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Organocatalytic Enantioselective Synthesis of Metabotropic Glutamate Receptor Ligands

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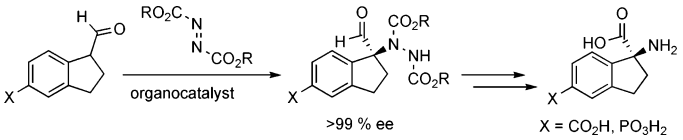
ABSTRACT



(*R*)-Proline catalyzes the amination reaction of functionalized indane carboxaldehydes and allows for the efficient enantioselective synthesis (>99% ee) of the metabotropic glutamate receptor ligands (*S*)-AIDA and (*S*)-APICA.

The catalytic asymmetric synthesis of chiral-nonracemic drugs has become an important focus for chemists in academia and industry.[1] New methodologies that limit the use of toxic substances and that are recognized as atom efficient are highly desirable. In this context, organocatalysis continues to attract attention.[2] Asymmetric organocatalysis utilizes organic molecules to induce chirality in various C−C, C−N, and C−O bond-forming reactions.[3] Many important chiral synthons have been obtained via organocatalysis. For example, efficient and stereoselective preparations of α- and β-amino acids,[4] amino alcohols,[5] diols,[6] and carbohydrates[7] have been reported. In continuation of our work in this area[8] we sought to demonstrate that organocatalysis can be useful in the preparation of various medicinally important compounds. In many cases, the syntheses of chiral ligands that show therapeutic potential need to be reevaluated in light of modern asymmetric techniques, especially when the molecules are prepared via chiral pool approaches.[9] Thus, with organocatalysis in mind, a more efficient route to the amino acids listed in Figure 1 was realized. AIDA and APICA

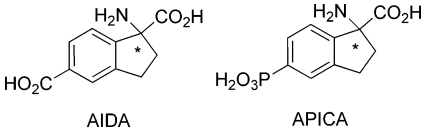


Figure 1. Metabotropic glutamate receptor ligands.

(Figure 1) are known antagonists of metabotropic glutamate receptors (mGluRs), G-protein-coupled receptors associated

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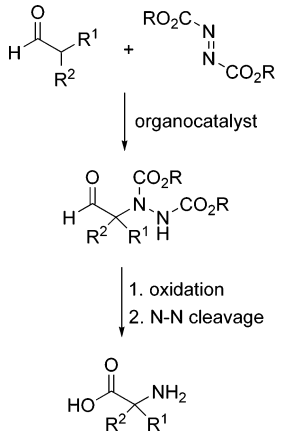
with various neurodegenerative diseases.[10] Their bioactivities have recently rendered them potential drugs of the future.[11] Both (*S*)-AIDA and (*S*)-APICA were found to be the active isomers in various biological assays.[12,13] Although the asymmetric synthesis of these compounds has been reported using chiral pool[12] and chiral ligand-exchange chromatography[13] approaches, there is still a need for a more direct asymmetric route that allows for the multigram preparation of these compounds and their analogues.

The (*S*)-proline-catalyzed amination of aldehydes has recently been reported as an efficient way to prepare chiral amino aldehydes.[14] As outlined in Scheme 1, the corresponding amino acids can be prepared by simple oxidation and N−N bond cleavage of the amino aldehyde adducts. Thus, utilizing this amination sequence, (*S*)-AIDA and (*S*)-APICA could be prepared via organocatalysis. Herein we report a practical and efficient organocatalytic enantioselective synthesis of (*S*)-AIDA and (*S*)-APICA where the amination of branched aldehyde donors is used as a key step.

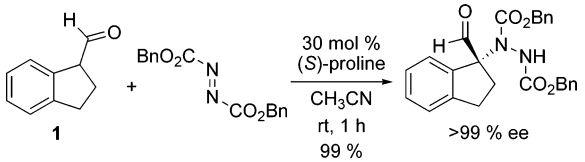
Scheme 1. Organocatalysis in the Preparation of Amino Acids



Brase and co-workers demonstrated that (*S*)-proline can catalyze the reaction of 2-phenylpropionaldehyde with diethylazodicarboxylate to give the corresponding amino aldehyde in 86% ee after 60 h in CH_2Cl_2.[14c] Although this substrate gave good ee, the reaction was fairly substrate dependent, and ees varied from 32 to 86% ee. One substrate that was not tested that was of particular interest to us was indane carboxyaldehyde **1**. Previously, we had found **1** to be a very reactive donor in the quaternary Mannich reaction, where it gave excellent enantio- and diastereoselectivity.[4] Because **1** contains the core structure of AIDA and APICA, the amination of **1** would provide the precursor amino aldehyde, which upon further elaboration would yield the corresponding amino acid.

As indicated in Scheme 2, the coupling of **1** to dibenzylazodicarboxylate (DBAD) is efficiently and selectively catalyzed by (*S*)-proline giving only one enantiomer in quantitative yield. Having demonstrated that high ees could be obtained using indane **1** as the donor, we devised syntheses of (*S*)-AIDA and (*S*)-APICA according to Schemes 3 and 4.

Scheme 2. (*S*)-Proline Catalyzed Amination of Indane Carboxaldehyde **1**



The synthesis of (*S*)-AIDA began with cyanation of commercially available 5-bromoindanone giving **3** in 78%.[15] Wittig olefination afforded **4** as a mixture of *E* and *Z* isomers, and upon hydrolysis of the cyano group and subsequent esterification, **5** was obtained in excellent yield. Various attempts to hydrolyze the enol ether **5** using mineral acids or PTSA resulted in low yields. However, when boron tribromide was used, the demethylation of **5** ensued without affecting the ester functionality,[16] thus providing indane aldehyde **6** in good yield. The functionalized indane **6** proved to be a good substrate for the amination reaction. When a slight excess of aldehyde was reacted with DBAD with 20 mol % (*R*)-proline at ambient temperature, the amination product was obtained in >99% ee and 96% yield in less than 4 h. Subsequent oxidation and esterification gave precursor **7**.

Initially, high-pressure hydrogenation over Ra−Ni was attempted in order to cleave the N−N bond.[14] Because yields were low (less than 10%), an alternative route was carried out utilizing SmI_2. We first applied a one-pot trifluoroacetylation−selective benzyloxycarbonyl deprotection protocol[17]

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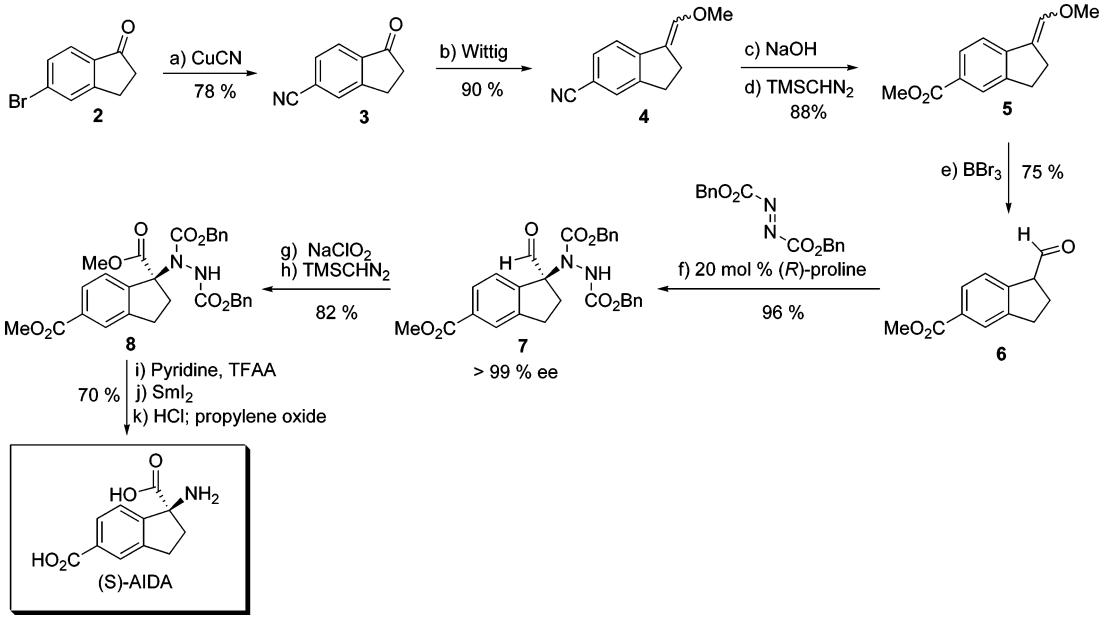
Scheme 3[a]

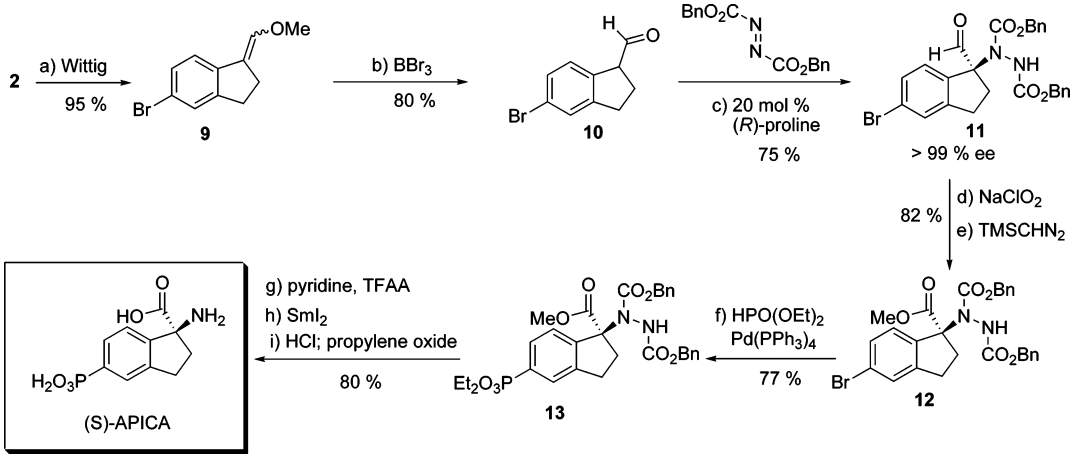


[a] Conditions: (a) CuCN, DMF, reflux, 12 h, 78%; (b) Ph_3PCH_2OMeCl, ^tKOBu, THF, −20 °C, 1 h, 90%; (c) NaOH, EtOH/H_2O, reflux, 4 h; (d) $TMSCHN_2$, MeOH/toluene, 10 min, 88%; (e) 2 equiv of BBr_3, CH_2Cl_2, −78 °C, 4 h, 75%; (f) DBAD, 20 mol % (*R*)-proline, CH_3CN, 4 h, 96%, >99% ee; (g) $NaClO_2$, 2-methyl-2-butene, $^tBuOH/H_2O$; (h) $TMSCHN_2$, MeOH/toluene, 10 min, 82%; (i) pyridine, 40 °C, 15 h, then trifluoroacetic anhydride, 48 h; (j) SmI_2, THF/MeOH, 30 min; (k) 6 M HCl, reflux, 48 h, then propylene oxide, 70%.

to provide the trifluoromethyl hydrazine. Cleavage of the N−N bond was then carried out with SmI_2 using a procedure slightly modified from that originally reported by Friestad.[18] Subsequent deprotection afforded (*S*)-AIDA.

The reaction sequence presented here was found to be very flexible and allowed for the preparation of the phosphonate analogue (*S*)-APICA from **2** (Scheme 4). After Wittig olefination and subsequent generation of aldehyde **10**, the (*R*)-proline-catalyzed amination furnished **11** in optically pure form. Oxidation to the acid followed by esterification afforded bromo-indane **12**, which underwent Pd(0)-catalyzed phosphonate coupling[12c] to give intermediate **13**. Transformation into the trifluoromethylacetyl-protected hydrazine allowed for the samarium-induced cleavage of the N−N bond.[19] Subsequent hydrolysis of the ester functionalities afforded (*S*)-APICA.

Scheme 4[a]



[a] Conditions: (a) Ph_3PCH_2OMeCl, ^tKOBu, THF, −20 °C, 1 h, 95%; (b) 2 equiv of BBr_3, CH_2Cl_2, −78 °C, 4 h, 80%; (c) DBAD, 20 mol % (*R*)-proline, CH_3CN, 4 h, 75%, >99% ee; (d) $NaOCl_2$, 2-methyl-2-butene, $^tBuOH/H_2O$; (e) $TMSCHN_2$, MeOH/toluene, 10 min, 82%; (f) diethyl phosphite, 10 mol % $Pd(PPh_3)_4$, toluene, reflux, 72 h, 77%; (g) pyridine, 40 °C, 15 h, then trifluoroacetic anhydride, 48 h; (h) SmI_2, THF/MeOH, 30 min; (i) 6 M HCl, reflux, 48 h, then propylene oxide, 80%.

In summary, organocatalysis was found to be an effective strategy that allowed for the enantioselective preparation of metabotropic glutamate receptor ligands (*S*)-AIDA and (*S*)-APICA in >99% ee. The synthetic route is general and should allow for the preparation of other analogues in optically pure form.[20] Importantly, the organocatalytic route can be readily scaled up, and either (*R*)- or (*S*)-products can be obtained using (*S*)- or (*R*)-proline, respectively, thus demonstrating the potential for organocatalysis in the preparation of other quaternary amino acids. With organocatalysis still in its infancy, its utility in the preparation of drugs and drug candidates has only recently become apparent;[3] further work in this area from our lab will be reported in due course.

Acknowledgment. This study was supported in part by the NIH (CA27489) and the Skaggs Institute for Chemical Biology.

Supporting Information Available: Full experimental details and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0512942

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(19) Hydrogenation of **13** over Ra−Ni gave the desired product in 65% yield.

(20) Preliminary results in our lab indicate that the tetrazole analogue can also be prepared via a similar synthetic route.

Organocatalytic Enantioselective Synthesis of Metabotropic Glutamate Receptor Ligands

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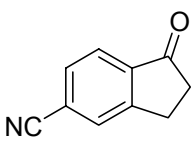
Supporting Information

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 an 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.

5-cyano-indanone (3). Prepared using a modified literature procedure.[1]

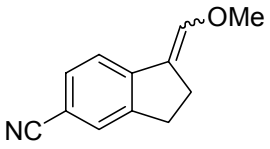


A dry 100 mL round bottom flask containing a magnetic stir bar was charged with copper cyanide (56 mmol, 5.1 g), 5-bromoindanone (47 mmol, 10 g), and DMF (40 mL). The round bottom flask was fitted with a condenser, placed under nitrogen and heated to 140 ºC for 16 hours. The reaction mixture was cooled to room temperature and diluted with 500 mL of dichloromethane. The solid was removed by vacuum filtration and the mother liquor washed with 2 × 150 mL saturated NH_4Ac and 150 mL brine. The organic layer was dried over $MgSO_4$, filtered and concentrated with silica and dry loaded onto an open faced silica column. Column was eluted with 500 mL of 30% ethyl acetate/hexane

[1] Matveeva, E. D.; Podrugina, T. A.; Morozkina, N. Y.; Zefirova, O. N.; Seregin, I. V.; Bachurin, S. O.; Pellicciari, R.; Zefirov, N. S. *Russ. J. Org. Chem.* **2002**, *38*, 1769-1774.

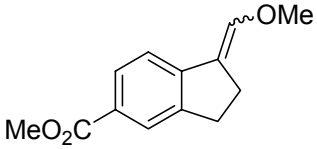
and 1000 mL of 40% ethyl acetate/hexane. Combined fractions were concentrated to yield 5.7 g of a pale yellow solid (37 mmol, 78% yield).

1-(methoxymethylene)-5-cyano-2,3-dihydro-1H-indene (4).



