ORGANIC LETTERS

2005
Vol. 7, No. 5
867−870

Total Synthesis of LFA-1 Antagonist BIRT-377 via Organocatalytic Asymmetric Construction of a Quaternary Stereocenter

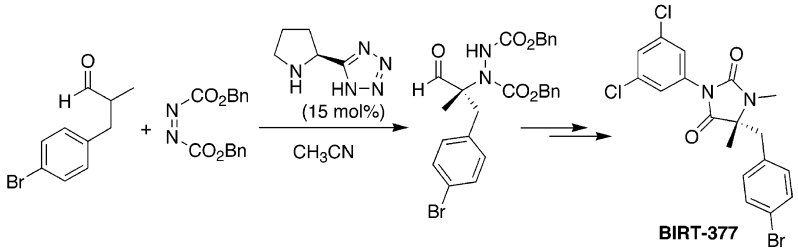
Naidu S. Chowdari and Carlos F. Barbas, III*

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

carlos@scripps.edu

Received December 22, 2004

ABSTRACT



A catalytic route for enantioselective total synthesis of cell adhesion inhibitor BIRT-377 is described. The quaternary stereocenter was constructed through L-proline-derived, tetrazole-catalyzed direct asymmetric α-amination of 3-(4-bromophenyl)-2-methylpropanal with dibenzyl azodicarboxylate. In the course of these studies, a one-pot trifluoro acetylation/selective benzyloxycarbonyl deprotection method was developed.

BIRT-377 (**1**) is a potent inhibitor of the interaction between intercellular adhesion molecule-1 (ICAM-1) and lymphocyte function-associated antigen-1 (LFA-1). BIRT-377 has potential for treatment of a number of inflammatory and immune disorders. Reported syntheses of BIRT-377 are based on a chiral pool approach involving Seebach's self-regeneration of stereocenters strategy.[1] Asymmetric synthesis of quaternary amino acids, like BIRT-377, is a challenging task since these types of stereocenters cannot be made by catalytic asymmetric hydrogenation. Some of these unusual amino acids are components of enzyme inhibitors and their incorporation into peptides has been used to modulate secondary and tertiary structural conformations.[2] Existing methods for the synthesis of quaternary amino acids include auxiliary controlled Strecker syntheses[3] and diastereoselective alkylation of chiral enolates.[4] Recently, asymmetric phase transfer catalysis reactions[5] and other catalytic methods[6] have been reported. However development of a highly economical and broadly useful catalytic method for synthesis of quaternary amino acids is highly desirable.

(1) (a) Yee, N. K. *Org. Lett.* **2000**, *2*, 2781. (b) Kapadia, S. R.; Spero, D. M.; Eriksson, M. *J. Org. Chem.* **2001**, *66*, 1903. (c) Stehle, S.; Nummy, L.; Yee, N. *Tetrahedron: Asymmetry* **2001**, *12*, 101. (d) *Tetrahedron Lett.* **2001**, *42*, 3231. (e) Yee, N.; Nummy, L. J.; Frutos, R. P.; Song, J. J.; Napolitano, E.; Byrne, D. P.; Jones, P. J.; Farina, V. *Tetrahedron: Asymmetry* **2003**, *14*, 3495.

(2) (a) Shirlin, D.; Gerhart, F.; Hornsperger, J. M.; Harmon, M.; Wagner, I.; Jung, M. *J. Med. Chem.* **1988**, *31*, 30. (b) Karle, I.; Kaul, R.; Roa, R. B.; Raghothama, S.; Balaram, P. *J. Am. Chem. Soc.* **1997**, *119*, 12048.

(3) (a) Ma, D.; Tian, H.; Zou, G. *J. Org. Chem.* **1999**, *66*, 1903. (b) Davis, F. A.; Lee, S.; Zhang, H.; Fanelli, D. L.; *J. Org. Chem.* **2000**, *65*, 8704.

(4) (a) Lee, S.-H.; Lee, E. K. *Bull. Korean Chem. Soc.* **2001**, *22*, 551. (b) Vedezs, E.; Fields, S. C.; Hayashi, R.; Hitchcock, S. R.; Powell, D. R.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 2460. (c) Spino, C.; Gobdout, C. *J. Am. Chem. Soc.* **2003**, *125*, 12106.

(5) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013.

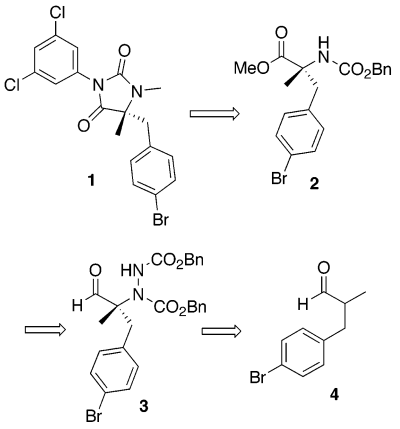
(6) (a) Trost, B. M.; Dogra, K.; *J. Am. Chem. Soc.* **2002**, *124*, 725. (b) Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3236. (c) Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532. (d) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867. (e) Saaby, S.; Bella, M.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8120. (f) Kato, N.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2004**, *45*, 3147.

10.1021/ol047368b CCC: $30.25
Published on Web 01/28/2005

Recently, proline- and proline derivative-catalyzed asymmetric aldol,[7] Mannich,[8] Michael,[9] Diels−Alder,[10] amination,[11] oxidation,[12] chlorination,[13] Robinson annulation,[14] and multicomponent or assembly reactions[15] have been developed. Our laboratory recently reported the synthesis of all carbon quaternary stereogenic centers via organocatalytic Aldol-,[7g] Mannich-,[8i] and Michael-type[9g] strategies. Here we report a direct catalytic asymmetric amination reaction for synthesis of an aldehyde containing an amino-substituted quaternary carbon center and the elaboration of this aldehyde into BIRT-377.

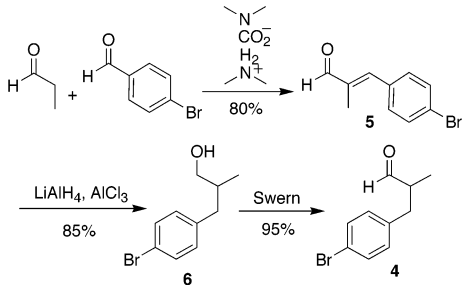
A retrosynthetic analysis of BIRT-377 leads to quaternary amino acid **2**, which we envisioned could be prepared by organocatalytic amination of aldehyde **4** (Scheme 1). We

Scheme 1. Retrosynthetic Analysis of BIRT-377



prepared the aldehyde **5** by condensation of propionaldehyde with 4-bromobenzaldehyde using dimethylammonium dimethyl carbamate[16] as a recoverable and reusable reaction medium and promoter (Scheme 2). Although selective

Scheme 2. Synthesis of 3-(4-Bromophenyl)-2-methylpropanal



double-bond reducing reagents are available,[17] we used $LiAlH_4$ reduction followed by oxidation as a more practical strategy. Accordingly, the unsaturated aldehyde was reduced with $LiAlH_4$ and oxidized using Swern conditions to afford aldehyde **4**.

We first evaluated the amination of aldehyde **4** with dibenzyl azodicarboxylate using a catalytic amount of L-proline (30 mol %) in CH_3CN at room temperature.[18] The reaction was complete in 5 days and provided the amino aldehyde in 90% yield with moderate enantioselectivity (44% ee). To improve enantioselectivity, we screened a number of catalysts and solvents. For example α-methyl-L-proline and (*S*)-4-(pyrrolidin-2-ylmethyl)morpholine with trifluoroacetic acid additive provided 69 and 57% ee, respectively. Tetrazole catalyst[19] (15 mol %) in CH_3CN gave the amination

(7) (a) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260. (c) Córdova, A.; Notz, W.; Barbas, C. F., III. *J. Org. Chem.* **2002**, *67*, 301. (d) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798. (e) Bogevig, A.; Kumaragurubaran, N.; Jorgensen, K. A. *Chem. Commun.* **2002**, 620. (f) Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D *J. Am. Chem. Soc.* **2003**, *125*, 5262. (g) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 2420. (h) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 1983. (i) Artikka, A.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2004**, *15*, 1831. (j) Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 3541. (k) Kofoed, J.; Nielsen, J.; Reymond, J.-L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2445. (l) Chandrasekhar, S.; Narsihmulu, Ch.; Reddy, N. R.; Sultana, S. S. *Chem. Commun.* **2004**, 2450. (m) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558.

(8) (a) Notz, W.; Sakthivel, K.; Bui, T.; Barbas, C, F., III. *Tetrahedron Lett.* **2001**, *42*, 199. (b) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842. (c) Córdova, A, Watanabe, S.-I.; Tanaka, F.; Notz, W.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1866. (d) Chowdari. N. S.; Ramachary, D. B.; Barbas, C, F., III. *Synlett.* **2003**, 1906. (e) Notz, W.; Tanaka, F.; Watanabe, S.-I.; Chowdari, N. S.; Thayumanavan, R.; Barbas, C. F., III. *J. Org. Chem.* **2003**, *68*, 9624. (f) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827. (g) Cobb, A. J. A.; Shaw, D. M.; Ley, S. V. *Synlett* **2004**, 558. (h) Zhuang, W.; Saaby, S.; Jorgensen, K. A. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 476. (i) Chowdari, N. S.; Suri, J. T.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 2507.

(9) (a) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, C, F., III. *Tetrahedron Lett.* **2001**, *42*, 4441. (b) Betancort, J. M.; Barbas, C, F., III. *Org. Lett.* **2001**, *3*, 3737. (c) Enders, D.; Seki, A. *Synlett* **2002**, 26. (d) Alexakis, A.; Andey, O. *Org. Lett.* **2002**, *4*, 3611. (e) Cobb, A. J. A.; Longbottom, D. A.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2002**, 1808. (f) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Tanaka, F.; Barbas, C, F., III. *Synthesis* **2004**, *9*, 1509. (g) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C, F., III. *Org. Lett.* **2004**, *6*, 2527.

(10) (a) Ramachary, D. B.; Chowdari. N. S.; Barbas, C, F., III. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 4233. (b) Ramachary, D. B.; Chowdari. N. S.; Barbas, C, F., III. *Synlett* **2003**, 1910. (c) Thayumanavan, R.; Ramachary, D. B.; Sakthivel, K.; Tanaka, F.; Barbas, C, F., III. *Tetrahedron Lett.* **2002**, *43*, 3817. (d) Ramachary, D. B.; Chowdari. N. S.; Barbas, C, F., III. *Tetrahedron Lett.* **2002**, *43*, 6743.

(11) (a) Bogevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W., Jorgensen, K. A. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1790. (b) Kumaragurubaran, N.; Juhl, K.; Zhuang, W., Bogevig, A.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254. (c) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656. (d) Vogt, H.; Vanderheiden, S.; Brase, S. *Chem. Commun.* **2003**, 2448. (e) Iwamura, H.; Mathew, S. P.; Blackmond, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 11770.

(12) (a) Zhong, G. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 4247. (b) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed. Engl.* **2003**, *43*, 1112. (c) Omiyama, N.; Torii, H.; Saito, S.; Yamamoto, H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5374.

(13) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C.*J. Am. Chem. Soc.* **2004**, *126*, 4108.

(14) Bui, T, Barbas, C, F., III. *Tetrahedron Lett.* **2000**, *41*, 6951.

(15) (a) Chowdari, N. S.; Ramachary, D. B.; Barbas, C. F., III. *Org. Lett.* **2003**, *5*, 1685. (b) Chowdari. N. S.; Ramachary, D. B.; Córdova, A.; Barbas, C, F., III. *Tetrahedron Lett.* **2002**, *43*, 9591. (c) Ramachary, D. B.; Barbas, C, F., III. *Chem. Eur. J.* **2004**, *10*, 5323.

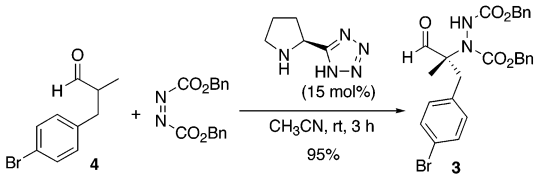
(16) Kreher, U. P.; Rosamilla, A. E.; Raston, C. L.; Scott, J. L.; Strauss, C. R.; *Org. Lett.* **2003**, *5*, 3107.

(17) (a) Saito, S.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 2928. (b) Keinan, E.; Greenspoon, N. *J. Am. Chem. Soc.* **1986**, *108*, 7314. (c) Brestensky, D. M.; Stryker, J. M. *Tetrahedron Lett.* **1989**, *30*, 5677.

(18) L-Proline was reported to be an excellent catalyst for amination of linear aldehydes (ref 11a,c) as well as α-aryl branched aldehydes, but failed to induce high ee's in cases involving α,α-dialkyl aldehydes (ref 11d).

