Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

Supporting Information

Upgrading furanic platforms to α-enaminones: tunable continuous flow hydrogenation of bio-based cyclopentenones

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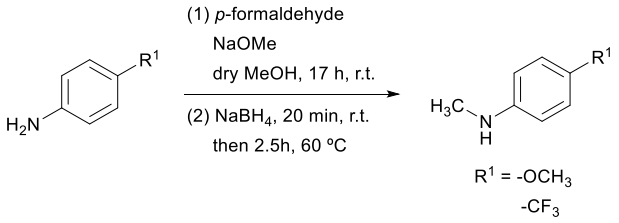
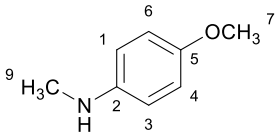
1. Preparation of Starting Materials

1.1. General procedure for the N-Methylation of para-Substituted Anilines

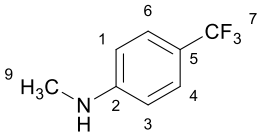


N-Methyl anilines were prepared according to a reported procedure.[1] To a suspension of NaOMe (1.26 equiv) in dry MeOH (40 mM) at 0℃, was slowly added *para*-substituted aniline (1 equiv) and paraformaldehyde (1.25 equiv) in portions, and the resultant reaction mixture stirred at room temperature for 17 hours. $NaBH_4$ (1.07 equiv) was then added in portions, at 0℃, and the reaction mixture was allowed to stir at room temperature for 20 minutes and finally stirred under reflux temperature for 2.5 hours. The reaction mixture was concentrated under reduced pressure, 1 M NaOH (20 mL) was added and the product extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, the solvent removed under reduced pressure and the crude product purified by flash column chromatography in silica gel (*n*-hexane/EtOAc).



4-methoxy-*N*-methylaniline was obtained as a dark yellow oil (0.125g, 43% yield) according to above general procedure. Analysis by NMR is consistent with the literature.[2]

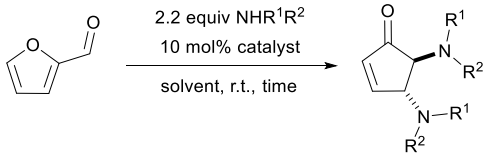
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.82 (dt, J = 7.8, 1.2 Hz, 2H, H4, H6), 6.66 – 6.54 (m, 2H, H1, H3), 3.76 (s, 3H, H7), 2.81 (s, 3H, H9) ppm.



N-methyl-4-(trifluoromethyl)aniline was obtained as a yellow oil (4.0904g, 84% yield). Analysis by NMR were consistent with the literature.[3]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 – 7.37 (m, 2H, H4, H6), 6.64 – 6.49 (m, 2H, H1, H3), 2.87 (s, 3H, H9) ppm.

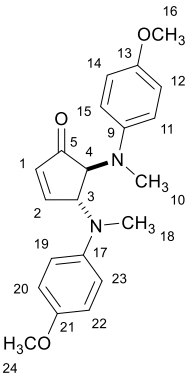
1.2. Preparation of trans-4,5-diamino-cyclopent-2-enones ***1a-1l***



Procedure I: *Trans*-4,5-diamino cyclopent-2-enones were available in the laboratory or prepared according to literature[4] as follows: To a solution of $Cu(OTf)_2$ (40 mg, 10 mol%) in water (1 mL) were added the corresponding amine (2.2 equiv) and furfural (100 mg, 1.04 mmol, 1 equiv). The reaction was stirred at room temperature for 5 minutes. The reaction mixture was diluted with distilled water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic phases were dried with $MgSO_4$ (anhydrous), filtered and the solvent evaporated under reduced pressure. When necessary, column chromatography in silica gel (*n*-hexane/EtOAc) was performed to obtain pure cyclopentenones. Analysis by NMR of all compounds was in accordance with literature.[4, 5] The novel cyclopentenones were characterized by NMR, HRMS and FTIR.

Procedure II: *Trans*-4,5-diamino cyclopent-2-enones were prepared according to literature[6] as follows: To a solution of $Dy(OTf)_3$ (10 mol%) in dry ACN (1 M) were added the corresponding amine (2.2 equiv) and furfural (1 equiv). The reaction was stirred at room temperature for 20 hours in the presence of 4Å MS. The reaction mixture was diluted with distilled water and extracted with ethyl acetate. The combined organic phases were dried with $MgSO_4$ (anhydrous), filtered and the solvent evaporated under reduced pressure. Column chromatography in silica gel (*n*-hexane/EtOAc) was performed to obtain pure cyclopentenones. The novel cyclopentenones were characterized by NMR, HRMS and FTIR.

- *Trans*-4,5-bis((4-methoxyphenyl)(methyl)amino)cyclopent-2-en-1-one **1b**



The product **1b** was obtained as a red oil (58 mg, quantitative yield) following Procedure I.

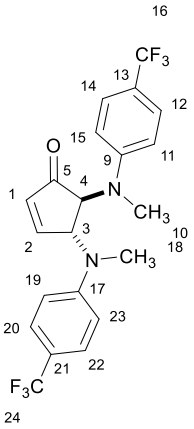
R_f (*n*-hexane/EtOAc – 4:1) = 0.13

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (dd, J = 6.2, 2.0 Hz, 1H, H2), 6.77 – 6.67 (m, 6H, H12, H14, H19, H22, H23), 6.57 – 6.52 (m, 2H, H11, H15), 6.40 (dd, J = 6.3, 2.1 Hz, 1H, H1), 4.94 (dt, J = 3.8, 2.1 Hz, 1H, H3), 4.20 (d, J = 3.5 Hz, 1H, H4), 3.73 (d, *J* = 3.7 Hz, 6H, H16, H24), 2.73 (d, *J* = 7.4 Hz, 6H, H10, H18) ppm.

^{13}C NMR APT (75 MHz, $CDCl_3$): δ 203.2 (C5), 161.9 (C2), 153.2 (C13), 152.7 (C21), 143.5 (C17), 143.5 (C9), 134.4 (C1), 117.2 (C19, C23), 116.1 (C11, C15), 114.6 (C12, C14, C20, C22), 70.1 (C4), 64.0 (C3), 55.8 (C24), 55.6 (C16), 36.9 (C10), 34.8 (C18) ppm.

HRMS (*m/z*) calculated for $C_{21}H_{24}N_2O_3$ ($[M+H]^+$):353.18652, found 353.18557.

- *Trans*-4,5-bis(methyl(4-(trifluoromethyl)phenyl)amino)cyclopent-2-en-1-one **1c**



The compound **1c** was obtained as a yellow solid (0.7618 g, 16% yield) following Procedure II.

R_f (*n*-hexane/EtOAc – 3:2) = 0.43

m.p. = 115-120℃

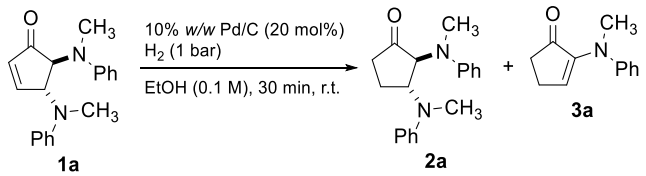
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (dd, J = 6.3, 2.0 Hz, 1H, H2), 7.40 – 7.33 (m, 4H, H12, H14, H20, H22), 6.72 – 6.66 (m, 2H, H19, H23), 6.57 – 6.50 (m, 3H, H1, H11, H15), 5.25 (dt, J = 4.1, 2.2 Hz, 1H, H3), 4.36 (d, J = 3.8 Hz, 1H, H4), 2.91 (s, 3H, H18), 2.86 (s, 3H, H10) ppm.

^{13}C NMR (75 MHz, $CDCl_3$)*: δ 200.7 (C5), 160.5 (C2), 151.2 (C17), 150.9 (C9), 135.3 (C1), 131.4 (C16, C24), 126.8-126.6 (C12, C14, C20, C22), 112.9 (C19, C23), 112.7 (C11, C15), 111.1 (C13, C21), 69.7 (C4), 62.0 (C3), 36.8 (C10), 33.5 (C18) ppm. *Carbon spectrum presented as APT

HRMS (*m/z*) calculated for $C_{21}H_{18}F_6N_2O$ ($[M+ H]^+$): 429.14109, found 429.14016.

FT-IR: 1705 cm^{-1} (C=O stretching); 1105 cm^{-1} and 1066 cm^{-1} (C-F stretching).

2. Hydrogenation of DCP under batch conditions

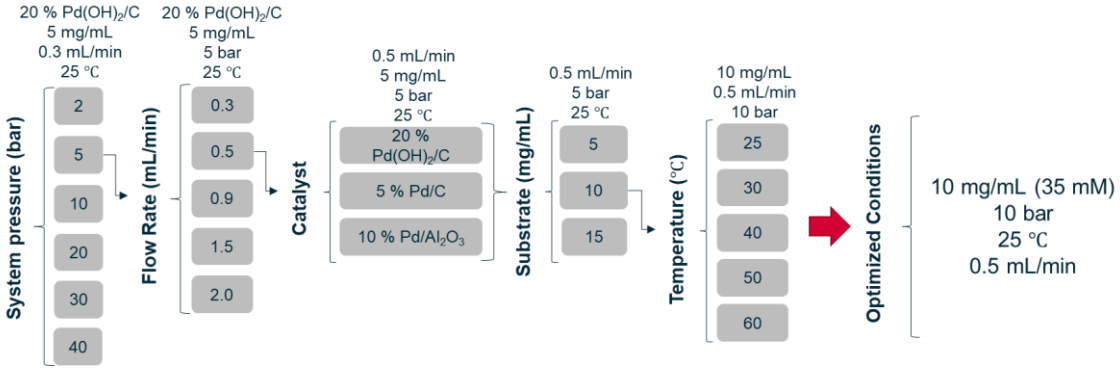


Scheme S1. Batch hydrogenation of DCP **1a** towards formation of cyclopentanone **2a** and α-enaminone **3a**.

The hydrogenation of DCP was initially performed under batch conditions using **1a** as model starting material. However, after 30 minutes we observed a mixture of products that were attributed to the hydrogenated cyclopentanone **2a** and the enaminone **3a** in 51% and 27% NMR yields (≈2:1 ratio) respectively (Scheme S1). Longer reaction times (17 h) led to an increase of **3a** up to 34% yield (≈1:1 ratio).

3. Continuous Flow Hydrogenation of *trans*-4,5-bis(methyl(phenyl)amino)cyclopent-2-enone 1a – Optimization of Reaction Parameters

Trans-4,5-bis(methyl(phenyl)amino)cyclopent-2-enone **1a** (20 mg, 0.068 mmol) was dissolved in distilled EtOH and injected at H-Cube® Mini Plus continuous flow reactor and a Thales Nano®, CatCart® 30 x 4 mm cartridge (65 µL reactor volume). Maintaining all the other constant, the reaction parameters were screened in the following order: system pressure (2, 5, 10, 20, 30, 40 bar), flow rate (0.3, 0.5, 0.9, 1.5, 2 mL/min), catalyst (20% $Pd(OH)_2/C$, 5% Pd/C, 10% Pd/Al_2O_3), substrate concentration (5, 10, 15 mg/mL), and temperature (25, 30, 40, 50, 60 °C) (Scheme). Optimized conditions were considered: 10 bar, 0.5 mL/min, 10 mg/mL (35 mM) and 25 °C. The reaction mixture was collected and the solvent evaporated under reduced pressure at 40°C and the crudes analysed by NMR in $CDCl_3$.



Scheme S2. Work flow diagram for optimization of continuous flow reaction conditions using H-Cube® Mini Plus hydrogenation reactor and *trans*-4,5-bis(methyl(phenyl)amino)cyclopent-2-enone **1a** as model substrate.

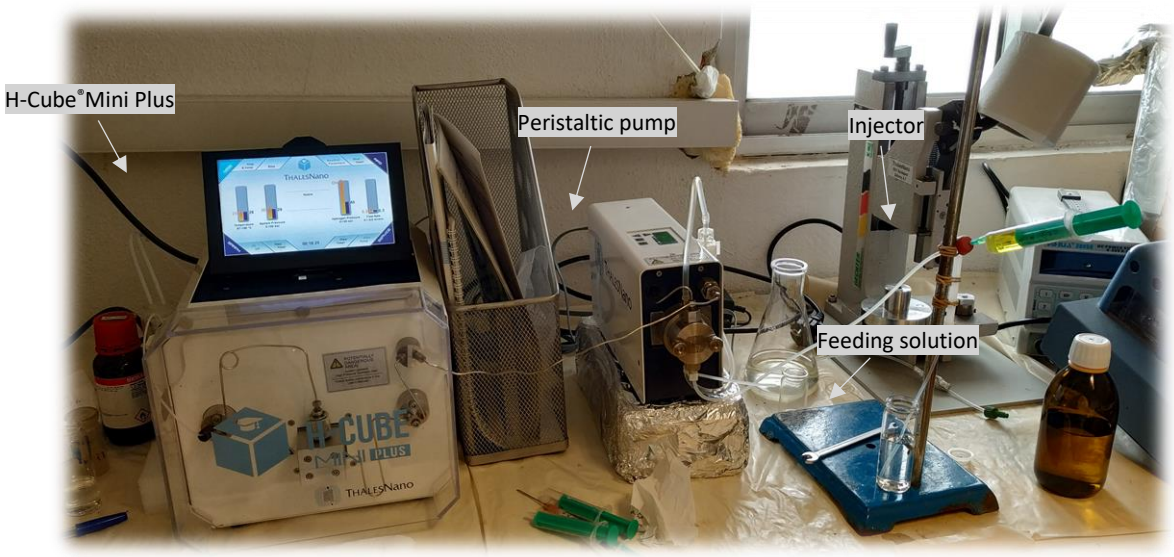
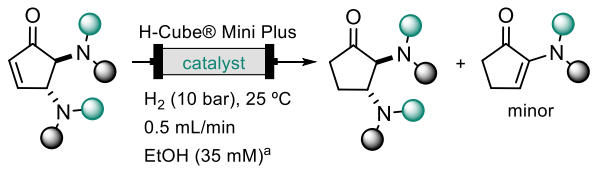


Figure S1. Continuous flow process setup for hydrogenation of *trans*-4,5-diamino-cyclopent-2-enones using H-Cube® Mini Plus reactor.

4. Scope of *trans*-4,5-Diamino-cyclopentanones 2a-2l

Table S1. Selectivity of species in crude containing a mixture of cyclopentanones **2** and α-enaminones **3**.

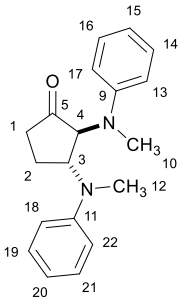


Catalyst: **A** - 5% Pd/C | **B** - 20% $Pd(OH)_2/C$ | **C** - 10% Pd/Al_2O_3

2a/3a	**2b/3b**	**2c/3c**	**2d/3d**	**2e/3e**	**2f/3f**
A - 82%/0%	A - 48%/0%	A - 83%/0%	A - 78%/0%	A - 40%/7%	A - 78%/8%
B - 88%/10%	B - 48%/0%	B - 99%/0%	B - 41%/0%	B - 53%/2%	B - 67%/6%
C - 80%/16%	C - 45%/32%	C - 94%/0%	C - 42%/0%	C - 48%/4%	C - 71%/9%

2g/3g	**2h/3h**	**2i/3i**	**2j/3j**	**2k/3k**
A - 0%/56%	A - 52%/0%	A - 66%/0%	A - 96%/0%	A - 69%/0%
B - 0%/70%	B - 93%/0%	B - 59%/0%	B - 59%/0%	B - 80%/0%
C - 0%/96%	C - 76%/0%	C - 56%/0%	C - 45%/5%	C - 78%/0%

***Trans*-2,3-bis(methyl(phenyl)amino)cyclopentan-1-one 2a**



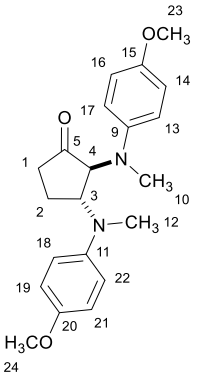
Trans-2,3-bis(methyl(phenyl)amino)cyclopentan-1-one **2a** was obtained as a transparent/white oil in 82% yield using 5 % Pd/C. The substrate concentration used was 35 mM.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (tdd, J = 7.2, 5.1, 2.2 Hz, 4H, H14, H16, H19, H21), 6.79 – 6.67 (m, 4H, H15, H18, H20, H22), 6.66 – 6.60 (m, 2H, H13, H17), 4.50 (td, J = 11.2, 6.2 Hz, 1H, H3), 4.37 (dd, J = 11.7, 1.5 Hz, 1H, H4), 2.67 (s, 3H, H12), 2.63 (s, 3H, H10), 2.63 – 2.52 (m, 1H, H1a), 2.40 – 1.98 (m, 3H, H1b, H2) ppm.

^{13}C NMR (75 MHz, $CDCl_3$)*: δ 213.6 (C5), 150.4 (C11), 150.0 (C9), 129.2 (C14, C26), 129.1 (C19, C21), 118.5 (C15), 118.3 (C20), 115.1 (C18, C22), 114.6 (C13, C17), 70.3 (C4), 60.2 (C3), 35.3 (C1), 34.5 (C10), 31.4 (C12), 21.5 (C2) ppm. * Spectrum presented as APT

HRMS (*m/z*) calculated for $C_{19}H_{22}N_2O$ ($[M+H]^+$): 295.18049, found 295.17963

***Trans*-2,3-bis((4-methoxyphenyl)(methyl)amino)cyclopentan-1-one 2b**



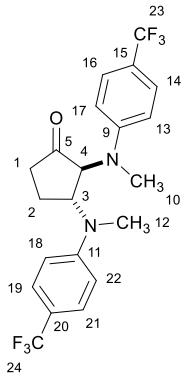
Trans-2,3-bis((4-methoxyphenyl)(methyl)amino)cyclopentan-1-one **2b** was obtained as a red oil in 48% yield using 5% Pd/C. The substrate concentration used was 24 mM.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.85 – 6.71 (m, 6H, H14, H16, H18, H19, H21, H22), 6.63 (td, *J* = 6.6, 2.5 Hz, 2H, H13, H17), 4.30 – 4.09 (m, 2H, H3, H4), 3.76 (s, 3H, H12), 3.75 (s, 3H, H10), 2.61 (d, *J* = 10.6 Hz, 6H, H23, H24), 2.54 – 2.45 (m, 1H, H1a), 2.28 – 1.94 (m, 3H, H1b, H2) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 214.7 (C5), 153.4 (C20), 152.8 (C15), 144.8 (C11), 144.5 (C9), 118.6 (C18, C22), 117.0 (C13, C17), 114.5 (C14, C16, C19, C21), 72.0 (C4), 61.8 (C3), 55.8 (C23, C24), 35.9 (C1), 35.1 (C10), 33.0 (C12), 22.6 (C2) ppm.

HRMS (*m/z*) calculated for $C_{21}H_{26}N_2O_3$ ([M+H - Amine]$^+$): 218.11756, found 218.11720.

***Trans*-2,3-bis(methyl(4-(trifluoromethyl)phenyl)amino)cyclopentan-1-one 2c**



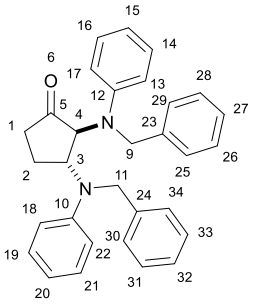
Trans-2,3-bis(methyl(4-(trifluoromethyl)phenyl)amino)cyclopentan-1-one **2c** was obtained as a yellow oil in 99% yield using 20% $Pd(OH)_2$/C. The substrate concentration was 17 mM.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43 – 7.35 (m, 4H, H14, H16, H19, H21), 6.73 – 6.66 (m, 2H, H18, H22), 6.64 - 6.58 (m, 2H, H13, H17) 4.60 (td, *J* = 11.2, 6.2 Hz, 1H, H3), 4.44 (dd, *J* = 11.6, 1.5 Hz, 1H, H4), 2.77 (s, 3H, H12), 2.69 (s, 3H, H10), 2.67 – 2.58 (m, 1H, H1a), 2.45 – 2.03 (m, 3H, H1b, H2) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 211.6 (C5), 152.3 (C11), 152.0 (C9), 126.6 (m, C14, C16, C19, C21), 113.4 (C18, C22), 113.1 (C13, C17), 69.8 (C4), 59.2 (C3), 35.1 (C1), 34.6 (C10), 31.2 (C12), 22.9 (C2).

HRMS (*m/z*) calculated for $C_{21}H_{20}F_6N_2O$ ([M+H-Amine]$^+$): 256.09438, found 256.09407.

***Trans*-2,3-bis(benzyl(phenyl)amino)cyclopentan-1-one 2d**



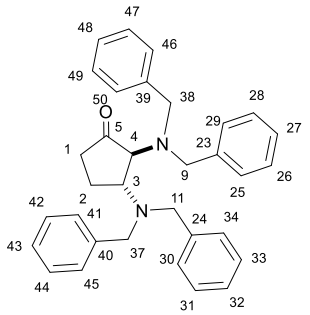
Trans-2,3-bis(benzyl(phenyl)amino)cyclopentan-1-one **2d** was obtained as a pale yellow oil in 78% yield using 5% Pd/C. The substrate concentration was 30 mM.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 – 7.02 (m, 14H, H14, H16, H19, H21, H25-H34), 6.86 – 6.57 (m, 6H, H13, H15, H17, H18, H20, H22), 4.90 – 4.72 (m, 1H, H3), 4.63 – 4.24 (m, 5H, H4, H9, H11), 2.64 – 2.42 (m, 1H, H1a), 2.41 – 2.19 (m, 2H, H1b, H2a), 1.86 (d, *J* = 10.4 Hz, 1H, H2b) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 213.9 (C5), 149.0 (C10), 148.4 (C12), 139.2 (C29), 138.8 (C28), 129.2 (C14, C17, C24, C26), 128.6 (C19, C21, C31, C33), 127.4 (C25, C29, C30, C34), 127.1 (C32), 126.8 (C27), 119.0 (C15), 118.5 (C20), 116.0 (C13, C17, C18, C22), 70.1 (C4), 58.8 (C3), 54.9 (C9), 49.2 (C11), 35.6 (C1), 23.1 (C2) ppm.

HRMS (*m/z*) calculated for $C_{31}H_{30}N_2O$ ([M+H]$^+$): 447.24364, found 447.24206; calculated for $C_{31}H_{30}N_2O$ ([M+H-Amine]$^+$): 264.13829, found 264.13774.

***Trans*-2,3-bis(dibenzylamino)cyclopentan-1-one 2e**



Trans-2,3-bis(dibenzylamino)cyclopentan-1-one **2e** was obtained in a mixture with the corresponding α-enaminone **3e**, as a white solid in 53% yield using 20% $Pd(OH)_2$/C. The substrate concentration was 18 mM.

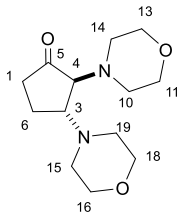
^{1}NMR (300 MHz, $CDCl_3$): δ 7.47 – 7.17 (m, 20H, H25-H34, H41-H50), 3.90 – 3.43 (m, H, H3, H4, H9, H11, H38, H37), 2.36 – 2.22 (m, 1H, H1a), 2.10 – 1.85 (m, 2H, H1b, H2a), 1.79 – 1.65 (m, 1H, H2b) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 218.1 (C5), 140.0 (C24, C40), 139.7 (C23, C39), 129.2 (C26, C28, C47, C49), 128.5 (C31, C33, C42, C44), 128.4 (C30, C34, C41, C45), 128.3 (C25, C29, C46, C50), 127.2 (C27, C48), 127.0 (C32, C43), 66.4 (C4), 58.7 (C3), 54.4 (C9, C38), 53.6 (C11, C37,), 36.6 (C1), 19.7 (C2) ppm.

m.p. = 131-135 ℃ (exp)

HRMS (*m/z*) calculated for $C_{33}H_{34}N_2O$ ($[M+H]^+$): 475.27494, found 475.27400.

***Trans*-2,3-dimorpholinocyclopentan-1-one 2f**



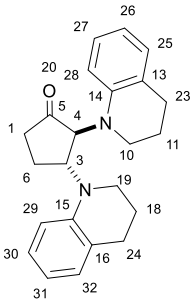
Trans-2,3-dimorpholinocyclopentan-1-one **2f** was obtained in a mixture with the corresponding α-enaminone **3f**, as a pale-yellow oil in 78% yield using 5% Pd/C. The substrate concentration was 35 mM.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.78 – 3.69 (m, 1H, H4), 3.65 (t, J = 4.7 Hz, 4H, H11, H13), 3.08 (dd, J = 9.8, 1.9 Hz, 4H, H16, H18), 3.02 – 2.89 (m, 3H, H3, H10), 2.79 (dt, J = 11.9, 4.8 Hz, 2H, H15), 2.73 – 2.58 (m, 4H, H14, H19), 2.45 – 2.30 (m, 1H, H1a), 2.23 – 1.93 (m, 2H, H1b, H2a), 1.78 – 1.59 (m, 1H, H2b) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 216.3 (C5), 73.9 (C4), 67.6 (C16, C18), 67.3 (C11, C13), 63.2 (C3), 51.2 (C15, C19), 49.7 (C10, C14), 36.9 (C1), 22.0 (C2) ppm.

HRMS (*m/z*) calculated for $C_{13}H_{22}N_2O_3$ ($[M+H]^+$): 255.17032, found 255.16972.

***Trans*-2,3-bis(3,4-dihydroquinolin-1-yl)cyclopentan-1-one 2h**



Trans-2,3-bis(3,4-dihydroquinolin-1-yl)cyclopentan-1-one **2h** was obtained as a white oil in 93% yield using 20% $Pd(OH)_2$/C. The substrate concentration was 30 mM.

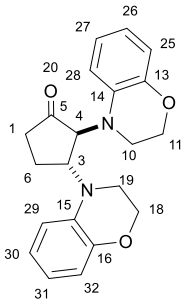
^{1}H NMR (300 MHz, $CDCl_3$). δ 7.10 – 6.87 (m, 4H, H25, H27, H30, H32), 6.68 (d, J = 8.3 Hz, 1H, H29), 6.60 (tt, J = 7.3, 1.2 Hz, 2H, H26, H31), 6.49 (d, J = 8.2 Hz, 1H, H28), 4.68 (td, J = 11.5, 5.6 Hz, 1H, H3), 4.52 (d, J = 12.1

Hz, 1H, H4), 3.35 – 3.12 (m, 2H, H19), 3.09 (d, J = 5.8 Hz, 2H, H10), 2.82 – 2.47 (m, 5H, H1a, H23, H24), 2.43 – 2.28 (m, 2H, H1b, H2a), 2.21 – 1.97 (m, 1H, H2b), 1.82 (dddd, J = 9.0, 6.2, 4.0, 1.4 Hz, 4H, H11, H18) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 213.4 (C5), 145.2 (C14), 145.0 (C15), 129.5 (C25), 129.4 (C32), 127.3 (C27), 127.0 (C30), 124.2 (C16), 124.0 (C13), 116.9 (C31), 116.6 (C26), 111.2 (C29), 111.1 (C28), 68.0 (C4), 56.3 (C3), 45.3 (C10), 41.7 (C19), 35.1 (C1), 28.3 (C24), 28.2 (C23), 22.4 (C18), 22.3 (C11), 20.7 (C2) ppm.

HRMS (*m/z*) calculated for $C_{23}H_{26}N_2O$ ([M+H-Amine]$^+$): 214.12264, found 214.12216.

***Trans*-2,3-bis(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)cyclopentan-1-one 2i**



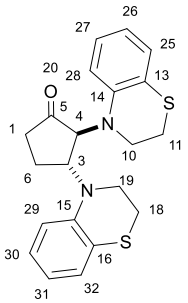
Trans-2,3-bis(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)cyclopentan-1-one **2i** was obtained as a yellow oil in 66% yield using 5% Pd/C. The substrate concentration was 34 mM.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.87 – 6.73 (m, 4H, H25, H27, H30, H32), 6.73 – 6.60 (m, 4H, H26, H28, H29, H31) 4.58 (td, J = 11.5, 5.4 Hz, 1H, H3), 4.44 (dd, J = 12.2, 1.5 Hz, 1H, H4), 4.40 – 4.16 (m, 2H, H11a, H18a), 4.12 (ddd, J = 7.8, 4.8, 3.1 Hz, 2H, H11b, H18b), 3.97 (tdd, J = 10.4, 6.8, 3.2 Hz, 4H, H10, H19), 2.73 – 2.44 (m, 1H, H1a), 2.44 – 2.29 (m, 2H, H1b, H2a), 2.13 – 1.91 (m, 1H, H2b) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 211.6 (C5), 144.7 (C16), 144.5 (C13), 134.1 (C14), 133.9 (C15), 121.7 (C27), 121.5 (C30), 118.7 (C31), 118.6 (C26), 117.2 (C32), 117.1 (C25), 112.3 (C29), 112.1 (C28), 67.0 (C4), 64.4 (C11, C18), 55.6 (C3), 43.5 (C10), 40.2 (C19), 34.8 (C1), 20.3 (C2) ppm.

HRMS: [M+H]$^+$ = 351.16948 *m/z* (exp) [351.17087 *m/z* calc]

***Trans*-2,3-bis(2,3-dihydro-4H-benzo[b][1,4]thiazin-4-yl)cyclopentan-1-one 2j**



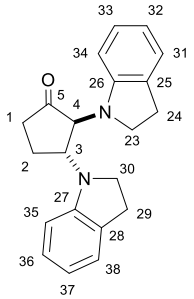
Trans-2,3-bis(2,3-dihydro-4H-benzo[b][1,4]thiazin-4-yl)cyclopentan-1-one **2j** was obtained as a yellow oil in 96% yield using 5% Pd/C. The substrate concentration was 5 mM.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.06 (ddd, J = 7.7, 2.6, 1.6 Hz, 2H, H25, H27), 6.96 (dtd, J = 8.3, 7.2, 1.6 Hz, 2H, H30, H32), 6.79 – 6.65 (m, 3H, H26, H28, H31), 6.59 (dd, J = 8.2, 1.2 Hz, 1H, H29), 4.47 (d, J = 3.2 Hz, 2H, H3, H4), 3.56 – 3.22 (m, 4H, H10, H19), 2.91 – 2.79 (m, 4H, H11, H18), 2.72 – 2.50 (m, 1H, H1a), 2.44 – 2.24 (m, 2H, H1b, H2a), 2.09 – 1.97 (m, 1H, H2b) ppm.

^{13}C NMR APT (75 MHz, $CDCl_3$): δ 212.7 (C5), 143.5 (C14, C15), 128.3 (C27), 128.1 (C25), 125.8 (C30), 125.7 (C32), 121.2 (C13, C16), 119.2 (C26, C31) 114.8 (C28), 114.3 (C29), 71.4 (C4), 58.4 (C3), 45.9 (C19), 42.1 (C10), 34.8 (C1), 27.1 (C18), 26.7 (C11), 21.9 (C2) ppm.

HRMS (*m/z*) calculated for $C_{21}H_{22}N_2OS_2$ ([M+H-Amine]$^+$): 232.07906, found 232.07840.

***Trans*-2,3-di(indolin-1-yl)cyclopentan-1-one 2k**



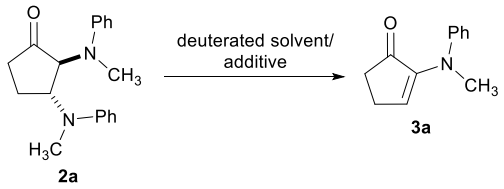
Trans-2,3-di(indolin-1-yl)cyclopentan-1-one **2k** was obtained as a yellow oil in 80% yield using 20% $Pd(OH)_2$/C. The substrate concentration was 33 mM.

^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.16 – 6.91 (m, 4H, H31, H33, H36, H38), 6.62 (tdd, J = 7.4, 3.6, 1.0 Hz, 2H, H32, H37), 6.40 (d, J = 7.9 Hz, 1H, H34), 6.27 (d, J = 7.8 Hz, 1H, H35), 4.37 (td, J = 11.3, 5.7 Hz, 1H, H3), 4.22 (dd, J = 12.0, 1.6 Hz, 1H, H4), 3.51 (dd, J = 9.3, 7.8 Hz, 3H, H23a, H30), 3.37 (td, J = 9.5, 7.8 Hz, 1H, H23b), 3.19 – 2.94 (m, 4H, H24, H29), 2.68 – 2.46 (m, 1H, H1a), 2.46 – 2.14 (m, 2H, H1b, H2a), 2.18 – 1.94 (m, 1H, H2b) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): *δ* 212.8 (C5), 150.7 (C27), 150.5 (C26), 129.9 (C25), 129.7 (C28), 127.5 (C36), 127.2 (C33), 124.9 (C31), 124.8 (C38), 117.7 (C32), 117.6 (C37), 106.4 (C34), 105.9 (C35), 65.0 (C4), 54.7 (C3), 49.0 (C23), 46.7 (C30), 35.6 (C1), 28.4 (C29), 28.3 (C24), 19.8 (C2) ppm.

HRMS (*m/z*) calculated for $C_{21}H_{22}N_2O$ ([M+H-Amine]$^+$): 200.10754, found 200.10680.

5. Stability studies of *trans*-2,3-bis(methyl(phenyl)amino)cyclopentan-1-one 2a in the presence of deuterated solvents and additives



Trans-4,5-bis(methyl(phenyl)amino)cyclopent-2-en-1-one (20 mg, 0.068 mmol) was dissolved in distilled EtOH and injected at H-Cube® Mini Plus continuous flow reactor under optimized conditions (10 bar, 0.5 mL/min, 10 mg/mL (35 mM) and 25 °C) using 5% Pd/C as catalyst. Different analyses were performed:

- After solvent evaporation at 30 °C the crudes were dissolved in different deuterated solvents (0.5 mL): $CDCl_3$, $NaHCO_3$ basified $CDCl_3$ and acetone-*d6*. The samples were analyzed over time (0, 10, 20, 30 and 40 h) at room temperature (25 °C) by ^1H NMR. The normalized increase in the percentage of 2-(methyl(phenyl)amino)cyclopent-2-en-1-one **3a** form was observed and plotted (Figure S2). The profile revealed a significant difference between non-neutralized $CDCl_3$ and the latter ones, where the ratio of **2a**: **3a** was reduced in the first case (1.2:8.8 vs 3:7). This was a preliminary indication that β-amine elimination was somewhat inhibited under slightly acidic conditions.

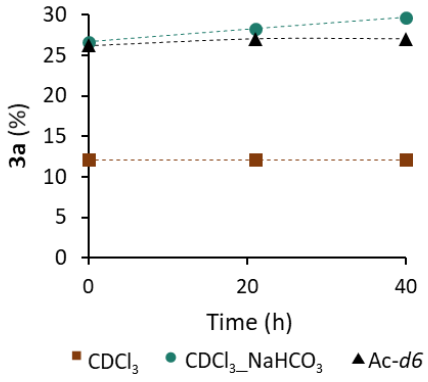


Figure S2. Percentage of α-enaminone **3a** over time in the presence of $CDCl_3$, $NaHCO_3$ basified $CDCl_3$ and acetone-d_6 at room temperature.

- Additives (0.5 equiv of *N*-methyl aniline, 28 % NH_3/H_2O, L-ascorbic acid, K_2CO_3, $Na_2HPO_4.2H_2O$, glacial acetic acid or formic acid) were added to the ethanolic solution collected directly from the H-Cube® Mini Plus reactor and the solvent evaporated under reduced pressure at 30 °C. The crudes were stored in the freezer overnight, dissolved in $CDCl_3$ and analyzed over time by ^1H NMR in the following sequence: days 0-1 → stored at 25 °C; days 1-6 → stored at 33 °C; days 6-14 → stored at 25 °C. The percentage of 2-(methyl(phenyl)amino)cyclopent-2-en-1-one **3a** observed was plotted (Figure S3/S4). NaH_2PO_4 successfully inhibited the formation of α-enaminone, even after 14 days. The inhibition of amine elimination by NaH_2PO_4

can be explained by its weak acidity. The possible protonation of free *N*-methyl aniline decreases its reactivity, preventing its action as base.

On the other hand, by adding K_2CO_3 as additive, the formation of α-enaminone **3a** was enhanced, possibly by base catalysed elimination of the amine. A suggested role of K_2CO_3 involves α-carbonyl deprotonation with subsequent enolate formation. This will lead to the elimination of β-amine to reform the thermodynamically favourable enone. Similar behaviour was observed in the presence of *N*-methylaniline, which also indicate a possible autocatalytic mechanism for the formation of **3a**. It is noteworthy that even in the absence of stirring the reaction occurs, despite not reaching full conversion after 7 hours.

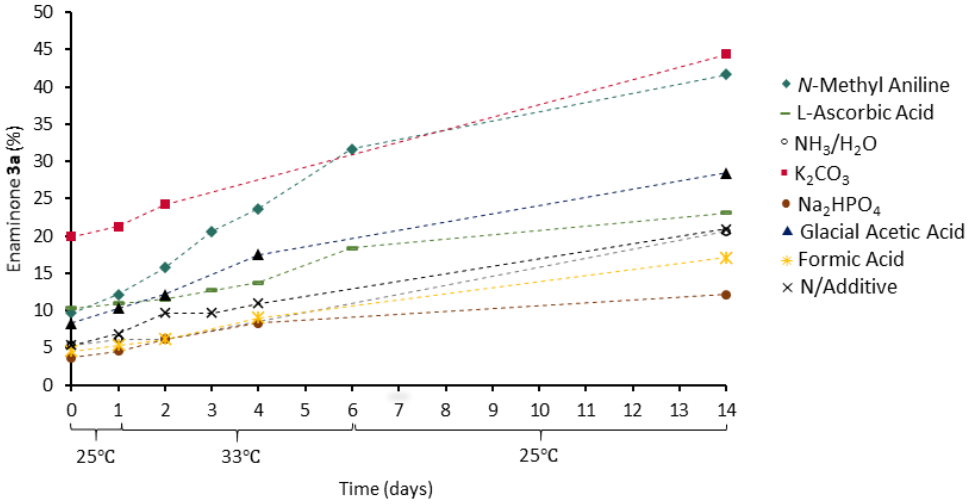


Figure S3. Stability studies of cyclopentanone **2a** in the presence of several additives in $CDCl_3$.

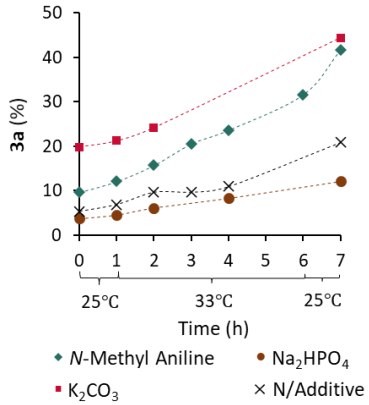
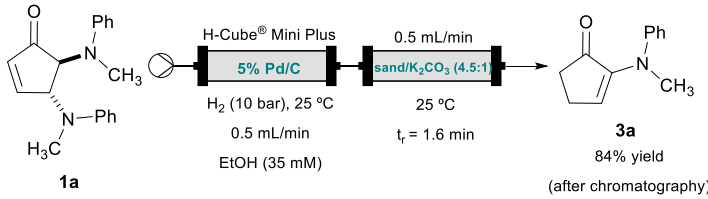


Figure S4. Simplified stability studies of cyclopentanone **2a** in the presence of several additives in $CDCl_3$. The results were calculated based on ^1H NMR experiments.

