Catalysts

Supporting Information

Asymmetric Synthesis of trans-3-Alkoxyamine-4-Oxygenated-2-Piperidinones Mediated by Transition-Metal-Free Dual C-H Oxidation and its CAL-B-Assisted Enzymatic Resolution

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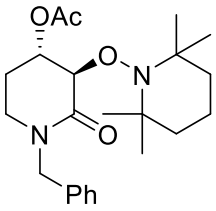
S1. Schematic representation for strategy a) resolution of the *rac-trans*-3 as the second substrate (for the fast-reacting enantiomer (3*S*,4*R*)-3) and strategy b) resolution of the *rac-trans*-2 intermediate as the first substrate (for the fast-reacting enantiomer (3*S*,4*R*)-2).S-18

General considerations

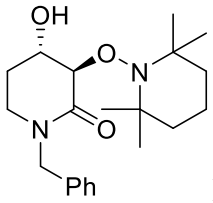
Commercially available reagents were used without further purification. All reactions were carried out under an inert argon atmosphere with dry solvents under anhydrous conditions unless otherwise noted. *Candida antarctica* lipase B (CAL-B) was obtained as Novozym® 435 (Novozymes Mexico). Solvents were used as technical grade and freshly distilled prior to use. Column chromatography (CC) was performed using silica gel (230-400 mesh) with solvents indicated in the text. Analytical grade solvents were purchased from Tecsiquim (*i*-PrOH), Caledon Laboratory Chemicals (*n*-hexane). NMR spectra were recorded with Bruker-500 (500 MHz) using as references: TMS for ^{1}H (0.0 ppm) and $CDCl_3$ for ^{13}C (77.16 ppm); chemical shifts (*d*) are reported in parts per million (ppm) and Hz for the coupling constants (*J*). The following abbreviations (or combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broadened. Melting points were not corrected and carried out using a Fisher-Scientific 12-144 melting point apparatus. Optical rotations were measured with an Autopol-III polarimeter using the sodium D line (589 nm).

Experimental section and characterization data



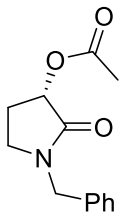
Method for 1-Benzyl-2-oxo-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)piperidin-4-yl acetate (rac-*trans*-**2)**: To a solution of 4-hydroxy-3-alkoxyaminolactam rac-*trans*-**3** (1.2 g, 3.33 mmol) and 4-DMAP (0.4 g, 3.33 mmol) in 33.3 mL of anhydrous CH_2Cl_2 at 0 ºC was added NEt_3 (0.5 g, 5.0 mmol) and acetic anhydride (1.02 g, 10 mmol). After 5 minutes, the reaction mixture was left to warm and stirred for 1 hour. Afterward, 20 mL of water was added, and both phases were separated. The aqueous phase was extracted with CH_2Cl_2 (25 mL × 3). The combined organic phases were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified using column chromatography [SiO_2, hexanes:EtOAc, 5:1] to give 1.2 g (90%) of rac-*trans*-**2** as a white solid. M.p.: 73-74 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.13 (br s, 6H), 1.25 (br s, 6H), 1.31-1.35 (m, 1H), 1.47-1.52 (br m, 5H), 1.90-1.95 (m, 1H), 2.01 (s, 3H), 2.28-2.35 (m, 1H), 3.21 (ddd, *J* = 12.5, 9.5, 6.0 Hz, 1H), 3.30 (ddd, *J* = 12.5, 7.5, 3.5 Hz, 1H), 4.29 (d, *J* = 15.0 Hz, 1H), 4.38 (d, *J* = 2.0 Hz, 1H), 4.94 (d, *J* = 15.0 Hz, 1H), 5.42 (q, *J* = 3.5 Hz, 1H), 7.25-7.33 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 17.2, 20.3, 20.7, 21.1, 23.0, 33.3, 33.9, 40.4(2C), 42.2, 50.1, 60.6(2C), 69.2, 80.7, 127.5,

128.2(2C), 128.6(2C), 136.9, 167.4, 169.9. HRMS (FAB$^+$) *m*/*z*: [M+H]$^+$ Calcd for $C_{23}H_{35}N_2O_4^+$ *m*/*z*: 403.5350, Found 403.2599.

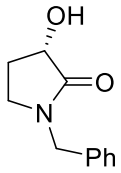


Method for (3*S*,4*R*)-1-benzyl-4-hydroxy-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)piperidin-2-one ((*u*)-*trans*-3). Enzymatic de-acylation reactions were carried out in sealed glass vials. The reactions consisted of the preparation of a solution of rac-*trans*-**2** 0.2 M in 2M2B, 2 to 4 equivalents of water, and 20 to 100 mg mL^{-1} of CAL-B (Novozym® 435). The reaction mixtures were stirred in a thermostated water bath at 45 °C or 60°C. At the end of the reaction, the enzyme was filtered off and washed with DCM. The solvent was evaporated in a vacuum. The residue was purified using column chromatography [SiO_2, Hex:EtOAc; 95:05 to 60:40] to give the product (*u*)-*trans*-**3** as a white solid. Yield 39%; $[\alpha]_D^{20}$ = +45.2 (*c* 1.0, $CHCl_3$) for the product obtained at 60°C. Spectral data for ^{1}H and ^{13}C NMR are consistent with the literature [**Error! Bookmark not defined.**]. δ: 1.21-187 (m, 18H), 2.06 (dq, *J* = 13.5, 3.8 Hz, 1H), 3.14-3.24 (m, 2H), 4.28 (d, *J* = 14.6 Hz, 1H), 4.33 (m, 1H), 4.53 (d, *J* = 8.7 Hz, 1H), 4.83 (d, *J* = 14.6 Hz, 1H), 6.37 (br, 1H), 7.23-7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) d: 17.2, 20.3, 20.7, 21.1, 23.0, 33.3, 33.9, 40.4(2C),

42.2, 50.1, 60.6(2C), 69.2, 80.7, 127.5, 128.2(2C), 128.6(2C), 136.9, 167.4, 169.9 HRMS (FAB$^+$) *m*/*z*: [M+H]$^+$ Calcd for $C_{21}H_{33}N_2O_3^+$ *m*/*z*: 361.4680, Found 361.2516.