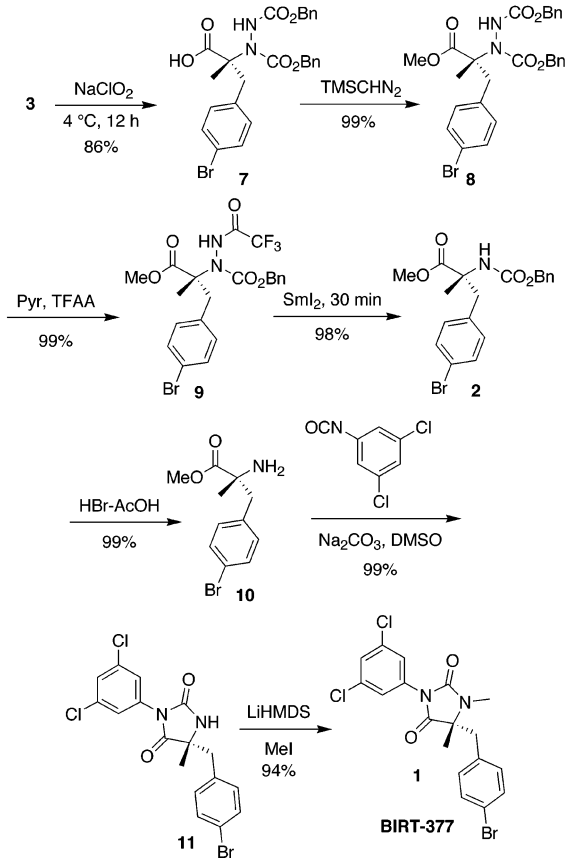
product (**3**) in 95% yield with 80% ee (Scheme 3). Upon recrystallization from ethyl acetate/hexane (3:7), the amino-aldehyde was obtained in >99% ee (71% yield).

Scheme 3. Organocatalytic Amination for the Synthesis of Quaternary Stereocenter



The amino aldehyde (**3**) was selectively oxidized with $NaClO_2$ at 4 °C to obtain the corresponding carboxylic acid (**7**) in 86% yield (Scheme 4). The carboxylic acid was treated

Scheme 4. Synthesis of BIRT-377

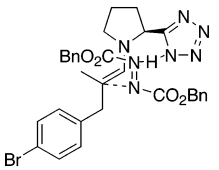


with (trimethylsilyl)diazomethane to afford the corresponding ester **8**. Next we attempted selective cleavage of the N−N bond in hydrazino ester **8** using SmI_2, which effectively cleaves trifluoroacetylated hydrazines,[20] but no product was obtained. We next tried trifluoroacetylation. Upon optimization we found that treatment of ester **8** with pyridine at 40 °C for 16 h followed by addition of trifluoroacetic anhydride (TFAA) gave the product **9** through selective removal of one of the carbamate groups. Although trifluoro acetic acid did not cleave any of the carbamate groups present in **8**, presumably the product formed after the trifluoroacetylation of product **8** underwent simultaneous carbamate cleavage. Selective N−N bond cleavage of **9** was readily achieved using SmI_2 and afforded the Cbz-protected quaternary amino acid methyl ester **2**. This one-pot trifluoroacetylation/selective benzyloxycarbonyl deprotection protocol should prove useful for the synthesis of a variety of Cbz-protected amino acids from precursors obtained through organocatalytic amination reactions.

When compound **2** was treated with 3,5-dichloroaniline in the presence of *n*BuLi, hydantoin **11** was obtained in 33% yield. Use of different bases such as NaOMe, NaH, or LDA did not provide any product. Better results were obtained when the Cbz group of **2** was removed with HBr/AcOH to give free amine **10**. The amine was treated with 3,5-dichlorophenyl isocyanate in the presence of Na_2CO_3 in dimethyl sulfoxide to obtain the hydantoin **11** in quantitative yield. *N*-methylation of hydantoin **11** was achieved using lithium bis(trimethylsilyl)amide to afford **1** in excellent yield (94%). The overall yield for the synthesis of BIRT-377 from aldehyde **4** in eight steps was 51%. The absolute stereochemistry of amino aldehyde was determined by comparison of optical rotation of **1** with the literature value.[21]

The synthesis of quaternary amino acids through organocatalytic amination reactions is challenging since the cis and trans enamines derived from α-branched aldehydes are energetically less distinct as compared to the cis and trans enamine intermediates in reactions involving linear aldehydes, and this leads to the low enantioselectivity observed for this class of amination reactions.[22] The higher reactivity and ee obtained with tetrazole catalyst relative to L-proline is ascribed to the lower pK_a and increased steric bulk of tetrazole relative to L-proline. Tetrazole and L- proline have pK_a's of ∼8 and ∼12, respectively, in DMSO. The hydrogen bonding interactions in the transition state of the reaction with the two catalysts are likely different and provide different levels of enantioselection. Based on the absolute configuration of the amino aldehyde and previous proline-catalyzed reactions,[7] we propose the transition state shown in Scheme 5. The approach of azodicarboxylate might be directed by interaction of the incoming nitrogen atom with the proton of the tetrazole of enamine intermediate.[11a,c]

Scheme 5. Transition State for Organocatalytic Amination of 3-(4-Bromophenyl)-2-methylpropanal



(19) Prepared according to literature procedure. See: Almquist, R. G.; Chao, W.-R.; White, C. J. *J. Med. Chem.* **1985**, *28*, 1067.
(20) Ding, H.; Friestad, G. K. *Org. Lett.* **2004**, *6*, 637.

In conclusion, we have developed the first catalytic asymmetric route to the total synthesis of BIRT-377. Quaternary amino aldehyde was constructed from readily available precursors using a small organic molecule catalyst. This method allows the synthesis of both enantiomers of BIRT-377. Analogues can be readily obtained by changing the α,α-disubstituted aldehyde and catalyst. Many of the steps reported here gave quantitative yields and did not require purification. Most of these reactions can be performed under operationally simple and safe conditions without the requirement for an inert atmosphere, dry solvents, or cooling equipment. This synthetic route should prove useful for high-throughput synthesis of BIRT-377 analogues. Full studies regarding scope of quaternary aminoaldehydes synthesis 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: Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL047368B

(21) $\alpha]^{25}_D = 131.6$ ($c = 1.0$, EtOH) [lit.[1e] $[\alpha]^{25}_D = 127.3$ ($c = 0.78$, EtOH)]; HPLC (Daicel Chirapak AD, hexane/EtOH/Et_2NH = 300:10:1, flow rate 1.0 mL/min, $\lambda = 254$ nm): $t_R = 15.62$ min, (+) **1** (BIRT-377); $t_R = 17.23$ min (−) **1**.

(22) The energy difference between cis and trans enamines of 3-(4-bromophenyl)-2-methyl propanal with L-proline is 0.266 kcal/mol, whereas propanal has a difference of 2.934 kcal/mol (based on MOPAC, PM3 calculations).

Total Synthesis of LFA-1 Antagonist BIRT-377 via Organocatalytic Asymmetric Construction of a Quaternary Stereocenter

Naidu S. Chowdari and Carlos F. Barbas III*

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

Supporting Information

General. Chemicals and solvents were either purchased *puriss p.A.* from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating. Flash chromatography was performed using silica gel Merck 60 (particle size 0.040-0.063 mm), ^1H NMR and ^{13}C NMR spectra were recorded on Bruker DRX-400, DRX-600 MHz. Chemical shifts are given in δ relative to tetramethylsilane (TMS), the coupling constants *J* are given in Hz. The spectra were recorded in $CDCl_3$ as solvent at room temperature, TMS served as internal standard (δ = 0 ppm) for ^1H NMR, and $CDCl_3$ was used as internal standard (δ = 77.0 ppm) for ^{13}C NMR. HPLC was carried out using a Hitachi organizer consisting of a D-2500 Chromato-Integrator, a L-4000 UV-Detector, and a L-6200A Intelligent Pump. Optical rotations were recorded on a Perkin Elemer 241 Polarimeter (λ=589 nm, 1 dm cell). High-resolution mass spectra were recorded on an IonSpec FTMS mass spectrometer with a DHB-matrix.

(*E*)-3-(4-bromophenyl)-2-methylacrylaldehyde (5): Method A. To a solution of dimethylammonium dimethyl carbamate (DIMCARB) (3 mL) and 4-bromobenzaldehyde (1.74 g, 9.4 mmol) in round-bottom flask was added propionaldehyde (1.36 mL, 18.6 mmol) and stirred at room temperature for 48 h. Then, DIMCARB was removed by distillation and the residue was diluted with 0.5 M H_2SO_4. The aqueous layer was extracted with CH_2Cl_2 and the combined organic phases were dried (Na_2SO_4), concentrated, and purified by flash column

chromatography (silica gel, hexanes/ethyl acetate = 95:5) to afford the desired product **5** (1.692 g, 80% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.05 (d, *J* = 0.9 Hz, 3H), 7.20 (s, 1H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.2 Hz, 2H), 9.58 (s, 1H).

Method B: To a cooled stirring solution of 4-bromobenzaldehyde (18.5 g, 0.1 mol) in MeOH (20 mL) 10% aqueous NaOH (4 mL) was added followed by slow addition of propionaldehyde (5.6 mL, 0.12 mol) over 3 h at room temperature. Then reaction mixture was stirred for an additional 2 h and cooled to 0 °C and quenched with 1 N HCl (15 mL). The precipitated solid was filtered and purified by flash column chromatography (silica gel, hexanes/ethyl acetate = 95:5) to afford the desired product **5** (17.55 g, 78% yield).

3-(4-bromophenyl)-2-methylpropan-1-ol (6): To a three neck round-bottom flask with $LiAlH_4$ (101.7 mmol, 1M ether solution) at 0 °C under N_2 was added aldehyde **5** (14.575 g, 64.78 mmol) in THF (300 mL) followed by $AlCl_3$ (34.98 mmol). The reaction temperature was increased to 65 °C and stirred for 11 h. The reaction was cooled to 0 °C and quenched with 2 N HCl (270 mL). Two layers are separated. The aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic phases were dried (Na_2SO_4), concentrated, and purified by flash column chromatography (silica gel, hexanes/ethyl acetate = 70:30) to afford the desired product **6** (12.609 g, 85% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.90 (d, *J* = 8.0 Hz, 3H), 1.91 (m, 1H), 2.38 (dd, *J* = 12.0, 8.0 Hz, 1H), 2.74 (dd, *J* = 12.0, 8.0 Hz, 1H), 3.50 (d, *J* = 4.0 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H).

3-(4-bromophenyl)-2-methylpropanal (4): To a three neck round-bottom flask with oxalyl chloride (5.475 mL, 60.34 mmol) in CH_2Cl_2 (125 mL) at -60 °C under N_2 was added DMSO (9.308 mL, 120.68 mmol) in CH_2Cl_2 (66 mL) followed by alcohol **6** (12.562 g, 54.85 mmol) in CH_2Cl_2 (55 mL) and stirred for 30 min. Et_3N (38.38 mL, 274.27 mmol) was added and the reaction mixture was stirred for 5 min and then allowed to warm to room temperature. The combined organic phases were washed with water and dried (Na_2SO_4), concentrated, and purified by flash column chromatography (silica gel, hexanes/ethyl acetate = 95:5) to afford the desired product **4** (11.828 g, 95% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.09 (d, *J* = 7.0 Hz, 3H), 2.55 (dd, *J* = 13.5, 8.2 Hz, 1H), 2.63 (m, 1H), 3.04 (dd, *J* = 13.5, 5.9 Hz, 1H), 7.04 (d, *J* =

8.2 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 9.70 (d, *J* = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.2, 35.9, 47.9, 120.3, 130.8, 131.6, 137.9, 203.9.

(*R*)-3-(4-bromophenyl)-2-(1,2-benzyloxycarbonylhydrazinyl)-2-methylpropanal (3): To a glass vial charged with (S)-5-(pyrrolidin-2-yl)-1H-tetrazole (104 mg, 0.75 mmol) was added CH_3CN (10 mL) followed by bis dibenzyl azodicarboxylate (1.59 g, 5 mmol), aldehyde **4** (1.703 g, 7.5 mmol) and the reaction was stirred at room temperature until completion as monitored by TLC (3 h). Then, a half saturated NH_4Cl solution and ethyl acetate were added with vigorous stirring, the layers were separated and the organic phase was washed with water. The combined organic phases were dried (Na_2SO_4), concentrated, and purified by flash column chromatography (silica gel, hexanes/ethyl acetate = 70:30) to afford the desired product **3** (2.489 g, 95% yield). Recrystallization from hexanes/ethyl acetate (70:30) furnished the mother liquor with >99% ee (71% yield). $[\alpha]^{25}_D$ = 82.0 (c = 1.0, $CHCl_3$); NMR spectrum exists as a mixture of rotamers at room temperature ($CDCl_3$, 600 MHz, 50 °C): δ 1.15 (s, 3H), 2.83 (bs, 1H), 3.28 (bs, 1H), 5.04 – 5.21 (m, 4H), 6.76 (bs, 2H), 7.31 (m, 12H), 9.67 (bs, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz, 50 °C) δ 18.28, 37.41, 68.18, 70.27, 128.20, 128.47, 128.54, 128.58, 128.64, 131.78, 131.86, 135.32, 150.25, 155.58, 193.30; HRMS for $C_{26}H_{26}BrN_2O5$ (MH^+): calcd 525.1027, obsd 525.1018; HPLC (Daicel Chirapak AS-H, hexane/isopropanol = 90 : 10, flow rate 1.0 mL/min, λ = 254 nm): t_R = 26.14 min (major), t_R = 33.36 min (minor).

(*R*)-3-(4-bromophenyl)-2-(1,2- benzyloxycarbonylhydrazinyl)-2-methylpropanoic acid (7): To a solution of amino aldehyde **3** (695 mg, 1.326 mmol) in *t*-BuOH-H_2O (5:1, 14 mL) at 4 °C $NaClO_2$ (5.30 mmol), NaH_2PO_4 (318 mg, 2.65 mmol) and 2-methtl-2-butene (5.3 mL of 2M THF solution, 10.61 mmol) was added and stirred for 12 h. After completion of the reaction as monitored by TLC the solvent was removed under vacuum. The crude material was extracted with ethyl acetate and washed with brine and water. The combined organic phases were dried (Na_2SO_4), concentrated, and purified by flash column chromatography (silica gel, methanol/ethyl acetate = 5:95) to afford the corresponding acid **7** as a white solid (616 mg, 86% yield). $[\alpha]^{25}_D$ = 10.2 (c = 0.5, MeOH); ^{1}H NMR (CD_3OD, 600 MHz, 50 °C): δ 1.71 (s, 3H), 3.37 (d, *J* = 13.2 Hz, 1H), 3.55 (bs, 1H), 5.40 – 5.48 (m, 5H), 7.29 (d, *J* = 7.8 Hz, 2H), 7.61 (m, 10H),

7.66 (d, J = 7.8 Hz, 2H); ^{13}C NMR (CD_3OD, 150 MHz, 50 °C) δ 21.35, 28.61, 69.17, 68.47, 69.42, 121.99, 129.10, 129.36, 129.56, 131.93, 132.39, 133.59, 134.12, 136.43, 137.32, 156.59, 175.78; HRMS for $C_{26}H_{25}BrN_2O_6Na$ (MNa^+): calcd 563.0788, obsd 563.0788.

