

Supplementary Information

Synthesis of (-)-Epibatidine

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General Methods: TLC analyses were performed on 0.25 mm silica gel plates, and were visualized with UV light, iodine chamber, 10% sulfuric acid or 10% PMA solution. Melting points were measured by means of open capillaries. All NMR spectra, i.e., ^1H , ^{13}C , DEPT, DQF-gCOSY, gHSQC, gHMBC, and NOE difference, were recorded on either 600 or 400 MHz NMR spectrometer, which provided all necessary data for the full assignment of each compound. HPLC analyses were carried out on a high-pressure mixing system with two pumps and a photodiodearray detector. The mass analyzer used for the HRMS is double focusing magnetic sector. The specific rotation values were recorded on the wavelength of 589 nm.

Materials: Chemicals, reagents and solvents were purchased from commercial suppliers. The reagents were used as received. Dichloromethane, pyridine, triethylamine, acetonitrile, DMSO and methanol were dried and distilled over calcium hydride under argon before use. Ether was dried and distilled over sodium-benzophenone ketyl under argon before use. THF was dried and distilled over potassium metal under argon before use. Toluene and benzene were dried and distilled over sodium metal under argon or argon before use. The reaction flasks were dried in a 110 °C oven and allowed to cool to room temperature in a desiccator over calcium sulfate and assembled under argon atmosphere.

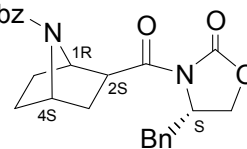
Separation of oxazolidinone diastereomers:

The racemic acid **3** (413 mg, 1.50 mmol, 1.0 eq.) was dissolved in one part of CH₂Cl₂ (~ 5 M). To the solution in an ice bath, was added SOCl₂ (3.0 eq.) followed by a drop of DMF under argon. Upon completion of addition, the ice bath was removed and the reaction mixture was allowed to be stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure to remove volatile substances, to yield a crude residue. The crude residue was diluted with one part of CH₂Cl₂ to give the crude acid chloride solution.

To a THF solution of (4*S*)-benzyl-2-oxazolidinone (319 mg, 1.80 mmol, 1.2 eq., ~ 0.3 M) at -50 °C under argon, BuLi (1.2 mL, 1.3 eq., 1.6 M in hexane) was slowly added by an additional funnel. The reaction mixture was allowed to be stirred at -50 °C for 1 h. The acid chloride solution was slowly cannulated to the oxazolidinone solution. The addition rate of the acid chloride solution was controlled so that the internal temperature was in the range between -40 to -50 °C. The resulting reaction mixture was allowed to be stirred at the temperature for 6 h. Upon completion of the reaction monitored by TLC analysis, chilled saturated NH₄Cl solution was added to quench the reaction, and the reaction mixture was concentrated under reduced pressure to remove excess organic solvent to yield a residue. The residue was partitioned with CH₂Cl₂ and water. The resulting aqueous layer was extracted with CH₂Cl₂ (X5). The combined organic layers were washed dried over anhydrous Na₂SO₄, and then concentrated to give crude product. Purification of the crude product by flash chromatography on silica gel, using EtOAc/n-Hex as the eluant afforded the titled product.

3-[(1*R*,2*S*,4*S*)-7-benzyloxycarbonyl-7-azabicyclo[2.2.1]heptane-2-carbonyl]-(4*S*)-benzyl-2-

oxazolidinone (4a): 290 mg, 0.667 mmol, 44%; white solid, mp 167-168 °C; R_f = 0.37, EtOAc/n-Hex = 1/2; $[\alpha]_D^{25} +25.6$ (c : 1.0, CHCl₃); ¹H-NMR (400 MHz, 25 °C, CDCl₃, δ): 1.47 (t, J = 7.2 Hz, 1H), 1.58-1.74 (m, 2H), 1.76-1.89 (m, 2H), 2.49 (ddd, J = 5.2, 5.2 and 10.4 Hz, 1H), 2.56-2.82 (m, 1H), 3.10-3.34 (m, 1H), 3.65 (dd, J = 5.2 and 8.4 Hz, 1H), 3.70 (brs, 0.5H), 3.97 (brs, 0.5H), 4.08-4.20 (m, 1H), 4.25 (brs, 0.5H), 4.38-4.45 (m, 2H), 4.63-4.68 (m, 0.5H), 4.94-5.15 (m, 2H), 7.06-7.40 (m, 10H); ¹³C-NMR (100 MHz, 25 °C, CDCl₃, δ): 28.9 (t), 29.6 (t), 31.8 (t), 37.6 (t), 47.7 (d), 55.4 (d), 56.3 (d), 60.2 (d), 66.2 (t), 66.8 (t), 127.2^{#1} (d), 127.9[#] (d),

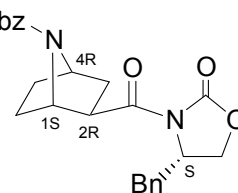


¹ #: These methine peaks in two phenyl groups can not be quantified by either peak heights or integral values due to deformation and overlapping.

128.36[#] (d), 128.38[#] (d), 128.8[#] (d), 129.3[#] (d), 135.2 (s), 136.5 (s), 153.5 (s), 155.1 (s), 172.2 (s); EI-HRMS (m/z): [M]⁺ calcd for C₂₅H₂₆N₂O₅⁺, 434.1842; found, 434.1832 (Δ= 2.3 ppm).

3-[(1*S*,2*R*,4*R*)-7-benzyloxycarbonyl-7-azabicyclo[2.2.1]heptane-2-carbonyl]-(4*S*)-benzyl-2-

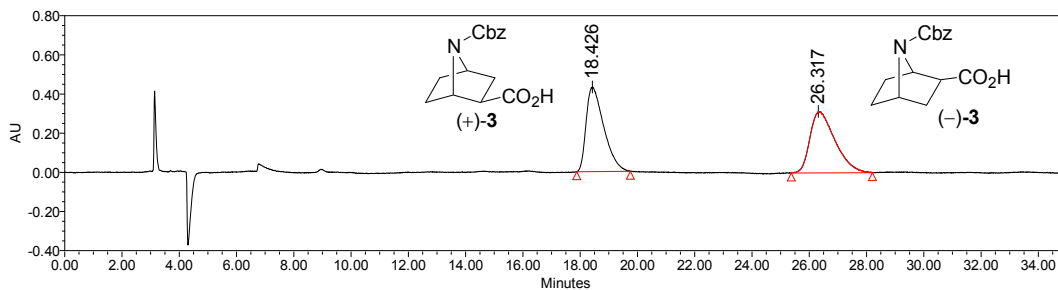
oxazolidinone (4b): 270 mg, 0.621 mmol, 41%; white solid, mp 110-111 °C; *R_f* = 0.29; EtOAc/*n*-Hex = 1/2; [α]_D²⁵ +83.5 (*c*: 1.0, CHCl₃); ¹H-NMR (400 MHz, 25 °C, CDCl₃, δ): 1.43-1.50 (m, 1H), 1.57 (t, *J* = 9.6 Hz, 1H), 1.72 (t, *J* = 8.4 Hz, 1H), 1.81-1.94 (m, 2H), 2.50 (brs, 1.5H), 2.78 (brs, 0.5H), 3.08 (brs, 0.5H), 3.30 (brs, 0.5H), 3.58 (dd, *J* = 5.2, and 8.4 Hz, 1H), 4.18 (brs, 2H), 4.44 (brs, 1H), 4.60 (brs, 2H), 4.84-5.24 (m, 2H), 7.00-7.60 (m, 10H); ¹³C-NMR (100 MHz, 25 °C, CDCl₃, δ): 28.7* (t), 29.5* (t), 31.8 (t), 37.5 (t), 47.5 (d), 55.3 (d), 56.1 (d), 60.1 (d), 66.3 (t), 66.8 (t), 127.1 (d), 127.8 (d, 2C), 128.3 (d, 2C), 128.8 (d, 3C), 129.4 (d, 2C), 135.3 (s), 136.5 (s), 153.5 (s), 154.9 (s), 172.2 (s); EI-HRMS (m/z): [M]⁺ calcd for C₂₅H₂₆N₂O₅⁺, 434.1842; found, 434.1834 (Δ= 1.8 ppm).



Hydrolysis of the oxazolidinone derivatives:

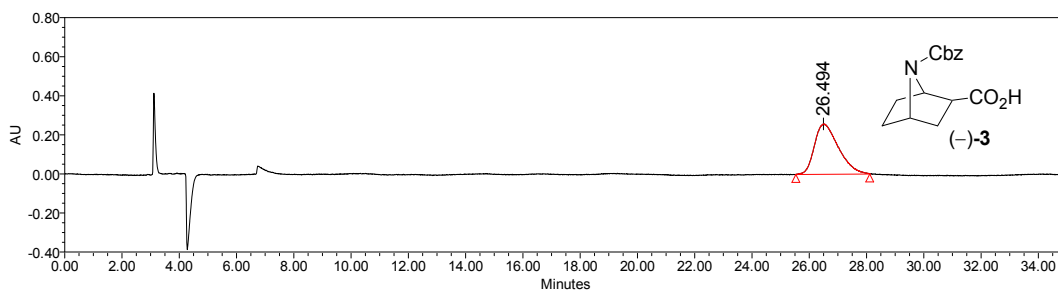
To a THF solution (2.5 mL) of oxazolidinone **4** (0.44 mmol, 1.0 eq.) in an ice bath, LiOH·H₂O (29.6 mg, 0.70 mmol, 1.6 eq.) was added followed by H₂O₂ (35%, 180 μL, 2 mmol, 4 eq.). The reaction mixture was allowed to be stirred at room temperature for 2 h. Upon completion of the reaction monitored by TLC analysis, a Na₂SO₃ solution (0.2 g dissolved in 1.5 mL) was added to quench the reaction, and the reaction mixture was concentrated under reduced pressure to remove excess organic solvent. H₂O (2 mL) was added to the aqueous solution. The resulting aqueous solution was washed with CH₂Cl₂ (2 mL X5), and covered with EtOAc (10 mL). The bilayer solution was acidified with a HCl solution (3 N) until pH was around 2. White precipitate was observed during acidification. After separation of the organic layer, the resulting aqueous layer was extracted with EtOAc (10 mL X 5). The combined organic layers were washed with brine (10 mL), and dried over anhydrous Na₂SO₄, and then concentrated to give the crude acid. Purification of the crude acid product by flash chromatography on silica gel, using EtOAc/*n*-Hex/AcOH as the eluant, gave the titled product as a colorless oil.

HPLC condition: CHIRACEL OD-H, 4.6 mm X 250 mm, 5 μm; Mobile phase A: 0.5% TFA in an IPA/*n*-Hex solution (v/v = 1/10); Mobile phase B: 0.5% TFA in pure *n*-Hex; isocratic, 50% A :50% B; flow rate 1.0 mL per min; detection UV 215 nm, *t_R*: 18.4 min for (+)-**3**, 26.3 min for (–)-**3**.

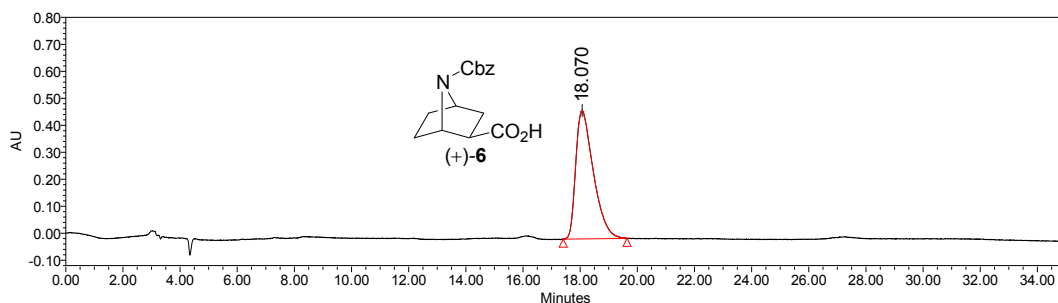


	Retention Time	Area	% Area	Height
1	18.426	18454909	49.31	432817
2	26.317	18972776	50.69	313734

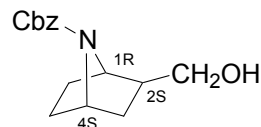
(-)-(1*R*,2*S*,4*S*)-7-benzyloxycarbonyl-7-azabicyclo[2.2.1]heptane-2-carboxylic acid (-)-3: 98%; colorless oil, $R_f = 0.24$; EtOAc/n-Hex = 1/4; $[\alpha]_D^{25} -8.6$ ($c: 1.0, \text{CHCl}_3$); $t_R: 26.5$ min for (-)-3.



(+)-(1*S*,2*R*,4*R*)-7-benzyloxycarbonyl-7-azabicyclo[2.2.1]heptane-2-carboxylic acid (+)-3: 93%; colorless oil, $R_f = 0.24$; EtOAc/n-Hex = 1/4; $[\alpha]_D^{25} +8.8$ ($c: 1.0, \text{CHCl}_3$); $t_R: 18.4$ min for (+)-3.

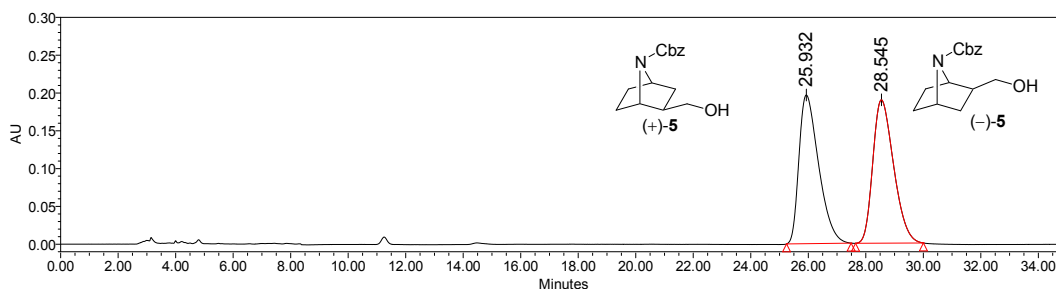


(-)-(1R,2S,4S)-7-benzyloxycarbonyl-7-azabicyclo[2.2.1]heptane-2-methanol

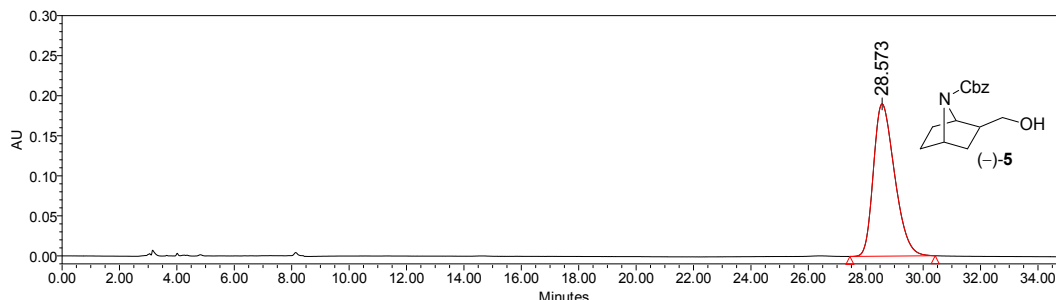


(5): To a solution of the acid **3** (9.16 g, 33.3 mmol, 1.0 eq.) in THF (80 mL) in an ice bath, was slowly added $\text{BH}_3 \cdot \text{SMe}_2$ solution (2 M, in THF, 35 mL, 69.9 mmol, 2.1 eq.). The reaction mixture was allowed to be stirred at room temperature for 5 h. Upon completion of the reaction monitored by TLC analysis, chilled water (48 mL) was added to quench the reaction, and the reaction mixture was concentrated under reduced pressure to remove excess organic solvent. The aqueous solution was partitioned with EtOAc (40 mL) and water (80 mL). The resulting aqueous layer was extracted with EtOAc (20 mL X5). The combined organic layers were washed with saturated NaHCO_3 (15 mL), brine (30 mL), and dried over anhydrous Na_2SO_4 . After removal of the solid dehydrating agent, the organic layer was concentrated under reduced pressure to give a crude product. Purification of the crude product by flash chromatography on silica gel, using EtOAc/n-Hex as the eluant, gave the titled product as a colorless oil (8.35 g, 32.0 mmol, 96%): $R_f = 0.36$, EtOAc/n-Hex = 4/1; $[\alpha]_D^{24} -19.4$ (c : 1.0, CHCl_3); $^1\text{H-NMR}$ (400 MHz, 25 °C, CDCl_3 , δ): 1.14-1.22 (m, 1H, H-3 exo), 1.30-1.42 (m, 2H, H-5 and H-6), 1.45 (dd, $J = 8.4$ and 12.4 Hz, 1H, H-3 endo), 1.70 (br, 2H, H-5 and H-6), 1.84-1.91 (m, 1H, H-2), 3.19-3.29 (m, 2H, CH_2OH), 3.80-4.10 (br, 1H, CH_2OH), 4.24 (brs, 2H, H-1 and H-4), 5.04 (brs, 2H, $-\text{OCH}_2\text{Ph}$), 7.21-7.28 (m, 1H, H-4' in Ph), 7.27-7.31 (m, 4H, H-2' and H-3' in Ph); $^{13}\text{C-NMR}$ (100 MHz, 25 °C, CDCl_3 , δ): 28.7 (t, 2C, C-5 and C-6), 32.9 (t, C-3), 45.1 (d, C-2), 55.4 (d, C-4), 57.1 (d, C-1), 64.1 (t, CH_2OH), 66.2 (t, OCH_2Ph), 127.2 (d, C-2 in Ph), 127.4 (d, C-4 in Ph), 127.9 (d, C-3 in Ph), 136.2 (s, C-1 in Ph), 155.2 (s, N-CO-O). EI-HRMS (m/z): $[\text{M}]^+$ calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_3^+$, 261.1365; found, 261.1368 ($\Delta = 1.1$ ppm).

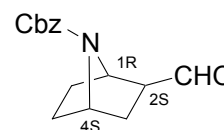
HPLC condition: Chiralcel OD-H, 250 mm X 4.6 mm, 5 μm ; Mobile phase A: IPA : n-Hex = 1 : 15 (v/v); Mobile phase B: pure n-Hex; isocratic, 50% A : 50% B; flow rate 1.0 mL per min; detection UV 215 nm, t_R : 25.9 min for (+)-**5**, 28.5 min for (-)-**5**.



	Retention Time	Area	% Area	Height
1	25.932	9340012	49.52	196658
2	28.545	9521818	50.48	189645



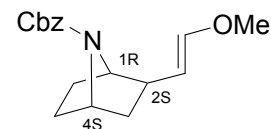
(+)-(1*R*,2*S*,4*S*)-7-benzoyloxycarbonyl-7-azabicyclo[2.2.1]heptane-2-carbaldehyde



(6): To a solution of alcohol **5** (5.52 g, 21.1 mmol, 1.0 eq.) in CH₂Cl₂ (150 mL) in an ice bath, was slowly added Dess-Martin periodinane reagent (10.75 g, 25.34 mmol, 1.2 eq.) in ~3 g portions. The reaction mixture was allowed to be stirred at room temperature for 3 h. Upon completion of the reaction monitored by TLC analysis, chilled saturated NaHCO₃ (245 mL) was added, followed by filtration with a celite pad to yield a filtrate. After separation of the organic layer, the resulting aqueous layer was extracted with CH₂Cl₂ (50 mL X5). The combined organic layers were dried over anhydrous Na₂SO₄. After removal of the solid dehydrating agent, the organic layers was concentrated under reduced pressure to give a crude product. Purification of the crude product by flash chromatography on silica gel, using EtOAc/n-Hex as the eluant, gave the titled product as a colorless oil (5.10 g, 19.7 mmol, 93%): *R_f* = 0.28, EtOAc/n-Hex = 1/2; [α]_D²³ +11.5 (*c*: 1.0, CHCl₃); ¹H-NMR (400 MHz, 25 °C, CDCl₃, δ): 1.34-1.50 (m, 3H, H-3, H-5 and H-6), 1.64-1.82 (m, 2H, H-5 and H-6), 2.08-2.16 (m, 1H, H-3), 2.44 (dd, *J* = 4.4 and 7.6 Hz, 1H, H-2), 4.30 (brs, 1H, H-4), 4.52 (brs, 1H, H-1), 4.92-5.05 (m, 2H, -OCH₂Ph), 7.20-7.29 (m, 5H, -Ph), 9.50 (s, 1H, -CHO); ¹³C-NMR (100 MHz, 25 °C, CDCl₃, δ): 28.9 (t, 2C, C-5 and C-6), 29.8 (t, C-3), 54.5 (d, C-2), 55.8 (d, C-4), 55.6 (d, C-1), 66.5 (t, OCH₂Ph), 127.5 (d, C-2 in Ph), 127.6 (d, C-4 in Ph), 128.0 (d, C-3 in Ph), 136.0 (s, C-1 in Ph), 154.7 (s, N-CO-O), 200.3 (d, CHO); EI-HRMS (*m/z*): [M]⁺ calcd for C₁₅H₁₇NO₃⁺, 259.1208; found, 259.1201 (Δ = 2.7 ppm).