Method for (*S*)-1-Benzyl-2-oxopyrrolidin-3-yl acetate (*S*-4): To an enantioenriched solution of (*u*)-trans-**2** (0.1 g, 0.25 mmol) in 8.3 mL of Et_2O at 0 ºC was added *m*-CPBA (77%; 0.17 g, 0.75 mmol) slowly. After 10 minutes of stirring at this temperature, NEt_3 (0.23 g, 2.25 mmol) and 5 mL of H_2O were added. The phases were separated, and the aqueous phase was extracted with Et_2O (3 × 8 mL). The combined organic phases were dried with Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified using column chromatography [SiO_2, hexanes/EtOAc; 4:1 until TEMPO came out of the column, then 1:1] to give 23.9 mg (50%) of *S*-**4** as a colorless oil. $[\alpha]_D^{25}$ = - 36.0 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.93 (tdd, *J* = 13.5, 9.5, 8.0 Hz, 1H), 2.16 (s, 3H), 2.50-2.56 (m, 1H), 3.21 (dt, *J* = 10.0, 7.5 Hz, 1H), 3.29 (td, *J* = 9.5, 2.5 Hz, 1H), 4.45 (d, *J* = 14.5 Hz, 1H), 4.54 (d, *J* = 14.5 Hz, 1H), 5.35 (t, *J* = 8.0 Hz, 1H), 7.24-7.36 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.1, 26.1, 43.1, 47.2, 71.4, 128.0, 128.4(2C), 129.0(2C), 135.7, 170.2, 170.5.



Method for (*S*)-1-Benzyl-3-hydroxypyrrolidin-2-one (*S*-5): To a solution of *S*-**4** (0.02 g, 0.086 mmol) in 2.9 mL of THF:H_2O (2:1) at 0 ºC was added LiOH (6.2 mg, 0.26 mmol). The reaction mixture was stirred and monitored with TLC. Upon completion, an aqueous solution of $KHSO_4$ was added until a pH of 1-2 was reached. Then, 10 mL of Et_2O was added, the phases were separated, and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phases were dried with Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified using column chromatography [SiO_2, EtOAc:EtOH; 1:2] to give 13 mg (79%) of *S*-**5** as a white solid. M.p.: 69-70 °C; $[\alpha]_D^{25}$ = - 79.0 (c = 0.55, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.91-1.99 (m, 1H), 2.39-2.45 (m, 1H), 3.15-3.27 (m, 2H), 4.01 (br, 1H), 4.41-4.51 (m, 3H), 7.23-7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.9, 43.2, 47.2, 70.2, 127.9, 128.3(2C), 128.9(2C), 135.8, 175.0.

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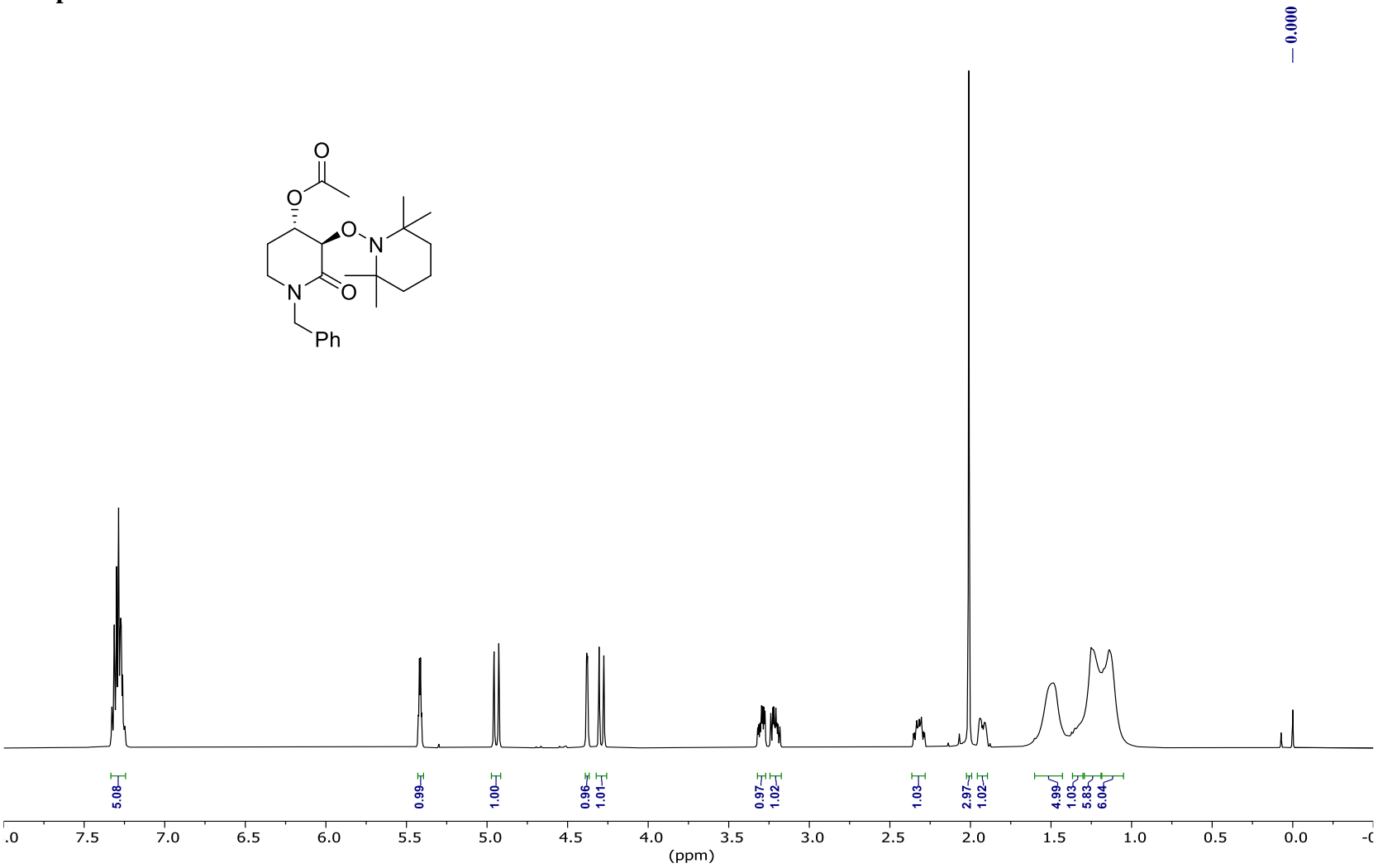
NMR Spectra


