Conjugate Addition of Lithiated Methyl Pyridines to Enones

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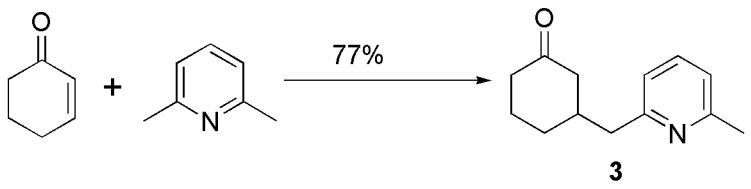
Supporting Information

Contents

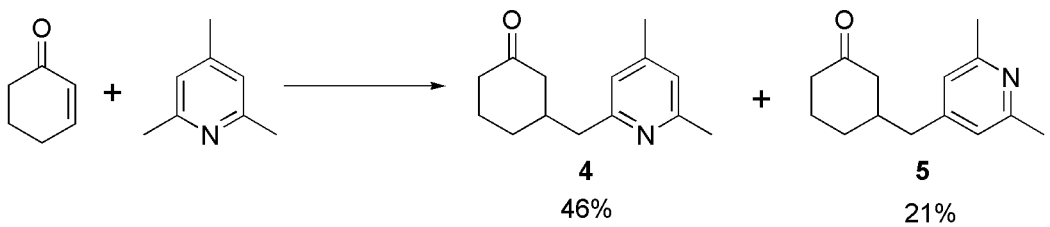
General:

^{1}H NMR and ^{13}C NMR spectra were recorded, as solutions in deuteriochloroform ($CDCl_3$) at 400 MHz, unless otherwise specialized, using residue solvent peaks as internal standards. ^{13}C multiplicities were determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methine carbons as "d" from methylene and quaternary carbons as "u". The infrared (IR) spectra were determined as neat oils. R_f values indicated refer to thin layer chromatography (TLC) on 2.5 x 10 cm, 250 μm analytical plates coated with silica gel GF, unless otherwise noted, and developed in the solvent system indicated. The elution solvent for chromatography is the same with the TLC solvent. All glassware was oven dried and rinsed with dry solvent before use. THF and diethyl ether were distilled from sodium metal/benzophenone ketyl under dry nitrogen. MTBE is methyl tert-butyl ether and PE is petroleum ether. All reactions were conducted under N_2 and stirred magnetically. All copper salts and all starting materials were used as received.



3

3-((6-Methylpyridin-2-yl)methyl)cyclohexanone (3). To a stirred solution of 2,6-lutidine (450 mg, 4.2 mmol) in THF (4 mL) was added *n*-BuLi (4.19 mmol, 1.8 mL, 2.33 M in hexane) at -78 ^{o}C. After stirring at 0 ^{o}C for 1 h, the reaction mixture was cooled to -30 ^{o}C and added over 2 min to a stirred suspension of CuBr•SMe_2 (410 mg, 2.0 mmol) in THF (4 mL) at -30 ^{o}C. After stirring for 2 h at -30 ^{o}C, the reaction mixture was cooled to -78 ^{o}C and a solution of 2-cyclohexen-1-one (110 mg, 1.14 mmol) in THF (3 mL) was added over 5 min. After stirring at -78 ^{o}C for 2 h, the reaction mixture was quenched with water (5 mL) and partitioned between CH_2Cl_2 (30 mL) and, sequentially, water (5 mL) and brine (15 mL). The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield ketone **3** (180 mg, 77% yield) as a pale yellow oil: TLC R_f (10% Et_2NH/PE) = 0.21; IR (cm^{-1}) 2933, 1708, 1587, 1456; ^{1}H NMR δ 7.40 (t, J = 7.5 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 6.85 (d, J = 7.5 Hz, 1H), 2.75 (m, 1H), 2.65 (m, 1H), 2.45 (s, 3H), 2.35-2.15 (m, 4H), 2.00 (m, 2H), 1.85 (m, 1H), 1.60 (m, 1H), 1.40 (m, 1H); ^{13}C NMR δ u 211.6, 158.7, 158.0, 47.6, 45.2, 41.4, 31.2, 25.2; d 136.5, 120.9, 120.5, 39.6, 24.5; HRMS calcd for $C_{13}H_{18}NO$ (MH^+) 204.1388, obsd 204.1385.



4 46%

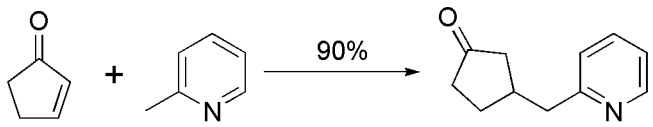
5 21%

3-((4,6-Dimethylpyridin-2-yl)methyl)cyclohexanone (4) and 3-((2,6-Dimethylpyridin-4-yl)methyl)cyclohexanone (5). To a stirred solution of 2,4,6-collidine (510 mg, 4.21 mmol) in THF (4 mL) was added *n*-BuLi (4.19 mmol, 1.8 mL, 2.33 M in hexane) at -78 ^{o}C. After stirring at 0 ^{o}C for 1 h, the reaction mixture was cooled to -30 ^{o}C and added over 2 min to a stirred suspension of CuBr•SMe_2 (427 mg, 2.07 mmol) in THF (4 mL) at -30 ^{o}C. After stirring for 2 h at -30 ^{o}C, the reaction mixture was cooled to -78 ^{o}C and a solution of 2-cyclohexen-1-one (93 mg, 0.97 mmol) in THF (3 mL) was added over 5 min. After stirring at -78 ^{o}C for 2 h, the reaction mixture was quenched with water (5 mL) and partitioned between CH_2Cl_2 (30 mL)and, sequentially, water (5 mL)and brine (15 mL). The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield ketone **4** (97 mg, 46% yield) as a pale yellow oil and ketone **5** (45 mg, 21% yield) as a pale yellow oil.

Ketone **4**: TLC R_f (5% Et_2NH/PE) = 0.35; IR (cm^{-1}) 2930, 1708, 1609, 1449; ^{1}H NMR δ 6.80 (s, 1H), 6.70 (s, 1H), 2.70 (m, 1H), 2.60 (m, 1H), 2.45 (s, 3H), 2.40-2.25 (m, 4H), 2.25 (s, 3H), 2.05 (m, 2H), 1.85 (m, 1H), 1.65 (m, 1H), 1.40 (m, 1H); ^{13}C NMR δ u 211.8, 158.5, 157.7, 147.4, 47.6, 45.1, 41.4, 31.3, 25.1; d 121.9, 121.5, 39.7, 24.4, 20.9; HRMS calcd for $C_{14}H_{20}NO$ (MH^+) 218.1545, obsd 218.1541.

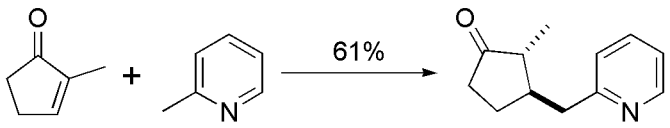
Ketone **5**: TLC R_f (5% Et_2NH/PE) = 0.26; IR (cm^{-1}) 1702, 1642, 1446; ^{1}H NMR δ 6.75 (s, 2H), 2.55 (m, 2H), 2.50 (s, 6H), 2.35 (m, 2H), 2.25 (m, 1H), 2.10-2.00 (m, 3H), 1.90 (m, 1H), 1.65 (m, 1H), 1.35 (m, 1H); ^{13}C NMR δ u 211.2, 157.7, 148.8, 47.7, 42.2, 41.3, 30.9, 25.1; d 121.0, 40.0, 24.4;. HRMS calcd for $C_{14}H_{20}NO$ (MH^+) 218.1545, obsd

218.1541.



