Supporting Information For: Anti-Markovnikov Hydroalkylation of Allylic Amine Derivatives via a Palladium-Catalyzed Reductive Cross-Coupling Reactive

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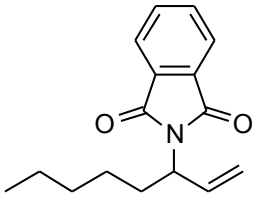
Table of Contents

General Considerations:

Dry dimethylacetamide (DMA) was purchased from Aldrich and stored over activated 3 Å molecular sieves (3 Å MS). 3 Å MS used in hydroalkylation reactions were powdered and activated by heating with a Bunsen burner while under vacuum. Palladium(II) chloride was purchased from Pressure Chemicals. Lindlar's catalyst was purchased from Strem chemicals. Granular Iodine was from J.T. Baker. Unless otherwise noted all chemicals were purchased from Aldrich or Acros and used without further purification. $[Pd(allyl)Cl]_2$, $[Pd(I^iPr)Cl_2]_2$ and $Pd(I^iPr)(OTs)_2$ were synthesized according to literature procedures.[1,2] All melting points are uncorrected and recorded on Thomas Hoover Unimelt capillary melting point apparatus. ^{1}H-NMR spectra were obtained at 300 MHz, 400 MHz or 500 MHz, chemical shifts are reported in ppm, and referenced to the $CHCl_3$ singlet at 7.26 ppm. ^{13}C-NMR spectra were obtained at 75MHz, 100 MHz or 126 MHz and referenced to the center peak of the $CHCl_3$ at 77.23 ppm. The abbreviations s, d, t, quint, dd, ddd, dt, m stand for the resonance multiplicities singlet, doublet, triplet, quintet, doublet of doublets, doublet of doublets of doublets, doublet of triplets and multiplet,

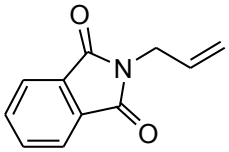
respectively. Thin-layer chromatography was performed with EMD silica gel 60 F254 plates eluting with solvents indicated, visualized by a 254 nm UV lamp and stained with phosphomolybdic acid (PMA). Flash chromatography was performed using EM reagent silica 60 (230-400 mesh). GC separations were performed with an HP6890 GC with a flame ionization detector equipped with a DB-5 column using a 50:1 split. IR spectra were recorded using a Thermo Nicolet FT-IR. HRMS data were obtained on a Waters LCP Premier XE instrument by ESI/TOF. SFC (supercritical fluid chromatography) analysis was performed at 40 °C, using a Thar instrument fitted with AD-H and OD columns.

Preparation of Substrates:



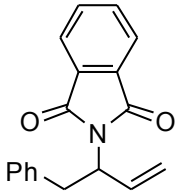
2-(oct-1-en-3-yl)isoindoline-1,3-dione:

This compound was prepared according to the literature procedure.[3] Analytical data matches the literature.[3]



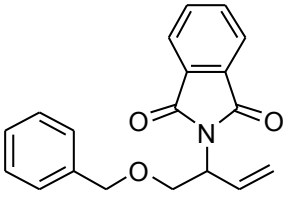
***N*-Allyl Phthalimide:**

This commercially available compound was prepared according to the literature procedure.[4] Analytical data matches the literature.[4]



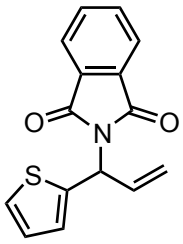
2-(1-phenylbut3-en-2-yl)isoindoline-1,3-dione

This compound was prepared according to the literature procedure.[3] Analytical data matches the literature.[3]

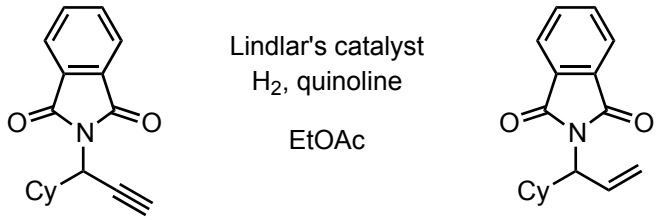


2-(1-(benzyloxy)but3-en-2-yl)isoindoline-1,3-dione

This compound was prepared according to the literature procedure.[3] Analytical data matches the literature. [3]

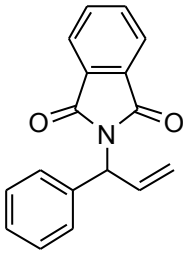


2-(1-(thiophen-2-yl)allyl)isoindoline-1,3-dione This compound was prepared according to the literature procedure.[3] Analytical data matches the literature.[3]

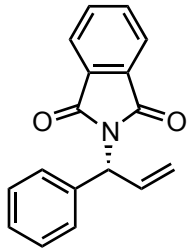


S1

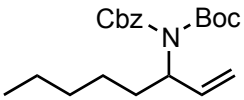
2-(1-cyclohexylallyl)isoindoline-1,3-dione. Lindlar's catalyst (palladium, 5% on calcium carbonate, lead-poisoned) (100 mg, 1 mg / 5 mg substrate), quinoline (121 mg, 0.94 mmol, 0.5 equiv.) and substrate **S1**[5] (500 mg, 1.87 mmol, 1.0 equiv.) were added to a 100 mL round-bottomed flask equipped with a magnetic stir-bar. Ethyl acetate (50 ml) was then added to the flask. The flask was placed under H_2 atmosphere by evacuation and refilling with a H_2 balloon (3×). The mixture was then stirred for 2 hours. Upon completion by TLC analysis, the reaction mixture was filtered through celite and concentrated. The product was purified by silica gel flash chromatography eluting with 10% ethyl acetate in hexanes to give the product as a white solid in 98% yield. Rf = 0.5 (10% EtOAc in Hexanes) M.P. = 57-59 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.75-1.33 (m, 5H), 1.46-2.23 (m, 6H), 4.34 (t, J = 9.9 Hz, 2H), 5.18 (d, J = 10.2 Hz, 1H), 5.28 (d, J = 12.9 Hz, 1H), 6.21-6.35 (m, 1H), 7.63-7.73 (m, 2H), 7.78-7.85 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 25.8, 25.9, 26.4, 30.0, 31.0, 38.2, 60.4, 119.2, 123.4, 132.1, 134.0, 135.1, 168.5. IR(neat): 3732 (w), 3628 (w), 2925 (m), 2851 (m), 1768 (m), 1705 (s), 1641 (w), 1467 (w), 1381 (m), 1352 (m), 1330 (w), 1074 (w), 912 (w), 718 (w) cm^{-1}. HRMS $(M+H)^+$: calcd. 270.1494, obsvd. 270.1497.



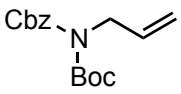
2-(1-phenylallyl)isoindoline-1,3-dione This compound was prepared according to the literature procedure.[3] Analytical data matches the literature.[3]



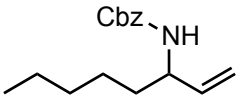
(*R*)-2-(1-phenylallyl)isoindoline-1,3-dione This compound was prepared according to the literature procedure.[3] Analytical data matches the literature.[3]



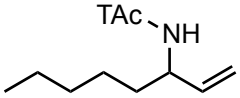
***N*-Cbz-*N*-Boc-3-amino-1-octene** This compound was prepared according to the literature procedure.[6] Analytical data matches the literature.[6]



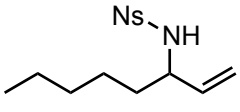
***N*-Boc-*N*-Cbz allylamine:** This compound was prepared according to the literature procedure.[6] Analytical data matches the literature.[6]



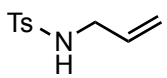
benzyl oct-1-en-3-ylcarbamate: This compound was prepared according to the literature procedure.[6] Analytical data matches the literature.[6]



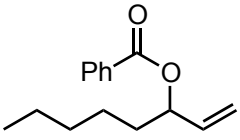
2,2,2-trichloro-*N*-(oct-1-en-3-yl)acetamide: This compound was prepared according to the literature procedure.[6] Analytical data matches the literature.[6]



2-nitro-*N*-(oct-1-en-3-yl)benzenesulfonamide: This compound was prepared according to the literature procedure.[6] Analytical data matches the literature.[6]



***N*-allyl-4-methylbenzenesulfonamide:** This compound was prepared according to the literature procedure.[7] Analytical data matches the literature.[8]



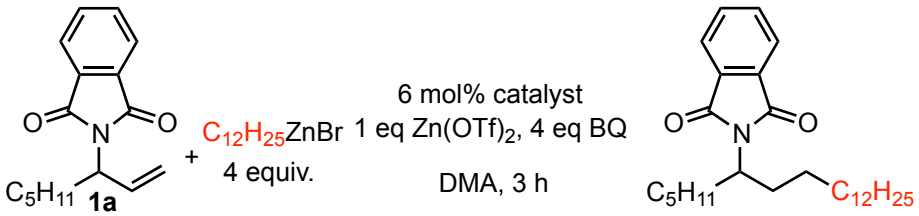
oct-1-en-3-yl benzoate: This compound was prepared according to the literature procedure.[9] Analytical data matches the literature.[10]

General Procedure for the Synthesis of OrganoZinc Reagents: A 25-mL round-bottomed flask was charged with 0.98 g of zinc powder (15.00 mmol, 1.50 equiv.) and heated to 80 °C under high vacuum for 3 hours. After back-filling with argon, DMA (to give a total volume of 10 mL) and then 0.76 g of iodine (0.30 mmol, 0.03 equiv.) were added. After the red color of iodine had faded (usually 3-5 minutes), the freshly distilled alkyl halide (10.00 mmol) was added. The colorless reaction mixture was stirred for 16 hours at 80 °C (the disappearance of the alkyl halide and the formation of the organozinc reagent can be monitored by ^{1}H NMR). The gray solution (~1.0 M) was transferred into a dry Schlenk flask via cannula. These organozinc solutions can be stored at room temperature under a dry atmosphere for several weeks without deterioration.[11-13]

Optimization for the Hydroalkylation Reaction:

The general procedure **A** described below was used with the following modifications. The reaction was performed on 0.10 mmol scale with ~10 wt% undecane used as an internal standard. After 3 h aliquots (~50 μL) were taken, passed through a small silica pipet with ethyl acetate and analyzed for conversion and product formation by gas chromatography. The modifications described below were applied in order to optimize the reaction.

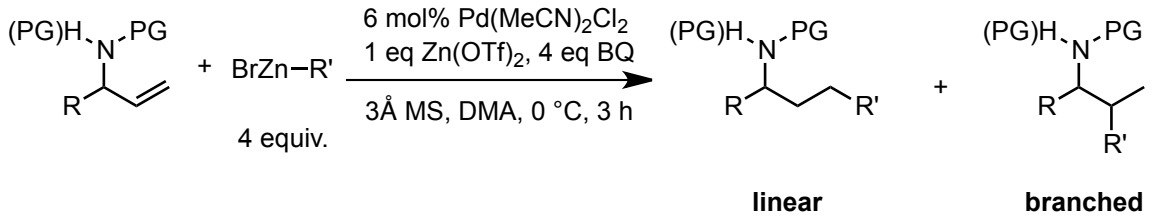
Modifications:



entry	catalyst	temp.	additive	% conv.[a]	% yield[a]	(l:b)[b]
1	$Pd(I^iPr)(OTs)_2$	RT	--	85	80	15:1
2	$Pd(MeCN)_2(OTs)_2$	RT	--	86	81	16:1
3	$Pd(MeCN)_2Cl_2$	RT	--	88	80	17:1
4	$Pd(MeCN)_2Cl_2$	0 °C	--	95	86	17:1
5	$Pd(MeCN)_2Cl_2$	0 °C	3Å MS	99	91	17:1

[a]Measured by GC using an internal standard. [b]Ratio of (linear:branched) product isomers determined by GC.

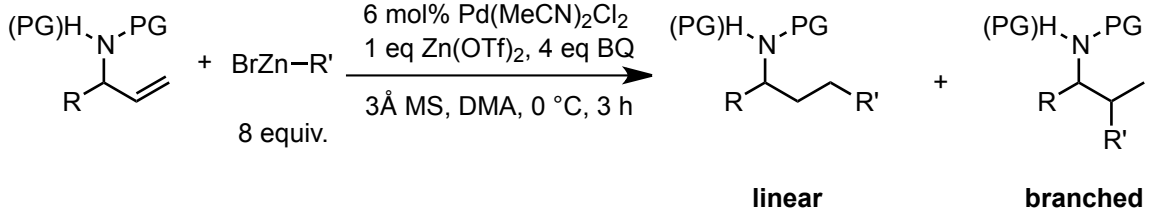
General Procedure A for the hydroalkylation of protected amines:



$Pd(MeCN)_2Cl_2$ (29.3 mg, 0.035 mmol, 0.07 equiv.), benzoquinone (216.2 mg, 2.0 mmol, 4.0 equiv.), $Zn(OTf)_2$ (181.8 mg, 0.5 mmol, 1.0 equiv.), and 250 mg of powdered 3 Å molecular sieves were added to an oven-dried, 25-ml, round-bottomed flask equipped with a stir-bar and a rubber septa. The system was flushed with argon by a needle for 15 minutes. Dry DMA (6.0 ml) was added to the reaction flask using a syringe. The substrate (0.5 mmol, 1.0 equiv.) was then added to the flask via a syringe. The flask was placed in an ice-water bath. The solution was stirred for 5 minutes. The alkylzinc bromide (2.0 ml, 2.0 mmol, 4 equiv.) was then added dropwise to the cooled solution. The reaction mixture was stirred for 3 hours at 0 °C.

After this time, the reaction was filtered through celite with ether (100 ml). The solution was transferred to a separatory funnel and washed with saturated NH_4Cl (30 ml). The organic layer was separated and washed with H_2O (2 x 30 ml) followed by brine (10 ml). The organic layer was then dried over anhydrous sodium sulfate. After filtration, the solvents were removed via rotary evaporation. The product was purified by flash chromatography.

General Procedure B for the hydroalkylation of protected amines:



$Pd(MeCN)_2Cl_2$ (29.3 mg, 0.035 mmol, 0.07 equiv.), benzoquinone (216.2 mg, 2.0 mmol, 4.0 equiv.), $Zn(OTf)_2$ (181.8 mg, 0.5 mmol, 1.0 equiv.), and 250 mg of powdered 3 Å molecular sieves were added to an oven-dried, 25-ml, round-bottomed flask equipped with a stir-bar and a rubber septa. The system was flushed with argon by a needle for 15 minutes. Dry DMA (4.0 ml) was added to the reaction flask using a syringe. The substrate (0.5 mmol, 1.0 equiv.) was then added to the flask via a syringe. The flask was placed in an ice-water bath. The solution was stirred for 5 minutes. The alkylzinc bromide (4.0 ml, 4.0 mmol, 8 equiv.) was then added dropwise to the cooled solution. The reaction mixture was stirred for 3 hours at 0 °C.

After this time, the reaction was filtered through celite with ether (100 ml). The solution was transferred to a separatory funnel and washed with saturated NH_4Cl (30 ml). The organic layer was separated and washed with H_2O (2 x 30 ml) followed by brine (10 ml). The organic layer was then dried over anhydrous sodium sulfate. After filtration, the solvents were removed via rotary evaporation. The product was purified by flash chromatography.

Product Purification/Characterization data:

Table 2, entry 1 (2-(icosan-6-yl)isoindoline-1,3-dione) (2a). The general procedure A was used. The product was purified by silica gel flash chromatography eluting with 3% ether in hexanes to give the product as a colorless oil in 87% yield, 17:1 (linear:branched). Rf = 0.4 (10% EtOAc in Hexanes) ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.74-0.91 (m, 6H), 1.07-1.35 (m, 30H), 1.60-1.76 (m, 2H), 1.96-2.15(m, 2H), 4.14 (app. sept, J = 5.1 Hz, 1H), 7.65-7.72 (dd, J = 5.5, 3.0 Hz, 2H), 7.77-7.84 (dd, J = 5.5, 3.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.2, 14.3, 22.7, 22.9, 26.5, 26.9, 29.5, 29.6, 29.7, 29.7, 29.8(2), 29.9(2), 30.5, 31.7, 32.1, 32.6, 32.7, 52.5, 123.3, 132.1, 134.0, 169.0. IR(neat): 3734 (w), 3628 (w), 2923 (m), 2853 (m), 1772 (w), 1710 (s), 1466 (w), 1370 (m), 1067 (w), 720(m), 688 (m) 651(w) cm^{-1}. HRMS $(M+H)^+$: calcd. 428.3529, obsvd. 428.3529.

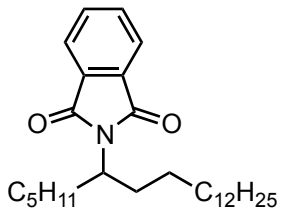
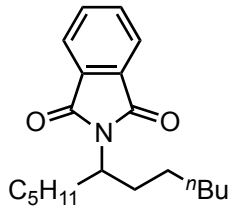


Table 2, entry 2 (2-(dodecan-6-yl)isoindoline-1,3-dione) (2b).). The general procedure A was used. The product was purified by silica gel flash chromatography eluting with 5% ethyl acetate in hexanes to give the



product as a colorless oil in 83% yield, 19:1 (linear:branched). Rf = 0.3 (5% EtOAc in Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.80 (t, J = 6.8 6H), 1.12-1.30 (m, 14H), 1.62-1.71 (m, 2H), 1.99-2.09 (m, 2H), 4.17 (app. Septet, J = 5.2 Hz, 1H), 7.68 (dd, J = 5.0, 3.0 Hz, 2H) 7.80 (dd, J = 5.5, 3.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.2(2), 22.7(2), 26.5, 26.8, 29.1, 31.7, 31.9, 32.6, 32.7, 52.5, 123.2, 132.1, 134.0, 169.0. IR(neat): 3850 (w), 3750 (m), 3620 (w), 3670 (m) 3620 (m), 2923 (w), 1754 (m), 1645 (w), 1373 (w), 720 (m), 668 (m), 657 (m) cm^{-1}. HRMS $(M+H)^+$: calcd. 316.2277, obsvd. 316.2276.

Table 2, entry 3 (2-(14-((*tert*-butyldiphenylsilyl)oxy)tetradecan-6-yl)isoindoline-1,3-dione) (2c). The general procedure B was used. The product was purified by silica gel flash chromatography eluting with 5% ethyl acetate in hexanes to give the product as a colorless oil in 69% yield, 9:1 (linear:branched). Rf = 0.3 (5% EtOAc in Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.85 (t, J = 7.0 3H), 1.05 (s, 9H), 1.16-1.37(m, 16H), 1.53(quin, J = 7.1, 2H), 1.66-1.75 (m, 2H), 2.03-2.14 (m, 2H), 3.64 (t, J = 6.8, 2H), 4.21 (app. septet, J = 5.1, 1H), 7.36-7.44 (m, 6H), 7.66-7.71 (m, 6H), 7.83 (dd, J = 5.5, 3.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.2, 19.4, 22.7, 25.9, 26.5, 26.9, 27.1, 29.5(2), 29.7, 31.7, 32,6, 32.7(2), 52.5, 64.2, 123.3, 127.8, 129.7, 132.1, 134.0, 134.4, 135.8, 169.0. IR(neat): 3846 (w), 2929 (m), 2856 (m), 1768 (m), 1709 (s), 1611 (w), 1370 (m), 1110 (m), 720 (m), 702 (m), 614 (m) cm^{-1}. HRMS $(M+Na)^+$: calcd. 620.3536, obsvd. 620.3536.

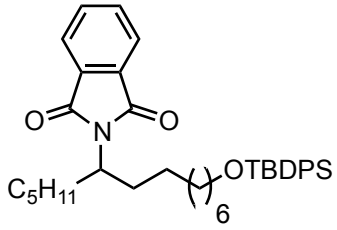


Table 2, entry 4 (2-(14-chlorotetradecan-6-yl)isoindoline-1,3-dione) (2d). The general procedure B was used. The product was purified by silica gel flash chromatography eluting with 10% ethyl acetate in hexanes to give the product as a colorless oil in 73% yield, >20:1 (linear:branched). Rf = 0.4 (10% EtOAc in Hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.83 (t, J = 6.6 Hz, 3H), 1.13-1.42 (m, 16H), 1.64-1.77(m, 4H), 1.98-2.14 (m, 2H), 3.50 (t, J = 6.8 Hz, 2H), 4.18 (app. septet, J = 5.2 Hz, 1H), 7.71 (dd, J = 5.7, 3.0 Hz, 2H), 7.82 (dd, J = 5.4, 3.0, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.2, 22.7, 26.5, 26.7, 27.0, 28.9, 29.3, 29.4, 31.6, 32.6(2), 32.7, 45.3, 52.4, 123.2, 132.0, 134.0, 169.0. IR(neat): 3727 (w), 3627 (w), 2925 (m), 2855 (m), 1770 (m), 1704 (s), 1466 (m), 1358 (m), 1067 (m), 870 (m), 718 (m), 668 (m) cm^{-1}. HRMS $(M+H)^+$: calcd. 378.2200, obsvd. 378.2202.

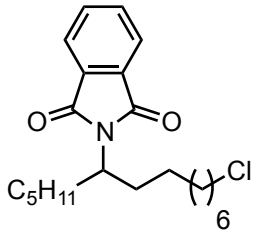


Table 1, entry 5 (9-(1,3-dioxoisoindolin-2-yl)tetradecyl pivalate) (2e). The general procedure B was used. The product was purified by silica gel flash chromatography eluting with 5% ethyl acetate in hexanes to give the product as a colorless oil in 72% yield, >20:1 (linear:branched). Rf = 0.4 (5% EtOAc in Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.80 (t, J = 7.0 Hz, 3H), 1.10-1.31 (m, 24H), 1.55 (quin, J = 7 Hz, 2H), 1.66 (m, 2H), 2.04 (m, 2H), 3.98 (t, J = 6.8 Hz, 2H), 4.16 (app. septet, J = 5.1 Hz, 1H), 7.68 (dd, J = 5.0, 3.0 Hz, 2H), 7.80 (dd, J = 5.5, 3.0 Hz, 2H).). ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.2, 22.7, 26.0, 26.5, 26.8, 27.4, 28.7, 29.3, 29.4, 29.5, 31.6, 32.6, 38.9, 52.4, 64.7, 123.2, 123.4, 132.0, 134.0, 169.0, 179.0. IR(neat): 3853 (w), 2710 (w), 2927 (m), 2856 (m), 1771 (m), 1707 (s), 1506 (m), 1070 (m), 870 (w), 720 (m), 668 (m) cm^{-1}. HRMS $(M+H)^+$: calcd. 444.3114, obsvd. 444.3114.

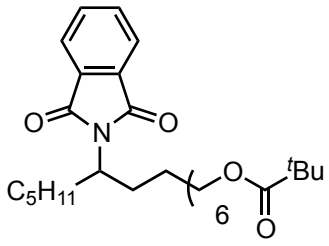


Table 1, entry 6 (2-(1-cyclohexylnonan-4-yl)isoindoline-1,3-dione) (2f). The general procedure A was used with the modification that the reaction was run at room temperature. The product was purified by silica gel flash chromatography eluting with 10% ethyl acetate in hexanes to give the product as a colorless oil in 47% yield, >20:1 (linear:branched). Rf = 0.4 (10% EtOAc in Hexanes) ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.71-0.86(m, 5H), 1.04-1.31 (m, 14H), 1.54-1.73 (m, 7H), 1.97-2.11 (m, 2H), 4.18 (app. septet, J = 5.1Hz, 1H), 7.69 (dd, J = 5.4, 3.0 Hz, 2H), 7.81 (dd, J = 5.4, 3.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 22.7, 24.1, 26.5, 26.6, 26.9, 31.7, 32.6, 33.0, 33.4, 33.6, 37.3, 37.7, 52.5, 123.3, 132.1, 134.0, 169.0. IR(neat): 3853 (w), 3744 (m), 3734 (w), 3675 (m) 3649 (m), 3628 (w), 2923 (w), 1734 (m), 1635 (w), 1373 (w), 720 (m), 668 (m), 655 (m) cm^{-1}. HRMS $(M+H)^+$: calcd. 356.2590, obsvd. 356.2587.

