Supporting Information

Formation of pentacyclic structures by a domino sequence on cyclic enamides

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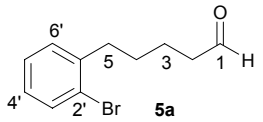
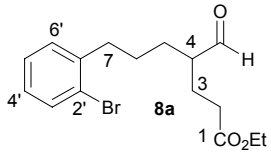
Contents

General: ^{1}H and ^{13}C NMR: Bruker Avance 400, spectra were recorded at 295 K in $CDCl_3$. Chemical shifts are calibrated to the residual proton and carbon resonance of the solvent: $CDCl_3$ (δH 7.25, δC 77.0 ppm). HRMS (FT-ICR): Bruker Daltonic APEX 2 with electron spray ionization (ESI). Analytical LC-MS: HP 1100 Series connected with an ESI MS detector Agilent G1946C, 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: J. T. Baker silica gel 43-60 µm. Thin-layer chromatography Machery-Nagel Polygram Sil G/UV_{254}. 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.



5a

5-(2-Bromophenyl)pentanal (5a): To a stirred solution of $Pd(OAc)_2$ (47.6 mg, 0.21 mmol), pentenylalcohol (1.53 mL, 14.8 mmol), triethylbenzylammonium chloride (2.4 g, 10.6 mmol) and $NaHCO_3$ (1.78 g, 21.2 mmol) in DMF (25 mL) was added iodobromobenzene **4a** (3.0 g, 10.6 mmol) and the resulting solution was heated at 40 °C for 24 h. The mixture was treated with aqueous NH_4Cl solution and then extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the solvent and purification of the crude material by flash chromatography (ethyl acetate/hexane, 1:19) furnished the aldehyde **5a** (1.78 g, 70%) as colorless oil. According to NMR analysis, a small amount of the branched aldehyde was present as well. ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 9.76 (s, 1H, CH=O), 7.51 (d, *J* = 8.7 Hz, 1H, 3'-H), 7.27–7.14 (m, 2H, Ar-H), 7.10–6.97 (m, 1H, Ar-H), 2.74 (t, *J* = 7.4 Hz, 2H, 5-H), 2.47 (dt, *J* = 7.4, 1.5 Hz, 2H, 2-H), 1.80–1.55 (m, 4H, 3-H, 4-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 202.4 (CH=O), 141.2 (C-1'), 132.8 (C-3'), 130.3 (CH), 127.6 (CH), 127.4 (CH), 124.3 (C-2'), 43.6 (C-5), 35.8 (C-2), 29.3 (C-4), 21.7 (C-3).

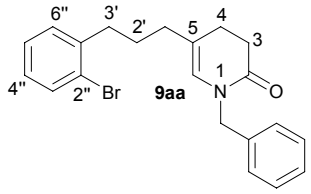


8a

Ethyl 7-(2-bromophenyl)-4-formylheptanoate (8a): To a magnetically stirred solution of aldehyde **5a** (2.38 g, 9.87 mmol) in C_6H_6 (10 mL) was added anhydrous K_2CO_3 (4.1 g, 29.6 mmol) followed by pyrrolidine (1.63 mL, 19.7 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 × 20 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to provide the crude enamine **7a**.

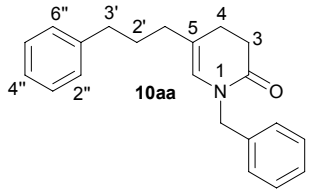
To the crude enamine**7a** in CH_3CN (10 mL) at 5 °C were added molecular sieves (4 Å, 2 g) followed by ethyl acrylate (1.88 mL, 15.8 mmol). The resultant mixture was stirred for 2 h at room temperature, and then refluxed for 2 h. After cooling of the mixture to room temperature, AcOH (3 mL) in H_2O (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 × 20 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, 1:8) furnished the aldehyde ester **8a** (2.1 g, 64% for two steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 9.59 (s, 1H, CH=O), 7.50 (dd, *J* = 7.9, 1.0 Hz, 1H, 3'-H), 7.20 (dt, *J* = 7.1, 1.0 Hz, 1H, Ar-H), 7.18 (dd, *J* = 7.7, 2.0 Hz, 1H, Ar-H), 7.04 (ddd, *J* = 9.2, 7.9, 2.0 Hz, 1H, Ar-H), 4.11 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 2.73 (t, *J* = 7.4 Hz, 2H, 7-H), 2.42–2.20 (m, 3H), 2.05–1.87 (m, 1H), 1.87–1.42 (m, 5H), 1.23 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 204.1 (CH=O), 172.9 (OC=O), 140.9 (C-1'), 132.8 (C-3'), 130.3

(CH), 127.7 (CH), 127.4 (CH), 124.3 (C-2'), 60.5 (OCH_2CH_3), 50.9 (C-4), 36.0 (C-7), 31.6 (C-2), 28.3 (CH_2), 27.1 (CH_2), 23.6 (C-3), 14.2 (OCH_2CH_3).



1-Benzyl-5-[3-(2-bromophenyl)propyl]-3,4-dihydropyridin-2(1*H*)-one (9aa): To a stirred solution of the 4-formylheptanoate **8a** (400 mg, 1.2 mmol) in CH_2ClCH_2Cl (3 mL) at room temperature, were added sequentially benzylamine (0.38 mL, 3.5 mmol) and AcOH (0.15 mL, 1.8 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 × 12 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, 4:6) furnished the cyclic enamide **9aa** (360 mg, 83%) as brown viscous oil. IR (neat): ν_{max}/cm^{-1} = 3063, 3030, 2925, 2838, 1667, 1496, 1437, 1410, 1211, 1022, 751, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.50 (dd, *J* = 7.9, 1.0 Hz, 1H, 3''-H), 7.37-7.17 (m, 5H, Ar-H), 7.18 (dd, *J* = 7.4, 1.0 Hz, 1H, Ar-H), 7.12 (dd, *J* = 7.4, 1.8 Hz, 1H, Ar-H), 7.03 (dt, *J* = 7.6, 1.8 Hz, 1H, Ar-H), 5.80 (s, 1H, 6-H), 4.67 (s, 2H, NCH_2Ph), 2.65 (2H, CH_2Ar) and 2.57 (2H, 1'-H) [2 t, *J* = 7.9 Hz], 2.28 (2H, 4-H) and 2.07 (2H, 3-H) [2 t, *J* = 7.9 Hz], 1.69 (quintet, *J* = 7.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 168.9 (NC=O), 141.3 (C-1''), 137.3 (C), 132.8 (C-3''), 130.3 (CH), 128.6 (2C, CH), 127.6 (CH), 127.5 (2C, CH), 127.4 (CH), 127.3 (CH), 124.3 (C-2''), 124.2 (C-6), 119.6 (C-5), 48.8 (NCH_2Ph), 35.6 (C-3'), 33.3 (C-1'), 31.2 (C-3), 27.6 (CH_2), 24.1(C-4); HRMS (ESI): $[M+H]^+$ calcd for $C_{21}H_{23}BrNO$ 384.0957, found 384.0957.

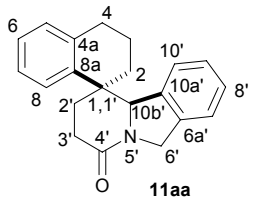
Palladium-catalyzed spiro cyclization of 5-(bromophenyl)propyl-substituted enamide 9aa: To a solution of the bromoenamide **9aa** (146 mg, 0.38 mmol) in anhydrous DMF (2.5 mL), in an oven dried Schlenk tube fitted with a rubber septum, were added biphenyl ligand[1] **12** (29.9 mg, 20 mol%), Cs_2CO_3 (495 mg, 1.52 mmol) and $Pd(OAc)_2$ (8.5 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 d. 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, 4:6) furnished as the first fraction the debromoenamide **10aa** (34 mg, 29%) as brown viscous oil. Further elution of the column using ethyl acetate/hexane (7:3) as eluent furnished the spiroamide **11aa** (59 mg, 51%) as a colorless solid, which was recrystallized from a mixture of CH_2Cl_2 and hexane.



1-Benzyl-5-(3-phenylpropyl)-3,4-dihydropyridin-2(1*H*)-one (10aa): IR (neat): ν_{max}/cm^{-1} = 2933, 2834, 1665, 1515, 1495, 1453, 1416, 1260, 1155, 1029, 703; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.38–7.02 (m, 10H, Ar-H), 5.75 (s, 1H, 6-H), 4.66 (s, 2H, NCH_2Ph), 2.56 (2H, CH_2Ph) and 2.54 (2H, C-1') [2 t, *J* = 7.4 Hz], 2.25 (2H, 4-H) and 2.01 (2H, 3-H) [2 t, *J* = 7.9 Hz], 1.69 (quintet, *J* = 7.37 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 168.8 (NC=O), 141.9 (C-1''), 137.3 (C),

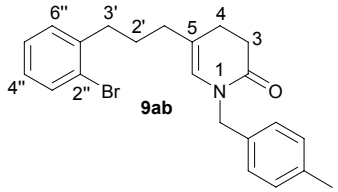
[1] H. Tomori, J. M. Fox and S. L. Buchwald, *J. Org. Chem.*, 2000, **65**, 5334-5341.

128.6 (2C, CH), 128.3 (4C, CH), 127.5 (2C, CH), 127.3 (CH), 125.7 (C-6), 124.1 (CH), 119.8 (C-5), 48.7 (NCH_2Ph), 35.1 (CH_2Ph), 33.1 (C-1'), 31.2 (C-3), 29.0 (CH_2), 24.1 (C-4); HRMS (ESI): $[M+H]^+$ calcd for $C_{21}H_{24}NO$ 306.1852, found 306.1852.



11aa

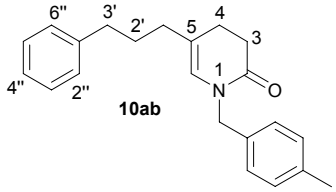
2',3,3',4,6',10b'-Hexahydro-2*H*,4'*H*-spiro[naphthalene-1,1'-pyrido[2,1-*a*]isoindol]-4'-one (11aa): m.p. 223–225 °C (hexane/CH_2Cl_2); IR (neat): ν_{max}/cm^{-1} = 3056, 2927, 2860, 1667, 1604, 1486, 1445, 1423, 1359, 1345, 1276, 1220, 1157, 758, 736, 720, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.20 (d, *J* = 7.6 Hz, 1H, 10'-H), 7.08 (t, *J* = 7.6 Hz, 1H, 8'-H), 6.93 (d, *J* = 7.6 Hz, 1H, Ar-H), 6.91 (t, *J* = 7.6 Hz, 1H, 9'-H), 6.84 (t, *J* = 7.6 Hz, 1H, Ar-H), 6.78 (d, *J* = 7.6 Hz, 1H, 7'-H), 6.69 (t, *J* = 7.6 Hz, 1H, Ar-H), 6.59 (d, *J* = 7.6 Hz, 1H, Ar-H), 4.91 (d, 1H) and 4.73 (d, 1H) [*J* = 15.8 Hz, 6'-H], 4.90 (s, 1H, 10b'-H), 2.90–2.72 (m, 2H), 2.60–2.40 (m, 2H), 2.32 (td, *J* = 14.2, 4.6 Hz, 1H), 2.20–1.80 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 172.3 (NC=O), 141.2 (C-8a), 138.7 (C-10a'), 137.0 (C-6a'), 136.0 (C-4a), 128.4 (CH), 127.5 (CH), 127.3 (CH), 127.1 (CH), 125.8 (CH), 125.5 (CH), 122.7 (CH), 122.6 (CH), 70.9 (C-10b'), 49.9 (C-6'), 42.5 (C-(1,1')), 38.9 (C-4), 36.4 (C-2'), 31.1 (C-3'), 30.6 (CH_2), 19.8 (CH_2); HRMS (ESI): $[M+H]^+$ calcd for $C_{21}H_{22}NO$ 304.1696, found 304.1695.



9ab

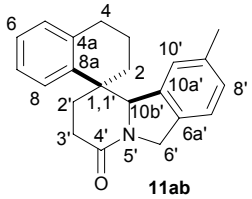
5-[3-(2-Bromophenyl)propyl]-1-(4-methylbenzyl)-3,4-dihydropyridin-2(1*H*)-one (9ab): As described for compound **9aa**, the formyl ester **8a** (2.0 g, 5.8 mmol) in CH_2ClCH_2Cl (10 mL) was reacted with 4-methylbenzylamine (1.5 mL, 11.7 mmol) and AcOH (0.33 mL, 5.9 mmol). Purification of the crude product by flash chromatography (ethyl acetate/hexane, 4:6) furnished the cyclic enamide **9ab** (1.7 g, 72%) as light brown viscous oil. IR (neat): ν_{max}/cm^{-1} = 3052, 3029, 2928, 2861, 1665, 1470, 1439, 1408, 1354, 1268, 1209, 1114, 1022, 958, 752, 658; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.50 (dd, *J* = 7.9, 1.3 Hz, 1H, 3''-H), 7.19 (dt, *J* = 7.9, 1.3 Hz, 1H, Ar-H), 7.17-7.06 (m, 1H, Ar-H), 7.13 (d, 2H) and 7.11 (d, 2H) [*J* = 8.9 Hz, Ar-H], 7.03 (dt, *J* = 7.9, 1.8 Hz, 1H, Ar-H), 5.79 (s, 1H, 6-H), 4.62 (s, 2H, NCH_2toluyl), 2.65 (2H, CH_2Ar) and 2.57 (2H, 1'-H) [2 t, *J* = 7.9 Hz], 2.31 (s, 3H, $ArCH_3$), 2.26 (2H, 4-H) and 2.06 (2H, 3-H) [2 t, *J* = 7.9 Hz], 1.68 (quintet, *J* = 7.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 168.8 (N*C*=O), 141.3 (C-1''), 137.0 (C), 134.3 (C), 132.8 (C-3''), 130.3 (CH), 129.3 (2C, CH), 127.6 (3C, CH), 127.4 (CH), 124.3 (C-2''), 124.2 (C-6), 119.5 (C-5), 48.5 (NCH_2toluyl), 35.6 (CH_2Ar), 33.4 (C-1'), 31.3 (C-3), 27.7 (CH_2), 24.1 (C-4), 21.1 ($ArCH_3$); HRMS (ESI): $[M+H]^+$ calcd for $C_{22}H_{25}BrNO$ 398.1114, found 398.1115.

Palladium-catalyzed spiro cyclization of 5-(bromophenyl)propyl-substituted enamide 9ab: The reaction was performed with the enamide **9ab** (125 mg, 0.31 mmol) in anhydrous DMF (2 mL) with biphenyl ligand **12** (24.7 mg, 20 mol%), Cs_2CO_3 (409 mg, 1.2 mmol) and $Pd(OAc)_2$ (7.0 mg, 10 mol%). After loading of the reagents at room temperature, the mixture was heated to 120 °C, as described for compound **9aa**. Purification of the crude product by flash chromatography (ethyl acetate/hexane, 2:3) first furnished the debromoenamide **10ab** (30 mg, 30%) as brown viscous oil. Further elution of the column using ethyl acetate/hexane (7:3) as eluent furnished the spiroisoindole **11ab** (46 mg, 46%) as a colorless solid, which was recrystallized from a mixture of CH_2Cl_2 and hexane.



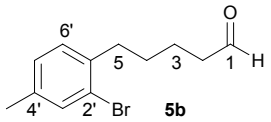
10ab

1-(4-Methylbenzyl)-5-(3-phenylpropyl)-3,4-dihydropyridin-2(1*H*)-one (10ab): IR (neat): ν_{max}/cm^{-1} = 3058, 3024, 2929, 2856, 1667, 1603, 1515, 1496, 1440, 1406, 1267, 1209, 1115, 1023, 959, 750, 700; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.30–7.12 (m, 3H, Ar-H), 7.13 (d, 2H) and 7.11 (d, 2H) [*J* = 8.9 Hz, Ar-H], 7.09 (d, *J* = 7.1 Hz, 2H, Ar-H), 5.74 (s, 1H, 6-H), 4.61 (s, 2H, NCH_2toluyl), 2.60–2.48 (m, 4H) [C-1', C-3'], 2.31 (s, 3H, $ArCH_3$), 2.23 (2H, 4-H) and 2.00 (2H, 3-H) [2 t, *J* = 7.9 Hz], 1.68 (quintet, *J* = 7.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 168.8 (NC=O), 141.9 (C-1''), 137.0 (C), 134.3 (C), 129.3 (2 C, CH), 128.4 (2 C, CH), 128.3 (2 C, CH), 127.6 (2 C, CH), 125.8 (CH), 124.0 (C-6), 119.7 (C-5), 48.5 (N-CH_2toluyl), 35.2 (C-3'), 33.2 (C-1'), 31.2 (C-3), 29.1 (CH_2), 24.1(C-4), 21.1 ($ArCH_3$); HRMS (ESI): $[M+H]^+$ calcd for $C_{22}H_{26}NO$ 320.2009, found 320.2011.



11ab

9'-Methyl-2',3,3',4,6',10b'-hexahydro-2*H*,4'*H*-spiro[naphthalene-1,1'-pyrido[2,1-*a*]isoindol]-4'-one (11ab): m.p. 196–198 °C; IR (neat): ν_{max}/cm^{-1} = 3053, 2924, 2862, 1760, 1723, 1664, 1604, 1487, 1436, 1344, 1265, 1221, 1099, 1040, 765, 738, 697; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.07 (d, *J* = 7.6 Hz, 1H, 8'-H), 6.94 (d, *J* = 7.4 Hz, 1H, 8-H), 6.88 (d, *J* = 7.4 Hz, 1H, 5-H), 6.84 (dt, *J* = 7.4,d 1.3 Hz, 1H, 7-H), 6.69 (t, *J* = 7.4 Hz, 1H, 6-H), 6.59 (d, *J* = 7.6 Hz, 1H, 7'-H), 6.58 (s, 1H, 10'-H), 4.86 (d, 1H) and 4.68 (d, 1H) [*J* = 15.8 Hz, 6'-H], 4.85 (s, 1H, 10b'-H), 2.93–2.76 (m, 2H), 2.58–2.38 (m, 2H), 2.37–2.22 (m, 1H), 2.20–1.80 (m, 5H), 2.07 (s, 3H, $ArCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 172.3 (NC=O), 141.2 (C-8a), 138.9 (C-10'), 137.0 (C), 136.6 (C-4a), 133.1 (C), 128.3 (CH), 128.2 (CH), 127.4 (CH), 125.7 (CH), 125.5 (CH), 123.1 (CH), 122.4 (CH), 70.8 (C-10b'), 49.7 (C-6'), 42.5 (C-(1,1')), 39.0 (C-4), 36.4 (C-2'), 31.1 (C-3'), 30.6 (CH_2), 21.2 ($ArCH_3$), 19.9 (CH_2); HRMS (ESI): $[M+H]^+$ calcd for $C_{22}H_{24}NO$ 318.1852, found 318.1852.



5b

5-(2-Bromo-4-methylphenyl)pentanal (5b): The reaction was performed as described for aldehyde **5a**. Thus, to a mixture of $Pd(OAc)_2$ (60.5 mg, 2 mol%), pentenylalcohol (2.2 mL, 25.2 mmol), triethylbenzylammonium chloride (3.1 g, 13.4 mmol) and $NaHCO_3$ (2.3 g, 26.9 mmol) in DMF (30 mL) was added iodobromide[2] **4b** (4.0 g, 13.4 mmol), followed by stirring of the mixture for 24 h at 40 °C. Purification of the crude material by flash chromatography (ethyl acetate/hexane, 1:19) furnished aldehyde **5b** (2.3 g, 67%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 9.76 (s, 1H, CH=O), 7.34 (s, 1H, 3'-H), 7.07 (1H, 5'-H) and 7.02 (1H, 6'-H) [2 d, *J* = 7.6 Hz], 2.70 (t, *J* = 7.4 Hz, 2H, 5-H), 2.46 (dt, *J* = 7.4, 1.5 Hz, 2H, 2-H), 2.28 (s, 3H, $ArCH_3$), 1.80–1.52 (m, 4H, 3-H, 4-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 202.5 (CH=O), 138.0 (C-1'), 137.5 (C-4'), 133.2 (CH), 130.0 (CH), 128.2 (CH), 124.1 (C-2'), 43.7 (C-5), 35.3 (C-2), 29.4 (C-4), 21.7 (C-3), 20.5 ($ArCH_3$).

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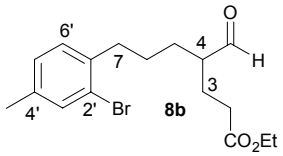
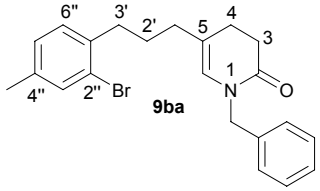
[2] (a) R. R. Bard, J. F. Bunnett and R. P. Traber, *J. Org. Chem.*, 1979, **44**, 4918-4924; (b) G. P. M. van Klink, H. J. R. de Boer, G. Schat, O. S. Akkerman, F. Bickelhaupt and A. L. Spek, *Organometallics*, 2002, **21**, 2119-2135.

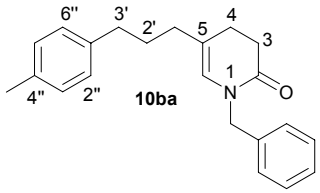


Ethyl 7-(2-bromo-4-methylphenyl)-4-formylheptanoate (8b): The reaction was performed with aldehyde **5b** (2.3 g, 9.0 mmol), pyrrolidine (1.5 mL, 18.0 mmol), K_2CO_3 (3.73 g, 27.0 mmol), molecular sieves (4 Å, 2 g) and ethyl acrylate (1.4 mL, 12.6 mmol) as described above (see **8a**). Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:8) furnished the aldehyde ester **8b** (2.1 g, 60% for two steps) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 9.59 (s, 1H, CH=O), 7.34 (s, 1H, 3'-H), 7.05 (1H, 5'-H) and 7.01 (1H, 6'-H) [2 d, J = 7.9 Hz], 4.12 (q, J = 7.1 Hz, 2H, OCH_2CH$_3$), 2.69 (t, J = 7.6 Hz, 2H, 7-H), 2.45–2.20 (m, 3H), 2.28 (s, 3H, ArCH$_3$), 2.10–1.40 (m, 6H), 1.24 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 204.1 (CH=O), 172.9 (OC=O), 137.7 (C-1'), 137.6 (C-4'), 133.2 (CH), 130.0 (CH), 128.2 (CH), 124.1 (C-2'), 60.5 (OCH$_2$CH$_3$), 50.9 (C-4), 35.5 (CH$_2$Ar), 31.6 (C-2), 28.3 (CH$_2$), 27.2 (CH$_2$), 23.6 (C-3), 20.5 (ArCH$_3$), 14.2 (OCH$_2$$CH_3$).

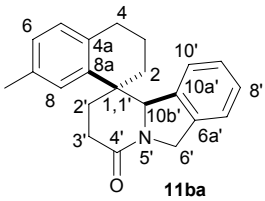


1-Benzyl-5-[3-(2-bromo-4-methylphenyl)propyl]-3,4-dihydropyridin-2(1*H*)-one (9ba): As described for compound **9aa**, the formyl ester **8b** (1.6 g, 4.5 mmol), dissolved in CH_2ClCH_2Cl (7 mL) was reacted with benzylamine (0.98 mL, 9.0 mmol) and AcOH (0.26 mL, 4.5 mmol). Purification of the crude product by flash chromatography (ethyl acetate/hexane, 4:6) as eluent furnished the cyclic enamide **9ba** (1.4 g, 78%) as light brown viscous oil. IR (neat): ν_{max}/cm^{-1} = 3030, 2925, 1666, 1606, 1491, 1440, 1410, 1270, 1211, 1038, 668; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.37–7.18 (m, 6H, Ar-H), 7.00 (s, 2H, Ar-H), 5.79 (s, 1H, 6-H), 4.66 (s, 2H, NCH$_2$Ph), 2.61 (2H, CH$_2$Ar) and 2.57 (2H, C-1') [2 t, J = 7.6 Hz], 2.28 (s, 3H, ArCH$_3$), 2.28 (2H, 4-H) and 2.05 (2H, 3-H) [2 t, J = 7.1 Hz], 1.66 (quintet, J = 7.63 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 168.9 (NC=O), 138.1 (C-1''), 137.5 (C), 137.3 (C), 133.2 (C-3''), 130.0 (CH), 128.6 (2 C, CH), 128.2 (CH), 127.5 (2 C, CH), 127.3 (CH), 124.2 (C-6), 124.0 (C-2''), 119.7 (C-5), 48.8 (NCH$_2$Ph), 35.1 (CH$_2$Ar), 33.3 (C-1'), 31.3 (C-3), 27.8 (CH$_2$), 24.1 (C-4), 20.5 (ArCH$_3$); HRMS (ESI): $[M + H]^+$ calcd for $C_{22}H_{25}BrNO$ 398.1114, found 398.1115.

Palladium-catalyzed spiro cyclization of 5-(bromophenyl)propyl-substituted enamide 9ba: The reaction was performed with the enamide **9ba** (116 mg, 0.29 mmol) in anhydrous DMF (2 mL) with biphenyl ligand[1] **12** (22.9 mg, 20 mol%), Cs_2CO_3 (380 mg, 1.2 mmol) and Pd(OAc)$_2$ (6.5 mg, 10 mol%). After loading of the reagents at room temperature, the mixture was heated to 120 °C, as described for compound **9aa**. Purification of the crude product by flash chromatography (ethyl acetate/hexane, 4:6) first furnished the debromoenamide **10ba** (25 mg, 27%) as brown viscous oil. Further elution using ethyl acetate-hexane (7:3) as eluent furnished the amide **11ba** (45 mg, 49%) as a colorless semi-solid, which was recrystallized from a mixture of CH_2Cl_2 and hexane.

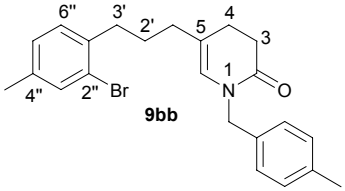


1-Benzyl-5-[3-(4-methylphenyl)propyl]-3,4-dihydropyridin-2(1*H*)-one (10ba): IR (neat): ν_{max}/cm^{-1} = 3030, 2928, 2838, 1665, 1606, 1515, 1496, 1411, 1268, 1212, 1029, 807, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.37–7.18 (m, 5H, Ar-H), 7.06 (d, 2H) and 6.98 (d, 2H) [*J* = 7.9 Hz, Ar-H], 5.75 (s, 1H, 6-H), 4.66 (s, 2H, NCH_2Ph), 2.56 (2H, 3'-H) and 2.50 (2H, 1'-H) [2 t, *J* = 7.6 Hz], 2.30 (s, 3H, $ArCH_3$), 2.25 (2H, 4-H) and 2.01 (2H, 3-H) [2 t, *J* = 7.6 Hz], 1.67 (quintet, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 168.9 (NC=O), 138.8 (C-1''), 137.4 (C), 135.2 (C), 129.0 (2 C, CH), 128.6 (2 C, CH), 128.2 (2 C, CH), 127.5 (2 C, CH), 127.4 (CH), 124.1 (C-6), 119.9 (C-5), 48.8 (NCH_2Ph), 34.7 (C-3'), 33.2 (C-1'), 31.3 (C-3), 29.2 (CH_2), 24.2 (C-4), 21.0 ($ArCH_3$); HRMS (ESI): $[M+H]^+$ calcd for $C_{22}H_{26}NO$ 320.2009, found 320.2009.



11ba

7-Methyl-2',3,3',4,6',10b'-hexahydro-2*H*,4'*H*-spiro[naphthalene-1,1'-pyrido[2,1-*a*]isoindol]-4'-one (11ba): m.p. 60–62 °C; IR (neat): ν_{max}/cm^{-1} = 3046, 2934, 2863, 1761, 1731, 1645, 1502, 1488, 1452, 1349, 1220, 738, 701; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.20 (d, *J* = 7.6 Hz, 1H, 10'-H), 7.07 (t, *J* = 7.6 Hz, 1H, 8'-H), 6.90 (t, *J* = 7.6 Hz, 1H, 9'-H], 6.81 (d, *J* = 7.9 Hz, 1H, 5-H) and 6.76 (d, *J* = 7.6 Hz, 1H, 7'-H), 6.64 (d, *J* = 7.9 Hz, 1H, 6-H), 6.36 (s, 1H, 8-H), 4.88 (d, 1H) and 4.75 (d, 1H) [*J* = 15.8 Hz, 6'-H], 4.87 (s, 1H, 10b'-H), 2.82–2.71 (m, 2H), 2.60–2.40 (m, 2H), 2.32 (td, *J* = 14.0, 4.1 Hz, 1H), 2.20–1.75 (m, 5H), 1.88 (s, 3H, $ArCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 172.5 (NC=O), 141.1 (C-8a), 138.8 (C-10a'), 135.9 (C-6a'), 134.9 (C-4a), 133.9 (C), 128.1 (CH), 127.9 (CH), 127.3 (CH), 127.0 (CH), 126.3 (CH), 122.4 (2 C, CH), 70.9 (C-10b'), 49.9 (C-6'), 42.7 (C-(1,1')), 38.9 (CH_2), 36.3 (C-2'), 31.2 (C-3'), 30.2 (CH_2), 20.8 ($ArCH_3$), 20.0 (CH_2); HRMS (ESI): $[M+H]^+$ calcd for $C_{22}H_{24}NO$ 318.1852, found 318.1852.

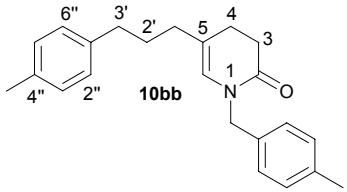


9bb

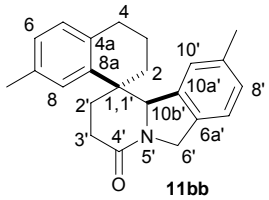
5-[3-(2-Bromo-4-methylphenyl)propyl]-1-(4-methylbenzyl)-3,4-dihydropyridin-2(1*H*)-one (9bb): As described for compound **9aa**, the formyl ester **8b** (700 mg, 2.0 mmol), dissolved in CH_2ClCH_2Cl (5 mL) was reacted with 4-methylbenzylamine (0.5 mL, 3.9 mmol) and AcOH (0.17 mL, 2.9 mmol). Purification of the crude product by flash chromatography (ethyl acetate/hexane, 4:6) as eluent furnished the cyclic enamide **9bb** (650 mg, 80%) as light brown viscous oil. IR (neat): ν_{max}/cm^{-1} = 3022, 2924, 2861, 1666, 1607, 1515, 1490, 1441, 1407, 1267, 1210, 1039, 819, 751, 703; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.34 (s, 1H, 3''-H), 7.13 (d, 2H) and 7.11 (d, 2H) [*J* = 8.9 Hz, Ar-H], 7.00 (s, 2H, Ar-H), 5.78 (s, 1H, 6-H), 4.62 (s, 2H, NCH_2toluyl), 2.60 (2H, 3'-H) and 2.56 (2H, 1'-H) [2 t, *J* = 7.6 Hz], 2.31 (s, 3H) and 2.28 (s, 3H) [2 $ArCH_3$], 2.26 (2H, 4-H) and 2.05 (2H, 3-H) [2 t, *J* = 7.6 Hz], 1.65 (quintet, *J* = 7.63 Hz, 2H, 2'-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 168.8 (NC=O), 138.1 (C-1''), 137.5 (C), 137.0 (C), 134.3 (C), 133.2 (C-3''), 130.0 (CH), 129.3 (2 C, CH), 128.2 (CH), 127.6 (2 C, CH), 124.2 (C-6), 124.1 (C-2''), 119.6 (C-5), 48.5 (NCH_2toluyl), 35.1 (C-3'), 33.3 (C-1'), 31.3 (C-3), 27.8 (CH_2), 24.1 (C-4), 21.1 (CH_3) and 20.5 (CH_3) [2 $ArCH_3$]; HRMS (ESI): $[M+H]^+$ calcd for $C_{23}H_{27}BrNO$ 412.1270, found 412.1270.

Palladium-catalyzed spiro cyclization of 5-(bromophenyl)propyl-substituted enamide 9bb: The reaction was performed with the enamide **9bb** (116 mg, 0.28 mmol) in anhydrous DMF (2 mL) with biphenyl ligand[1] **12** (22 mg, 20 mol%), Cs_2CO_3 (367 mg, 1.1 mmol) and $Pd(OAc)_2$ (6.3 mg, 10 mol%). After loading of the reagents at room temperature, the mixture was heated to 120 °C, as

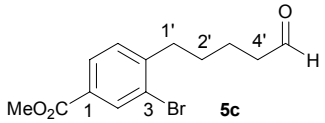
described for compound **9aa**. Purification of the crude product mixture by flash chromatography (ethyl acetate/hexane, 4:6) first furnished the debromoeanamide **10bb** (28 mg, 30%) as brown viscous oil. Further elution (ethyl acetate/hexane, 7:3) provided amide **11bb** (46 mg, 49%) as a colorless solid, which was recrystallized from a mixture of CH_2Cl_2 and hexane.



1-(4-Methylbenzyl)-5-[3-(4-methylphenyl)propyl]-3,4-dihydropyridin-2(1*H*)-one (10bb): IR (neat): ν_{max}/cm^{-1} = 3019, 2925, 2855, 1666, 1606, 1515, 1441, 1376, 1334, 1267, 1209, 1022, 751, 703; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.14 (d, 2H) and 7.12 (d, 2H) [*J* = 8.1 Hz, Ar-H], 7.07 (d, 2H) and 6.99 (d, 2H) [*J* = 7.9 Hz, Ar-H], 5.75 (s, 1H, 6-H), 4.62 (s, 2H, NCH_2toluyl), 2.55 (2H, 3'-H) and 2.50 (2H, 1'-H) [2 t, *J* = 7.6 Hz], 2.32 (s, 3H) and 2.31 (s, 3H) [2 $ArCH_3$], 2.24 (2H, 4-H) and 2.01 (2H, 3-H) [2 t, *J* = 7.6 Hz], 1.67 (quintet, *J* = 7.6 Hz, 2H, 2'-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 168.8 (NC=O), 138.8 (C-1''), 137.0 (C), 135.2 (C), 134.3 (C), 129.2 (2 C, CH), 128.9 (2 C, CH), 128.2 (2 C, CH), 127.6 (2 C, CH), 124.0 (C-6), 119.8 (C-5), 48.5 (NCH_2toluyl), 34.7 (C-3'), 33.2 (C-1'), 31.2 (C-3), 29.2 (CH_2), 24.1 (C-4), 21.0 (CH_3) and 20.9 (CH_3) [2 $ArCH_3$]; HRMS (ESI): $[M+H]^+$ calcd for $C_{23}H_{28}NO$ 334.2165, found 334.2167.



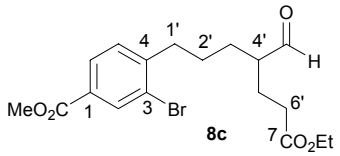
7,9'-Dimethyl-2',3,3',4,6',10b'-hexahydro-2*H*,4'*H*-spiro[naphthalene-1,1'-pyrido[2,1-*a*]isoindol]-4'-one (11bb): m.p. 141–143 °C; IR (neat): ν_{max}/cm^{-1} = 3051, 2926, 2860, 1644, 1514, 1488, 1436, 1344, 1265, 1184, 1099, 761, 733, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.07 (1H, 8'-H) and 6.87 (1H, 7'-H) [2 d, *J* = 7.6 Hz], 6.81 (1H, 5-H) and 6.63 (1H, 6-H) [2 d, *J* = 7.6 Hz], 6.56 (s, 1H, 10'-H), 6.37 (s, 1H, 8-H), 4.83 (d, 1H) and 4.70 (d, 1H) [*J* = 15.8 Hz, 6'-H], 4.82 (s, 1H, 10b'-H), 2.78 (d, 1H) and 2.76 (d, 1H) [*J* = 3.1 Hz, 4-H], 2.60-2.38 (m, 2H), 2.30 (td, *J* = 14.0, 4.1 Hz, 1H), 2.20–1.70 (m, 5H), 2.07 (s, 3H) and 1.89 (s, 3H) [2 $ArCH_3$]; ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 172.5 (NC=O), 141.1 (C-8a), 138.9 (C-10a'), 136.6 (C-6a'), 134.9 (C-4a), 133.9 (C), 132.9 (C), 128.2 (CH), 128.0 (CH), 127.8 (CH), 126.3 (CH), 123.0 (CH), 122.1 (CH), 70.8 (C-10b'), 49.7 (C-6'), 42.7 (C-(1,1')), 39.0 (C-4), 36.3 (C-2'), 31.2 (C-3'), 30.2 (CH_2), 21.2 (CH_3) and 20.8 (CH_3) [2 $ArCH_3$], 20.0 (CH_2); HRMS (ESI): $[M+H]^+$ calcd for $C_{23}H_{26}NO$ 332.2009, found 332.2010.



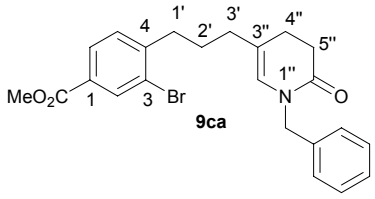
Methyl 3-bromo-4-(5-oxopentyl)benzoate (5c): The reaction was performed as described for the compound **5a**. Thus, to a mixture of $Pd(OAc)_2$ (43.5 mg, 2 mol%), pentenylalcohol (1.4 mL, 13.7 mmol), triethylbenzylammonium chloride (2.2 g, 9.7 mmol) and $NaHCO_3$ (1.64 g, 19.5 mmol) in DMF (25 mL) was added iodobromide[3] **4c** (3.3 g, 9.7 mmol), followed by stirring of the mixture for 24 h at 40 °C. Purification of the crude material by flash chromatography (ethyl acetate/hexane, 1:4)

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

furnished aldehyde **5c** (1.0 g, 34%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 9.50 (s, 1H, CH=O), 7.92 (d, *J* = 1.8 Hz, 1H, 2-H), 7.61 (dd, *J* = 7.9, 1.8 Hz, 1H, 6-H), 7.00 (d, *J* = 7.9 Hz, 1H, 5-H), 3.63 (s, 3H, CO_2CH_3), 2.52 (t, *J* = 7.6 Hz, 2H, 1'-H), 2.22 (dt, *J* = 7.6, 1.5 Hz, 2H, 4'-H), 1.55–1.25 (m, 4H, 2'-H, 3'H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 202.0 (CH=O), 165.6 (OC=O), 146.4 (C-4), 133.8 (C-2), 130.0 (C-6), 129.6 (C-1), 128.4 (C-5), 124.2 (C-3), 52.2 (CO_2CH_3), 43.5 (C-1'), 35.9 (C-4'), 28.9 (C-2'), 21.6 (C-3').

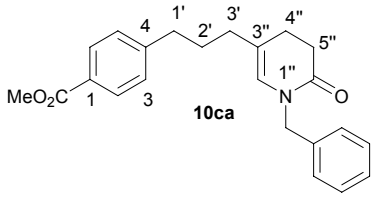


Methyl 3-bromo-4-(7-ethoxy-4-formyl-7-oxoheptyl)benzoate (8c): The reaction was performed with aldehyde **5c** (1.0 g, 3.3 mmol), pyrrolidine (0.55 mL, 6.7 mmol), K_2CO_3 (1.4 g, 10 mmol), molecular sieves (4 Å, 1 g) and ethyl acrylate (0.5 mL, 4.7 mmol) as described above (see **8a**). Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:3) furnished the aldehyde ester **8c** (900 mg, 67% for two steps) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 9.59 (s, 1H, CH=O), 8.18 (d, *J* = 1.8 Hz, 1H, 2-H), 7.87 (dd, *J* = 7.88 Hz, 1H, 6-H), 7.26 (d, *J* = 7.9 Hz, 1H, 5-H), 4.11 (q, *J* = 7.12 Hz, 2H, OCH_2CH_3), 3.89 (s, 3H, CO_2CH_3), 2.78 (t, *J* = 7.6 Hz, 2H, CH_2Ar), 2.47–2.20 (m, 3H), 2.05–1.87 (m, 1H), 2.87–1.43 (m, 5H), 1.23 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 203.9 (CH=O), 172.8 (C-7'), 165.7 (OC=O), 146.2 (C-4,), 133.9 (C-2), 130.1 (C-6), 129.7 (C-1), 128.5 (C-5), 124.2 (C-3), 60.5 (OCH_2CH_3), 52.3 (CO_2CH_3), 50.8 (C-4'), 36.1 (CH_2Ar), 31.5 (C-6'), 28.3 (CH_2), 26.8 (CH_2), 23.6 (C-5'), 14.2 (OCH_2CH_3).

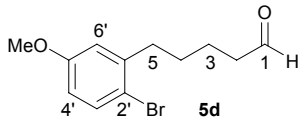


Methyl 4-[3-(1-benzyl-6-oxo-1,4,5,6-tetrahydropyridin-3-yl)propyl]-3-bromobenzoate (9ca): As described for compound **9aa**, the formyl ester **8c** (680 mg, 1.7 mmol), dissolved in CH_2ClCH_2Cl (4 mL) was reacted with benzylamine (0.56 mL, 5.1 mmol) and AcOH (0.1 mL, 1.7 mmol). Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:1) furnished the cyclic enamide **9ca** (600 mg, 79%) as light brown viscous oil. IR (neat): ν_{max}/cm^{-1} = 3030, 2948, 1723, 1667, 1602, 1496, 1435, 1410, 1286, 1256, 1211, 1113, 1040, 763, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 8.17 (d, *J* = 1.8 Hz, 1H, 2-H), 7.84 (dd, *J* = 7.9, 1.8 Hz, 1H, 6-H), 7.40–7.15 (m, 5H, Ar-H), 7.17 (d, *J* = 7.9 Hz, 1H, 5-H), 5.79 (s, 1H, 2''-H), 4.66 (s, 2H, NCH_2Ph), 3.89 (s, 3H, CO_2CH_3), 2.68 (2H, 1'-H) and 2.57 (2H, 3'-H) [2 t, *J* = 7.6 Hz], 2.27 (2H, 4''-H) and 2.06 (2H, 5'-H) [2 t, *J* = 7.9 Hz], 1.69 (quintet, *J* = 7.63 Hz, 2H, 2'-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 168.8 (NC=O), 165.7 (OC=O), 146.5 (C-4), 137.2 (C), 133.9 (C-2), 130.1 (C-6), 129.6 (C-1), 128.6 (2 C, CH), 128.4 (C-5), 127.5 (2 C, CH), 127.3 (CH), 124.4 (C-2''), 124.2 (C-3), 119.2 (C-3''), 52.2 (CO_2CH_3), 48.7 (NCH_2Ph), 35.6 (C-1'), 33.3 (C-3'), 31.2 (C-5''), 27.3 (CH_2), 24.0 (C-4''); HRMS (ESI): $[M+H]^+$ calcd for $C_{23}H_{25}BrNO_3$ 442.1012, found 442.1014.

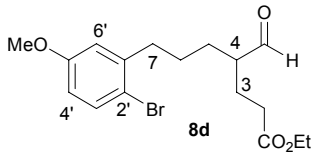
Palladium-catalyzed spiro cyclization of 5-(bromophenyl)propyl-substituted enamide 9ca: The reaction was performed with the enamide **9ca** (106 mg, 0.24 mmol) in anhydrous DMF (2 mL) with Ph_3P (12.5 mg, 20 mol%), Cs_2CO_3 (312 mg, 0.96 mmol) and $Pd(OAc)_2$ (5.3 mg, 10 mol%). After loading of the reagents at room temperature, the mixture was heated to 120 °C, as described for compound **9aa**. Purification of the crude material by flash chromatography (ethyl acetate/hexane, 1:1) furnished the debromoenamide **10ca** (25 mg, 29%) as brown viscous oil. The pentacyclic compound **11ca** was not observed.



Methyl 4-[3-(1-benzyl-6-oxo-1,4,5,6-tetrahydropyridin-3-yl)propyl]benzoate (10ca): IR (neat): ν_{max}/cm^{-1} = 3030, 2939, 1720, 1666, 1609, 1496, 1435, 1409, 1279, 1179, 1110, 1020, 763, 703; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.91 (d, 2H) and 7.13 (d, 2H) [J = 8.4 Hz, Ar-H], 7.40–7.15 (m, 5H, Ar-H), 5.73 (s, 1H, 2''-H), 4.65 (s, 2H, NCH_2Ph), 3.89 (s, 3H, CO_2CH_3), 2.58 (2H, 1'-H) and 2.56 (2H, 3'-H) [2 t, J = 7.6 Hz], 2.24 (2H, 4''-H) and 2.00 (2H, 5''-H) [2 t, J = 7.9 Hz], 1.70 (quintet, J = 7.6 Hz, 2H, 2'-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 168.8 (NC=O), 167.1 (OC=O), 147.4 (C-4), 137.3 (C), 129.7 (2 C, CH), 128.6 (2 C, CH), 128.4 (2 C, CH), 127.9 (C), 127.6 (2 C, CH), 127.4 (CH), 124.3 (C-2''), 119.5 (C-3''), 52.0 (CO_2CH_3), 48.8 (NCH_2Ph), 35.1 (C-1'), 33.1 (C-3'), 31.2 (C-5''), 28.7 (CH_2), 24.1 (C-4''); HRMS (ESI): $[M+H]^+$ calcd for $C_{23}H_{26}NO_3$ 386.1727, found 386.1726.

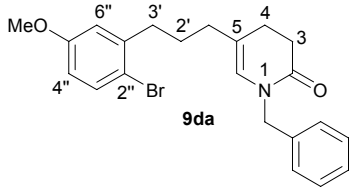


5-(2-Bromo-5-methoxyphenyl)pentanal (5d): The reaction was performed as described for compound **5a**. Thus, to a mixture of $Pd(OAc)_2$ (57 mg, 2 mol%), pentenylalcohol (1.8 mL, 17.9 mmol), triethylbenzylammonium chloride (2.9 g, 12.8 mmol) and $NaHCO_3$ (2.1 g, 25.5 mmol) in DMF (30 mL) was added iodobromide[4] **4d** (4.0 g, 12.8 mmol), followed by stirring of the mixture for 24 h at 40 °C. Purification of the crude material by flash chromatography (ethyl acetate/hexane, 1:9) furnished aldehyde **5d** (2.5 g, 72%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 9.76 (s, 1H, CH=O), 7.38 (d, J = 8.7 Hz, 1H, 3'-H), 6.74 (d, J = 3.05 Hz, 1H, 6'-H), 6.61 (dd, J = 8.7, 3.1 Hz, 1H, 4'-H), 3.76 (s, 3H, OCH_3), 2.69 (t, J = 7.1 Hz, 2H, 5-H), 2.47 (dt, J = 7.1, 1.5 Hz, 2H, 2-H), 1.80–1.55 (m, 4H, 3-H, 4-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 202.4 (CH=O), 158.9 (C-5'), 142.2 (C-1'), 133.2 (C-3'), 116.0 (CH), 114.8 (C-2'), 113.1 (CH), 55.4 (OCH_3), 43.6 (C-5), 36.0 (C-2), 29.3 (C-4), 21.7 (C-3).



