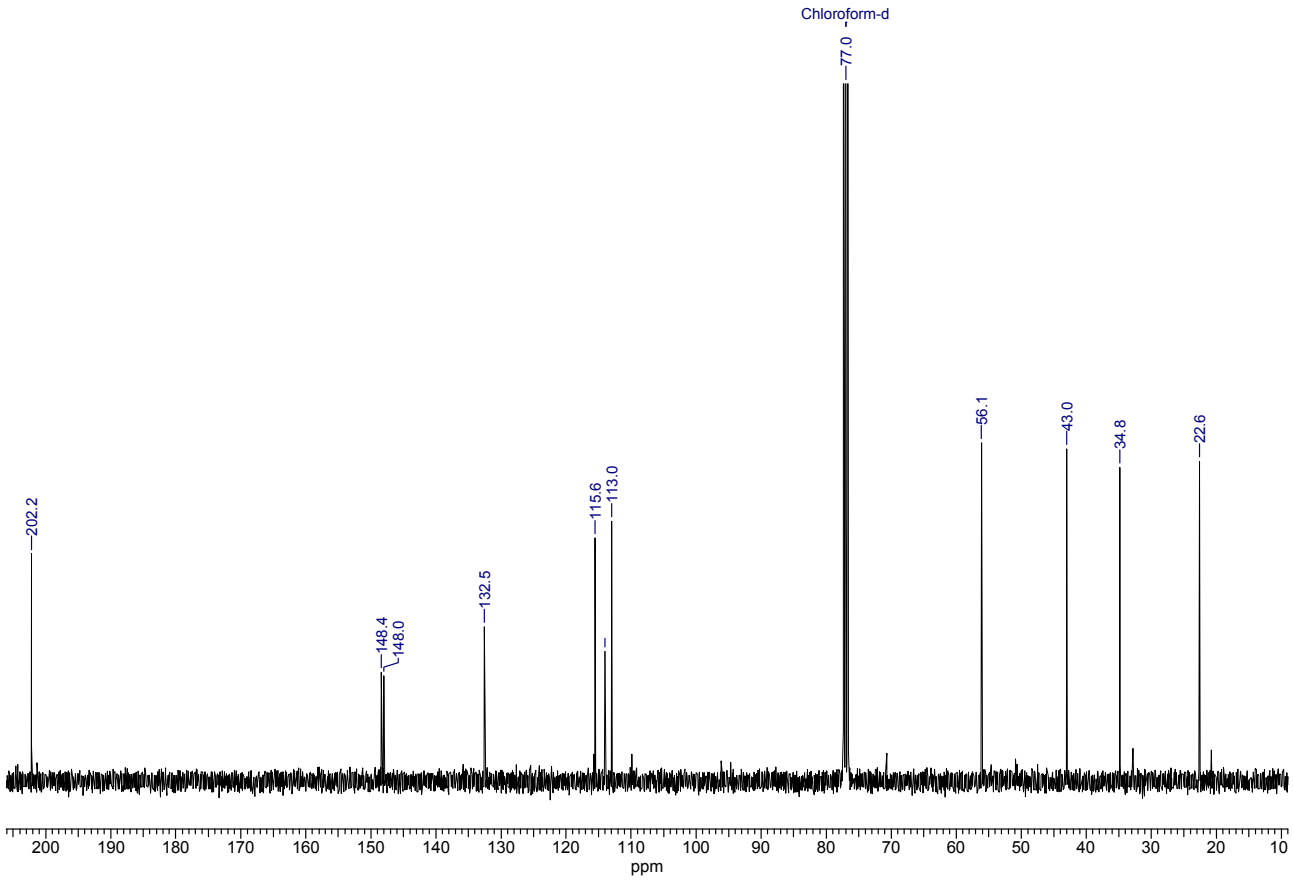

MeO
4
3
2
O
6
7
1,3'
2'
4'
N
Bn
6'
5'
O
14d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

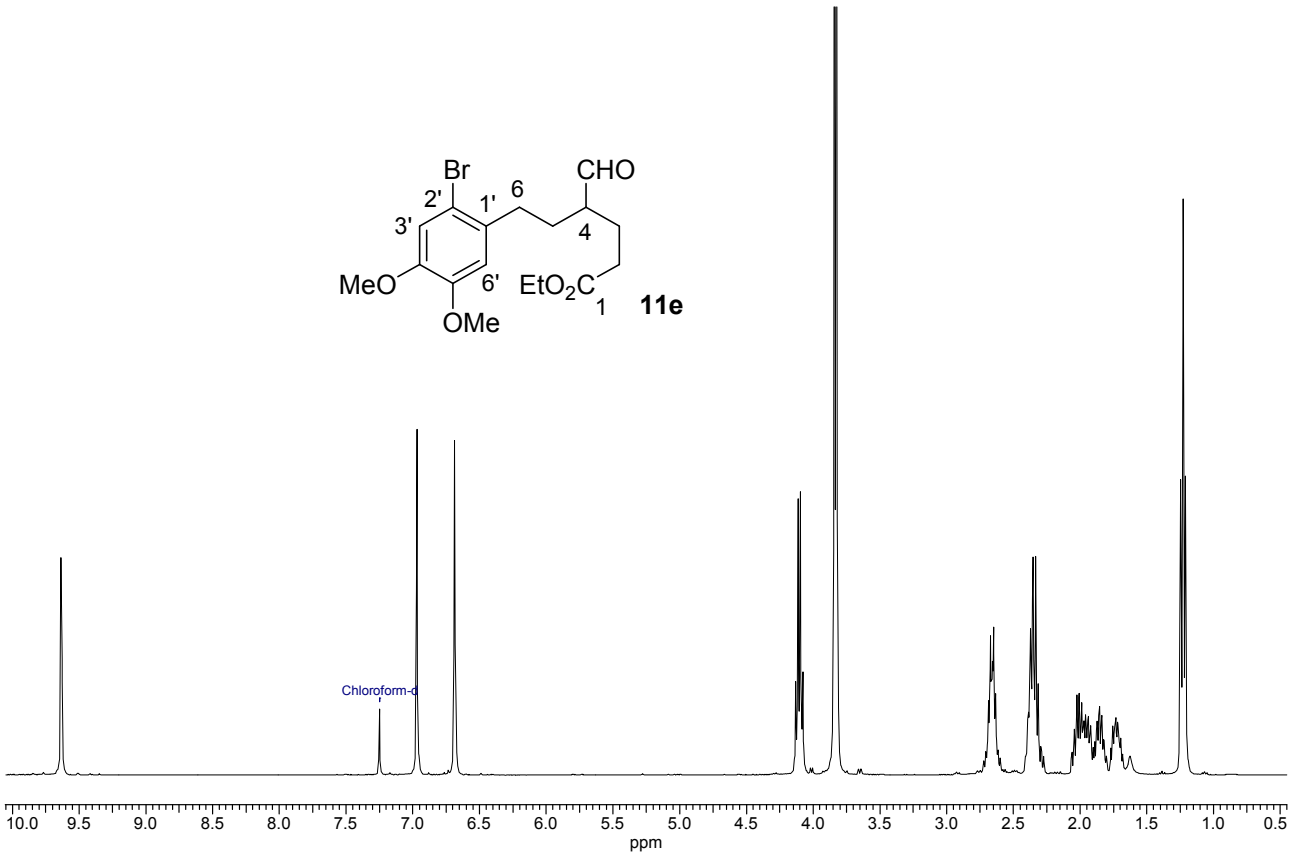

Chloroform-d
77.0
128.8
128.3
127.3
123.7
112.6
110.4
55.4
54.2
43.3
36.8
30.3
30.1
28.9
175.6
172.2
159.9
145.5
137.4
136.3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

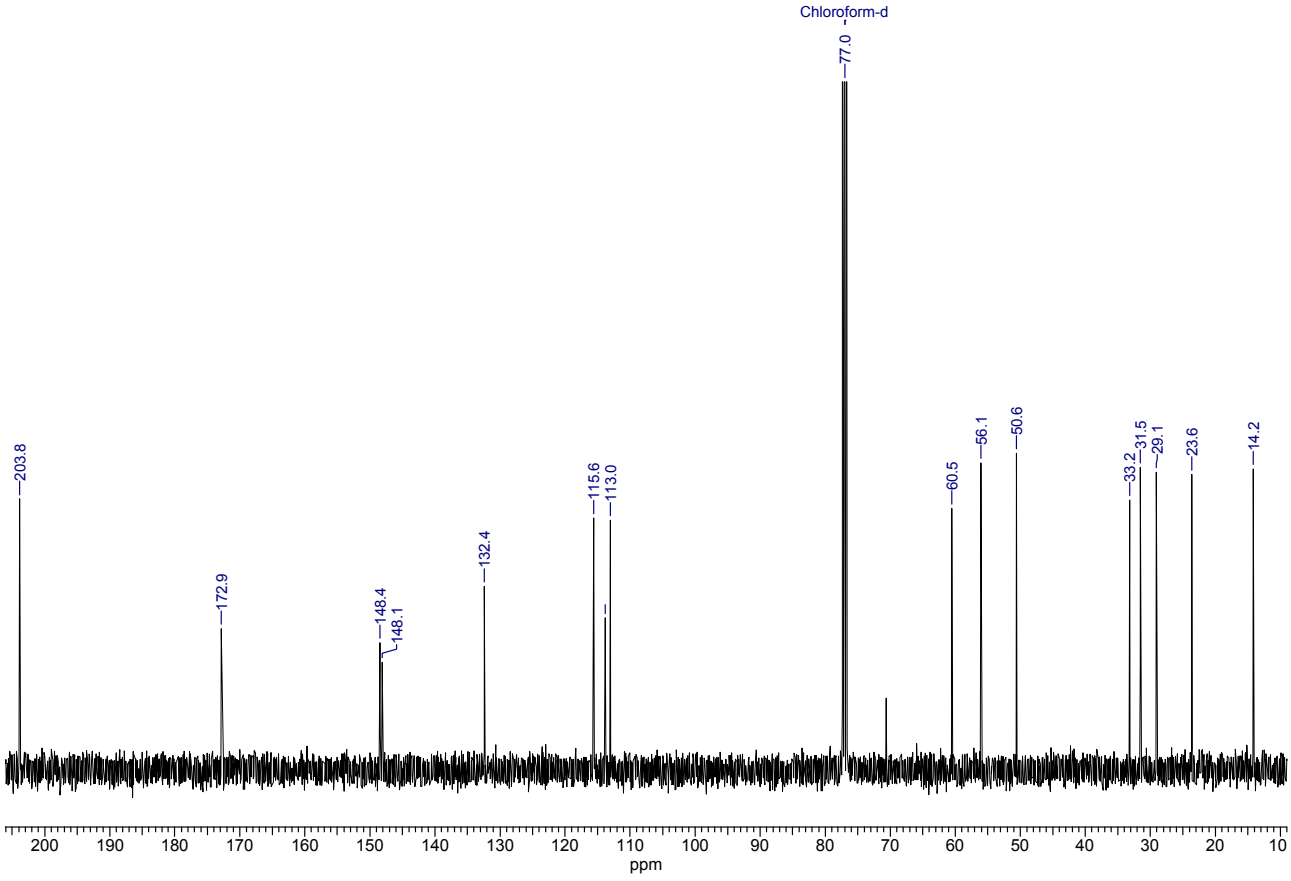

MeO
4
3
2
6
7
1,3'
2'
4'
6'
N
Bn
5'
O
15d
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