A suspension of methoxymethyl(triphenylphosphoniumchloride) (179 mmols, 62 g) in THF (250 mL) was cooled to -20 ^{o}C and ^{t}BuOK (149 mmols, 149 mL of 1.0 M solution in THF) was slowly added dropwise to give an orange solution. After 10 minutes a solution of **3** (74.4 mmols, 11.7 g) in THF (200 mL) was added dropwise and the mixture was stirred for 30 minutes and then was warmed to ambient temperature and stirred for an additional hour. The mixture was filtered through a fritted funnel and the filtrate concentrated *in vacuo.* The residue was precipitated with EtOAc/hexane (1:2, 150 mL) and filtered. The filtrate was concentrated and the residue purified by flash chromatography (5-20 % EtOAc in hexane gradient elution) to give **4** as a colorless oil which solidified at -20 ^{o}C. Yield: 90 %. NMR showed a 2:1 mixture of E and Z isomers. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.85 (d, J = 8.4 Hz, 0.34H), 7.43 (m, 1.3H), 7.37 (d, J = 8.0 Hz, 0.69H), 7.28 (d, J = 8.0 Hz 0.66H), 6.76 (t, J = 2.6 Hz, 0.69H), 6.29 (t, J = 1.89 Hz, 0.35H), 3.78 (s, 1.8H), 3.77 (s, 0.93H), 2.98 (m, 2H), 2.77 (m, 1.29H), 2.72 (m, 0.64H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.9, 145.8, 145.4, 144.8, 144.3, 143.1, 130.7, 130.6, 129.6, 128.6, 127.8, 125.1, 120.5, 119.9, 119.8, 118.6, 115.3, 108.9, 108.6. HRMS for $C_{12}H_{12}NO$ $[MH]^+$: calcd 186.0919, obsd 186.0916.

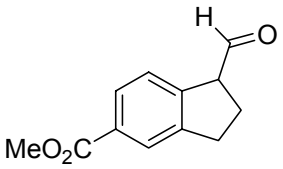
Methyl 1-(methoxymethylene)-2,3-dihydro-1H-indene-5-carboxylate (5). Cyano ether **4**



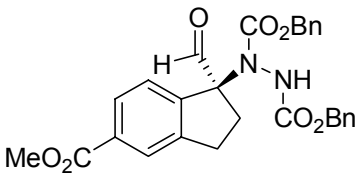
(24.3 mmols, 4.5284 g) dissolved in EtOH/H_2O (1:1, 100 mL) was treated with NaOH (121.5 mmols, 4.86 g) and heated to reflux for 4h. The reaction mixture was concentrated under vacuum, and the residue dissolved in ice H_2O (20 mL). The pH was carefully adjusted to pH 3 with conc. HCl. The aqueous layer was extracted with EtOAc (4 × 50 mL), dried over $MgSO_4$, filtered, and the filtrate concentrated *in vacuo*. The residue was dissolved in toluene/MeOH (1:2, 40 mL), cooled to 0 °C, and $TMSCHN_2$ (*ca*. 64 mmols, 32 mL of 2.0 M solution in diethyl ether) was added dropwise over 10 minutes. The solution was warmed to ambient temperature and stirred for 10

minutes and then quenched with AcOH (until bubbling subsided). The solvent was removed *in vacuo* and the residue subjected to flash chromatography (dry loaded, 10-25 % EtOAc in hexane gradient elution) to give **5** as a separable mixture (foam). Yield: 88 %. ^{1}H NMR ($CDCl_3$, 500 MHz), Z isomer: δ 7.83 (m, 3H), 6.20 (t, J = 1.8 Hz, 1H), 3.86 (s, 3H), 3.71 (s, 3H), 2.95 (m, 2H), 3.76 (dt, J_1 = 1.9 Hz, J_2 = 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.1, 145.2, 144.7, 143.2, 128.0, 127.5, 125.4, 124.1, 118.4, 60.2, 51.6, 30.0, 27.0. HRMS for $C_{13}H_{15}O_3$ $[MH]^+$: calcd 219.1016, obsd 219.1009.

Methyl 1-formyl-2,3-dihydro-1H-indene-5-carboxylate (6). Ether **5** (3.99 mmols, 0.8703 g) was dissolved in CH_2Cl_2 (20 mL) and cooled to -78 °C under argon. BBr_3 (8.0 mmols, 8 mL of 1.0 M solution in hexane) was added dropwise over 10 minutes and the mixture was stirred for 4 h. The mixture was carefully quenched with aqueous $NaHCO_3$ (30 mL, sat. solution) and allowed to reach ambient temperature. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was eluted through a plug of silica gel and the fractions were combined and concentrated *in vacuo* to give **6** as a foam. Yield: 94 %. The product was > 75 % pure by proton NMR and was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz), δ 9.69 (d, J = 2.1 Hz, 1H), 7.94 (m, 3H), 3.90 (s, 3H), 3.02 (m, 2H), 3.02 (m, 2H), 2.47 (m, 1H), 2.38 (m, 1H). HRMS for $C_{12}H_{13}O_3$ $[MH]^+$: calcd 205.0859, obsd 205.0854.

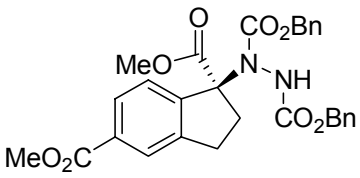


(S)-methyl 1-formyl-1-[1,2-hydrazinedicarboxylic acid-bis(phenylmethyl)ester]-2,3-dihydro-1H-indene-5-carboxylate (7). To a suspension of (*R*)- proline (0.4 mmols, 46.1 mg) in CH_3CN (5 mL) was added dibenzyldiazodicarboxylate (DBAD, 2 mmols, 0.597 g) and aldehyde **6** (2.8 mmols, 0.597 g). The reaction was carefully monitored by TLC (30 % EtOAc/hexane) and after consumption of DBAD (4 h) the reaction mixture was treated with sat. NH_4Cl (10 mL), extracted with EtOAc, dried over MgSO4, and filtered. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (10-30 %



EtOAc in hexane gradient elution) to give **7** as a foam. Yield: 96%. ^{1}H NMR ($CDCl_3$, 500 MHz), mixture of rotamers: δ 9.89-9.58 (m, 1H), 7.96-7.10 (m, 13H), 5.26-5.04 (m, 4H), 3.95 (s, 3H), 3.28-2.26 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 193.1, 166.1, 155.9, 141.6, 135.4, 135.2, 131.2, 128.5, 128.4, 120.3, 128.1, 127.8, 126.7, 125.5, 81.6, 68.8, 67.7, 60.3, 52.1, 31.4, 30.1. HRMS for $C_{28}H_{27}N_2O_7$ $[MH]^+$: calcd 503.1813, obsd 503.1813; $[\alpha]_D$ = + 15.75 ^{o} (c = 2.4, $CHCl_3$); HPLC (Daicel Chirapak AD, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm): t_R = 15.16 min (major), t_R = 24.58 min (minor), > 99 % ee.

(S)-methyl 1-formyl-1-[1,2-hydrazinedicarboxylic acid-bis(phenylmethyl)ester]-2,3-dihydro-1H-indene-5-carboxylate (8). Aldehyde **7** (2.2 mmols, 1.0934 g) was dissolved in



^{t}BuOH/H_2O (5:1, 44 mL) along with NaH_2PO_4 (4.4 mmols, 0.528 g) and 2-methyl-2butene (15.4 mmols, 7.7 mL of 2.0 M solution in THF). The solution was cooled to 4 ^{o}C and $NaClO_2$ (8.8 mmols, 0.796 g) was added. After 12 h reaction mixture was concentrated and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. The residue was dissolved in toluene:MeOH (1:2, 15 mL mL) and $TMSCHN_2$ (3 mL of 2.0 M solution in diethyl ether) was added dropwise until bubbling subsided. The excess $TMSCHN_2$ was quenched with a few drops of AcOH. The solvent was removed *in vacuo* and the residue purified by flash chromatography (10-30 % EtOAc in hexane gradient elution) to give 8 as a white foam. Yield: 82 %. ^{1}H NMR ($CDCl_3$, 500 MHz), mixture of rotamers: δ 7.88-7.00 (m, 13H), 5.16-4.86 (m, 4H), 3.89 (s, 3H), 3.60 (bs, 3H), 3.27-3.18 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.4, 166.7, 155.4, 146.6, 142.4, 135.4, 131.1, 128.4, 128.2, 128.0, 127.9, 127.6, 126.3, 126.1, 78.1, 68.4, 68.3, 68.2, 67.6, 67.5, 67.1, 60.3, 52.8, 52.1, 35.2, 35.1, 30.2, 30.0. HRMS for $C_{29}H_{29}N_2O_8$ $[MH]^+$: calcd 533.1918, obsd 533.1900; $[\alpha]_D$ = + 94.11^{o} (c = 1.26, $CHCl_3$).

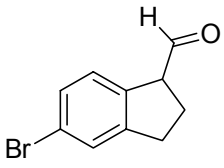
(S)-AIDA. Ester **8** (1.5 mmols, 0.8234 g) was dissolved in pyridine (10 mL) and heated at 40 °C for 15 h. The solution was cooled to 0 °C and trifluoroacetic anhydride (6 mmols, 1.26 g) was slowly added. The mixture was stirred at ambient temperature for 48 h and the solvent was removed *in vacuo*. The residue was dissolved in water and extracted with EtOAc, dried over $MgSO_4$, and filtered. The filtrate was eluted through a plug of silica gel and the fractions collected and concentrated *in vacuo*. The residue was dissolved in MeOH (10 mL) and argon was bubbled through the solution for 5 minutes. SmI_2 (40 mL of 0.1 M solution in THF) was carefully added under argon until the blue color persisted for more than 2 minutes and the solution was stirred for 30 minutes. The solvent was removed *in vacuo* and the residue was dissolved in NH_4Cl (sat.) and extracted with EtOAc. The organic layers were dried over $MgSO_4$ and filtered through a plug of celite. The filtrate was concentrated *in vacuo* to give an orange foam that was dissolved in 6 M HCl (10 mL) and heated to reflux for 48 h. The solvent was removed *in vacuo* and the residue was dissolved in EtOH (10 mL) and propylene oxide (2 mL). The mixture was heated to 60 °C for 30 minutes and then concentrated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$:MeOH:AcOH, 5:3:1) to give a yellow glass. Yield: 70 % over 4 steps. NMR was in accordance with the literature.[2] ^{1}H NMR (D_2O, 500 MHz) δ 8.03 (s, 1H), 7.97 (d, J = 5.6 Hz, 1H), 7.53 (d, J = 5.9 Hz, 1H), 3.27 (m, 2H), 2.94 (m, 1H), 2.48 (m, 1H); HRMS for $C_{11}H_{12}NO_4$ $[MH]^+$: calcd 222.0761, obsd 222.0767; $[\alpha]_D$ = + 86.1 ° (c = 0.44, 6 M HCl), lit. + 86.3 ° (c = 0.8, 6 M HCl).[2]

5-bromo-1-(methoxymethylene)-2,3-dihydro-1H-indene (9) A suspension of methoxymethyl(triphenylphosphoniumchloride) (110 mmols, 37.8 g) in THF (250 mL) was cooled to -20 °C and ^{t}BuOK (90 mmols, 90 mL of 1.0 M solution in THF) was slowly added dropwise to give an orange solution. After 10 minutes a solution of **2** (45 mmols, 9.498 g) in THF (200 mL) was added dropwise and the mixture was stirred for 30 minutes and then was warmed to ambient temperature and stirred for an additional hour. The mixture was filtered through a fritted funnel and the filtrate concentrated *in vacuo.* The residue was precipitated with EtOAc/hexane (1:2,

150 mL) and filtered. The filtrate was concentrated and the residue purified by flash chromatography (0-5 % EtOAc in hexane gradient elution) to give **9** as a yellow oil which solidified at -20 °C. Yield: 95 %. Gave a 2:1 mixture of E and Z isomers**.**

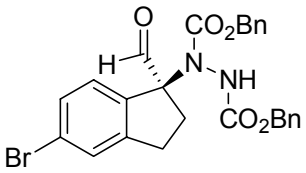
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.66 (d, J = 8.2 Hz, 0.41H), 7.31 (m, 1.6H), 7.21 (dd, J_1 = 1.8 Hz, J_2 = 8.1 Hz, 0.61H), 7.10 (d, J = 8.2, Hz, 0.64H), 6.63 (t, J = 2.6 Hz, 0.66H), 6.18 (t, J = 1.83, 0.3H), 3.73 (s, 3H), 2.94 (m, 2H), 2.75 (m, 1H), 2.68, (dt, J_1 = 1.8 Hz, J_2 = 7.5 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.6, 147.0, 141.6, 140.4, 139.5, 139.1, 133.8, 133.6, 129.4, 129.3, 128.7, 128.5, 128.4, 128.2, 127.6, 126.1, 120.7, 119.8, 119.5, 119.2, 60.3, 60.2, 30.4, 30.2, 27.2, 26.0. HRMS for $C_{11}H_{12}BrO$ $[MH]^+$: calcd 239.0066, obsd 239.0071.

Methyl 1-formyl-2,3-dihydro-1H-indene-5-carboxylate (10). Ether **9** (21.49 mmols, 5.14 g) was dissolved in CH_2Cl_2 (100 mL) and cooled to -78 °C under argon. BBr_3 (50 mmols, 50 mL of 1.0 M solution in hexane) was added dropwise over 10 minutes and the mixture was stirred for 4 h. The mixture was carefully poured into an ice-slurry of aqueous $NaHCO_3$ (200 mL, sat. solution), stirred vigorously and allowed to reach ambient temperature. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the residue quickly subjected to flash chromatography (1-10% EtOAc in hexane gradient elution) to give 10 as a foam. Yield: 3.87 g, 80 %. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.65 (d, J = 2.4 Hz, 1H), 7.427 (s, 2H), 7.35 (d, J = 8.0 Hz, 1H), 7.17 (d, J = 8.0 Hz 1H), 3.89 (t, J = 6.2 Hz, 1H), 3.01 (m, 2H), 2.45 (m, 1H), 2.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.9, 147.0, 137.4, 129.8, 128.3, 126.3, 122.0, 57.2, 31.5, 25.6. HRMS for $C_{10}H_{10}BrO$ $[MH]^+$: calcd 224.9915, obsd 224.9911.



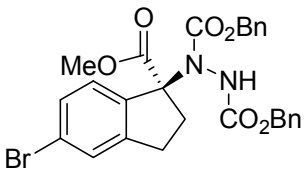
[2] Ma, D.; Tian, H.; Zou, G. *J. Org. Chem.* **1999,** *64,* 120-125.

(S)-methyl 1-formyl-1-[1,2-hydrazinedicarboxylic acid-bis(phenylmethyl)ester]-2,3-dihydro-1H-indene-5-carboxylate (11). To a suspension of (R)-proline (2.6 mmols, 0.3 g) in



CH_3CN (30 mL) was added dibenzyldiazodicarboxylate (DBAD, 10.3 mmols, 3.07 g) and aldehyde **9** (15.4 mmols, 3.465 g). The reaction was carefully monitored by TLC (30 % EtOAc/hexane) and after consumption of DBAD (4 h) the reaction mixture was concentrated to ca. 10 mL, treated with sat. NH_4Cl (10 mL), extracted with EtOAc, dried over $MgSO_4$, and filtered. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (10-40 % EtOAc in hexane gradient elution) to give **11** as a foam. Yield: 4.04 g, 75 %. ^{1}H NMR ($CDCl_3$, 500 MHz) mixture of rotamers, δ 9.78 – 9.47 (m, 2H), 7.39 – 7.01 (m, 13H), 5.21 – 5.01 (m, 4H), 3.11 – 2.71(m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 193.4, 192.8, 171.2, 155.78, 148.1, 136.1, 135.45, 135.3, 134.75, 129.8, 128.7, 128.3, 128.2, 127.8, 127.6, 127.0, 126.7, 123.8, , 81.3, 68.6, 67.9, 67.5, 60.3, 31.3, 30.1; HRMS for $C_{26}H_{24}BrN_2O_5$ $[MH]^+$: calcd 523.0863, obsd 523.0871. $[\alpha]_D$ = + 20.90 ^{o} (c = 2.45, $CHCl_3$); HPLC (Daicel Chirapak OD-H, hexane/isopropanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm): t_R = 23.48 min (minor), t_R = 29.19 min (major), > 99 % ee.