2-[(1R,2S,4S)-7-benzyloxycarbonyl-7-azabicyclo[2.2.1]heptan-2-yl]-

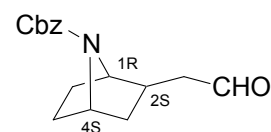
methoxyethene (7): To a solution of methoxymethyltriphenylphosphonium chloride ($\text{Ph}_3\text{PCH}_2\text{OCH}_3\cdot\text{Cl}$, 4.49 g, 13.1 mmol, 2.0 eq.) in THF (60 mL) at -50



$^{\circ}\text{C}$, was slowly added NaHMDS solution (2.0 M in THF, 6.5 mL, 13.1 mmol, 2.0 eq.). After stirred at -50 $^{\circ}\text{C}$ for 30 min, the yellow solution became an orange solution. To the ylide solution at -50 $^{\circ}\text{C}$, was slowly added an aldehyde **6** (1.700 g, 6.556 mmol, 1.0 eq.) solution in THF (20 mL). The reaction mixture was allowed to be stirred at room temperature for 4 h. Upon completion of the reaction monitored by TLC analysis, the solution was concentrated under reduced pressure to a crude residue. The crude residue was partitioned with ether (75 mL) and water (75 mL). After separation of the organic layer, the resulting aqueous layer was extracted with ether (20 mL X5). The combined organic layers were dried over anhydrous Na_2SO_4 , and then concentrated under reduced pressure to give a crude product. Purification of the crude product by flash chromatography on silica gel, using EtOAc/n-Hex as the eluant, gave the titled product as a colorless oil (1.658 g, 5.769 mmol, 88%): $R_f = 0.59$, EtOAc/n-Hex = 1/2; $^1\text{H-NMR}$ (400 MHz, 25 $^{\circ}\text{C}$, CDCl_3 , δ): 1.28-1.50 (m, 3H), 1.62-1.78 (m, 3H), 2.17-2.23 (m, 0.6H), 2.70-2.76 (m, 0.4H), 3.35 (brs, 1.8H), 3.50 (s, 1.2H), 4.01 (d, $J = 16$ Hz, 1H), 4.18-4.34 (m, 1.5H), 4.59 (t, $J = 9.6$ Hz, 0.5H), 5.02-5.14 (m, 2H), 5.70 (d, $J = 6.0$ Hz, 0.4H), 6.27 (d, $J = 12.8$ Hz, 0.6H), 7.20-7.44 (m, 5H); $^{13}\text{C-NMR}$ (100 MHz, 25 $^{\circ}\text{C}$, CDCl_3 , δ): 28.7 (t, 4C), 37.8 (t), 40.0 (t), 41.9 (d, 2C), 55.2 (q), 55.7 (d), 55.8 (d), 59.1 (q), 61.5 (d), 62.0 (d), 66.17 (t), 66.21 (t), 106.6 (d), 110.7 (d), 127.44 (d, 2C), 127.46 (d, 2C), 127.51 (d), 127.56 (d), 128.04 (d, 2C), 128.09 (d, 2C), 136.6 (s, 2C), 144.7 (d), 146.2 (d), 155.2 (s, 2C); EI-HRMS (m/z): $[\text{M}]^+$ calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_3^+$, 287.1521; found, 287.1511 ($\Delta = 3.5$ ppm).

(-)-(1R,2S,4S)-7-benzyloxycarbonyl-7-azabicyclo[2.2.1]heptan-2-

ylacetaldehyde (8): To a solution of enol ether **7** (4.61 g, 16.0 mmol, 1.0 eq.) in THF (70 mL) in an ice bath, was slowly added HCl solution (1 M in THF, 16 mL).

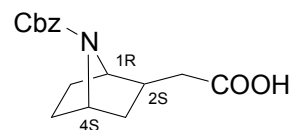


The reaction mixture was allowed to be stirred at room temperature for 2 h. Upon completion of the reaction monitored by TLC analysis, the reaction mixture was concentrated under reduced pressure to afford a residue. The crude residue was partitioned with EtOAc (40 mL) and water (40 mL). After separation of the organic layer, the resulting aqueous layer was extracted with EtOAc (15 mL X5). The combined organic layers were washed with saturated NaHCO_3 (55 mL), brine (15 mL), and dried over

anhydrous Na₂SO₄. After removal of the solid dehydrating agent, the organic layer was concentrated under reduced pressure to give a crude product. Purification of the crude product by flash chromatography on silica gel, using EtOAc/n-Hex as the eluant, gave the titled product as a colorless oil (4.02 g, 14.7 mmol, 92%): colorless oil, *R_f* = 0.33; EtOAc/n-Hex = 1/2; [α]_D²⁵ -1.8 (*c*: 1.0, CHCl₃); ¹H-NMR (400 MHz, 25 °C, CDCl₃, δ): 1.16-1.23 (m, 1H, H-3), 1.30 (t, *J* = 8.8 Hz, 1H, H-5), 1.40 (t, *J* = 8.8 Hz, 1H, H-6), 1.55-1.75 (m, 3H, H-3, H-5 and H-6), 2.04-2.11 (m, 1H, H-2), 2.19-2.26 (m, 1H, -CH₂CHO), 2.45 (br, 1H, -CH₂CHO), 3.94 (brs, 1H, H-1), 4.21 (brs, 1H, H-4), 4.99 (d, *J* = 12.4 Hz, 1H, -OCH₂Ph), 5.03 (d, *J* = 12.4 Hz, 1H, -OCH₂Ph), 7.18-7.24 (m, 1H, H-4 in Ph), 7.23-7.28 (m, 4H, H-2' and H-3' in Ph), 9.56 (s, 1H, -CHO); ¹³C-NMR (100 MHz, 25 °C, CDCl₃, δ): 28.6 (t, C-5), 28.7 (t, C-6), 36.4 (d, C-2), 37.2 (t, C-3), 49.4 (t, -CH₂CHO), 55.8 (d, C-4), 59.8 (d, C-1), 66.3 (t, OCH₂Ph), 127.5 (d, C-2 in Ph), 127.6 (d, C-4 in Ph), 128.1 (d, C-3 in Ph), 136.3 (s, C-1 in Ph), 155.2 (s, N-CO-O), 201.0 (d, -CH₂CHO); EI-HRMS (*m/z*): [M]⁺ calcd for C₁₆H₁₉NO₃⁺, 273.1365; found, 273.1361 (Δ = 1.5 ppm).

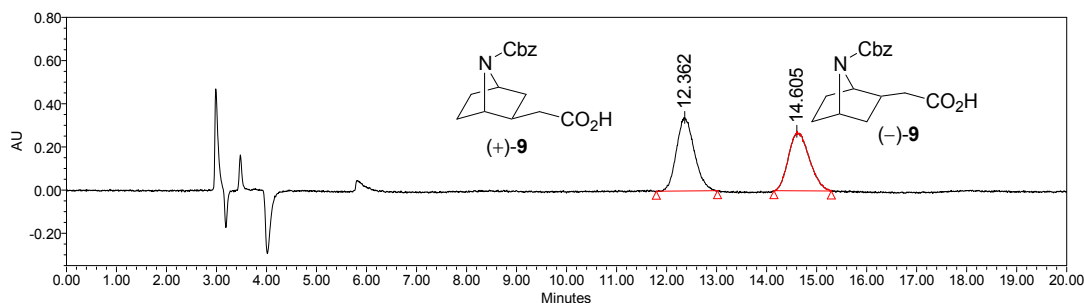
(-)-(1*R*,2*S*,4*S*)-7-benzyloxycarbonyl-7-azabicyclo[2.2.1]heptan-2-ylacetic acid (9):

To a solution of aldehyde **8** (171 mg, 0.626 mmol, 1.0 eq.) in acetone (1.3 mL) in an ice bath, was slowly added Jones' reagent (1.34 M, 600 μL, 0.8 mmol, 1.3 eq.). The reaction mixture was allowed to be stirred at the ice bath for 1 h. Upon completion of the reaction monitored by TLC analysis, IPA (1 mL) was added to quench the reaction, followed by addition of brine (2.0 mL) and CH₂Cl₂ (4 mL). The resulting aqueous solution was extracted with CH₂Cl₂ (2 mL X4). The combined organic layers were dried over anhydrous Na₂SO₄. After removal of the solid dehydrating agent, the organic layer was concentrated under reduced pressure to give a crude product. Purification of the crude product by flash chromatography on silica gel, using EtOAc/n-Hex/AcOH as the eluant, gave the titled product as a colorless oil (172 mg, 0.594 mmol, 95%): *R_f* = 0.23; EtOAc/n-Hex = 1/1; [α]_D²⁶ -5.9 (*c*: 1.0, CHCl₃); ¹H-NMR (400 MHz, 25 °C, CDCl₃, δ): 1.32-1.42 (m, 2H, H-3 and H-5), 1.46 (t, *J* = 8.8 Hz, 1H, H-6), 1.62-1.82 (m, 3H, H-3, H-5 and H-6), 2.04-2.11 (m, 1H, H-2), 2.09-2.24 (m, 1H, -CH₂COOH), 2.40 (br, 1H, -CH₂COOH), 4.12 (brs, 1H, H-1), 4.30 (brs, 1H, H-4), 5.09 (s, 2H, -OCH₂Ph), 7.24-7.35 (m, 5H in Ph), 8.60 (brs, 1H, -COOH); ¹³C-NMR (100 MHz, 25 °C, CDCl₃, δ): 28.8 (t, 2C, C-5 and C-6), 37.1 (t, C-3), 38.9 (d, C-2), 39.4 (t, -CH₂COOH), 56.1 (d, C-4), 60.0 (d, C-1), 66.8 (t, OCH₂Ph), 127.7 (d, C-2 in Ph), 127.8 (d, C-4 in Ph), 128.3 (d, C-3 in Ph), 136.4 (s,

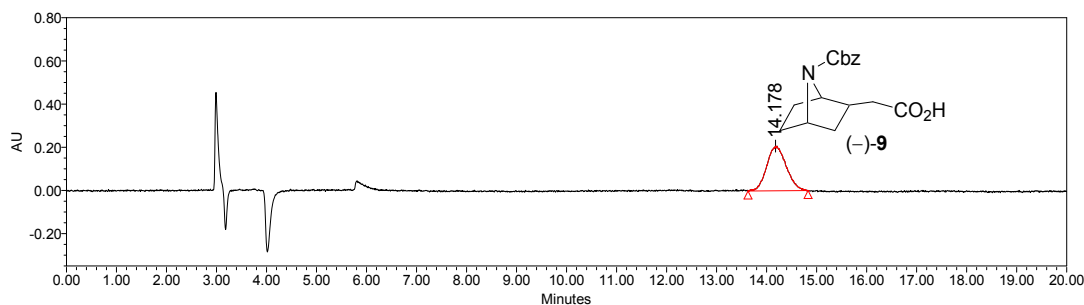


C-1 in Ph), 155.6 (s, N-CO-O), 177.3 (s, -CH₂COOH); EI-HRMS (m/z): [M]⁺ calcd for C₁₆H₁₉NO₄⁺, 289.1314; found, 289.1305 (Δ = 3.1 ppm).

HPLC condition: Chiralcel OD-H, 250 mm X 4.6 mm, 5 μm; Mobile phase A: 0.5% TFA in an IPA/n-Hex solution (v/v = 1/10); Mobile phase B: 0.5% TFA in pure n-Hex; isocratic, 70% A : 30% B; flow rate 1.0 mL per min; detection UV 215 nm, t_R: 12.4 min for (+)-**9**, 14.6 min for (-)-**9**.



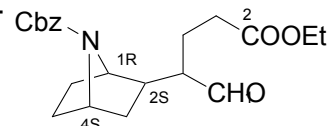
	Retention Time	Area	% Area	Height
1	12.362	8556779	50.53	342164
2	14.605	8378835	49.47	282511



Ethyl 4-[(1'R,2'S,4'S)-7-benzyloxycarbonyl-7-azabicyclo[2.2.1]heptan-2-yl]-

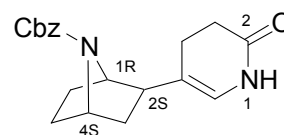
5-oxo-pentanoate(10): To a solution of aldehyde **9** (3.00 g, 11.0 mmol, 1.0 eq.) in CH₃CN (7.3 mL) in an ice bath, was slowly added

diethyltrimethylsilylamine (TMSNEt₂, 2.1 mL, 11.0 mmol, 1.0 eq.) and ethyl acrylate (1.8 mL, 16.5 mmol, 1.5 eq.). The reaction mixture was allowed to be refluxed for 13 h. Upon completion of the reaction monitored by TLC analysis, the reaction mixture was concentrated under reduced pressure to yield a residue. Purification of the crude residue product by flash chromatography on silica gel, using EtOAc/n-Hex as the eluant, gave the titled product glutarate semialdehyde **10** as a colorless oil (3.32 g,



8.89 mmol, 81%): R_f = 0.23; EtOAc/n-Hex = 1/3; $^1\text{H-NMR}$ (400 MHz, 25 °C, CDCl_3 , δ): 1.13 (t, J = 7.2 Hz, 3H), 1.26-1.42 (m, 2.5H), 1.42-1.57 (m, 1.5H), 1.58-1.76 (m, 3H), 1.78-1.90 (m, 2H), 2.00-2.24 (m, 3H), 4.00 (dd, J = 7.2, 14.4 Hz, 2H), 4.03-4.10 (m, 0.5H), 4.21 (br, 1.5H), 4.94-5.04 (m, 2H), 7.17-7.20 (m, 1H), 7.21-7.27 (m, 4H), 9.44 (s, 0.5H), 9.54 (brs, 0.5H); $^{13}\text{C-NMR}$ (100 MHz, 25 °C, CDCl_3 , δ): 13.8 (q, 2C), 21.4 (t), 22.2 (t), 28.6-29.3 (t, 4C), 30.9 (t), 31.0 (t), 34.9 (t, 2C), 42.8 (d, 2C), 54.4 (d), 54.8 (d), 55.7 (d), 56.0 (d), 57.7 (d), 58.1 (d), 60.11 (t), 60.14 (t), 66.36 (t), 60.39 (t), 127.52 (d, 2C), 127.55 (d, 2C), 127.65 (d), 127.66 (d), 128.09 (d, 2C), 128.11 (d, 2C), 136.27 (s), 136.28 (s), 150 (s, 2C), 172.26 (s), 172.31 (s), 203.0 (d), 203.4 (d); ESI-HRMS (m/z): $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{21}\text{H}_{27}\text{NO}_5\cdot\text{H}]^+$, 374.1967; found, 374.1969 (Δ = 0.5 ppm).

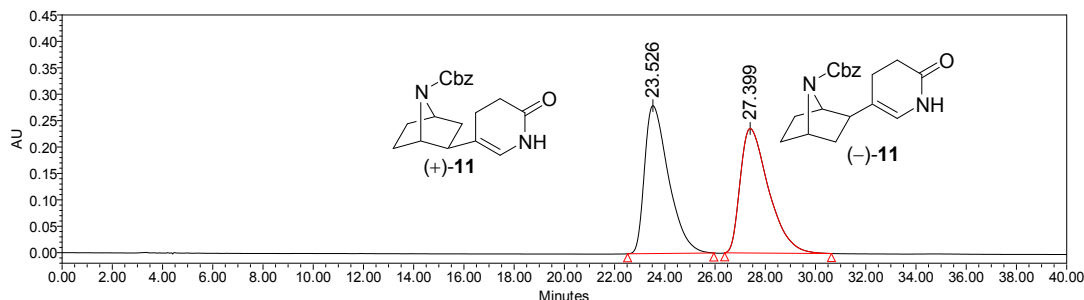
(-)-5-[(1'R,2'S,4'S)-7-benzyloxycarbonyl-7-azabicyclo[2.2.1]heptan-2-yl]-



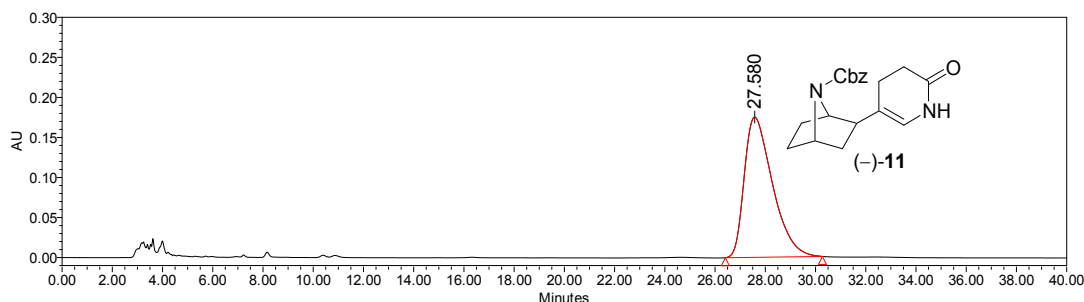
3,4-dihydropyrid-2-one (11): To a solution of glutarate semialdehyde **10** (350 mg, 0.937 mmol, 1.0 eq.) in benzene (1.0 mL) in an ice bath, was slowly added

ammonium acetate (87 mg, 1.13 mmol, 1.2 eq.) and acetic acid (80 μL , 1.40 mmol, 1.5 eq). The reaction mixture was allowed to be refluxed for 2.5 h. Upon completion of the reaction monitored by TLC analysis, a NaHCO_3 solution (5%, 4 mL) was added to quench the reaction at the ice bath, followed by addition of brine (5 mL) and ether (5 mL). The resulting aqueous solution was extracted with ether (3 mL X5). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4 , and then concentrated under reduced pressure to give a crude product. Purification of the crude product by flash chromatography on silica gel, using $\text{MeOH}/\text{CH}_2\text{Cl}_2$ as the eluant, gave the titled product as a white solid (287 mg, 0.879 mmol, 93%): mp 127-128 °C, R_f = 0.33; $\text{MeOH}/\text{CH}_2\text{Cl}_2$ = 1/10; $[\alpha]_{\text{D}}^{25}$ -1.3° (c : 1.0, CHCl_3); $^1\text{H-NMR}$ (400 MHz, 25 °C, CDCl_3 , δ): 1.36-1.46 (m, 2H, H-5 and H-6), 1.58-1.66 (m, 2H, H-3), 1.72 (brs, 2H, H-5 and H-6), 2.18 (brs, 2H, H-4 in pyridone), 2.27 (t, J = 6.8 Hz, 1H, H-2), 2.28-2.38 (m, 2H, H-3 in pyridone), 4.04-4.20 (m, 1H, H-1), 4.32 (brs, 1H, H-4), 4.98-5.08 (m, 2H, $-\text{OCH}_2\text{Ph}$), 5.78 (brs, 1H, H-6 in pyridone), 7.22-7.34 (m, 5H, -Ph), 7.93 (s, 1H, -NH); $^{13}\text{C-NMR}$ (100 MHz, 25 °C, CDCl_3 , δ): 22.5 (t, C-4 in pyridone), 28.9 (t, 2C, C-5 and C-6), 30.1 (t, C-3 in pyridone), 35.9 (t, C-3), 46.2 (d, C-2), 55.6 (d, C-4), 59.5 (d, C-1), 66.5 (t, OCH_2Ph), 119.4 (d, C-6 in pyridone), 119.7 (s, C-5 in pyridone), 127.8 (d, C-2 in Ph), 127.9 (d, C-4 in Ph), 128.3 (d, C-3 in Ph), 136.5 (s, C-1 in Ph), 154.6 (s, N-CO-O), 171.1 (s, C-2 in pyridone); EI-HRMS (m/z): $[\text{M}]^+$ calcd for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_3^+$, 326.1630; found, 326.1631 (Δ = 0.3 ppm).

HPLC condition: Chiralcel OD-H, 250 mm X 4.6 mm, 5 μ m; Mobile phase A: IPA : n-Hex = 1 : 4 (v/v); Mobile phase B: pure n-Hex; isocratic, 70% A : 30% B; flow rate 1.0 mL per min; detection UV 258 nm, t_R : 23.5 min for (+)-**11**, 27.4 min for (-)-**11**.

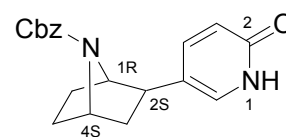


	Retention Time	Area	% Area	Height
1	23.526	18534751	50.10	280066
2	27.399	18460616	49.90	235872



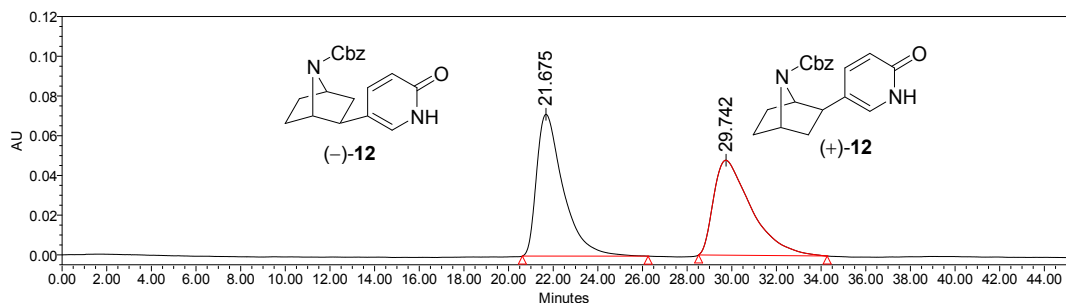
(+)-5-[(1'R,2'S,4'S)-7-benzyloxycarbonyl-7-azabicyclo[2.2.1]heptan-2-yl]-2-pyridine (12):

To a solution of dihydropyridone **11** (245 mg, 0.751 mmol, 1.0 eq.) in benzene (3.7 mL), was added MnO_2 (65 mg, 0.75 mmol, 1.0 eq.). The reaction mixture was allowed to be refluxed for 13 h. Additional MnO_2 was added in 65 mg portions every hour until total amount reaches to 9.0 equivalent. Upon completion of the reaction monitored by TLC analysis, the reaction mixture was filtered with a celite pad to yield a filtrate. The filtrate was concentrated under reduced pressure to give a crude residue. Purification of the crude product by flash chromatography on silica gel, using $\text{MeOH}/\text{CH}_2\text{Cl}_2$ as the eluant to give the titled product as a yellow solid (220 mg, 0.678 mmol, 90%): mp 78-80 $^\circ\text{C}$, $R_f = 0.24$; $\text{MeOH}/\text{CH}_2\text{Cl}_2 = 1/10$; $[\alpha]_D^{23} +21.9$ (c : 1.0, CHCl_3); $^1\text{H-NMR}$ (400 MHz, 25 $^\circ\text{C}$, CDCl_3 , δ): 1.40-1.56 (m, 2H, H-5 and H-6), 1.66-1.80 (m, 3H, H-3,

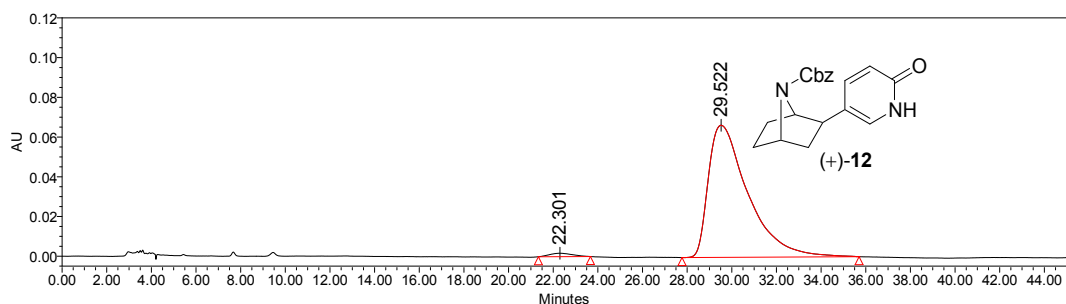


H-5 and H-6), 1.88 (dd, $J = 9.2$ and 12.0 Hz, 1H, H-3 endo), 2.61 (dd, $J = 4.4$ and 8.0 Hz, 1H, H-2), 4.14 (brs, 1H, H-1), 4.39 (brs, 1H, H-4), 5.06 (s, 2H, $-\text{OCH}_2\text{Ph}$), 6.46 (d, $J = 9.2$ Hz, 1H, H-3 in pyridone), 7.18 (s, 1H, H-6 in pyridone), 7.29 (brs, 5H -Ph), 7.40 (d, $J = 9.2$ Hz, 1H, H-4 in pyridone), 13.3 (s, 1H, -NH); ^{13}C -NMR (100 MHz, 25 °C, CDCl_3 , δ): 28.8 (t, C-5), 30.8 (t, C-6), 39.3 (t, C-3), 44.4 (d, C-2), 56.0 (d, C-4), 62.0 (d, C-1), 66.8 (t, OCH_2Ph), 120.1 (d, C-3 in pyridone), 124.0 (s, C-5 in pyridone), 127.8 (d, C-2 in Ph), 127.9 (d, C-4 in Ph), 128.4 (d, C-3 in Ph), 131.5 (d, C-6 in pyridone), 136.4 (s, C-1 in Ph), 141.7 (d, C-4 in pyridone), 155.3 (s, $\text{N}-\text{CO}-\text{O}$), 164.6 (s, C-2 in pyridone); EI-HRMS (m/z): $[\text{M}]^+$ calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_3^+$, 324.1474; found, 324.1480 ($\Delta = 1.9$ ppm).