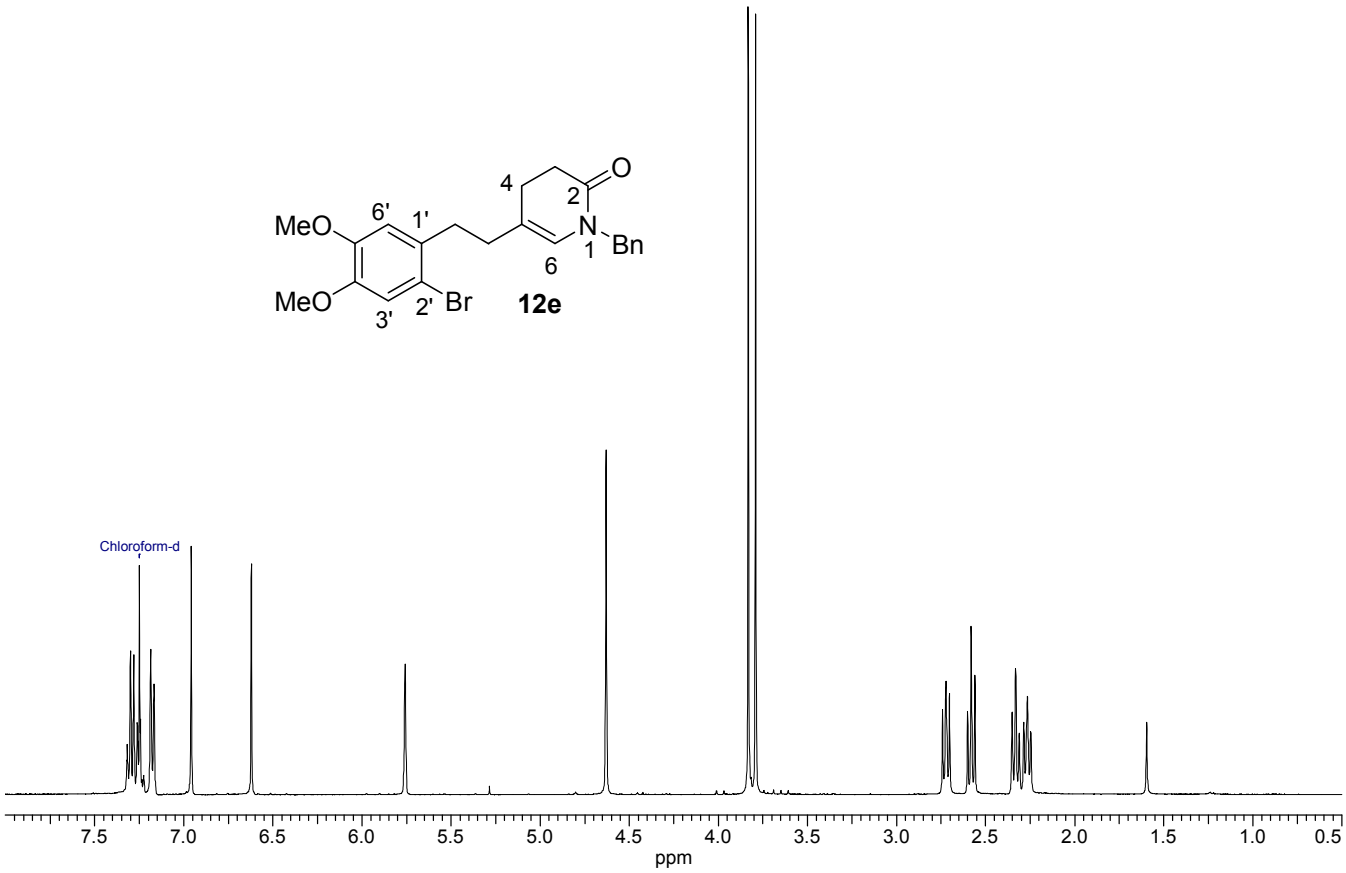

Chloroform-d
77.0
128.5
128.4
127.4
123.2
112.4
110.2
169.5
159.6
145.0
138.9
137.0
56.1
55.4
50.3
45.8
35.3
32.0
29.7
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

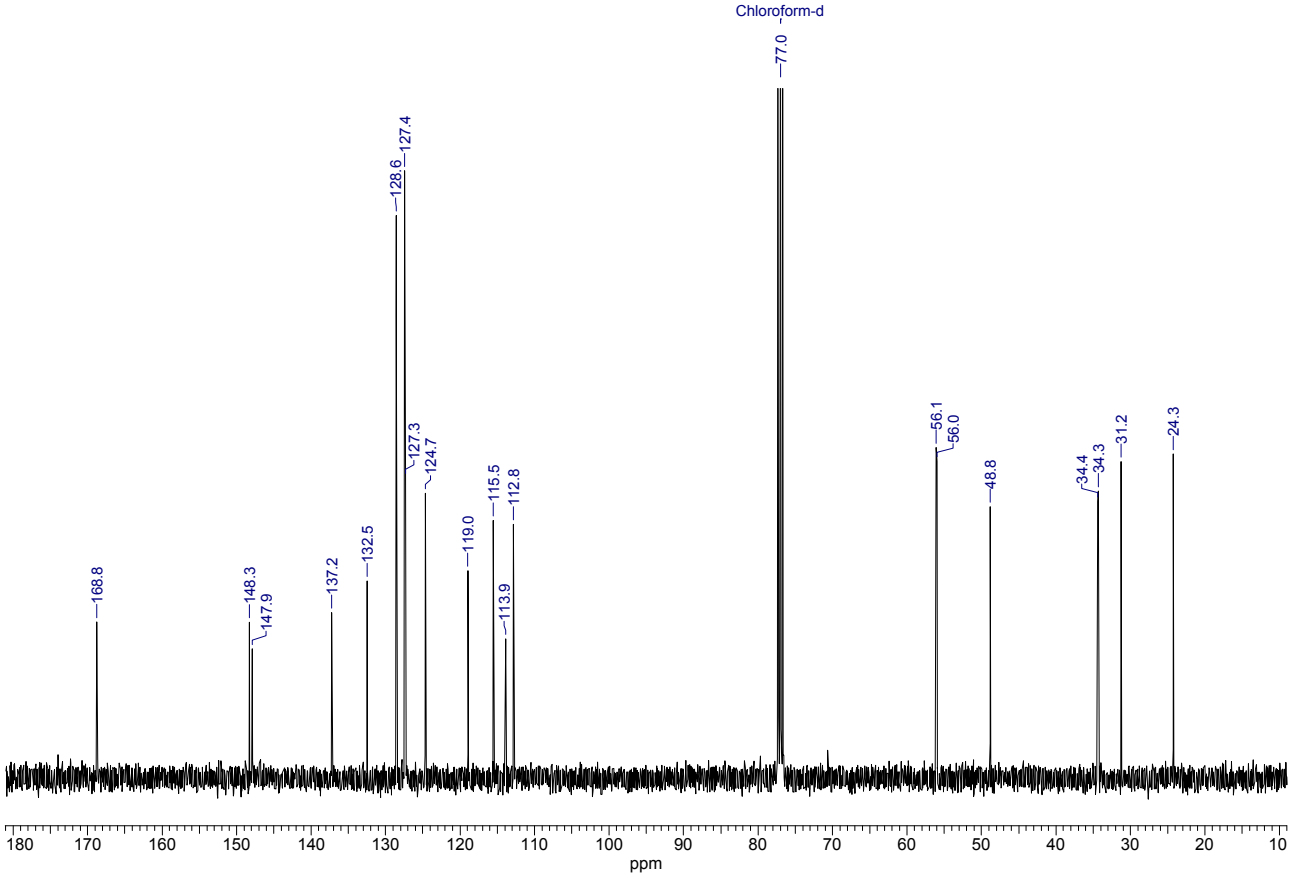

MeO
6'
1'
4
2
CHO
MeO
3'
2'
Br
9e
Chloroform-d
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm

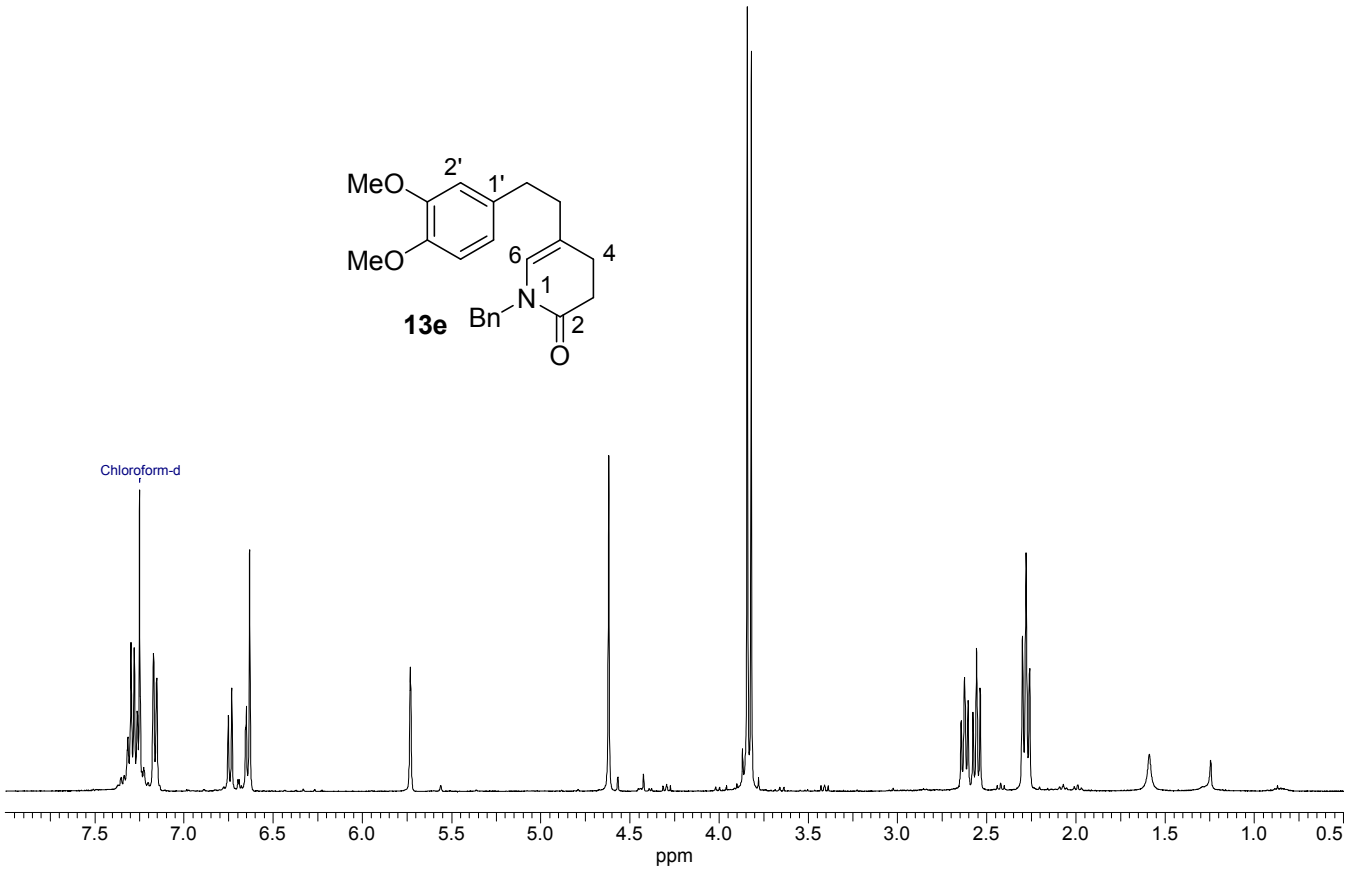

Chloroform-d
77.0
202.2
148.4
148.0
132.5
115.6
113.0
56.1
43.0
34.8
22.6
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

