Dual Catalyst System provides the Shortest Pathway for *l*-Menthol Synthesis

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Supporting Information

General Information. All melting points (mp) are uncorrected. ^{1}H- and ^{13}C-NMR were measured on a Bruker DRX-500 spectrometer (Bruker Co.). Mass spectra were performed on a Hitachi M-80B (Hitachi Ltd.). Optical rotations were measured on a JASCO P-1020 digital polarimeter (JASCO Co.). IR spectra were taken with a Nicolet AVATAR 360 FT-IR infrared spectrometer (Thermo Fisher Scientific Co.). Hydrogenation reaction was performed on personal synthesizer "Chemi Station" (EYELA). Gas liquid chromatography (GLC) was performed on Shimadzu GC-2010AF (Shimadzu) instrument using DB-WAX (30m×0.32mm×0.5μm) and Beta DEX^{TM} 225 (30m×0.25mm×0.25μm) columns.

Preparation of citral (*E*/*Z* mixture), *E*-citral, and *Z*-citral

Citral (*E*/*Z* mixture) is commercially available. *E*- and *Z*-citral were prepared by fractional distillation from the *E*/*Z* mixture. All citrals were distilled prior to asymmetric hydrogenation.

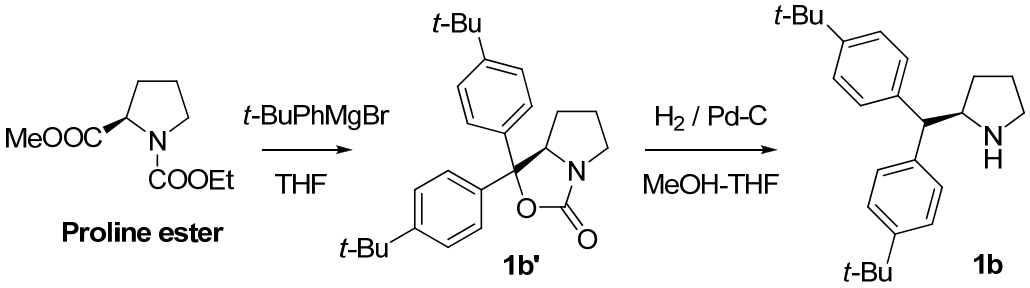
Amine catalyst 1a, 1e, 2-4

Amine **1a, 1e** and **2-4** were purchased from SIGMA-ALDRICH. They were used directly in the following reaction.

(2S)-2-(ditolylmethyl)pyrrolidine (1d)

Amine **1d** was synthesized according to the literature using (*S*)-proline as a starting material.[1]

(2R)-2-[bis(4-*tert*-butylphenyl)methyl]pyrrolidine (1b)



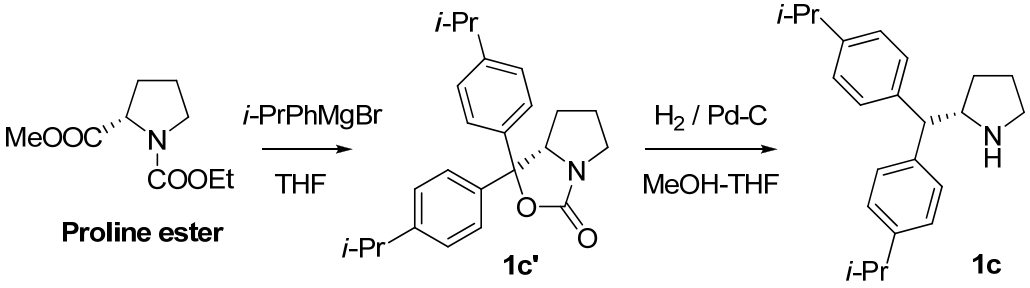
Oxazolidinone **1b'** [3] was synthesized following the same procedure with **1c'** (yield 50.0 %).

mp 248-251 ^{0}C (lit.[3] mp 240-243 ^{0}C). $[\alpha]_D^{20}$ = +143.7 (c = 0.44, CH_2Cl_2) (lit.[3] $[\alpha]_D^{rt}$ = +125 (c = 0.44, CH_2Cl_2)). IR (KBr) ν_{max} cm^{-1} 2960, 1750, 1510, 1470, 1390. ^{1}H-NMR (500 MHz; $CDCl_3$; Me_4Si) δ 7.25-7.46 (8H, m), 4.50 (1H, dd, *J* = 5.6, 10.5 Hz), 3.72 (1H, m), 3.22 (1H, m), 1.96 (1H, m), 1.84 (1H, m), 1.71 (1H, m), 1.25 (18H, s), 1.13 (1H, m). ^{13}C-NMR (125 MHz; $CDCl_3$; Me_4Si) δ 160.63, 151.09, 150.44, 140.65, 137.34, 125.53, 125.41, 125.16, 125.07, 85.90, 69.62, 45.99, 34.48, 34.47, 31.27, 31.23, 29.00, 24.90.

Amine **1b** was synthesized following the same procedure with amine **1c** except for using oxazolidinone **1b'** instead of oxazolidinone **1c'** (yield 74.3 %).

mp 124-125 ^{0}C. $[\alpha]_D^{20}$ = -7.1 (c = 0.52, CH_2Cl_2). IR (KBr) ν_{max} cm^{-1} 3320, 2960, 1510, 1460, 1400. ^{1}H-NMR (500 MHz; $CDCl_3$; Me_4Si) δ 7.18-7.30 (8H, m), 3.78 (1H, m), 3.66 (1H, d, *J* = 10.2 Hz), 3.02 (1H, m), 2.84 (1H, m), 1.74 (3H, m), 1.60 (1H, br), 1.38 (1H, m), 1.25 (18H, s). ^{13}C-NMR (125 MHz; $CDCl_3$; Me_4Si) δ 148.87, 148.81, 140.93, 140.78, 127.66, 127.64, 125.46, 125.22, 62.64, 57.65, 46.18, 34.32, 31.37, 30.65, 24.72. HRMS (ESI) Found 350.2843 $[M+H]^+$ Calcd. for $C25H35N+H^+$ 350.2842.

***(2S)*-2-[bis(4-*iso*-propylphenyl)methyl]pyrrolidine (1c)**



A solution of proline ester[2] 10.05 g (50.0 mmol) in THF 50 mL was added dropwise to a solution of *i*-PrPhMgBr in THF 140 mL (0.714 mol/L, 100.0 mmol) under N_2 at 5 ^{0}C. To solution was warmed to room temperature and then heated under reflux for 3 h. The reaction mixture was then added to an ice cold solution of NH_4Cl and the aqueous layer extracted into EtOAc. The combined organic layer was washed with brine and dried

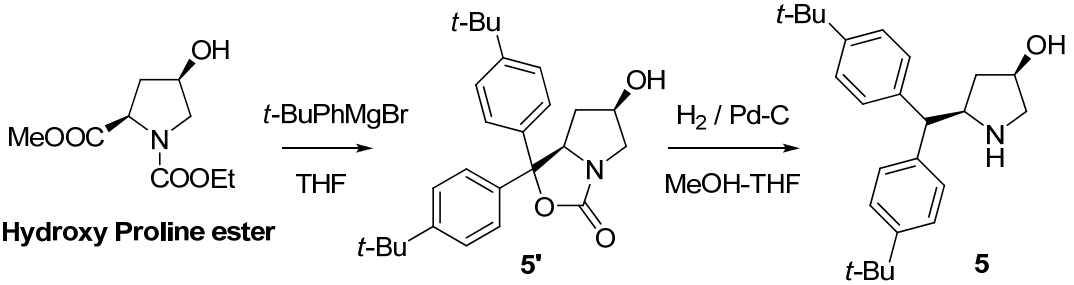
over Na_2SO_4. The solvent was removed under reduced pressure to give oxazolidinone **1c'** as a white crystalline solid, which was recrystallised from MeOH (6.66 g, yield 36.7 %).