HPLC condition: Chiralcel OD-H, 250 mm X 4.6 mm, 5 μm ; Mobile phase A: IPA : n-Hex = 1 : 4 (v/v); Mobile phase B: pure n-Hex; isocratic, 80% A : 20% B; flow rate 1.0 mL per min; detection UV 310 nm, t_{R} : 21.7 min for (-)-**12**, 29.7 min for (+)-**12**.



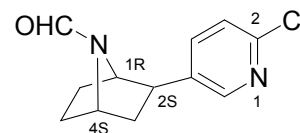
	Retention Time	Area	% Area	Height
1	21.675	5894555	51.26	71377
2	29.742	5603737	48.74	47797



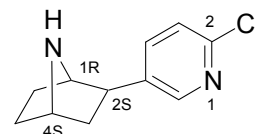
	Retention Time	Area	% Area	Height
1	22.301	123305	1.48	1727
2	29.522	8210735	98.52	66521

5-[(1'R,2'S,4'S)-7-formyl-7-azabicyclo[2.2.1]heptan-2-yl]-2-chloropyridine

(13): To a mixture of pyridone **12** (190 mg, 0.586 mmol, 1.0 eq.) and DMF (300 μ L, 3.87 mmol, 6.6 eq.) in an ice bath, was slowly added POCl₃ (300 μ L, 3.22 mmol, 5.5 eq.). The reaction mixture was allowed to be stirred at 80 °C for 8.5 h. Upon completion of the reaction monitored by TLC analysis, chilled CH₂Cl₂ (1 mL) was added. The reaction mixture was transferred to a chilled biphasic solution of NaOH (1 N, 5 mL) and CH₂Cl₂ (5 mL). The pH value was controlled in the range of 9~10. The aqueous solution was extracted with CH₂Cl₂ (4 mL X5). The combined organic layers were dried over anhydrous Na₂SO₄ and then concentrated under reduced pressure to give a crude product. Purification of the crude product by flash chromatography on silica gel, using MeOH/CH₂Cl₂/Et₃N as the eluant to give the titled product as a yellow oil (101 mg, 0.427 mmol, 73%): R_f = 0.43; MeOH/CH₂Cl₂ = 1/20; ¹H-NMR (400 MHz, 25 °C, CDCl₃, δ): ² 1.55-1.90 (m, 10H), 2.06 (dd, J = 8.8 and 12.4 Hz, 1H), 2.15 (dd, J = 9.2 and 12.4 Hz, 1H), 2.99 (t, J = 4.0 Hz, 1H), 3.01 (t, J = 4.0 Hz, 1H), 3.89 (d, J = 4.0 Hz, 1H), 4.27 (t, J = 4.4 Hz, 1H), 4.61 (d, J = 4.4 Hz, 1H), 4.78 (t, J = 4.8 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H), 7.43 (dd, J = 2.4 and 8.8 Hz, 1H), 7.53 (dd, J = 2.8 and 8.8 Hz, 1H), 7.99 (s, 1H), 8.16 (d, J = 2.0 Hz, 1H), 8.17 (s, 1H), 8.19 (d, J = 2.0 Hz, 1H); ¹³C-NMR (100 MHz, 25 °C, CDCl₃, δ): 28.2 (t), 29.1 (t), 29.8 (t), 30.7 (t), 38.7 (t), 41.2 (t), 44.1 (d), 44.8 (d), 51.6 (d), 55.3 (d), 56.6 (d), 61.8 (d), 124.2 (d), 124.4 (d), 136.4 (d), 136.8 (d), 138.5 (s), 139.0 (s), 148.4 (d), 148.7 (d), 149.4 (s), 149.8 (s), 157.2 (d), 157.6 (d). EI-HRMS (m/z): [M]⁺ calcd for C₁₂H₁₃ClN₂O⁺, 236.0716; found, 236.0712 (Δ = 1.7 ppm).

**(-)-5-[(1'R,2'S,4'S)-7-azabicyclo[2.2.1]heptan-2-yl]-2-chloropyridine**

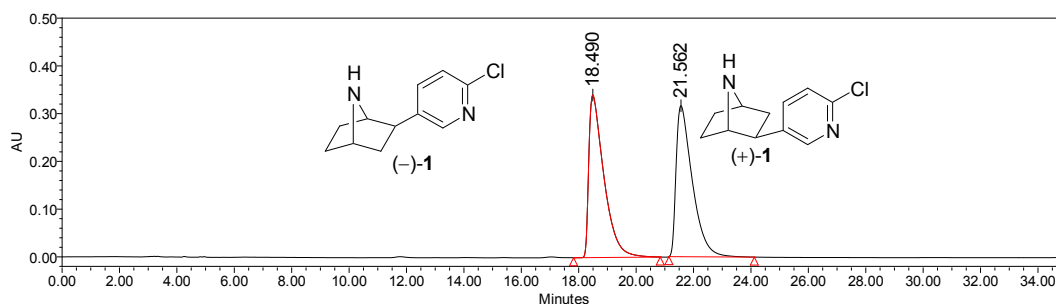
(epibatidine, 1): To a solution of formamide **13** (107 mg, 0.452 mmol, 1.0 eq.) in MeOH (0.4 mL) in an ice bath, was slowly added HCl in methanol solution (5%, 0.6 mL). The reaction mixture was allowed to be stirred at 60 °C for 2 h. Upon completion of the reaction monitored by TLC analysis, chilled CH₂Cl₂ (1 mL) was added. The reaction mixture was transferred to a chilled biphasic solution of K₂CO₃ (10%, 8 mL) and CH₂Cl₂ (5 mL). The pH value was controlled in the range of 9~10. The aqueous solution was extracted with CH₂Cl₂ (3 mL X5). The combined organic layers were dried over anhydrous Na₂SO₄ and then concentrated under reduced pressure to give a crude product. Purification of the crude product by flash chromatography on silica gel,



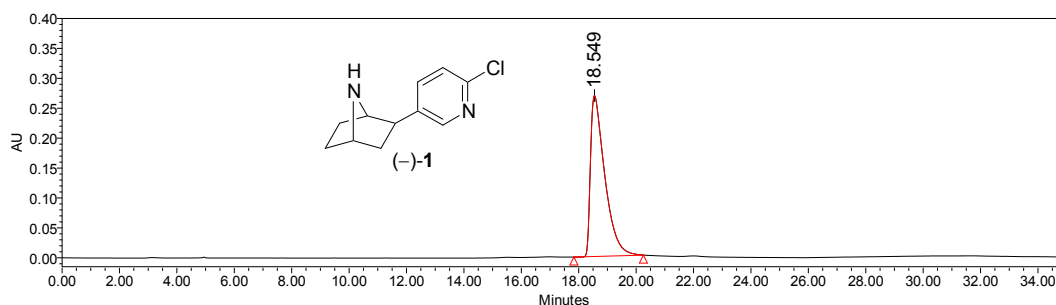
² The product appears as an equal amount of E/Z mixture.

using MeOH/CH₂Cl₂/NEt₃ as the eluant to give the titled product as a yellow oil (87 mg, 0.417 mmol, 92%): $R_f = 0.15$; MeOH/CH₂Cl₂/NEt₃ = 1/20/0.2; $[\alpha]_D^{25} -6.8$ ($c: 1.0$, CHCl₃), [lit.³ $[\alpha]_D^{25} -6.5$ ($c: 1.0$, CHCl₃)]; ¹H-NMR (400 MHz, 25 °C, CDCl₃, δ): 1.42-1.55 (m, 5H, H-3, H-5 X2 and H-6 X2), 1.69 (s, 1H, NH), 1.83 (dd, $J = 8.8$ and 12.0 Hz, 1H, H-3 endo), 2.69 (dd, $J = 4.4$ and 8.8 Hz, 1H, H-2), 3.48 (brs, 1H, H-1), 3.72 (t, $J = 4.0$ Hz, 1H, H-4), 7.15 (d, $J = 8.4$ Hz, 1H, H-3 in pyridine), 7.70 (dd, $J = 2.4$ and 8.0 Hz, 1H, H-4 in pyridine), 8.20 (d, $J = 2.4$ Hz, 1H, H-6 in pyridine); ¹³C-NMR (100 MHz, 25 °C, CDCl₃, δ): 30.0 (t, C-5), 31.2 (t, C-6), 40.2 (t, C-3), 44.3 (d, C-2), 56.0 (d, C-4), 62.6 (d, C-1), 123.7 (d, C-3 in pyridine), 137.6 (d, C-4 in pyridine), 141.0 (s, C-5 in pyridine), 148.6 (d, C-6 in pyridine), 148.7 (s, C-2 in pyridine). EI-HRMS (m/z): $[M]^+$ calcd for C₁₁H₁₃ClN₂⁺, 208.0767; found, 208.0763 ($\Delta = 1.9$ ppm).

HPLC condition: Chiralcel OD-H, 250 mm X 4.6 mm, 5 μ m; Mobile phase A: 0.1% Et₂NH in an IPA/n-Hex solution ($v/v = 1/15$); Mobile phase B: pure n-Hex; isocratic, 50% A : 50% B; flow rate 1.0 mL per min; detection UV 274 nm, t_R : 18.5 min for (-)-**1**, 21.6 min for (+)-**1**.

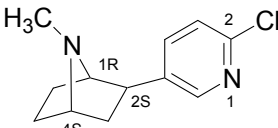


	Retention Time	Area	% Area	Height
1	18.490	12450854	50.11	340284
2	21.562	12396237	49.89	316282

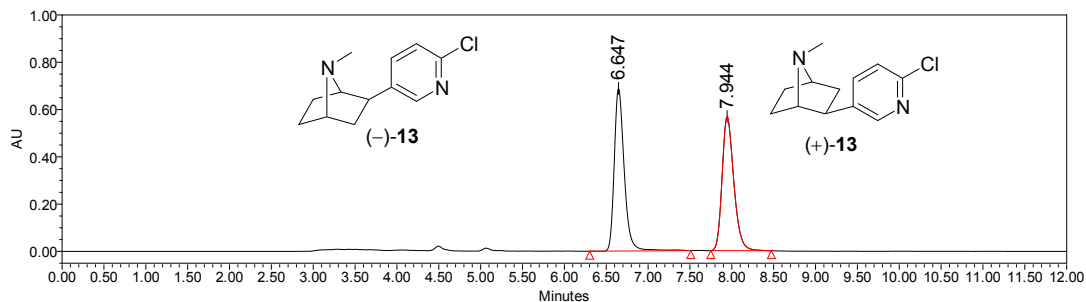


³ Fletcher, S. R.; Baker, R.; Chambers, M. S.; Herbert, R. H.; Hobbs, S. C.; Thomas, S. R.; Verrier, H. M.; Watt, A. P.; Ball, R. G. *J. Org. Chem.* **1994**, *59*, 1771.

(+)-5-[(1'R,2'S,4'S)-7-methyl-7-azabicyclo[2.2.1]heptan-2-yl]-2-

chloropyridine: (*N*-methyl-epibatidine, **14):** To a THF solution (2 mL) of  LiAlH₄ (72 mg, 1.90 mmol, 5.0 eq.) and Et₃N•HCl (262 mg, 1.90 mmol, 5.0 eq.) in an ice bath, was slowly added a solution of formamide **13** (90 mg, 0.380 mmol, 1.0 eq.) in THF (2 mL). The reaction mixture was allowed to be stirred at room temperature overnight. Upon completion of the reaction monitored by TLC analysis, chilled CH₂Cl₂ (1 mL) was added, followed by slow addition of a NaOH solution (10%, 1.5 mL). The reaction mixture was allowed to be stirred for another 10 min until white precipitate has been settled down. After separation of the precipitate, the filtrate was concentrated under reduced pressure to give a crude product. Purification of the crude product by flash chromatography on silica gel, using MeOH/CH₂Cl₂/NEt₃ as the eluant to give the titled product as a yellow solid (64 mg, 0.287 mmol, 76%): mp 76-78 °C, *R*_f = 0.28; MeOH/CH₂Cl₂ = 1/20; [α]_D²⁵ +18.5 (*c*: 1.0, CHCl₃); ¹H-NMR (400 MHz, 25 °C, CDCl₃, δ): 1.34-1.44 (m, 2H, H-5 and H-6), 1.58-1.66 (m, 1H, H-3), 1.80 (dd, *J* = 9.6 and 11.6 Hz, 1H, H-3 endo), 1.84-1.94 (m, 2H, H-5 and H-6), 2.21 (s, 3H, NCH₃) 2.61 (dd, *J* = 4.8 and 9.2 Hz, 1H, H-2), 3.09 (d, *J* = 4.0 Hz, 1H, H-1), 3.29 (t, *J* = 4.0 Hz, 1H, H-4), 7.17 (d, *J* = 8.4 Hz, 1H, H-3 in pyridine), 7.85 (dd, *J* = 2.0 and 8.0 Hz, 1H, H-4 in pyridine), 8.25 (d, *J* = 2.0 Hz, 1H, H-6 in pyridine); ¹³C-NMR (100 MHz, 25 °C, CDCl₃, δ): 25.4 (t, C-5), 26.3 (t, C-6), 34.5 (q, NCH₃), 41.5 (t, C-3), 45.3 (d, C-2), 61.1 (d, C-4), 67.4 (d, C-1), 123.6 (d, C-3 in pyridine), 138.0 (d, C-4 in pyridine), 141.7 (s, C-5 in pyridine), 148.6 (s, C-2 in pyridine), 148.8 (d, C-6 in pyridine); EI-HRMS (*m/z*): [M]⁺ calcd for C₁₂H₁₅ClN₂⁺, 222.0924; found, 222.0927 (Δ = 1.4 ppm).

HPLC condition: Chiralcel OD-H, 250 mm X 4.6 mm, 5 μ m; Mobile phase A: 0.1% Et₂NH in an IPA/n-Hex solution (v/v = 1/15); Mobile phase B: pure n-Hex; isocratic, 50% A : 50% B; flow rate 1.0 mL per min; detection UV 273 nm, t_R : 6.6 min for (-)-**14**, 7.9 min for (+)-**14**.



	Retention Time	Area	% Area	Height
1	6.647	5701753	50.89	687950
2	7.944	5502199	49.11	567187

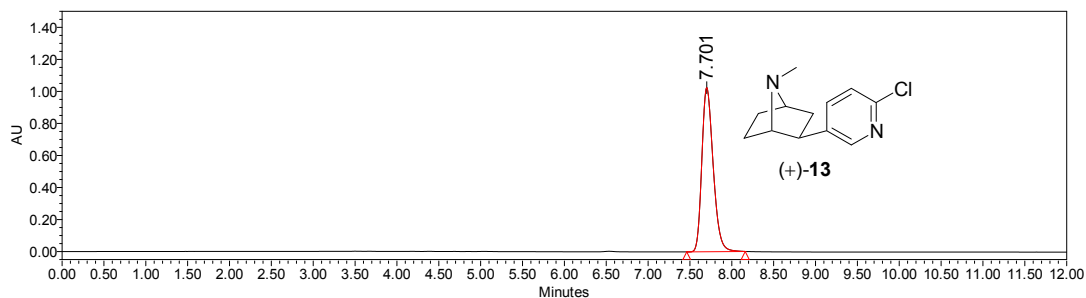


Table 1. Crystal data and structure refinement for **4a**.

Identification code	corn	
Empirical formula	C ₂₅ H ₂₆ N ₂ O ₅	
Formula weight	434.48	
Temperature	150(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 8.2328(2) Å	α = 90°.
	b = 12.2627(2) Å	β = 90°.
	c = 21.8139(4) Å	γ = 90°.
Volume	2202.25(8) Å ³	
Z	4	
Density (calculated)	1.310 Mg/m ³	
Absorption coefficient	0.750 mm ⁻¹	
F(000)	920	
Crystal size	0.42 x 0.40 x 0.32 mm ³	
Theta range for data collection	4.05 to 72.34°.	
Index ranges	-9 ≤ h ≤ 10, -9 ≤ k ≤ 14, -26 ≤ l ≤ 19	
Reflections collected	8398	
Independent reflections	4239 [R(int) = 0.0196]	
Completeness to theta = 72.34°	98.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.96097	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	4239 / 0 / 290	
Goodness-of-fit on F ²	1.013	
Final R indices [I > 2σ(I)]	R1 = 0.0315, wR2 = 0.0839	
R indices (all data)	R1 = 0.0338, wR2 = 0.0855	
Absolute structure parameter	0.07(15)	
Extinction coefficient	0.0038(3)	
Largest diff. peak and hole	0.180 and -0.142 e.Å ⁻³	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **4a**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
O(1)	2288(1)	3644(1)	1364(1)	26(1)
O(2)	2368(2)	5290(1)	896(1)	35(1)
O(3)	-1037(2)	4695(1)	1840(1)	34(1)
O(4)	-2567(1)	1506(1)	1442(1)	34(1)
O(5)	-1535(1)	1229(1)	2374(1)	30(1)
N(1)	814(2)	3901(1)	517(1)	26(1)
N(2)	-1493(2)	2929(1)	2029(1)	22(1)
C(1)	3336(2)	3584(1)	2921(1)	28(1)
C(2)	3513(2)	2840(2)	3397(1)	36(1)
C(3)	3954(2)	1777(2)	3272(1)	38(1)
C(4)	4207(2)	1449(1)	2671(1)	35(1)
C(5)	4028(2)	2185(1)	2197(1)	30(1)
C(6)	3593(2)	3263(1)	2318(1)	24(1)
C(7)	3430(2)	4074(1)	1807(1)	28(1)
C(8)	1842(2)	4368(1)	924(1)	25(1)
C(9)	-308(2)	3000(1)	660(1)	25(1)
C(10)	-819(2)	2646(2)	13(1)	35(1)
C(11)	-787(2)	3734(2)	-351(1)	42(1)
C(12)	-328(2)	4563(2)	145(1)	33(1)
C(13)	-1773(2)	4705(1)	587(1)	35(1)
C(14)	-1767(2)	3626(1)	956(1)	25(1)
C(15)	-1430(2)	3820(1)	1632(1)	24(1)
C(16)	-1930(2)	1860(1)	1896(1)	25(1)
C(17)	-576(2)	1844(1)	2814(1)	28(1)
C(18)	-913(2)	3038(1)	2662(1)	21(1)
C(19)	-2158(2)	3584(1)	3084(1)	25(1)
C(20)	-1453(2)	3702(1)	3719(1)	23(1)
C(21)	-1849(2)	2978(1)	4182(1)	36(1)
C(22)	-1079(3)	3033(2)	4746(1)	45(1)
C(23)	100(2)	3816(2)	4854(1)	40(1)
C(24)	483(2)	4552(1)	4400(1)	36(1)
C(25)	-289(2)	4497(1)	3834(1)	29(1)

Table 3. Bond lengths [\AA] and angles [$^\circ$] for **4a**.