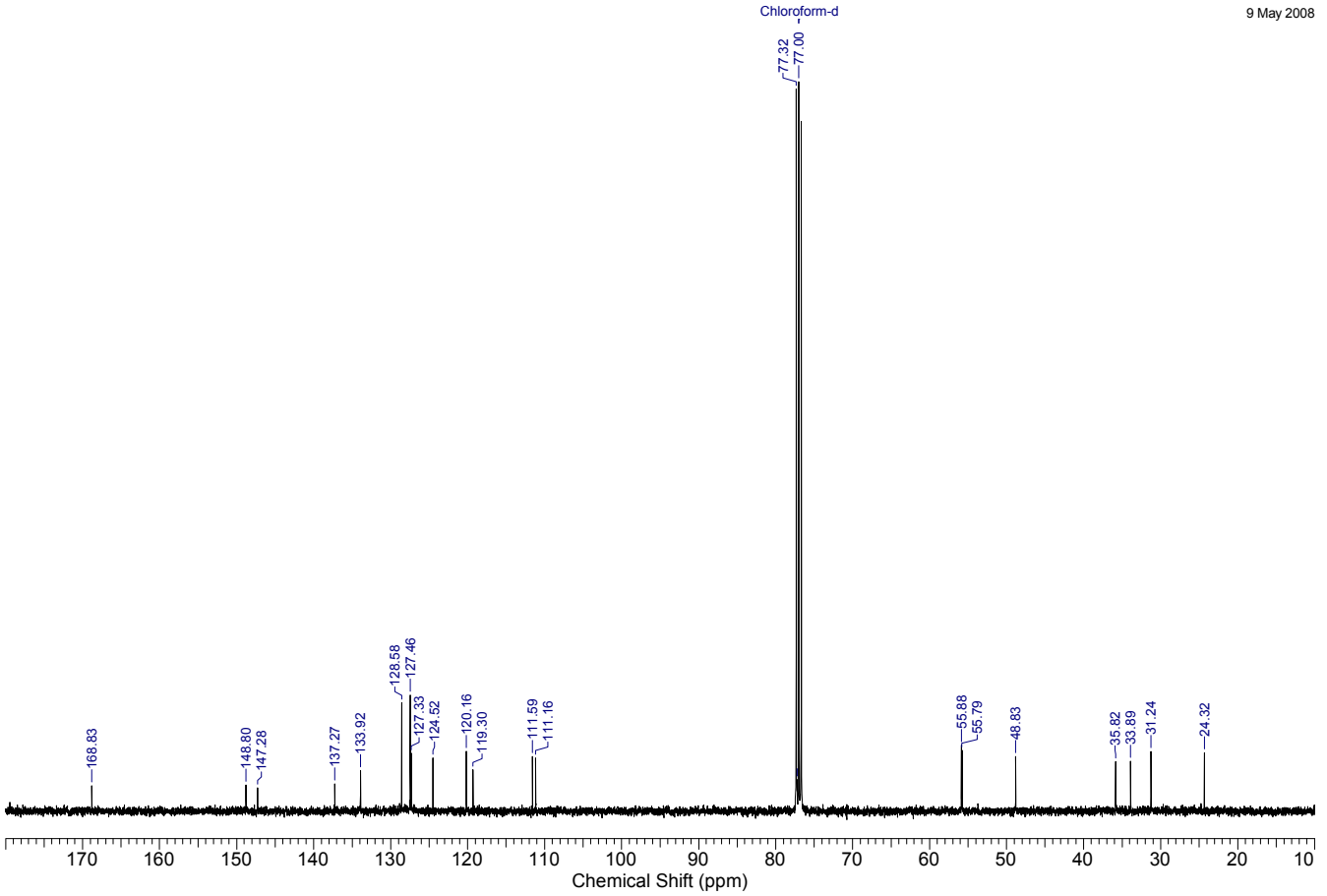

Br
CHO
2'
1'
6
3'
4
MeO
6'
EtO2C
1
OMe
11e
Chloroform-d
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm

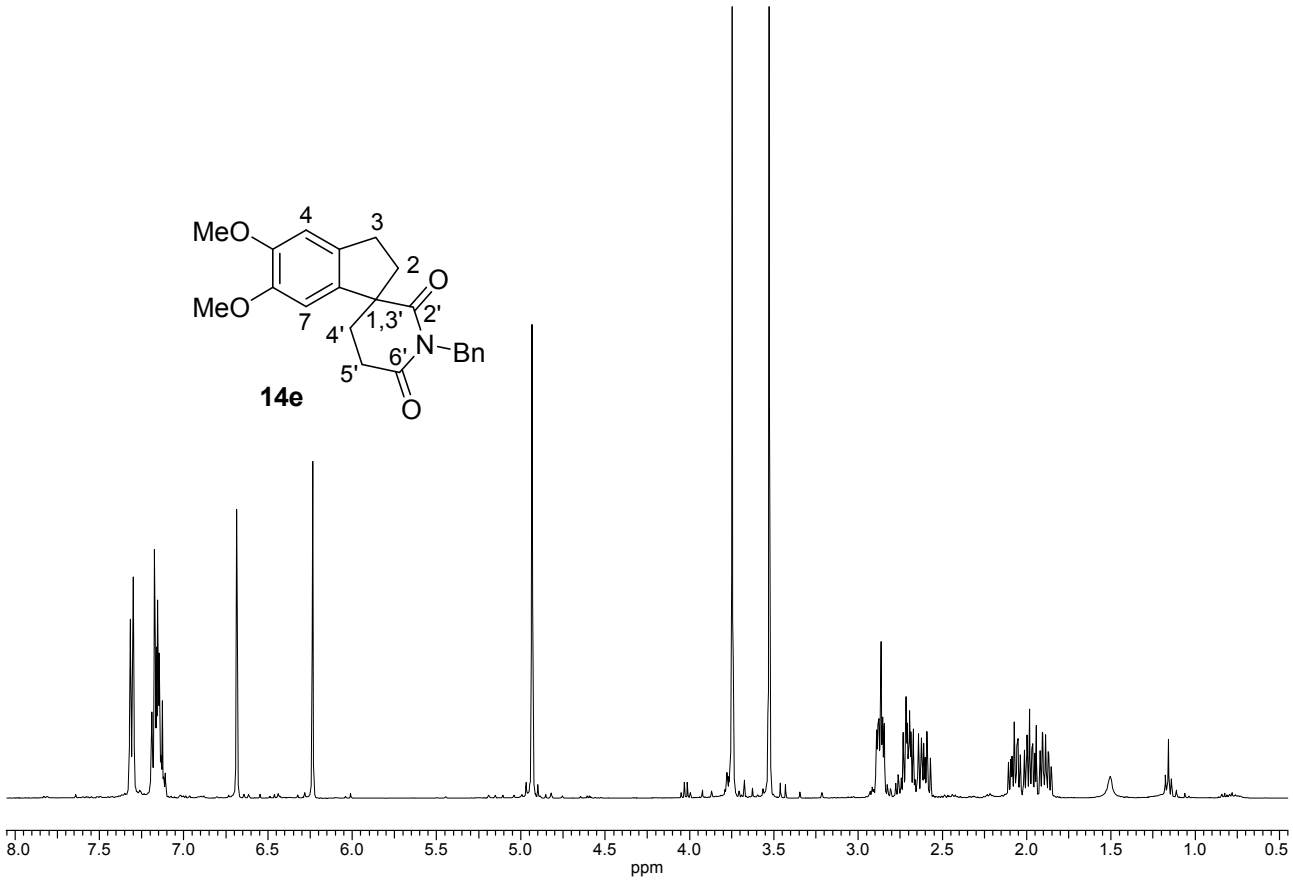

Chloroform-d
77.0
203.8
172.9
148.4
148.1
132.4
115.6
113.0
60.5
56.1
50.6
33.2
31.5
29.1
23.6
14.2
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm


MeO
MeO
Br
Bn
O
N
1
2
4
6
6'
1'
2'
3'
12e
Chloroform-d
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
ppm