mp 121-124 ^{0}C. $[\alpha]_D^{20}$ = -154.5 (c = 0.44, CH_2Cl_2). IR (KBr) ν_{max} cm^{-1} 2960, 1750, 1510, 1460, 1380. ^{1}H-NMR (500 MHz; $CDCl_3$; Me_4Si) δ 7.15-7.46 (8H, m), 4.50 (1H, dd, *J* = 5.5, 10.5 Hz), 3.72 (1H, m), 3.23 (1H, m), 2.88 (2H, m), 1.96 (1H, m), 1.84 (1H, m), 1.71 (1H, m), 1.23 (12H, d, *J* = 6.9Hz), 1.13 (1H, m) ^{13}C-NMR (125 MHz; $CDCl_3$; Me_4Si) δ 160.63, 148.87, 148.17, 141.05, 137.80, 126.57, 126.26, 125.87, 125.45, 85.98, 69.58, 46.02, 33.70, 33.67, 29.03, 24.93, 23.87, 23.85. HRMS (ESI) Found 386.2090 $[M+Na]^+$ Calcd. for C24H29NO2+Na$^+$ 386.2091.

A mixture of Oxazolidinone **1c'** 6.00 g (16.5 mmol) and 10%-Pd/C 120 mg (2 wt%) in MeOH/THF (2:1 v/v) 90 mL was stirred under H_2 atmosphere at room temperature for 4 d. The catalyst was filtered off and the solvent removed under reduced pressure. Purification over SiO_2 gave the title compound as a white crystalline solid (2.44 g, yield 46.0 %).

mp 64-68 ^{0}C. $[\alpha]_D^{20}$ = +12.5 (c = 0.47, CH_2Cl_2). IR (KBr) ν_{max} cm^{-1} 3320, 2960, 1510, 1460, 1400. ^{1}H-NMR (500 MHz; $CDCl_3$; Me_4Si) δ 7.08-7.28 (8H, m), 3.78 (1H, m), 3.67 (1H, d, *J* =10.2 Hz), 3.02 (1H, m), 2.83 (3H, m), 1.75 (3H, m), 1.38 (1H, m), 1.18 (12H, d) ^{13}C-NMR (125 MHz; $CDCl_3$; Me_4Si) δ 146.62, 146.54, 141.22, 127.91, 127.89, 126.62, 126.39, 62.59, 57.83, 46.18, 33.62, 33.59, 30.62, 24.73, 23.96. HRMS (ESI) Found 322.2519 $[M+H]^+$ Calcd. for C23H31N+H$^+$ 322.2529.

***(2R,4R)*-2-[bis(4-*tert*-butylphenyl)methyl]-4-hydroxypyrrolidine (5)**



A solution of hydroxy proline ester 6.10 g (30.0 mmol) in THF 50 mL was added dropwise to a solution of *t*-BuPhMgBr in THF 165 mL (0.545 mol/L, 90.0 mmol) under N_2 at 5 ^{0}C. To solution was warmed to room temperature and then heated under reflux for 2.5 h. The reaction mixture was then added to an ice cold solution of NH_4Cl and the aqueous layer extracted into EtOAc. The combined organic layer was washed with H_2O and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the title compound as a white crystalline solid, which was recrystallised from

Hexane/EtOAc (1:6 v/v) (7.87 g, yield 64.4 %).
mp 219-221 ^{0}C. $[\alpha]_D^{20}$ = 153.7 (c = 0.44, CH_2Cl_2). IR (KBr) ν_{max} cm^{-1} 3320, 2960, 1760, 1460, 1370. ^{1}H-NMR (500 MHz; $CDCl_3$; Me_4Si) δ 7.27-7.45 (8H, m), 4.61 (1H, dd, *J* =7.3, 8.7 Hz), 4.51 (1H, m), 3.74 (1H, dd, *J*= 3.1, 12.4 Hz), 3.34 (1H, dd, *J* = 5.8, 12.4 Hz), 2.11(1H, m), 1.78 (1H, d, *J* = 4.4 Hz), 1.40 (1H, m), 1.30 (s, 18H). ^{13}C-NMR (125 MHz; $CDCl_3$; Me_4Si) δ 160.88, 151.25, 150,69, 140.46, 137.06, 125.62, 125.47, 125.43, 125.31, 86.46, 72.57, 68.15, 55.42, 38.36, 34.52, 31.29. 31.25. HRMS (ESI) Found 408.2526 $[M+H]^+$ Calcd. for C26H33NO3+H^+ 408.2533.

A mixture of oxazolidinone **5'** 3.00 g (7.36 mmol) and 10%-Pd/C 300 mg (10 wt%) in MeOH/THF (1:1 v/v) 60 mL was stirred under H_2 atmosphere at room temperature for 26 h. The catalyst was filtered off and the solvent removed under reduced pressure. Purification over Al_2O_3 gave the title compound as a white crystalline solid (2.34 g, yield 87.0 %).
mp 114-116 ^{0}C. $[\alpha]_D^{20}$ = 6.3 (c = 0.43, CH_2Cl_2). IR (KBr) ν_{max} cm^{-1} 3210, 2960, 1510, 1460, 1360. ^{1}H-NMR (500 MHz; $CDCl_3$; Me_4Si) δ 7.19-7.31 (8H, m), 4.30 (1H, m), 3.84 (1H, d, *J* = 10.3 Hz), 3.77 (1H, m), 2.98 (1H, d, *J* = 11.1 Hz), 2.88 (1H, dd, *J* = 4.8, 11.1 Hz), 2.12 (3H, m), 1.42 (1H, dddd, *J* = 1.4, 2.8, 7.1, 14.2 Hz), 1.27 (18H, s). ^{13}C-NMR (125 MHz; $CDCl_3$; Me_4Si) δ 149.13, 149.06, 140.43, 140.16, 127.67, 127.60, 125.56, 125.35, 72.11, 61.95, 57.80, 55.66, 41.00, 34.35, 34.33, 31.36. HRMS (ESI) Found 366.2796 $[M+H]^+$ Calcd. for C25H35NO+H^+ 366.2791.

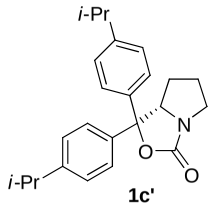
Typical procedure (asymmetric hydrogenation of citral)

A mixture of citral (*E*/*Z* = 50/50) 2.00 g (13.1 mmol), TFA・**1b** salt 115 mg (0.249 mmol) and 5%-Pd/$BaSO_4$ 28 mg (0.1 mol%) in *t*-BuOH/H_2O (92:8 v/v) 2.0 mL was stirred under N_2 atmosphere at 50 ^{0}C for 1 h. To the mixture was then introduced H_2 gas. After stirring for 21 h at 50 ^{0}C, the reaction mixture was filtered Celite and organic phase was analyzed by GLC (octadecane was used as an internal standard) to afford (*R*)-citronellal (74% yield, 84% ee).

