Organic Syntheses

Indole-Catalyzed Bromolactonization: Preparation of Bromolactone in Lipophilic Media

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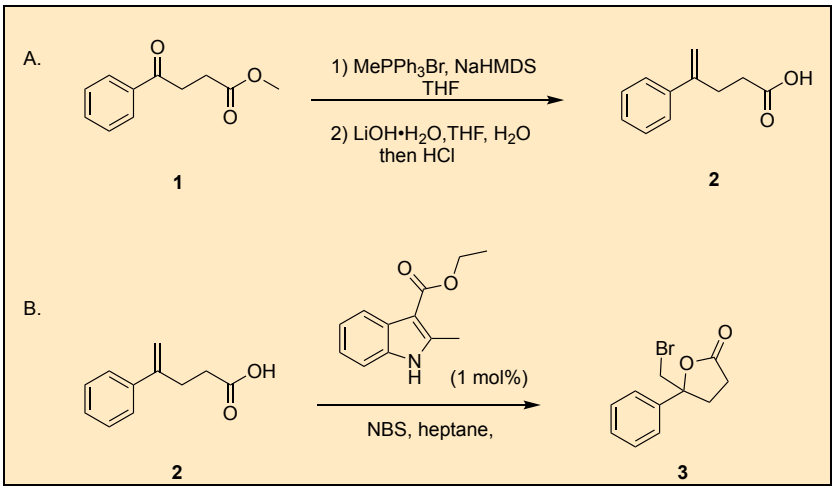
Checked by Zhaobin Han and Kuiling Ding



Procedure (Note 1)

A. *4-Phenyl-4-pentenoic acid* (**2**). A cloudy white suspension of methyltriphenylphosphonium bromide (25.51 g, 70.0 mmol, 1.87 equiv) (Note 2) in anhydrous toluene (70 mL) (Note 3) is placed in an oven-dried, 250-mL reaction flask equipped with a magnetic stir bar (2.5 x 0.8 cm Teflon-coated) (Note 4) and a reflux condenser capped with a rubber septum. An inert gas inlet is inserted via a needle, and the solution is cooled to 0 °C (ice water bath temperature). Sodium bis(trimethylsilyl)amide (NaHMDS, 67.5 mL, 67.5 mmol, 1.8 equiv, 1 M

DOI: 10.15227/orgsyn.095.0256

solution in THF) (Note 5) is added dropwise by syringe to the suspension under a nitrogen atmosphere over 15 min. The resulting solution is allowed to stir for 45 min and is then cooled to –78 °C using a dry ice-acetone bath. Methyl 3-benzoylpropionate (7.21 g, 37.5 mmol, 1 equiv) (Note 6) is added dropwise by syringe over 5 min. The reaction mixture is warmed to 22 °C for 2 h and is the heated to reflux for 40 h under a nitrogen atmosphere (Figure 1). The reaction is monitored by ^{1}H NMR investigation of the crude sample (Note 7). Upon cooling to 22 °C, the reaction is quenched by the addition of saturated aqueous ammonium chloride (100 mL) and the resulting slurry is diluted with water (100 mL). The organic layer is separated and the aqueous layer is extracted with EtOAc (100 mL x 3). The combined organic extracts are washed with brine (100 mL), dried over anhydrous Na_2SO_4 (5.0 g), filtered, and concentrated by rotary evaporation. The residue is purified by flash column chromatography on silica gel (hexane/EtOAc : 10:1) to give 5.16 g of methyl 4-phenyl-4-pentenoate (**1**) as pale yellow oil (Note 7).

Figure 1. Reaction setup for synthesis of 1

Into a 500-mL reaction flask containing a magnetic teflon-coated stir bar (2.5 x 0.8 cm) is added a solution of methyl 4-phenyl-4-pentenoate (**1**) (5.49 g, 28.9 mmol, 1 equiv) in THF (100 mL) and H_2O (100 mL) containing LiOH•H_2O (12.1 g, 289.0 mmol, 10.0 equiv) (Note 8) at 22 °C. The mixture is

stirred for 12 h (monitored by silica TLC using hexane/ethyl acetate : 5/1) (Note 7) and then diluted with water (150 mL). The aqueous fraction is washed with diethyl ether (3 x 100 mL) and acidified with 2 M HCl to pH 2. After extraction of the aqueous phase with EtOAc (3 x 150 mL), the combined organic extracts are washed with brine (200 mL), dried over Na_2SO_4 (5.0 g), filtered and concentrated under reduced pressure to give the desired alkenoic acid **2** as a white solid, which is purified by flash column chromatography (silica, pure EtOAc) to yield 4.77 g of 4-phenyl-4-pentenoic acid (**2**) (28.6 mmol, 72% from methyl 3-benzoylpropionate) as a white solid (Note 9).

*B. 5-(Bromomethyl)-5-phenyldihydrofuran-2(3H)-one (**3**).* An oven-dried, 1-L reaction flask equipped with a teflon-coated magnetic stir bar (5.0 x 2.0 cm, ovoid-shaped) and a glass stopper (Figure 2) is charged with a mixture of alkenoic acid **2** (3.97 g, 22.5 mmol, 1.0 equiv) and ethyl 2-methylindole-3-carboxylate (46.2 mg, 0.225 mmol, 0.01 equiv) (Note 10) in heptane (450 mL) (Note 11) at 22 °C, to which is added *N*-bromosuccinimide (4.81 g, 27 mmol, 1.2 equiv) (Note 12) in three portions with five min intervals in the absence of light (the flask is wrapped with aluminum foil tightly). The resulting mixture is vigorously stirred at 22 °C in the dark till completion. The reaction is monitored by ^{1}H NMR (Note 13). After 48 h the insoluble succinimide is filtered and washed with a mixture of diethyl ether/hexane (ratio 4:5) (3 x 45 mL). The combined filtrate is concentrated under reduced pressure. The remaining

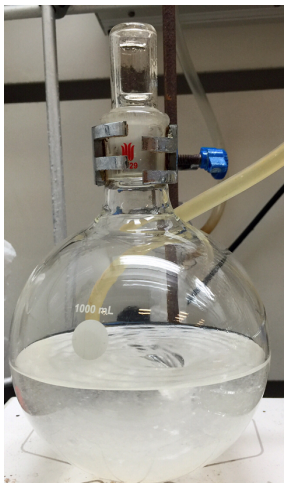


Figure 2. Reaction setup for synthesis of 3

solvent is removed under a high vacuum (1.0 mm Hg), and without using column chromatography, 5.01 g (87% yield) of 5-(bromomethyl)-5-phenyldihydrofuran-2(3H)-one (**3**) is obtained as a pale-yellow oil with a purity of 99%, as determined by ^{1}H NMR spectroscopy (Note 13).

