EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201200210

Functionalized Phosphanyl-Phosphonic Acids as Unusual Complexing Units as Analogues of Fosmidomycin

Sonia Montel,[a] Camille Midrier,[a] Jean-Noël Volle,[a] Ralf Braun,[b] Klaus Haaf,[b] Lothar Willms,[b] Jean-Luc Pirat,[a] and David Virieux*[a]

Dedicated to Professor Henri-Jean Cristau on the occasion of his 70th birthday

Keywords: Synthetic methods / Natural products / Enzymes / Inhibitors / Phosphorus / Palladium / Arylation

Fosmidomycin (**1a**) and FR-90098 are potent inhibitors of 1-deoxy-D-xylulose-5-phosphate reductoisomerase (DXR), the second enzyme of the non-mevalonate (MEP) pathway responsible for the biosynthesis of isoprenoids. This paper describes the synthesis of four types of targets bearing a phosphanyl-phosphonic acid motif as the common core for the inhibition of DXR. In these structures, the hydroxamic acid was replaced by various chelators based on a phosphinic acid linked to different functional groups capable of forming five- or six-membered chelating rings.

Introduction

The non-mevalonate pathway is an alternative metabolic pathway leading to the formation of isopentenyl pyrophosphate and is widely found in higher plants, protozoa, and bacteria, but, interestingly, there is no equivalent pathway in mammals. Identifying a non-mevalonate pathway inhibitor would greatly contribute to the search for safer antibiotics, antimalarials, and, for our interests, herbicides.[1] The unique properties of 1-deoxy-D-xylulose-5-phosphate reductoisomerase (DXR), the central enzyme of the non-mevalonate pathway, make it a remarkable and attractive target for drug design. Fosmidomycin (**1a**), a phosphonohydroxamic acid isolated from *Streptomyces lavendulae*, acts as an inhibitor of DXR and still remains, along with its *N*-acetyl homologue FR90098 (**1b**), one of the most potent inhibitors ever known.[2] The X-ray diffraction analyses of the co-crystals of DXR and fosmidomycin and DXR and deoxyxylulose phosphate (DXP, **2**) show that the phosphonic or phosphate group interacts with a highly specific and polar pocket in the enzyme site, allowing only few structural modifications (Figure 1).[3] In contrast, the cation-complexing unit represented by the hydroxamic acid offers fine-tuning possibilities for the complexation abilities as well as potential secondary interactions with the cofactor (NADPH), generally embedded in the active site. Although X-ray crystal structures of the complex of DXR with fosmidomycin have been solved, the rational design of new potent inhibitors by docking methods is obviously complicated, because DXR undergoes a dramatic conformational change induced by the inclusion of the substrate or fosmidomycin. In addition, the latter is known as a slow-binding inhibitor, and the ternary complexes constituted by DXR, NADPH, and fosmidomycin in the early stage or in the tight-binding mode deeply differ from each other.[4]

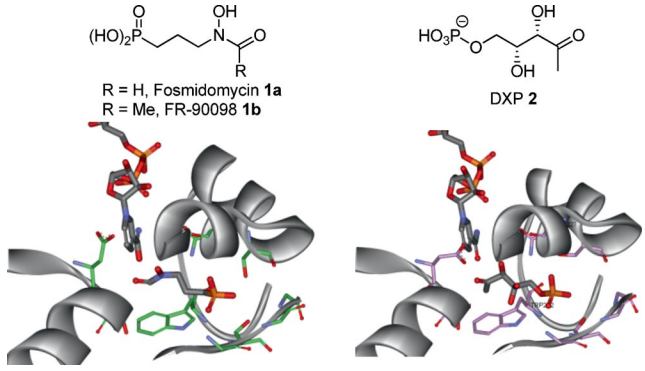


Figure 1. X-ray crystal structure of DXR active site with fosmidomycin (**1a**) or DXP (**2**) and NADPH.

Phosphinic acids are often employed as complexing units particularly in the inhibition of matrix metalloproteinases (MMPs), a family of zinc-dependent endoproteinases.[5] Of the many published inhibitors of DXR, a large majority contain the hydroxamic acid functionality which is already present in fosmidomycin, resulting in less effort toward other classes of inhibitors. From a structural point of view,

[a] Institut Charles Gerhardt, UMR 5253, AM2N, ENSCM, 8, Rue de l'Ecole Normale, 34296 Montpellier, France
Fax: +33-4-67144319
E-mail: david.virieux@enscm.fr
[b] Bayer CropScience AG, Chemistry Frankfurt, G 836, Industriepark Höchst, 65926 Frankfurt am Main, Germany
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201200210.

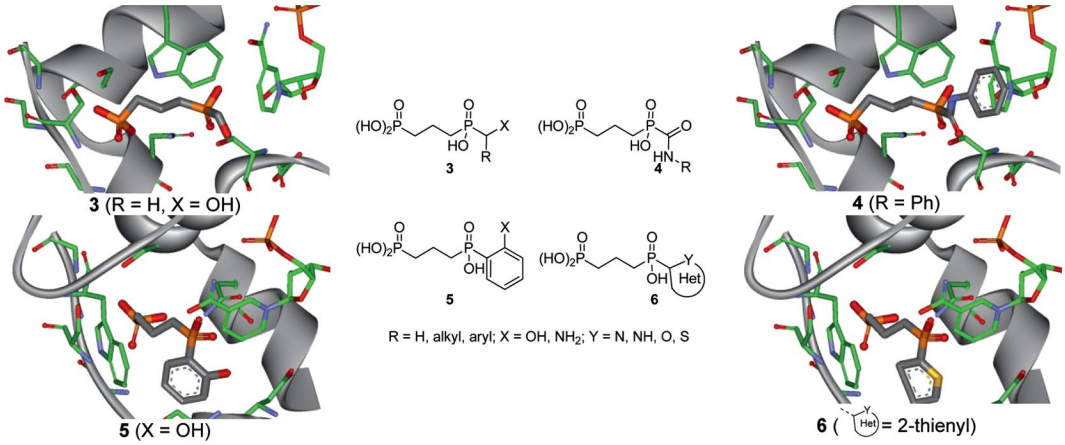


Figure 2. Modified chelators **3**–**6**, analogues of fosmidomycin (**1a**), docked in the active site of DXR.

the tetrahedral geometry of the phosphinic acid group could directly mimic the tetrahedral alcohol function of DXP (**2**). As a consequence, phosphinate-based inhibitors may possess useful properties, derived from their better complexation capabilities associated with the presence of a side chain that can bind in other specific pockets of the enzyme.[6] In accordance with this feature, the presence of other heteroatoms would lead to original chelators through the formation of potential five- or six-membered chelating rings (Figure 2).[7] Similarly, the modulations of the hardness and softness parameters and the hybridization of these heteroatoms would allow modifications in the complexing abilities. For these purposes, four types of targets (i.e. **3**–**6**) were designed (see Figure 2) to explore the molecular diversity and structurally embedded rigid or flexible chelating unit.

Results and Discussion

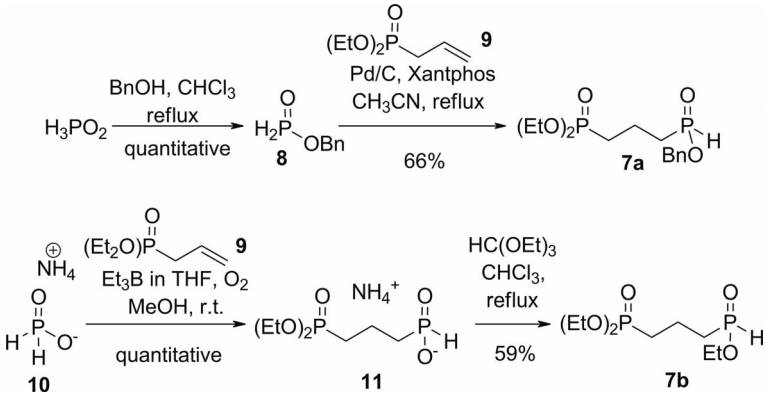
Syntheses of the Diethyl (3-Alkoxyphosphinoylpropyl)-phosphinate Precursors 7a and 7b

All of the target structures were synthesized from the 3-phosphinoylpropylphosphonates **7a** (R = Bn) or **7b** (R = Et), versatile building blocks, which were readily available on a multigram scale from cheap and commercially available reagents. Indeed, **7a** and **7b** were considered as key precursors to introduce chemical diversity by exploiting the outstanding reactivity associated with the P–H bond.

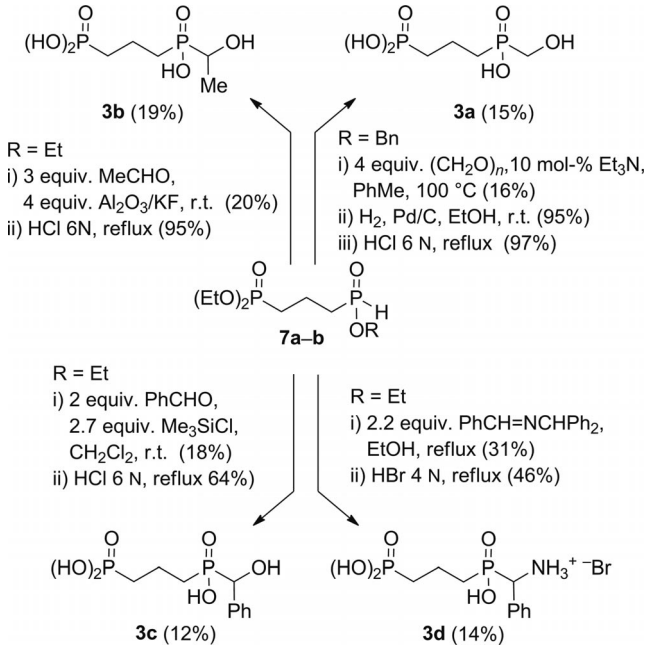
O-Benzyl phosphonophosphinate **7a** was obtained by the esterification of dry hypophosphorous acid with benzyl alcohol in refluxing chloroform (Scheme 1).[8] Then, a palladium-catalyzed hydrophosphinylation was performed with Pd/C and Xanthphos as the ligand to afford **7a** in 66% overall yield.[9] The *O*-ethyl phosphinate **7b** was synthesized from ammonium hypophosphite (**10**) by radical addition to diethyl allylphosphonate (**9**), mediated by triethylborane and oxygen.[10] The resulting acid **11** was then transformed into the corresponding ester **7b** in 59% overall yield using triethyl orthoformate in refluxing chloroform.

α-Hydroxy and α-Amino Phosphanylphosphonic Acids 3a–d

Starting from the two precursors **7a** and **7b**, the molecular diversity was then introduced by introducing an α-substituted hydroxy- or aminomethyl group to the reactive *H*-phosphinate function. Although the target structures **3** presented some similarities, the chemical behavior of the aldehyde and imine reagents were quite different and required specific reaction conditions (Scheme 2).



Scheme 1. Synthesis of phosphanyl-*H*-phosphinates **7a** and **7b**.

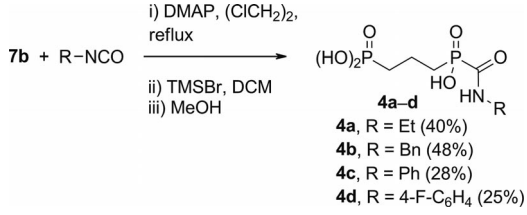


Scheme 2. α-Hydroxy and α-amino phosphanylphosphonic acids **3a**–**d**.

Three different aldehydes (formaldehyde, acetaldehyde, and benzaldehyde) were used to introduce the α-hydroxy group. Formaldehyde was thermally depolymerized from the paraformaldehyde, and upon heating to reflux for 1 h, the reaction resulted in complete consumption of the starting material.[11] The pure product was obtained in a modest crude NMR yield of 56% and was finally isolated in a 16% yield after two successive flash chromatography purifications, which were necessary because of the product's polarity. For acetaldehyde, the Texier–Boullet et al. methodology, which uses preadsorbed potassium fluoride on alumina as a base, was preferentially applied and gave the expected product in 20% yield.[12] For benzaldehyde, silyl-Abramov conditions were advantageously used to obtain the expected structure. Hydrogenolysis of the *O*-benzyl phosphinate was achieved using hydrogen and a Pd/C catalyst. Finally, hydrolysis of both phosphinic and phosphonic esters was effective under acidic conditions affording **3a**–**c**, respectively, in low overall yields. The α-aminobenzyl derivative **3d** was synthesized in a 14% overall yield in two steps from **7b** by the addition of the corresponding imine and then full deprotection using hydrobromic acid.

Carbamoylphosphanylphosphonic Acids 4a–d

α-Ketophosphinates are scarcely described in the literature, but they are proven to be useful chelating agents. For example, they inhibit human calpain I, a calcium-dependent cysteine protease.[13] Carbamoylphosphinates **4a**–**d** were synthesized by the condensation of phosphono-*H*-phosphinate **7b** with various isocyanates (Scheme 3).[14] Different conditions were established for the optimization of this reaction using phenyl isocyanate as the reactant. Both the direct basic activation (with cesium carbonate, sodium hydride, and potassium *tert*-butoxide) as well as the formation of the silylphosphonite by reaction of **7b** with trimethylsilyl chloride were attempted, but the best yields were obtained by using 4-(dimethylamino)pyridine (DMAP) in refluxing dichloroethane. The cleavage of both the phosphonic and phosphinic ester moieties mediated by trimethylsilyl bromide then resulted in the formation of the deprotected carbamoylphosphanylphosphonic acids **4a**–**d** in quantitative yields.



Scheme 3. Synthesis of Carbamoylphosphanylphosphonic acids **4a**–**d**.