— 0.000
O
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O
N
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7.0
6.5
6.0
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5.0
4.5
4.0
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3.0
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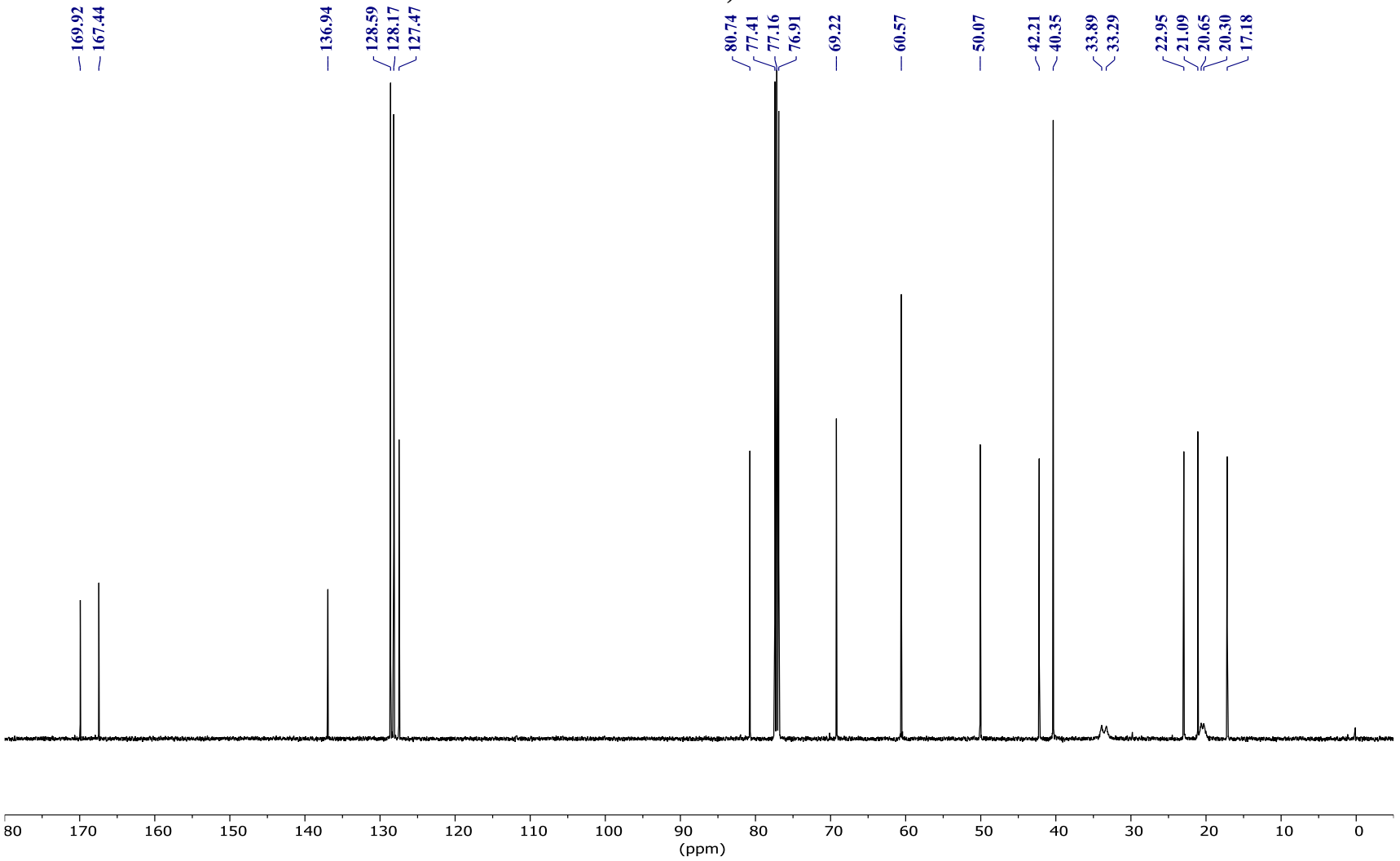
2.0
1.5
1.0
0.5
0.0
(ppm)

NMR spectra for 1-Benzyl-2-oxo-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)piperidin-4-yl acetate (rac-*trans*-**2**): ^{1}H-NMR (500 MHz, $CDCl_3$).



