ORGANIC LETTERS

2005
Vol. 7, No. 7
1383−1385

Mimicking Dihydroxy Acetone Phosphate-Utilizing Aldolases through Organocatalysis: A Facile Route to Carbohydrates and Aminosugars†

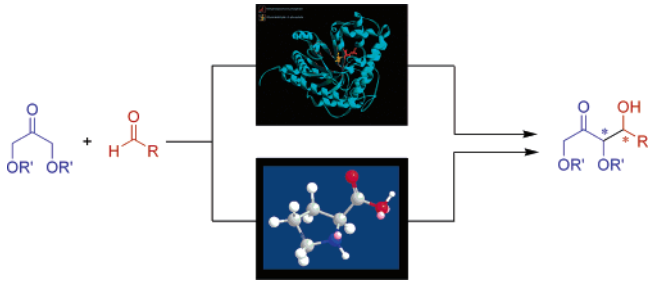
Jeff T. Suri, Dhevalapally B. Ramachary, and Carlos F. Barbas, III*

The Skaggs Institute for Chemical Biology and the Departments of Chemistry and Molecular Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

carlos@scripps.edu

Received February 6, 2005

ABSTRACT



A practical and environmentally friendly organocatalytic strategy designed to mimic the DHAP aldolases has been developed and shown to be effective in the preparation of carbohydrates and aminosugars. (*S*)-Proline and (*S*)-2-pyrrolidine-tetrazole catalyzed the aldol reaction between dihydroxy acetone variants such as 1,3-dioxan-5-one and 2,2-dimethyl-1,3-dioxan-5-one with aldehydes to give the corresponding polyols in good yields with very high ees.

Dihydroxy acetone phosphate-utilizing aldolases such as FDP aldolase have been developed into exceptionally powerful tools for the asymmetric synthesis of carbohydrates and their derivatives.[1] Enzymes of this family catalyze the aldol addition of dihydroxy acetone phosphate (DHAP) with a range of aldehyde acceptors to form a new C−C bond while creating two hydroxy-substituted stereogenic centers. Typically, these reactions take place with complete stereospecificity, and with the appropriate aldolase enzyme, all four stereoisomers can be generated with high levels of stereocontrol.[2] DHAP aldolases have been used to prepare a diverse range of stereochemically complex carbohydrates and azasugars,[3] molecules of great significance in medicinal chemistry and glycobiology.[4]

Although many attempts have been made to effect these same transformations using lithium- and boron-enolate chemistries,[5] highly stereoselective catalytic reactions have

† This report is cordially dedicated to Professor C.-H. Wong for his many contributions in enzymatic carbohydrate synthesis.

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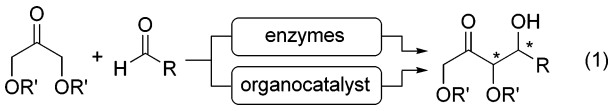
10.1021/ol0502533 CCC: $30.25
Published on Web 03/01/2005

remained elusive.[6] Organocatalysis has emerged as a simple and yet powerful methodology in asymmetric enamine-based chemistries. In analogy to enzymes, organocatalysis allows for the direct coupling of aldehydes and ketones with a variety of electrophiles without the use of preformed enolates. Many reactions have been reported, and in some cases, remarkably high levels of stereoselectivity have been achieved.[7] In studies aimed at recapitulating the chemistry of aldolase enzymes with organocatalysis,[8] we report here the efficacy of this approach in aldol reactions between dihydroxy acetone derivatives and aldehyde acceptors, with the ultimate goal being to mimic the aldolase enzymes and achieve complete stereocontrol (eq 1) without the substrate restrictions endemic to natural enzymes.



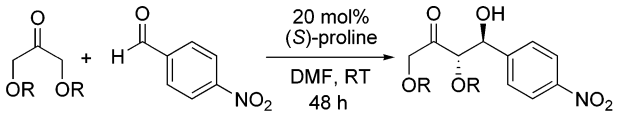
(1)

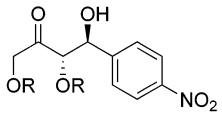
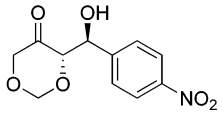
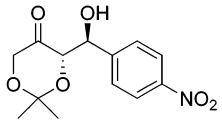
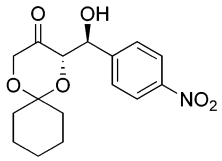
In earlier studies, we reported that under aqueous buffered conditions, (*S*)-proline can catalyze the aldol reaction between unprotected dihydroxy acetone and various aldehydes.[8b] Although moderate ees were obtained (up to 63% ee), the diastereoselectivity was low for almost all cases,[9] hampering the general utility of this reaction in asymmetric synthesis. To overcome this shortcoming we have now investigated the aldol reaction between various protected versions of dihydroxy acetone[10] and nitrobenzaldehyde in the presence of proline or (*S*)-2-pyrrolidine-tetrazole[8f] (Table 1).

In DMF at ambient temperature, the reaction with dihydroxy acetone was very sluggish, providing minimal product after 48 h (entry 1), a reaction hampered by dimerization of this ketone in organic solvent. The benzyl-protected ketone as well as the silyl-protected version (entries 2 and 3) also gave small amounts of product. However, the cyclic derivatives (entries 4−9) were found to be suitable substrates for this aldol reaction, giving polyol products in excellent yield after 48 h.[11] The degree of stereoselectivity was dependent on the protecting group. For example, 1,3-dioxan-5-one underwent aldolization, giving product with high ee and dr (entries 4 and 5, up to 94% ee and 15:1 dr), while 1,5-dioxaspiro[5.5]undecan-3-one gave the corresponding adduct with much less stereoselectivity (entries 9 and 10, up to 67% ee and 5:1 dr). At subambient temperatures, 2,2-dimethyl-1,3-dioxan-5-one gave good ees and diastereoselectivity (entries 6−8). X-ray crystallographic analysis of this adduct revealed the major product to be anti with respect to the newly formed hydroxyl group, and the absolute configuration was 3*S*,4*S* (see Supporting Information). This stereochemical outcome is in accordance with other (*S*)-proline-catalyzed aldol reactions.[7]

The scope of this reaction was then demonstrated using the commercially available 2,2-dimethyl-1,3-dioxan-5-one and various aliphatic, aromatic, and oxy- and amine-substituted acceptors (Table 2). In contrast to the aromatic substrates, greater stereoselectivity was provided with aliphatic substrates. For example, when isovaleraldehyde was

Table 1. Dihydroxy Acetone Derivatives in Direct Aldol Reaction



entry	R	product	%yield[a]	*anti*:*syn*[b]	%ee[b]
1	H		trace	-	-
2	Bn				
3	TIPS				
4	-CH_2-		89	2:1	92
5			91	15:1	94[c]
6	-$C(CH_3)_2$-		89	2:1	60
7			90	6:1	93[c]
8			86	16:1	95[c,d]
9	-$C(C_5H_{10})$-		85	5:1	59
10			62	5:1	67[c]

[a] Isolated yield after column chromatography. [b] Determined by chiral-phase HPLC analysis. [c] Performed at 4 °C. [d] Performed with 20 mol % (*S*)-2-pyrrolidine-tetrazole[8f] as a catalyst.

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(6) Excellent stereoselectivities have been obtained using chiral auxiliaries; see: (a) Enders, D.; Ince, S. J.; Bonnekessel, M.; Runsink, J.; Raabe, G. *Synlett* **2002**, 962−966. (b) Enders, D.; Ince, S. J. *Synthesis* **2002**, 619−624. (c) Enders, D.; Hundertmark, T. *Tetrahedron Lett.* **1999**, *40*, 4169−4172.

(7) For reviews see: (a) Dalko, P. I.; Moisan, L. *Angew Chem. Int. Ed.* **2004**, *43*, 5138−5175. (b) Dalko, P. I.; Moisan, L. *Angew Chem. Int. Ed.* **2001**, 40, 3726−3748. (c) *Acc. Chem. Res.* **2004**, *37*, special issue on organocatalysis.

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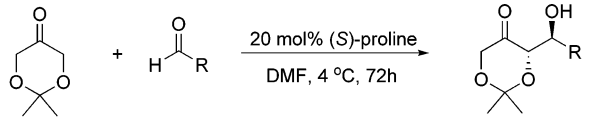
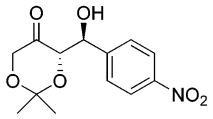
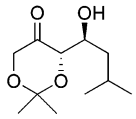
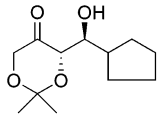
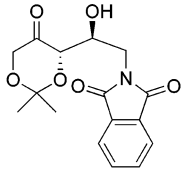
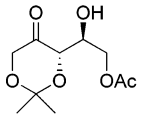
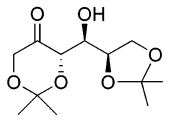
(9) Two substrates gave drs of >20:1 but without any ee.

(10) Following our initial submission, Enders et al. published an extensive review related to the use of 2,2-dimethyl 2,2-dimethyl-1,3-dioxan-5-one in synthetic chemistry and a complementary study of its use under proline catalysis. See: (a) Enders, D.; Voith, M.; Lenzen, A. *Angew. Chem., Int. Ed.* **2005**, *44*, ASAP. (b) Enders, D.; Grondal, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1210−1212.

(11) Significantly, 4-thianone has been used as a masked cyclic ketone surrogate of the unreactive 3-pentanone for proline catalysis. See: (a) Ward, D. E.; Jheengut, V. *Tetrahedron Lett.* **2004**, *45*, 8347−8350. (b) Nyberg, A. I.; Usano, A.; Pihko, P. M. *Synlett* **2004**, *11*, 1891−1896.

Table 2. Stereoselective Direct Coupling of 2,2-Dimethyl-1,3-dioxan-5-one with Aldehyde Acceptors



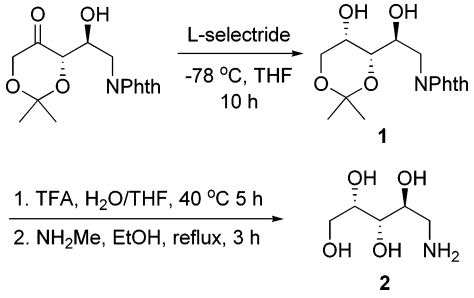
entry	R	product	%yield[a]	*anti*:*syn*[b]	%ee[c]
1	*p*-$NO_2C_6H_5$		89	6:1	93[d]
2	$CH_2{}^iPr$		75	10:1	98
3	C_5H_9		67	99:1	97
4	CH_2Phth		75	55:1	98
5	CH_2OAc		60	>15:1	98
6	-CH(OCMe$_2$O)CH$_2$-		40	>15:1	94

[a] Isolated yield. [b] Determined by HPLC and NMR analysis. [c] Determined by chiral-phase HPLC analysis. [d] Reaction time = 48 h.

the donor, the corresponding adduct was obtained in 98% ee and with 10:1 dr (entry 2). The product of the reaction with cyclopentane carboxaldehyde (entry 3) was obtained in 97% ee with no other diastereomer observed. When oxy- and amino-substituted aldehydes were reacted with proline and 2,2-dimethyl-1,3-dioxan-5-one (entries 4−6), the reactions proceeded with high levels of stereocontrol (>94% ee, >15:1 dr), giving the corresponding polyols and aminols (entries 4−7). Significantly, these aldol products are protected azasugars (entry 4) and carbohydrates (L-ribulose and D-tagatose, entries 5 and 6), compounds that are otherwise most efficiently prepared via enzymatic reactions[1b] or from the chiral pool.[12] Unlike natural aldolase enzymes, we found that reactions with imines and alkenes, Mannich and Michael-type reactions, were also facile, suggesting the synthetic scope of this methodology will reach beyond that observed with enzymes with respect to electrophile range.[13]

Reactions were readily performed on a gram scale, and deprotection and further elaboration of the aldol products allowed for the rapid construction of carbohydrate architectures. For example, treatment of the aldol adducts with Dowex resin in H_2O/THF gave the corresponding dihydroxy products in quantitative yield (see Supporting Information). The phthalimido-protected aldol product was reduced with (L)-Selectride to give the stereochemically rich polyol **1** (Scheme 1).[14] Deprotection with TFA and methylamine-induced cleavage of the phthalimide group afforded 1-amino-1-deoxy-D-lyxitol **2**,[15] a carbohydrate construct traditionally prepared from the chiral pool of naturally occurring sugars.

Scheme 1. Synthesis of 1-Amino-1-deoxy-D-lyxitol



In summary, we have demonstrated the effectiveness of organocatalysis in the preparation of carbohydrates and aminosugars in a strategy designed to mimic the DHAP aldolases. This efficient strategy promises simplified routes to complex carbohydrates and their derivatives.

Acknowledgment. This study was supported in part by the NIH (CA27489) and the Skaggs Institute for Chemical Biology. We thank Dr. Raj K. Chadha for X-ray structural analysis and Rajeswari Thayumanavan for technical assistance.

Supporting Information Available: Experimental procedures, characterization data, and X-ray files. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Ekeberg, D.; Morgenlie, S.; Stenstrom, Y. *Carbohydr. Res.* **2002**, *337*, 779−786.
(13) Results concerning Mannich-type and Michael reactions will be reported in due course.
(14) Enders, D.; Muller-Huwen, A. *Eur. J. Org. Chem.* **2004**, 1732−1739.
(15) Blanc-Muesser, M.; Defaye, J.; Horton, D. *Carbohydr. Res.* **1979**, *68*, 175−187.

Mimicking Dihydroxy Acetone Phosphate Utilizing Aldolases Through Organocatalysis: A Facile Route to Carbohydrates and Aminosugars.

Jeff T. Suri, Dhevalapally B. Ramachary, and Carlos F. Barbas III*

Contribution from The Skaggs Institute for Chemical Biology and the Departments of Chemistry and Molecular Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California

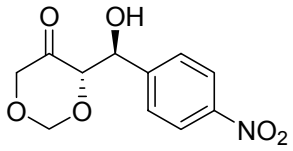
Supporting Information

General. Chemicals and solvents were either purchased *puriss p.A.* from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating; or with a solution of ninhydrin in EtOH followed by heating. Flash chromatography was performed using silica gel Merck 60 (particle size 0.040-0.063 mm), ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-500 MHz instrument and were referenced internally to the residual solvent peak. HPLC was carried out using a Hitachi organizer consisting of a D-2500 Chromato-Integrator, a L-4000 UV-Detector, and a L-6200A Intelligent Pump. Optical rotations were recorded on a Perkin Elemer 241 Polarimeter (λ=589 nm, 1 dm cell). High-resolution mass spectra were recorded on an IonSpec TOF mass spectrometer. 1,3-Bis(triisopropylsilyloxy)propan-2-one (Table 1, entry 3) and 1,5-Dioxaspiro[5.5]undecan-3-one (Table 1, entries 8,9) were prepared according to the literature procedure.[1] 1,3-Dioxan-5-one (Table 1, entries 4,5) was prepared by PCC oxidation of 1,3-dioxan-5-ol in CH_2Cl_2.

General experimental procedure for the aldol reaction (Table 1): To a glass vial charged with DMF (200 μL) was added ketone (0.5 mmols), aldehyde (0.1 mmols) and *S*-proline (0.02 mmols, 2.3 mg) the reaction was stirred at ambient temperature or at 4 ^{o}C for the appropriate time until the reaction was complete by TLC. Then, a half saturated NH_4Cl solution and ethyl acetate were added with vigorous stirring, the layers were separated and the organic phase was washed with brine. The organic phase was dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, mixtures of hexanes/ethyl acetate) to afford the desired Aldol product.

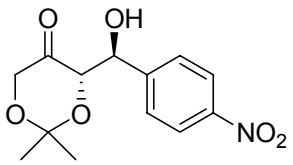
General procedure for derivatization of aliphatic substrates for HPLC analysis. The aldol adduct (1 equiv) in CH_2Cl_2 (1 mL/0.5 mmols) was treated with 3,5-dinitrobenzoyl chloride (1.1 equiv) and DMAP (1.1 equiv) and stirred for 1 h. The solution was filtered through a small plug of silica gel and analyzed by HPLC.

(S)-4-((S)-Hydroxy(4-nitrophenyl)methyl)-1,3-dioxan-5-one (Table 1, entry 4):



^{1}H NMR ($CDCl_3$, 500 MHz), major product: δ 8.20 (d, *J* = 8.7 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 5.07 (d, *J* = 5.9 Hz, 1H), 4.90 (d, *J* = 6, Hz 1H), 4.30 (d, *J* = 2.5 Hz, 1H), 3.76 (bs, 1H), 2.94 (s, 1H), 2.87 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 205.75, 162.61, 145.8, 128.1, 123.26, 91.5, 93.4, 72.99, 72.44. HRMS for $C_{11}H_{10}NO_6$ $[M-H]^-$: calcd 252.0514, obsd 252.0511; HPLC (Daicel Chiralcel OJ-H, hexane/isopropanol = 80 : 20, flow rate 1.0 mL/min, λ = 254 nm): t_R = 31.17 min (*anti*, major), t_R = 33.92 min (*anti*, minor), t_R = 36.11 min (*syn*). $[\alpha]_D$ = – 18.42 (c = 0.73, $CHCl_3$).

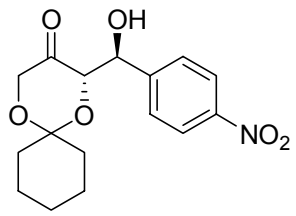
(S)-4-((S)-Hydroxy(4-nitrophenyl)methyl)-2,2-dimethyl-1,3-dioxan-5-one (Table 1, entry 6):



Column chromotography provided a separable diastereomeric mixture. ^{1}H NMR ($CDCl_3$, 500 MHz), major product: δ 8.20 (d, *J* = 8.8 Hz, 2H), 7.59 (d, *J* = 8.6 Hz, 2H), 4.99 (d, *J* = 7.9 Hz, 1H), 4.278 (dd, J_1 = 1.4, J_2 = 17.7 Hz, 1H), 4.08 (d, *J* = 17.7 Hz, 1H), 3.81 (bs, 1H), 1.381 (s, 3H), 1.209 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 210.557, 147.655,

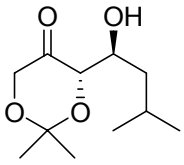
146.432, 127.858, 123.136, 101.386, 75.770, 71.719, 66.554, 23.441, 23.250. HRMS for $C_{13}H_{15}NO_6Na$ (MNa^+): calcd 304.0792, obsd 304.0788; HPLC (Daicel Chirapak OD-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL/min, λ = 254 nm): t_R = 9.08 min (*anti*, major), t_R = 10.34 min (*anti*, minor), t_R = 13.98 min (*syn*). $[\alpha]_D$ = – 125.1 (c = 0.666, $CHCl_3$).