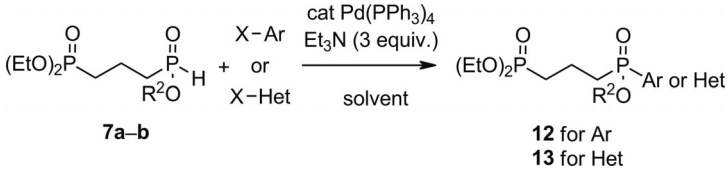
Aryl and Heteroarylphosphinoylphosphonic Acids 5 and 6

Metal-cation chelation is an important feature recognized in the development of new biologically active molecules.[15] In this context, the heterocyclic core of some complexing agents have demonstrated their efficiency, particularly in chelation therapy of iron by siderophores.[16] In this context, Arbusov and Michaelis–Becker reactions provide easy and useful procedures to form carbon–phosphorus bonds, but these methods are not directly applicable to the formation of sp^2-hybridized aromatic carbon atoms, even if a direct S_NAr process is presumed. As originally illustrated by Hirao et al., one of the best approaches is the palladium-catalyzed arylation of P–H reagents using aryl halides, preferentially an aryl bromide or iodide.[17] A striking detail specific to this method is the full regioselectivity of the arylation, that is, the P–C bond formation takes place exclusively at the position initially occupied by the bromide or iodide on the arylating agent, and a full retention of configuration at the phosphorus center is jointly observed during the transformation of the P–H bond into a P–Ar bond.[18]

Using $Pd(PPh_3)_4$

Because the palladium(0) catalyst is involved in such coupling reactions, we first used a catalytic amount of tetrakis(triphenylphosphane)palladium in the presence of triethylamine. The experimental results are listed in Table 1. According to the literature, when bromobenzene was used, the ^{31}P NMR yields (Table 1, Entry 2) were efficient as expected. However, the *O*-benzyl-protected phosphinate **7a** (Table 1, Entry 1) gave arylphosphinate **12a** (Ar = Ph), and concomitantly a small percentage of **7a** underwent debenzylation, which was confirmed by the presence of benzyl alcohol in GC–MS. Different solvents were also tried. In general, ethanol resulting in better conversions, but lower

Table 1. Palladium(0)-catalyzed arylation of **7a** and **7b**.



	Ar–X[a]	Conditions	Conversion (^{31}P NMR yield)
12a-Bn	Ph–Br	**7a**, 3% "Pd", PhMe, reflux, 4 d	100% (32%)
12a-Et	Ph–Br	**7b**, 10% "Pd", EtOH, 80 °C, 14 h	97% (72%)
12a-Et	Ph–I	**7b**, 10% "Pd", EtOH, 80 °C, 14 h	29% (16%)
13a	2-bromopyridine	**7b**, 10% "Pd", THF/EtOH, 10:1, reflux, 8 h	76% (4%)
13b	5-bromo-1-methyl-1*H*-imidazole	**7b**, 30% "Pd", PhMe/EtOH, 2:1, reflux, 14 h	74% (–)
13c	2-bromothiazole	**7b**, 30% "Pd", PhMe, reflux, 3 h	64% (–)

[a] Ar–X (1.5 equiv.) was used.

^{31}P NMR yields, because of the formation of tetraethyl propyl-1,3-diphosphonate. Its formation could be attributed either to oxidation and esterification steps or to a likely attack by the ethanol on the phosphorus atom of the Ar–Pd–P intermediate complex.

The phosphinylation of heterocycles were problematic, because a target could not be isolated when 2-bromopyridine, 2-bromothiazole, or 2-bromoimidazole were used. The complexation abilities of the resulting heteroarylphosphinates or precursor **7b** could induce this lack of reactivity.

Using $PdCl_2$

Another method involving a palladium(II) complex as the precursor was tried, as such air-stable complexes are generally easier to handle. In the literature, the Pd^{II} complex is reduced in situ to Pd^0 by treatment with triethylsilane under an inert atmosphere.[19] However, in many examples, ligands such as phosphanes can behave as reducing agents. After optimization of the conditions with bromobenzene as the model reagent, four of the protected arylphosphinates **12a**–**d** were obtained in isolated yields ranging from 51% to 62% (Table 2).

Table 2. Palladium(II)-catalyzed arylation of **7b**.

	Ar–X[a]	^{31}P NMR yield	Yield
12a-Et	Ph–Br	75%	62%
12b	2-AcOC_6H_4Br	70%	54%
12c	2-MeOC_6H_4Br	81%	61%
12d	2-AcHNC_6H_4Br	78%	51%
13a	2-bromopyridine	20%	–
13d	2-bromothiophene	5%	–

[a] Ar–X (1.5 equiv.) and $PdCl_2$ (10 mol-%) were used.

Using Pd_2dba_3

On the basis of these insights, specific conditions were developed to enable the cross-coupling step with heteroaryl halides. The efficiency in the formation of the 2-pyridylphosphonates was increased by the replacement of triphenylphosphane with bidentate ligands in the catalytic system.[20] This system exhibited a higher efficiency than $Pd(PPh_3)_4$ partly because of better reductive elimination given its bidentate character. Gratifyingly, the conditions developed for the use of dppf and Pd_2dba_3 permitted the successful formation of 2-pyridyl, 2-pyrimidinyl, and 2-[4-(trifluoromethyl)pyridyl] derivatives in yields ranging from 66 to 74% (Table 3). To the best of our knowledge, this is the first cross-coupling reaction between an *H*-phosphinate and heteroaryl chlorides.[21] To confirm the mechanism of the coupling, a palladium-free reaction was performed giving no conversion of **7b**, excluding a direct S_NAr process. Then, 2-bromothiophene and 2-bromothiazole were converted successfully into **13d** and **13c**, respectively, in 50% and 65% isolated yields. The coupling of the 5-(1-methyl-1*H*-imidazolyl) derivative gave **13b** in 84% for the ^{31}P NMR yield. Unfortunately, **13b** was unstable during flash chromatography. To circumvent this problem, the purification of **13b** was conducted by trituration and multiple extractions, which resulted in this low yield.

Table 3. Palladium(II)- and dppf-catalyzed arylation of **7b**.

	Heteroaryl halide	Time[a]	Yield (^{31}P NMR yield)
13a	2-bromopyridine	14 h	74% (96%)
13b	5-bromo-1-methyl-1*H*-imidazole	14 h	30% (84%)
13c	2-bromothiazole	15 h	65% (84%)
13d	2-bromothiophene	15 h	50% (80%)
13e	2-chloropyrimidine	7 h	68% (80%)
13f	2-chloro-4-trifluoromethylpyridine	3 h	66% (88%)

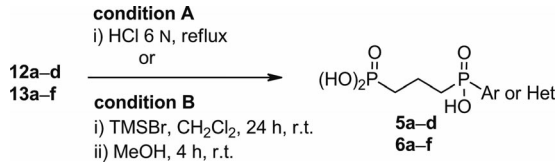
[a] Pd_2dba_3 (5 mol-%), dppf (10 mol-%), NEt_3 (3 equiv.), PhMe, 80 °C.

Deprotection

The deprotection of phosphanyl-phosphinic esters **12a**–**d** and **13a**–**f** was performed using refluxing HCl (6 N) or TMSBr (trimethylsilyl bromide) in dichloromethane at room temperature followed by methanolysis.[22] 2-Acetyl derivative **12b** and 2-anilinyl derivative **12d** were deprotected using trimethylsilyl bromide to afford phosphanyl-phosphonic triacids **5b** and **5d**, respectively, along with the *O*-

and *N*-acetyl-protected compounds (Table 4). The proportion of the deprotected phenol or amine depended on the use of water or methanol in the solvolysis reaction. Acetyl groups were fully removed using a solution of HCl (1 N) in methanol. When pyrimidinylphosphinate **13e** and thiazolylphosphinate **13c** were subjected to the deprotection conditions, both TMSBr and HCl quantitatively unexpectedly led to the formation of the propane-1,3-diphosphonic acid.[23] Under acidic conditions, a possible protonation of the heterocycle would induce the nucleophilic attack of water on the phosphorus atom, and consequently cleave the phosphorus–carbon bond.

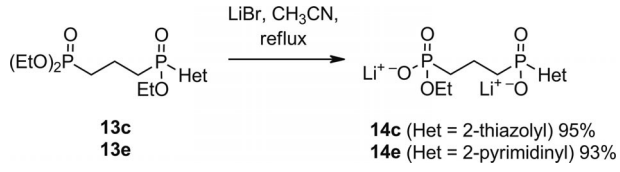
Table 4. Deprotection of aryl and heteroaryl phosphinates **12** and **13**.



	Ar or Het	Conditions	Yield
5b	2-AcOC$_6$H$_4$	B[a]	89%
5d	2-AcHNC$_6$H$_4$	B[b]	90%
6a	2-pyridyl	B	95%
6c	2-thiazolyl	A or B	–
6d	2-thienyl	B	87%
6e	2-pyrimidinyl	A or B	–
6f	2-(4-trifluoromethyl)pyridyl	B	91%

[a] The crude reaction mixture issued from B contained a 3:2 ratio of *O*-acetyl derivative **12b** and **12b**. [b] The crude reaction mixture issued from B contained a 2:1 ratio of *N*-acetyl derivative **12d** and **12d**.

Lithium bromide was used for the cleavage of the ester functions to obtain the free phosphinic acids from 2-thiazolylphosphinate **13c** and 2-pyrimidinylphosphinate **13e** (Scheme 4). Heating of **13c** and **13e** in acetonitrile at reflux with LiBr gave the expected lithium salts **14c** and **14e** in 95% and 93% yields, respectively.



Scheme 4. Nucleophilic deprotection of phosphinates **13c** and **13e**.

Conclusions

In summary, the syntheses of four new families of fosmidomycin analogues were accomplished using triethyl (3-phosphanylpropyl)phosphonate (**7b**) as a central scaffold. Owing to the presence of the P–H bond, a divergent procedure introduced chemical diversity into the cation-complexing subunit of fosmidomycin (**1a**) to afford original chelating functionalities. Interestingly, the palladium-catalyzed couplings of heteroaryl halides and, particularly, some heteroaryl chlorides were successfully applied to a fosmidomycin-related structure, clearly broadening the scope and usefulness of this reaction.

Living systems in nature are complex, therefore, all of the fosmidomycin analogues were tested directly on different weed plants in a greenhouse using a specific formulation by Bayer CropScience for highly polar compounds. In such conditions, no significant in vivo activity was observed.

Experimental Section

General Methods: All of the reactions were performed under a nitrogen atmosphere unless otherwise stated. Unless specified, all of the reagents and starting materials were purchased from commercial sources and used as received. The solvents were distilled prior to use. Analytical thin layer chromatography (TLC) was performed using precoated plates of silica gel 60F$_{254}$, and the visualizations were achieved by UV light (254 nm) or by treatment with a phosphomolybdic acid or permanganate solution as developing agents followed by heating. Purifications by flash chromatography were performed with silica gel (60 Å, 35–70 μm) or prepacked columns (from 12 to 120 g scale) of silica (35–70 μm). ^{1}H NMR spectroscopic data were recorded at 400 or 250 MHz. ^{13}C NMR spectroscopic data were recorded at 100 or 62.5 MHz, and ^{31}P NMR spectroscopic data were recorded at 162 or 101 MHz. The chemical shifts are reported in ppm, and the coupling constants (*J*) are reported in Hz. The chemical shift values are referenced against the residual proton in the deuterated solvents. In the ^{13}C NMR spectra, signals corresponding to C, CH, CH$_2$, or CH$_3$ were assigned from the JMOD sequence. The multiplicities are given as s (singlet), d (doublet), t (triplet), q (quadruplet), and m (multiplet). Low and high resolution mass spectra were recorded with a time-of-flight mass spectrometer using electrospray ionization (ESI), with H$_3$PO$_4$ (0.1% in water/acetonitrile, 1:1) as the internal reference.

Benzyl Hypophosphite (8): Into a 50-mL three-necked flask equipped with a heavy solvent extractor and condenser were introduced dry hypophosphorous acid (2.0 g, 0.03 mol), chloroform (30 mL), and benzyl alcohol (12.5 mL, 0.12 mol). The reaction mixture was heated at reflux for 14 h. After cooling, the benzene was removed by concentration under vacuum using a distillation apparatus and keeping the temperature below 30 °C. A mixture of benzyl hypophosphite and benzyl alcohol was obtained quantitatively as a colorless liquid and used directly without further purification. ^{31}P NMR (161.97 MHz, CDCl$_3$): δ = 12.37 (s) ppm. ^{1}H NMR (400.13 MHz, CDCl$_3$): δ = 4.94 (d, $^3J_{H,P}$ = 10.6 Hz, 2 H), 6.95 (d, $^1J_{H,P}$ = 564.6 Hz, 2 H), 7.04–7.21 (m, 5 H) ppm.

Ammonium Hypophosphite (10): Into a 3-L Erlenmeyer flask was introduced aqueous hypophosphorus acid (50 wt.-%/wt., 100 g, 0.76 mol), and the mixture was cooled in an ice bath and stirred. Then, an aqueous solution of ammonia (28%, 60 mL, 0.88 mol) was slowly added. After the complete addition, the reaction mixture was stirred for 20 min at room temperature. Acetone (2 L) was poured into the reaction mixture, and the resulting white solid was filtered and washed with acetone (300 mL). The salt was then dried under vacuum to afford ammonium hypophosphite (61.8 g, 83%) as a white solid which was stored in a Schlenk tube under nitrogen. ^{31}P NMR (101.25 MHz, CDCl$_3$): δ = 7.83 (s) ppm. ^{31}P NMR with coupling ^{1}H (101.25 MHz, CDCl$_3$): δ = 7.83 (t, $^1J_{P,H}$ = 518.5 Hz) ppm.