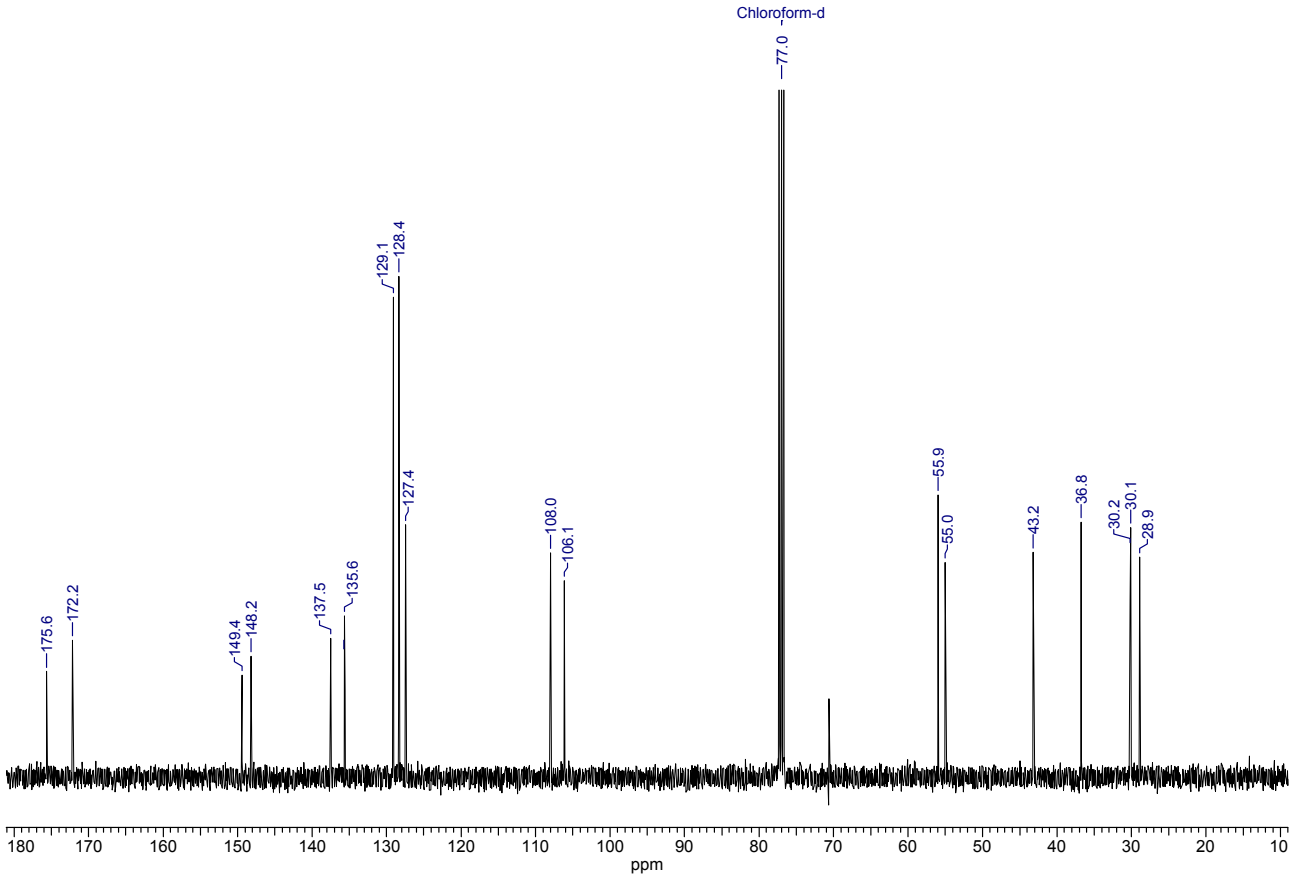

Chloroform-d
77.0
168.8
148.3
147.9
137.2
132.5
128.6
127.4
127.3
124.7
119.0
115.5
113.9
112.8
56.1
56.0
48.8
34.4
34.3
31.2
24.3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

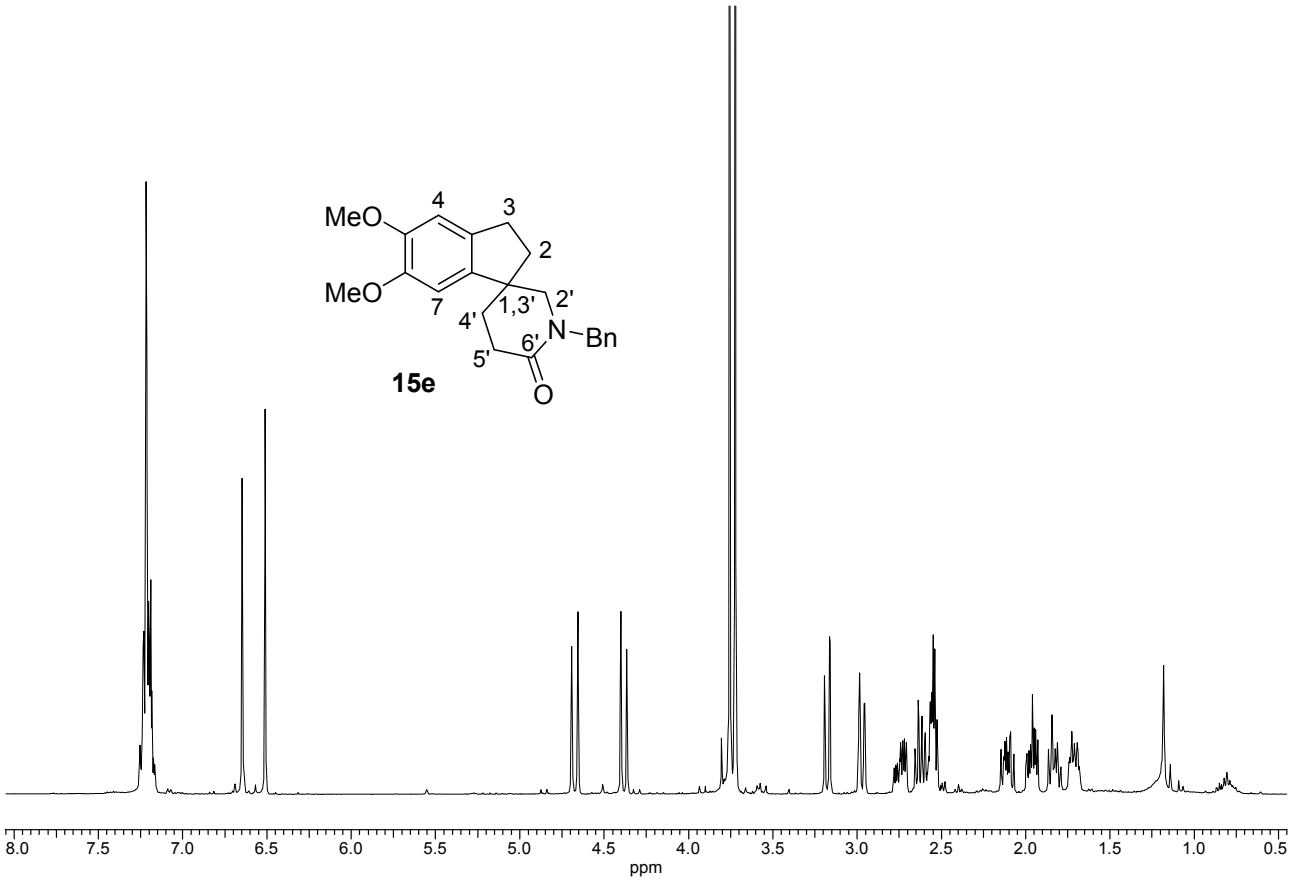

MeO
MeO
2'
1'
6
4
1
N
Bn
2
O
13e
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

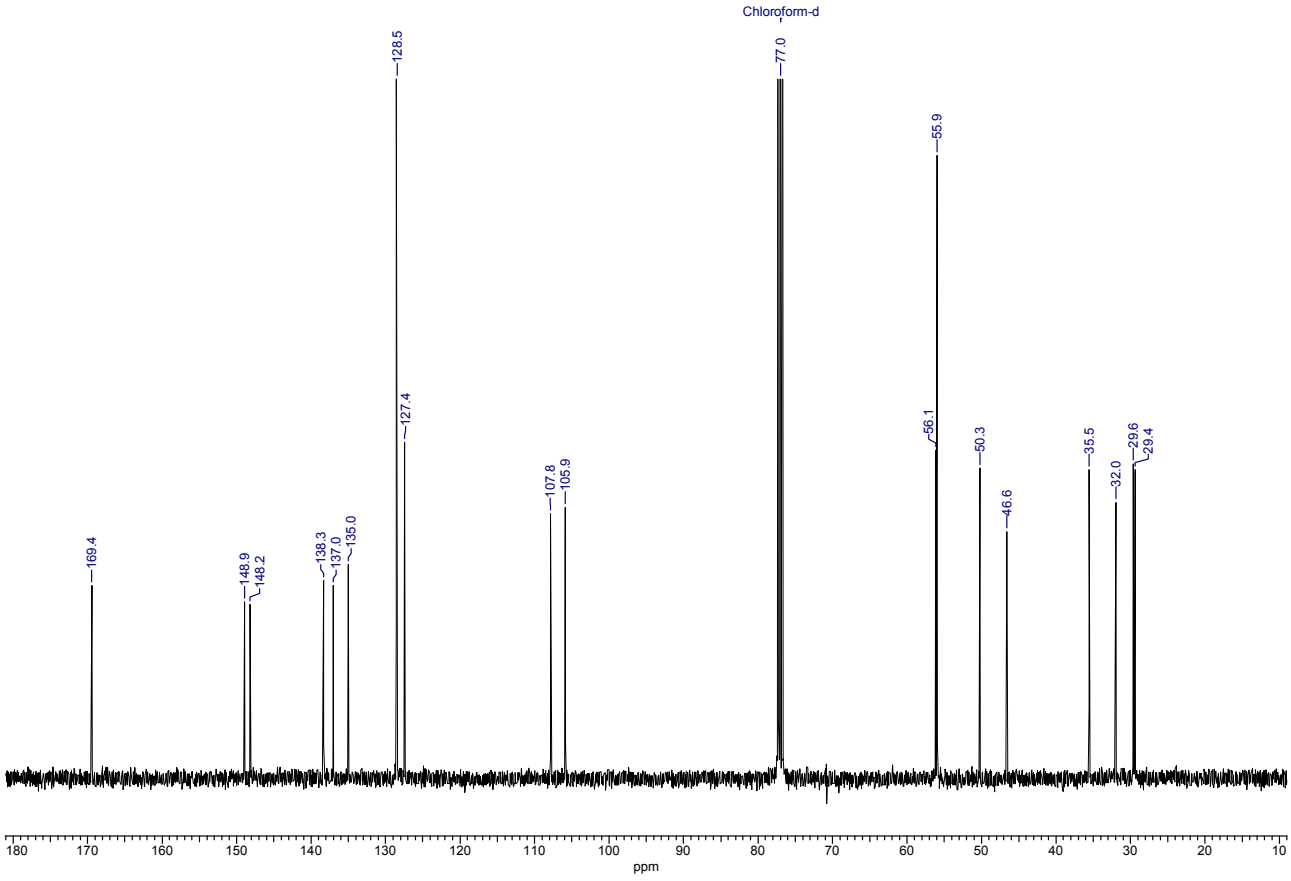

Chloroform-d
9 May 2008
77.32
77.00
168.83
148.80
147.28
137.27
133.92
128.58
127.46
127.33
124.52
120.16
119.30
111.59
111.16
55.88
55.79
48.83
35.82
33.89
31.24
24.32
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
Chemical Shift (ppm)

