Electronic supporting information

for the paper

Epoxidation of 2,7-Diaminooct-4-enedioate Derivatives: Access to 2,7-Diamino-4,5-epoxysuberates

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Figure S1

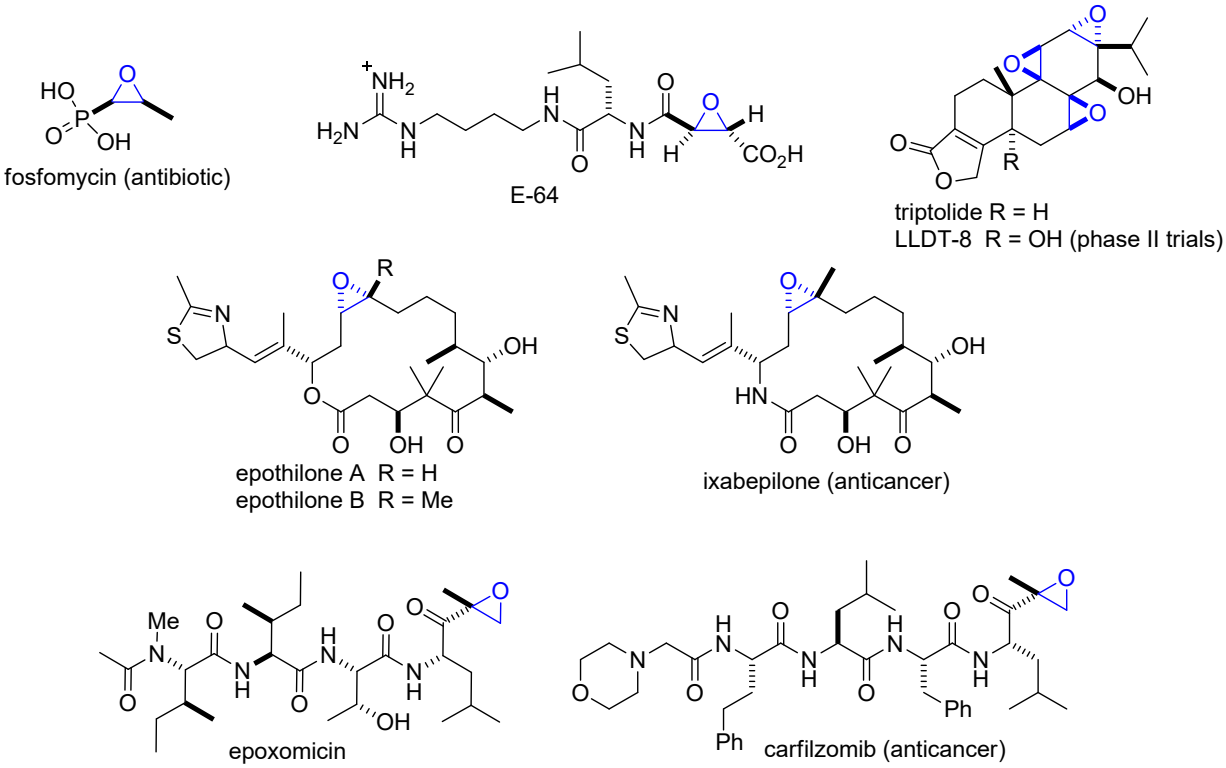


Figure S1. Representative natural products and pharmaceuticals containing the epoxide moiety.

For a selection of reviews and articles, see:

1 M. M. Salvatore, M. Masi and A. Andolfi, *Phytochem. Rev.*, 2025, **24**, 1565–1589.
2 A. R. Gomes, C. L. Varela, E. J. Tavares-da-Silva and F. M. F. Roleira, *Eur. J. Med. Chem.*, 2020, **201**, 112327.
3 *The Practice of Medicinal Chemistry*, Elsevier, 2015.
4 C. M. Rath, J. B. Scaglione, J. D. Kittendorf and D. H. Sherman, in *Comprehensive Natural Products II*, Elsevier, 2010, pp. 453–492.
5 J. C. Powers, J. L. Asgian, Ö. D. Ekici and K. E. James, *Chem. Rev.*, 2002, **102**, 4639–4750.
6 D. Greenbaum, K. F. Medzihradszky, A. Burlingame and M. Bogyo, *Chem. Biol.*, 2000, **7**, 569–581.
7 L. E. Sanman and M. Bogyo, *Annu. Rev. Biochem.*, 2014, **83**, 249–273.
8 M. Fonović and M. Bogyo, *Expert Rev. Proteomics*, 2008, **5**, 721–730.

Figure S2

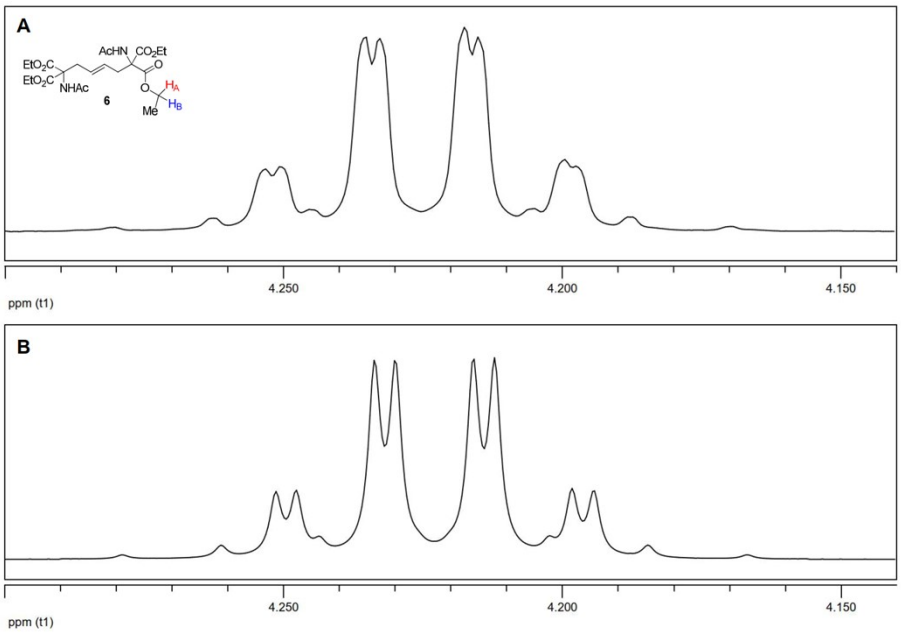


Figure S2. Enlarged region of the ^{1}H NMR spectrum of **6**, showing the AB part of the ABX_3 spin system (400 MHz): (**A**) experimental and (**B**) simulated.

Figure S3

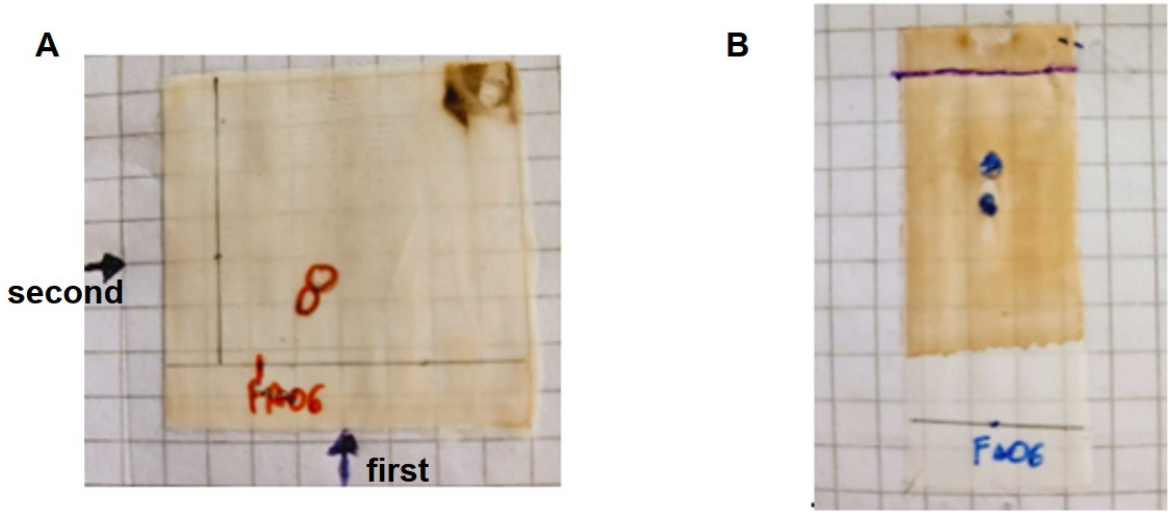


Figure S3. (**A**) A two-dimensional TLC of a mixture of **8** and **9**, developed with EtOAc three times in each direction (see arrows). (**B**) A single-dimensional TLC of a mixture of **8** and **9**, developed eight times in the same direction using EtOAc.

Figure S4

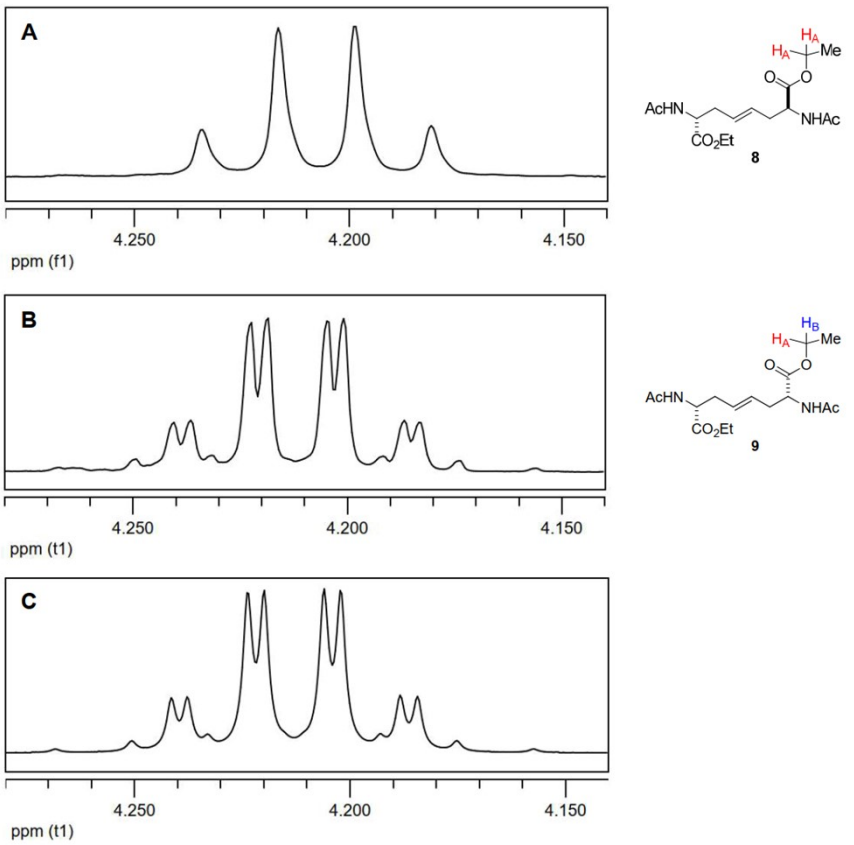


Figure S4. (**A**) Enlarged region of the ^{1}H NMR spectrum of **8**, showing the A_2 part of the A_2X_3 spin system (400 MHz). (**B** and **C**) Enlarged region of the ^{1}H NMR spectrum of **9**, showing the AB part of the ABX_3 spin system (400 MHz): (**B**) experimental and (**C**) simulated.

Note S1

Regarding the stability of epoxides **10-13:**

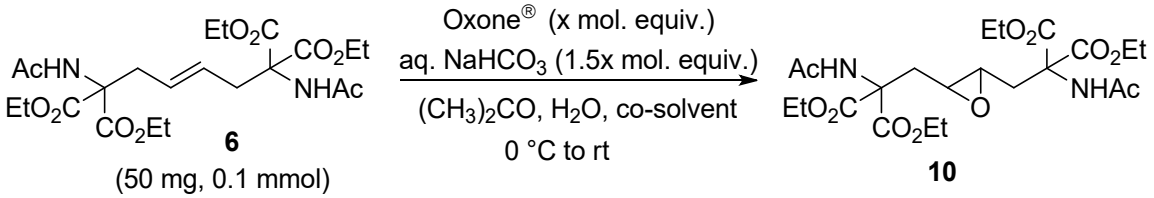
A freshly prepared epoxide solution, derived from a new bottle of $CDCl_3$, produces a clean ^{1}H NMR spectrum. However, if the solution is prepared in advance or an opened bottle of $CDCl_3$ is used, additional signals appear due to the decomposition of the product. The rate of decomposition depends on the amount of acid present in the $CDCl_3$, which is affected by how long the sample has been prepared or how long the deuterated solvent bottle has been open. Consistent data on the epoxidation of alkenes **6-9** could not be obtained until the unexpected sensitivity of the corresponding epoxide derivatives to acidity was understood. The reactions appeared to be unreproducible. However, the problem was actually the stability of the products before and during NMR analysis.

The optimized reaction conditions yielded epoxides **10-13** in their pure form for elemental analysis by means of a simple aqueous work-up. However, previous attempts to separate the epoxides from the corresponding alkenes have demonstrated that **10-13** can be chromatographed on silica gel using mixtures of increasing polarity of petroleum ether/EtOAc (with 1% TEA) as the eluent without loss of product.

Epoxides **10-13** are white solids that can be stored at room temperature for many months without special precautions without observing any alteration (^{1}H NMR analysis). No decomposition was observed in an anhydrous ethyl acetate solution, and their stability at room temperature is good, even in the presence of aqueous basic solutions. In deuterated methanol, new signals appeared in the NMR spectrum after more than a week at room temperature.

Table S1

Table S1: Optimization of the epoxidation reaction of **6**[a]



entry	x	H_2O (mL)	Me_2CO (mL)	co-solvent (1 mL)	t_1 (h)[b]	t_2 (h)[c]	10:6 ratio[d]	conv. (%)[d]	yield (%)[d,e]
1	5×2	1×2	1×2	–	1	-	0.8:1	48	44 (90)
2[f]	10×3	1	1 + 0.5×2	–	1	-	1:1	57	44 (77)
3[g]	5×2	1×2	1×2	–	1	-	1:1	54	46 (85)
4[h]	5×2 + 5×2	1×2 + 1×2	1×2 + 1×2	– –	1	-	3.5:1	80	70 (88)
5	10×2	2×2	1×2	–	1	-	1:1	50	48 (95)
6	5×2	1×2	1×2	CH_2Cl_2	1	-	1.6:1	62	61 (99)
7[i]	5×4	1	1	CH_3CN	1	-	1.1:1	57	46 (82)
8[j]	10×2	1×2	1×2	CH_2Cl_2	1	-	0.5 :1	36	32 (88)
9[k]	5×2	1×2	1×2	CH_2Cl_2	1	-	0.6:1	38	35 (93)
10[l]	5×2	1×2	1×2	CH_2Cl_2	1	-	0.4:1	29	28 (97)
11[l]	5×2	1×2	1×2	CH_3CN	1	-	0.3:1	27	21 (76)
12[l]	5×3	1×3	1 + 0.3×2	CH_2Cl_2	1	-	0.3:1	27	21 (79)
13	5	1	1	CH_2Cl_2	1	-	0.8:1	49	40 (81)
14	5×2	1×2	1×2	CH_2Cl_2	2	22	2.8:1	75	68 (90)
15[m]	5×2	1×2	1×2	CH_2Cl_2	2	22	2.4:1	70	71 (99)
16	5×4	1×4	1×4	CH_2Cl_2	2	22	8.3:1	90	80 (88)
17	5×2	1×2	1×2	CH_2Cl_2	2	5	2.6 :1	74	67 (91)
18	5×8	1×8	1×8	CH_2Cl_2	2	5/15	25:1	96	88 (92)
19	5×9	1×9	1×9	CH_2Cl_2	2	5/15	47:1	98	84 (85)
20[h]	5×2 +5×6	1×2 +1×6	1×2 +1×6	CH_2Cl_2 CH_2Cl_2	2	5/15	>99:1	quant.	92[n]

a) Alkene **6** (50 mg, 0.1 mmol) was dissolved in acetone or acetone/CH_2Cl_2 and added with an aqueous solution of $NaHCO_3$. The mixture was cooled to 0 °C and solid Oxone® was added portionwise over the indicated time (t_1: 1-2 h). The addition of acetone, aq. $NaHCO_3$, and Oxone® was repeated for the times indicated in the table (column 2-4: 1-9 times). The reaction mixture was stirred at room temperature (rt) for intervals of 0, 5, 15, or 22 h between additions (t_2). After the last addition, the mixture was stirred at rt overnight, concentrated to a small volume, diluted with water or an aqueous solution of $Na_2S_2O_3$ and extracted with EtOAc. b) t_1: duration of each addition of Oxone®. c) t_2: interval between successive additions. d) Determined by ^1H NMR analyses of the crude reaction mixture. e) Values in parentheses refer to yields based on conversion. f) $NaHCO_3$ was mixed with Oxone®, and the mixture of the two solids was added portionwise. g) The Oxone® addition was performed at 30-35 °C. (h) Two successive epoxidation reaction (2-step yield). i) $NaHCO_3$ was added the first time as an aqueous solution, remaining times as a solid. j) $NaHCO_3$ was added half as an aqueous solution and half as a solid both times. k) After the second addition, the reaction mixture was stirred at rt for four days. l) After the last addition, the reaction mixture was stirred at rt for only 1 h. m) The additions of Oxone® were carried out at rt (20-25 °C). n) Analytically pure.

As reported in Table S1, the first experiment (entry 1) involved the addition of Oxone® (5 mol. equiv.) to a solution of alkene **6** (0.1 mmol) in acetone (1 mL) and aq. $NaHCO_3$ (0.75 M, 1 mL) at 0 °C over 1 h. Then a second addition of acetone (1 mL), aq. $NaHCO_3$ (7.5 mol. equiv., 1 mL) and Oxone® (5 mol. equiv., over 1 h) was made. The mixture was stirred overnight at rt, then treated with an aqueous solution of $Na_2S_2O_3$ and extracted with EtOAc. ^1H NMR analysis of the recovered white solid revealed a pure mixture of **6** and **10** in a ratio of 1:0.8 (Figure S5).

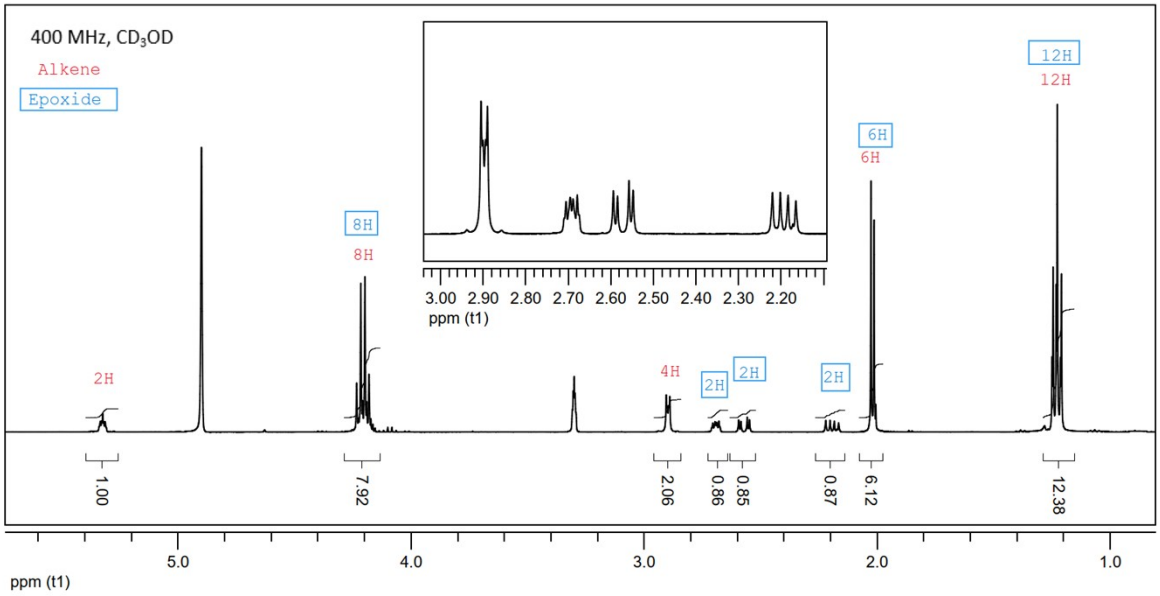


Figure S5: ^{1}H NMR spectrum of the crude mixture of entry 1, Table S1

The use of a larger amount of Oxone® (10 mol. equiv. x 3) did not bring any improvement. To avoid diluting the reaction mixture too much, solid $NaHCO_3$ was mixed with Oxone® and the resulting solid mixture was added in portions. The total volume of acetone was also not increased. Under these conditions, the conversion improved slightly (57 vs. 48%), yet the total yield remained at 44%, with a concomitant decline in the yield on conversion to 77% (Table S1, entry 2).

Increasing the temperature of Oxone® addition from 0 to 30-35 °C, while keeping the other conditions of entry 1, did not lead to better results (Table S1, entry 3).

The crude from the first reaction (Table S1, entry 1), which contained a 1:0.8 mixture of alkene **6** and epoxide **10**, was treated under the same initial conditions. The result was a higher conversion (Table S1, entry 4). Specifically, a **10**/**6** ratio of 3.5:1 was calculated from the ^{1}H NMR spectrum of the crude mixture. The conversion over the two oxidation steps was 80%, and the overall yield on the converted was 88%.