Diethyl Allylphosphonate (9): Into a 250-mL two-necked flask equipped with a condenser were introduced triethyl phosphite (80 mL, 0.48 mol) and allyl bromide (60 mL, 0.72 mol). The reaction mixture was stirred for 14 h at 160 °C, and then it was distilled under reduced pressure (82–85 °C, 2 Torr) to yield a colorless liquid (78.8 g, 92%). ^{31}P NMR (161.97 MHz, $CDCl_3$): δ = 27.7 (s) ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.34 (t, $^3J_{H,H}$ = 7.0 Hz, 6 H), 2.64 (m, $^2J_{H,P}$ = 21.9 Hz, $^3J_{H,H}$ = 7.4 Hz, $^4J_{H,H}$ = 1.2 Hz, 2 H), 4.06–4.20 (m, 4 H), 5.12–5.35 (m, 2 H), 5.70–5.92 (m, 1 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 16.2 (d, $^3J_{C,P}$ = 6.0 Hz), 31.5 (d, $^1J_{C,P}$ = 139.0 Hz), 61.7 (d, $^2J_{C,P}$ = 6.7 Hz), 119.5 (d, $^3J_{C,P}$ = 14.5 Hz), 127.3 (d, $^2J_{C,P}$ = 11.2 Hz) ppm.

Diethyl 3-(Benzyloxy-*H*-phosphinoyl)propylphosphonate (7a): Into a 500-mL three-necked flask equipped with a condenser were added acetonitrile (125 mL), palladium on charcoal (10%, 883 mg, 0.83 mmol), and Xantphos (526 mg, 0.907 mmol). The resulting mixture was stirred at room temperature for 10 min. A solution of alkyl hypophosphorus ester (249 mmol) and diethyl allylphosphonate 9 (14.7 g, 82.5 mmol) in acetonitrile (125 mL) was added. The reaction was heated at reflux for 18 h and then was filtered through Celite at room temperature. After concentration under vacuum, the benzyl alcohol was removed under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/EtOH, from 100:0 to 70:30) to yield a yellow oil (18.2 g, 66%). ^{31}P NMR (161.97 MHz, $CDCl_3$): δ = 30.17 (d, $^4J_{P,P}$ = 4.0 Hz), 37.16 (d, $^4J_{P,P}$ = 4.0 Hz) ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.33 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H), 1.82–2.02 (m, 6 H), 4.06–4.12 (m, 4 H), 5.03–5.31 (m, 2 H), 7.15 (d, $^1J_{H,P}$ = 534.9 Hz, 1 H) 7.37–7.41 (m, 5 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 14.6 (dd, $^2J_{C,P}$ = 4.4 Hz, $^2J_{C,P}$ = 2.2 Hz), 16.4 (d, $^3J_{C,P}$ = 5.8 Hz), 26.2 (dd, $^1J_{C,P}$ = 141.3 Hz, $^3J_{C,P}$ = 15.4 Hz), 28.3 (dd, $^1J_{C,P}$ = 92.2 Hz, $^3J_{C,P}$ = 13.9 Hz), 61.7 (d, $^2J_{C,P}$ = 6.6 Hz), 67.8 (d, $^2J_{C,P}$ = 6.6 Hz), 128.7–128.1 (m, 4 C) ppm. HRMS (ESI): calcd. for $C_{14}H_{25}O_5P_2$ 335.1177; found 335.1155.

Ammonium 3-(Diethoxyphosphonyl)propyl-*H*-phosphinate (11): Into a 1-L open flask were introduced ammonium hypophosphite (20.7 g, 0.25 mol), diethyl allylphosphonate (17.8 g, 0.1 mol), and methanol (490 mL). After complete dissolution of the salts, triethylborane (1 M solution in tetrahydrofuran, 20 mL, 0.02 mol) was added slowly. The resulting mixture was stirred vigorously for 4 h. After concentration under vacuum, the resulting crude mixture was dried under high vacuum to remove the traces of methanol, and then chloroform (250 mL) was added. The mixture was stirred in a sonic bath for 30 min. A white suspension formed and was filtered. The resulting filtrate was concentrated and dried to yield **11** (25.0 g, quantitative) as a colorless oil. ^{31}P NMR (161.97 MHz, $CDCl_3$): δ = 26.58 (s), 31.52 (d, $^4J_{P,P}$ = 3.96 Hz) ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.25 (t, $^3J_{H,H}$ = 7.1 Hz, 6 H), 1.57–1.98 (m, 6 H), 3.98–4.05 (m, 4 H), 6.93 (d, $^1J_{H,P}$ = 506.3 Hz, 1 H), 7.73 (s, 4 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 15.2 (d, $^2J_{C,P}$ = 4.3 Hz), 16.4 (d, $^3J_{C,P}$ = 6.6 Hz), 26.0 (dd, $^1J_{C,P}$ = 140.5 Hz, $^3J_{C,P}$ = 14.6 Hz), 31.9 (dd, $^1J_{C,P}$ = 91.5 Hz, $^3J_{C,P}$ = 14.6 Hz), 61.7 (d, $^2J_{C,P}$ = 6.6 Hz) ppm. HRMS (ESI): calcd. for $C_7H_{19}O_5P_2$ 245.0708; found 245.0731.

Diethyl 3-(Ethoxy-*H*-phosphinoyl)propylphosphonate (7b): Into a 500-mL two-necked flask equipped with a condenser were introduced, under nitrogen, **11** (25 g, 0.095 mol), chloroform (250 mL), and triethyl orthoformate (31.6 mL, 0.190 mol). The resulting mixture was heated at reflux for 13 h. After concentration under vacuum, the resulting crude mixture was purified by column chromatography on silica gel (EtOAc/EtOH, from 100:0 to 70:30) to give **7b** (15.2 g, 59%) as a colorless liquid. ^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 26.45 (d, $^4J_{P,P}$ = 3.7 Hz), 33.22 (d, $^4J_{P,P}$ = 3.7 Hz) ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.28 (t, $^3J_{H,H}$ = 7.0 Hz, 6 H), 1.32 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H), 1.77–1.92 (m, 6 H), 4.00–4.18 (m, 6 H), 7.06 (d, $^1J_{H,P}$ = 531.8 Hz, 1 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 14.5 (m), 16.2 (d, $^3J_{C,P}$ = 5.9 Hz), 16.4 (d, $^3J_{C,P}$ = 5.9 Hz), 26.1 (dd, $^1J_{C,P}$ = 142.0 Hz, $^3J_{C,P}$ = 14.6 Hz), 29.07 (dd, $^1J_{C,P}$ = 93.7 Hz, $^3J_{C,P}$ = 14.6 Hz), 61.7 (d, $^2J_{C,P}$ = 6.6 Hz), 62.6 (d, $^2J_{C,P}$ = 6.6 Hz) ppm. HRMS (ESI): calcd. for $C_9H_{23}O_5P_2$ 273.1021; found 273.1007.

3-[Hydroxy(hydroxymethyl)phosphinoyl]propylphosphonic Acid (3a)

Diethyl 3-[Benzyloxy(hydroxymethyl)phosphinoyl]propylphosphonate: Into a 50-mL two-necked flask under nitrogen were introduced **7a** (4.0 g, 11.9 mmol), dry toluene (20 mL), triethylamine (166 μL, 1.19 mmol), and paraformaldehyde (0.72 g, 23.9 mmol). The reaction mixture was heated at reflux. After completely dissolving the paraformaldehyde, the reaction was heated for 1 h. After cooling and concentration, the crude residue was dissolved in chloroform (100 mL), and the resulting mixture was washed with water (2 × 10 mL). The organic phase was dried with $MgSO_4$ and then concentrated. The resulting residue was purified twice by column chromatography on silica gel (EtOAc/EtOH, from 100:0 to 70:30) to give the product (0.70 g, 16%) as a yellow oil. ^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 30.80 (d, $^4J_{P,P}$ = 3.95 Hz), 54.31 (d, $^4J_{P,P}$ = 3.95 Hz) ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.22 (t, $^3J_{H,H}$ = 7.0 Hz, 6 H), 1.72–1.95 (m, 6 H), 3.71–3.96 (m, 2 H), 4.93–4.02 (m, 4 H), 4.94–5.04 (m, 2 H), 7.23–7.32 (m, 5 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 15.1 (dd, $^2J_{C,P}$ = 4.4 Hz, $^2J_{C,P}$ = 2.9 Hz), 16.4 (d, $^3J_{C,P}$ = 6.6 Hz), 26.1 (dd, $^1J_{C,P}$ = 88.55 Hz, $^3J_{C,P}$ = 14.63 Hz), 26.2 (dd, $^1J_{C,P}$ = 140.51 Hz, $^3J_{C,P}$ = 13.2 Hz), 58.3 (d, $^1J_{C,P}$ = 105.38 Hz), 61.7 (d, $^2J_{C,P}$ = 6.6 Hz), 66.2 (d, $^2J_{C,P}$ = 5.8 Hz), 127.9 (s), 128.6 (s), 128.4 (s), 136.4 (d, $^3J_{C,P}$ = 5.1 Hz) ppm. HRMS (ESI): calcd. for $C_{15}H_{27}O_6P_2$ 365.1283; found 365.1296.

Diethyl 3-[Hydroxy(hydroxymethyl)phosphinoyl]propylphosphonate: Into a Schlenk tube under nitrogen were introduced 10% Pd/C (60 mg) and diethyl 3-[benzyloxy(hydroxymethyl)phosphinoyl]-propylphosphonate (600 mg, 1.64 mmol) in EtOH (40 mL). The reaction mixture was vigorously stirred at room temp. for 12 h under a hydrogen atmosphere (1 atm). Then, the Pd/C was filtered through Celite, and the EtOH was removed under vacuum to yield the product (0.43 g, 95%) as a colorless oil. ^{31}P NMR (161.97 MHz, $CDCl_3$): δ = 31.45 (d, $^4J_{P,P}$ = 4.0 Hz), 50.18 (br. s) ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.26 (t, $^3J_{H,H}$ = 7.1 Hz, 6 H), 1.78–1.95 (m, 6 H), 3.70–3.95 (m, 2 H), 3.97–4.07 (m, 4 H), 7.73 (br. s, 2 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 15.07 (s), 16.4 (d, $^3J_{C,P}$ = 5.9 Hz), 26.1 (dd, $^1J_{C,P}$ = 140.5 Hz, $^3J_{C,P}$ = 13.2 Hz), 26.5 (dd, $^1J_{C,P}$ = 87.8 Hz, $^3J_{C,P}$ = 18.3 Hz), 59.1 (d, $^1J_{C,P}$ = 106.1 Hz), 61.8 (d, $^2J_{C,P}$ = 6.6 Hz) ppm. HRMS (ESI): calcd. for $C_8H_{21}O_6P_2$ 275.0813; found 275.0784.

3-[Hydroxy(hydroxymethyl)phosphinoyl]propylphosphonic Acid (3a): Into a 25-mL two-necked flask equipped with a condenser were introduced, respectively, diethyl 3-[hydroxy-(hydroxymethyl)phosphinoyl]propylphosphonate (0.36 g, 1.32 mmol), water (2 mL), and hydrochloric acid (35% solution, 4.8 mL). The reaction mixture was heated at reflux for 4 h and then concentrated under vacuum. Compound **3a** (280 mg, 97%) was obtained without further purification as a white foam. ^{31}P NMR (161.97 MHz, D_2O): δ = 29.57 (d, $^4J_{P,P}$ = 5.9 Hz), 50.97 (d, $^4J_{P,P}$ = 5.9 Hz) ppm. ^{1}H NMR (400.13 MHz, D_2O): δ = 1.72–1.85 (m, 6 H), 3.70 (d, $^2J_{H,P}$ = 5.0 Hz, 2 H) ppm. ^{13}C NMR (100.61 MHz, D_2O): δ = 14.9 (t, $^2J_{C,P}$ = 3.7 Hz), 26.1 (dd, $^1J_{C,P}$ = 88.6 Hz, $^3J_{C,P}$ = 16.1 Hz,), 27.2 (dd, $^1J_{C,P}$ = 133.9 Hz, $^3J_{C,P}$ = 14.6 Hz), 57.8 (d, $^1J_{C,P}$ = 108.3 Hz) ppm. HRMS (ESI): calcd. for $C_4H_{13}O_6P_2$ 219.0187; found 219.0212.