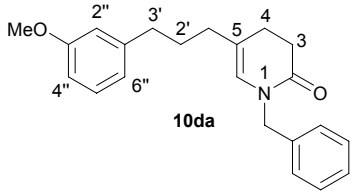
Ethyl 7-(2-bromo-5-methoxyphenyl)-4-formylheptanoate (8d): The reaction was performed with aldehyde **5d** (2.5 g, 9.2 mmol), pyrrolidine (1.5 mL, 18.4 mmol), K_2CO_3 (3.8 g, 27.7 mmol), molecular sieves (4 Å, 2 g) and ethyl acrylate (1.4 mL, 12.9 mmol) as described above. Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:6) furnished the aldehyde ester **8d** (2.3 g, 67% for two steps) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 9.60 (s, 1H, CH=O), 7.40 (d, J = 8.9 Hz, 1H, 3'-H), 6.73 (d, J = 3.1 Hz, 1H, 6'-H), 6.61 (dd, J = 8.9, 3.1 Hz, 1H, 4'-H), 4.11 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 3.76 (s, 3H, OCH_3), 2.69 (t, J = 7.6 Hz, 2H, 7-H), 2.43–2.20 (m, 3H), 2.08-1.88 (m, 1H), 1.88–1.45 (m, 5H), 1.24 (t, J = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 204.1 (CH=O), 172.9 (OC=O), 158.9 (C-5'), 141.9 (C-1'), 133.3 (C-3'), 116.0 (CH), 114.8 (C-2'), 113.2 (CH), 60.5 (OCH_2CH_3), 55.4 (OCH_3), 50.9 (C-4), 36.2 (CH_2Ar), 31.6 (C-2), 28.3 (CH_2), 27.1 (CH_2), 23.6 (C-3), 14.2 (OCH_2CH_3).

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

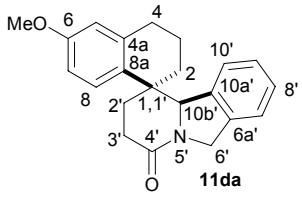


1-Benzyl-5-[3-(2-bromo-5-methoxyphenyl)propyl]-3,4-dihydropyridin-2(1*H*)-one (9da): As described for compound **9aa**, the formyl ester **8d** (1.8 g, 4.8 mmol) in CH_2ClCH_2Cl (8 mL) was reacted with benzylamine (1.0 mL, 9.7 mmol) and AcOH (0.3 mL, 4.8 mmol). Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:1) furnished the cyclic enamide **9da** (1.4 g, 70%) as light brown viscous oil. IR (neat): ν_{max}/cm^{-1} = 3062, 3029, 2934, 2835, 1666, 1594, 1572, 1471, 1411, 1277, 1241, 1212, 1162, 1054, 1012, 735, 701; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.42 (d, *J* = 8.7 Hz, 1H, 3''-H), 7.40–7.20 (m, 5H, Ar-H), 6.74 (d, *J* = 3.1 Hz, 1H, 6''-H), 6.65 (dd, *J* = 8.7, 3.1 Hz, 1H, 4'-H), 5.84 (s, 1H, 6-H), 4.71 (s, 2H, NCH_2Ph), 3.79 (s, 3H, OCH_3), 2.65 (2H, 3'-H) and 2.62 (2H, 1'-H) [2 t, *J* = 7.6 Hz], 2.32 (2H, 4-H) and 2.11 (2H, 3-H) [2 t, *J* = 7.9 Hz], 1.72 (quintet, *J* = 7.63 Hz, 2H, 2'-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 168.8 (NC=O), 158.9 (C-5''), 142.3 (C-1''), 137.3 (C), 133.2 (C-3''), 128.6 (2 C, CH), 127.4 (2 C, CH), 127.3 (CH), 124.2 (C-6), 119.6 (C-5), 116.1 (CH), 114.8 (C-2''), 112.9 (CH), 55.3 (OCH_3), 48.7 (NCH_2Ph), 35.8 (C-3'), 33.3 (C-1'), 31.2 (C-3), 27.7 (CH_2), 24.1 (C-4); HRMS (ESI): $[M+H]^+$ calcd for $C_{22}H_{25}BrNO_2$ 414.1063, found 414.1063.

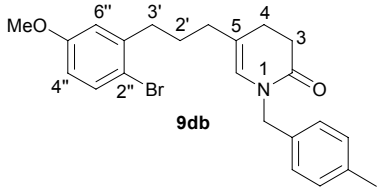
Palladium-catalyzed spiro cyclization of 5-(bromophenyl)propyl-substituted enamide 9da: The reaction was performed with the enamide **9da** (100 mg, 0.24 mmol) in anhydrous DMF (2 mL) using biphenyl ligand[1] **12** (19.0 mg, 20 mol%), Cs_2CO_3 (314 mg, 0.97 mmol) and $Pd(OAc)_2$ (5.4 mg, 10 mol%). After loading of the reagents at room temperature, the mixture was heated to 120 °C, as described for compound **9aa**. Purification of the crude product mixture by flash chromatography (ethyl acetate/hexane, 1:1) first furnished the debromoenamide **10da** (20 mg, 25%) as brown viscous oil. Further elution of the column (ethyl acetate/hexane, 4:1) provided the polycyclic amide **11da** (40 mg, 50%) as a colorless solid, which was recrystallized from a mixture of CH_2Cl_2 and hexane.



1-Benzyl-5-[3-(3-methoxyphenyl)propyl]-3,4-dihydropyridin-2(1*H*)-one (10da): IR (neat): ν_{max}/cm^{-1} = 3062, 3029, 2934, 2856, 2835, 1667, 1601, 1584, 1488, 1454, 1264, 1211, 1153, 1040, 778; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.38–7.11 (m, 6H, Ar-H), 6.77–6.62 (m, 3H, Ar-H), 5.76 (s, 1H, 6-H), 4.66 (s, 2H, NCH_2Ph), 3.77 (s, 3H, OCH_3), 2.56 (2H, 3'-H) and 2.52 (2H, 1'-H) [2 t, *J* = 7.6 Hz], 2.25 (2H, 4-H) and 2.01 (2H, 3-H) [2 t, *J* = 7.9 Hz], 1.68 (quintet, *J* = 7.6 Hz, 2H, 2'-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 168.9 (NC=O), 159.6 (C-3''), 143.6 (C-1''), 137.3 (C), 129.3 (C-5''), 128.6 (2 C, CH), 127.5 (2 C, CH), 127.3 (CH), 124.1 (C-6), 120.8 (C-6''), 119.8 (C-5), 114.3 (CH), 110.9 (CH), 55.1 (OCH_3), 48.8 (NCH_2Ph), 35.2 (C-3'), 33.2 (C-1'), 31.2 (C-3), 29.0 (CH_2), 24.2 (C-4); HRMS (ESI): $[M+H]^+$ calcd for $C_{22}H_{26}NO_2$ 336.1958, found 336.1959.



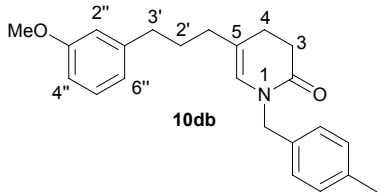
6-Methoxy-2',3,3',4,6',10b'-hexahydro-2*H*,4'*H*-spiro[naphthalene-1,1'-pyrido[2,1-*a*]isoindol]-4'-one (11da): m.p. 158–160 °C; IR (neat): ν_{max}/cm^{-1} = 3050, 2934, 2837, 1760, 1728, 1660, 1610, 1500, 1453, 1345, 1251, 1129, 1040, 761, 738, 701; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.20 (d, *J* = 7.6 Hz, 1H, 10'-H), 7.09 (t, *J* = 7.6 Hz, 1H, 8'-H), 6.93 (t, *J* = 7.6 Hz, 1H, 9'-H], 6.79 (d, *J* = 7.6 Hz, 1H, 7'-H), 6.49 (d, *J* = 8.7 Hz, 1H, 8-H), 6.45 (d, *J* = 2.80 Hz, 1H, 7-H), 6.27 (dd, *J* = 8.7, 2.8 Hz, 1H, 5-H), 4.90 (d, 1H) and 4.71 (1H, d) [*J* = 15.5 Hz, 6'-H], 4.87 (s, 1H, 10b'-H), 3.61 (s, 3H, OCH_3), 2.86–2.71 (m, 2H), 2.55–2.36 (m, 2H), 2.28 (td, *J* = 14.0, 4.6 Hz, 1H), 2.18–2.05 (m, 2H), 2.05–1.78 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 172.3 (NC=O), 156.9 (C-6), 138.8 (C-10a'), 138.3 (C-8a), 136.0 (C-4a), 133.3 (C-6a'), 128.6 (CH), 127.3 (CH), 127.1 (CH), 122.7 (2 C, CH), 112.6 (CH), 112.3 (CH), 70.9 (C-10b'), 54.9 (OCH_3), 49.8 (C-6'), 41.8 (C-(1,1')), 38.8 (C-4), 36.5 (C-2'), 31.0 (C-3'), 30.9 (CH_2), 19.8 (CH_2),; HRMS (ESI): $[M+H]^+$ calcd for $C_{22}H_{24}NO_2$ 334.1802, found 334.1802.



9db

5-[3-(2-Bromo-5-methoxyphenyl)propyl]-1-(4-methylbenzyl)-3,4-dihydropyridin-2(1*H*)-one (9db): As described for compound **9aa**, the formyl ester **8d** (1.5 g, 4.0 mmol) in CH_2ClCH_2Cl (7 mL) was reacted with 4-methylbenzylamine (1.0 mL, 8.1 mmol) and AcOH (0.23 mL, 4.0 mmol). Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:1) furnished the cyclic enamide **9db** (1.3 g, 78%) as light brown viscous oil. IR (neat): ν_{max}/cm^{-1} = 3033, 2933, 1665, 1601, 1515, 1487, 1438, 1262, 1209, 1153, 1114, 1038, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.38 (d, *J* = 8.7 Hz, 1H, 3''-H), 7.11 (d, 2H) and 7.10 (d, 2H) [*J* = 8.9 Hz, Ar-H], 6.69 (d, *J* = 3.1 Hz, 1H, 6'-H), 6.61 (dd, *J* = 8.7, 3.1 Hz, 1H, 4'-H), 5.79 (s, 1H, 6-H), 4.62 (s, 2H, NCH_2toluyl), 3.75 (s, 3H, OCH_3), 2.60 (2H, 3'-H) and 2.56 (2H, 1'-H) [2 t, *J* = 7.6 Hz], 2.31 (s, 3H, $ArCH_3$), 2.26 (2H, 4-H) and 2.06 (2H, 3-H) [2 t, *J* = 7.9 Hz], 1.67 (quintet, *J* = 7.6 Hz, 2H, 2'-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 168.8 (NC=O), 158.9 (C-5''), 142.3 (C-1''), 137.0 (C), 134.3 (C), 133.2 (C-3''), 129.3 (2 C, CH), 127.5 (2 C, CH), 124.2 (C-6), 119.5 (C-5), 116.1 (CH), 114.8 (C-2''), 112.9 (CH), 55.4 (OCH_3), 48.5 (NCH_2toluyl), 35.8 (C-3'), 33.4 (C-1'), 31.3 (C-3), 27.7 (CH_2), 24.1 (C-4), 21.1 ($ArCH_3$); HRMS (ESI): $[M+H]^+$ calcd for $C_{23}H_{27}BrNO_2$ 428.1220, found 428.1220.

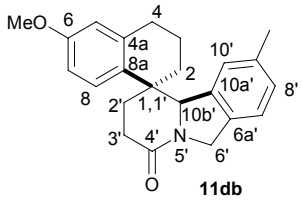
Palladium-catalyzed spiro cyclization of 5-(bromophenyl)propyl-substituted enamide 9db: The reaction was performed with the enamide **9db** (140 mg, 0.32 mmol) in anhydrous DMF (2.5 mL) with biphenyl ligand[1] **12** (25.7 mg, 20 mol%), Cs_2CO_3 (426 mg, 1.3 mmol) and $Pd(OAc)_2$ (7.3 mg, 10 mol%). After loading of the reagents at room temperature, the mixture was heated to 120 °C, as described for compound **9aa**. Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:1) first furnished the debromoenamide **10db** (34 mg, 30%) as brown viscous oil. Further elution of the column (ethyl acetate/hexane, 4:1) provided the amide **11db** (50 mg, 44%) as a colorless solid, which was recrystallized from a mixture of CH_2Cl_2 and hexane.



10db

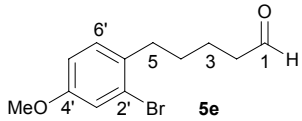
5-[3-(3-Methoxyphenyl)propyl]-1-(4-methylbenzyl)-3,4-dihydropyridin-2(1*H*)-one (10db): IR (neat): ν_{max}/cm^{-1} = 3033, 2931, 2851, 1665, 1640, 1573, 1499, 1433, 1344, 1241, 1229, 1041, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.17 (t, *J* = 7.9 Hz, 1H, 5''-H), 7.13 (d, 2H) and 7.11 (d,

2H) [J = 8.9 Hz, Ar-H], 6.72 (dd, J = 7.9, 2.3 Hz, 1H, 4''-H), 6.68 (d, J = 7.9, 3.1 Hz, 1H, 6''-H), 6.67 (s, 1H, 2''-H), 5.75 (s, 1H, 6-H), 4.61 (s, 2H, NCH_2toluyl), 3.78 (s, 3H, OCH_3), 2.54 (2H, 3'-H) and 2.52 (2H, 1'-H) [2 t, J = 7.6 Hz], 2.31 (s, 3H, $ArCH_3$), 2.24 (2H, 4-H) and 2.01 (2H, 3-H) [2 t, J = 7.9 Hz], 1.68 (quintet, J = 7.63 Hz, 2H, 2'-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 168.8 (NC=O), 159.6 (C-5''), 143.6 (C-1''), 137.0 (C), 134.3 (C), 129.3 (2 C, CH), 129.2 (CH), 127.6 (2 C, CH), 124.0 (CH, C-6), 120.8 (CH), 119.7 (C-5), 114.2 (CH), 110.9 (CH), 55.1 (OCH_3), 48.5 (NCH_2toluyl), 35.2 (C-3'), 33.2 (C-1'), 31.3 (C-3), 29.0 (CH_2), 24.1 (C-4), 21.1 ($ArCH_3$); HRMS (ESI): $[M+H]^+$ calcd for $C_{23}H_{28}NO_2$ 350.2115, found 350.2115.



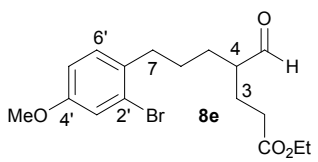
11db

6-Methoxy-9'-methyl-2',3,3',4,6',10b'-hexahydro-2*H*,4'*H*-spiro[naphthalene-1,1'-pyrido[2,1-*a*]isoindol]-4'-one (11db): m.p. 202–204 °C; IR (neat): ν_{max}/cm^{-1} = 3033, 2931, 2859, 1665, 1640, 1609, 1572, 1499, 1434, 1344, 1241, 1220, 1041, 734, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.07 (1H, 8'-H) and 6.89 (1H, 7'-H) [2 d, J = 7.6 Hz], 6.60 (s, 1H, 10'-H), 6.51 (d, J = 8.7 Hz, 1H, 8-H), 6.46 (d, J = 2.8 Hz, 1H, 5-H), 6.29 (dd, J = 8.7, 2.8 Hz, 1H, 7-H), 4.85 (d, 1H) and 4.66 (d, 1H) [J = 15.3 Hz, 6'-H], 4.83 (s, 1H, 10b'-H), 3.62 (s, 3H, OCH_3), 2.90–2.70 (m, 2H), 2.60–2.35 (m, 2H), 2.26 (td, J = 14.0, 4.6 Hz, 1H), 2.19–1.75 (m, 5H), 2.10 (s, 3H, $ArCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 172.3 (NC=O), 156.9 (C-6), 138.9 (C-10a'), 138.3 (C-8a), 136.7 (C-4a), 133.4 (C), 133.1 (C-6a'), 128.5 (CH), 128.3 (CH), 123.2 (CH), 122.4 (CH), 112.5 (CH), 112.3 (CH), 70.8 (C-10b'), 54.9 (OCH_3), 49.7 (C-6'), 41.8 (C-(1,1')), 38.9 (C-4), 36.5 (C-2'), 31.0 (C-3'), 30.9 (CH_2), 21.3 ($ArCH_3$), 19.8 (CH_2); HRMS (ESI): $[M+H]^+$ calcd for $C_{23}H_{26}NO_2$ 348.1958, found 348.1958.



5e

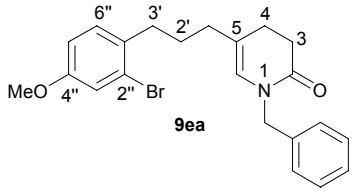
5-(2-Bromo-4-methoxyphenyl)pentanal (5e): The reaction was performed as described for compound **5a**. Thus, to a mixture of $Pd(OAc)_2$ (57.4 mg, 2 mol%), pentenylalcohol (1.8 mL, 17.9 mmol), triethylbenzylammonium chloride (2.9 g, 12.8 mmol) and $NaHCO_3$ (2.1 g, 25.5 mmol) in DMF (30 mL) was added iodobromide[5] **4e** (4.0 g, 12.8 mmol), followed by stirring of the mixture for 24 h at 40 °C. Purification of the crude material by flash chromatography (ethyl acetate/hexane, 1:9) furnished aldehyde **5e** (2.35 g, 68%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 9.76 (s, 1H, CH=O), 7.08 (d, J = 8.7 Hz, 1H, 6'-H), 7.07 (d, J = 2.8 Hz, 1H, 3'-H), 6.77 (dd, J = 8.7, 2.8 Hz, 1H, 5'-H), 3.75 (s, 3H, OCH_3), 2.67 (t, J = 7.6 Hz, 2H, 5-H), 2.45 (dt, J = 7.6, 1.5 Hz, 2H, 2-H), 1.75–1.52 (m, 4H, 3-H, 4-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 202.4 (CH=O), 158.3 (C-4'), 133.1 (C-1'), 130.5 (C-6'), 124.3 (C-2'), 117.8 (CH), 113.5 (CH), 55.4 (OCH_3), 43.6 (C-5), 34.8 (C-2), 29.6 (C-4), 21.6 (C-3).



8e

[5] (a) K. Orito, T. Hatakeyama, M. Takeo and H. Suginome, *Synthesis*, 1995, 1273-1277; (b) T. Jensen, H. Pedersen, B. Bang-Andersen, R. Madsen and M. Joergensen, *Angew. Chem.*, 2008, **120**, 902-904; *Angew. Chem. Int. Ed.*, 2008, **47**, 888-890.

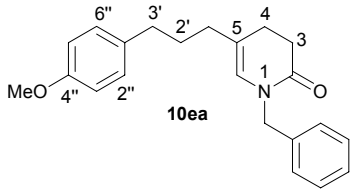
Ethyl 7-(2-bromo-4-methoxyphenyl)-4-formylheptanoate (8e): The reaction was performed with aldehyde **5e** (2.35 g, 8.6 mmol), pyrrolidine (1.4 mL, 17.2 mmol), K_2CO_3 (3.6 g, 26 mmol), molecular sieves (4 Å, 2 g) and ethyl acrylate (1.3 mL, 12.1 mmol) as described above. Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:6) furnished the aldehyde ester **8e** (2.1 g, 68% for two steps) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 9.58 (s, 1H, CH=O), 7.07 (d, *J* = 8.7 Hz, 1H, 6'-H), 7.06 (d, *J* = 3.8 Hz, 1H, 3'-H), 6.77 (dd, *J* = 8.7, 2.8 Hz, 1H, 5'-H), 4.11 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 3.76 (s, 3H, OCH_3), 2.66 (t, *J* = 7.6 Hz, 2H, 7-H), 2.43–2.20 (m, 3H), 2.03–1.87 (m, 1H), 1.88–1.40 (m, 5H), 1.23 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 204.1 (CH=O), 172.9 (OC=O), 158.3 (C-4'), 132.9 (C-1'), 130.5 (C-6'), 124.3 (C-2'), 117.9 (CH), 113.6 (CH), 60.5 (OCH_2CH_3), 55.5 (OCH_3), 50.9 (C-4), 35.0 (CH_2Ar), 31.6 (C-2), 28.2 (CH_2), 27.4 (CH_2), 23.6 (C-3), 14.2 (OCH_2CH_3).



9ea

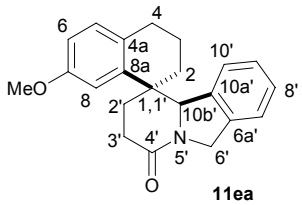
1-Benzyl-5-[3-(2-bromo-4-methoxyphenyl)propyl]-3,4-dihydropyridin-2(1*H*)-one (9ea): As described for compound **9aa**, the formyl ester **8e** (2.1 g, 5.66 mmol), dissolved in CH_2ClCH_2Cl (10 mL) was reacted with benzylamine (1.2 mL, 11.3 mmol) and AcOH (0.32 mL, 5.6 mmol). Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:1) furnished the cyclic enamide **9ea** (1.4 g, 80%) as a colorless solid, which was recrystallized from a mixture of CH_2Cl_2 and hexane, m.p. 86–88 °C. IR (neat): ν_{max}/cm^{-1} = 3063, 3029, 2935, 2835, 1665, 1604, 1566, 1493, 1454, 1409, 1267, 1240, 1211, 1028, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.40–7.20 (m, 5H, Ar-H), 7.07 (d, *J* = 2.5 Hz, 1H, 3''-H), 7.01 (d, *J* = 8.4 Hz, 1H, 6''-H), 6.75 (dd, *J* = 8.4, 2.5 Hz, 1H, 5''-H), 5.79 (s, 1H, 6-H), 4.66 (s, 2H, NCH_2Ph), 3.75 (s, 3H, OCH_3), 2.65–2.52 (m, 4H, 1'-H, 3'-H), 2.27 (2H, 4-H) and 2.05 (2H, 3-H) [2 t, *J* = 7.9 Hz], 1.65 (quintet, *J* = 7.6 Hz, 2H, 2'-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 168.9 (NC=O), 158.3 (C-4''), 137.3 (C), 133.2 (C-1''), 130.5 (C-6''), 128.6 (2 C, CH), 127.5 (2 C, CH), 127.3 (CH), 124.3 (C-2''), 124.2 (C-6), 119.7 (C-5), 117.8 (CH), 113.6 (CH), 55.5 (OCH_3), 48.8 (NCH_2Ph), 34.6 (C-3'), 33.2 (C-1'), 31.3 (CH_2, C-3), 27.9 (C-2'), 24.1 (C-4); HRMS (ESI): $[M+H]^+$ calcd for $C_{22}H_{25}BrNO_2$ 414.1063, found 414.1063.

Palladium-catalyzed spiro cyclization of 5-(bromophenyl)propyl-substituted enamide 9ea: The reaction was performed with the enamide **9ea** (110 mg, 0.26 mmol) in anhydrous DMF (2 mL) with biphenyl ligand[1] **12** (21 mg, 20 mol%), Cs_2CO_3 (346 mg, 1.1 mmol) and $Pd(OAc)_2$ (5.9 mg, 10 mol%). After loading of the reagents at room temperature, the mixture was heated to 120 °C, as described for compound **9aa**. Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:1) first furnished the enamide **10ea** (30 mg, 34%) as brown viscous oil. This compound however, was not obtained pure. Further elution of the column (ethyl acetate-hexane, 4:1) furnished the polycyclic amide **11ea** (40 mg, 45%) as a colorless solid, which was recrystallized from a mixture of CH_2Cl_2 and hexane.



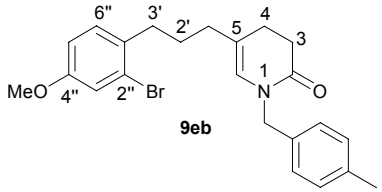
10ea

1-Benzyl-5-[3-(4-methoxyphenyl)propyl]-3,4-dihydropyridin-2(1*H*)-one (10ea). This compound was not obtained pure.



11ea

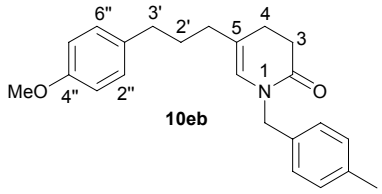
7-Methoxy-2',3,3',4,6',10b'-hexahydro-2*H*,4'*H*-spiro[naphthalene-1,1'-pyrido[2,1-*a*]isoindol]-4'-one (11ea): m.p. 195–197 °C; IR (neat): ν_{max}/cm^{-1} = 3057, 2934, 1759, 1659, 1608, 1496, 1484, 1437, 1351, 1241, 1120, 998, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.21 (d, *J* = 7.6 Hz, 1H, 10'-H), 7.10 (t, *J* = 7.6 Hz, 1H, 8'-H), 6.93 (t, *J* = 7.6 Hz, 1H, 9'-H], 6.83 (d, *J* = 8.7 Hz, 1H, 5-H), 6.77 (d, *J* = 7.6 Hz, 1H, 7'-H), 6.43 (dd, *J* = 8.7, 2.5 Hz, 1H, 6-H), 6.12 (d, *J* = 2.5 Hz, 1H, 8-H), 4.90 (d, 1H) and 4.76 (d, 1H) [*J* = 16.0 Hz, 6'-H], 4.89 (s, 1H, 10b'-H), 3.39 (s, 3H, OCH_3), 2.76 (d, 1H) and 2.74 (d, 1H) [*J* = 3.8 Hz], 2.57–2.41 (m, 2H), 2.32 (td, *J* = 14.0, 4.6 Hz, 1H), 2.20–1.70 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 172.5 (NC=O), 157.3 (C-7), 142.1 (C-8a), 138.8 (C-10a'), 135.8 (C-6a'), 129.4 (C-4a), 129.3 (CH), 127.5 (CH), 127.2 (CH), 122.7 (2 C, CH), 113.2 (CH), 111.3 (CH), 70.8 (C-10b'), 54.9 (OCH_3), 49.9 (C-6'), 42.8 (C-(1,1')), 38.6 (C-4), 36.2 (C-2'), 31.1 (C-3'), 29.7 (CH_2), 20.0 (CH_2); HRMS (ESI): $[M+H]^+$ calcd for $C_{22}H_{24}NO_2$ 334.1802, found 334.1803.



9eb

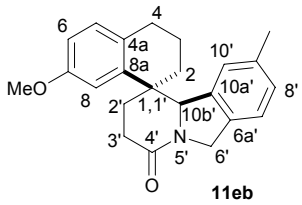
5-[3-(2-Bromo-4-methoxyphenyl)propyl]-1-(4-methylbenzyl)-3,4-dihydropyridin-2(1*H*)-one (9eb): As described for compound **9aa**, the formyl ester **8e** (700 mg, 1.9 mmol) in CH_2ClCH_2Cl (4 mL) was reacted with 4-methylbenzylamine (0.5 mL, 3.8 mmol) and AcOH (0.16 mL, 2.8 mmol). Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:1) furnished the cyclic enamide **9eb** (630 mg, 78%) as light brown viscous oil. IR (neat): ν_{max}/cm^{-1} = 3033, 2935, 2835, 1664, 1604, 1515, 1492, 1407, 1239, 1209, 1035, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.13 (d, 2H) and 7.11 (d, 2H) [*J* = 8.9 Hz, Ar-H], 7.06 (d, *J* = 2.5 Hz, 1H, 3''-H), 7.01 (d, *J* = 8.4 Hz, 1H, 6''-H), 6.75 (dd, *J* = 8.4, 2.5 Hz, 1H, 5''-H), 5.78 (s, 1H, 6-H), 4.62 (s, 2H, NCH_2toluyl), 3.76 (s, 3H, OCH_3), 2.64–2.50 (m, 4H, 1'-H, 3'-H), 2.31 (s, 3H, $ArCH_3$), 2.26 (2H, 4-H) and 2.04 (2H, 3-H) [2 t, *J* = 7.9 Hz], 1.64 (quintet, *J* = 7.6 Hz, 2H, 2'-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 168.8 (NC=O), 158.3 (C-4''), 137.0 (C), 134.3 (C-1''), 133.2 (C), 130.6 (C-6''), 129.3 (2 C, CH), 127.5 (2 C, CH), 124.3 (C-2''), 124.1 (C-6), 119.6 (C-5), 117.8 (CH), 113.6 (CH), 55.5 (OCH_3), 48.5 (NCH_2toluyl), 34.6 (C-3'), 33.3 (C-1'), 31.3 (C-3), 27.9 (CH_2), 24.1 (C-4), 21.1 ($ArCH_3$); HRMS (ESI): $[M+H]^+$ calcd for $C_{23}H_{27}BrNO_2$ 428.1220, found 428.1218.

Palladium-catalyzed spiro cyclization of 5-(bromophenyl)propyl-substituted enamide 9eb: The reaction was performed with the enamide **9eb** (108 mg, 0.25 mmol) in anhydrous DMF (2 mL) with biphenyl ligand[1] **12** (20 mg, 20 mol%), Cs_2CO_3 (328 mg, 1.0 mmol) and $Pd(OAc)_2$ (5.7 mg, 10 mol%). After loading of the reagents at room temperature, the mixture was heated to 120 °C, as described for compound **9aa**. Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:1) first furnished the debromoenamide **10eb** (25 mg, 28%) as brown viscous oil. Further elution of the column using ethyl acetate-hexane (4:1) as eluent furnished the polycyclic amide **11eb** (38 mg, 43%) as a colorless solid, which was recrystallized from a mixture of CH_2Cl_2 and hexane.



10eb

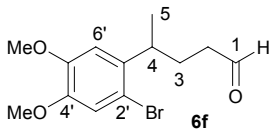
5-[3-(4-Methoxyphenyl)propyl]-1-(4-methylbenzyl)-3,4-dihydropyridin-2(1*H*)-one (10eb): IR (neat): ν_{max}/cm^{-1} = 3025, 2930, 2834, 1666, 1611, 1583, 1512, 1441, 1377, 1246, 1106, 1036, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.14 (s, 4H, Ar-H), 7.00 (d, 2H) and 6.79 (d, 2H) [*J* = 8.6 Hz, Ar-H], 5.73 (s, 1H, 6-H), 4.61 (s, 2H, NCH_2toluyl), 3.77 (s, 3H, OCH_3), 2.54 (2H, 3'-H) and 2.47 (2H, 1'-H) [2 t, *J* = 7.6 Hz], 2.32 (s, 3H, Ar-CH_3), 2.23 (2H, 4-H) and 1.99 (2H, 3-H) [2 t, *J* = 7.9 Hz], 1.65 (quintet, *J* = 7.6 Hz, 2H, 2'-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 168.8 (NC=O), 157.7 (C-4''), 137.0 (C), 134.3 (C-1''), 134.0 (C), 129.2 (4 C, CH), 127.6 (2 C, CH), 124.0 (C-6), 119.7 (C, C-5), 113.7 (2 C, CH), 55.2 (OCH_3), 48.5 (NCH_2toluyl), 34.2 (C-3'), 33.1 (C-1'), 31.3 (C-3), 29.3 (CH_2), 24.1 (C-4), 21.1 ($ArCH_3$); HRMS (ESI): $[M+H]^+$ calcd for $C_{23}H_{28}NO_2$ 350.2115, found 350.2115.



11eb

7-Methoxy-9'-methyl-2',3,3',4,6',10b'-hexahydro-2*H*,4'*H*-spiro[naphthalene-1,1'-pyrido[2,1-*a*]isoindol]-4'-one (11eb): m.p. 176–178 °C; IR (neat): ν_{max}/cm^{-1} = 3064, 2927, 2857, 1726, 1661, 1609, 1500, 1437, 1344, 1238, 1119, 1038, 732, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.08 (1H, 8'-H) and 6.90 (1H, 7'-H) [2 d, *J* = 7.6 Hz], 6.84 (d, *J* = 8.4 Hz, 1H, 5-H), 6.57 (s, 1H, 10'-H), 6.43 (dd, *J* = 8.4, 2.4 Hz, 1H, 6-H), 6.12 (d, *J* = 2.5 Hz, 1H, 8-H), 4.85 (d, 1H) and 4.71 (d, 1H) [*J* = 15.8 Hz, 6'-H], 4.84 (s, 1H, 10b'-H), 3.40 (s, 3H, OCH_3), 2.77 (d, 1H) and 2.75 (d, 1H) [*J* = 3.8 Hz, 4-H], 2.58–2.38 (m, 2H), 2.30 (td, *J* = 14.0, 4.6 Hz, 1H), 2.20–1.70 (m, 5H), 2.08 (s, 3H, $ArCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 172.5 (NC=O), 157.3 (C-7), 142.2 (C-8a), 139.0 (C-10a'), 136.8 (C-6a'), 132.9 (C), 129.4 (C-4a), 129.1 (CH), 128.4 (CH), 123.2 (CH), 122.3 (CH), 113.3 (CH), 111.1 (CH), 70.7 (C-10b'), 54.9 (OCH_3), 49.7 (C-6'), 42.8 (C-(1,1')), 38.7 (C-4), 36.2 (C-2'), 31.1 (C-3'), 29.7 (CH_2), 21.3 ($ArCH_3$), 20.0 (CH_2); HRMS (ESI): $[M+H]^+$ calcd for $C_{23}H_{26}NO_2$ 348.1958, found 348.1957.

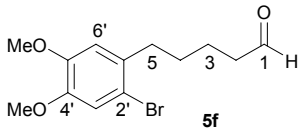
4-(2-Bromo-4,5-dimethoxyphenyl)pentanal (6f) and 5-(2-Bromo-4,5-dimethoxyphenyl)pentanal (5f): The reaction was performed as described for compound **5a**. Thus, to a mixture of $Pd(OAc)_2$ (56 mg, 2 mol%), pentenylalcohol (1.8 mL, 17.5 mmol), triethylbenzylammonium chloride (2.8 g, 12.5 mmol) and $NaHCO_3$ (2.1 g, 25 mmol) in DMF (30 mL) was added iodobromide **4f** (4.3 g, 12.5 mmol), followed by stirring of the mixture for 24 h at 40 °C. Purification of the crude material by flash chromatography (ethyl acetate/hexane, 1:4) first furnished the branched aldehyde **6f** (700 mg, 18%) as colorless oil. Further elution of the column (ethyl acetate/hexane, 1:3) furnished the linear aldehyde **5f** (2.8 g, 74%) as colorless oil.



6f

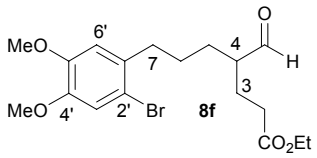
^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 9.70 (s, 1H, CH=O), 6.98 (s, 1H, Ar-H) and 6.67 (s, 1H, Ar-H), 3.84 (s, 3H) and 3.83 (s, 3H) [2 OCH_3], 3.28–3.12 (m, 1H, 4-H), 2.53–2.36 (m, 1H) and 2.36–2.23 (m, 1H) [2-H], 1.98–1.75 (m, 2H, 3-H), 1.21 (d, *J* = 6.9 Hz, 3H, 4-CH_3); ^{13}C NMR (100 MHz,

$CDCl_3$): δ[ppm] = 202.1 (CH=O), 148.8 (C), 147.9 (C), 136.7 (C-1'), 115.4 (CH), 114.3 (C-2'), 109.5 (CH), 56.1 (OCH_3), 56.0 (OCH_3), 41.9 (C-2), 37.1 (C-4), 29.6 (C-3), 21.4 (C-5).



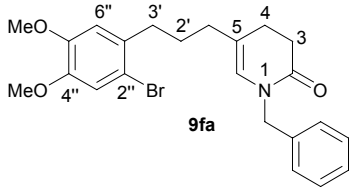
5f

^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 9.75 (s, 1H, CH=O), 6.96 (s, 1H, Ar-H), 6.68 (s, 1H, Ar-H), 3.83 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 2.65 (t, J = 7.6 Hz, 2H, 5-H), 2.46 (dt, J = 7.1, 1.5 Hz, 2H, 2-H), 1.76–1.52 (m, 4H, 3-H, 4-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 202.4 (CH=O), 148.3 (C), 147.8 (C), 133.1 (C-1'), 115.5 (CH), 113.9 (C-2'), 112.8 (CH), 56.1 (OCH_3), 56.0 (OCH_3), 43.6 (C-5), 35.4 (C-2), 29.6 (C-4), 21.6 (C-3).



8f

Ethyl 7-(2-bromo-4,5-dimethoxyphenyl)-4-formylheptanoate (8f): The reaction was performed with aldehyde **5f** (2.8 g, 9.3 mmol), pyrrolidine (1.5 mL, 18.5 mmol), K_2CO_3 (3.8 g, 27.8 mmol), molecular sieves (4 Å, 2 g) and ethyl acrylate (1.4 mL, 12.9 mmol) as described above. Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:3) furnished the aldehyde ester **5f** (2.3 g, 63% for two steps) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 9.58 (s, 1H, CH=O), 6.96 (s, 1H, Ar-H), 6.66 (s, 1H, Ar-H), 4.09 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 3.83 (s, 3H, OCH_3), 3.81 (3H, s, OCH_3), 2.64 (t, J = 7.6 Hz, 2H, 7-H), 2.42–2.20 (m, 3H), 2.05–1.85 (m, 1H), 1.85–1.40 (m, 5H), 1.22 (t, J = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 204.0 (CH=O), 172.8 (OC=O), 148.3 (C), 147.8 (C), 132.9 (C-1'), 115.5 (CH), 113.9 (C-2'), 112.8 (CH), 60.4 (OCH_2CH_3), 56.1 (OCH_3), 56.0 (OCH_3), 50.8 (C-4), 35.6 (C-7), 31.5 (C-2), 28.2 (CH_2), 27.4 (CH_2), 23.5 (C-3), 14.1 (OCH_2CH_3).

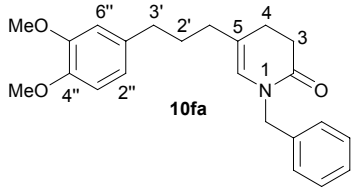


9fa

1-Benzyl-5-[3-(2-bromo-4,5-dimethoxyphenyl)propyl]-3,4-dihydropyridin-2(1*H*)-one (9fa): As described for compound **9aa**, the formyl ester **8f** (2.0 g, 4.9 mmol) in CH_2ClCH_2Cl (10 mL) was reacted with benzylamine (1.1 mL, 10.0 mmol) and AcOH (0.3 mL, 4.9 mmol). Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:1) furnished the cyclic enamide **9fa** (2.0 g, 90%) as a colorless solid, which was recrystallized from a mixture of CH_2Cl_2 and hexane, m.p. 110–112 °C; IR (neat): ν_{max}/cm^{-1} = 3062, 3029, 2932, 2838, 1664, 1603, 1508, 1439, 1410, 1381, 1337, 1255, 1215, 1163, 1030, 959, 855, 731, 701; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.40–7.15 (m, 5H, Ar-H), 6.97 (s, 1H, Ar-H), 6.63 (s, 1H, Ar-H), 5.80 (s, 1H, 6-H), 4.66 (s, 2H, NCH_2Ph), 3.83 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 2.58 (t, J = 7.6 Hz, 4H, 1'-H, 3'-H), 2.28 (2H, 4-H) and 2.06 (2H, 3-H) [2 t, J = 7.9 Hz], 1.65 (quintet, J = 7.9 Hz, 2H, 2'-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 168.9 (NC=O), 148.3 (C), 147.8 (C), 137.3 (C), 133.3 (C-1''), 128.6 (2 C, CH), 127.4 (2 C, CH), 127.3 (CH), 124.2 (C-6), 119.7 (C-5), 115.5 (CH), 113.9 (C-2''), 112.9 (CH), 56.1, 56.0 (2 OCH_3), 48.8 (NCH_2Ph), 35.3 (C-3'), 33.3 (C-1'), 31.3 (C-3), 28.1 (CH_2), 24.1 (C-4); HRMS (ESI): $[M+H]^+$ calcd for $C_{23}H_{27}BrNO_3$ 444.1169, found 444.1168.

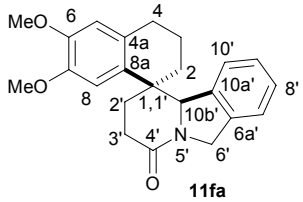
Palladium-catalyzed spiro cyclization of 5-(bromophenyl)propyl-substituted enamide 9fa: The reaction was performed with the enamide **9fa** (120 mg, 0.27 mmol) in anhydrous DMF (2 mL) with Ph_3P (14 mg, 20 mol%), Cs_2CO_3 (352 mg, 1.1 mmol) and $Pd(OAc)_2$ (6.1 mg, 10 mol%). After

loading of the reagents at room temperature, the mixture was heated to 120 °C, as described for compound **9aa**. Purification of the crude product mixture by flash chromatography (ethyl acetate/hexane, 1:1) first furnished the debromoenamide **10fa** (30 mg, 30%) as brown viscous oil. Further elution of the column (ethyl acetate/hexane, 9:1) furnished the polycyclic amide **11fa** (50 mg, 51%) as a colorless solid, which was recrystallized from a mixture of CH_2Cl_2 and hexane.



10fa

1-Benzyl-5-[3-(3,4-dimethoxyphenyl)propyl]-3,4-dihydropyridin-2(1*H*)-one (10fa): IR (neat): ν_{max}/cm^{-1} = 2934, 2834, 1662, 1606, 1514, 1493, 1453, 1416, 1360, 1259, 1236, 1155, 1029, 732, 704; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.37–7.18 (m, 5H, Ar-H), 6.75 (d, 1H, *J* = 7.9 Hz, Ar-H), 6.62 (d, 1H, *J* = 7.9 Hz, Ar-H), 6.63 (s, 1H, 2''-H), 5.75 (s, 1H, 6-H), 4.66 (s, 2H, NCH_2Ph), 3.84 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 2.56 (t, *J* = 7.6 H, 2H, 3'-H), 2.49 (t, *J* = 7.6 H, 2H, 1'-H), 2.25 (t, *J* = 7.9 Hz, 2H, 4-H), 2.01 (t, *J* = 7.9 Hz, 2H, 3-H), 1.66 (quintet, *J* = 7.6 Hz, 2H, 2'-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 168.8 (NC=O), 148.8 (C), 147.1 (C), 137.3 (C), 134.5 (C-1''), 128.6 (2 C, CH), 127.5 (2 C, CH), 127.3 (CH), 124.0 (C-6), 120.1 (C-6''), 119.9 (C-5), 111.6 (CH), 111.1 (CH), 55.9 (OCH_3), 55.7 (OCH_3), 48.7 (NCH_2Ph), 34.8 (C-3'), 33.1 (C-1'), 31.2 (C-3), 29.3 (CH_2), 24.1 (C-4); HRMS (ESI): $[M+H]^+$ calcd for $C_{23}H_{28}NO_3$ 366.2064, found 366.2063.



11fa

6,7-Dimethoxy-2',3,3',4,6',10b'-hexahydro-2*H*,4'*H*-spiro[naphthalene-1,1'-pyrido[2,1-*a*]isoindol]-4'-one (11fa): m.p. 173–175 °C; IR (neat): ν_{max}/cm^{-1} = 3055, 2933, 2857, 1664, 1604, 1590, 1488, 1437, 1345, 1255, 1215, 1120, 722, 696; ^{1}H NMR (400 MHz, $CDCl_3$): δ[ppm] = 7.20 (d, *J* = 7.6 Hz, 1H, 10'-H), 7.09 (t, *J* = 7.6 Hz, 1H, 8'-H), 6.93 (t, *J* = 7.6 Hz, 1H, 9'-H], 6.75 (d, *J* = 7.6 Hz, 1H, 7'-H), 6.39 (s, 1H, 8-H), 6.06 (s, 1H, 5-H), 4.89 (d, 1H) and 4.76 (d, 1H) [*J* = 16.0 Hz, 6'-H], 4.87 (s, 1H, 10b'-H), 3.72 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 2.85–2.65 (m, 2H), 2.58–2.40 (m, 2H), 2.31 (td, *J* = 14.0, 4.3 Hz, 1H, 1H), 2.20–1.75 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm] = 172.6 (NC=O), 146.8 (C-7), 146.7 (C-6), 138.9 (C-10a'), 135.7 (C-8a), 132.9 (C-6a'), 129.4 (C-4a), 127.6 (CH), 127.3 (CH), 122.9 (CH), 122.5 (CH), 110.5 (CH), 110.0 (CH), 70.8 (C-10b'), 55.4 (OCH_3), 55.3 (OCH_3), 49.9 (C-6'), 42.2 (C-(1,1')), 38.3 (C-4), 36.1 (C-2'), 31.1 (C-3'), 30.0 (CH_2), 19.9 (CH_2); HRMS (ESI): $[M+H]^+$ calcd for $C_{23}H_{26}NO_3$ 364.1907, found 364.1905.