O(1)-C(8)	1.3570(17)
O(1)-C(7)	1.4491(17)
O(2)-C(8)	1.2122(18)
O(3)-C(15)	1.2094(18)
O(4)-C(16)	1.2020(18)
O(5)-C(16)	1.3390(18)
O(5)-C(17)	1.4548(18)
N(1)-C(8)	1.356(2)
N(1)-C(9)	1.4725(19)
N(1)-C(12)	1.4829(19)
N(2)-C(16)	1.3903(18)
N(2)-C(15)	1.3959(18)
N(2)-C(18)	1.4677(17)
C(1)-C(2)	1.389(2)
C(1)-C(6)	1.391(2)
C(1)-H(1A)	0.9500
C(2)-C(3)	1.381(3)
C(2)-H(2A)	0.9500
C(3)-C(4)	1.387(2)
C(3)-H(3A)	0.9500
C(4)-C(5)	1.379(2)
C(4)-H(4A)	0.9500
C(5)-C(6)	1.394(2)
C(5)-H(5A)	0.9500
C(6)-C(7)	1.499(2)
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(9)-C(10)	1.535(2)
C(9)-C(14)	1.5650(19)
C(9)-H(9A)	1.0000
C(10)-C(11)	1.552(3)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(11)-C(12)	1.533(2)
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-C(13)	1.541(2)
C(12)-H(12A)	1.0000
C(13)-C(14)	1.549(2)
C(13)-H(13A)	0.9900
C(13)-H(13B)	0.9900
C(14)-C(15)	1.520(2)
C(14)-H(14A)	1.0000
C(17)-C(18)	1.526(2)
C(17)-H(17A)	0.9900
C(17)-H(17B)	0.9900

C(18)-C(19)	1.5310(19)
C(18)-H(18A)	1.0000
C(19)-C(20)	1.5089(19)
C(19)-H(19A)	0.9900
C(19)-H(19B)	0.9900
C(20)-C(21)	1.384(2)
C(20)-C(25)	1.390(2)
C(21)-C(22)	1.386(2)
C(21)-H(21A)	0.9500
C(22)-C(23)	1.385(3)
C(22)-H(22A)	0.9500
C(23)-C(24)	1.376(3)
C(23)-H(23A)	0.9500
C(24)-C(25)	1.390(2)
C(24)-H(24A)	0.9500
C(25)-H(25A)	0.9500

C(8)-O(1)-C(7)	114.11(11)
C(16)-O(5)-C(17)	110.24(11)
C(8)-N(1)-C(9)	124.73(12)
C(8)-N(1)-C(12)	121.51(13)
C(9)-N(1)-C(12)	97.42(12)
C(16)-N(2)-C(15)	128.16(12)
C(16)-N(2)-C(18)	111.53(11)
C(15)-N(2)-C(18)	120.08(11)
C(2)-C(1)-C(6)	120.38(15)
C(2)-C(1)-H(1A)	119.8
C(6)-C(1)-H(1A)	119.8
C(1)-C(2)-C(3)	119.98(16)
C(1)-C(2)-H(2A)	120.0
C(3)-C(2)-H(2A)	120.0
C(4)-C(3)-C(2)	120.02(16)
C(4)-C(3)-H(3A)	120.0
C(2)-C(3)-H(3A)	120.0
C(3)-C(4)-C(5)	120.12(16)
C(3)-C(4)-H(4A)	119.9
C(5)-C(4)-H(4A)	119.9
C(4)-C(5)-C(6)	120.45(15)
C(4)-C(5)-H(5A)	119.8
C(6)-C(5)-H(5A)	119.8
C(1)-C(6)-C(5)	119.06(14)
C(1)-C(6)-C(7)	120.10(14)
C(5)-C(6)-C(7)	120.83(14)
O(1)-C(7)-C(6)	108.18(12)
O(1)-C(7)-H(7A)	110.1
C(6)-C(7)-H(7A)	110.1
O(1)-C(7)-H(7B)	110.1
C(6)-C(7)-H(7B)	110.1
H(7A)-C(7)-H(7B)	108.4

O(2)-C(8)-O(1)	123.41(14)
O(2)-C(8)-N(1)	125.70(14)
O(1)-C(8)-N(1)	110.81(13)
N(1)-C(9)-C(10)	100.91(12)
N(1)-C(9)-C(14)	101.60(11)
C(10)-C(9)-C(14)	107.89(12)
N(1)-C(9)-H(9A)	114.9
C(10)-C(9)-H(9A)	114.9
C(14)-C(9)-H(9A)	114.9
C(9)-C(10)-C(11)	102.87(13)
C(9)-C(10)-H(10A)	111.2
C(11)-C(10)-H(10A)	111.2
C(9)-C(10)-H(10B)	111.2
C(11)-C(10)-H(10B)	111.2
H(10A)-C(10)-H(10B)	109.1
C(12)-C(11)-C(10)	102.30(12)
C(12)-C(11)-H(11A)	111.3
C(10)-C(11)-H(11A)	111.3
C(12)-C(11)-H(11B)	111.3
C(10)-C(11)-H(11B)	111.3
H(11A)-C(11)-H(11B)	109.2
N(1)-C(12)-C(11)	100.29(13)
N(1)-C(12)-C(13)	102.10(11)
C(11)-C(12)-C(13)	109.03(15)
N(1)-C(12)-H(12A)	114.6
C(11)-C(12)-H(12A)	114.6
C(13)-C(12)-H(12A)	114.6
C(12)-C(13)-C(14)	103.06(13)
C(12)-C(13)-H(13A)	111.2
C(14)-C(13)-H(13A)	111.2
C(12)-C(13)-H(13B)	111.2
C(14)-C(13)-H(13B)	111.2
H(13A)-C(13)-H(13B)	109.1
C(15)-C(14)-C(13)	111.78(13)
C(15)-C(14)-C(9)	109.71(12)
C(13)-C(14)-C(9)	101.94(12)
C(15)-C(14)-H(14A)	111.0
C(13)-C(14)-H(14A)	111.0
C(9)-C(14)-H(14A)	111.0
O(3)-C(15)-N(2)	118.08(13)
O(3)-C(15)-C(14)	123.58(13)
N(2)-C(15)-C(14)	118.24(12)
O(4)-C(16)-O(5)	122.60(14)
O(4)-C(16)-N(2)	128.76(14)
O(5)-C(16)-N(2)	108.64(12)
O(5)-C(17)-C(18)	104.83(11)
O(5)-C(17)-H(17A)	110.8
C(18)-C(17)-H(17A)	110.8
O(5)-C(17)-H(17B)	110.8

C(18)-C(17)-H(17B)	110.8
H(17A)-C(17)-H(17B)	108.9
N(2)-C(18)-C(17)	100.15(10)
N(2)-C(18)-C(19)	112.71(11)
C(17)-C(18)-C(19)	114.25(12)
N(2)-C(18)-H(18A)	109.8
C(17)-C(18)-H(18A)	109.8
C(19)-C(18)-H(18A)	109.8
C(20)-C(19)-C(18)	109.56(11)
C(20)-C(19)-H(19A)	109.8
C(18)-C(19)-H(19A)	109.8
C(20)-C(19)-H(19B)	109.8
C(18)-C(19)-H(19B)	109.8
H(19A)-C(19)-H(19B)	108.2
C(21)-C(20)-C(25)	118.68(14)
C(21)-C(20)-C(19)	121.18(14)
C(25)-C(20)-C(19)	119.95(13)
C(20)-C(21)-C(22)	120.62(16)
C(20)-C(21)-H(21A)	119.7
C(22)-C(21)-H(21A)	119.7
C(23)-C(22)-C(21)	120.35(16)
C(23)-C(22)-H(22A)	119.8
C(21)-C(22)-H(22A)	119.8
C(24)-C(23)-C(22)	119.48(15)
C(24)-C(23)-H(23A)	120.3
C(22)-C(23)-H(23A)	120.3
C(23)-C(24)-C(25)	120.18(16)
C(23)-C(24)-H(24A)	119.9
C(25)-C(24)-H(24A)	119.9
C(20)-C(25)-C(24)	120.66(15)
C(20)-C(25)-H(25A)	119.7
C(24)-C(25)-H(25A)	119.7

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **4a**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
O(1)	27(1)	24(1)	27(1)	0(1)	-7(1)	-2(1)
O(2)	41(1)	30(1)	35(1)	7(1)	-1(1)	-8(1)
O(3)	53(1)	22(1)	26(1)	-1(1)	2(1)	-1(1)
O(4)	34(1)	34(1)	33(1)	-11(1)	-4(1)	-5(1)
O(5)	37(1)	21(1)	31(1)	0(1)	1(1)	-2(1)
N(1)	26(1)	31(1)	22(1)	1(1)	-1(1)	1(1)
N(2)	23(1)	22(1)	20(1)	-3(1)	0(1)	-1(1)
C(1)	18(1)	34(1)	32(1)	-6(1)	-2(1)	4(1)
C(2)	28(1)	53(1)	26(1)	1(1)	-1(1)	0(1)
C(3)	30(1)	44(1)	41(1)	16(1)	-6(1)	-5(1)
C(4)	30(1)	28(1)	47(1)	1(1)	-10(1)	2(1)
C(5)	24(1)	32(1)	33(1)	-5(1)	-2(1)	3(1)
C(6)	15(1)	30(1)	27(1)	-2(1)	-3(1)	0(1)
C(7)	27(1)	28(1)	29(1)	-1(1)	-7(1)	-5(1)
C(8)	24(1)	28(1)	23(1)	2(1)	3(1)	3(1)
C(9)	24(1)	30(1)	21(1)	-6(1)	-1(1)	0(1)
C(10)	28(1)	52(1)	25(1)	-15(1)	0(1)	-1(1)
C(11)	38(1)	70(1)	19(1)	-2(1)	-3(1)	4(1)
C(12)	34(1)	45(1)	21(1)	9(1)	-1(1)	6(1)
C(13)	36(1)	43(1)	25(1)	7(1)	-2(1)	14(1)
C(14)	23(1)	33(1)	20(1)	0(1)	-1(1)	6(1)
C(15)	24(1)	25(1)	22(1)	0(1)	2(1)	4(1)
C(16)	20(1)	26(1)	29(1)	-4(1)	4(1)	-3(1)
C(17)	32(1)	27(1)	26(1)	0(1)	-4(1)	2(1)
C(18)	19(1)	23(1)	19(1)	-1(1)	-1(1)	-2(1)
C(19)	20(1)	31(1)	24(1)	-2(1)	0(1)	1(1)
C(20)	23(1)	25(1)	21(1)	-4(1)	3(1)	2(1)
C(21)	49(1)	32(1)	25(1)	-2(1)	4(1)	-10(1)
C(22)	74(1)	36(1)	24(1)	3(1)	-2(1)	-1(1)
C(23)	48(1)	47(1)	26(1)	-10(1)	-10(1)	17(1)
C(24)	30(1)	42(1)	37(1)	-17(1)	-1(1)	-1(1)
C(25)	30(1)	28(1)	28(1)	-4(1)	5(1)	-3(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **4a**.

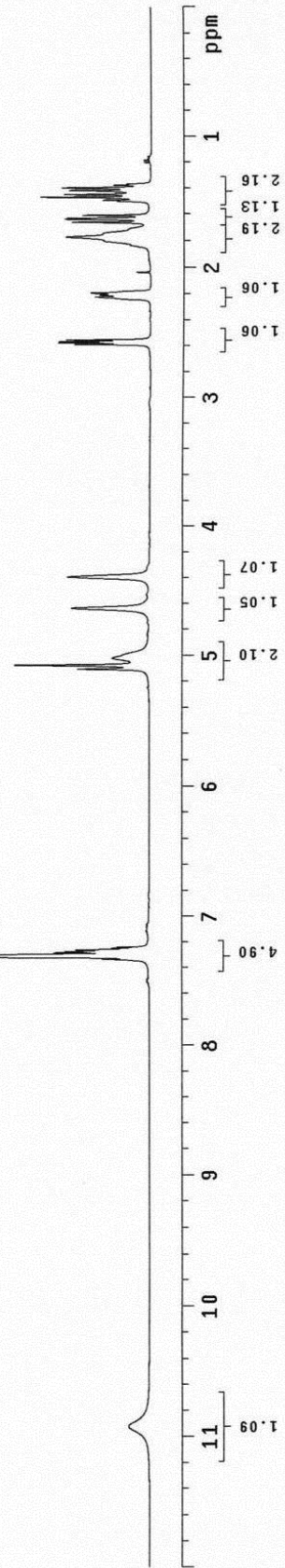
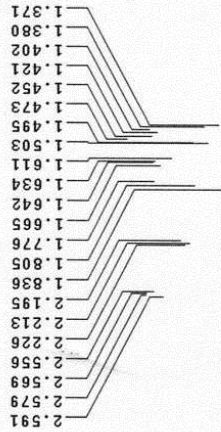
	x	y	z	U(eq)
H(1A)	3037	4316	3009	34
H(2A)	3331	3063	3808	43
H(3A)	4085	1270	3597	46
H(4A)	4505	717	2585	42
H(5A)	4202	1956	1786	35
H(7A)	3033	4779	1970	34
H(7B)	4499	4198	1611	34
H(9A)	164	2408	919	30
H(10A)	-1921	2323	14	42
H(10B)	-44	2112	-161	42
H(11A)	35	3713	-682	51
H(11B)	-1864	3899	-530	51
H(12A)	137	5261	-15	40
H(13A)	-2803	4797	359	42
H(13B)	-1611	5341	859	42
H(14A)	-2807	3218	897	30
H(17A)	594	1676	2769	34
H(17B)	-916	1673	3239	34
H(18A)	126	3460	2669	25
H(19A)	-2448	4311	2919	30
H(19B)	-3158	3137	3101	30
H(21A)	-2656	2438	4112	43
H(22A)	-1361	2531	5060	54
H(23A)	640	3844	5239	48
H(24A)	1276	5099	4474	44
H(25A)	-18	5008	3523	34

3 ¹H NMR

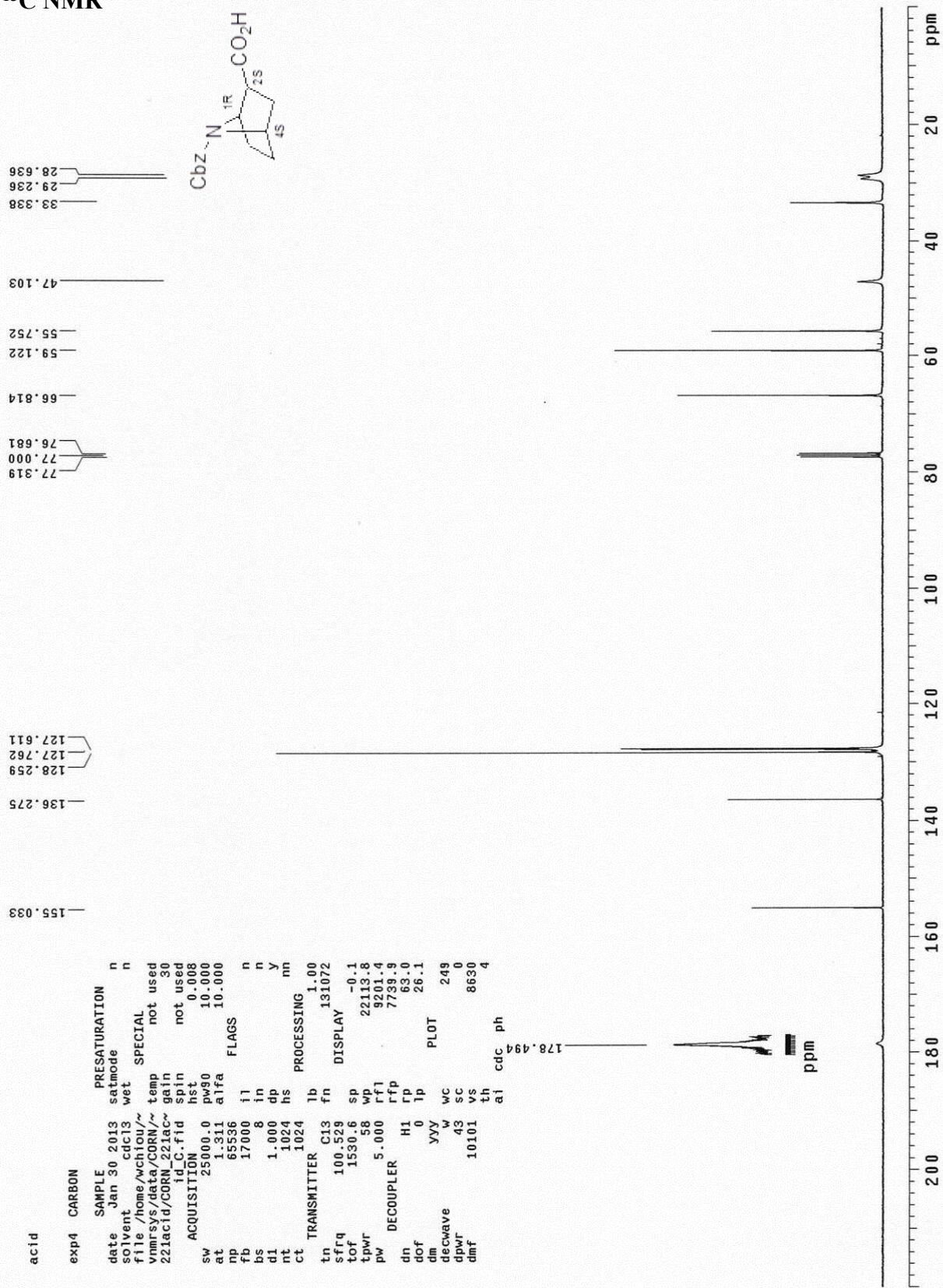
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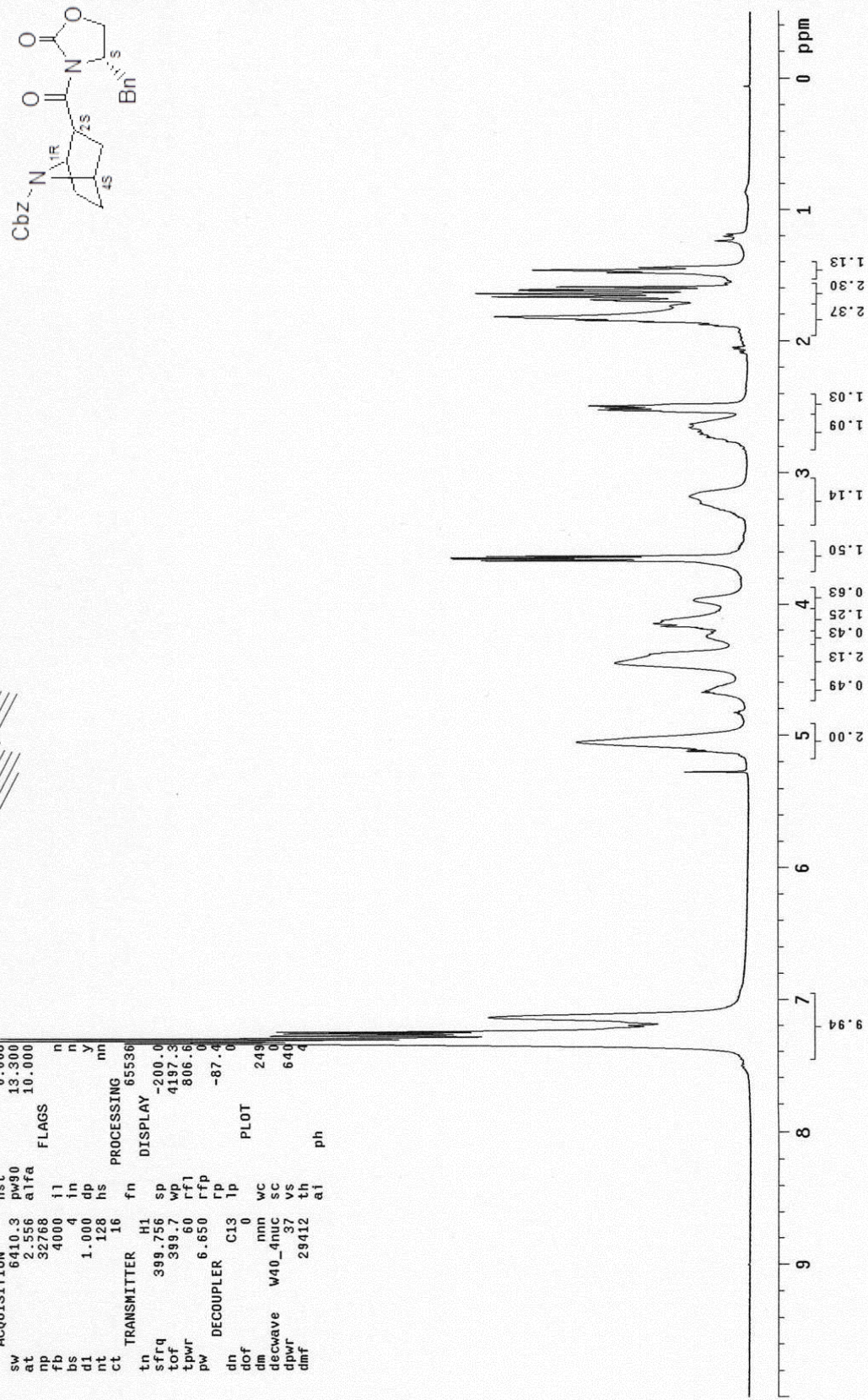
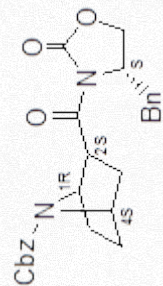