NMR spectra for 1-Benzyl-2-oxo-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)piperidin-4-yl acetate (rac-*trans*-**2**): ^{13}C-NMR (125 MHz, $CDCl_3$).

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Sample: JEG16-1P01                 Operator name M.en ITA Victoria Labastida G.
Note : Dr.Escalante/ Centro de Investigaciones Químicas UAEM

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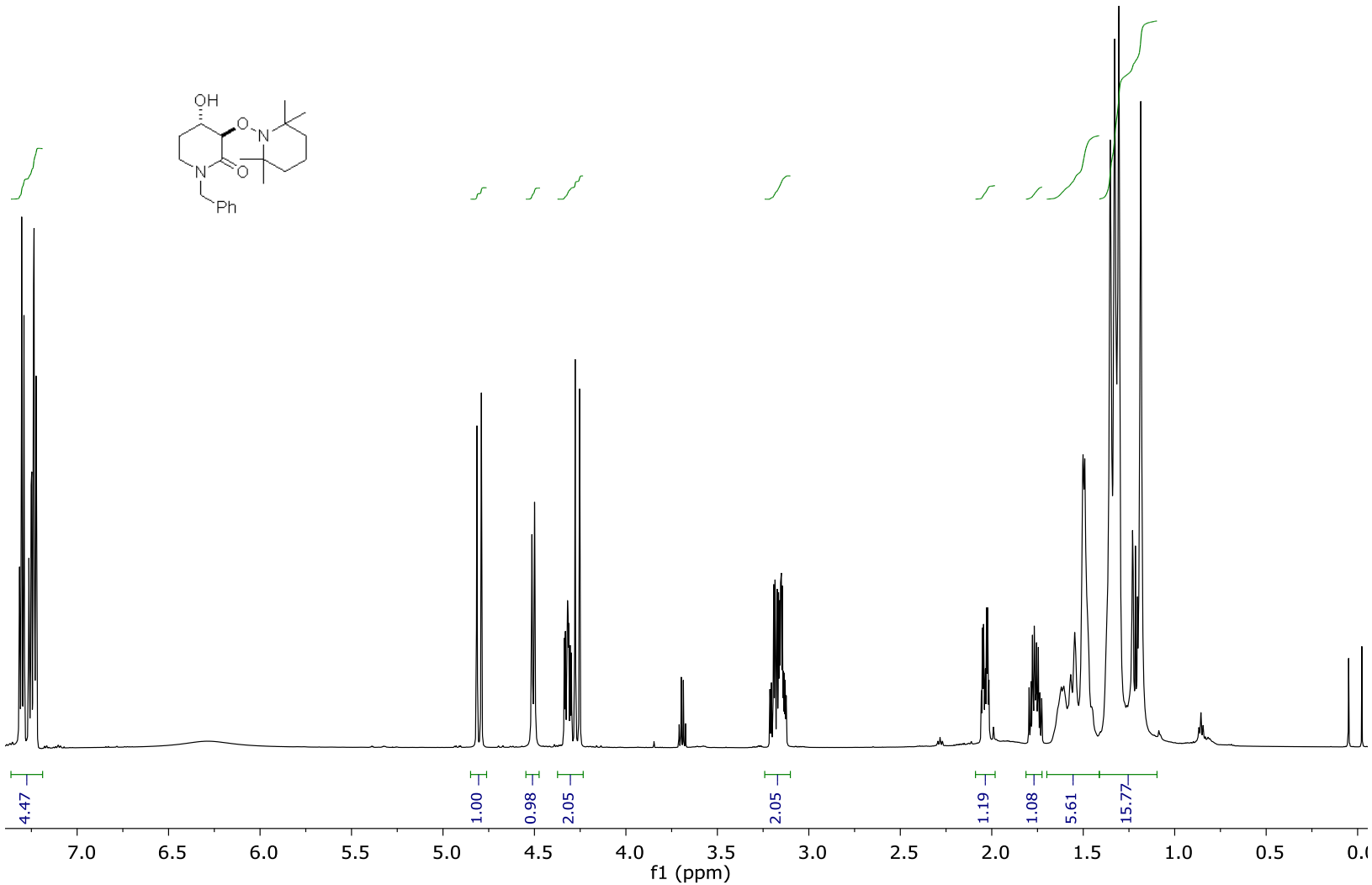
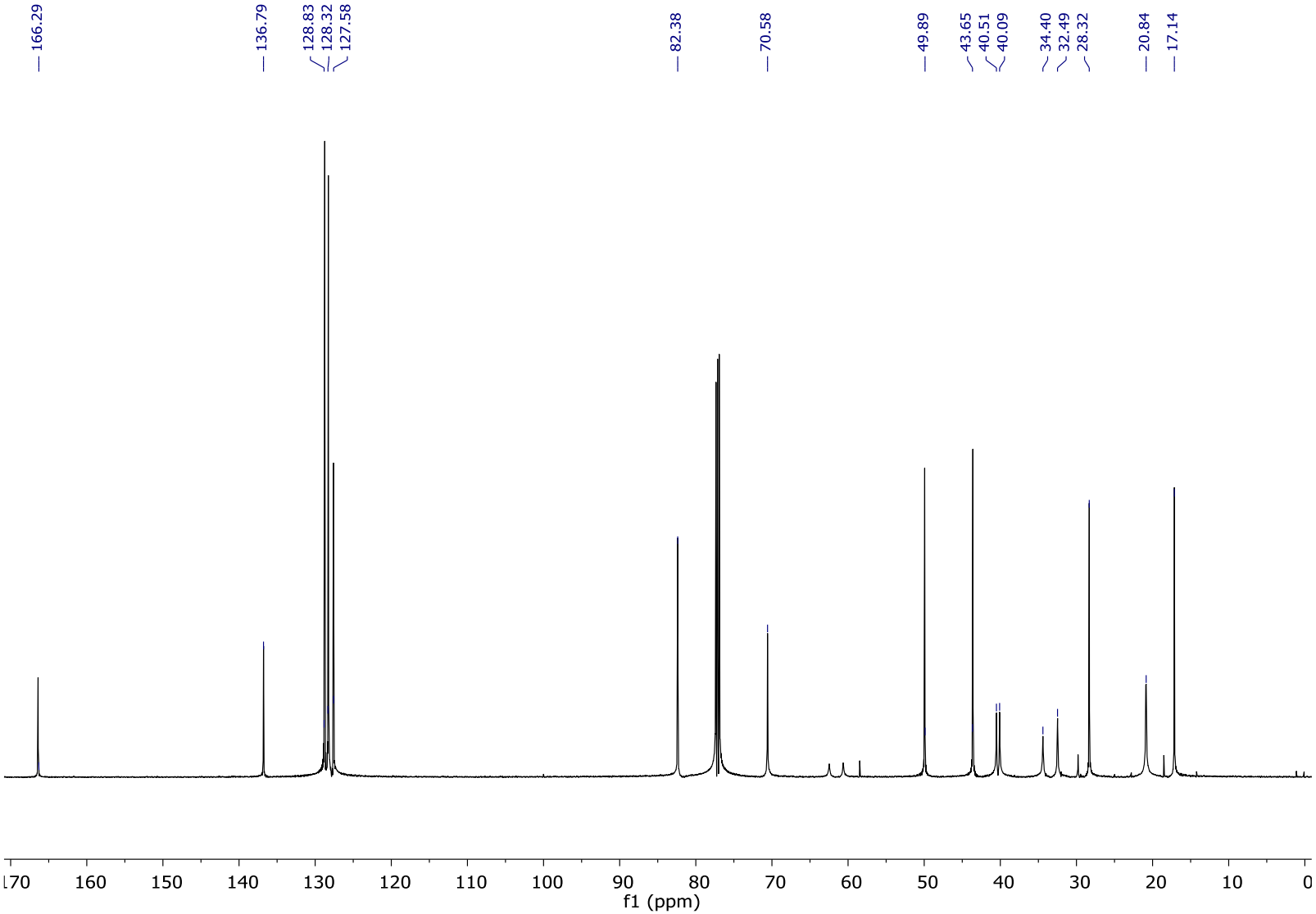
NMR spectra for 1-Benzyl-2-oxo-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)piperidin-4-yl acetate (rac-*trans*-**2**): HRMS (Fab^+).