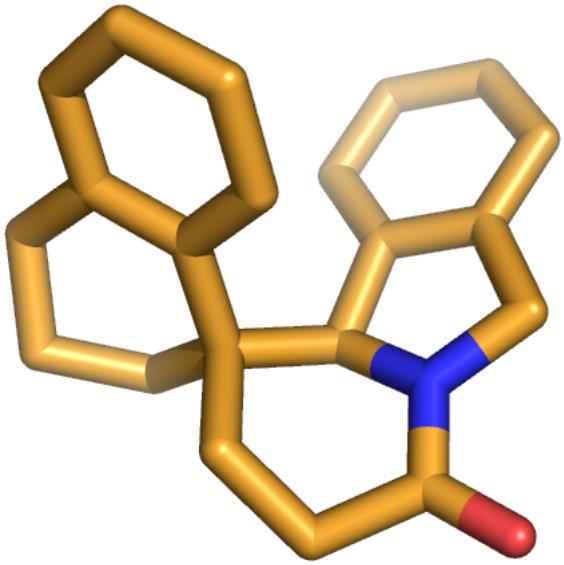
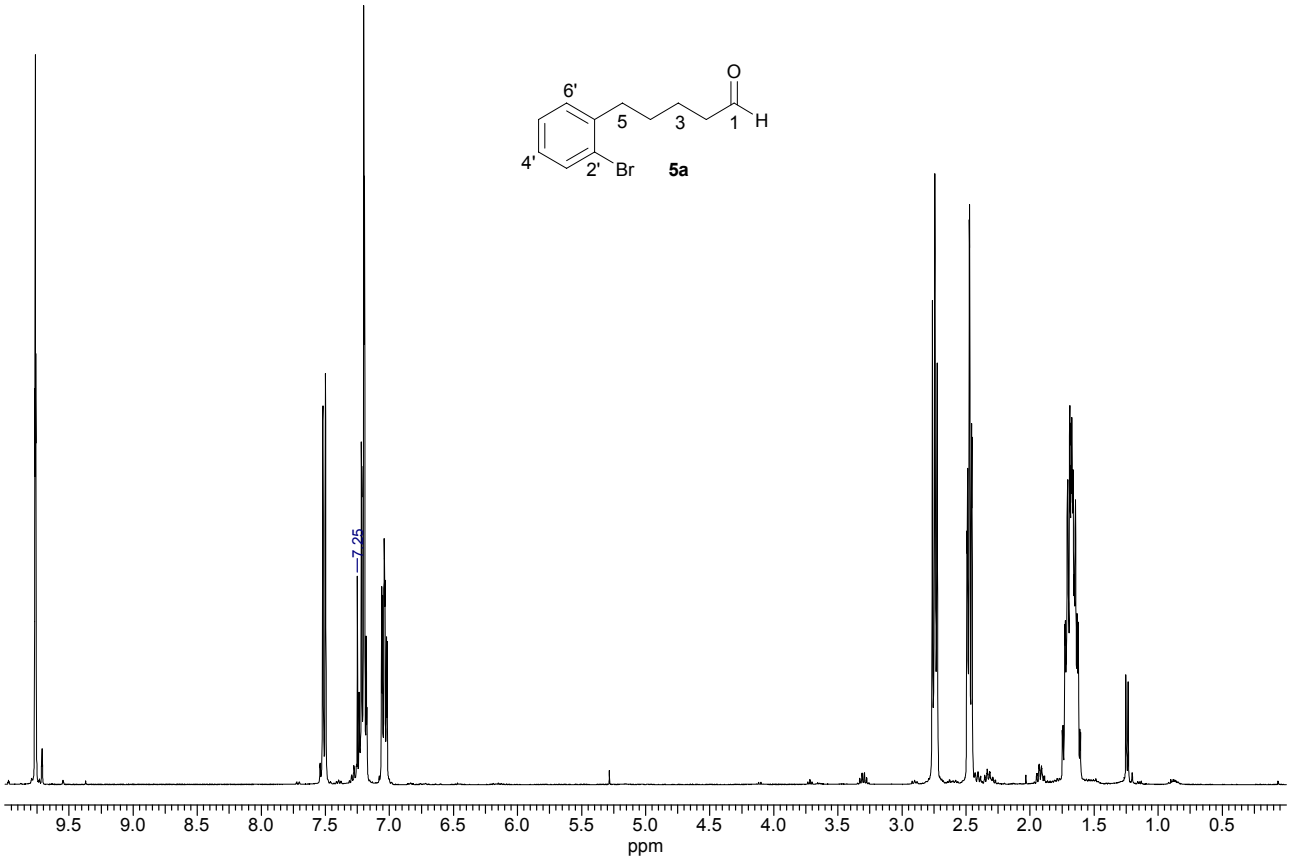
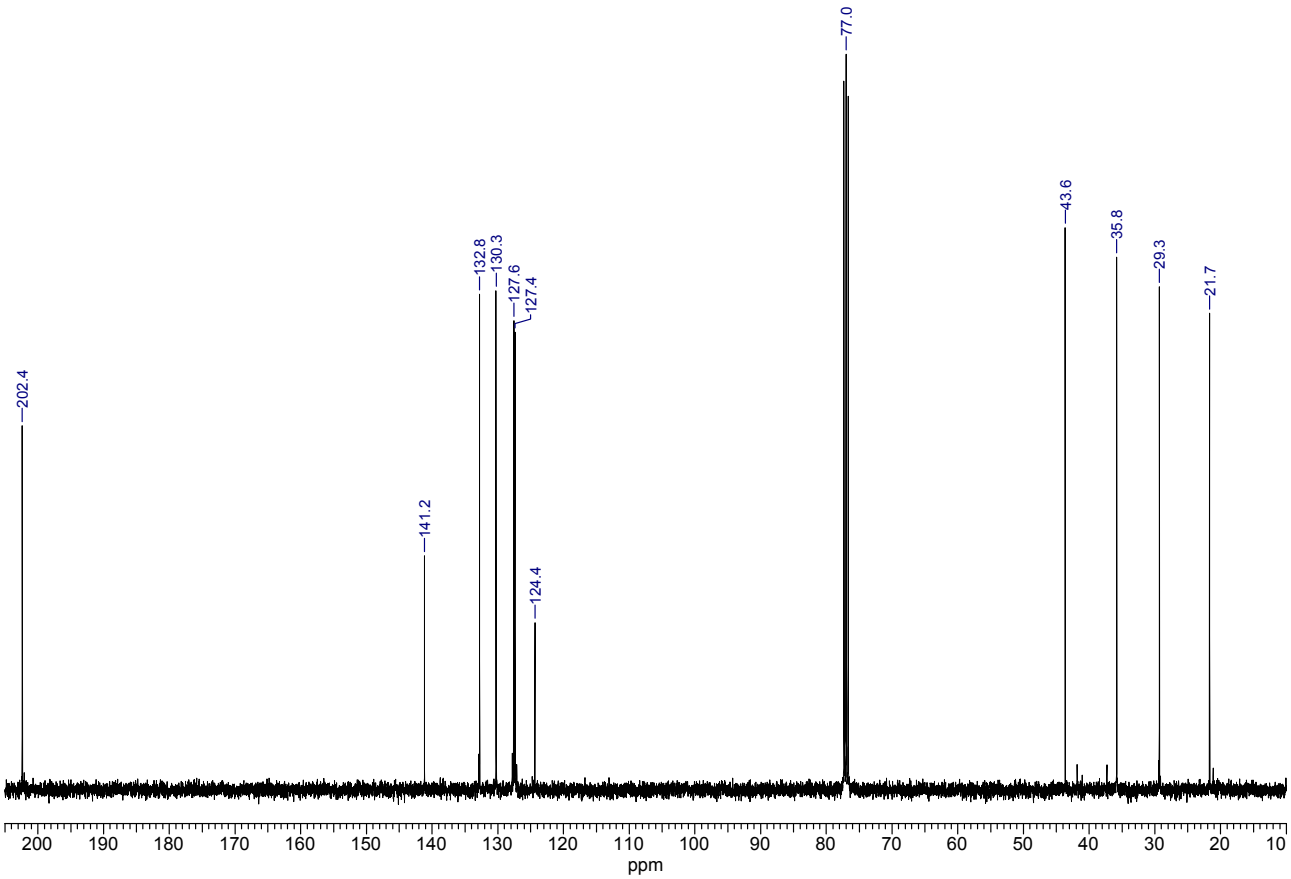
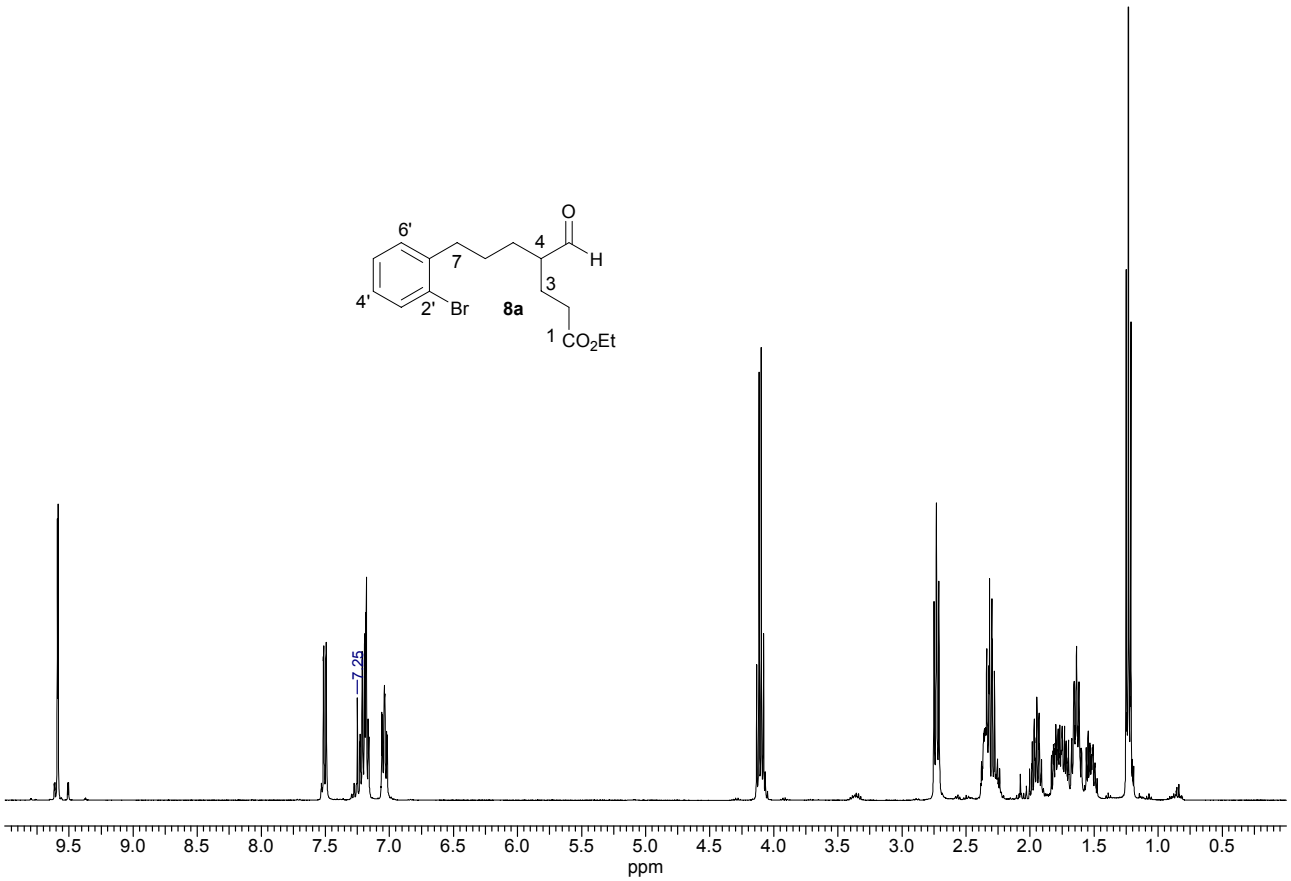
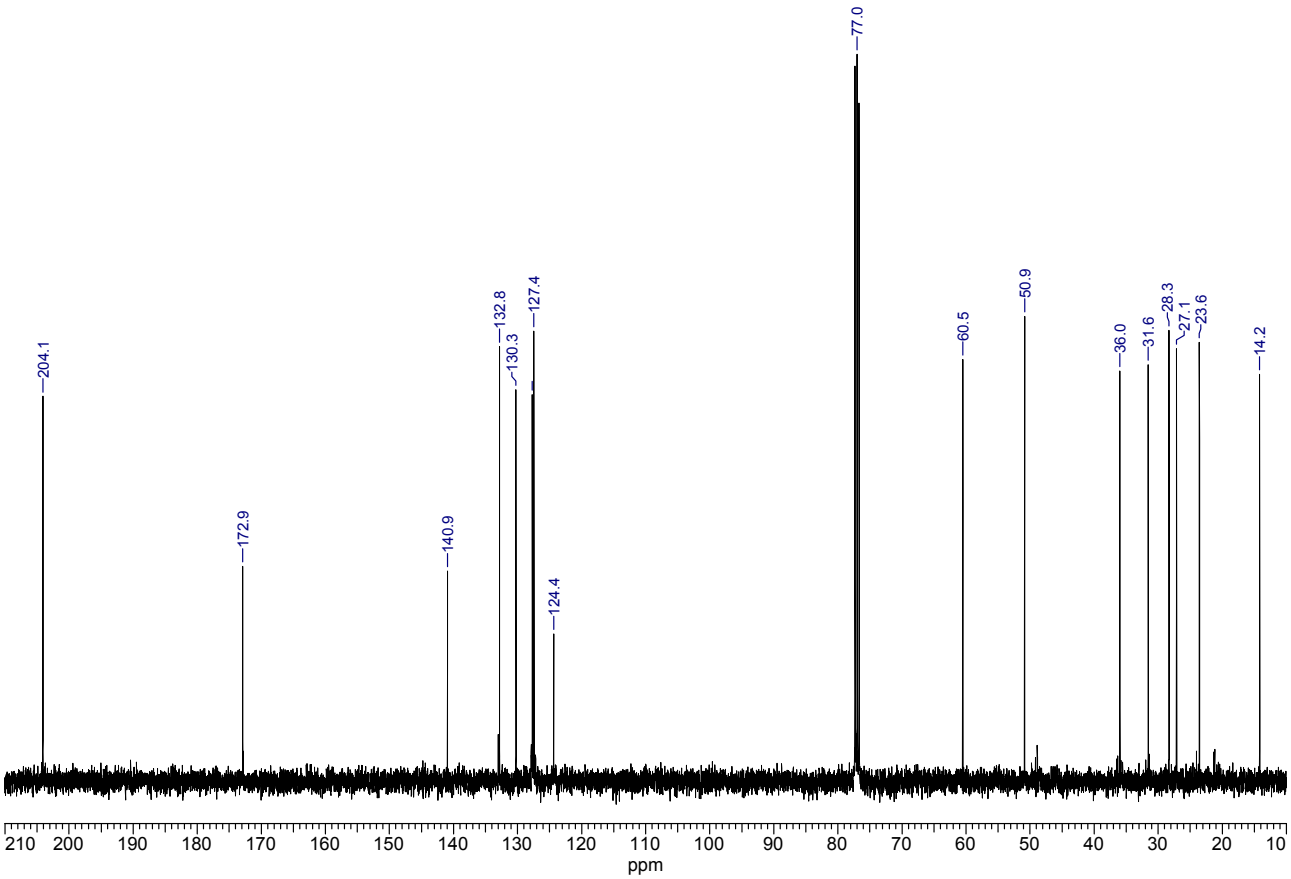


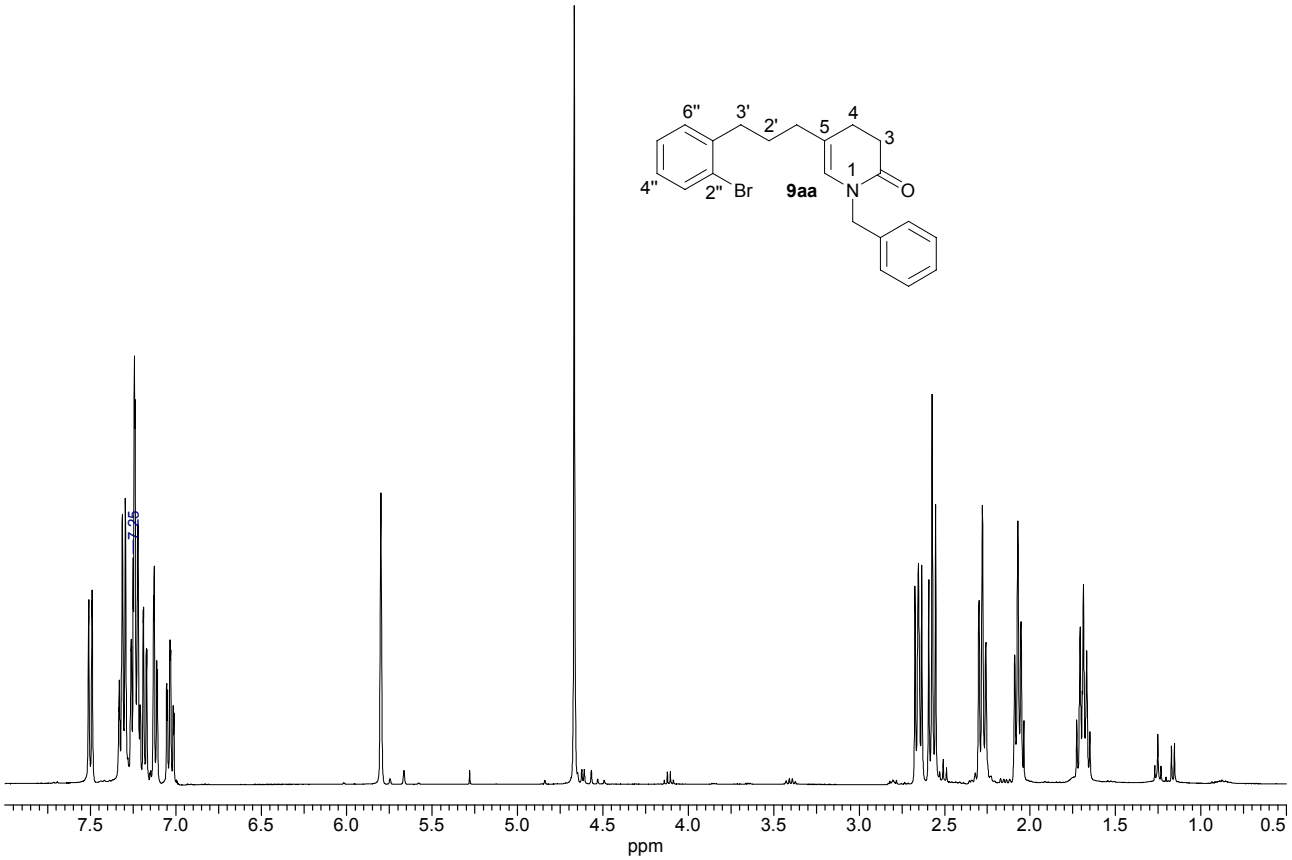
Fig. 1 X-ray structure of pentacycle **11aa**.

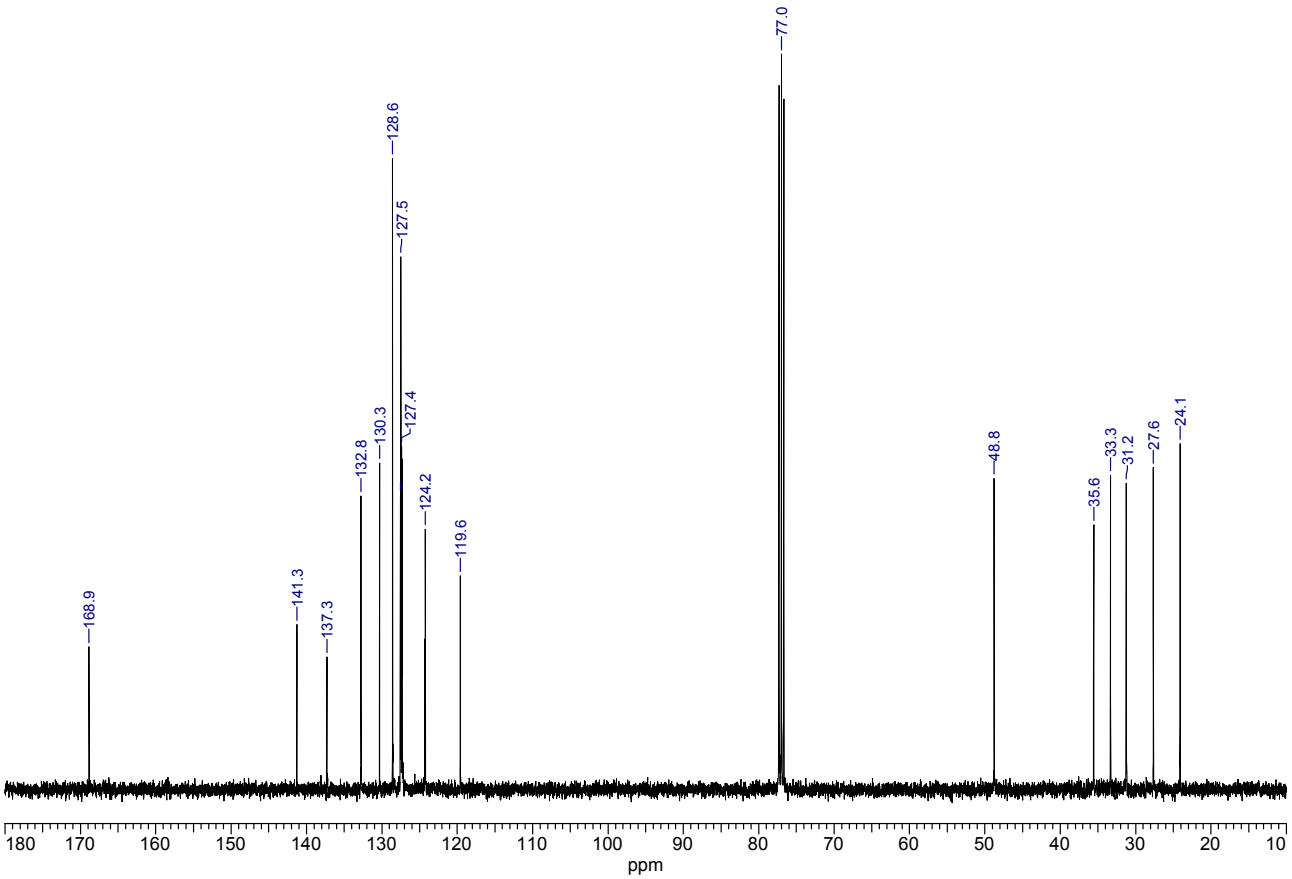


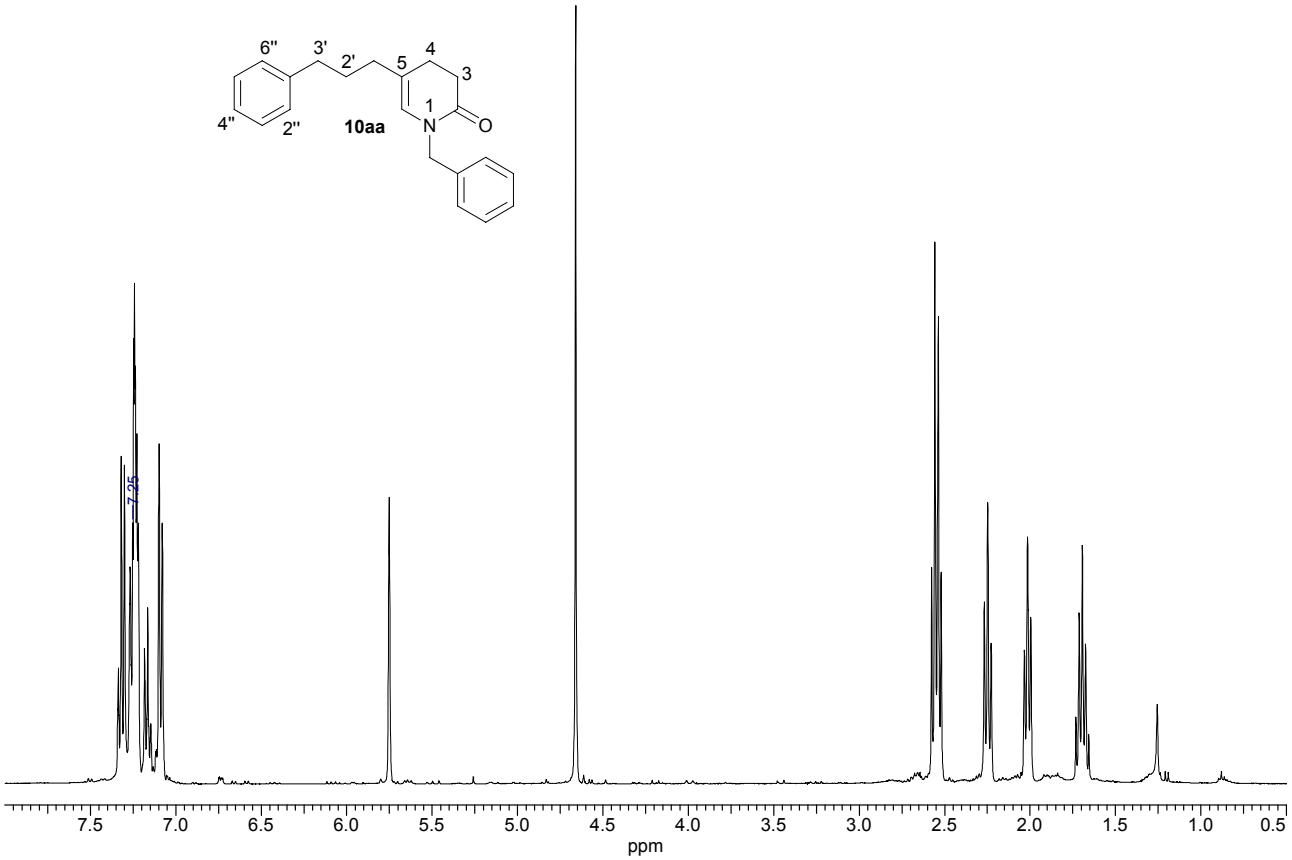








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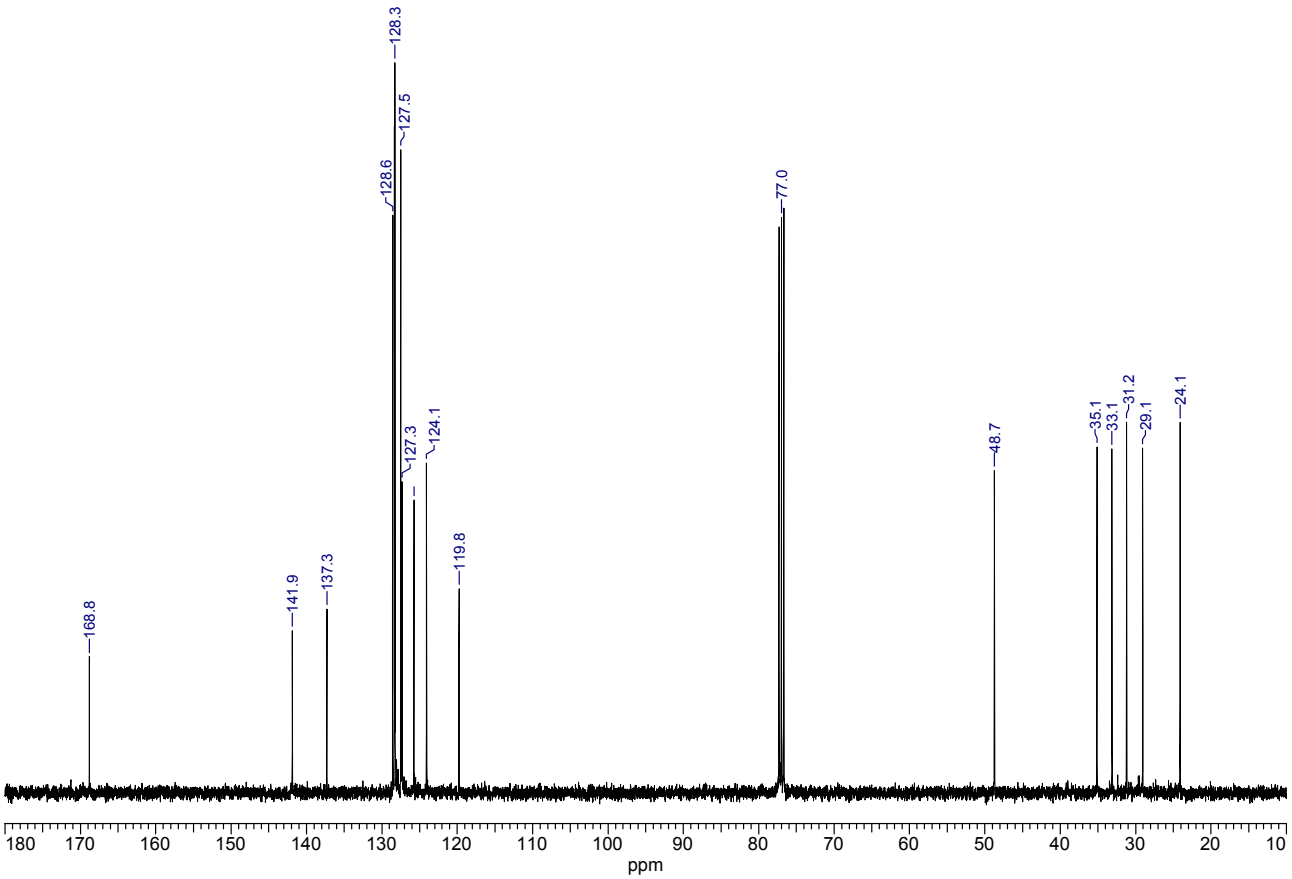
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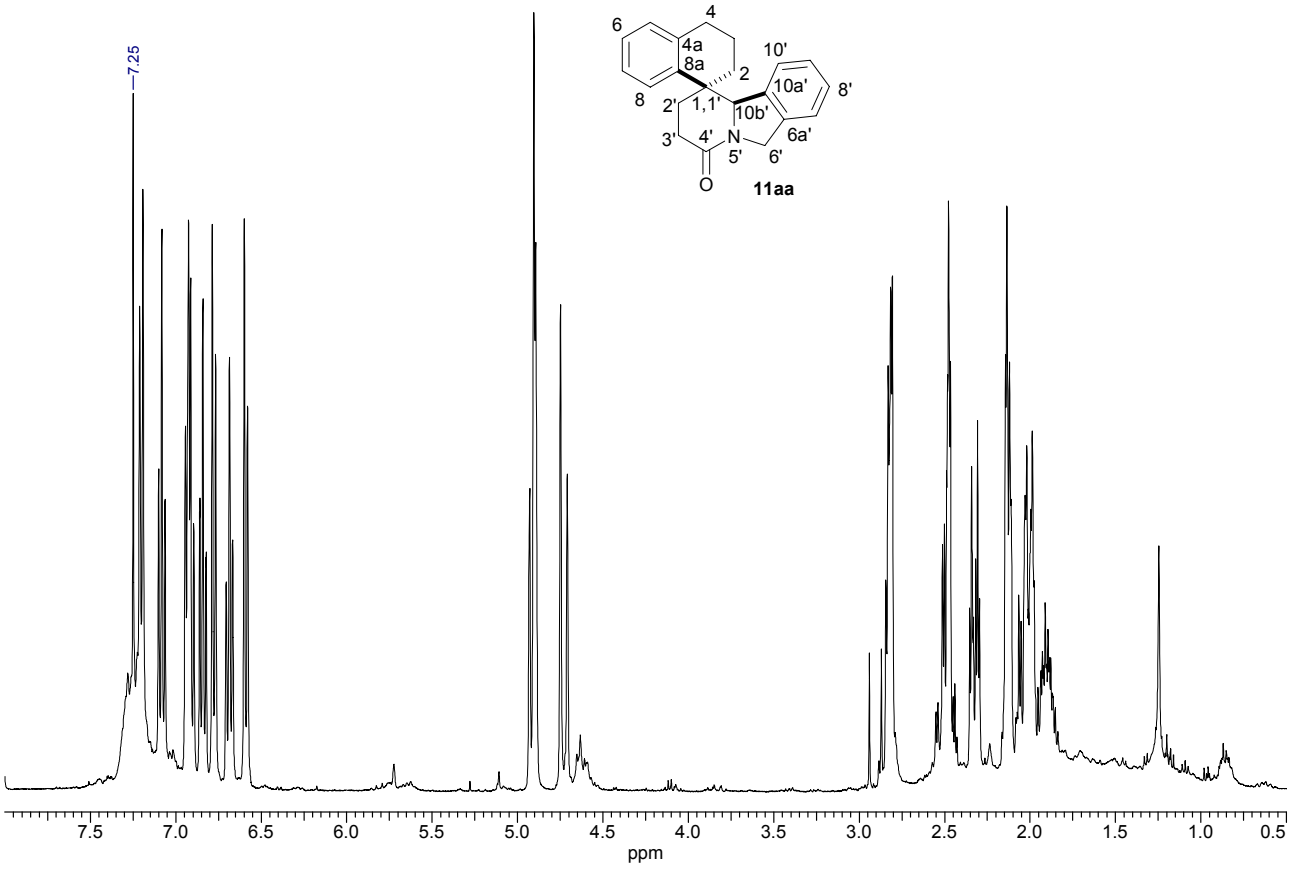
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10b'
3'
4'
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5'
6'
O
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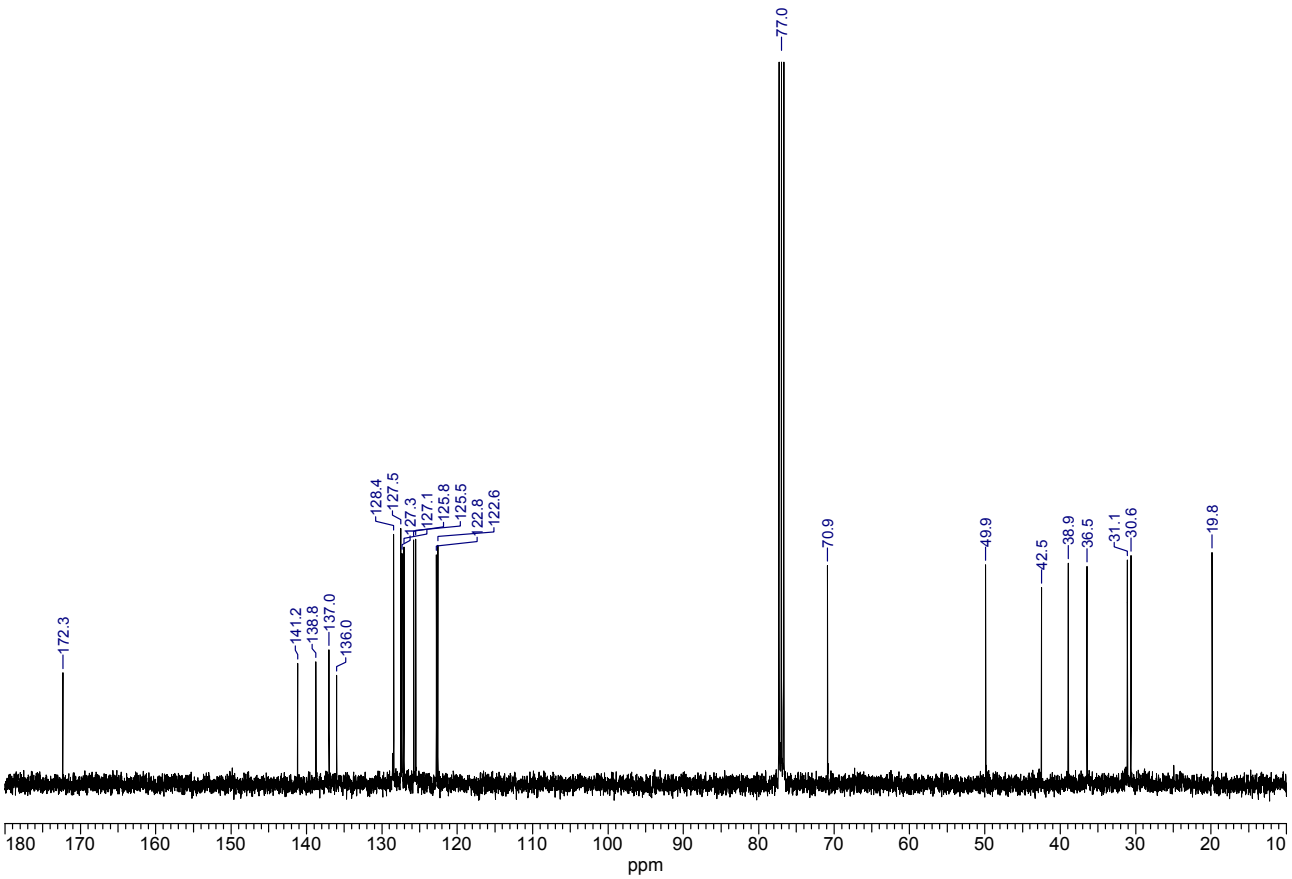
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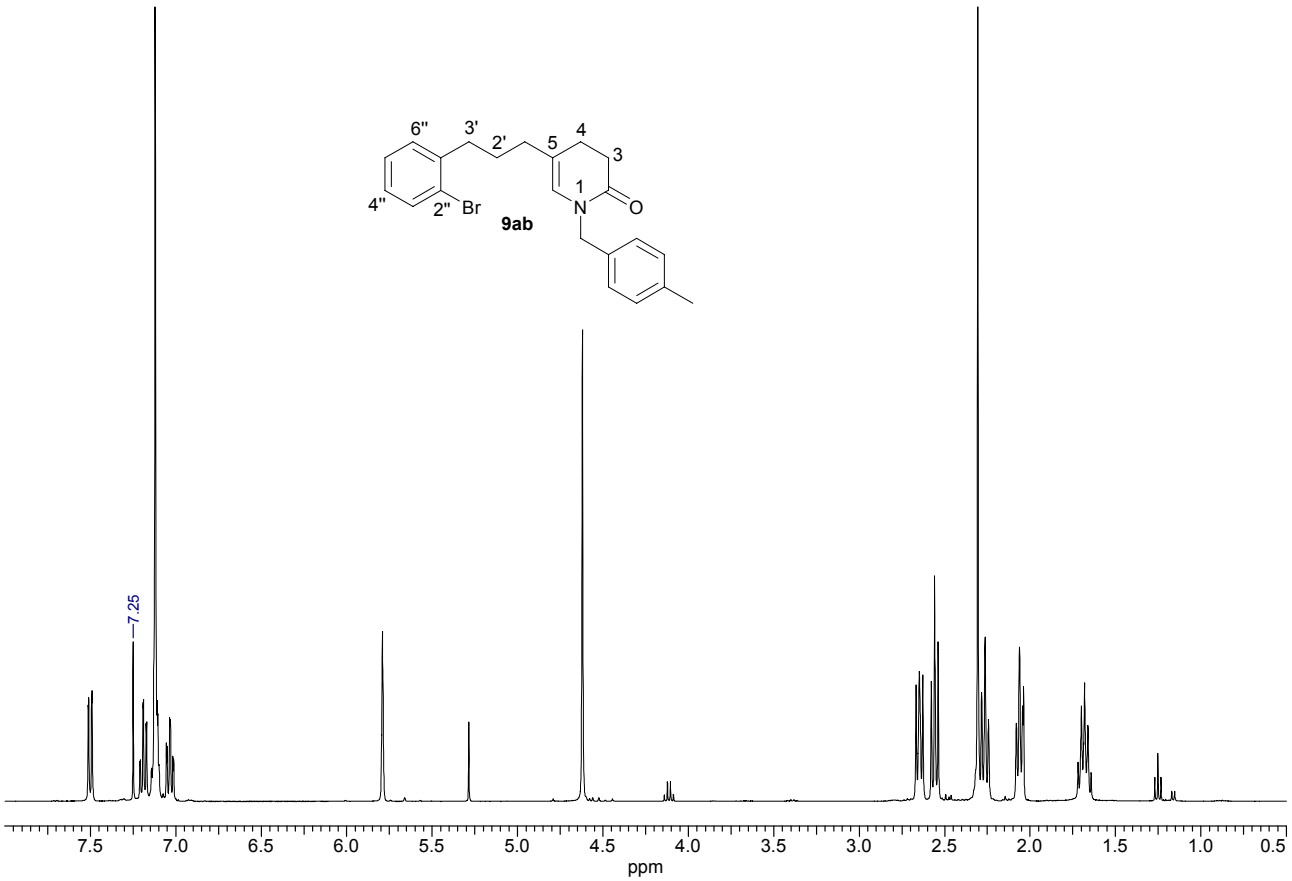
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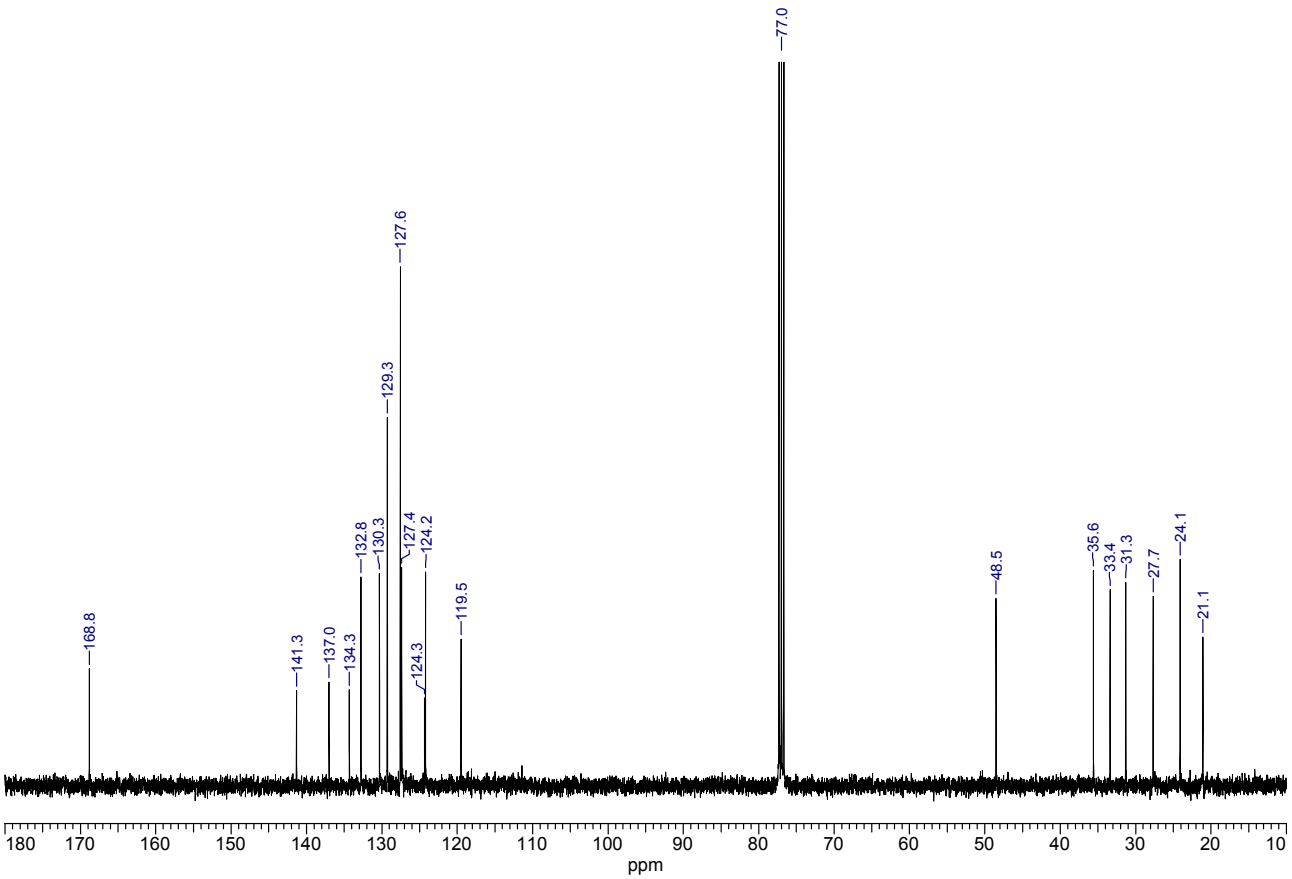
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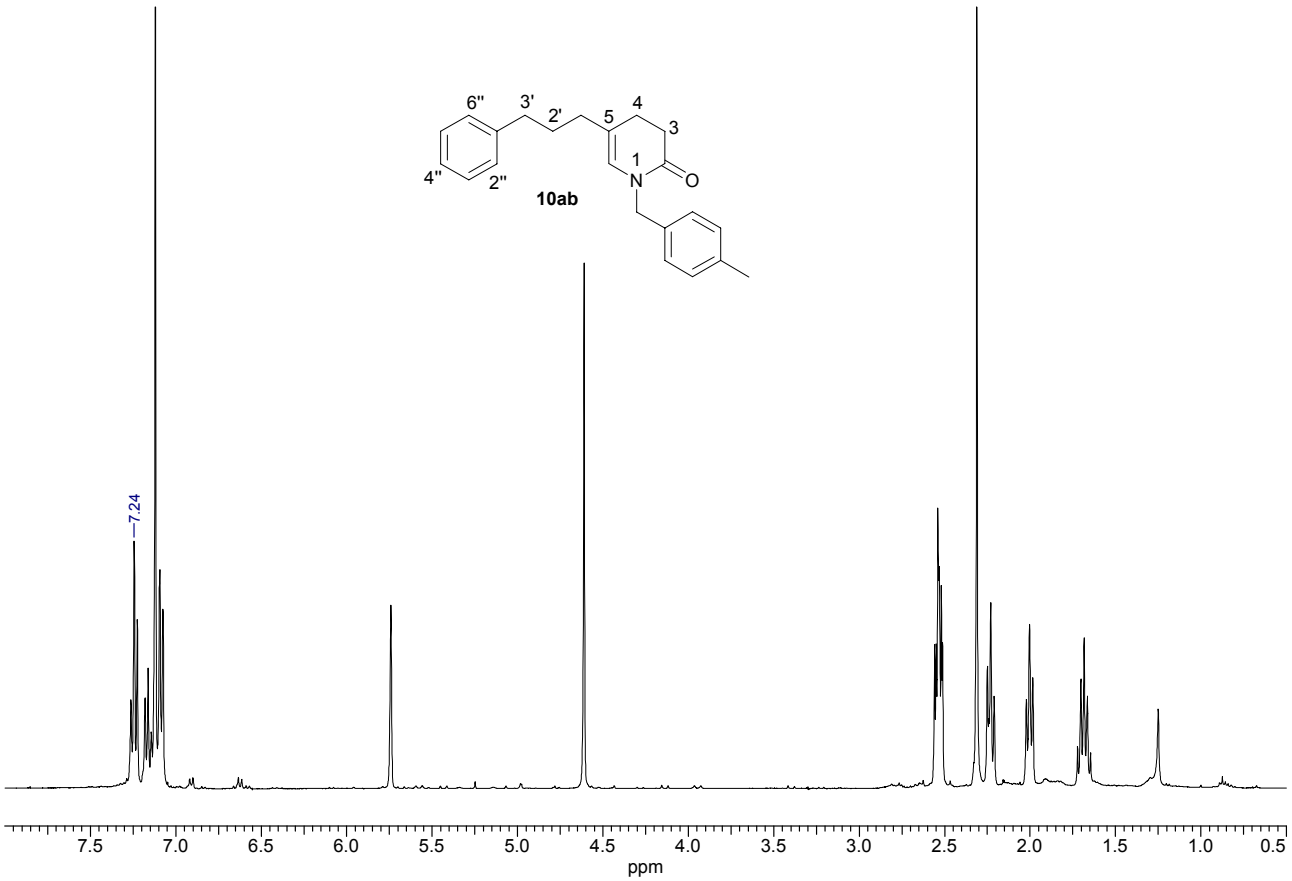
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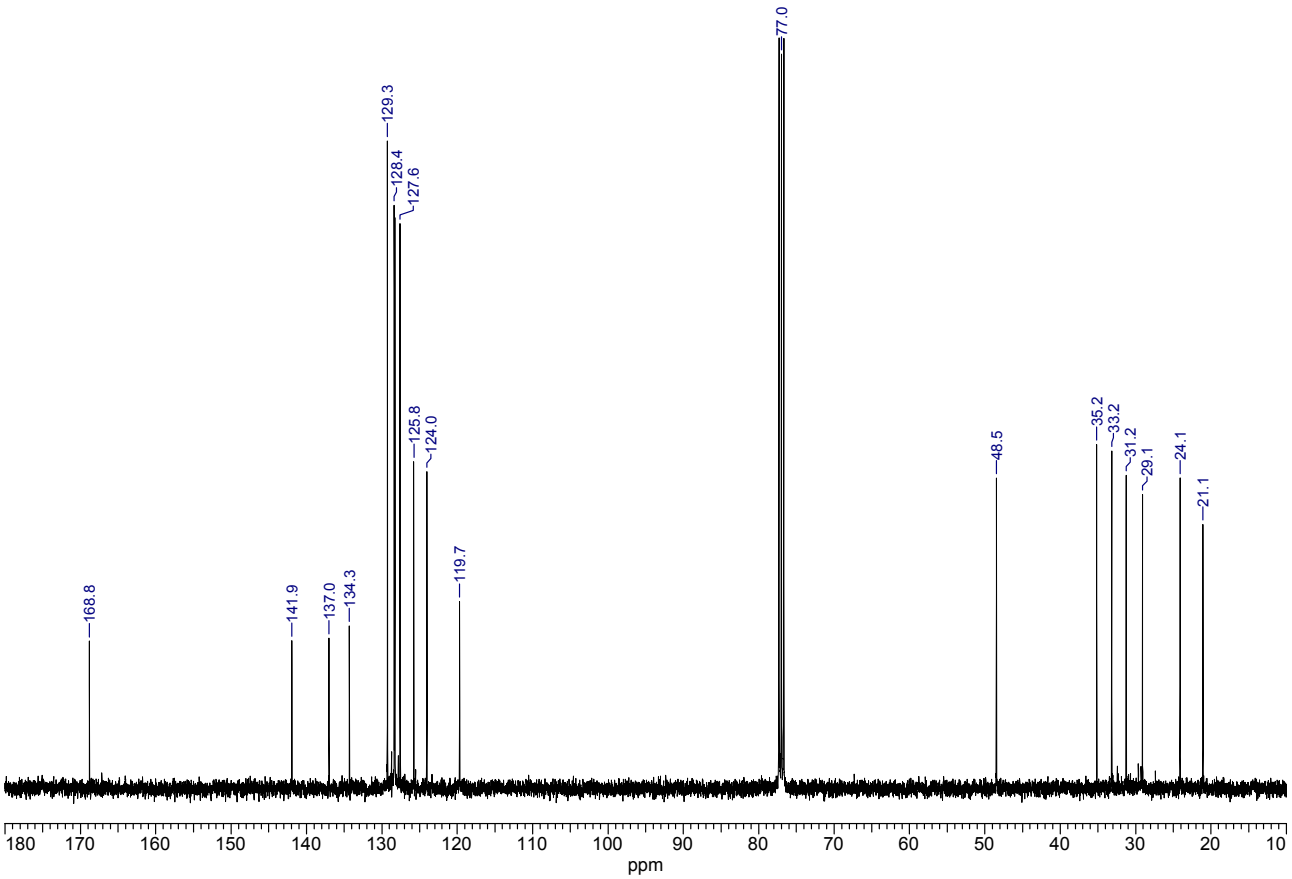
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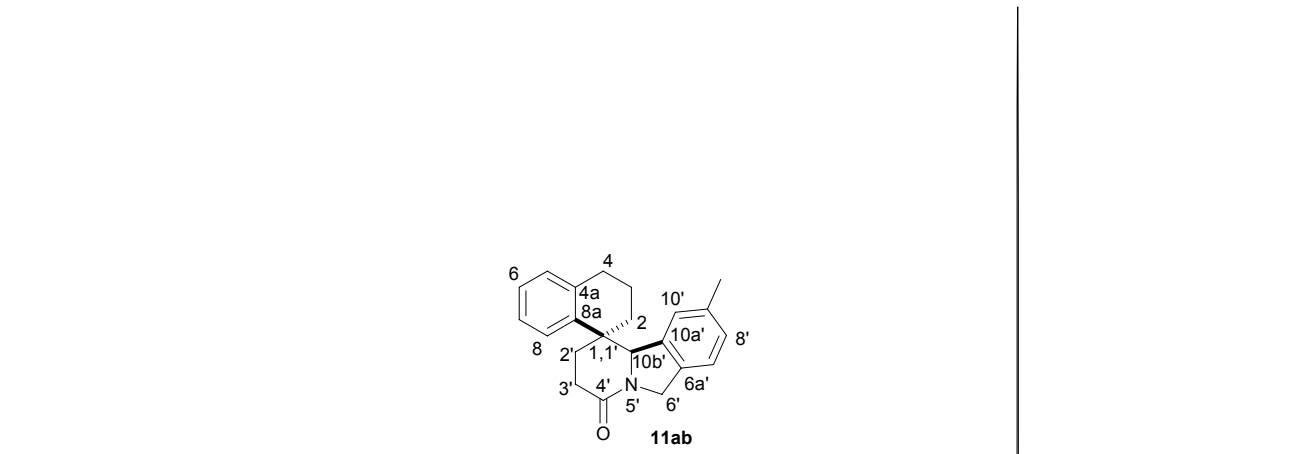
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5'
6'
6a'
O

