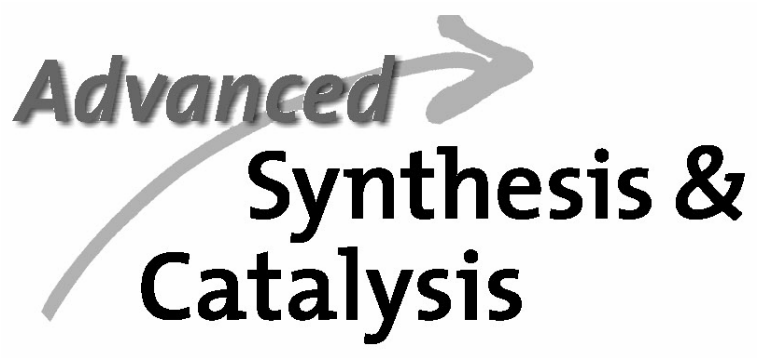


Supporting Information

Supporting Information

Organocatalytic *anti*-Mannich Reactions with Dihydroxyacetone and Acyclic Dihydroxyacetone Derivatives: A Facile Route to Amino Sugars

Haile Zhang, S. S. V. Ramasastry, Fujie Tanaka, 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

General: For thin layer chromatography (TLC), silica gel plates VWR GL60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot H_2O$ (10 g), and conc. H_2SO_4 (60 mL) in H_2O (940 mL) followed by heating or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), and acetic acid (10 mL) in ethanol (900 mL) followed by heating. Flash column chromatography was performed using Bodman silica gel 32-63, 60Å. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DRX-500 and Varian INOVA-400. Proton chemical shifts are given in relative to tetramethylsilane (0.00 ppm) in $CDCl_3$ or to the residual proton signals of the deuterated solvent in CD_3OD (3.31 ppm). Carbon chemical shifts were internally referenced to the deuterated solvent signals in $CDCl_3$ (77.00 ppm) or CD_3OD (49.00 ppm). High-resolution mass spectra were recorded on an Agilent ESI-TOF mass spectrometer. Enantiomeric excesses were determined by chiral-phase HPLC using a Hitachi instrument.

Preparation of protected dihydroxyacetones:

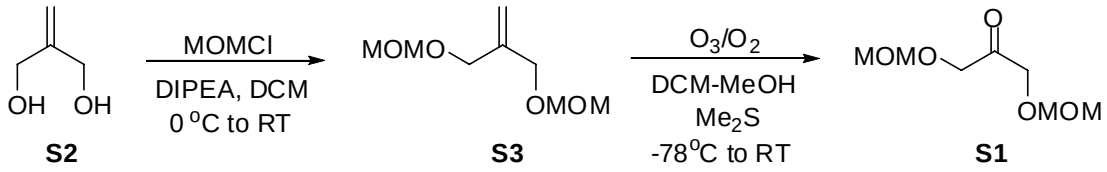
1,3-Dihydroxyacetone dimer was purchased from Aldrich and was used without further purification.

Bn-protected dihydroxyacetone was prepared according to the literature methods.[1,2]

TBS-protected dihydroxyacetone was prepared according to the literature method.[3]

MOM-protected dihydroxyacetone **S1** was prepared as following procedure (**Scheme S1**).

Scheme 1: Synthesis of MOM-protected dihydroxyacetone S1.



6-Methylene-2,4,8,10-tetraoxaundecane (S3)

To an ice-cold solution of 2-methylene-1,3-propanediol **S2** (3.5 g, 39.8 mmol) in methylene chloride (25 mL) was added diisopropylethyl amine (17.3 mL, 99.4 mmol). After stirring for 10 min at the same temperature, chloromethyl methyl ether (6.65 mL, 87.5 mmol) was added drop wise and the reaction mixture was stirred for 10 h at room temperature. It was then poured into dilute HCl. The mixture was extracted with methylene chloride and the organic layers were combined and washed with brine, dried (Na_2SO_4), concentrated, and purified by flash column chromatography (hexanes/ethyl acetate) to afford the desired product **S3**.

2,4,8,10-Tetraoxaundecan-6-one (**S1**):

Ozone was passed through a methylene chloride-methanol (25 mL, 5:1) solution of **S3** (5.2 g, 29.5 mmol) at -78 °C, till the reaction mixture turned pale blue in color. Dimethyl sulfide (8.6 mL, 118 mmol) was then added to the reaction mixture and stirred for 12 h at room temperature. Solvents were removed under reduced pressure and the reaction mixture was purified by flash column chromatography (hexanes/ethyl acetate) to afford **S1** in 72% yield for two steps.

General procedure for Two-component Mannich-type reactions of DHA (Table 1 and Table 2):

Reactions were performed in a closed system (a vial with a cap). An inert atmosphere of nitrogen or argon was not necessary for the reactions. To a solution of *N*-PMP-protected preformed imine (0.5 mmol, 1 equiv) in anhydrous 1-methyl-2-pyrrolidinone (NMP, 0.5 mL) was added 1,3-dihydroxyacetone dimer (0.5 mmol, 1 equiv; 2 equiv as monomer) followed by O-*t*Bu-L-Thr (0.1 mmol, 0.2 equiv) and 5-methyl-1*H*-tetrazole (0.05 mmol, 0.1 equiv) at room temperature. The reaction was stirred at room temperature for the time as indicated in Table 1 and Table 2. The reaction mixture

was worked up by addition of saturated ammonium chloride, and extracted with AcOEt. The organic layers were washed with water and brine, dried over Na_2SO_4, filtered, concentrated in vacuo, and purified by flash column chromatography (AcOEt/hexane) to afford the corresponding Mannich adducts as an *anti*/*syn* mixture. Racemic standards were prepared using (±)-tryptophan and phenylphosphinic acid.

General procedure for Three-component Mannich reactions of DHA (Table 2, entries 5-7):

A mixture of NMP (0.5 mL), *p*-anisidine (0.5 mmol, 1 equiv) and aldehyde (0.5 mmol, 1 equiv), was stirred at 25^{o}C for 0.5 h. Then, to the mixture, added 1,3-dihydroxyacetone dimer (0.5 mmol, 1 equiv; 2 equiv as monomer), O-*t*Bu-L-Thr (0.1 mmol, 0.2 equiv) and additive 5-methyl-1*H*-tetrazole (0.05 mmol, 0.1 equiv). The reaction was stirred at room temperature for the time as indicated in Table 2. The reaction mixture was worked up by addition of saturated ammonium chloride, and extracted with AcOEt. The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, concentrated in vacuo, and purified by flash column chromatography (AcOEt/hexane) to afford the corresponding Mannich adducts as an *anti*/*syn* mixture. Racemic standards were prepared using (±)-tryptophan and phenylphosphinic acid.

General procedure for the O-*t*Bu-L-Thr-catalyzed Mannich reaction of Bn-protected DHA and *N*-PMP-protected preformed imine (Table 3).

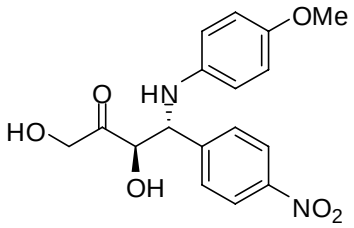
To a solution of Bn-protected-dihydroxyacetone (0.45 mmol, 1.5 equiv) in anhydrous NMP (0.3 mL), imine (0.3 mmol, 1 equiv) and O-*t*Bu-L-Thr (0.06 mmol, 0.2 equiv) were added followed by 5-methyl-1*H*-tetrazole (0.03 mmol, 0.1 equiv) at room temperature. The reaction was stirred at room temperature until the imine was consumed as monitored by TLC. The reaction mixture was worked up by addition of saturated ammonium chloride, and extracted with AcOEt. The organic layers were washed with water and brine, dried over Na_2SO_4, filtered, concentrated in vacuo, and purified by flash column chromatography (AcOEt/hexane) to afford the corresponding Mannich adducts as an *anti*/*syn* mixture. Racemic standards were prepared using (±)-tryptophan and phenylphosphinic acid.

General procedure for the O-*t*Bu-L-Thr-catalyzed Mannich reaction of MOM-protected DHA and *N*-PMP-protected preformed imine (Table 4).

To a solution of MOM-protected-dihydroxyacetone (0.5 mmol, 2 equiv) in anhydrous NMP (0.25 mL), imine (0.25 mmol, 1 equiv) and O-*t*Bu-L-Thr (0.05 mmol, 0.2 equiv) were added followed by 5-methyl-1*H*-tetrazole (0.025 mmol, 0.1 equiv) at room temperature. The reaction was stirred at room temperature until the imine was consumed as monitored by TLC. The reaction mixture was worked up by addition of saturated ammonium chloride, and extracted with AcOEt. The organic layers were washed with water and brine, dried over Na_2SO_4, filtered, concentrated in vacuo, and purified by flash column chromatography (AcOEt/hexane) to afford the corresponding Mannich adducts as an *anti*/*syn* mixture. Racemic standards were prepared using (±)-tryptophan and phenylphosphinic acid.

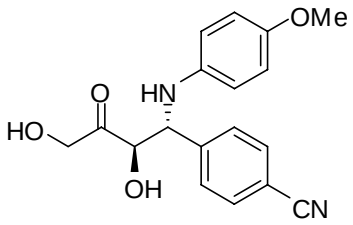
Characterizations of Mannich products 8 and 9 were previously reported.

(3*R*,4*R*)-1,3-Dihydroxy-4-(*p*-methoxyphenylamino)-4-(*p*-nitrophenyl)butan-2-one (1)



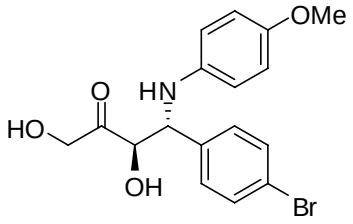
^{1}H NMR (500 MHz, $CDCl_3$): major diastereomer δ 3.69 (s, 3H), 4.10 (d, 1H, J = 20.0 Hz), 4.41 (d, 1H, J = 20.0 Hz), 4.77 (d, 1H, J = 4.5 Hz), 4.87 (d, 1H, J = 4.5 Hz), 655 (d, 2H, J = 9.0 Hz), 6.70 (d, 2H, J = 9.0 Hz), 7.46 (d, 2H, J = 8.5 Hz), 8.12 (d, 2H, J = 8.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): major diastereomer δ 55.6, 60.6, 67.1, 77.1, 115.0, 116.0, 123.8, 128.7, 139.0, 147.6, 153.3, 210.2. HRMS: calcd for $C_{17}H_{19}N_2O_6$ (MH^+) 347.1238, found 347.1236. HPLC (Daicel Chiralpak OJ-H, hexane/*i*-PrOH = 75:25, flow rate 1.0 mL/min, λ = 254 nm), t_R (*anti* major enantiomer) = 78.4 min, t_R (*anti* minor enantiomer) = 52.2 min, t_R (*syn* major enantiomer) = 28.8 min, t_R (*syn* minor enantiomer) = 34.8 min.

(3*R*,4*R*)-4-(*p*-Cyanophenyl)-1,3-dihydroxy-4-(*p*-methoxyphenylamino)butan-2-one (2)



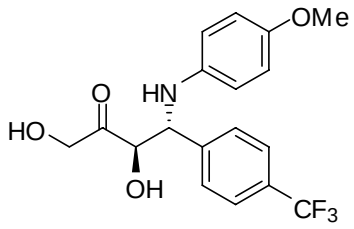
^{1}H NMR (500 MHz, $CDCl_3$): major diastereomer δ 3.69 (s, 3H), 4.08 (d, 1H, J = 20.0 Hz), 4.39 (d, 1H, J = 20.0 Hz), 4.74 (d, 1H, J = 4.0 Hz), 4.82 (d, 1H, J = 4.0 Hz), 6.54 (d, 2H, J = 9.0 Hz), 6.70 (d, 2H, J = 9.0 Hz), 7.41 (d, 2H, J = 8.5 Hz), 7.56 (d, 2H, J = 8.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): major diastereomer δ 55.6, 60.8, 67.1, 77.1, 111.9, 114.9, 115.9, 118.4, 128.5, 132.4, 139.1, 143.2, 153.2, 210.3. HRMS: calcd for $C_{18}H_{19}N_2O_4$ (MH^+) 327.1339, found 327.1340. HPLC (Daicel Chiralpak OJ-H, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R (*anti* major enantiomer) = 82.4 min, t_R (*anti* minor enantiomer) = 76.5 min, t_R (*syn* major enantiomer) = 39.8 min, t_R (*syn* minor enantiomer) = 46.2 min.

(3*R*,4*R*)-4-(*p*-Bromophenyl)-1,3-dihydroxy-4-(*p*-methoxyphenylamino)butan-2-one (3)



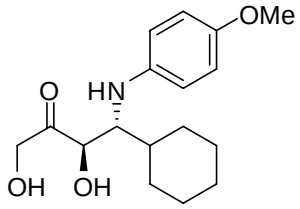
^{1}H NMR (500 MHz, $CDCl_3$): *anti*- δ 3.69 (s, 3H), 3.99 (d, 1H, J = 20.0 Hz), 4.31 (d, 1H, J = 20.0 Hz), 4.67 (d, 1H, J = 3.5 Hz), 4.71 (d, 1H, J = 3.5 Hz), 6.55 (d, 2H, J = 8.5 Hz), 6.70 (d, 2H, J = 8.5 Hz), 7.14 (d, 2H, J = 8.5 Hz), 7.41 (d, 2H, J = 8.5 Hz). *Syn*- δ 3.67 (s, 3H), 4.57 (m, 3H), 4.79 (s, 1H), 6.46 (d, 2H, J = 8.5 Hz), 6.66 (d, 2H, J = 8.5 Hz), 7.19 (d, 2H, J = 8.5 Hz), 7.43 (d, 2H, J = 8.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): mixture of diastereomers (*anti*:*syn* = 2:1) δ 55.6, 59.3, 60.6, 66.5, 67.1, 77.1, 78.8, 114.9, 115.5, 116.0, 1216, 122.2, 128.8, 129.2, 131.8, 136.3, 138.0, 139.4, 152.7, 153.0, 209.8, 210.6. HRMS: calcd for $C_{17}H_{19}BrNO_4$ (MH^+) 380.0492, found 380.0493. HPLC (Daicel Chiralpak AD, hexane/*i*-PrOH = 95:5, flow rate 0.8 mL/min, λ = 254 nm), t_R (*anti* major enantiomer) = 93.9 min, t_R (*anti* minor enantiomer) = 79.7 min, t_R (*syn* major enantiomer) = 85.9 min, t_R (*syn* minor enantiomer) = 72.5 min.

(3*R*,4*R*)-1,3-Dihydroxy-4-(*p*-methoxyphenylamino)-4-(*p*-trifluoromethylphenyl)butan-2-one (4)



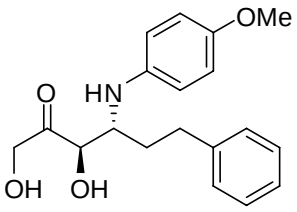
^{1}H NMR (500 MHz, $CDCl_3$): major diastereomer δ 3.70 (s, 3H), 4.07 (d, 1H, J = 20.0 Hz), 4.36 (d, 1H, J = 20.0 Hz), 4.74 (d, 1H, J = 4.0 Hz), 4.82 (d, 1H, J = 4.0 Hz), 6.57 (d, 2H, J = 9.0 Hz), 6.72 (d, 2H, J = 9.0 Hz), 7.41 (d, 2H, J = 8.5 Hz), 7.56 (d, 2H, J = 8.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): major diastereomer δ 55.6, 60.9, 67.1, 77.1, 114.9, 116.0, 123.8 (q, J = 270.6 Hz), 125.7 (q, J = 3.8 Hz), 128.0, 130.4 (q, J = 32.5 Hz), 139.3, 141.4, 153.2, 210.2. HRMS: calcd for $C_{18}H_{19}F_3NO_4$ (MH^+) 370.1261, found 370.1261. HPLC (Daicel Chiralpak OJ-H, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R (*anti* major enantiomer) = 54.7 min, t_R (*anti* minor enantiomer) = 46.6 min, t_R (*syn* major enantiomer) = 28.6 min, t_R (*syn* minor enantiomer) = 33.3 min.

(3*R*,4*R*)-4-Cyclohexyl-1,3-dihydroxy-4-(4-methoxyphenylamino)butan-2-one (5)



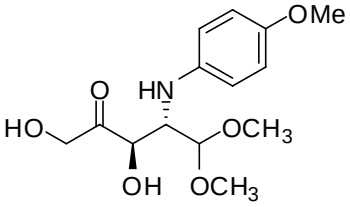
^{1}H NMR (400 MHz, $CDCl_3$): major diastereomer δ 0.99-1.30 (m, 5H), 1.50-1.90 (m, 6H), 3.20-3.50 (br s, 2H), 3.41 (t, 1H, J = 7.6 Hz), 3.50 (dd, 1H, J = 10.0 Hz, 2.8 Hz), 3.72 (s, 3H), 4.36 (d, 2H, J = 22.8 Hz), 4.44 (d, 1H, J = 4.0 Hz), 4.47 (d, 1H, J = 2.8 Hz), 6.50 (d, 2H, J = 12.0 Hz), 6.71 (2H, J = 11.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): major diastereomer δ 26.13, 26.17, 26.18, 26.23, 30.3, 41.2, 55.6, 61.1, 66.0, 75.2, 114.7, 114.9, 141.5, 152.2, 211.9. HRMS: calcd for $C_{17}H_{26}NO_4$ (MH^+) 308.1856, found 308.1852. HPLC (Daicel Chiralpak OJ-H, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R (*anti* major enantiomer) = 67.3 min, t_R (*anti* minor enantiomer) = 47.3 min, t_R (*syn* major enantiomer) = 31.4 min, t_R (*syn* minor enantiomer) = 28.0 min.

(3*R*,4*R*)-1,3-Dihydroxy-4-(4-methoxyphenylamino)-6-phenylhexan-2-one (6)



^{1}H NMR (400 MHz, $CDCl_3$): major diastereomer δ 1.46-1.60 (m, 1H), 1.78-2.10 (m, 1H), 2.56-2.90 (m, 2H), 3.06 (brs, 1H), 3.56 (td, 1H, J = 13.6 Hz, 3.3 Hz), 3.75 (s, 3H), 3.81 (d, 1H, J = 14.8 Hz), 4.44 (d, 2H, J = 12.4 Hz), 4.43 (dd, 1H, J = 17.6 Hz, 4.0 Hz), 6.61 (d, 2H, J = 12.0 Hz), 6.80 (d, 2H, J = 11.6 Hz), 7.10-7.32 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): major diastereomer δ 31.4, 32.0, 55.7, 56.8, 66.6, 75.6, 115.1, 116.1, 126.21, 126.25, 128.3, 128.48, 128.54, 128.56, 211.0. HRMS: calcd for $C_{19}H_{24}NO_4$ (MH^+) 330.1700, found 308.1709. HPLC (Daicel Chiralpak AD, hexane/*i*-PrOH = 93:7, flow rate 1.0 mL/min, λ = 254 nm), t_R (*anti* major enantiomer) = 30.1 min, t_R (*anti* minor enantiomer) = 47.1 min, t_R (*syn* major enantiomer) = 39.5 min, t_R (*syn* minor enantiomer) = 33.4 min.

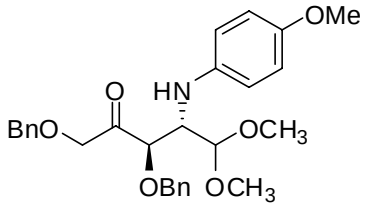
(3*R*,4*S*)-1,3-Dihydroxy-5,5-dimethoxy-4-(*p*-methoxyphenylamino)pentan-2-one (7)



^{1}H NMR (500 MHz, $CDCl_3$): mixture of diastereomers (*anti*:*syn* = 1:1) δ 3.32 (s, 3H x 1/2), 3.41 (s, 3H x 1/2), 3.43 (3H x 1/2), 3.45 (s, 3H x 1/2), 3.73 (s, 3H x 1/2), 3.74 (s, 3H x 1/2), 3.89 (t, 1H x 1/2, J = 3.0 Hz), 4.03(dd, 1H x 1/2, J = 3.0 Hz, 5.0 Hz), 4.36-4.66 (m, 4H), 6.61 (d, 2H x 1/2, J = 9.0 Hz), 6.69 (d, 2H x 1/2, J = 9.0 Hz), 6.75 (d, 2H x 1/2, J = 9.0 Hz), 6.79 (d, 2H x 1/2, J = 9.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): mixture of diastereomers (*anti*:*syn* = 1:1) δ 55.0, 55.6, 56.4, 57.0, 57.3, 58.3, 58.4, 66.6, 67.2, 74.8, 75.4, 105.8, 105.9, 114.9, 115.0, 115.7, 115.8, 139.6, 140.1, 153.0, 153.2, 211.5, 212.1. HRMS: calcd for $C_{14}H_{22}NO_6$ (MH^+) 300.1442, found 300.1442. HPLC (Daicel Chiralpak OJ-H, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R (*anti* major enantiomer) = 21.8 min, t_R (*anti* minor enantiomer) = 19.8 min, t_R (*syn* major enantiomer) = 27.9 min, t_R (*syn* minor enantiomer) =

16.7 min.

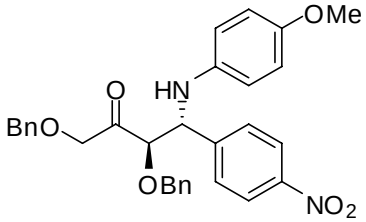
(3*R*,4*S*)-1,3-Bis(benzyloxy)-5,5-dimethoxy-4-(*p*-methoxyphenylamino)pentan-2-one(10)



^{1}H NMR (500 MHz, $CDCl_3$): major diastereomer δ 3.26 (s, 3H), 3.28 (s, 3H), 3.71 (s, 1H), 4.08 (dd, 1H, J = 3.5, 7.0 Hz, 4.18 (d, 1H, J = 17.0 Hz), 4.33 (d, 1H, J = 3.5 Hz), 4.35 (d, 1H, J = 4.5 Hz), 4.38(d, 1H, J = 10.0 Hz), 4.53-4.55 (m, 3H), 4.63 (d, 2H, J = 11.5 Hz), 6.55 (d, 2H, J = 9.0 Hz), 6.66 (d, 2H, J = 9.0 Hz), 7.21-7.35 (m, 10 Hz).^{13}C NMR (125 MHz, $CDCl_3$): major diastereomer δ 52.2, 55.4, 55.7, 58.2, 73.4, 74.0, 74.4, 81.6, 102.7,114.9, 115.1, 127.9, 128.0, 128.1, 128.4, 137.3, 137.4, 140.4, 152.6, 206.7. HRMS: calcd for $C_{28}H_{34}NO_6$ (MH^+) 480.2381, found 480.2374. HPLC (Daicel Chiralcel AD, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm): t_R (*anti* major enantiomer) = 18.0 min; t_R (*anti* minor enantiomer) = 20.2 min, t_R (*syn* major enantiomer) = 11.8 min, t_R (*syn* minor enantiomer) = 20.2 min. Based on the dr determined by ^{1}HNMR and the ee of *syn* enantiomer which obtained from OD-H column (see the following), area of t_R 20.2 min was corrected to give ee value.

HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm): t_R (*anti* enantiomer) = 16.9 min, t_R (*syn* major enantiomer) = 11.3 min, t_R (*syn* minor enantiomer) = 21.2 min.

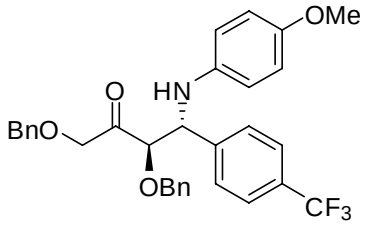
(3*R*,4*R*)-1,3-Bis(benzyloxy)-4-(*p*-methoxyphenylamino)-4-(*p*-nitrophenyl)butan-2-one (11)



^{1}H NMR (500 MHz, $CDCl_3$): major diastereomer δ 3.68 (s, 3H), 3.89 (d, 1H, J = 18 Hz), 4. 11 (d, 1H, J = 18 Hz), 4.24 (brs, 1H), 4.33 (d, 1H, J = 11.5 Hz), 4.38 (d, 1H, J = 5.5 Hz), 4.46 (s, 2H), 4.57 (d, 1H, J = 11.5 Hz), 4.78 (d, 1H, J = 5.5 Hz), 6.37 (d, 2H, J = 9.0 Hz), 6.65 (d, 2H, J = 9.0 Hz), 7.16-7.34 (m,

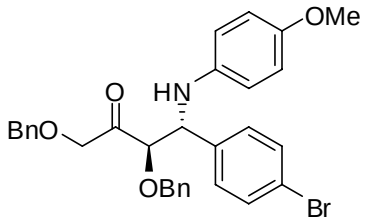
10H), 7.42 (d, 2H, J = 9.0 Hz), 8.08 (d, 2H, J = 9.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): major diastereomer δ 55.6, 59.7, 73.3, 73.6, 74.0, 84.4, 114.8, 115.4, 123.6, 128.0, 128.2, 128.3, 128.6, 128.72, 128.74, 136.2, 136.5, 139.2, 146.4, 147.5, 152.9, 207.4. HRMS: calcd for $C_{31}H_{31}N_2O_6$ (MH^+) 527.2177, found 527.2176. HPLC (Daicel Chiralpak AD, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R (*anti* major enantiomer) = 44.8 min, t_R (*anti* minor enantiomer) = 37.3 min, t_R (*syn* major enantiomer) = 15.8 min, t_R (*syn* minor enantiomer) = 18.8 min.

(3*R*,4*R*)-1,3-Bis(benzyloxy)-4-(*p*-methoxyphenylamino)-4-(*p*-trifluoromethylphenyl)butan-2-one (12)



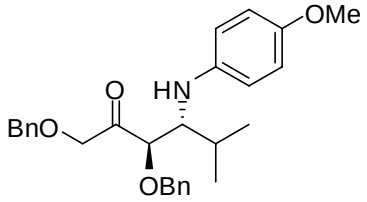
^{1}H NMR (500 MHz, $CDCl_3$): major diastereomer δ 3.67 (s, 3H), 3.88 (d, 1H, J = 18 Hz), 4. 11 (d, 1H, J = 18 Hz), 4.29-4.37 (m, 4H), 4.44 (d, 1H, J = 12.0 Hz), 4.54 (d, 1H, J = 12.0 Hz), 4.74 (d, 1H, J = 6.0 Hz), 6.40 (d, 2H, J = 9.0 Hz), 6.65 (d, 2H, J = 9.0 Hz), 7.11-7.36 (m, 10H), 7.39 (d, 2H, J = 8.5 Hz), 7.51 (d, 2H, J = 8.5 Hz) ^{13}C NMR (125 MHz, $CDCl_3$): major diastereomer δ 55.5, 59.8, 73.3, 73.5, 73.9, 84.6, 114.8, 115.4, 124.0 (q, J = 270.4 Hz), 125.3 (q, J = 3.8 Hz), 127.9, 128.1, 128.2, 128.4, 128.5, 128.6, 129.9 (q, J = 32.0 Hz), 136.4, 136.7, 139.5, 142.9, 152.7, 207.7. HRMS: calcd for $C_{32}H_{31}F_3NO_4$ (MH^+) 550.2200, found 550.2200. HPLC (Daicel Chiralpak OD-H, hexane/*i*-PrOH = 50:50, flow rate 0.5 mL/min, λ = 254 nm), t_R (*anti* major enantiomer) = 36.9 min, t_R (*anti* minor enantiomer) = 24.3 min, t_R (*syn* major enantiomer) = 18.6 min, t_R (*syn* minor enantiomer) = 28.8 min.

(3*R*,4*R*)-1,3-Bis(benzyloxy)-4-(*p*-bromophenyl)-4-(*p*-methoxyphenylamino)butan-2-one (13)



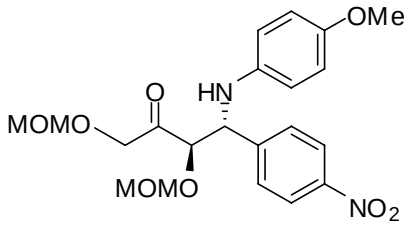
^{1}H NMR (500 MHz, $CDCl_3$): major diastereomer δ 3.62 (s, 3H), 3.79 (d, 1H, J = 18.5 Hz), 4.04 (d, 1H, J = 18.5 Hz), 4.26-4.31 (m, 3H), 4.38 (d, 1H, J = 11.5 Hz), 4.48 (d,1H, J = 11.5 Hz), 4.60 (d, 1H, J = 5.0 Hz), 6.36 (d, 2H, J = 9.0 Hz), 6.60 (d, 2H, J = 9.0 Hz), 7.09-7.33 (m, 14H). ^{13}C NMR (125 MHz, $CDCl_3$): major diastereomer δ 55.6, 59.7, 73.2, 73.6, 73.9, 84.7, 114.8, 115.4, 121.8, 127.95, 128.04, 128.1, 128.4, 128.5, 128.6, 129.5, 131.6, 136.5, 136.8, 137.7, 139.6, 152.7, 207.9. HRMS: calcd for $C_{31}H_{31}BrNO_4$ (MH^+) 560.1431, found 560.1431. HPLC (Daicel Chiralpak AD, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R (*anti* major enantiomer) = 23.7 min, t_R (*anti* minor enantiomer) = 17.7 min, t_R (*syn* major enantiomer) = 10.4 min, t_R (*syn* minor enantiomer) = 13.7 min.

(3*R*,4*R*)-1,3-Bis(benzyloxy)-4-(*p*-methoxyphenylamino)-5-methylhexan-2-one (14)



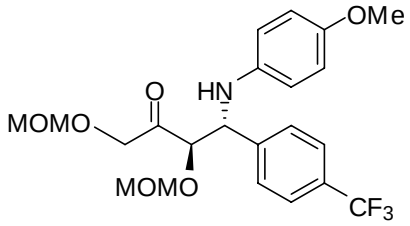
^{1}H NMR (500 MHz, $CDCl_3$): mixture of diastereomers (*anti*:*syn* = 2:1), * denotes *syn* diastereomer δ 0.88 (d, 3H* x 1/3, J = 6.8 Hz), 0.90 (d, 3H x 2/3, J = 6.8 Hz), 0.92 (d, 3H x 2/3, J = 6.8 Hz), 0.93 (d, 3H* x 1/3, J = 6.8 Hz), 1.95 (m, 1H* x 1/3), 2.00 (m, 1H x 2/3), 3.48 (d, 1H* x 1/3, J = 7.5 Hz,), 3.63 (t, 1H x 2/3, J = 4.5 Hz), 3.70 (s, 1H* x 1/3), 3.71 (s, 1H x 2/3), 4.12-4.64 (m, 7H), 6.43 (d, 2H* x 1/3, J = 9.0 Hz), 6.49 (d, 2H x 2/3, J = 9.0 Hz), 6.67 (d, 2H* x 1/3, J = 9.0 Hz), 6.69 (d, 2H x 2/3, J = 9.0 Hz), 7.20-7.37 (m, 10 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): mixture of diastereomers (*anti*:*syn* = 2:1) δ 17.10, 19.83, 20.06, 20.71, 29.88, 31.77, 55.69, 61.21, 62.27, 73.13, 73.23, 73.37, 73.49, 73.57, 73.73, 74.33, 83.76, 83.53, 114.32, 114.87, 114.92, 127.83, 127.88, 127.90, 127.95, 128.05, 128.08, 128.21, 128.25, 128.39, 128.42, 128.49, 128.50, 128.51, 136.98, 137.04, 137.17, 137.20, 141.54, 142.14, 151.83, 152.28, 209.19, 209.91. HRMS: calcd for $C_{28}H_{34}NO_4$ (MH^+) 448.2482, found 448.2470. HPLC (Daicel Chiralpak AD, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R (*anti* major enantiomer) = 7.3 min, t_R (*anti* minor enantiomer) = 8.5 min, t_R (*syn* major enantiomer) = 10.8 min, t_R (*syn* minor enantiomer) = 6.2 min.

(3*R*,4*R*)-1,3-Bis(methoxymethyl)-4-(*p*-methoxyphenylamino)-4-(*p*-nitrophenyl)butan-2-one (15)



1H NMR (500 MHz, $CDCl_3$): major diastereomer δ 3.30 (s, 3H), 3.34 (s, 3H), 3.68 (s 3H), 4.02 (d, 1H, J = 18.3 Hz), 4.27 (d, 1H, J = 18.3 Hz), 4.50 (d, 1H, J = 5.8 Hz), 4.62 (m, 5H), 4.88 (s, 1H), 6.48 (d, 2H, J = 9.0 Hz), 6.68 (d, 2H, J = 9.0 Hz), 7.52 (d, 2H, J = 9.0 Hz), 8.16 (d, 2H, J = 9.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): major diastereomer δ 55.6, 55.7, 56.5, 59.7, 71.2, 83.7, 96.4, 97.9, 114.9, 115.3, 123.6, 128.7, 139.3, 146.4, 147.5, 152.9, 206.3. HRMS: calcd for $C_{21}H_{27}N_2O_8$ (MH^+) 435.1762, found 435.1759. HPLC (Daicel Chiralcel AD, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm): t_R (*anti* major enantiomer) = 57.7 min, t_R (*anti* minor enantiomer) = 27.4 min, (*syn* major enantiomer) = 17.7 min, t_R (*syn* minor enantiomer) = 15.0 min.

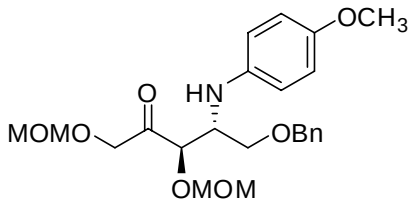
(3*R*,4*R*)-1,3-Bis(methoxymethyl)-4-(*p*-methoxyphenylamino)-4-(*p*-trifluoromethylphenyl)butan-2-one (16)



^{1}H NMR (400 MHz, $CDCl_3$): major diastereomer δ 3.27 (s, 3H), 3.33 (s, 3H), 3.70 (s, 3H), 3.76 (d, 1H, J = 14.8 Hz), 3.94 (d, 1H, J = 24.4 Hz), 4.21 (d, 1H, J = 24.4 Hz), 4.47-4.70 (m, 5H), 6.50 (d, 2H, J = 12.0 Hz), 6.70 (d, 2H, J = 12.0 Hz), 7.47 (d, 2H, J = 11.6 Hz), 7.57 (d, 2H, J = 11.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): major diastereomer δ 55.5, 55.6, 56.4, 59.8, 71.2, 83.8, 96.3, 97.8, 114.8, 115.0, 115.2, 125.4, 125.5, 127.5, 128.1, 139.6, 152.6, 206.5. HRMS: calcd for $C_{22}H_{27}F_3NO_6$ (MH^+) 458.1785, found 458.1789. HPLC (Daicel Chiralpak AD, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254

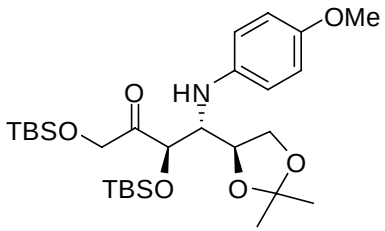
nm), t_R (*anti* major enantiomer) = 63.6 min, t_R (*anti* minor enantiomer) = 29.1 min, t_R (*syn* major enantiomer) = 15.8 min, t_R (*syn* minor enantiomer) = 14.0 min.

(3*R*,4*R*)-5-Benzyloxy-1,3-bis(methoxymethyl)-4-(*p*-methoxyphenylamino)pentan-2-one(17)



^{1}H NMR (400 MHz, $CDCl_3$): major diastereomer δ 3.30 (s, 3H), 3.35 (s, 3H), 3.51-3.63 (m, 1H), 3.73 (s, 3H), 4.00-4.13 (m, 1H), 4.30-4.70 (m, 10 H), 6.61 (d, 2H, J = 8.8 Hz), 6.75 (d, 2H, J = 8.8 Hz), 7.20-7.40 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): major diastereomer δ 55.5, 55.7, 56.3, 56.6, 67.7, 71.6, 73.2, 80.4, 96.3, 97.8, 114.6, 114.9, 115.8, 127.7, 127.8, 137.7, 140.2, 152.8, 206.6. HRMS: calcd for $C_{23}H_{32}NO_7$ (MH^+) 434.2173, found 434.2174. HPLC (Daicel Chiralpak AS-H, hexane/*i*-PrOH = 92:8, flow rate 1.0 mL/min, λ = 254 nm), t_R (*anti* major enantiomer) = 42.9 min, t_R (*anti* minor enantiomer) = 35.4 min, t_R (*syn* major enantiomer) = 30.0 min, t_R (*syn* minor enantiomer) = 19.2 min.

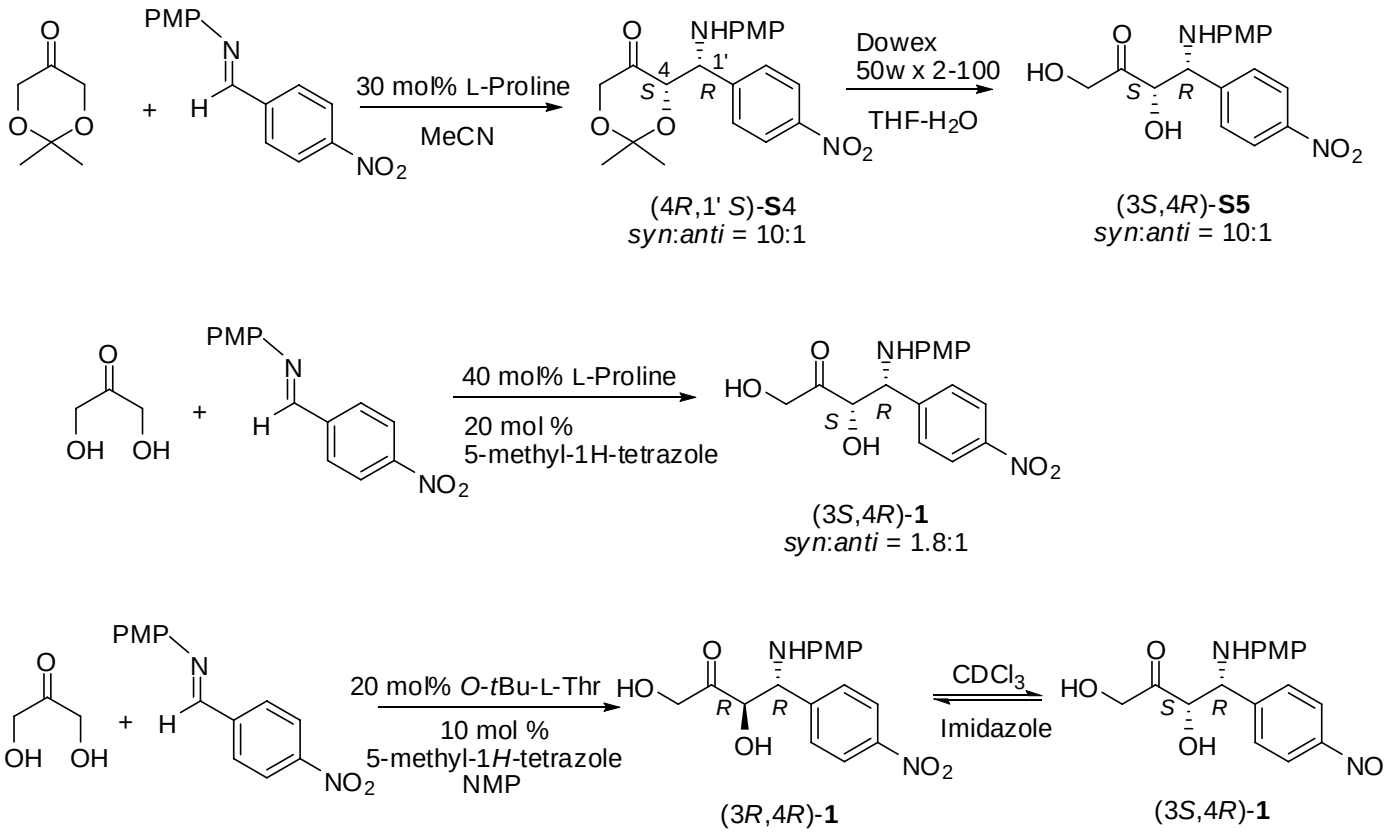
(3*R*,4*R*)-1,3-Bis(*tert*-butyldimethylsiloxy)-4-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-(*p*-methoxyphenylamino)-2-one (18)



^{1}H NMR (500 MHz, $CDCl_3$): δ -0.05 (s, 3H), 0.02(s, 3H) ,0.08 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 0.96 (s, 9H), 1.30 (s, 3H), 1.35 (s, 3H), 3.41 (d, 1H, J = 10.0 Hz), 3.74 (s, 3H), 3.85 (dd, 1H, J = 9.0 Hz, 5.5 Hz), 3.89 (t, 1H, J = 9.0 Hz), 4.08 (dd, 1H, J = 8.5 Hz, 6.0 Hz), 4.14-4.19 (m, 1H), 4.37 (d, 1H, J = 17.3 Hz), 4.51 (d, 1H, J = 6.0 Hz), 4.75(d, 1H, J = 17.3 Hz), 6.64 (d, 2H, J = 10.0 Hz), 6.77 (d, 2H, J = 10.0 Hz,), ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.4, -5.3, -4.9, -4.7, 18.2, 18.5, 25.4, 25.8, 25.9, 26.2, 55.7, 60.9, 67.9, 68.4, 74.2, 76.7, 109.8, 114.9, 115.1, 139.8, 152.6, 209.3. HRMS: calcd for $C_{28}H_{52}NO_6Si_2$ (MH^+) 554.3328, found 554.3337.

Determination of absolute stereochemistry of unprotected DHA *anti*-Mannich adduct 1:

Scheme S2

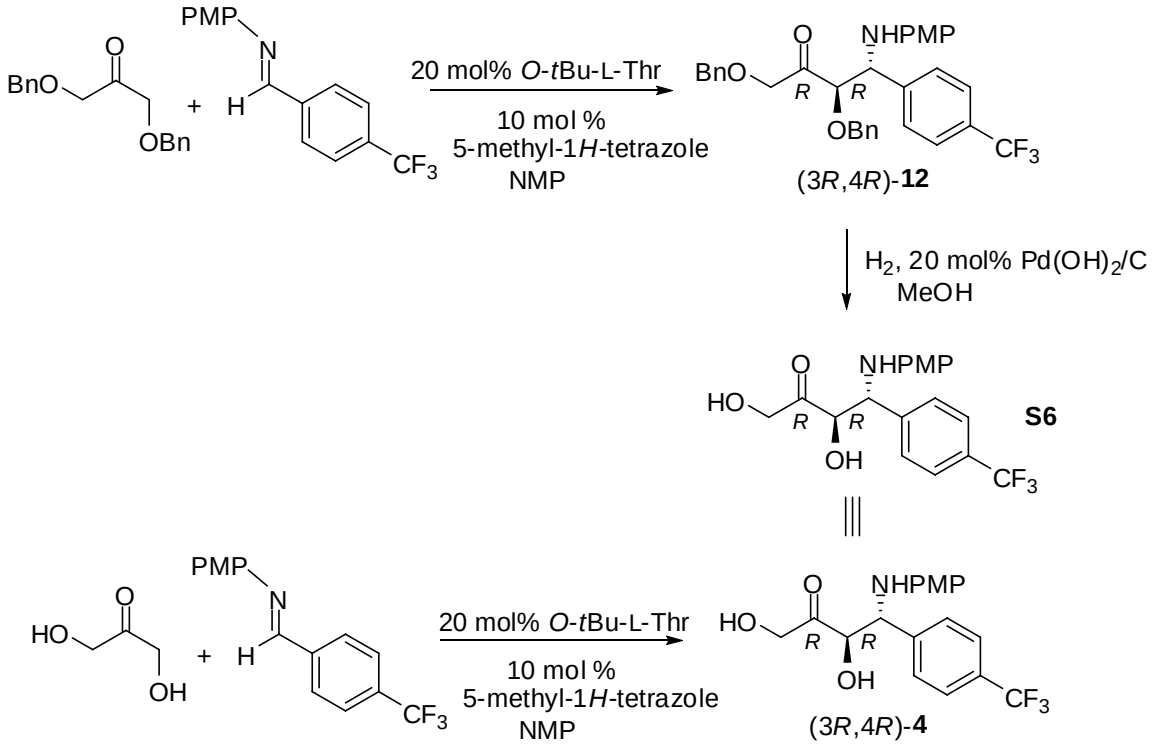


Syn-Mannich product (4*R*,1′*S*)-**S4** (*syn*:*anti* = 10:1, *syn* 53% ee) was synthesized[4] using (*S*)-proline, 2,2-dimethyl-1,3-dioxan-5-one, and *N*-PMP-protected preformed imine. This *syn*-Mannich product was transformed to (3*S*,4*R*)-**S5** (*syn:anti* = 10:1, *syn* 54% ee) using reported[5] procedures. Comparison of the HPLC traces confirmed the absolute configuration of Mannich product *syn*-**1** obtained by the (*S*)-proline catalysis to be 3*R*,4*S*.