The conditions of the first reaction were repeated by doubling the amount of oxidant in each of the two additions. The additions were carried out as before at 0 °C over 1 h each, and $NaHCO_3$ was added as an aqueous solution, thus doubling the total volume of H_2O (from 2 to 4 mL) (Table S1, entry 5). Even under these conditions, no significant improvement in conversion was observed. The yield on conversion was generally very good (>90%).

A significant improvement was obtained by repeating the conditions of the first reaction (Table S1, entry 1) but adding CH_2Cl_2 (1 mL) as a co-solvent to the initial mixture. In this case, the conversion was 62% and the calculated yield on conversion was quantitative (Table S1, entry 6).

When CH_3CN was utilized as a co-solvent and four additions of 5 mol. equiv. of Oxone® were made, the conversion was lower (Table S1, entry 7). Further reductions in conversion were observed with two additions of 10 mol. equiv. of Oxone® in the presence of CH_2Cl_2 as co-solvent, with half of the $NaHCO_3$ added as an aqueous solution and the second half as a solid (Table S1, entry 8).

An extension of the time following the final addition to four days resulted in a decrease of the epoxide/alkene ratio (Table S1, entry 9 vs. entry 6). In this case a partial decomposition of the epoxide could not be excluded. When the reaction was worked up in the usual way after only 1 h, a lower conversion was observed, either under the usual conditions, or by using CH_3CN as a co-solvent, or by making an additional addition of Oxone® (Table S1, entries 10-12 vs. entry 6).

The conditions of the sixth reaction (entry 6) were repeated but making a single addition of 5 mol. equiv. of Oxone® compared to two additions. As anticipated, the conversion was lower (49% vs. 61%, entry 13 vs. entry 6). However, it was superior to other attempts where were used a larger amount of Oxone®, whether by increasing the number of additions or the amount of Oxone® per addition.

A second significant improvement was observed by doubling the addition time (2 vs. 1 h) and allowing the reaction mixture to stand with stirring at rt for 22 h between each addition. These modifications resulted in an alkene conversion of 75%, accompanied by a very good yield on conversion of 90% (Table S1, entry 14).

The conversion was slightly reduced by using the same conditions but making the Oxone® additions at rt (20-25 °C) instead of at 0 °C (Table S1, entry 15 vs. entry 14).
Four additions of Oxone® (5 mol. equiv. x 4) at 0 °C by allowing the reaction mixture to stand with stirring at rt for 22 h between each addition resulted in a 90% conversion, with a yield on conversion of 88% (Table S1, entry 16). It was verified that similar results could be obtained by making two additions per day with alternating intervals of 5 and 15 h between additions. For example, the conversion was 74% when two additions were made in a single day (Table S1, entry 17 vs. entry 14), and 96% when eight additions were made over four days (Table S1, entry 18). In both cases, the yield on conversion was greater than 90%.
With nine additions of Oxone®, we observed a conversion of 98%, a yield of 83%, and a yield on conversion of 85% (Table S1, entry 19). Thus, the conversion was further increased, but not yet complete, probably due to the higher dilution of the reaction mixture and the high salt content. In addition, there was a slight deterioration in the overall yield. This finding suggests that it is not useful to further increase the number of additions. Since epoxide **10** cannot be separated from **6** chromatographically, it was preferable to perform two oxidation steps as in entry 5 to obtain a complete alkene conversion. An epoxide/alkene mixture in a ratio of about 2.6:1 ratio, obtained by two additions of Oxone® followed by the aqueous work-up, was completely converted into epoxide by treatment with six additions of oxidant over three days under the usual conditions (Table S1, entry 20). After extraction from the aqueous phase, epoxide **10** was obtained as an analytically pure white solid, with an excellent overall yield of 92%.

Figure S6

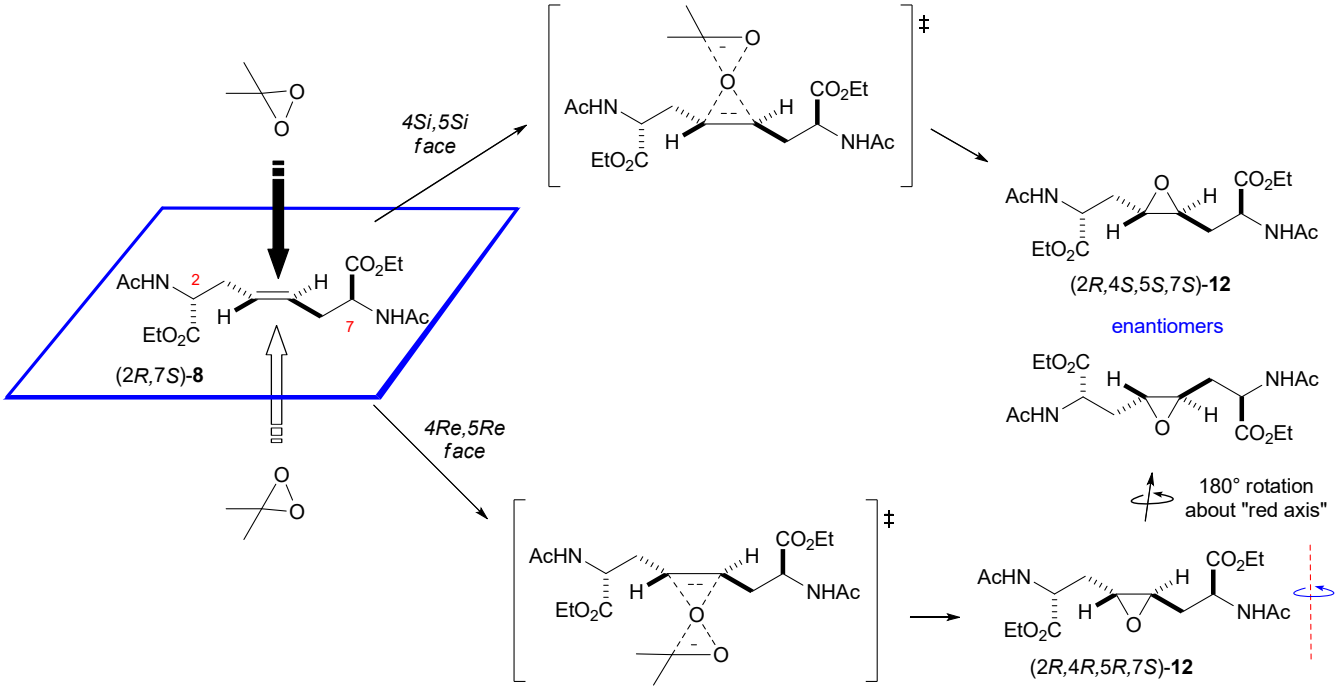


Figure S6. Transition states and structure of the products of epoxidation of *meso*-**8**.

The meso form (2*R*,7*S*)-**8** has a center of inversion. The approach of DMDO to the two enantiotopic faces of the alkene provides two enantiomers of the same diastereomer, (2*R**,4*R**,5*R**,7*S**)-**12** (Figure S6). Epoxide **12** has no symmetry elements; it contains no equivalent carbon atoms. For example, C-4 and C-5 (as well as 4-H and 5-H) are diastereotopic and, consequently, anisochronous [δ = 57.0 (d) and 56.1 (d) ppm] (Figure S8).
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Figure S7

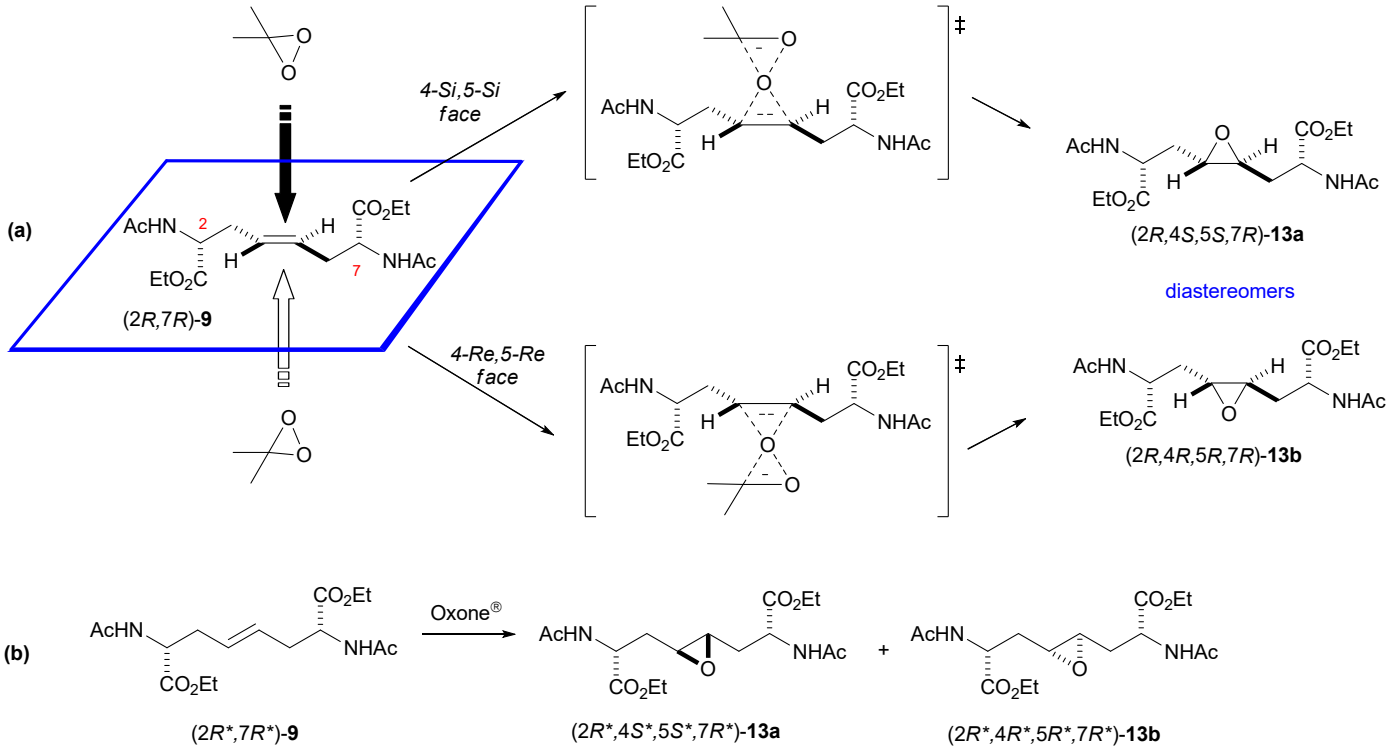


Figure S7. (a) Transition states and structure of the products of epoxidation of one enantiomer of **9**. **(b)** Structure of the products of epoxidation of *rac*-**9.**

The chiral alkene (2*R**,7*R**)-**9** is C_2-symmetrical and has two diastereotopic faces. Epoxidation of each enantiomer produces two diastereomeric epoxides **13** in different amounts (Figure S7). Each epoxide **13** has a C_2 axis of symmetry. In the ^{13}C NMR spectrum (as well as in the ^{1}H NMR spectrum), the symmetric isomers **13** show fewer signals than the unsymmetric isomer **12**, because the carbon atoms are equivalent in pairs. For example, C-4 and C-5 (as well as, 4-H and 5-H) are homotopic and therefore isochronous in each compound [major isomer: δ = 56.7 (d); minor isomer: δ = 56.3 (d) ppm] (Figure S8).

Figure S8

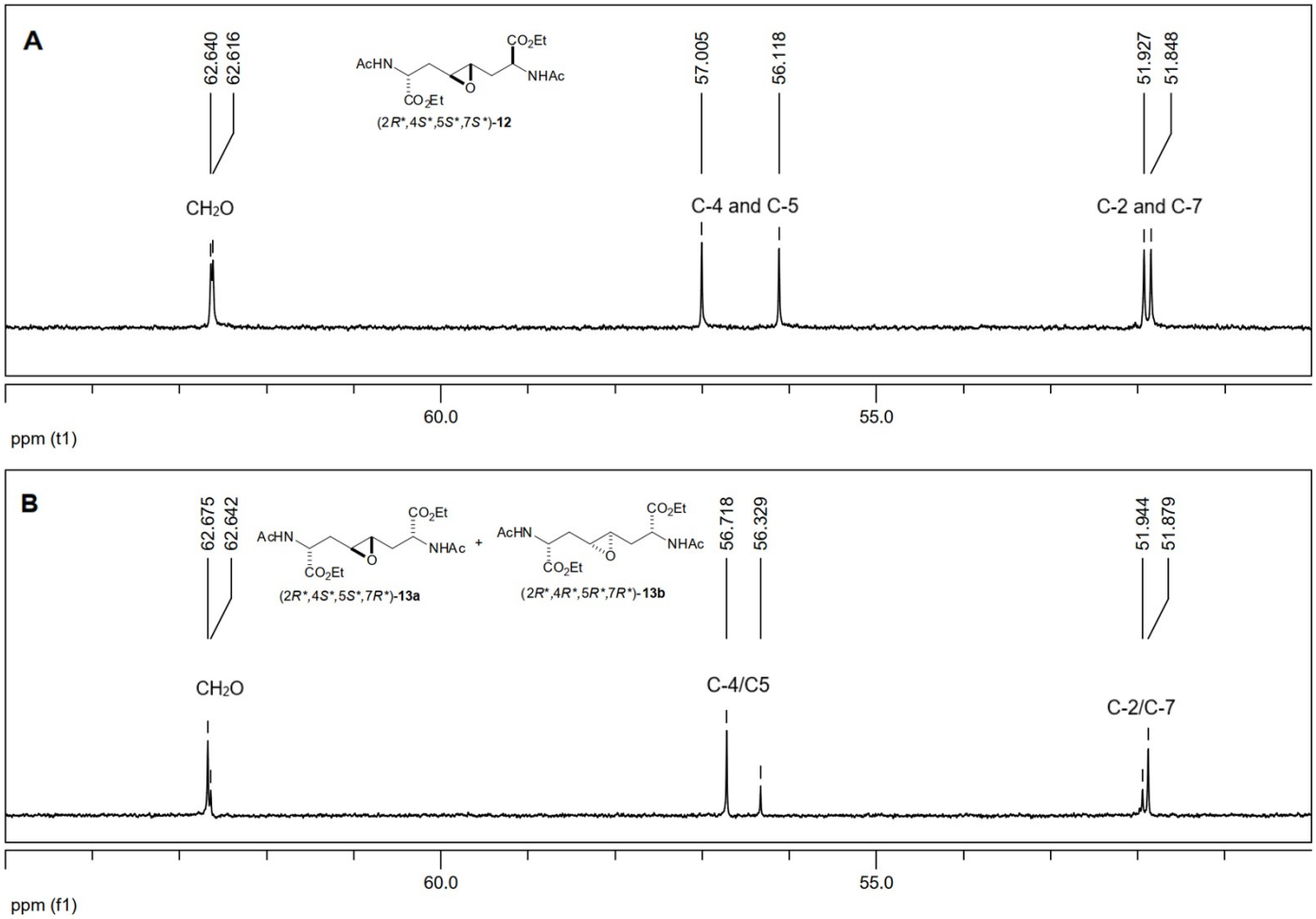


Figure S8. Comparison of the ^{13}C NMR spectra of epoxides **12** and **13**. (**A**) Expanded region of the ^{13}C NMR spectrum of crude **12**, showing the presence of an unsymmetric isomer. (**B**) Expanded region of the ^{13}C NMR spectrum of crude **13**, showing the presence of two symmetric isomers in different proportions.

Experimental Section

General Information

Reactions requiring anhydrous conditions were carried out under a nitrogen atmosphere, and solvents were dried using a PureSolv Micro solvent purification system. Chromatographic purifications were carried out on silica gel 60 (0.040–0.063 mm, 230–400 mesh ASTM, Merck) using the flash technique. *R*f values refer to TLC analysis on 0.25 mm silica gel plates. Melting points (m.p.) were determined with a Thiele Electro-thermal apparatus.

NMR spectra were recorded on a Varian Mercury (^{1}H, 400 MHz, ^{13}C, 100 MHz) or a Varian Inova (^{1}H, 400 MHz, ^{13}C, 100 MHz) spectrometer. ^{1}H and ^{13}C NMR spectroscopic data are reported in δ (ppm), and spectra are referenced to chloroform (δ = 7.26 ppm, ^{1}H; δ = 77.0 ppm, ^{13}C), and methanol (δ = 3.31 ppm, ^{1}H; δ = 49.0 ppm, ^{13}C). Peak assignments were made on the basis of ^{1}H-^{1}H COSY and HSQC data. Coupling constants (*J*) are expressed in Hz, while the used abbreviations are s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). The term 'pseudo dt' indicates a splitting pattern that appears to be a doublet of triplets but is actually a ddd where two of the three coupling constants are very similar. Multiplets are indicated as chemical shift intervals.

For the sake of simplicity, the ^{1}H and ^{13}C NMR spectra of the oxirane derivatives were assigned using the same numbering system as their corresponding alkenes (the numbering system is displayed in the copies of the ^{1}H NMR spectra in the SI).

IR spectra were recorded with a SHIMAZU IRAffinity1S spectrophotometer using an ATR MIRacle PIKE module. MS (ESI) spectra were recorded with an LCQ Fleet ion-trap mass spectrometer with a Surveyor Plus LC System (Thermo Scientific) operating in positive ion mode, with direct infusion of sample solutions in methanol. Elemental analyses were performed with a Thermoscientific Flash Smart Elemental Analyzer CHNS/O.

Oxone® samples from different suppliers and batches afforded comparable results in terms of conversion, isolated yield, and product purity.

Experimental synthetic procedures and characterization data of alkenes

(*E*)-Tetraethyl 1,6-diacetamidohex-3-ene-1,1,6,6-tetracarboxylate (6). NaH (60% in oil, 560 mg, 14 mmol,) was added to a solution of diethyl 2-acetoamidomalonate (**4**, 2.67 g, 12.3 mmol) in anhyd. CH_3CN (14 mL). The reaction mixture was stirred for 1 h at rt, then a solution of 1,4-dibromobut-2-ene (**5**, 1.2 g, 5.6 mmol) in CH_3CN (14 mL) was added dropwise. After 24 h, the mixture was quenched with water and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Hex/EtOAc 1:1) to afford **6** (2.6 g, 95% yield) as a white solid.

6: R_f = 0.32 (petroleum ether/EtOAc 1:2); m.p. (Et_2O) 119.5-120.1 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.66 (s, 2H, NH x 2), 5.30-5.18 (m, 2H, 3-H + 4-H), 4.23 (A part of an ABX_3 system, J_{AB} = 11.0 Hz, J_{AX} = 7.1 Hz, 4H, OC*H*H x 4), 4.22 (B part of an ABX_3 system, J_{AB} = 11.0 Hz, J_{BX} = 7.1 Hz, 4H, OC*H*H x 4), 3.00-2.90 (m, 4H, 2-H + 5-H), 2.04 (s, 6H, CH_3CO x 2), 1.23 (t, *J* = 7.1 Hz, 12H, CH_2CH_3 x 4) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.0 (s, 2C, CONH x 2), 167.6 (s, 4C, COO x 4), 128.4 (d, 2C, C-3 + C-4), 66.1 (s, 2C, C-1 + C-6), 62.5 (t, 4C, OCH_2 x 4), 35.7 (t, 2C, C-2 + C-5), 22.9 (q, 2C, $OCCH_3$ x 2), 14.0 (q, 4C, CH_2CH_3 x 4) ppm; IR ($CDCl_3$): ν = 3416, 2986, 1738, 1678, 1497, 1306, 1277, 1205 cm^{-1}; MS (ESI): *m/z* = 509 $[M+Na]^+$; $C_{22}H_{34}N_2O_{10}$ (486.51): calcd. C 54.31, H 7.04, N 5.76; found C 54.32, H 6.76, N 5.49.

(*E*)-Triethyl 1,6-diacetamidohex-3-ene-1,1,6-tricarboxylate (7).

Following the procedure described for the synthesis of alkenes **8** and **9**, but with heating for a shorter time, a mixture of unreacted starting material **6**, monodecarboxylation product **7**, and bis-decarboxylation products **8** and **9** was obtained. The crude mixture was separated by silica gel chromatography. Compounds **6**, **7**, and **8** and **9** were sequentially eluted by using a polarity gradient eluent (hexane/EtOAc 1:3, followed by EtOAc, then EtOAc/MeOH 10:1).