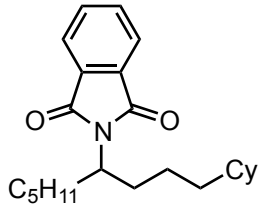
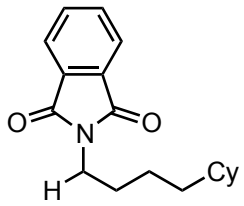


Table 1, entry 7 (2-(4-cyclohexylbutyl)isoindoline-1,3-dione) (2g). The general procedure A was used with the modification that the reaction was run at room temperature. The product was purified by silica gel flash chromatography eluting with 5% ethyl acetate in hexanes to give the product as a white solid in 54% yield, 2:1 (linear:branched). Rf = 0.3 (10% EtOAc in Hexanes). M.P. = 64-66 °C ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.70-0.95 (m, 2H), 0.70-0.95 (m, 3H) Minor, 1.01-1.81 (m, 15H), 2.04-2.15 (m, 1H) minor, 3.45 (dd, J = 13.3, 8.3 Hz, 1H) minor, 3.54 (dd, *J* = 13.3, 6.3, Hz, 1H) minor , 3.66 (t, J = 7.3 Hz, 2H), 7.68-7.72 (m, 2H) 7.81-7.85 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.0(minor), 24.4, 26.5, 26.6, 26.7, 26.9(2), 29.2, 29.7, 33.1, 33.6, 34.3, 35.0, 37.2, 37.8, 38.3, 42.6, 44.8 123.4 (minor), 123.4 (major), 123.4 (major), 132.3 (minor), 132.4 (major), 134.0 (major), 134.1(minor), 169.0 (minor) 168.7 (major). IR(neat): 2921 (m), 2850 (m), 1773 (m), 1712 (s), 1466 (m), 1437 (m),



1396 (m), 1369 (m), 1054 (m), 720(m) cm^{-1}. HRMS $(M+H)^+$: calcd. 286.1807, obsvd. 286.1814.

Table 1, entry 8 (2-(1-phenylhexadecan-2-yl)isoindoline-1,3-dione) (2h). The general procedure A was used. The product was purified by silica gel flash chromatography eluting with 5% ethyl acetate in hexanes to give the product as a white solid in 91% yield 9:1 (linear:branched). Rf = 0.4 (10% EtOAc in Hexanes). M.P. = 40-41 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, J = 6.8 Hz, 3H), 1.11-1.37 (m, 26H), 1.68-1.83 (m, 1H), 2.10-2.25 (m, 1H), 3.10 (dd, J = 13.8, 6.0 Hz, 1H), 3.31 (dd, J = 13.8, 9.9 Hz, IH), 4.49 (app. septet, J = 5.2 Hz, IH), 7.10-7.21 (m, 5H), 7.65 (dd, J = 5.4, 3.3 Hz, 2H), 7.74 (dd, J = 6.6, 3.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.4, 22.9, 26.9, 29.5, 29.6, 29.7, 29.8(2), 29.9(2), 32.2, 32.3, 39.0, 53.7,123.2, 126.5, , 128.6, 129.1, 131.9, 133.9, 138.6, 168.8. IR(neat): 3853 (w), 3744 (m), 3734 (w), 3675 (m) 3649 (m), 3628 (w), 2923 (w), 1707 (s), 1635 (w), 1373 (w), 720 (m), 668 (m), 655 (m) cm^{-1}. HRMS $(M+H)^+$: calcd. 448.3216, obsvd. 448.3224.

Table 1, entry 9 (2-(1-(benzyloxy)-10-chlorodecan-2-yl)isoindoline-1,3-dione) (2i). The general procedure B was used. The product was purified by silica gel flash chromatography eluting with 10% ethyl acetate in hexanes to give the product as a colorless oil in 73% yield, >20:1 (linear:branched). Rf = 0.3 (10% EtOAc in Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.22-1.46 (m, 10H), 1.67-1.80 (m, 3H), 2.02-2.12 (m, 1H), 3.52 (t, J = 6.8 Hz, 2H), 3.71 (dd, J = 9.8, 5.3 Hz, 1H), 4.04 (t, J = 9.8 Hz, 1H), 4.48-4.58 (m, 3H), 7.21-7.32 (m, 5H), 7.74 (dd, J = 5.5, 3.0 Hz, 2H), 7.85 (dd, J = 5.3, 3.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 26.4, 26.9, 28.9(2), 29.2, 29.3, 32.7, 45.3, 51.5, 69.9, 72.9, 123.3, 127.7, 128.5, 132.1, 134.0, 138.2, 168.9. IR(neat): 3727 (w), 2928 (m), 2856 (m), 1772 (m), 1707 (s), 1466 (w), 1454 (m), 1373 (m), 1099 (m), 720 (m), 698 (m) cm^{-1}. HRMS $(M+Na)^+$: calcd. 450.1812, obsvd. 450.1807.

Table 1, entry 10 (2-(1-(thiophen-2-yl)heptyl)isoindoline-1,3-dione) (2j). The general procedure A was used. The product was purified by silica gel flash chromatography eluting with 5% ethyl acetate in hexanes to give the product as a yellow oil in 63% yield, >20:1 (linear:branched). Rf = 0.4 (10% EtOAc in Hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 (t, J = 6.9 Hz, 3H), 1.18-1.38 (m, 8H), 2.22-2.36 (m, 1H), 2.47-2.63 (m, 1H), 5.57 (dd, J = 9.5, 6.8 Hz, 1H), 6.93 (dd, J = 5.1, 3.6 Hz, 1H), 7.13-7.15 (m, 1H), 7.21 (dd, J = 5.1, 1.2 Hz, 1H), 7.70 (dd, J = 5.4, 3.0 Hz, 2H), 7.82 (dd, J = 5.4, 3.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 22.7, 27.0, 28.9, 31.8, 33.1, 50.2, 123.5, 125.3, 126.4, 126.7, 132.0, 134.2, 143.0, 168.1. IR(neat): 3727 (w), 2926 (m), 2856 (m), 1772 (m), 1707 (s), 1466 (w), 1386 (m), 1330

(m), 1081 (m), 718 (m), 668 (m) cm^{-1}. HRMS $(M+Na)^+$: calcd. 350.1191, obsvd. 350.1187.

Table 1, entry 11 (2-(1-cyclohexylpentadecyl)isoindoline-1,3-dione) (2k). The general procedure A was used. The product was purified by silica gel flash chromatography eluting with 5% ethyl acetate in hexanes to give the product as a colorless oil in 78% yield, >20:1 (linear:branched). Rf = 0.4 (10% EtOAc in Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.85 (t, J = 7.3 Hz, 3H), 0.88-1.30 (m, 29H), 1.45-1.78 (m, 5H), 1.89-2.13 (m, 3H), 3.87 (dt, J = 10.8, 4.0 Hz, 1H), 7.68 (dd, J = 5.5, 3.0 Hz, 2H), 7.80 (dd, J = 5.3, 3.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.3, 22.9, 26.0, 26.1, 26.5, 26.9, 29.1, 29.5(2), 29.7(2), 29.8(3), 29.9(2), 30.4, 31.0, 32.1, 39.7, 57.6, 123.3, 132.0, 134.0, 169.1. IR(neat): 3727 (w), 3627 (w), 2916 (m), 2849 (m), 2024 (m), 1699 (s), 1396 (w), 719 (m), 668 (m), 656 (m) cm^{-1}. HRMS $(M+H)^+$: calcd. 440.3529, obsvd. 440.3539.

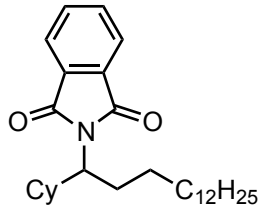


Table 1, entry 12 (2-(1-phenylheptyl)isoindoline-1,3-dione) (2l). The general procedure A was used. The product was purified by silica gel flash chromatography eluting with 5% ethyl acetate in hexanes to give the product as a colorless oil in 66% yield, >20:1 (linear:branched). Rf = 0.3 (5% EtOAc in Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.85 (t, J = 7.0 Hz, 3H), 1.20-1.44 (m, 8H), 2.27 (app. sextet, J = 7.1 Hz, 1H), 2.58 (m, 1H), 5.33 (dd, J = 10, 6.5 Hz, 1H), 7.23-7.35 (m, 3H), 7.53-7.57 (m, 2H), 7.67 (dd, J = 5.5, 3.0 Hz, 2H), 7.79 (dd, J = 5.5, 3.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.2, 22.7, 27.2, 29.1, 31.1, 31.8, 55.3, 123.3, 127.9, 128.4, 128.7, 132.1, 134.1, 140.1, 168.6. IR(neat): 3853 (w), 3743 (w), 2954 (m), 2925 (m) 2856 (m), 1771 (m), 1660 (s), 1456 (m), 1386 (m), 1352 (s), 1071 (m), 698 (m), 604 (m) cm^{-1}. HRMS $(M+H)^+$: calcd. 322.1807, obsvd. 322.1813.

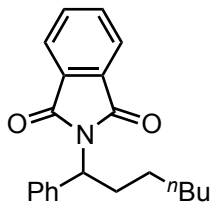


Table 2, *tert*-butyl 2-(((benzyloxy)carbonyl)(dodecan-6-yl)amino)acetate (3a). The general procedure A was used. The product was purified by silica gel flash chromatography eluting with 2% ethyl acetate in hexanes to give the product as a colorless oil in 68% yield, >20:1 (linear:branched). Rf = 0.3 (2% EtOAc in Hexanes).). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82-0.89 (m, 6H), 1.16-1.30 (m, 15H), 1.43 (s, 9H), 1.44-1.54 (m, 2H), 1.70-1.86 (m, 2H), 4.16 (app. septet, J = 5.0 Hz, 1H), 5.20 (s, 2H), 7.27-7.41 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.2, 14.3, 22.8(2), 26.4, 26.7, 28.1, 29.3, 31.9, 32.0, 33.7(2), 58.7, 68.3, 82.5, 128.4(2), 128.7, 136.0, 153.4, 155.1. IR(neat): 3853 (w), 3837 (w), 3844 (w), 3649 (w), 2956 (m), 2928 (s), 2858 (m), 1742 (s), 1702 (s), 1497 (w), 1392 (m), 1135 (m), 748 (m), 668 (m) cm^{-1}. HRMS $(M+Na)^+$: calcd. 442.2933, obsvd. 442.2927.

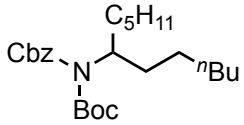


Table 2, *tert*-butyl 2-(((benzyloxy)carbonyl)(heptyl)amino)acetate (3b). The general procedure A was used. The product was purified by silica gel flash chromatography eluting with 2% ethyl acetate in hexanes to give the product as a colorless oil in 71% yield, 8:1 (linear:branched). Rf = 0.2 (2% EtOAc in Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87 (t, J = 7.0 Hz, 3H), 1.17-1.32 (m, 8H), 1.47 (s, 9H), 1.50-1.60 (m, 2H), 3.62 (t, J = 7.5 Hz, 2H), 5.22 (s, 2H), 7.29-7.42 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.3, 22.8, 26.9, 28.2, 29.2(2), 32.0, 46.9, 68.4, 82.8, 128.4, 128.5, 128.7, 136.0, 152.4, 154.2. IR(neat): 3853 (w), 3743 (w), 3628 (w), 2928 (m), 2857 (m), 1746 (s), 1718 (s), 1456 (m), 1124 (m), 778 (m), 696 (m) cm^{-1}. HRMS $(M+Na)^+$: calcd. 372.2151, obsvd. 372.2138.

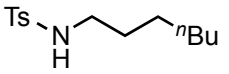
Table 2, benzyl dodecan-6-ylcarbamate (3c). The general procedure A was used. The product was purified by silica gel flash chromatography eluting with 10% ethyl acetate in hexanes to give the product as a white solid in 82% yield, >20:1 (linear:branched). Rf = 0.3 (10% EtOAc in Hexanes). M.P. = 64-65 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, J = 6.6, 6H), 1.09-1.55 (m, 18H), 3.47-3.69 (m, 1H), 4.45 (d, J = 9.0 Hz), 5.09 (s, 2H), 7.27-7.38 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.3(2), 22.8, 25.7, 26.0, 29.5, 29.9, 32.0, 35.6, 35.7, 61.6, 66.7, 128.3(2), 128.7, 137.0, 156.3. . IR(neat): 3324 (br), 2955 (m), 2926 (m), 2857 (m), 1689 (s), 1519 (m), 1457 (m), 1378 (w), 1246 (w), 819 (s), 724 (m), 679 (m), 652 (m) cm^{-1}. IR(neat): 3734 (w), 3628 (w), 3320 (br), 2923 (s), 2853 (m), 1686 (s), 1539 (m), 1274 (m), 1112 (w), 750 (w), 726 (w), 668 (m) cm^{-1}. HRMS $(M+Na)^+$: calcd. 342.2409, obsvd. 342.2397.

Table 2, 2,2,2-trichloro-*N*-(dodecan-6-yl)acetamide (3d). The general procedure A was used. The product was purified by silica gel flash chromatography eluting with 5% ethyl acetate in hexanes to give the product as a white solid in 72% yield, >20:1 (linear:branched). Rf = 0.4 (5% EtOAc in Hexanes). M.P. = 35-36 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (m, 6H), 1.10-1.64 (m, 18H), 3.88 (m, 1H), 6.30 (d, J = 9.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2(2), 22.7(2), 25.6, 25.9, 29.3, 31.8, 31.9, 35.0(2), 52.2, 93.3, 161.6. IR(neat): 3324 (br), 2955 (m), 2926 (m), 2857 (m), 1689 (s), 1519 (m), 1457 (m), 1378 (w), 1246 (w), 819 (s), 724 (m), 679 (m), 652 (m) cm^{-1}. HRMS $(M+Na)^+$: calcd. 352.0978, obsvd. 352.0975.

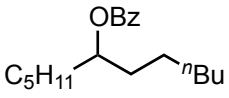
Table 2, *N*-(dodecan-6-yl)-2-nitrobenzenesulfonamide (3e). The general procedure A was used. The product was purified by silica gel flash chromatography eluting with 10% ethyl acetate in hexanes to give the product as a colorless oil in 43% yield, >20:1 (linear:branched). Rf = 0.4 (10% EtOAc in Hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.76-0.85 (m, 6H), 1.05-

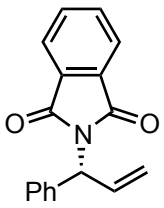
1.52 (m, 18H), 3.43 (m, 1H), 5.09 (d, J = 8.4 Hz, 1H), 7.69-7.75 (m, 2H), 7.82-7.87 (m, 1H), 8.11-8.16 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 14.2, 22.6, 22.7, 25.2, 25.5, 29.1, 31.7, 31.8, 35.4, 35.5, 125.4, 130.6, 133.0, 133.4, 135.6, 147.9. IR(neat): 3852 (w), 3732 (w), 3628 (w), 2929 (m), 2857 (m), 1537 (w), 1442 (w), 1414 (w), 1358 (w), 1168 (m), 1123 (w), 859 (w), 783 (w), 742 (w) cm^{-1}. HRMS $(M+Na)^+$: calcd. 393.1824, obsvd. 393.1818.

Table 2, *N*-heptyl-4-methylbenzenesulfonamide (3f). The general procedure A was used. The product was purified by silica gel flash chromatography eluting with 10% ethyl acetate in hexanes to give the product as a colorless oil in 44% yield, >20:1 (linear:branched). Rf = 0.4 (10% EtOAc in Hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, J = 6.8 Hz, 3H), 1.09- 1.50 (m, 10H), 2.43 (s, 3H), 2.93 (q, J = 6.8 Hz, 2H), 4.25 (t, J = 5.7 Hz, 1H), 7.31 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 8.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2, 21.7, 22.7, 26.7, 28.9 29.7, 31.8, 43.4, 127.3, 129.9, 137.2, 143.5. IR(neat): 3853 (w), 3733 (w), 3628 (w), 3283 (m), 2928 (m), 2051 (w), 1684 (m), 1652 (w), 1540 (w), 1326 (w), 1160 (m), 1094 (w), 814 (w), 615 (m) cm^{-1}. HRMS $(M+Na)^+$: calcd. 292.1347, obsvd. 292.1330.

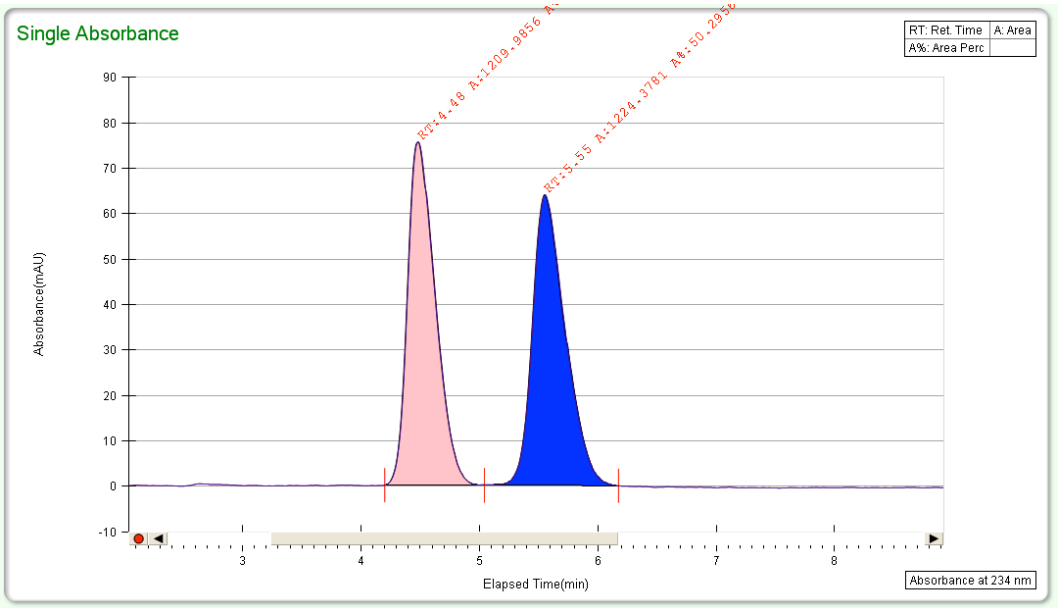


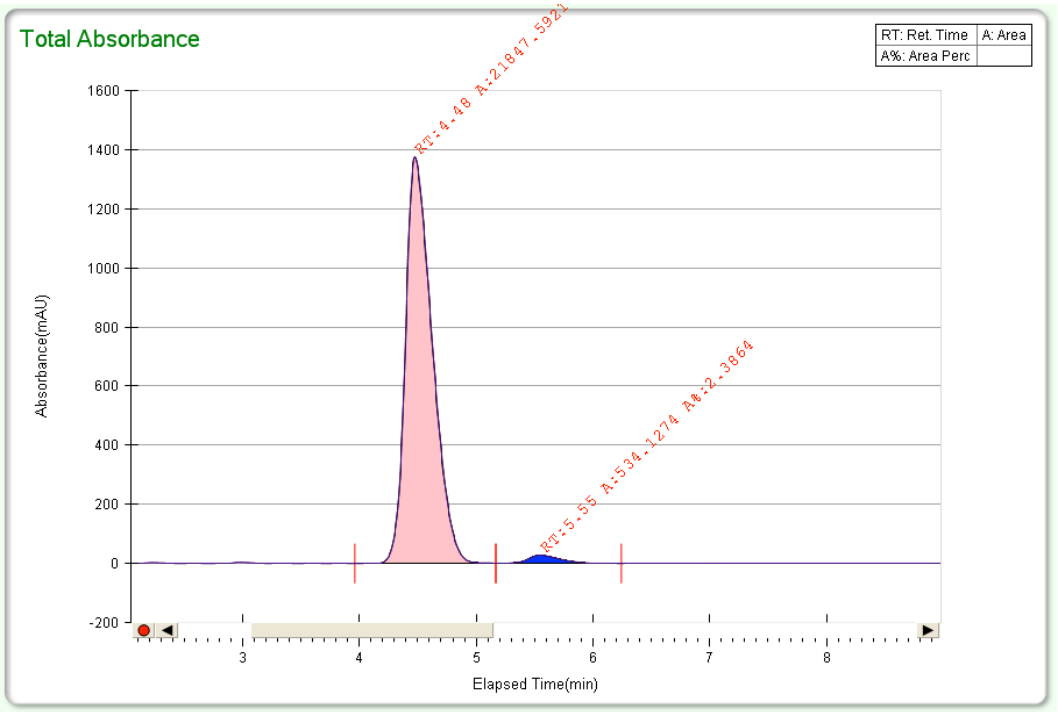
dodecan-6-yl benzoate (4b). The general procedure A was used. The product was purified by silica gel flash chromatography eluting with 5% ethyl acetate in hexanes to give the product as a slightly yellow oil in 65% yield, >20:1 (linear:branched). Rf = 0.5 (10% EtOAc in Hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (m, 6H), 1.18-1.43 (m, 14H), 1.66 (m, 4H), 5.13 (quin., J = 6.2 Hz, 1H), 7.40-7.59 (m, 3H), 8.03-8.08 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 14.3, 22.8(2), 25.2, 25.5, 29.5, 32.0(2), 34.4(2), 75.3, 128.5, 129.7, 131.1, 132.9, 166.6. IR(neat): 2927 (m), 2858 (m), 1715 (s), 1451 (m), 1269 (s), 1109 (m), 1026 (m), 708 (m), 669 (w) cm^{-1}. HRMS $(M+Na)^+$: calcd. 313.2144, obsvd. 313.2139.

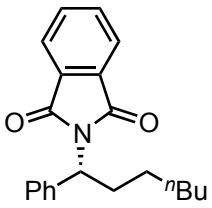




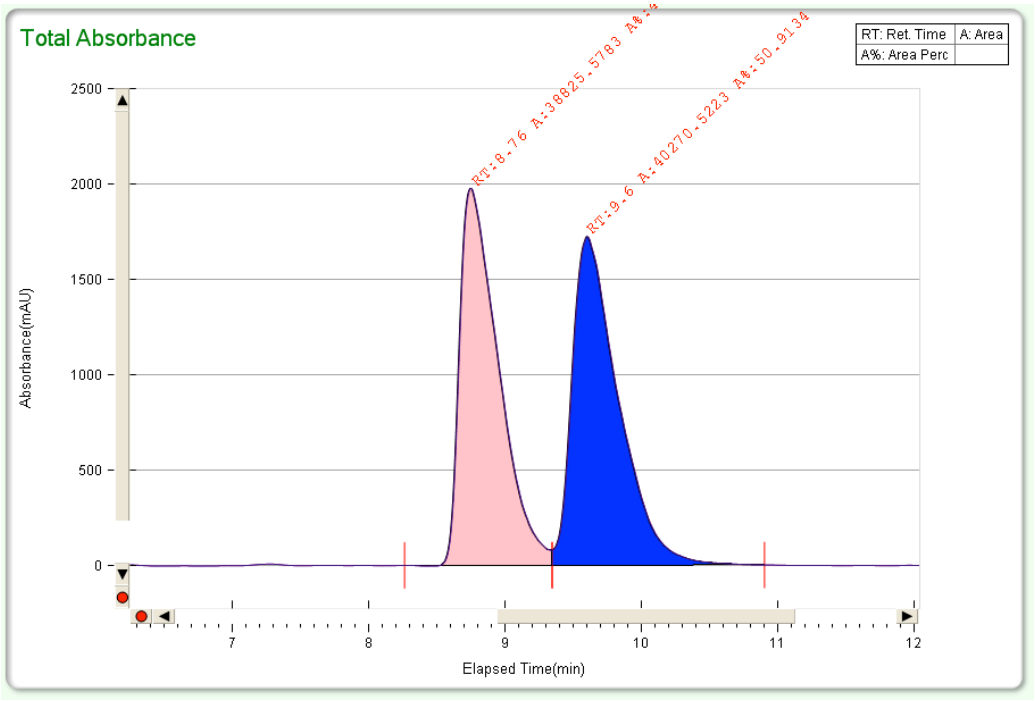
Separation of enantiomers by SFC. ChiraCel OD column, isochratic 3 mL/min, 4% MeOH, 160 bar, 40 °C, 4.48 min (major), 5.55 min (minor).

