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Combination of gold and redox enzyme catalysis to access valuable enantioenriched aliphatic β-chlorohydrins

Electronic Supporting Information

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I. Compounds described in this contribution

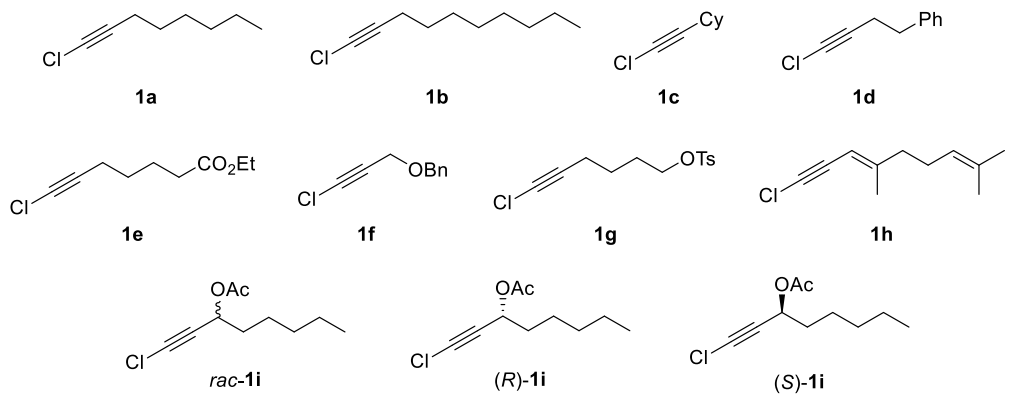


Figure S1. Structure of chloroalkynes **1a-i** studied in this contribution.

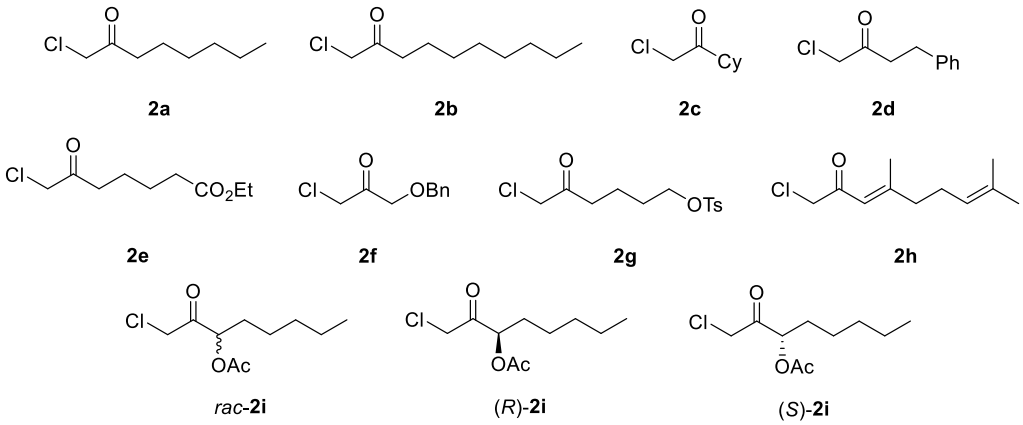


Figure S2. Structure of prochiral α-chloromethyl ketones **2a-i** studied in this contribution.

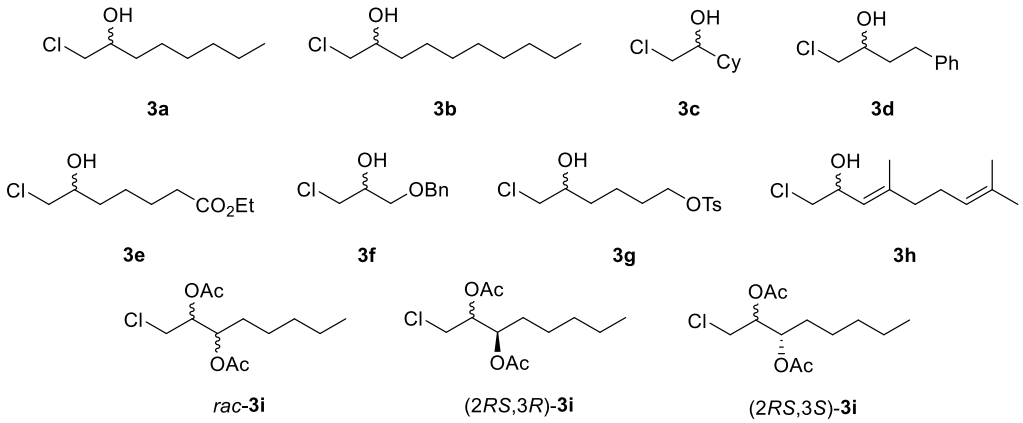
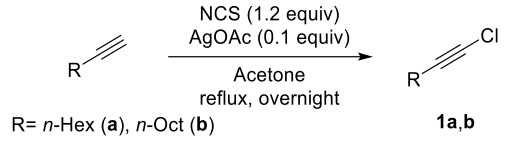


Figure S3. Structure of chlorohydrins **3a-h** and diester **3i** studied in this contribution.

II. General protocol for the synthesis of alkynes 1a-i and kinetic resolution of oct-1-yn-3-ol

II.1. Synthesis of alkynes 1a and 1b

Compounds **1a** and **1b** were synthesized following an adapted procedure to the one described by Nicolai *et al* (Scheme S1).[1]



Scheme S1. Synthesis of chlorinated alkynes **1a** and **1b** from the corresponding terminal alkynes.

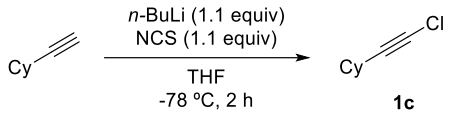
N-chlorosuccinimide (NCS, 3.2 g, 24 mmol, 1.20 equiv) and silver acetate (AgOAc, 333.9 mg, 2.4 mmol, 0.10 equiv) were added in this order to a solution of the corresponding acetylene (20 mmol, 1.0 equiv) in acetone (80 mL), and the solution was refluxed overnight. After this time, the mixture was poured into ice, and the resulting aqueous layer extracted with pentane (3 × 20 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4, filtered, and the solvent evaporated under reduced pressure. Purification by column chromatography (SiO_2, pentane) afforded the corresponding chlorinated alkyne **1a** or **1b** as smelly colorless oils (2.57 g and 3.21 g, 89% and 93% isolated yield, respectively). The spectroscopic data of compounds **1a** and **1b** matched with the ones previously reported in the literature.[1]

1-Chlorooct-1-yne (1a): Colorless oil. R_f (pentane): 0.80. IR: ν 2956, 2930, 2859, 2244, 1467, 1379, 1084, 726 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 2.19 (*t*, *J* = 7.0 Hz, 2H), 1.57–1.47 (*m*, 2H), 1.44–1.26 (*m*, 6H), 0.91 (*m*, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 69.8 (C), 56.9 (C), 31.3 (CH_2), 28.5 (CH_2), 28.3 (CH_2), 22.5 (CH_2), 18.8 (CH_2), 14.0 (CH_3).

1-Chlorodec-1-yne (1b): Colorless oil. R_f (10% Et_2O/pentane): 0.85. IR: ν 2958, 2925, 2855, 2317, 1468, 1083, 724 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 2.18 (*t*, *J* = 7.0 Hz, 2H), 1.51 (*quint*, *J* = 7.1 Hz, 2H), 1.42–1.29 (*m*, 10H), 0.90 (*t*, *J* = 6.6 Hz, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 69.7 (C), 56.9 (C), 31.8 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.8 (CH_2), 28.4 (CH_2), 22.7 (CH_2), 18.9 (CH_2), 14.1 (CH_3).

II.2. Synthesis of alkyne 1c

Compound **1c** was synthesized following an adapted procedure to the one described by Bai *et al* (Scheme S2).[2]



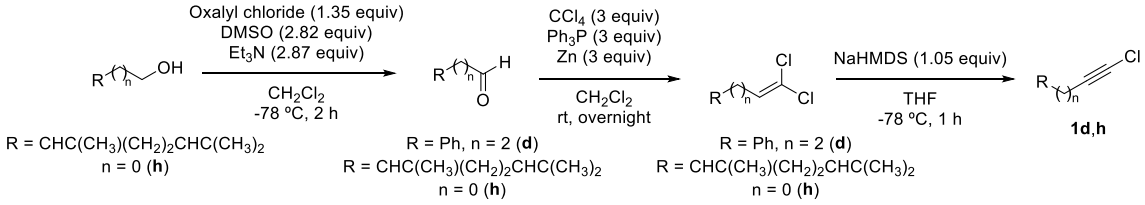
Scheme S2. Synthesis of chlorinated alkyne **1c**.

N-butyllithium (2.4 M solution in hexanes, 4.6 mL, 11 mmol, 1.1 equiv) was added to a solution of ethynylcyclohexane (1.3 mL, 10 mmol, 1.0 equiv) in THF (30 mL) under nitrogen atmosphere, and the mixture was stirred for 15 min at –78 ºC before the addition of *N*-chlorosuccinimide (NCS, 1.49 g, 11 mmol, 1.1 equiv). The reaction was then allowed to gradually warm to room temperature and subsequently quenched with an aqueous saturated NH_4Cl solution (15 mL). The aqueous layer was extracted with Et_2O (3 x 30 mL), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum. Purification by column chromatography (SiO_2, pentane) afforded the corresponding chlorinated alkyne **1c** as a smelly colorless oil (1.23 g, 86% of isolated yield).

(Chloroethynyl)cyclohexane (1c): Colorless oil. R_f (pentane): 0.80. IR: ν 3005, 2990, 2929, 2855, 2319, 1462, 1275, 1267, 1261, 1049, 742 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 2.44 (*apparent td*, *J* = 9.0, 4.5 Hz, 1H), 1.84–1.67 (*m*, 4H), 1.53–1.28 (*m*, 6H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 81.9 (C), 65.1 (C), 32.3 ($2CH_2$), 29.5 (CH_2), 25.8 (CH), 24.8 ($2CH_2$).

II.3. Synthesis of alkynes 1d and 1h

Alkynes **1d** and **1h** were synthesized through a Corey-Fuchs reaction.[3] In the case of alkyne **1h**, the development of a previous Swern oxidation to obtain an aldehyde was performed by adapting the protocol previously described by Marx and Tidwell (Scheme S3).[4]



Scheme S3. Synthesis of chlorinated alkynes **1d** and **1h**.

Oxalyl chloride (1.5 mL, 17.5 mmol, 1.35 equiv) and dimethylsulfoxide (DMSO, 2.6 mL, 36.6 mmol, 2.82 equiv) were diluted with CH_2Cl_2 (25 mL) under nitrogen atmosphere and the mixture was stirred at –78 ºC. After 15 min, (*E*)-3,7-dimethylocta-2,6-dien-1-ol (2.3 mL, 12.97 mmol, 1.0 equiv) was added and stirred for further 30 min. Then, Et_3N (5.2 mL, 37.2 mmol, 2.87 equiv) was added. The reaction was then allowed to gradually warm to room temperature, quenched with H_2O (25 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with an aqueous saturated $NaHCO_3$ solution (30 mL) and then, dried over Na_2SO_4, filtered and concentrated in vacuum.

In the second step, carbon tetrachloride (CCl_4, 5.7 mL, 60 mmol, 3.0 equiv), triphenylphosphine (Ph_3P, 15.8 g, 60 mmol, 3.0 equiv) and Zn (3.9 g, 60 mmol, 3.0 equiv) were stirred in CH_2Cl_2 (100 mL) for 15 min at rt under nitrogen atmosphere. After that, the corresponding aldehyde was added dropwise. After 16 h, the black solution was concentrated in the rotary evaporator until approx. 50 mL of mixture remained. The residue was then purified via flash chromatography on silica gel (100% hexane) to obtain the desired 2,2-dichlorovinylated derivatives as yellow oils.

Subsequently, a 1 M solution of NaHMDS in THF (10.05 mL, 10.05 mmol, 1.05 equiv) was added dropwise at –78 ºC to a stirred solution of the corresponding 2,2-dichlorovinylated derivative (10 mmol) in THF (25 mL). After 1 h, the reaction was

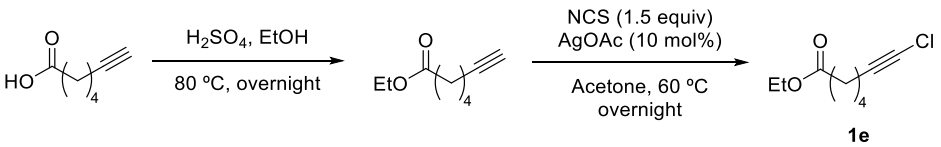
warmed to 0 ºC, quenched with an aqueous saturated NH_4Cl solution (20 mL) and diluted with H_2O (25 mL). Then, the solution was extracted with Et_2O (3 x 20 mL), washed with brine (2 x 20 mL), and the combined organic extracts dried over Na_2SO_4, filtered, and the solvent removed by evaporation under reduced pressure. Compounds **1d** and **1h** were isolated by column chromatography (SiO_2, 100% hexane) to obtain the desired chlorinated alkynes **1d** and **1h** (1.19 g and 1.10 g, 72 and 60% isolated yield, respectively). The spectroscopic data of compound **1d** matched with the ones already reported in the literature.[5]

(4-Chlorobut-3-yn-1-yl)benzene (1d): Colorless oil. R_f (hexane): 0.49. IR: ν 3028, 2928, 2859, 1604, 1454, 1076, 744, 696 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 7.36–7.22 (*m*, 5H), 2.85 (*t*, *J* = 7.6 Hz, 2H), 2.49 (*t*, *J* = 7.5 Hz, 2H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 140.7 (C), 128.9 (2CH), 128.8 (2CH), 126.8 (CH), 69.4 (C), 58.4 (C), 35.2 (CH_2), 21.4 (CH_2).

(*E*)-1-Chloro-4,8-dimethylnona-3,7-dien-1-yne (1h): Colorless oil. R_f (pentane): 0.83. IR: ν 2966, 2913, 1625, 1439, 1376, 1273, 829, 754, 419 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 5.22 (*m*, 1H), 5.08 (*m*, 1H), 2.12 (*m*, 4H), 1.90 (*s*, 3H), 1.70 (*s*, 3H), 1.62 (*s*, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 154.4 (C), 132.7 (C), 123.7 (CH), 104.0 (CH), 69.5 (C), 68.1 (C), 39.0 (CH_2), 26.5 (CH_2), 26.1 (CH_3), 19.8 (CH_3), 18.1 (CH_3).

II.4. Synthesis of alkyne 1e

Compound **1e** was synthesized through esterification of hept-6-ynoic acid with ethanol and chemical chlorination of the resulting ethyl hept-6-ynoate. Both steps were performed following an adapted procedure to the one described by Nicolai *et al* (Scheme S4).[1]



Scheme S4. Synthesis of chlorinated alkyne **1e**.

Hept-6-ynoic acid (1 g, 7.9 mmol), a concentrated H_2SO_4 aqueous solution (0.88 mL) and ethanol (EtOH, 7.1 mL) were stirred at 80 ºC overnight. After that, the reaction was cooled at rt and quenched with H_2O (5 mL). The solution was extracted with Et_2O (3 x

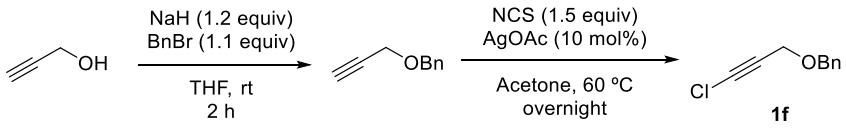
15 mL) and the combined organic extracts dried over Na_2SO_4, filtered, and the solvent removed by evaporation under reduced pressure, yielding ethyl hept-6-ynoate that was used without further purification for the next step.

Then, NCS (1.58 g, 11.85 mmol, 1.50 equiv) and AgOAc (132 mg, 0.79 mmol, 0.10 equiv) were added in this order to the previous obtained ester (7.9 mmol, 1.0 equiv) in acetone (25 mL), and the solution was refluxed overnight. After this time, the mixture was poured into ice, and the resulting aqueous layer extracted with pentane (3 × 20 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4, filtered, and the solvent evaporated under reduced pressure. Purification by column chromatography (SiO_2, 10% Et_2O/pentane) afforded the corresponding chlorinated alkyne **1e** as a smelly colorless oil (1.00 g, 67% isolated yield).

Ethyl 7-chlorohept-6-ynoate (1e): Colorless oil. R_f (10% Et_2O/pentane): 0.55. IR: ν 2938, 2239, 1732, 1298, 1273, 1178, 1028, 756, 747 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 4.14 (*qt*, *J* = 7.1, 1.3 Hz, 2H), 2.32 (*td*, *J* = 7.4, 1.7 Hz, 2H), 2.21 (*td*, *J* = 7.0, 1.6 Hz, 2H), 1.78–1.67 (*m*, 2H), 1.60–1.49 (*m*, 2H), 1.27 (*tt*, *J* = 7.1, 1.3 Hz, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 173.9 (C), 69.5 (C), 60.8 (CH_2), 57.9 (C), 34.2 (CH_2), 28.1 (CH_2), 24.4 (CH_2), 18.9 (CH_2), 14.7 (CH_3). HRMS (ESI$^+$, m/z): calcd for $(C_9H_{14}ClO_2)^+$ $(M+H)^+$: 189.0677; found 189.0682.

II.5. Synthesis of alkyne 1f

Compound **1f** was synthesized by first protecting the alcohol function with a benzyl group and subsequent chlorination of the terminal alkyne (Scheme S5).



Scheme S5. Synthesis of chlorinated alkyne **1f**.

A solution of prop-2-yn-1-ol (883 µL, 15 mmol, 1.0 equiv) in THF (30 mL) was added dropwise to a solution of NaH (720 mg, 18 mmol, 1.2 equiv) in THF (15 mL), and the resulting mixture was stirred 30 min at 0 ºC under nitrogen atmosphere. After that, benzyl bromide (1.95 mL, 16.5 mmol, 1.1 equiv) was added and the reaction was then allowed

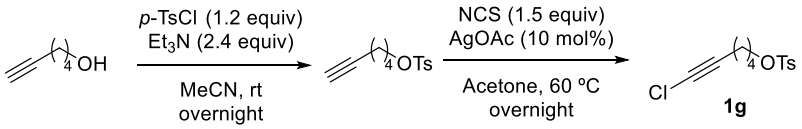
to gradually warm to room temperature and stirred 2 h at rt. After this time, the reaction was quenched with an aqueous saturated NH_4Cl solution (25 mL), and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum. Purification by column chromatography (SiO_2, 5% EtOAc/hexane) afforded the corresponding benzylated alkyne.

Then, NCS (2.85 g, 21.38 mmol, 1.5 equiv) and AgOAc (357 mg, 2.14 mmol, 0.1 equiv) were added in this order to the previous obtained benzylated alkyne (14.25 mmol, 1.0 equiv) in acetone (40 mL), and the solution was refluxed overnight. After this time, the mixture was poured into ice, and the resulting aqueous layer extracted with pentane (3 × 40 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered, and the solvent evaporated under reduced pressure. Purification by column chromatography (SiO_2, 5% EtOAc/hexane) afforded the corresponding chlorinated alkyne **1f** as a smelly colorless oil (2.12 g, 77% isolated yield). The spectroscopic data of compound **1f** matched with the ones already reported in the literature.[6]

{[(3-Chloroprop-2-yn-1-yl)oxy]methyl}benzene (1f): Colorless oil. R_f (5% EtOAc/hexane): 0.68. IR: ν 3005, 2990, 2858, 1275, 1267, 1261, 1089, 748, 696 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ.7.43–7.31 (*m*, 5H), 4.62 (*s*, 2H), 4.21 (*s*, 2H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 137.6 (C), 128.9 (2CH), 128.5 (2CH), 128.4 (CH), 72.1 (CH_2), 65.8 (C), 65.1 (C), 57.9 (CH_2). HRMS (ESI^+, m/z): calcd for $(C_{10}H_{10}ClO)^+$ $(M+H)^+$: 181.0415; found 181.0420.

II.6. Synthesis of alkyne 1g

Compound **1g** was synthesized by first protecting the alcohol moiety with a tosyl group and next via chemical chlorination of the terminal alkyne (Scheme S6).



Scheme S6. Synthesis of chlorinated alkyne **1g**.

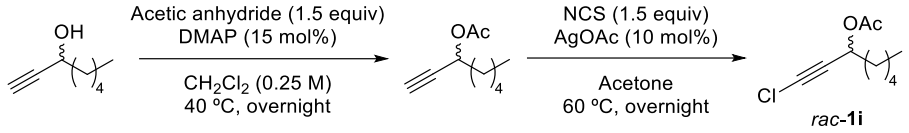
Hex-5-yn-1-ol (1.00 g, 10.2 mmol, 1.0 equiv), *p*-toluensulfonyl chloride (2.33 g, 12.24 mmol, 1.2 equiv) and Et_3N (3.40 mL, 24.5 mmol, 2.4 equiv) were dissolved in dry MeCN (50 mL) and stirred overnight at rt under nitrogen atmosphere. After this time, the reaction was quenched with H_2O (25 mL), and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum. Purification by column chromatography (SiO_2, 30% EtOAc/hexane) afforded the corresponding tosylated derivative. The spectroscopic data of the compound matched with the ones already reported in the literature.[7]

Then, NCS (1.30 g, 9.77 mmol, 1.5 equiv) and AgOAc (108.5 mg, 0.65 mmol, 0.1 equiv) were added in this order to a solution of the obtained hex-5-yn-1-yl 5-methylbenzenesulfonate (6.51 mmol, 1.0 equiv) in acetone (25 mL). The solution was refluxed overnight, and then the mixture was poured into ice, extracting the resulting aqueous layer with pentane (3 × 20 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4, filtered, and the solvent evaporated under reduced pressure. Purification by column chromatography (SiO_2, 50% EtOAc/hexane) afforded the corresponding chlorinated alkyne **1g** as a smelly colorless oil (1.68 g, 74% isolated yield).

6-Chlorohex-5-yn-1-yl 4-methylbenzenesulfonate (1g): Colorless oil. R_f (50% EtOAc/hexane): 0.89. IR: ν 2954, 2925, 1598, 1357, 1175, 1097, 933, 816, 666, 556 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 7.81 (*d*, *J* = 8.3 Hz, 2H), 7.37 (*d*, *J* = 7.9 Hz, 2H), 4.06 (*t*, *J* = 6.3 Hz, 2H), 2.47 (*s*, 3H), 2.17 (*t*, *J* = 6.9 Hz, 2H), 1.76 (*dq*, *J* = 8.0, 6.0 Hz, 2H), 1.55 (*quint*, *J* = 7.0 Hz, 2H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 144.8 (C), 133.1 (C), 129.9 (2CH), 127.9 (2CH), 69.8 (C+CH_2), 68.6 (C), 27.8 (CH_2), 24.2 (CH_2), 21.6 (CH_3), 18.1 (CH_2). HRMS (ESI^+, m/z): calcd for $(C_{13}H_{15}ClNaO_3S)^+$ $(M+Na)^+$: 309.0323; found 309.0332.

II.7. Synthesis of alkyne 1i

Compound **1i** was synthesized by first protecting the alcohol moiety with an acetyl group and next via chemical chlorination of the terminal alkyne (Scheme S7).



Scheme S7. Synthesis of racemic chlorinated alkyne **1i**.

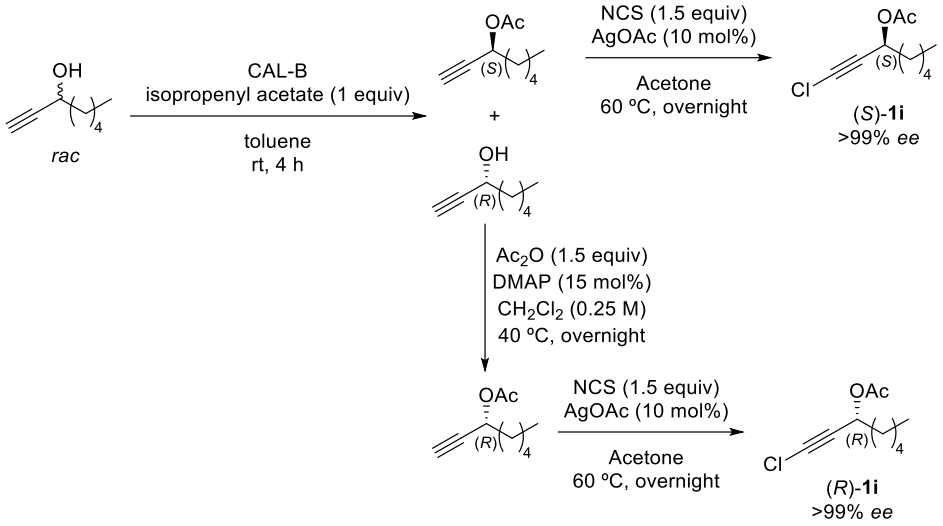
Oct-1-yn-3-ol (2.00 g, 15.85 mmol, 1.0 equiv), acetic anhydride (2.25 mL, 23.78 mmol, 1.5 equiv) and DMAP (284 mg, 2.39 mmol, 0.15 equiv) were dissolved in CH_2Cl_2 (65 mL), and stirred overnight at 40 ºC. After this time, the reaction was quenched with H_2O (25 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum, affording the corresponding acetate intermediate.

Then, NCS (1.19 g, 8.92 mmol, 1.5 equiv) and AgOAc (99 mg, 0.59 mmol, 0.1 equiv) were added in this order to a solution of the so-obtained oct-1-yn-3-yl acetate (5.94 mmol, 1.0 equiv) in acetone (25 mL). The solution was refluxed overnight, and after this time, the mixture was poured into ice, and the resulting aqueous layer extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4, filtered, and the solvent evaporated under reduced pressure. Purification by column chromatography (SiO_2, 10% Et_2O/pentane) afforded the corresponding chlorinated alkyne **1i** as a smelly colorless oil (1.16 g, 48% isolated yield).

1-Chlorooct-1-yn-3-yl acetate (1i): Colorless oil. R_f (50% Et_2O/pentane): 0.81. IR: ν 3045, 2929, 2861, 2244, 1740, 1369, 1273, 1257, 1219, 1017, 765, 749 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 5.33 (*t*, *J* = 6.7 Hz, 1H), 2.09 (*s*, 3H), 1.79–1.70 (*m*, 2H), 1.47–1.26 (*m*, 6H), 0.90 (*t*, *J* = 6.8 Hz, 3H). ^{13}C-NMR (75.5 MHz, CDCl3): δ 170.4 (C), 67.3 (C), 64.6 (CH), 64.4 (C), 35.0 (CH_2), 31.6 (CH_2), 25.0 (CH_2), 22.9 (CH_2), 21.4 (CH_3), 14.4 (CH_3). HRMS (ESI^+, m/z): calcd for $(C_{10}H_{16}ClO_2)^+$ $(M+H)^+$: 203.0833; found 203.0843.

II.8. Kinetic resolution of oct-1-yn-3-ol

Both acetylated **1i** enantiomers were obtained through lipase-catalyzed kinetic resolution of oct-1-yn-3-ol following an adapted procedure to the one described by Zhu *et al* (Scheme S8).[8]



Scheme S8. Kinetic resolution of oct-1-yn-3-ol and synthesis of chlorinated alkynes (*S*)- and (*R*)-**1i**.

A suspension of racemic oct-1-yn-3-ol (2.24 g, 16 mmol, 1.0 equiv), isopropenyl acetate (1.76 mL, 16 mmol, 1.0 equiv) and immobilized CAL-B (Novozyme 435®, 320 mg) in toluene (80 mL) was stirred at rt for 4 h. After this time, the suspension was filtered off, washed (10 mL), and the solvent evaporated under reduced pressure. Purification by column chromatography (SiO_2, 30% Et_2O/hexane) afforded the corresponding optically active (*R*)-alcohol (987 mg, 44% isolated yield) and (*S*)-acetate (1.37 g, 47% isolated yield) both in enantiopure form (see Section X for analytical details).

On one hand, the enantiopure (*S*)-acetate was subjected to a chlorination reaction following the usual procedure: NCS (1.50 g, 11.25 mmol, 1.5 equiv) and AgOAc (125 mg, 0.75 mmol, 0.1 equiv) were added in this order to a solution of (*S*)-oct-1-yn-3-yl acetate (1.37 g, 7.5 mmol, 1.0 equiv) in acetone (30 mL). The solution was refluxed overnight, and after this time, the mixture was poured into ice, and the resulting aqueous layer extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4, filtered, and the solvent evaporated under reduced

pressure. Purification by column chromatography (SiO_2, 30% Et_2O/hexane) afforded the corresponding chlorinated alkyne (*S*)-**1i** (>99% *ee*) as a smelly colorless oil (1.10 g, 32% isolated yield).

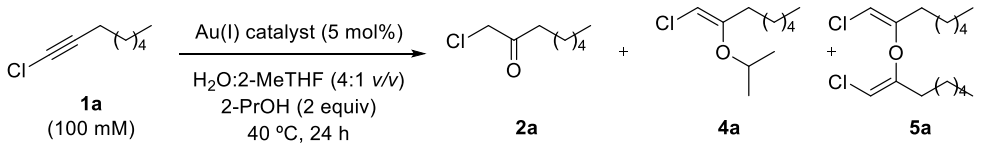
On the other hand, the unreacted (*R*)-alcohol from the lipase-catalyzed kinetic resolution was chemically acetylated. Therefore, (*R*)-oct-1-yn-3-ol (987 mg, 7.78 mmol, 1.0 equiv), acetic anhydride (1.12 mL, 11.67 mmol, 1.5 equiv) and DMAP (146 mg, 1.17 mmol, 0.15 equiv) were dissolved in CH_2Cl_2 (25 mL), and stirred overnight at 40 ºC. After this time, the reaction was quenched with H_2O (25 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum. The resulting crude without further purification was subjected to the chlorination reaction. Thus, NCS (1.56 g, 11.67 mmol, 1.5 equiv) and AgOAc (130 mg, 0.78 mmol, 0.1 equiv) were added in this order to a solution of the so-obtanined (*R*)-oct-1-yn-3-yl acetate (7.78 mmol, 1.0 equiv) in acetone (25 mL). The solution was refluxed overnight, and after this time, the mixture was poured into ice, and the resulting aqueous layer extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4, filtered, and the solvent evaporated under reduced pressure. Purification by column chromatography (SiO_2, 10% Et_2O/pentane) afforded the corresponding chlorinated alkyne (*R*)-**1i** (>99 *ee*) as a smelly colorless oil (1.28 g, 37% isolated yield).

The spectroscopic data of optically active **1i** enantiomers matched with those reported for the racemic compound that have been previously displayed. For the optical rotation value, see Section XI.

The absolute configuration of both enantiomers was assigned based on the known stereopreference of the CAL-B.

III. Optimization of the gold(I)-catalyzed hydration process of alkyne 1a

Table S1. Screening of gold(I) catalysts in the hydration reaction of 1-chlorooct-1-yne (**1a**).



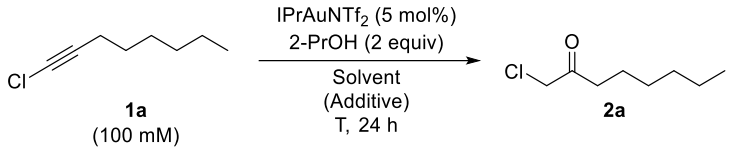
Entry	Catalyst	**1a** (%)[a]	**2a** (%)[a]	By-products (%)[a]
1	--	>99	<1	<1
2	$IPrAuNTf_2$	<1	99	1
3	$IPrAu(MeCN)SbF_6$	21	68	11
4	$JohnPhosAu(MeCN)SbF_6$	62	37	1
5	$JohnPhosAuNTf_2$	<1	91	9
6	$BrettPhosAuNTf_2$	<1	96	4
7	Ph_3PAuCl	53	<1	47

[a] Product percentages were determined by GC analysis.

1-Chlorooctan-2-one (2a):[9] Yellowish oil (190 mg, 96%). R_f (5% EtOAc/hexane): 0.60. IR: ν 1693 and 769 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 4.07 (*s*, 2H), 2.58 (*t*, *J* = 7.4 Hz, 2H), 1.61 (*quint*, *J* = 7.3 Hz, 2H), 1.29 (*m*, 6H), 0.88 (*t*, *J* = 6.9 Hz, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 202.8 (C), 48.2 (CH_2), 39.7 (CH_2), 31.5 (CH_2), 28.7 (CH_2), 23.6 (CH_2), 22.5 (CH_2), 14.0 (CH_3). HRMS (ESI^+, m/z): calcd for $(C_8H_{16}ClO)^+$ $(M+H)^+$: 163.0889; found 163.0883.

(*Z*)-1-Chloro-2-{[(*Z*)-1-chlorooct-1-en-2-yl]oxy}oct-1-ene (5a):[9] Yellowish oil. R_f (hexane): 0.46. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 5.44 (*t*, *J* = 1.3 Hz, 2H), 2.12 (*m*, 4H), 1.56–1.48 (*m*, 4H), 1.30 (*m*, 12H), 0.89 (*m*, 6H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 153.2 (2C), 100.1 (2CH), 32.3 ($2CH_2$), 31.5 ($2CH_2$), 28.7 ($2CH_2$), 26.6 ($2CH_2$), 22.5 ($2CH_2$), 14.1 ($2CH_3$). HRMS (ESI^+, m/z): calcd for $(C_{16}H_{29}Cl_2O)^+$ $(M+H)^+$: 307.1590; found 307.1587.

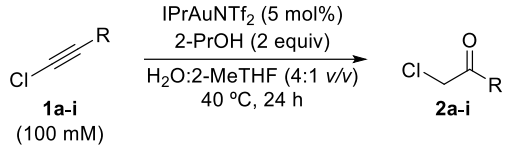
Table S2. Screening of the reaction medium, temperature and equivalents of 2-PrOH in the hydration process of **1a** using $IPrAuNTf_2$ (5 mol%).



Entry	Reaction medium[a]	T (ºC)	1a (%)[b]	2a (%)[b]	By-products (%)[b]
1	H_2O:MeCN (4:1)	40	12	67	21
2	H_2O:THF (4:1)	40	<1	72	28
3	H_2O:2-Me-THF (4:1)	40	<1	99	1
4	H_2O:*n*-Heptane (4:1)	40	3	78	19
5	H_2O:MTBE (4:1)	40	<1	63	37
6	Buffer Tris-HCl pH 8.0 (20 mM):2-Me-THF (4:1)	40	<1	85	15
7	Buffer PO_4^{3-} pH 7.5 (50 mM):2-Me-THF (4:1)	40	54	34	12
8	H_2O:2-Me-THF (95:5)	40	<1	42	58
9	H_2O:2-Me-THF (9:1)	40	<1	48	52
10	H_2O:2-Me-THF (85:15)	40	<1	79	21
11	H_2O:2-Me-THF (4:1)	20	<1	88	12
12	H_2O:2-Me-THF (4:1)	30	<1	91	9
13	H_2O:2-Me-THF (4:1)	45	<1	84	16
14	H_2O:2-PrOH (4:1)	40	<1	35	65
15	H_2O	40	<1	86	14
16	TPGS-750-M[c]	40	<1	60	40
17	H_2O:DES[d] (4:1)	40	<1	86	14
18[e]	H_2O:2-Me-THF (4:1)	40	<1	93	7
19[f]	H_2O:2-Me-THF (4:1)	40	<1	92	8

[a] Volume/volume ratios appear in parentheses unless otherwise stated.
[b] Product percentages were determined by GC analysis.
[c] This is a commercially available water solution that includes the surfactant in 2% w/v.
[d.] Deep Eutectic Solvent formed by ChCl:Gly (1:2 mol/mol).
[e] [**1a**] = 150 mM.
[f] [**1a**] = 200 mM.

IV. Full characterization of α-halomethyl ketones 2 obtained through gold(I)-catalyzed hydration



1-Chlorooctan-2-one (2a):[9] Yellowish oil (190 mg, 96%). See Section III for full compound characterization.

1-Chlorodecan-2-one (2b):[10] Yellowish oil (212 mg, 96%). R_f (10% EtOAc/hexane): 0.65. IR: ν 2924, 2855, 1733, 1719, 1459, 1401, 1378, 1131, 1069, 770, 759, 747, 725 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 4.09 (*s*, 2H), 2.60 (*t*, *J* = 7.4 Hz, 2H), 1.63 (*m*, 2H), 1.34–1.27 (*m*, 10H), 0.90 (*t*, *J* = 6.7 Hz, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 202.8 (C), 48.2 (CH_2), 39.7 (CH_2), 31.8 (CH_2), 29.3 (CH_2), 29.1 ($2CH_2$), 23.6 (CH_2), 22.6 (CH_2), 14.0 (CH_3). HRMS (ESI^+, m/z): calcd for $(C_{10}H_{19}ClNaO)^+$ $(M+Na)^+$: 213.1017; found 213.1027.

2-Chloro-1-cyclohexylethan-1-one (2c):[11] Yellowish oil (200 mg, 89%). R_f (2% EtOAc/hexane): 0.54. IR: ν 2929, 2855, 1722, 1709, 1450, 1396, 1371, 1275, 1267, 1261, 768, 742 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 4.18 (*s*, 2H), 2.64 (*tt*, *J* = 11.2, 3.3 Hz, 1H), 1.90–1.78 (*m*, 4H), 1.69 (*m*, 1H), 1.46–1.19 (*m*, 5H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 205.0 (C), 47.8 (CH_2), 47.3 (CH), 28.4 ($2CH_2$), 25.6 (CH_2), 25.5 ($2CH_2$). HRMS (ESI^+, m/z): calcd for $(C_8H_{13}ClNaO)^+$ $(M+Na)^+$: 183.0547; found 183.0548.

1-Chloro-4-phenylbutan-2-one (2d):[11] Yellowish oil (182 mg, 82%). R_f (10% EtOAc/hexane): 0.38. IR: ν 3028, 2929, 1733, 1721, 1717, 1454, 1398, 1257, 1083, 1065, 752, 698, 552, 495 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 7.35–7.20 (*m*, 5H), 4.06 (*s*, 2H), 2.97 (*m*, 4H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 201.9 (C), 140.3 (C), 128.6 (2CH), 128.3 (2CH), 126.4 (CH), 48.3 (CH_2), 41.3 (CH_2), 29.6 (CH_2). HRMS (ESI^+, m/z): calcd for $(C_{10}H_{11}ClNaO)^+$ $(M+Na)^+$: 205.0391; found 205.0399.

Ethyl 7-chloro-6-oxoheptanoate (2e):[12] Yellowish oil (180 mg, 82%). R_f (50% Et_2O/pentane): 0.49. IR: ν 2980, 2939, 1723, 1374, 1177, 1027, 768, 414 cm^{-1}. ^{1}H-NMR

(300.13 MHz, $CDCl_3$): δ 4.13 (*m*, 4H), 2.64 (*m*, 2H), 2.33 (*m*, 2H), 1.67 (*m*, 4H), 1.26 (*t*, *J* = 7.1 Hz, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 202.8 (C), 173.8 (C), 60.8 (CH_2), 48.7 (CH_2), 39.7 (CH_2), 34.4 (CH_2), 24.6 (CH_2), 23.3 (CH_2), 14.7 (CH_3). HRMS (ESI^+, m/z): calcd for $(C_9H_{16}ClO_3)^+$ $(M+H)^+$: 207.0782; found 207.0785.

1-Benzyloxy-3-chloropropan-2-one (2f):[13] Yellowish oil (180 mg, 82%). R_f (20% EtOAc/hexane): 0.45. IR: ν 3005, 2990, 1741, 1275, 1267, 1261, 1097, 763, 750, 698 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 7.43–7.33 (*m*, 5H), 4.63 (*s*, 2H), 4.32 (*s*, 2H), 4.27 (*s*, 2H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 200.3 (C), 136.6 (C), 128.7 (2CH), 128.3 (CH), 128.0 (2CH), 73.7 (CH_2), 73.6 (CH_2), 46.7 (CH_2). HRMS (ESI^+, m/z): calcd for $(C_{10}H_{11}ClNaO_2)^+$ $(M+Na)^+$: 221.0340; found 221.0347.

6-Chloro-5-oxohexyl 4-methylbenzenesulfonate (2g):[11] Yellowish oil (189 mg, 89%). R_f (50% EtOAc/hexane): 0.65. IR: ν 2961, 2923, 2868, 1716, 1579, 1469, 1455, 1328, 1276, 1153, 768, 749, 736, 704, 548 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 7.79 (*d*, *J* = 8.2 Hz, 2H), 7.37 (*d*, *J* = 8.0 Hz, 2H), 4.04 (*m*, 4H), 2.60 (*t*, *J* = 6.4 Hz, 2H), 2.47 (*s*, 3H), 1.69 (*m*, 4H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 202.0 (C), 144.9 (C), 133.0 (C), 129.9 (2CH), 127.9 (2CH), 70.0 (CH_2), 48.1 (CH_2), 38.6 (CH_2), 28.0 (CH_2), 21.7 (CH_2), 19.5 (CH_3). HRMS (ESI^+, m/z): calcd for $(C_{13}H_{17}ClNaO_4S)^+$ $(M+Na)^+$: 327.0428; found 327.0444.

V. Full characterization of β-chlorohydrins 3 obtained after chemical reduction of α-chloro ketones 2

Full characterizations of alcohols **3a**-**d**,**f**,**h** appear below, while the obtained specific rotation values of the enantioenriched derivatives appear in Section XI (Table S20):

1-Chlorooctan-2-ol (3a):[14] Yellowish oil (29 mg, 88%). R_f (10% EtOAc/hexane): 0.37. IR: ν 3375, 3005, 2987, 1275, 1260 and 763 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 3.79 (*m*, 1H), 3.63 (*dd*, *J* = 11.0, 3.2 Hz, 1H), 3.47 (*dd*, *J* = 11.1, 7.1 Hz, 1H), 2.22 (*br s*, 1H), 1.57–1.47 (*m*, 2H), 1.30 (*m*, 8H), 0.87 (*t*, *J* = 6.9 Hz, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 71.5 (CH), 50.6 (CH_2), 34.2 (CH_2), 31.7 (CH_2), 29.2 (CH_2), 25.5 (CH_2), 22.6 (CH_2), 14.1 (CH_3). HRMS (ESI^+, m/z): calcd for $(C_8H_{17}ClNaO)^+$ $(M+Na)^+$: 187.0866; found 187.0870.

1-Chlorodecan-2-ol (3b):[15] Yellowish oil (33 mg, 86%). R_f (10% EtOAc/hexane): 0.40. IR: ν 3347, 3005, 1275, 1267, 1261, 769, 759 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 3.82 (*m*, 1H), 3.66 (*dd*, *J* = 11.0, 3.2 Hz, 1H), 3.50 (*dd*, *J* = 11.1, 7.1 Hz, 1H), 2.16 (*d*, *J* = 4.8 Hz, 1H), 1.55 (*m*, 2H), 1.30 (*m*, 12H), 0.90 (*t*, *J* = 6.7 Hz, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 71.5 (CH), 50.6 (CH_2), 34.2 (CH_2), 31.9 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 25.5 (CH_2), 22.7 (CH_2), 14.1 (CH_3). HRMS (ESI^+, m/z): calcd for $(C_{10}H_{21}ClNaO)^+$ $(M+Na)^+$: 215.1173; found 215.1176.

2-Chloro-1-cyclohexylethan-1-ol (3c):[16] Yellowish oil (22 mg, 68%). R_f (20% EtOAc/pentane): 0.25. IR: ν 3367, 3005, 1275, 1267, 1261, 741, 726 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 3.76–3.68 (*m*, 1H), 3.61–3.52 (*m*, 2H), 2.20 (*s*, 1H), 1.92 (*m*, 1H), 1.82–1.65 (*m*, 4H), 1.52 (*m*, 1H), 1.35–1.00 (*m*, 5H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 75.6 (CH), 49.2 (CH_2), 41.3 (CH), 29.0 (CH_2), 28.3 (CH_2), 26.3 (CH_2), 26.0 (CH_2), 25.9 (CH_2). HRMS (ESI^+, m/z): calcd for $(C_8H_{15}ClNaO)^+$ $(M+Na)^+$: 185.0704; found 185.0709.

1-Chloro-4-phenylbutan-2-ol (3d):[17] Yellowish oil (34 mg, 91%). R_f (30% EtOAc/hexane): 0.51. IR: ν 3414, 3364, 2951, 2911, 1600, 1423, 1344, 1091, 1076, 854, 754, 728, 700, 597, 510, 474, 466 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 7.36–7.21 (*m*, 5H), 3.85 (*m*, 1H), 3.66 (*dd*, *J* = 11.1, 3.3 Hz, 1H), 3.53 (*dd*, *J* = 11.1, 7.0 Hz, 1H), 2.87–

2.73 (*m*, 2H), 2.32 (*d*, *J* = 3.9 Hz, 1H), 1.88 (*m*, 2H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 141.3 (C), 128.5 (2CH), 128.4 (2CH), 126.1 (CH), 70.6 (CH), 50.5 (CH_2), 35.8 (CH_2), 31.8 (CH_2). HRMS (ESI^+, m/z): calcd for $(C_{10}H_{13}ClNaO)^+$ $(M+Na)^+$: 207.0547; found 207.0551.

1-Benzyloxy-3-chloropropan-2-ol (3f):[18] Yellowish oil (36 mg, 89%). R_f (10% EtOAc/hexane): 0.12. IR: ν 3359, 2989, 2962, 1275, 1267, 1261, 1098, 764, 750 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 7.42–7.33 (*m*, 5H), 4.59 (*s*, 2H), 4.10–3.99 (*m*, 1H), 3.73–3.52 (*m*, 4H), 2.57 (*d*, *J* = 5.6 Hz, 1H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 137.6 (C), 128.5 (2CH), 128.0 (CH), 127.8 (2CH), 73.6 (CH_2), 70.8 (CH_2), 70.3 (CH), 46.1 (CH_2).

(*E*)-1-Chloro-4,8-dimethylnona-3,7-dien-2-ol (3h):[19] Yellowish oil (30 mg, 74%). R_f (10% Et_2O/pentane): 0.17. IR: ν 3347, 2967, 2916, 2849, 1668, 1441, 1276, 1259, 1060, 1003, 763, 749 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 5.20 (*d*, *J* = 8.2 Hz, 1H), 5.08 (*t*, *J* = 6.6 Hz, 1H), 4.57 (*dt*, *J* = 7.9, 4.1 Hz, 1H), 3.63–3.43 (*m*, 2H), 2.31 (*m*, 1H), 2.13–2.00 (*m*, 4H), 1.72 (*s*, 3H), 1.69 (*s*, 3H), 1.61 (*s*, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 141.7 (C), 131.9 (C), 123.6 (CH), 123.0 (CH), 68.8 (CH), 49.7 (CH_2), 39.5 (CH_2), 26.3 (CH_2), 25.6 (CH_3), 17.7 (CH_3), 16.9 (CH_3). HRMS (ESI^+, m/z): calcd for $(C_{11}H_{19}ClNaO)^+$ $(M+Na)^+$: 225.1017; found 225.1023. (*S*)-**3h**, *ee* >99%, $[\alpha]_D^{20}$: –3.5 (*c* 1.0, $CHCl_3$).

VI. Experimental protocols and screening results for the reduction of α-chloromethyl ketones using different ADHs

VI.1. Bioreduction of 2a using ADH-A

α-Chloroketone **2a** (2.4 mg, 0.015 mmol), 2-Me-THF (120 μL), 2-PrOH (0.03 mmol, 2.4 μL), a NADH aqueous solution (10 mM, 60 μL), distilled water (420 μL) and lyophilized cells of *E. coli* overexpressing ADH-A (10 mg) were successively added to a 1.5 mL-Eppendorf tube. Then, the recipient was closed and kept under orbital shaking at 220 rpm at 40 °C for 24 h. After this time, the solution was extracted with Et_2O (3 x 0.5 mL), the organic layers combined, dried over anhydrous Na_2SO_4 and filtered. The solution was concentrated, measuring then the reaction conversion and the enantiomeric excess of alcohol **3a** by GC analyses.

