Enzymatic Dynamic Kinetic Resolution of (±)-*cis*-*N*-(Alkoxycarbonyl)cyclopentane-1,2-diamines based on Spontaneous Racemization

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General Spectroscopic and Experimental Data

Lipase B from *Candida antarctica* (CAL-B, available immobilized on polyacrylamide as Novozyme 435, 7300 PLU/g) was supplied by Novo Nordisk Co. For the enzymatic reactions, ethyl acetate of spectrophotometric grade (stored with 4 Å molecular sieves), other anhydrous solvents and (±)-1-phenylethyl acetate were used. Thin-layer chromatography was performed on precoated TLC plates of Merck silica gel $60F_{254}$, using a potassium permanganate solution as developing reagent. Merck silica gel 60 (particle size, 40 - 63 μm) was used for column chromatography. Optical rotations were measured at the sodium D line at 20 °C. Mass spectra (*m*/*z*) were recorded in ElectronSpray Ionisation (ESI) and Electron Impact (EI). ^{1}H NMR and proton-decoupled ^{13}C NMR spectra ($CDCl_3$ solutions) were recorded using AC-300 or DPX-300 (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz) and AV-400 MHz (^{1}H, 400.13 MHz and ^{13}C, 100.63 MHz) spectrometers using the δ scale (ppm) for chemical shifts; calibration was made on the $CDCl_3$ (^{13}C, 76.95 ppm) or the residual $CHCl_3$ (^{1}H, 7.26 ppm).

Experimental Procedures

***tert*-Butyl (±)-*trans*-(2-hydroxycyclopentyl)carbamate, (±)-2a**. (±)-*trans*-2-Aminocyclopentanol hydrochloride (12.0 mmol) was dissolved in methanol (40 mL) and Na_2CO_3 (12.0 mmol) and di-*tert*-butyl dicarbonate (14.0 mmol) were added to the solution. After stirring 24 h at room temperature, solvent was evaporated and the residue extracted with CH_2Cl_2. The usual work-up of the organic phase gave pure (±)-**2a** with 83% yield. M.p.: 105.6-106.8 ºC (Lit.[1] m.p.: 103 ºC). Spectroscopic data are in good agreement with those previously published.[1]

General procedure for the synthesis of carbamates (±)-2b-d.

[1] Page, M. F. Z.; Jalisatgi, S. S.; Maderna, A.; Hawthorne, M. F. *Synthesis* **2008**, 555-563.

To a solution of 2-aminocyclopentanol hydrochloride (7.3 mmol) in water (15 mL), sodium carbonate (14.6 mmol) and the corresponding alkyl chloroformate (8.7 mmol) were added. After 24 h stirring at room temperature, the reaction mixture was extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined, washed with brine (20 mL), dried with Na_2SO_4, and evaporated under reduced pressure to give the corresponding pure product, except in the case of (±)-**2b**.

Benzyl (±)-*trans*-(2-hydroxycyclopentyl)carbamate, (±)-2b. The solid crude material was repeatedly washed with warm hexane to remove benzylic alcohol. Thus, pure product was isolated as a white solid. Yield: 94%; m.p.: 59.1-60.4 ºC (Lit.[2] m.p.: 57-59 ºC). Spectroscopic data were in good agreement with the literature.[2]

Allyl (±)-*trans*-(2-hydroxycyclopentyl)carbamate, (±)-2c. Yield: 97%; colourless oil; ^{1}H NMR (300 MHz): δ (ppm) = 1.38 (m, 1H), 1.54-1.82 (m, 3H), 1.90-2.16 (m, 2H), 3.58-3.80 [m + br s, 2H, CH-NH + OH (3.75)], 4.00 (q, 1H, ^3J = 6.3 Hz, CH-OH), 4.55 (d, 2H, ^3J = 5.5 Hz, CH_2-O), 4.93 (br s, 1H, NH), 5.21 (dd, 1H, $^3J_{cis}$ = 10.4 Hz, $|^2J|$ = 1.0 Hz, =C*H*H), 5.30 (dd, 1H, $^3J_{trans}$ = 17.2 Hz, $|^2J|$ = 1.0 Hz, =CH*H*), 5.90 (m, 1H, HC=); ^{13}C NMR (100.6 MHz): δ (ppm) = 20.4 (CH_2), 29.7 (CH_2), 31.6 (CH_2), 59.9 (CH), 65.4 (CH_2), 78.2 (CH), 117.4 (CH_2), 132.4 (CH), 156.9 (C=O); MS (ESI), *m/z* (%) = 186 (100) [M + H]$^+$; elemental analysis (%) calcd. for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56; found: C, 58.15; H, 8.34; N, 7.49.

Ethyl (±)-*trans*-(2-hydroxycyclopentyl)carbamate, (±)-2d. Yield: 92%; colourless oil; ^{1}H NMR (300 MHz): δ (ppm) = 1.23 (t, 3H, ^3J = 7.1 Hz, CH_3), 1.28-1.45 (m, 1H), 1.57-1.83 (m, 3H), 1.89-2.17 (m, 2H), 3.66 (m, 1H, CH-N), 3.88 (br s, 1H, OH), 3.98 (q, 1H, ^3J = 6.3 Hz, CH-O), 4.10 (q, 2H, ^3J = 7.1 Hz, CH_2-O), 4.87 (br s, 1H, NH); ^{13}C NMR (100.6 MHz): δ (ppm) = 14.3 (CH_3), 20.5 (CH_2), 29.9 (CH_2), 31.8 (CH_2), 60.0 (CH), 60.8 (CH_2), 78.6 (CH), 157.4 (C=O); MS (ESI), *m/z* (%) = 174 (100) [M + H]$^+$, 258 (48) [2M − NHCOOEt]$^+$; elemental analysis (%) calcd. for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09; found: C, 55.21; H, 8.45; N, 8.38.

Alkyl (±)-*cis*-(2-azidocyclopentyl)carbamates. General Procedure.

Triethylamine (30.0 mmol) and the corresponding alkyl (±)-*trans*-(2-hydroxycyclopentyl)carbamate (±)-**2a-d** (10.0 mmol) were dissolved in CH_2Cl_2 (12 mL). The solution was coolded at 0 ºC, and methanesulfonyl chloride (16.0 mmol) was added, under a nitrogen atmosphere, during 10 min. After 3 h at 0 ºC (for **2a**) or 50 min at rt (for **2b**-**d**), the solvent was eliminated under reduced pressure. The crude

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[2] Maestro, A.; Astorga, C.; Gotor, V. *Tetrahedron: Asymmetry* **1997**, *8*, 3153-3159.

was dissolved in CH_2Cl_2 and the resulting organic solution successively washed with 1 M aq. $NaHSO_4$, water and brine. After dried with Na_2SO_4, solvent was evaporated under reduced pressure yielding the corresponding (±)-*trans*-mesylate, which was used without purification in the following reaction. Thus, a mixture of the crude mesylate and NaN_3 (30.0 mmol) was dissolved in anhydrous DMF (17 mL) and the solution was heated at 50 ºC for 24 h. After this time, CH_2Cl_2 was added and the organic solution repeatedly washed with water. The organic layer was dried with Na_2SO_4, the solvents were eliminated, and the resulting crude was purified by flash chromatography (hexane-ethyl acetate 6:1) to yield the pure product.

***tert*-Butyl (±)-*cis*-(2-azidocyclopentyl)carbamate, (±)-3a**. Yield: 54%; m.p.: 75.3-76.4 ºC. Spectroscopic data are in good agreement with those previously published for optically active **3a**.[3]

Benzyl (±)-*cis*-(2-azidocyclopentyl)carbamate, (±)-3b. Yield: 69%; colourless oil; ^{1}H NMR (300 MHz): δ (ppm) = 1.45 (m, 1H), 1.63 (m, 1H), 1.72-2.06 (m, 4H), 4.03 (m, 2H, H-1 and H-2), 5.03 (br s, 1H, NH), 5.11 (AB system, 2H, $|^2J|$ = 12.3 Hz, CH_2-O), 7.36 (m, 5H); ^{13}C NMR (75.5 MHz): δ (ppm) = 19.7 (CH_2), 28.6 (CH_2), 28.8 (CH_2), 54.9 (CH), 64.0 (CH), 66.6 (CH_2), 127.89 (CH), 127.92 (CH), 128.3 (CH), 136.2 (C), 155.7 (C=O); MS (ESI), *m/z* (%) = 283 (92) $[M + Na]^+$, 233 (45) 102 (100); elemental analysis calcd. for $C_{13}H_{16}N_4O_2$: C, 59.99; H, 6.20; N, 21.52; found: C, 60.27; H, 6.03; N, 21.80.

Allyl (±)-*cis*-(2-azidocyclopentyl)carbamate, (±)-3c. Yield: 67%; colourless oil; ^{1}H NMR (400 MHz): δ (ppm) = 1.45 (m, 1H), 1.56-1.64 (m, 1H), 1.72-2.11 (m, 4H), 4.01 (br s, 2H, H-1 and H-2), 4.56 (d, 2H, ^3J = 5.4 Hz, CH_2-O), 5.00 (br s, 1H, NH), 5.20 (dd, 1H, $^3J_{cis}$ = 10.4 Hz, $|^2J|$ = 1.4 Hz, =C*H*H), 5.30 (dd, 1H, $^3J_{trans}$ = 17.2 Hz, $|^2J|$ = 1.4 Hz, =CH*H*), 5.91 (m, 1H, HC=); ^{13}C NMR (100.6 MHz): δ (ppm) = 19.7 (CH_2), 28.5 (CH_2), 28.8 (CH_2), 54.9 (CH), 64.0 (CH_2), 65.4 (CH), 117.4 (CH_2), 132.6 (CH), 155.6 (C=O); MS (ESI), *m/z* (%) = 211 (60) $[M + H]^+$, 183 (100); elemental analysis calcd. for $C_9H_{14}N_4O_2$: C, 51.42; H, 6.71; N, 26.65; found: C, 51.26; H, 6.97; N, 26.43.

Ethyl (±)-*cis*-(2-azidocyclopentyl)carbamate, (±)-3d. Yield: 68%; colourless oil; ^{1}H NMR (400 MHz): δ (ppm) = 1.21 (t, 3H, ^3J = 7.1 Hz), 1.36-1.48 (m, 1H), 1.52-1.64 (m, 1H), 1.72-1.96 (m, 4H), 3.98 (m, 2H), 4.08 (q, 2H, ^3J = 7.1 Hz), 4.99 (br s, 1H, NH); ^{13}C NMR (100.6 MHz): δ (ppm) = 14.4 (CH_3), 19.8 (CH_2), 28.7 (CH_2), 28.9 (CH_2), 54.9 (CH), 60.8 (CH_2), 64.1 (CH), 156.0 (C=O); MS (ESI), *m/z* (%) = 199 (58) $[M + H]^+$, 171 (100); elemental analysis calcd. for $C_8H_{14}N_4O_2$: C, 48.47; H, 7.12; N, 28.26; found: C, 48.25; H, 7.00; N, 28.39.

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[3] Govindaraju, T.; Kumar, V. A.; Ganesh, K. N. *J. Org. Chem.* **2004**, *69*, 5725-5734.

***tert*-Butyl (±)-*cis*-(2-aminocyclopentyl)carbamate, (±)-5a**. A suspension of (±)-**3a** (2.20 mmol) and Pd-C (10%, 230 mg) in deoxygenated methanol (30 mL) was stirred for 23 h under a hydrogen atmosphere. The reaction mixture was filtered through Celite®, and the filtrate was evaporated to yield a crude, which was purified by flash chromatography (ethyl acetate and ethyl acetate:methanol 4:1 were successively used as eluents). Yield: 79%; colourless oil; ^{1}H NMR (400 MHz): δ (ppm) = 1.30-1.55 (m + s, 12H. Singlet to 1.39 corresponds to Bu^t), 1.69 (m, 1H), 1.89 (m, 2H), 2.23 (br s, 2H, NH_2), 3.29 (q, 1H, ^3J = 5.7 Hz, H-2), 3.76 (br m, 1H, H-1), 5.14 (br s, 1H, NH); ^{13}C NMR (100.6 MHz): δ (ppm) = 20.2 (CH_2), 28.2 (3×CH_3), 29.7 (CH_2), 32.4 (CH_2), 53.0 (CH), 54.6 (CH), 78.9 (C), 155.8 (C=O); MS (ESI), *m/z* (%) = 201 (100) $[M + H]^+$; elemental analysis calcd. for $C_{10}H_{20}N_2O_2$: C, 59.97; H, 10.07; N, 13.99; found: C, 60.23; H, 10.33; N, 13.81.

General procedure for the Staudinguer reduction of (±)-*cis*-(2-azidocyclopentyl)carbamates 3b-d.

Triphenylphosphine (4.32 g, 16.5 mmol) was added to a solution of the corresponding azidocarbamate (±)-**3b-d** (13.8 mmmol) in THF-H_20 (10:1, 55 mL). After stirring at room temperature during 72h, solvents were eliminated under reduced pressure and the resulting crude was purified by flash chromatography (a gradient of ethyl acetate to ethyl acetate-methanol was used as eluent).

Benzyl (±)-*cis*-(2-aminocyclopentyl)carbamate, (±)-5b. Yield: 89%; white solid; m.p.: 61.6-63.0 ºC; ^{1}H NMR (300 MHz): δ (ppm) = 1.30-1.62 [m + s, 5H. Singlet corresponds to NH_2 (1.45)], 1.74 (m, 1H), 1.84-2.02 (m, 2H), 3.34 (m, 1H, H-2), 3.84 (m, 1H, H-1), 5.09 (s, 2H, CH_2-O), 5.38 (br d, 1H, ^3J = 6.5 Hz, NH), 7.20-7.40 (m, 5H); ^{13}C NMR (75 MHz): δ (ppm) = 19.6 (CH_2), 28.8 (CH_2), 31.8 (CH_2), 52.5 (CH), 54.6 (CH), 65.6 (CH_2), 127.2 (CH), 127.3 (CH), 127.7 (CH), 136.0 (C), 155.7 (C=O); MS (ESI), *m/z* (%) = 235 (100) $[M + H]^+$, 257 (40) $[M + Na]^+$, 469 (60) $[2M + H]^+$; elemental analysis calcd. for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96; found: C, 66.39; H, 7.98; N, 12.15.

Allyl (±)-*cis*-(2-aminocyclopentyl)carbamate, (±)-5c. Yield: 84%; colourless oil; ^{1}H NMR (400 MHz): δ (ppm) = 1.39 (m, 1H), 1.45-1.59 (m, 4H, NH_2 + 2H), 1.64-1.78 (m, 1H), 1.84-1.98 (m, 2H), 3.35 (q, 1H, ^3J = 5.6 Hz, H-2), 3.81 (br m, 1H, H-1), 4.55 (br s, 2H, CH_2-O), 5.19 (d, 1H, $^3J_{cis}$ = 10.3 Hz, =C*H*H), 5.29 (dd, 1H, $^3J_{trans}$ = 17.2 Hz, $|^2J|$ = 1.3 Hz, =CH*H*), 5.35 (br s, 1H, NH), 5.91 (ddt, 1H, $^3J_{trans}$ = 17.2 Hz, $^3J_{cis}$ = 10.3 Hz, ^3J = 5.6 Hz, HC=); ^{13}C NMR (100.6 MHz): δ (ppm) = 19.6 (CH_2), 28.8 (CH_2), 31.7 (CH_2), 52.4 (CH), 54.4 (CH), 64.4 (CH_2), 116.4 (CH_2), 132.3 (CH), 155.5 (C=O); MS (ESI), *m/z* (%) = 185 (100) $[M + H]^+$; elemental analysis calcd. for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21; found: 58.39; H, 8.97; N, 15.45.

Ethyl (±)-*cis*-(2-aminocyclopentyl)carbamate, (±)-5d. Yield: 79%; colourless oil; ^{1}H NMR (400 MHz): δ (ppm) = 1.22 (t, 3H, ^3J = 7.1 Hz), 1.37 (m, 1H), 1.56 (m, 2H), 1.62-1.80 [br s + m, 3H, br s corresponds to NH_2 (1.66)], 1.94 (m, 2H), 3.33 (q, 1H, ^3J = 5.6 Hz, H-2), 3.81 (br m, 1H, H-1), 4.08 (q, 2H, ^3J = 7.1 Hz), 5.25 (br d, 1H, NH, ^3J = 6.1 Hz); ^{13}C NMR (100.6 MHz): δ (ppm) = 14.2 (CH_3), 20.0 (CH_2), 29.4 (CH_2), 32.4 (CH_2), 52.8 (CH), 54.8 (CH), 60.1 (CH_2), 156.2 (C=O); MS (ESI), *m/z* (%) = 173 (100) $[M + H]^+$; elemental analysis calcd. for $C_8H_{16}N_2O_2$: C, 55.79; H, 9.36; N, 16.27; found: C, 55.68; H, 9.59; N, 16.08.

Enzymatic kinetic resolution of *tert*-butyl (±)-(2-aminocyclopentyl)carbamate, (±)-5a.

tert-Butyl methyl ether (5.0 mL) and (±)-1-phenylethyl acetate (3.0 mmol) were added under nitrogen atmosphere to a mixture of racemic amino carbamate (±)-**5a** (200 mg, 1.0 mmol), CAL-B (100 mg) and 4 Å molecular sieves (25 mg). The suspension was shaken at 28 ºC and 200 rpm during 6 days. The solvent was removed under vacuum, CH_2Cl_2 was added to the suspension and the enzyme filtered. After, the enzyme was successively washed with CH_2Cl_2 and aq. 3N NaOH. Both layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). All the organic layers were combined, dried with Na_2SO_4 and concentrated in vacuo to give a residue. Flash chromatography (hexane:ethyl acetate 1:1, ethyl acetate and ethyl acetate:methanol 4:1 were successively used as eluents) of the residue yielded pure enantioenriched compounds **5a** and **6a**.

***tert*-Butyl (1*R*,2*S*)-(2-aminocyclopentyl)carbamate, (1*R*,2*S*)-5a**. Yield: 41%. $[\alpha]_D^{20}$ = +7.8, ee = 97%.