Imidazole isomerization [6] of the *anti*-**1** obtained from the O-*t*Bu-L-Thr-catalyzed reaction afforded the *syn*-product possessing a (3*R*,4*S*) configuration, which was the product of the (*S*)-proline-catalyzed reaction. This result confirmed that the major *anti*-product **1** generated from the O-*t*Bu-L-Thr-catalyzed reaction had a (3*R*,3*R*) configuration.

Determination of absolute stereochemistry of Bn-protected DHA *anti*-Mannich adduct 12:

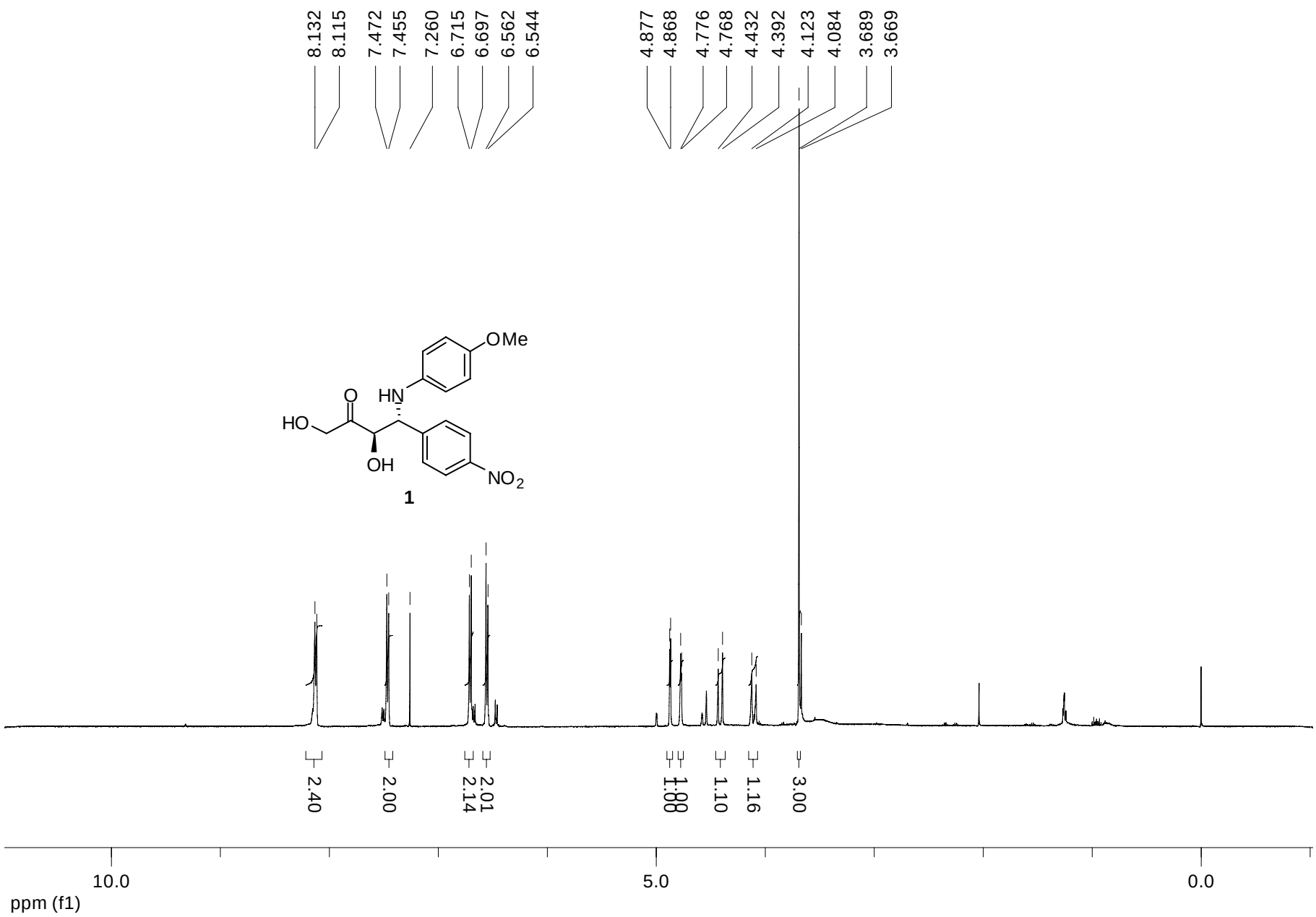
Scheme S3



The Mannich Product **12** was hydrogenolyzed in methanol in the presence of 20% $Pd(OH)_2/C$ under hydrogen to give the Mannich product **S6.** The major enantiomer of diol **S6** showed the same HPLC retention time as the major enantiomer of **4**, which was the O-*t*Bu-L-Thr catalyzed *anti*-Mannich adduct of dihydroxyacetone and *p*-trifluoromethylbenzaldehyde. Because the absolute configuration of **4** is (3*R*,4*R*) which had confirmed by the above method (See **Scheme 2**), major enantiomer of **12** must be (3*R*,4*R*).

References:

1. K. S. Kim, and S. D. Hong, *Tetrahedron Lett*., 2000, **41**, 5909.
2. H. O. Kim, H. W. Baek, H. R. Moon, D.-K. Kim, M. W. Chun, and L. S. Jeong, *Org. Biomol. Chem*., 2004, **2**, 1164.
3. M. Sodeoka, H. Yamada, and M. Shibasaki, *J. Am. Chem. Soc*., 1990, **112**, 4906.
4. D. Enders, C. Grondal, M. Vrettou, and G.. Raabe, *Angew. Chem. Int. Ed*., 2005, **44**, 4079.
5. M. Kitamura, M. Isobe, Y. Ichikawa, and T. Goto, *J. Am. Chem. Soc.*, 1984, **106**, 3252.
6. D. E. Ward, M. Sales, and P. Sasmal, *J. Org. Chem.*, 2004, **69**, 4808.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7.260
6.715
6.697
6.562
6.544
4.877
4.868
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4.768
4.432
4.392
4.123
4.084
3.689
3.669
OMe
HN
O
HO
OH
NO2
1
2.40
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2.01
1.08
1.10
1.16
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10.0
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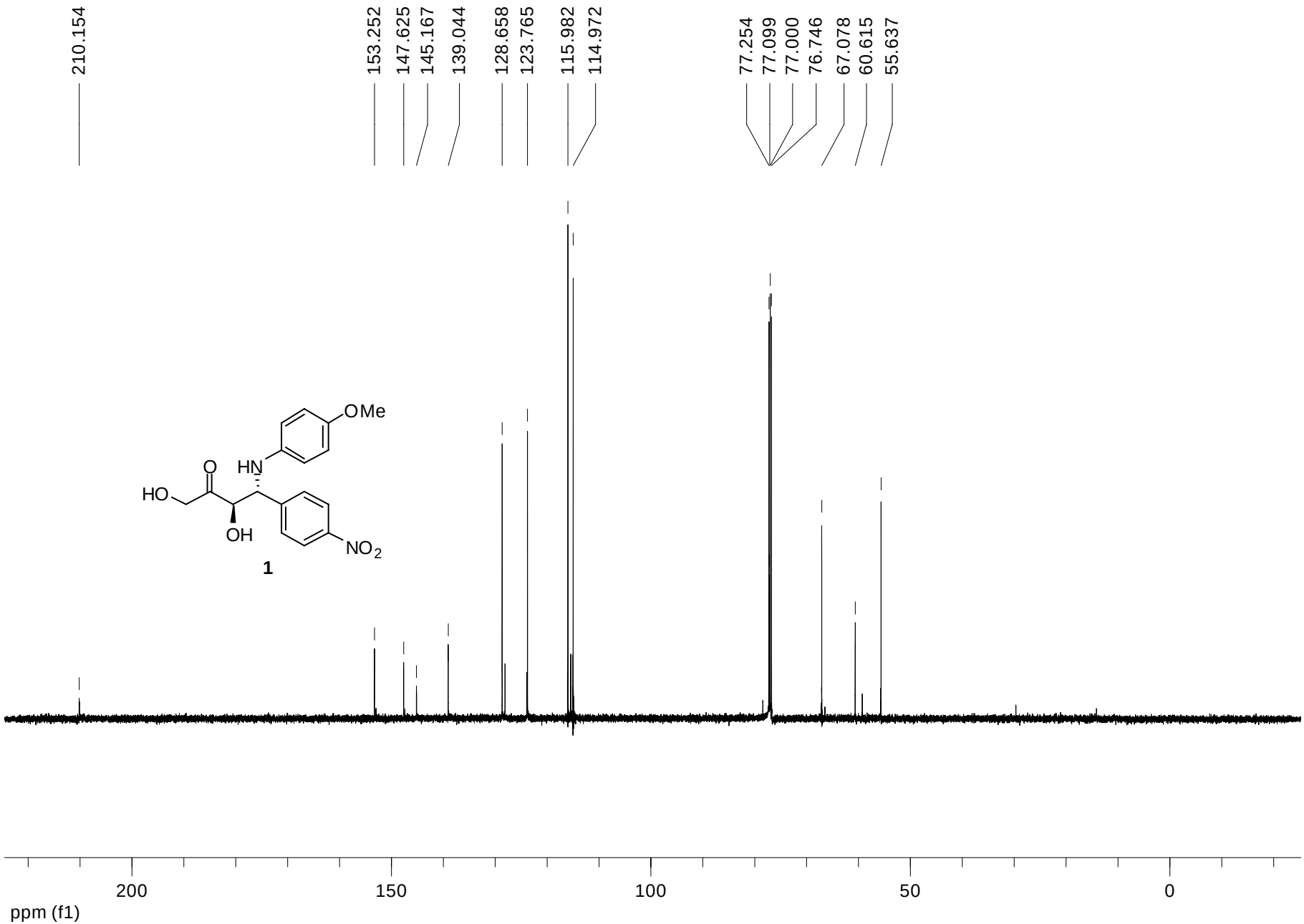
ppm (f1)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123.765
115.982
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77.254
77.099
77.000
76.746
67.078
60.615
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O
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OH
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1
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150
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50
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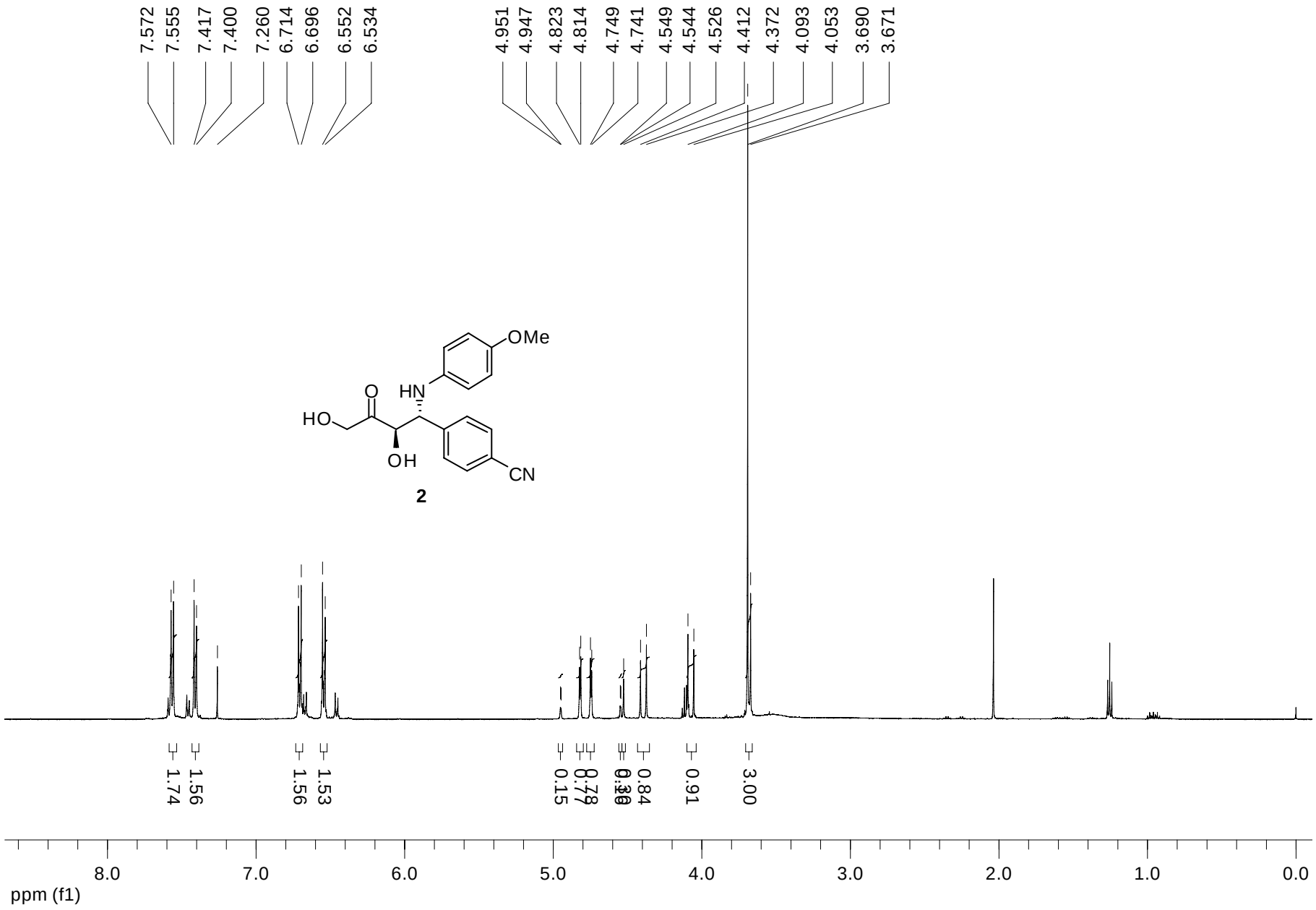
ppm (f1)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4.814
4.749
4.741
4.549
4.544
4.526
4.412
4.372
4.093
4.053
3.690
3.671
OMe
HN
O
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OH
CN
2
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1.56
1.56
1.53
0.15
0.84
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5.0
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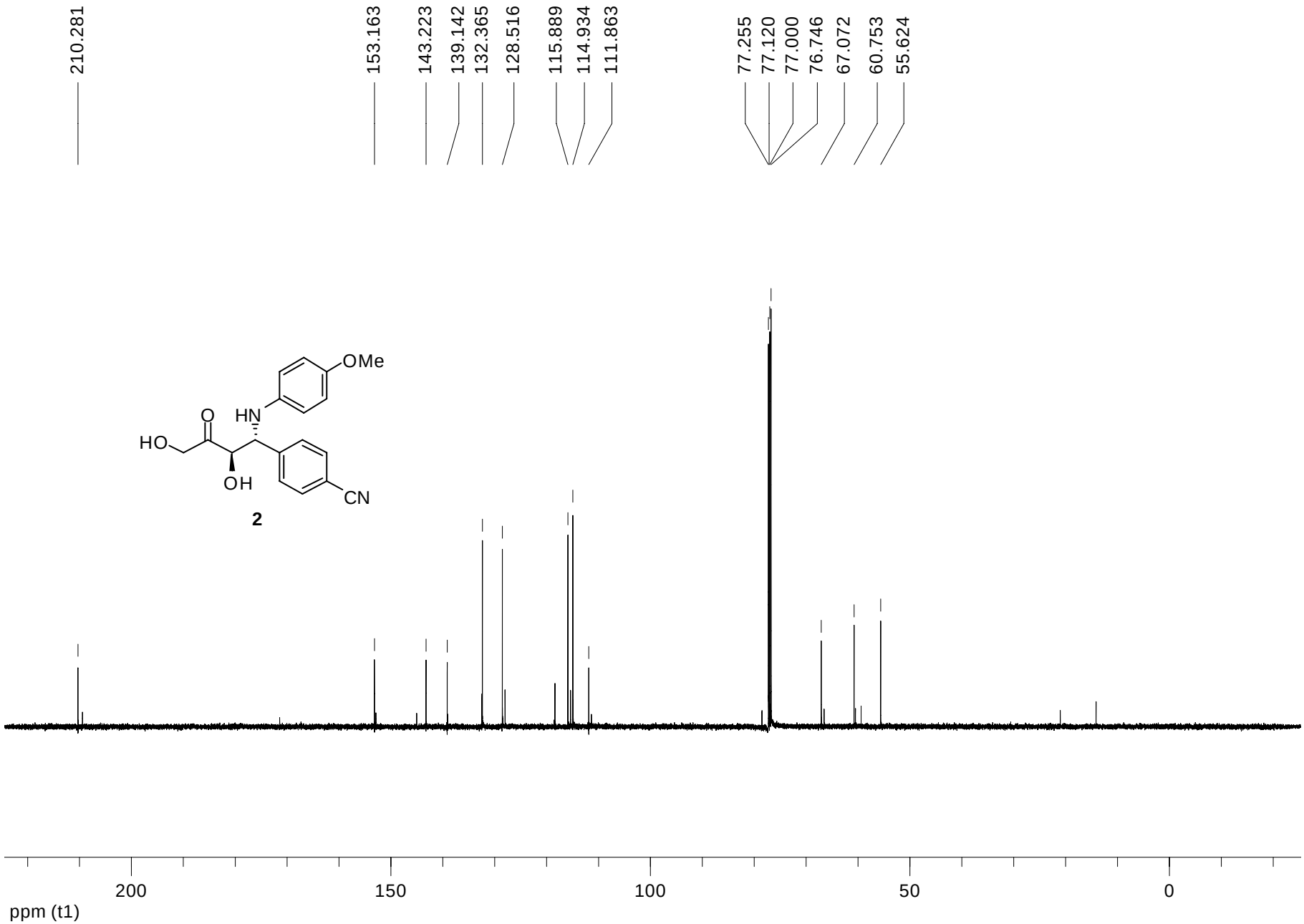
ppm (f1)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77.000
76.746
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CN
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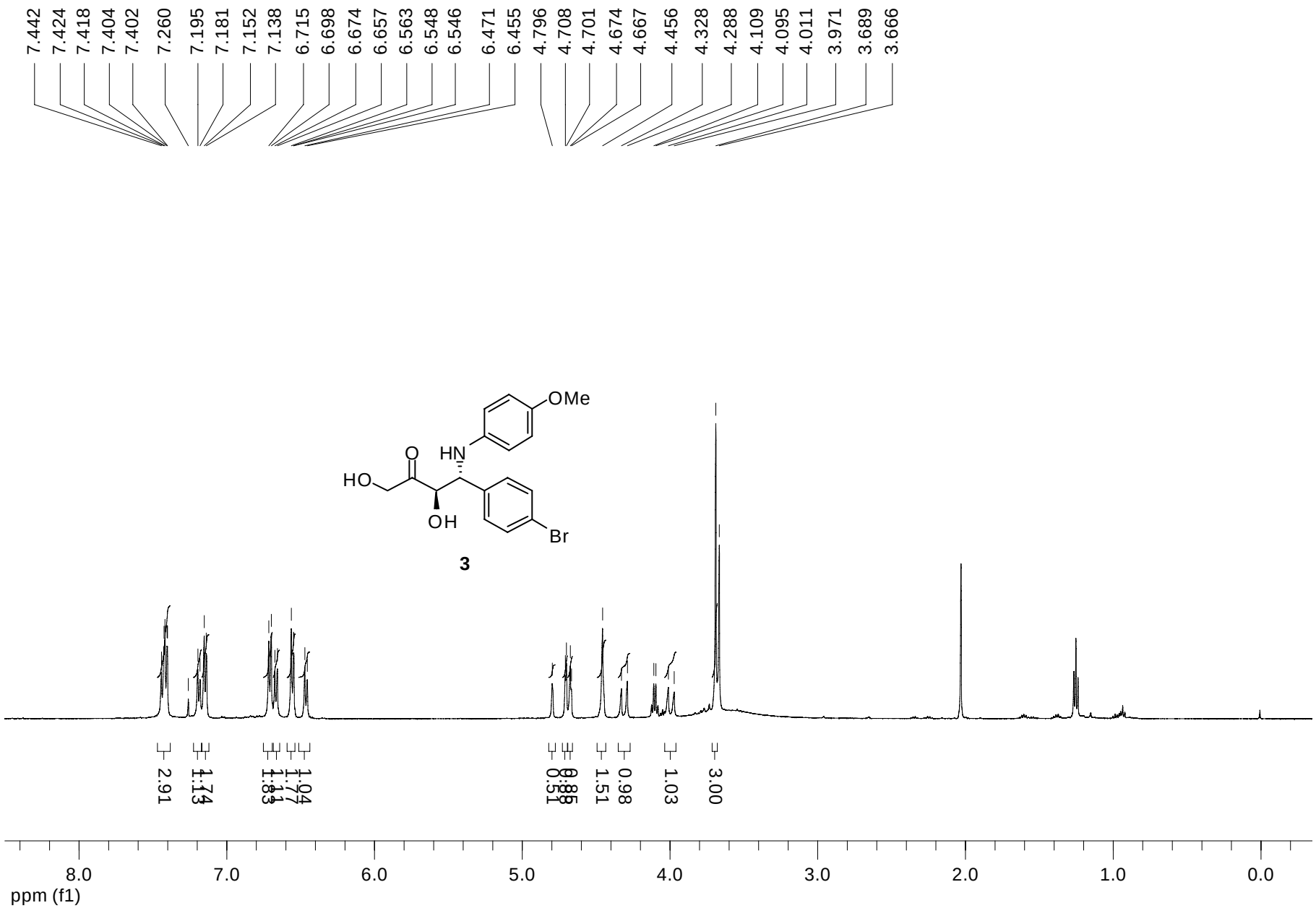
100
50
0
ppm (t1)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6.563
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6.546
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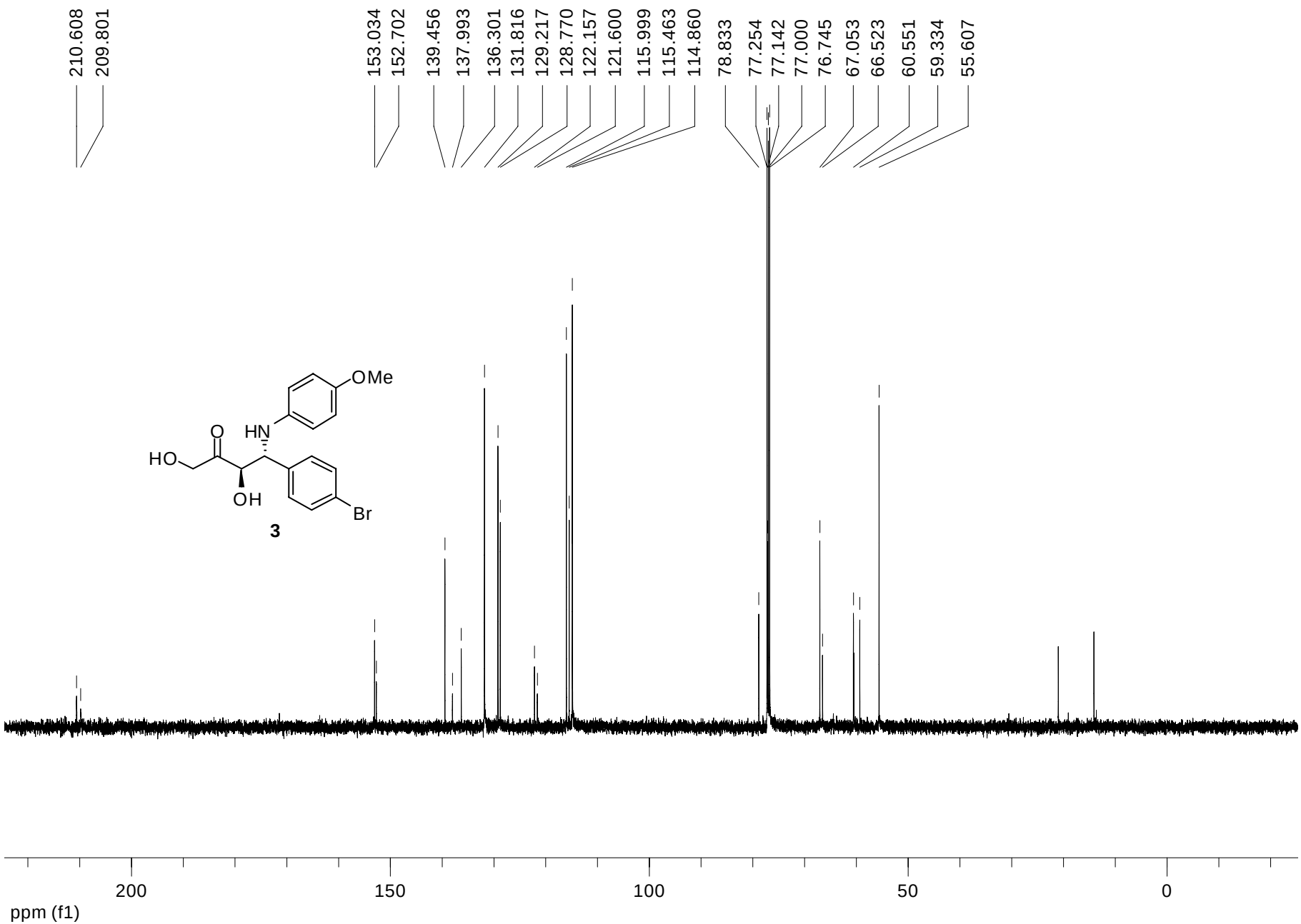
ppm (f1)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115.999
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77.254
77.142
77.000
76.745
67.053
66.523
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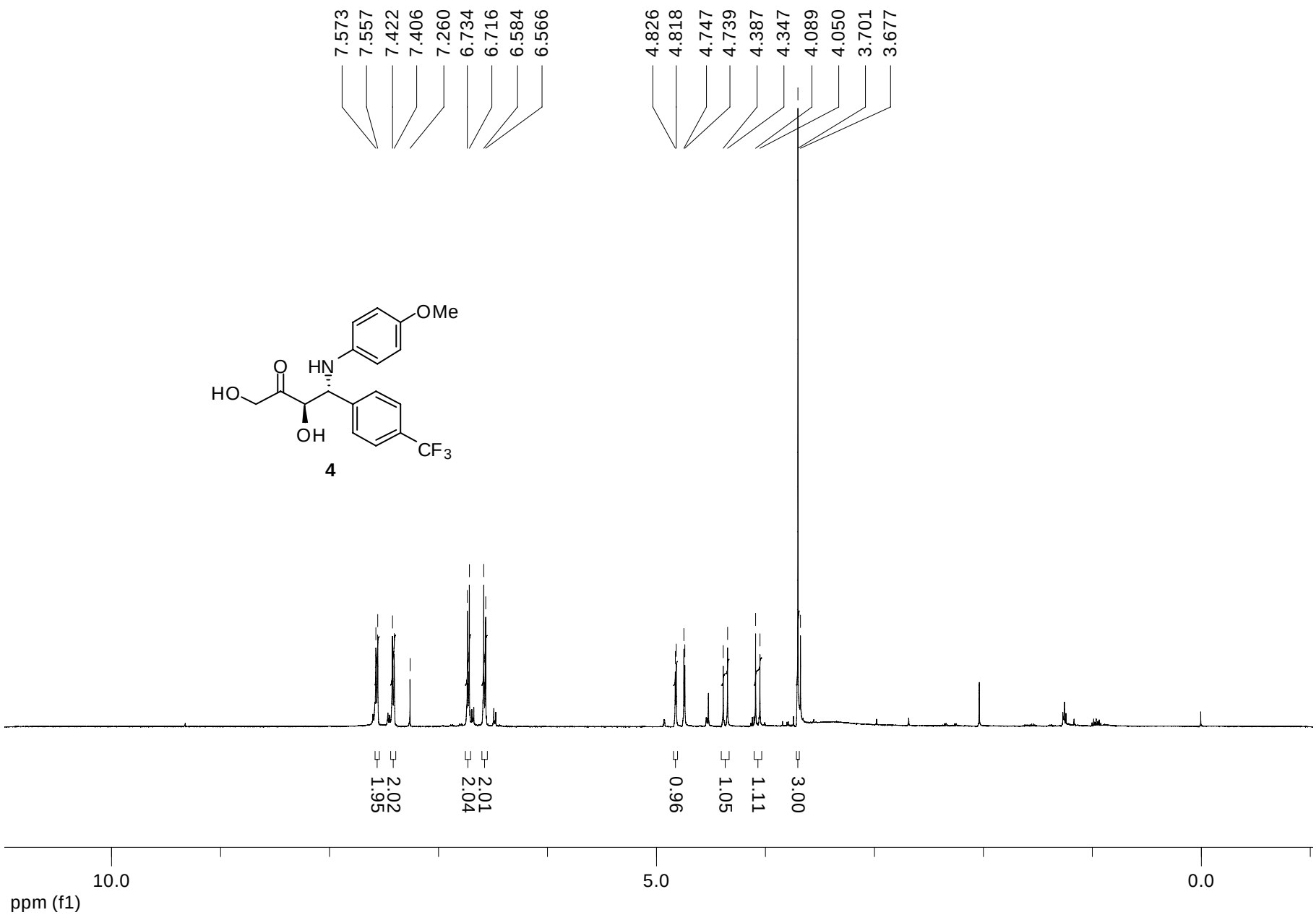
ppm (f1)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4.739
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4.347
4.089
4.050
3.701
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HO
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2.01
0.96
1.05
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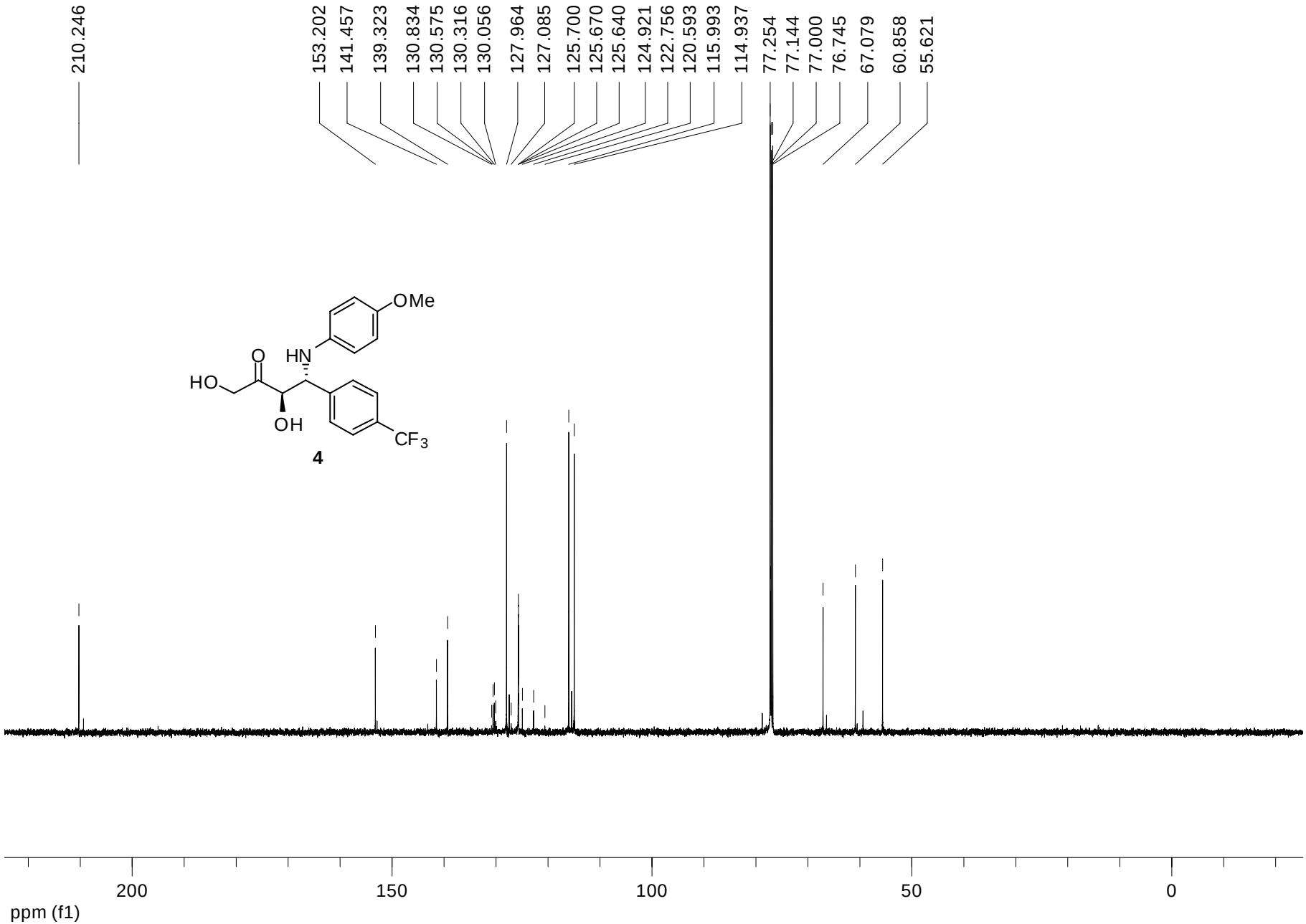
5.0
0.0
ppm (f1)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125.640
124.921
122.756
120.593
115.993
114.937
77.254
77.144
77.000
76.745
67.079
60.858
55.621
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O
HO
OH
CF3
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100
50
0
ppm (f1)