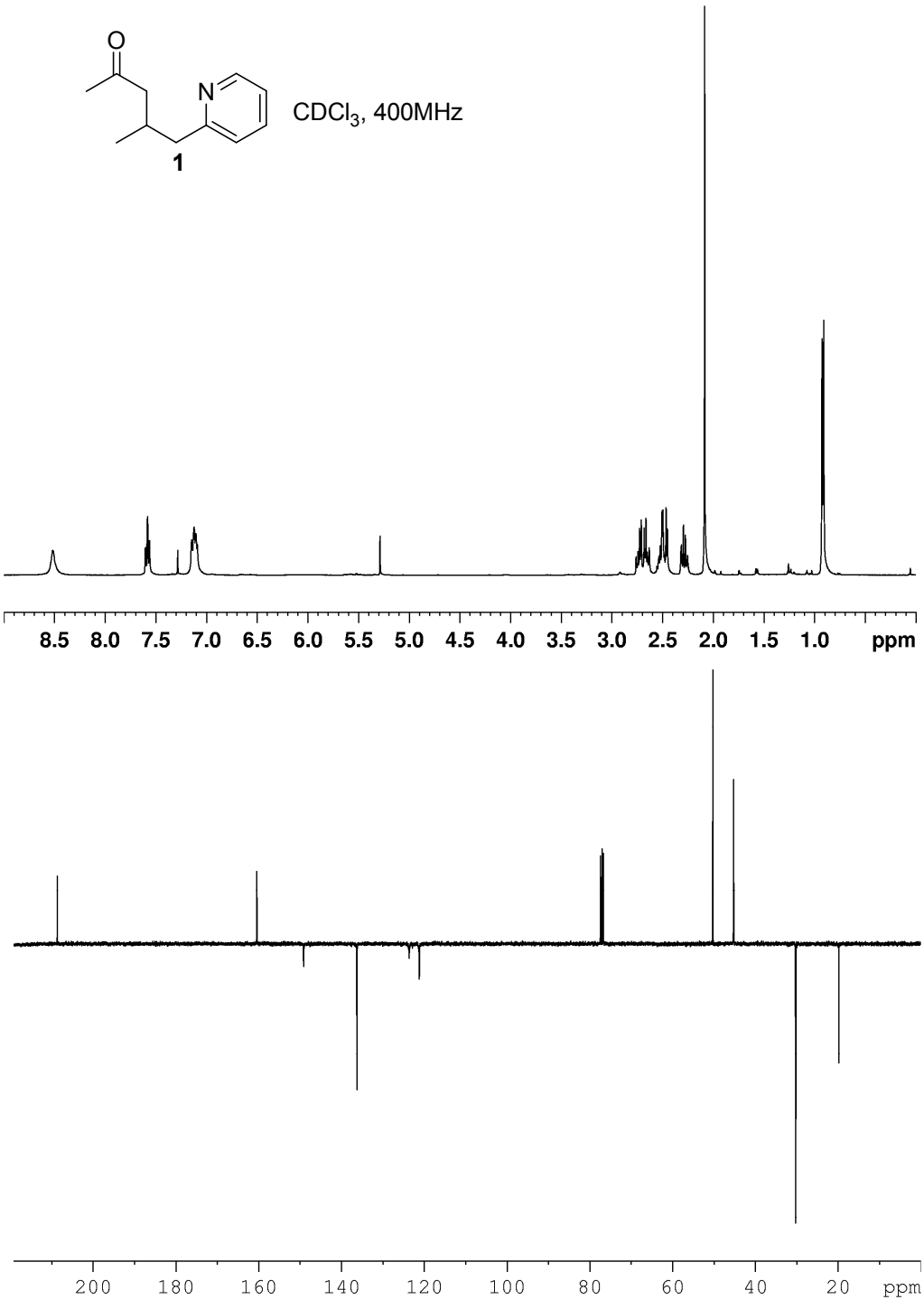
6

3-(Pyridin-2-ylmethyl)cyclopentanone (6). To a stirred solution of 2-picoline (395 mg, 4.25 mmol) in THF (4 mL) was added *n*-BuLi (4.19 mmol, 1.8 mL, 2.33 M in hexane) at -78 ^{o}C. After stirring at 0 ^{o}C for 1 h, the reaction mixture was cooled to -30 ^{o}C and added over 2 min to a stirred suspension of CuBr•SMe_2 (412 mg, 2.0 mmol) in THF (4 mL) at -30 ^{o}C. After stirring for 2 h at -30 ^{o}C, the reaction mixture was cooled to -78 ^{o}C and a solution of 2-cyclopeten-1-one (93 mg, 1.13 mmol) in THF (3 mL) was added over 5 min. After stirring at -78 ^{o}C for 2 h, the reaction mixture was quenched with water (5 mL) and partitioned between CH_2Cl_2 (30 mL) and, sequentially, water (5 mL) and brine (15 mL). The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield ketone **6** (178 mg, 90% yield) as a pale yellow oil: TLC R_f (20% MTBE/CH_2Cl_2) = 0.24; IR (cm^{-1}) 2957, 1736, 1593, 1437; ^{1}H NMR δ 8.50 (app s, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.05 (m, 2H), 2.85 (d, J = 7.3 Hz, 2H), 2.65 (m, 1H), 2.25 (m, 2H), 2.05 (m, 2H), 1.85 (m, 1H), 1.60 (m, 1H); ^{13}C NMR δ u 219.1, 159.9, 44.8, 43.6, 38.4, 29.1; d 149.4, 136.4, 123.2, 121.4, 37.4; HRMS calcd for $C_{11}H_{14}NO$ (MH^+) 176.1075, obsd 176.1067.