***tert*-Butyl (1*S*,2*R*)-[(2-acetylamino)cyclopentyl]carbamate, (1*S*,2*R*)-6a**. Yield: 45%; white solid; m.p.: 118.9-120.2 ºC; $[\alpha]_D^{20}$ = +11.4 (*c* 1.0 in $CHCl_3$), ee = 98%; ^{1}H NMR (300 MHz): δ (ppm) = 1.40-1.85 [m + s, 13H. Singlet corresponds to Bu^t (1.44)], 1.90-2.20 [m + s, 5H. Singlet corresponds to CH_3 (1.96)], 3.94 (quintet, 1H, ^3J = 6.2 Hz, H-1), 4.13 (br m, 1H, H-2), 4.76 (br s, 1H, NH), 6.11 (br s, 1H, NH); ^{13}C NMR (100.6 MHz): δ (ppm) = 20.0 (CH_2), 23.1 (CH_3), 28.2 (3×CH_3), 29.4 (CH_2), 29.8 (CH_2), 52.9 (CH), 53.4 (CH), 79.2 (C), 156.2 (C=O) 170.4 (C=O, Ac); MS (ESI), *m/z* (%) = 243 (45) $[M + H]^+$, 485 (100) $[2M + Na]^+$; HRMS (EI) calcd. for $C_{10}H_{17}NO_2$ $[M - (CH_2{=}C{=}O) - (NH_3)]^{\bullet+}$: 183.1259; found: 183.1255. Elemental analysis calcd. for $C_{12}H_{22}N_2O_3$: C, 59.48; H, 9.15; N, 11.56; found: C, 59.63; H, 9.02; N, 11.79.

Enzymatic dynamic kinetic resolution of alkyl (±)-(2-aminocyclopentyl)carbamates (±)-5a-d.

To a mixture of racemic amino carbamate (±)-**5a**-**d** (1.2 mmol) and CAL-B (120 mg) under a nitrogen atmosphere, a mixture of anhydrous TBME-Et_3N (10:1; 7.2 mL) and (±)-1-phenylethyl acetate (575 μL,

3.6 mmol) were added. The suspension was circularly shaken at 50 ºC and 200 rpm during 9 days. After, the enzyme was filtered and washed with methanol. Once solvents were eliminated, the crude was submitted to flash chromatography (a gradient of hexane-ethyl acetate 10:1 to ethyl acetate was used as eluent) to yield pure the corresponding acetamide.

Benzyl (1*S*,2*R*)-[(2-acetylamino)cyclopentyl]carbamate, (1*S*,2*R*)-6b. Yield: 94%; white solid; m.p.: 143.3-144.7 ºC; $[\alpha]_D^{20}$ = +61.2 (*c* 1.0 in $CHCl_3$), ee = 96%; ^{1}H NMR (300 MHz): δ (ppm) = 1.42-1.75 (m, 4H), 1.91 (s, 3H), 2.07 (m, 2H), 4.02 (quintet, 1H, ^3J = 5.8 Hz), 4.18 (quintet, 1H, ^3J = 5.8 Hz), 5.02 (br s, 1H, NH), 5.10 (s, 2H, CH_2-O), 5.98 (br s, 1H, NH), 7.35 (m, 5H, Ph); ^{13}C NMR (75.5 MHz): δ (ppm) = 20.1 (CH_2), 23.1 (CH_3), 29.4 (CH_2), 29.9 (CH_2), 53.0 (CH), 54.1 (CH), 66.7 (CH_2), 128.0 (CH), 128.4 (CH), 136.3 (C), 156.6 (C=O), 170.6 (C=O, Ac); MS (ESI), *m/z* (%) = 277 (100) $[M + H]^+$, 553 (38) $[2M + H]^+$; HRMS (EI) calcd. for $C_{15}H_{20}N_2O_3$ ($M^{\bullet+}$): 276.1474; found: 276.1479.

Allyl (1*S*,2*R*)-[(2-acetylamino)cyclopentyl]carbamate, (1*S*,2*R*)-6c. Yield: 85%; white solid; m.p.: 107.2-108.5 ºC; $[\alpha]_D^{20}$ = +20.4 (*c* 1.0 in $CHCl_3$), ee = 97%; ^{1}H NMR (300 MHz): δ (ppm) = 1.42-1.78 (m, 4H), 1.90-2.20 [m + s, 5H. Singlet corresponds to CH_3 (2.00)], 4.01 (br s, 1H, H-1), 4.19 (br m, 1H, H-2), 4.56 (d, 2H, ^3J = 5.5 Hz), 5.02 (br s, 1H, NH), 5.22 (dd, 1H, $^3J_{cis}$ = 10.4 Hz, $|^2J|$ = 1.4 Hz, =C*H*H), 5.32 (dd, 1H, $^3J_{trans}$ = 17.2 Hz, $|^2J|$ = 1.4 Hz, =CH*H*), 5.92 (m, 1H, =CH), 6.13 (br s, 1H, NH); ^{13}C NMR (75.5 MHz): δ (ppm) = 20.1 (CH_2), 23.1 (CH_3), 29.4 (CH_2), 30.0 (CH_2), 53.0 (CH), 54.0 (CH), 65.6 (CH_2), 117.7 (CH_2), 132.7 (CH), 156.5 (C=O), 170.7 (C=O, Ac); MS (ESI), *m/z* (%) = 249 (80) [M + Na]$^+$, 475 (100) $[2M + Na]^+$; HRMS (EI) calcd. for $C_9H_{13}NO_2$ $[M - (CH_2{=}C{=}O) - (NH_3)]^{\bullet+}$: 167.0946; found: 155.0949. Elemental analysis calcd. for $C_{11}H_{18}N_2O_3$: C, 58.39; H, 8.02; N, 12.38; found: C, 58.12; H, 8.31; N, 12.09.

Ethyl (1*S*,2*R*)-[(2-acetylamino)cyclopentyl]carbamate, (1*S*,2*R*)-6d. Yield: 72%; white solid; m.p.: 125.6-127.3 ºC; $[\alpha]_D^{20}$ = +19.9 (*c* 1.0 in $CHCl_3$), ee = 95%; ^{1}H NMR (300 MHz): δ (ppm) = 1.24 (t, 3H, ^3J = 7.1 Hz), 1.42-1.80 (m, 3H), 1.90-2.18 [m + s, 5H. Singlet corresponds to CH_3 (1.97)], 3.99 (quintet, 1H, ^3J = 6.1 Hz), 4.10-4.30 [q + m, 3H. Quartet corresponds to CH_2-O (4.11 ppm, ^3J = 7.2 Hz)], 5.03 (br s, 1H, NH), 6.10 (br s, 1H, NH); ^{13}C NMR (75.5 MHz): δ (ppm) = 14.5 (CH_3), 20.0 (CH_2) 23.1 (CH_3), 29.5 (CH_2), 30.0 (CH_2), 52.8 (CH), 53.8 (CH), 60.7 (CH_2), 156.9 (C=O), 170.7 (C=O, Ac); MS (ESI), *m/z* (%) = 237 (100) [M + Na]$^+$; HRMS (EI) calcd. for $C_8H_{13}NO_2$ $[M - (CH_2{=}C{=}O) - (NH_3)]^{\bullet+}$: 155.0946; found: 155.0951. Elemental analysis calcd. for $C_{10}H_{18}N_2O_3$: C, 56.06; H, 8.47; N, 13.07; found: C, 56.29; H, 8.53; N, 12.89.

Determination of the enantiomeric excesses.

The ee for each optically active compound involved in the enzymatic reactions was determined by chiral HPLC using Chiralpak IA (25 cm × 4.6 mm i.d.) or Chiralpak AS (25 cm × 4.6 mm i.d.) columns.

The products isolated from the enzymatic reactions, that is, acetamides, were directly analyzed:

For *tert*-butyl (±)-2-[(acetylamino)cyclopentyl]carbamate: Chiralpak AS, hexane/ethanol 93:7, 0.8 mL/min, 20 ºC; t_R = 10.0 (1*S*,2*R*) and 11.4 (1*R*,2*S*) min; R_S = 1.3.

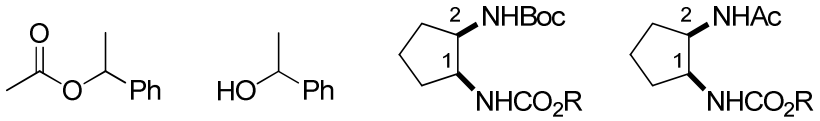
For benzyl (±)-2-[(acetylamino)cyclopentyl]carbamate: Chiralpak AS, hexane/ethanol 90:10, 0.8 mL/min, 20 ºC; t_R = 13.9 (1*S*,2*R*) and 18.7 (1*R*,2*S*) min; R_S = 2.3. At 30 ºC; t_R = 13.0 (1*S*,2*R*) and 16.4 (1*R*,2*S*) min; R_S = 2.9.

For allyl (±)-2-[(acetylamino)cyclopentyl]carbamate: Chiralpak IA, hexane/ethanol 94:6, 1.0 mL/min, 25 ºC; t_R = 14.3 (1*S*,2*R*) and 15.9 (1*R*,2*S*) min; R_S = 1.5.

For ethyl (±)-2-[(acetylamino)cyclopentyl]carbamate: Chiralpak IA, hexane/ethanol 96:4, 0.9 mL/min, 25 ºC; t_R = 24.3 (1*S*,2*R*) and 26.3 (1*R*,2*S*) min; R_S = 1.3.

In order to analyze the ee of the remaining substrate isolated in the reaction of amino-Boc **5a**, it was previously transformed into the acetamide (acetyl chloride, Et_3N, CH_2Cl_2). For the other remaining amino carbamates, see below.

Monitorization of the enzymatic DKRs of alkyl (±)-*cis*-2-(aminocyclopentyl)carbamates (±)-5b-d: Aliquots of 50 μL were taken periodically and treated with di-*tert*-butyl dicarbonate (Boc_2O). After 5 min, organic solvents were eliminated obtaining a crude, which consisted of a mixture of four compounds: 1-phenylethyl acetate, 1-phenylethanol, biscarbamate (alkyl *tert*-butyl cyclopentane-1,2-diylbiscarbamate proceeding from the reaction of the remaining amino carbamate with Boc_2O) and acetamide (see below).



b: R = Bn; **c**: R = Allyl; **d**: R = Et

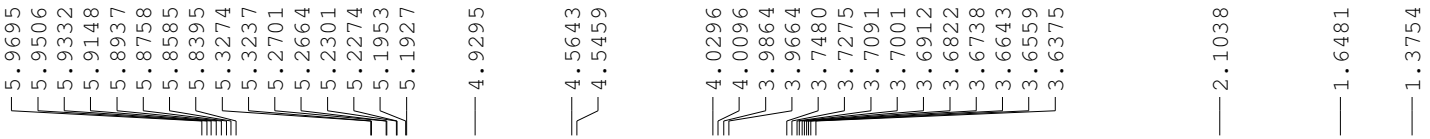
These crudes were analyzed by chiral HPLC and conditions and reaction times were as follows:

Reactions using (±)-5b as substrate: Chiralpak IA, hexane/ethanol 96:4 (7 min) and then, 85:15, 30 ºC, 0.8 mL/min. (±)-1-Phenylethyl acetate: t_R = 4.9 (*R*) and 5.2 (*S*) min, R_S = 1.4. (±)-1-Phenylethanol: t_R =

9.2 (*R*) and 9.7 (*S*) min; R_S = 1.5. (±)-Biscarmate: t_R = 13.6 (1*S*,2*R*) and 18.8 (1*R*,2*S*) min; R_S = 11.3. (±)-Acetamide: t_R = 16.4 (1*S*,2*R*) and 17.0 (1*R*,2*S*) min; R_S = 1.5.

Reaction using (±)-5c as substrate: Chiralpak IA, hexane/ethanol 94:6, 20 ºC, 0.8 mL/min. (±)-1-Phenylethyl acetate: t_R = 5.0 (*R*) and 5.3 (*S*) min. (±)-1-Phenylethanol: t_R = 8.0 (*R*) and 8.4 (*S*) min. (±)-Biscarmate: t_R = 11.2 (1*S*,2*R*) and 14.1 (1*R*,2*S*) min; R_S = 4.9. (±)-Acetamide: t_R = 20.0 (1*S*,2*R*) and 22.6 (1*R*,2*S*) min; R_S = 1.8.

Reaction using (±)-5d as substrate: Chiralpak IA, hexane/ethanol 96:4, 20 ºC, 0.8 mL/min. (±)-1-Phenylethyl acetate: t_R = 5.2 (*R*) and 5.5 (*S*) min. (±)-1-Phenylethanol: t_R = 9.7 (*R*) and 10.3 (*S*) min. (±)-Biscarmate: t_R = 14.3 (1*S*,2*R*) and 16.5 (1*R*,2*S*) min; R_S = 3.4. (±)-Acetamide: t_R = 32.3 (1*S*,2*R*) and 36.3 (1*R*,2*S*) min; R_S = 1.7.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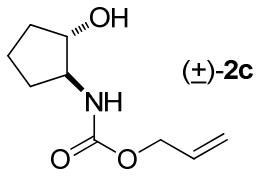
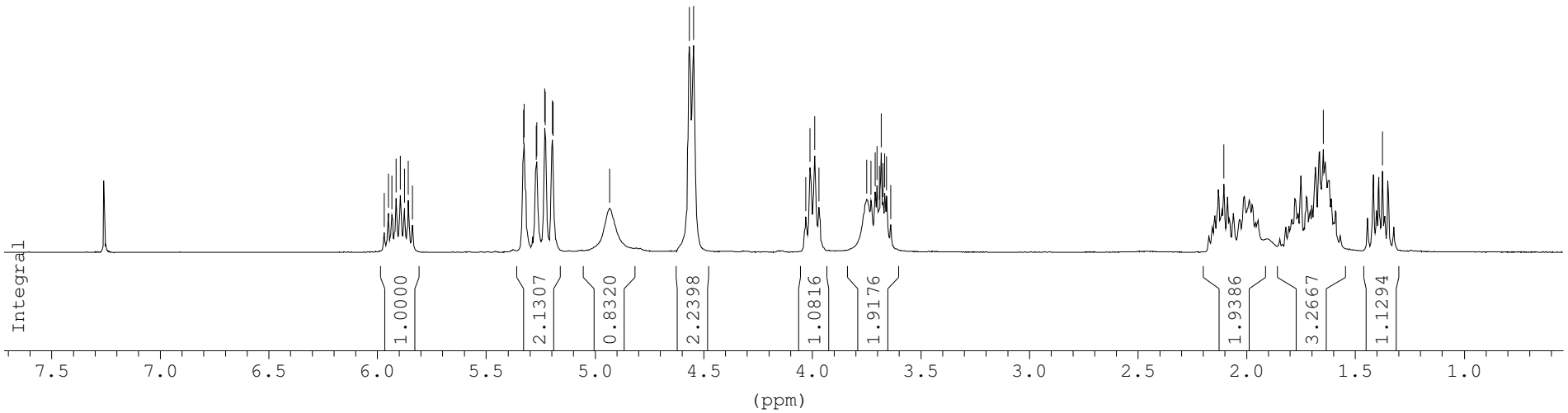
5.9332
5.9148
5.8937
5.8758
5.8585
5.8395
5.3274
5.3237
5.2701
5.2664
5.2301
5.2274
5.1953
5.1927
4.9295
4.5643
4.5459
4.0296
4.0096
3.9864
3.9664
3.7480
3.7275
3.7091
3.7001
3.6912
3.6822
3.6738
3.6643
3.6559
3.6375
2.1038
1.6481
1.3754