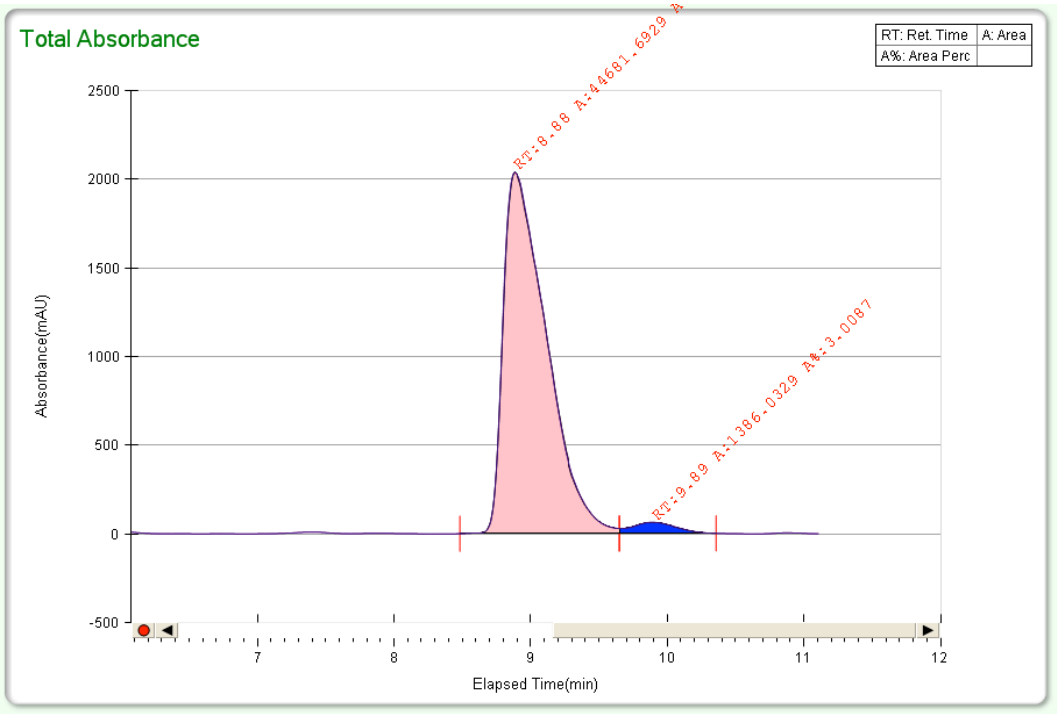






Separation of enantiomers by SFC. ChiraCel AD-H column, isochratic 3 mL/min, 3% IPA, 160 bar, 40 °C, 8.8 min (major), 9.6 min (minor).[4]





References:

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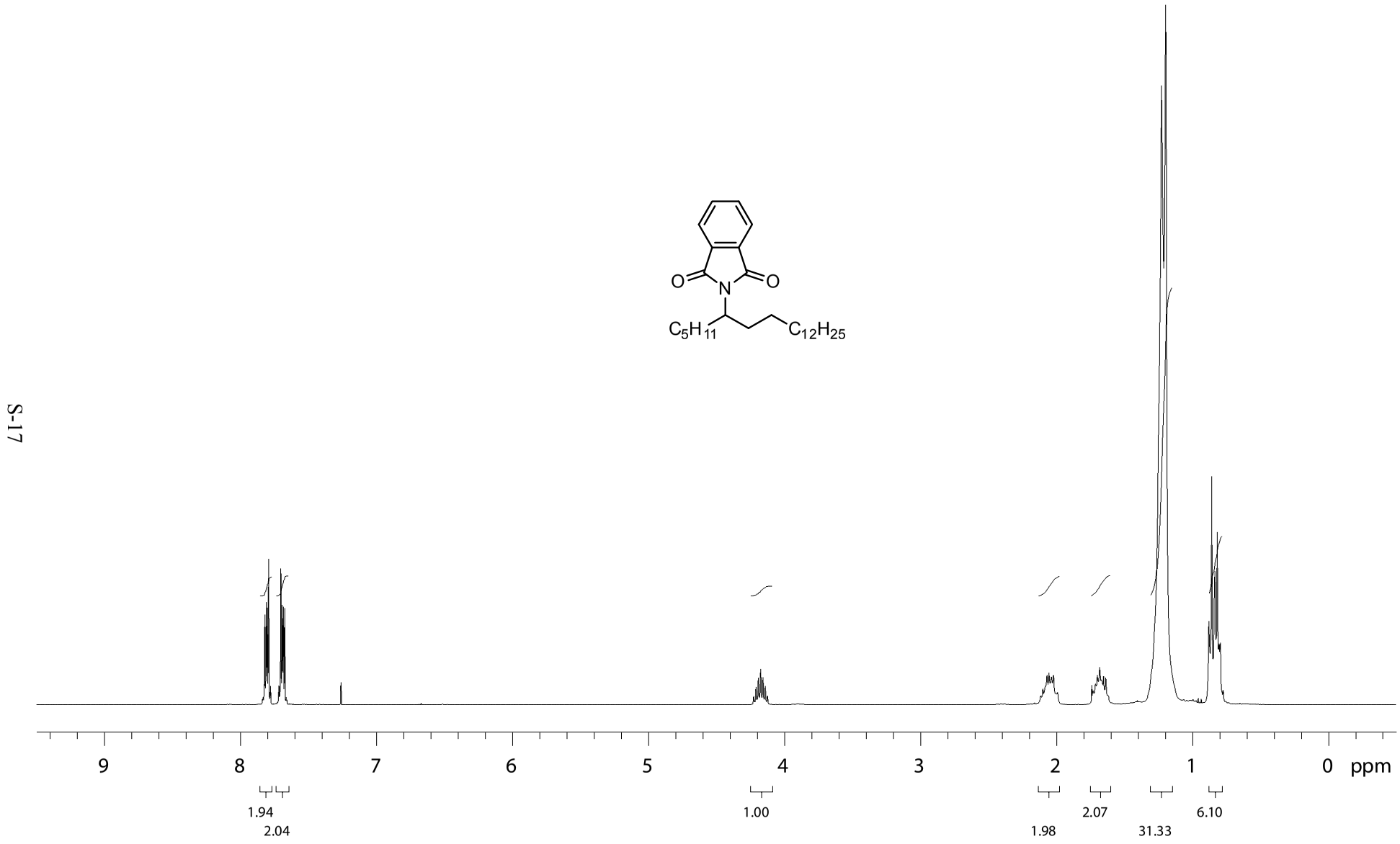
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C5H11
C12H25
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8
7
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1.00
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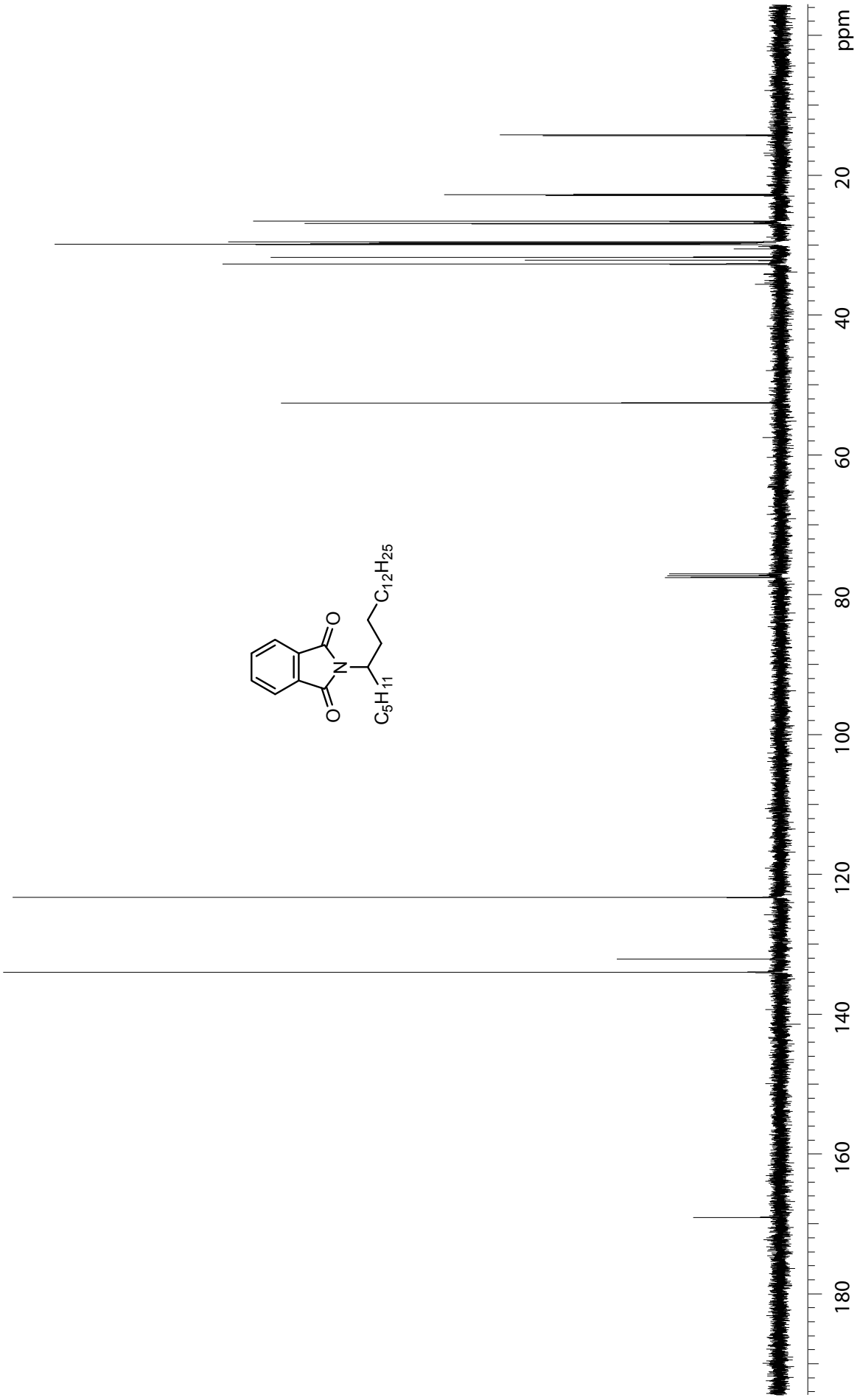
2.07
31.33
6.10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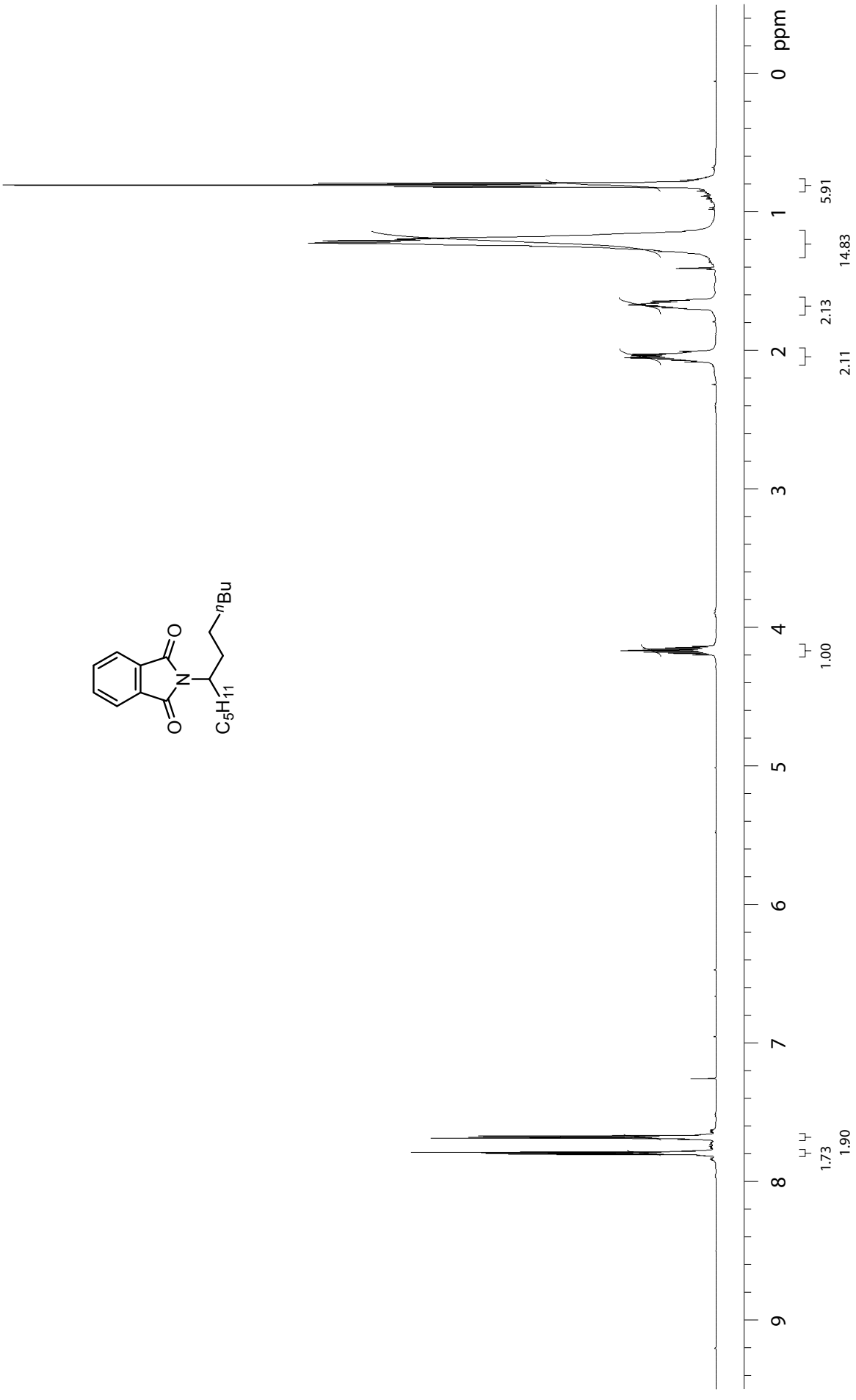
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^{n}Bu
C_5H_{11}
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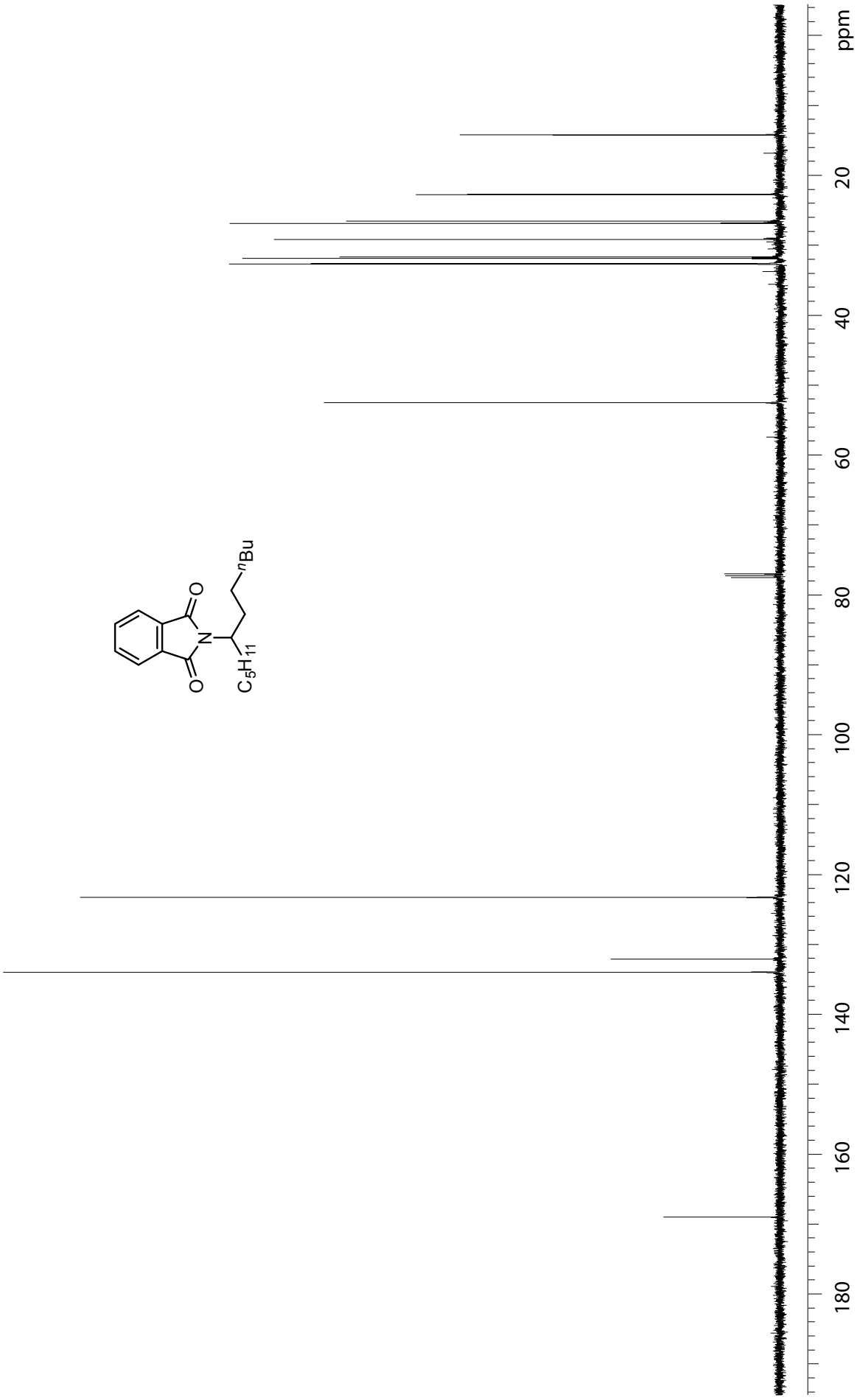
1.90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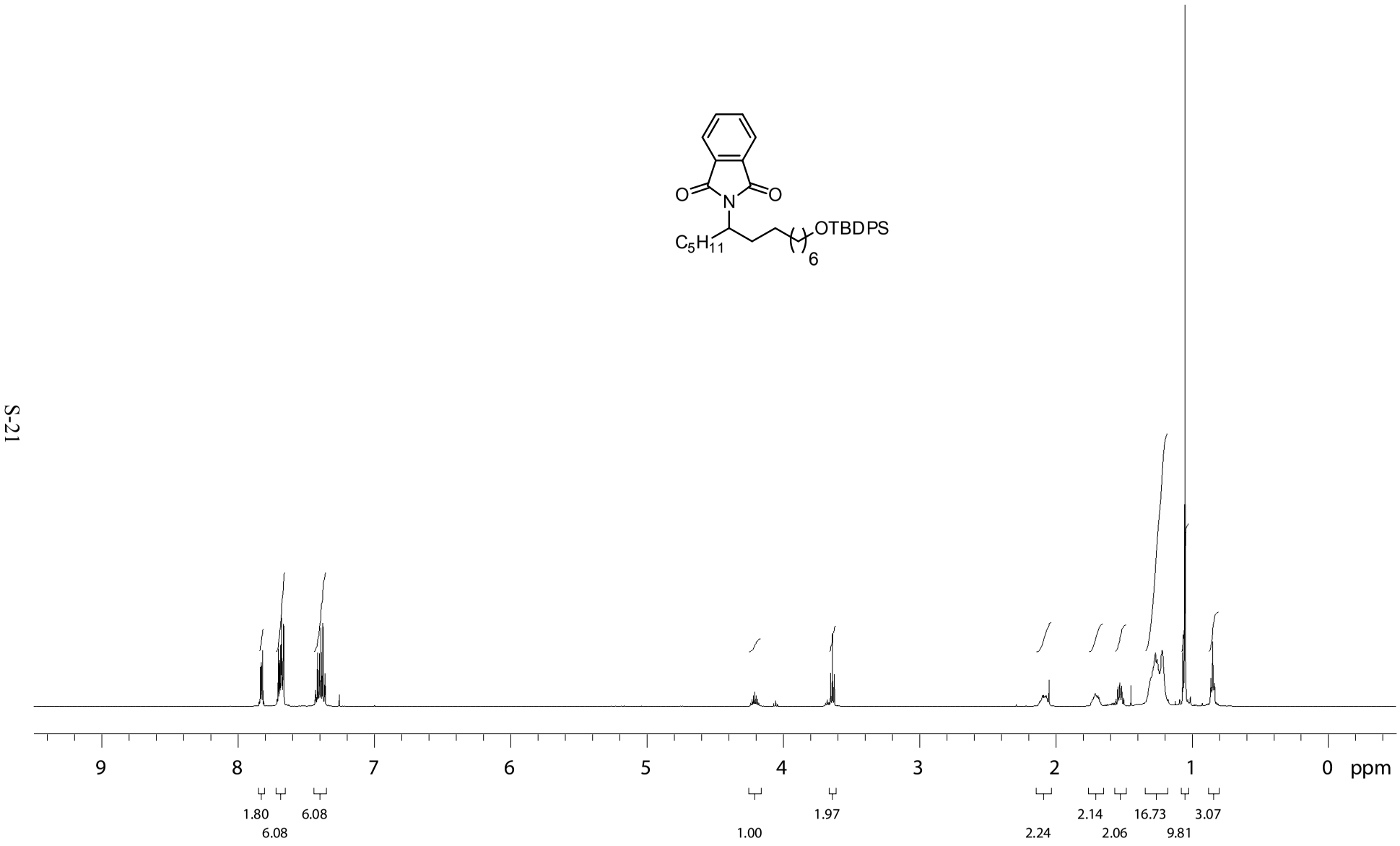
O
N
^{n}Bu
C_5H_{11}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C5H11
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7
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1
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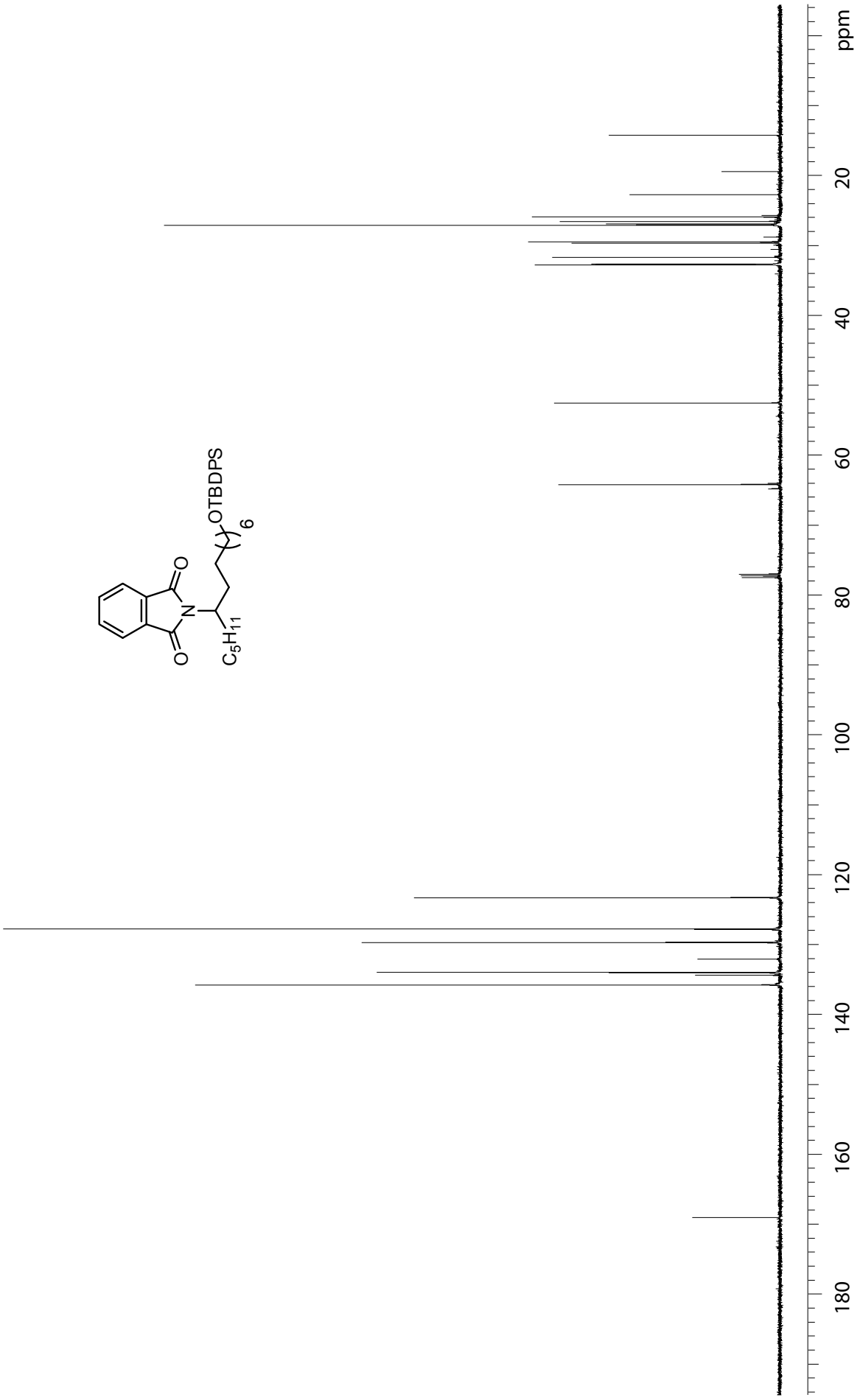