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4.436
4.399
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3.522
3.515
3.497
3.490
3.436
3.417
3.398
1.881
1.832
1.825
1.779
1.740
1.728
1.716
1.706
1.689
1.678
1.669
1.653
1.642
1.632
1.581
1.579
1.534
1.266
1.257
1.247
1.231
1.221
1.206
1.183
1.164
1.157
1.146
1.127
1.117
O
NHPMP
OH
OH
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2.00
0.96
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1.51
3.09
10.90
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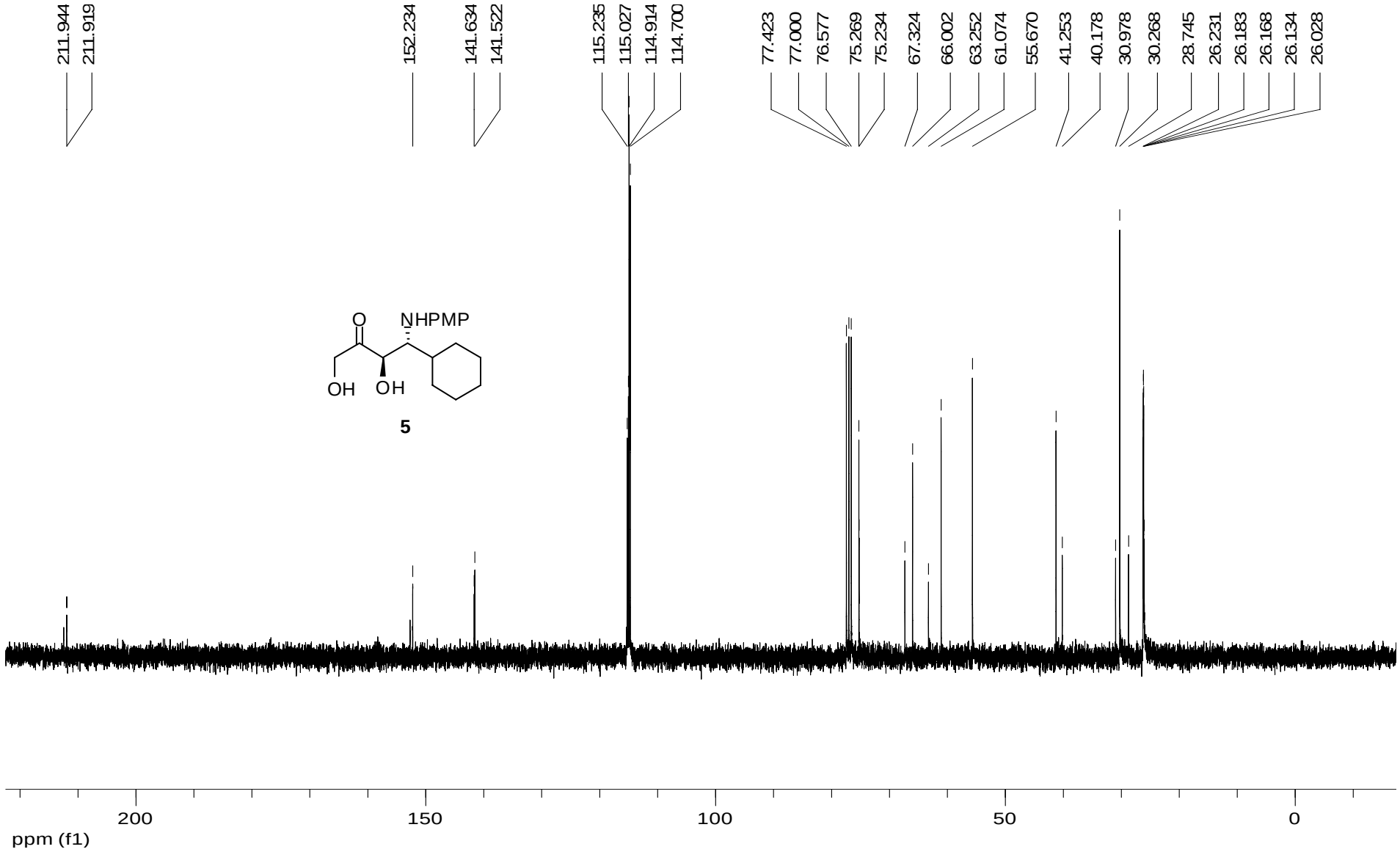
ppm (f1)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75.234
67.324
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63.252
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55.670
41.253
40.178
30.978
30.268
28.745
26.231
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26.134
26.028
O
NHPMP
OH
OH
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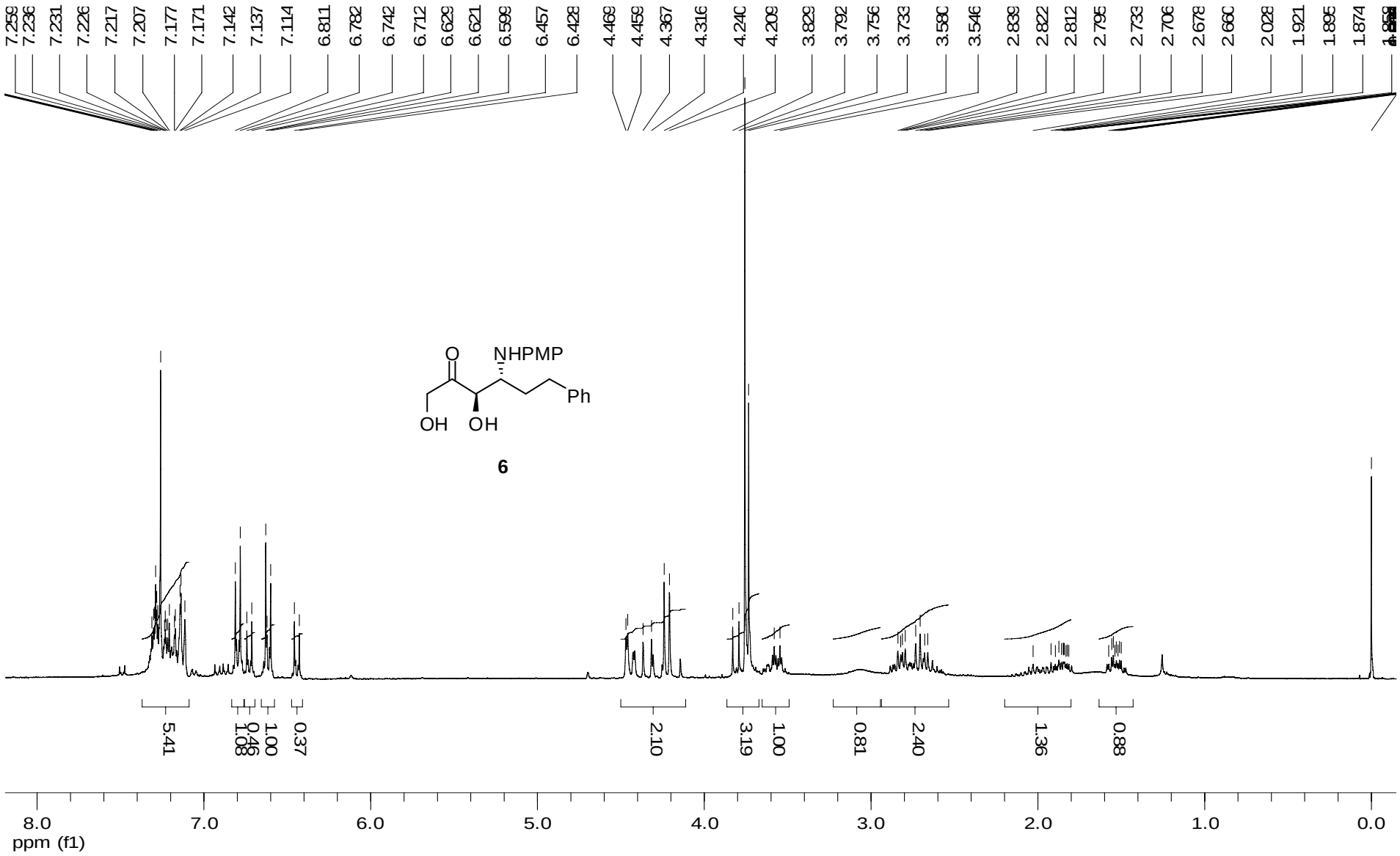
ppm (f1)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7.171
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7.137
7.114
6.811
6.782
6.742
6.712
6.629
6.621
6.599
6.457
6.428
4.468
4.459
4.367
4.316
4.240
4.209
3.829
3.792
3.756
3.733
3.580
3.546
2.839
2.822
2.812
2.795
2.733
2.706
2.678
2.660
2.028
1.921
1.895
1.874
O
NHPMP
Ph
OH
OH
6
5.41
1.08
0.46
1.00
0.37
2.10
3.19
1.00
0.81
2.40
1.36
0.88
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7.0
6.0
5.0
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3.0
2.0
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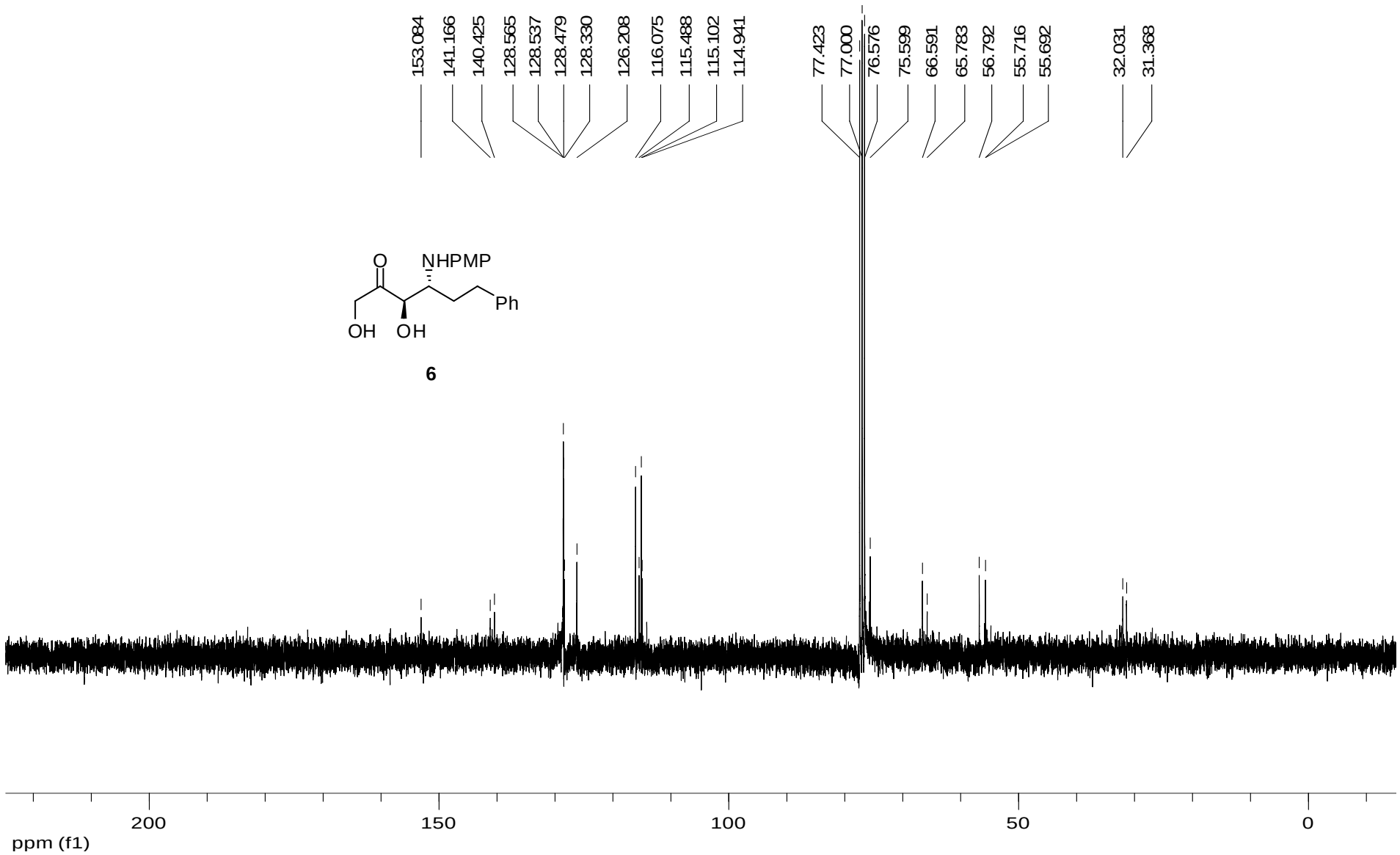
0.0
ppm (f1)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77.000
76.576
75.599
66.591
65.783
56.792
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O
NHPMP
Ph
OH
OH
6
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50
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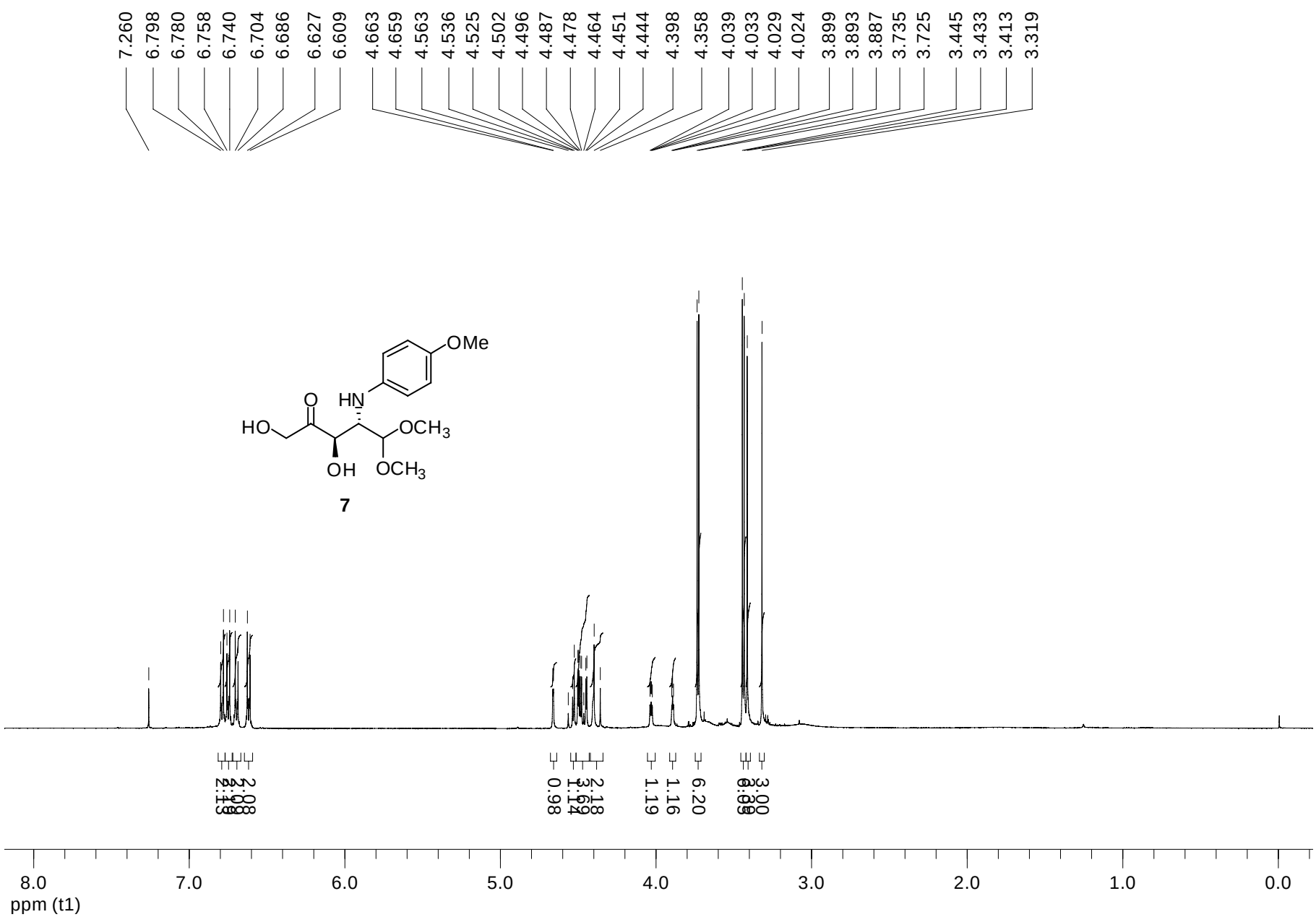
ppm (f1)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4.659
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4.536
4.525
4.502
4.496
4.487
4.478
4.464
4.451
4.444
4.398
4.358
4.039
4.033
4.029
4.024
3.899
3.893
3.887
3.735
3.725
3.445
3.433
3.413
3.319
OMe
HN
O
HO
OCH3
OH
OCH3
7
2.13
2.08
0.98
1.14
3.69
2.18
1.19
1.16
6.20
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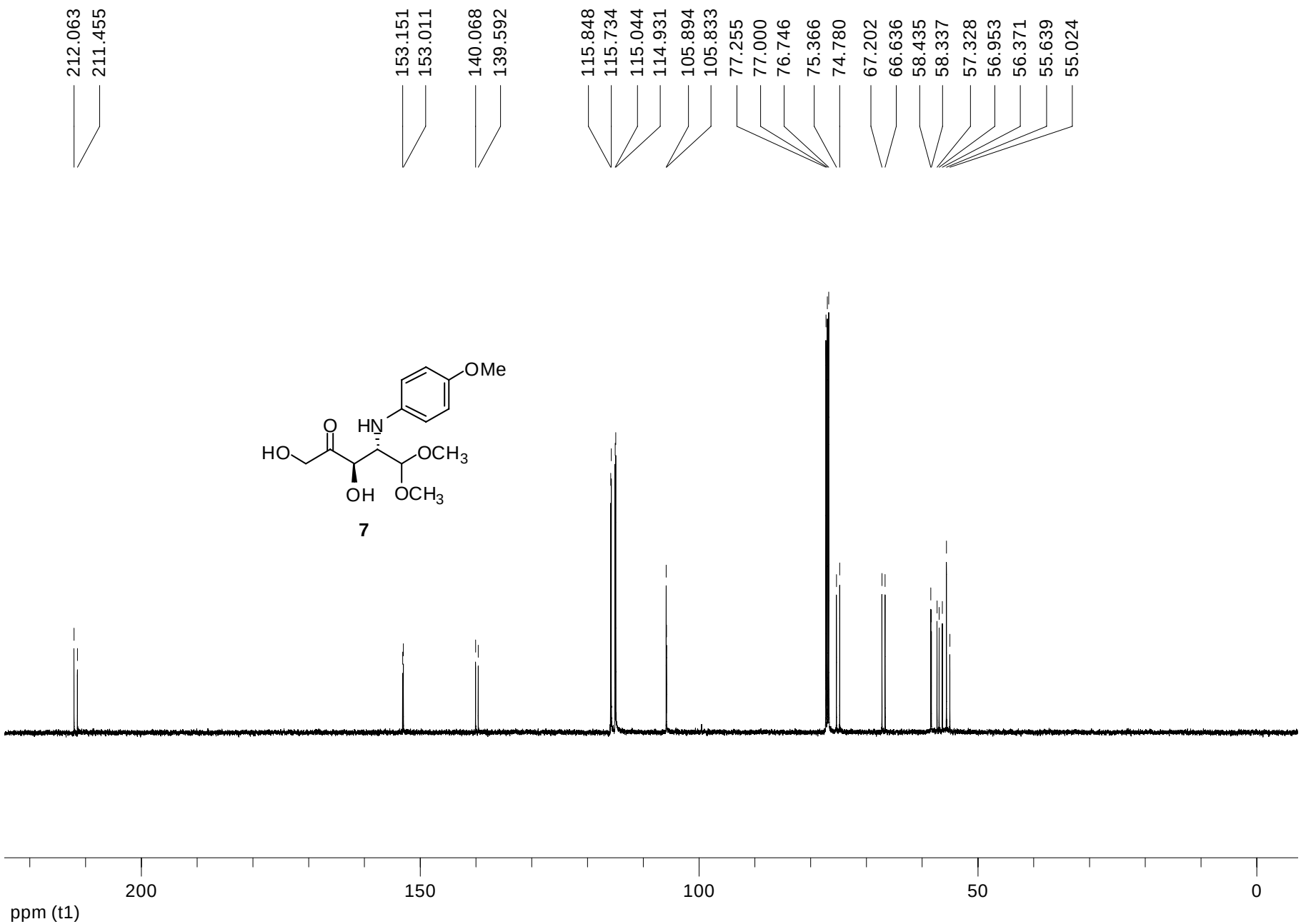
ppm (t1)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77.000
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74.780
67.202
66.636
58.435
58.337
57.328
56.953
56.371
55.639
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OMe