NMR spectra for **1-benzyl-4-hydroxy-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)piperidin-2-one** (*u*)-*trans*-**3.**



NMR spectra for **1-benzyl-4-hydroxy-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)piperidin-2-one** (*u*)-*trans*-**3.**

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CENTRO DE INVESTIGACIONES QUÍMICAS

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Note : Dr.Escalante   Centro de Investigaciones Químicas UAEM

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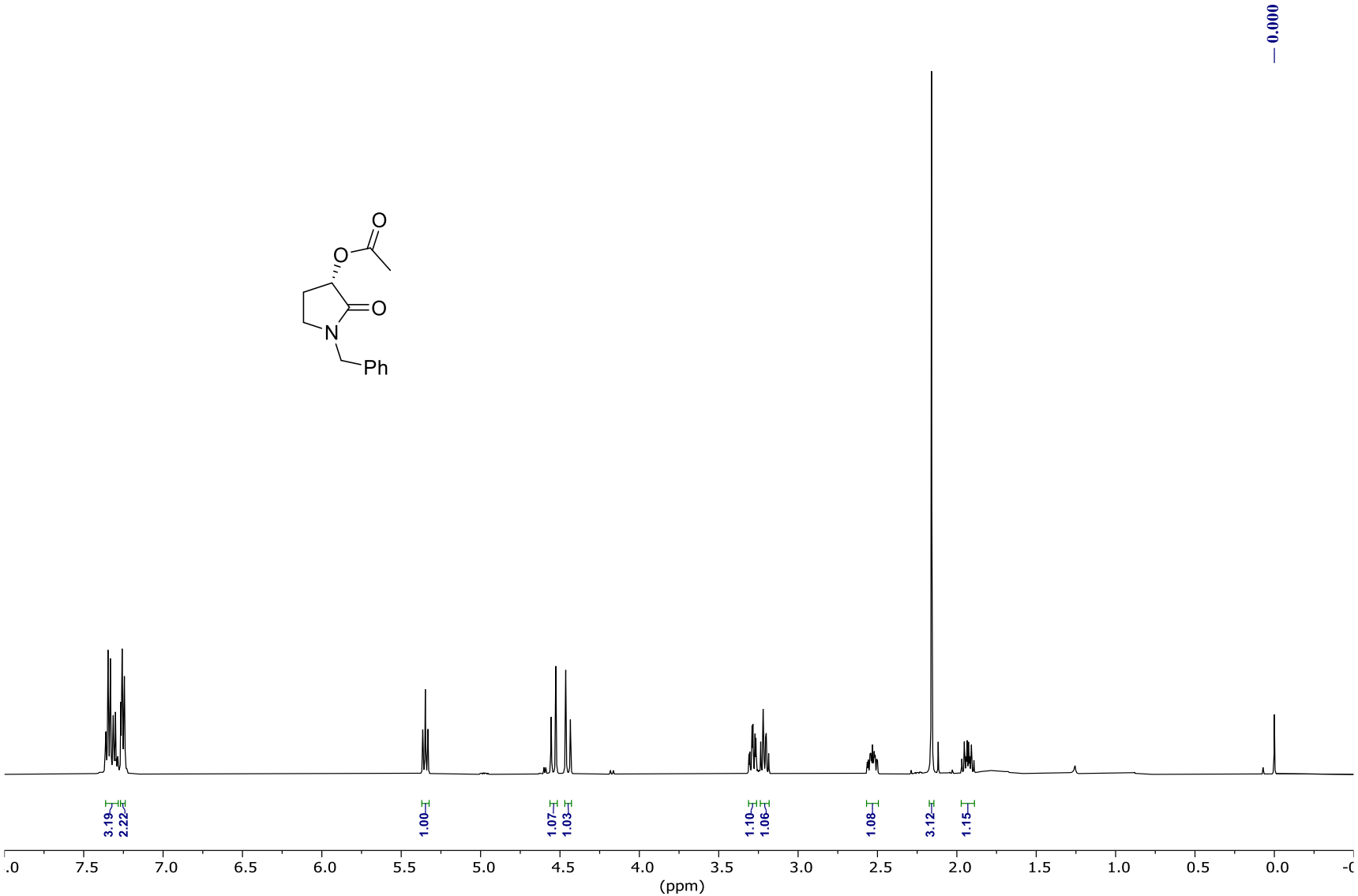
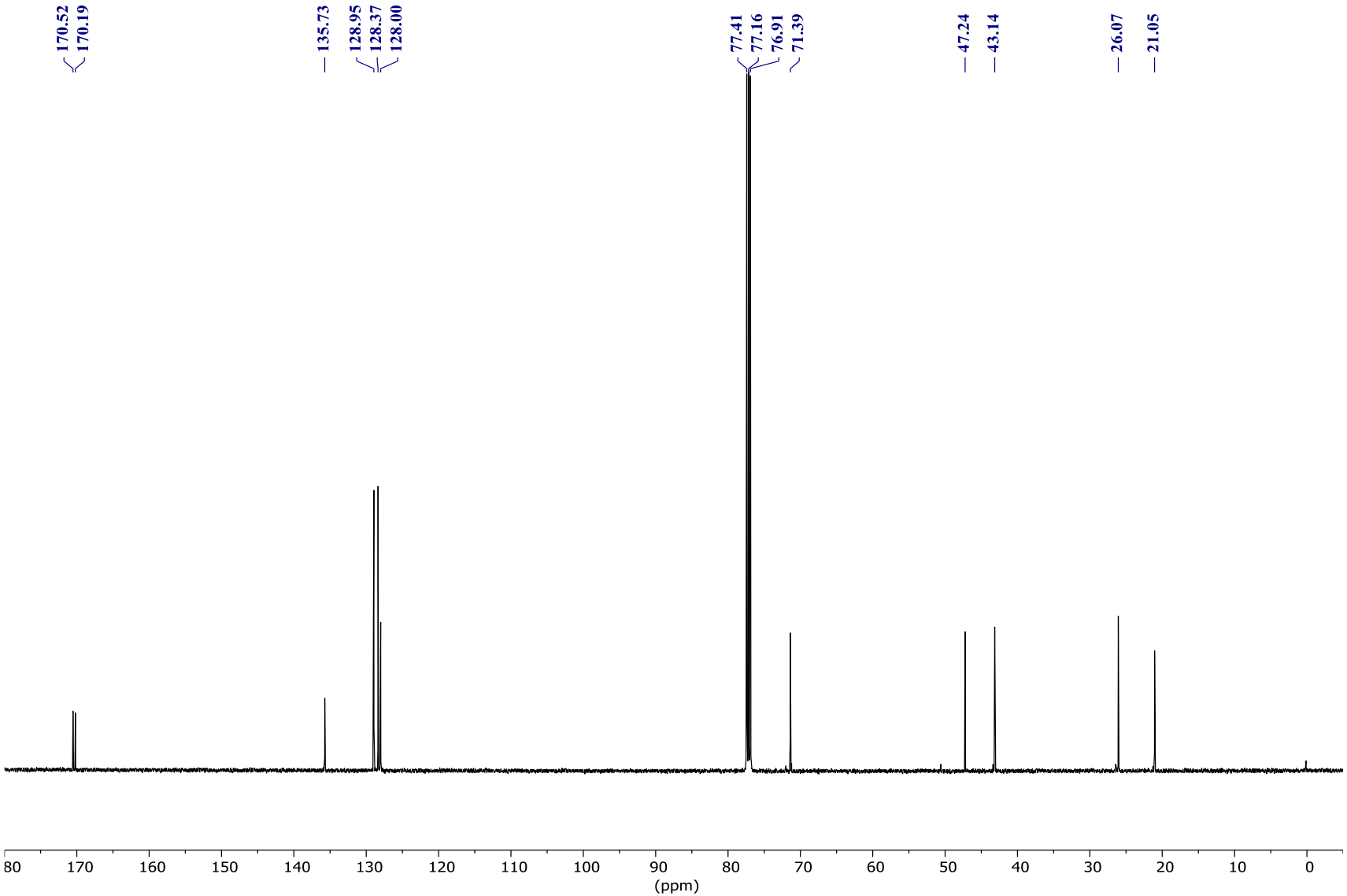
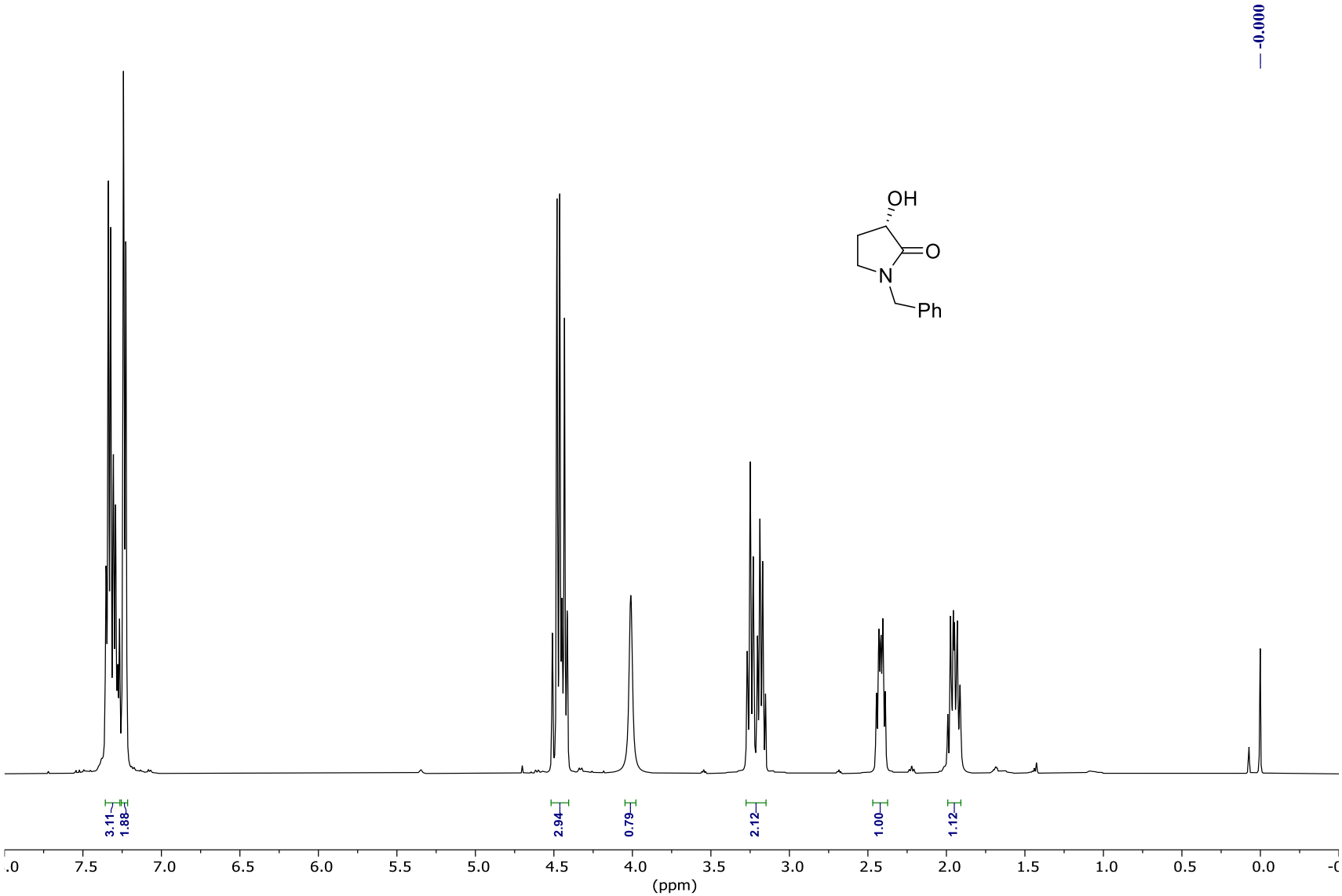