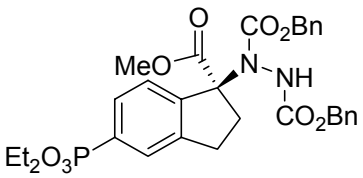
(S)-methyl 1-formyl-1-[1,2-hydrazinedicarboxylic acid-bis(phenylmethyl)ester]-2,3-dihydro-1H-indene-5-carboxylate (12). Aldehyde **11** (3.4 g, 6.5 mmols) was dissolved in



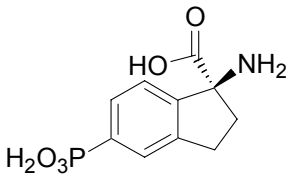
^{t}BuOH/H_2O (5:1, 120 mL) along with NaH_2PO_4 (13 mmols, 1.56 g) and 2-methyl-2butene (46 mmols, 23 mL of 2.0 M solution in THF). The solution was cooled to 4 deg and $NaClO_2$ (26 mmols, 2.35 g) was added. After 12 h the reaction mixture was concentrated and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. The residue was dissolved in toluene:MeOH (30 mL, 1:2) and $TMSCHN_2$ (13 mmols, 6.5 mL of 2.0 M solution in ether) was added slowly. The reaction mixture was quenched with AcOH (ca. 0.5 mL) until bubbling subsided. The solvent was removed *in vacuo* and the residue purified by flash chromatography (10-40 % EtOAc in hexane gradient elution) to give 12 as a colorless foam. Yield: 2.906 g, 81 % over two steps. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.47 – 7.14

(m, 13H), 5.26 – 4.96 (m, 4H), 3.70 (s, 3H), 3.33 – 2.82 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.7, 171.1, 155.5, 148.8, 136.8, 135.5, 129.5, 128.5, 128.3, 128.2, 128.0, 127.7, 123.9, 77.9, 68.4, 68.3, 67.3, 60.4, 52.9, 35.3, 30.3, 30.1; HRMS for $C_{27}H_{26}BrN_2O_6$ $[MH]^+$: calcd 553.0969, obsd 553.0968; $[\alpha]_D$ = + 49.48 ^{o} (c = 2.45, $CHCl_3$).

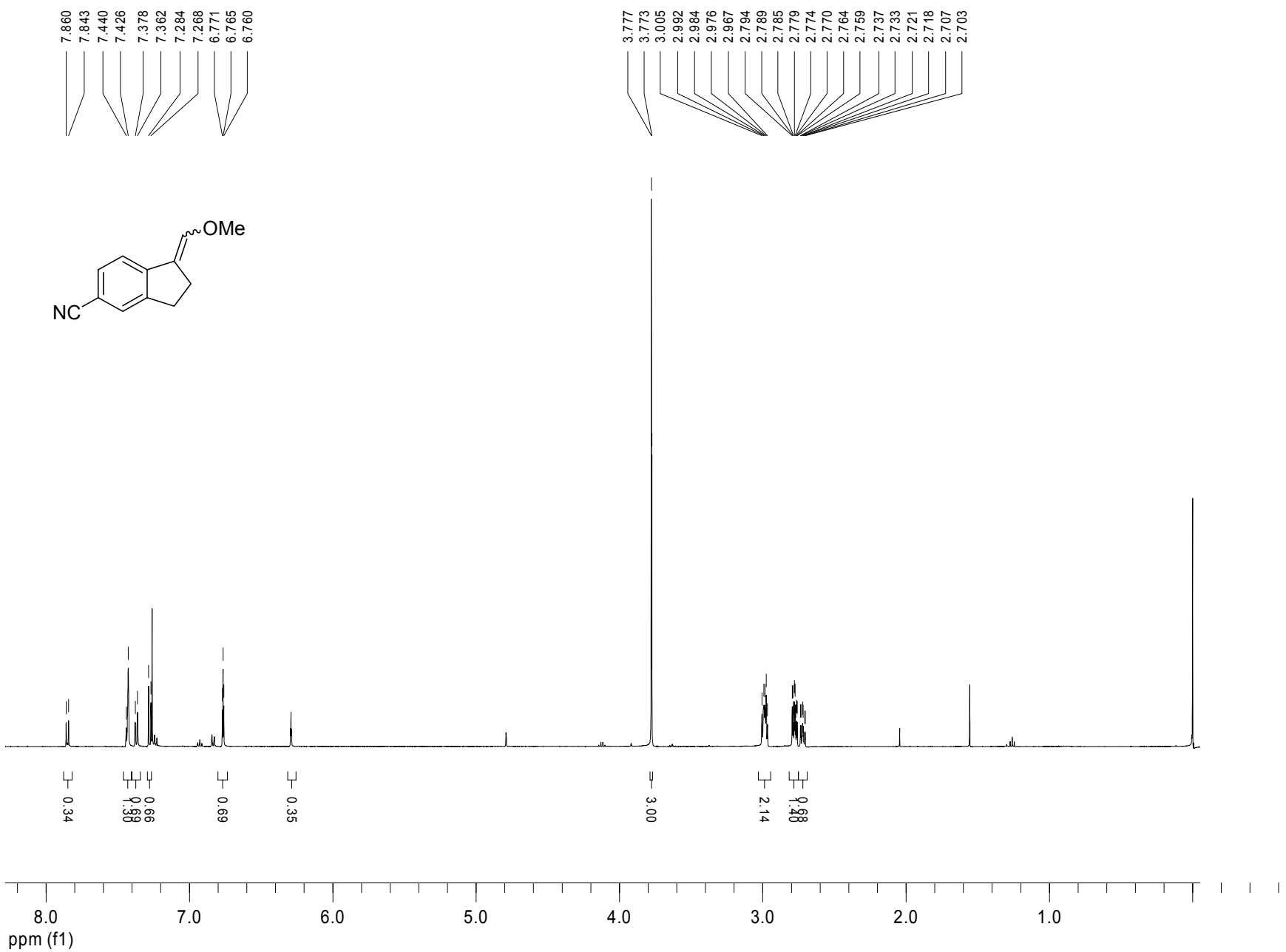
(S)-methyl 1-formyl-1-[1,2-hydrazinedicarboxylic acid-bis(phenylmethyl)ester]-2,3-dihydro-1H-indene-5-carboxylate (13). In a pressure tube, ester **12** (2.419 g, 4.37 mmols) was dissolved in toluene (10 mL) along with diethyl phosphite (22 mmols, 2.81 mL), $Pd(PPh_3)_4$ (0.437 mmols, 0.505 g), and triethylamine (22, 3.1 mL). The mixture was degassed with argon for 2 minutes, the tube was sealed, and the mixture heated to 115 °C for 72 h. The solvent was removed *in vacuo* and the residue purified by flash chromatography (30-80 % EtOAc in hexane gradient elution) to give **13** as a colorless foam. Yield: 1.966 g, 74 %. Starting material was also recovered (0.1 g); yield based on recovered staring material: 77 %. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.69 – 7.07 (m, 13H), 5.16 – 4.79 (m, 4H), 4.13 – 4.02 (m, 4H), 3.61 (bs, 3H), 3.23 – 2.84 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.3, 155.7, 155.4, 146.5, 142.2, 135.4, 132.0, 131.9, 131.8, 129.7, 129.6, 128.7, 128.4, 128.1, 127.9, 127.6, 126.6, 78.2, 68.4, 67.3, 62.1, 52.8, 35.1, 30.4; ^{31}P ($CDCl_3$) δ 29.7, 19.4; HRMS for $C_{31}H_{36}N_2O_9P$ $[MH]^+$: calcd 611.2153, obsd 611.2139; $[\alpha]_D$ = + 44.21 ^{o} (c = 2.98, $CHCl_3$).



(S)-APICA. Ester **13** (2.9 mmols, 1.76 g) was dissolved in pyridine (20 mL) and heated at 40 ^{o}C for 15 h. The solution was cooled to 0 ^{o}C and trifluoroacetic acid (11.6 mmols, 2.44 g) was slowly added. The mixture was stirred at ambient temperature for 48 h and the solvent was removed *in vacuo*. The residue was dissolved in water and extracted with EtOAc, dried over $MgSO_4$, and filtered. The filtrate was eluted through a plug of silica gel and the fractions collected and concentrated *in vacuo*. The residue was dissolved in MeOH (20 mL) and argon was bubbled through the solution for 5 minutes. SmI_2 (80 mL of 0.1 M solution in THF) was carefully added under argon until the blue color persisted for more than 2 minutes and the