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical). See also "Identifying and Evaluating Hazards in Research Laboratories" (American Chemical Society, 2015) which is available via the associated website "Hazard Assessment in Research Laboratories" at https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with methyltriphenylphosphonium bromide, toluene, sodium bis(trimethylsilyl)amide, tetrahydrofuran, methyl 3-benzoylpropionate, ammonium chloride, ethyl acetate, silica gel, brine, sodium sulfate, hexane, lithium hydroxide, diethyl ether, hydrochloric acid, ethyl 2-methylindole-3-carboxylate, heptane, *N*-bromosuccinimide, and succinimide.
2. Methyltriphenylphosphonium bromide was purchased from Acros, (98% purity, white solid) and used as received.
3. Toluene was purchased from Merck, (≥99.9% purity, colorless liquid) and was dried over INERT Pure Solv Solvent Purification System before use.

4. All glassware was thoroughly washed and dried in an oven at 110 °C. Teflon-coated magnetic stirring bars were washed with acetone and dried.
5. Sodium bis(trimethylsilyl)amide was purchased from Sigma-Aldrich, (1.0 M solution in THF) and used as received.
6. Methyl 3-benzoylpropionate was purchased from Sigma-Aldrich, (CDS001561, colorless liquid) and used as received. The checkers purchased methyl 3-benzoylpropionate (>98%) from Tokyo Chemical Industry Co., Ltd. and used it as received.
7. The product was purified by flash chromatography on a column (5 x 40 cm) of 100 g of silica gel and eluted with hexane/EtOAc (10:1), R_f = 0.60 in hexane/EtOAc (5:1). A second reaction on the same scale provided 5.13 g (76%) of methyl 4-phenyl-4-pentenoate (**1**). The product exhibits the following characteristics: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.48 (t, *J* = 8.0 Hz, 2H), 2.84 (t, *J* = 7.6 Hz, 2H), 3.66 (s, 3H), 5.09 (s, 1H), 5.31 (s, 1H), 7.25 – 7.43 (m, 5H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.4, 32.9, 51.5, 112.7, 126.0, 127.5, 128.3, 140.4, 146.7, 173.4 . IR (film): 2951, 1734, 1494, 1155, 897, 777, 701 cm^{-1}; HRMS (ESI, $[M+H]^+$) *m*/*z* calcd for $C_{12}H_{15}O_2$: 191.1067. Found: 191.1068. The purity of product **1** was determined using ^{1}H QNMR analysis. ^{1}H QNMR was performed using a mixture of methyl 4-phenyl-4-pentenoate (25.4 mg) and ethylene carbonate (7.1 mg) (Alfa Aesar, ⩾99% purity, white solid) as an internal standard in $CDCl_3$. The purity was calculated according to standard method as 99 wt%.
8. $LiOH \bullet H_2O$ was purchased from Sigma-Aldrich, (⩾98.0% purity, white solid) and used as received.
9. The product was purified by flash chromatography on a column (5 x 40 cm) of 100 g of silica gel and eluted with pure EtOAc, R_f = 0.65 in EtOAc. A second reaction on the same scale provided 4.71 g of **2** (71% from methyl 3-benzoylpropionate). The product exhibits the following characteristics: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.54 (t, *J* = 7.6 Hz, 2H), 2.85 (t, *J* = 7.6 Hz, 2H), 5.11 (d, *J* = 1.2 Hz, 1H), 5.33 (s, 1H), 7.24–7.43 (m, 5H), 11.58 (br s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.0, 33.0, 112.9, 126.0, 127.6, 128.4, 140.3, 146.4, 179.9 IR (film): 3051, 2922, 1693, 920, 777, 701
cm^{-1}; HRMS (ESI, $[M-H]^-$) *m*/*z* calcd for $C_{11}H_{11}O_2$: 175.0765. Found: 175.0764; Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.02; H, 6.87. The purity of product **2** was determined using ^{1}H QNMR analysis.

^{1}H QNMR was performed using a mixture of **2** (20.1 mg) and 1,3,5-trimethoxybenzene (7.0 mg) (Alfa Aesar, ⩾99% purity, white solid) as an internal standard in $CDCl_3$. The purity was calculated according to standard method as 99 wt%.

10. Ethyl 2-methylindole-3-carboxylate was purchased from Sigma-Aldrich, (99.0% purity, white solid) and used as received.
11. *n*-Heptane was purchased from Acros, (99.83% purity, colorless liquid) and used as received.
12. *N*-Bromosuccinimide was purchased from Alfa Aesar (99% purity, white solid) and recrystallized before use.
13. A second reaction on the same scale provided 5.00 g (88%) of **3**. The product **3** exhibits the following characteristics: R_f = 0.67 in CH_2Cl_2; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.49 – 2.63 (m, 2H), 2.76 – 2.90 (m, 2H), 3.70 (d, *J* = 11.2 Hz, 1H), 3.75 (d, *J* = 11.6 Hz, 1H), 7.33 – 7.46 (m, 5H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.8, 32.2, 40.9, 86.2, 124.7, 128.4, 128.6, 140.5, 175.4. IR (film): 1773, 1153, 928, 766, 700 cm^{-1}; HRMS (ESI, $[M+H]^+$) *m*/*z* calcd for $C_{11}H_{12}BrO_2$: 255.0015. Found: 255.0015. The purity of product **3** was determined using ^{1}H QNMR analysis. ^{1}H QNMR was performed using a mixture of **3** (40.7 mg) and ethylene carbonate (5.5 mg) (Alfa Aesar, ⩾99% purity, white solid) as an internal standard in $CDCl_3$. The purity was calculated according to standard method as 99.0 wt%.

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no

significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

Discussion

Lactone is a privileged heterocycle, as it is the essential unit in many natural products and drug molecules. As a result, synthesis of functionalized lactones has steadily attracted a great deal of interest among organic chemists. A significant amount of research has been well documented over the past few decades.