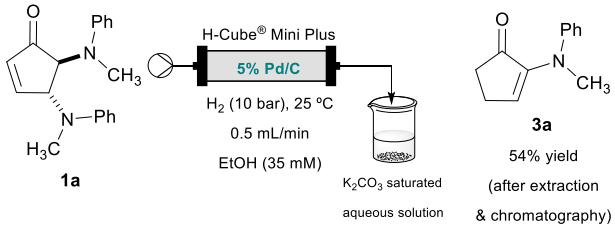
6. Studies on the Formation of 2-(methyl(phenyl)amino)cyclopent-2-en-1-one 3a

Trans-4,5-bis(methyl(phenyl)amino)cyclopent-2-en-1-one (20 mg, 0.068 mmol) was dissolved in distilled EtOH (2 mL, 35 mM) and injected at H-Cube® Mini Plus continuous flow reactor. The hydrogenation reaction was performed under the optimized conditions. The reaction mixture was reacted with K_2CO_3 using three different methodologies:

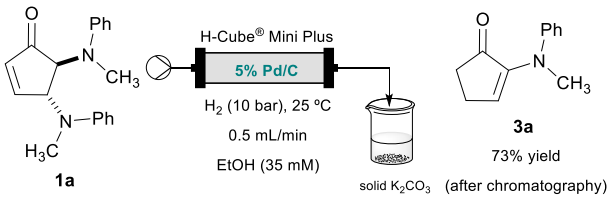
- Using an empty Agilent (15 cm x 4.6 mm) HPLC column filled with a mixture of sand:K_2CO_3 (4.5:1, 2.574 g) with 1.6 min residence time. The reaction mixture was collected and the solvent evaporated under reduced pressure at 40 ℃;

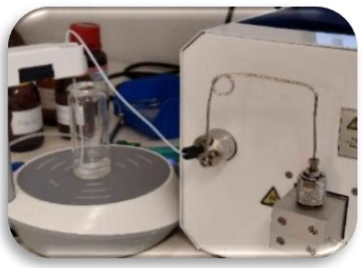


- Collection of the reaction mixture into a flask containing a saturated aqueous solution of K_2CO_3 (2 mL) for 40 minutes at room temperature. Extraction with DCM (3 x 5 mL) was performed and the combined organic phases were dried with $MgSO_4$ (anhydrous), filtered and the solvent evaporated under reduced pressure at 40 ℃;



- Collection of the reaction mixture into a flask containing solid K_2CO_3 (1 equiv) for 40 minutes at room temperature. K_2CO_3 was filtered and the reaction mixture redissolved in DCM, followed by a second filtration and solvent evaporation under reduced pressure at 40 ℃.

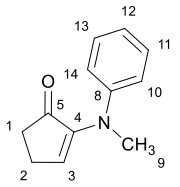




In all cases, pure enaminone **3a** was obtained after column chromatography in silica using *n*-hexane/EtOAc (4:1). Concerning the first approach, system pressure complications were observed during the hydrogenation reaction. Stirring with a saturated aqueous solution leads to lower yields (54%) despite full conversion. However, the simple use of solid K_2CO_3 afforded the desired product in high yields.

7. Scope of α-Enaminones 3a-3l

2-(methyl(phenyl)amino)cyclopent-2-en-1-one 3a



2-(methyl(phenyl)amino)cyclopent-2-en-1-one **3a** was obtained as a yellow oil in 70% isolated yield using 20% $Pd(OH)_2/C$.

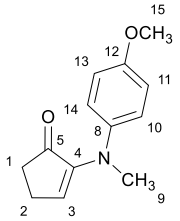
R_f (*n*-hexane/EtOAc – 4:1) = 0.42

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 – 7.18 (m, 2H, H10, H14), 7.02 – 6.91 (m, 3H, H11, H13), 6.84 (t, J = 3.1 Hz, 1H, H3), 3.19 (s, 3H, H9), 2.66 – 2.56 (m, 2H, H2), 2.55 – 2.43 (m, 2H, H1) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 204.9 (C5), 149.1 (C4), 147.7 (C8), 140.1 (C3), 129.0 (C10, C14), 122.0 (C12), 120.0 (C11, C13), 39.7 (C9), 34.9 (C1), 23.8 (C2) ppm.

The NMR characterization is consistent with literature.[7]

2-((4-methoxyphenyl)(methyl)amino)cyclopent-2-en-1-one 3b



2-((4-methoxyphenyl)(methyl)amino)cyclopent-2-en-1-one **3b** was obtained as a pale brown solid in 83% isolated yield using 5% Pd/C.

R_f (*n*-hexane/EtOAc – 4:1) = 0.44

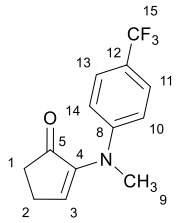
m.p. = 71-75 ℃ (exp)

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96 – 6.89 (m, 2H, H10, H14), 6.86 – 6.79 (m, 2H, h11, H13), 6.53 (td, J = 3.2, 0.8 Hz, 1H, H3), 3.78 (d, J = 0.8 Hz, 3H, H15), 3.14 (d, J = 0.8 Hz, 3H, H9), 2.59 – 2.52 (m, 2H, H2), 2.50 – 2.43 (m, 2H; H1) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 205.6 (C5), 155.8 (C12), 150.2 (C4), 141.0 (C8), 135.7 (C3), 123.4 (C10, C14), 114.4 (C11, C13), 55.6 (C15), 40.8 (C9), 36.6 (C1), 23.5 (C2) ppm.

HRMS (*m/z*) calculated for $C_{13}H_{15}NO_2$ ($[M+H]^+$): 218.11756, found 218.11701.

2-(methyl(4-(trifluoromethyl)phenyl)amino)cyclopent-2-en-1-one 3c



2-(methyl(4-(trifluoromethyl)phenyl)amino)cyclopent-2-en-1-one **3c** was obtained as yellow oil in 79% isolated yield using 20% $Pd(OH)_2/C$.

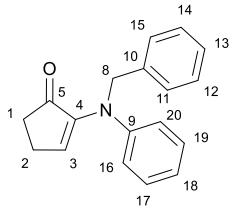
R_f (*n*-hexane/EtOAc – 4:1) = 0.44

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 – 7.42 (m, 2H, H11, H13), 7.15 (t, J = 3.1 Hz, 1H, H3), 6.92 – 6.86 (m, 2H, H10, H14), 3.22 (s, 3H, H9), 2.68 (dtd, J = 7.4, 4.4, 3.7, 2.4 Hz, 2H, H2), 2.56 – 2.51 (m, 2H, H1) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 205.6 (C5), 150.1 (C8), 148.5 (C4), 145.8 (C3), 126.2 (q, C11, C13), 124.7 (q, C15), 122.1 (q, C12), 117.2 (C10, C14), 39.0 (C9), 34.5 (C1), 25.1 (C2) ppm.

HRMS (*m/z*) calculated for $C_{13}H_{12}F_3NO$ ($[M+H]^+$): 256.09438, found 256.09389.

2-(benzyl(phenyl)amino)cyclopent-2-en-1-one 3d



2-(benzyl(phenyl)amino)cyclopent-2-en-1-one **3d** was obtained as an orange oil in 82% isolated yield using 5% Pd/C.

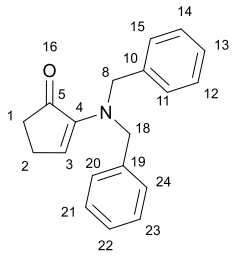
R_f (*n*-hexane/EtOAc – 9:1) = 0.49

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 – 7.30 (m, 7H, H11-H15, H17, H29), 7.08 – 7.02 (m, 3H, H16, H18, H20), 6.99 (t, *J* = 3.1 Hz, 1H, H3), 5.02 (s, 2H, H8), 2.73 – 2.65 (m, 2H, H2), 2.64 – 2.56 (m, 2H, H1) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 204.7 (C5), 147.5 (C9), 147.0 (C4), 141.6 (C3), 138.8 (C10), 129.0 (C14, C19), 128.7 (C12, C14), 127.0 (C13), 126.9 (C11, C15), 121.8 (C18), 119.9 (C16, C20), 55.5 (C8), 34.9 (C1), 23.9 (C2) ppm.

HRMS (*m/z*) calculated for $C_{18}H_{17}NO$ ($[M+H]^+$): 264.13884, found 264.13772.

2-(dibenzylamino)cyclopent-2-en-1-one 3e



2-(dibenzylamino)cyclopent-2-en-1-one **3e** was obtained as yellow oil in 42% isolated yield using 20% $Pd(OH)_2/C$.

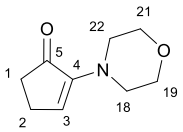
R_f (*n*-hexane) = 0.17 – it was necessary to elute 2x to see separation from the free amine spot.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 – 7.18 (m, 10H, H11-H15, H19-H24), 6.07 (t, J = 3.2 Hz, 1H, H3), 4.40 (s, 4H, H8, H18), 2.50 – 2.44 (m, 2H, H2), 2.44 – 2.38 (m, 2H, H1) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 205.5 (C5), 148.2 (C4), 138.4 (C10, C19), 132.0 (C3), 128.5 (C12, C14, C21, C23), 128.0 (C11, C15, C20, C24), 127.1 (C13, C22), 53.4 (C8, C18), 35.7 (C2), 23.2 (C1) ppm.

The NMR characterization is in accordance with literature.[8]

2-morpholinocyclopent-2-en-1-one 3f



2-morpholinocyclopent-2-en-1-one **3f** was obtained as a yellow oil in 43% isolated yield using 5% Pd/C.

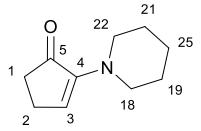
R_f (*n*-hexane/EtOAc – 4:1) = 0.5

^{1}H NMR (300 MHz, CDCl3): *δ* 6.35 (t, J = 3.1 Hz, 1H, H3), 3.79 – 3.70 (m, 4H, H19, H21), 3.09 – 3.00 (m, 4H, H18, H22), 2.48 (ddd, J = 5.5, 4.1, 2.5 Hz, 2H, H2), 2.43 – 2.36 (m, 2H, H1) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): *δ* 205.2 (C5), 150.8 (C4), 133.8 (C3), 66.7 (C19, C21), 48.5 (C18, C22), 35.3 (C1), 23.4 (C2) ppm.

The NMR characterization is in accordance with literature.[8]

2-(piperidin-1-yl)cyclopent-2-en-1-one 3g



2-(piperidin-1-yl)cyclopent-2-en-1-one **3g** was isolated as a brown oil in 16 % isolated yield from the hydrogenation reaction using 10% Pd/Al_2O_3 without treatment with K_2CO_3.

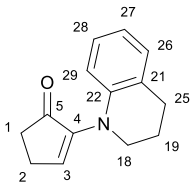
R_f (*n*-hexane/EtOAc – 9:1) = 0.52

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.35 (t, J = 3.1 Hz, 1H, H3), 3.05 – 2.95 (m, 4H, H18, H22), 2.52 – 2.44 (m, 2H, H2), 2.44 – 2.37 (m, 2H, H1), 1.70 – 1.59 (m, 4H, H19, H21), 1.57 – 1.50 (m, 2H, H25) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 205.7 (C5), 151.9 (C4), 133.6 (C3), 49.5 (C8, C22), 35.4 (C1), 25.5 (C19, C21), 24.5 (C25), 23.5 (C2) ppm.

The NMR characterization is in accordance with literature.[8]

2-(3,4-dihydroquinolin-1-yl)cyclopent-2-en-1-one 3h



2-(3,4-dihydroquinolin-1-yl)cyclopent-2-en-1-one **3h** was obtained as a yellow oil in 81% yield using 20% $Pd(OH)_2/C$.

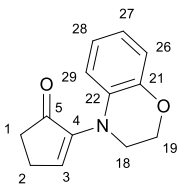
R_f (*n*-hexane/EtOAc – 4:1) = 0.20

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08 (d, J = 3.0 Hz, 1H, H3), 7.06 – 6.96 (m, 2H, H28, H27), 6.77 (td, J = 7.4, 1.2 Hz, 1H, H26), 6.68 (dd, J = 8.1, 1.2 Hz, 1H, H29), 3.57 – 3.47 (m, 2H, H18), 2.79 (t, J = 6.5 Hz, 2H, H25), 2.68 – 2.59 (m, 2H, H2), 2.59 – 2.47 (m, 2H, H1), 2.01 – 1.87 (m, 2H, H11) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 205.4 (C5), 148.7 (C4), 144.3 (C3), 142.6 (C21, C22), 129.4 (C27), 126.2 (C28), 119.8 (C26), 117.9 (C29), 48.0 (C18), 34.6 (C1), 27.4 (C25), 24.0 (C2), 22.2 (C11) ppm.

HRMS (*m/z*) calculated for $C_{14}H_{15}NO$ ($[M+H]^+$): 214.12319, found 214.12222.

2-(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)cyclopent-2-en-1-one 3i



2-(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)cyclopent-2-en-1-one **3i** was obtained as a yellow oil in 72% yield using 20% $Pd(OH)_2/C$.

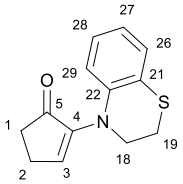
R_f (*n*-hexane/EtOAc – 9:1) = 0.41

^1H NMR (300 MHz, $CDCl_3$): δ 7.05 (t, J = 3.1 Hz, 1H, H3), 6.97 – 6.72 (m, 4H, H26-H29), 4.21 – 4.13 (m, 2H, H19), 3.76 – 3.67 (m, 2H, H18), 2.66 – 2.56 (m, 2H, H2), 2.56 – 2.48 (m, 2H, H1) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 205.4 (C5), 147.6 (C4), 146.1 (C21), 142.6 (C3), 130.7 (C22), 122.2 (C28), 120.7 (C27), 120.0 (C29), 117.6 (C26), 64.2 (C19), 45.5 (C18), 34.8 (C1), 23.9 (C2) ppm.

HRMS (*m/z*) calculated for $C_{13}H_{13}NO_2$ ($[M+H]^+$): 216.10245, found 216.10171.

2-(2,3-dihydro-4H-benzo[b][1,4]thiazin-4-yl)cyclopent-2-en-1-one 3j



2-(2,3-dihydro-4H-benzo[b][1,4]thiazin-4-yl)cyclopent-2-en-1-one **3j** was obtained as a yellow oil in 48% yield using 5% Pd/C.

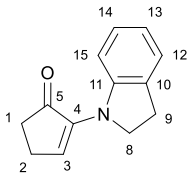
R_f (n-hexane/EtOAc – 4:1) = 0.25

^1H NMR (300 MHz, $CDCl_3$): *δ* 7.11 (ddd, J = 7.6, 1.7, 0.6 Hz, 1H, H28), 6.98 – 6.82 (m, 3H, H26, H27, H29), 6.81 (t, J = 3.0 Hz, 1H, H3), 3.98 – 3.89 (m, 2H, H18), 3.05 – 2.95 (m, 2H, H19), 2.65 – 2.47 (m, 4H, H1, H2) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): *δ* 204.9 (C5), 148.4 (C4), 143.2 (C3), 140.9 (C22), 127.7 (C28), 124.7 (C26), 123.1 (C27), 122.8 (C29), 120.5 (C21), 45.6 (C18), 35.1 (C1), 26.2 (C19), 23.8 (C2) ppm.

HRMS (*m/z*) calculated for $C_{13}H_{13}NOS$ ($[M+H]^+$): 232.07961, found 232.07875.

2-(indolin-1-yl)cyclopent-2-en-1-one 3k



2-(indolin-1-yl)cyclopent-2-en-1-one **3k** was obtained as a yellow oil in 60% isolated yield using 20% $Pd(OH)_2/C$.

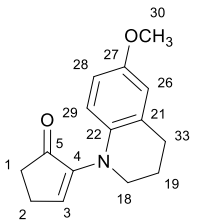
R_f (*n*-hexane/EtOAc -9:1) = 0.5

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 – 7.04 (m, 2H, H13, H14), 6.99 (t, J = 3.2 Hz, 1H, H3), 6.83 (d, J = 8.0 Hz, 1H, H15), 6.76 (td, J = 7.4, 1.0 Hz, 1H, H12), 3.96 (t, J = 8.5 Hz, 2H, H8), 3.07 (t, J = 8.5 Hz, 2H, H9), 2.67 (ddd, J = 7.5, 3.3, 1.8 Hz, 2H, H2), 2.57 – 2.46 (m, 2H, H1) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 205.4 (C5), 147.0 (C11), 145.0 (C4), 136.0 (C3), 131.1 (C10), 127.2 (C14), 125.0 (C13), 119.6 (C12), 110.6 (C15), 51.3 (C8), 34.5 (C1), 28.6 (C9), 24.2 (C2) ppm.

HRMS (*m/z*) calculated for $C_{13}H_{13}NO$ ($[M+H]^+$): 200.10754, found 200.10665.

2-(6-methoxy-3,4-dihydroquinolin-1(2H)-yl)cyclopent-2-en-1-one 3l



2-(6-methoxy-3,4-dihydroquinolin-1(2H)-yl)cyclopent-2-en-1-one **3l** was obtained as a yellow oil in 83% isolated yield using 10% Pd/Al_2O_3.

R_f (*n*-hexane/EtOAc – 4:1) = 0.15

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.83 (t, J = 3.1 Hz, 1H, H3), 6.69 (d, J = 9.7 Hz, 1H, H26), 6.62 (ddd, J = 4.0, 3.1, 2.3 Hz, 2H, H28, H29), 3.75 (s, 3H, H30), 3.57 – 3.47 (m, 2H, H33), 2.76 (t, J = 6.6 Hz, 2H, H18), 2.62 – 2.54 (m, 2H, H2), 2.54 – 2.46 (m, 2H, H1), 1.85 (tdd, J = 6.7, 5.6, 4.2 Hz, 2H, H19) ppm.

13C NMR (75 MHz, $CDCl_3$): δ 205.5 (C5), 154.0 (C27), 149.5 (C4), 141.2 (C3), 136.6 (C22), 128.5 (C21), 120.9 (C29), 114.2 (C26), 112.5 (C28), 55.7 (C30), 47.4 (C33), 35.0 (C1), 27.6 (C18), 23.8 (C2), 22.0 (C1 9) ppm.

HRMS (*m/z*) calculated for $C_{15}H_{17}NO_2$ ($[M+H]^+$): 244.13375, found 244.13276.

8. 5% Pd/C Catalyst Reuse Experiments

A single cartridge of 5% Pd/C was reused up to 1229 times the reactor volume (65 µL) with a loading of about 200 mg at 35 mM in EtOH of substrate **1a**. The optimized continuous flow conditions to obtain the corresponding α-enaminone **3a** were used.

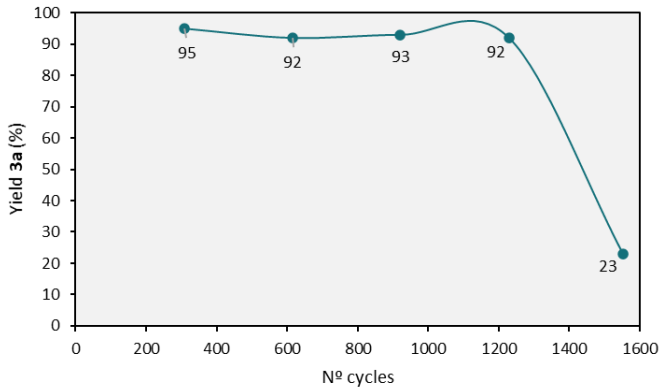


Figure S5. 5% Pd/C catalyst reuse experiments using substrate **1a** in 35mM.

Table S2. Experimental data for the 5% Pd/C catalyst reuse experiments using 35 mM substrate concentration.

Cycle	Nº reactor volumes	**1a** (g)	Yield **3a** (%)
1	309	0.201	95
2	306	0.199	92
3	306	0.199	93
4	308	0.200	92
5	323	0.210	23

A single cartridge of 5% Pd/C was reused up to 231 times the reactor volume (65 µL) with a loading of about 275 mg at 173 mM in EtOH of substrate **1a**. The optimized continuous flow conditions to obtain the corresponding α-enaminone **3a** were used.

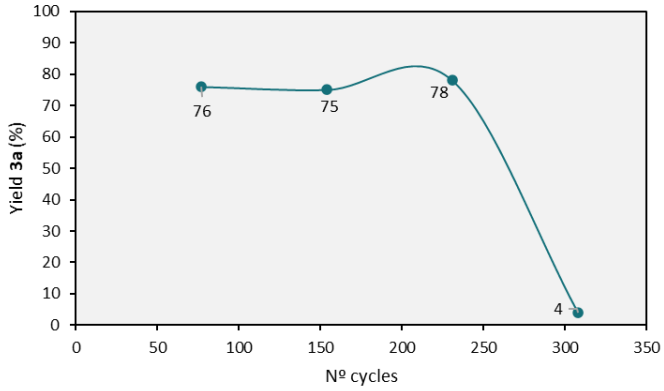


Figure S6. 5% Pd/C catalyst reuse experiments using substrate **1a** in 173 mM.

Table S3. Experimental data for the 5% Pd/C catalyst reuse experiments using 173 mM substrate concentration.

Cycle	Nº reactor volumes	**1a** (g)	Yield **3a** (%)
1	77	0.2747	76
2	77	0.2747	75
3	77	0.2747	78
4	77	0.2747	4

9. Deuteration Experiments during Continuous Flow Hydrogenation of 4,5-*trans*-bis(methyl(phenyl)amino)cyclopent-2-en-1-one 1a

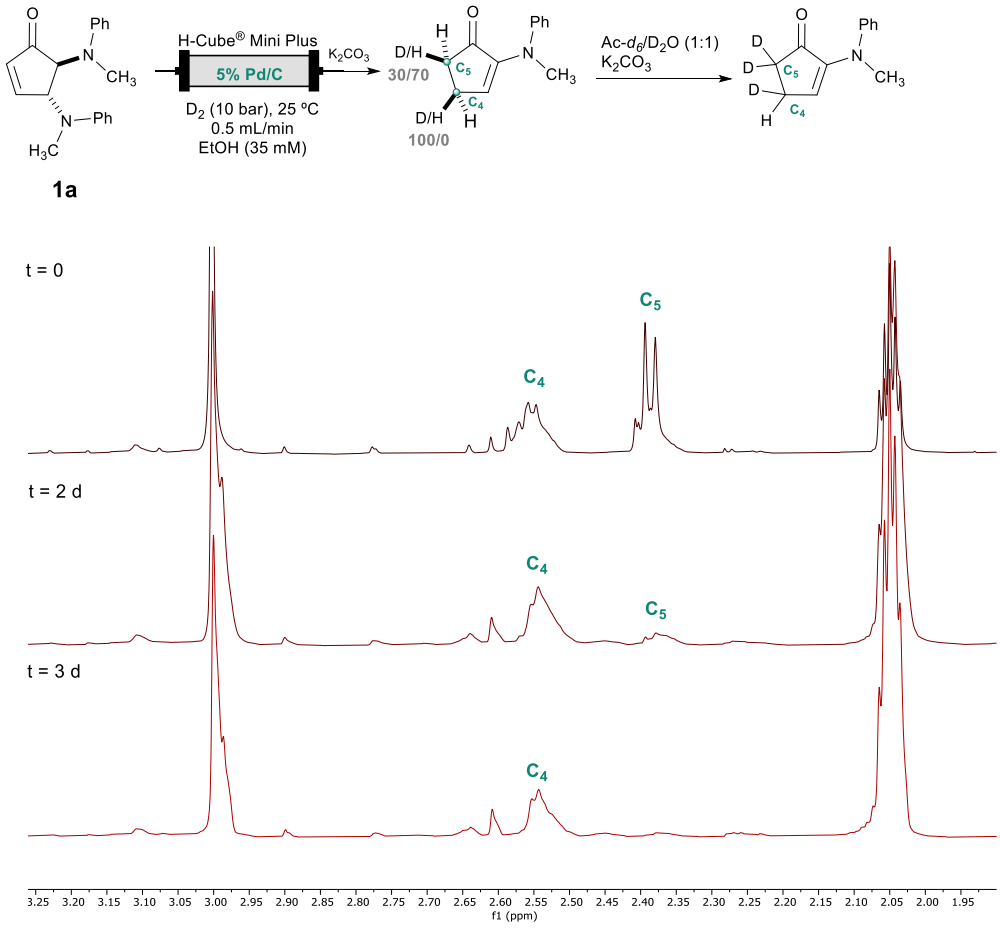
Before starting the reaction H-Cube® Mini Plus was previously prepared for deuteration experiments in the following manner:

- The exterior reservoir containing normal water was removed and replaced by another reservoir containing heavy water.
- The outlet channel was separated from the inlet channel in order to avoid contamination.
- The water purge was turn on for 15-20 minutes in order to fill the apparatus.
- An inert cartridge (available with the equipment) was inserted and a simulation of the experiment was performed.
- The 5% Pd/C cartridge was inserted, a simulation of the experiment was performed and finally the actual experiment was performed.

The hydrogenation of **1a** was performed using 5% Pd/C cartridge. Before the experiment, the catalyst was pre-treated for 10 min at full D_2 mode and 0.5 $mLmin^{-1}$ pure solvent. Then, a 35 mM solution of DCP **1a** in EtOH was passed through the cartridge at full D_2 mode (10 bar), 0.5 $mLmin^{-1}$ flow rate at 25 °C. The reaction solution was collected into a flask containing solid K_2CO_3 with constant stirring for 40 minutes at room temperature. After filtration through cotton pipette, EtOH was evaporated under reduced pressure at 40 °C. The crude mixture was redissolved in DCM and a second filtration was performed, followed by evaporation. The crude was analysed by dissolution in Ac-d_6/D_2O (1:1) at t=0. Then K_2CO_3 was added to the NMR tube and the deuteration at C_5 was observed over time for three days.

Replacing the distilled water for deuterated water on the hydrogenation apparatus allows the release of D_2, therefore affording the corresponding deuterated products. The deuteration occurred in 30% on position C_5 and 100 % on position C_4. This observation is not in accordance to the expected 100% of D on the C5 position, from the concerted syn insertion of deuterium. This can be explained by the enolizable C5 position that may reduce the D/H ratio.

Treatment of the deuterated α-enaminone **3a** with K_2CO_3 in acetone-d_6/D_2O (1:1) allowed the deuteration in position C_5 after 3 days being consistent with enolizable C5 position (Scheme S3).



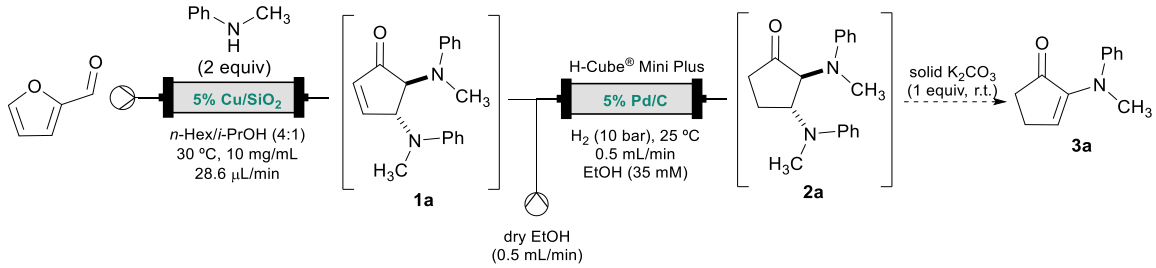
Scheme S3. Deuterium-labelling experiments during hydrogenation of DCP **1a** over time in Acetone-d_6/D_2O (1:1) in the presence of K_2CO_3.

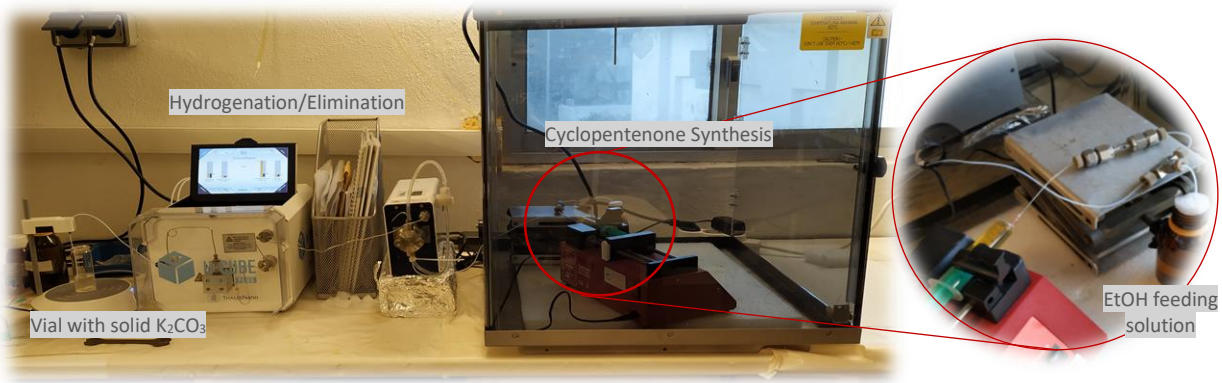
10. Sequential Continuous Flow Process for Direct Transformation of Furfural into 2-(methyl(phenyl)amino)cyclopent-2-en-1-one 3a

A previously described continuous flow system for the preparation of DCP from furfural[5] was coupled with the herein described hydrogenation setup. The sequential reaction was able to afford α-enaminone **3a** directly from furfural.

Experimental Procedure: A packed bed metal reactor (5 cm x 0.4 cm i.d.) was weighted and filled with 5% Cu/SiO_2 catalyst. A mixture of *n*-hexane/*i*-PrOH (4:1) was injected in the reactor and warmed to 30 ℃ in an oven. A mixture of furfural (1 equiv, 0.043 mL, 0.519 mmol) and *N*-methylaniline (2 equiv, 0.1183 mL, 0.895 mmol) was dissolved in *n*-hexane/*i*-PrOH (4:1) (5 mL, 10 mg/mL) and injected at 28.6 µL/min with a syringe pump. A stock solution of EtOH was feeding the H-Cube® Mini Plus reactor for hydrogenation of the intermediate cyclopentenone **2a** at 0.5 mL/min through a 5% Pd/C catalyst. The crude was collected to a vial containing solid K_2CO_3 (1 equiv, 0.073 g) and stirred at room temperature during the total time of the experiment. The corresponding α-enaminone **3a** (0.0171 g) was purified by column chromatography in *n*-hexane/EtOAc (4:1) in 17 % yield (1 g L^{-1} h^{-1}).

Cyclopentenone Synthesis Packed Bed Metal Reactor Setup Parameters	
$m_{reactor}$	60.0559 g
$m_{reactor+catalyst}$	60.3486 g
$m_{reactor+catalyst+solvent}$	60.6496
$m_{solvent}$	0.301 g
$V_{solvent}$ (d = 0.7019 g/mL)	0.429 mL
Residence time (t_r)	15 min
Flow rate	28.6 µL/min





Scheme S4. Sequential continuous flow synthesis of α-enaminone directly from furfural coupling a previously reported continuous flow synthesis of cyclopentenone **1a** and the herein described tandem hydrogenation/elimination reaction.

Catalyst leaching measurement of Cu and Pd were conducted through Inductively Coupled-Plasma Atomic Emission Spectroscopy (ICP-AES) analyses using the crude sample obtained from the sequential flow process.

The analysis was carried out on a Horiba Jobin Yvon ULTIMA sequential ICP, using the Horiba Jobin Yvon ICP Analyst 5.4 software. A monochromator with a Czerny Turner spectrometer was used. The gas used was Argon. Instrument configuration and general experimental conditions are summarized. For each sample three determinations were performed and average results were reported.

Instrument	ICP Ultima
RF generator power	1.05 kw
RF frequency	40.68 MHz
Plasma gas flow rate	12 L/min
Carrier gas flow rate	1.0 L/min
Sample introduction	Miramist nebulizer
Misting chamber	Cyclonic glass chamber
Observation method	Radial
Injector tube diameter	3 mm

Sample preparation: 6.78 mg sample/1 mL in 50% (*v/v*) HCl:H_2O (dilution factor = 148)

Blank sample: 50% (*v/v*) HCl:H_2O

Standards preparation in 50% (*v/v*) HCl:H_2O

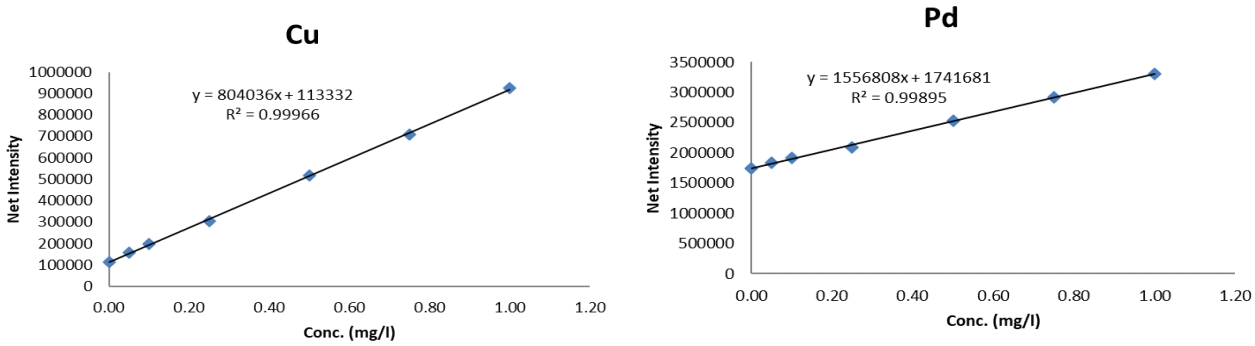


Figure S7. Cu and Pd calibration curves prior extraction and chromatographic purification.

Table S4. Cu and Pd content analysis by ICP-AES in crude sample obtained from sequential process prior extraction and chromatographic purification.

Sample	Conc (mg/L)	Net Intensity	Sample	Conc (mg/L)	Net Intensity
Blank	0.00	112485	Blank	<Limit of detection	1741764
Crude	0.46	485492	Crude	<Limit of detection	1740861
Cu	679 ppm/mg sample		Pd	<1.63 ppm/mg sample	

The amount of Cu in the crude sample was determined after extraction with EtOAc.

Sample preparation: 13.3 mg sample/1 mL in 50% (*v/v*) HCl:H_2O (dilution factor = 75)

Blank sample: 50% (*v/v*) HCl:H_2O

Standards preparation in 50% (*v/v*) HCl:H_2O

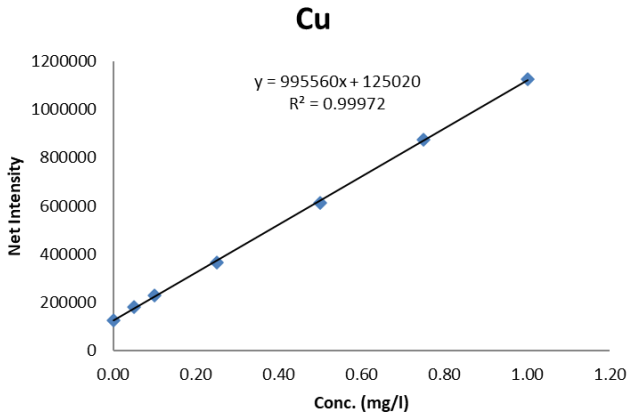


Figure S8. ICP-AES calibration curves for Cu quantification after extraction of crude sample.

Table S5. Results obtained from ICP-AES analysis after extraction.

Sample	Cu Conc (mg/L)	Net Intensity
Blank	0.01	133402
Crude (ext)	1.11	1228652
Cu	83.5 ppm/mg sample	

Additional catalyst leaching measurement of Pd was conducted through ICP-AES analyses using the crude sample obtained from the continuous flow hydrogenation reaction.

Sample preparation: 100.92 mg sample/1.1 mL in 50% (*v/v*) HCl:H_2O (dilution factor = 10.9)

Blank sample: 50% (*v/v*) HCl:H_2O

Standards preparation in 50% (*v/v*) HCl:H_2O

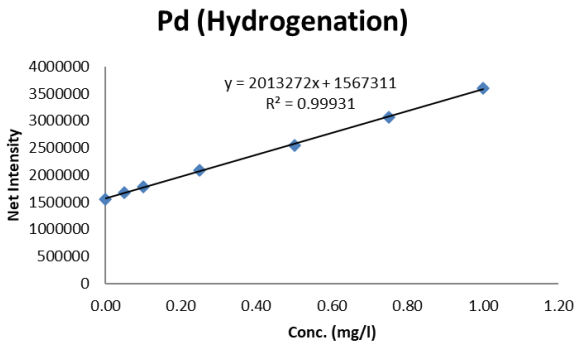


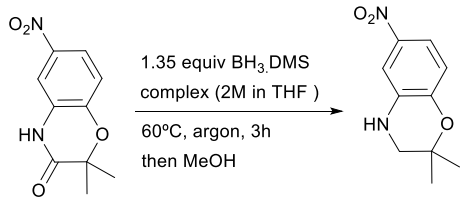
Figure S9. ICP-AES calibration curves for Pd quantification in the crude sample of the continuous flow hydrogenation reaction.

Table S6. Results obtained from ICP-AES analysis of Pd.

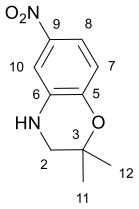
Sample	Pd Conc (mg/L)	Net Intensity
Blank	<limit of detection	1565035
Crude	<limit of detection	1570166
Pd	< 0.16 ppm	

11. Total Synthesis of 2-(2,2-dimethyl-6-nitro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)cyclopent-2-en-1-one 3n

11.1. Reduction of 2,2-dimethyl-6-nitro-2H-benzo[b][1,4]oxazin-3(4H)-one



Amide (0.0992 g, 0.446 mmol) was placed in a previously dried and degassed round bottom flask (5 mL). BH_3.DMS complex (2M in THF, 0.3 mL, 0.603 mmol, 1.35 equiv) was added dropwise at 0℃. Then the reaction was allowed to stir at 60℃ for 3 hours. MeOH (1 mL) was slowly added and the reaction was stirred for additional 30 minutes. The reaction mixture was diluted with distilled H_2O (3 mL) and extracted with EtOAc (4 x 3 mL). The combined organic phases were dried with $MgSO_4$ (anhydrous), filtered and the solvent evaporated under reduced pressure. The crude was purified by fast vacuum filtration through silica to obtain the desired amine.



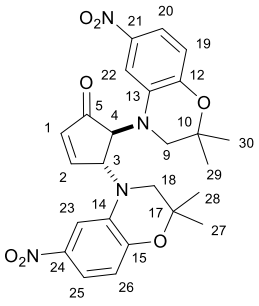
2,2-dimethyl-6-nitro-3,4-dihydro-2H-benzo[b][1,4]oxazine was obtained as a yellow solid (86.7 mg, 93% yield). The compound was characterized by ^{1}H NMR in $CDCl_3$ and was consistent with literature.[9]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (dd, J = 8.8, 2.6 Hz, 1H, H8), 7.50 (d, J = 2.7 Hz, 1H, H10), 6.78 (dd, J = 8.8, 0.6 Hz, 1H, H7), 3.14 (d, J = 2.6 Hz, 2H, H2), 1.37 (s, 6H, H11, H12) ppm.

*11.2. Synthesis of trans-5-(2,2-dimethyl-6-nitro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)-4-(2,2-dimethyl-7-nitro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)cyclopent-2-en-1-one **1n***

Cyclopentenone **1n** was prepared according to literature[6] as follows: To a solution of $Dy(OTf)_3$ (60 mol%)* in dry ACN (1 M) were added the corresponding amine (2.2 equiv) and furfural (1 equiv). The reaction was stirred at room temperature for 20 hours in the presence of 4Å MS. The reaction mixture was diluted with distilled water and extracted with ethyl acetate. The combined organic phases were dried with $MgSO_4$ (anhydrous), filtered and the solvent evaporated under reduced pressure. Column chromatography in silica gel (*n*-hexane/EtOAc) was performed to obtain pure cyclopentenone. *The results were similar using $Sc(OTf)_3$ (60 mol%).

4,5-trans-4,5-bis(2,2-dimethyl-6-nitro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)cyclopent-2-en-1-one 1n



4,5-*trans*-4,5-bis(2,2-dimethyl-6-nitro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)cyclopent-2-en-1-one **1n** was obtained as an orange solid (5.6 mg, 5% yield).