7

(2*R,3*R**)-2-Methyl-3-(pyridin-2-ylmethyl)cyclopentanone (7).** To a stirred solution of 2-picoline (390 mg, 4.19 mmol) in THF (4 mL) was added *n*-BuLi (4.19 mmol, 1.8 mL, 2.33 M in hexane) at -78 ^{o}C. After stirring at 0 ^{o}C for 1 h, the reaction mixture was cooled to -30 ^{o}C and added over 2 min to a stirred suspension of CuBr•SMe_2 (425 mg, 2.06 mmol) in THF (4 mL) at -30 ^{o}C. After stirring for 2 h at -30 ^{o}C, the reaction mixture was cooled to -78 ^{o}C and a solution of 2-methyl-2-cyclopentenone (96 mg, 1.0 mmol) in THF (3 mL) was added over 5 min. After stirring at -78 ^{o}C for 2 h, the reaction mixture was quenched with water (5 mL) and partitioned between CH_2Cl_2 (30 mL) and, sequentially, water (5 mL) and brine (15 mL). The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield ketone **7** (115 mg, 61% yield) as a pale yellow oil: TLC R_f (20% MTBE/CH_2Cl_2) = 0.30; IR (cm^{-1}) 1734, 1643, 1438; ^{1}H NMR δ 8.50 (app s, 1H), 7.60 (m, 1H), 