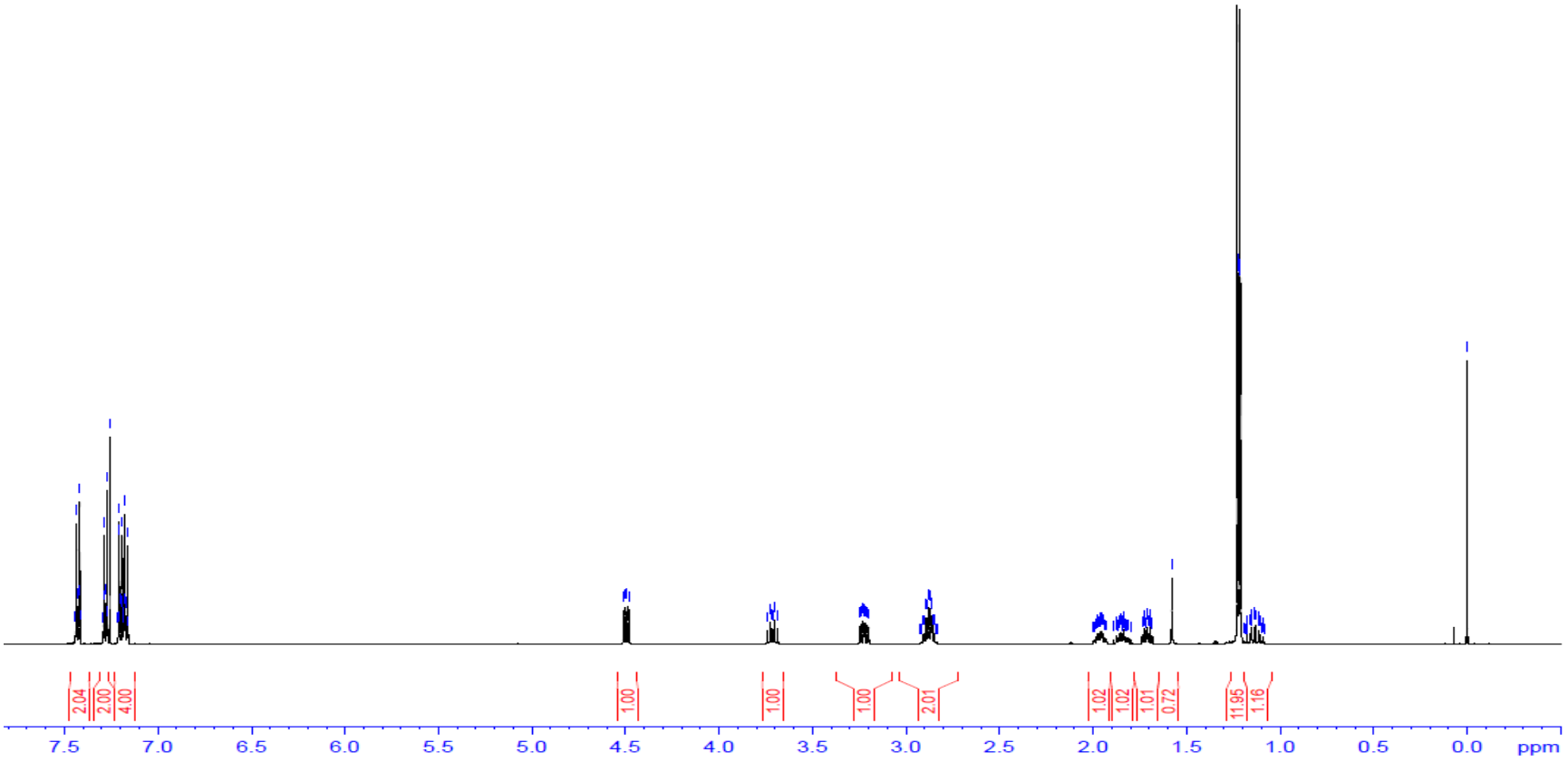
References

(1) C. Y. Ho; Y. C. Chen; M. K. Wong; D. Yang *J. Org. Chem.* **2005** , 70, 898-906.
(2) D. J. Bailey; D. O'Hagan; M. Tavasli *Tetrahedron: Asymmetry* **1997**, 8, 149-153.
(3) U. Groselj; D. Seebach; D. M. Badine; W. B. Schweizer; A. K. Beck; I. Krossing; P. Klose; Y. Hayashi; T. Uchimaru *Helv. Chim. Acta.* **2009**, 92, 1225-1259.

^{1}H NMR ($CDCl_3$):



1c'



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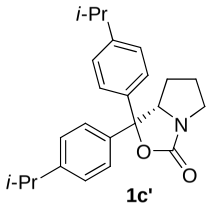

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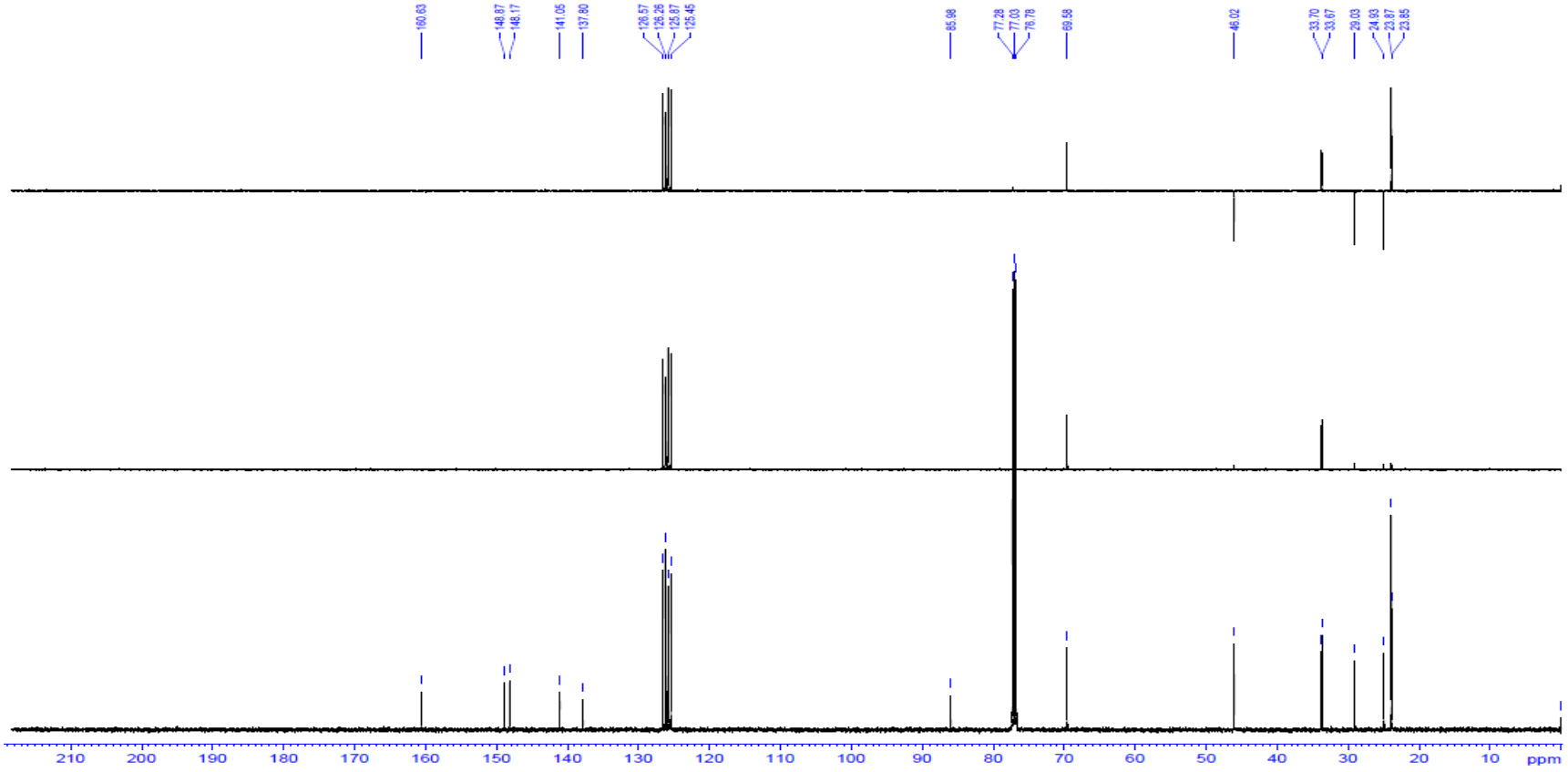