OH
NH
O
O

(±)-**2c**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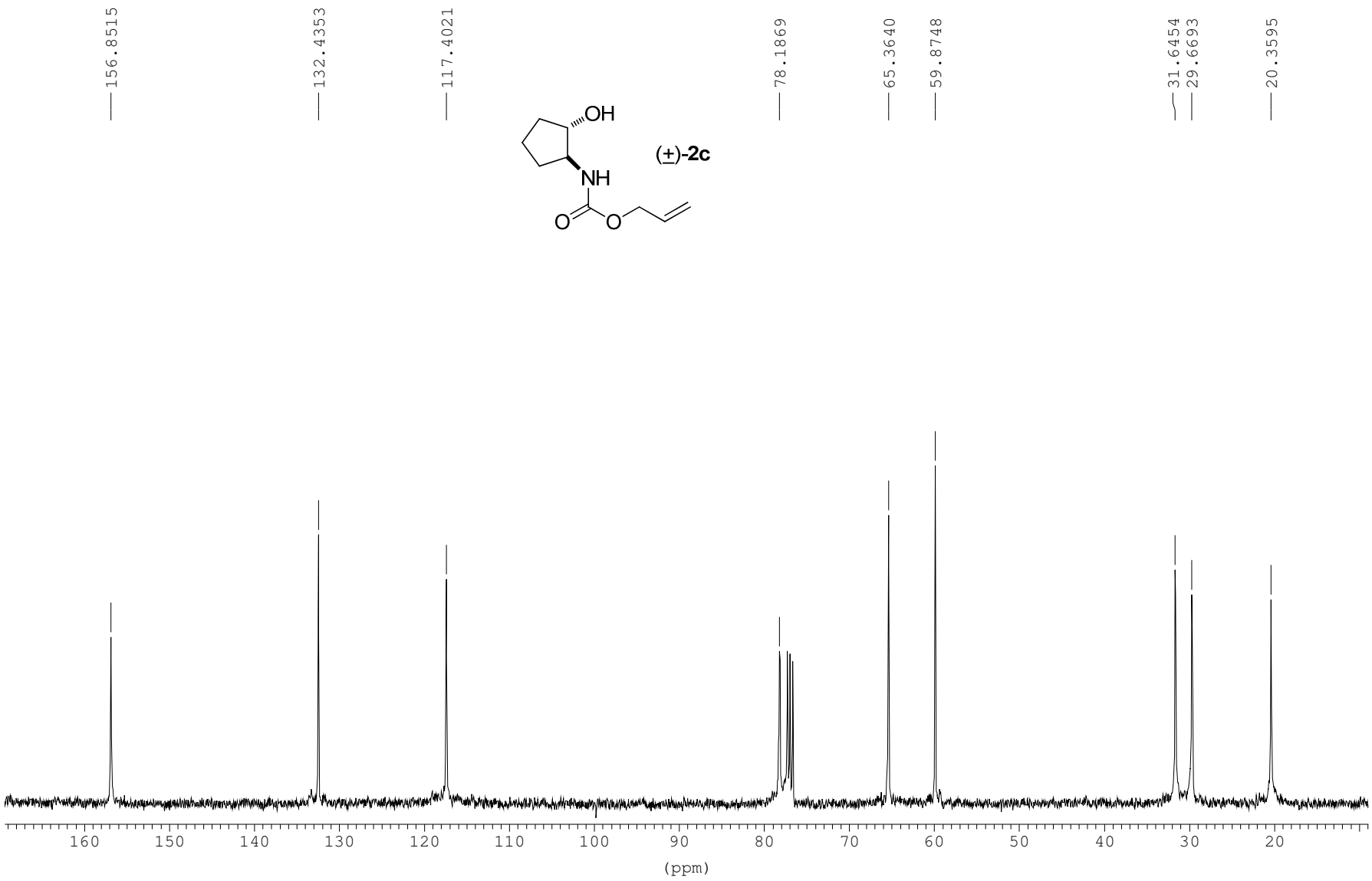
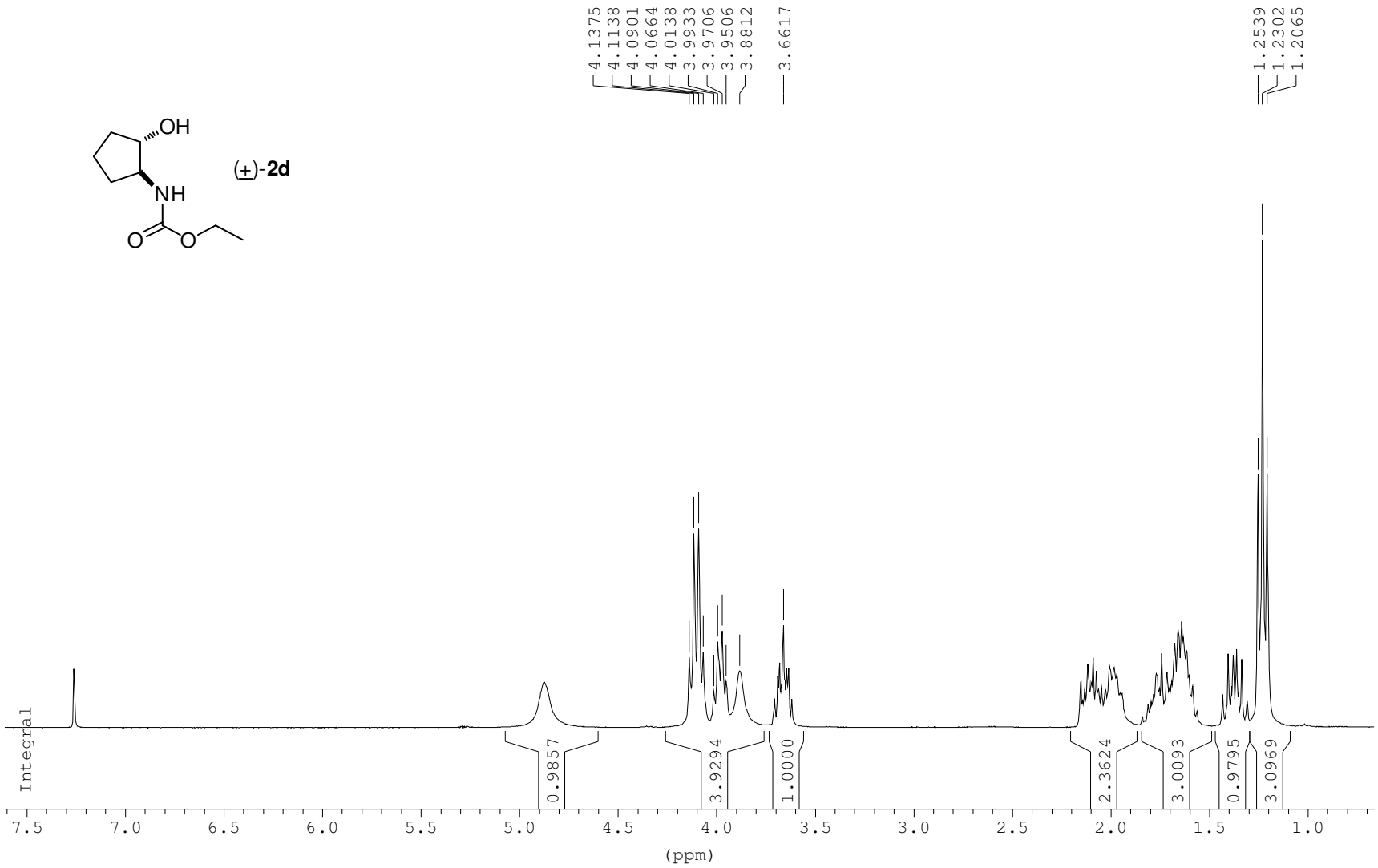
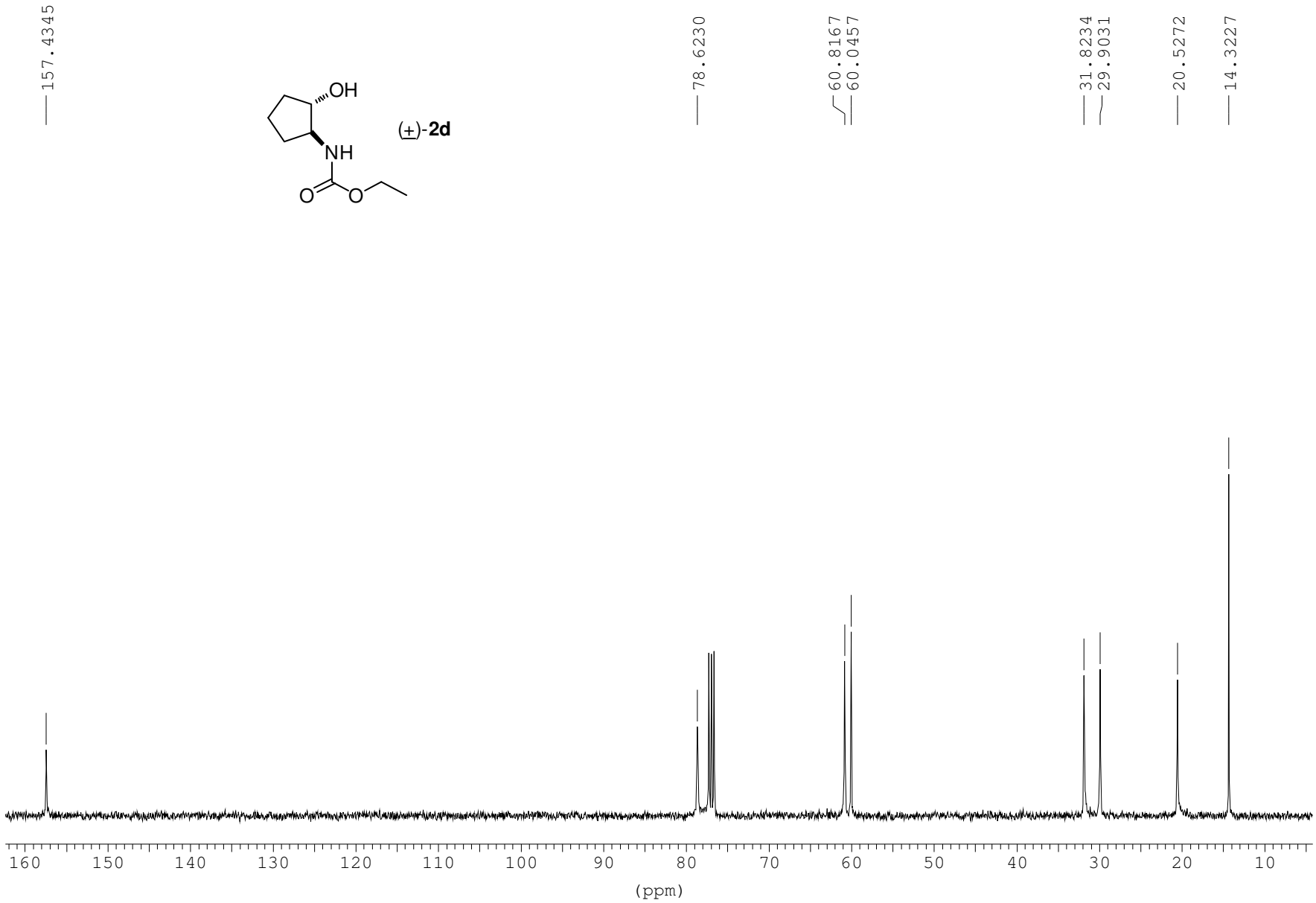
0.8320
2.2398
1.0816
1.9176
1.9386
3.2667
1.1294
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)


156.8515
132.4353
117.4021
78.1869
65.3640
59.8748
31.6454
29.6693
20.3595
OH
NH
O
O
(±)-2c
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
(ppm)


OH
NH
O
O
(±)-2d
4.1375
4.1138
4.0901
4.0664
4.0138
3.9933
3.9706
3.9506
3.8812
3.6617
1.2539
1.2302
1.2065
Integral
0.9857
3.9294
1.0000
2.3624
3.0093
0.9795
3.0969
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
(ppm)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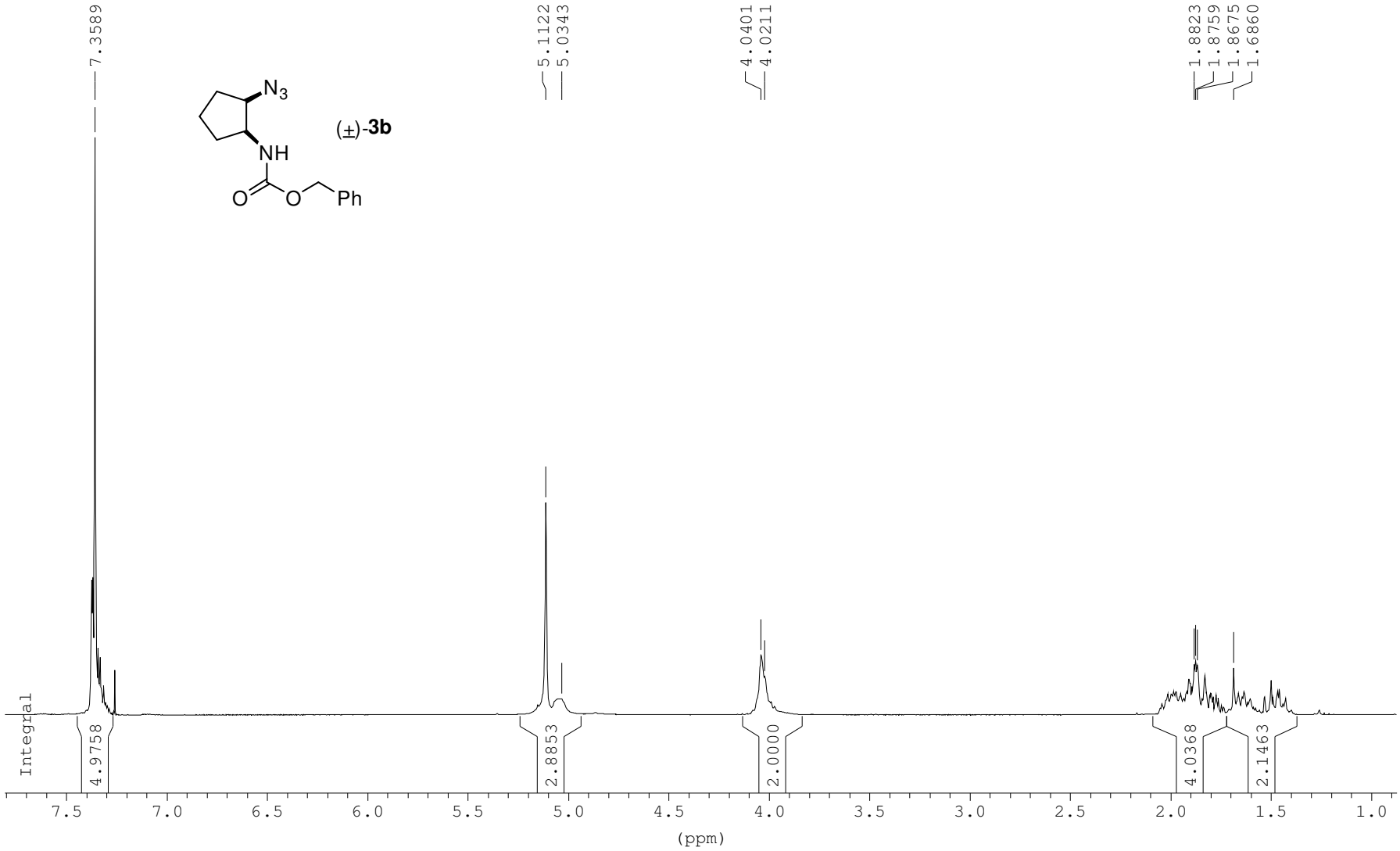
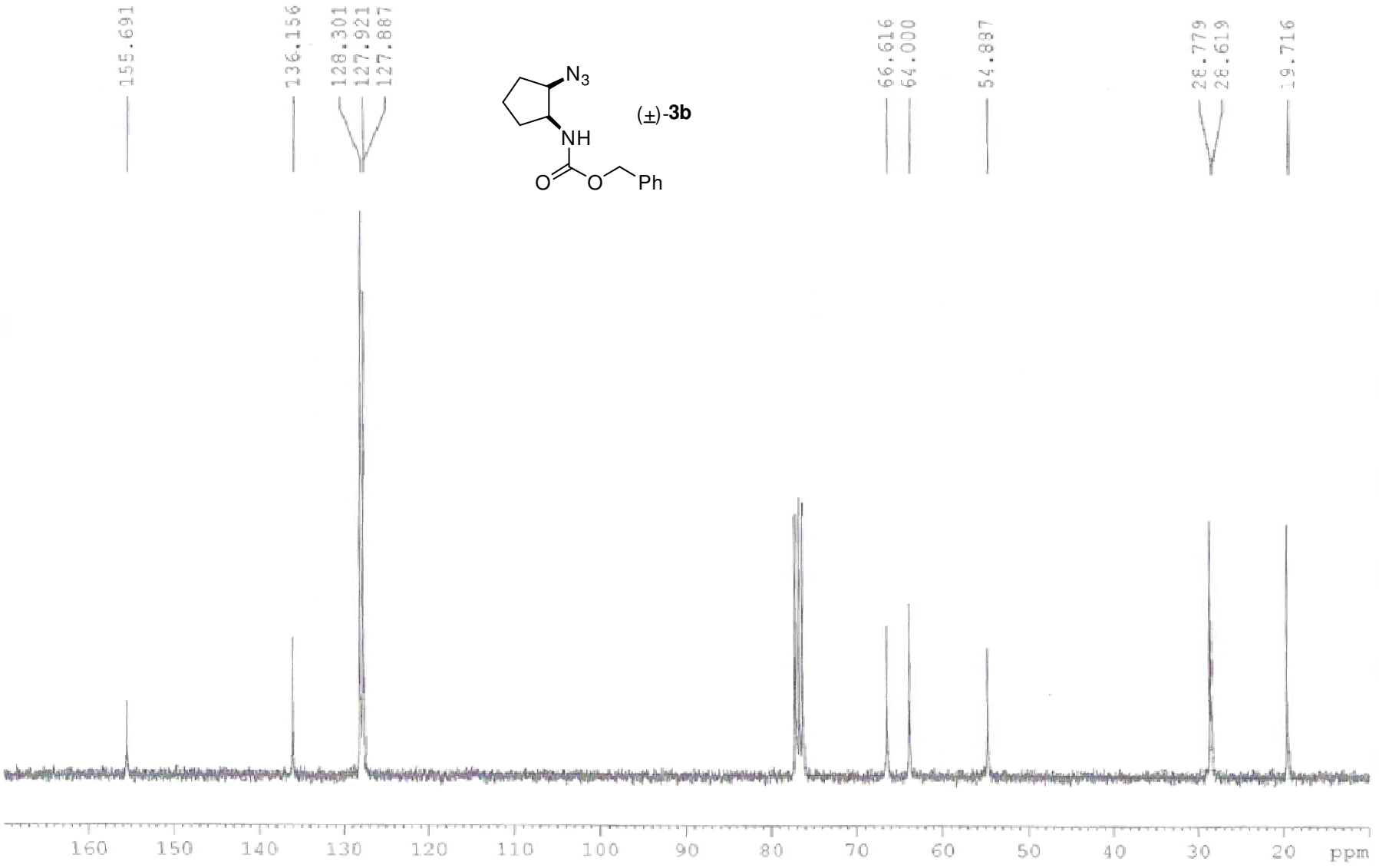
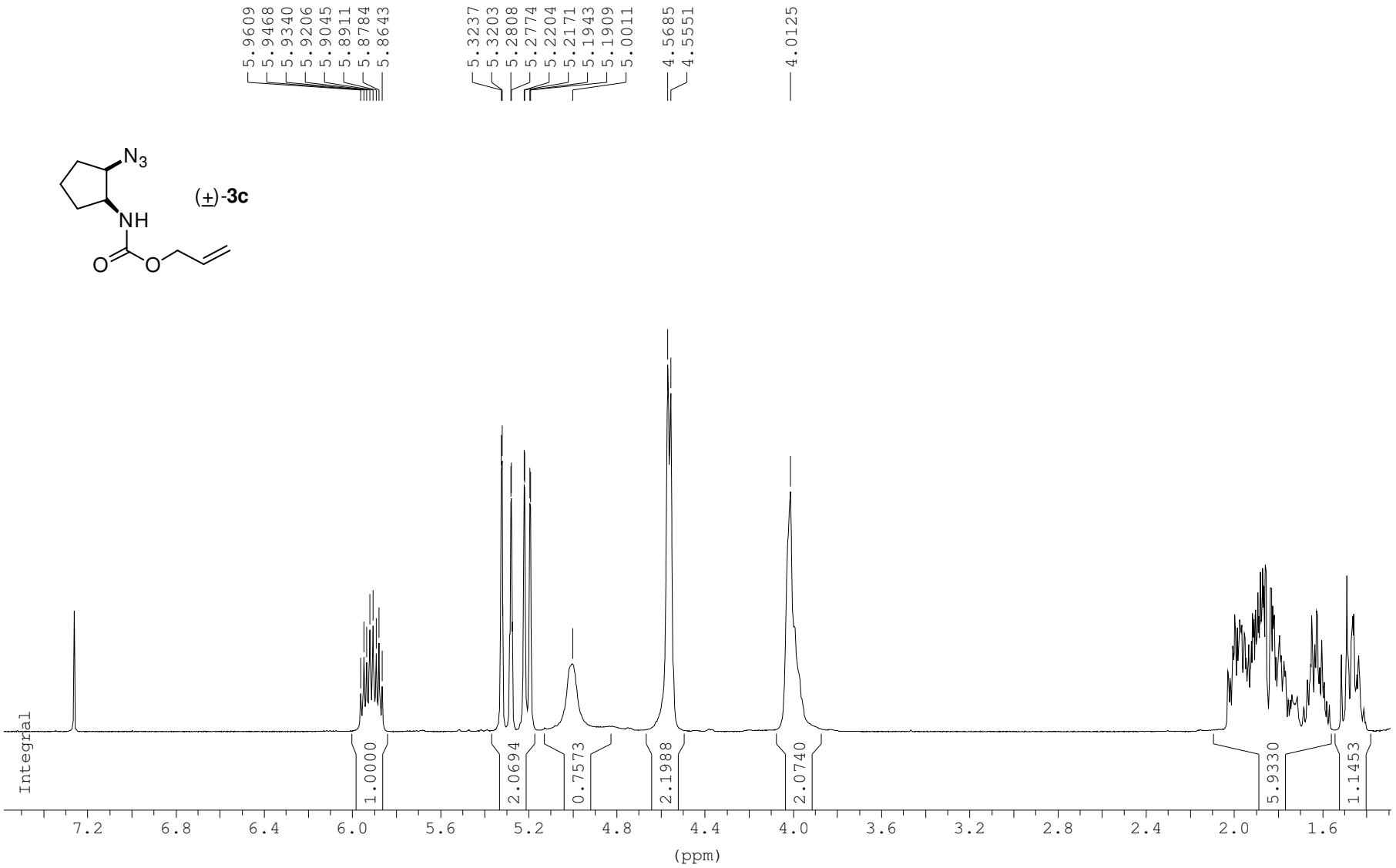
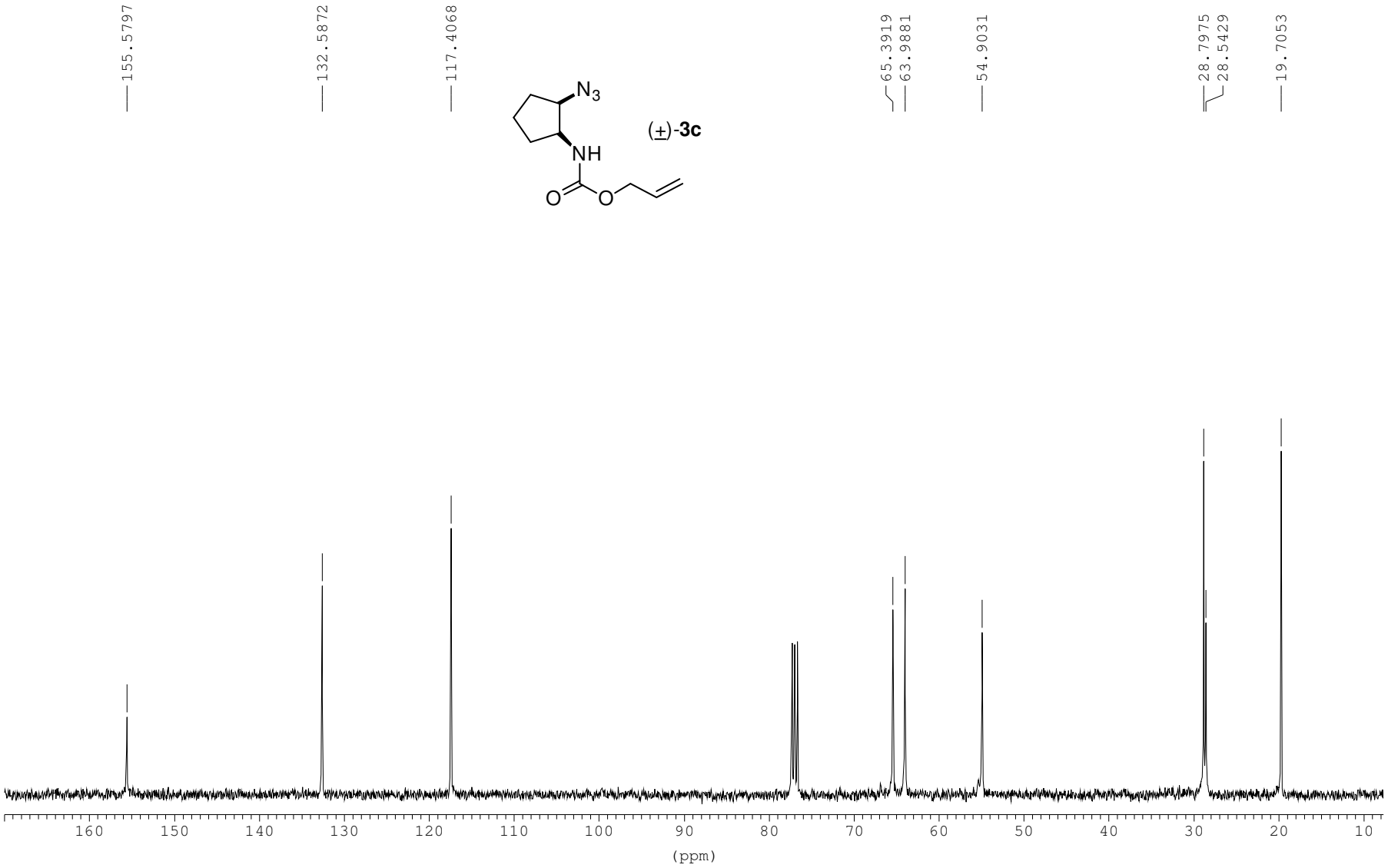
78.6230
60.8167
60.0457
31.8234
29.9031
20.5272
14.3227
OH
NH
O
O
(±)-2d
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