VI.2. Bioreduction of 2a using ADH-T, TeSADH and SyADH

α-Chloroketone **2a** (2.4 mg, 0.015 mmol), 2-Me-THF (120 μL), 2-PrOH (0.03 mmol, 2.4 μL), a NADPH aqueous solution (10 mM, 60 μL), distilled water (420 μL) and lyophilized cells of *E. coli* overexpressing the corresponding ADH (10 mg) were successively added to a 1.5 mL-Eppendorf tube. Then, the recipient was closed and kept under orbital shaking at 220 rpm at 40 °C for 24 h. After this time, the solution was extracted with Et_2O (3 x 0.5 mL), the organic layers combined, dried over anhydrous Na_2SO_4 and filtered. The solution was concentrated, measuring then the reaction conversion and the enantiomeric excess of alcohol **3a** by GC analyses.

VI.3. Bioreduction of 2a using LbADH

α-Chloroketone **2a** (2.4 mg, 0.015 mmol), 2-Me-THF (126 μL), 2-PrOH (0.03 mmol, 2.4 μL), a NADPH aqueous solution (10 mM, 60 μL), a $MgCl_2$ aqueous solution (10 mM, 60 μL), distilled water (384 μL) and lyophilized cells of *E. coli* overexpressing *Lb*ADH (10 mg) were successively added to a 1.5 mL-Eppendorf tube. Then, the recipient was closed and kept under orbital shaking at 220 rpm at 40 °C for 24 h. After this time, the solution was extracted with Et_2O (3 x 0.5 mL), the organic layers combined, dried over anhydrous

Na_2SO_4 and filtered. The solution was concentrated, measuring then the reaction conversion and the enantiomeric excess of alcohol **3a** by GC analyses.

VI.4. Bioreduction of 2a using commercial evo.1.1.200

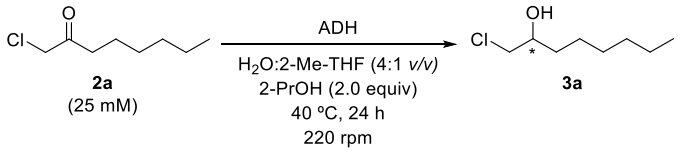
α-Chloroketone **2a** (2.4 mg, 0.015 mmol), 2-Me-THF (126 μL), 2-PrOH (0.03 mmol, 2.4 μL), a NADH aqueous solution (10 mM, 60 μL), a $MgCl_2$ aqueous solution (10 mM, 60 μL), distilled water (384 μL) and evo.1.1.200 (2.4 mg) were successively added to a 1.5 mL-Eppendorf tube. Then, the recipient was closed and kept under orbital shaking at 220 rpm at 40 °C for 24 h. After this time, the solution was extracted with Et_2O (3 x 0.5 mL), the organic layers combined, dried over anhydrous Na_2SO_4 and filtered. The solution was concentrated, measuring then the reaction conversion and the enantiomeric excess of alcohol **3a** by GC analyses.

VI.5. Bioreduction of 2a using commercial ADHs from Codexis

The selected commercially available Codexis KRED (2.4 mg) was added to a 1.5 mL Eppendorf tube containing α-chloroketone **2a** (2.4 mg, 0.015 mmol), 2-Me-THF (126 μL), 2-PrOH (0.03 mmol, 2.4 μL), a NADPH aqueous solution (10 mM, 60 μL), a $MgCl_2$ aqueous solution (10 mM, 60 μL) and distilled water (384 μL). Then, the recipient was closed and kept under orbital shaking at 220 rpm at 40 °C for 24 h. After this time, the product was extracted with Et_2O (3 × 0.5 mL), the organic layers combined, dried over anhydrous Na_2SO_4 and filtered. The solution was concentrated, measuring then the reaction conversion and the enantiomeric excess of alcohol **3a** by GC analyses.

VI.6. Summary of results in the bioreduction of ketone 2a

Table S3. Screening of different ADHs for the asymmetric bioreduction of **2a**.[a]

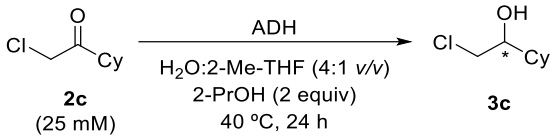


Entry	ADH[b]	**3a** (%)[c]	**3a** *ee* (%)[d]
1	ADH-A	>99	>99 (*R*)
2	ADH-T	68	71 (*R*)
3	*Te*SADH	<1	*n.d.*
4	*Sy*ADH	36	62 (*S*)
5	*Lb*ADH	>99	>99 (*S*)
6	evo.1.1.200	97	>99 (*S*)
7	KRED-P1-A04	97	>99 (*S*)
8	KRED-P1-A12	65	76 (*S*)
9	KRED-P1-B02	97	84 (*S*)
10	KRED-P1-B05	48	70 (*S*)
11	KRED-P1-B10	81	86 (*S*)
12	KRED-P1-B12	98	>99 (*S*)
13	KRED-P1-C01	99	79 (*S*)
14	KRED-P1-H08	99	58 (*S*)
15	KRED-P2-B02	99	<1
16	KRED-P2-C02	98	60 (*S*)
17	KRED-P2-C11	95	80 (*S*)
18	KRED-P2-D03	95	46 (*S*)
19	KRED-P2-D11	98	>99 (*S*)
20	KRED-P2-D12	97	>99 (*S*)
21	KRED-P2-G03	99	35 (*S*)
22	KRED-P2-H07	98	86 (*S*)
23	KRED-P3-B03	96	>99 (*R*)
24	KRED-P3-G09	98	>99 (*R*)
25	KRED-P3-H12	98	>99 (*R*)

[a] See Sections VI.1 to VI.5 for general procedures with all tested enzymes.
[b] The coupled-substrate system employing 2-PrOH as cosubstrate was used for cofactor recycling purposes.
[c] Product percentages were determined by GC analysis (see Section X for further details).
[d] Enantiomeric excess values were determined by GC analysis using a chiral column after acetylation of the halohydrin obtained in the reaction crude with acetic anhydride and DMAP. The configuration of the major enantiomer appears in parentheses. Change in the CIP priority. *n.d.*: not determined.

VI.7. Summary of results in the bioreduction of ketone 2c

Table S4. Screening of different ADHs for the asymmetric bioreduction of **2c**.[a]



Entry	ADH	**3c** (%)[b]	**3c** *ee* (%)[c]
1	ADH-A	51	>99 (*R*)
2	ADH-T	41	>99 (*R*)
3	*Te*SADH	<1	*n.d.*
4	*Sy*ADH	<1	*n.d.*
5	*Lb*ADH	98	>99 (*S*)
6	evo.1.1.200	>99	>99 (*S*)
7	KRED-P1-A04	>99	>99 (*S*)
8	KRED-P1-A12	97	>99 (*S*)
9	KRED-P1-B02	98	85 (*S*)
10	KRED-P1-B05	9	*n.d.*
11	KRED-P1-B10	98	81 (*S*)
12	KRED-P1-B12	98	95 (*S*)
13	KRED-P1-C01	>99	<1
14	KRED-P1-H08	99	<1
15	KRED-P2-B02	98	<1
16	KRED-P2-C02	96	10 (*S*)
17	KRED-P2-C11	97	97 (*S*)
18	KRED-P2-D03	98	55 (*S*)
19	KRED-P2-D11	>99	6 (*S*)
20	KRED-P2-D12	72	87 (*S*)
21	KRED-P2-G03	98	91 (*S*)
22	KRED-P2-H07	97	>99 (*S*)
23	KRED-P3-B03	15	60 (*R*)
24	KRED-P3-G09	6	*n.d.*
25	KRED-P3-H12	26	96 (*R*)

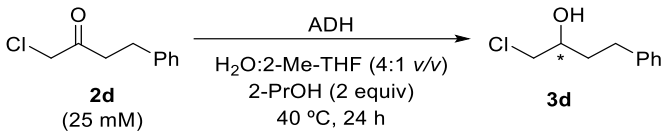
[a] Procedures already applied to ketone **2a** were used for the bioreduction of **2c** considering the mmol substrate/weight enzyme ratio.

[b] Product percentages were determined by GC analysis.

[c] Enantiomeric excess values were determined by GC analysis using a chiral column after acetylation of the halohydrin obtained in the reaction crude with acetic anhydride and DMAP. The configuration of the major enantiomer appears in parentheses. Change in the CIP priority. *n.d.*: not determined.

VI.8. Summary of results in the bioreduction of ketone 2d

Table S5. Screening of different ADHs for the asymmetric bioreduction of **2d**.[a]

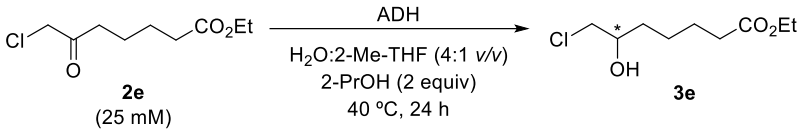


Entry	ADH	**3d** (%)[b]	**3d** *ee* (%)[c]
1	ADH-A	>99	>99 (*R*)
2	ADH-T	98	>99 (*R*)
3	*Te*SADH	47	>99 (*R*)
4	*Hl*ADH	3	*n.d.*
5	*Lb*ADH	99	>99 (*S*)
6	evo.1.1.200	99	>99 (*S*)
7	KRED-P1-A04	99	>99 (*S*)
8	KRED-P1-A12	99	>99 (*S*)
9	KRED-P1-B05	55	>99 (*S*)
10	KRED-P1-B10	98	>99 (*S*)
11	KRED-P1-B12	99	>99 (*S*)
12	KRED-P1-C01	98	<1
13	KRED-P1-H08	98	80 (*S*)
14	KRED-P2-B02	98	<1
15	KRED-P2-C02	96	<1
16	KRED-P2-C11	99	<1
17	KRED-P2-D03	99	>99 (*S*)
18	KRED-P2-D11	99	<1
19	KRED-P2-D12	92	86 (*S*)
20	KRED-P2-G03	99	42 (*S*)
21	KRED-P2-H07	99	94 (*S*)
22	KRED-P3-B03	93	>99 (*S*)
23	KRED-P3-G09	64	26 (*R*)
24	KRED-P3-H12	80	74 (*R*)

[a] Procedures already applied to ketone **2a** were used for the bioreduction of **2d** considering the mmol substrate/weight enzyme ratio.
[b] Product percentages were determined by HPLC analysis.
[c] Enantiomeric excess values were determined by chiral HPLC analysis. The configuration of the major enantiomer appears in parentheses. Change in the CIP priority. *n.d.*: not determined.

VI.9. Summary of results in the bioreduction of ketone 2e

Table S6. Screening of different ADHs for the asymmetric bioreduction of **2e**.[a]

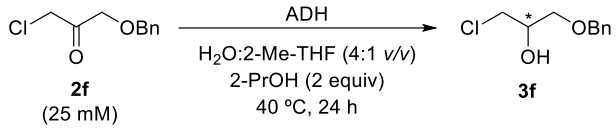


Entry	ADH	**3e** (%)[b]	**3e** *ee* (%)[c]
1	ADH-A	>99	>99 (*R*)
2	ADH-T	10	*n.d.*
3	*Te*SADH	48	*n.d.*
4	*Hl*ADH	21	*n.d.*
5	*Lb*ADH	99	>99 (*S*)
6	evo.1.1.200	99	>99 (*S*)
7	KRED-P1-A04	99	>99 (*S*)
8	KRED-P1-A12	98	>99 (*S*)
9	KRED-P1-B02	98	86 (*S*)
10	KRED-P1-B05	35	*n.d.*
11	KRED-P1-B10	99	>99 (*S*)
12	KRED-P1-B12	98	94 (*S*)
13	KRED-P1-C01	99	58 (*S*)
15	KRED-P2-B02	>99	<1
16	KRED-P2-C02	99	22 (*S*)
18	KRED-P2-D03	99	30 (*S*)
19	KRED-P2-D11	99	>99 (*S*)
20	KRED-P2-D12	91	>99 (*S*)
21	KRED-P2-G03	99	>99 (*S*)
22	KRED-P2-H07	99	>99 (*S*)
23	KRED-P3-B03	>99	46 (*S*)
24	KRED-P3-G09	41	*n.d.*
25	KRED-P3-H12	70	<1

[a] Procedures already applied to ketone **2a** were used for the bioreduction of **2e** considering the mmol substrate/weight enzyme ratio.
[b] Product percentages were determined by GC analysis.
[c] Enantiomeric excess values were determined by GC analysis using a chiral column after acetylation of the halohydrin obtained in the reaction crude with acetic anhydride and DMAP. The configuration of the major enantiomer appears in parentheses. Change in the CIP priority. *n.d.*: not determined.

VI.10. Summary of results in the bioreduction of ketone 2f

Table S7. Screening of different ADHs for the asymmetric bioreduction of **2f**.[a]

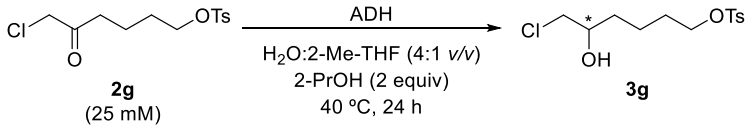


Entry	ADH	**3f** (%)[b]	**3f** *ee* (%)[c]
1	ADH-A	99	>99 (*R*)
2	ADH-T	20	*n.d.*
3	*Te*SADH	89	40 (*S*)
4	*Hl*ADH	40	*n.d.*
5	*Lb*ADH	>99	>99 (*S*)
6	evo.1.1.200	99	>99 (*S*)
7	KRED-P1-A04	99	>99 (*S*)
8	KRED-P1-A12	98	>99 (*S*)
9	KRED-P1-B02	70	>99 (*S*)
10	KRED-P1-B05	61	>99 (*S*)
11	KRED-P1-B10	>99	>99 (*S*)
12	KRED-P1-B12	97	>99 (*S*)
13	KRED-P1-C01	>99	68 (*S*)
14	KRED-P1-H08	93	<1
15	KRED-P2-B02	95	42 (*S*)
16	KRED-P2-C02	>99	76 (*S*)
17	KRED-P2-C11	97	>99 (*S*)
18	KRED-P2-D03	>99	>99 (*S*)
19	KRED-P2-D11	>99	>99 (*S*)
20	KRED-P2-D12	>99	40 (*S*)
21	KRED-P2-G03	>99	>99 (*S*)
22	KRED-P2-H07	>99	>99 (*S*)
23	KRED-P3-B03	>99	>99 (*R*)
24	KRED-P3-G09	65	>99 (*R*)
25	KRED-P3-H12	91	>99 (*R*)

[a] Procedures already applied to ketone **2a** were used for the bioreduction of **2f** considering the mmol substrate/weight enzyme ratio.
[b] Product percentages were determined by HPLC analysis.
[c] Enantiomeric excess values were determined by HPLC analysis. The configuration of the major enantiomer appears in parentheses. Change in the CIP priority. *n.d.*: not determined.

VI.11. Summary of results in the bioreduction of ketone 2g

Table S8. Screening of different ADHs for the asymmetric bioreduction of **2g**.[a]

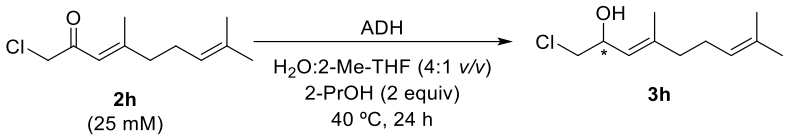


Entry	ADH	**3g** (%)[b]	**3g** *ee* (%)[c]
1	ADH-A	99	>99 (*R*)
2	ADH-T	35	96 (*R*)
3	*TeS*ADH	11	90 (*R*)
4	*Hl*ADH	11	30 (*R*)
5	*Lb*ADH	>99	>99 (*S*)
6	evo.1.1.200	>99	>99 (*S*)
7	KRED-P1-A04	>99	>99 (*S*)
8	KRED-P1-A12	>99	>99 (*S*)
9	KRED-P1-B02	>99	98 (*S*)
10	KRED-P1-B05	28	96 (*S*)
11	KRED-P1-B10	99	98 (*S*)
12	KRED-P1-B12	99	94 (*S*)
13	KRED-P1-C01	99	90 (*S*)
14	KRED-P1-H08	99	90 (*S*)
15	KRED-P2-B02	99	64 (*S*)
16	KRED-P2-C02	99	34 (*S*)
17	KRED-P2-C11	99	>99 (*S*)
18	KRED-P2-D03	99	62 (*S*)
19	KRED-P2-D11	99	>99 (*S*)
20	KRED-P2-D12	88	94 (*S*)
21	KRED-P2-G03	99	>99 (*S*)
22	KRED-P2-H07	99	>99 (*S*)
23	KRED-P3-B03	98	80 (*R*)
24	KRED-P3-G09	66	50 (*R*)
25	KRED-P3-H12	91	86 (*R*)

[a] Procedures already applied to ketone **2a** were used for the bioreduction of **2g** considering the mmol substrate/weight enzyme ratio.
[b] Product percentages were determined by HPLC analysis.
[c] Enantiomeric excess values were determined by HPLC analysis. The configuration of the major enantiomer appears in parentheses. Change in the CIP priority.

VI.12. Summary of results in the bioreduction of ketone 2h

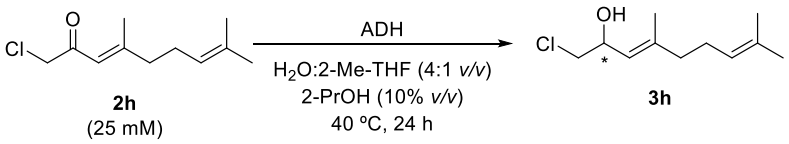
Table S9. Screening of different ADHs for the asymmetric bioreduction of **2h**.[a]



Entry	ADH	3i (%)[b]	3i *ee* (%)[c]
1	ADH-A	2	*n.d.*
2	ADH-T	<1	*n.d.*
3	*Te*SADH	<1	*n.d.*
4	*Lb*ADH	53	>99 (*S*)
5	*Hl*ADH	49	>99 (*S*)
6	evo.1.1.200	<1	*n.d.*
7	KRED-P1-A04	55	>99 (*S*)
8	KRED-P1-A12	10	*n.d.*
10	KRED-P1-B02	45	>99 (*S*)
11	KRED-P1-B05	<1	*n.d.*
12	KRED-P1-B10	6	*n.d.*
13	KRED-P1-B12	14	*n.d.*
14	KRED-P1-C01	18	*n.d.*
15	KRED-P1-H08	6	*n.d.*
16	KRED-P2-B02	51	<1
17	KRED-P2-C02	11	*n.d.*
18	KRED-P2-C11	27	*n.d.*
19	KRED-P2-D03	14	*n.d.*
20	KRED-P2-D11	36	*n.d.*
21	KRED-P2-D12	4	*n.d.*
22	KRED-P2-G03	48	>99 (*R*)
23	KRED-P2-H07	56	>99 (*S*)
24	KRED-P3-B03	20	*n.d.*
25	KRED-P3-G09	68	88 (*R*)
26	KRED-P3-H12	<1	*n.d.*

[a] Procedures already applied to ketone **2a** were used for the bioreduction of **2h** considering the mmol substrate/weight enzyme ratio.
[b] Product percentages were determined by GC analysis.
[c] Enantiomeric excess values were determined by GC analysis using a chiral column after acetylation of the halohydrin obtained in the reaction crude with acetic anhydride and DMAP. The configuration of the major enantiomer appears in parentheses. Change in the CIP priority. *n.d.*: not determined.

Table S10. Screening of different ADHs for the asymmetric bioreduction of **2h** using a higher amount of 2-PrOH.[a]



2h (25 mM) → **3h**

Entry	ADH	**3h** (%)[b]	**3h** *ee* (%)[c]
1	*Lb*ADH	93	>99 (*S*)
2	*Hl*ADH	<1	*n.d.*
3	KRED-P1-A04	94	>99 (*S*)
4	KRED-P1-B02	>99	>99 (*S*)
5	KRED-P2-B02	92	>99 (*S*)
6	KRED-P2-G03	68	88 (*R*)
7	KRED-P2-H07	87	>99 (*S*)
8	KRED-P3-G09	10	*n.d.*

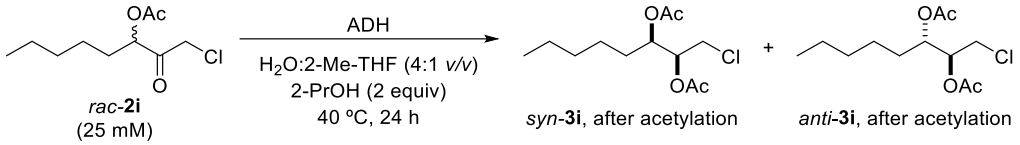
[a] Procedures already applied to ketone **2a** were used for the bioreduction of **2h** considering the mmol substrate/weight enzyme ratio.

[b] Product percentages were determined by GC analysis.

[c] Enantiomeric excess values were determined by GC analysis using a chiral column after acetylation of the halohydrin obtained in the reaction crude with acetic anhydride and DMAP. The configuration of the major enantiomer appears in parentheses. Change in the CIP priority. *n.d.*: not determined.

VI.13. Summary of results in the bioreduction of racemic and optically active ketone 2i

Table S11. Screening of different ADHs for the asymmetric bioreduction of *rac*-**2i**.[a]



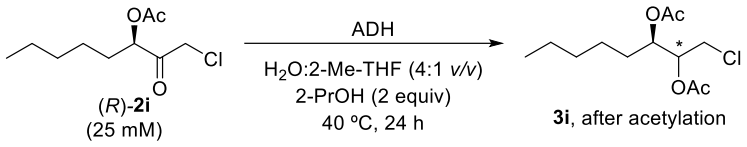
Entry	ADH	**3i** (%)[b]	**3i** *de* (%)[c]	**3i** *ee* (%)[c]	
				syn	*anti*
1	ADH-A	50	96 (*anti*)	*n.d.*	>99 (2*R*,3*R*)
2	ADH-T	42	>99 (*anti*)	*n.d.*	88 (2*R*,3*R*)
3	*Te*SADH	40	>99 (*anti*)	*n.d.*	86 (2*R*,3*R*)
4	*Hl*ADH	34	>99 (*anti*)	*n.d.*	>99 (2*R*,3*R*)
5	*Lb*ADH	56	82 (*anti*)	*n.d.*	>99 (2*S*,3*S*)
6	evo.1.1.200	>99	<1	95 (2*S*,3*R*)	>99 (2*S*,3*S*)
7	KRED-P1-A04	82	36 (*anti*)	95 (2*S*,3*R*)	>99 (2*S*,3*S*)
8	KRED-P1-A12	64	60 (*syn*)	>99 (2*S*,3*R*)	95 (2*S*,3*S*)
9	KRED-P1-B02	98	<1	95 (2*S*,3*R*)	96 (2*S*,3*S*)
10	KRED-P1-B05	40	>99 (*anti*)	*n.d.*	94 (2*S*,3*S*)
11	KRED-P1-B10	32	>99 (*anti*)	*n.d.*	92 (2*S*,3*S*)
12	KRED-P1-B12	84	18 (*syn*)	>99 (2*S*,3*R*)	94 (2*S*,3*S*)
13	KRED-P1-C01	80	36 (*syn*)	>99 (2*S*,3*R*)	95 (2*S*,3*S*)
14	KRED-P1-H08	43	59 (*anti*)	95 (2*S*,3*R*)	>99 (2*S*,3*S*)
15	KRED-P2-B02	94	18 (*anti*)	96 (2*R*,3*S*)	>99 (2*R*,3*R*)
16	KRED-P2-C02	59	72 (*anti*)	96 (2*R*,3*S*)	>99 (2*R*,3*R*)
17	KRED-P2-C11	78	26 (*anti*)	>99 (2*S*,3*R*)	>99 (2*S*,3*S*)
18	KRED-P2-D03	81	42 (*anti*)	96 (2*S*,3*R*)	>99 (2*S*,3*S*)
19	KRED-P2-D11	98	4 (*syn*)	>99 (2*S*,3*R*)	96 (2*S*,3*S*)
20	KRED-P2-D12	66	54 (*anti*)	96 (2*S*,3*R*)	>99 (2*S*,3*S*)
21	KRED-P2-G03	>99	24 (*anti*)	96 (2*S*,3*R*)	>99 (2*S*,3*S*)
22	KRED-P2-H07	92	20 (*syn*)	>99 (2*S*,3*R*)	96 (2*S*,3*S*)
23	KRED-P3-B03	32	>99 (*anti*)	*n.d.*	>99 (2*R*,3*R*)
24	KRED-P3-G09	48	>99 (*anti*)	*n.d.*	>99 (2*R*,3*R*)
25	KRED-P3-H12	30	>99 (*anti*)	*n.d.*	>99 (2*R*,3*R*)

[a] Procedures already applied to ketone **2a** were used for the bioreduction of *rac*-**2i** considering the mmol substrate/weight enzyme ratio.

[b] Product percentages were determined by GC analysis.

[c] Enantio- and diastereomeric excess values were determined by GC analysis using a chiral column after acetylation of the halohydrin obtained in the reaction crude with acetic anhydride and DMAP. The configuration of the major enantiomer of each isomer appears in parentheses. Change in the CIP priority.

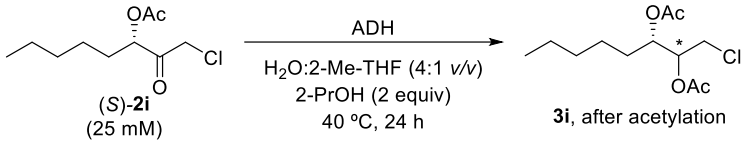
Table S12. Screening of different ADHs for the asymmetric bioreduction of (*R*)-**2i**.[a]



Entry	ADH	**3i** (%)[b]	**3i** *de* (%)[c]	**3i** *ee* (%)[c]
1	ADH-A	>99	>99 (*anti*)	>99 (2*R*,3*R*)
2	evo.1.1.200	>99	>99 (*syn*)	>99 (2*S*,3*R*)
3	KRED-P1-A04	>99	>99 (*syn*)	>99 (2*S*,3*R*)
4	KRED-P1-B02	>99	>99 (*syn*)	>99 (2*S*,3*R*)
5	KRED-P2-B02	>99	96 (*anti*)	>99 (2*R*,3*R*)
6	KRED-P2-C02	>99	82 (*anti*)	>99 (2*R*,3*R*)
7	KRED-P2-G03	>99	38 (*syn*)	>99 (2*S*,3*R*)

[a] Procedures already applied to ketone **2a** were used for the bioreduction of (*R*)-**2i** considering the mmol substrate/weight enzyme ratio.
[b] Product percentages were determined by GC analysis.
[c] Enantio- and diastereomeric excess values were determined by GC analysis using a chiral column after acetylation of the halohydrin obtained in the reaction crude with acetic anhydride and DMAP. The configuration of the major enantiomer of each isomer appears in parentheses. Change in the CIP priority.

Table S13. Screening of different ADHs for the asymmetric bioreduction of (*S*)-**2i**.[a]

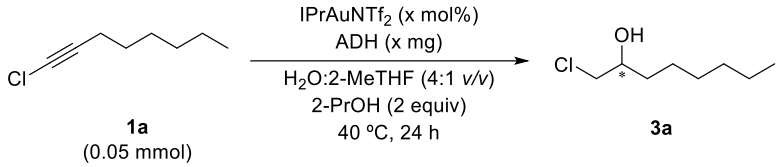


Entry	ADH	**3i** (%)[b]	**3i** *de* (%)[c]	**3i** *ee* (%)[c]
1	ADH-A	>99	>99 (*syn*)	>99 (2*R*,3*S*)
2	evo.1.1.200	>99	>99 (*anti*)	>99 (2*S*,3*S*)
3	KRED-P1-A04	>99	>99 (*anti*)	>99 (2*S*,3*S*)
4	KRED-P1-B02	>99	>99 (*anti*)	>99 (2*S*,3*S*)
5	KRED-P2-B02	>99	94 (*syn*)	>99 (2*R*,3*S*)
6	KRED-P2-C02	>99	62 (*syn*)	>99 (2*R*,3*S*)
7	KRED-P2-G03	>99	94 (*anti*)	>99 (2*S*,3*S*)

[a] Procedures already applied to ketone **2a** were used for the bioreduction of (*S*)-**2i** considering the mmol substrate/weight enzyme ratio.
[b] Product percentages were determined by GC analysis.
[c] Enantio- and diastereomeric excess values were determined by GC analysis using a chiral column after acetylation of the halohydrin obtained in the reaction crude with acetic anhydride and DMAP. The configuration of the major enantiomer of each isomer appears in parentheses. Change in the CIP priority.

VII. Optimization of the one-pot hydration-bioreduction cascade starting from alkyne 1a

Table S14. Optimization of the hydration-bioreduction cascade starting from **1a**.



1a (0.05 mmol) **3a**

Entry	Enzyme (mg)	$IPrAuNTf_2$ (mol%)	Vessel[a]	Concentration (mM)	Stirring	**1a** (%)[a]	**2a** (%)[b]	By-products (%)[b]	**3a** (%)[b]	**3a** *ee* (%)[c]
1	ADH-A[d] (2)	2	Vial	100	Magnetic	69	<1	3	28	>99 (*R*)
2	ADH-A[d] (2)	2	Vial	100	220 rpm[e]	58	<1	4	38	>99 (*R*)
3	ADH-A[d] (2)	2	Eppendorf	100	220 rpm[e]	48	1	11	40	>99 (*R*)
4	ADH-A[d] (2)	5	Vial	100	Magnetic	9	<1	13	78	>99 (*R*)
5	ADH-A[d] (2)	6	Vial	100	Magnetic	<1	<1	4	96	>99 (*R*)
6	*Lb*ADH (10)	2	Vial	100	Magnetic	<1	<1	10	90	>99 (*S*)
7	*Lb*ADH (10)	2	Vial	100	220 rpm[e]	<1	<1	7	93	>99 (*S*)
8	*Lb*ADH (10)	6	Vial	100	220 rpm[e]	<1	<1	2	98	>99 (*S*)
9	KRED-P2-D11 (2)	2	Vial	100	Magnetic	34	<1	9	57	>99 (*S*)
10	KRED-P2-D11 (2)	2	Vial	100	220 rpm[e]	3	30	2	65	>99 (*S*)
11	KRED-P2-D11 (2)	3	Vial	100	220 rpm[e]	14	1	5	80	>99 (*S*)

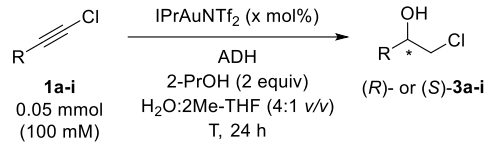
Table S14 continuation.

Entry	Enzyme (mg)	IPrAuNTf$_2$ (mol%)	Vessel[a]	Concentration (mM)	Stirring	**1a** (%)[b]	**2a** (%)[b]	By-products (%)[a]	**3a** (%)[b]	**3a** *ee* (%)[c]
12	KRED-P2-D11 (2)	4	Vial	100	220 rpm[e]	<1	<1	7	93	>99 (*S*)
13	KRED-P2-D11 (2)	5	Vial	100	220 rpm[e]	<1	<1	8	92	>99 (*S*)
14	KRED-P2-D11 (2)	6	Vial	100	220 rpm[e]	<1	<1	9	91	>99 (*S*)
15	KRED-P2-D11 (3)	4	Vial	100	220 rpm[e]	<1	75	9	16	>99 (*S*)
16	KRED-P2-D11 (5)	4	Vial	100	220 rpm[e]	<1	16	19	65	>99 (*S*)
17	KRED-P2-D11 (7)	4	Vial	100	220 rpm[e]	<1	<1	7	93	>99 (*S*)
18	KRED-P2-D11 (7)	4	Vial	150	220 rpm[c]	<1	<1	10	90	>99 (*S*)
19	KRED-P2-D11 (7)	4	Vial	200	220 rpm[e]	<1	<1	13	87	>99 (*S*)
20	KRED-P2-D11 (10)	4	Vial	100	220 rpm[e]	<1	<1	7	93	>99 (*S*)

[a] Vial: glass vial (19 x 130 x 3 mm). Eppendorf (1.5 mL).
[b] Product percentages were determined by GC analysis.
[c] Enantiomeric excess values were determined by GC analysis using a chiral column after acetylation of the halohydrin obtained in the reaction crude with acetic anhydride and DMAP. The configuration of the major enantiomer appears in parentheses.
[d.] ADH-A semi-purified by heat treatment.
[e] Orbital shaking.

VIII. Scope of the one-pot cascade process

Table S15. Scope of the concurrent cascade via gold-catalyzed hydration and stereoselective bioreduction of alkynes **1a**-**i**.



Entry	Compound	R	Enzyme	Stirring	T (ºC)	$IPrAuNTf_2$ (mol%)	**1** (%)[a]	**2** (%)[a]	By-products (%)[a]	**3** (%)[a]	**3** *ee* (%)[b]
1	**1a**	C_6H_{13}	ADH-A	Magnetic	40	6	<1	<1	4	96	>99 (*R*)
2	**1a**	C_6H_{13}	*Lb*ADH	220 rpm[c]	40	6	<1	<1	2	98	>99 (*S*)
3	**1b**	C_8H_{17}	ADH-A	Magnetic	40	5	<1	9	10	81	>99 (*R*)
4	**1b**	C_8H_{17}	*Lb*ADH	220 rpm[c]	40	5	<1	<1	7	93	>99 (*S*)
5	**1c**	Cy	*Lb*ADH	220 rpm[c]	40	5	<1	<1	18	82	>99 (*S*)
6	**1d**	$PhCH_2CH_2$	ADH-T	Magnetic	40	5	<1	<1	<1	>99	>99 (*R*)
7	**1d**	$PhCH_2CH_2$	*Lb*ADH	220 rpm[c]	40	5	<1	<1	<1	>99	>99 (*S*)
8	**1e**	$EtO_2C(CH_2)_4$	ADH-A	Magnetic	40	5	<1	2	<1	98	>99 (*R*)
9	**1e**	$EtO_2C(CH_2)_4$	*Lb*ADH	220 rpm[c]	40	5	<1	9	<1	91	>99 (*S*)
10	**1f**	$BnOCH_2$	ADH-A	Magnetic	45	7.5	<1	<1	40	60	>99 (*R*)
11	**1f**	$BnOCH_2$	*Lb*ADH	220 rpm[c]	45	7.5	19	5	<1	76	>99 (*S*)

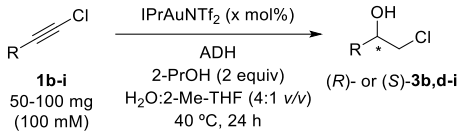
Table S15 continuation.

Entry	Compound	R	Enzyme	Stirring	T (ºC)	IPrAuNTf$_2$ (mol%)	**1** (%)[a]	**2** (%)[a]	By-products (%)[a]	**3** (%)[a]	**3** *ee* (%)[b]
12	**1g**	TsO(CH$_2$)$_4$	ADH-A	Magnetic	40	5	<1	40	<1	60	>99 (*R*)
13	**1g**	TsO(CH$_2$)$_4$	*Lb*ADH	220 rpm[c]	40	5	<1	<1	<1	>99	>99 (*S*)
14	**1h**[d]	(CH$_3$)$_2$C=CH(CH$_2$)$_2$(CH$_3$)C=CH	*Lb*ADH	220 rpm[c]	40	5	<1	6	<1	94	>99 (*S*)
15	(*R*)-**1i**	H$_3$C(CH$_2$)$_4$CH(OAc)	KRED-P2-B02	220 rpm[c]	40	5	<1	<1	<1	>99	96% *de*, >99 *ee* (2*R*,3*R*)
16	(*R*)-**1i**	H$_3$C(CH$_2$)$_4$CH(OAc)	evo.1.1.200	Magnetic	40	5	<1	<1	<1	>99	>99% *de*, >99 *ee* (2*S*,3*R*)
17	(*S*)-**1i**	H$_3$C(CH$_2$)$_4$CH(OAc)	KRED-P2-B02	220 rpm[c]	40	5	<1	2	<1	98	>99% *de*, >99 *ee* (2*R*,3*S*)
18	(*S*)-**1i**	H$_3$C(CH$_2$)$_4$CH(OAc)	evo.1.1.200	Magnetic	40	5	<1	<1	<1	>99	>99% *de*, >99 *ee* (2*S*,3*S*)

[a] Product percentages were determined by GC analysis.
[b] Enantiomeric excess values were determined by GC analysis using a chiral column after acetylation of the halohydrin obtained in the reaction crude with acetic anhydride and DMAP, except for alcohol **3d**, **3f** and **3g** where HPLC analyses were required.
[c] Orbital shaking.
[d] 10% *v/v* of 2-PrOH was employed.

IX. Scale-up of the one-pot cascade hydration-bioreduction processes

Table S16. Scale-up of the one-pot cascade hydration-bioreduction processes.



Entry	Compound	R	Amount of alkyne (mg)	Enzyme	Stirring	T (ºC)	$IPrAuNTf_2$ (mol%)	**3** (%)[a]	**3** *ee* (%)[b]
1	**1b**	C_8H_{17}	100	ADH-A	Magnetic	40	5	72	>99 (*R*)
2	**1b**	C_8H_{17}	100	*Lb*ADH	220 rpm[c]	40	5	86	>99 (*S*)
3	**1c**	Cy	50	*Lb*ADH	220 rpm[c]	40	5	73	>99 (*S*)
4	**1d**	$PhCH_2CH_2$	50	*Lb*ADH	220 rpm[c]	40	5	88	>99 (*S*)
5	**1e**	$EtO_2C(CH_2)_4$	50	ADH-A	Magnetic	40	5	81	>99 (*R*)
6	**1f**	$BnOCH_2$	100	*Lb*ADH	220 rpm[c]	45	7.5	63	>99 (*S*)
7	**1g**	$TsO(CH_2)_4$	50	*Lb*ADH	220 rpm[c]	40	5	87	>99 (*S*)
8	**1h**[d]	$(CH_3)_2C=CH(CH_2)_2(CH_3)C=CH$	50	*Lb*ADH	220 rpm[c]	40	5	75	>99 (*S*)
9	(*R*)-**1i**	$H_3C(CH_2)_4CH(OAc)$	50	KRED-P2-B02	220 rpm[c]	40	5	83	96% *de*, >99 *ee* (2*R*,3*R*)
10	(*R*)-**1i**	$H_3C(CH_2)_4CH(OAc)$	50	evo.1.1.200	Magnetic	40	5	85	>99% *de*, >99 *ee* (2*S*,3*R*)

[a] Isolated yields after chromatographic column.
[b] Enantio- and diastereomeric excess values were determined by GC analysis using a chiral column after acetylation of the halohydrin obtained in the reaction crude with acetic anhydride and DMAP, except for alcohol **3d**, **3f** and **3g** where HPLC analyses were required.
[c] Orbital stirring.
[d.] 10% *v/v* of 2-PrOH was employed.

X. Analytical data

X.1. GC analyses for the determination of product percentages

An Agilent HP-1 (30 m x 0.32 mm x 0.25 μm, 12.2 psi N_2) or a DB-1701 column (30 m x 0.25 cm x 0.25 μm, 12.2 psi N_2) were used for the determination of the conversion values in the cascade and sequential protocols. The experimental conditions are indicated in Table S17.

Table S17. GC analytical conditions and retention times for the determination of conversion values.

Entry	Substrate	Column	Program[a]	Retention time (min)
1	**1a**	HP-1	70/0/2/94/0/15/200/5	4.1
2	**2a**	HP-1	70/0/2/94/0/15/200/5	8.4
3	**3a**	HP-1	70/0/2/94/0/15/200/5	9.4
4	**1b**	HP-1	70/0/2/94/0/15/200/5	10.8
5	**2b**	HP-1	70/0/2/94/0/15/200/5	14.9
6	**3b**	HP-1	70/0/2/94/0/15/200/5	15.6
7	**1c**	HP-1	70/0/2/94/0/15/200/5	4.9
8	**2c**	HP-1	70/0/2/94/0/15/200/5	9.9
9	**3c**	HP-1	70/0/2/94/0/15/200/5	11.2
10	**1e**	HP-1	70/0/2/94/0/15/200/5	12.4
11	**2e**	HP-1	70/0/2/94/0/15/200/5	15.7
12	**3e**	HP-1	70/0/2/94/0/15/200/5	16.2
13	**1h**	DB-1701	70/0/5/100/2/1/130/2/20/200/1	18.4
14	**2h**	DB-1701	70/0/5/100/2/1/130/2/20/200/1	37.5
15	**3h**	DB-1701	70/0/5/100/2/1/130/2/20/200/1	38.8
16	**1i**	HP-1	90/0/1/120/2/20/200/0	9.0
17	**2i**	HP-1	90/0/1/120/2/20/200/0	16.1
18	**3i**	HP-1	90/0/1/120/2/20/200/0	26.1 (*anti*); 27.3 (*syn*)

[a] GC program: initial temp. (ºC) / time (min) / ramp (ºC/min) / temp. (ºC) / time (min) / ramp (ºC/min) / temp. (ºC) / time (min) / ramp (ºC/min) / final temp. (ºC) / time (min).

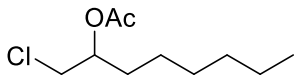
X.2. GC analyses for the determination of ee values of 1i, 2i and 3a-c,e,h,i

Chiralsil Dex CB (30 m x 0.32 m x 0.25 μm, 12.2 psi N_2) or Chirasil RtbDEXse (30 m x 0.25 mm x 0.25 μm, 12.2 psi N_2) was employed for the determination of the enantiomeric excess values of ester **1i**, keto ester **2i** and alcohols **3a-c**,**e**,**h**,**i** (Table S18).

Table S18. GC analyses for the determination of the *ee* values of keto ester **2i** and alcohols **3a-c**,**e**,**h**,**i**.

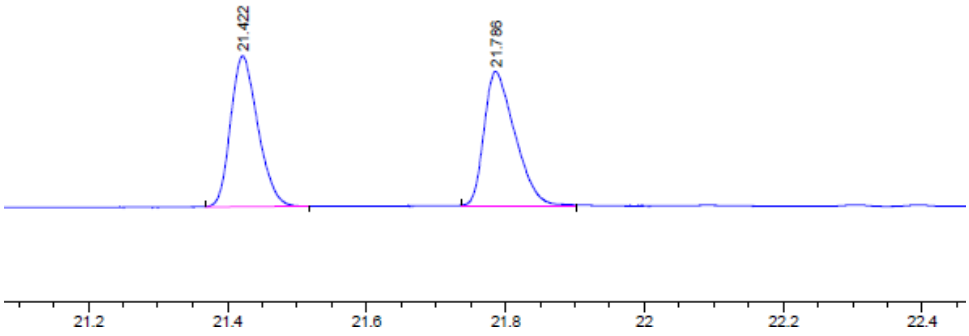
Entry	Compound	Column	Program[a]	Retention time (min)[b]	
1	**3a**	Chiralsil Dex CB	70/3/5/180/1	21.4 (*R*)	21.8 (*S*)
2	**3b**	Chiralsil Dex CB	70/3/5/180/1	28.2 (*R*)	28.9 (*S*)
3	**3c**	Chiralsil RtbDEXse	70/3/5/180/1	39.6 (*R*)	40.0 (*S*)
4	**3e**	Chiralsil Dex CB	70/3/5/160/10/2/ 180/5	30.2 (*R*)	30.9 (*S*)
5	**3h**	Chiralsil Dex CB	70/3/5/180/1	24.6 (*R*)	24.7 (*S*)
6	**1i**	Chiralsil Dex CB	70/3/5/180/1	35.0 (*R*)	35.2 (*S*)
7	**2i**	Chiralsil Dex CB	70/3/5/180/1	22.0 (*R*)	22.2 (*S*)
8	**3i**	Chiralsil Dex CB	70/3/5/180/1	24.2 (2*R*,3*R*), 24.3 (2*S*,3*S*)	24.6 (2*R*,3*S*), 24.7 (2*S*,3*R*)

[a] GC program: initial temp. (ºC) / time (min) / ramp (ºC/min) / temp. (ºC) / time (min) / ramp (ºC/min) / final temp. (ºC) / time (min).
[b] Alcohols were *in situ* acetylated employing DMAP and acetic anhydride.

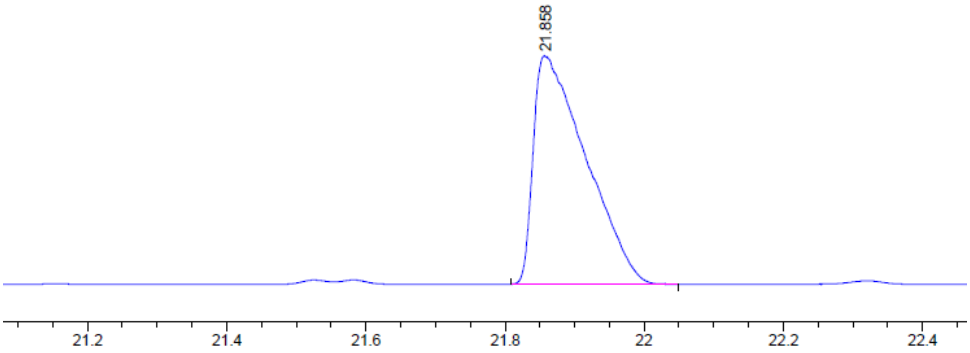


3a

Acetylated racemic alcohol **3a**



Acetylated alcohol (*S*)-**3a** in >99% *ee* (after bioreduction with *Lb*ADH)



Acetylated alcohol (*R*)-**3a** in >99% *ee* (after bioreduction with ADH-A)

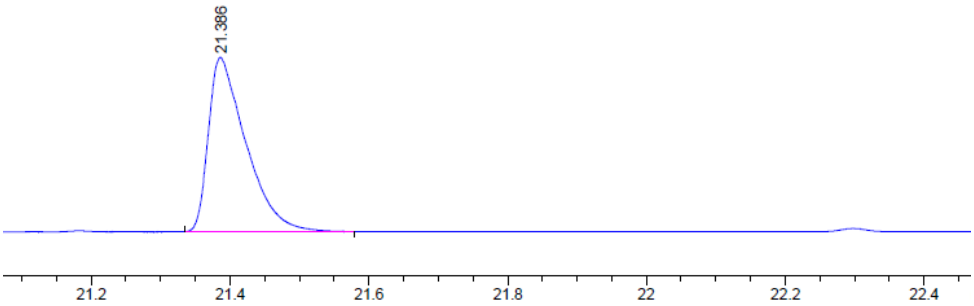
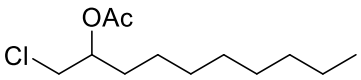
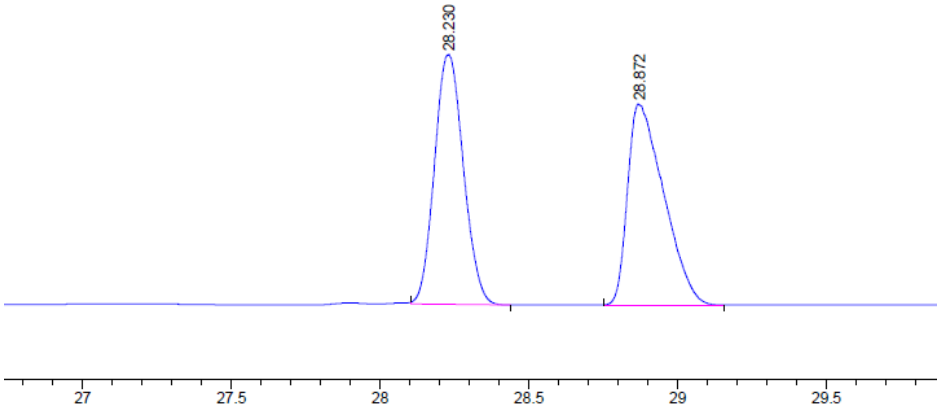


Figure S4. GC chromatograms of acetylated racemic halohydrin and optically active **3a** obtained using selective ADHs.