3 ¹³C NMR

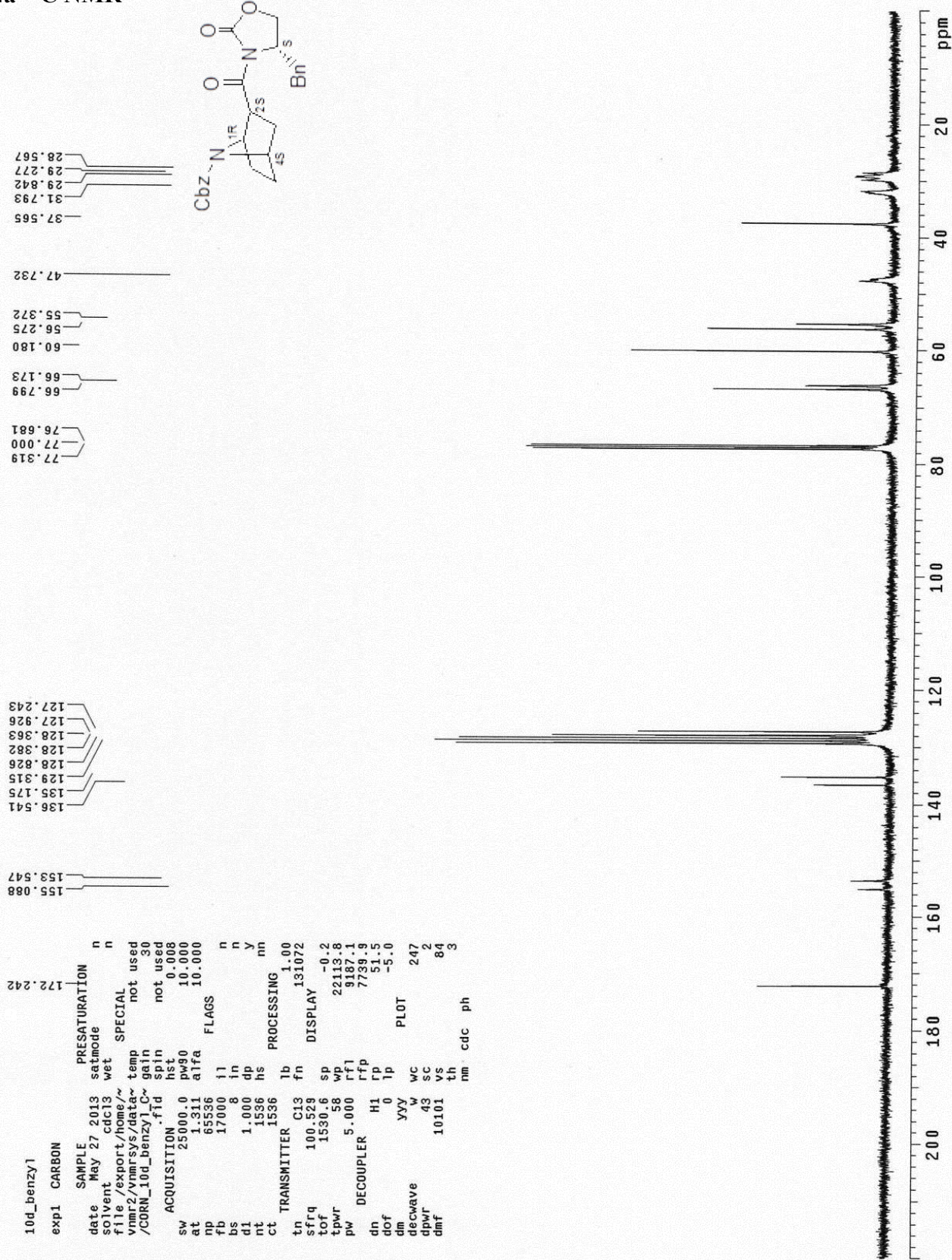


4a ¹H NMR

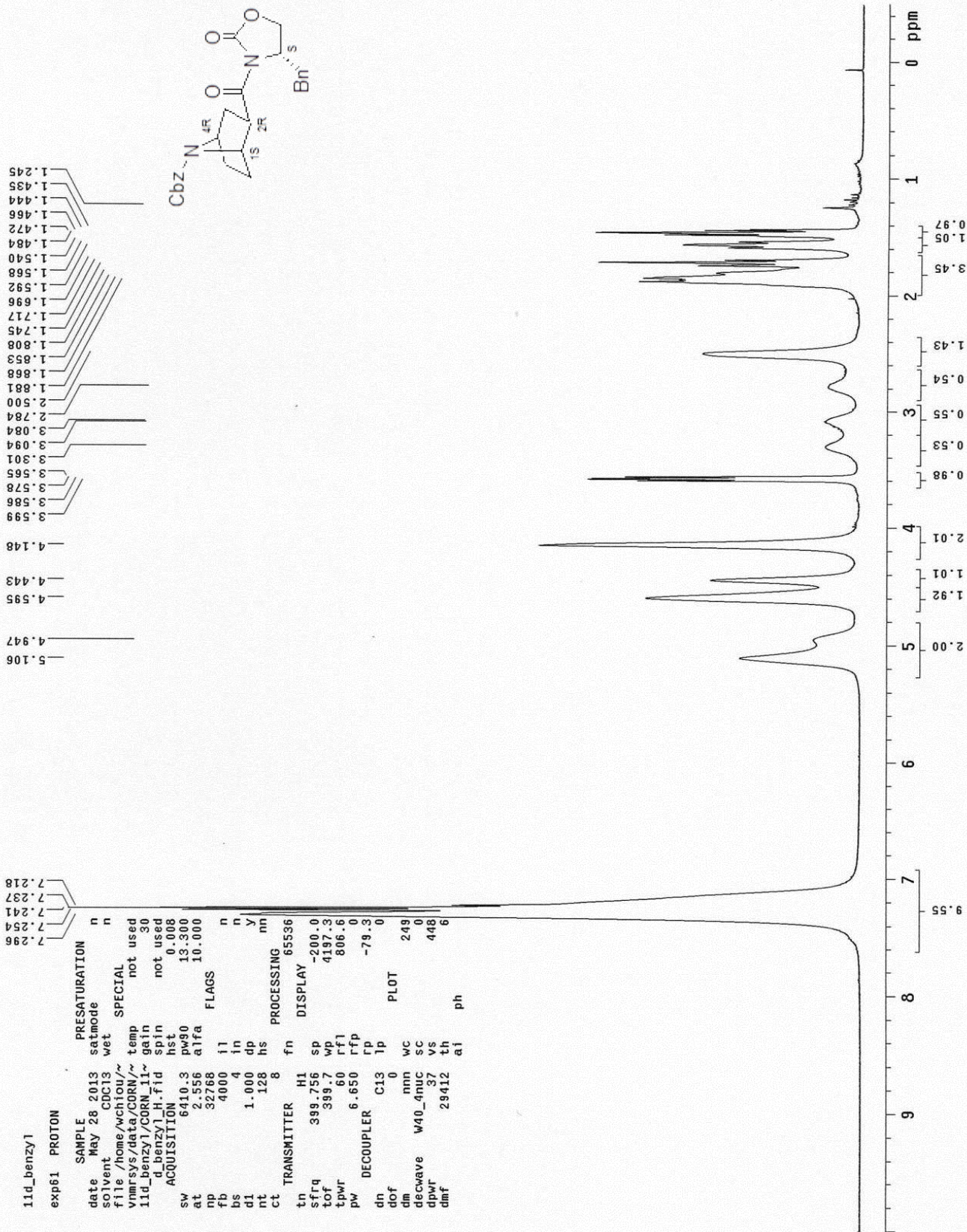
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4a ¹³C NMR



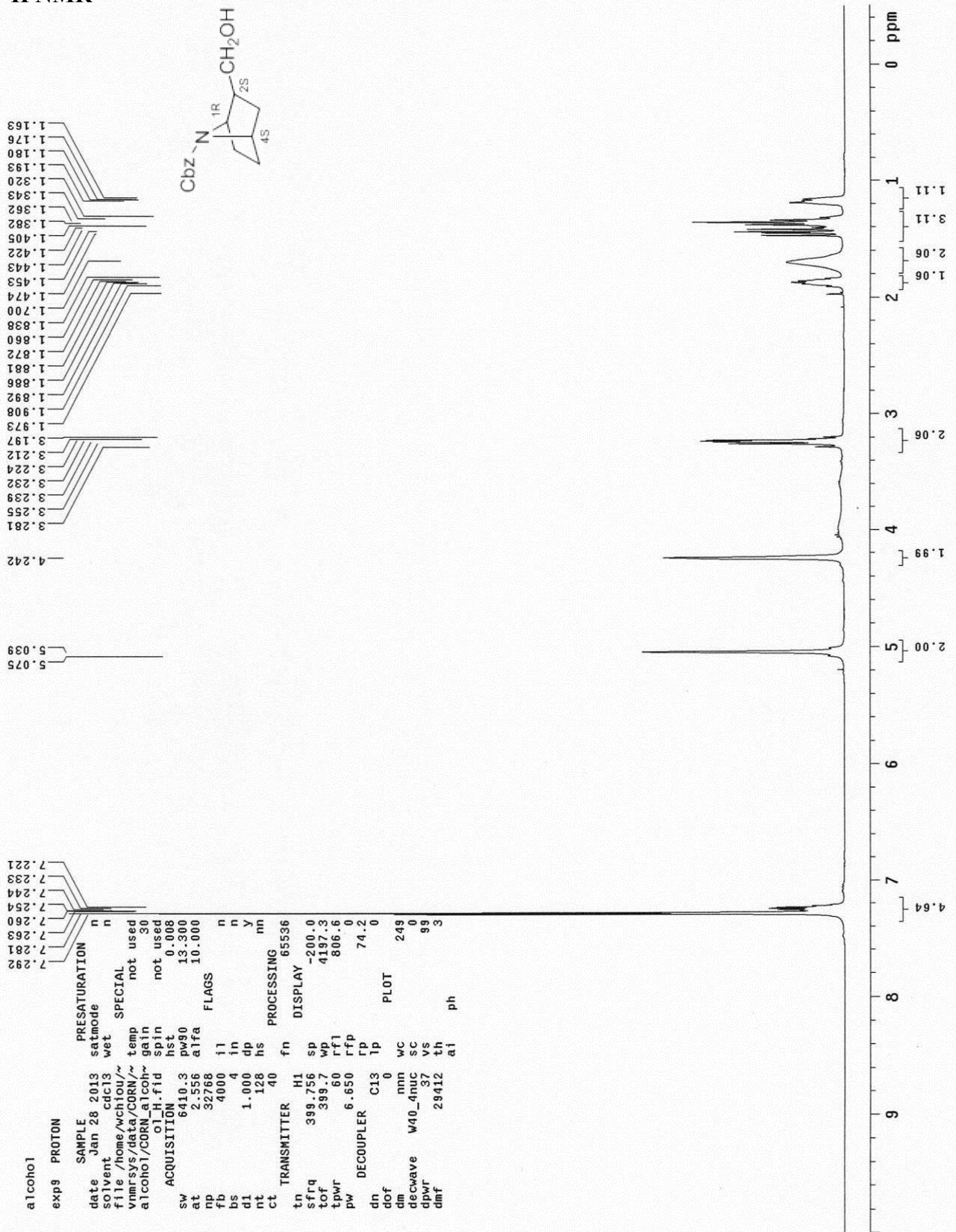
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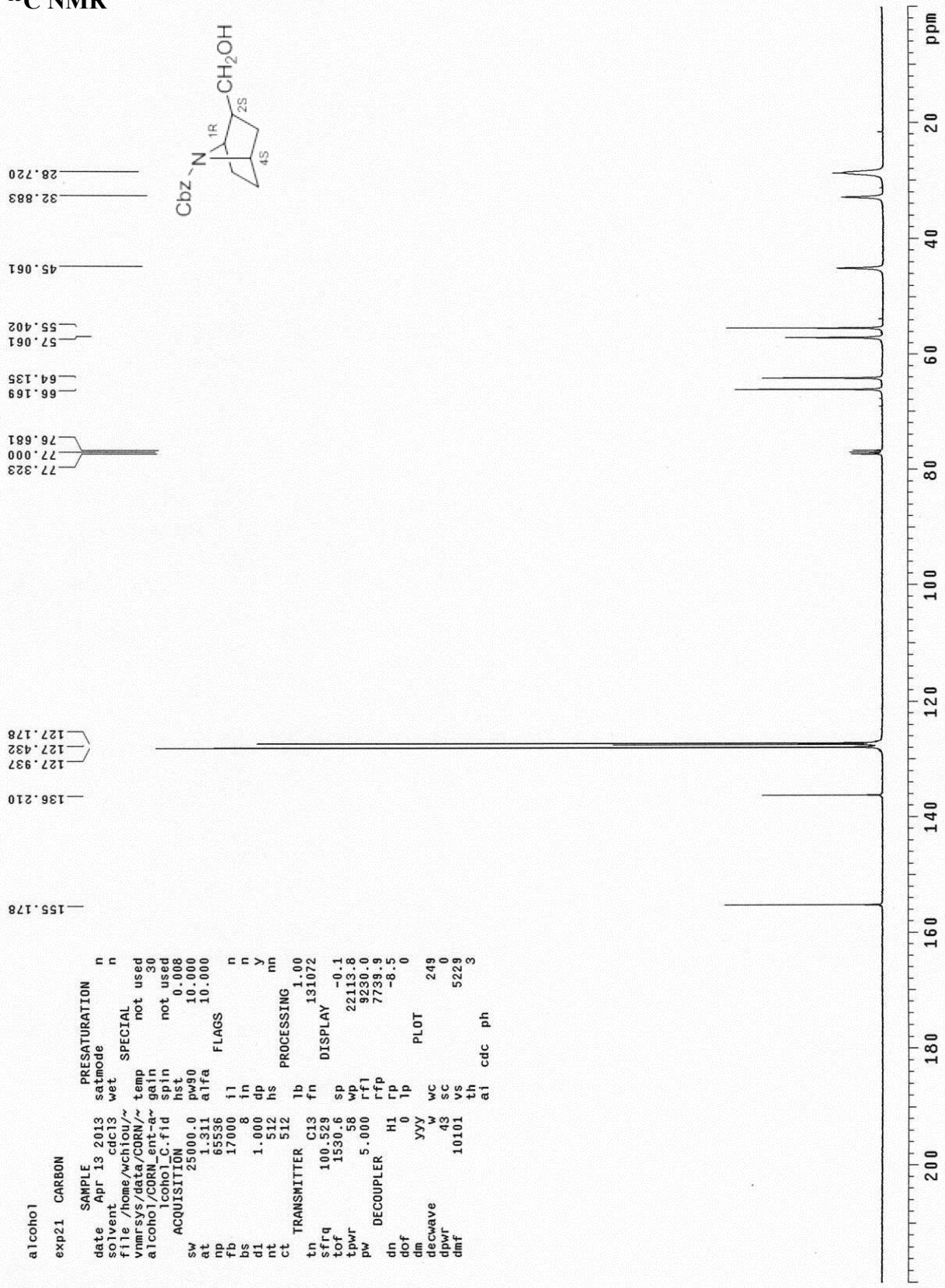
4b ¹³C NMR



5 ¹H NMR



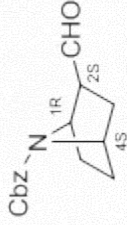
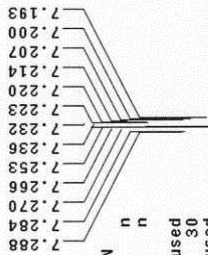
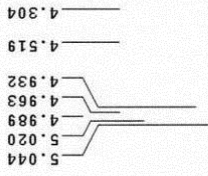
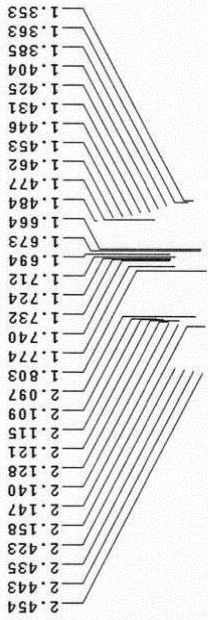
5 ¹³C NMR



```

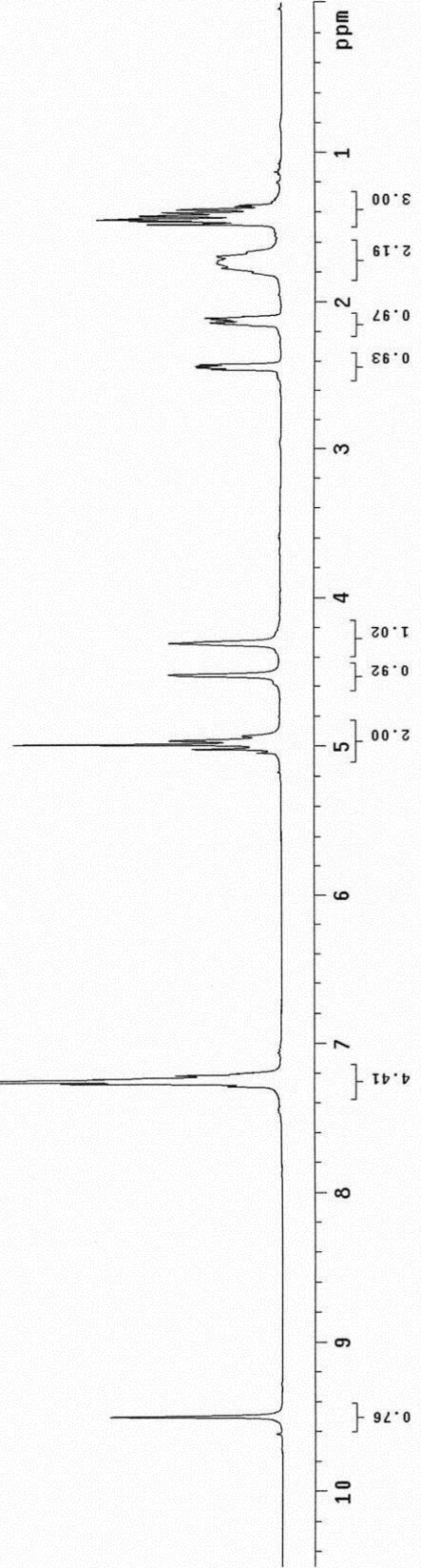
alcohol
exp21 CARBON
SAMPLE PRESATURATION
date Apr 13 2013 satmode n
solvent cdc13 wet n
file /home/wchiou/~
nmrSYS/data/CORN/~ temp SPECIAL not used
alcohol/CORN_ent-a~ gain 30
lcohol_C.fid spin not used
ACQUISITION hst 0.008
sw 25000.0 pw90 10.000
at 1.311 alfa 10.000
np 65536 il FLAGS n
fb 17000 8 in n
bs 1.000 dp Y
nt 512 hs PROCESSING nm
ct 512 lb 1.00
tn TRANSMITTER C13 fn 131072
sfrq 100.529 DISPLAY -0.1
tof 1530.6 sp 22113.8
tpwr 58 wp 9230.0
pw 5.000 rfp 7739.9
DECOUPLER H1 rp -8.5
dn 0 lp 0
dm YVY WC PLOT 249
decwave W WC 0
dprf 43 SC 5229
dmf 10101 VS 3
al cdc ph
  