7.3589
5.1122
5.0343
4.0401
4.0211
1.8823
1.8759
1.8675
1.6860
N3
NH
O
O
Ph
(±)-3b
Integral
4.9758
2.8853
2.0000
4.0368
2.1463
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
(ppm)


155.691
136.156
128.301
127.921
127.887
66.616
64.000
54.897
28.779
28.619
19.716
N3
NH
O
O
Ph
(±)-3b
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


5.9609
5.9468
5.9340
5.9206
5.9045
5.8911
5.8784
5.8643
5.3237
5.3203
5.2808
5.2774
5.2204
5.2171
5.1943
5.1909
5.0011
4.5685
4.5551
4.0125
N3
NH
O
O
(±)-3c
Integral
1.0000
2.0694
0.7573
2.1988
2.0740
5.9330
1.1453
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
(ppm)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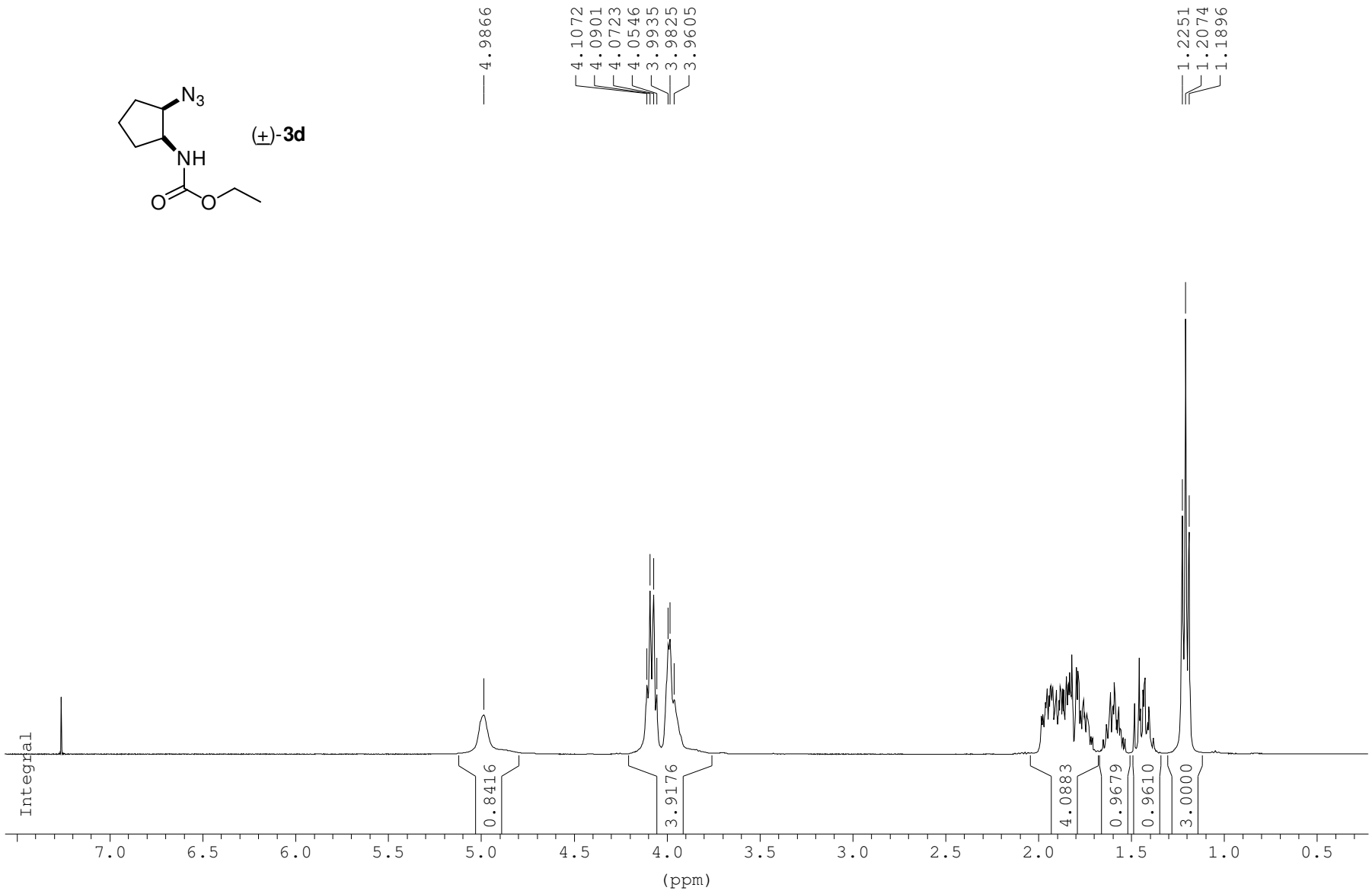
132.5872
117.4068
65.3919
63.9881
54.9031
28.7975
28.5429
19.7053
N3
NH
O
O
(±)-3c
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


(±)-3d
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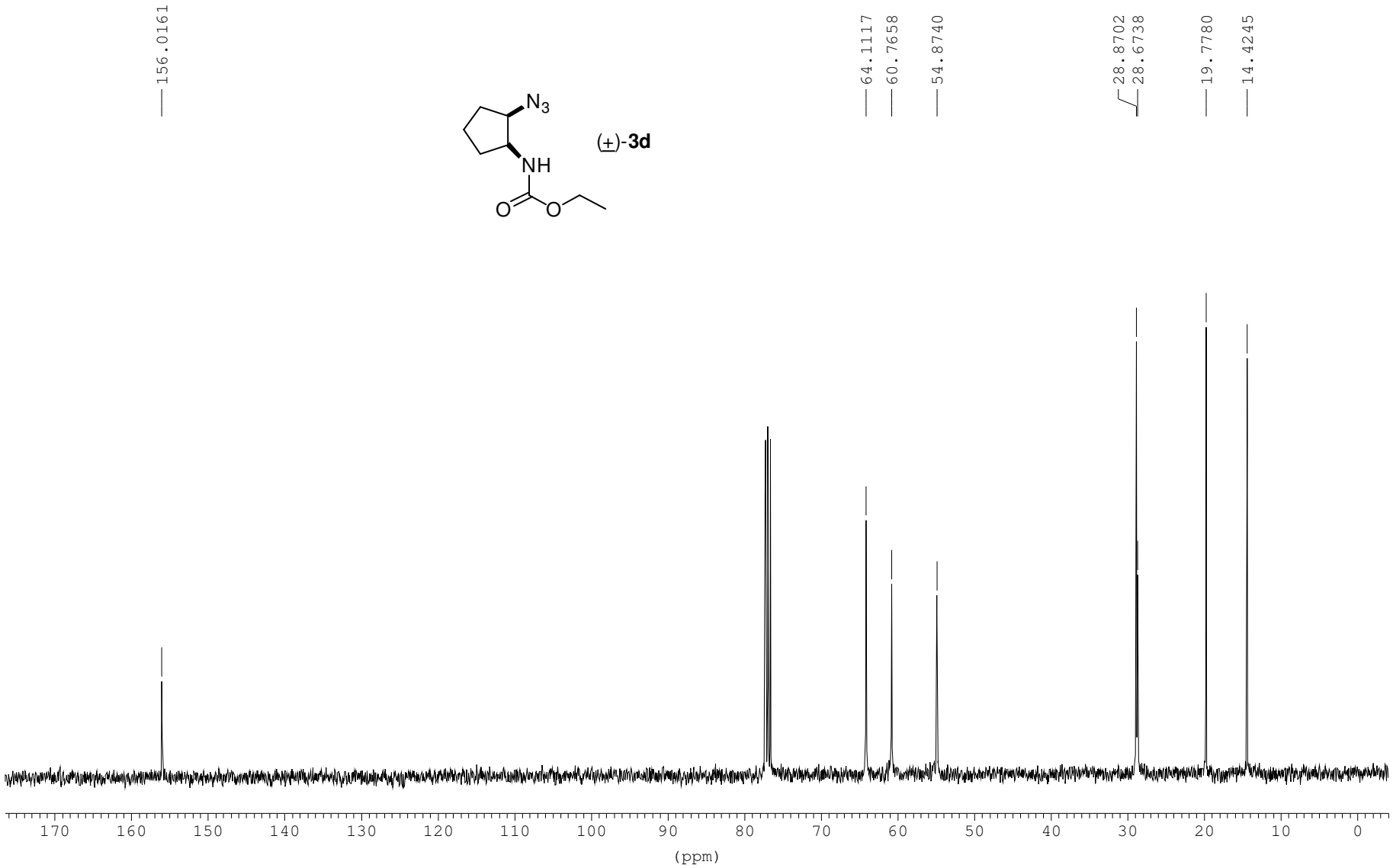
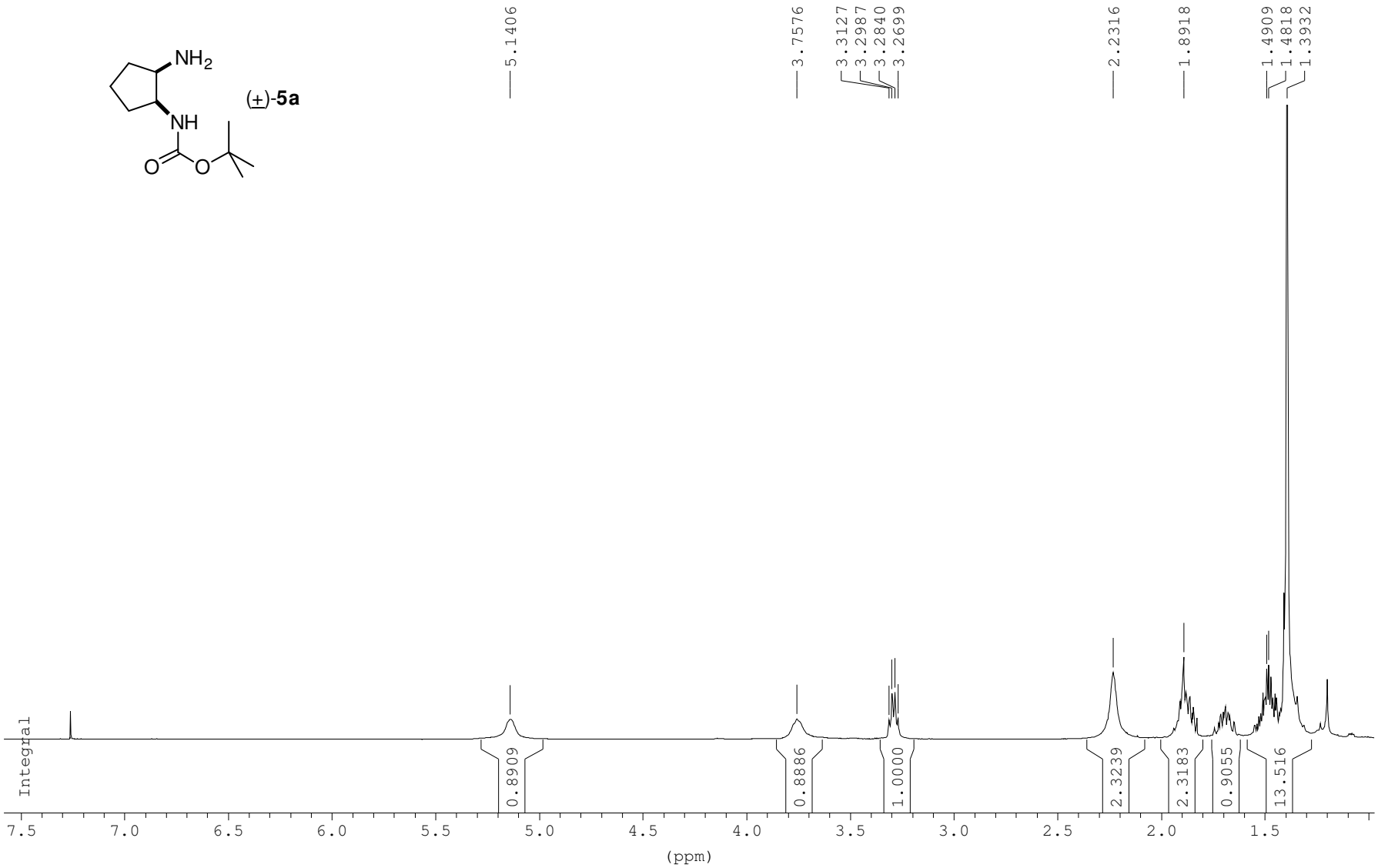
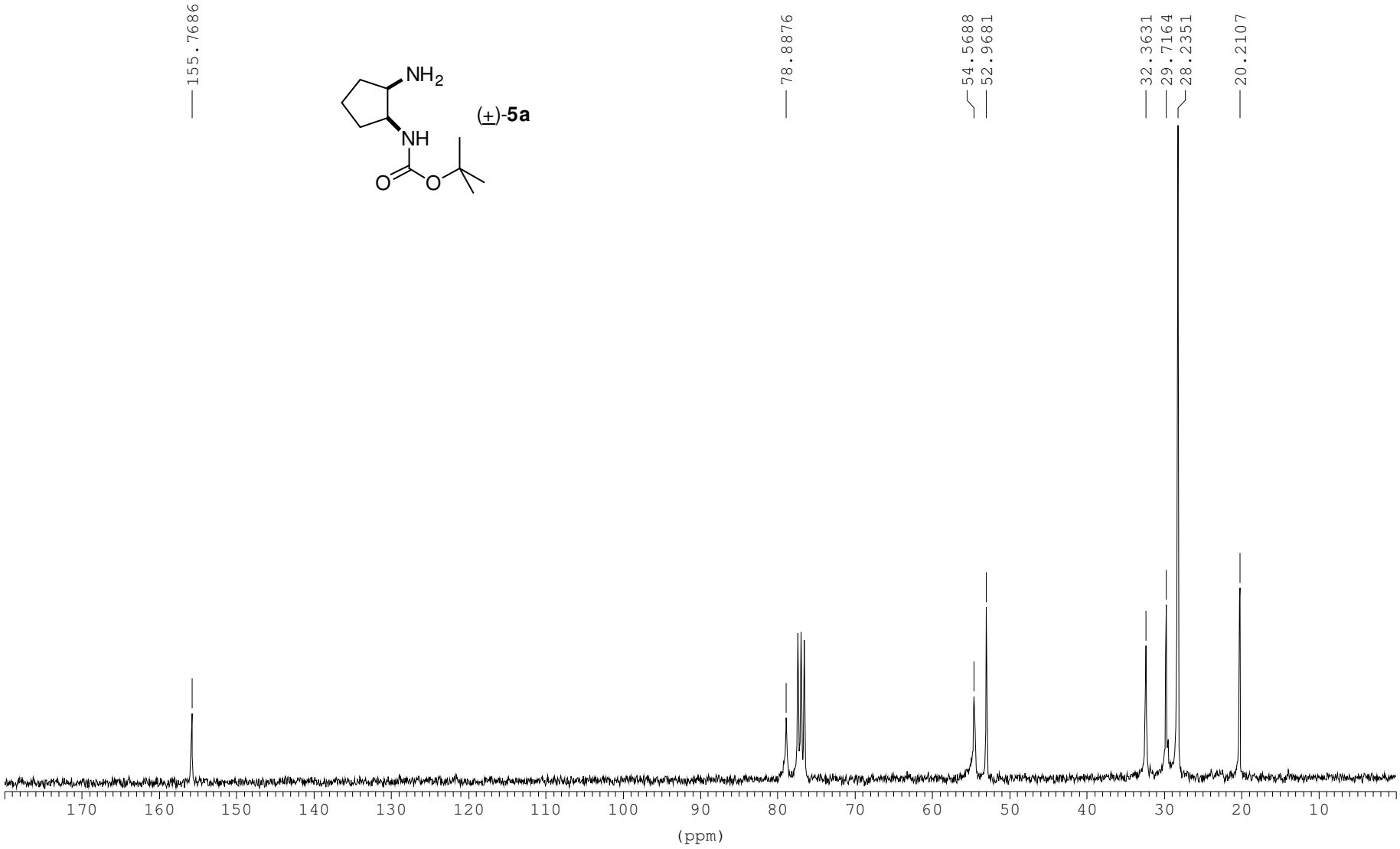
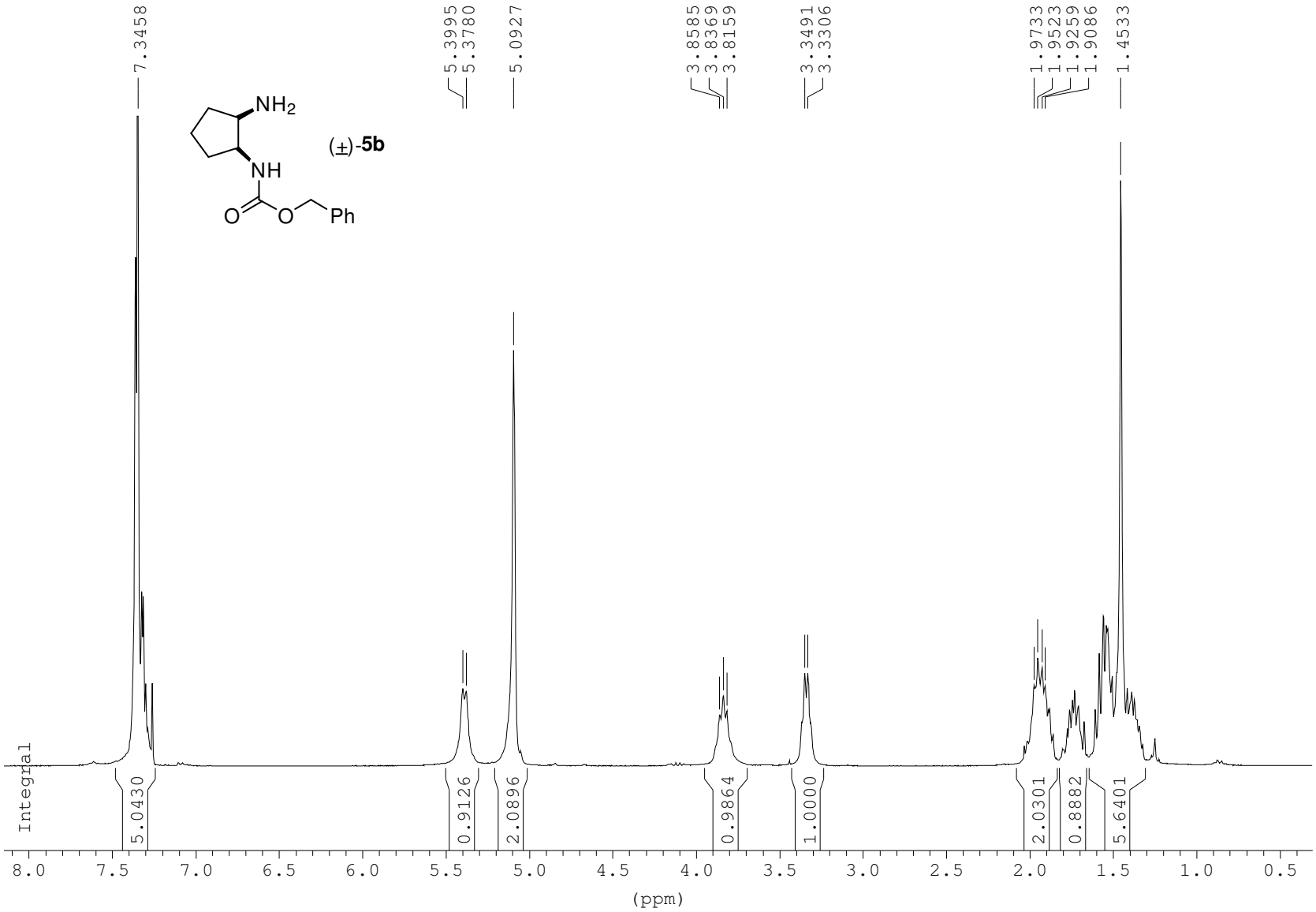
4.1072
4.0901
4.0723
4.0546
3.9935
3.9825
3.9605
1.2251
1.2074
1.1896
Integral
0.8416
3.9176
4.0883
0.9679
0.9610
3.0000
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)