solution was stirred for 30 minutes. The solvent was removed *in vacuo* and the residue was dissolved in NH_4Cl (sat.) and extracted with EtOAc. The organic layers were dried over $MgSO_4$ and filtered through a plug of celite. The filtrate was concentrated *in vacuo* to give an orange foam that was dissolved in 6 M HCl (20 mL) and heated to reflux for 48 h. The solvent was removed *in vacuo* and the residue was dissolved in EtOH (20 mL) and propylene oxide (2 mL). The mixture was heated to 60 ^{o}C for 30 minutes and then cooled. The precipitate was collected and washed with EtOH to give a yellow powder. Yield: 80 % over 4 steps. NMR was in accordance with the literature.[2] ^{1}H NMR (D_2O, 500 MHz) δ 7.72 (d, J = 12.7 Hz, 1H), 7.67 (m, 1H), 7.43 (d, J = 7.0 Hz, 1H), 3.22 (m, 2H), 2.82 (dt, J_1 = 7.4 Hz, J_2 = 14.4 Hz, 1H), 2.41 (dt, J_1 = 6.7 Hz, J_2 = 13.8 Hz, 1H); ^{13}C NMR (D_2O, 125 MHz) δ 33.2, 38.0, 72.8, 125.9, 126.0, 130.1, 132.3, 139.0, 140.7, 144.9, 147.7, 178.7; ^{31}P (D_2O) δ 6.0; HRMS for $C_{10}H_{13}NO_5P$ $[MH]^+$: calcd 258.0526, obsd 258.0516; $[\alpha]_D$ = + 65.7 ^{o} (c = 1.7, 6 M HCl), lit. + 66.8 ^{o} (c = 1.7, 6 M HCl).[2]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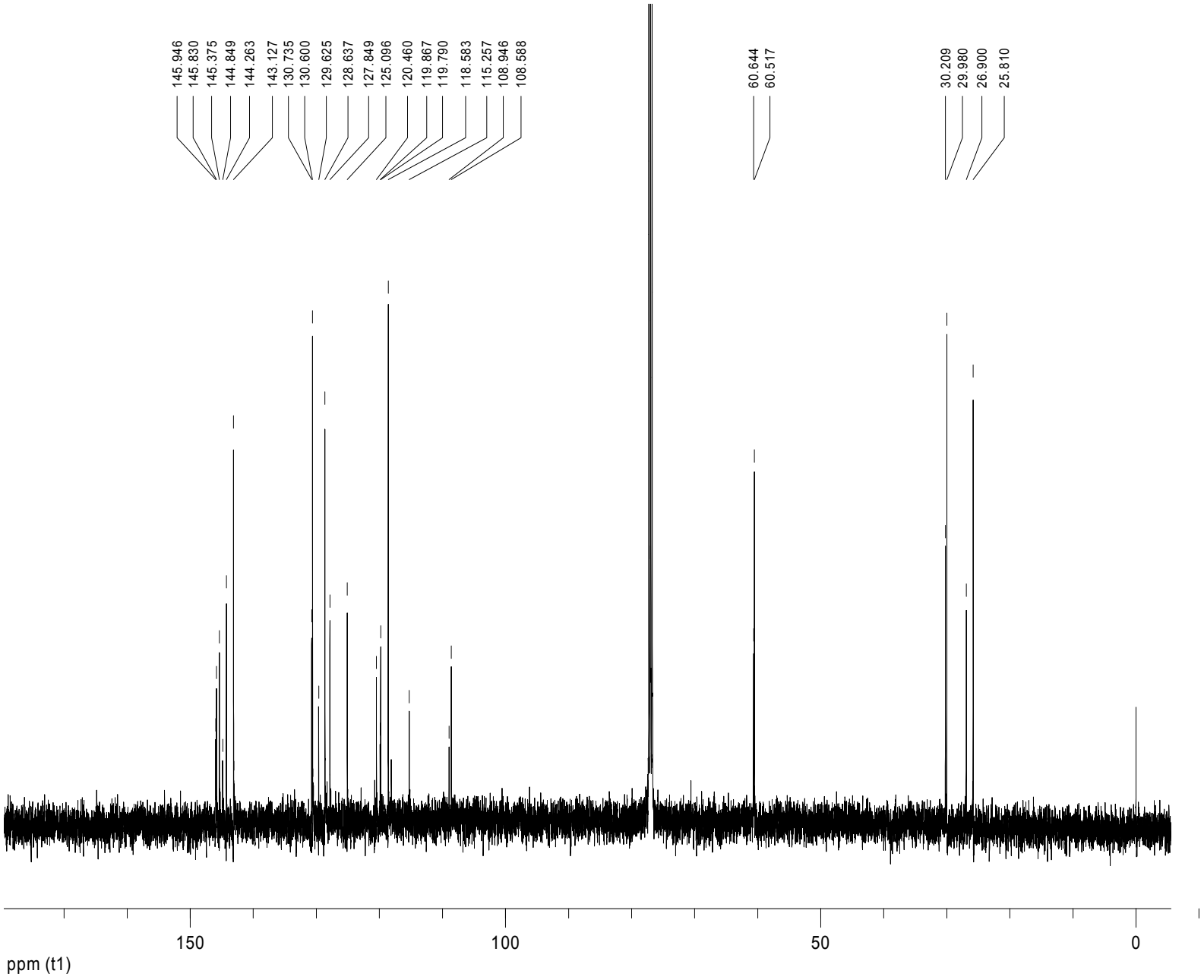
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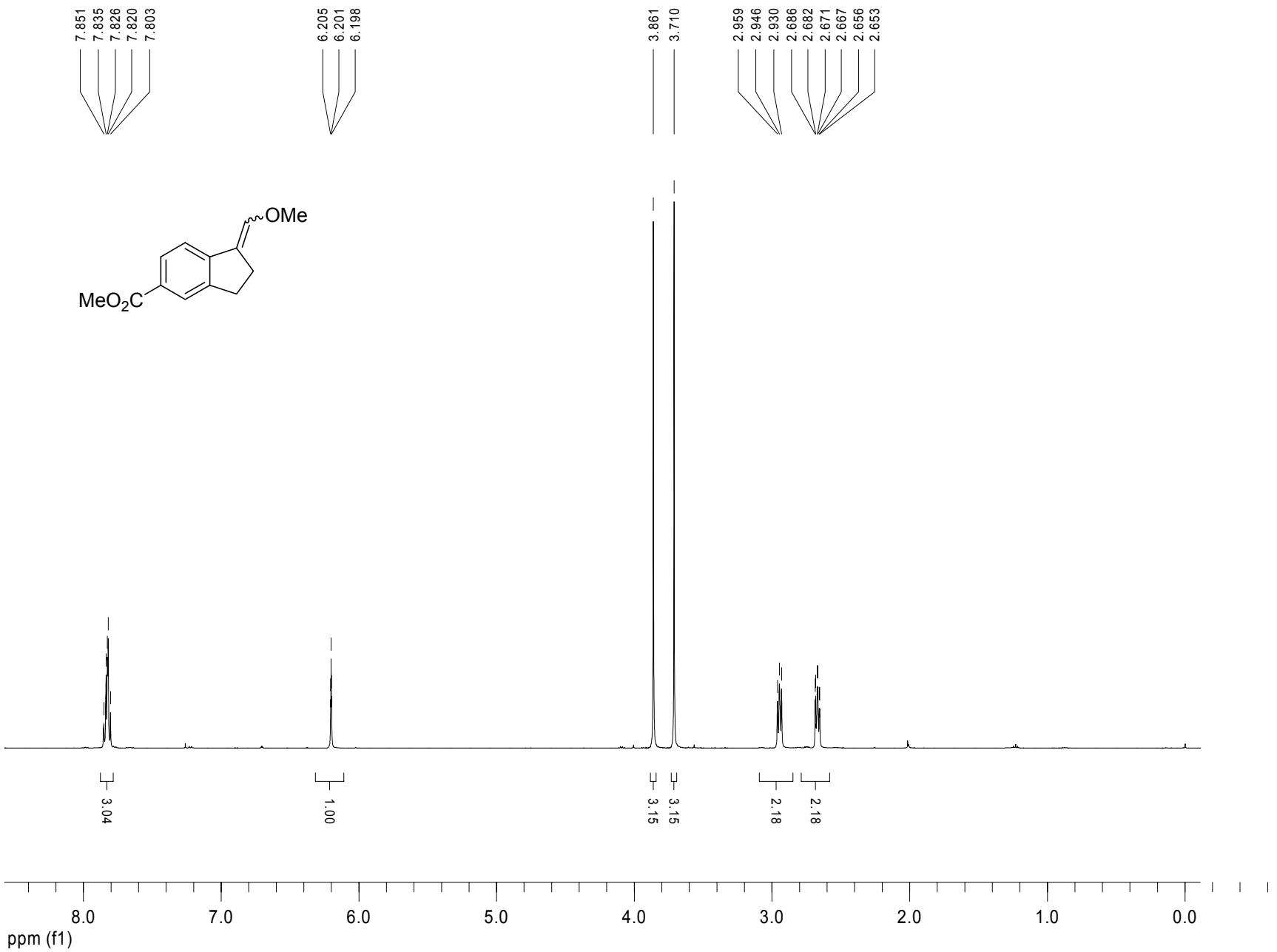