```

6 ¹H NMR

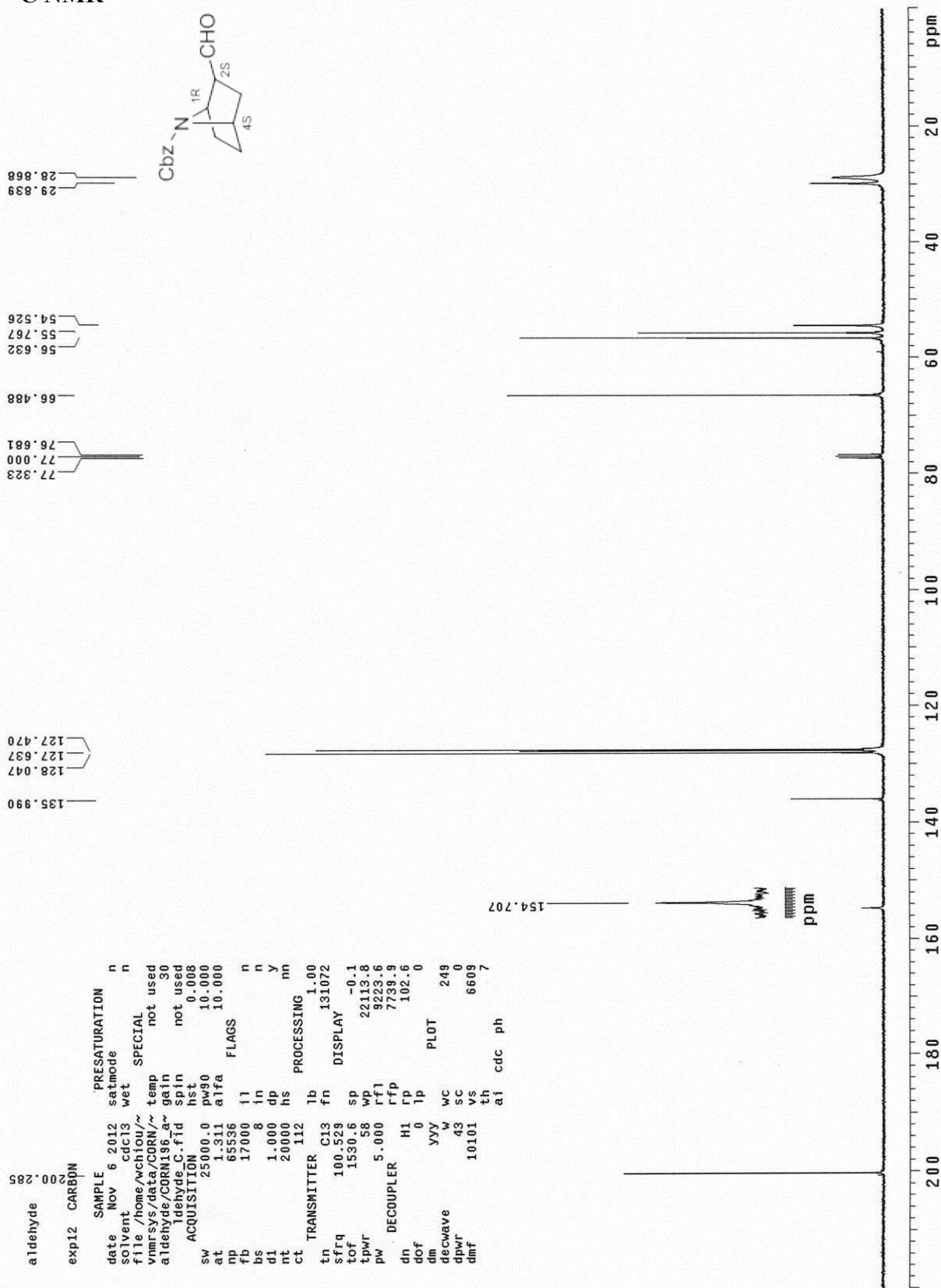


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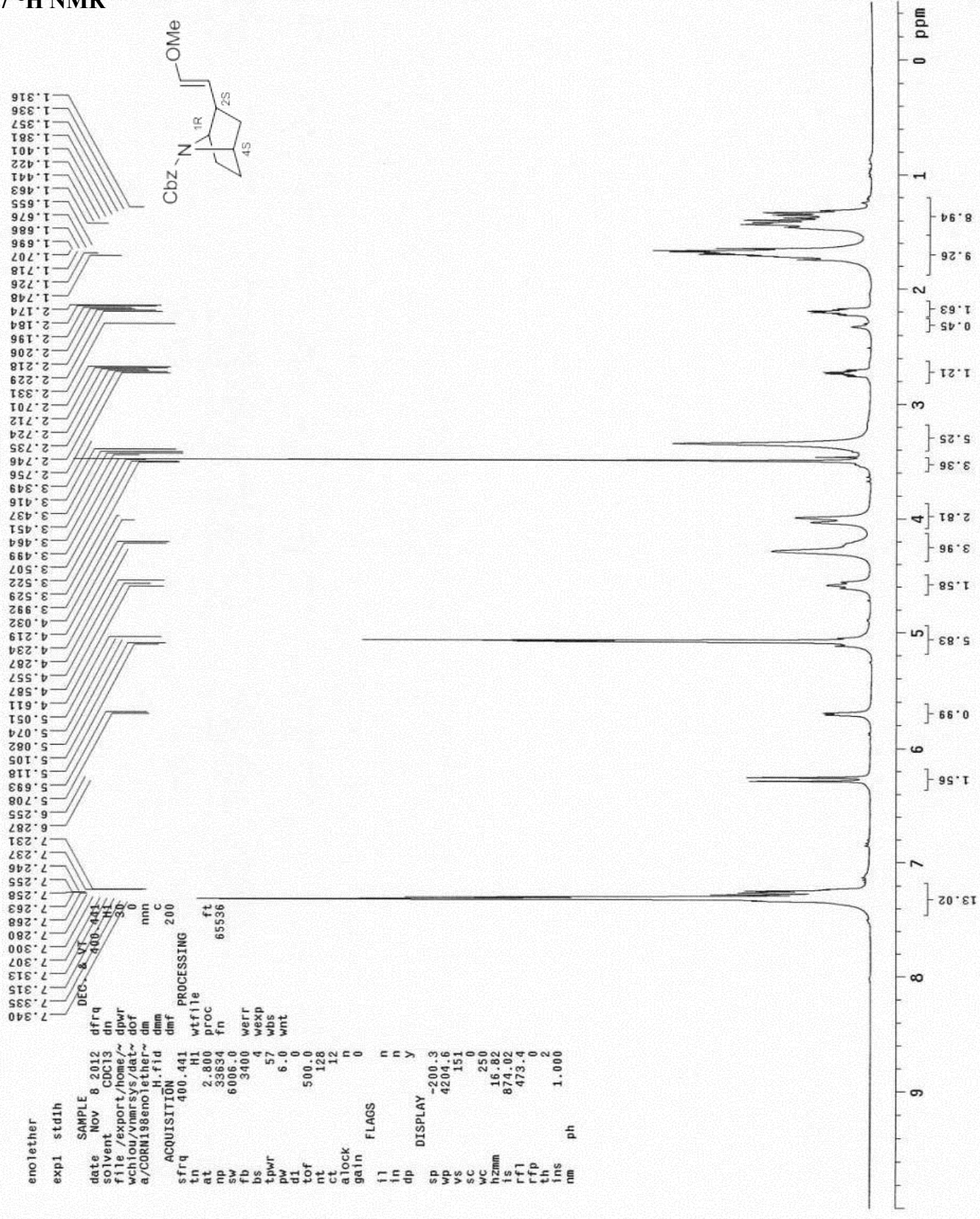
aldehyde
exp12 PROTON
date Nov 6 2012 satmode n
solvent cdc13 wet n
file /home/wchou/~
vnmrshs/data/CORN/~
aldehyde/CORN196_a~
aldehyde.H.fid spin
ACQUISITION hst 0.008
sw 6410.3 pw90 13.300
at 2.556 a1fa 10.000
np 32768
fb 4000 i1 n
bs 4 in n
di 1.000 dp y
nt 128 hs
ct TRANSMITTER I2 fn 65536
tn HI
sfrq 399.756 sp -0.1
tof 399.7 wp 4197.3
tpwr 60 rfl 806.6
pw 6.650 rfp 0
DECOUPLER C13 rp 89.5
dn 0 lp 0
dof 0 PLOT
dim nnn wc 249
deccave W40_4muc SC 0
dpwr 37 ss 96
dmf 29412 th 3
a1 ph
  
```



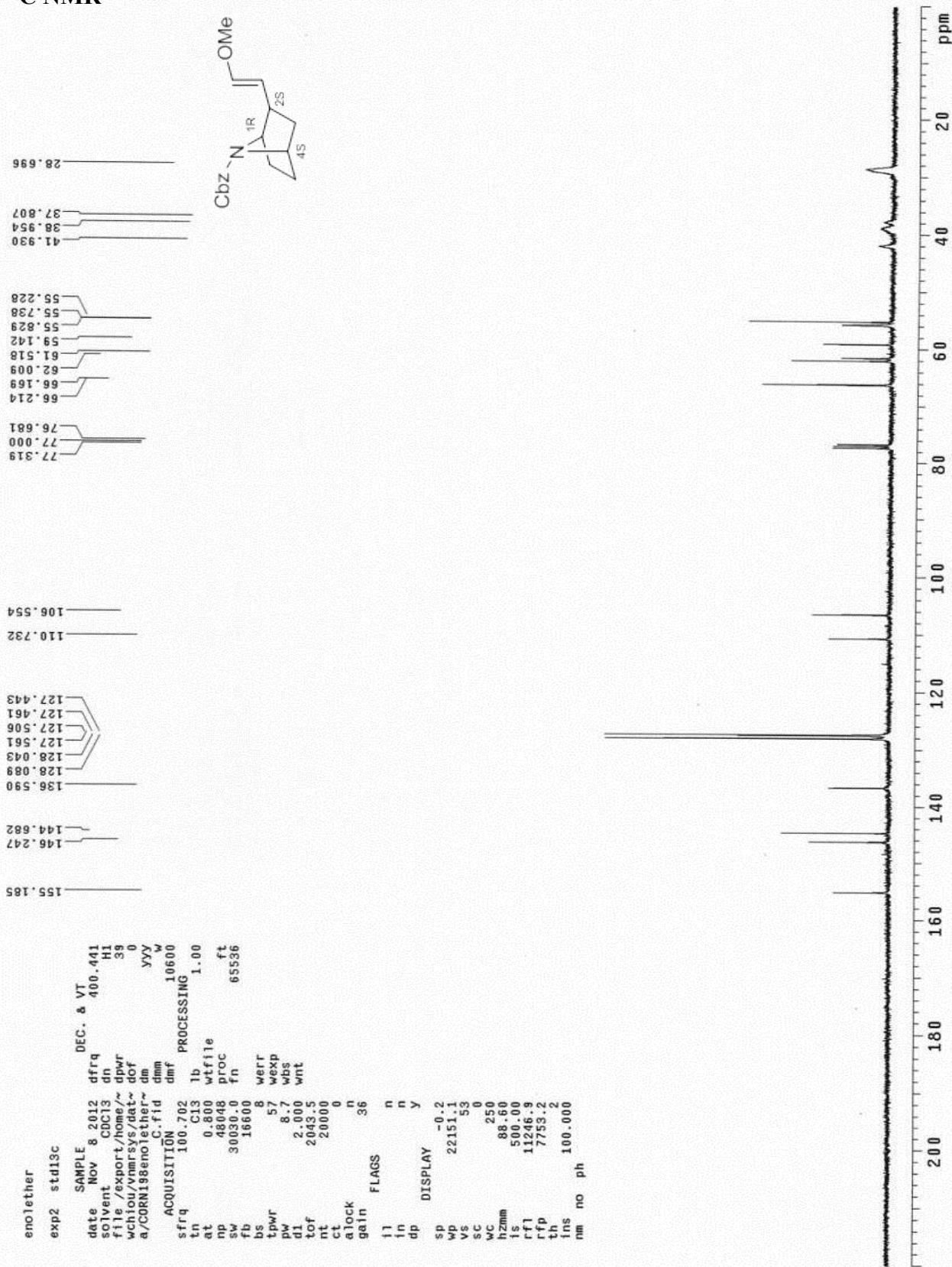
6 ¹³C NMR



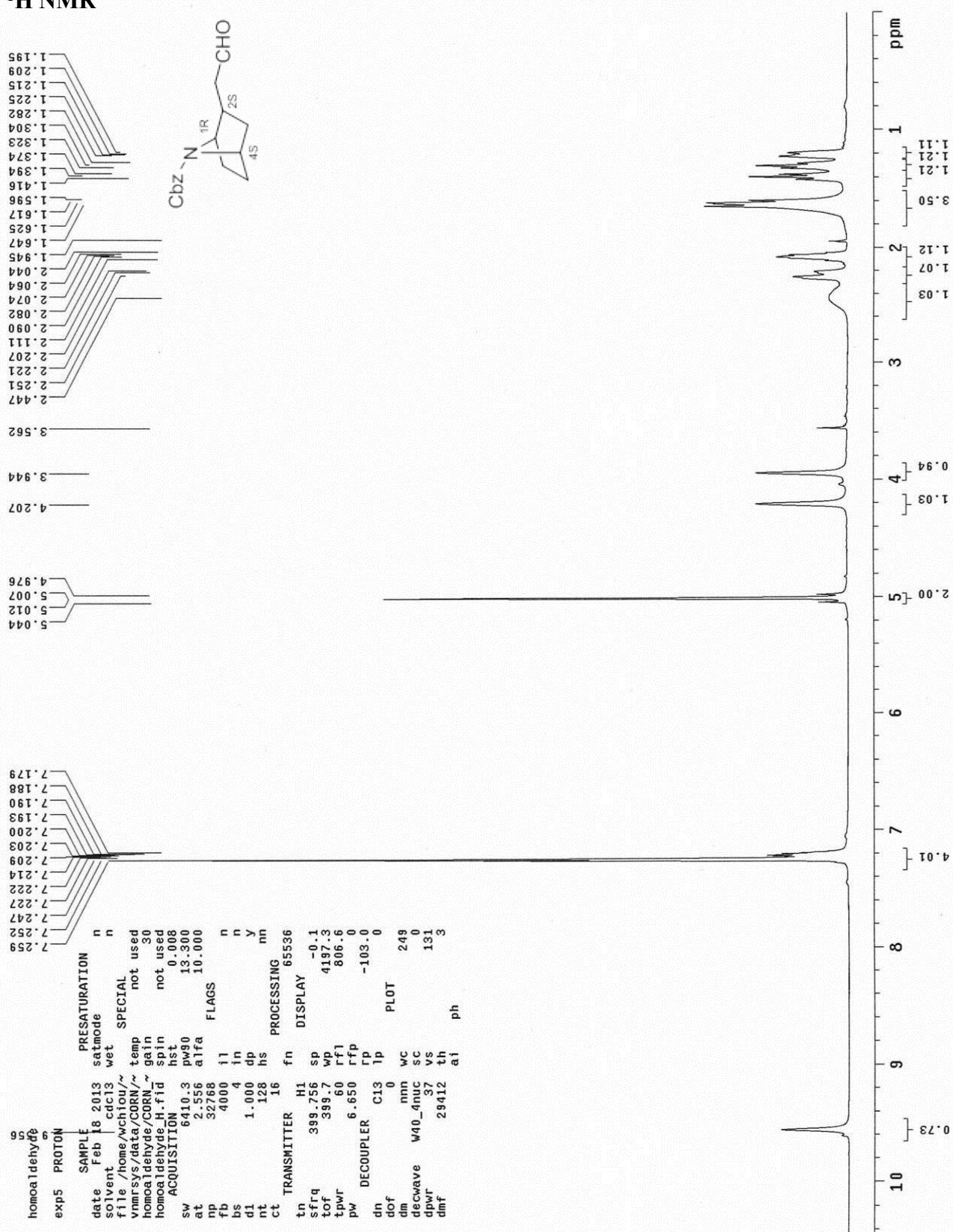
7 ¹H NMR



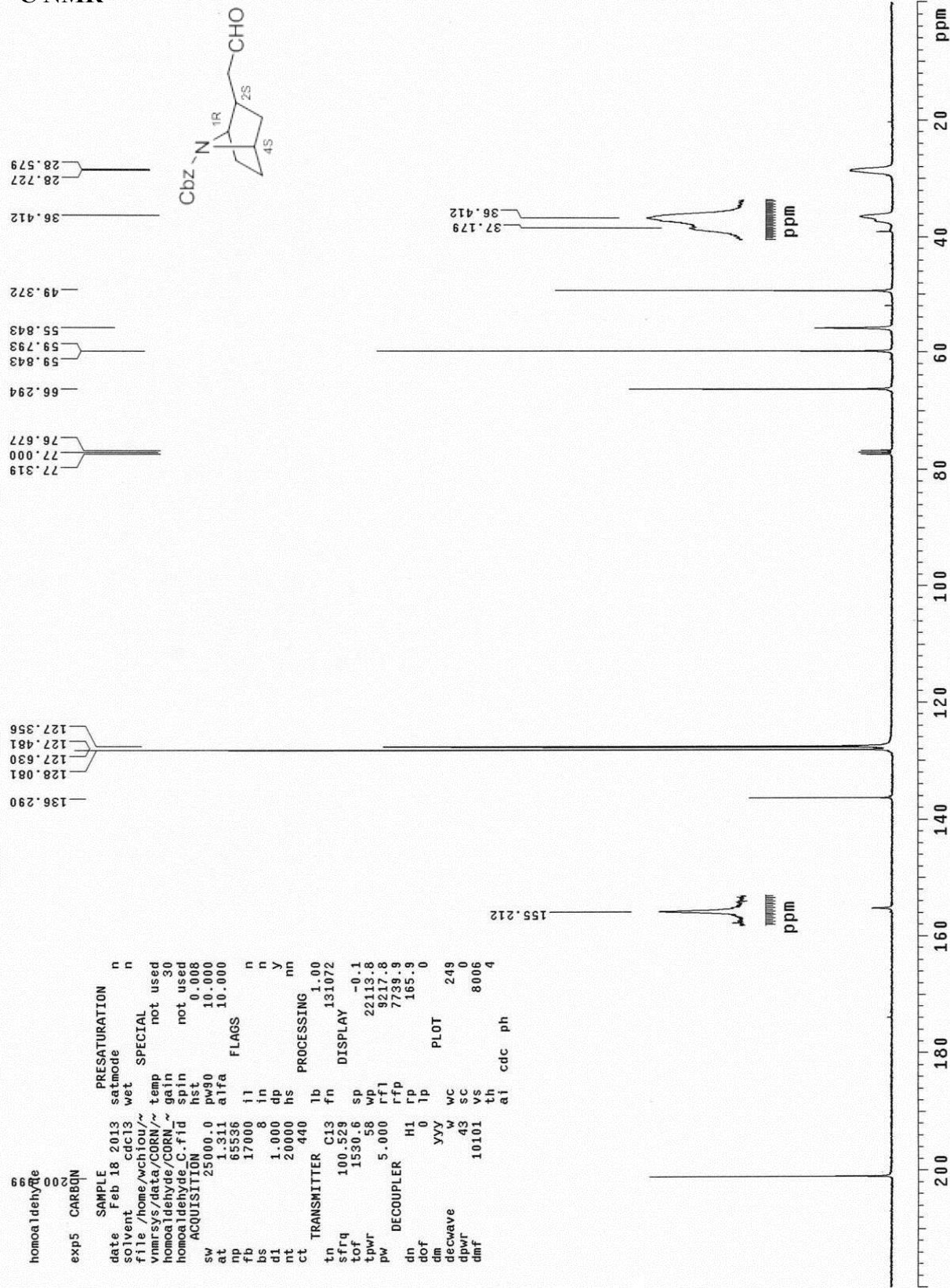
7 ¹³C NMR



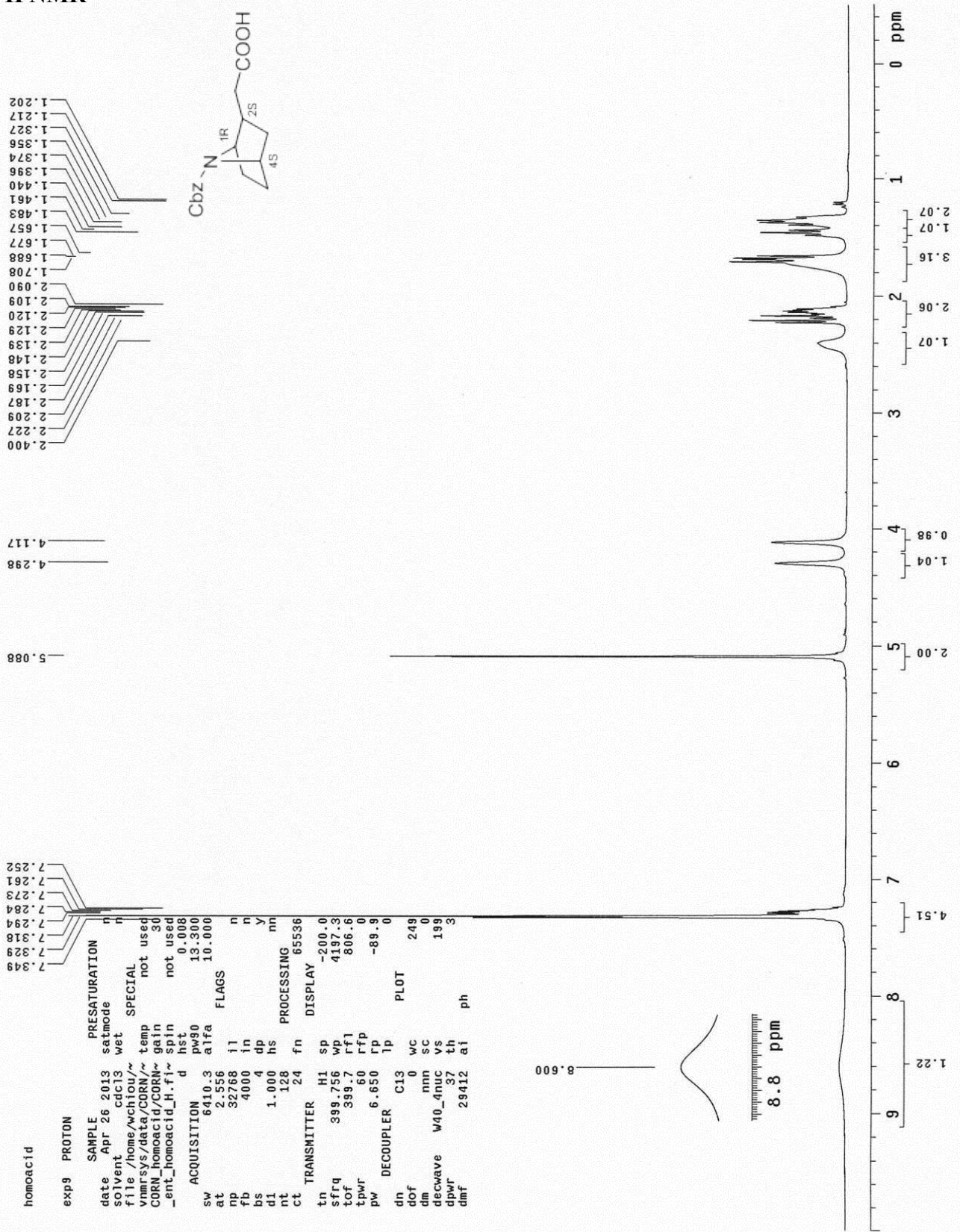
8 ¹H NMR



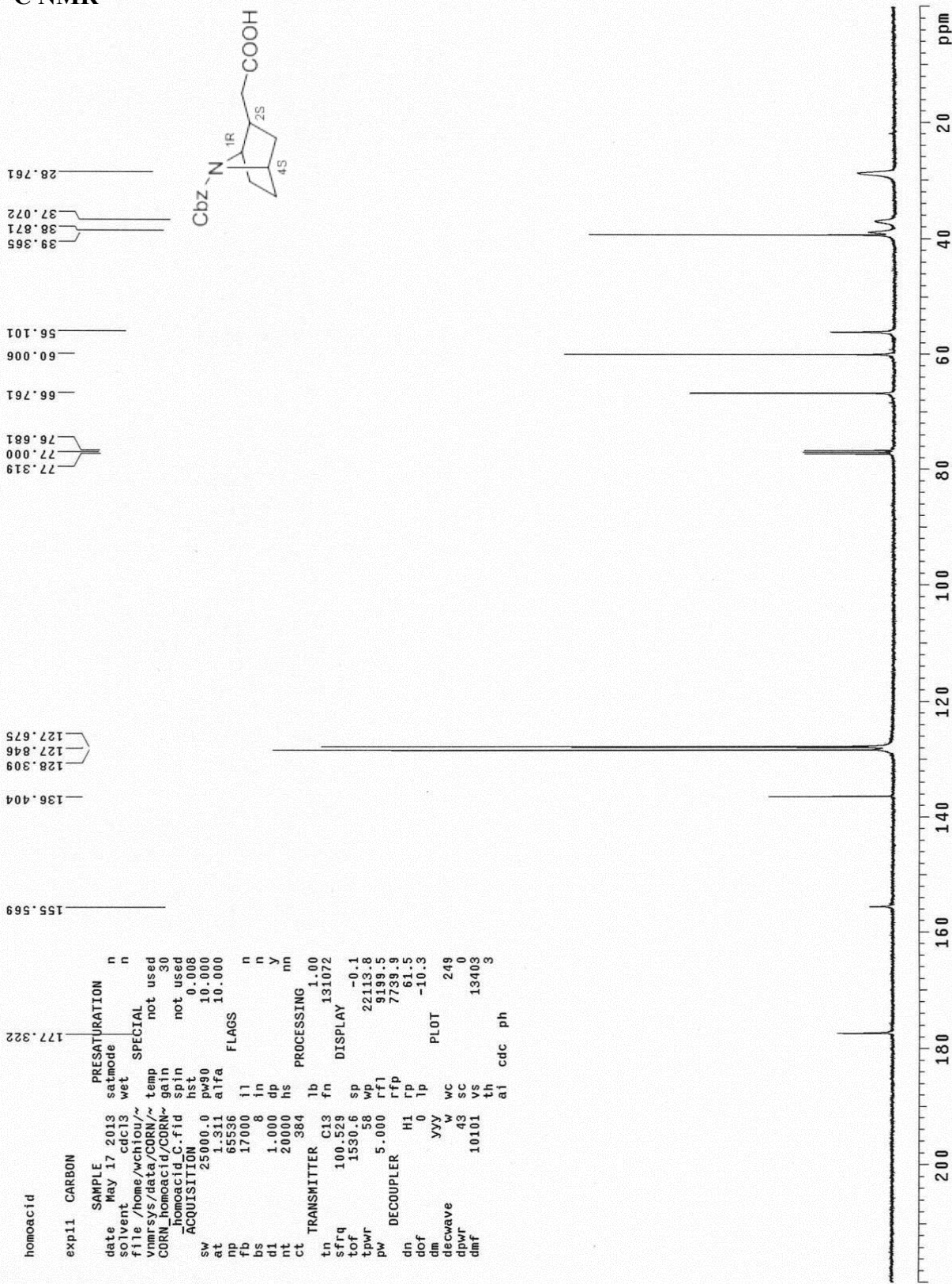
8 ¹³C NMR



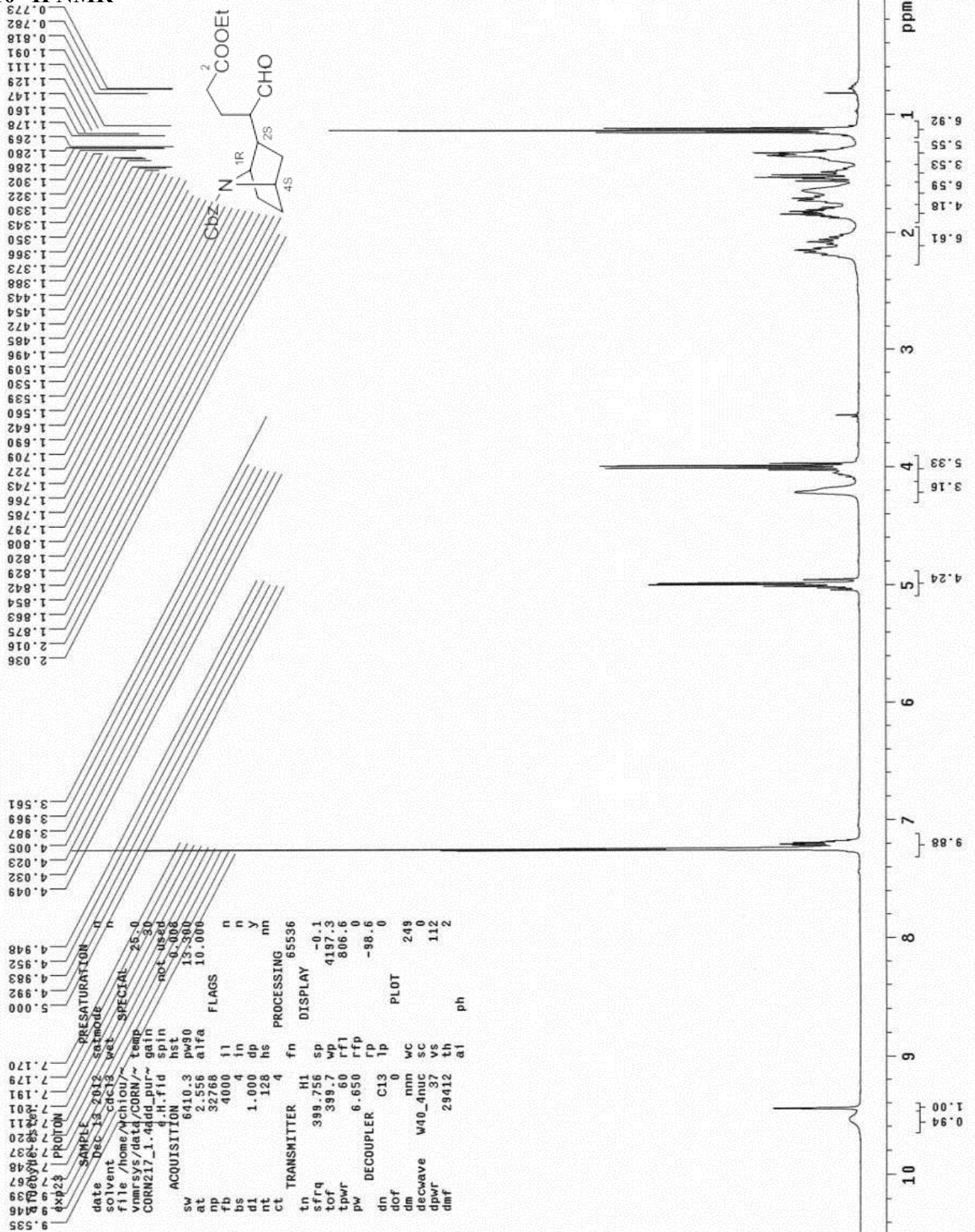
9 ¹H NMR



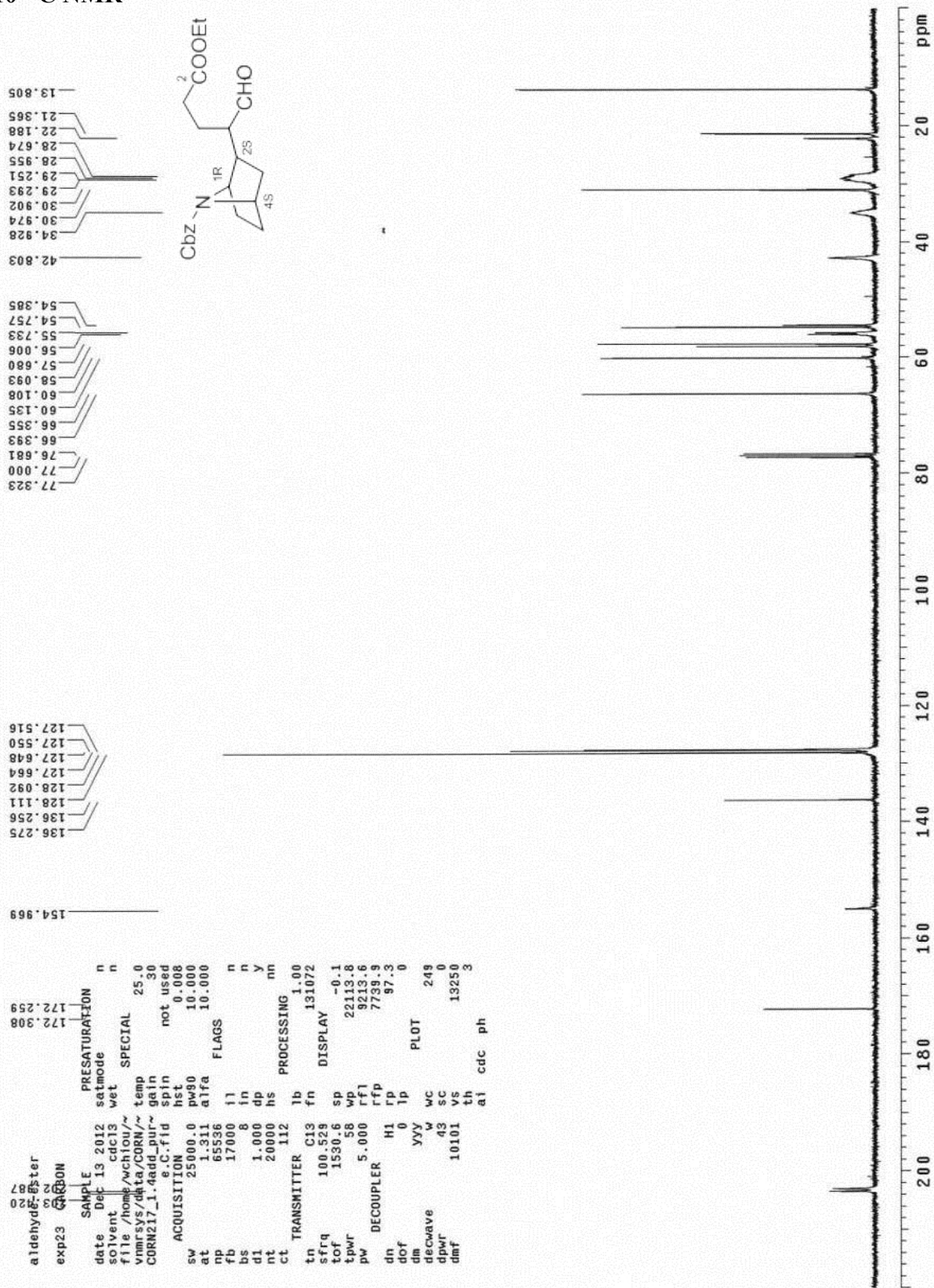
9 ¹³C NMR



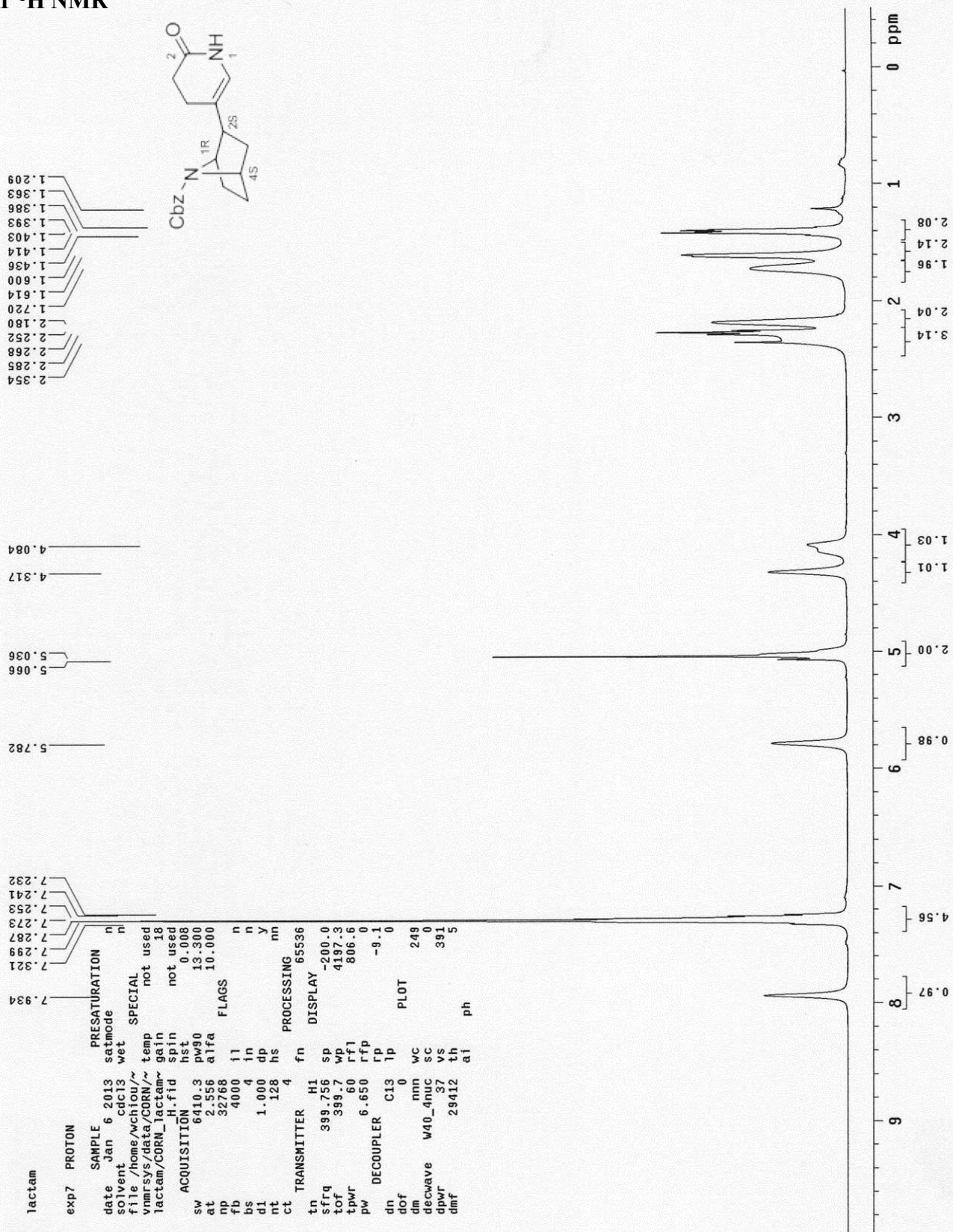
10 ¹H NMR



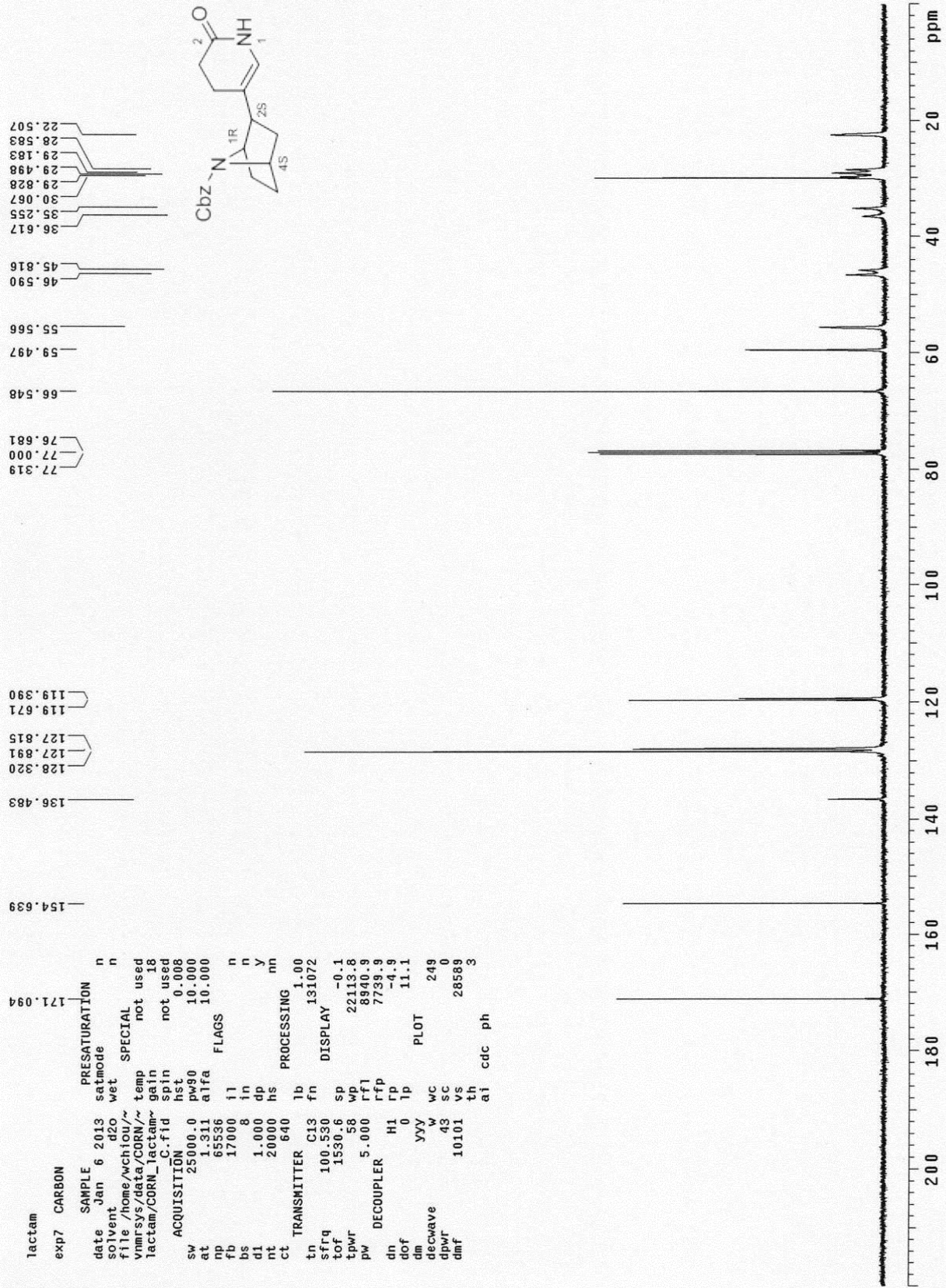
10¹³C NMR



11 ¹H NMR



11 ¹³C NMR

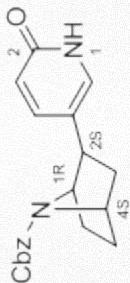


12 ¹H NMR

2.627
2.615
2.606
2.595
1.904
1.874
1.851
1.716
1.685
1.531
1.510
1.486
1.473
1.451
1.431

4.139
4.385
5.061

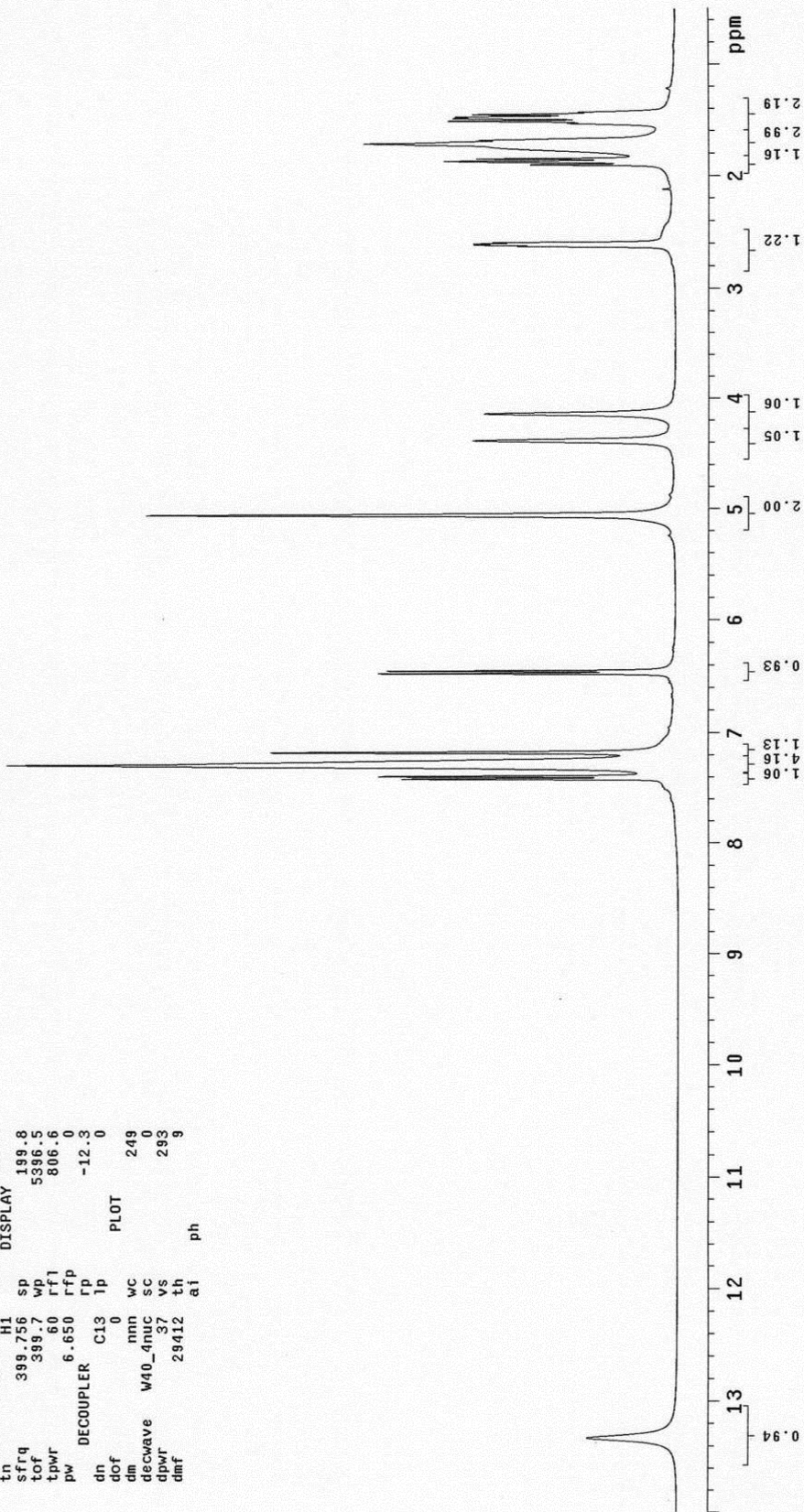
6.450
6.473
7.177
7.291
7.392
7.416



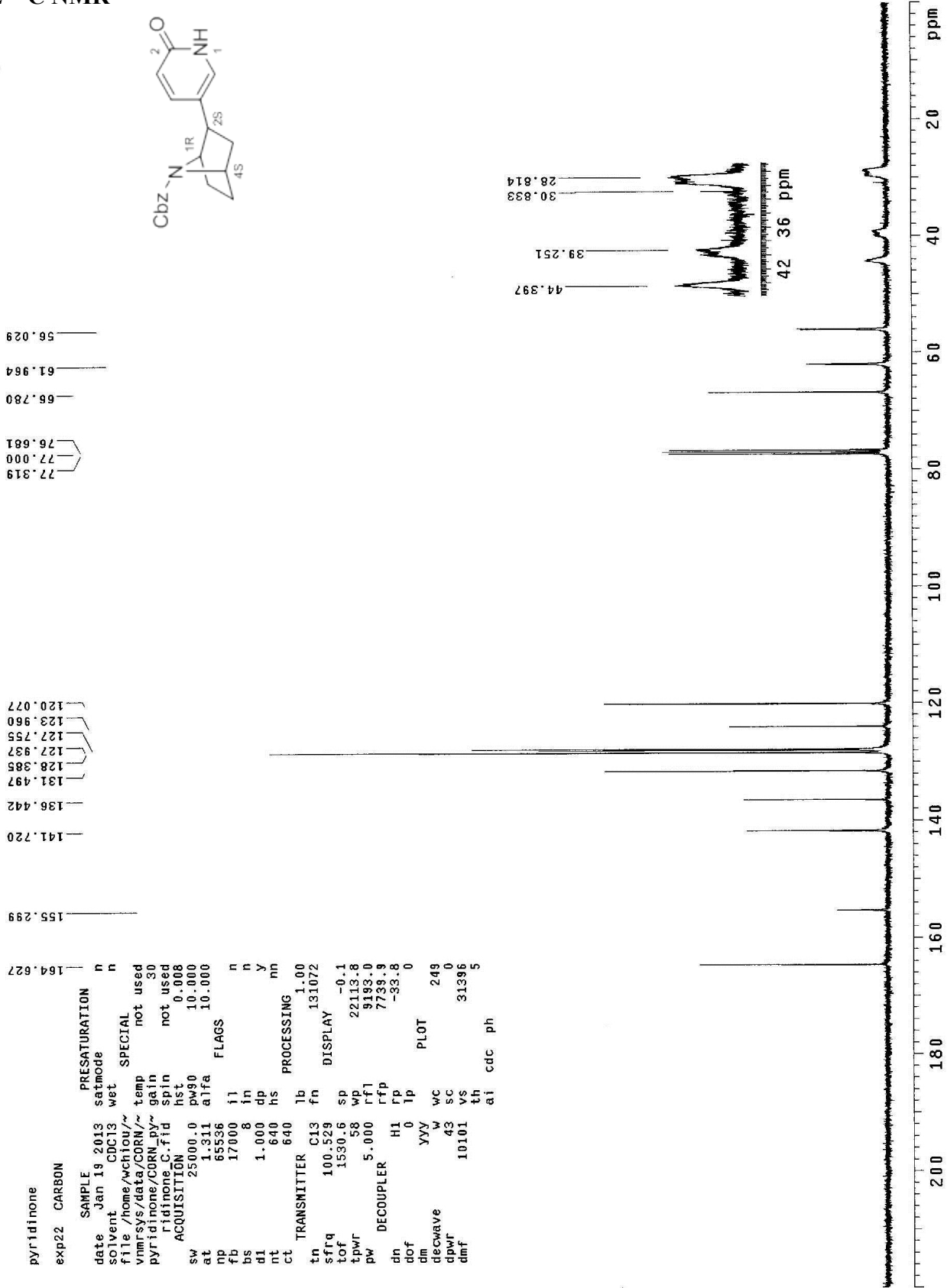
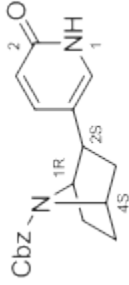
```

