Electronic Supplementary Material (ESI) for RSC Advances.

Environmentally Benign Diastereoselective Synthesis of Granatane and Tropane Aldol Derivatives

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Supporting information

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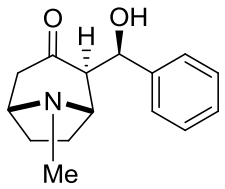
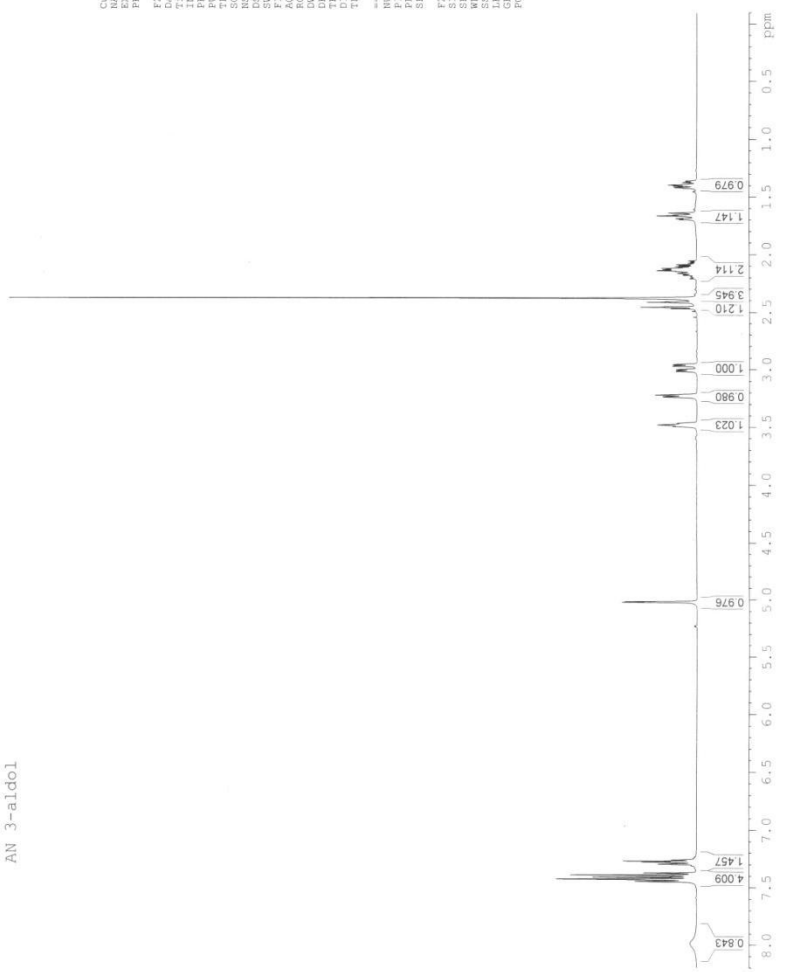
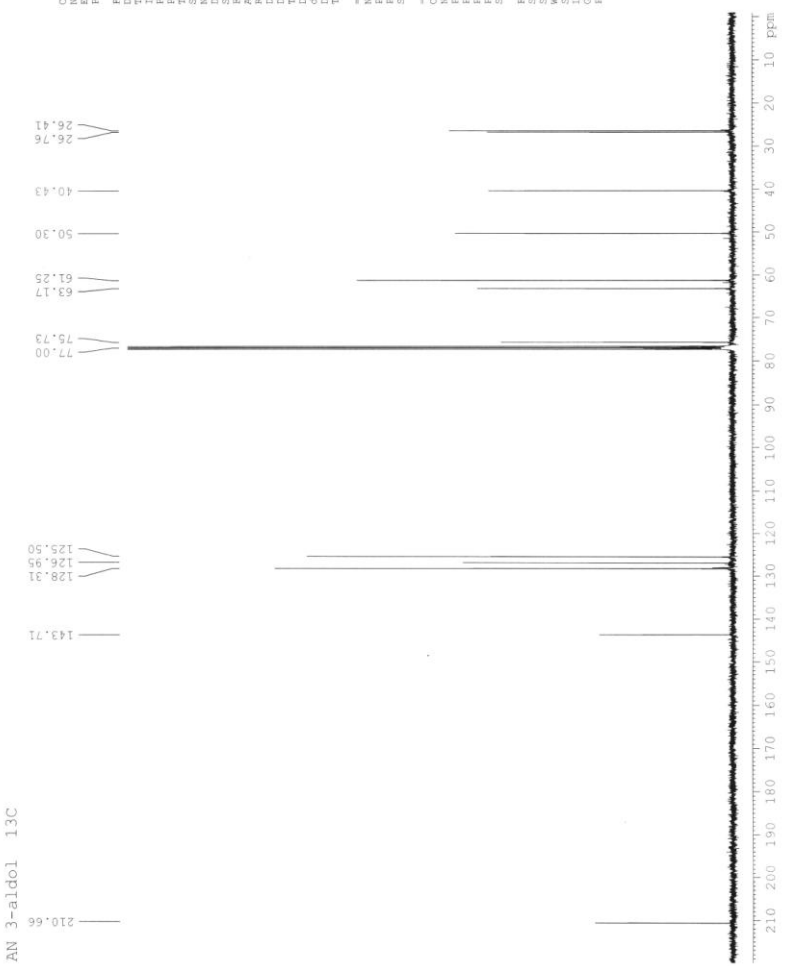
Granatanone (**5**, pseudopelletierine) was synthesized by an adapted literature procedure.[1] Acetonedicarboxylic acid (1.461 g, 10 mmol) was added to a cooled (0 °C) solution of methylamine hydrochloride (0.810 g, 12 mmol) and glutaraldehyde (25% solution; 3.8 mL, 10 mmol) in water (10 mL). The mixture was adjusted to pH = 4 with 10% aqueous AcONa and stirred overnight at rt. Then the mixture was acidified to pH = 2 with 10% aqueous HCl and washed with diethyl ether (2 × 10 mL – wash discarded). The aqueous layer was basified with saturated $NaHCO_3$ to pH = 8 and extracted with DCM (5 × 10 mL). The combined extracts were dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude product was sublimed (Kugelrohr, 80 °C, 1.1 Torr) to give granatanone (1.241 g, 81%) as a white solid. **^{1}H-NMR**: 3.35-3.28 (m, 2H), 2.75 (dd, *J* = 16.7 Hz, 6.6 Hz, 2H), 2.62 (s, 3H), 2.24 (d, *J* = 16.8 Hz, 2H), 2.02-1.89 (m, 2H), 1.58-1.47 (m, 4H); **^{13}C-NMR**: 210.5, 55.5, 41.7, 41.0, 29.4, 15.8.

exo,syn-2-(hydroxy(phenyl)methyl)-8-methyl-8-azabicyclo[3.2.1]octan-3-one (*exo,syn*-3a)







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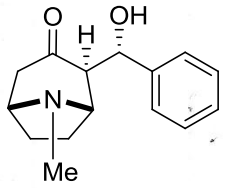

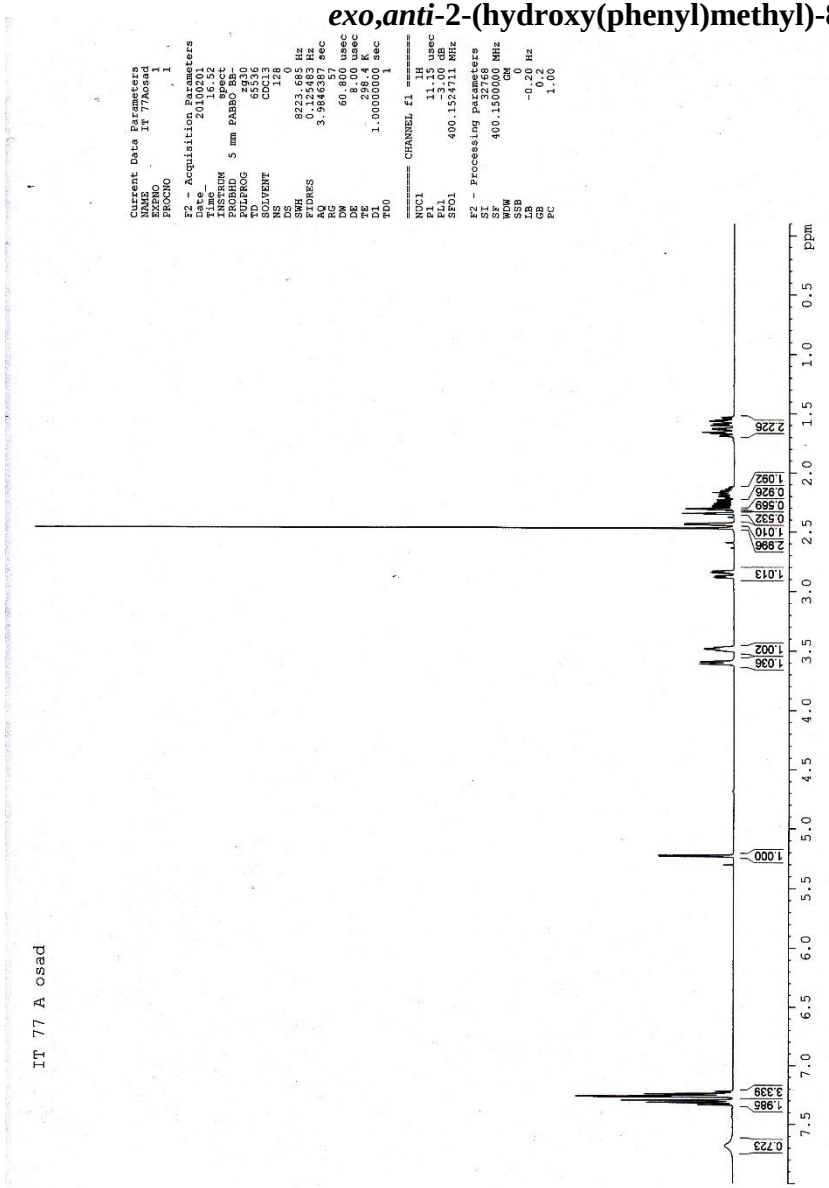

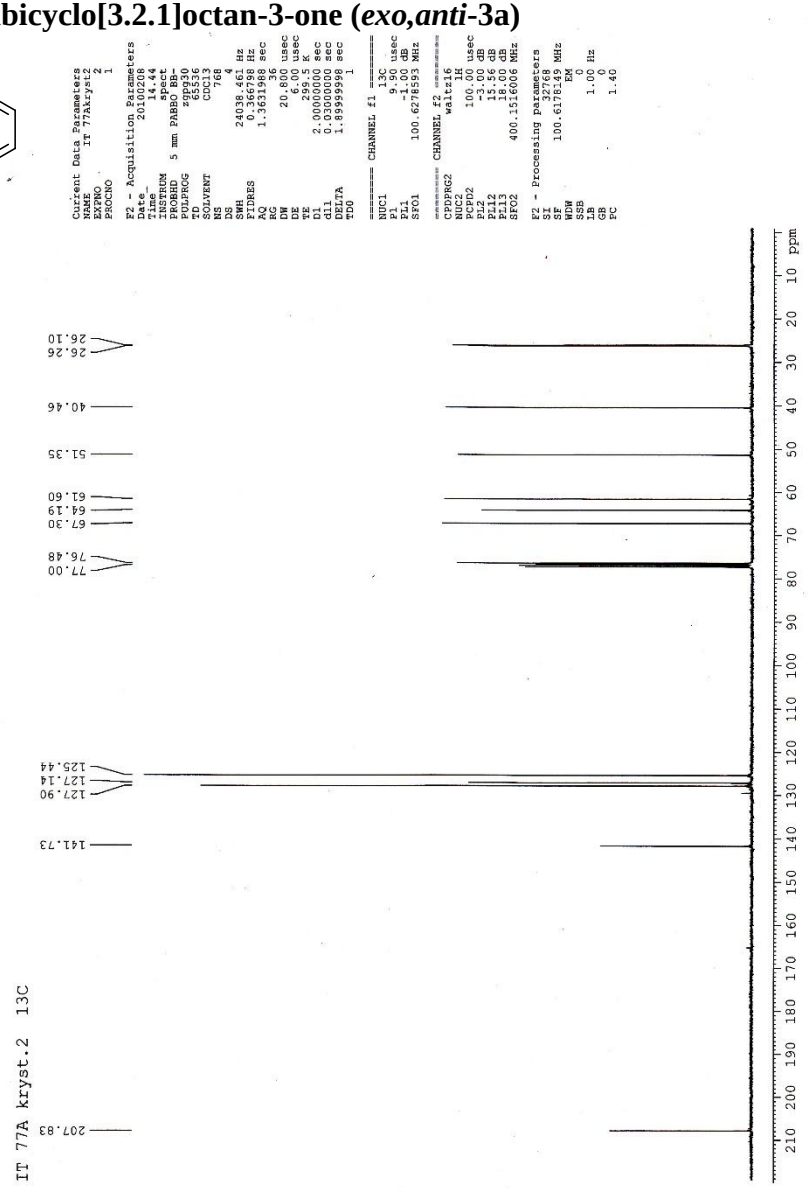

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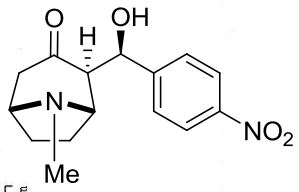

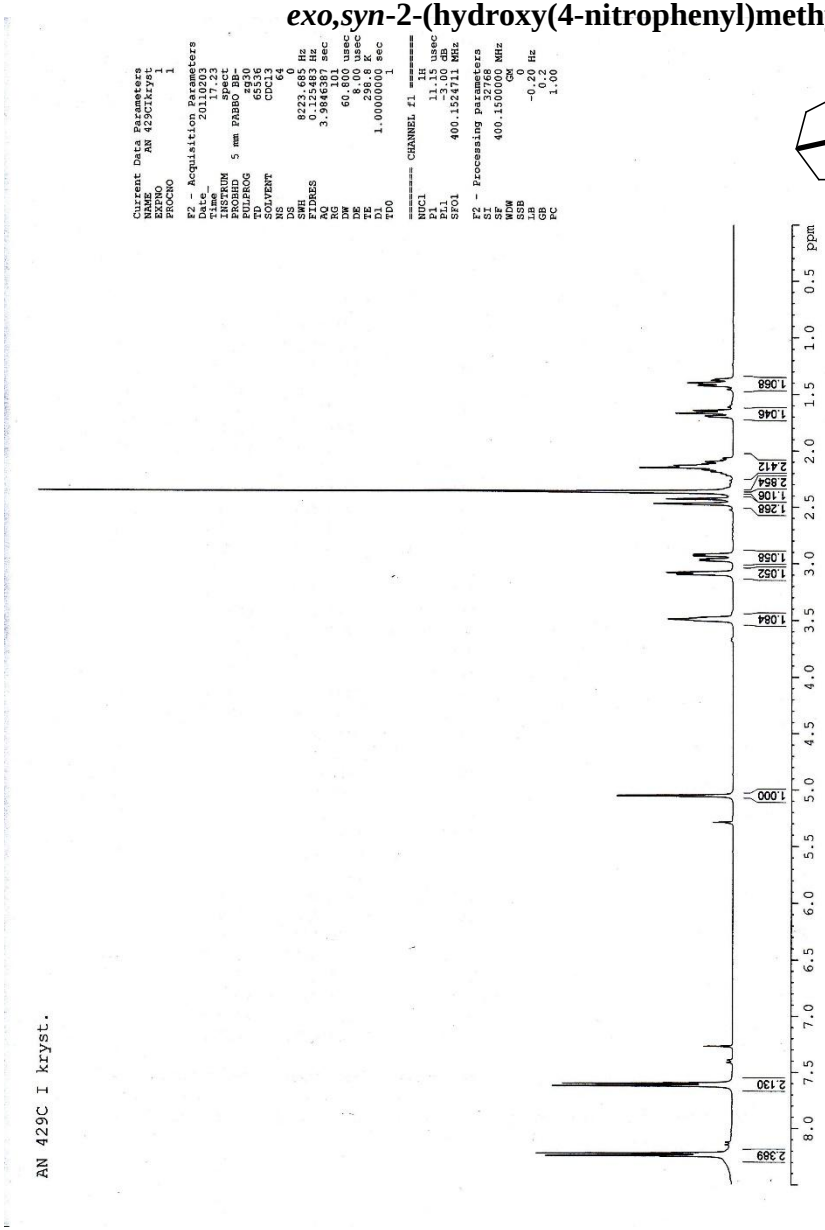

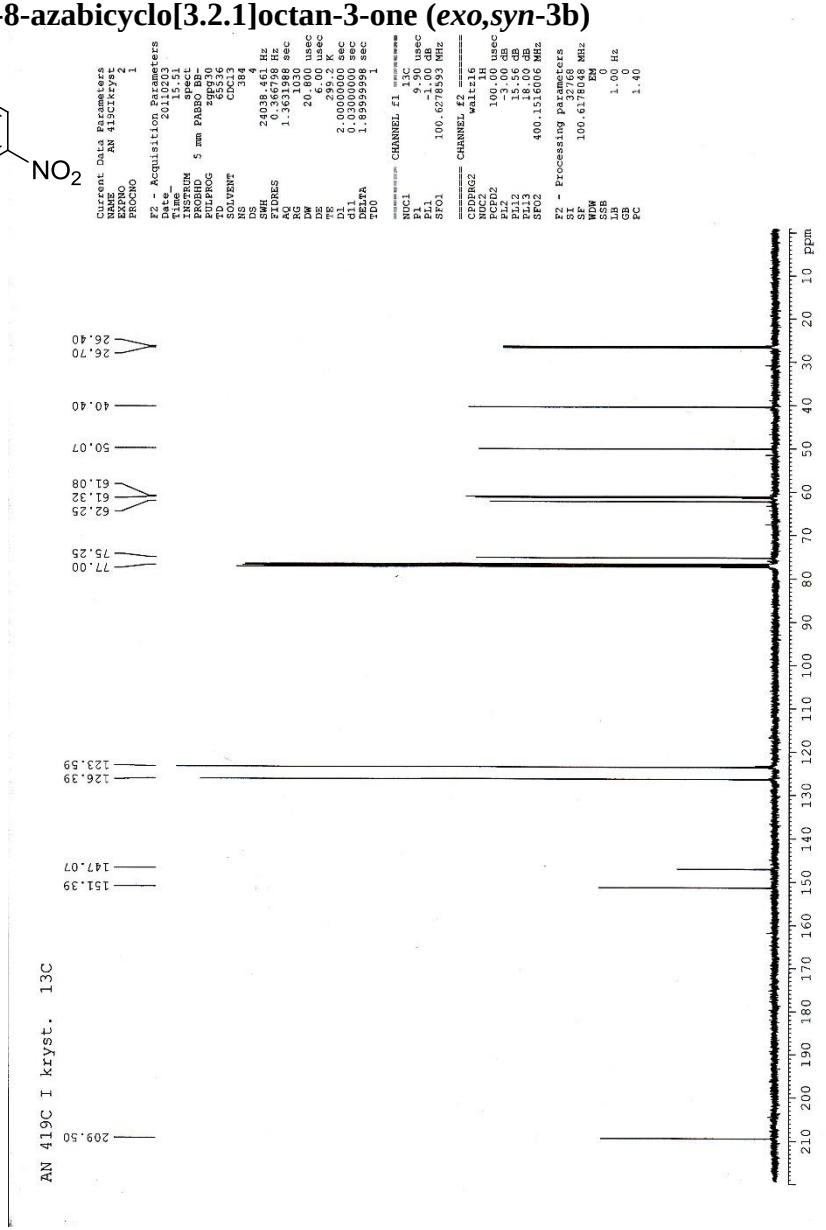

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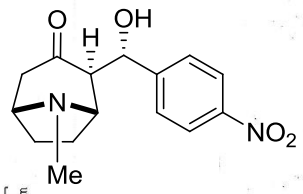

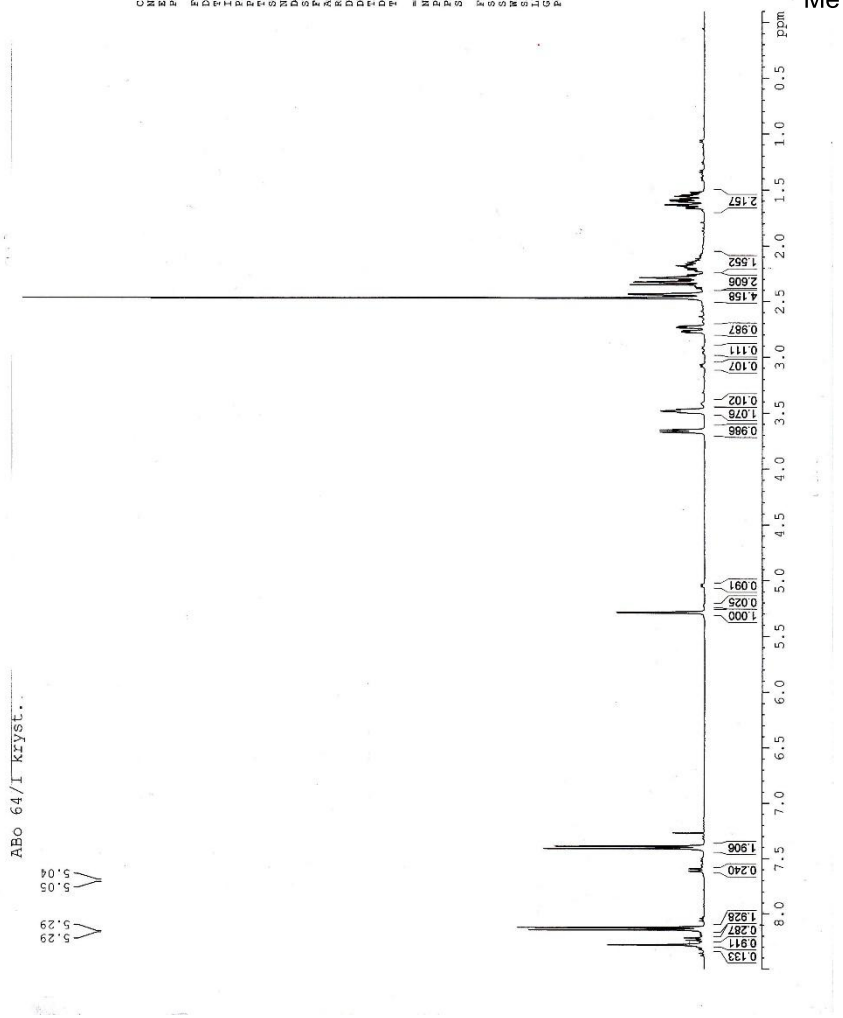

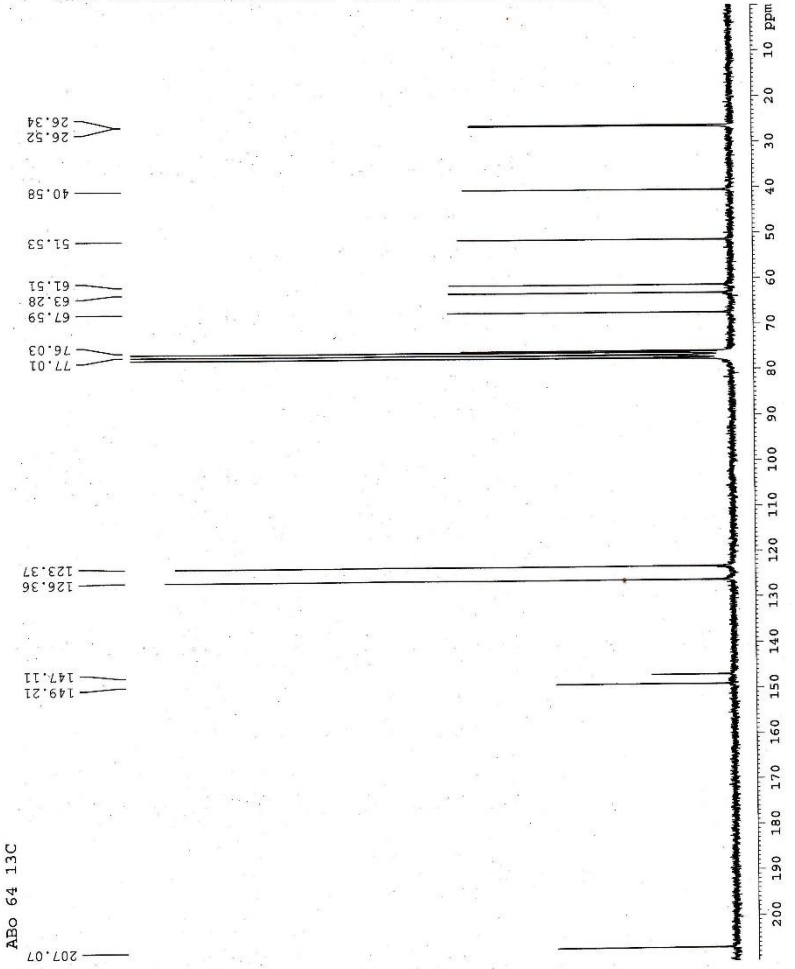

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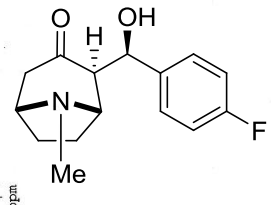