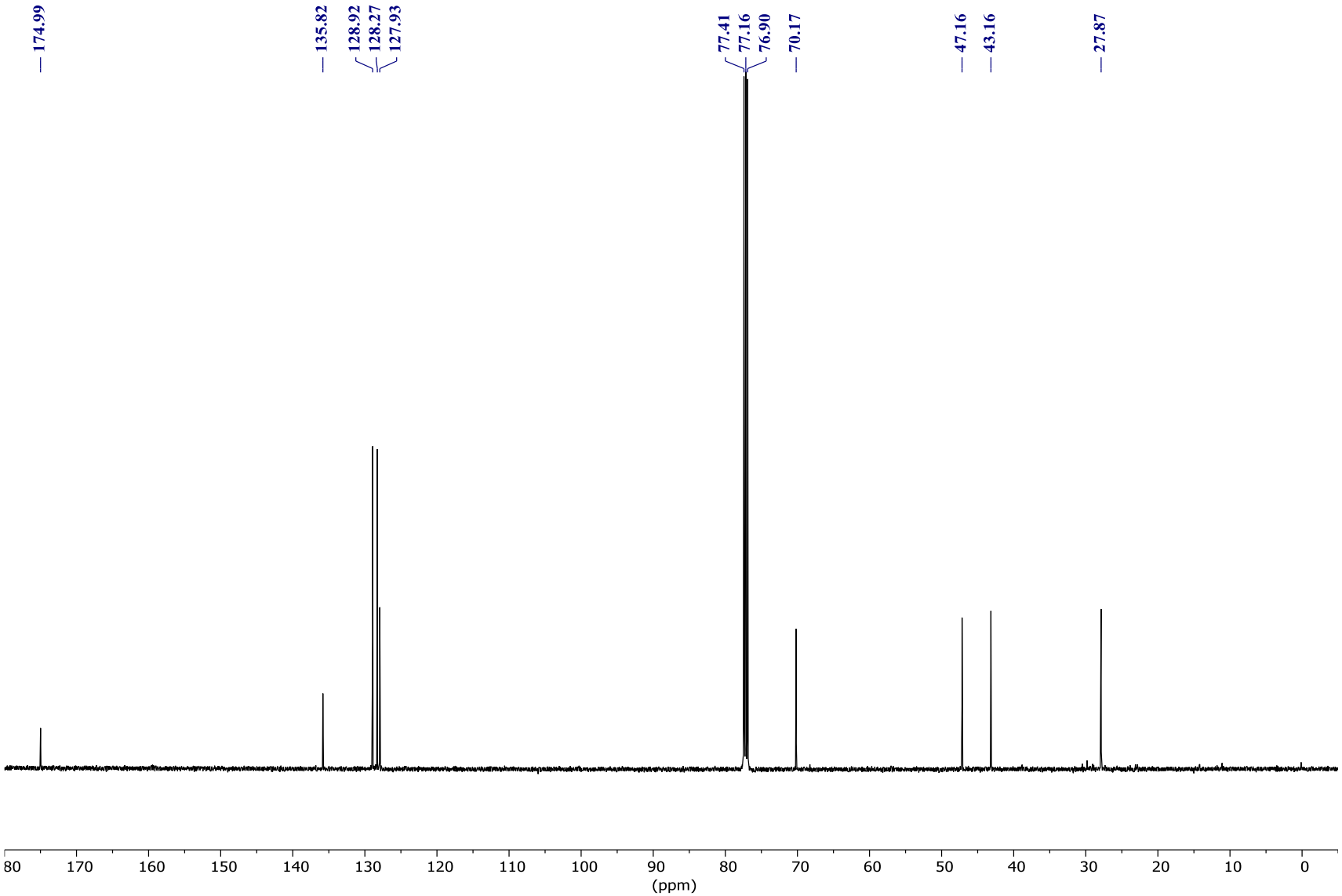
NMR spectra for (*S*)-1-Benzyl-2-oxopyrrolidin-3-yl acetate (*S*-**4**): ^{1}H-NMR (500 MHz, $CDCl_3$).