ppm (t1)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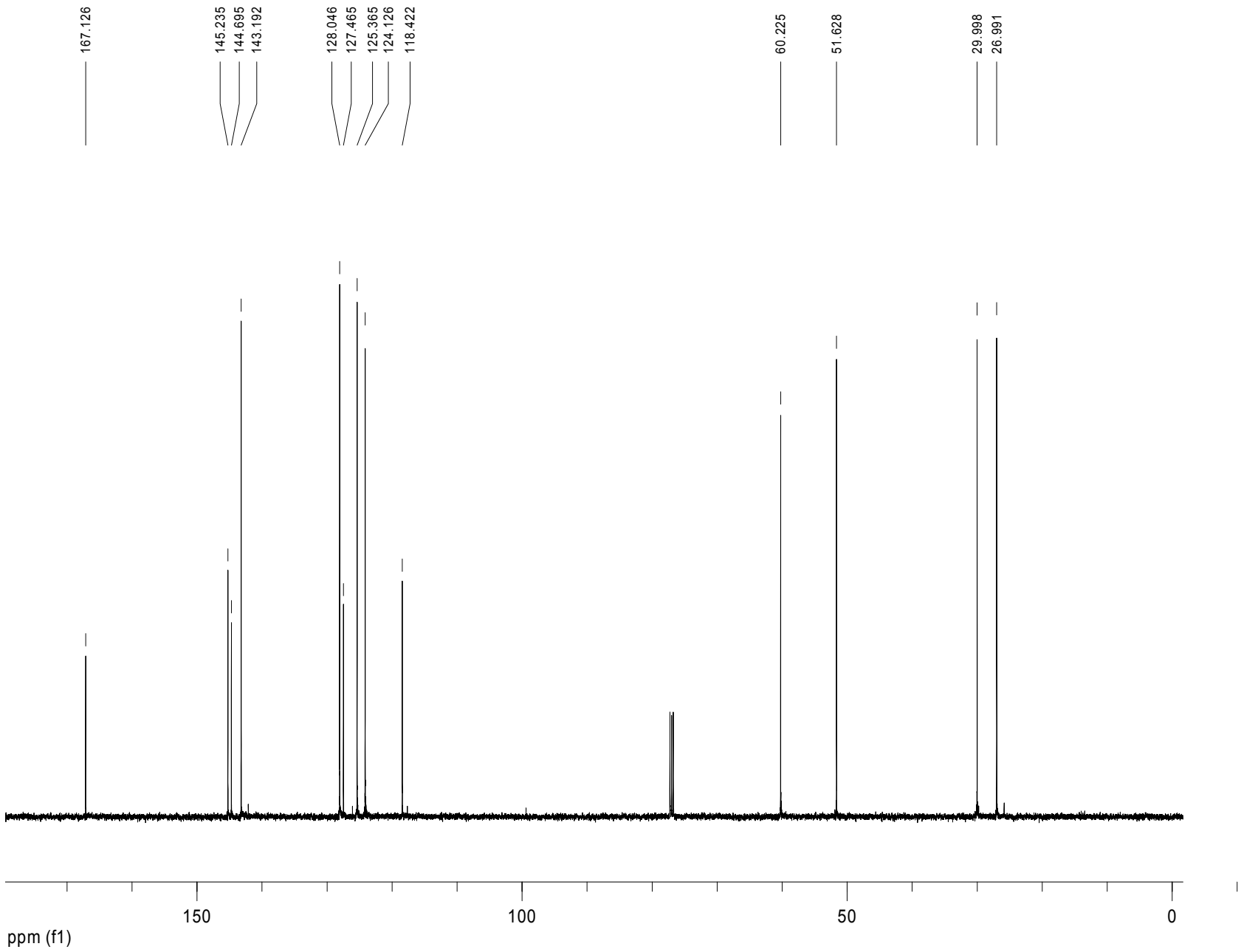
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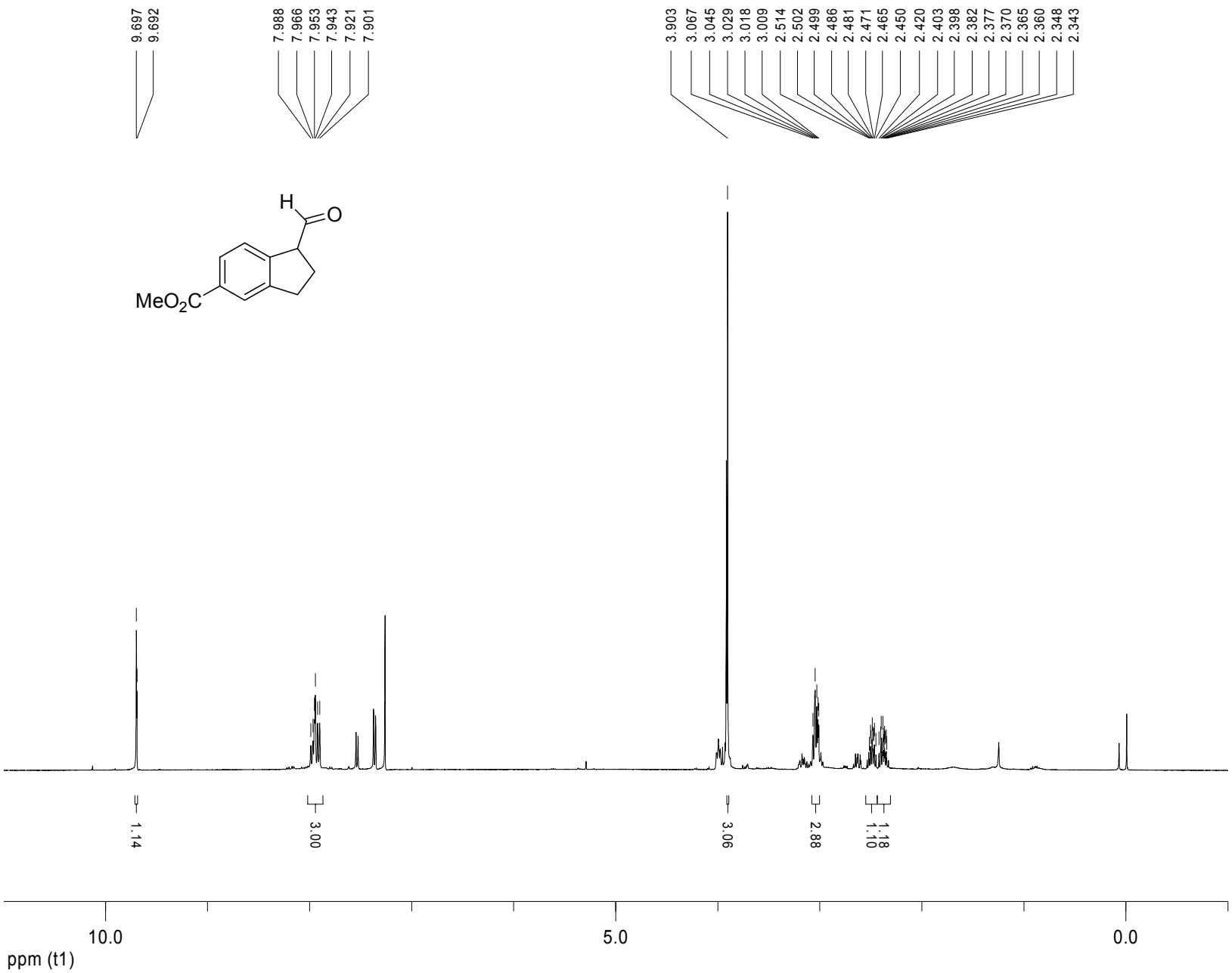
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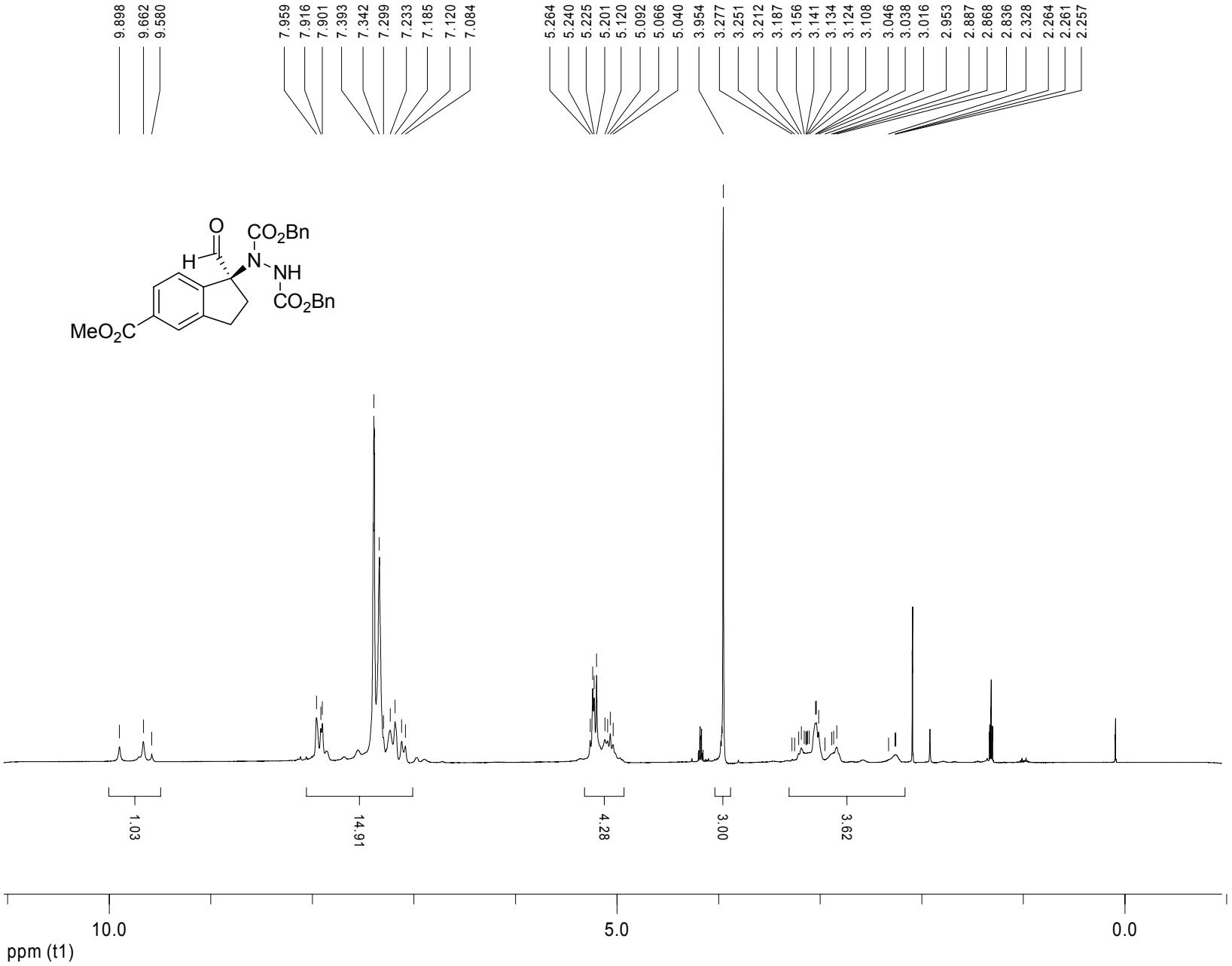
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3.156
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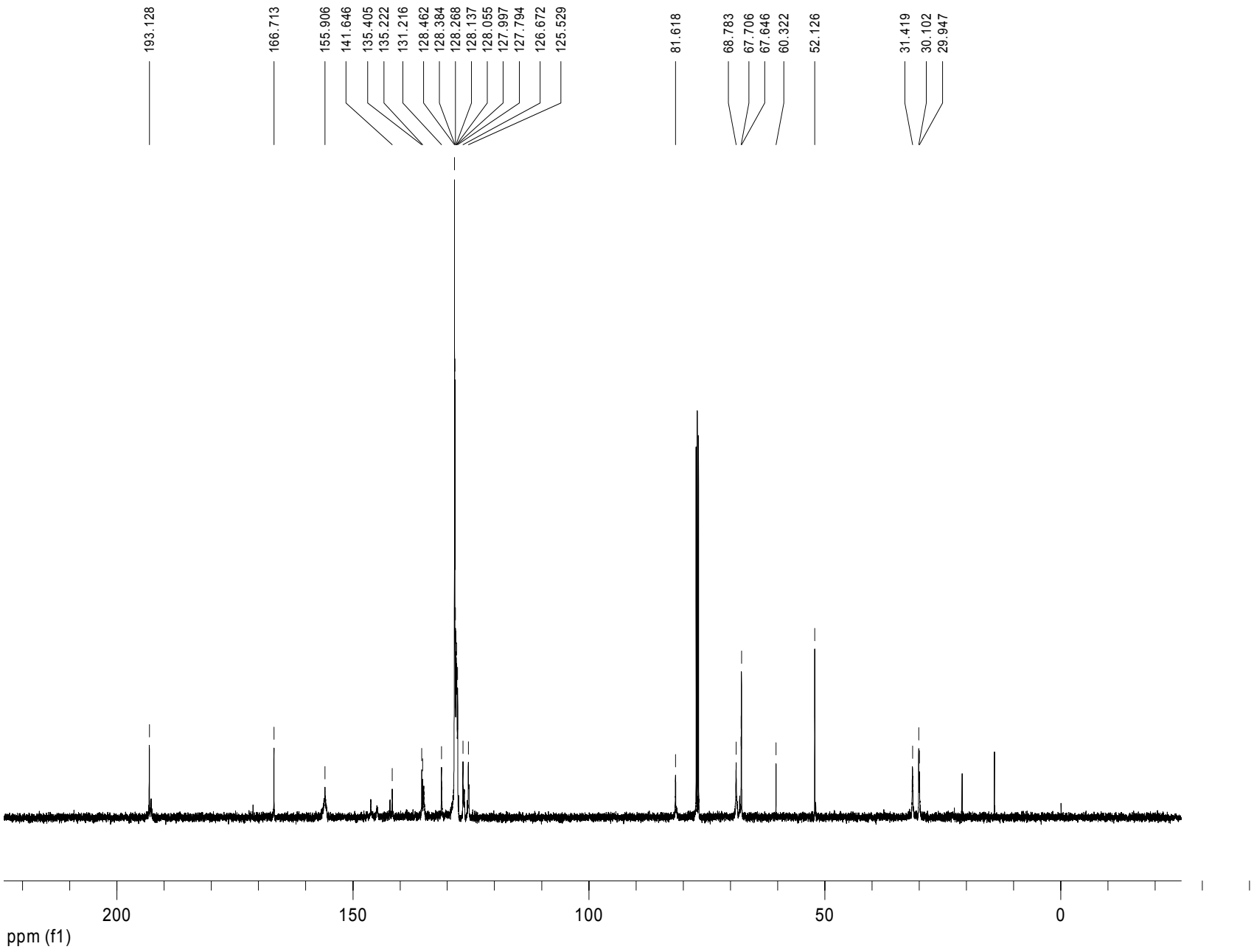
ppm (t1)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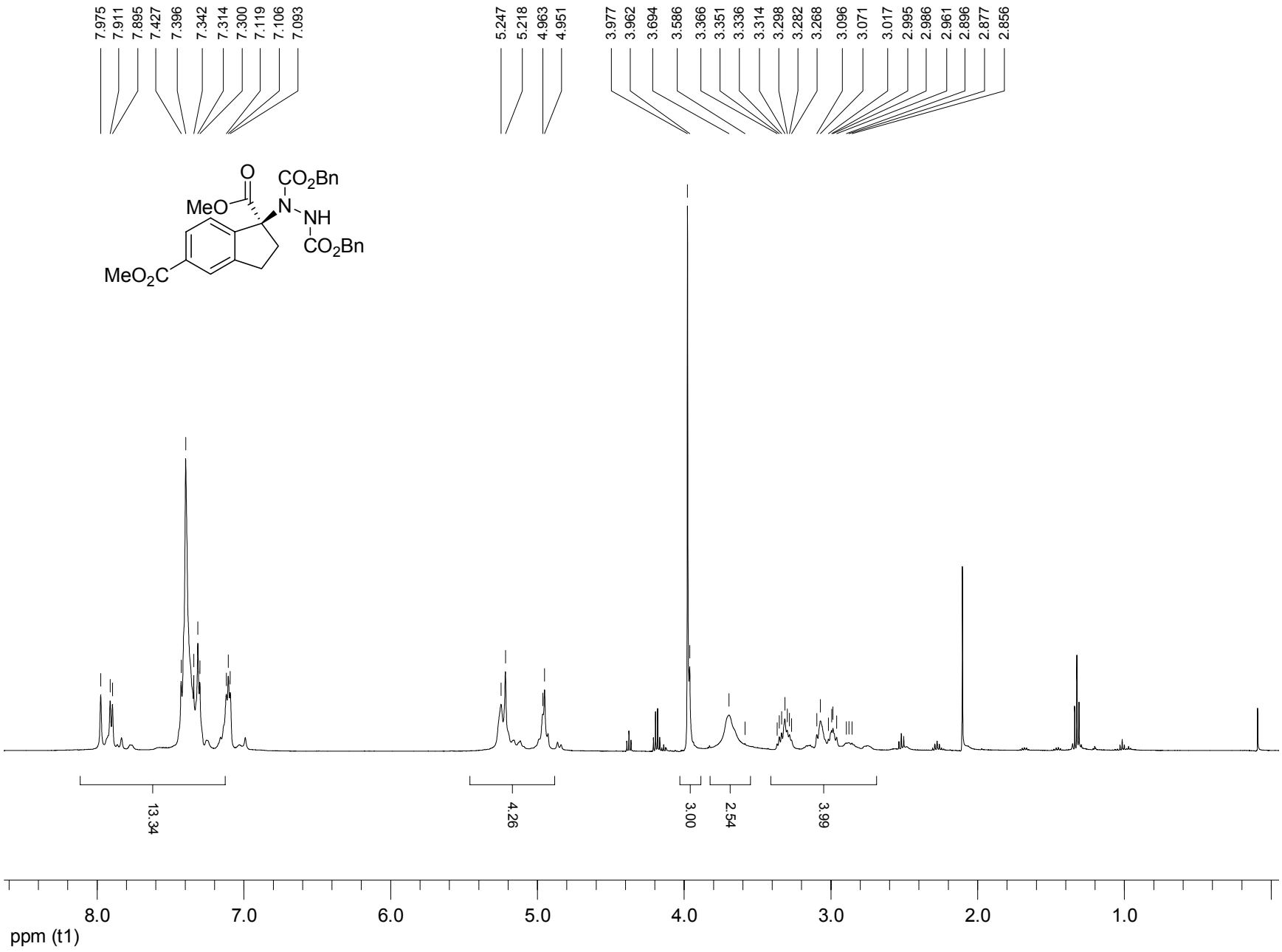
166.713
155.906
141.646
135.405
135.222
131.216
128.462
128.384
128.268
128.137
128.055
127.997
127.794
126.672
125.529
81.618
68.783
67.706
67.646
60.322
52.126
31.419
30.102
29.947
200
150
100
50
0
ppm (f1)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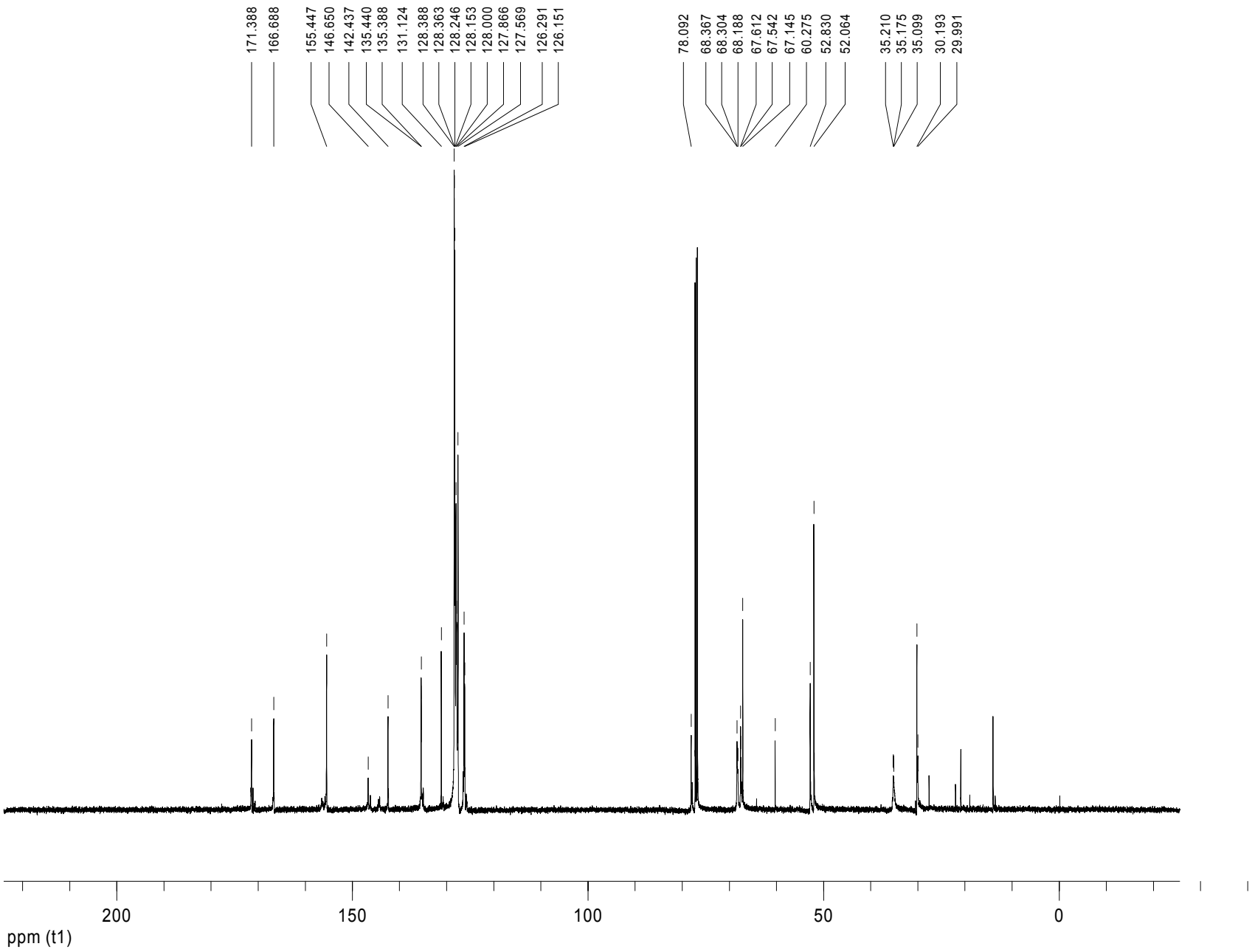
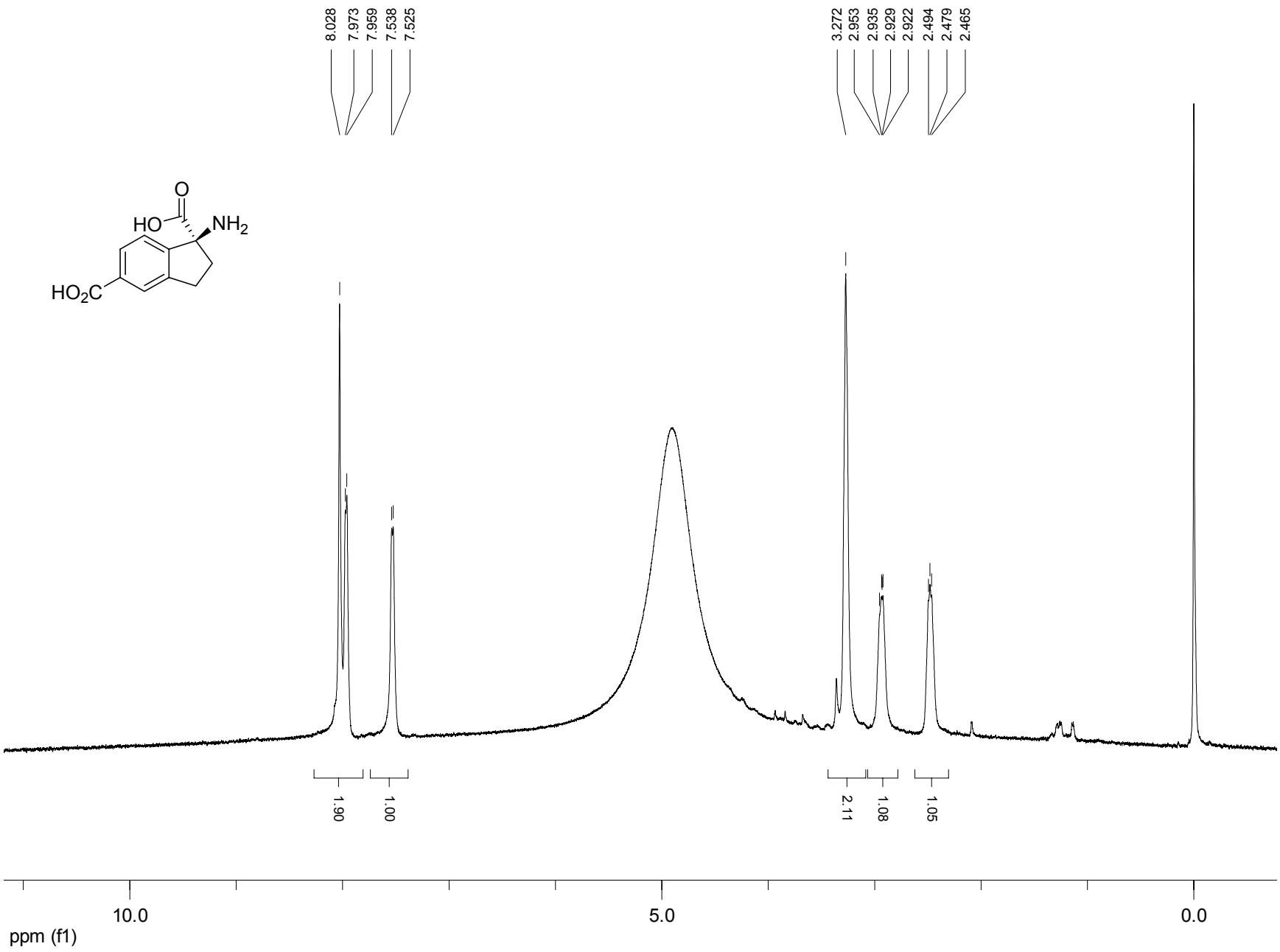
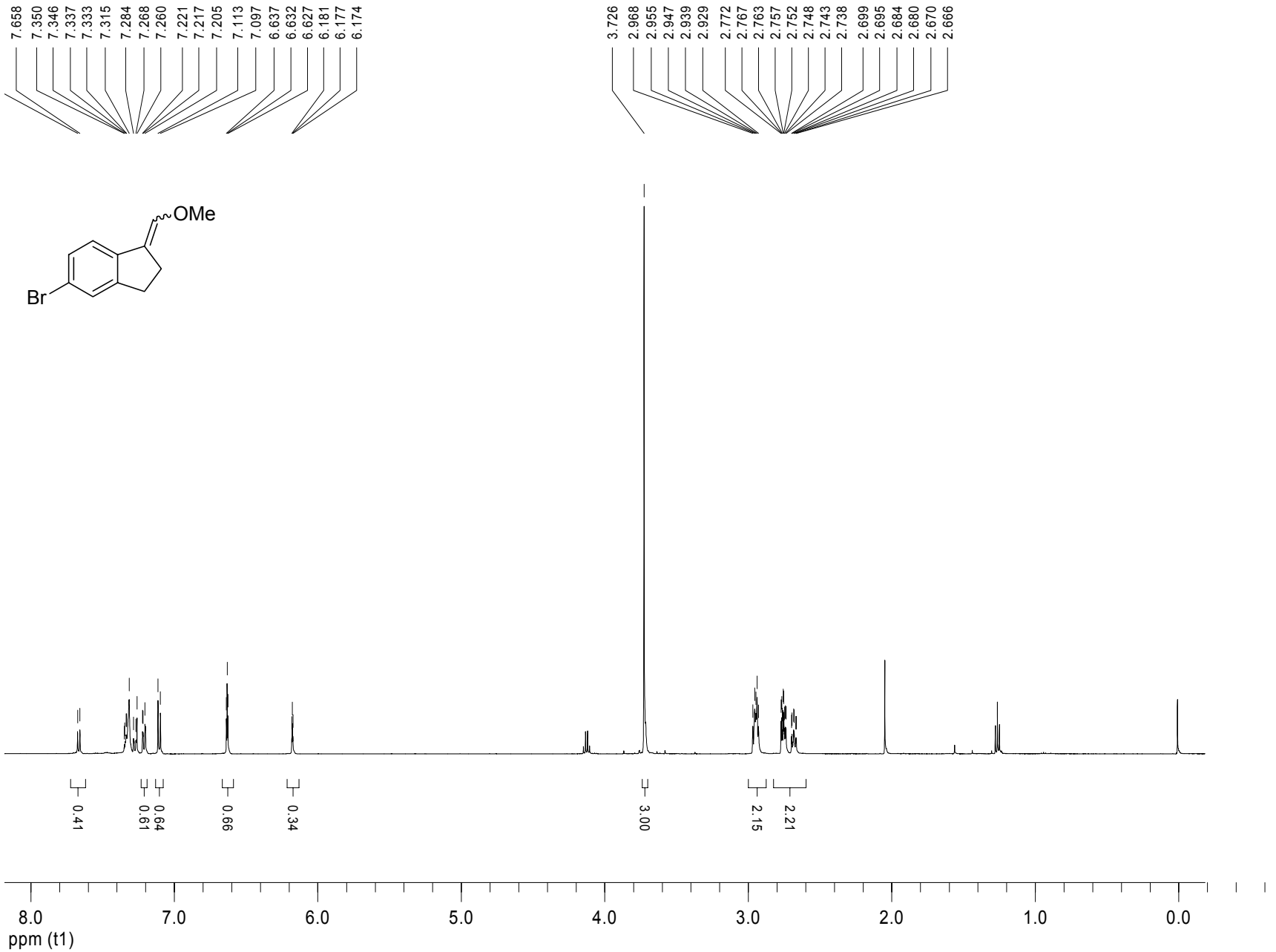
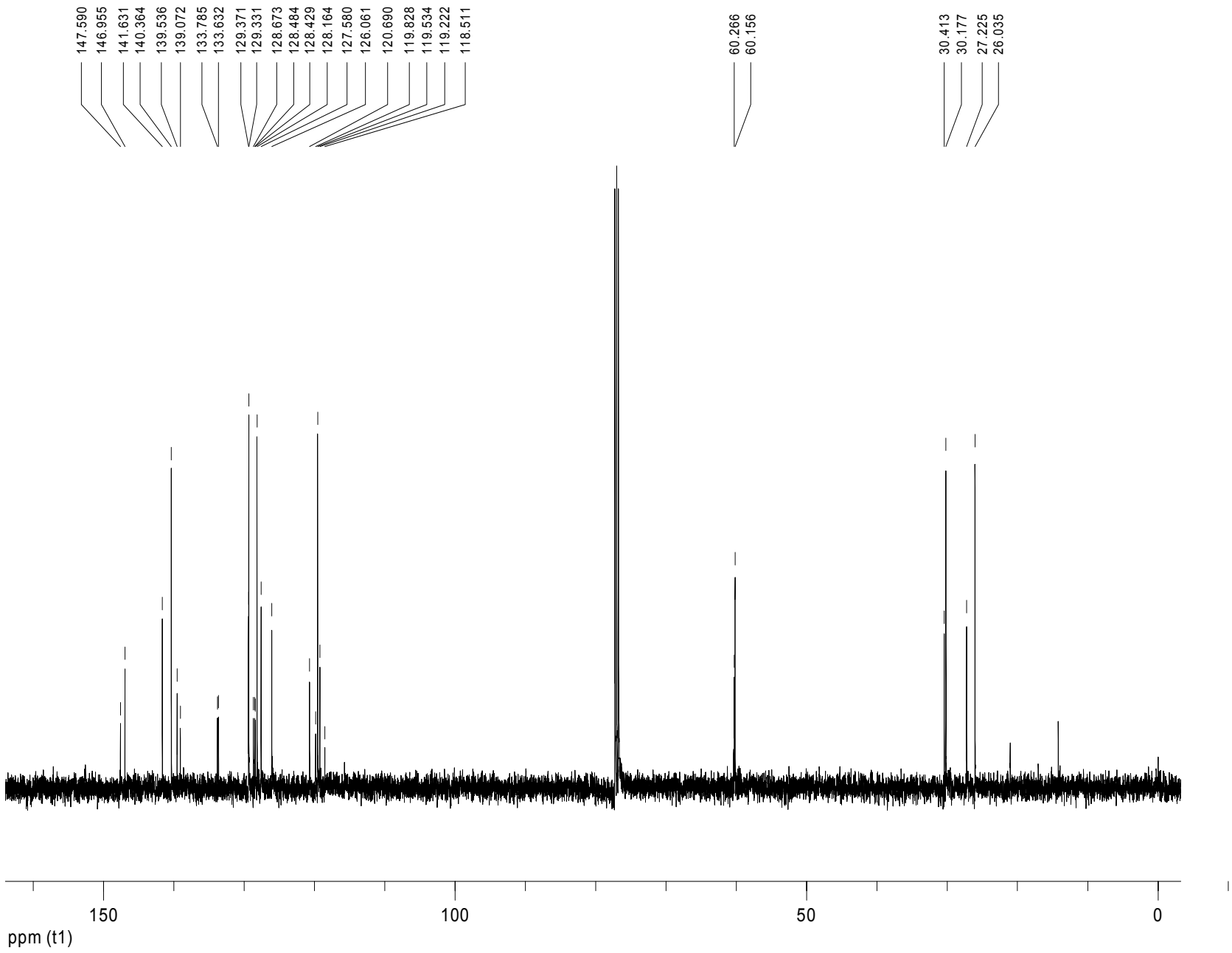
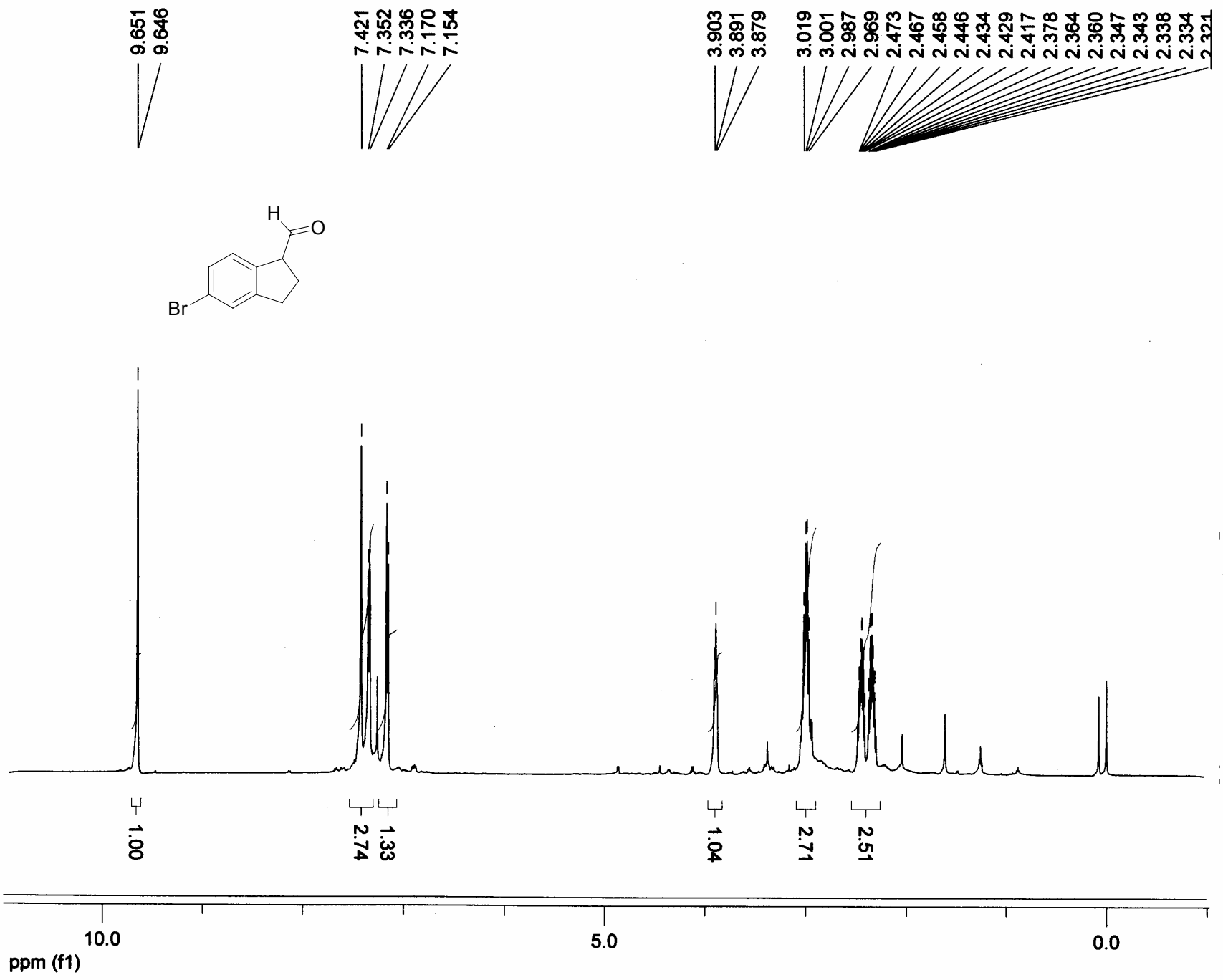
7.911
7.895
7.427
7.396
7.342
7.314
7.300
7.119
7.106
7.093
5.247
5.218
4.963
4.951
3.977
3.962
3.694
3.586
3.366
3.351
3.336
3.314
3.298
3.282
3.268
3.096
3.071
3.017
2.995
2.986
2.961
2.896
2.877
2.856
O
CO2Bn
MeO
N
NH
CO2Bn
MeO2C
13.34
4.26
3.00
2.54
3.99
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