(S)-4-((S)-hydroxy(4-nitrophenyl)methyl)1,5-Dioxaspiro[5.5]undecan-3-one (Table 1, entry 9): Column chromotography provided a separable diastereomeric mixture.

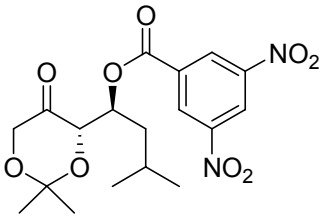


^{1}H NMR ($CDCl_3$, 500 MHz), major product: δ 8.214 (d, *J* = 8.4, 2H), 7.60 (d, *J* = 8.5, 2H), 5.00 (d, J = 8.2, 1H), 4.40-4.41 (m, 2H), 4.09 (d, J = 17.7 Hz, 1H), 1.81-1.168 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 211.176, 147.450, 146.645, 127.913, 123.112, 101.477, 77.477, 75.496, 71.911, 66.320, 32.939, 31.894, 24.874, 22.579, 22.194, δ HRMS for $C_{16}H_{19}NO_6$ (MH^+): calcd 322.1285, obsd 322.1288; HPLC (Daicel Chirapak OD-H, hexane/isopropanol = 95:5, flow rate 0.5 mL/min, λ = 254 nm): t_R = 38.38 min (*anti*, major), t_R = 41.42 min (*anti*, minor),), t_R = 48.67 min (*syn*, minor),), t_R = 68.64 min (*anti*, minor) $[\alpha]_D$ = – 68.16 (c = 0.6 $CHCl_3$).

(S)-4-((S)-1-hydroxy-3-methylbutyl)-2,2-dimethyl-1,3-dioxan-5-one (Table 2, entry 2):

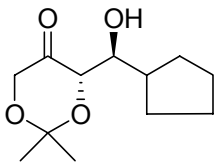


^{1}H NMR ($CDCl_3$, 500 MHz) : δ 4.24 (dd, J_1 = 1.4 Hz, J_2 = 17.3 Hz, 1H), 4.05 (dd, J_1 = 1.3 Hz, J_2= 6.5 Hz, 1H), 4.00 (d, *J* = 17.3, 1H), 3.972-3.934 (m, 1H), 2.87 (bs, 1H), 1.897-1.842 (m, 1H), 1.456 (s, 3H), 1.428 (s, 3H), 0.934 (d, *J* = 6.7 Hz, 3H), 0.900 (d, *J* = 6.9, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 210.94, 100.9, 76.507, 68.84, 66.74, 41.19, 24.02, 23.84, 23.749, 23.425, 21.428. HRMS for $C_{11}H_{20}O_4Na$ (MNa^+): calcd 239.1254, obsd 239.1256. $[\alpha]_D$ = – 211.5 (c = 0.667 $CHCl_3$).



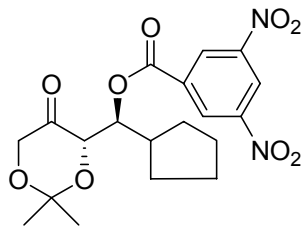
HPLC (Daicel Chirapak OJ-H, hexane/*i*-PrOH = 95:5, flow rate 1.0 mL/min, λ = 254 nm): t_R = 31.92 min (major, *anti*), t_R = 35.73 min (minor, anti) t_R = 49.07 min (*syn*).

(S)-4-((S)-cyclopentyl(hydroxy)methyl)-2,2-dimethyl-1,3-dioxan-5-one (Table 2, entry 3):

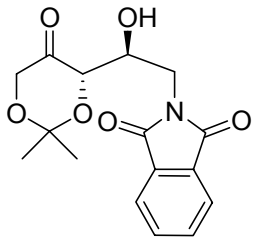


^{1}H NMR ($CDCl_3$, 500 MHz) : δ 4.26 (d, *J* = 16.4 Hz, 1H), 4.12 (d, *J* = 6.8 Hz, 1H), 4.01 (d, *J* = 17.3 Hz, 1H), .83, (m, 1H), 2.96 (d, *J* = 2.6 Hz), 2.27-2.21 (m, 1H), 1.69-1.49 (m, 8H), 1.47 (s, 3H), 1.44 (s, 3H).

^{1}H NMR ($CDCl_3$, 500 MHz) : δ 9.31 (t, *J* = 2.1 Hz, 1H), 9.20 (d, *J* = 2.1, 2H), 5.65 (dd, J_1 =4.8 Hz, J_2 = 7.4 Hz, 1H), 4.597 (dd, J_1 = 1.0 Hz, J_2 = 4.7 Hz), 4.37 (dd, J_1 = 1.3 Hz, J_2 = 17.2 Hz, 1H), 4.11 (d, *J* = 17.2 Hz, 1H), 2.72-2.64 (m, 1H), 1.88-1.62 (m, 8H), 1.543 (d, *J* = 19.7 Hz), 1.55 (s, 3H), 1.52 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.4, 162.05, 148.70, 133.99, 129.44, 122.4, 101.0, 77.6, 74.87, 66.988, 40.22, 28.93, 28.48, 25.36, 24.90, 24.15, 23.34. HRMS for $C_{19}H_{22}N_2O_9Na$ (MNa^+): calcd 445.1217, obsd 445.1217. HPLC (Daicel Chirapak AD, hexane/*i*-PrOH = 95:5, flow rate 1.0 mL/min, λ = 254 nm): t_R = 12.90 min (major), t_R = 15.12 min (minor). $[\alpha]_D$ = – 88.2 (c = 0.833 $CHCl_3$).

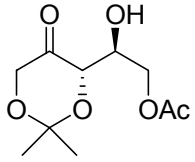


2-((S)-2-((S)-2,2-dimethyl-5-oxo-1,3-dioxan-4-yl)-2-hydroxyethyl)isoindoline-1,3-dione



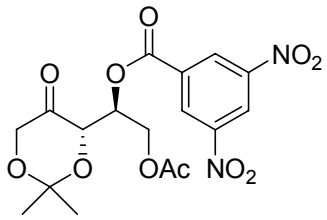
(Table 2, entry 4): ^{1}H NMR ($CDCl_3$, 500 MHz) : δ 7.86 (d, *J* = 3.0 Hz, 1H), 7.85 (d, *J* = 3.0 Hz, 1H), 7.72 (d, *J* = 3.0 Hz, 1H), 7.71 (d, *J* = 3.0 Hz, 1H), 4.32 (m, 2H), 4.29 (d, *J* = 18 Hz, 1H), 4.02 (d, *J* = 17.5 Hz, 1H), 3.97 – 3.93 (m, 2H), 3.24 (d, *J* = 4.5 Hz, 1H, O-*H*), 1.47 (s, CH_3, 3H), 1.34 (s, CH_3, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 209.5, 168.6, 134.0, 132.0, 123.3, 101.2, 75.6, 68.2, 66.6, 39.9, 23.5, 23.5. HRMS for $C_{16}H_{17}NO_6Na$ (MNa^+): calcd 342.0948, obsd 342.0943; HPLC (Daicel Chirapak AD, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm): t_R = 23.07min (minor, *anti*), t_R = 38.37 min (major, *anti*). $[\alpha]_D$ = – 114.3 (c = 0.315 $CHCl_3$).

(S)-2-((S)-2,2-dimethyl-5-oxo-1,3-dioxan-4-yl)-2-hydroxyethyl acetate (Table 2, entry 5):



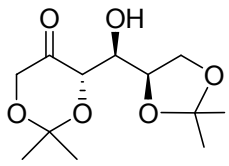
^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.34 – 4.18 (m, 4H), 4.13 (m, 1H), 4.04 (d, *J* = 17.5 Hz, 1H), 3.20 (d, *J* = 3.5 Hz, 1H, O-*H*), 2.08 (s, COCH_3, 3H), 1.44 (s, CH_3, 3H), 1.41 (s, CH_3, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 210.6,

170.9,101.3, 72.9, 68.8, 66.5, 64.2, 23.6, 23.4, 20.8. HRMS for $C_{10}H_{16}O_6Na$ (MNa^+): calcd 255.0839, obsd 255.0832; $[\alpha]_D = -82.6$ (c = 0.615 $CHCl_3$).

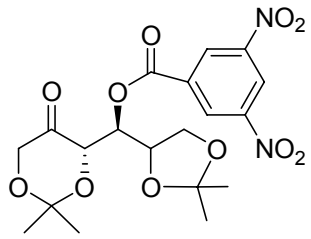


^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.22 (br t, *J* = 2.0 Hz, 1H), 9.11 (s, 1H), 9.10 (s, 1H), 5.71 (m, 1H), 4.67 (d, *J* = 5.5 Hz, 1H), 4.45 (m, 2H), 4.31 (d, *J* = 17.5 Hz, 1H), 4.10 (m, 1H), 2.05 (s, COC*H*$_3$, 3H), 1.49 (s, C*H*$_3$, 3H), 1.46 (s, C*H*$_3$, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 205.7, 170.4, 161.6, 148.6, 133.2, 129.5, 122.6, 101.6, 72.2, 71.6, 66.7, 61.5, 23.5, 23.4. HRMS for $C_{17}H_{18}N_2O_{11}$ (MH^+): calcd 427.0983, obsd 427.0995;HPLC (Daicel Chirapak AD, hexane/*i*-PrOH = 95:5, flow rate 1.0 mL/min, λ = 254 nm): t_R = 45.18 min (*anti,* major), t_R = 73.04 min (*anti*, minor), t_R = 54.03 min (*syn*). $[\alpha]_D = -58.5$ (c = 0.54 $CHCl_3$).

(S)-4-((S)-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)-2,2-dimethyl-1,3-dioxan-5-one (Table 2, entry 6): ^{1}H NMR and ^{13}C NMR were in accordance with lit. values.[2] ^{1}H NMR



($CDCl_3$, 500 MHz): δ 4.28-4.24 (m, 3H), 4.03 (d, *J* = 17.5 Hz, 1H), 3.98 (dd, J_1 = 6.6 Hz, J_2= 8.2 Hz, 1H), 3.86-3.81 (m, 2H), 3.19 (d, 3.5 Hz, 1H), 1.45 (s, 3H), 1.41 (s, 3H), 1.40 (s, 3H), 1.34 (s, 3H);); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 210.4, 109.2, 101.3, 75.2, 73.4, 70.1, 66.7, 65.6, 26.3, 25.6, 23.6, 23.5. HRMS for $C_{12}H_{20}O_6$ (MH^+): calcd 261.1333, obsd 261.1328; $[\alpha]_D = -157.9$ (c = 1.61 $CHCl_3$), lit. -167.2 (c = 1.1 $CHCl_3$). Mp = 102-104 ^{o}C, lit. 103-105^{o}C.



^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.23 (br d, *J* = 8.0 Hz, 1H), 9.16 (s, 1H), 9.13 (s, 1H), 5.51 (br dd, *J* = 6.5, 3.5 Hz, 1H), 4.67 (m, 1H), 4.57 (m, 1H), 4.31 (AB q, *J* = 14.0 Hz, 1H), 4.14 – 3.99 (m, 2H), 3.81 (dd, *J* = 7.5, 5.0 Hz, 1H), 1.53 (s, C*H*$_3$, 3H), 1.47 (s, C*H*$_3$, 3H), 1.44 (s, C*H*$_3$, 3H), 1.34 (s, C*H*$_3$, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 207.5, 162.8, 149.5, 134.5, 130.6, 130.4, 110.6, 102.5, 74.6, 73.4, 72.5, 67.7, 66.3, 27.1, 26.0, 25.8, 24.4. HRMS: $C_{19}H_{22}N_2O_{11}Na$ (MNa^+): calcd 477.1116, obsd 477.1110; HPLC (Daicel Chirapak AD, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm): t_R = 10.6 min (*anti,* major), t_R = 19.80 min (*anti*, minor).

General procedure for deprotection with resin. 2-((S)-2-((S)-2,2-dimethyl-5-oxo-1,3-dioxan-4-yl)-2-hydroxyethyl)isoindoline-1,3-dione (0.05 mmols, 18 mg) dissolved in H_2O (200 μL) and THF (300 μL) was stirred with Dowex 50WX2-100 resin (prewashed with H_2O) for 12 h at RT. The solution was filtered and the filtrate concentrated to give 2-((2S,3S)-2,3,5-trihydroxy-4-oxopentyl)isoindoline-1,3-dione (Yield: 100 %); no purification was necessary. ^{1}H NMR (dDMSO, 500 MHz): δ 7.88-7.82 (m, 4H), 5.70 (d, J = 5.3 Hz, 1H), 5.31 (d, J = 5.4 Hz, 1H), 4.90 (t, J = 5.9 Hz, 1H) 4.32 (dq, J_1 = 6.0 Hz, J_2 = 19.4 Hz, 2H), 4.03-3.96 (m, 2H), 3.73 (dd, J_1 = 9.2 Hz, J_2 = 13.8 Hz, 1H), 3.56 (dd, J_1 = 3.13 Hz, J_2 = 13.1 Hz, 1H); ^{13}C NMR (dDMSO, 125 MHz) δ 211.0, 167.9, 134.1, 131.7, 122.8, 76.3, 69.0, 66.4, 41.0. HRMS for $C_{13}H_{13}NNaO_6$ (MNa^+): calcd 302.0635, obsd 302.0634.

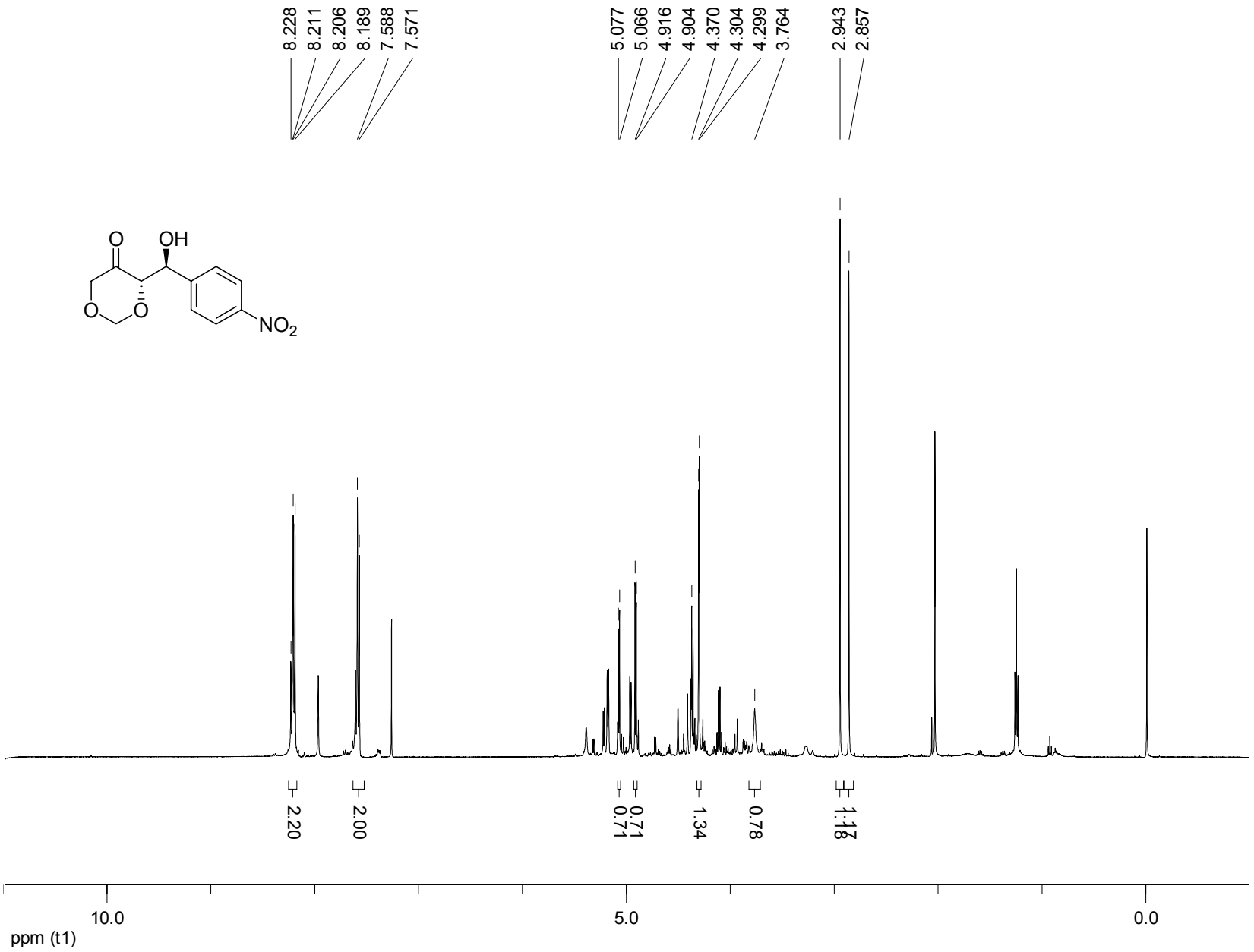
2-((S)-2-hydroxy-2-((4S,5S)-5-hydroxy-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)isoindoline-1,3-dione (1): A solution of 2-((S)-2-((S)-2,2-dimethyl-5-oxo-1,3-dioxan-4-yl)-2-hydroxyethyl)isoindoline-1,3-dione (58 mg, 0.18 mmols) in THF (1.2 mL) was cooled to -78 ^{o}C under argon and L-selectride® (0.19 mL of 1.0 M in THF) was added dropwise. The solution was stirred and allowed to slowly reach room temperature over 5 h at which time it was quenched with 0.5 mL of an aqueous NH_4Cl (sat.) solution. H_2O_2 (100 μL of 30 % aq. solution) was added followed by NaOH (0.1 N, 100 μ mL) and the solution stirred for 30 min. The aqueous layer was extracted with EtOAc and dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (gradient elution of 40% EtOAc/hexane to 100 % EtOAc to give a white solid (Yield: 50 %). ^{1}H NMR (MeOD, 500 MHz): δ 7.86-7.78 (m, 4H), 4.15-4.04 (m, 2H), 3.89 (dd, J_1 = 5.7 Hz, J_2 = 13.9 Hz, 2H), 3.80-3.73 (m, 3H) 3.62 (d, J = 1.5 Hz, 1H), 1.41 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (MeOD, 125 MHz) δ 170.1, 135.3, 133.6, 124.0, 99.8, 75.8, 67.2, 67.0, 63.5, 42.8, 29.4, 18.7. HRMS for $C_{16}H_{19}NNaO_6$ (MNa^+): calcd 344.1105, obsd 344.1101.