R_f (n-hexane/EtOAc – 3:2) = 0.33

m.p. = 222-224℃ (exp)

^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.61 (dd, J = 6.3, 2.1 Hz, 1H, H2), 7.50 (dd, J = 8.7, 2.4 Hz, 2H, H20, H25), 7.41 (d, J = 2.5 Hz, 1H, H23), 7.21 – 7.11 (m, 1H, H22), 6.77 (d, J = 8.8 Hz, 2H, H19, H26), 6.65 (dd, J = 6.4, 2.0 Hz, 1H, H1, H3), 5.40 (s, 1H, H4), 4.51 (s, 1H), 3.15 (dd, J = 12.2, 8.6 Hz, 2H, H9), 3.01 (dd, J = 11.3, 7.4 Hz, 2H, H18), 1.48 –1.33 (m, 12H, H29, H30, H27, H28) ppm.

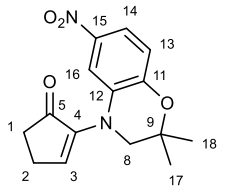
^{13}C NMR (75 MHz, CDCl*3*): *δ* 200.1 (C5), 149.8 (C2), 149.4 (C12), 149.1 (C15), 141.3 (C21), 141.2 (C25), 136.7 (C1), 131.7 (C13, C14), 117.5 (C19, C26), 115.8 (C20, C25), 107.0 (C23), 106.3 (C22), 74.3 (C10, C17), 59.5 (C3, C4), 50.9 (C9, C18), 25.8 (C27, C28), 25.0 (C29, C30) ppm.

HRMS (*m/z*) calculated for $C_{25}H_{26}N_4O_7$ ($[M+H]^+$): 495.18797, found 495.18764.

FT-IR: 1709 cm^{-1} (C=O stretching); 1503 cm^{-1} (N-O stretching)

Using the usual conditions of 0.5 mL min^{-1} at 35 mM substrate concentration a different enaminone than the pretended was obtained instead. The proposed structure is the bis-reduction product, including nitro group reduction to the primary amine. Preliminary indication of the formation of compound 3p was obtained by HRMS where the experimental molecular ion $[M+H]^+$ was 259.14410 *m/z*.

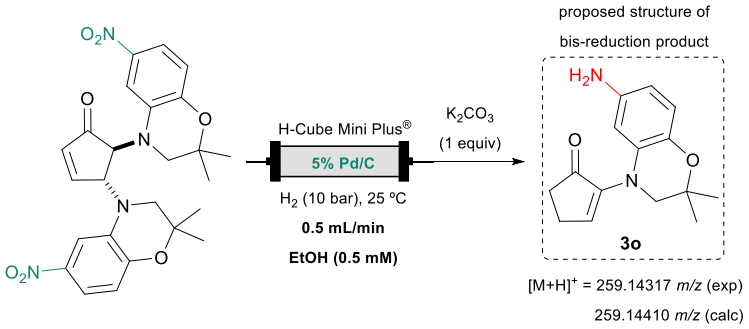
2-(2,2-dimethyl-6-nitro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)cyclopent-2-en-1-one 3n



2-(2,2-dimethyl-6-nitro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)cyclopent-2-en-1-one **3n** was obtained as a dark yellow oil (11 mg, 71% yield).

R_f (n-hexane/EtOAc – 3:2) = 0.6

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 – 7.22 (m, 2H), 6.84 – 6.80 (m, 1H), 6.46 – 6.38 (m, 1H), 3.00 (s, 2H), 2.31 – 2.25 (m, 2H), 2.16 – 2.10 (m, 2H), 0.90 (s, 6H) ppm.



Scheme S5. Proposed product structure **3o** using the normal continuous flow hydrogenation conditions as attempt to obtain the nitro substituted α-enaminone **3n**.

12. Quantitative and Qualitative Green Metrics (CHEM21 toolkit[10])

The green metrics for the described "Hydrogenation/Elimination" process were accessed using an increased substrate concentration (173 mM) and the conditions from the first 1229 cycles in the catalyst reuse experiments.

The following equations represent the calculation of:

- Reaction Mass Efficiency (RME)

$$RME = \frac{mass\ of\ isolated\ product}{total\ mass\ of\ reactants} \times 100$$

- Atom Economy (AE)

$$AE = \frac{molecular\ weight\ of\ product}{total\ molecualr\ weight\ of\ reactants} \times 100$$

- Optimum Efficiency (OE)

$$OE = \frac{RME}{AE} \times 100$$

- Reaction Mass Intensity (RMI): is one of the most important parameters, accounting also the volume of solvents, catalysts and reagents used in the reaction. It is called "Process Mass Intensity (PMI)" when the work-up solvents are accounted.

$$mass\ intensity = \frac{total\ mass\ in\ a\ process\ or\ process\ step}{mass\ of\ product}$$

All the information to calculate the previous parameters for all the methods is given in the following tables.

Table S7. Data for quantitative green metrics calculation in *This Work*.

This Work

role	chemical	mass (g)	Volume (mL)	MW	density (g/mL)
reactant	Cyclopentenone	0.8241	-	292	-
catalyst	5% Pd/C	0.15	-	-	-
reagent	K_2CO_3	0.525	-	-	-
solvent	EtOH	-	15	-	0.789
workup solvent	EtOH	-	1	-	0.789
workup solvent	EtOAc	-	40	-	0.902
workup solvent	*n*-hexane	-	160	-	0.665
Product	**3a**	0.402	-	187	-

Table S8. Data for quantitative green metrics calculation in *Method 1*.

Method 1

role	chemical	mass (g)	Volume (mL)	MW	density (g/mL)
reactant	Cyclopentanone	0.084	-	84	-
reactant	*N*-Methylaniline	0.054	-	107	-
catalyst	Pt electrode	-	-	-	-
reagent	Electrolyte (KI)	0.084	-	166	-
solvent	MeOH	-	5	-	0.792
Product	**3a**	0.075	-	187	-

Table S9. Data for quantitative green metrics calculation in *Method 2*.

Method 2

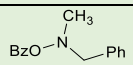
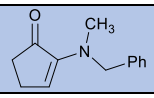
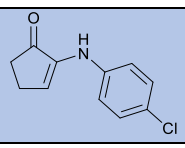
role	chemical	mass (g)	Volume (mL)	MW	density (g/mL)
reactant	Cyclopentanone	0.017	-	84	-
reactant		0.113	-	225	-
catalyst	$Sc(OTf)_3$	0.010	-	492	-
catalyst	CuCl	0.002	-	99	-
reagent	Bis(4-bromophenyl)amine	0.020	-	327	-
solvent	ACN	-	2	-	0.786
Product		0.029	-	201	-

Table S10. Data for quantitative green metrics calculation in *Method 3*.

Method 3

role	chemical	mass (g)	Volume (mL)	MW	density (g/mL)
reactant	Cyclopentanone	0.025	-	84	-
reactant	*p*-chloroaniline	0.026	-	128	
catalyst	$AgSbF_6$	0.007	-	344	-
reagent	3Å MS	0.400	-	-	-
reagent	$TEMPO^+ PF_6^-$	0.020	-	301	-
solvent	DCE	-	1	-	1.253
workup solvent	EtOAc	-	10	-	0.902
Product		0.026	-	208	-

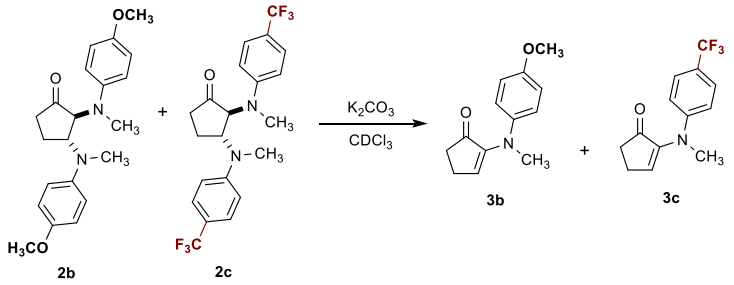
The quantitative green metrics of the process starting from furfural were accessed. For that, the reaction parameters (i.e. reactants, catalyst, reaction solvent and workup solvent) of the continuous flow synthesis of DCP **1a**[5] were added and included in the above described metrics for the "This Work" method.

Table S11. Data for quantitative green metrics calculation of the process starting from furfural.

This work, from furfural

role	chemical	mass (g)	Volume (mL)	MW	density (g/mL)
reactant	furfural	0.27	-	96	-
reactant	*N*-methyl aniline	0.6	-	107	
catalyst	$Cu(OTf)_2$	0.01	-	-	-
catalyst	5% Pd/C	0.150	-	-	-
reagent	K_2CO_3	0.53	-	-	-
solvent	EtOH	-	15	-	0.79
solvent	H_2O	-	0.28		1
solvent (workup)	MTBE	-	2		0.74
solvent (workup)	EtOAc	-	40		0.902
solvent (workup)	*n*-hexane	-	160		0.665
Product	**3a**	0.402	-	187	-

13. NMR Competitive Studies for Evaluation of the Electronic Effects of the Aryl Amine Substituent on the Elimination Reaction



Scheme S6. Competitive NMR studies of cyclopentanones **2b** and **2c** in $CDCl_3$ in the presence of K_2CO_3.

Table S12. ^1H NMR data from the competitive experiments between cyclopentanones **2a**/**2b**, **2a**/**2c** and **2b**/**2c**.

	H vs CF_3			H vs OCH_3			OCH_3 vs CF_3		
Time (d)	**H**	**CF_3**	**ratio CF_3/H**	**H**	**OCH_3**	**ratio OCH_3/H**	**OMe**	**CF_3**	**ratio OCH_3/CF_3**
0	1	1	1	1	1	1	1	1	1
2	1	0.42	0.42	0.96	1	1.041666667	1	0.24	0.24
8	0.16	0	0	0.66	1	1.515151515	0.77	0	0

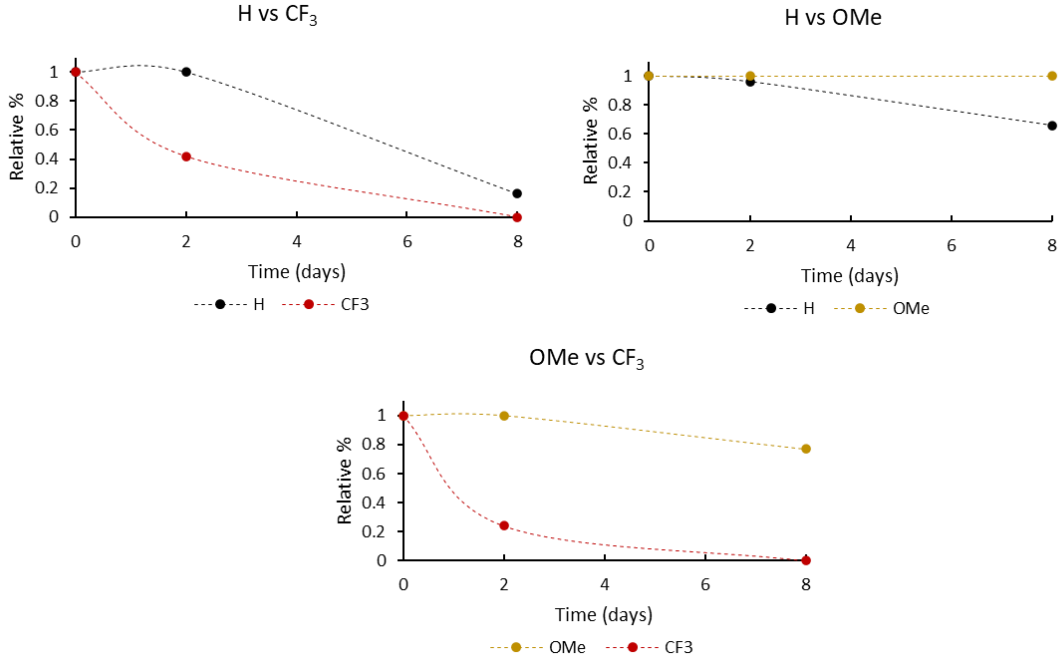


Figure S10. Relative percentage of each cyclopentanone **2a**, **2b** and **2c** in the NMR competitive experiments over time.

The cumulative concentrations of **2a/2b** and **2a/2c** are depicted in Scheme S11. After 8 days (192 h) there was no evidence of cyclopentanone **2c**. This suggests that the electron rich arylamines inhibit the elimination. On the contrary, electron poor **2c** underwent fast elimination and after 192 h was observed full conversion of the cyclopentanone. Additionally, it is noteworthy that the rate of elimination of **2a** was

increased when in combination with **2c**. This is in accordance with our previous findings that the free amine is catalysing the elimination. In this case, the fast elimination in **2c** will increase the concentration of free base, therefore increasing the rate of elimination in comparison with the experiment done with the pair **2a/2b**.

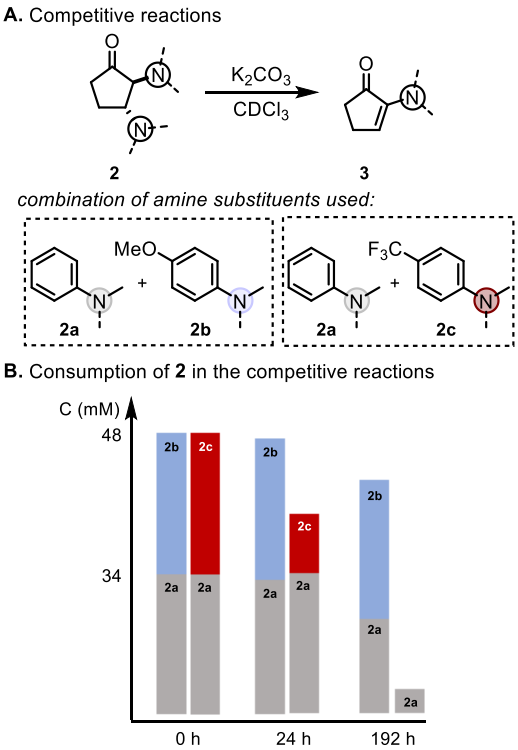
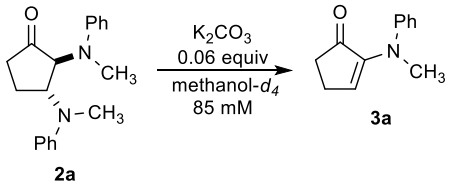


Figure S11. Evaluation of electronic effects of the aryl amine substituent on the elimination reaction through competitive 1H NMR experiments between cyclopentanone **2a** and derivatives **2b** and **2c** in the presence of K_2CO_3.

14. NMR Kinetic Studies

Cyclopentanone **2a** (0.010 g, 0.034 mmol) and internal standard 1,3,5-trimethoxybenzene (0.33 equiv, 0.0019 g) was dissolved in methanol-d_4 (0.400 mL). A first ^{1}H NMR was performed at t=0. After addition of K_2CO_3 (0.06 equiv, 0.28 mg) the conversion into α-enaminone **3a** was monitored by ^{1}H NMR over 1h40.



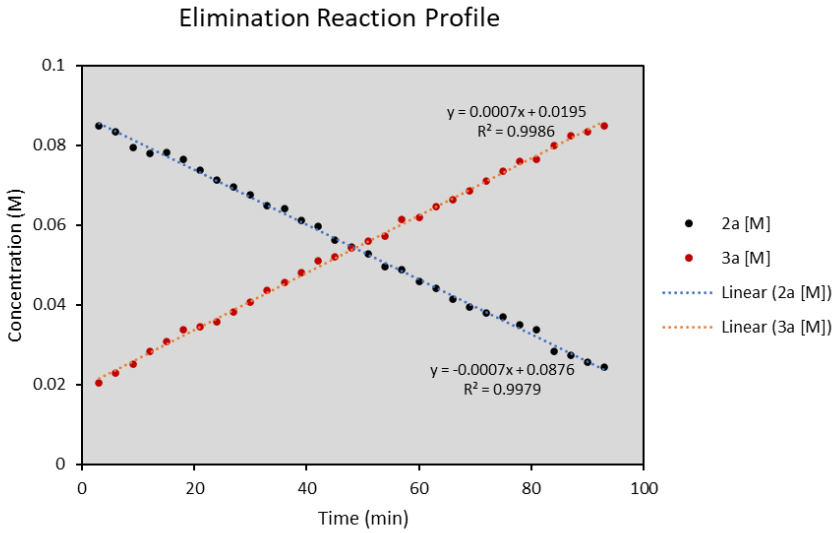


Figure S12. Cyclopentanone (CPa) **2a** and α-enaminone (En) **3a** reaction profile over time in the presence of K_2CO_3 in methanol-d_4 determined by ^{1}H NMR experiments.

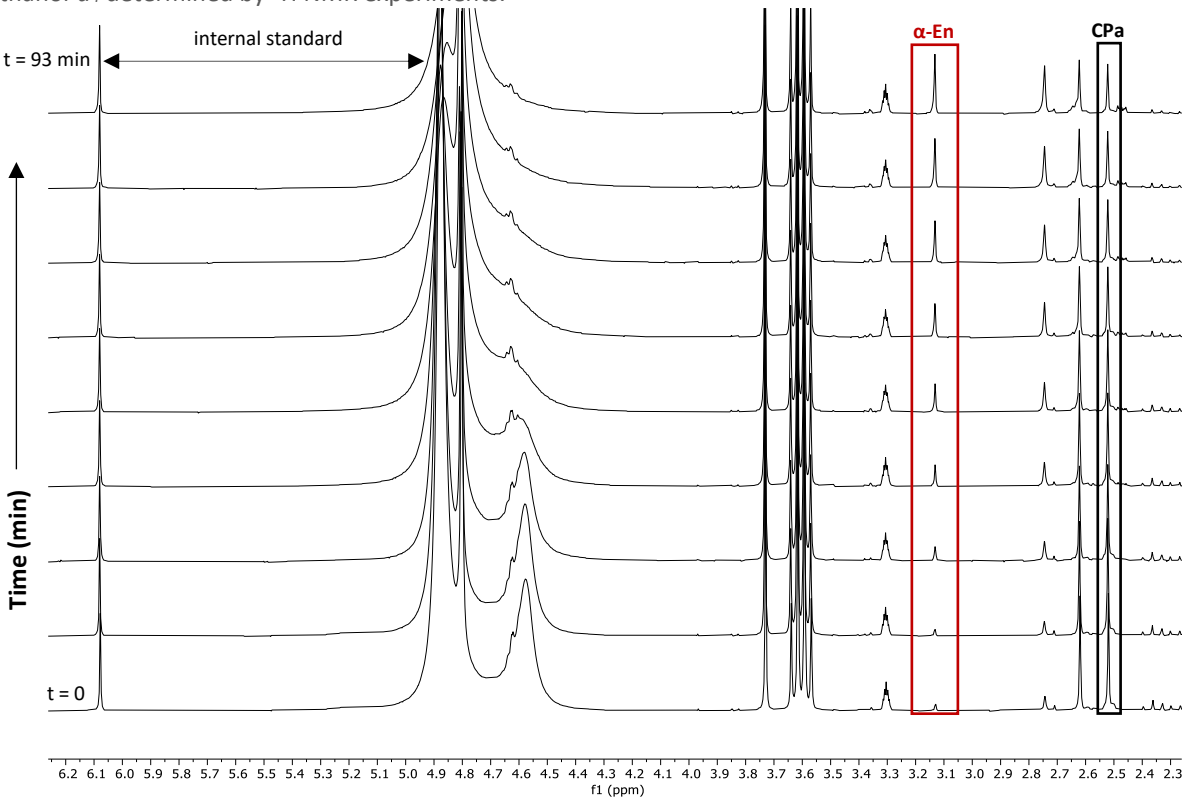


Figure S13. Selected ^{1}H NMR spectra in methanol-d_4 of the β-amine elimination of cyclopentanone **2a** into α-enaminone **3a** in the presence of K_2CO_3.

15. Computational Studies

Computational Details

Density functional theory (DFT) calculations were performed using the Gaussian 09 software package[11] and structural representations were generated with CYLview20.[12] All the geometry optimizations were carried out using the standard B3LYP functional and 6-31G(d) basis set. All of the optimized geometries were verified by frequency computations as minima (zero imaginary frequencies) or transition states (a single imaginary frequency corresponding to the desired reaction coordinate). Single-point energy calculations on the optimized geometries were then evaluated using the long-range corrected hybrid functional ωB97X-D developed by Head-Gordon and co-workers[13] and the valence triple-zeta Def2 TZVPP basis set, with solvent effects (ethanol) calculated by means of the Polarizable Continuum Model (PCM) initially devised by Tomasi and coworkers,[14-17] with radii and non-electrostatic terms of the SMD solvation model, developed by Truhler and co-workers.[18] The free energy values presented along the manuscript and SI were derived from the electronic energy values obtained at the ωB97X D/Def2 TZVPP//B3LYP/6-31G(d) level, including solvent effects, and corrected by using the thermal and entropic corrections based on structural and vibration frequency data calculated at the B3LYP/6-31G(d) level.

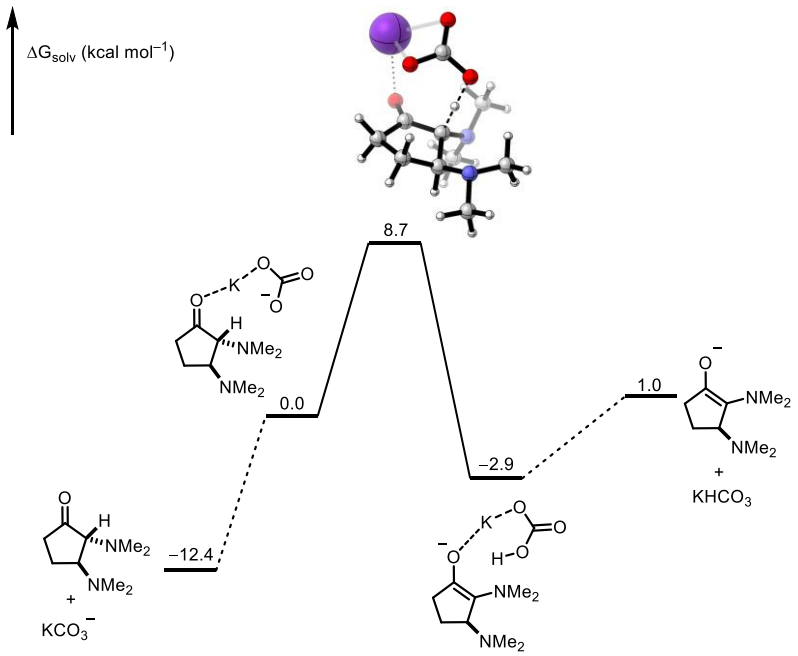


Figure S14. Free energy profile for the deprotonation of 2-derived ketone promoted by KCO3−. DFT calculations were performed at the ωB97XD/Def2 TZVPP/PCM(ethanol)//B3LYP/6-31G(d) level of theory.

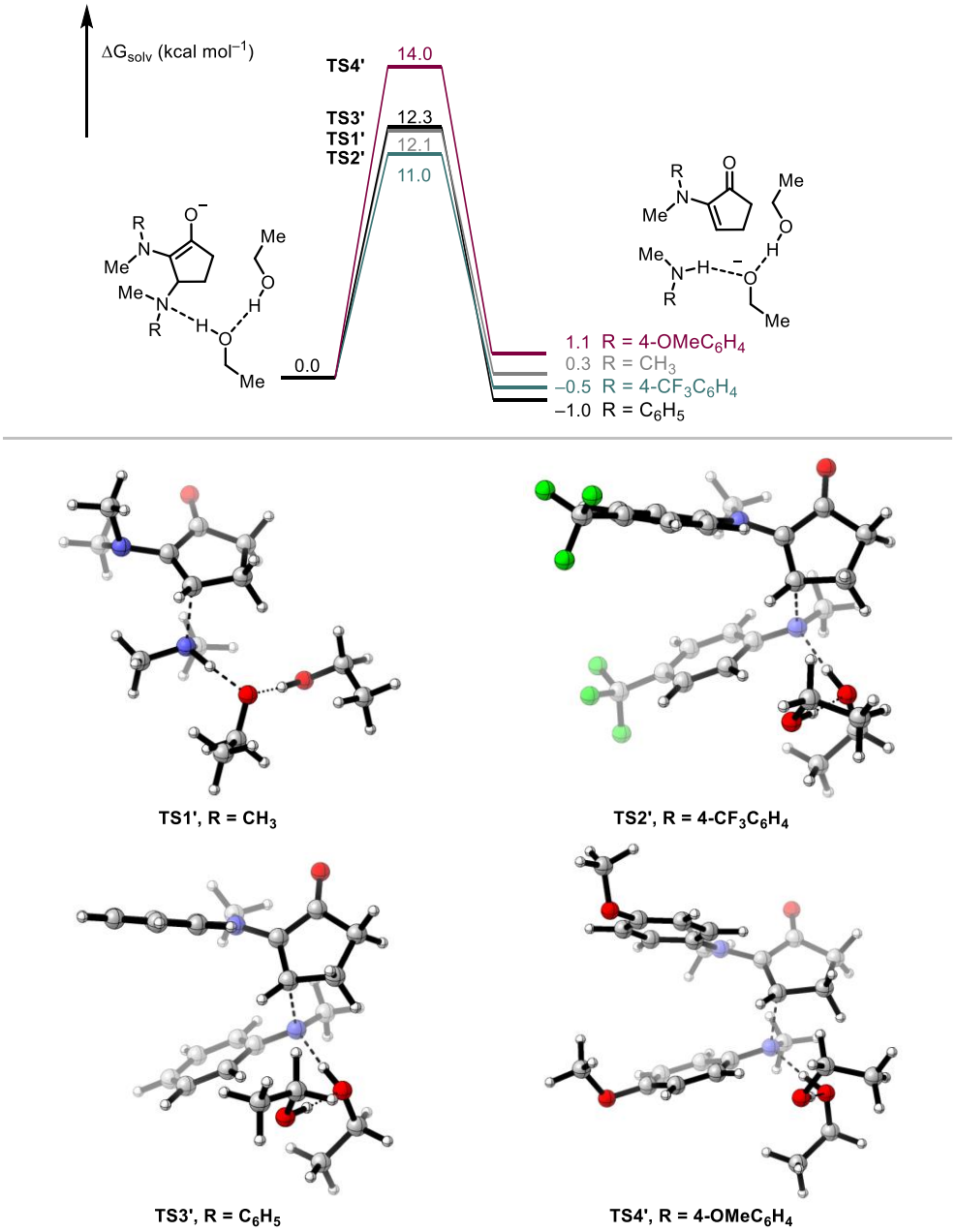


Figure S15. Free energy profile for the cleavage of the C–N bond of 2-derived enolate promoted by 2 molecules of ethanol. DFT calculations were performed at the ωB97XD/Def2 TZVPP/PCM(ethanol)//B3LYP/6-31G(d) level of theory.

	SCF energy (Hartree)	Free energy correction (Hartree)	Free energy (Hartree)	Relative ΔG (kcal mo^{-1})
KCO3-	-864.46939048	-0.001510	-864.470900595	
KCO_3H	-863.97362515	-0.014945	-863.988569650	
ketone	-538.554015566	0.229778	-538.324237479	
enolate	-538.036236617	0.215633	-537.820603307	
[ketone-KCO_3]$^-$	-1402.527640716	0.214834	-1402.312807129	0.0
TS	-1402.505626993	0.214123	-1402.291503902	8.7
[enolate-KCO_3H]$^-$	-848.180056228	0.341484	-847.838572678	-2.9
TS1'_R	-848.200224112	0.361072	-847.839151722	0.0

TS1'	-848.178221760	0.358427	-847.819795002	12.1
TS1'_P	-848.192530962	0.353811	-847.838719809	0.3
TS3'_R	-1231.70353967	0.458350	-1231.24519015	0.0
TS3'	-1231.68103054	0.455435	-1231.22559602	12.3
TS3'_P	-1231.69324120	0.446392	-1231.24684947	-1.0
TS2'_R	-1905.92131970	0.456085	-1750.459673	0.0
TS2'	-1905.90136946	0.453736	-1750.438687	11.0
TS2'_P	-1905.91397165	0.447997	-1750.454631	-0.5
TS4'_R	-1460.76894980	0.515500	-1460.253450290	0.0
TS4'	-1460.74205020	0.510979	-1460.231071170	14.0
TS4'_P	-1460.75562346	0.503991	-1460.251632580	1.1

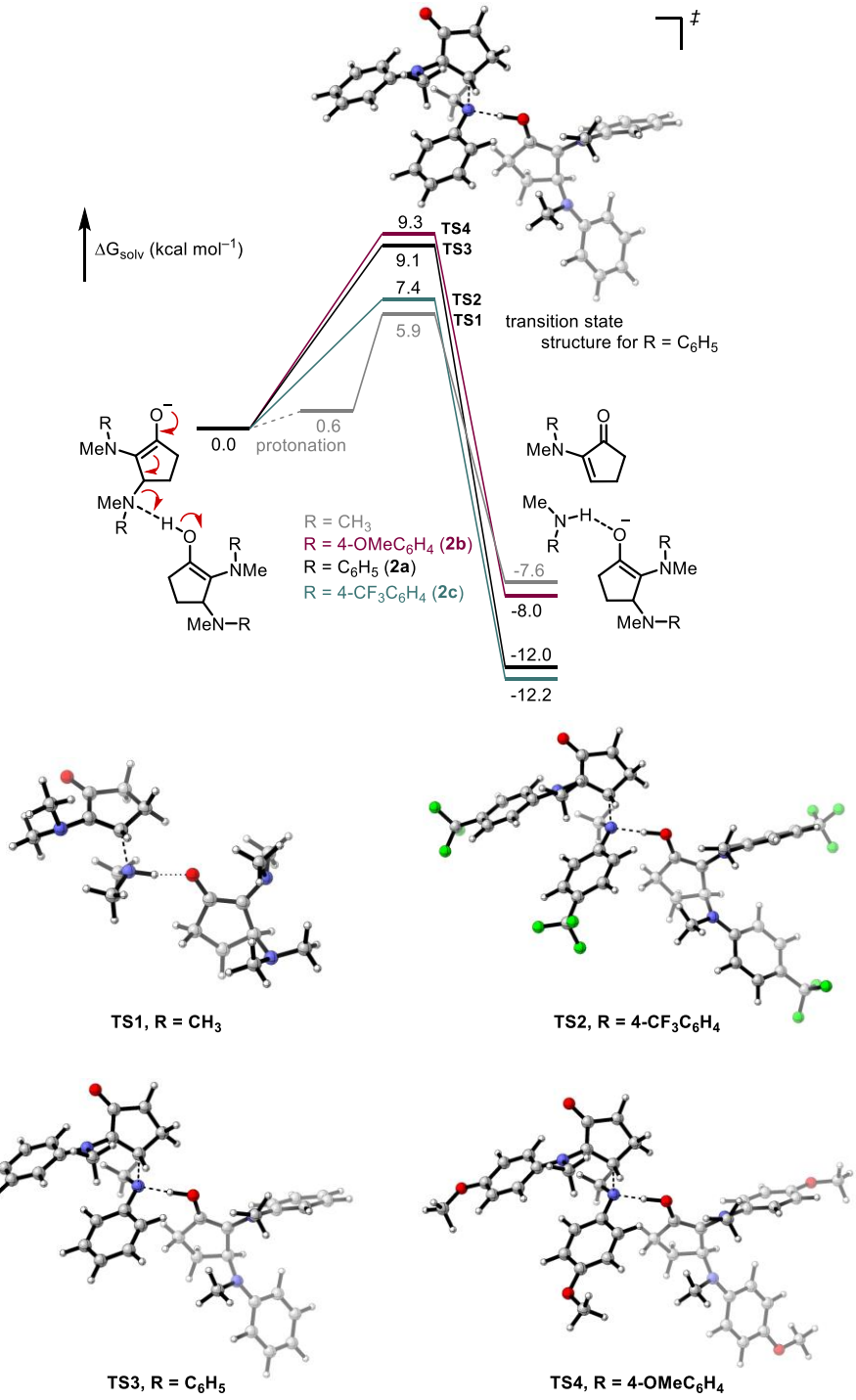
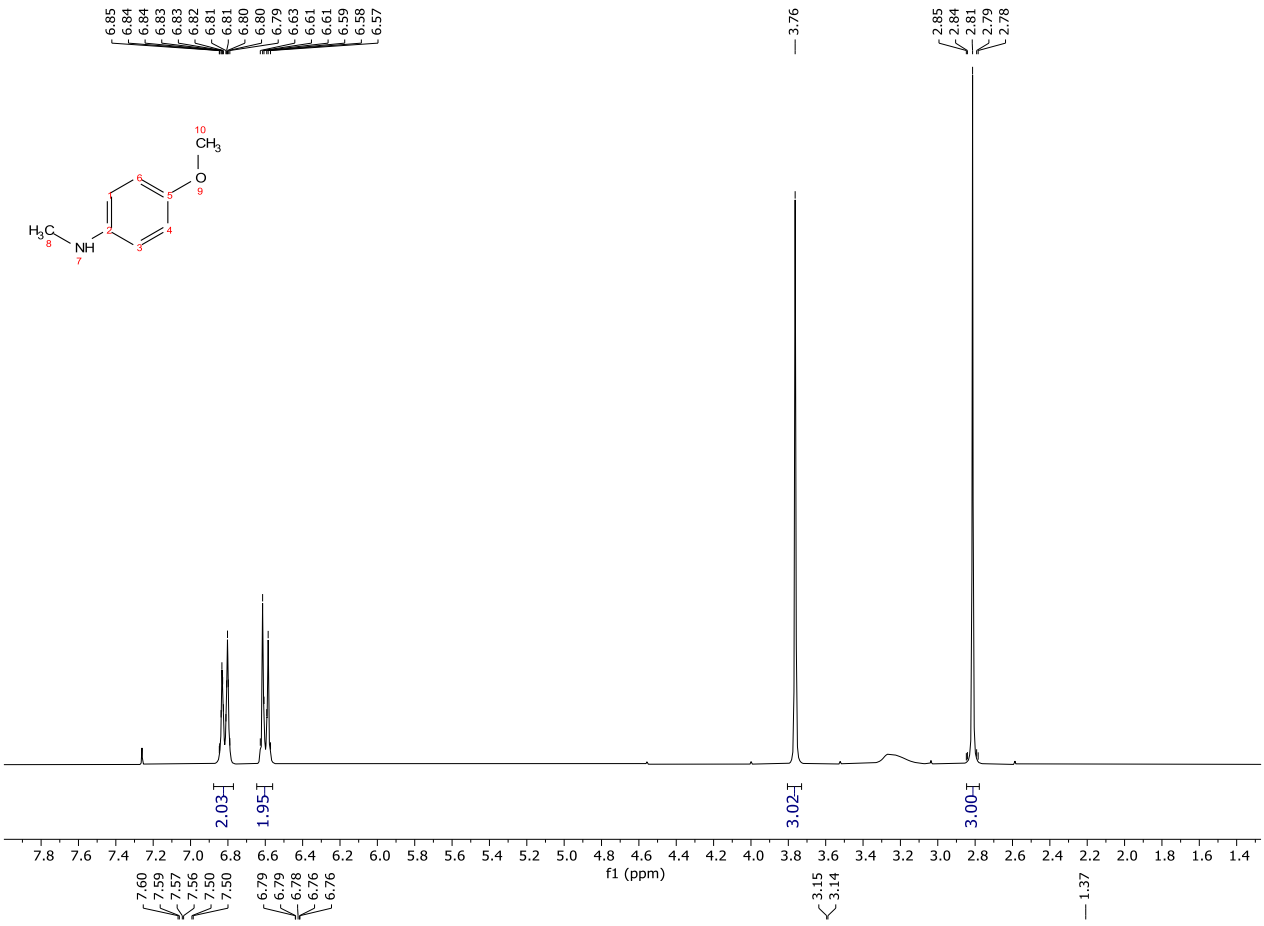
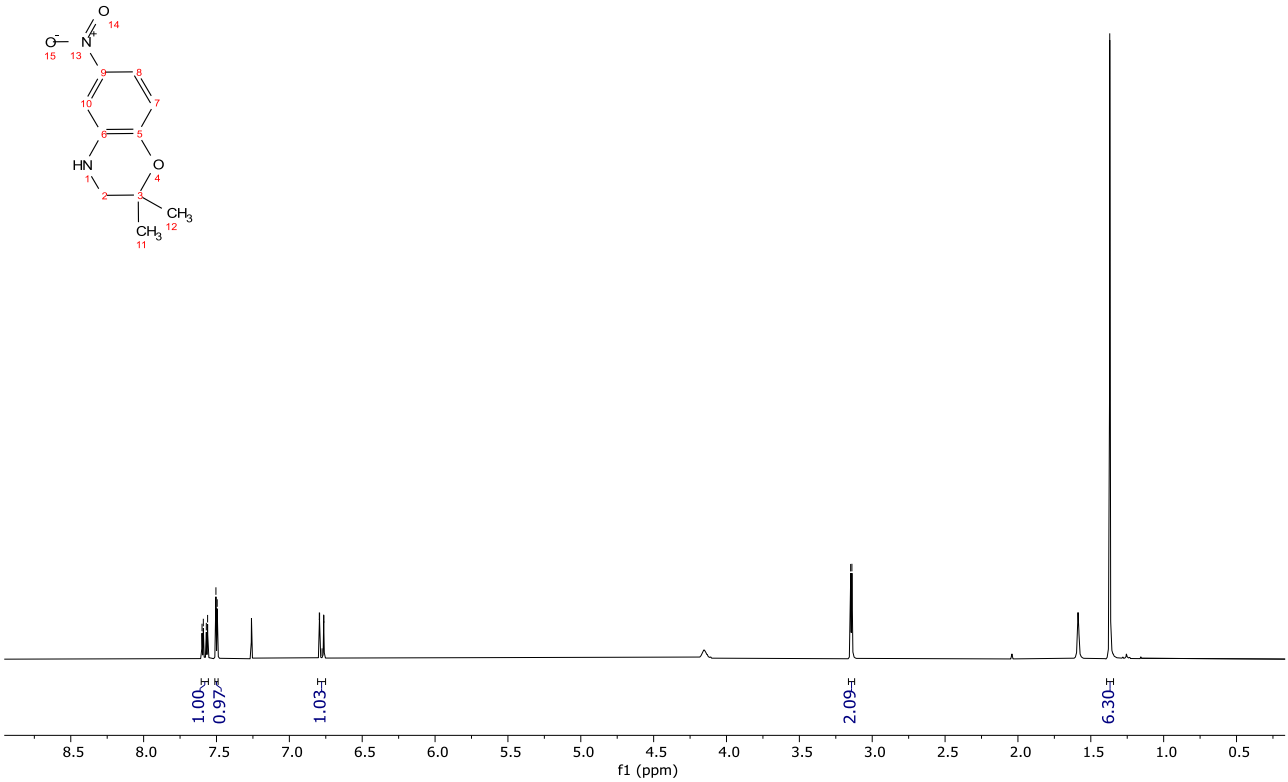


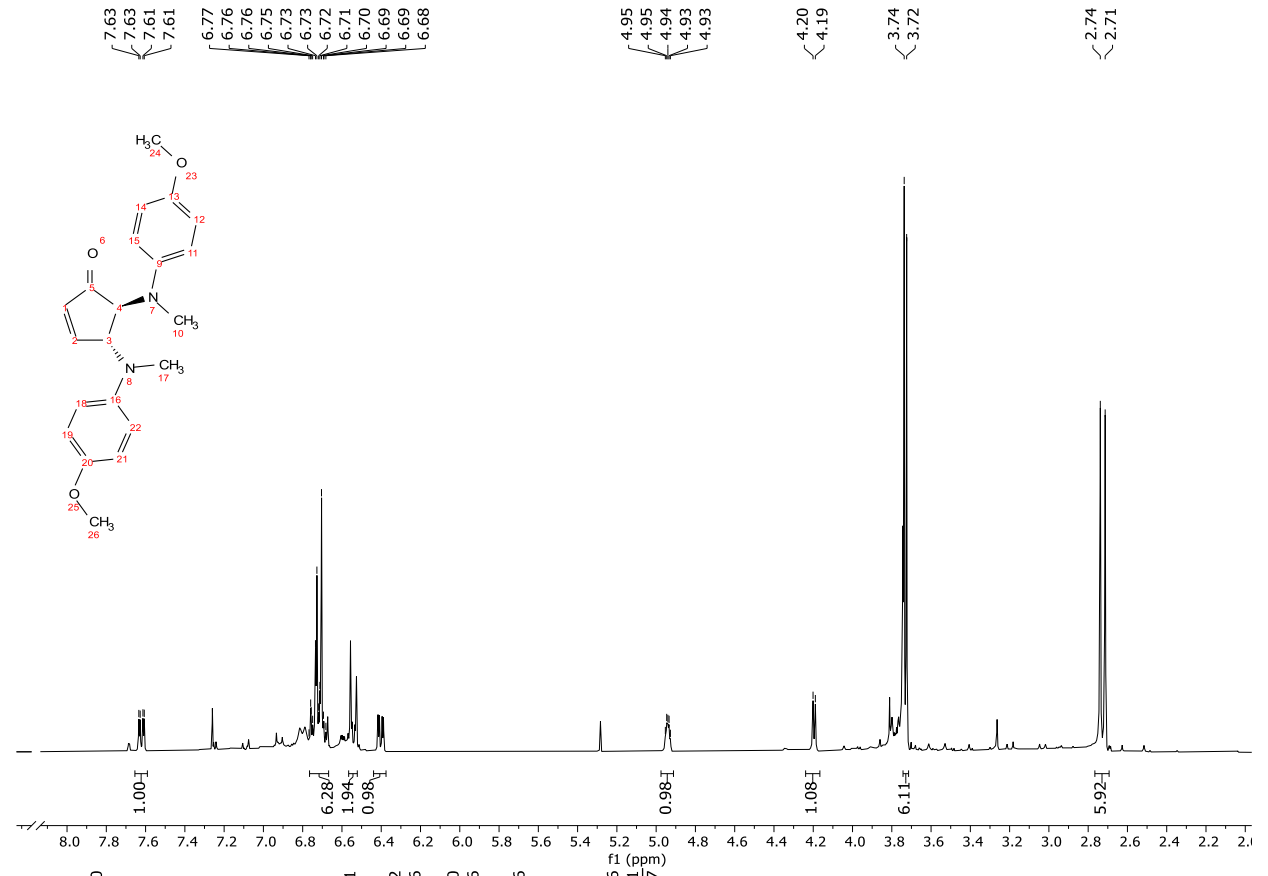
Figure S16. Gibbs free energy profiles (ωB97X-D/Def2-TZVPP/PCM (SMD,ethanol)//B3LYP/6-31G(d)) for the elimination reaction of DCP.