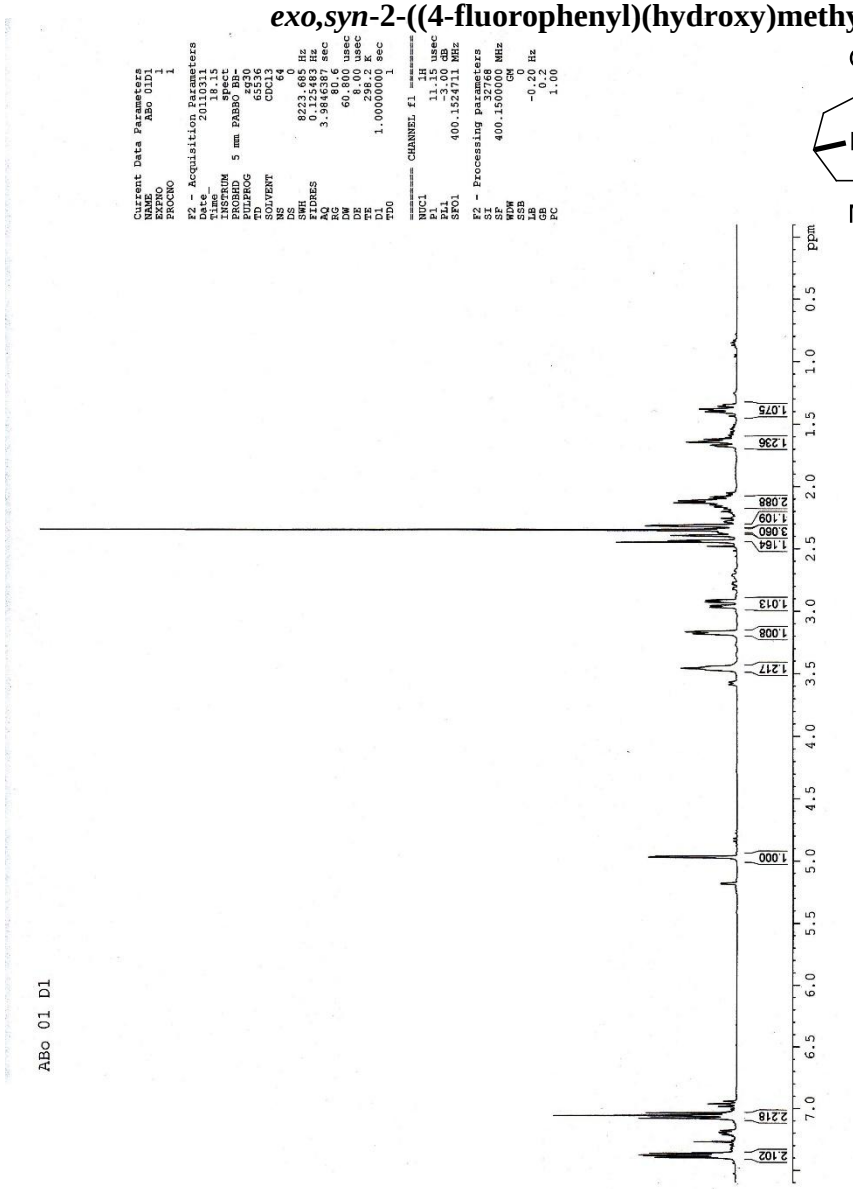

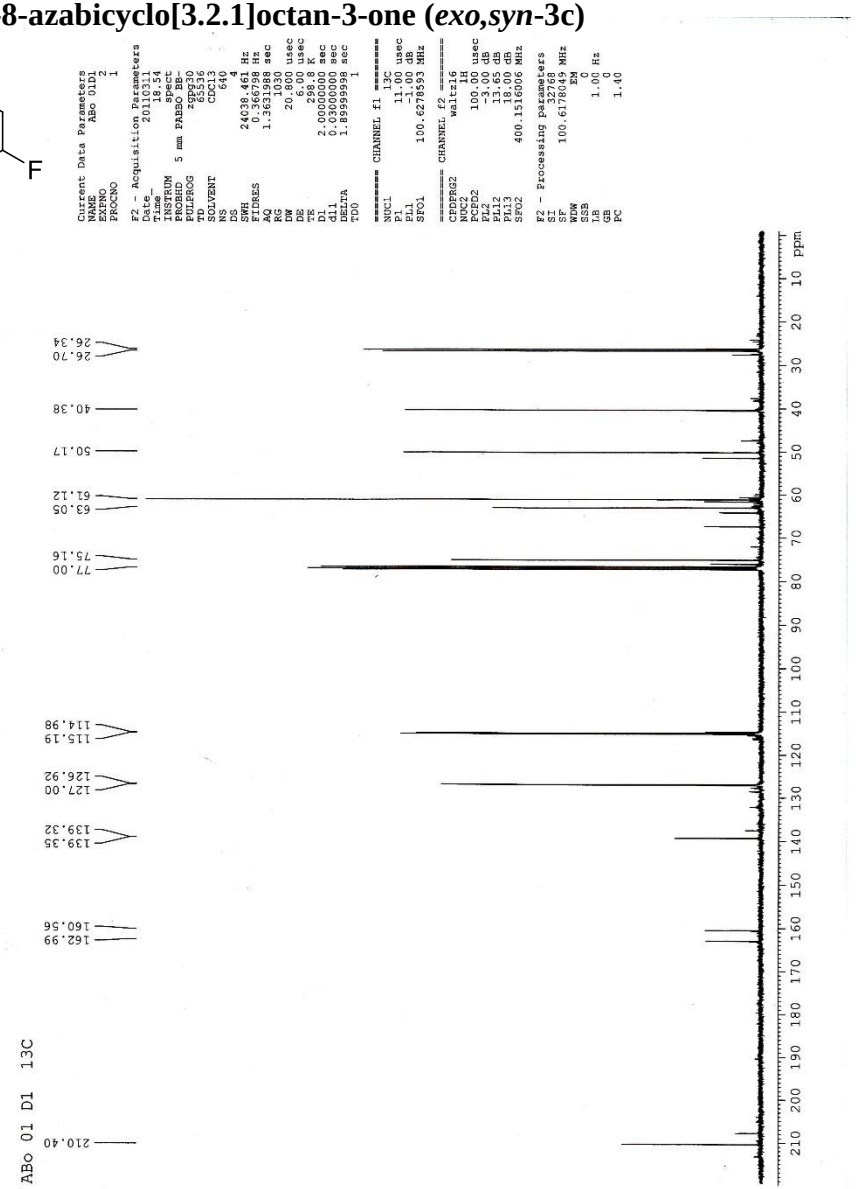

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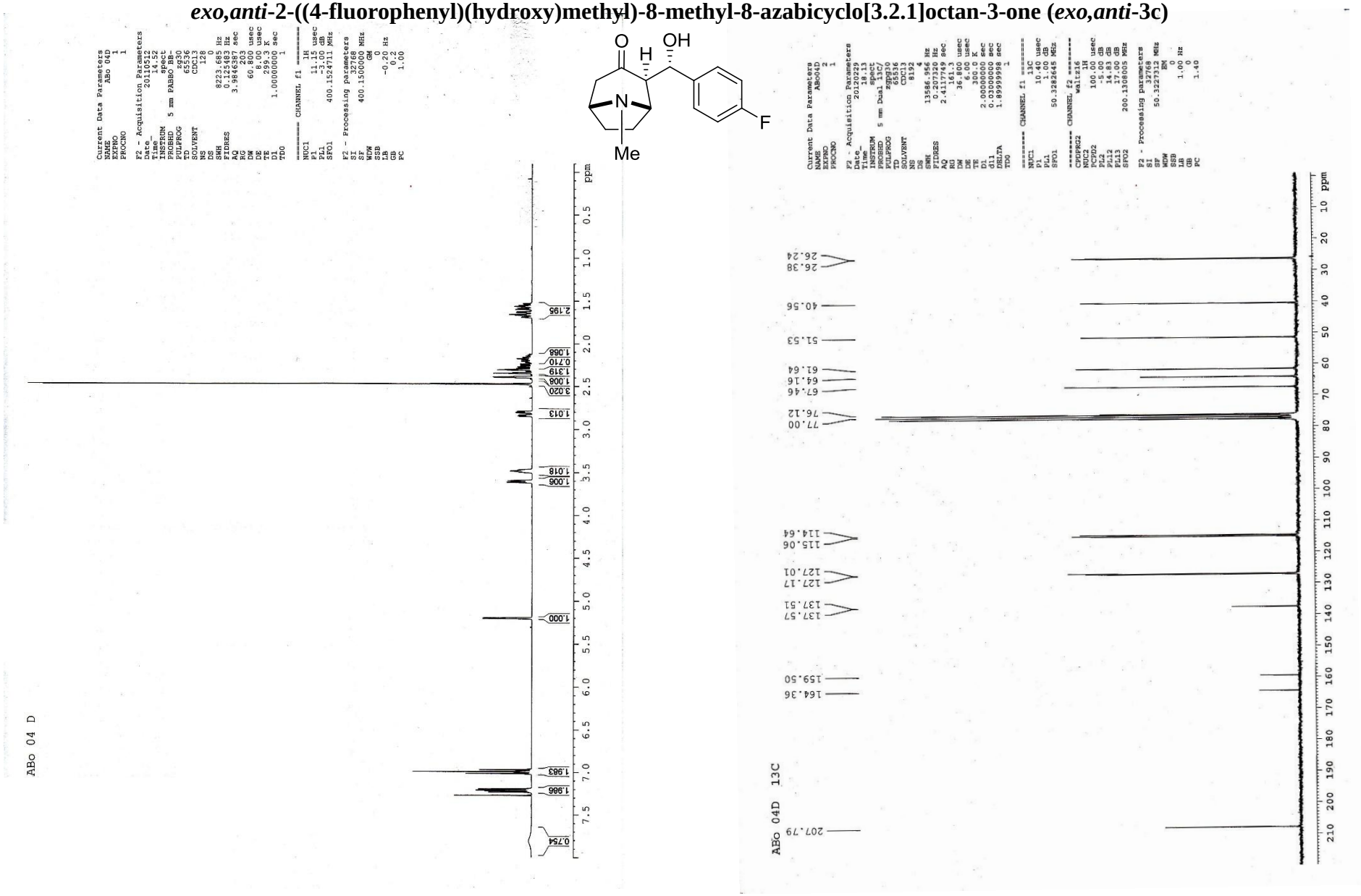

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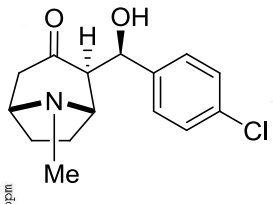

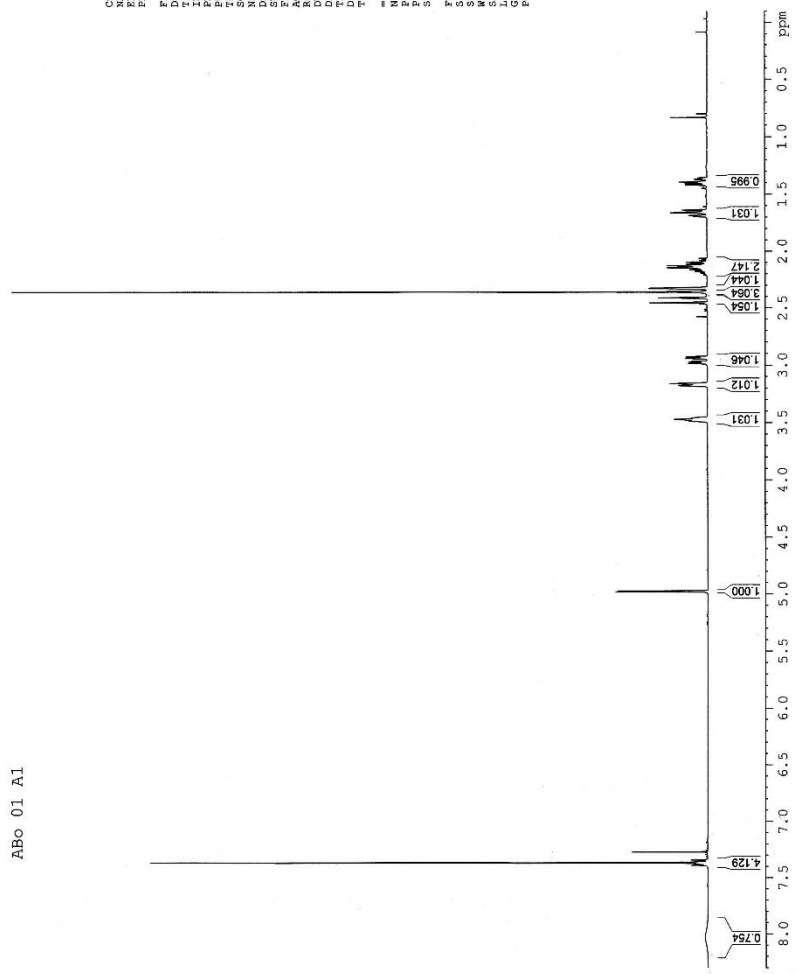

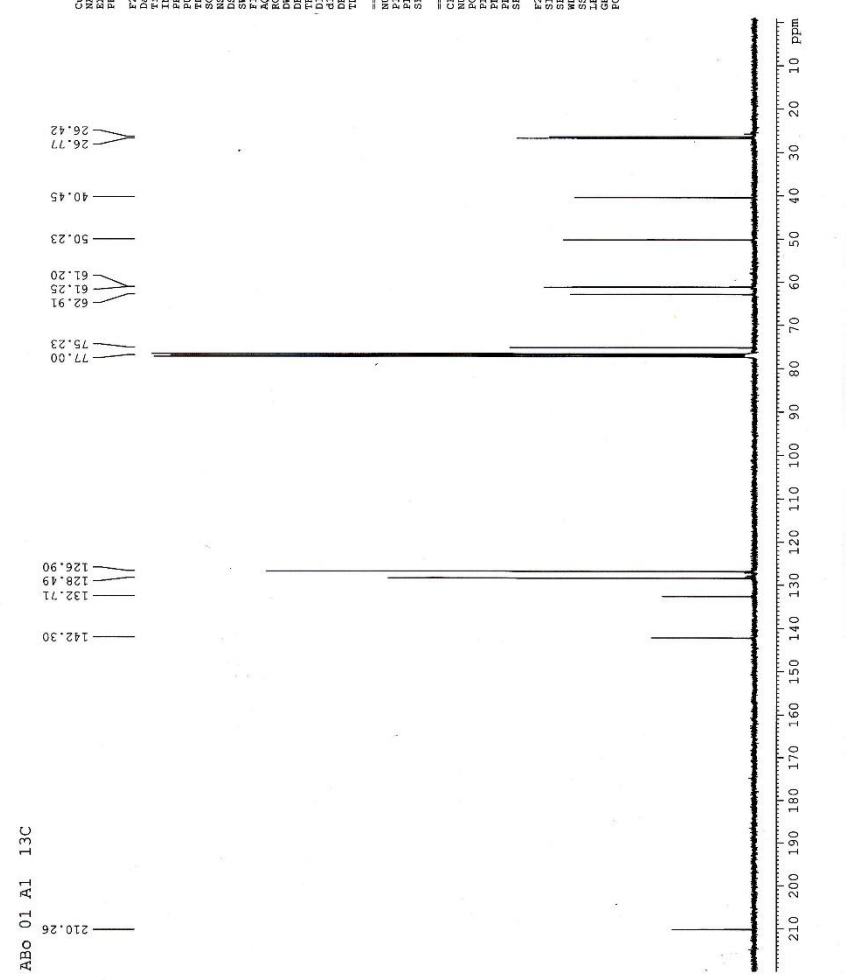

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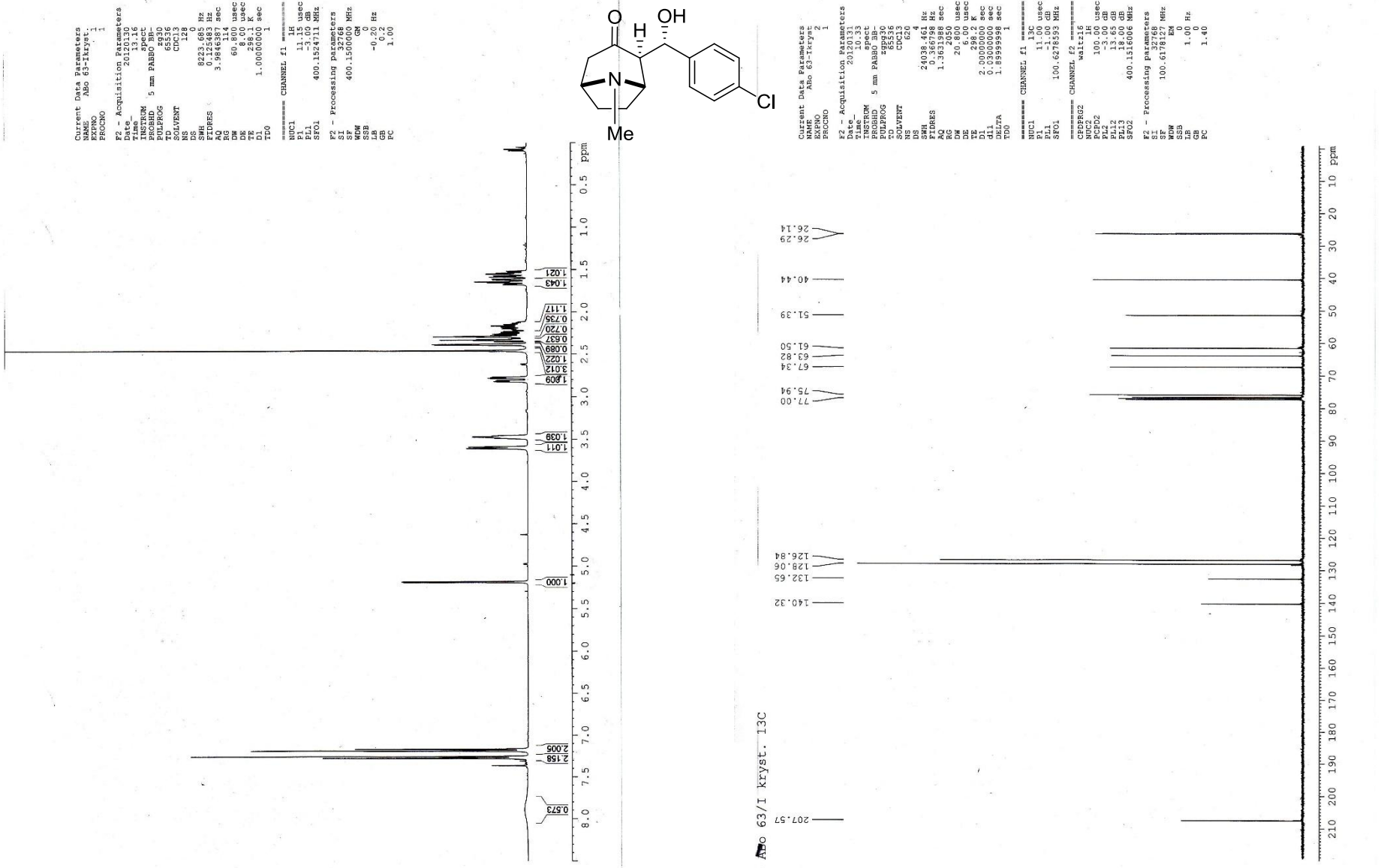

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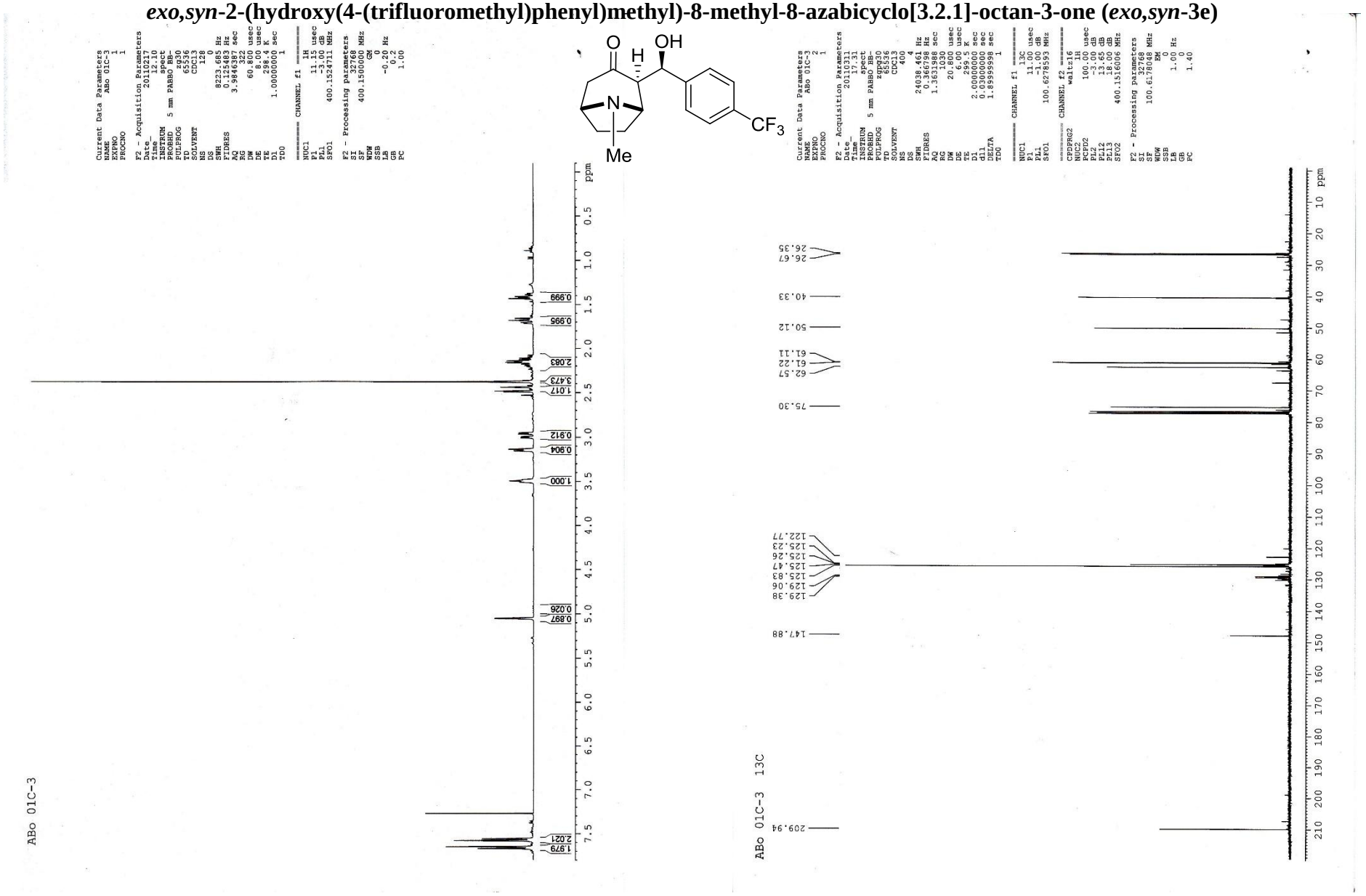