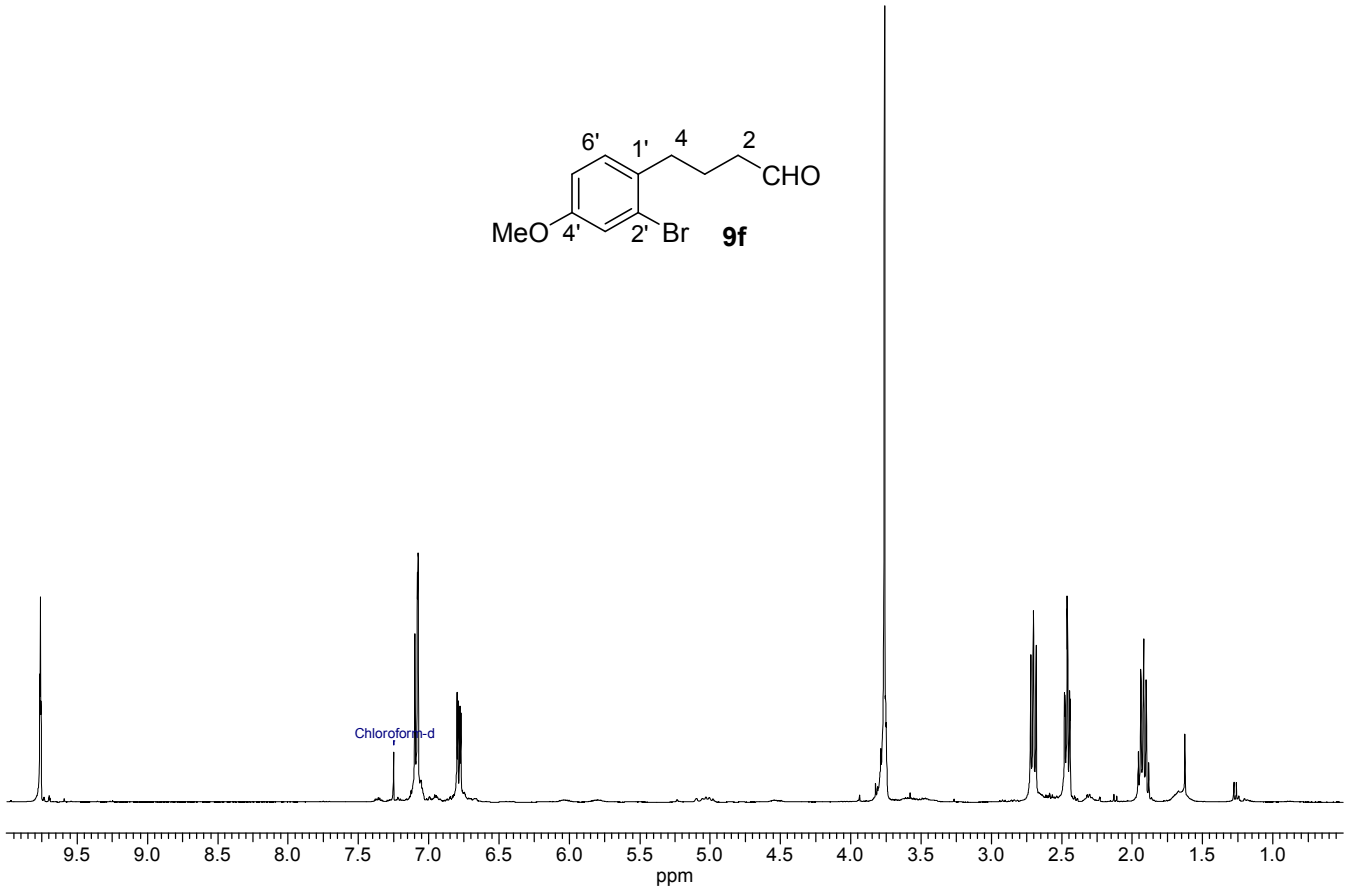

MeO
MeO
4
3
2
O
7
1,3'
2'
4'
N
Bn
6'
5'
O
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

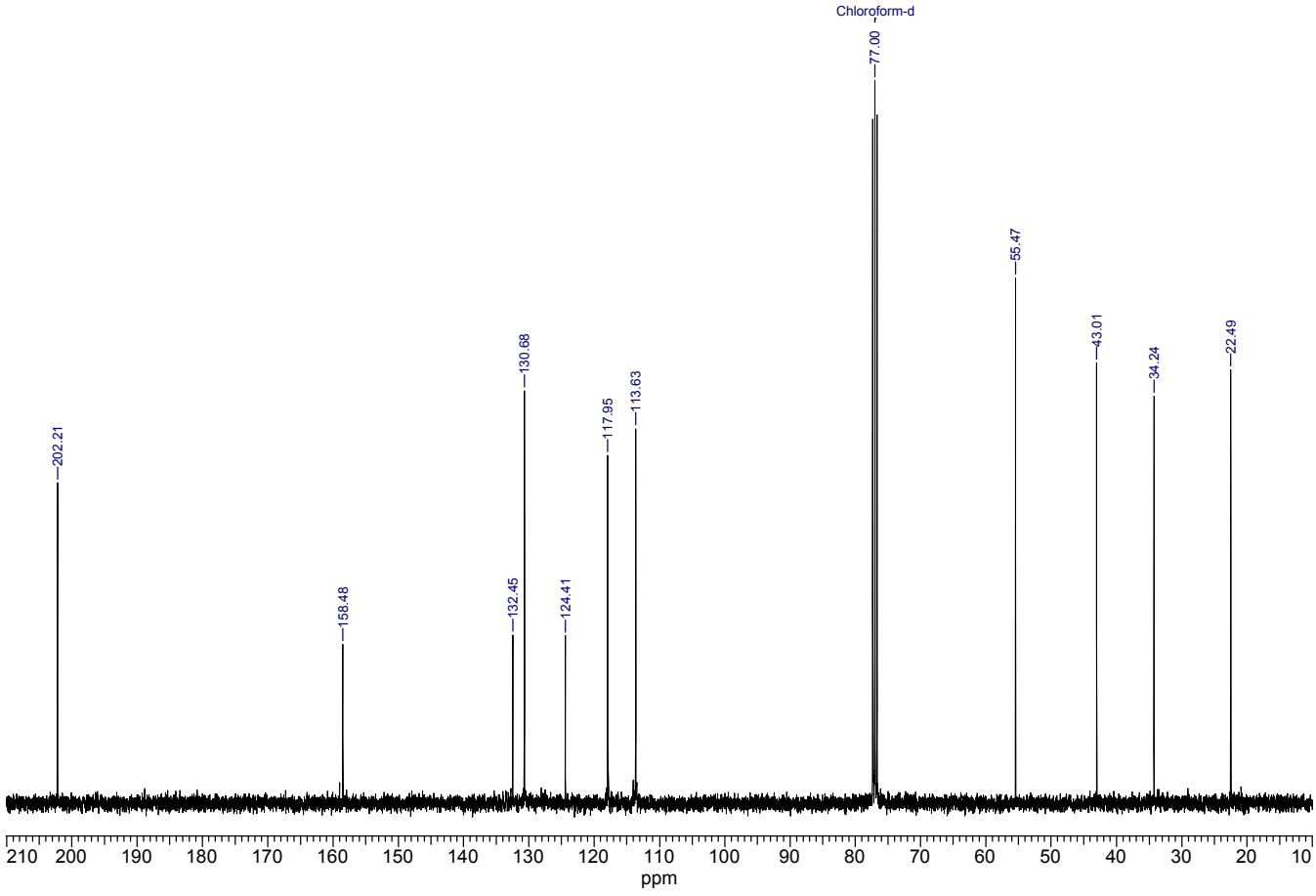
14e

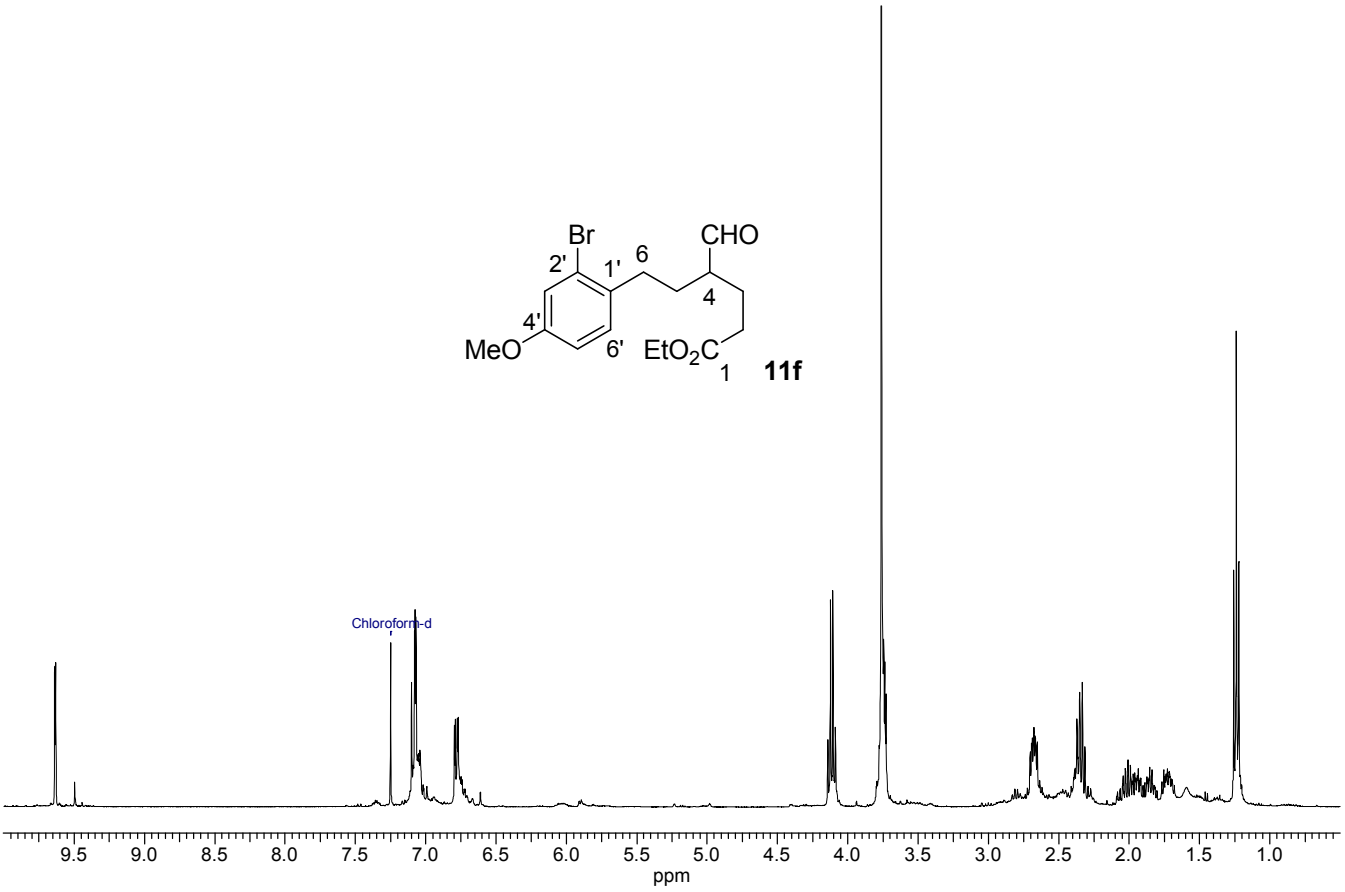

Chloroform-d
77.0
175.6
172.2
149.4
148.2
137.5
135.6
129.1
128.4
127.4
108.0
106.1
55.9
55.0
43.2
36.8
30.2
30.1
28.9
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