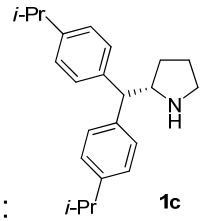

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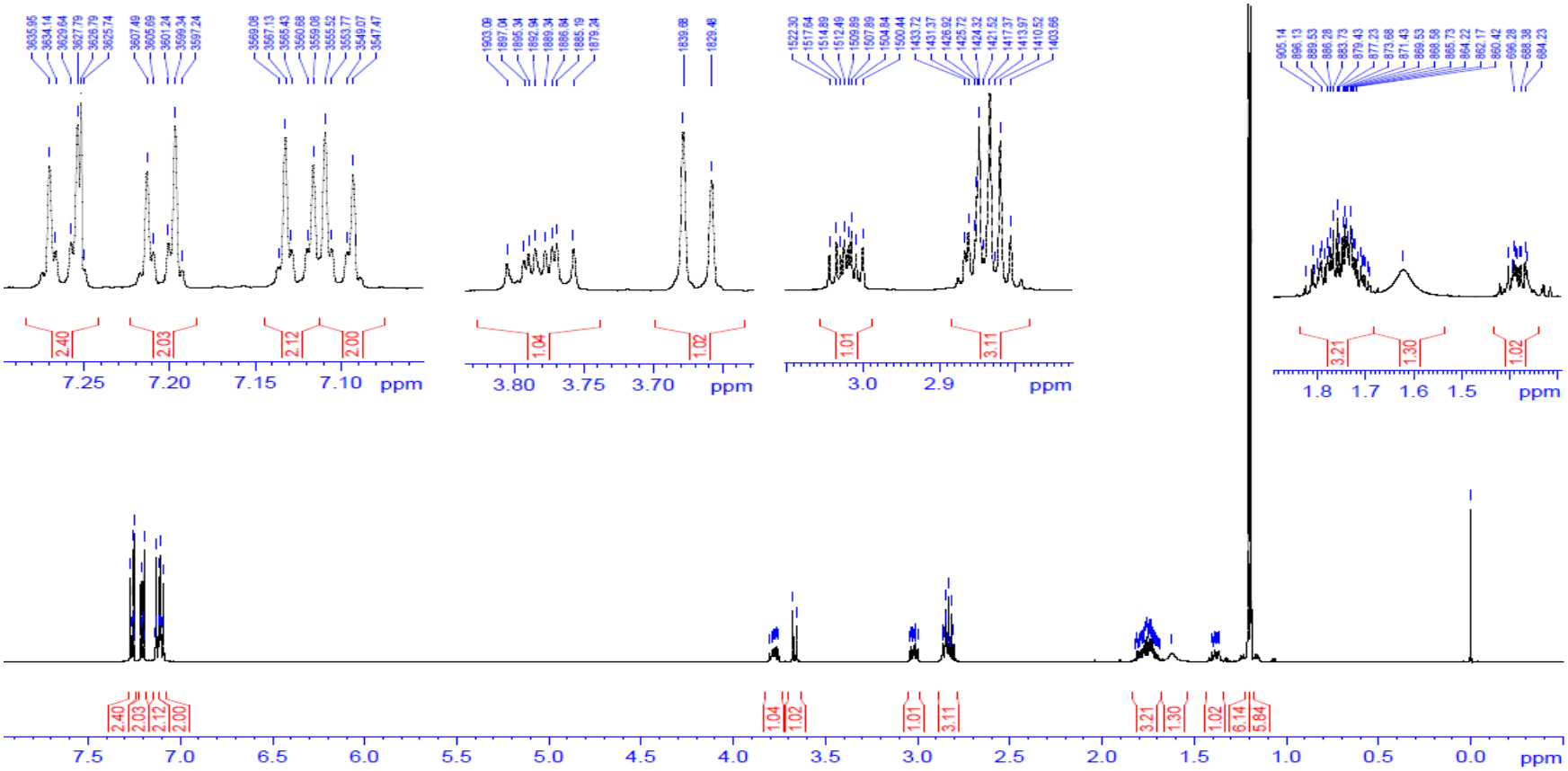

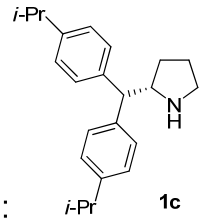

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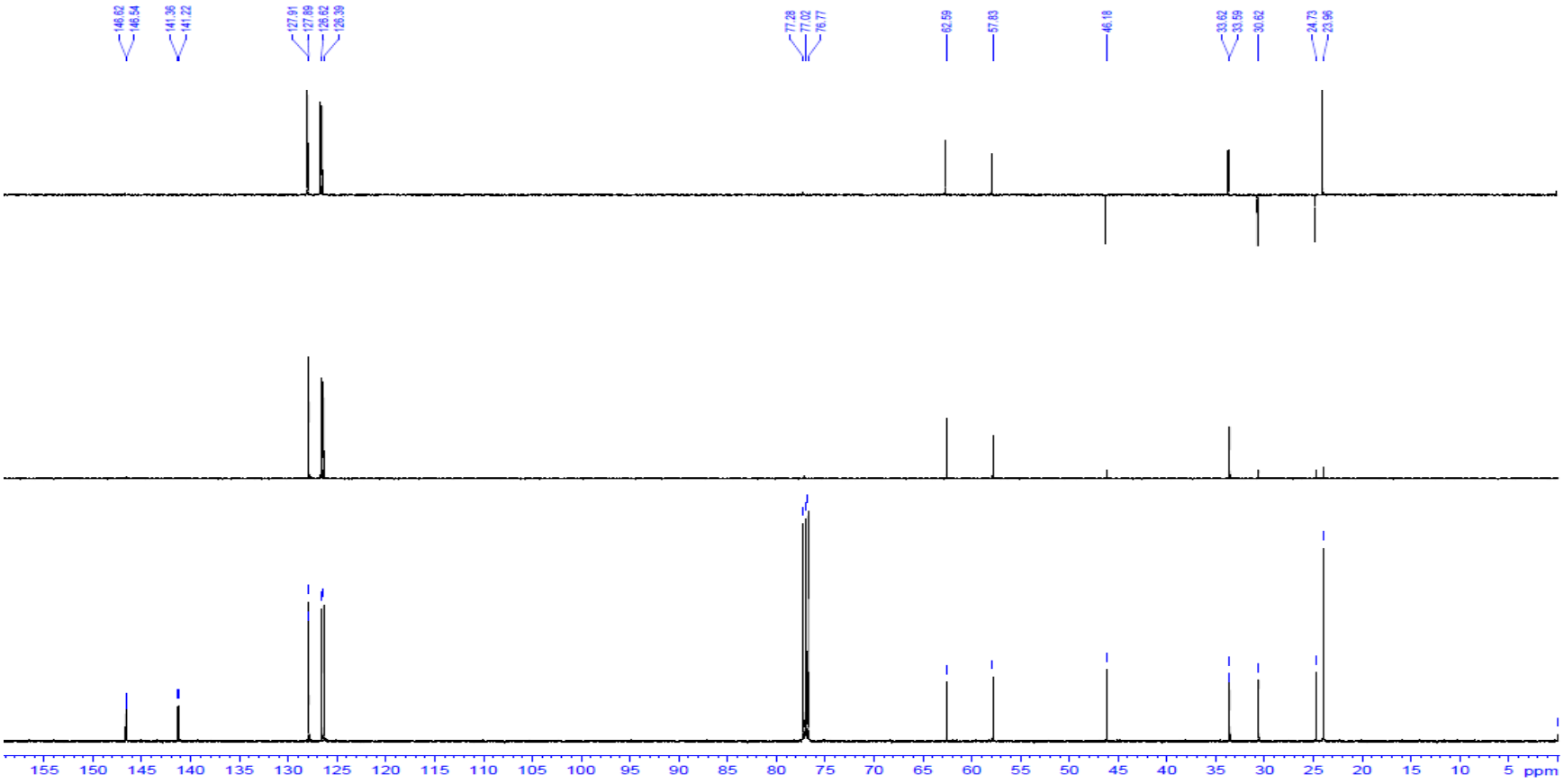