1-Amino-1-Deoxy-D-Lyxitol (2): TFA (23 μL) was added to a solution of **1** (0.063 mmols, 20.3 mg) in THF/H_2O (3:1, 1 mL) and the mixture was heated at 40 ^{o}C for 6 h. The reaction was quenched with saturated $NaHCO_3$ (1 mL) and brine (1 mL) and extracted with THF. The organic layer was dried over NaCl and $MgSO_4$

and concentrated *in vacuo* to give the phthalimide protected intermediate as a crude mixture. The mixture was dissolved in EtOH (1 mL), treated with methylamine (1.5 mL, 30 % in EtOH), and heated to reflux for 3 h.[3] The solvent was removed *in vacuo* and the residue purified by column chromatography (dry loading, gradient elution with 10 % MeOH/CH_2Cl_2 to 50 % MeOH/CH_2Cl_2; then with 100 % AcOH) to give a colorless solid (60 % over two steps). The product was isolated as the acetate salt and its spectroscopic data were identical to those in the literature for the HCl salt.[4] ^{1}H NMR (D_2O with TSP, 500 MHz): δ 3.94 (m, 2H), 3.67 (d, J = 6.4 Hz, 2H), 3.58 (dd, J_1 = 1.7 Hz, J_2 = 8 Hz, 1H), 3.39 (dd, J_1 = 3.2 Hz, J_2 = 13.2 Hz, 1H), 3.05 (dd, J_1 = 9.2 Hz, J_2 = 13.2 Hz), 2.90 (d, J = 3.2 Hz, 1H, *OH*); ^{13}C NMR (D_2O with TSP, 125 MHz) δ 74.76, 70.06, 65.66, 45.20. HRMS for $C_{17}H_{23}NO_4Na$ (M^+): calcd 152.0917, obsd 152.0923.

References:

1. Kim, K. S.; Hong, S. D. *Tetrahedron Lett.* **2000**, *41*, 5909-5913.
2. Majewski, M.; Nowak, P. *J. Org. Chem.* **2000**, *65*, 5152-5160.
3. Motawia, M. S.; Meldal, M.; Sofan, M.; Stein, P.; Pedersen, E. B.; Nielsen, C. *Synthesis* **1995**, 265-70.
4. Blanc-Muesser, M.; Defaye, J.; Horton, D. *Carbohydr. Res.* **1979**, *68*, 175-187.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NO2
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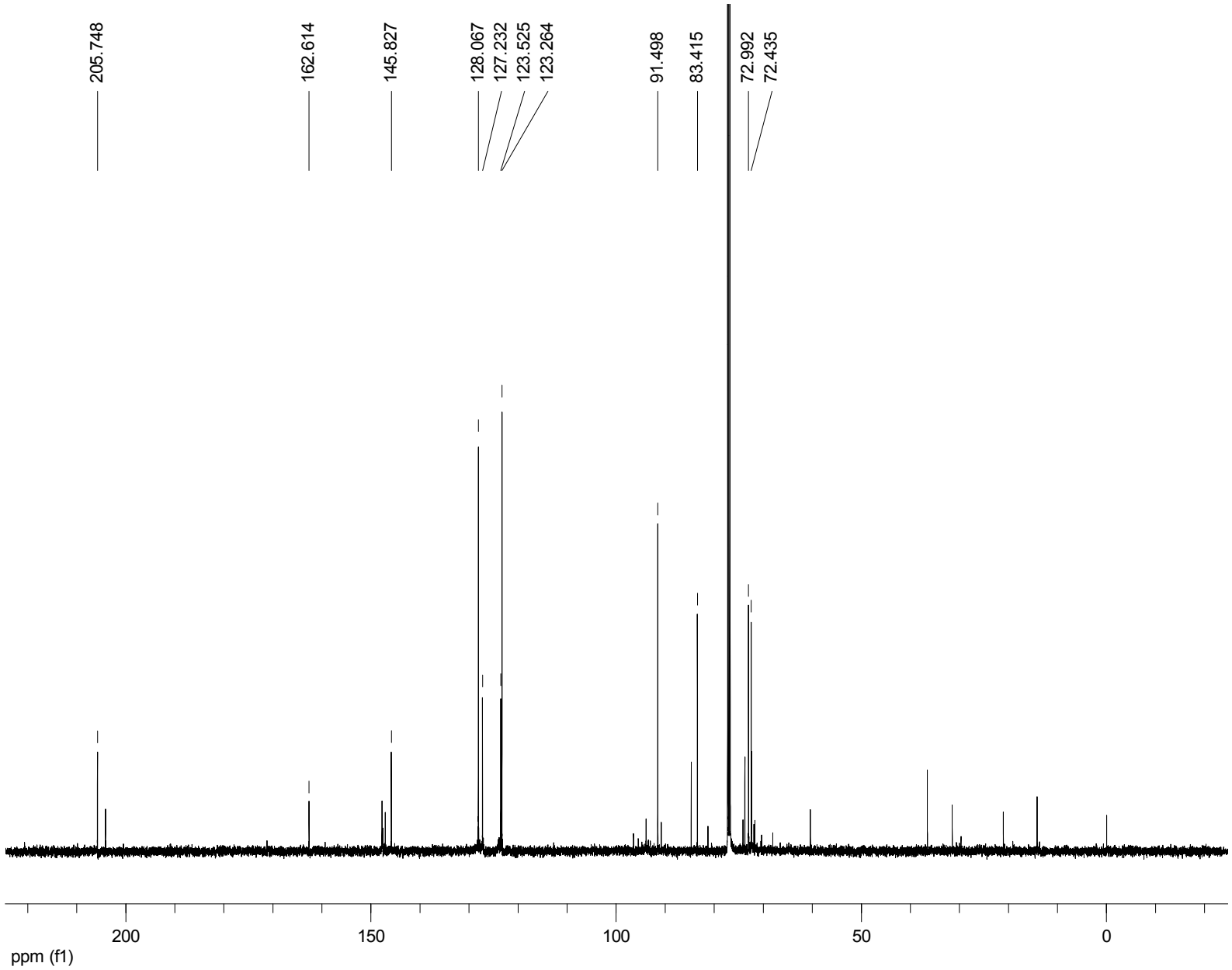
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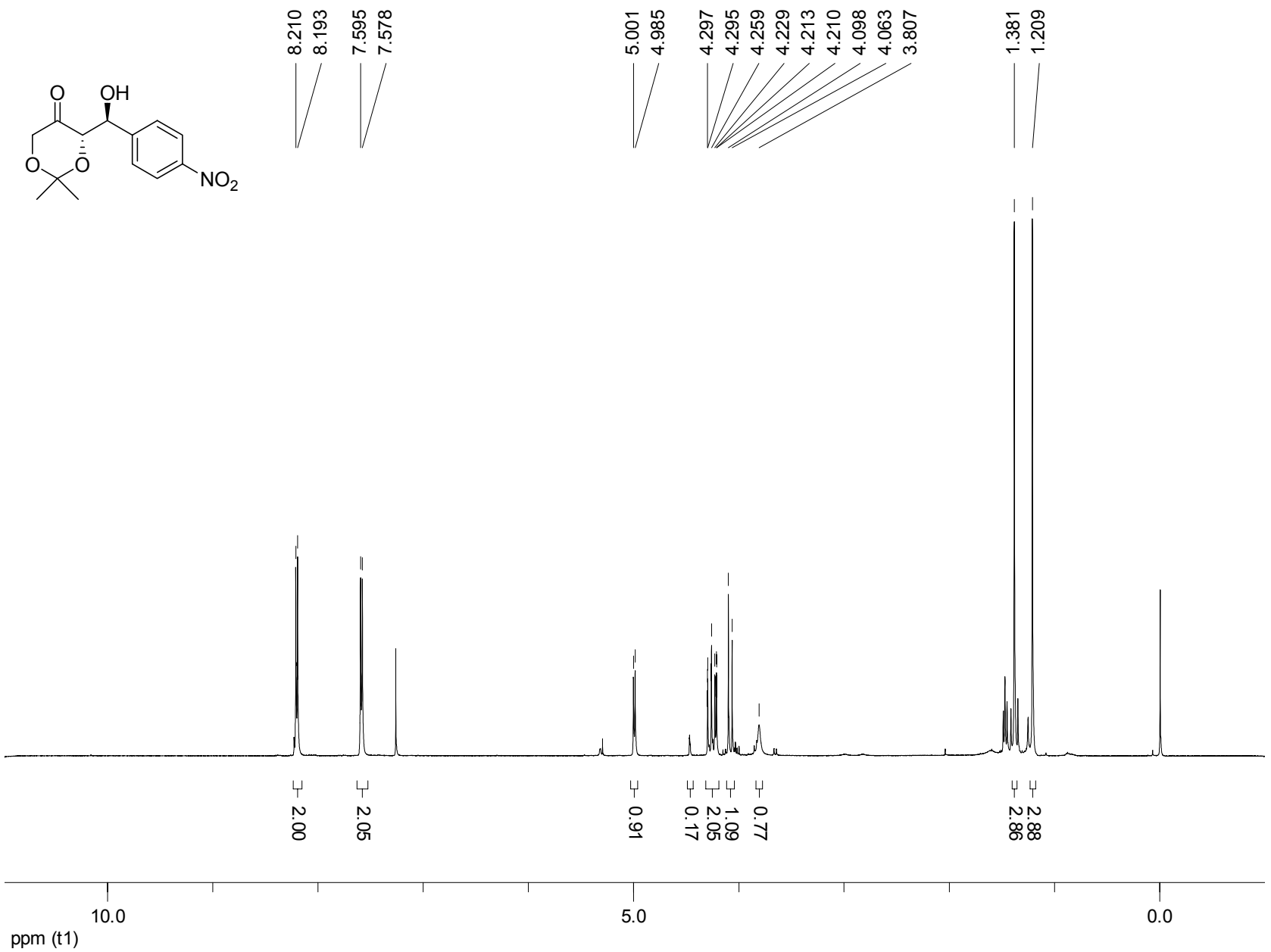
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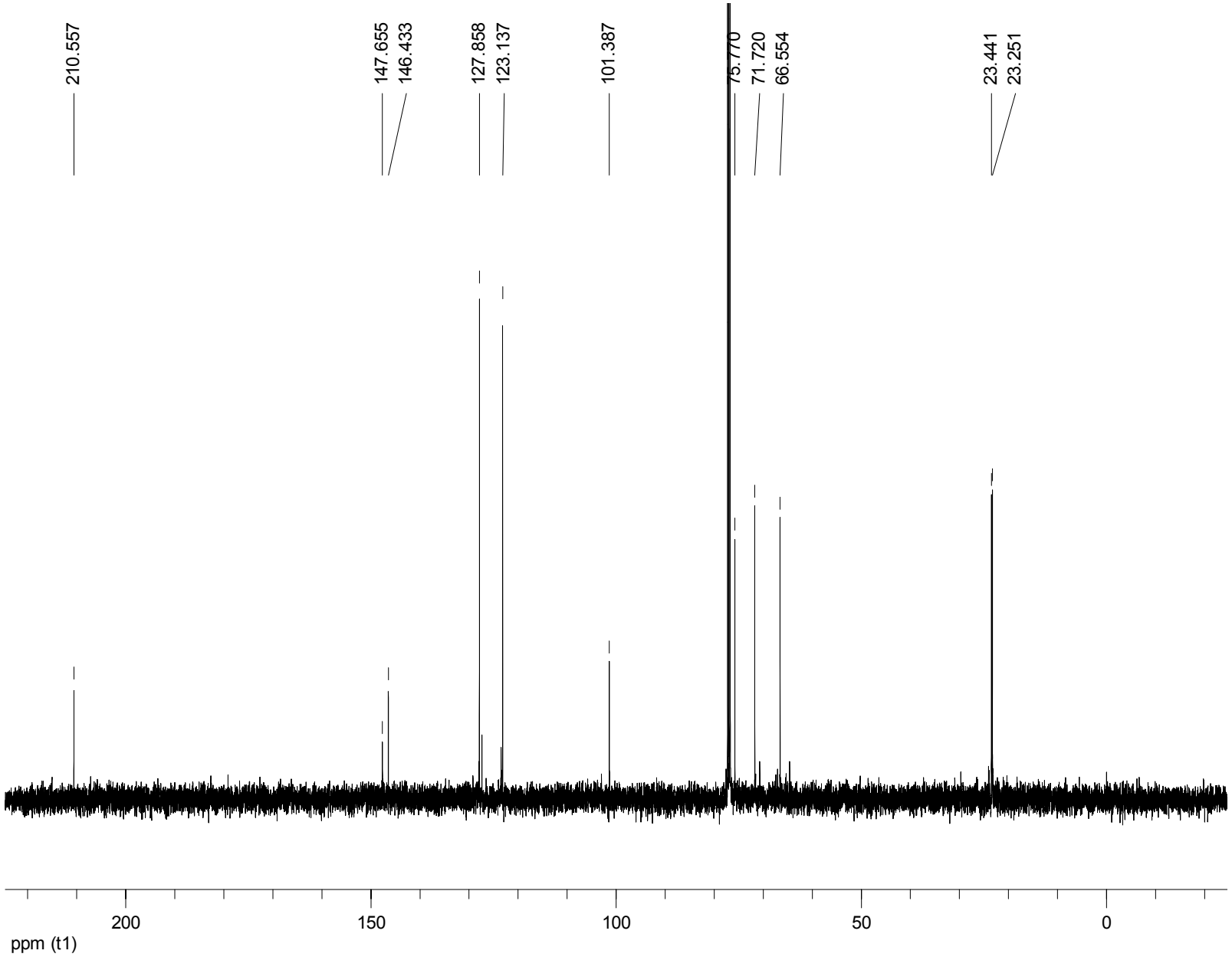
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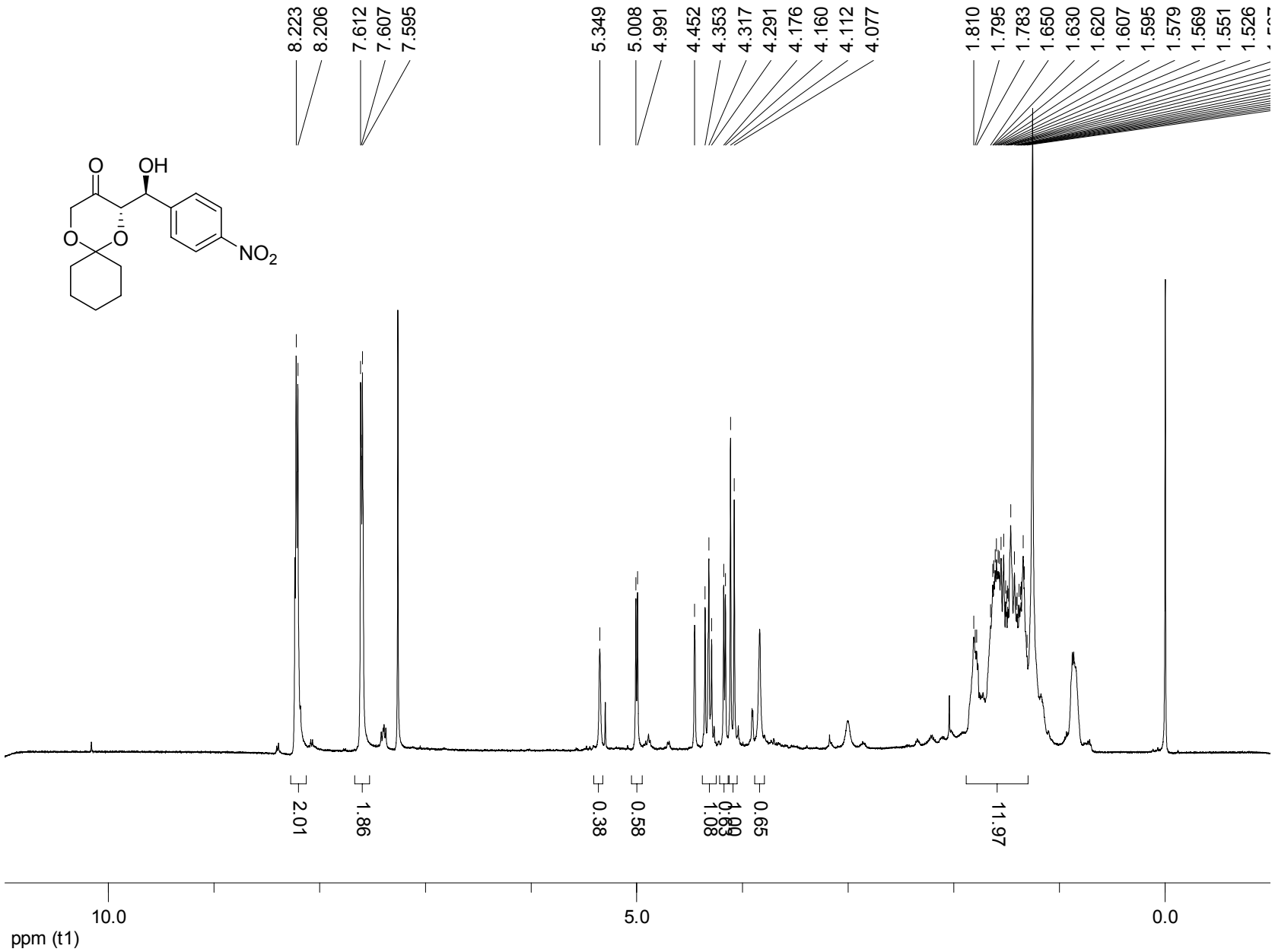
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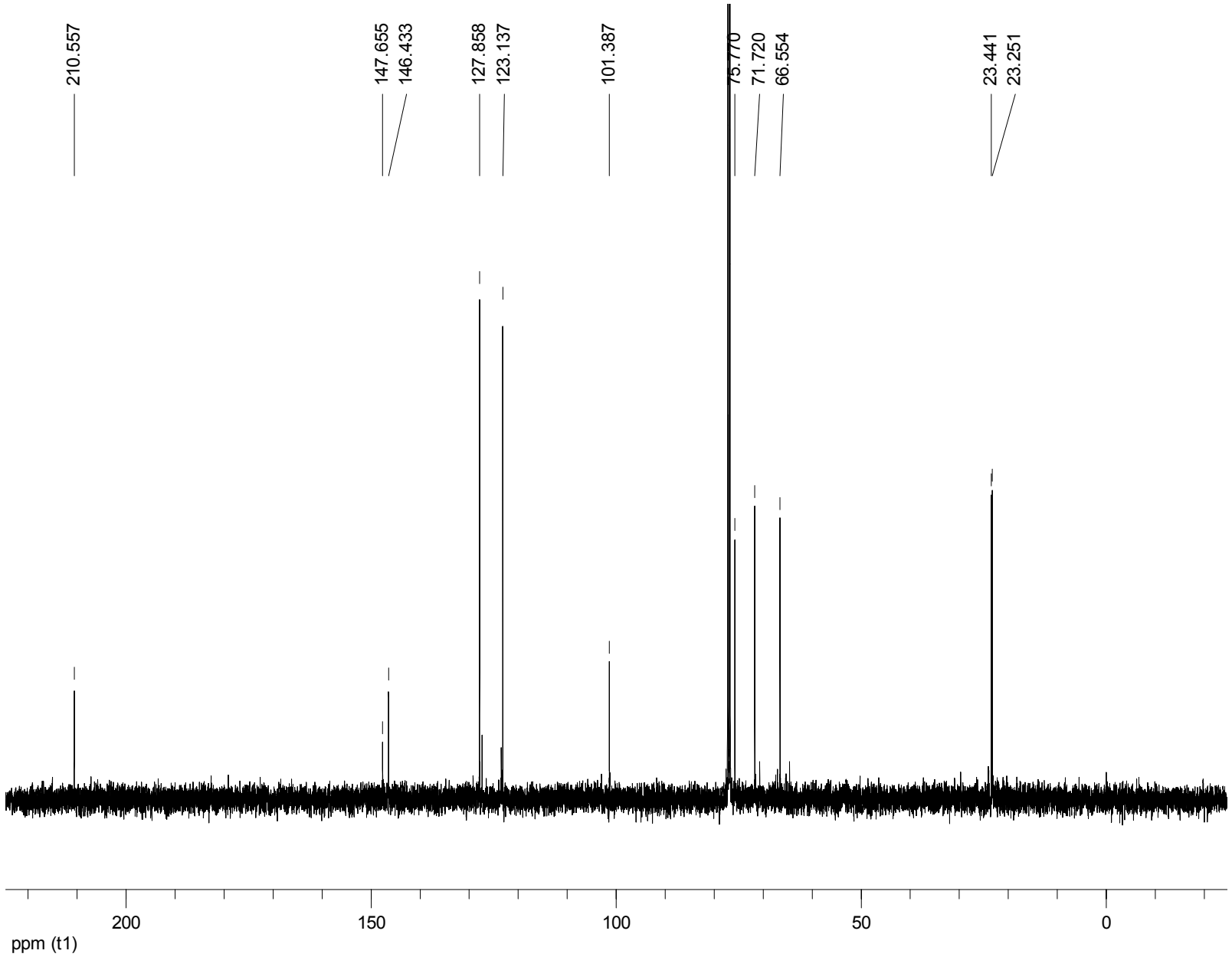
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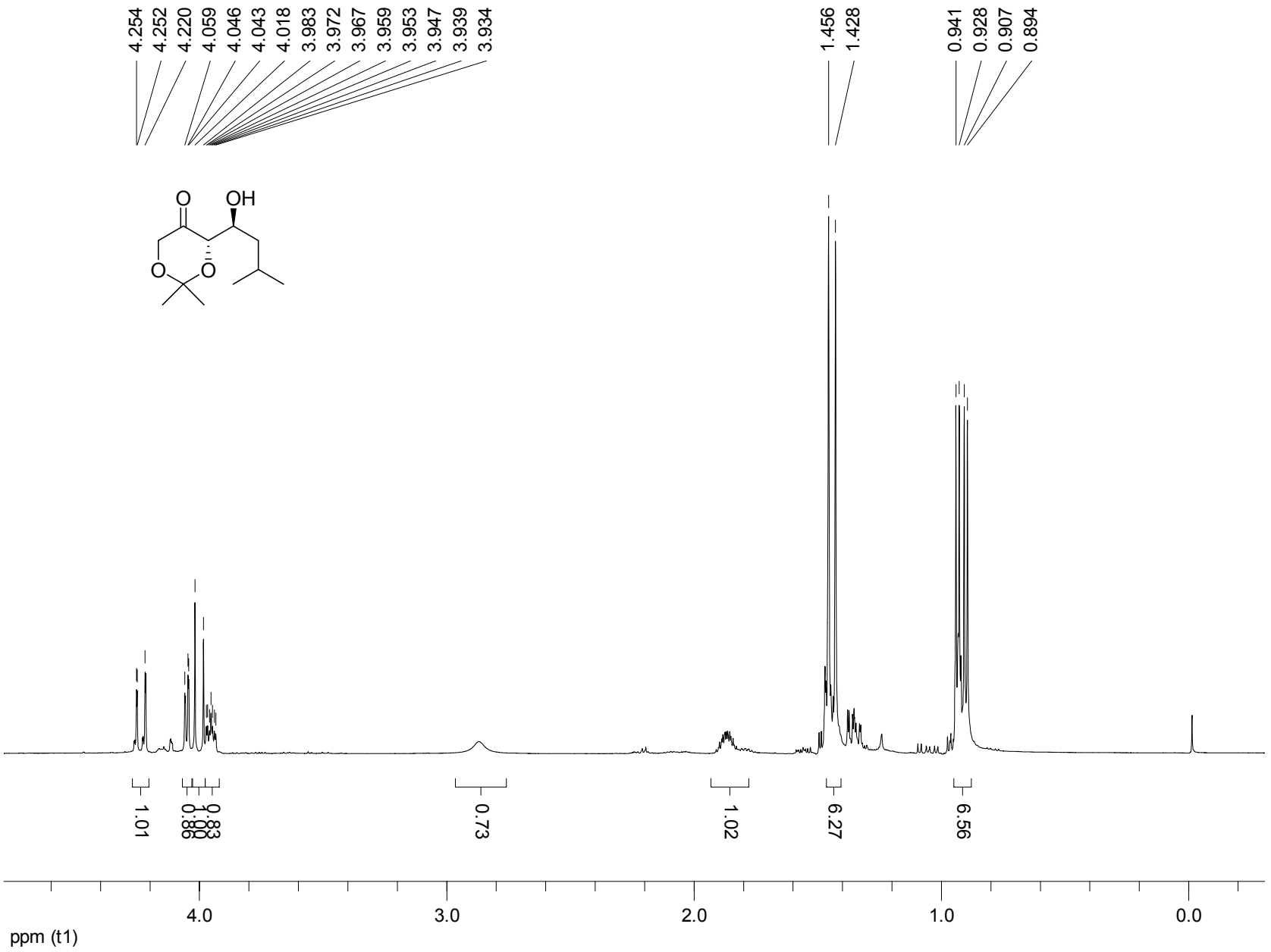
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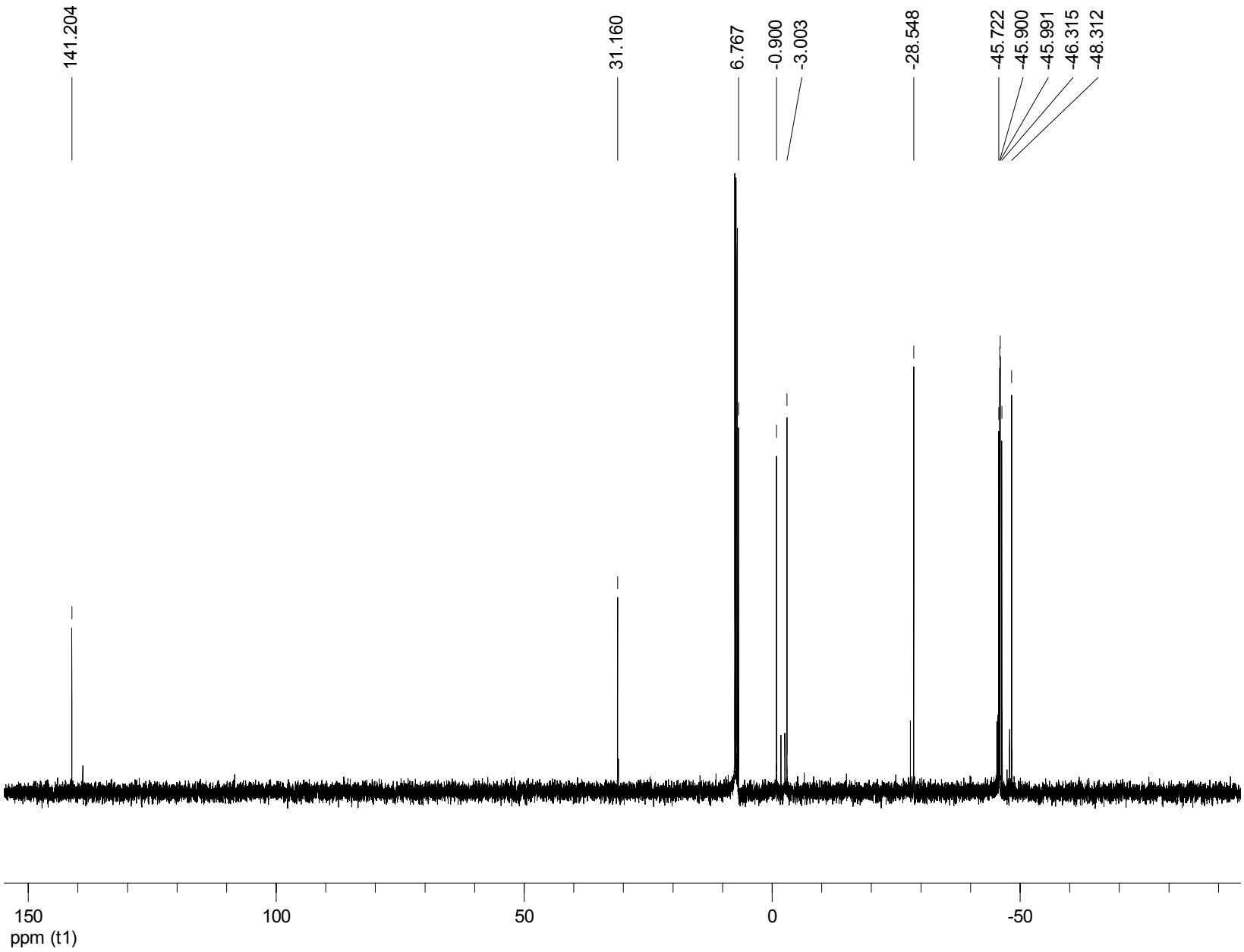
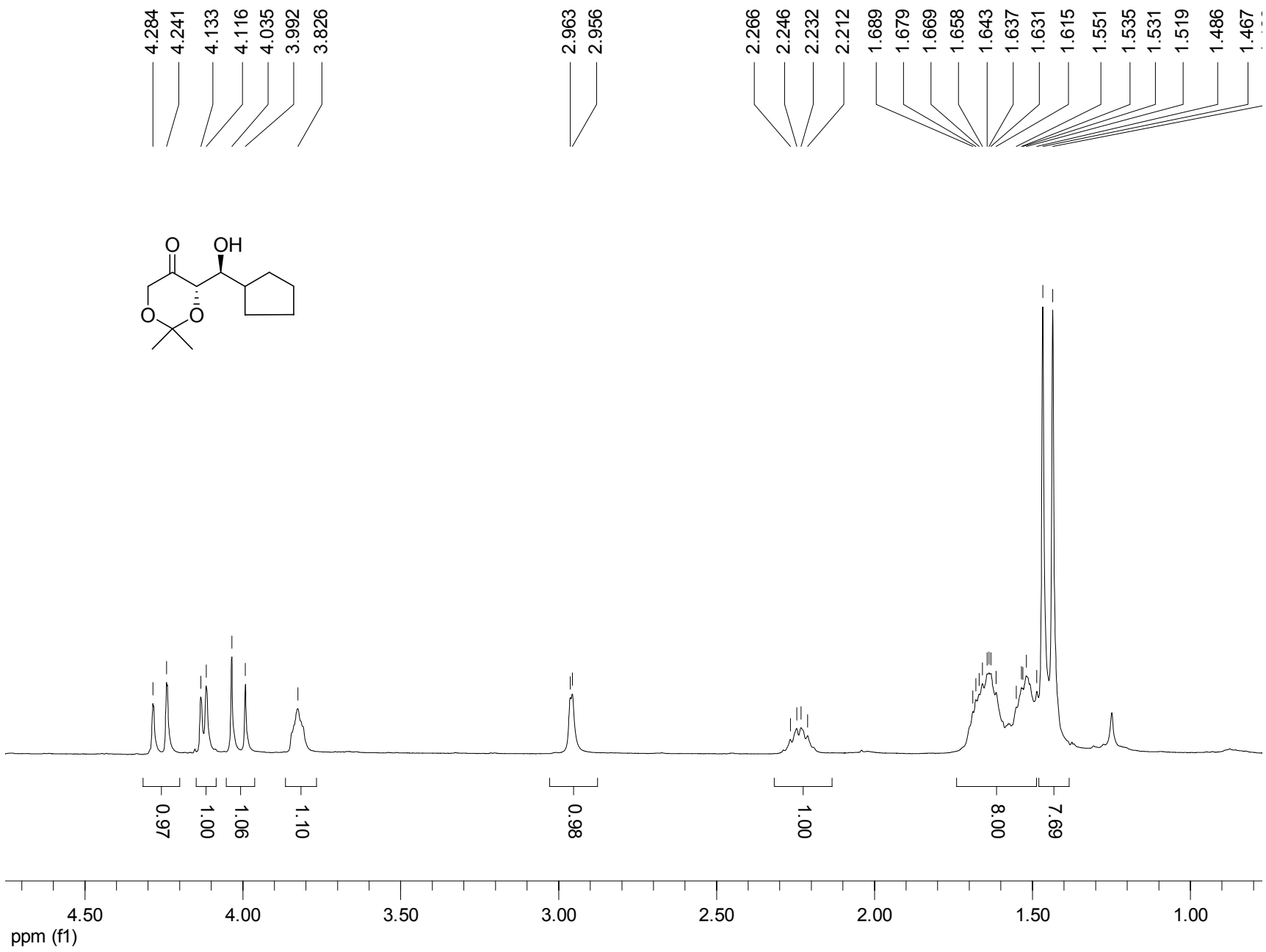
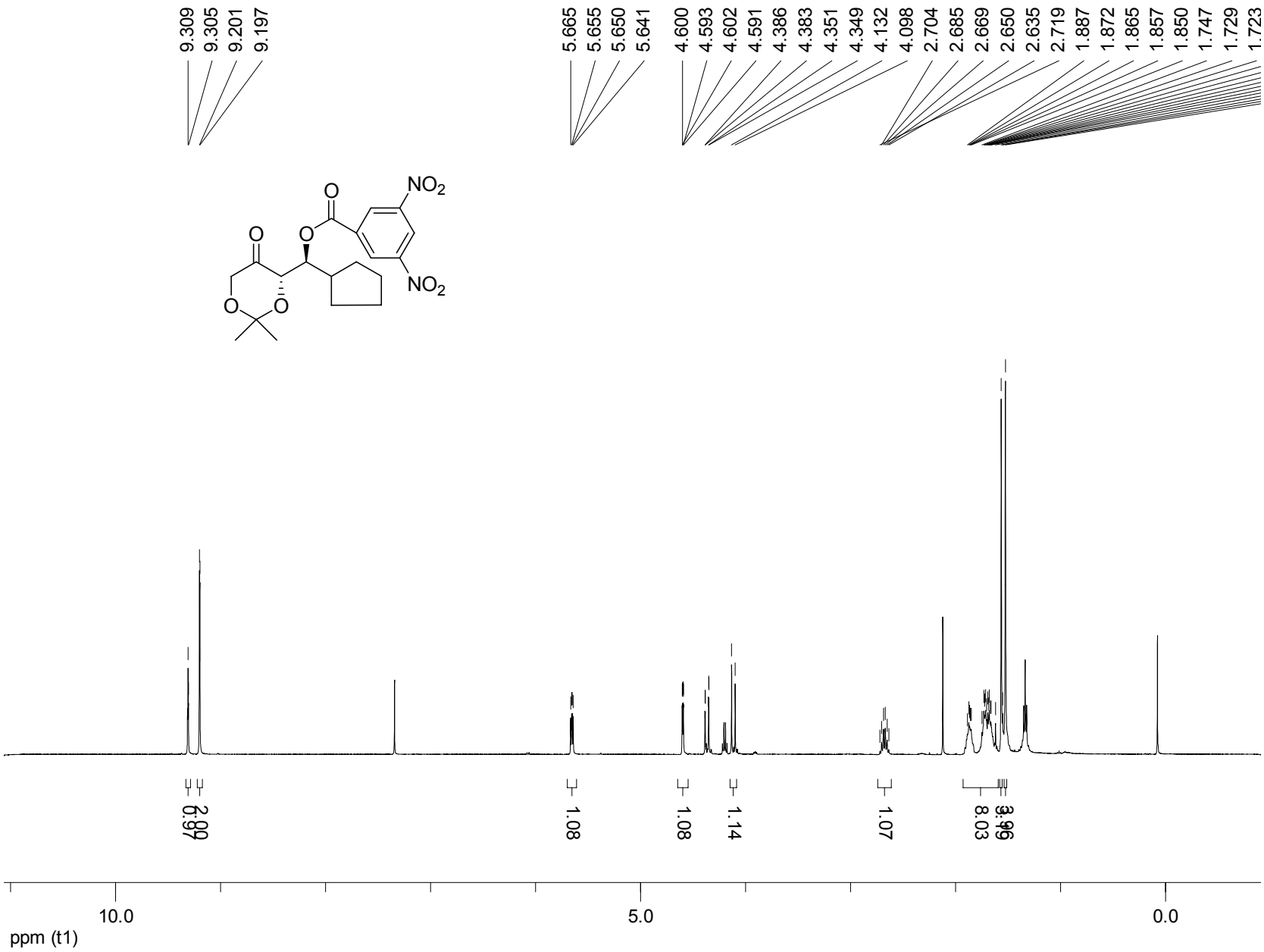
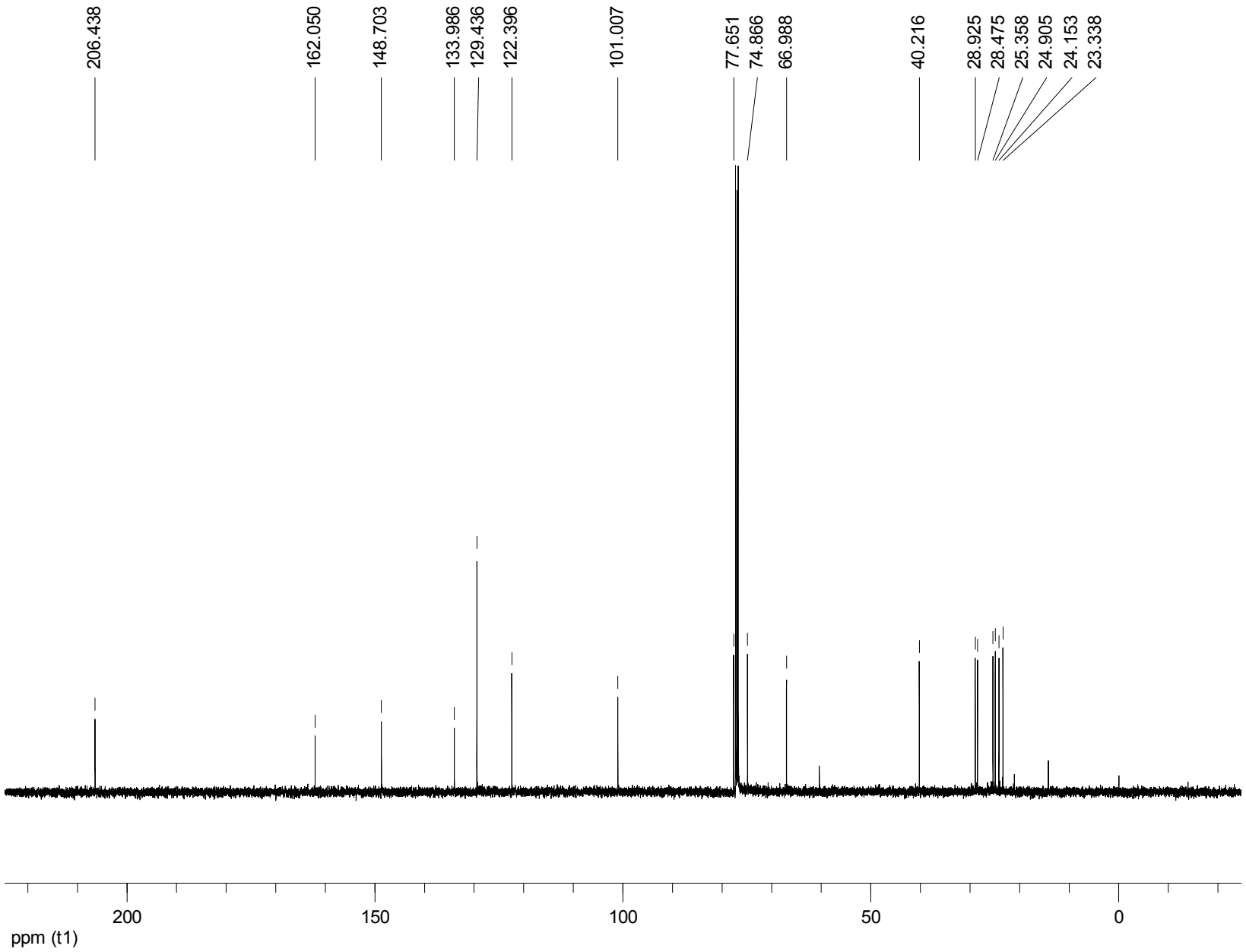
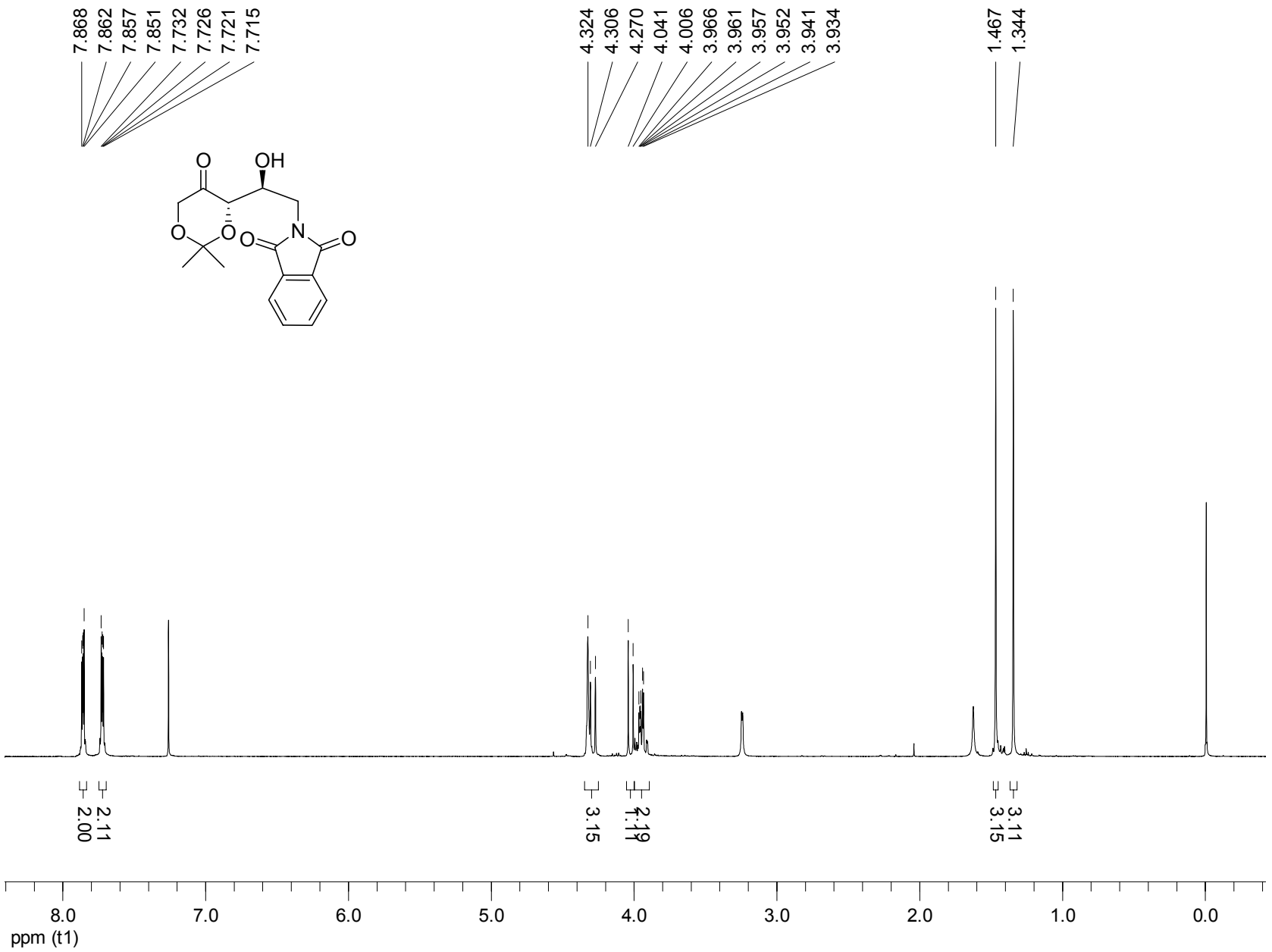
6.56
4.0
3.0
2.0
1.0
0.0
ppm (t1)