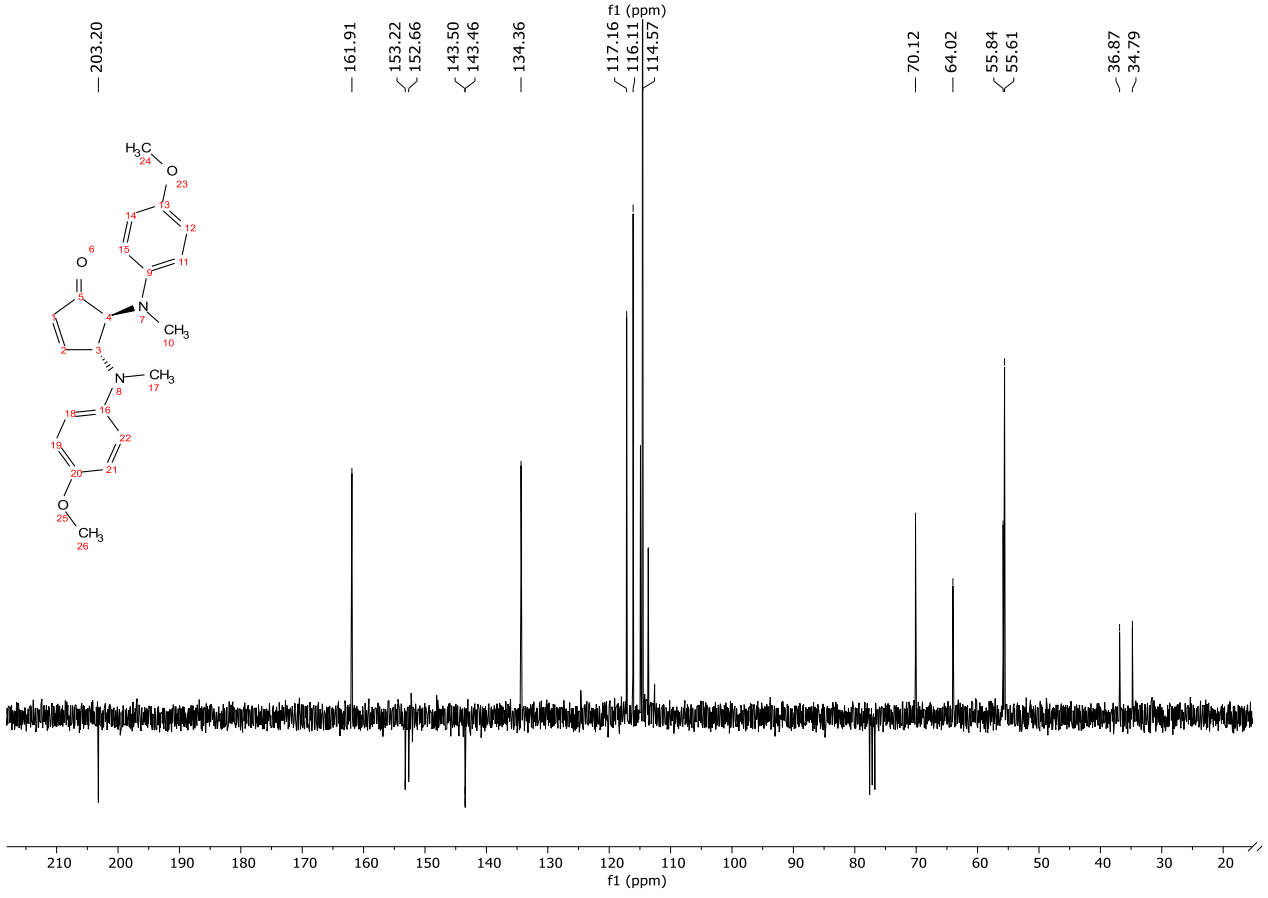
	SCF energy (Hartree)	Free energy correction (Hartree)	Free energy (Hartree)	Relative ΔG (kcal mol^{-1})
TS1_R_0	-1076.59308160	0.463122	-1076.129960	0.0
TS1_R	-1076.59149054	0.462424	-1076.129067	0.6
TS1	-1076.58139378	0.460906	-1076.120488	5.9
TS1_P	-1076.59519189	0.453135	-1076.142057	-7.6
TS2_R	-3192.03176056	0.650788	-3191.380973	0.0
TS2	-3192.01775097	0.648534	-3191.369217	7.4
TS2_P	-3192.04139266	0.641020	-3191.400373	-12.2
TS3_R	-1843.59783554	0.657227	-1842.940608	0.0
TS3	-1843.58020992	0.654127	-1842.926083	9.1
TS3_P	-1843.60482910	0.645023	-1842.959806	-12.0
TS4_R	-2301.73146719	0.773092	-2300.958375	0.0
TS4	-2301.71273979	0.769199	-2300.943540	9.3
TS4_P	-2301.73471305	0.763602	-2300.971111	-8.0
TS1'_R	-693.12236904	0.287435	-692.834934	0.0
TS1'	-693.08444249	0.282299	-692.802144	20.6
TS1'_P	-693.10130969	0.278549	-692.822761	7.6
TS3'_R	-1076.62403956	0.383126	-1076.240914	0.0
TS3'	-1076.59665806	0.381120	-1076.215538	15.9
TS3'_P	-1076.60433445	0.372616	-1076.231718	5.8
TS2'_R	-1750.84098482	0.381312	-1750.459673	0.0
TS2'	-1750.81729795	0.378611	-1750.438687	13.2
TS2'_P	-1750.82600908	0.371378	-1750.454631	3.2
TS4'_R	-1305.69364923	0.442935	-1305.250714	0.0
TS4'	-1305.66697246	0.439967	-1305.227005	14.9
TS4'_P	-1305.67015408	0.430044	-1305.240110	6.7

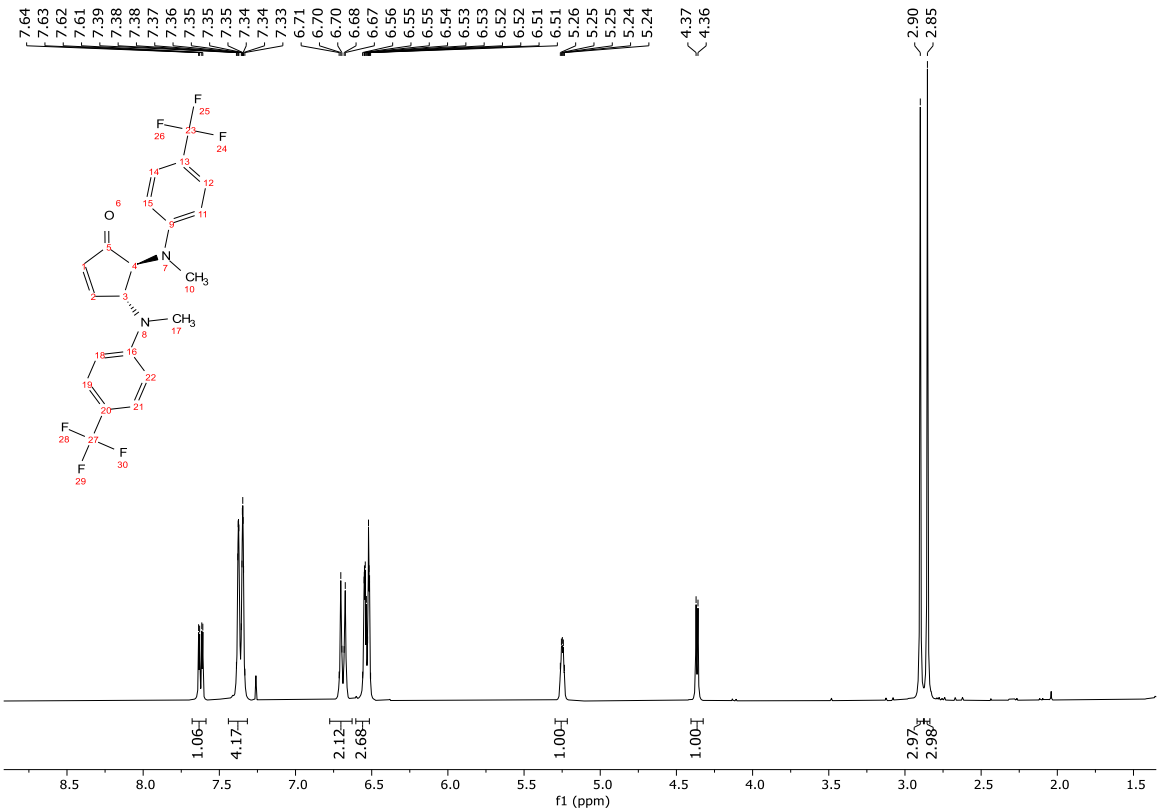




16. NMR Spectra of Compounds


7.63
7.63
7.61
7.61
6.77
6.76
6.76
6.75
6.73
6.73
6.72
6.71
6.70
6.69
6.69
6.68
4.95
4.95
4.94
4.93
4.93
4.20
4.19
3.74
3.72
2.74
2.71
1.00
6.28
1.94
0.98
0.98
1.08
6.11
5.92
f1 (ppm)


203.20
161.91
153.22
152.66
143.50
143.46
134.36
117.16
116.11
114.57
70.12
64.02
55.84
55.61
36.87
34.79
f1 (ppm)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7.62
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7.37
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7.35
7.35
7.35
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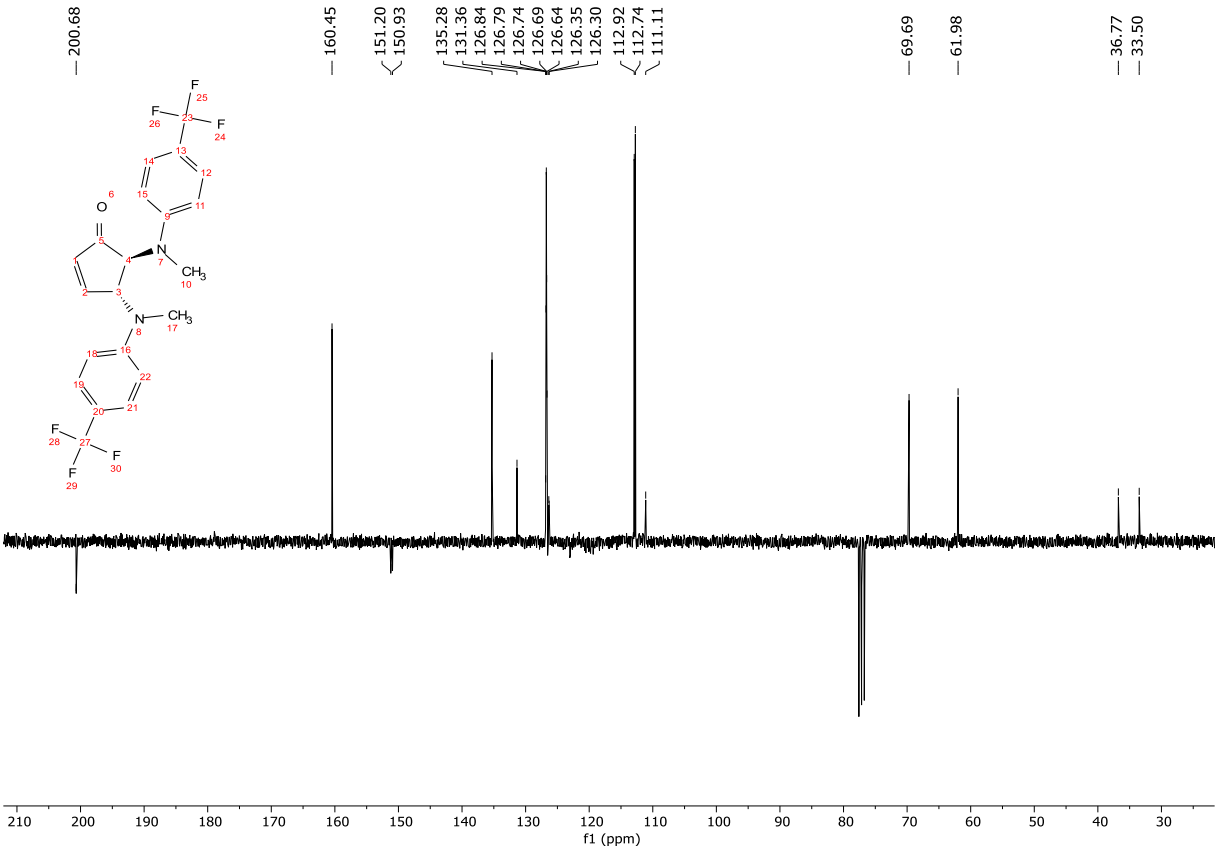
7.34
7.33
6.71
6.70
6.70
6.68
6.67
6.56
6.55
6.55
6.54
6.53
6.53
6.52
6.52
6.51
6.51
5.26
5.25
5.25
5.24
5.24
4.37
4.36
2.90
2.85
1.06
4.17
2.12
2.68
1.00
1.00
2.97
2.98
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)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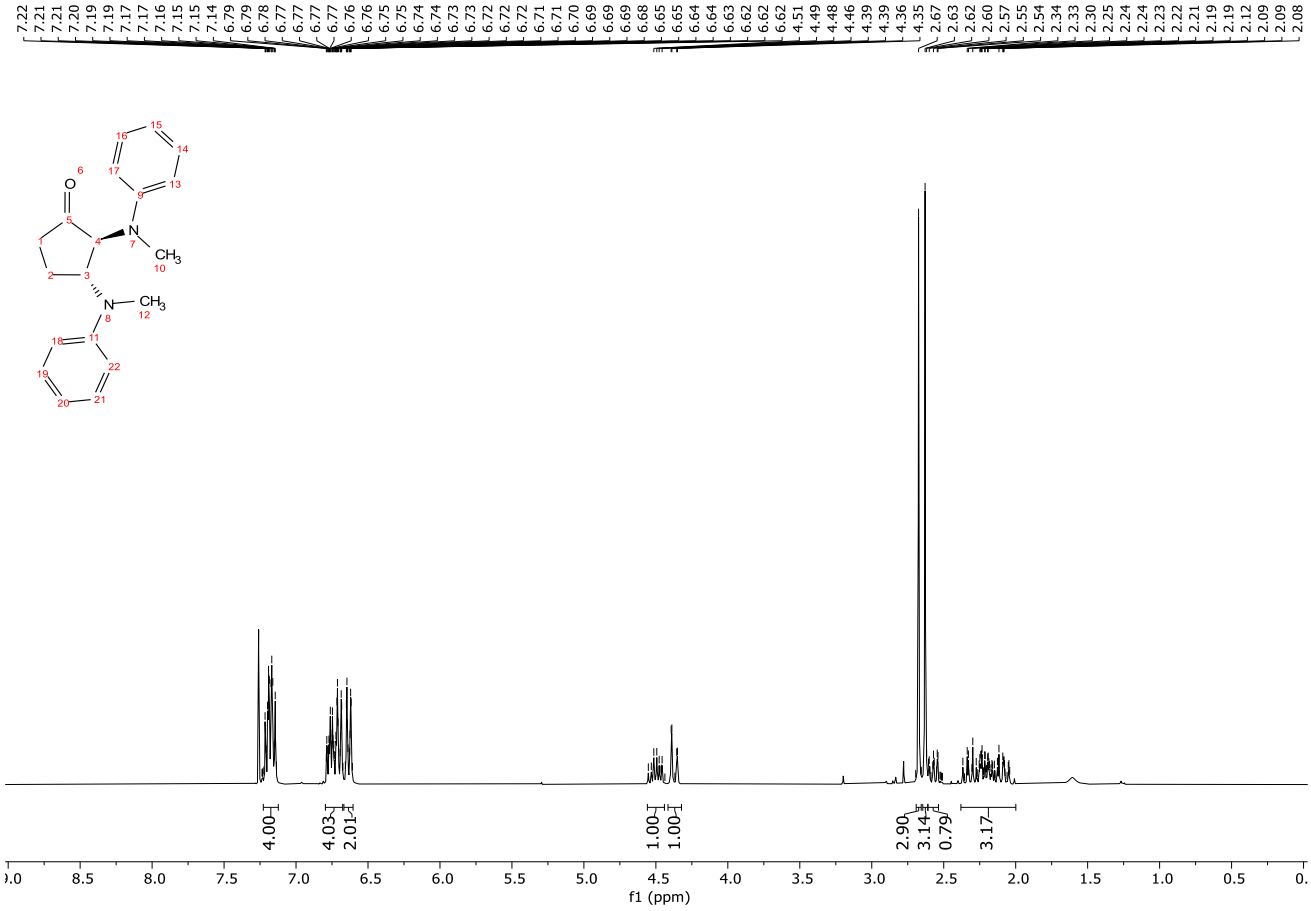
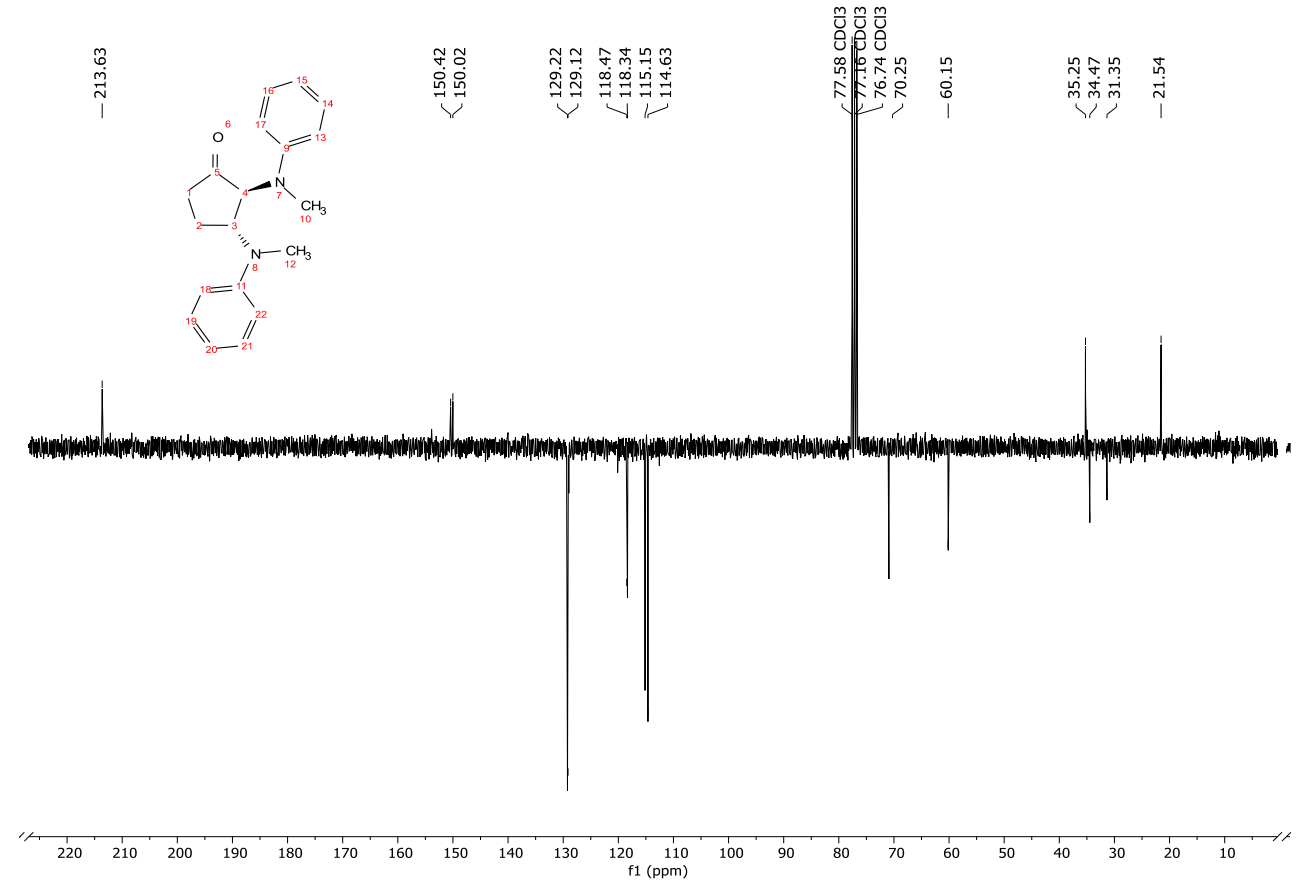
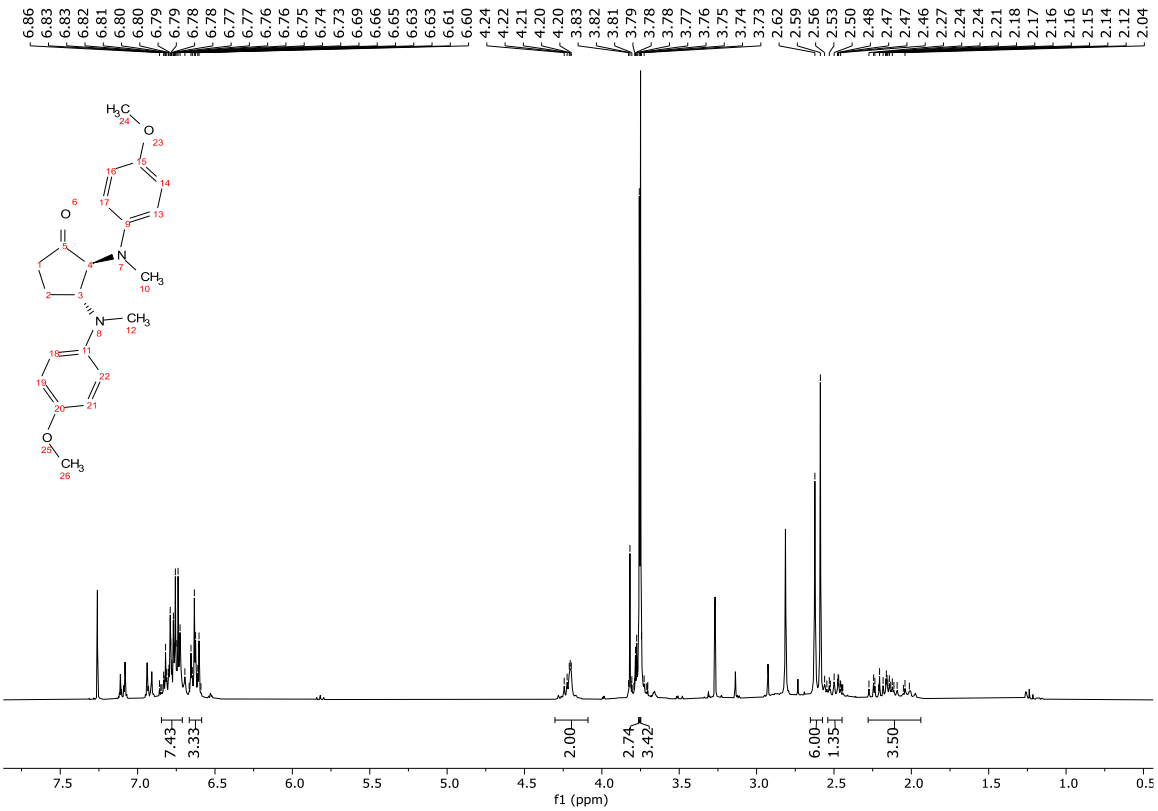
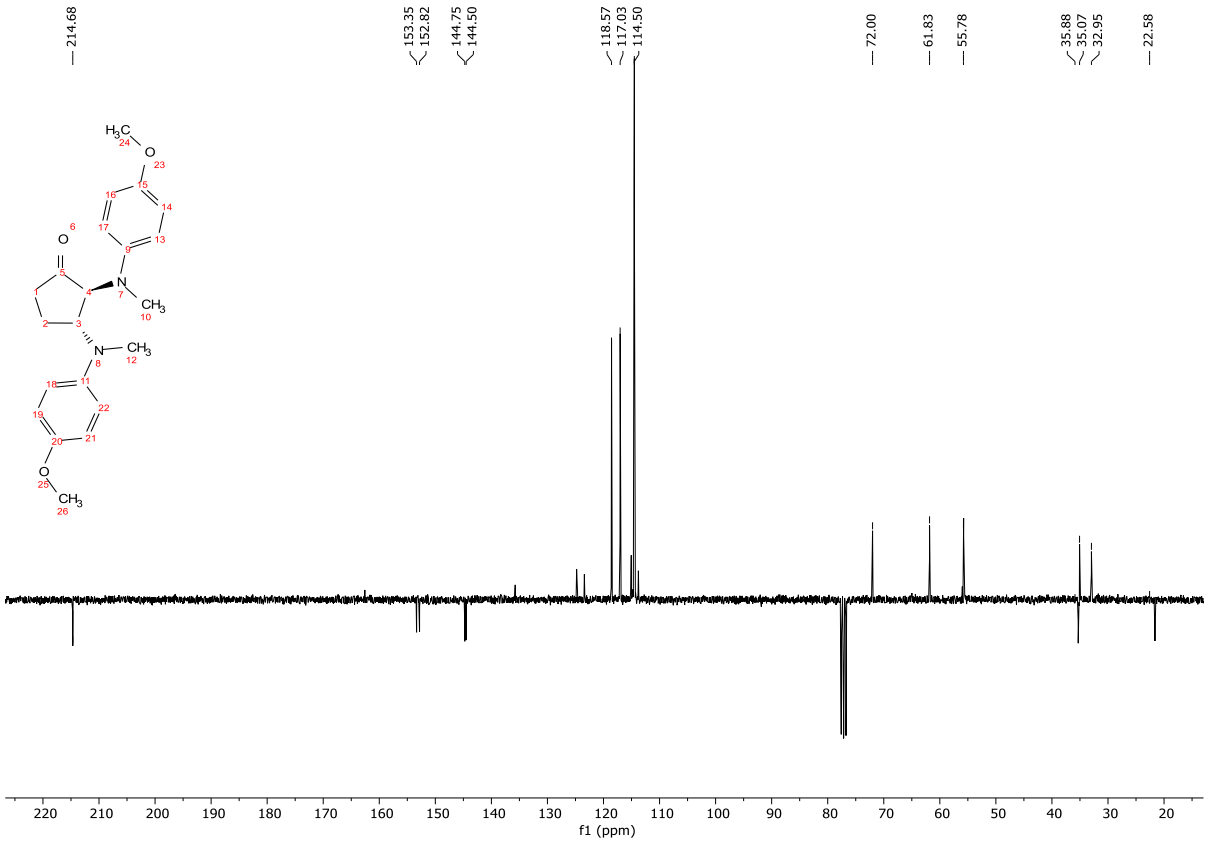
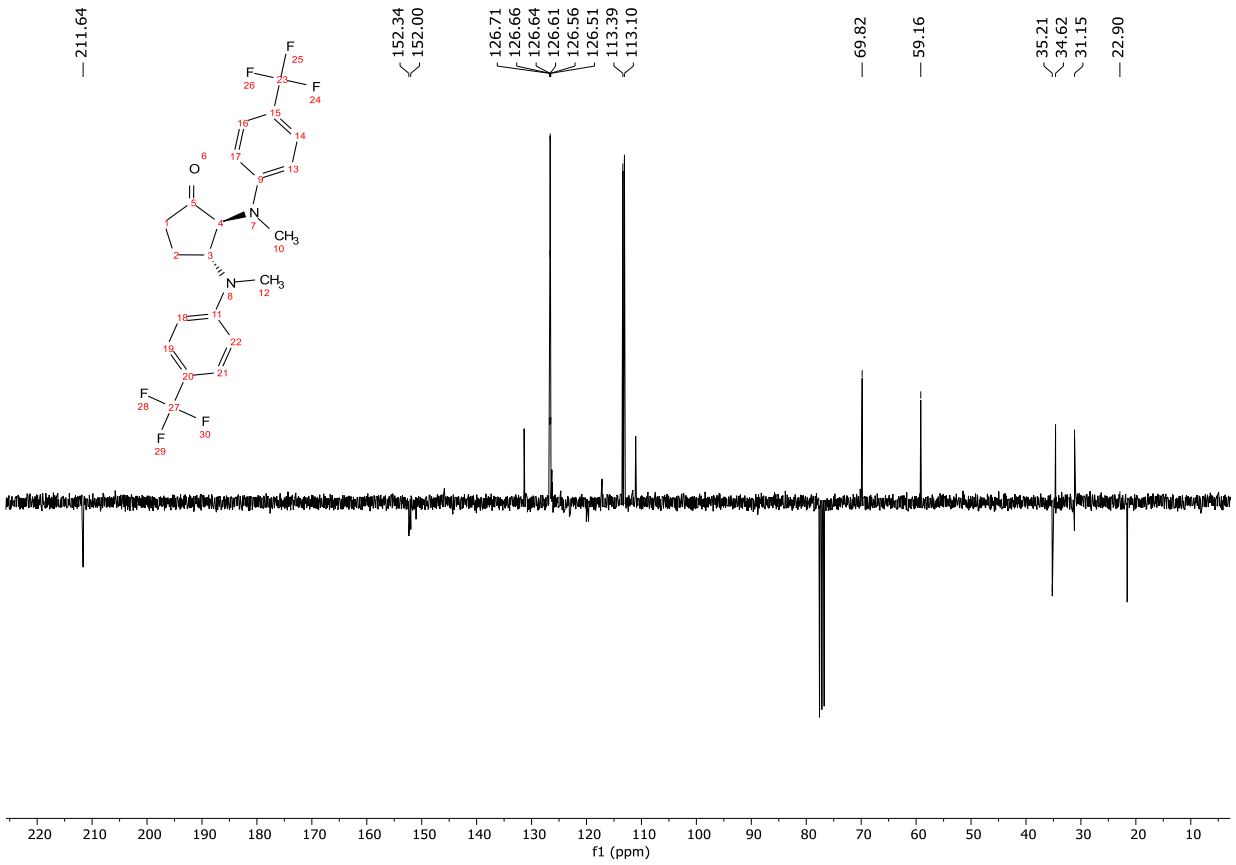
151.20
150.93
135.28
131.36
126.84
126.79
126.74
126.69
126.64
126.35
126.30
112.92
112.74
111.11
69.69
61.98
36.77
33.50
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
f1 (ppm)

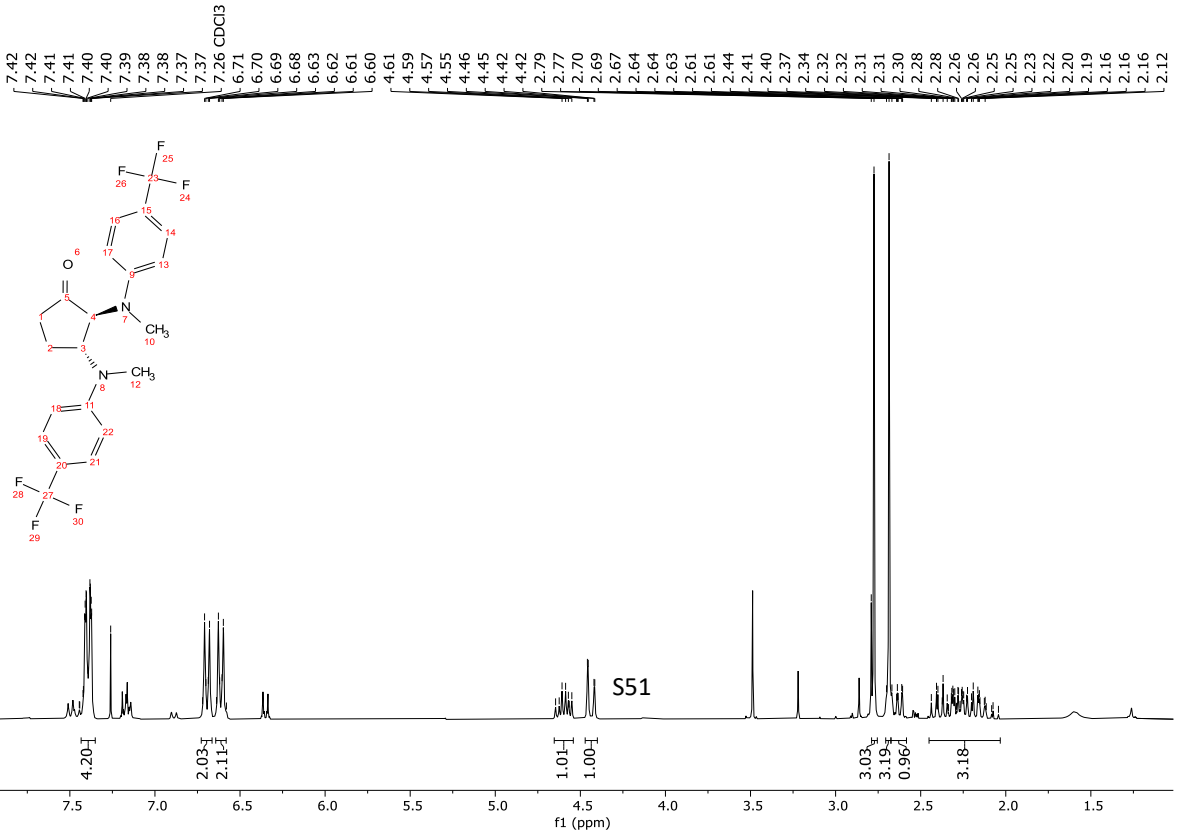

7.22 7.21 7.21 7.20 7.19 7.19 7.17 7.17 7.16 7.15 7.15 7.14 6.79 6.79 6.78 6.77 6.77 6.77 6.77 6.76 6.76 6.75 6.75 6.74 6.74 6.73 6.73 6.72 6.72 6.72 6.71 6.71 6.70 6.69 6.69 6.69 6.68 6.65 6.65 6.64 6.64 6.63 6.62 6.62 6.62 4.51 4.49 4.48 4.46 4.39 4.39 4.36 4.35 2.67 2.63 2.62 2.60 2.57 2.55 2.54 2.34 2.33 2.30 2.25 2.24 2.24 2.23 2.22 2.21 2.19 2.19 2.12 2.09 2.09 2.08
4.00
4.03
2.01
1.00
1.00
2.90
3.14
0.79
3.17
f1 (ppm)

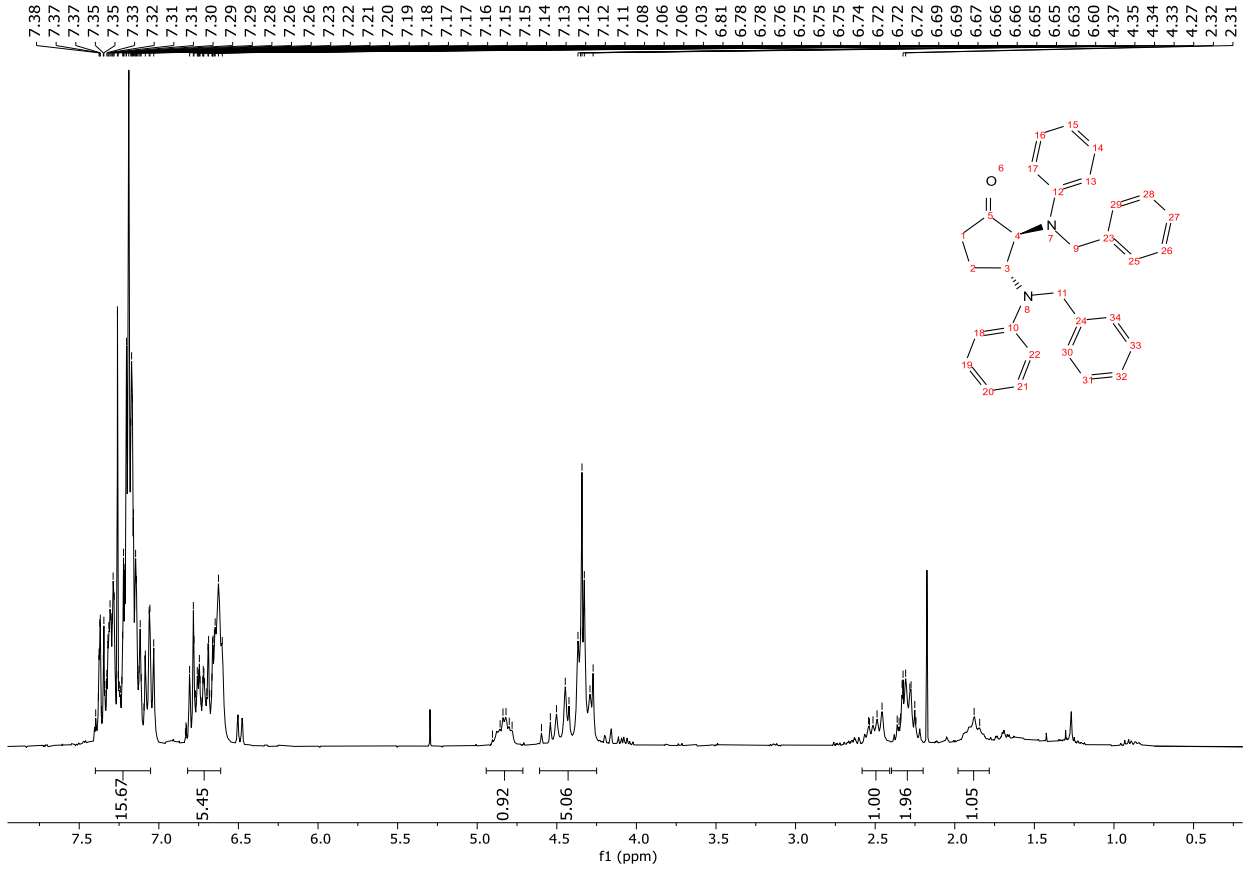

213.63
150.42
150.02
129.22
129.12
118.47
118.34
115.15
114.63
77.58 CDCl3
77.16 CDCl3
76.74 CDCl3
70.25
60.15
35.25
34.47
31.35
21.54
f1 (ppm)