Halolactonization, which can be dated back to 1954, remains one of the superior ways to construct lactones with an easily manipulated halogen handle.[2] The resulting lactones are oftentimes pharmaceutically important drug cores. To avoid handling toxic liquid bromine, alternative electrophilic halolactonization reactions have become more popular in recent decades.[3] *N*-Bromosuccinimide (NBS) is one of the inexpensive electrophilic halogen sources that can be handled with ease.[4] However, the Br carrier (succinimide) is soluble in both polar and halogenated solvents, which complicates the purification process particularly for large-scale reactions. Halogenation in nonpolar solvents (e.g., heptane) is uncommon in literature due to the insolubility of polar halogenating sources, although some of the nonpolar solvents are attractive reaction media in industrial processes.[5]

Previously, we have exploited the use of a 1*H*-indole-3-carboxylate-based solid-liquid phase-transfer organocatalyst in the bromolactonization reaction of olefinic carboxylic acids in lipophilic solvent.[6] The 1*H*-indole-3-

carboxylate system can be readily constructed using a two-step sequence starting from aniline.[7]

This new type of halogen activation using a structurally simple indole organocatalyst can be applied to various electrophilic halogenation reactions. The major side product for halogenation is succinimide, which is insoluble in non-polar solvents. This methodology allows succinimide to be removed easily via simple filtration without the need to use column chromatography and thus saving time and money in the purification of the desired halogenation products.

In summary, 1*H*-indole-3-carboxylate has been identified to be an efficient organocatalyst for large-scale bromolactonization of alkenoic acids in green lipophilic media such as heptane. The reaction is operationally simple: the lactonization can be performed at room temperature and the workup process can be facilitated by filtration. Considering the practicality of this type of catalytic halogenation reaction, significant further applications are expected.

References

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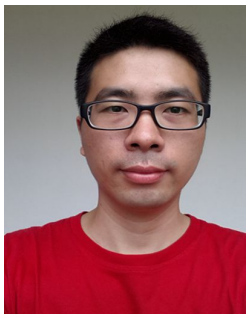
Appendix
Chemical Abstracts Nomenclature (Registry Number)

Methyltriphenylphosphonium bromide; (1779-49-3)
Toluene; (108-88-3)
NaHMDS: Sodium bis(trimethylsilyl)amide; (1070-89-9)
LiOH•H_2O: Lithium hydroxide monohydrate; (1310-66-3)
Ethyl 2-methylindole-3-carboxylate; (53855-47-3)
n-Heptane; (142-82-5)
N-Bromosuccinimide; (128-08-5)

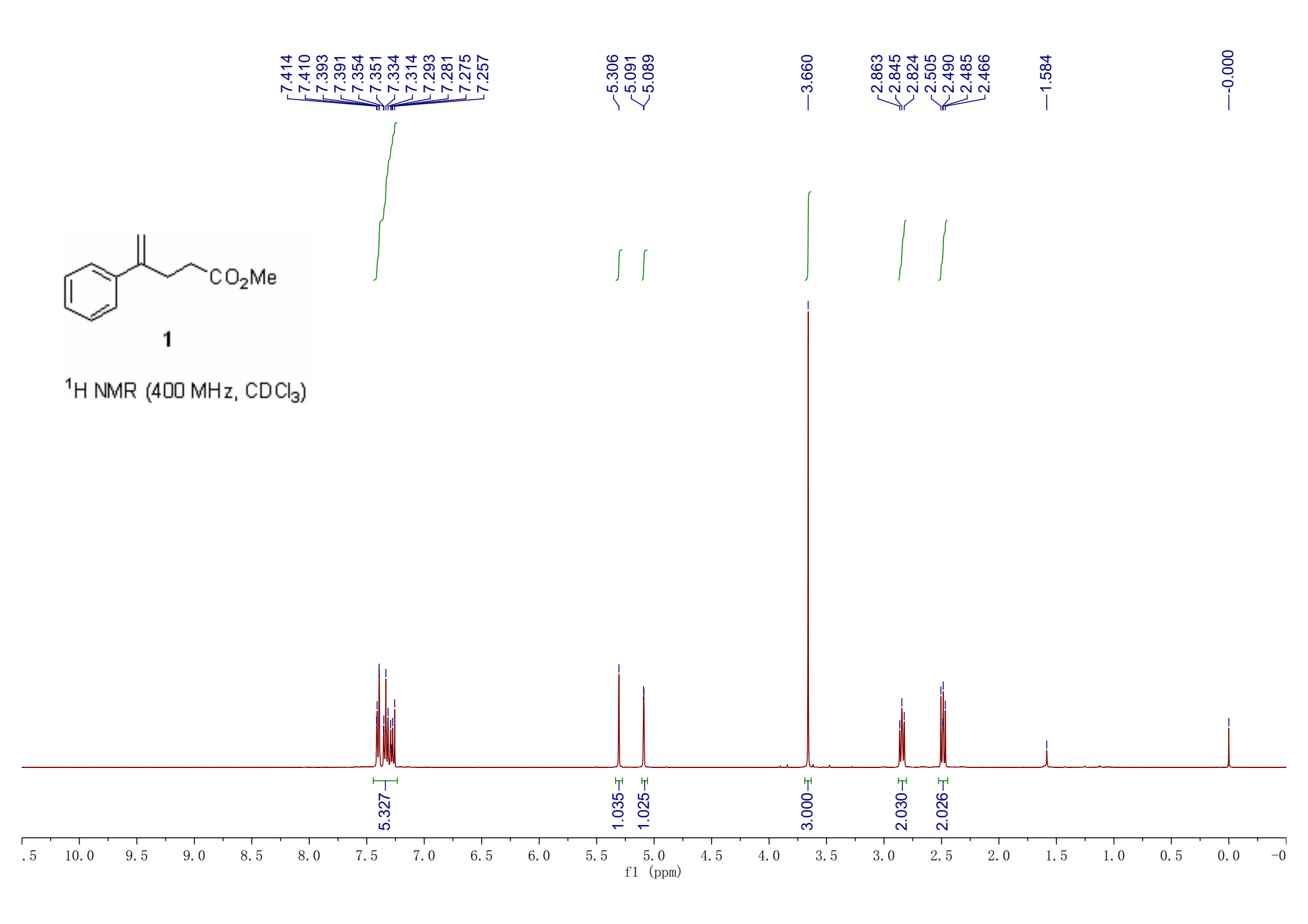
Zhihai Ke received his Ph.D. degree from The Chinese University of Hong Kong in 2012 under the direction of Prof. Hak-Fun Chow. He joined Prof. Ying-Yeung Yeung's research group at the National University of Singapore as a postdoctoral fellow in late 2012. In Aug 2015, he moved back to The Chinese University of Hong Kong as a Research Assistant Professor, dedicating his efforts to the development of novel organic synthetic methods.



Tao Chen was born in 1985 in Jiangsu, China. He obtained his B.S. degree from Soochow University in 2008. After receiving an M.S. degree from the same university in 2011, he started Ph.D. study under the supervision of Prof. Ying-Yeung Yeung in National University of Singapore in the same year. He received his Ph.D. degree in 2016, after which he joined the research group of Prof. Shunsuke Chiba as a postdoctoral fellow at the Nanyang Technological University.