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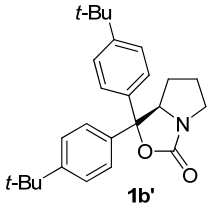

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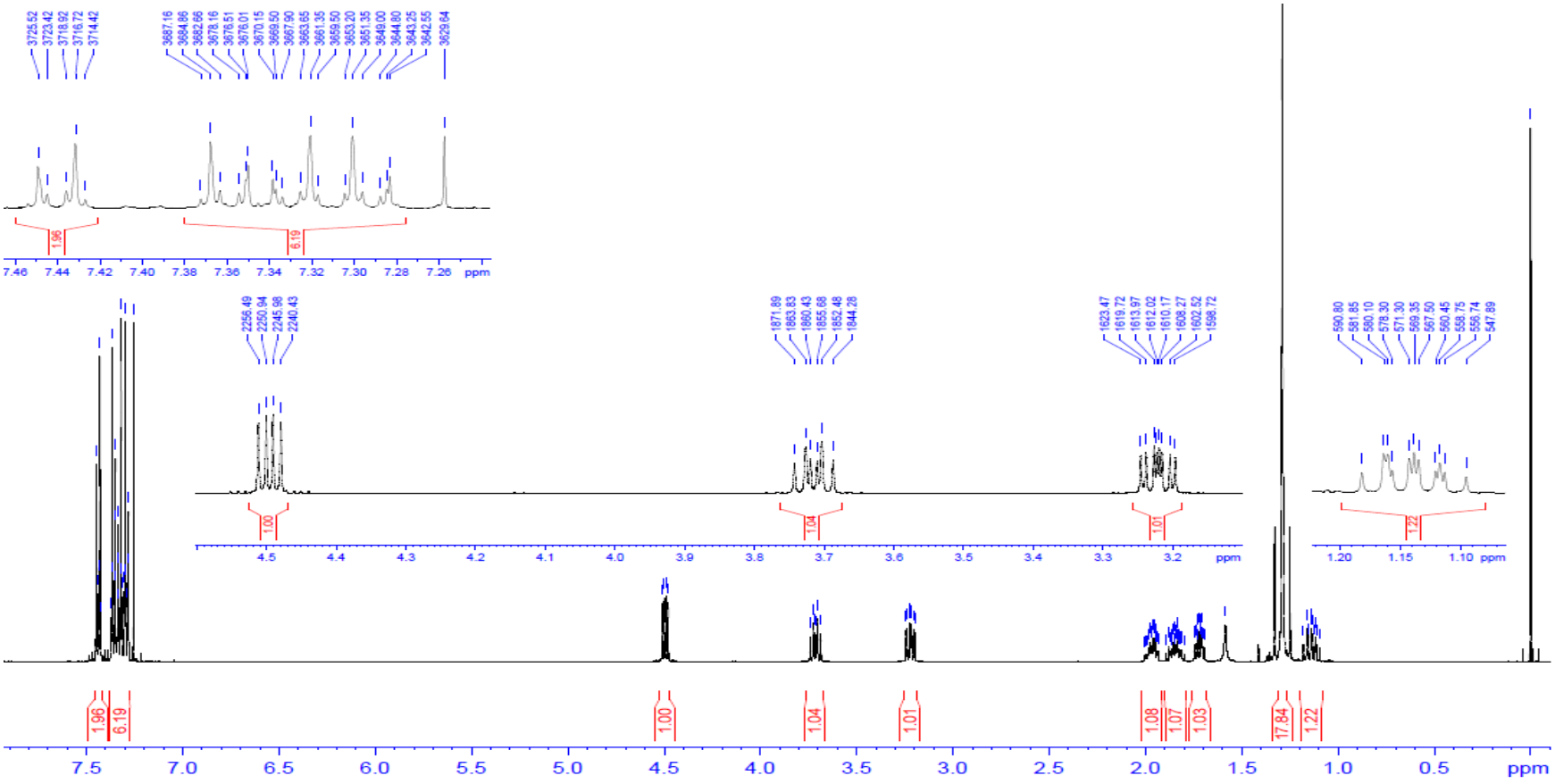

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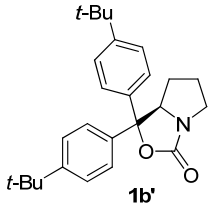