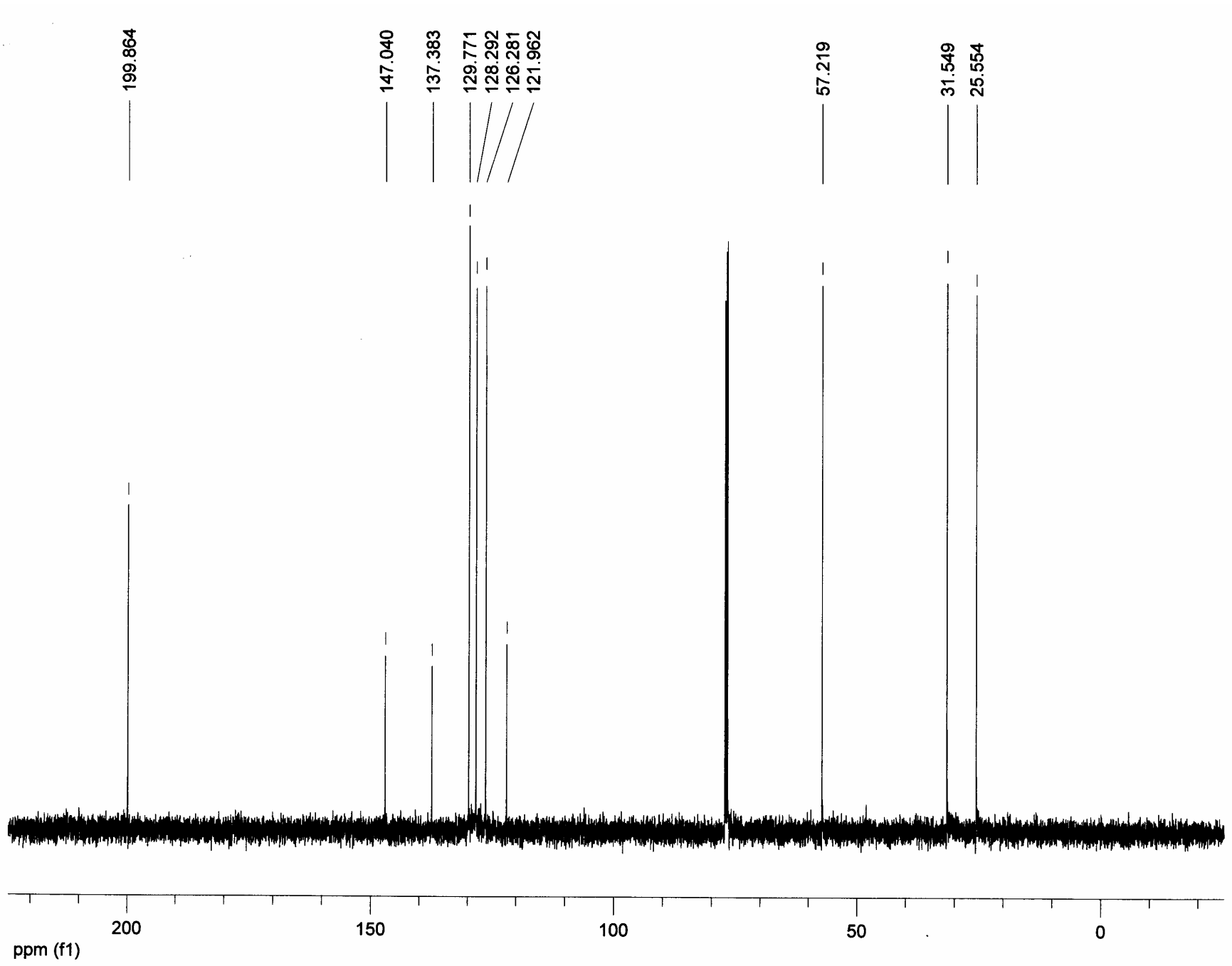

171.388
166.688
155.447
146.650
142.437
135.440
135.388
131.124
128.388
128.363
128.246
128.153
128.000
127.866
127.569
126.291
126.151
78.092
68.367
68.304
68.188
67.612
67.542
67.145
60.275
52.830
52.064
35.210
35.175
35.099
30.193
29.991
200
150
100
50
0
ppm (t1)

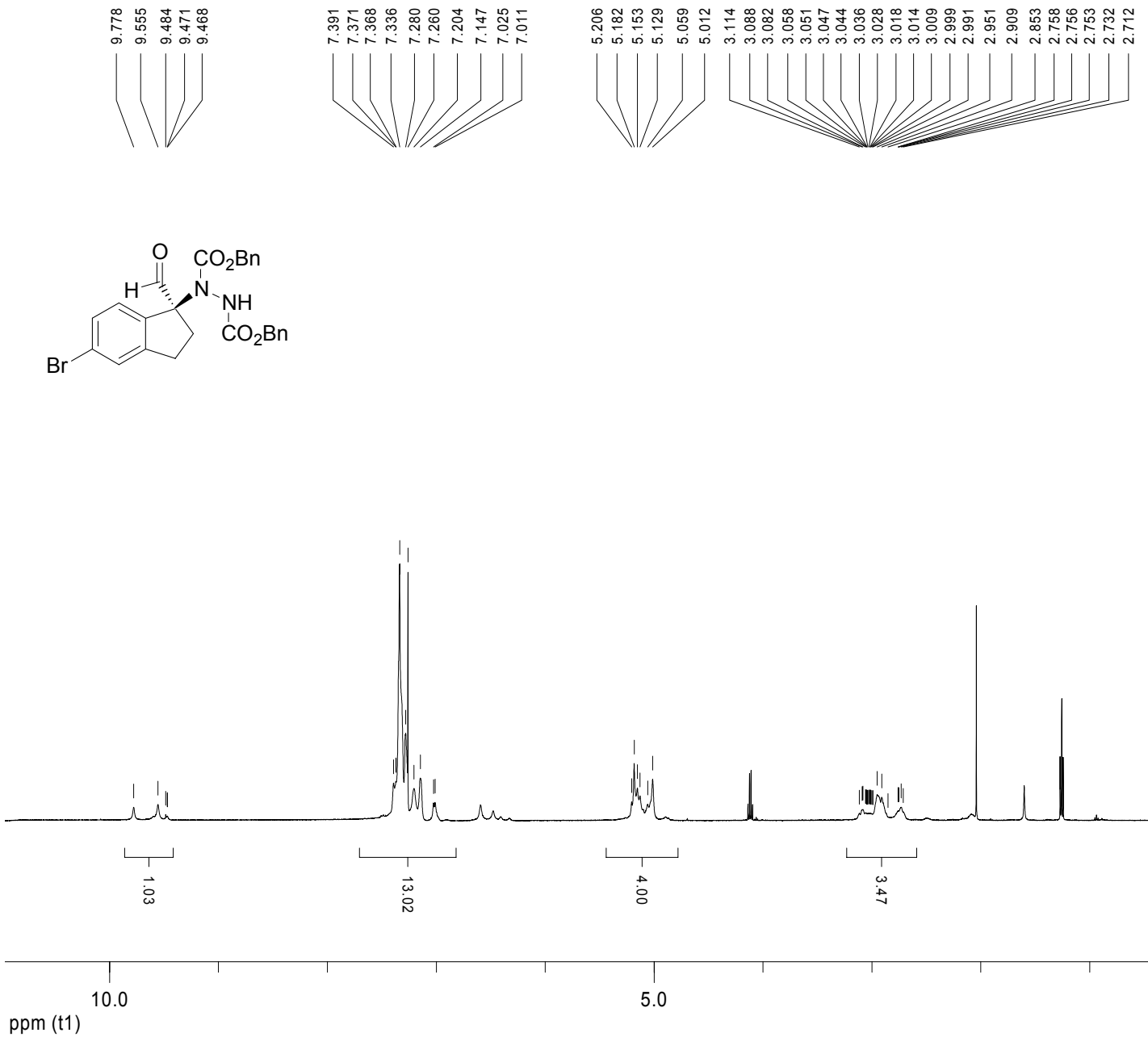

8.028
7.973
7.959
7.538
7.525
3.272
2.953
2.935
2.929
2.922
2.494
2.479
2.465
HO
O
NH2
HO2C
1.90
1.00
2.11
1.08
1.05
10.0
5.0
0.0
ppm (f1)