HN
O
HO
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OH
OCH3
7
200
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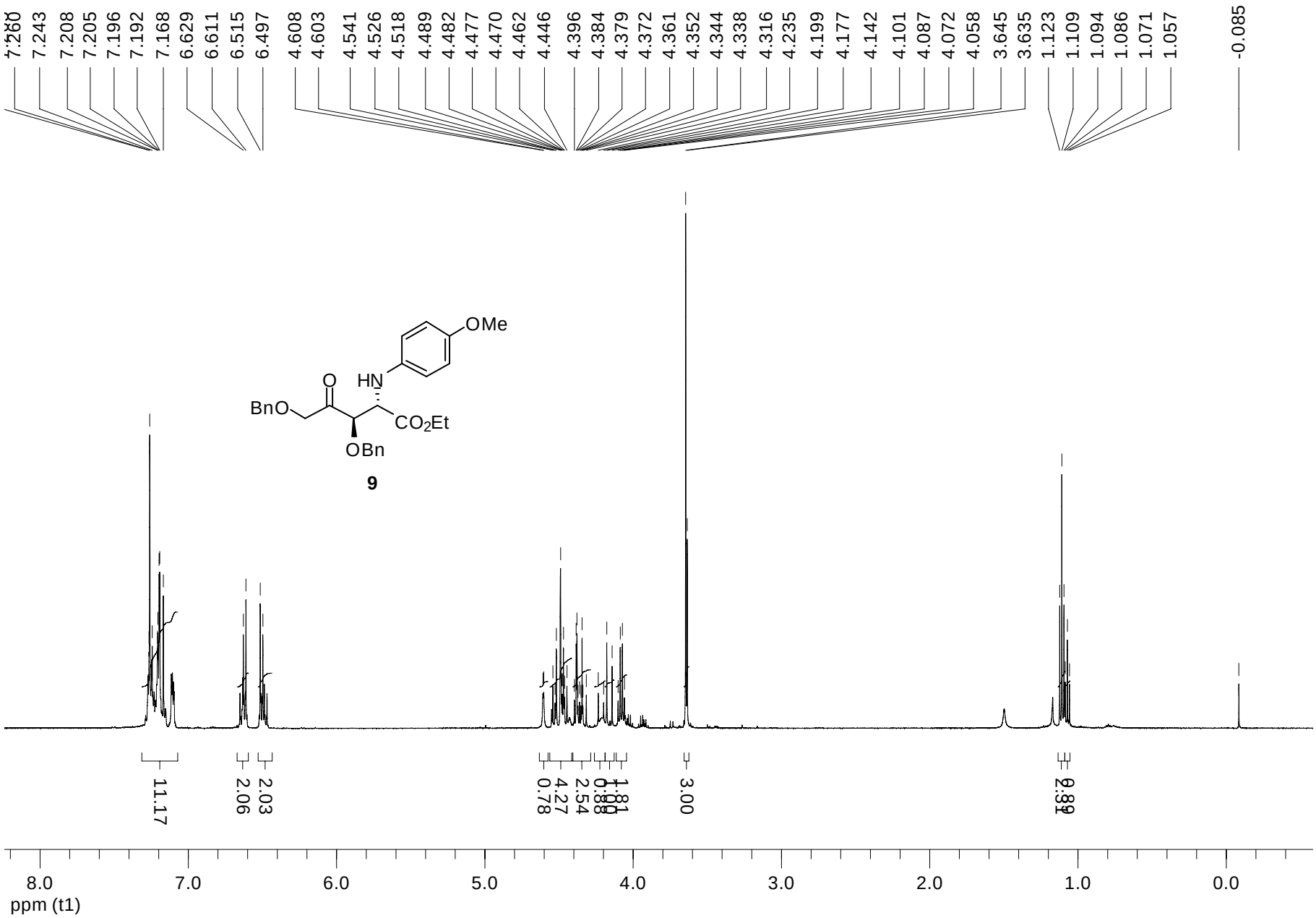
100
50
0
ppm (t1)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7.192
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6.629
6.611
6.515
6.497
4.608
4.603
4.541
4.526
4.518
4.489
4.482
4.477
4.470
4.462
4.446
4.396
4.384
4.379
4.372
4.361
4.352
4.344
4.338
4.316
4.235
4.199
4.177
4.142
4.101
4.087
4.072
4.058
3.645
3.635
1.123
1.109
1.094
1.086
1.071
1.057
-0.085
OMe
HN
O
BnO
CO2Et
OBn
9
11.17
2.06
2.03
0.78
4.27
2.54
3.00
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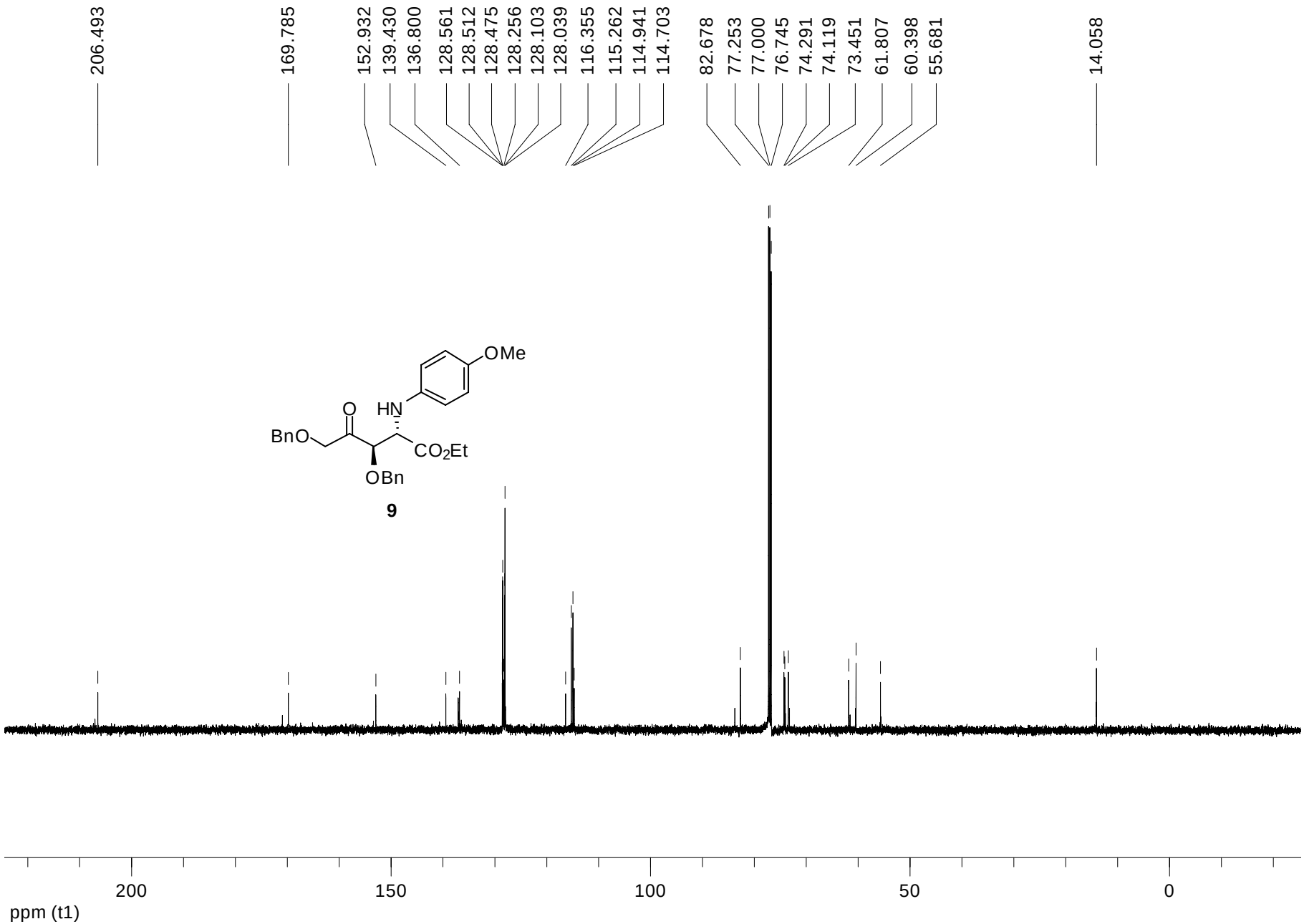
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)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128.039
116.355
115.262
114.941
114.703
82.678
77.253
77.000
76.745
74.291
74.119
73.451
61.807
60.398
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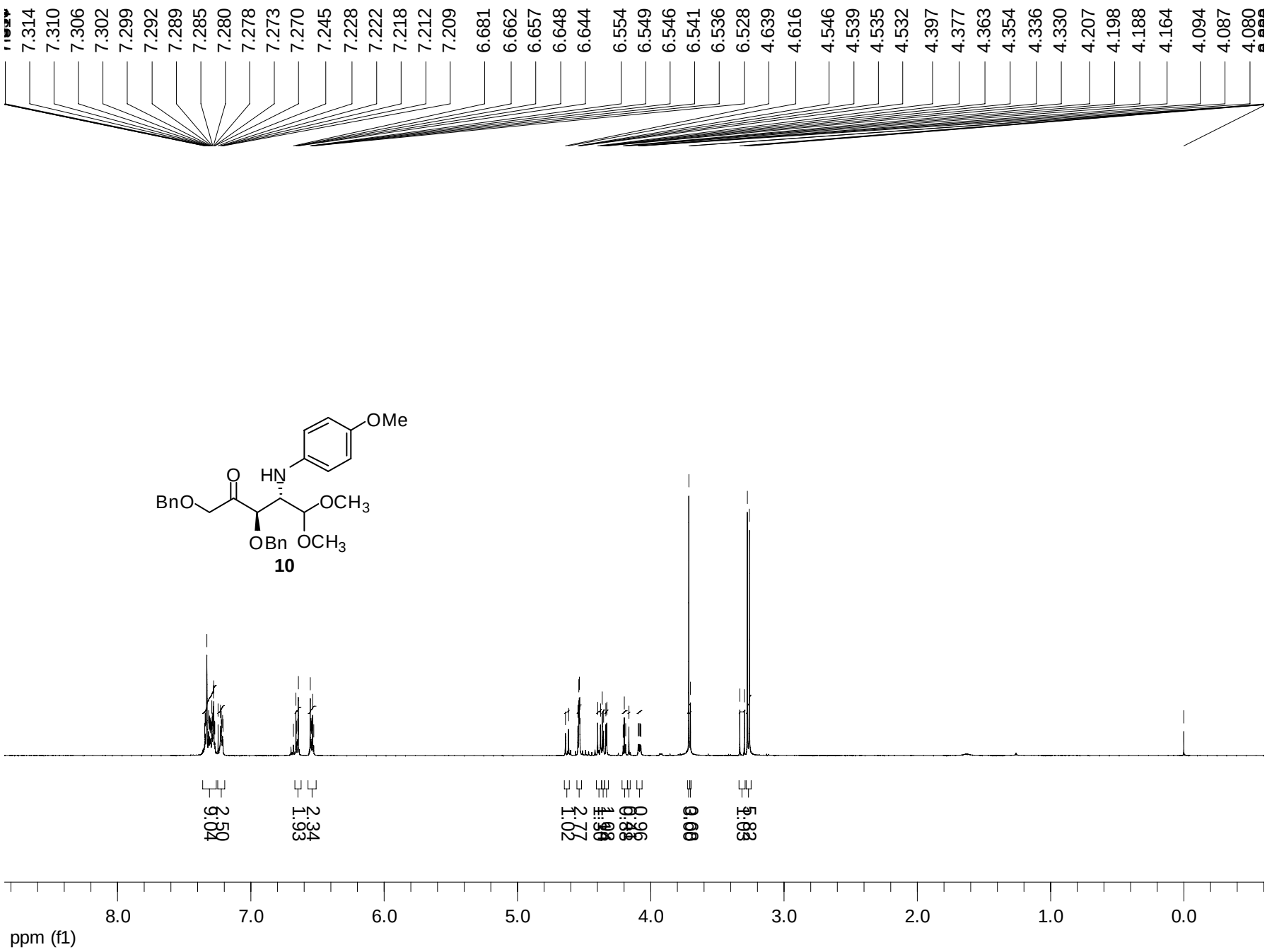
OMe
HN
O
BnO
CO2Et
OBn
9
200
150
100
50
0
ppm (t1)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7.292
7.289
7.285
7.280
7.278
7.273
7.270
7.245
7.228
7.222
7.218
7.212
7.209
6.681
6.662
6.657
6.648
6.644
6.554
6.549
6.546
6.541
6.536
6.528
4.639
4.616
4.546
4.539
4.535
4.532
4.397
4.377
4.363
4.354
4.336
4.330
4.207
4.198
4.188
4.164
4.094
4.087
4.080
OMe
HN
O
BnO
OCH3
OBn
OCH3
10
2.50
2.34
1.93
1.72
2.77
1.00
0.88
0.96
1.00
5.83
8.0
7.0
6.0
5.0
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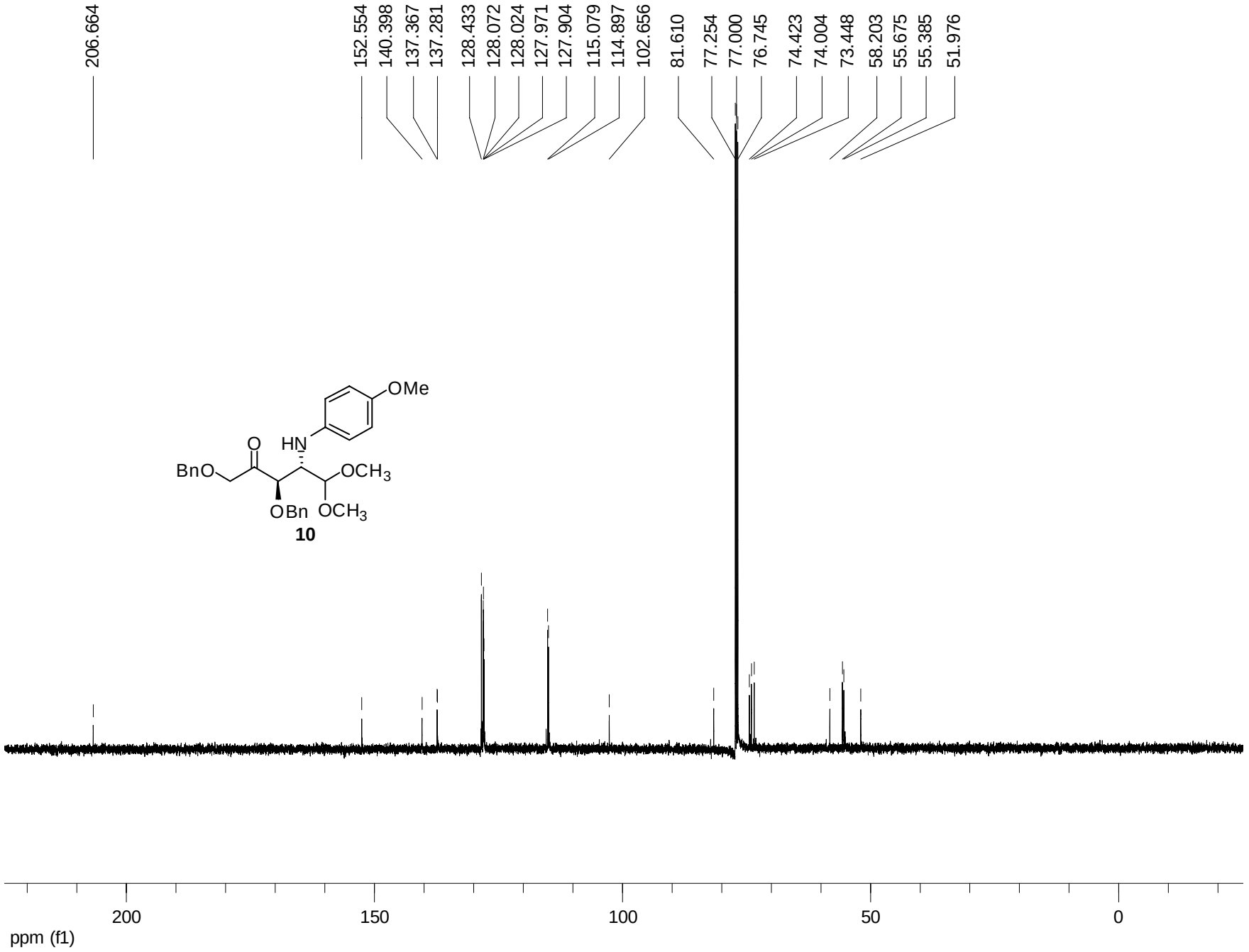
3.0
2.0
1.0
0.0
ppm (f1)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77.254
77.000
76.745
74.423
74.004
73.448
58.203
55.675
55.385
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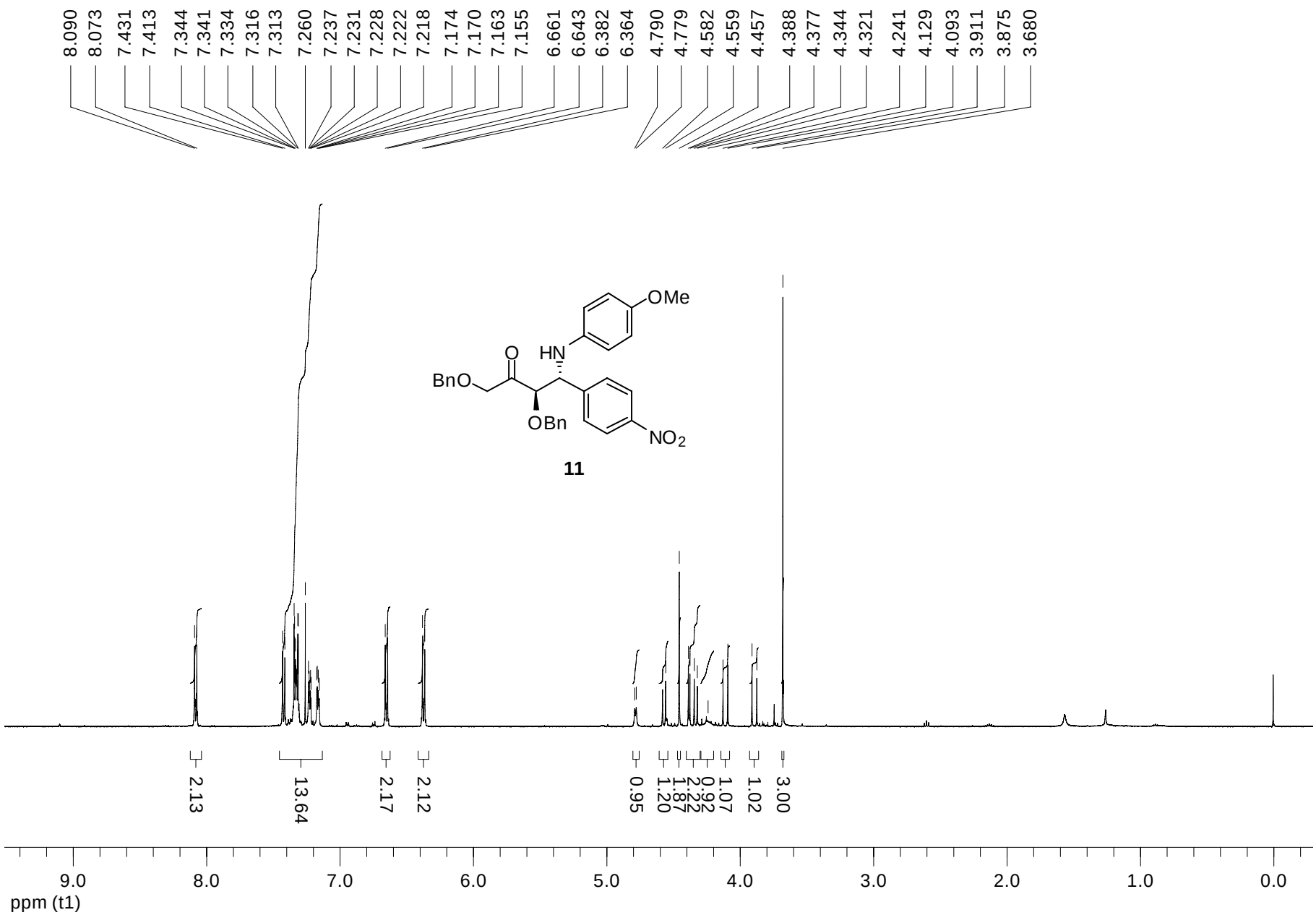
HN
O
BnO
OCH3
OBn
OCH3
10
200
150
100
50
0
ppm (f1)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7.313
7.260
7.237
7.231
7.228
7.222
7.218
7.174
7.170
7.163
7.155
6.661
6.643
6.382
6.364
4.790
4.779
4.582
4.559
4.457
4.388
4.377
4.344
4.321
4.241
4.129
4.093
3.911
3.875
3.680
OMe
HN
O
BnO
OBn
NO2
11
2.13
13.64
2.17
2.12
0.95
1.20
1.87
2.22
0.92
1.07
1.02
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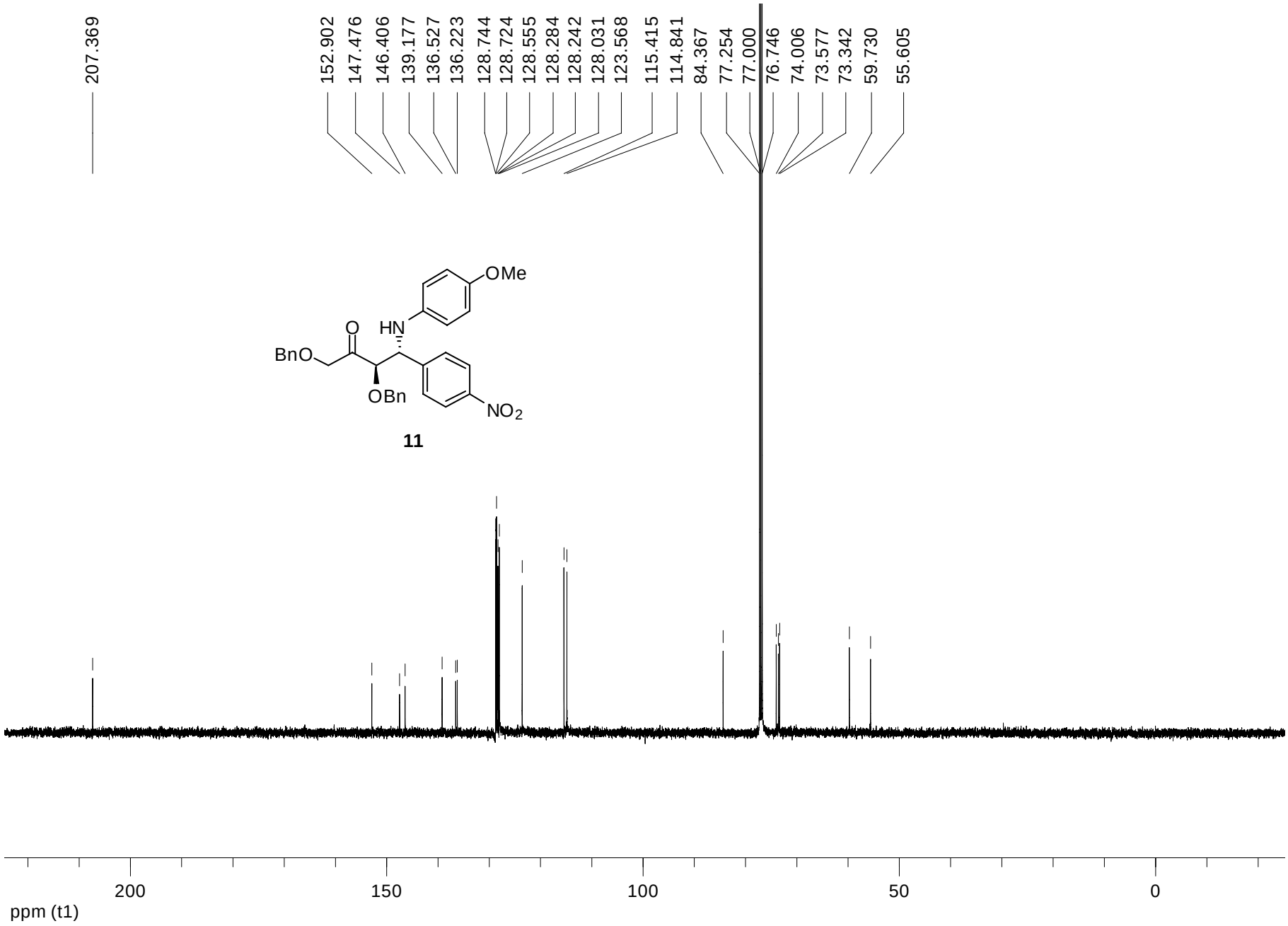
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)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128.242
128.031
123.568
115.415
114.841
84.367
77.254
77.000
76.746
74.006
73.577
73.342
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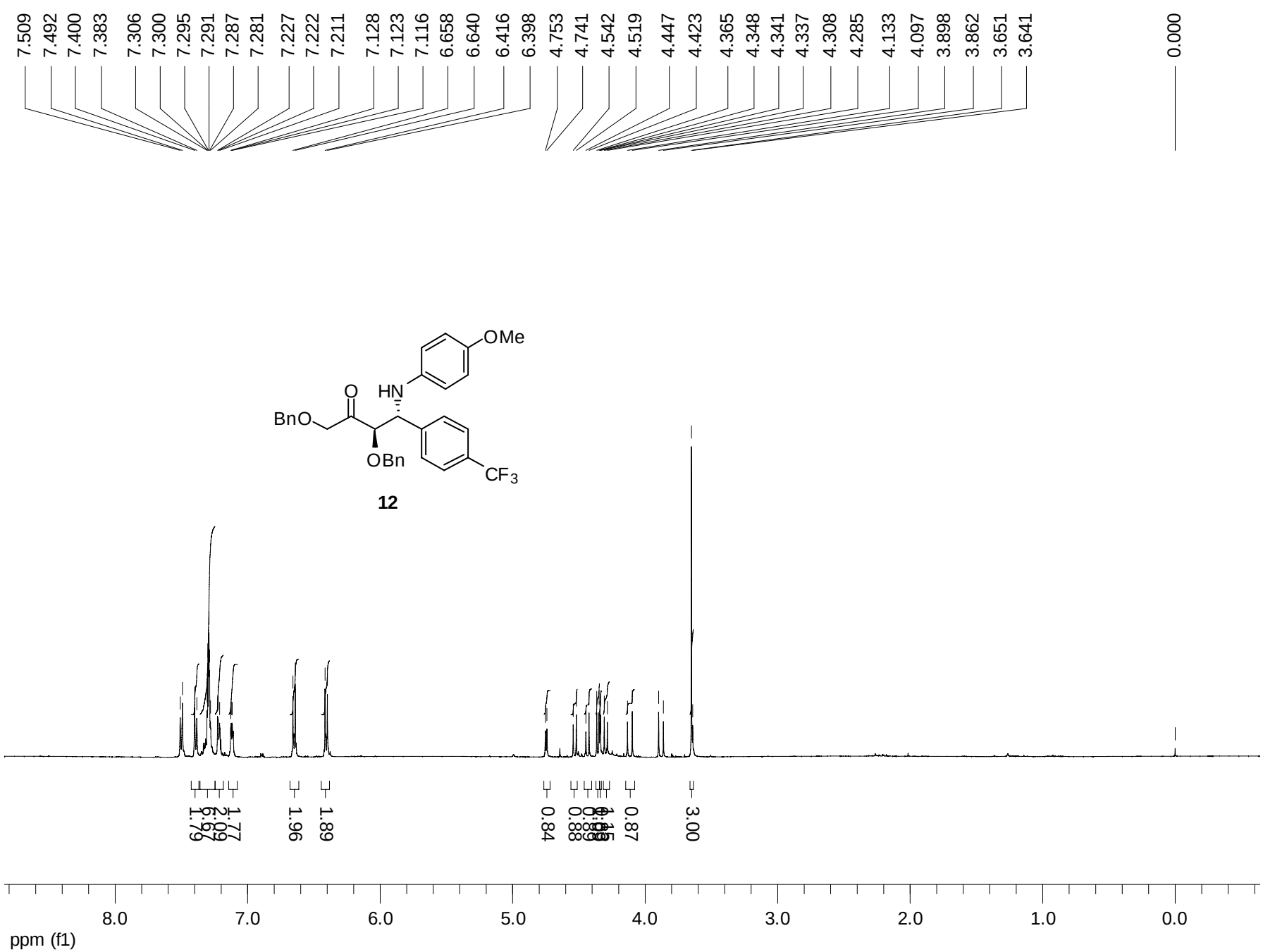
OMe
HN
O
BnO
OBn
NO2
200
150
100
50
0
ppm (t1)