Ying-Yeung Yeung received his B.Sc. (2001) at The Chinese University of Hong Kong. He continued his graduate research in the same university under the supervision of Prof. Tony K. M. Shing. After four years research dedicated to natural product synthesis, Dr. Yeung moved to the USA to conduct postdoctoral research with Prof. E. J. Corey at Harvard University. In 2008, he joined National University of Singapore, Department of Chemistry. In 2015, he moved to The Chinese University of Hong Kong as an Associate Professor. His research interests include asymmetric catalysis, green oxidation, and methodology development.

Dr. Zhaobin Han graduated from the Department of Chemistry, Nanjing University in 2003. He received his Ph.D. degree from Shanghai Institute of Organic Chemistry under the supervision of Prof. Kuiling Ding and Prof. Xumu Zhang in 2009, working on development of novel chiral ligands for asymmetric catalysis. He is currently an Associate Professor in the same institute and his research interests focus on the development of efficient catalytic methods for organic synthesis based on homogeneous catalysis.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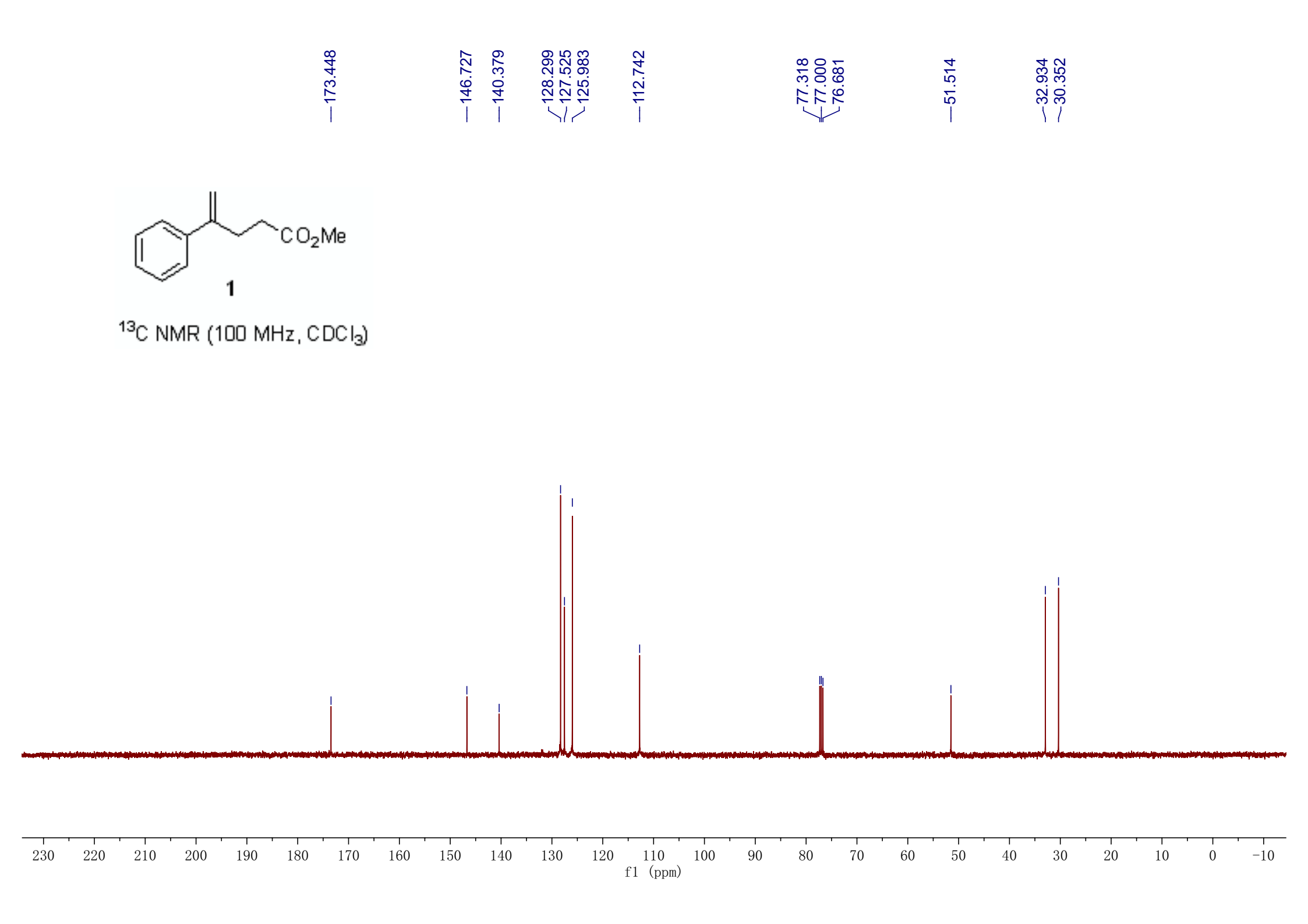
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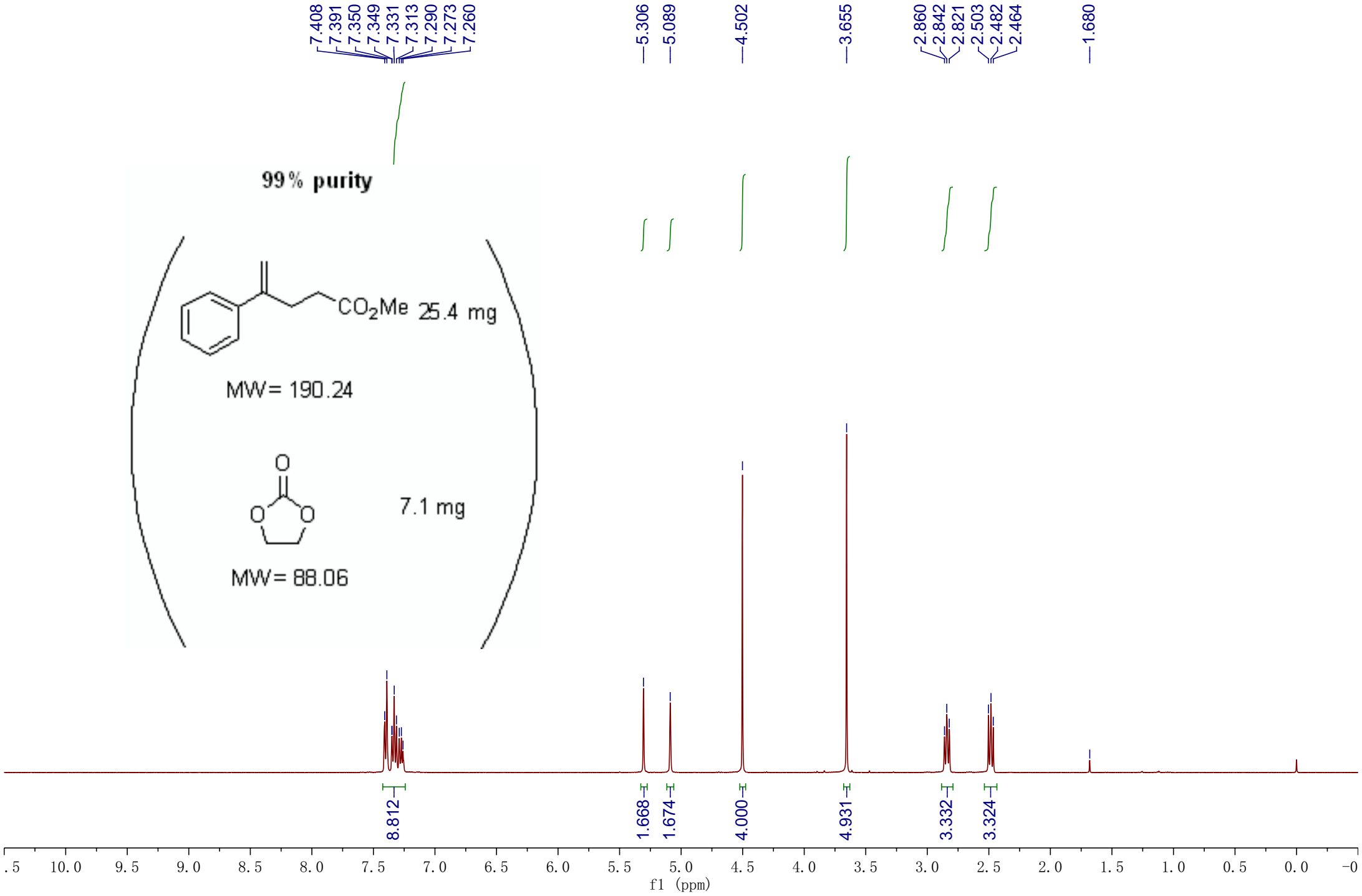
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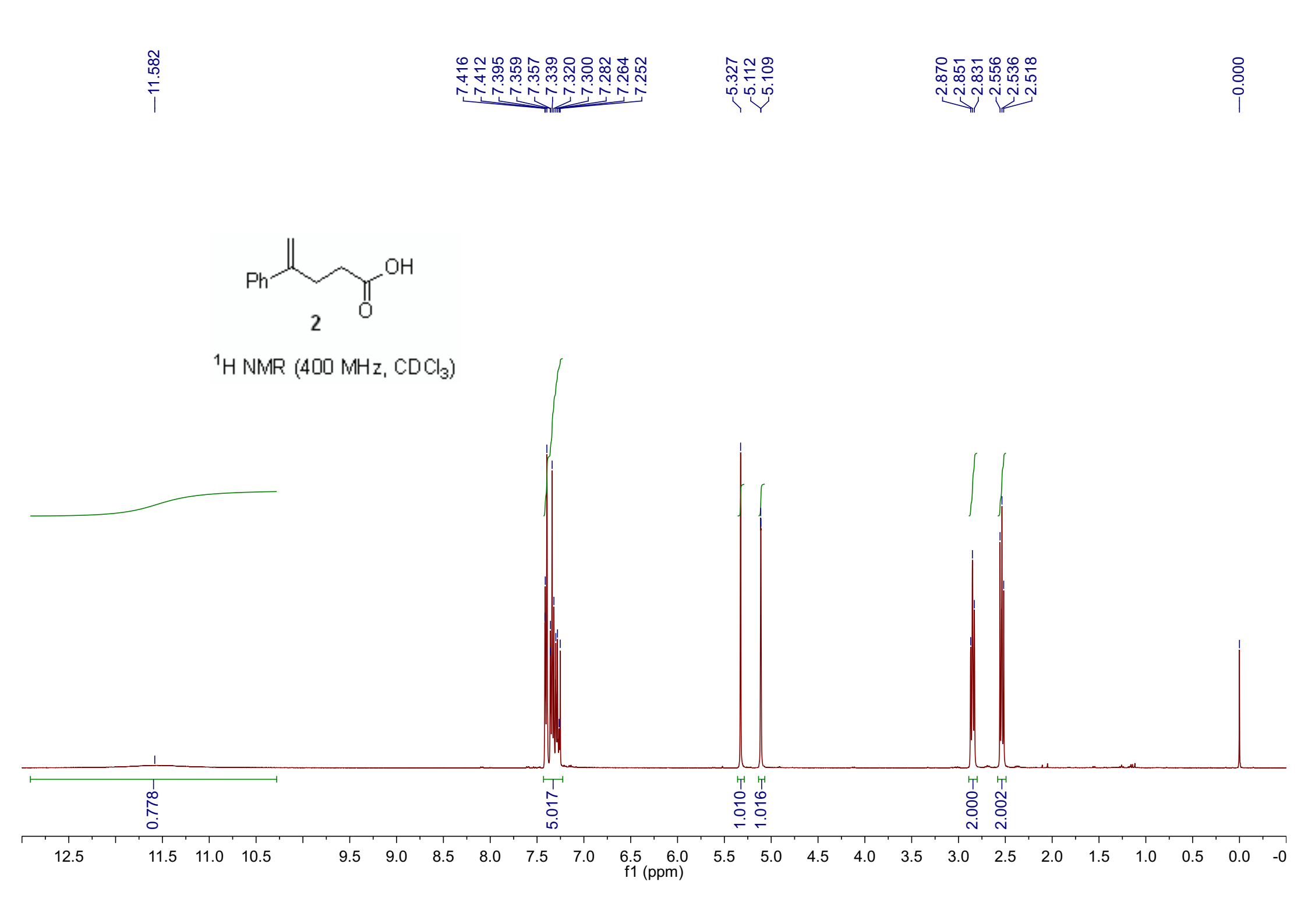