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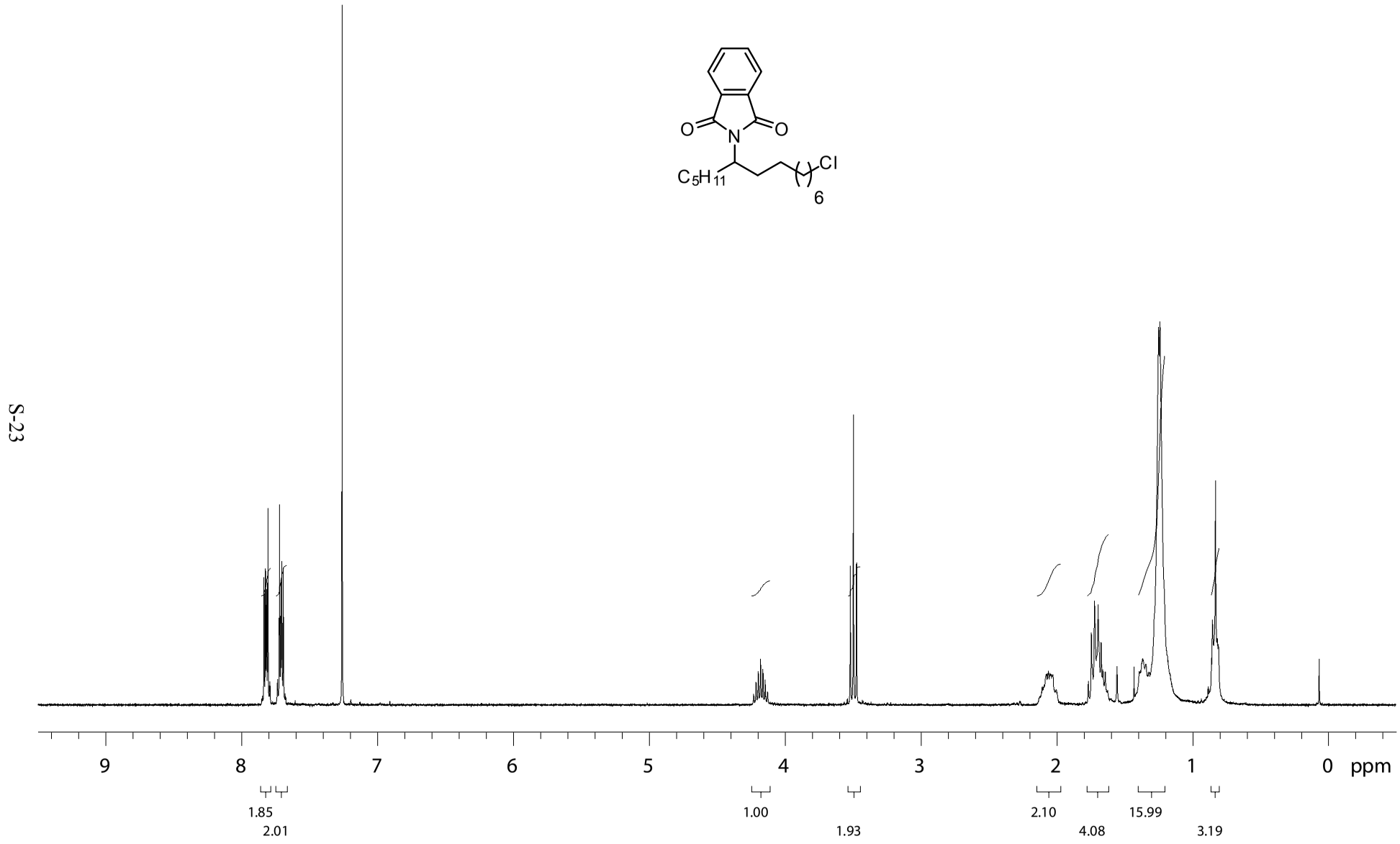
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C5H11
Cl
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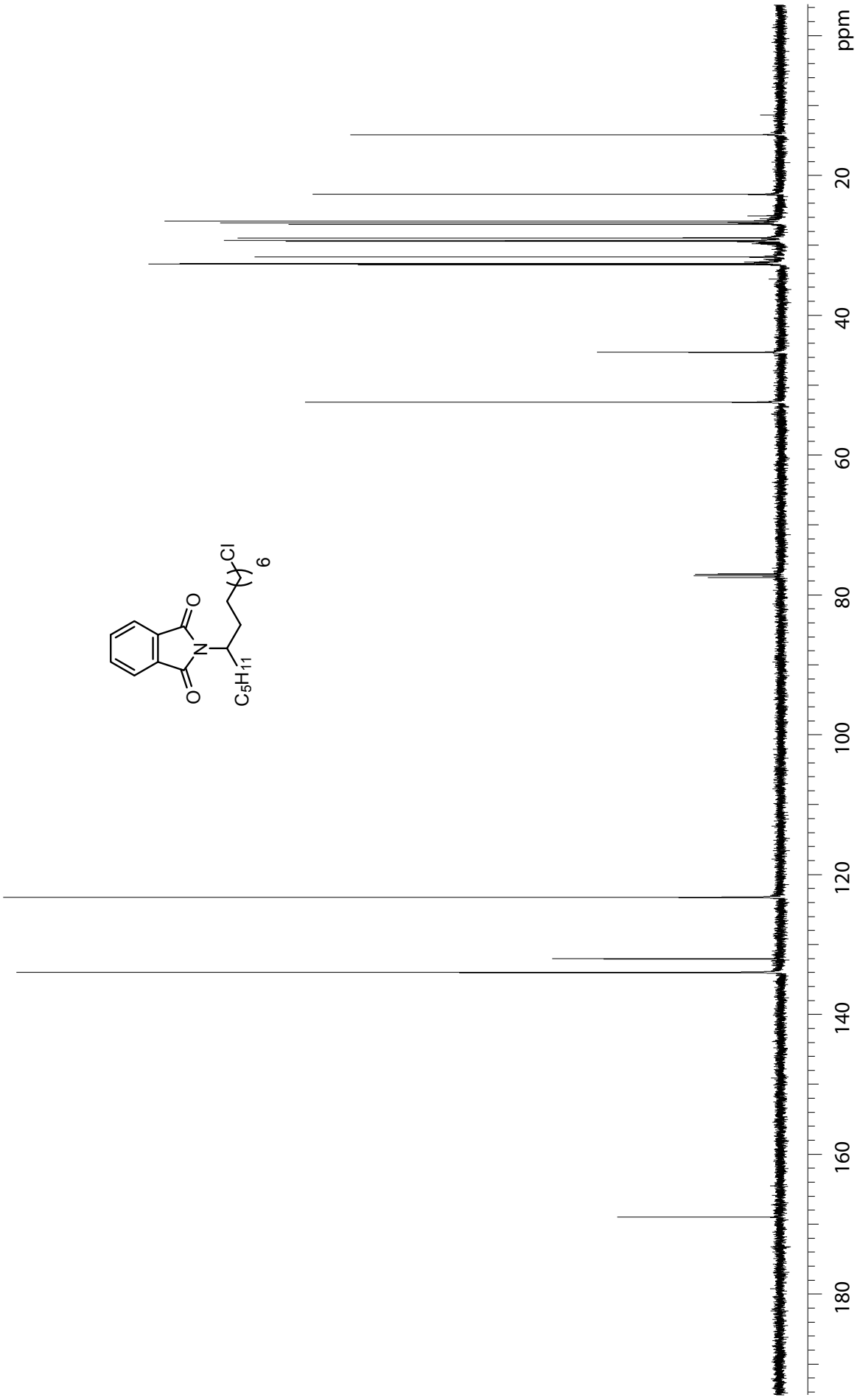
4.08
15.99
3.19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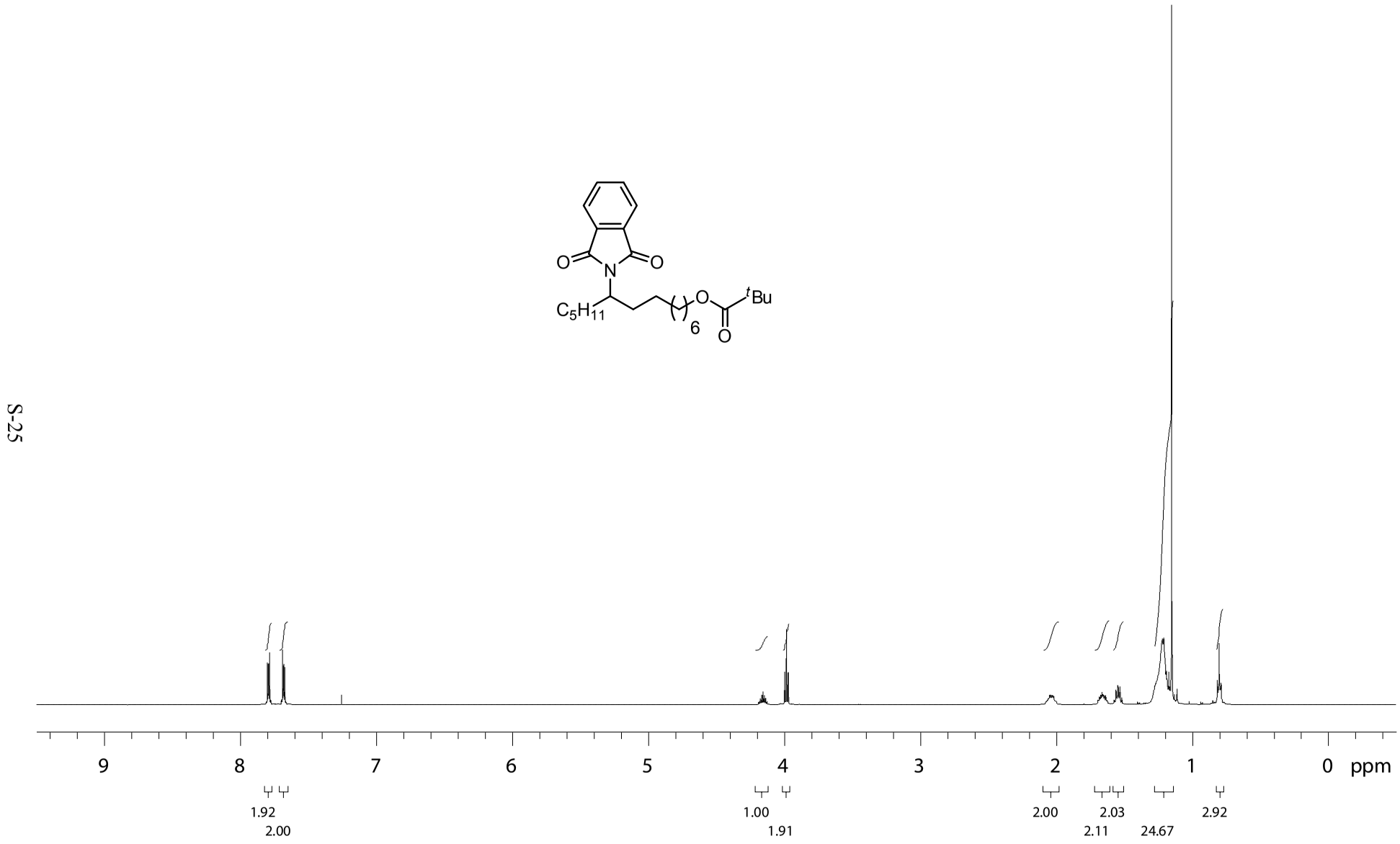
C5H11
Cl
6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O
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7
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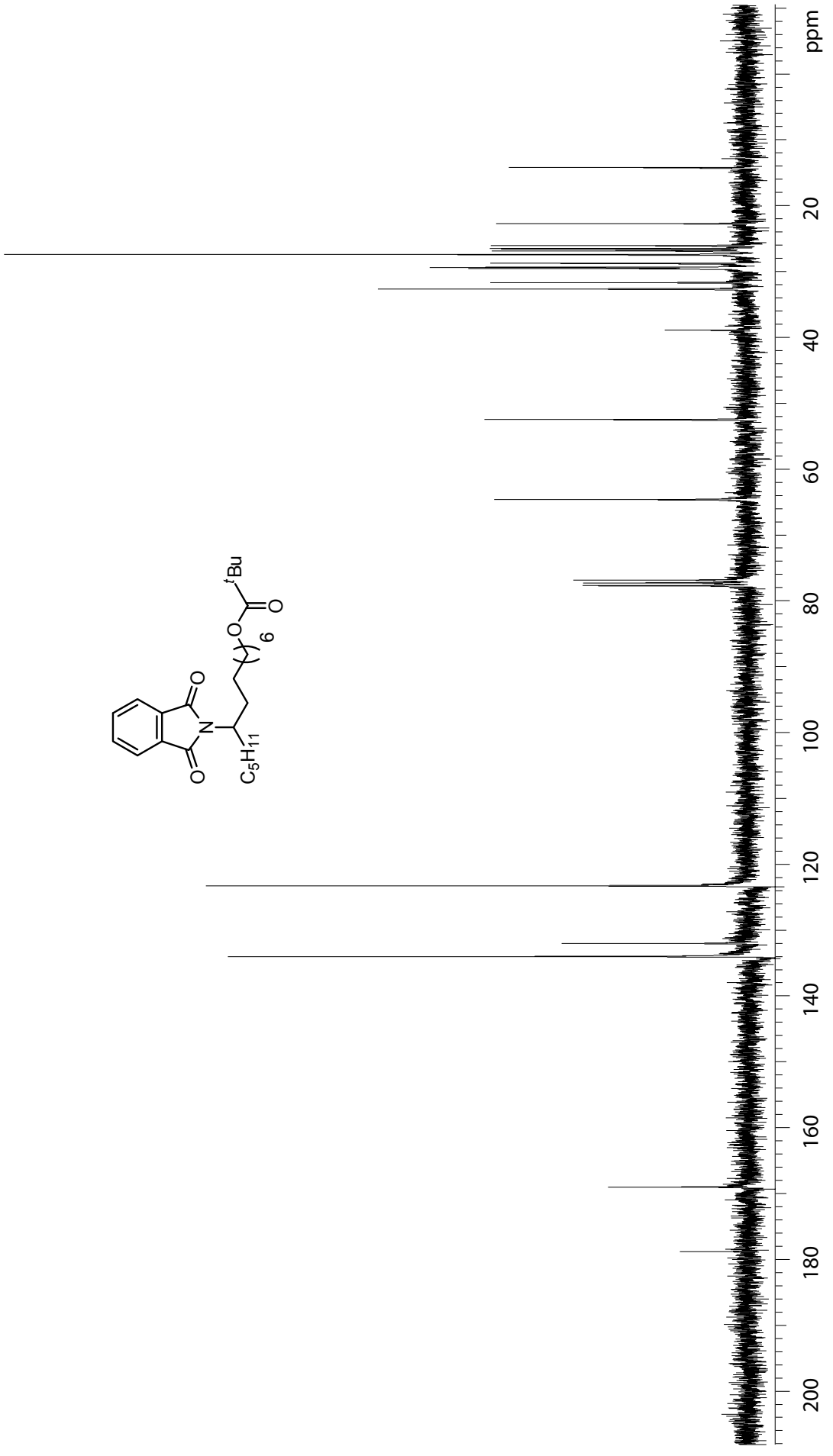
2.11
24.67
2.92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tBu
O
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120
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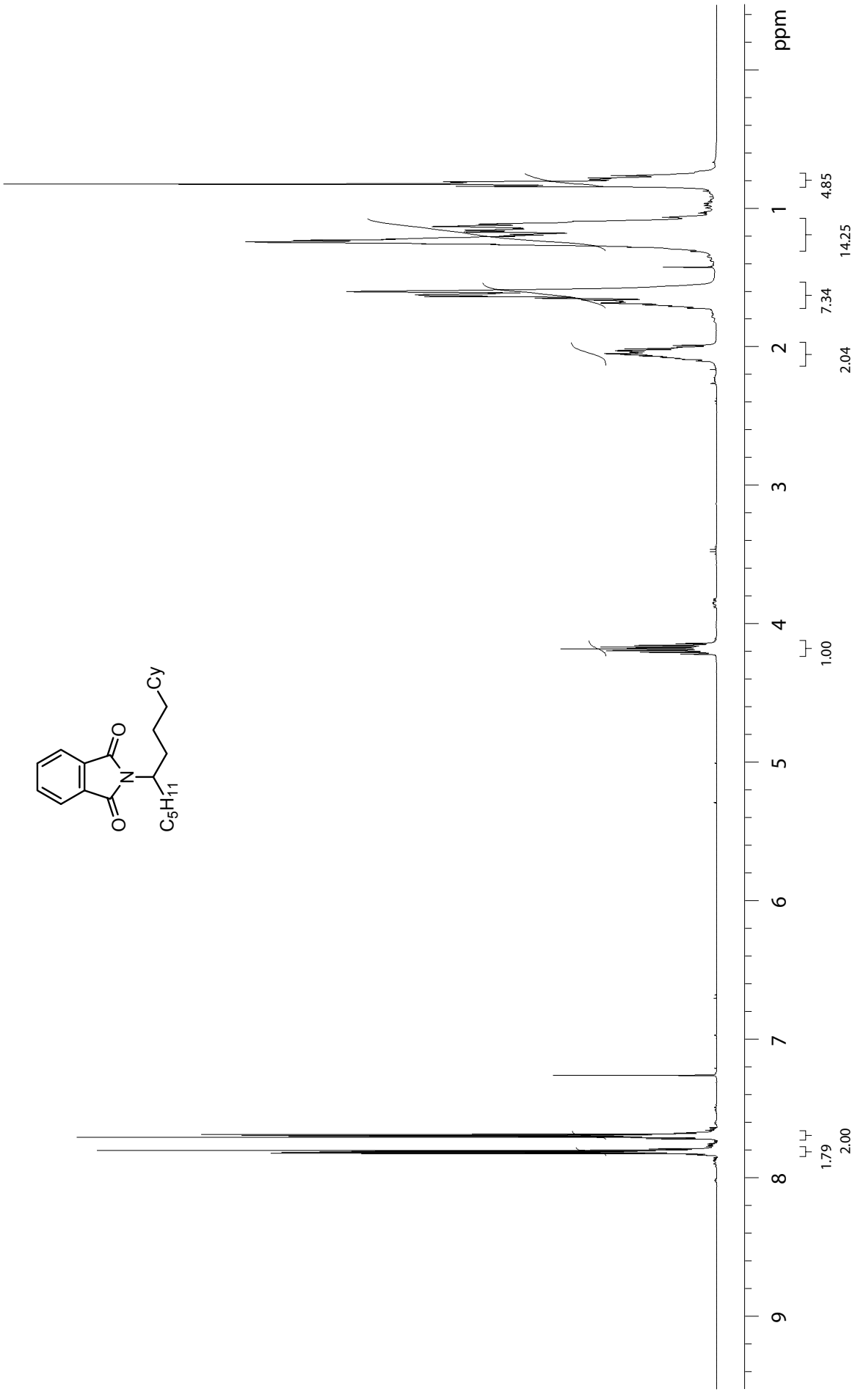
180
200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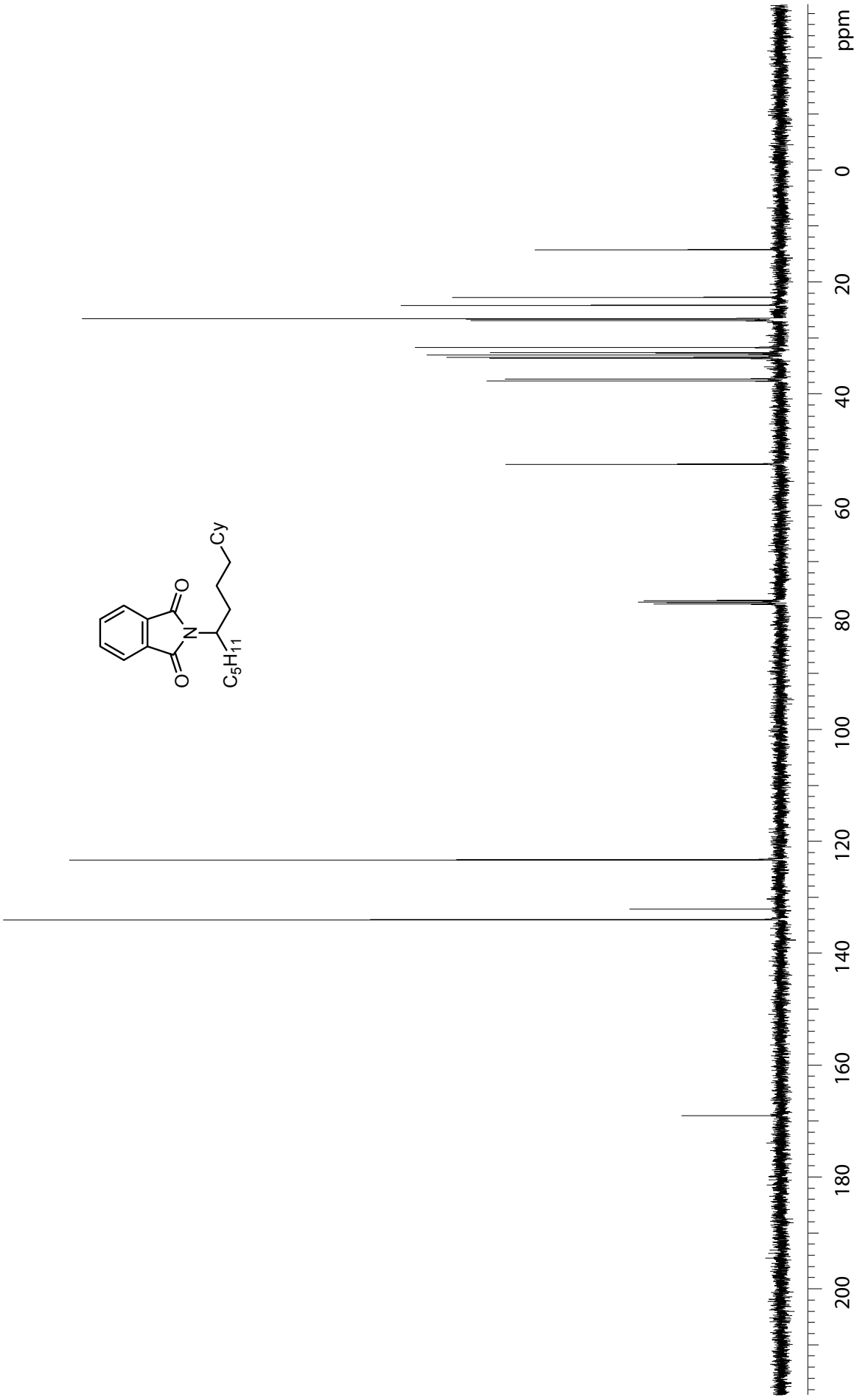
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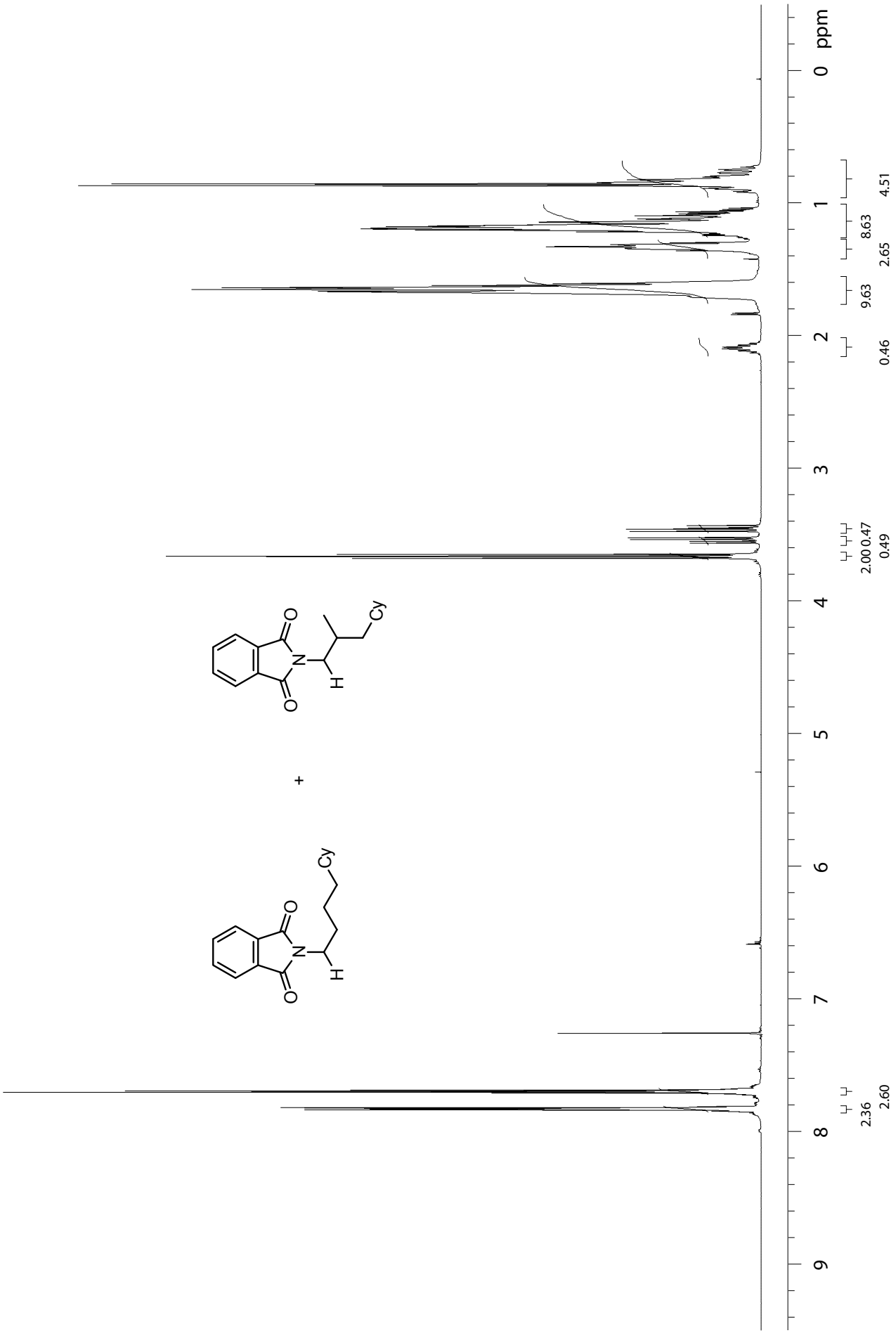