11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7.227
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7.211
7.128
7.123
7.116
6.658
6.640
6.416
6.398
4.753
4.741
4.542
4.519
4.447
4.423
4.365
4.348
4.341
4.337
4.308
4.285
4.133
4.097
3.898
3.862
3.651
3.641
0.000
OMe
HN
O
BnO
OBn
CF3
12
1.79
1.96
1.89
0.84
0.88
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2.0
1.0
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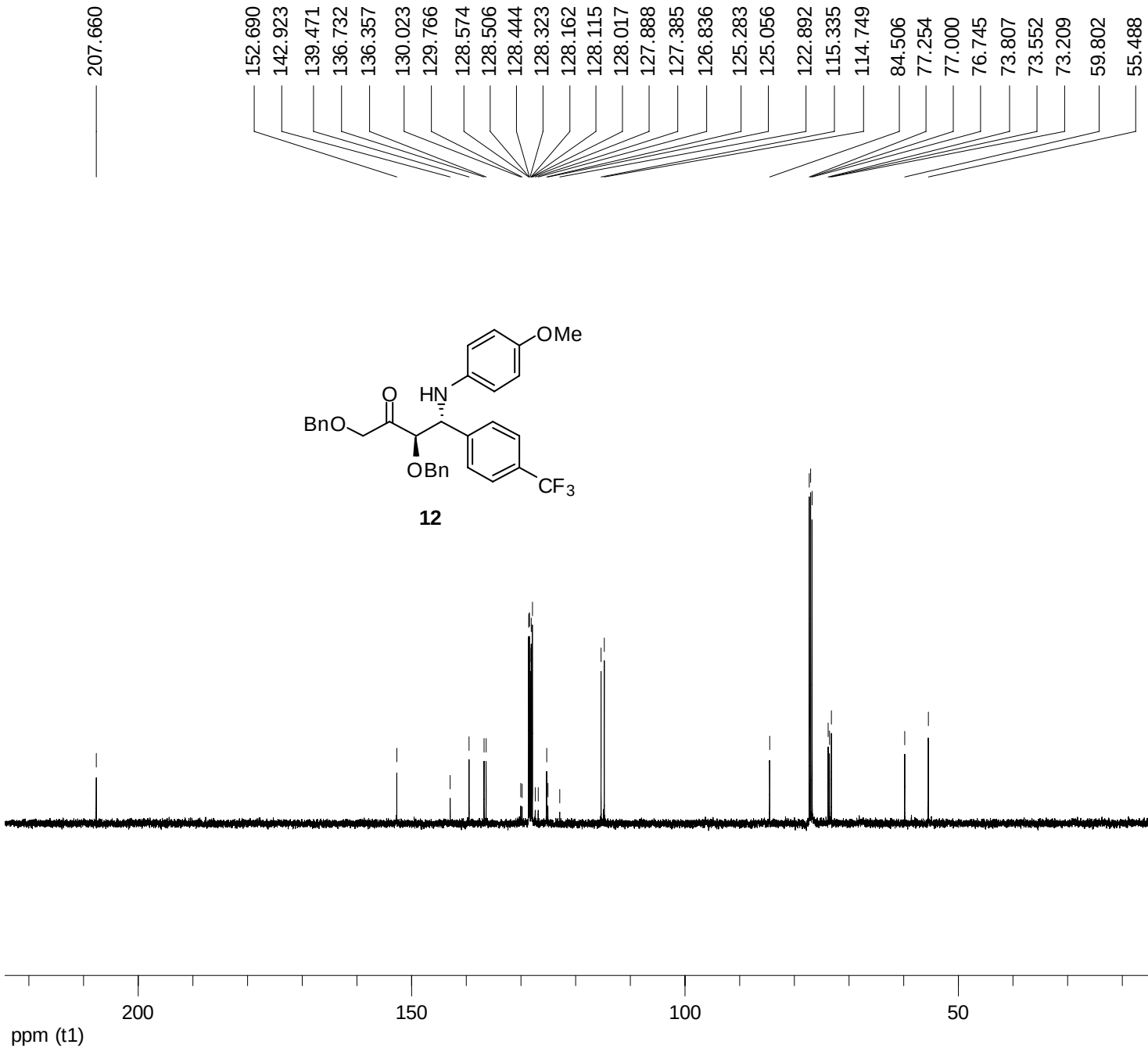
ppm (f1)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128.115
128.017
127.888
127.385
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125.283
125.056
122.892
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114.749
84.506
77.254
77.000
76.745
73.807
73.552
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HN
O
BnO
OBn
CF3
12
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100
50
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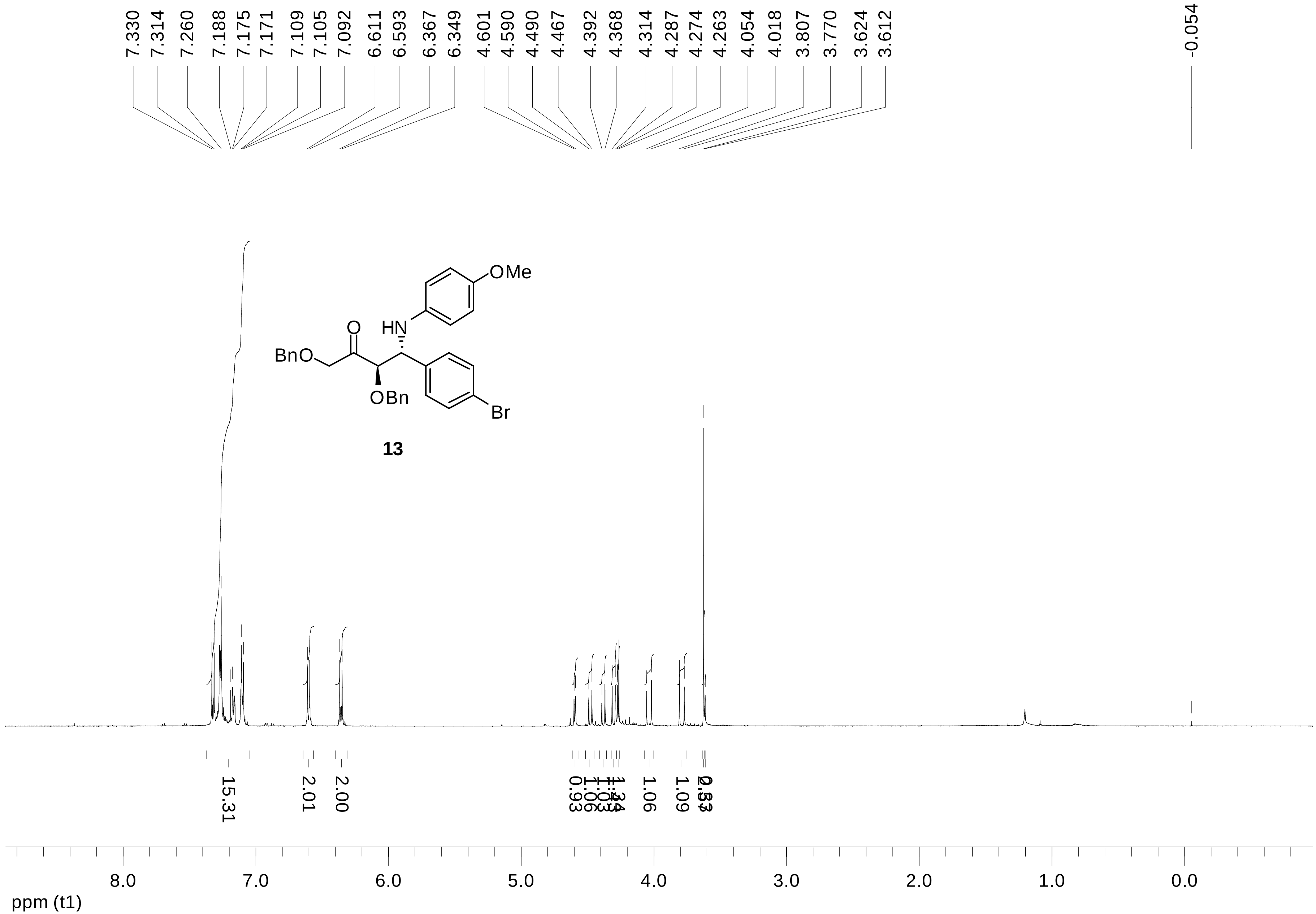
ppm (t1)