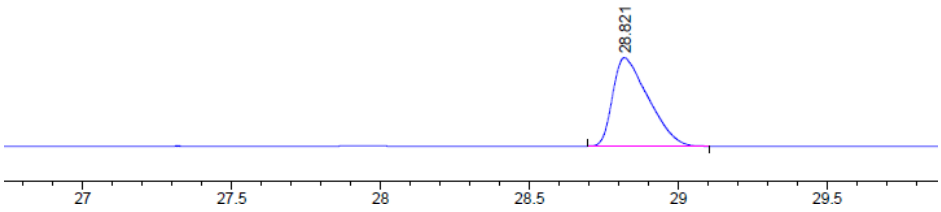


3b

Acetylated racemic alcohol **3b**



Acetylated alcohol (*S*)-**3b** in >99% *ee* (after bioreduction with *Lb*ADH)



Acetylated alcohol (*R*)-**3b** in >99% *ee* (after bioreduction with ADH-A)

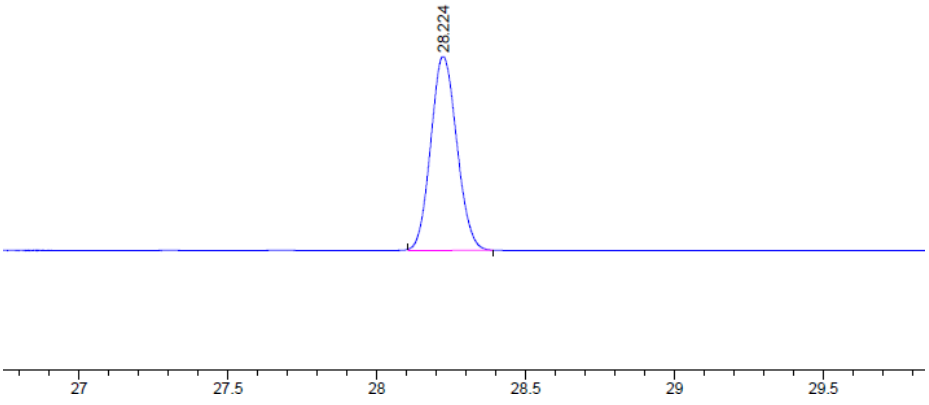
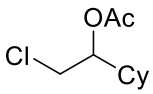
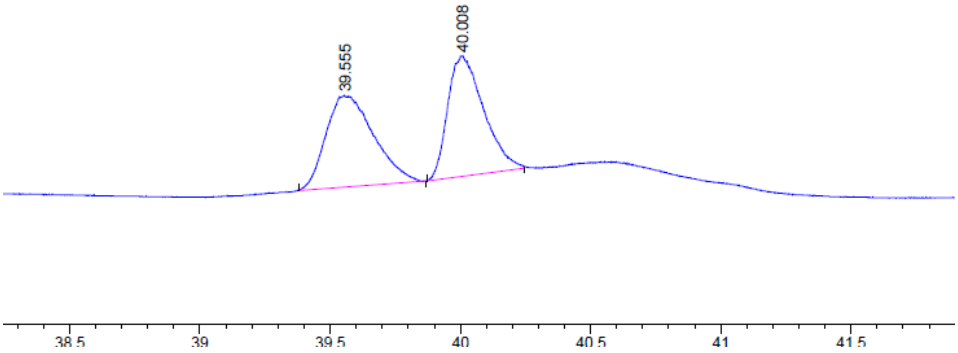


Figure S5. GC chromatograms of acetylated racemic halohydrin and optically active **3b** obtained using selective ADHs.



3c

Acetylated racemic alcohol **3c**



Acetylated alcohol (*S*)-**3c** in >99% *ee* (after bioreduction with *Lb*ADH)

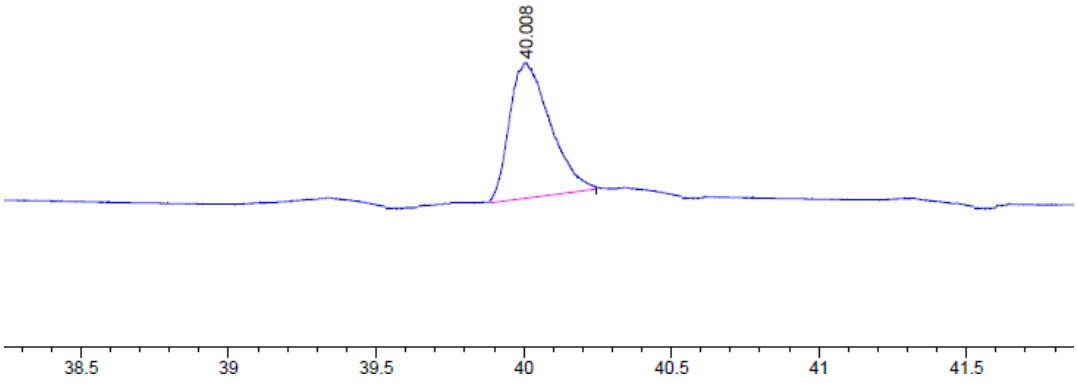
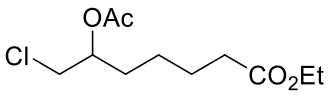
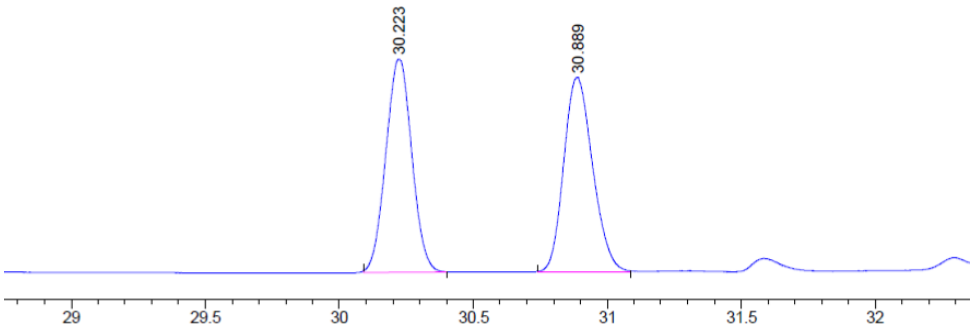


Figure S6. GC chromatograms of acetylated racemic halohydrin and optically active **3c** obtained using *Lb*ADH.

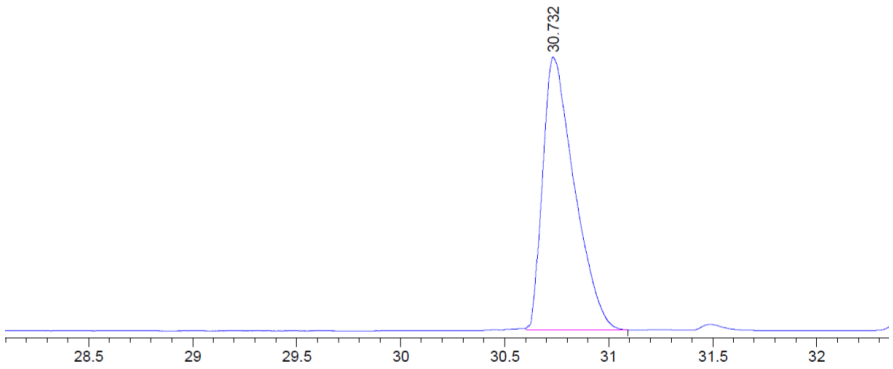


3e

Acetylated racemic alcohol **3e**



Acetylated alcohol (*S*)-**3e** in >99% *ee* (after bioreduction with *Lb*ADH)



Acetylated alcohol (*R*)-**3e** in >99% *ee* (after bioreduction with ADH-A)

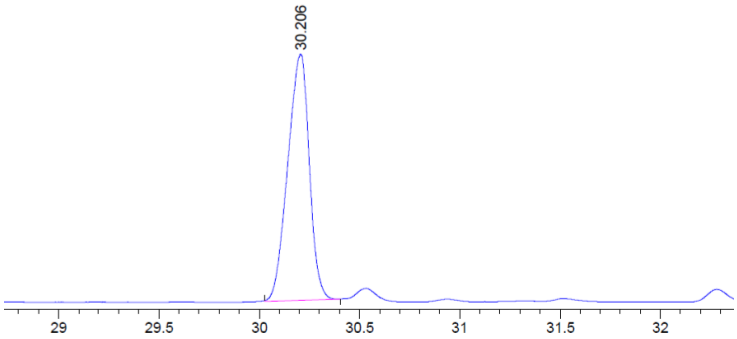
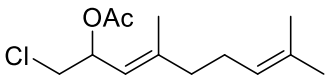
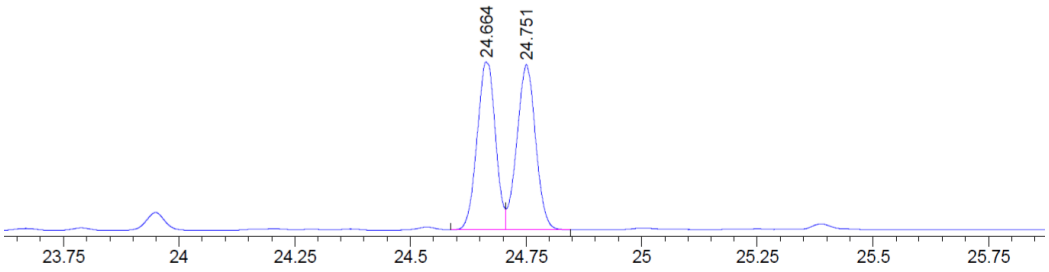


Figure S7. GC chromatograms of acetylated racemic halohydrin and optically active **3e** obtained using selective ADHs.

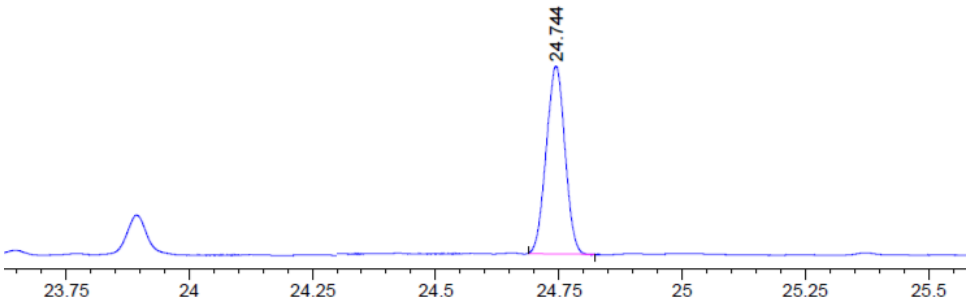


3h

Acetylated racemic alcohol **3h**



Acetylated alcohol (*S*)-**3h** in >99% *ee* (after bioreduction with *Lb*ADH)



Acetylated alcohol (*R*)-**3h** in >99% *ee* (after bioreduction with ADH-A)

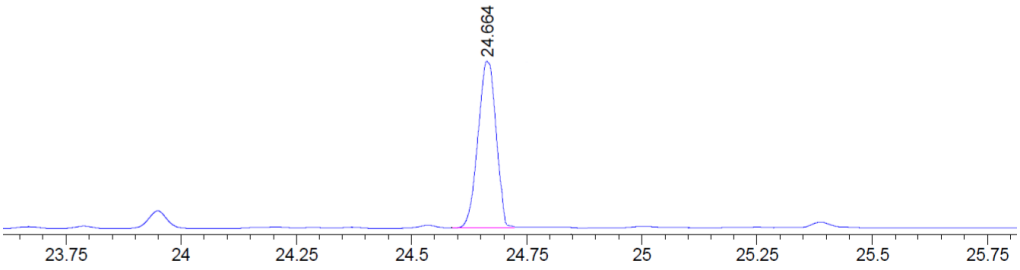
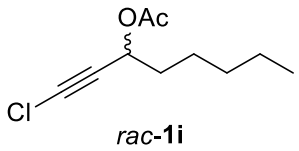
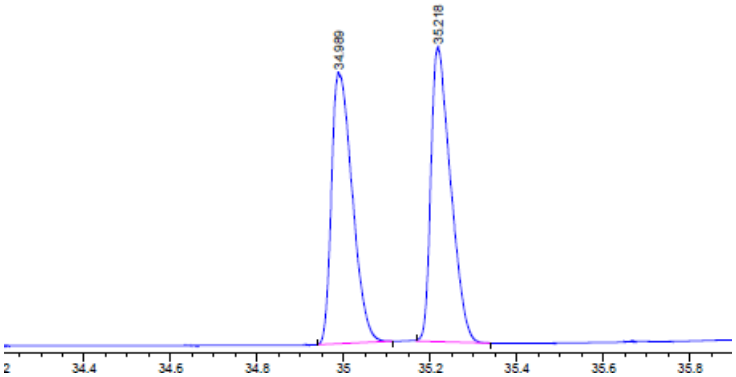


Figure S8. GC chromatograms of acetylated racemic halohydrin and optically active **3h** obtained using selective ADHs.

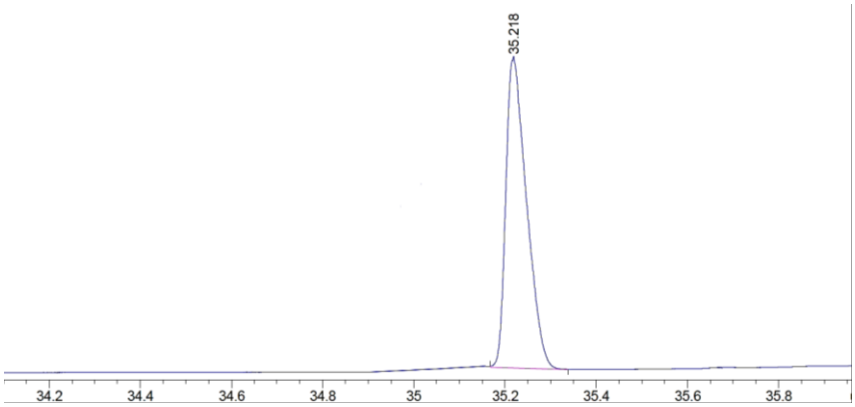


rac-**1i**

Acetylated racemic alcohol **1i**



Acetylated alcohol (*S*)-**1i** in >99% *ee* (after kinetic resolution with CAL-B)



Acetylated alcohol (*R*)-**1i** in >99% *ee* (after kinetic resolution with CAL-B)

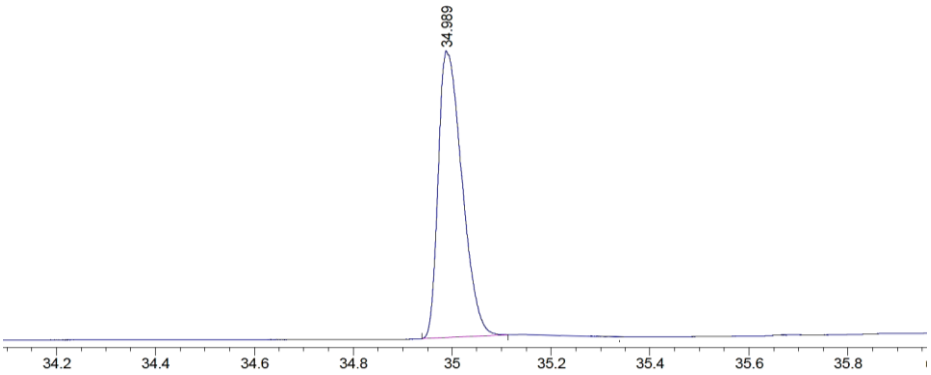
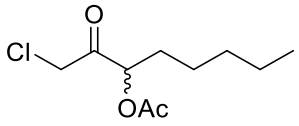
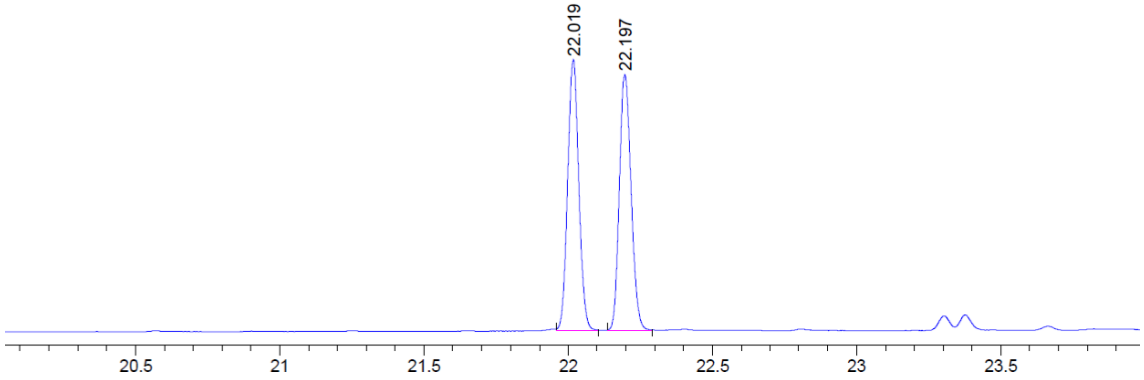


Figure S9. GC chromatograms of acetylated racemic alcohol and optically active **1i** obtained using selective CAL-B.

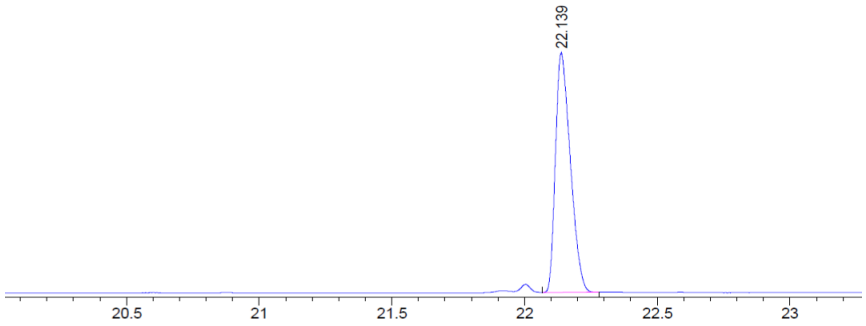


rac-**2i**

Acetylated racemic alcohol **2i**



Acetylated alcohol (*S*)-**2i** in >99% *ee* (after kinetic resolution with CAL-B)



Acetylated alcohol (*R*)-**2i** in >99% *ee* (after kinetic resolution with CAL-B)

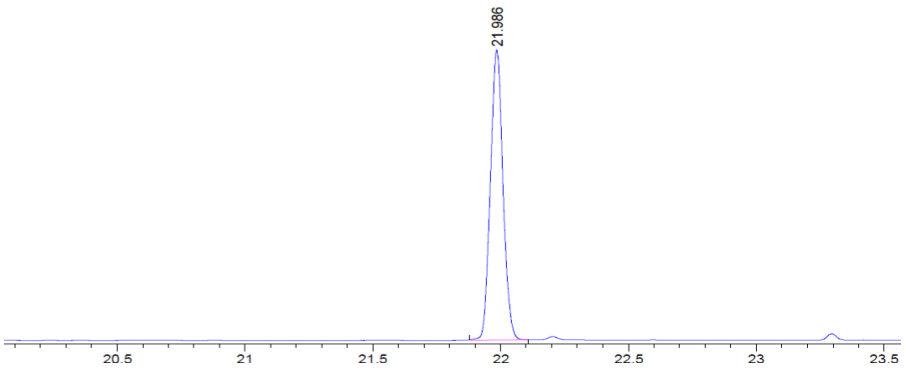
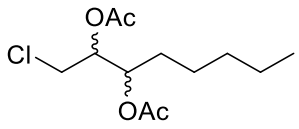
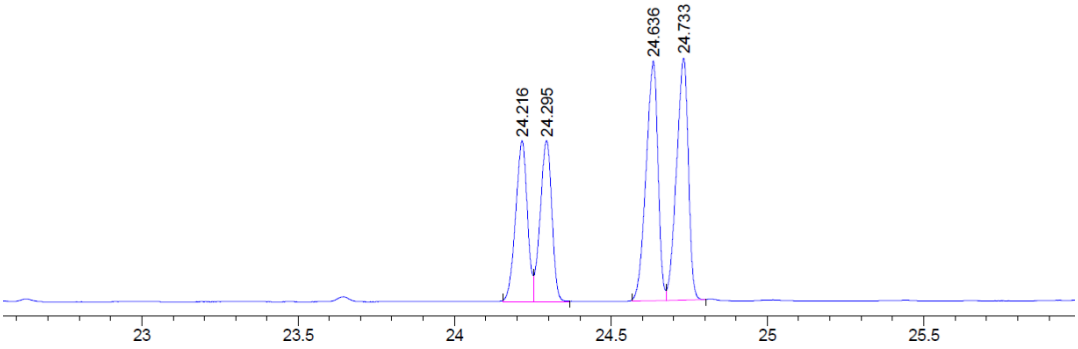


Figure S10. GC chromatograms of acetylated racemic halohydrin and optically active **2i** obtained using CAL-B.

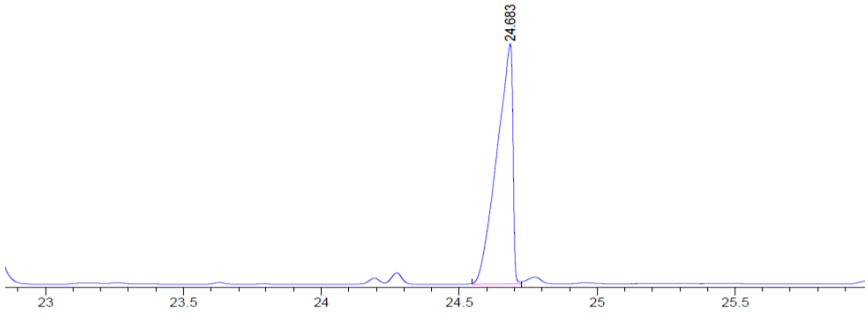


rac-**3i**

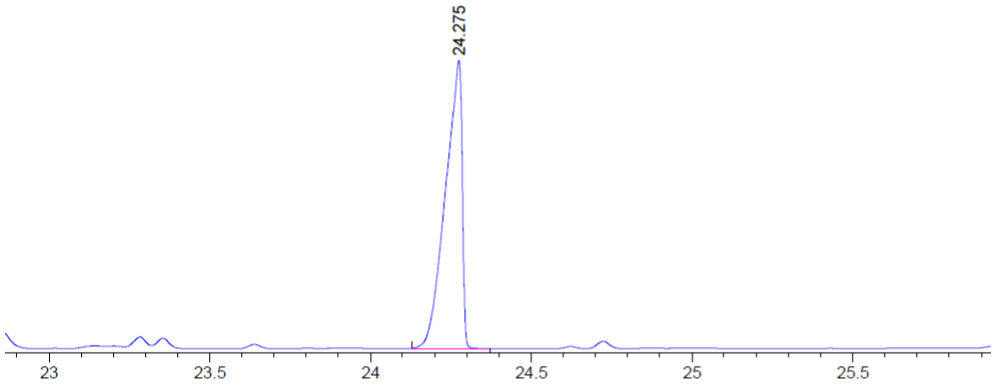
Diacetylated racemic diol **3i**



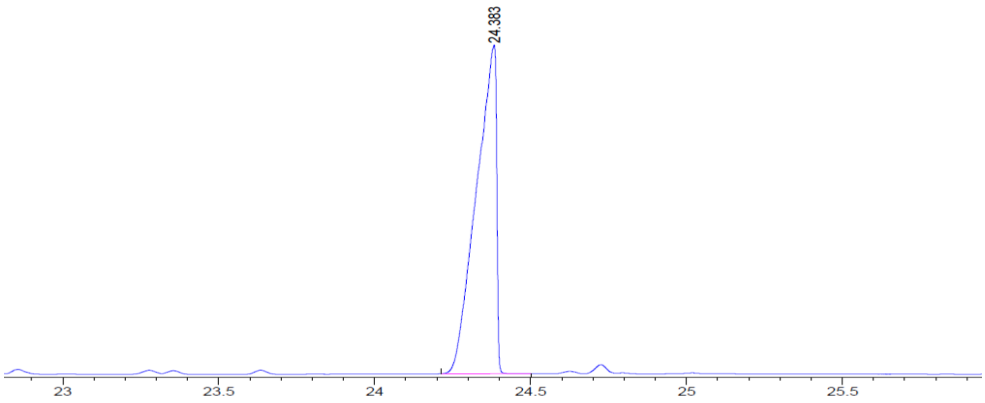
Diacetylated diol (2*R*,3*S*)-**3i** in >99% *de*, >99% *ee* (after bioreduction of (*S*)-**2i** with KRED-P2-B02)



Diacetylated diol (2*R*,3*R*)-**3i** in >99% *de*, >99% *ee* (after bioreduction of (*R*)-**2i** with KRED-P2-B02)



Diacetylated diol (2*S*,3*S*)-**3i** in >99% *de*, >99% *ee* (after bioreduction of (*S*)-**2i** with evo.1.1.200)



Diacetylated diol (2*S*,3*R*)-**3i** in 96% *de*, >99% *ee* (after bioreduction of (*R*)-**2i** with evo.1.1.200)

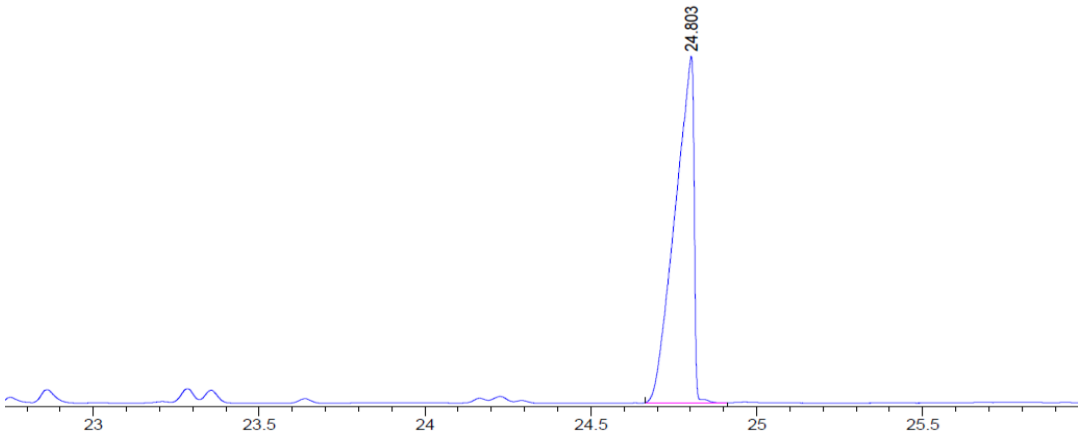


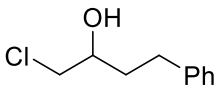
Figure S11. GC chromatograms of racemic and optically active diacetylated **3i** obtained using selective ADHs.

X.3. HPLC analyses for the determination of product percentages and enantiomeric excess values in reactions towards 3d,f,g

For the cascade and sequential approaches towards the synthesis of halohydrins **3d**,**f**,**g**, the determination of the conversion values and the enantiomeric excess values were performed through HPLC analyses using different columns and conditions as specified in the Experimental Section of the manuscript and in Table S19.

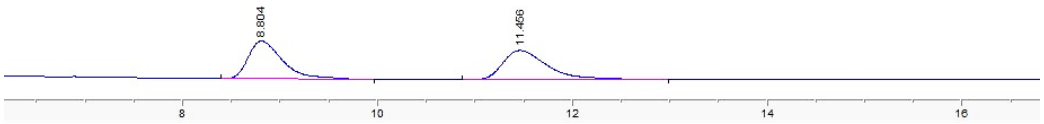
Table S19. HPLC analytical conditions and retention times of alcohols **3d**,**f**-**g** (temperature column: 30 ºC).

Entry	Compound	Column	Flow (mL/min)	*n*-Hexane/propan-2-ol (*v/v*)	Retention time (min)
1	**1d**	Chiralcel OD-H	0.8	90:10	11.0
2	**2d**	Chiralcel OD-H	0.8	90:10	13.6
3	**3d**	Chiralcel OD-H	0.8	90:10	8.8 (*R*), 11.4 (*S*)
4	**1f**	Chiralcel OD-H	0.8	95:5	16.3
5	**2f**	Chiralcel OD-H	0.8	95:5	22.8
6	**3f**	Chiralcel OD-H	0.8	95:5	14.5 (*S*), 17.3 (*R*)
7	**1g**	Chiralpak AD-H	1.0	85:15	6.4
8	**2g**	Chiralpak AD-H	1.0	85:15	17.5
9	**3g**	Chiralpak AD-H	1.0	85:15	21.8 (*R*), 22.5 (*S*)

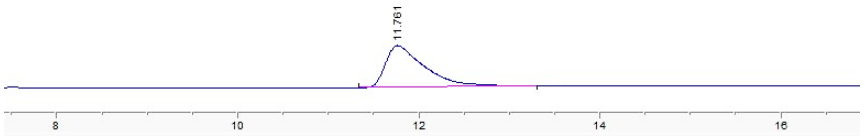


3d

HPLC separation for both enantiomers of racemic alcohol **3d**

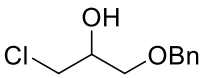


Alcohol (*S*)-**3d** in >99% *ee* (after bioreduction with *Lb*ADH)



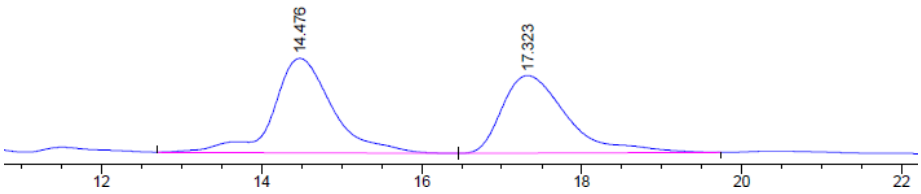
Alcohol (*R*)-**3d** in >99% *ee* (after bioreduction with ADH-T)

Figure S12. HPLC chromatograms of racemic halohydrin and optically active **3d** obtained using selective ADHs.

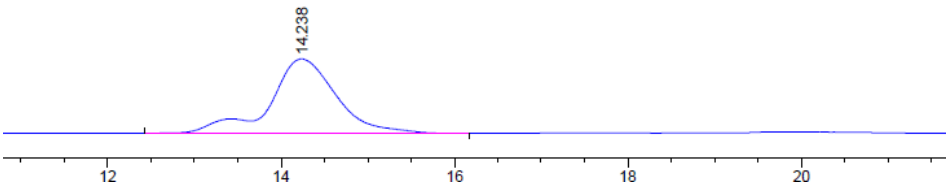


3f

HPLC separation for both enantiomers of racemic alcohol **3f**



Alcohol (*S*)-**3f** in >99% *ee* (after bioreduction with *Lb*ADH)



Alcohol (*R*)-**3f** in >99% *ee* (after bioreduction with ADH-A)

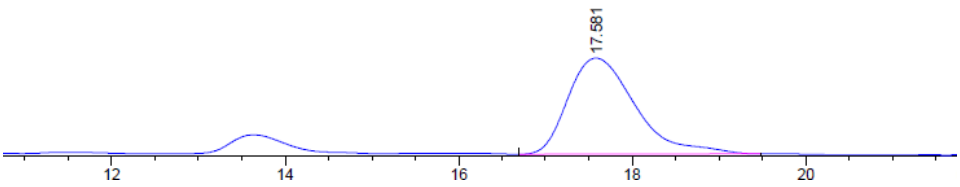
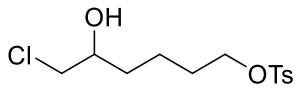
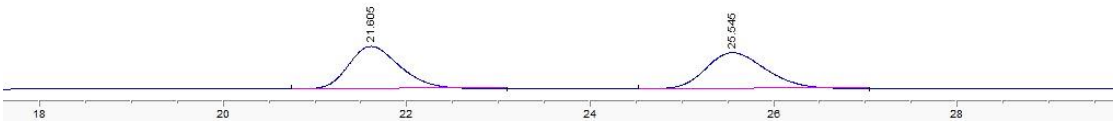


Figure S13. HPLC chromatograms of racemic halohydrin and optically active **3f** obtained using selective ADHs.

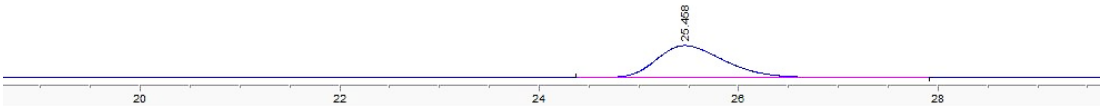


3g

HPLC separation for both enantiomers of racemic alcohol **3g**



Alcohol (*S*)-**3g** in >99% *ee* (after bioreduction with *Lb*ADH)



Alcohol (*R*)-**3g** in >99% *ee* (after bioreduction with ADH-A)

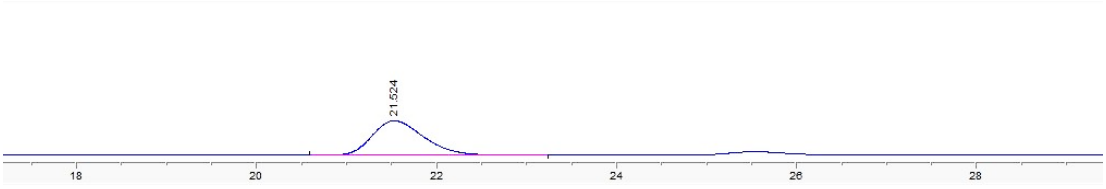


Figure S14. HPLC chromatograms of racemic halohydrin and optically active **3g** obtained using selective ADHs.

XI. Optical rotation values of derivatives 3a-i obtained through the concurrent cascade approach

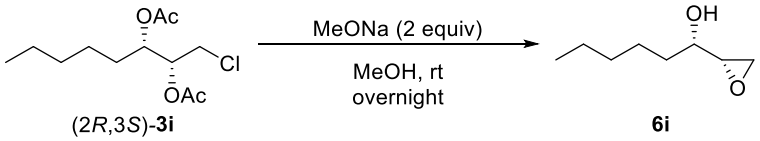
Table S20. Specific rotation of chiral halohydrins obtained through the gold(I)/ADH cascade.

Entry	Enzyme	Compound	*ee* (%)[a]	Experimental $[\alpha]_D^{20}$
1	*Lb*ADH	**3a**	>99 (*S*)[b]	+2.4 (*c* 1.0, $CHCl_3$)[d]
2	ADH-A	**3a**	>99 (*R*)[b]	–3.5 (*c* 1.0, $CHCl_3$)[d]
3	*Lb*ADH	**3b**	>99 (*S*)[b]	+27.0 (*c* 1.0, $CHCl_3$)
4	ADH-A	**3b**	>99 (*R*)[b]	–32.9 (*c* 1.0, $CHCl_3$)
5	ADH-A	**3c**	>99 (*R*)[b]	–6.5 (*c* 1.0, $CHCl_3$)[e]
6	*Lb*ADH	**3d**	>99 (*S*)[c]	–8.7 (*c* 1.0, $CHCl_3$)
7	ADH-A	**3e**	>99 (*R*)[b]	+0.7 (*c* 1.0, $CHCl_3$)
8	*Lb*ADH	**3f**	>99 (*S*)[c]	–1.6 (*c* 1.0, $CHCl_3$)[f]
9	ADH-A	**3f**	>99 (*R*)[c]	+1.4 (*c* 1.0, $CHCl_3$)[g]
10	*Lb*ADH	**3g**	>99 (*S*)[c]	–78.2 (*c* 1.0, $CHCl_3$)
11	*Lb*ADH	**3h**	>99 (*S*)[b]	–3.5 (*c* 1.0, $CHCl_3$)
12	CAL-B	**1i**	>99 (*S*)[b]	–91.1 (*c* 1.0, $CHCl_3$)
13	CAL-B	**2i**	>99 (*R*)[b]	+8.5 (*c* 1.0, $CHCl_3$)
14	evo.1.1.200	**3i**	*de* >99, *ee* >99 (2*S*,3*R*)[b]	+1.2 (*c* 1.0, $CHCl_3$)
15	KRED-P2-B02	**3i**	*de* 96, *ee* >99 (2*R*,3*R*)[b]	+8.9 (*c* 1.0, $CHCl_3$)

[a] Absolute configuration of the compounds **3a-i** in parentheses.
[b] Enantiomeric excess values were measured by GC analysis.
[c] Enantiomeric excess values were measured by HPLC analysis.
[d] Optical rotation values were compared with those already described in the literature.[14]
[e] Optical rotation values were compared with those already described in the literature.[16]
[f] Optical rotation values were compared with those already described in the literature.[20]
[g] Optical rotation values were compared with those already described in the literature.[21]

XII. Synthesis and characterization of epoxide 6i to determine the absolute configuration of compound 3i

Compound **6i** was synthesized through basic hydrolysis of diester (2*R*,3*S*)-**3i** with sodium methoxide in methanol (Scheme S9).



Scheme S9. Synthesis of epoxide **6i**.

Compound (2*R*,3*S*)-**3i** (60 mg, 0.23 mmol, 1 equiv) was dissolved in methanol (5 mL) and sodium methoxide (24.5 mg, 0.45 mmol, 2 equiv) was added and stirred overnight at rt. After this time, the reaction was quenched with H_2O (5 mL) and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum. Purification by column chromatography (SiO_2, 80% Et_2O/pentane), afforded the corresponding epoxide derivative **6i** (55 mg, 85% isolated yield). The spectroscopic data and the optical rotation of this compound matched with the ones already reported in the literature.[22]

(*S*)-1-((*S*)-Oxiran-2-yl)hexan-1-ol (6i): Colorless oil. R_f (80% Et_2O/pentane): 0.57. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.42 (*quint*, *J* = 5.6 Hz, 1H), 3.06–2.93 (*m*, 1H), 2.83 (*t*, *J* = 4.5 Hz, 1H), 2.72 (*dd*, *J* = 5.0, 2.8 Hz, 1H), 2.27 (*d*, *J* = 5.2 Hz, 1H), 1.68–1.13 (*m*, 8H), 0.90 (*t*, *J* = 6.6 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 72.2 (CH), 55.9 (CH), 45.6 (CH_2), 34.7 (CH_2), 32.2 (CH_2), 25.4 (CH_2), 22.9 (CH_2), 14.4 (CH_3). $[\alpha]_D^{20}$ = +1.6 (1.0 *c*, $CHCl_3$). Lit:[20] $[\alpha]_D^{26}$ = +4.4 (0.1 *c*, $CHCl_3$).

XIII. Reference section

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XIV. NMR spectra

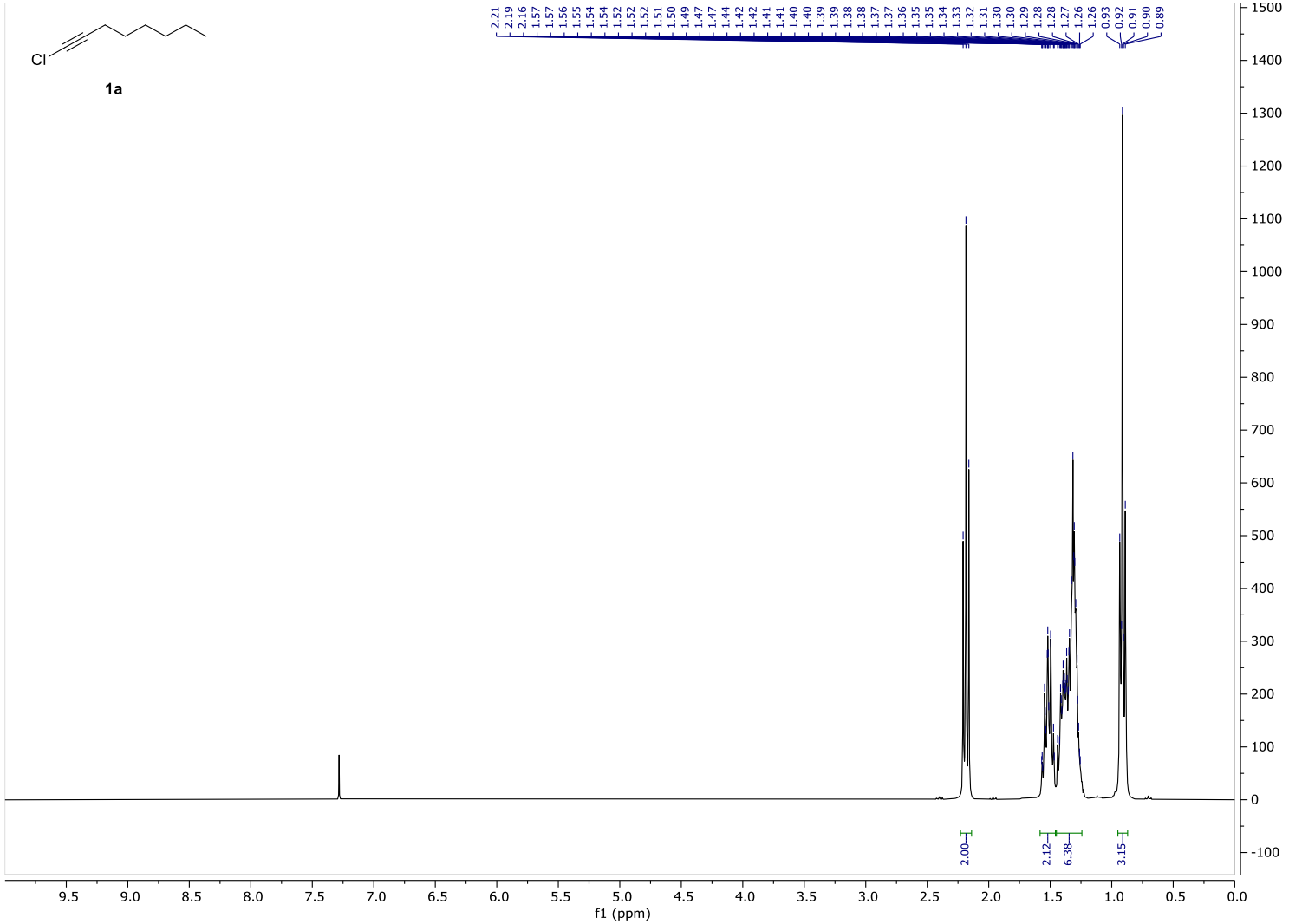

Figure S15. ^{1}H-NMR spectrum ($CDCl_3$) of compound **1a**.

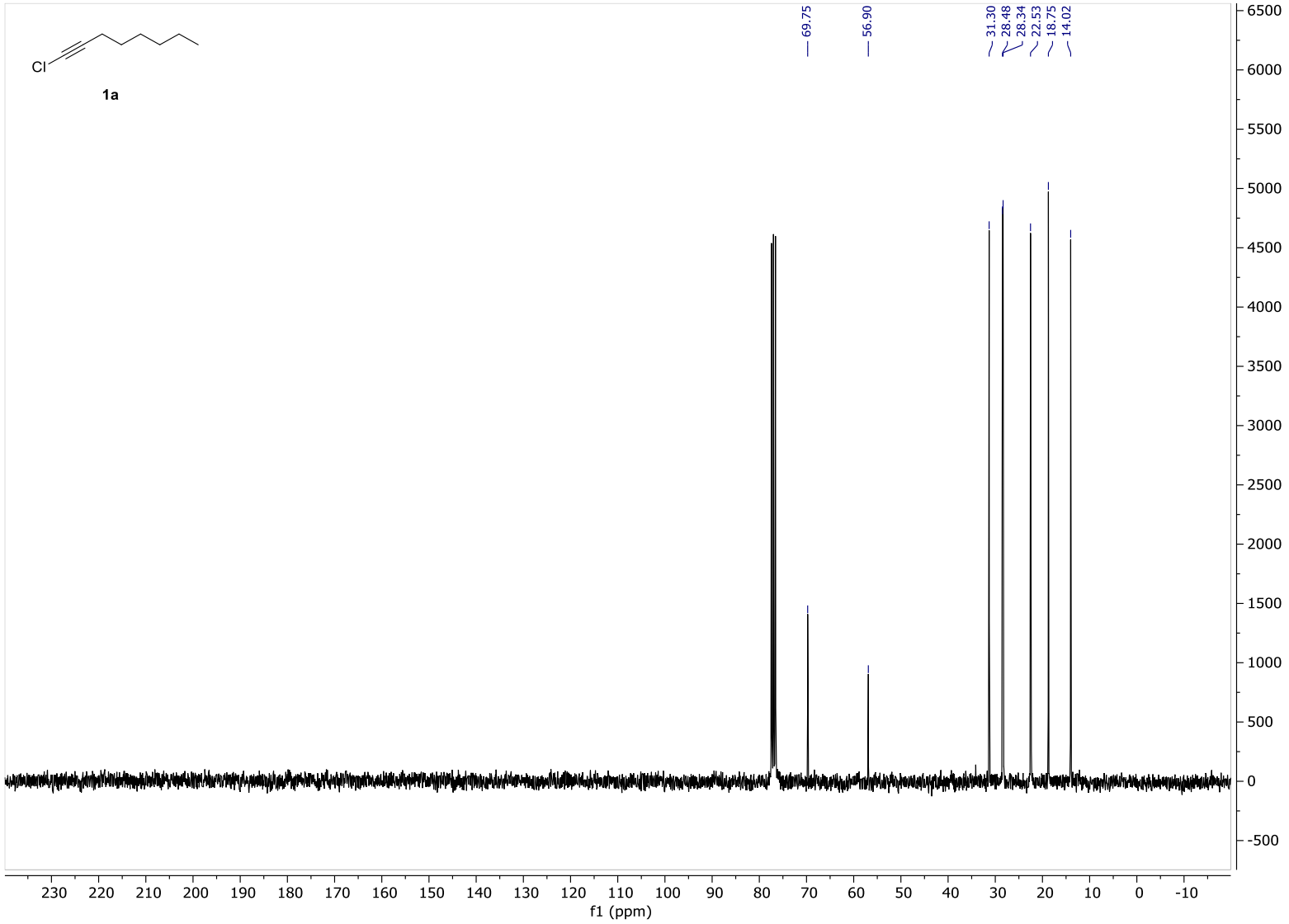

Figure S16. ^{13}C-NMR spectrum ($CDCl_3$) of compound **1a**.

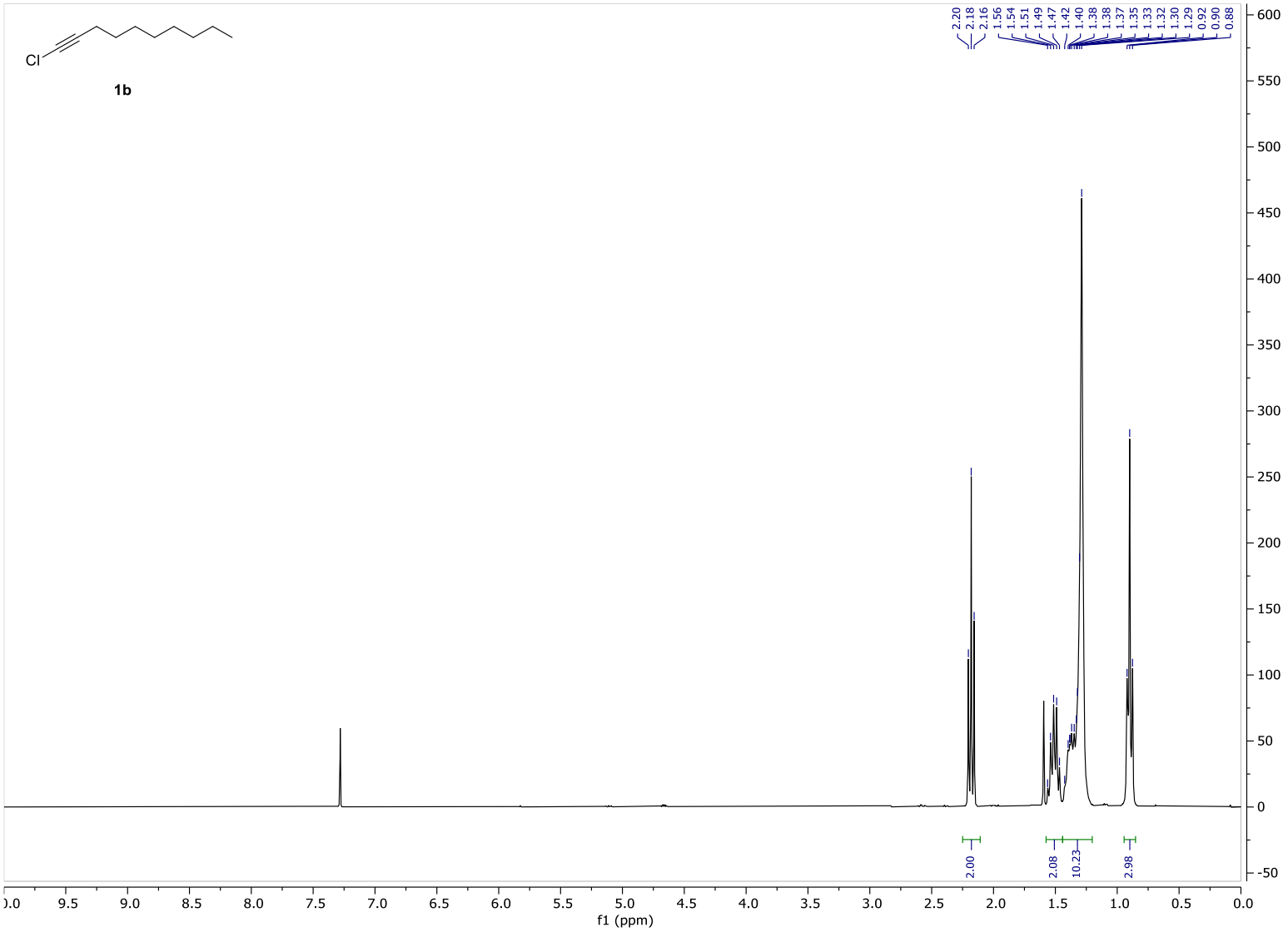

Figure S17. ^{1}H-NMR spectrum ($CDCl_3$) of compound **1b**.