(*R*)-Methyl 3-(4-bromophenyl)-2-(1,2- benzyloxycarbonylhydrazinyl)-2-methylpropanoate (8): To a solution of amino acid **7** (471 mg, 0.872 mmol) in toluene-MeOH (2:1, 20 mL) (trimethylsilyl)diazomethane (0.872 mL of 2 M solution in hexanes, 1.744 mmol) was added and stirred at room temperature for 10 min. Then the excess of trimethyl silyl diazomethane was quenched by drop wise addition of acetic acid. The solvent was removed under vacuum and the residue was purified by flash column chromatography (silica gel, hexanes/ethyl acetate = 70:30) to afford the desired product **8** (478 mg, 99% yield). $[\alpha]^{25}_D$ = 42.8 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz, 50 °C): δ 1.40 (s, 3H), 2.97 (bs, 1H), 3.26 (bs, 1H), 3.57 (s, 3H), 5.06 – 5.16 (m, 4H), 6.83 (bs, 1H), 7.29 (m, 14H); ^{13}C NMR ($CDCl_3$, 150 MHz, 50 °C) δ 21.06, 41.21, 52.24, 67.94, 68.40, 107.95, 128.29, 128.12, 128.36, 128.54, 131.69, 131.95, 134.98, 135.65, 154.95, 156.19, 173.04; HRMS for $C_{27}H_{27}BrN_2O_6Na$ (MNa^+): calcd 577.0945, obsd 577.0941.

(*R*)-Methyl 3-(4-bromophenyl)-2-methyl-2-(1-benzyloxycarbonyl-2-(2,2,2-trifluoroacetyl)hydrazinyl)propanoate (9): A solution of amino acid ester **8** (453 mg, 0.817 mmol) in pyridine (2 mL) was heated at 40 °C for 18 h. Then the reaction was cooled to 0 °C and trifluoroacetic anhydride (0.596 mL, 4.29 mmol) was added and stirred at room temperature for 48 h. The volatiles were removed under vacuum and the residue was purified by flash column chromatography (silica gel, hexanes/ethyl acetate = 70:30) to afford the desired product **9** (417 mg, 99% yield). $[\alpha]^{25}_D$ = 14.3 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz, 50 °C): δ 1.43 (s, 3H), 3.12 (bs, 1H), 3.37 (bs, 1H), 3.64 (s, 3H), 5.13 (d, J = 12.0 Hz, 1H), 5.22 (d, J = 12.0 Hz, 1H), 6.94 (bs, 2H), 7.30 – 7.37 (m, 7H); ^{13}C NMR ($CDCl_3$, 150 MHz, 50 °C) δ 21.24, 41.08, 52.66, 67.83, 69.08, 114.59, 116.51, 121.60, 128.33, 128.67, 128.71, 131.66, 132.20, 134.29, 135.09, 156.60, 156.85, 172.92; HRMS for $C_{21}H_{20}BrF_3N_2O_5Na$ (MNa^+): calcd 539.0408, obsd 539.0405.

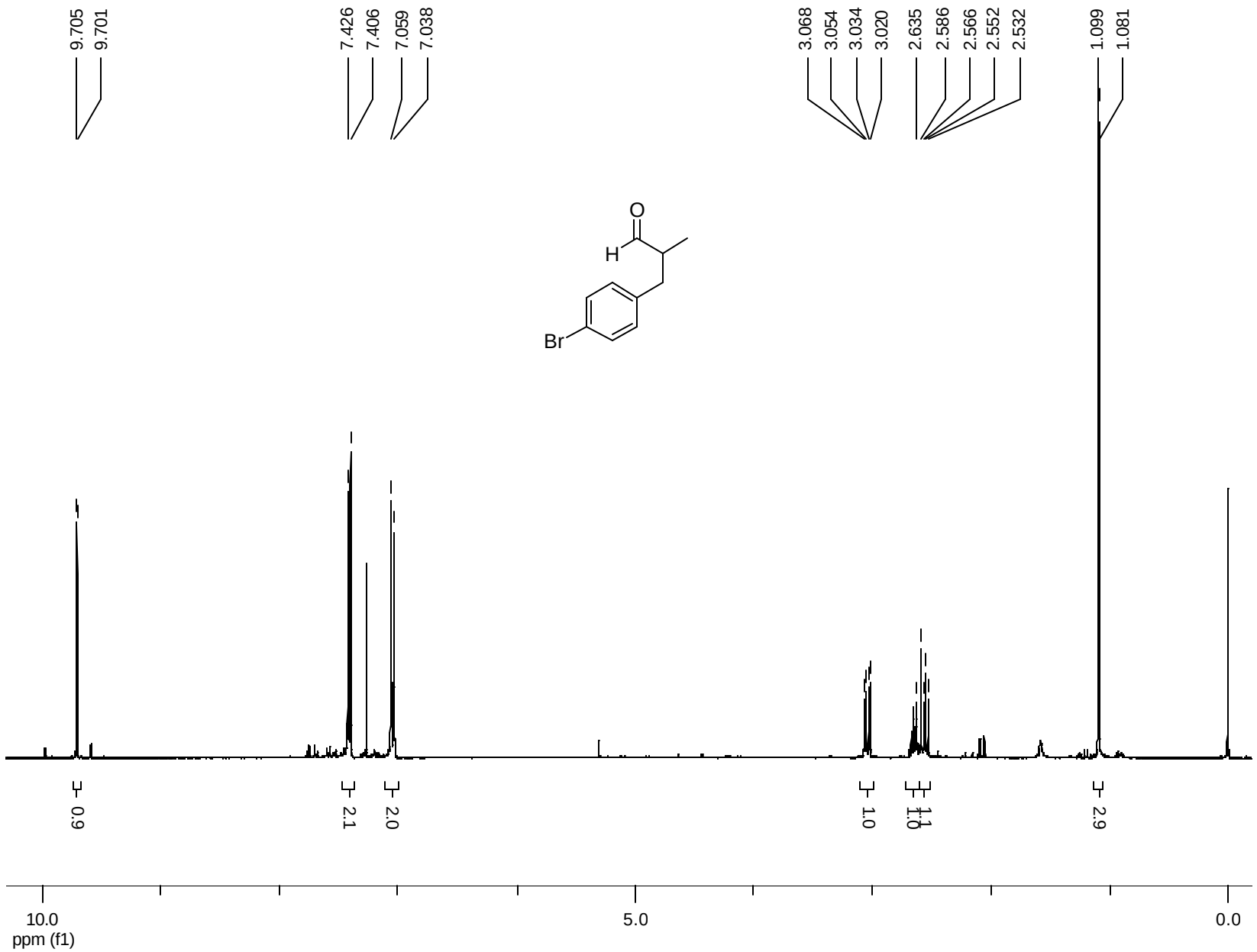
(*R*)-Methyl 2-(benzyloxycarbonyl)-3-(4-bromophenyl)-2-methylpropanoate (2): To a solution of amino acid ester **9** (361 mg, 0.7 mmol) in MeOH (1.4 mL) 0.1 M solution of samarium iodide in THF (47.5 mL) was added under N_2 and stirred at room temperature for 30 min. The volatiles were removed under vacuum and the residue was purified by flash column chromatography (silica gel, hexanes/ethyl acetate = 70:30) to afford the desired product **2** (278 mg, 98% yield). $[\alpha]^{25}_D = -44.1$ (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz, 50 °C): δ 1.61 (s, 3H), 3.13 (d, *J* = 13.8 Hz, 1H), 3.38 (d, *J* = 13.8 Hz, 1H), 3.72 (s, 3H), 5.07 (d, *J* = 12.6 Hz, 1H), 5.15 (d, *J* = 12.6 Hz, 1H), 5.38 (bs, 1H), 6.83 (d, *J* = 7.8 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz, 50 °C) δ 23.80, 41.11, 52.59, 60.78, 66.53, 121.02, 128.20, 128.52, 131.36, 131.55, 135.25, 136.66, 154.62, 173.78; HRMS for $C_{19}H_{20}BrNO_4Na$ (MNa^+): calcd 428.0468, obsd 428.0470.

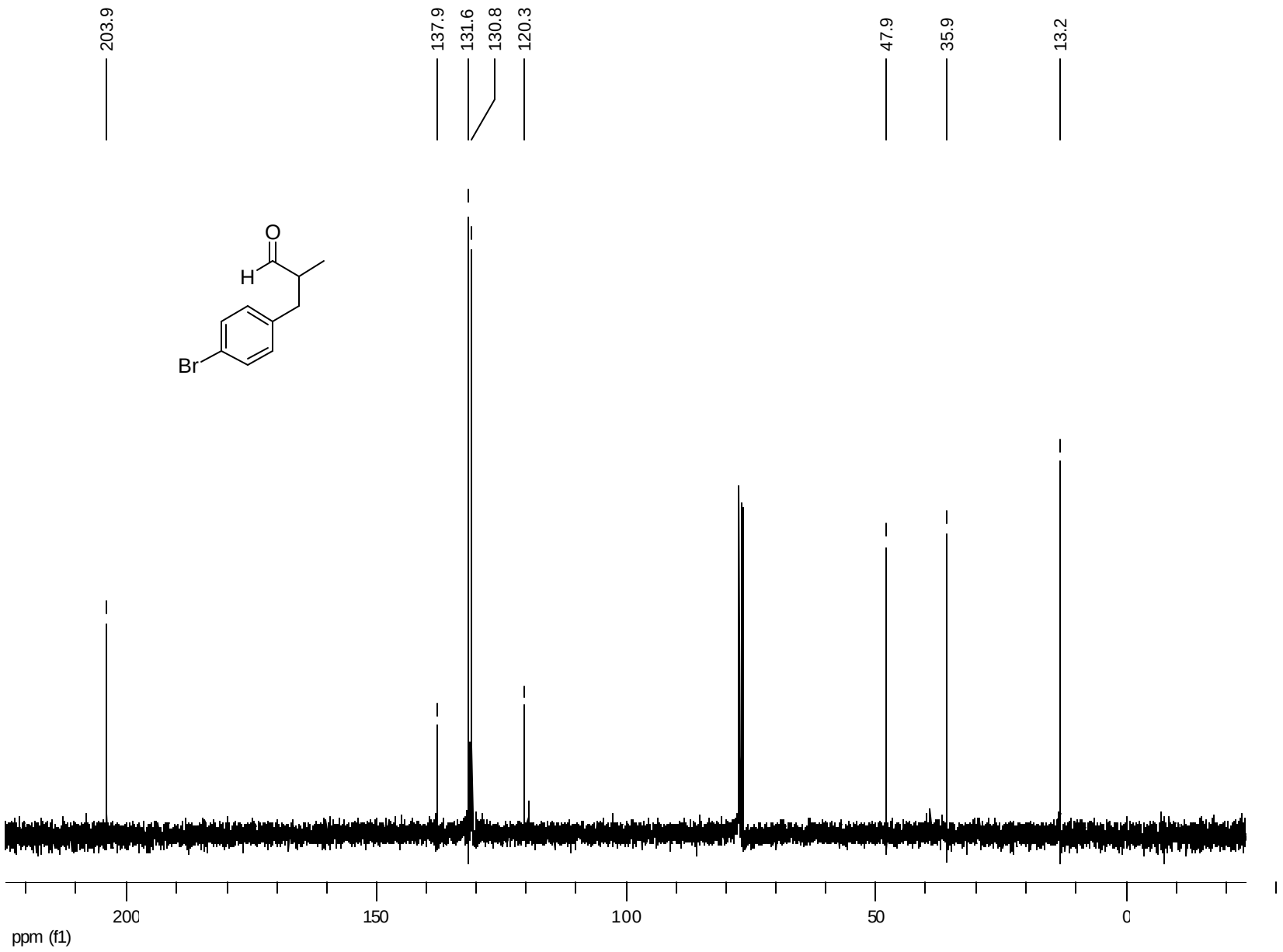
(*R*)-Methyl 2-amino-3-(4-bromophenyl)-2-methylpropanoate (10): To a solution of amino acid ester **2** (156 mg, 0.385 mmol) in AcOH (1.0 mL) 33% HBr in AcOH solution (0.7 mL) was added and stirred at room temperature for 24 h. The volatiles were removed under vacuum and the residue was diluted with ethyl acetate and water. The aqueous layer was neutralized with sat aq $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to afford the pure product **10** (103 mg, 99% yield). $[\alpha]^{25}_D$ = 17.4 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.39 (s, 3H), 1.80 (bs, 2H), 2.77 (d, *J* = 13.2 Hz, 1H), 3.08 (d, *J* = 13.2 Hz, 1H), 3.70 (s, 3H), 7.03 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.43, 46.09, 52.22, 58.78, 121.06, 131.44, 131.64, 135.41, 177.08; HRMS for $C_{11}H_{15}BrNO_2$ (MH^+): calcd 272.0281, obsd 272.0274.

