A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

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.

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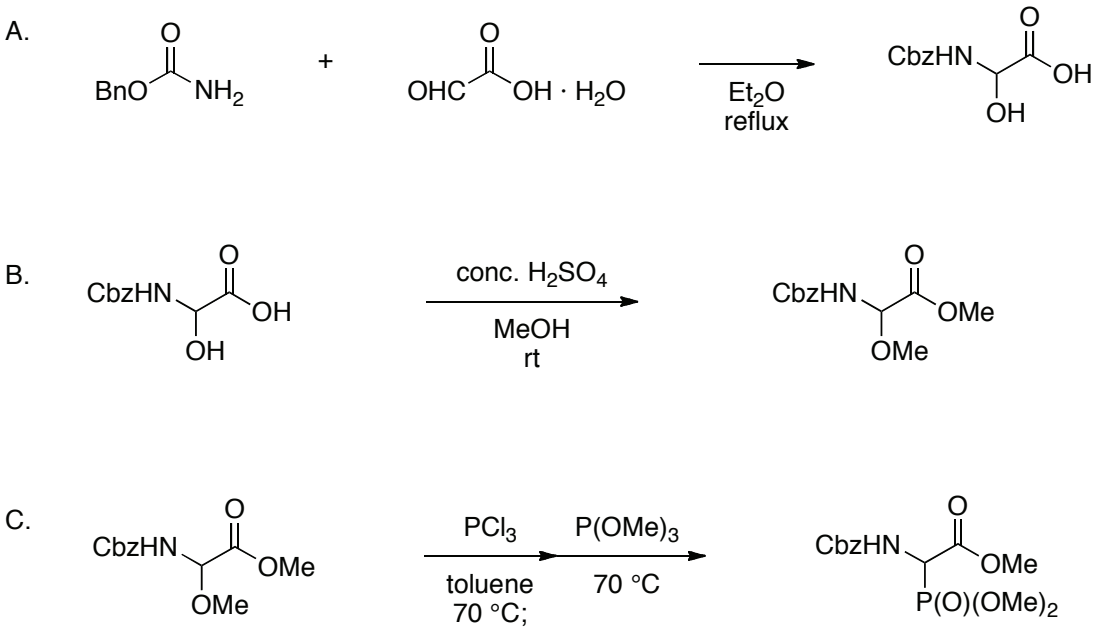
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

PREPARATION OF HORNER-WADSWORTH-EMMONS REAGENT: METHYL 2-BENZYLOXYCARBONYLAMINO-2-(DIMETHOXY- PHOSPHINYL)ACETATE



Submitted by Hiroki Azuma,[1] Kentaro Okano,[1] Tohru Fukuyama,[2] and Hidetoshi Tokuyama.[1]
Checked by Alistair Boyer and Mark Lautens.

1. Procedure

A. α-*Hydroxy-N-benzyloxycarbonylglycine.* A 500-mL three-necked round-bottomed flask equipped with an overhead mechanical stirrer (teflon paddle, 75 x 20 mm), a glass stopper, and a reflux condenser fitted with an inert gas inlet (Note 1) is charged with benzyl carbamate (30.23 g, 200 mmol, 1.0 equiv) (Note 2) and glyoxylic acid monohydrate (20.25 g, 220 mmol, 1.1 equiv) (Note 3). The flask is evacuated and backfilled with inert gas, the glass stopper is removed under a stream of inert gas and the flask is charged with anhydrous Et_2O (200 mL) (Note 4). The resulting translucent solution is heated under reflux for 12 h (Note 5) with stirring at a rate of 200 rpm. Over this time, the product precipitates to give a white suspension. The white precipitate is collected by filtration, washed with hexanes-Et_2O (1:1) (6 x 10 mL) (Note 6), and dried *in vacuo* to yield α-hydroxy-*N*-benzyloxycarbonylglycine as fine white crystals

Org. Synth. **2011**, *88*, 152-161
Published on the Web 1/14/2011

(32.80–35.37 g, 73–79%) (Note 7).

B. *Methyl α-methoxy-N-benzyloxycarbonylglycinate.* A 1-L one-necked, round-bottomed flask equipped with a Teflon-coated magnetic stir bar (octagonal, 38 mm) is charged with α-hydroxy-*N*-benzyloxycarbonylglycine (22.52 g, 100 mmol, 1.0 equiv) and anhydrous MeOH (200 mL) (Note 8). An inert gas inlet is attached (Note 1), and the flask is cooled to 1 °C (internal temperature). The gas inlet is temporarily removed and to the translucent solution is added conc. H_2SO_4 (5.0 mL) (Note 9) with a pipette over 5 min. The gas inlet is replaced, the cooling bath is then removed, and the mixture is stirred at room temperature for 15 h (Note 10). The reaction mixture is cooled to 1 °C (internal temperature) to which is added sat. aq. $NaHCO_3$ (120 mL) (Note 11) accompanied with vigorous gas evolution. The pH of the solution after addition is determined to be ca. 7. Methanol is removed under reduced pressure on a rotary evaporator (30 °C, 40 mmHg), and the residue is transferred into a 300-mL separatory funnel with the aid of water (50 mL) and EtOAc (200 mL). After partitioning, the aqueous layer is extracted with EtOAc (2 x 200 mL). The combined organic extracts are transferred into a 1-L separatory funnel and are washed with sat. aq. NaCl (1 x 200 mL), dried over $MgSO_4$ (20 g), and filtered (washing with 2 x 20 mL of EtOAc). The filtrate is concentrated under reduced pressure on a rotary evaporator (30 °C, 40 mmHg) and the residue is thoroughly dried *in vacuo* to give methyl α-methoxy-*N*-benzyloxycarbonylglycinate as a white solid (24.26–24.56 g, 96–97%) (Note 12).