156.0161
64.1117
60.7658
54.8740
28.8702
28.6738
19.7780
14.4245
N3
NH
O
O
(±)-3d
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)


NH2
NH
O
O
(±)-5a
5.1406
3.7576
3.3127
3.2987
3.2840
3.2699
2.2316
1.8918
1.4909
1.4818
1.3932
Integral
0.8909
0.8886
1.0000
2.3239
2.3183
0.9055
13.516
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
(ppm)


155.7686
78.8876
54.5688
52.9681
32.3631
29.7164
28.2351
20.2107
NH2
NH
O
O
(±)-5a
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


7.3458
5.3995
5.3780
5.0927
3.8585
3.8369
3.8159
3.3491
3.3306
1.9733
1.9523
1.9259
1.9086
1.4533
NH2
NH
O
O
Ph
(±)-5b
Integral
5.0430
0.9126
2.0896
0.9864
1.0000
2.0301
0.8882
5.6401
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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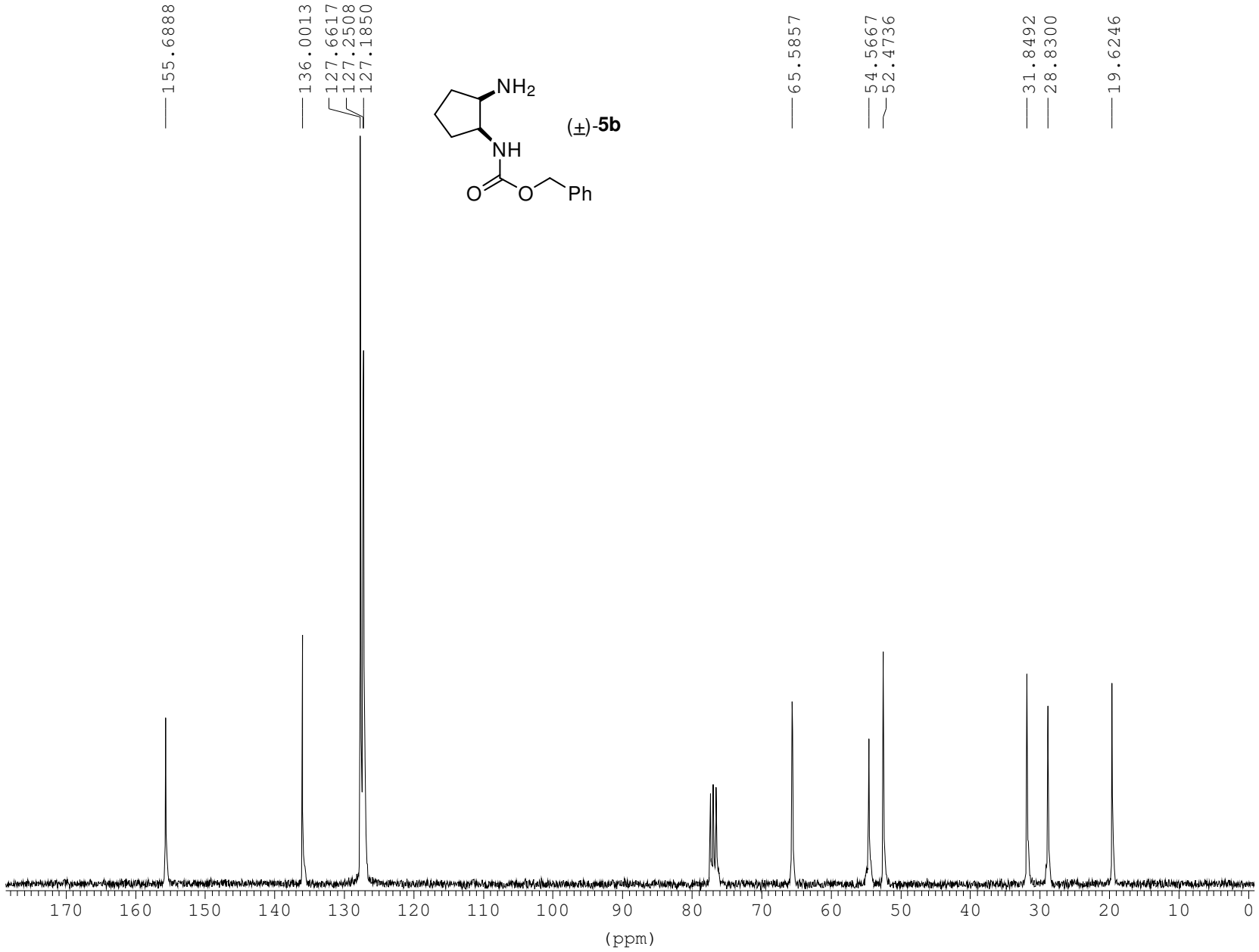
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)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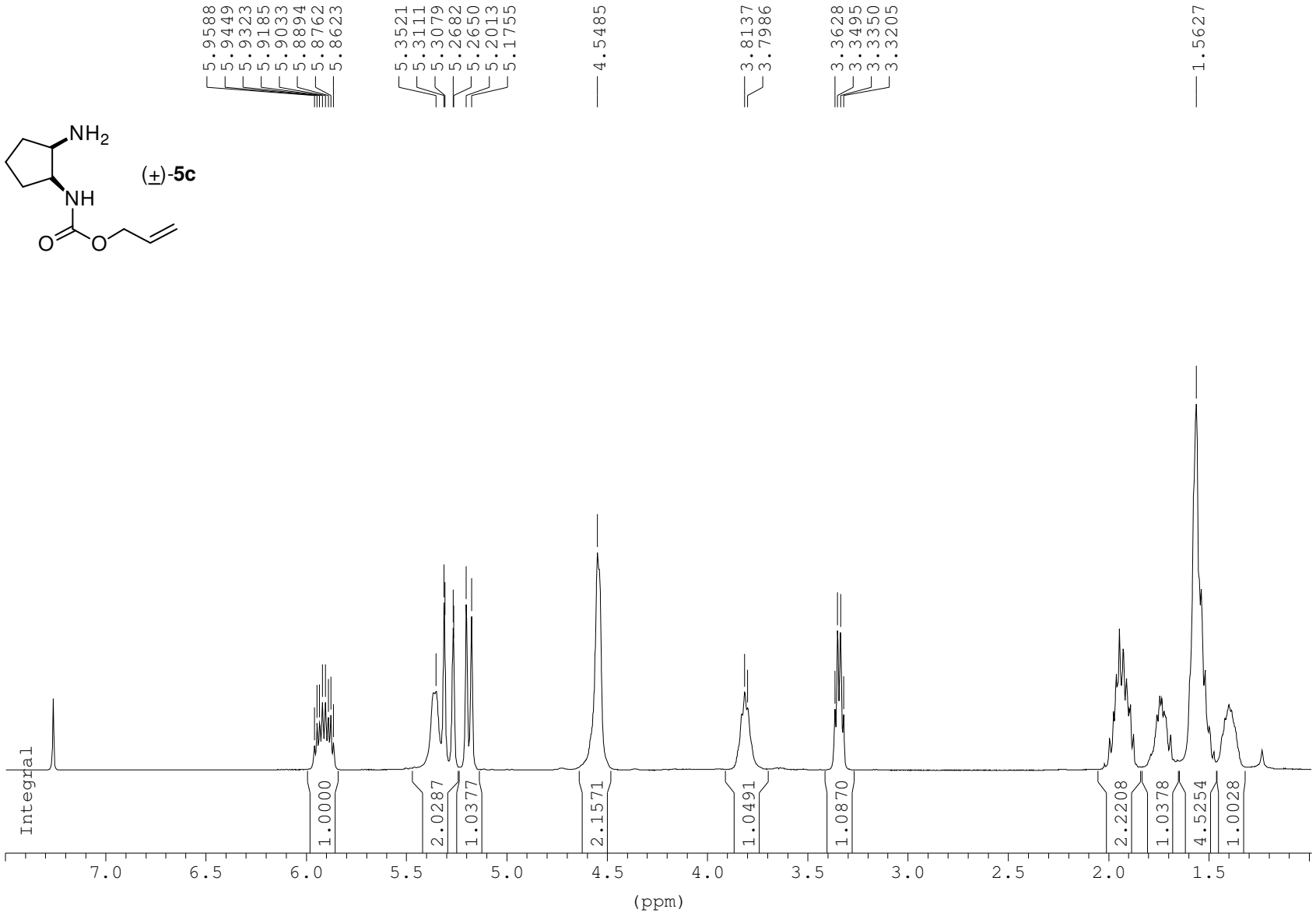
127.6617
127.2508
127.1850
65.5857
54.5667
52.4736
31.8492
28.8300
19.6246
NH2
NH
O
O
Ph
(±)-5b
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)


5.9588
5.9449
5.9323
5.9185
5.9033
5.8894
5.8762
5.8623
5.3521
5.3111
5.3079
5.2682
5.2650
5.2013
5.1755
4.5485
3.8137
3.7986
3.3628
3.3495
3.3350
3.3205
1.5627
NH2
NH
O
O
(±)-5c
Integral
1.0000
2.0287
1.0377
2.1571
1.0491
1.0870
2.2208
1.0378
4.5254
1.0028
7.0
6.5
6.0
5.5
5.0
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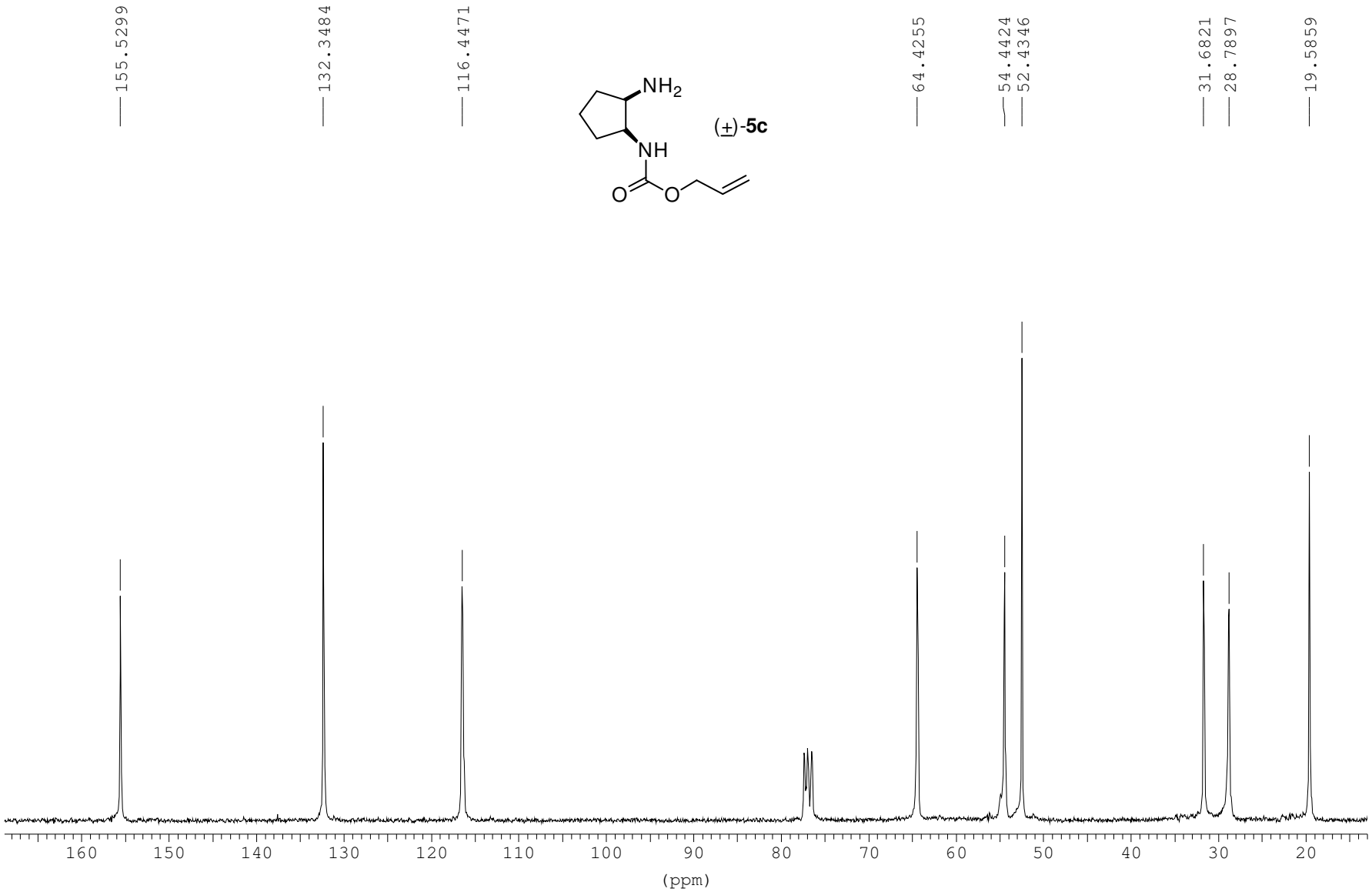
4.0
3.5
3.0
2.5
2.0
1.5
(ppm)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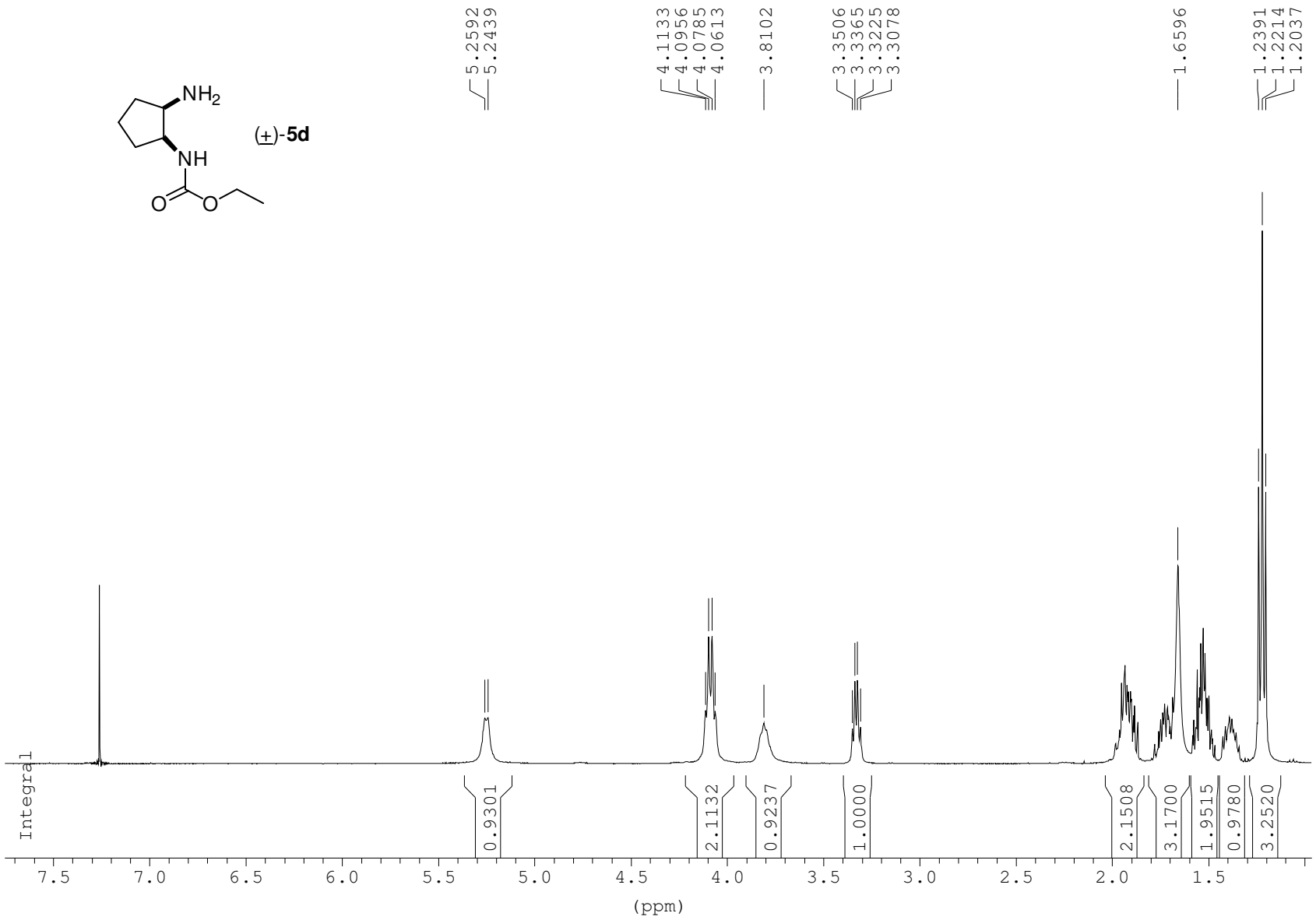
116.4471
64.4255
54.4424
52.4346
31.6821
28.7897
19.5859
NH2
NH
O
O
(±)-5c
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
(ppm)