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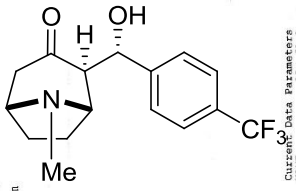

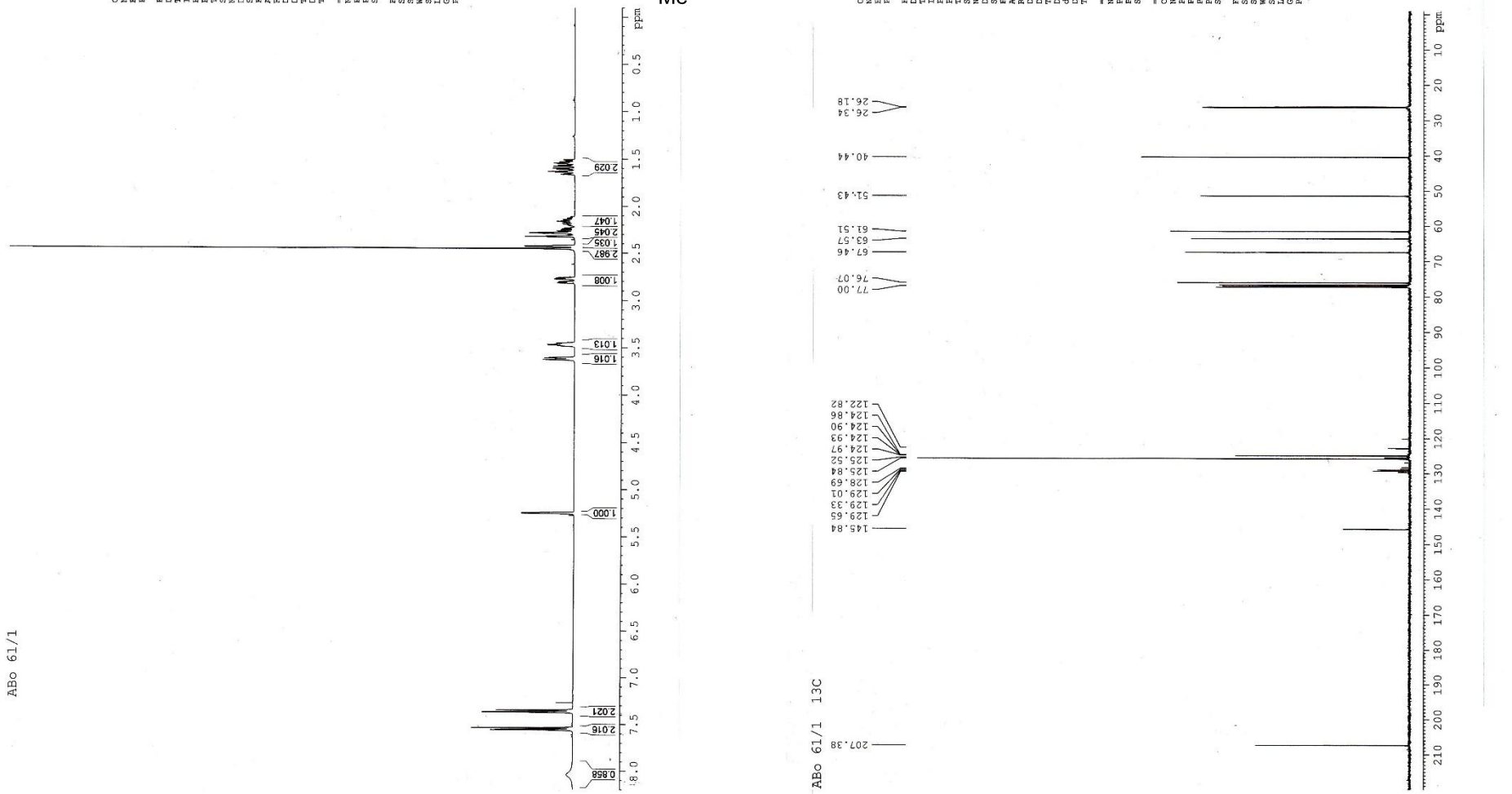

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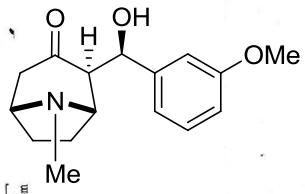

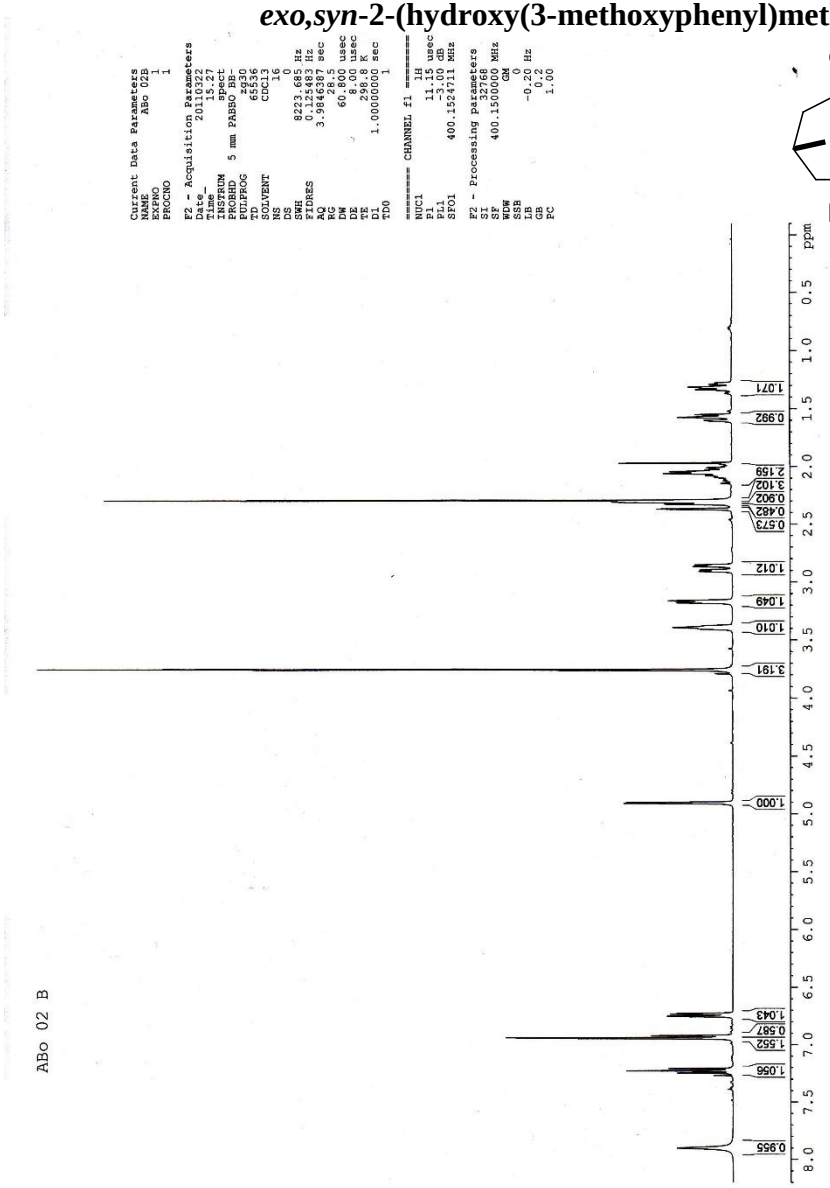

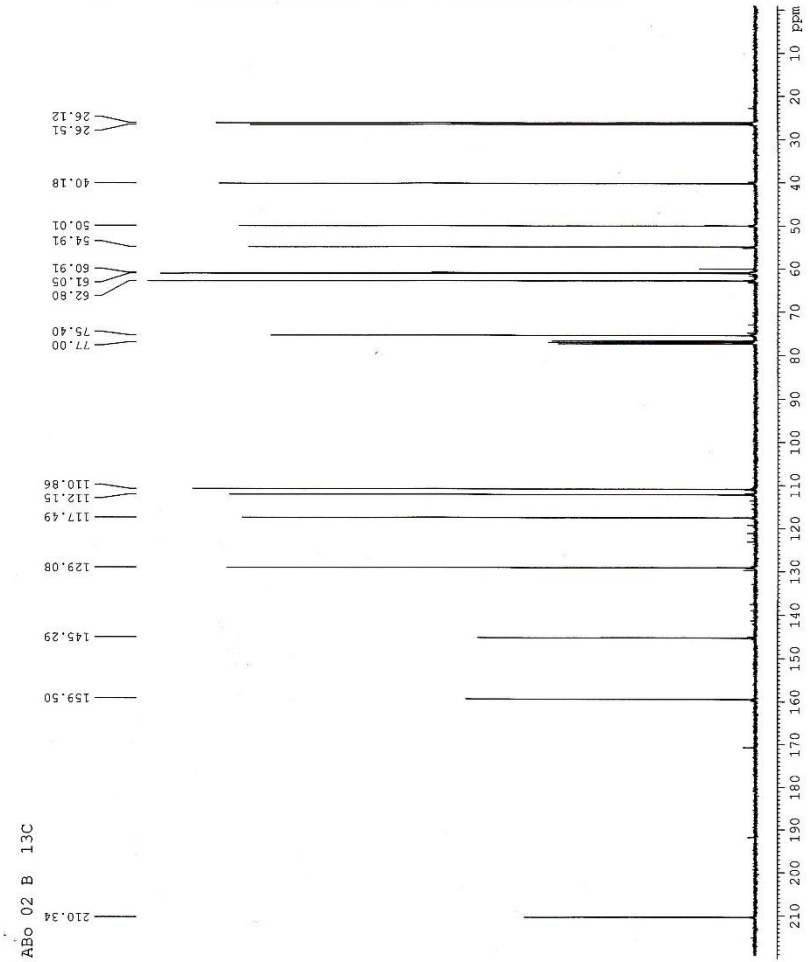

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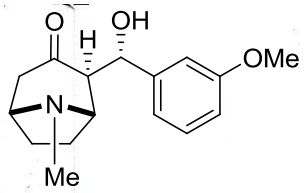

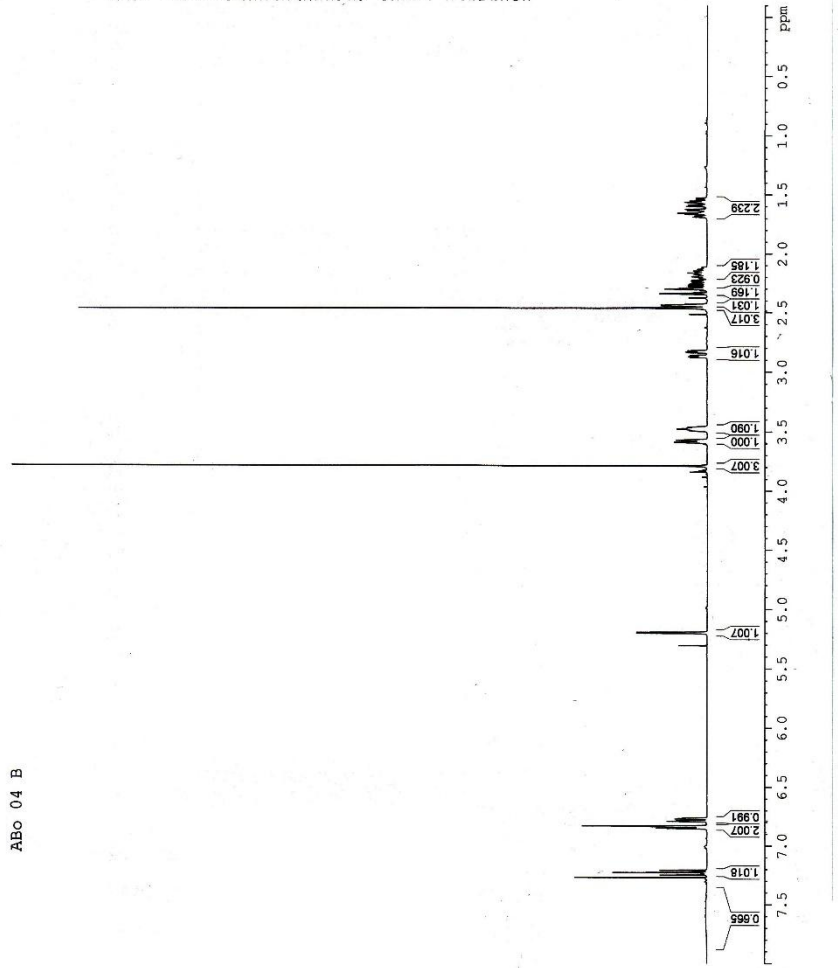

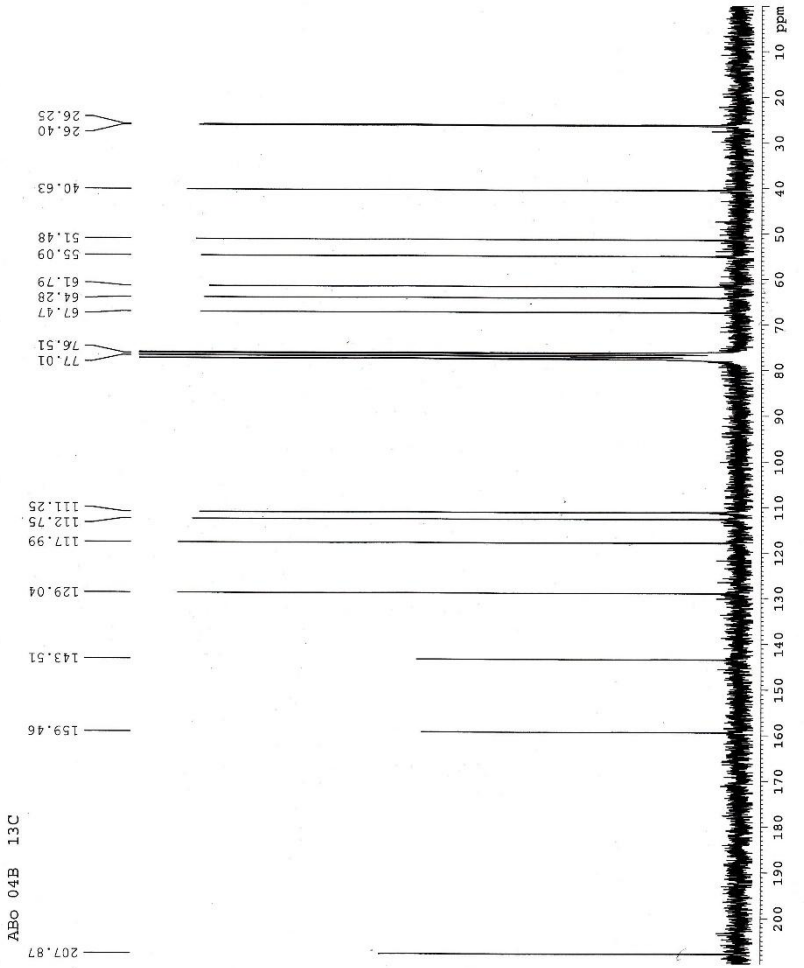

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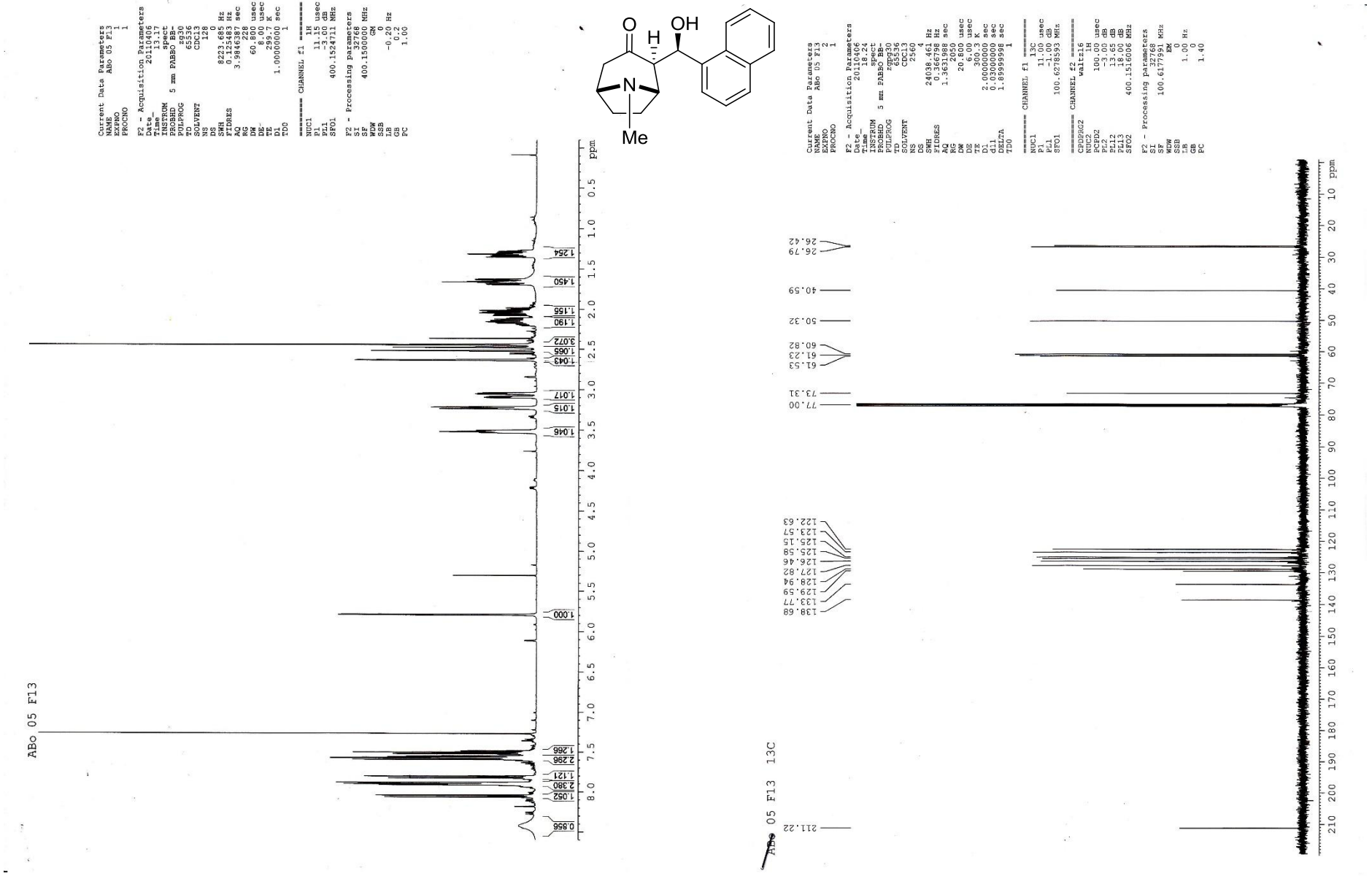

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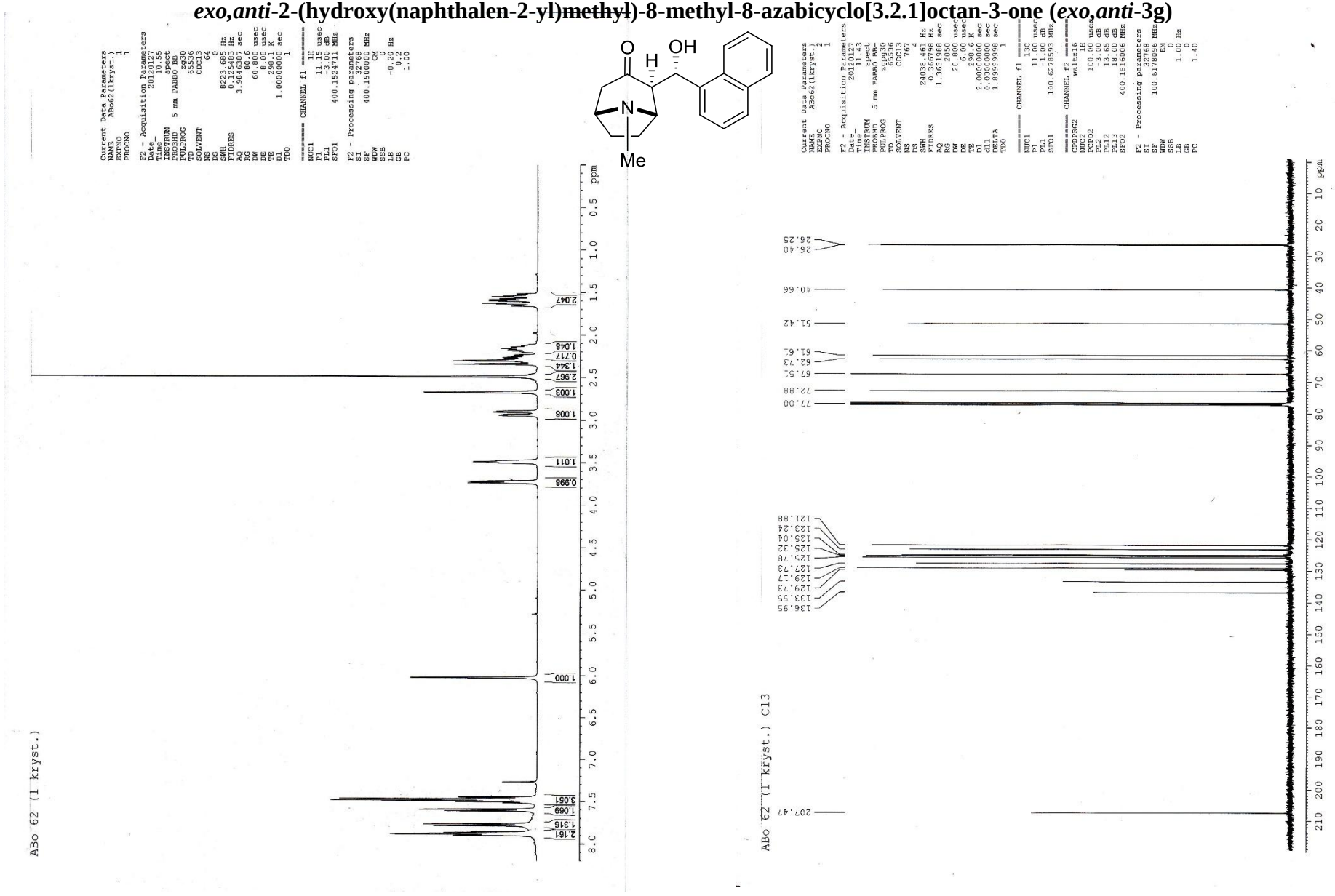