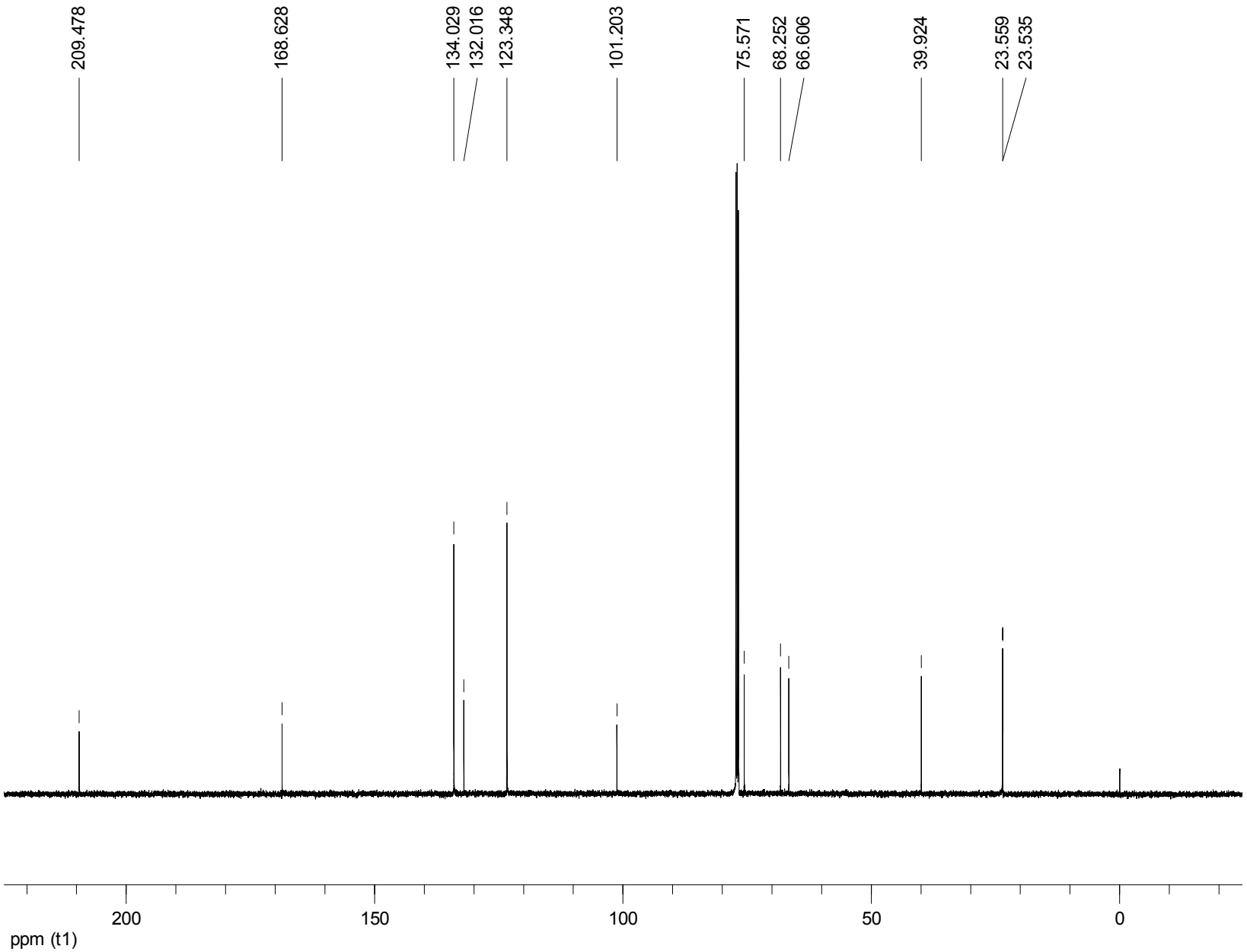

141.204
31.160
6.767
-0.900
-3.003
-28.548
-45.722
-45.900
-45.991
-46.315
-48.312
150
100
50
0
-50
ppm (t1)

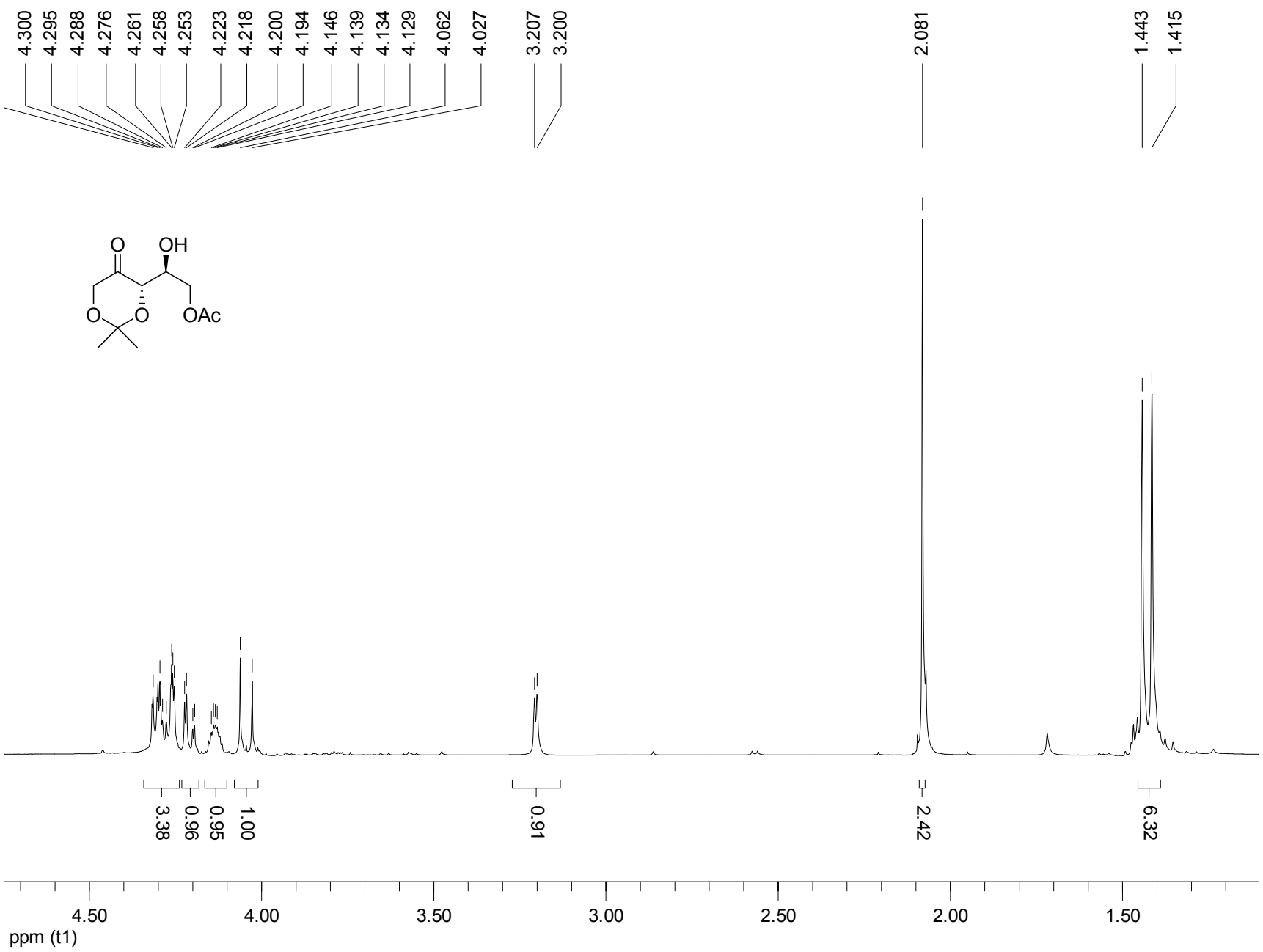

4.284
4.241
4.133
4.116
4.035
3.992
3.826
2.963
2.956
2.266
2.246
2.232
2.212
1.689
1.679
1.669
1.658
1.643
1.637
1.631
1.615
1.551
1.535
1.531
1.519
1.486
1.467
O
OH
O
O
0.97
1.00
1.06
1.10
0.98
1.00
8.00
7.69
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
ppm (f1)

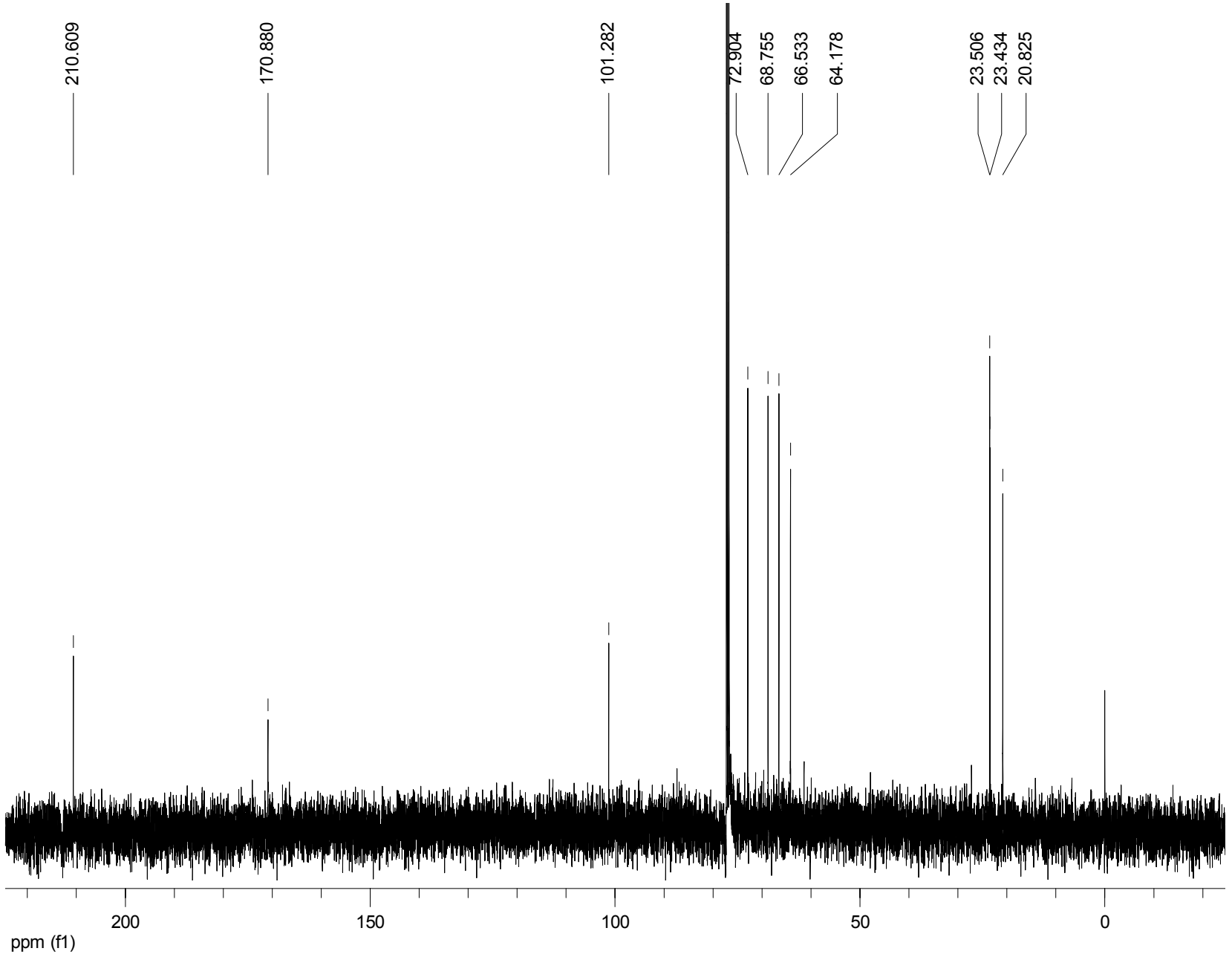

9.309
9.305
9.201
9.197
5.665
5.655
5.650
5.641
4.600
4.593
4.602
4.591
4.386
4.383
4.351
4.349
4.132
4.098
2.704
2.685
2.669
2.650
2.635
2.719
1.887
1.872
1.865
1.857
1.850
1.747
1.729
1.723
O
O
O
O
O
O
NO2
NO2
2.00
2.07
1.08
1.08
1.14
1.07
8.03
3.96
10.0
5.0
0.0
ppm (t1)