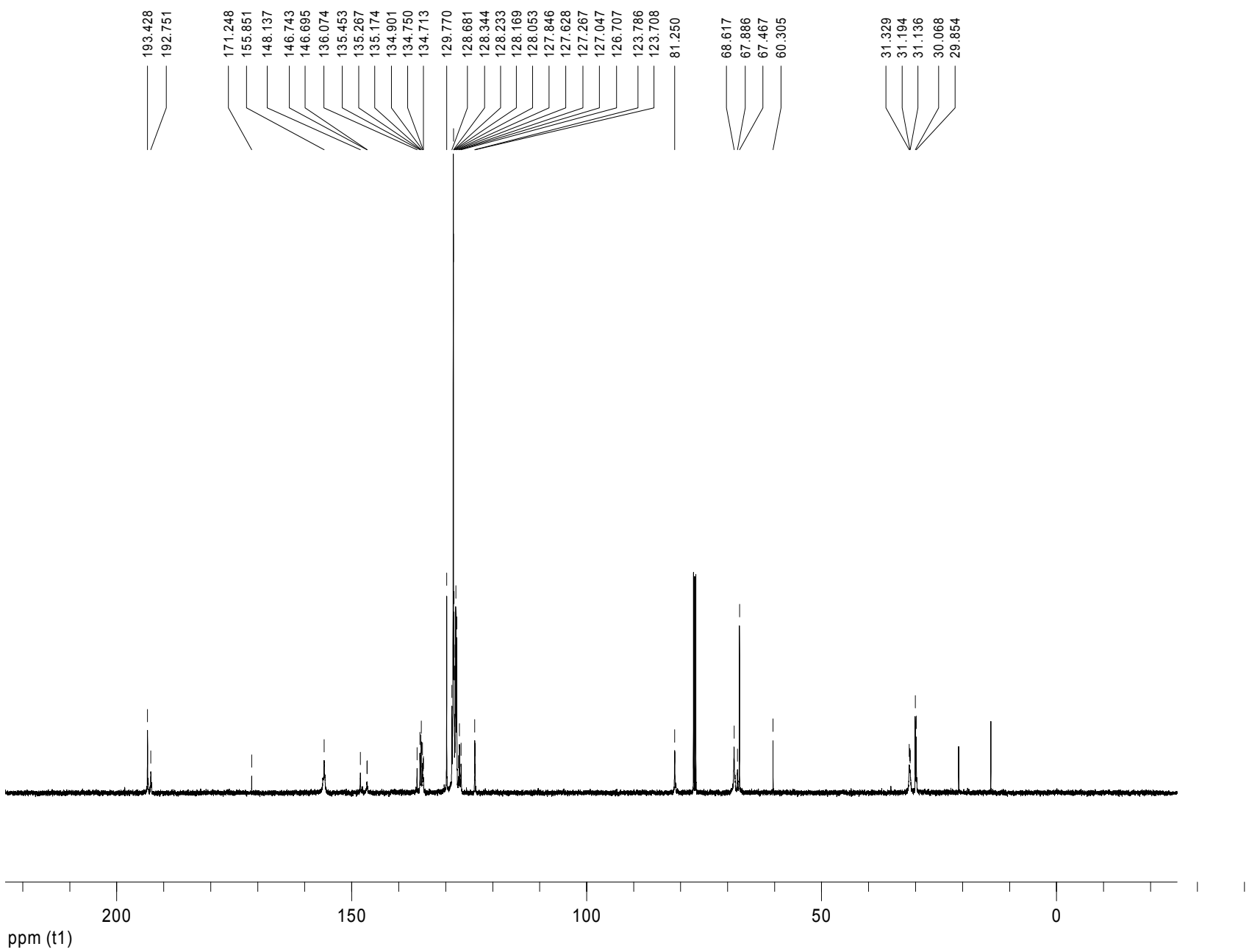

7.658
7.350
7.346
7.337
7.333
7.315
7.284
7.268
7.260
7.221
7.217
7.205
7.113
7.097
6.637
6.632
6.627
6.181
6.177
6.174
3.726
2.968
2.955
2.947
2.939
2.929
2.772
2.767
2.763
2.757
2.752
2.748
2.743
2.738
2.699
2.695
2.684
2.680
2.670
2.666
OMe
Br
0.41
0.61
0.64
0.66
0.34
3.00
2.15
2.21
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

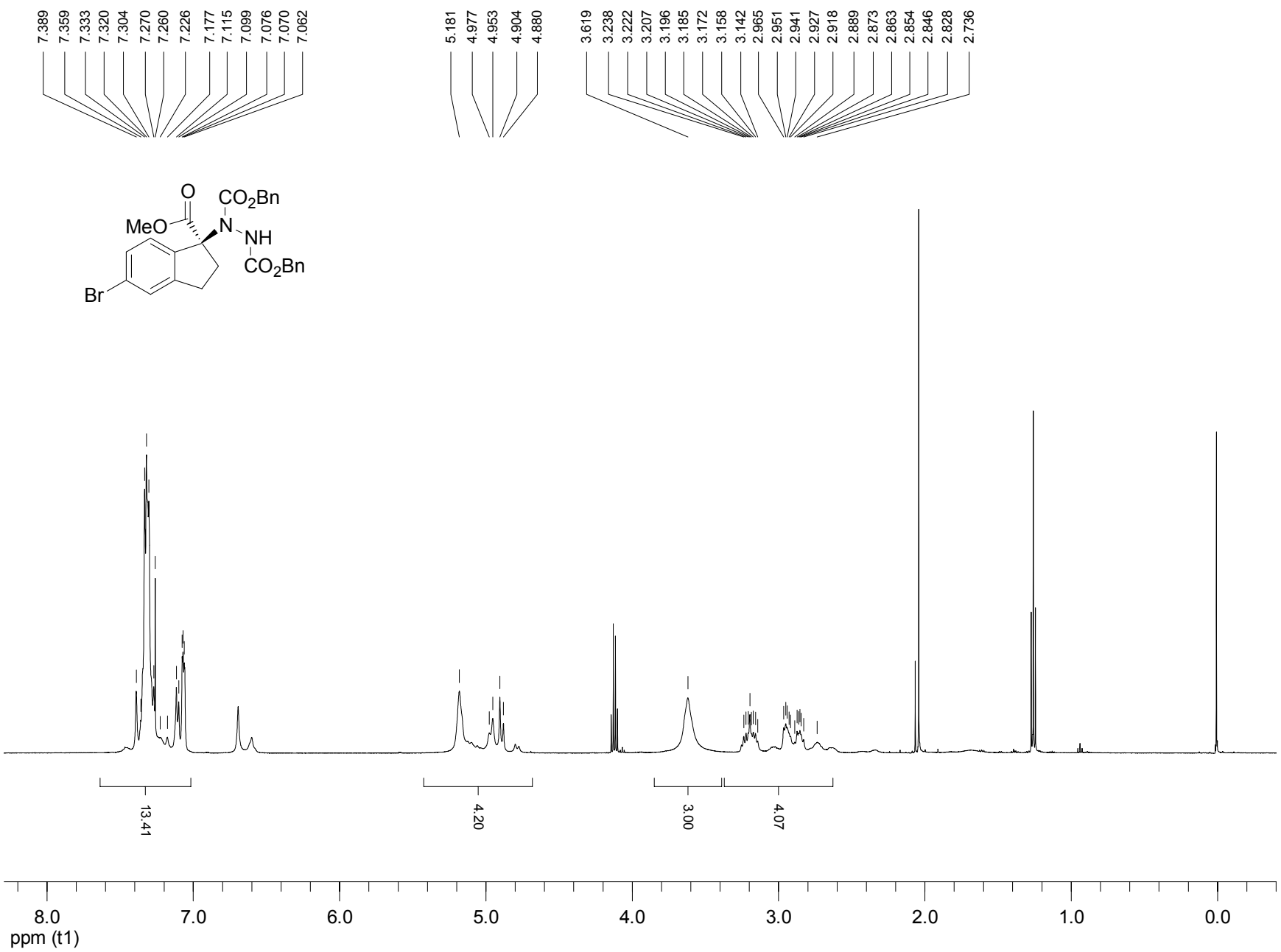

147.590
146.955
141.631
140.364
139.536
139.072
133.785
133.632
129.371
129.331
128.673
128.484
128.429
128.164
127.580
126.061
120.690
119.828
119.534
119.222
118.511
60.266
60.156
30.413
30.177
27.225
26.035
150
100
50
0
ppm (t1)


9.651
9.646
7.421
7.352
7.336
7.170
7.154
3.903
3.891
3.879
3.019
3.001
2.987
2.969
2.473
2.467
2.458
2.446
2.434
2.429
2.417
2.378
2.364
2.360
2.347
2.343
2.338
2.334
2.321
H
O
Br
1.00
2.74
1.33
1.04
2.71
2.51
10.0
5.0
0.0
ppm (f1)


199.864
147.040
137.383
129.771
128.292
126.281
121.962
57.219
31.549
25.554
200
150
100
50
0
ppm (f1)


9.778
9.555
9.484
9.471
9.468
7.391
7.371
7.368
7.336
7.280
7.260
7.204
7.147
7.025
7.011
5.206
5.182
5.153
5.129
5.059
5.012
3.114
3.088
3.082
3.058
3.051
3.047
3.044
3.036
3.028
3.018
3.014
3.009
2.999
2.991
2.951
2.909
2.853
2.758
2.756
2.753
2.732
2.712
O
CO2Bn
H
N
NH
CO2Bn
Br
1.03
13.02
4.00
3.47
10.0
5.0
0.0
ppm (t1)


193.428
192.751
171.248
155.851
148.137
146.743
146.695
136.074
135.453
135.267
135.174
134.901
134.750
134.713
129.770
128.681
128.344
128.233
128.169
128.053
127.846
127.628
127.267
127.047
126.707
123.786
123.708
81.250
68.617
67.886
67.467
60.305
31.329
31.194
31.136
30.068
29.854
200
150
100
50
0
ppm (t1)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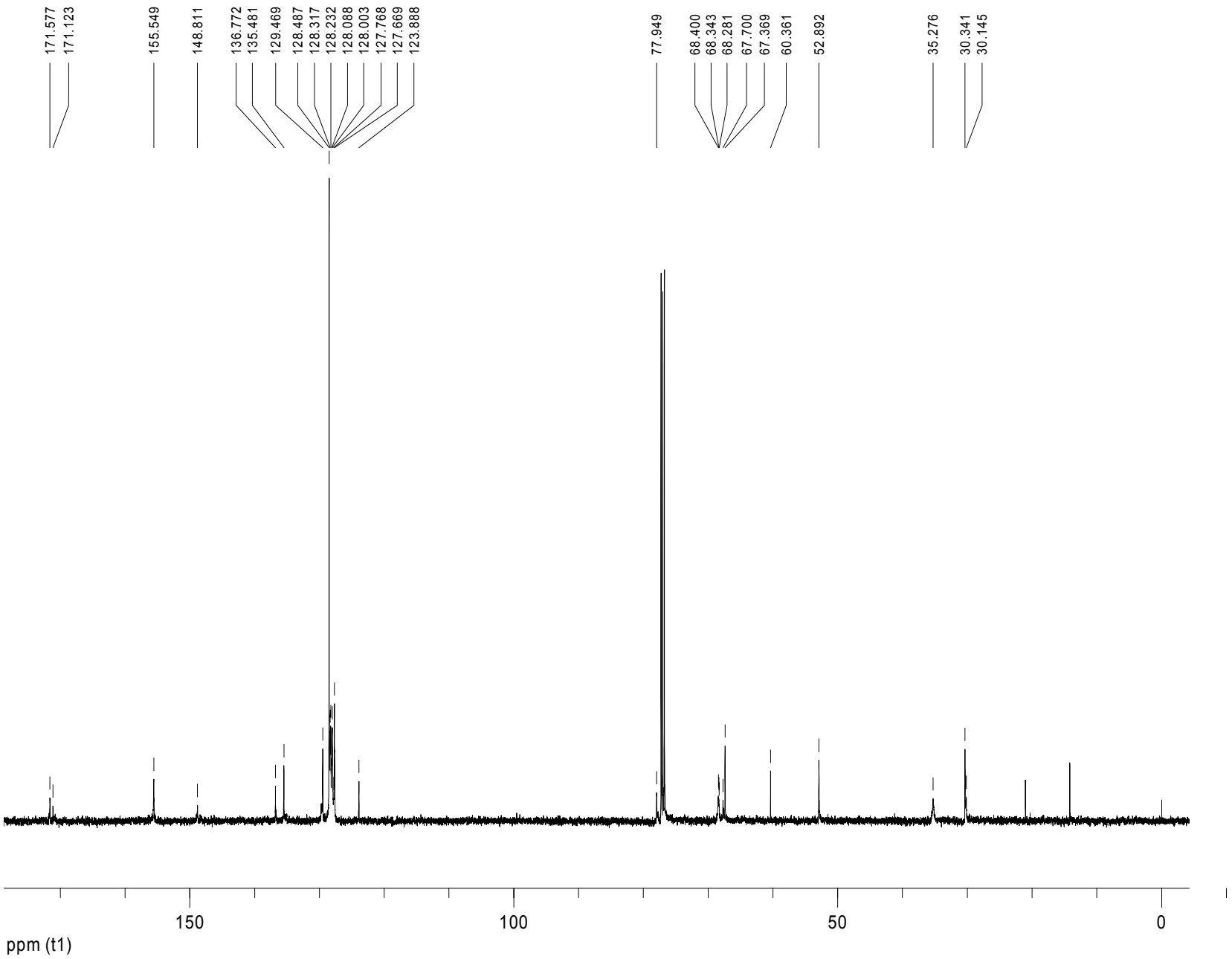
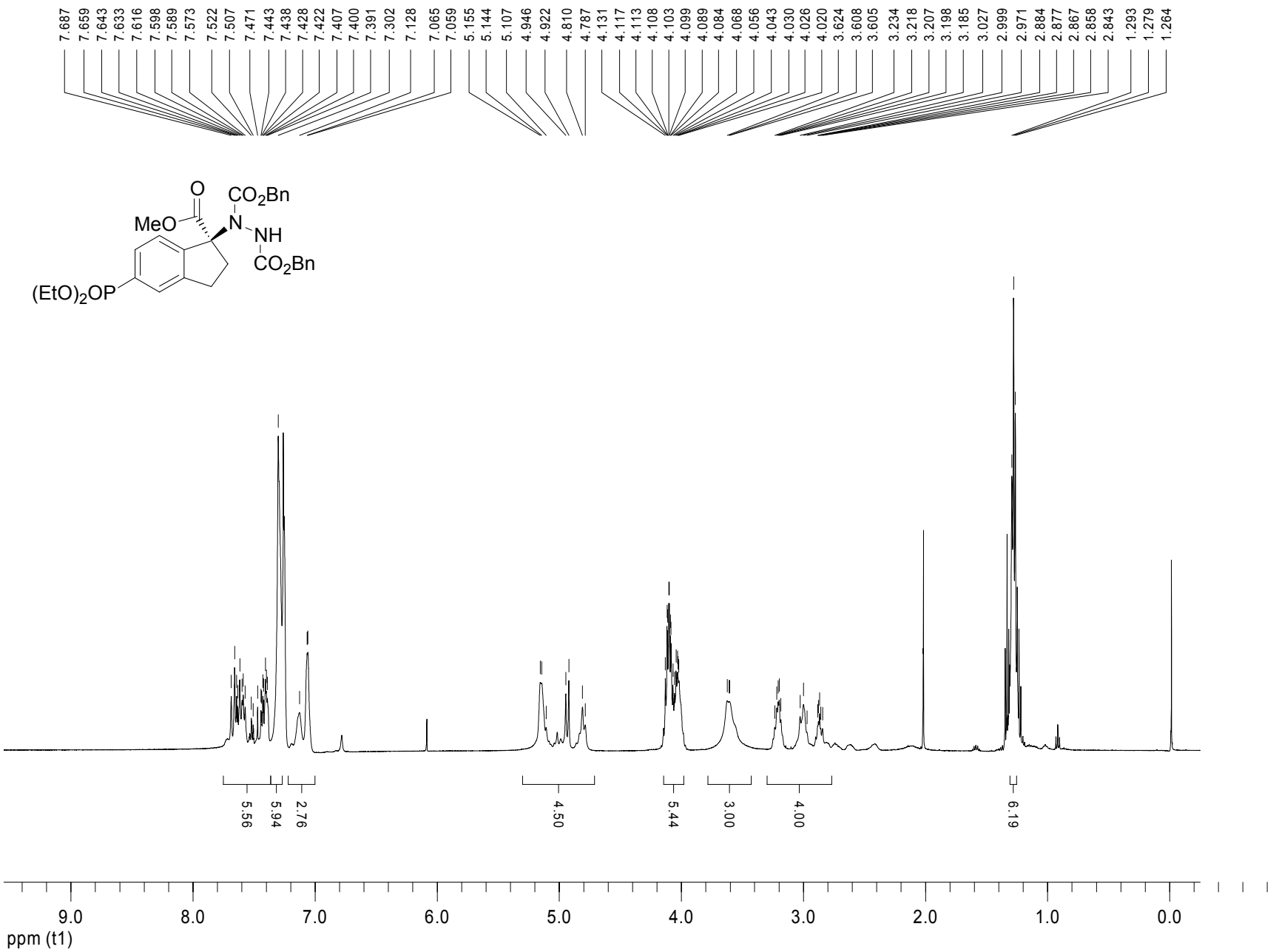
7.359
7.333
7.320
7.304
7.270
7.260
7.226
7.177
7.115
7.099
7.076
7.070
7.062
5.181
4.977
4.953
4.904
4.880
3.619
3.238
3.222
3.207
3.196
3.185
3.172
3.158
3.142
2.965
2.951
2.941
2.927
2.918
2.889
2.873
2.863
2.854
2.846
2.828
2.736
O
CO2Bn
MeO
N
NH
CO2Bn
Br
13.41
4.20
3.00
4.07
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