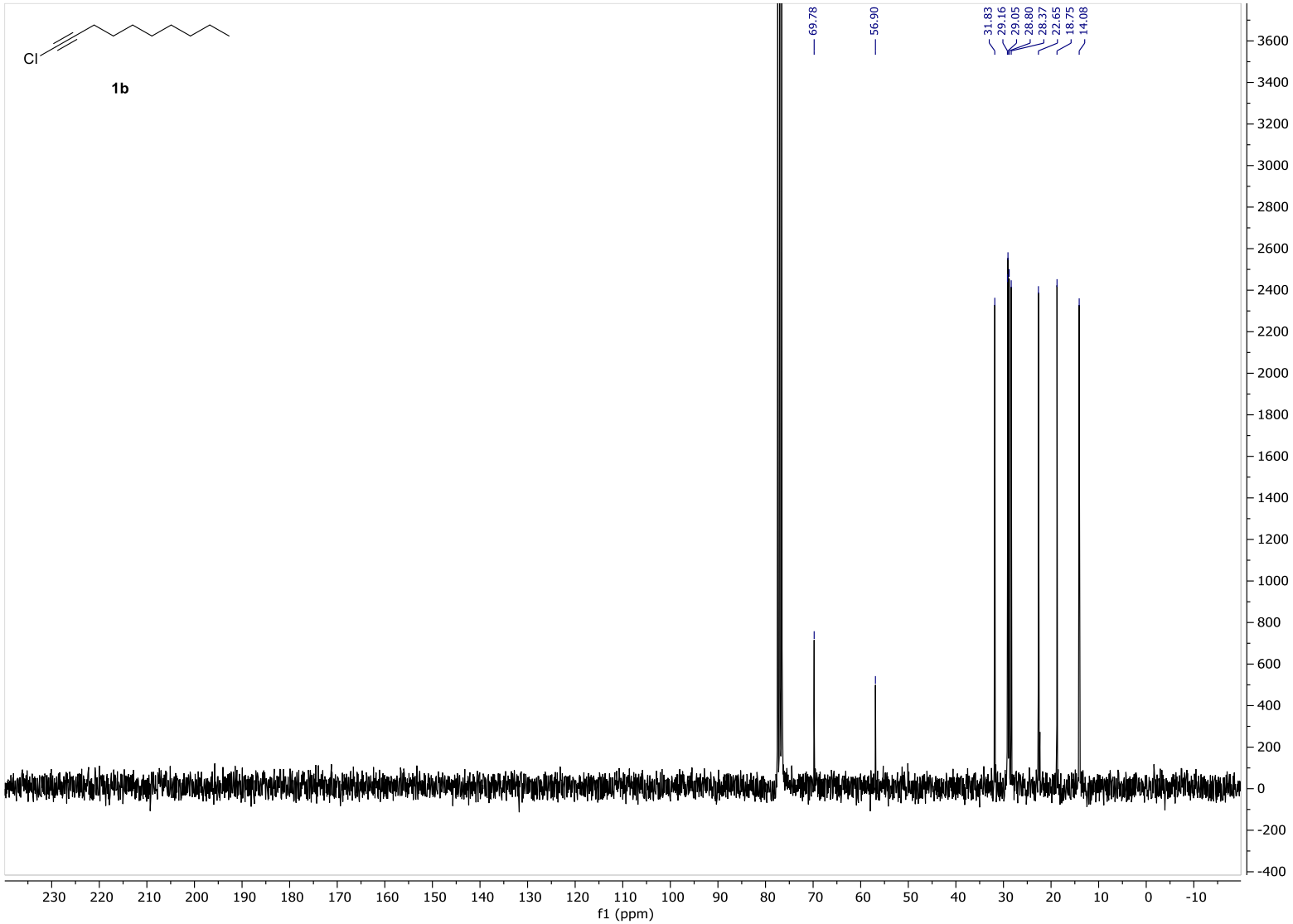

Figure S18. ^{13}C-NMR spectrum ($CDCl_3$) of compound **1b**.

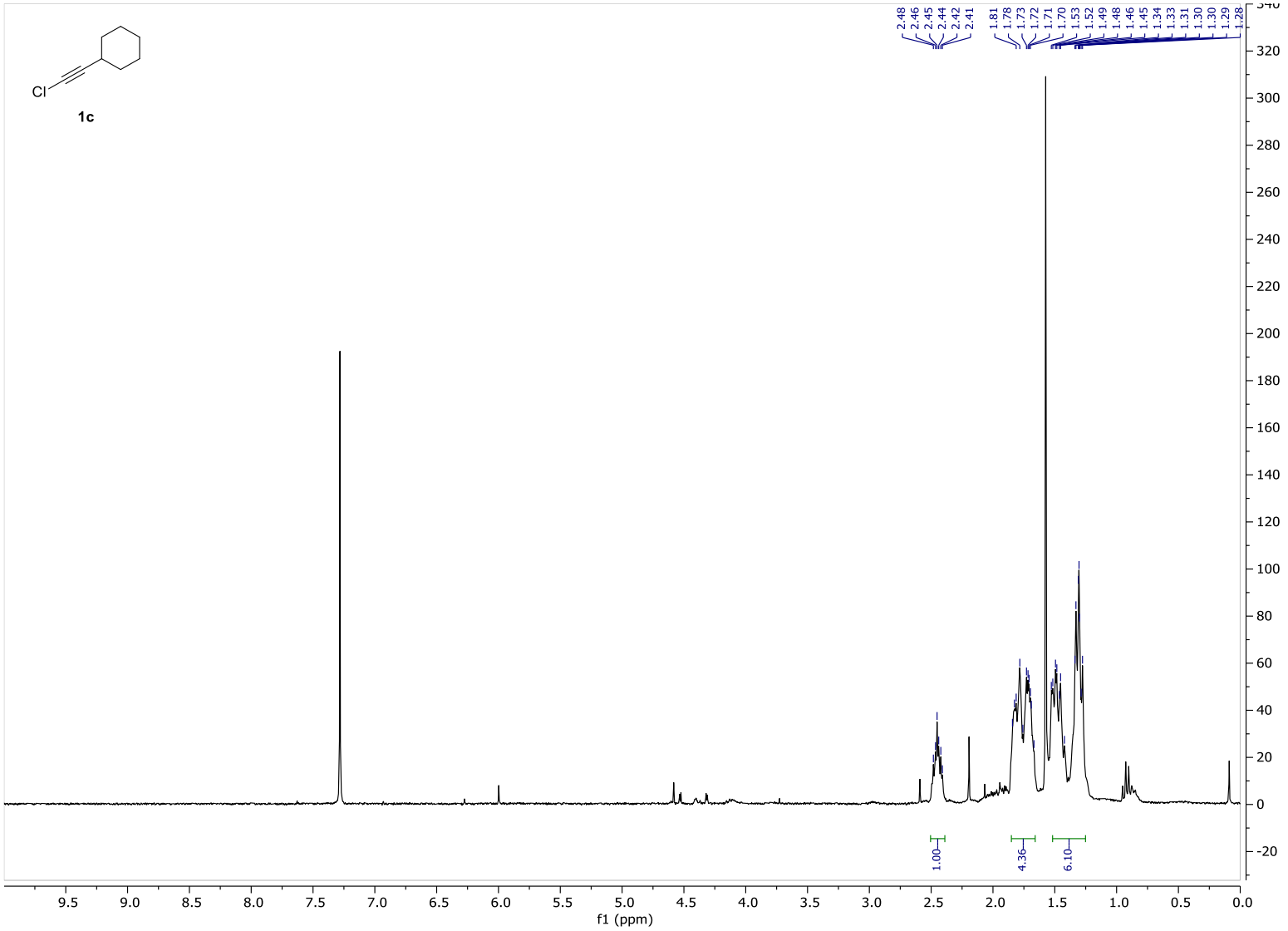

Figure S19. ^{1}H-NMR spectrum ($CDCl_3$) of compound **1c**.

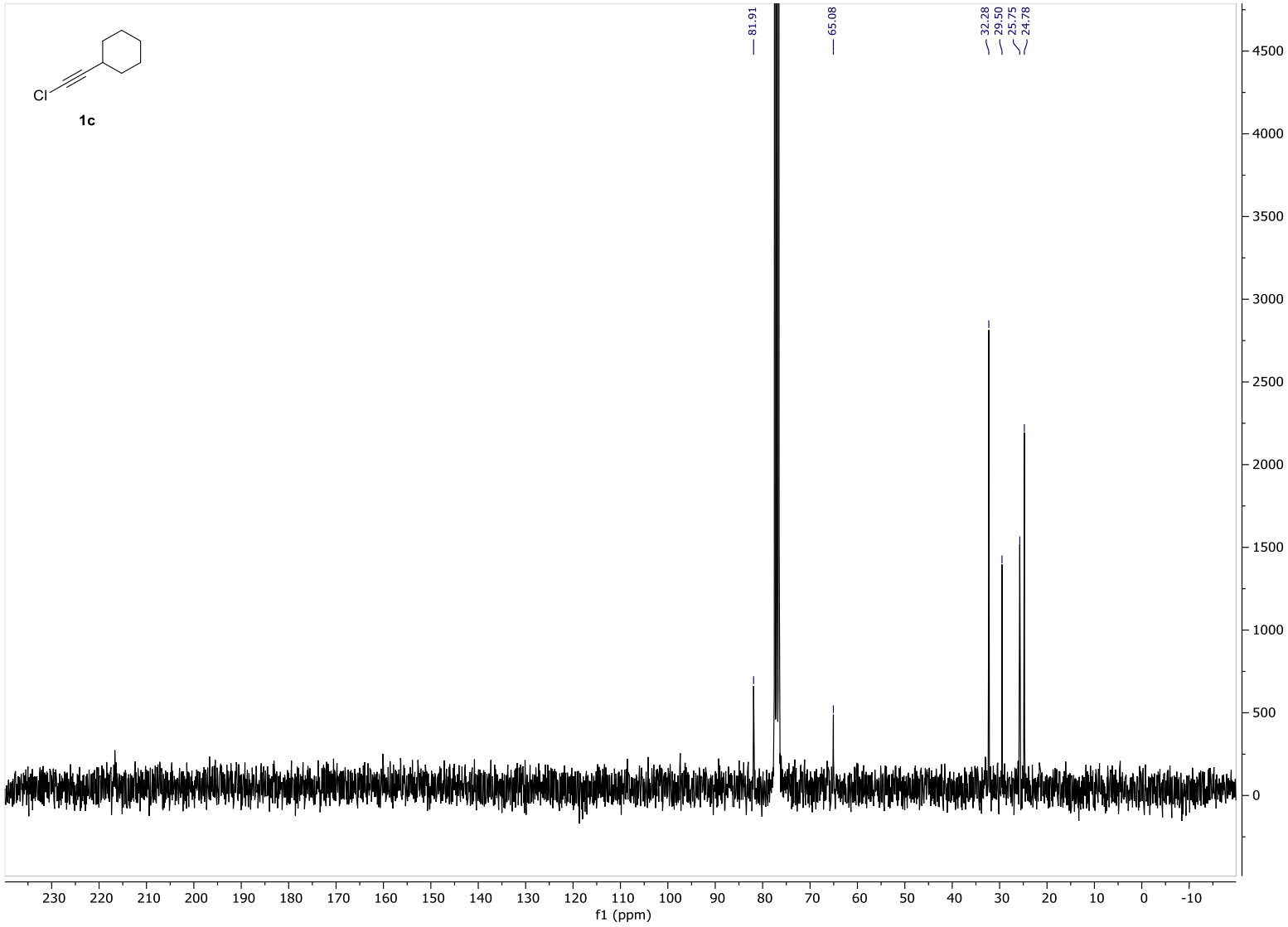

Figure S20. ^{13}C-NMR spectrum ($CDCl_3$) of compound **1c**.

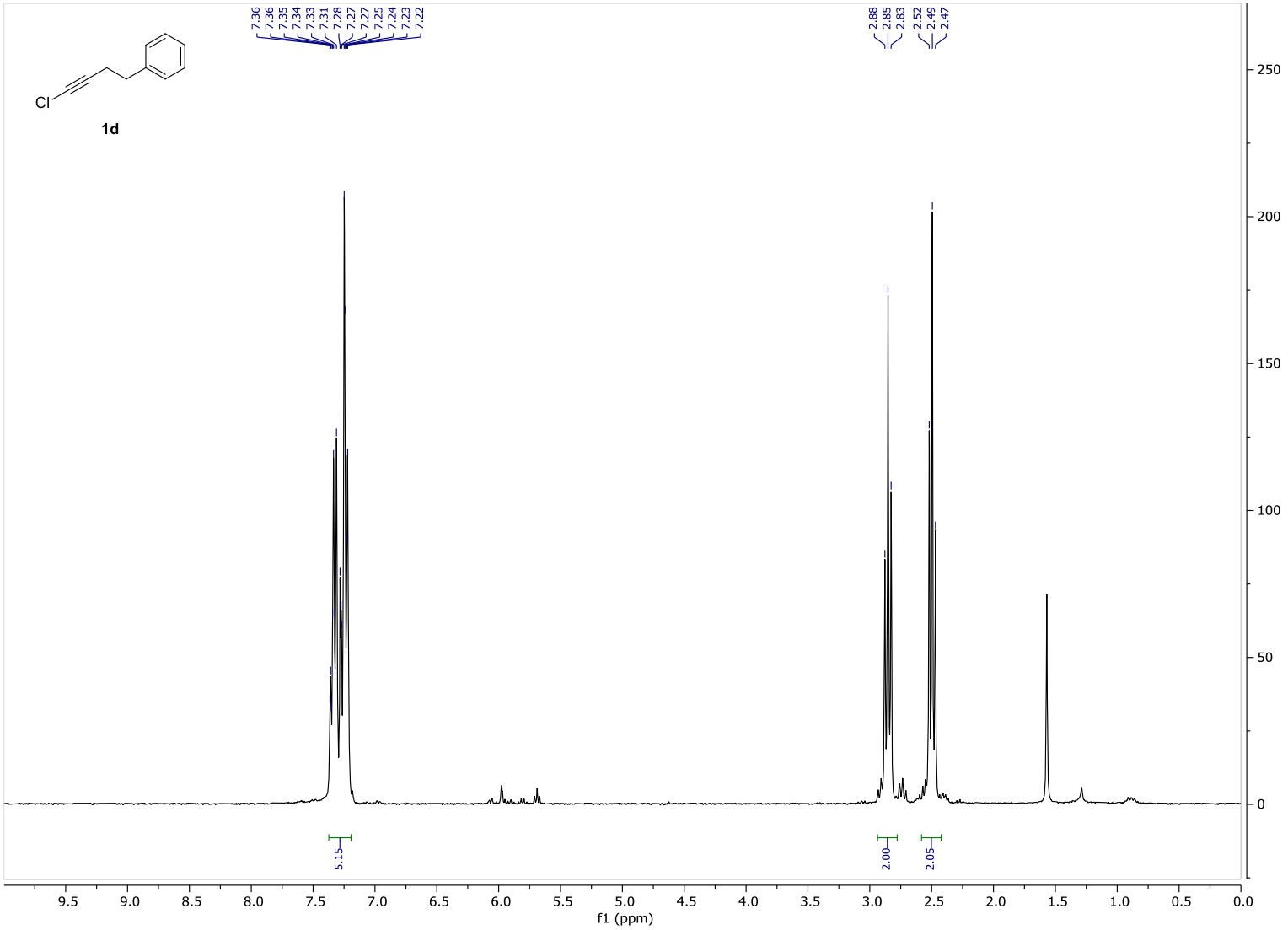

Figure S21. ^{1}H-NMR spectrum ($CDCl_3$) of compound **1d**.

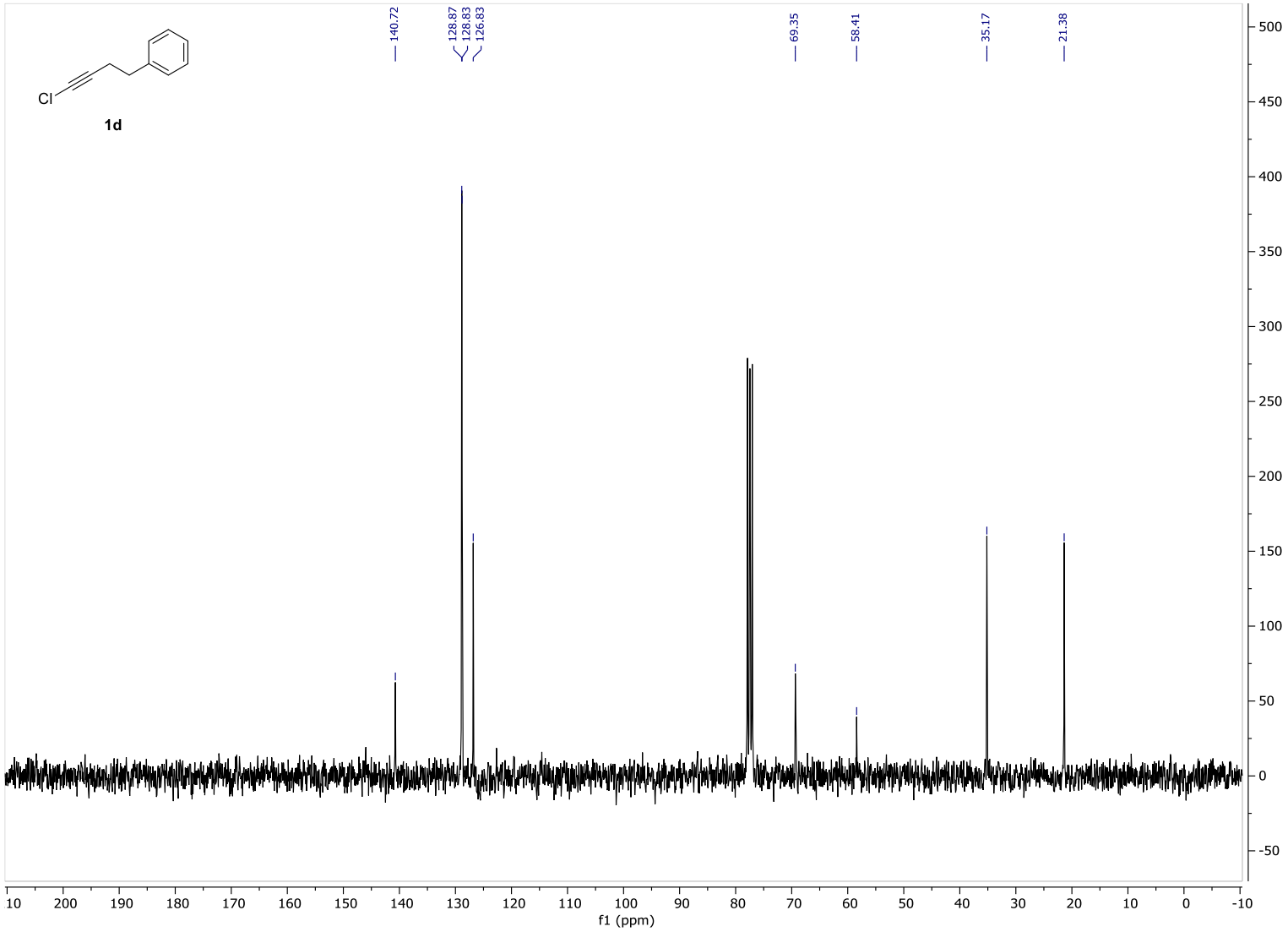

Figure S22. ^{13}C-NMR spectrum ($CDCl_3$) of compound **1d**.

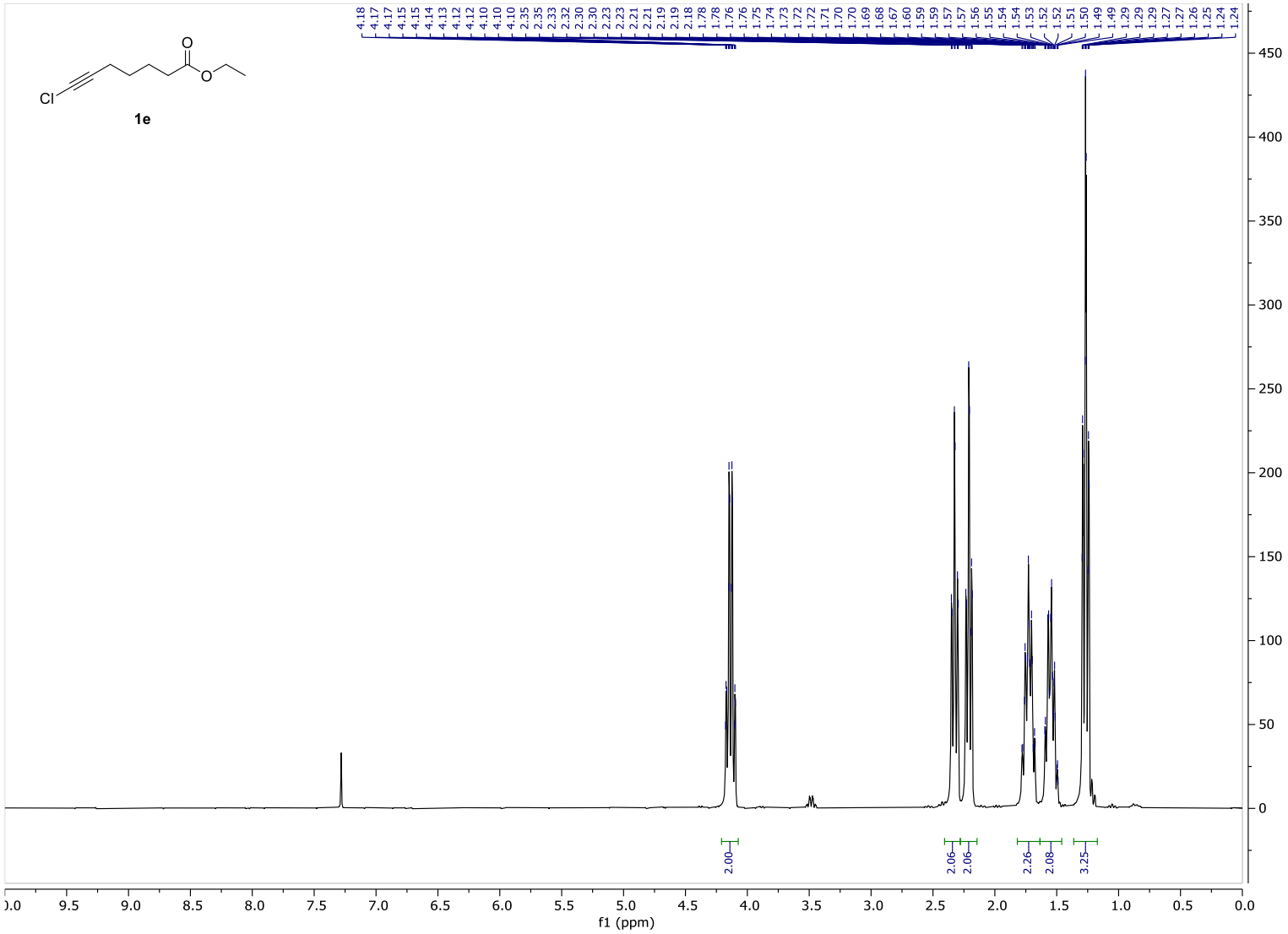

Figure S23. ^{1}H-NMR spectrum ($CDCl_3$) of compound **1e**.

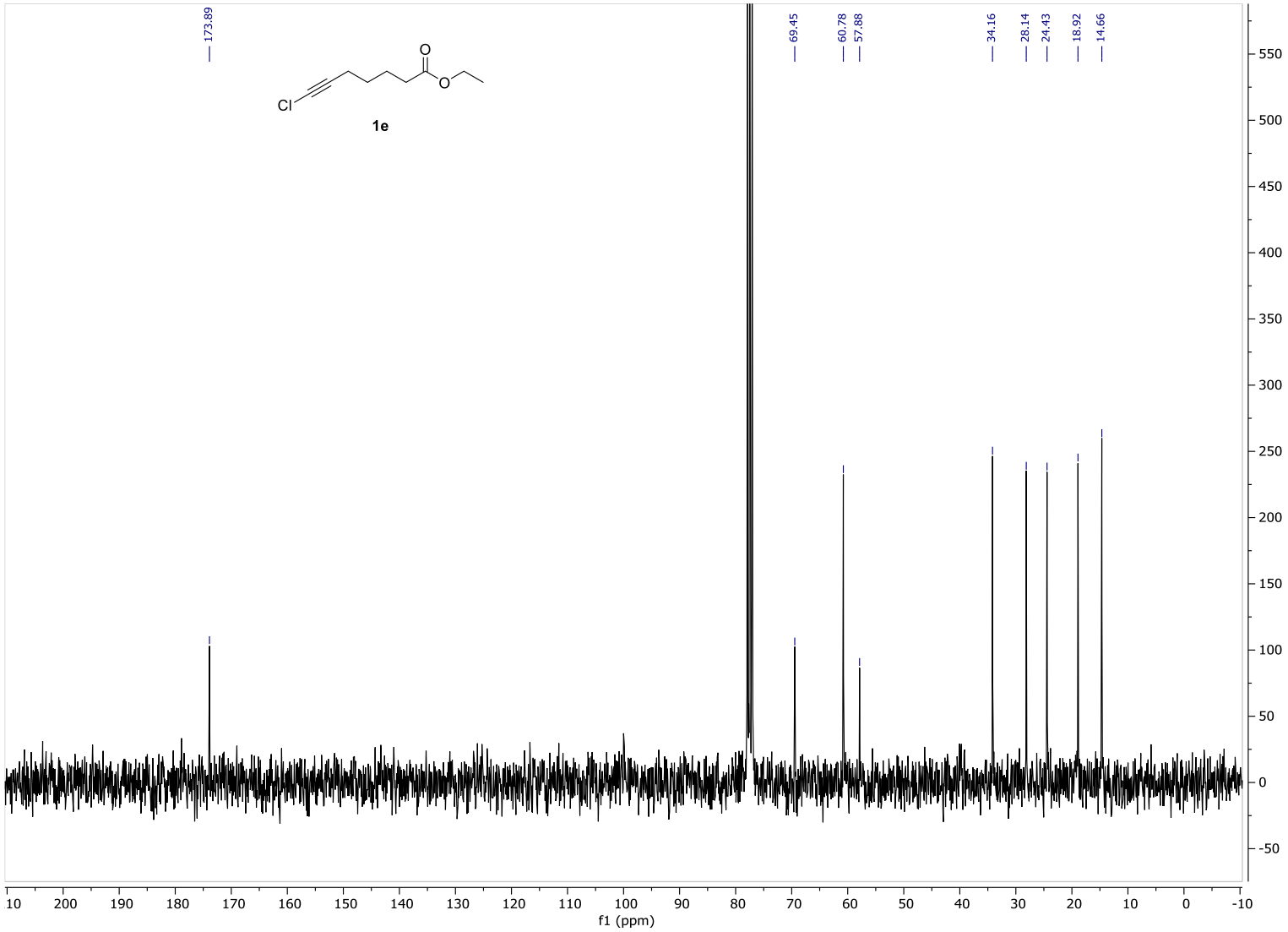

Figure S24. ^{13}C-NMR spectrum ($CDCl_3$) of compound **1e**.

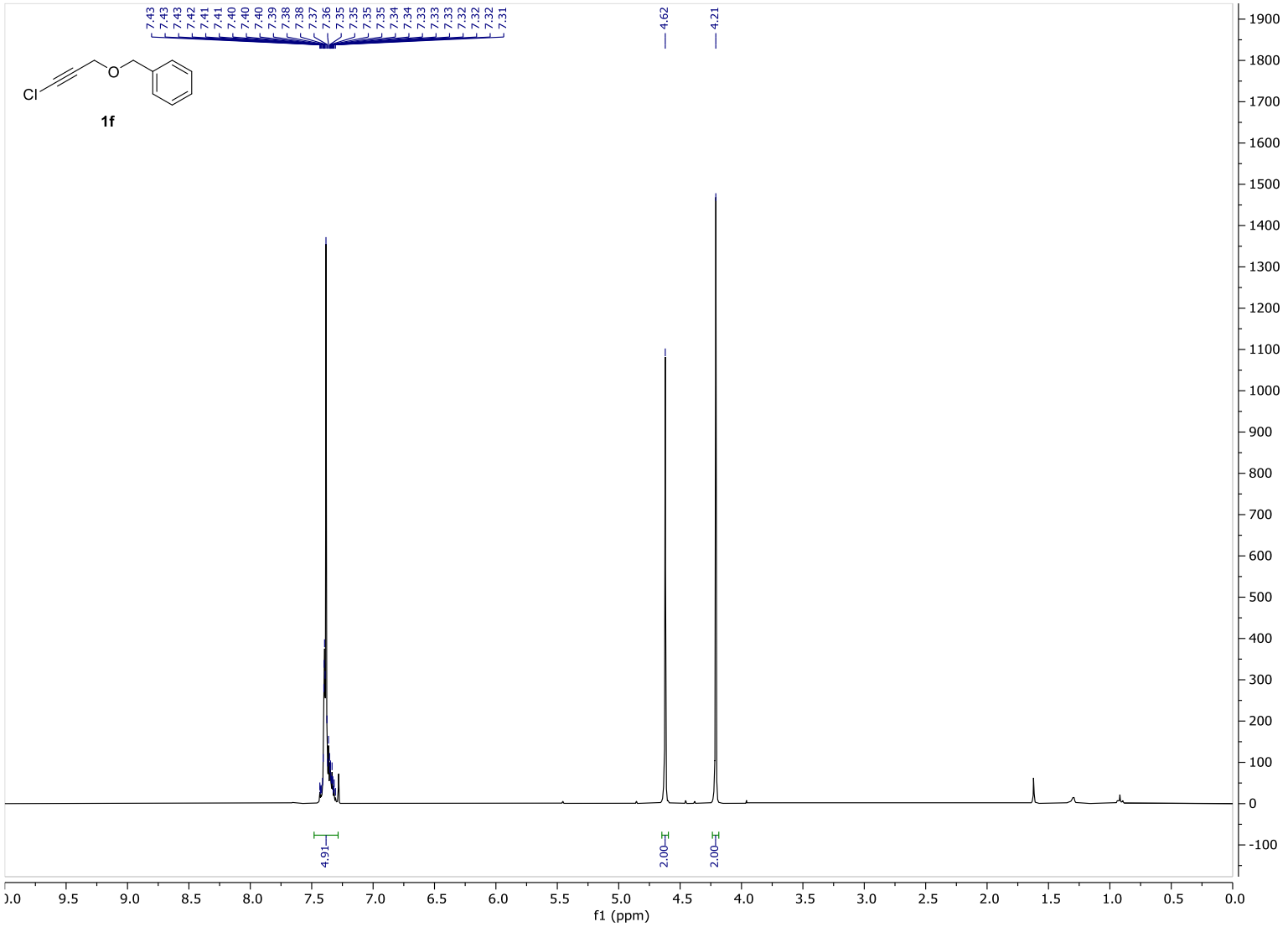

Figure S25. ^{1}H-NMR spectrum ($CDCl_3$) of compound **1f**.

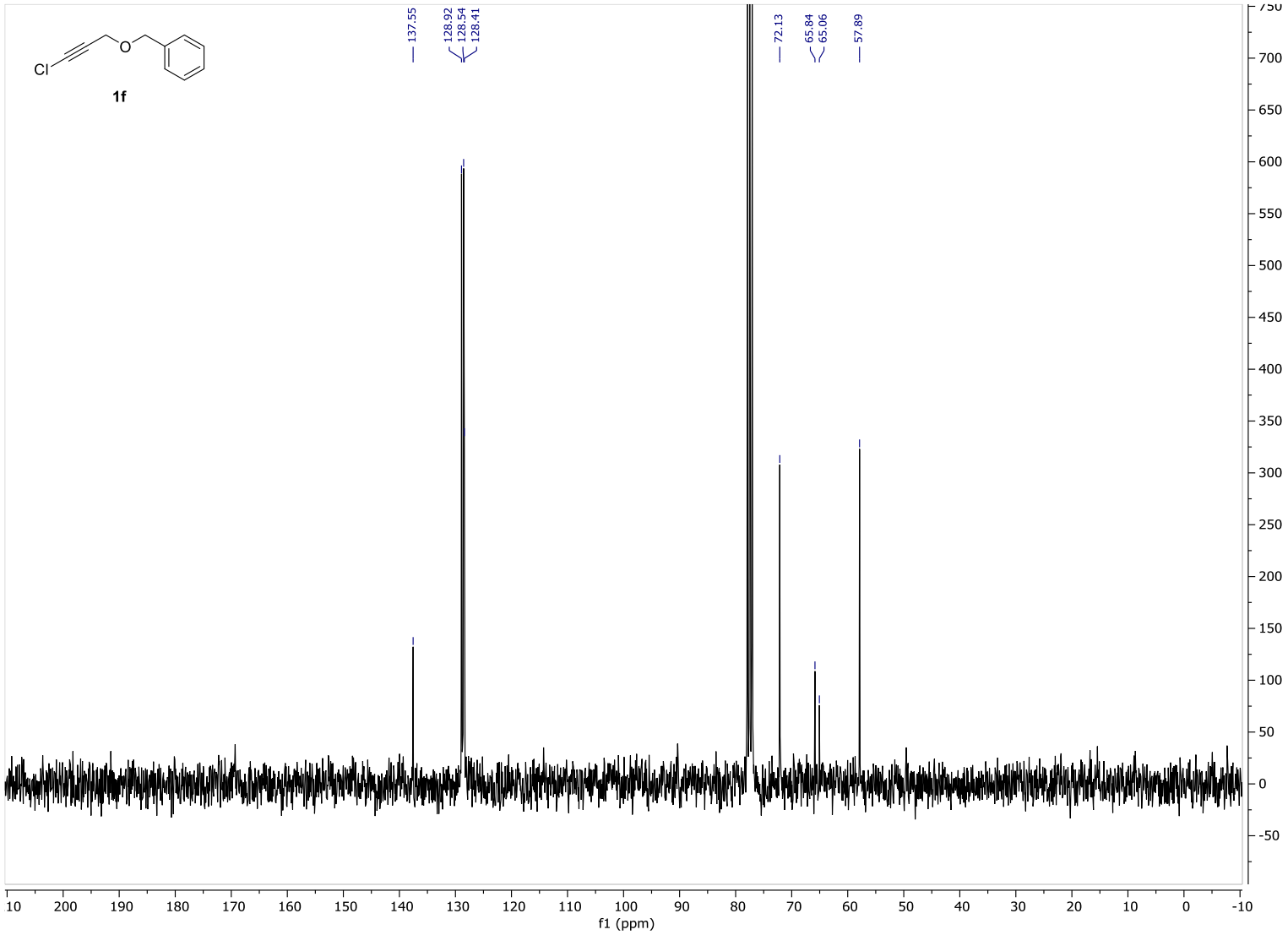

Figure S26. ^{13}C-NMR spectrum ($CDCl_3$) of compound **1f**.

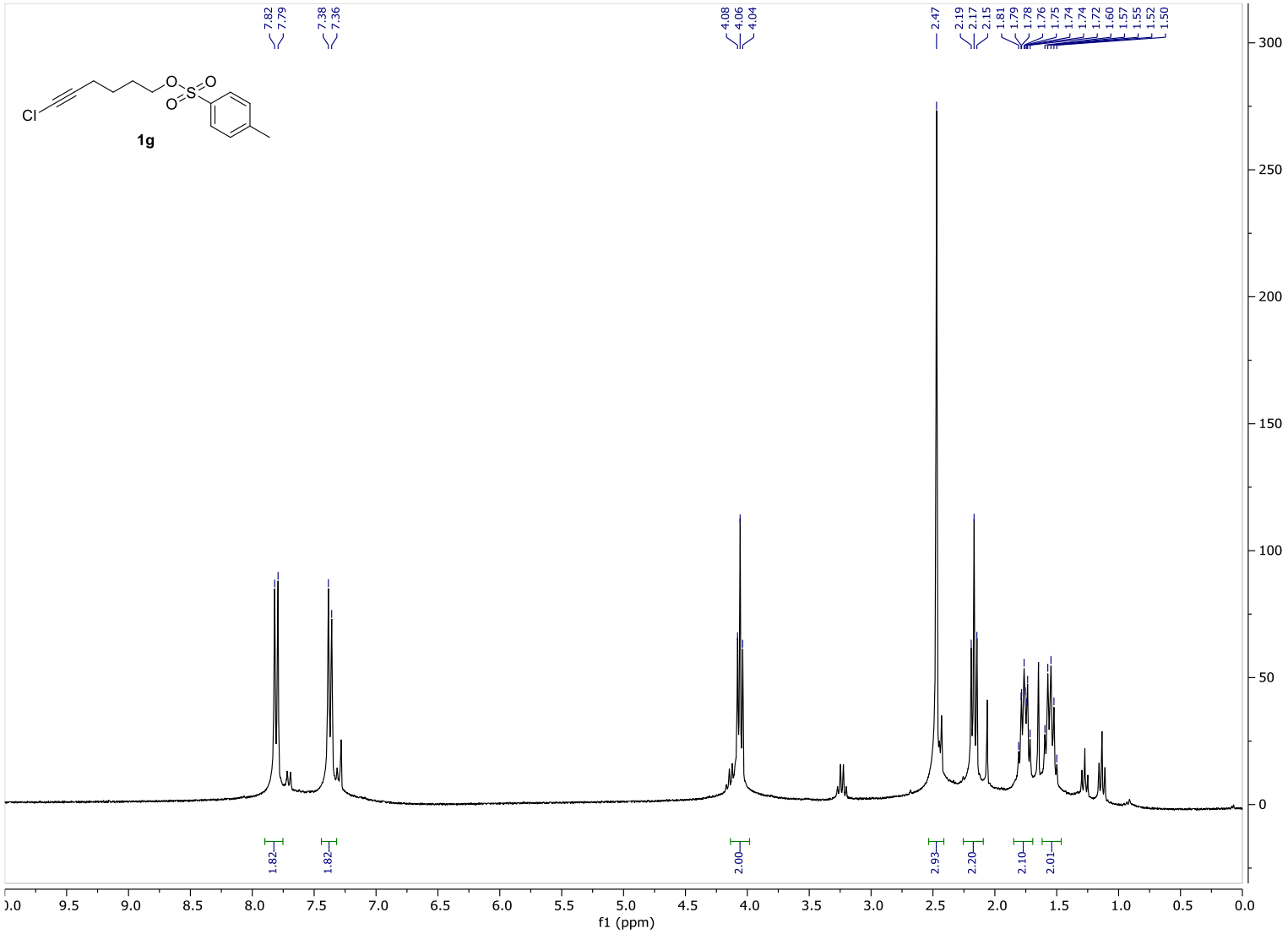

Figure S27. ^{1}H-NMR spectrum ($CDCl_3$) of compound **1g**.

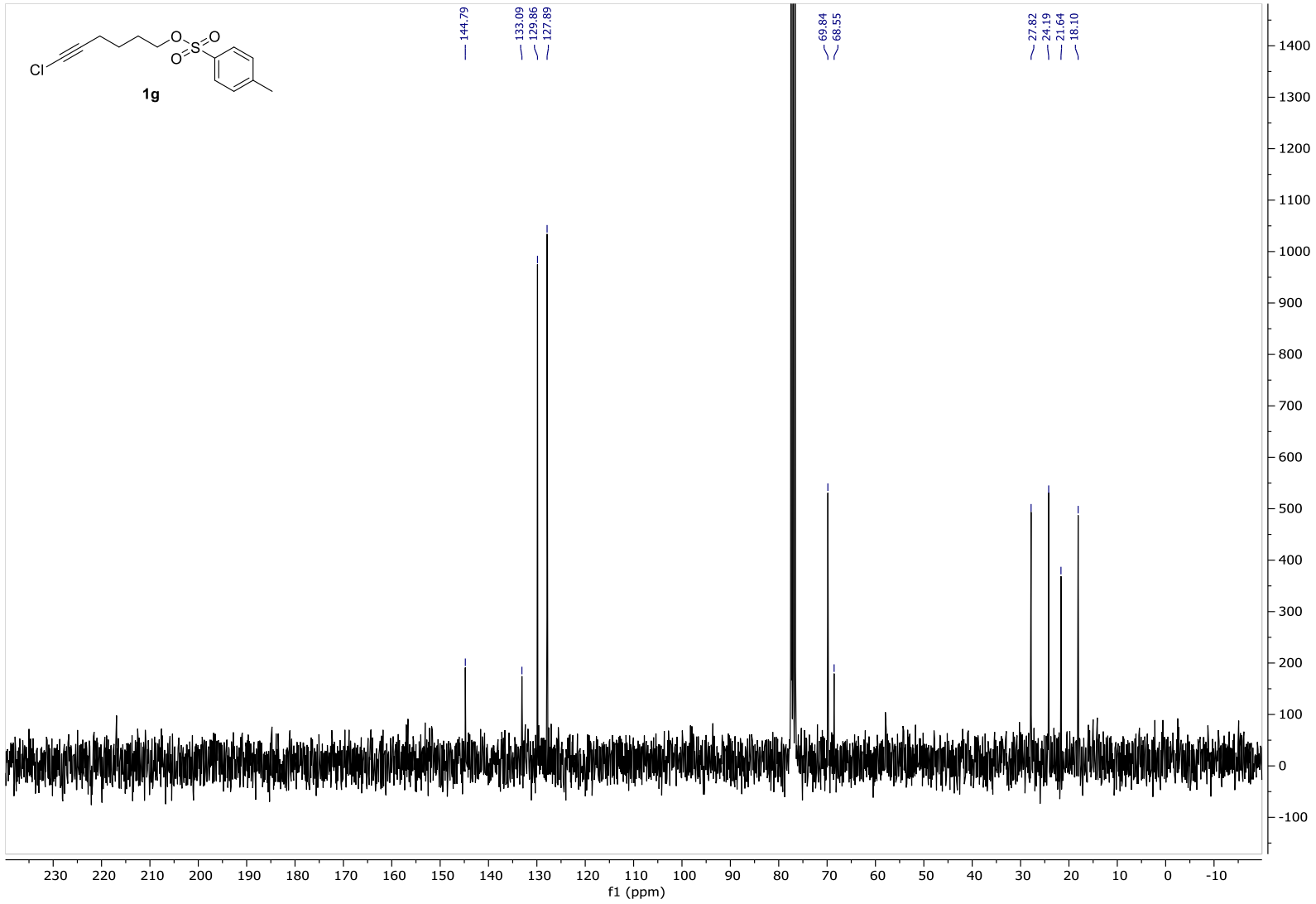

Figure S28. ^{13}C-NMR spectrum ($CDCl_3$) of compound **1g**.

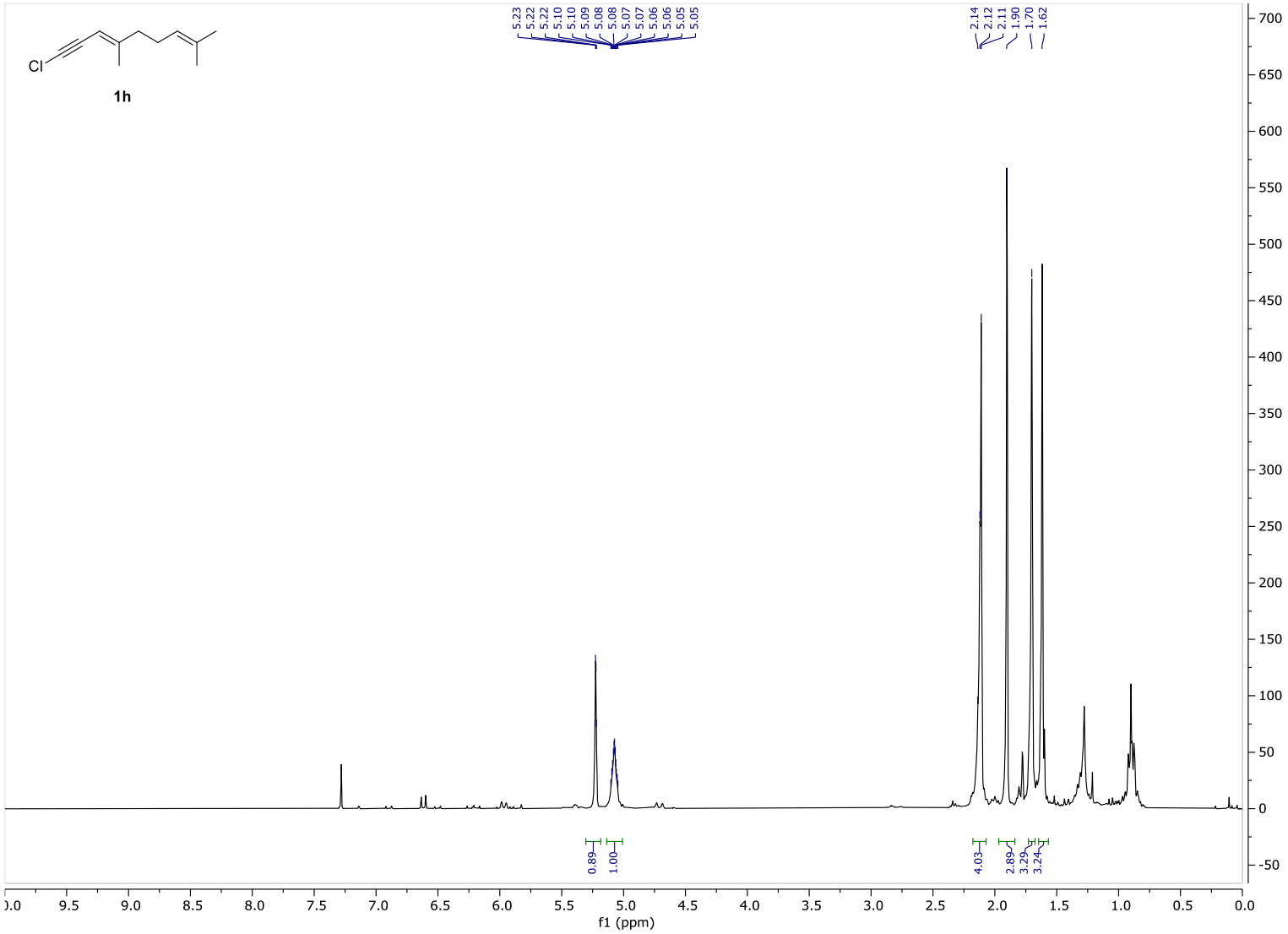

Figure S29. ^{1}H-NMR spectrum ($CDCl_3$) of compound **1h**.