11ab

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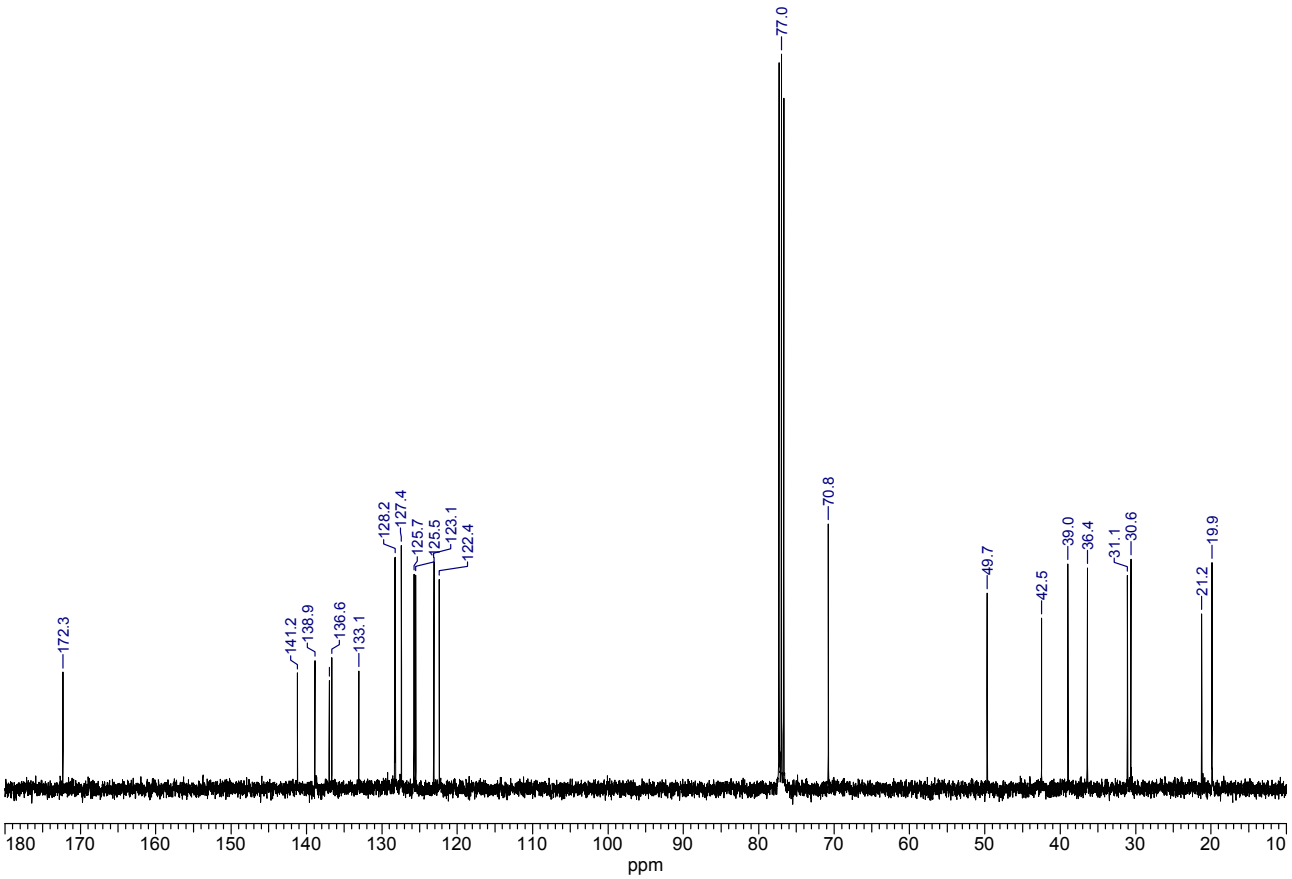
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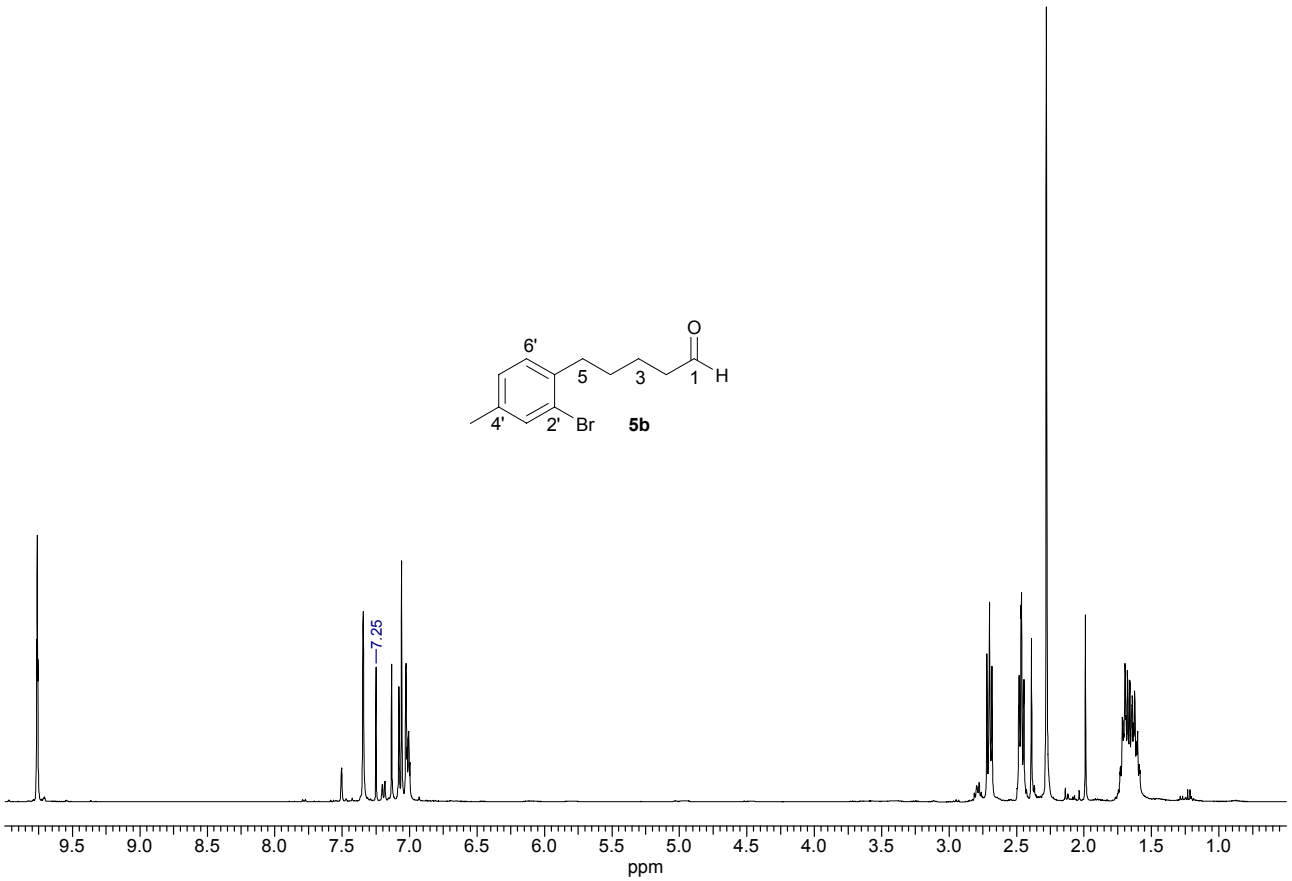
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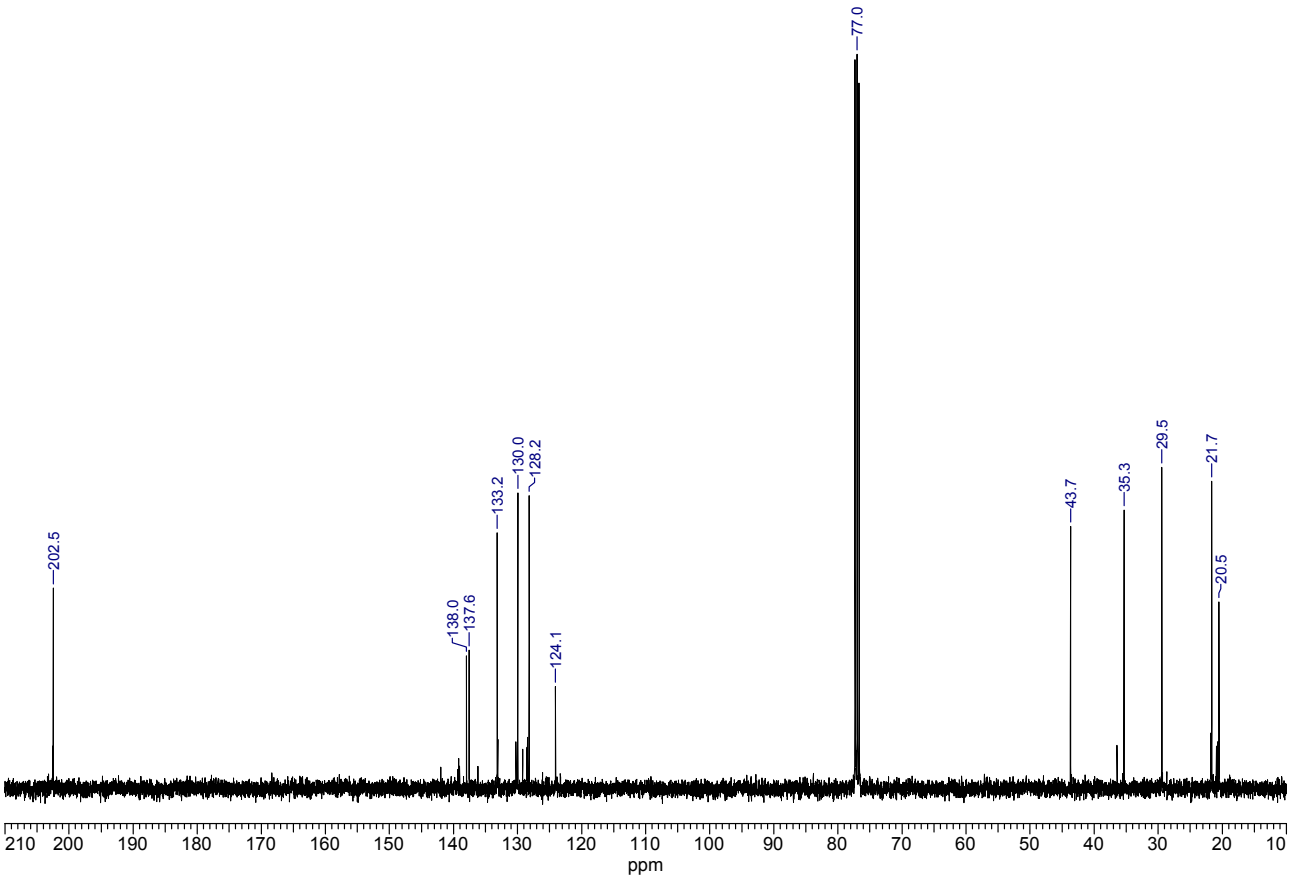
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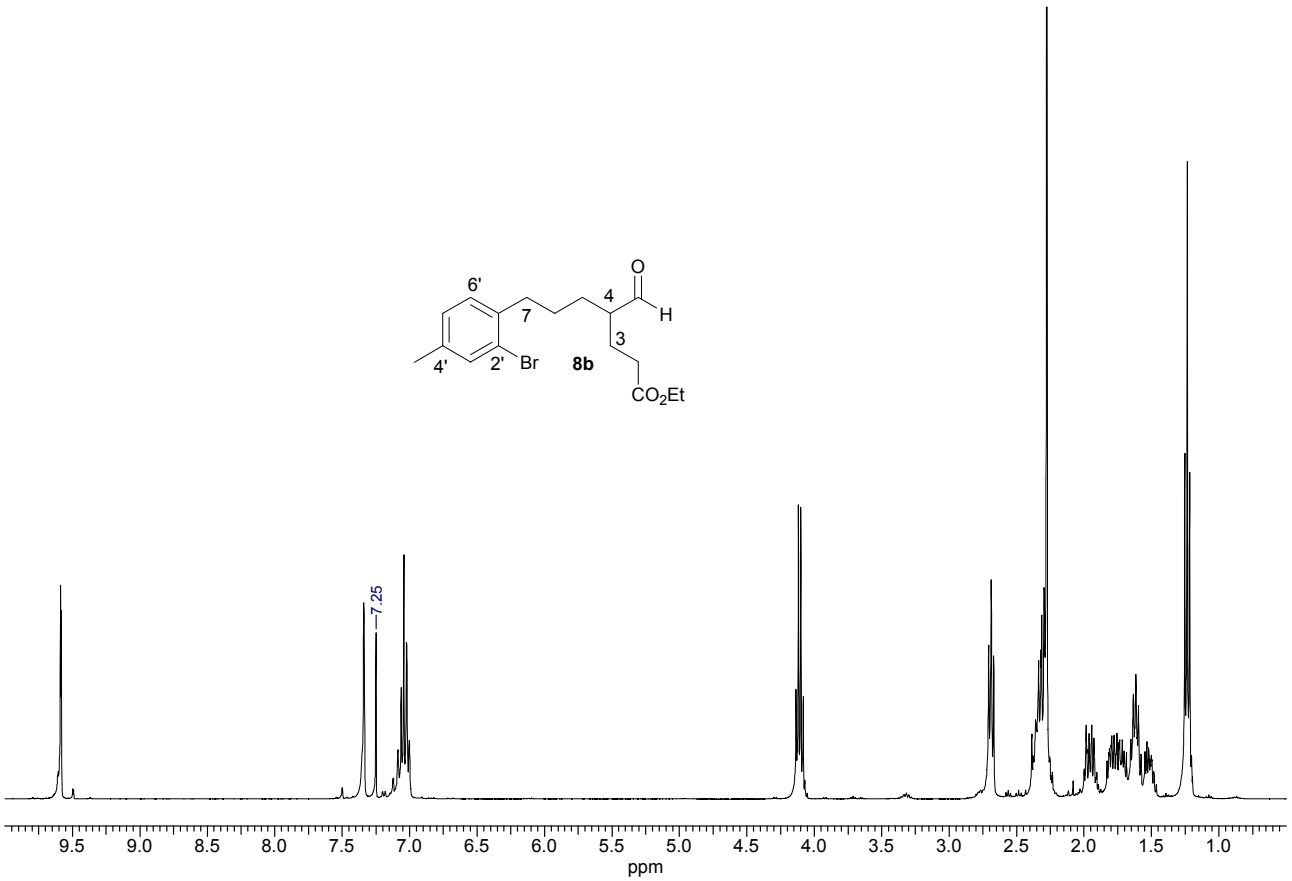
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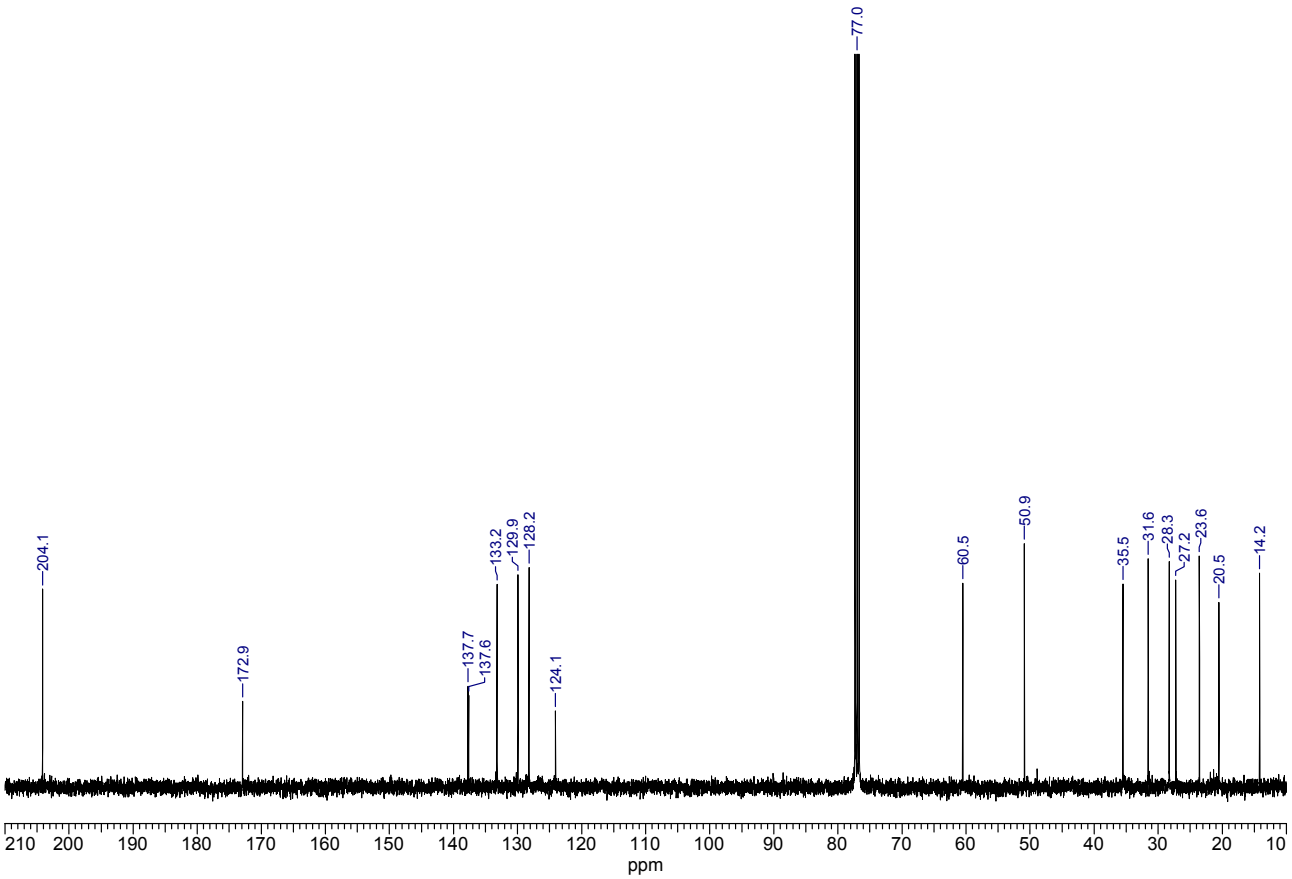
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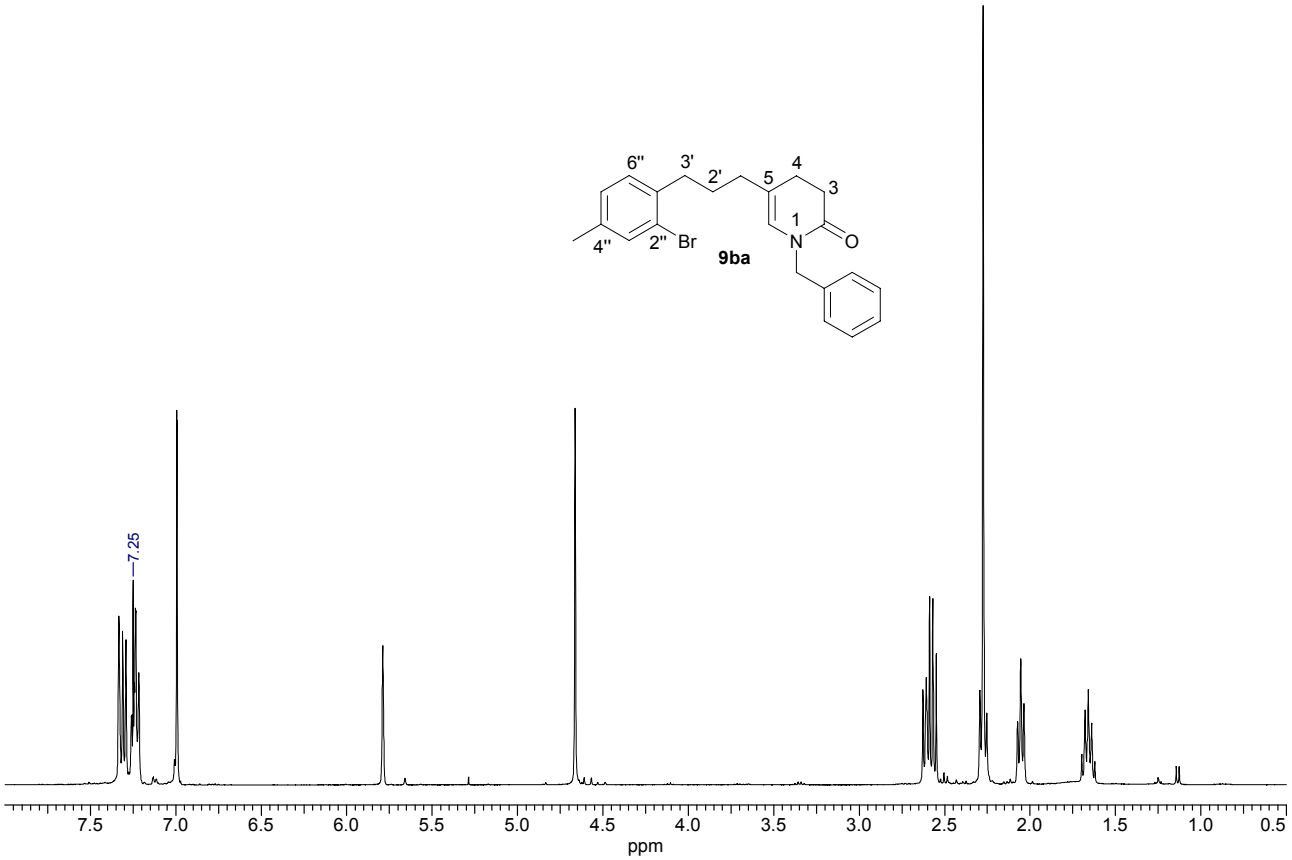
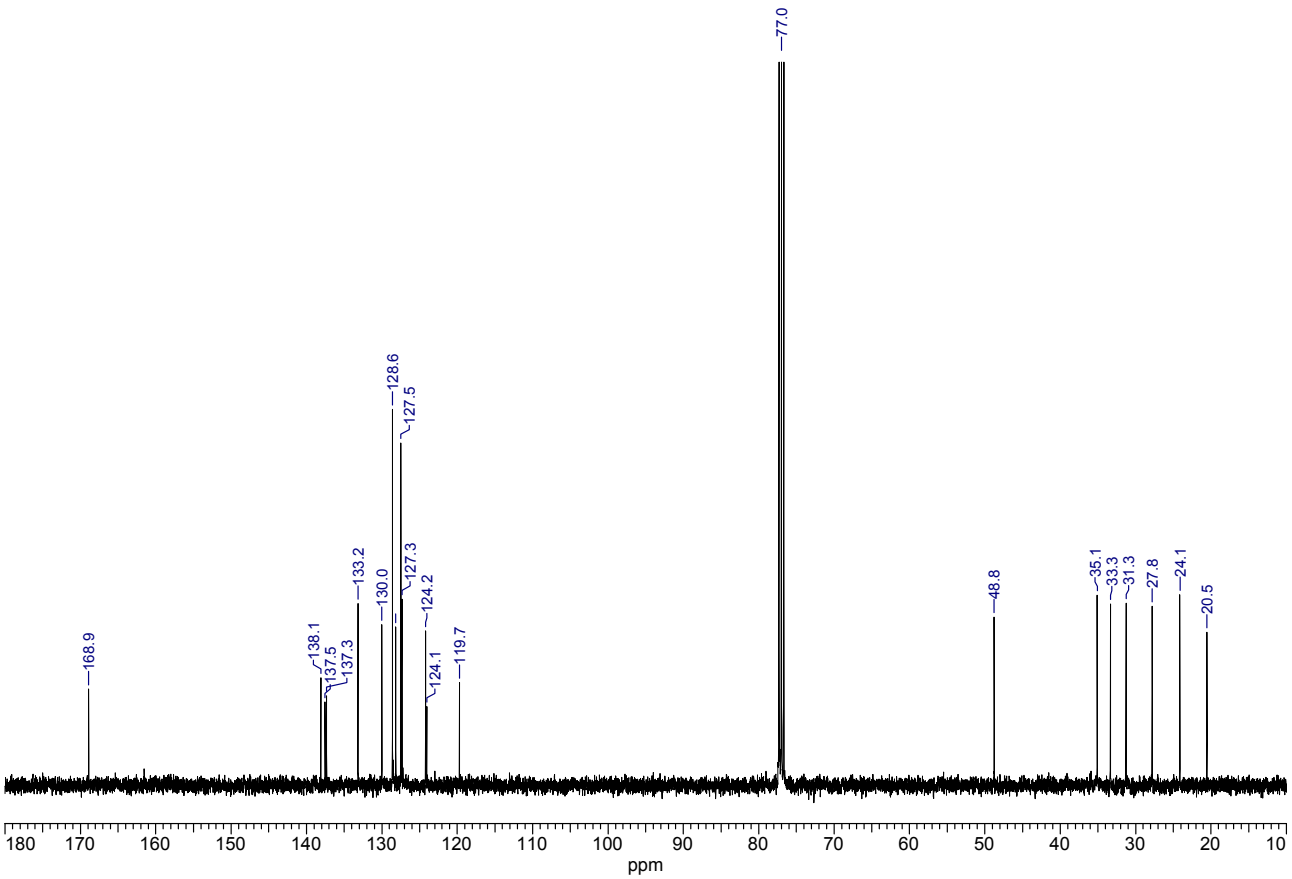
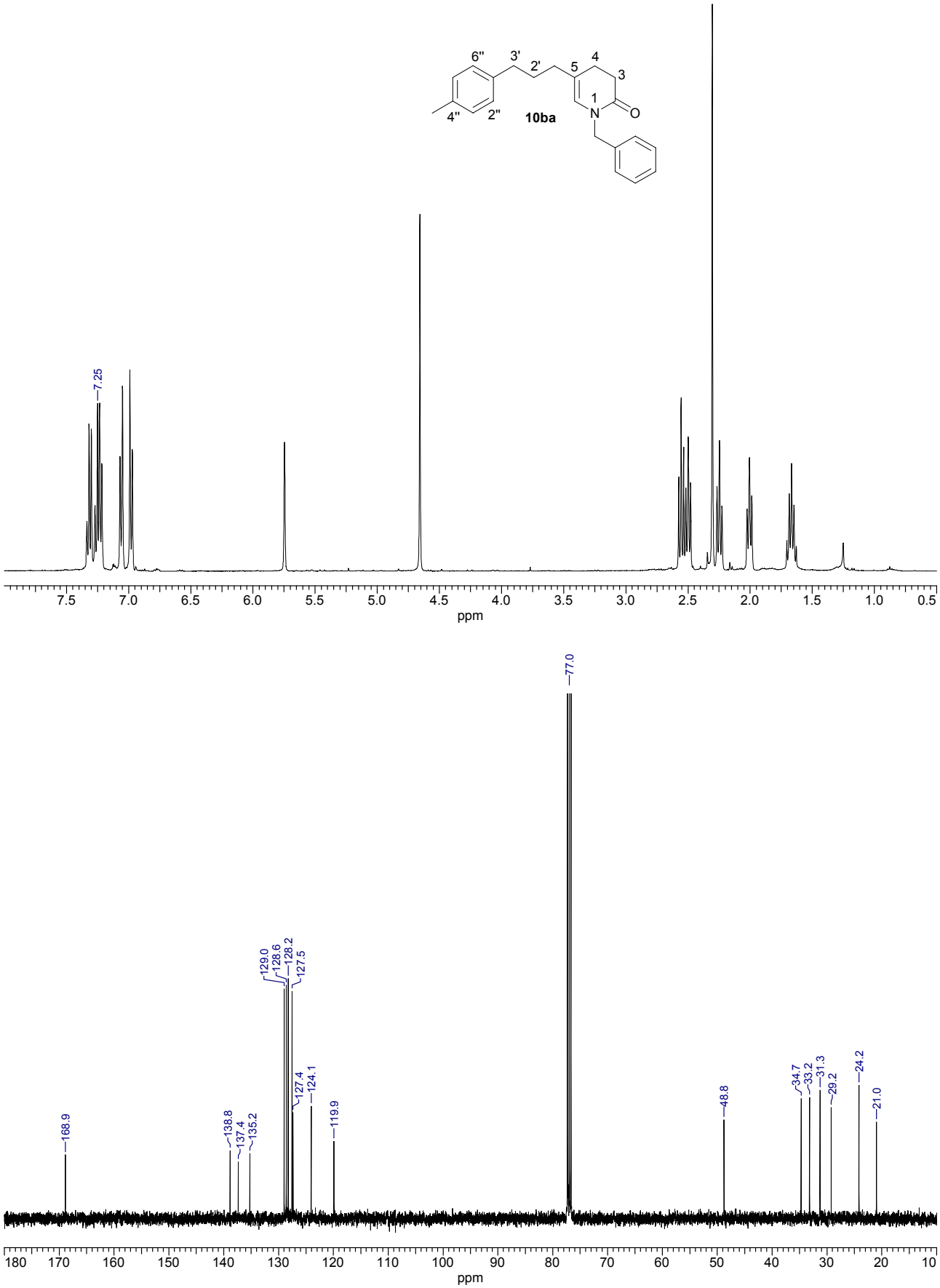
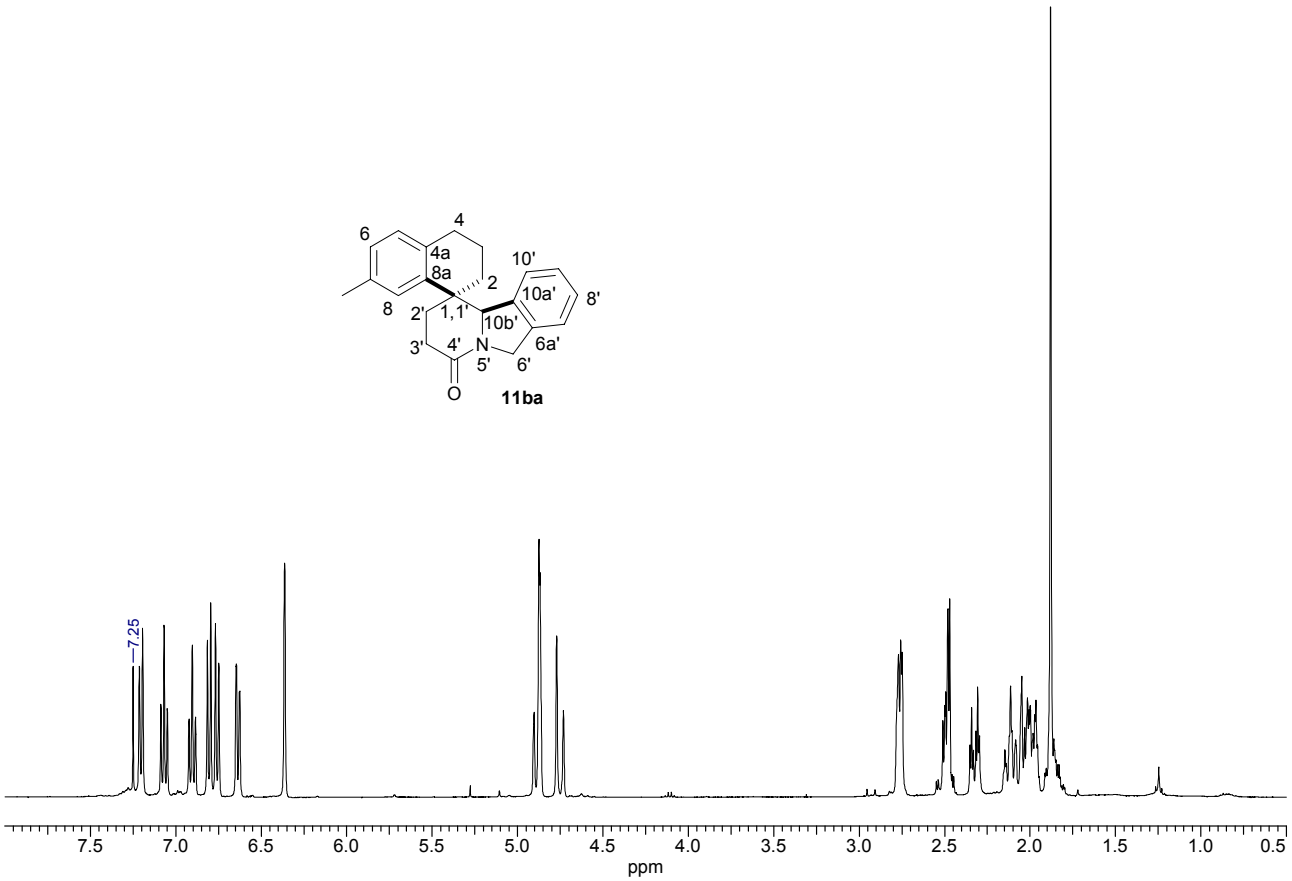


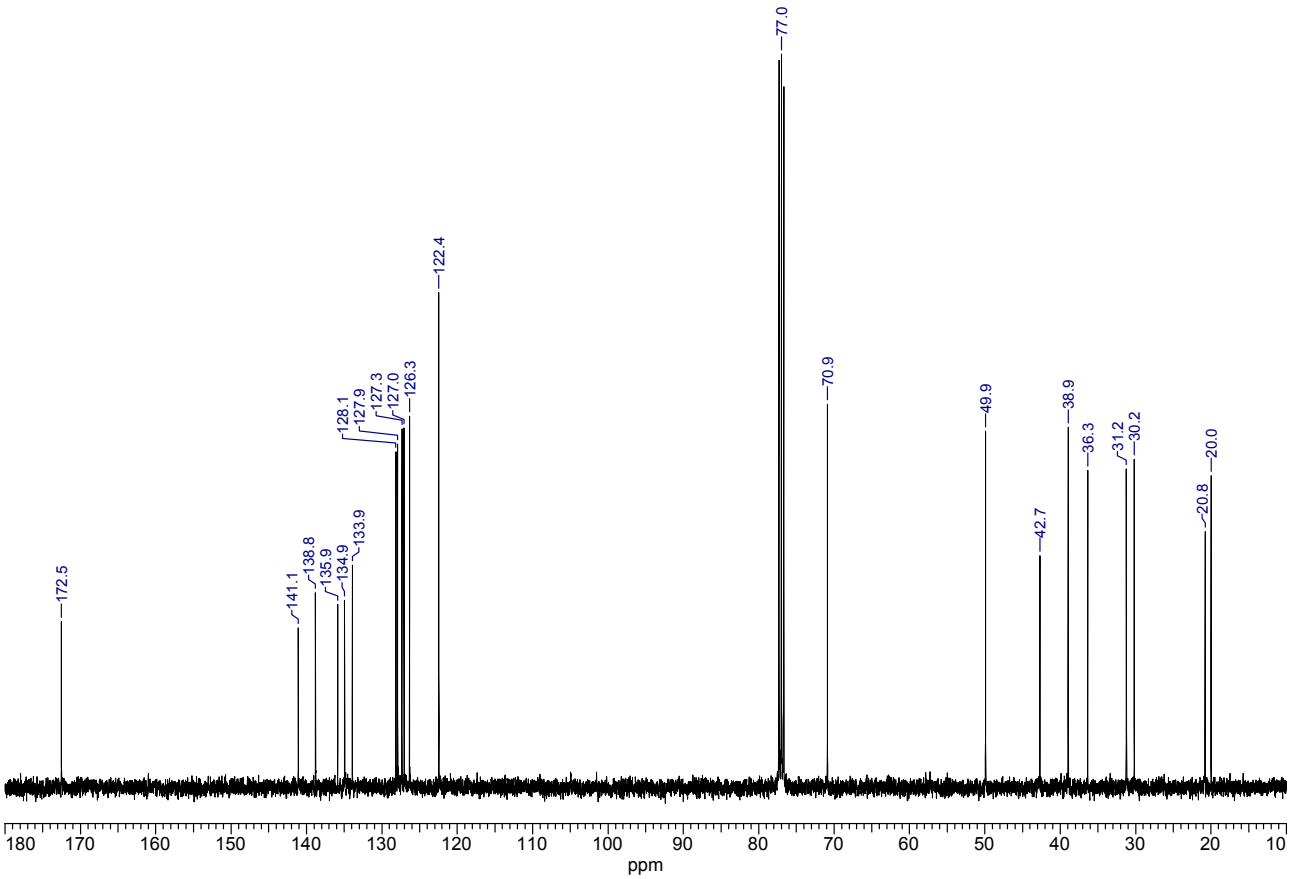


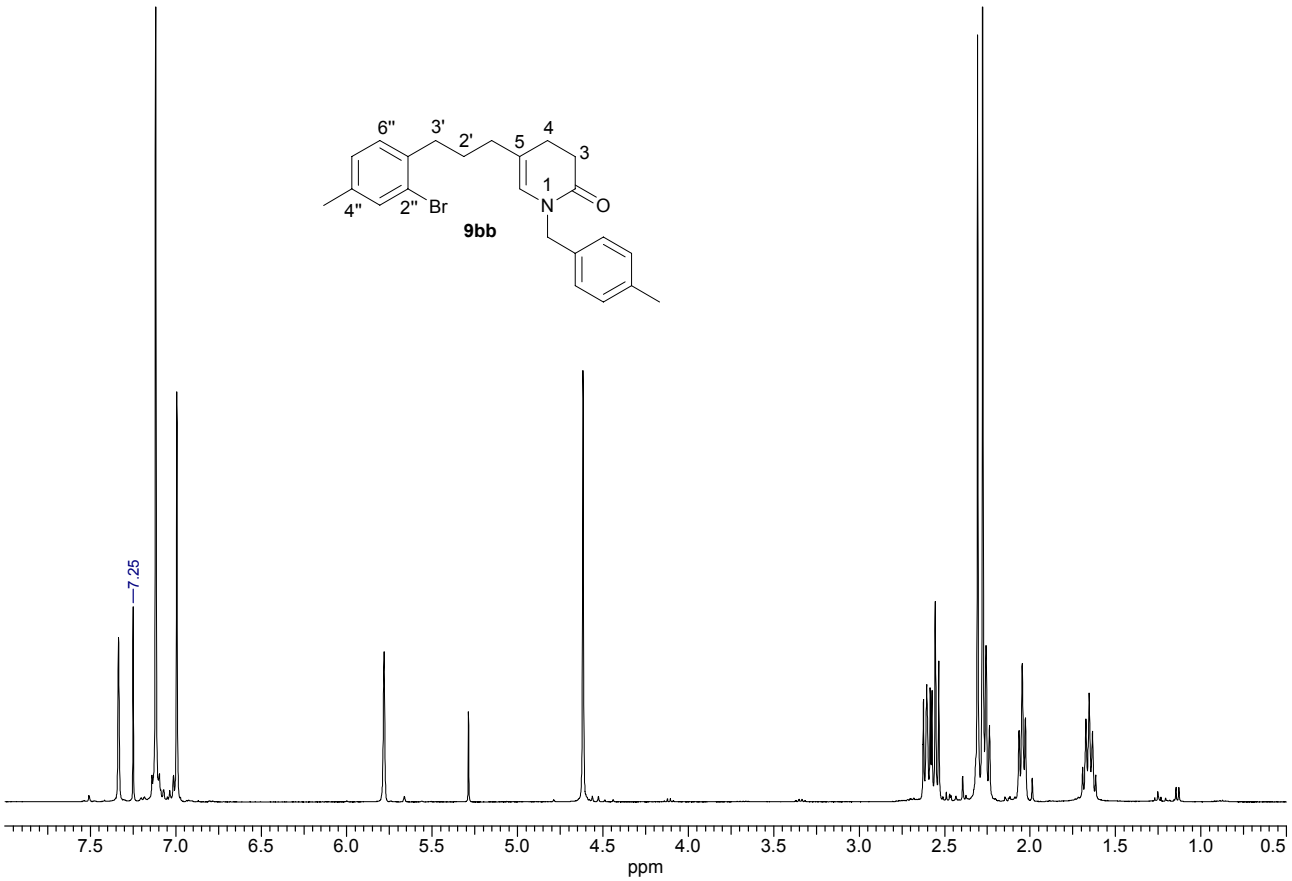

6''
3'
2'
5
4
3
1
N
O
4''
2''
10ba
7.25
ppm
77.0
129.0
128.6
128.2
127.5
127.4
124.1
119.9
168.9
138.8
137.4
135.2
48.8
34.7
33.2
31.3
29.2
24.2
21.0
ppm