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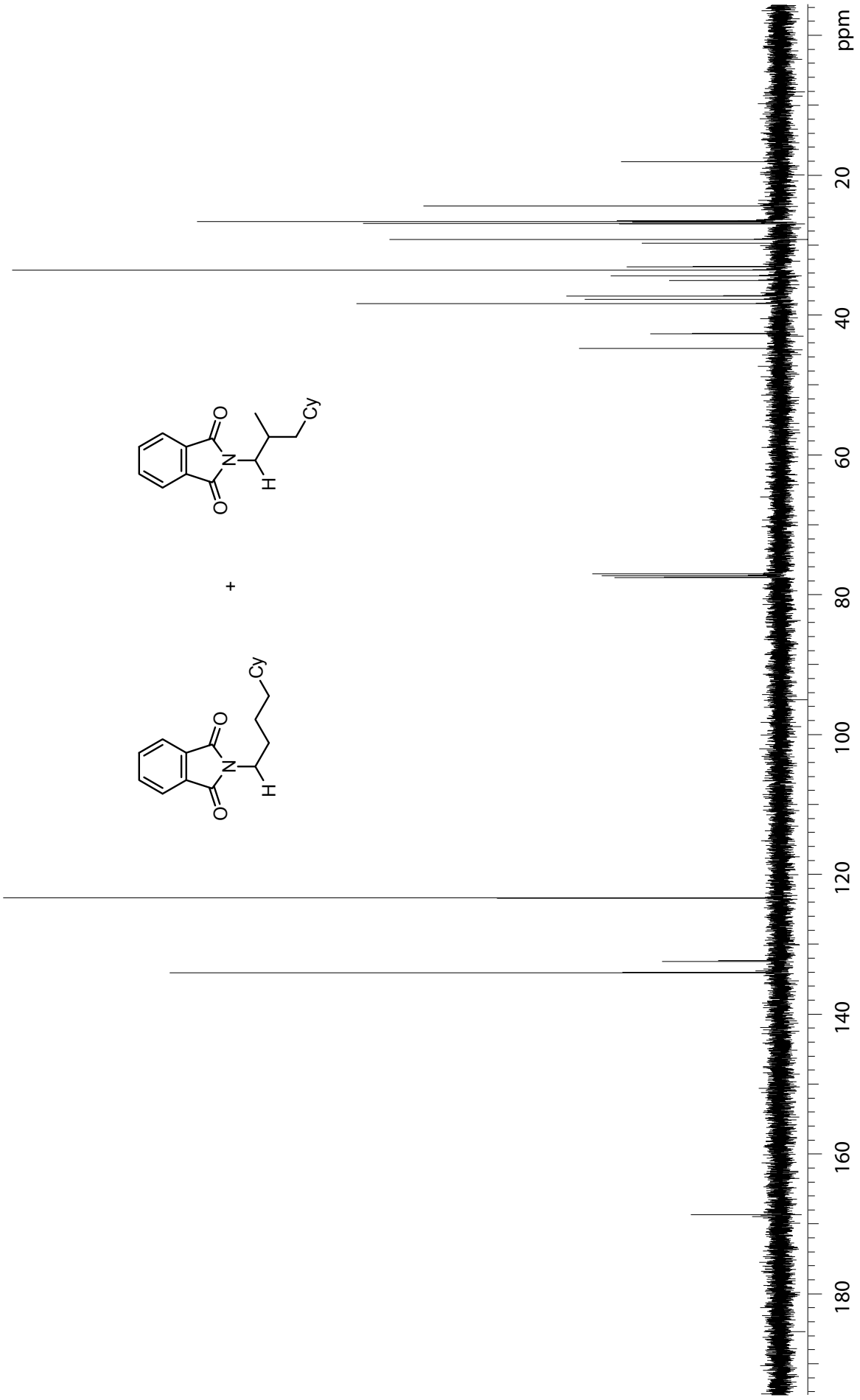
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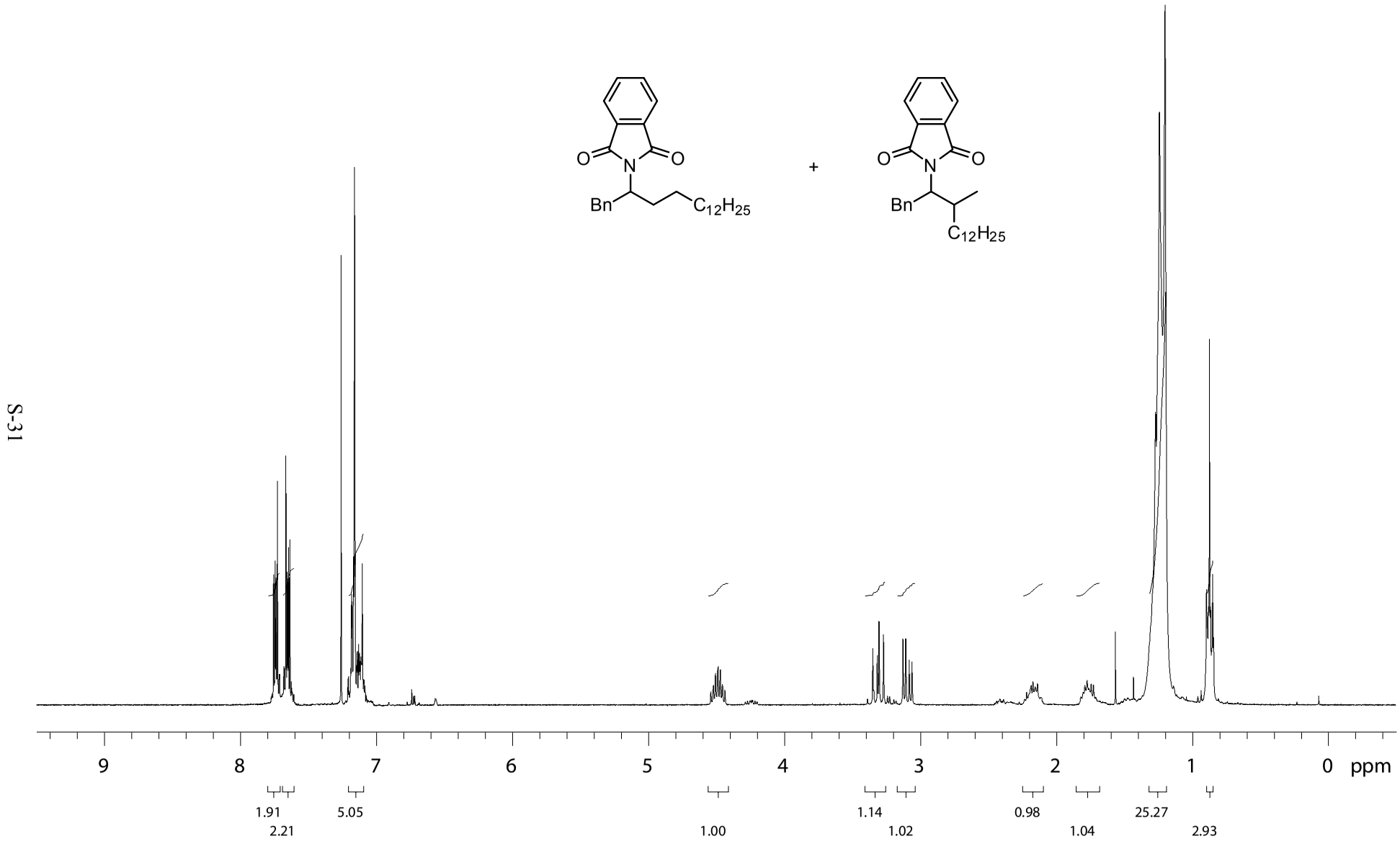
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7
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3
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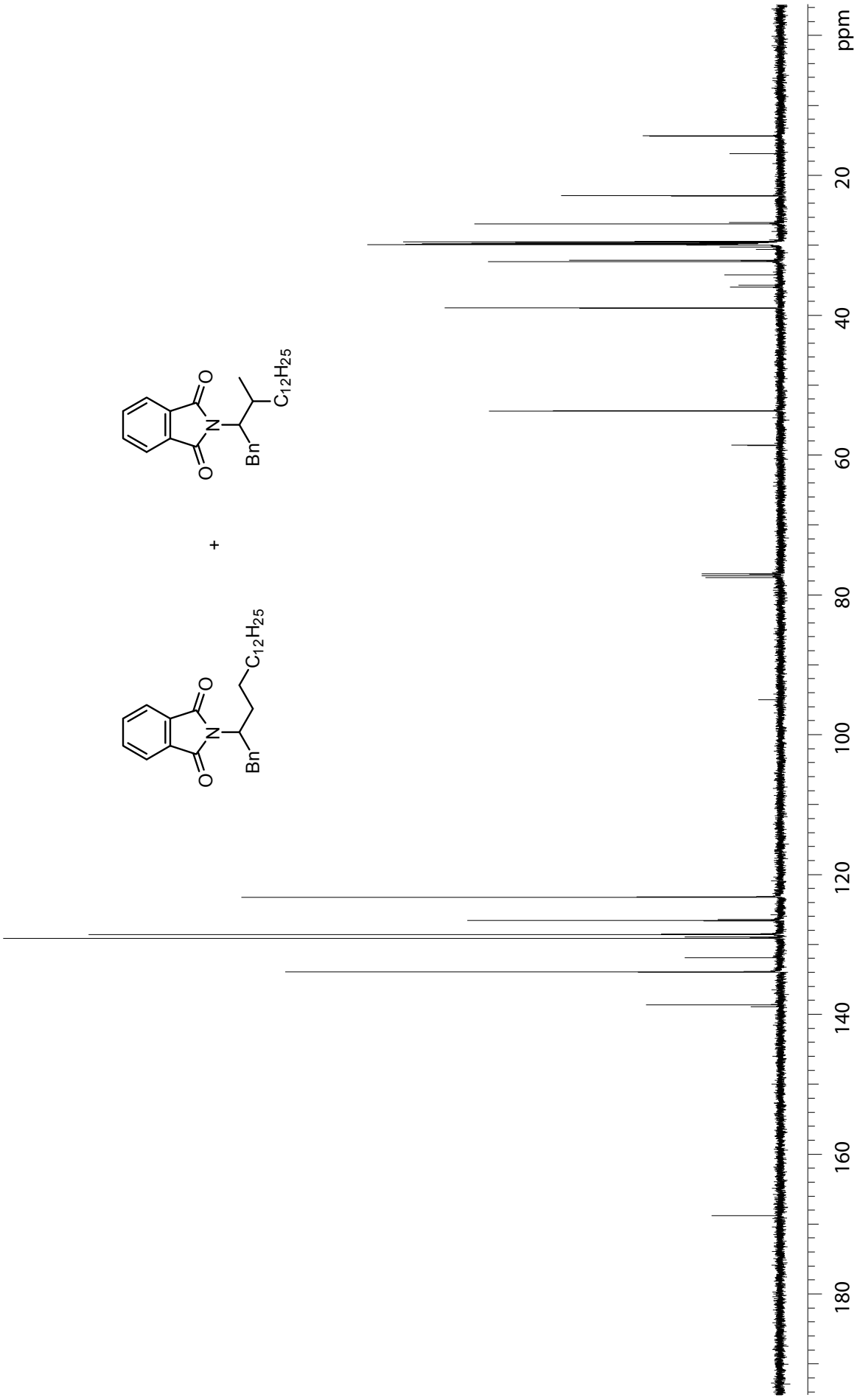
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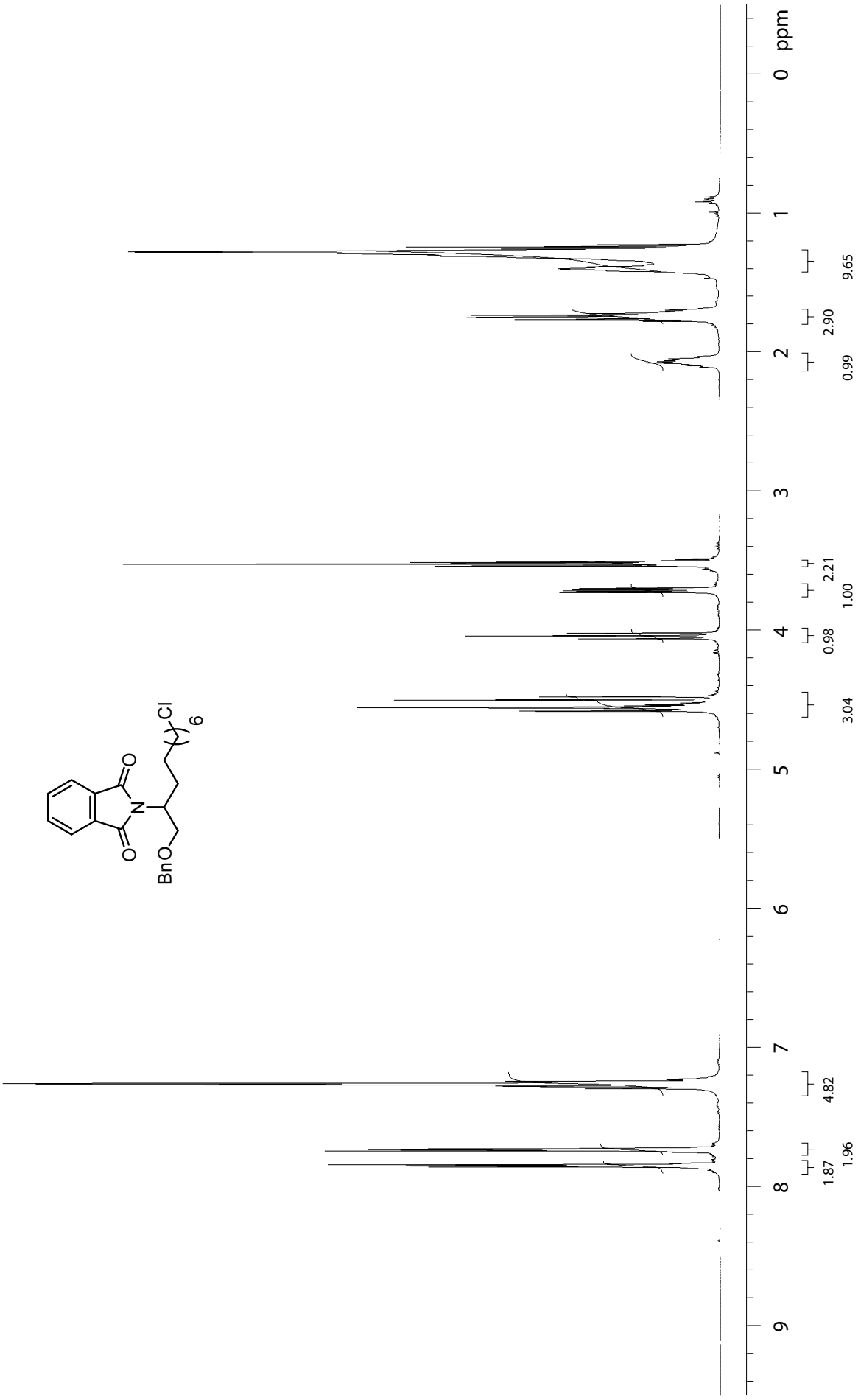
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Cl
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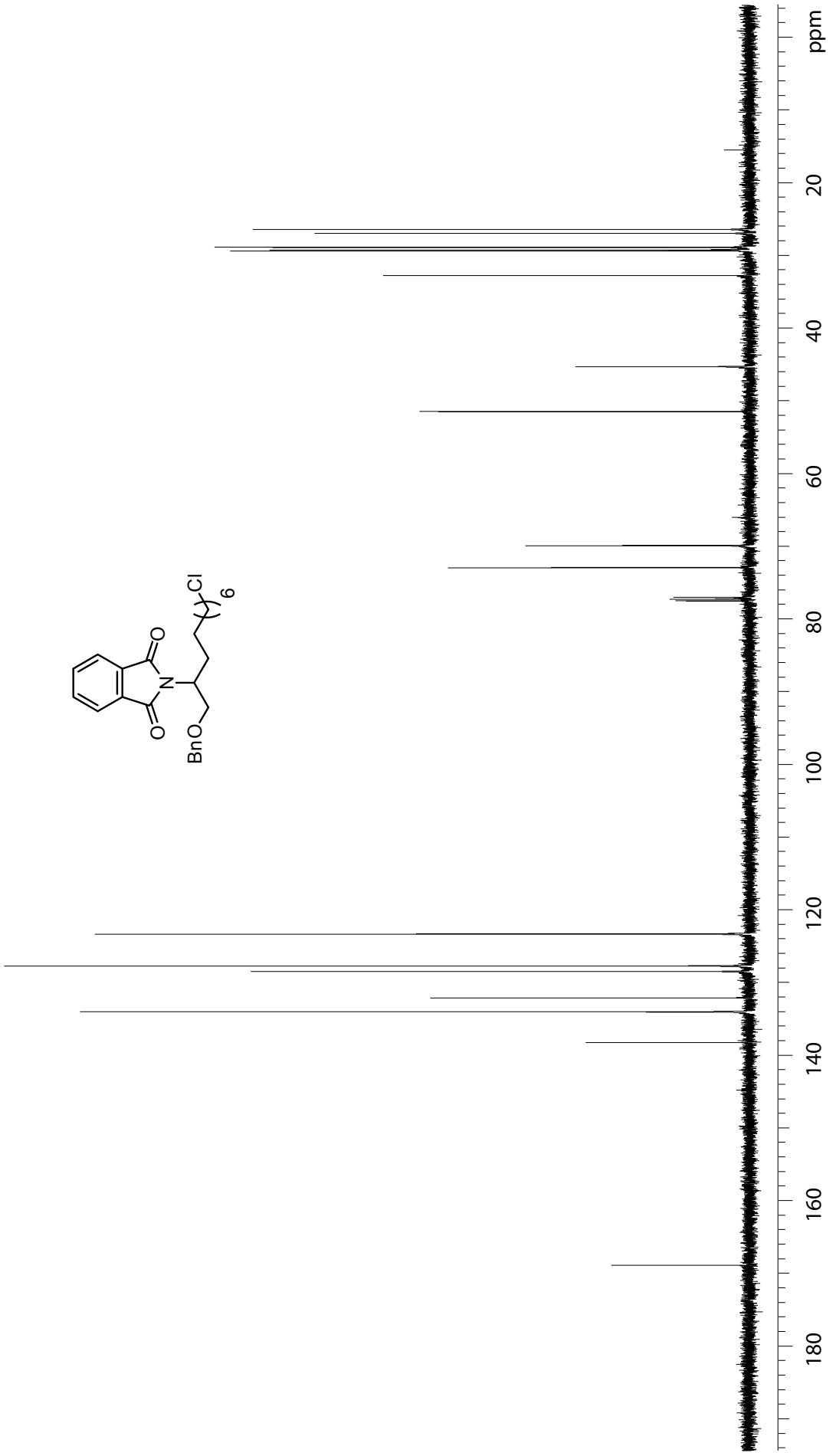
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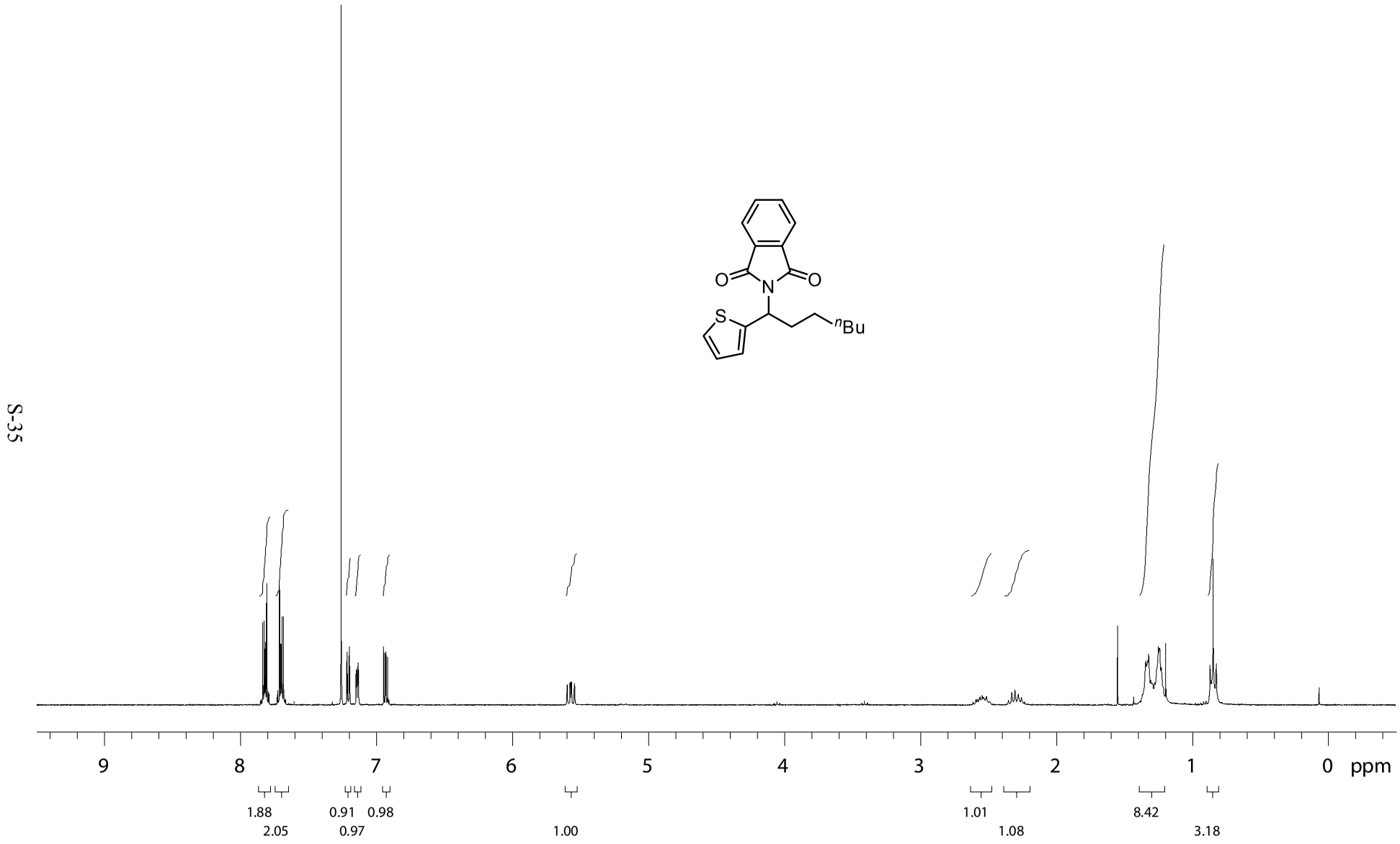
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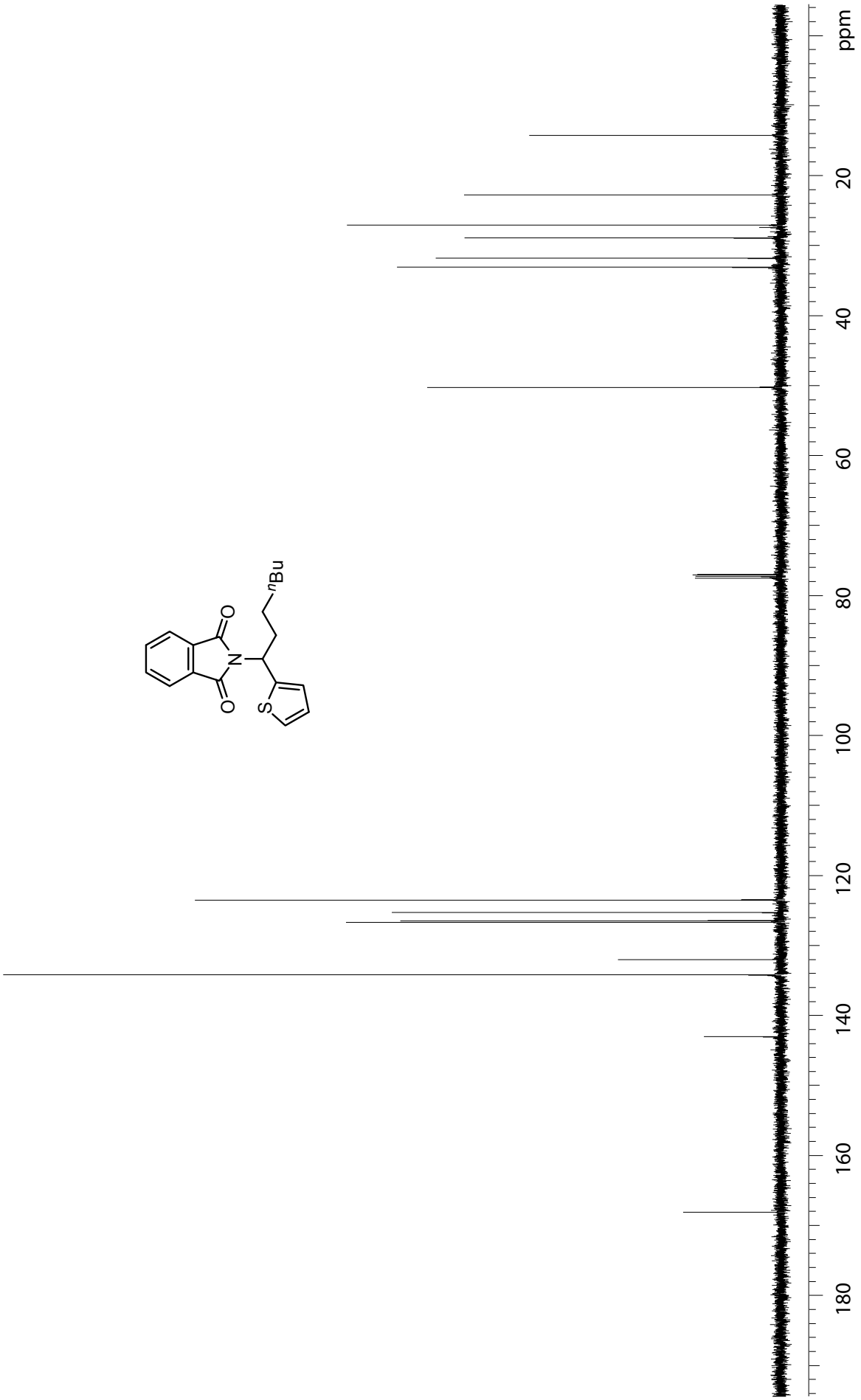
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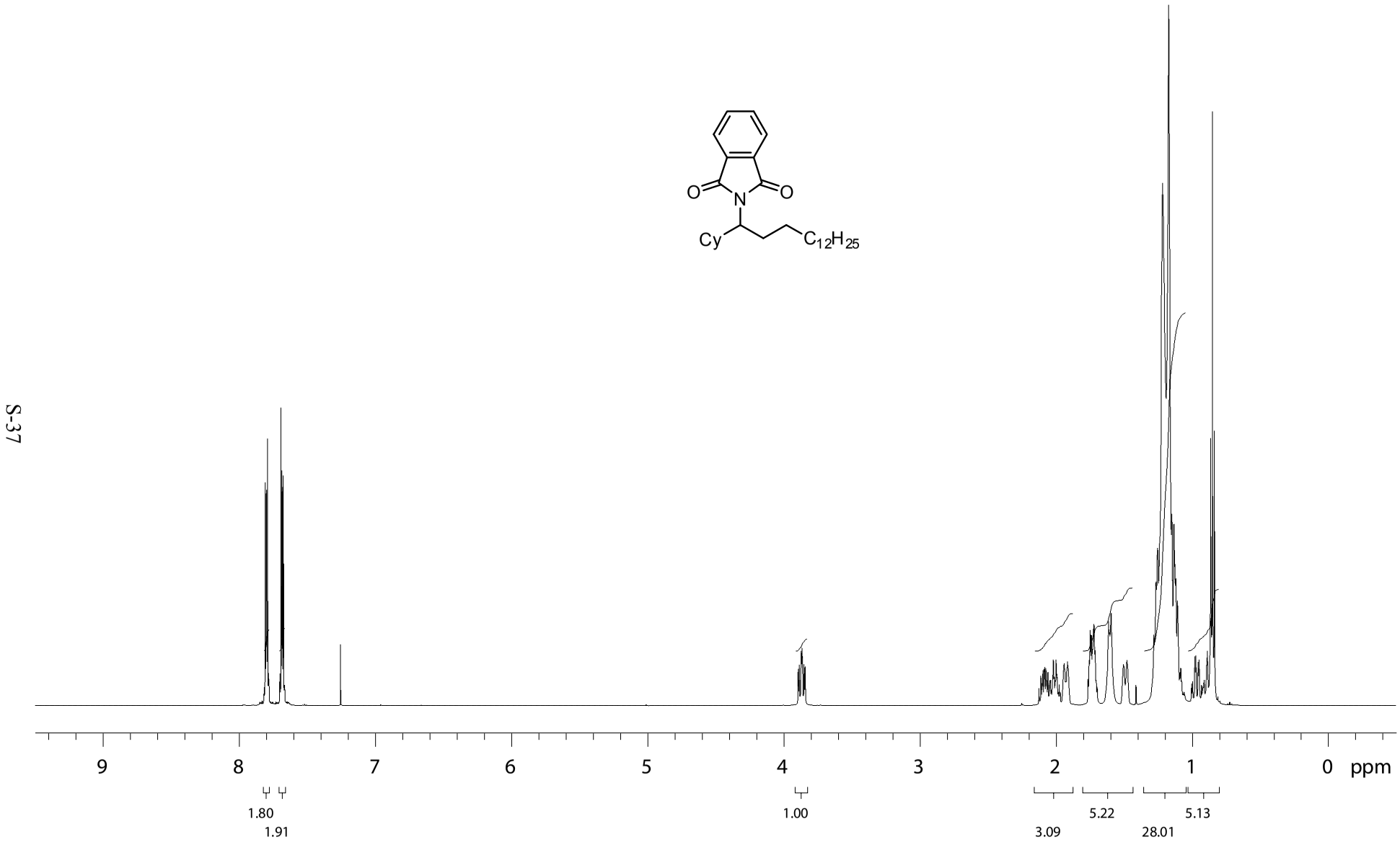
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$C_{12}H_{25}$