C. *Methyl 2-benzyloxycarbonylamino-2-(dimethoxyphosphinyl)acetate.* A 500-mL flame-dried, two-necked, round-bottomed flask (Note 13) equipped with a Teflon-coated magnetic stir bar (octagonal, 38 mm), a rubber septum, and an inert gas inlet (Note 1) is charged with methyl α-methoxy-*N*-benzyloxycarbonylglycinate (20.27 g, 80.0 mmol, 1.0 equiv). The flask is evacuated and backfilled with inert gas. The flask is charged with anhydrous toluene (80 mL) (Note 14), and the resulting solution is heated at 70 °C. Phosphorus trichloride (6.98 mL, 11.0 g, 80.0 mmol, 1.0 equiv) (Note 15) is added to the solution over 5 min via a syringe. After stirring at 70 °C for 26 h (Note 16), trimethyl phosphite (9.44 mL, 9.93 g, 80.0 mmol, 1.0 equiv) (Note 17) is added to the mixture over 5 min via a syringe. The resulting mixture is stirred at 70 °C for an additional 2 h (Note 18). All volatile materials are removed under reduced pressure (40 then 10 mmHg, bath temperature: 70 °C) in a general distillation apparatus (a distillation head, a distillation adapter, and a receiver flask) to give a yellow

viscous oil. The oil is transferred into a 300-mL separatory funnel with the aid of EtOAc (100 mL). The solution is washed with sat. aq. $NaHCO_3$ (3 x 50 mL). The combined aqueous washings are extracted with EtOAc (1 x 50 mL). The combined organic extracts are washed with sat. aq. NaCl (1 x 50 mL), dried over Na_2SO_4 (10 g), filtered (washing with 10 mL EtOAc), and concentrated on a rotary evaporator under reduced pressure (30 °C, 40 mmHg) to give a pale yellow oil (27.26 g). Upon addition of hexanes (40 mL) to the oil with vigorous stirring at room temperature, a white solid precipitates which is collected by filtration, washed with ice-cold hexanes (5 x 20 mL), and dried *in vacuo* to afford methyl 2-benzyloxycarbonylamino-2-(dimethoxyphosphinyl)acetate as a fine white powder (22.59–23.08 g, 85–87%) (Note 19).

2. Notes

1. The use of either argon or nitrogen had no impact on the yield of the reaction.

2. Benzyl carbamate (99%) was purchased from Sigma-Aldrich Co. and used as received without further purification.

3. Glyoxylic acid monohydrate (98%) was purchased from Sigma-Aldrich Co. and used as received without further purification.

4. Et_2O (puriss., dried over molecular sieves, ≤0.005% H_2O) was purchased from Sigma-Aldrich Co. and used as received without further purification (submitters used >99.5%, water content: <0.05% from Kanto Chemical Company, Inc).

5. The submitters observed an incomplete reaction at 12 h and longer reaction time and/or higher reaction temperature did not improve the conversion.

6. Concentration of the combined washings gave 13.35 g of the desired product: α–hydroxy-*N*-benzyloxycarbonylglycine, with a trace of glyoxylic acid monohydrate.

7. The submitters report a yield of 58%. Data for product (without further purification): R_f = 0.60 (H_2O-MeOH-*n*-BuOH-EtOAc = 1:1:1:2; Merck silica gel 60F-254 aluminium-backed plates; visualized at 254-nm and with an ethanol solution of $Ce_2(SO_4)_3$ and phosphomolybdic acid followed by heating); mp = 198–200 °C (Et_2O); IR (film): 3333, 3039, 2946, 1732, 1694, 1542, 1536, 1454, 1340, 1266, 1246, 1085 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 5.05 (s, 2 H), 5.22 (d, J = 8.8 Hz, 1 H), 7.27–7.41

(m, 5 H), 8.13 (d, J = 8.8 Hz, 1 H); The submitters report an additional ^{1}H NMR resonance at 6.26 (br s, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 66.2, 73.9, 128.5 (2 × C), 128.5, 129.0 (2 × C), 137.5, 156.2, 171.7; HRMS. [M + H]+ calcd. for $C_{10}H_{12}NO_5$: 226.0715. Found: 226.0716; Anal. calcd. for $C_{10}H_{11}NO_5$: C, 53.33; H, 4.92; N, 6.22. Found: C, 53.20; H, 5.27; N, 6.14.

8. Methanol (puriss., absolute, dried over molecular sieves, ≤0.01% H_2O) was purchased from Sigma-Aldrich Co. and used as received without further purification (submitters used 99.8%, water content: <50 ppm from Wako Pure Chemical Industries, Ltd.).

9. Conc. H_2SO_4 (95.0–98.0%) was purchased from Caledon Laboratories Ltd. and used as received without further purification (submitters used 95.0% from Wako Pure Chemical Industries, Ltd.).

10. The reaction typically requires 15 h to consume all the α-hydroxy-*N*-benzyloxycarbonylglycine and is monitored by TLC analysis. The R_f values of the starting material and the product are baseline and 0.71, respectively (CH_2Cl_2-MeOH = 19:1; Merck silica gel 60F-254 aluminium-backed plates; visualized at 254-nm and with an ethanol solution of $Ce_2(SO_4)_3$ and phosphomolybdic acid followed by heating).

11. The submitters sometimes observed the solidification of the reaction mixture upon cooling to 0 °C. In this situation, the reaction mixture is warmed to room temperature and ice-cold sat. aq. $NaHCO_3$ (0 °C) is added at room temperature.

12. Data for product (without further purification): R_f = 0.40 (hexanes-EtOAc = 2:1; Merck silica gel 60F-254 aluminium-backed plates; visualized at 254-nm and with an ethanol solution of $Ce_2(SO_4)_3$ and phosphomolybdic acid followed by heating); mp = 70–72 °C (EtOAc); IR (film): 3310, 3035, 2947, 1752, 1716, 1686, 1542, 1455, 1439, 1362, 1259, 1221, 1197, 1103 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.47 (s, 3 H), 3.81 (s, 3 H), 5.14 (d, J = 12.3 Hz, 1 H), 5.17 (d, J = 12.3 Hz, 1 H), 5.36 (d, J = 9.4 Hz, 1 H), 5.84 (br s, 1 H), 7.31–7.39 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 52.8, 56.2, 67.4, 80.6, 128.1, 128.3, 128.5, 135.7, 155.6, 167.9; HRMS. $[M + Na]^+$ calcd. for $C_{12}H_{15}NNaO_5$: 276.0848. Found: 276.0846; Anal. calcd. for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.83; H, 6.21; N, 5.56.