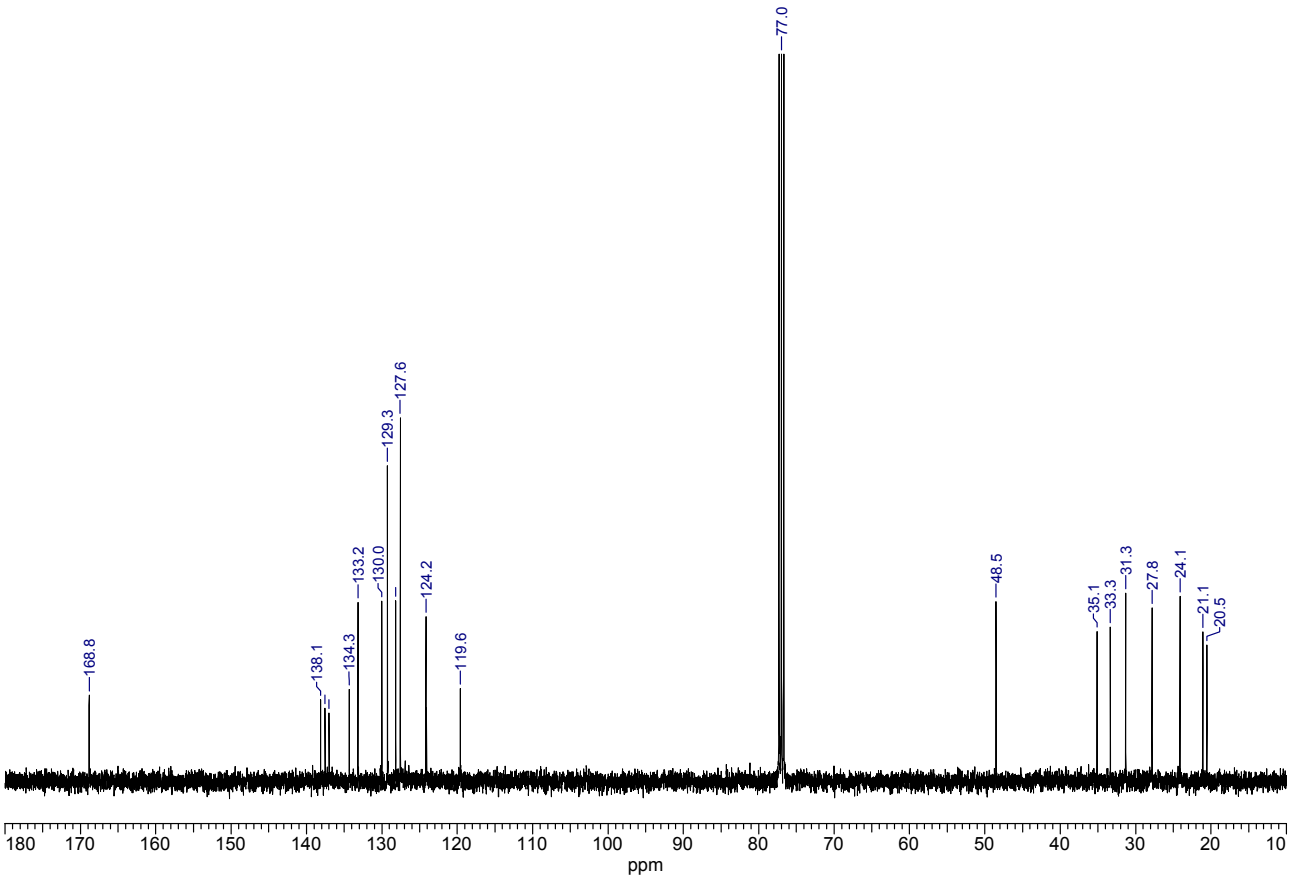

7.25
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

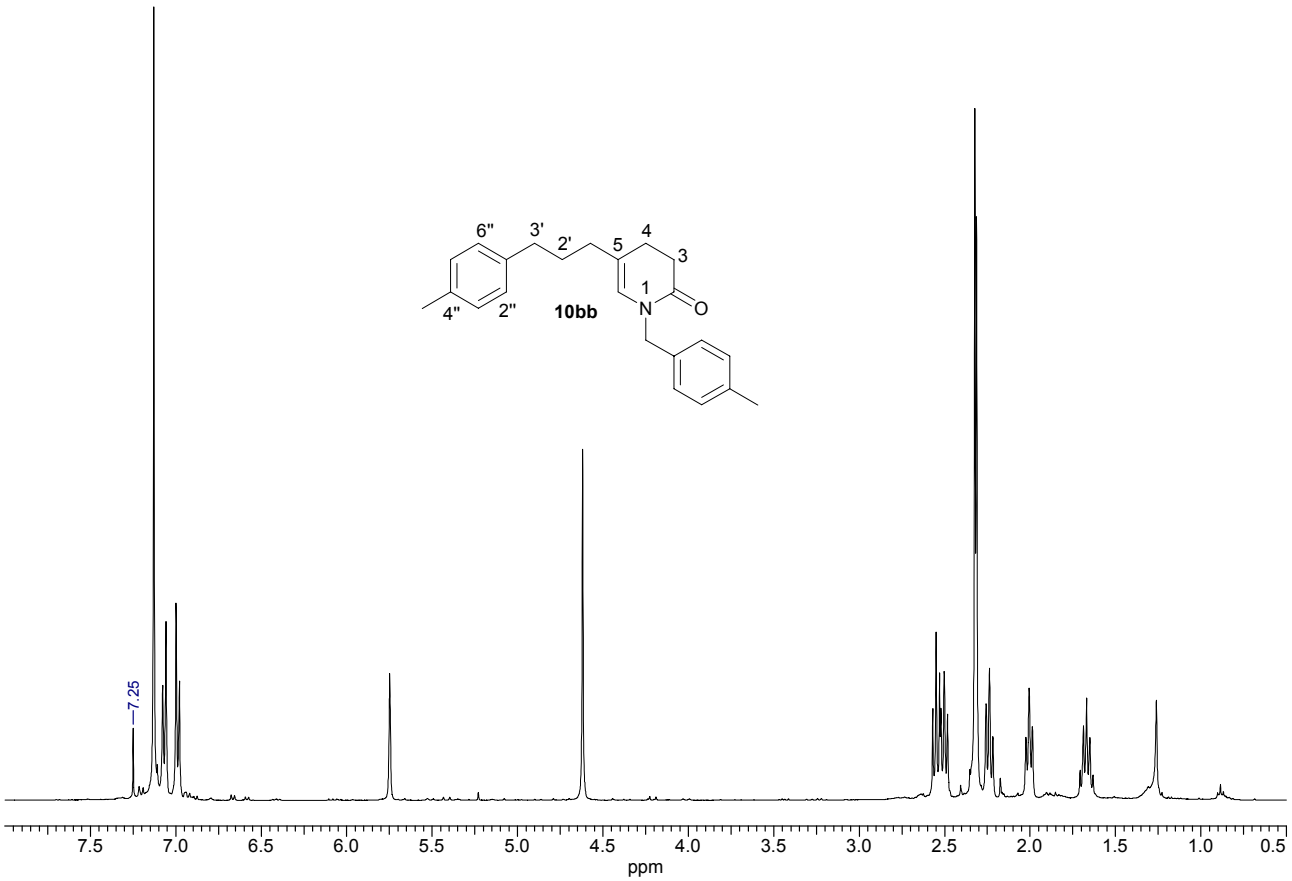
4
6
4a
8a
10'
2
10a'
8'
8
2'
1,1'
10b'
3'
4'
N
6a'
5'
6'
O

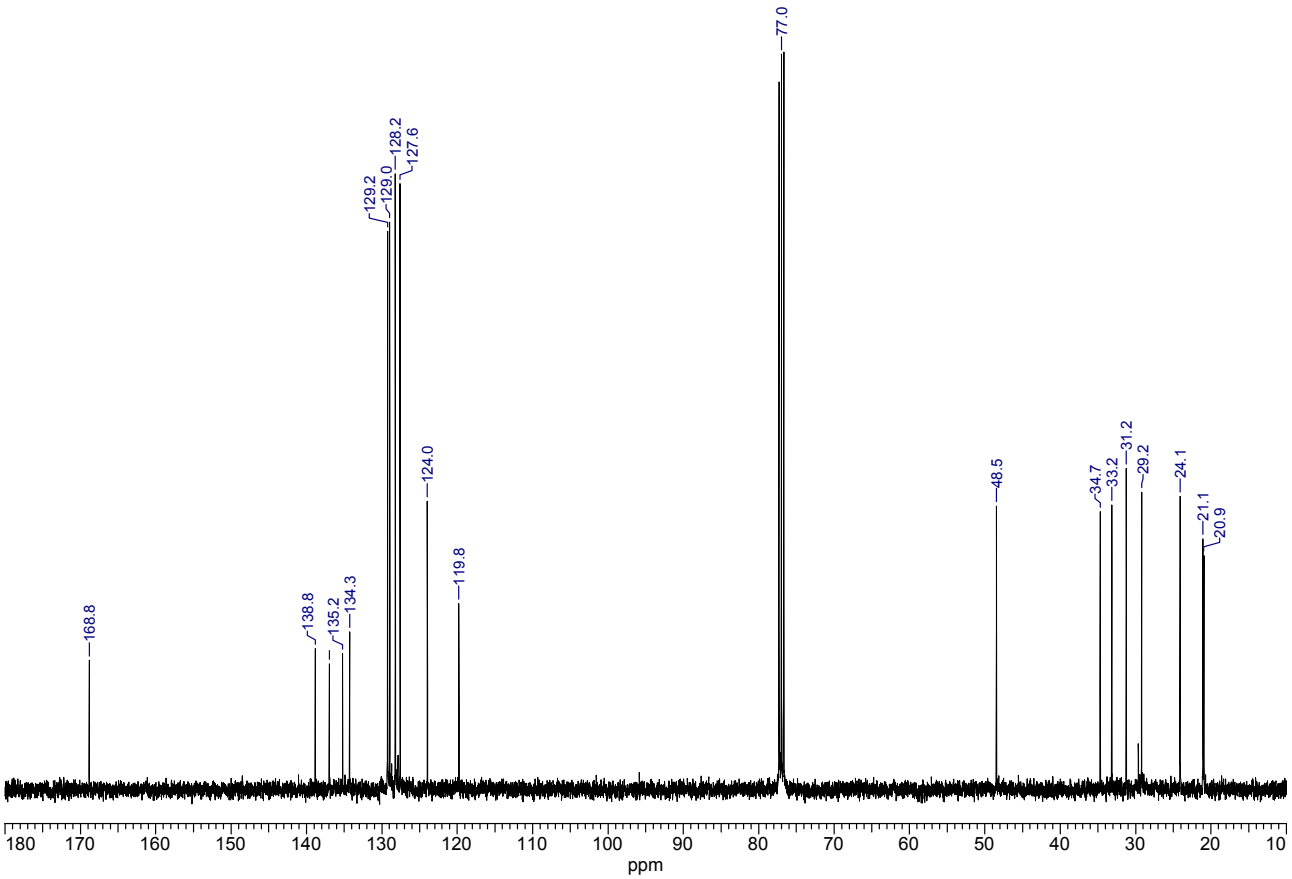
11ba

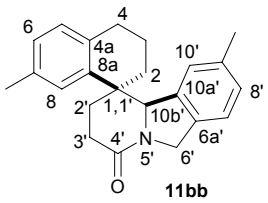

77.0
122.4
70.9
49.9
38.9
36.3
31.2
30.2
20.8
20.0
42.7
128.1
127.9
127.3
127.0
126.3
133.9
138.8
135.9
134.9
141.1
172.5
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


6"
3'
2'
5
4
3
1
N
O
4"
2"
Br
9bb
7.25
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


77.0
168.8
138.1
134.3
133.2
130.0
129.3
127.6
124.2
119.6
48.5
35.1
33.3
31.3
27.8
24.1
21.1
20.5
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

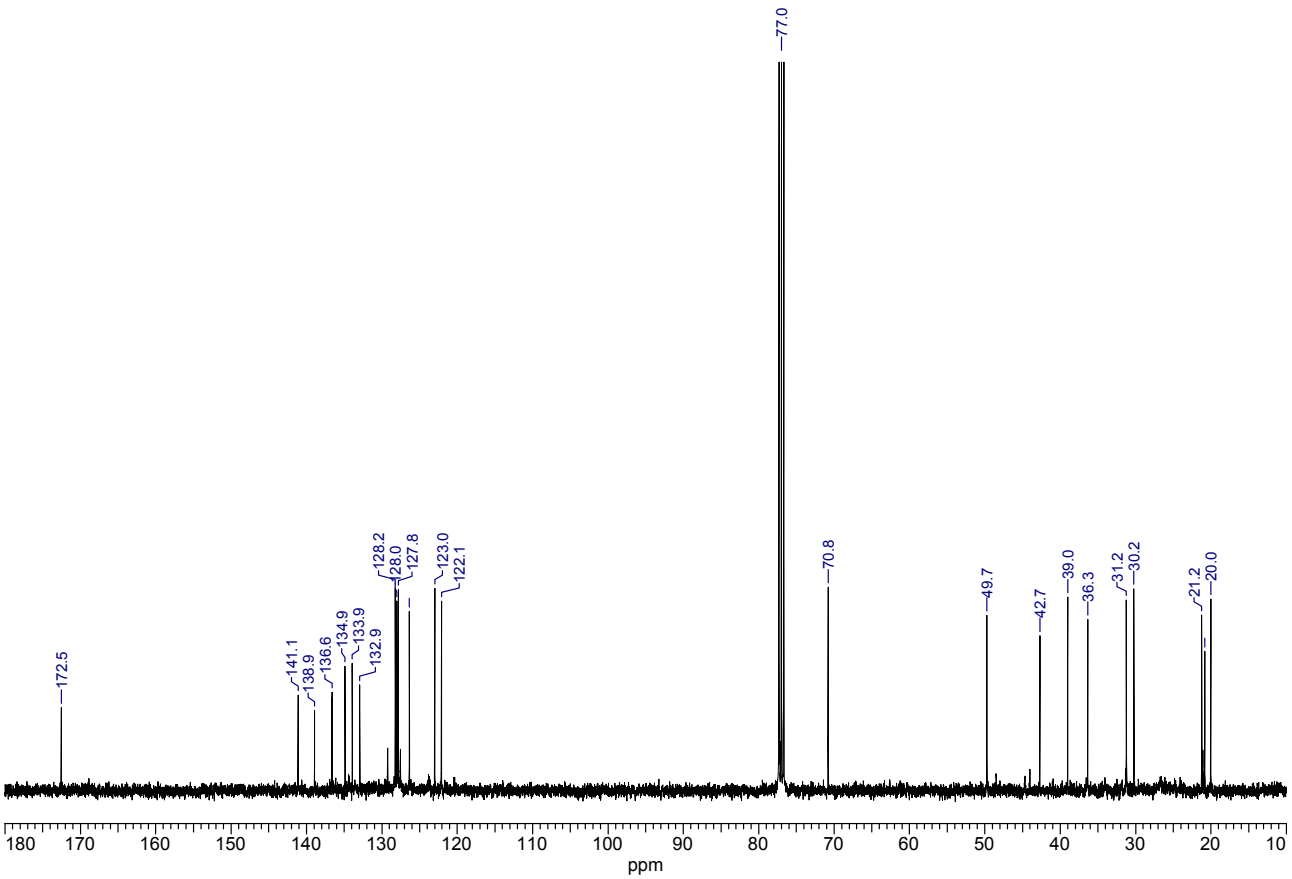

6"
3'
2'
5
4
3
1
N
O
4"
2"
10bb
7.25
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

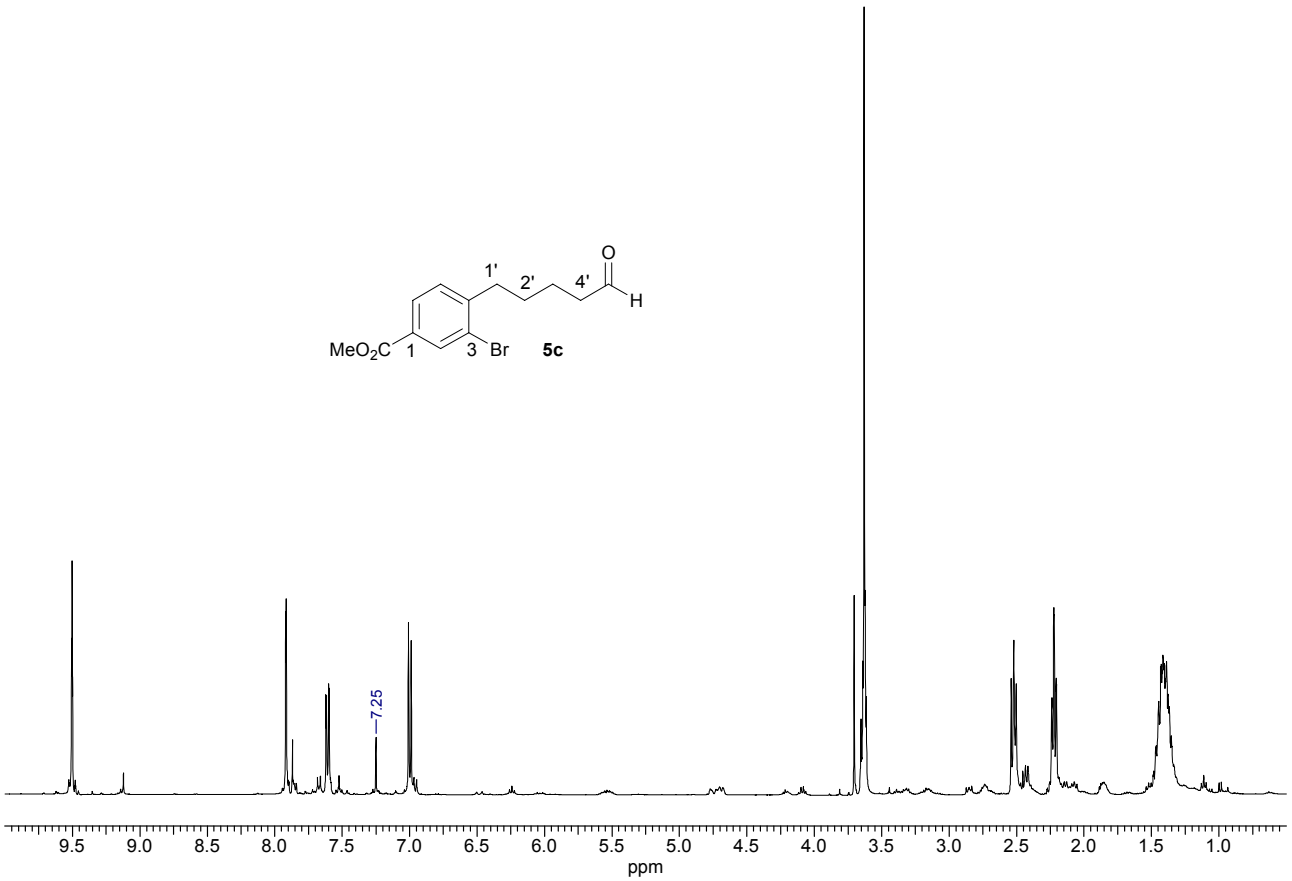

168.8
138.8
135.2
134.3
129.2
129.0
128.2
127.6
124.0
119.8
77.0
48.5
34.7
33.2
31.2
29.2
24.1
21.1
20.9
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

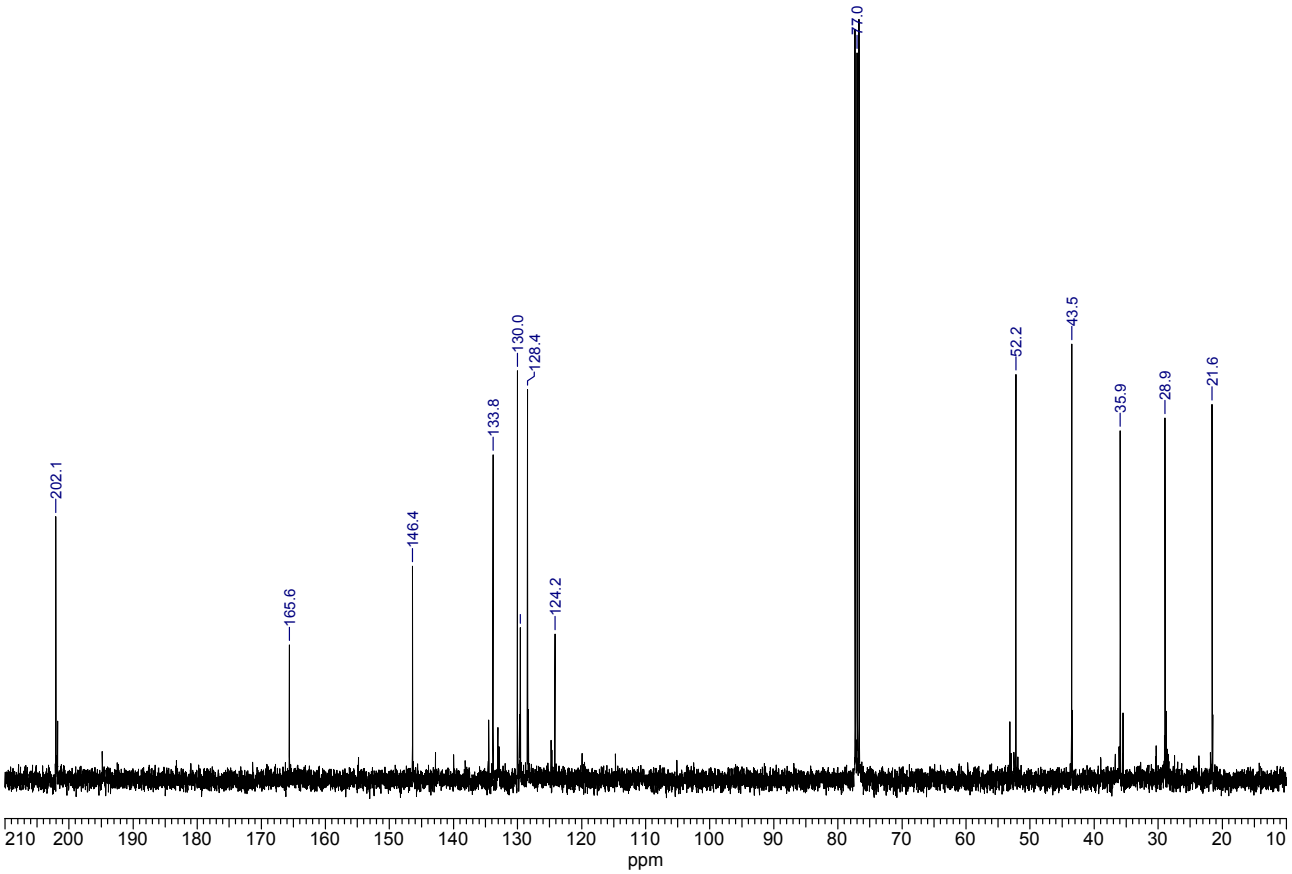

4
6
4a
8a
2
10'
10a'
8'
8
2'
1,1'
10b'
3'
4'
N
5'
6'
6a'
O

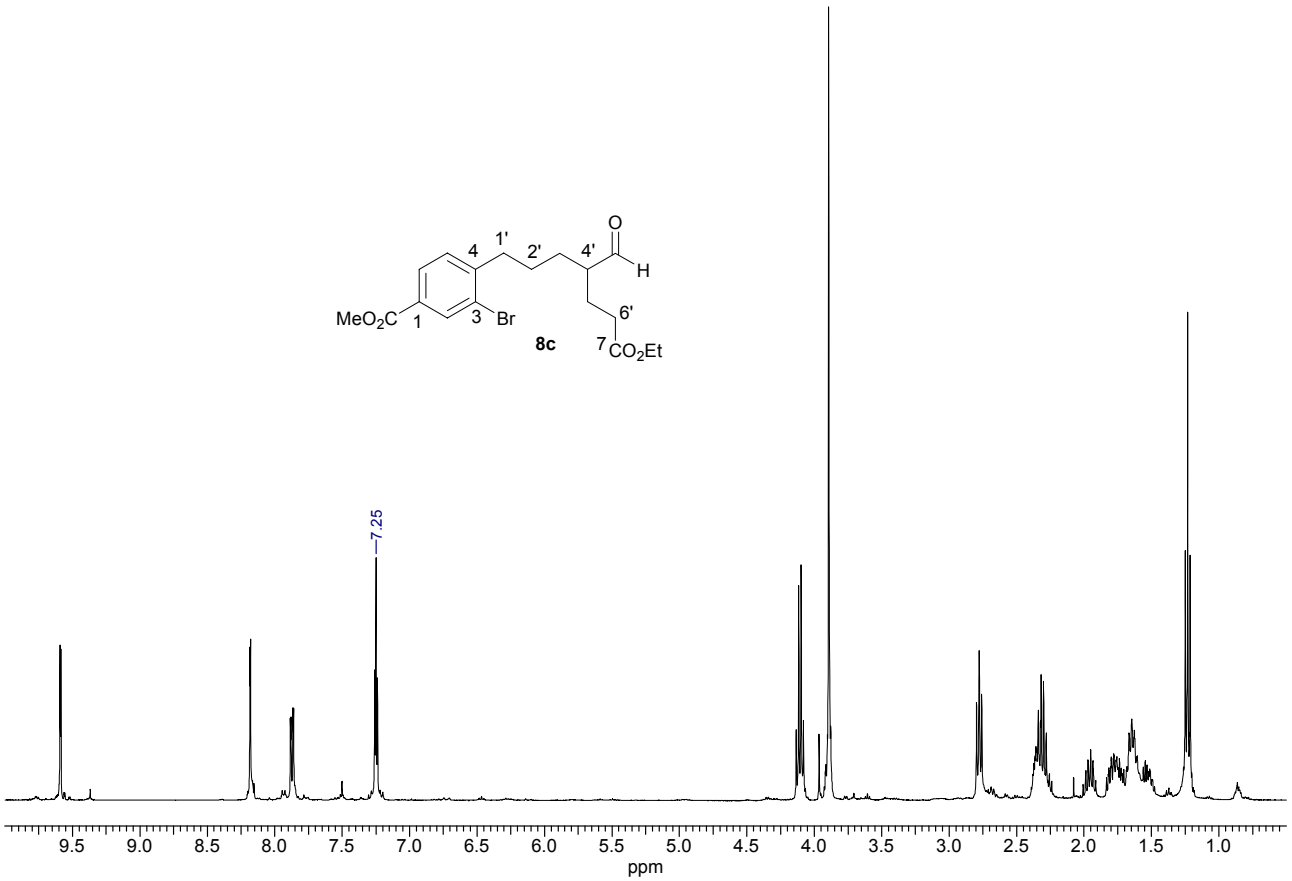
11bb

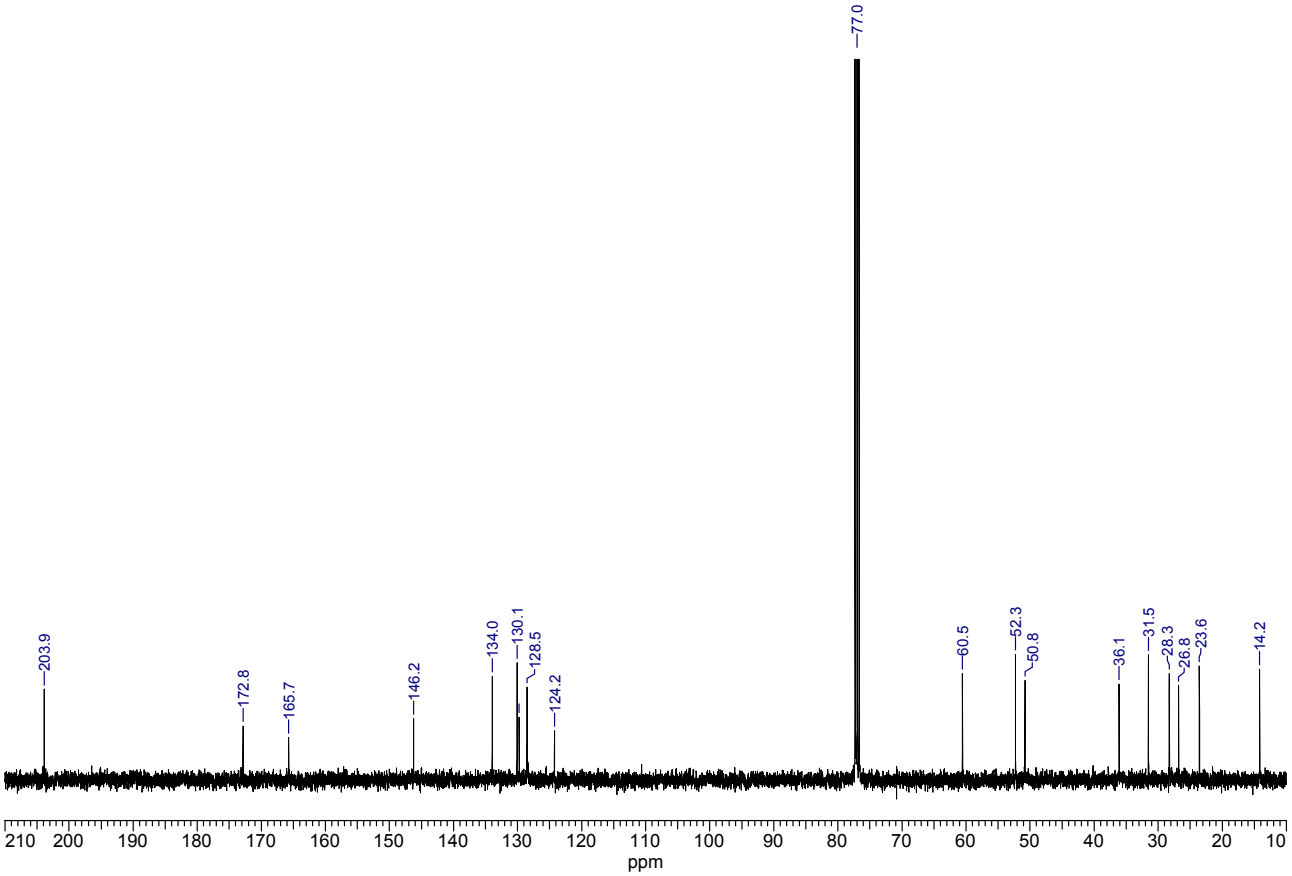
7.25
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

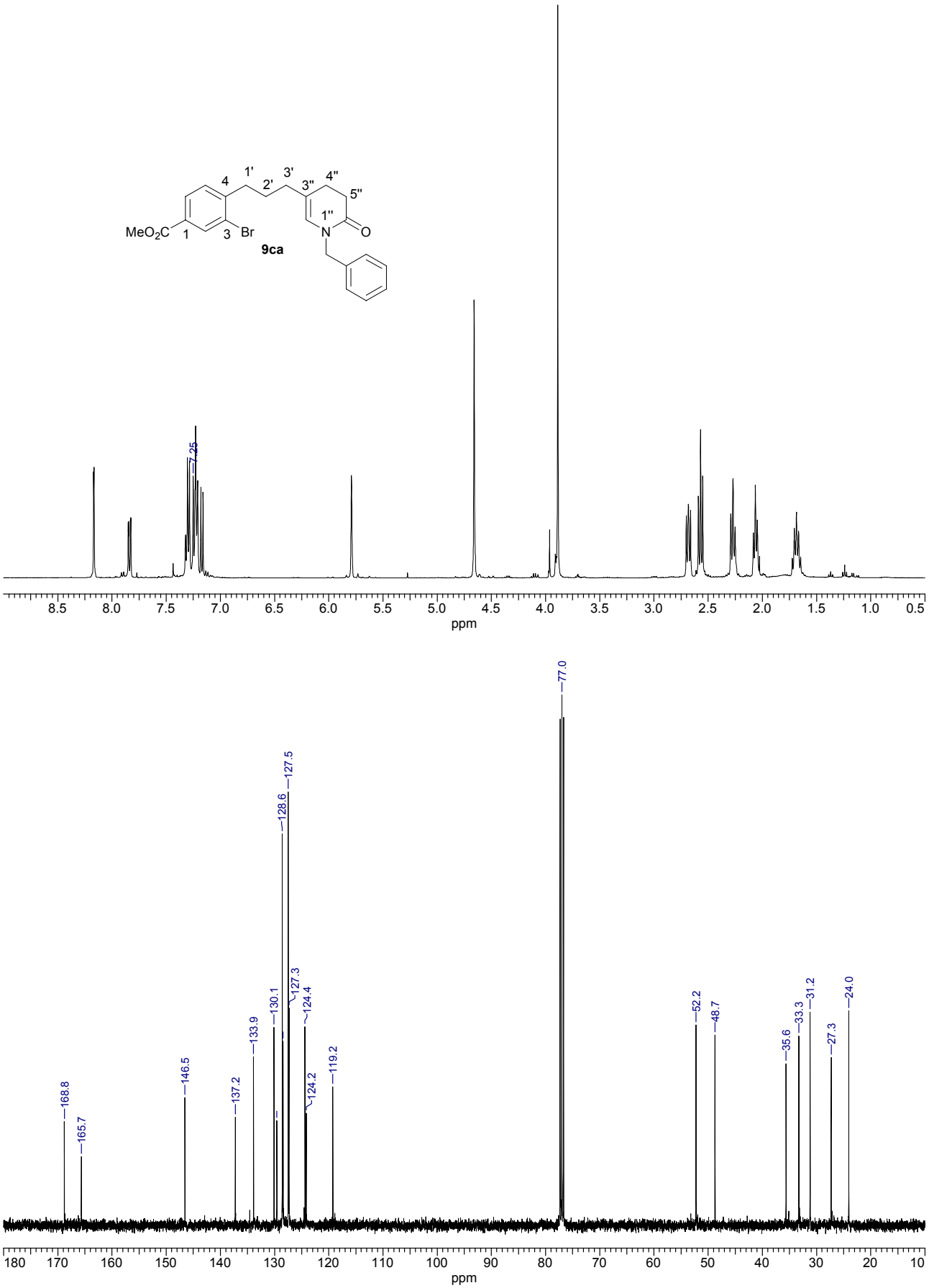

77.0
172.5
141.1
138.9
136.6
134.9
133.9
132.9
128.2
128.0
127.8
123.0
122.1
70.8
49.7
42.7
39.0
36.3
31.2
30.2
21.2
20.0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

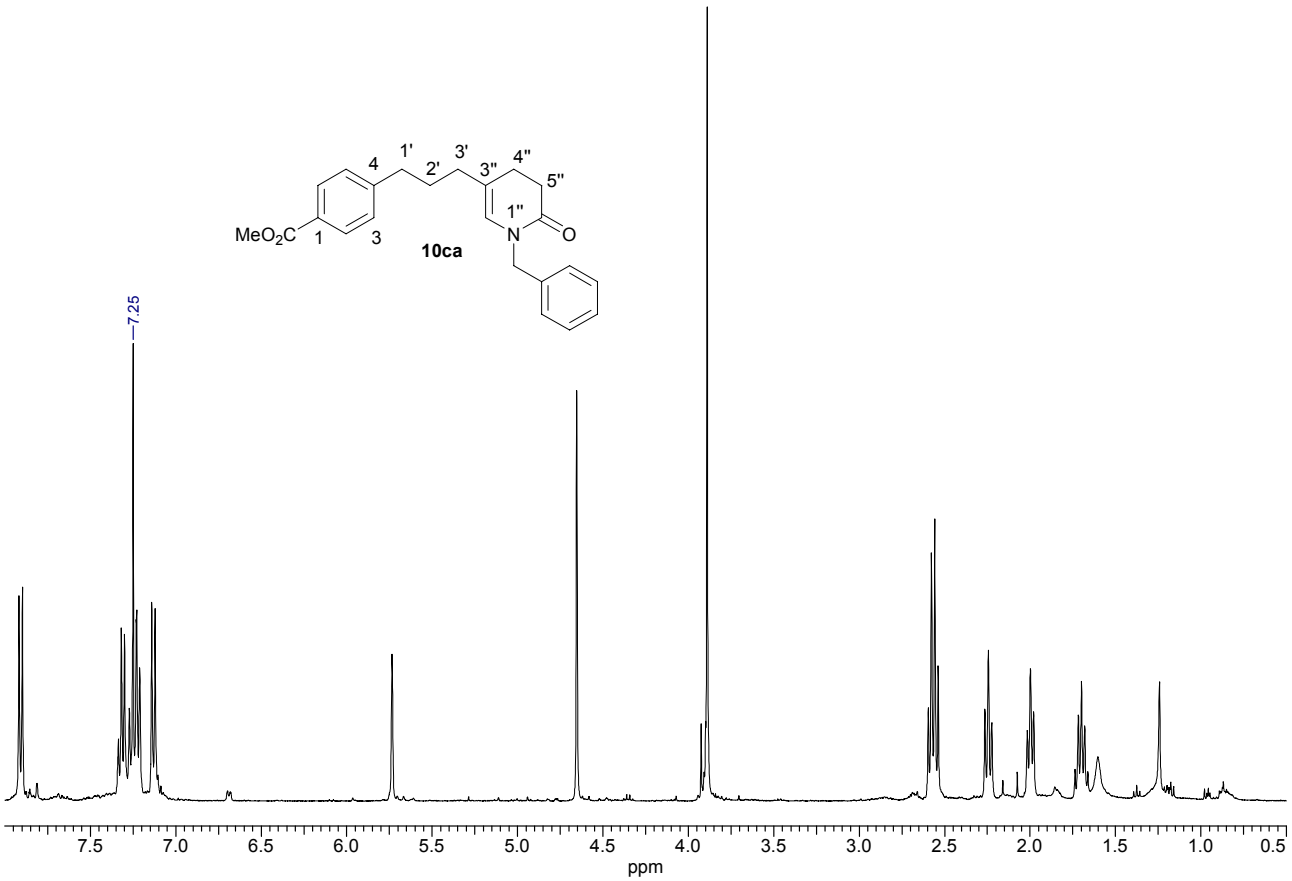


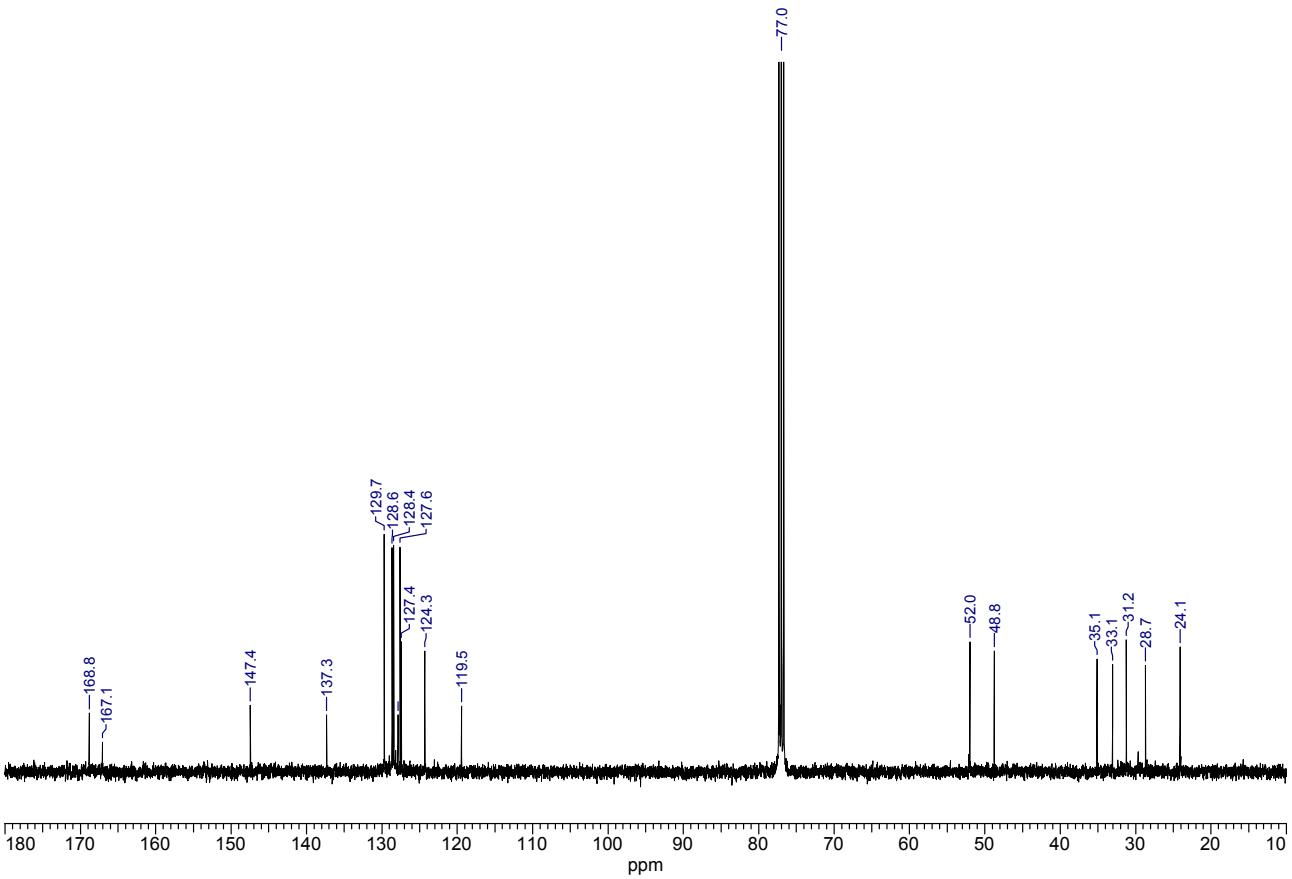


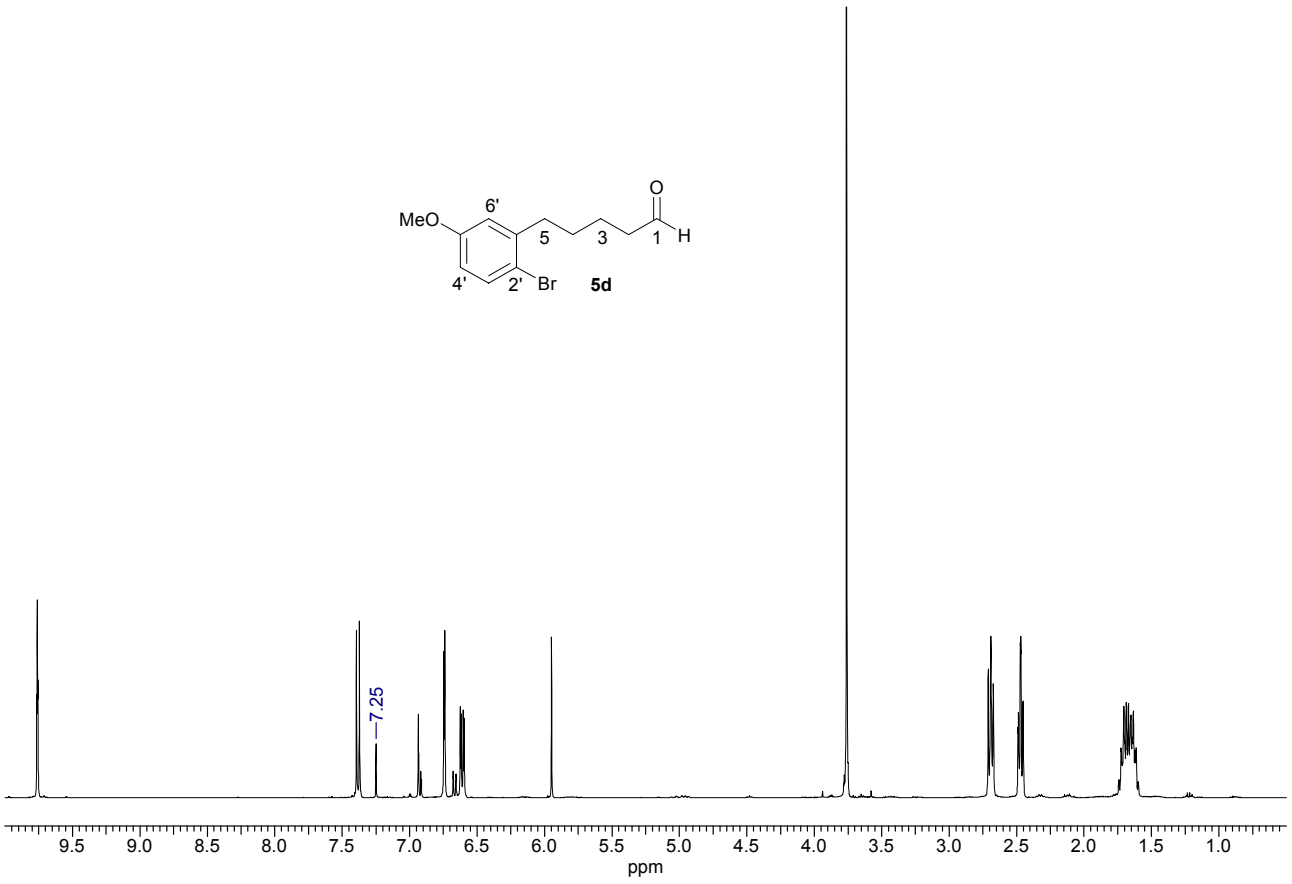

MeO2C
Br
CO2Et
O
H
1
2'
3
4
4'
6'
7
1'
8c
7.25
ppm

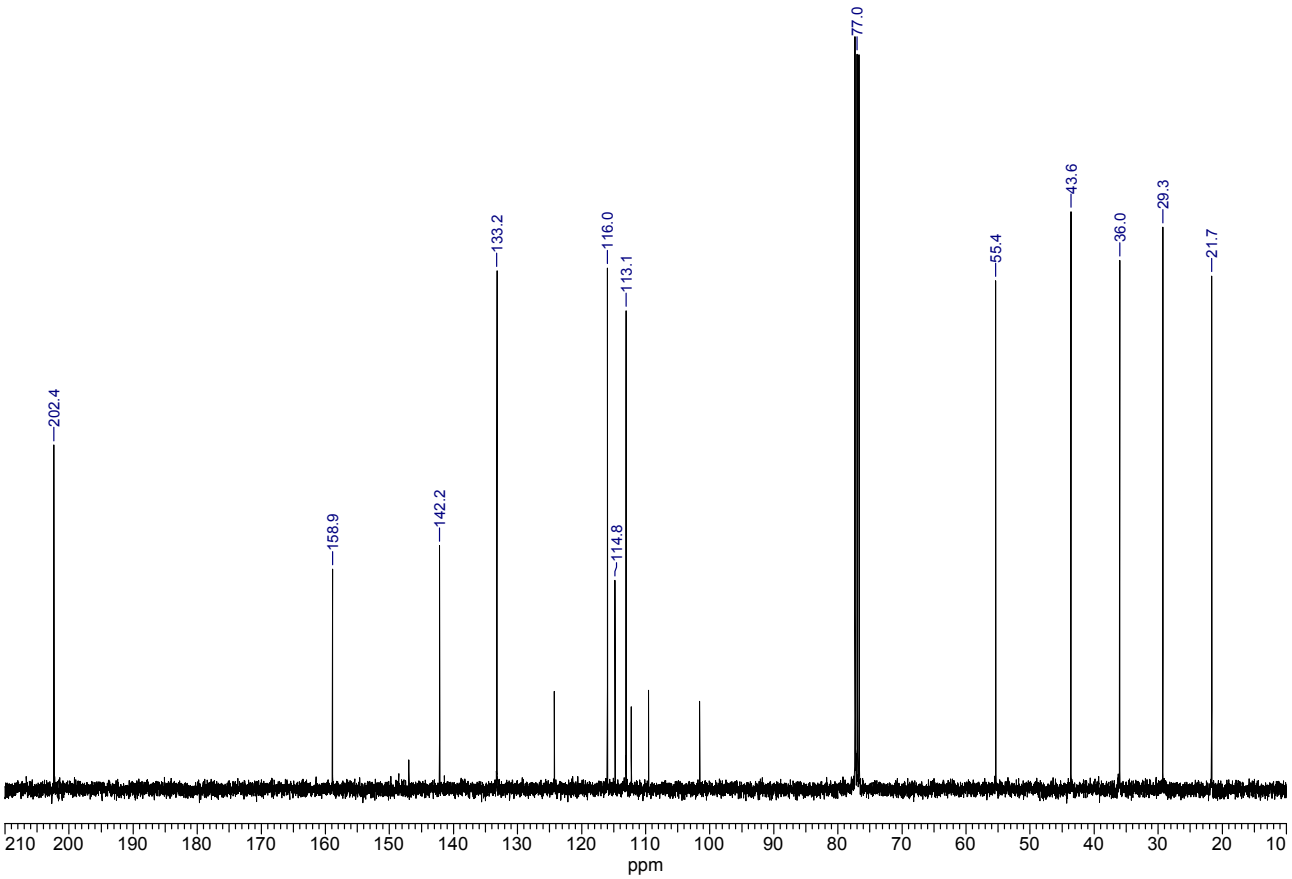

77.0
203.9
172.8
165.7
146.2
134.0
130.1
128.5
124.2
60.5
52.3
50.8
36.1
31.5
28.3
26.8
23.6
14.2
ppm