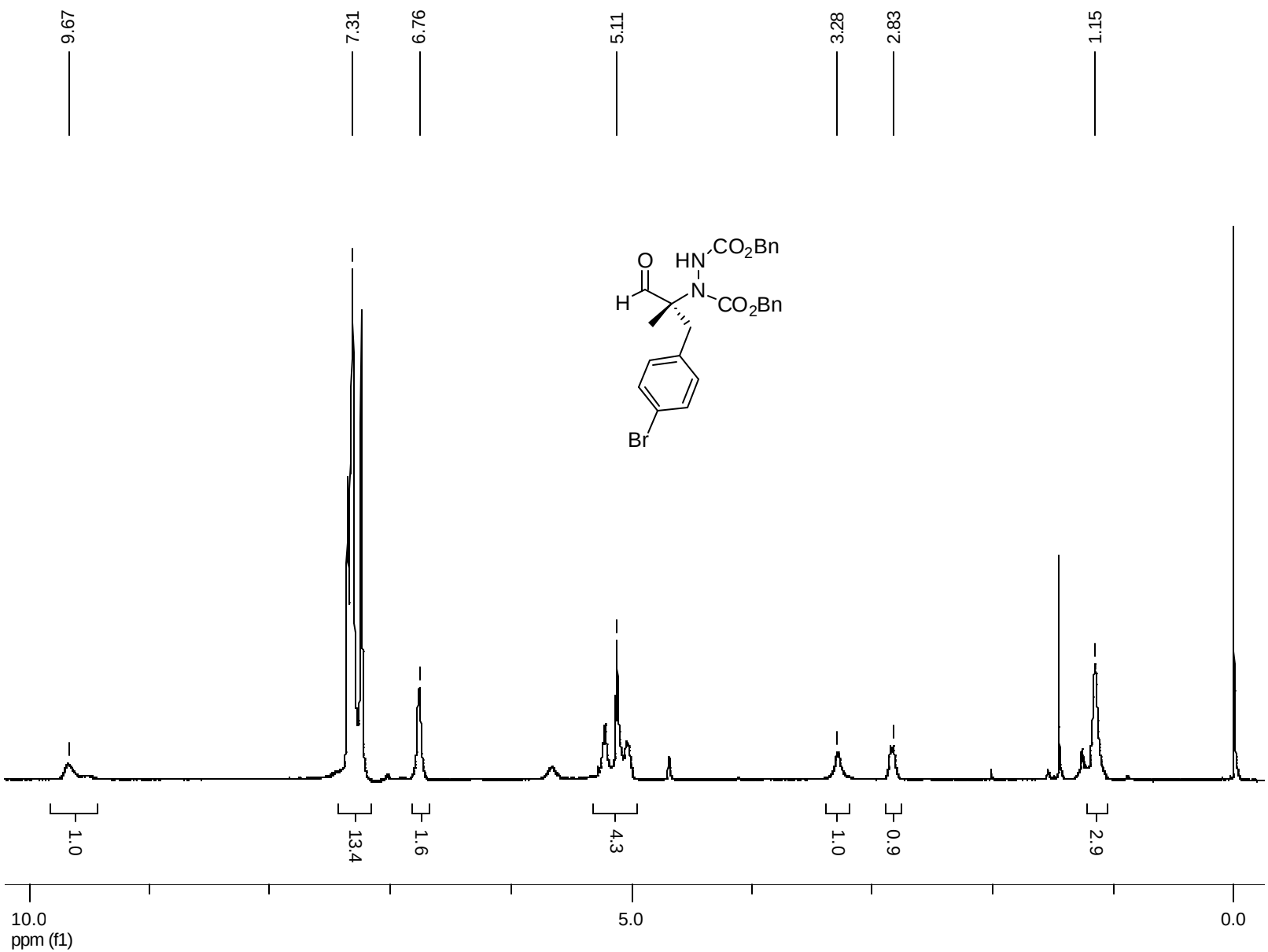
(*R*)-5-(4-bromobenzyl)-3-(3,5-dichlorophenyl)-5-methylimidazolidine-2,4-dione (11): A solution of amine **10** (87 mg, 0.321 mmol) and 3,5-dichlorophenyl isocyanate (60 mg, 0.321 mmol) in dry DMSO (0.6 mL) was stirred at room temperature for 1 h. Then sodium carbonate (68 mg, 0.642 mmol) was added and stirred at 120 °C for 12 h. The reaction mixture was brought to room temperature and diluted with ethyl acetate and washed with water and aq NH_4Cl solution. The organic phase was dried (Na_2SO_4), concentrated, and purified by flash column chromatography (silica gel, hexanes/ethyl acetate = 70:30) to afford the desired product

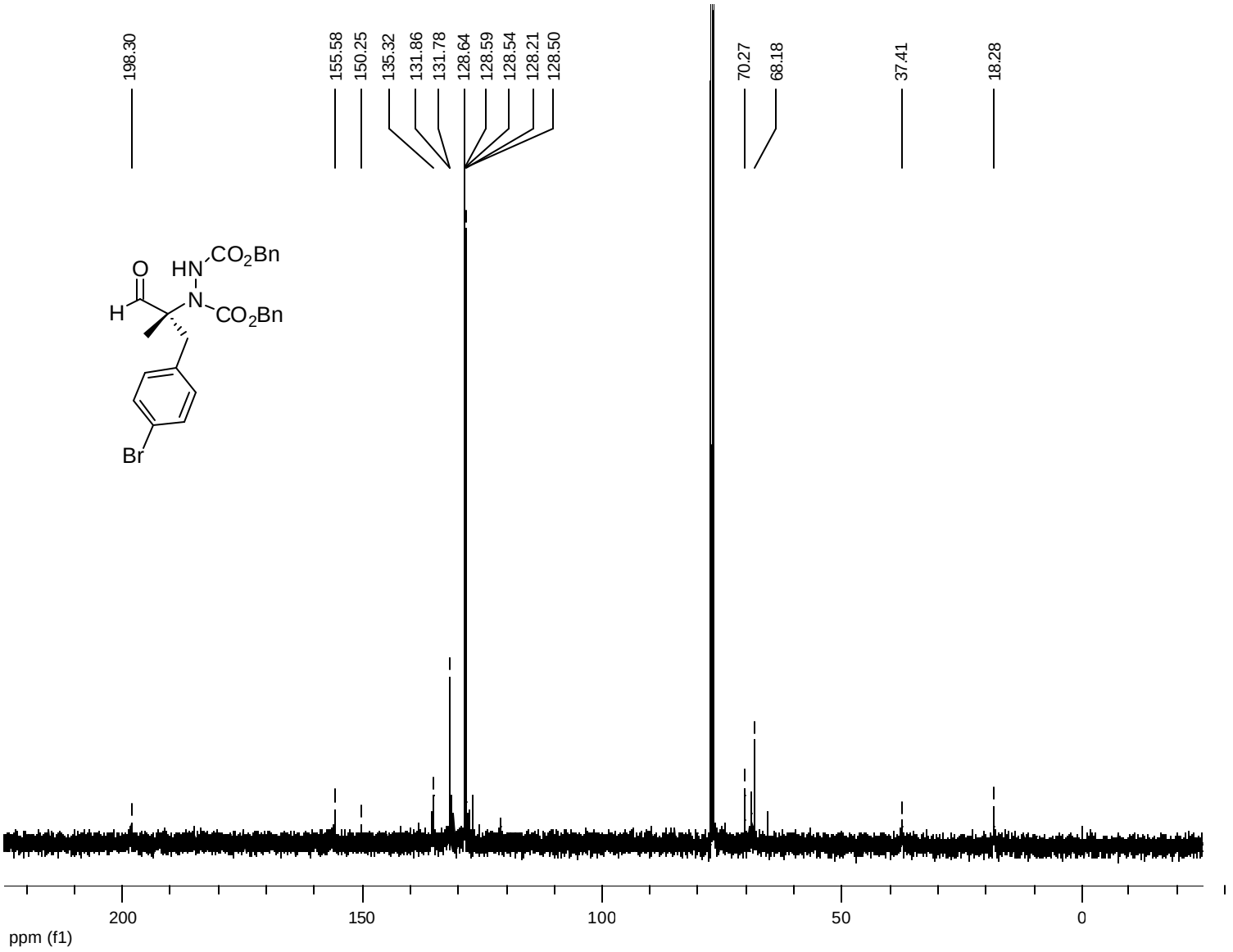
11 (135 mg, 99% yield). $[\alpha]^{25}_D$ = 119.5 (c = 0.86, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.61 (s, 3H), 2.92 (d, *J* = 13.6 Hz, 1H), 3.14 (d, *J* = 13.6 Hz, 1H), 5.84 (bs, 1H), 7.01 (d, *J* = 1.6 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 7.34 (t, *J* = 1.6 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.7, 43.7, 62.5, 122.1, 124.5, 128.5, 132.8, 131.7, 132.7, 135.2, 154.0, 174.0; HRMS for $C_{17}H_{12}BrCl_2N_2O_2$ ($M\text{-}H^+$): calcd 424.9465, obsd 424.9445.

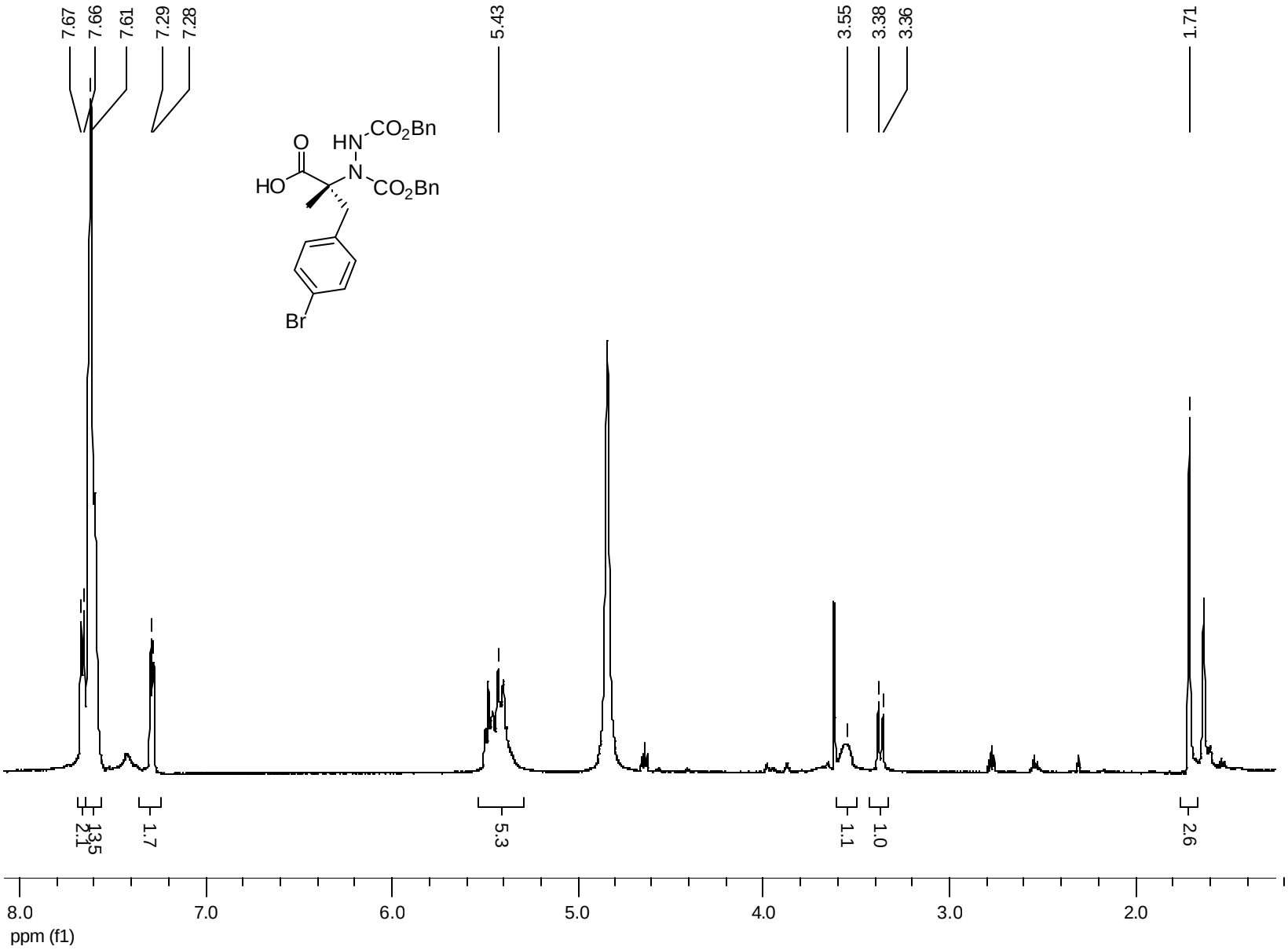
(*R*)-5-(4-bromobenzyl)-3-(3,5-dichlorophenyl)-1,5-dimethylimidazolidine-2,4-dione (1): To a solution of hydantoin **11** (118 mg, 0.2769 mmol) in DMF (1 mL) at 4 °C lithium bi(trimethylsilyl)amide (0.321 mmol of 1M THF solution) followed by iodomethane (26 μL, 0.415 mmol) were added and stirred at room temperature for 3 h. The reaction mixture was diluted with water and extracted with ethyl acetate (3 x 5 mL). The combined organics were washed with aq NH_4Cl solution and dried (Na_2SO_4), concentrated, and purified by flash column chromatography (silica gel, hexanes/ethyl acetate = 70:30) to afford the desired product **1** (115 mg, 94% yield). $[\alpha]^{25}_D$ = 131.6 (c = 1.0, EtOH); HPLC (Daicel Chirapak AD, hexane/EtOH/Et_2NH = 300:10:1, flow rate 1.0 mL/min, λ = 254 nm): t_R = 15.62 min, (+) **1** (BIRT-377); t_R = 17.23 min (-) **1**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.63 (s, 3H), 2.97 (d, *J* = 14.0 Hz, 1H), 3.08 (s, 3H), 3.10 (d, *J* = 15.2 Hz, 1H), 6.84 (d, *J* = 2.0 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 7.29 (t, *J* = 2.0 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.0, 25.3, 40.7, 65.6, 121.9, 124.5, 128.3, 131.1, 131.8, 132.8, 133.0, 135.0, 153.4, 173.3; HRMS for $C_{18}H_{16}BrCl_2N_2O_2$ (MH^+): calcd 440.9767, obsd 440.9759.