13. The use of an oversize flask allows for the removal of the reagents and solvent at the end of the reaction without the loss of product through bumping.

14. Toluene (dried max. 0.001% H_2O, puriss.) was purchased from Sigma-Aldrich Co. and used as received without further purification (submitters used 99.5%, water content: <30 ppm from Wako Pure Chemical Industries, Ltd.).

15. Phosphorus trichloride (ReagentPlus, 99%) was purchased from Sigma-Aldrich Co. and used as received without further purification (submitters used 99.0% from Wako Pure Chemical Industries, Ltd.).

16. The reaction typically requires 22–26 h to consume all the methyl α-methoxy-*N*-benzyloxycarbonylglycinate and is monitored by TLC analysis. The R_f values of the starting material and the intermediate are 0.71 and 0.50, respectively (CH_2Cl_2-MeOH = 19:1; Merck silica gel 60F-254 aluminium-backed plates; visualized at 254-nm and with an ethanol solution of $Ce_2(SO_4)_3$ and phosphomolybdic acid followed by heating). The intermediate of the reaction is *methyl N-benzyloxycarbonyl-α-chloroglycinate*. A small amount of the reaction mixture was concentrated *in vacuo* and analyzed by ^{1}H spectroscopy: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.86 (s, 3 H), 5.10–5.24 (m, 2 H), 6.18 (br s, 1 H), 7.32–7.40 (m, 5 H).[3]

17. Trimethyl phosphite (>99%) was purchased from Sigma-Aldrich Co. and used as received without further purification.

18. The reaction typically requires 2 h to consume all the intermediate and is monitored by TLC analysis. The R_f values of the intermediate and the product are 0.50 and 0.45, respectively (CH_2Cl_2-MeOH = 19:1; Merck silica gel 60F-254 aluminium-backed plates; visualized at 254-nm and with an ethanol solution of $Ce_2(SO_4)_3$ and phosphomolybdic acid followed by heating).

19. Data for product (without further purification): R_f = 0.45 (EtOAc; Merck silica gel 60F-254 aluminium-backed plates; visualized at 254-nm and with an ethanol solution of $Ce_2(SO_4)_3$ and phosphomolybdic acid followed by heating); mp = 77–78 °C (hexanes); IR (film): 3229, 3034, 2963, 1749, 1716, 1535, 1427, 1332, 1277, 1240, 1213, 1030 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.79 (d, $^3J_{H\text{-}P}$ = 11.0 Hz, 3 H), 3.82 (d, $^3J_{H\text{-}P}$ = 11.2 Hz, 3 H), 3.84 (s, 3 H), 4.93 (dd, $^2J_{H\text{-}P}$ = 22.3, J = 9.2 Hz, 1 H), 5.16 (d, J = 12.0 Hz, 1 H), 5.16 (d, J = 12.0 Hz, 1 H), 5.58 (d, J = 9.6 Hz, 1 H), 7.31–7.39 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 52.0 (d, $^1J_{C\text{-}P}$ = 148 Hz), 53.3, 53.9 (d, $^2J_{C\text{-}P}$ = 6.8 Hz), 54.1 (d, $^2J_{C\text{-}P}$ = 6.5 Hz), 67.5, 128.1, 128.3, 128.5, 135.8, 155.5 (d, $^3J_{C\text{-}P}$ = 7.2 Hz), 167.1; HRMS. [M + H] calcd. for $C_{13}H_{19}NO_7P$: 332.0899. Found: 332.0905; Anal. calcd. for $C_{13}H_{18}NO_7P$: C, 47.14; H, 5.48; N, 4.23. Found: C, 47.51; H, 5.74; N, 4.34.

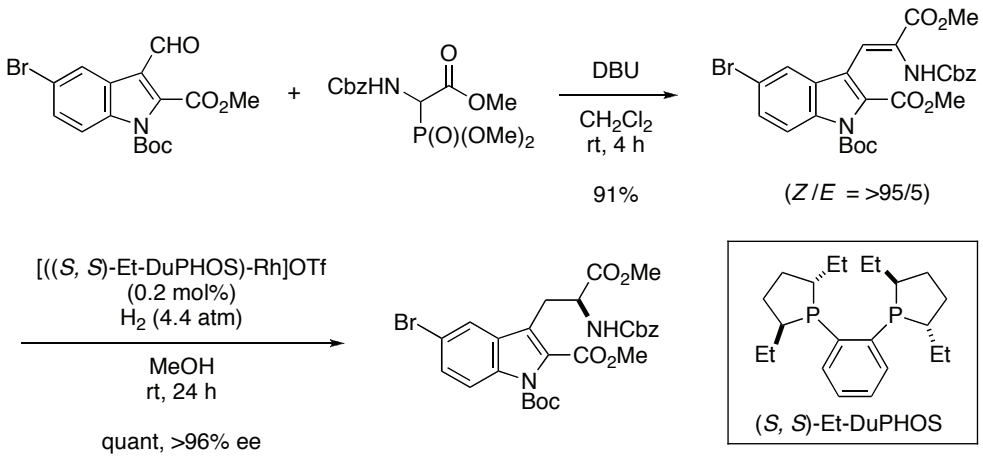
Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academic Press; Washington, DC, 1995.