3-[Hydroxy(1-hydroxyethyl)phosphinoyl]propylphosphonic Acid (3b)

Diethyl 3-[Ethoxy(1-hydroxyethyl)phosphinoyl]propylphosphonate: Into a 25-mL two-necked flask under nitrogen was introduced **7b** (4.0 g, 14.7 mmol). The starting material was stirred in an ice bath, and then acetaldehyde (1.67 mL, 29.4 mmol) was added. Potassium fluoride preabsorbed on alumina (6.8 g, 58.8 mmol, 1:1, w/w) was added in portions, and the resulting mixture was vigorously stirred at room temp. for 5 h. Dichloromethane (50 mL) was added, and then the reaction mixture was stirred for 30 min. The mixture was filtered through Celite to remove the solid. The filtrate was concentrated, and the residue was purified twice by column chromatography on silica gel (EtOAc/EtOH, from 100:0 to 70:30) to yield the product (0.90 g, 20%) as a colorless oil. ^{31}P NMR (161.97 MHz, $CDCl_3$, diastereomer A): δ = 30.89 (d, $^4J_{P,P}$ = 4.0 Hz, 38%), 53.48 (br. s, 38%) ppm. ^{31}P NMR (161.97 MHz, $CDCl_3$, diastereomer B): δ = 31.03 (d, $^4J_{P,P}$ = 4.0 Hz, 62%), 54.20 (br. s, 62%) ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.26 (t, $^3J_{H,H}$ = 7.1 Hz, 9 H), 1.35 (dd, $^3J_{H,P}$ = 13.4 Hz, $^3J_{H,H}$ = 7.3 Hz, diastereomer B) and 1.37 (dd, $^3J_{H,P}$ = 15.1 Hz, $^3J_{H,H}$ = 7.1 Hz, diastereomer A) (3 H), 1.78–2.04 (m, 6 H), 3.87–3.95 (m, 1 H), 3.98–4.08 (m, 6 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 15.1 (t, $^2J_{C,P}$ = 3.7 Hz, diastereomer B), 15.3 (t, $^2J_{C,P}$ = 3.7 Hz, diastereomer A), 16.4–16.8 (m), 24.8 (dd, $^1J_{C,P}$ = 85.6 Hz, $^3J_{C,P}$ = 14.6 Hz, diastereomer A), 25.3 (dd, $^1J_{C,P}$ = 85.3 Hz, $^3J_{C,P}$ = 14.6 Hz, diastereomer B), 26.3 (dd, $^1J_{C,P}$ = 140.5 Hz, $^3J_{C,P}$ = 13.2 Hz, diastereomer A), 26.4 (dd, $^1J_{C,P}$ = 141.2 Hz, $^3J_{C,P}$ = 13.9 Hz, diastereomer B), 61.0–61.7 (m), 64.7 (d, $^2J_{C,P}$ = 7.6 Hz, diastereomer A), 64.7 (d, $^2J_{C,P}$ = 8.3 Hz, diastereomer B) ppm. HRMS (ESI): calcd. for $C_{11}H_{27}O_6P_2$ 317.1283; found 317.1256.

3-[Hydroxy(1-hydroxyethyl)phosphinoyl]propylphosphonic Acid (3b): Into a 25-mL two-necked flask equipped with a condenser were introduced, respectively, diethyl 3-[ethoxy(1-hydroxyethyl)phosphinoyl]propylphosphonate (0.79 g, 2.5 mmol), water (2 mL), and hydrochloric acid (35% solution, 4.8 mL). The reaction mixture was heated at reflux for 5 h and then was concentrated under vacuum. Compound **3b** (0.55 g, 95%) was obtained without further purification as a white foam. ^{31}P NMR (161.97 MHz, D_2O): δ = 32.31 (d, $^4J_{P,P}$ = 5.9 Hz), 56.22 (d, $^4J_{P,P}$ = 5.9 Hz) ppm. ^{1}H NMR (400.13 MHz, D_2O): δ = 1.24 (dd, $^3J_{H,P}$ = 15.7 Hz, $^3J_{H,H}$ = 7.2 Hz, 3 H), 1.70–1.85 (m, 6 H), 3.90 (qd, $^3J_{H,H}$ = 7.2 Hz, $^2J_{H,P}$ = 1.5 Hz, 1 H) ppm. ^{13}C NMR (100.61 MHz, D_2O): δ = 14.6 (t, $^2J_{C,P}$ = 4.4 Hz), 14.96 (s), 24.8 (dd, $^1J_{C,P}$ = 86.4 Hz, $^3J_{C,P}$ = 16.4 Hz), 27.1 (dd, $^1J_{C,P}$ = 134.7 Hz, $^3J_{C,P}$ = 14.6 Hz), 64.2 (d, $^1J_{C,P}$ = 111.2 Hz) ppm. HRMS (ESI): calcd. for $C_5H_{15}O_6P_2$ 233.0344; found 233.0367.

3-[Hydroxy(hydroxybenzyl)phosphinoyl]propylphosphonic Acid (3c)

Diethyl 3-[Ethoxy(hydroxybenzyl)phosphinoyl]propylphosphonate: Into a 5-mL two-necked flask under nitrogen was introduced **7b** (1.0 g, 3.67 mmol). The mixture was stirred in an ice bath, and then trimethylsilyl chloride (1.3 mL, 9.91 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 1 h. Benzaldehyde (779 mg, 7.34 mmol) was added, and then the reaction was stirred for an additional 1 h at 0 °C. Dichloromethane (2 mL) was then added, and the reaction was stirred at room temperature for 20 h. Extraction between acetonitrile (100 mL) and hexane (2 × 100 mL) was performed and the acetonitrile layer was concentrated. The crude residue was dissolved in chloroform (100 mL), and the resulting mixture was extracted with water (2 × 5 mL). The organic phase was dried with $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography on silica gel (EtOAc/EtOH, from 100:0 to 70:30) to yield the product (0.25 g, 18%) as a colorless oil. ^{31}P NMR (161.97 MHz, $CDCl_3$, diastereomer A): δ = 30.80 (d, $^4J_{P,P}$ = 5.4 Hz, 50%), 50.35 (br. s, 50%) ppm. ^{31}P NMR (161.97 MHz, $CDCl_3$, diastereomer B): δ = 30.91 (d, $^4J_{P,P}$ = 5.0 Hz, 50%), 52.60 (br. s, 50%) ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.12 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H), 1.20 (t, $^3J_{H,H}$ = 7.1 Hz, 6 H), 1.62–1.79 (m, 6 H), 3.73–4.01 (m, 6 H), 4.85 (d, $^2J_{H,P}$ = 7.7 Hz, 0.5 H, diastereomer), 4.93 (d, $^2J_{H,P}$ = 8.7 Hz, 0.5 H, diastereomer), 7.20–7.40 (m, 5 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 14.9–15.1 (m), 16.4 (d, $^3J_{C,P}$ = 5.9 Hz), 16.6 (d, $^3J_{C,P}$ = 5.8 Hz), 16.6 (d, $^3J_{C,P}$ = 5.8 Hz), 25.1 (dd, $^1J_{C,P}$ = 88.5 Hz, $^3J_{C,P}$ = 14.6 Hz), 25.6 (dd, $^1J_{C,P}$ = 88.5 Hz, $^3J_{C,P}$ = 15.4 Hz), 26.3 (dd, $^1J_{C,P}$ = 140.5 Hz, $^3J_{C,P}$ = 13.2 Hz), 25.1 (dd, $^1J_{C,P}$ = 140.5 Hz, $^3J_{C,P}$ = 13.2 Hz), 61.4–61.7 (m), 71.8 (d, $^1J_{C,P}$ = 103.2 Hz), 72.2 (d, $^1J_{C,P}$ = 102.5 Hz), 126.5 (d, $^4J_{C,P}$ = 5.1 Hz), 127.1 (d, $^4J_{C,P}$ = 5.1 Hz), 127.8 (d, $^5J_{C,P}$ = 2.2 Hz), 128.0 (d, $^5J_{C,P}$ = 2.2 Hz), 128.2 (d, $^5J_{C,P}$ = 2.2 Hz), 128.3 (d, $^5J_{C,P}$ = 2.2 Hz), 136.8 (s) ppm. HRMS (ESI): calcd. for $C_{16}H_{29}O_6P_2$ 379.1439; found 379.1423.

3-[Hydroxy(hydroxybenzyl)phosphinoyl]propylphosphonic Acid (3c): Into a 25-mL two-necked flask equipped with a condenser were introduced, respectively, diethyl 3-[ethoxy(hydroxybenzyl)phosphinoyl]propylphosphonate (0.50 g, 1.33 mmol), water (2 mL), and hydrochloric acid (35% solution, 4.8 mL). The reaction mixture was heated at reflux for 5 h and then concentrated under vacuum. The crude residue was purified by precipitation from a mixture of methanol and chloroform (1 mL/10 mL). The resulting solid was filtered and washed with chloroform to afford **3c** (250 mg, 64%) as a yellow foam. ^{31}P NMR (161.97 MHz, D_2O): δ = 29.20 (d, $^4J_{P,P}$ = 5.9 Hz), 48.65 (d, $^4J_{P,P}$ = 5.9 Hz) ppm. ^{1}H NMR (400.13 MHz, D_2O): δ = 1.70–1.95 (m, 6 H), 4.89 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H), 7.21–7.31 (m, 5 H) ppm. ^{13}C NMR (100.61 MHz, D_2O): δ = 15.0 (t, $^2J_{C,P}$ = 4.4 Hz), 25.5 (dd, $^1J_{C,P}$ = 87.8 Hz, $^3J_{C,P}$ = 16.1 Hz), 27.4 (dd, $^1J_{C,P}$ = 133.9 Hz, $^3J_{C,P}$ = 14.6 Hz), 71.7 (d, $^1J_{C,P}$ = 107.6 Hz), 127.0 (d, $J_{C,P}$ = 5.1 Hz), 128.4 (d, $J_{C,P}$ = 2.9 Hz), 128.6 (d, $J_{C,P}$ = 2.2 Hz), 136.0 (d, $J_{C,P}$ = 1.5 Hz) ppm. HRMS (ESI): calcd. for $C_{10}H_{17}O_6P_2$ 295.0500; found 295.0513.

3-[Hydroxy(aminobenzyl)phosphinoyl]propylphosphonic Acid Hydrobromide (3d)

Diethyl 3-[Ethoxy(diphenylmethylaminobenzyl)phosphinoyl]propylphosphonate: Into a 50-mL three-necked flask equipped with a condenser were dissolved, under nitrogen, **7b** (1 g, 3.67 mmol) and *N*-benzylidene-1,1-diphenylmethanamine (2.17 g, 8.04 mmol) in anhydrous EtOH (20 mL). The reaction mixture was heated at reflux for 15 d. After cooling and filtration, the reaction mixture was concentrated under vacuum. Purification of the resulting residue was performed by column chromatography on silica gel (EtOAc/EtOH, from 100:0 to 95:05) to yield the product (0.61 g, 31%) as a yellow oil. ^{31}P NMR (161.97 MHz, $CDCl_3$, diastereomer A): δ = 30.66 (d, $^4J_{P,P}$ = 5.9 Hz, 53%), 51.17 (d, $^4J_{P,P}$ = 5.9 Hz, 53%) ppm. ^{31}P NMR (161.97 MHz, $CDCl_3$, diastereomer B): δ = 30.85 (d, $^4J_{P,P}$ = 5.9 Hz, 47%), 50.68 (d, $^4J_{P,P}$ = 5.9 Hz, 47%) ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.18–1.27 (m, 9 H), 1.54–2.06 (m, 6 H), 3.16–3.22 and 3.61–3.68 (m, 1 H), 3.62 (d, $^2J_{H,P}$ = 15.4 Hz) and 3.74 (d, $^2J_{H,P}$ = 16.2 Hz, 1 H), 3.85–4.40 (m, 5 H), 4.10 (s, 1 H), 7.10–7.38 (m, 15 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 15.1 (t, $^2J_{C,P}$ = 4.4 Hz), 15.5 (t, $^2J_{C,P}$ = 4.4 Hz), 16.3–16.9 (m), 26.4 (dd, $^1J_{C,P}$ = 140.5 Hz, $^3J_{C,P}$ = 13.9 Hz), 26.6 (dd, $^1J_{C,P}$ = 140.5 Hz, $^3J_{C,P}$ = 13.9 Hz), 27.0 (dd, $^1J_{C,P}$ = 92.9 Hz, $^3J_{C,P}$ = 15.4 Hz), 27.6 (dd, $^1J_{C,P}$ = 92.2 Hz, $^3J_{C,P}$ = 16.1 Hz), 59.7 (d, $^1J_{C,P}$ = 101.7 Hz), 60.1 (d, $^1J_{C,P}$ = 98.8 Hz), 61.2–62.1 (m, $^2J_{C,P}$ = 7.32 Hz, $^2J_{C,P}$ = 6.6 Hz), 63.6 (d, $^3J_{C,P}$ = 4.4 Hz), 63.8 (d, $^3J_{C,P}$ = 2.9 Hz), 127.0–128.9 (m), 135.3 (d, $^2J_{C,P}$ = 3.7 Hz), 135.5 (s), 141.8, 142.0, 143.6, 143.7 ppm. HRMS (ESI): calcd. for $C_{29}H_{40}NO_5P_2$ 544.2382; found 544.2364.

3-[Hydroxy(aminobenzyl)phosphinoyl]propylphosphonic Acid Hydrobromide (3d): Into a 25-mL two-necked flask equipped with a condenser were introduced, respectively, diethyl 3-[ethoxy(diphenylmethylaminobenzyl)phosphinoyl]propylphosphonate (600 mg, 1.1 mmol), water (2.5 mL), and hydrobromic acid (47% solution, 2.58 mL). The reaction mixture was heated at reflux for 3 h. After concentration under vacuum, the crude residue was dissolved in a minimum of water. Acetone was added to precipitate **3d**. After removal of the supernatant, the residue was washed with acetone to yield **3d** (189 mg, 46%) as a yellow foam. ^{31}P NMR (161.97 MHz, D_2O): δ = 29.31 (s), 34.44 (s) ppm. ^{1}H NMR (400.13 MHz, D_2O): δ = 1.40–1.65 (m, 6 H), 4.30 (d, $^2J_{P,H}$ = 10.4 Hz, 1 H), 7.27–7.49 (m, 5 H) ppm. ^{13}C NMR (100.61 MHz, D_2O): δ = 15.3 (t, $^2J_{C,P}$ = 3.7 Hz), 27. 6 (dd, $^1J_{C,P}$ = 133.2 Hz, $^3J_{C,P}$ = 15.4 Hz), 28.3 (dd, $^1J_{C,P}$ = 95.9 Hz, $^3J_{C,P}$ = 16.1 Hz), 85.6 (d, $^1J_{C,P}$ = 85.6 Hz), 127.6 (d, $J_{C,P}$ = 4.4 Hz), 128.6 (d, $J_{C,P}$ = 1.5 Hz), 129.1 (d, $J_{C,P}$ = 1.5 Hz), 131.1 (d, $J_{C,P}$ = 2.9 Hz) ppm. HRMS (ESI): calcd. for $C_{10}H_{18}NO_5P_2$ 294.0660; found 294.0634.