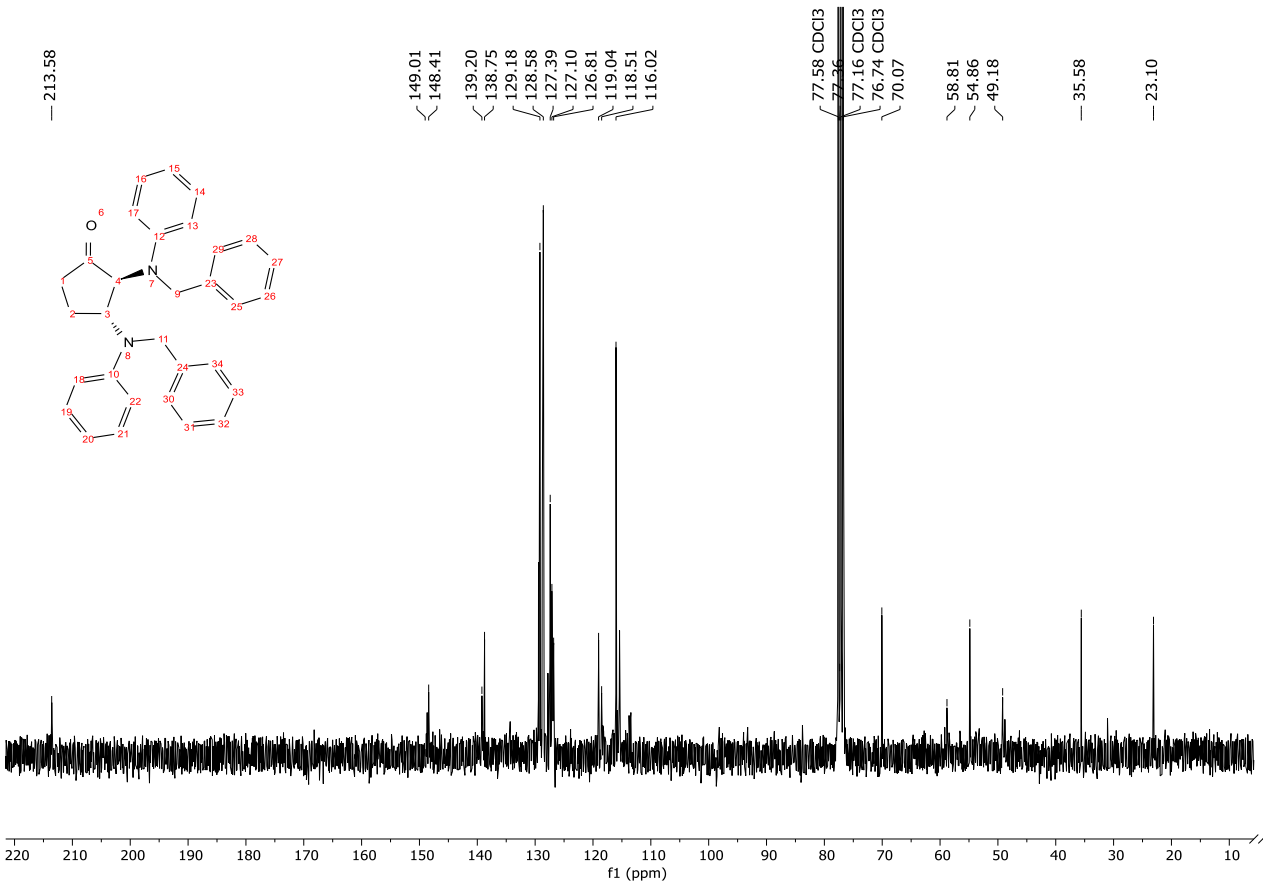

6.86 6.83 6.83 6.82 6.81 6.80 6.80 6.79 6.79 6.78 6.78 6.77 6.77 6.76 6.76 6.75 6.74 6.73 6.69 6.66 6.65 6.63 6.63 6.61 6.60
4.24 4.22 4.21 4.20 4.20 3.83 3.82 3.81 3.79 3.78 3.78 3.77 3.76 3.75 3.74 3.73
2.62 2.59 2.56 2.53 2.50 2.48 2.47 2.47 2.46 2.27 2.24 2.24 2.21 2.18 2.17 2.16 2.16 2.15 2.14 2.12 2.04
7.43 3.33 2.00 2.74 3.42 6.00 1.35 3.50
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

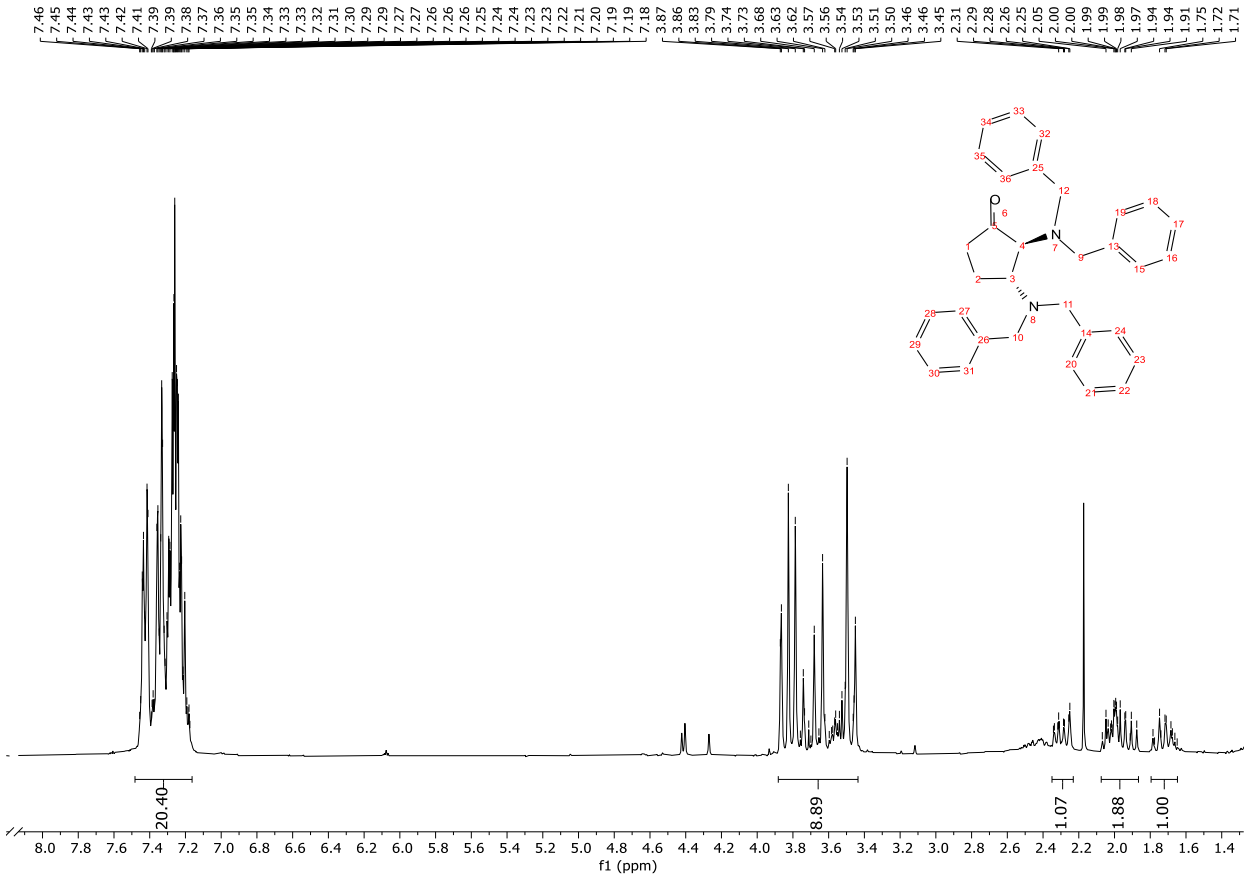

214.68
153.35 152.82 144.75 144.50 118.57 117.03 114.50 72.00 61.83 55.78 35.88 35.07 32.95 22.58
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
f1 (ppm)

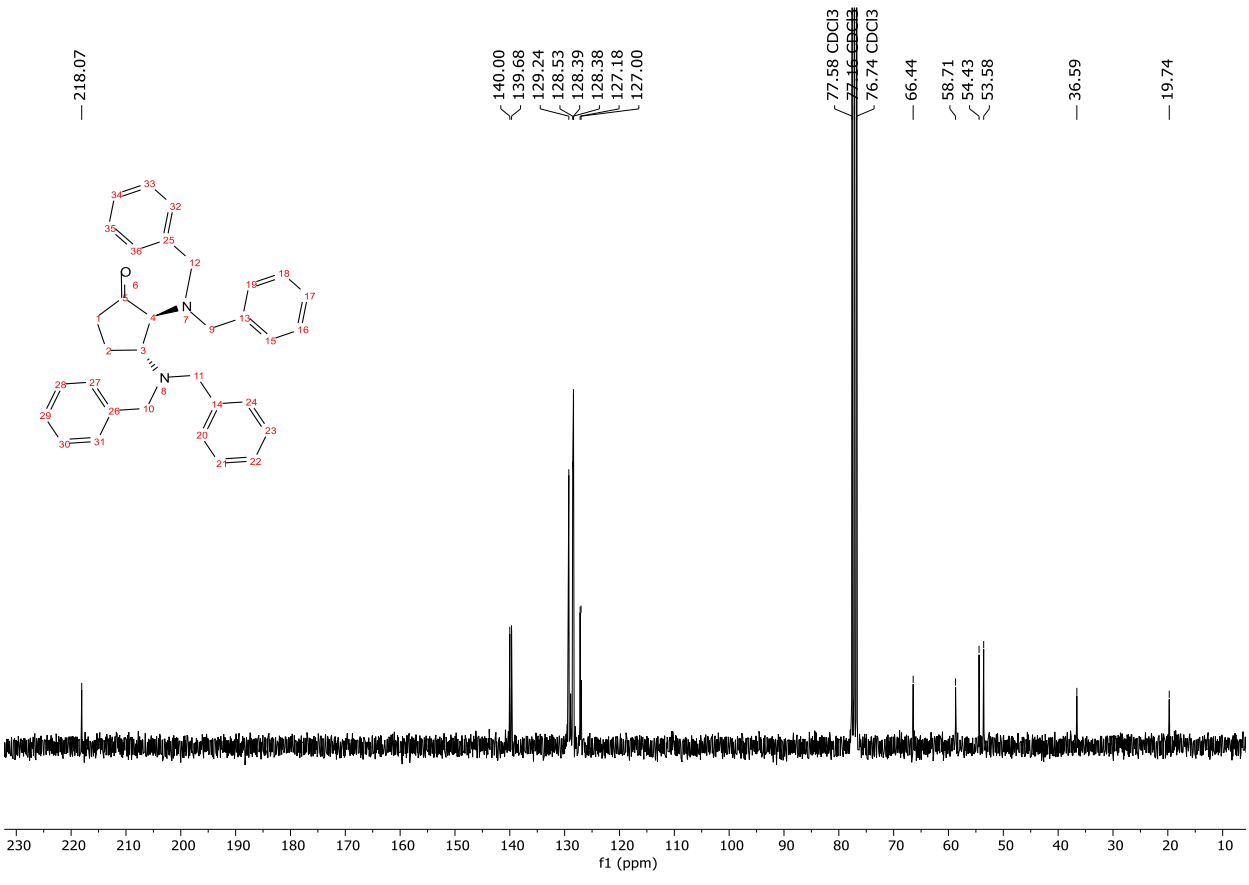

211.64
152.34
152.00
126.71
126.66
126.64
126.61
126.56
126.51
113.39
113.10
69.82
59.16
35.21
34.62
31.15
22.90
f1 (ppm)

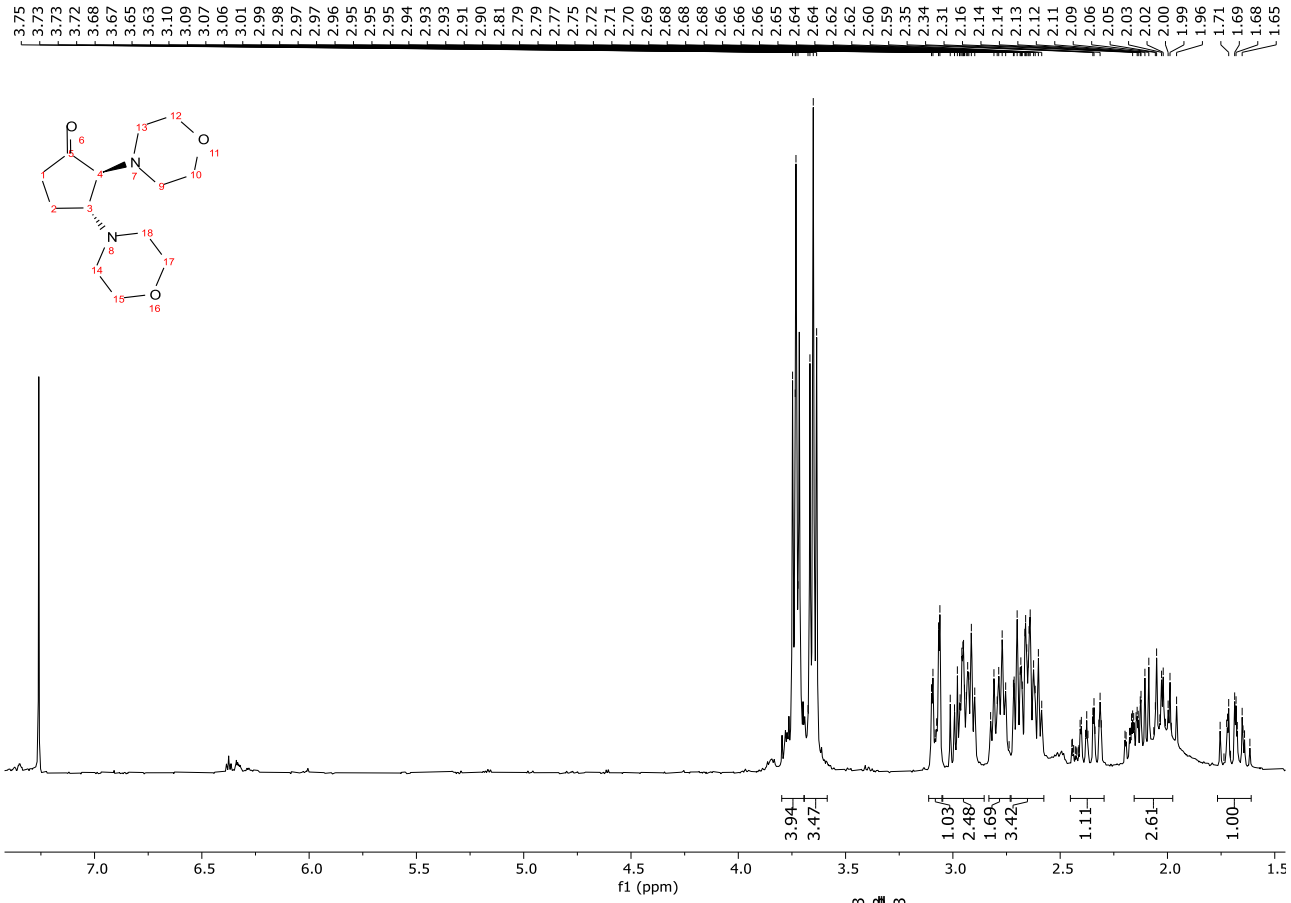

CDCl3
f1 (ppm)
S51

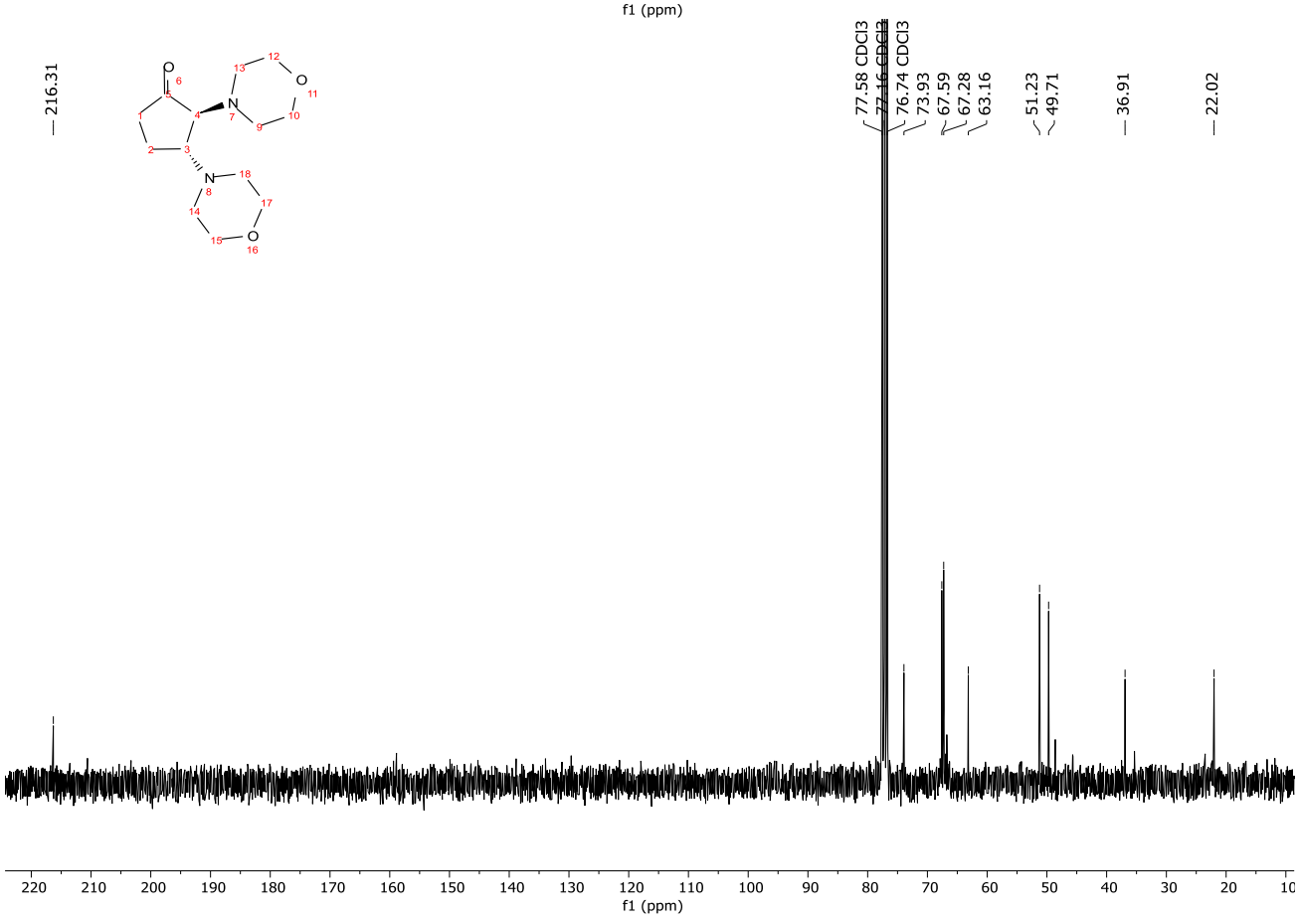

7.38 7.37 7.37 7.35 7.35 7.33 7.32 7.31 7.31 7.30 7.29 7.29 7.28 7.26 7.26 7.23 7.22 7.21 7.20 7.19 7.18 7.17 7.17 7.16 7.15 7.15 7.14 7.13 7.12 7.12 7.11 7.08 7.06 7.06 7.03 6.81 6.78 6.78 6.76 6.75 6.75 6.75 6.74 6.72 6.72 6.72 6.69 6.69 6.67 6.66 6.66 6.65 6.65 6.63 6.60 4.37 4.35 4.34 4.33 4.27 2.32 2.31
15.67
5.45
0.92
5.06
1.00
1.96
1.05
f1 (ppm)


213.58
149.01 148.41 139.20 138.75 129.18 128.58 127.39 127.10 126.81 119.04 118.51 116.02
77.58 CDCl3 77.36 77.16 CDCl3 76.74 CDCl3 70.07
58.81 54.86 49.18
35.58
23.10
f1 (ppm)


7.46 7.45 7.44 7.43 7.43 7.42 7.41 7.39 7.39 7.38 7.37 7.36 7.35 7.35 7.34 7.33 7.33 7.32 7.31 7.30 7.29 7.29 7.27 7.27 7.26 7.26 7.26 7.25 7.24 7.24 7.23 7.23 7.22 7.21 7.20 7.19 7.19 7.18
3.87 3.86 3.83 3.79 3.74 3.73 3.68 3.63 3.62 3.57 3.56 3.54 3.53 3.51 3.50 3.46 3.45
2.31 2.29 2.28 2.26 2.25 2.05 2.00 2.00 1.99 1.99 1.98 1.97 1.94 1.94 1.91 1.75 1.72 1.71
20.40
8.89
1.07
1.88
1.00
8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4
f1 (ppm)


218.07
140.00
139.68
129.24
128.53
128.39
128.38
127.18
127.00
77.58 CDCl3
77.16 CDCl3
76.74 CDCl3
66.44
58.71
54.43
53.58
36.59
19.74
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


3.75 3.73 3.73 3.72 3.68 3.67 3.65 3.63 3.10 3.09 3.07 3.06 3.01 2.99 2.98 2.97 2.97 2.96 2.95 2.95 2.95 2.94 2.93 2.93 2.91 2.90 2.81 2.79 2.79 2.77 2.75 2.72 2.71 2.70 2.69 2.68 2.68 2.68 2.66 2.66 2.66 2.65 2.64 2.64 2.62 2.62 2.60 2.59 2.35 2.34 2.31 2.16 2.14 2.14 2.13 2.12 2.11 2.09 2.06 2.05 2.03 2.02 2.00 1.99 1.96 1.71 1.69 1.68 1.65
3.94
3.47
1.03
2.48
1.69
3.42
1.11
2.61
1.00
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5
f1 (ppm)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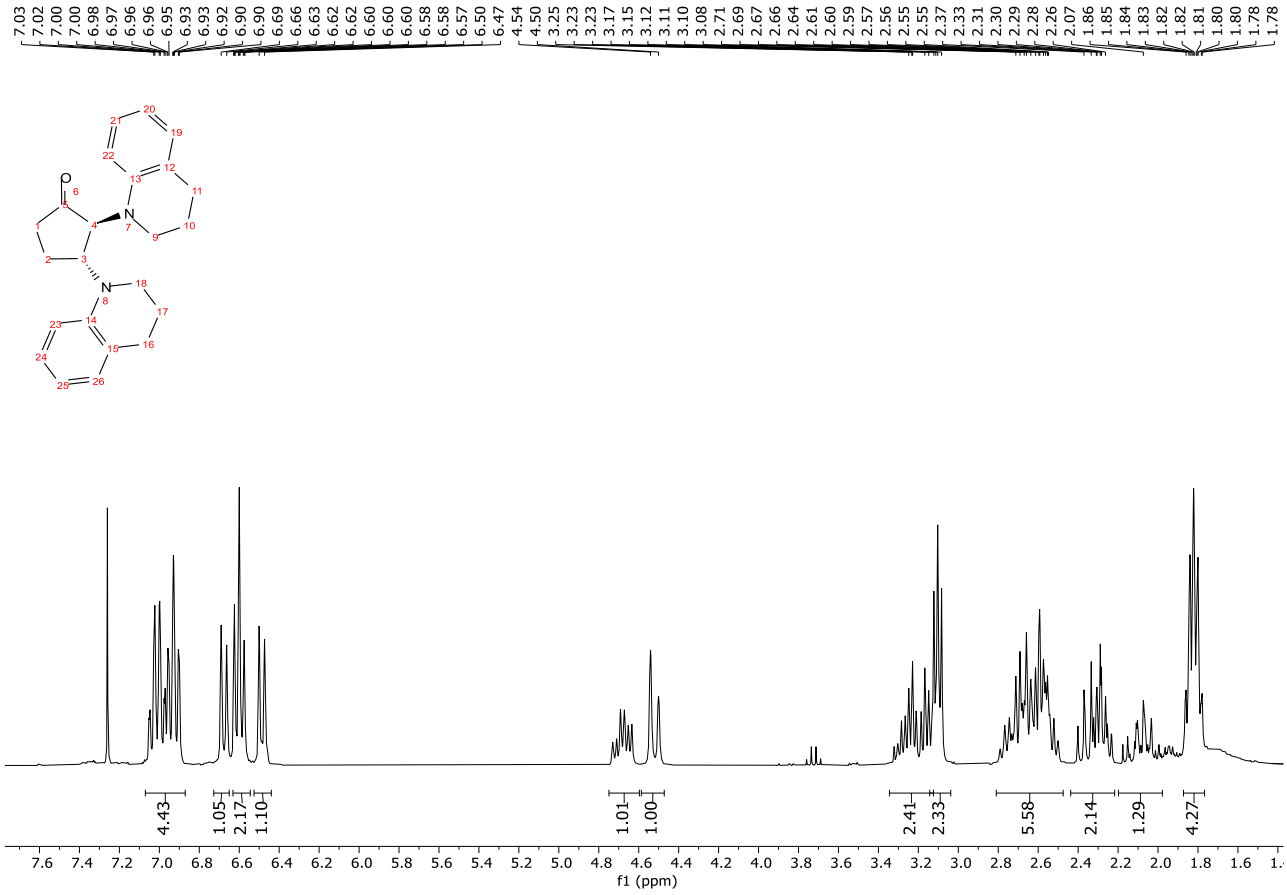
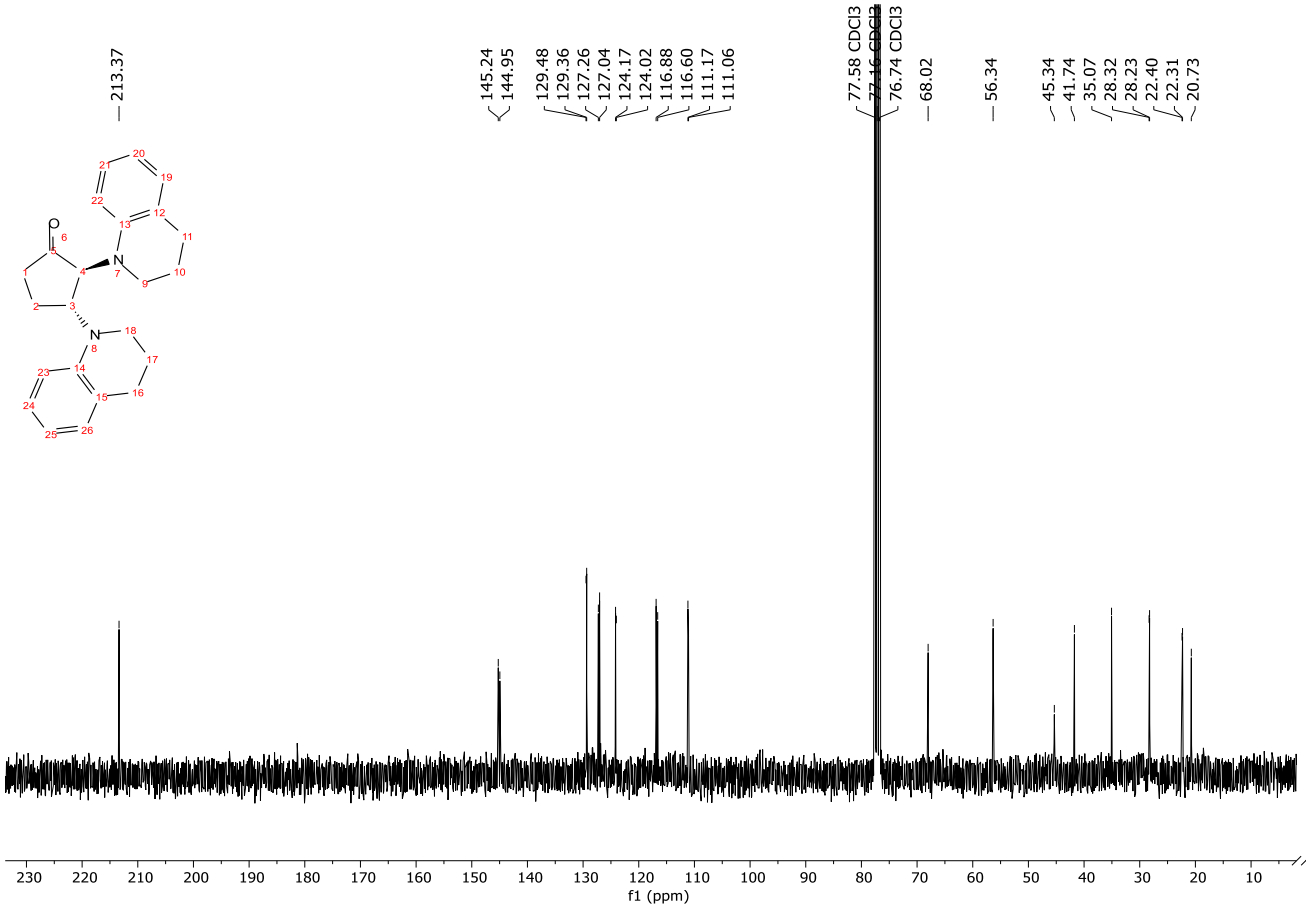
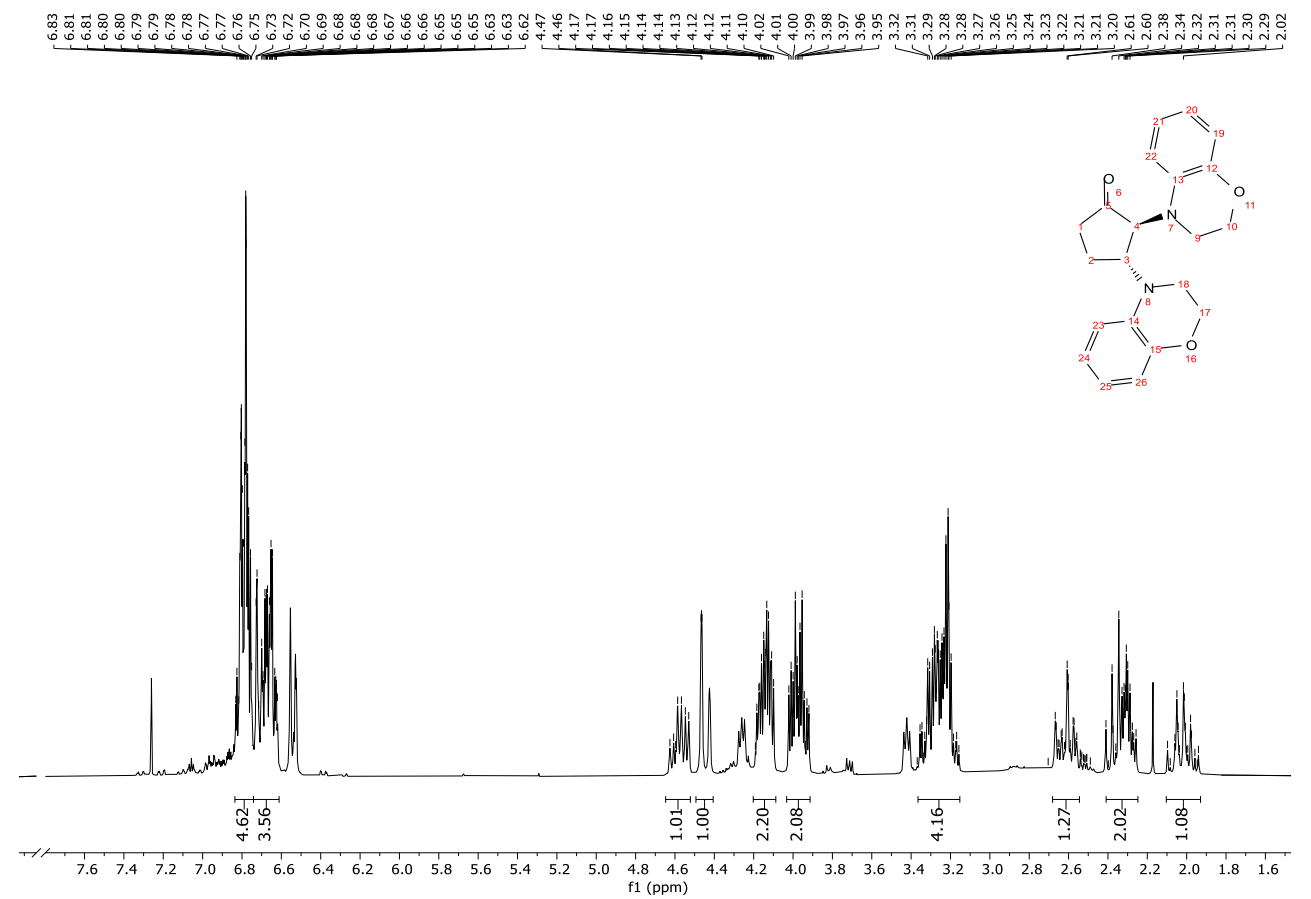
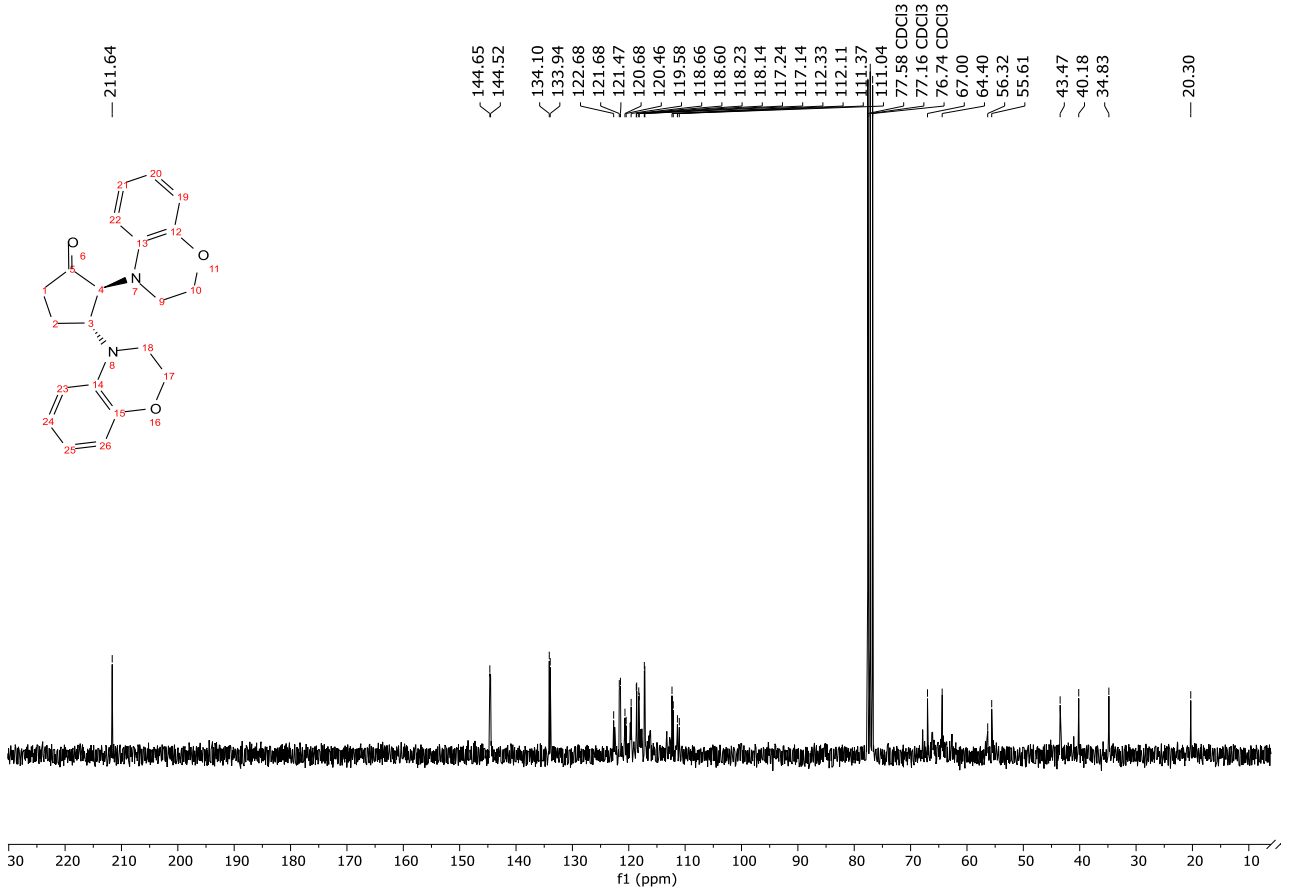
77.58 CDCl3
77.16 CDCl3
76.74 CDCl3
73.93
67.59
67.28
63.16
51.23
49.71
36.91
22.02
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


7.03 7.02 7.00 7.00 6.98 6.97 6.96 6.96 6.95 6.93 6.93 6.92 6.90 6.90 6.69 6.66 6.63 6.62 6.62 6.60 6.60 6.60 6.58 6.58 6.57 6.50 6.47
4.54 4.50 3.25 3.23 3.23 3.17 3.15 3.12 3.11 3.10 3.08 2.71 2.69 2.67 2.66 2.64 2.61 2.60 2.59 2.57 2.56 2.55 2.55 2.37 2.33 2.31 2.30 2.29 2.28 2.26 2.07 1.86 1.85 1.84 1.83 1.82 1.82 1.81 1.80 1.80 1.78 1.78
O
N
N
4.43
1.05
2.17
1.10
1.01
1.00
2.41
2.33
5.58
2.14
1.29
4.27
7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6
f1 (ppm)


213.37
145.24
144.95
129.48
129.36
127.26
127.04
124.17
124.02
116.88
116.60
111.17
111.06
77.58 CDCl3
77.16 CDCl3
76.74 CDCl3
68.02
56.34
45.34
41.74
35.07
28.32
28.23
22.40
22.31
20.73
f1 (ppm)