3. Discussion

The Horner-Wadsworth-Emmons (HWE) olefination[4] has the following advantages over the Wittig reaction; 1) the phosphonate carbanions are more nucleophilic than phosphorus ylides, and even unreactive hindered ketones react readily in HWE olefinations; 2) water-soluble phosphonate byproducts facilitate the purification process; and 3) the product olefin geometry can be switched by the Corey-Kwiatkowski modification,[4a,5] the Still-Gennari modification,[4b,6] or the Ando modification.[7]

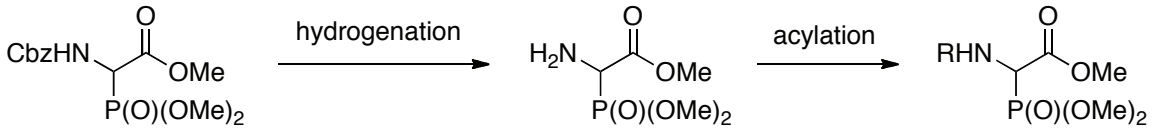
The present procedure describes a convenient and scalable preparation of the HWE reagent[8] that gives the (*Z*)-dehydroamino acid derivative, which allows facile access to Cbz-protected α-amino acid methyl esters via Rh-catalyzed enantioselective hydrogenation[9] (Scheme 1).

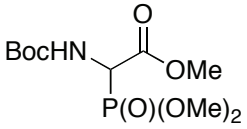
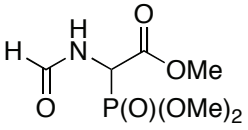
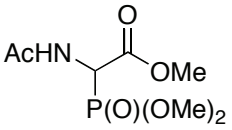


Scheme 1. Preparation of tryptophan derivative

The Cbz group in the HWE reagent is converted to a variety of protecting groups via hydrogenolysis followed by acylation[8b] (Table 1).

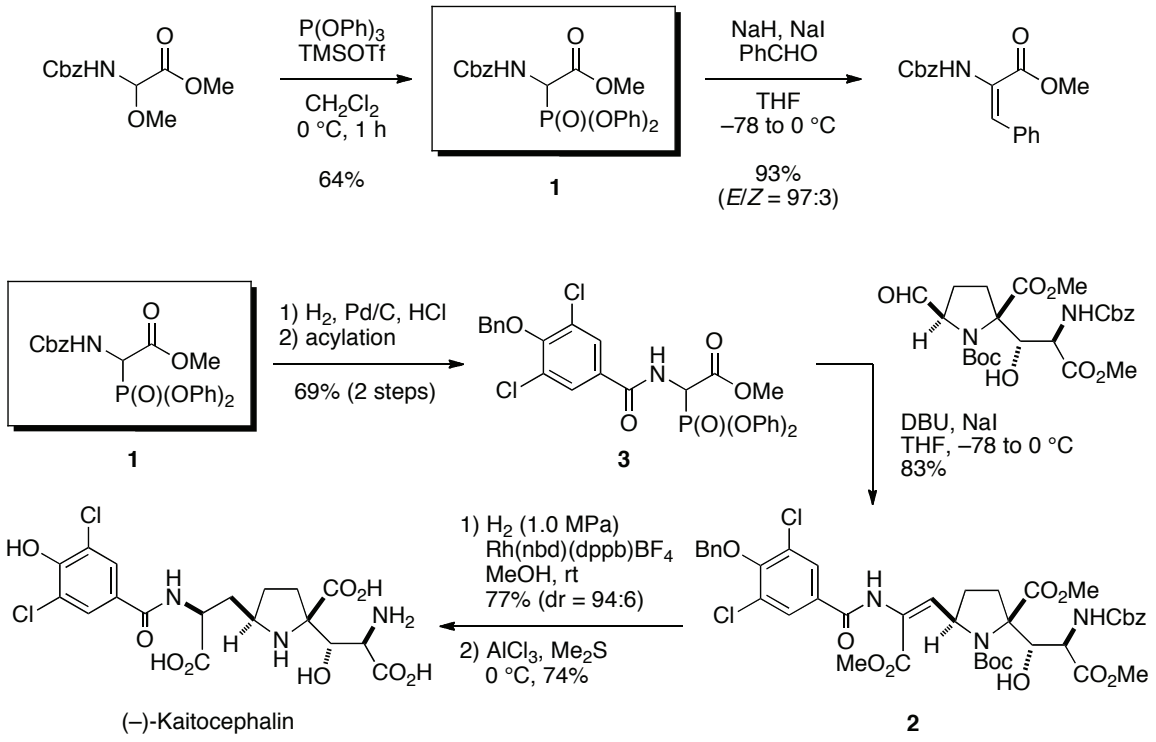
Table 1. Preparation of a series of related HWE reagents



hydrogenation	acylation	product
H_2 (3 atm), Pd/C MeOH, rt, 87%	Boc_2O CH_2Cl_2, rt, 80%	
H_2 (3 atm), Pd/C MeOH, rt, 87%	HCO_2H, DCC CH_2Cl_2, rt, 81%	
H_2 (3 atm), Pd/C Ac_2O, MeOH, rt, 91%[a]	–	

[a] Debenzylation and acylation were carried out in one pot without isolation of the primary amine.

Recently, Ohfune and Shinada reported modified synthesis of a new Ando-type HWE reagent **1** providing an (*E*)-encarbamate.[10] The reagent was prepared from a hemiaminal, the product of step B in this procedure, by treatment with $P(OPh)_3$ and TMSOTf. Treatment of benzaldehyde with phosphonate **1** provided the corresponding (*E*)-dehydrophenylalanine derivative with excellent stereoselectivity (97:3). Their (–)-kaitocephalin synthesis features a substrate-controlled diastereoselective hydrogenation of (*E*)-enamide **2** prepared from the corresponding phosphonate **3** readily prepared from **1** (Scheme 2).



Scheme 2. Total synthesis of (–)-kaitocephalin featuring (*E*)-selective olefination and substrate-controlled diastereoselective hydrogenation

1. Graduate School of Pharmaceutical Sciences, Tohoku University, Aramaki, Aoba-ku, Sendai 980-8578, Japan.

This work was supported by The Ministry of Education, Culture, Sports, Science and Technology, Japan.