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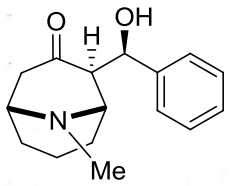

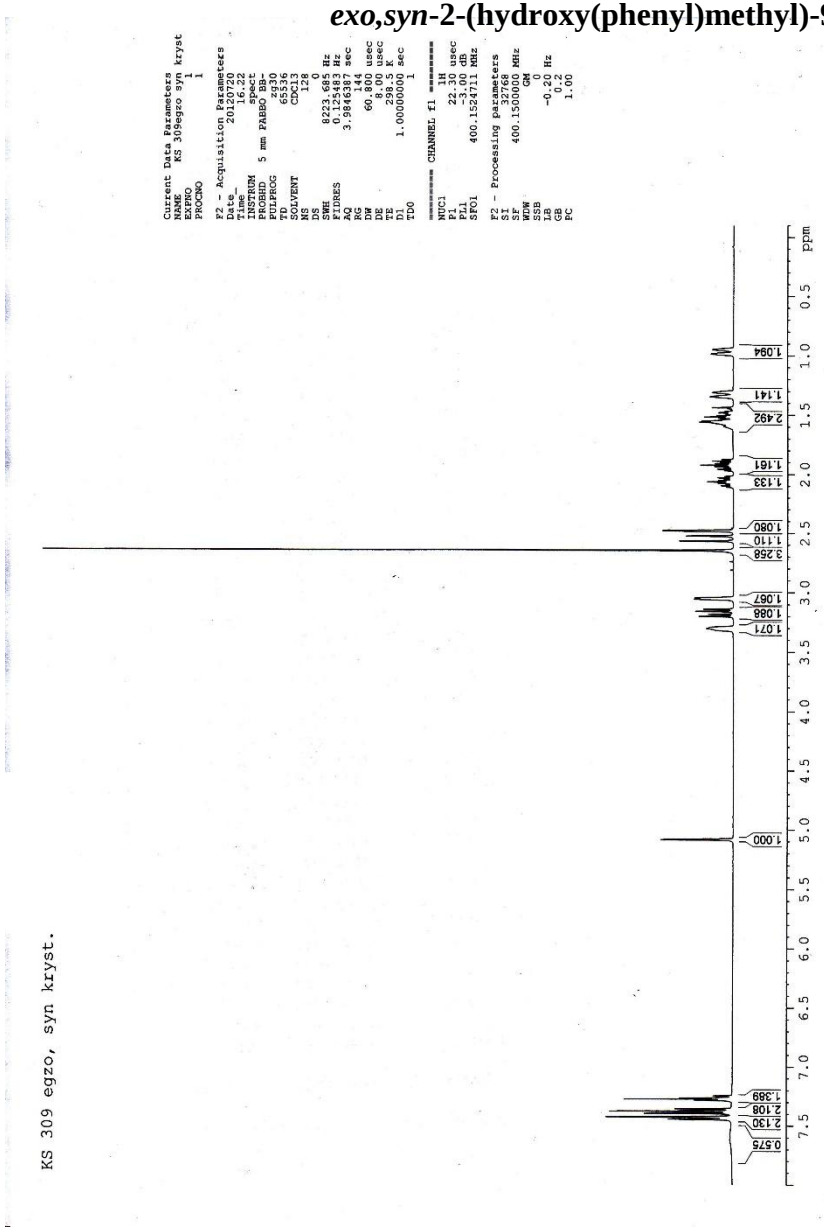

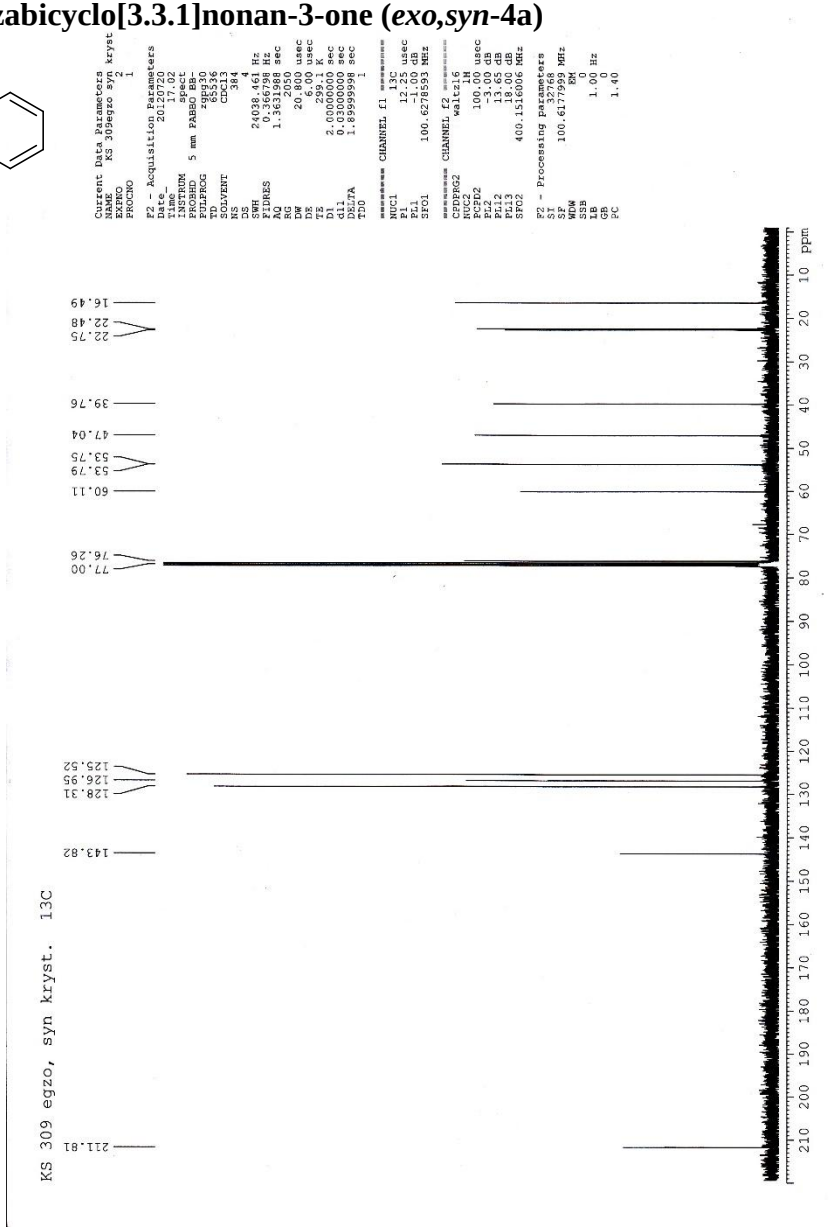

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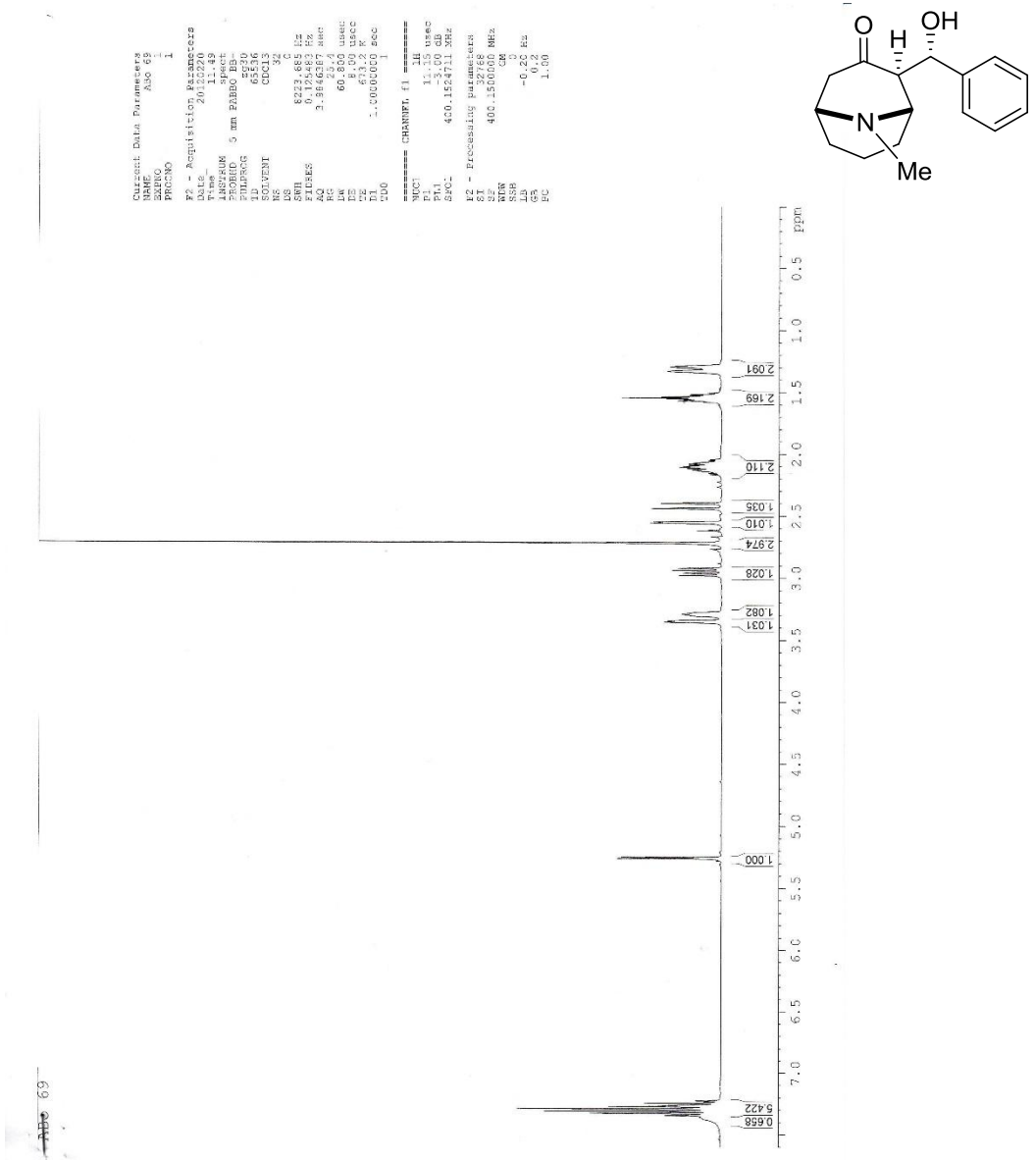

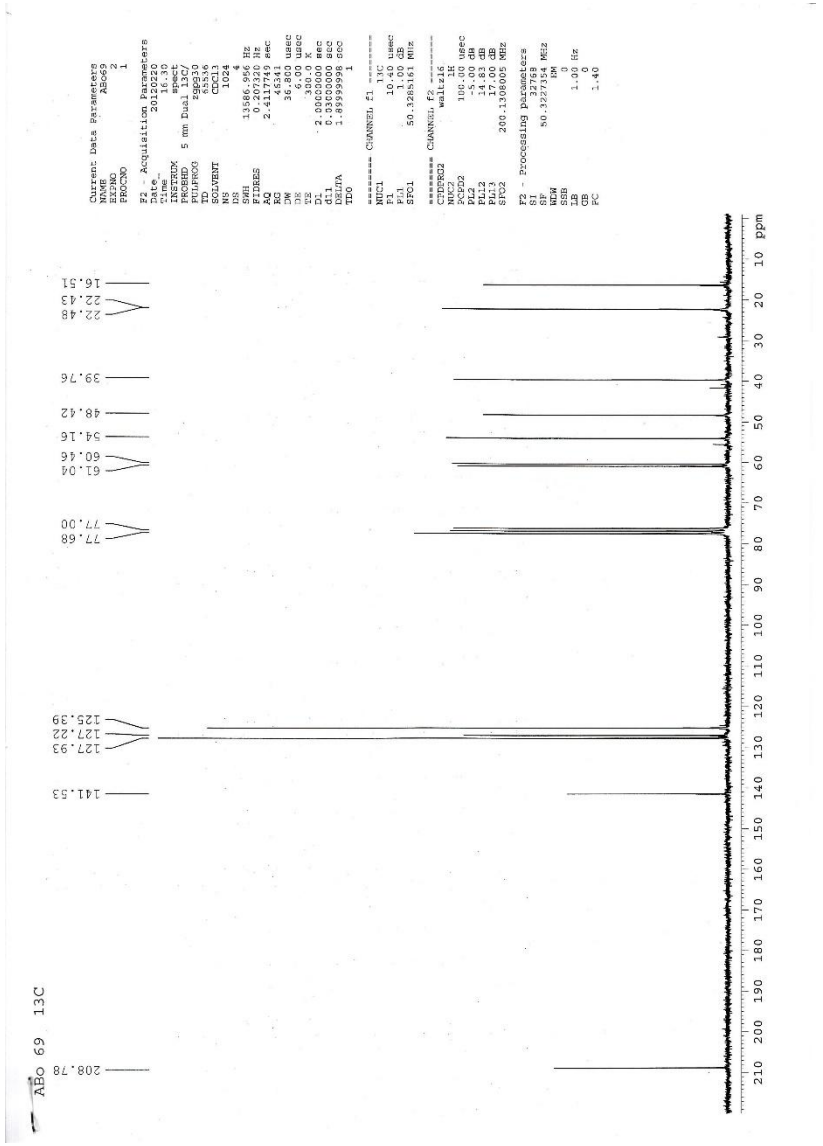

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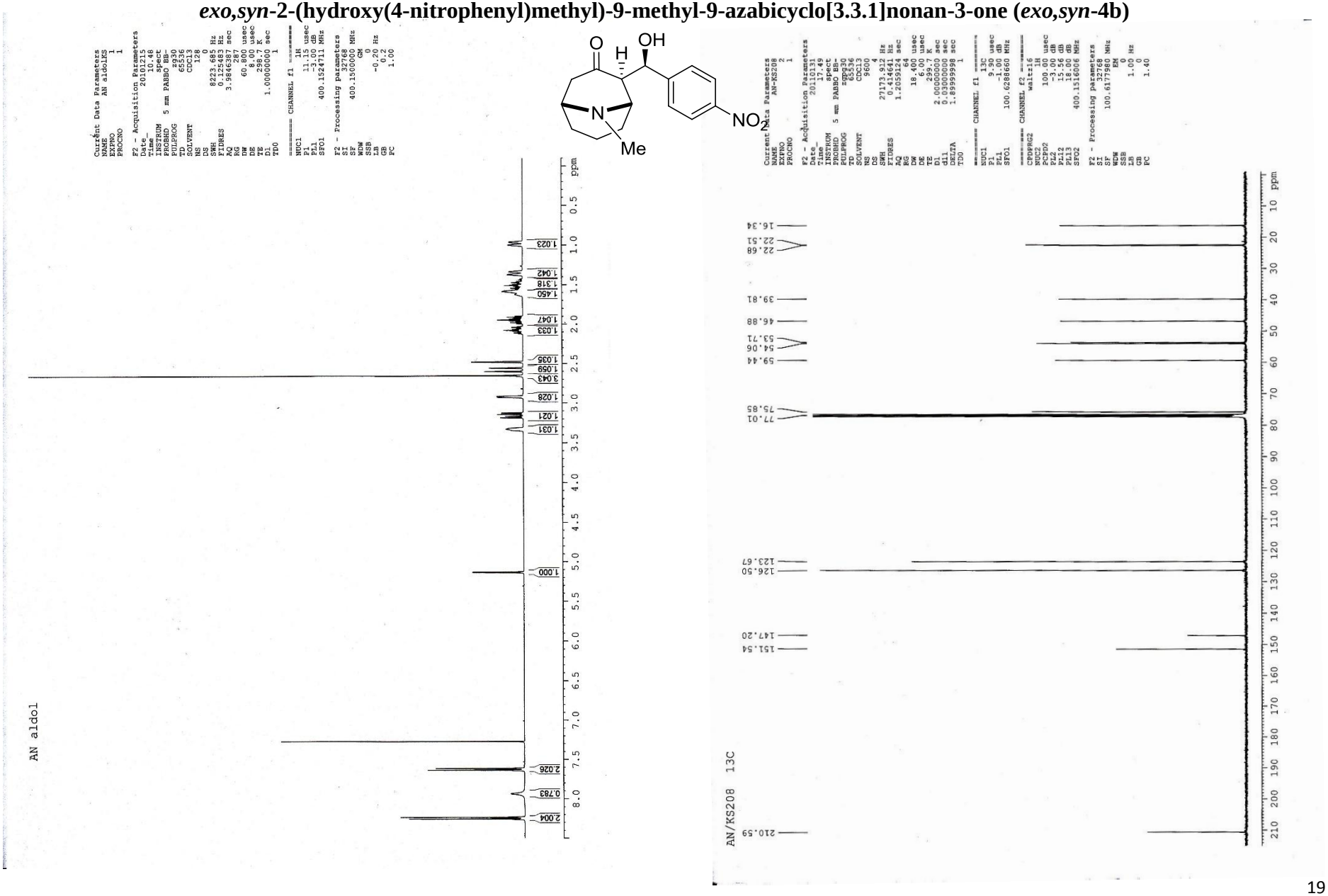

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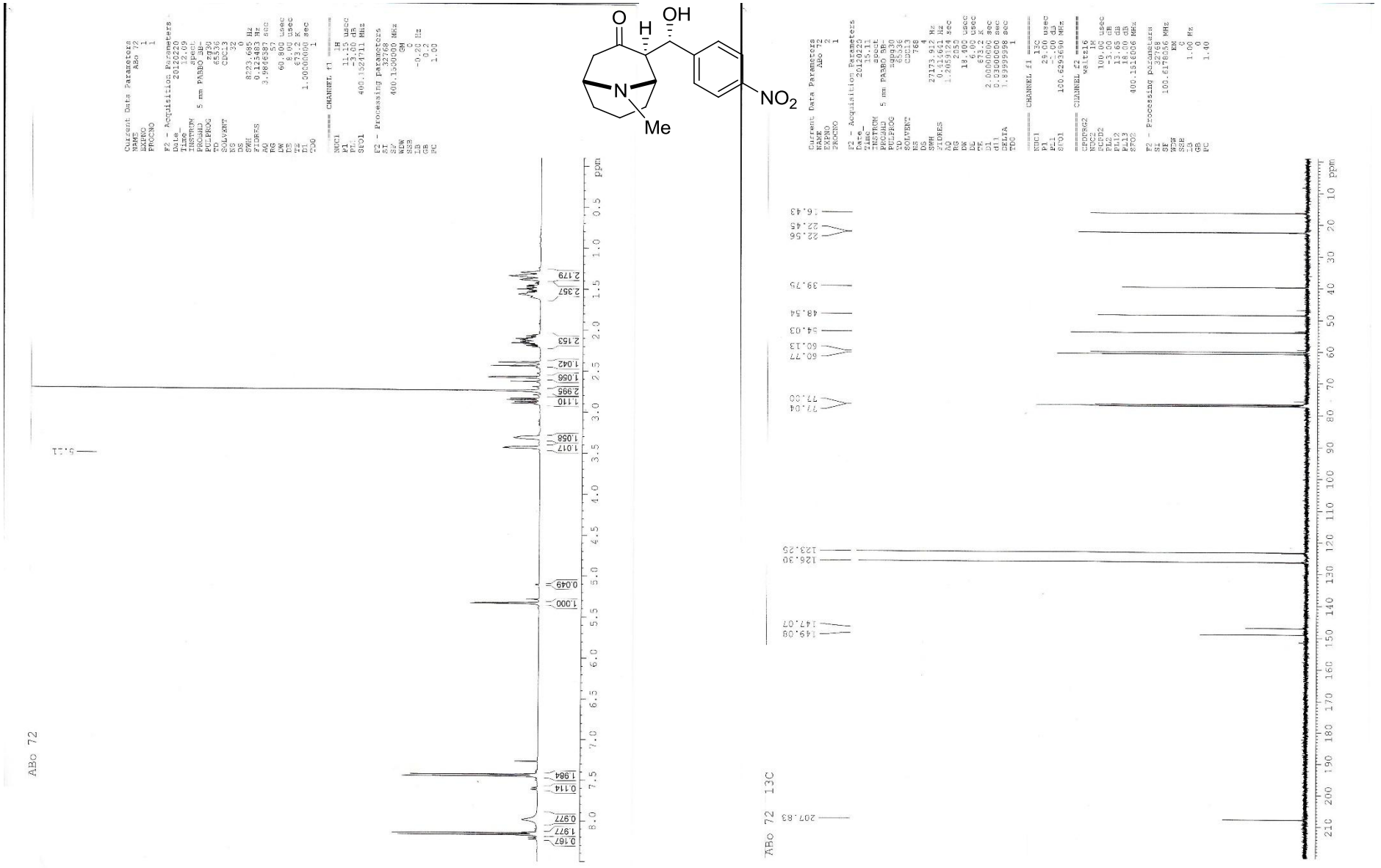