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7.105
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6.367
6.349
4.601
4.590
4.490
4.467
4.392
4.368
4.314
4.287
4.274
4.263
4.054
4.018
3.807
3.770
3.624
3.612
-0.054
OMe
HN
O
BnO
OBn
Br
13
15.31
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2.00
0.93
1.06
1.06
1.09
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1.0
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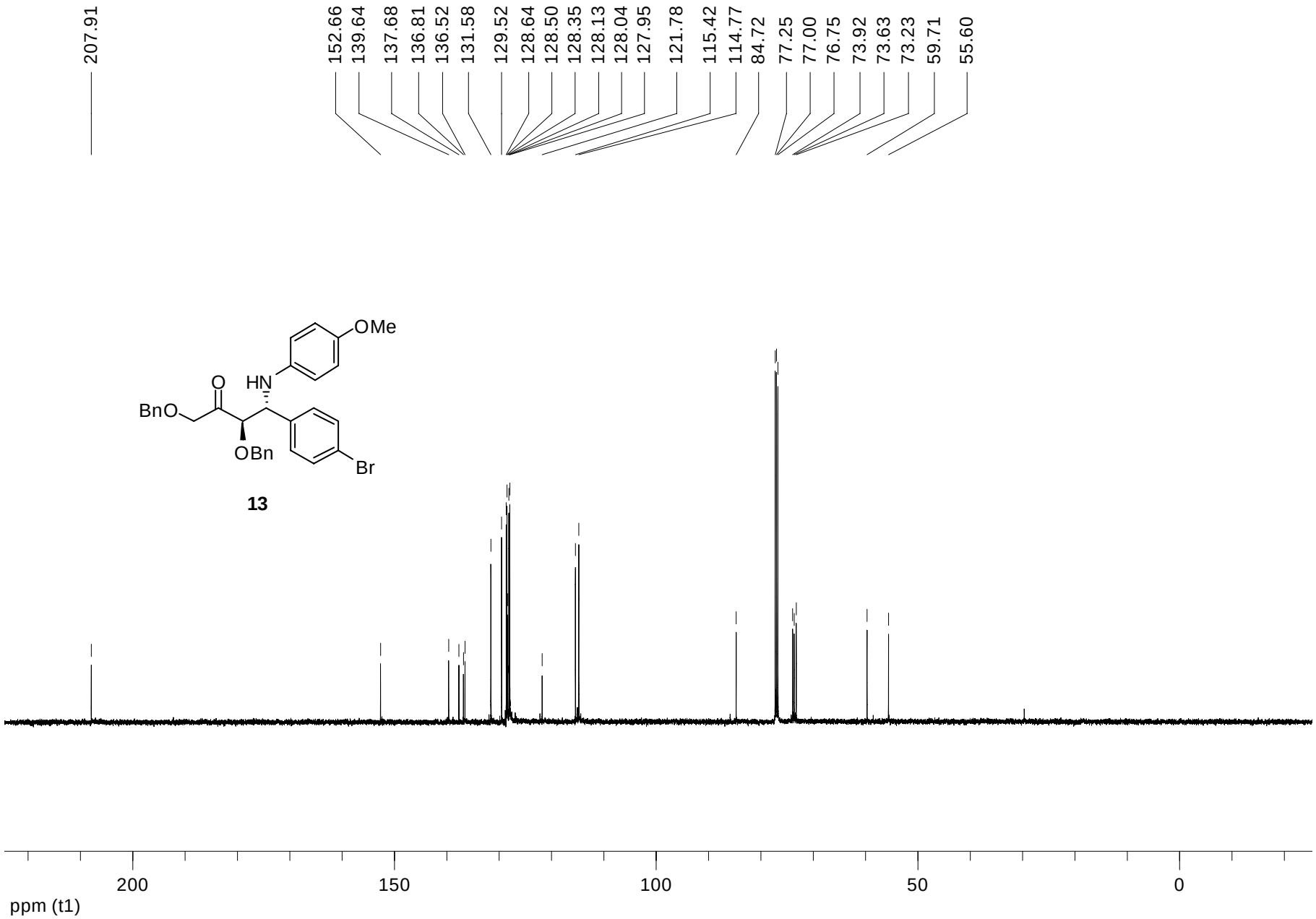
ppm (t1)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128.04
127.95
121.78
115.42
114.77
84.72
77.25
77.00
76.75
73.92
73.63
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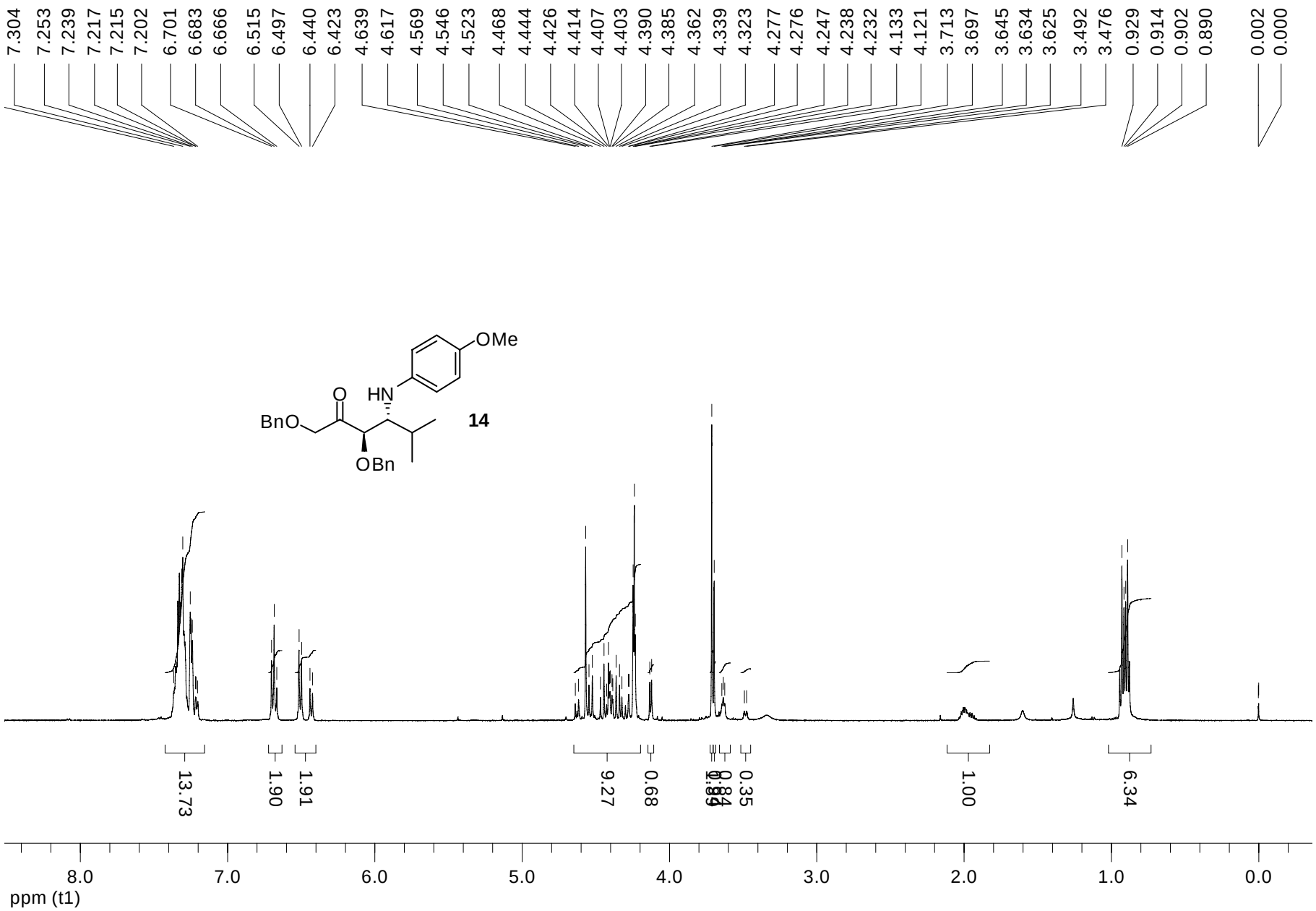
OMe
HN
O
BnO
OBn
Br
13
200
150
100
50
0
ppm (t1)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6.423
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4.617
4.569
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4.523
4.468
4.444
4.426
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4.276
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4.238
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3.713
3.697
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3.634
3.625
3.492
3.476
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0.914
0.902
0.890
0.002
0.000
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HN
O
BnO
OBn
14
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1.91
9.27
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0.35
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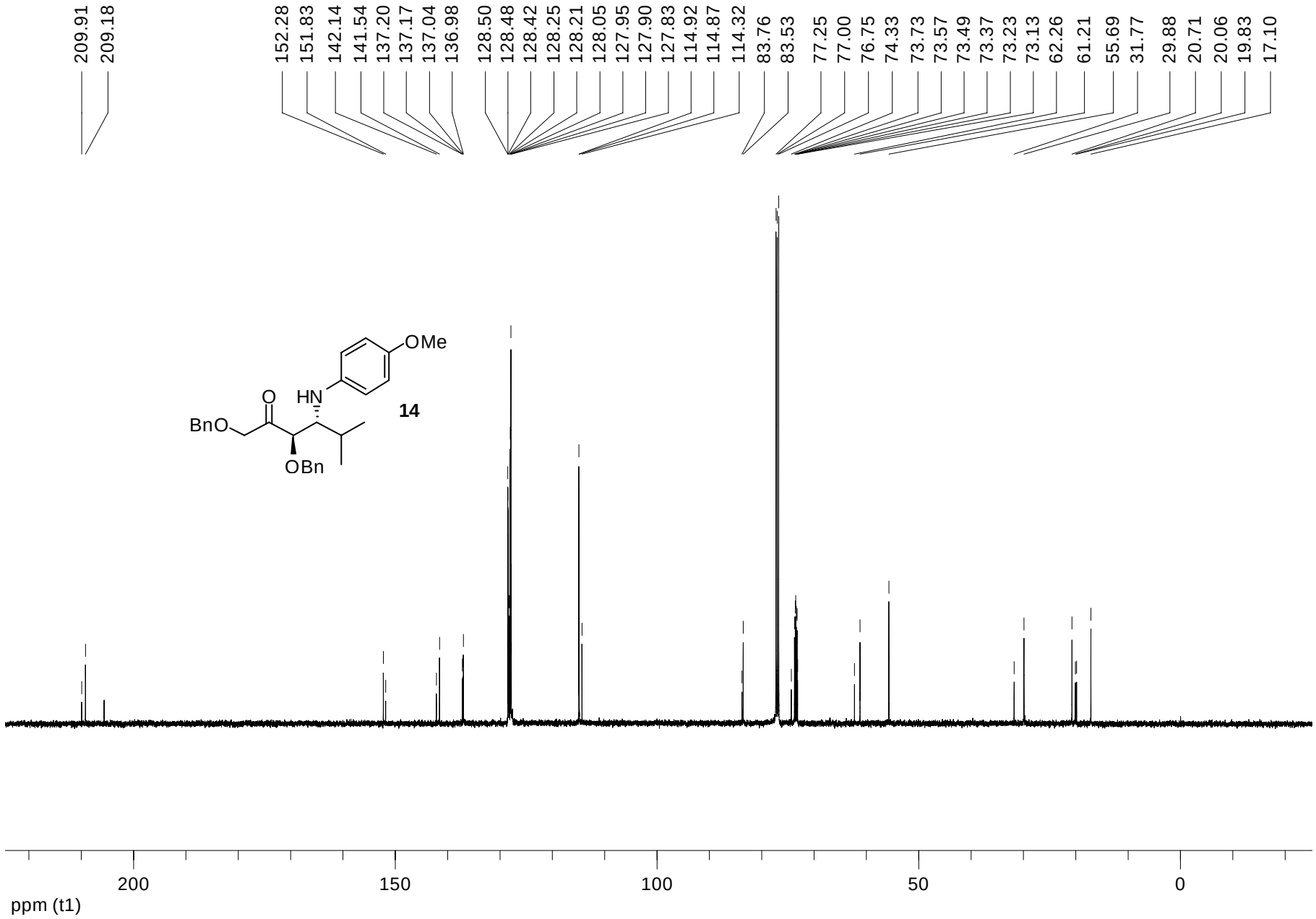
ppm (t1)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128.21
128.05
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127.90
127.83
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114.87
114.32
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83.53
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73.73
73.57
73.49
73.37
73.23
73.13
62.26
61.21
55.69
31.77
29.88
20.71
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17.10
OMe
HN
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BnO
OBn
14
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50
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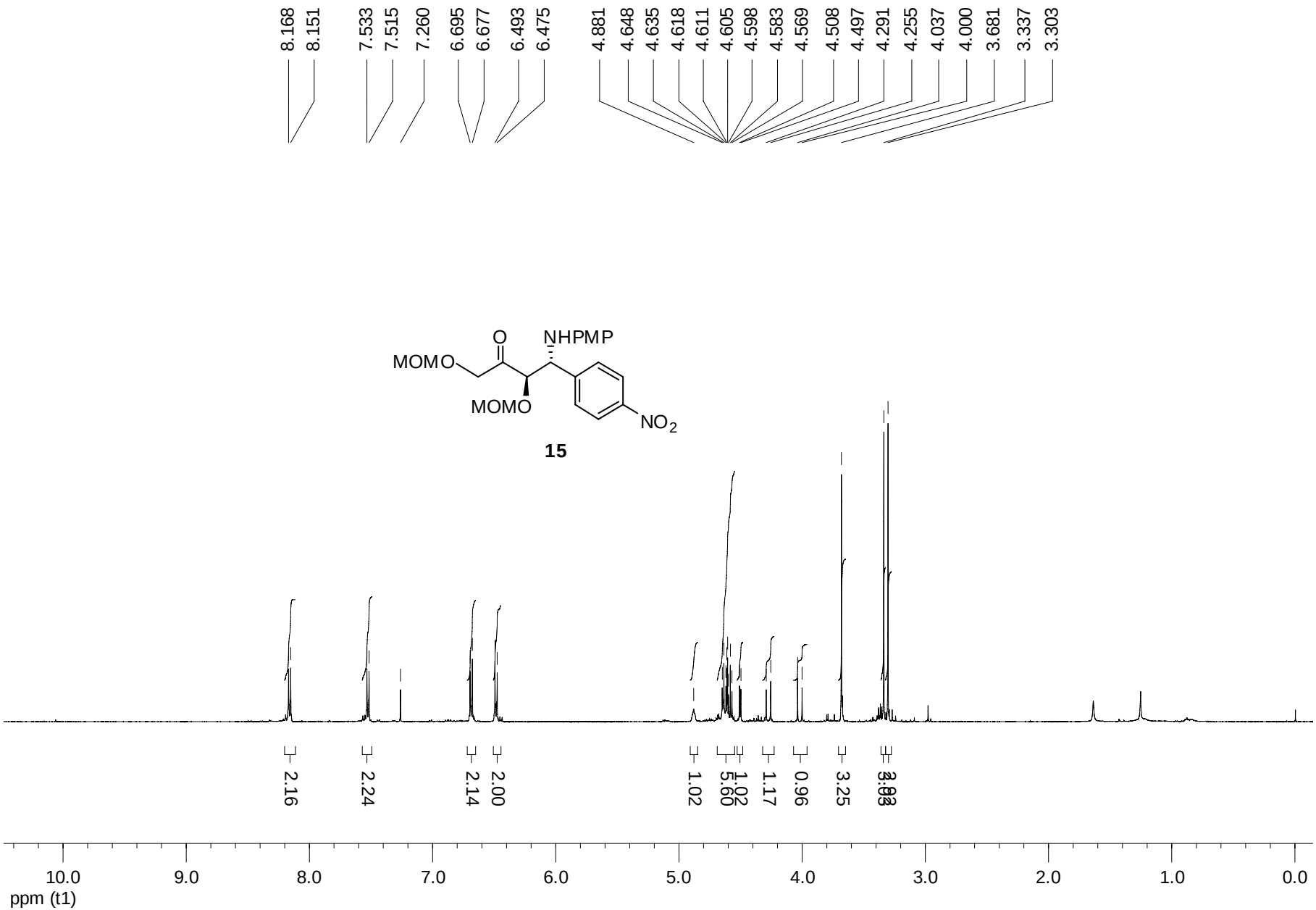
ppm (t1)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4.618
4.611
4.605
4.598
4.583
4.569
4.508
4.497
4.291
4.255
4.037
4.000
3.681
3.337
3.303
MOMO
O
NHPMP
MOMO
NO2
15
2.16
2.24
2.14
2.00
1.02
5.60
1.02
1.17
0.96
3.25
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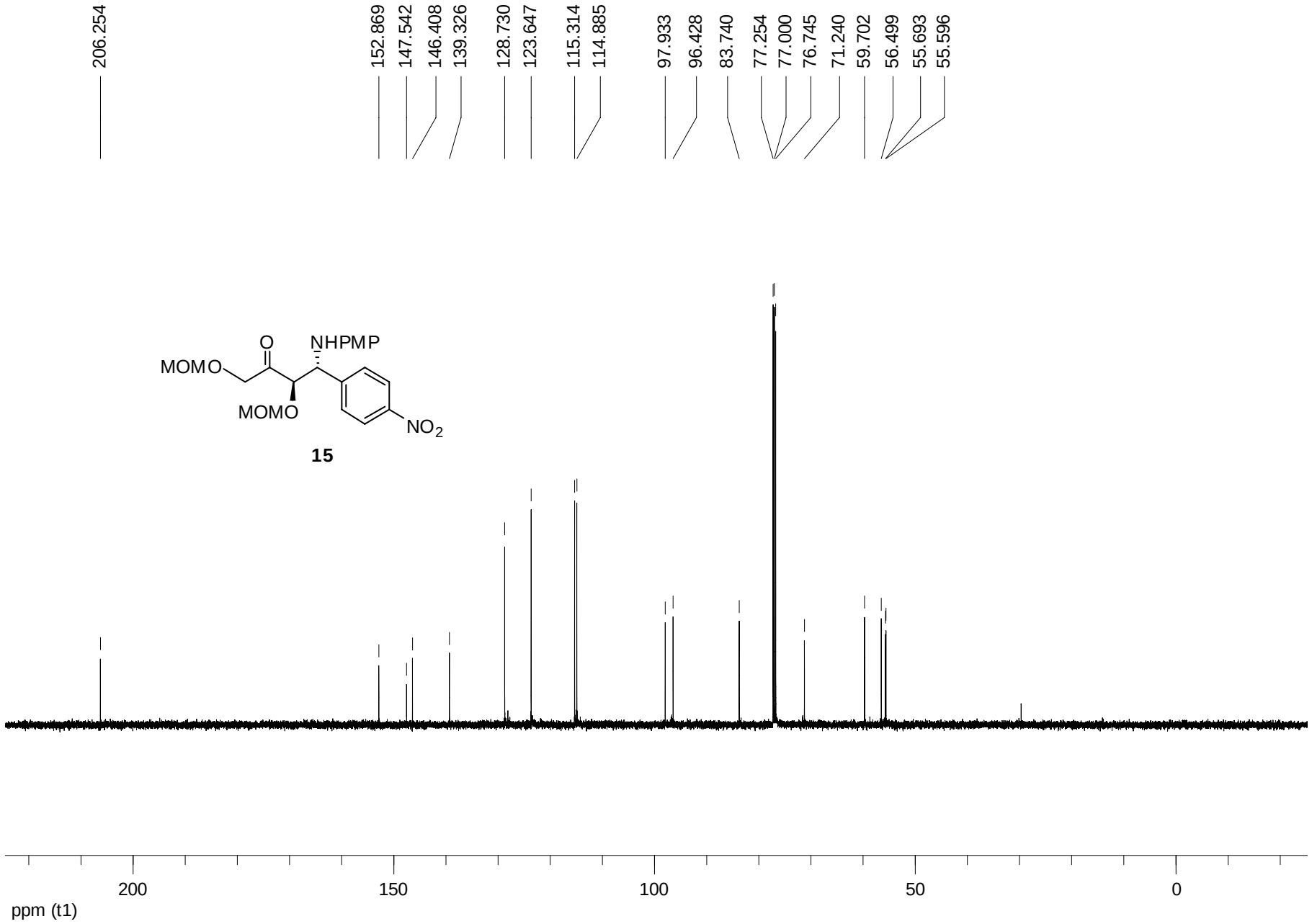
ppm (t1)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96.428
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77.000
76.745
71.240
59.702
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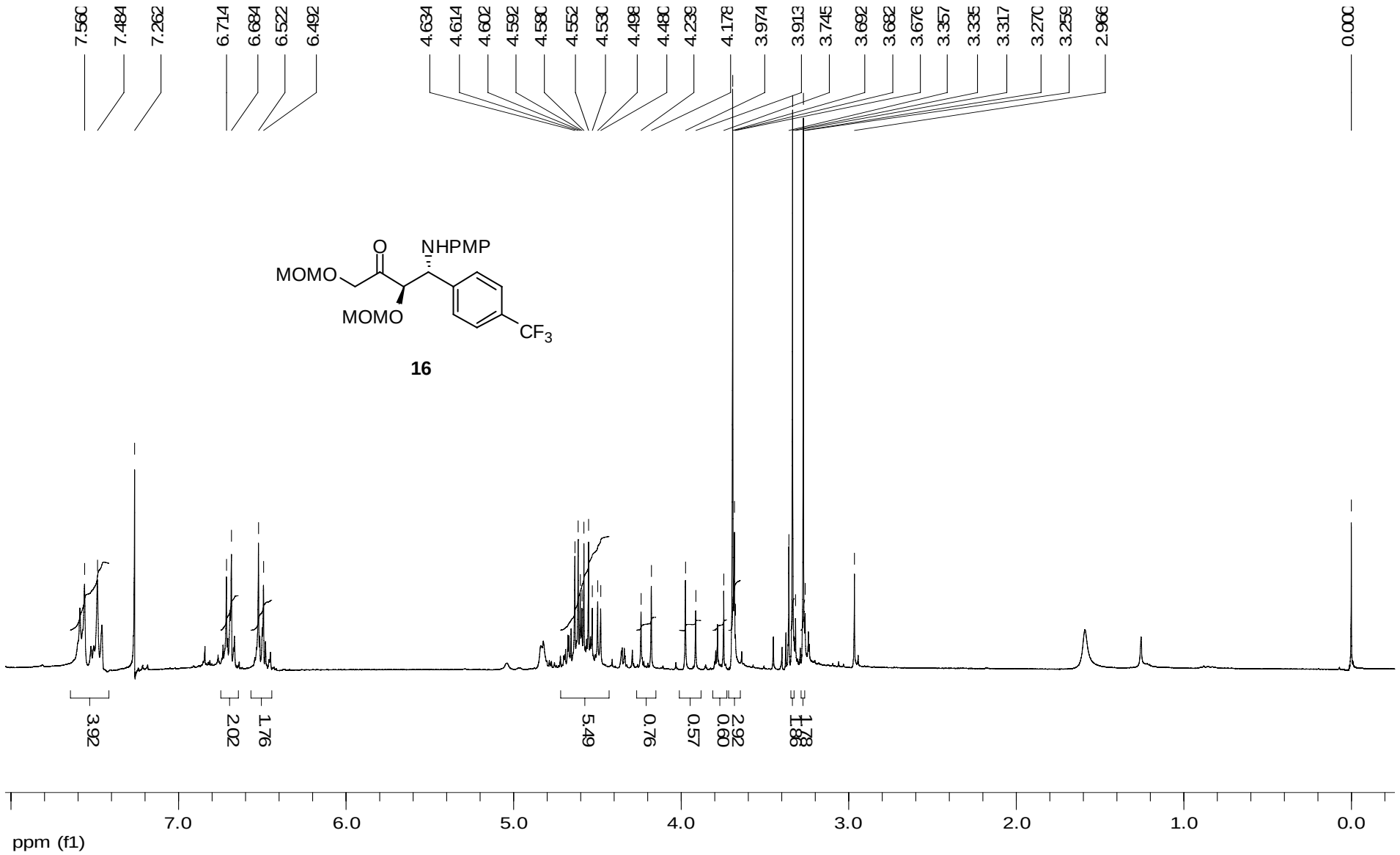
O
NHPMP
MOMO
MOMO
NO2
15
200
150
100
50
0
ppm (t1)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3.259
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0.000
O
NHPMP
MOMO
MOMO
CF3
16
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2.02
1.76
5.49
0.76
0.57
0.60
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2.0
1.0
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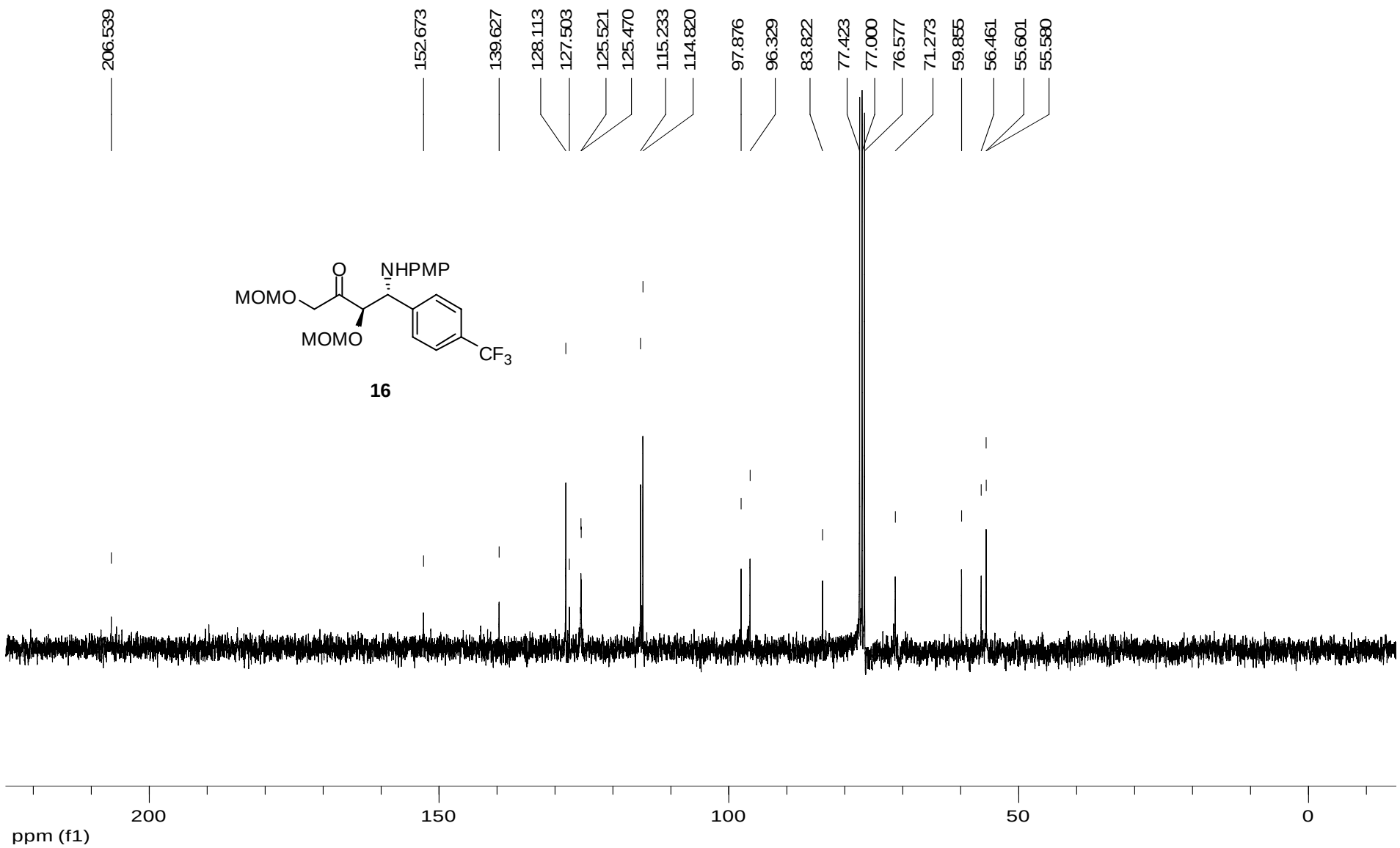
ppm (f1)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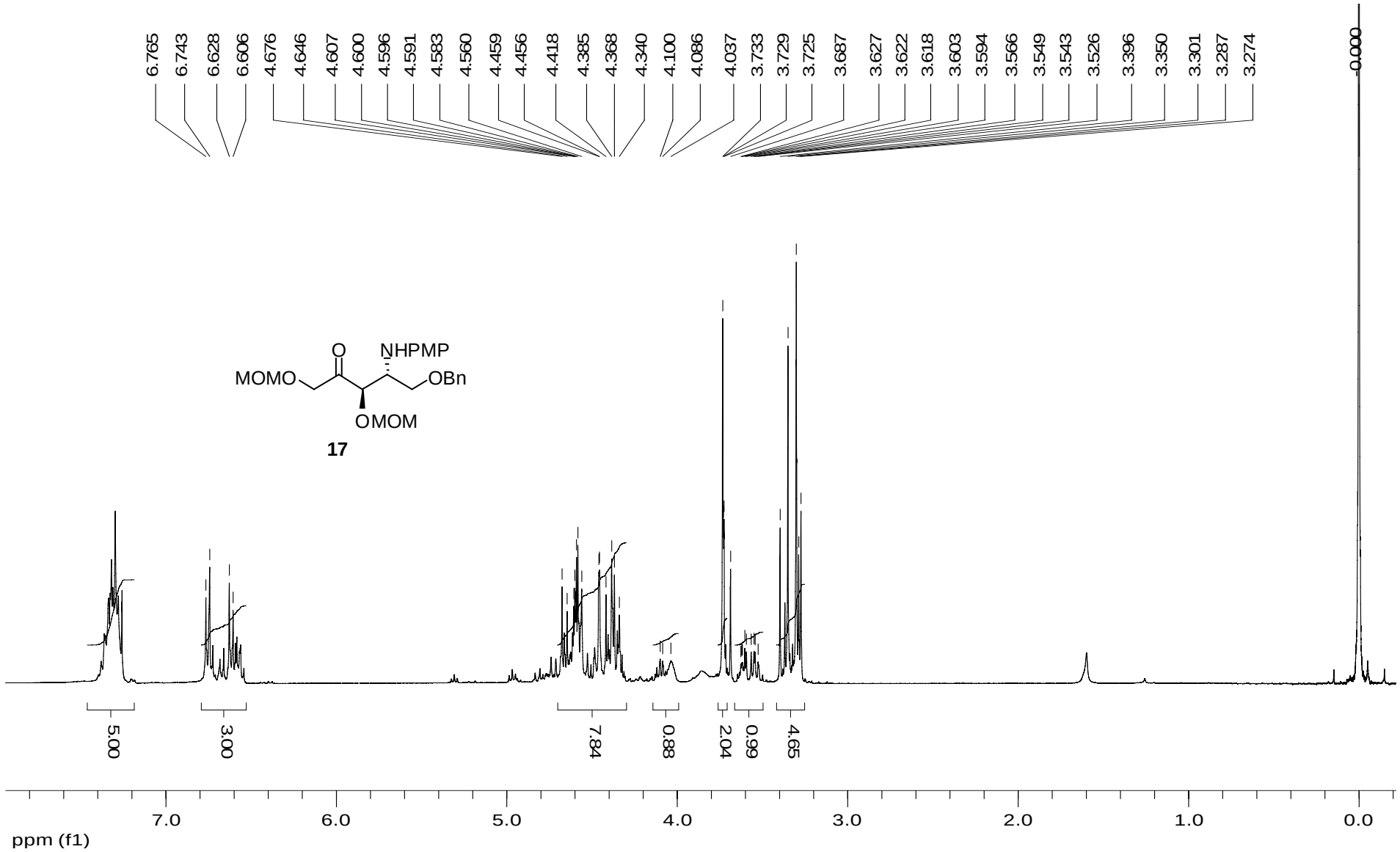
77.423
77.000
76.577
71.273
59.855
56.461
55.601
55.580
O
NHPMP
MOMO
MOMO
CF3
16
200
150
100
50
0
ppm (f1)