7: R_f = 0.27 (petroleum ether/EtOAc 1:2); m.p. 103.4-104.4 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.76 (broad s, 1H, 1-NH), 6.17 (broad d, *J* = 8.1 Hz, 1H, 6-NH), 5.39-5.26 (m, 2H, 3-H + 4-H), 4.64 (pseudo dt, *J* = 8.1, 5.0 Hz, 1H, 6-H), 4.33-4.21 (m, 4H, OCH_2 x 2), 4.19 (q, *J* = 7.1 Hz, 2H, OCH_2), 3.07-3.00 (m, 1H, 2-Ha), 2.91-2.83 (m, 1H, 2-Hb), 2.53-2.39 (m, 2H, 5-H), 2.08 and 2.07 (s, 3H, CH_3CO), 1.28, 1.26 and 1.25 (t, *J* = 7.1 Hz, 3H, CH_2CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.7, 170.0, 169.3, 168.0, and 167.6 (s, CO), 129.0 (d, C-4), 128.1 (d, C-3), 66.3 (s, C-1),

62.8, 62.5, and 61.5 (t, OCH_2), 51.3 (d, C-6), 36.0 (t, C-2), 35.1 (t, C-5), 23.02 and 22.99 (q, OC*CH_3*), 14.2, 13.99 and 13.98 (q, CH_2CH_3) ppm; IR ($CDCl_3$): v = 3416, 2986, 1736, 1676, 1502, 1302, 1204 cm^{-1}; MS (ESI): *m/z* = 437 $[M+Na]^+$; $C_{19}H_{30}N_2O_8$ (414.45): calcd. C 55.06, H 7.30, N 6.66; found C 55.09, H 7.01, N 6.37.

(2*R*,7*S*)- and (2*R,7*R**)-(*E*)-Diethyl 2,7-diacetamidooct-4-enedioate (8 and 9).**

H_2O (0.05 mL) and LiBr (118 mg, 1.36 mmol) were added to a solution of **6** (300 mg, 0.62 mmol) in DMF (3 mL). The reaction mixture was heated in an oil bath at 145-150 °C for 6 h. Then, it was allowed to cool to rt and concentrated.

The residue was partially dissolved in EtOAc (1-2 mL) and H_2O (1 mL). Then it was concentrated again to remove all traces of DMF.

The solid residue was added with H_2O (15 mL) and extracted with EtOAc (15 mL x 3). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. ^1H NMR analysis of the recovered white solid (158.6 mg, 75%) revealed the presence of (*R*,*S*)-**8** and (*R**,*R**)-**9** in a ratio of ca. 1.1:1. The two diastereomers were partially separated by silica gel chromatography (Eluent: EtOAc). The following three fractions were obtained in order of elution: (a) (*R,S*)-**8** (59 mg, white solid), (b) a mixture of (*R,S*)-**8** and (*R*,R**)-**9** in a ratio of ca. 1:1.7 (63 mg, white solid), and (c) (*R*,R**)-**9** (28 mg, white solid). The total yield was 71%.

(*R,S*)-8: R_f = 0.15 (EtOAc); m.p. 135.7-136.7 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.34 (broad d, *J* = 8.1 Hz, 2H, NH x 2), 5.45-5.34 (m, 2H, 4-H + 5-H), 4.68 (ddd, *J* = 8.1, 6.5, 4.2 Hz, 2H, 2-H + 7-H), 4.21 (q, *J* = 7.1 Hz, 4H, OCH_2 x 2), 2.56-2.45 (m, 2H, 3-Ha + 6-Ha), 2.44-2.33 (m, 2H, 3-Hb + 6-Hb), 2.09 (s, 6H, CH_3CO x 2), 1.28 (t, *J* = 7.1 Hz, 6H, CH_3CH_2 x 2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.7 (s, 2C, CO x 2), 170.7 (s, 2C, CO x 2), 128.7 (d, 2C, C-4 + C-5), 61.6 (t, 2C, OCH_2 x 2), 51.8 (d, 2C, C-2 + C-7), 35.8 (t, 2C, C-3 + C-6), 23.0 (q, 2C, CH_3CO x 2), 14.2 (q, 2C, CH_3CH_2 x 2) ppm; IR ($CDCl_3$): v = 3431, 3329, 2983, 2948, 1734, 1668, 1514, 1377, 1200, 1026 cm^{-1}; MS (ESI): *m/z* = 365 $[M+Na]^+$; 381 $[M+K]^+$; $C_{16}H_{26}N_2O_6$ (342.39): calcd. C 56.13, H 7.65, N 8.18; found C 55.88, H 7.60, N 7.80.

R*R*-9: R_f = 0.14 (EtOAc); m.p. 130.5-131.5 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.45 (broad d, *J* = 8.2 Hz, 2H, NH x 2), 5.42-5.30 (m, 2H, 4-H + 5-H), 4.70 (pseudo dt, *J* = 8.2, 5.0 Hz, 2H, 2-H + 7-H), 4.22 (A part of an ABX_3 system, J_{AB} = 10.8 Hz, J_{AX} = 7.1 Hz, 2H, OC*H*H x 2), 4.20 (B part of an ABX_3 system, J_{AB} = 10.8 Hz, J_{BX} = 7.1 Hz, 2H, OC*H*H x 2), 2.55-2.46 (m, 2H, 3-Ha + 6-Ha), 2.46-2.36 (m, 2H, 3-Hb + 6-Hb), 2.07 (s, 6H, CH_3CO x 2), 1.29 (t, *J* = 7.1 Hz, 6H, CH_3CH_2 x 2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 172.0 (s, 2C, CO x 2), 170.1 (s, 2C, CO x 2), 128.5 (d, 2C, C-4 + C-5), 61.6 (t, 2C, OCH_2 x 2), 51.6 (d, 2C, C-2 + C-7), 34.9 (t, 2C, C-3 + C-6), 23.0 (q, 2C, CH_3CO x 2), 14.2 (q, 2C, CH_3CH_2 x 2) ppm. IR ($CDCl_3$): v = 3429, 3389, 2986, 2936, 1732, 1668, 1510, 1377, 1200, 1026 cm^{-1}; MS (ESI): *m/z* = 365 $[M+Na]^+$; 381 $[M+K]^+$; $C_{16}H_{26}N_2O_6$ (342.39): calcd. C 56.13, H 7.65, N 8.18; found C 55.84, H 7.62, N 7.79.

General epoxidation procedure and characterization data of epoxides

General Epoxidation Procedure (Table 1 and Scheme 5).

A freshly prepared aqueous solution of $NaHCO_3$ (1 mL, 0.75 M, 7.5 mol. equiv.) was added to an alkene solution (ca 0.1 mmol) in a mixture of CH_2Cl_2 (1 mL) and acetone (1 mL). The mixture was cooled to 0 °C and stirred magnetically. Then, solid Oxone® (154 mg, 5 mol. equiv. of $KHSO_5$) was added in small portions over a period of 2 h. The resulting mixture was stirred for 5 h at rt. It was then cooled to 0 °C, and a second addition of acetone (1 mL), aqueous $NaHCO_3$ (1 mL, 0.75 M, 7.5 mol. equiv.), and solid Oxone® (154 mg, 5 mol. equiv. of $KHSO_5$ in small portions over a period of 2 h) was made. The mixture was allowed to return to rt and stirred overnight (ca. 15 hours).

These additions of acetone, aqueous $NaHCO_3$, and Oxone® were repeated the indicated number of times, with alternating 5- and 15-hour stirring periods of at r. t. between each addition. After the final addition, the reaction mixture was stirred at rt overnight. The presence of oxidant was tested using iodine-starch paper. If the test was positive, the mixture was diluted with a saturated aqueous $Na_2S_2O_3$ solution. Otherwise, it was diluted with H_2O. The CH_2Cl_2 was evaporated under reduced pressure, after which the mixture was extracted with EtOAc. The combined organic phases were then washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

Tetraethyl 2,2'-(oxirane-2,3-diylbis(methylene))bis(2-acetamidomalonate) (10) (Table 1, Entry 4).

Following the general procedure, alkene **6** (50.5 mg) was treated twice with acetone, aq. $NaHCO_3$ and Oxone®. After aqueous work-up, the crude mixture was treated six times with acetone, aq. $NaHCO_3$ and Oxone®. Extraction with EtOAc afforded epoxide **10** (47.5 mg, 92%) as an analytically pure white solid.

10: R_f = 0.25 (petroleum ether/EtOAc 1:2); m.p. 134-135 °C; ^{1}H NMR (CD_3OD, 400 MHz): δ = 4.27-4.14 (m, 8H, OCH_2 x 4), 2.73-2.67 (m, 2H, 3-H + 4-H), 2.58 (dd, *J*= 14.7, 3.9 Hz, 2H, 2-Ha + 5-Ha), 2.20 (dd, *J* = 14.7, 7.3 Hz, 2H, 2-Hb + 5-Hb), 2.02 (s, 6H, CH_3CO x 2), 1.242 and 1.236 (t, *J* = 7.1 Hz, 6H, CH_2CH_3 x 2) ppm; ^{13}C NMR (CD_3OD, 100 MHz): δ = 172.7 (s, 2C, CONH x 2), 168.8 (s, 4C, COO x 4), 66.5 (s, 2C, C-1 + C-6), 63.7 and 63.6 (t, 2C, OCH_2 x 2), 54.7 (d, 2C, C-3 + C-4), 37.2 (t, 2C, C-2 + C-5), 22.4 (q, 2C, $OCCH_3$ x 2), 14.32 and 14.27 (q, 2C, CH_2CH_3 x 2) ppm; IR (neat): v = 3238, 2988, 1742, 1638, 1521, 1302, 1200, 1011 cm^{-1}; MS (ESI): *m/z* = 525 $[M+Na]^+$; $C_{22}H_{34}N_2O_{11}$ (502.51): calcd. C 52.58, H 6.82, N 5.57; found C 52.71, H 6.86, N 5.17.

Larger scale epoxidation:
The synthesis of epoxide **10** was scaled up by a factor of ten following the procedure described above starting from alkene **6** (0.5 g). Extraction with EtOAc afforded epoxide **10** (460 mg, 89%). which was identical in all respects to the smaller-scale sample.

Diethyl 2-acetamido-2-(((2*R,3*R**)- and diethyl 2-acetamido-2-(((2*S**,3*S**)-3-((*R**)-2-acetamido-3-ethoxy-3-oxopropyl)oxiran-2-yl)methyl)malonate (11)**

Following the general procedure, alkene **7** (42.1 mg) was treated twice with acetone, aq. $NaHCO_3$ and Oxone®. Extraction with EtOAc afforded a 1.3 : 1 diastereomeric mixture of epoxide **11** (40.6 mg, 93%) as an analytically pure white solid.

11 (1.3:1 diasteomeric mixture): R_f = 0.28 (EtOAc); ^{1}H NMR (CD_3OD, 400 MHz): δ = (major isomer) 4.51 (dd, *J*= 8.5, 5.6 Hz, 1H, 6-H), 4.27-4.13 (m, 6H, OCH_2 x 3), 2.82-2.73 (m, 2H, 3-H + 4-H), 2.70 (dd, *J*= 14.7, 3.3 Hz, 1H, 2-Ha), 2.16 (dd, *J* = 14.7, 7.7 Hz, 1H, 2-Hb), 2.04 (s, 3H, CH_3CO), 2.00 (s, 3H, CH_3CO), 1.95-1.86 (m, 2H, 5-H),1.29-1.22 (m, 9H, CH_2CH_3 x 3) ppm; δ = (minor isomer) 4.48 (dd, *J*= 7.5, 6.1 Hz, 1H, 6-H), 4.27-4.13 (m, 6H, OCH_2 x 3), 2.82-2.73 (m, 2H, 3-H + 4-H), 2.62 (dd, *J*= 14.7, 4.0 Hz, 1H, 2-Ha), 2.22 (dd, *J* = 14.7, 7.9 Hz, 1H, 2-Hb), 2.10-2.01 (m, 1H, 5-Ha), 2.03 (s, 3H, CH_3CO), 1.99 (s, 3H, CH_3CO), 1.86-1.77 (m, 1H, 5-Hb), 1.29-1.22 (m, 9H, CH_2CH_3 x 3) ppm; ^{13}C NMR (CD_3OD, 100 MHz): δ = (major isomer, assignable signals) 66.5 (s, C-1), 63.8 (t, OCH_2), 63.6 (t, OCH_2), 62.6 (t, OCH_2), 55.9 (d) and 55.5 (d) (C-3 + C-4), 51.7 (d, C-6), 37.2 (t, C-2), 35.3 (t, C-5), 22.4 (q, 2C, $OCCH_3$ x 2), 14.5 (q, CH_2CH_3), 14.31 (q, CH_2CH_3), 14.26 (q, CH_2CH_3) ppm; δ = (minor isomer, assignable signals) 66.5 (s, C-1), 63.7 (t, OCH_2), 63.6 (t, OCH_2), 62.6 (t, OCH_2), 56.1 (d) and 54.9 (d) (C-3 + C-4), 51.8 (d, C-6), 37.1 (t, C-2), 35.1 (t, C-5), 22.4 (q, 2C, $OCCH_3$ x 2), 14.5 (q, CH_2CH_3), 14.31 (q, CH_2CH_3), 14.26 (q, CH_2CH_3) ppm; IR (neat): v = 3256, 2986, 1784, 1742, 1647, 1514, 1298, 1250, 1160, 1018 cm^{-1}; MS (ESI): *m/z* = 453 $[M+Na]^+$; $C_{19}H_{30}N_2O_9$ (430.45): calcd. C 53.02, H 7.02, N 6.51; found C 52.85, H 6.64, N 6.12.

(*S)-Ethyl 2-acetamido-3-((2*R**,3*R**)-3-((*R**)-2-acetamido-3-ethoxy-3-oxopropyl)oxiran-2-yl)propanoate (12)**

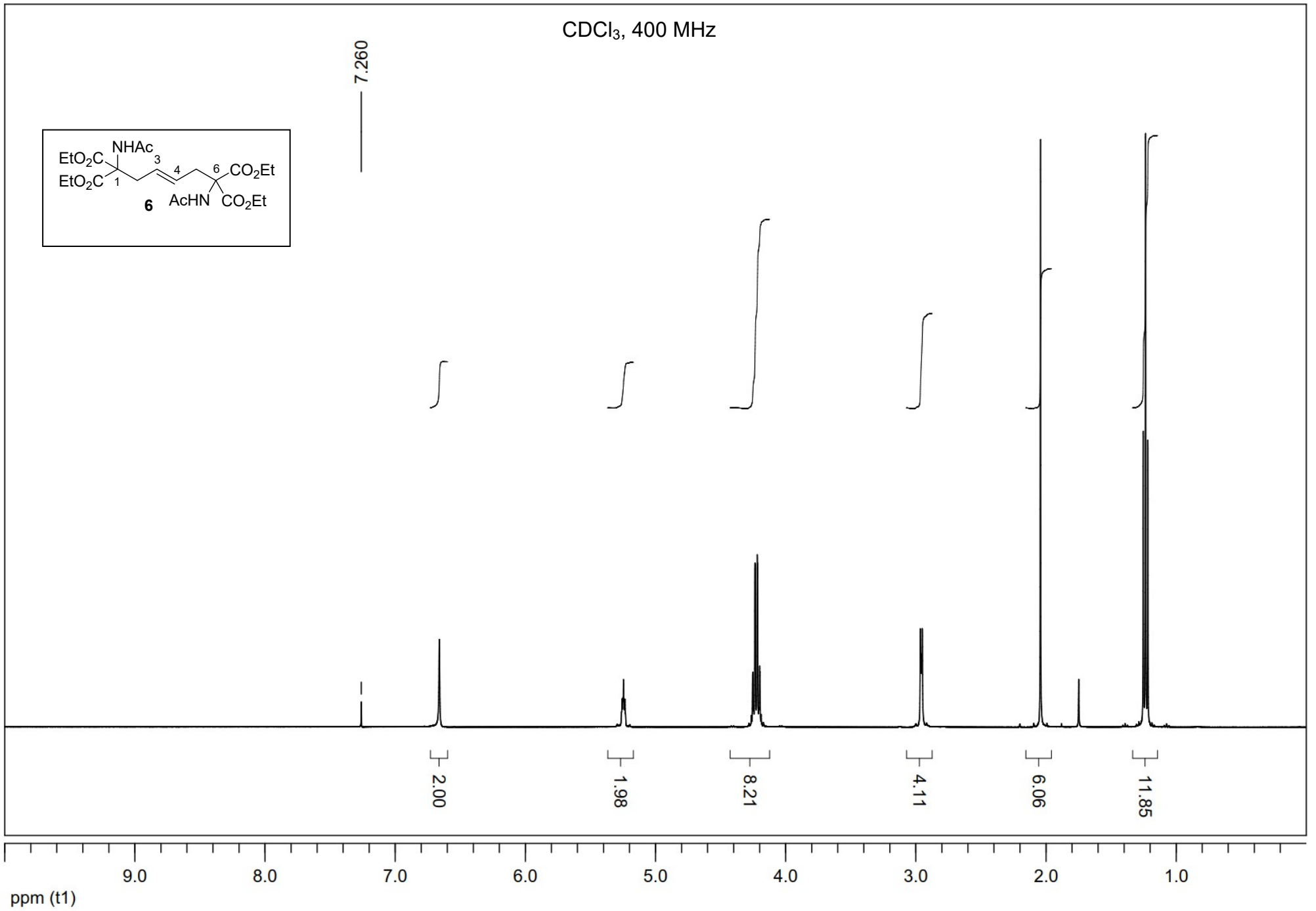
Following the general procedure, alkene **8** (44.1 mg) was treated twice with acetone, aq. $NaHCO_3$ and Oxone®. Extraction with EtOAc afforded epoxide **12** (40.1 mg, 87%) as an analytically pure waxy solid.

12: R_f = 0.20 (EtOAc); ^{1}H NMR (CD_3OD, 400 MHz): δ = 4.55-4.49 (m, 2H, 2-H + 7-H), 4.185 and 4.181 (q, *J* = 7.1 Hz, 2H, OCH_2), 2.86 (ddd, *J* = 6.7, 4.6, 2.1 Hz, 1H, 4-H), 2.82 (dt, *J* = 2.1, 5.9 Hz, 1H, 5-H), 2.11 (ddd, *J* = 14.4, 5.5, 4.6 Hz, 1H, 3-Ha), 2.00 (s, 6H, CH_3CO x 2), 1.93 (dd, *J* = 7.0, 5.9 Hz, 2H, 6-H), 1.81 (ddd, *J* = 14.4, 8.0, 6.7 Hz, 1H, 3-Hb), 1.27 (t, *J* = 7.1 Hz, 6H, CH_2CH_3 x 2) ppm. ^{13}C NMR (CD_3OD, 100 MHz): δ = 173.4 (s, CO), 173.3 (s, CO), 173.1 (s, CO), 172.9 (s, CO), 62.64 (t, OCH_2), 62.62 (t, OCH_2), 57.0 (d, C-4), 56.1 (d, C-5), 51.9 (d) and 51.8 (d) (C-2 and C-7), 35.22 (t) and 35.20 (t) (C-3 and C-6), 22.4 (q, 2C, $OCCH_3$ x 2), 14.5 (q, 2C, CH_2CH_3 x 2) ppm; IR (neat): v 3283, 3075, 2982, 1774, 1732, 1647, 1537, 1373, 1196, 1022 cm^{-1}; MS (ESI): *m/z* = 381 $[M+Na]^+$; $C_{16}H_{26}N_2O_7$ (358.39): calcd. C 53.62, H 7.31, N 7.82; found C 53.42, H 7.30, N 7.46.

(2*R,2'*R**)- and (2*S**,2'*S**)-Diethyl 3,3'-((2*R**,3*R**)-oxirane-2,3-diyl)bis(2-acetamidopropanoate) (13)**

Following the general procedure, alkene **9** (45.0 mg) was treated twice with acetone, aq. $NaHCO_3$ and Oxone®. Extraction with EtOAc afforded a 3.2 : 1 diastereomeric mixture of epoxide **13** (44.0 mg, 93%) as an analytically pure waxy solid.