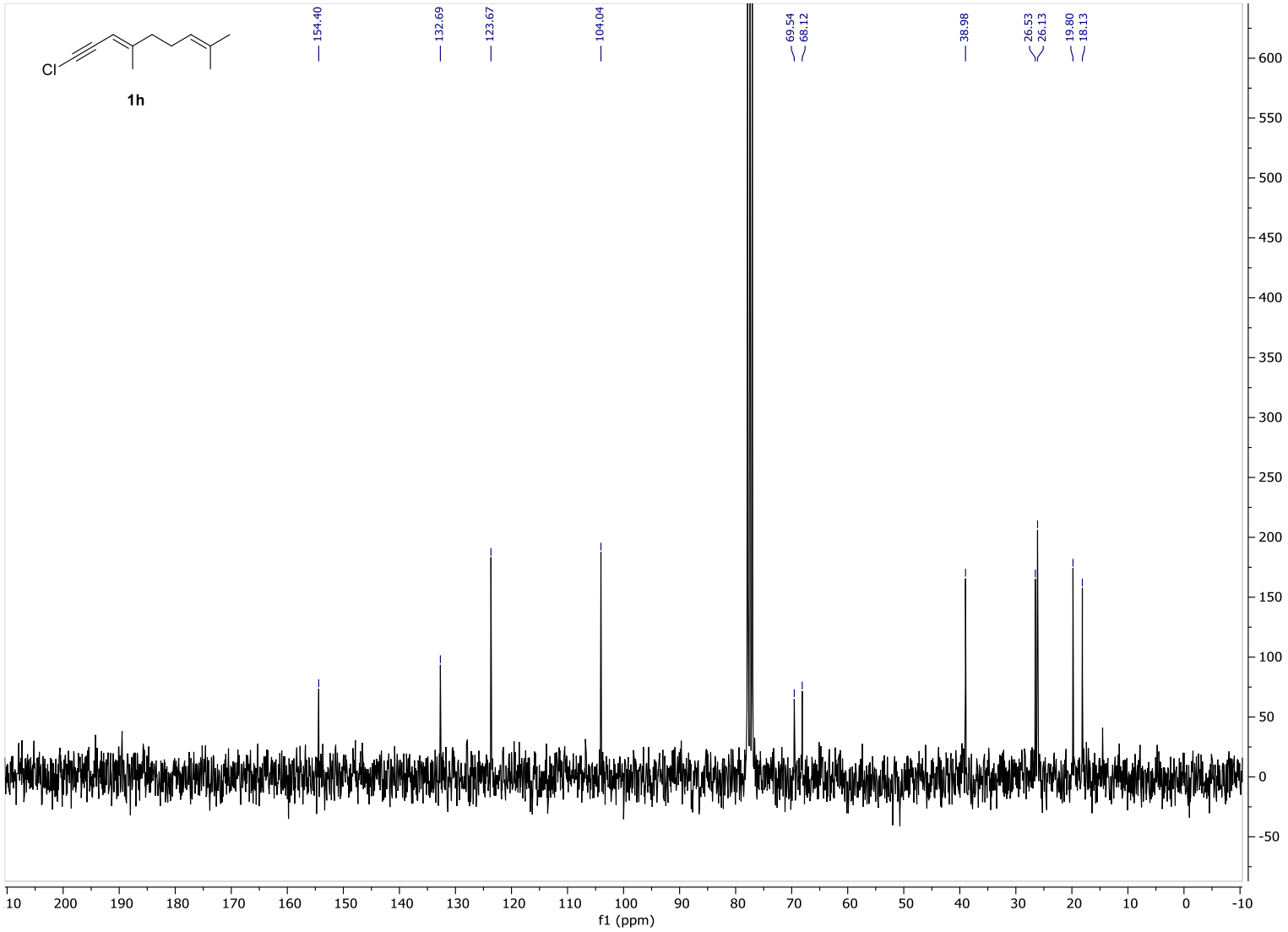

Figure S30. ^{13}C-NMR spectrum ($CDCl_3$) of compound **1h**.

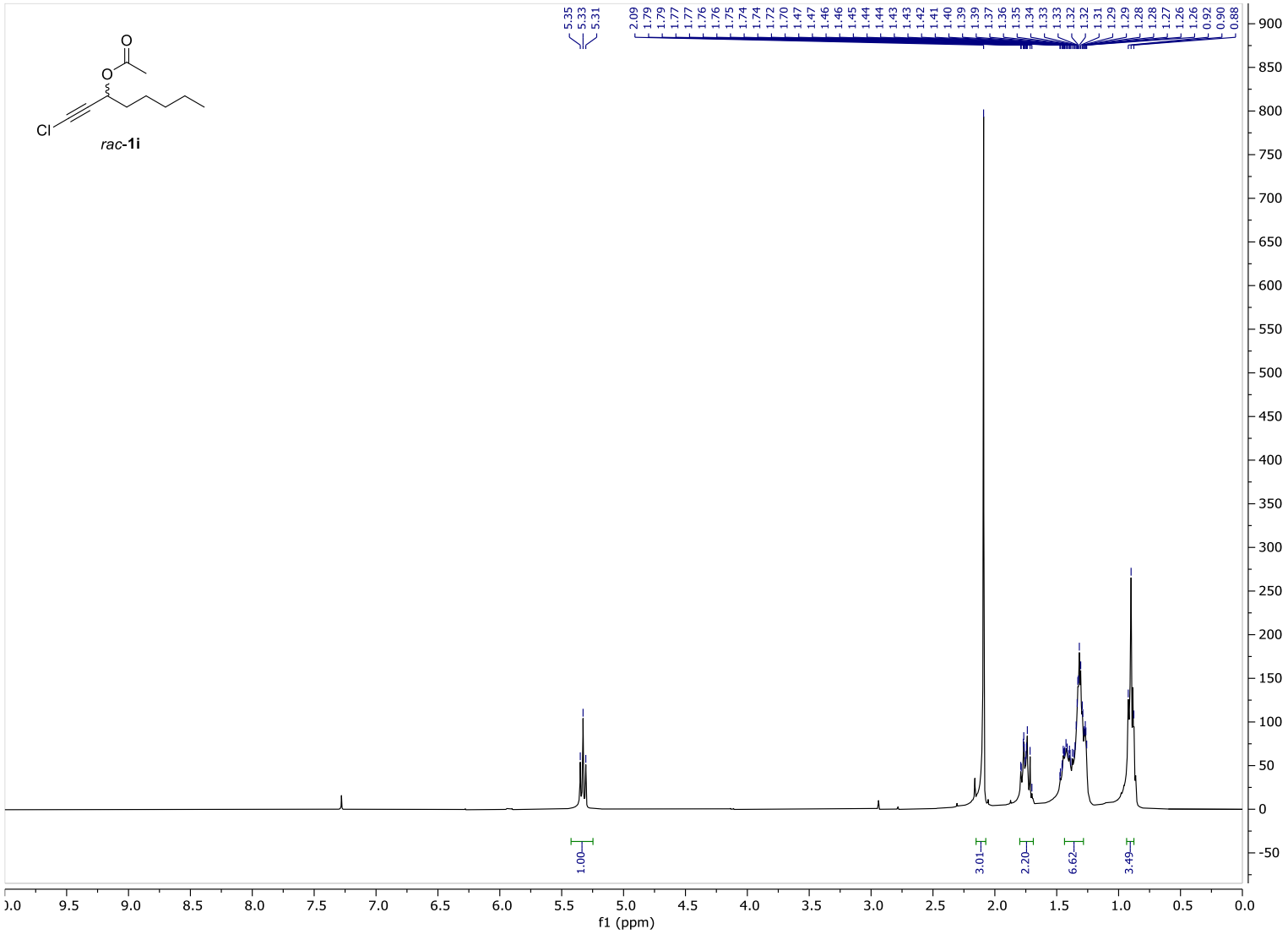

Figure S31. ^{1}H-NMR spectrum ($CDCl_3$) of compound **1i**.

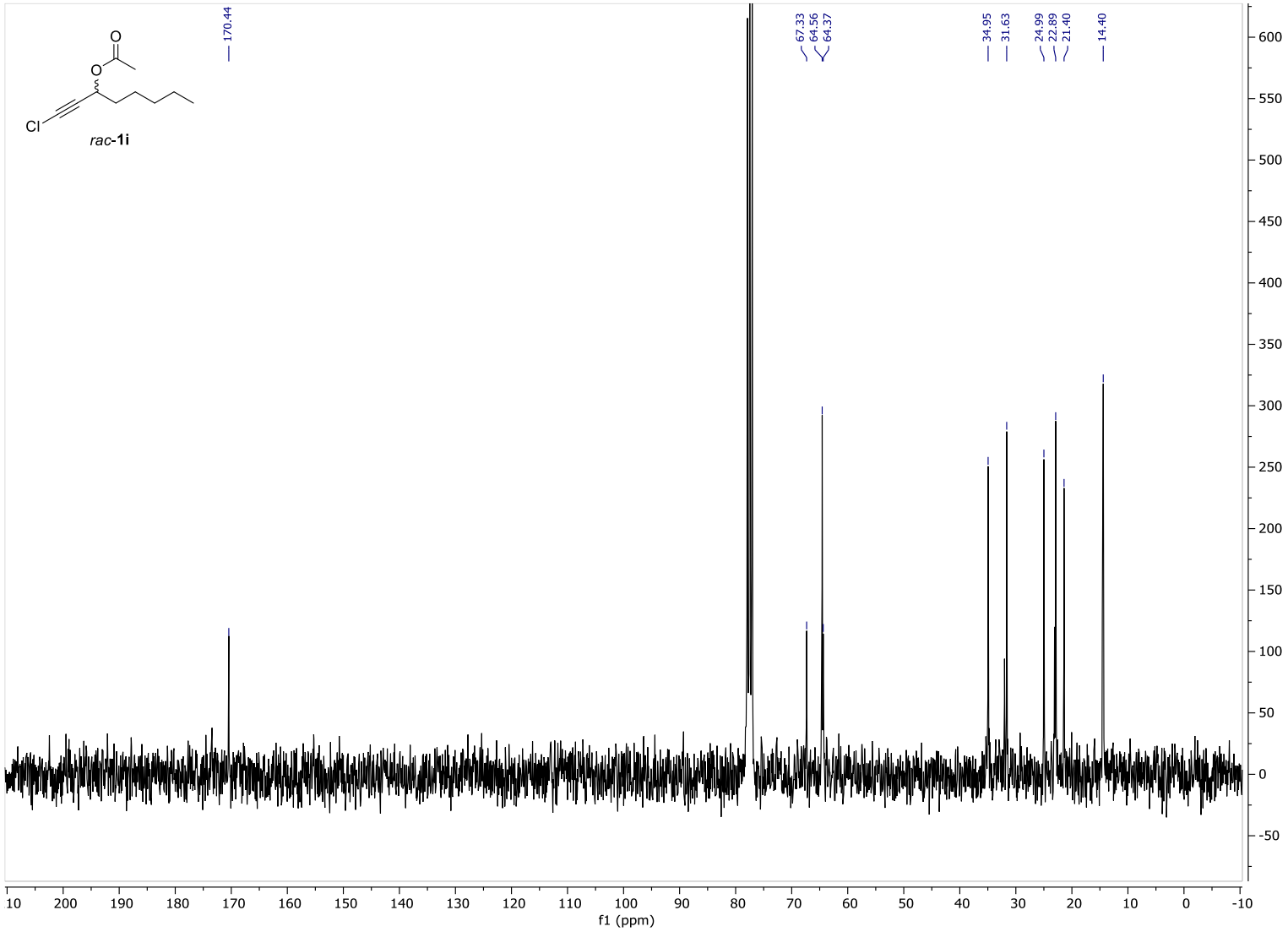

Figure S32. ^{13}C-NMR spectrum ($CDCl_3$) of compound **1i**.

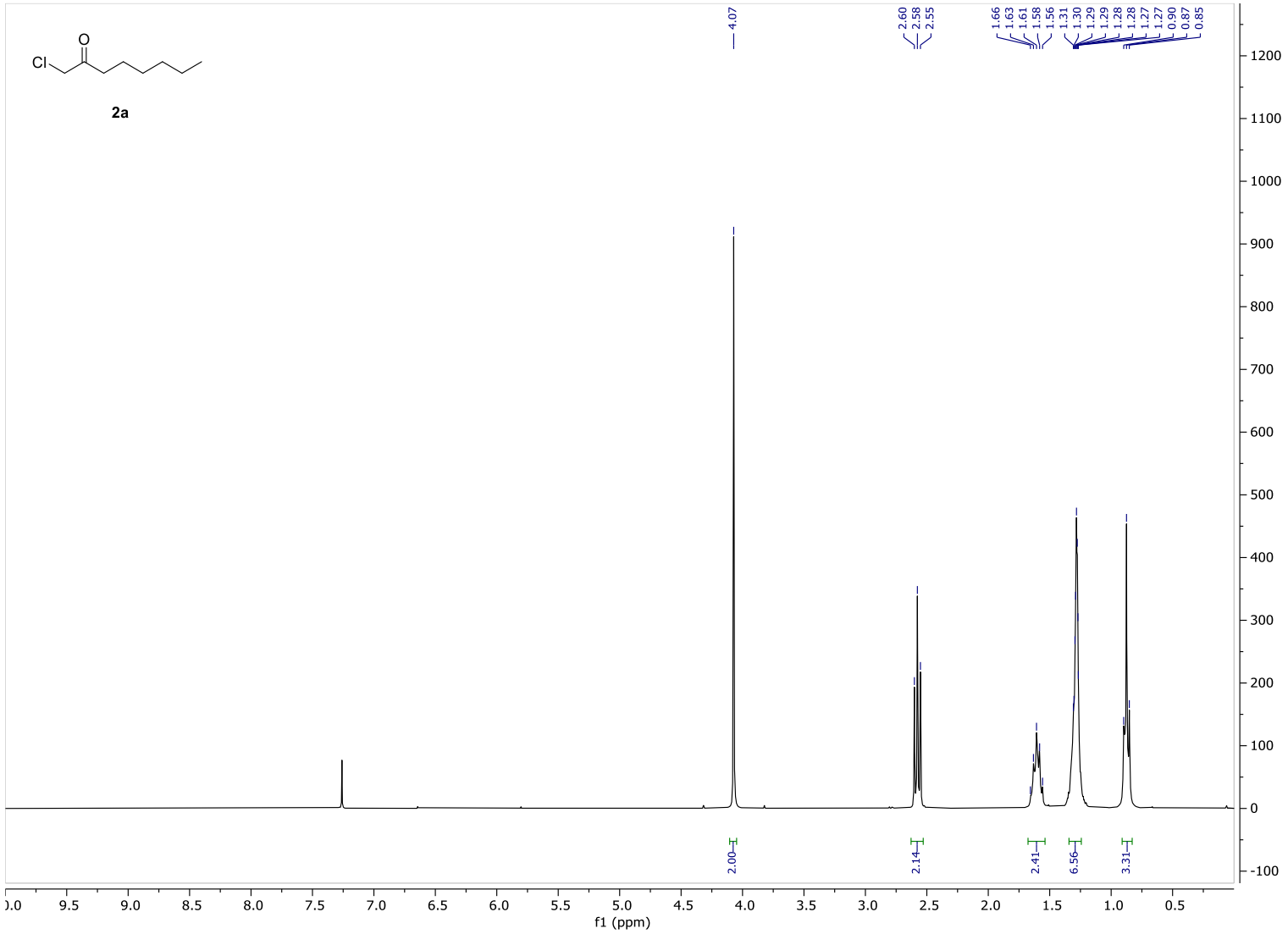

Figure S33. ^{1}H-NMR spectrum ($CDCl_3$) of compound **2a**.

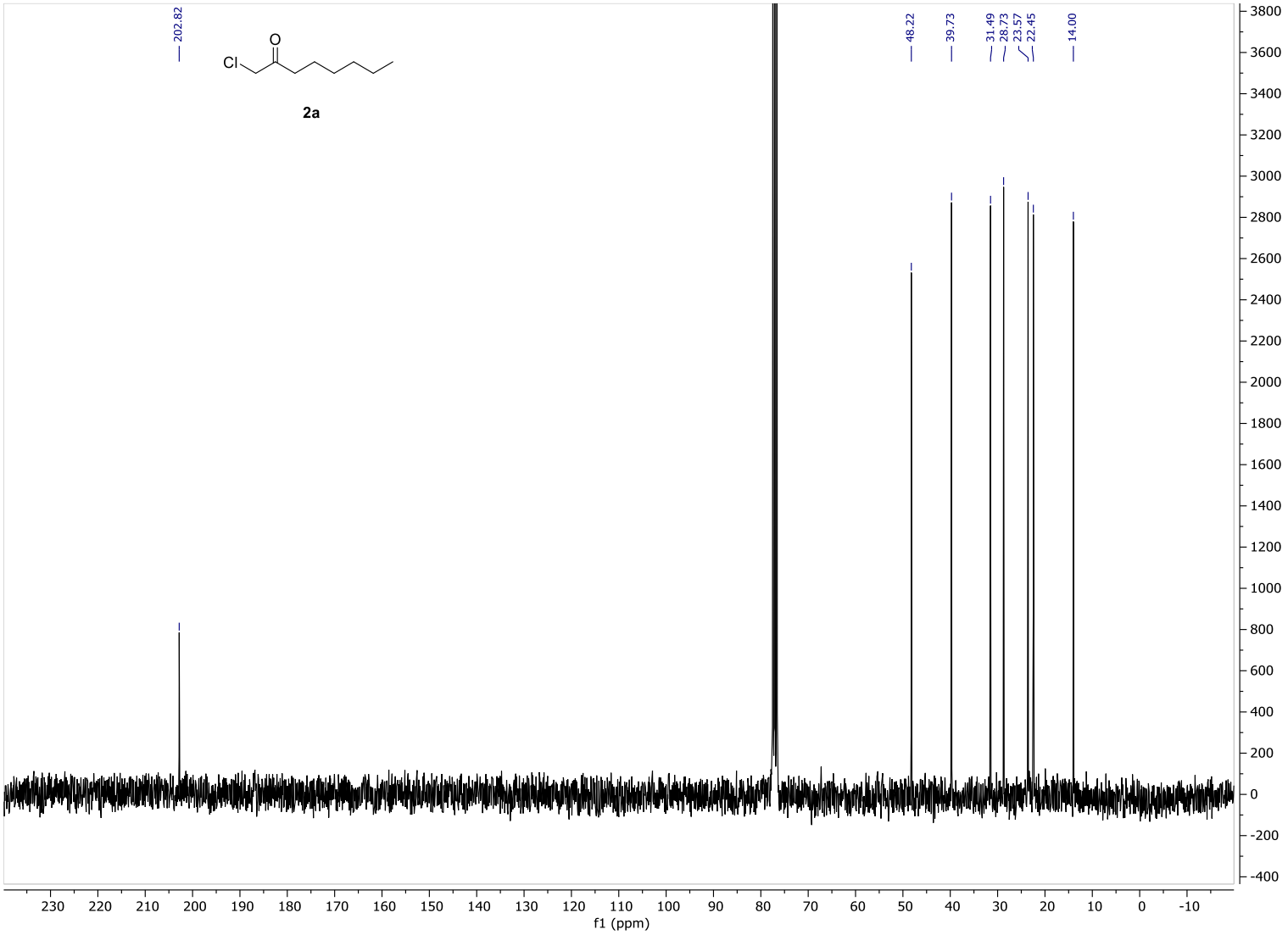

Figure S34. ^{13}C-NMR spectrum ($CDCl_3$) of compound **2a**.

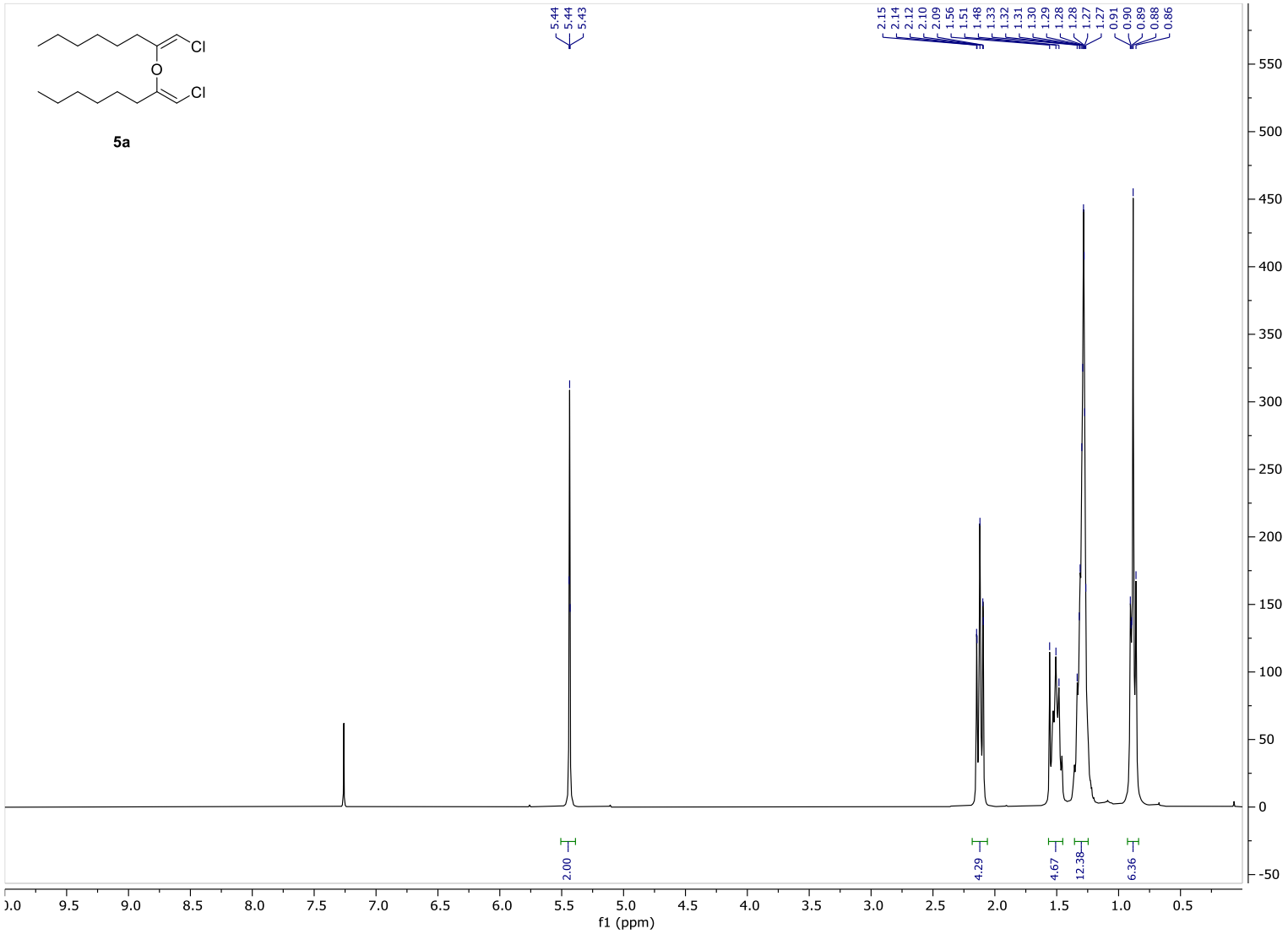

Figure S35. ^{1}H-NMR spectrum ($CDCl_3$) of by-product **5a** detected in the hydration of **1a**.

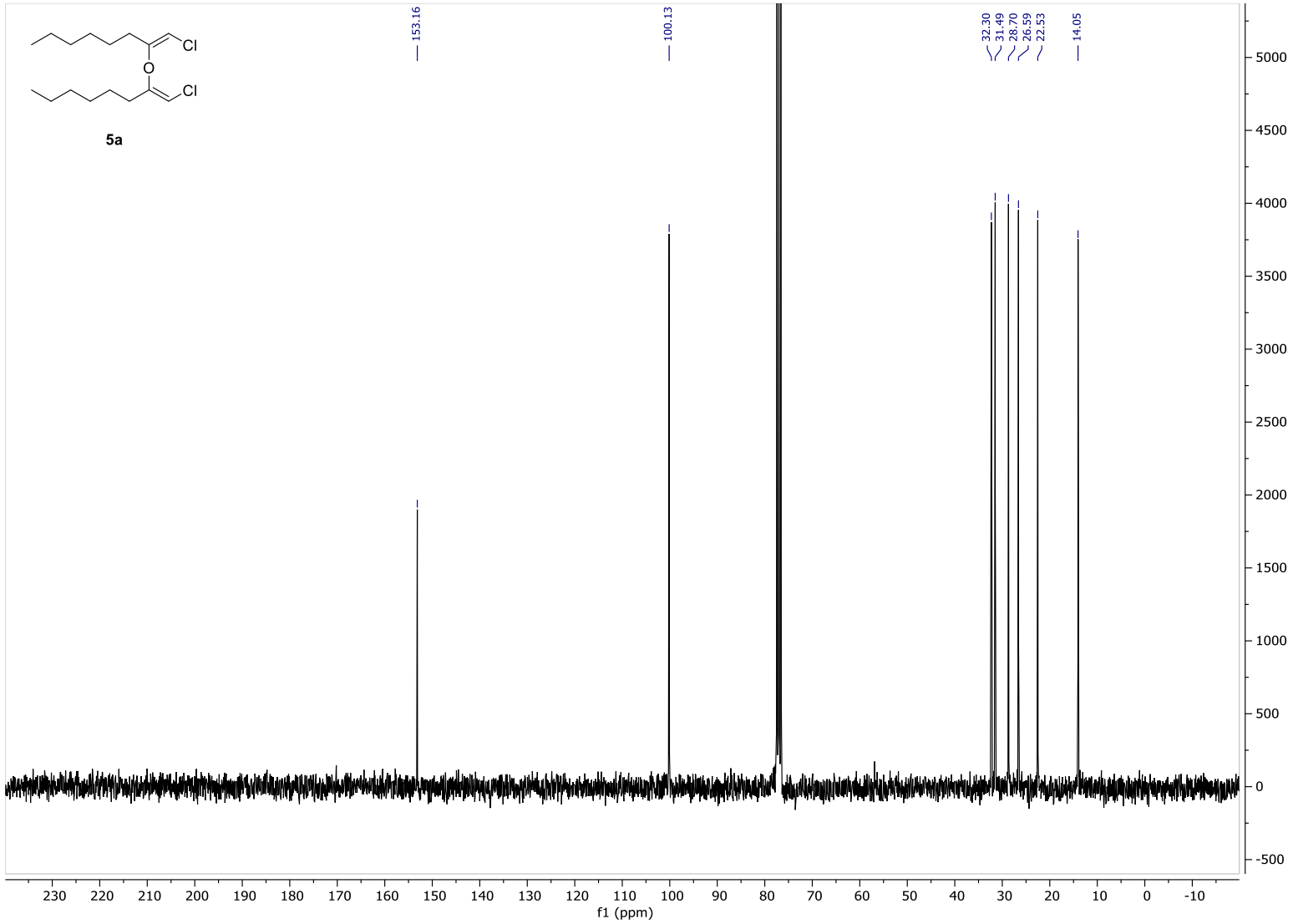

Figure S36. ^{13}C-NMR spectrum ($CDCl_3$) of by-product **5a** detected in the hydration of **1a**.

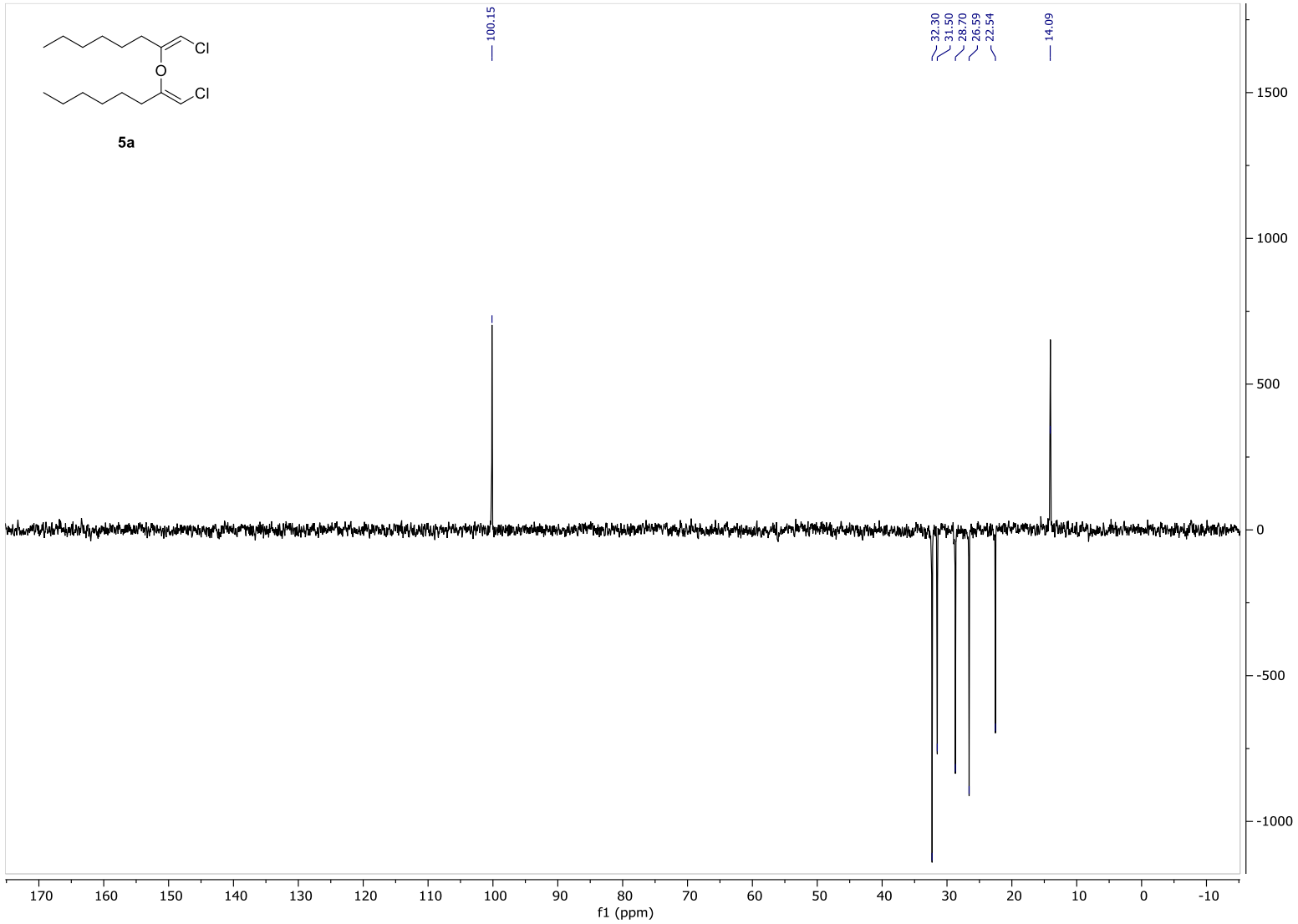

Figure S37. DEPT-NMR spectrum ($CDCl_3$) of by-product **5a** detected in the hydration of **1a**.

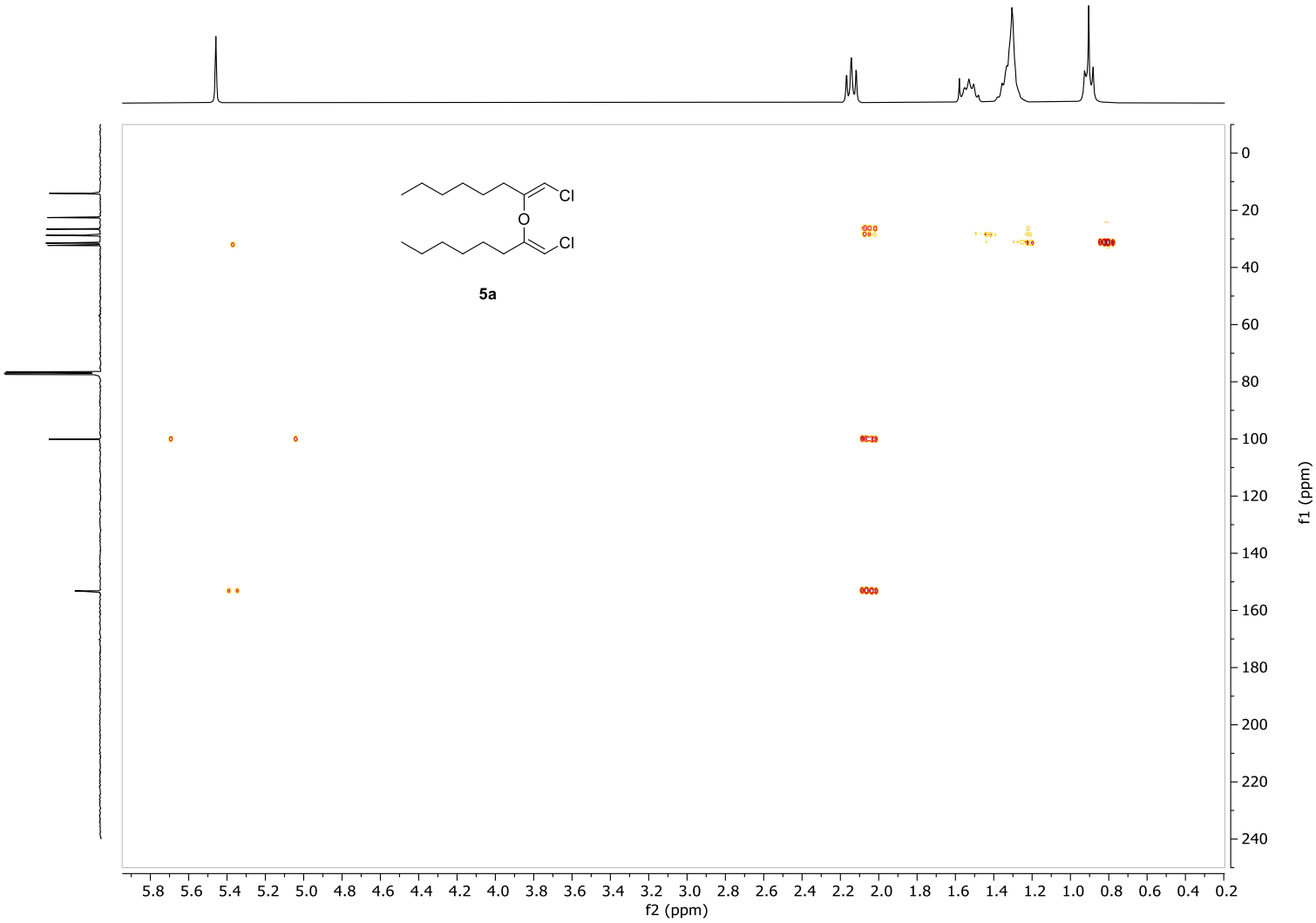

Figure S38. HMBC-NMR spectrum ($CDCl_3$) of by-product **5a** detected in the hydration of **1a**.

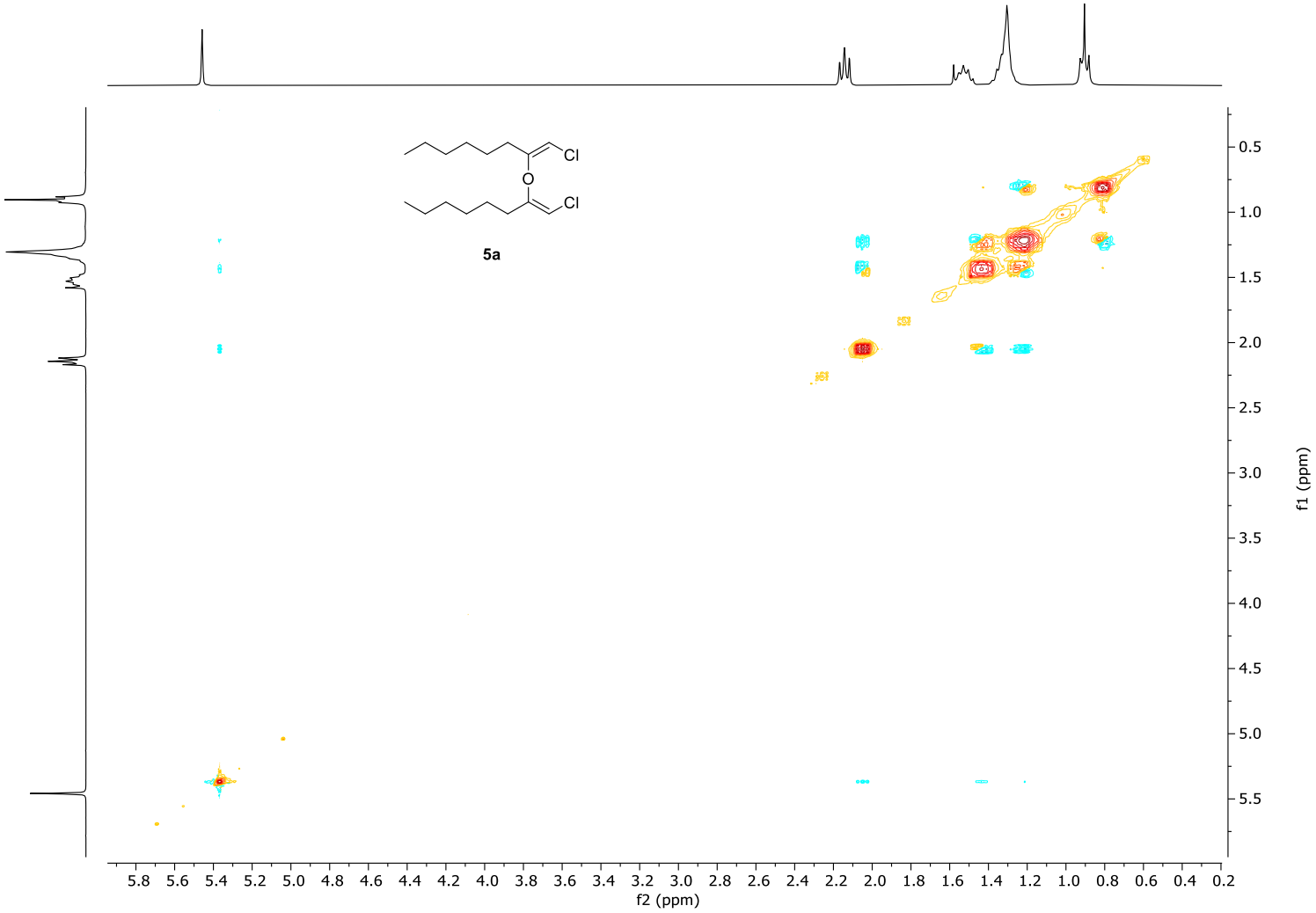

Figure S39. NOESY-NMR spectrum ($CDCl_3$) of by-product **5a** detected in the hydration of **1a**.

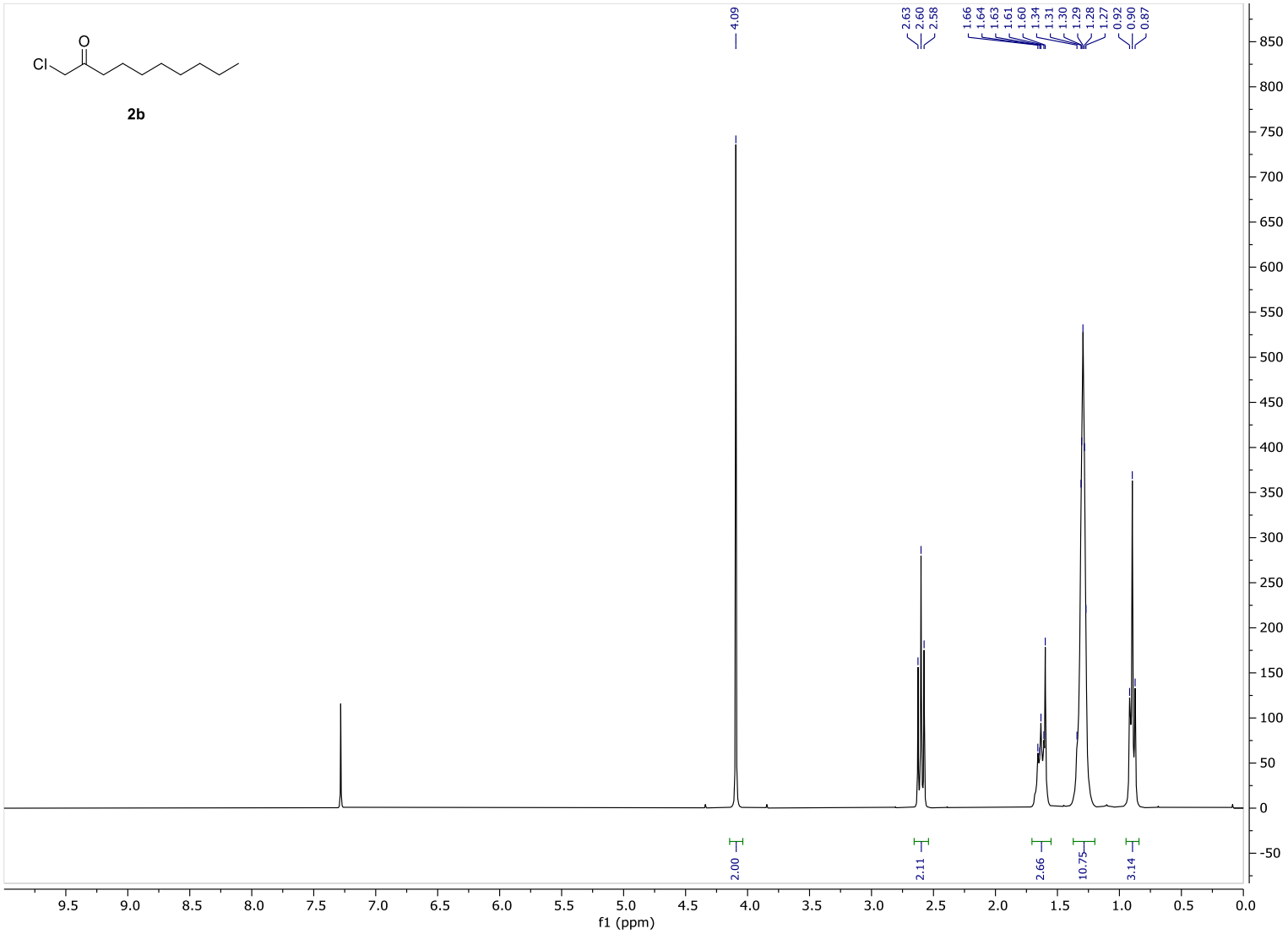

Figure S40. ^{1}H-NMR spectrum ($CDCl_3$) of compound **2b**.

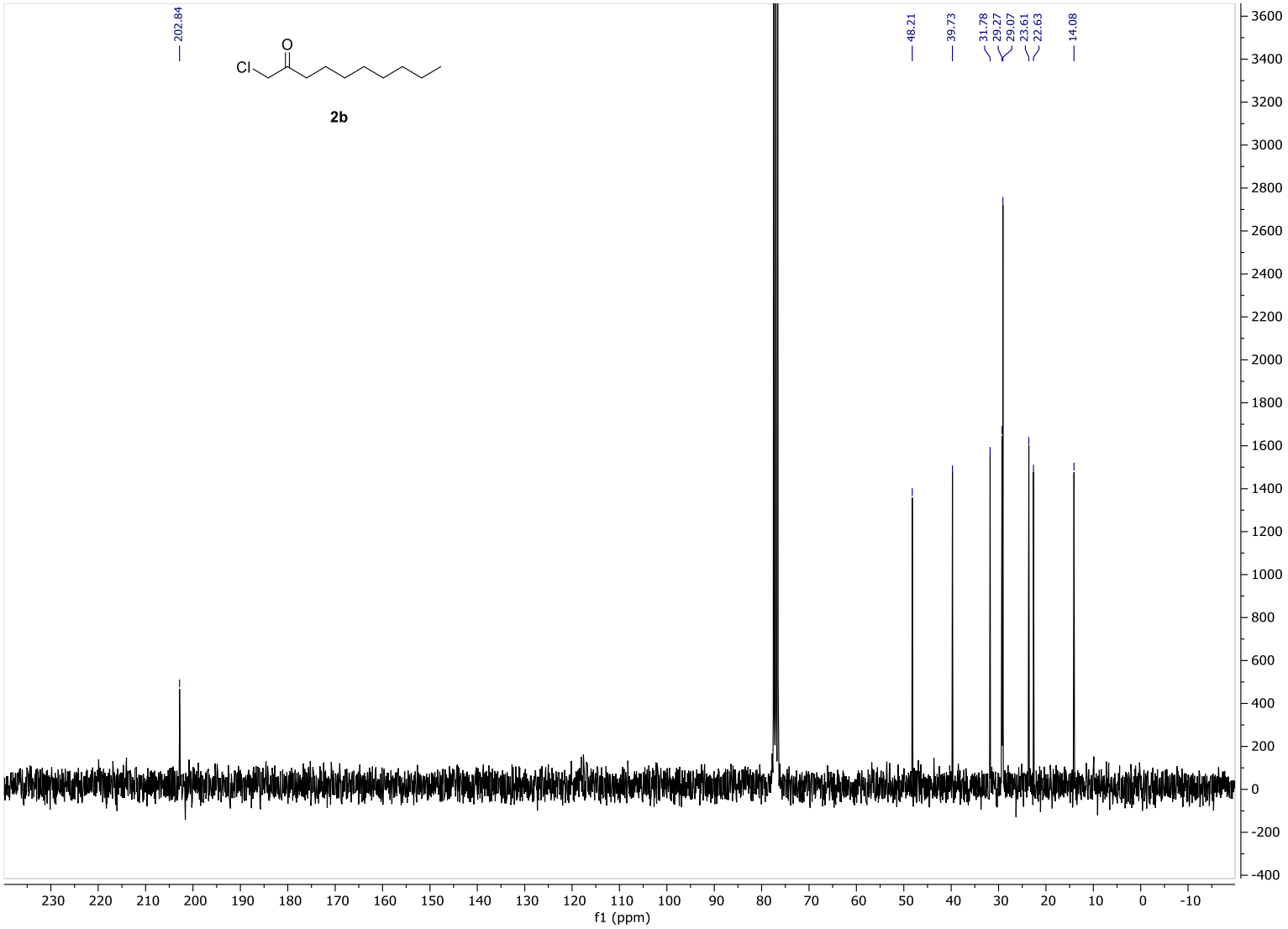

Figure S41. ^{1}H and ^{13}C-NMR spectrum ($CDCl_3$) of compound **2b**.

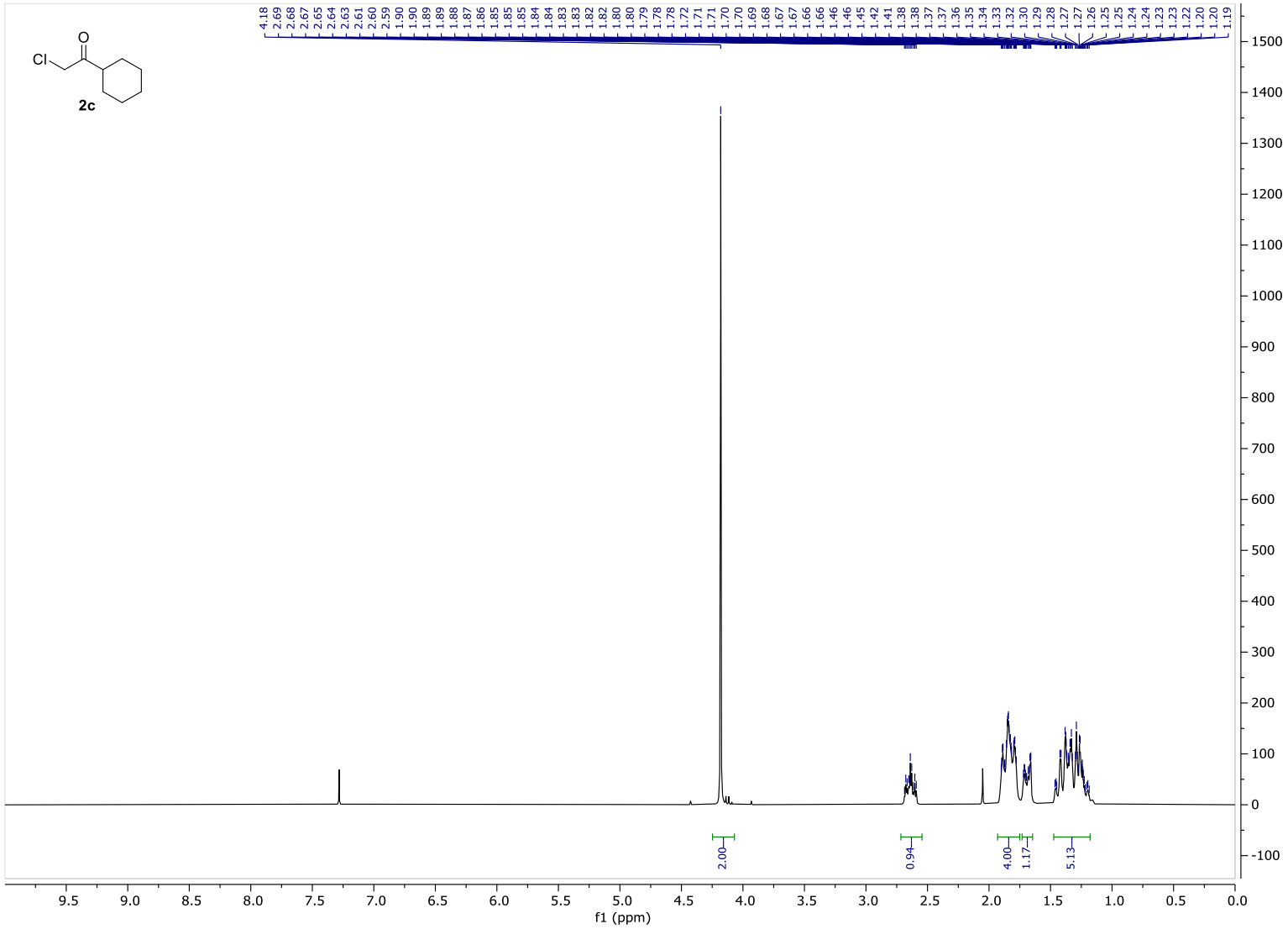

Figure S42. ^{1}H-NMR spectrum ($CDCl_3$) of compound **2c**.