pyridinone
exp21 PROTON
SAMPLE
date Jan 15 2013 satmode n
solvent cdc13 wet SPECIAL n
file /home/wchiou/~ temp not used
vnmrsvs/data/CORN/~ gain 30
pyridinone/CORN_by not used
ridinone_H.ftid spin 0.008
ACQUISITION hst 13.300
sw 6410.3 pw90 10.000
at 2.556 aifa 10.000
np 32768
fb 4000
bs 4
d1 1.000 dp in n
nt 128 hs
ct TRANSMITTER 36 fn 65536
tn H1 DISPLAY 199.8
sfrq 399.756 sp 5386.5
tof 399.7 wp 806.6
tpwr 60 rfi 0
pw 6.650 rfp -12.3
dn DECOUPLER C13 lp 0
dof 0 PLOT
dm mnn WC 249
decwave W40_4nuc SC 0
dpwr 37 vs 293
dmf 29412 th ai 9

```



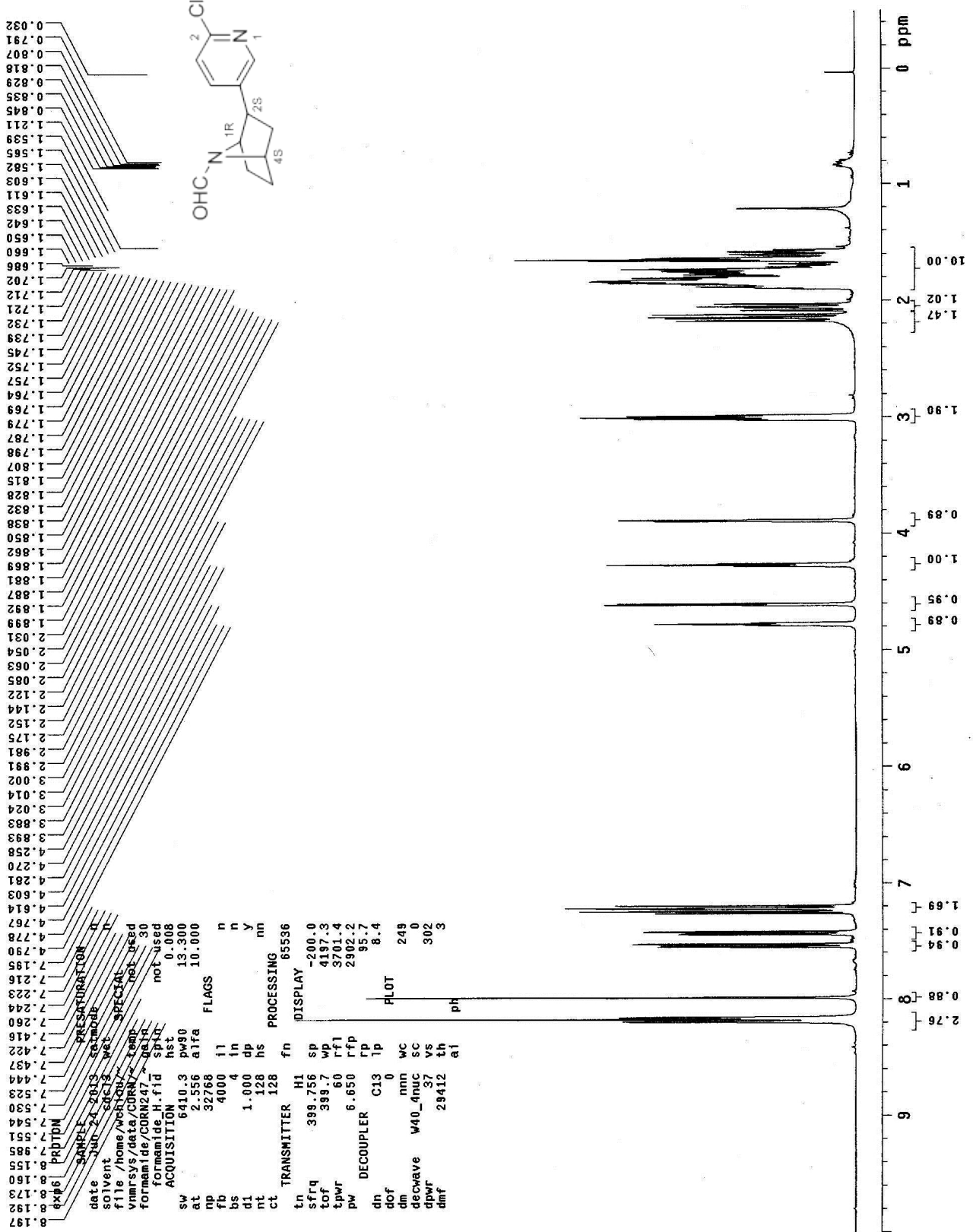
12 ¹³C NMR