7.10 (m, 2H), 3.10 (m, 1H), 2.70 (m, 1H), 2.30 (m, 1H), 2.20-1.80 (m, 4H), 1.50 (m, 1H), 1.00 (d, J = 7.0 Hz, 3H); ^{13}C NMR δ u 220.7, 159.9, 42.9, 37.3, 27.3; d 149.4, 136.4, 123.5, 121.4, 50.1, 45.0, 12.7; HRMS calcd for $C_{12}H_{16}NO$ (MH^+) 190.1232, obsd 190.1230.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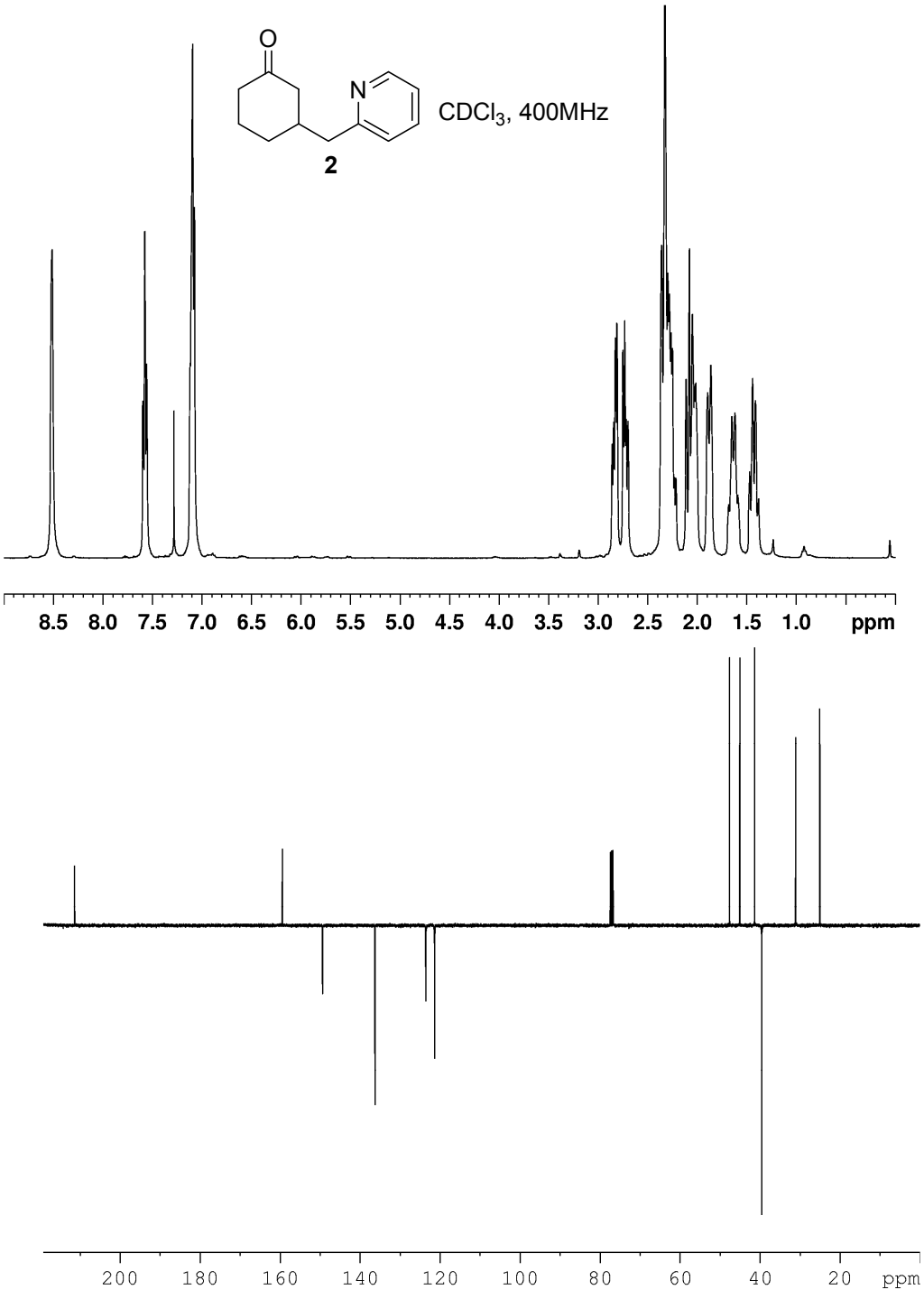
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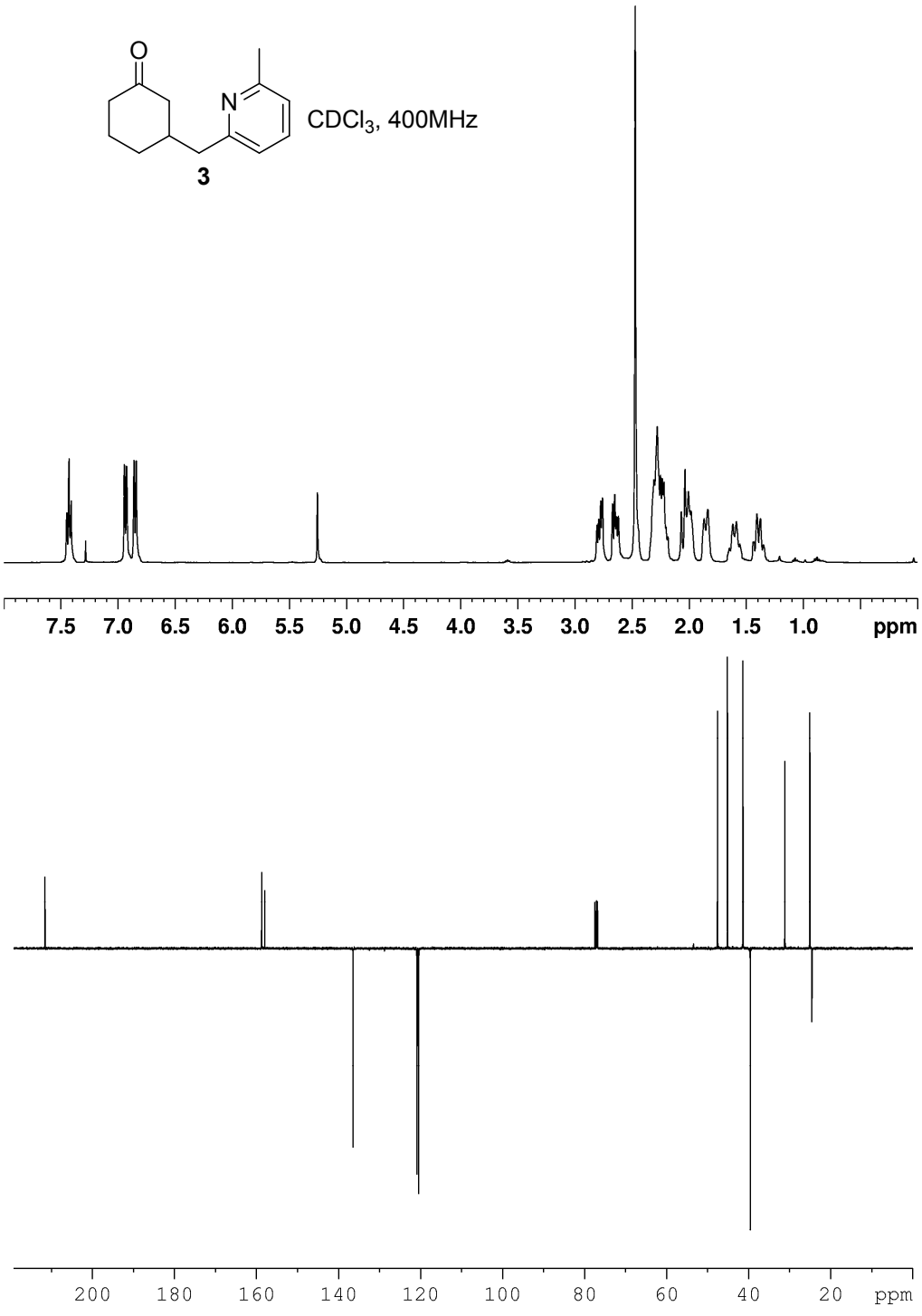