6.765
6.743
6.628
6.606
4.676
4.646
4.607
4.600
4.596
4.591
4.583
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4.459
4.456
4.418
4.385
4.368
4.340
4.100
4.086
4.037
3.733
3.729
3.725
3.687
3.627
3.622
3.618
3.603
3.594
3.566
3.549
3.543
3.526
3.396
3.350
3.301
3.287
3.274
0.000
O
NHPMP
MOMO
OBn
OMOM
17
5.00
3.00
7.84
0.88
2.04
0.69
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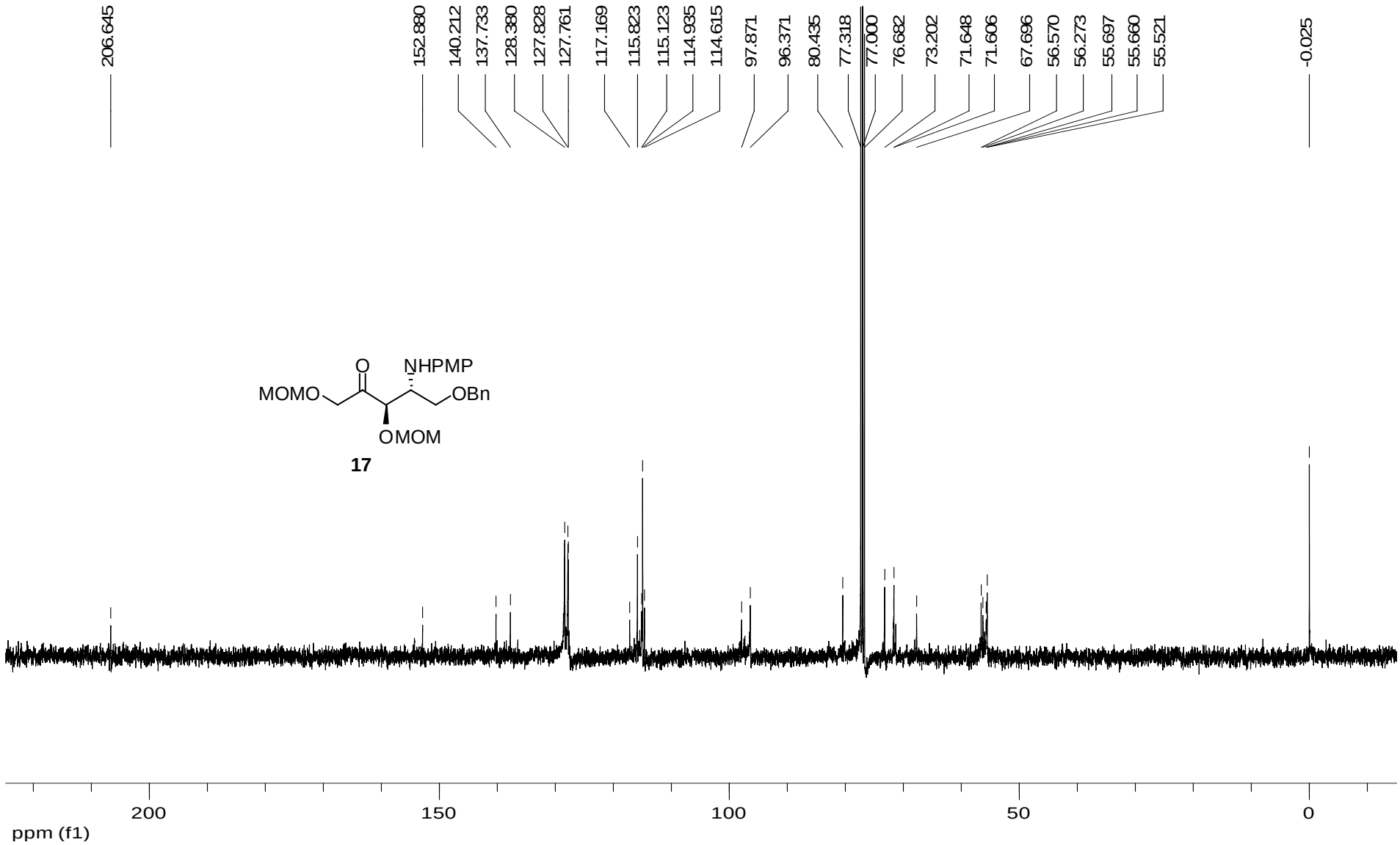
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)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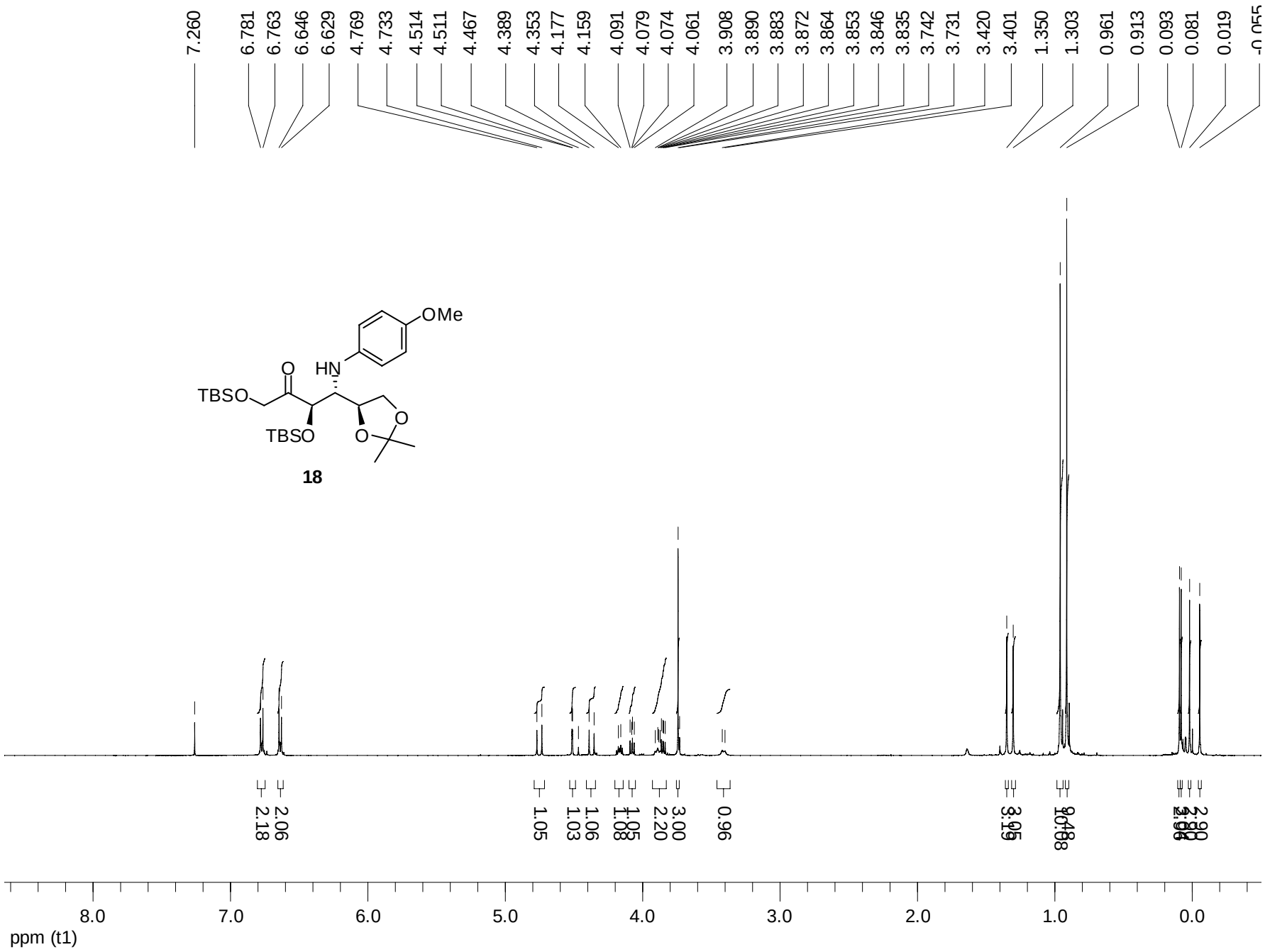
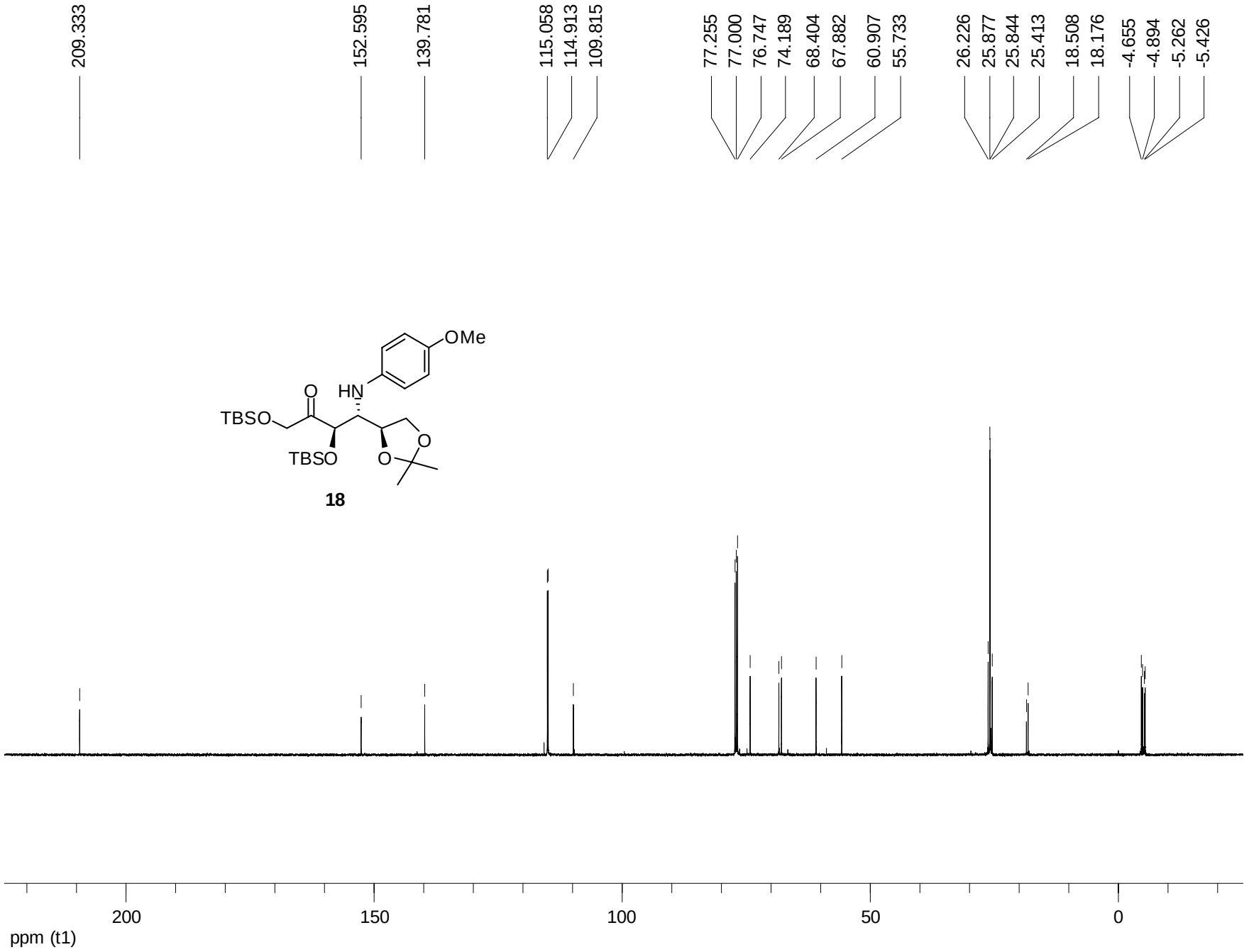
152.880
140.212
137.733
128.380
127.828
127.761
117.169
115.823
115.123
114.935
114.615
97.871
96.371
80.435
77.318
77.000
76.682
73.202
71.648
71.606
67.696
56.570
56.273
55.697
55.660
55.521
-0.025
O
NHPMP
MOMO
OBn
OMOM
17
200
150
100
50
0
ppm (f1)


7.260
6.781
6.763
6.646
6.629
4.769
4.733
4.514
4.511
4.467
4.389
4.353
4.177
4.159
4.091
4.079
4.074
4.061
3.908
3.890
3.883
3.872
3.864
3.853
3.846
3.835
3.742
3.731
3.420
3.401
1.350
1.303
0.961
0.913
0.093
0.081
0.019
OMe
HN
O
TBSO
TBSO
O
O
18
2.18
2.06
1.05
1.03
1.06
1.08
1.05
2.20
3.00
0.96
3.15
3.05
10.88
2.90
2.90
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)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114.913
109.815
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76.747
74.189
68.404
67.882
60.907
55.733
26.226
25.877
25.844
25.413
18.508
18.176
-4.655
-4.894
-5.262
-5.426
OMe
HN
O
TBSO
TBSO
O
O
18
200
150
100
50
0
ppm (t1)