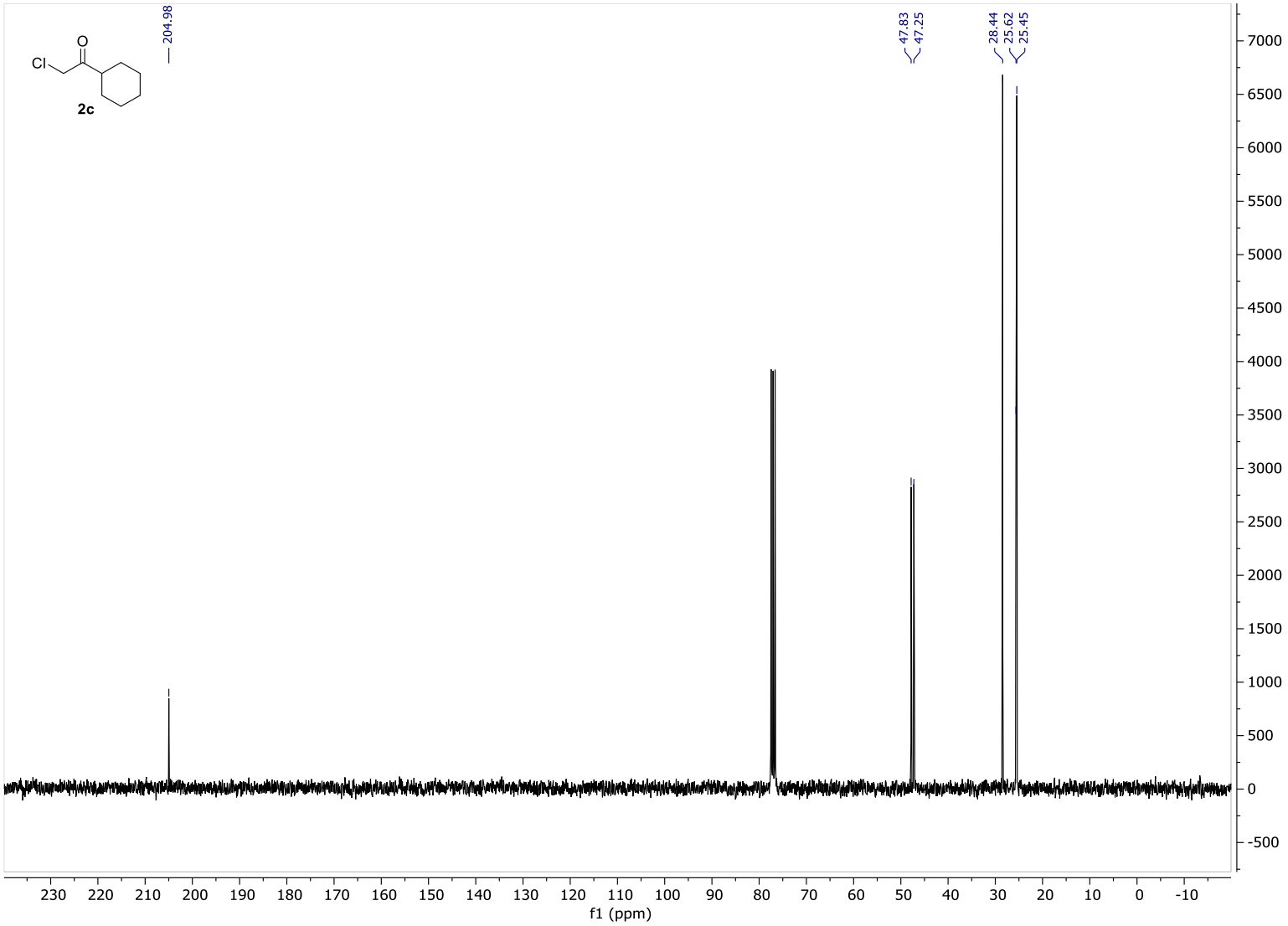

Figure S43. ^{13}C-NMR spectrum ($CDCl_3$) of compound **2c**.

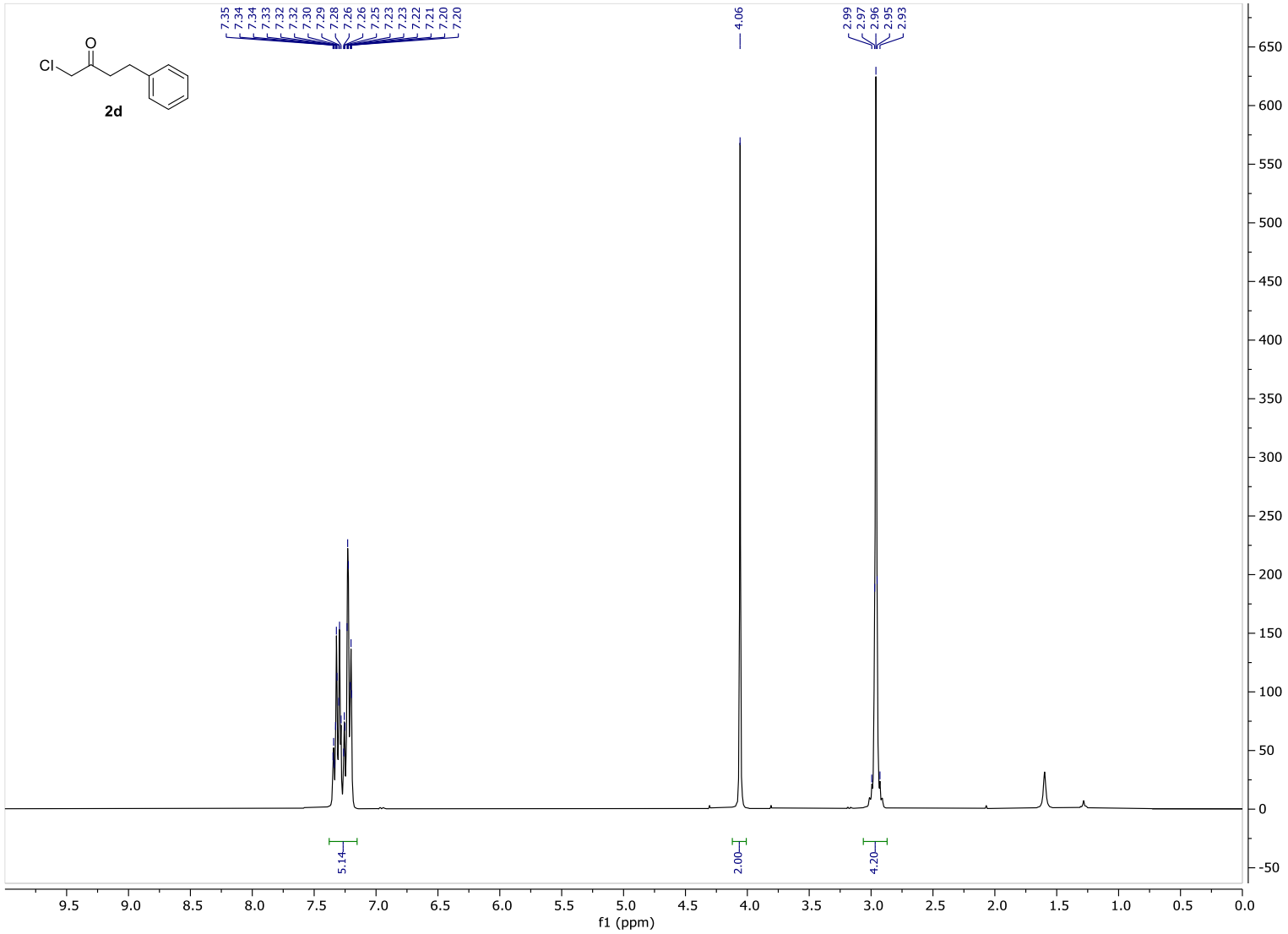

Figure S44. ^{1}H-NMR spectrum ($CDCl_3$) of compound **2d**.

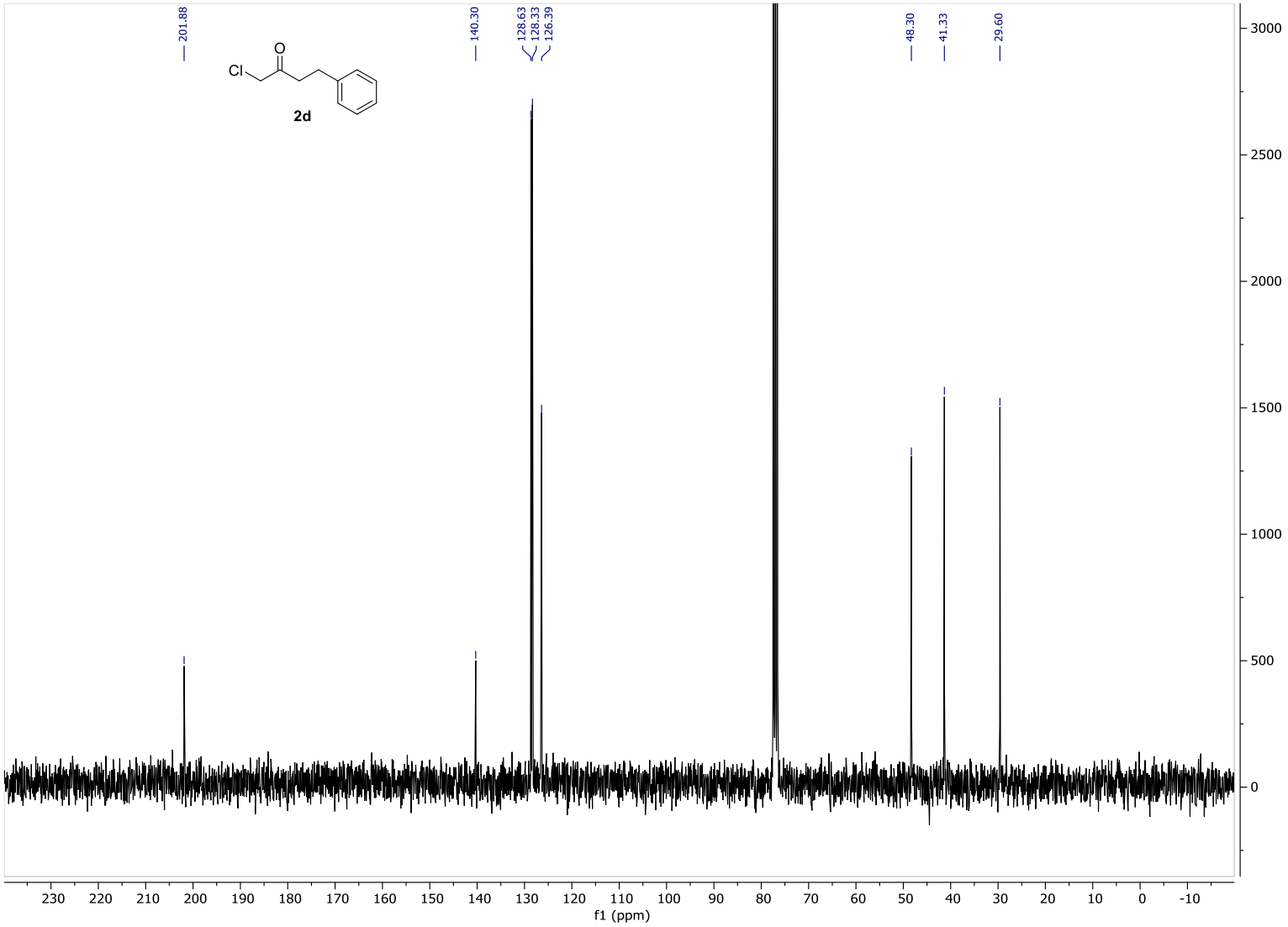

Figure S45. ^{13}C-NMR spectrum ($CDCl_3$) of compound **2d**.

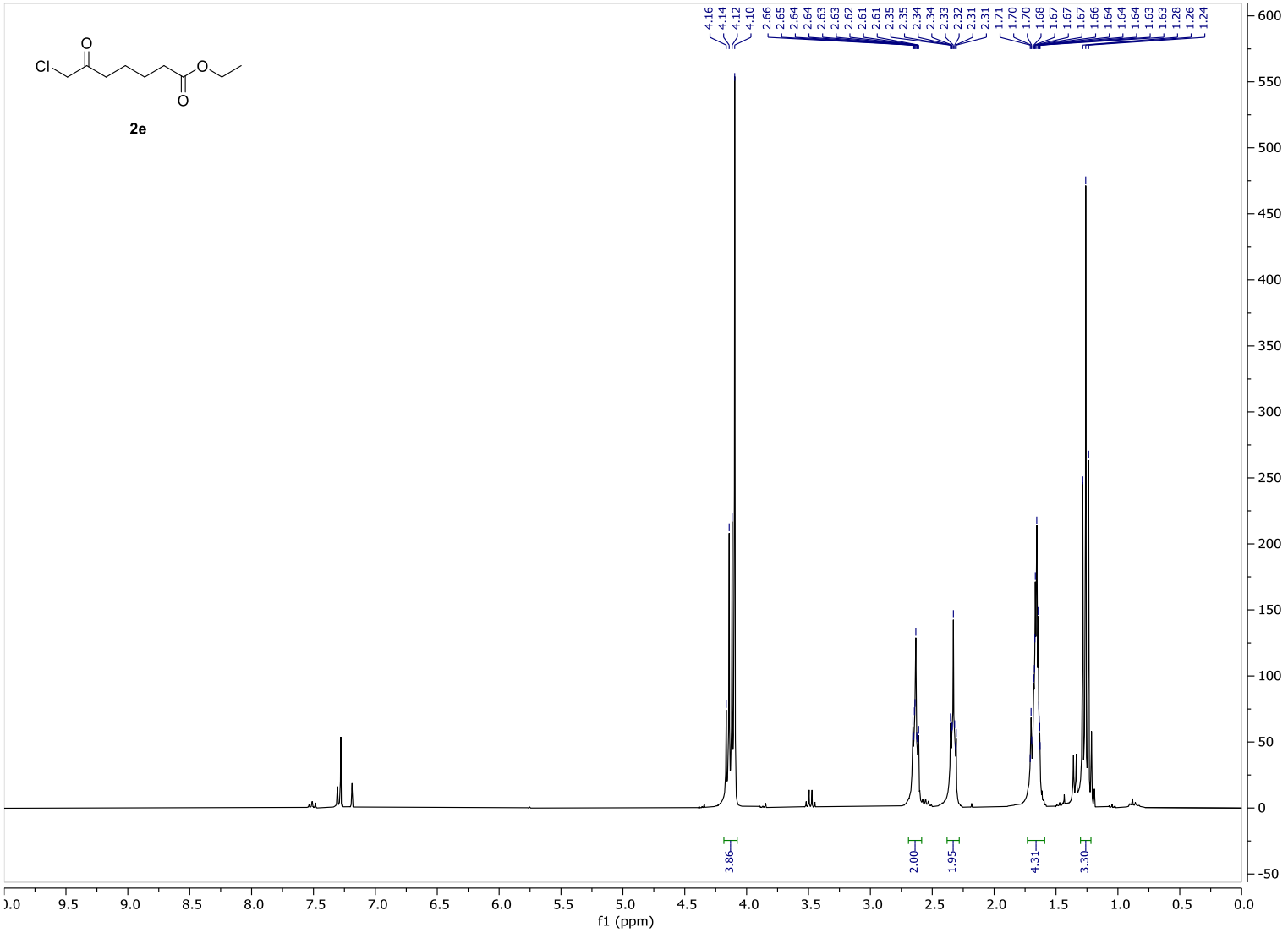

Figure S46. ^{1}H-NMR spectrum ($CDCl_3$) of compound **2e**.

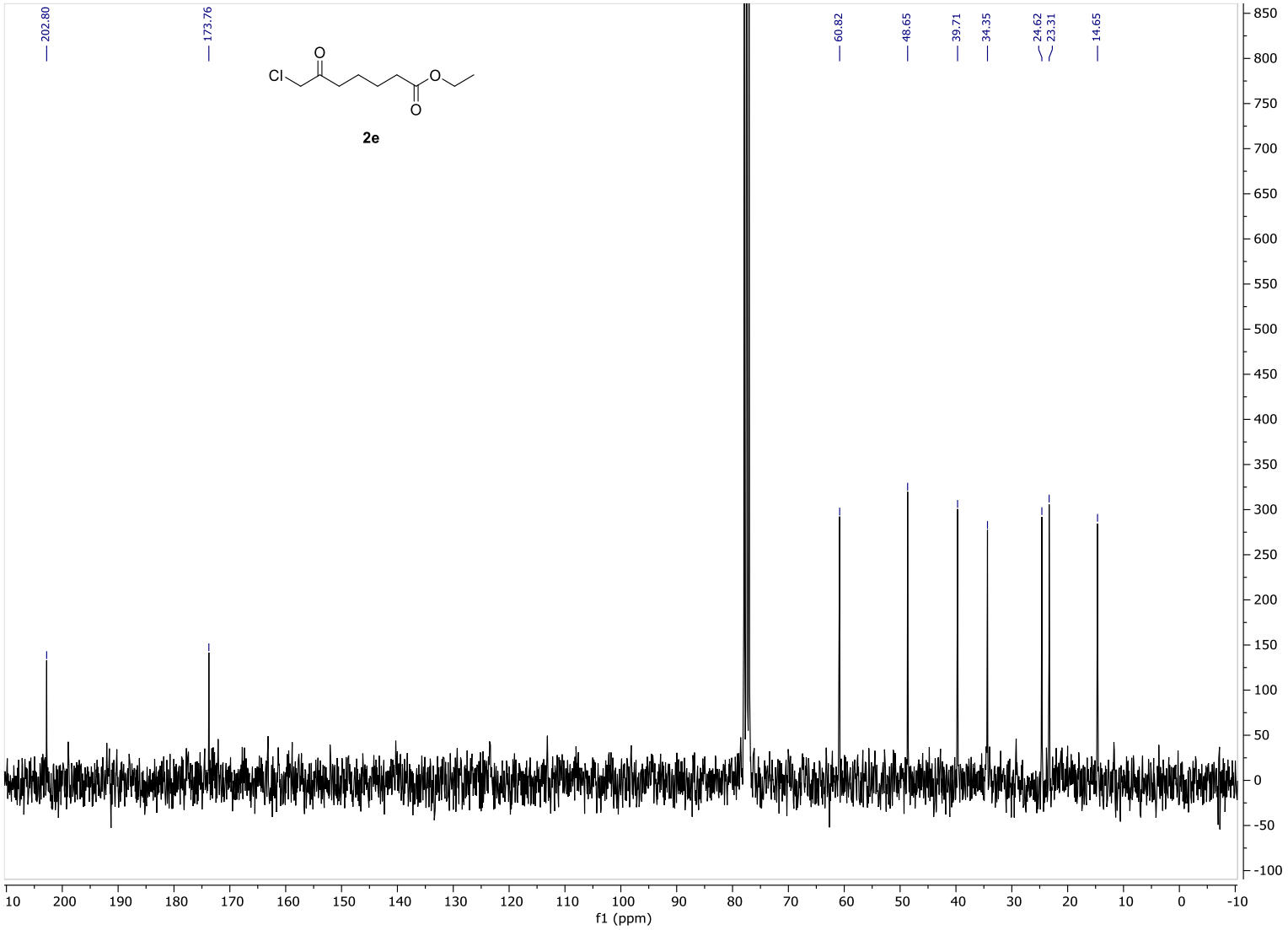

Figure S47. ^{13}C-NMR spectrum ($CDCl_3$) of compound **2e**.

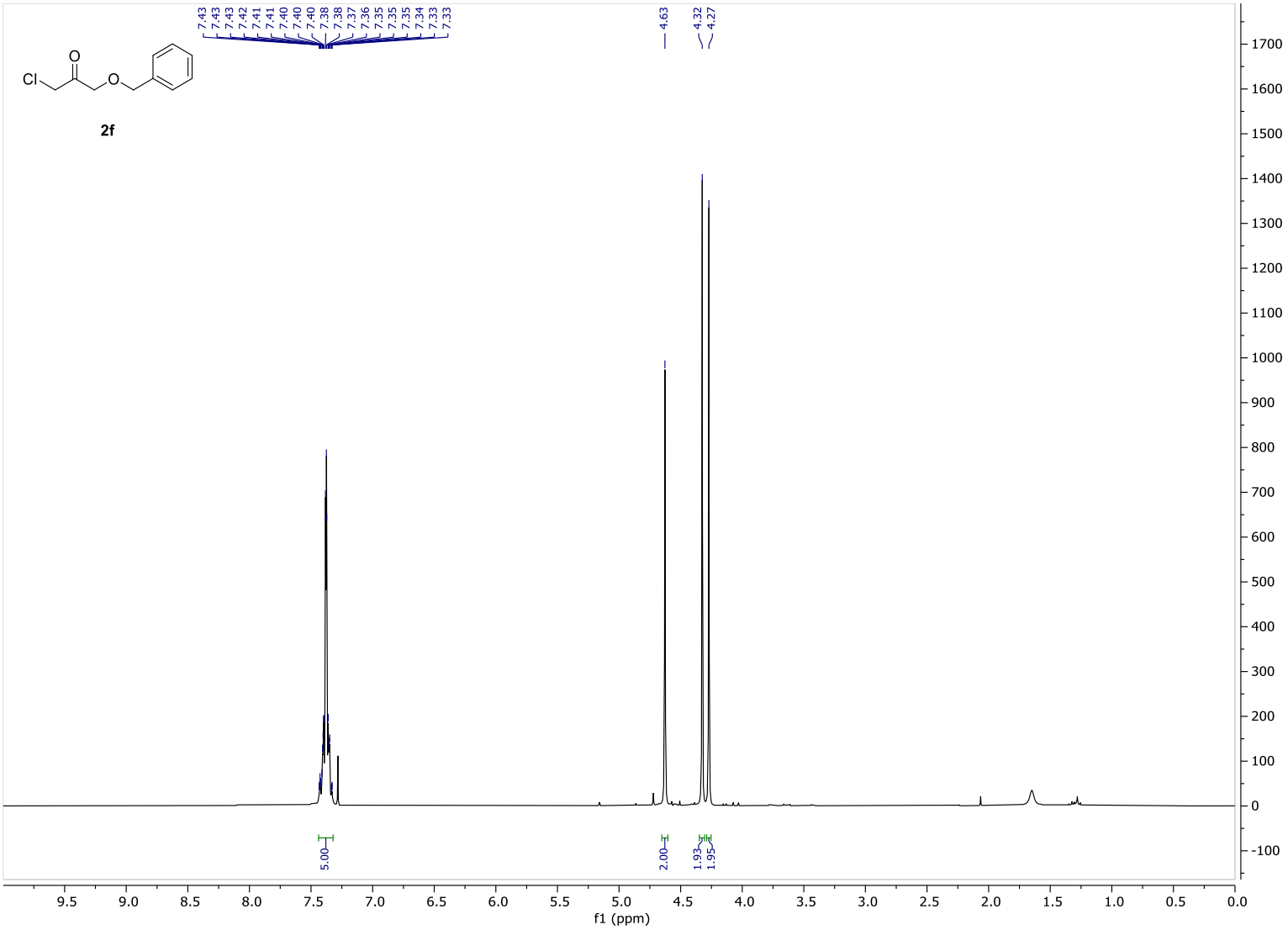

Figure S48. ^{1}H-NMR spectrum ($CDCl_3$) of compound **2f**.

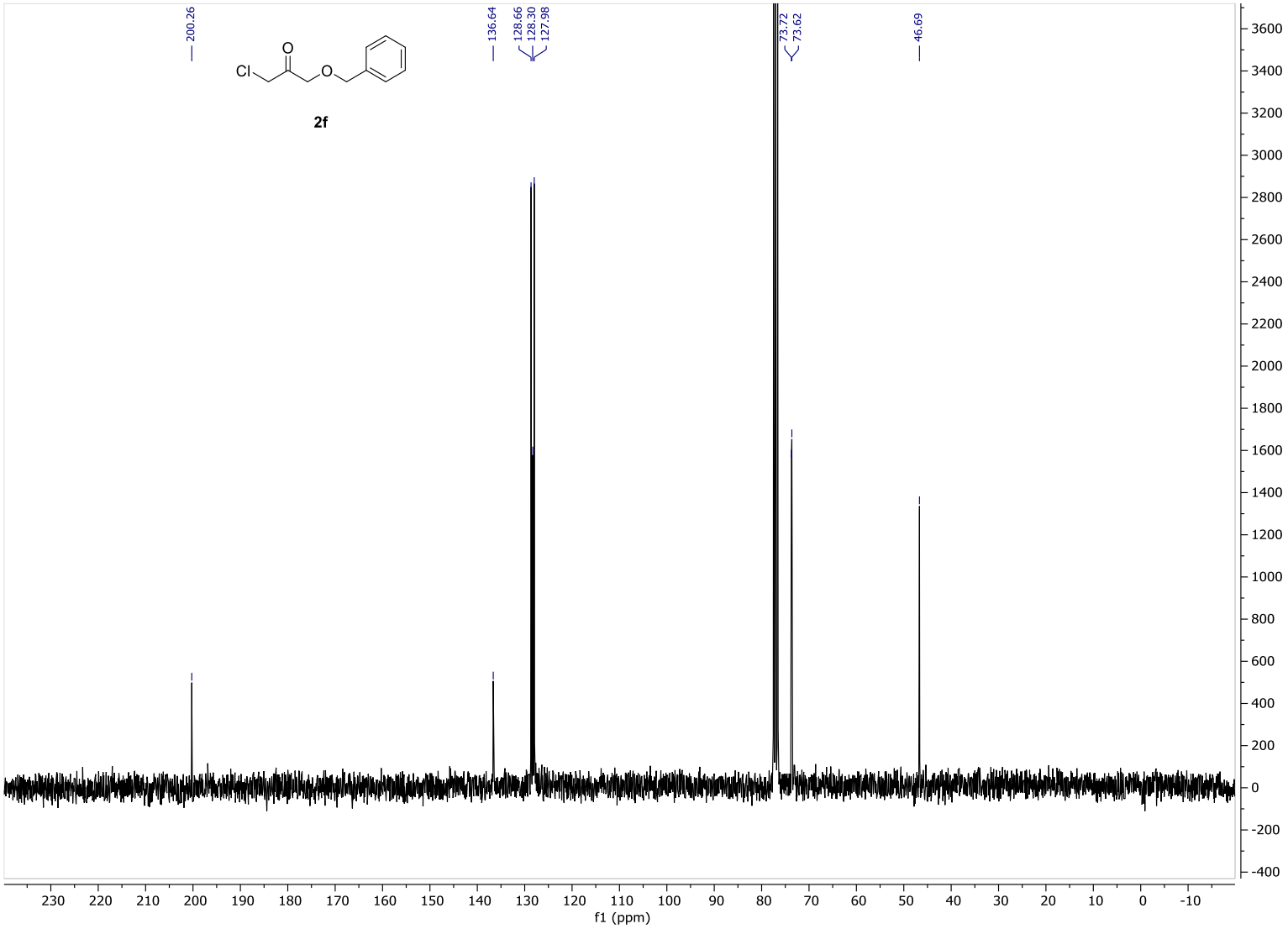

Figure S49. ^{13}C-NMR spectrum ($CDCl_3$) of compound **2f**.

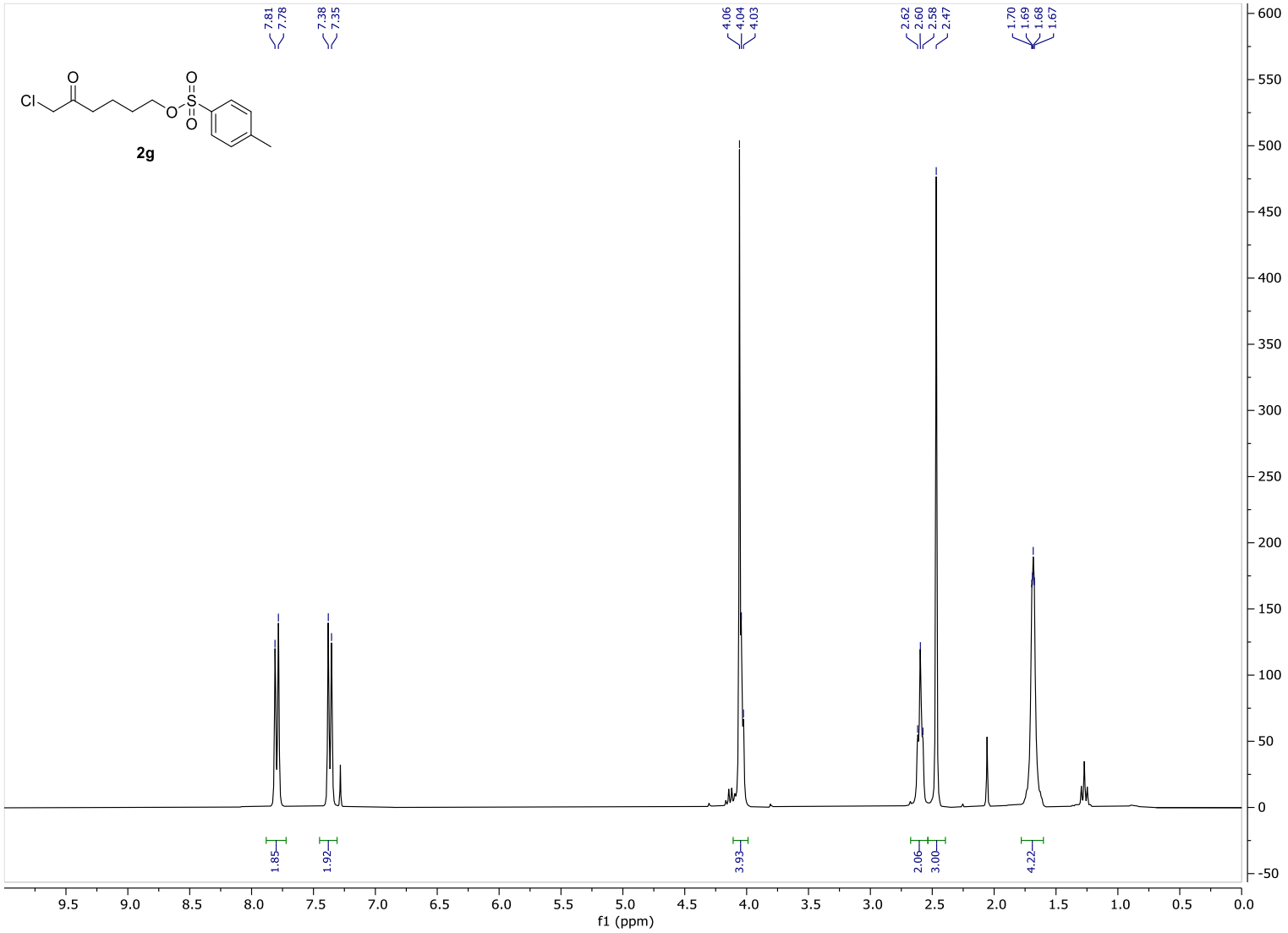

Figure S50. ^{1}H-NMR spectrum ($CDCl_3$) of compound **2g**.

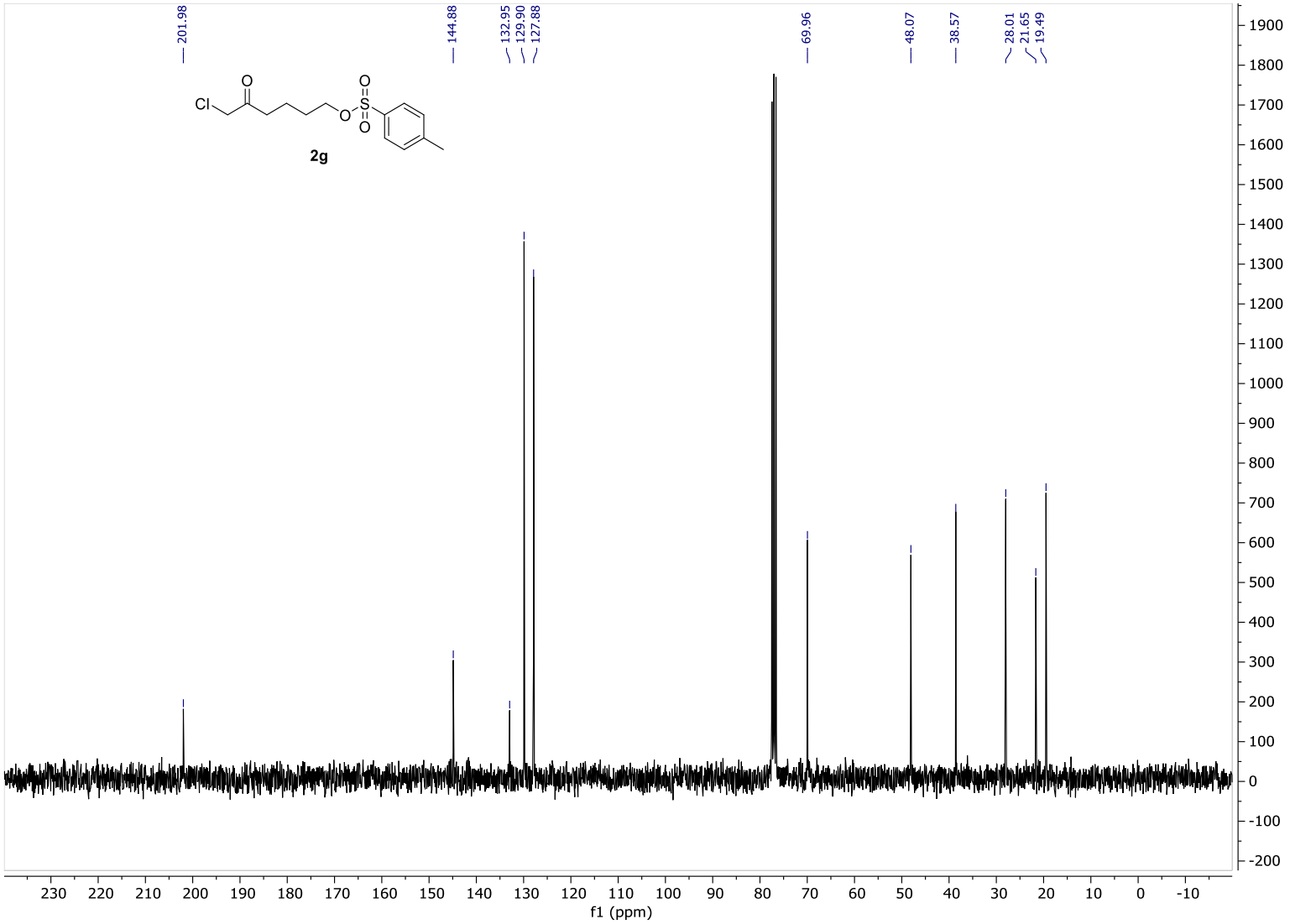

Figure S51. ^{13}C-NMR spectrum ($CDCl_3$) of compound **2g**.

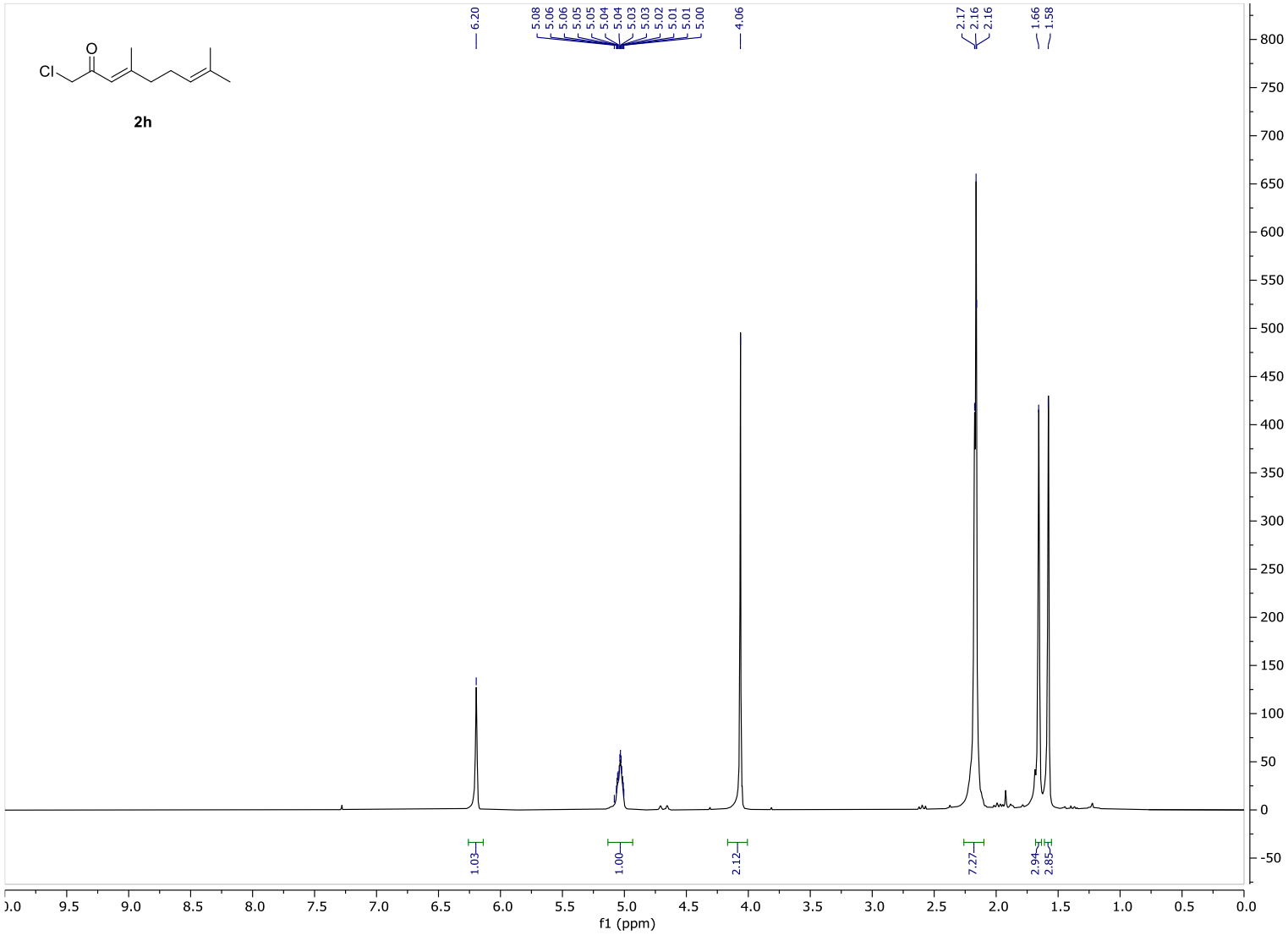

Figure S52. ^{1}H-NMR spectrum ($CDCl_3$) of compound **2h**.

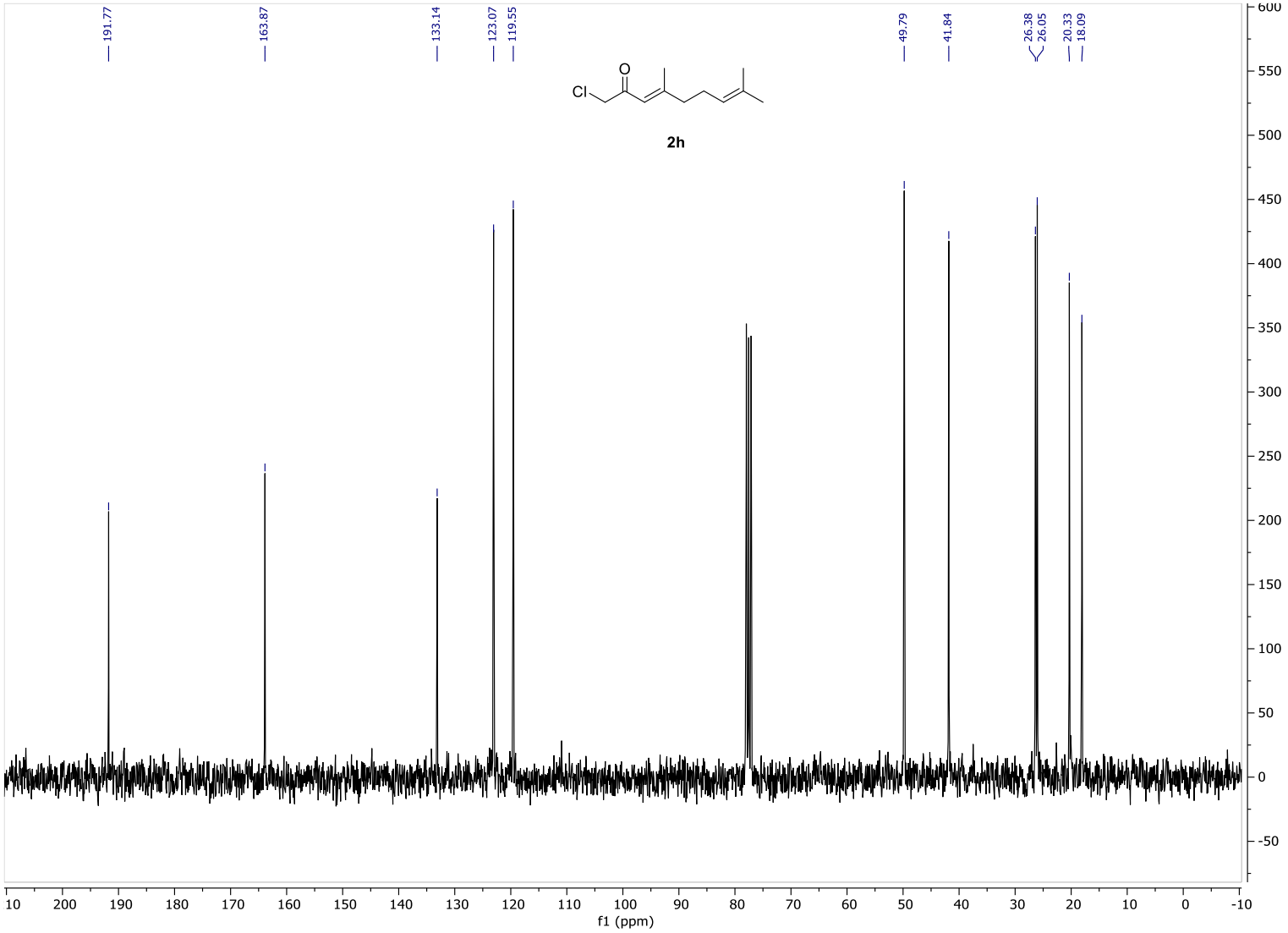

Figure S53. ^{13}C-NMR spectrum ($CDCl_3$) of compound **2h**.

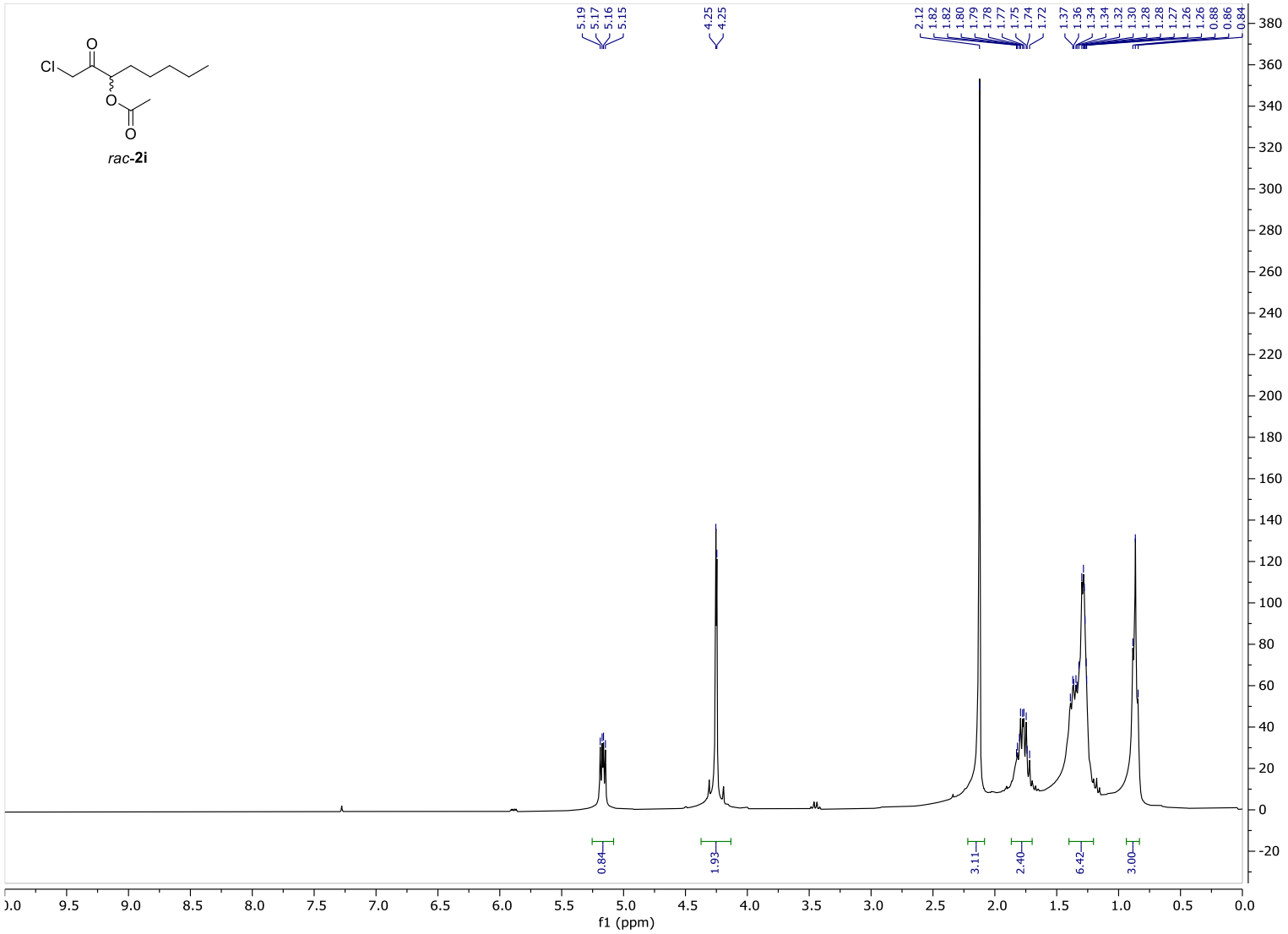

Figure S54. ^{1}H-NMR spectrum ($CDCl_3$) of compound **2i**.