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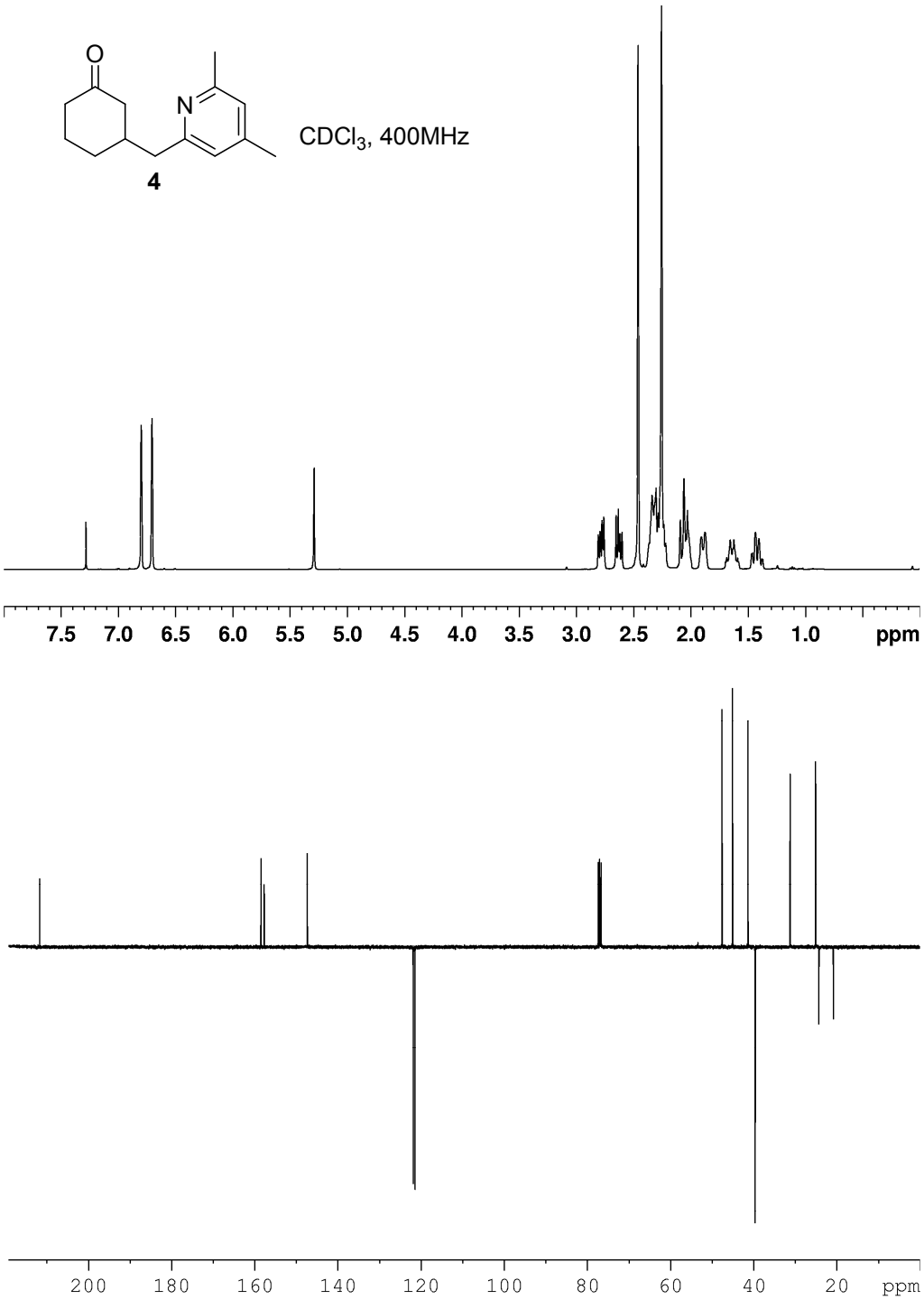
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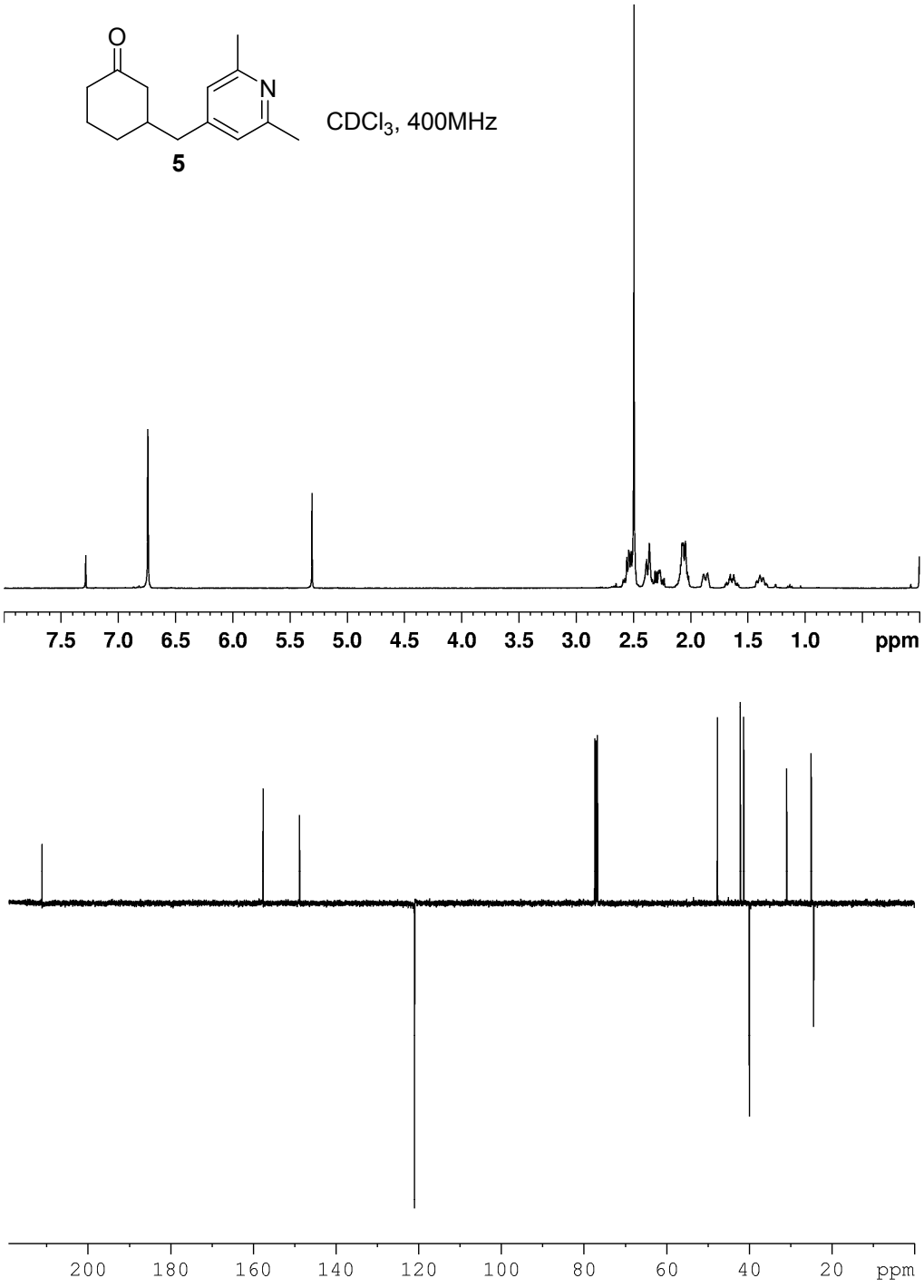
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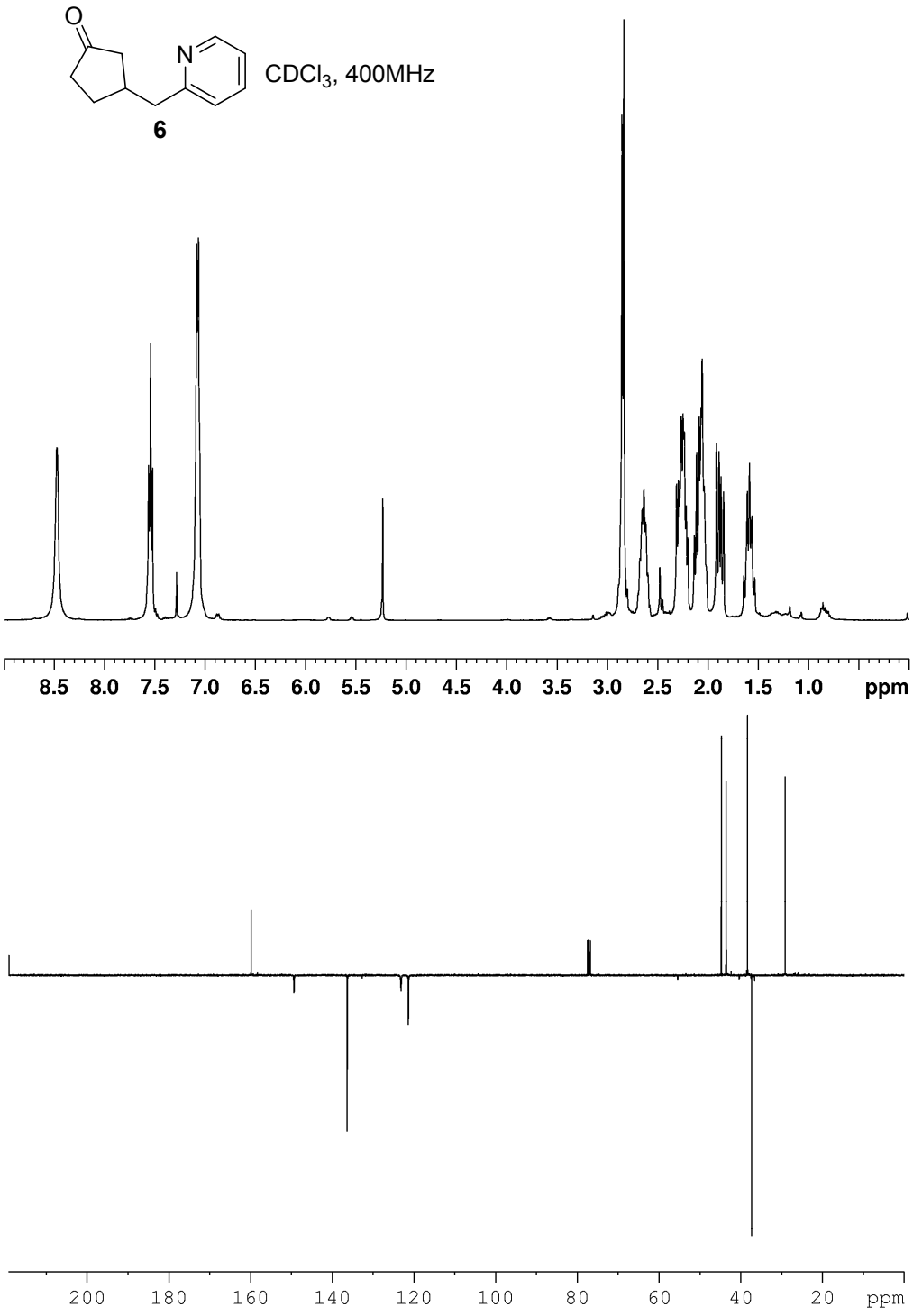
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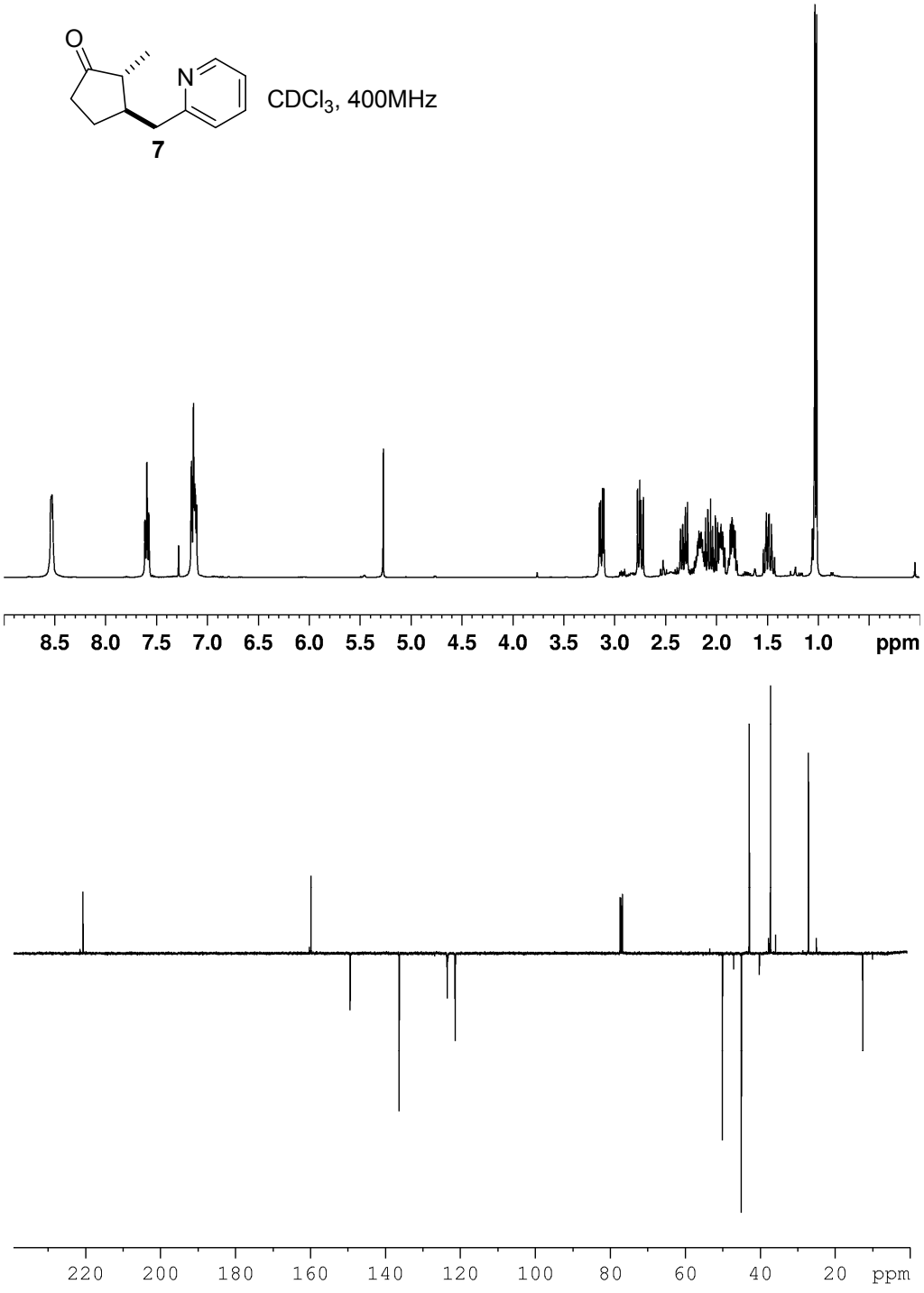
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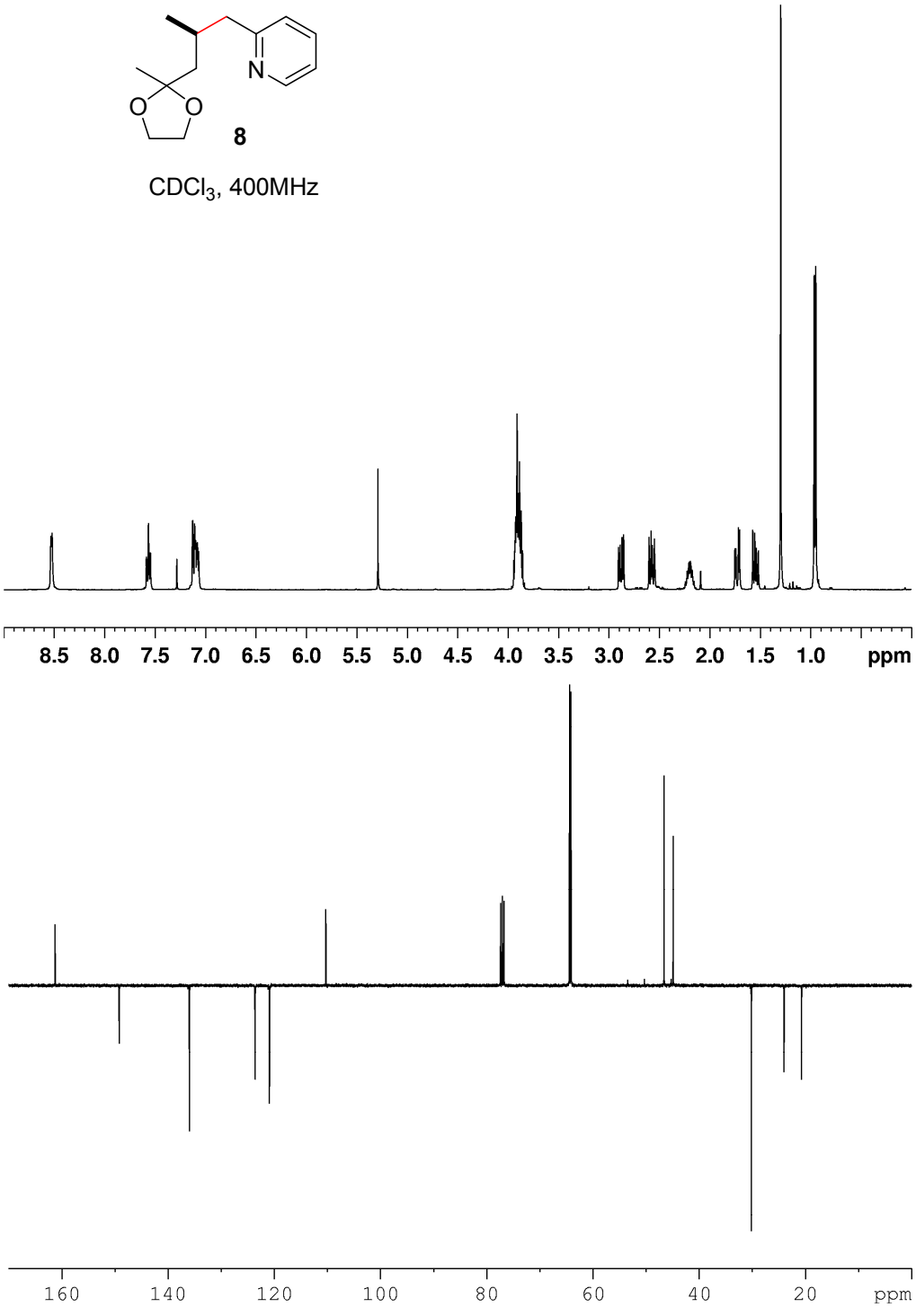
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O