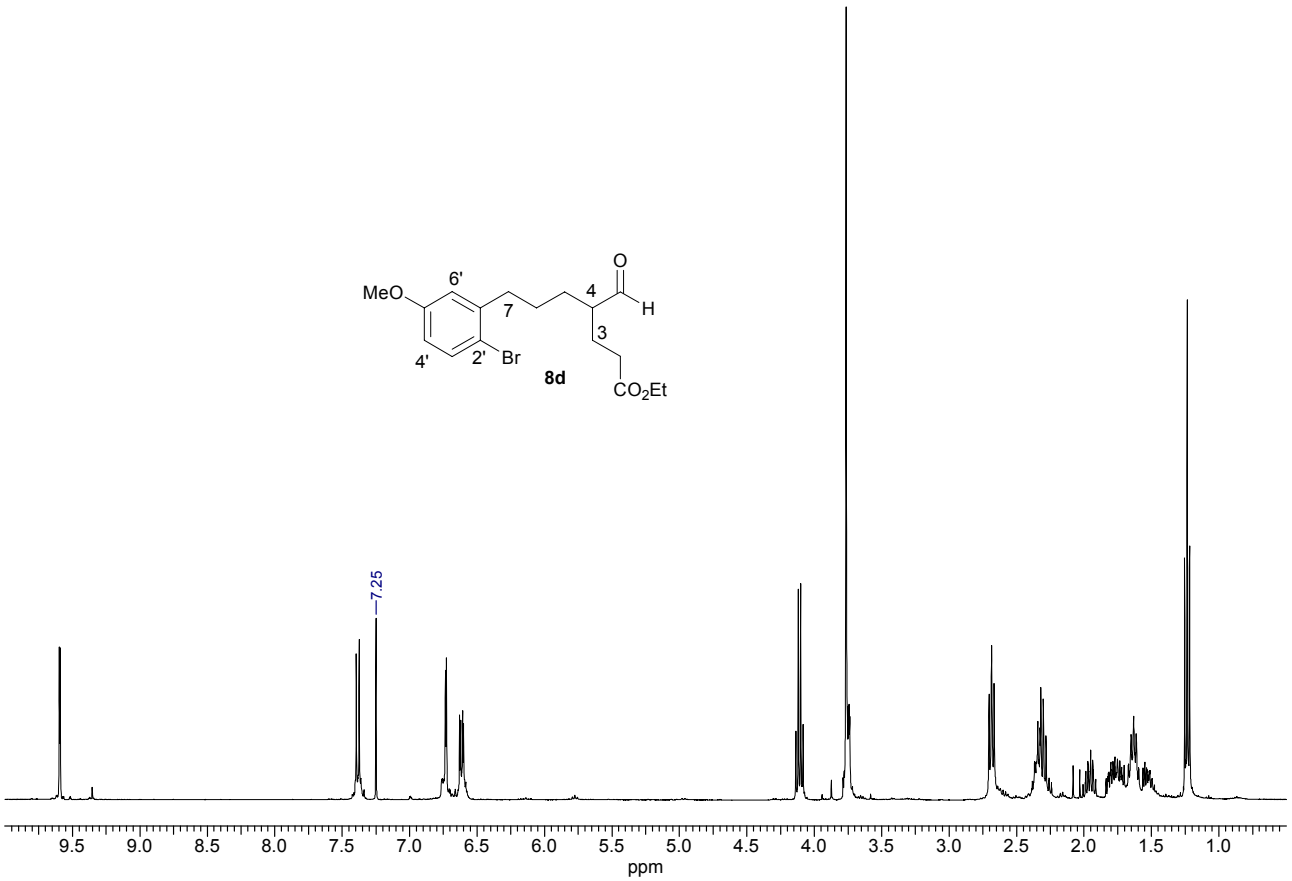

MeO2C
Br
9ca
7.25
77.0
168.8
165.7
146.5
137.2
133.9
130.1
128.6
127.5
127.3
124.4
124.2
119.2
52.2
48.7
35.6
33.3
31.2
27.3
24.0
ppm
ppm

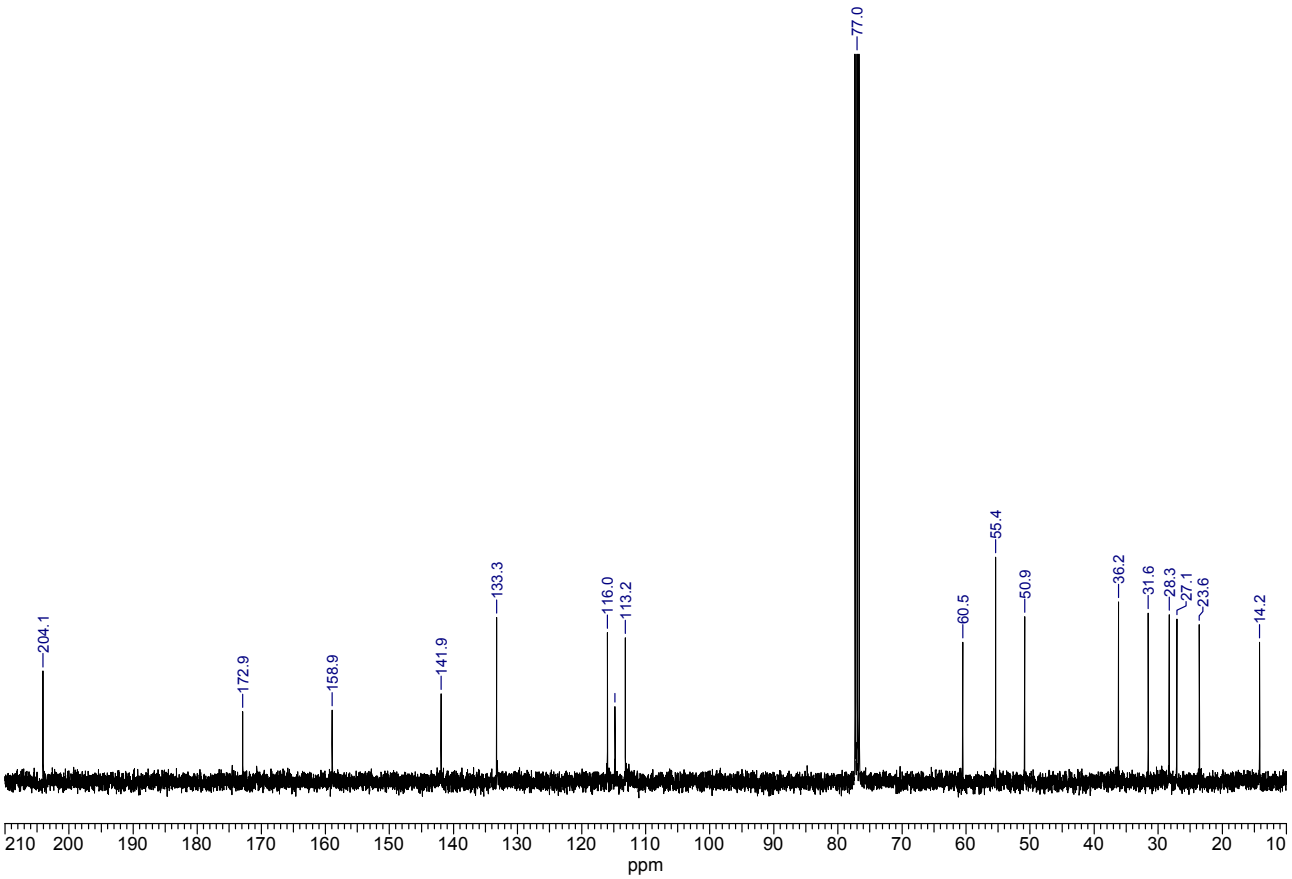

1'
3'
4"
4
2'
3"
5"
1"
MeO2C
1
3
N
O
10ca
7.25
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

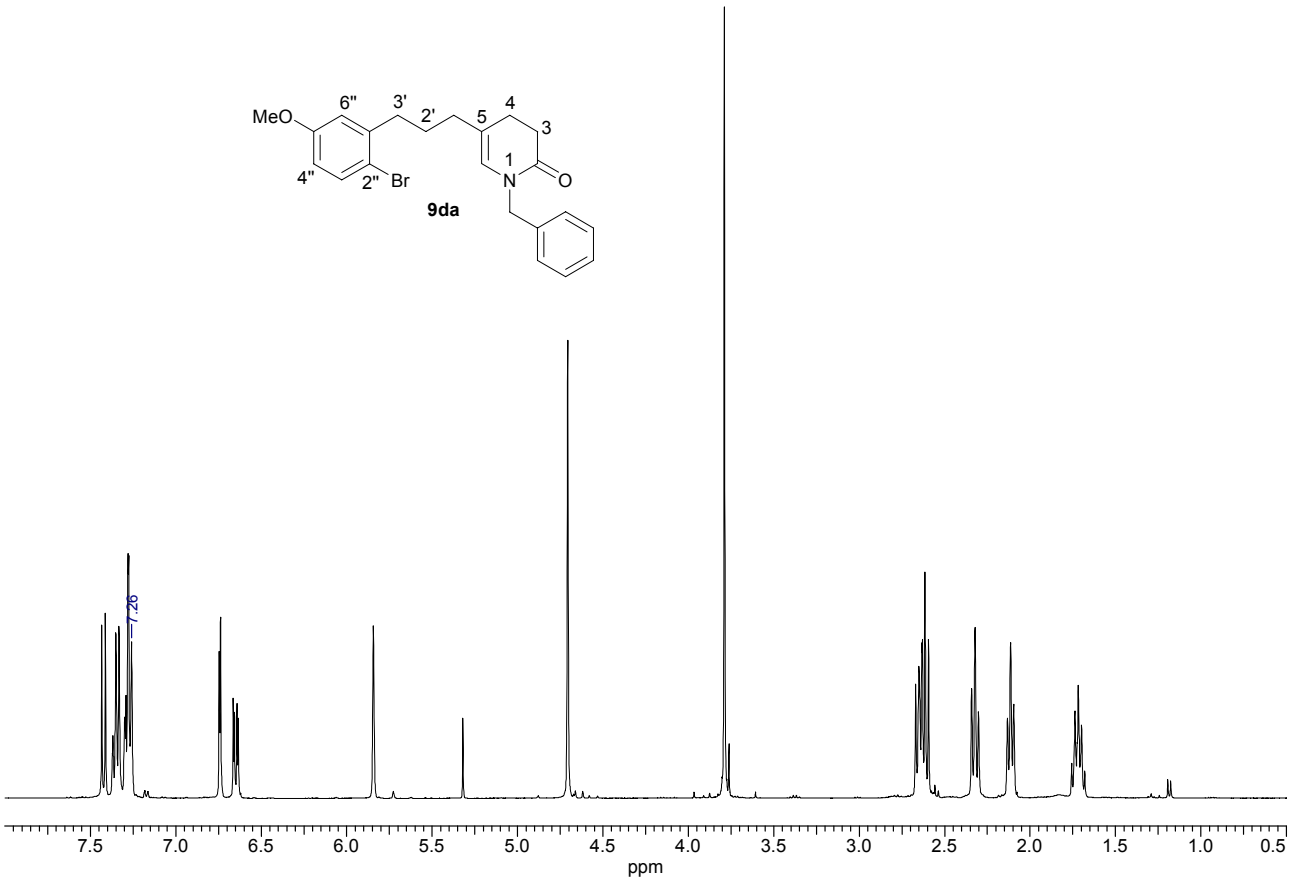

77.0
129.7
128.6
128.4
127.6
127.4
124.3
119.5
168.8
167.1
147.4
137.3
52.0
48.8
35.1
33.1
31.2
28.7
24.1
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

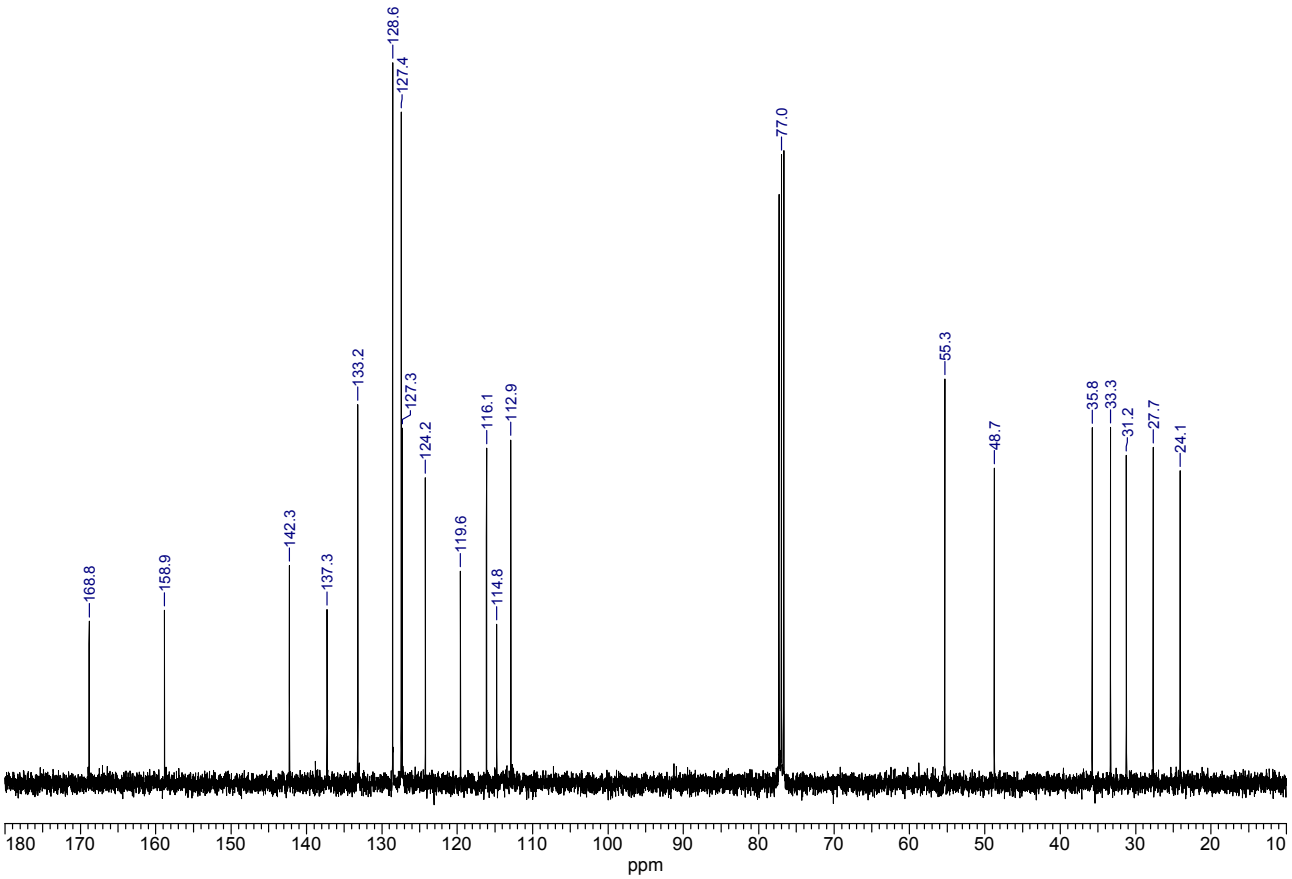

MeO
6'
5
3
1
O
H
4'
2'
Br
5d
7.25
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm

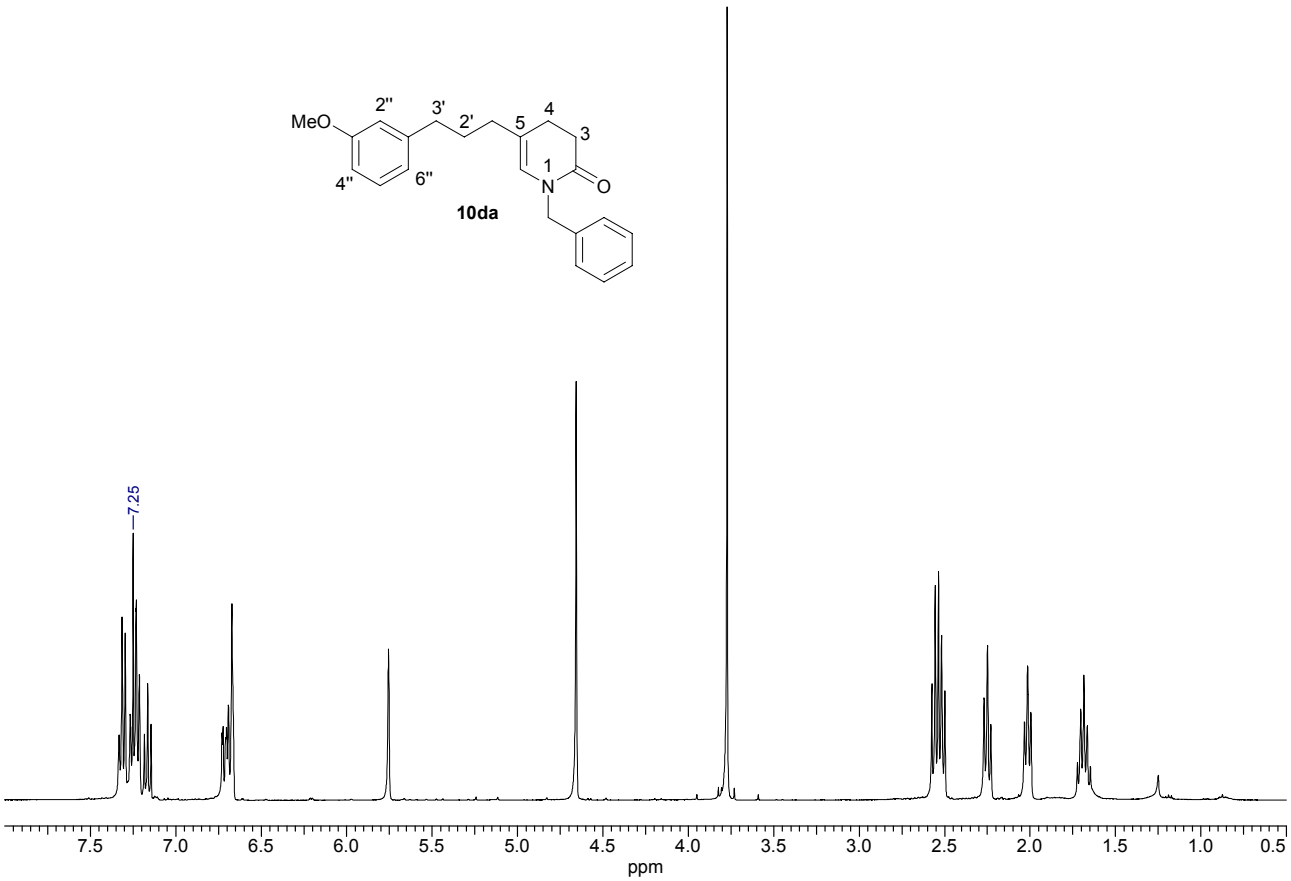

202.4
158.9
142.2
133.2
116.0
114.8
113.1
77.0
55.4
43.6
36.0
29.3
21.7
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

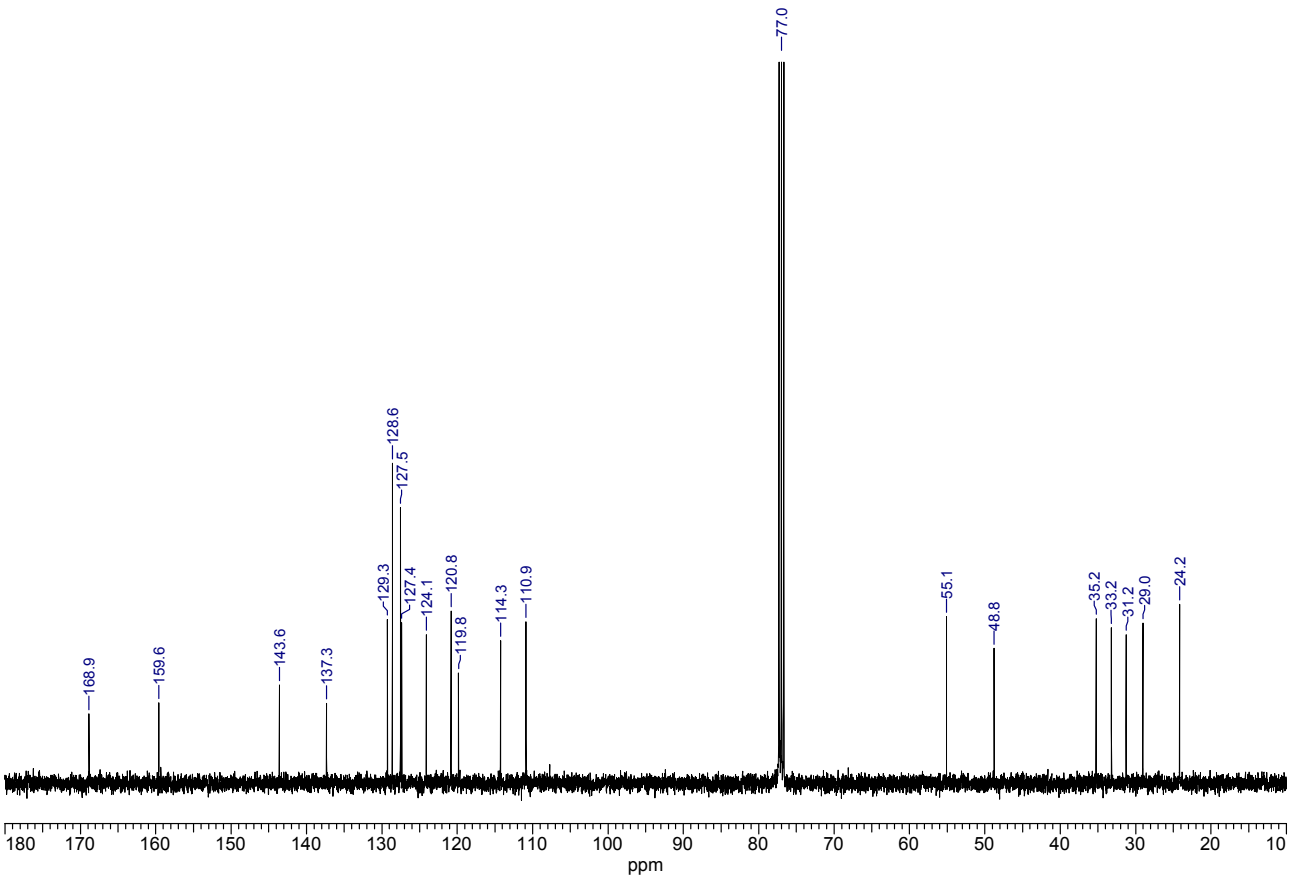

MeO
6'
4
O
H
7
3
4'
2'
Br
8d
CO2Et
7.25
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm

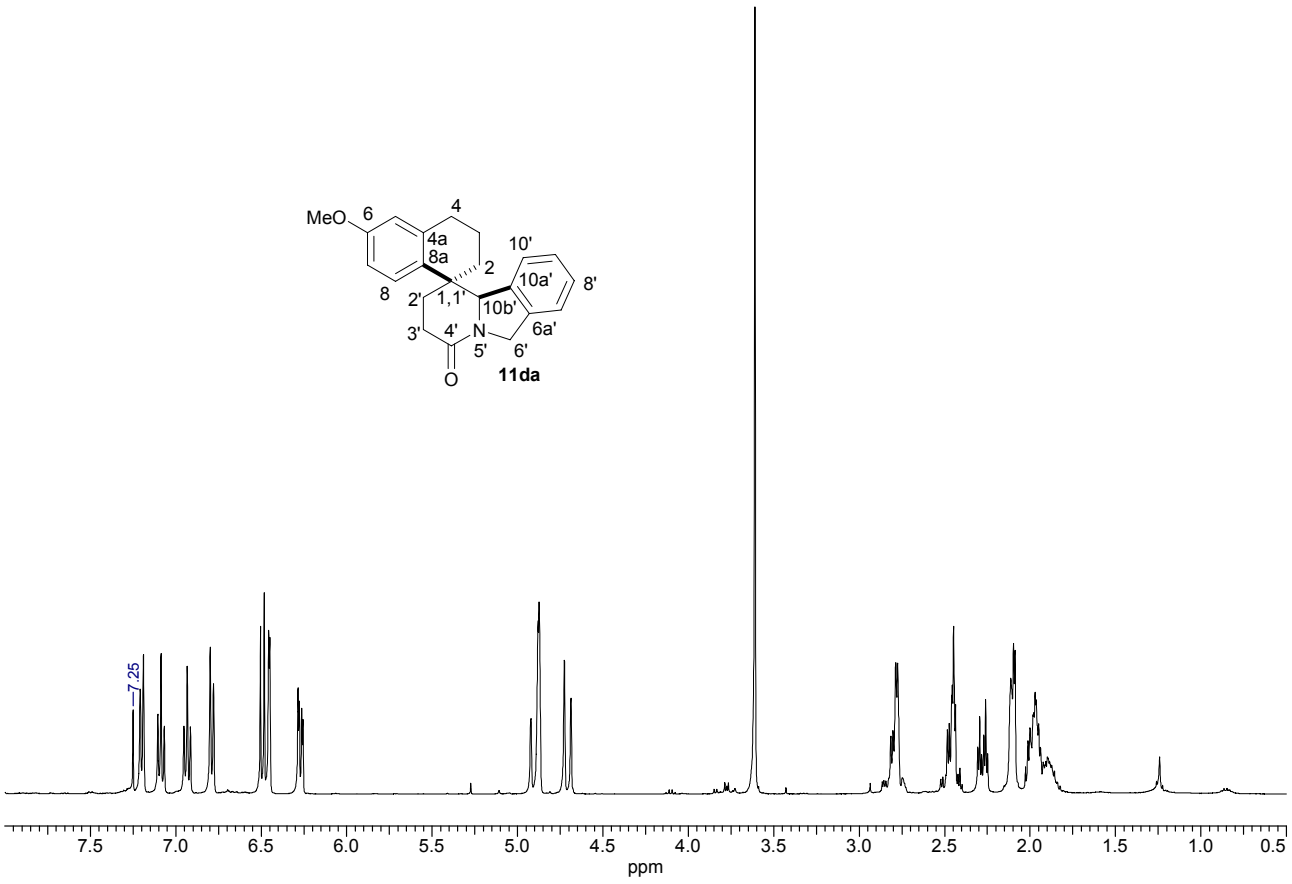

77.0
204.1
172.9
158.9
141.9
133.3
116.0
113.2
60.5
55.4
50.9
36.2
31.6
28.3
27.1
23.6
14.2
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

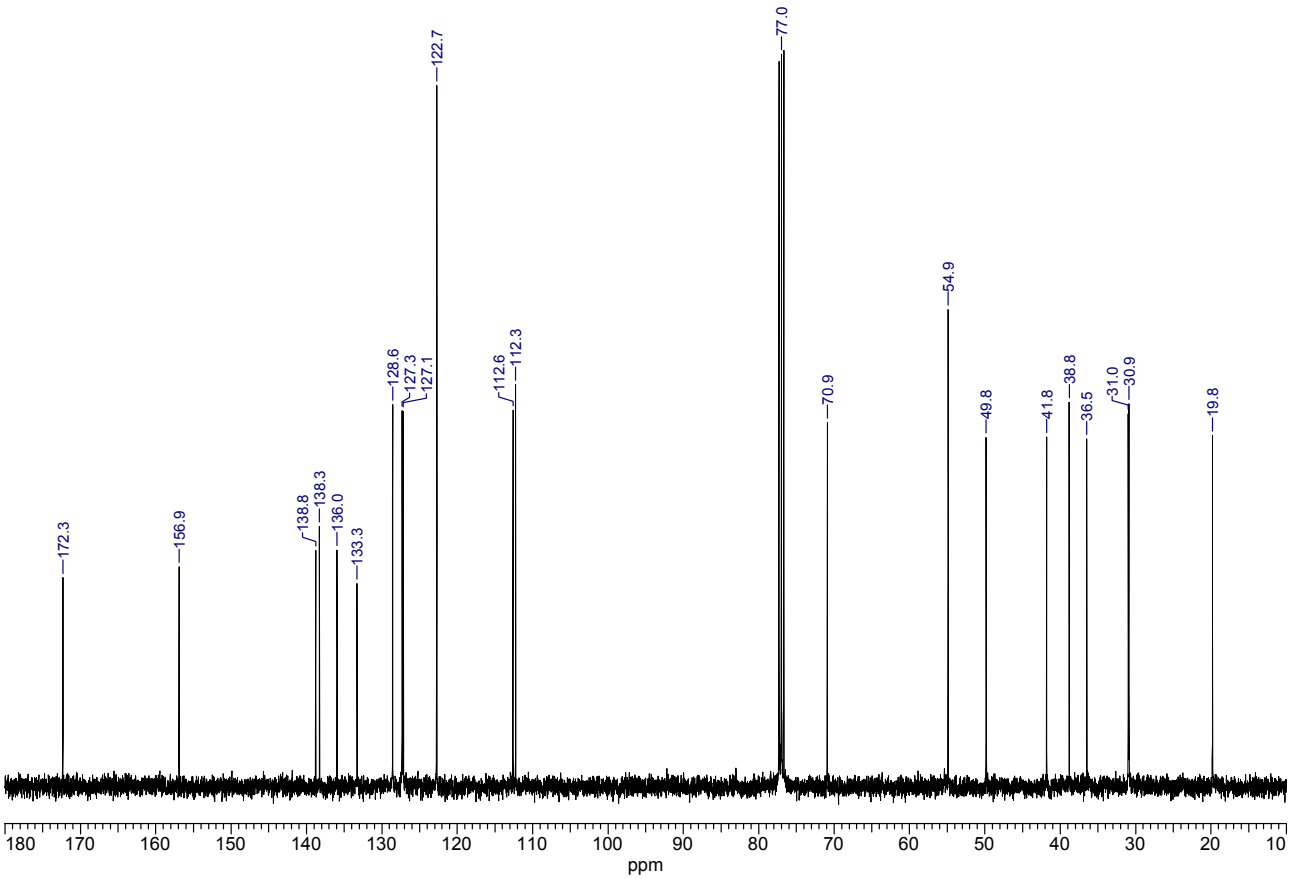

MeO
6"
3'
2'
5
4
3
1
N
O
4"
2"
Br
9da
7.26
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

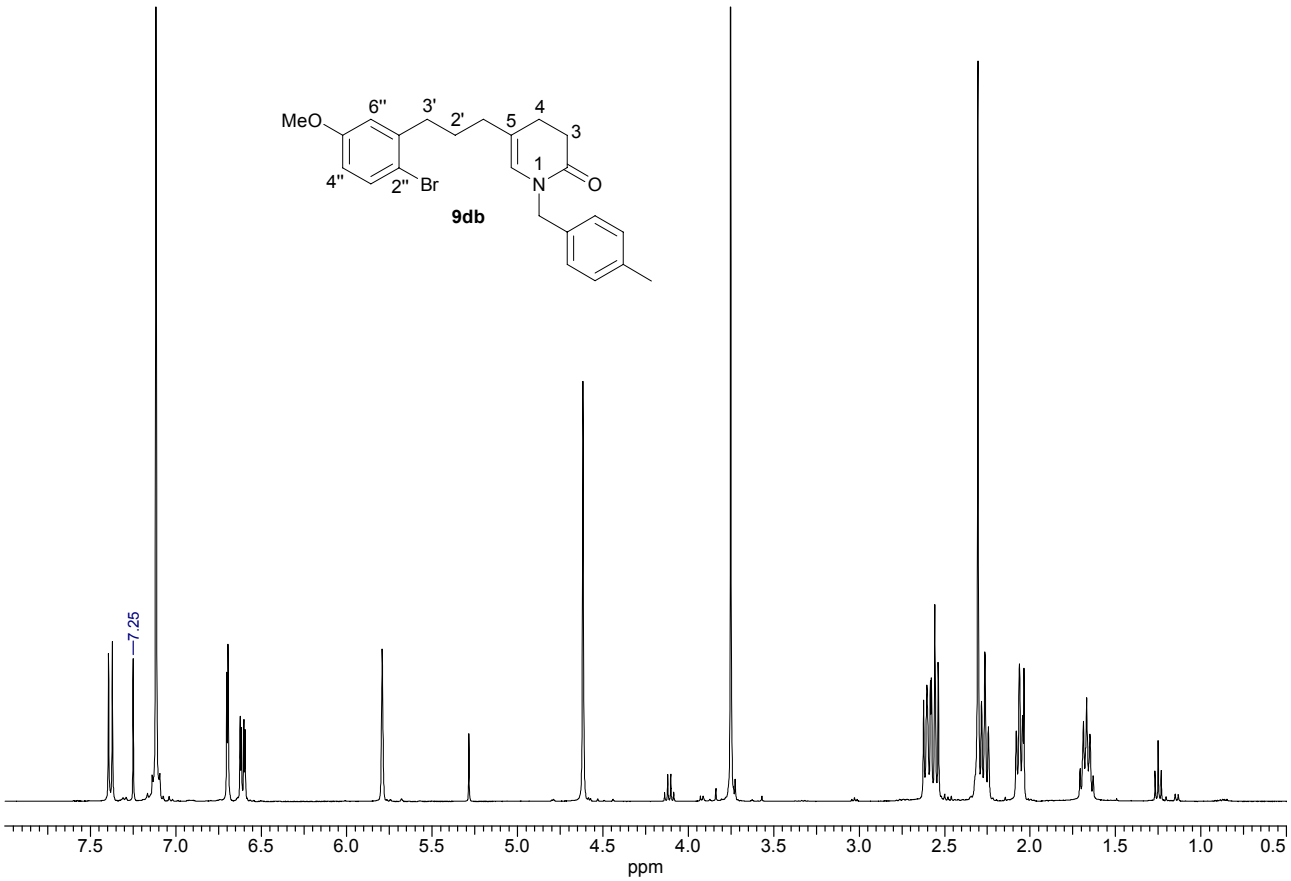

168.8
158.9
142.3
137.3
133.2
128.6
127.4
127.3
124.2
119.6
116.1
114.8
112.9
77.0
55.3
48.7
35.8
33.3
31.2
27.7
24.1
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

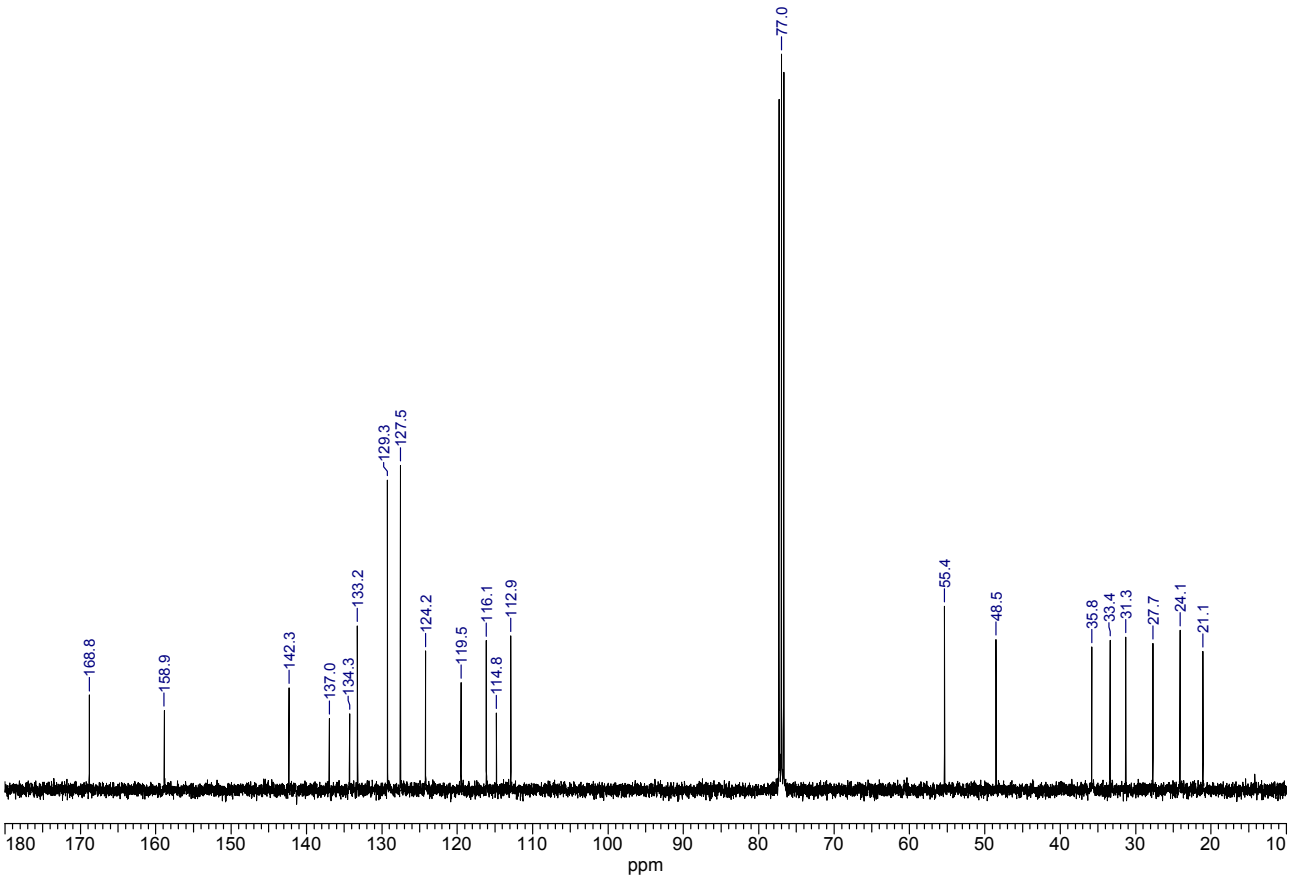

MeO
2''
3'
2'
5
4
3
1
N
O
4''
6''
10da
7.25
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

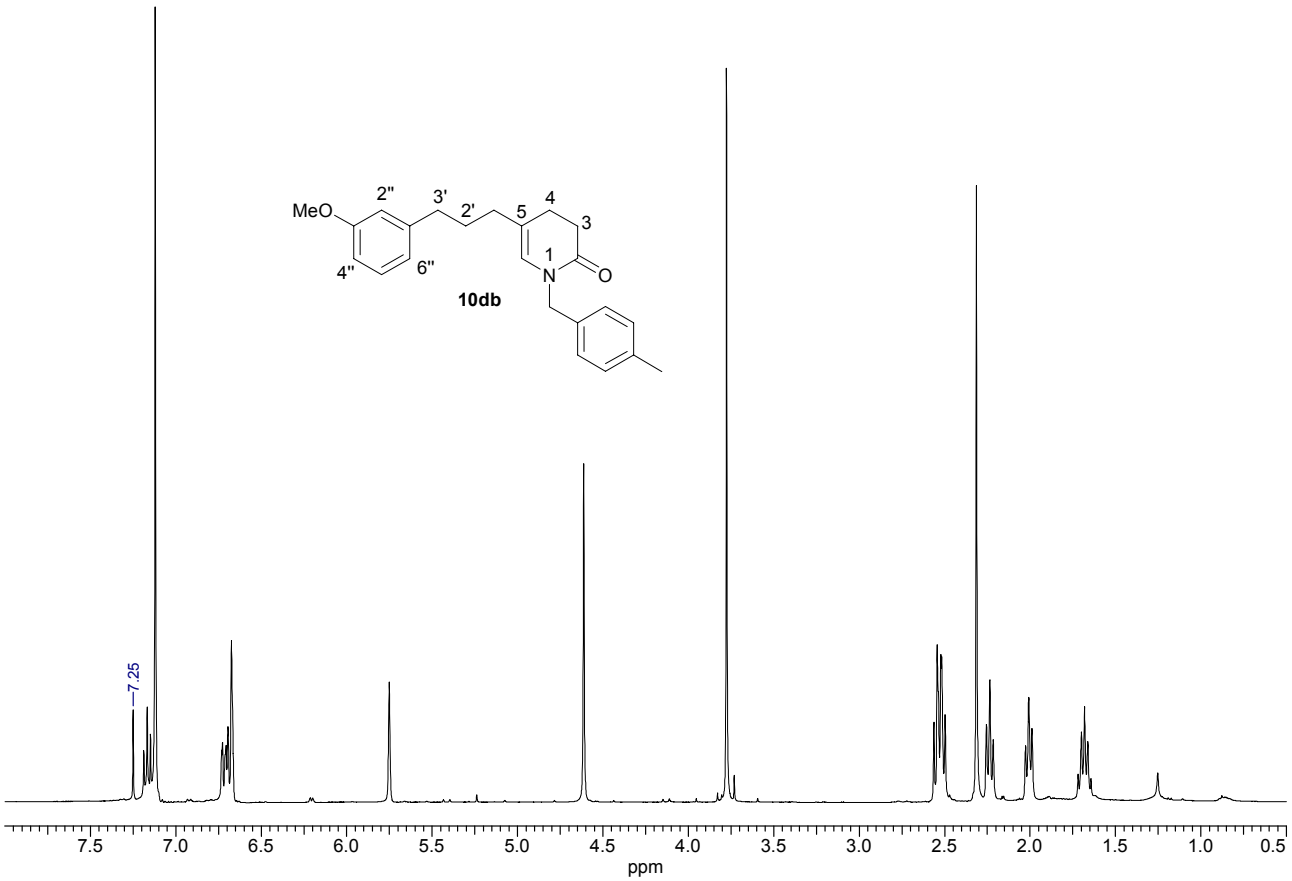

77.0
168.9
159.6
143.6
137.3
129.3
128.6
127.5
127.4
124.1
120.8
119.8
114.3
110.9
55.1
48.8
35.2
33.2
31.2
29.0
24.2
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

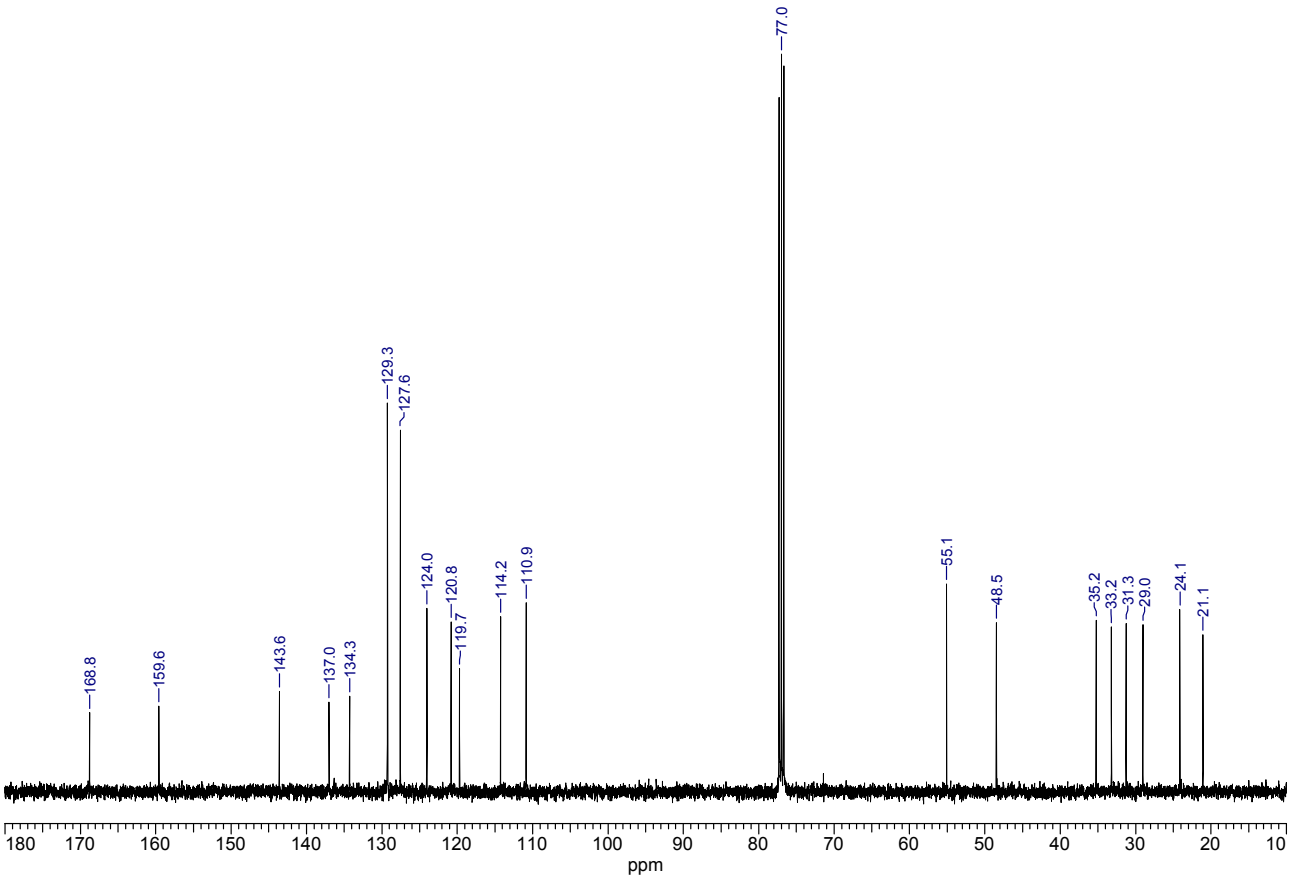

MeO
6
4
4a
8a
10'
2
10a'
8'
8
2'
1,1'
10b'
3'
4'
N
5'
6'
6a'
O
11da
7.25
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