6.83 6.81 6.81 6.80 6.80 6.79 6.79 6.78 6.78 6.77 6.77 6.76 6.75 6.73 6.72 6.70 6.69 6.68 6.68 6.68 6.67 6.66 6.66 6.65 6.65 6.65 6.63 6.62
4.47 4.46 4.17 4.17 4.16 4.15 4.14 4.14 4.13 4.12 4.12 4.11 4.10 4.02 4.01 4.00 3.99 3.98 3.97 3.96 3.95
3.32 3.31 3.29 3.28 3.28 3.27 3.26 3.25 3.24 3.23 3.22 3.21 3.21 3.20 2.61 2.60 2.38 2.34 2.32 2.31 2.31 2.30 2.29 2.02
4.62
3.56
1.01
1.00
2.20
2.08
4.16
1.27
2.02
1.08
f1 (ppm)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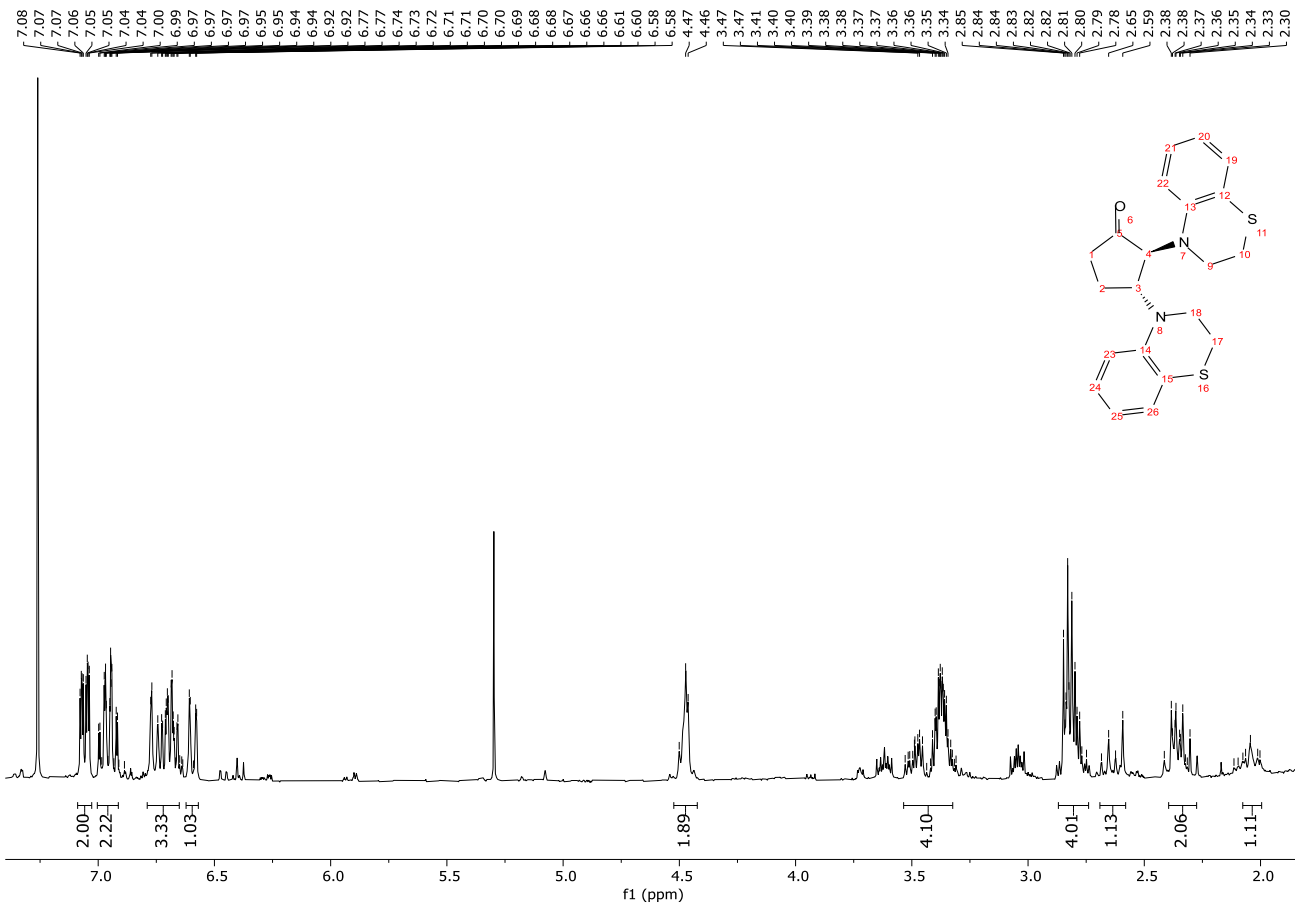
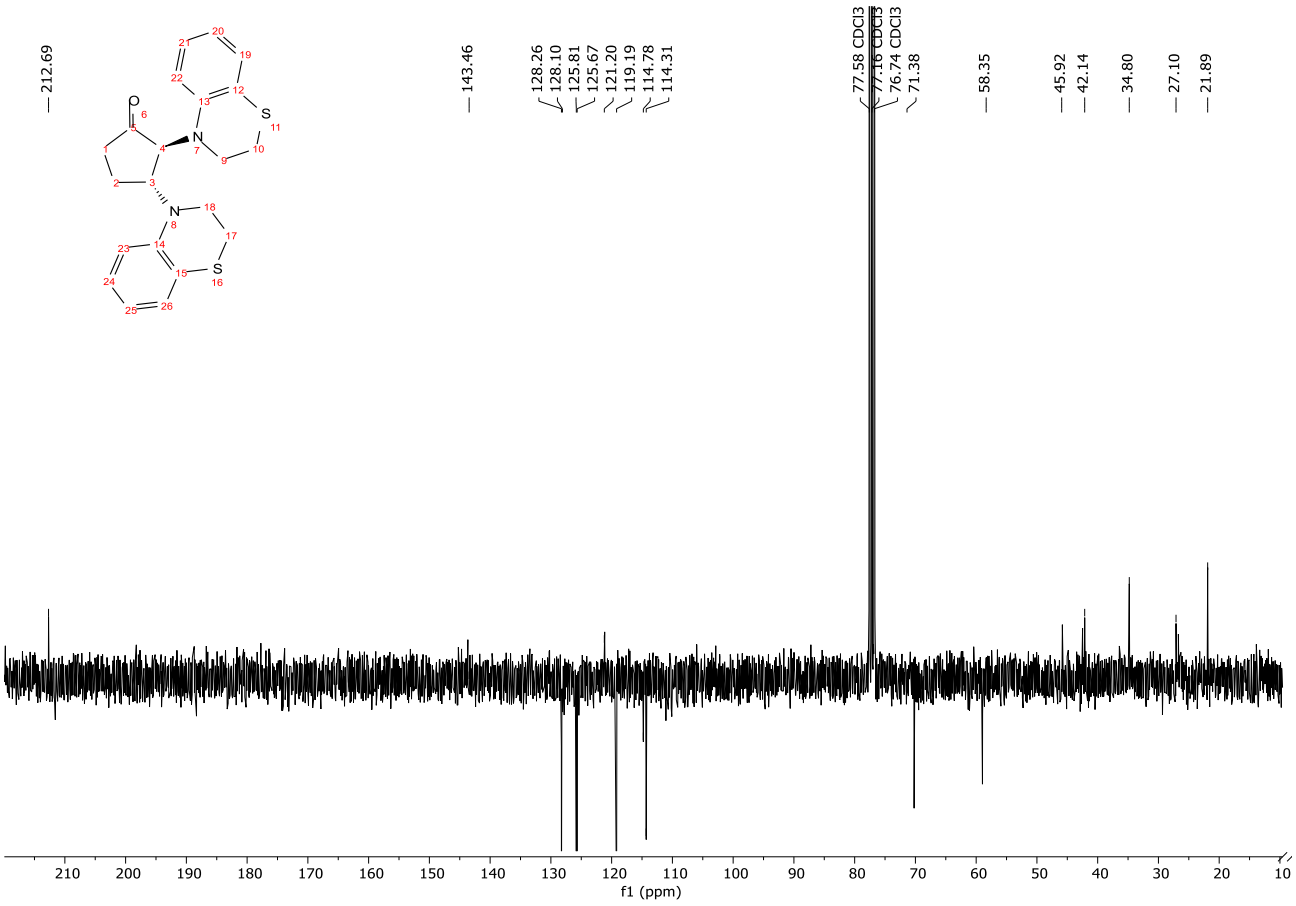
144.52
134.10
133.94
122.68
121.68
121.47
120.68
120.46
119.58
118.66
118.60
118.23
118.14
117.24
117.14
112.33
112.11
111.37
111.04
77.58 CDCl3
77.16 CDCl3
76.74 CDCl3
67.00
64.40
56.32
55.61
43.47
40.18
34.83
20.30
f1 (ppm)


2.00
2.22
3.33
1.03
1.89
4.10
4.01
1.13
2.06
1.11
f1 (ppm)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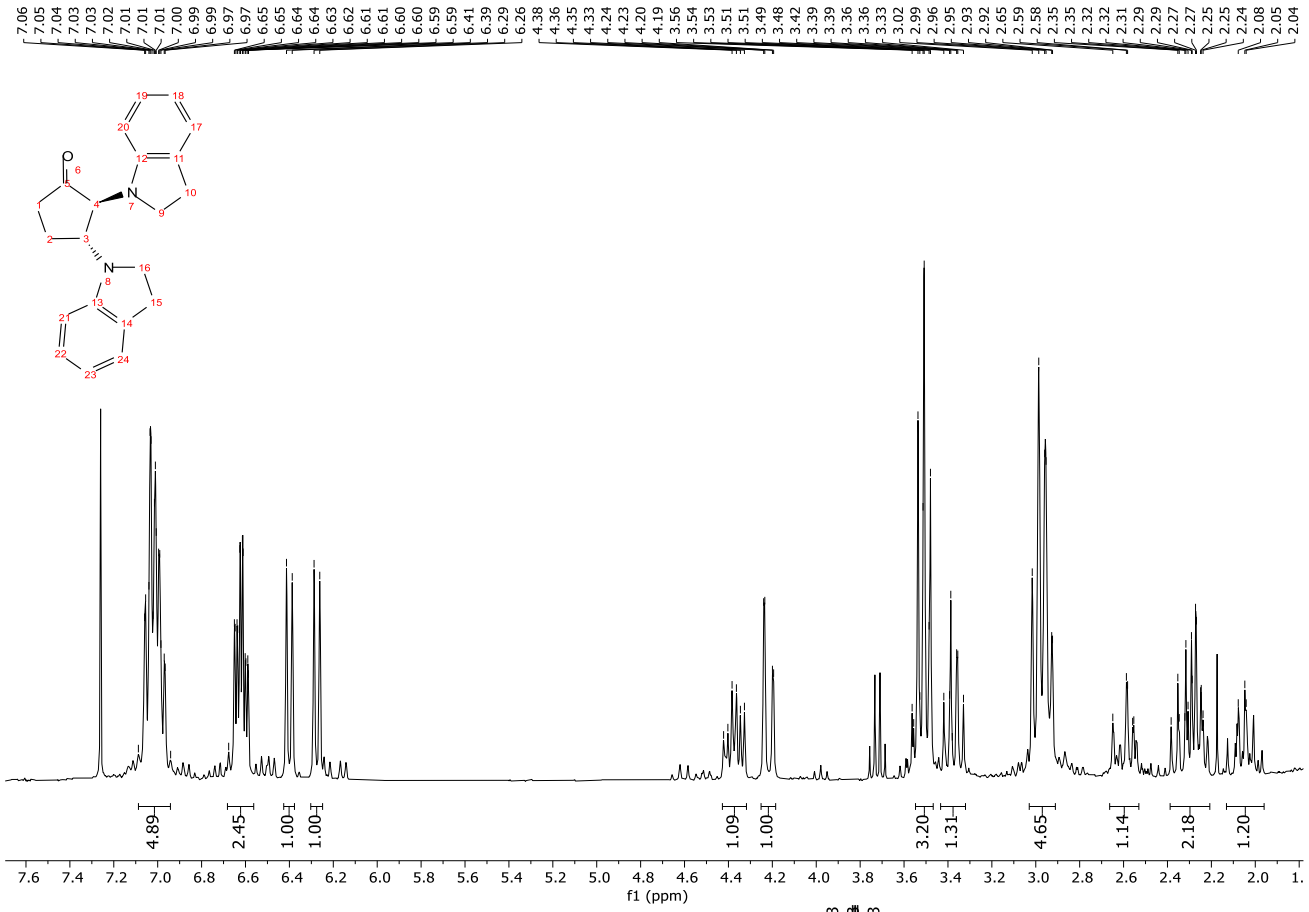
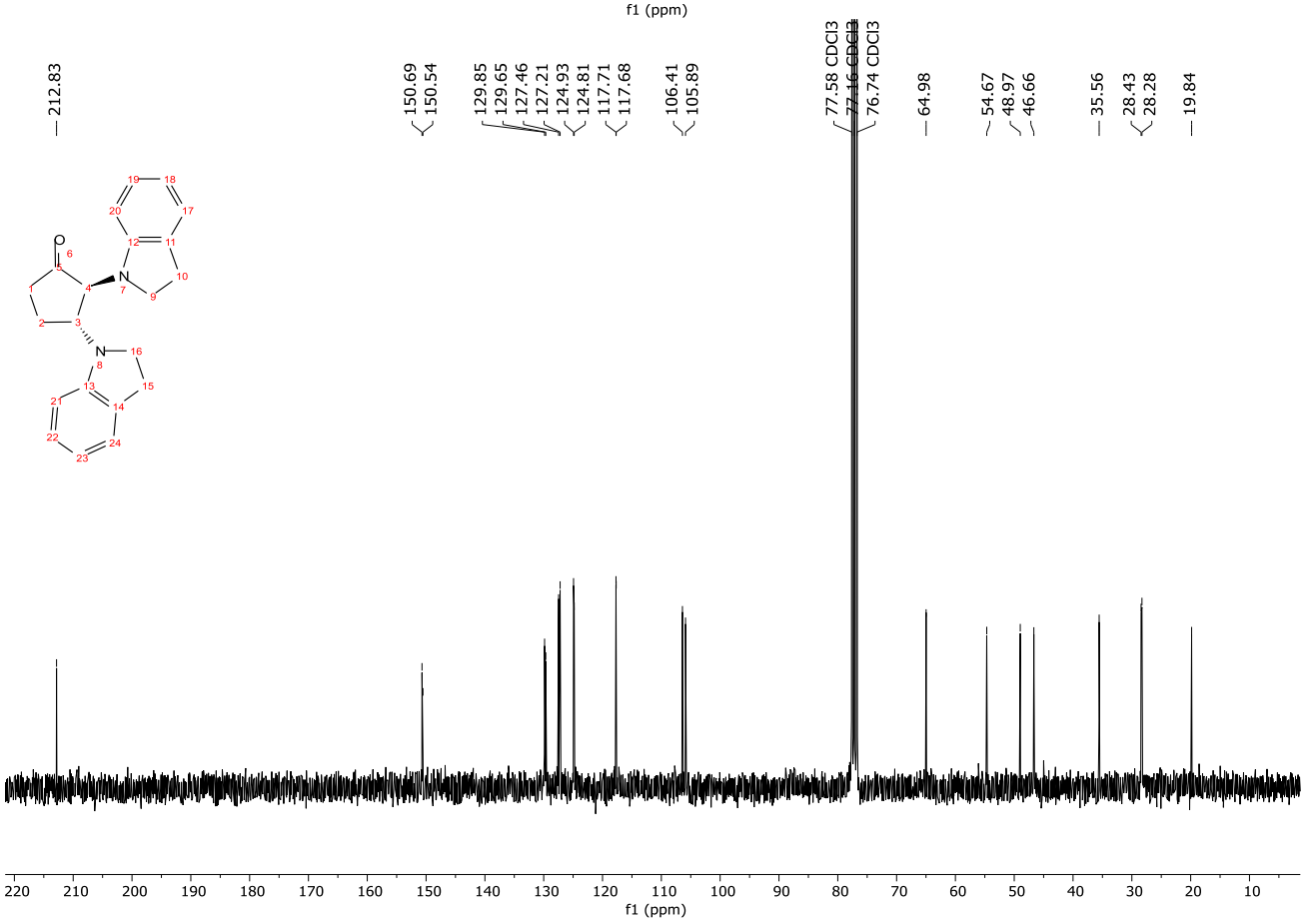
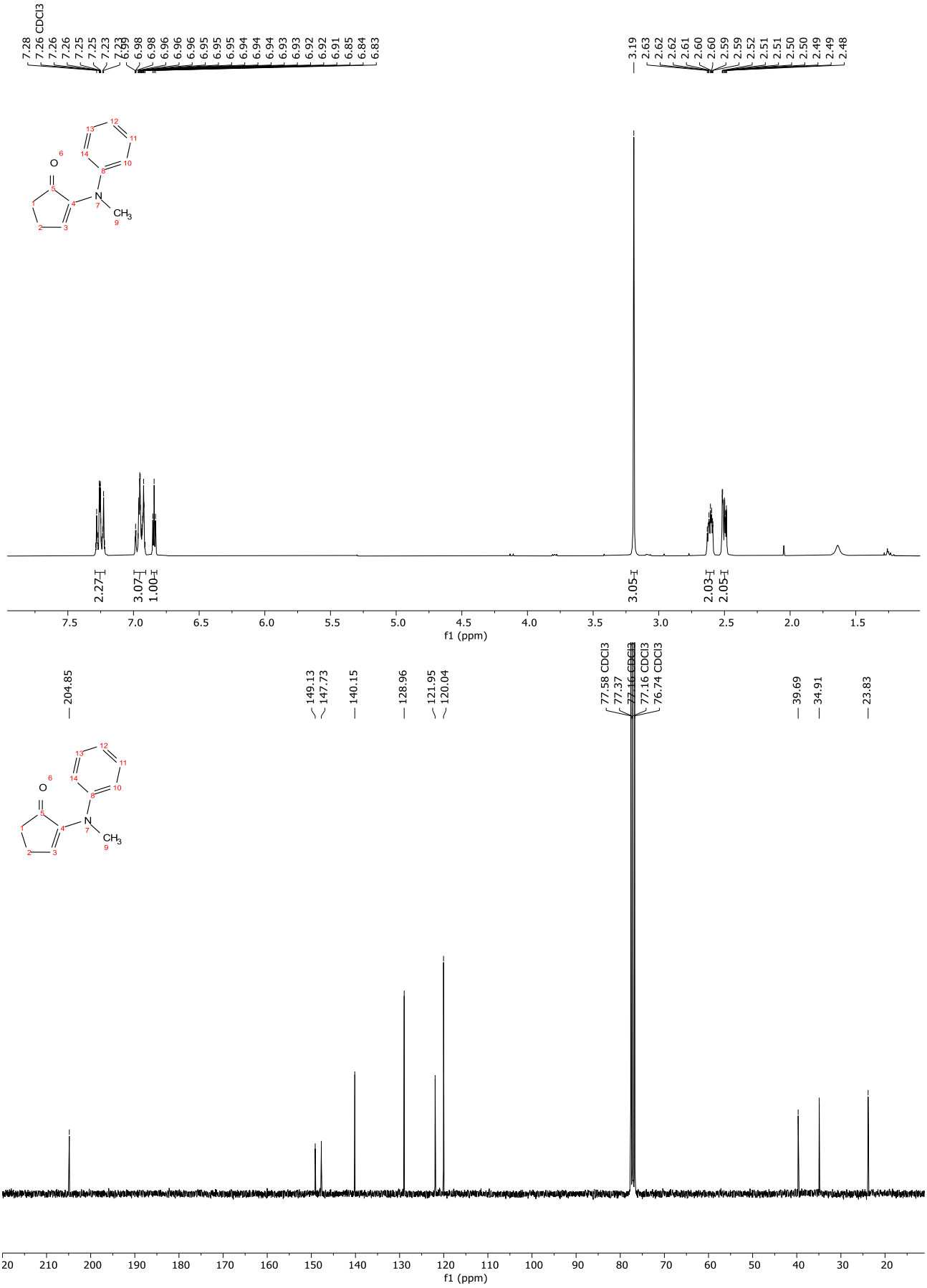
128.26
128.10
125.81
125.67
121.20
119.19
114.78
114.31
77.58 CDCl3
77.16 CDCl3
76.74 CDCl3
71.38
58.35
45.92
42.14
34.80
27.10
21.89
f1 (ppm)


7.06 7.05 7.04 7.03 7.03 7.02 7.01 7.01 7.01 7.00 6.99 6.99 6.97 6.97 6.65 6.65 6.64 6.64 6.63 6.62 6.61 6.61 6.60 6.60 6.59 6.59 6.41 6.39 6.29 6.26
4.38 4.36 4.35 4.33 4.24 4.23 4.20 4.19 3.56 3.54 3.53 3.51 3.51 3.49 3.48 3.42 3.39 3.39 3.36 3.36 3.33 3.02 2.99 2.96 2.95 2.93 2.92 2.65 2.59 2.58 2.35 2.35 2.32 2.32 2.31 2.29 2.29 2.27 2.27 2.25 2.25 2.24 2.08 2.05 2.04
4.89 2.45 1.00 1.00 1.09 1.00 3.20 1.31 4.65 1.14 2.18 1.20
f1 (ppm)


212.83
150.69 150.54 129.85 129.65 127.46 127.21 124.93 124.81 117.71 117.68 106.41 105.89
77.58 CDCl3 77.16 CDCl3 76.74 CDCl3
64.98 54.67 48.97 46.66 35.56 28.43 28.28 19.84
f1 (ppm)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7.26
7.26
7.25
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6.98
6.98
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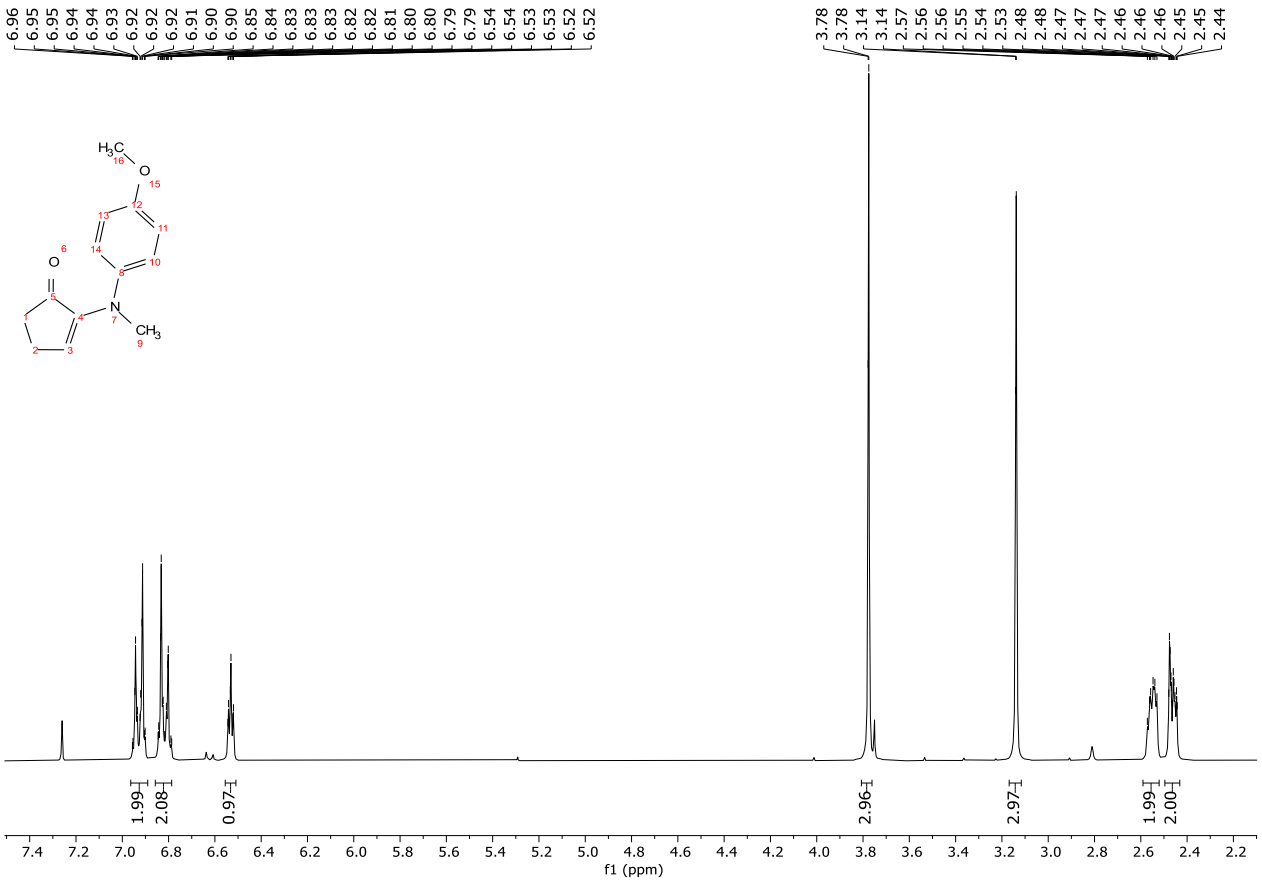
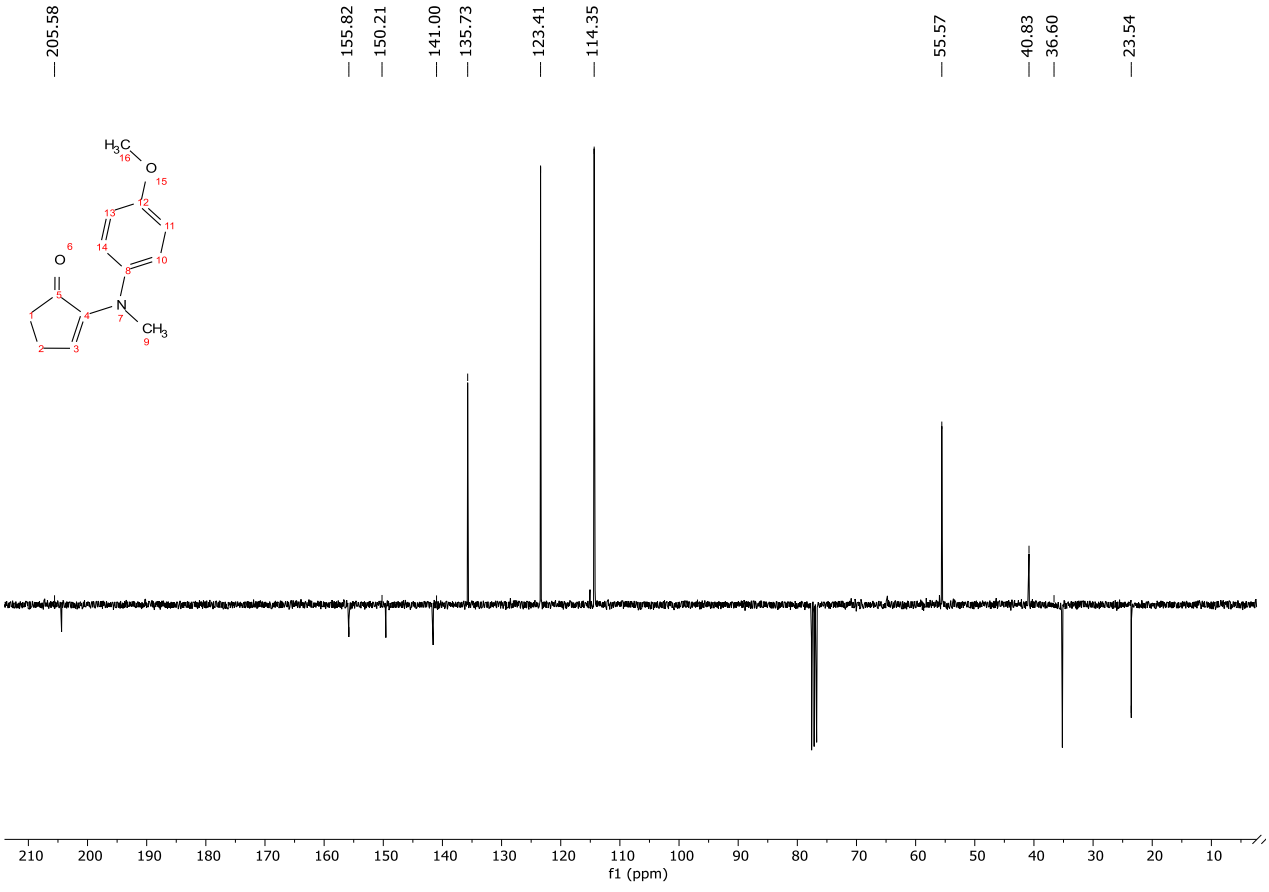
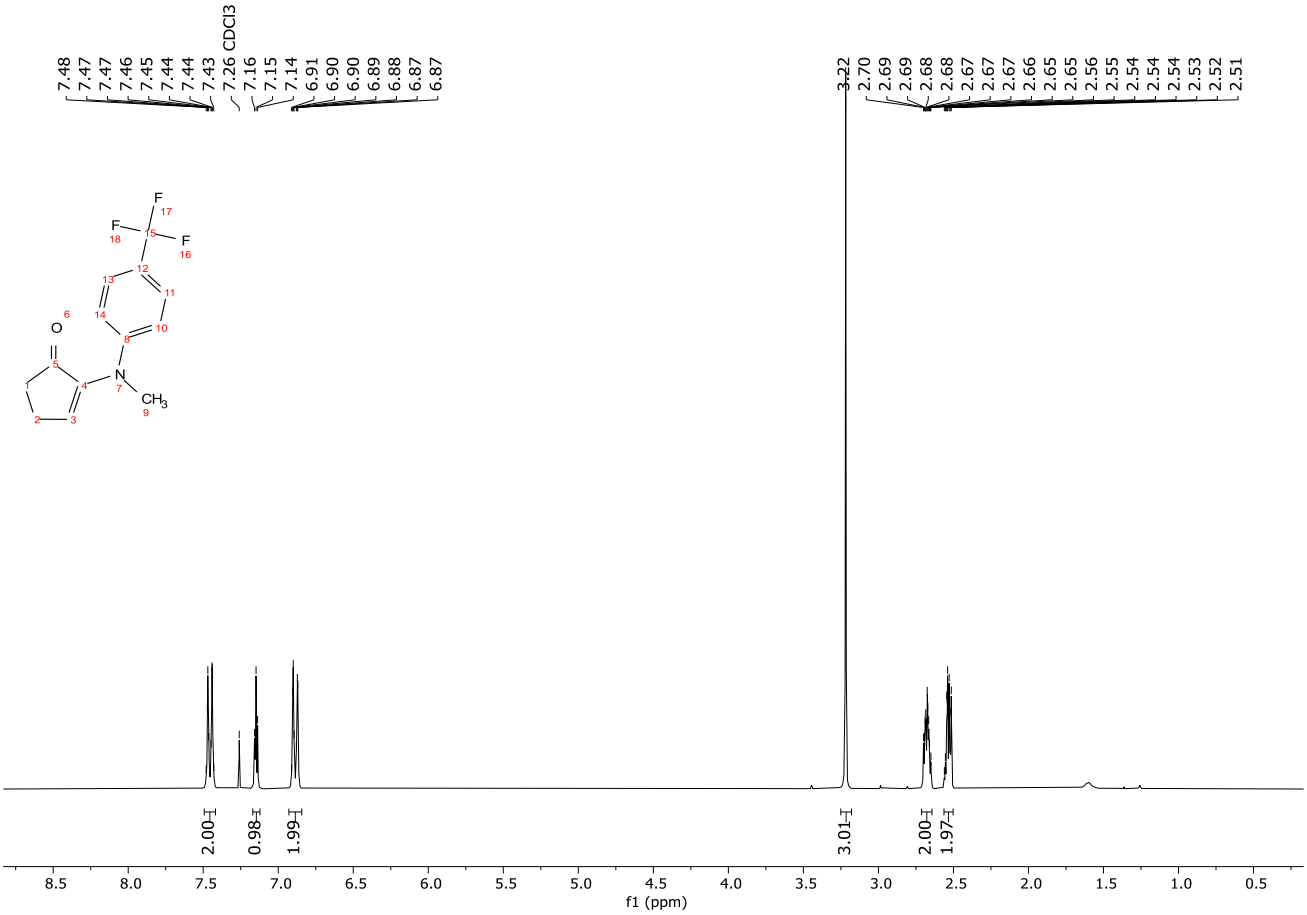
2.49
2.48
O
N
CH3
2.27
3.07
1.00
3.05
2.03
2.05
f1 (ppm)
204.85
149.13
147.73
140.15
128.96
121.95
120.04
77.58 CDCl3
77.37
77.16 CDCl3
76.74 CDCl3
39.69
34.91
23.83
f1 (ppm)


6.96 6.95 6.95 6.94 6.94 6.93 6.92 6.92 6.92 6.91 6.90 6.90 6.85 6.84 6.83 6.83 6.82 6.82 6.81 6.80 6.80 6.79 6.79 6.54 6.54 6.53 6.53 6.52 6.52
3.78 3.78 3.14 3.14 2.57 2.56 2.56 2.55 2.54 2.53 2.48 2.47 2.47 2.46 2.46 2.45 2.45 2.44
1.99 2.08 0.97 2.96 2.97 1.99 2.00
7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2
f1 (ppm)


205.58
155.82
150.21
141.00
135.73
123.41
114.35
55.57
40.83
36.60
23.54
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)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7.47
7.47
7.46
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7.44
7.43
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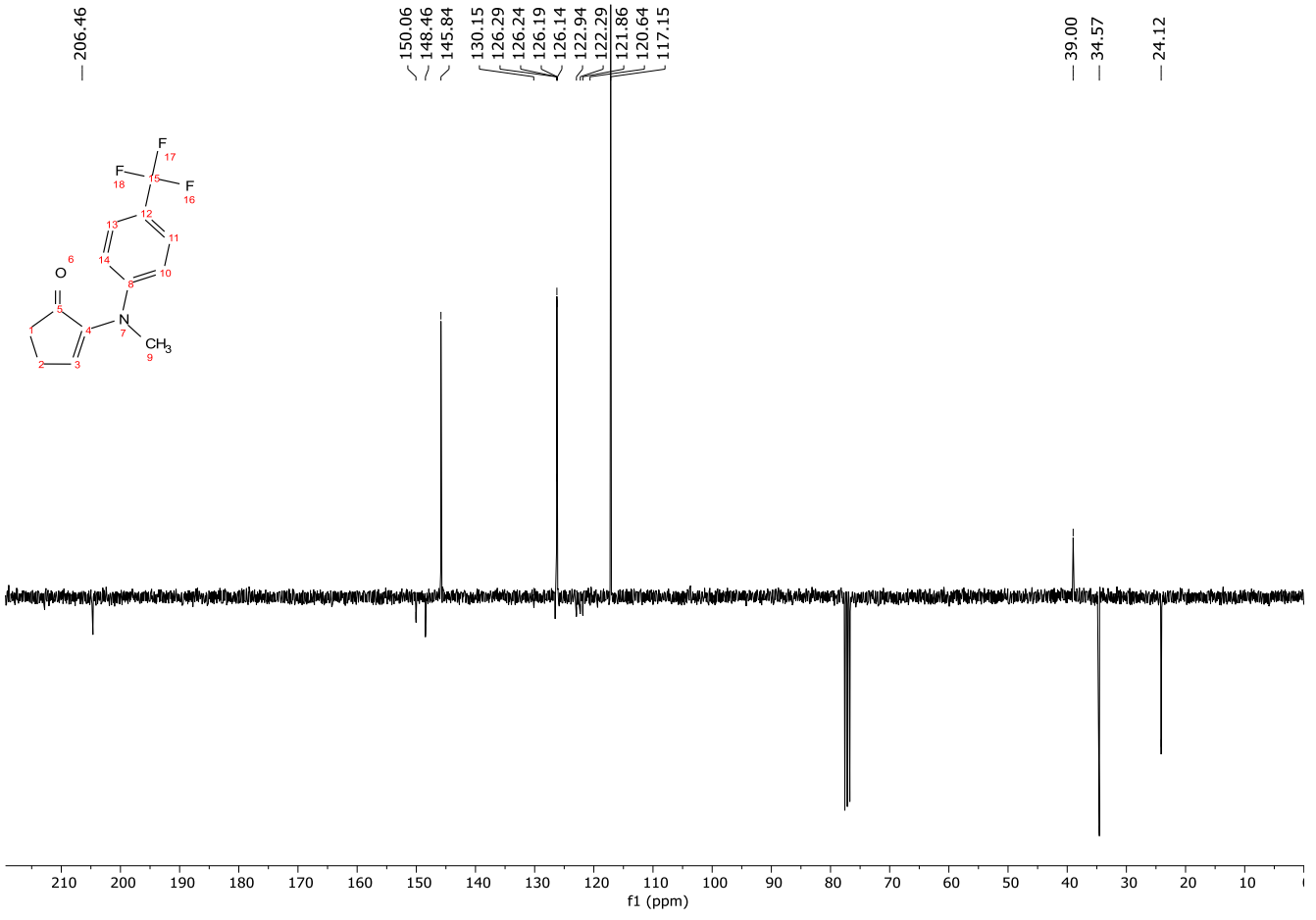
7.16
7.15
7.14
6.91
6.90
6.90
6.89
6.88
6.87
6.87
3.22
2.70
2.69
2.69
2.68
2.68
2.67
2.67
2.67
2.66
2.65
2.65
2.56
2.55
2.54
2.54
2.54
2.53
2.52
2.51
F
F
F
O
N
CH3
2.00
0.98
1.99
3.01
2.00
1.97
f1 (ppm)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145.84
130.15
126.29
126.24
126.19
126.14
122.94
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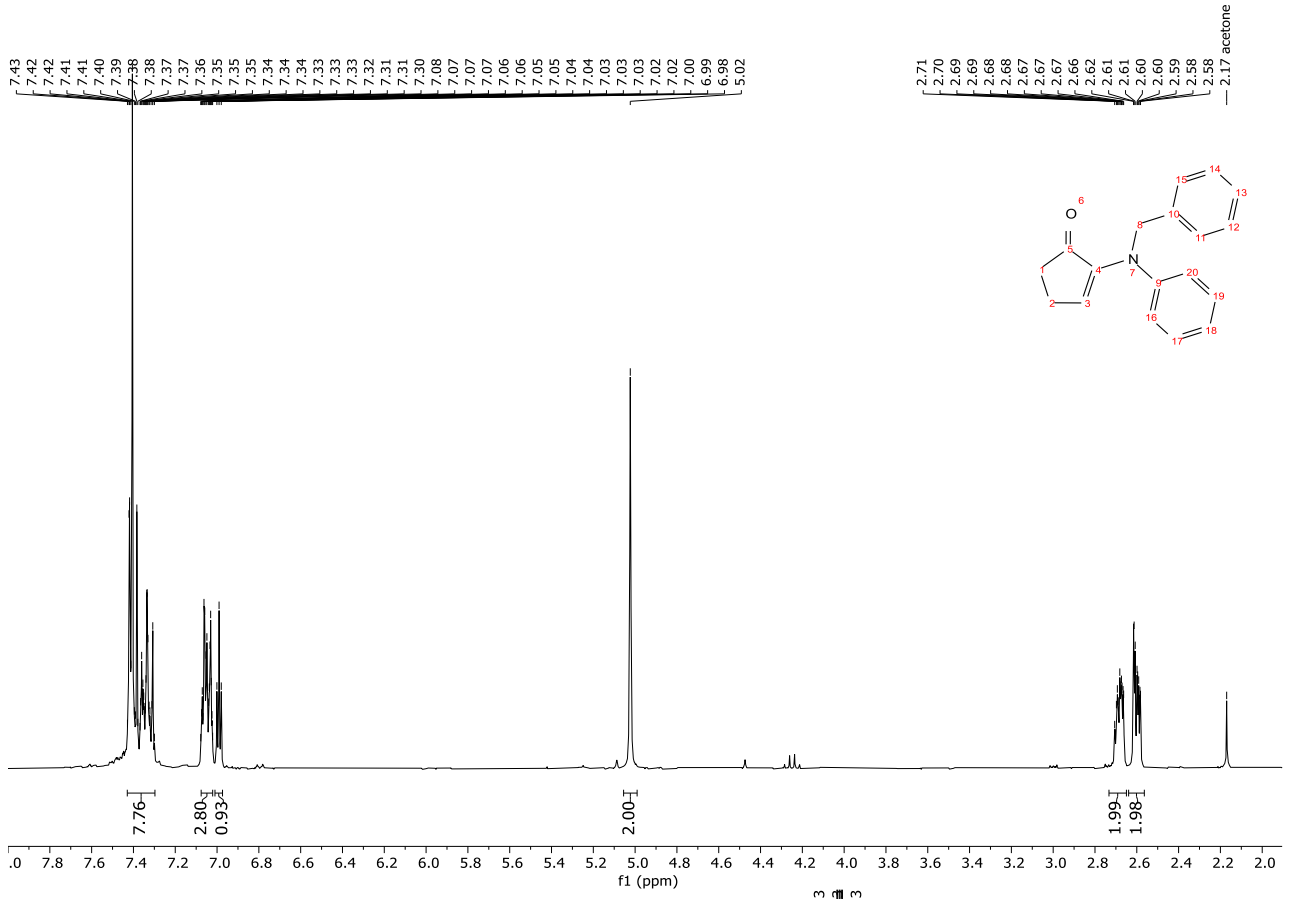
117.15
39.00
34.57
24.12
F
F
F
O
N
CH3
f1 (ppm)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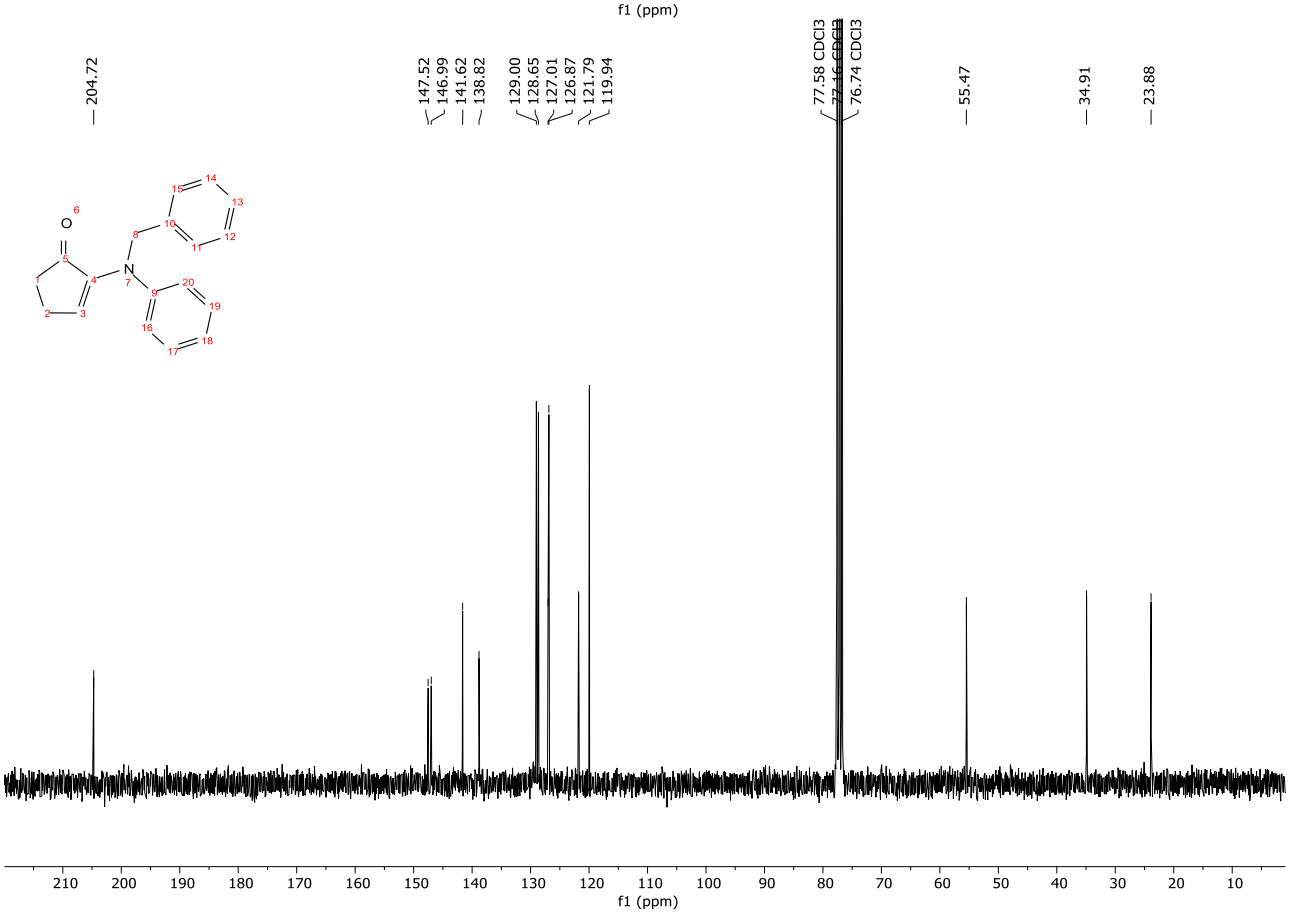
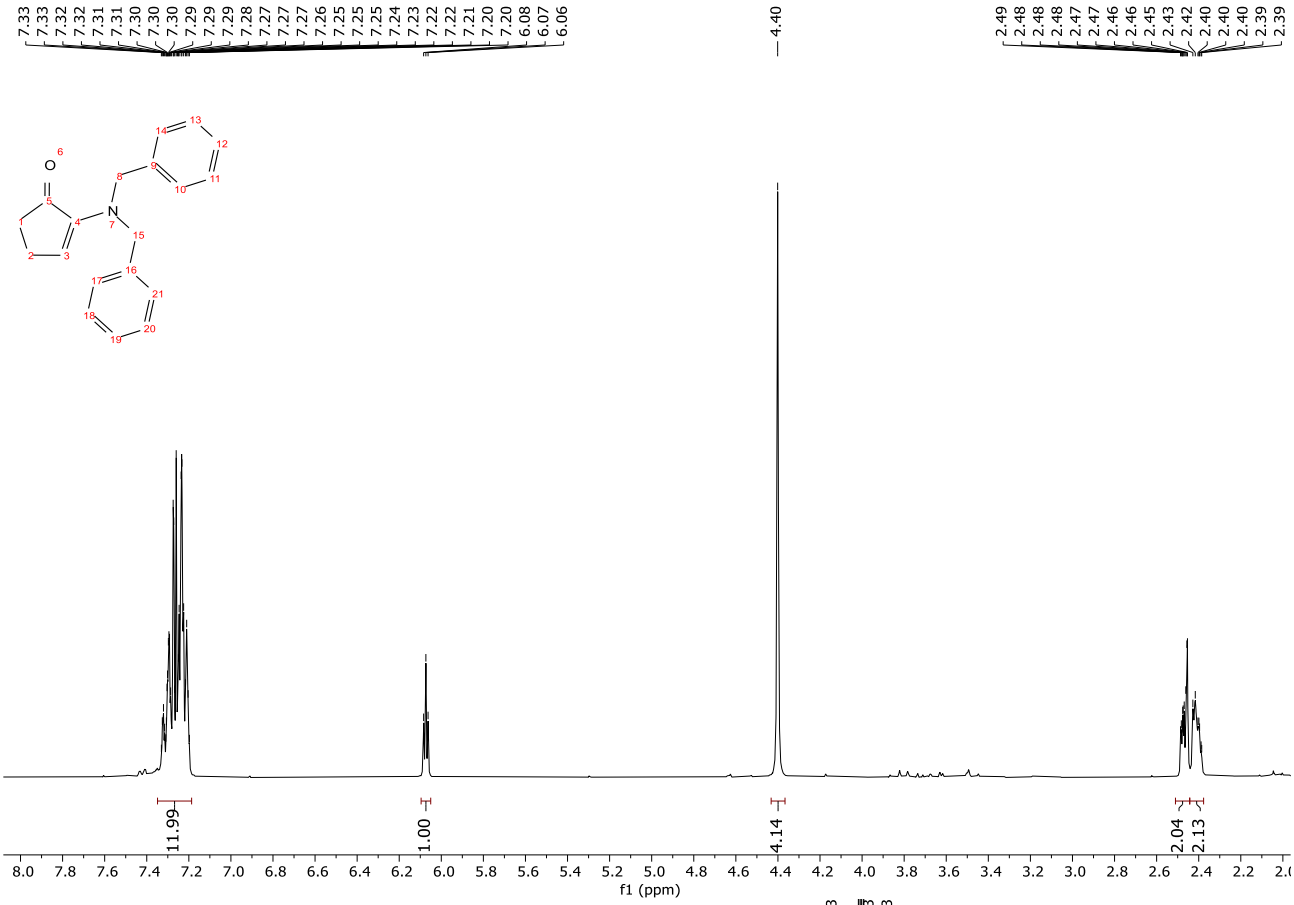
2.71 2.70 2.69 2.69 2.68 2.67 2.67 2.67 2.66 2.62 2.61 2.61 2.60 2.60 2.59 2.58 2.58 2.17 acetone
7.76
2.80
0.93
2.00
1.99
1.98
f1 (ppm)