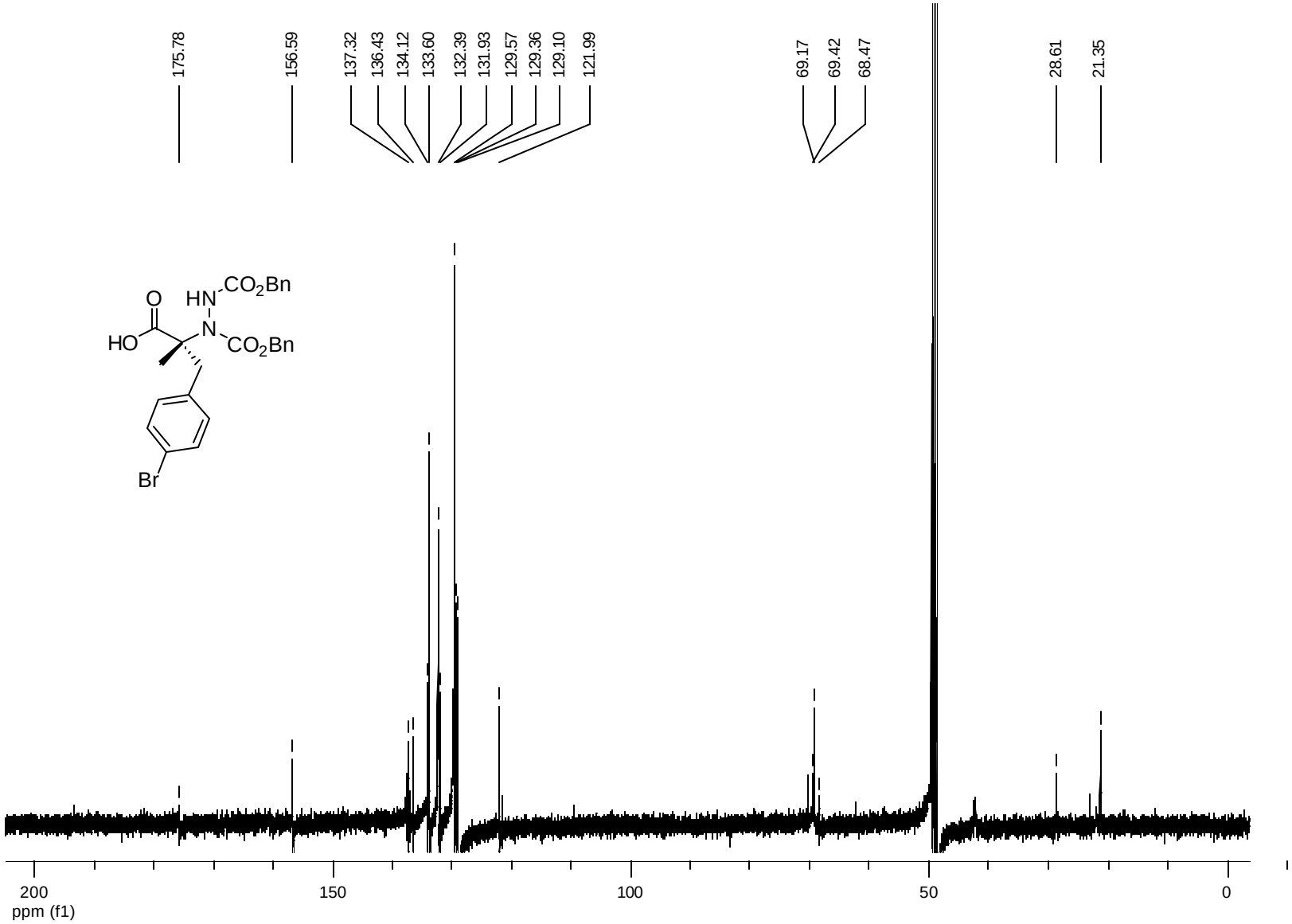

9.705
9.701
7.426
7.406
7.059
7.038
3.068
3.054
3.034
3.020
2.635
2.586
2.566
2.552
2.532
1.099
1.081
O
H
Br
0.9
2.1
2.0
1.0
1.1
1.0
2.9
10.0
ppm (f1)
5.0
0.0

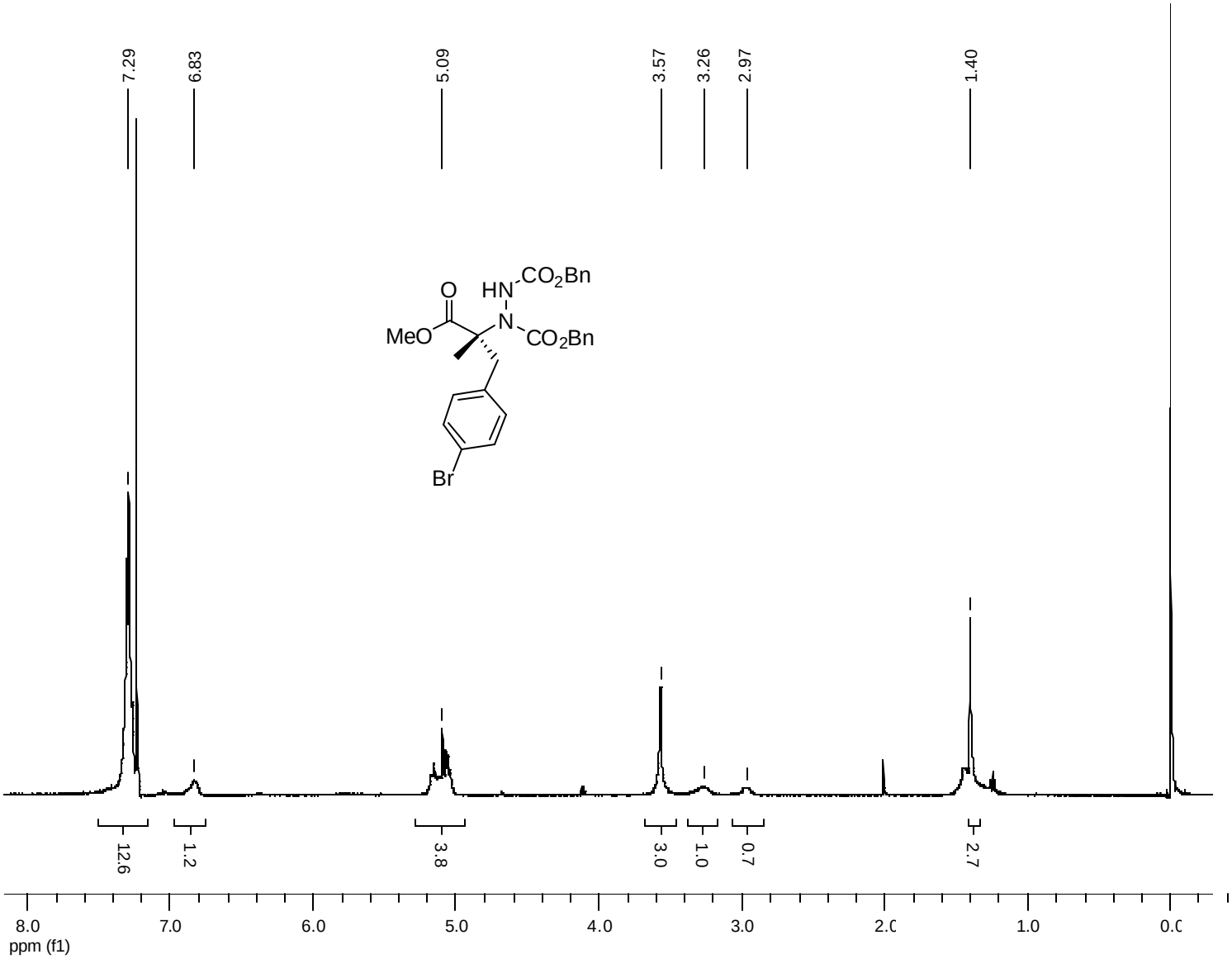

203.9
137.9
131.6
130.8
120.3
47.9
35.9
13.2
O
H
Br
200
150
100
50
0
ppm (f1)

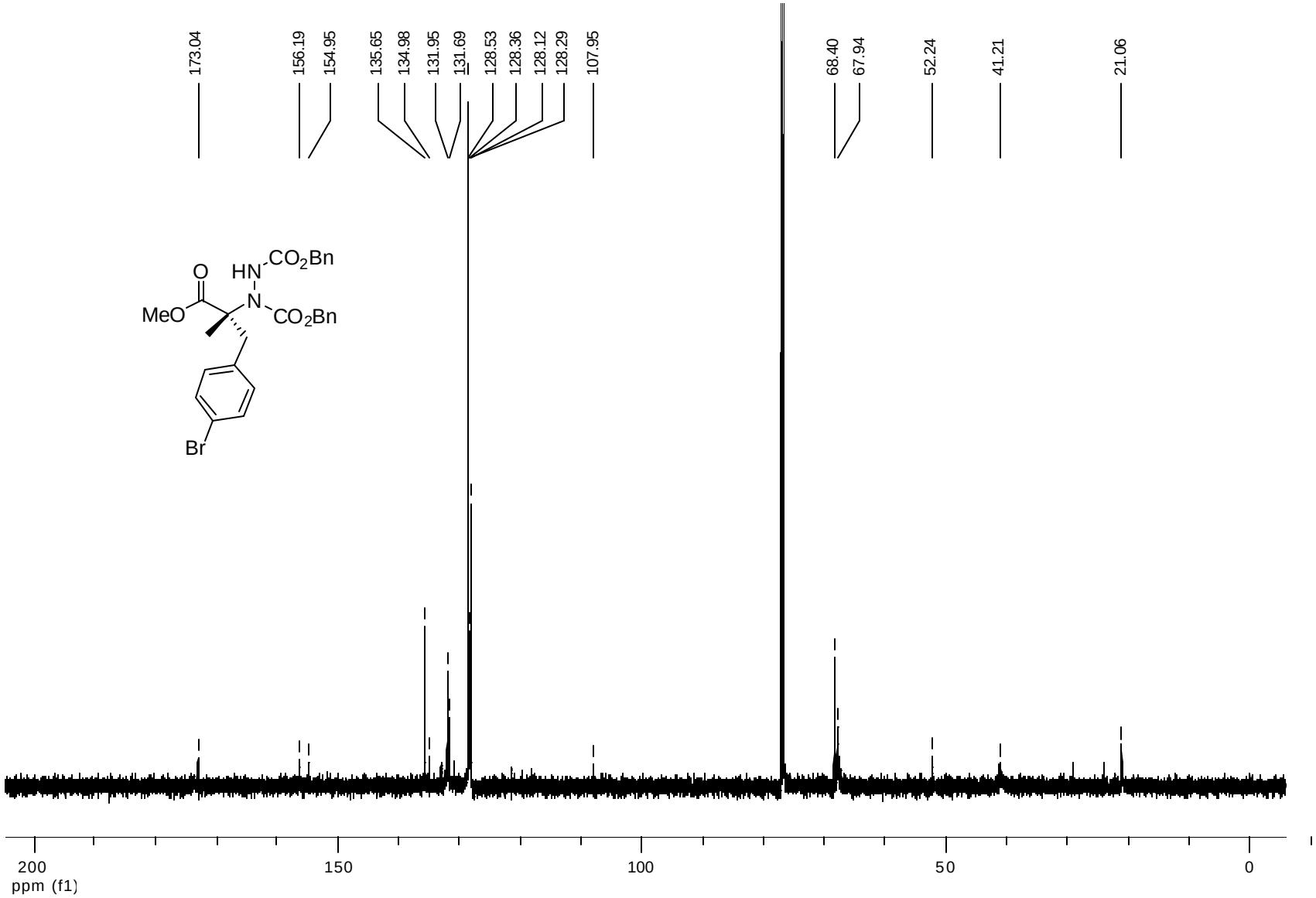

9.67
7.31
6.76
5.11
3.28
2.83
1.15
O
HN
CO2Bn
H
N
CO2Bn
Br
1.0
13.4
1.6
4.3
1.0
0.9
2.9
10.0
ppm (f1)
5.0
0.0