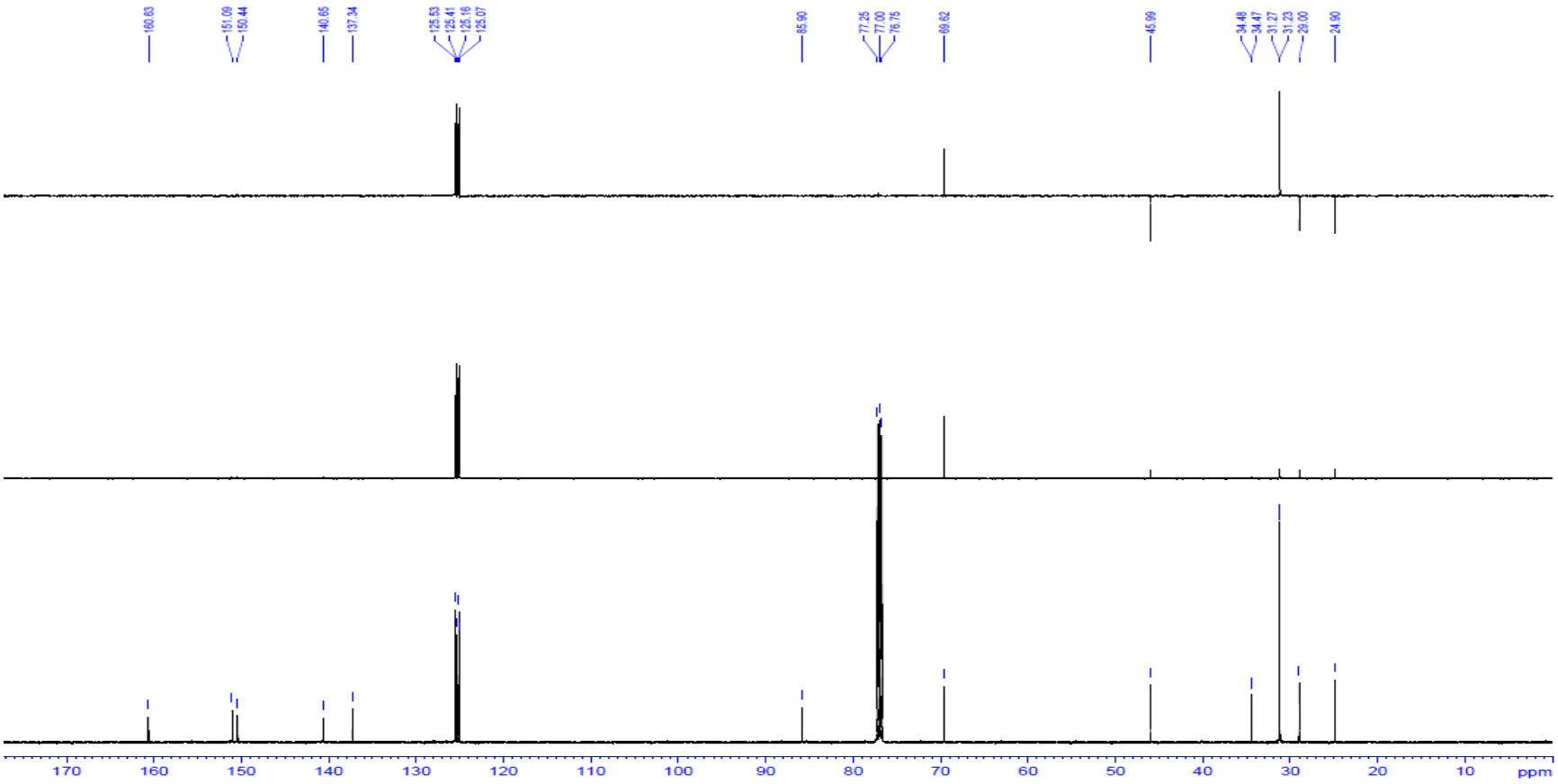

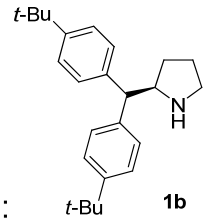

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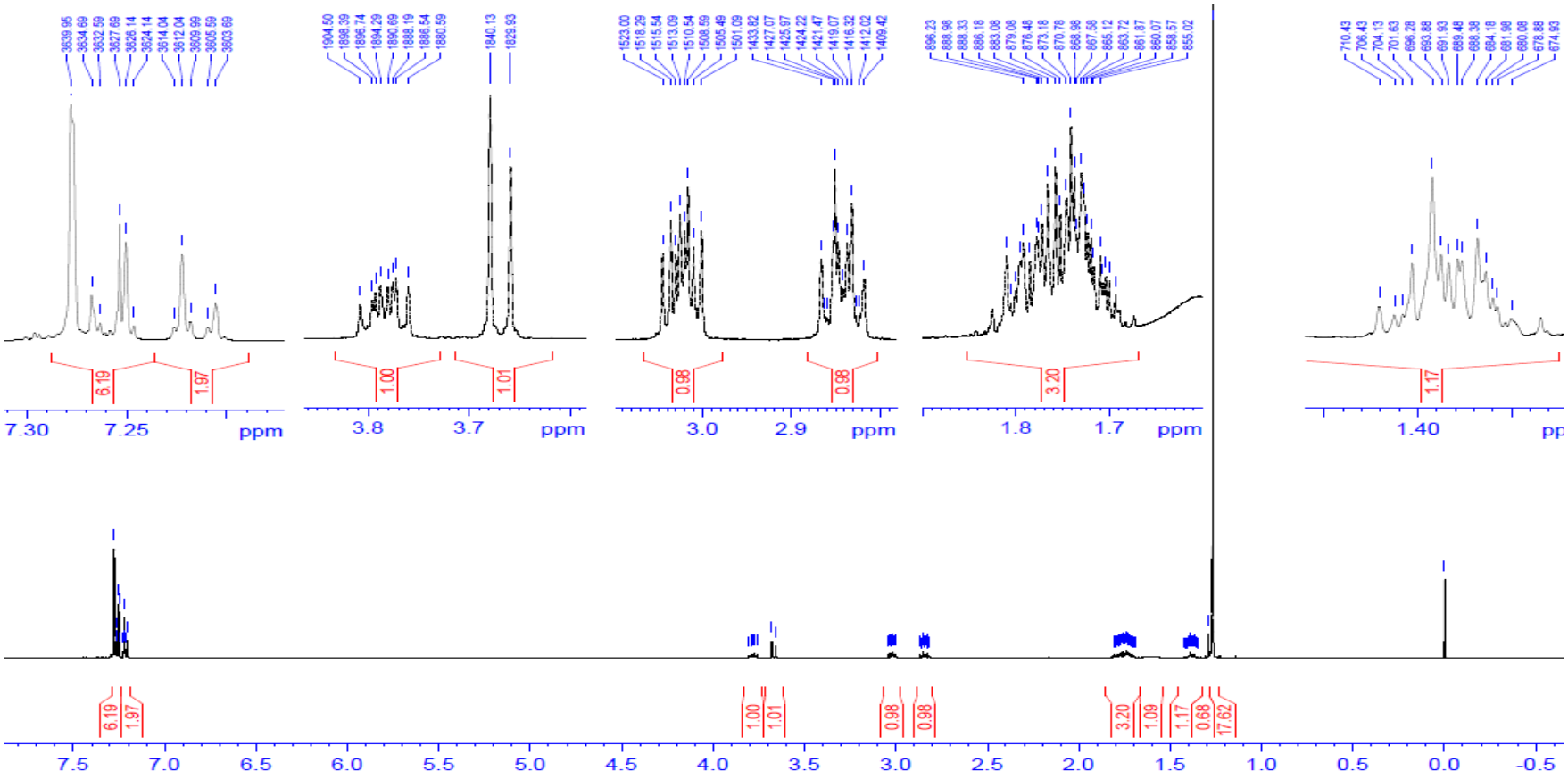