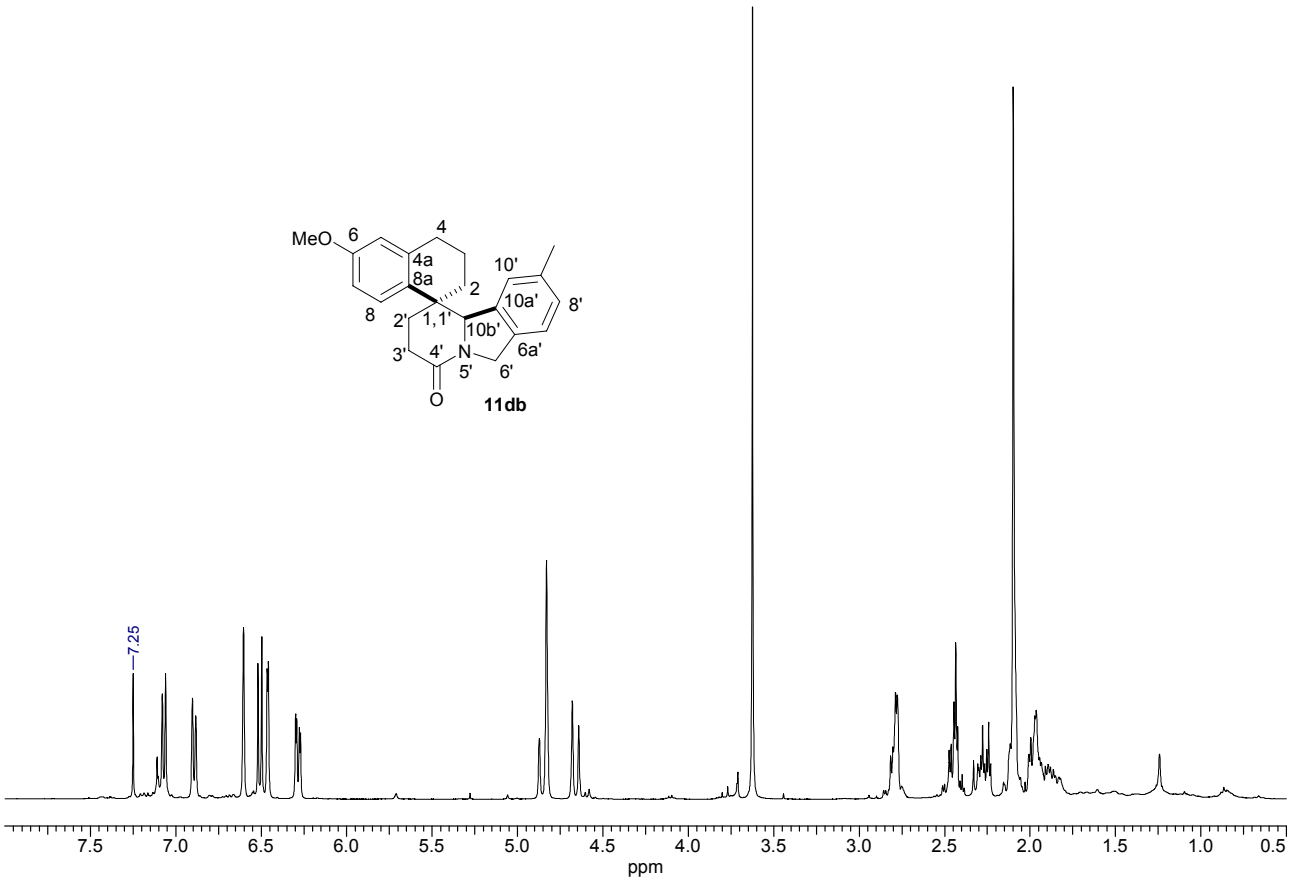

172.3
156.9
138.8
138.3
136.0
133.3
128.6
127.3
127.1
122.7
112.6
112.3
77.0
70.9
54.9
49.8
41.8
38.8
36.5
31.0
30.9
19.8
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

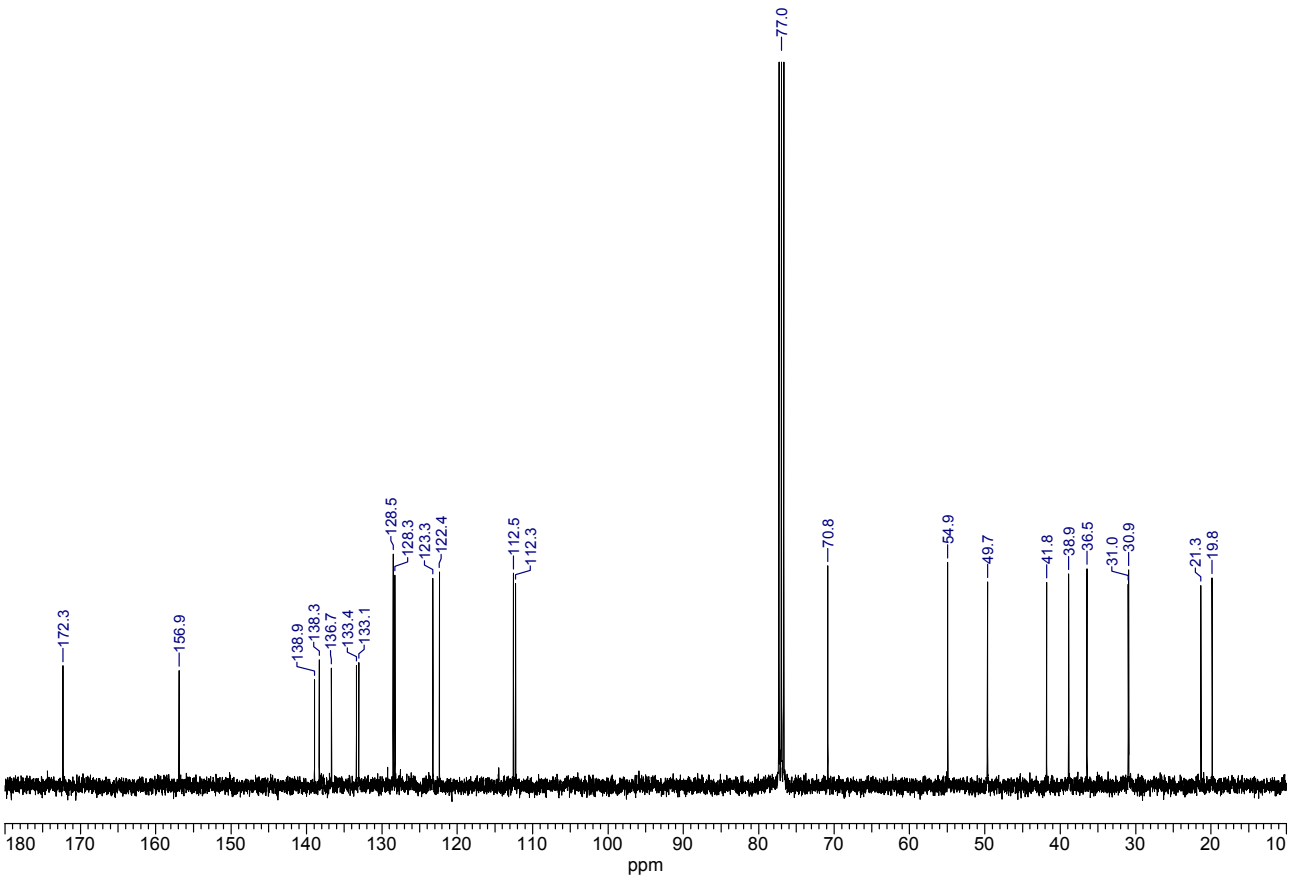

MeO
6''
3'
2'
5
4
3
1
N
O
4''
2''
Br
9db
7.25
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

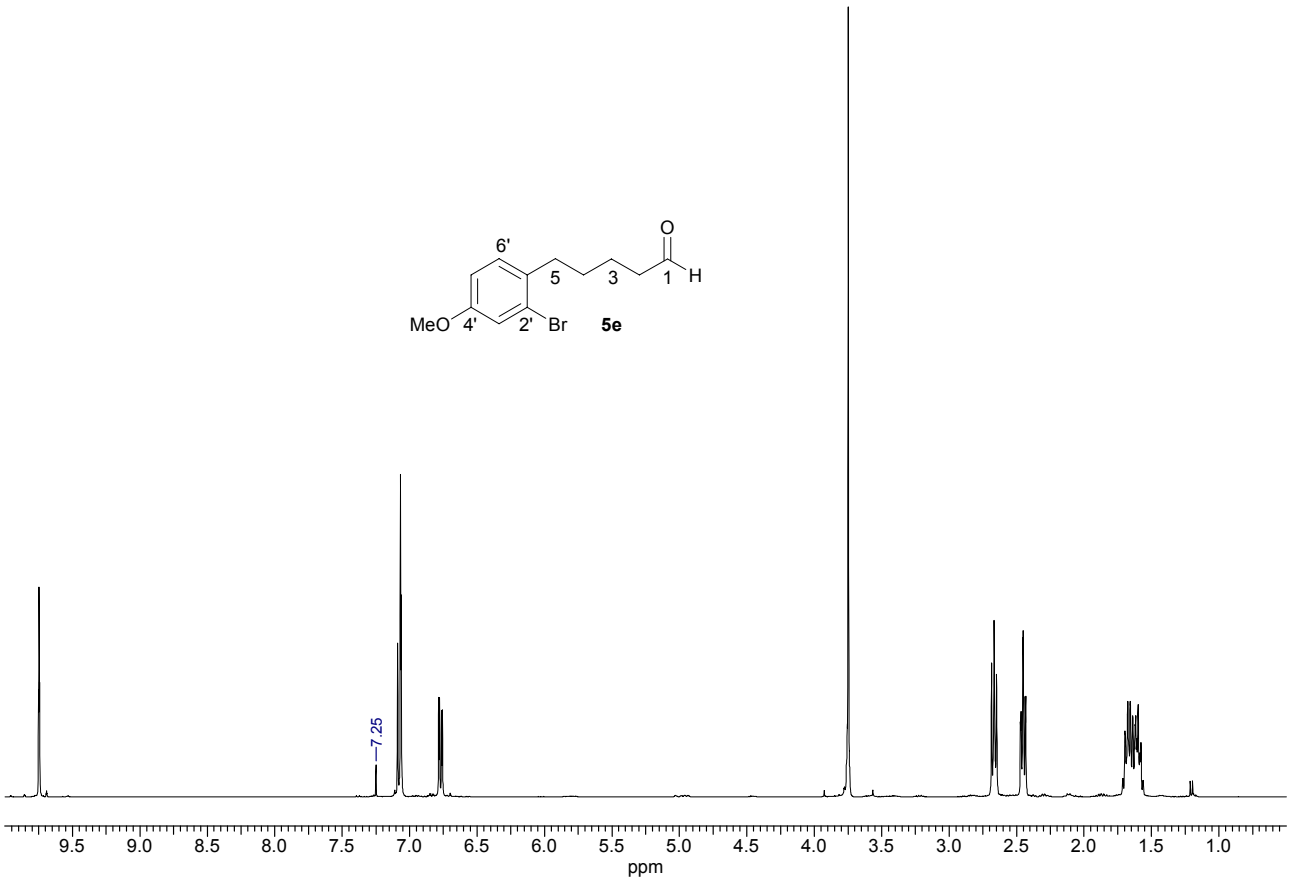

168.8
158.9
142.3
137.0
134.3
133.2
129.3
127.5
124.2
119.5
116.1
114.8
112.9
77.0
55.4
48.5
35.8
33.4
31.3
27.7
24.1
21.1
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

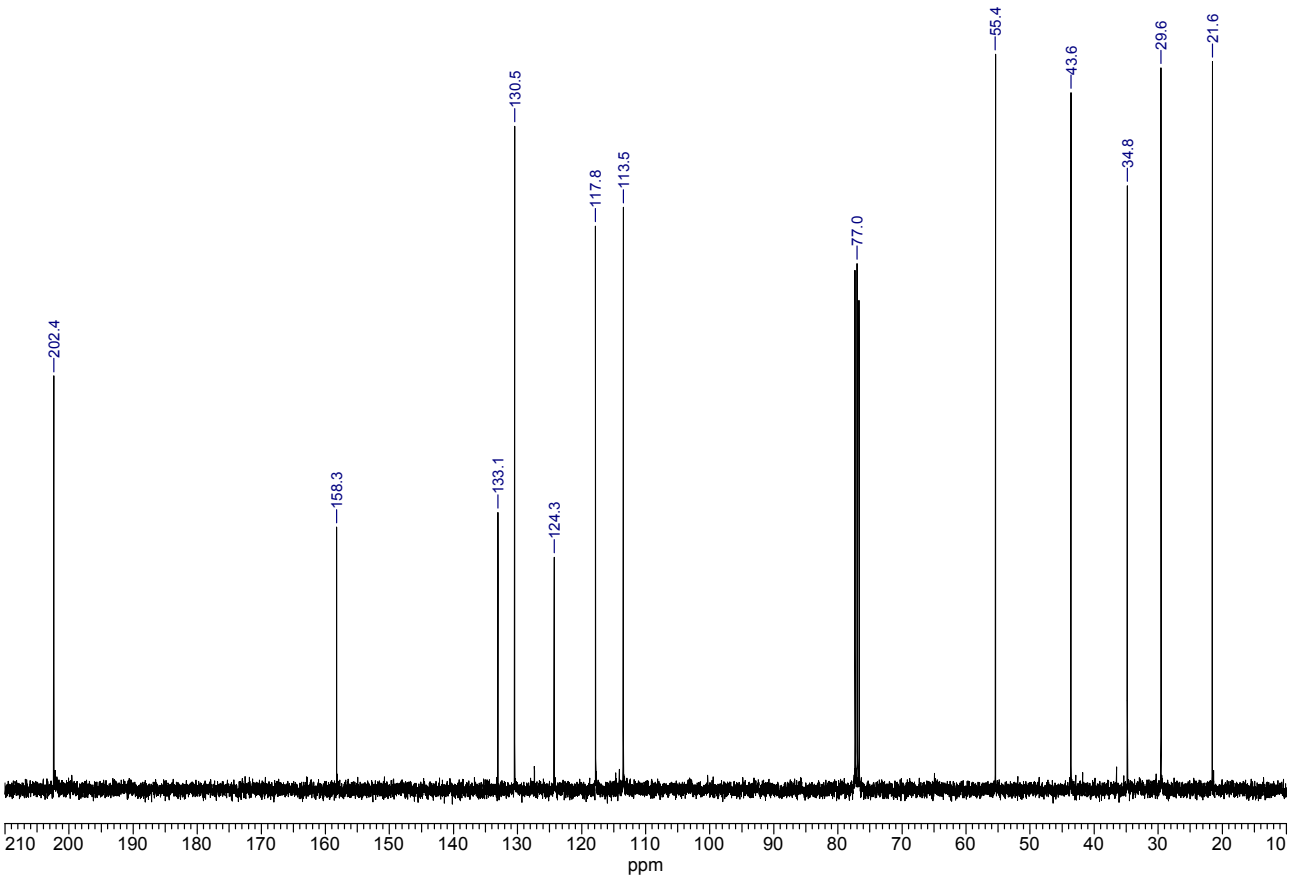

MeO
2"
3'
2'
5
4
3
1
N
O
4"
6"
10db
7.25
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

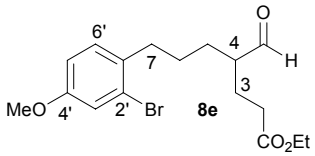

168.8
159.6
143.6
137.0
134.3
129.3
127.6
124.0
120.8
119.7
114.2
110.9
77.0
55.1
48.5
35.2
33.2
31.3
29.0
24.1
21.1
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm





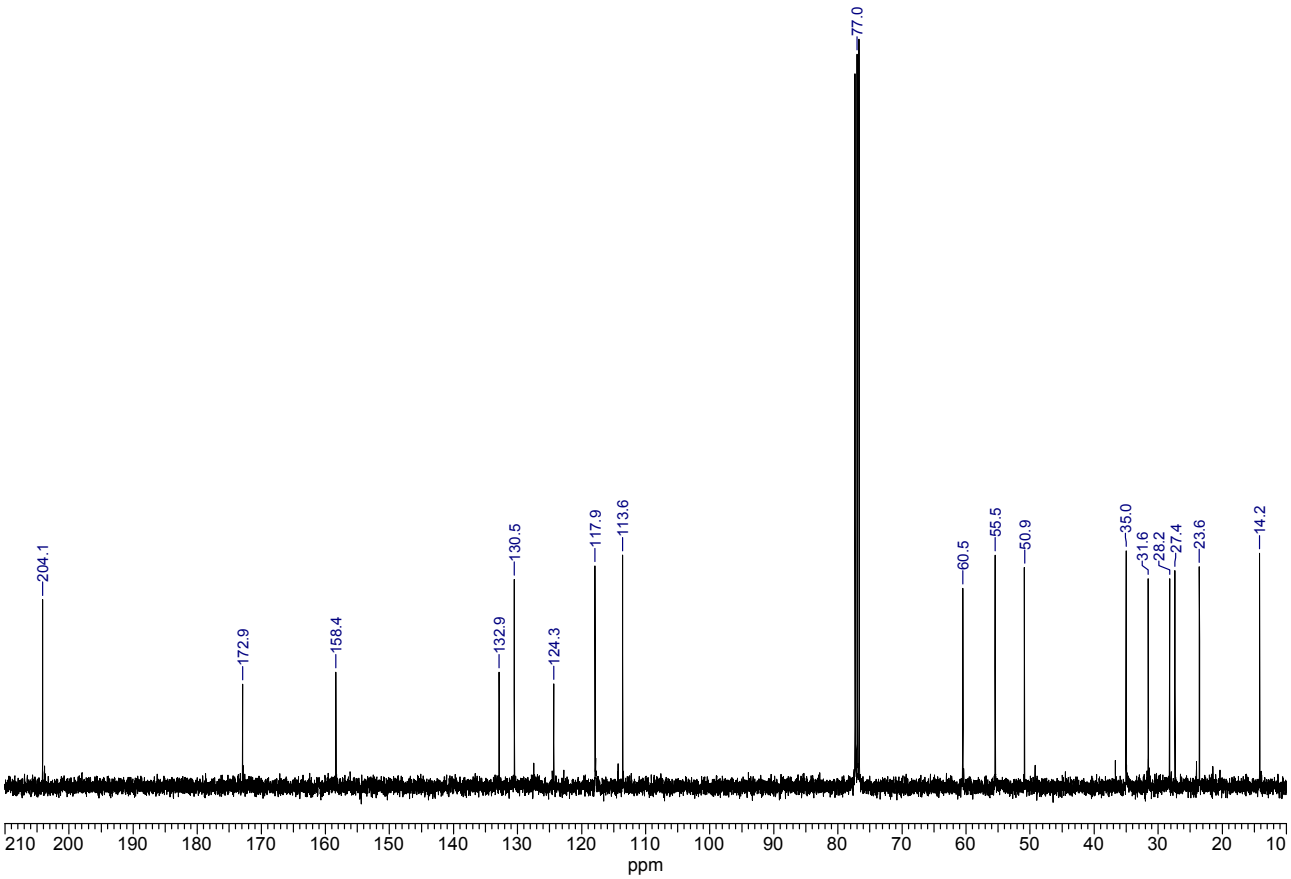

6'
5
3
1
O
H
MeO
4'
2'
Br
5e
7.25
ppm

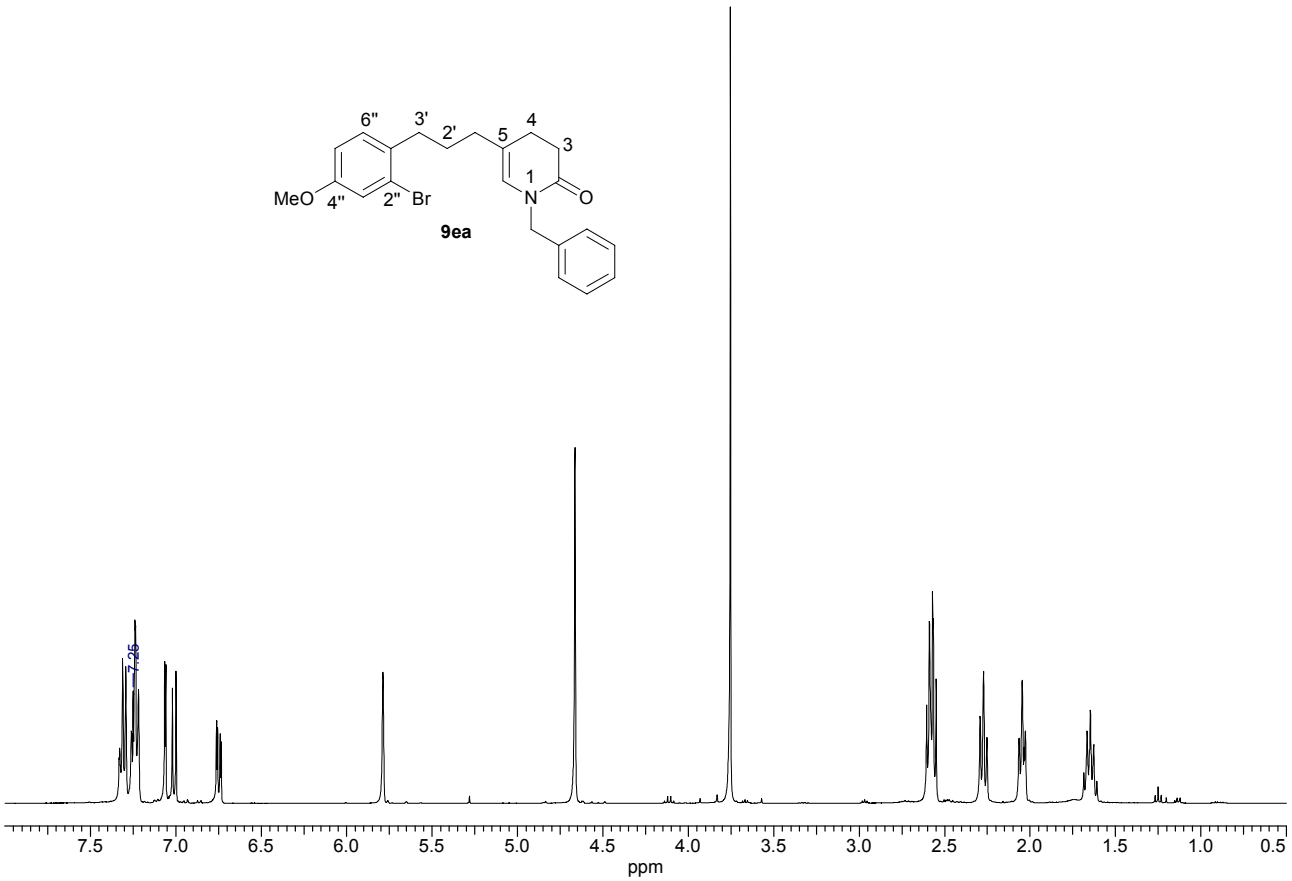

202.4
158.3
133.1
130.5
124.3
117.8
113.5
77.0
55.4
43.6
34.8
29.6
21.6
ppm

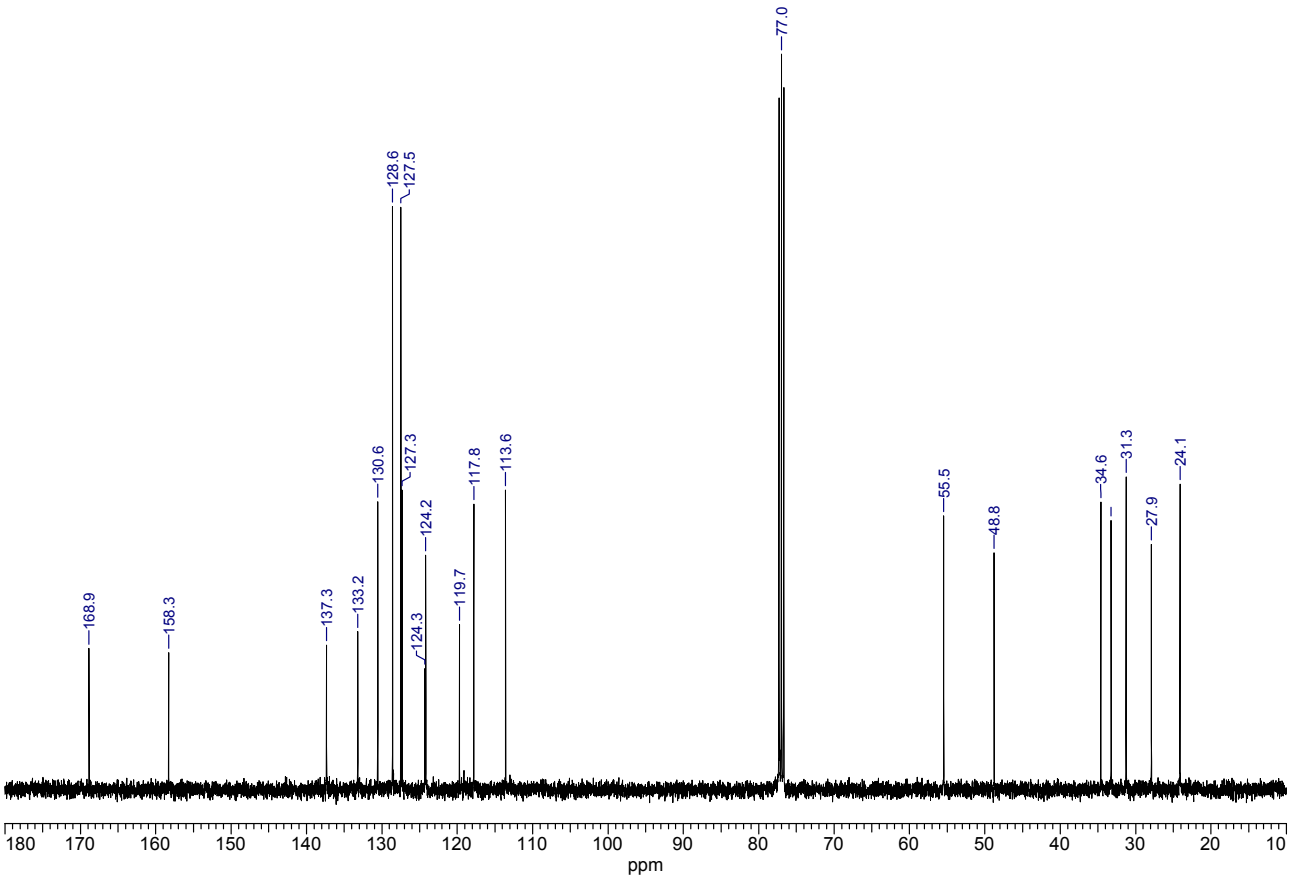

6'
7
4
O
H
3
MeO
4'
2'
Br
CO2Et

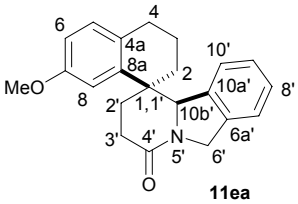
8e

7.25
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


77.0
204.1
172.9
158.4
132.9
130.5
124.3
117.9
113.6
60.5
55.5
50.9
35.0
31.6
28.2
27.4
23.6
14.2
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

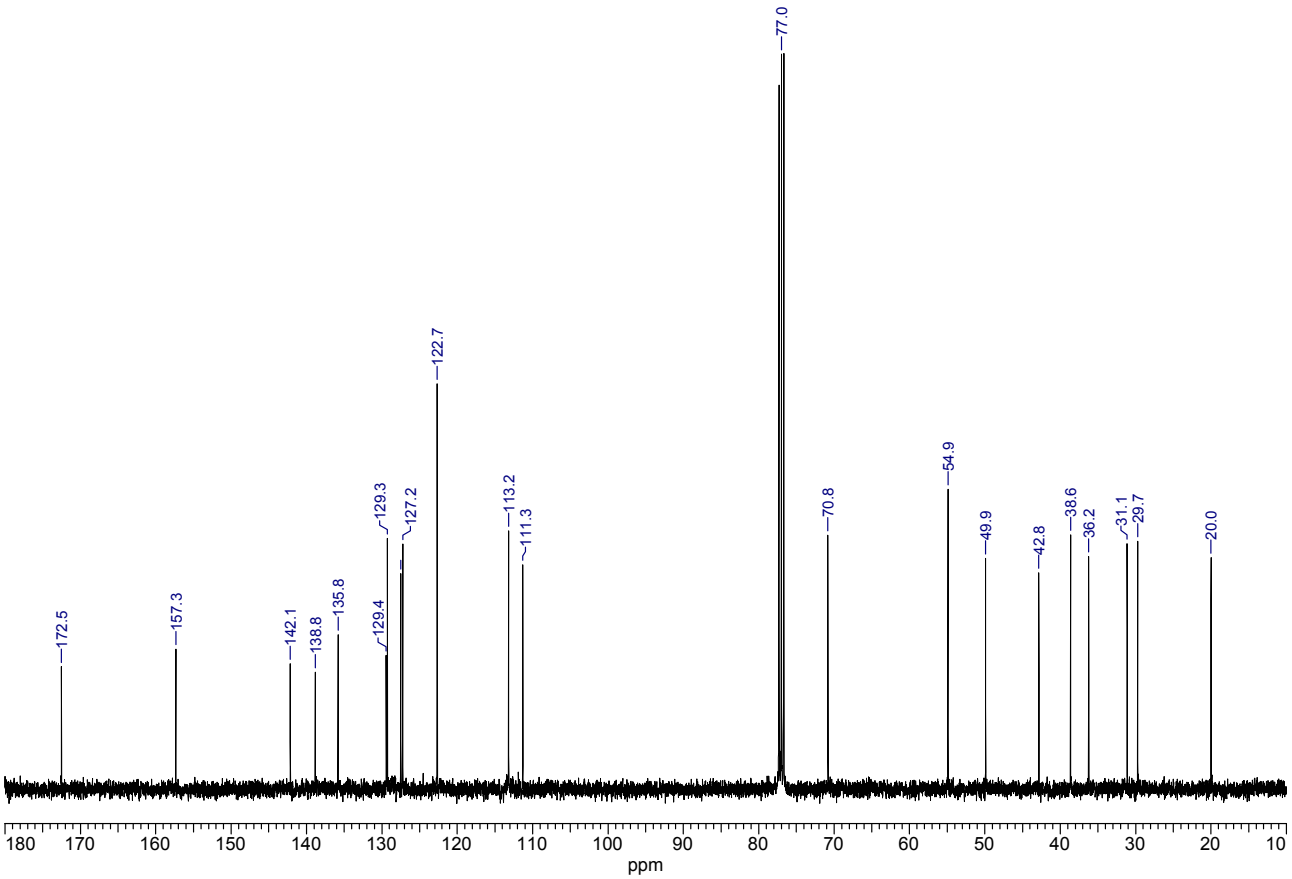

6"
3'
2'
5
4
3
1
N
O
MeO
4"
2"
Br
9ea
7.25
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

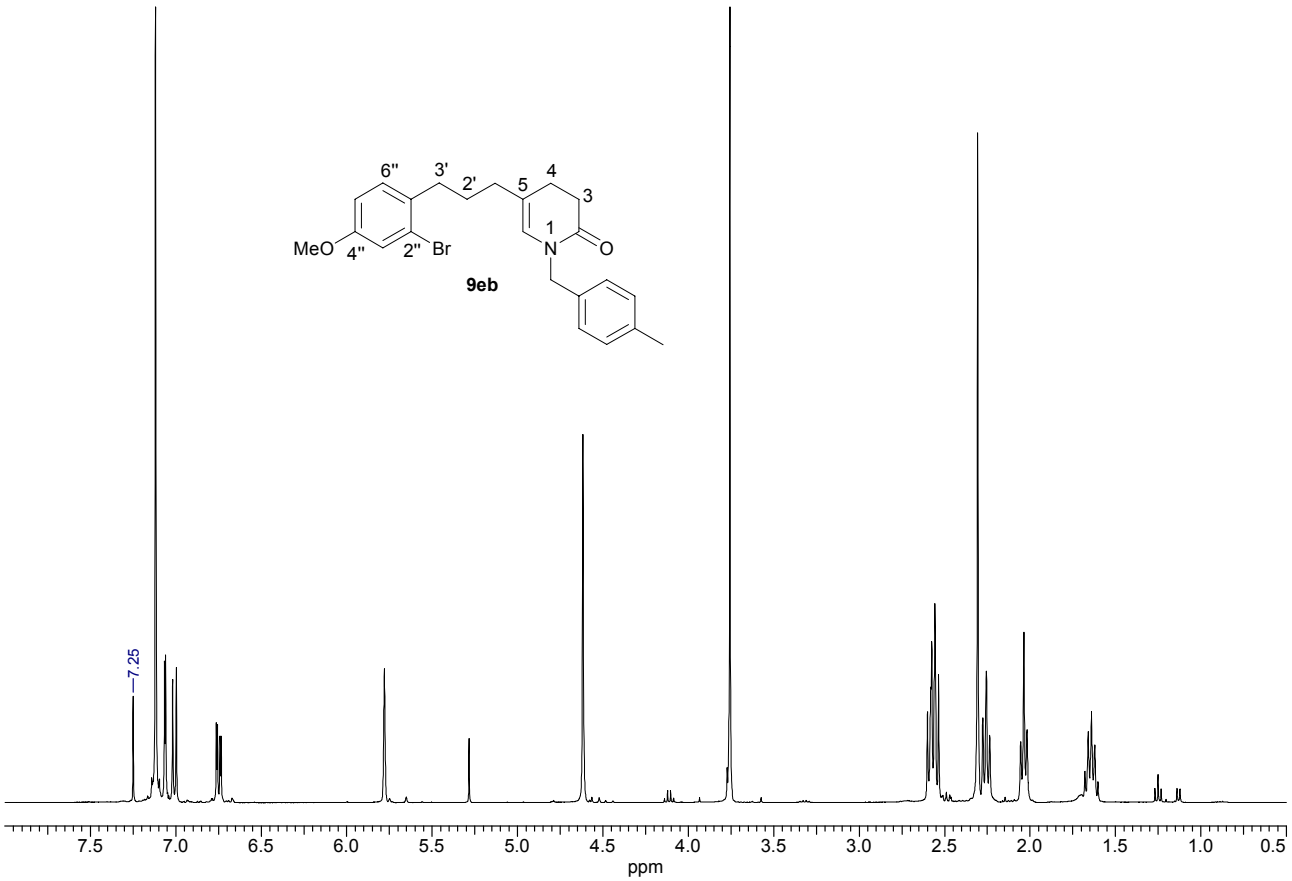

168.9
158.3
137.3
133.2
130.6
128.6
127.5
127.3
124.3
124.2
119.7
117.8
113.6
77.0
55.5
48.8
34.6
31.3
27.9
24.1
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

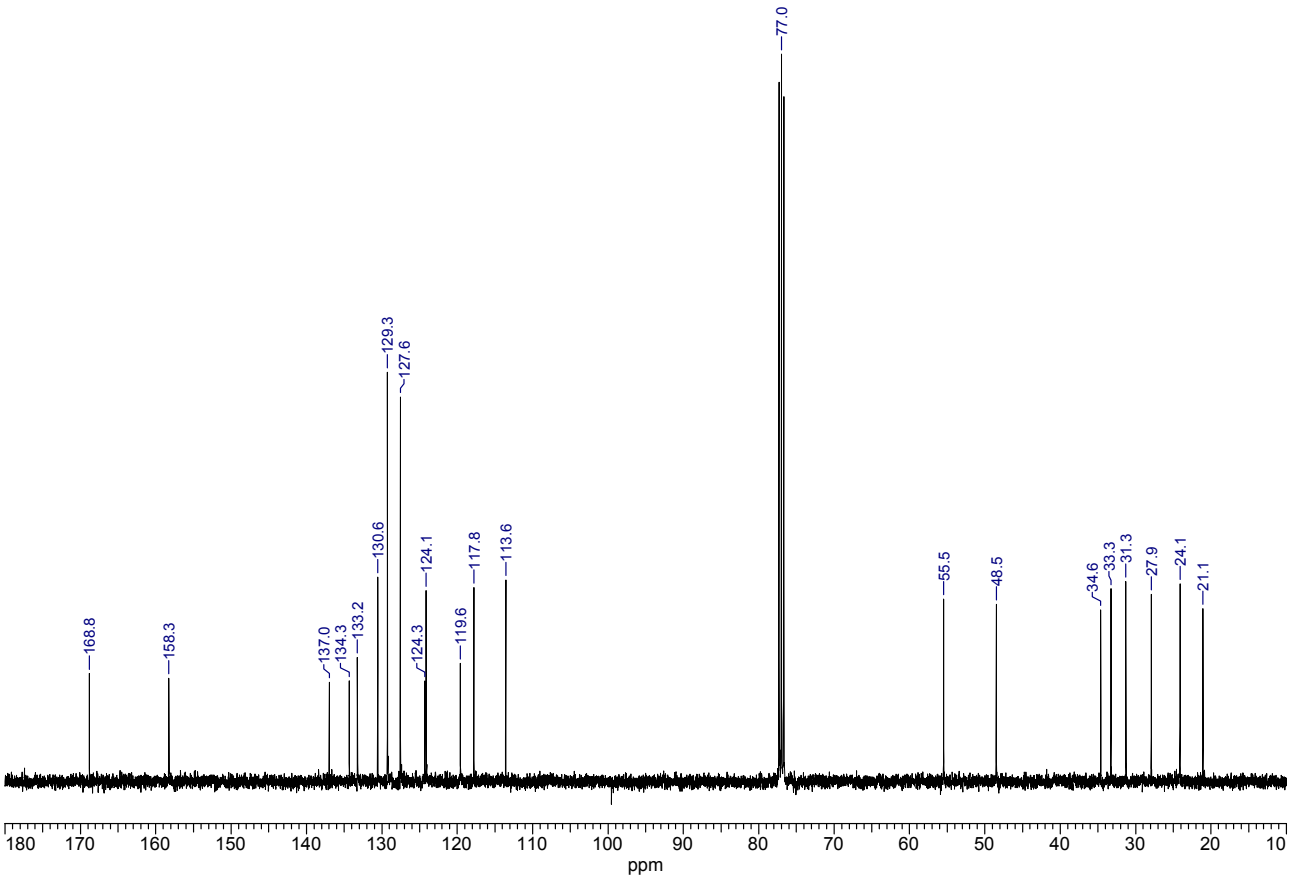

4
6
4a
10'
8a
2
MeO
8
10a'
8'
2'
1,1'
10b'
3'
4'
N
6a'
5'
6'
O

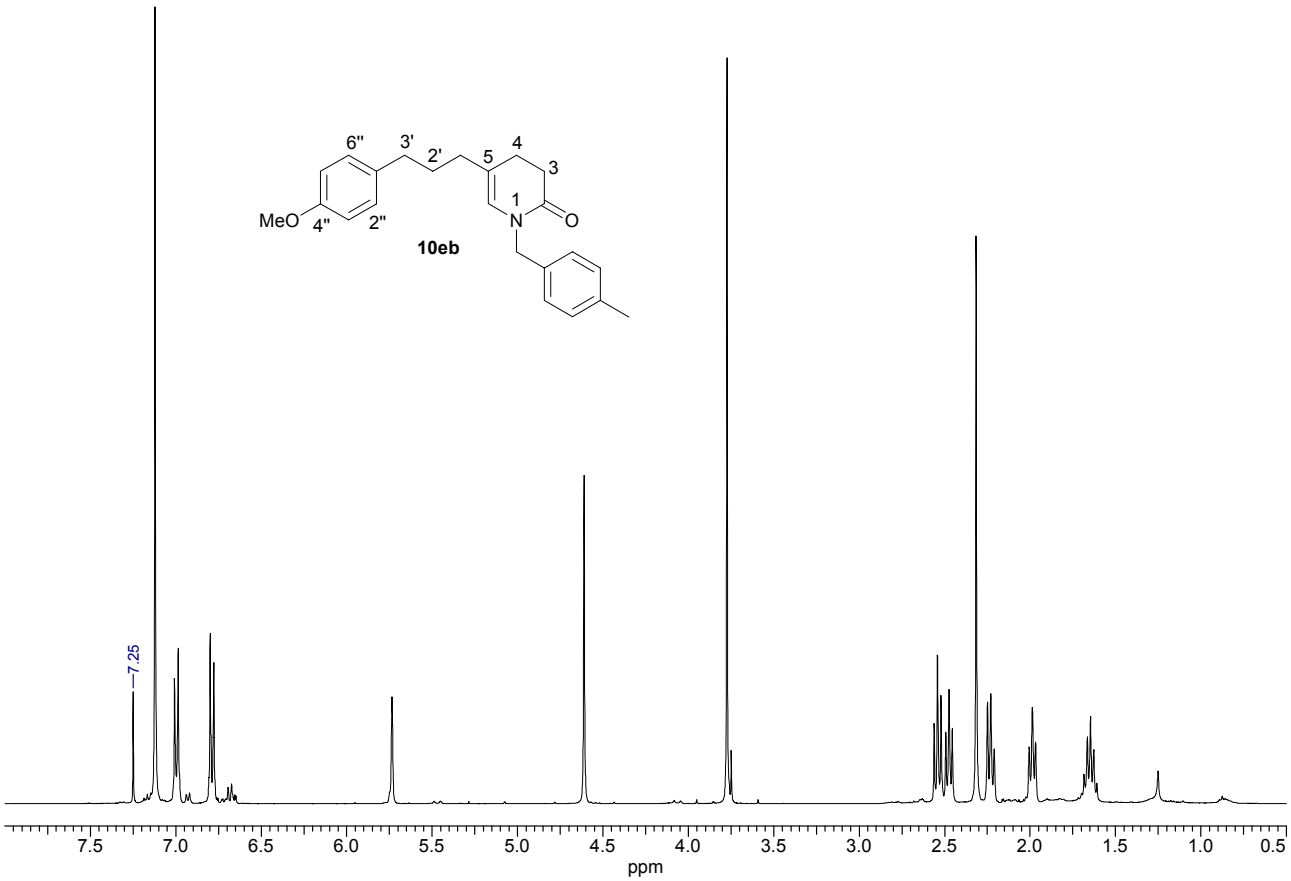
11ea

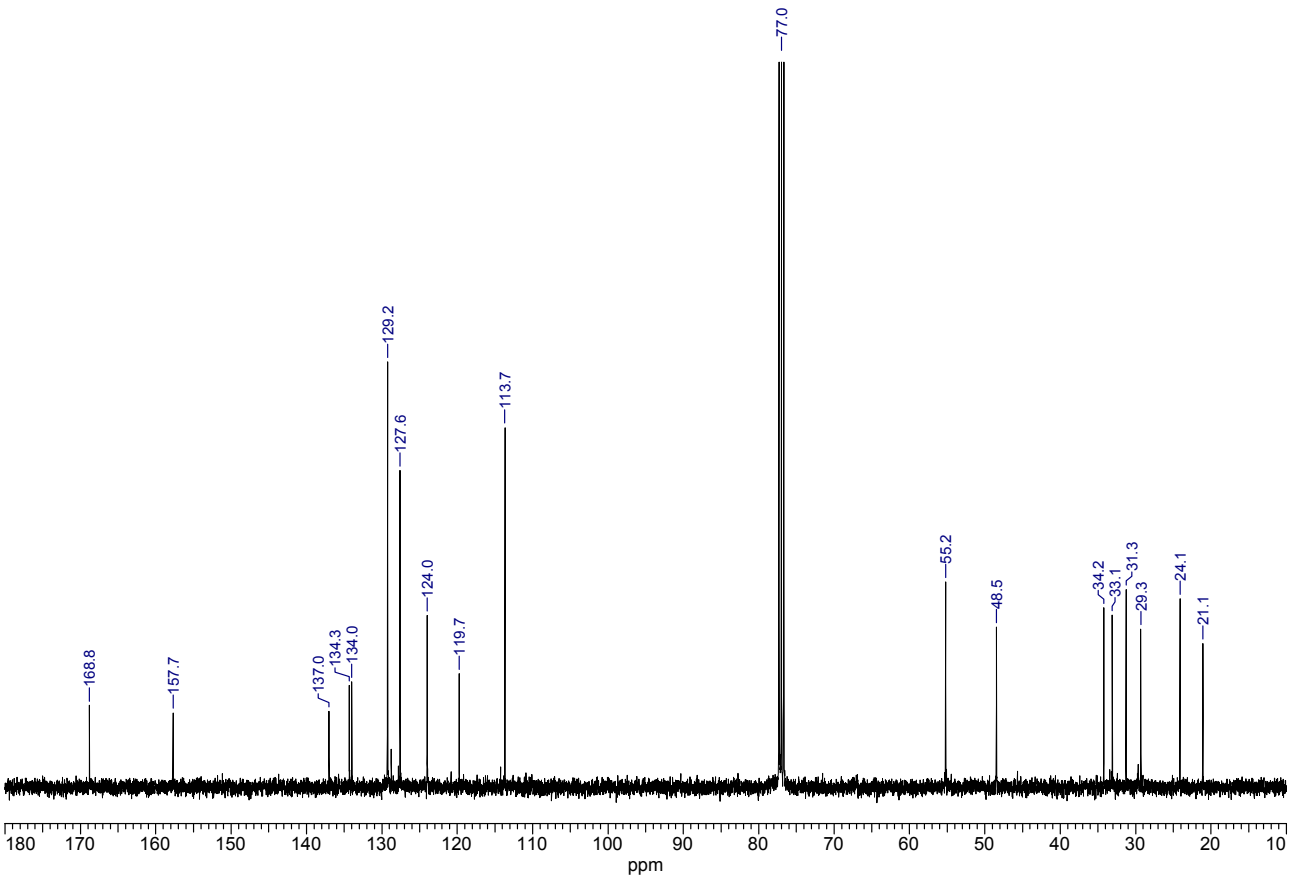
7.25
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