```

pyridinone
exp22 CARBON
SAMPLE PRESATURATION
date Jan 19 2013 satmode n
solvent CDCl3 wet n
file /home/wchiou/~ SPECIAL
vnmrSYS/data/CORN/~ temp not used
pyridinone/CORN_py gain 30
ridinone_C_fid spin not used
ACQUISITION hst 0.008
sw 25000.0 pw90 10.000
at 1.311 alfa 10.000
np 65536
fb 17000 fl n
bs 8 in n
dl 1.000 dp y
nt 640 hs PROCESSING mn
ct 640 lb 1.00
TRANSMITTER C13 fn 131072
tn 100.529 sfrq
tof 1530.6 sp -0.1
tpwr 58 wd 22113.8
pw 5.000 rfl 9193.0
DECOUPLER H1 rp 7739.9
dn 0 lp -33.8
dof 0
dm YYY PLOT
decwave w WC 249
dppwr 43 SC 0
dmf 10101 vs 31396
ai cdc ph 5
  
```

13 H NMR



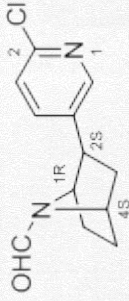
13 ¹³C NMR

61.808
56.598
55.311
51.649
44.826
44.059
41.179
38.720
30.723
29.775
29.099
28.238

77.319
77.000
76.681

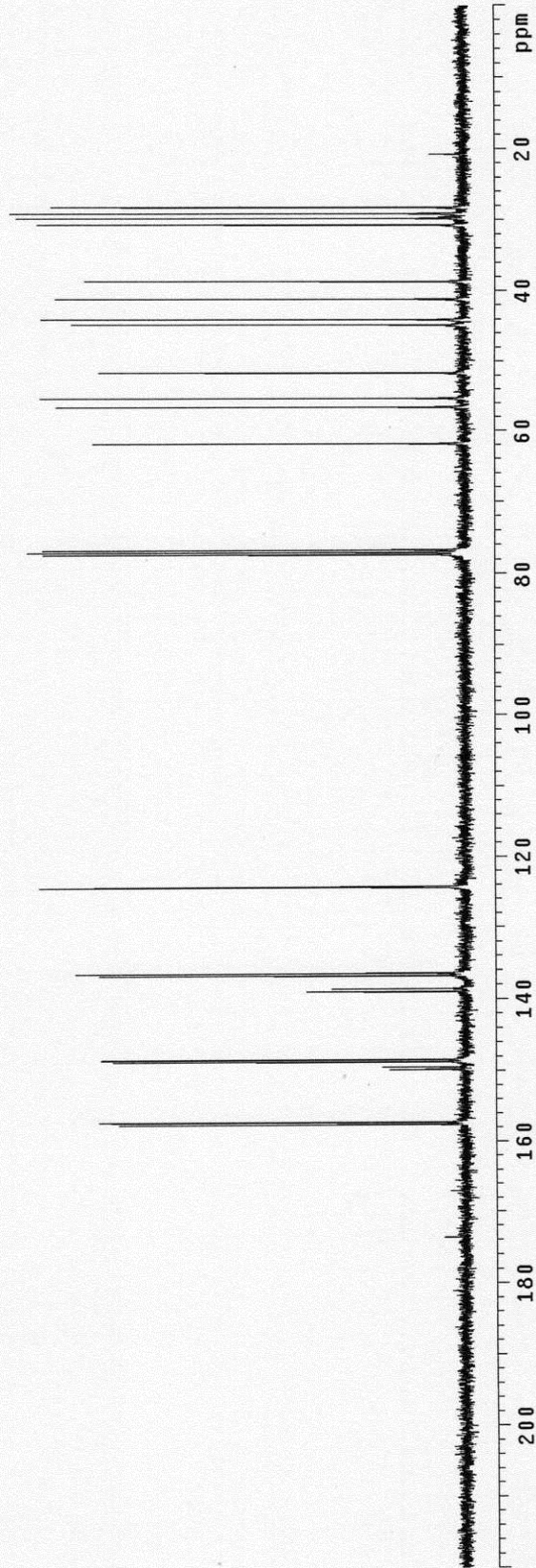
124.244
124.958

136.407
136.760
138.533
138.954
148.404
148.692
149.440
149.770
157.235
157.553

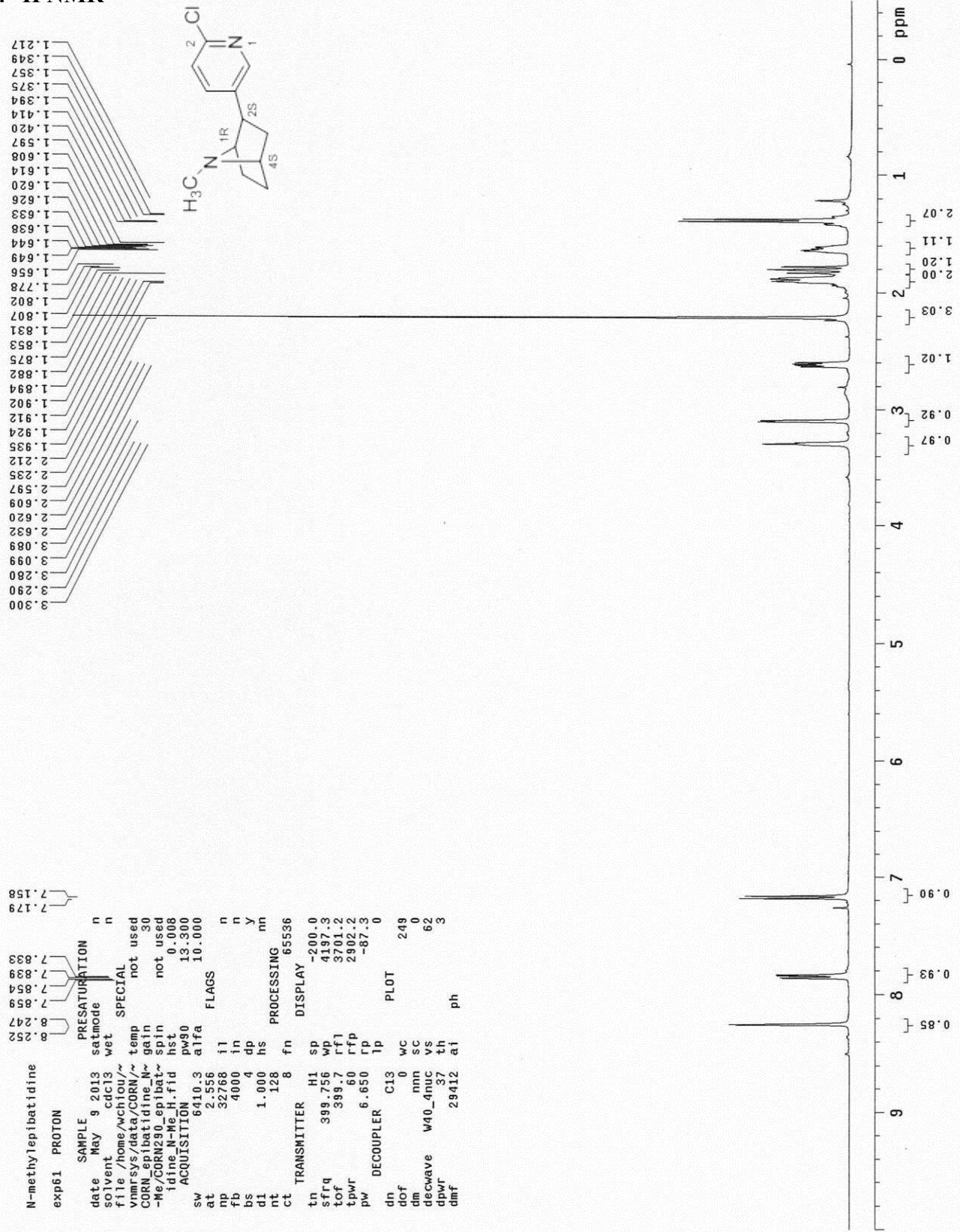


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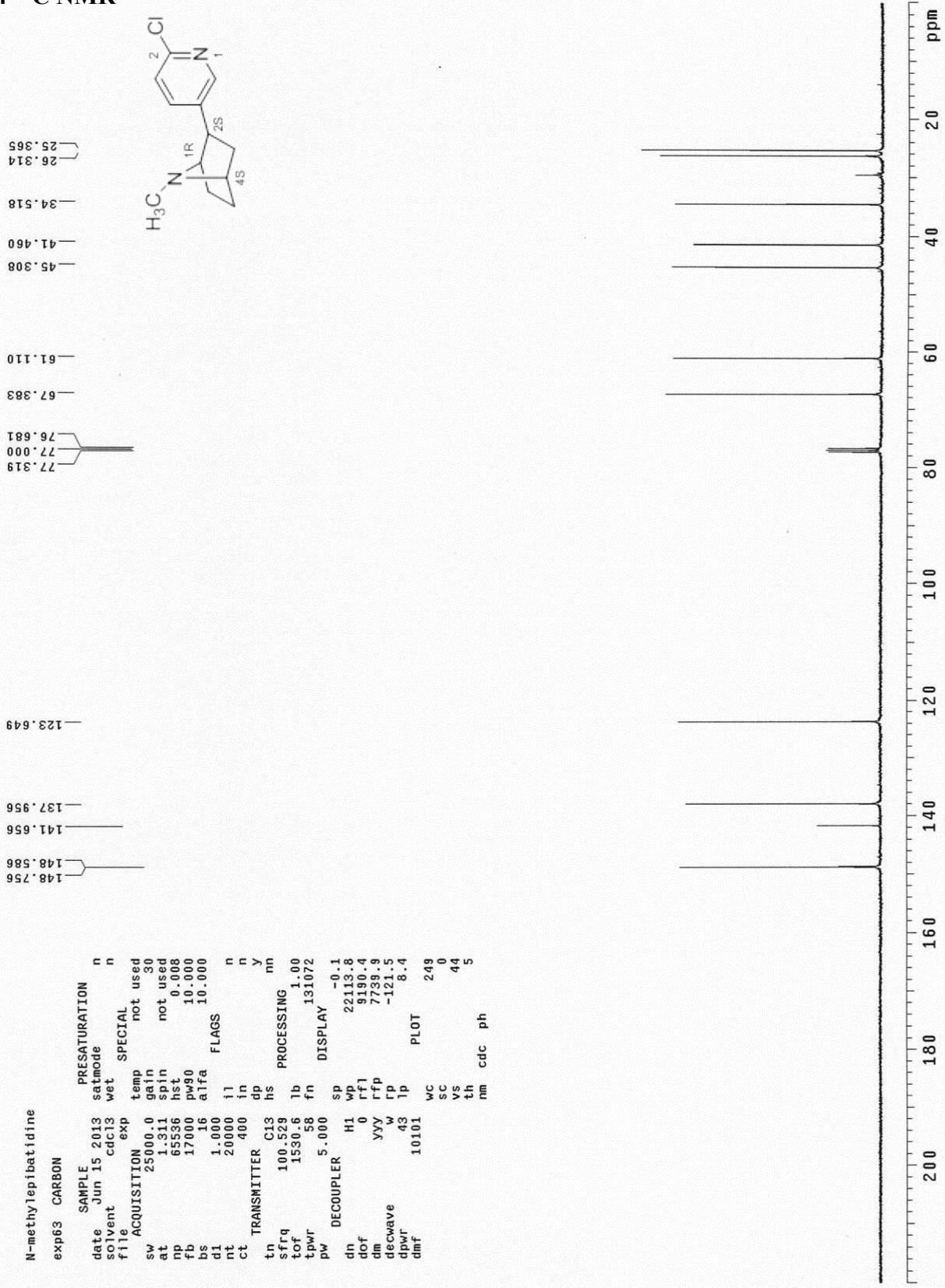
formamide
exp5 CARBON
SAMPLE PRESATURATION
date Feb 22 2013 satmode n
solvent cdc13 wet n
file /home/vchiou/~ SPECIAL not used
vnmrsys/data/CORN/~ temp not used
CORN247f1_POC13_DM~ gain 30
F/CORN247f1_POC13~ spin not used
C.fid hst 0.008
ACQUISITION pw90 10.000
sw 25000.0 alfa 10.000
at 1.311 i1
np 65536 in
fb 17000 in n
bs 8 dp n
d1 1.000 hs
nt 512 lb
ct 512 fn 131072
TRANSMITTER C13 DISPLAY -0.1
tn 100.529 sp 22113.8
sftq 1530.6 wp 9193.4
tof 58 rfl 7739.9
tpwr 5.000 rfp 164.6
pw DECOUPLER H1 lp
dn dof 0
dim 0 YVY WC 249
dm dechve W SC 0
dipwr 43 VS 50641
dmf 10101 th ai cdc ph 9
  
```



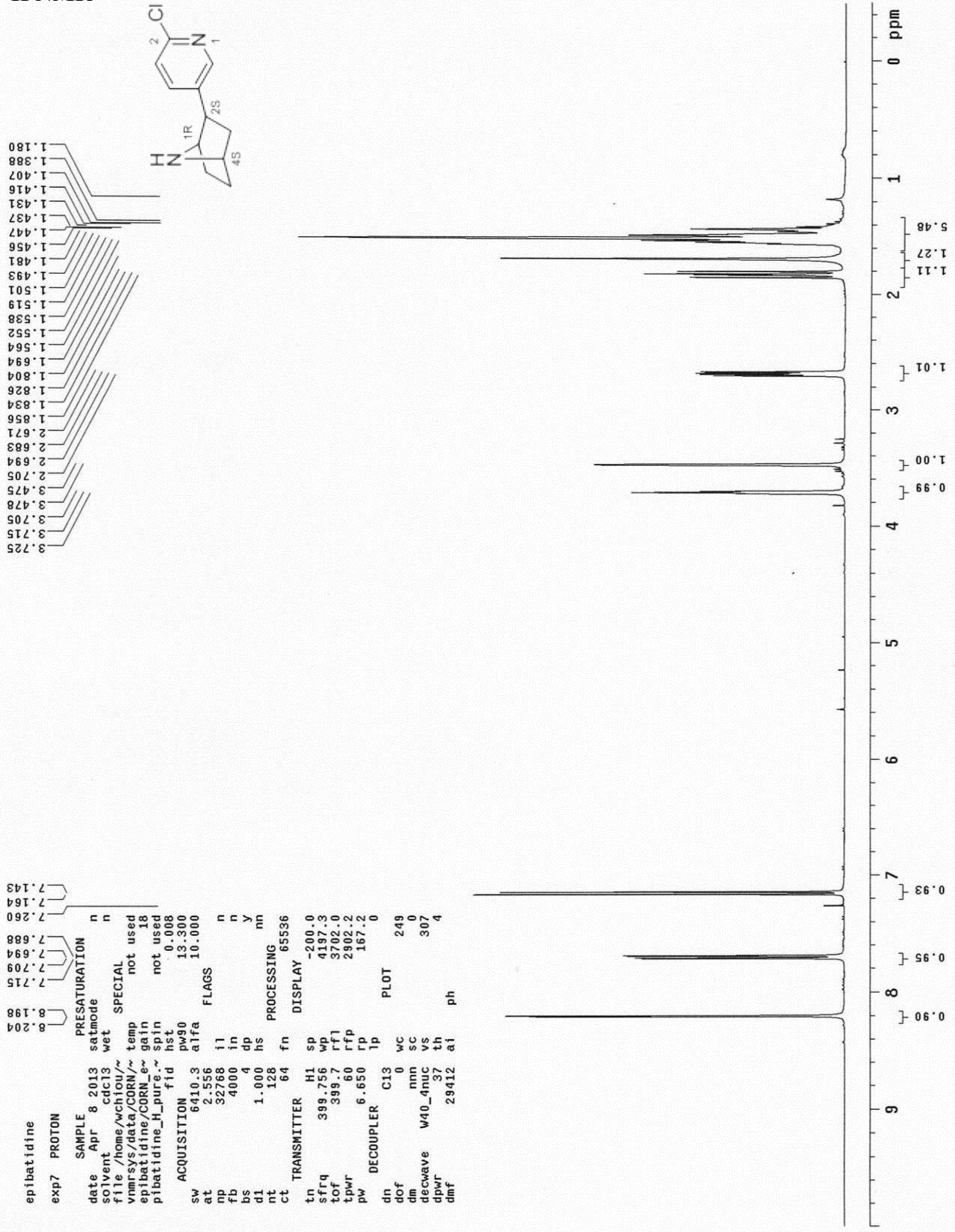
14 ¹H NMR



14 ¹³C NMR



1 H NMR



1 ¹³C NMR