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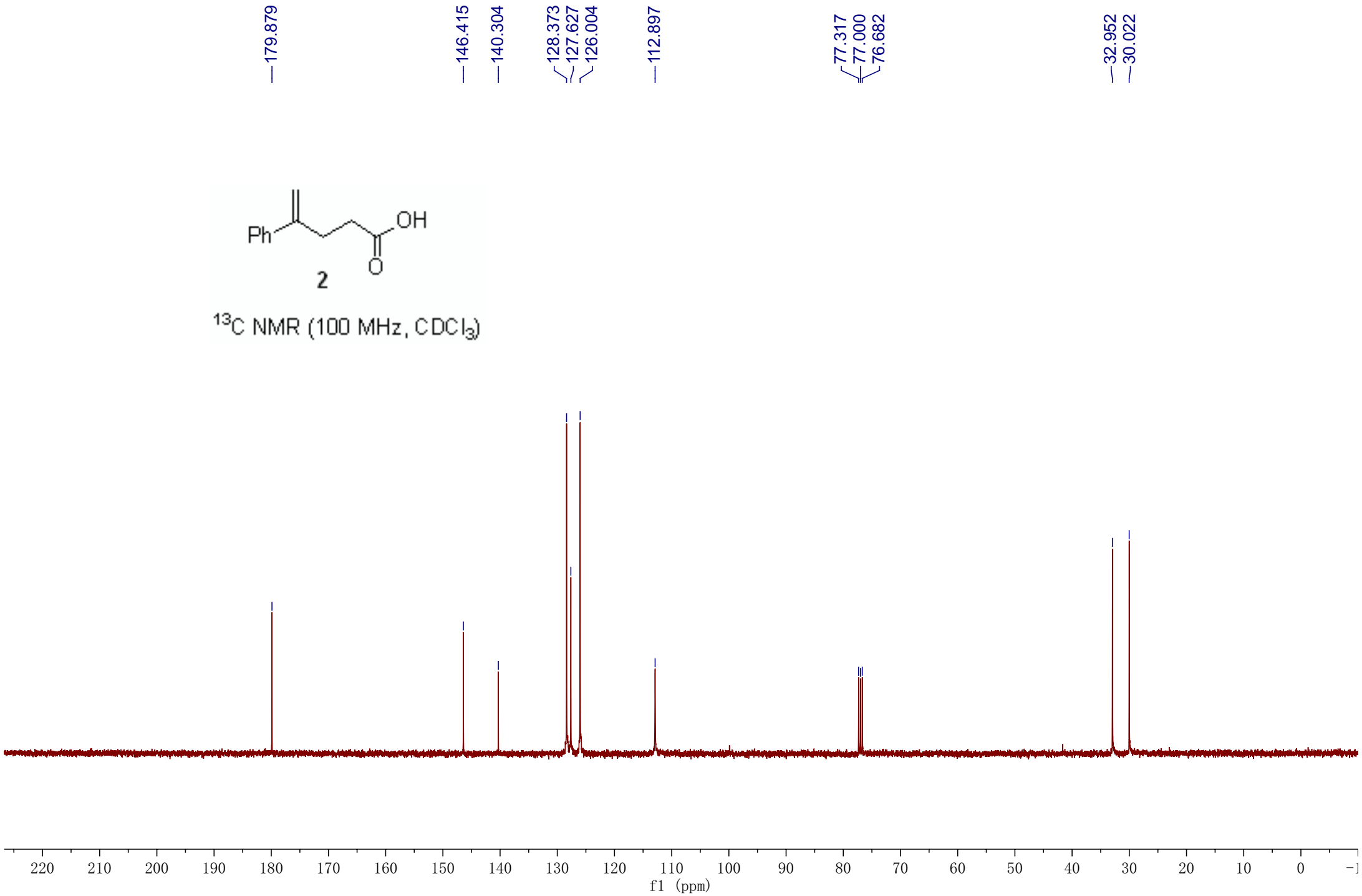
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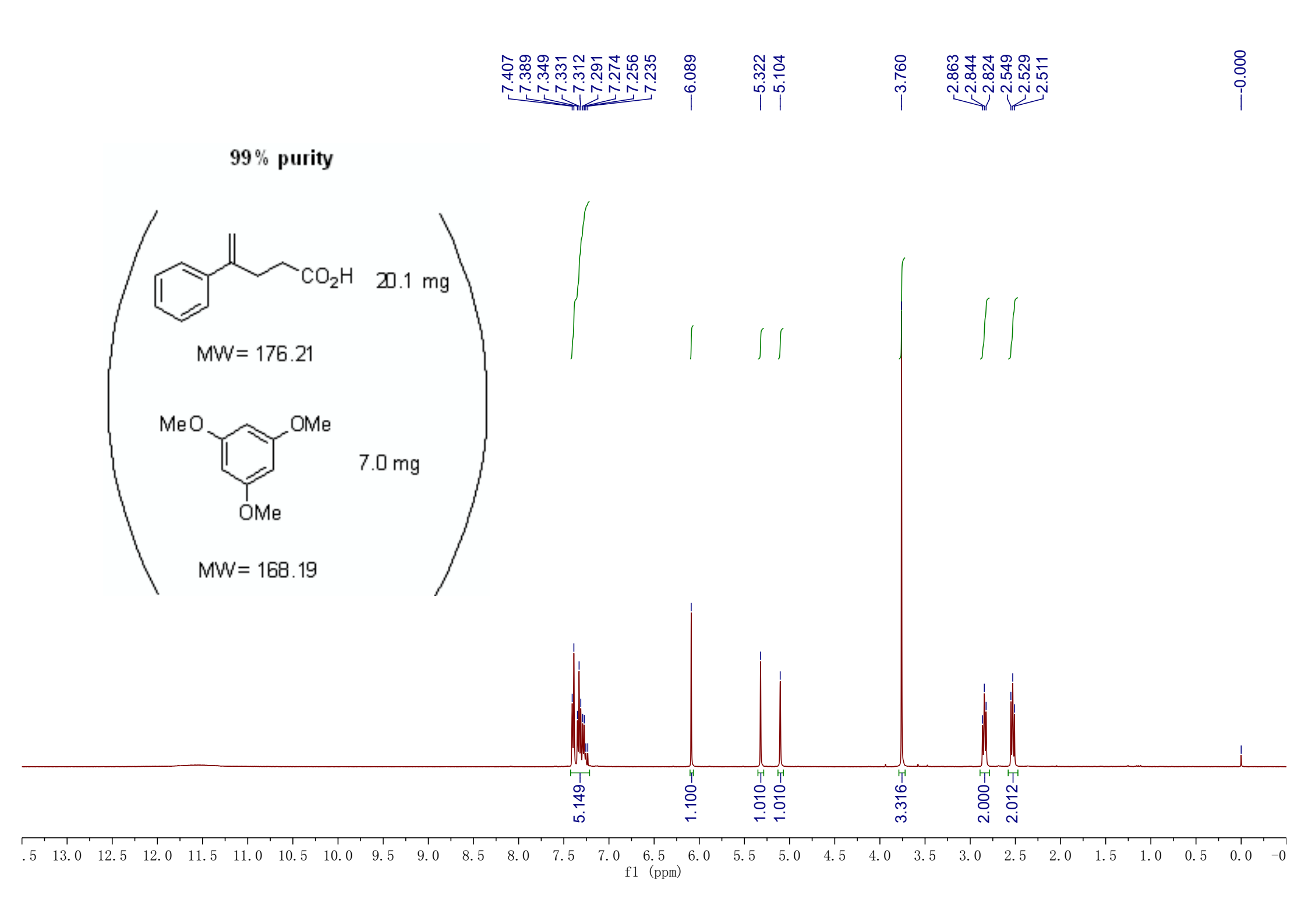
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2.511
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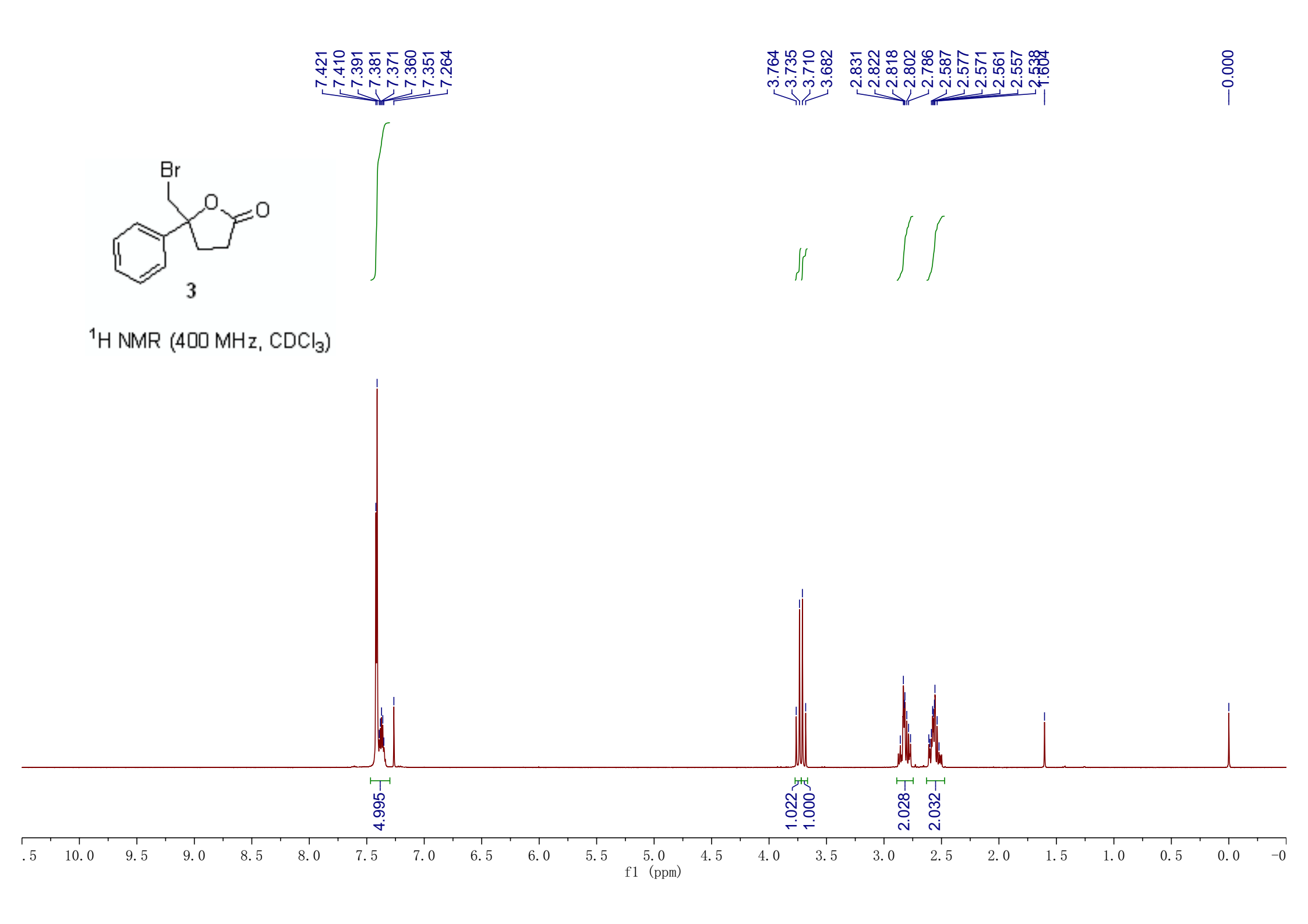
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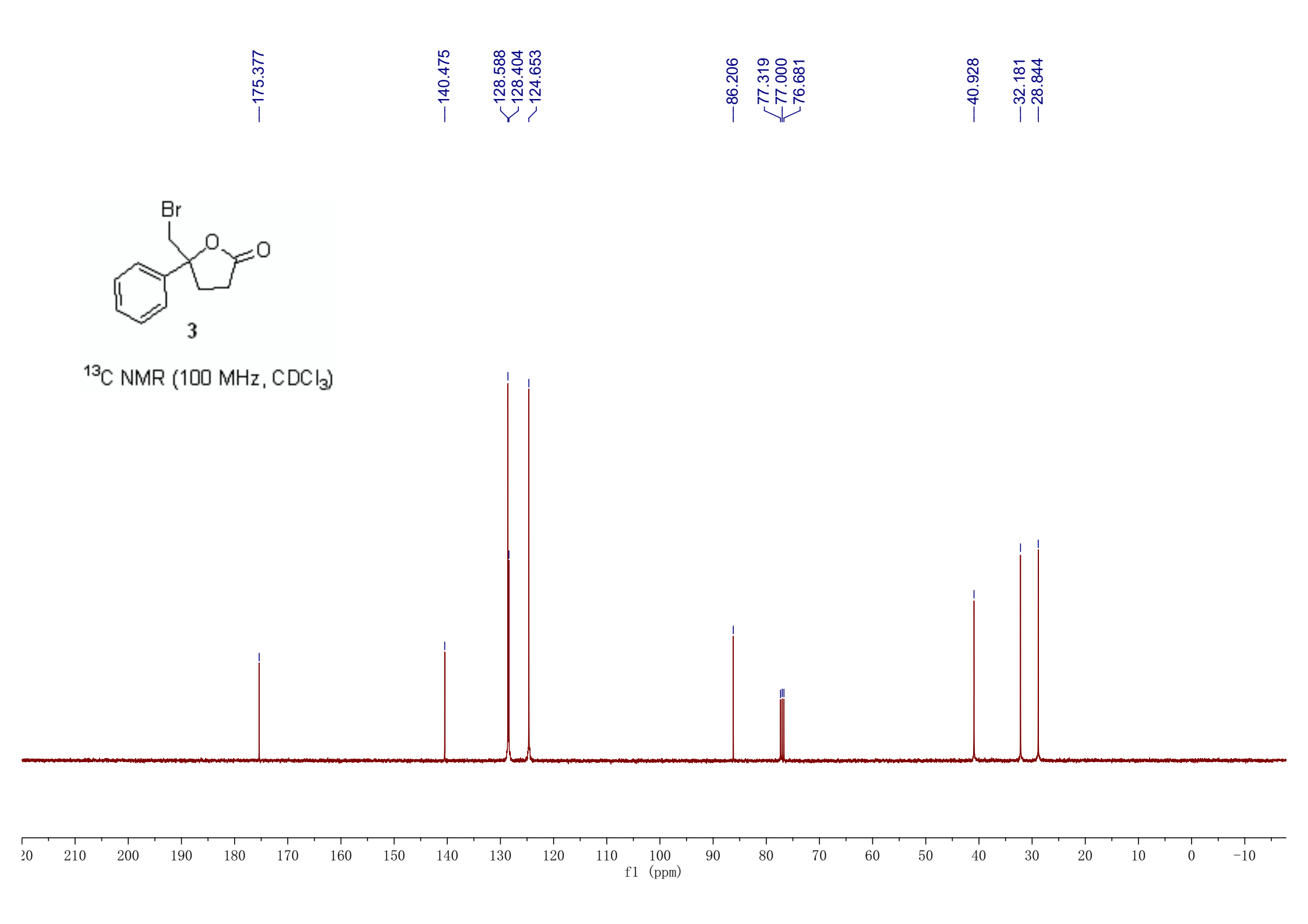
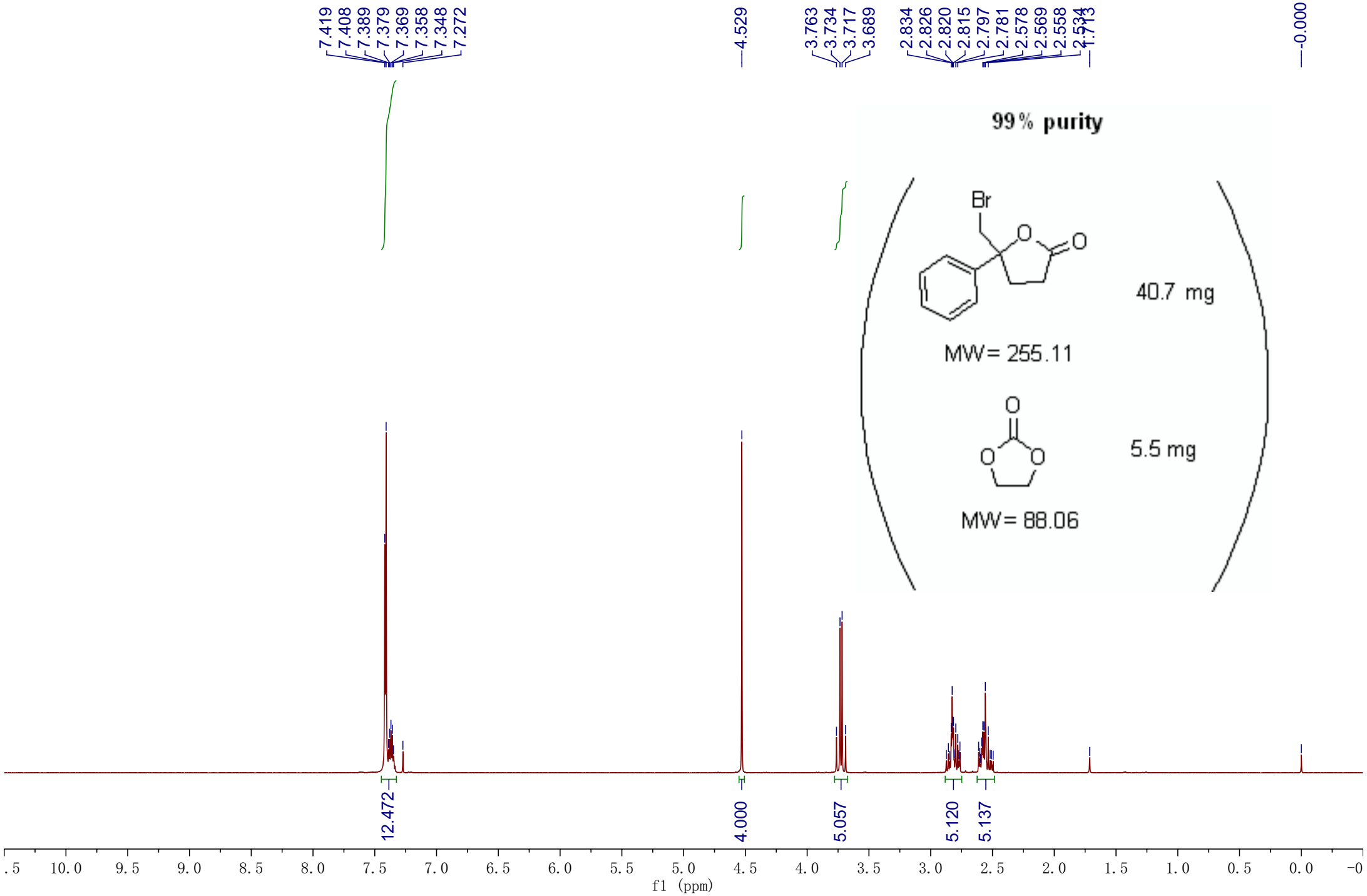
2.822
2.818
2.802
2.786
2.587
2.577
2.571
2.561
2.557
2.538
1.604
0.000
Br
O
O
3
1H NMR (400 MHz, CDCl3)
4.995
1.022
1.000
2.028
2.032
f1 (ppm)


175.377
140.475
128.588
128.404
124.653
86.206
77.319
77.000
76.681
40.928
32.181
28.844
Br
O
O
3
13C NMR (100 MHz, CDCl3)
f1 (ppm)


7.419
7.408
7.389
7.379
7.369
7.358
7.348
7.272
4.529
3.763
3.734
3.717
3.689
2.834
2.826
2.820
2.815
2.797
2.781
2.578
2.569
2.558
2.534
1.713
0.000
99% purity
Br
O
O
40.7 mg
MW= 255.11
O
O
O
5.5 mg
MW= 88.06
12.472
4.000
5.057
5.120
5.137
f1 (ppm)