



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

## Working with Hazardous Chemicals

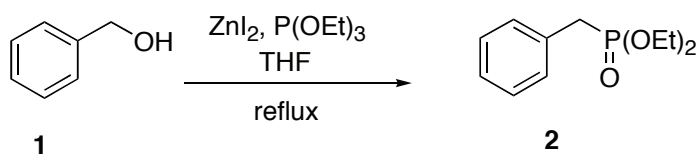
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*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

## Direct Conversion of Benzylic and Allylic Alcohols to Diethyl Phosphonates



Submitted by Rebekah M. Richardson and David F. Wiemer.<sup>1</sup>

Checked by Laura S. Kocsis and Kay M. Brummond.

### 1. Procedure

A flame-dried 100-mL, two-necked, round-bottomed flask equipped with a cylindrical Teflon-coated magnetic stir bar (1.5 cm x 0.7 cm), a rubber septum, and a reflux condenser is maintained under an atmosphere of argon during the course of the reaction. The flask is charged with zinc iodide (12.2 g, 38.2 mmol, 1.2 equiv) (Note 1) and is evacuated and refilled with argon three times. Tetrahydrofuran (35 mL) (Note 2) is added by syringe to provide a white liquid with undissolved solid still present. Triethyl phosphite (8.2 mL, 48 mmol, 1.5 equiv) (Note 3) is added using a 5-mL disposable syringe, and the solution becomes colorless with a small quantity of solid still present. Benzyl alcohol (3.3 mL, 32 mmol, 1.0 equiv) (Note 4) is added using a disposable syringe. The reaction mixture is heated at reflux for 16 h (oil bath, 75 °C) (Note 5), at which time the reaction turns yellow and clear. The solution is allowed to cool for 10 min, slowly placed under vacuum, and concentrated at 2 mmHg for 5.5 h to remove volatiles (Note 6). The residue is then transferred to a 500-mL separatory funnel with diethyl ether (2 x 10 mL) and 2 N NaOH (2 x 10 mL), and diluted with additional diethyl ether (90 mL). The organic phase is washed with 2 N NaOH (350 mL) (Note 7), the aqueous phase is extracted with diethyl ether (3 x 125 mL), and the combined organic phase is dried over 12 g of MgSO<sub>4</sub>. The solution is then filtered through a bed of Celite<sup>®</sup> (24 g) in a 350-mL coarse porosity sintered glass funnel, washed with diethyl ether (3 x 50 mL), and the filtrate is concentrated by rotary evaporation (23 °C, 10 mmHg) to afford a yellow oil. After transfer to a 25-mL round-bottomed flask equipped with a magnetic stir bar (Note 8), the product is purified via a short-path distillation with an 8-cm head under vacuum (0.5 mmHg) and collected with

a fraction cutter or “cow” apparatus. A forerun of 1.2–1.6 g is collected, followed by product **2** distilling at 115–122 °C (0.5 mmHg) (Note 9) as a colorless oil (5.11 g, 70%) (Notes 10, 11, and 12).

## 2. Notes

1.  $\text{ZnI}_2$  ( $\geq 98\%$ ) was obtained from Sigma-Aldrich and used as received. The bottle was purged with argon after each use due to the hygroscopic nature of the chemical.

2. Anhydrous 99.9%, inhibitor free tetrahydrofuran was obtained from Sigma-Aldrich and purified with alumina using the Sol-Tek ST-002 solvent purification system directly prior to use. The submitters report that anhydrous tetrahydrofuran ( $\geq 99\%$  containing 250 ppm BHT as inhibitor) was obtained from Sigma-Aldrich and distilled from sodium benzophenone ketyl immediately prior to use.

3. Triethyl phosphite (98%) was obtained from Sigma-Aldrich and used as received. The bottle was purged with argon after each use to minimize air oxidation.

4. Benzyl alcohol ( $\geq 99\%$ ) was obtained from Sigma-Aldrich and used as received.

5. A longer reaction time is not detrimental to the reaction yield. The submitters performed the reaction for 12 h.

6. The vacuum was attached at the head of the condenser in the round-bottomed flask. Occasional bumping occurs, and the condenser traps any material that bumps so that the residue can later be transferred to the separatory funnel for extraction, rather than being lost in the vacuum line. Alternatively, a rotary evaporator can be used to remove volatile materials, as long as care is taken to minimize oxidation of excess triethyl phosphite (bp  $\sim 156$  °C) to the less volatile triethyl phosphate (bp  $\sim 215$  °C).

7. The initial washing with 2 N NaOH causes the aqueous phase to become cloudy with white precipitate. After dilution with 90 mL diethyl ether and 350 mL 2 N NaOH, the aqueous layer is colorless and slightly cloudy. After the first ether extraction, there is no visible precipitate in the aqueous layer.

8. The submitters report that if left sitting overnight, the initial colorless oil sometimes turns yellow. The checkers only observed a crude yellow oil.

9. The temperature of the oil bath was increased by 25 °C increments from 50–150 °C every ten minutes to ensure collection of pure product. The forerun was collected from 100–105 °C. The submitters report that at pressures of 0.1 mmHg and 0.15 mmHg, the product was obtained distilling at 100–105 °C, and at pressures of 0.25 mmHg the product was obtained distilling at 108–115 °C.

10. Diethyl benzylphosphonate **2** has the following physical and spectroscopic properties: TLC analysis was performed on SiliCycle Inc. SiliaPlate silica gel plates (w/ UV254, glass-backed, 250 μm) and was visualized as a blue spot with cerium molybdate followed by heating.  $R_f = 0.23$  in 70% EtOAc in hexane; IR (neat) 2983, 1247, 1027  $\text{cm}^{-1}$ ; LRMS (TOF MSMS ES+)  $m/z$  (%): 229 (28), 201 (38), 173 (100); HRMS (TOF MS ES+)  $[M+H]^+$  calcd for  $\text{C}_{11}\text{H}_{18}\text{O}_3\text{P}$ , 229.0994; found, 229.1004;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.23 (t,  $J_{\text{HH}} = 7.2$  Hz, 6 H), 3.14 (d,  $J_{\text{HP}} = 21.6$  Hz, 2 H), 3.96–4.04 (m, 4 H), 7.24–7.30 (m, 5 H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 16.2 (d,  $J_{\text{CP}} = 6.0$  Hz, 2C), 33.7 (d,  $J_{\text{CP}} = 137.0$  Hz), 62.0 (d,  $J_{\text{CP}} = 7.0$  Hz, 2C), 126.7 (d,  $J_{\text{CP}} = 3.0$  Hz), 128.4 (d,  $J_{\text{CP}} = 3.0$  Hz, 2C), 129.7 (d,  $J_{\text{CP}} = 6.0$  Hz, 2C), 131.5 (d,  $J_{\text{CP}} = 8.0$  Hz);  $^{31}\text{P}$  (121 MHz,  $\text{CDCl}_3$ )  $\delta$ : 26.4.

11. A yield of 70% was obtained on full scale, while a yield of 65% was obtained on half scale. The submitters report a 76% yield when reaction is performed on full scale. On small scale, products were typically purified through flash column chromatography on silica gel with yields of 80–90%.

12. The distillation gives material of  $\geq 98\%$  purity by  $^{31}\text{P}$  NMR, which is sufficiently pure for most applications. To obtain an analytical sample, a portion of the distillate (0.2 mL) was purified by flash column chromatography [7.3 g silica gel, 2.5 x 45 cm glass column, diethyl ether-pentane (8:2) as eluent (Note 13)] to give 0.193 g (90% yield) of compound **2** as a colorless oil.

13. Standard grade silica gel (230 x 400 mesh) was obtained from Sorbent Technologies and used as received. In a typical purification, collecting 9-mL fractions, compound **2** would elute in fractions 11–27 as the pure product. The submitters reported that compound **2** elutes in fraction 4 as a slight mixture and fractions 5–11 as the pure product when ethyl acetate – hexanes (7:3) is used as eluent. The combined organic fractions were concentrated by rotary evaporation (23 °C, 10 mmHg) and then at 2 mmHg. Analysis by HPLC showed a single peak with a retention time of 17.6 min using 70% ethyl acetate-hexanes as the eluent and a flow rate of 4 mL/min.

HPLC experiments were conducted using a Varian Dynamax column (250 x 10.0 mm) and Varian UV/Vis detector operating at 254 nm.

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### 3. Discussion

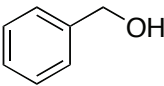
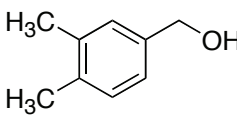
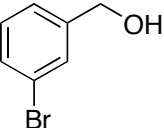
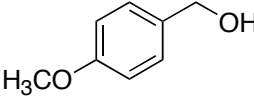
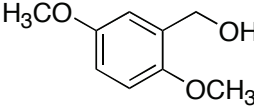
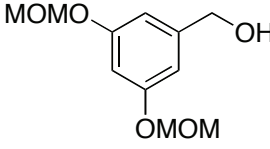
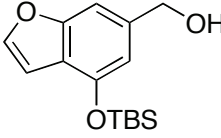
Activated phosphonate esters serve as reagents in Horner-Wadsworth-Emmons reactions. Their synthesis often relies upon a classic three-step protocol involving formation of the mesylate from an alcohol, conversion to the corresponding halide, and a final Michaelis-Arbuzov reaction.<sup>2-4</sup> In some cases, this sequence has proven problematic<sup>5</sup> or difficult to conduct on a larger scale. This method allows for an inexpensive, one-flask procedure for conversion of benzylic and allylic alcohols to the corresponding phosphonates through treatment with triethyl phosphite and ZnI<sub>2</sub>.<sup>6,7</sup>

Optimal reaction conditions can be slightly modified for each substrate with solvents including tetrahydrofuran, *N,N*-dimethylformamide, and toluene, and temperatures of 66–140 °C. The best yields often were obtained when the zinc-mediated reaction was conducted at 66 °C, an improvement upon the generally high temperatures required for the Michaelis-Arbuzov reaction.<sup>3</sup>

The reaction conditions are applicable to benzylic alcohols with varying electron donating or withdrawing substituents, and to furan systems (Table 1). Primary and secondary allylic alcohols (Table 2) also were

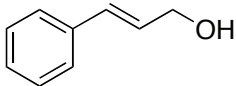
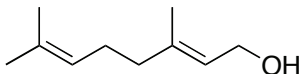
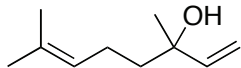
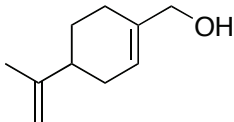
converted to phosphonates under parallel reaction conditions. As demonstrated in Table 2, tertiary allylic alcohols appear to undergo rearrangement to the primary allylic phosphonate. Application of this protocol to aliphatic systems led to mixed ester phosphonate and hydrogen phosphonate products, demonstrating the importance of a stabilized carbocation.

**Table 1.** Preparation of Benzyl Phosphonates<sup>a</sup>

Entry	Starting Alcohol	Rxn Temp °C	Solvent	Purified <sup>b</sup> Yield (%)
1 <sup>c</sup>		66	THF	76
2		110	Toluene	69
3		140	Toluene	71
4		66	THF	85
5		66	THF	81
6		66	THF	57 <sup>d</sup>
7		140	Toluene	64

<sup>a</sup>Reactions were carried out overnight using 3.0 equivalents of P(OEt)<sub>3</sub> and 1.5 equivalents of ZnI<sub>2</sub>.<sup>6b</sup> <sup>b</sup>Products were purified through flash column chromatography using varying ratios of EtOAc in hexanes. <sup>c</sup>Reaction was carried out using 1.5 equivalents of P(OEt)<sub>3</sub> and 1.2 equivalents of ZnI<sub>2</sub>. <sup>d</sup>70% based on recovered starting material.

**Table 2.** Preparation of Allylic Phosphonates<sup>a</sup>

Entry	Starting Alcohol	P(OEt) <sub>3</sub> equiv	Rxn Temp °C	Purified <sup>b</sup> Yield (%)
1		3.1	110	81
2 <sup>c</sup>		2.1	110	70
3		3.0	140	21 <sup>d</sup>
4		3.0	140	78

<sup>a</sup>Reactions were carried out overnight using 1.5 equivalents of ZnI<sub>2</sub> in toluene.<sup>6</sup> <sup>b</sup>Products were purified through flash column chromatography using varying ratios of EtOAc in hexanes. <sup>c</sup>Reaction was carried out using 1.1 equivalents of ZnI<sub>2</sub>. <sup>d</sup>The tertiary alcohol rearranged to form diethyl geranylphosphonate as the product.

1. Department of Chemistry, University of Iowa, Iowa City, IA, 52242. E-mail: david-wiemer@uiowa.edu. Funding from the University of Iowa Graduate College, in the form of a Presidential Fellowship to R. M. R., and the Roy J. Carver Charitable Trust is gratefully acknowledged.
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6. (a) Presented in part at the 240<sup>th</sup> ACS National Meeting, Boston, MA, August, 2010: Richardson, R. M.; Barney, R. J.; Wiemer, D. F. ORGN-1059. (b) Barney, R. J.; Richardson, R. M.; Wiemer, D. F. *J. Org. Chem.* **2011**, *76*, 2875–2879. (c) Richardson, R. M.; Barney, R. J.; Wiemer, D. F. *Tetrahedron Lett.* **2012**, *53*, 6682–6684.
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## Appendix

### Chemical Abstracts Nomenclature (Registry Number)

Zinc Iodide; (10139-47-6)

Triethyl Phosphite; (122-52-1)

Benzyl Alcohol; (100-51-6)\



David F. Wiemer was born and raised in southeastern Wisconsin. He received a B.S. degree in Chemistry from Marquette University, earned the Ph.D. degree at the University of Illinois, and was an NIH postdoctoral fellow at Cornell University. He joined the faculty in the Department of Chemistry at the University of Iowa as an assistant professor, and now holds the rank of F. Wendell Miller Professor of Chemistry. His research interests include synthetic methodology based on organophosphorus chemistry, synthesis of phosphonate analogues of isoprenoid phosphates as potential enzyme inhibitors, and synthesis of biologically active natural products, especially potential anti-cancer agents.





Rebekah Richardson was born in Peoria, IL. She graduated from Knox College with a B.A. in chemistry in 2007, where she performed undergraduate research at the USDA in Peoria. She then joined the group of Professor David F. Wiemer at the University of Iowa in 2007 as a recipient of the University of Iowa Presidential Graduate Fellowship. Her research focuses on C-P bond formation and natural product total synthesis.



Laura Kocsis was born in 1987 in Easton, Pennsylvania. In 2009, she received her B.S. degree in chemistry from Carnegie Mellon University in Pittsburgh, Pennsylvania. She is currently pursuing graduate studies at the University of Pittsburgh under the guidance of Prof. Kay Brummond. Her research currently focuses on exploring the novel synthesis and photophysical properties of functionalized cyclopenta[*b*]naphthalenes generated via a dehydrogenative Diels-Alder reaction.

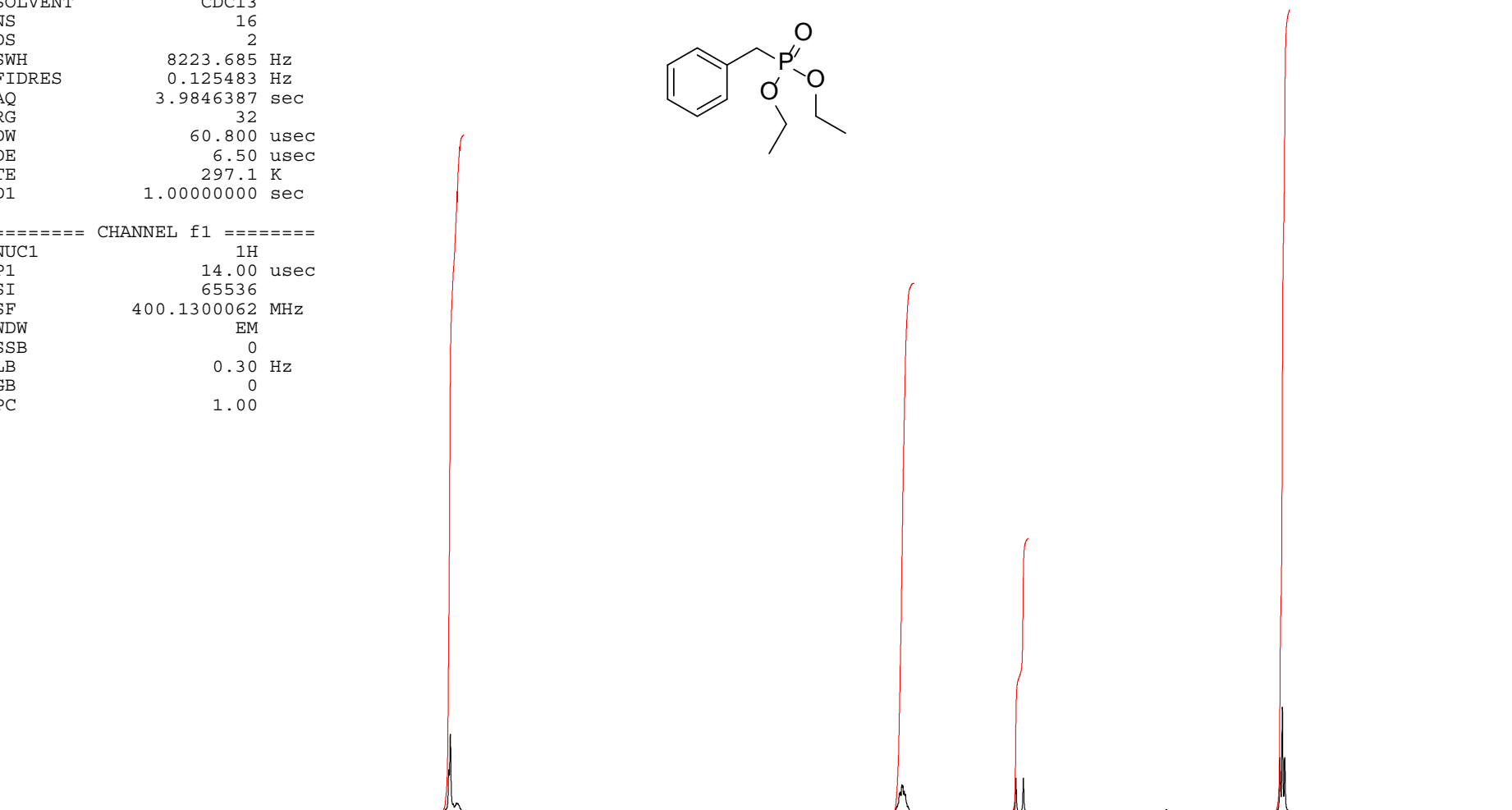
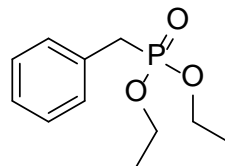
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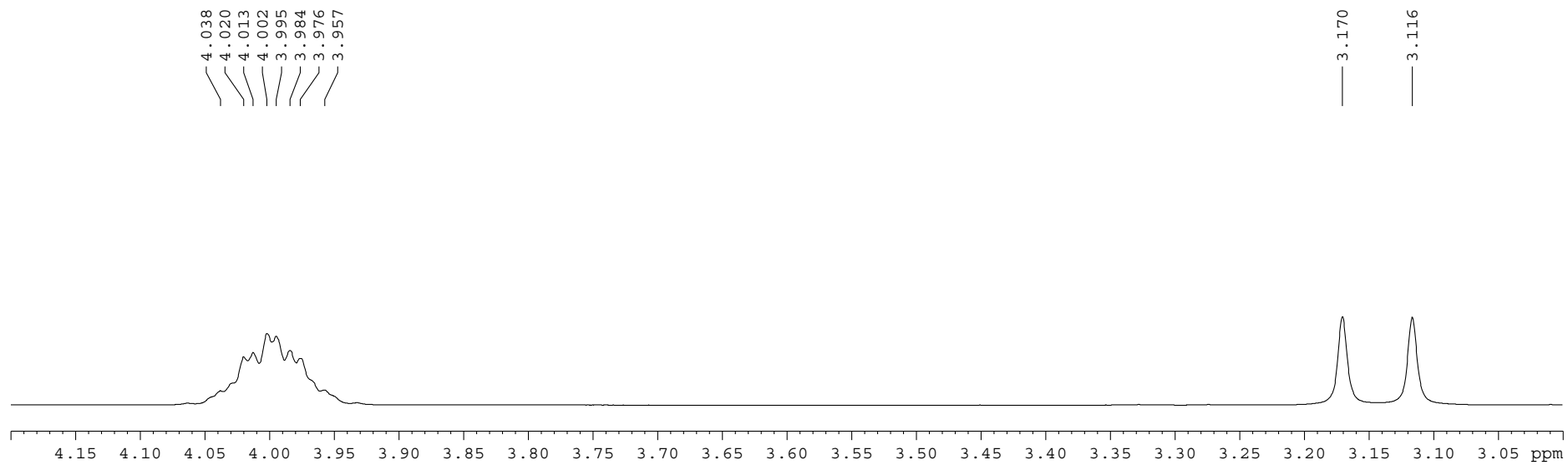
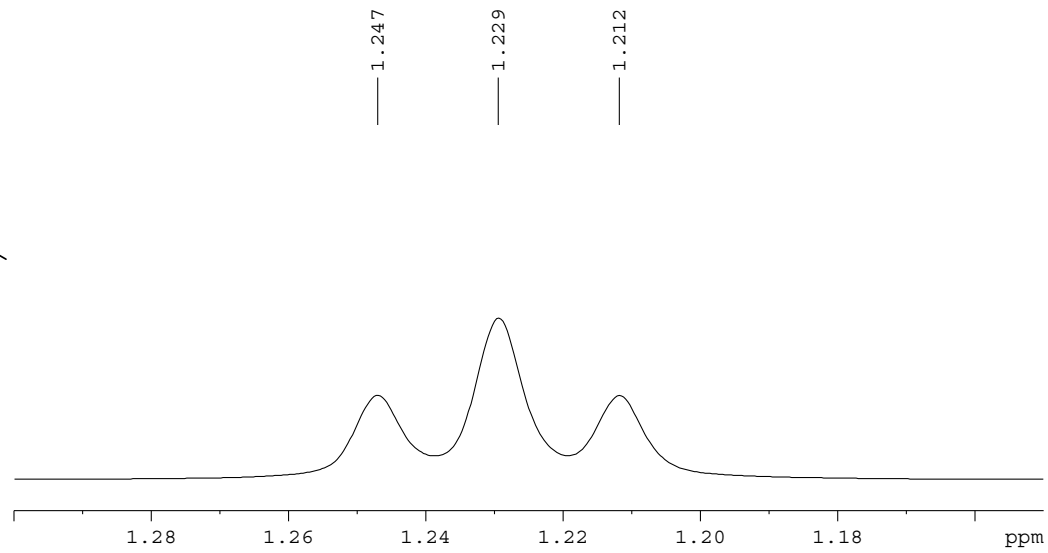
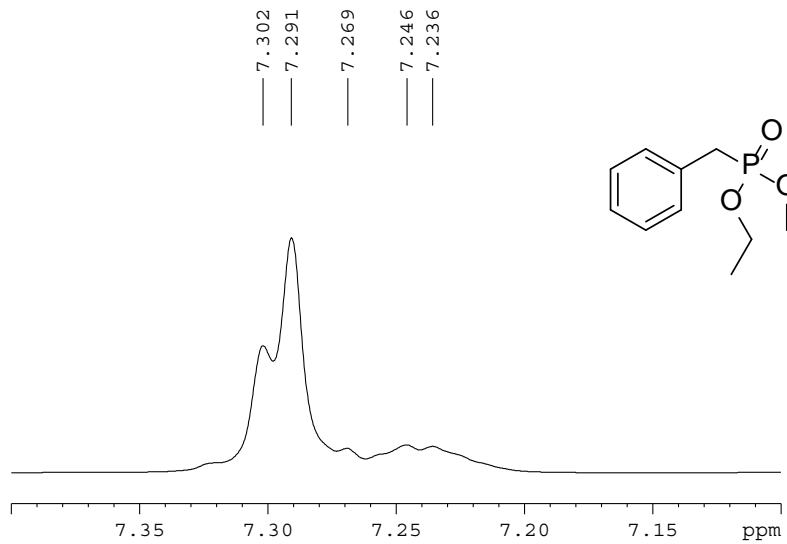
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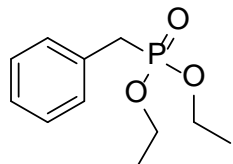
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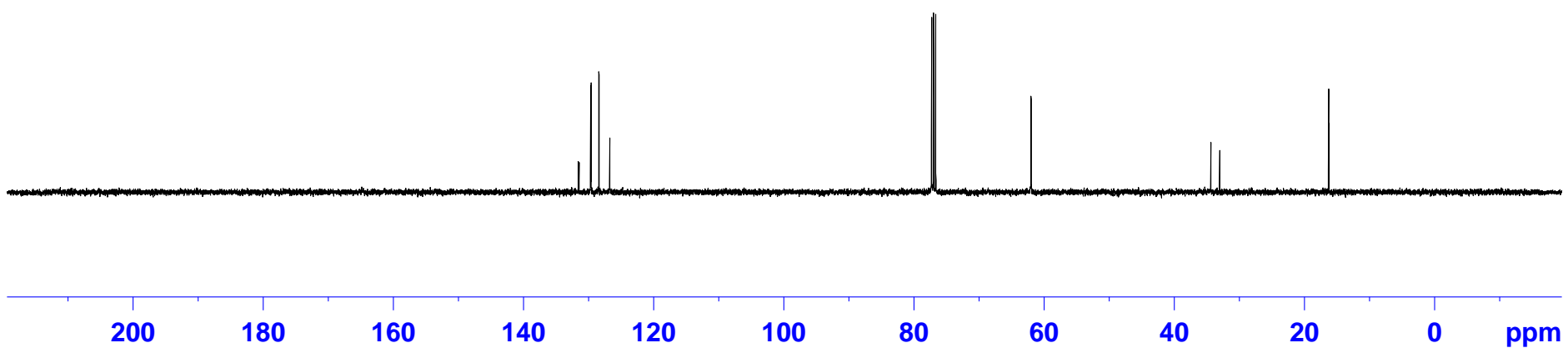
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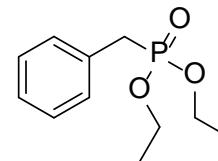
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