MeO
MeO
4
3
2
1,3'
2'
4'
N
Bn
6'
5'
7
O
15e
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
ppm

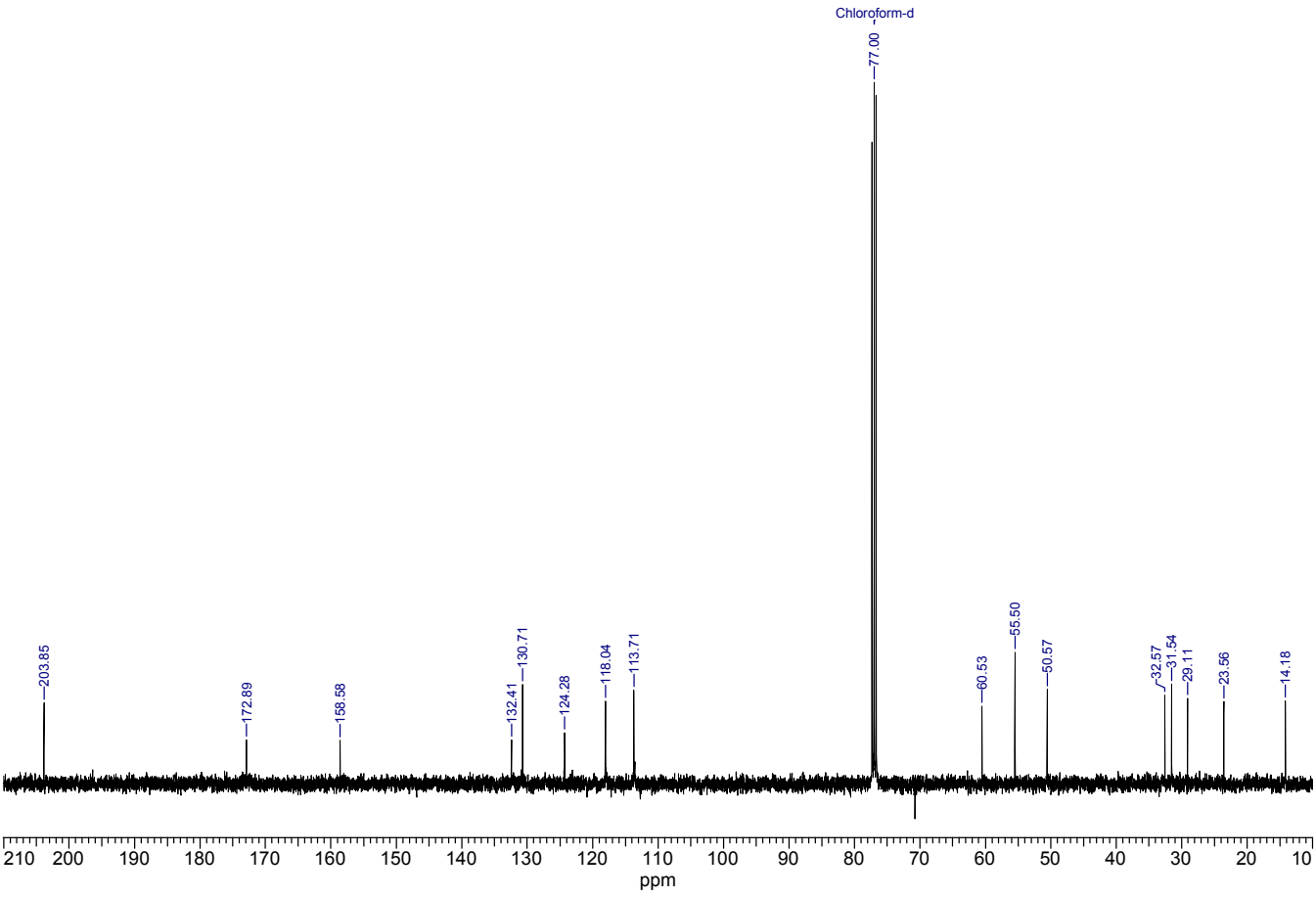

Chloroform-d
169.4
148.9
148.2
138.3
137.0
135.0
128.5
127.4
107.8
105.9
77.0
56.1
55.9
50.3
46.6
35.5
32.0
29.6
29.4
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

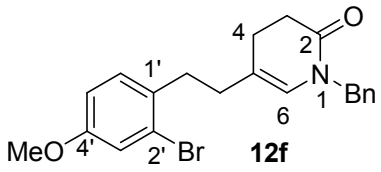

6'
1'
4
2
CHO
MeO
4'
2'
Br
9f
Chloroform-d
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm


Chloroform-d
77.00
202.21
158.48
132.45
130.68
124.41
117.95
113.63
55.47
43.01
34.24
22.49
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm


Br
CHO
2'
1'
6
4
4'
MeO
6'
EtO2C
1
Chloroform-d
9.5 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
ppm