2. Graduate School of Pharmaceutical Sciences, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan.

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3101. (b) Crépy, K. V. L.; Imamoto, T. *Adv. Synth. Catal*. **2003**, *345*, 79. For a review on enantioselective hydrogenation, see: (c) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.
10. Hamada, M.; Shinada, T.; Ohfune, Y. *Org. Lett.* **2009**, *11*, 4664.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

Benzyl carbamate: Carbamic acid, Phenylmethyl ester; (621-84-1)
Glyoxylic acid monohydrate: Acetic acid, 2,2-dihydroxy-; (563-96-2)
Sulfuric acid: Sulfuric acid; (7664-93-9)
Phosphorous trichloride: Phosphorous trichloride; (7719-12-2)
Trimethylphosphite: Phosphorous acid, trimethyl ester; (121-45-9)

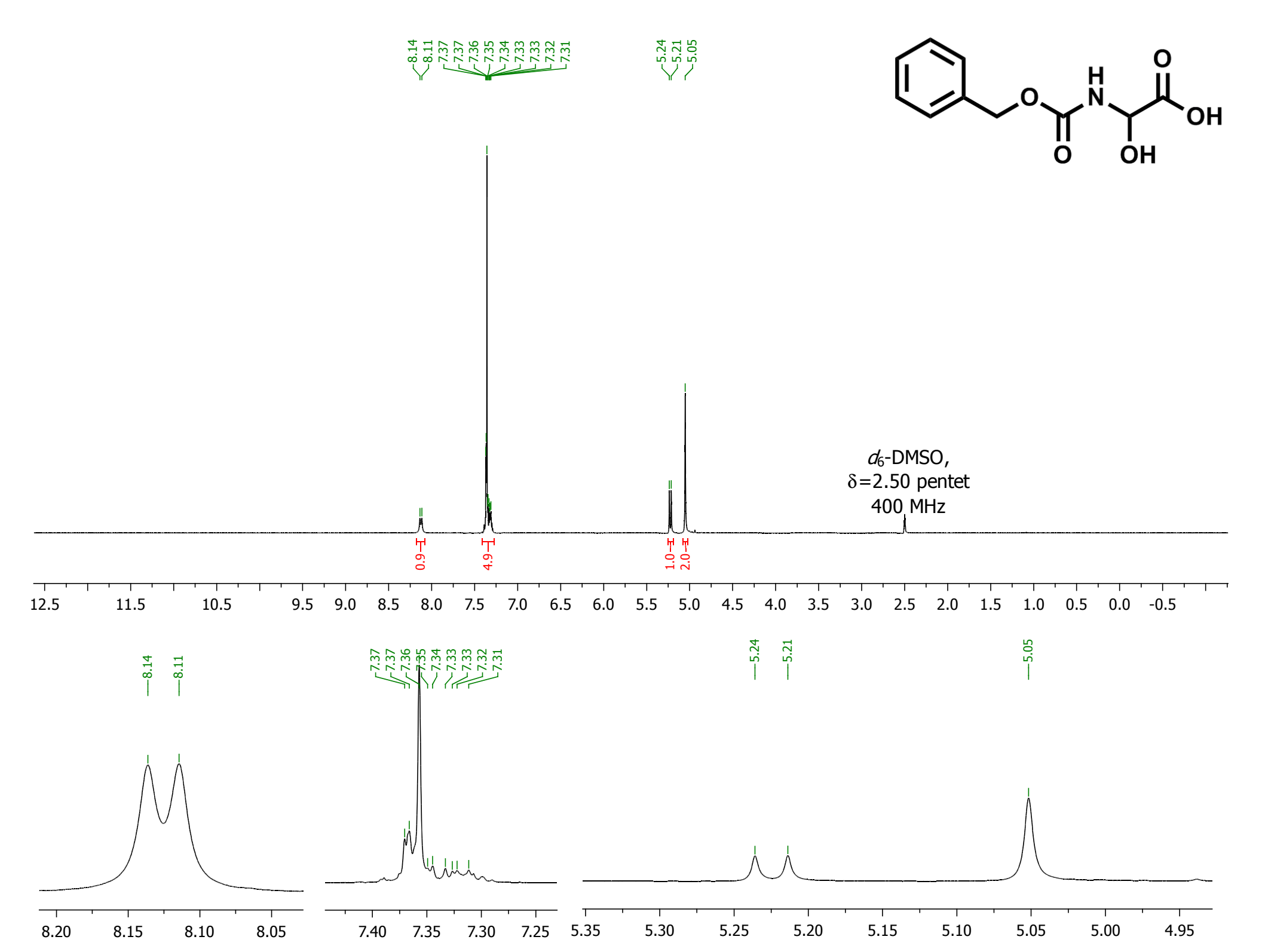
Hidetoshi Tokuyama was born in Yokohama in 1967. He received his Ph.D. in 1994 from Tokyo Institute of Technology under the direction of Professor Ei-ichi Nakamura. He spent one year (1994-1995) at the University of Pennsylvania as a postdoctoral fellow with Professor Amos B. Smith, III. He joined the group of Professor Tohru Fukuyama at the University of Tokyo in 1995 and was appointed Associate Professor in 2003. In 2006, he moved to Tohoku University, where he is currently Professor of Pharmaceutical Sciences. His research interest is on the development of synthetic methodologies and total synthesis of natural products.

Hiroki Azuma was born in Fukushima in 1987. He received his B.S. in 2009 from the Faculty of Pharmaceutical Sciences, Tohoku University, where he carried out undergraduate research in the laboratories of Professor Hideo Takeuchi. In the same year, he then began his doctoral studies at the Graduate School of Pharmaceutical Sciences, Tohoku University under the supervision of Professor Hidetoshi Tokuyama. His research focuses on the total synthesis of azaspirocyclic natural products.