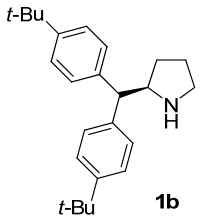

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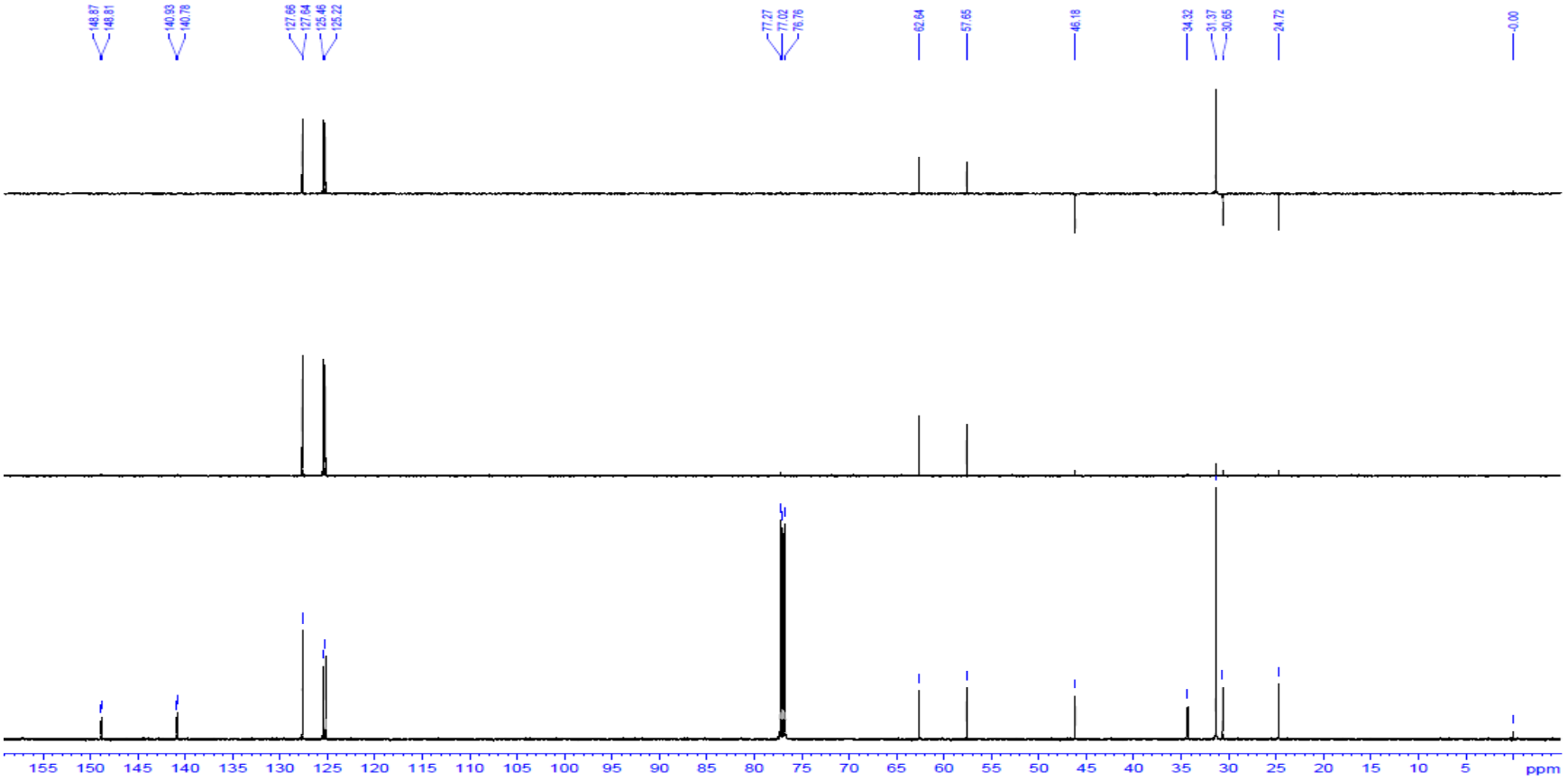

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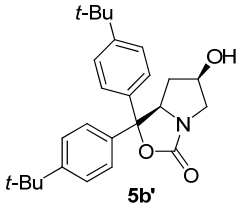

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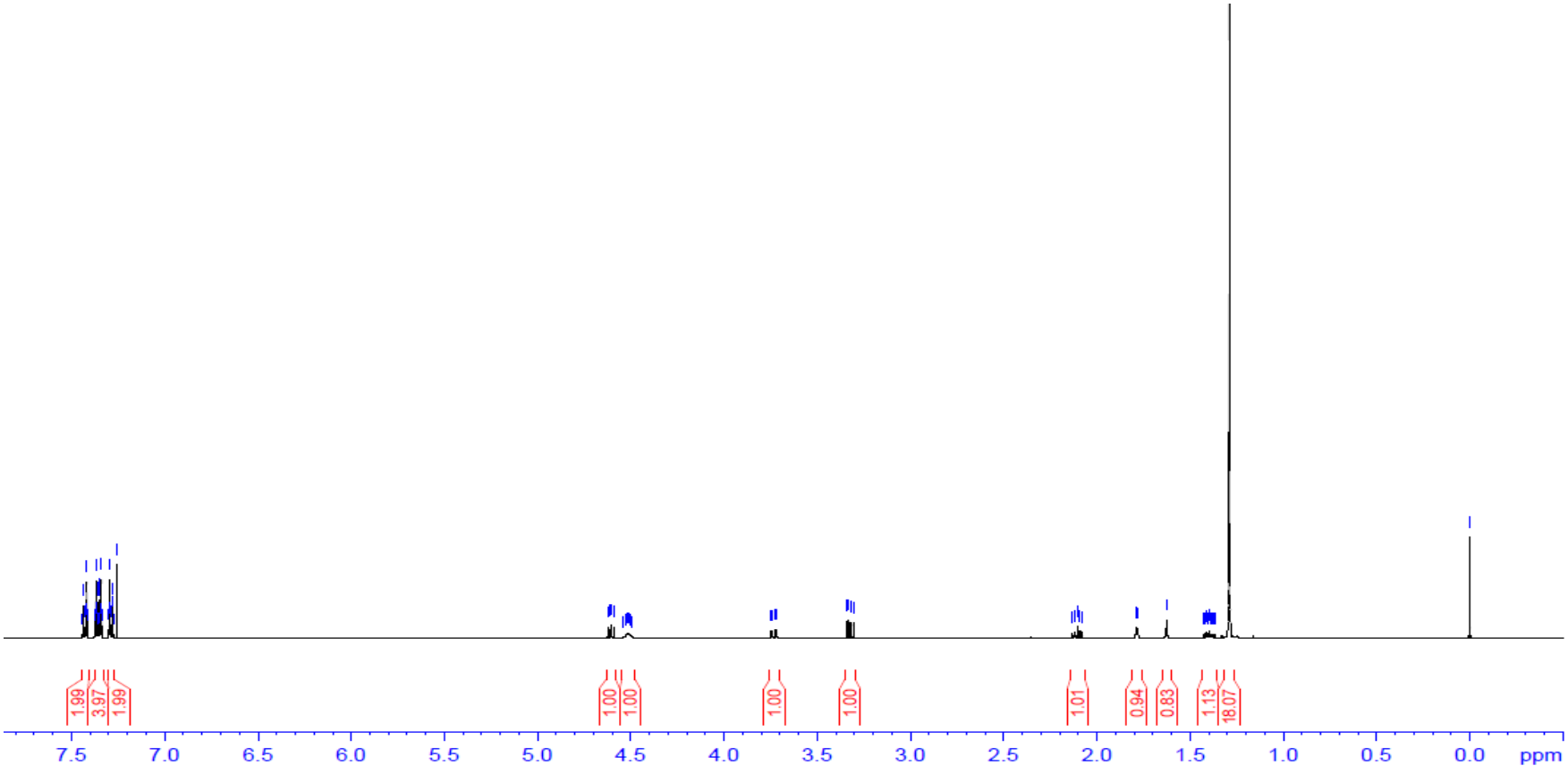

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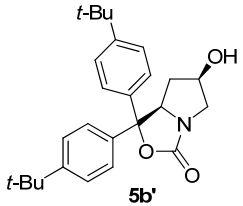