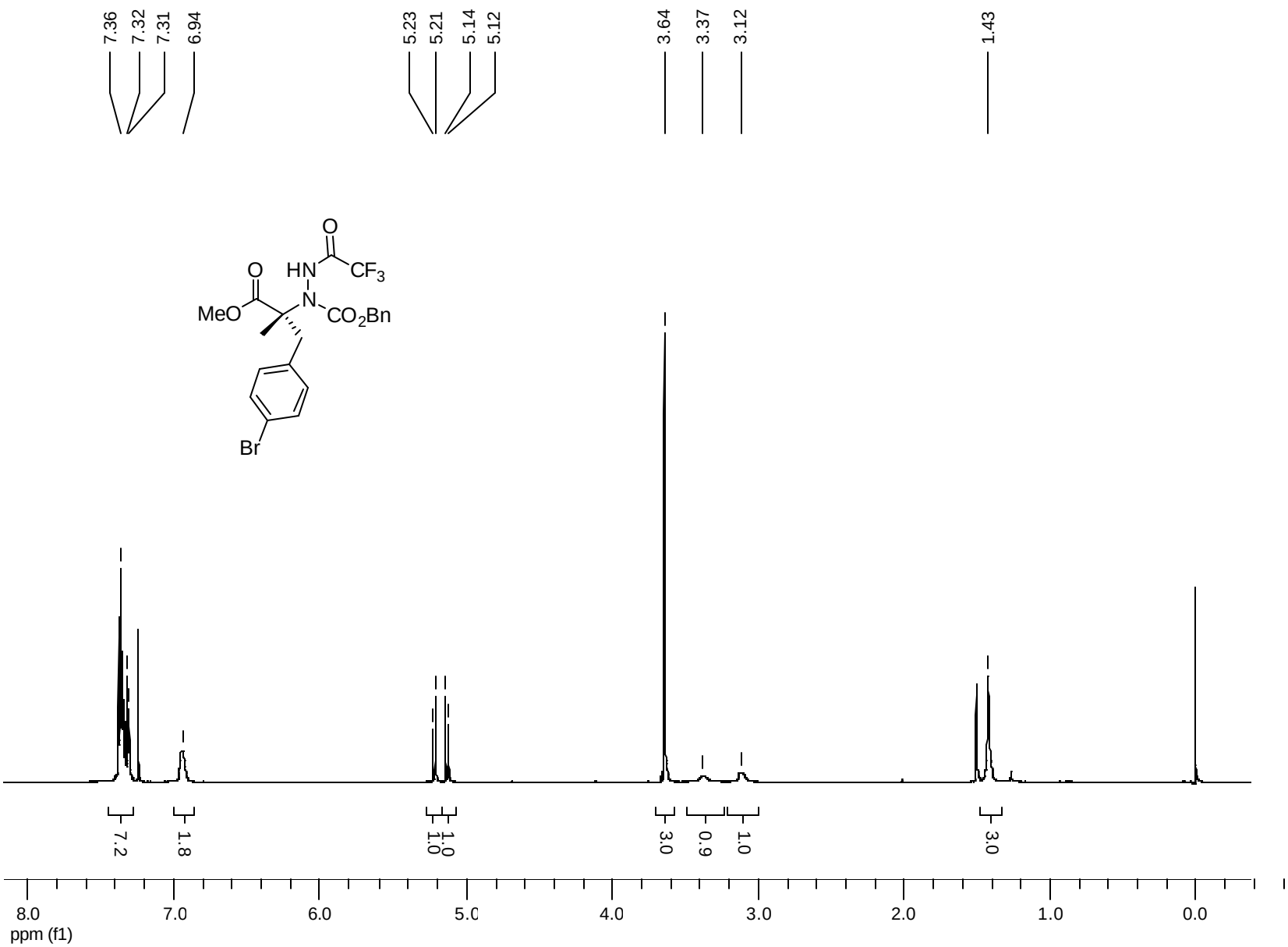

198.30
155.58
150.25
135.32
131.86
131.78
128.64
128.59
128.54
128.21
128.50
70.27
68.18
37.41
18.28
O
HN
CO2Bn
H
N
CO2Bn
Br
200
150
100
50
0
ppm (f1)

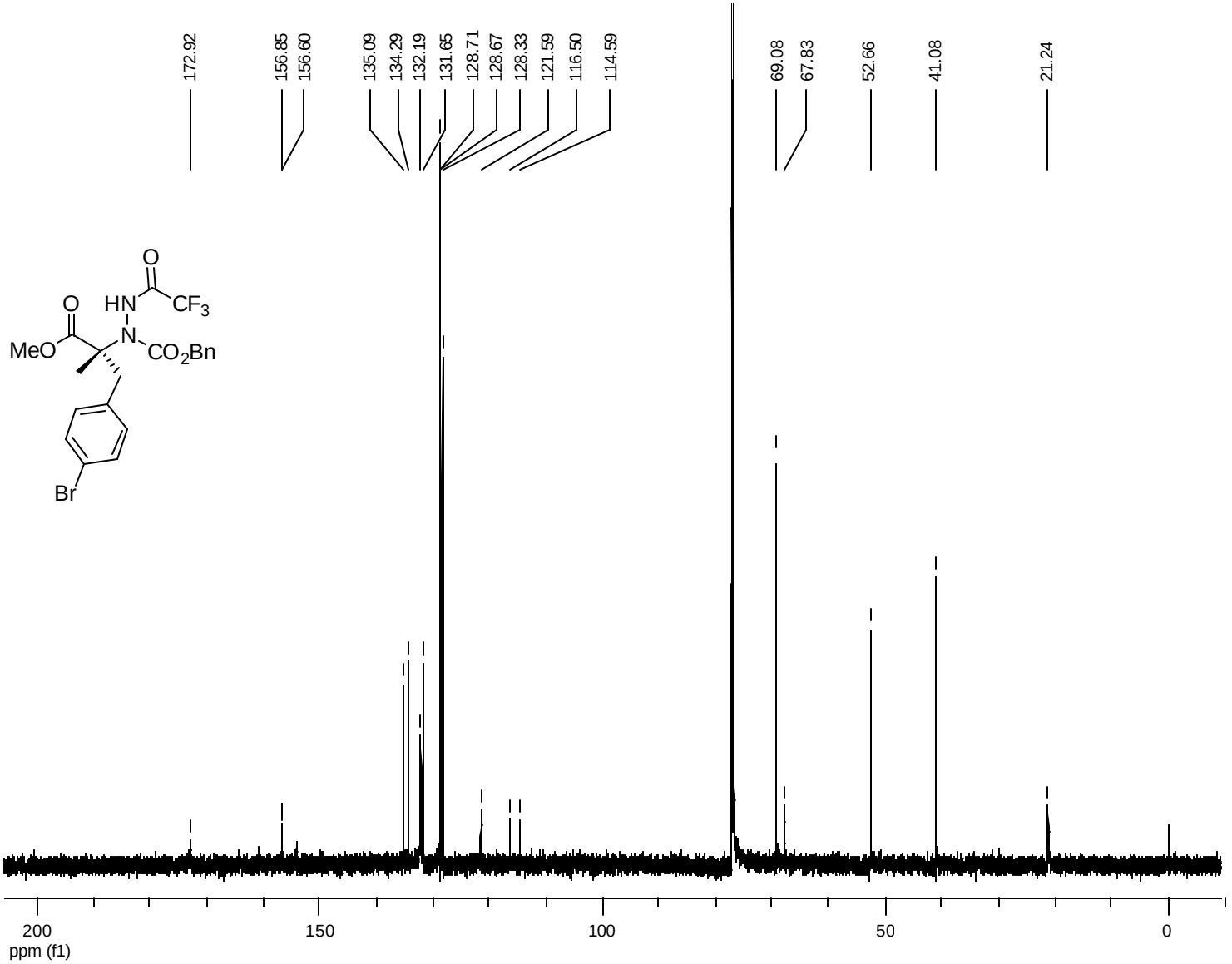

7.67
7.66
7.61
7.29
7.28
5.43
3.55
3.38
3.36
1.71
O
HO
HN
CO2Bn
N
CO2Bn
Br
2.1
1.35
1.7
5.3
1.1
1.0
2.6
8.0
7.0
6.0
5.0
4.0
3.0
2.0
ppm (f1)

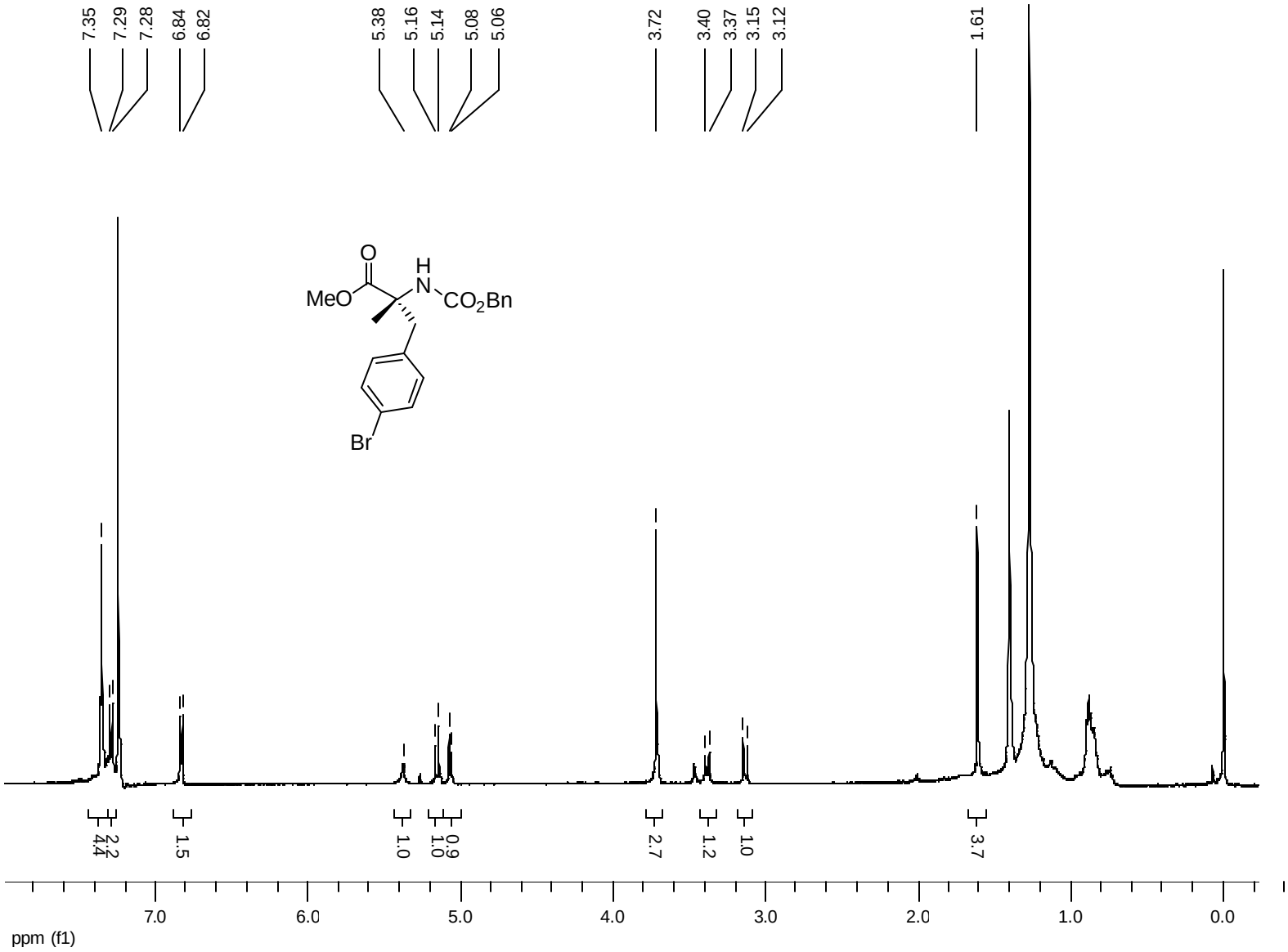

175.78
156.59
137.32
136.43
134.12
133.60
132.39
131.93
129.57
129.36
129.10
121.99
69.17
69.42
68.47
28.61
21.35
O
HO
HN
CO2Bn
N
CO2Bn
Br
200
150
100
50
0
ppm (f1)

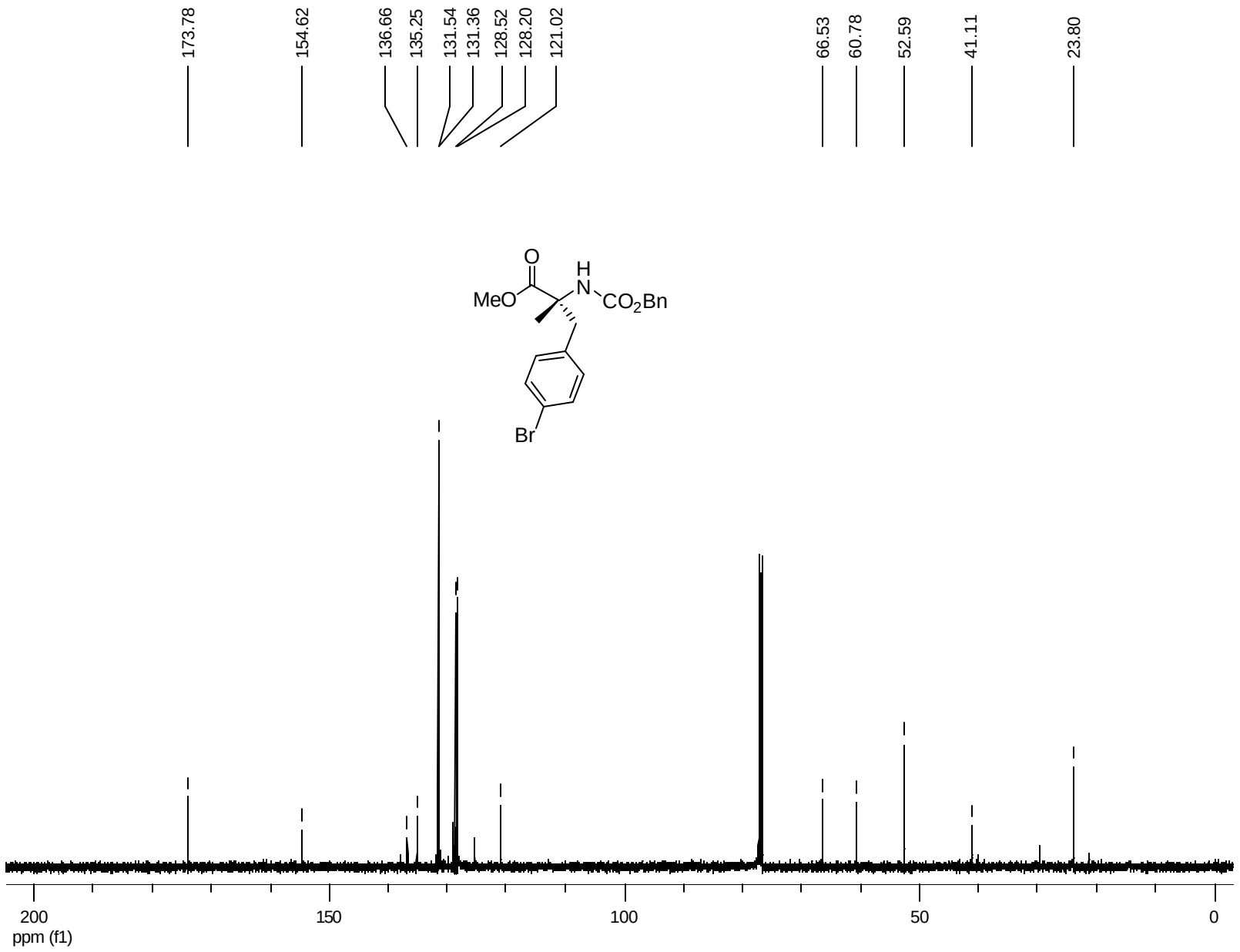

7.29
6.83
5.09
3.57
3.26
2.97
1.40
O
HN
CO2Bn
MeO
N
CO2Bn
Br
12.6
1.2
3.8
3.0
1.0
0.7
2.7
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