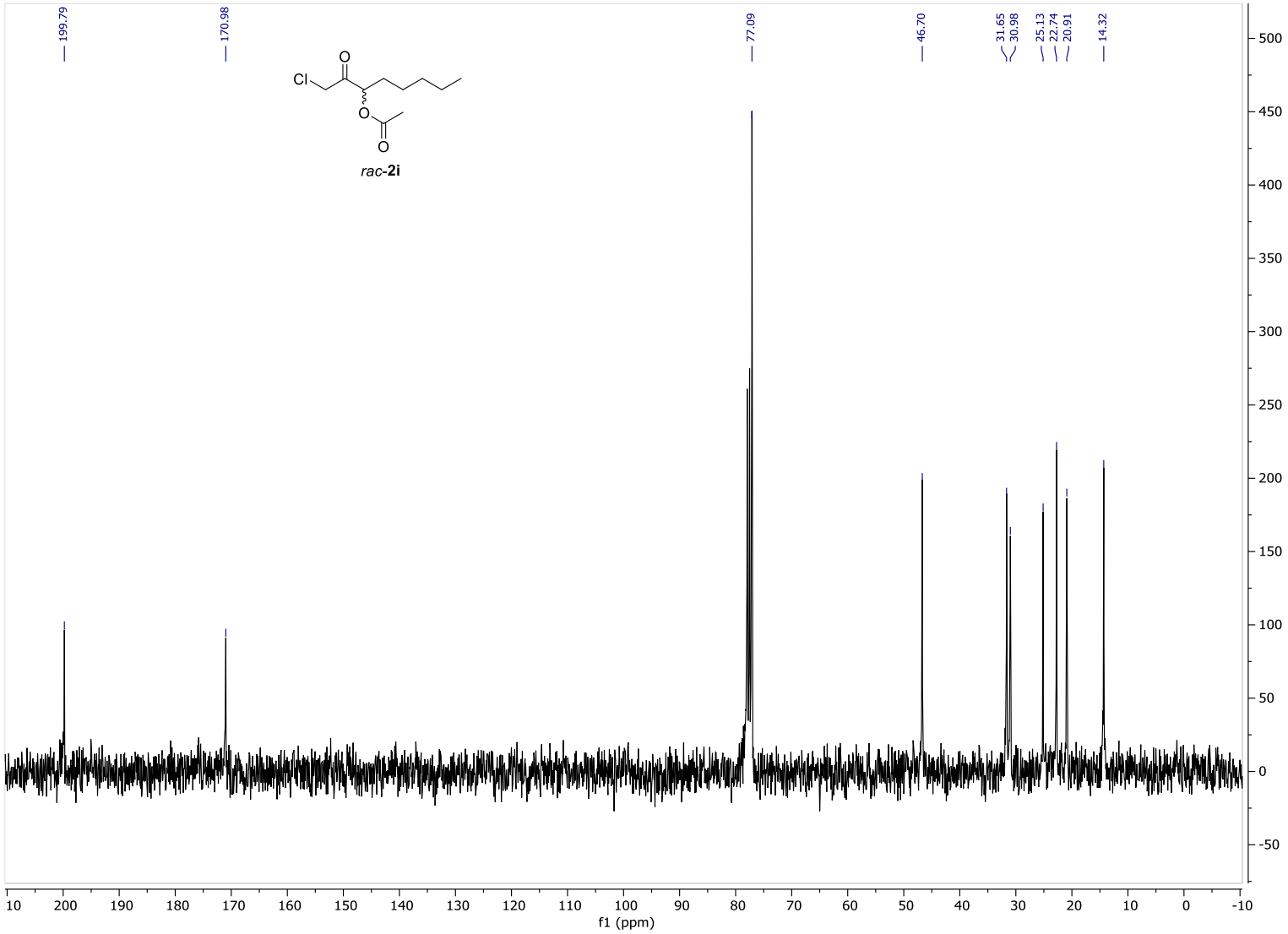

Figure S55. ^{13}C-NMR spectrum ($CDCl_3$) of compound **2i**.

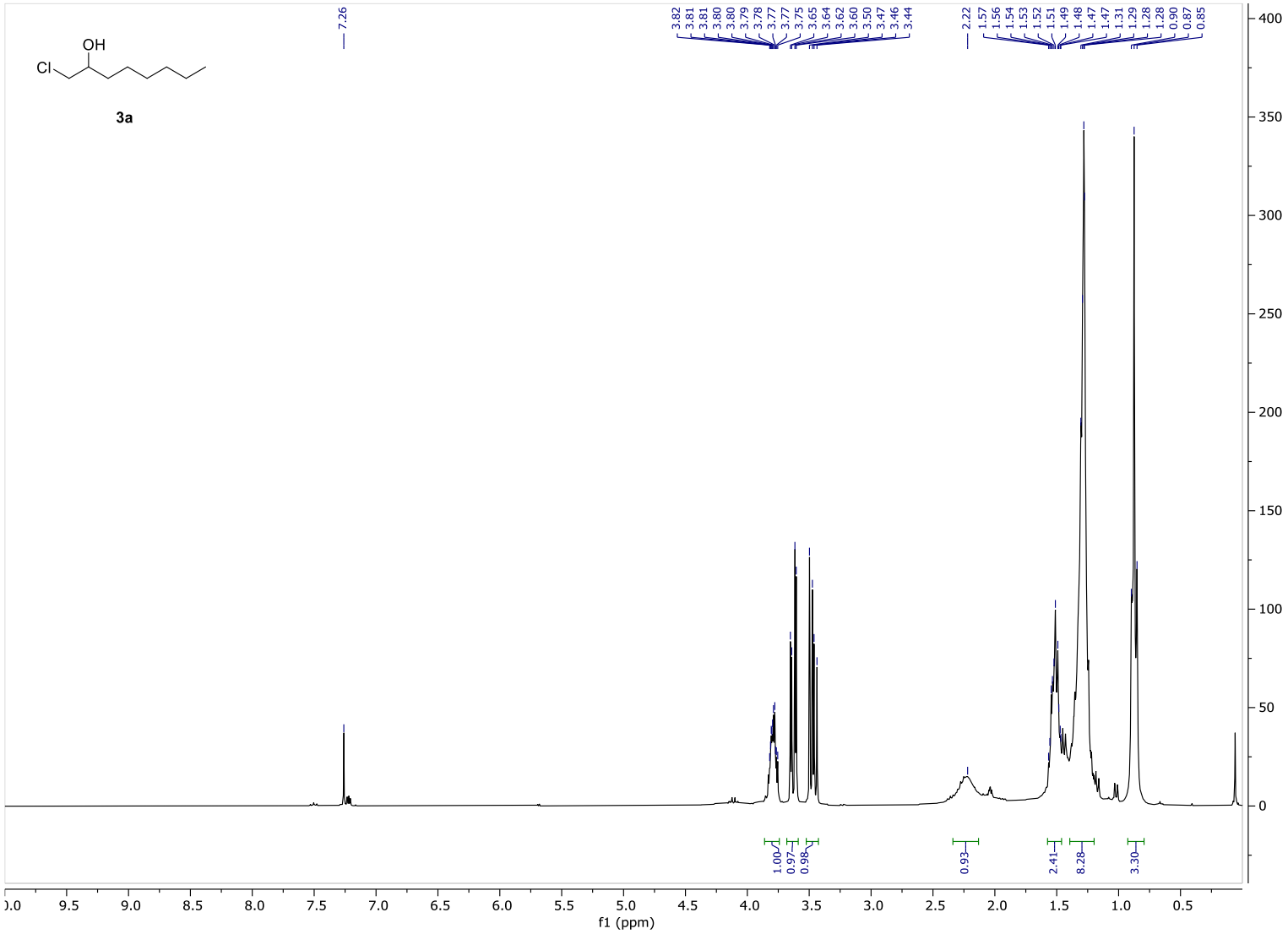

Figure S56. ^{1}H-NMR spectrum ($CDCl_3$) of compound **3a**.

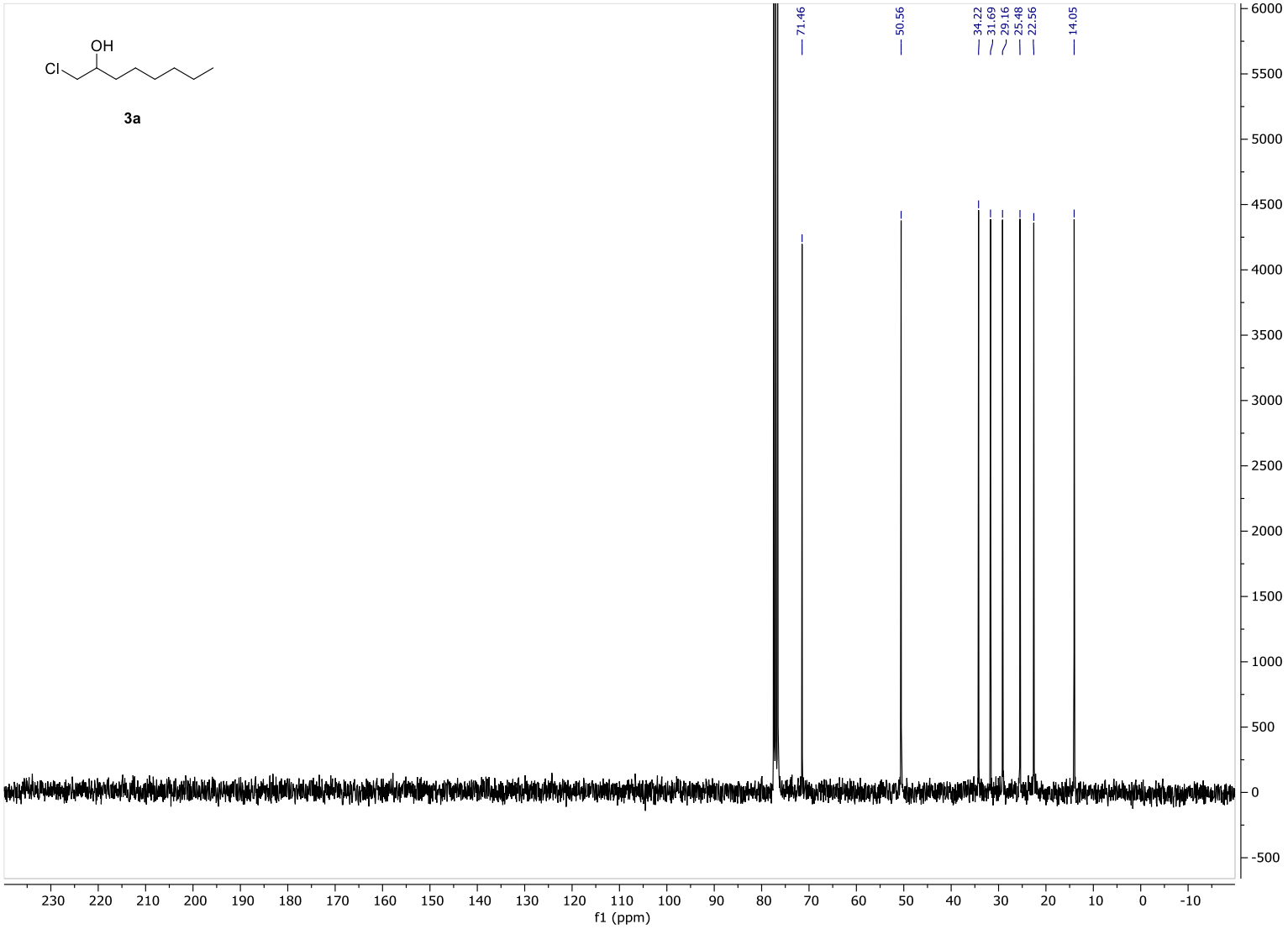

Figure S57. ^{1}H and ^{13}C-NMR spectrum ($CDCl_3$) of compound **3a**.

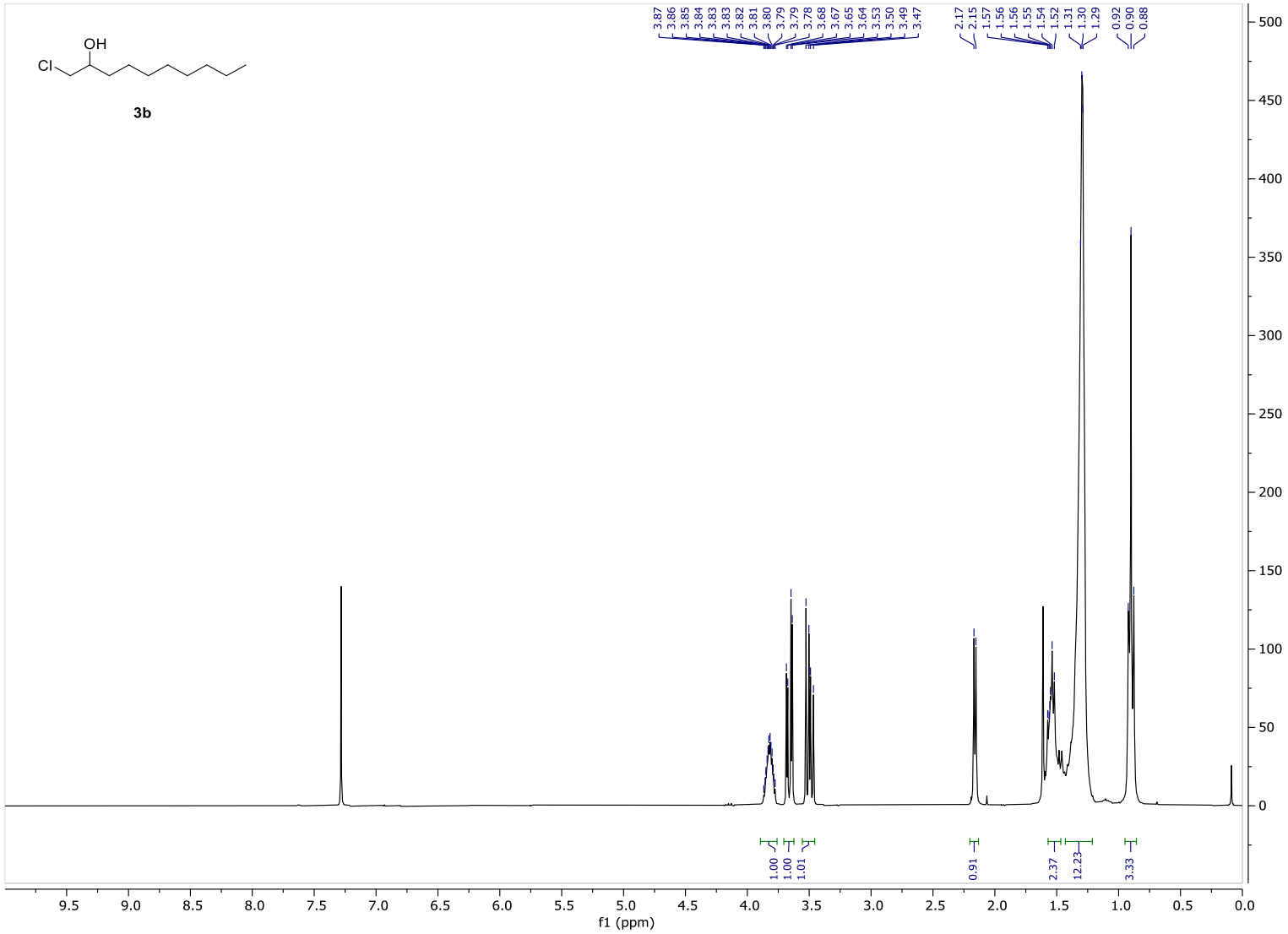

Figure S58. ^{1}H-NMR spectrum ($CDCl_3$) of compound **3b**.

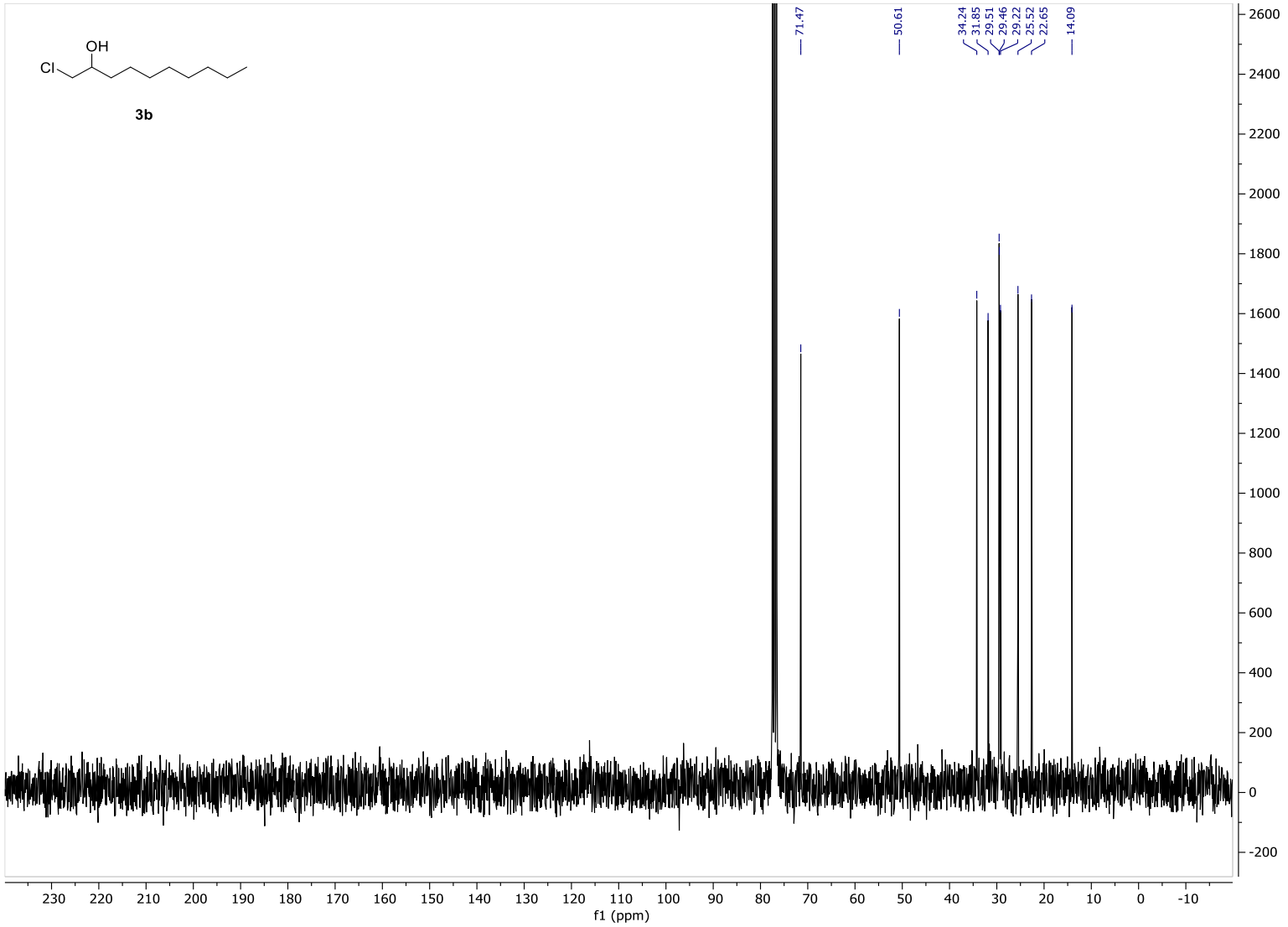

Figure S59. ^{13}C-NMR spectrum ($CDCl_3$) of compound **3b**.

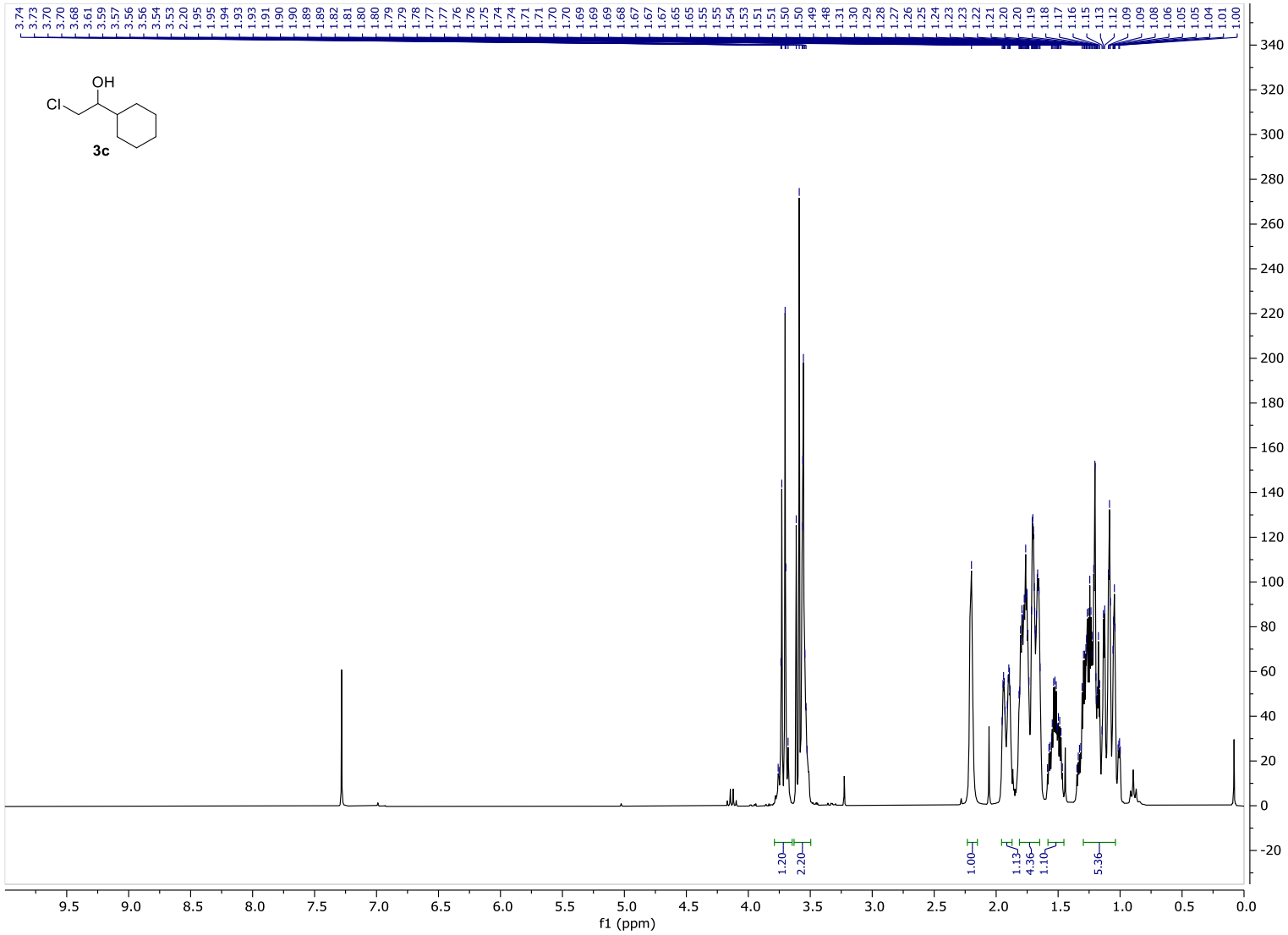

Figure S60. ^{1}H-NMR spectrum ($CDCl_3$) of compound **3c**.

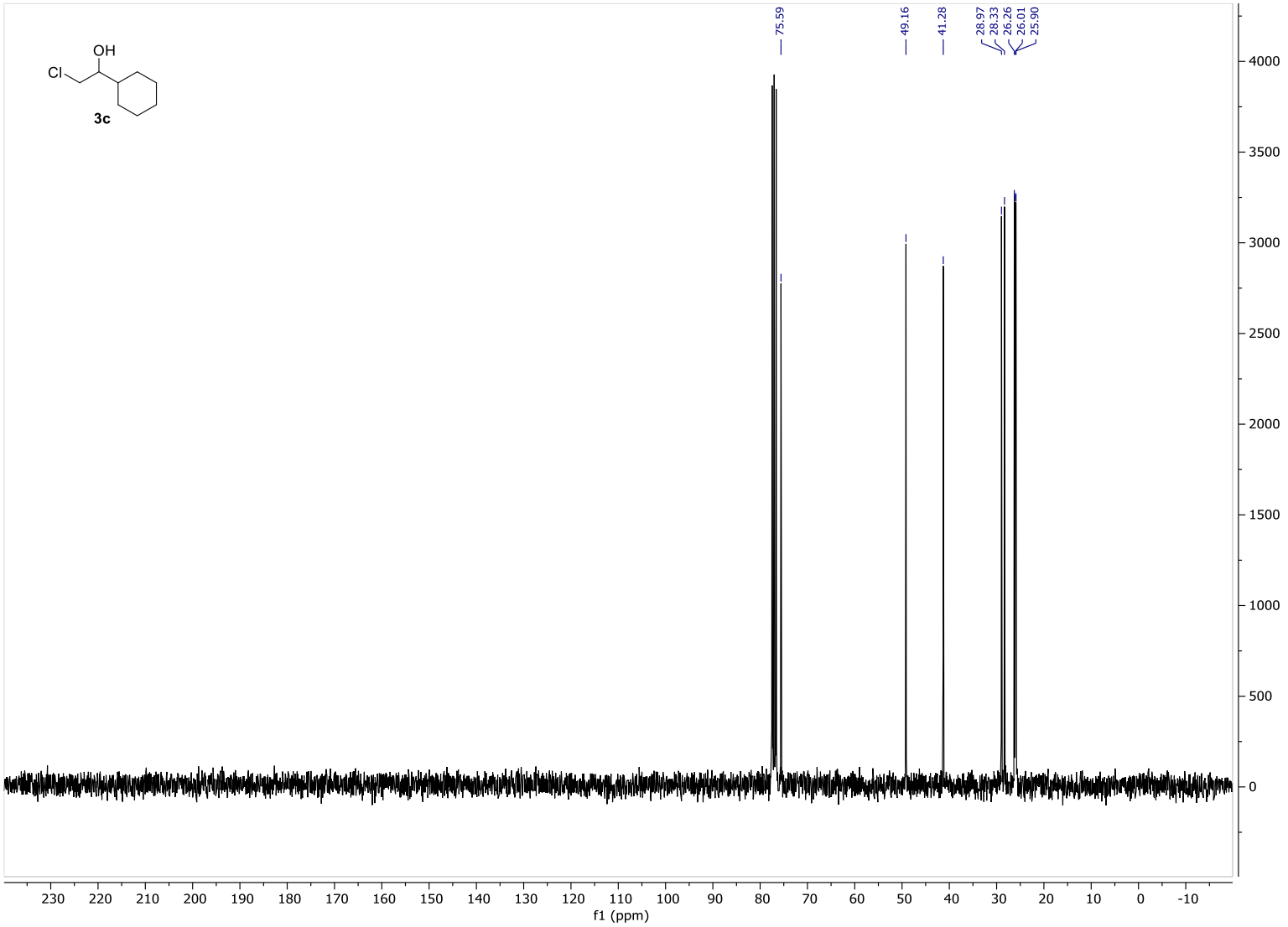

Figure S61. ^{13}C-NMR spectrum ($CDCl_3$) of compound **3c**.

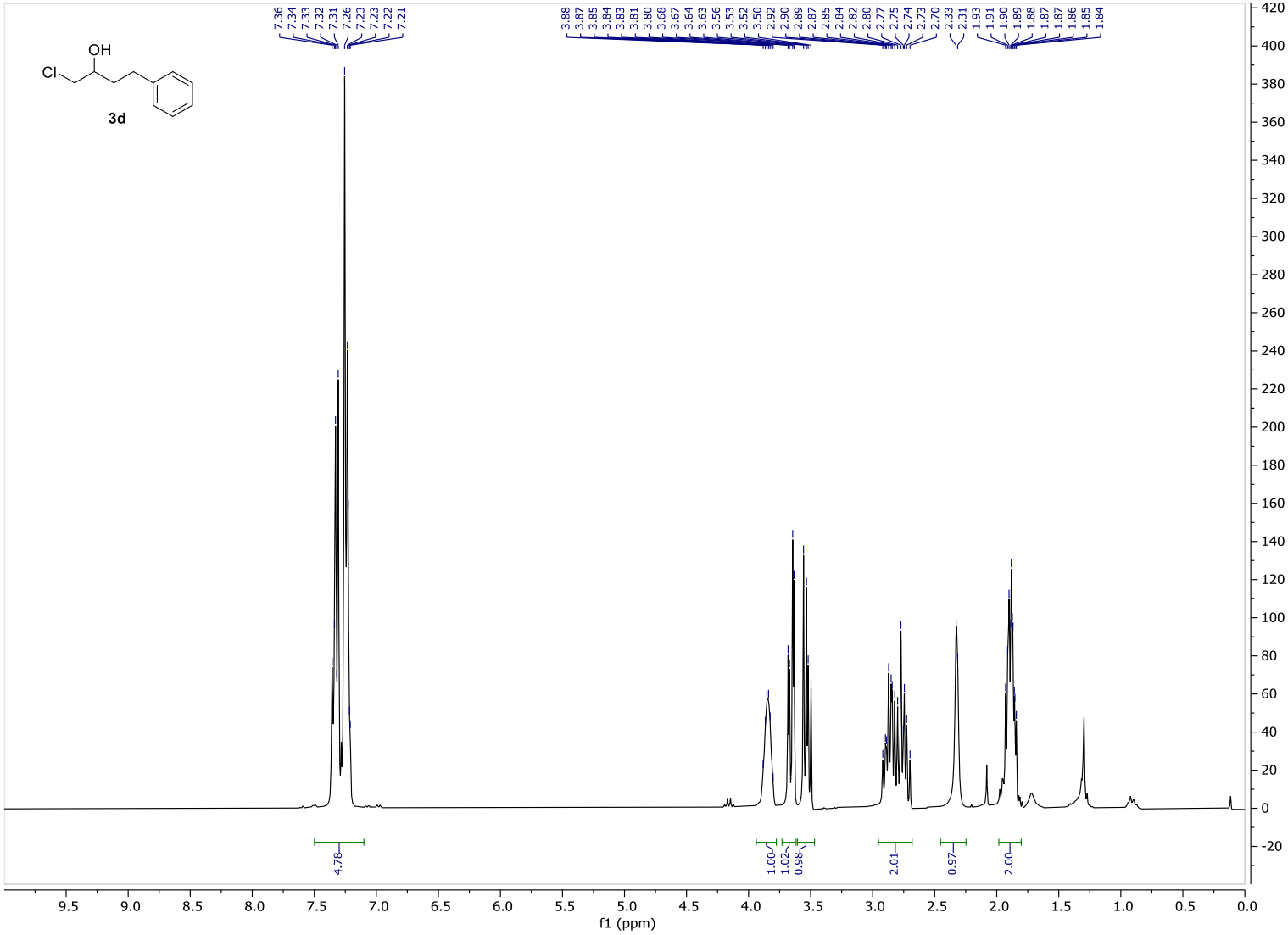

Figure S62. ^{1}H-NMR spectrum ($CDCl_3$) of compound **3d**.

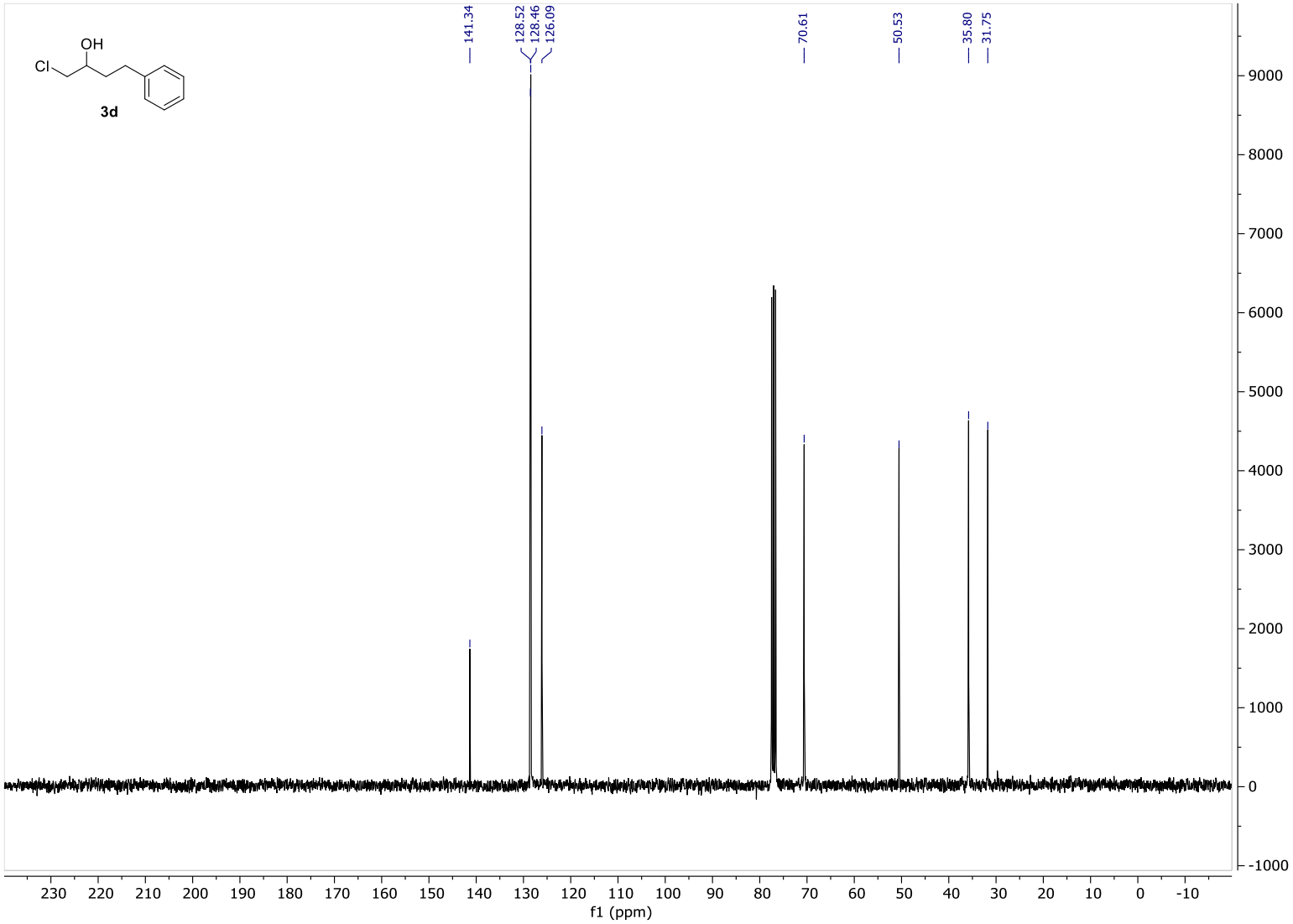

Figure S63. ^{13}C-NMR spectrum ($CDCl_3$) of compound **3d**.

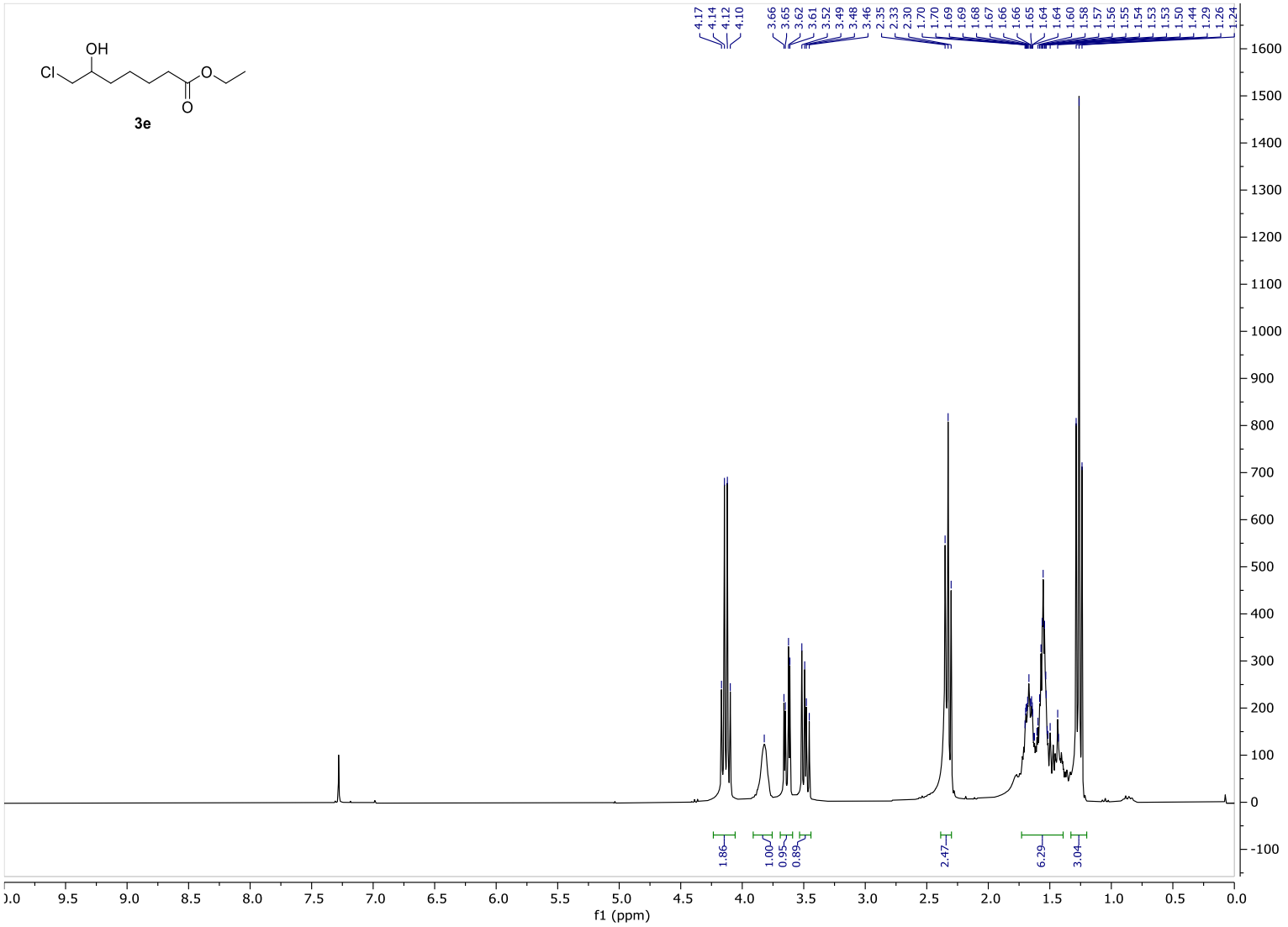

Figure S64. ^{1}H-NMR spectrum ($CDCl_3$) of compound **3e**.

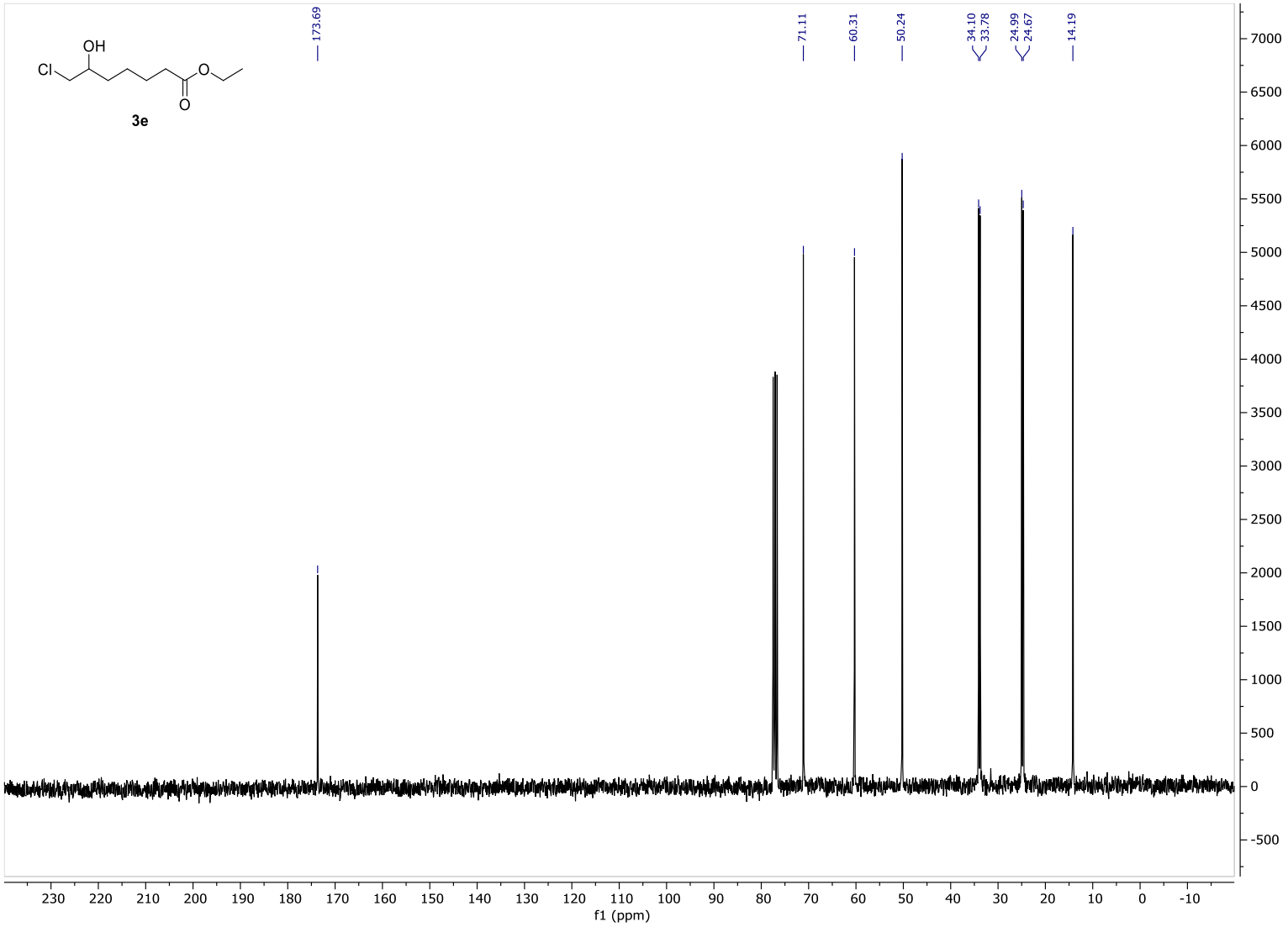

Figure S65. ^{13}C-NMR spectrum ($CDCl_3$) of compound **3e**.

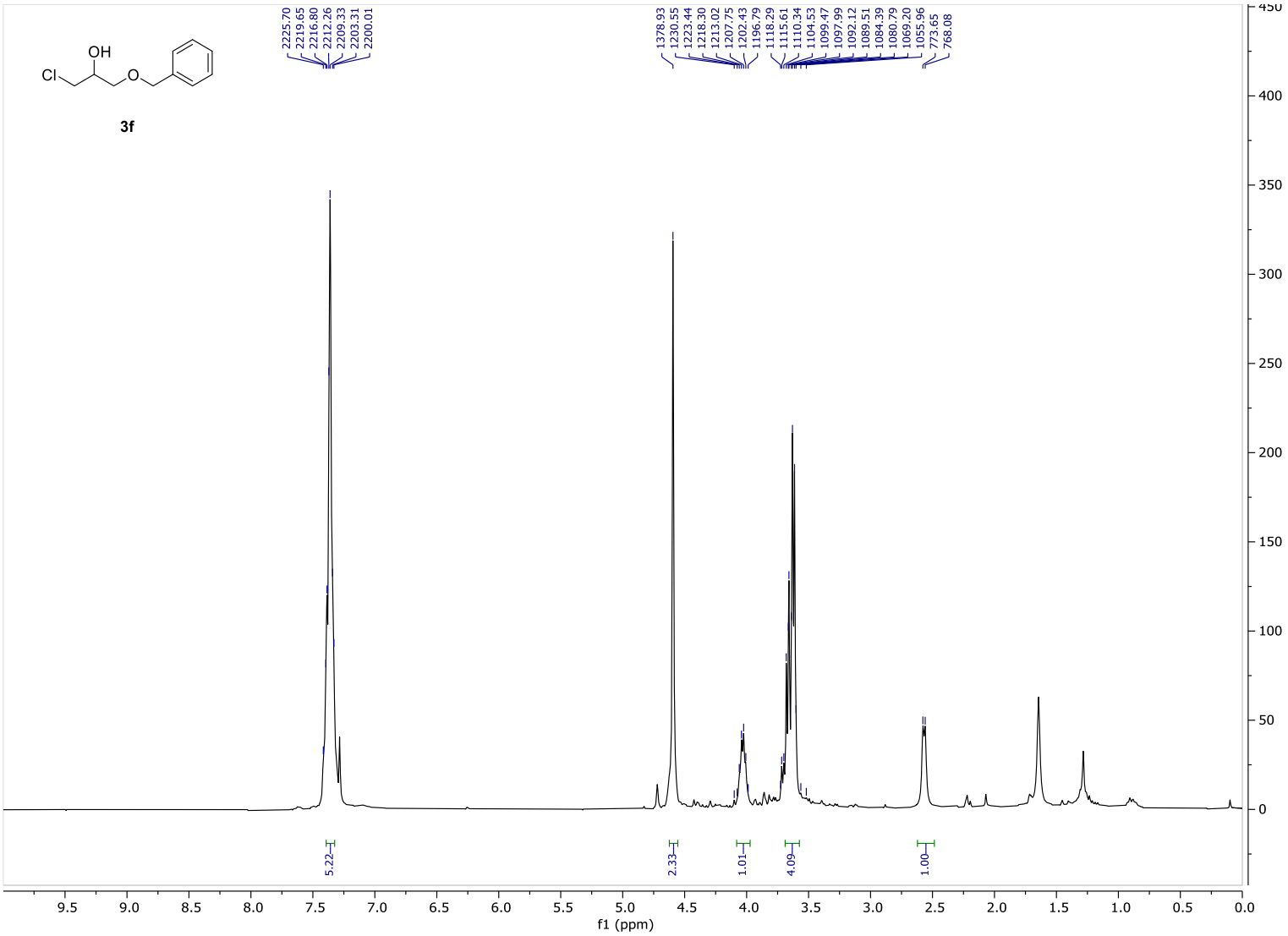

Figure S66. ^{1}H-NMR spectrum ($CDCl_3$) of compound **3f**.

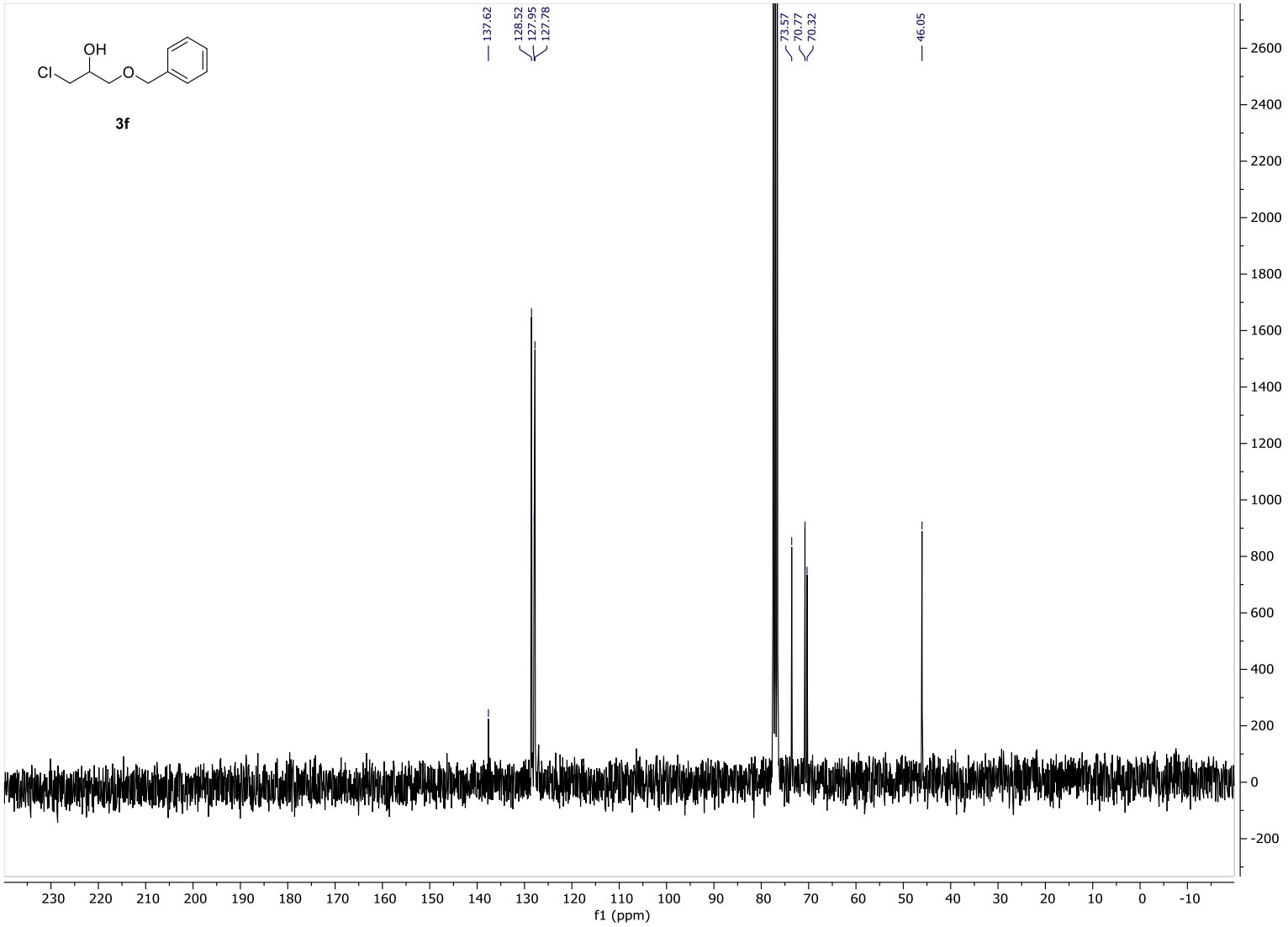

Figure S67. ^{13}C-NMR spectrum ($CDCl_3$) of compound **3f**.