O
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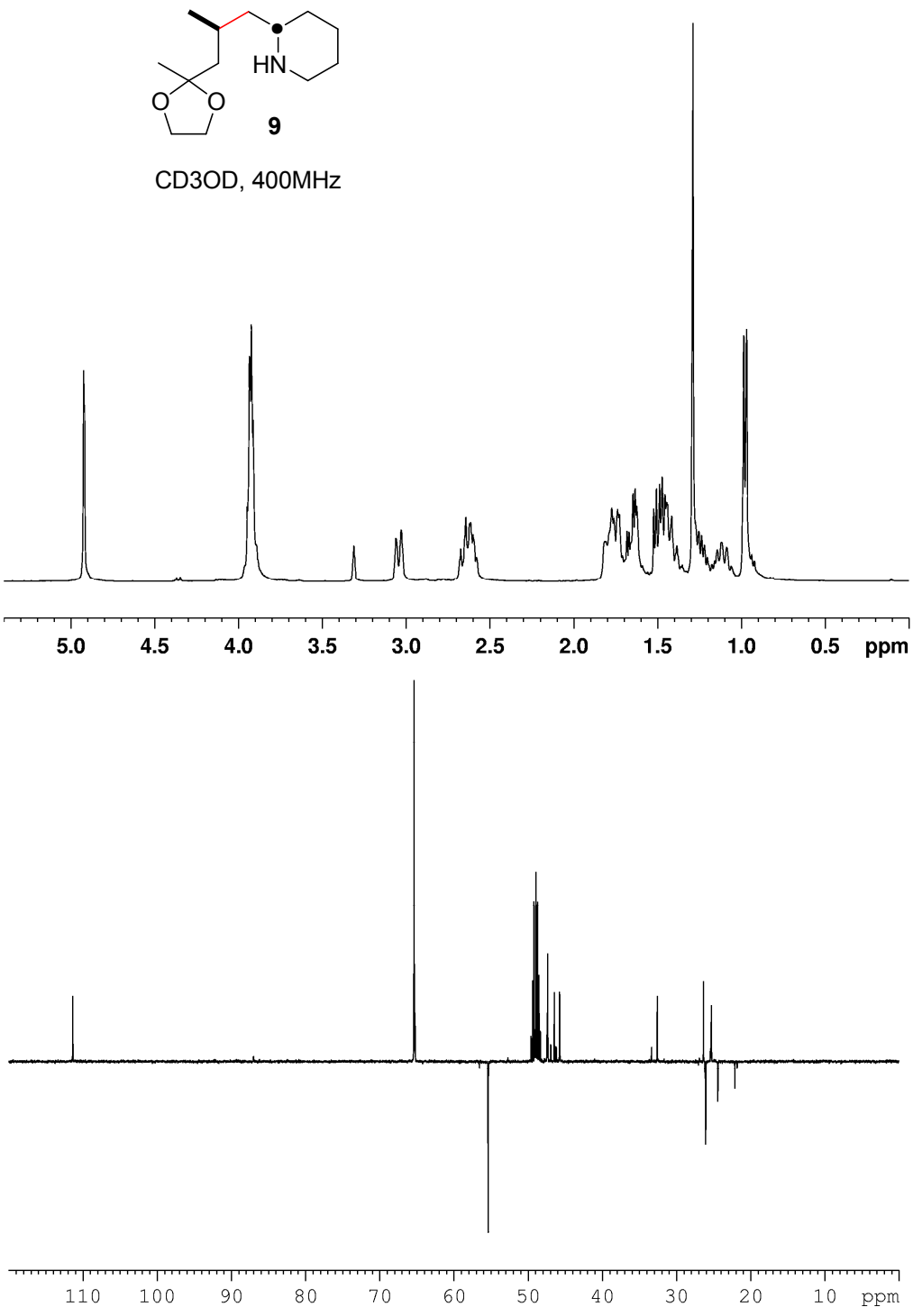
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2.5
2.0
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1.0
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ppm
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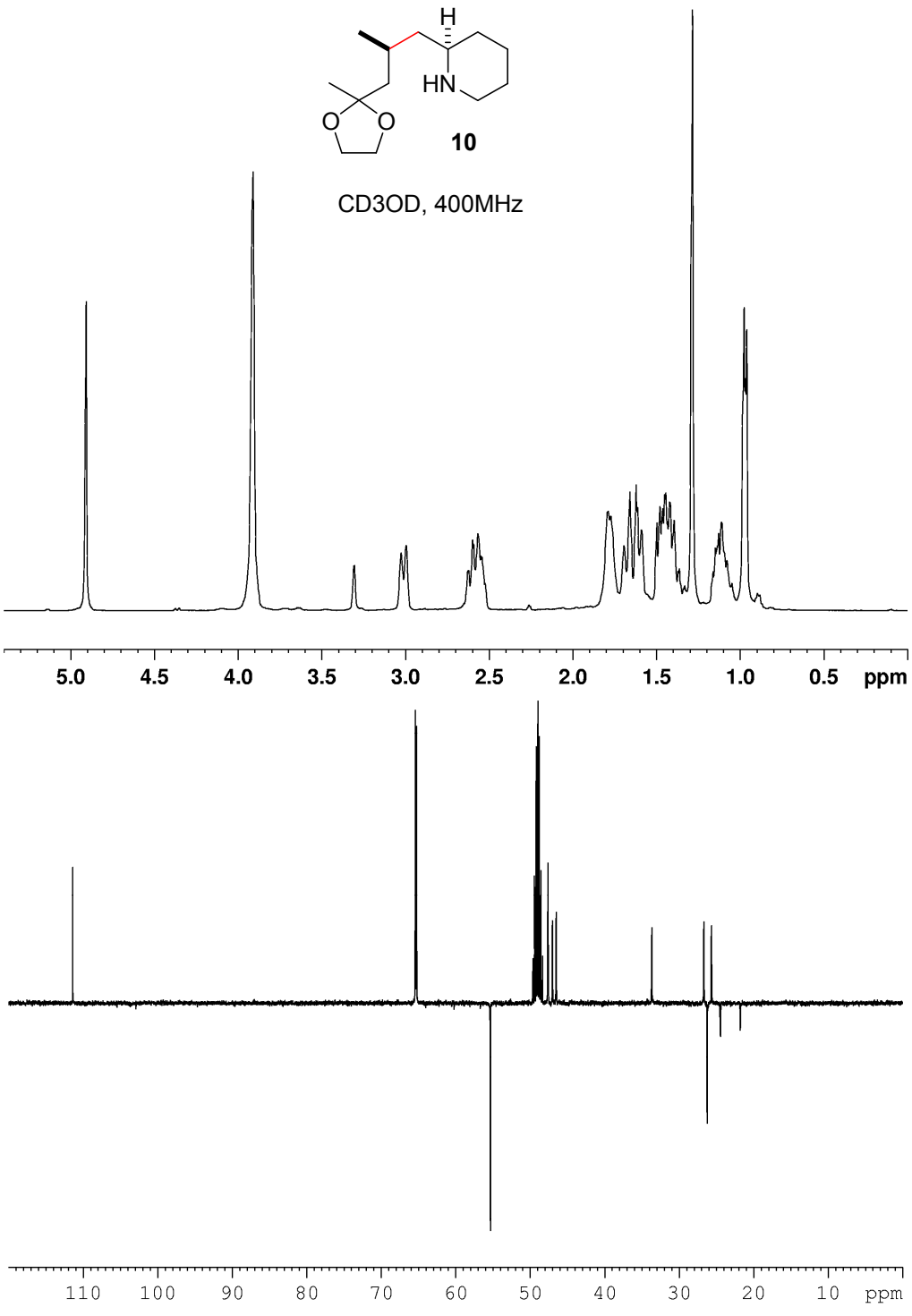
100
90
80
70
60
50
40
30
20
10
ppm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O
O
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2.5