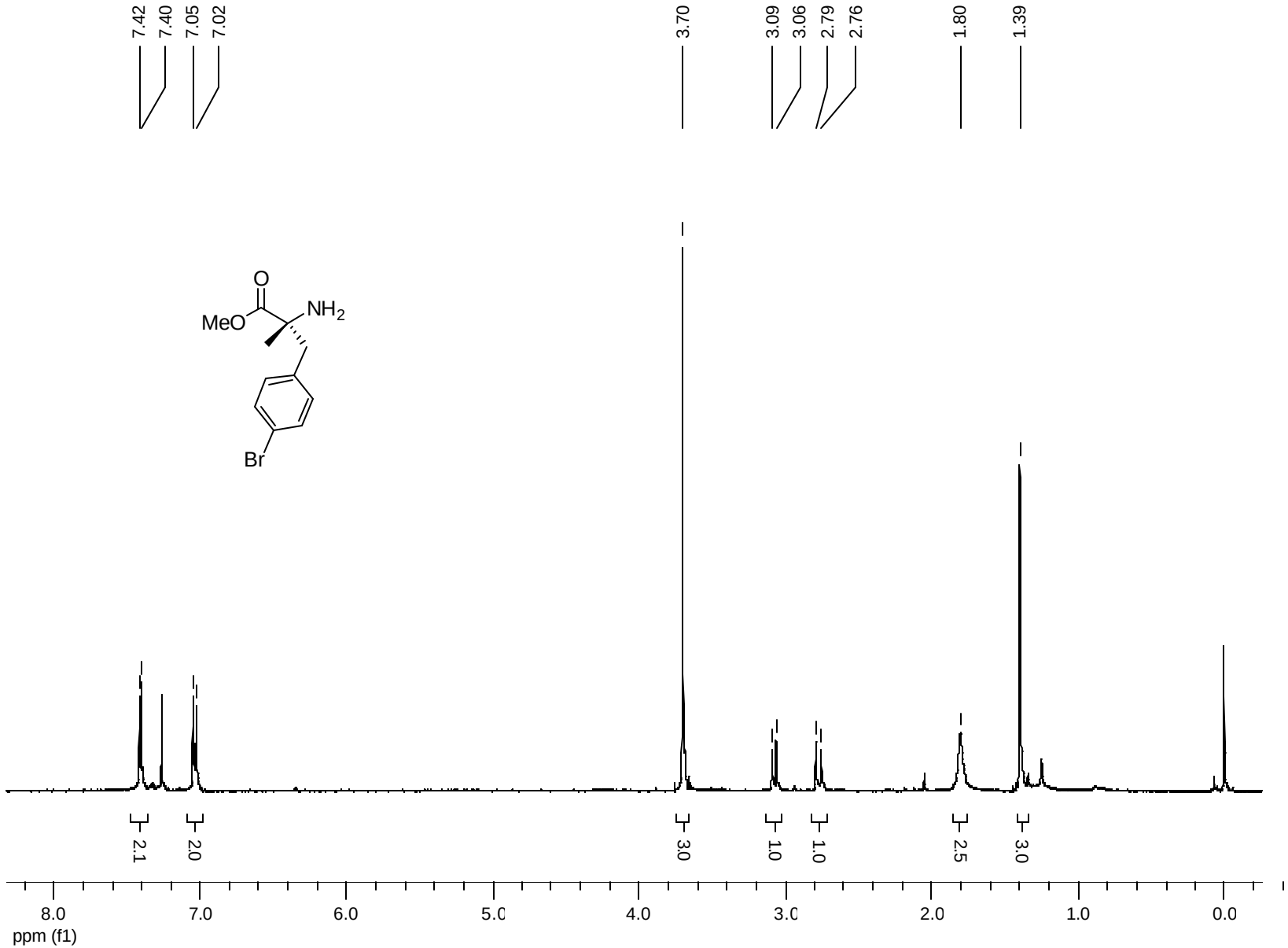

173.04
156.19
154.95
135.65
134.98
131.95
131.69
128.53
128.36
128.12
128.29
107.95
68.40
67.94
52.24
41.21
21.06
O
HN
CO2Bn
MeO
N
CO2Bn
Br
200
150
100
50
0
ppm (f1)

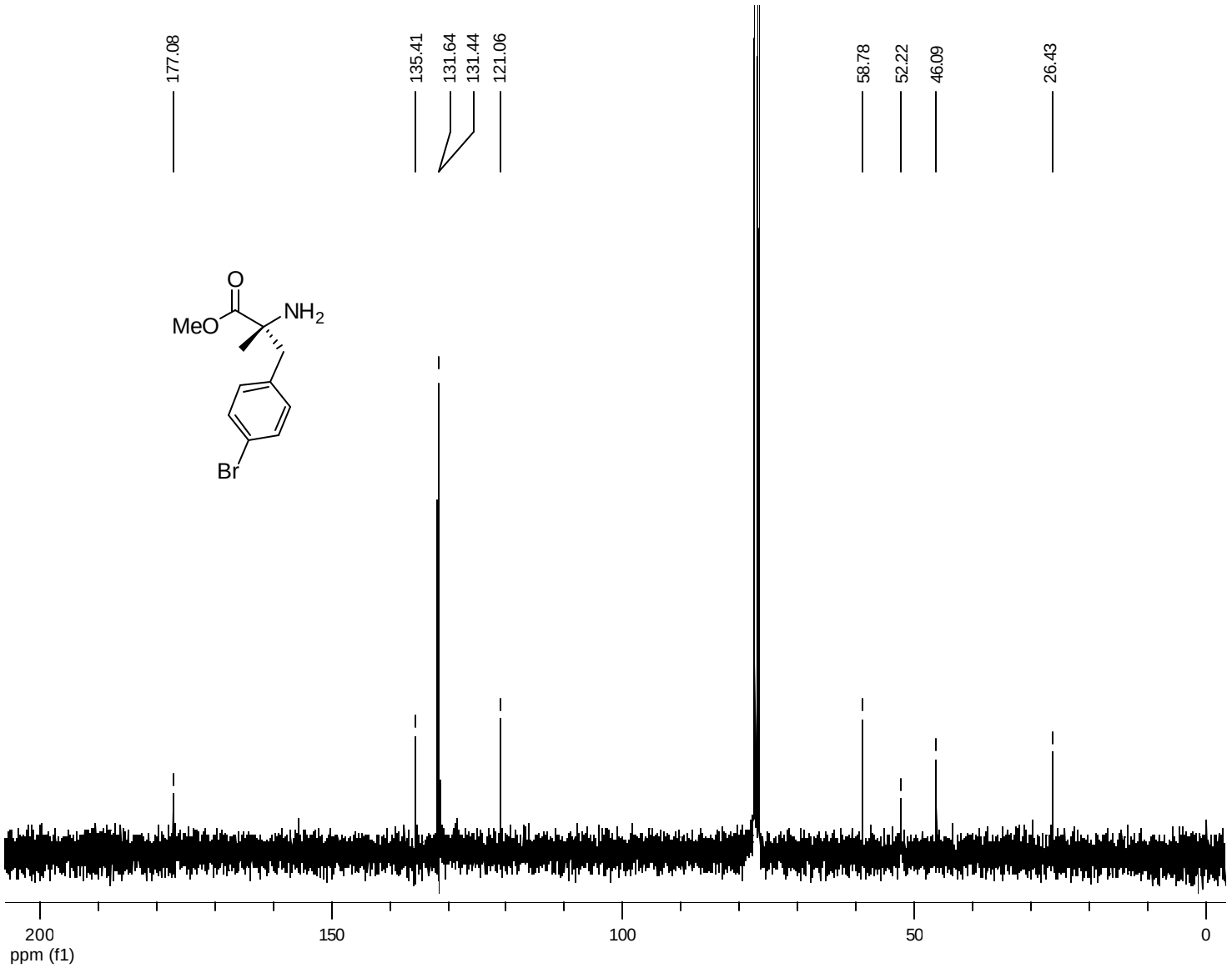

7.36
7.32
7.31
6.94
5.23
5.21
5.14
5.12
3.64
3.37
3.12
1.43
O
HN
CF3
O
MeO
N
CO2Bn
Br
7.2
1.8
1.0
1.0
3.0
0.9
1.0
3.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

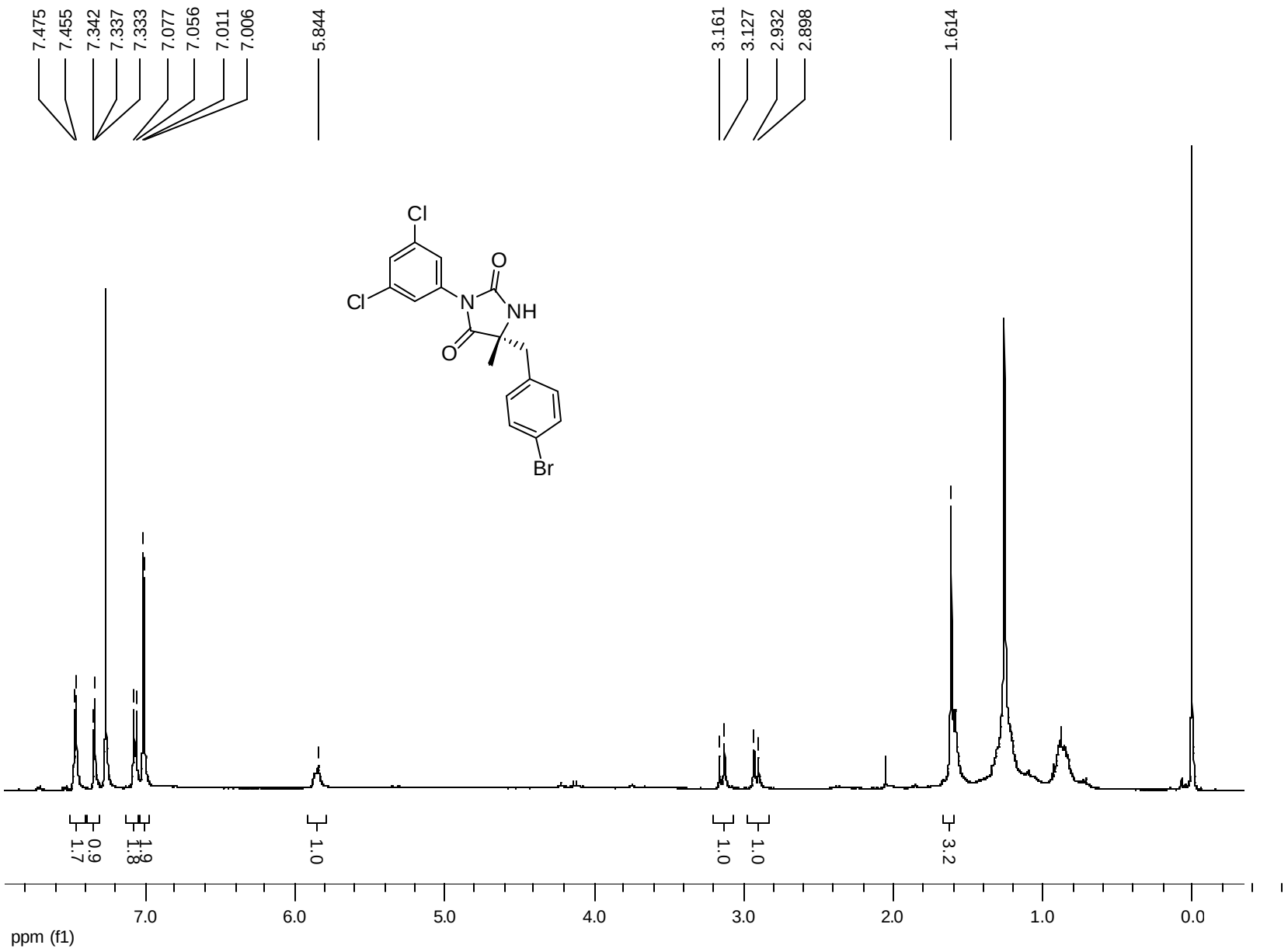

172.92
156.85
156.60
135.09
134.29
132.19
131.65
128.71
128.67
128.33
121.59
116.50
114.59
69.08
67.83
52.66
41.08
21.24
O
HN
CF3
O
MeO
N
CO2Bn
Br
200
150
100
50
0
ppm (f1)