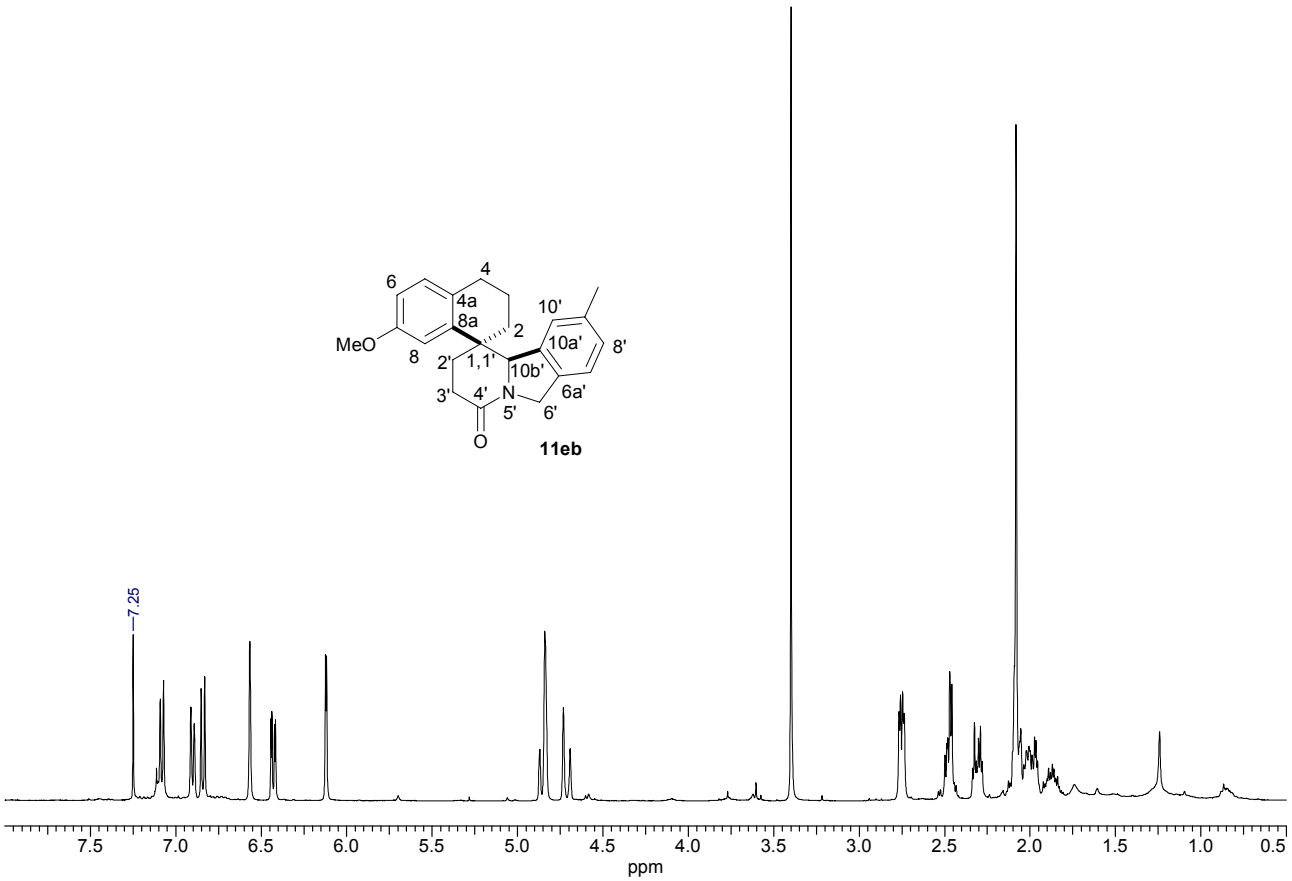

77.0
122.7
129.3
127.2
113.2
111.3
54.9
70.8
49.9
42.8
38.6
36.2
31.1
29.7
20.0
172.5
157.3
142.1
138.8
135.8
129.4
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

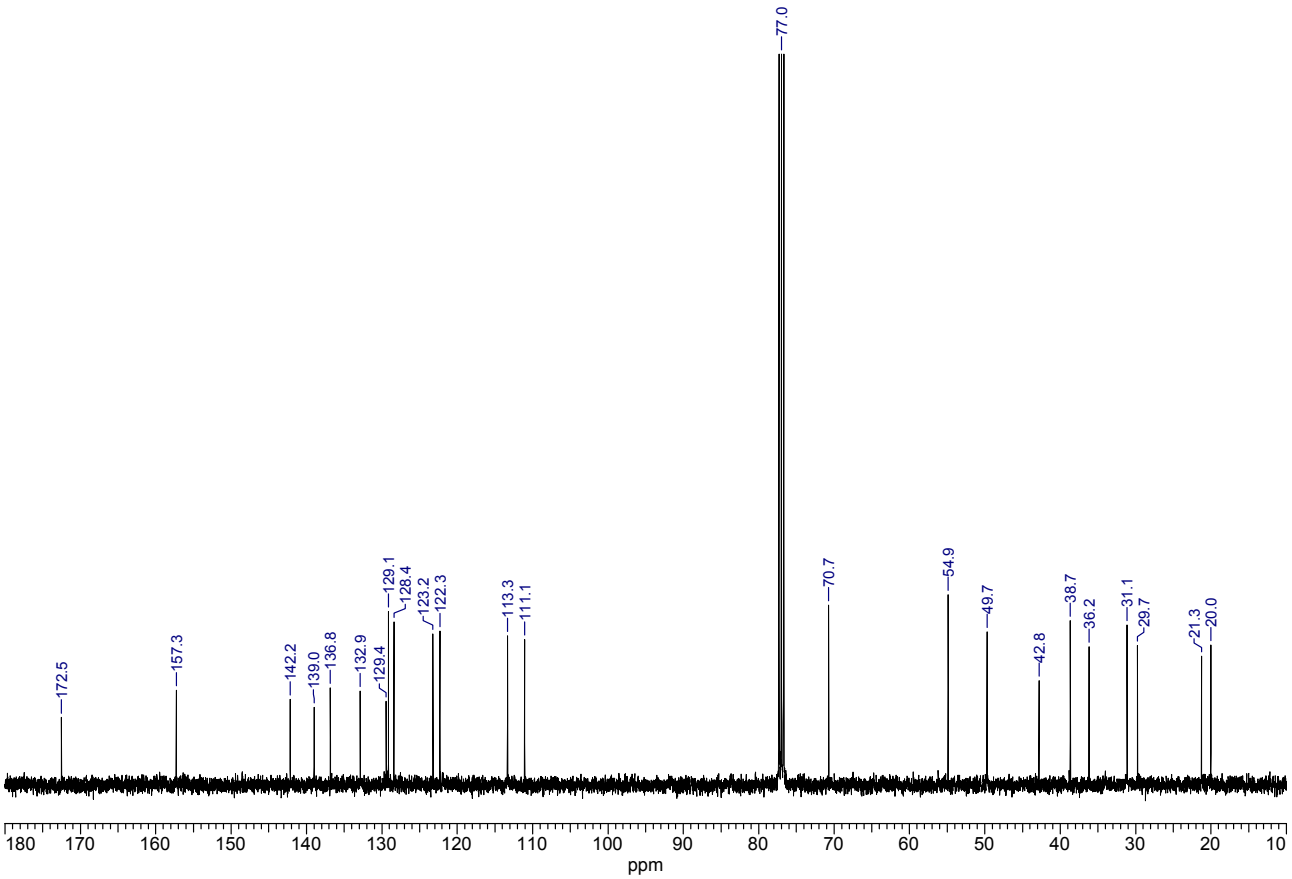

6''
3'
2'
5
4
3
1
N
O
MeO
4''
2''
Br
9eb
7.25
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

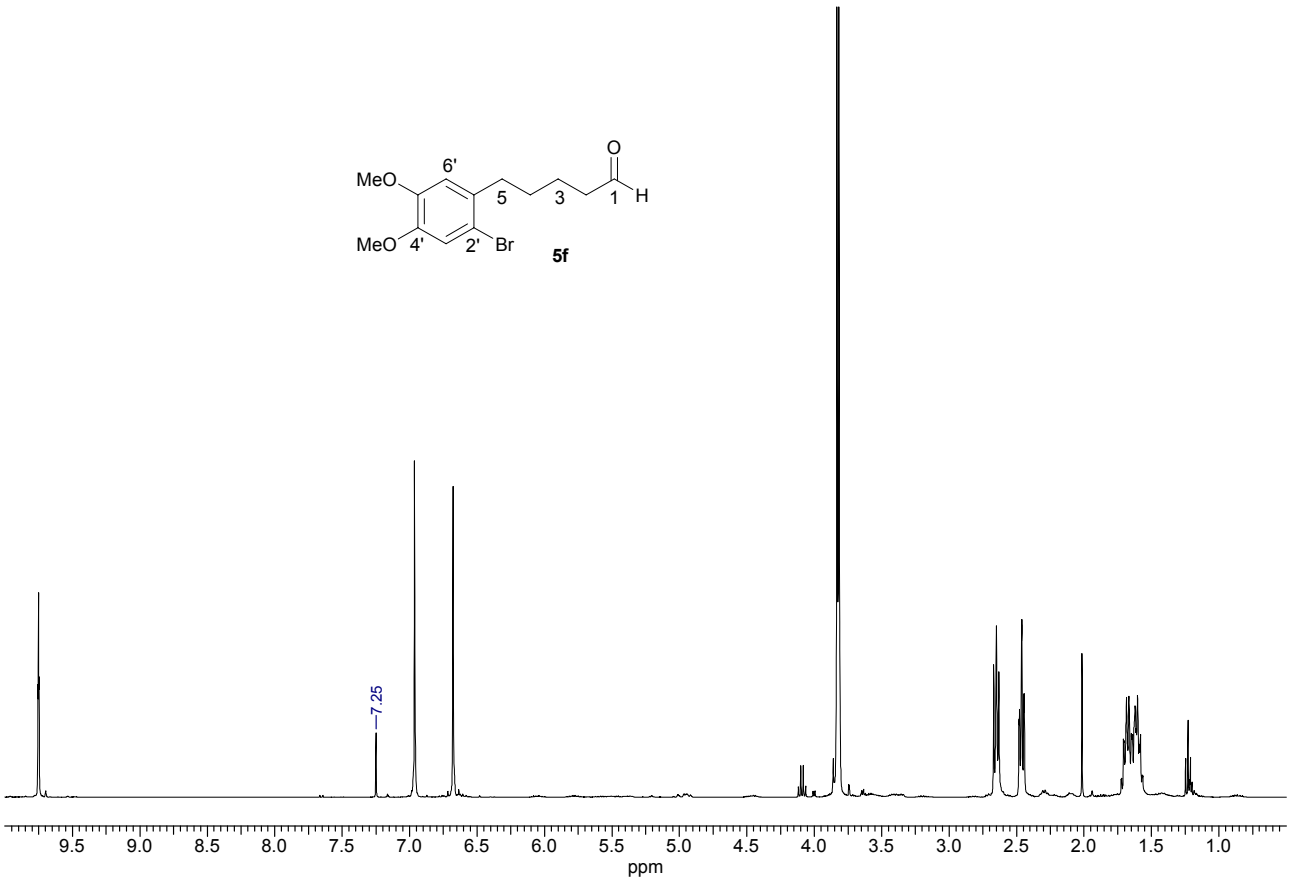

77.0
168.8
158.3
137.0
134.3
133.2
129.3
127.6
130.6
124.1
124.3
119.6
117.8
113.6
55.5
48.5
34.6
33.3
31.3
27.9
24.1
21.1
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

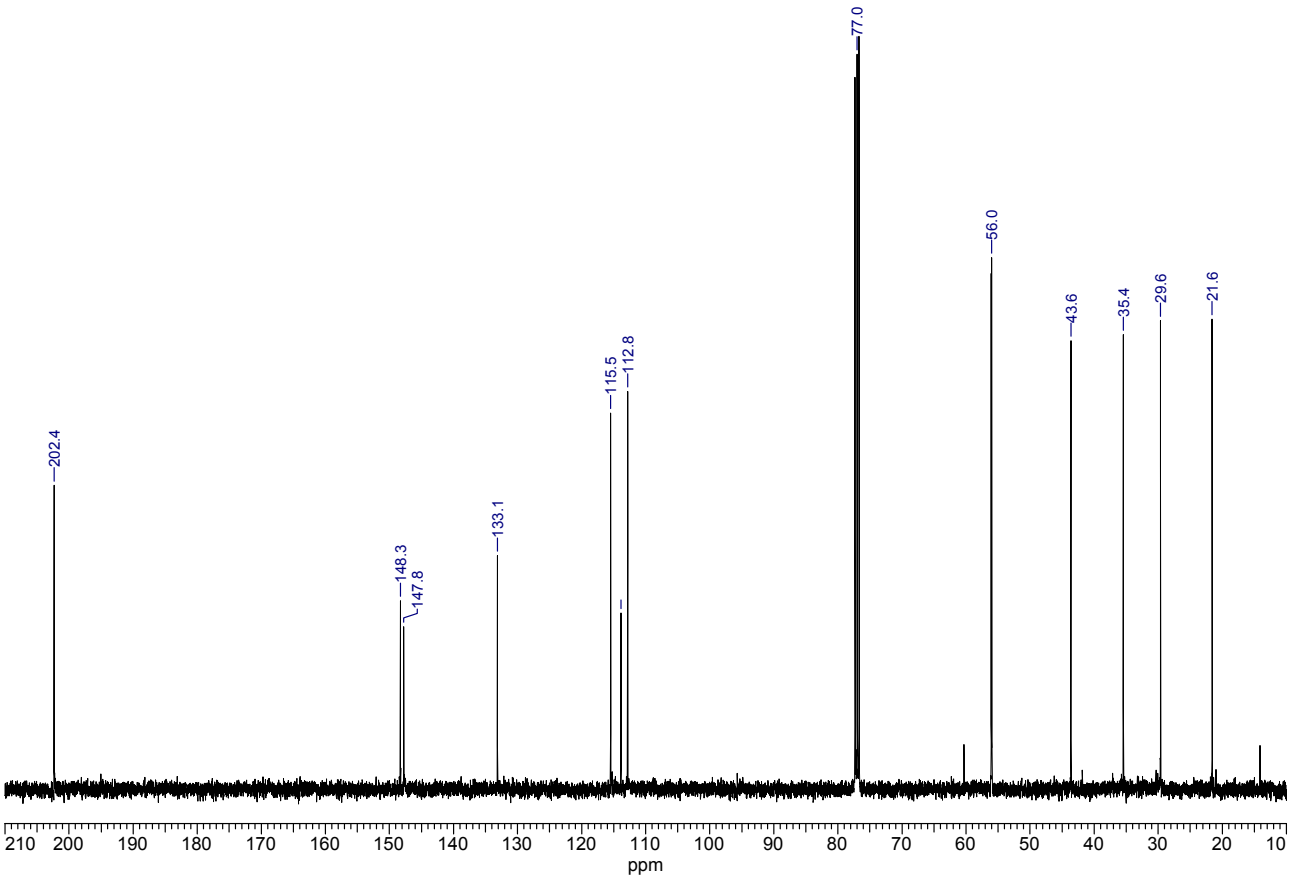


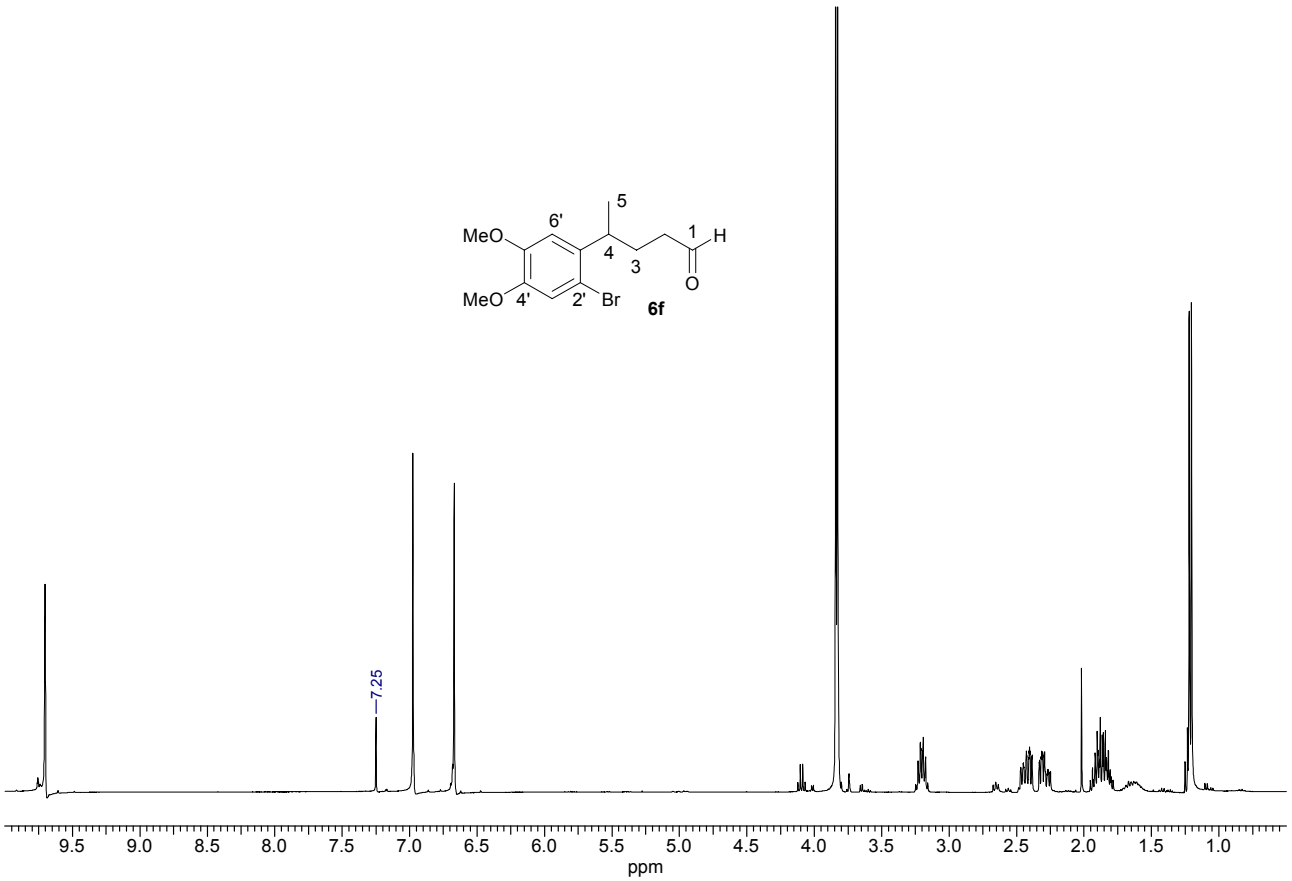


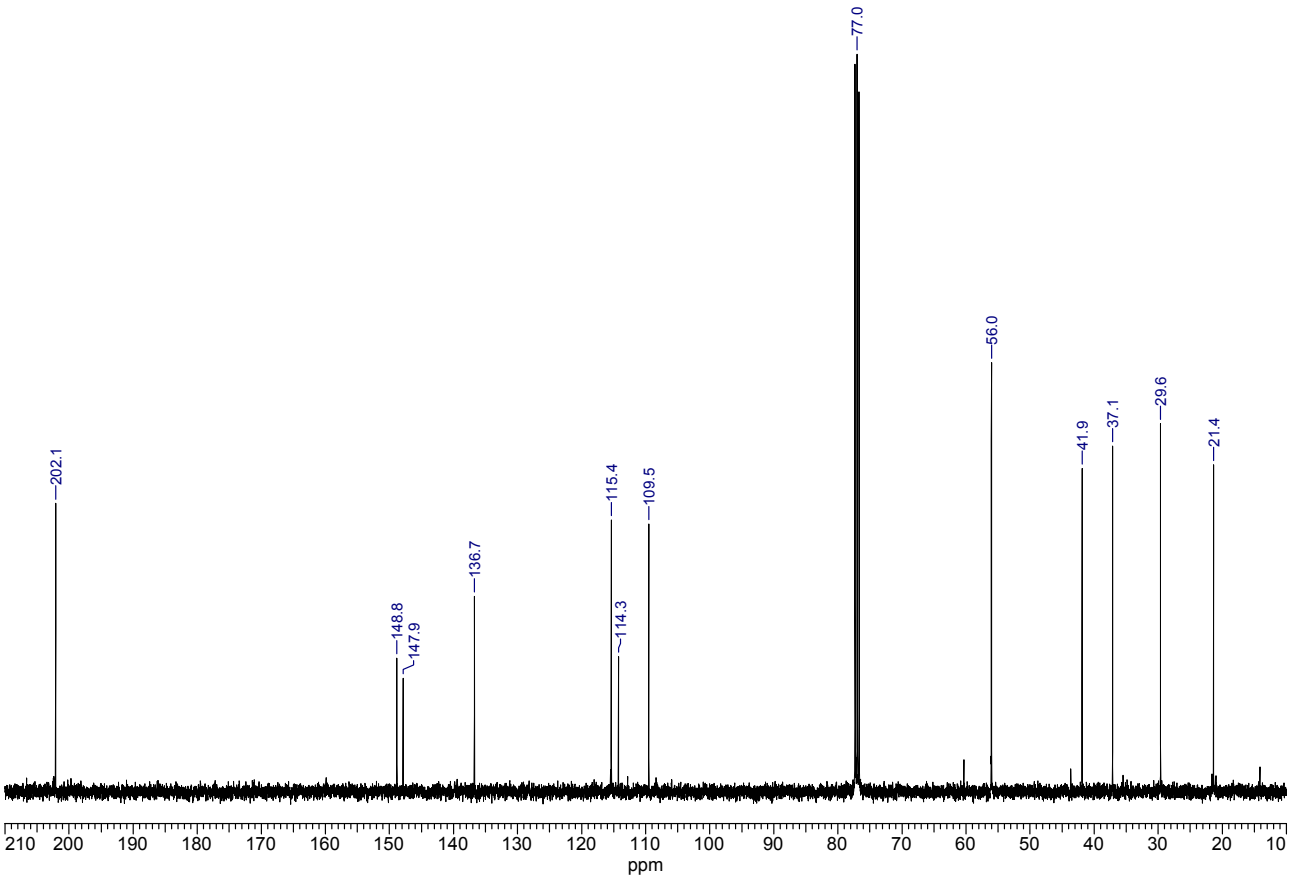

6
4
4a
8a
2
10'
MeO
8
2'
1,1'
10a'
8'
10b'
3'
4'
N
5'
6a'
6'
O
11eb
7.25
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

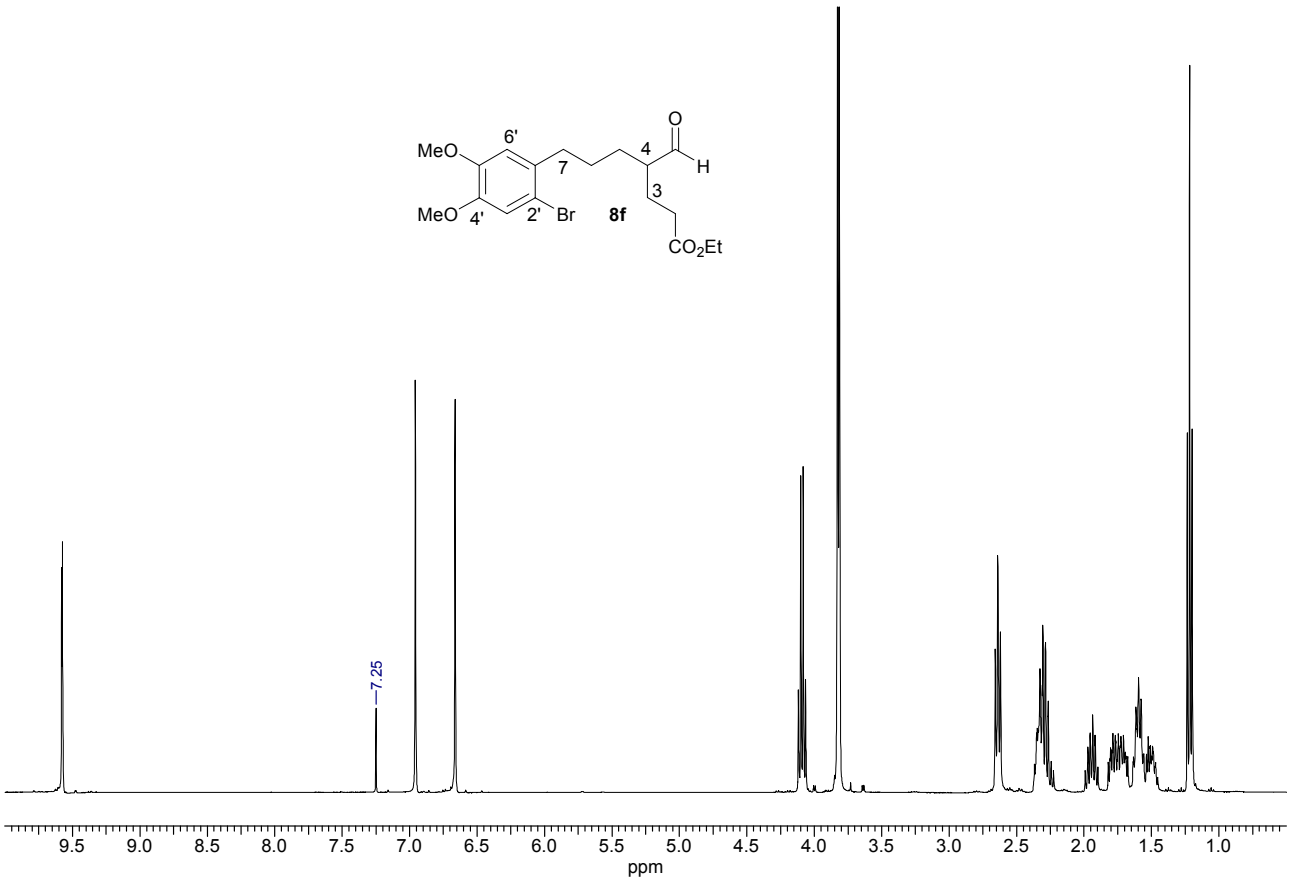

77.0
172.5
157.3
142.2
139.0
136.8
132.9
129.4
129.1
128.4
123.2
122.3
113.3
111.1
70.7
54.9
49.7
42.8
38.7
36.2
31.1
29.7
21.3
20.0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

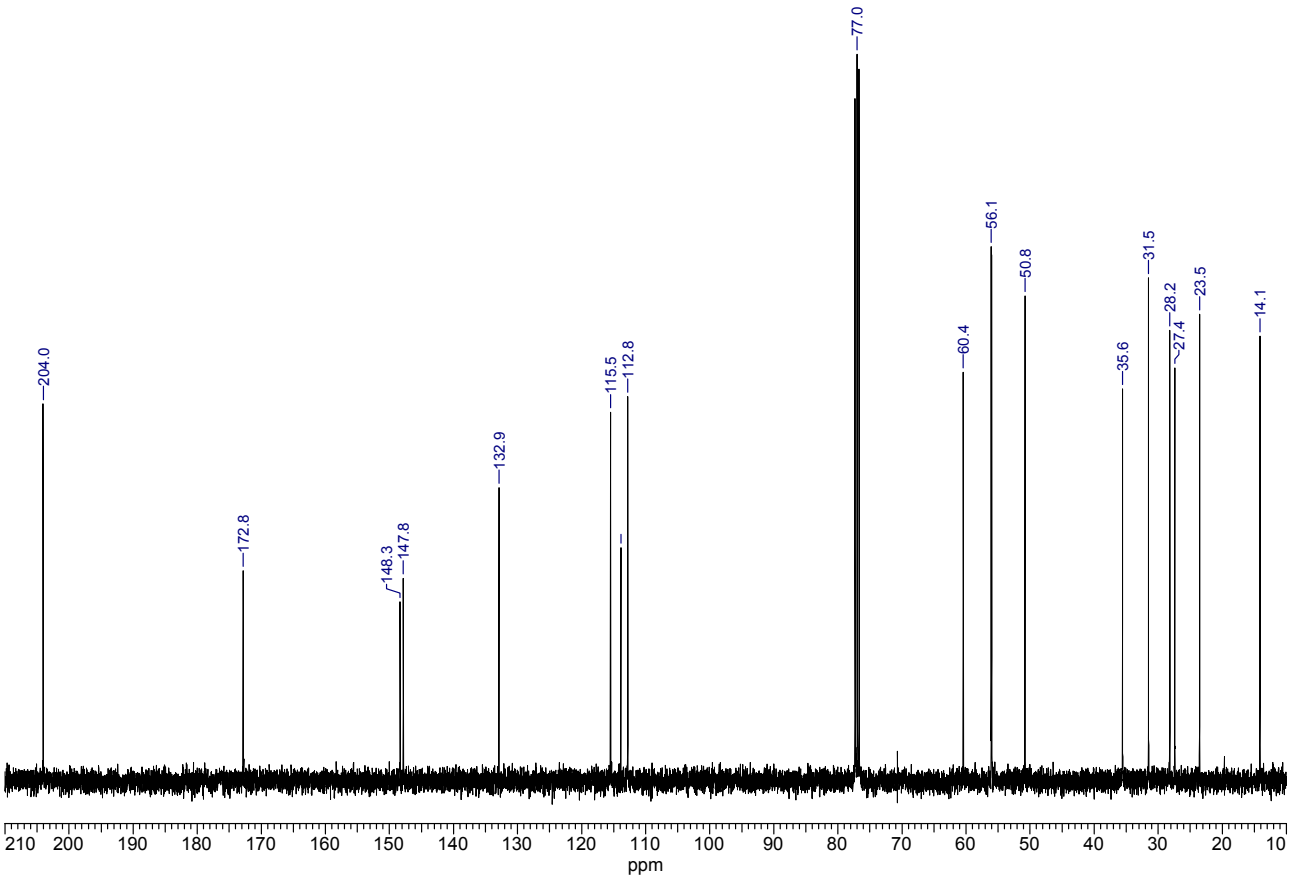


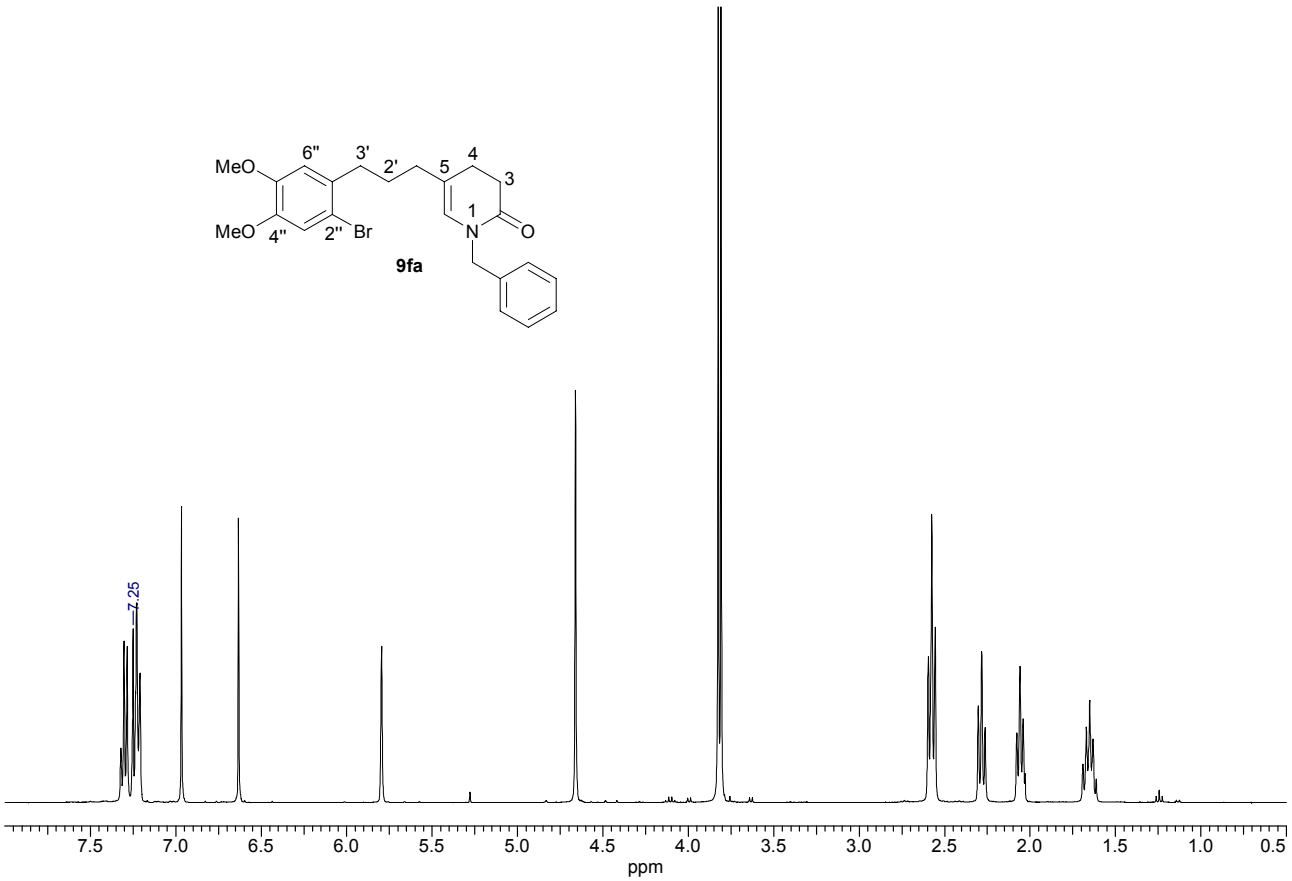


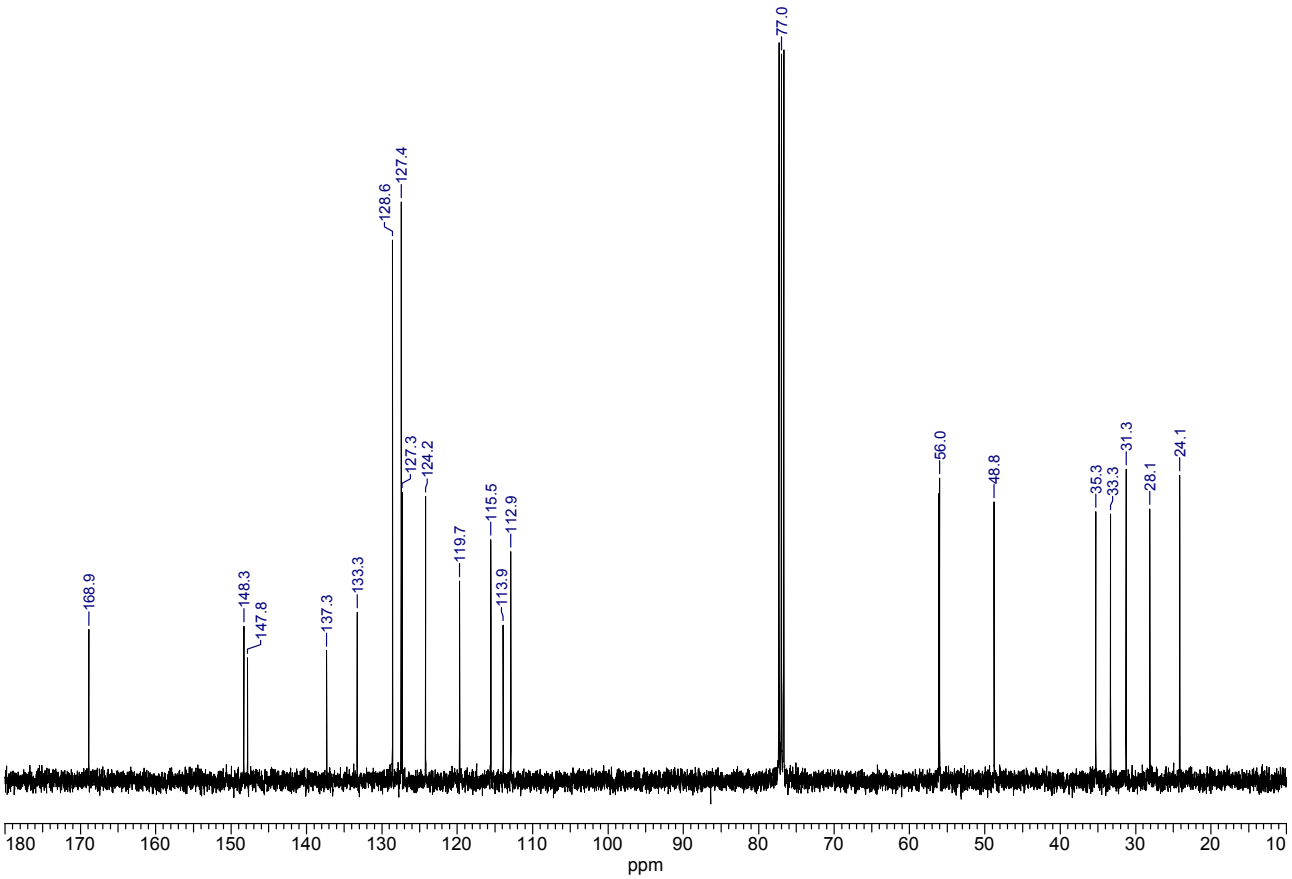

MeO
MeO
6'
5
1
H
4
3
4'
2'
Br
O
6f
7.25
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm

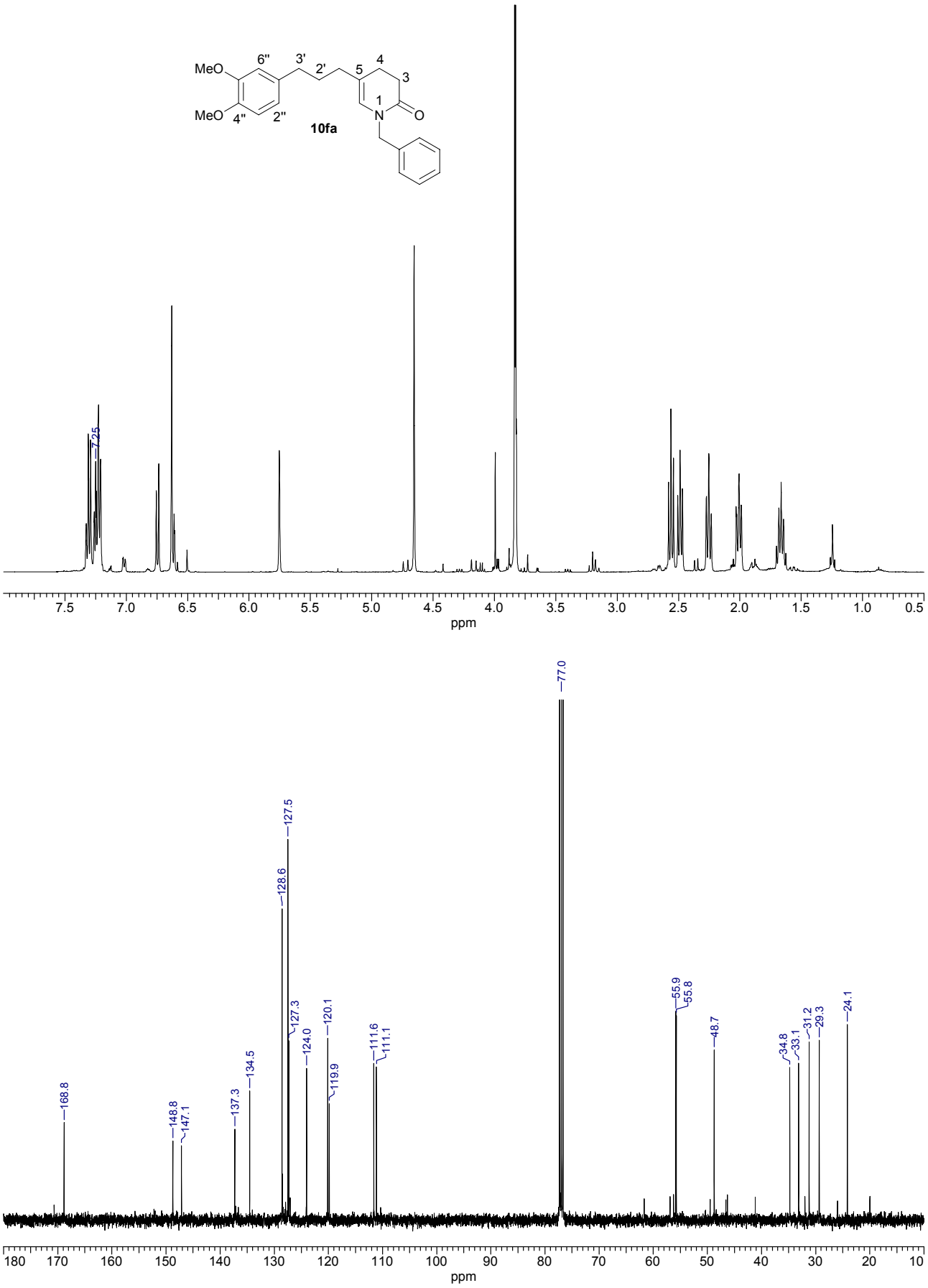

202.1
148.8
147.9
136.7
115.4
114.3
109.5
77.0
56.0
41.9
37.1
29.6
21.4
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

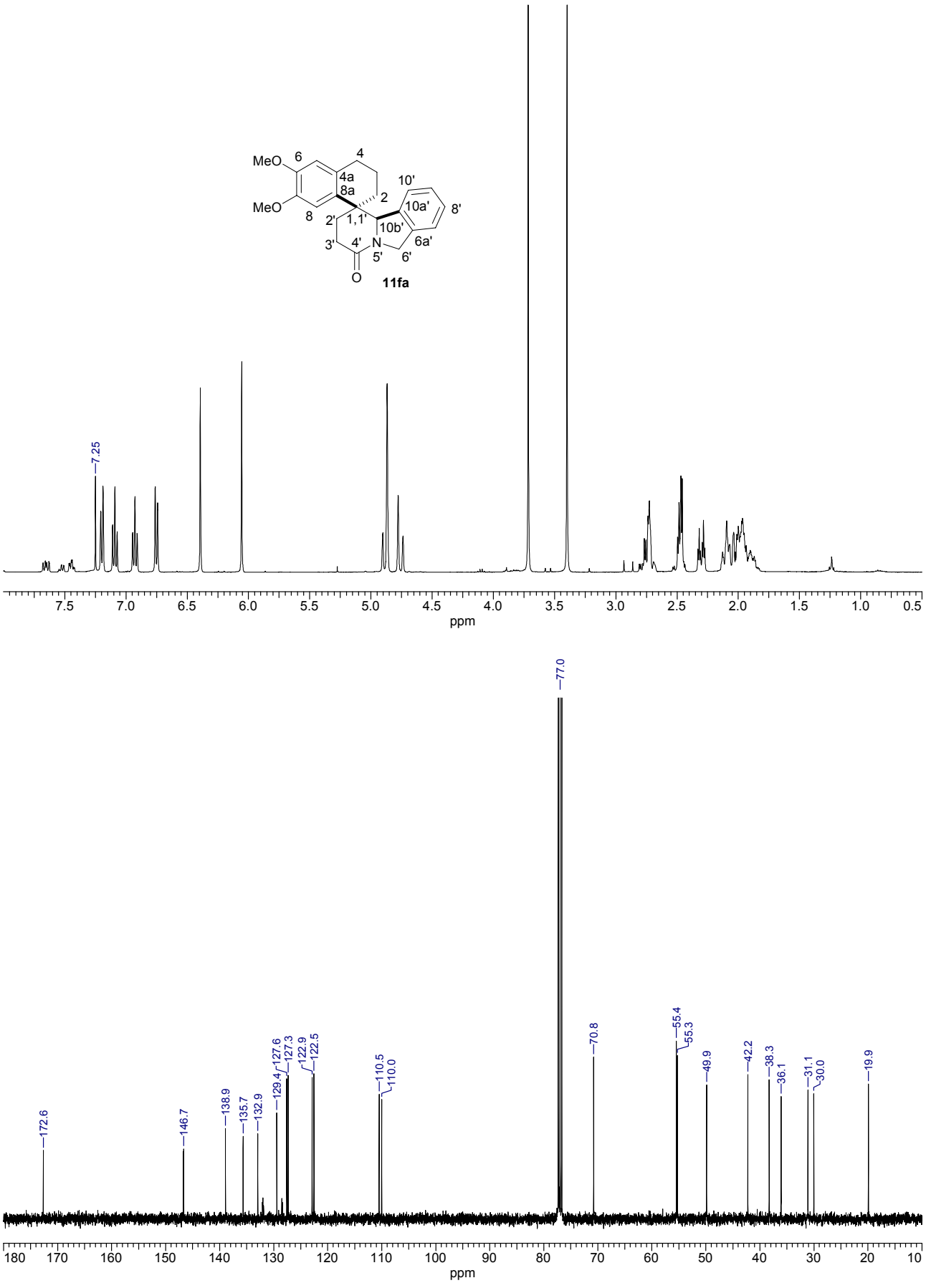

MeO
MeO
6'
4'
2'
Br
7
4
3
O
H
CO2Et
8f
7.25
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm


204.0
172.8
148.3
147.8
132.9
115.5
112.8
77.0
60.4
56.1
50.8
35.6
31.5
28.2
27.4
23.5
14.1
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm


MeO
MeO
6"
3'
2'
5
4
3
1
N
O
4"
2"
Br
9fa
7.25
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


168.9
148.3
147.8
137.3
133.3
128.6
127.4
127.3
124.2
119.7
115.5
113.9
112.9
77.0
56.0
48.8
35.3
33.3
31.3
28.1
24.1
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


MeO
MeO
6"
3'
2'
5
4
3
1
N
O
4"
2"
10fa
7.25
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
77.0
127.5
128.6
127.3
124.0
120.1
119.9
111.6
111.1
168.8
148.8
147.1
137.3
134.5
55.9
55.8
48.7
34.8
33.1
31.2
29.3
24.1
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


MeO
6
4
4a
8a
10'
2
MeO
8
10a'
8'
2'
1,1'
10b'
3'
4'
N
6a'
5'
6'
O
11fa
7.25
ppm
77.0
70.8
55.4
55.3
49.9
42.2
38.3
36.1
31.1
30.0
19.9
172.6
146.7
138.9
135.7
132.9
129.4
127.6
127.3
122.9
122.5
110.5
110.0
ppm