Kentaro Okano was born in Tokyo in 1979. He received his B.S. in 2003 from Kyoto University, where he carried out undergraduate research under the supervision of Professor Tamejiro Hiyama. He then moved to the laboratories of Professor Tohru Fukuyama at the University of Tokyo and started his Ph.D. research on synthetic studies toward antitumor antibiotic yatakemycin by means of the copper-mediated aryl amination strategy. In 2007, he started his academic carrier at Tohoku University, where he is currently an assistant professor in Professor Hidetoshi Tokuyama's group. His current research interest is natural product synthesis based on the development of new synthetic methodologies.

Tohru Fukuyama received his Ph.D. in 1977 from Harvard University with Yoshito Kishi. He remained in Kishi's group as a postdoctoral fellow until 1978 when he was appointed as Assistant Professor of Chemistry at Rice University. After seventeen years on the faculty at Rice, he returned to his home country and joined the faculty of the University of Tokyo in 1995, where he is currently Professor of Pharmaceutical Sciences. He has primarily been involved in the total synthesis of complex natural products of biological and medicinal importance. He often chooses target molecules that require development of new concepts in synthetic design and/or new methodology for their total synthesis.

Alistair Boyer was born in 1982 in Warrington, UK. He obtained his M.Sci. at the University of Cambridge in 2004, completing his masters project with Prof. Andrew B. Holmes. He stayed at Cambridge to perform his Ph.D. studies under the supervision of Prof. Steven V. Ley working on the synthesis of azadirachtin. In 2009, he moved to Toronto, Canada to become a postdoctoral research associate in the group of Prof. Mark Lautens, investigating novel rhodium-catalyzed reactions.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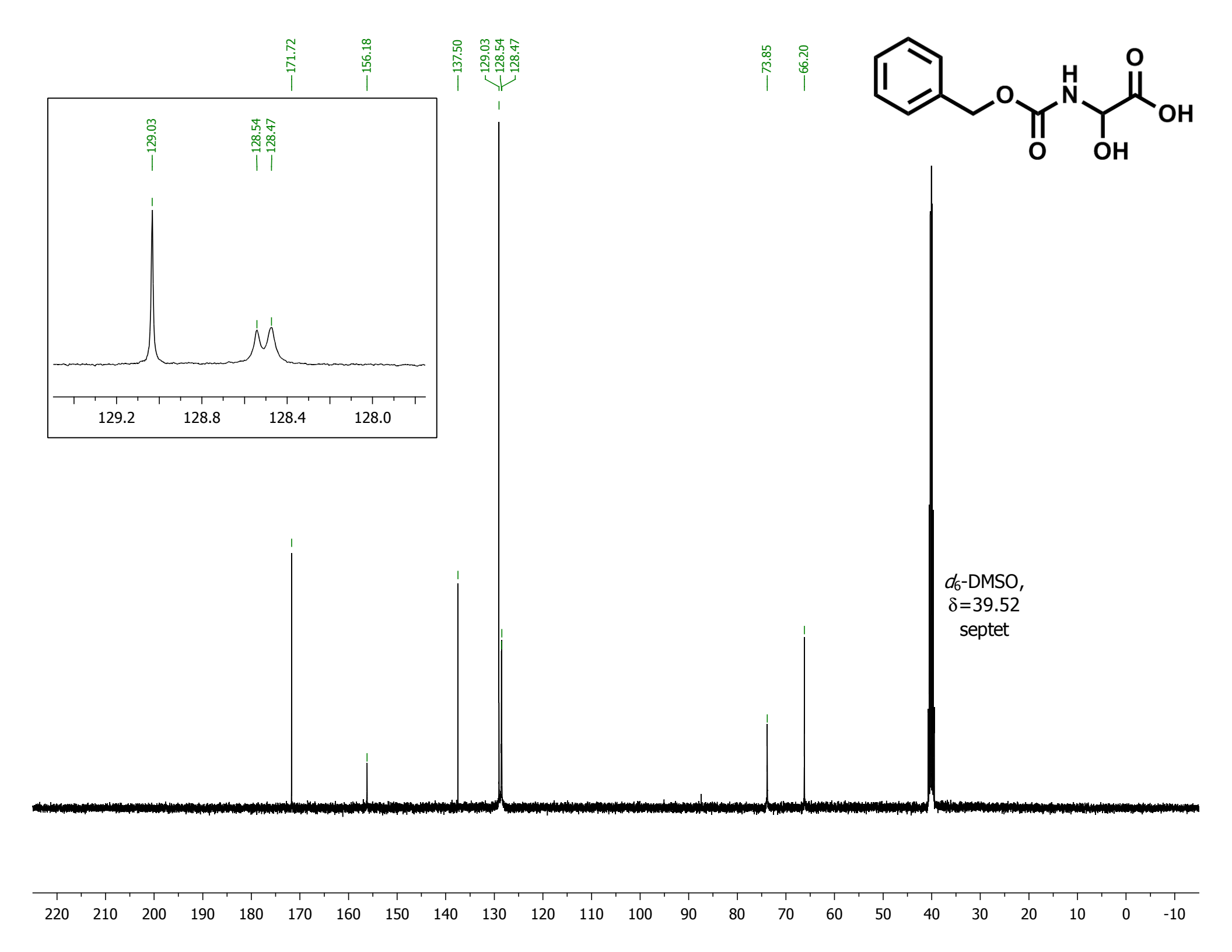