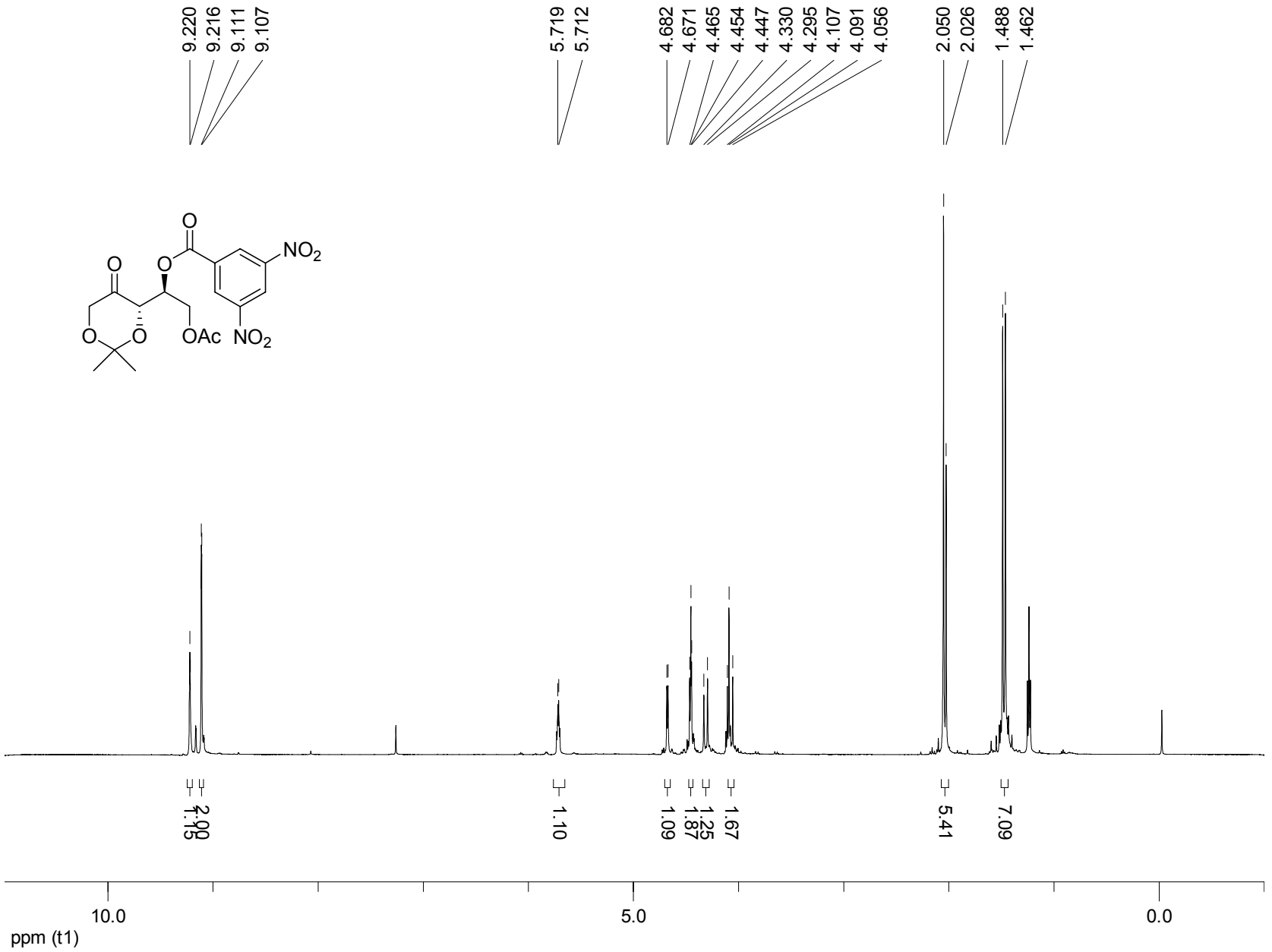

206.438
162.050
148.703
133.986
129.436
122.396
101.007
77.651
74.866
66.988
40.216
28.925
28.475
25.358
24.905
24.153
23.338
200
150
100
50
0
ppm (t1)

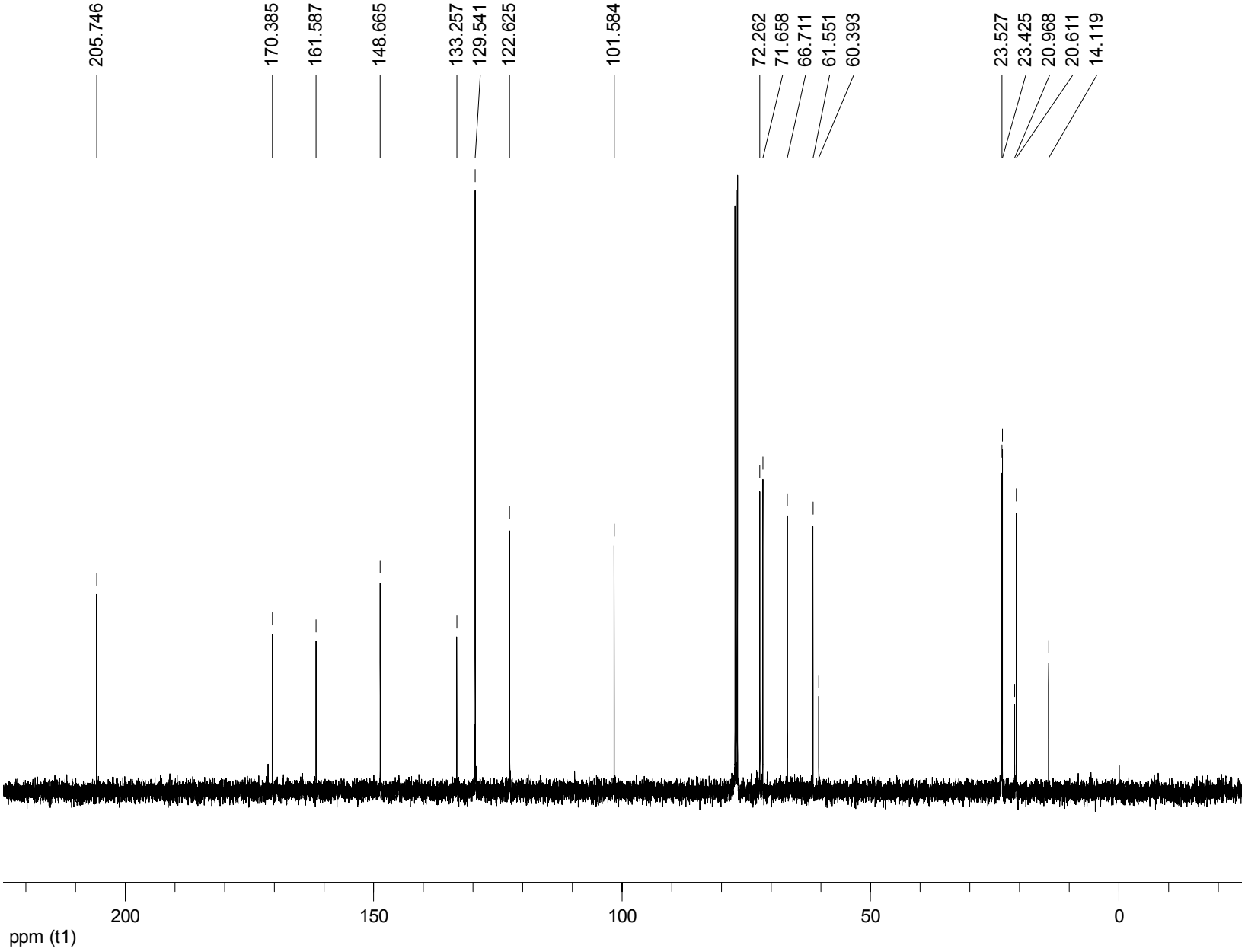

7.868
7.862
7.857
7.851
7.732
7.726
7.721
7.715
4.324
4.306
4.270
4.041
4.006
3.966
3.961
3.957
3.952
3.941
3.934
1.467
1.344
O
OH
O
O
O
N
O
2.00
2.11
3.15
2.19
1.11
3.15
3.11
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

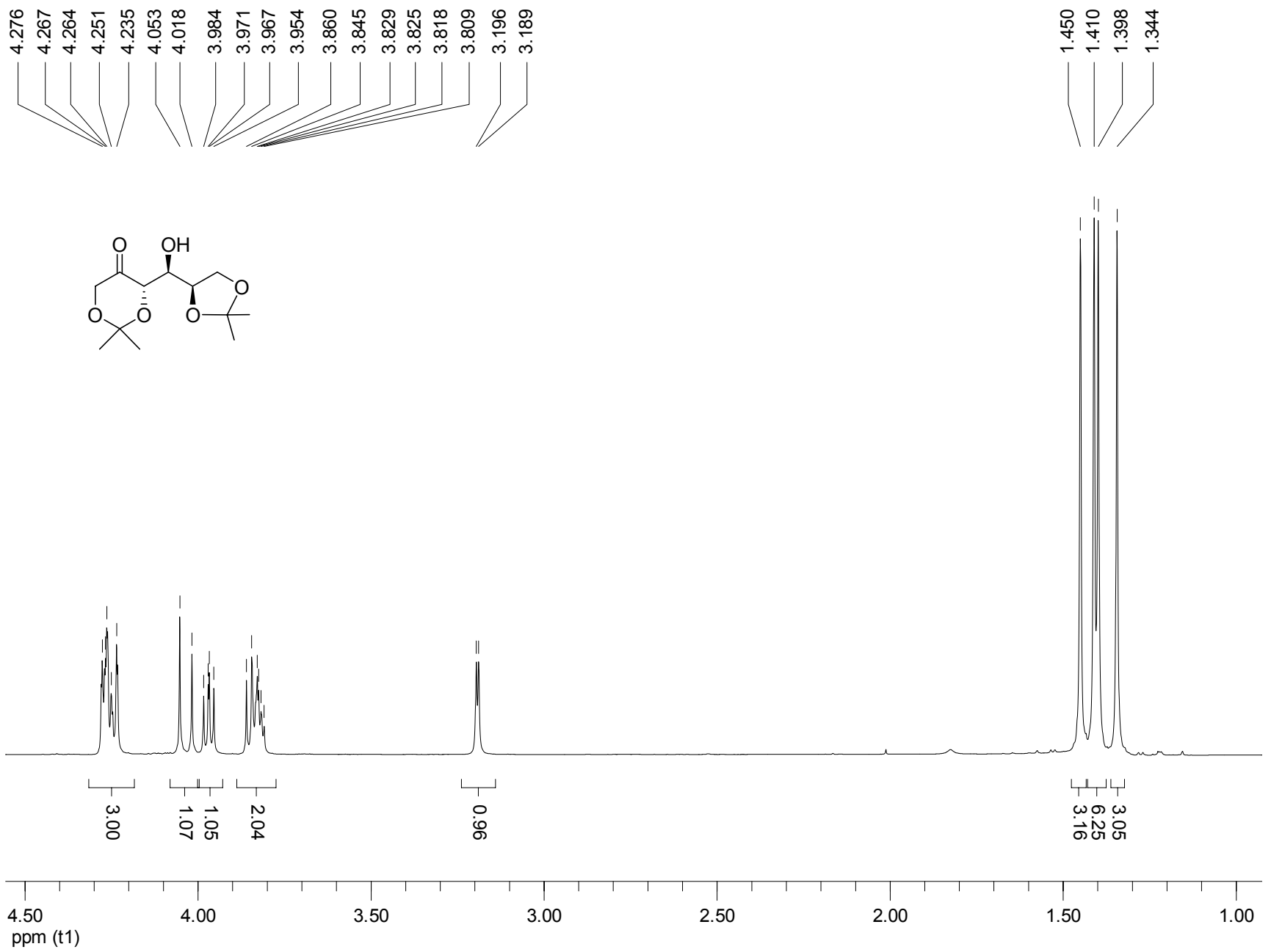

209.478
168.628
134.029
132.016
123.348
101.203
75.571
68.252
66.606
39.924
23.559
23.535
200
150
100
50
0
ppm (t1)

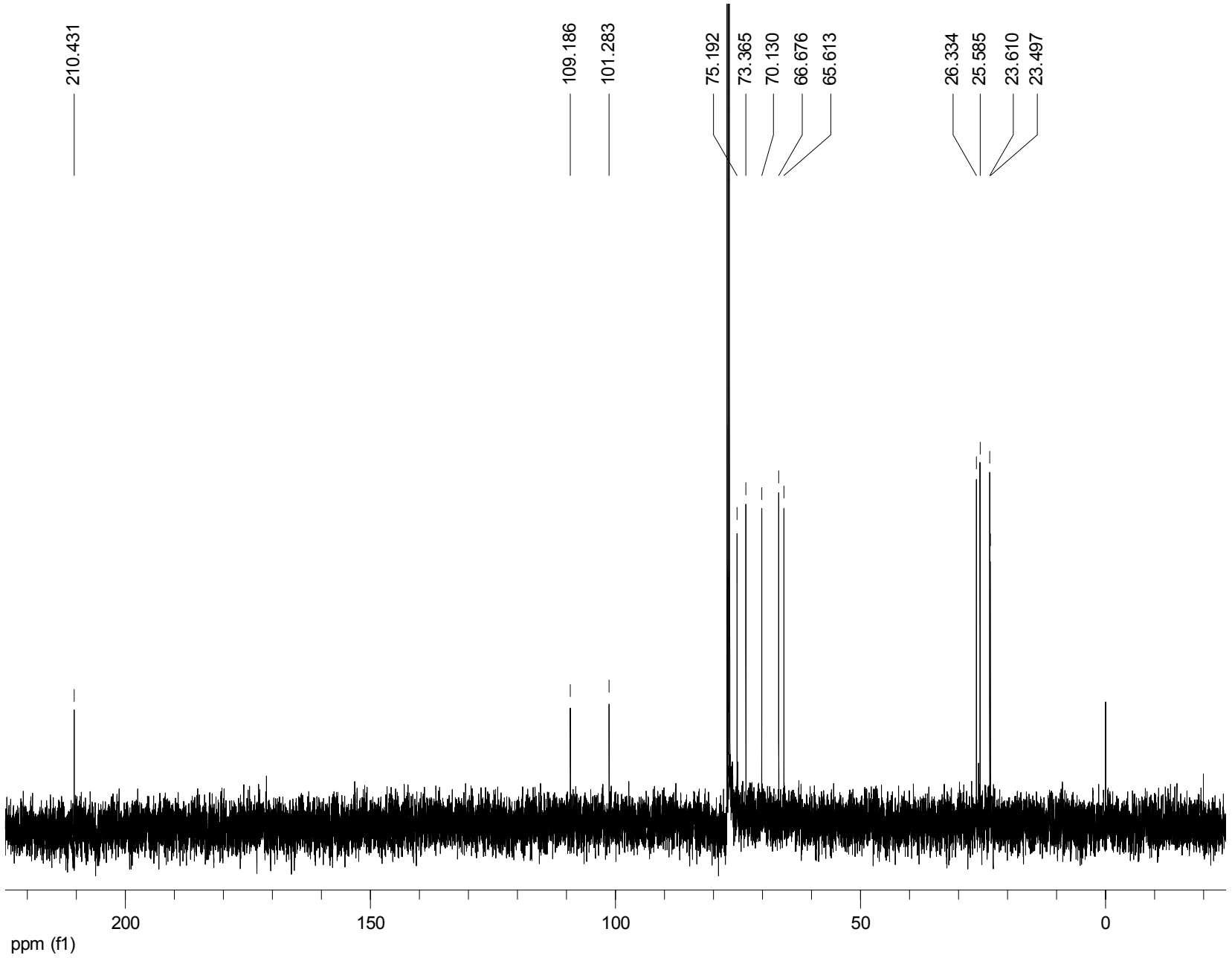

4.300
4.295
4.288
4.276
4.261
4.258
4.253
4.223
4.218
4.200
4.194
4.146
4.139
4.134
4.129
4.062
4.027
3.207
3.200
2.081
1.443
1.415
O
OH
O
O
OAc
3.38
0.96
0.95
1.00
0.91
2.42
6.32
4.50
4.00
3.50
3.00
2.50
2.00
1.50
ppm (t1)