NH2
NH
O
O
(±)-5d
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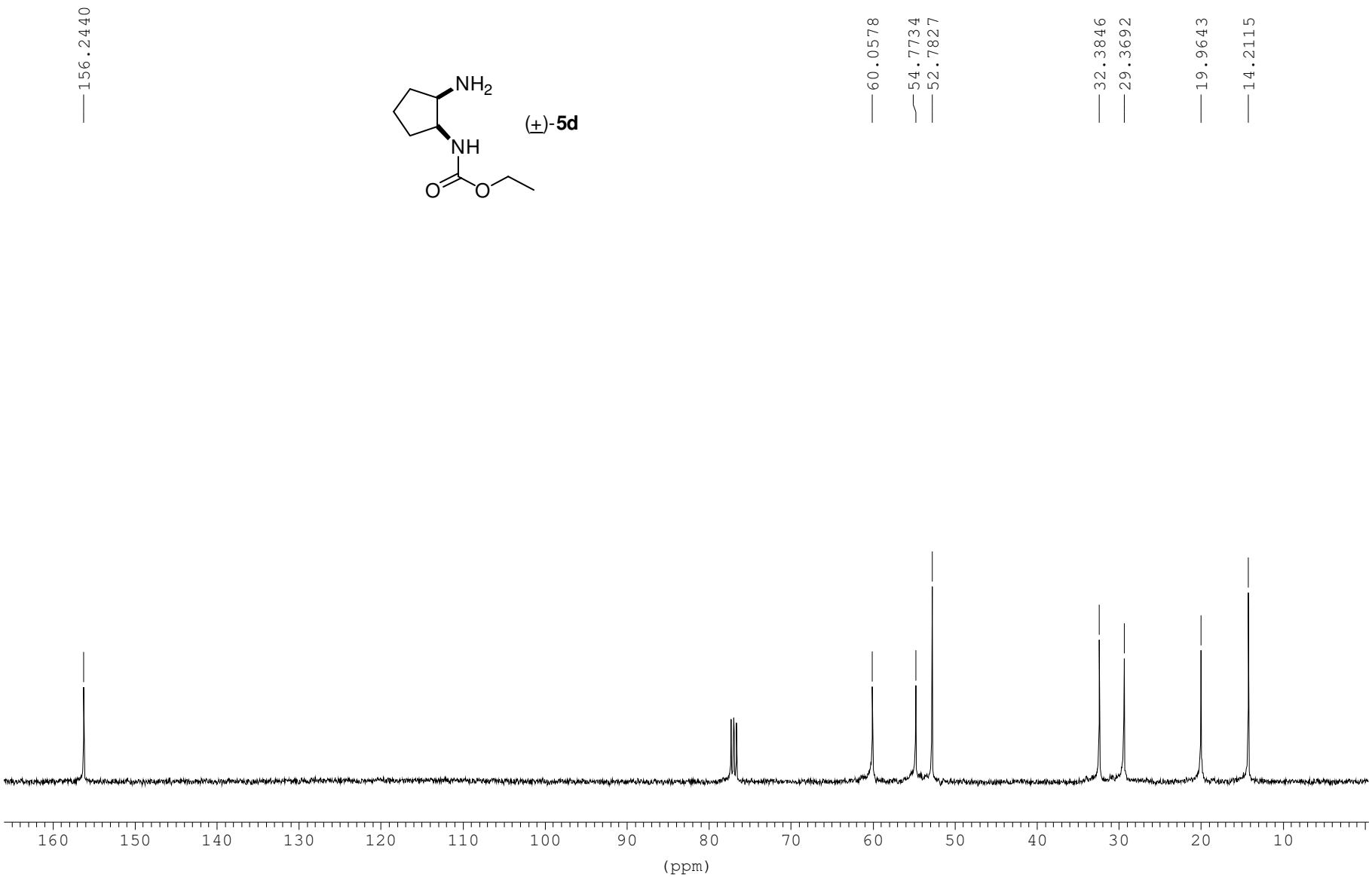
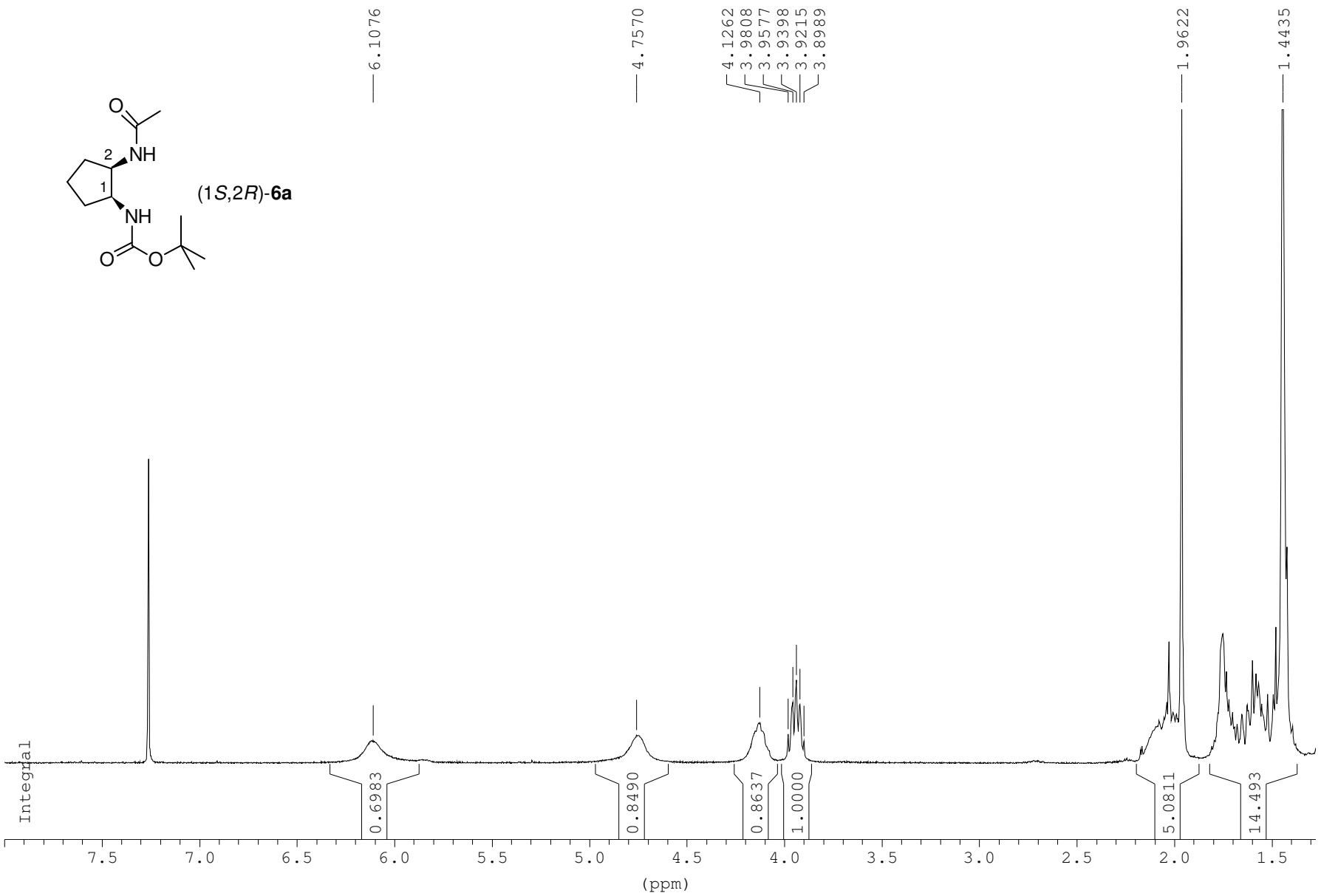
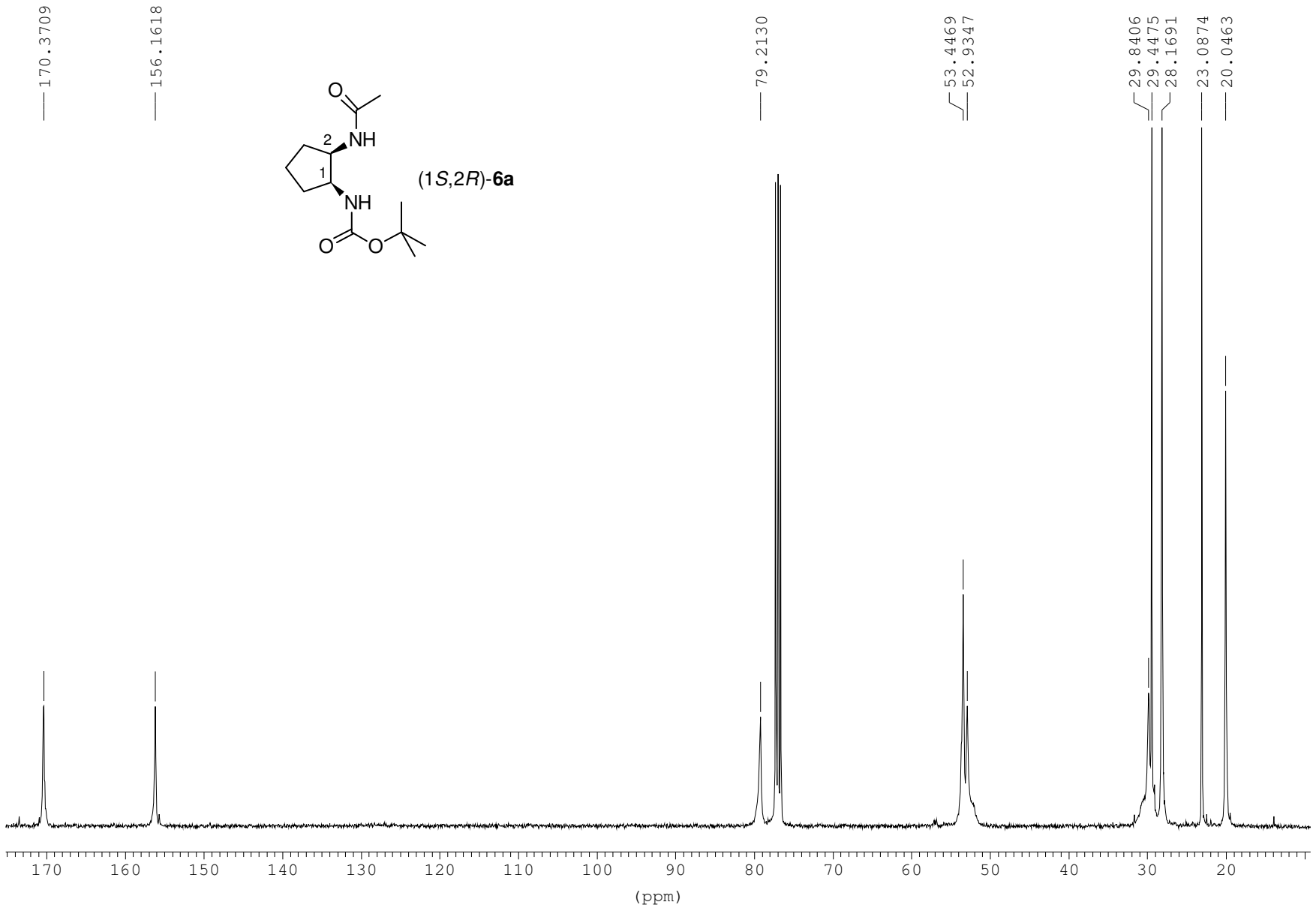
5.2439
4.1133
4.0956
4.0785
4.0613
3.8102
3.3506
3.3365
3.3225
3.3078
1.6596
1.2391
1.2214
1.2037
Integral
0.9301
2.1132
0.9237
1.0000
2.1508
3.1700
1.9515
0.9780
3.2520
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
(ppm)


156.2440
60.0578
54.7734
52.7827
32.3846
29.3692
19.9643
14.2115
NH2
NH
O
O
(±)-5d
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


6.1076
4.7570
4.1262
3.9808
3.9577
3.9398
3.9215
3.8989
1.9622
1.4435
(1S,2R)-6a
Integral
0.6983
0.8490
0.8637
1.0000
5.0811
14.493
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
(ppm)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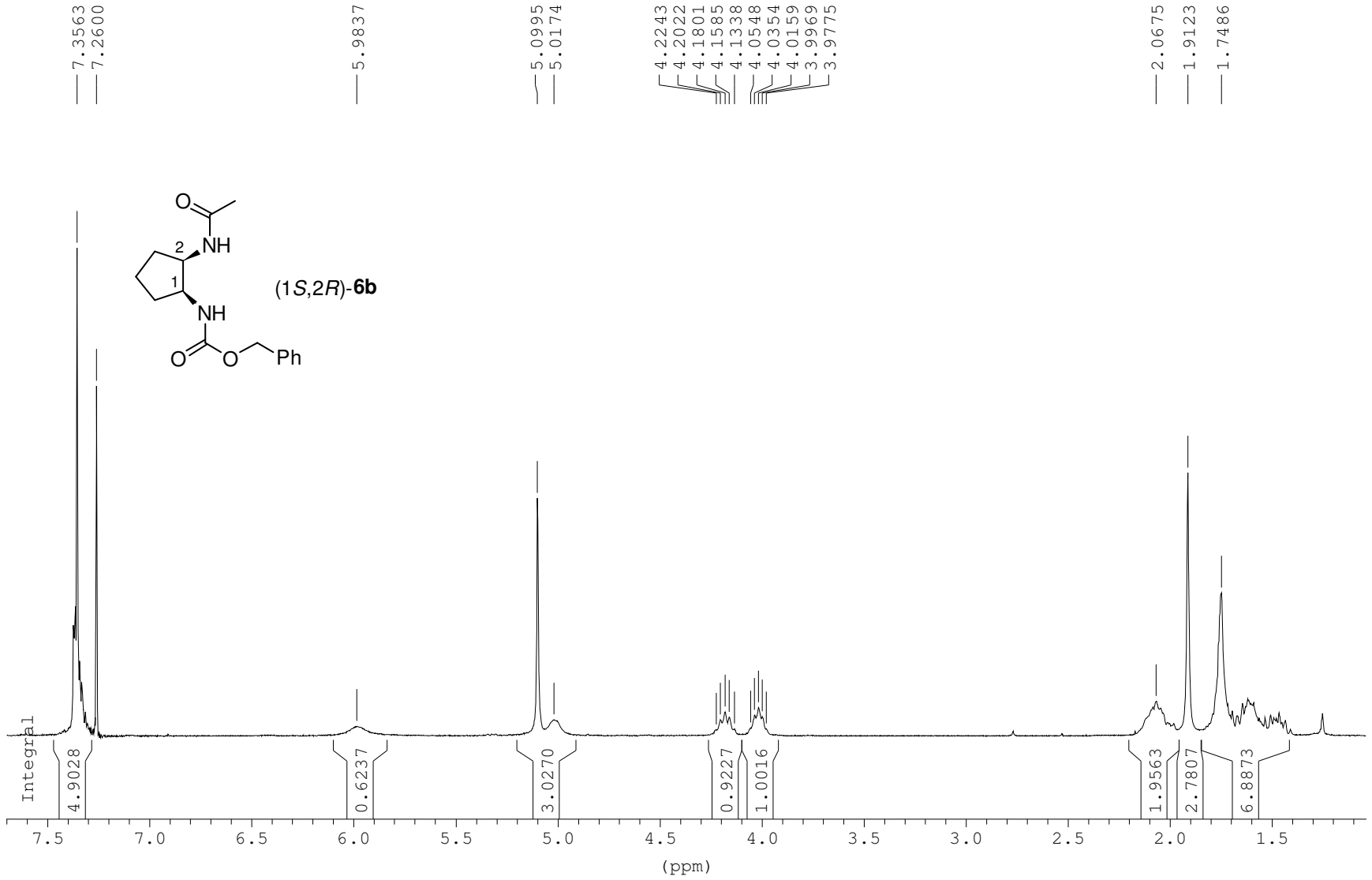
156.1618
79.2130
53.4469
52.9347
29.8406
29.4475
28.1691
23.0874
20.0463
O
NH
2
1
NH
O
O
(1S,2R)-6a
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
(ppm)