NMR spectra for (*S*)-1-Benzyl-2-oxopyrrolidin-3-yl acetate (*S*-**4**): ^{13}C-NMR (125 MHz, $CDCl_3$).



NMR spectra for (S)-1-Benzyl-3-hydroxypyrrolidin-2-one (*S*-**5**): ^{1}H-NMR (500 MHz, $CDCl_3$).



NMR spectra for (*S*)-1-Benzyl-3-hydroxypyrrolidin-2-one (*S*-**5**): ^{13}C-NMR (125 MHz, $CDCl_3$).

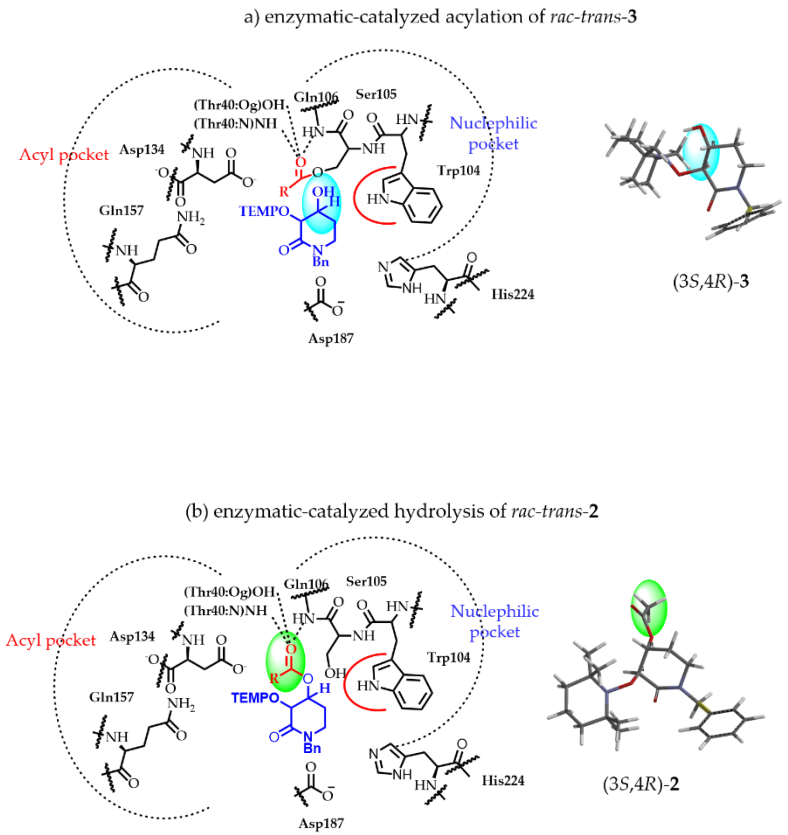


Figure S1. Schematic representation for: a) resolution of the *rac-trans*-**3** as the second substrate (for enantiomer (3*S*,4*R*)) and b) resolution of the *rac-trans*-**2** intermediate as the first substrate (for the fast-reacting enantiomer (3*S*,4*R*)-**2**).