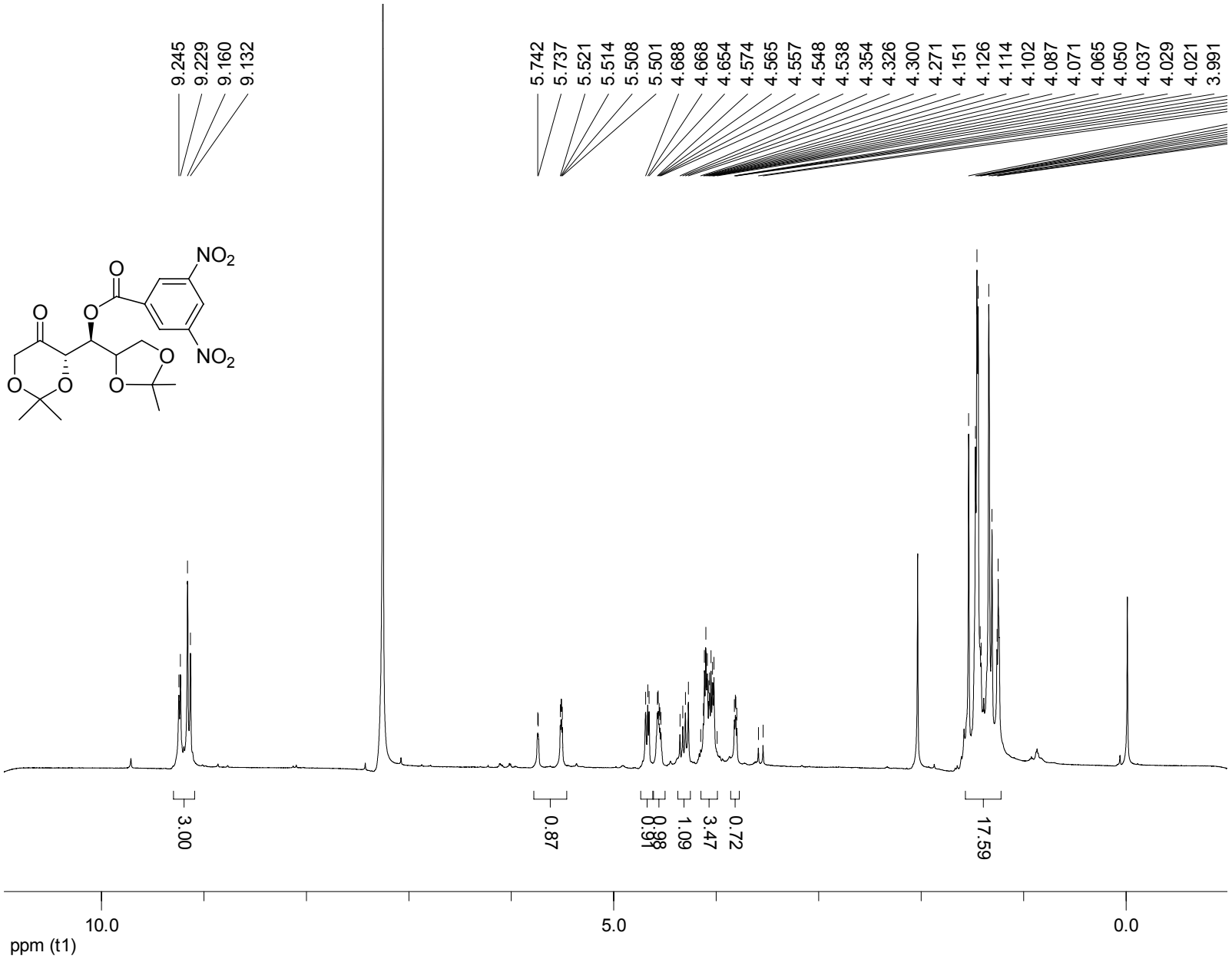

210.609
170.880
101.282
72.904
68.755
66.533
64.178
23.506
23.434
20.825
200
150
100
50
0
ppm (f1)

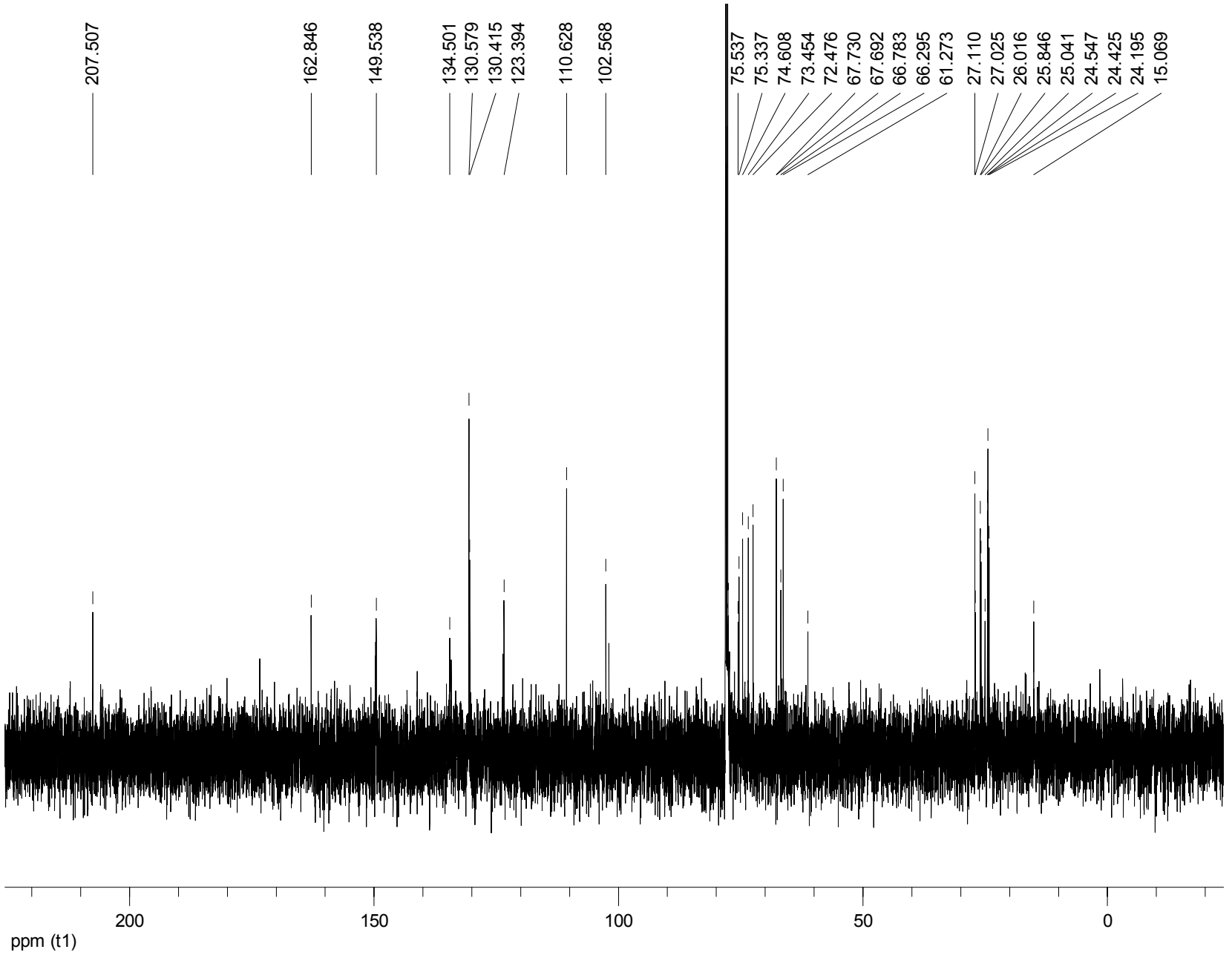

9.220
9.216
9.111
9.107
5.719
5.712
4.682
4.671
4.465
4.454
4.447
4.330
4.295
4.107
4.091
4.056
2.050
2.026
1.488
1.462
O
O
O
O
O
NO2
OAc
NO2
4.15
2.00
1.10
1.09
1.87
1.25
1.67
5.41
7.09
10.0
5.0
0.0
ppm (t1)

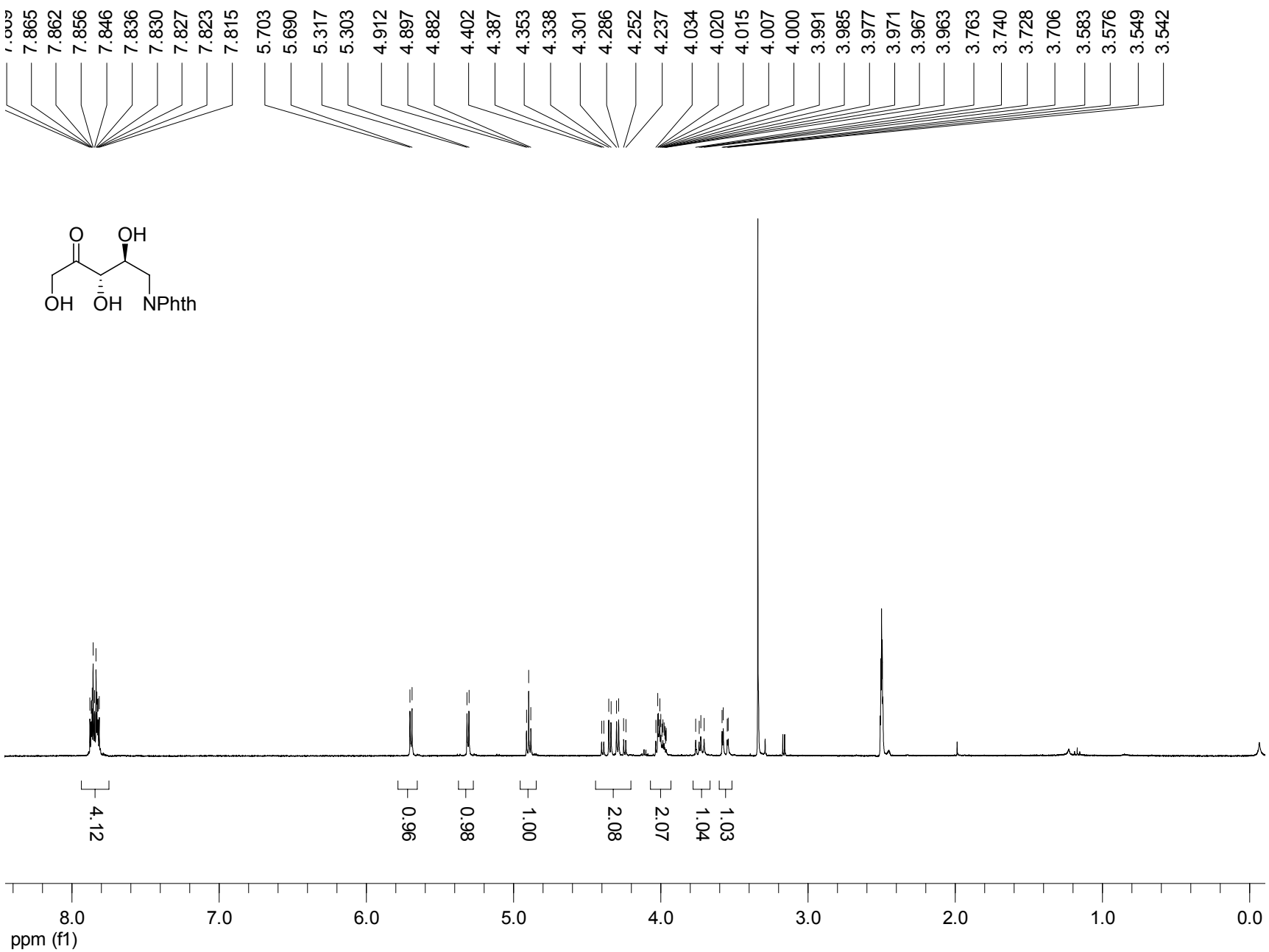

205.746
170.385
161.587
148.665
133.257
129.541
122.625
101.584
72.262
71.658
66.711
61.551
60.393
23.527
23.425
20.968
20.611
14.119
200
150
100
50
0
ppm (t1)

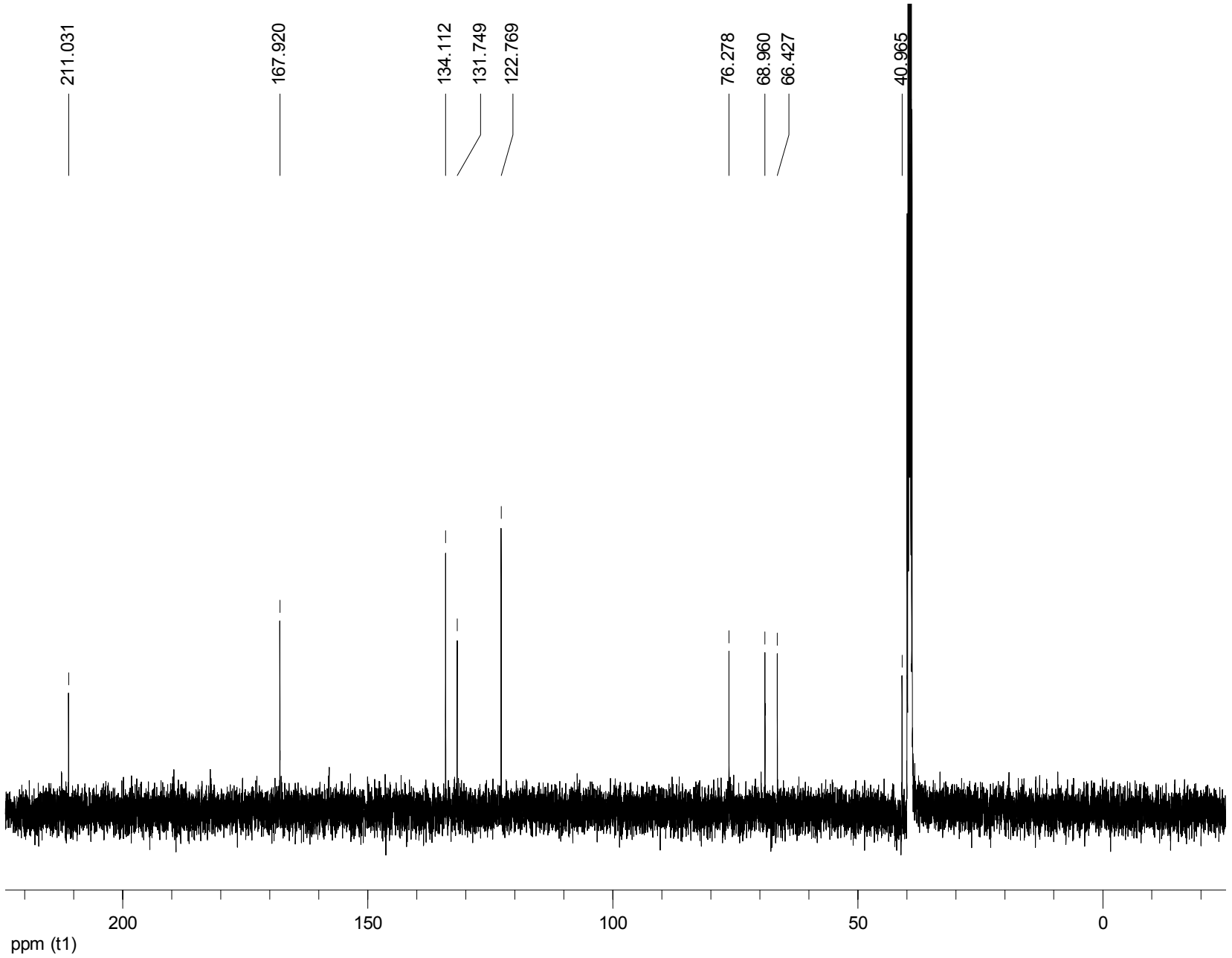

4.276
4.267
4.264
4.251
4.235
4.053
4.018
3.984
3.971
3.967
3.954
3.860
3.845
3.829
3.825
3.818
3.809
3.196
3.189
1.450
1.410
1.398
1.344
O
OH
O
O
O
O
3.00
1.07
1.05
2.04
0.96
3.16
6.25
3.05
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
ppm (t1)

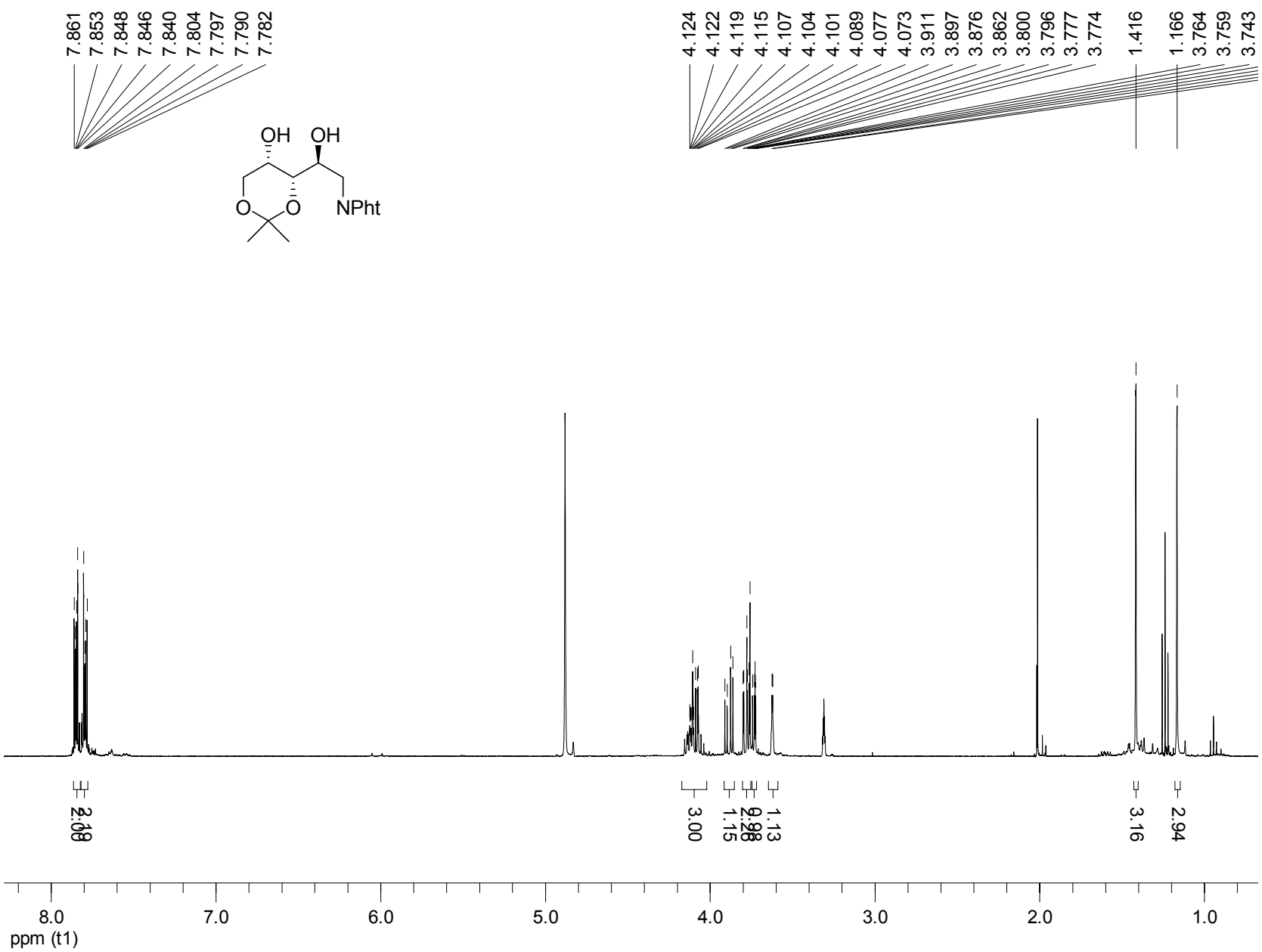

210.431
109.186
101.283
75.192
73.365
70.130
66.676
65.613
26.334
25.585
23.610
23.497
200
150
100
50
0
ppm (f1)