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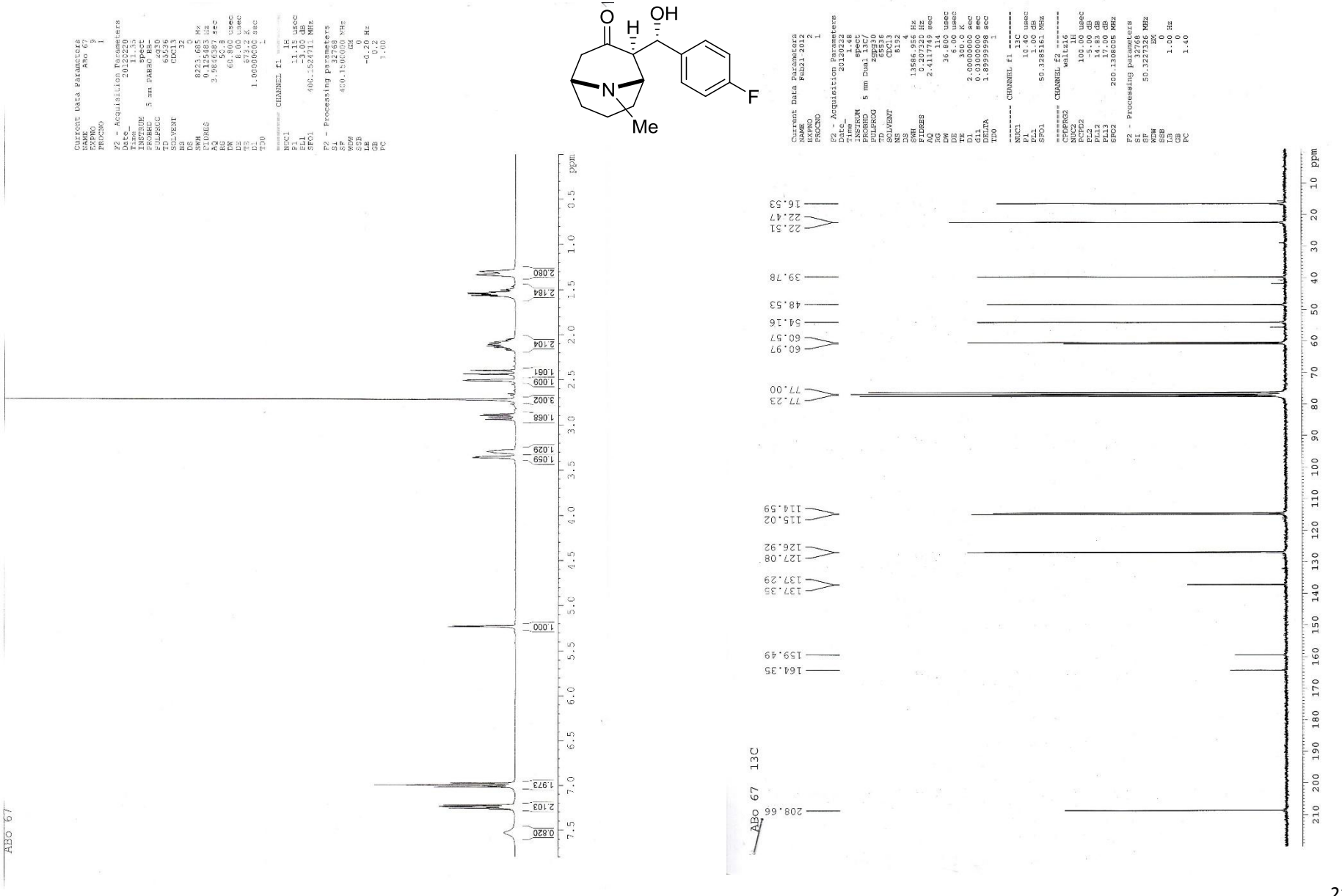

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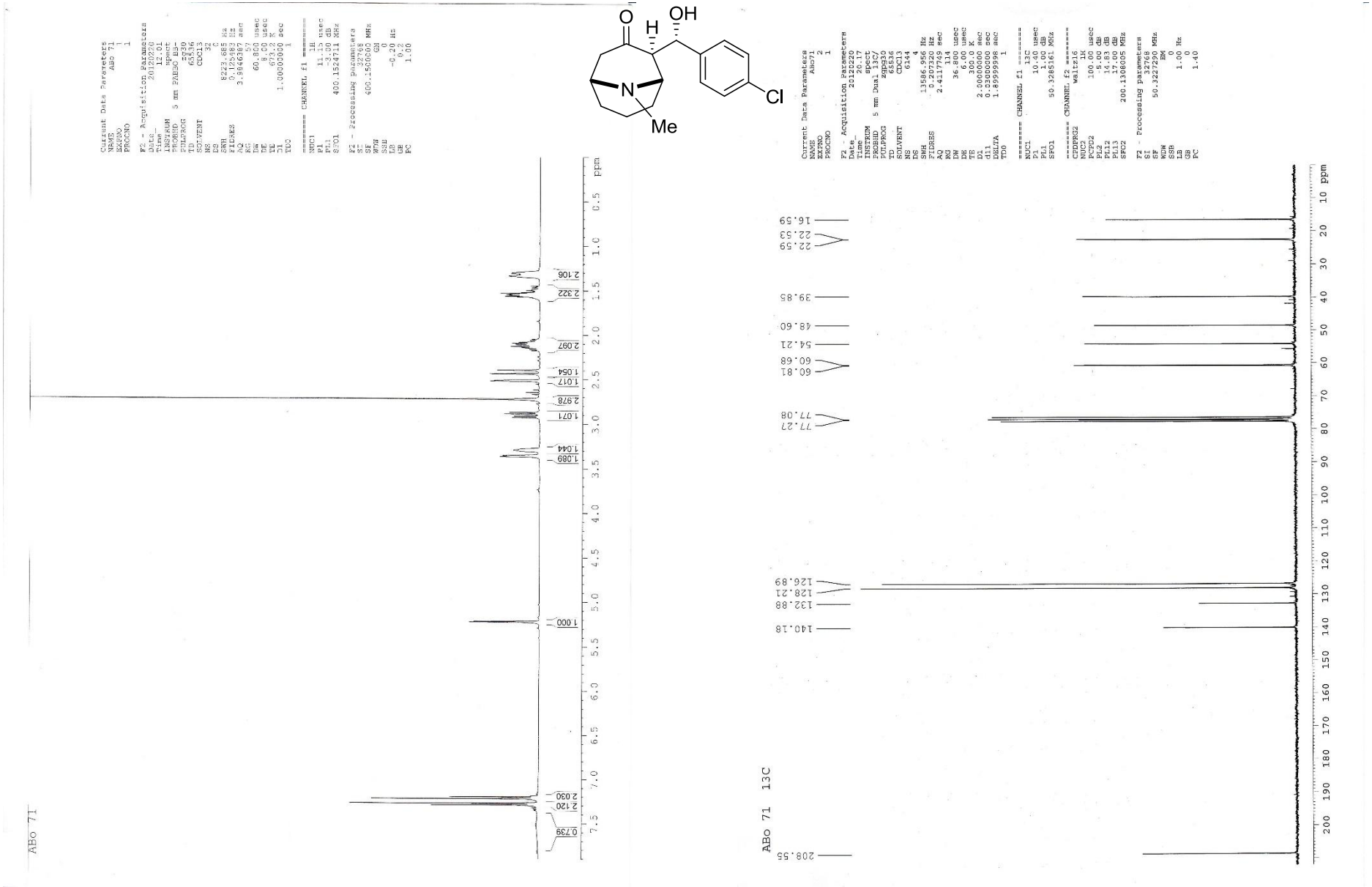

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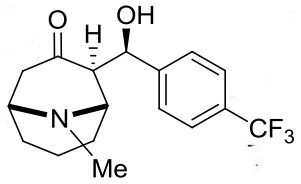

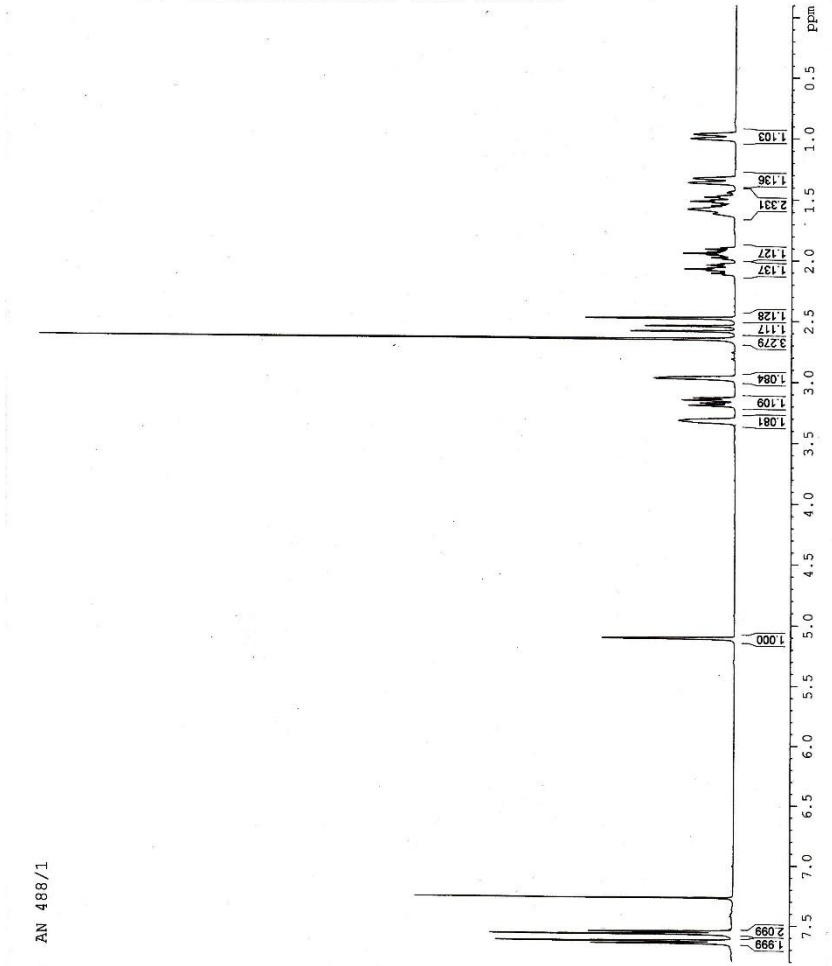

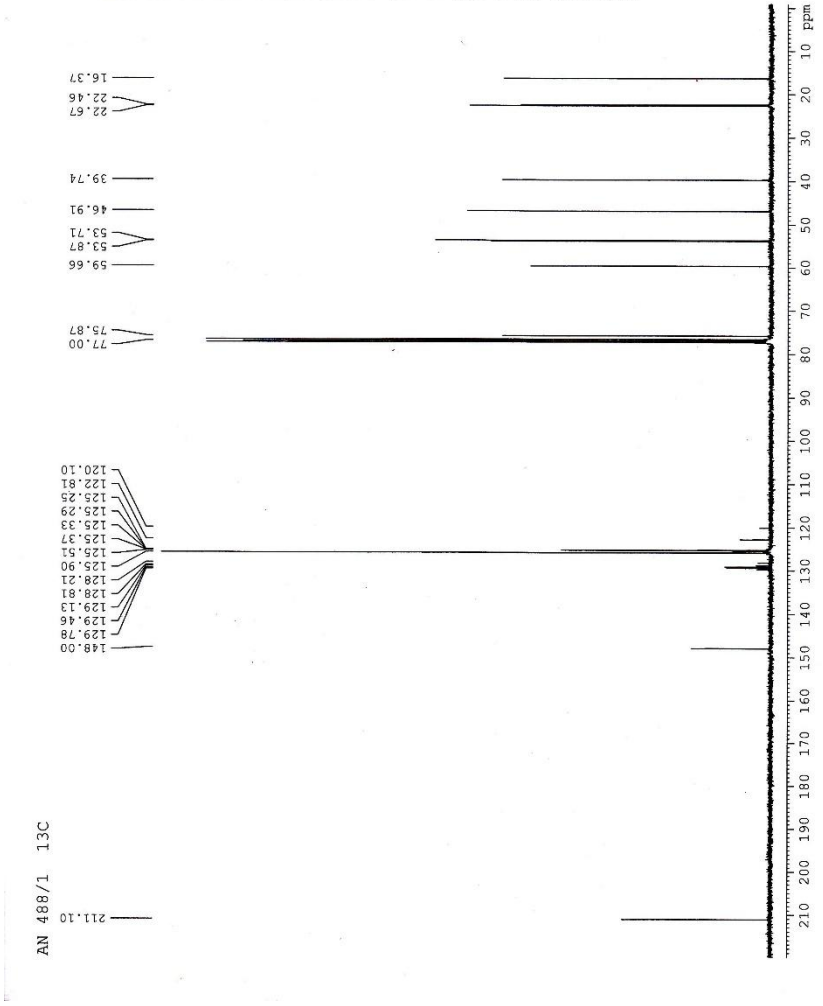

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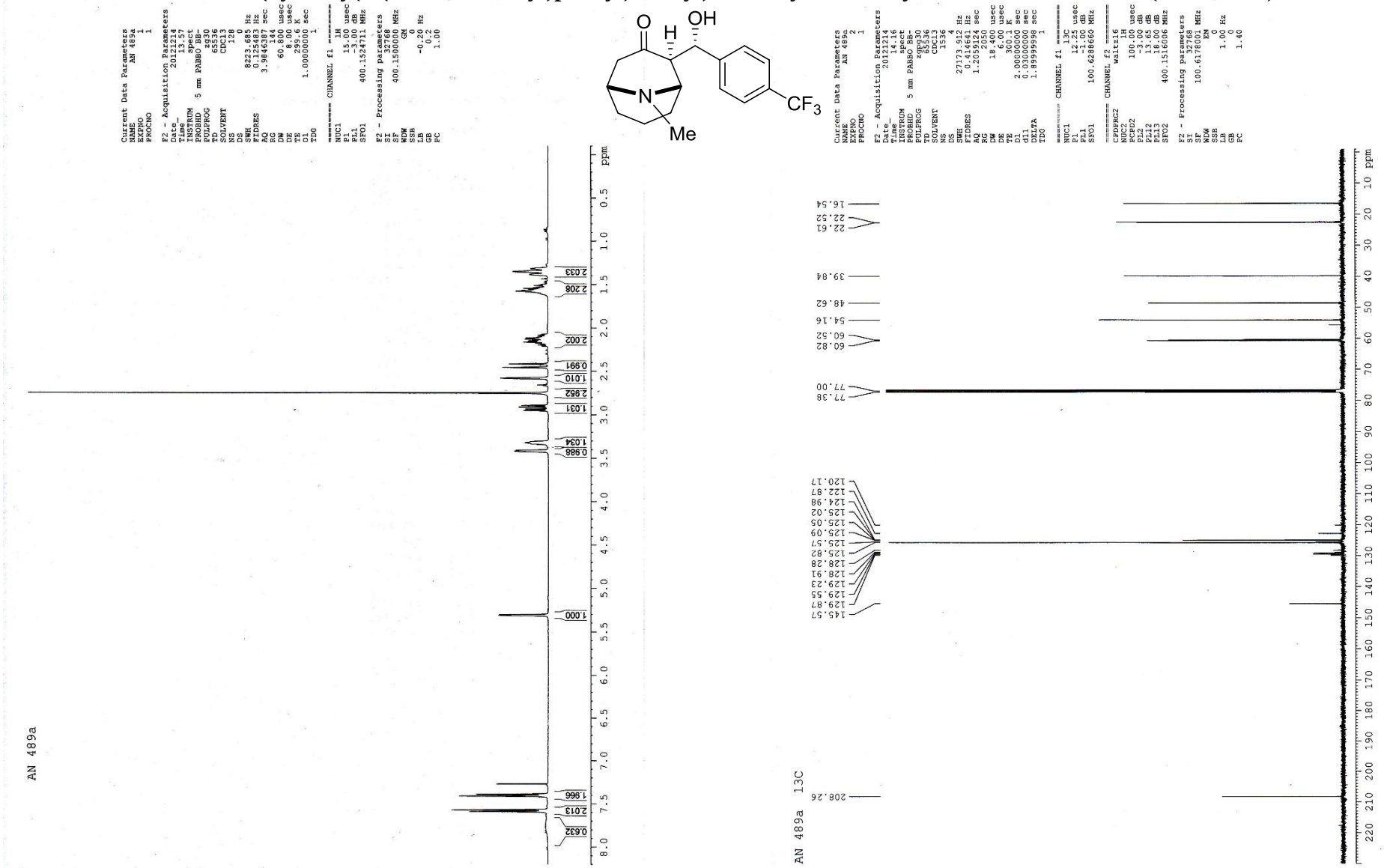

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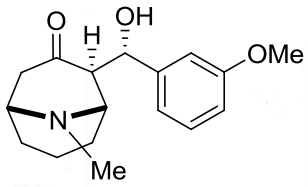