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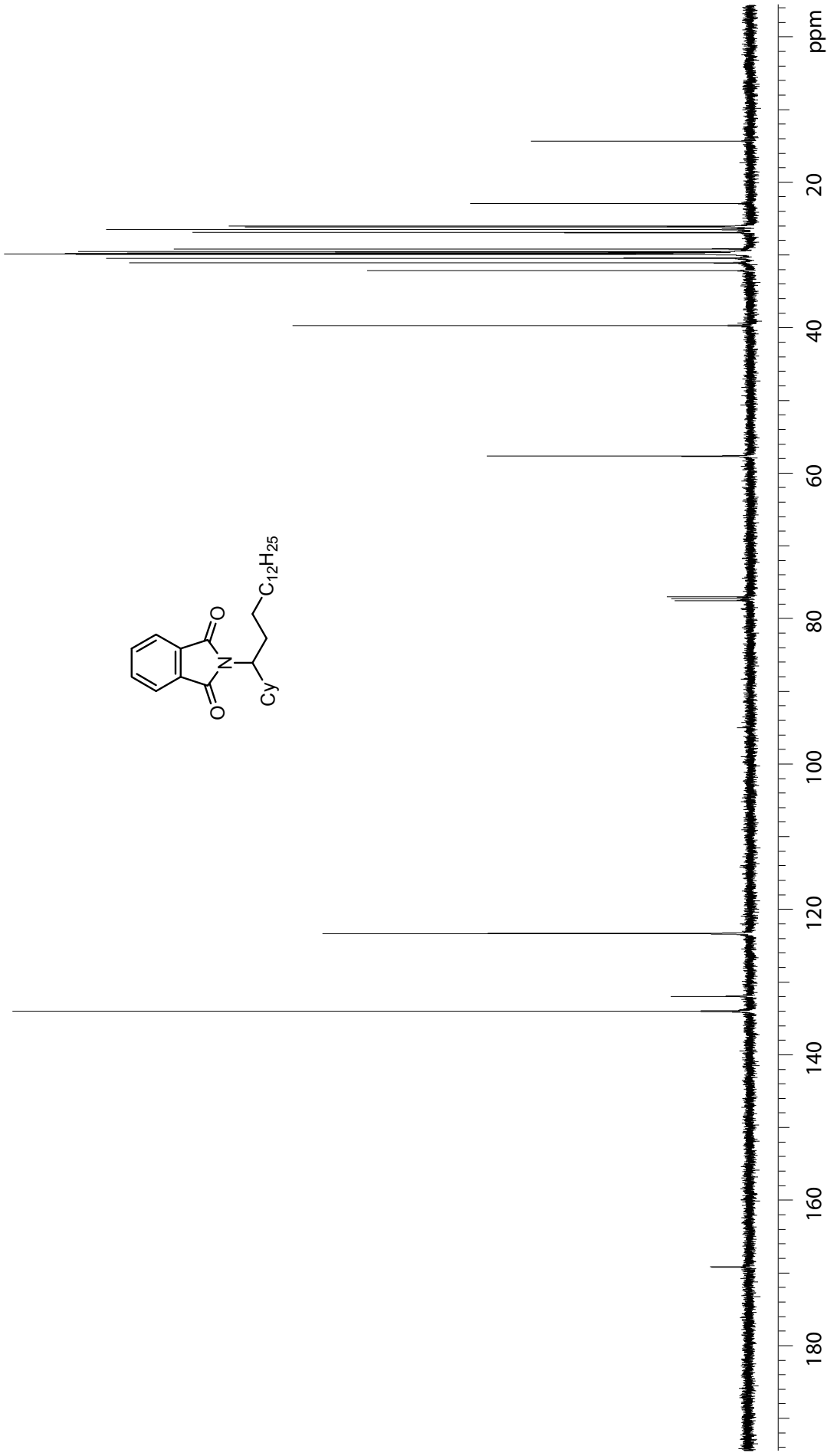
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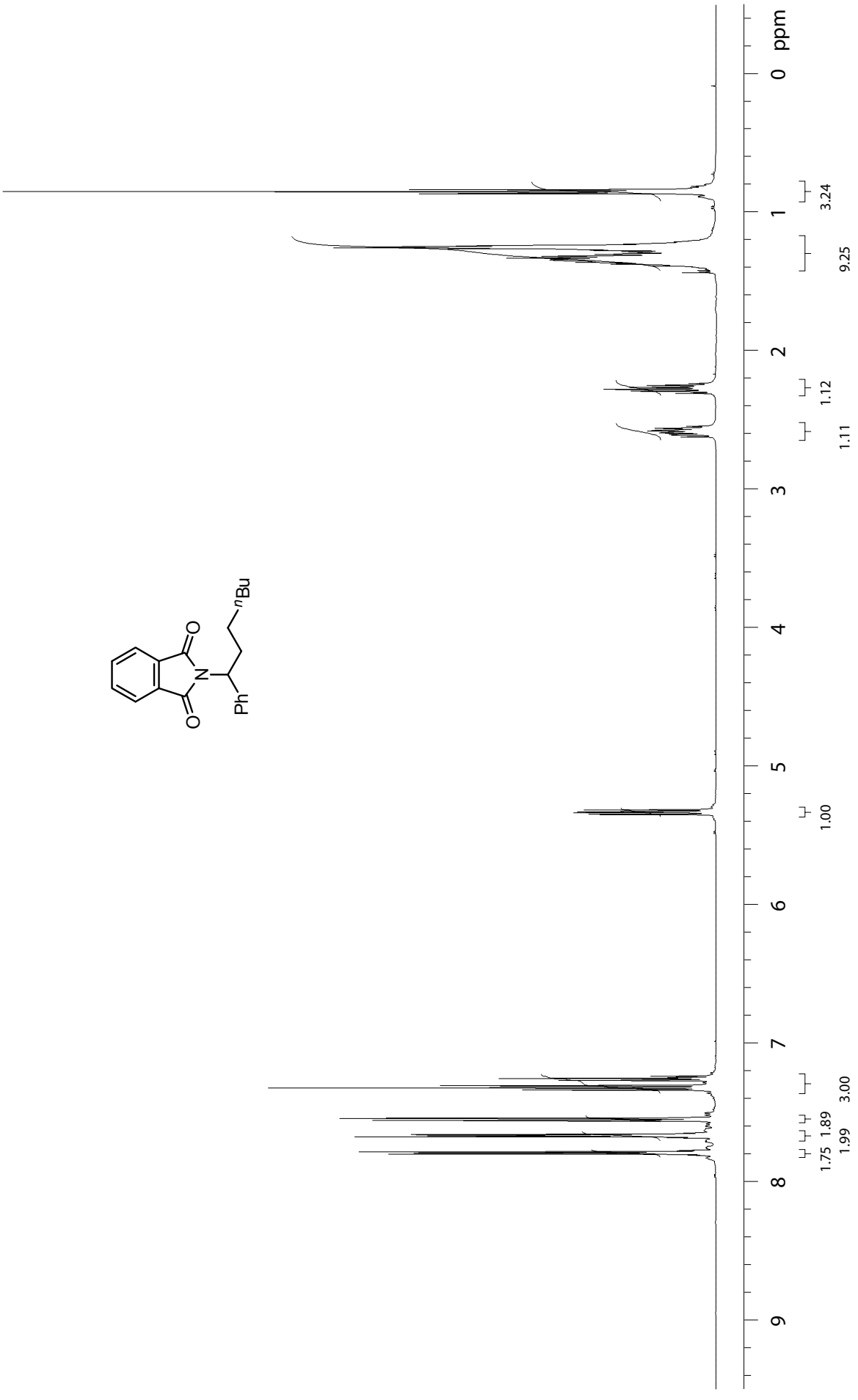
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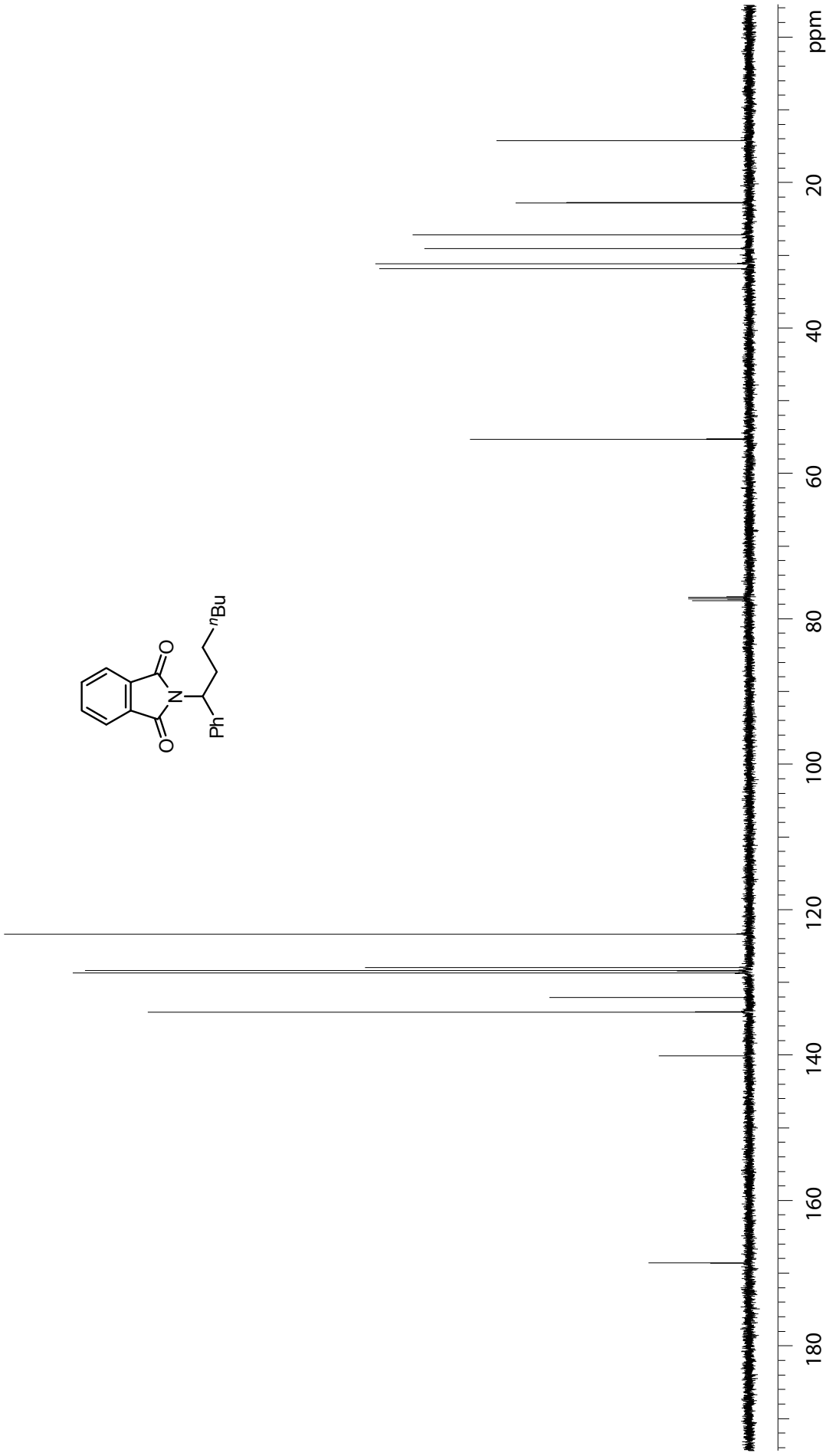
3.00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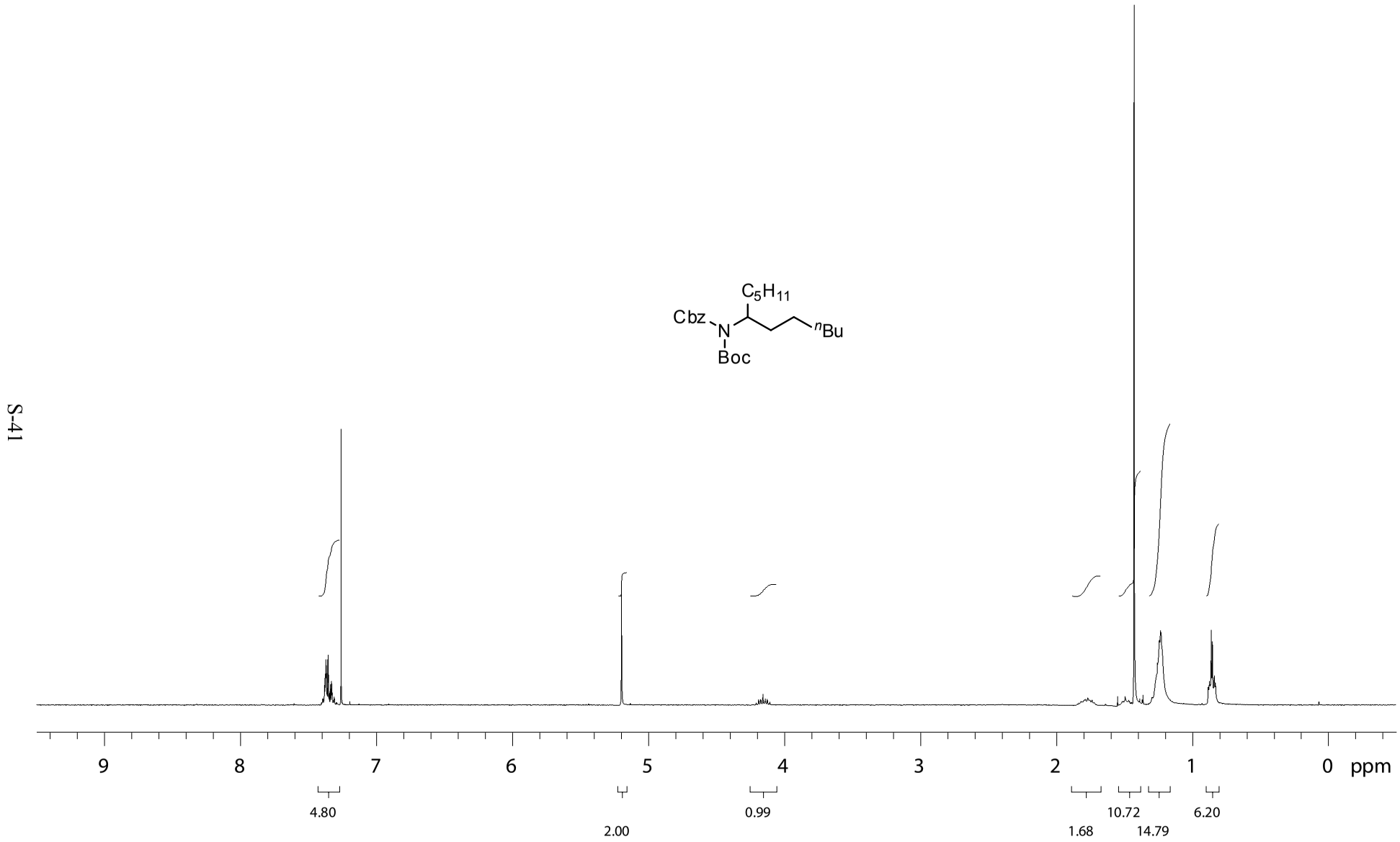
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nBu
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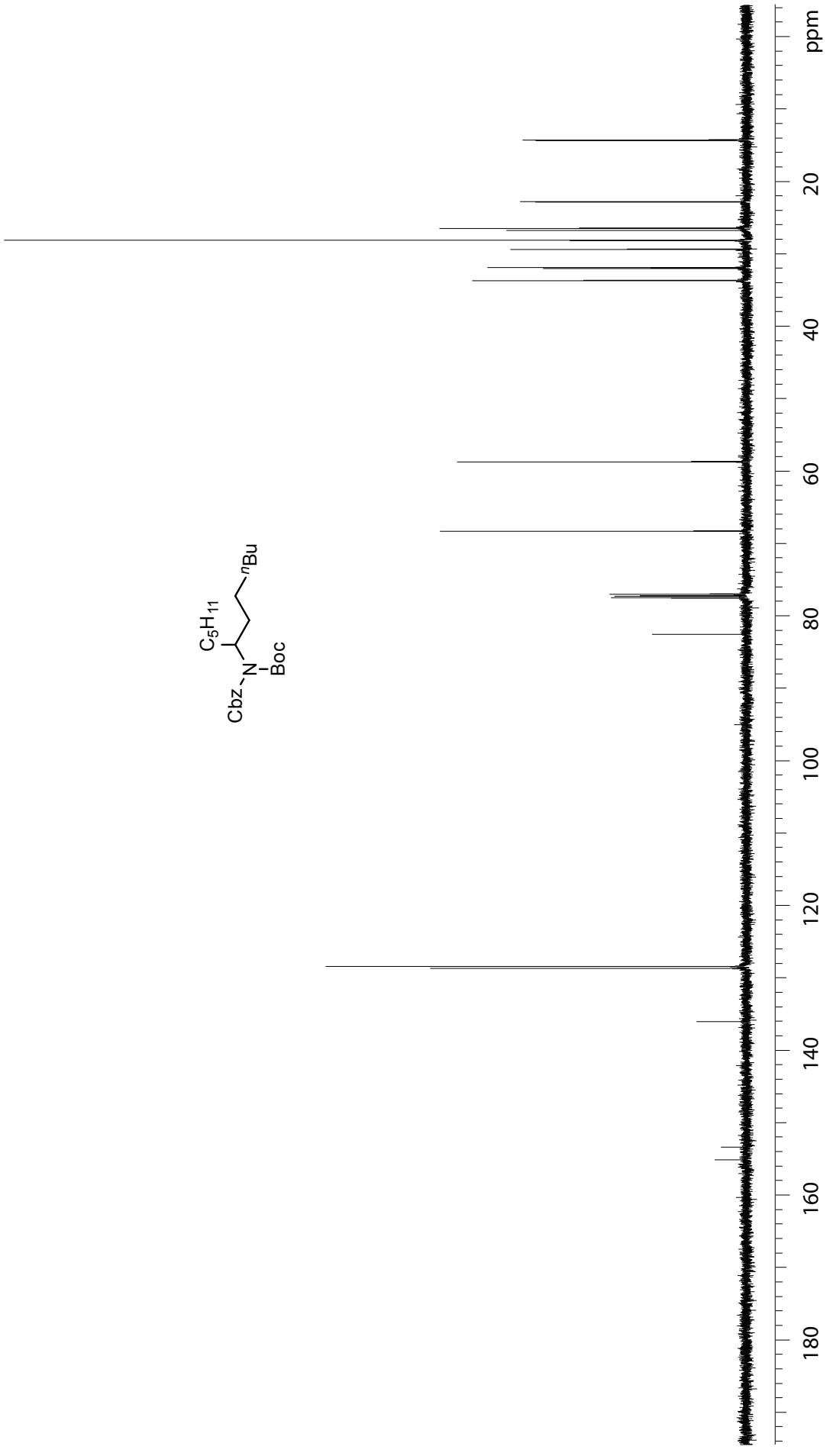
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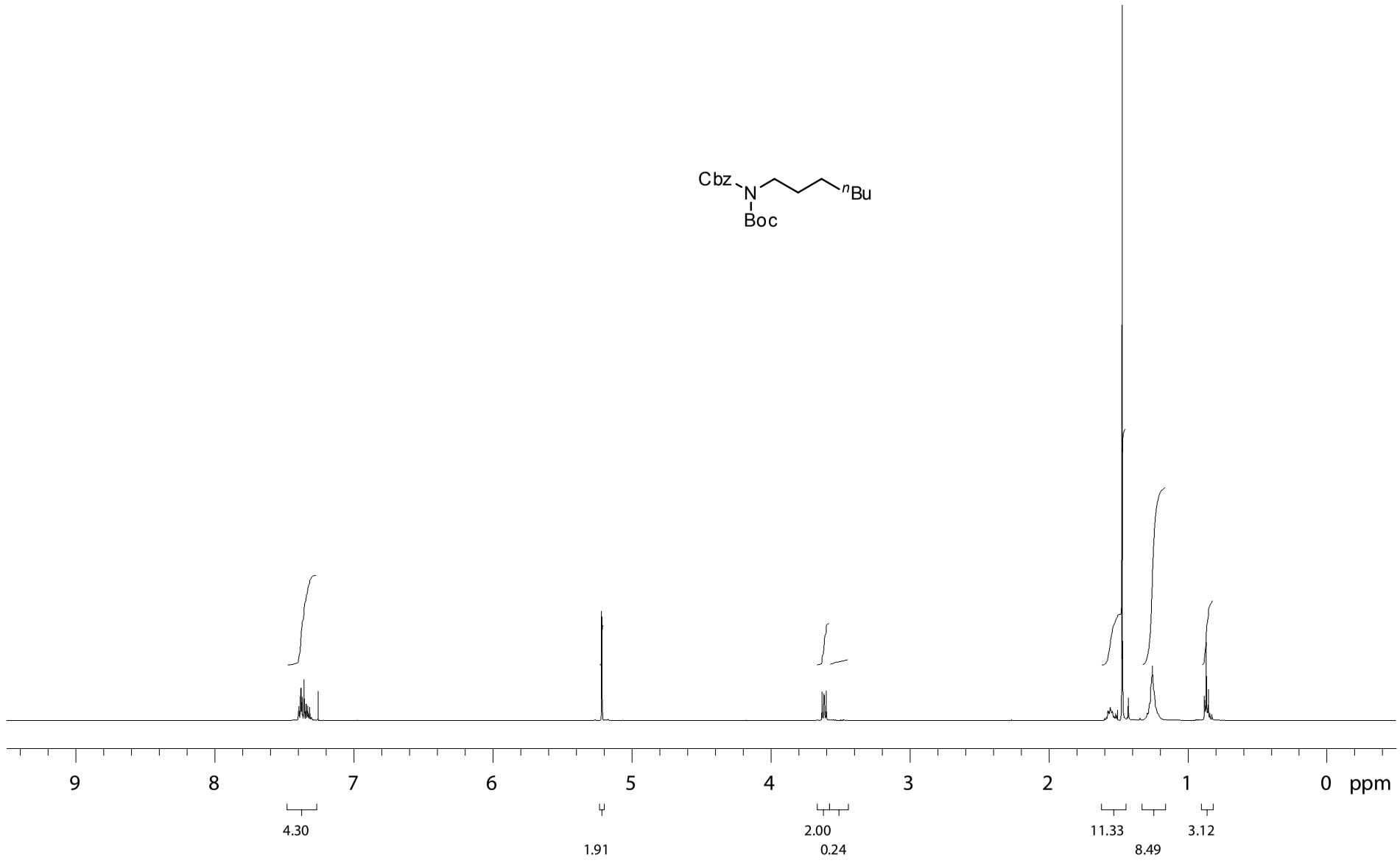
Boc
C5H11
nBu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Boc
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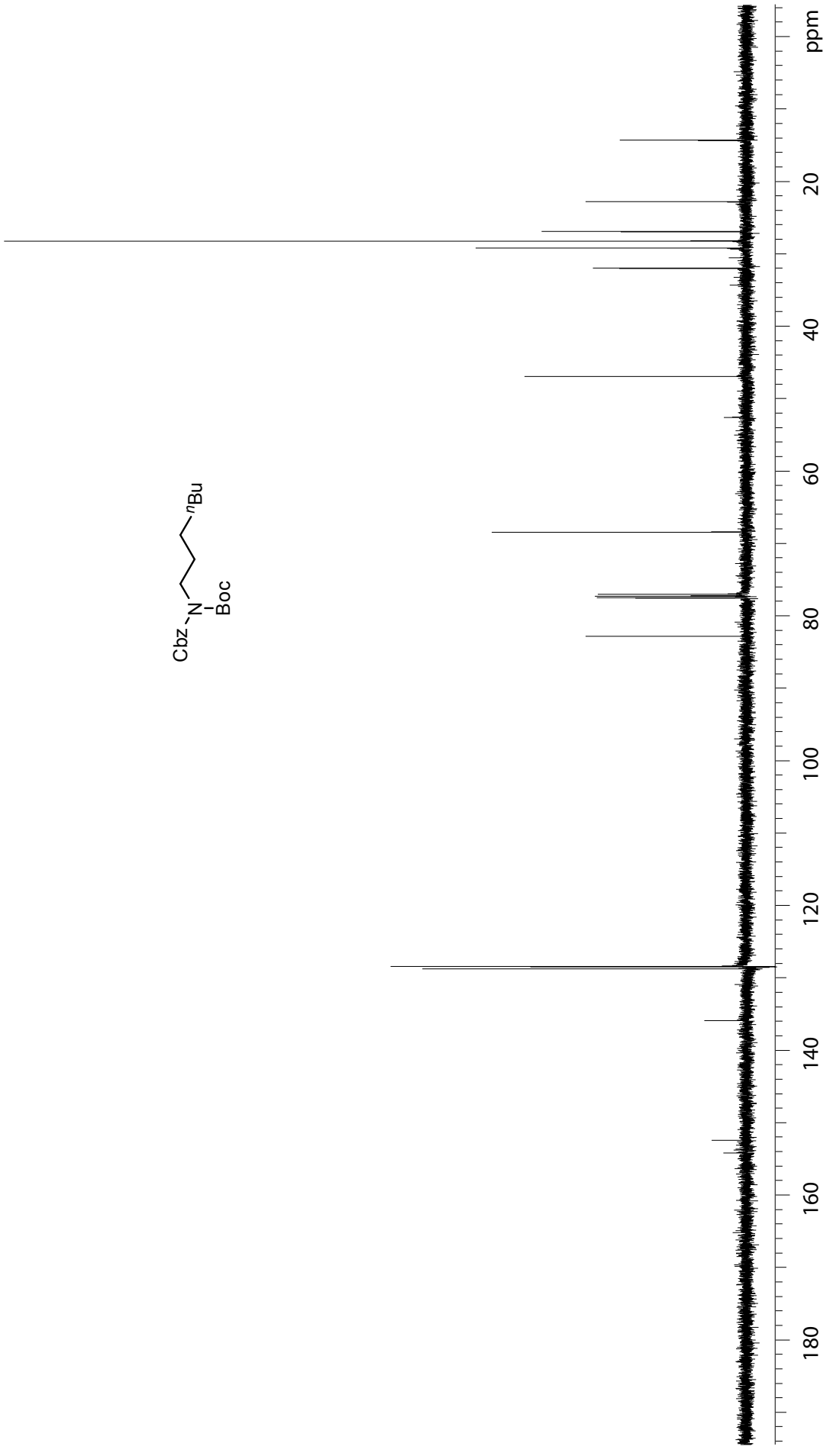
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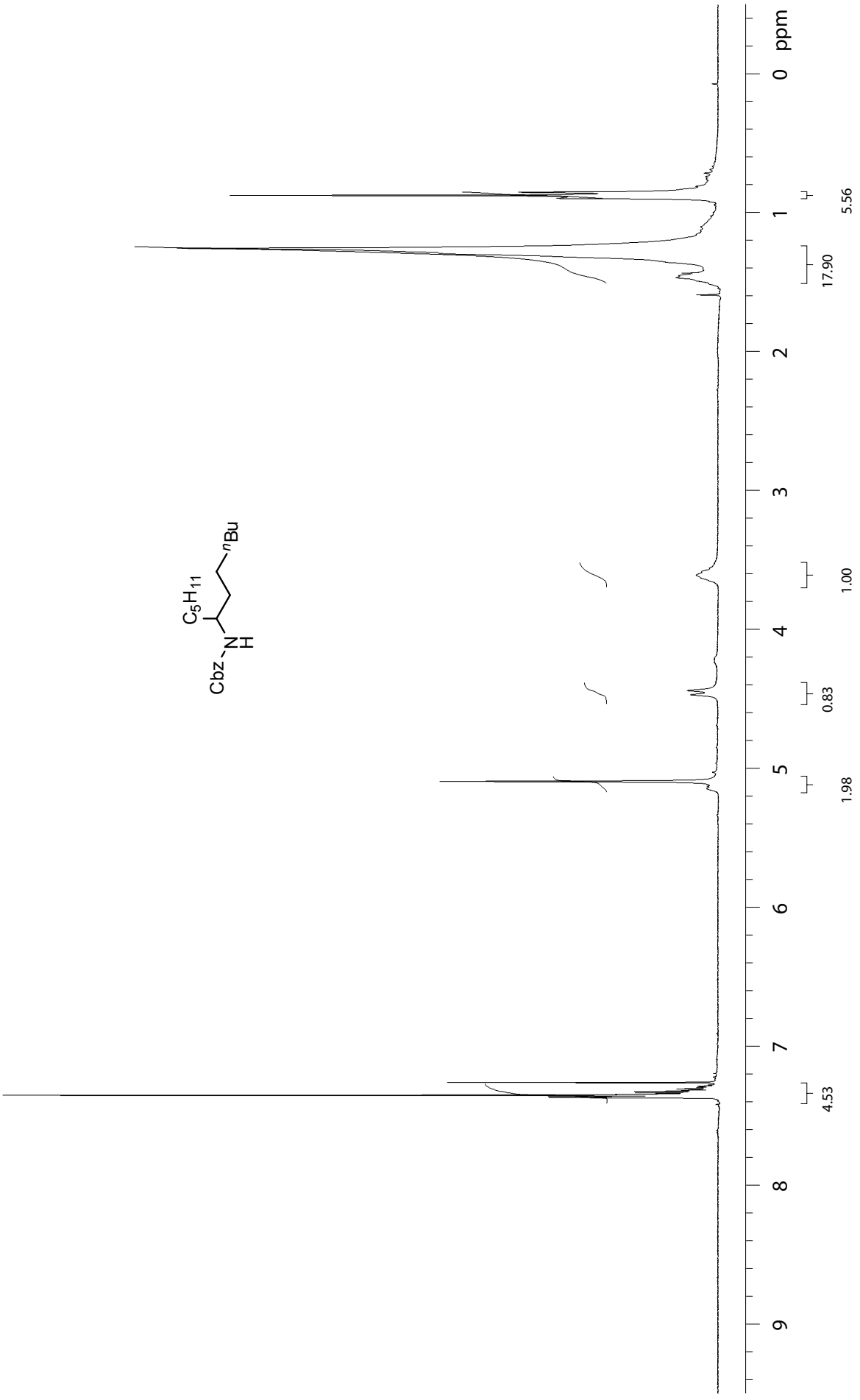
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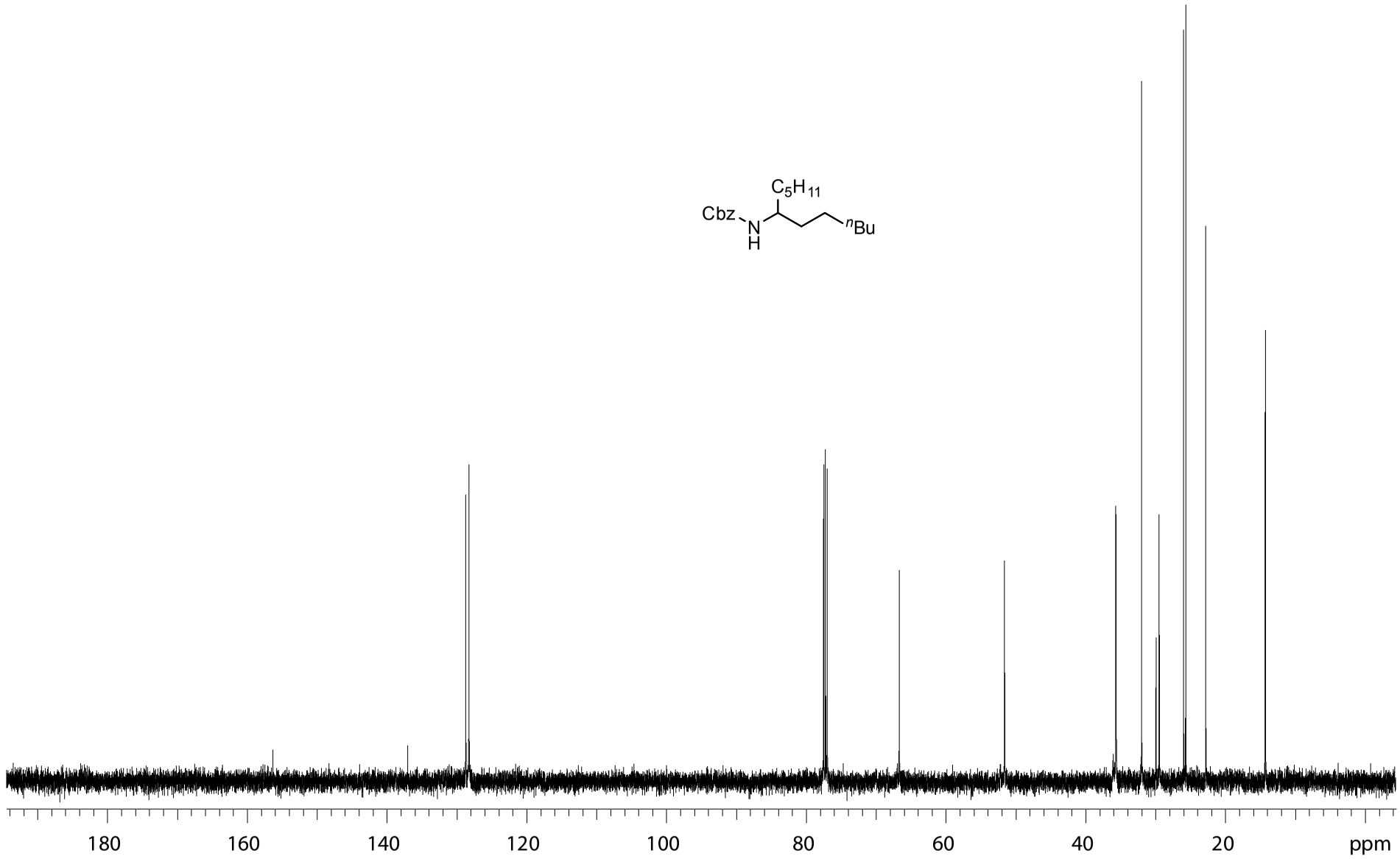
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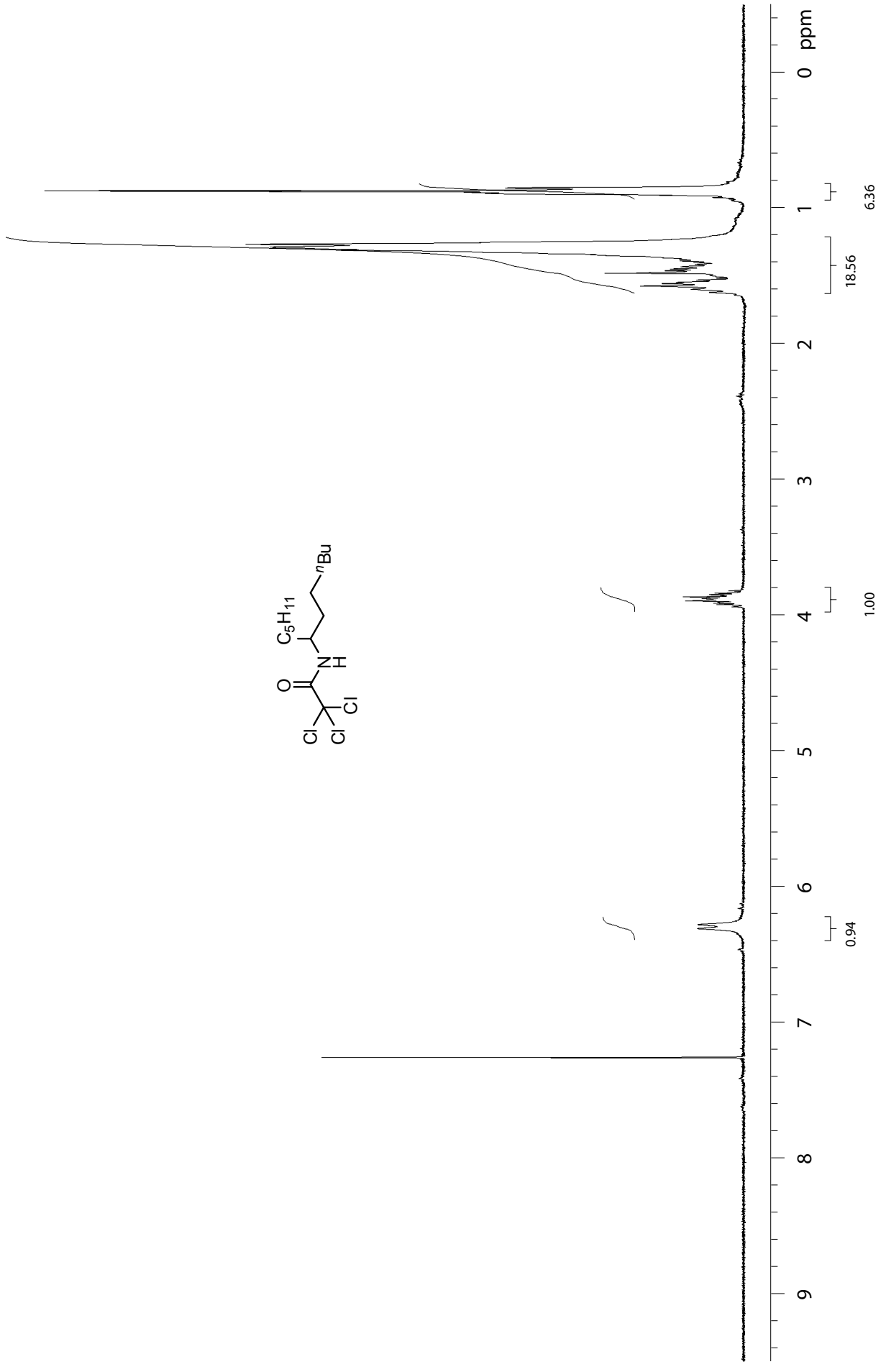