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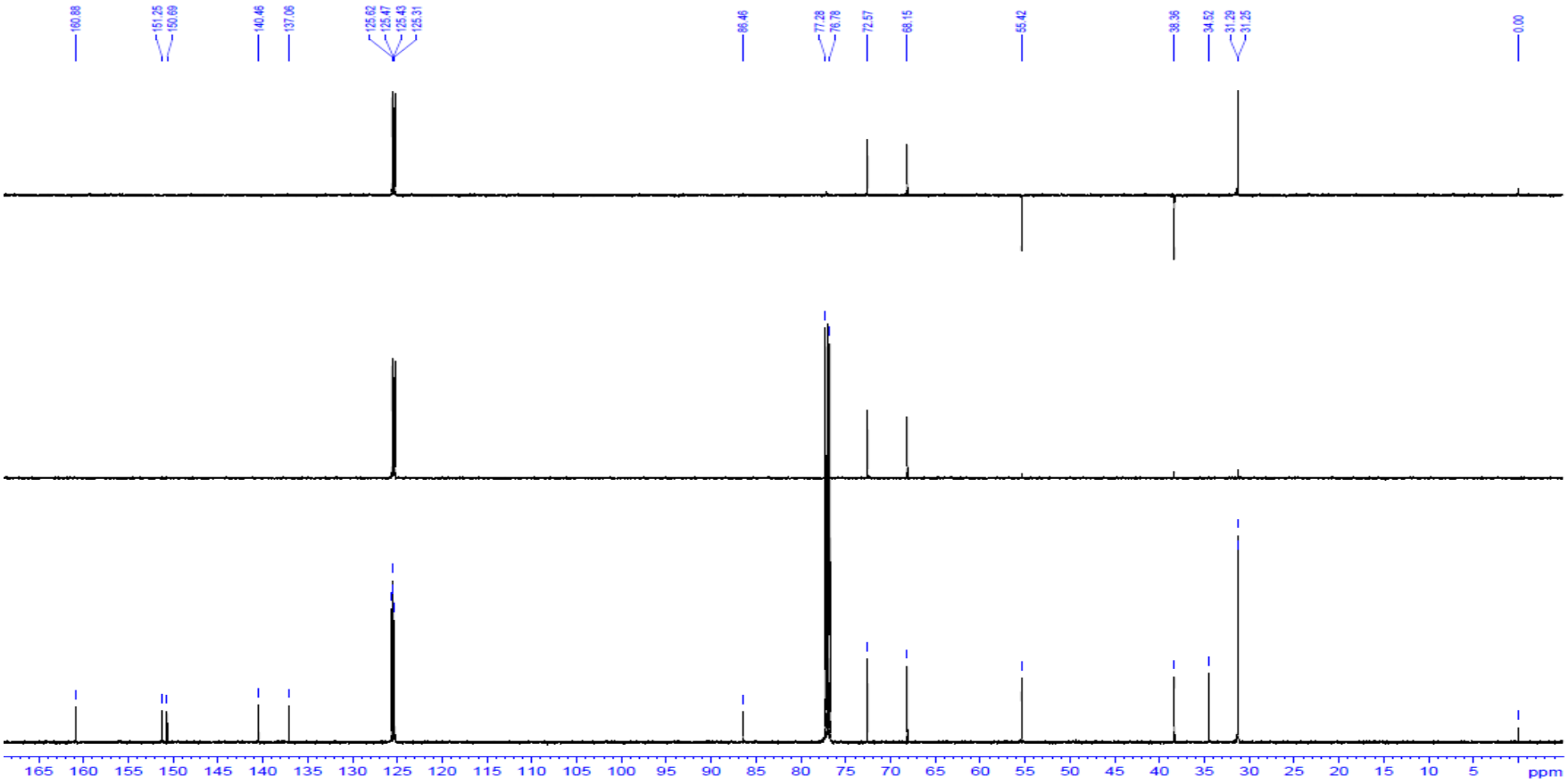

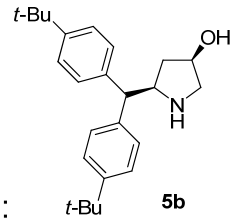

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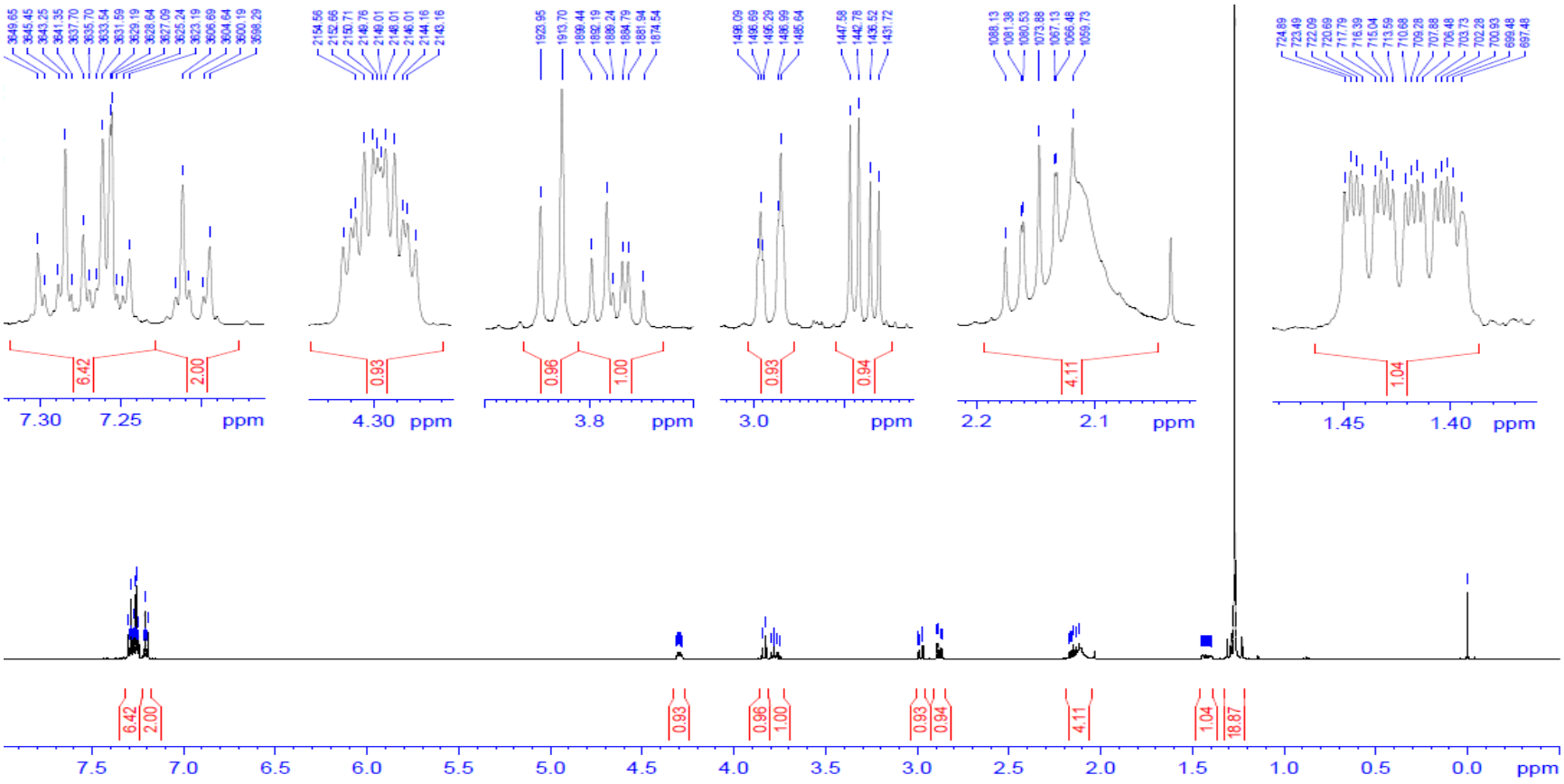

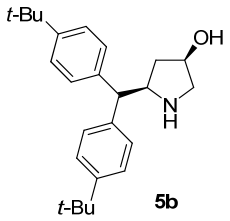

5b

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