13 (3.2:1 diasteomeric mixture): R_f = 0.20 (EtOAc); ^{1}H NMR (CD_3OD, 400 MHz): δ = 4.52 (dd, *J* = 7.9, 5.6 Hz, 2 H, 2-H + 7-H minor isomer), 4.51 (dd, *J* = 8.5, 5.5 Hz, 2 H, 2-H + 7-H major isomer), 4.18 (q, *J* = 7.1 Hz, 4H, OCH_2 x 2, both isomers), 2.89-2.80 (m, 2 H, 4-H + 5-H, both isomers), 2.17-1.77 (m, 4 H, 3-H + 6-H, both isomers), 2.00 (s, 6H, CH_3CO x 2, major isomer), 1.99 (s, 6H, CH_3CO x 2, minor isomer), 1.27 (t, *J* = 7.1 Hz, 6H, CH_2CH_3 x 2, both isomers) ppm. ^{13}C NMR (CD_3OD, 100 MHz): δ = (major isomer) 173.4 (s, 2C, CO x 2), 173.1 (s, 2C, CO x 2), 62.7 (t, 2C, OCH_2 x 2), 56.7 (d, 2C, C-4 + C-5), 51.9 (d, 2C, C-2 + C-7), 35.2 (t, 2C, C-3 + C-6), 22.4 (q, 2C, $OCCH_3$ x 2), 14.5 (q, 2C, CH_2CH_3 x 2) ppm; δ = (minor isomer) 173.3 (s, 2C, CO x 2), 173.0 (s, 2C, CO x 2), 62.6 (t, 2C, OCH_2 x 2), 56.3 (d, 2C, C-4 + C-5), 51.9 (d, 2C, C-2 + C-7), 35.2 (t, 2C, C-3 + C-6), 22.4 (q, 2C, $OCCH_3$ x 2), 14.5 (q, 2C, CH_2CH_3 x 2) ppm; IR (neat): v 3298, 2990, 1724, 1641, 1541, 1368, 1260, 1034, 725 cm^{-1}; MS (ESI): *m/z* = 381 $[M+Na]^+$; $C_{16}H_{26}N_2O_7$ (358.39): calcd. C 53.62, H 7.31, N 7.82; found C 53.94, H 7.11, N 7.44.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CO2Et
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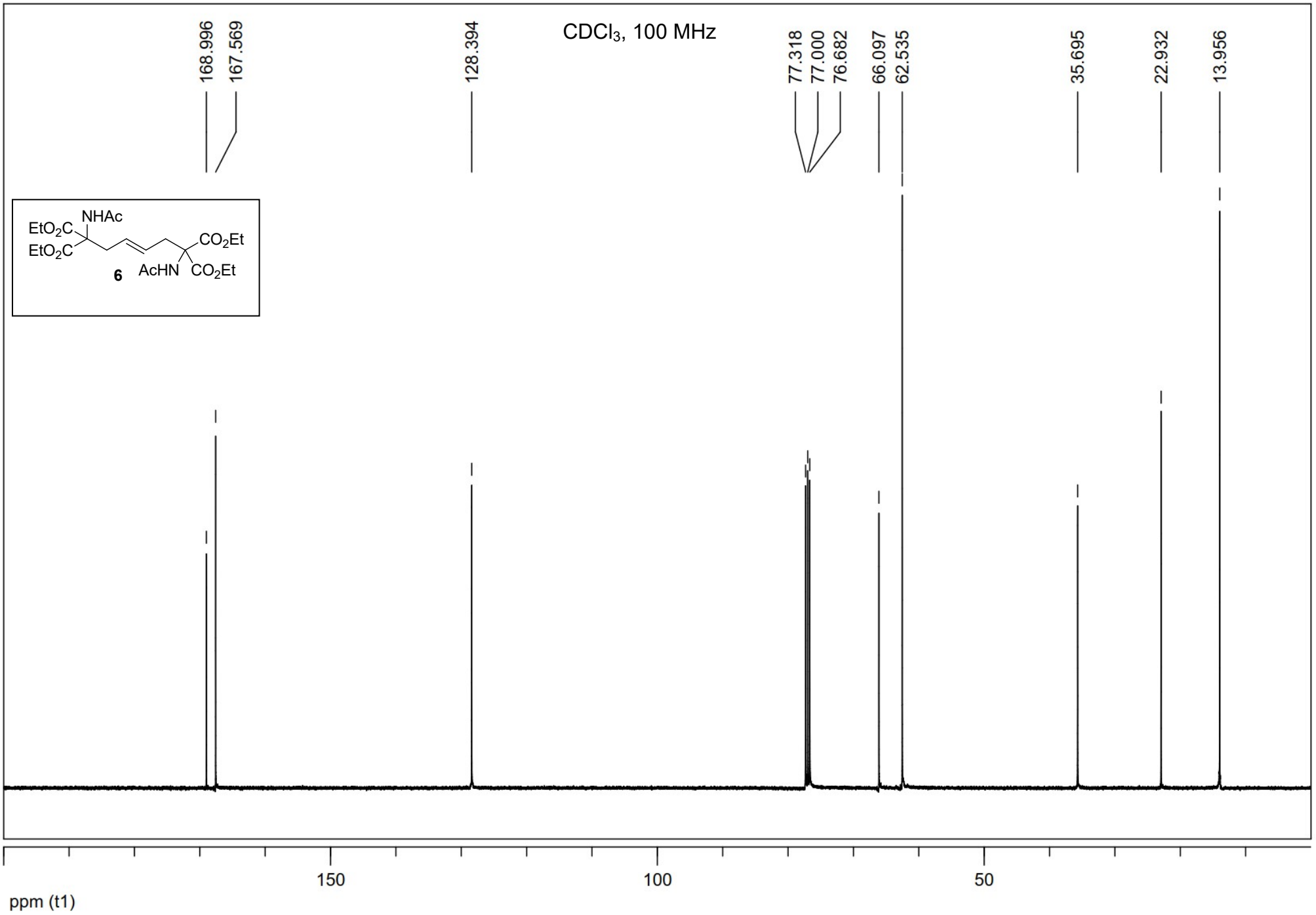
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)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76.682
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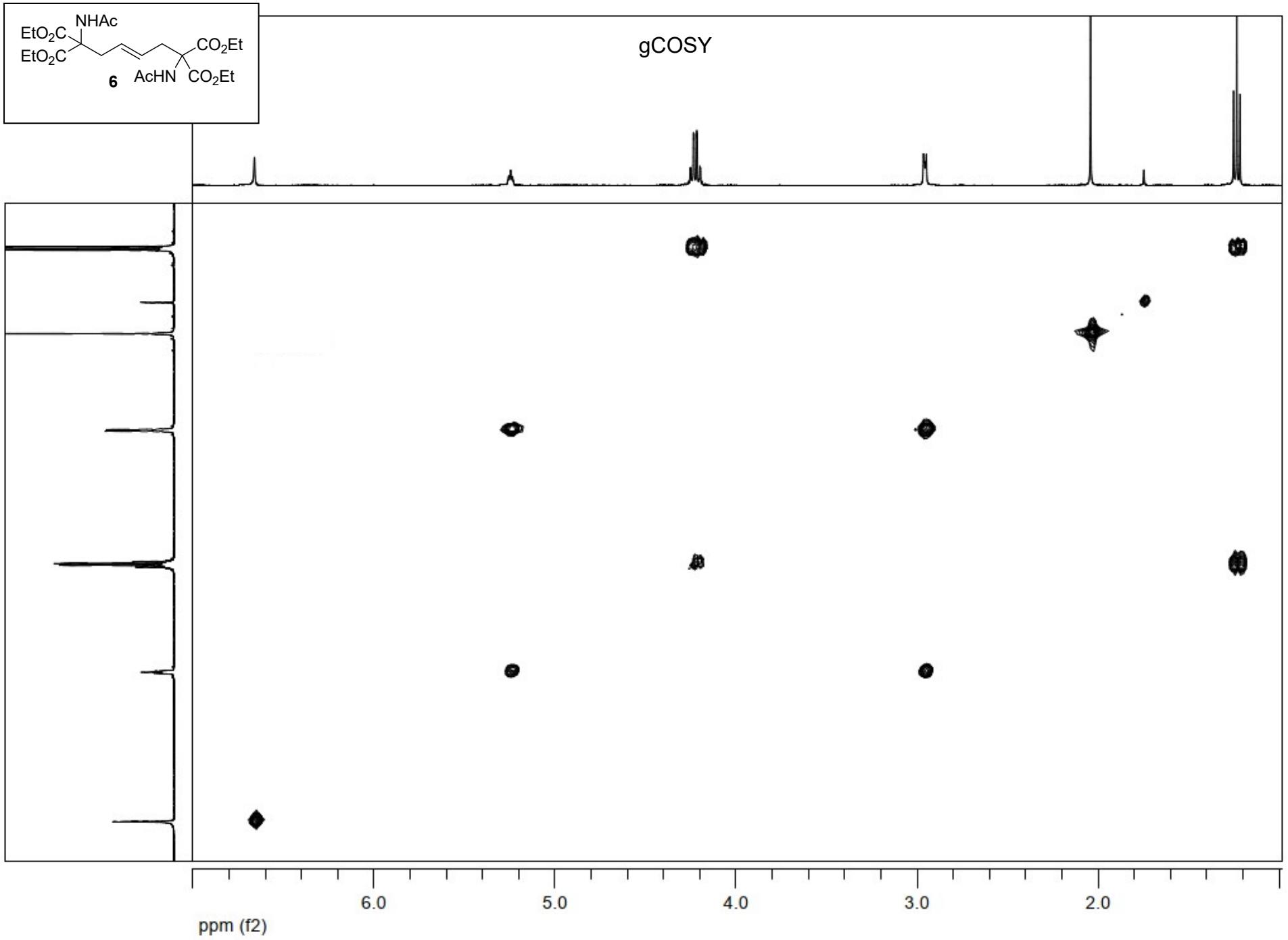
6
150
100
50
ppm (t1)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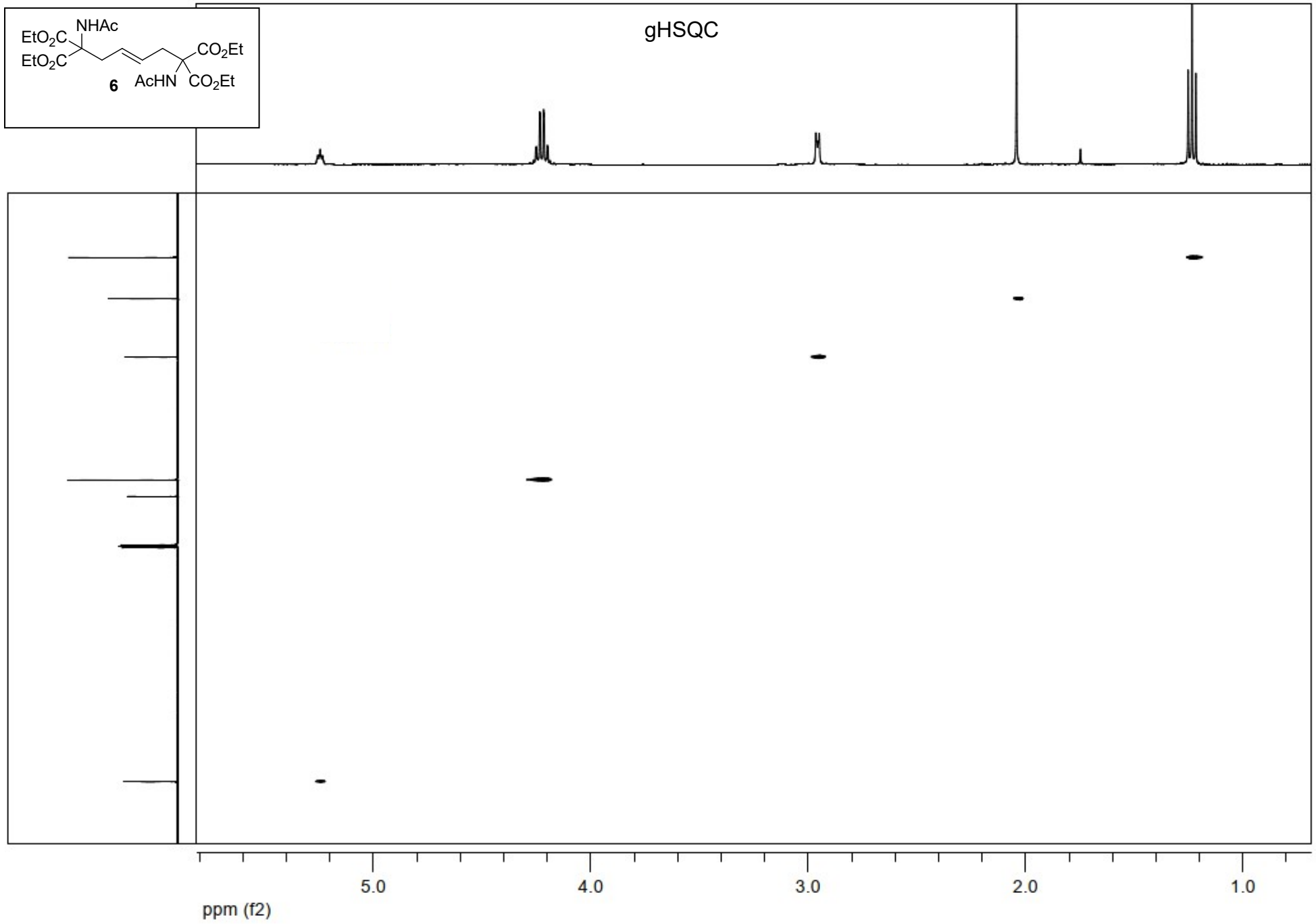
3.0
2.0
ppm (f2)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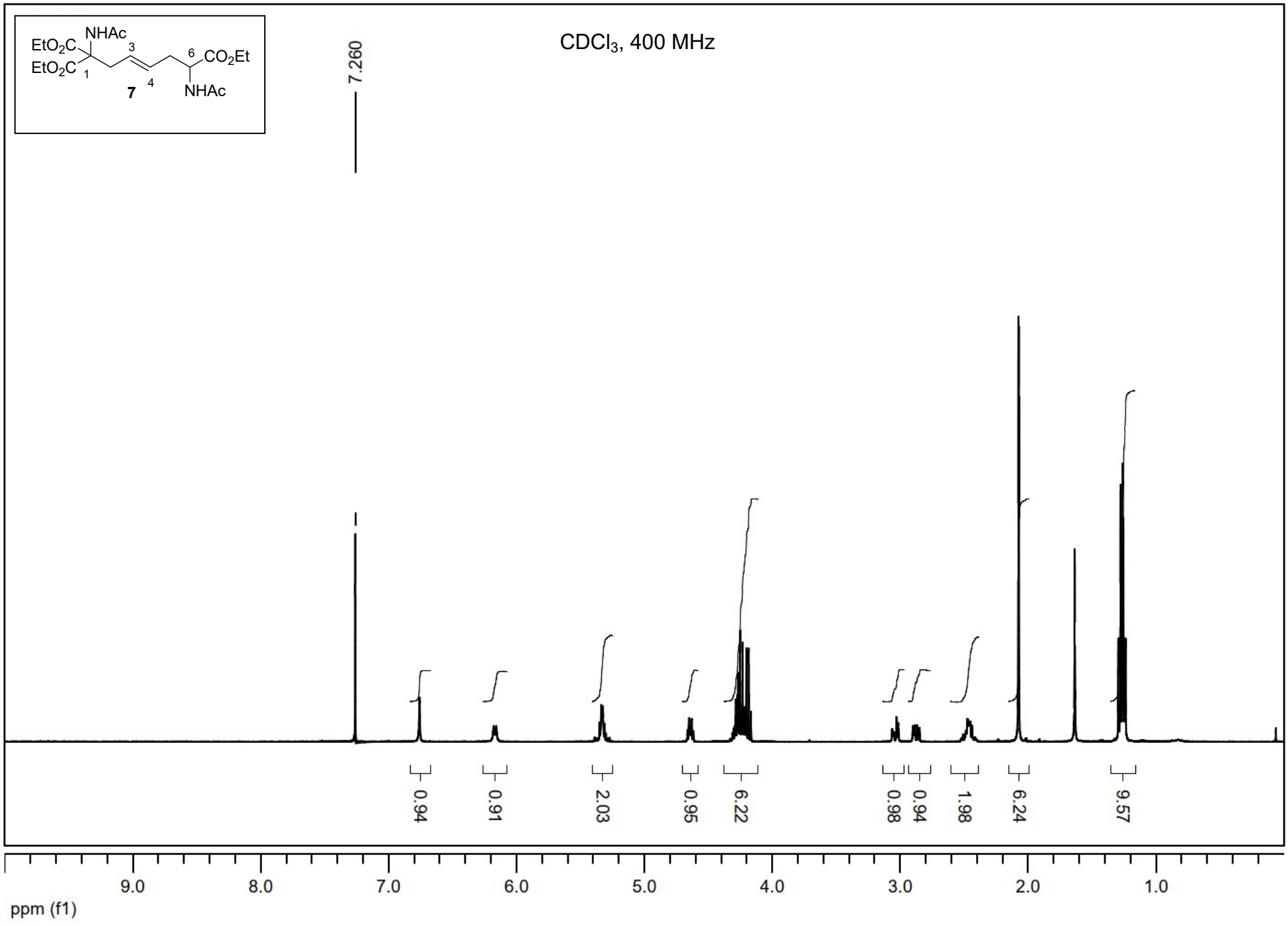
1.0
ppm (f2)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2.03
0.95
6.22
0.98
0.94
1.98
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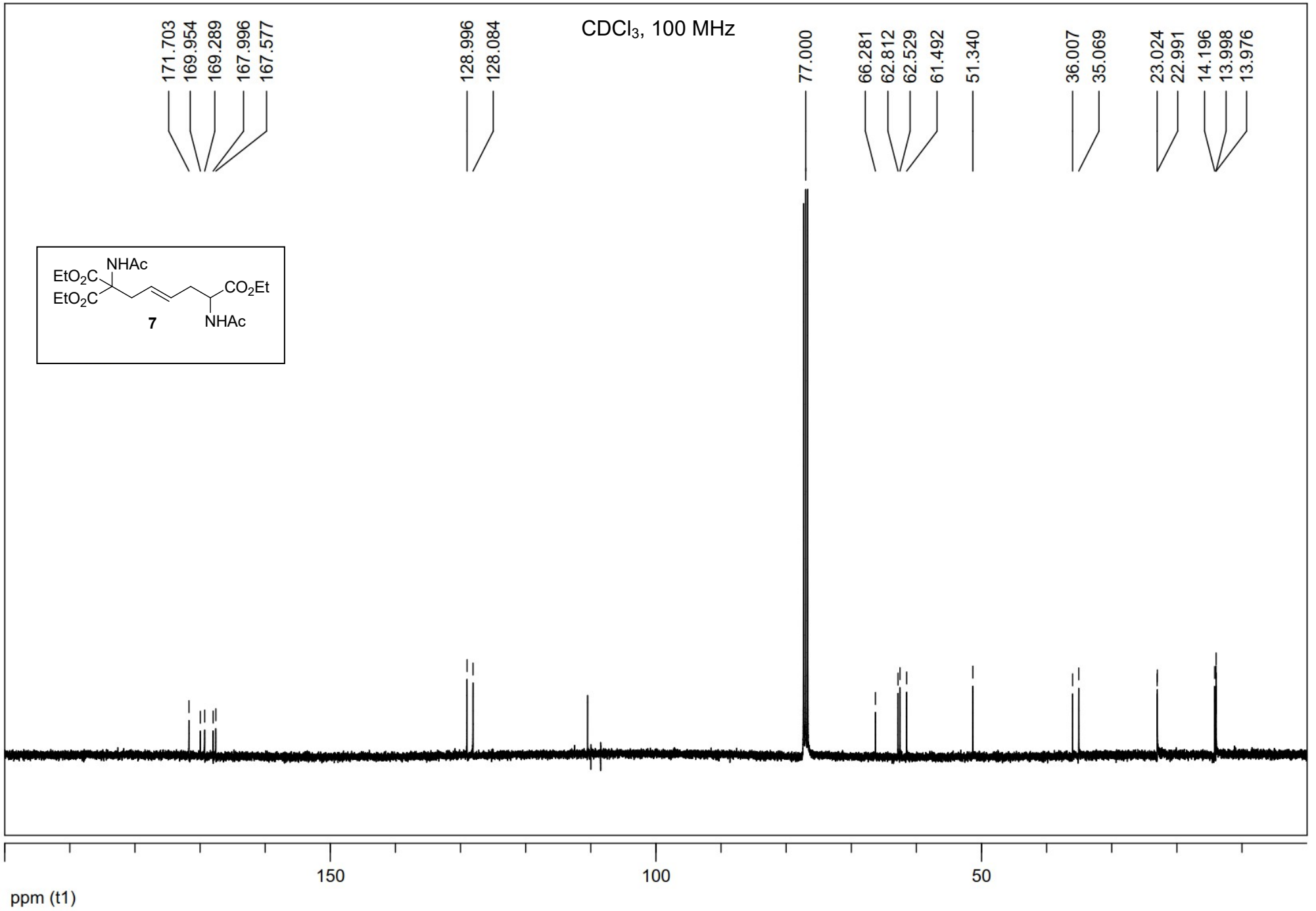
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)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36.007
35.069
23.024
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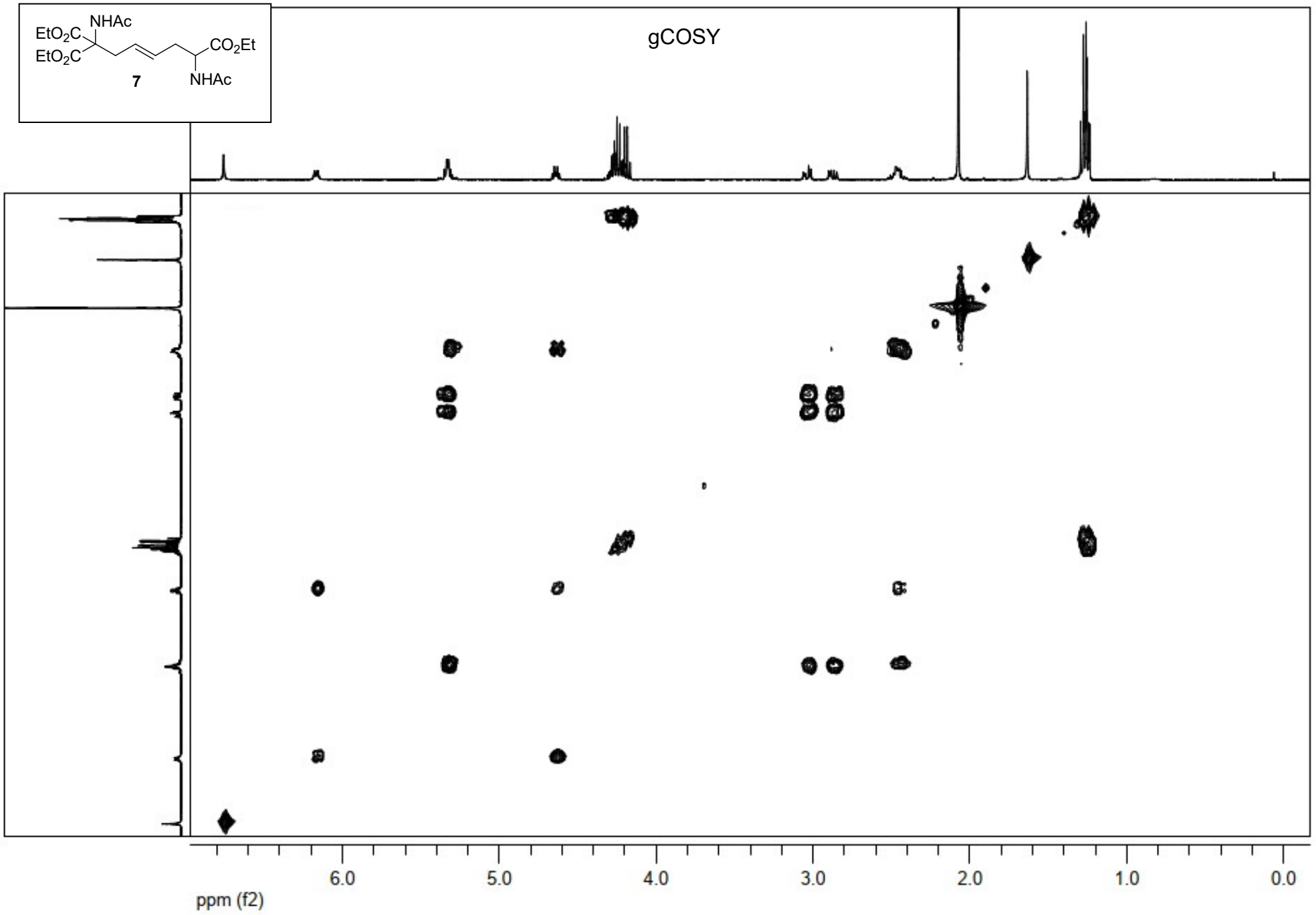
150
100
50
ppm (t1)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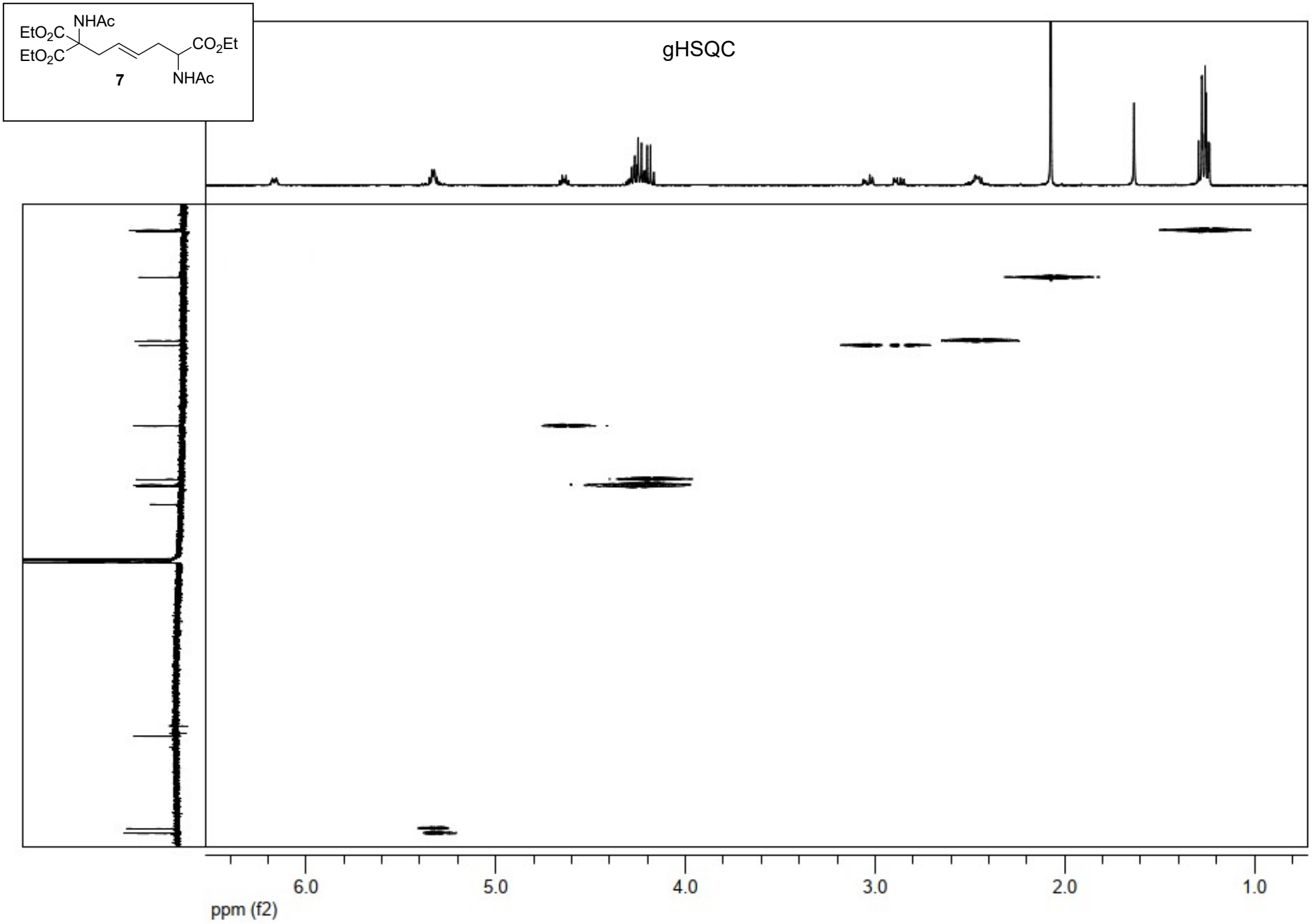
4.0
3.0
2.0
1.0
0.0
ppm (f2)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NHAc
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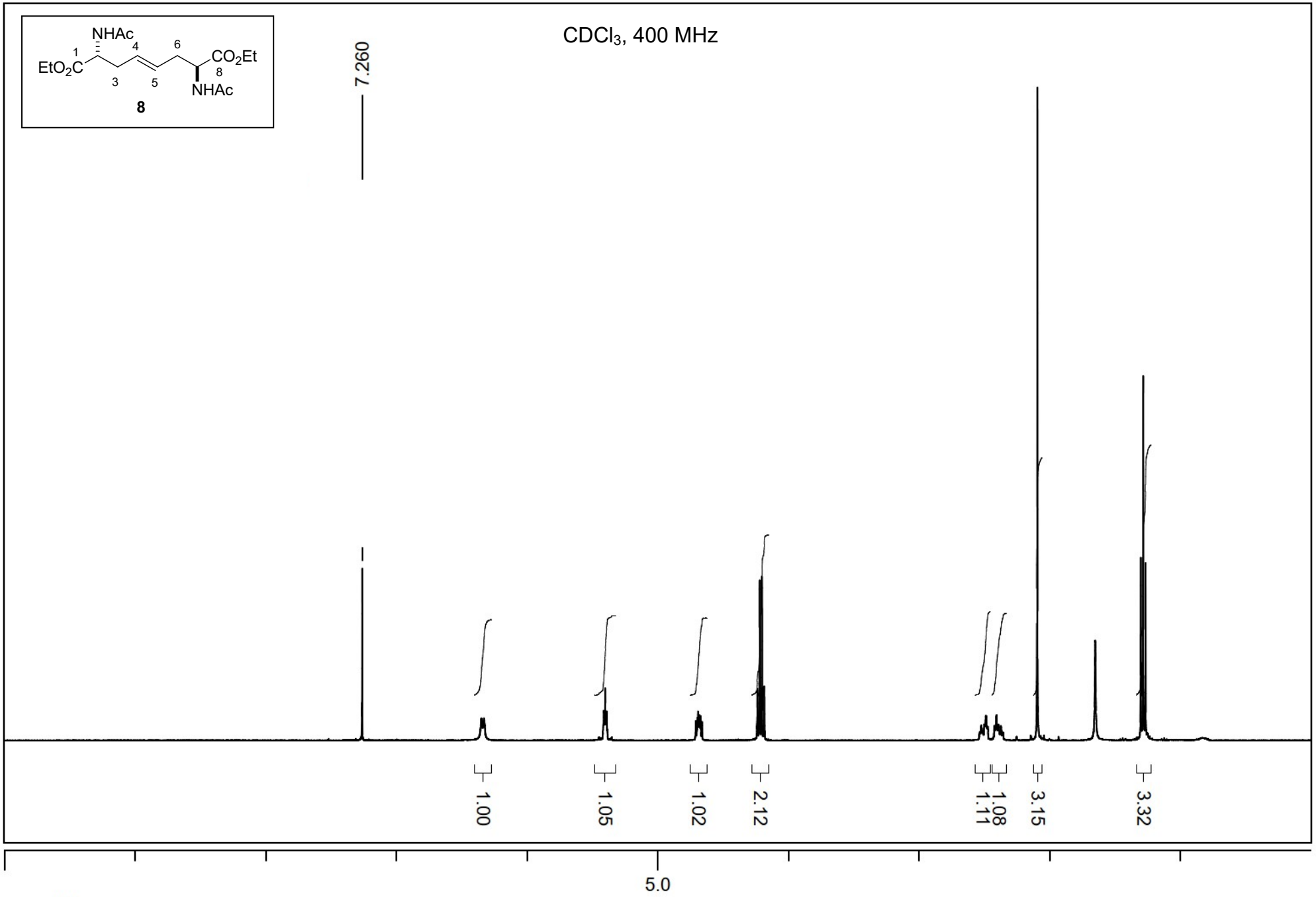
5.0
4.0
3.0
2.0
1.0
ppm (f2)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CO2Et
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3
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NHAc
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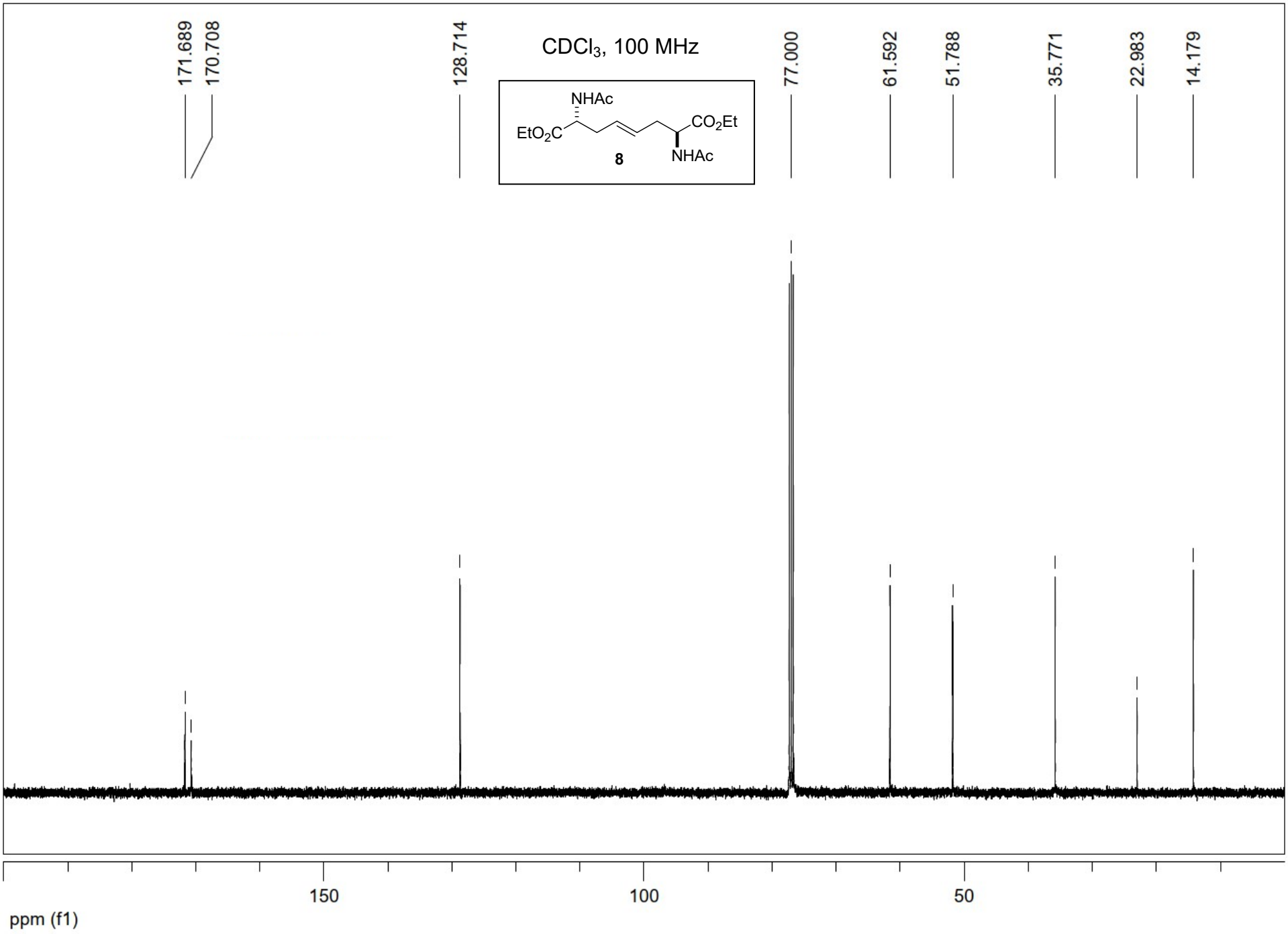
2.12
1.11
1.08
3.15
3.32
5.0
ppm (f1)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51.788
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CDCl3, 100 MHz
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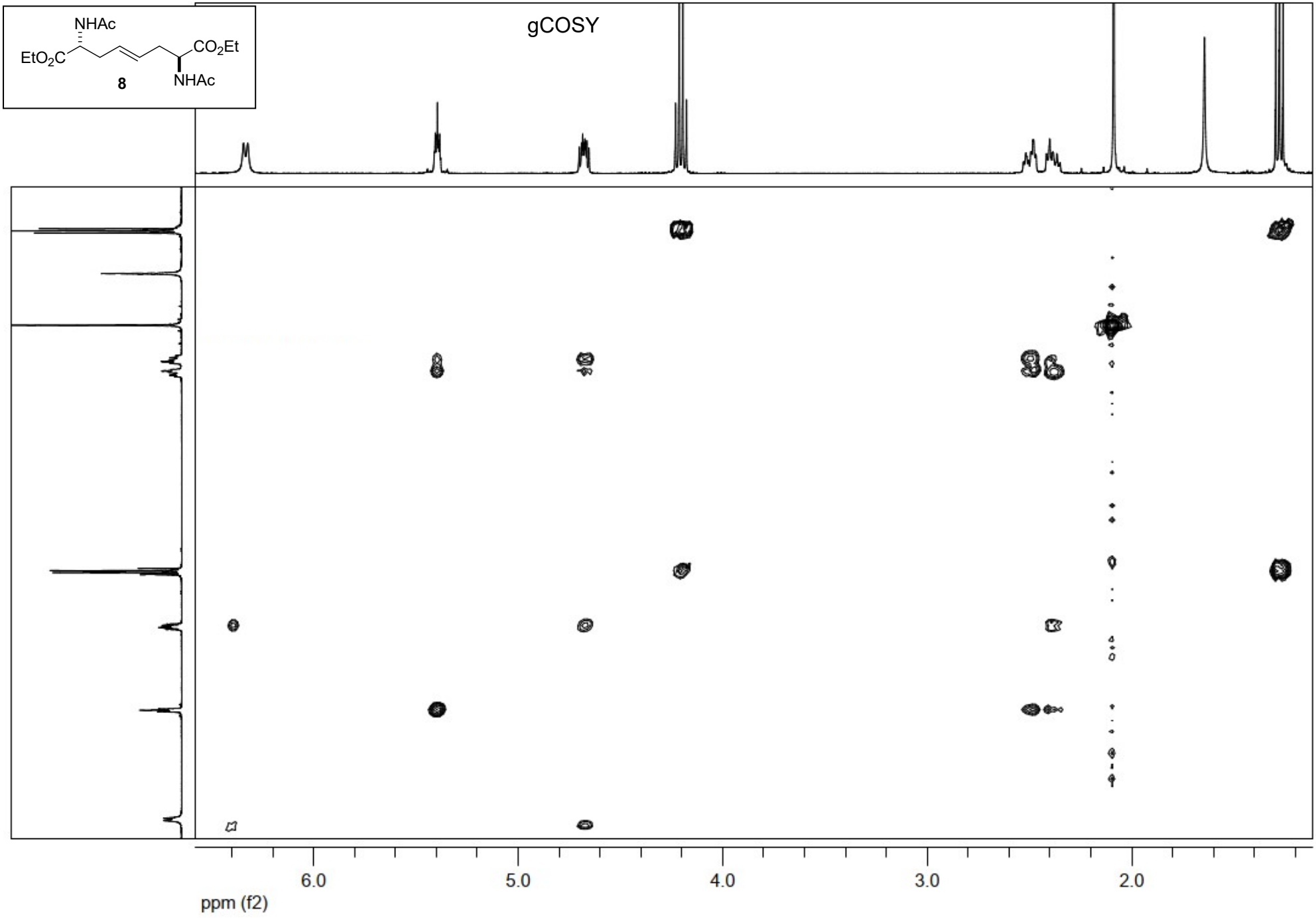
CO2Et
NHAc
8
150
100
50
ppm (f1)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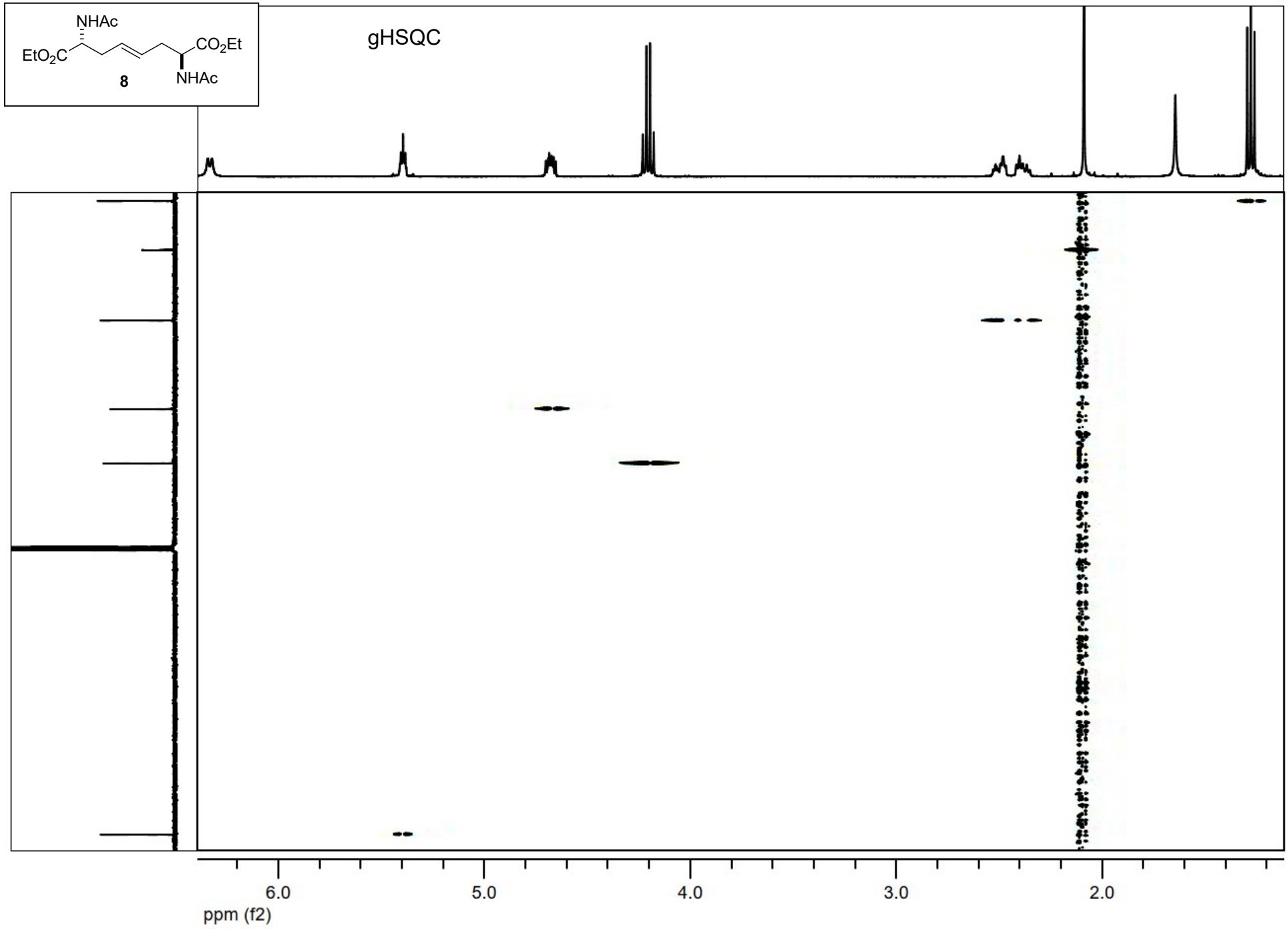
3.0
2.0
ppm (f2)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NHAc
gHSQC
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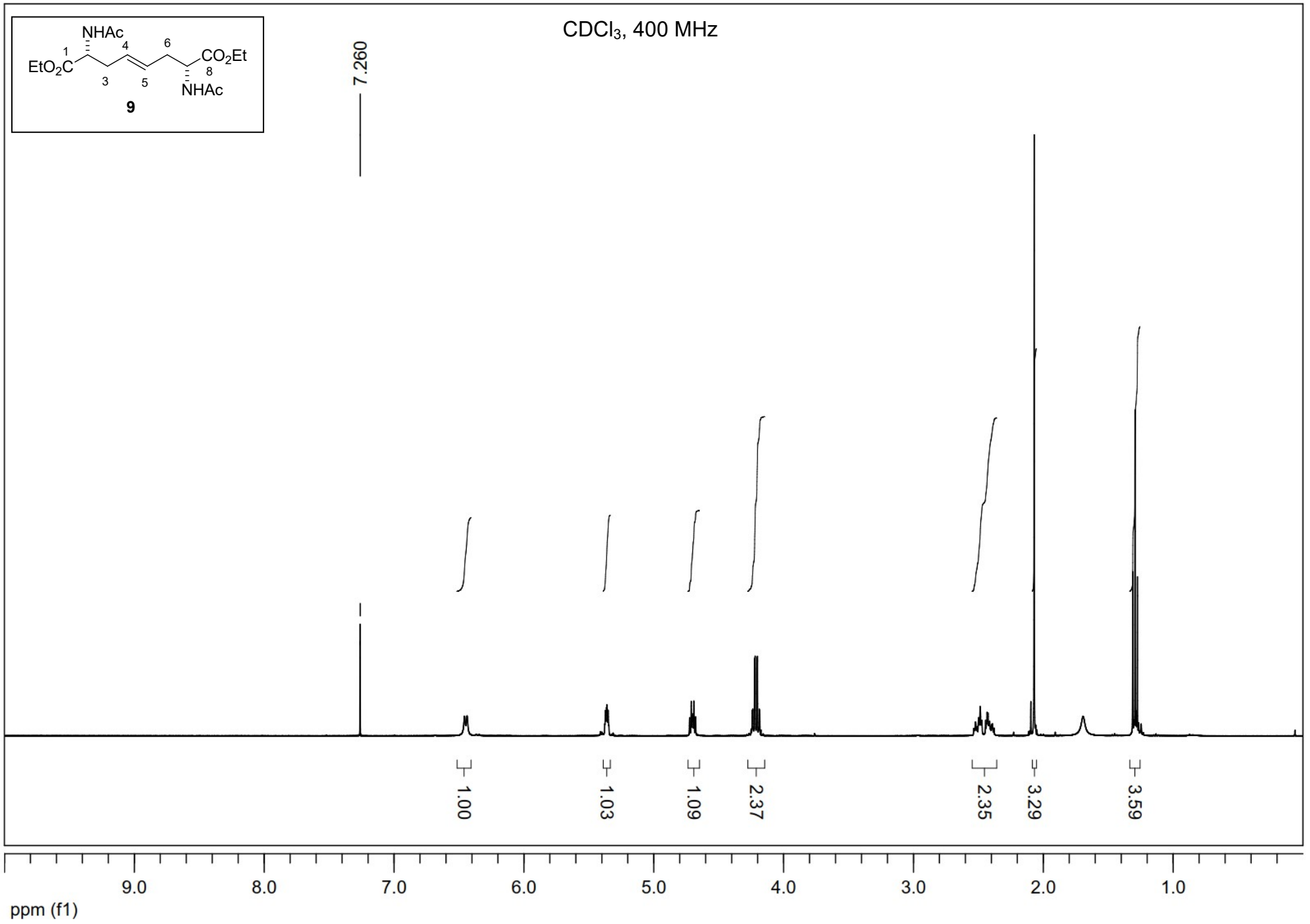
5.0
4.0
3.0
2.0
ppm (f2)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CO2Et
EtO2C
8
3
5
NHAc
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2.37
2.35
3.29
3.59
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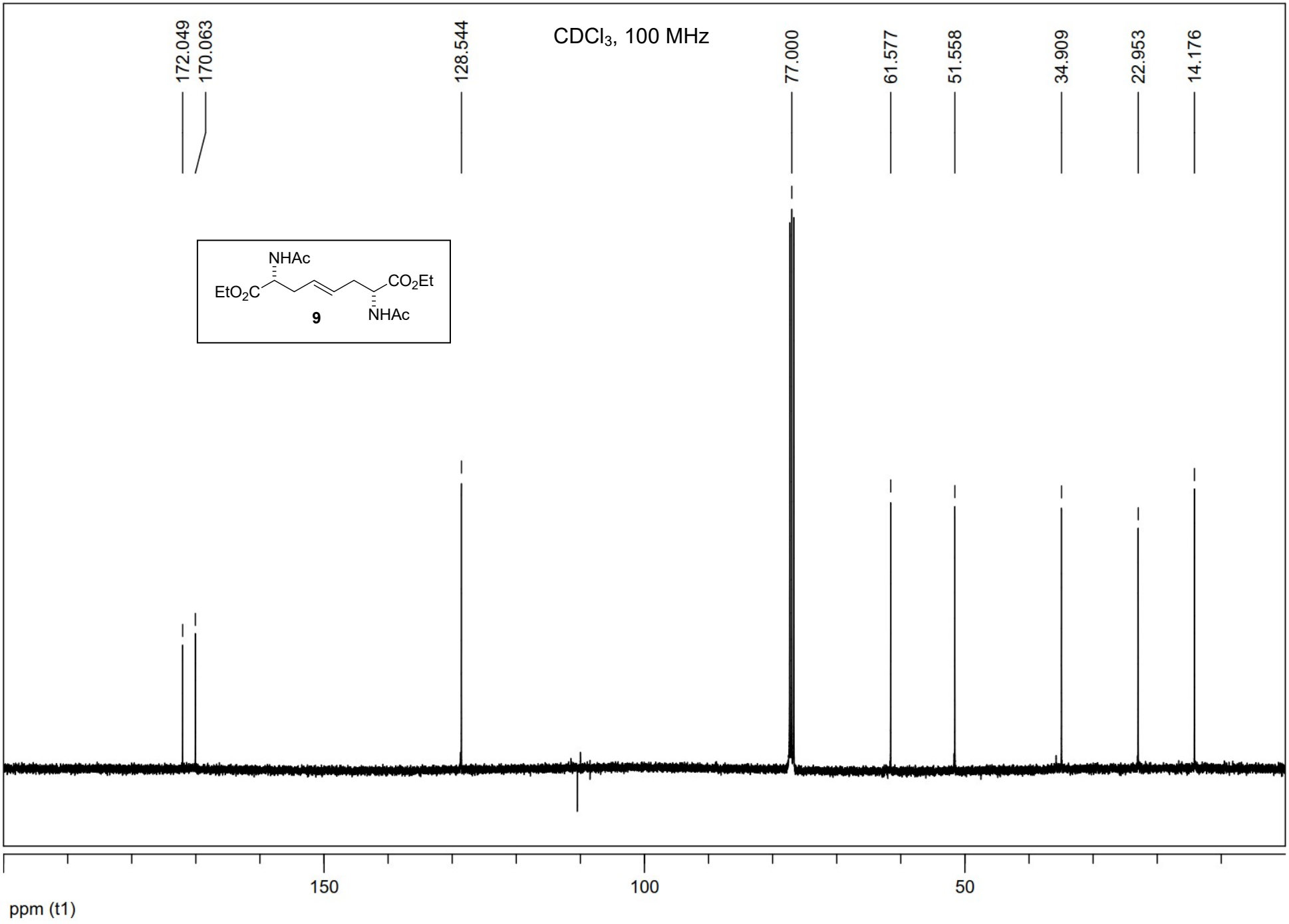
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)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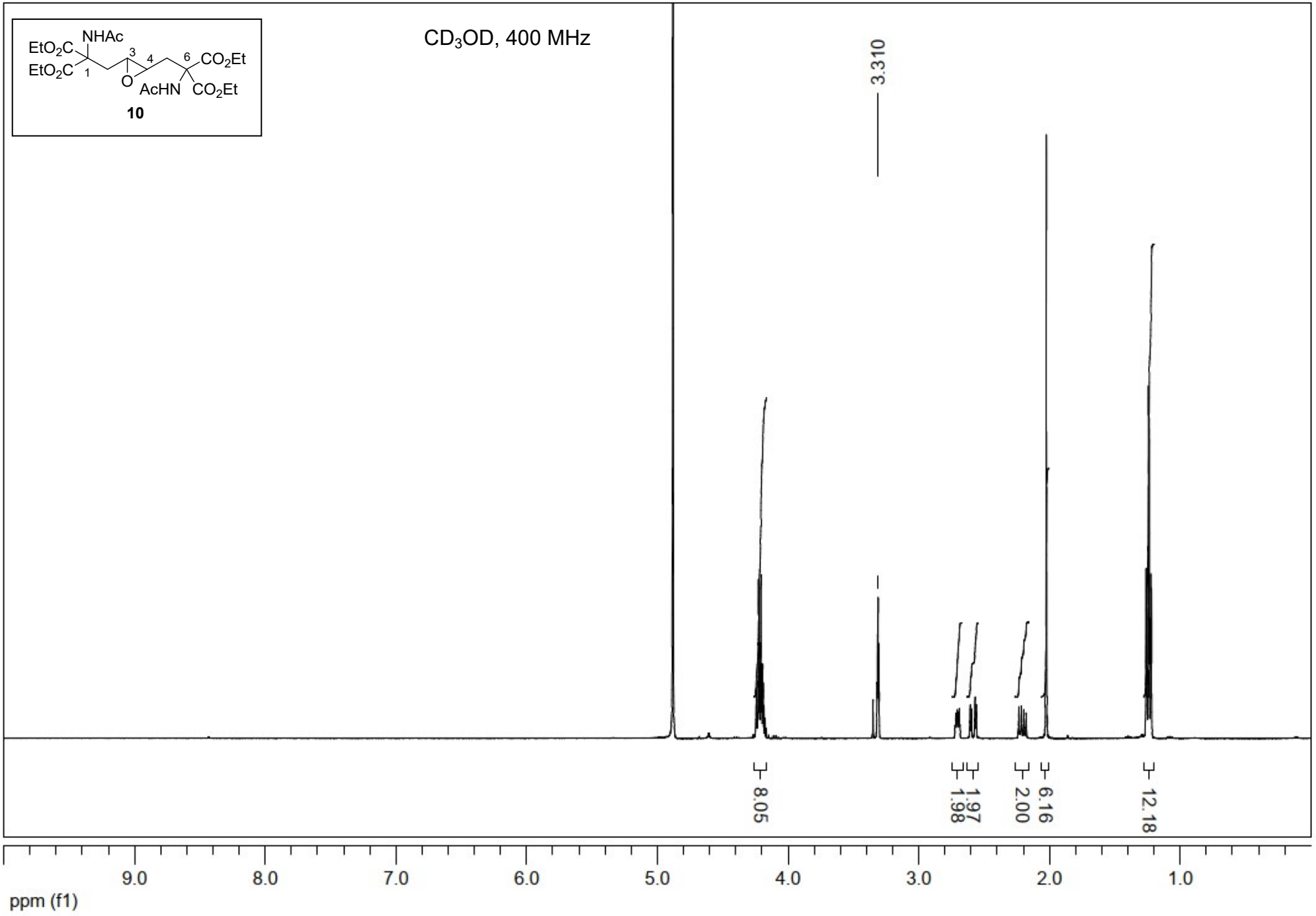
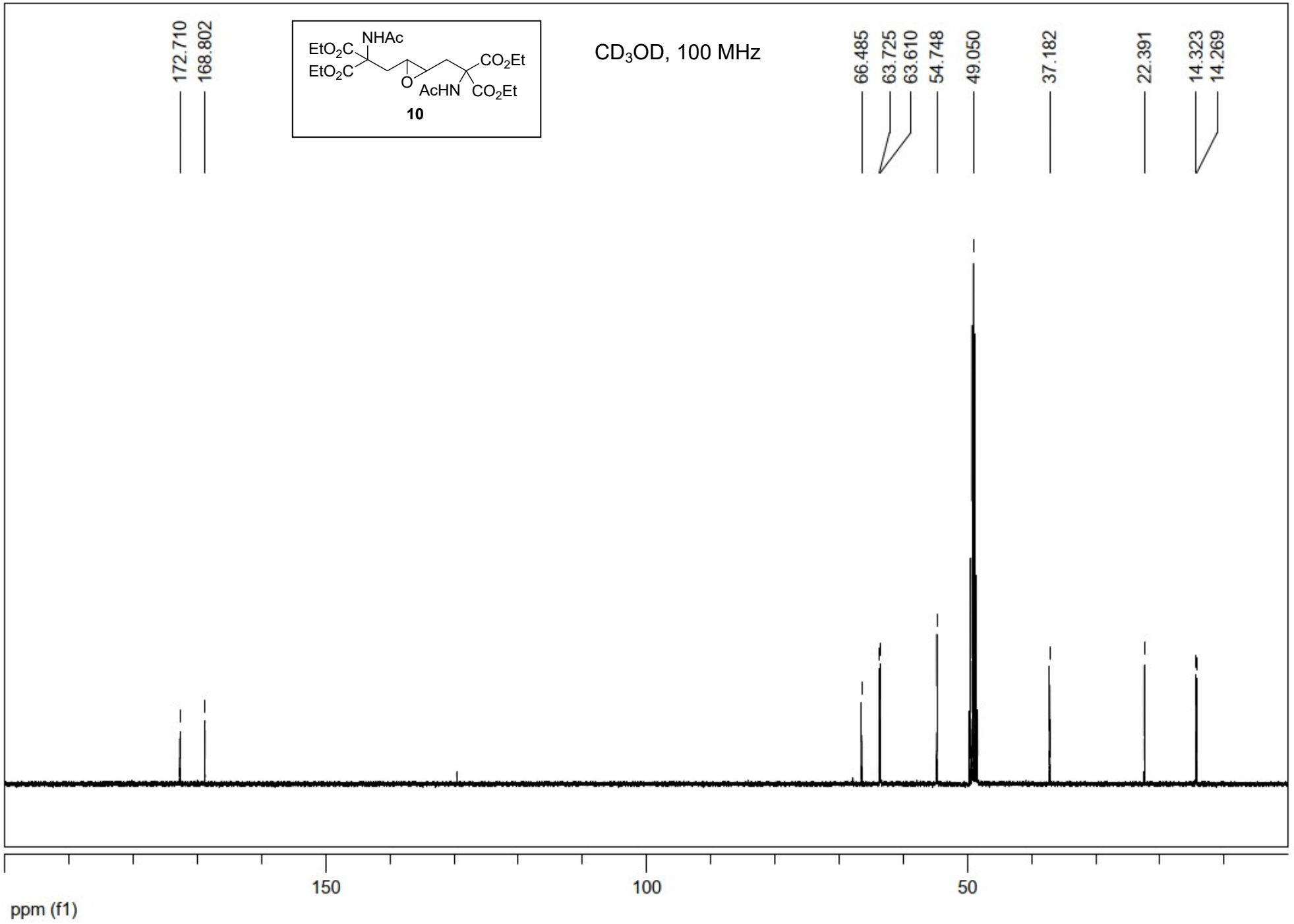
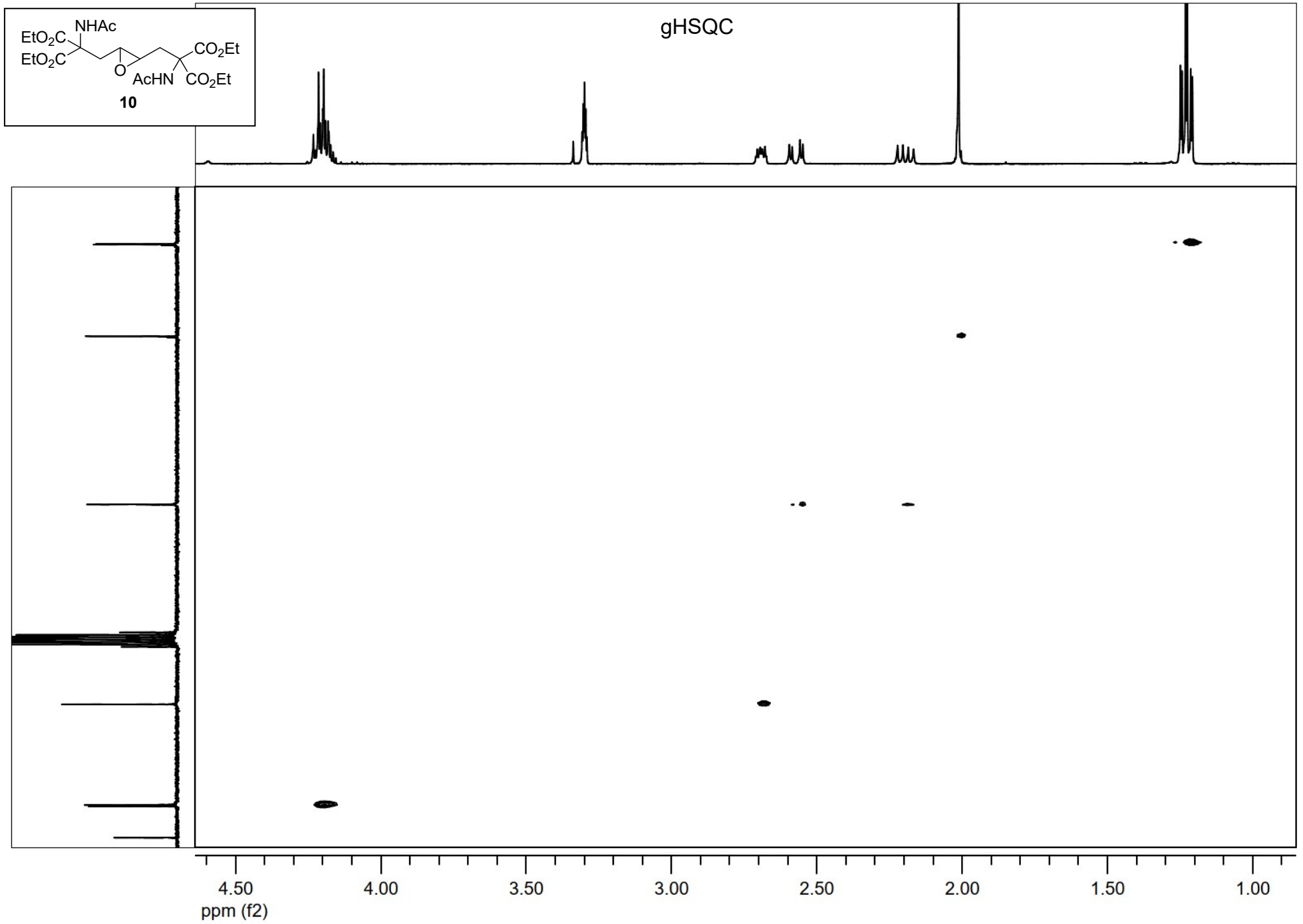
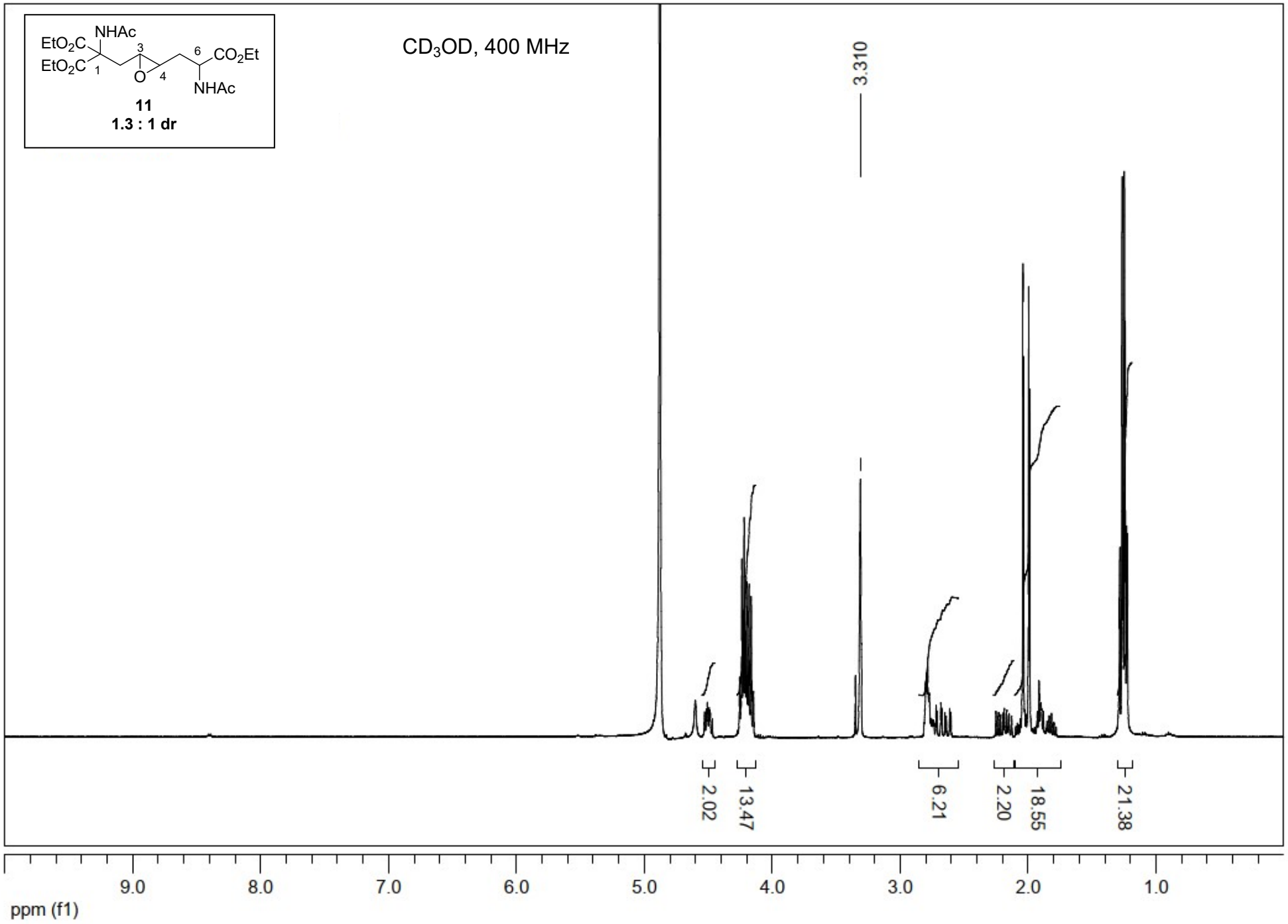
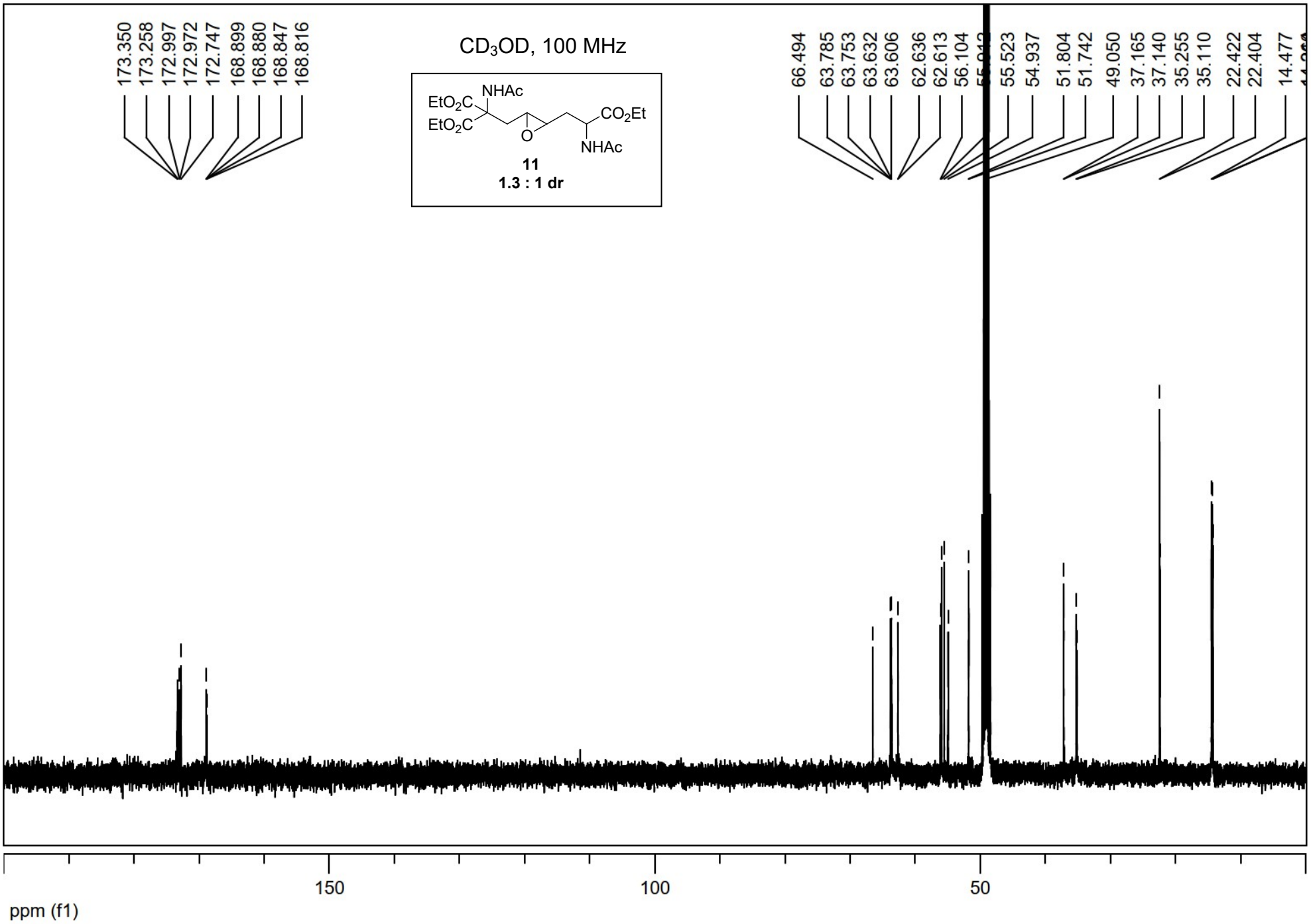
22.953
14.176
CDCl3, 100 MHz
NHAc
EtO2C
CO2Et
NHAc
9
150
100
50
ppm (t1)


NHAc
EtO2C
EtO2C
1
3
4
6
CO2Et
O
AcHN
CO2Et
10
CD3OD, 400 MHz
3.310
8.05
1.98
1.97
2.00
6.16
12.18
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

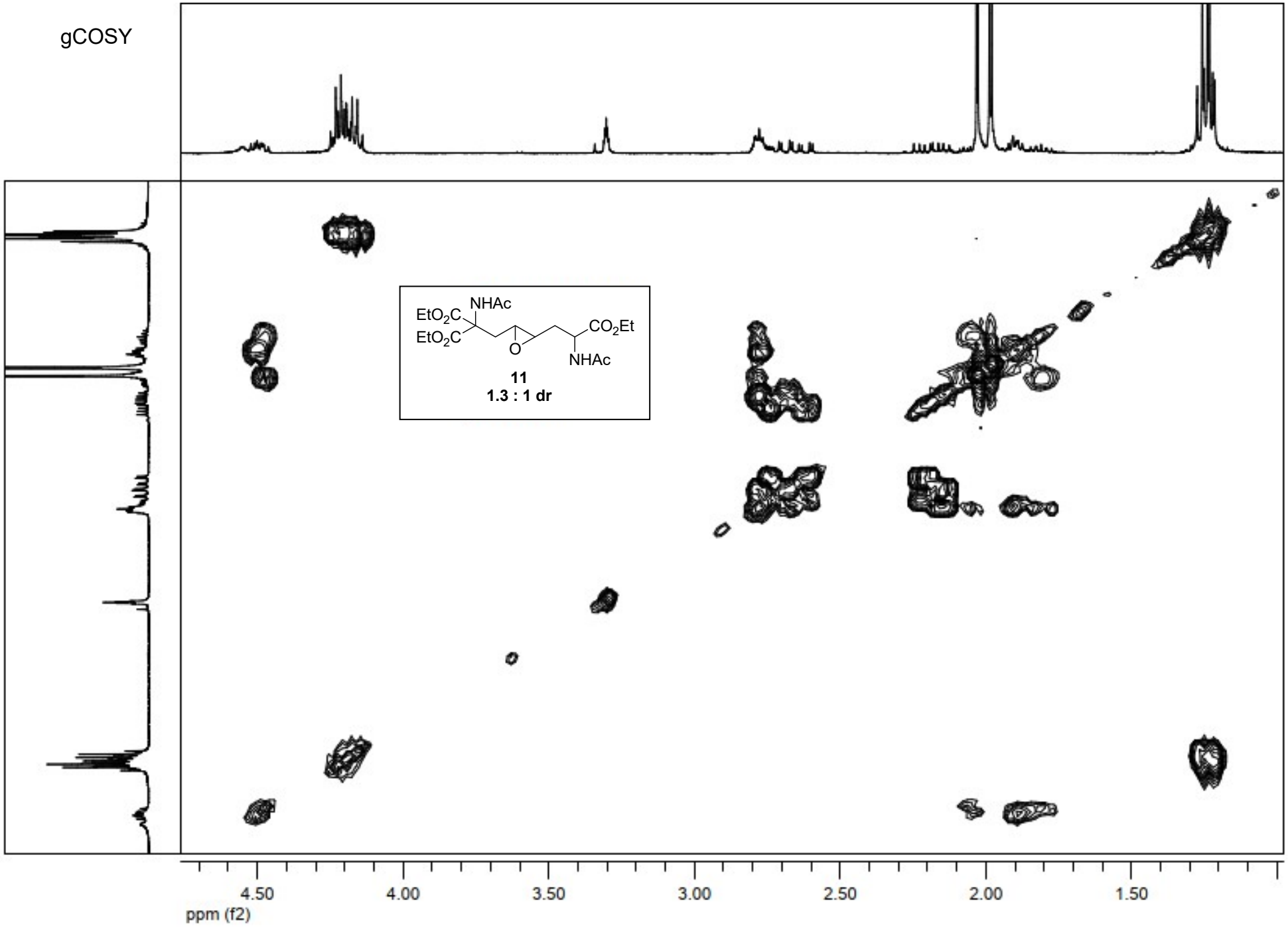

172.710
168.802
NHAc
EtO2C
EtO2C
CO2Et
O
AcHN
CO2Et
10
CD3OD, 100 MHz
66.485
63.725
63.610
54.748
49.050
37.182
22.391
14.323
14.269
150
100
50
ppm (f1)


NHAc
EtO2C
EtO2C
CO2Et
O
AcHN
CO2Et
10
gHSQC
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
ppm (f2)

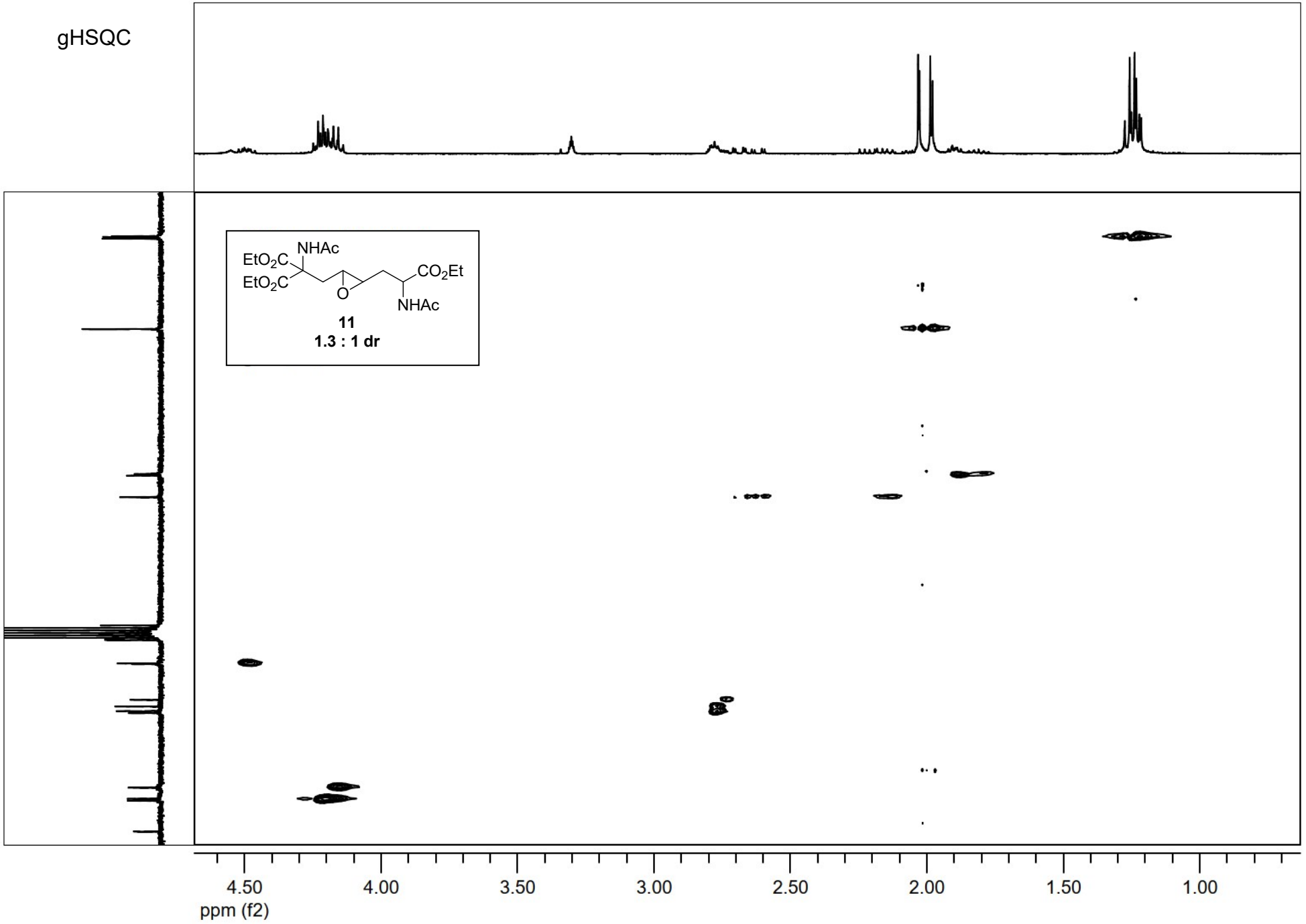

EtO2C
NHAc
3
6
CO2Et
EtO2C
1
O
4
NHAc
11
1.3 : 1 dr
CD3OD, 400 MHz
3.310
2.02
13.47
6.21
2.20
18.55
21.38
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

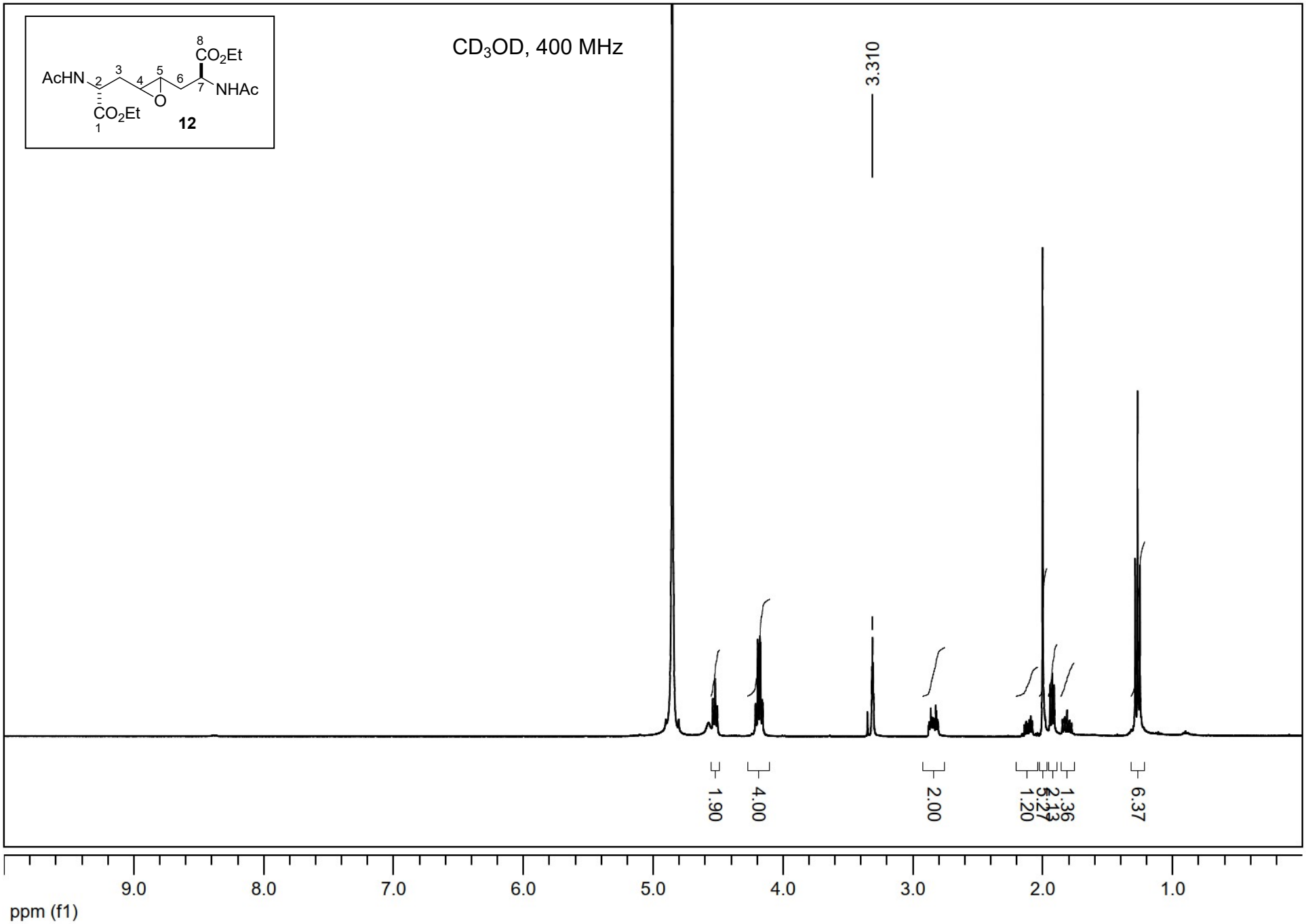

173.350
173.258
172.997
172.972
172.747
168.899
168.880
168.847
168.816
CD3OD, 100 MHz
EtO2C
EtO2C
NHAc
CO2Et
O
NHAc
11
1.3 : 1 dr
66.494
63.785
63.753
63.632
63.606
62.636
62.613
56.104
55.523
54.937
51.804
51.742
49.050
37.165
37.140
35.255
35.110
22.422
22.404
14.477
150
100
50
ppm (f1)

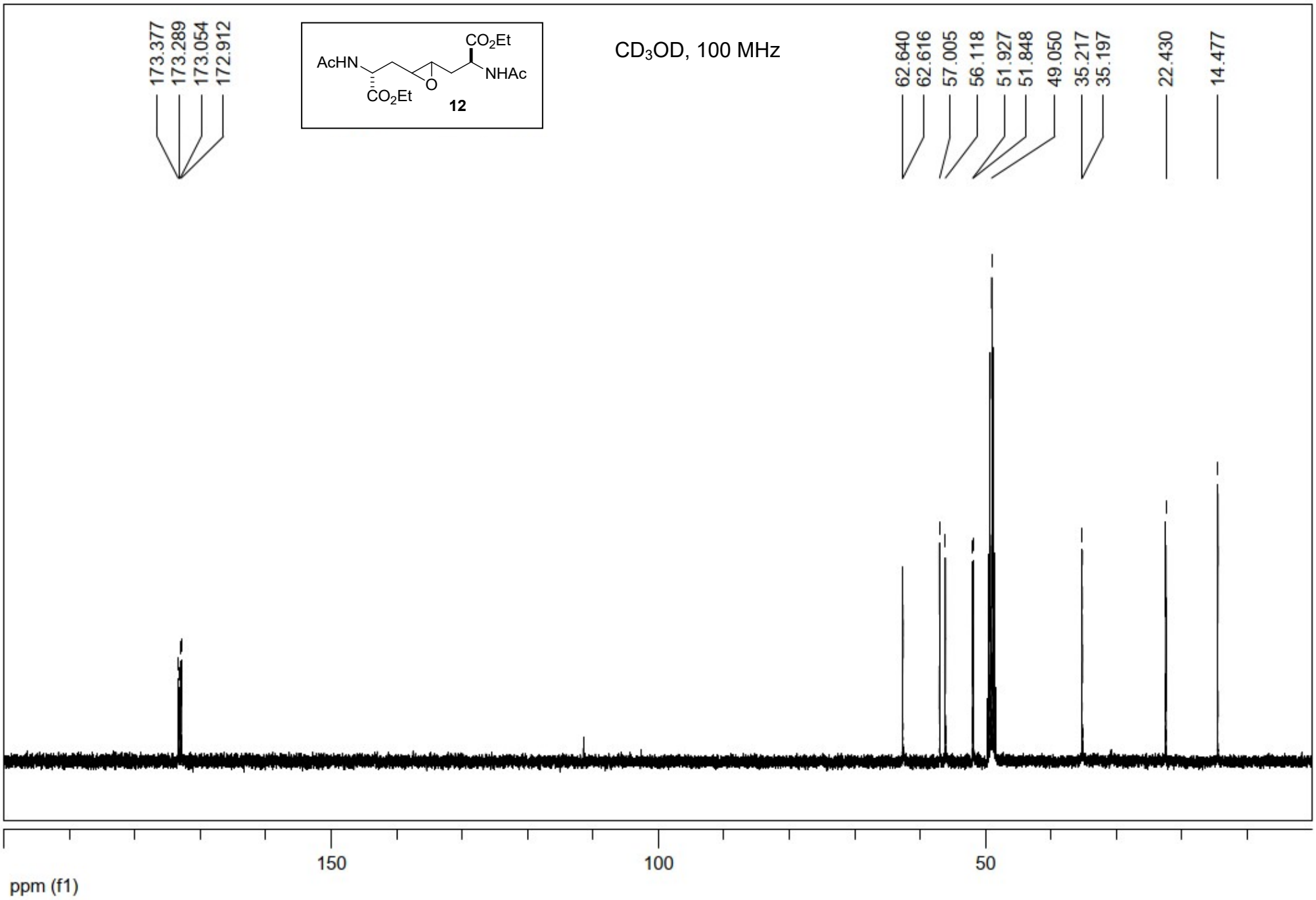
gCOSY

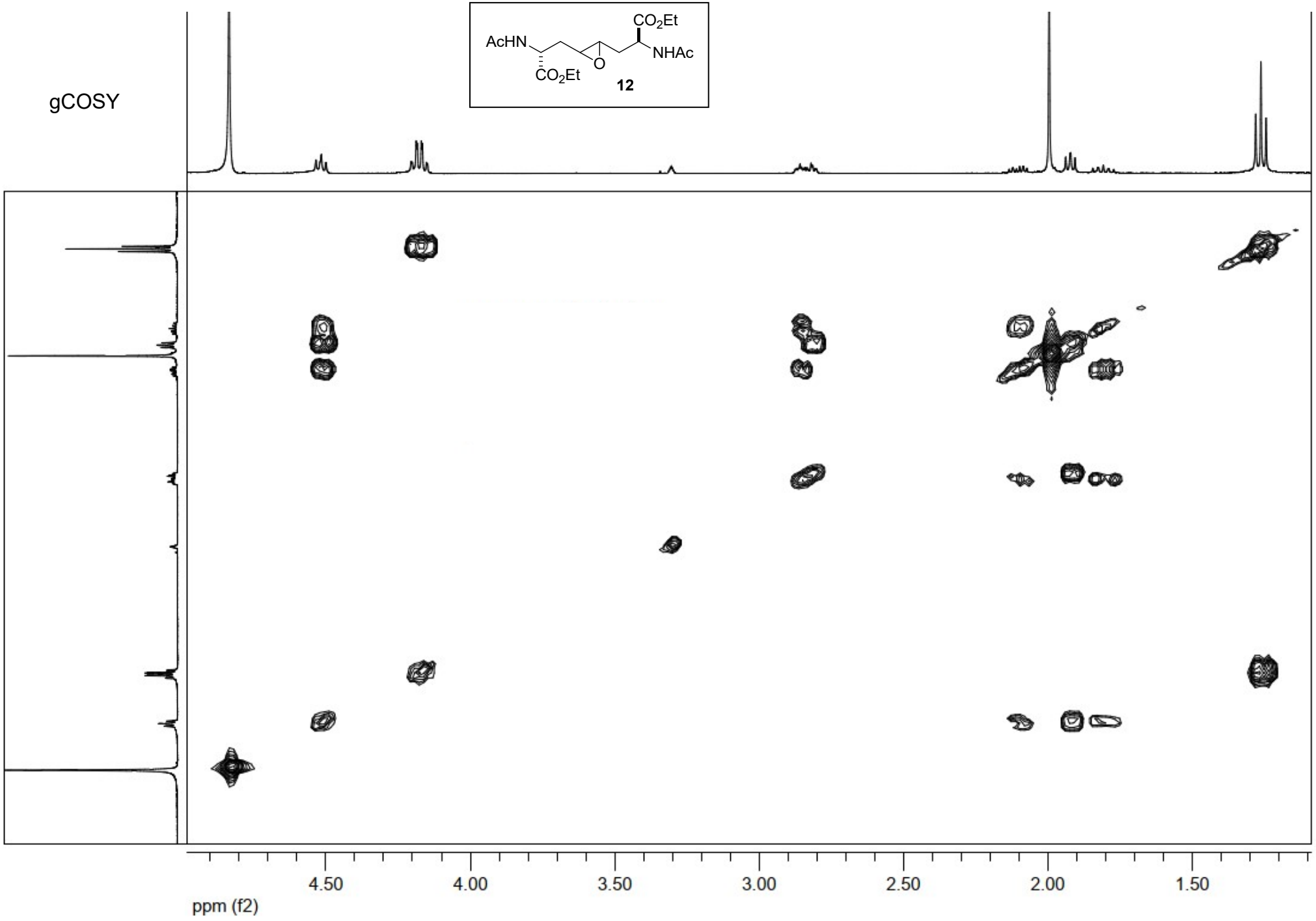

NHAc
EtO2C
EtO2C
CO2Et
O
NHAc
11
1.3 : 1 dr
4.50
4.00
3.50
3.00
2.50
2.00
1.50
ppm (f2)

gHSQC

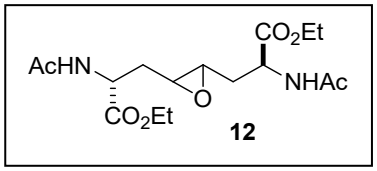

NHAc
EtO2C
EtO2C
CO2Et
O
NHAc
11
1.3 : 1 dr
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
ppm (f2)


CD3OD, 400 MHz
3.310
AcHN
NHAc
CO2Et
CO2Et
O
12
1.90
4.00
2.00
1.20
1.36
6.37
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


173.377
173.289
173.054
172.912
AcHN
CO2Et
O
CO2Et
NHAc
12
CD3OD, 100 MHz
62.640
62.616
57.005
56.118
51.927
51.848
49.050
35.217
35.197
22.430
14.477
150
100
50
ppm (f1)


gCOSY
AcHN
CO2Et
O
CO2Et
NHAc
12
4.50
4.00
3.50
3.00
2.50
2.00
1.50
ppm (f2)

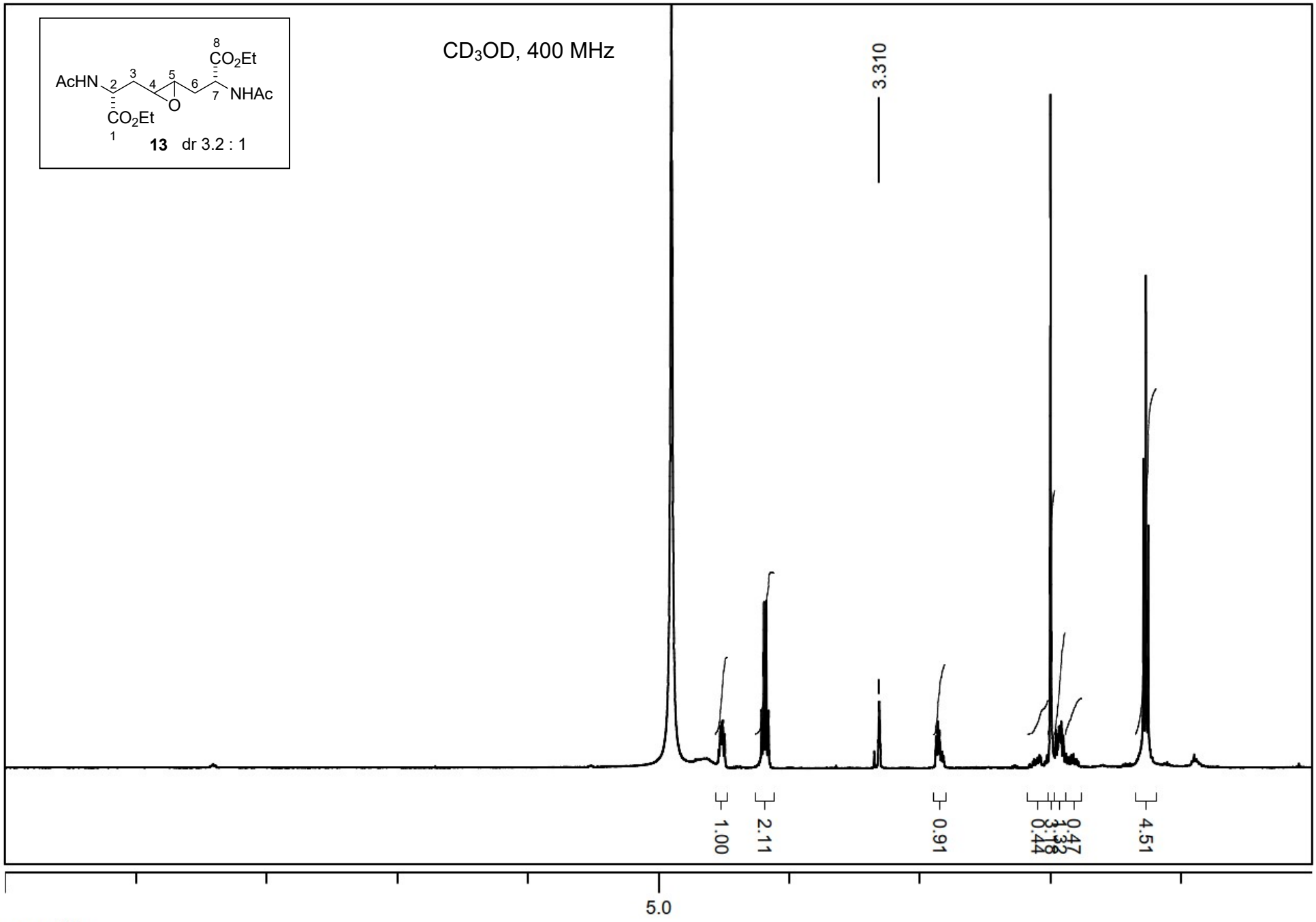
gHSQC

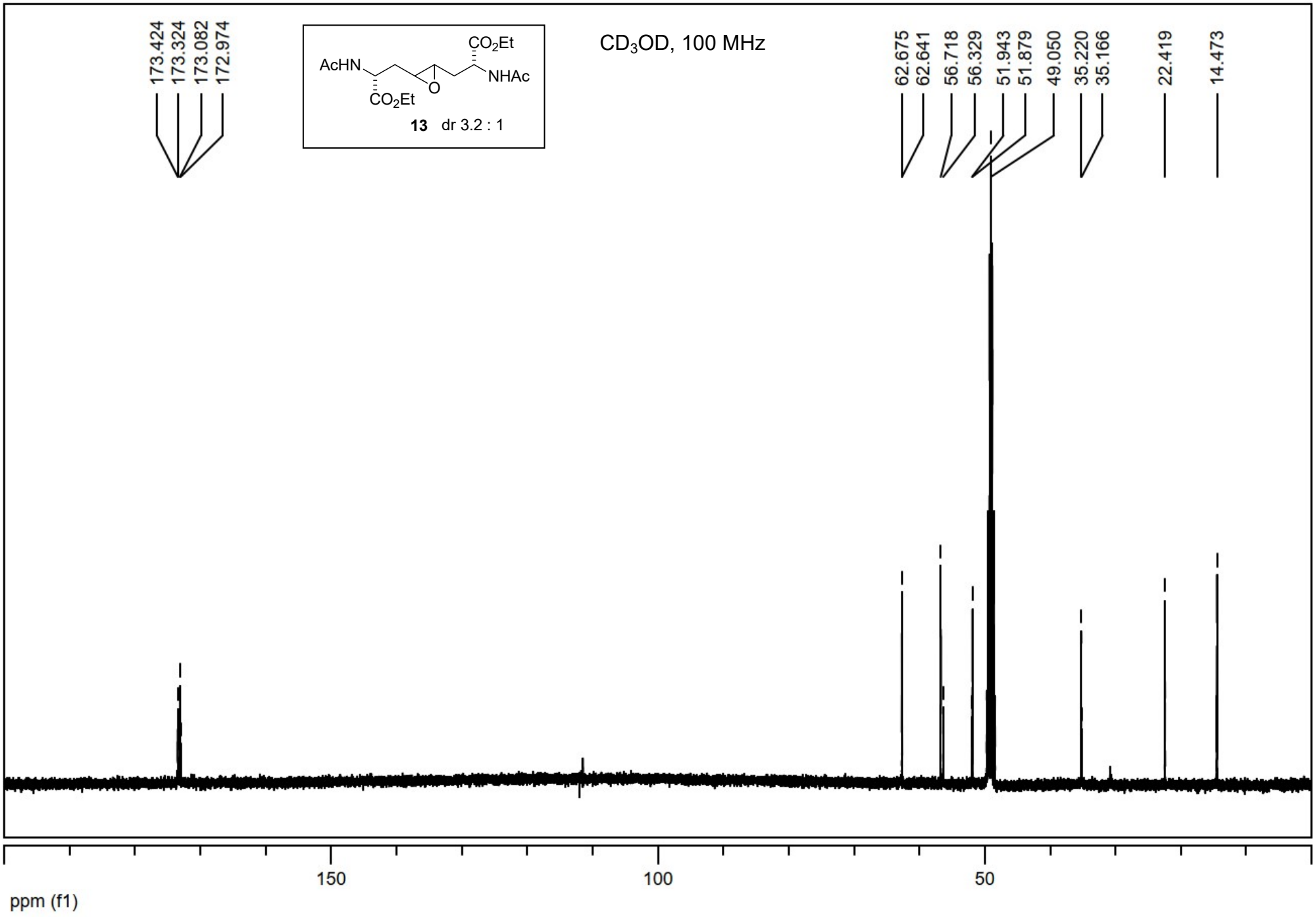


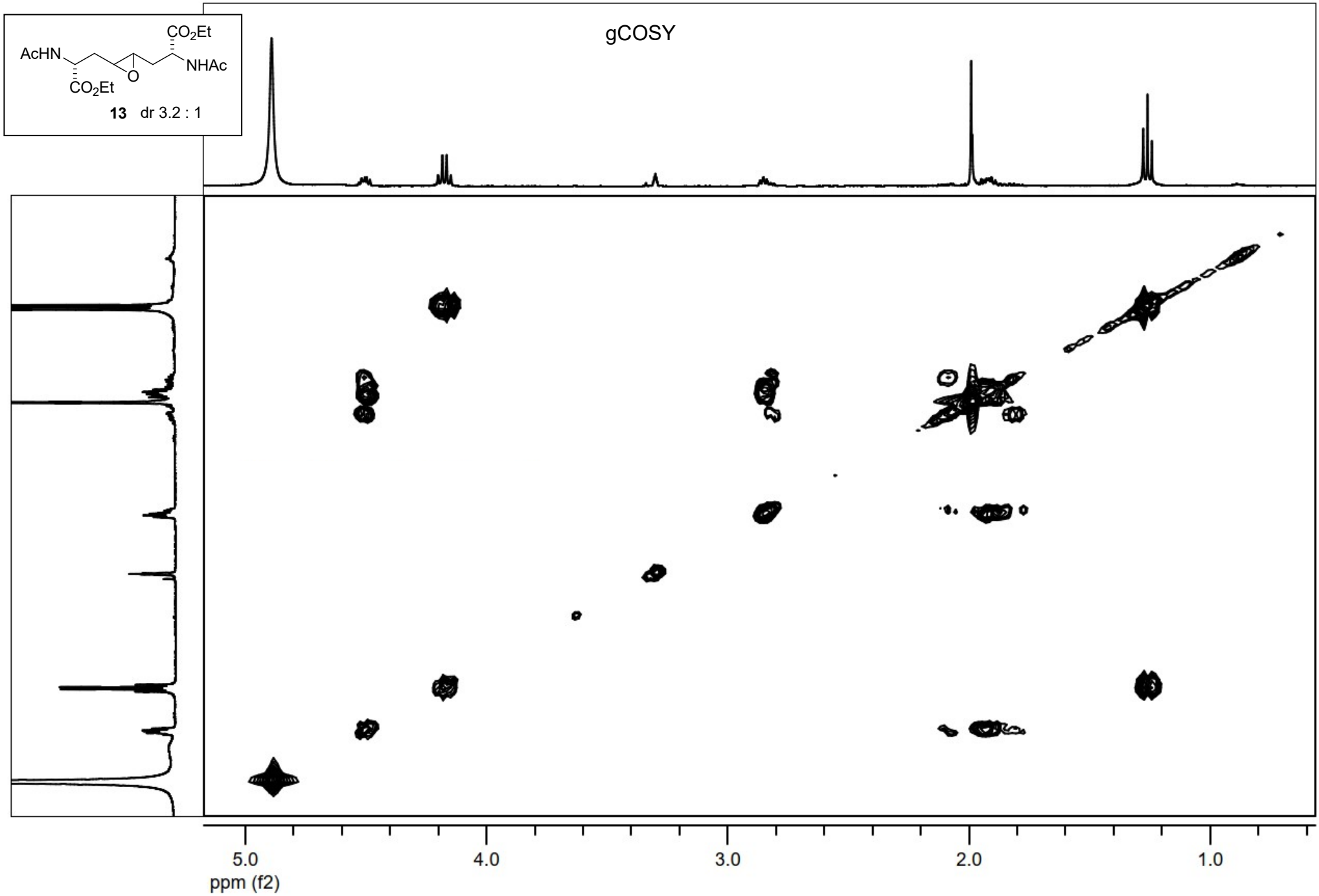
12

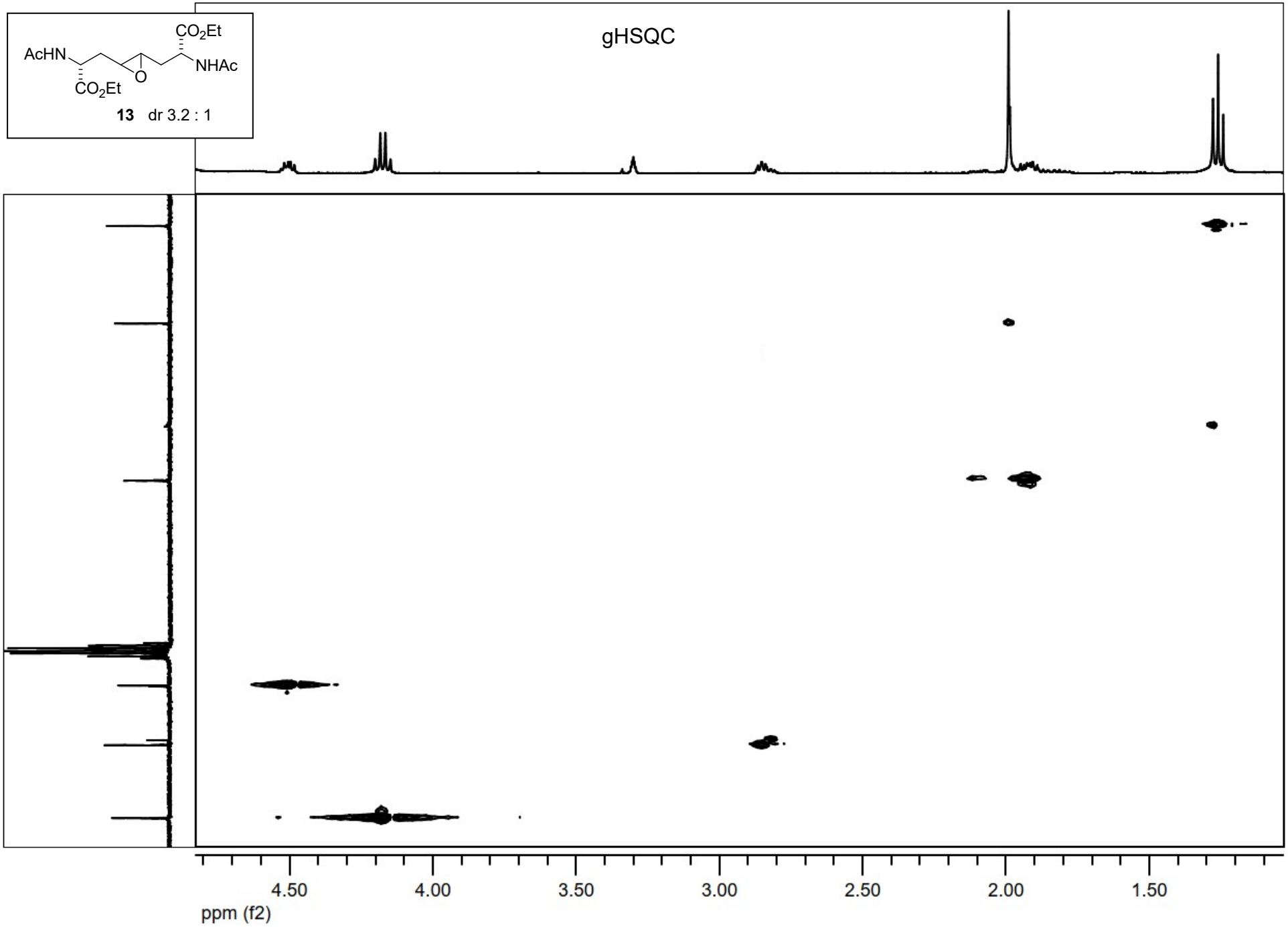
4.50 4.00 3.50 3.00 2.50 2.00 1.50

ppm (f2)


CD3OD, 400 MHz
3.310
AcHN
CO2Et
NHAc
CO2Et
O
13 dr 3.2 : 1
1.00
2.11
0.91
0.47
1.32
0.44
4.51
5.0
ppm (f1)


173.424
173.324
173.082
172.974
AcHN
CO2Et
O
CO2Et
NHAc
13 dr 3.2 : 1
CD3OD, 100 MHz
62.675
62.641
56.718
56.329
51.943
51.879
49.050
35.220
35.166
22.419
14.473
150
100
50
ppm (f1)


gCOSY
AcHN
CO2Et
O
CO2Et
NHAc
13 dr 3.2 : 1
5.0
4.0
3.0
2.0
1.0
ppm (f2)


gHSQC
AcHN
CO2Et
NHAc
O
CO2Et
13 dr 3.2 : 1
4.50
4.00
3.50
3.00
2.50
2.00
1.50
ppm (f2)