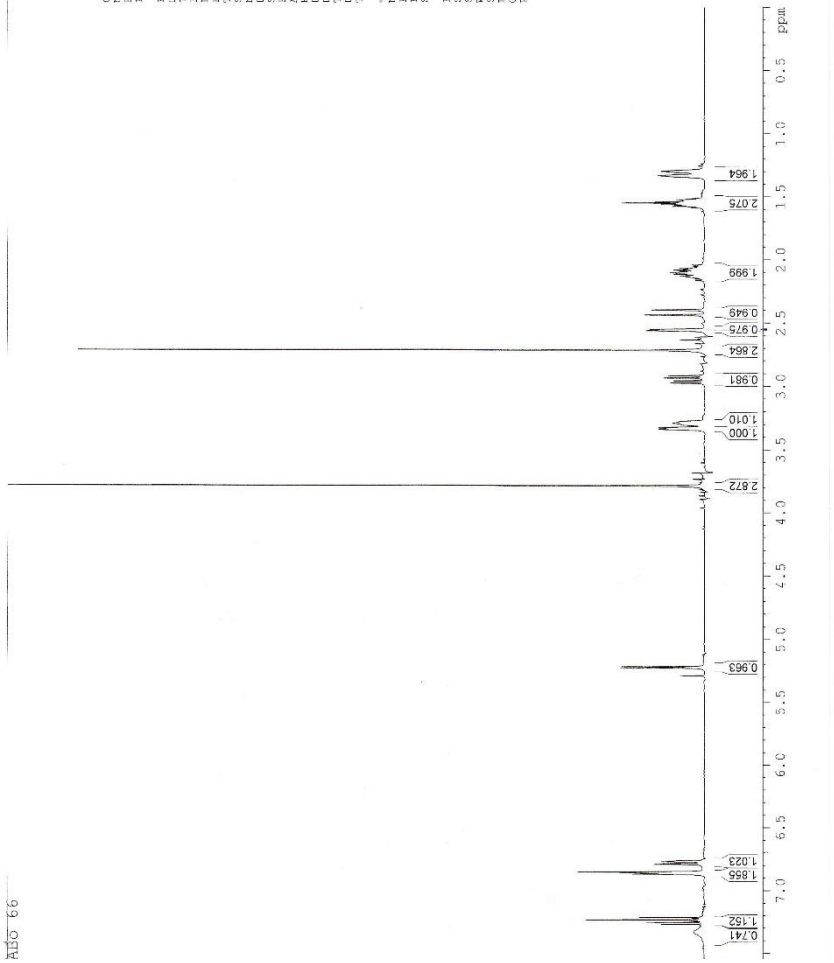

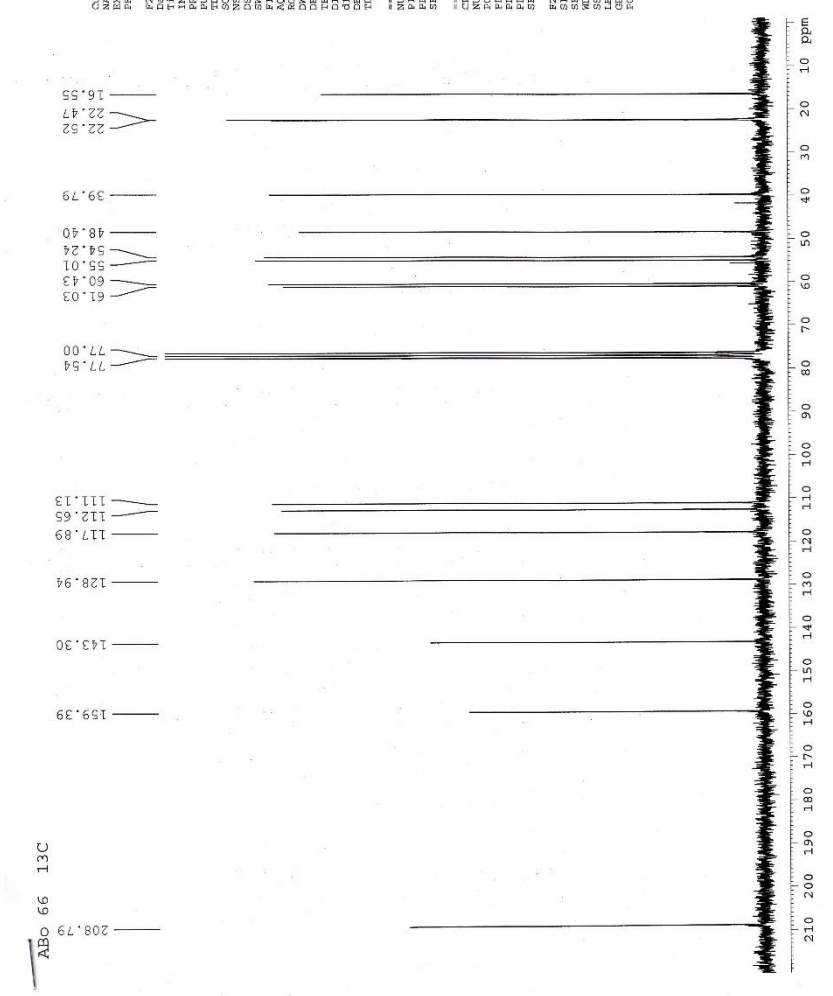

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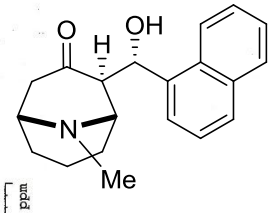
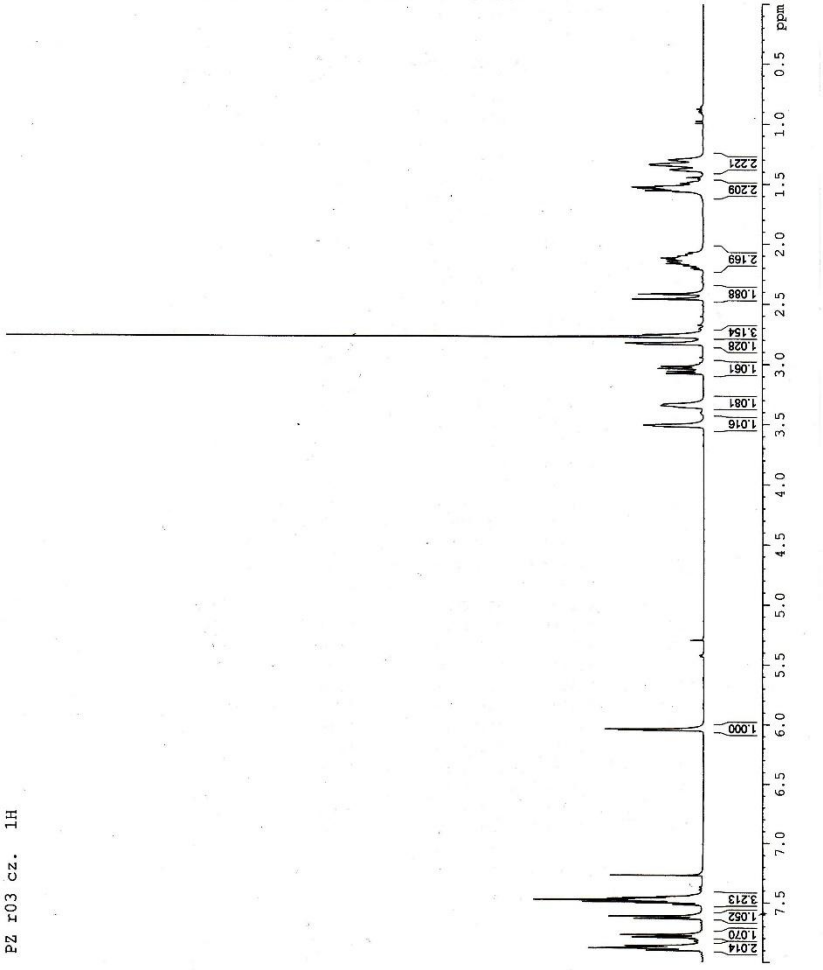
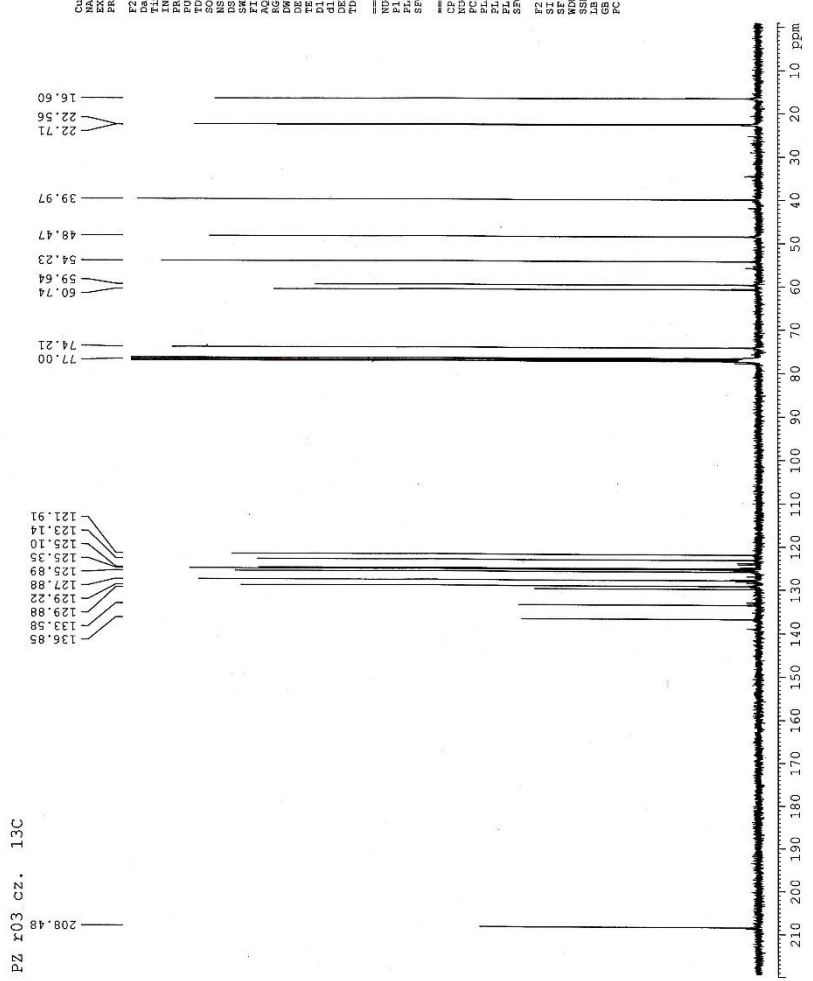
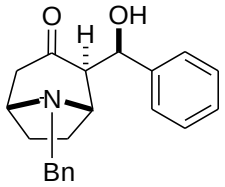
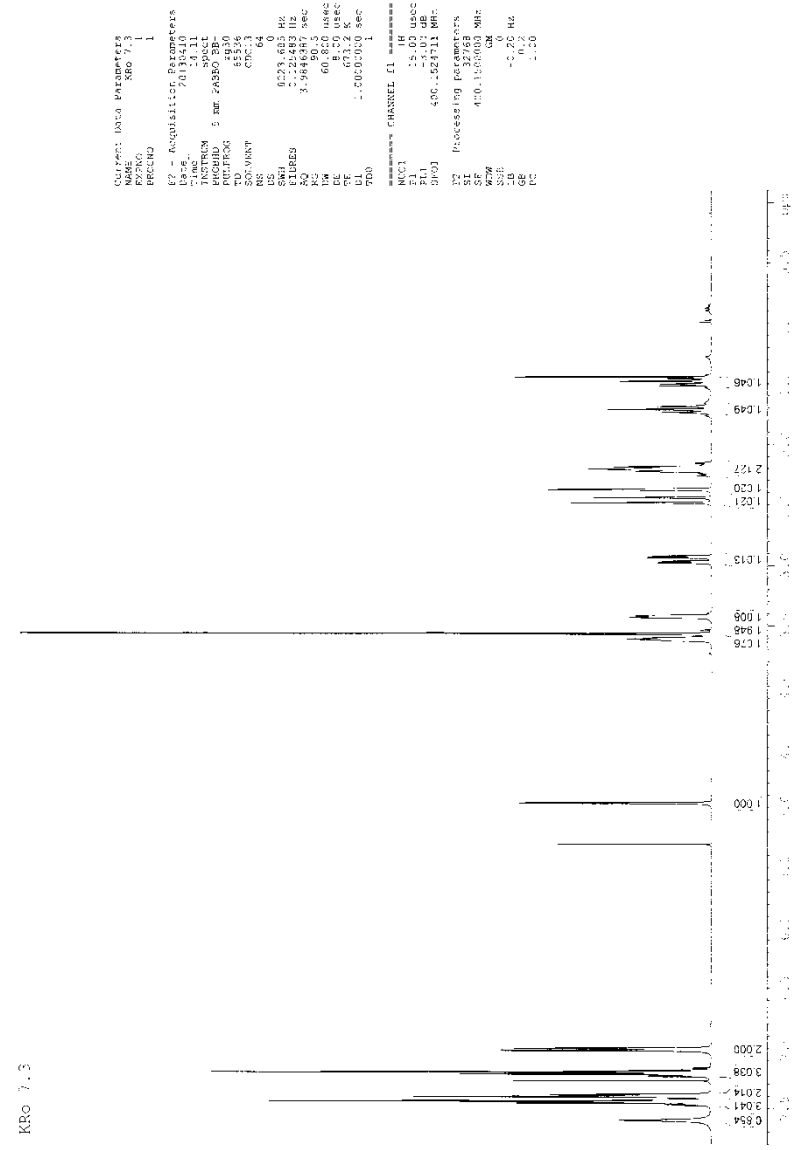


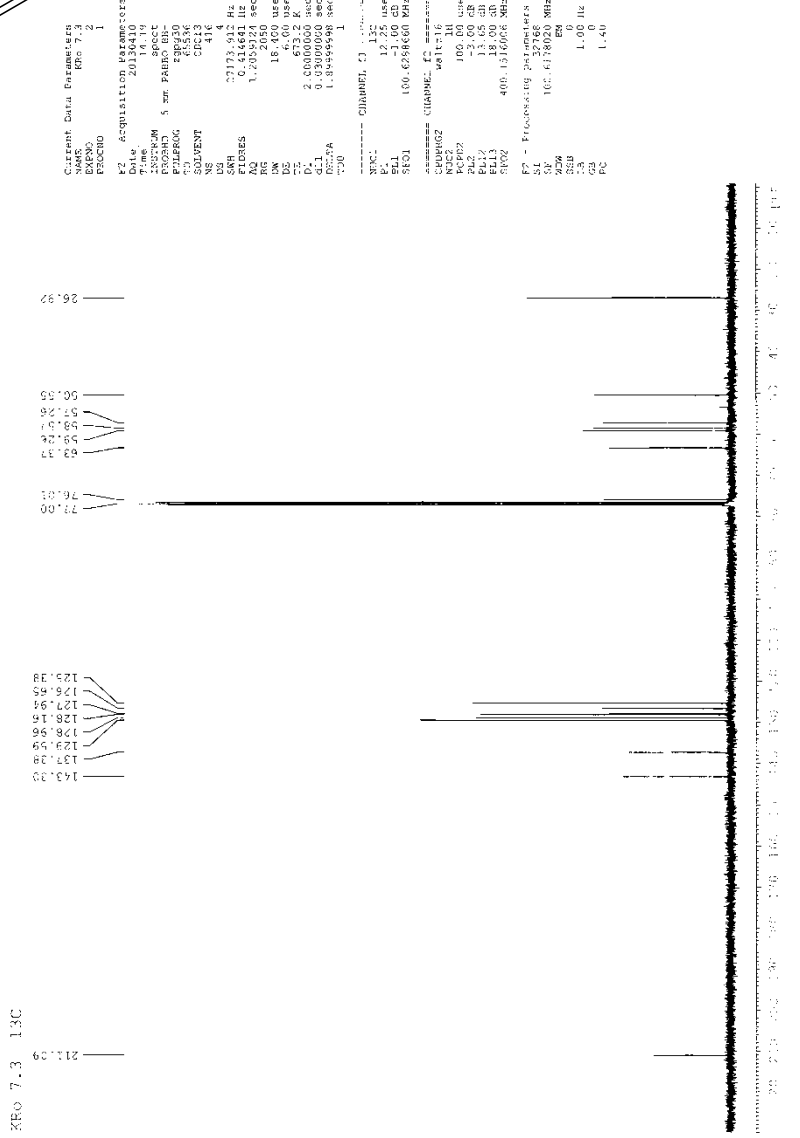




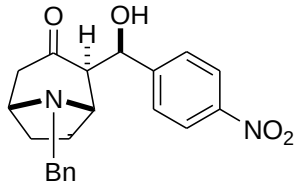
exo,syn-8-benzyl-2-(hydroxy(phenyl)methyl)-8-aza-bicyclo[3.2.1]octan-3-one (_exo,syn_-14a)

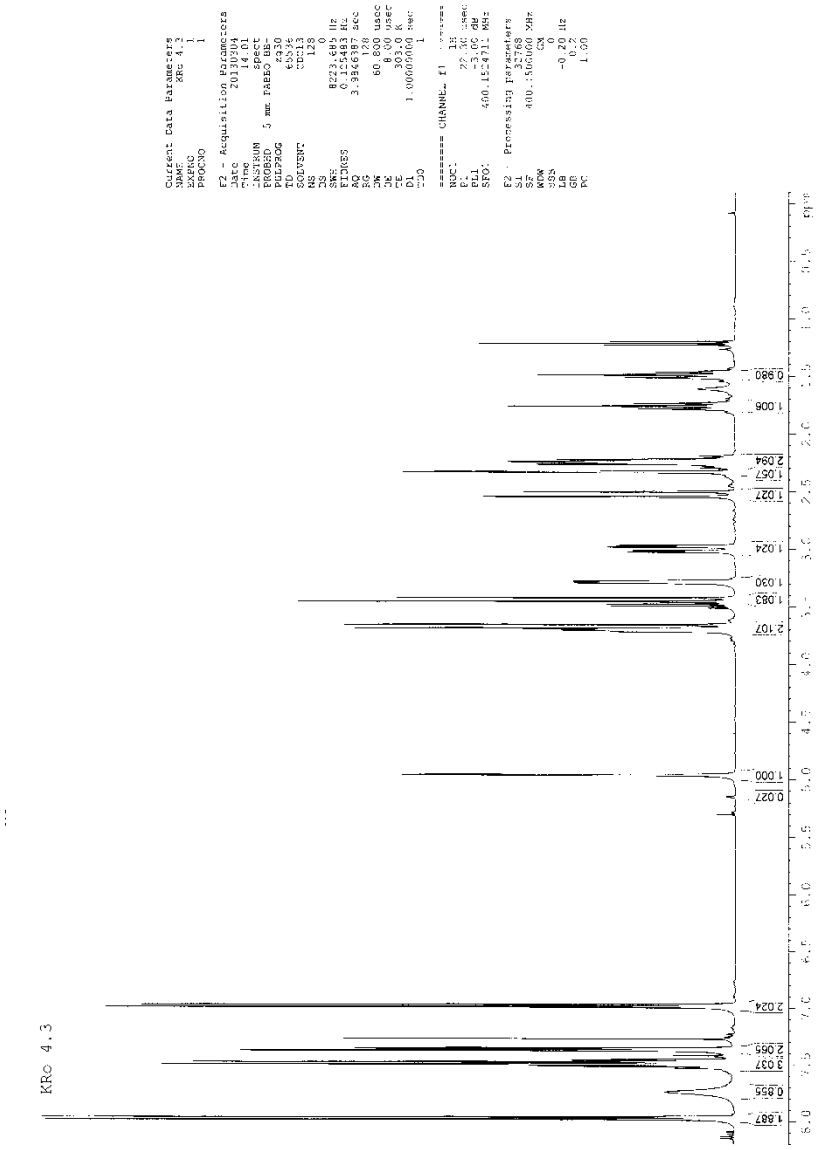


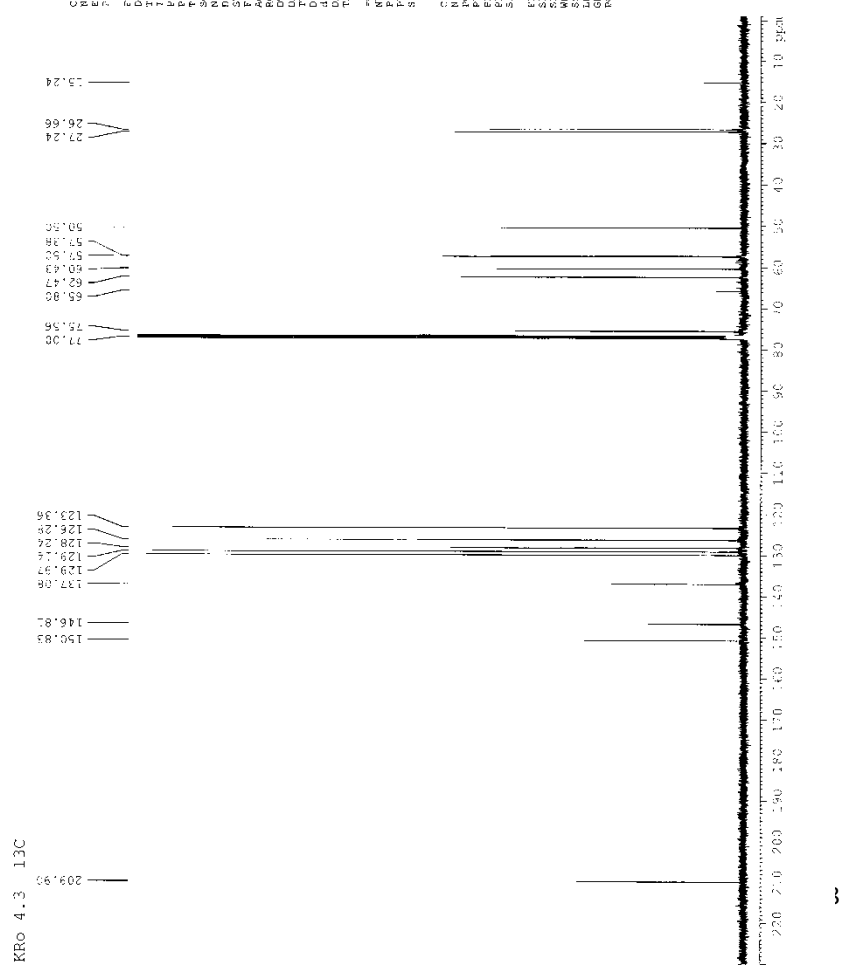




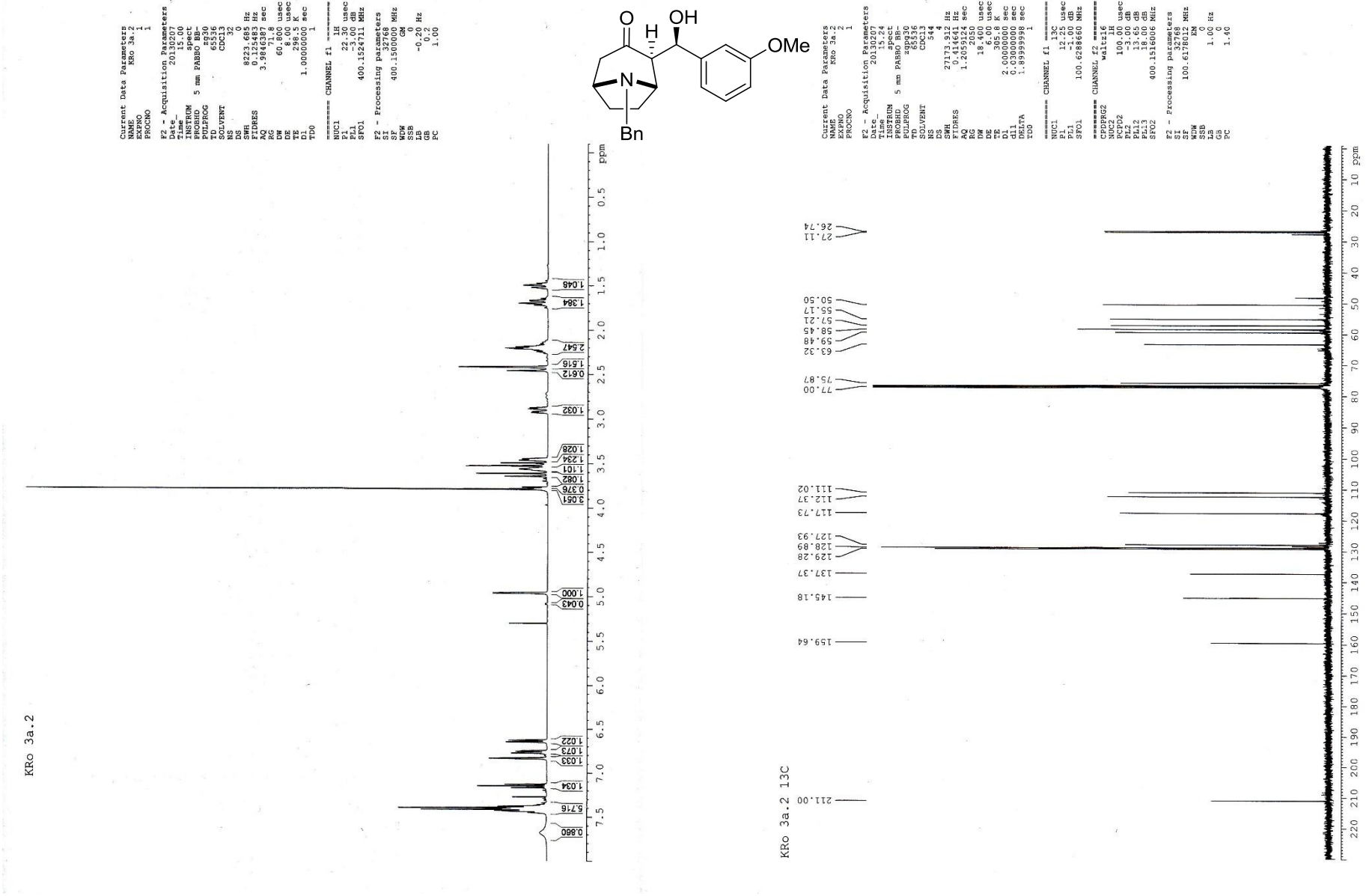
exo,syn-8-benzyl-2-(hydroxy(4-nitrophenyl)methyl)-8-aza-bicyclo[3.2.1]octan-3-one (_exo,syn_-14b)



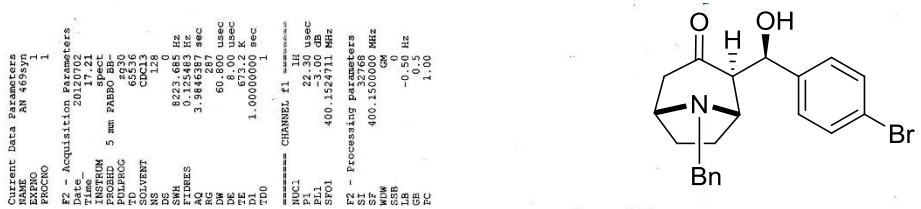


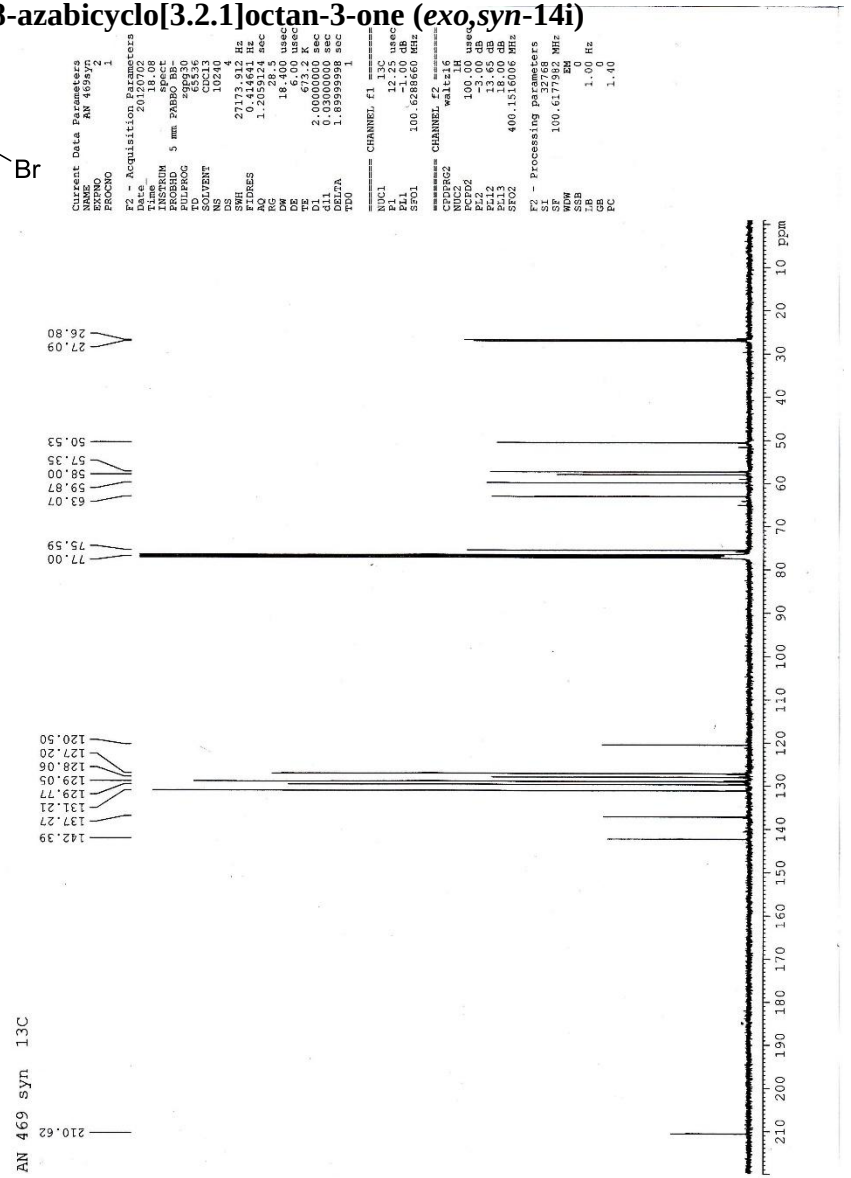


exo,syn-8-benzyl-2-(hydroxy(3-methoxyphenyl)methyl-8-azabicyclo[3.2.1]octan-3-one (_exo,syn_-14f)