204.72
147.52 146.99 141.62 138.82 129.00 128.65 127.01 126.87 121.79 119.94
77.58 CDCl3 77.16 CDCl3 76.74 CDCl3
55.47
34.91
23.88
f1 (ppm)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4.40
2.49 2.48 2.48 2.48 2.47 2.47 2.46 2.46 2.45 2.43 2.42 2.40 2.40 2.40 2.39 2.39
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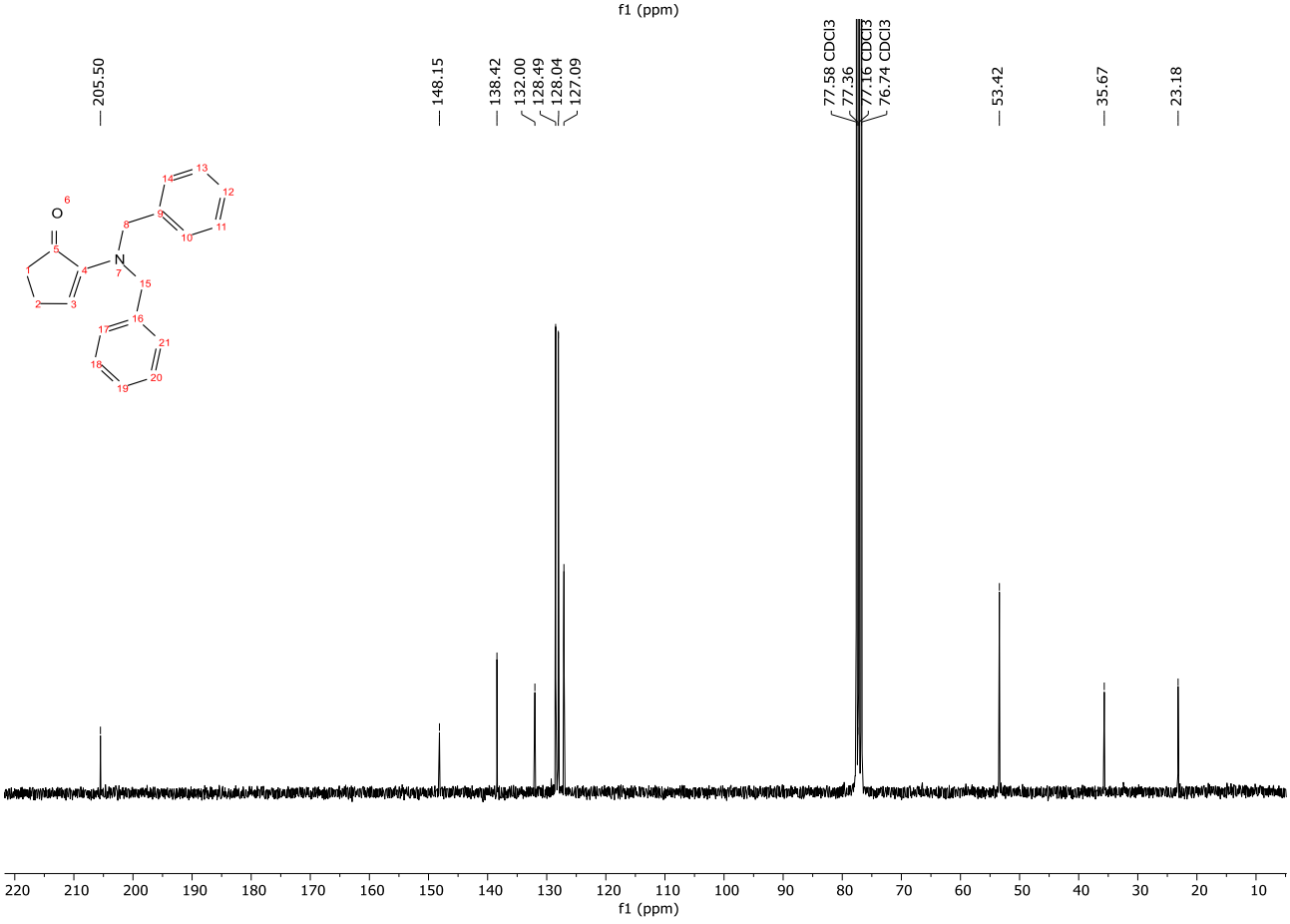
1.00
4.14
2.04
2.13
f1 (ppm)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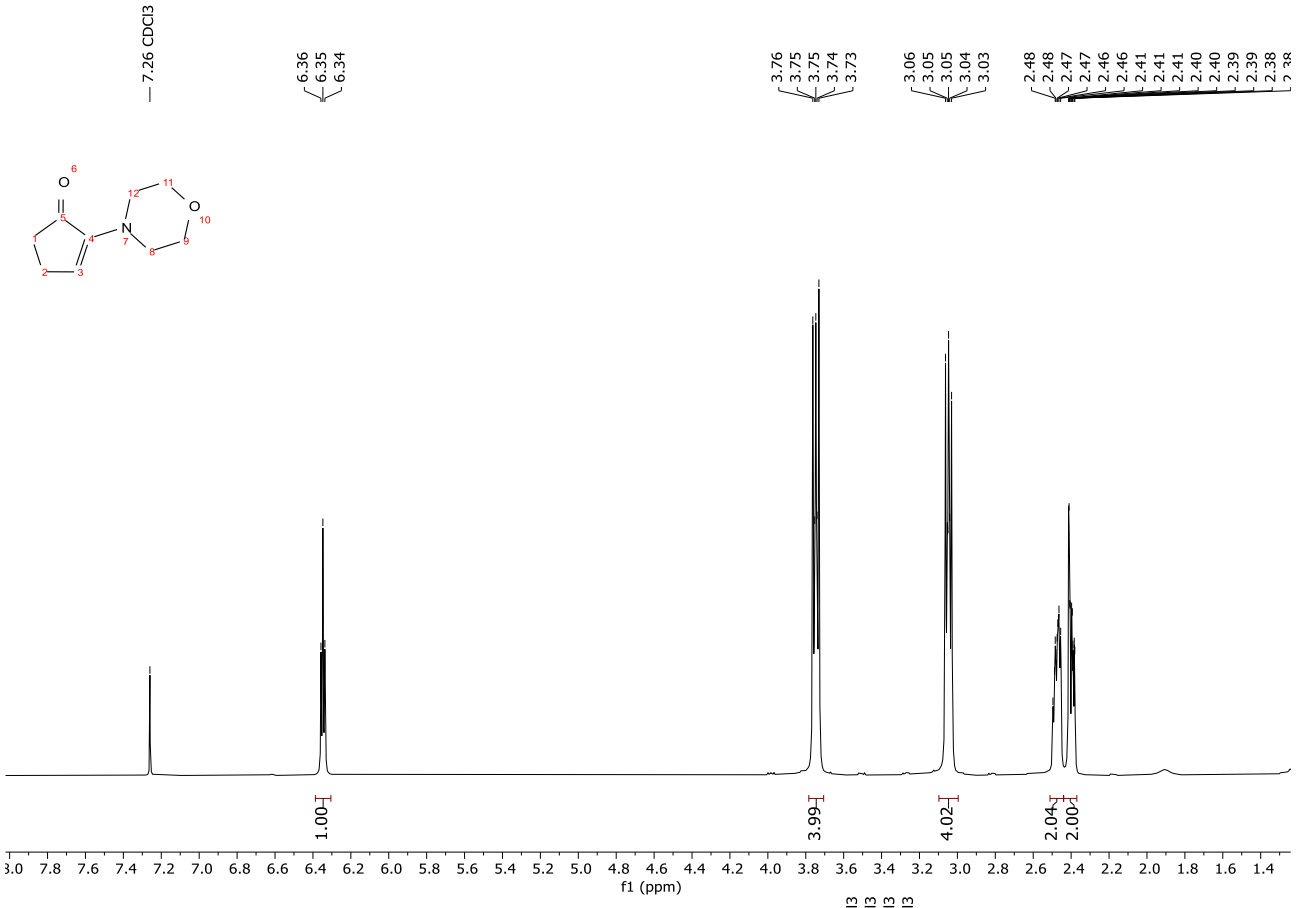
138.42
132.00
128.49
128.04
127.09
77.58 CDCl3
77.36
77.16 CDCl3
76.74 CDCl3
53.42
35.67
23.18
f1 (ppm)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6.35
6.34
3.76
3.75
3.75
3.74
3.73
3.06
3.05
3.05
3.04
3.03
2.48
2.48
2.47
2.47
2.46
2.46
2.41
2.41
2.41
2.40
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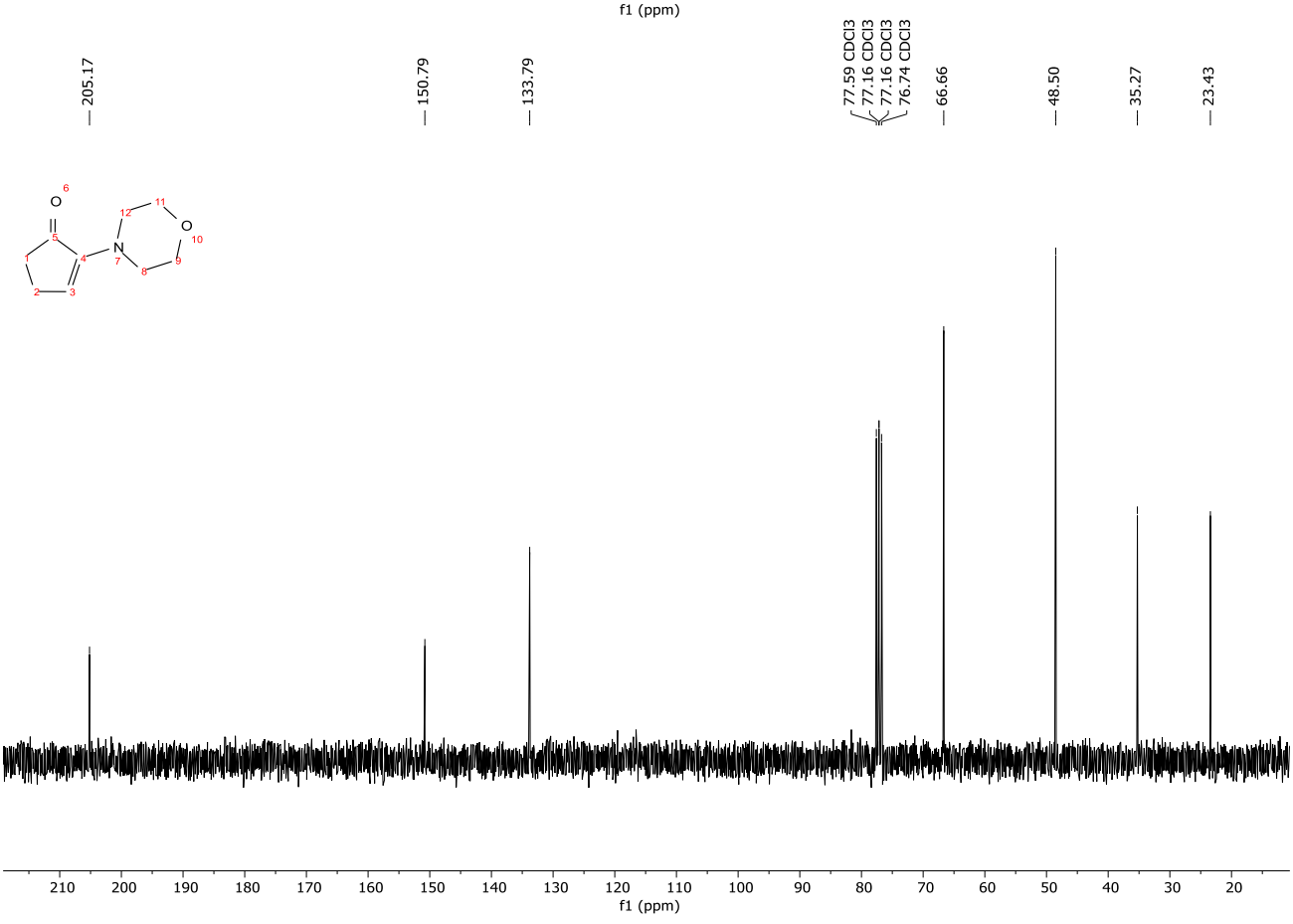
2.39
2.39
2.38
1.00
3.99
4.02
2.04
2.00
f1 (ppm)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150.79
133.79
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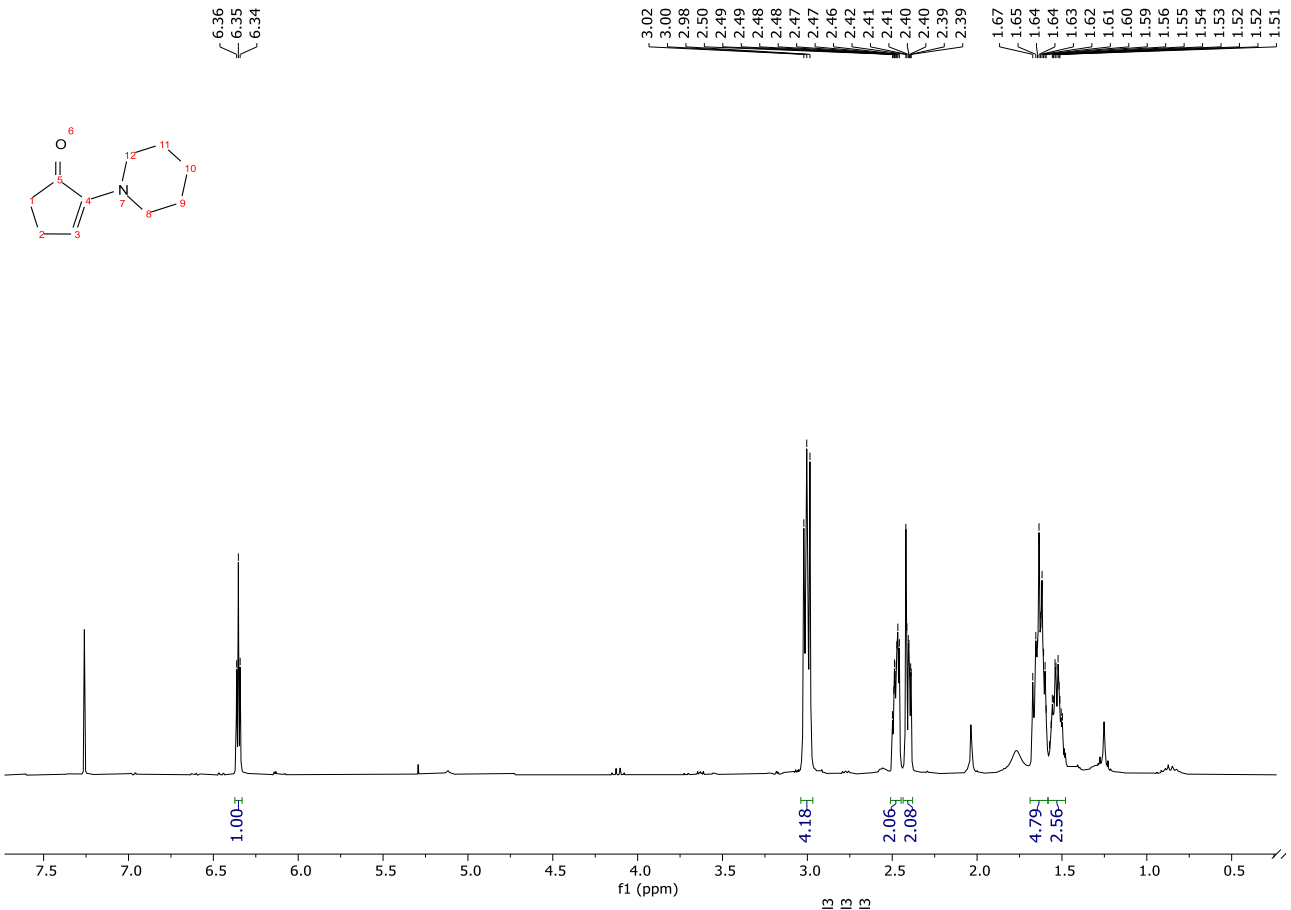
77.16 CDCl3
77.16 CDCl3
76.74 CDCl3
66.66
48.50
35.27
23.43
f1 (ppm)


6.36
6.35
6.34
3.02
3.00
2.98
2.50
2.49
2.49
2.48
2.48
2.47
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2.46
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2.41
2.41
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1.59
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1.53
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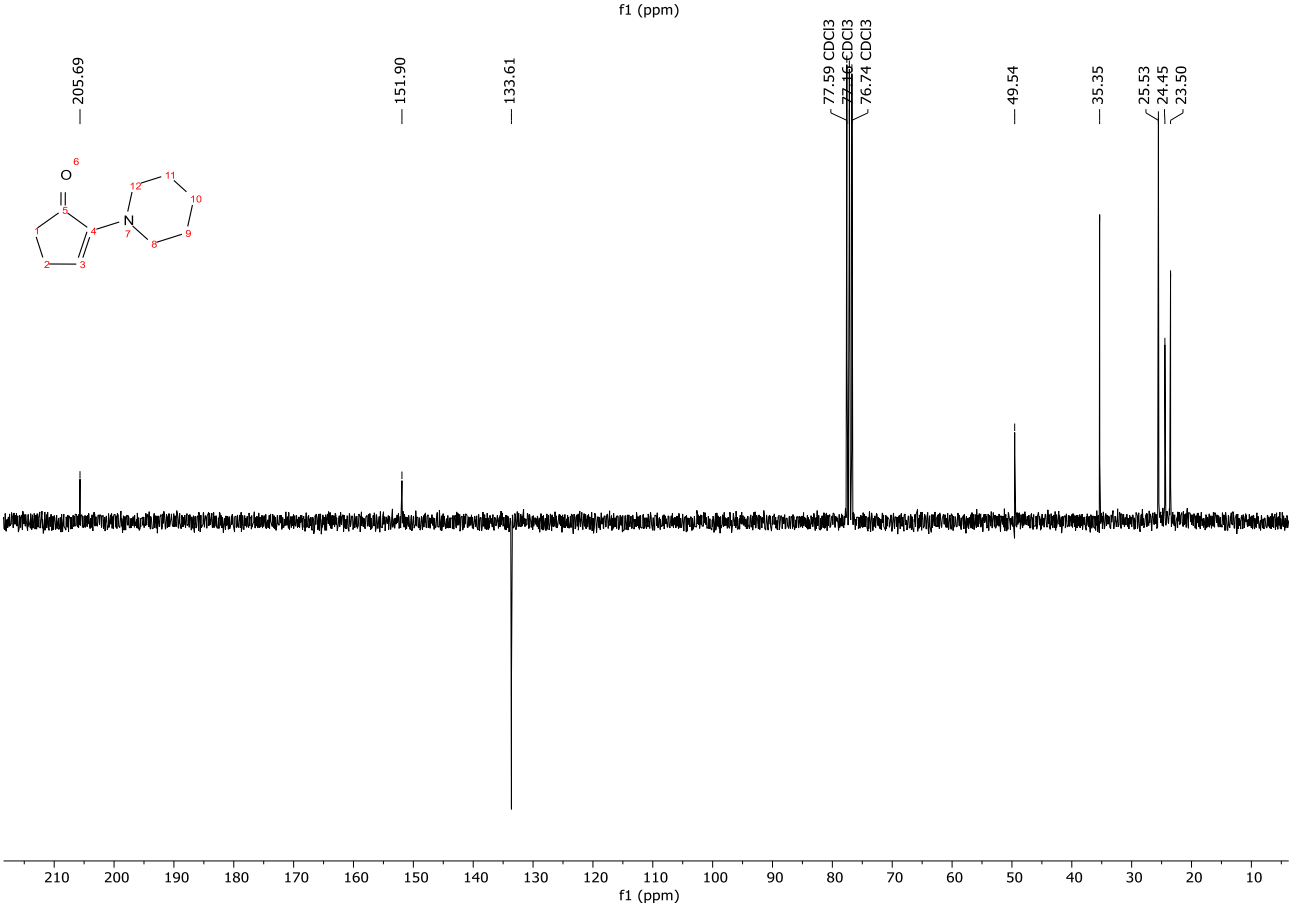
1.52
1.51
1.00
4.18
2.06
2.08
4.79
2.56
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)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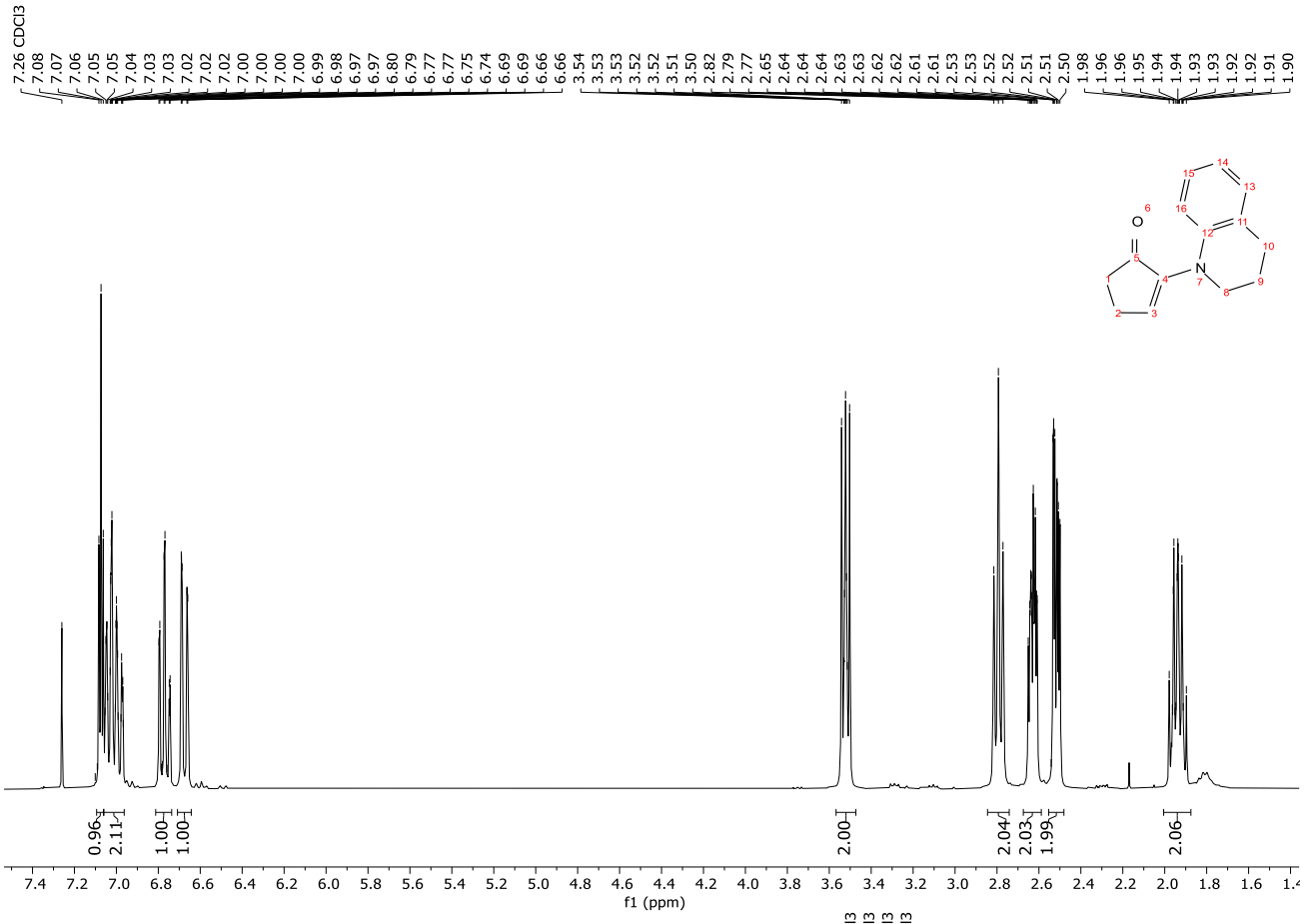
77.59 CDCl3
77.16 CDCl3
76.74 CDCl3
49.54
35.35
25.53
24.45
23.50
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)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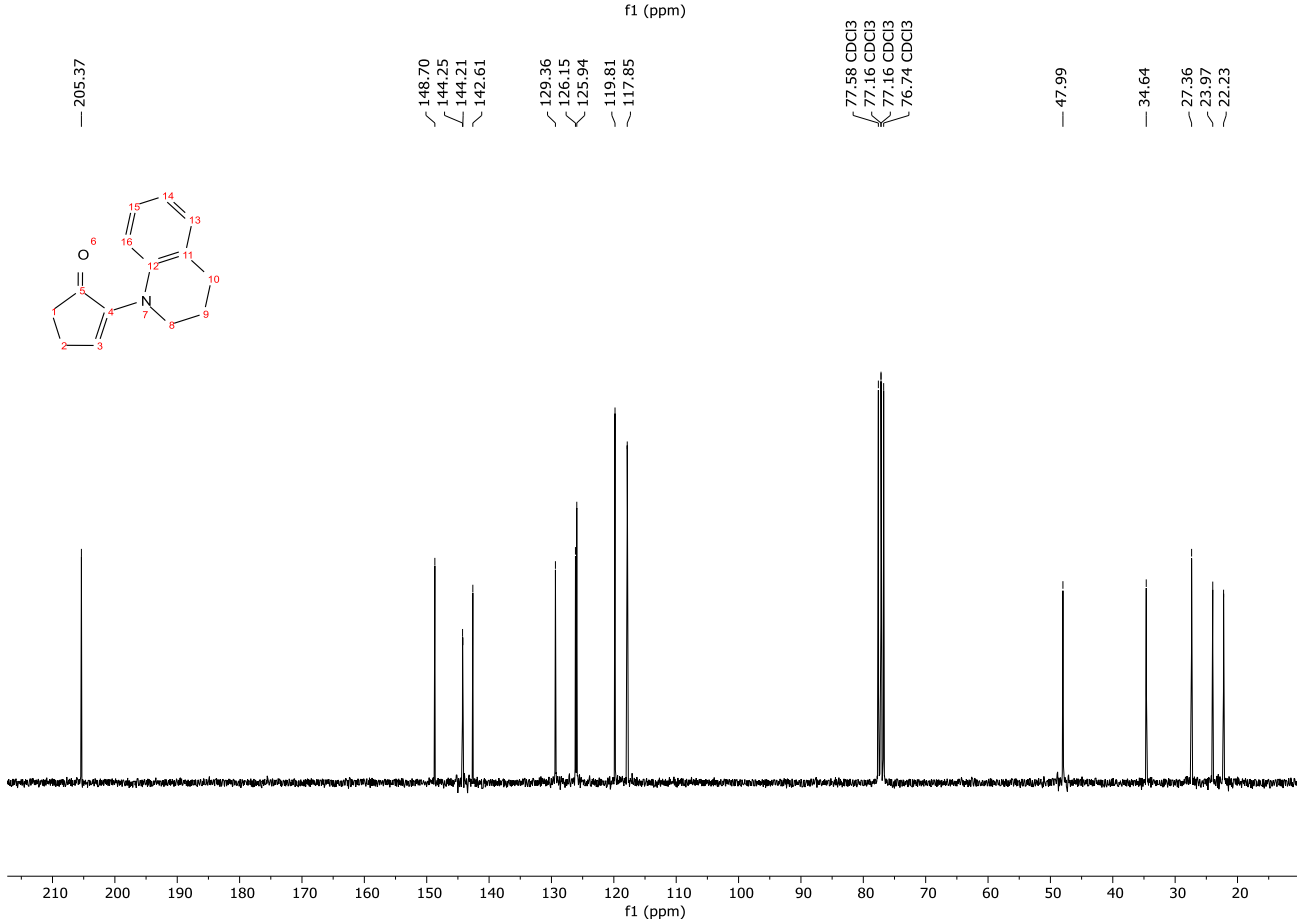
1.00
1.00
2.00
2.04
2.03
1.99
2.06
f1 (ppm)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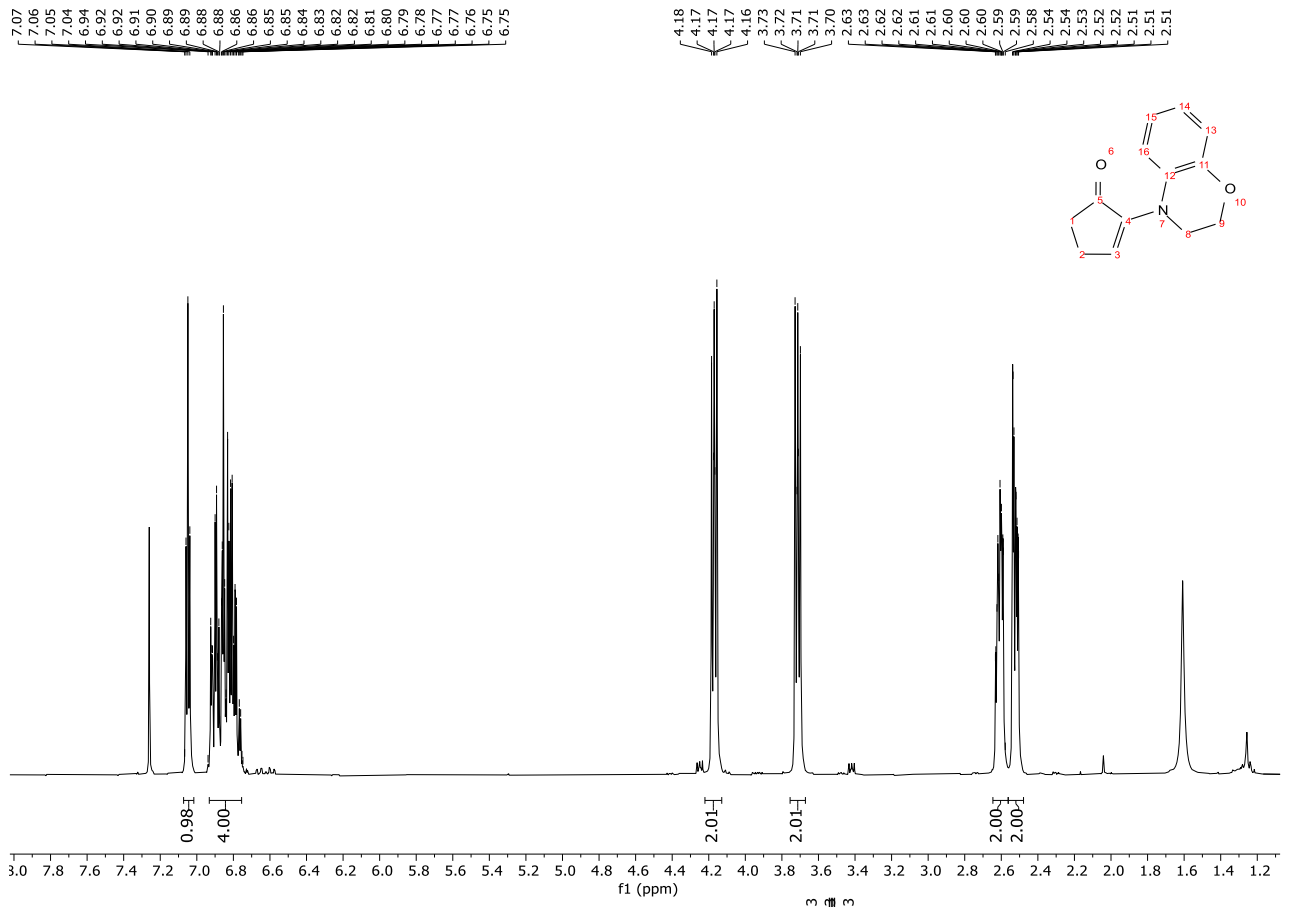
148.70
144.25
144.21
142.61
129.36
126.15
125.94
119.81
117.85
77.58 CDCl3
77.16 CDCl3
77.16 CDCl3
76.74 CDCl3
47.99
34.64
27.36
23.97
22.23
f1 (ppm)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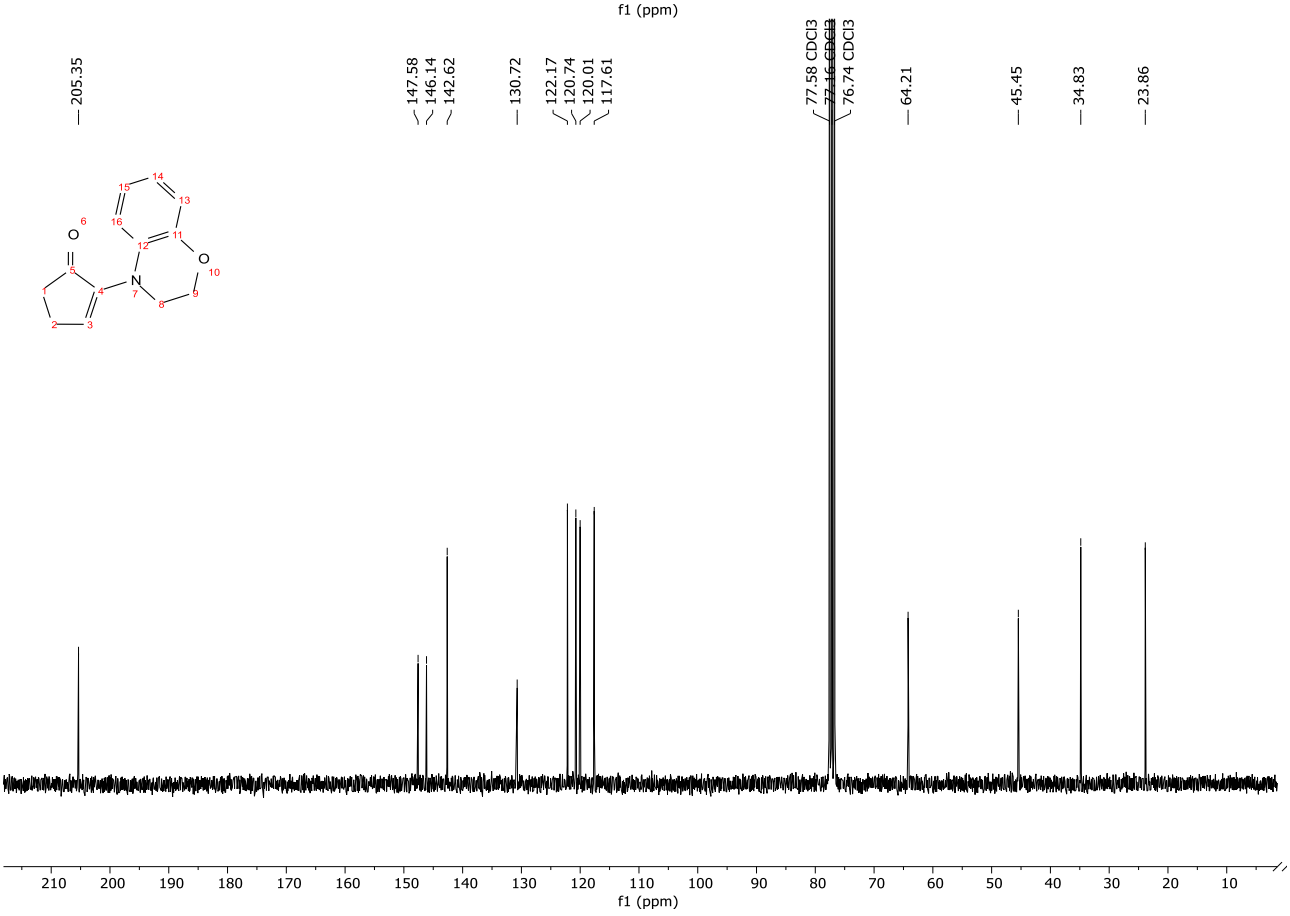
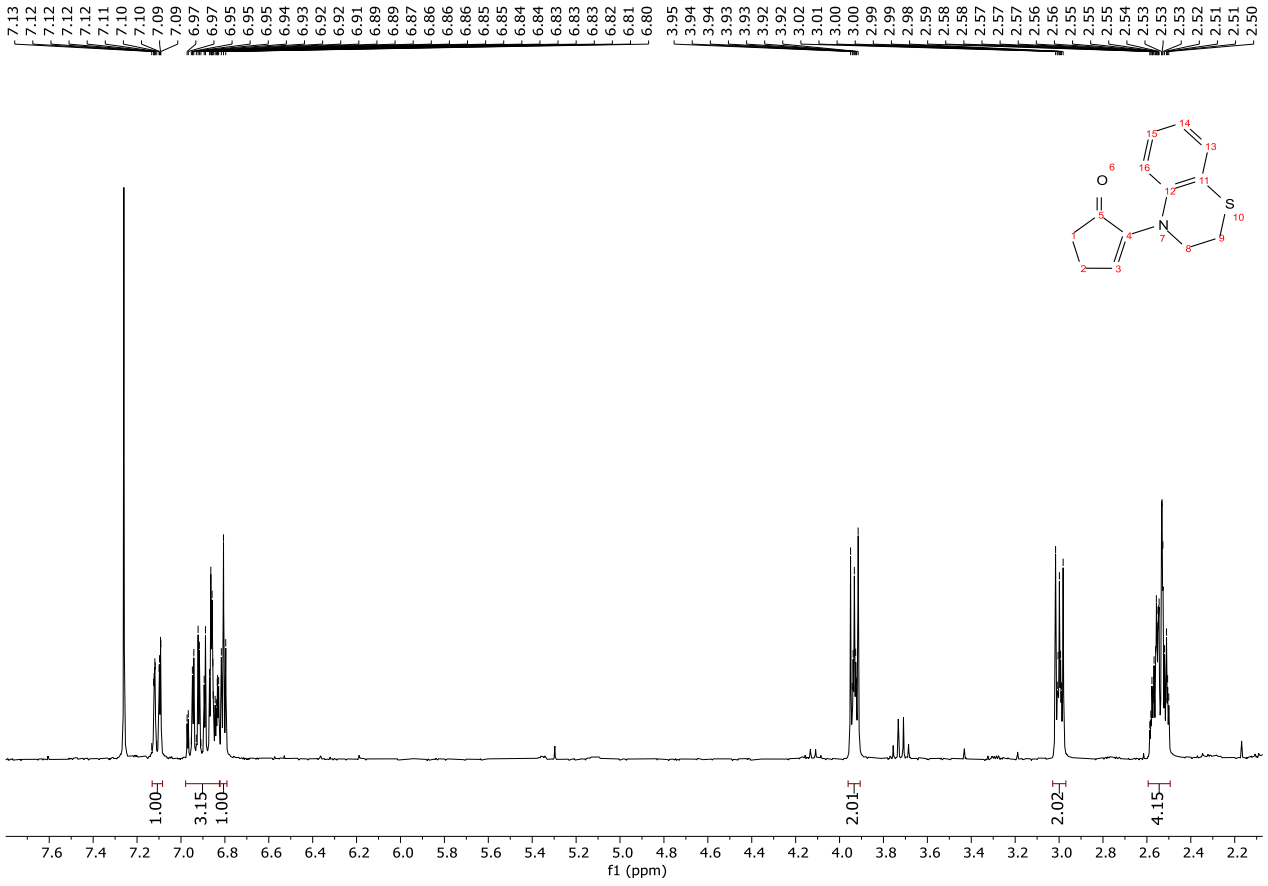
4.18 4.17 4.17 4.17 4.16 3.73 3.72 3.71 3.71 3.70 2.63 2.63 2.62 2.62 2.61 2.61 2.60 2.60 2.60 2.60 2.59 2.59 2.58 2.54 2.54 2.53 2.52 2.52 2.51 2.51 2.51 2.51
0.98
4.00
2.01
2.01
2.00
2.00
f1 (ppm)