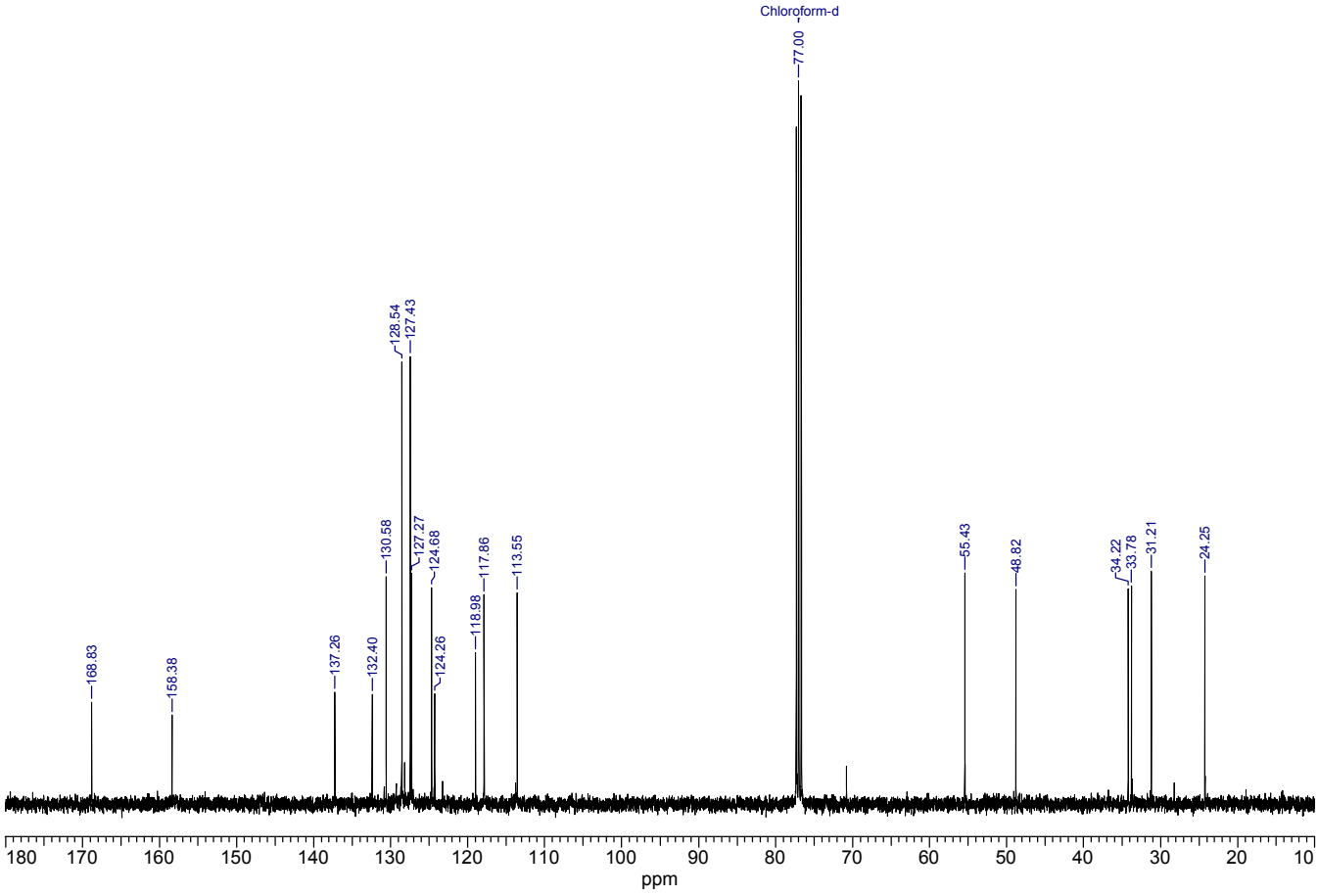
11f

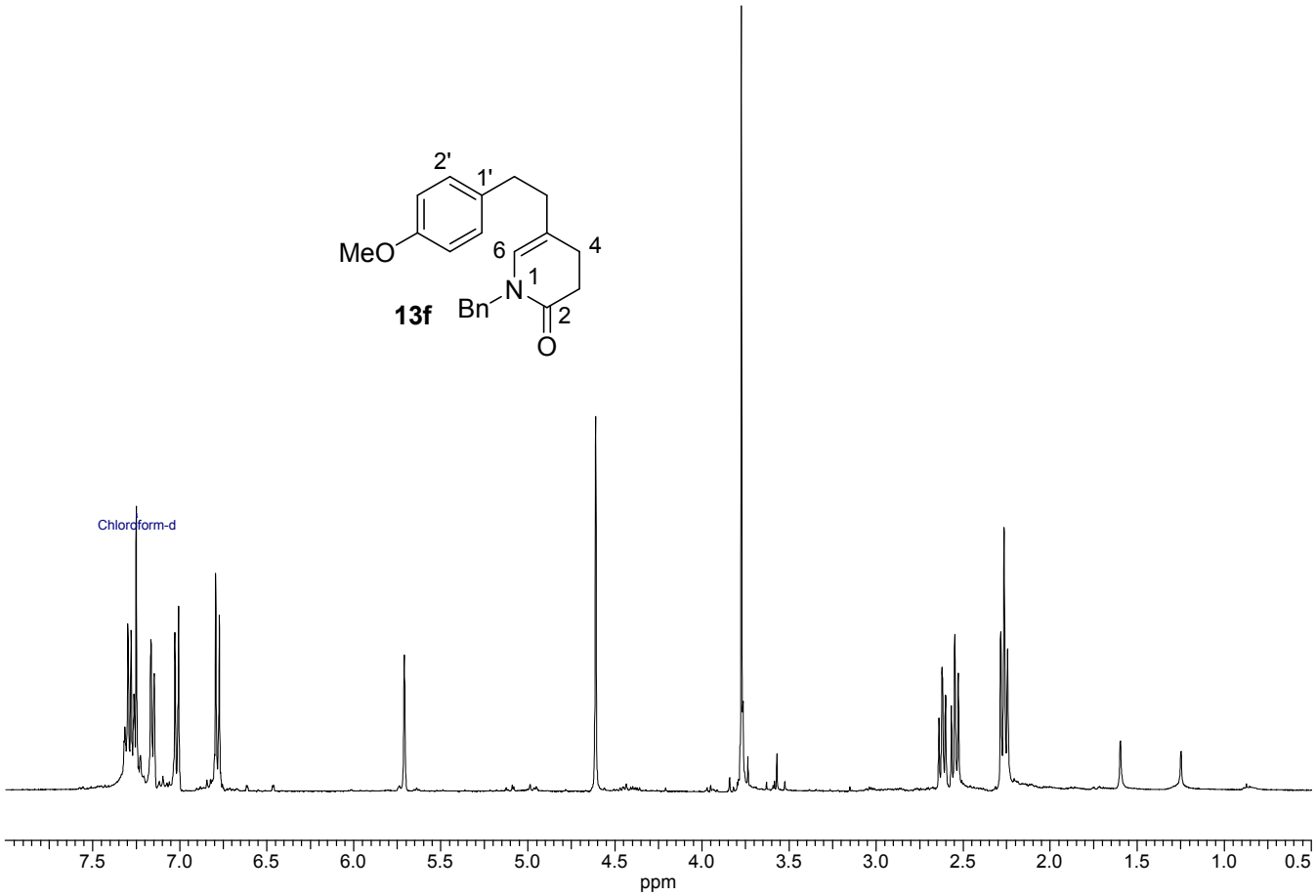

Chloroform-d
77.00
203.85
172.89
158.58
132.41
130.71
124.28
118.04
113.71
60.53
55.50
50.57
32.57
31.54
29.11
23.56
14.18
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm


4
O
2
1'
N
Bn
1
6
MeO
4'
2'
Br

12f

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
ppm


Chloroform-d
77.00
128.54
127.43
130.58
127.27
124.68
117.86
113.55
168.83
158.38
137.26
132.40
124.26
118.98
55.43
48.82
34.22
33.78
31.21
24.25
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