General Procedures for the Syntheses of Carbamoylphosphinates 4a–d: Into a 50-mL two-necked flask equipped with a condenser were introduced, respectively, **7b** (1.5 g, 5.51 mmol), dry dichloroethane (30 mL), the isocyanate (from 2 to 3 equiv.), and 4-(dimethylamino)pyridine (from 0.2 to 0.5 equiv.) under nitrogen. The reaction mixture was refluxed from 4 to 7 d. After concentration under vacuum, the residue was purified by column chromatography on silica gel (AcOEt/EtOH, from 100:0 to 50:50) to give the protected product. Into a 50-mL two-necked flask were introduced the carbamoyl-protected phosphinate (1 mmol) and dry dichloromethane (20 mL). The mixture was cooled in an ice bath, and trimethylsilyl bromide (12 mmol) was added. The reaction mixture was stirred at room temperature overnight and then concentrated in vacuo to dryness. Finally, methanol (20 mL) was poured into the flask, and the resulting mixture was stirred at room temperature for 1 h and then concentrated under vacuum. After extraction using chloroform and water, the aqueous phase was evaporated under vacuum, and **4a**–**d** were obtained in quantitative yield without further purification.

3-[(*N*-Ethylcarbamoyl)hydroxyphosphinoyl]propylphosphonic Acid (4a)

Diethyl 3-[(*N*-Ethylcarbamoyl)ethoxyphosphinoyl]propylphosphonate: From ethyl isocyanate (3 equiv.) and DMAP (0.5 equiv.) and heating at reflux for 5 d to yield the product (757 mg, 40%) as a yellow oil. ^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 30.03 (d, $^4J_{P,P}$ = 6.1 Hz), 33.76 (d, $^4J_{P,P}$ = 6.1 Hz) ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.22 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H), 1.25 (t, $^3J_{H,H}$ = 7.0 Hz, 6 H), 1.27 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H), 1.85–2.09 (m, 6 H), 3.39–3.43 (m, 2 H), 3.99–4.16 (m, 6 H), 7.20 (br. m, 1 H) ppm. ^{13}C NMR (100.61 MHz,$CDCl_3$): δ = 14.2 (s), 14.7 (s), 16.1 (d, $^3J_{C,P}$ = 5.8 Hz), 16.2 (d, $^3J_{C,P}$ = 5.8 Hz), 25.8 (dd, $^1J_{C,P}$ = 95.9 Hz, $^3J_{C,P}$ = 16.1 Hz), 26.1 (dd, $^1J_{C,P}$ = 141.2 Hz, $^3J_{C,P}$ = 14.6 Hz), 34.1 (d, $^3J_{C,P}$ = 5.1 Hz), 61.4 (d, $^2J_{C,P}$ = 6.6 Hz), 62.1 (d, $^2J_{C,P}$ = 6.6 Hz), 167.3 (d, $^1J_{C,P}$ = 145.6 Hz) ppm. HRMS (ESI): calcd. for $C_{12}H_{28}NO_6P_2$ 344.1388; found 344.1392.

3-[(*N*-Ethylcarbamoyl)hydroxyphosphinoyl]propylphosphonic Acid (4a): Yellow oil (259 mg, quantitative). ^{31}P NMR (161.97 MHz, D_2O): δ = 27.62 (d, $^4J_{P,P}$ = 6.5 Hz), 30.24 (d, $^4J_{P,P}$ = 6.5 Hz) ppm. ^{1}H NMR (400.13 MHz, D_2O): δ = 0.99 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H), 1.59–1.82 (m, 6 H), 3.15 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H) ppm. ^{13}C NMR (100.61 MHz, D_2O): δ = 13.4 (s), 15.1 (dd, $^2J_{C,P}$ = 2.2 Hz, $^2J_{C,P}$ = 2.9 Hz), 27.0 (dd, $^1J_{C,P}$ = 133.9 Hz, $^3J_{C,P}$ = 15.4 Hz), 27.5 (dd, $^1J_{C,P}$ = 93.7 Hz, $^3J_{C,P}$ = 16.1 Hz), 34.2 (d, $^3J_{C,P}$ = 5.1 Hz), 172.8 (d, $^1J_{C,P}$ = 146.4 Hz) ppm. HRMS (ESI): calcd. for $C_6H_{16}NO_6P_2$ 260.0453; found 260.0439.

3-[(*N*-Benzylcarbamoyl)hydroxyphosphinoyl]propylphosphonic Acid (4b)

Diethyl 3-[(*N*-Benzylcarbamoyl)ethoxyphosphinoyl]propylphosphonate: From benzyl isocyanate (2.5 equiv.) and DMAP (0.2 equiv.) and heating at reflux for 4 d to yield the product (1.07 g, 48%) as a yellow oil. ^{31}P NMR (161.97 MHz, $CDCl_3$): δ = 30.18 (d, $^4J_{P,P}$ = 5.9 Hz), 33.88 (d, $^4J_{P,P}$ = 5.9 Hz) ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.25 (t, $^3J_{H,H}$ = 7.1 Hz, 6 H), 1.25 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H), 1.75–2.03 (m, 6 H), 3.88–4.08 (m, 6 H), 4.42 (dd, $^2J_{H,H}$ = –14.60 Hz, $^3J_{H,H}$ = 5.27 Hz, 1 H), 4.48 (dd, $^2J_{H,H}$ = –14.60 Hz, $^3J_{H,H}$ = 6.08 Hz, 1 H), 7.20–7.30 (m, 5 H), 7.55 (br. m, 1 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 14.9 (dd, $^2J_{C,P}$ = 4.4 Hz, $^2J_{C,P}$ = 2.2 Hz), 16.3 (d, $^3J_{C,P}$ = 5.8 Hz), 16.5 (d, $^3J_{C,P}$ = 5.8 Hz), 26.1 (dd, $^1J_{C,P}$ = 95.9 Hz, $^3J_{C,P}$ = 16.1 Hz), 26.4 (dd, $^1J_{C,P}$ = 141.2 Hz, $^3J_{C,P}$ = 14.6 Hz), 43.4 (d, $^3J_{C,P}$ = 5.1 Hz), 61.7 (d, $^2J_{C,P}$ = 6.6 Hz), 62.5 (d, $^2J_{C,P}$ = 6.6 Hz), 128.0 (s), 128.90 (s), 136.7 (s), 167.8 (d, $^1J_{C,P}$ = 145.2 Hz) ppm. HRMS (ESI): calcd. for $C_{17}H_{30}NO_6P_2$ 406.1548; found 406.1548.

3-[(*N*-Benzylcarbamoyl)hydroxyphosphinoyl]propylphosphonic Acid (4b): Yellow foam (321 mg, quantitative. ^{31}P NMR (161.97 MHz, D_2O): δ = 27.13 (d, $^4J_{P,P}$ = 5.9 Hz), 30.27 (d, $^4J_{P,P}$ = 5.9 Hz) ppm. ^{1}H NMR (400.13 MHz, D_2O): δ = 1.59–1.79 (m, 6 H), 4.31 (s, 2 H), 7.17–7.24 (m, 5 H) ppm. ^{13}C NMR (100.61 MHz, D_2O): δ = 15.2 (dd, $^2J_{C,P}$ = 2.2 Hz, $^2J_{C,P}$ = 2.9 Hz), 27.0 (dd, $^1J_{C,P}$ = 133.9 Hz, $^3J_{C,P}$ = 15.4 Hz), 27.7 (dd, $^1J_{C,P}$ = 94.4 Hz, $^3J_{C,P}$ = 16.8 Hz), 127.2 (s), 127.48 (s), 128.8 (s), 137.2 (s), 173.5 (d, $^1J_{C,P}$ = 144.9 Hz) ppm. HRMS (ESI): calcd. for $C_{11}H_{18}NO_6P_2$ 322.0608; found 322.0609.

3-[Hydroxy(*N*-phenylcarbamoyl)phosphinoyl]propylphosphonic Acid (4c)

Diethyl 3-[Ethoxy(*N*-phenylcarbamoyl)phosphinoyl]propylphosphonate: From phenyl isocyanate (2 equiv.) and DMAP (0.3 equiv.) and heating at reflux for 7 d to yield the product (604 mg, 28%) as a yellow oil. ^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 30.13 (d, $^4J_{P,P}$ = 5.0 Hz), 33.93 (d, $^4J_{P,P}$ = 5.0 Hz) ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.23 (t, $^3J_{H,H}$ = 7.1 Hz, 6 H), 1.28 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H), 1.79–2.10 (m, 6 H), 3.96–4.06 (m, 4 H), 4.07–4.17 (m, 2 H), 7.10–7.14 (m, 1 H), 7.28–7.32 (m, 2 H), 7.61–7.63 (m, 2 H), 9.29 (s, 1 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 15.0 (dd, $^2J_{C,P}$ = 4.4 Hz, $^2J_{C,P}$ = 2.9 Hz), 16.3 (d, $^3J_{C,P}$ = 5.8 Hz), 16.4 (d, $^3J_{C,P}$ = 5.9 Hz), 26.0 (dd, $^1J_{C,P}$ = 96.6 Hz, $^3J_{C,P}$ = 16.1 Hz), 26.3 (dd, $^1J_{C,P}$ = 141.2 Hz, $^3J_{C,P}$ = 14.6 Hz), 61.7 (d, $^2J_{C,P}$ = 6.6 Hz), 62.8 (d, $^2J_{C,P}$ = 7.3 Hz), 120.0 (s), 125.65 (s), 129.16 (s), 136.6 (d, $^3J_{C,P}$ = 9.5 Hz), 166.7 (d, $^1J_{C,P}$ = 146.4 Hz) ppm. HRMS (ESI): calcd. for $C_{16}H_{28}NO_6P_2$ 392.1392; found 392.1392.

3-[Hydroxy(*N*-phenylcarbamoyl)phosphinoyl]propylphosphonic Acid (4c): Brown foam (307 mg, quantitative). ^{31}P NMR (161.97 MHz, D_2O): δ = 26.33 (s), 30.10 (d, $^4J_{P,P}$ = 5.9 Hz) ppm ^{1}H (400.13 MHz, D_2O): δ = 1.78–1.85 (m, 6 H), 7.43–7.21 (m, 5 H) ppm. ^{13}C NMR (100.61 MHz, D_2O): δ = 14.0 (t, $^2J_{C,P}$ = 3.8 Hz, $^2J_{C,P}$ = 2.9 Hz), 26.3–28.9 (m), 122.52 (s), 126.4 (s), 129.2 (s), 135.5 (dd, $^3J_{C,P}$ = 8.8 Hz), 174.9 (s) ppm. HRMS (ESI): calcd. for $C_{10}H_{16}NO_6P_2$ 308.0450; found 308.0453.

3-[(*N*-4-Fluorophenylcarbamoyl)hydroxyphosphinoyl]propylphosphonic Acid (4d)

Diethyl 3-[Ethoxy(*N*-4-fluorophenylcarbamoyl)phosphinoyl]propylphosphonate: From 4-fluorophenyl isocyanate (2 equiv.) and DMAP (0.3 equiv.) and heating at reflux for 4 d to yield the product (564 mg, 25%) as a brown foam. ^{31}P NMR (101.25 MHz,

$CDCl_3$): δ = 30.09 (d, $^4J_{P,P}$ = 5.9 Hz), 33.92 (d, $^4J_{P,P}$ = 5.9 Hz) ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.24 (t, $^3J_{H,H}$ = 7.2 Hz, 6 H), 1.30 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H), 1.77–2.11 (m, 6 H), 3.95–4.14 (m, 6 H), 6.97–7.02 (m, 2 H), 7.54–7.55 (m, 2 H), 8.92 (s, 1 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 15.0 (dd, $^2J_{C,P}$ = 3.7 Hz, $^2J_{C,P}$ = 2.9 Hz), 16.2 (d, $^3J_{C,P}$ = 5.8 Hz), 16.3 (d, $^3J_{C,P}$ = 5.8 Hz), 26.0 (dd, $^1J_{C,P}$ = 96.7 Hz, $^3J_{C,P}$ = 15.4 Hz), 26.2 (dd, $^1J_{C,P}$ = 142.0 Hz, $^3J_{C,P}$ = 15.4 Hz), 61.6 (d, $^2J_{C,P}$ = 6.6 Hz), 62.7 (d, $^2J_{C,P}$ = 7.3 Hz), 115.5 (d, $^2J_{C,F}$ = 22.7 Hz), 122.1 (d, $^3J_{C,F}$ = 8.0 Hz), 133.1 (d, $^3J_{C,P}$ = 10.2 Hz), 159.8 (d, $^1J_{C,F}$ = 245.2 Hz), 166.2 (d, $^1J_{C,P}$ = 147.1 Hz) ppm. HRMS (ESI): calcd. for $C_{16}H_{27}FNO_6P_2$ 410.1294; found 410.1298.

3-[(*N*-4-Fluorophenylcarbamoyl)hydroxyphosphinoyl]propylphosphonic Acid (4d): Yellow foam (325 mg, quantitative). ^{31}P NMR (161.97 MHz, D_2O): δ = 26.64 (s), 30.35 (d, $^4J_{P,P}$ = 5.9 Hz) ppm. ^{1}H NMR (400.13 MHz, D_2O): δ = 1.67–1.83 (m, 6 H), 7.00–7.04 (m, 2 H), 7.31–7.34 (m, 2 H) ppm. ^{13}C NMR (100.61 MHz, D_2O): δ = 14.0 (t, $^2J_{C,P}$ = 3.7 Hz, $^2J_{C,P}$ = 2.9 Hz), 26.9 (dd, $^1J_{C,P}$ = 133.9 Hz, $^3J_{C,P}$ = 15.4 Hz), 27.4 (dd, $^1J_{C,P}$ = 94.4 Hz, $^3J_{C,P}$ = 16.8 Hz), 115.6 (d, $^2J_{C,F}$ = 23.4 Hz), 124.3 (d, $^3J_{C,F}$ = 8.8 Hz), 131.3 (dd, $^3J_{C,P}$ = 8.8 Hz, $^3J_{C,F}$ = 2.2 Hz), 160.2 (d, $^1J_{C,F}$ = 243.0 Hz), 171.6 (d, $^1J_{C,P}$ = 147.8 Hz) ppm. HRMS (ESI): calcd. for $C_{10}H_{15}FNO_6P_2$ 326.0347; found 326.0359.

General Procedure for the Coupling Between 7b and Substituted Bromobenzene Using Palladium Dichloride: Into a 25-mL two-necked flask equipped with a condenser were introduced palladium dichloride (64 mg, 0.368 mmol), triphenylphosphane (292 mg, 1.104 mmol), and dry toluene (10 mL). The mixture was stirred at room temperature for 5 min. Then, **7b** (1.0 g, 3.68 mmol), the substituted bromobenzene derivatives (5.52 mmol), and triethylamine (1.54 mL, 11.04 mmol) were added. The reaction mixture was stirred at reflux for 14 h and then concentrated under vacuum. The crude residue was dissolved in ethyl acetate (50 mL), and the resulting mixture was filtered through Celite. The filtrate was concentrated, and the residue was purified by column chromatography on silica gel (EtOAc/EtOH, from 100:0 to 85:15).

Diethyl 3-(Ethoxy-phenylphosphinoyl)propylphosphonate (12a): Colorless oil (794 mg, 62%). ^{31}P NMR (161.97 MHz, $CDCl_3$): δ = 30.63 (d, $^4J_{P,P}$ = 5.3 Hz), 43.53 (d, $^4J_{P,P}$ = 5.3 Hz) ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.19 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H), 1.21 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H), 1.23 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H) 1.70–2.04 (m, 6 H), 3.72–3.85 (m, 1 H), 3.92–4.06 (m, 5 H), 7.39–7.45 (m, 2 H), 7.47–7.52 (m, 1 H), 7.67–7.74 (m, 2 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 15.5 (dd, $^2J_{C,P}$ = 4.4 Hz, $^2J_{C,P}$ = 2.9 Hz), 16.4–16.5 (m), 26.3 (dd, $^1J_{C,P}$ = 140.5 Hz, $^3J_{C,P}$ = 15.1 Hz), 30.3 (dd, $^1J_{C,P}$ = 100.3 Hz, $^3J_{C,P}$ = 14.6 Hz), 60.6 (d, $^2J_{C,P}$ = 6.6 Hz), 61.6 (d, $^2J_{C,P}$ = 6.6 Hz), 128.7 (d, $^3J_{C,P}$ = 12.4 Hz), 130.5 (d, $^1J_{C,P}$ = 123.7 Hz), 131.6 (d, $^2J_{C,P}$ = 10.2 Hz), 132.4 (d, $^4J_{C,P}$ = 2.9 Hz) ppm. HRMS (ESI): calcd. for $C_{15}H_{27}O_5P_2$ 349.1334; found 349.1319.

Diethyl 3-[(2-Acetyloxyphenyl)ethoxyphosphinoyl]propylphosphonate (12b): Colorless oil (807 mg, 54%). ^{31}P NMR (161.97 MHz, $CDCl_3$): δ = 30.64 (d, $^4J_{P,P}$ = 5.9 Hz), 40.33 (d, $^4J_{P,P}$ = 5.9 Hz) ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.18 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H), 1.21 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H), 1.23 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H), 1.72–2.20 (m, 6 H), 2.26 (s, 3 H), 3.60–3.69 (m, 1 H), 3.92–4.09 (m, 5 H), 7.07 (ddd, $^3J_{H,H}$ = 8.1 Hz, $^4J_{H,P}$ = 4.8 Hz, $^4J_{H,H}$ = 0.9 Hz, 1 H), 7.31 (tdd, $^3J_{H,H}$ = 7.6 Hz, $^4J_{H,P}$ = 2.3 Hz, $^4J_{H,H}$ = 0.9 Hz, 1 H), 7.53 (dddd, $^3J_{H,H}$ = 8.1 Hz, $^3J_{H,H}$ = 7.6 Hz, $^4J_{H,H}$ = $^5J_{H,P}$ = 1.8 Hz, 1 H), 7.89 (ddd, $^3J_{H,H}$ = 7.6 Hz, $^3J_{H,P}$ = 12.4 Hz, $^4J_{H,H}$ = 1.8 Hz, 1 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 15.3 (dd, $^2J_{C,P}$ = 2.9 Hz, $^2J_{C,P}$ = 4.4 Hz), 16.2–16.5 (m), 21.15 (s), 26.3 (dd, $^1J_{C,P}$ = 141.1 Hz, $^3J_{C,P}$ = 14.6 Hz), 30.2 (dd, $^1J_{C,P}$ = 103.2 Hz, $^3J_{C,P}$ = 15.4 Hz), 61.0 (d, $^2J_{C,P}$ = 6.6 Hz), 61.6 (d, $^2J_{C,P}$ = 5.9 Hz), 123.1 (d, $^1J_{C,P}$ = 123.1 Hz), 123.7 (d, $^3J_{C,P}$ = 6.6 Hz), 126.3 (d, $^3J_{C,P}$ = 11.0 Hz), 134.0 (d, $^4J_{C,P}$ = 1.5 Hz), 135.1 (d, $^2J_{C,P}$ = 5.8 Hz), 152.1 (d, $^2J_{C,P}$ = 3.7 Hz), 169.1 (s) ppm. HRMS (ESI): calcd. for $C_{17}H_{29}O_7P_2$ 407.1389; found 407.1380.

Diethyl 3-[Ethoxy(2-methoxyphenyl)phosphinoyl]propylphosphonate (12c): Colorless oil (849 mg, 61%). ^{31}P NMR (161.97 MHz, $CDCl_3$): δ = 30.95 (d, $^4J_{P,P}$ = 5.9 Hz), 42.04 (d, $^4J_{P,P}$ = 5.9 Hz) ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.24 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H), 1.27 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H), 1.29 (t, $^3J_{H,H}$ = 7.7 Hz, 3 H), 1.75–2.24 (m, 6 H), 3.72–3.84 (m, 1 H), 3.88 (s, 3 H), 3.99–4.11 (m, 5 H), 6.94 (dd, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,P}$ = 5.7 Hz, 1 H), 7.07 (tdd, $^3J_{H,H}$ = 7.5 Hz, $^4J_{H,P}$ = 1.8 Hz, $^4J_{H,H}$ = 0.9 Hz, 1 H), 7.53 (dddd, $^3J_{H,H}$ = 8.3 Hz, $^3J_{H,H}$ = 7.5 Hz, $^5J_{H,P}$ = 2.2 Hz, $^4J_{H,H}$ = 1.8 Hz, 1 H), 7.92 (ddd, $^3J_{H,P}$ = 12.8 Hz, $^3J_{H,H}$ = 7.5 Hz, $^4J_{H,H}$ = 1.8 Hz, 1 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 15.3 (t, $^2J_{C,P}$ = 2.9 Hz), 16.3–16.4 (m), 26.4 (dd, $^1J_{C,P}$ = 140.5 Hz, $^3J_{C,P}$ = 14.6 Hz), 29.7 (dd, $^1J_{C,P}$ = 102.5 Hz, $^3J_{C,P}$ = 16.1 Hz), 55.5 (s), 60.4 (d, $^2J_{C,P}$ = 6.6 Hz), 61.5 (d, $^2J_{C,P}$ = 6.6 Hz), 110.8 (d, $^3J_{C,P}$ = 7.3 Hz), 117.8 (d, $^1J_{C,P}$ = 120.7 Hz), 120.8 (d, $^3J_{C,P}$ = 11.7 Hz), 134.5 (d, $^4J_{C,P}$ = 2.2 Hz), 135.7 (d, $^2J_{C,P}$ = 5.8 Hz), 160.6 (d, $^1J_{C,P}$ = 4.4 Hz) ppm. HRMS (ESI): calcd. for $C_{16}H_{29}O_6P_2$ 379.1439; found 379.1417.

Diethyl 3-[(2-Acetylaminophenyl)ethoxyphosphinoyl]propylphosphonate (12d): Light yellow oil (760 mg, 51%). ^{31}P NMR (161.97 MHz, $CDCl_3$): δ = 30.32 (d, $^4J_{P,P}$ = 4.0 Hz), 49.32 (d, $^4J_{P,P}$ = 4.0 Hz) ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.20 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H), 1.23 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H), 1.25 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H), 1.73–2.02 (m, 6 H), 2.13 (s, 3 H), 3.78–3.84 (m, 1 H), 3.95–4.09 (m, 5 H), 7.04 (tdd, $^3J_{H,H}$ = 7.4 Hz, $^4J_{H,P}$ = 2.8 Hz, $^4J_{H,H}$ = 0.9 Hz, 1 H), 7.22 (ddd, $^3J_{H,P}$ = 13.1 Hz, $^3J_{H,H}$ = 7.4 Hz, $^4J_{H,H}$ = 1.4 Hz, 1 H), 7.53 (ddd, $^3J_{H,H}$ = 8.5 Hz, $^3J_{H,H}$ = 7.4 Hz, $^4J_{H,H}$ = 1.4 Hz, 1 H), 8.55 (ddd, $^3J_{H,H}$ = 8.5 Hz, $^4J_{H,P}$ = 5.1 Hz, $^4J_{H,H}$ = 0.9 Hz, 1 H), 11.05 (s, 1 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 15.2 (dd, $^2J_{C,P}$ = 4.4 Hz, $^2J_{C,P}$ = 2.9 Hz), 16.3–16.5 (m): δ = 25.28 (s), 26.2 (dd, $^1J_{C,P}$ = 141.2 Hz, $^3J_{C,P}$ = 15.4 Hz), 30.8 (dd, $^1J_{C,P}$ = 103.2 Hz, $^3J_{C,P}$ = 13.9 Hz), 61.3 (d, $^2J_{C,P}$ = 7.3 Hz), 61.6 (d, $^2J_{C,P}$ = 5.9 Hz), 114.6 (d, $^1J_{C,P}$ = 116.4 Hz), 120.7 (d, $^3J_{C,P}$ = 8.0 Hz), 122.9 (d, $^3J_{C,P}$ = 12.4 Hz), 131.5 (d, $^2J_{C,P}$ = 8.8 Hz), 134.0 (d, $^4J_{C,P}$ = 2.2 Hz), 143.0 (d, $^1J_{C,P}$ = 5.1 Hz), 169.1 (s) ppm. HRMS (ESI): calcd. for $C_{17}H_{30}NO_6P_2$ 406.1548; found 406.1527.

General Procedure for the Coupling of 7b and Substituted Heteroaryl Halides Using Bis(dibenzylidene)dipalladium: Into a 25-mL two-necked flask equipped with a condenser were introduced bis(tribenzylidene)dipalladium (169 mg, 0.184 mmol), (diphenylphosphanyl)ferrocene (204 mg, 0.368 mmol), and dry toluene (15 mL). The mixture was stirred at room temperature for 5 min. Finally, **7b** (1 g, 3.68 mmol), the heteroaryl halide (5.52 mmol), and triethylamine (1. 54 mL, 11.04 mmol) were successively added, and the reaction mixture was stirred at 80 °C for 12 h. The mixture was concentrated under vacuum, and the resulting residue was dissolved in ethyl acetate (50 mL). The mixture was filtered through Celite. The filtrate was concentrated, and the residue was purified using different techniques depending on the substrate.

Diethyl 3-[Ethoxy(2-pyridyl)phosphinoyl]propylphosphonate (13a): 2-Bromopyridine was used as the starting material for this reaction. The crude material was purified by column chromatography on silica gel (EtOAc/EtOH, from 100:0 to 80:20) to yield the product (950 mg, 74%) as a yellow oil. ^{31}P NMR (161.97 MHz, $CDCl_3$): δ = 30.59 (d, $^4J_{P,P}$ = 6.9 Hz), 40.14 (d, $^4J_{P,P}$ = 6.9 Hz) ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.27 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H), 1.28 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H), 1.30 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H), 1.81–2.22 (m, 6 H), 3.80–3.89 (m, 1 H), 4.02–4.14 (m, 5 H), 7.44 (dddd, $^3J_{H,H}$ =

7.8 Hz, $^{3}J_{H,H}$ = 4.8 Hz, $^{5}J_{H,P}$ = 2.1 Hz, $^{4}J_{H,H}$ = 1.2 Hz, 1 H), 7.84 (dddd, $^{4}J_{H,P}$ = 10.0 Hz, $^{3}J_{H,H}$ = 7.8 Hz, $^{3}J_{H,H}$ = 7.7 Hz, $^{4}J_{H,H}$ = 1.6 Hz, 1 H), 8.07 (dddd, $^{3}J_{H,H}$ = 7.7 Hz, $^{3}J_{H,P}$ = 5.5 Hz, $^{4}J_{H,H}$ = 1.2 Hz, $^{5}J_{H,H}$ = 1.1 Hz, 1 H), 8.79 (ddd, $^{3}J_{H,H}$ = 4.8 Hz, $^{4}J_{H,H}$ = 1.6 Hz, $^{5}J_{H,H}$ = 1.1 Hz, 1 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 15.4 (t, $^{2}J_{C,P}$ = 3.7 Hz), 16.4 (d, $^{3}J_{C,P}$ = 5.8 Hz), 26.4 (dd, $^{1}J_{C,P}$ = 140.5 Hz, $^{3}J_{C,P}$ = 14.6 Hz), 27.9 (dd, $^{1}J_{C,P}$ = 101.0 Hz, $^{3}J_{C,P}$ = 16.4 Hz), 61.1 (d, $^{2}J_{C,P}$ = 6.6 Hz), 61.5 (d, $^{2}J_{C,P}$ = 6.6 Hz), 126.0 (d, $^{4}J_{C,P}$ = 3.7 Hz), 128.3 (d, $^{2}J_{C,P}$ = 21.2 Hz), 136.2 (d, $^{3}J_{C,P}$ = 9.5 Hz), 150.5 (d, $^{3}J_{C,P}$ = 19.7 Hz), 153.8 (d, $^{1}J_{C,P}$ = 153.0 Hz) ppm. HRMS (ESI): calcd. for $C_{14}H_{26}NO_5P_2$ 350.1286; found 350.1285.

Diethyl 3-[Ethoxy-(1-methylimidazol-5-yl)phosphinoyl]propylphosphonate (13b): 5-Bromo-1-methyl-1*H*-imidazole was used as the starting material. The target compound was not stable on silica gel and was purified by extraction. The first extraction of the crude material was performed using hexane and acetonitrile. The acetonitrile layer was concentrated, and the residue was dissolved in chloroform. The resulting mixture was washed with water. The chloroform phase was dried with $MgSO_4$ and concentrated. The residue was dissolved in a minimum amount of chloroform, and ether was added. The filtrate was concentrated, and the oil obtained was triturated with ether (4×). The combined filtrates were concentrated, and the oil obtained triturated with hexane (4×). Finally, the oily residue was dissolved in ether, and the mixture was treated with active charcoal. The filtrate was extracted with water, and the aqueous phase was concentrated to dryness to yield the product (380 mg, 30%) as a colorless oil. ^{31}P NMR (161.97 MHz, $CDCl_3$): δ = 30.43 (d, $^{4}J_{P,P}$ = 4.9 Hz), 33.62 (d, $^{4}J_{P,P}$ = 4.9 Hz) ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.21–1.29 (m, 9 H), 1.75–1.99 (m, 6 H), 3.83 (s, 3 H), 3.88–3.94 (m, 1 H), 3.94–4.04 (m, 4 H), 4.04–4.12 (m, 1 H), 7.37 (s, 1 H), 7.53 (d, $^{3}J_{H,P}$ = 2.1 Hz, 1 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 15.3 (dd, $^{2}J_{C,P}$ = 4.4 Hz, $^{2}J_{C,P}$ = 2.9 Hz), 16.3 (d, $^{3}J_{C,P}$ = 6.6 Hz), 16.4 (d, $^{3}J_{C,P}$ = 5.9 Hz), 26.0 (dd, $^{1}J_{C,P}$ = 141.24 Hz, $^{3}J_{C,P}$ = 15.4 Hz), 31.3 (dd, $^{1}J_{C,P}$ = 109.0 Hz, $^{3}J_{C,P}$ = 13.9 Hz), 33.7 (s), 61.2 (d, $^{2}J_{C,P}$ = 6.6 Hz), 61.6 (d, $^{2}J_{C,P}$ = 6.6 Hz), 121.8 (d, $^{1}J_{C,P}$ = 147.1 Hz), 139.7 (d, $^{2\text{ or }3}J_{C,P}$ = 16.1 Hz), 143.0 (d, $^{2\text{ or }3}J_{C,P}$ = 11.7 Hz) ppm. HRMS (ESI): calcd. for $C_{13}H_{27}N_2O_5P_2$ 353.1395; found 353.1390.

Diethyl 3-[Ethoxy(2-thiazolyl)phosphinoyl]propylphosphonate (13c): 2-Bromothiazole was used as the starting material for this reaction. The crude material was purified by column chromatography on silica gel (EtOAc/EtOH, from 100:0 to 85:15) to yield the product (845 mg, 65%) as a yellow oil. ^{31}P NMR (161.97 MHz, $CDCl_3$): δ = 30.35 (d, $^{4}J_{P,P}$ = 5.9 Hz), 34.30 (d, $^{4}J_{P,P}$ = 5.9 Hz) ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.27–1.32 (m, 9 H), 1.82–2.27 (m, 6 H), 3.84–3.99 (m, 1 H), 4.01–4.18 (m, 4 H), 4.14–4.23 (m, 1 H), 7.73 (dd, $^{3}J_{H,H}$ = 2.9 Hz, $^{4}J_{H,P}$ = 2.9 Hz, 1 H), 8.15 (dd, $^{3}J_{H,H}$ = 2.9 Hz, $^{4}J_{H,P}$ = 1.1 Hz, 1 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 15.2 (t, $^{2}J_{C,P}$ = 4.4 Hz), 16.3 (d, $^{3}J_{C,P}$ = 6.6 Hz), 16.4 (d, $^{3}J_{C,P}$ = 5.9 Hz), 26.2 (dd, $^{1}J_{C,P}$ = 141.25 Hz, $^{3}J_{C,P}$ = 15.4 Hz), 29.3 (dd, $^{1}J_{C,P}$ = 106.8 Hz, $^{3}J_{C,P}$ = 16.1 Hz), 61.6 (d, $^{2}J_{C,P}$ = 6.6 Hz), 61.9 (d, $^{2}J_{C,P}$ = 6.6 Hz), 125.2 (s), 146.2 (d, $^{3}J_{C,P}$ = 22.7 Hz), 161.9 (d, $^{1}J_{C,P}$ = 155.14 Hz) ppm. HRMS (ESI): calcd. for $C_{12}H_{24}NO_5P_2S$ 356.0850; found 356.0850.

Diethyl 3-[Ethoxy(2-thienyl)phosphinoyl]propylphosphonate (13d): 2-Bromothiophene was used as the starting material. The crude material was purified by column chromatography on silica gel (EtOAc/EtOH, from 100:0 to 80:20) to yield the product (640 mg, 50%) as a yellow oil. ^{31}P NMR (161.97 MHz, $CDCl_3$): δ = 30.52 (d, $^{4}J_{P,P}$ = 5.9 Hz), 37.22 (d, $^{4}J_{P,P}$ = 5.9 Hz) ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.22 (t, $^{3}J_{H,H}$ = 7.0 Hz, 3 H), 1.23 (t, $^{3}J_{H,H}$ = 7.0 Hz, 3 H), 1.24 (t, $^{3}J_{H,H}$ = 7.1 Hz, 3 H), 1.75–2.03 (m, 6 H), 3.84–3.91 (m, 1 H), 3.95–4.09 (m, 5 H), 7.15 (ddd, $^{3}J_{H,H}$ = 4.8 Hz, $^{3}J_{H,H}$ = 3.6 Hz, $^{4}J_{H,P}$ = 2.3 Hz, 1 H), 7.55 (ddd, $^{3\text{ or }4}J_{H,P}$ = 6.8 Hz, $^{3}J_{H,H}$ = 3.6 Hz, $^{4}J_{H,H}$ = 1.0 Hz, 1 H), 7.67 (ddd, $^{3}J_{H,H}$ = 4.8 Hz, $^{3\text{ or }4}J_{H,P}$ = 4.6 Hz, $^{3}J_{H,H}$ = 1.0 Hz, 1 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 15.1 (t, $^{2}J_{C,P}$ = 3.7 Hz), 16.3–16.4 (m), 26.1 (dd, $^{1}J_{C,P}$ = 141.2 Hz, $^{3}J_{C,P}$ = 15.4 Hz), 31.4 (dd, $^{1}J_{C,P}$ = 108.3 Hz, $^{3}J_{C,P}$ = 15.4 Hz), 61.0 (d, $^{2}J_{C,P}$ = 6.6 Hz), 61.5 (d, $^{2}J_{C,P}$ = 6.6 Hz), 128.4 (d, $^{3}J_{C,P}$ = 14.6 Hz), 130.8 (d, $^{1}J_{C,P}$ = 133.8 Hz), 133.6 (d, $^{3}J_{C,P}$ = 5.5 Hz), 136.4 (d, $^{2}J_{C,P}$ = 10.9 Hz) ppm. HRMS (ESI): calcd. for $C_{13}H_{25}O_5P_2S$ 355.0898; found 355.0890.

Diethyl 3-[Ethoxy(2-pyrimidinyl)phosphinoyl]propylphosphonate (13e): 2-Chloropyrimidine was used as the starting material. The crude material was purified by column chromatography on silica gel (EtOAc/EtOH, from 100:0 to 85:15) to yield the product (876 mg, 68%) as a yellow oil. ^{31}P NMR (161.97 MHz, $CDCl_3$): δ = 30.52 (d, $^{4}J_{P,P}$ = 6.9 Hz), 35.95 (d, $^{4}J_{P,P}$ = 6.9 Hz) ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.26–1.34 (m, 9 H), 1.83–2.29 (m, 6 H), 4.01–4.11 (m, 4 H), 4.14–4.24 (m, 1 H), 4.26–4.40 (m, 1 H), 7.41 (m, 1 H), 7.84 (m, 2 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 15.2 (t, $^{2}J_{C,P}$ = 4.4 Hz), 16.3 (d, $^{3}J_{C,P}$ = 6.6 Hz), 16.4 (d, $^{3}J_{C,P}$ = 5.9 Hz), 26.4 (dd, $^{1}J_{C,P}$ = 140.5 Hz, $^{3}J_{C,P}$ = 14.6 Hz), 27.6 (dd, $^{1}J_{C,P}$ = 101.0, $^{3}J_{C,P}$ = 16.1 Hz), 61.5 (d, $^{2}J_{C,P}$ = 6.6 Hz), 62.1 (d, $^{2}J_{C,P}$ = 7.3 Hz), 122.3 (d, $^{4}J_{C,P}$ = 2.9 Hz), 156.9 (d, $^{3}J_{C,P}$ = 14.6 Hz), 166.0 (d, $^{1}J_{C,P}$ = 185.9 Hz) ppm. HRMS (ESI): calcd. for $C_{13}H_{25}N_2O_5P_2$ 351.1239; found 351.1246.

Diethyl 3-{Ethoxy[5-(trifluoromethyl)pyridin-2-yl]phosphinoyl}propylphosphonate (13f): 2-Chloro-4-(trifluoromethyl)pyridine was used as the starting material. The crude material was purified by column chromatography on silica gel (EtOAc/EtOH, from 100:0 to 70:30) to yield the product (1.00 g, 66%) as a colorless oil. ^{31}P NMR (161.97 MHz, $CDCl_3$): δ = 30.36 (d, $^{4}J_{P,P}$ = 5.9 Hz), 38.89 (d, $^{4}J_{P,P}$ = 5.9 Hz) ppm. ^{19}F NMR (376.50 MHz, $CDCl_3$): δ = –62.80 (s, 3 F) ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.21 (t, $^{3}J_{H,H}$ = 7.0 Hz, 3 H), 1.22 (t, $^{3}J_{H,H}$ = 7.1 Hz, 3 H), 1.24 (t, $^{3}J_{H,H}$ = 7.0 Hz, 3 H), 1.75–2.20 (m, 6 H), 3.78–3.85 (m, 1 H), 3.95–4.10 (m, 5 H), 8.03 (dddd, $^{3}J_{H,H}$ = 7.9 Hz, $^{3}J_{H,P}$ = 3.1 Hz, $^{4}J_{H,H}$ = 2.0 Hz, $^{4}J_{H,F}$ = 0.7 Hz, 1 H), 8.15 (dd, $^{3}J_{H,H}$ = 7.9 Hz, $^{3}J_{H,P}$ = 5.1 Hz, 1 H), 8.96 (s, 1 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 15.2 (dd, $^{2}J_{C,P}$ = 4.4 Hz, $^{2}J_{C,P}$ = 2.9 Hz), 16.3 (d, $^{3}J_{C,P}$ = 5.8 Hz), 26.3 (dd, $^{1}J_{C,P}$ = 141.2 Hz, $^{3}J_{C,P}$ = 14.6 Hz), 27.7 (dd, $^{1}J_{C,P}$ = 101.0 Hz, $^{3}J_{C,P}$ = 15.4 Hz), 61.4 (d, $^{2}J_{C,P}$ = 6.6 Hz), 61.5 (d, $^{2}J_{C,P}$ = 6.6 Hz), 122.9 (q, $^{1}J_{C,F}$ = 274.4 Hz), 127.9 (d, $^{3}J_{C,P}$ = 21.2 Hz), 128.46 (qd, $^{2}J_{C,F}$ = 32.9 Hz, $^{4}J_{C,P}$ = 2.9 Hz), 131.9 (dq, $^{3}J_{C,P}$ = 9.5 Hz, $^{3}J_{C,F}$ = 2.9 Hz), 147.1 (dq, $^{3}J_{C,P}$ = 20.5 Hz, $^{3}J_{C,F}$ = 3.7 Hz), 158.0 (d, $^{1}J_{C,P}$ = 149.3 Hz) ppm. HRMS (ESI): calcd. for $C_{15}H_{25}F_3NO_5P_2$ 418.1160; found 418.1167.