7.3563
7.2600
5.9837
5.0995
5.0174
4.2243
4.2022
4.1801
4.1585
4.1338
4.0548
4.0354
4.0159
3.9969
3.9775
2.0675
1.9123
1.7486
(1S,2R)-6b
Integral
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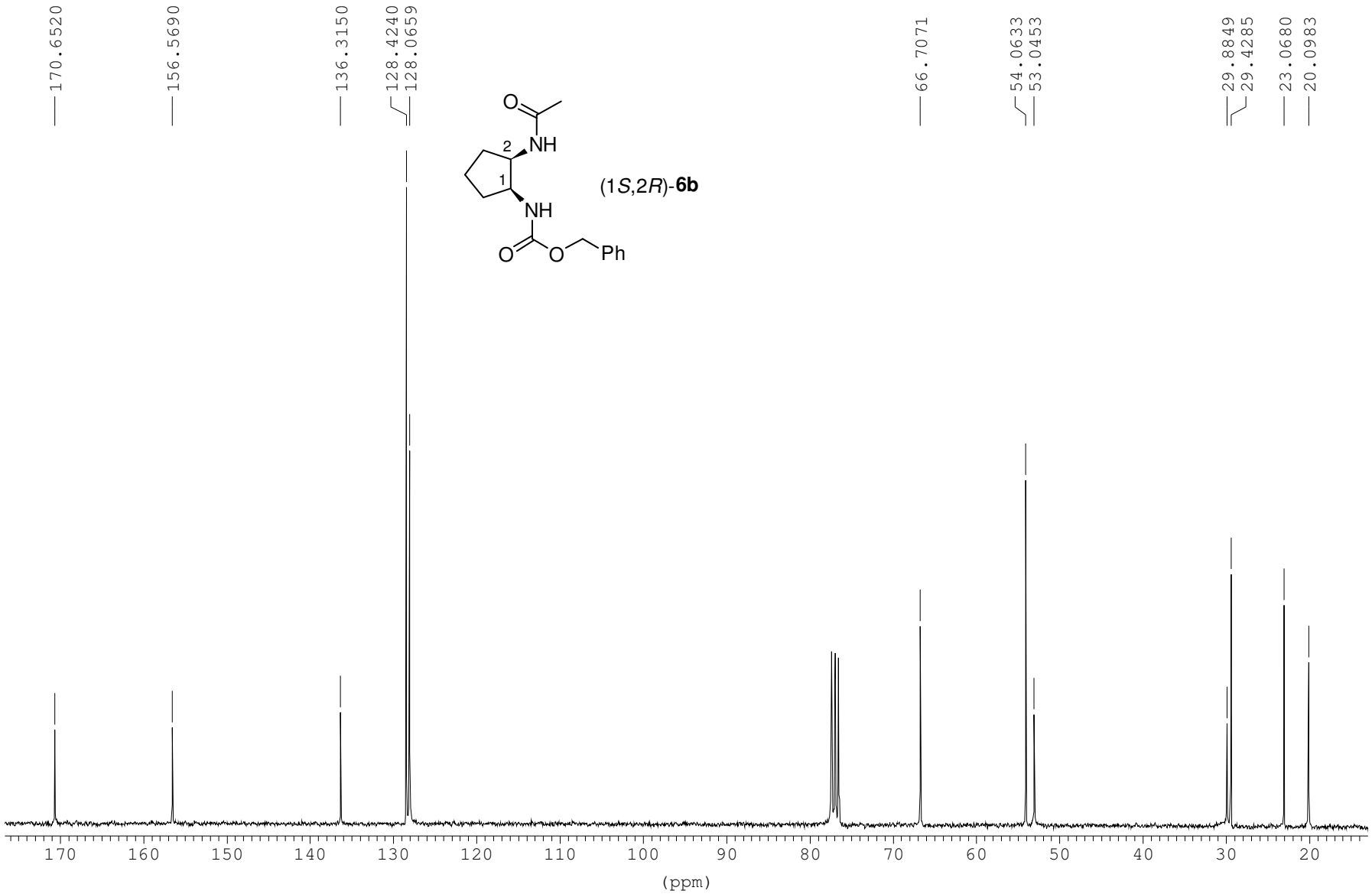
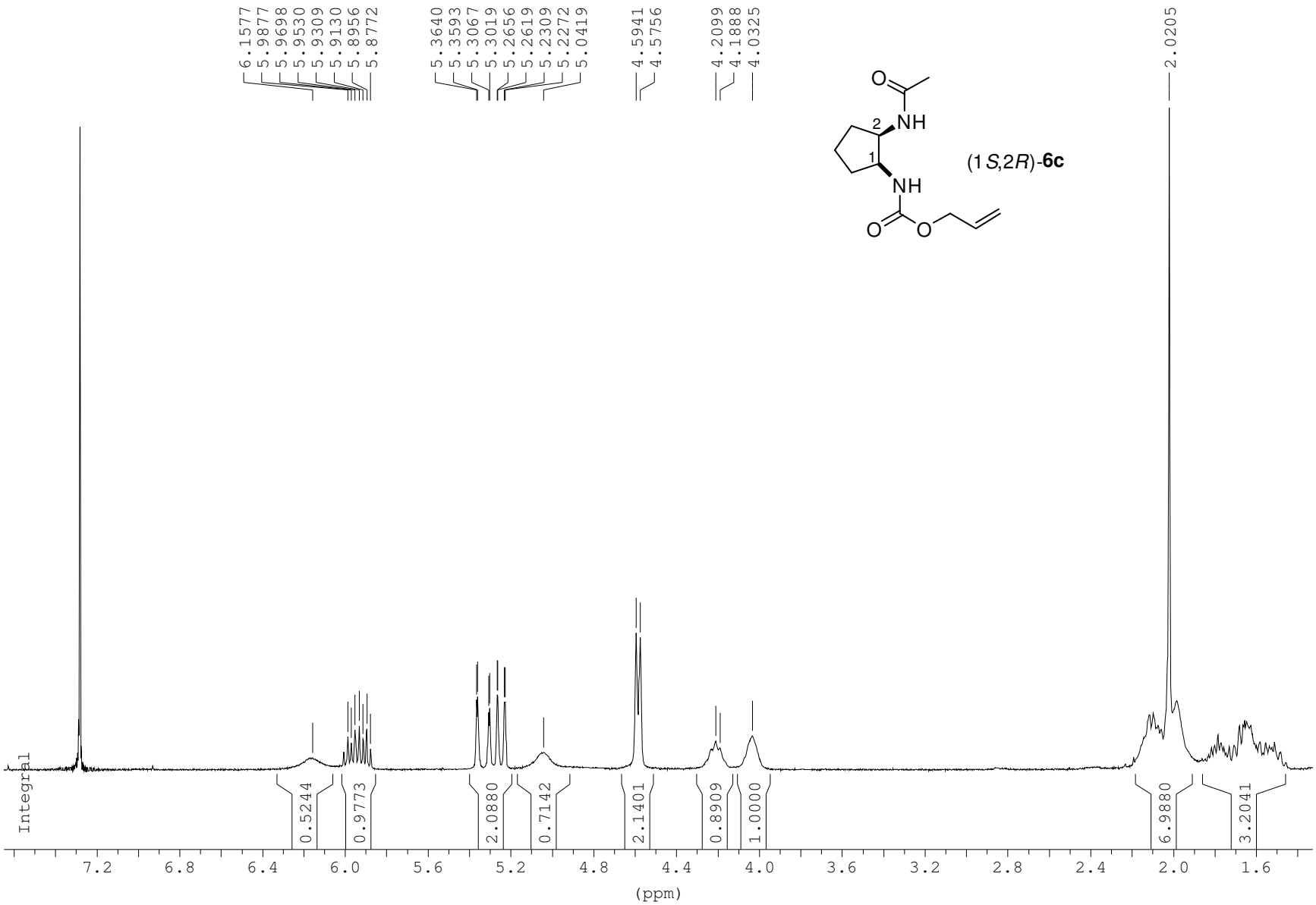
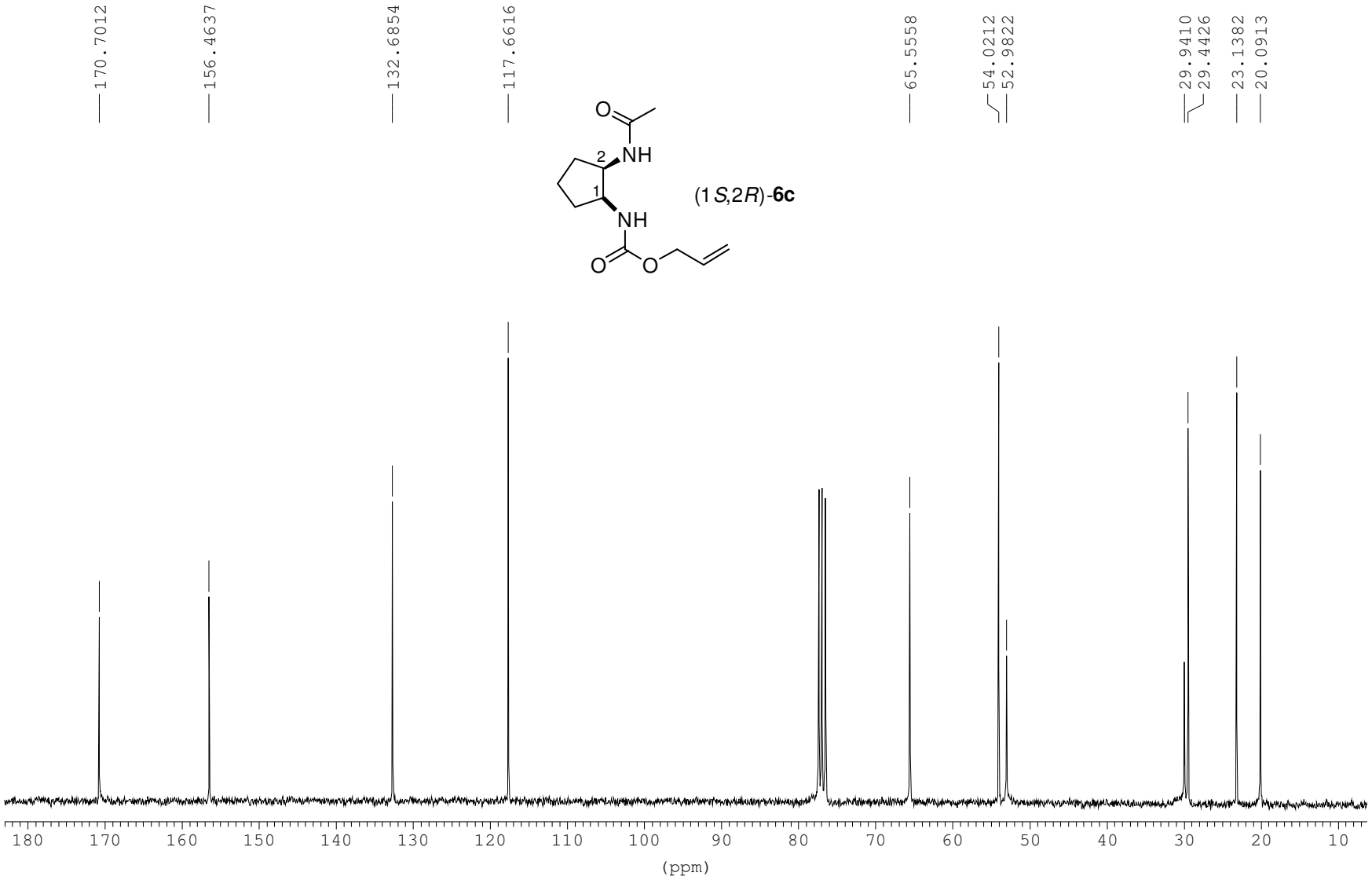
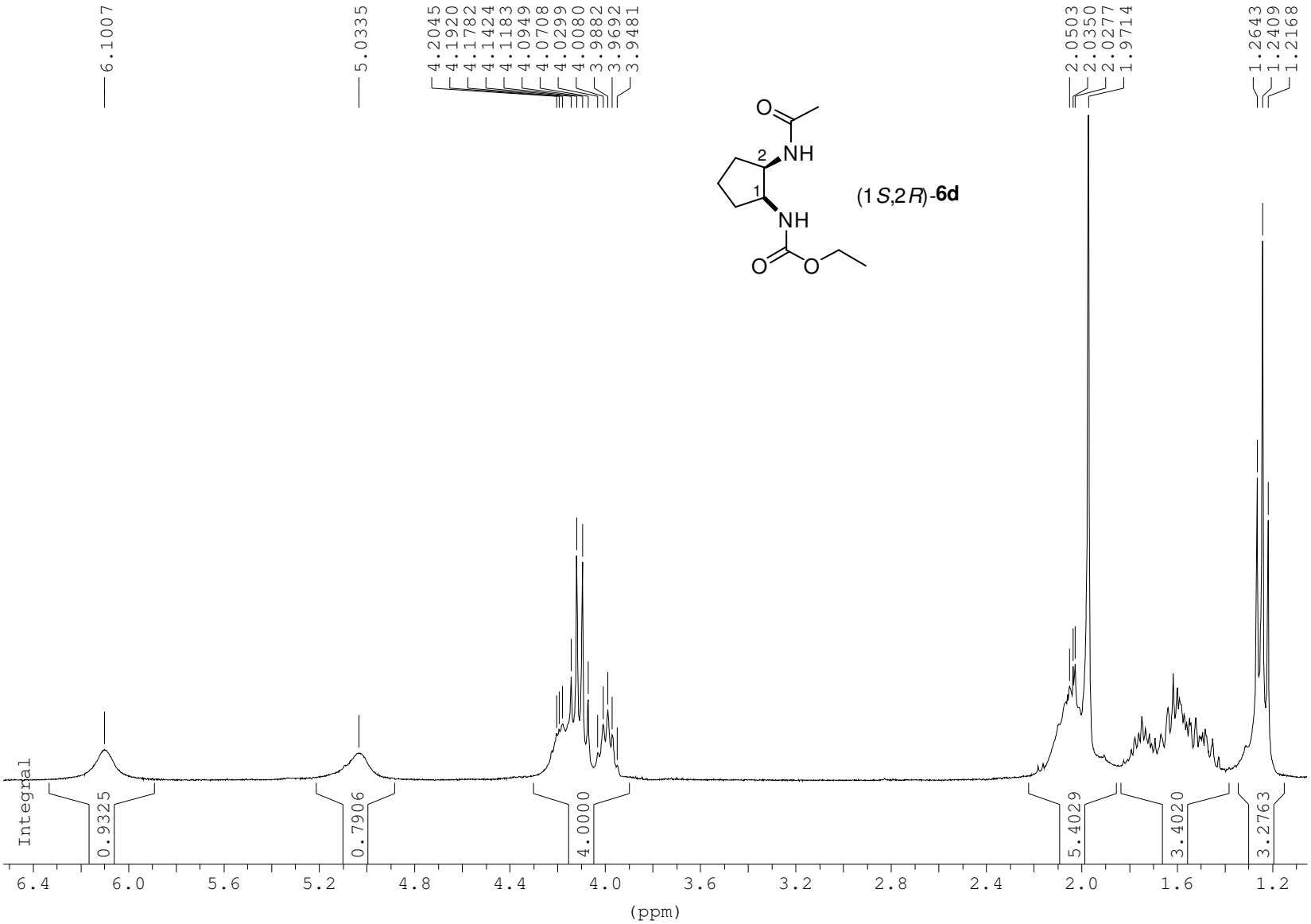
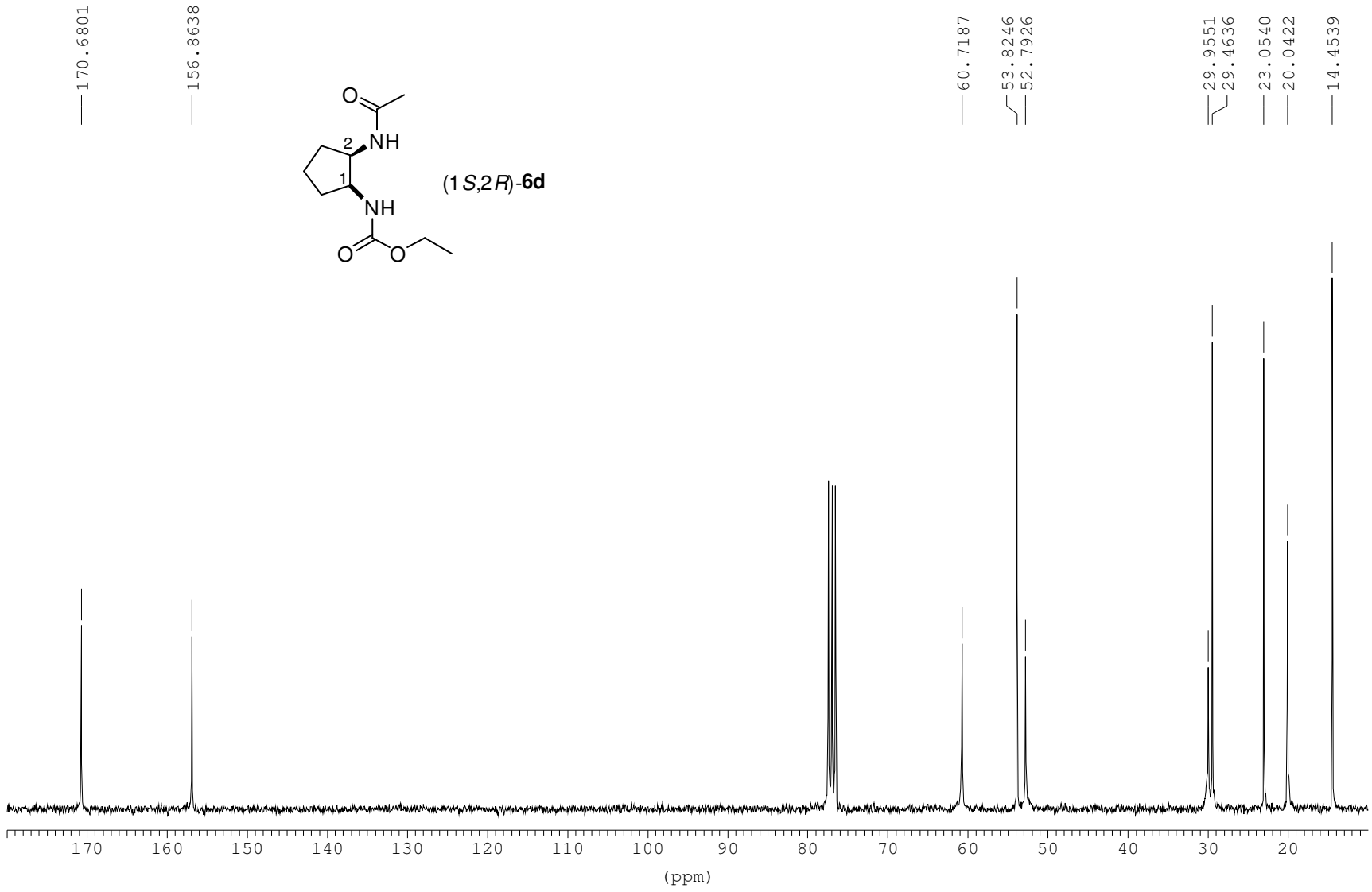
0.6237
3.0270
0.9227
1.0016
1.9563
2.7807
6.8873
(ppm)


