



(1) (10.0 g, 45.3 mmol, 1.0 equiv) and sulfur (1.45 g, 45.3 mmol, 1.0 equiv). The flask is charged with dry THF (75 mL) via a syringe and flushed with argon (Notes 2, 3, and 4). The reaction mixture is heated in an oil bath at 60 °C (bath temperature) and stirred for 23 h under an argon atmosphere (Figure 1). The reaction mixture is a pale yellow homogeneous solution. The reaction progress is monitored by TLC analysis (Figure 2) (Note 5) and  $^{31}\text{P}$  NMR (Note 6). After consumption of **1**, the straight glass tube is replaced with an ammonia-gas line inlet, and the reflux condenser is replaced with a glass stopper. The small glass stopper is replaced with a pressure-resistant rubber hose attached to a 3-way glass stopcock to discharge the excess of ammonia gas into a water bath. The mixture is cooled to 0 °C in an ice bath, and the ammonia gas, set to a constant gas-feed at a pressure of approx. 0.015 MPa is bubbled into the reaction mixture through a glass tube at 0 °C for 0.5 h (Figure 3). Then the ice-bath and ammonia-gas line inlet are removed and the reaction mixture is stirred at room temperature for 2 h under air with the precipitated ammonium chloride (Figure 4). The reaction progress is monitored by TLC analysis (Figure 5) (Note 7). The solvent is removed using a rotary evaporator (30 °C, 64 mmHg). The resulting crude product containing **2** and ammonium chloride is placed on a sintered glass filter, which is washed with chloroform (3 x 20 mL) (Note 8) under reduced pressure into a 300-mL one-necked, round-bottomed flask (Figure 6). The filtrate is concentrated using a rotary evaporator (30 °C, 64 mmHg), and the flask is fitted with a 2.5-cm Teflon-coated oval magnetic stirring bar. The crude solid product is dissolved in chloroform (40 mL), and heated in an oil bath at 70 °C (bath temperature). *n*-Hexane (70 mL) is slowly added to the hot chloroform solution (Note 9). The solution is allowed to cool to room temperature and left standing for 4 h, and then cooled in a refrigerator (4 °C) for 24 h. The resulting crystals are collected by filtration with a Hirsch funnel (Figure 7) and washed with a mixed solvent of *n*-hexane and  $\text{CHCl}_3$  (5/1, 3 x 3 mL). The collected crystals are dried in vacuo (60 °C, 0.1 mmHg) for 5 h to provide 7.84 g of phosphinothioic amide **2** (77% yield) as colorless crystals (Figure 8) (Notes 10 and 11). The purity of phosphinothioic amide **2** is assessed at >98 wt% by quantitative  $^1\text{H}$  NMR in  $\text{CDCl}_3$  using dimethyl fumarate as a standard (Note 12).



Figure 1. Reaction setup Step A

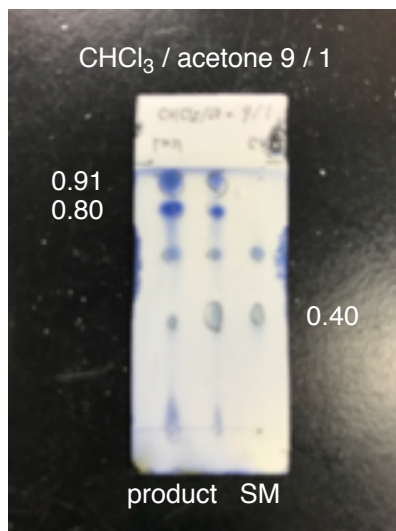


Figure 2. TLC image



Figure 3. Addition of ammonia



Figure 4. Precipitated ammonium chloride

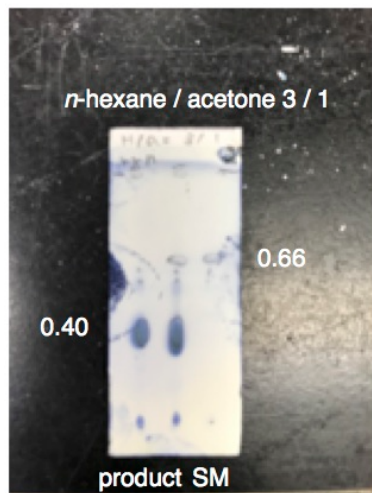


Figure 5. TLC image 2

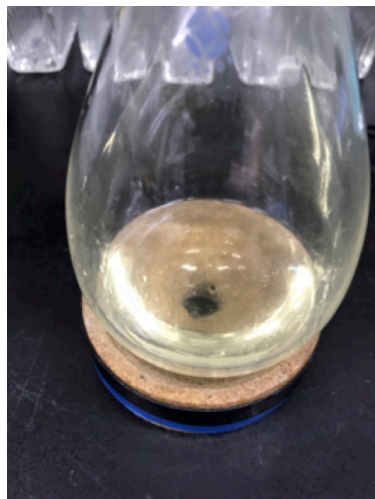


Figure 6. After filtration

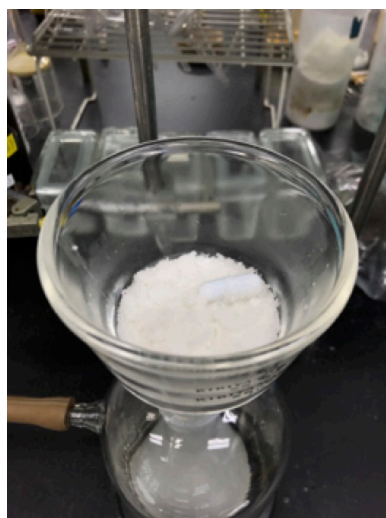


Figure 7. Filtration

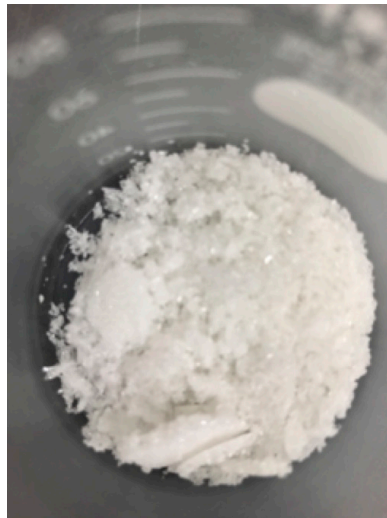


Figure 8. Phosphinothioic amide 2

B. *P,P*-Diphenyl-*N*-(1-phenylethylidene)phosphinothioic amide (**4**).<sup>4</sup> A 50 mL one-necked round-bottomed flask equipped with a 2.5-cm Teflon-coated oval magnetic stirring bar is charged with phosphinothioic amide **2** (7.00 g, 30 mmol, 1.0 equiv) and (1,1-dimethoxyethyl)benzene (**3**) (4.99 g, 30 mmol, 1.0 equiv) (Note 13). The flask is equipped with a reflux condenser (15 cm)



without tap water flow (air-cooling), and the mixture is heated to 130 °C (oil bath temperature) under air (Figures 9 and 10). After stirring for 1 h, another portion of acetal **3** (4.99 g, 30 mmol, 1.0 equiv) (Note 13) is added dropwise at that temperature. After further stirring for 1 h, the mixture is cooled to room temperature (Figure 11), the reaction progress is checked by TLC analysis (Note 14). The mixture is transferred to a 300 mL one-necked round-bottomed flask using 15 mL EtOAc (Note 15) and 20 g neutral silica gel (Note 16) is added. The mixture is concentrated first by a rotary evaporator (30 °C, 64 mmHg) and then under high vacuum (rt, 0.2 mmHg) for 40 min (Figure 12). The crude mixture is applied on top of the silica gel column (a glass column charged with 7 x 10 cm, 210 g of neutral silica gel) (Note 16), and eluted with 550 mL of a mixed solvent of EtOAc and *n*-hexane (1/10) (Notes 9 and 15), followed by 500 mL of a mixed solvent of EtOAc and *n*-hexane (1/5). At this point, collection of the eluent is begun (100-mL fractions each), and collection is continued while using 1.9 L of a mixed solvent of EtOAc/*n*-hexane (1/5). The product is contained in fractions 2–17, which are concentrated using a rotary evaporator (65 mmHg, 30 °C). The residue is dissolved in 50 mL hot EtOAc (50 °C), and 150 mL *n*-hexane is added (Notes 9 and 15). The solution is allowed to cool to room temperature, and further cooled in a refrigerator (4 °C) for 24 h. The resulting crystals are collected by suction filtration on a Hirsch funnel (Figure 13), washed with 100 mL *n*-hexane, and transferred to a 50-mL vial and dried in vacuo (rt, 0.2 mmHg) for 4 h to provide 2.64 g of ketimine **4** (26% yield) as colorless crystals (Figure 14) (Notes 17 and 18). The purity of ketimine **4** is assessed at >98 wt% by quantitative <sup>1</sup>H NMR in CDCl<sub>3</sub> using dimethyl fumarate as a standard (Note 12).



Figure 9. Reaction setup Step B  
(Before heating)



Figure 10. Reaction setup Step B  
(while heating at 130 °C)



Figure 11. After cooling

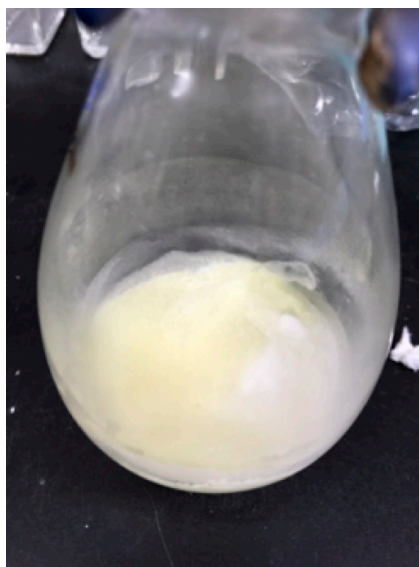


Figure 12. After vacuum

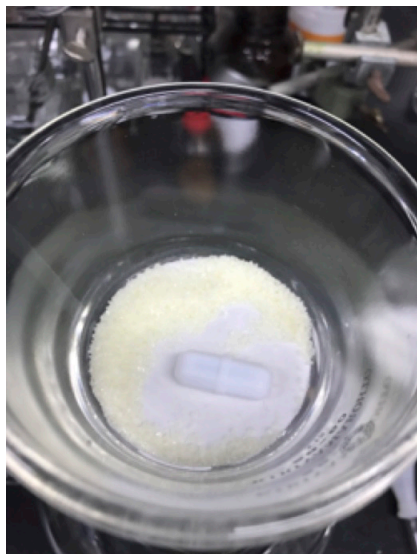


Figure 13. Filtration

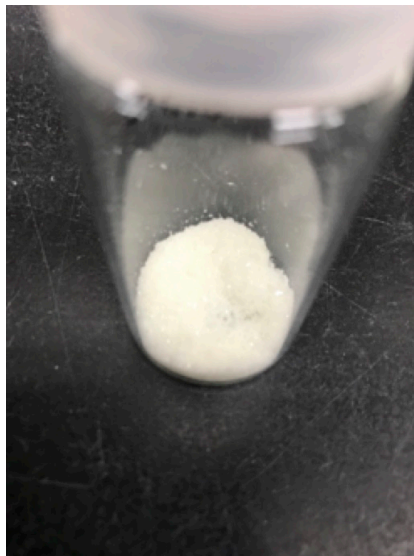


Figure 14. Purified product 4

C. (*R*)-Diethyl 1-((diphenylphosphorothioyl)amino)-1-phenylethylphosphonate (**6**).<sup>5</sup> An oven-dried 20 mL two-necked round-bottomed flask equipped with a 1.5-cm Teflon-coated oval magnetic stirring bar, 3-way glass stopcock with an argon balloon, and a rubber septum is charged with 1,2-bis((2*R*,5*R*)-2,5-diphenylphospholano)ethane ((*R,R*)-Ph-BPE, 122 mg, 0.24 mmol, 0.02 equiv) (Note 19) and tetrakis(acetonitrile)copper(I) hexafluorophosphate [ $\text{Cu}(\text{CH}_3\text{CN})_4$ ]PF<sub>6</sub>, 89.5 mg, 0.24 mmol, 0.02 equiv) (Note 20). The flask is evacuated and backfilled with an argon (3 times). Dry THF (2 mL) (Note 4) is added under an argon atmosphere (Note 21), and the mixture is stirred at room temperature for 1.5 h to give a solution of the chiral Cu(I) complex, which is stored at room temperature and used within 1 h.

An oven-dried 100-mL two-necked round-bottomed flask equipped with a 2.5-cm Teflon-coated oval magnetic stirring bar, a 3-way glass stopcock with an argon balloon, and a rubber septum is charged with *P,P*-diphenyl-*N*-(1-phenylethylidene)phosphinothioic amide (**4**) (4.03 g, 12 mmol, 1.0 equiv). The flask is evacuated (rt, 5 min) and backfilled with argon gas (3 times) (Figure 15). Dry THF (44 mL) (Note 4) is added via a syringe under an argon atmosphere. The mixture is stirred for 2 min to give a clear solution (Figure 16). The catalyst solution (2.0 mL) containing Cu (I)

complex (0.24 mmol, 0.02 equiv), which is prepared in the procedure described above, is transferred (using 4.0 mL dry THF for rinsing) via a syringe at room temperature under argon atmosphere (Figure 17). After stirring for 5 min, triethylamine (836  $\mu$ L, 6 mmol, 0.5 equiv) (Note 22) is added via a syringe under an argon atmosphere. Diethyl phosphite (**5**) (2.94 mL, 24 mmol, 2.0 equiv) (Note 23) is added via a syringe under an argon atmosphere (Figure 18). The flask is evacuated and backfilled with argon gas (3 times), and attached to nitrogen-gas line inlet (Figure 19). After stirring at room temperature for 72 h under continuous nitrogen flow (Figure 20), the reaction progress is checked by TLC analysis (Note 24). To the mixture is added neutral silica gel (10 g) (Note 16) and the volatiles are removed under reduced pressure (80 mmHg, 40  $^{\circ}$ C). The resulting residue is applied to the top of silica gel column (a glass column charged with 7  $\times$  10 cm, 210 g of neutral silica gel), and eluted with 600 mL of a mixed solvent of EtOAc/*n*-hexane (1/2) (Notes 9 and 15), followed by 1.0 L of a mixed solvent of EtOAc/*n*-hexane (2/3). At this point, collection of eluents (100 mL fractions) is begun and continued with 2.5 L of a mixed solvent of EtOAc/*n*-hexane (2/3). The desired product is contained in fractions 6–26, which are concentrated using a rotary evaporator (80 mmHg, 40  $^{\circ}$ C). The resulting residue is transferred to a 50-mL round-bottomed flask using EtOAc (30 mL) (Note 15), and dried in vacuo (0.1 mmHg at 90  $^{\circ}$ C for 12 h) to provide 5.02 g of phosphonate **6** (88% yield) as a brown viscous oil (Figures 21 and 22). The purity of phosphonate **6** is assessed at >98 wt% by quantitative  $^1\text{H}$  NMR in  $\text{CDCl}_3$  using dimethyl fumarate as a standard (Note 12), and the enantiopurity of **6** is determined to be 95% ee by HPLC analysis (Notes 25, 26, and 27).



Figure 15. Reaction setup Step C (charged starting material)



Figure 16. Reaction setup Step C (dissolved starting material)

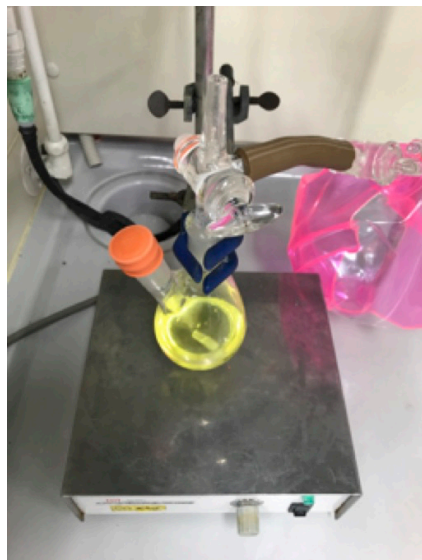


Figure 17. Reaction setup Step C (after addition of catalyst)



Figure 18. Reaction setup Step C (after addition of diethyl phosphite)





Figure 19. Reaction setup Step C  
(under nitrogen flow)

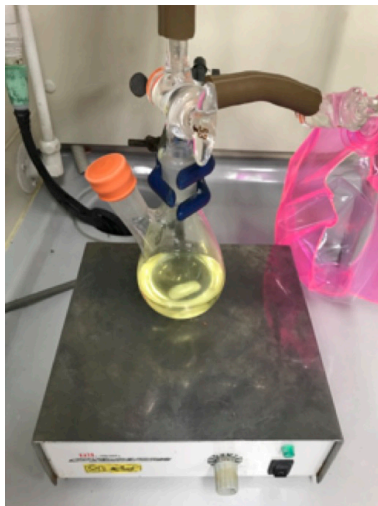


Figure 20. Reaction setup Step C  
(after 72 h of stirring)



Figure 21. Purified product 6  
(before drying)

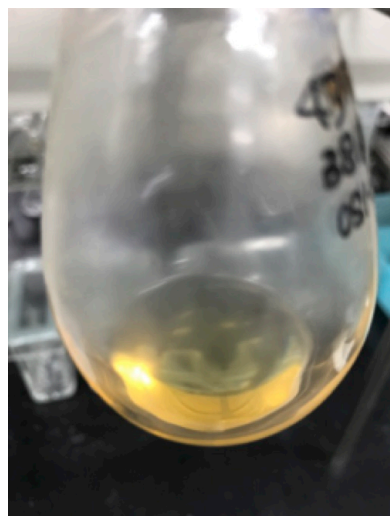
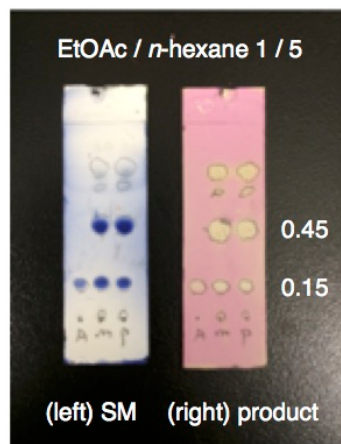


Figure 22. Purified product 6  
(after drying)

## Notes

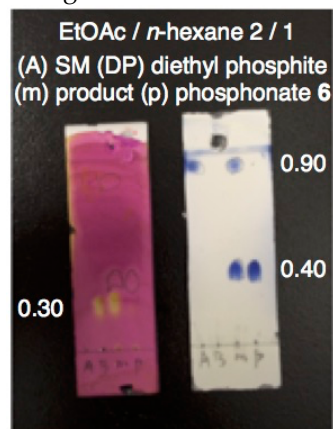
1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out 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 chlorodiphenylphosphine, sulfur, tetrahydrofuran, ammonia, ammonium chloride, chloroform, *n*-hexane, dimethyl fumarate, (1,1-dimethoxyethyl)benzene, ethyl acetate, silica gel, 1,2-bis((2*R*,5*R*)-2,5-diphenylphospholano)ethane, tetrakis(acetonitrile)copper(I) hexafluorophosphate, triethylamine, and diethyl phosphite.
2. Chlorodiphenylphosphine (96%) was purchased from Sigma-Aldrich Co., Inc. and used as received.
3. Sulfur (99%, reagent grade) was purchased from Sigma-Aldrich Co., Inc. and used as received.
4. Dry THF (>99.5%) was purchased from Kanto Chemical Co., Inc., which was purified under argon by using an Organic Solvent Pure Unit (Wako Pure Chemical Industries, Ltd.).
5. TLC plates were purchased from Merck Millipore, Co., Inc. (silica gel 60 F254).
6. During the sulfurization, several spots appeared on TLC, caused by decomposition of *P,P*-diphenyl-phosphinothioic chloride, ( $R_f$  0.91 and 0.80, chloroform/acetone = 9/1). The checkers judged the endpoint of sulfuration with  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ ), confirming disappearance of the peak of chlorodiphenylphosphine (**1**) ( $\delta$  81.8 ppm) and

- appearance of the peak of *P,P*-diphenyl-phosphinothioic chloride ( $\delta$  80.0 ppm). The sampling was performed by taking a 10- $\mu$ L fraction of the reaction mixture using a gas-tight syringe, which was diluted with  $\text{CDCl}_3$  (0.7 mL) in an NMR tube.
7. The amination progress was monitored by TLC analysis (*n*-hexane/acetone = 3/1) using ceric ammonium molybdate stain (Figure 5). The phosphinothioic amide **2** appeared at  $R_f$  = 0.40 (blue).
  8. Chloroform (>99.0%) was purchased from Kanto Chemical Co., Inc. and used as received.
  9. *n*-Hexane (96%) was purchased from Wako Pure Chemical Industries and used as received.
  10. A second reaction on the same scale provided 8.10 g (77%) of **2**, and a third reaction on the same scale gave 7.84 g (74%) of **2**.
  11. Phosphinothioic amide, *P,P*-diphenyl (**2**) is bench-stable and has the following spectroscopic properties:  $R_f$  0.40 (*n*-hexane/acetone = 3/1); mp 108–109 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.90 (brs, 2H), 7.42–7.49 (m, 6H), 7.96–8.00 (m, 4H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 128.4, 128.5, 131.1, 131.2, 131.6, 131.7, 134.8, 135.5;  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ )  $\delta$ : 55.4; IR ( $\text{CHCl}_3$ ):  $\nu$  3344, 3228, 3106, 3054, 1551, 1475, 1440, 1306  $\text{cm}^{-1}$ ; HRMS (ESI-TOF) Anal. calcd. for  $\text{C}_{12}\text{H}_{13}\text{NPS}$   $m/z$  234.0501  $[\text{M}+\text{H}]^+$ , found 234.0503.
  12. Dimethyl fumarate (>98%) was purchased from Tokyo Chemical Industry (TCI, product number F0069) and used as received.
  13. (1,1-Dimethoxyethyl)benzene (97%) was purchased from Alfa Aesar Co., Inc. and used as received.
  14. The reaction progress was monitored by TLC analysis ( $\text{EtOAc}/n$ -hexane, 1/5) using ceric ammonium molybdate or potassium permanganate stain (see Figure). The starting material **2** appeared at  $R_f$  = 0.15 (blue with ceric ammonium molybdate), and the ketimine **4** appeared at  $R_f$  = 0.45 (blue with ceric ammonium molybdate).



15. EtOAc (99%) was purchased from Wako Pure Chemical Industries and used as received.
16. Neutral silica gel was purchased from Kanto Chemical Co., Inc. (silica gel 60N; spherical, 40–50  $\mu\text{m}$ ).
17. A second reaction on the same scale provided 3.40 g (34%) of **4**, and a third reaction on the same scale gave 4.13 g (41%) of **4**.
18. *P,P*-Diphenyl-*N*-(1-phenylethylidene)phosphinothioic amide (**4**) is bench-stable and has the following spectroscopic properties:  $R_f$  0.45 (EtOAc/*n*-hexane = 1/5); mp 129–131  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.80 (d, 3H,  $J$  = 1.5 Hz), 7.42–7.49 (m, 8H), 7.54–7.57 (m, 1H), 8.03–8.07 (m, 6H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 22.4 (d,  $J$  = 17 Hz), 127.9, 128.3, 128.4, 128.5, 131.08, 131.11, 131.2, 132.5, 136.1, 136.8, 139.9, 140.1, 183.4 (d,  $J$  = 8.3 Hz);  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ )  $\delta$ : 47.4; IR ( $\text{CHCl}_3$ ):  $\nu$  3048, 1626, 1591, 1574, 1475, 1434, 1370, 1307, 1266  $\text{cm}^{-1}$ ; HRMS (ESI-TOF) Anal. calcd. for  $\text{C}_{20}\text{H}_{19}\text{NP}$   $m/z$  336.0970  $[\text{M}+\text{H}]^+$ , found 336.0973.
19. (–)-1,2-Bis((2*R*,5*R*)-2,5-diphenylphospholan-1-yl)ethane ((*R,R*)-Ph-BPE, Kanata purity) was purchased from Sigma-Aldrich Co., Inc. and used as received.
20. Tetrakis(acetonitrile)copper(I) hexafluorophosphate ( $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{PF}_6$ ) (97%) was purchased from Sigma-Aldrich Co., Inc. and used as received.
21. Although the use of a dry box is recommended, (*R,R*)-Ph-BPE and  $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{PF}_6$  can be quickly weighed under air.
22. Triethylamine (99%) was purchased from Wako Pure Chemical Industries and distilled from calcium hydride before use.

23. Diethyl phosphite (>98%) was purchased from Tokyo Chemical Industry and distilled under vacuum (4.0 mmHg, 50 °C) before use.
24. The reaction progress was monitored by TLC analysis (EtOAc/*n*-hexane = 2/1) using ceric ammonium molybdate or potassium permanganate stain (see Figure). The ketimine starting material **4** appeared at  $R_f = 0.90$  (blue), and the hydrophosphonylation product appeared at  $R_f = 0.40$  (blue) using ceric ammonium molybdate stain. The diethyl phosphite starting material **5** appeared at  $R_f = 0.30$  (yellow) using potassium permanganate stain.



25. A second reaction on the same scale provided 4.41 g (78%) of **6**, and a third reaction on the same scale gave 5.28 g (93%) of **6**.
26. (*R*)-Diethyl-1-((diphenylphosphorothioyl)amino)-1-phenylethyl phosphonate (**6**) is bench-stable and has the following spectroscopic properties:  $R_f$  0.40 (EtOAc/*n*-hexane = 2/1);  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.09 (t, 1H,  $J = 7.0$  Hz), 1.31 (t, 1H,  $J = 7.0$  Hz), 1.98 (d, 3H,  $J = 17.3$  Hz), 3.51–3.55 (m, 1H), 3.80–3.84 (m, 1H), 3.95 (t, 1H,  $J = 7.6$  Hz), 4.06–4.14 (m, 2H), 7.28–7.30 (m, 1H), 7.34–7.39 (m, 4H), 7.43–7.52 (m, 4H), 7.56–7.57 (m, 2H), 7.80–7.84 (m, 2H), 8.16–8.20 (m, 2H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$ : 16.2 (d,  $J = 5.5$  Hz), 16.4 (d,  $J = 6.1$  Hz), 19.8 (t,  $J = 5.1$  Hz), 58.7, 59.7, 63.2 (d,  $J = 7.7$  Hz), 63.7 (d,  $J = 7.1$  Hz), 127.37, 127.40, 127.49, 127.51, 127.83, 127.85, 128.1, 128.2, 128.4, 128.5, 130.86, 130.94, 131.45, 131.47, 131.49, 131.50, 132.1, 132.2, 135.5, 135.7, 136.2, 136.4, 140.3;  $^{31}\text{P}$  NMR (162 MHz,  $\text{CDCl}_3$ )  $\delta$ : 53.1 (d,  $J = 40$  Hz), 24.5 (d,  $J = 40$  Hz); IR ( $\text{CHCl}_3$ ):  $\nu$  3373, 3048, 2979, 2926, 2903, 1496, 1481, 1440, 1394, 1237  $\text{cm}^{-1}$ ; HRMS (ESI-TOF) Anal. calcd. for  $\text{C}_{24}\text{H}_{29}\text{O}_3\text{NaP}_2\text{S}$   $m/z$  496.1236  $[\text{M}+\text{Na}]^+$ , found 496.1242;  $[\alpha]_{\text{D}}^{24}$  46.5 ( $c$  1.00,  $\text{CHCl}_3$ ); Enantiomeric excess of the



product was determined to be 95% ee by HPLC analysis on chiral stationary phase (CHIRALPAK IA ( $\phi$  0.46 cm x 25 cm), 2-propanol/*n*-hexane = 1/9, flow rate 1.0 mL/min, detection at 254 nm,  $t_R$  = 9.6 min (minor), 12.8 min (major)).

27. The Cu(I) catalyst (2 mol%, 0.02 equiv) and triethylamine (50 mol%, 0.5 equiv) were used for better reproducibility in terms of enantioselectivity on a >5 g scale reaction.

## 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](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.

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## Discussion

Significant progress in the field of asymmetric catalysis over the last two decades allows for the construction of tetrasubstituted stereogenic centers in a catalytic and enantioselective manner.  $\alpha$ -Amino phosphonic acids are important synthetic targets in medicinal chemistry because these compounds serve as alternatives to  $\alpha$ -amino acids.<sup>6</sup> The growing interest in  $\alpha,\alpha$ -disubstituted  $\alpha$ -amino acids for higher metabolic stability has increased the demand for corresponding  $\alpha,\alpha$ -disubstituted  $\alpha$ -amino phosphonic acids, inspiring synthetic chemists to develop robust synthetic methodologies for these substrates.

In this context, a pioneering catalytic asymmetric process for the synthesis of nonracemic  $\alpha,\alpha$ -disubstituted  $\alpha$ -amino phosphonic acids was reported by Ito et al. by enantioselective allylation of  $\alpha$ -acetoamido- $\beta$ -keto phosphonates, although the enantioselectivity was not satisfactory.<sup>7</sup> Nakamura and Shibata et al. later reported highly enantioselective hydrophosphonylation of secondary phosphites to *N*-sulfonyl ketimines promoted by cinchona alkaloids to afford this class of compounds.<sup>8,9</sup> Although this catalytic system exhibited broad generality for aromatic *N*-sulfonyl ketimines and aliphatic substrates gave lower enantioselectivity, Shibasaki et al. later devised a cooperative catalytic system to render a highly enantioselective reaction of both aromatic and aliphatic ketimines.<sup>5</sup> The use of soft Lewis basic *N*-thiophosphinoylketimines was key to promote the reaction with the soft Lewis acid (chiral Cu(I) complex)/Brønsted base ( $\text{Et}_3\text{N}$ ) cooperative catalyst. In small scale reactions, as little as 0.5% of catalyst loading was sufficient to reach completion and the chiral Cu(I) complex could be recovered. For large scale reactions, the use of 2 mol% of catalyst is recommended to ensure high enantioselectivity.

## References

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#### Appendix

##### Chemical Abstracts Nomenclature (Registry Number)

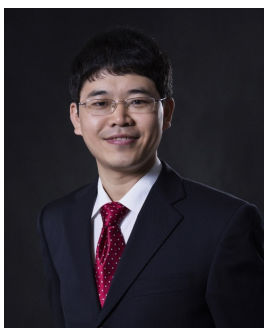
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 Sulfur (7704-34-9)  
 Tetrahydrofuran (109-99-9)  
 Ammonia (7664-41-7)  
 Ammonium chloride (12125-02-9)  
 Dimethyl fumarate (624-49-7)  
 Phosphinothioic chloride, *P,P*-diphenyl- (1015-37-8)  
 (1,1-Dimethoxyethyl)benzene (4316-35-2)  
*P,P*-Diphenyl-N-(1-phenylethylidene)phosphinothioic amide (945492-04-6)  
 1,2-Bis((2*R*,5*R*)-2,5-diphenylphospholano)ethane (528565-79-9)  
 Tetrakis(acetonitrile)copper(I) hexafluorophosphate (64443-05-6)  
 Triethylamine (121-44-8)  
 Diethyl phosphite (762-04-9)  
 (*R*)-Diethyl (1-((diphenylphosphorothioyl)amino)-1-phenylethyl)phosphonate (1446718-96-2)



Shaoquan Lin received his B.Sc. in Applied Chemistry from the Southwest University of Science and Technology (SWUST) in 2009. He obtained his M.Sc. in Organic Chemistry (2013) from the Shanghai Institute of Organic Chemistry (SIOC) under the supervision of Professor Xiuli Sun and Professor Yong Tang. He is now a research student in Professor M. Shibasaki's laboratory at the Institute of Microbial Chemistry, working on asymmetric catalysis chemistry.



Yasunari Otsuka received his Ph.D. from Kanazawa University in 2011 under the supervision of Professor Chisato Mukai. He pursued postdoctoral studies in the laboratory of Professor Shibasaki's group in 2011–2013 at the Institute of Microbial Chemistry (BIKAKEN), Tokyo. He moved to the Hiyoshi branch of BIKAKEN (Dr. Miyake's group) in 2013 as a researcher. He is currently a senior researcher at the laboratory of medicinal chemistry of BIKAKEN (Dr. Takahashi's group). His research interests include the synthesis of antibiotics based on sugar chemistry.



Liang Yin received his B.Sc. and M.Sc. from Nankai University, and his Ph.D. from the University of Tokyo under the supervision of Professors Masakatsu Shibasaki and Motomu Kanai. He pursued his postdoctoral studies in the Corey Lab at Harvard University, then continued his postdoctoral studies in the Shibasaki Lab at the Institute of Microbial Chemistry. In 2014, he began his independent academic career as a "Bairen" Professor at Shanghai Institute of Organic Chemistry. His research interests are focused on the development of asymmetric catalysis and their application to the synthesis of natural products and pharmaceutically active compounds.



Naoya Kumagai received his Ph.D. in Pharmaceutical Sciences at the University of Tokyo in 2005 under the supervision of Professor Masakatsu Shibasaki, and pursued postdoctoral studies in the laboratory of Professor Stuart L. Schreiber at Harvard University in 2005–2006. He returned to Professor Shibasaki's group at the University of Tokyo as an assistant professor in 2006. He is currently a chief researcher at the Institute of Microbial Chemistry, Tokyo. His research interests include the development of new methodologies in asymmetric catalysis and their application to bio-inspired dynamic processes.

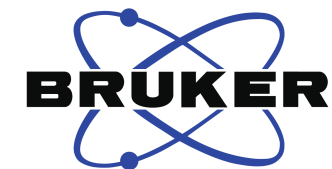


Masakatsu Shibasaki received his Ph.D. from the University of Tokyo in 1974 with Professor Shun-ichi Yamada before beginning his postdoctoral studies with Professor E. J. Corey (Harvard University). In 1977, he joined Teikyo University as an Associate Professor. In 1983, he moved to Sagami Chemical Research Center as a group leader, and in 1986, he assumed a professorship at Hokkaido University before returning to the University of Tokyo as a Professor in 1991. Currently, he is a director of the Institute of Microbial Chemistry (Tokyo). His research interests include asymmetric catalysis and medicinal chemistry of biologically significant compounds.



Ayumu Matsuda received his M.S. degree in 2016 at Tokyo Institute of Technology under the direction of Professor Keisuke Suzuki, and he is currently a doctoral student. His research efforts focus on the total synthesis of natural products.



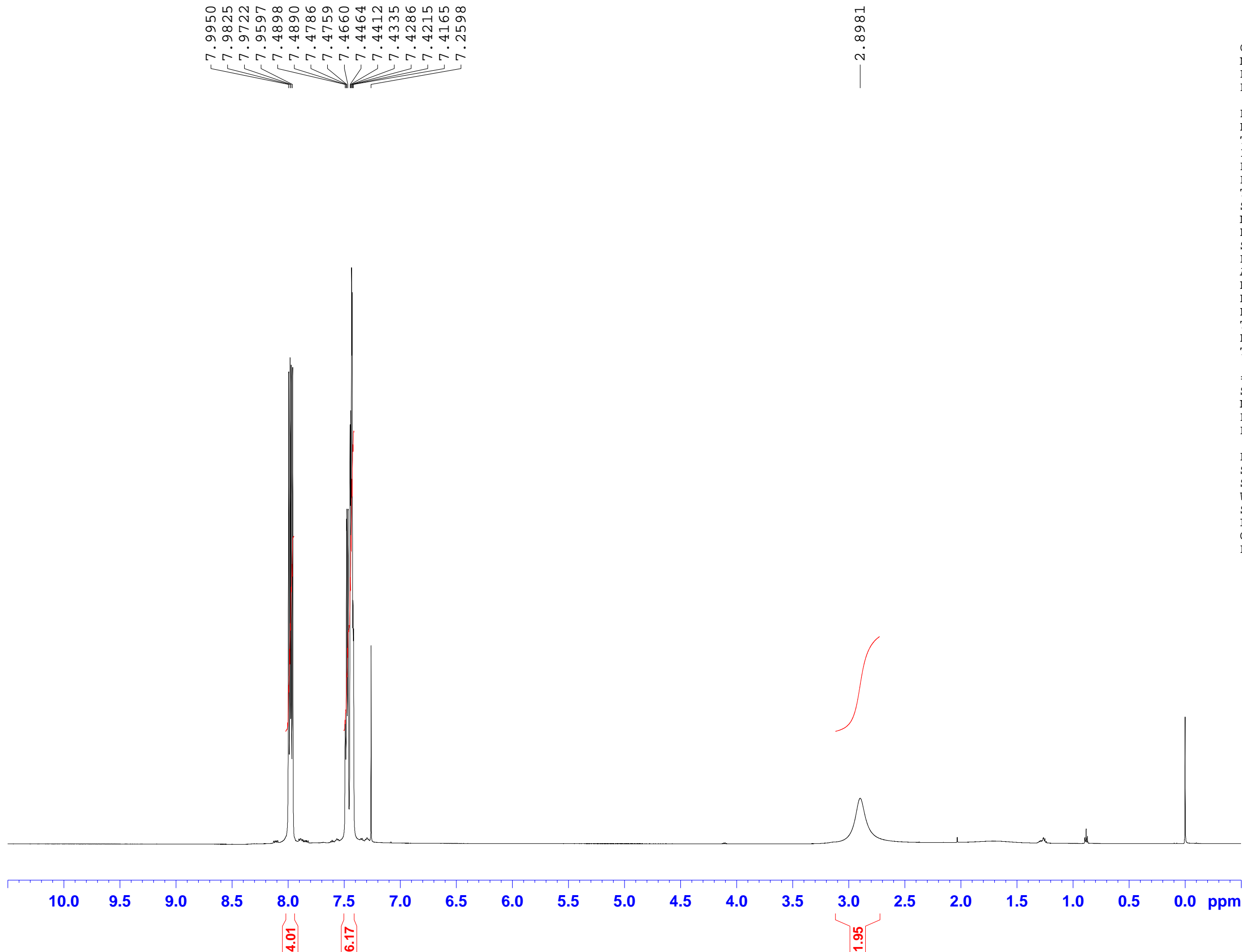


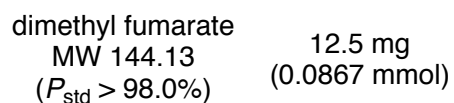
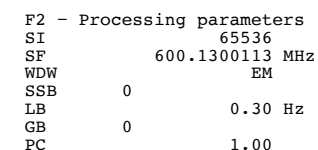
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FIDRES 0.183399 Hz  
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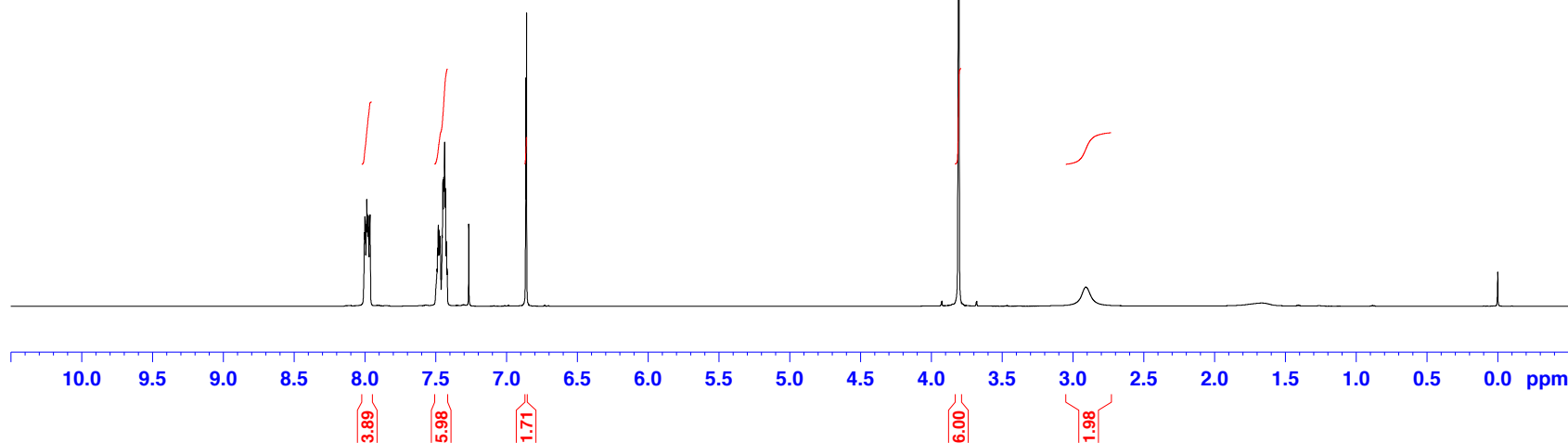
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LB 0.30 Hz  
GB 0  
PC 1.00





$$P_{\text{pdt}} = \text{Molar Ratio}_{\text{NMR}} \times \frac{0.0845 \text{ mmol}_{\text{pdt}}}{0.0867 \text{ mmol}_{\text{std}}} \times >98.0\% > 98\%$$





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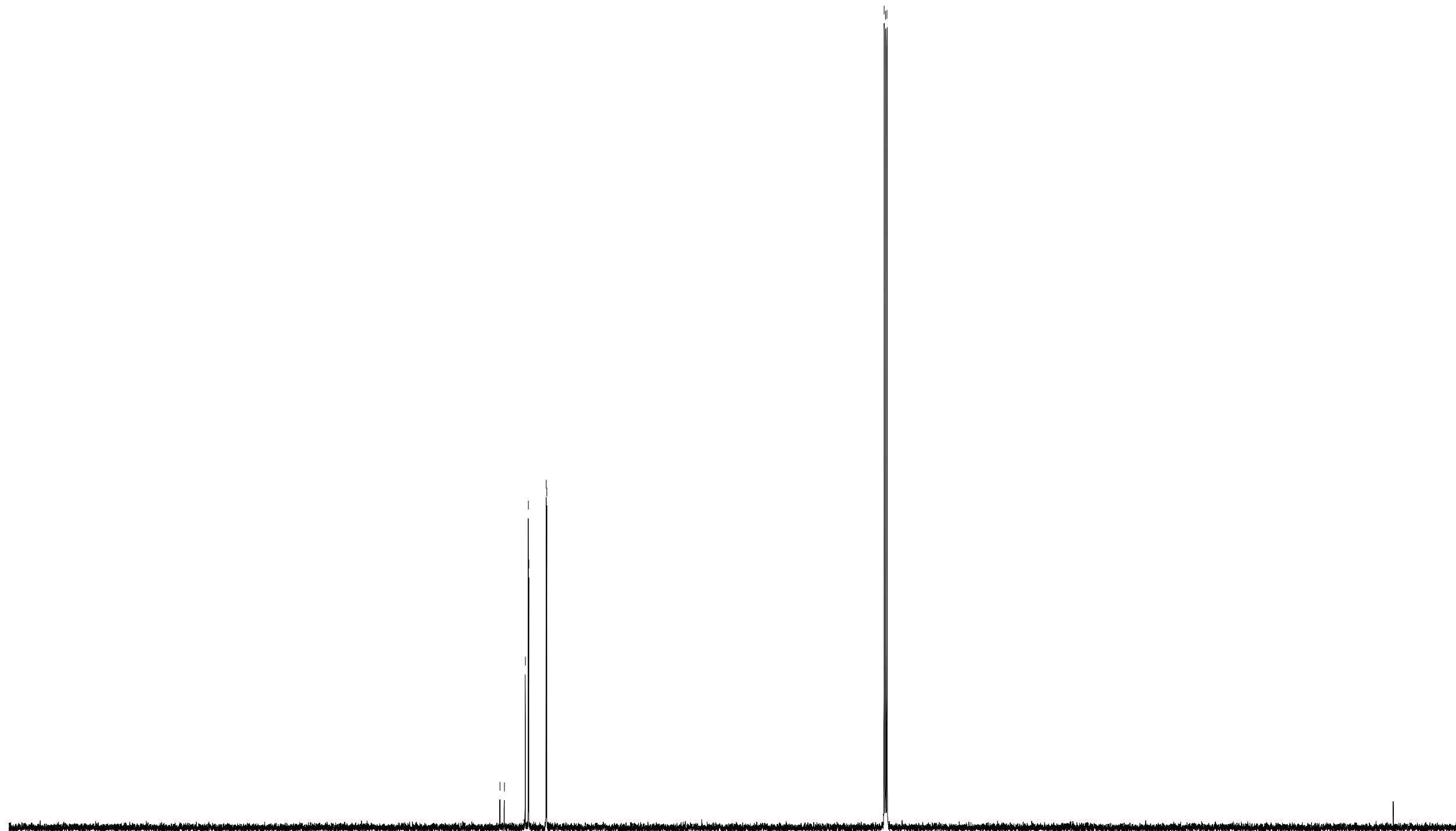
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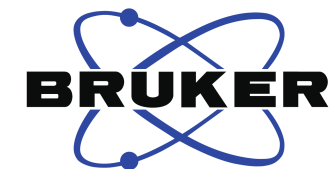
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131.6434  
131.1896  
131.1134  
128.4779  
128.3906

77.2111  
76.9994  
76.7876



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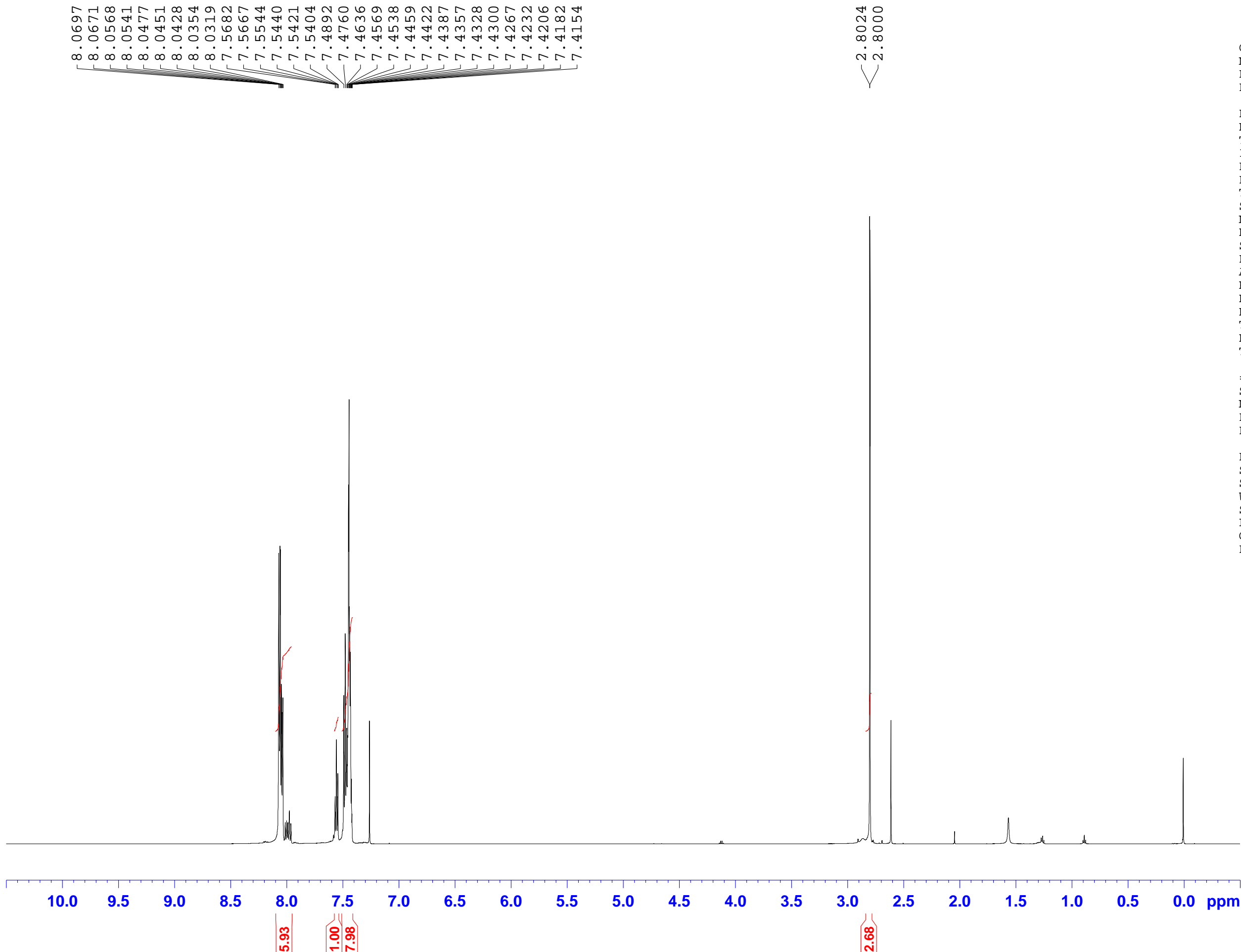


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SOLVENT CDCl3  
NS 16  
DS 2  
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FIDRES 0.183399 Hz  
AQ 2.7262976 sec  
RG 17.5  
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DE 10.00 use  
TE 300.0 K  
D1 1.00000000 sec  
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 FIDRES 0.183399 Hz  
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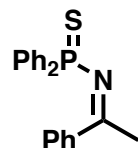
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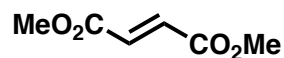
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7.5402  
7.5298  
7.5279  
7.4752  
7.4622  
7.4498  
7.4318  
7.4302  
7.4285  
7.4250  
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7.2599  
6.8578

3.7988

2.7888  
2.7864



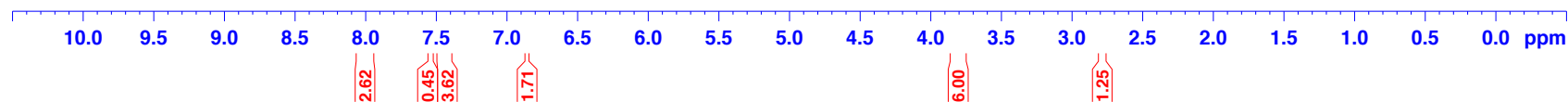
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 MW 335.40 (0.0641 mmol)



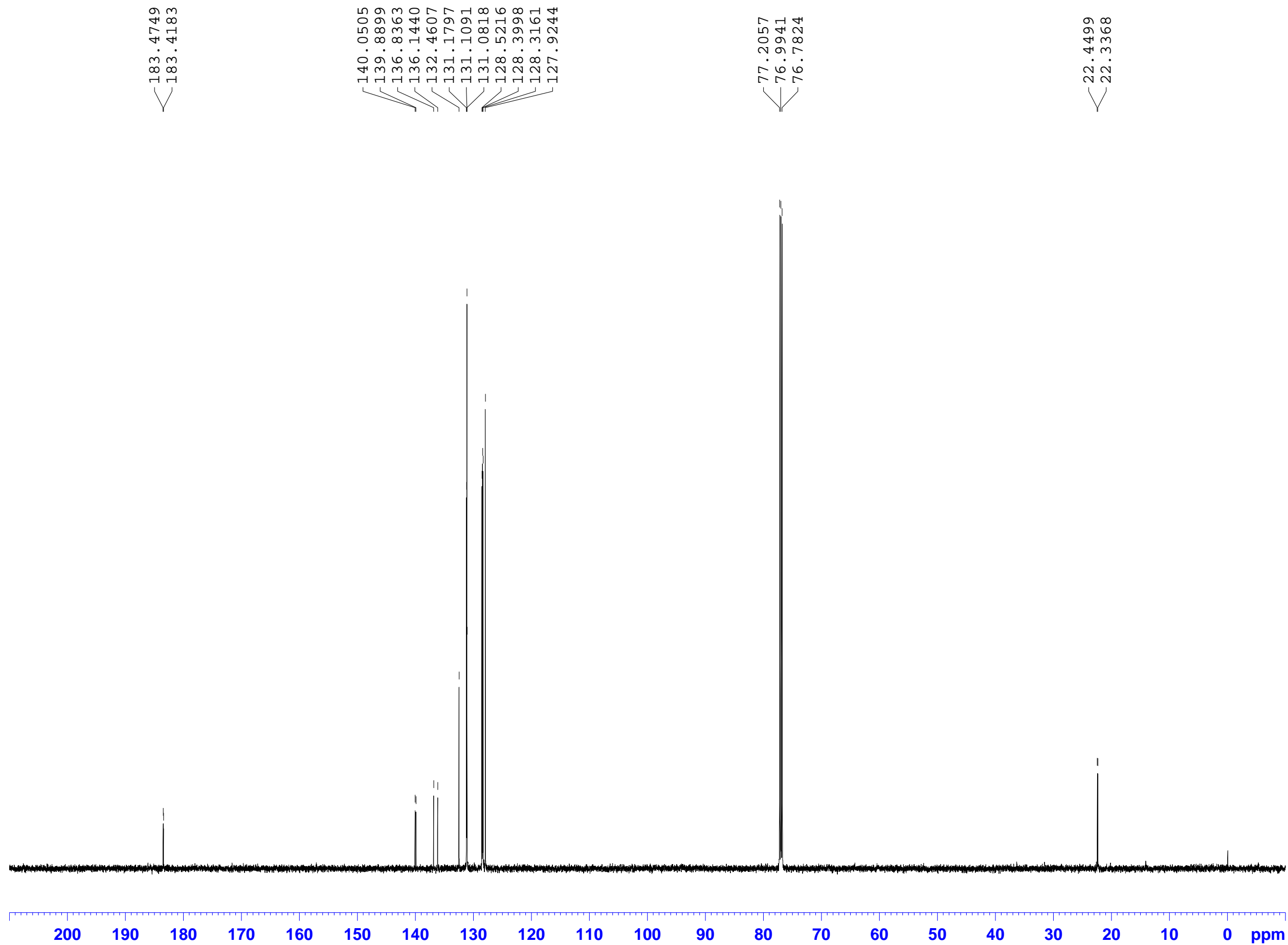
dimethyl fumarate  
 MW 144.13  
 ( $P_{\text{std}} > 98.0\%$ ) 21.2 mg  
 (0.147 mmol)

$$\text{Molar Ratio}_{\text{NMR}} = \frac{6.00 \div 6}{2.62 \div 6} = 2.29$$

$$P_{\text{pdt}} = \text{Molar Ratio}_{\text{NMR}} \times \frac{0.0641 \text{ mmol}_{\text{pdt}}}{0.147 \text{ mmol}_{\text{std}}} \times >98.0\% > 98\%$$







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SOLVENT CDCl3  
NS 600  
DS 4  
SWH 36057.691 Hz  
FIDRES 0.550197 Hz  
AQ 0.9087659 sec  
RG 175.56  
DW 13.867 use  
DE 6.50 use  
TE 298.0 K  
D1 2.00000000 sec  
D11 0.03000000 sec  
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PCPD2 70.00 use  
PLW2 22.00000000 W  
PLW12 0.64652997 W  
PLW13 0.31680000 W

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SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40

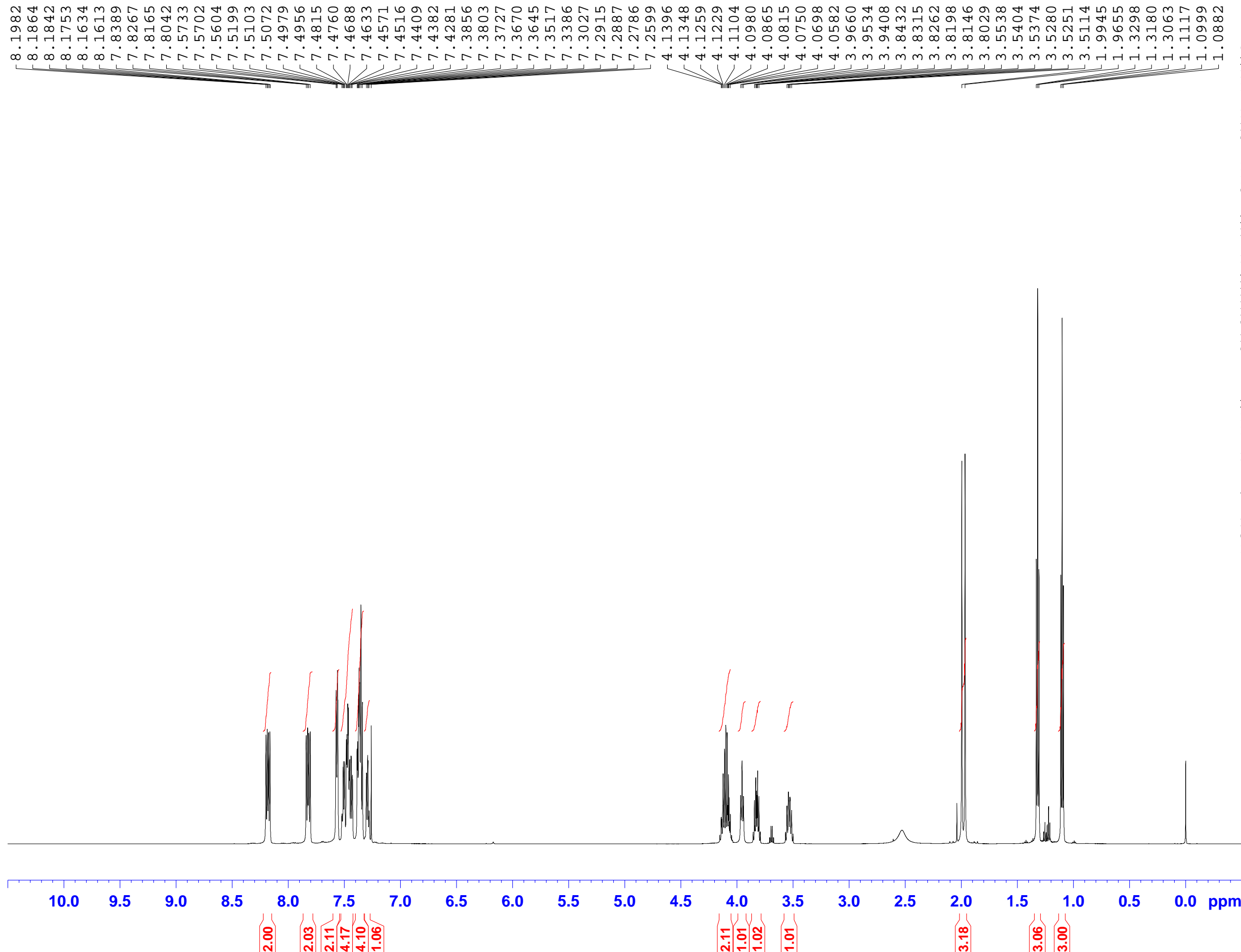


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PROCNO 1

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PROBHD 5 mm CPPBBO BB  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 16  
DS 2  
SWH 12019.230 Hz  
FIDRES 0.183399 Hz  
AQ 2.7262976 sec  
RG 17.5  
DW 41.600 use  
DE 10.00 use  
TE 300.0 K  
D1 1.00000000 sec  
TD0 1

===== CHANNEL f1 =====  
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NUC1 1H  
P1 12.00 use  
PLW1 23.00000000 W

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SSB 0  
LB 0.30 Hz  
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PC 1.00



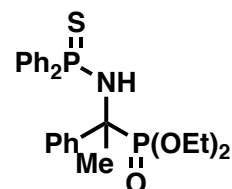
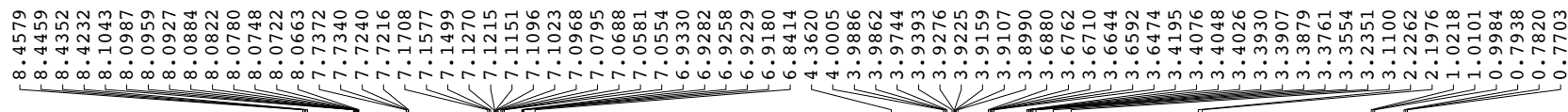


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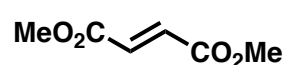
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 DS 2  
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 FIDRES 0.183399 Hz  
 AQ 2.7262976 sec  
 RG 17.5  
 DW 41.600 use  
 DE 10.00 use  
 TE 300.0 K  
 D1 1.00000000 sec  
 TD0 1

===== CHANNEL f1 =====  
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 NUC1 1H  
 P1 12.00 use  
 PLW1 23.00000000 W

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 PC 1.00



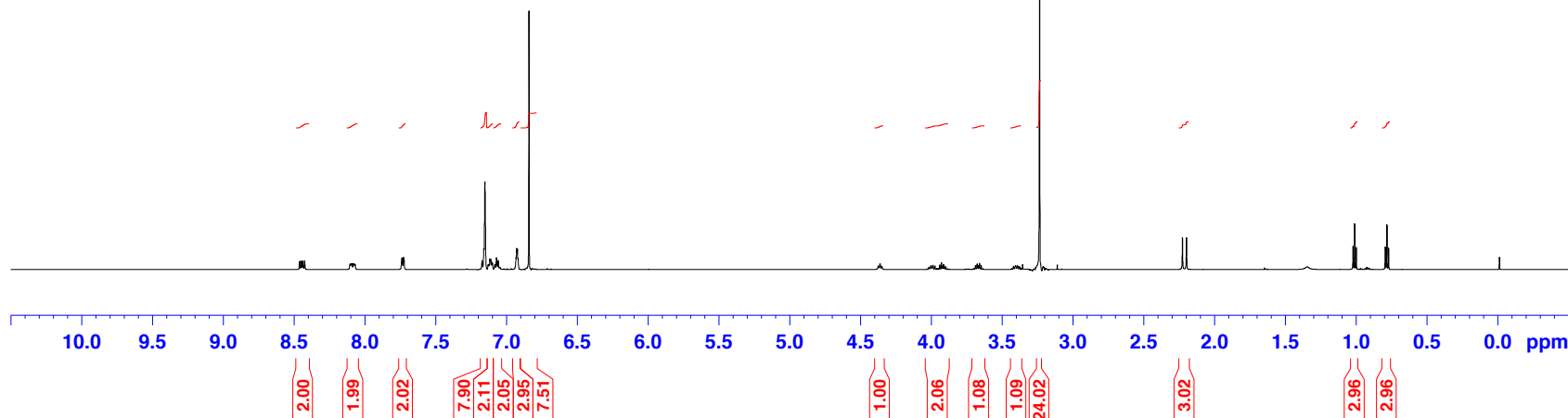
**6**  
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 (0.0275 mmol)

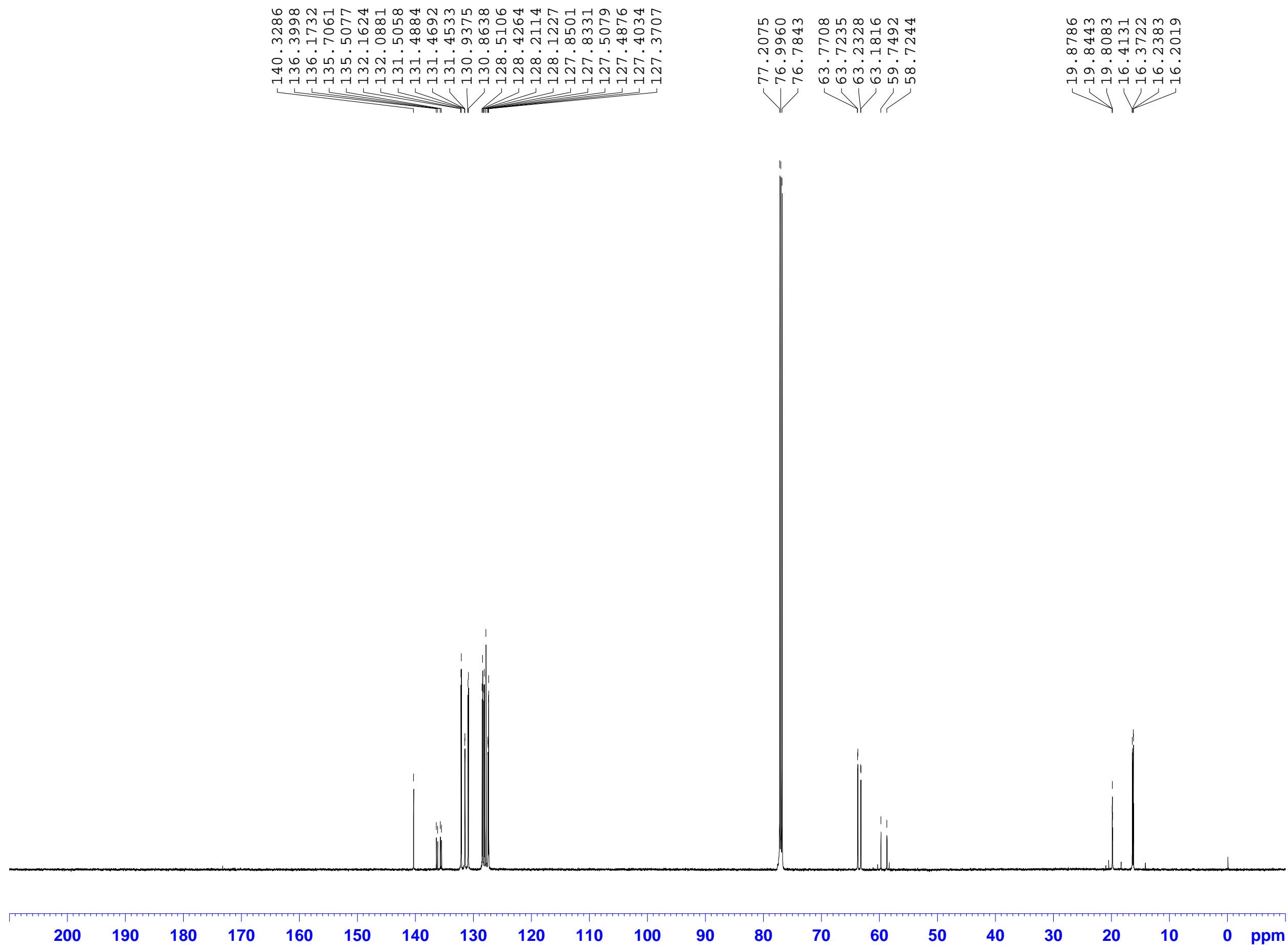


dimethyl fumarate  
 MW 144.13 15.9 mg  
 ( $P_{\text{std}} > 98.0\%$ ) (0.110 mmol)

$$\text{Molar Ratio}_{\text{NMR}} = \frac{24.0 \div 6}{2.00 \div 2} = 4.00$$

$$P_{\text{pdt}} = \text{Molar Ratio}_{\text{NMR}} \times \frac{0.0275 \text{ mmol}_{\text{pdt}}}{0.111 \text{ mmol}_{\text{std}}} \times >98.0\% > 98\%$$





Current Data Parameters  
NAME OS-C-1  
EXPNO 11  
PROCNO 1

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SOLVENT CDCl3  
NS 512  
DS 4  
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FIDRES 0.550197 Hz  
AQ 0.9087659 sec  
RG 175.56  
DW 13.867 use  
DE 18.00 use  
TE 300.0 K  
D1 2.00000000 sec  
D11 0.03000000 sec  
TD0 1

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NUC1 13C  
P1 10.00 use  
PLW1 70.00000000 W

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NUC2 1H  
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PLW2 14.00000000 W  
PLW12 0.64286000 W  
PLW13 0.32335001 W

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PC 1.40