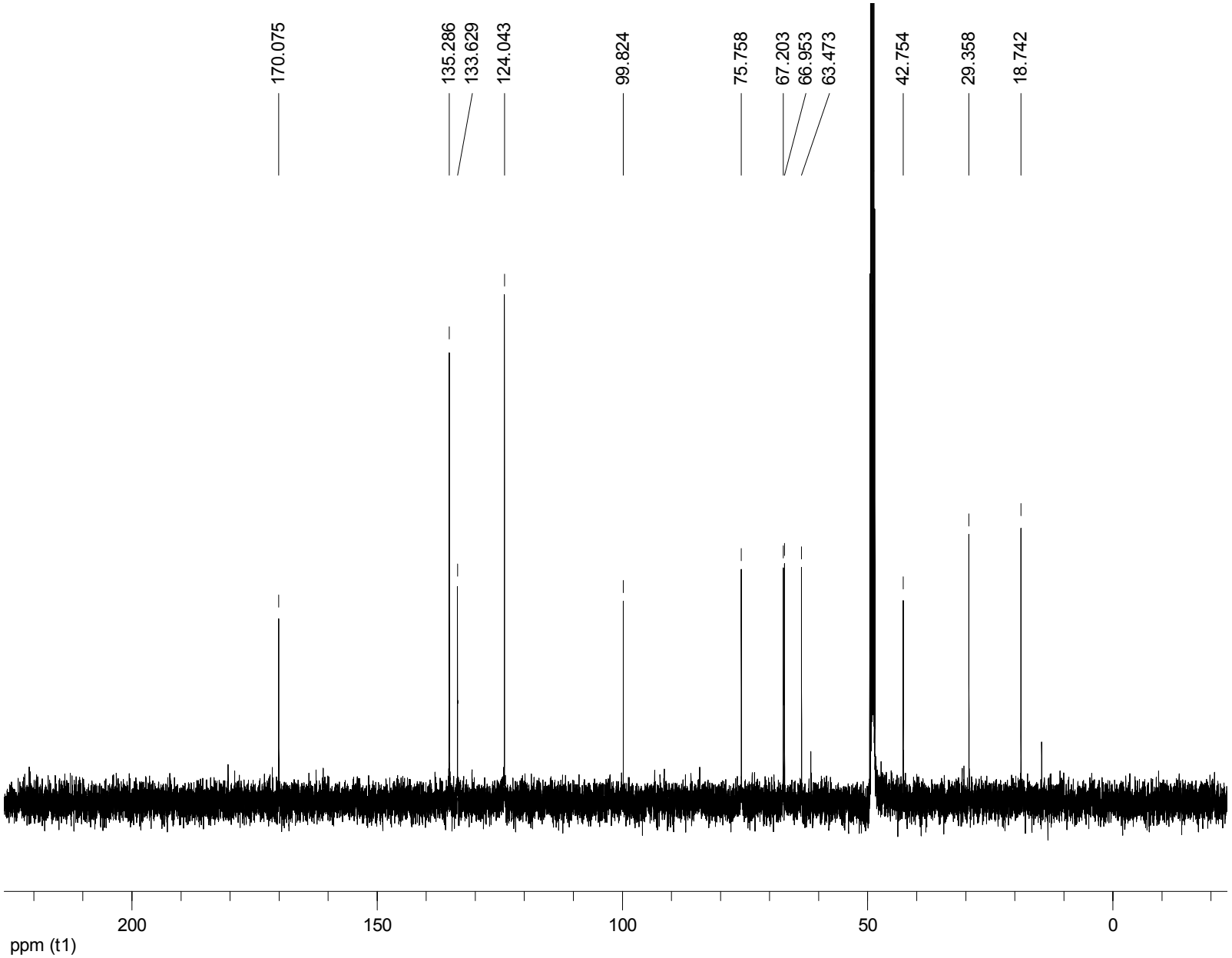

9.245
9.229
9.160
9.132
5.742
5.737
5.521
5.514
5.508
5.501
4.688
4.668
4.654
4.574
4.565
4.557
4.548
4.538
4.354
4.326
4.300
4.271
4.151
4.126
4.114
4.102
4.087
4.071
4.065
4.050
4.037
4.029
4.021
3.991
NO2
NO2
O
O
O
O
O
O
O
3.00
0.87
0.91
0.98
1.09
3.47
0.72
17.59
10.0
5.0
0.0
ppm (t1)

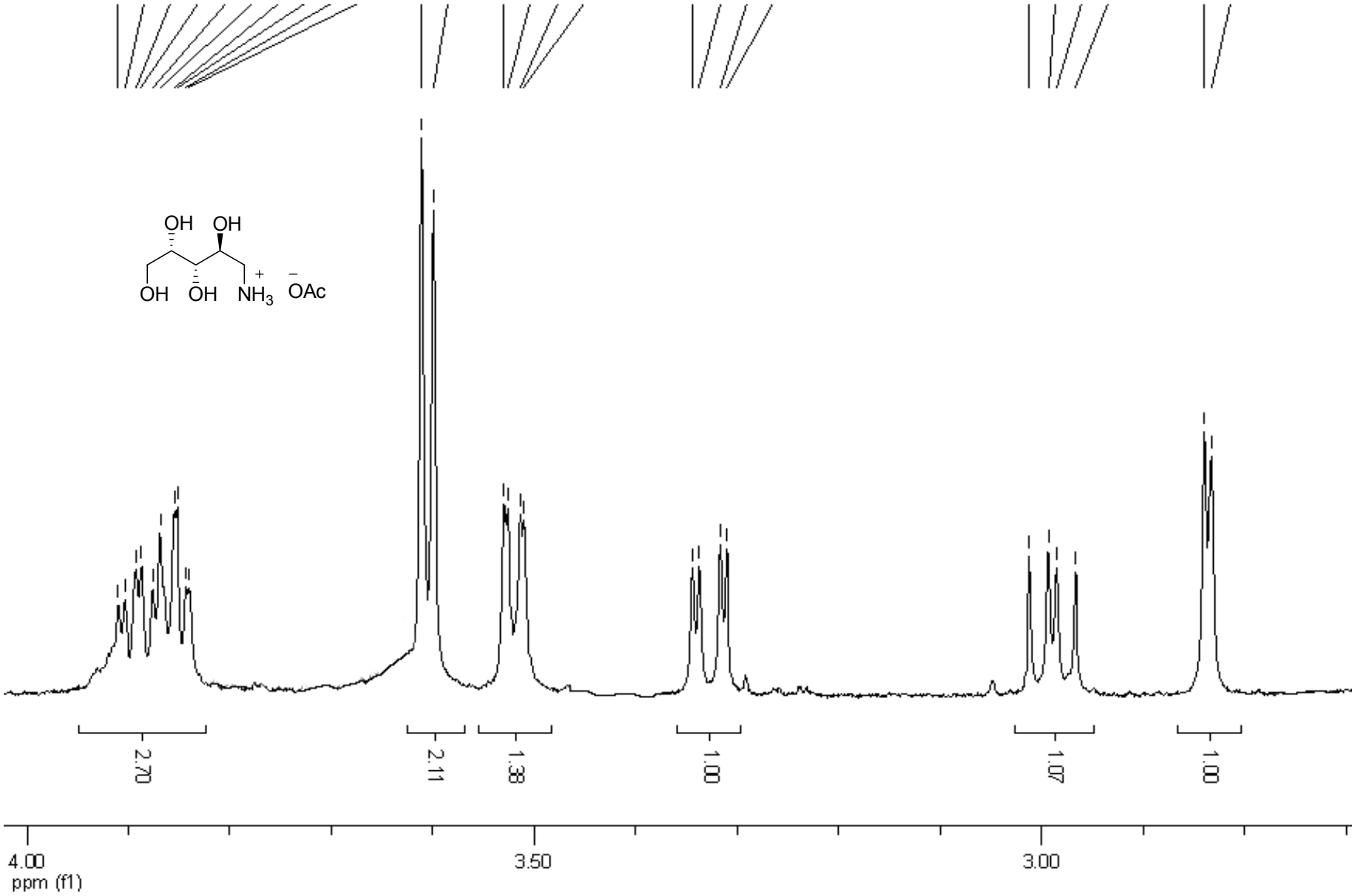

207.507
162.846
149.538
134.501
130.579
130.415
123.394
110.628
102.568
75.537
75.337
74.608
73.454
72.476
67.730
67.692
66.783
66.295
61.273
27.110
27.025
26.016
25.846
25.041
24.547
24.425
24.195
15.069
200
150
100
50
0
ppm (t1)

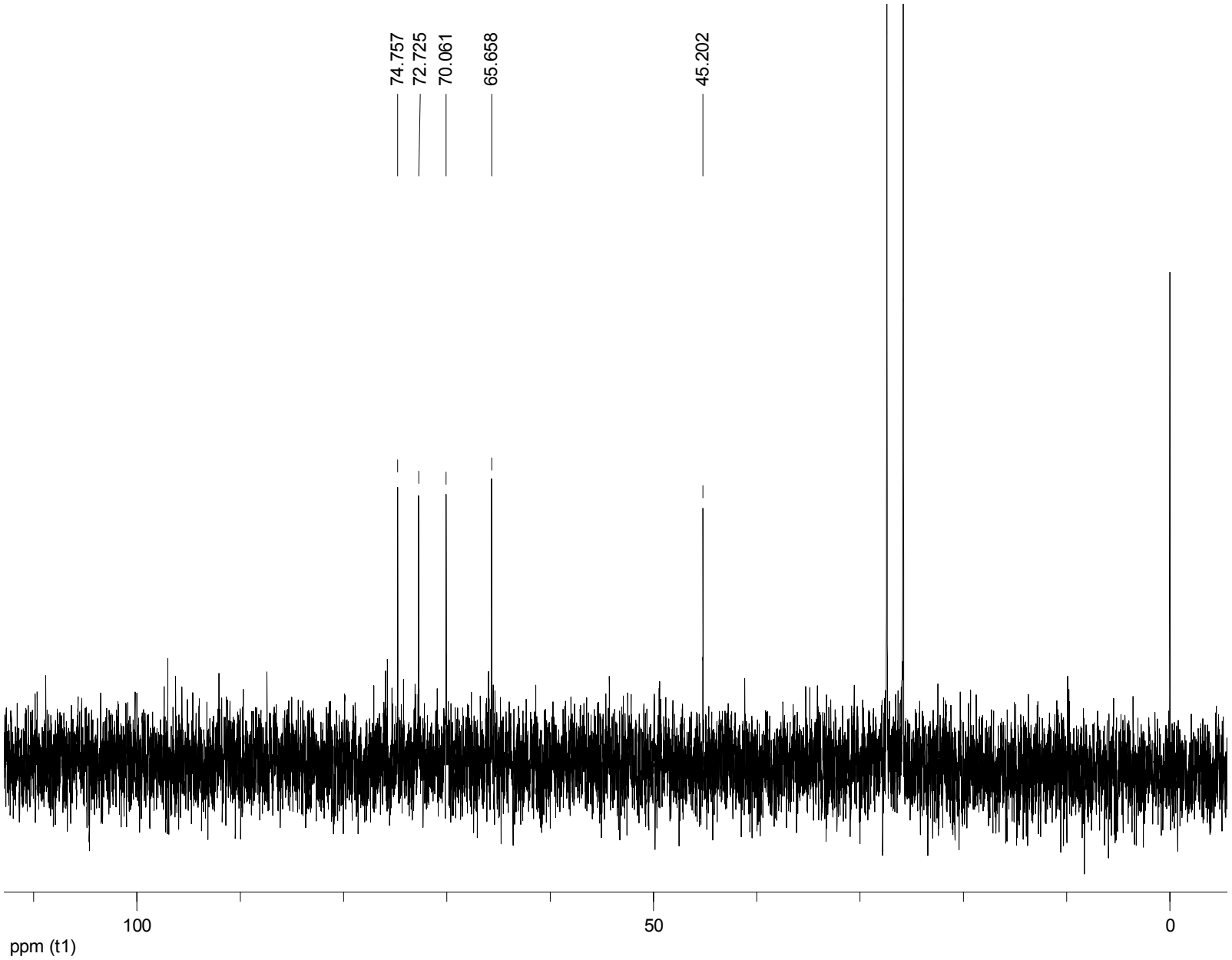

7.865
7.862
7.856
7.846
7.836
7.830
7.827
7.823
7.815
5.703
5.690
5.317
5.303
4.912
4.897
4.882
4.402
4.387
4.353
4.338
4.301
4.286
4.252
4.237
4.034
4.020
4.015
4.007
4.000
3.991
3.985
3.977
3.971
3.967
3.963
3.763
3.740
3.728
3.706
3.583
3.576
3.549
3.542
O
OH
OH
OH
NPhth
4.12
0.96
0.98
1.00
2.08
2.07
1.04
1.03
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

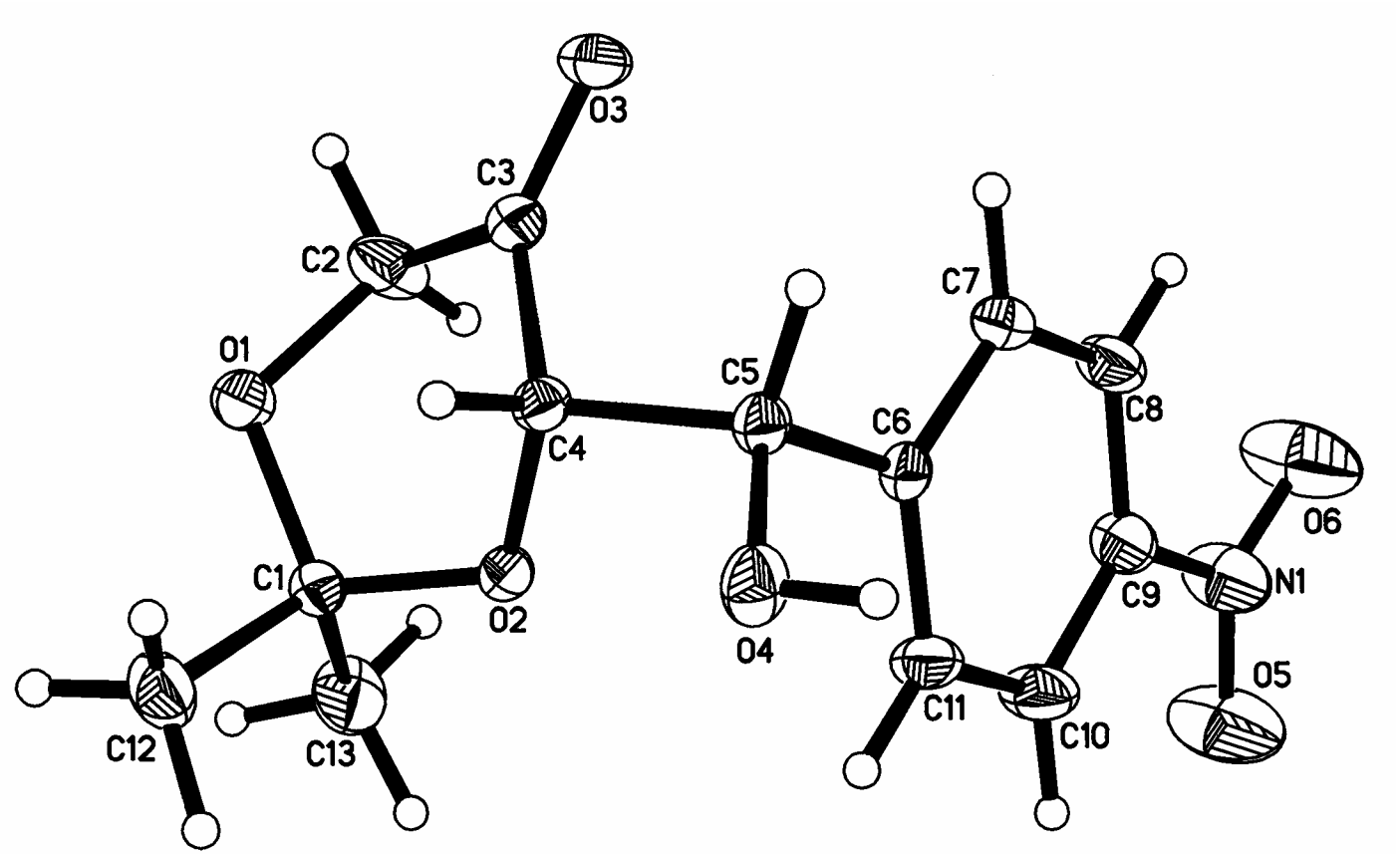

211.031
167.920
134.112
131.749
122.769
76.278
68.960
66.427
40.965
200
150
100
50
0
ppm (t1)


7.861
7.853
7.848
7.846
7.840
7.804
7.797
7.790
7.782
4.124
4.122
4.119
4.115
4.107
4.104
4.101
4.089
4.077
4.073
3.911
3.897
3.876
3.862
3.800
3.796
3.777
3.774
1.416
1.166
3.764
3.759
3.743
OH
OH
O
O
NPht
2.00
3.00
1.15
1.13
3.16
2.94
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)


170.075
135.286
133.629
124.043
99.824
75.758
67.203
66.953
63.473
42.754
29.358
18.742
200
150
100
50
0
ppm (t1)


OH
OH
OH
OH
NH3
OAc
2.70
2.11
1.38
1.00
1.07
1.00
4.00
ppm (f1)
3.50
3.00


74.757
72.725
70.061
65.658
45.202
100
50
0
ppm (t1)



X-ray structure o f (S)-4-((S)-Hydroxy(4-nitrophenyl)methyl)-2,2-dimethyl-1,3-dioxan-5-one (Table 1, entry 6).