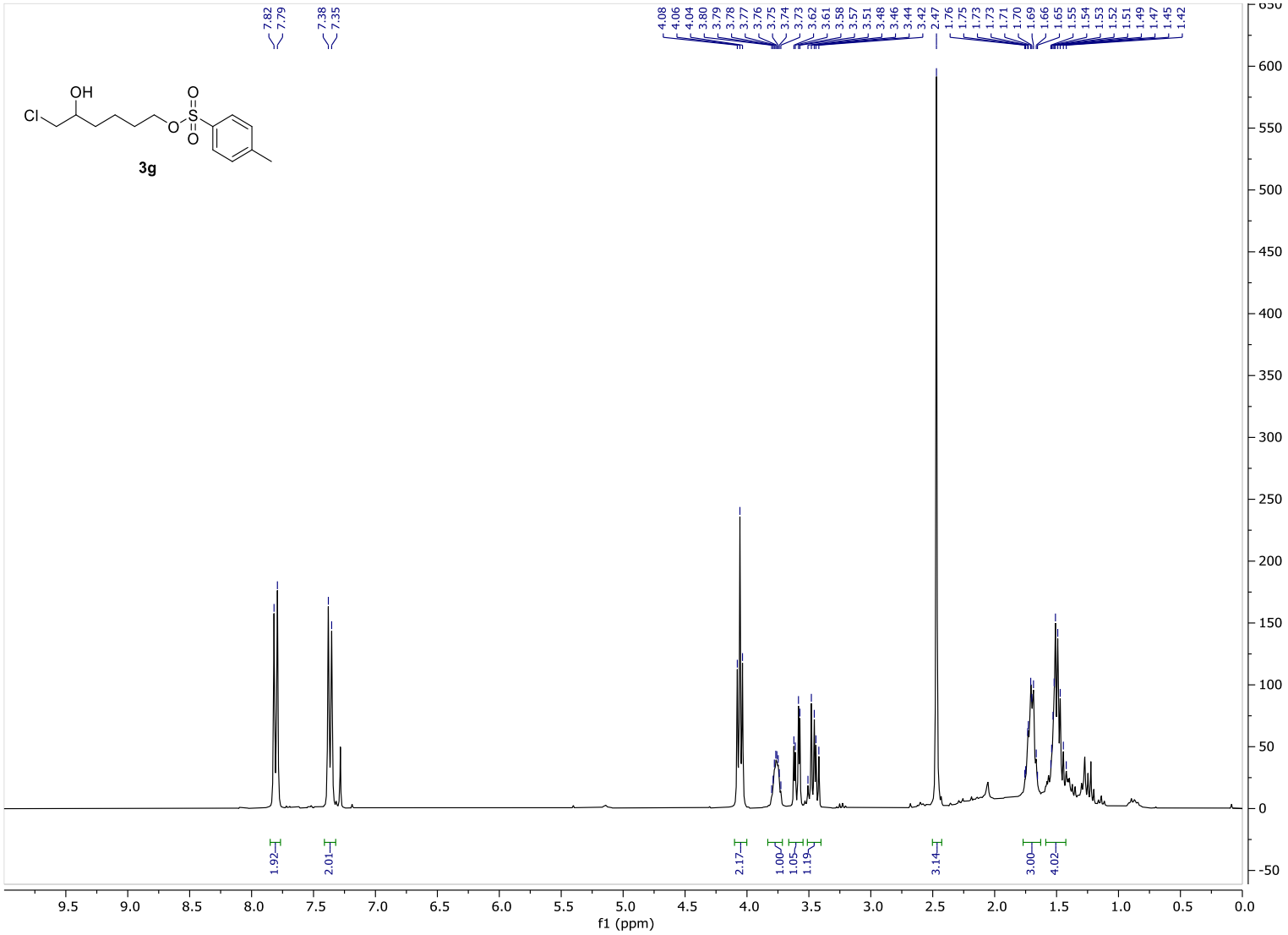

Figure S68. ^{1}H-NMR spectrum ($CDCl_3$) of compound **3g**.

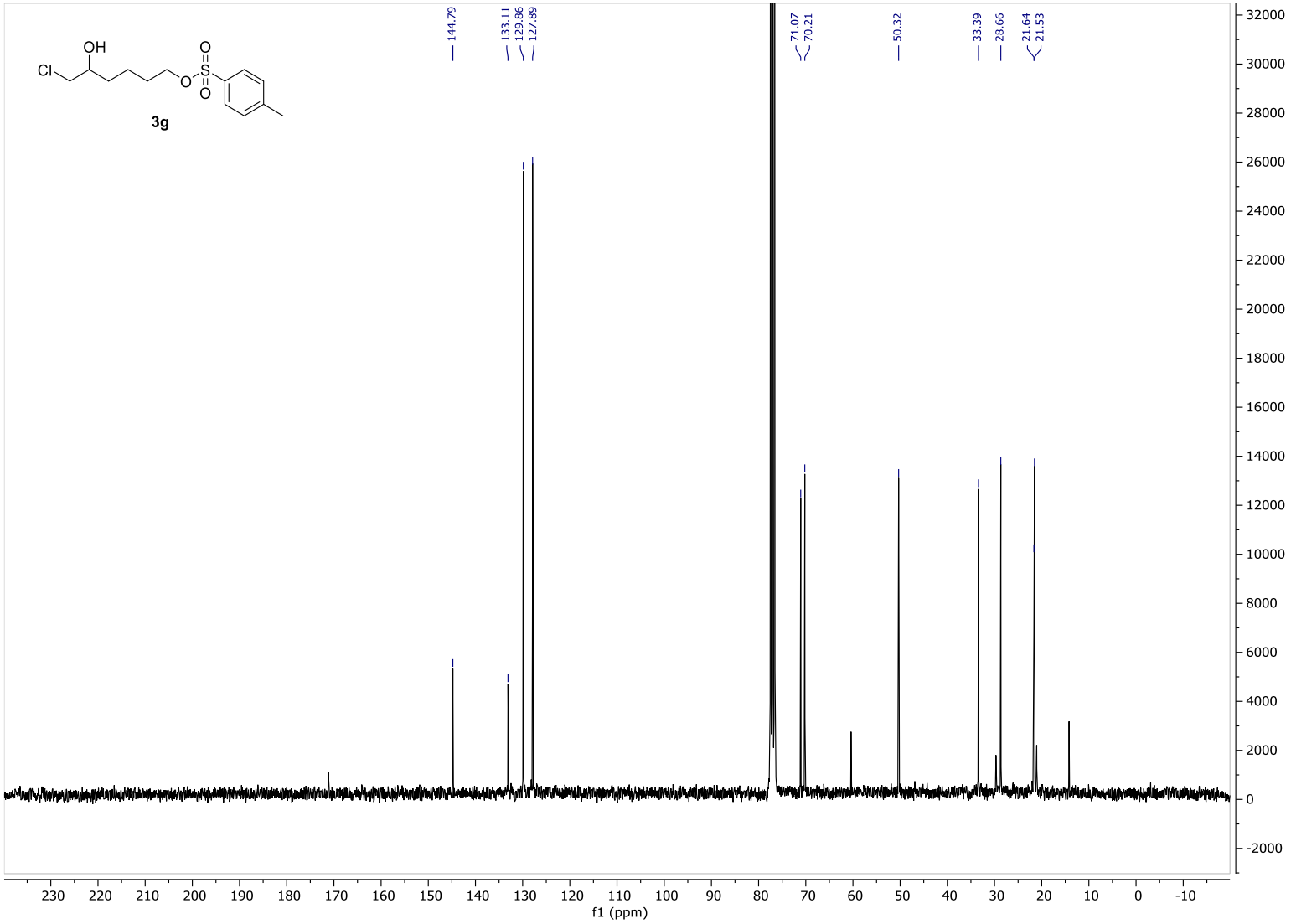

Figure S69. ^{13}C-NMR spectrum ($CDCl_3$) of compound **3g**.

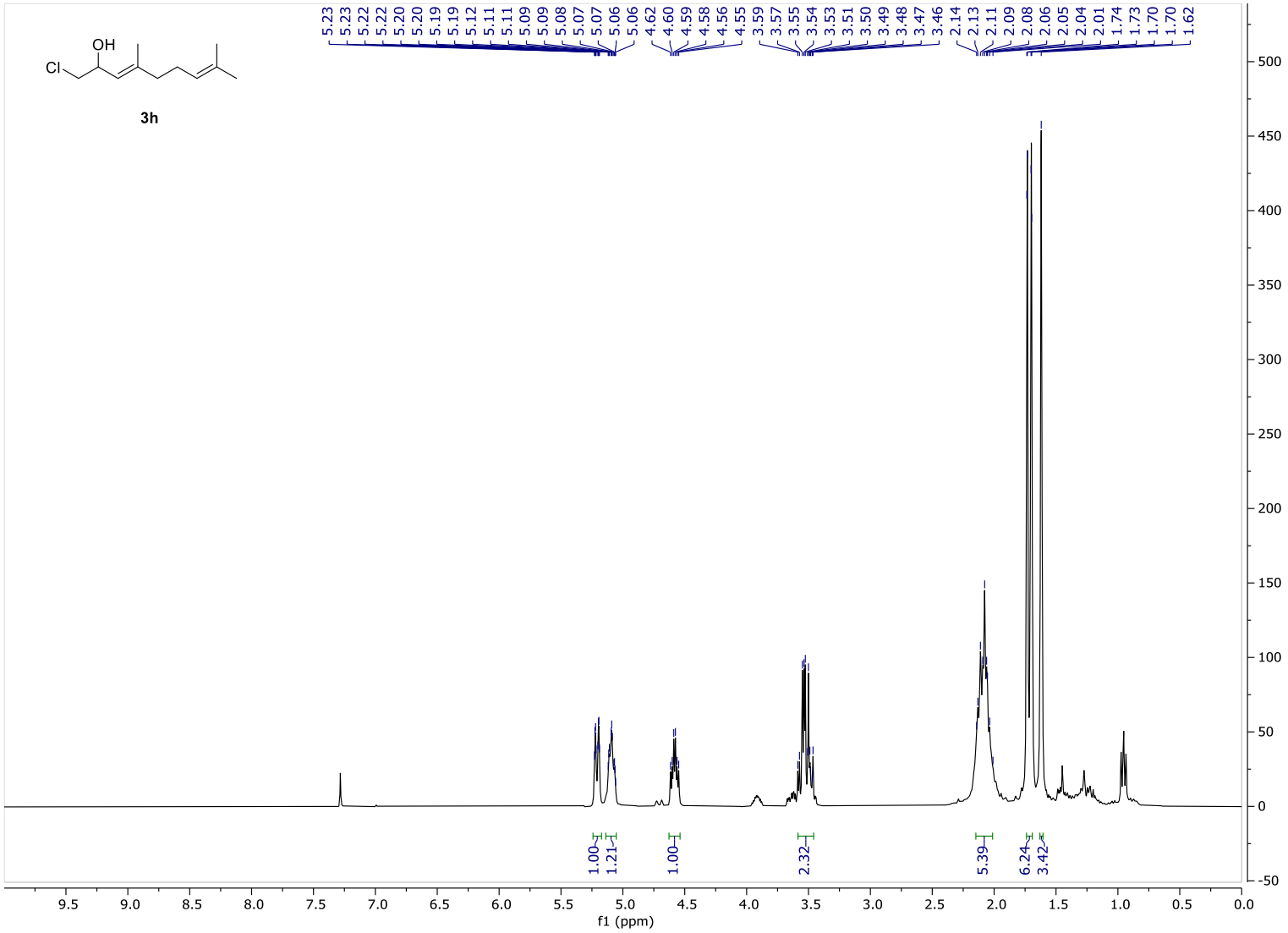

Figure S70. ^{1}H-NMR spectrum ($CDCl_3$) of compound **3h**.

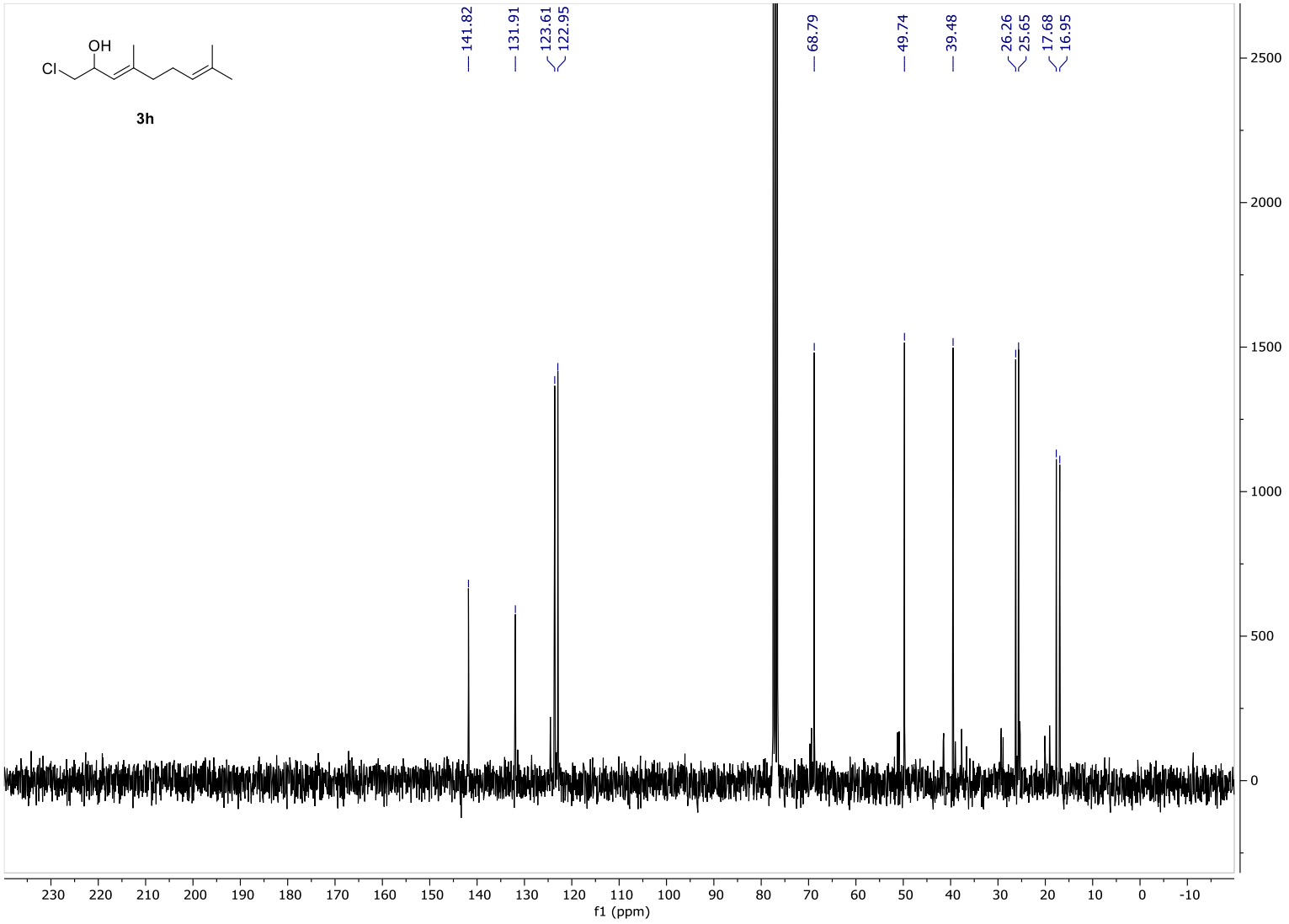

Figure S71. ^{13}C-NMR spectrum ($CDCl_3$) of compound **3h**.

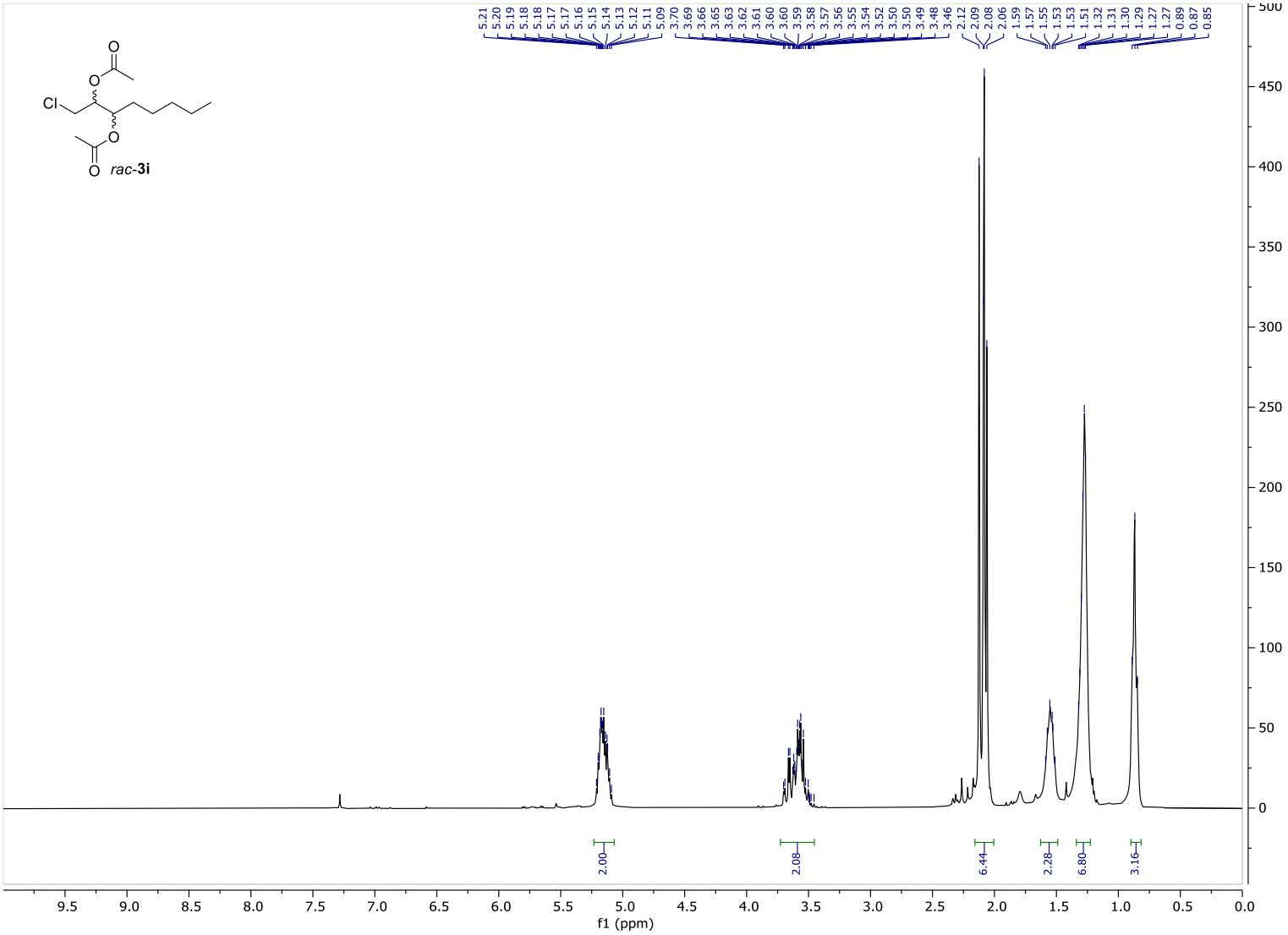

Figure S72. ^{1}H-NMR spectrum ($CDCl_3$) of compound *rac*-**3i**.

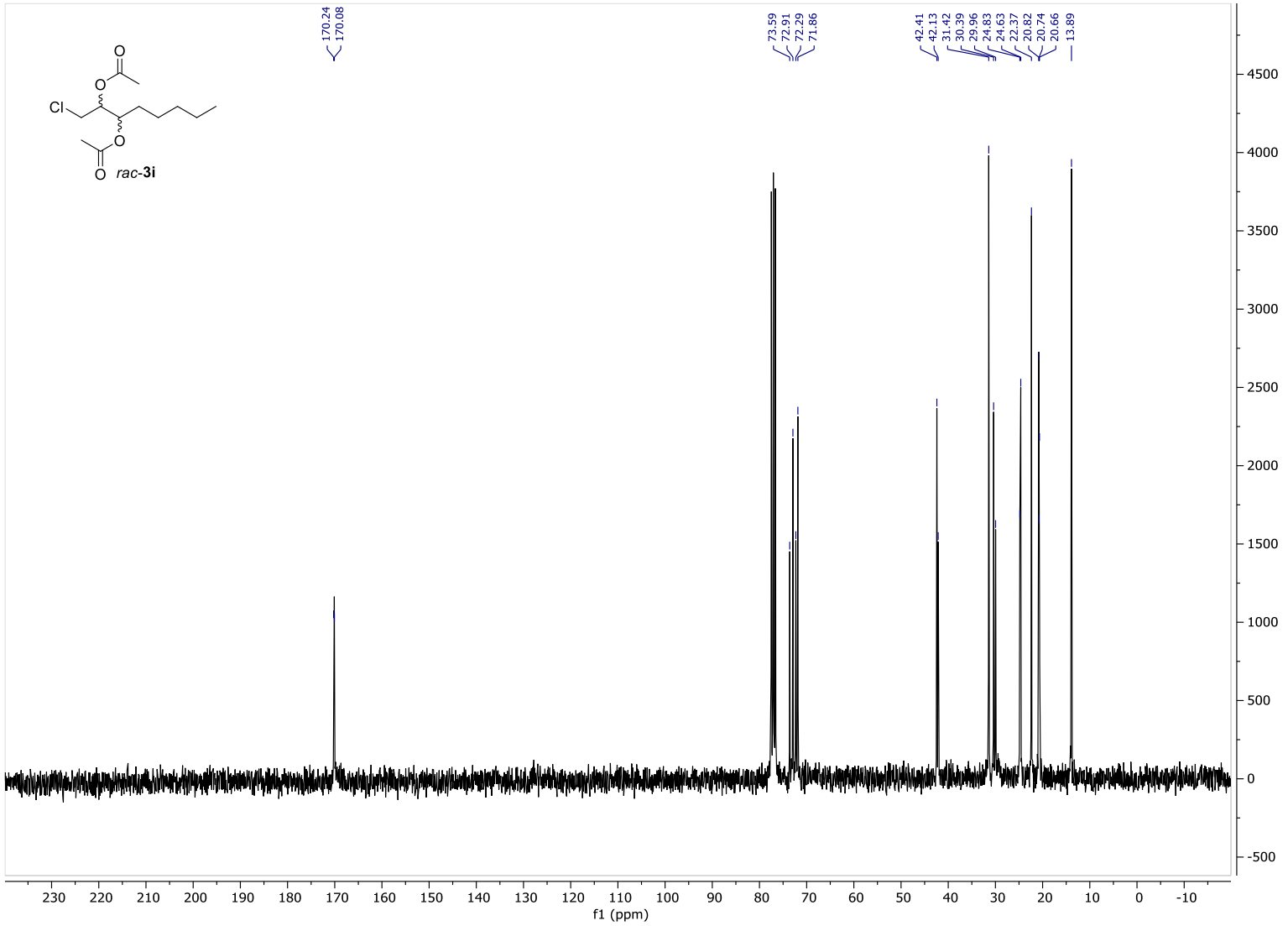

Figure S73. ^{13}C-NMR spectrum ($CDCl_3$) of compound *rac*-**3i**.

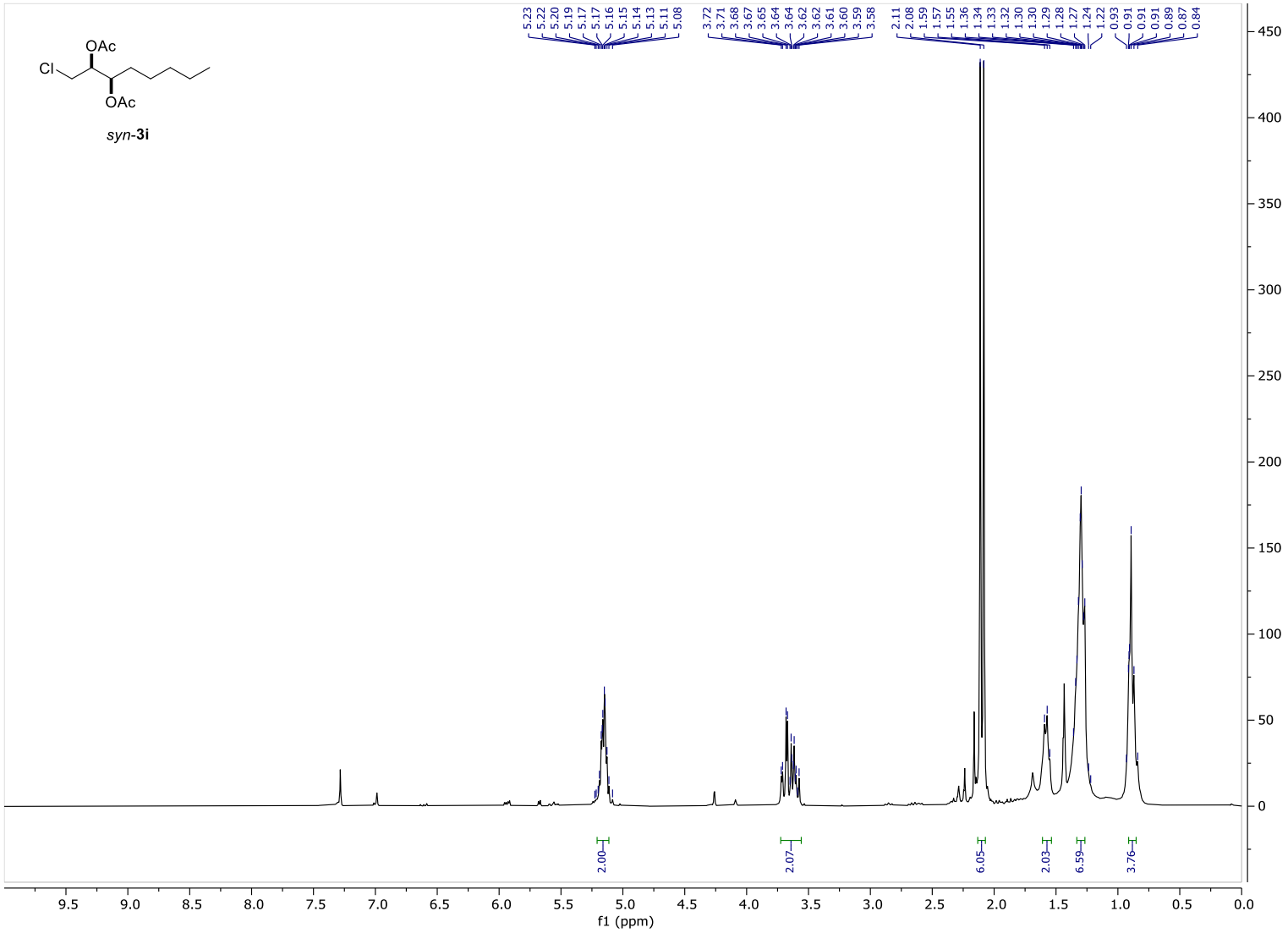

Figure S74. ^{1}H-NMR spectrum ($CDCl_3$) of compound *syn*-**3i**.

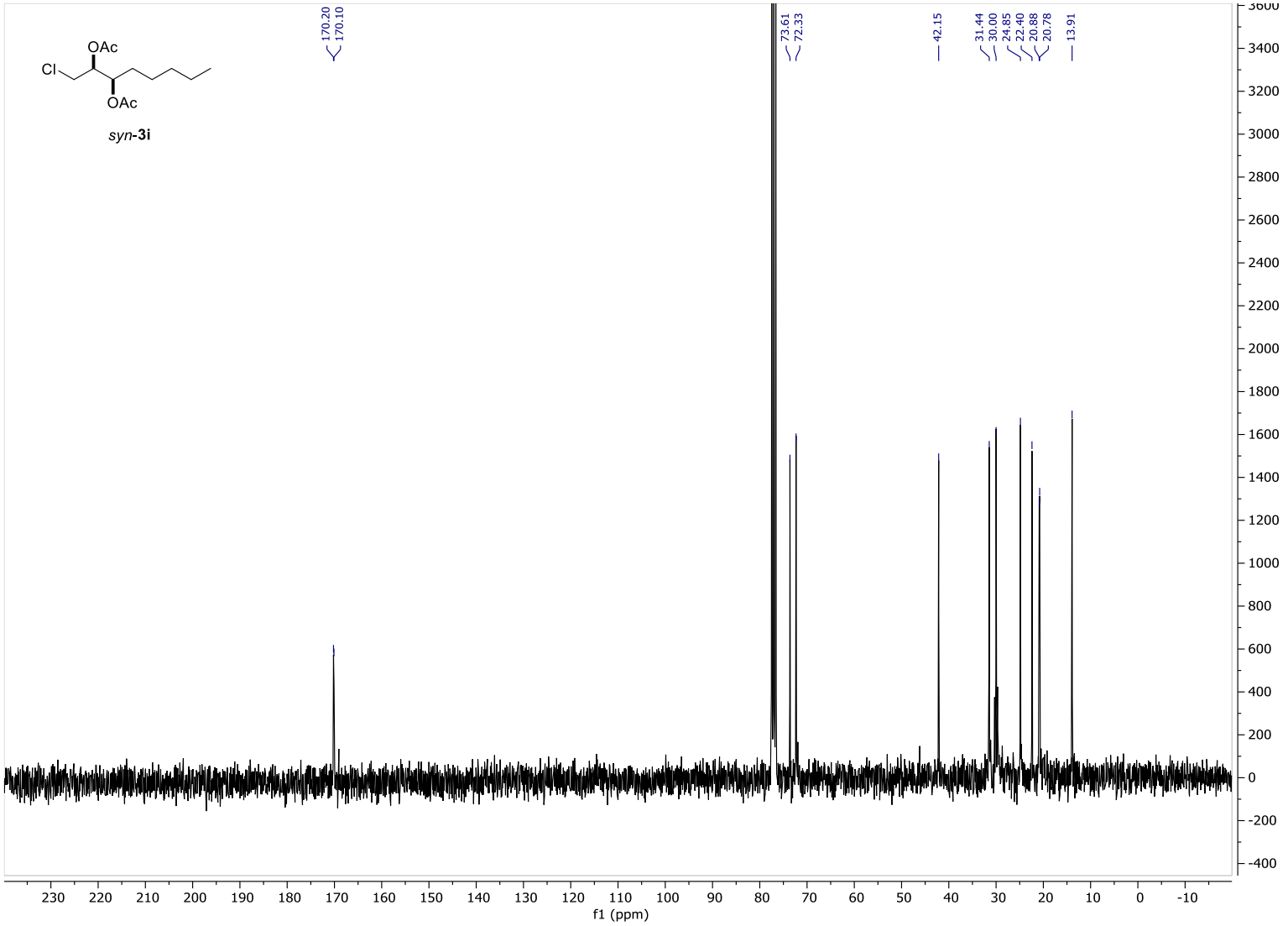

Figure S75. ^{13}C-NMR spectrum ($CDCl_3$) of compound *syn*-**3i**.

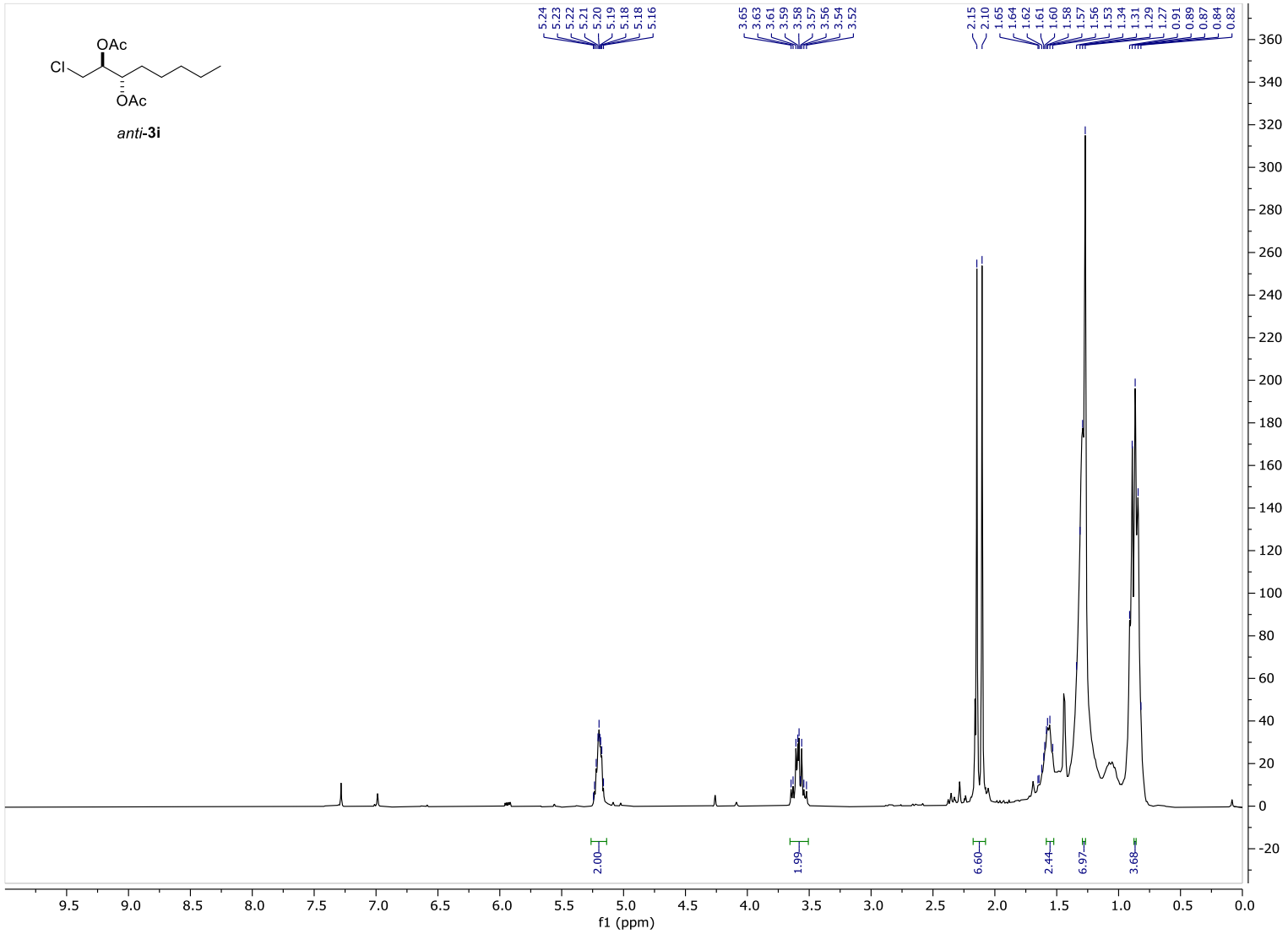

Figure S76. ^{1}H-NMR spectrum ($CDCl_3$) of compound *anti*-**3i**.

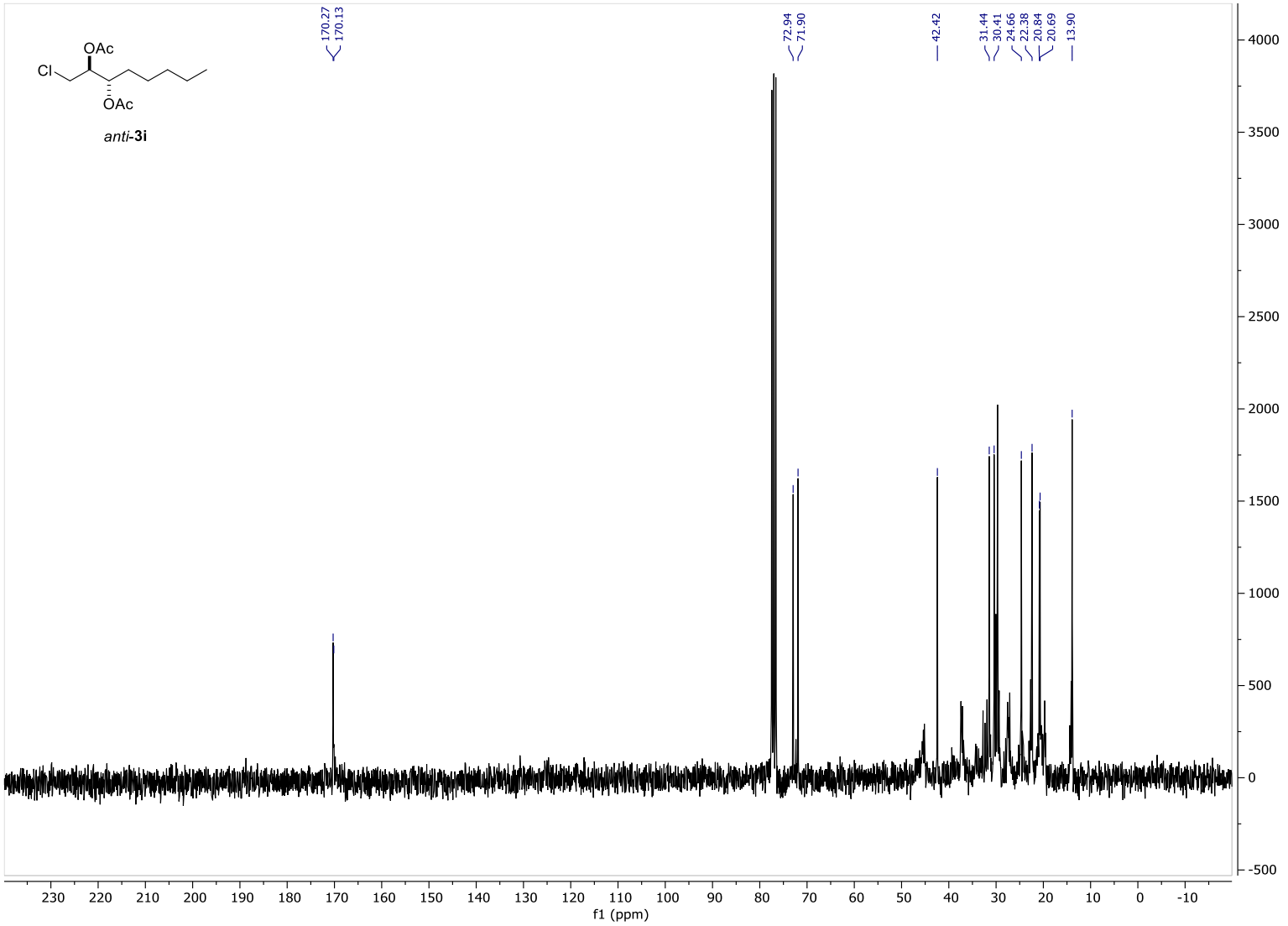

Figure S77. ^{1}H and ^{13}C-NMR spectrum ($CDCl_3$) of compound *anti*-**3i**.

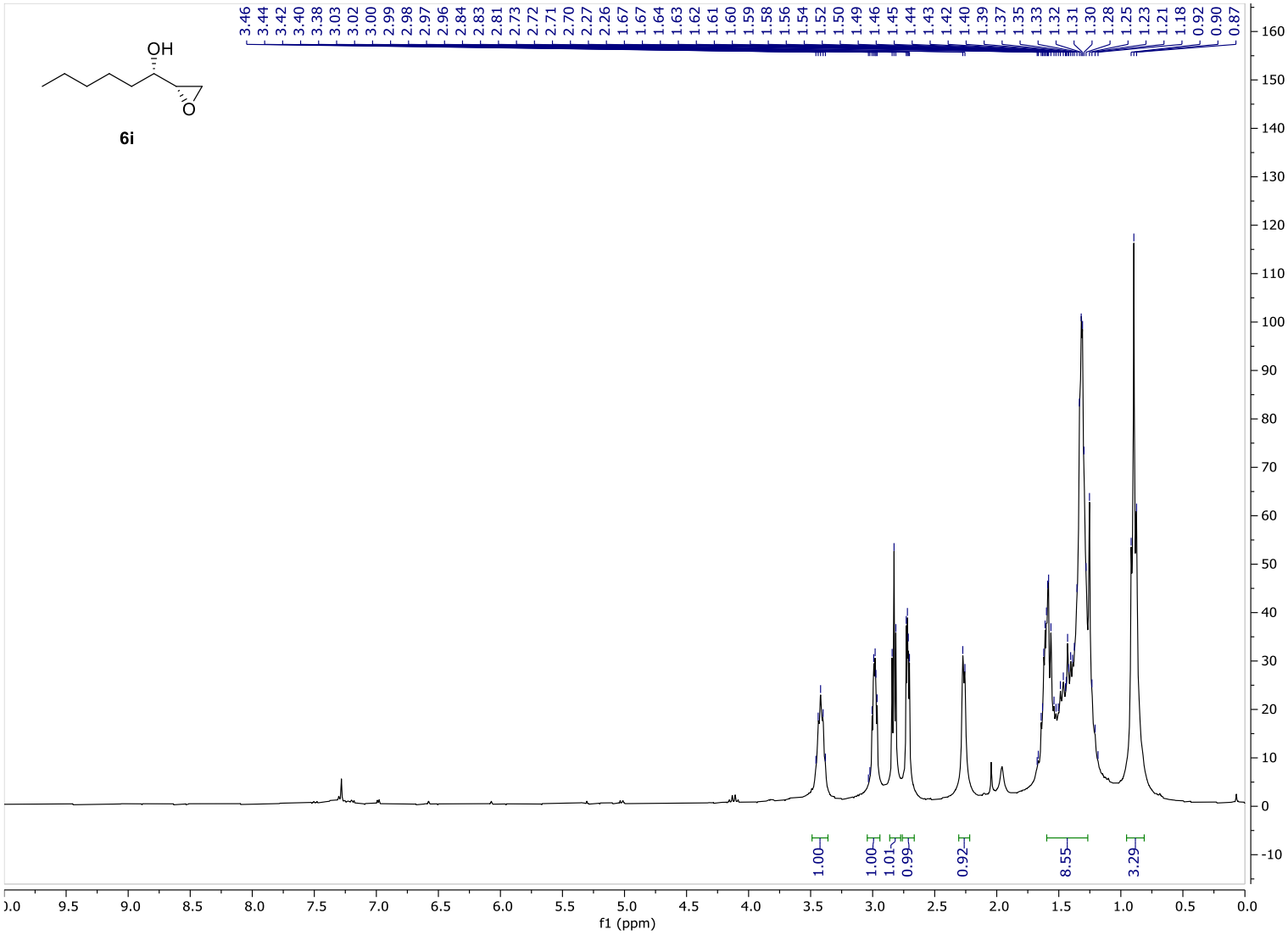

Figure S78. ^{1}H-NMR spectrum ($CDCl_3$) of compound **6i**.

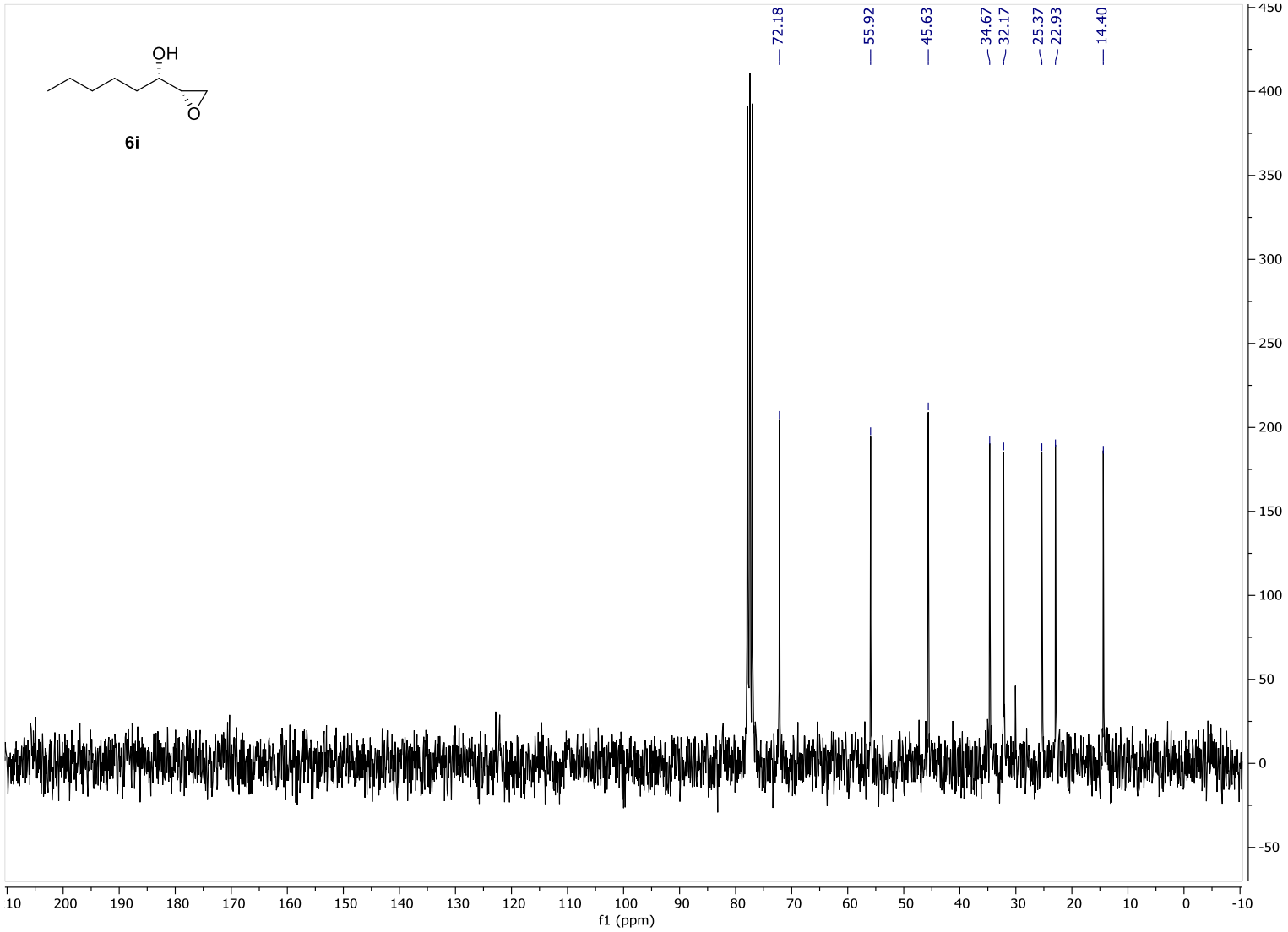

Figure S79. ^{13}C-NMR spectrum ($CDCl_3$) of compound **6i**.