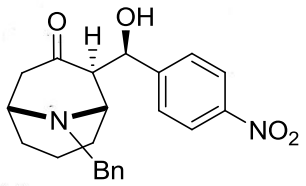


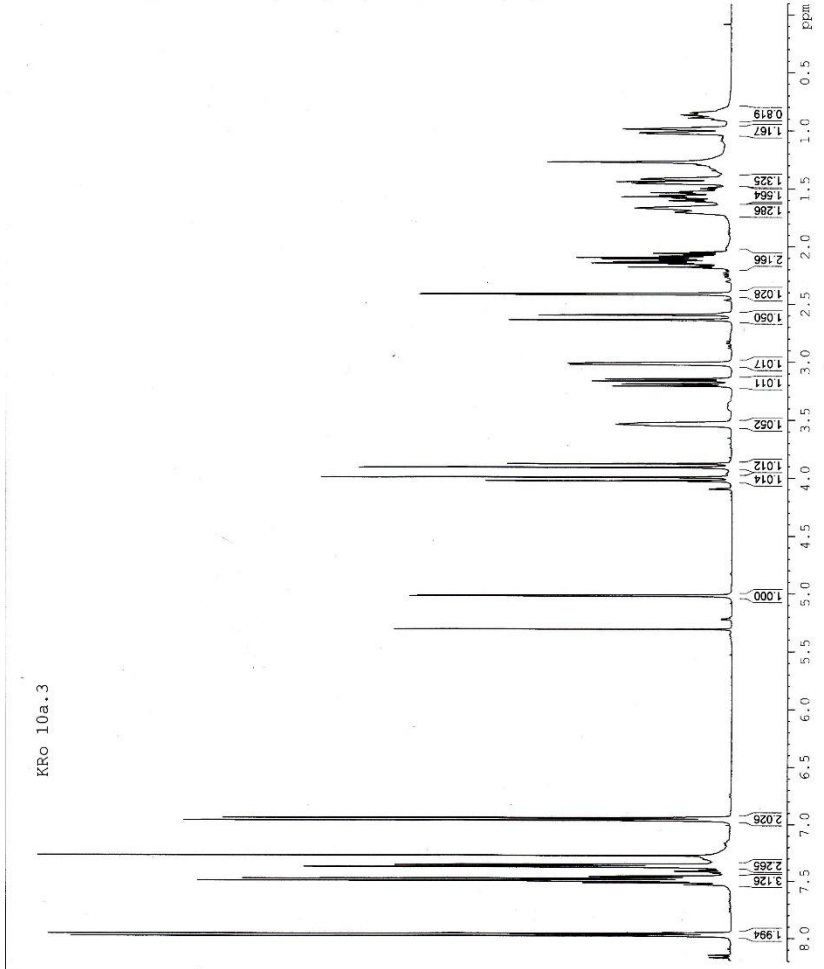
exo,syn-8-benzyl-2-((4-bromophenyl)(hydroxy)methyl)-8-azabicyclo[3.2.1]octan-3-one (_exo,syn_-14i)

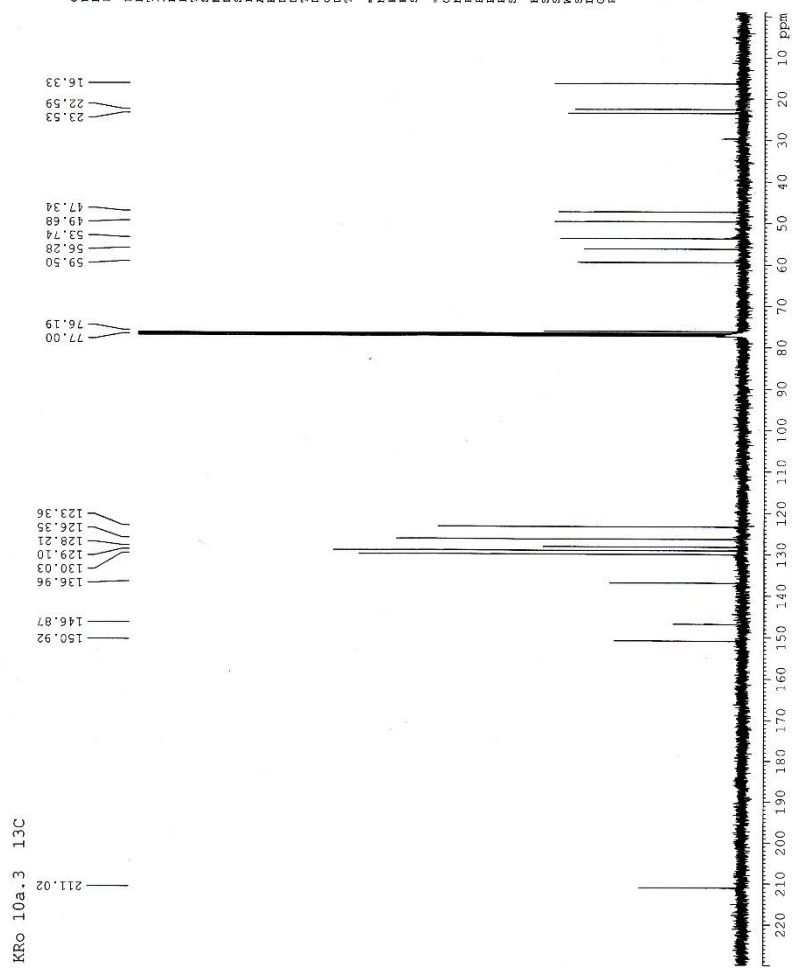




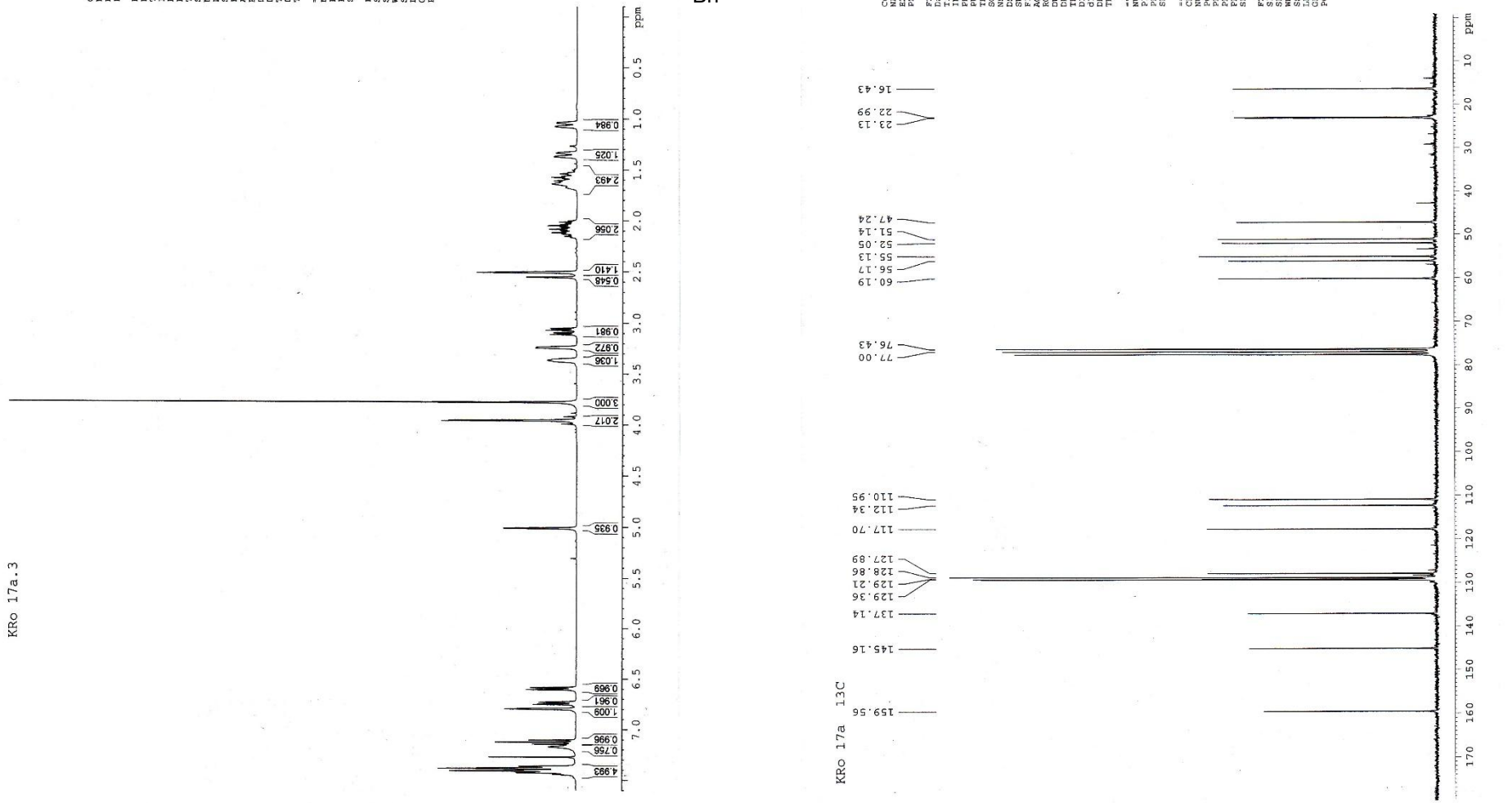
exo,syn-9-benzyl-2-(hydroxy(4-nitrophenyl)methyl)-9-azabicyclo[3.3.1]nonan-3-one (_exo,syn_-15b)



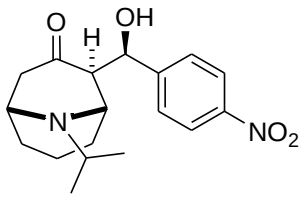


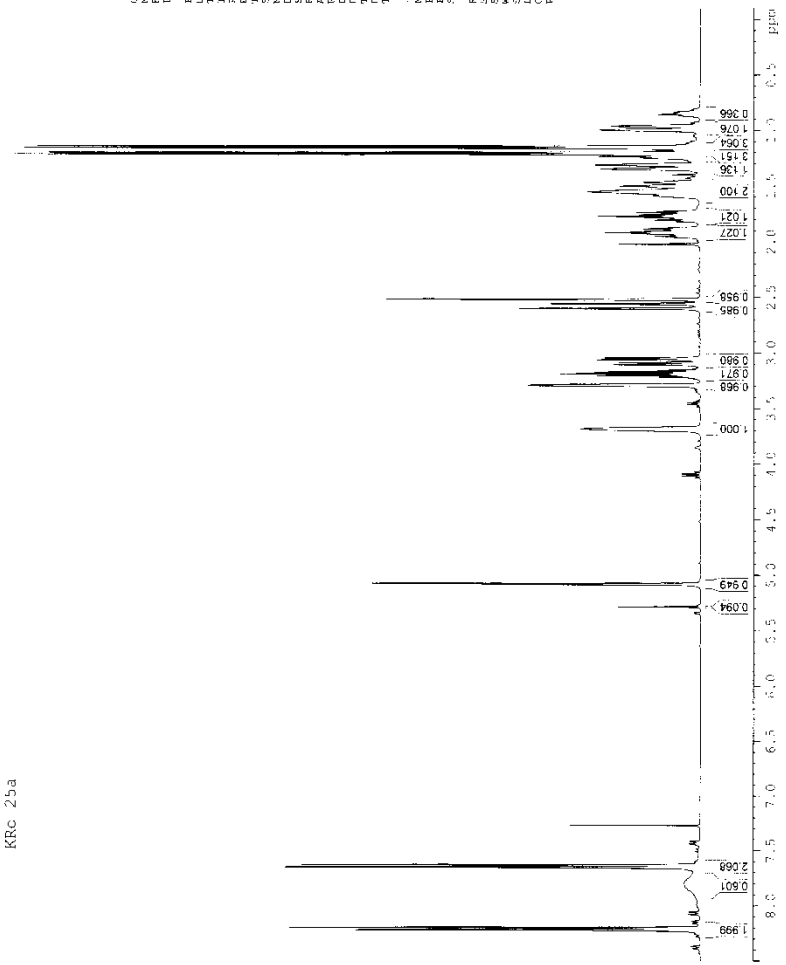


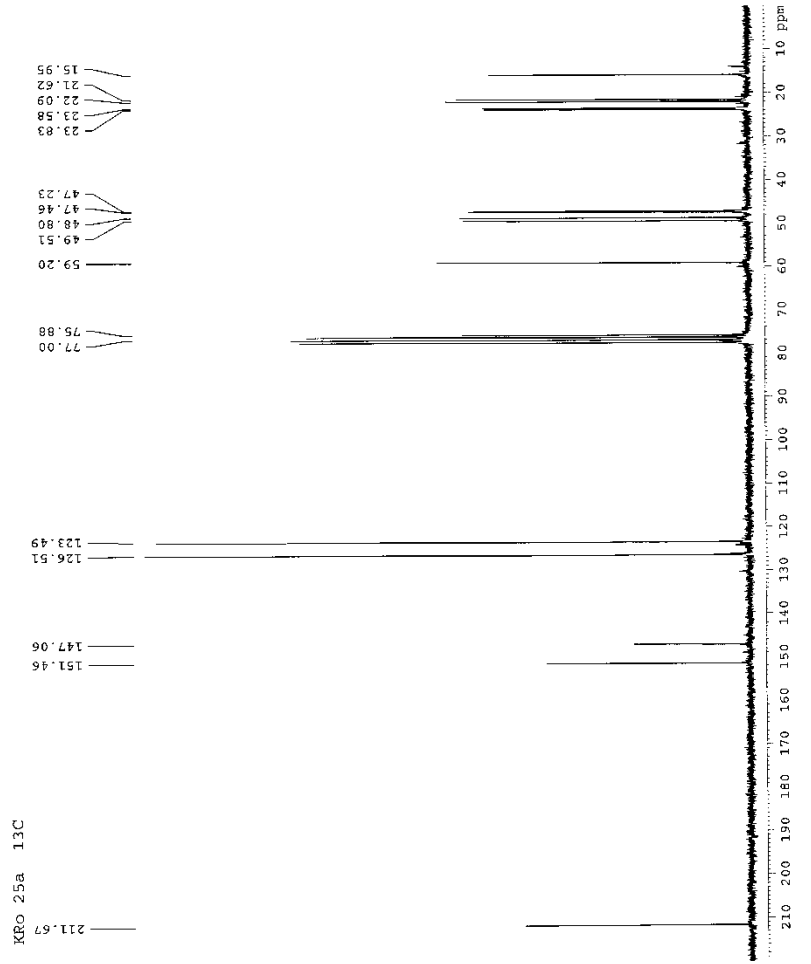
exo,syn-9-benzyl-2-(hydroxy(3-methoxyphenyl)methyl)-9-azabicyclo[3.3.1]nonan-3-one (_exo,syn_-15f)



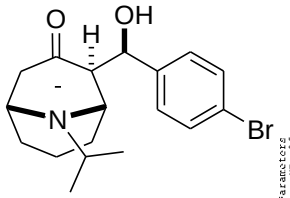
exo,syn-2-(hydroxy(4-nitrophenyl)methyl)-9-isopropyl-9-aza-bicyclo[3.3.1]nonan-3-one (_exo,syn_-17b)

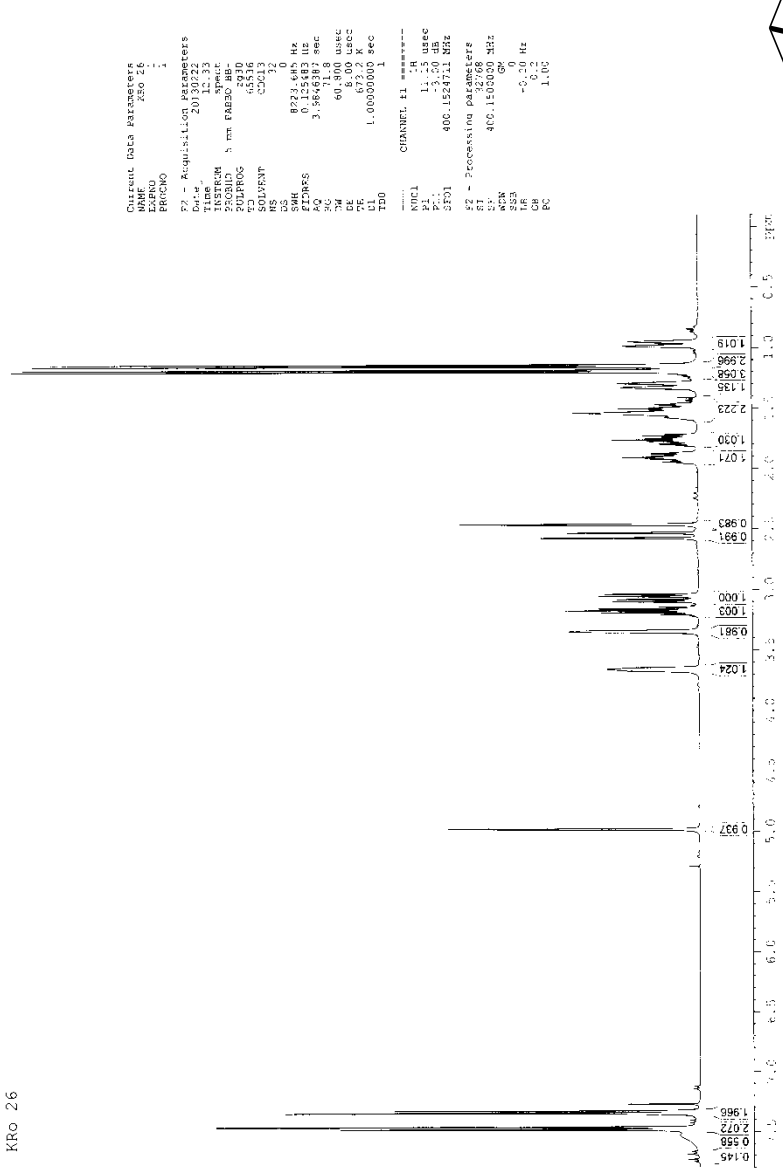


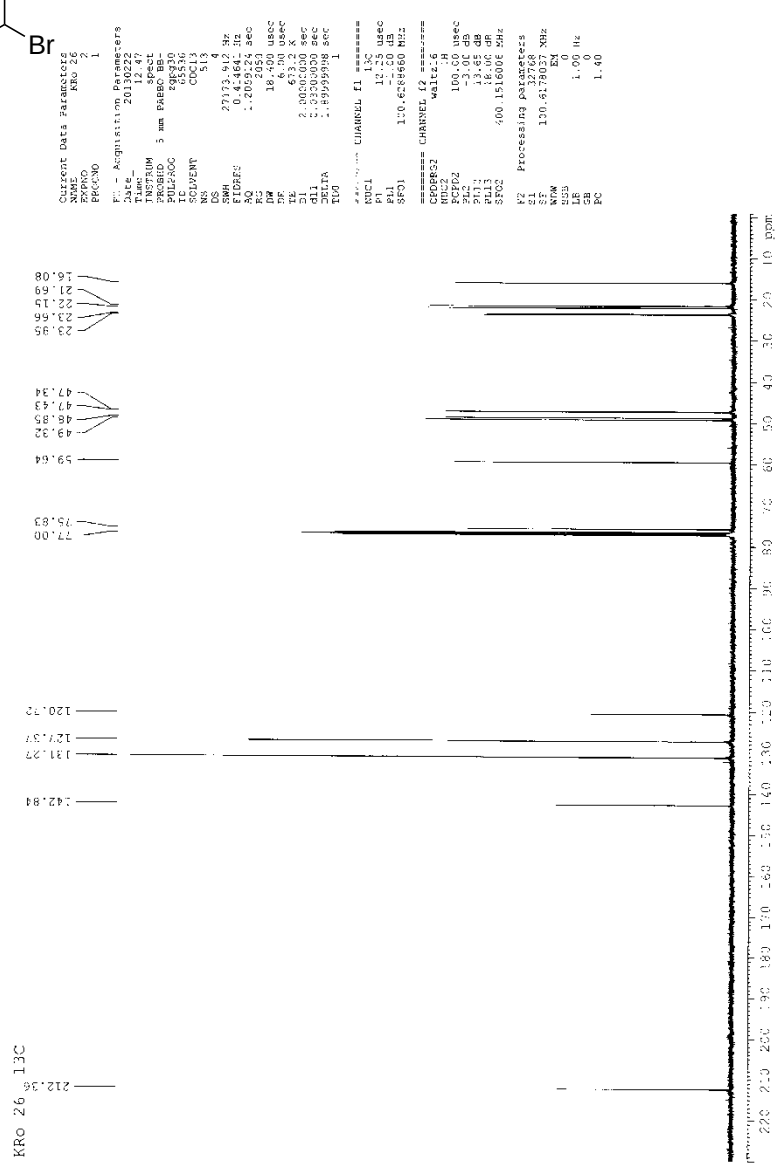




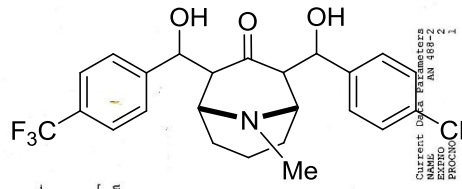
exo,syn-2-((4-bromophenyl)(hydroxy)methyl)-9-isopropyl-9-aza-bicyclo[3.3.1]nonan-3-one (_exo,syn_-17i)