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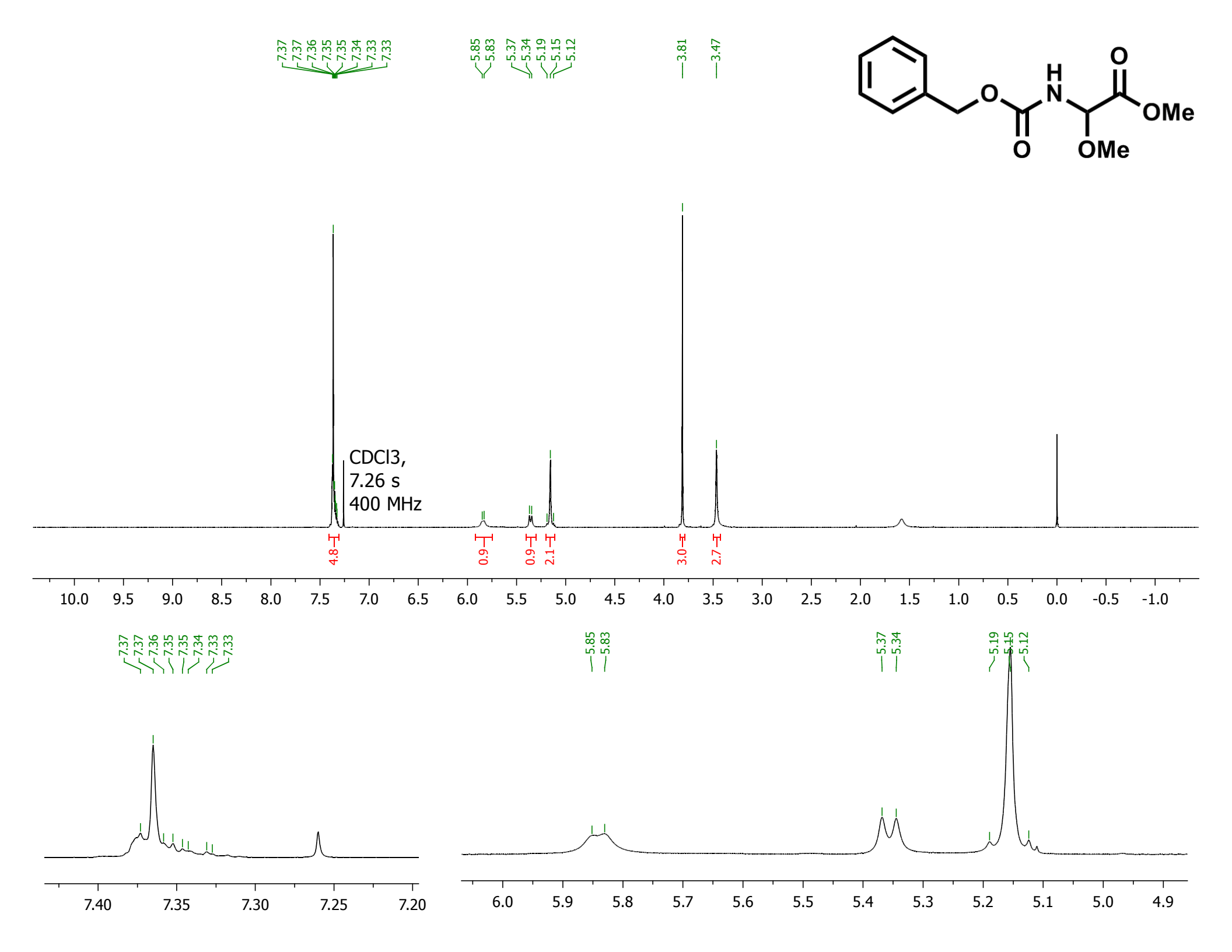
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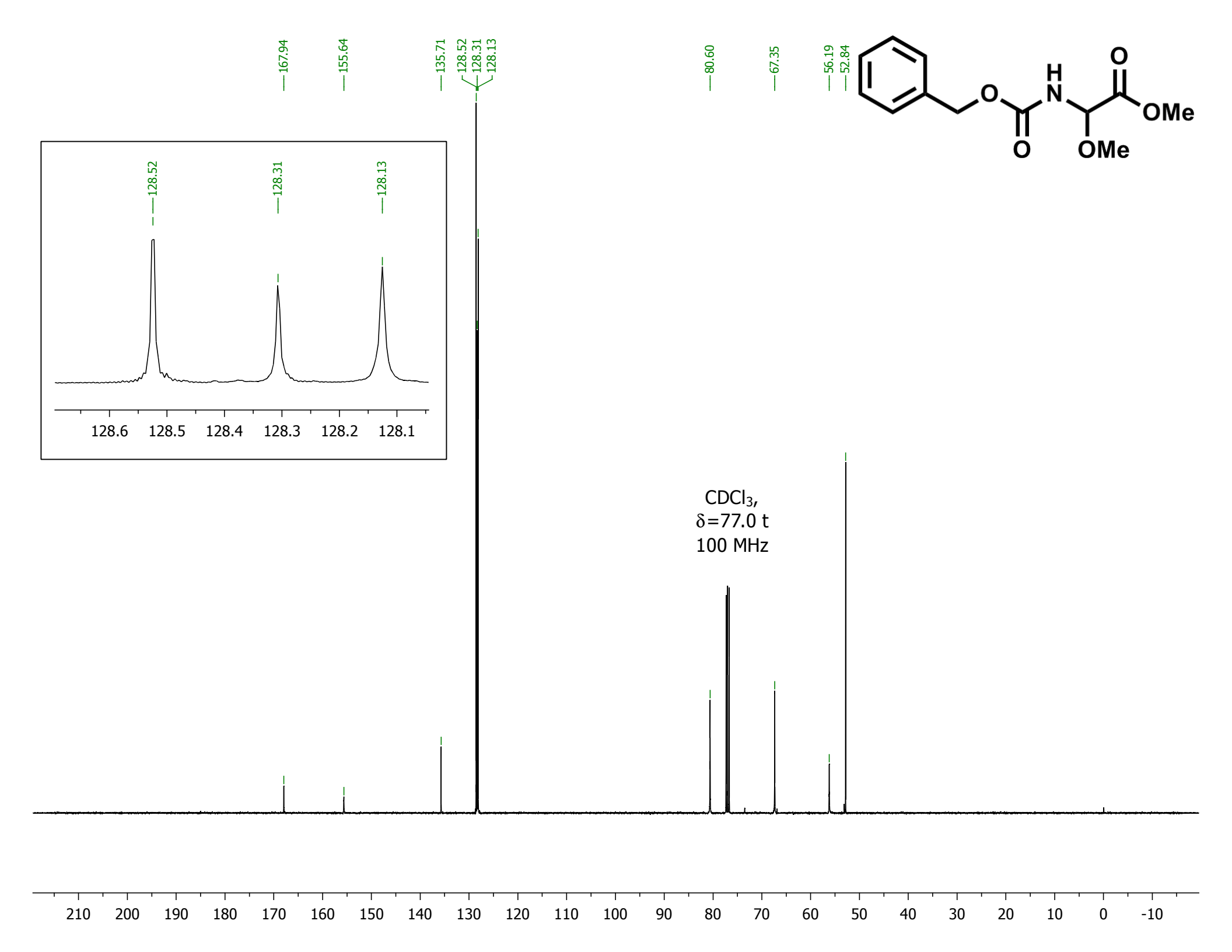
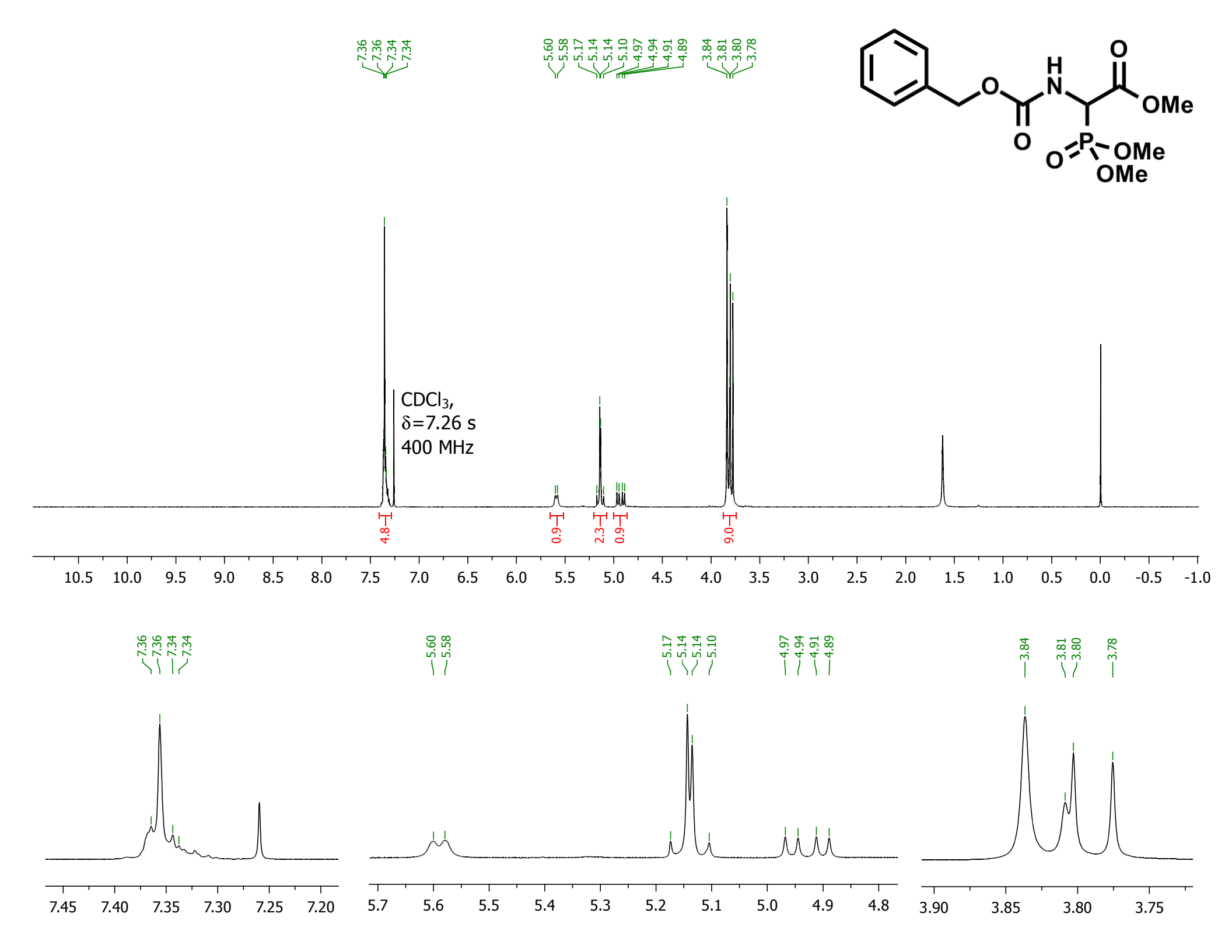
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
7.40
7.35
7.30
7.25
7.20
6.0
5.9
5.8
5.7
5.6
5.5
5.4
5.3
5.2
5.1
5.0
4.9


167.94
155.64
135.71
128.52
128.31
128.13
80.60
67.35
56.19
52.84
O
H
N
O
OMe
O
OMe
128.52
128.31
128.13
128.6
128.5
128.4
128.3
128.2
128.1
CDCl3,
δ=77.0 t
100 MHz
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


7.36
7.36
7.34
7.34
5.60
5.58
5.17
5.14
5.14
5.10
4.97
4.94
4.91
4.89
3.84
3.81
3.80
3.78
O
H
N
O
OMe
O
O
P
OMe
OMe
CDCl3,
δ=7.26 s
400 MHz
4.8
0.9
2.3
0.9
9.0
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
7.45 7.40 7.35 7.30 7.25 7.20
5.7 5.6 5.5 5.4 5.3 5.2 5.1 5.0 4.9 4.8
3.90 3.85 3.80 3.75