171.577
171.123
155.549
148.811
136.772
135.481
129.469
128.487
128.317
128.232
128.088
128.003
127.768
127.669
123.888
77.949
68.400
68.343
68.281
67.700
67.369
60.361
52.892
35.276
30.341
30.145
150
100
50
0
ppm (t1)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7.633
7.616
7.598
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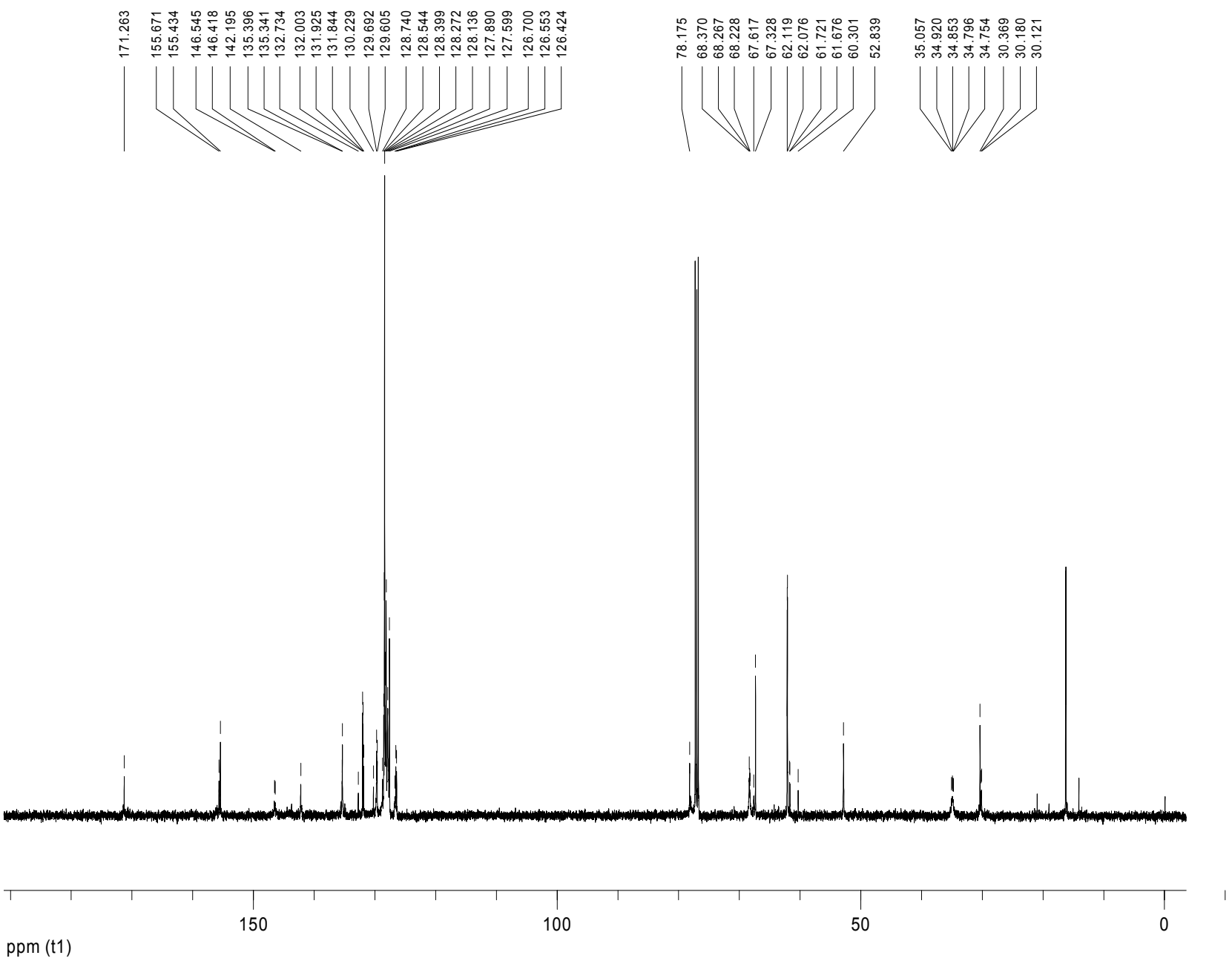
7.573
7.522
7.507
7.471
7.443
7.438
7.428
7.422
7.407
7.400
7.391
7.302
7.128
7.065
7.059
5.155
5.144
5.107
4.946
4.922
4.810
4.787
4.131
4.117
4.113
4.108
4.103
4.099
4.089
4.084
4.068
4.056
4.043
4.030
4.026
4.020
3.624
3.608
3.605
3.234
3.218
3.207
3.198
3.185
3.027
2.999
2.971
2.884
2.877
2.867
2.858
2.843
1.293
1.279
1.264
O
CO2Bn
MeO
N
NH
CO2Bn
(EtO)2OP
5.56
5.94
2.76
4.50
5.44
3.00
4.00
6.19
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)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146.418
142.195
135.396
135.341
132.734
132.003
131.925
131.844
130.229
129.692
129.605
128.740
128.544
128.399
128.272
128.136
127.890
127.599
126.700
126.553
126.424
78.175
68.370
68.267
68.228
67.617
67.328
62.119
62.076
61.721
61.676
60.301
52.839
35.057
34.920
34.853
34.796
34.754
30.369
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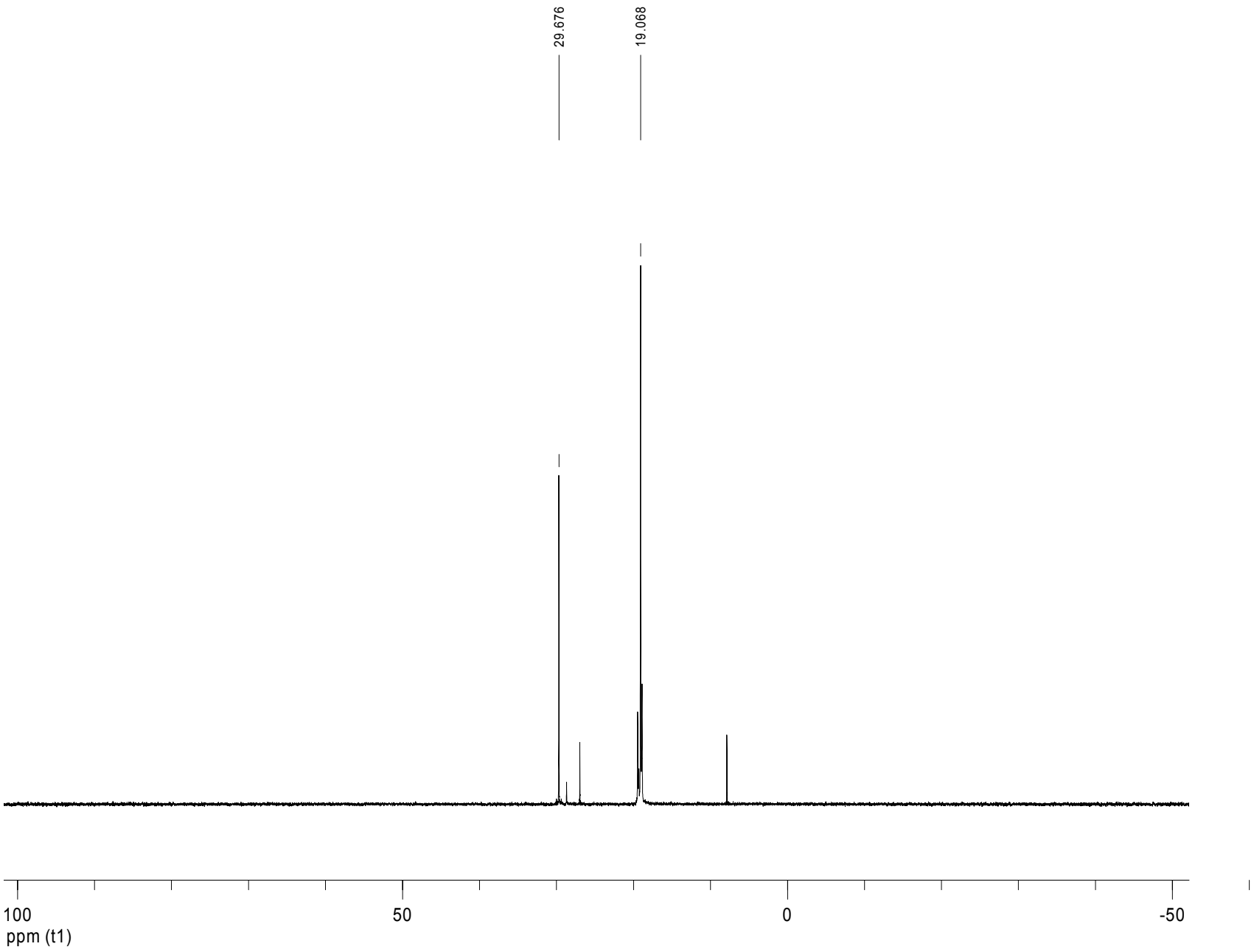
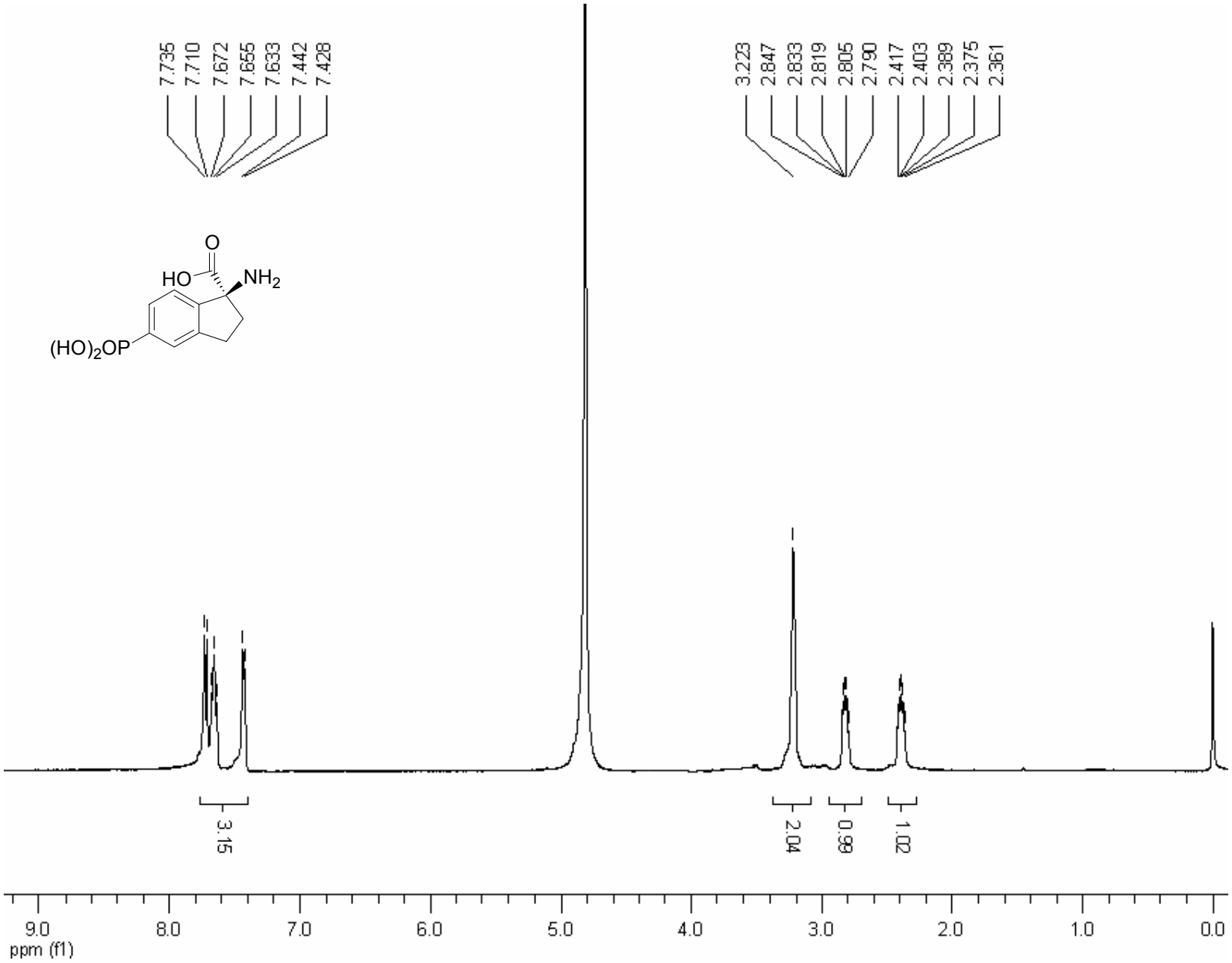
30.121
150
100
50
0
ppm (t1)


29.676
19.068
100
50
0
-50
ppm (t1)


7.735
7.710
7.672
7.655
7.633
7.442
7.428
3.223
2.847
2.833
2.819
2.805
2.790
2.417
2.403
2.389
2.375
2.361
O
HO
NH2
(HO)2OP
3.15
2.04
0.99
1.02
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)