2'
1'
MeO
6
4
N
1
Bn
2
O
13f
Chloroform-d
7.5
7.0
6.5
6.0
5.5
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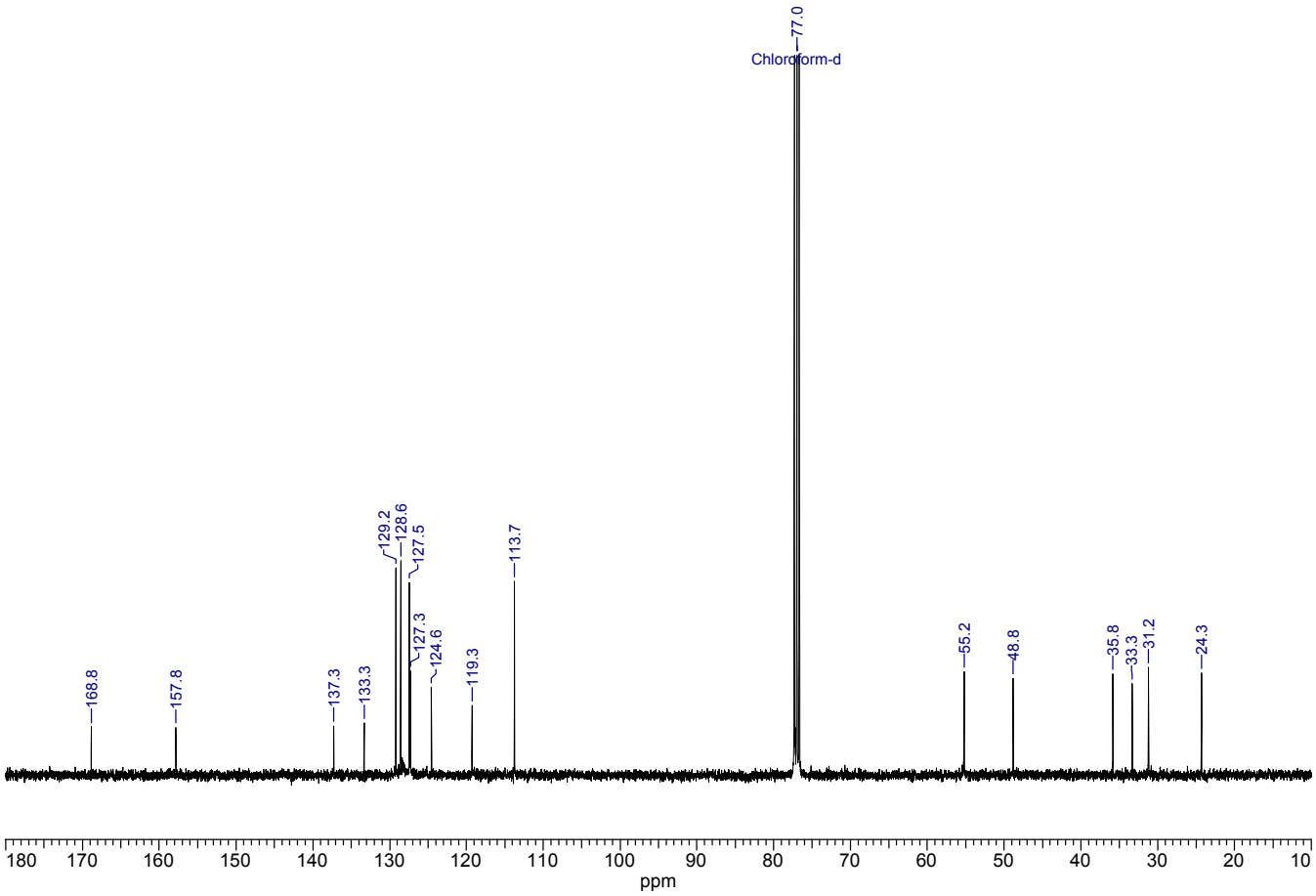
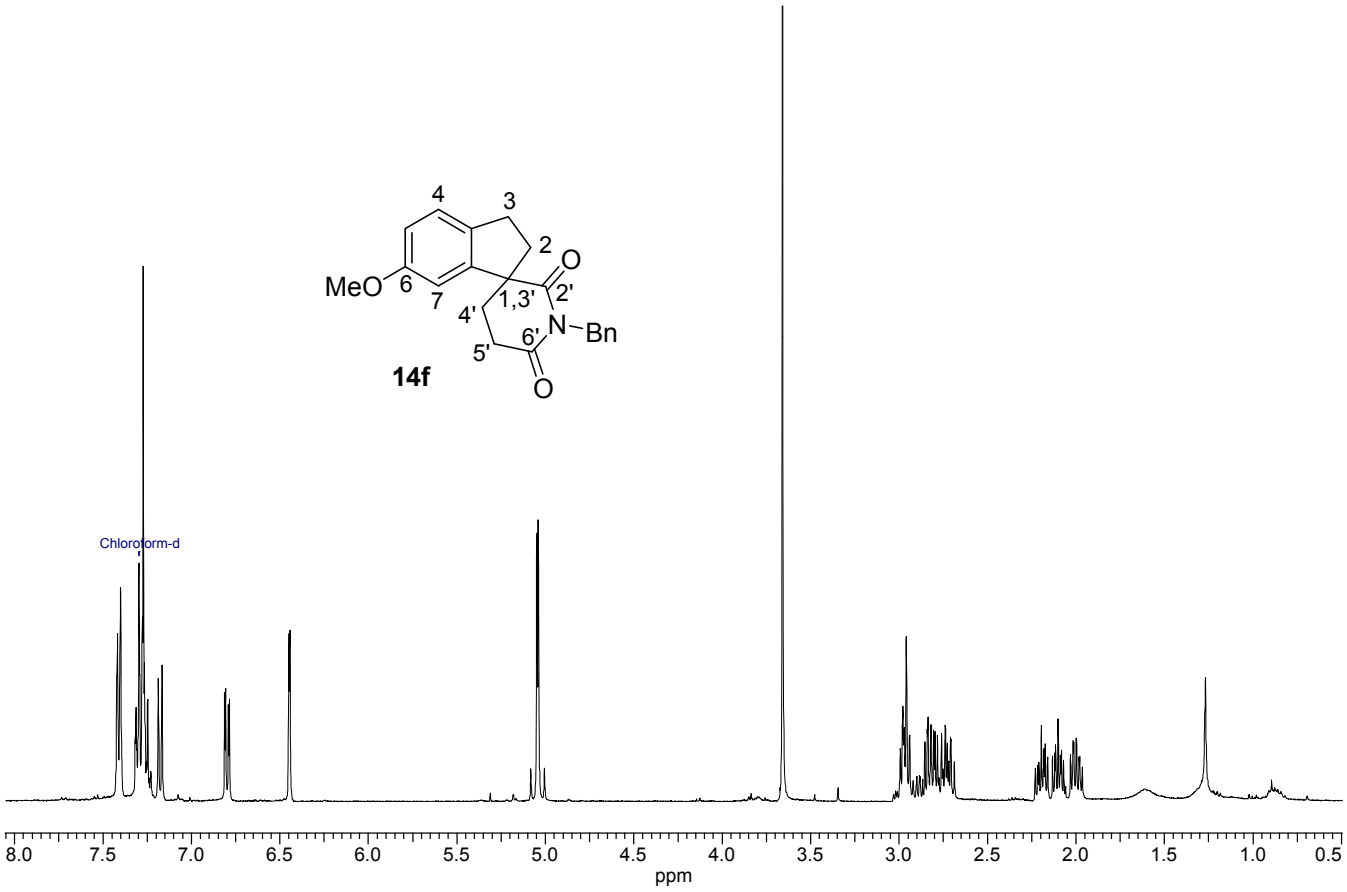
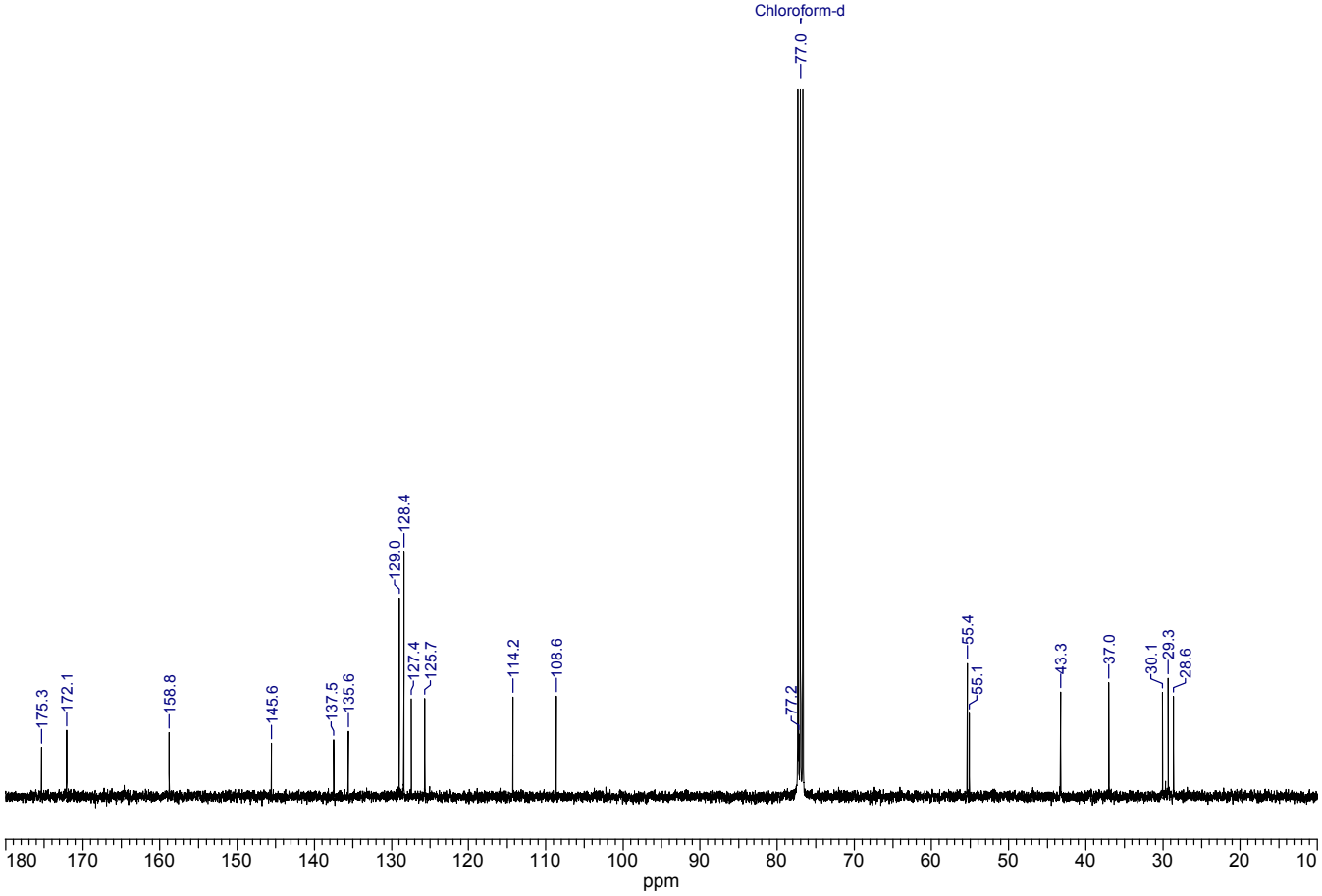
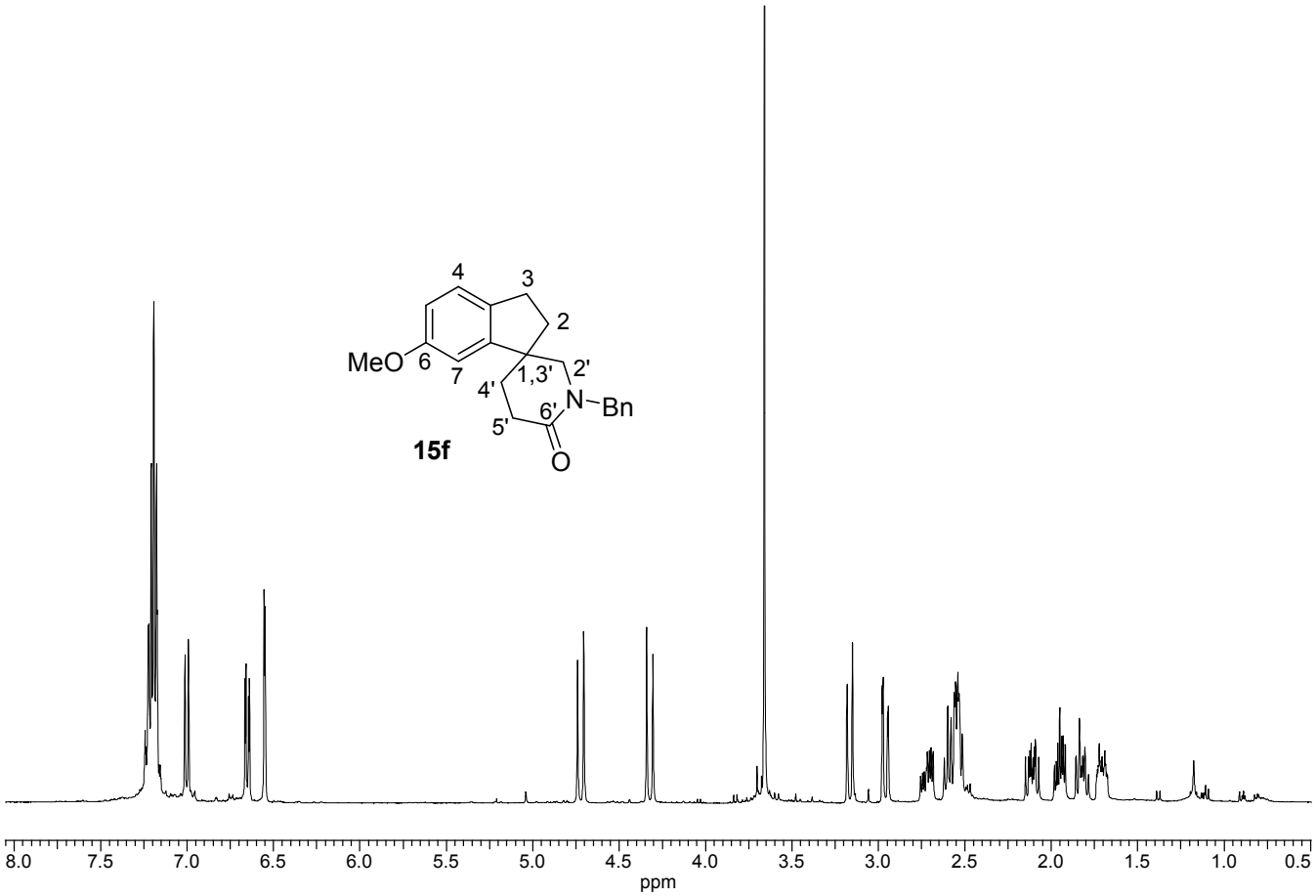
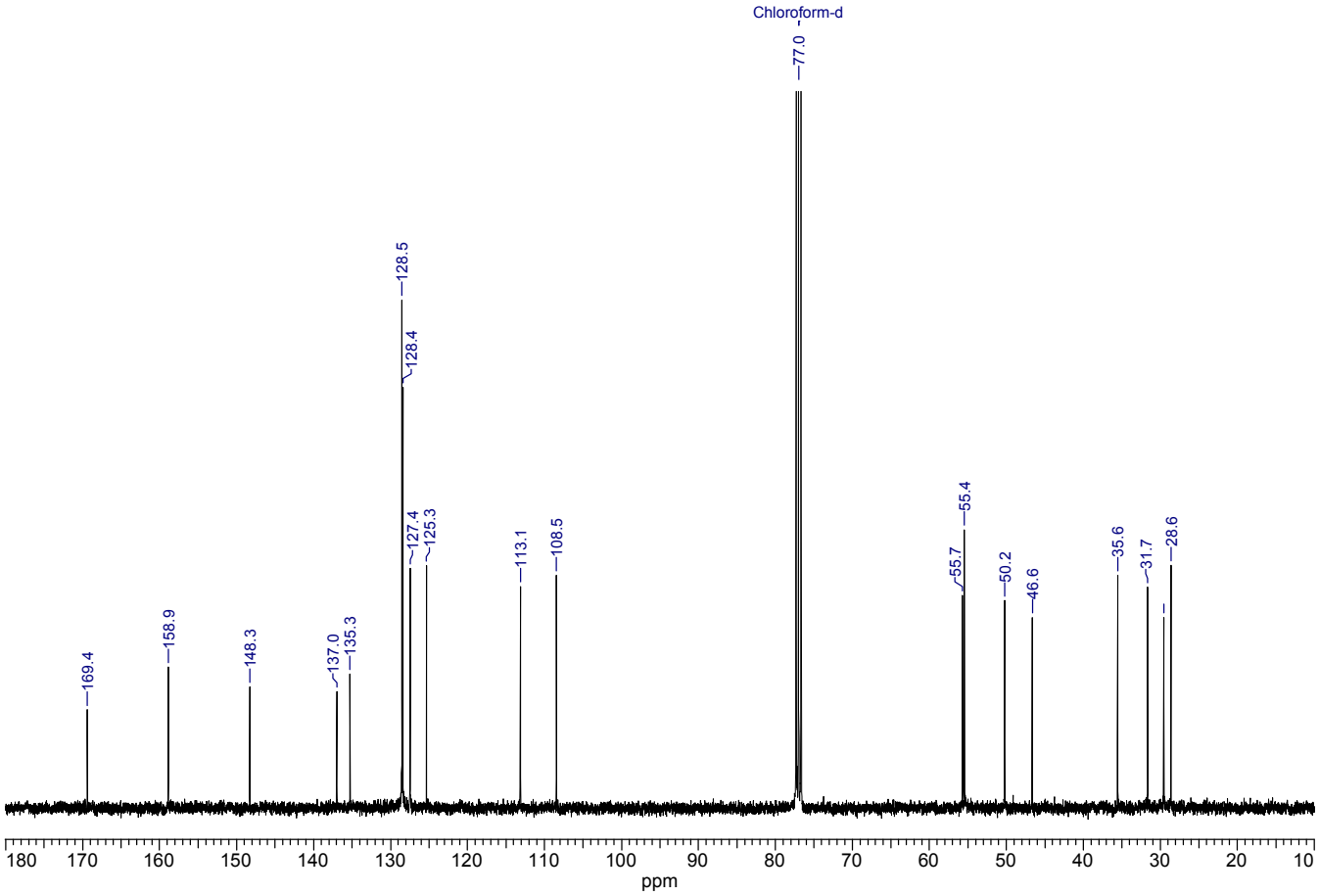
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


77.0
Chloroform-d
168.8
157.8
137.3
133.3
129.2
128.6
127.5
127.3
124.6
119.3
113.7
55.2
48.8
35.8
33.3
31.2
24.3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


4
3
2
O
MeO
6
7
1,3'
2'
4'
N
Bn
6'
5'
O
14f
Chloroform-d
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
ppm


Chloroform-d
77.0
175.3
172.1
158.8
145.6
137.5
135.6
129.0
128.4
127.4
125.7
114.2
108.6
77.2
55.4
55.1
43.3
37.0
30.1
29.3
28.6
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


4
3
2
MeO
6
7
1,3'
2'
4'
6'
N
Bn
5'
O
15f
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
ppm


Chloroform-d
77.0
128.5
128.4
127.4
125.3
113.1
108.5
169.4
158.9
148.3
137.0
135.3
55.7
55.4
50.2
46.6
35.6
31.7
28.6
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm