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# Rapid and Efficient Synthesis of Unsymmetrical Phosphinic Acids R′P(O)OHR′′

Cécile Fougère,[a] Erwann Guénin,[a] Julie Hardouin,[a] and Marc Lecouvey*[a]

**Keywords:** Phosphinic acids / Phosphorus / Peptidomimetics / Amines / Organophosphorus chemistry

A new synthesis of unsymmetrical phosphinic acids R′P(O)OHR′′ has been evaluated. The first P–C bond was formed by base-promoted H-phosphinate alkylation of a protected H-phosphinate, which is easier and safer to handle. A one-pot methodology was developed for the second P–C bond formation reaction that involves the sila-Arbuzov reaction. This methodology was then extended to the synthesis of a dialkylphosphinic acid with an amino functionality.


## Introduction

Organophosphorus compounds are important substrates in the study of biochemical processes and tetracoordinate pentavalent phosphorus compounds are widely used as biologically active compounds.[1] In recent years, the synthesis of α-substituted phosphoryl derivatives (phosphonic and phosphinic acids) has attracted considerable attention[2] due to their biological activities and application as enzyme inhibitors,[3] antimetabolites,[4] and antibiotics.[5] Of the many phosphorus compounds, phosphinic acids are increasingly being used in peptidomimetic design.[6,7] It has been shown that these pseudopeptides are transition-state analogue inhibitors of peptidases and in this role they are typically tightly binding and specific.[8–10]

From the simplest starting materials, hypophosphorous acid ($H_3PO_2$), the synthesis of phosphinic-containing molecules requires the formation of two P–C bonds. New reactions are continuously being developed for the efficient synthesis of such compounds.[11,12] However, most of the methods reported for their preparation are not general and suffer from severe limitations:[7,13] A large excess of reagents, the direct formation of symmetrical dialkylphosphinate or the instability and handling difficulties of the starting materials. Thus, new methods using more general and milder conditions are required to allow the preparation of functionalized dialkylphosphinates.

Herein we report the development of a simple and efficient synthesis of dialkylphosphinic acids. The methodology uses H-phosphinates as intermediates, ideal synthons in organophosphorus chemistry.

[a] Chimie Biomoléculaire et Bionanomatériaux, CSPBAT FRE CNRS 3043, Université Paris 13, UFR SMBH,
74, rue Marcel Cachin, 93017 Bobigny Cedex, France
Fax: +33-1-48387625
E-mail: marc.lecouvey@smbh.univ-paris13.fr
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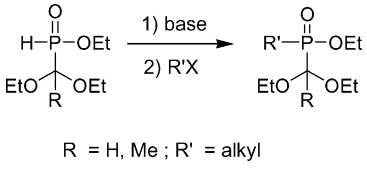
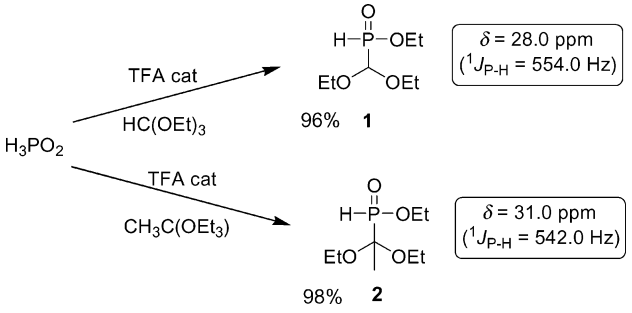
## Results and Discussion

We used the protected acid P–H synthon originally described by Gallagher and Honegger[14] to perform the first base-promoted alkylation reaction (Scheme 1).



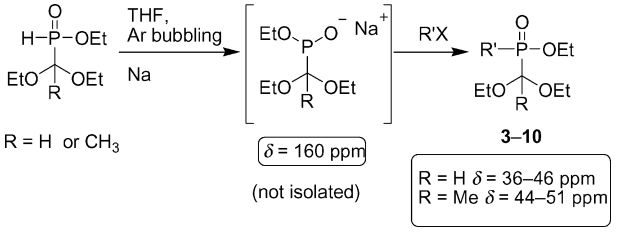

Scheme 1. Preparation of protected H-phosphinates.

This so-called Ciba-Geigy reagent is very attractive as it can easily be obtained from $H_3PO_2$ in high yield and in large quantities. Moreover, this reagent has the advantage of being safer to use than hypophosphorus acid or other pyrophoric starting materials such as bis(trimethylsiloxy)-phosphane [$(TMSO)_2PH$ also called BTSP].[13,15] The H-phosphinates **1** and **2** were prepared from anhydrous hypophosphorous acid and triethyl orthoacetate (2.2 equiv.) or triethyl orthoformate (2.2 equiv.) with TFA as catalyst (0.2 equiv.) by adapting the existing protocol (Scheme 2). The reactions were monitored by $^{31}P$ NMR and were completed after 1 or 3 hours, respectively. Note that a longer reaction time led to product degradation. The two compounds were obtained in good yields and high purity after distillation [b.p. (**1**) 75 °C (3 Torr); b.p. (**2**) 65 °C (3 Torr)]. Many examples of base-promoted H-phosphinate alkylation have been reported in the literature. The most important work was performed by Montchamp and co-workers, who described various examples of the deprotonation reaction using LDA or LHMDS and the subsequent reaction with electrophiles. These reactions were carried out simultaneously at –78 °C.[11]




Scheme 2. Preparation of H-phosphinates **1** and **2**.

In this work we preferred to form the sodium alkylphosphinate intermediate, which can react with electrophiles (Scheme 3). Montchamp and co-workers found that the use of sodium metal in the synthesis of nucleophilic phosphinate species was unsuccessful[11] probably due to competition with the Wurtz reaction as both sodium and halogenoalkanes were added together.




Scheme 3. Preparation of alkylphosphinates.

In the first step, sodium alkylphosphinates were obtained in 15 min at room temperature by the reaction of an excess of sodium metal with compound **1** or **2** in THF with argon bubbling. The reaction was monitored by $^{31}$P NMR and when the signal of the starting material had disappeared, the sodium excess was removed. Note that the reaction proceeds properly with 1 equiv. of sodium, the excess only secures completion of the reaction. The use of sodium hydride was also evaluated (1.1 equiv.), but the results were less encouraging. In the second step, alkyl halides were added at room temperature under argon. Compound **2** and the resulting sodium alkylphosphinate were slightly more reactive than compound **1** and its sodium anion. The reaction was complete in 15 min to 16 h depending on the reactivity of the electrophile and with the less reactive isopropyl bromide, heating was even necessary (Table 1). Nevertheless, with simple deoxygenation by bubbling argon through the solvent prior to reaction, no competitive oxidation of the anion took place, even when heating at reflux for 16 h. These compounds were then purified on neutral aluminium oxide because of the sensitivity of such protected alkyl phosphinates towards acids.

The next stage of the synthesis exploited the latent P–H functionality to form the second P–C bond. We explored two different pathways depending on the reactivity of the protected alkylated phosphinate intermediates **3**–**10**

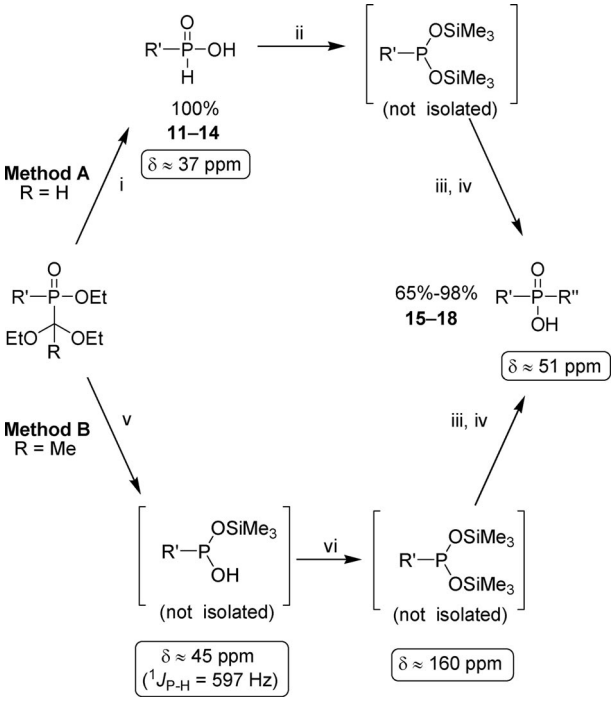
Table 1. Reaction of sodium alkylphosphinates with alkylhalides.

| Product | Conditions | R | R′X | Isolated yield [%] |
|---|---|---|---|---|
| **3** | THF, room temp., 15 min | H | $CH_3I$ | 100 |
| **4** | THF, room temp., 3 h | H | BnBr | 95 |
| **5** | THF, room temp., 10 h | H | $C_{12}H_{23}Br$ | 96 |
| **6** | THF, reflux, 16 h | H | *i*PrBr | 70 |
| **7** | THF, room temp., 15 min | $CH_3$ | $CH_3I$ | 90 |
| **8** | THF, room temp., 3 h | $CH_3$ | BnBr | 97 |
| **9** | THF, room temp., 10 h | $CH_3$ | $C_{12}H_{23}Br$ | 88 |
| **10** | THF, reflux, 16 h | $CH_3$ | *i*PrBr | 86 |

(Scheme 4). To perform the second alkylation we chose to proceed by the sila-Arbuzov reaction. When starting from alkylphosphinates with ketal protection (products **3**–**6**, method A), direct silylation was not possible irrespective of the conditions used, probably due to the greater stability of the ketal protection. Typical acidic deprotection, which quantitatively yielded the unprotected alkylphosphinic acids (**11**–**14**), was used.[16] Persilylation of these pentavalent phosphorus acids led to highly reactive P$^{III}$-silylated intermediates, which underwent the Arbuzov reaction with alkyl halides or Michael addition with methyl methacrylate. The phosphinic acids were treated with trimethylsilyl bromide (TMSBr) in the presence of triethylamine at 0 °C for 30 min. The reaction was followed by $^{31}$P NMR and when no starting material remained, the halide derivatives or methyl methacrylate was added. The reaction mixture was stirred at room temperature for 20 min to 24 h depending on the reactant. With primary alkyl halides, the reactions were rapid and efficient (Table 2) except for the reaction with dodecyl bromide. In this case the degradation (oxidation or hydrolysis) of the silylated intermediate was always quicker than the reaction with the fatty alkyl bromide. With methyl methacrylate, the reaction was slower but still gave a good yield. Although allowing the synthesis of the desired products, this method was not satisfactory as it could not be used for products bearing protection that could potentially be removed in acidic media as is often the case in the synthesis of bioactive compounds with an amino functionality. Thus, we tried to develop a "one-pot" method that does not require deprotection with mineral acids.

When starting from alkylphosphinates with ketal protection (products **7**–**10**, method B), direct silylation was possible. The partial silylation of such compounds has already been observed by various authors.[8] Such a strategy has already been documented using the BTSP approach,[15] but to the best of our knowledge complete silylation has never been described in the literature starting from such protected alkylphosphinates. However, a TMSCl/ethanol mixture was once used to fully deprotect such compounds,[8] which indicates the possibility of complete silylation. Thus, we evaluated several reaction conditions, monitoring them by $^{31}$P NMR, and we now propose the following methodology. First, the protected monoalkylphosphinate was treated with an excess of TMSBr to obtain the monosilylated H-phosphinate. The reaction was performed by bubbling argon through the solution to avoid oxidation and to slowly evap-



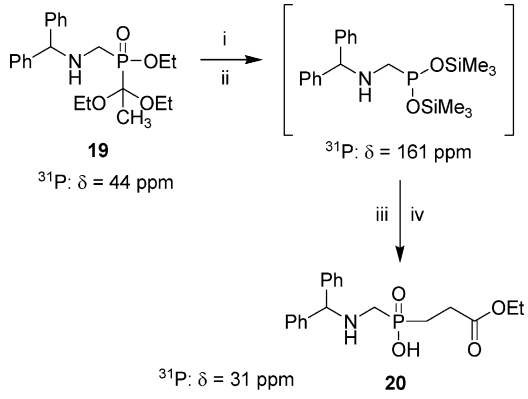

Scheme 4. Synthesis of dialkylphosphinic acids. Reagents and conditions: (i) 37% HCl, reflux, 24 h; (ii) TMSBr, $Et_3N$, DCM, 0 °C, 30 min; (iii) R′′X or $CH_2$=C($CH_3$)COOMe, 20 min to 24 h; (iv) EtOH; (v) TMSBr, DCM, 30 min; (vi) $Et_3N$.

Table 2. Synthesis of dialkylphosphinic acids (n.d. = not done).

| Entry | R′ | Electrophile | Yield [%] Method A | Method B |
|---|---|---|---|---|
| **15a** | $CH_3$ | $C_{12}H_{25}Br$ | failed | failed |
| **15b** | $CH_3$ | BnBr | 85 | failed |
| **15c** | $CH_3$ | $CH_2$=C($CH_3$)COOMe | 80 | failed |
| **16a** | Bn | $C_{12}H_{25}Br$ | failed | failed |
| **16b** | Bn | $CH_3I$ | 65 | 76 |
| **16c** | Bn | $CH_2$=C($CH_3$)COOMe | 93 | 88 |
| **16d** | Bn | $BrCH_2COOEt$ | n.d. | 86 |
| **16e** | Bn | $CH_2$=CHCOOMe | n.d. | 96 |
| **17a** | $C_{12}H_{25}$ | BnBr | 88 | 84 |
| **17b** | $C_{12}H_{25}$ | $CH_3I$ | 88 | 75 |
| **17c** | $C_{12}H_{25}$ | $CH_2$=C($CH_3$)COOMe | 92 | 81 |
| **17d** | $C_{12}H_{25}$ | $BrCH_2COOEt$ | n.d. | 98 |
| **17e** | $C_{12}H_{25}$ | $CH_2$=CHCOOMe | n.d. | 97 |
| **18a** | *i*Pr | $C_{12}H_{25}Br$ | failed | failed |
| **18b** | *i*Pr | BnBr | 75 | 70 |
| **18c** | *i*Pr | $CH_3I$ | 89 | 95 |
| **18d** | *i*Pr | $CH_2$=C($CH_3$)COOMe | 76 | 82 |
| **18e** | *i*Pr | $BrCH_2COOEt$ | n.d. | 92 |
| **18f** | *i*Pr | $CH_2$=CHCOOMe | n.d. | 85 |

orate the ethyl bromide formed. When no starting material remained, triethylamine was added to the mixture to allow further silylation. Neither of the silylated intermediates was isolated, but their formation was assessed before the next stage. Finally, the bromide derivatives or methyl methacrylate was added and the reaction was stirred for 20 min to 24 h depending on the reactant (Table 2). As before, the reactions were efficient. Methyl methacrylate was still less reactive than the other reactants, but when the more reactive methyl acrylate was used the reaction worked readily without the formation of oxidation products. Once again dodecyl bromide failed to react. We also evaluated the use of ethyl bromoacetate, which was less reactive than benzyl bromide but it still reacted efficiently. The silylation of the protected methylphosphinate **7** was also efficient but the bis(trimethylsilyl) methylphosphonite, although detected by $^{31}P$ NMR ($\delta$ = 165 ppm), was too volatile (b.p. < 20 °C) and evaporated before reacting under argon.

Finally we applied the conditions of method B to the synthesis of a dialkylphosphinic acid with an amino functionality (Scheme 5). Usually such compounds are obtained by using a methodology that requires several protection and deprotection steps both for the amine and the phosphinate. Moreover, depending on the amine protecting group used when synthesizing such pseudo-peptides, pseudo-diketopiperazine was formed.[10] Here, we chose to use compound **19**, a [(diphenylmethyl)amino]methylenephosphinate protected as a ketal, as the starting material. It was easily obtained, as already described, from the reaction of triazinane with compound **2**. A previous report has already shown the compatibility of nitrogen in sila-Arbuzov chemistry.[17] The addition to **19** under argon bubbling of, successively, TMSBr and $Et_3N$ readily yielded the silylated intermediate, which then reacted at room temperature with ethyl bromopropionate to afford compound **20** in 70% yield.




Scheme 5. Synthesis of α-aminophosphinic acid **20**. Reagents and conditions: (i) TMSBr, DCM, 30 min; (ii) $Et_3N$; (iii) ethyl bromopropionate 24 h; (iv) EtOH.

## Conclusions

We have reported the novel synthesis of unsymmetrical dialkylphosphinic acids from the protected acid P–H synthon under mild conditions. The first P–C bond formation was easily achieved by a base-promoted H-phosphinate alkylation methodology. For the formation of the second P–C bond, a "one-pot" methodology based on the sila-Arbuzov reaction was developed. This mild methodology is applicable to the production of a dialkylphosphinic with an amino functionality. Further investigations exploring the synthesis of more functionalized products will be reported in due course.

## Experimental Section

**General:** All reagents used in the reactions described in this manuscript are commercial and were used without purification, except for methyl methacrylate, which was distilled just before the reaction. The phosphinic acid was purchased from Aldrich as an aqueous solution and dehydrated under vacuum by heating the solution at 30 °C. Particular care was taken when heating this solution as phosphinic acid readily decomposes to give pyrophoric byproducts. The solvents used were distilled in the presence of the drying agents listed below. Tetrahydrofuran was distilled from sodium and benzophenone, dichloromethane and acetonitrile were distilled from $P_2O_5$, and toluene was distilled from sodium. NMR spectra were recorded with Varian Unity Inova 500 ($^{13}$C: 125.9 MHz; $^{1}$H: 500.6 MHz) and Gemini 200 ($^{31}$P: 80.9 MHz) spectrometers. The chemical shifts are given in parts per million (ppm) on the $\delta$ scale. The solvent peak was used as a reference value ($^{1}$H NMR: $CDCl_3$ 7.26 ppm, $CD_3OD$ 3.31 ppm, $D_2O$ 4.79 ppm; $^{13}$C NMR: $CDCl_3$ 77.2 ppm, $CD_3OD$ 49.0 ppm). The data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, and br. = broad). $^{31}$P NMR spectra were recorded with phosphoric acid (85%) as the external reference. High- and low-resolution mass spectra were recorded with a MALDI-TOF mass spectrometer (Biflex IV, Bruker Daltonique) with 2,5-dihydroxybenzoic acid as the matrix. The IR spectra were recorded by using a Nicolet FTIR 380 spectrometer. All melting points were measured by using a Stuart SMP3 melting point apparatus and are uncorrected. It proved difficult to obtain reliable elemental analytical data for most of the compounds, which were very hygroscopic. Flash chromatography was performed on neutral alumina oxide using reagent-grade ethyl acetate and hexane. All reactions were performed in flame-dried glassware under argon with magnetic stirring unless otherwise noted.

**Synthesis of Phosphinates 1 and 2:** TFA (0.2 equiv.) was added to the anhydrous phosphinic acid (0.15 mol; 10 g) followed by triethyl orthoformate (2.2 equiv.) or triethyl orthoacetate (2.2 equiv.). The mixture was stirred at room temperature (R = $CH_3$: 1 h; R = H: 3 h). The solution was then concentrated under reduced pressure, taken up in $CHCl_3$, and washed with saturated aqueous $NaHCO_3$. The combined organic layers were dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was distilled under reduced pressure.

**Ethyl (Diethoxymethyl)phosphinate (1):** Colorless oil; b.p. 75 °C/3 Torr; yield 28.21 g, 96%. $^{1}$H NMR (500.9 MHz, $CDCl_3$): $\delta$ = 1.24 (t, $^{3}J_{H,H}$ = 7.2 Hz, 6 H, $COCH_2CH_3$), 1.38 (t, $^{3}J_{H,H}$ = 7.2 Hz, 3 H, $POCH_2CH_3$), 3.62–3.81 (br., 4 H, $COCH_2CH_3$), 4.23 (q, $^{3}J_{H,H}$ = 7.5 Hz, 2 H, $POCH_2CH_3$), 4.70 (d, $^{2}J_{P,H}$ = 9.0 Hz, 1 H, CH), 6.90 (d, $^{1}J_{P,H}$ = 554.0 Hz, 1 H, PH) ppm. $^{13}$C NMR {$^{1}$H} (125.9 MHz, $CDCl_3$): $\delta$ = 100.4 (d, $^{1}J_{P,C}$ = 154.0 Hz, CH), 65.6 (s, $POCH_2$), 63.2 (s, $COCH_2$), 16.5 (s, $COCH_2CH_3$), 15.3 (s, $POCH_2CH_3$) ppm. $^{31}$P NMR (80.9 MHz, $CDCl_3$): $\delta$ = 28 (dd, $^{2}J_{P,H}$ = 9.0, $^{1}J_{P,H}$ = 554.0 Hz) ppm.

**Ethyl (1,1-Diethoxyethyl)phosphinate (2):** Clear and colorless oil; b.p. 65 °C/3 Torr; yield 31.03 g, 98%. $^{1}$H NMR (500.9 MHz, $CDCl_3$): $\delta$ = 1.18 (br., 6 H, $COCH_2CH_3$), 1.34 (t, $^{3}J_{H,H}$ = 7.5 Hz, 3 H, $POCH_2CH_3$), 1.46 (d, $^{3}J_{P,H}$ = 16.0 Hz, 3 H, $CH_3$), 3.73–3.62 (br., 4 H, $COCH_2CH_3$), 4.19–4.16 (br., 2 H, $POCH_2CH_3$), 6.90 (d, $^{1}J_{P,H}$ = 549.0 Hz, 1 H, PH) ppm. $^{13}$C NMR {$^{1}$H} (125.9 MHz, $CDCl_3$): $\delta$ = 15.5 ($COCH_2CH_3$), 16.5 ($POCH_2CH_3$), 19.1 (d, $^{2}J_{P,C}$ = 12.5 Hz, $CH_3$), 57.9 (d, $^{3}J_{P,C}$ = 6.3 Hz, $COCH_2$), 63.8 ($POCH_2$), 101.0 (d, $^{1}J_{P,C}$ = 145.5 Hz, C) ppm. $^{31}$P NMR (80.9 MHz, $CDCl_3$): $\delta$ = 28 (dd, $^{2}J_{P,H}$ = 9.0, $^{1}J_{P,H}$ = 554.0 Hz) ppm.

**General Method for the Synthesis of Alkylphosphinates:** Sodium metal, in large excess, was added to the phosphinate (1 equiv., 30 mmol) in dried THF (50 mL) under argon bubbling. The reaction was monitored by $^{31}$P NMR and when the signal of the starting material had disappeared, the sodium excess was removed. The bromide compound was added dropwise. Reaction completion was obtained in 15 min to 16 h depending on the reactivity of the electrophile. Heating (50 °C) for 12 h was even necessary with the less reactive isopropyl bromide. The solvent was removed under reduced pressure and the mixture was taken up in $CHCl_3$. The organic layer was washed with saturated aqueous $NaHCO_3$, dried with $MgSO_4$, filtered, and evaporated under reduced pressure.

**Ethyl (Diethoxymethyl)methylphosphinate (3):** Clear oil; yield 6.29 g, 100%. $^{1}$H NMR (500.9 MHz, $CDCl_3$): $\delta$ = 1.32 (br., 9 H, $OCH_2CH_3$), 1.48 (d, $^{2}J_{PH}$ = 16.0 Hz, 3 H, $PCH_3$), 3.62–4.00 (br., 4 H, $CHOCH_2CH_3$), 4.18 (br., 2 H, $POCH_2CH_3$), 4.65 (d, $^{2}J_{P,H}$ = 6.0 Hz, 1 H, PCH) ppm. $^{13}$C NMR {$^{1}$H} (125.9 MHz, $CDCl_3$): $\delta$ = 10.8 (d, $^{1}J_{P,C}$ = 94.1 Hz, $PCH_3$), 15.3 ($POCH_2CH_3$), 16.8 ($POCH_2CH_3$), 61.4 ($CHOCH_2CH_3$), 65.5 ($POCH_2CH_3$), 101 (d, $^{1}J_{P,C}$ = 145.5 Hz, PCH) ppm. $^{31}$P NMR {$^{1}$H} (80.9 MHz, $CDCl_3$): $\delta$ = 39 ppm.

**Ethyl Benzyl(diethoxymethyl)phosphinate (4):** Clear oil; yield 8.15 g, 95%. $^{1}$H NMR (500.9 MHz, $CDCl_3$): $\delta$ = 1.24 (br., 9 H, $CH_3$), 3.20 (d, $^{2}J_{P,H}$ = 12.1 Hz, 2 H, $PCH_2$), 3.57–3.86 (br., 4 H, $COCH_2CH_3$), 4.08 (br., 2 H, $POCH_2CH_3$), 4.57 (d, $^{2}J_{P,H}$ = 6.0 Hz, 1 H, CH), 7.29 (s, 5 H, $C_6H_5$) ppm. $^{13}$C NMR {$^{1}$H} (125.9 MHz, $CDCl_3$): $\delta$ = 15.3 ($CH_3$), 16.7 ($CH_3$), 33.6 (d, $^{1}J_{P,C}$ = 84.1 Hz, $CH_2$), 62.0 ($COCH_2$), 65.4 ($POCH_2$), 100.0 (d, $^{1}J_{P,C}$ = 144.3 Hz, C), 126.8, 128.6, 130.2, 131.0 ($C_6H_5$) ppm. $^{31}$P NMR {$^{1}$H} (80.9 MHz, $CDCl_3$): $\delta$ = 40 ppm.

**Ethyl (Diethoxymethyl)dodecylphosphinate (5):** Fluid and colorless oil; yield 10.49 g, 96%. $^{1}$H NMR (500.9 MHz, $CDCl_3$): $\delta$ = 0.84 [t, $^{3}J_{H,H}$ = 6.0 Hz, 3 H, $CH_3(CH_2)_{10}$], 1.19–1.32 [br., 29 H, $CH_3(CH_2)_{10}$, $OCH_2CH_3$], 1.63 (d, $^{2}J_{P,H}$ = 6.0 Hz, 1 H, PCH), 1.80 (td, $^{2}J_{P,H}$ = 6.0, $^{3}J_{H,H}$ = 8.2 Hz, 2 H, $PCH_2$), 3.91–3.37 (br., 4 H, $CHOCH_2CH_3$), 4.25–4.07 (br., 2 H, $POCH_2CH_3$) ppm. $^{13}$C NMR {$^{1}$H} (125.9 MHz, $CDCl_3$): $\delta$ = 14.1 [$CH_3(CH_2)_{10}$], 15.2 ($OCH_2CH_3$), 16.7 ($OCH_2CH_3$), 25.4 (d, $^{1}J_{P,C}$ = 89.1 Hz, $PCH_2$), 29.1 [$CH_3(CH_2)_{10}$], 29.3 [$CH_3(CH_2)_{10}$], 29.6 [$CH_3(CH_2)_{10}$], 30.9 [$CH_3(CH_2)_{10}$], 31.9 [$CH_3(CH_2)_{10}$], 61.3 ($CHOCH_2CH_3$), 65.3 ($POCH_2CH_3$), 101.0 (d, $^{1}J_{P,C}$ = 140.5 Hz, PCH) ppm. $^{31}$P NMR {$^{1}$H} (80.9 MHz, $CDCl_3$): $\delta$ = 46 ppm.

**Ethyl (Diethoxymethyl)isopropylphosphinate (6):** Blue oil; yield 5.00 g, 70%. $^{1}$H NMR (500.9 MHz, $CDCl_3$): $\delta$ = 0.90–1.18 (br., 15 H, $CH_3CHP$, $OCH_2CH_3$), 1.91 (br., 1 H, $CH_3CHP$), 3.53 (br., 2 H, $CHOCH_2CH_3$), 3.71 (br., 2 H, $CHOCH_2CH_3$), 4.05 (br., 2 H, $POCH_2CH_3$), 4.58 (d, $^{2}J_{P,H}$ = 10.2 Hz, 1 H, PCH) ppm. $^{13}$C NMR {$^{1}$H} (125.9 MHz, $CDCl_3$): $\delta$ = 15.0 ($CH_3CHP$), 15.3 ($CHOCH_2CH_3$), 16.7 ($POCH_2CH_3$), 25.5 (d, $^{1}J_{P,C}$ = 89.1 Hz, $CH_3CHP$), 61.4 ($POCH_2CH_3$), 65.1 ($CHOCH_2CH_3$), 65.4 ($CHOCH_2CH_3$), 101.0 (d, $^{1}J_{P,C}$ = 135.5 Hz, $PCHOCH_2CH_3$) ppm. $^{31}$P NMR {$^{1}$H} (80.9 MHz, $CDCl_3$): $\delta$ = 36 ppm.

**Ethyl Methyl(1,1-diethoxyethyl)phosphinate (7):** Colorless oil; yield 6.07 g, 90%. $^{1}$H NMR (500.9 MHz, $CDCl_3$): $\delta$ = 1.14–1.16 (br., 6 H, $PCOCH_2CH_3$), 1.26 (t, $^{3}J_{H,H}$ = 7.1 Hz, 3 H, $POCH_2CH_3$), 1.4 (d, $^{3}J_{P,H}$ = 15.2 Hz, 3 H, $PCCH_3$), 1.43 (d, $^{2}J_{P,H}$ = 16.1 Hz, 3 H, $PCH_3$), 3.58–3.66 (br., 4 H, $PCHOCH_2CH_3$), 4.11–4.21 (br., 2 H, $POCH_2CH_3$) ppm. $^{13}$C NMR {$^{1}$H} (125.9 MHz, $CDCl_3$): $\delta$ = 11.7 (d, $^{1}J_{P,C}$ = 87.8 Hz, $PCH_3$), 15.5 and 16.5 ($PCOCH_2CH_3$), 16.8 (d, $^{3}J_{P,C}$ = 6.3 Hz, $POCH_2CH_3$), 20.5 (d, $^{2}J_{P,C}$ = 11.3 Hz, $PCCH_3$), 57.8 and 58.1 (d, $^{3}J_{P,C}$ = 12.5 Hz, $PCOCH_2CH_3$), 61.6 (d, $^{2}J_{P,C}$ =

5.2 Hz, PO*C*H$_2$CH$_3$), 101.0 (d, $^1J_{P,C}$ = 142.7 Hz, P*C*CH$_3$) ppm. $^{31}$P NMR {$^1$H} (80.9 MHz, CDCl$_3$): $\delta$ = 46 ppm.

**Ethyl (1,1-Diethoxyethyl)benzylphosphinate (8):** Clear oil; yield 8.79 g, 97%. $^1$H NMR (500.9 MHz, CDCl$_3$): $\delta$ = 1.16–1.23 (br., 6 H, COCH$_2$C*H*$_3$), 1.29 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, COCH$_2$C*H*$_3$), 1.40 (d, $^3J_{P,H}$ = 15.3 Hz, 3 H, C*H*$_3$), 3.15 (d, $^2J_{P,H}$ = 16.0 Hz, 2 H, C*H*$_2$), 3.55–3.68 (br., 4 H, COC*H*$_2$CH$_3$), 3.95–4.11 (br., 2 H, POC*H*$_2$CH$_3$), 7.22–7.26 (br., 5 H, C$_6$*H*$_5$) ppm. $^{13}$C NMR {$^1$H} (125.9 MHz, CDCl$_3$): $\delta$ = 15.4 (COCH$_2$*C*H$_3$), 16.6 (POCH$_2$*C*H$_3$), 19.1 (d, $^2J_{P,C}$ = 12.6 Hz, PC*C*H$_3$), 33.8 (d, $^2J_{P,C}$ = 75.3 Hz, *C*H$_2$), 58.0 (CO*C*H$_2$), 61.9 (PO*C*H$_2$), 101.4 (d, $^1J_{P,C}$ = 140.2 Hz, *C*), 126.9, 128.5, 130.4, 131.5 (*C*$_6$H$_5$) ppm. $^{31}$P NMR {$^1$H} (80.9 MHz, CDCl$_3$): $\delta$ = 44 ppm.

**Ethyl (1,1-Diethoxyethyl)dodecylphosphinate (9):** Clear oil; yield 10.04 g, 88%. $^1$H NMR (500.9 MHz, CDCl$_3$): $\delta$ = 0.80 [t, $^3J_{H,H}$ = 7.2 Hz, 3 H, C*H*$_3$(CH$_2$)$_{10}$], 1.11–1.32 [br., 29 H, CH$_3$(C*H*$_2$)$_{10}$, OCH$_2$C*H*$_3$], 1.42 (d, $^2J_{P,H}$ = 16.1 Hz, 2 H, PC*H*$_2$), 3.55–3.68 (br., 4 H, PCOC*H*$_2$CH$_3$), 3.95–4.11 (m, 2 H, POC*H*$_2$CH$_3$) ppm. $^{13}$C NMR {$^1$H} (125.9 MHz, CDCl$_3$): $\delta$ = 14.3 [CH3(CH$_2$)$_{10}$], 15.4 (PCOCH$_2$*C*H$_3$), 16.6 (POCH$_2$*C*H$_3$), 29.3–29.7 [CH$_3$(*C*H$_2$)$_{10}$], 20.7 (d, $^2J_{P,C}$ = 13.5 Hz, PC*C*H$_3$), 31.1 (d, $^2J_{P,C}$ = 75.3 Hz, P*C*H$_2$), 57.6 (PCO*C*H$_2$CH$_3$), 61.9 (PO*C*H$_2$CH$_3$), 101.4 ($^1J_{P,C}$ = 140.0 Hz, P*C*OCH$_2$CH$_3$) ppm. $^{31}$P NMR {$^1$H} (80.9 MHz, CDCl$_3$): $\delta$ = 49 ppm.

**Ethyl (1,1-Diethoxyethyl)isopropylphosphinate (10):** Colorless oil; yield 6.55 g, 86%. $^1$H NMR (500.9 MHz, CDCl$_3$): $\delta$ = 1.03–1.28 [br., 15 H, OCH$_2$C*H*$_3$, (C*H*$_3$)$_2$CHP], 1.44 (d, $^3J_{P,H}$ = 16.0 Hz, 3 H, PCC*H*$_3$), 1.86–2.02 (br., 1 H, CH$_3$C*H*P), 3.56–3.79 (br., 4 H, PCOC*H*$_2$CH$_3$), 4.01–4.28 (br., 2 H, POC*H*$_2$CH$_3$) ppm. $^{13}$C NMR {$^1$H} (125.9 MHz, CDCl$_3$): $\delta$ = 15.4 (PCOCH$_2$*C*H$_3$), 15.6 (PCOCH$_2$*C*H$_3$), 15.8 (*C*H$_3$CHP), 16.0 (*C*H$_3$CHP), 16.8 (POCH$_2$*C*H$_3$), 20.8 (d, $^2J_{P,C}$ = 11.3 Hz, PC*C*H$_3$), 26.0 (d, $^1J_{P,C}$ = 87.8 Hz, CH$_3$*C*HP), 57.6 (PCO*C*H$_2$CH$_3$), 58.2 (PCO*C*H$_2$CH$_3$); 61.5 (PO*C*H$_2$CH$_3$), 101.7 (d, $^1J_{P,C}$ = 133.0 Hz, P*C*CH$_3$) ppm. $^{31}$P NMR {$^1$H} (80.9 MHz, CDCl$_3$): $\delta$ = 51 ppm.

**General Method for the Synthesis of Alkylphosphinic Acids:** A suspension of alkylphosphinate (20 mmol) in HCl solution (50 mL, 12 M) was heated at reflux for 24 h. The mixture was coevaporated with water (3 × 100 mL) under reduced pressure. The residue was then dried under high vacuum at 50 °C for 24 h.

**Methylphosphinic Acid (11):** Clear oil and colorless; yield 1.6 g, 100%. $^1$H NMR (500.9 MHz; D$_2$O): $\delta$ = 1.50 (d, $^2J_{P,H}$ = 6.0 Hz, 3 H, PC*H*$_3$), 7.15 (d, $^1J_{P,H}$ = 554.9 Hz, 1 H, P*H*), 12.23 (s, 1 H, O*H*) ppm. $^{13}$C NMR {$^1$H} (125.9 MHz; D$_2$O): $\delta$ = 22.4 (d, $^1J_{P,C}$ = 87.2 Hz) ppm. $^{31}$P NMR (80.9 MHz; D$_2$O): $\delta$ = 35 (dd, $^1J_{P,H}$ = 554.9, $^2J_{P,H}$ = 6.0 Hz) ppm. HRMS: calcd. for [MH]$^+$ 81.0; found 80.8.

**Benzylphosphinic Acid (12):** Colorless oil; yield 3.12 g, 100%. $^1$H NMR (500.9 MHz, CDCl$_3$): $\delta$ = 3.10 (d, $^2J_{P,H}$ = 16.0 Hz, 2 H, C*H*$_2$), 6.92 (d, $^1J_{P,H}$ = 559.0 Hz, 1 H, P*H*), 7.27 (br., 5 H, C$_6$*H*$_5$), 9.87 (s, 1 H, PO*H*) ppm. $^{13}$C NMR {$^1$H} (125.9 MHz, CDCl$_3$): $\delta$ = 37.0 (d, $^1J_{P,C}$ = 89.10 Hz, *C*H$_2$), 127.6, 129.2, 130.0, 130.1 (*C*$_6$H$_5$) ppm. $^{31}$P NMR (80.9 MHz, CDCl$_3$): $\delta$ = 35 (d, $^1J_{P,H}$ = 554.9, $^2J_{P,H}$ = 16.0 Hz) ppm. HRMS: calcd. for [MH]$^+$ 157.03; found 157.02.

**Dodecylphosphinic Acid (13):** White solid; yield 4.68 g, 100%. $^1$H NMR (500.9 MHz, CDCl$_3$): $\delta$ = 0.85 [t, $^3J_{H,H}$ = 6.9 Hz, 3 H, C*H*$_3$(CH$_2$)$_{10}$], 1.23 [br., 20 H, CH$_3$(C*H*$_2$)$_{10}$], 1.78 (br., 2 H, C*H*$_2$P), 7.21 (d, $^1J_{P,H}$ = 559.0 Hz, 1 H, P*H*), 7.97 (s, 1 H, O*H*) ppm. $^{13}$C NMR {$^1$H} (125.9 MHz, CDCl$_3$): $\delta$ = 14.2 [*C*H$_3$(CH$_2$)$_{10}$], 20.7 (*C*H$_2$CH$_2$CH$_2$P), 22.8 (CH$_3$*C*H$_2$), 29.3 (*C*H$_2$CH$_2$P), 29.5 [CH$_3$CH$_2$(C*H*$_2$)$_6$], 29.7 [CH$_3$CH$_2$(C*H*$_2$)$_6$], 29.8 [CH$_3$CH$_2$(C*H*$_2$)$_6$], 30.5 (d, $^1J_{P,C}$ = 16.8 Hz, *C*H$_2$P), 32.1 (PCH$_2$CH$_2$*C*H$_2$) ppm. $^{31}$P NMR (80.9 MHz, CDCl$_3$): $\delta$ = 39 (d, $^1J_{P,H}$ = 542.8 Hz) ppm. HRMS: calcd. for [MH]$^+$ 235.17; found 235.20.

**Isopropylphosphinic Acid (14):** Blue oil; yield 1.76 g, 100%. $^1$H NMR (500.9 MHz, CDCl$_3$): $\delta$ = 1.12 (dd, $^3J_{H,H}$ = 20.1, $^3J_{P,H}$ = 50.0 Hz, 6 H, C*H*$_3$), 1.88 (br., 1 H, C*H*), 6.85 (d, $^1J_{P,H}$ = 550.2 Hz, 1 H, P*H*) ppm. $^{13}$C NMR {$^1$H} (125.9 MHz, CDCl$_3$): $\delta$ = 14.0 (*C*H$_3$), 27.5 [d, $^1J$(P,C) = 95.3 Hz, *C*H] ppm. $^{31}$P NMR (80.9 MHz, CDCl$_3$): $\delta$ = 44 (d, $^1J_{P,H}$ = 550.5 Hz) ppm. HRMS: calcd. for [MH]$^+$ 109.3; found 109.17.

**General Method for the Synthesis of Dialkylphosphinic Acids. Method A:** Triethylamine (3 equiv.) and bromotrimethylsilane (3 equiv.) were added under Ar to an ice-cold solution of alkylphosphinic acid (20 mmol) in dry $CH_2Cl_2$ (10 mL). The mixture was stirred for 30 min at 0 °C. The bromide derivative (1 equiv.) was then added dropwise. The solution was stirred at room temperature for 20 min to 24 h depending on the alkyl bromide. The mixture was cooled to 0 °C and absolute ethanol was added to quench the reaction. After 30 min, the solvent was removed and the residue was taken up in distilled water and extracted with ethyl acetate. The organic layer was dried under $MgSO_4$, filtered, and evaporated under reduced pressure to give the crude product.

**Method B:** Bromotrimethylsilane (7 equiv.) was added to the alkylphosphinate (20 mmol) in acetonitrile (20 mL) under argon bubbling. Triethylamine (2 equiv.) was added, followed 5 min later by the bromide derivative (1 equiv.). The mixture was cooled to 0 °C and absolute ethanol was added to quench the reaction. After 30 min, the solvent was removed and the residue was taken up in distilled water and extracted with ethyl acetate. The organic layer was dried under $MgSO_4$, filtered, and evaporated under reduced pressure to give the crude product.

**Benzyl(methyl)phosphinic Acid (15b or 16b):** The product was taken up in water (20 mL) and washed with diethyl ether (3 × 20 mL) and submitted to reversed-phase column chromatography (water/methanol, 1:1). $R_f$ = 0.88. White solid; yield 2.21 g, 65% (Method A); 2.58 g, 76% (Method B). $^1$H NMR (500.9 MHz, CDCl$_3$): $\delta$ = 1.26 (d, $^2J_{P,H}$ = 12.2 Hz, 3 H, C*H*$_3$), 3.03 (d, $^2J_{P,H}$ = 18.0 Hz, 2 H, C*H*$_2$), 7.24 (s, 5 H, C$_6$*H*$_5$), 9.76 (s, 1 H, PO*H*) ppm. $^{13}$C NMR {$^1$H} (125.9 MHz, CDCl$_3$): $\delta$ = 14.2 (d, $^1J_{P,C}$ = 95.4 Hz, *C*H$_3$), 38.8 (d, $^1J_{P,C}$ = 87.8 Hz, *C*H$_2$), 127.0, 128.8, 129.9, 130.0 (*C*$_6$H$_5$) ppm. $^{31}$P NMR {$^1$H} (80.9 MHz, CDCl$_3$): $\delta$ = 54 ppm.

**Methyl 3-[Hydroxy(methyl)phosphinoyl]-2-methylpropionate (15c):** Purification: the mixture is taken up in water (20 mL) and washed with diethyl ether (3 × 20 mL) and subjected to reversed-phase column chromatography (100% water). $R_f$ = 0.65. White solid; yield 2.88 g, 80% (Method A). $^1$H NMR (500.9 MHz, CDCl$_3$): $\delta$ = 1.26 (d, $^3J_{H,H}$ = 6.0 Hz, 3 H, PCH$_2$CHC*H*$_3$), 1.44 (d, $^2J_{P,H}$ = 16.0 Hz, 3 H, PC*H*$_3$), 1.76 (qt, $^3J_{H,H}$ = 7.5, $^3J_{H,H}$ = 6.5 Hz, 1 H, PCH$_2$C*H*), 2.28 (br., 1 H, PC*H*$_2$), 2.85 (br., 1 H, PC*H*$_2$), 3.66 (s, 3 H, OC*H*$_3$), 10.77 (s, 1 H, O*H*) ppm. $^{13}$C NMR {$^1$H} (125.9 MHz, CDCl$_3$): $\delta$ = 15.8 (d, $^1J_{P,C}$ = 94.1 Hz, P*C*H$_3$), 19.2 (d, $^3J_{P,C}$ = 10.0 Hz, PCH$_2$CH*C*H$_3$), 34.12 (d, $^1J_{P,C}$ = 102.9 Hz, P*C*H$_2$), 34.13 (PCH$_2$*C*H), 52.2 (O*C*H$_3$), 176.1 (*C*OOCH$_3$) ppm. $^{31}$P NMR {$^1$H} (80.9 MHz, CDCl$_3$): $\delta$ = 56 ppm.

**Methyl 3-[Benzyl(hydroxy)phosphinoyl]-2-methylpropionate (16c):** The product was purified by column chromatography (60 Å silica gel) using hexane/ethyl acetate (2:8) as eluent. $R_f$ = 0.84. Colorless oil; yield 4.76 g, 93% (Method A); 4.50 g, 88% (Method B). $^1$H NMR (500.9 MHz, CDCl$_3$): $\delta$ = 1.21 (d, $^3J_{H,H}$ = 7.2 Hz, 3 H, C*H*$_3$), 1.76 (td, $^3J_{H,H}$ = 7.1, $^3J_{H,H}$ = 7.2 Hz, 1 H, C*H*), 2.28 (br., 1 H,

$CH_2CH$), 2.85 (br., 1 H, $CH_2CH$), 3.02 (d, $^2J_{P,H}$ = 17.4 Hz, 2 H, $CH_2C_6H_5$), 3.63 (s, 3 H, $OCH_3$), 7.21–7.27 (br., 5 H, $C_6H_5$), 9.12 (s, 1 H, PO*H*) ppm. $^{13}C$ NMR {$^1H$} (125.9. $CDCl_3$): $\delta$ = 19.0 ($CH_3$), 31.3 (d, $^1J_{P,C}$ = 94.1 Hz, $CH_2C_6H_5$), 33.7 (C*H*), 38.0 (d, $^1J_{P,C}$ = 87.8 Hz, $CH_2CH$), 52.2 ($OCH_3$), 127.0, 128.8, 130.0, 131.6 ($C_6H_5$), 176.1 (*C*O) ppm. $^{31}P$ NMR {$^1H$} (80.9 MHz, $CDCl_3$): $\delta$ = 53 ppm.

**Benzyl(2-ethoxy-2-oxoethyl)phosphinic Acid (16d):** The mixture was taken up in water(40 mL) and washed with diethyl ether (3 × 40 mL) and the product was extracted with ethyl acetate (3 × 40 mL). The organic phase was dried with $MgSO_4$, filtered, and evaporated under reduced pressure. Colorless oil; yield 4.16 g, 86% (Method B). $^1H$ NMR (500.9 MHz, $CDCl_3$): $\delta$ = 1.27 (t, $^3J_{H,H}$ = 6.5 Hz, 3 H, $OCH_2CH_3$), 2.76 (d, $^1J_{P,H}$ = 17.5 Hz, 2 H, $PCH_2Ph$), 3.25 (d, $^1J_{P,H}$ = 18.5 Hz, 2 H, $PCH_2CO$), 4.18 (q, $^3J_{HH}$ = 7.5 Hz, 2 H, $OCH_2CH_3$), 7.28 (br., 5 H, $C_6H_5$) ppm. $^{13}C$ NMR {$^1H$} (125.9 MHz, $CDCl_3$): $\delta$ = 13.4 ($OCH_2CH_3$), 35.0 ($^1J_{P,C}$ = 131.0 Hz, $PCH_2Ph$), 35.7 ($^1J_{P,C}$ = 138.7 Hz, $PCH_2CO$), 60.9 ($OCH_2CH_3$), 126.4–130.4 ($C_6H_5$), 165.7 (*C*O) ppm. $^{31}P$ NMR {$^1H$} (80.9 MHz, $CDCl_3$): $\delta$ = 45.7 ppm.

**Methyl 3-[Benzyl(hydroxy)phosphinoyl]propionate (16e):** The mixture was taken up in water (40 mL) and washed with diethyl ether (3 × 40 mL) and the product was extracted with ethyl acetate (3 × 40 mL). The organic phase was dried with $MgSO_4$, filtered, and evaporated under reduced pressure. Colorless oil; yield 4.18 g, 96% (Method B). $^1H$ NMR (500.9 MHz, $CDCl_3$): $\delta$ = 1.92 (m, 2 H, $PCH_2CH_2$), 2.50 (m, 2 H, $PCH_2CH_2$), 3.07 (d, $^1J_{P,H}$ = 17.0 Hz, 2 H, $PCH_2Ph$), 3.68 (s, 3 H, $OCH_3$), 7.28 (br., 5 H, $C_6H_5$), 9.10 (s, 1 H, O*H*) ppm. $^{13}C$ NMR {$^1H$} (125.9 MHz, $CDCl_3$): $\delta$ = 23.3 (d, $^1J_{P,C}$ = 95.6 Hz, $PCH_2CH_2$), 26.3 ($PCH_2CH_2$), 37.5 (d, $^1J_{P,C}$ = 88.1 Hz, $PCH_2Ph$), 52.2 ($OCH_3$), 127.2–131.5 ($C_6H_5$), 173.0 (*C*O) ppm. $^{31}P$ NMR {$^1H$} (80.9 MHz, $CDCl_3$): $\delta$ = 53 ppm.

**Benzyl(dodecyl)phosphinic Acid (17a):** The mixture was taken up in water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic phase was dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The product was precipitated in diethyl ether. White solid; yield 5.41 g, 88% (Method A); 5.16 g, 84% (Method B). $^1H$ NMR (500.9 MHz, $CDCl_3$): $\delta$ = 0.86 [t, $^3J_{H,H}$ = 7.5 Hz, 3 H, $CH_3(CH_2)_{10}$], 1.23 [br., 20 H, $CH_3(CH_2)_{10}$], 1.50 [br., 2 H, $PCH_2(CH_2)_{10}$], 3.01 (d, $^2J_{P,H}$ = 20.0 Hz, 2 H, $PCH_2Ph$), 6.92 (br., 1 H, *OH*), 7.24 (br., 5 H, $C_6H_5$) ppm. $^{13}C$ NMR {$^1H$} (125.9 MHz, $CDCl_3$): $\delta$ = 14.3 [$CH_3(CH_2)_{10}$], 21.5 ($PCH_2CH_2CH_2$), 22.8 ($CH_3CH_2$), 28.8 [d, $^1J_{P,C}$ = 130.6 Hz, $PCH_2(CH_2)_{10}$], 29.5 and 29.8 [$CH_3CH_2CH_2(CH_2)_6$], 30.8 (d, $^2J_{P,C}$ = 16.0 Hz, $PCH_2CH_2$), 32.1 ($CH_3CH_2CH_2$), 37.3 (d, $^1J_{P,C}$ = 86.5 Hz, $PCH_2Ph$), 126.9–132.1 ($C_6H_5$) ppm. $^{31}P$ NMR {$^1H$} (80.9 MHz, $CDCl_3$): $\delta$ = 56 ppm.

**Dodecyl(methyl)phosphinic Acid (17b):** The mixture was taken up in water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic phase was dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The product was precipitated in diethyl ether. White solid; yield 4.37 g, 88% (Method A); 3.72 g, 75% (Method B). $^1H$ NMR (500.9 MHz, $CDCl_3$): $\delta$ = 0.85 (t, $^3J_{H,H}$ = 6.9 Hz, 3 H, $CH_3CH_2$), 1.22–1.37 [br., 18 H, $CH_3(CH_2)_9$], 1.43 (d, $^2J_{P,H}$ = 16.2 Hz, 3 H, $PCH_3$), 1.56 (br., 2 H, $PCH_2CH_2$), 1.68 (br., 2 H, $PCH_2$), 6.90 (br., 1 H, O*H*) ppm. $^{13}C$ NMR {$^1H$} (125.9 MHz, $CDCl_3$): $\delta$ = 14.3 [$CH_3(CH_2)_{10}$], 15.6 (d, $^1J_{P,C}$ = 101.4 Hz, $PCH_3$), 22.4 [d, $^1J_{P,C}$ = 106.9 Hz, $PCH_2(CH_2)_{10}$], 29.3–32.1 [$PCH_2$-$(CH_2)_{10}$] ppm. $^{31}P$ NMR {$^1H$} (80.9 MHz, $CDCl_3$): $\delta$ = 58 ppm.

**Methyl 3-[Dodecyl(hydroxy)phosphinoyl]-2-methylpropionate (17c):** After several attempts at purification, we failed to obtain the pure product. Crude yield 8.84 g, 92% (Method A); 7.78 g, 81% (Method B). $^{31}P$ NMR {$^1H$} (80.9 MHz, $CDCl_3$): $\delta$ = 51 ppm.

**Dodecyl(2-ethoxy-2-oxoethyl)phosphinic Acid (17d):** The mixture was taken up in water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic phase was dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The product was precipitated in diethyl ether. White solid; yield 6.25 g, 98% (Method B). $^1H$ NMR (500.9 MHz, $CDCl_3$): $\delta$ = 0.83 [t, $^3J_{H,H}$ = 6.5 Hz, 3 H, $CH_3(CH_2)_{10}$], 1.23 [m, 19 H, $CH_3(CH_2)_8$, $OCH_2CH_3$], 1.33 (m, 2 H, $PCH_2CH_2CH_2$), 1.55 (m, 2 H, $PCH_2CH_2$), 1.81 [m, 2 H, $PCH_2(CH_2)_{10}$], 2.91 (d, $^1J_{P,H}$ = 17.5 Hz, 2 H, $PCH_2CO$), 4.14 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, $OCH_2CH_3$), 9.84 (s, 1 H, O*H*) ppm. $^{13}C$ NMR {$^1H$} (125.9 MHz, $CDCl_3$): $\delta$ = 14.3 [$CH_3(CH_2)_{10}$], 21.6 ($OCH_2CH_3$), 22.6 ($PCH_2CH_2$), 28.4–32.1 [$CH_3(CH_2)_7$, $PCH_2CH_2$], 37.5 (d, $^1J_{P,C}$ = 80.5 Hz, $PCH_2CO$), 61.7 ($OCH_2CH_3$), 166.7 (*C*O) ppm. $^{31}P$ NMR {$^1H$} (80.9 MHz, $CDCl_3$): $\delta$ = 51 ppm.

**Dodecyl(3-methoxy-3-oxopropyl)phosphinic Acid (17e):** The mixture was taken up in water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic phase was dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The product was precipitated in diethyl ether. White solid; yield 6.18 g, 97% (Method B). $^1H$ NMR (500.9 MHz, $CDCl_3$): $\delta$ = 0.84 (t, $^3J_{H,H}$ = 6.5 Hz, 3 H, $CH_3CH_2$), 1.21 [m, 16 H, $CH_3(CH_2)_8$], 1.30 (m, 2 H, $PCH_2CH_2CH_2$), 1.57 (m, 2 H, $PCH_2CH_2CH_2$), 1.85 [m, 2 H, $PCH_2(CH_2)_{10}$], 2.62 (m, 2 H, $PCH_2CH_2CO$), 2.94 (m, 2 H, $PCH_2CH_2CO$), 3.66 (s, 3 H, $OCH_3$), 10.21 (s, 1 H, O*H*) ppm. $^{13}C$ NMR {$^1H$} (125.9 MHz, $CDCl_3$): $\delta$ = 14.3 ($CH_3CH_2$), 24.2 (d, $^1J_{PH}$ = 93.1 Hz, $PCH_2CH_2CO$), 26.5 ($PCH_2CH_2CO$), 26.5–32.1 [$P(CH_2)_{11}$], 52.2 ($OCH_3$), 173.1 (*C*O) ppm. $^{31}P$ NMR {$^1H$} (80.9 MHz, $CDCl_3$): $\delta$ = 58 ppm.

**Benzyl(isopropyl)phosphinic Acid (18b):** The mixture was taken up in water (20 mL) and washed with diethyl ether (3 × 20 mL) and subjected to reversed-phase column (water/methanol, 8:2). $R_f$ = 0.69. White solid; yield 5.17 g, 75% (Method A); 4.83 g, 70% (Method B). $^1H$ NMR (500.9 MHz, $CDCl_3$): $\delta$ = 1.0 (d, $^3J_{H,H}$ = 7.0 Hz, 6 H, $CH_3$), 1.68 (br., 1 H, PC*H*), 2.97 (d, $^2J_{P,H}$ = 15.3 Hz, 2 H, $PCH_2$), 7.18–7.25 (br., 5 H, $C_6H_5$) ppm. $^{13}C$ NMR {$^1H$} (125.9 MHz, $CDCl_3$): $\delta$ = 15.2 ($CH_3$), 26.7 (d, $^1J_{P,C}$ = 95.4 Hz, P*C*H), 34.6 (d, $^1J_{P,C}$ = 81.6 Hz, $PCH_2$), 126.8–131.9 ($C_6H_5$) ppm. $^{31}P$ NMR {$^1H$} (80.9 MHz, $CDCl_3$): $\delta$ = 59 ppm.

**Isopropyl(methyl)phosphinic Acid (18c):** The mixture was taken up in water (20 mL) and washed with diethyl ether (3 × 20 mL) and subjected to reversed-phase column (water/methanol, 8:2). $R_f$ = 0.76. White solid; yield 2.17 g, 89% (Method A); 2.51 g, 95% (Method B). $^1H$ NMR (500.9 MHz, $CDCl_3$): $\delta$ = 1.06 (d, $^3J_{H,H}$ = 7.0 Hz, 6 H, $CH_3CH$), 1.30 (d, $^2J_{P,H}$ = 13.1 Hz, 3 H, $PCH_3$), 1.76 (br., 1 H, PC*H*), 8.9 (s, 1 H, O*H*) ppm. $^{13}C$ NMR {$^1H$} (125.9 MHz, $CDCl_3$): $\delta$ = 12.0 (d, $^1J_{P,C}$ = 89.6 Hz, $PCH_3$), 15.8 ($CH_3CH$), 29.0 (d, $^1J_{P,H}$ = 98.0 Hz, P*C*H) ppm. $^{31}P$ NMR {$^1H$} (80.9 MHz, $CDCl_3$): $\delta$ = 53 ppm.

**Methyl 3-[Hydroxy(isopropyl)phosphinoyl]-2-methylpropionate (18d):** The mixture was taken up in water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic phase was dried with $MgSO_4$, filtered, and evaporated under reduced pressure. Yellow oil; yield 3.16 g, 76% (Method A); 3.41 g, 82% (Method B). $^1H$ NMR (500.9 MHz, $CDCl_3$): $\delta$ = 1.11 (d, $^3J_{H,H}$ = 7.1 Hz, 6 H, $CH_3CH$), 1.30 (d, $^3J_{H,H}$ = 6.5 Hz, 3 H, $PCH_2CHCH_3$), 1.76 (t, $^3J_{H,H}$ = 7.0 Hz, 1 H, $PCH_2CH$), 1.93 (br., 1 H, $CH_3CH$), 2.19 (br., 1 H, $PCH_2$), 2.92 (br., 1 H, $PCH_2$), 3.65 (s, 3 H, $OCH_3$), 8.9 (s, 1 H, O*H*) ppm. $^{13}C$ NMR {$^1H$} (125.9 MHz, $CDCl_3$): $\delta$ = 15.2 ($CH_3CH$), 19.2 ($PCH_2CHCH_3$), 28.5 (d, $^1J_{P,C}$ = 93.5 Hz, P*C*H), 29.5 (d, $^1J_{P,C}$ = 87.7 Hz, $PCH_2$), 33.6 ($PCH_2CH$), 52.2 ($OCH_3$),

176.3 (*C*O) ppm. $^{31}$P NMR {$^1$H} (80.9 MHz, $CDCl_3$): $\delta$ = 61 ppm.

(**2-Ethoxy-2-oxoethyl)isopropylphosphinic Acid (18e):** The mixture was taken up in water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic phase was dried with $MgSO_4$, filtered, and evaporated under reduced pressure. Yellow oil; yield 3.56 g, 92% (Method B). $^1$H NMR (500.9 MHz, $CDCl_3$): $\delta$ = 1.15 (dd, $^3J_{H,H}$ = 7.0, $^3J_{P,H}$ = 15.0 Hz, 6 H, C*H*$_3$CH), 1.22 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH$_2$C*H*$_3$), 2.01 (m, 1 H, *H*$_2$), 2.90 (d, $^1J_{P,H}$ = 16.5 Hz, 2 H, PC*H*$_2$), 4.13 (q, $^3J_{H,H}$ = 6.5 Hz, 2 H, OC*H*$_2$) ppm. $^{13}$C NMR {$^1$H} (125.9 MHz, $CDCl_3$): $\delta$ = 14.2 (OCH$_2$*C*H$_3$), 15.2 (*C*H$_3$CH), 27.8 (d, $^1J_{P,C}$ = 100.4 Hz, CH$_3$*C*H), 35.5 (d, $^1J_{P,C}$ = 77.8 Hz, P*C*H$_2$), 61.6 (O*C*H$_2$), 166.9 (*C*O) ppm. $^{31}$P NMR {$^1$H} (80.9 MHz, $CDCl_3$): $\delta$ = 52 ppm.

**Isopropyl(3-methoxy-3-oxopropyl)phosphinic Acid (18f):** The mixture was taken up in water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic phase was dried with $MgSO_4$, filtered, and evaporated under reduced pressure. Yellow oil; yield 2.94 g, 76% (Method B). $^1$H NMR (500.9 MHz, $CDCl_3$): $\delta$ = 1.13 (dd, $^3J_{H,H}$ = 7.0, $^3J_{P,H}$ = 15.0 Hz, 6 H, C*H*$_3$CH), 1.82 (m, 1 H, CH$_3$C*H*), 1.96 (m, 2 H, PC*H*$_2$), 2.60 (m, 2 H, PCH$_2$C*H*$_2$), 3.66 (s, 3 H, OC*H*$_3$), 8.76 (s, 1 H, O*H*) ppm. $^{13}$C NMR {$^1$H} (125.9 MHz, $CDCl_3$): $\delta$ = 15.3 (*C*H$_3$CH), 21.4 (d, $^1J_{PC}$ = 90.2 Hz, CH$_3$*C*H), 26.2 (PCH$_2$*C*H$_2$), 27.9 (d, $^1J_{P,C}$ = 95.5 Hz, P*C*H$_2$), 52.1 (O*C*H$_3$), 173.2 (*C*O) ppm. $^{31}$P NMR {$^1$H} (80.9 MHz, $CDCl_3$): $\delta$ = 60 ppm.

**Synthesis of α-Aminophosphinic Acid (20):** To (aminoalkyl)phosphinate (80 mmol) in acetonitrile (50 mL), bromotrimethylsilane (7 equiv.) was added under argon bubbling. The mixture was stirred for 20 min. Triethylamine (6 equiv.) was added, followed by ethyl bromopropionate (1.2 equiv.). The mixture was stirred at 35 °C for 6 h. The mixture was cooled to 0 °C, and absolute ethanol was added to quench the reaction. After 30 min, the solvent was removed, and the residue was taken up in distilled water and washed with diethyl ether (3 × 100 mL). The compound was extracted with chloroform (100 mL). The organic layer was dried with $MgSO_4$ and filtered. The chloroform layer was cooled at 0 °C and the product precipitated to give a white solid. Yield: 62% (Method B). $^1$H NMR (500.9 MHz; $CDCl_3$): δ = 1.22 (t, 3H, $^3J_{H,H}$ = 7.5 Hz, C*H*$_3$), 1.85 (br., 2 H, PC*H*$_2$CH$_2$), 2.51 (br., 2 H, PCH$_2$C*H*$_2$), 2.97 (d, 2 H, $^2J_{P,H}$ = 9.1 Hz, NHC*H*$_2$P), 4.10 (q, 2 H, $^3J_{H,H}$ = 6.5 Hz, OC*H*$_2$), 5.66 (s, 1 H, C*H*), 7.39 (br., 2 H, *p*-C$_6$*H*$_5$), 7.48 (br., 4 H, *m*-C$_6$*H*$_5$), 7.55 (br., 4 H, *o*-C$_6$*H*$_5$) ppm. $^{13}$C NMR {$^1$H} (125.9 MHz, $CDCl_3$): δ = 14.5 (*C*H$_3$), 27.1 (d, $^1J_{P,C}$ = 102.3 Hz, P*C*H$_2$CH$_2$), 28.6 (PCH$_2$*C*H$_2$), 46.1 (d, $^1J_{P,C}$ = 110.1 Hz, NHC*H*$_2$P), 62.0 (O*C*H$_2$), 68.7 (*C*H), 129.2, 130.4, 130.6, 137.0 (*C*$_6$H$_5$), 176.3 (*C*O) ppm. $^{31}$P NMR {$^1$H} (80.9 MHz, $CDCl_3$): δ = 27 ppm. HRMS: calcd. for $[MH]^+$ 362.17; found 362.17.

**Supporting Information** (see also the footnote on the first page of this article): $^1$H, $^{31}$P, and $^{13}$C NMR spectra for all compounds.

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