Synthesis of Functionalized Dialkyl Ketones From Carboxylic Acid Derivatives and Alkyl Halides

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Supporting Information

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I. Methods

NMR Spectroscopy:

^{1}H and ^{13}C NMR spectra were acquired on 500 MHz or 400 MHz (proton) Bruker NMR instruments and data analysis was performed using the iNMR software package (version 4.2.0, Nucleomatica, August 2011). NMR chemical shifts are reported in ppm and referenced to the residual solvent peak as an internal standard (for $CDCl_3$ δ = 7.260 ppm, ^{1}H; δ = 77.160 ppm ^{13}C). Chemical shifts are reported in parts per million (ppm).

Gas Chromatography:

GC analyses were performed on an Agilent 7890A GC equipped with dual DB-5 columns (20 m x 180 µm x 0.18 µm), dual FID detectors and with hydrogen as the carrier gas. The analysis method used in all cases was 1 µL inj. of sample, inj. temp of 300 °C, 100:1 split ratio, initial inlet pressure was 20.3 psi but varied as the column flow was held constant at 1.8 mL/min for the duration of the run. Initial oven temperature of 50 °C was held for 0.46 min followed by a temperature ramp up to 300 °C at 65 °C/min and finally the temperature was held at 300 °C for 0.69 min. Total run time was ~ 5 min. FID temperature was 325 °C. Dodecane (Aldrich) was used as an internal standard for GC analysis of catalytic reactions.

GC analysis of reaction mixtures was accomplished by removal a 10 µL aliquot with a 50 µL gas-tight syringe which was quenched with 50 µL of 1 M aqueous $NaHSO_4$, diluted with ethyl ether [1 mL], and filtered through a short silica pad [0.75 cm] in a pipette packed with glass wool. The filtrate was analyzed by GC.

High Resolution Mass Spectrometry:

High resolution mass spectra (HRMS) under electrospray (ESI) and electron impact (EI) ionization methods were obtained from Mass Spectrometry Laboratory at University of Illinois at Champaign-Urbana. The 70-VSE mass spectrometer (EI HRMS) was purchased in part with a grant from the Division of Research Resources, National Institutes of Health (RR 04648). The Q-Tof Ultima (ESI HRMS) mass spectrometer was purchased in part with a grant from the National Science Foundation, Division of Biological Infrastructure (DBI-0100085).

Thin Layer / Column Chromatography:

Thin layer chromatography was performed on EMD Chemcials TLC Silica Gel 60 F254 plates. Visualization was accomplished with p-anisaldehyde, potassium permanganate, or ninhydrin stains after inspection under UV light. Flash chromatography was performed using EMD silica gel 60, particle size 0.040-0.063 mm using standard flash techniques. Biotin labeled compounds (**2f** and **17**) were purified on a Combiflash Rf 200 (Teledyne Isco) using Redisep Rf Gold normal-phase silica columns.

Elemental Analysis:

Elemental analysis data for compounds **1g**, **3**, **13**, and **16** were obtained from the CENTC Elemental Analysis Facility at the University of Rochester, funded by NSF CHE-0650456.

II. Chemicals

Nickel Sources:

$NiCl_2$(1,2-dimethoxyethane) ($NiCl_2$(dme)) was purchased from Strem or synthesized according to the literature procedure.[1] The stoichiometry of the $NiCl_2$(dme) was found to be variable and the dme is

[1] Ward, L. G. L.; Pipal, J. R., *Inorg. Synth.* **2007**, *13*, 154.

easily lost upon exposure to vacuum. The molecular weight of $NiCl_2$(dme) was corrected for the actual amount of dme present as determined by elemental analysis and a slight excess of ligand is preferred to avoid excess nickel, which results in diminished yields. $NiCl_2$(dme) was stored under nitrogen.

Ligands:

4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy) was purchased from Aldrich or synthesized according to the literature procedure.[2] 2,2'-Dipyridyl and 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine were purchased from Aldrich.

Reducing Agents:

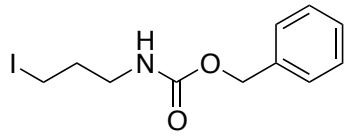
Manganese powder -325 mesh (Aldrich) and zinc dust < 10 micron (Aldrich) were used as received.

Solvent:

Anhydrous *N,N*-dimethylacetamide (Aldrich) was stored over activated 4 Å molecular sieves. Water content was routinely measured using Karl-Fisher titration (Metrohm) and was less than 70 ppm.

Alkyl Halides:

2-bromoheptane (Aldrich) and (1-chloroethyl)benzene (**2d**) (TCI) used as received. 2-iodoheptane[3] (**2c**), tert-butyl (3-iodopropyl)carbamate[4] (**2e**), (5-iodopent-1-yn-1-yl)triisopropylsilane[5,6] (**2f**), tert-butyl(3-iodopropoxy)dimethylsilane[7,8] **2i**), (E)-pinacol(5-iodo-1-pentenyl)boronate[9] (**2j**) were synthesized using the literature procedures. Benzyl (3-iodopropyl)carbamate (**2h**) was made from the known protected amino alcohol by the procedure of Hesse.[4] 1-iodooctane (**2a**) (Aldrich), (**2i**), and (**2c**) were filtered through a dry, activated, basic alumina pad (1.5 cm) under nitrogen before use.



Benzyl (3-iodopropyl)carbamate (2h) [84792-78-9].[10]

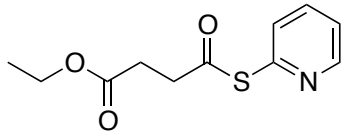
The procedure was adapted from the method of Hesse and coworkers.[4] A round bottom flask containing a teflon-coated magnetic stir bar was charged with triphenylphosphine (2.670 g, 10.25 mmol), imidizole (0.700 g, 10.28 mmol), and 60 mL dichloromethane. This solution was cooled to 0 °C, then was added I_2 (2.6 g, 10.24 mmol) portion wise under nitrogen with stirring. After warming to rt (22 °C) the mixture was stirred for 15 minutes, after which was added benzyl (3-hydroxypropyl)carbamate[11] (1.8 g, 8.6 mmol) drop-wise as a solution in 10 mL of dichloromethane. After stirring at 22 °C for 5 hours the reaction was filtered, then washed successively with DI water, saturated sodium thiosulfate, brine, then dried over $MgSO_4$ and concentrated in vacuo. Purification by SiO_2 column chromatography (3:1 hexane: ethyl acetate) the rosy red product was dissolved 5 mL ethyl acetate and was washed with saturated sodium thiosulfate (1 x 2 mL), then 2 mL sat. brine. Drying over $MgSO_4$ and concentration in vacuo afforded 2.162 g (79% yield) of the title compound a vibrant pineapple-yellow oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.37-7.36 (m, 5H), 5.10 (s, 2H), 4.84 (s, br,

[2] Hadda, T. B.; Le Bozec, H. *Polyhedron*, **1988**, *7*, 575.
[3] Schrim, M.; Besendorf, H., *Arch. Pharm.* **1942**, 64.
[4] Hesse, M.; Ensch, C. *Helv. Chim. Acta.* **2002**, *85*, 1659.
[5] Layton, M. E.; Morales, C. A.; Shair, M. D., *J. Am. Chem. Soc.* **2002**, *124*, 773.
[6] Begley, M. J.; Patterson, G.; Robertson, G. M., *J. Chem. Soc. Perkin Trans. 1*, 1988, 1085.
[7] Darwish, T. A.; Evans, R. A.; James, M.; Malic, N.; Triani, G. Hanley, T. L., *J. Am. Chem. Soc.* **2010**, *132*, 10748.
[8] Girard, S.; Deslongchamps, P., *Can. J. Chem.* **1992**, *70*, 1265.
[9] Tucker, C. E.; Greve, B.; Klein, W.; Knochel, P., *Organometallics* **1994**, *13*, 94.
[10] Dai, C.; Narayanam, J. M. R.; Stephenson, C. R. J., *Nat. Chem.* **2011**, *3*, 140.
[11] Stark, P. A.; Thrall, B. D.; Meadows, G. G.; Mahmoud, M., A-M., *J. Med. Chem.* **1992**, *35*, 4264.

1H), 3.30 (q, *J* = 6.4 Hz, 2H), 3.19 (t, *J* = 6.7 Hz, 2H), 2.04 (quintet, *J* = 6.6 Hz, 2H). ^{13}C NMR (126 MHz; $CDCl_3$): δ 156.5, 136.5, 128.7, 128.35, 128.31, 67.0, 41.6, 33.3, 3.0.

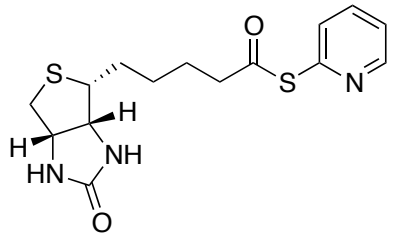
Carboxylic Acid Derivitives:

Ethyl succinyl chloride (**1b)** (Acros), trimethylacetyl chloride (**1c**) (Aldrich), 3,3-dimethylbutryl chloride (**1f**) (Aldrich), cyclopropanecarbonyl chloride (**1d**) (TCI), cyclohexanecarbonyl chloride (**1e**) (Aldrich), and biotin (Chem-Impex International) were used as received.



Ethyl 4-oxo-4-(pyridin-2-ylthio)butanoate (1b).

The procedure was adapted from the method of Masashi and coworkers.[12] A round bottom flask containing a teflon-coated magnetic stir bar was charged with Et_3N (7.00 mL, 50.2 mmol), 2-mercaptopyridine (5.51g, 49.5 mmol), 100 mL of dry THF, and a teflon-coated magnetic stir bar was cooled to 0°C under nitrogen. To this solution, ethyl succinyl chloride (7.10 mL, 49.8 mmol) was added drop-wise with stirring. A precipitate formed and the cooling bath was removed. After stirring for 6 h, the crude reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was taken up in ethyl acetate (60 mL), washed twice with saturated brine (30 mL), dried over $MgSO_4$, filtered, and the filtrate was again concentrated in vacuo. Purification by flash chromatography (2.75:1 hexanes:ethyl acetate) afforded 9.00 g (75% yield) of the title compound as a bright yellow, viscous oil. ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.62 (d, *J* = 4.8 Hz, 1H), 7.74 (td, *J* = 7.7, 1.9 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.29 (dd, *J* = 7.5, 4.9 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.04 (t, *J* = 6.9 Hz, 2H), 2.69 (t, *J* = 6.9 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz; $CDCl_3$): δ 195.3, 171.8, 151.2, 150.5, 137.4, 130.4, 123.8, 61.0, 38.8, 29.2, 14.3. HRMS (ESI): $[M + H]^+$ Calc. for $C_{11}H_{13}NO_3S$: 240.0687; found: 240.0694.



S-(2-pyridyl) 5-[(3AS,4S,6AR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl]pentanthiolate (1g).

The procedure was adapted from the method of Brown and coworkers.[13] Commercial biotin was dried under high vacuum at 40 °C in a vacuum oven to remove any residual water. A round bottom flask containing a teflon-coated magnetic stir bar was charged with 30 mL of dry acetonitrile, 2,2'-dipyridyl disulfide (1.039 g, 4.72 mmol), and triphenylphosphine (1.237 g, 4.72 mmol). The resulting mixture was stirred at 22 °C under nitrogen for 15 minutes. The yellow solution was cooled to 0 °C and biotin (0.768 g, 3.144 mmol) was added in one portion. The reaction was allowed to warm to 22 °C and was stirred for 16 hours. The reaction mixture was then concentrated in vacuo and the crude product was purified by column chromatography (SiO_2, 4:1 ethyl acetate/hexanes followed by acetone to elute product) to afford 874.9 mg (82% yield) of the title compound as a dull chartreuse, amorphous solid. ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.61 (d, *J* = 3.8 Hz, 1H), 7.73 (td, *J* = 7.7, 1.7 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.29-7.26 (m, 1H), 6.25 (s, 1H), 5.59 (s, br, 1H), 4.48 (t, *J* = 6.1 Hz, 1H), 4.29 (t, *J* = 5.8 Hz, 1H), 3.13 (q, *J* = 5.9 Hz, 1H), 2.88 (dd, *J* = 12.8, 4.9 Hz, 1H), 2.80-2.65 (m, 3H), 1.85-1.60 (m, *J* = 7.5 Hz, 4H), 1.55-1.40 (m, 2H). ^{13}C NMR (101 MHz; $CDCl_3$): δ 196.7, 163.9, 151.6, 150.5, 137.3, 130.3, 123.6,

[12] Masashi, A.; Shigeru, S.; Hisashi, T.; Mukaiyama, T., *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1777.
[13] Brown, P.; Calvert, S. H.; Chapman, P. C. A.; Cosham, S. C.; Eglington, A. J.; Elliot, R. L.; Harris, M. A.; Hinks, J. D.; Lowther, J.; Merrikin, D. J.; Pearson, M. J.; Ponsford, R. J.; Syms, J. V., *J. Chem. Soc. Perkin Trans. 1* **1991**, 881.

62.1, 60.2, 55.6, 43.9, 40.7, 28.41, 28.31, 25.4. EA: Calc. for $C_{15}H_{19}N_3O_2S_2$: 53.39% C, 5.67% H, 12.45% N; found: 53.370% C, 5.610% H, 12.270% N. Mp: 138.1 - 142.5 °C.

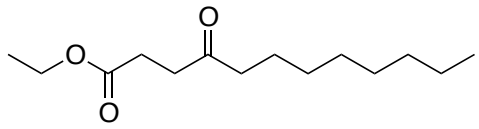
III. General Procedures for Synthesis of Ketones From Alkyl Halides and Carboxylic Acid Derivatives.

Procedure A. For Liquid Substrates:

On the bench, an oven-dried 1-dram vial containing a teflon-coated magnetic stir bar was charged with $NiCl_2$(dme) (10.5 mg, 0.0478 mmol), 4,4'-di-*tert*-butyl-2,2'-bipyridine (14.8 mg, 0.0551 mmol), and the appropriate metal reductant, either zinc dust (< 10 micron, 198 mg, 3.00 mmol) or manganese powder (-325 mesh, 165 mg, 3.0 mmol). The vial was then sealed by means of a screw cap fitted with a PTFE-faced silicone septum. To the vial, 2 mL of DMA was added under a low flow of nitrogen (needle). The resulting mixture was shaken for 15 seconds to dissolve the catalyst and then stirred (1300 rpm) at rt (~ 22 °C) until the reaction mixture's color was green-black (~30 minutes for Mn, ~1 hour for Zn). After cooling to 0 °C, the alkyl halide (1.00 mmol) and carboxylic acid derivative were added sequentially under nitrogen by syringe. The nitrogen line was then removed and the vial was stirred (1300 rpm) at 0 °C (ice/water bath) for until judged complete (less than 1 % alkyl halide remaining) by GC analysis (12-26 h). In order to remove the DMA, the reaction mixture was poured into 100 mL of water and the resulting mixture was extracted with ethyl acetate (4 × 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and the filtrate was concentrated in vacuo to yield the crude product. Pure products were then obtained after flash chromatography. In some instances the reaction mixture was filtered through a pad of celite (ethyl acetate rinse) before the aqueous workup to avoid problems with salts during the extractions.

Procedure B. For Solid Substrates:

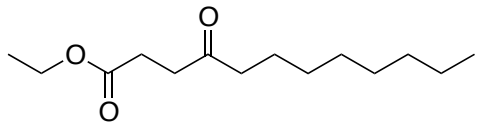
The reaction is setup as procedure A, except a smaller amount of DMA (0.75 mL) was added to the $NiCl_2$(dme), bipyridine, and reductant mixture. The remaining 1.25 mL DMA were used to quantitatively transfer the solid substrates into the reaction via syringe after stirring the catalyst mixture at rt for 1 h. An additional 1 mL of DMA was sometimes required to transfer sparingly soluble substrates.



Ethyl 4-oxododecanoate (3) (Table 2, Entry 1) [59941-35-4].[14]

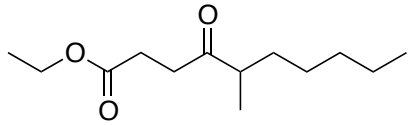
General procedure A was followed with manganese, 1-iodooctane (180 µL, 1.00 mmol), and ethyl succinyl chloride (214 µL, 1.50 mmol). Reaction was judged complete after 19 hours. Purification by flash chromatography (15:1 hexanes:ethyl acetate) afforded 209 mg (86% yield) of the title compound as a pale yellow oil which stained purple with *p*-anisaldehyde stain. ^{1}H NMR spectrum matched the literature reference but it was named incorrectly as ethyl 4-oxotridecanoate. ^{1}H NMR (400 MHz; $CDCl_3$): δ 4.12 (q, *J* = 7.1 Hz, 2H), 2.71 (t, *J* = 6.5 Hz, 2H), 2.56 (t, *J* = 6.6 Hz, 2H), 2.43 (t, *J* = 7.5 Hz, 2H), 1.64-1.50 (m, 2H), 1.30-1.23 (m, 13H), 0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz; $CDCl_3$): δ 209.4, 173.0, 60.7, 43.0, 37.2, 32.0, 29.51, 29.37, 29.28, 28.2, 24.0, 22.8, 14.33, 14.25. EA: Calc. for $C_{14}H_{26}O_3$: 69.380% C, 10.810% H; found: 69.081% C, 10.801% H.

[14] Yamashita, M.; Tasika, H.; Uchida, M., *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1257.



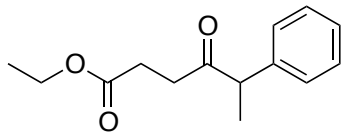
Ethyl 4-oxododecanoate (3) (Table 2, Entry 2) [59941-35-4].[14]

General procedure A was followed with zinc dust, 1-iodooctane (180 µL, 1.00 mmol), and ethyl 4-oxo-4-(pyridin-2-ylthio)butanoate (**1b**) (239 mg, 1.00 mmol). Reaction was judged complete after 30 hours. Purification by SiO_2 chromatography (15:1 hexanes:ethyl acetate) afforded 178.5 mg (74% yield) of the title compound as a pale yellow oil which stained medium purple with *p*-anisaldehyde stain. ^1H and ^{13}C NMR spectra matched those reported for the material synthesized from ethyl succinyl chloride (above).



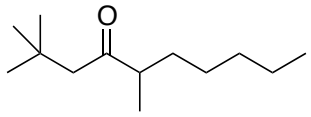
Ethyl 5-methyl-4-oxodecanoate (4) (Table 2, Entry 3).

General procedure A was followed using manganese, 2-iodoheptane (226mg, 1.00 mmol), and ethyl succinyl chloride (214 µL, 1.50 mmol). Reaction was judged complete after 15 hours. Purification by SiO_2 chromatography (20:1 hexanes:ethyl acetate) afforded 208 mg (91% yield) of the title compound as a pale yellow oil which stained medium purple with *p*-anisaldehyde stain. ^1H NMR (400 MHz; $CDCl_3$): δ 4.11 (q, J = 7.1 Hz, 2H), 2.74 (q, J = 6.5 Hz, 2H), 2.61-2.48 (m, 3H), 1.73-1.56 (m, 1H), 10.37-1.19 (m, 10H), 1.08 (d, J = 6.9 Hz, 3H), 0.86 (t, J = 6.9 Hz, 3H).[15] ^{13}C NMR (101 MHz; $CDCl_3$): δ 212.9, 173.0, 60.7, 46.4, 35.7, 33.1, 32.0, 28.1, 27.0, 22.6, 16.4, 14.3, 14.2. HRMS (ESI): $[M + H]^+$ Calc. for $C_{13}H_{24}O_3$: 229.1804; found: 229.1805.



Ethyl 4-oxo-5-phenylhexanoate (5) (Table 2, Entry 4) [1284190-95-9].[16]

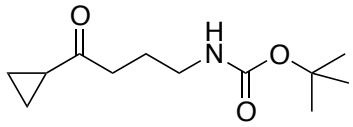
General procedure A was followed with 2-iodoheptane (226mg, 1.00 mmol), manganese, and 2 equiv of ethyl succinyl chloride (285 µL, 2.00 mmol). Reaction was judged complete after 20 hours. Purification by flash chromatography (20:1 hexanes:ethyl acetate) afforded a 9.1:1[17] mixture of the title compound (113.7 mg, 49% yield), and diethyl succinate (9.3 mg) as a pale yellow oil. The product could be could be visualized on TLC with *p*-anisaldehyde stain. ^1H NMR (400 MHz; $CDCl_3$): δ 7.31 (t, J = 1.7 Hz, 2H), 7.27-7.21 (m, 3H), 4.09 (q, J = 7.1 Hz, 2H), 3.79 (q, J = 7.0 Hz, 1H), 2.74-2.52 (m, 3H), 2.47-2.37 (m, 1H), 1.41 (d, J = 7.0 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz; $CDCl_3$): δ 209.2, 172.9, 140.6, 129.1, 128.0, 127.3, 60.7, 53.1, 35.7, 28.3, 17.5, 14.3. HRMS (ESI): $[M + Na]^+$ Calc. for $C_{14}H_{18}O_3$: 257.1154; found: 257.1161.



2,2,5-trimethyldecan-4-one (6) (Table 2, Entry 5).

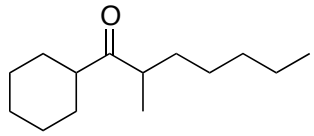
[15] Compound 6 was used as a model to assign the ^1H NMR peak integrations.
[16] Available from Aurora Fine Chemicals LLC., 01/25/2012.
[17] GC retention time, LRMS-EI$^+$, and ^1H NMR shifts of the byproduct matched that of diethyl succinate.

General procedure A was followed using manganese, 2-iodoheptane (226mg, 1.00 mmol) and 3,3-dimethylbutryl chloride (208 µL, 1.50 mmol). Reaction was judged complete after 20 hours. Purification by SiO_2 chromatography (40:1 hexanes:ethy acetate) afforded 163 mg (82% yield) of the title compound as a pale yellow oil which stained grey-tan with *p*-anisaldehyde stain. Protons in the 2-heptyl side-chain were assigned after analysis of the COSY spectrum (copy included below with ^1H and ^{13}C spectra). ^1H NMR (400 MHz; $CDCl_3$): δ 2.46 (m, 1H, -C(CH_3)*H*-), 2.35 (d, *J* = 15.4 Hz, 1H, -C(CH_3)$_3$C(H)*H*-), 2.29 (d, *J* = 15.4 Hz, 1H, C(CH_3)$_3$C(H)*H*-), 1.63-1.55 (m, 1H, -(CO)CH(CH_3)C(H)*H*-), 1.35-1.19 (m, 7H, -(CO)CH(CH_3)C(H)*H*-) and -(CH_2)$_3$$CH_3$), 1.02-1.01 (m, 12H, C($CH_3$)$_3$- and -CH$CH_3$), 0.87 (t, *J* = 6.9 Hz, 3H, -$CH_2$$CH_3$). ^{13}C NMR (101 MHz; $CDCl_3$): δ 214.8, 53.7, 47.7, 33.0, 32.1, 29.9, 27.1, 22.7, 16.1, 14.2, 9.6. HRMS (ESI): $[M + H]^+$ Calc. for $C_{13}H_{26}O$: 199.2062; found: 199.2067.



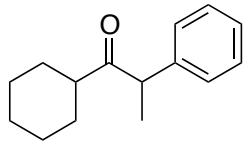
***Tert*-butyl (4-cyclopropyl-4-oxobutyl)carbamate (7) (Table 2, Entry 6).**

General procedure B was followed using manganese powder, *tert*-butyl (3-iodopropyl)carbamate (285 mg, 1.00 mmol), and cyclopropanecarbonyl chloride (137 µL, 1.51 mmol). The crude reaction mixture was filtered through celite before aqueous workup. Purification by flash chromatography (5:1 hexanes:ethyl acetate) afforded 178.4 mg (78% yield) of the title compound as a dull orange-yellow, amorphous solid which stained medium-purple with *p*-anisaldehyde stain and light brown with ninhydrin stain. ^1H NMR (500 MHz; $CDCl_3$): δ 4.70-4.45 (m, br, 1H), 3.18-3.10 (m, 2H), 2.61 (t, *J* = 7.1 Hz, 2H), 1.97-1.88 (m, 1H), 1.85-1.75 (m, 2H), 1.45 (s, 9H), 1.05-0.99 (m, 2H), 0.90-0.85 (m, 2H). ^{13}C NMR (126 MHz; $CDCl_3$): δ 210.6, 156.1, 79.1, 40.7, 40.2, 28.5, 26.4, 24.2, 20.6, 10.8. HRMS (ESI): $[M + H]^+$ Calc. for $C_{12}H_{21}NO_3$: 228.1600; found: 228.1603. Mp: 45.3 – 54.5 °C.



1-cyclohexyl-2-methylheptan-1-one (8) (Table 2, Entry 7).

General procedure A was followed using manganese, 2-iodoheptane (226 mg, 1.00 mmol), and cyclohexanecarbonyl chloride (200 µL, 1.50 mmol). The reaction was judged complete after 20 hours. Purification by flash chromatography (40:1 hexanes:ethyl acetate) afforded 151.2 mg (72% yield) of the title compound as a pale yellow oil which stained grey-tan with *p*-anisaldehyde stain. ^1H NMR (400 MHz; $CDCl_3$): δ 2.65 (m, *J* = 6.7 Hz, 1H), 2.47-2.40 (m, 1H), 1.77 (m, 4H), 1.68-1.58 (m, 2H), 1.37-1.15 (m, 12H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.86 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz; $CDCl_3$): δ 218.0, 50.0, 44.7, 33.2, 32.1, 28.8, 28.6, 27.3, 26.02, 25.91, 25.88, 22.7, 16.9, 14.2. HRMS (EI): $[M]^+$ Calc. for $C_{14}H_{26}O$: 210.1984; found: 210.1985.

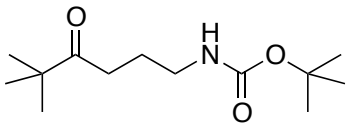


1-cyclohexyl-2-phenylpropan-1-one (9) (Table 2, Entry 8) [117269-69-9].[18]

General procedure A was followed using manganese, (1-chloroethyl)benzene (133 µL, 1.00 mmol), and cyclohexanecarbonyl chloride (200 µL, 1.50 mmol). Substrates were added at rt (22 °C) instead of 0 °C. The reaction was reacted at 30 °C not 0 °C until judged complete after 20 hours. Purification by

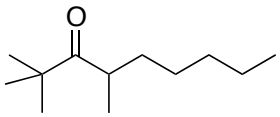
[18] Berk, S. C.; Yeh, M. C. P.; Jeong, N,; Knochel, P., *Organometallics* **1990**, *9*, 3053.

SiO_2 chromatography (40:1 hexanes:ethyl acetate) afforded 72.3 mg (33% yield) of the title compound as a pale yellow oil which stained bright cyan with *p*-anisaldehyde stain. The ^1H and ^{13}C NMR spectra matched the literature reference. ^1H NMR (500 MHz; $CDCl_3$): δ 7.33-7.30 (m, 2H), 7.26-7.20 (m, 3H), 3.90 (q, *J* = 6.9 Hz, 1H), 2.40 (tt, *J* = 11.3, 3.5 Hz, 1H), 1.85-1.43 (m, 5H), 1.36 (d, *J* = 6.9 Hz, 3H), 1.27-1.05 (m, 6H). ^{13}C NMR (126 MHz; $CDCl_3$): δ 214.0, 140.9, 128.9, 128.1, 127.1, 51.3, 49.6, 29.6, 28.5, 26.06, 25.91, 25.4, 18.3. HRMS (ESI): $[M + Na]^+$ Calc. for $C_{15}H_{20}O$: 239.1412; found: 239.1411.



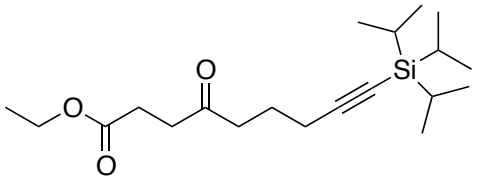
***Tert*-butyl (5,5-dimethyl-4-oxohexyl)carbamate (10) (Table 2, Entry 9).**

General procedure B was followed using manganese powder, *tert*-butyl (3-iodopropyl)carbamate (285 mg, 1.00 mmol), and trimethylacetyl chloride (185 µL, 1.57 mmol). The reaction was judged complete after 30 hours. The crude reaction mixture was filtered through celite before aqueous workup. Purification by flash chromatography (3:1 hexanes:ethyl acetate) afforded 222 mg (91% yield) of the title compound as a dull orange-yellow, amorphous solid which stained medium purple with *p*-anisaldehyde stain and light brown with ninhydrin stain. ^1H NMR (500 MHz; $CDCl_3$): δ 4.55 (s, br, 1H), 3.12 (q, *J* = 5.9 Hz, 2H), 2.52 (t, *J* = 7.0 Hz, 2H), 1.83-1.65 (m, 2H), 1.43 (s, 9H), 1.13 (s, 9H). ^{13}C NMR (126 MHz; $CDCl_3$) 215.5, 156.1, 78.9, 44.0, 40.1, 33.6, 28.4, 26.4, 24.1. HRMS (ESI): $[M + H]^+$ Calc. for $C_{13}H_{25}NO_3$: 244.1913; found: 244.1923. Mp: 33.9 - 43.7 °C.



2,2,4-trimethylnonan-3-one (11) (Table 2, Entry 10) [32557-59-8].[19]

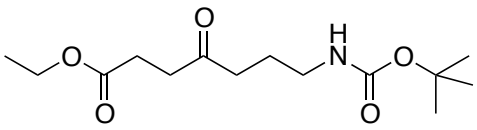
General procedure A was followed using manganese, 2-iodoheptane (226 mg, 1.00 mmol), and trimethylacetyl chloride (185 µL, 1.50 mmol). The reaction was judged complete after 13 hours. Purification by SiO_2 chromatography (50:1 hexanes:ethyl acetate) afforded 123 mg (67% yield) of the title compound as a pale yellow oil which stained grey-tan with *p*-anisaldehyde stain. ^1H NMR (500 MHz; $CDCl_3$): δ 2.97 (m, 1H), 1.62-1.52 (m, 1H), 1.30-1.20 (m, 7H), 1.14 (s, 9H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.86 (t, *J* = 7.0 Hz, 3H).[15] ^{13}C NMR (126 MHz; $CDCl_3$): δ 220.1, 44.7, 39.7, 34.5, 32.1, 27.5, 26.4, 22.7, 18.6, 14.2. HRMS (ESI): $[M + H]^+$ Calc. for $C_{12}H_{24}O$: 185.1905; found: 185.1907.



Ethyl 4-oxo-9-(triisopropylsilyl)non-8-ynoate (12) (Table 3, Entry 1).

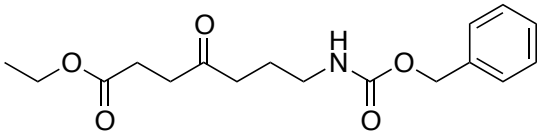
General procedure A was followed using manganese powder, (5-iodopent-1-yn-1-yl)triisopropylsilane (350 mg, 1.00 mmol), and ethyl succinyl chloride (214 µL, 1.50 mmol). The reaction was judged complete after 20 hours. Purification by flash chromatography (20:1 hexanes: ethyl acetate) afforded 218 mg (62% yield) of the title compound as a pale yellow oil which stained tan-grey with p-anisaldehyde stain and bright yellow with $KMnO_4$ stain. ^1H NMR (400 MHz; $CDCl_3$): δ 4.12 (q, *J* = 7.1 Hz, 2H), 2.72 (t, *J* = 6.6 Hz, 2H), 2.63 (t, *J* = 7.3 Hz, 2H), 2.57 (t, *J* = 6.6 Hz, 2H), 2.29 (t, *J* = 6.8 Hz, 2H), 1.81 (m, 2H), 1.25 (d, *J* = 14.3 Hz, 3H), 1.05 (m, 21H). ^{13}C NMR (101 MHz; $CDCl_3$): δ 208.6, 172.9, 108.0, 81.3, 60.8, 41.3, 37.4, 28.1, 22.9, 19.3, 18.8, 14.3, 11.4. HRMS (ESI): $[M + H]^+$ Calc. for $C_{20}H_{36}O_3Si$: 353.2512; found: 352.2513.

[19] Meyers, A. I.; Smith, E. M.; Ao, M. S., *J. Org. Chem.* **1973**, *38*, 2129.



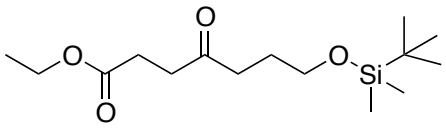
Ethyl 7-((*tert*-butoxycarbonyl)amino)-4-oxoheptanoate (13) (Table 3, Entry 2).

General procedure B was followed using manganese powder, *tert*-butyl (3-iodopropyl)carbamate (285 mg, 1.00 mmol), and ethyl succinyl chloride (214 µL, 1.50 mmol). The reaction was judged complete after 17 hours. The crude reaction mixture was filtered through celite before aqueous workup. Purification by flash chromatography (3:1 hexanes:ethyl acetate) afforded 236 mg (82% yield) of the title compound as a dull orange-yellow, amorphous solid which stained medium purple with *p*-anisaldehyde stain and light brown with ninhydrin stain. ^{1}H NMR (400 MHz; $CDCl_3$): δ 4.60 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.12 (q, *J* = 6.5 Hz, 2H), 2.71 (t, *J* = 6.5 Hz, 2H), 2.58 (t, *J* = 6.5 Hz, 2H), 2.50 (t, *J* = 7.2 Hz, 2H), 1.77 (m, 2H), 1.43 (s, 9H), 1.24 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz; $CDCl_3$): δ 208.6, 172.9, 156.2, 79.3, 60.8, 40.01, 39.9, 37.2, 28.5, 28.2, 24.2, 14.3. EA: Calc. for $C_{14}H_{25}NO_5$: 58.52% C, 8.77% H, 4.87% N; found: 58.29% C, 8.74% H, 4.51% N. Mp: 33.9 - 43.7 °C.



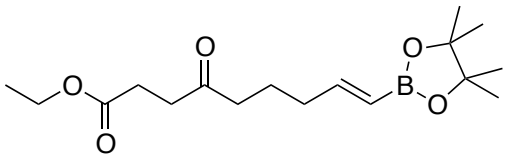
Ethyl 7-(((benzyloxy)carbonyl)amino)-4-oxoheptanoate (14) (Table 3, Entry 3).

General procedure B was followed using manganese powder, *tert*-butyl (3-iodopropyl)carbamate (319.1 mg, 1.00 mmol), and ethyl succinyl chloride (214 µL, 1.50 mmol). The reaction was judged complete after 17 hours. The crude reaction mixture was filtered through celite before aqueous workup. Purification by flash chromatography (3:1 hexanes:ethyl acetate) afforded 276 mg (86% yield) of the title compound as a pale yellow, amorphous solid which stained medium purple with *p*-anisaldehyde stain and light brown with ninhydrin stain. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.36-7.28 (m, 5H), 5.08 (s, 2H), 4.89 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.20 (q, *J* = 6.5 Hz, 2H), 2.69 (t, *J* = 6.3 Hz, 2H), 2.57 (t, *J* = 6.4 Hz, 2H), 2.52 (t, *J* = 7.0 Hz, 2H), 1.80 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz; $CDCl_3$): δ 208.5, 172.8, 156.6, 136.7, 128.5, 128.3, 128.1, 66.6, 60.6, 40.4, 39.7, 37.1, 28.0, 23.9, 14.2. HRMS (ESI): $[M + H]^+$ Calc. for $C_{17}H_{23}NO_5$: 322.1654; found: 322.1647. Mp: 44.8 - 45.2 °C.



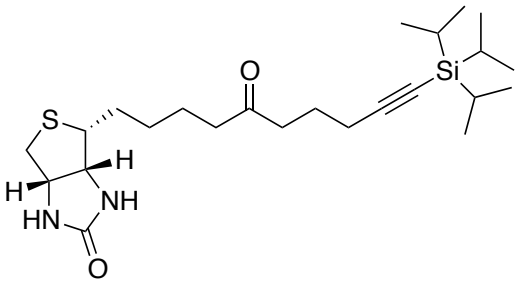
Ethyl 7-((*tert*-butyldimethylsilyl)oxy)-4-oxoheptanoate (15) (Table 3, Entry 4).

General procedure A was followed using manganese powder, *tert*-butyl(3-iodopropoxy)dimethylsilane (300 mg, 1.00 mmol), and ethyl succinyl chloride (214 µL, 1.50 mmol). The reaction was judged complete after 20 hours. Purification by flash chromatography (20:1 hexanes:ethyl acetate) afforded 251 mg (83% yield) of the title compound as a pale yellow oil which stained bright yellow with p-anisaldehyde stain. ^{1}H NMR (400 MHz; $CDCl_3$): δ 4.11 (q, *J* = 7.1 Hz, 2H), 3.60 (t, *J* = 6.1 Hz, 2H), 2.72 (t, *J* = 6.6 Hz, 2H), 2.54 (dt, *J* = 15.2, 7.0 Hz, 4H), 1.82-1.76 (m, 2H), 1.24 (t, *J* = 7.2 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 6H). ^{13}C NMR (101 MHz; $CDCl_3$): δ 208.9, 172.9, 62.3, 60.7, 39.3, 37.2, 28.1, 27.0, 26.1, 18.4, 14.3, -5.2. HRMS (ESI): $[M + H]^+$ Calc. for $C_{15}H_{30}O_4Si$: 303.1992; found: 303.1992.



(E)-ethyl 4-oxo-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)non-8-enoate (16) (Table 3, Entry 5).

General procedure A was followed using zinc dust, (E)-pinacol(5-iodo-1-pentenyl)boronate (322 mL, 1.00 mmol), and ethyl 4-oxo-4-(pyridin-2-ylthio)butanoate (**1b**) (239 mg, 1 mmol). The reaction was judged complete after 36 hours. Purification by flash chromatography (6:1 hexanes:ethyl acetate) afforded 184 mg, (58% yield) of the title compound as a pale yellow oil which stained medium-purple with *p*-anisaldehyde stain. ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.56 (dt, *J* = 17.9, 6.4 Hz, 1H), 5.43 (dt, *J* = 17.9, 1.4 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 2.69 (t, *J* = 6.5 Hz, 2H), 2.55 (t, *J* = 6.6 Hz, 2H), 2.45 (t, *J* = 7.5 Hz, 2H), 2.15 (qd, *J* = 6.9, 1.0 Hz, 2H), 1.72 (m, 2H), 1.25 (s, 12H), 1.23 (t, *J* = 3.3 Hz, 3H). ^{13}C NMR (126 MHz; $CDCl_3$): δ 208.8, 172.9, 153.3, 83.2, 60.7, 42.1, 37.2, 35.1, 28.1, 24.9, 22.3, 14.3.[20] EA: Calc. for $C_{17}H_{29}BO_5$: 62.98% C, 9.02% H; found: 63.05% C, 9.22% H.

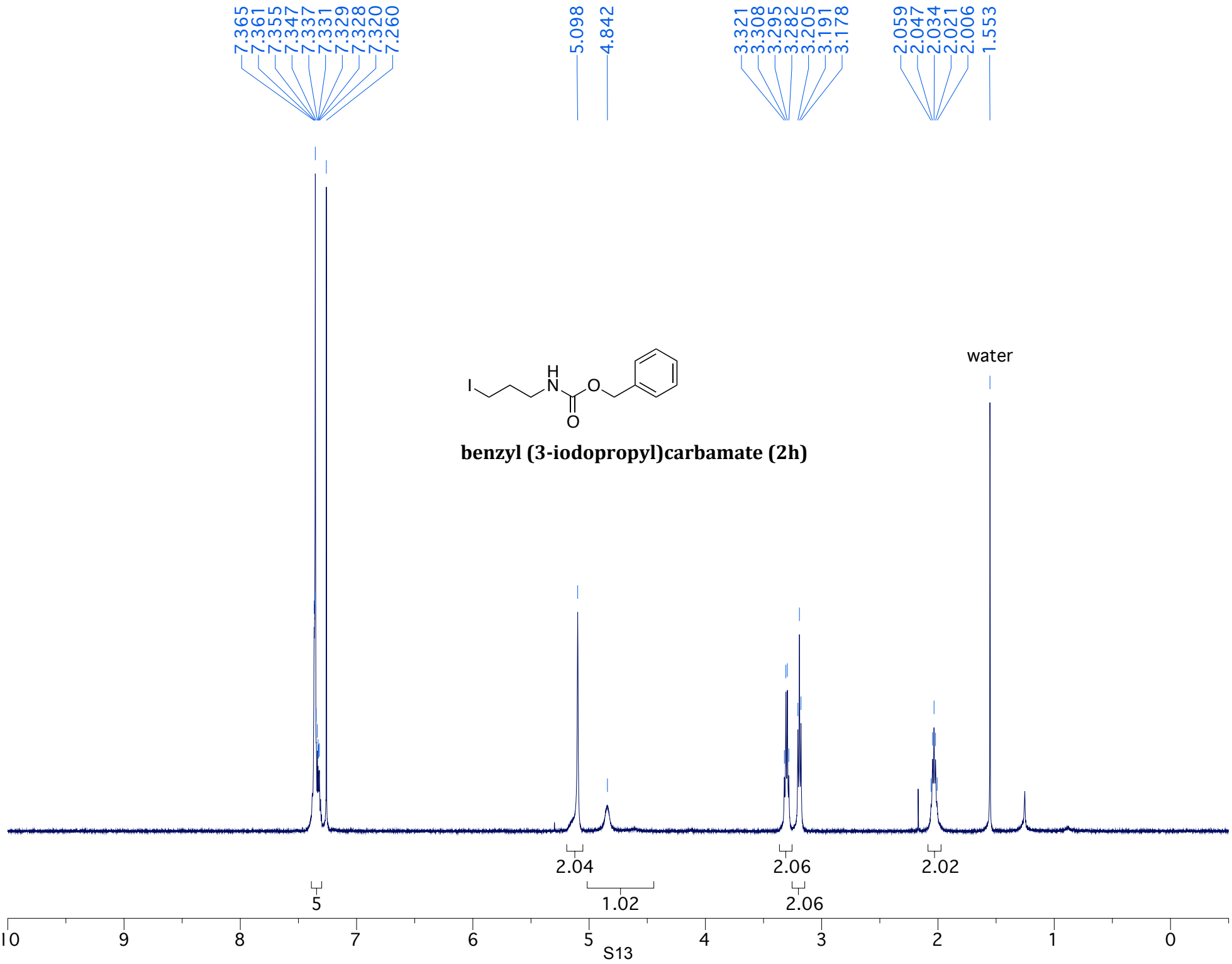


(3a*R*,4*R*,6a*S*) -4-(5-oxo-10-(triisopropylsilyl)dec-9-yn-1-yl)tetrahydro-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one (17) (Table 3, Entry 6).

Run 1. General procedure B was followed using zinc powder and (5-iodopent-1-yn-1-yl)triisopropylsilane (350 mg, 1.00 mmol). **1g** (337.1 mg, 1.00 mmol) was transferred using 2.25 mL of DMA. The reaction was judged complete after 30 hours. The crude reaction mixture was filtered through celite and then extracted from water with ethyl acetate (12 x 20 mL). Concentration in vacuo, followed by flash chromatography (3:2 ethyl acetate:hexanes followed by 3:2 acetone:hexanes to elute product) afforded 191.4 mg (42% yield) of the title compound as a dull green-yellow sticky solid which stained medium purple with *p*-anisaldehyde stain, bright yellow with $KMnO_4$, and light brown with ninhydrin stain. **Run 2**: Same as run 1 but on half-scale. The reaction was extracted (25 x 10 mL EtOAc) from 50 mL water. Purification by chromatography (3:2 ethyl acetate:hexanes followed by 1:1 acetone hexanes to elute product) afforded 68 mg (30% yield) of the title compound as a pale yellow, sticky solid. ^{1}H and ^{13}C spectra matched those for run 1. ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.98 (s, br, 1H), 5.71 (s, br, 1H), 4.49 (m, br, 1H), 4.29 (m, br, 1H), 3.14 (q, *J* = 5.8 Hz, 1H), 2.89 (dd, *J* = 12.7, 4.7 Hz, 1H), 2.72 (d, *J* = 12.6 Hz, 1H), 2.55 (d, *J* = 7.3 Hz, 2H), 2.41 (t, *J* = 7.3 Hz, 2H), 2.27 (t, *J* = 6.8 Hz, 2H), 1.76 (m, 2H), 1.72-1.50 (m, *J* = 7.8 Hz, 4H), 1.42-1.36 (m, 2H), 1.06-1.04 (m, 21H). ^{13}C NMR (126 MHz; $CDCl_3$): δ 210.3, 163.9, 107.7, 80.7, 61.8, 60.0, 55.3, 42.3, 40.9, 40.4, 28.28, 28.20, 23.3, 22.5, 18.9, 18.3, 11.0. HRMS (ESI): $[M + H]^+$ Calc. for $C_{24}H_{42}N_2O_2SSi$: 451.2815; found: 451.2786.

[20] The =*C*(H)Bpin resonance was not observed in our ^{13}C spectrum. This is the case for the B-C carbon of other reported vinyl boronic esters. See: (a) Shirakawa, K.; Aarase, A.; Hoshi, M. *Synthesis* **2004**, 1814; (b) Brown, H. C.; Imai, T., *Organometallics* **1984**, *3*, 1392.

IV. Spectra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3.295
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3.205
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3.178
2.059
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2.034
2.021
2.006
1.553
water
H
N
O
I
O
benzyl (3-iodopropyl)carbamate (2h)
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2.06
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7
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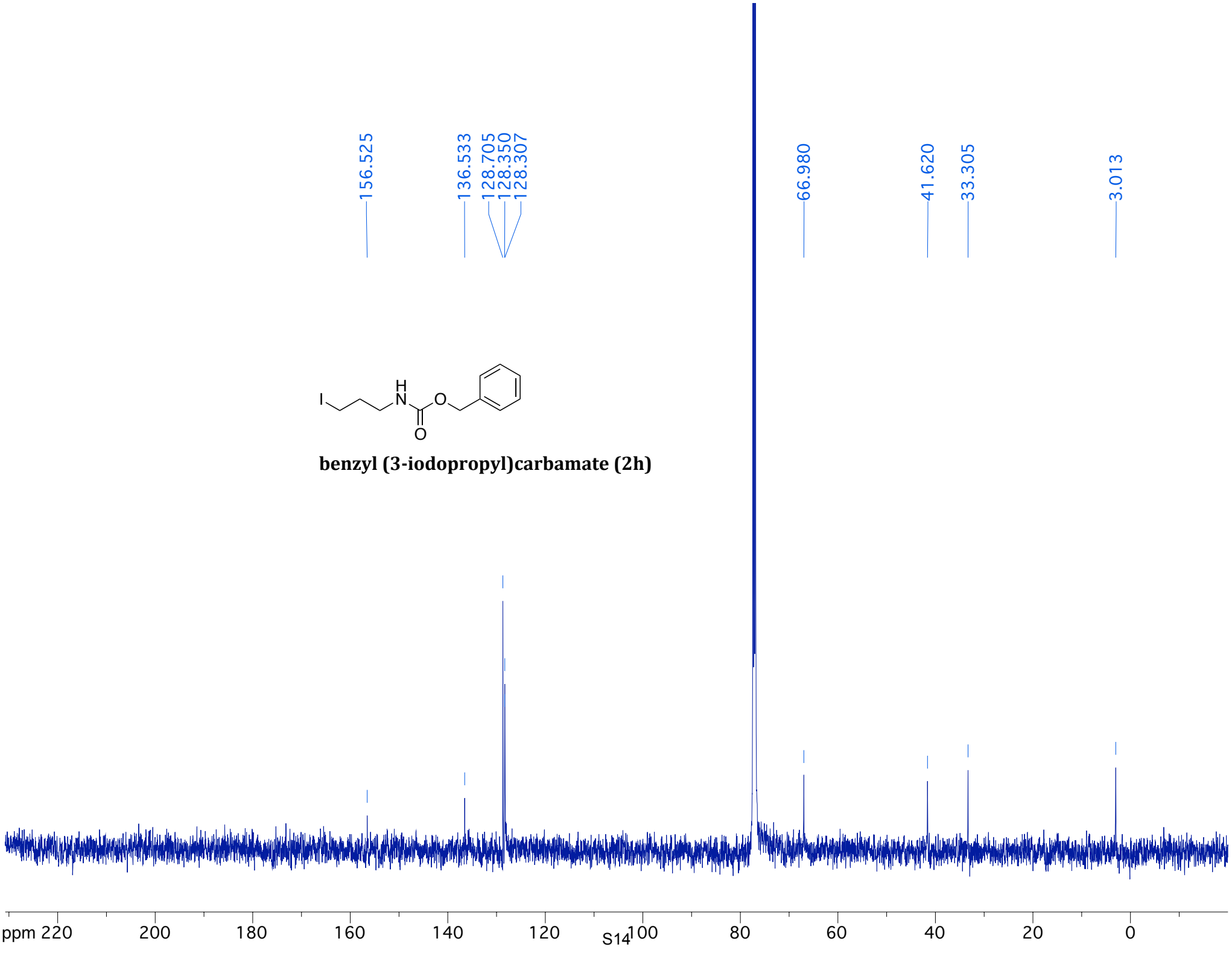
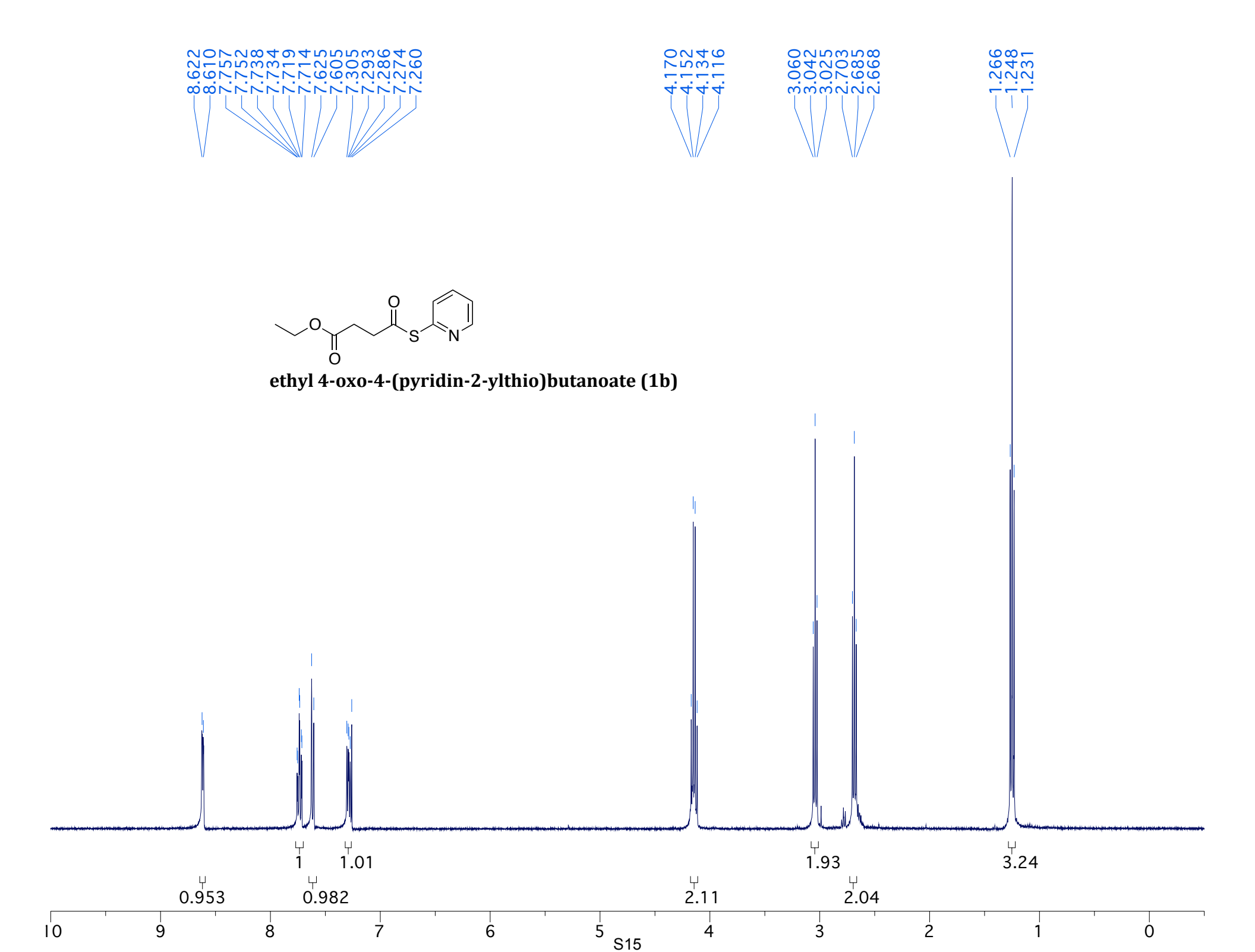
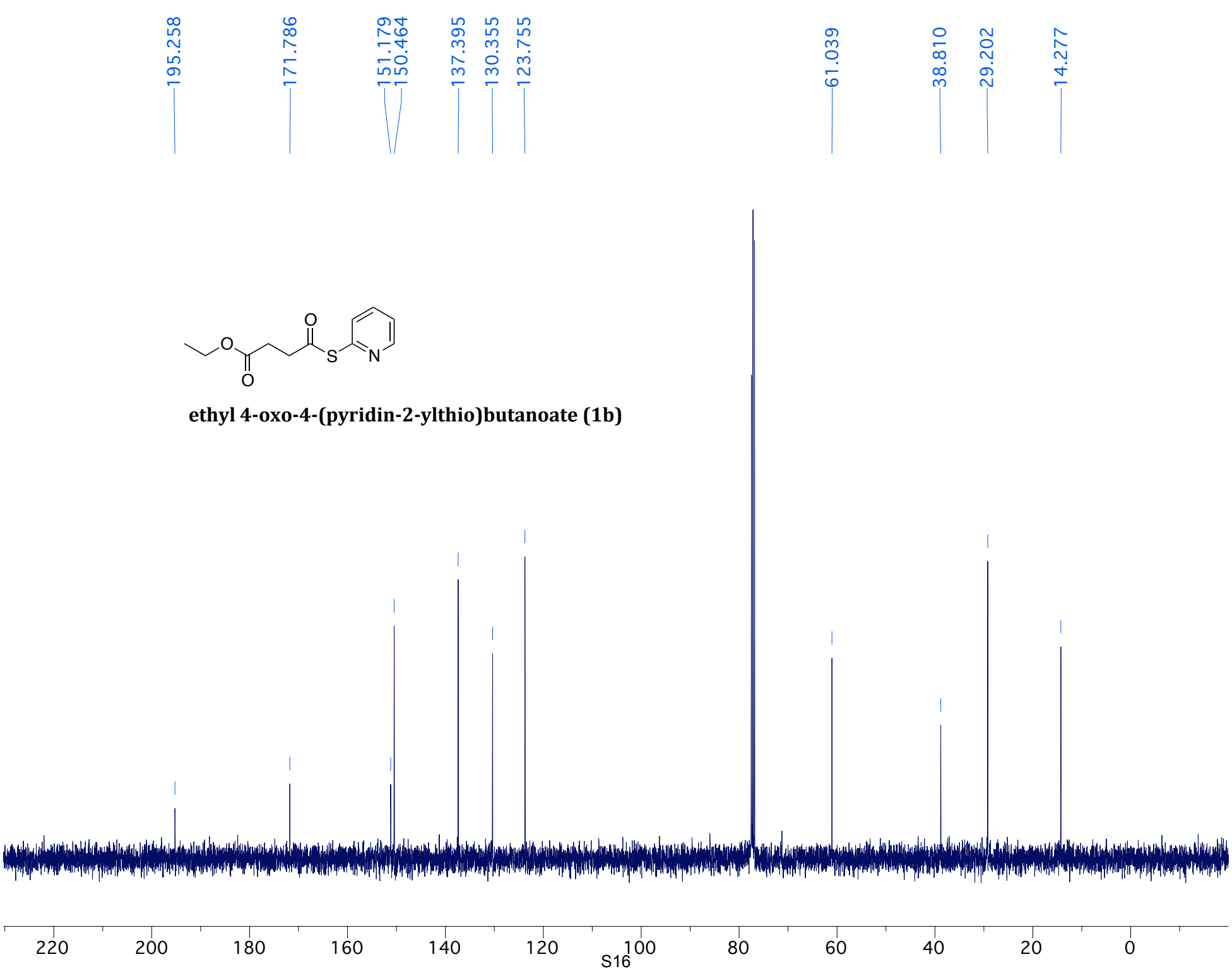


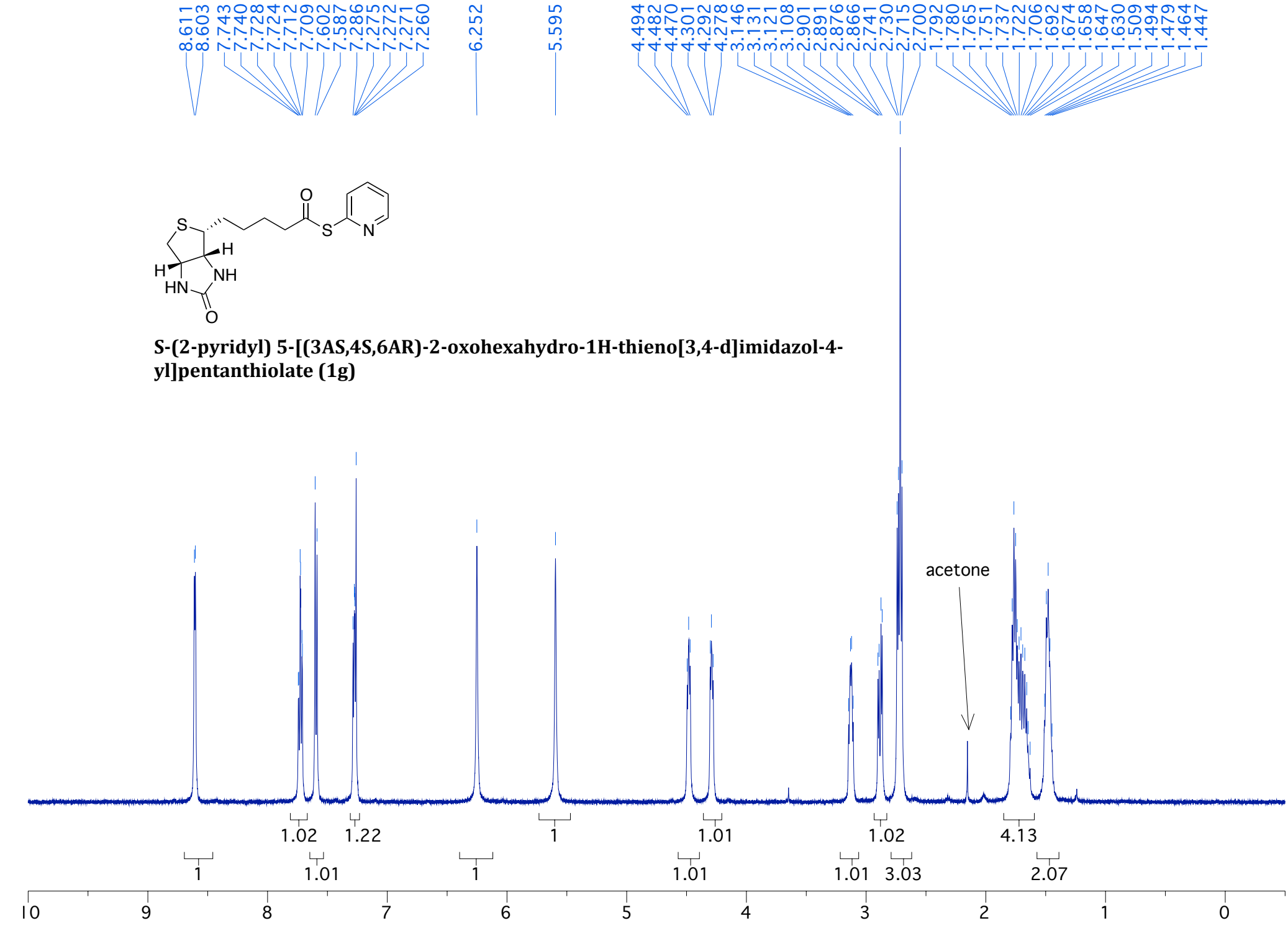
benzyl (3-iodopropyl)carbamate (2h)



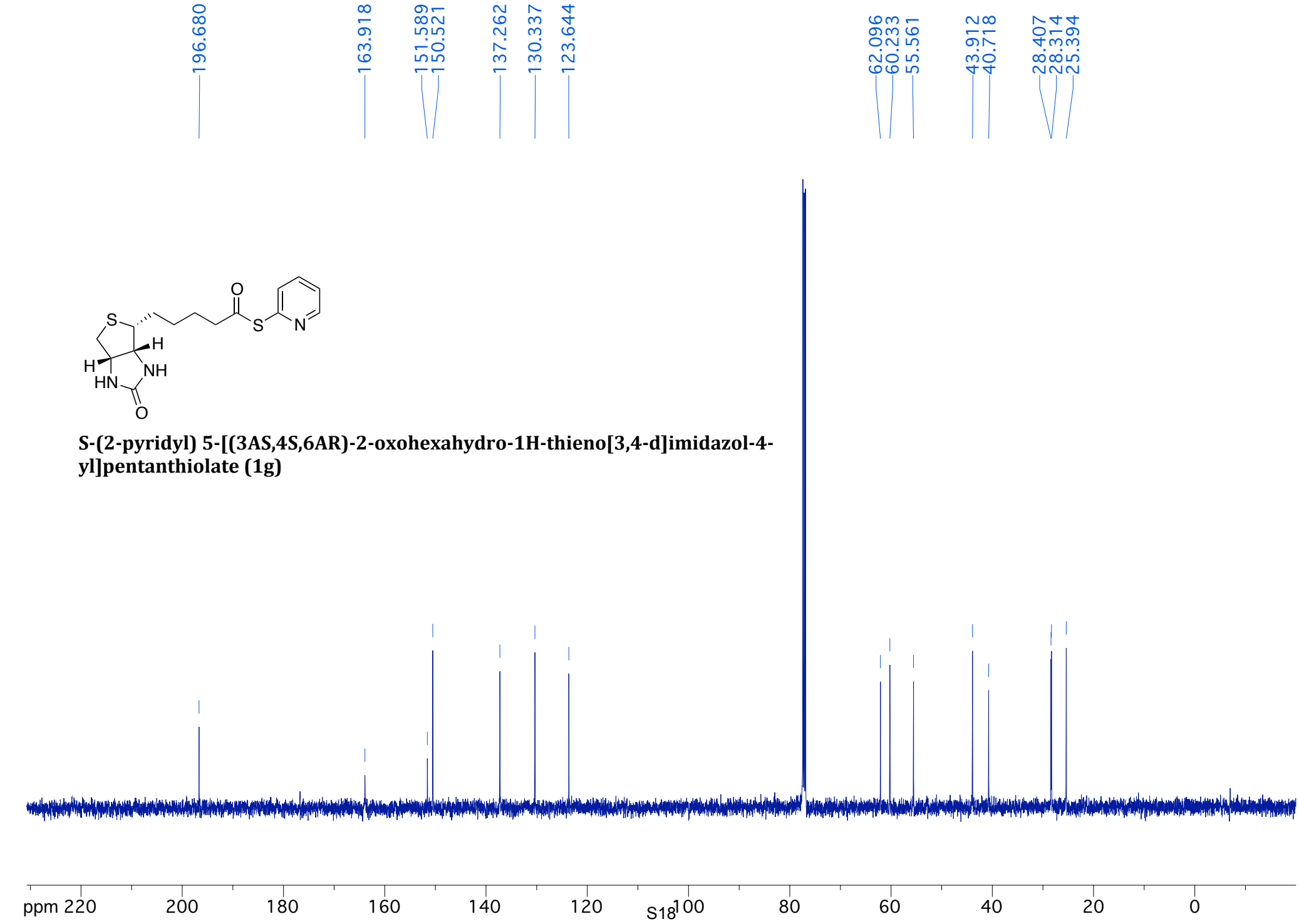
ethyl 4-oxo-4-(pyridin-2-ylthio)butanoate (1b)



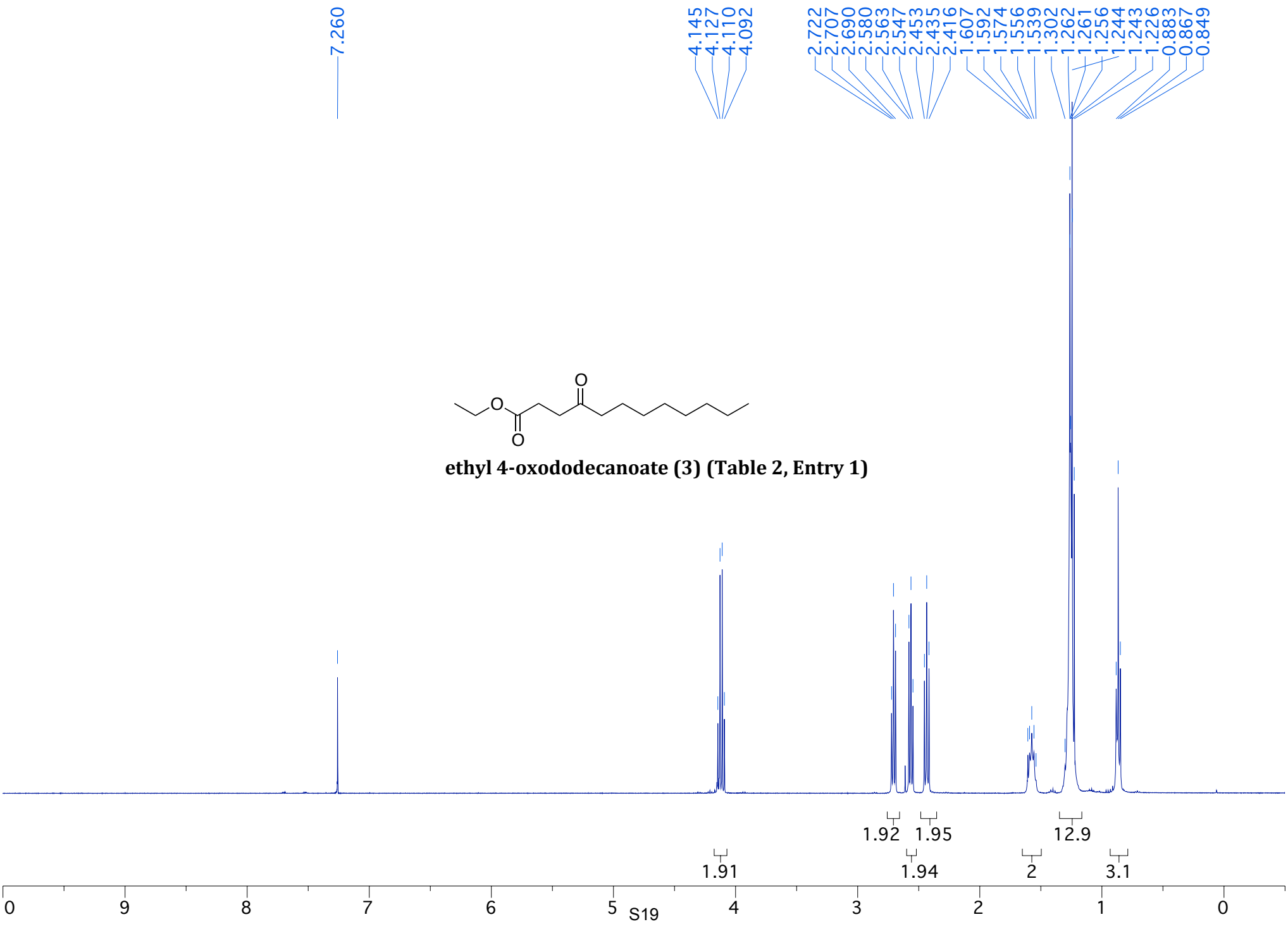
ethyl 4-oxo-4-(pyridin-2-ylthio)butanoate (1b)



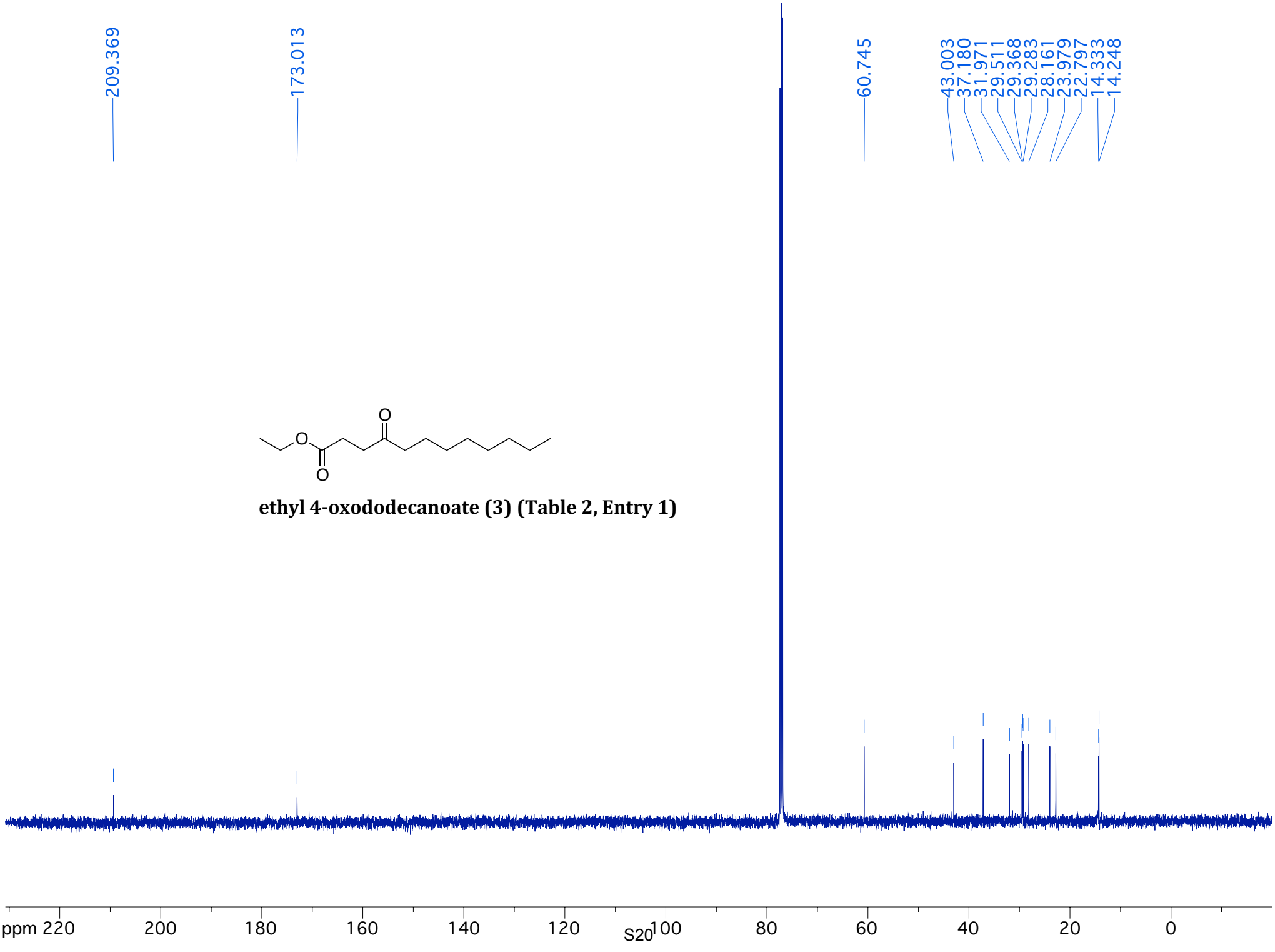
S-(2-pyridyl) 5-[(3AS,4S,6AR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl]pentanthiolate (1g)



S-(2-pyridyl) 5-[(3AS,4S,6AR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl]pentanthiolate (1g)



ethyl 4-oxododecanoate (3) (Table 2, Entry 1)



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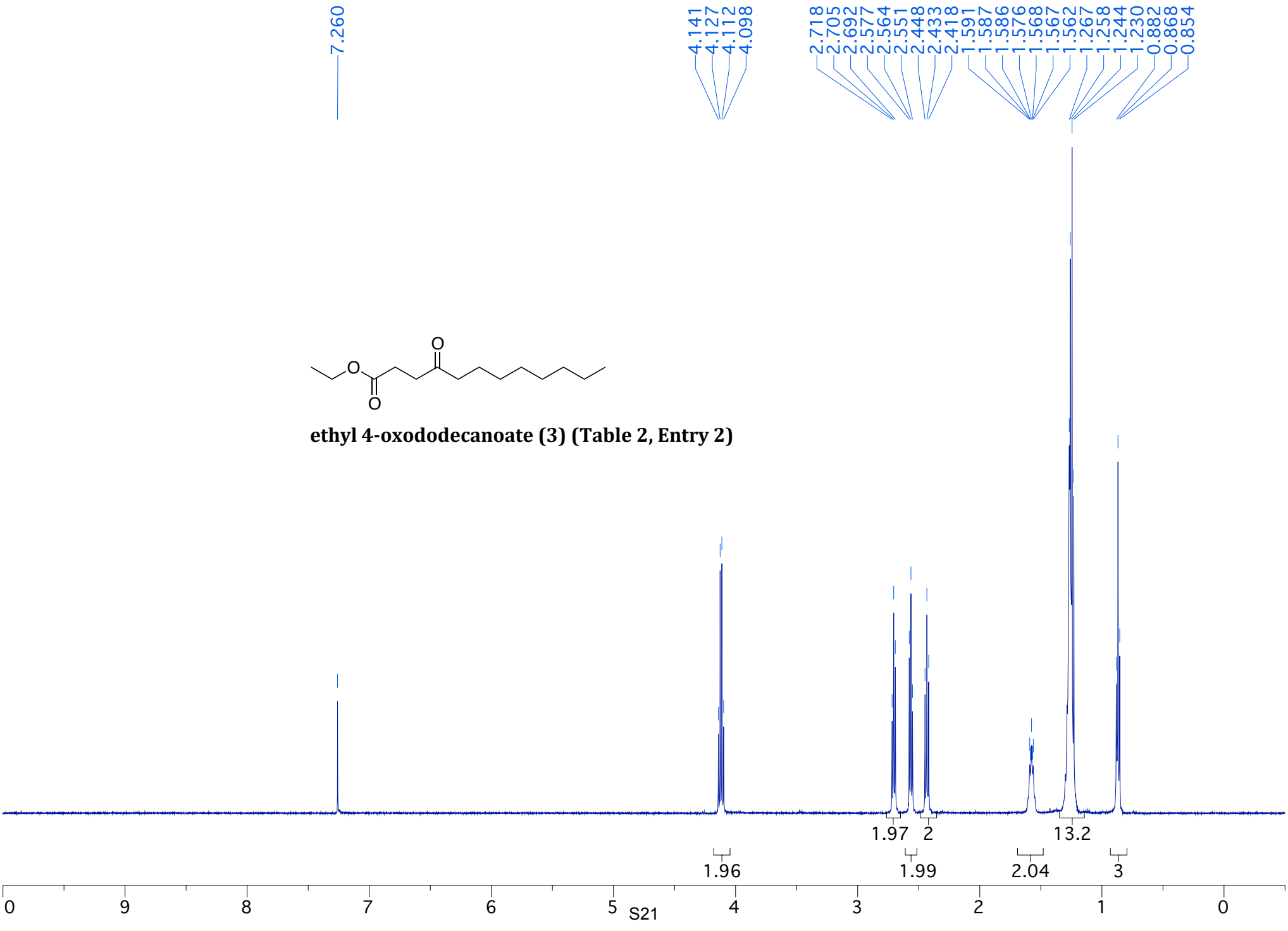
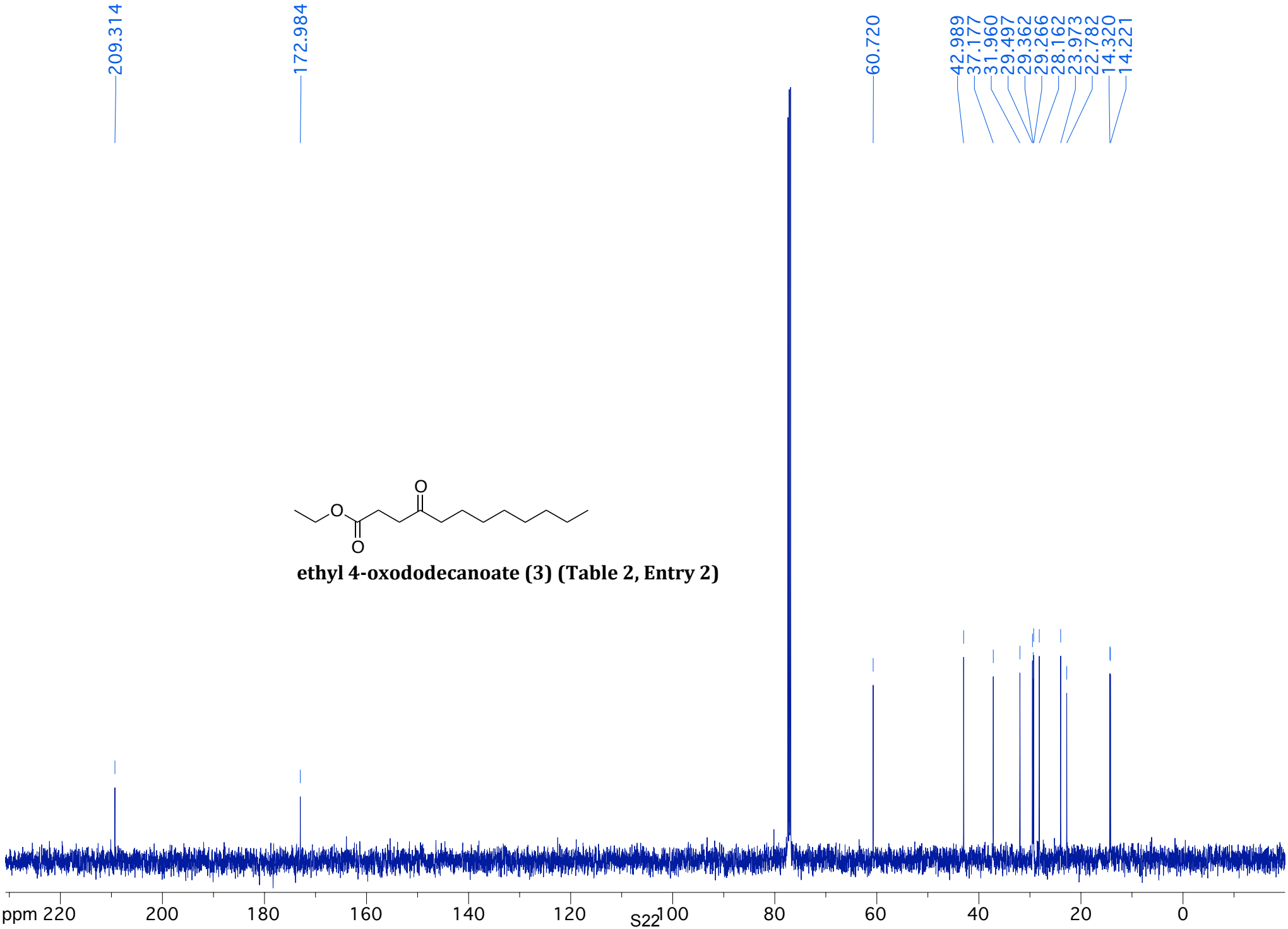
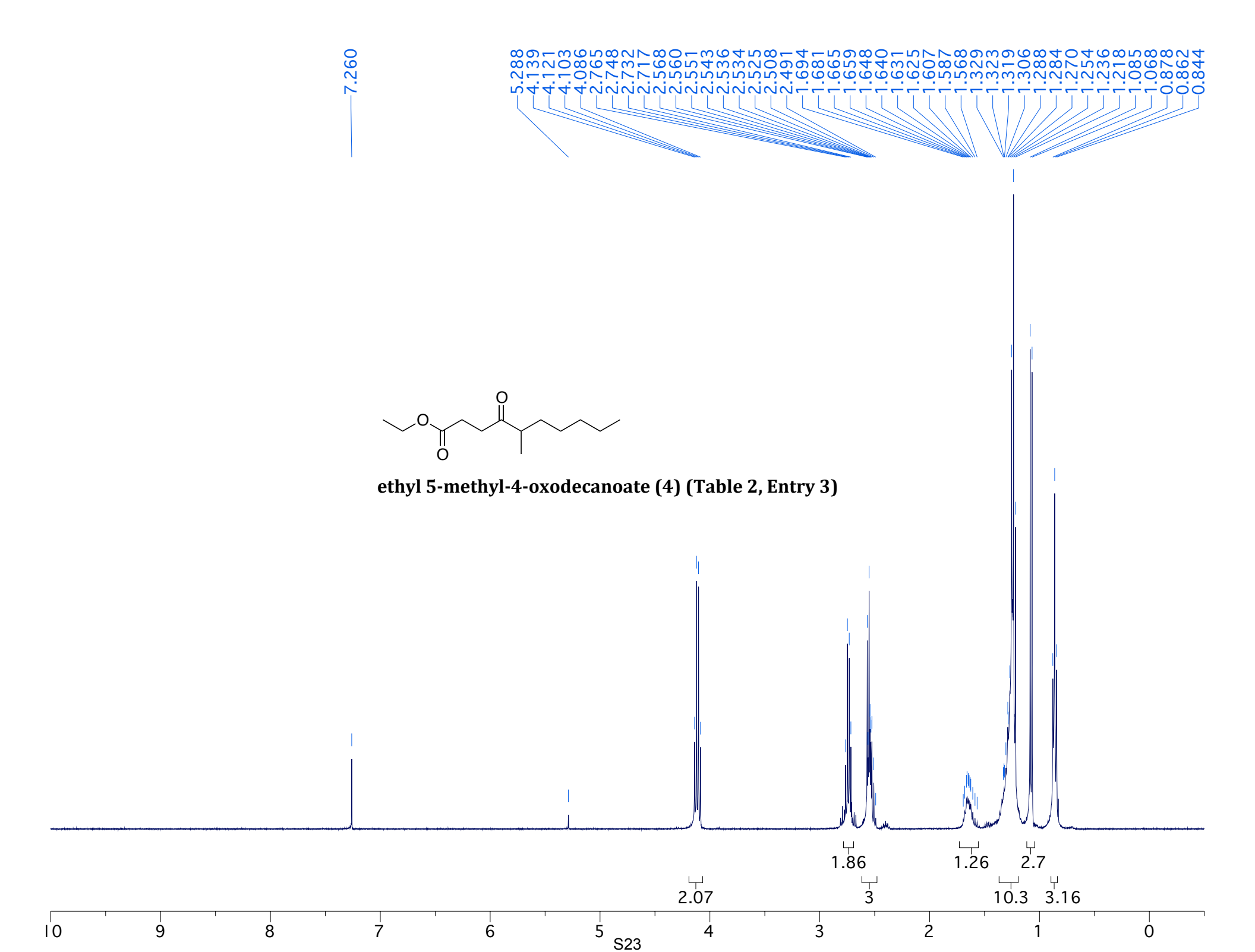


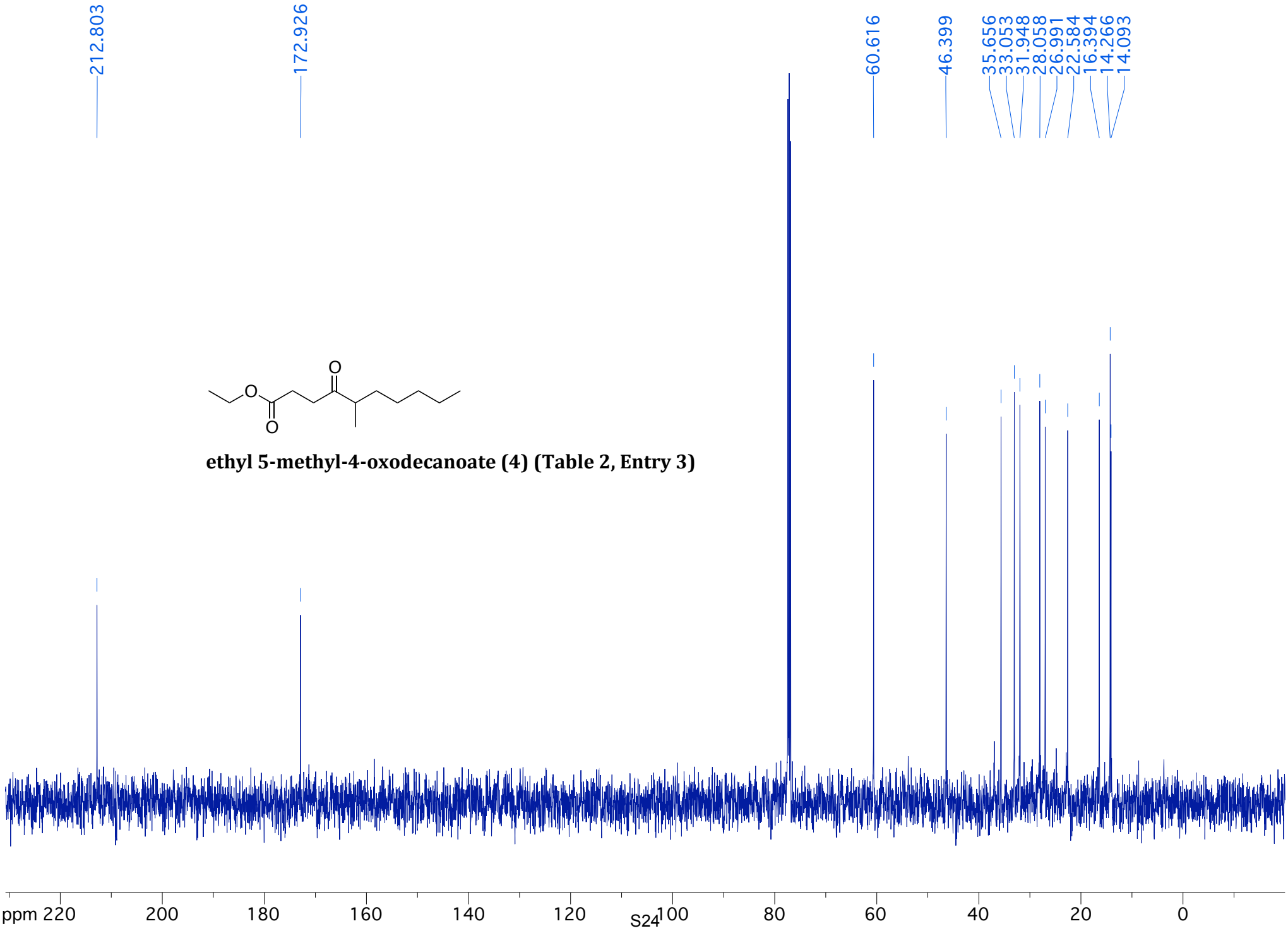
ethyl 4-oxododecanoate (3) (Table 2, Entry 2)



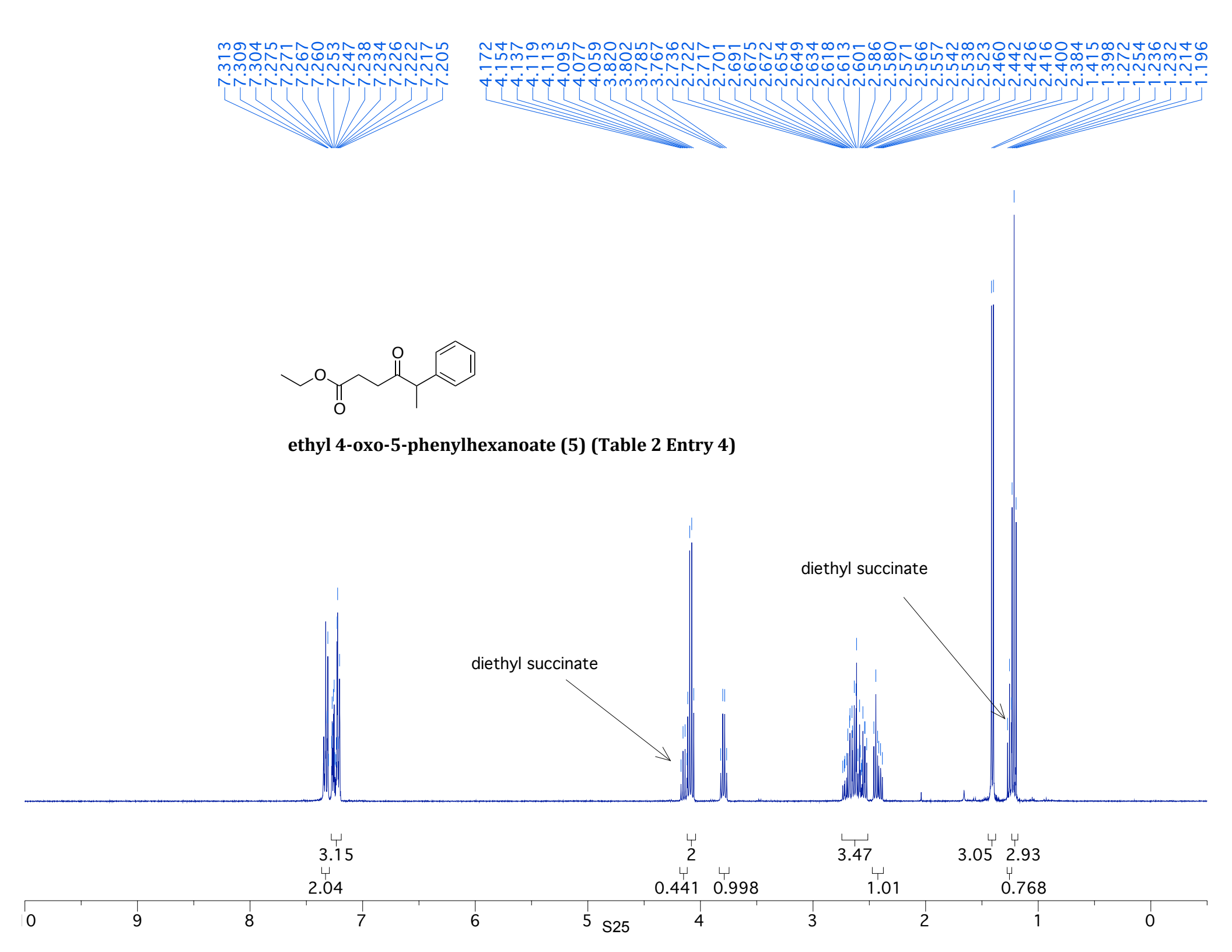
ethyl 4-oxododecanoate (3) (Table 2, Entry 2)



ethyl 5-methyl-4-oxodecanoate (4) (Table 2, Entry 3)



ethyl 5-methyl-4-oxodecanoate (4) (Table 2, Entry 3)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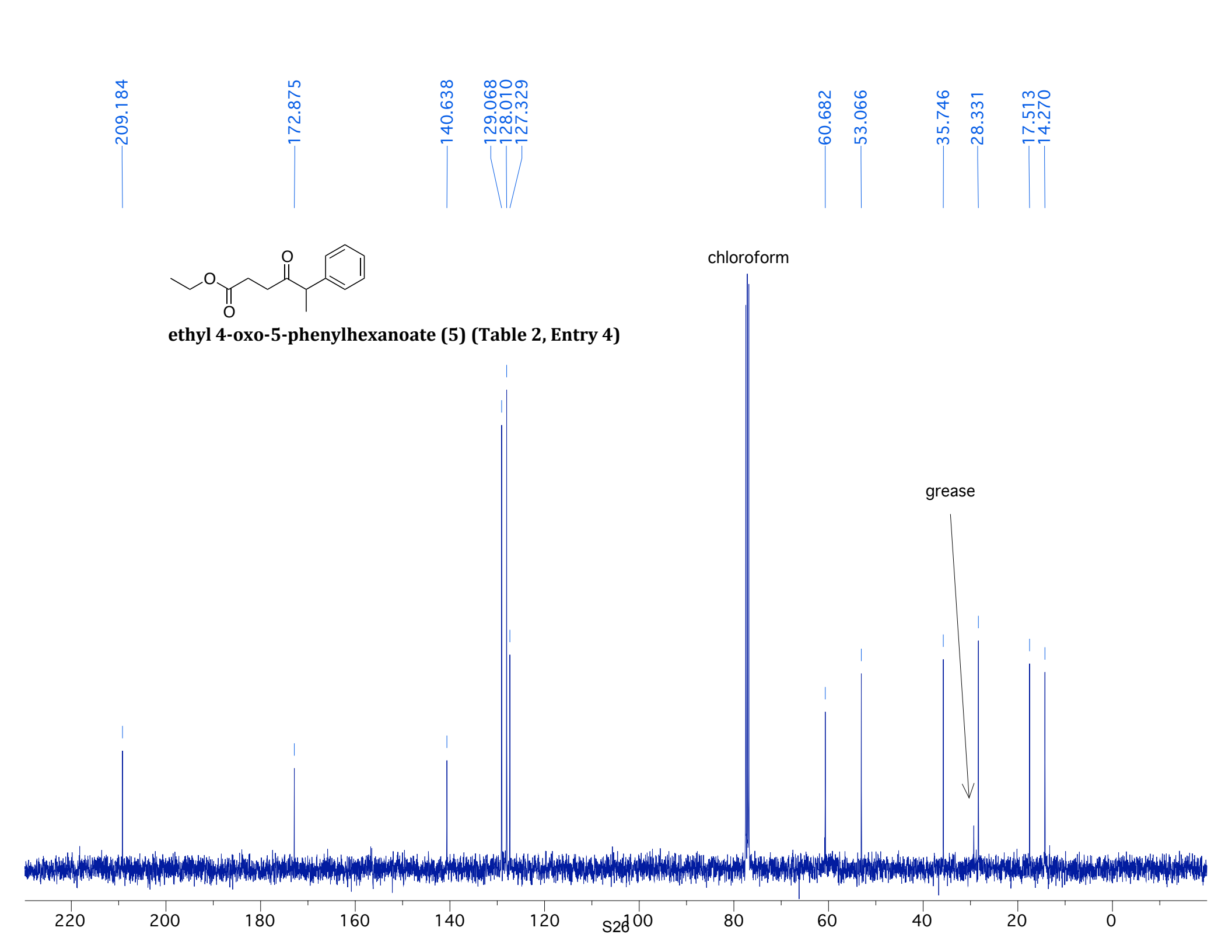
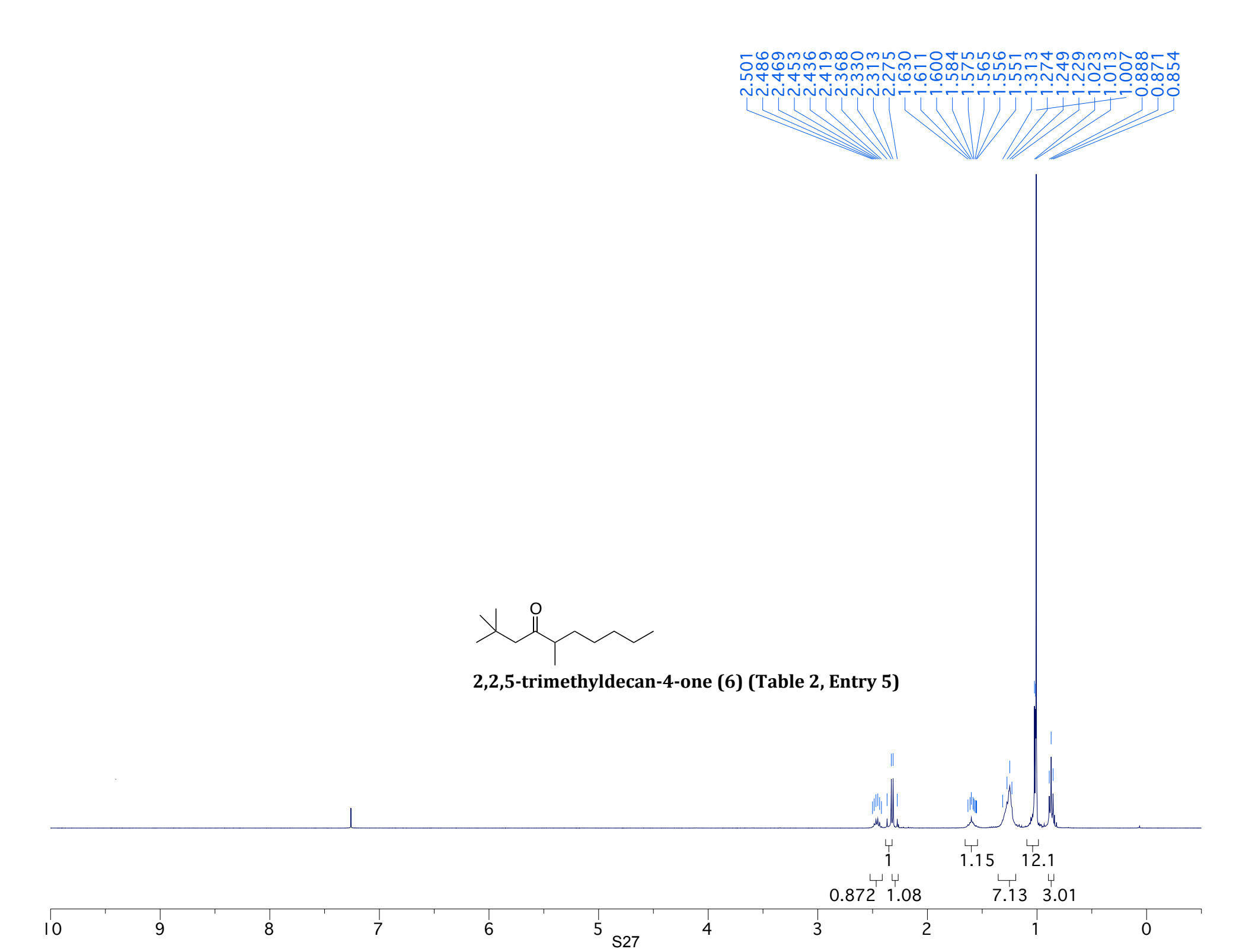
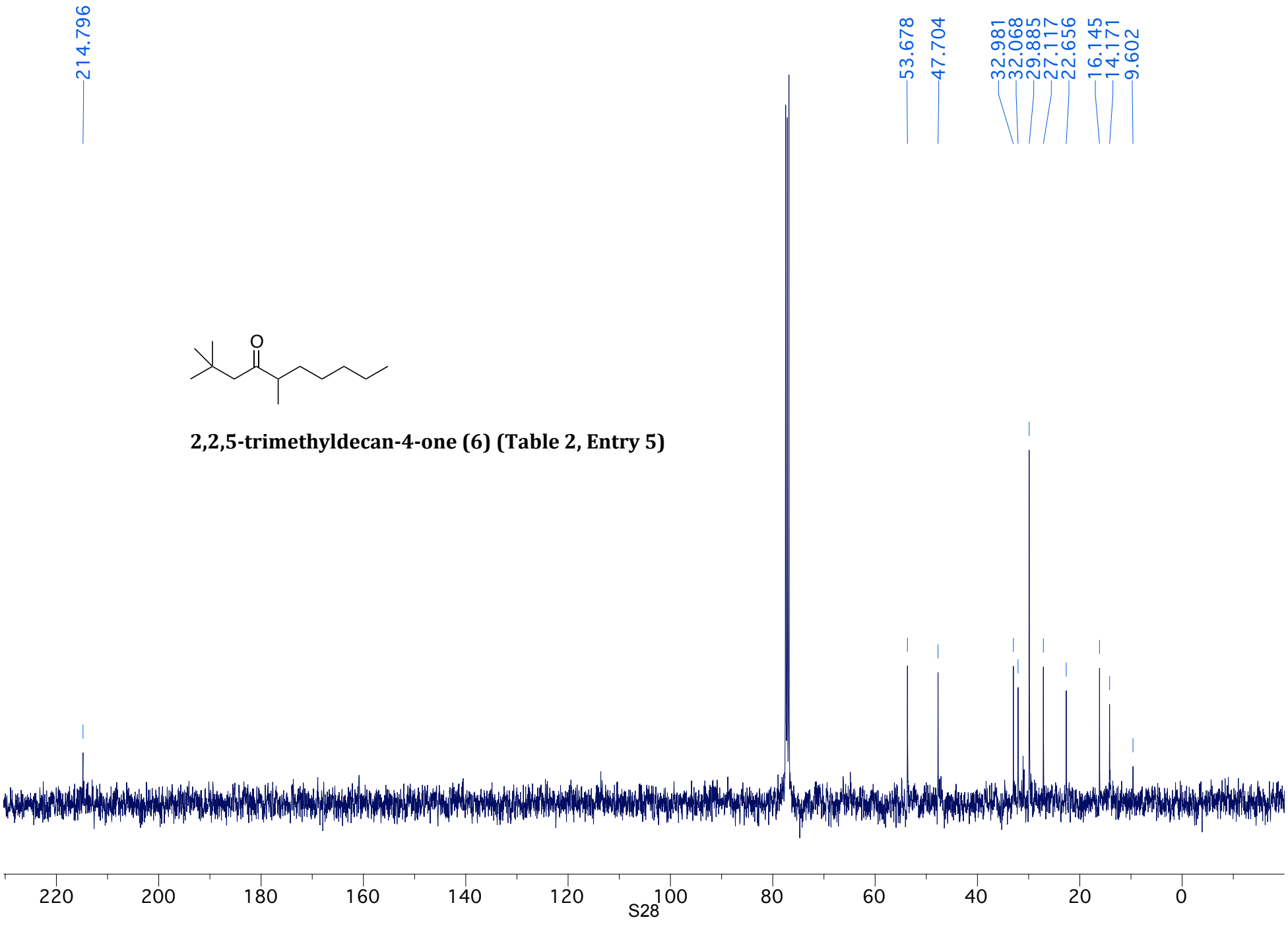
7.275
7.271
7.267
7.260
7.253
7.247
7.238
7.234
7.226
7.222
7.217
7.205
4.172
4.154
4.137
4.119
4.113
4.095
4.077
4.059
3.820
3.802
3.785
3.767
2.736
2.722
2.717
2.701
2.691
2.675
2.672
2.654
2.649
2.634
2.618
2.613
2.601
2.586
2.580
2.571
2.566
2.557
2.542
2.538
2.523
2.460
2.442
2.426
2.416
2.400
2.384
1.415
1.398
1.272
1.254
1.236
1.232
1.214
1.196
O
O
O
ethyl 4-oxo-5-phenylhexanoate (5) (Table 2 Entry 4)
diethyl succinate
diethyl succinate
3.15
2.04
2
0.441
0.998
3.47
1.01
3.05
2.93
0.768
0
9
8
7
6
5
4
3
2
1
0



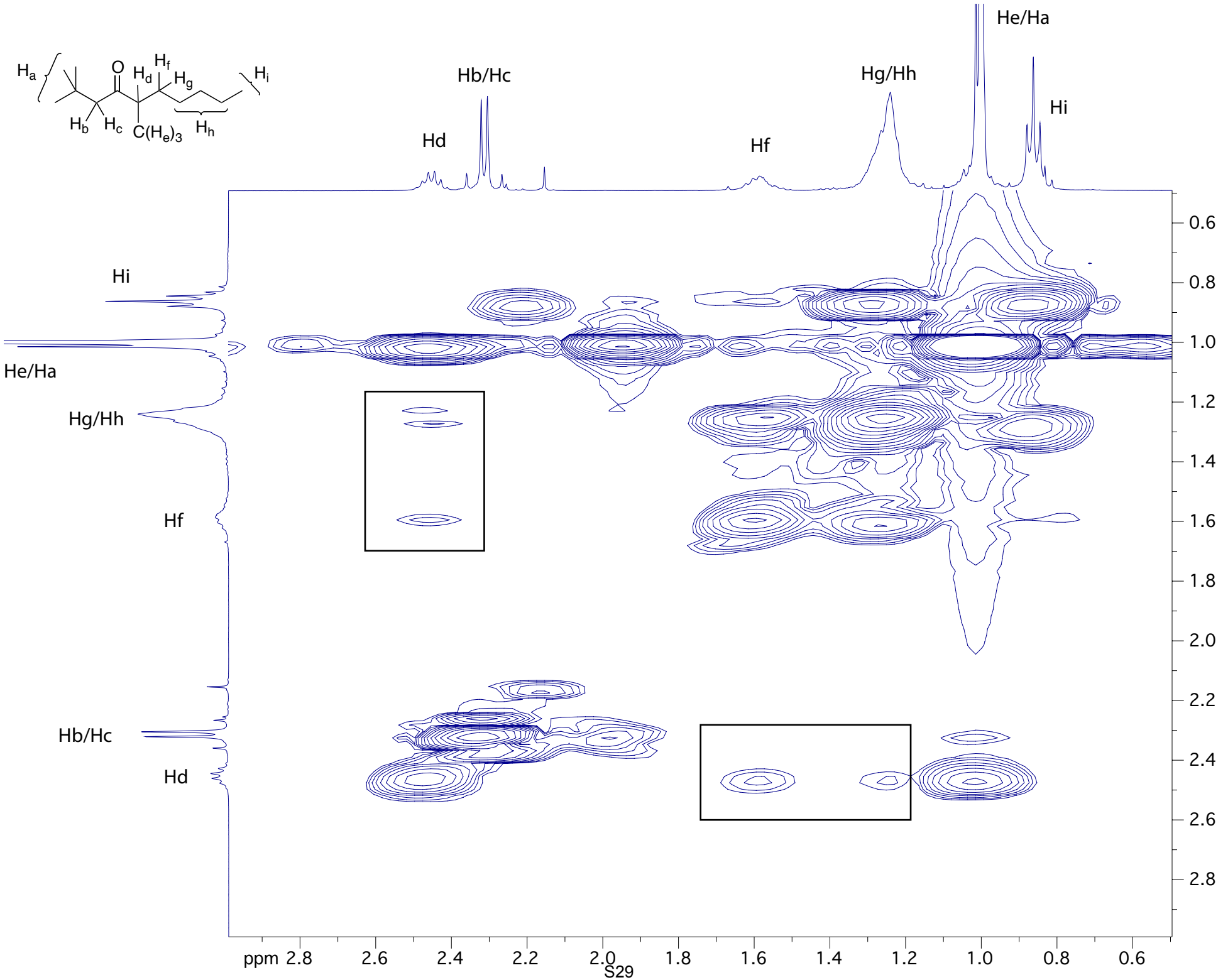
ethyl 4-oxo-5-phenylhexanoate (5) (Table 2, Entry 4)

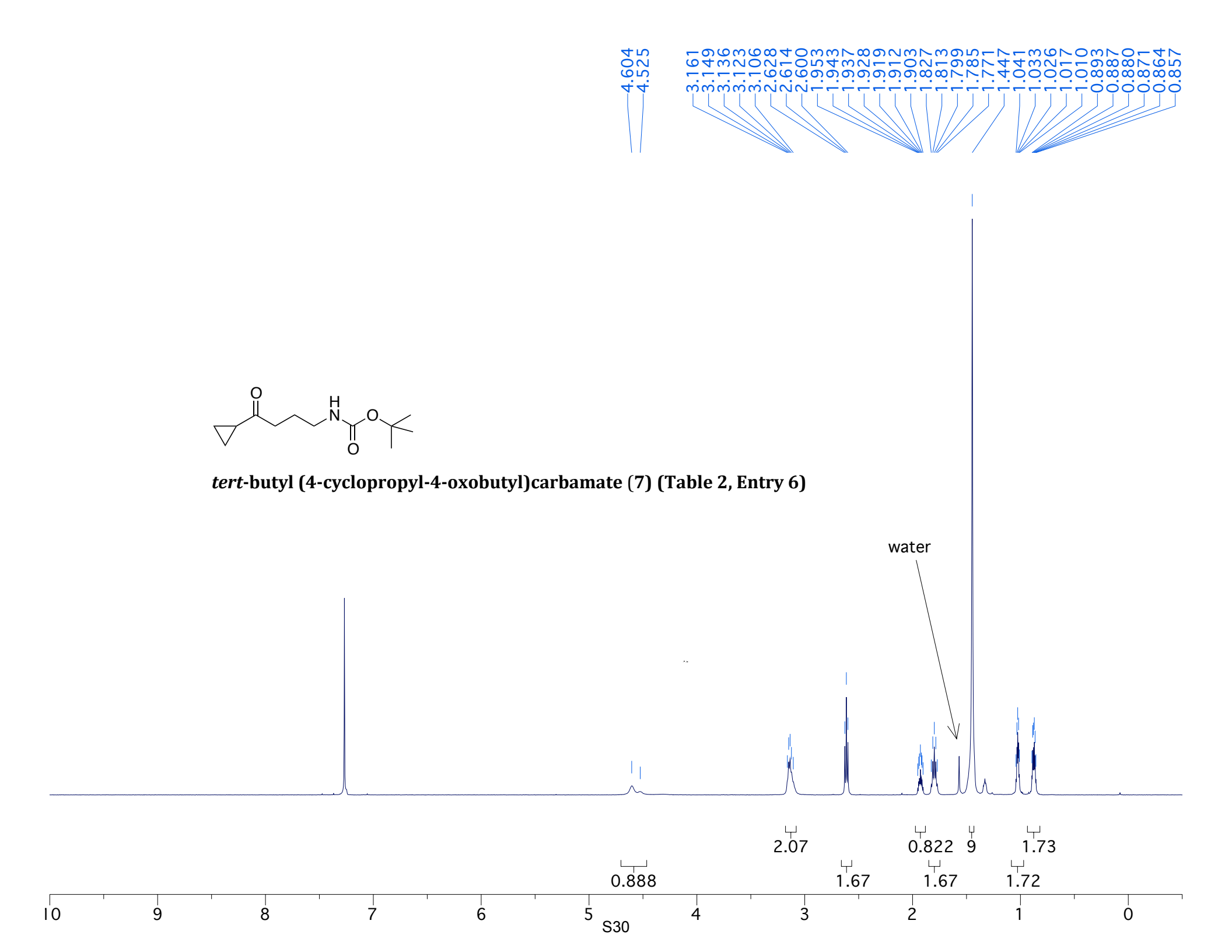


2,2,5-trimethyldecan-4-one (6) (Table 2, Entry 5)

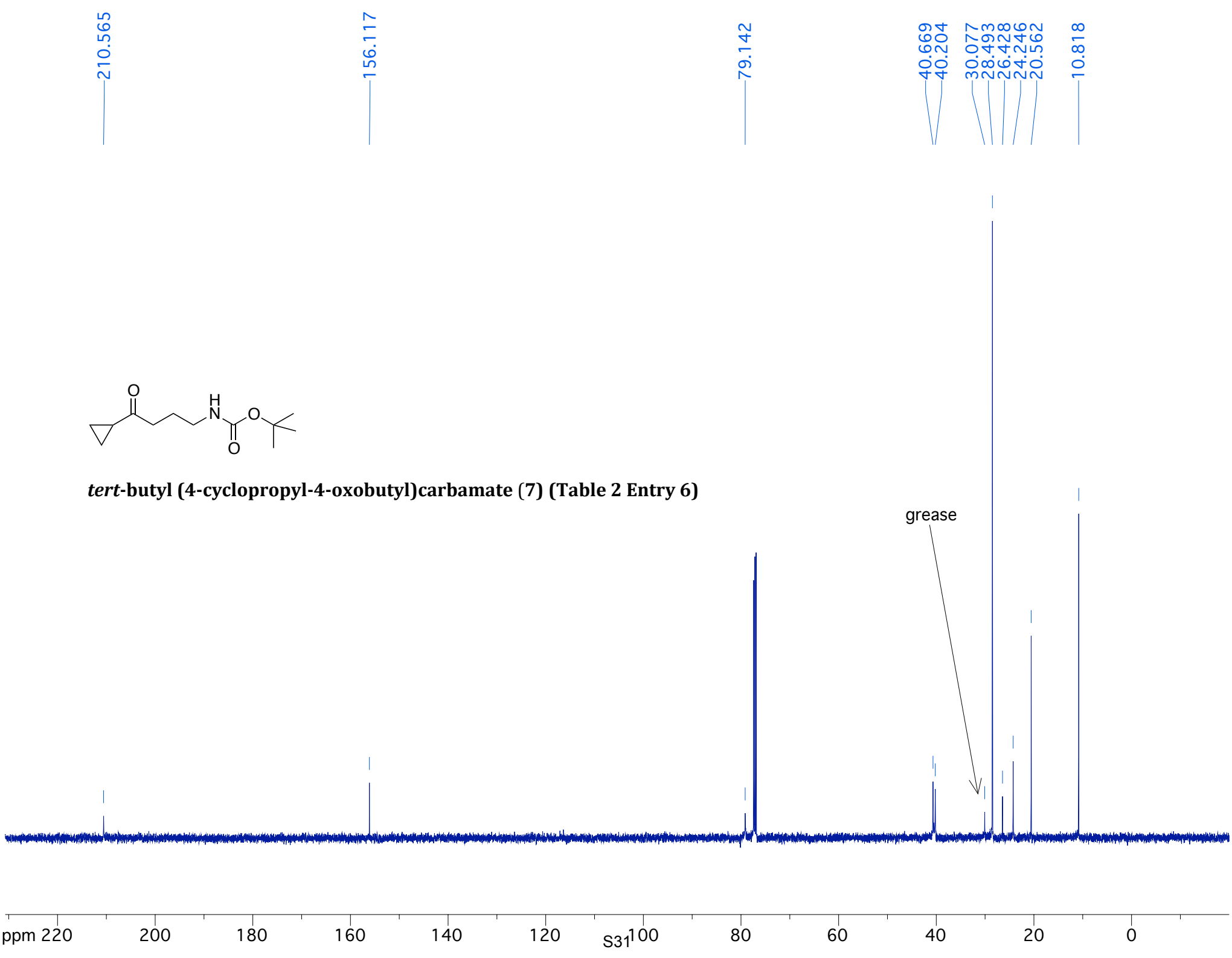


2,2,5-trimethyldecan-4-one (6) (Table 2, Entry 5)

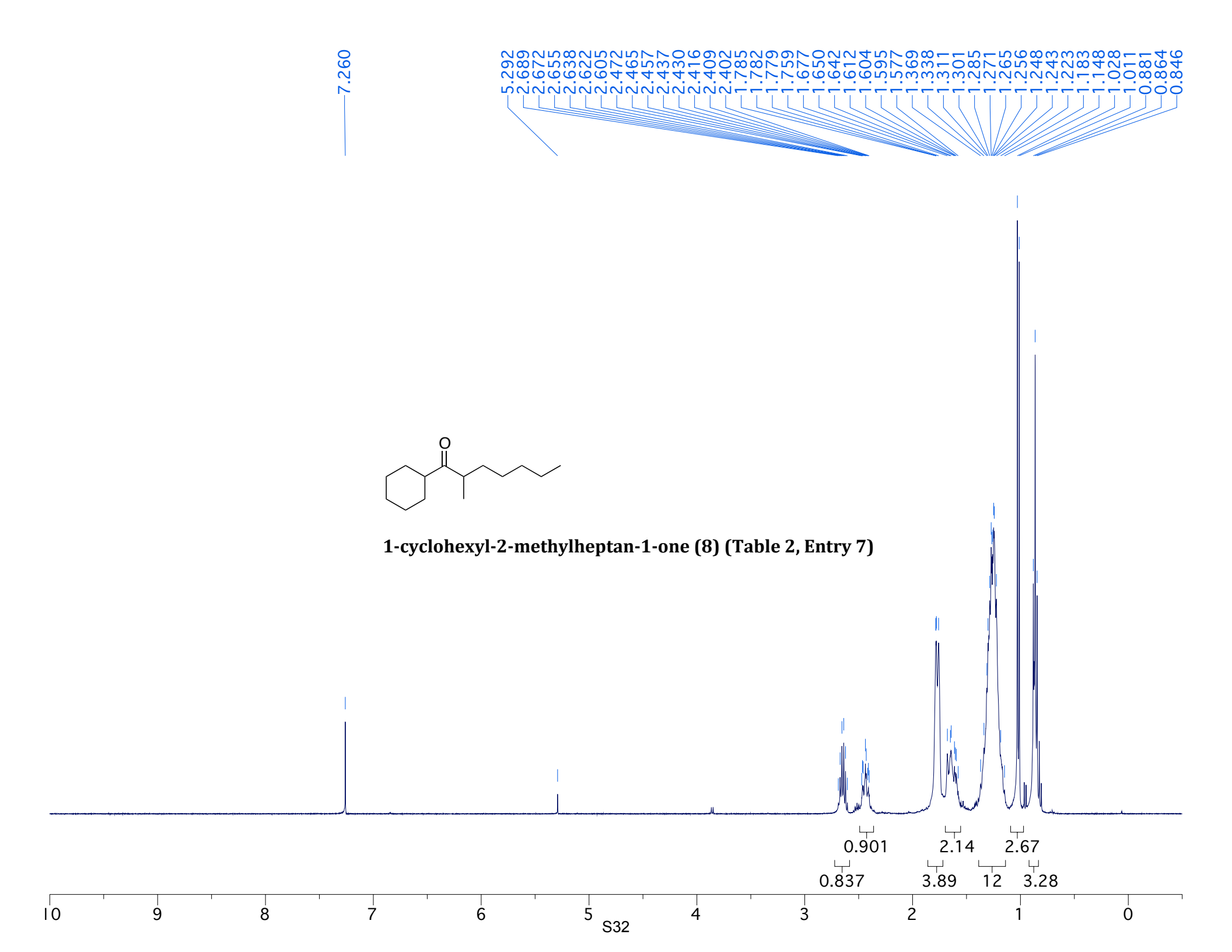

Ha
O
Hf
Hd
Hg
Hi
Hb
Hc
C(He)3
Hh
He/Ha
Hb/Hc
Hg/Hh
Hi
Hd
Hf
Hi
He/Ha
Hg/Hh
Hf
Hb/Hc
Hd
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
ppm 2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6



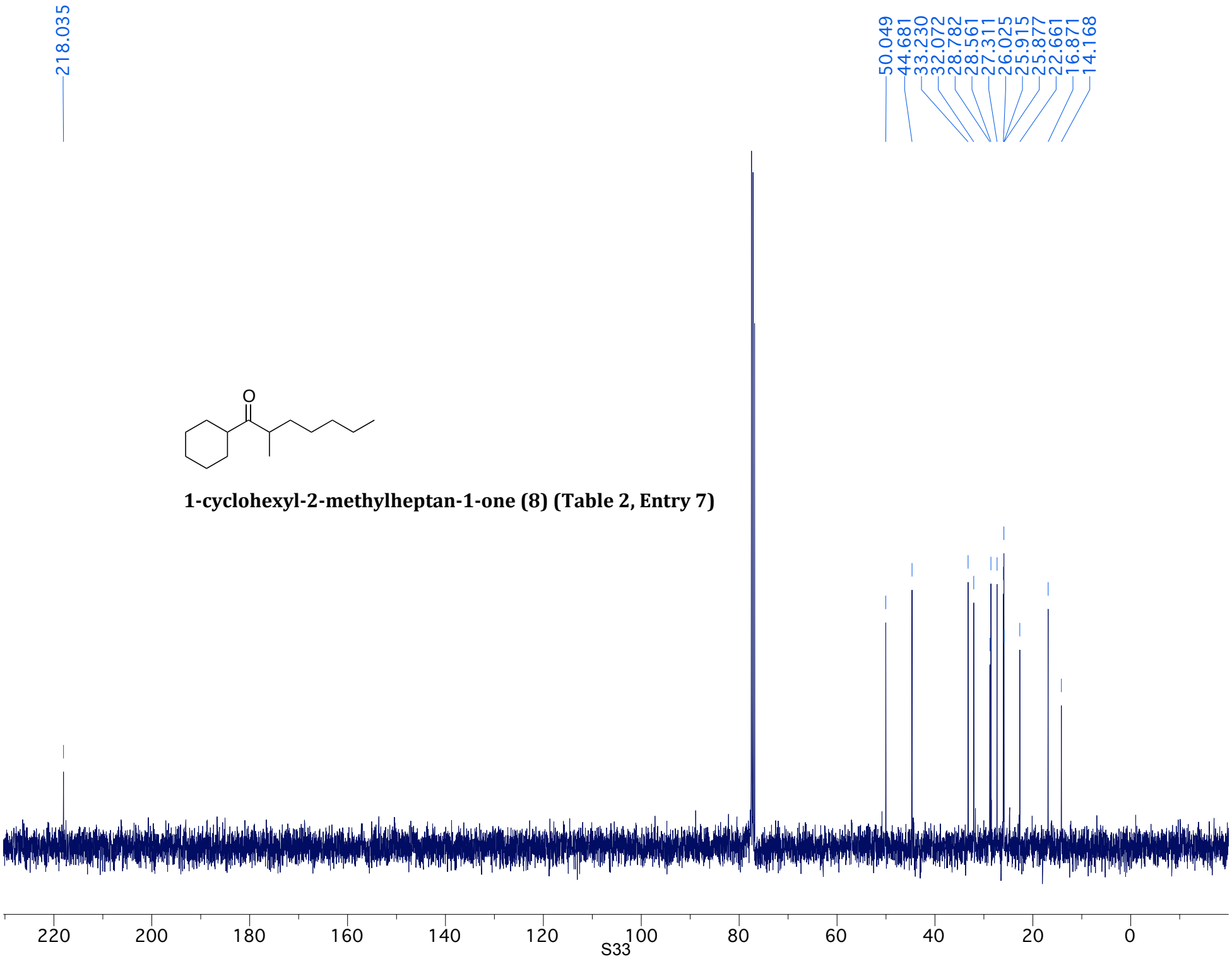
***tert*-butyl (4-cyclopropyl-4-oxobutyl)carbamate (7) (Table 2, Entry 6)**



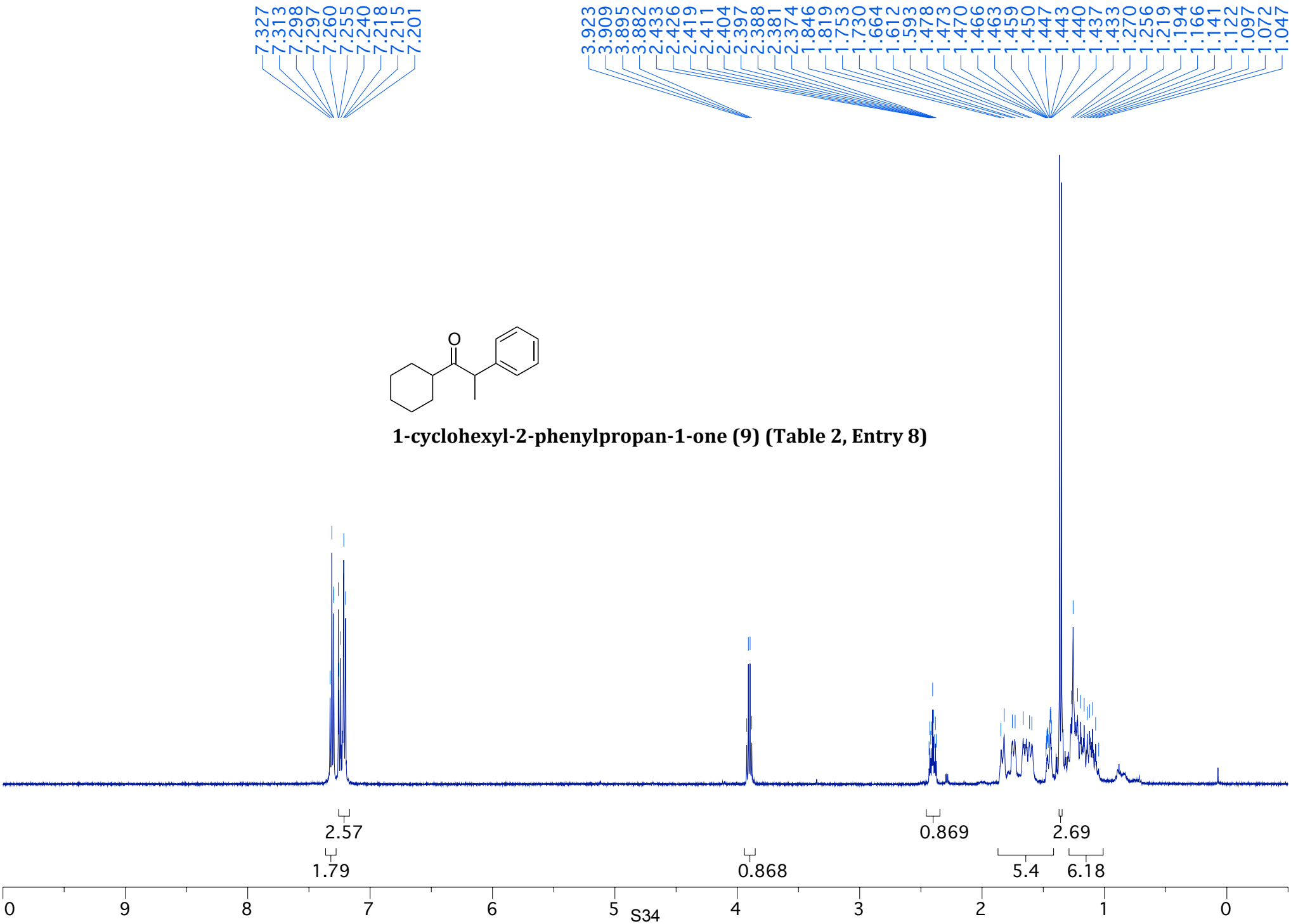
***tert*-butyl (4-cyclopropyl-4-oxobutyl)carbamate (7) (Table 2 Entry 6)**



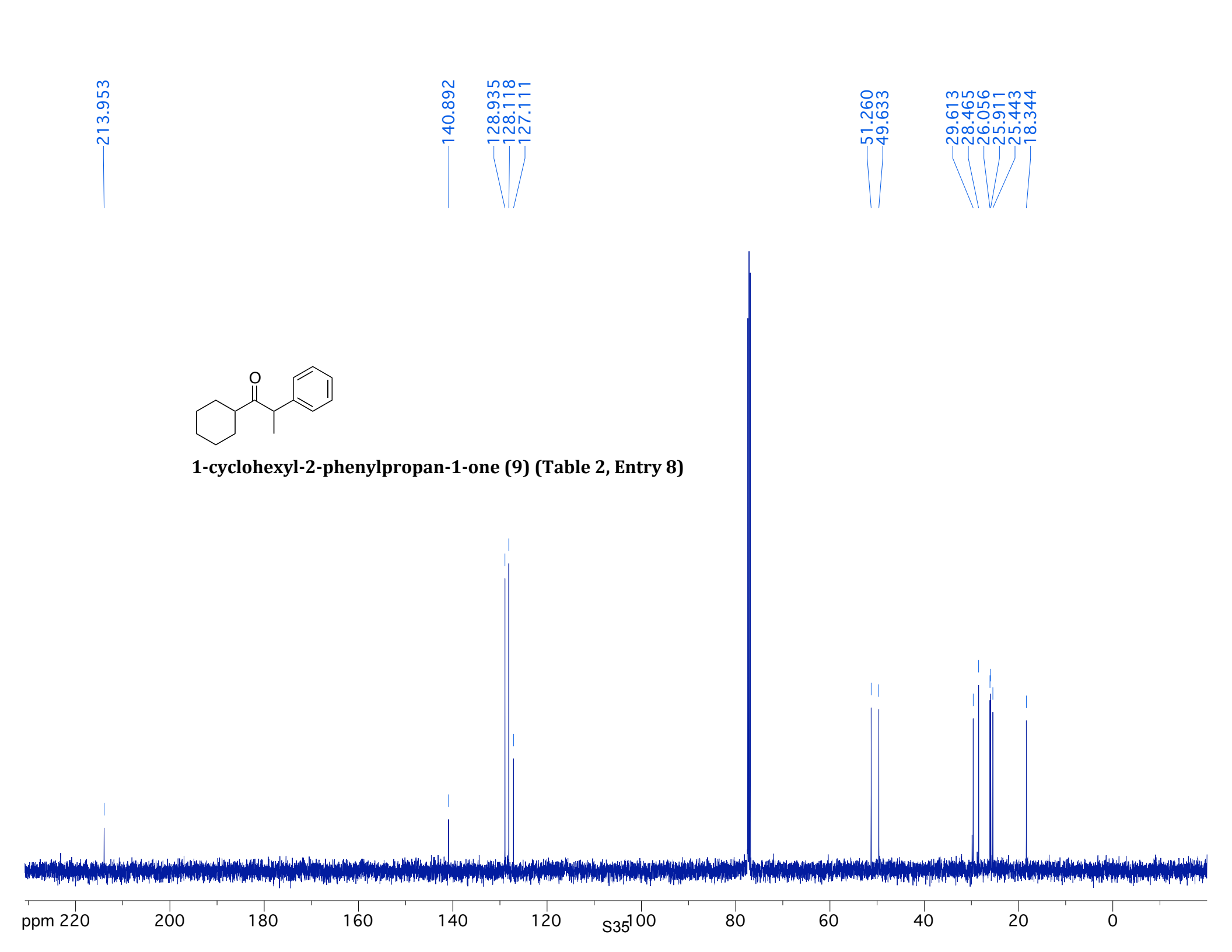
1-cyclohexyl-2-methylheptan-1-one (8) (Table 2, Entry 7)



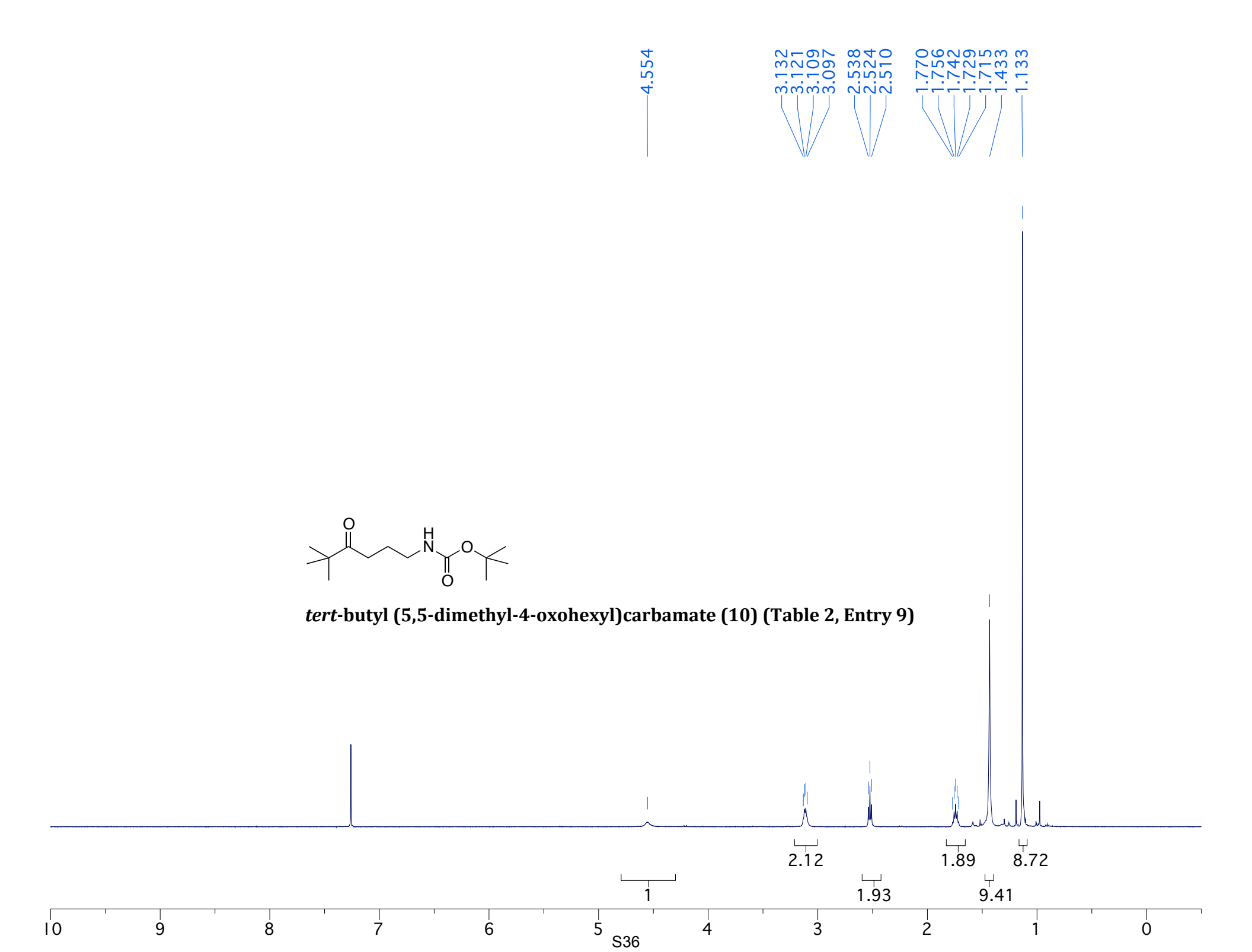
1-cyclohexyl-2-methylheptan-1-one (8) (Table 2, Entry 7)



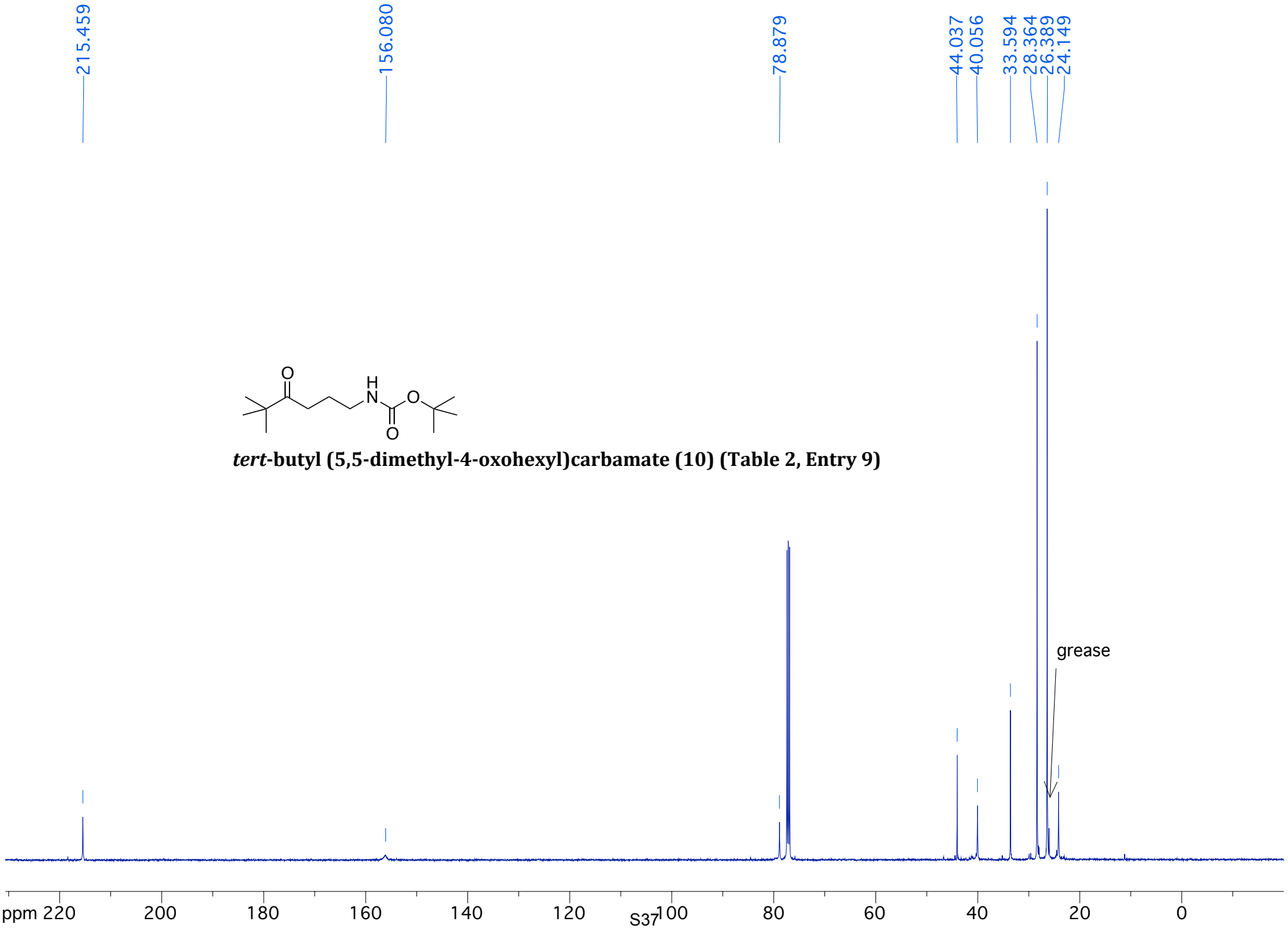
1-cyclohexyl-2-phenylpropan-1-one (9) (Table 2, Entry 8)



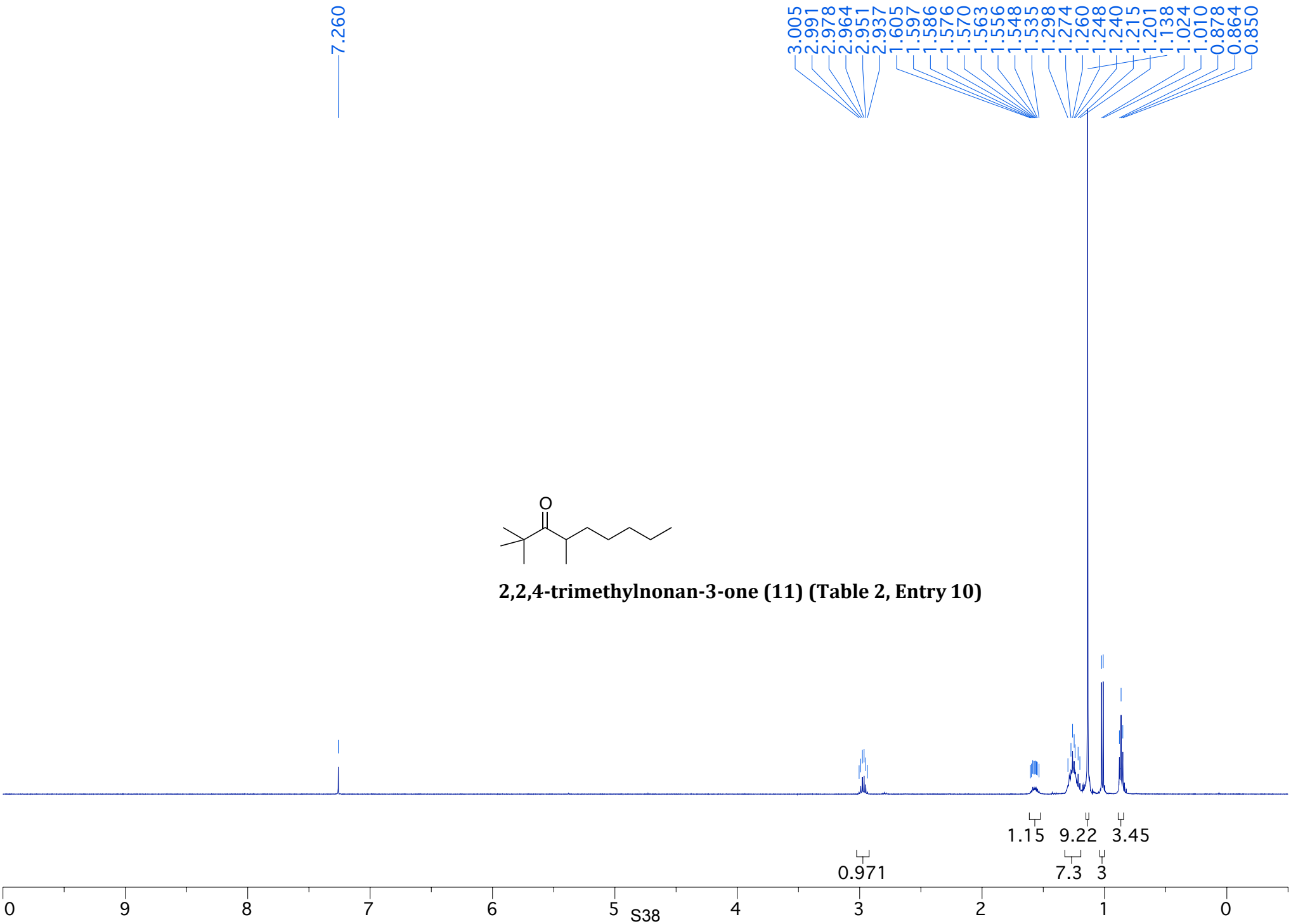
1-cyclohexyl-2-phenylpropan-1-one (9) (Table 2, Entry 8)



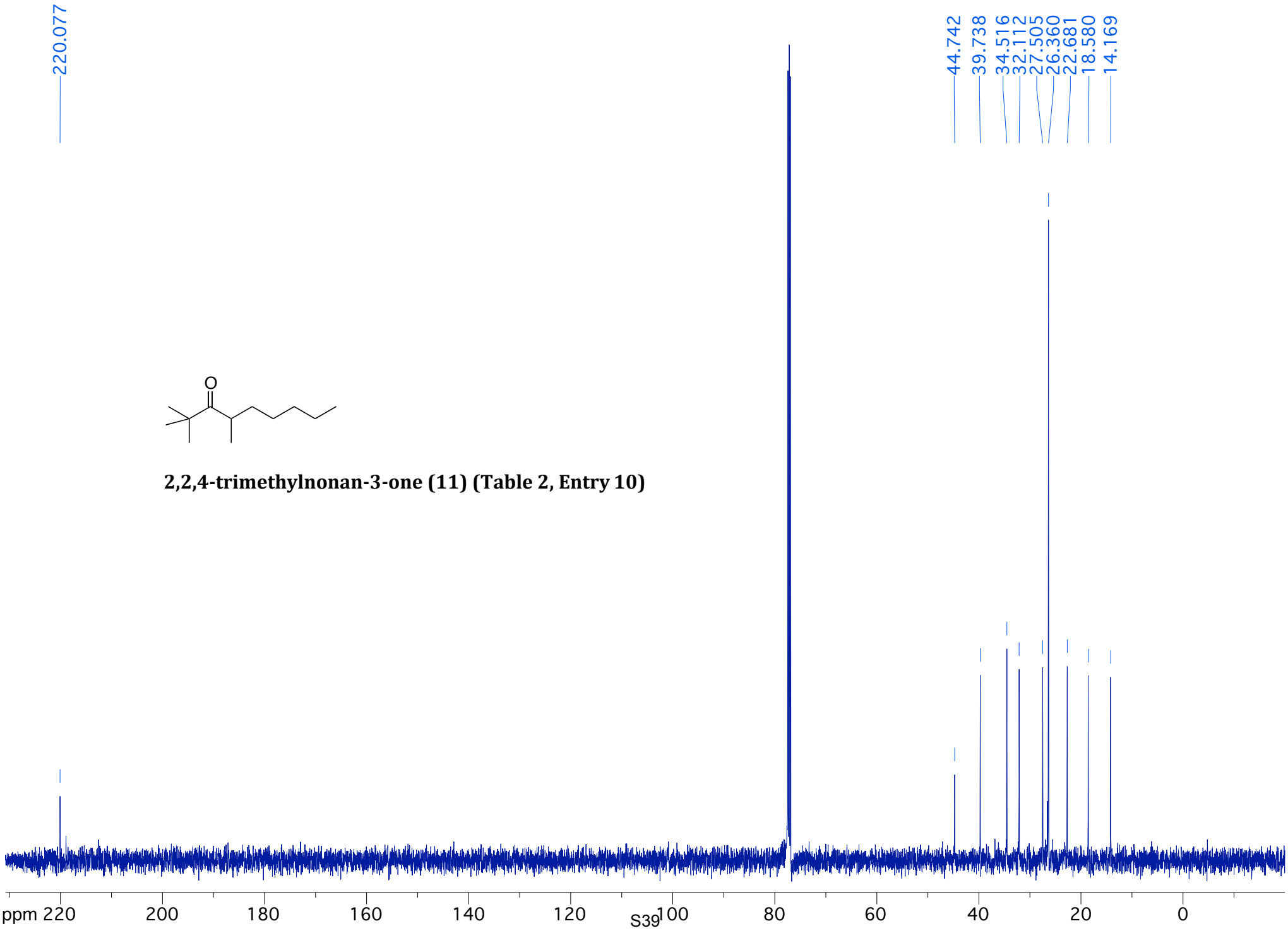
***tert*-butyl (5,5-dimethyl-4-oxohexyl)carbamate (10) (Table 2, Entry 9)**



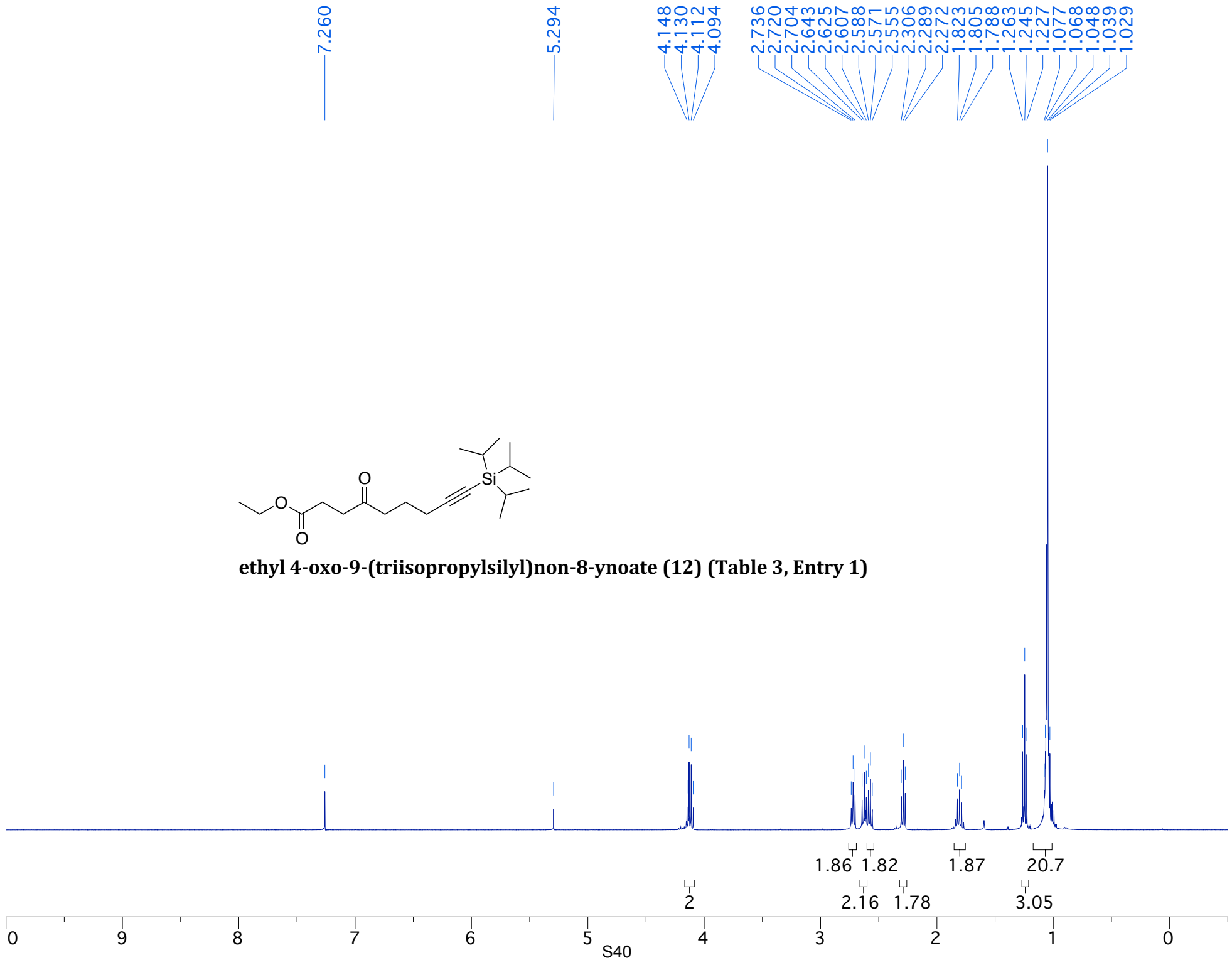
***tert*-butyl (5,5-dimethyl-4-oxohexyl)carbamate (10) (Table 2, Entry 9)**



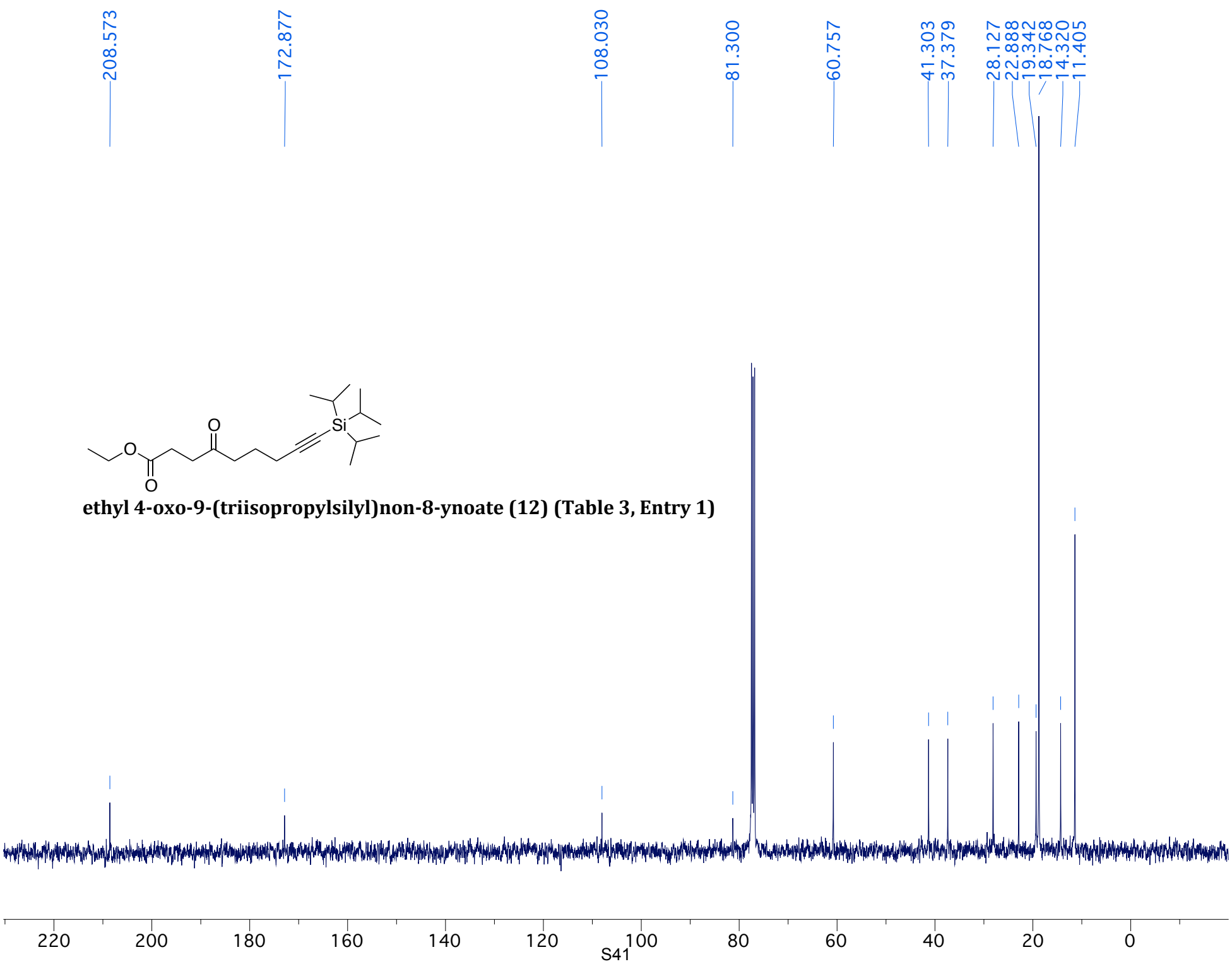
2,2,4-trimethylnonan-3-one (11) (Table 2, Entry 10)



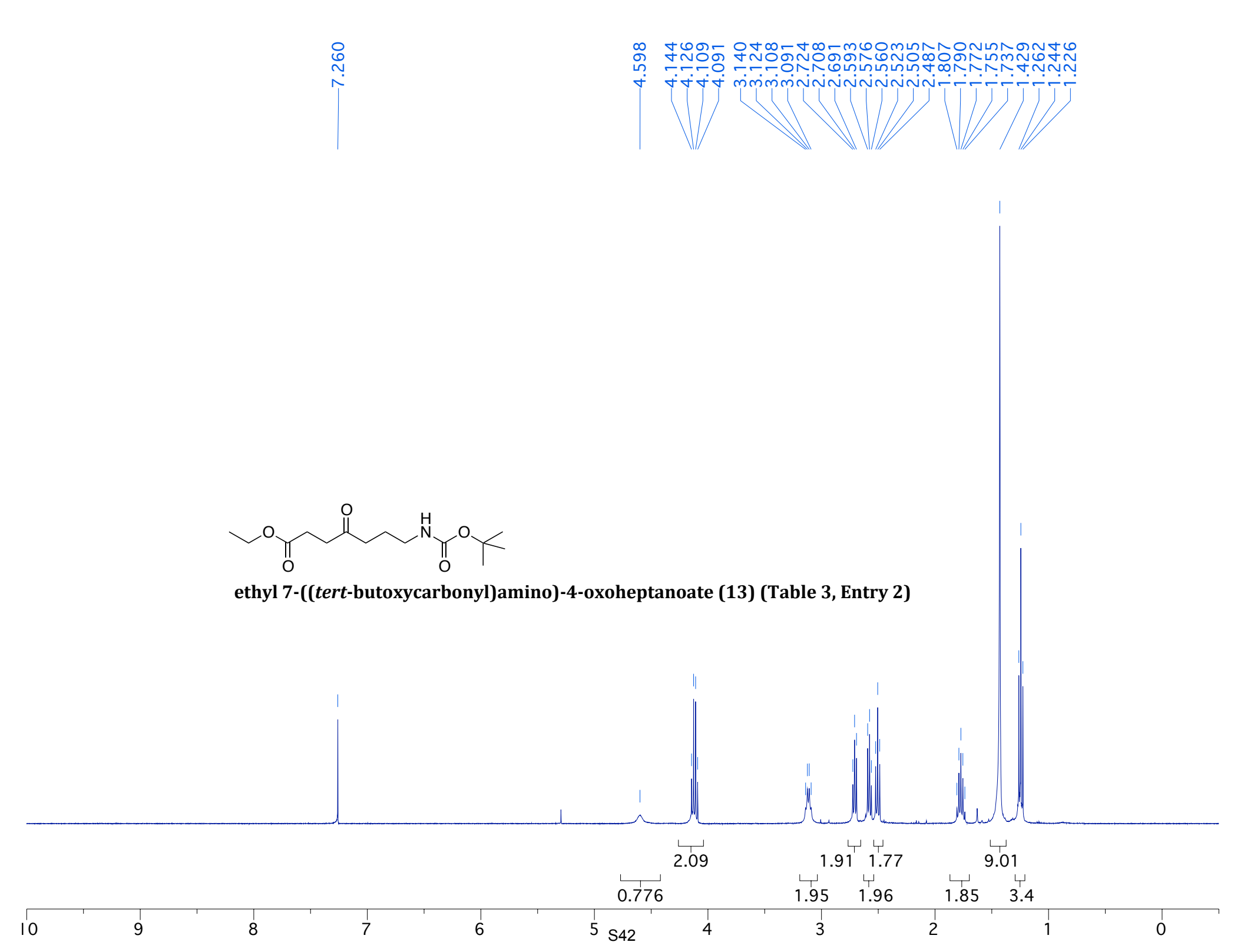
2,2,4-trimethylnonan-3-one (11) (Table 2, Entry 10)



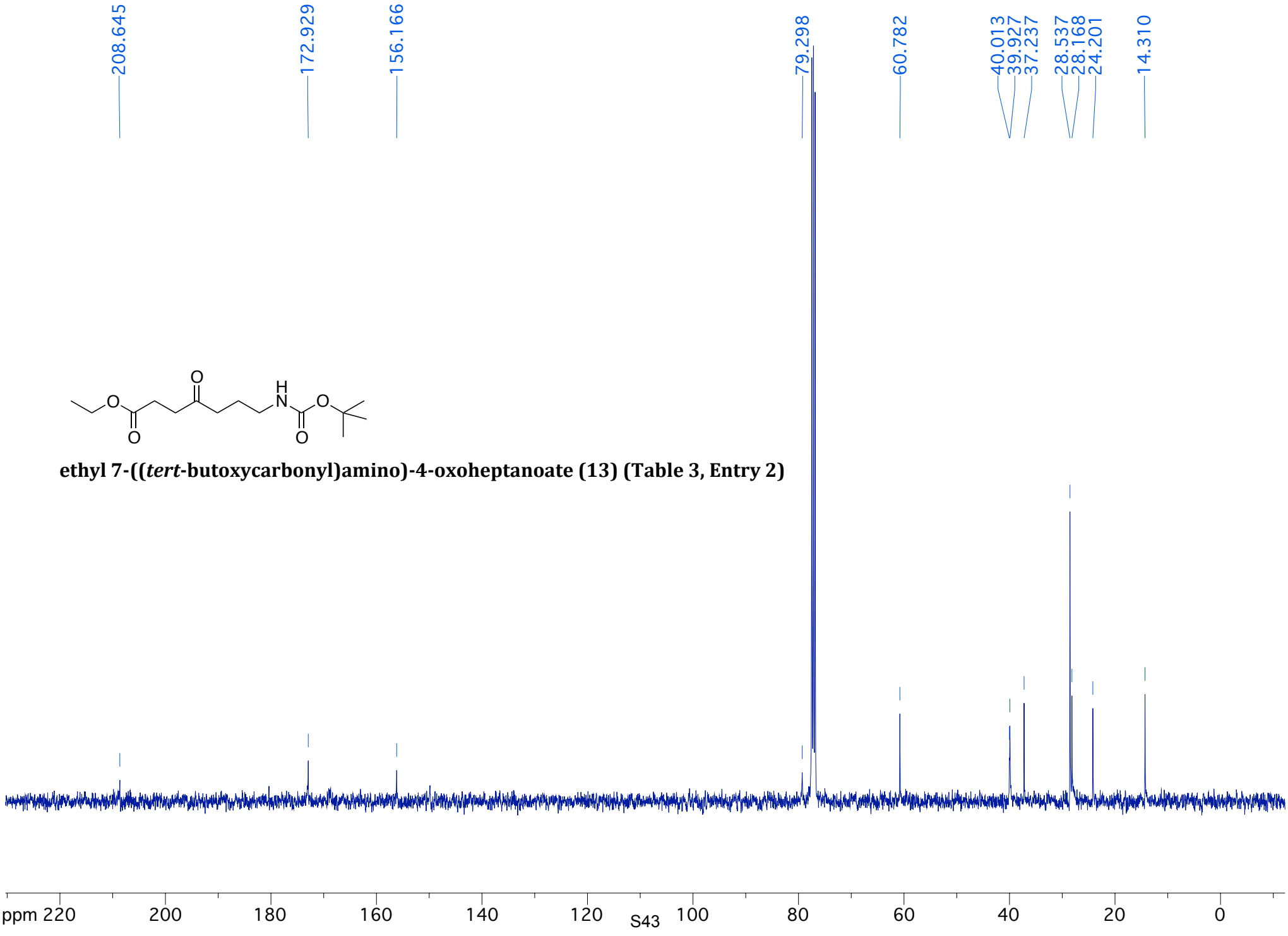
ethyl 4-oxo-9-(triisopropylsilyl)non-8-ynoate (12) (Table 3, Entry 1)



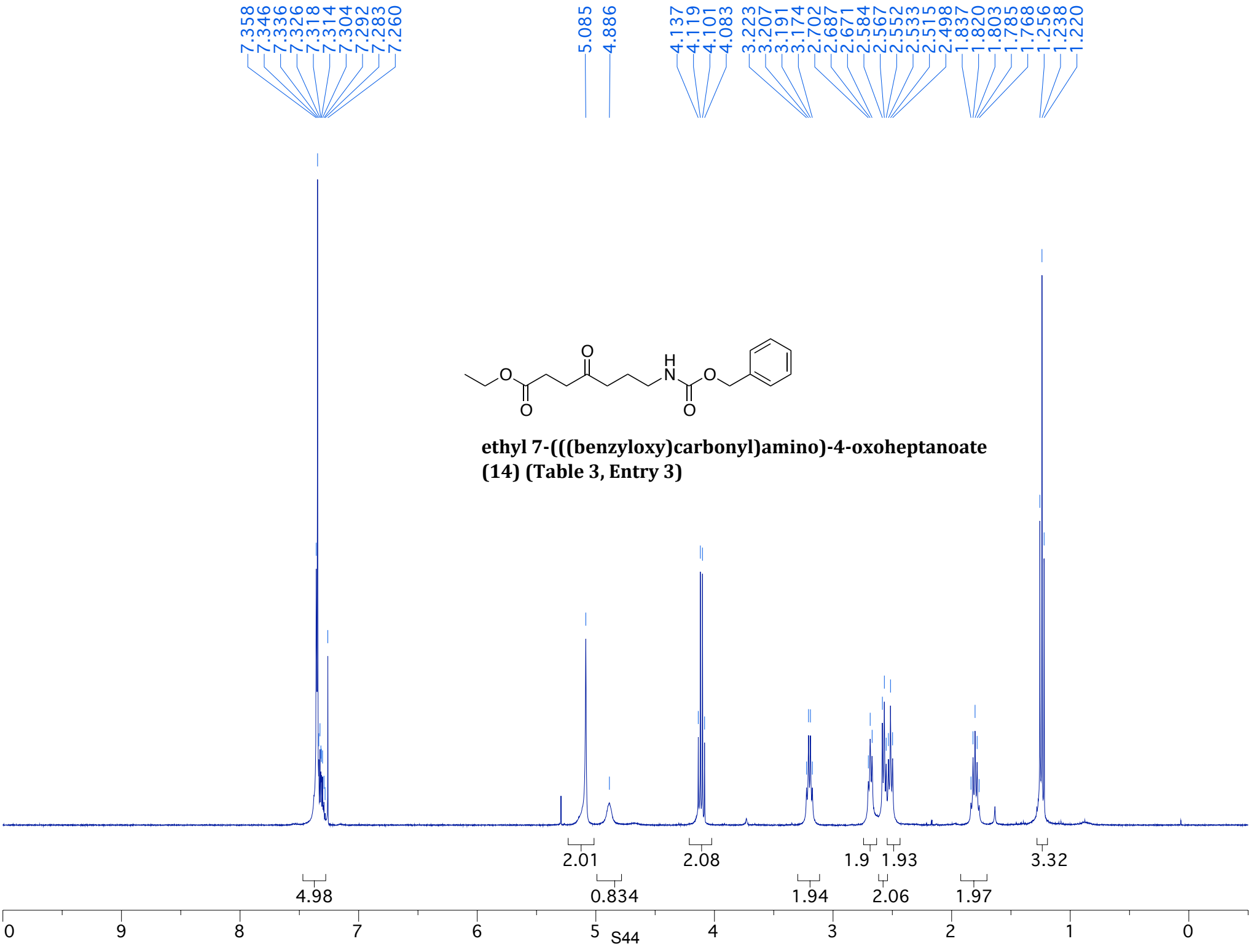
ethyl 4-oxo-9-(triisopropylsilyl)non-8-ynoate (12) (Table 3, Entry 1)



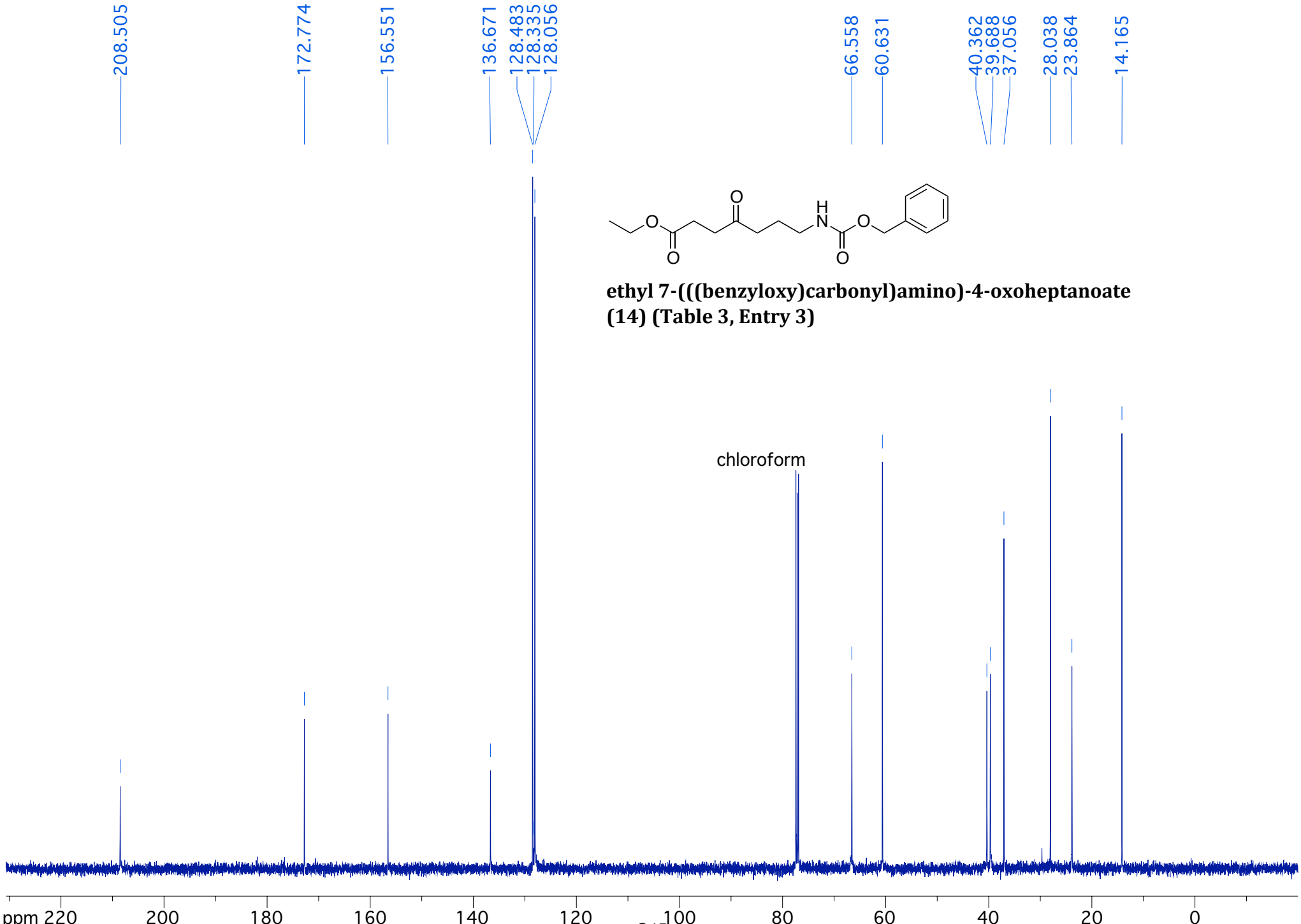
ethyl 7-((*tert*-butoxycarbonyl)amino)-4-oxoheptanoate (13) (Table 3, Entry 2)



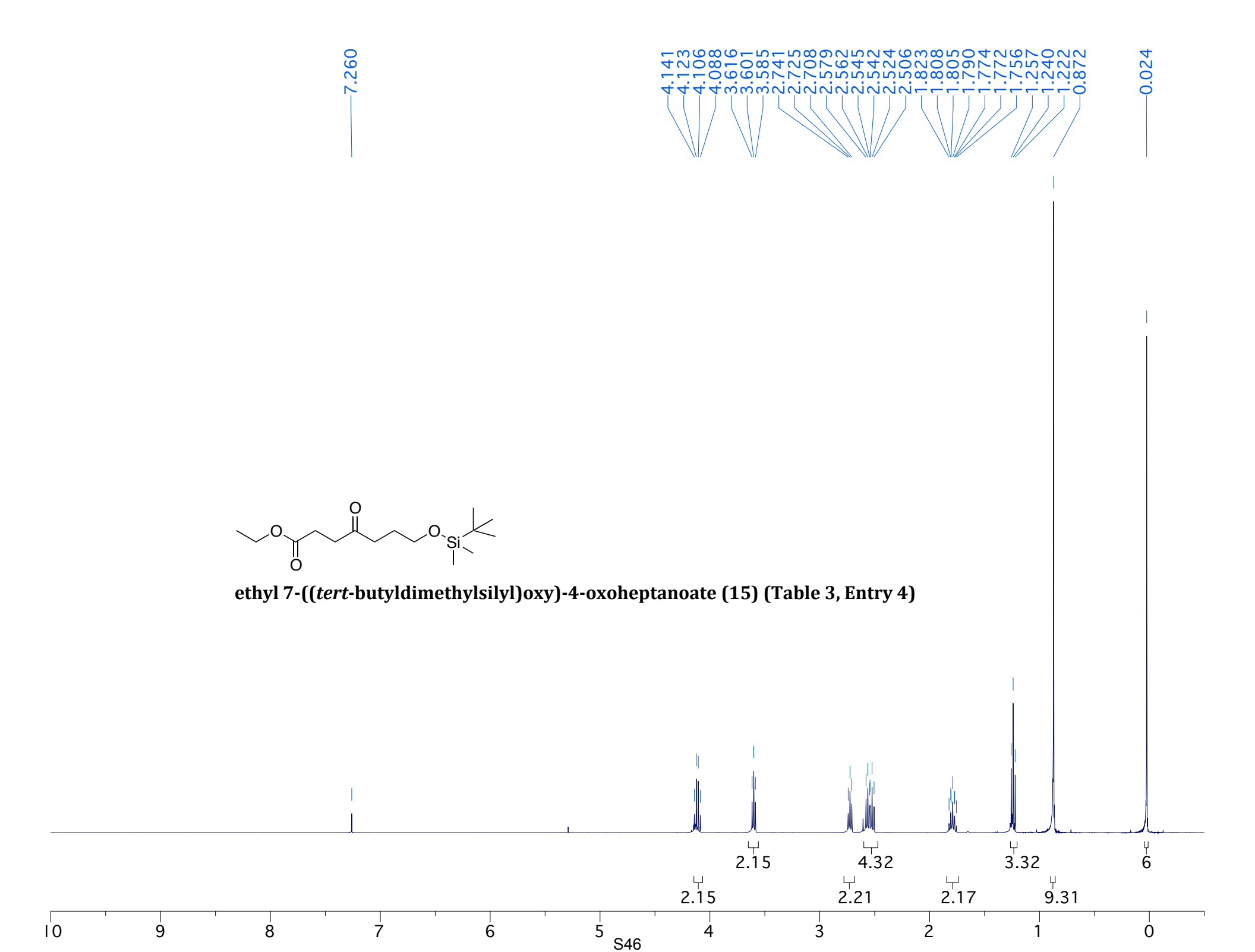
ethyl 7-((*tert*-butoxycarbonyl)amino)-4-oxoheptanoate (13) (Table 3, Entry 2)



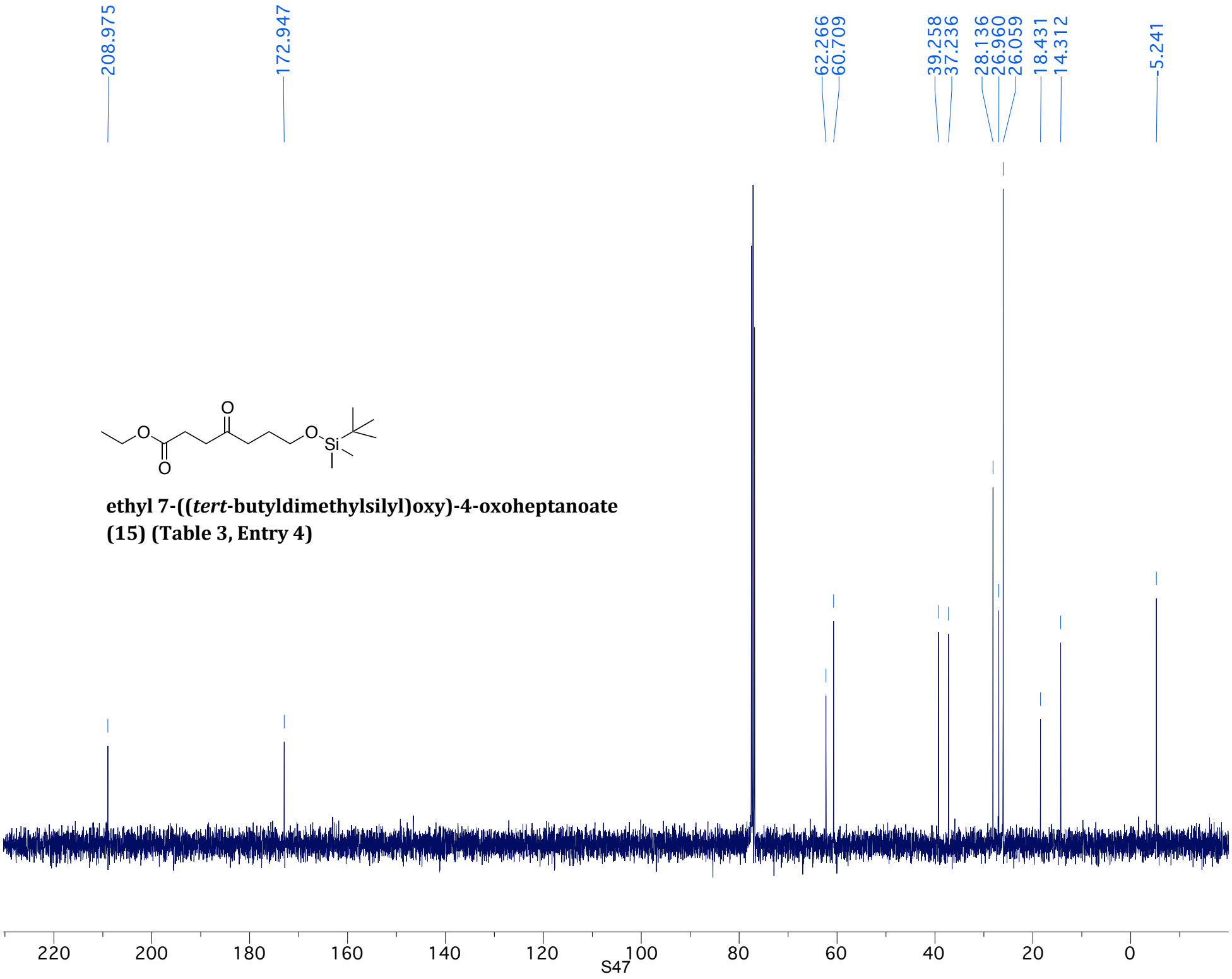
ethyl 7-(((benzyloxy)carbonyl)amino)-4-oxoheptanoate (14) (Table 3, Entry 3)



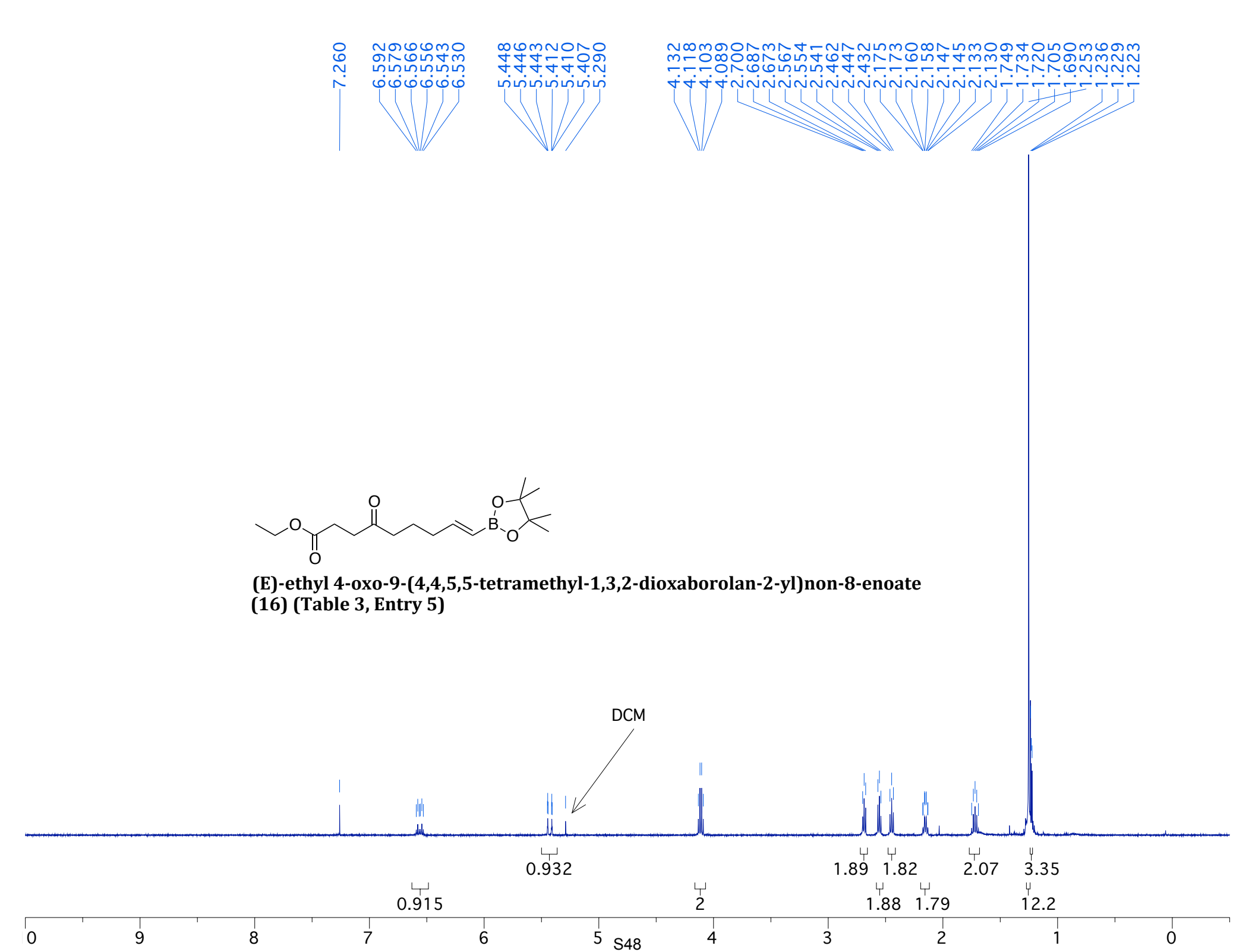
ethyl 7-(((benzyloxy)carbonyl)amino)-4-oxoheptanoate (14) (Table 3, Entry 3)



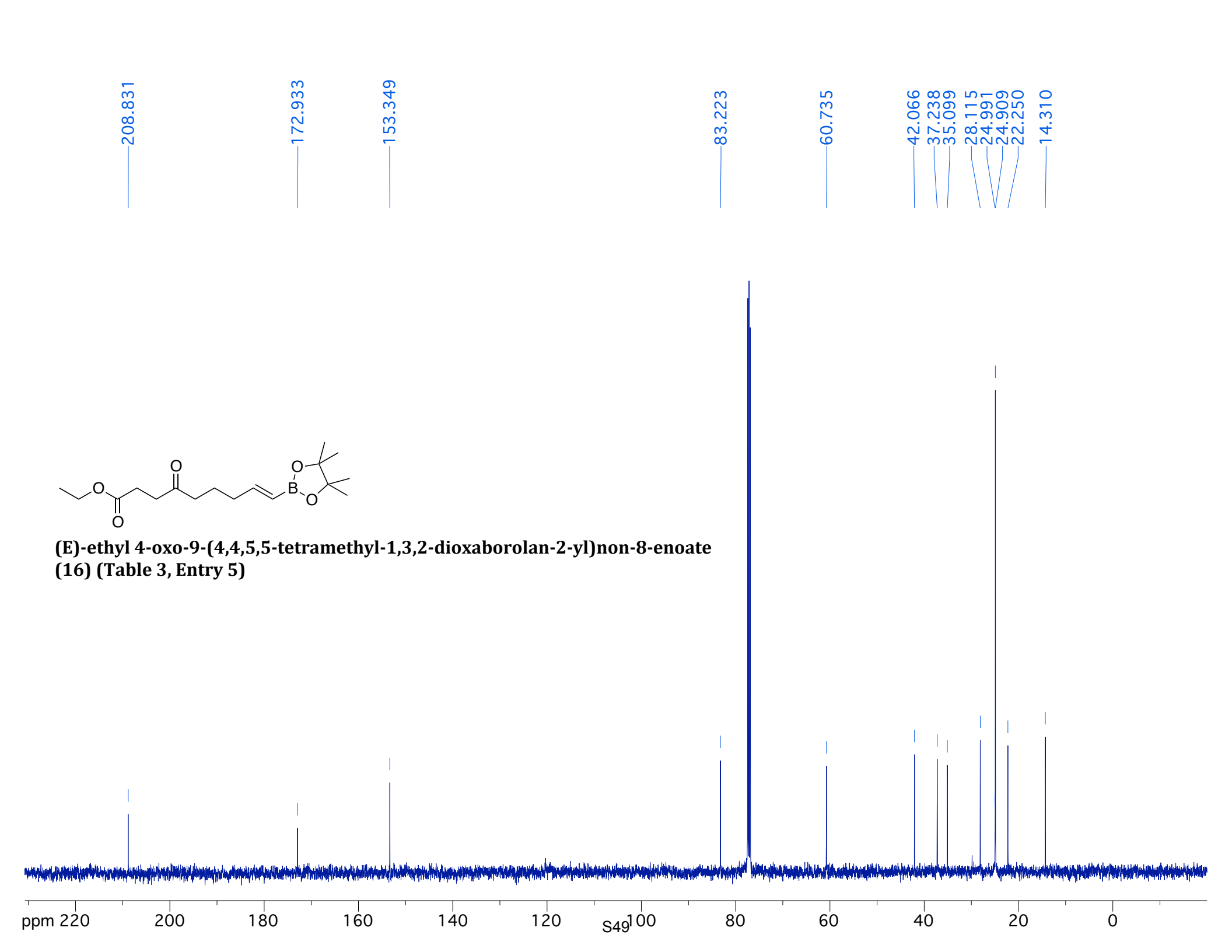
ethyl 7-((*tert*-butyldimethylsilyl)oxy)-4-oxoheptanoate (15) (Table 3, Entry 4)



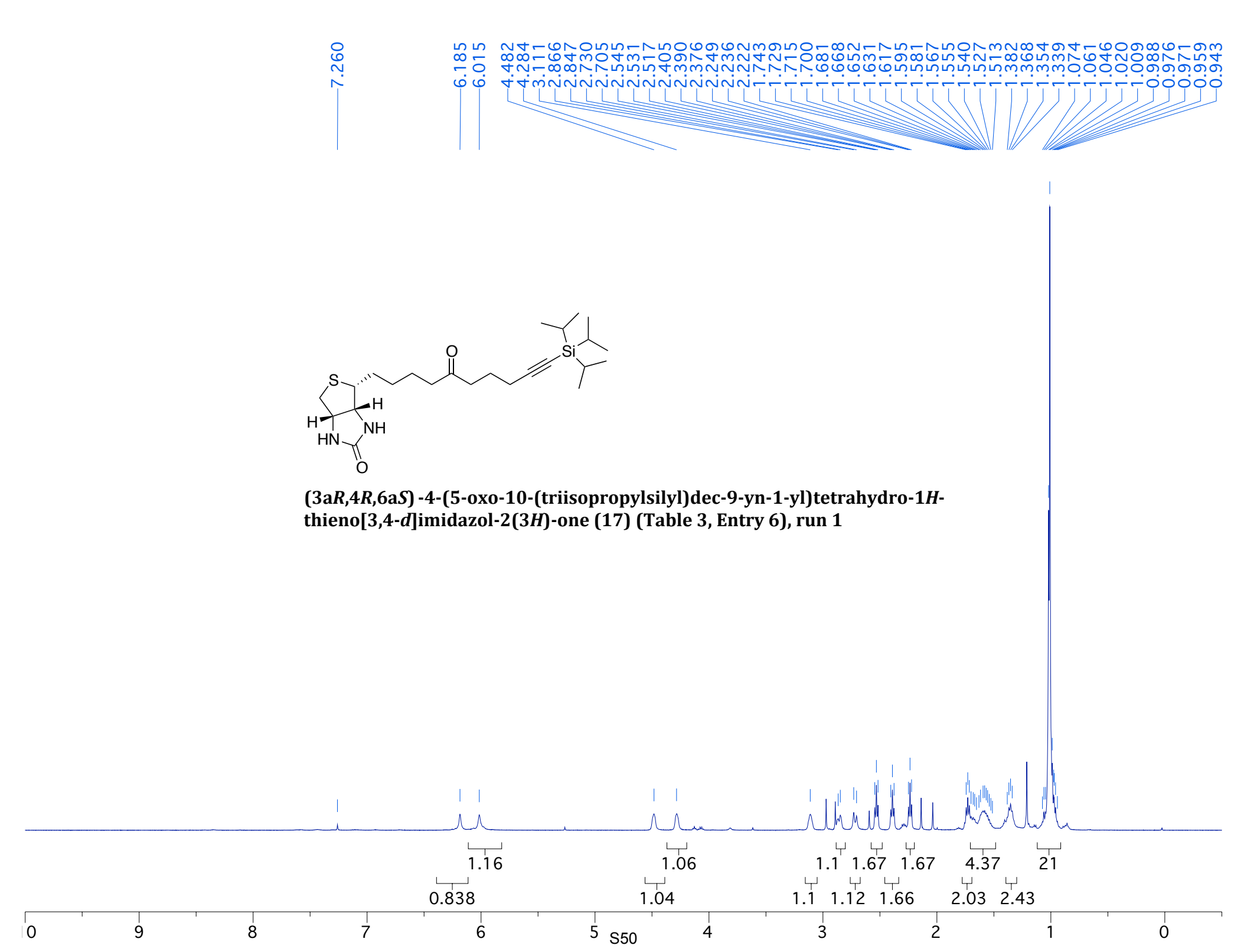
ethyl 7-((*tert*-butyldimethylsilyl)oxy)-4-oxoheptanoate (15) (Table 3, Entry 4)



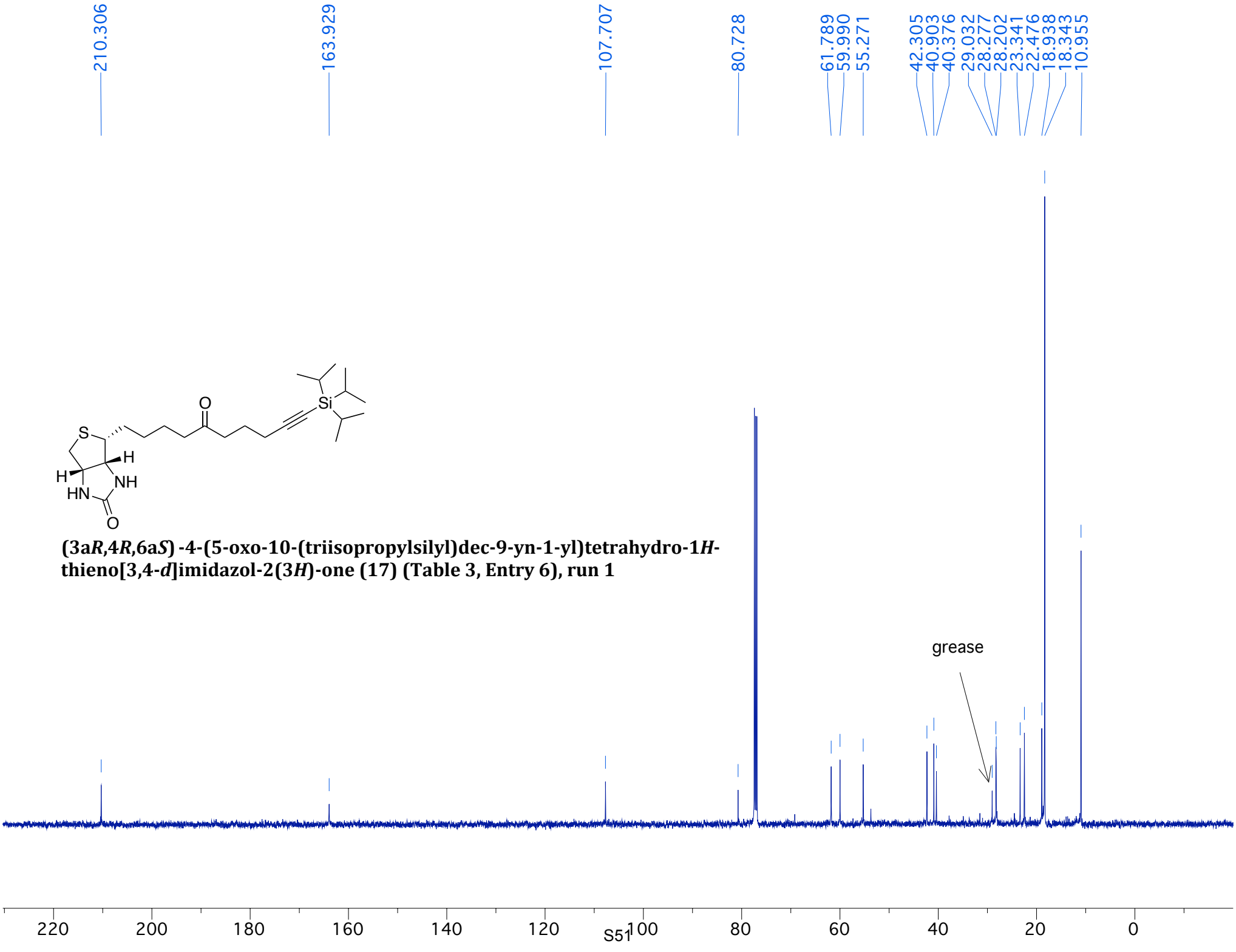
(E)-ethyl 4-oxo-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)non-8-enoate (16) (Table 3, Entry 5)



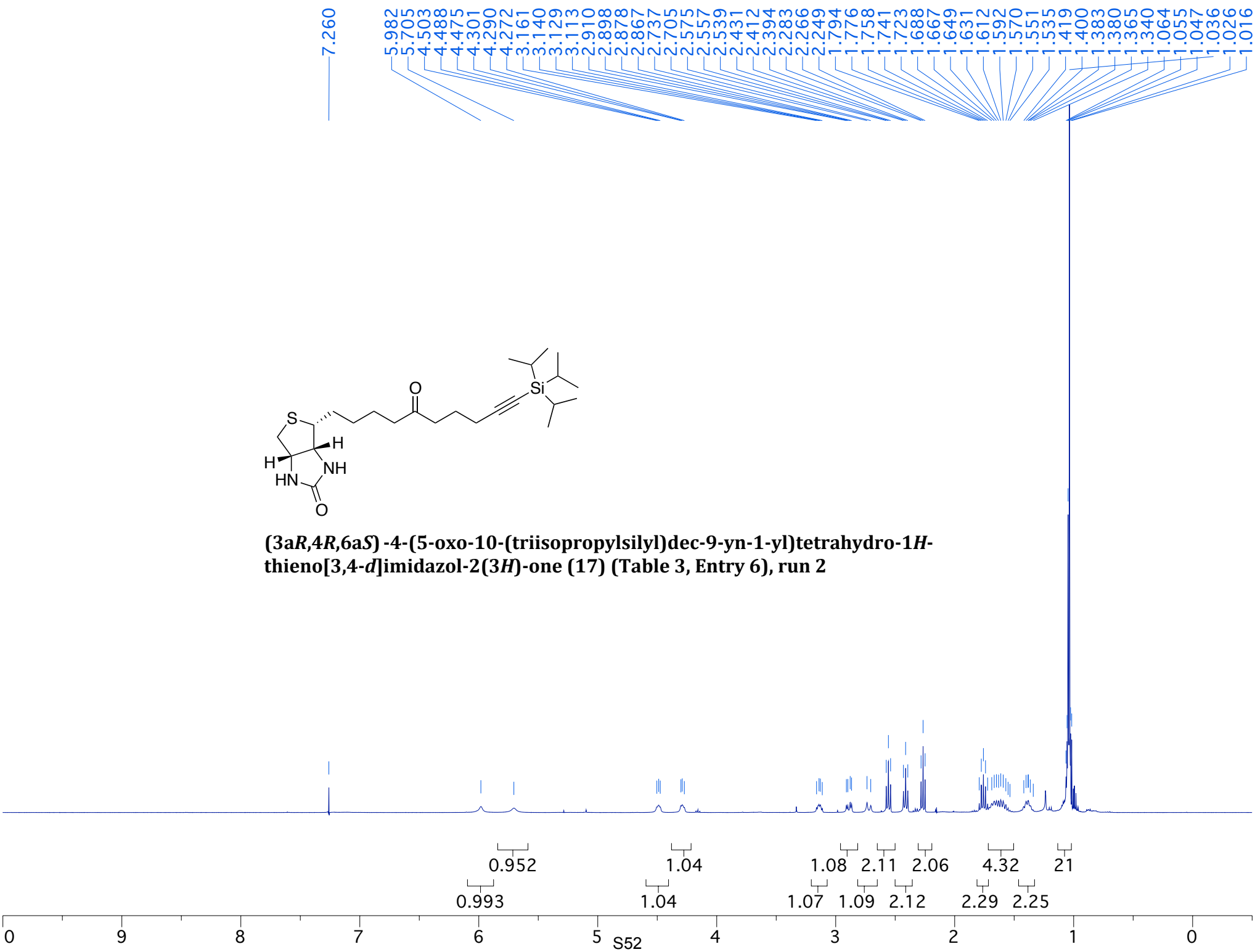
(E)-ethyl 4-oxo-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)non-8-enoate (16) (Table 3, Entry 5)



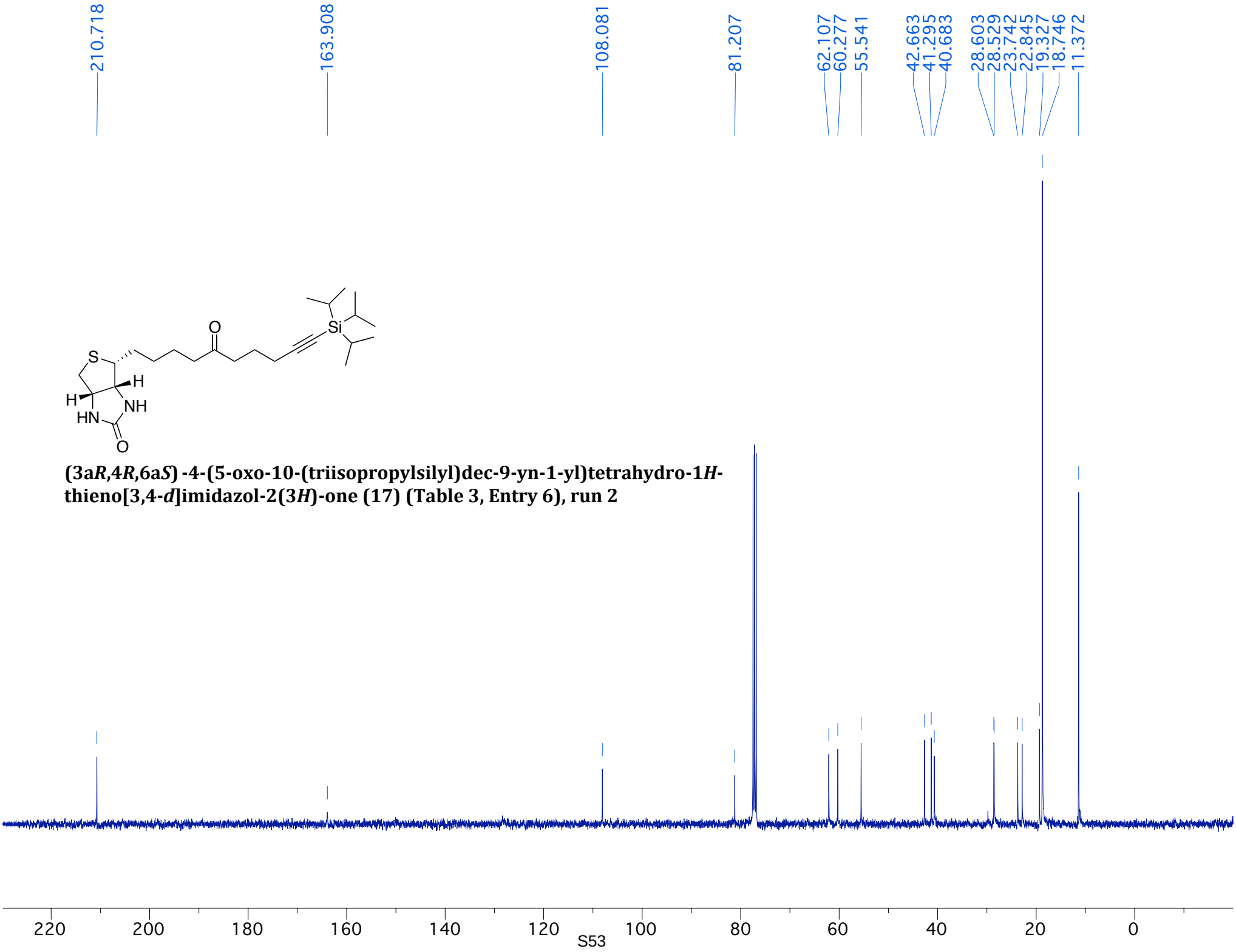
(3a*R*,4*R*,6a*S*) -4-(5-oxo-10-(triisopropylsilyl)dec-9-yn-1-yl)tetrahydro-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one (17) (Table 3, Entry 6), run 1



(3a*R*,4*R*,6a*S*) -4-(5-oxo-10-(triisopropylsilyl)dec-9-yn-1-yl)tetrahydro-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one (17) (Table 3, Entry 6), run 1



(3a*R*,4*R*,6a*S*) -4-(5-oxo-10-(triisopropylsilyl)dec-9-yn-1-yl)tetrahydro-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one (17) (Table 3, Entry 6), run 2



(3a*R*,4*R*,6a*S*) -4-(5-oxo-10-(triisopropylsilyl)dec-9-yn-1-yl)tetrahydro-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one (17) (Table 3, Entry 6), run 2