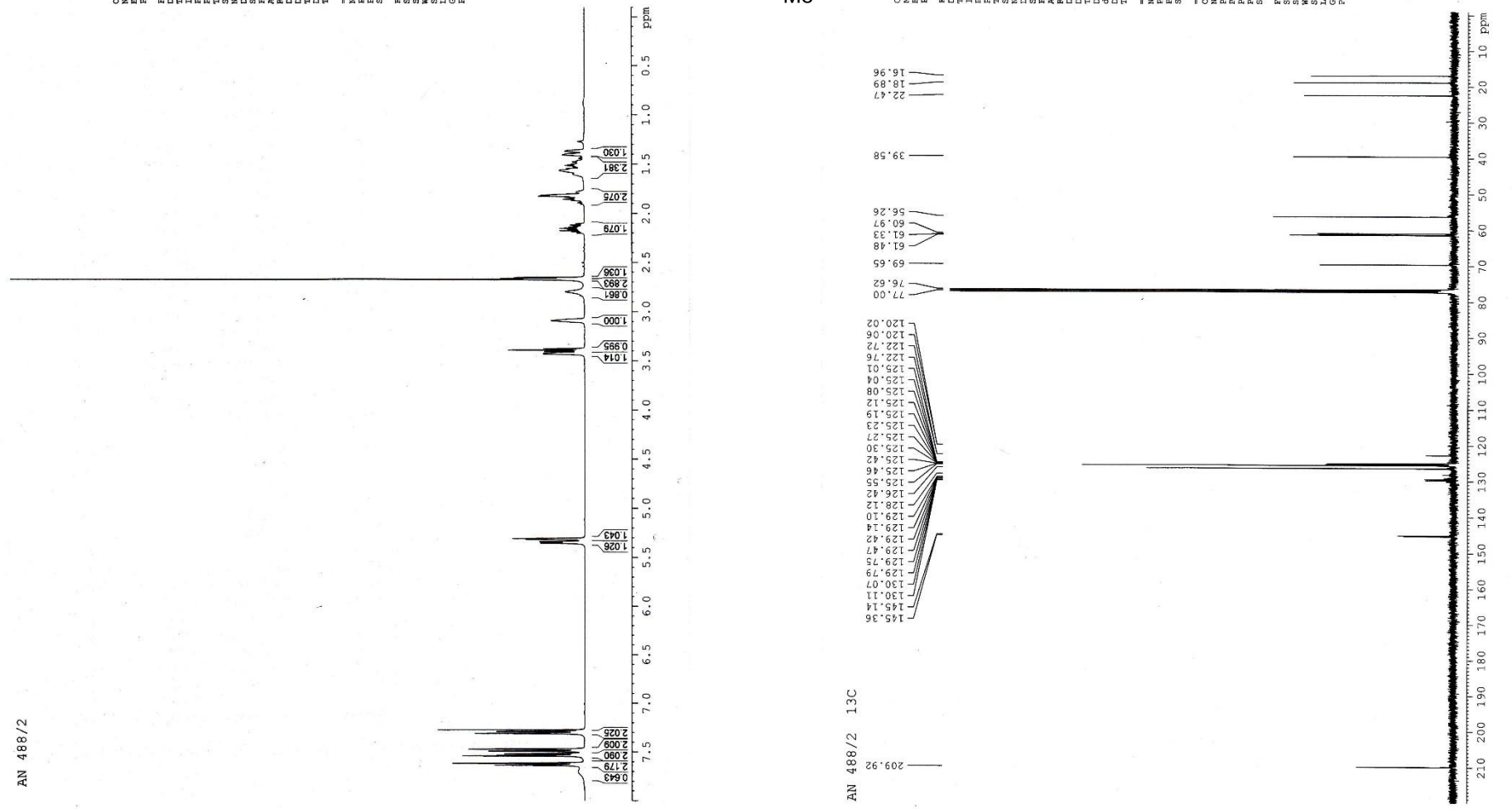




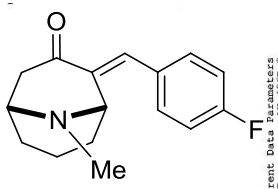


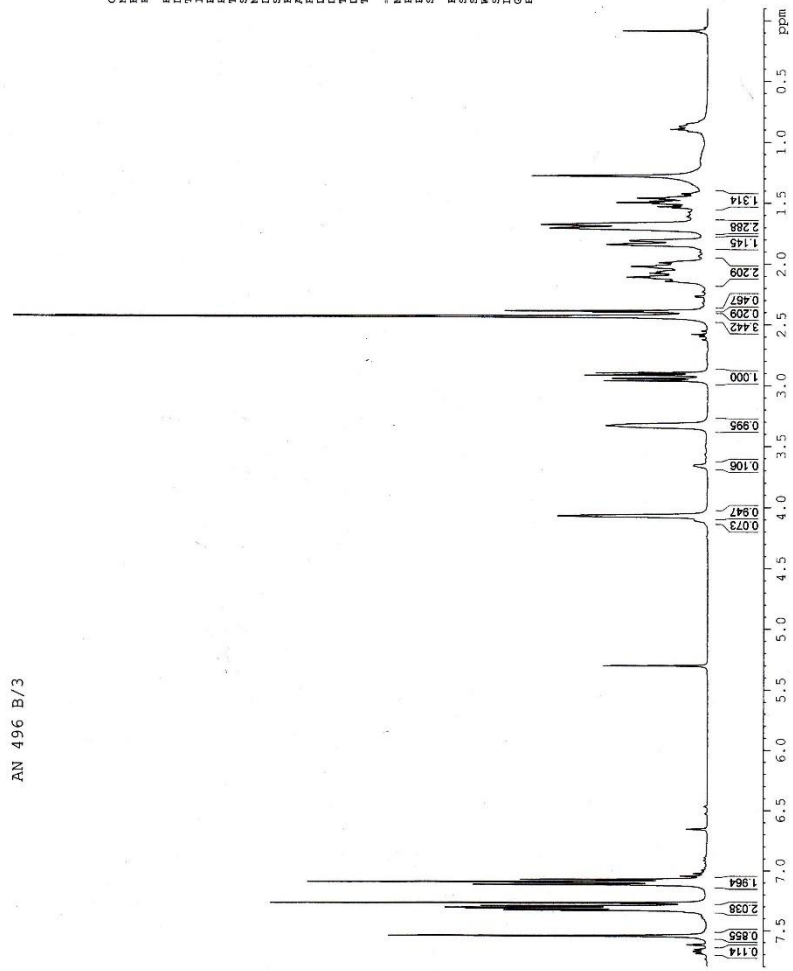
2,4-bis(hydroxy(4-(trifluoromethyl)phenyl)methyl)-9-methyl-9-azabicyclo[3.3.1]nonan-3-one (5e)

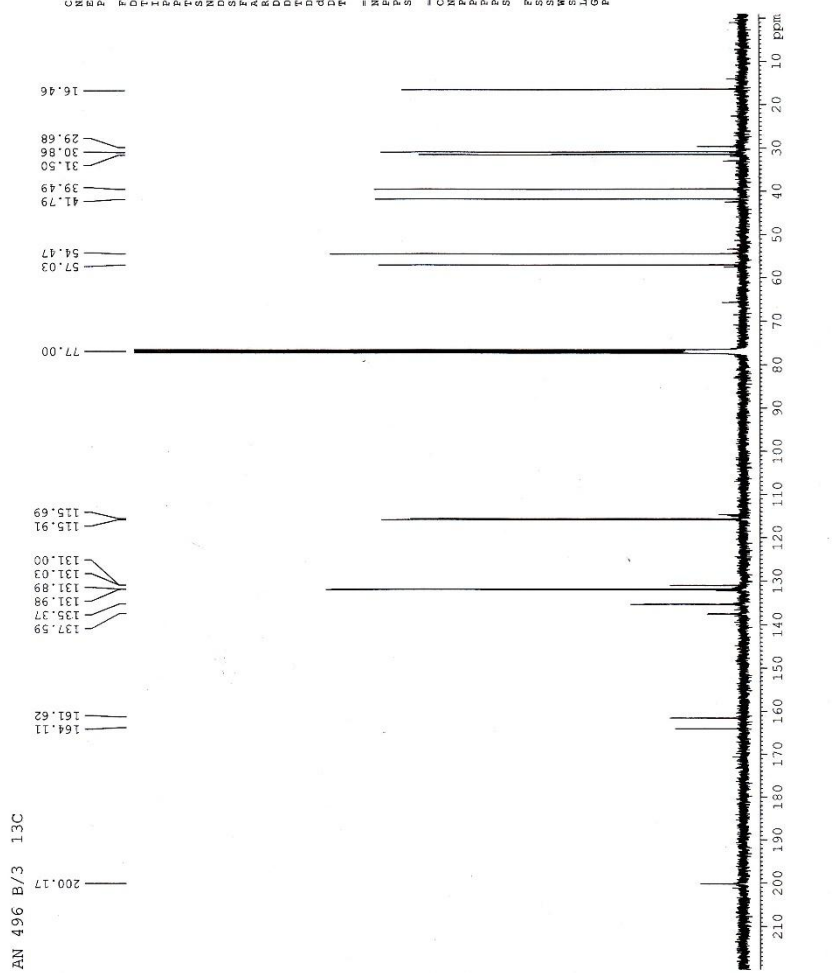




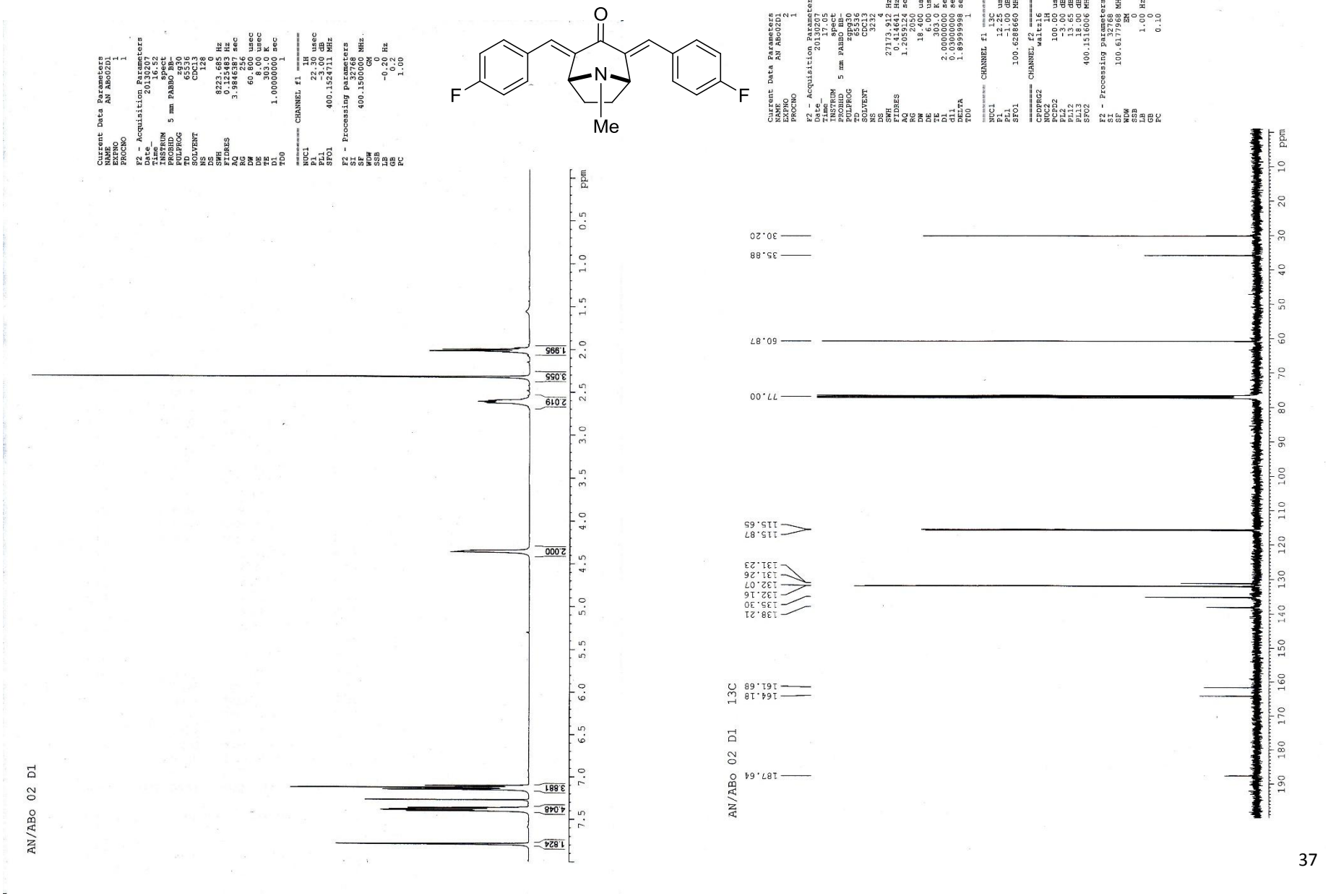
(*E*)-2-(4-fluorobenzylidene)-9-methyl-9-azabicyclo[3.3.1]nonan-3-one (7c)



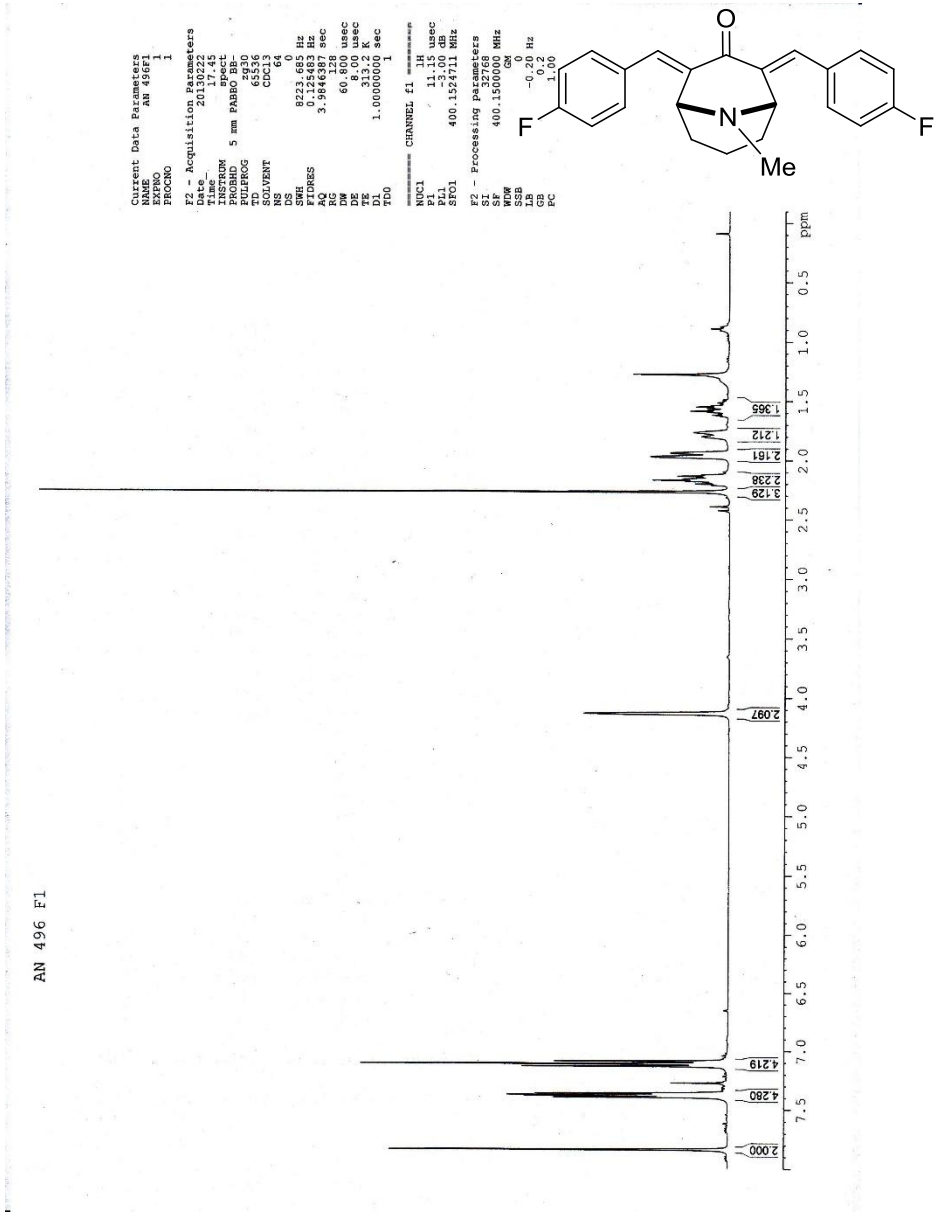


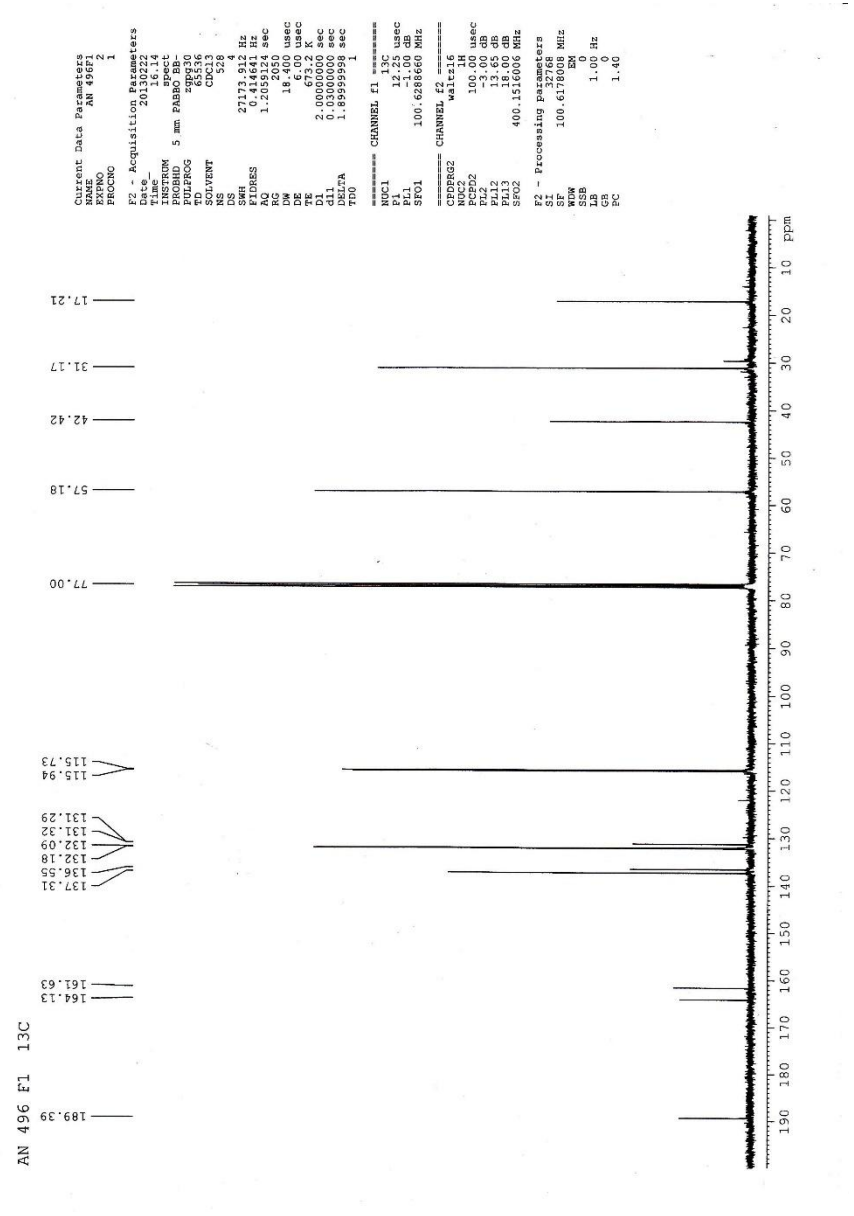


(2*E*,4*E*)-2,4-bis(4-fluorobenzylidene)-8-methyl-8-azabicyclo[3.2.1]octan-3-one (8c)



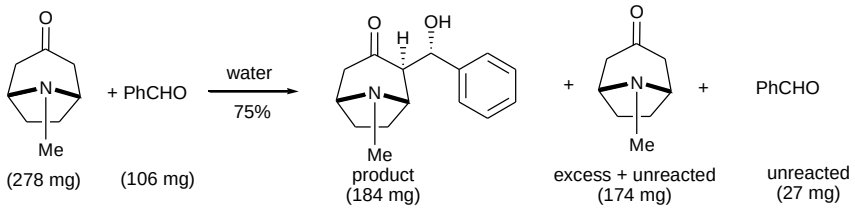
(2*E*,4*E*)-2,4-bis(4-fluorobenzylidene)-9-methyl-9-azabicyclo[3.3.1]nonan-3-one (9c)





E-factor

1.



(278 mg) (106 mg) product (184 mg) excess + unreacted (174 mg) unreacted (27 mg)

FOR ONE RUN OF THE REACTION

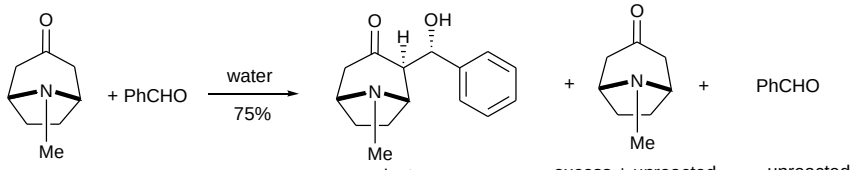
Total amount of reactants: 278 mg + 106 mg = 384 mg

Amount of final product: 1 • 184 = 184 mg, assuming yield = 75% for one run

Amount of waste: (384 mg – 184 mg) = 200 mg

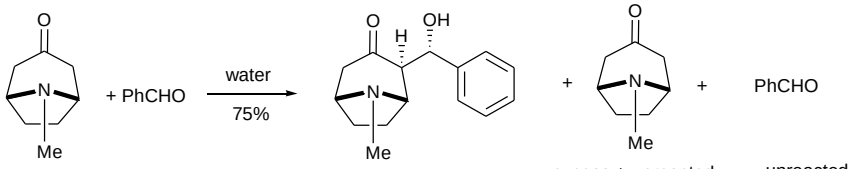
E-Factor = Amount of waste / Amount of product = 200 mg / 184 mg = **1.09**

2.



(104 mg) (79 mg) product (184 mg) excess + unreacted (174 mg) unreacted (27 mg)

3.



(104 mg) (79 mg) product (184 mg) excess + unreacted (174 mg) unreacted (27 mg)

FOR THREE RUNS OF THE REACTION

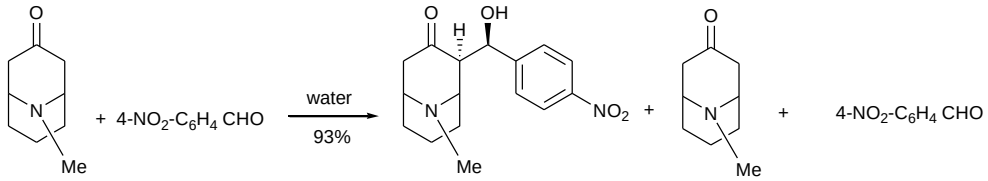
Total amount of reactants: 278 mg + 106 mg + 2 • 104 mg + 2 • 79 mg = 750 mg

Amount of final product: 3 • 184 = 552 mg, assuming yield = 75% in each cycle

Amount of waste: (750 mg – 552 mg) = 198 mg

E-Factor = Amount of waste / Amount of product = 198 mg / 552 mg = **0.36**

1.



(306 mg) (151 mg) product (283 mg) excess + unreacted (164 mg) unreacted (11 mg)

FOR ONE RUN OF THE REACTION

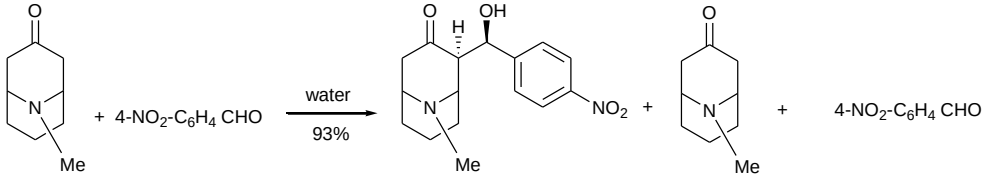
Total amount of reactants: 306 mg + 151 mg = 457 mg

Amount of final product: 1 • 283 = 283 mg, assuming yield = 93% for one run

Amount of waste: (457 mg – 283 mg) = 174 mg

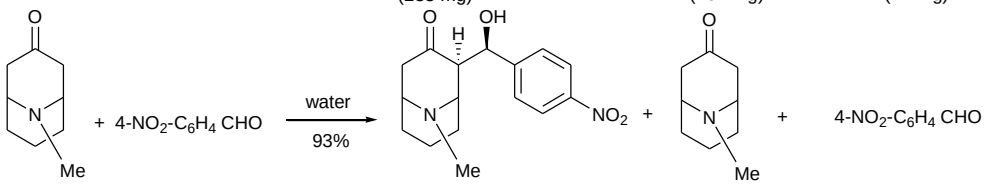
E-Factor = Amount of waste / Amount of product = 174 mg / 283 mg = **0.61**

2.



(142 mg) (140 mg) product (283 mg) excess + unreacted (164 mg) unreacted (11 mg)

3.



(142 mg) (140 mg) product (283 mg) excess + unreacted (164 mg) unreacted (11 mg)

FOR THREE RUNS OF THE REACTION

Total amount of reactants: 306 mg + 151 mg + 2 • 142 mg + 2 • 140 mg = 1021 mg

Amount of final product: 3 • 283 = 849 mg, assuming yield = 93% in each cycle

Amount of waste: (1021 mg – 849 mg) = 172 mg

E-Factor = Amount of waste / Amount of product = 172 mg / 849 mg = **0.20**