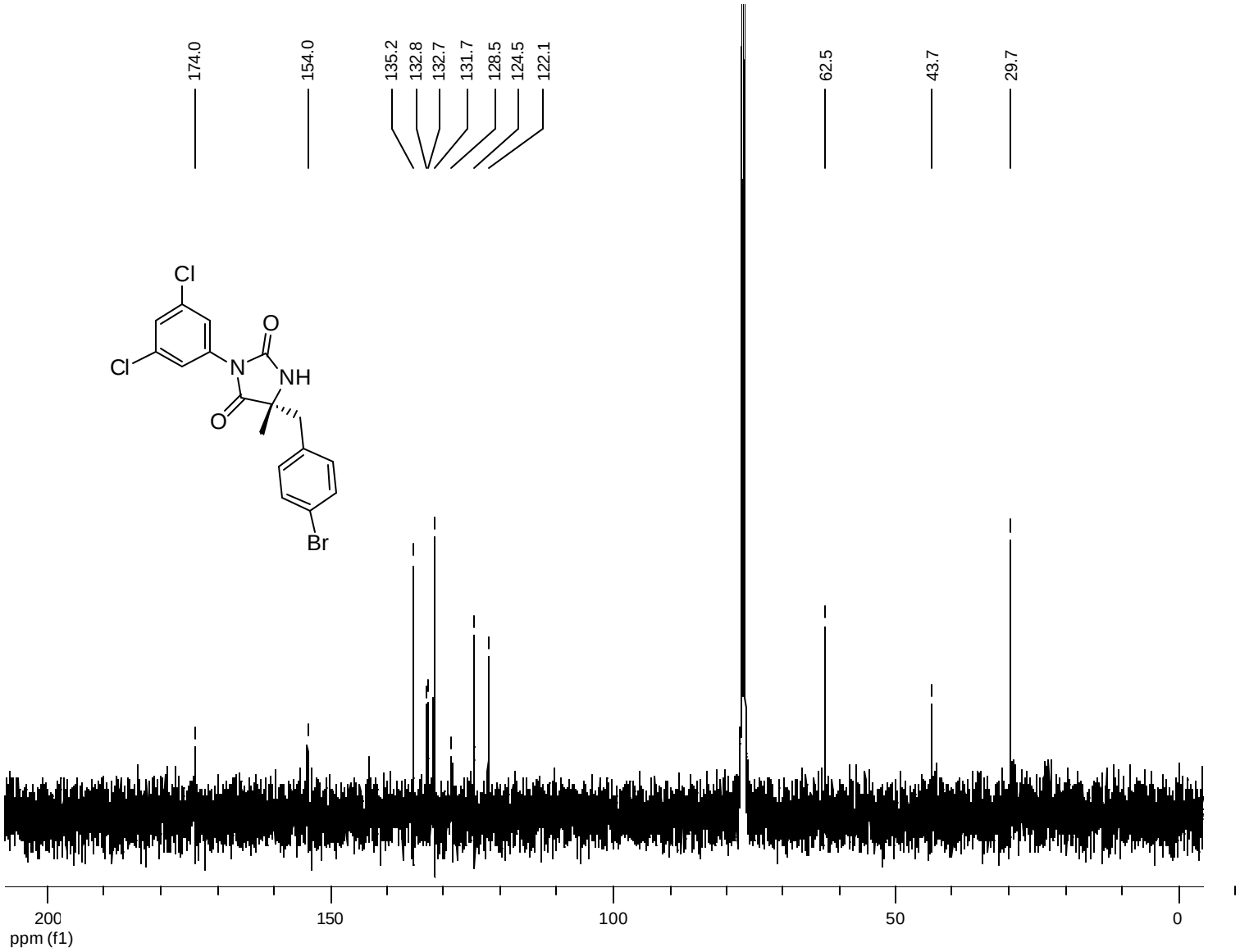

7.35
7.29
7.28
6.84
6.82
5.38
5.16
5.14
5.08
5.06
3.72
3.40
3.37
3.15
3.12
1.61
O
H
N
MeO
CO2Bn
Br
4.4
2.2
1.5
1.0
1.0
0.9
2.7
1.2
1.0
3.7
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

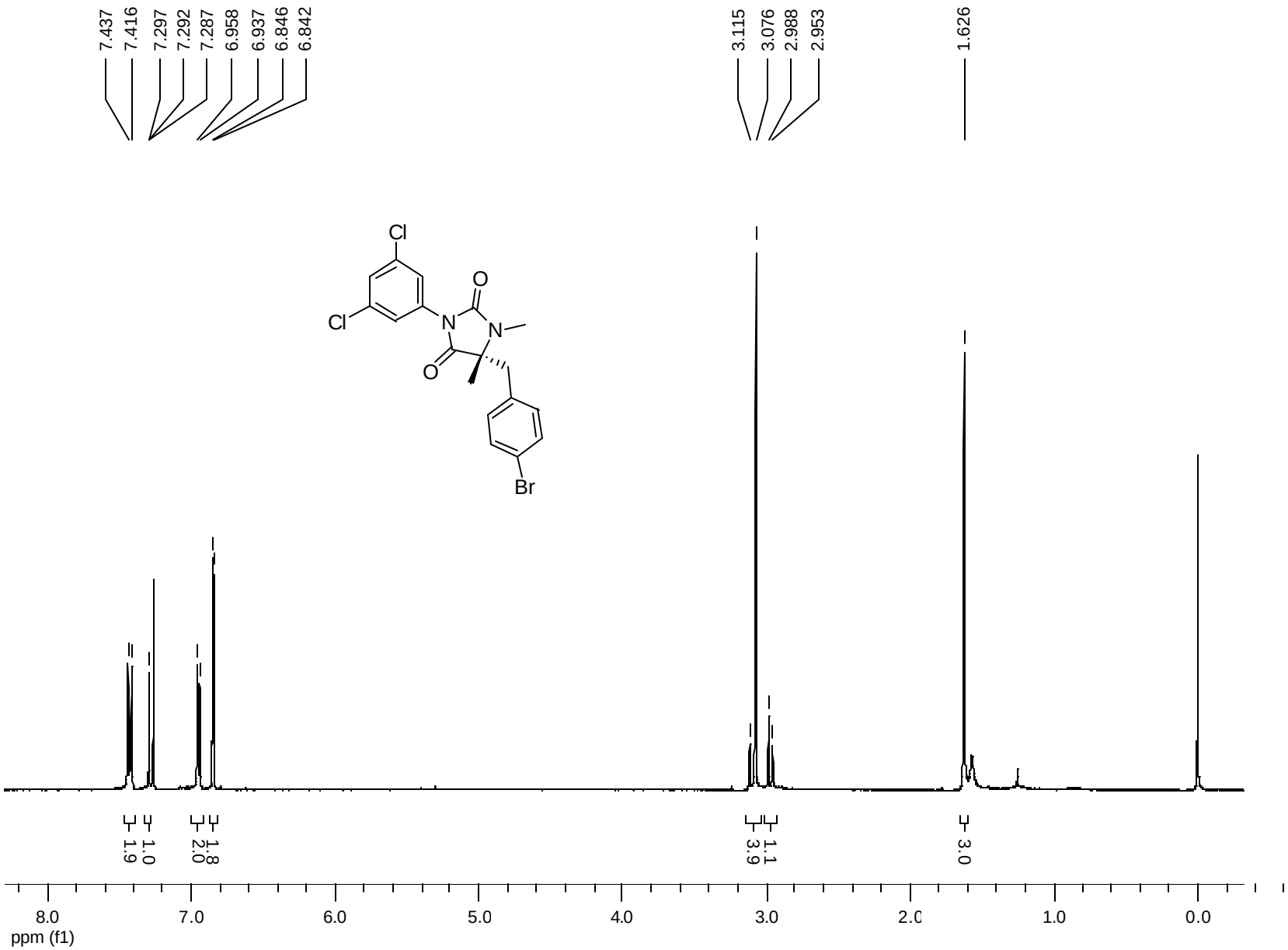

173.78
154.62
136.66
135.25
131.54
131.36
128.52
128.20
121.02
66.53
60.78
52.59
41.11
23.80
O
H
N
MeO
CO2Bn
Br
200
150
100
50
0
ppm (f1)

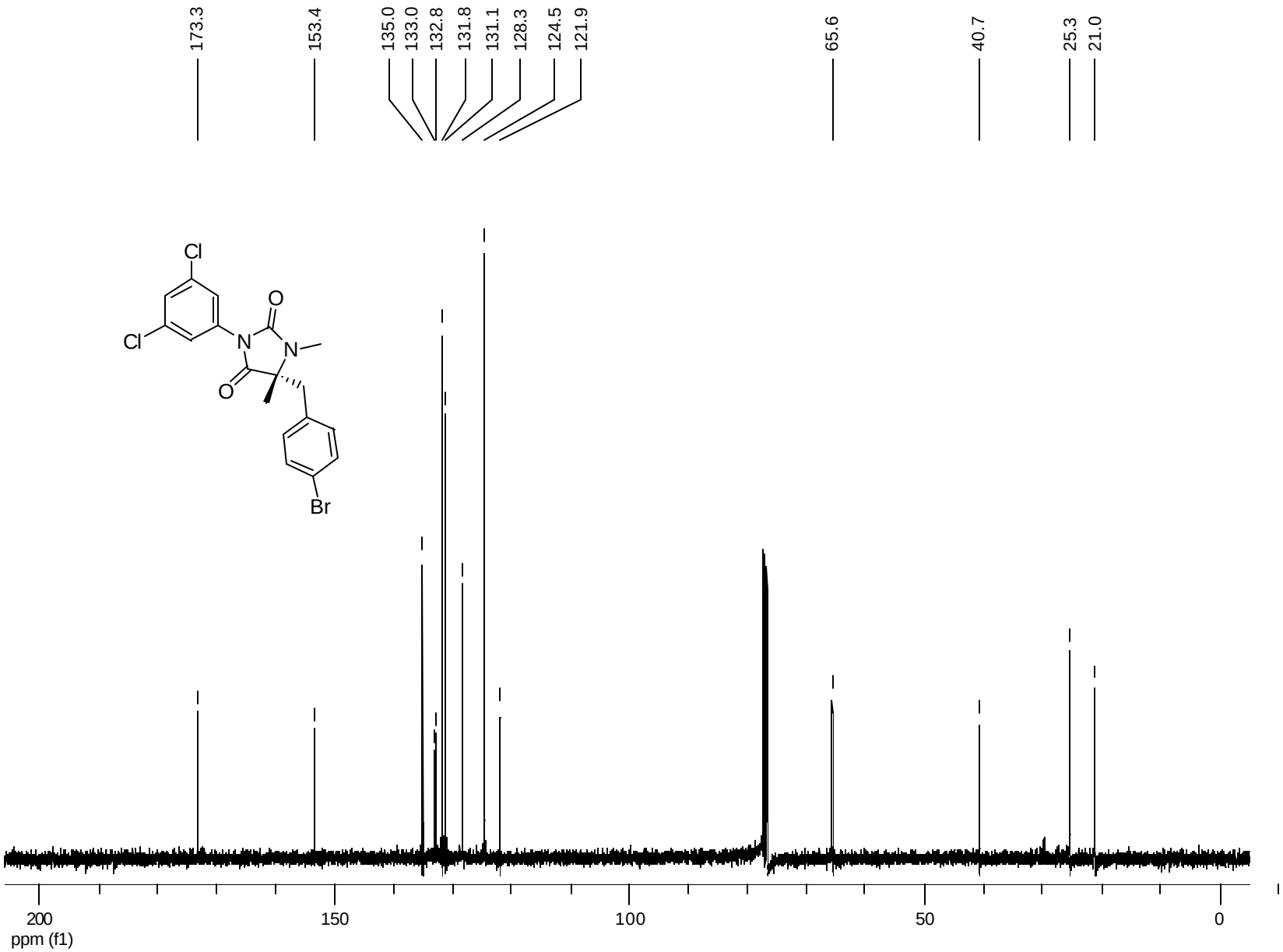

7.42
7.40
7.05
7.02
3.70
3.09
3.06
2.79
2.76
1.80
1.39
O
MeO
NH2
Br
2.1
2.0
3.0
1.0
1.0
2.5
3.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)


177.08
135.41
131.64
131.44
121.06
58.78
52.22
46.09
26.43
O
MeO
NH2
Br
200
150
100
50
0
ppm (f1)


7.475
7.455
7.342
7.337
7.333
7.077
7.056
7.011
7.006
5.844
3.161
3.127
2.932
2.898
1.614
Cl
Cl
N
O
NH
O
Br
1.7
0.9
1.8
1.9
1.0
1.0
1.0
3.2
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)


174.0
154.0
135.2
132.8
132.7
131.7
128.5
124.5
122.1
62.5
43.7
29.7
Cl
Cl
O
N
NH
O
Br
200
150
100
50
0
ppm (f1)


7.437
7.416
7.297
7.292
7.287
6.958
6.937
6.846
6.842
3.115
3.076
2.988
2.953
1.626
Cl
Cl
N
N
O
O
Br
1.9
1.0
2.0
1.8
3.9
1.1
3.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)


173.3
153.4
135.0
133.0
132.8
131.8
131.1
128.3
124.5
121.9
65.6
40.7
25.3
21.0
Cl
Cl
O
O
N
N
Br
200
150
100
50
0
ppm (f1)