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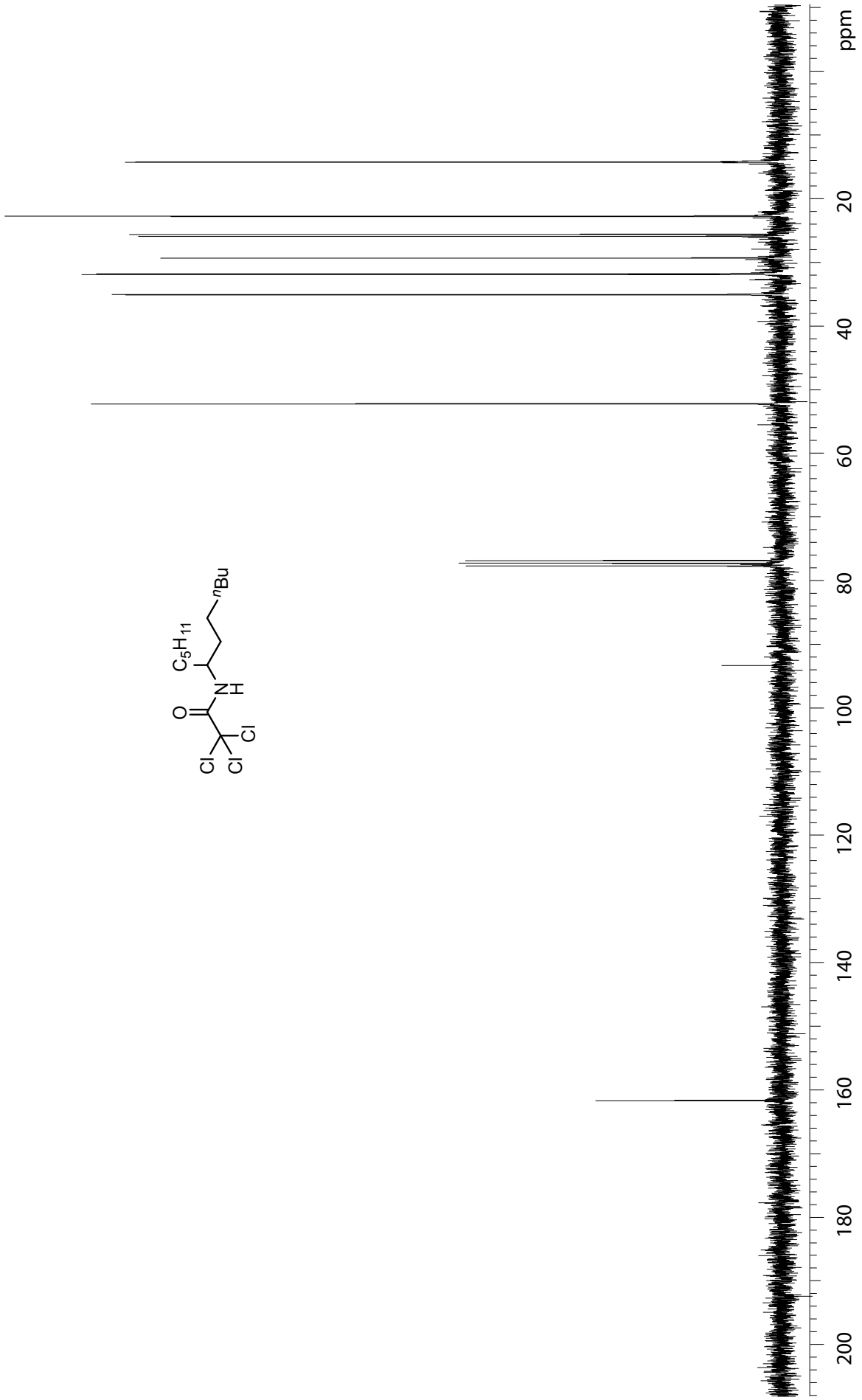
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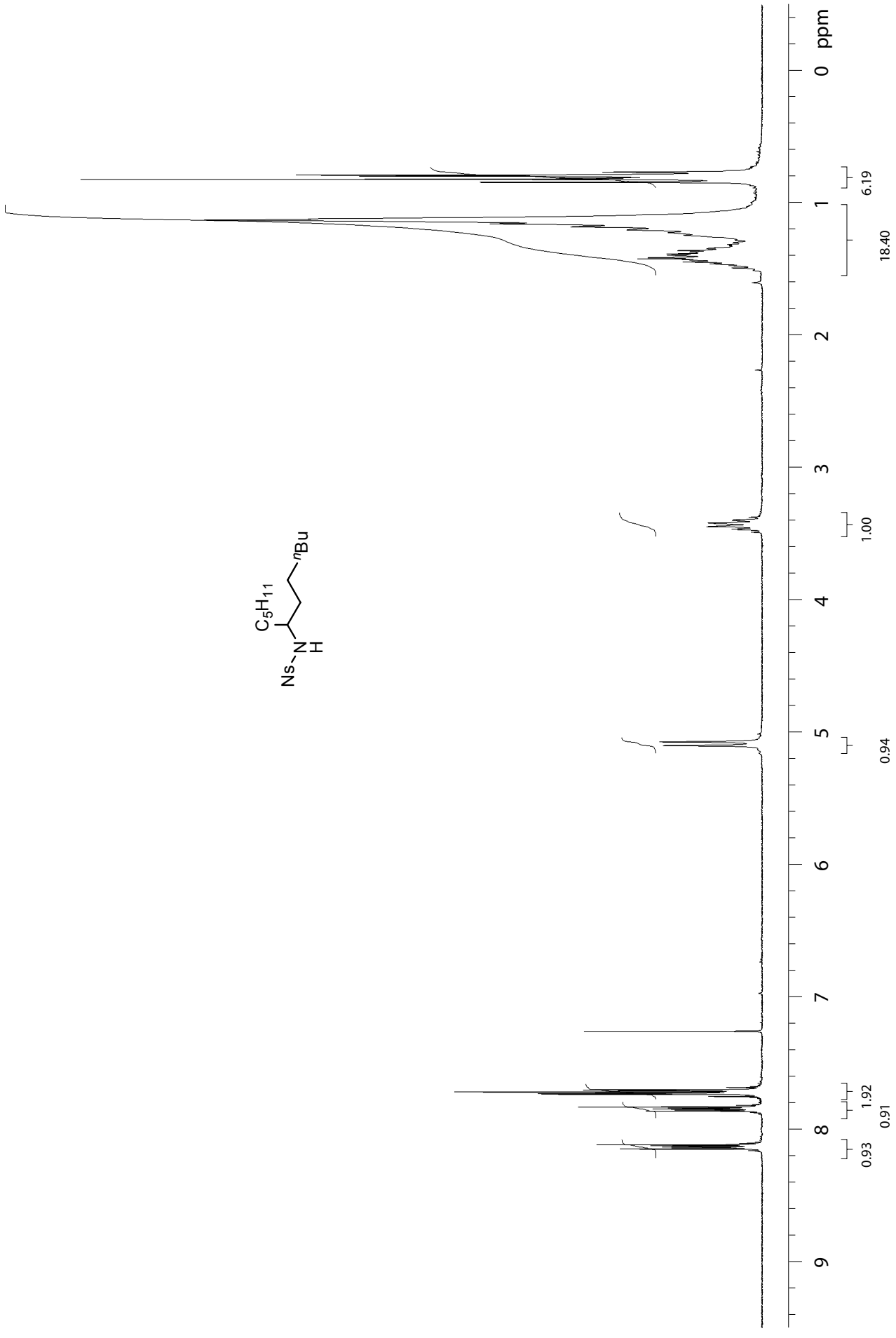
Cl
Cl
C5H11
nBu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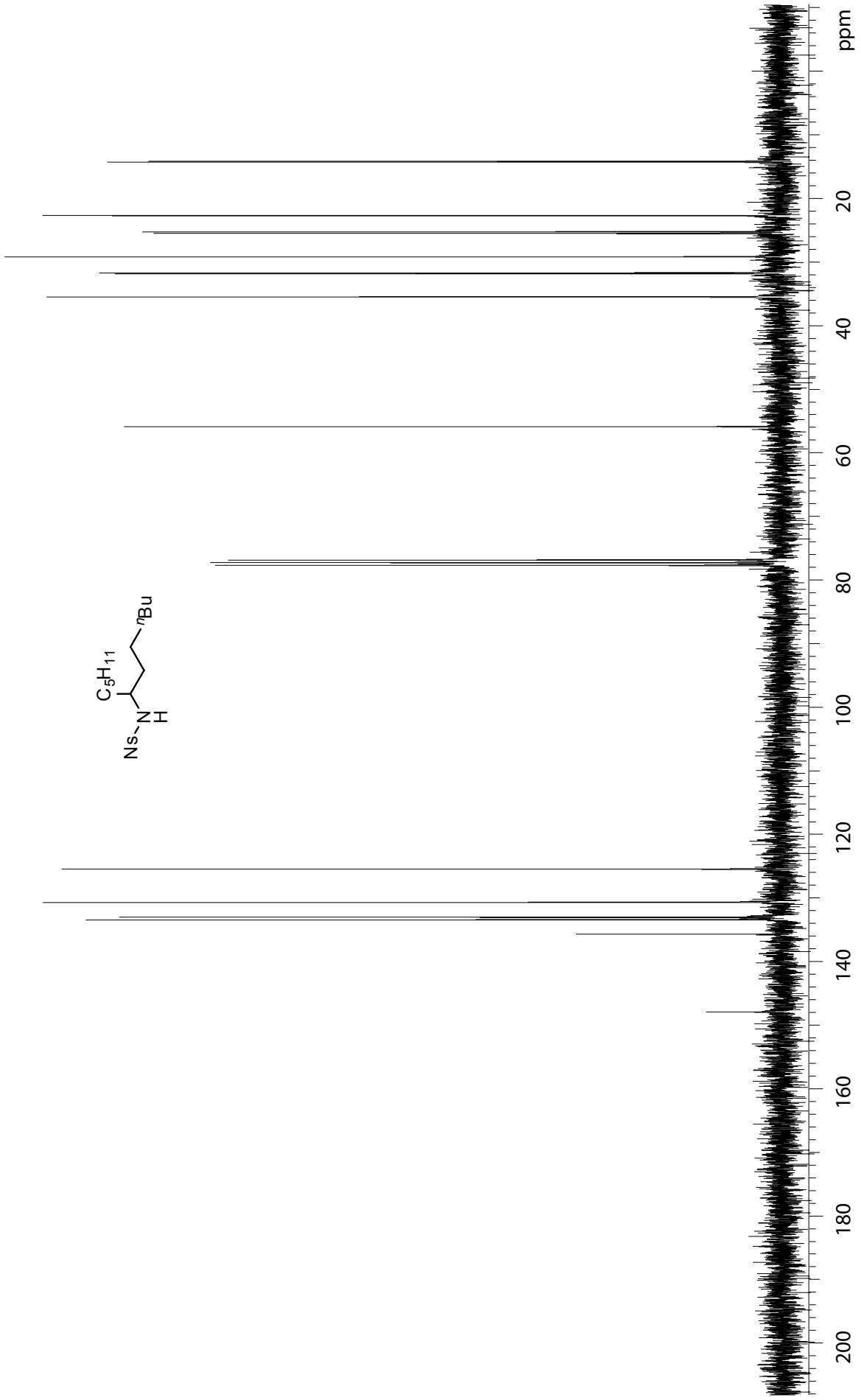
C5H11
nBu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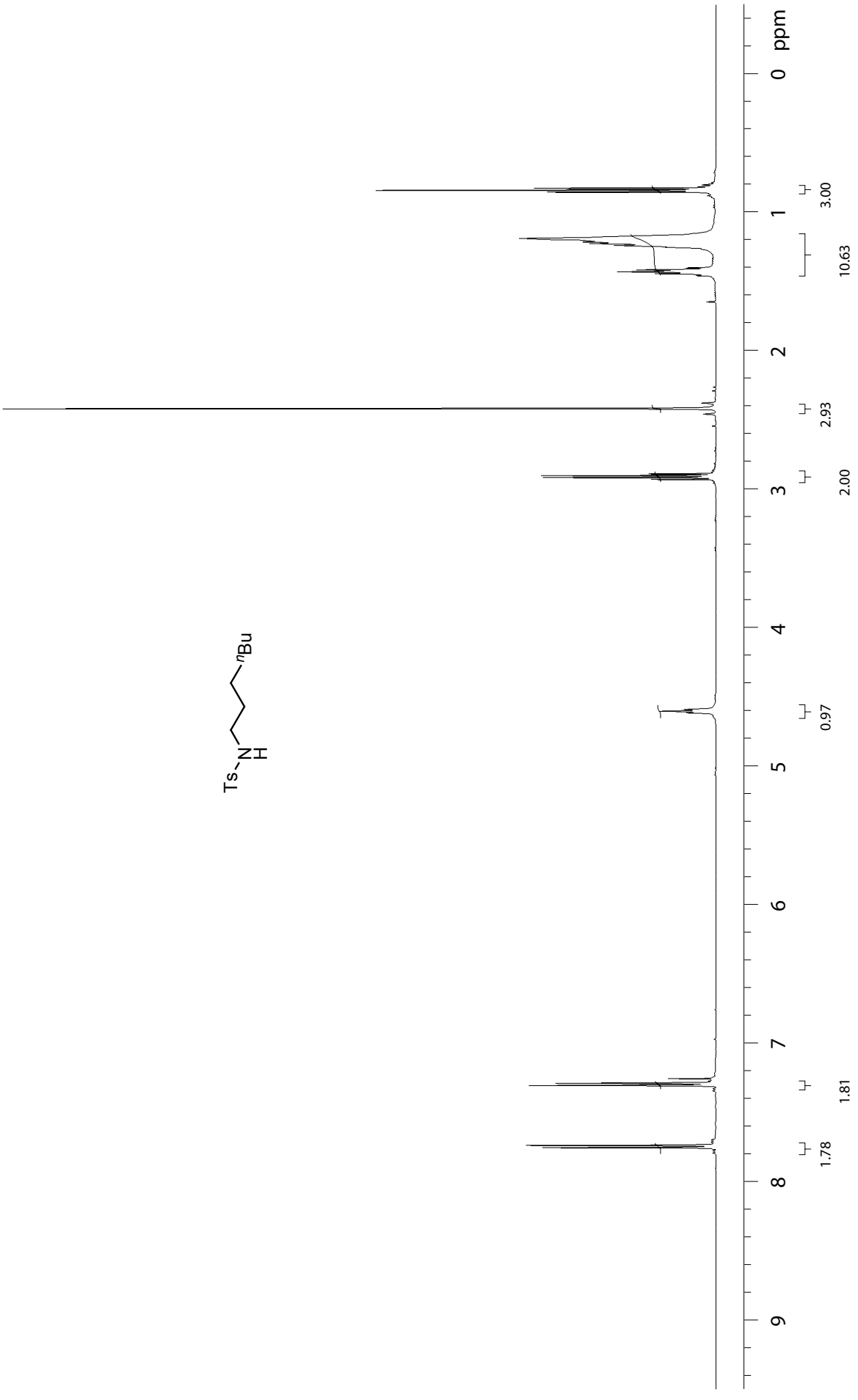
nBu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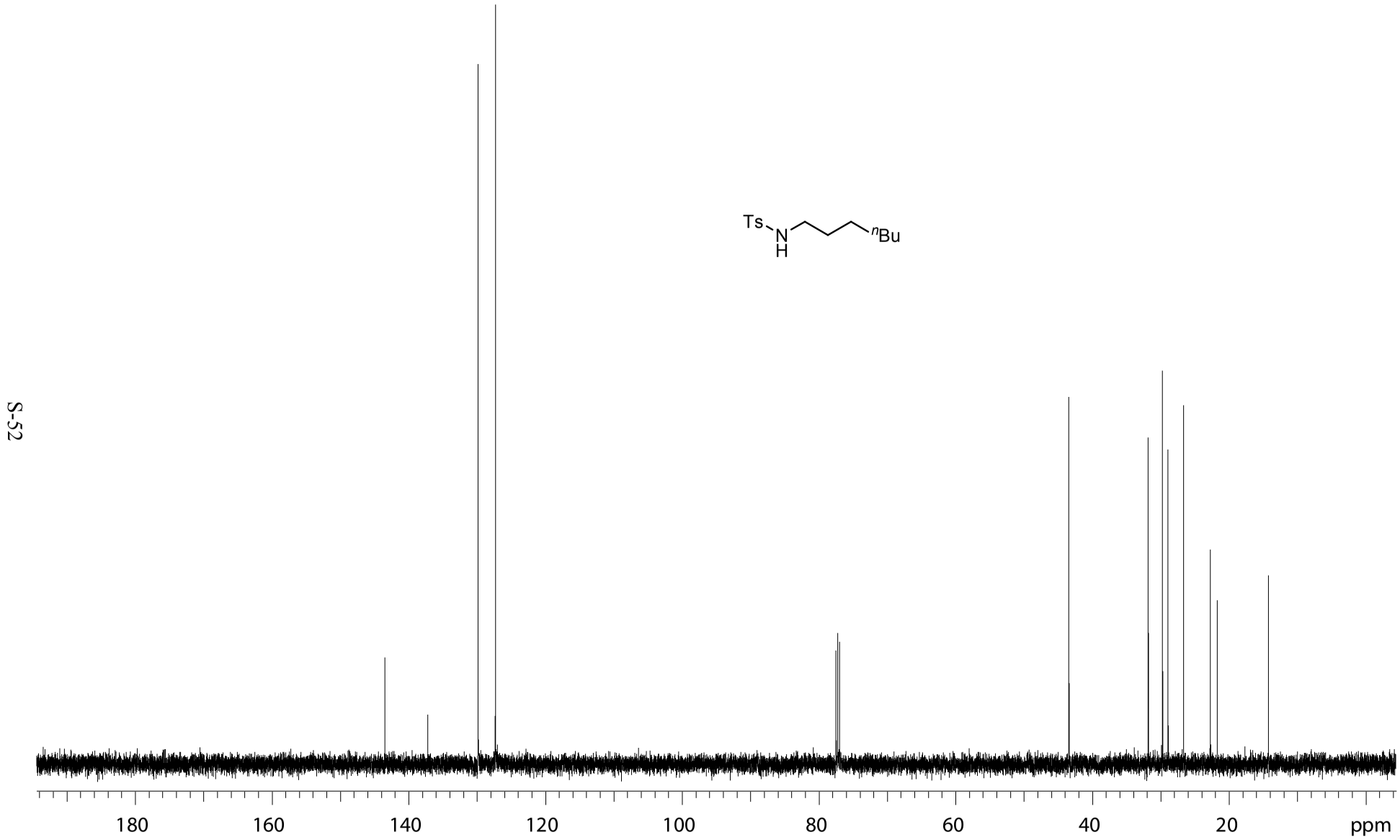
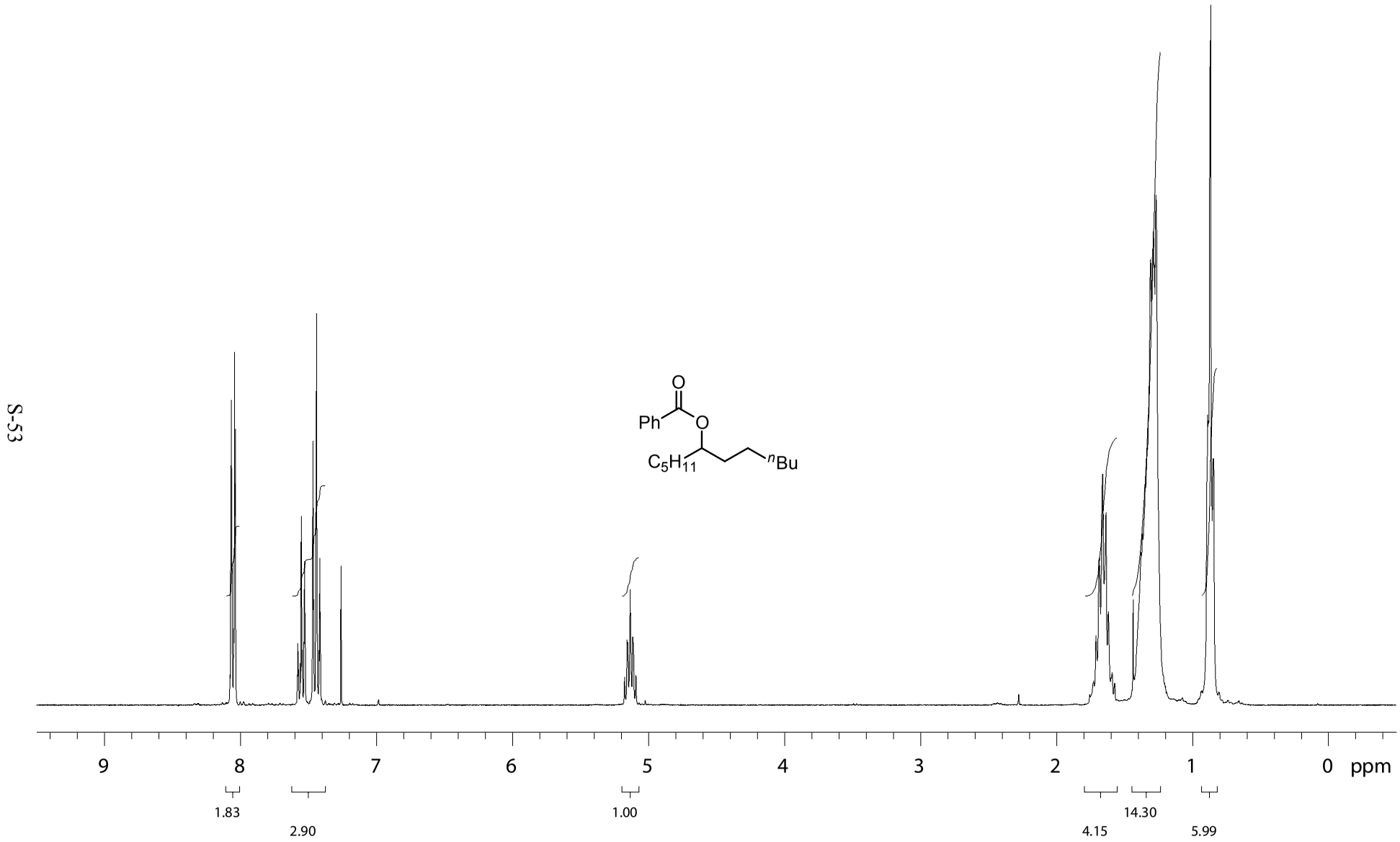
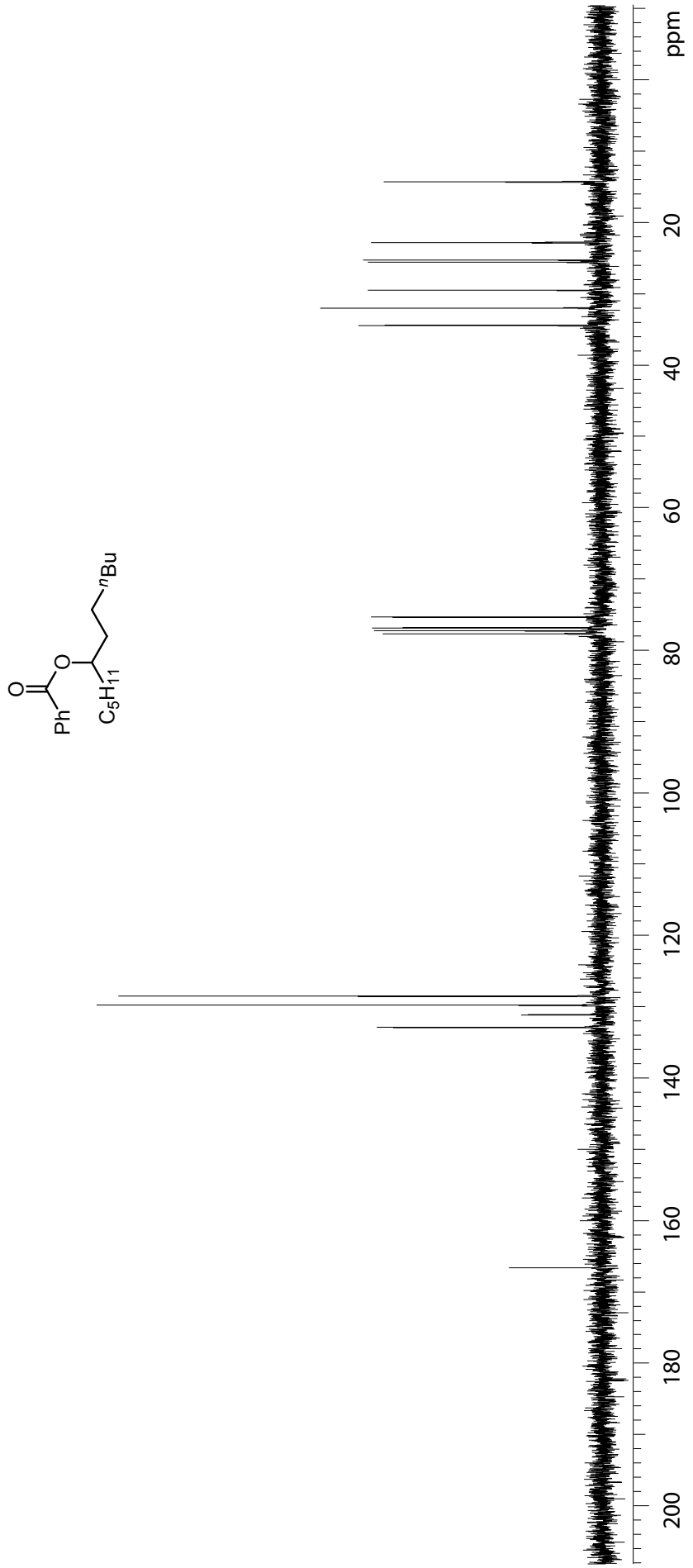
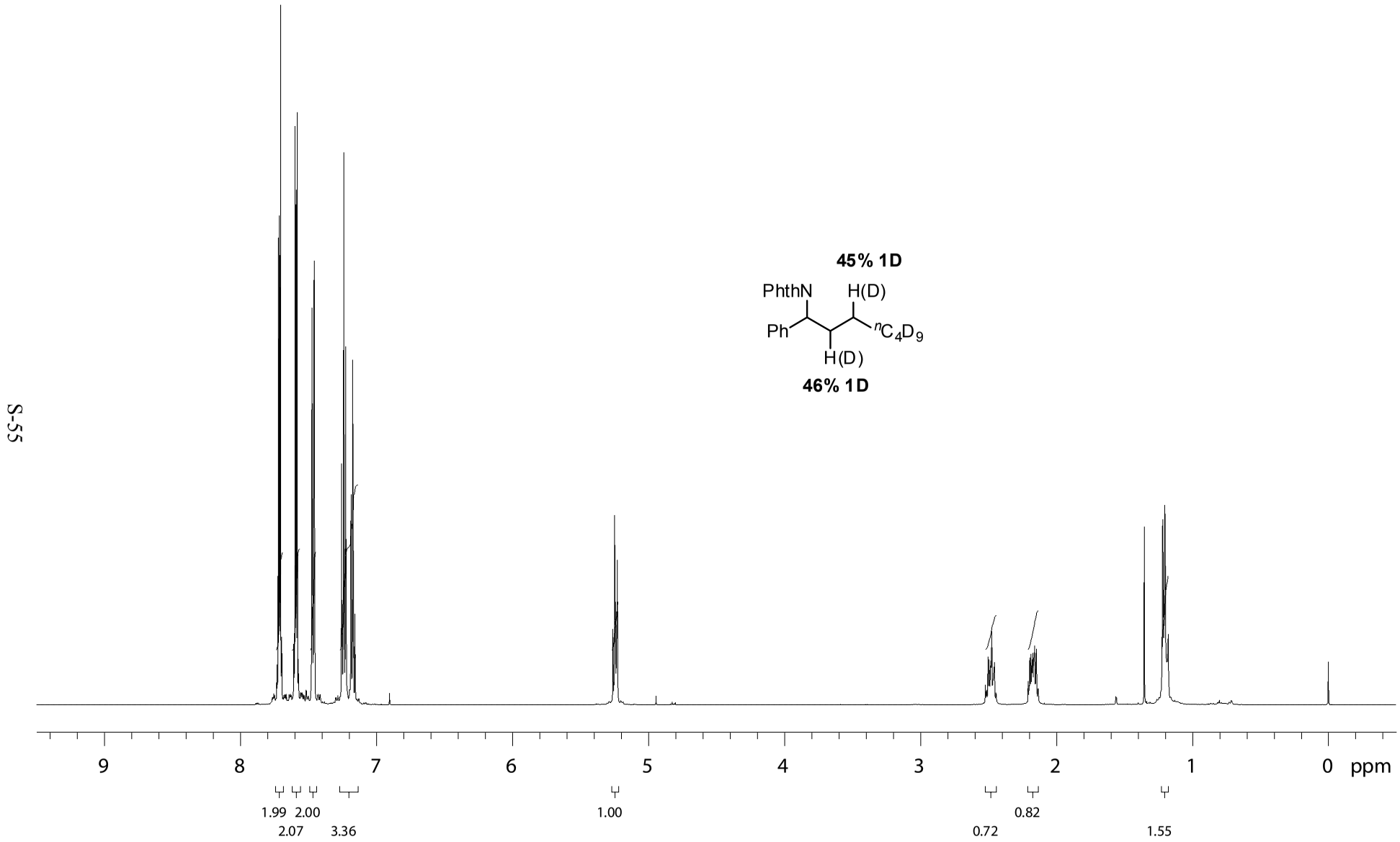
3
4
5
6
7
8
9
ppm
3.00
10.63
2.93
2.00
0.97
1.81
1.78


Ts
N
H
nBu
180
160
140
120
100
80
60
40
20
ppm


O
Ph
O
C5H11
nBu
9
8
7
6
5
4
3
2
1
0
ppm
1.83
2.90
1.00
4.15
14.30
5.99


O
Ph
O
C5H11
nBu
ppm
20
40
60
80
100
120
140
160
180
200


45% 1D
PhthN
H(D)
Ph
nC4D9
H(D)
46% 1D
9
8
7
6
5
4
3
2
1
0
ppm
1.99
2.00
2.07
3.36
1.00
0.72
0.82
1.55