170.6520
156.5690
136.3150
128.4240
128.0659
66.7071
54.0633
53.0453
29.8849
29.4285
23.0680
20.0983
O
NH
2
1
NH
O
O
Ph
(1S,2R)-6b
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
(ppm)


6.1577
5.9877
5.9698
5.9530
5.9309
5.9130
5.8956
5.8772
5.3640
5.3593
5.3067
5.3019
5.2656
5.2619
5.2309
5.2272
5.0419
4.5941
4.5756
4.2099
4.1888
4.0325
2.0205
O
NH
2
1
NH
O
O
O
(1S,2R)-6c
Integral
0.5244
0.9773
2.0880
0.7142
2.1401
0.8909
1.0000
6.9880
3.2041
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
(ppm)


170.7012
156.4637
132.6854
117.6616
65.5558
54.0212
52.9822
29.9410
29.4426
23.1382
20.0913
O
2
NH
1
NH
O
O
(1S,2R)-6c
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


6.1007
5.0335
4.2045
4.1920
4.1782
4.1424
4.1183
4.0949
4.0708
4.0299
4.0080
3.9882
3.9692
3.9481
2.0503
2.0350
2.0277
1.9714
1.2643
1.2409
1.2168
(1S,2R)-6d
Integral
0.9325
0.7906
4.0000
5.4029
3.4020
3.2763
(ppm)


170.6801
156.8638
60.7187
53.8246
52.7926
29.9551
29.4636
23.0540
20.0422
14.4539
O
NH
2
1
NH
O
O
(1S,2R)-6d
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
(ppm)

AS2006 H:EtOH 93:7 0.8 ml/min 20 °C 13 bar

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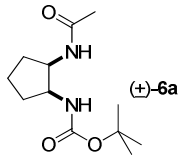
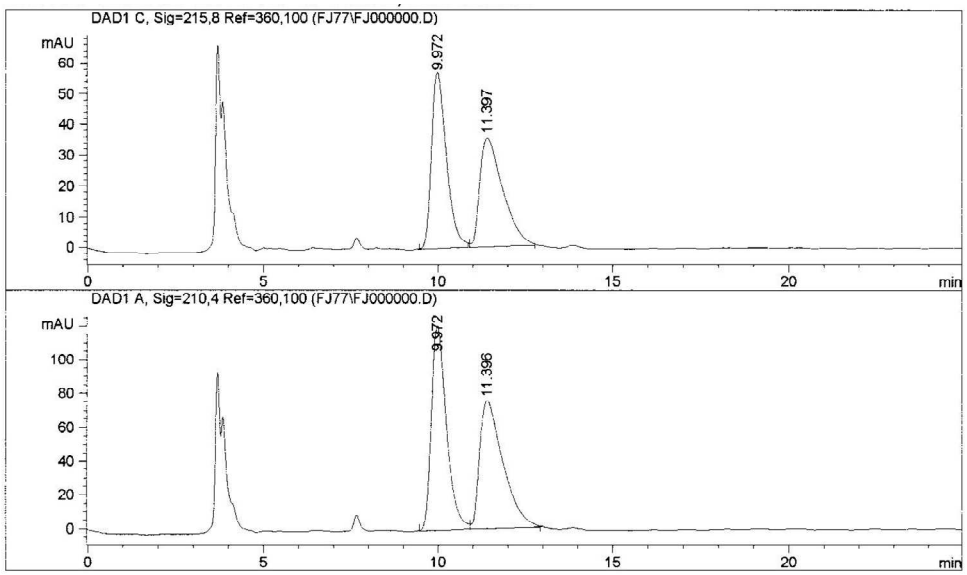
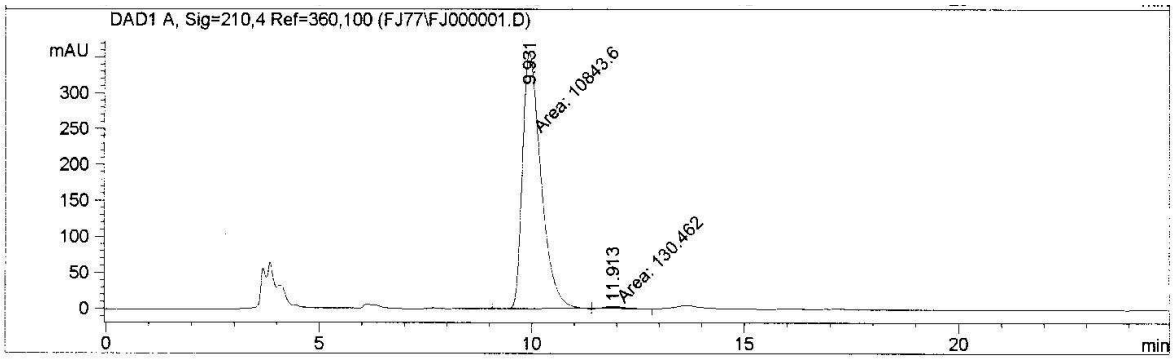
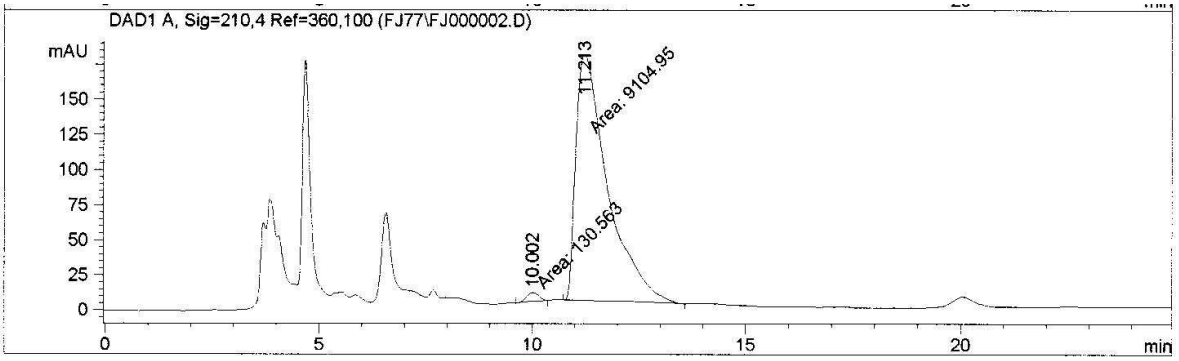


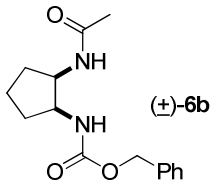


Product isolated in the KR of (±)-**5a**: (1*S*,2*R*)-**6a** (ee = 98%)



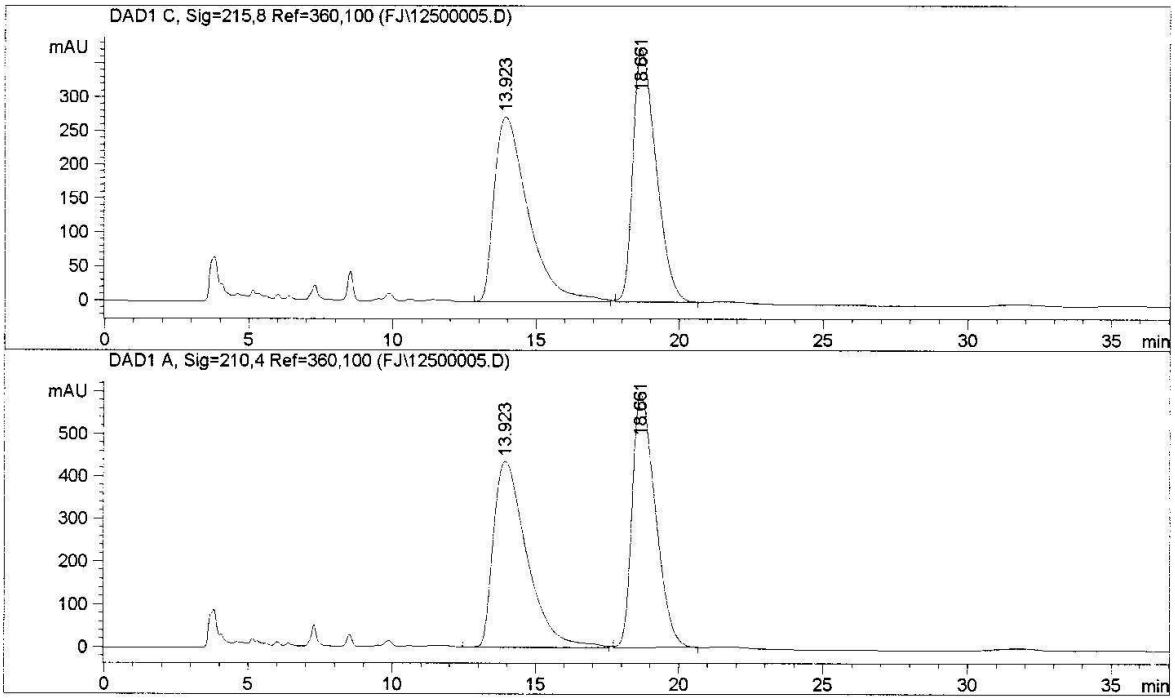
Substrate isolated in the KR of (±)-**5a**: (1*R*,2*S*)-**5a**, which is transformed into (1*R*,2*S*)-**6a** (ee = 97%).



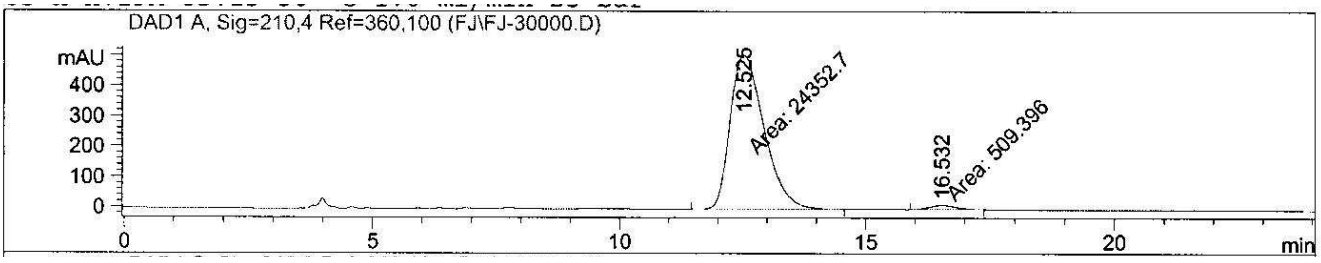


(±)-**6b**

AS-APH H:EtOH 90:10 0.8mL/min 20 °C 13 bar



Product isolated in the DKR of (±)-**5b**: (1*S*,2*R*)-**6b** (ee = 96%). Analysis was carried out at 30 ºC.



FJ-305rac
Chiralpak IA H:EtOH 94:6 1.0 ml/min 25 °C 29 BAR

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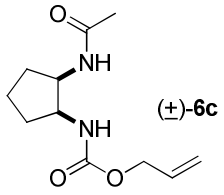
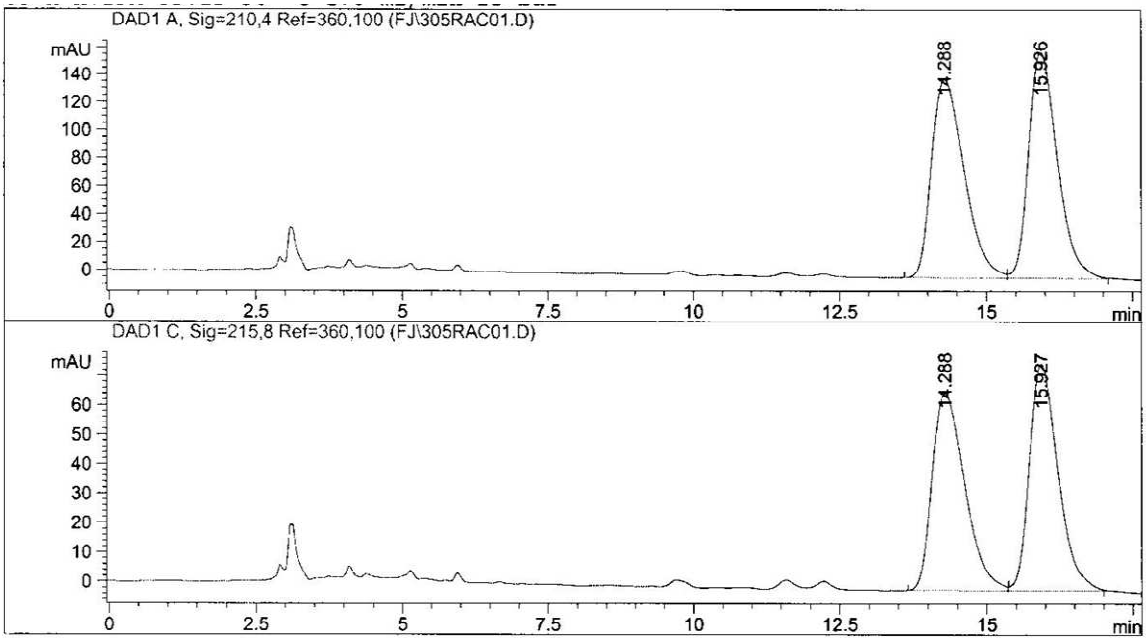
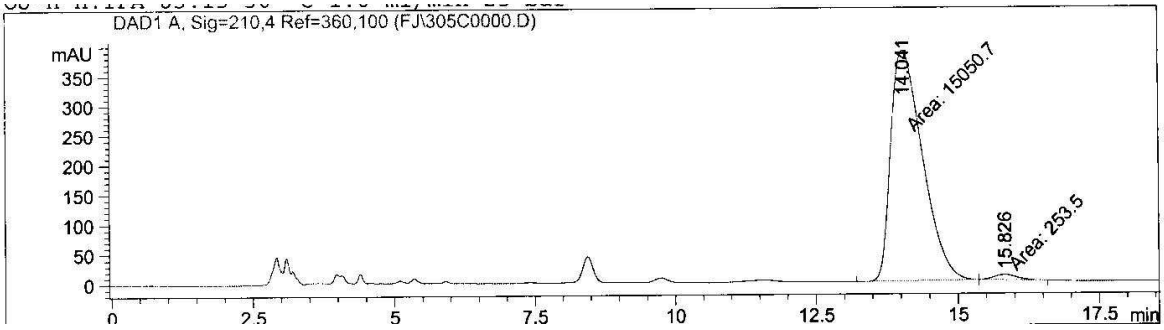


(±)-**6c**



Product isolated in the DKR of (±)-**5c**: (1*S*,2*R*)-**6c** (ee = 97%).



FJ-304rac
Chiralpak IA H:EtOH 96:4 0.9 ml/min 25 °C 25 BAR

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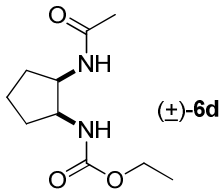
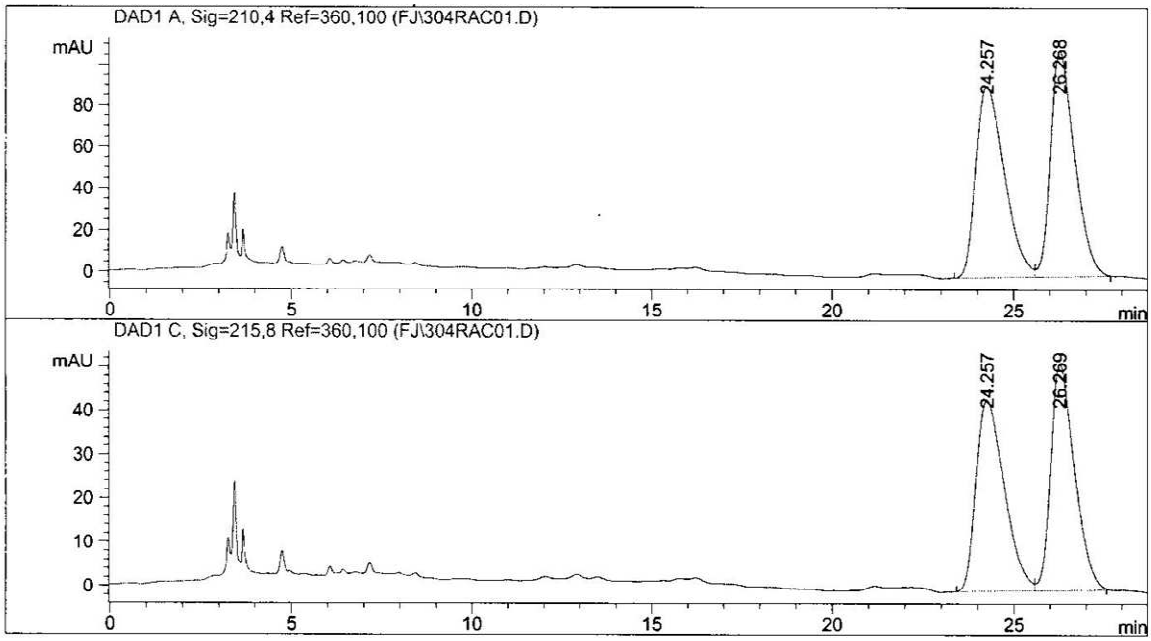


(±)-**6d**



Product isolated in the DKR of (±)-**5d**: (1*S*,2*R*)-**6d** (ee = 95%).