205.35
147.58 146.14 142.62 130.72 122.17 120.74 120.01 117.61
77.58 CDCl3 77.16 CDCl3 76.74 CDCl3
64.21 45.45 34.83 23.86
f1 (ppm)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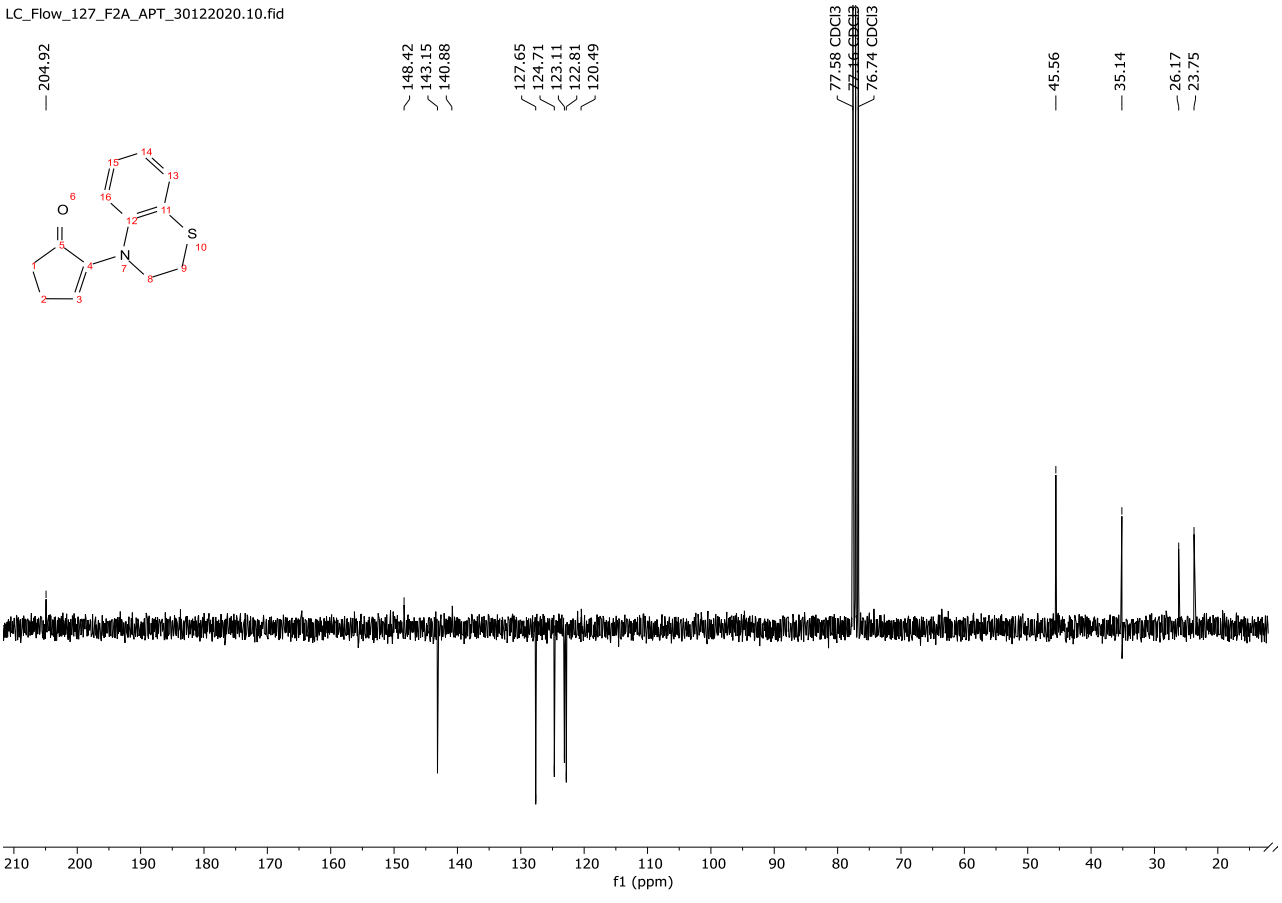
3.95 3.94 3.94 3.93 3.93 3.92 3.92 3.02 3.01 3.00 3.00 2.99 2.99 2.98 2.59 2.58 2.58 2.57 2.57 2.57 2.56 2.56 2.55 2.55 2.55 2.54 2.53 2.53 2.53 2.52 2.51 2.51 2.50
O
S
N
1.00
3.15
1.00
2.01
2.02
4.15
f1 (ppm)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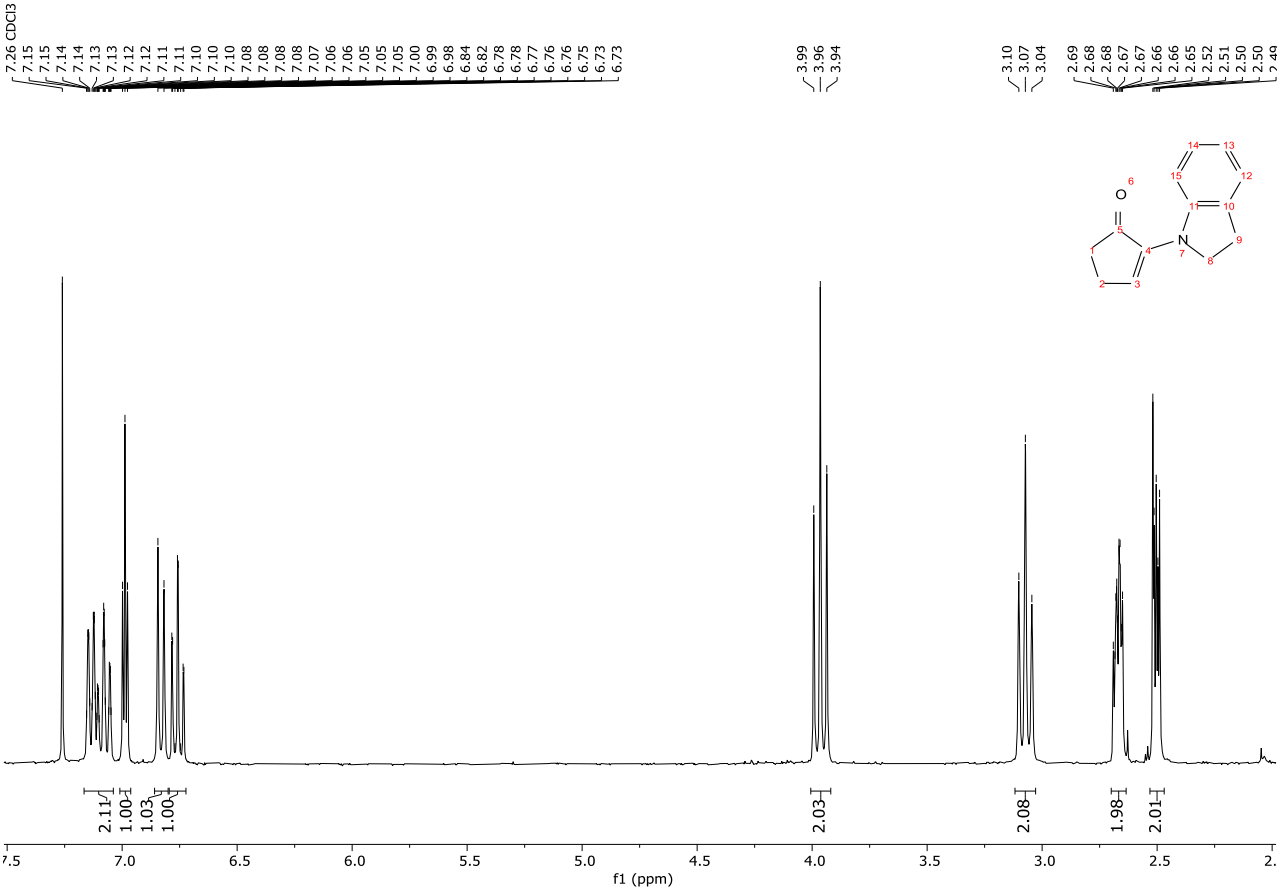
204.92
148.42
143.15
140.88
127.65
124.71
123.11
122.81
120.49
77.58 CDCl3
77.16 CDCl3
76.74 CDCl3
45.56
35.14
26.17
23.75
O
S
N
f1 (ppm)


7.26 CDCl3
7.15
7.14
7.13
7.12
7.11
7.10
7.08
7.07
7.06
7.05
7.00
6.99
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6.75
6.73
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3.96
3.94
3.10
3.07
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2.68
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2.65
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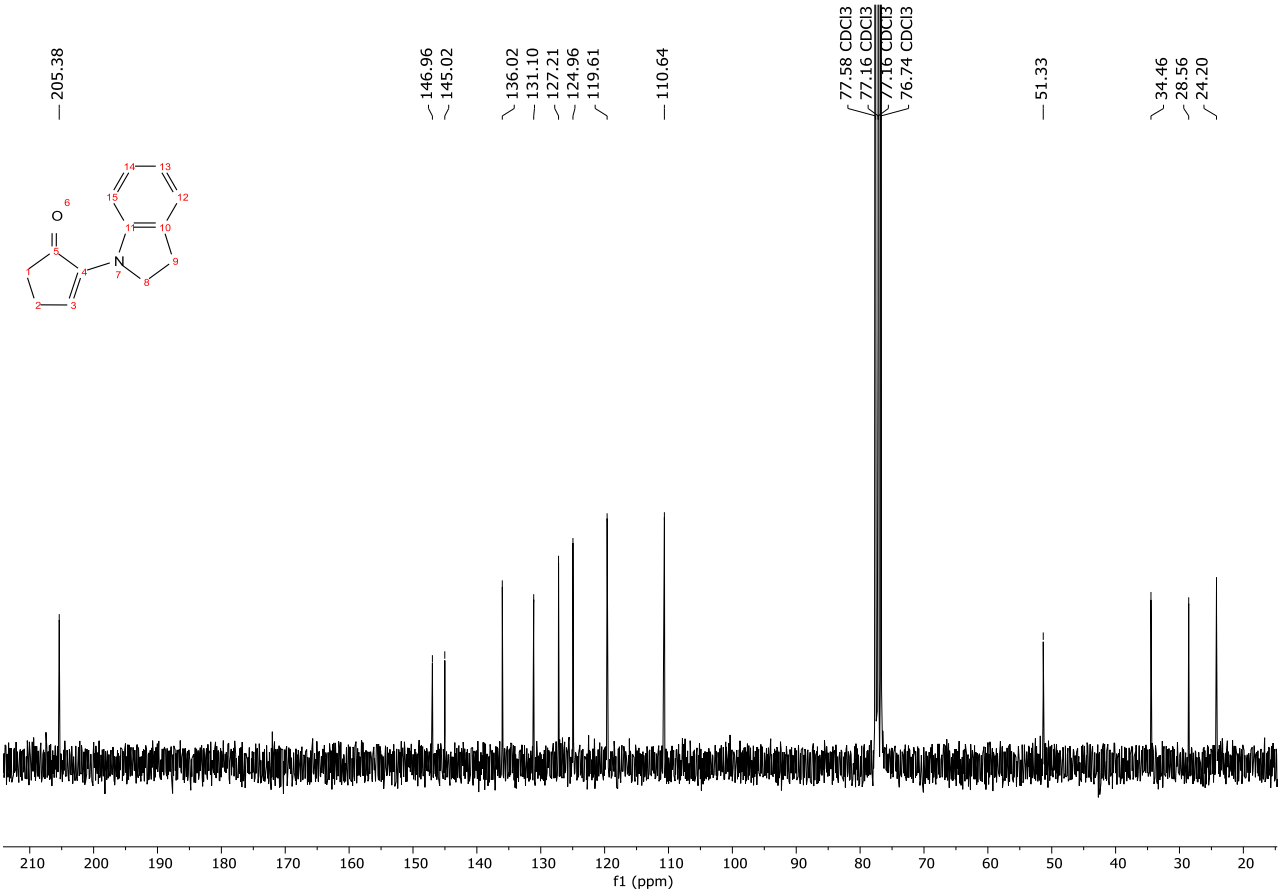
1.00
2.03
2.08
1.98
2.01
f1 (ppm)


205.38
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145.02
136.02
131.10
127.21
124.96
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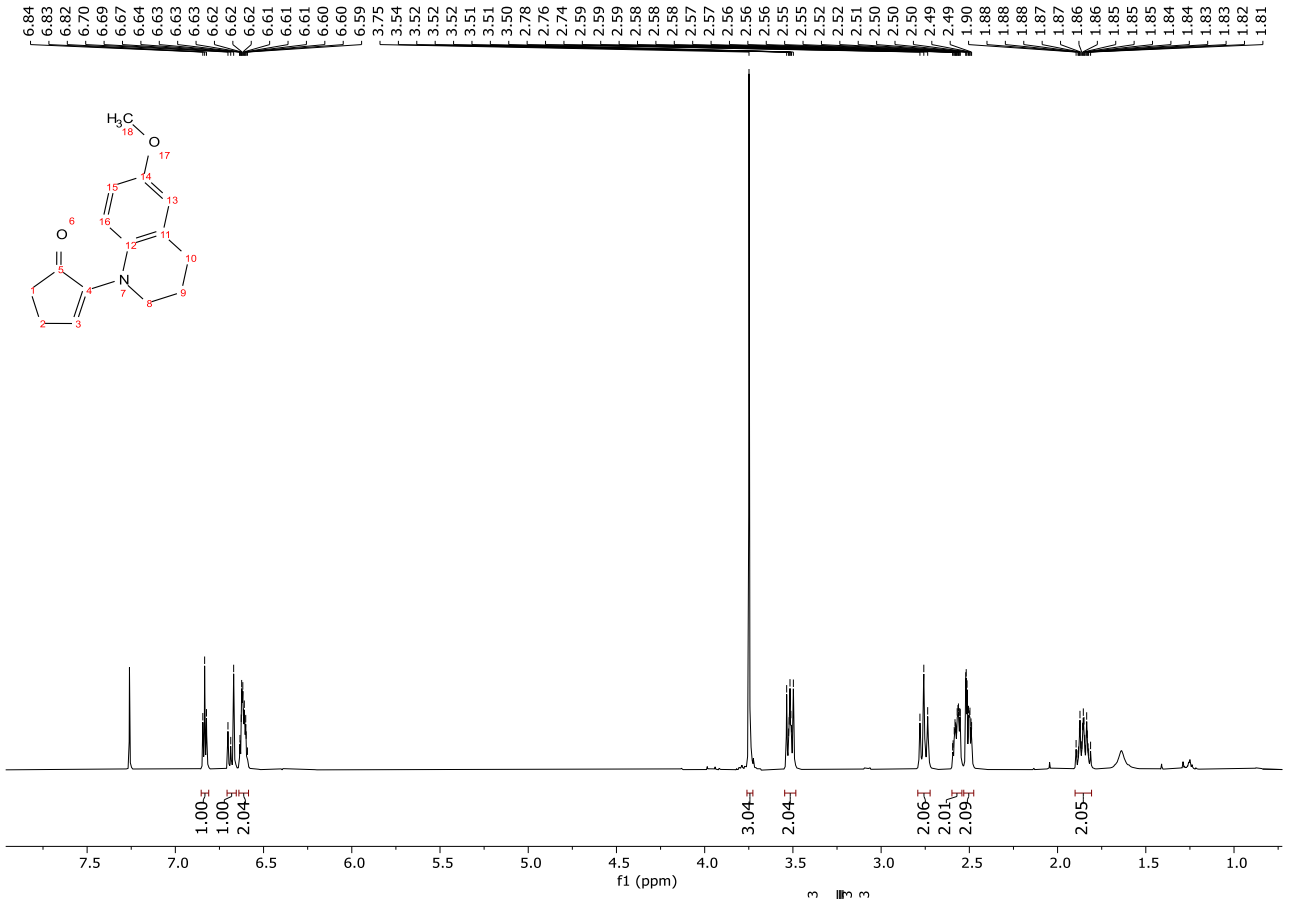
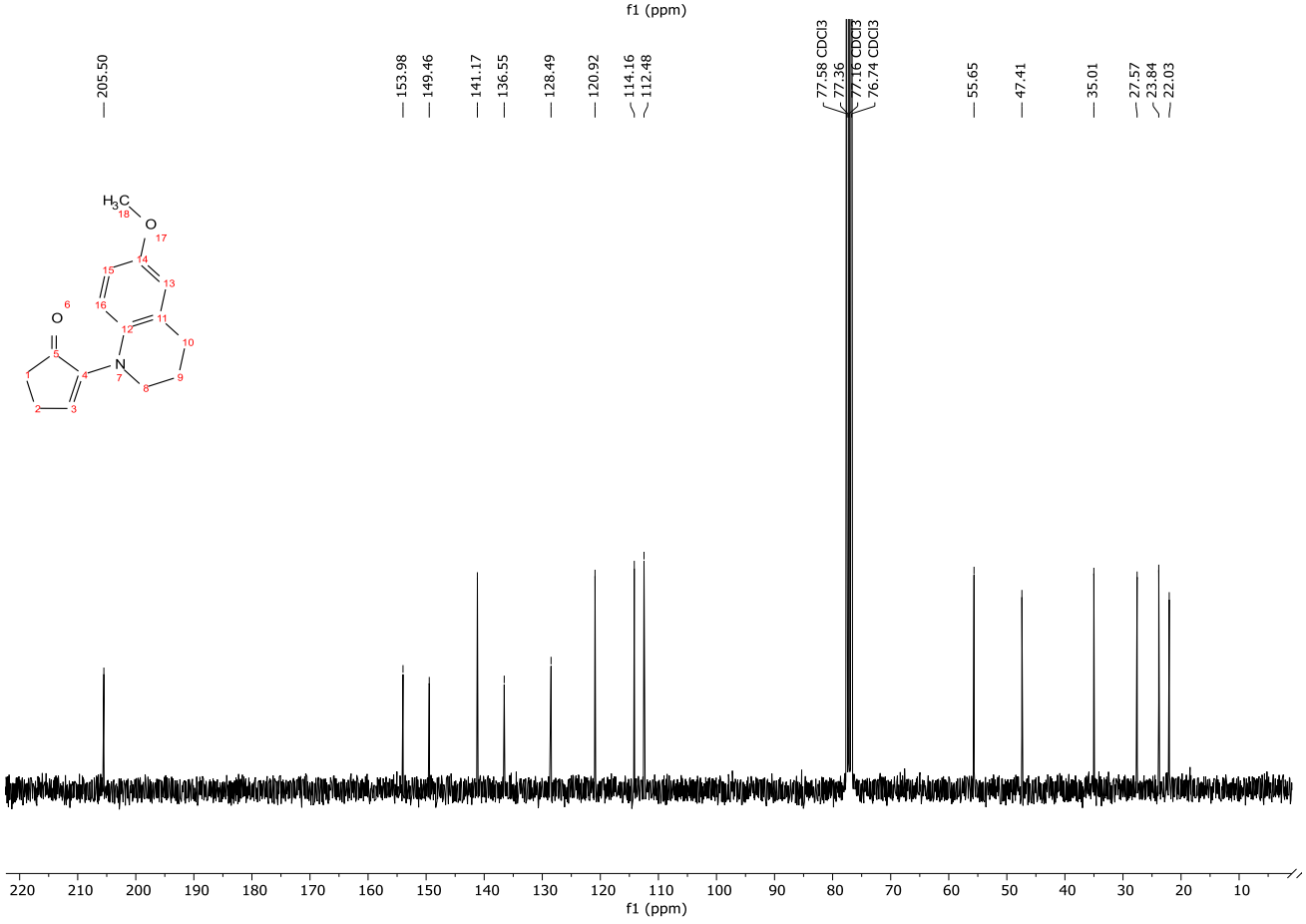
110.64
77.58 CDCl3
77.16 CDCl3
76.74 CDCl3
51.33
34.46
28.56
24.20
f1 (ppm)


6.84 6.83 6.82 6.70 6.69 6.67 6.64 6.63 6.63 6.63 6.62 6.62 6.62 6.61 6.61 6.61 6.60 6.60 6.59
3.75 3.54 3.52 3.52 3.52 3.51 3.51 3.50 2.78 2.76 2.74 2.59 2.59 2.59 2.58 2.58 2.58 2.57 2.57 2.56 2.56 2.56 2.55 2.55 2.52 2.52 2.51 2.50 2.50 2.50 2.49 2.49 1.90 1.88 1.88 1.88 1.87 1.87 1.86 1.86 1.85 1.85 1.85 1.84 1.84 1.83 1.82 1.81
1.00 1.00 2.04 3.04 2.04 2.06 2.01 2.09 2.05
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)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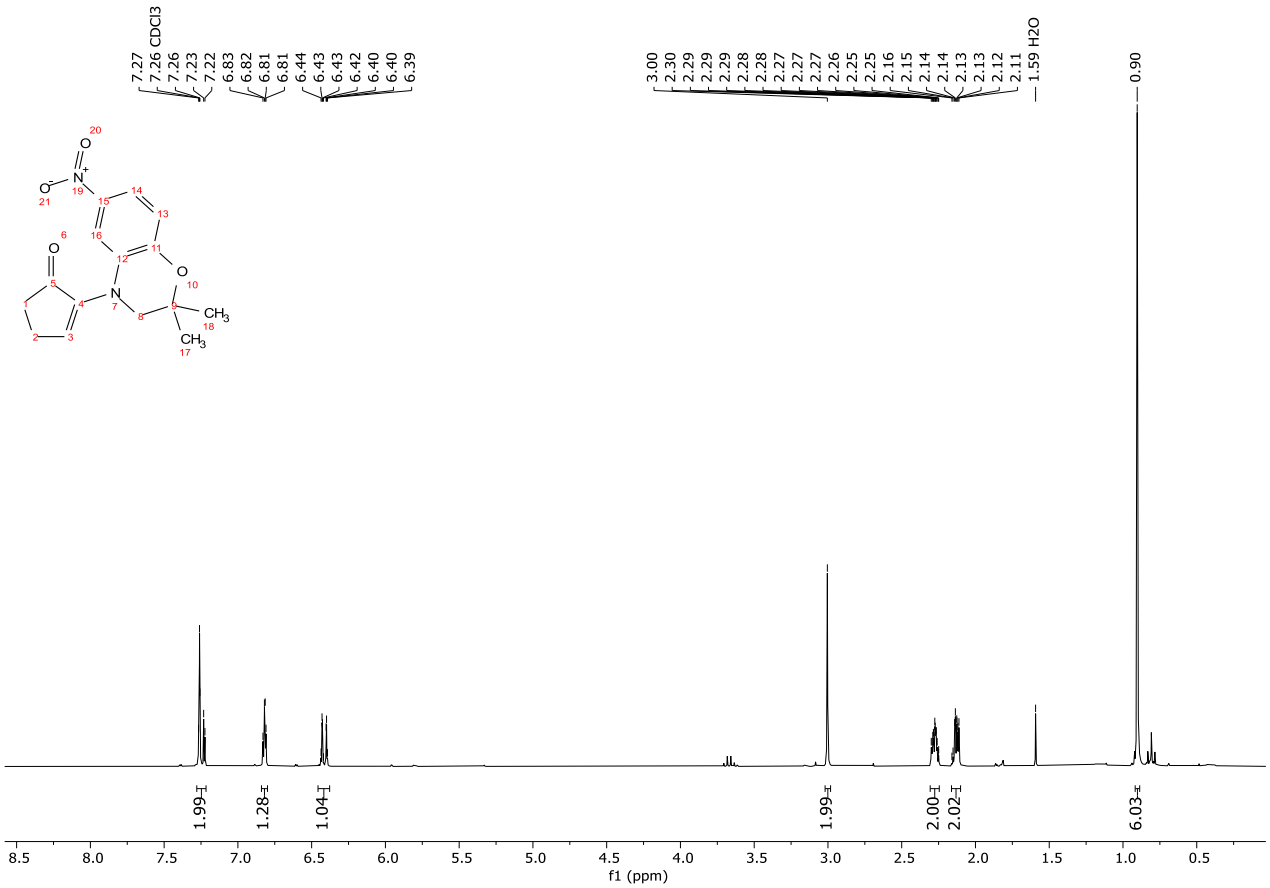
153.98 149.46 141.17 136.55 128.49 120.92 114.16 112.48
77.58 CDCl3 77.36 77.16 CDCl3 76.74 CDCl3
55.65 47.41 35.01 27.57 23.84 22.03
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)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7.26 CDCl3
7.26
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7.22
6.83
6.82
6.81
6.81
6.44
6.43
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6.39
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2.29
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2.27
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2.26
2.25
2.25
2.16
2.15
2.14
2.14
2.13
2.13
2.12
2.11
1.59 H2O
0.90
1.99
1.28
1.04
1.99
2.00
2.02
6.03
8.5
8.0
7.5
7.0
6.5
6.0
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5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
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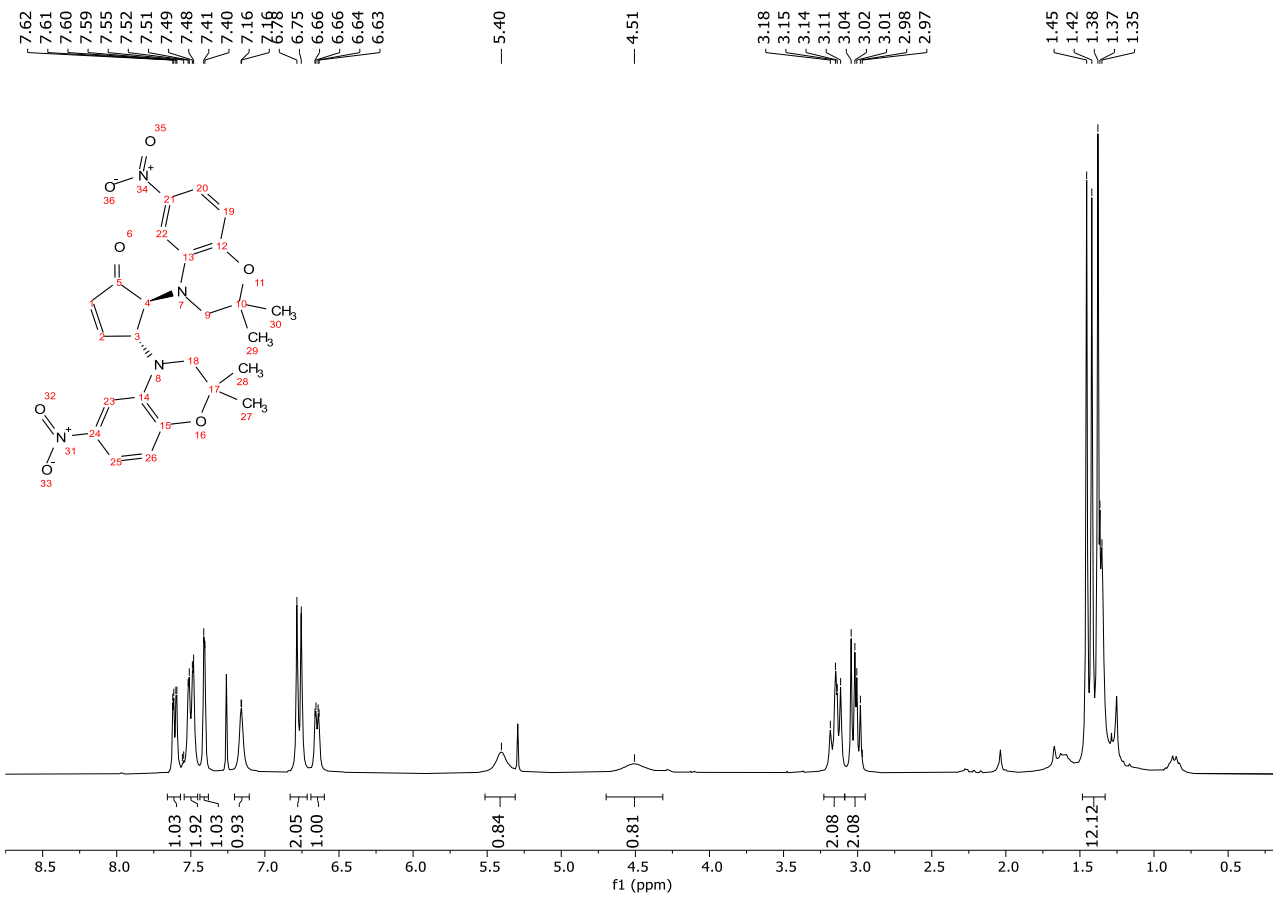
0.5
f1 (ppm)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6.63
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3.02
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2.97
1.45
1.42
1.38
1.37
1.35
1.03
1.92
1.03
0.93
2.05
1.00
0.84
0.81
2.08
2.08
12.12
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7.0
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6.0
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3.0
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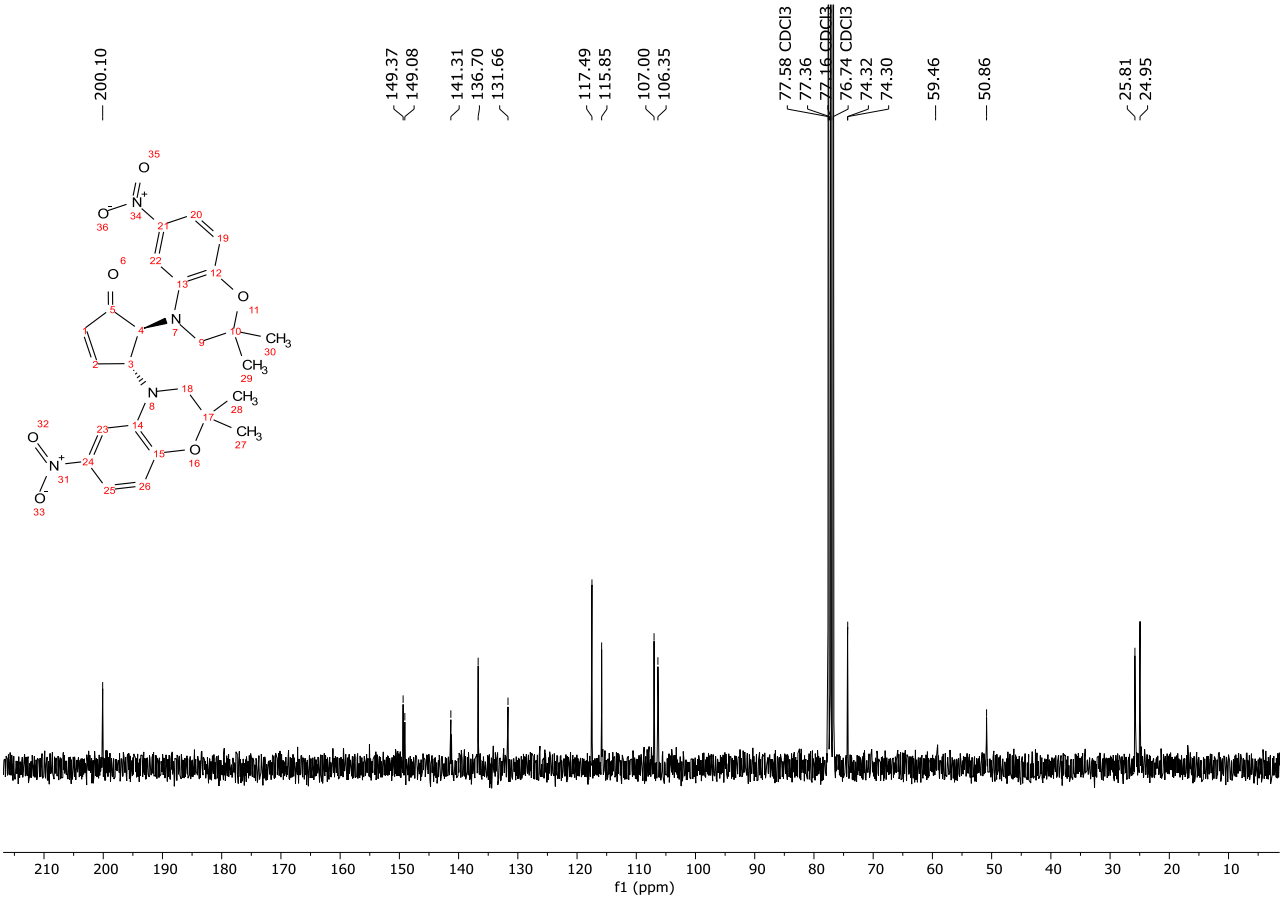
1.5
1.0
0.5
f1 (ppm)



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Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Ö. Farkas; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J., Gaussian 09 Revision d.01, Gaussian Inc., Wallingford CT, 201, 2009.
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