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80
70
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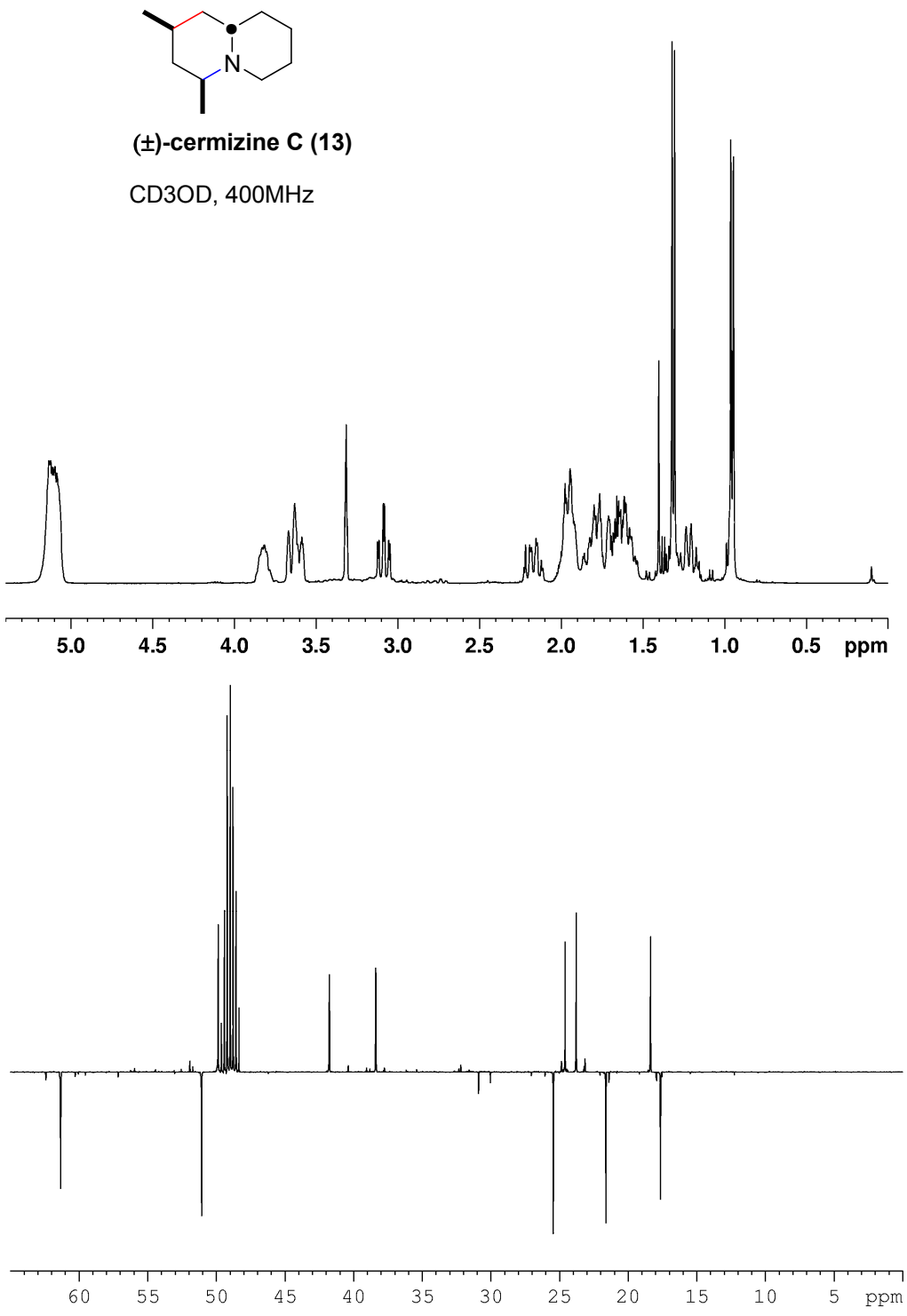
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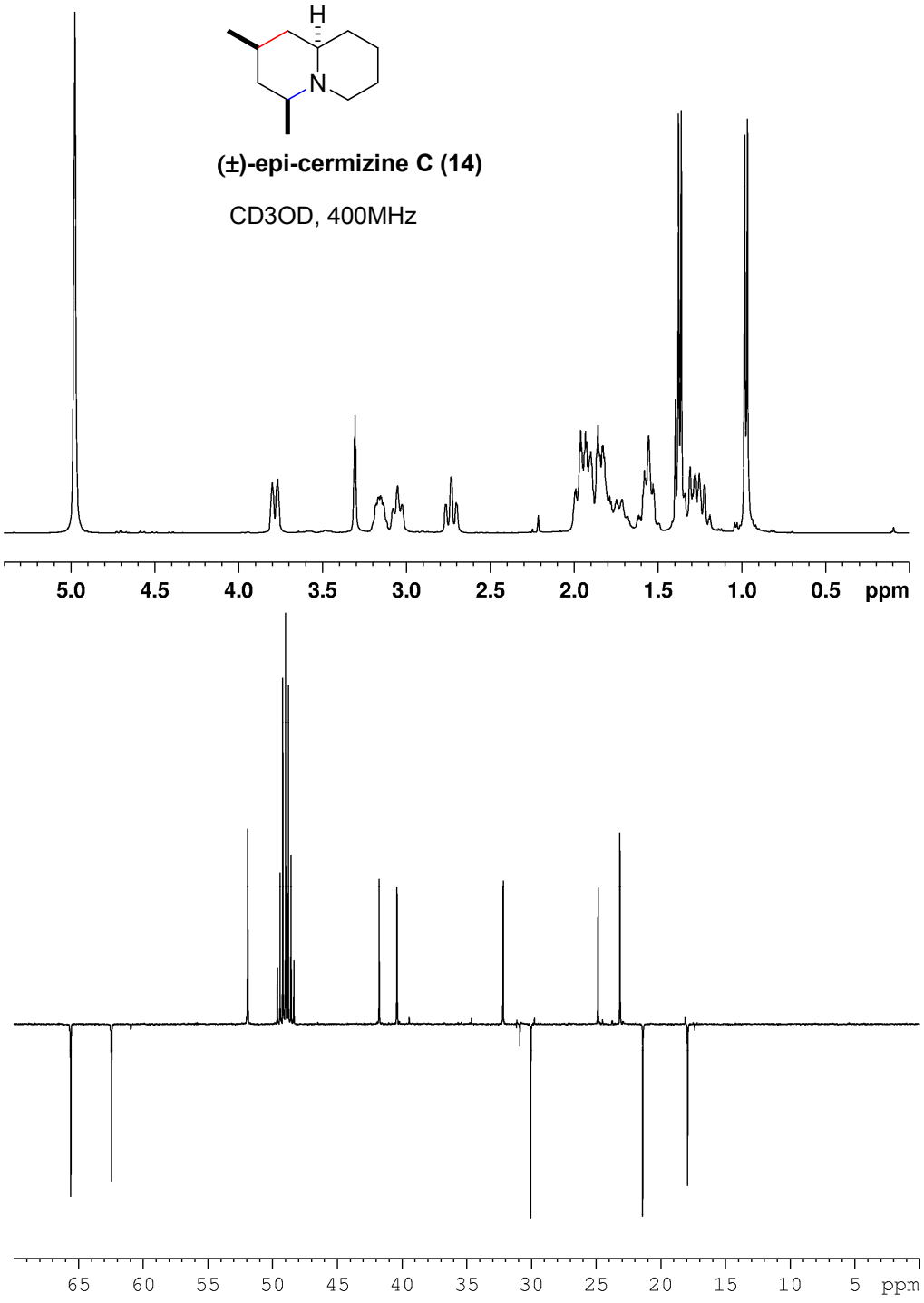
40
35
30
25
20
15
10
5
ppm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ppm
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50
45
40
35
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25
20
15
10
5
ppm