3-(Hydroxy-phenylphosphinoyl)propylphosphonic Acid (5a): Into a 25-mL two-necked flask equipped with a condenser were introduced, respectively, **12a** (300 mg, 0.861 mmol), water (1.6 mL), and hydrochloric acid (35% solution, 1.6 mL). The reaction mixture was heated to reflux for 20 h and then concentrated under vacuum to yield the product (200 mg, 88%) as a white foam. ^{31}P NMR (161.97 MHz, D_2O): δ = 29.33 (d, $^{4}J_{P,P}$ = 5.9 Hz), 43.34 (d, $^{4}J_{P,P}$ = 5.9 Hz) ppm. ^{1}H NMR (400.13 MHz, D_2O): δ = 1.56–1.72 (m, 4 H), 1.89–1.97 (m, 2 H), 7.40–7.46 (m, 2 H), 7.49–7.54 (m, 1 H), 7.60–7.66 (m, 2 H) ppm. ^{13}C NMR (100.61 MHz, D_2O): δ = 15.59 (t, $^{2}J_{C,P}$ = 3.9 Hz, CH_2-2), 27.18 (dd, $^{1}J_{C,P}$ = 134.7 Hz, $^{3}J_{C,P}$ = 16.1 Hz, CH_2-1), 29.96 (dd, $^{1}J_{C,P}$ = 96.6, $^{3}J_{C,P}$ = 16.1 Hz, CH_2-3), 128.81 (d, $^{3}J_{C,P}$ = 13.2 Hz, CH-6), 130.68 (d, $^{2}J_{C,P}$ = 10.2 Hz, CH-5), 131.05 (d, $^{1}J_{C,P}$ = 127.3 Hz, C-4), 132.63 (d, $^{4}J_{C,P}$ = 2.2 Hz, CH-7) ppm. HRMS (ESI): calcd. for $C_9H_{15}O_5P_2$ 265.0395; found 265.0392.

General Procedure for the Deprotection of Substituted Arylphosphinoylphosphonates Using Trimethylsilyl Bromide: Into a 50-mL three-necked flask were introduced **12b** or **12d** (1 mmol) and dry dichloromethane (10 mL). The solution was cooled in an ice bath, and trimethylsilyl bromide (1.9 mL, 15 mmol) was added. The reaction mixture was stirred at room temperature for 14 h and concentrated to dryness under vacuum. Finally, methanol (10 mL) was added, and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under vacuum, and the crude residue was dissolved once again in methanol (10 mL). Aqueous HCl (1 M solution, 2 mL) was added, and the resulting solution was stirred at room temperature for 16 h. After concentration under vacuum, the desired compound was obtained.

3-[Hydroxy(2-hydroxyphenyl)phosphinoyl]propylphosphonic Acid (5b): Slightly yellow foam (250 mg, 89%). ^{31}P NMR (161.97 MHz, D_2O): δ = 30.04 (d, $^4J_{P,P}$ = 5.9 Hz), 44.25 (d, $^4J_{P,P}$ = 5.9 Hz) ppm. ^{1}H NMR (400.13 MHz, D_2O): δ = 1.57–1.72 (m, 4 H), 1.98–2.08 (m, 2 H), 6.82 (dd, $^3J_{H,H}$ = 8.0 Hz, $^4J_{H,P}$ = 5.6 Hz, 1 H), 6.9 (td, $^3J_{H,H}$ = 8.0 Hz, $^4J_{H,P}$ = 2.4 Hz, 1 H), 7.36 (td, $^3J_{H,H}$ = 8.0 Hz, $^4J_{H,P}$ = 0.9 Hz, 1 H), 7.46 (ddd, $^3J_{H,P}$ = 13.0 Hz, $^3J_{H,H}$ = 8.0 Hz, $^4J_{H,H}$ = 2.4 Hz, 1 H) ppm. ^{13}C NMR (100.61 MHz, D_2O): δ = 15.3 (t, $^2J_{C,P}$ = 2.7 Hz), 26.9 (dd, $^1J_{C,P}$ = 134.6 Hz, $^3J_{C,P}$ = 16.1 Hz), 29.7 (dd, $^1J_{C,P}$ = 97.3 Hz, $^3J_{C,P}$ = 16.1 Hz), 115.7 (d, $^1J_{C,P}$ = 125.9 Hz, C-4), 116.1 (d, $^3J_{C,P}$ = 8.0 Hz), 120.1 (d, $^3J_{C,P}$ = 11.7 Hz), 132.5 (d, $^4J_{C,P}$ = 6.6 Hz), 134.9 (d, $^2J_{C,P}$ = 2.2 Hz), 158.5 (d, $^1J_{C,P}$ = 5.1 Hz) ppm. HRMS (ESI): calcd. for $C_9H_{15}O_6P_2$ 281.0344; found 281.03400.

2-[Hydroxy(3-phosphonopropyl)phosphinoyl]benzenammonium Chloride (5d): Yellow oil (283 mg, 90%). ^{31}P NMR (161.97 MHz, D_2O): δ = 30.19 (d, $^4J_{P,P}$ = 6.9 Hz), 39.27 (s) ppm. ^{1}H NMR (400.13 MHz, D_2O): δ = 1.56–1.72 (m, 4 H), 1.85–1.92 (m, 2 H), 7.32 (dd, $^3J_{H,H}$ = 7.8 Hz, $^4J_{H,P}$ = 4.1 Hz, 1 H), 7.47 (t, $^3J_{H,H}$ = 7.8 Hz, 1 H), 7.57 (t, $^3J_{H,H}$ = 7.5 Hz, 1 H), 7.66 (ddd, $^3J_{H,P}$ = 12.3 Hz, $^3J_{H,H}$ = 7.5 Hz, $^4J_{H,H}$ = 1.2 Hz, 1 H) ppm. ^{13}C NMR (100.61 MHz, D_2O): δ = 15.1 (t, $^2J_{C,P}$ = 2.9 Hz), 26.7 (dd, $^1J_{C,P}$ = 134.7, $^3J_{C,P}$ = 16.8 Hz), 31.6 (dd, $^1J_{C,P}$ = 99.5 Hz, $^3J_{C,P}$ = 15.4 Hz), 124.3 (d, $^3J_{C,P}$ = 8.1 Hz), 126.0 (d, $^1J_{C,P}$ = 100.7 Hz), 129.4 (d, $^3J_{C,P}$ = 11.0 Hz), 132.0 (d, $^2J_{C,P}$ = 3.6 Hz), 133.2 (d, $^2J_{C,P}$ = 8.0 Hz), 133.6 (d, $^4J_{C,P}$ = 1.4 Hz) ppm. HRMS (ESI): calcd. for $C_9H_{16}NO_5P_2$ 280.0504; found 280.0500.

General Procedure for the Deprotection of Substituted Heteroarylphosphinoylphosphonates Using Trimethylsilyl Bromide: Into a 50-mL three-necked flask were introduced **13a**, **13d**, or **13f** (1 mmol) and dry dichloromethane (10 mL). The mixture was cooled in an ice bath, and trimethylsilyl bromide (1.9 mL, 15 mmol) was added. The reaction mixture was stirred at room temperature for 14 h and then concentrated to dryness under vacuum. Finally, methanol (10 mL) was poured into the flask, and the resulting mixture was stirred at room temperature for 2 h and concentrated again under vacuum. Purification was not required for these compounds.

3-(Hydroxy-2-pyridylphosphinoyl)propylphosphonic Acid (6a): Yellow oil (251 mg, 95%). ^{31}P NMR (161.97 MHz, D_2O): δ = 26.73 (d, $^4J_{P,P}$ = 5.9 Hz), 32.84 (d, $^4J_{P,P}$ = 5.9 Hz) ppm. ^{1}H NMR (400.13 MHz, D_2O): δ = 1.54–1.74 (m, 4 H), 1.83–1.91 (m, 2 H), 8.00 (t, $^3J_{H,H}$ = 6.0 Hz, 1 H), 8.15 (t, $^3J_{H,H}$ = 6.0 Hz, 1 H), 8.53 (t, $^3J_{H,H}$ = 7.72 Hz, 1 H), 8.61 (d, $^3J_{H,H}$ = 6.0 Hz, 1 H) ppm. ^{13}C NMR (100.61 MHz, D_2O): δ = 18.0 (t, $^2J_{C,P}$ = 2.9 Hz), 29.4 (dd, $^1J_{C,P}$ = 133.9 Hz, $^3J_{C,P}$ = 16.8 Hz), 33.3 (dd, $^1J_{C,P}$ = 103.9 Hz, $^3J_{C,P}$ = 15.4 Hz), 131.2 (d, $^4J_{C,P}$ = 1.5 Hz), 132.5 (d, $^2J_{C,P}$ = 10.2 Hz), 144.8 (d, $^3J_{C,P}$ = 5.1 Hz), 149.5 (d, $^3J_{C,P}$ = 6.6 Hz), 153.5 (d, $^1J_{C,P}$ = 109.0 Hz) ppm. HRMS (ESI): calcd. for $C_8H_{14}NO_5P_2$ 266.0347; found 266.0340.

3-(Hydroxy-2-thienylphosphinoyl)propylphosphonic Acid (6d): Yellow oil (235 mg, 87%). ^{31}P NMR (161.97 MHz, D_2O): δ = 29.94 (s), 35.88 (s) ppm. ^{1}H NMR (400.13 MHz, D_2O): δ = 1.50–1.60 (m, 4 H), 1.79–1.85 (m, 2 H), 7.02 (s, 1 H), 7.55 (dd, $^{3\text{ or }4}J_{H,P}$ = 7.0 Hz, $^3J_{H,H}$ = 3.3 Hz, 1 H), 7.67 (t, $^3J_{H,H}$ = 4.7 Hz, $^{3\text{ or }4}J_{H,P}$ = 4.7 Hz, 1 H) ppm. ^{13}C NMR (100.61 MHz, D_2O): δ = 15.7 (t, $^2J_{C,P}$ = 3.7 Hz), 27.0 (dd, $^1J_{C,P}$ = 133.9 Hz, $^3J_{C,P}$ = 15.4 Hz), 31.4 (dd, $^1J_{C,P}$ = 103.9 Hz, $^3J_{C,P}$ = 16.8 Hz), 128.6 (d, $^3J_{C,P}$ = 14.6 Hz), 132.4 (d, $^1J_{C,P}$ = 137.6 Hz), 133.5 (d, $^3J_{C,P}$ = 5.8 Hz), 135.4 (d, $^2J_{C,P}$ = 10.9 Hz) ppm. HRMS (ESI): calcd. for $C_7H_{13}O_5P_2S$ 270.9959; found 270.9953.

3-Hydroxy-[2-(5-trifluoromethylpyridyl)phosphinoyl]propylphosphonic Acid (6f): Yellow oil (303 mg, 91%). ^{31}P NMR (161.97 MHz, D_2O): δ = 26.47 (br. s), 30.12 (d, $^4J_{P,P}$ = 5.9 Hz) ppm. ^{19}F NMR (376.50 MHz, D_2O): δ = –63.21 (s, 3 F) ppm. ^{1}H NMR (400.13 MHz, D_2O): δ = 1.53–1.77 (m, 4 H), 1.88–1.98 (m, 2 H), 8.29 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H), 8.73 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H), 9.14 (s, 1 H) ppm. ^{13}C NMR (100.61 MHz, D_2O): δ = 15.4 (t, $^2J_{C,P}$ = 2.9 Hz), 26.9 (dd, $^1J_{C,P}$ = 134.7 Hz, $^3J_{C,P}$ = 16.8 Hz), 30.2 (dd, $^1J_{C,P}$ = 103.2 Hz, $^3J_{C,P}$ = 16.1 Hz), 121.5 (q, $^1J_{C,F}$ = 272.9 Hz), 129.8 (d, $^3J_{C,P}$ = 12.4 Hz), 130.2 (s), 141.83 (s), 142.3 (s), 156.3 (d, $^1J_{C,P}$ = 115.9 Hz) ppm. HRMS (ESI): calcd. for $C_9H_{13}NO_5P_2F_3$ 334.0221; found 334.0212.

General Procedure for the Deprotection Using Lithium Bromide: Into a 5-mL sealed tube were introduced **13c** or **13e** (0.43 mmol) and dry acetonitrile (5 mL). The solution was stirred at room temperature, and lithium bromide (225 mg, 2.6 mmol) was added. The resulting mixture was heated at reflux and stirred for 5 d. After cooling, the white solid formed was filtered and washed with acetonitrile. The solid was dried under vacuum.

Dilithium Compound 4c: Yellow solid (127 mg, 95%). ^{31}P NMR (161.97 MHz, D_2O): δ = 26.17 (d, $^4J_{P,P}$ = 7.9 Hz), 27.30 (d, $^4J_{P,P}$ = 7.9 Hz) ppm. ^{1}H NMR (400.13 MHz, D_2O): δ = 1.04 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H), 1.40–1.51 (m, 4 H), 1.82–1.90 (m, 2 H), 3.69 (qu, $^3J_{H,H}$ = $^3J_{H,P}$ = 7.0 Hz, 2 H), 7.72 (dd, $^3J_{H,H}$ = 2.9 Hz, $^4J_{H,P}$ = 1.9 Hz, 1 H), 7.94 (d, $^3J_{H,H}$ = 2.9 Hz, 1 H) ppm. ^{13}C NMR (100.61 MHz, D_2O): δ = 15.8 (d, $^3J_{C,P}$ = 5.8 Hz), 16.7 (t, $^2J_{C,P}$ = 3.6 Hz), 27.2 (dd, $^1J_{C,P}$ = 133.9, $^3J_{C,P}$ = 16.1 Hz), 31.8 (dd, $^1J_{C,P}$ = 102.4, $^3J_{C,P}$ = 16.1 Hz), 60.4 (d, $^2J_{C,P}$ = 5.8 Hz), 124.0 (s), 144.7 (d, $^3J_{C,P}$ = 19.8 Hz), 169.1 (d, $^1J_{C,P}$ = 142.7 Hz) ppm. HRMS (ESI): calcd. for $C_8H_{16}NO_5P_2S$ 300.0224; found 300.0228.

Dilithium Compound 14e: Yellow solid (123 mg, 93%). ^{31}P NMR (161.97 MHz, D_2O): δ = 27.47 (d, $^4J_{P,P}$ = 7.6 Hz), 28.16 (d, $^4J_{P,P}$ = 7.6 Hz) ppm. ^{1}H NMR (400.13 MHz, D_2O): δ = 1.06 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H), 1.51–1.57 (m, 4 H), 1.87–1.95 (m, 2 H, CH_2-3), 3.72 (qu, $^3J_{H,H}$ = $^4J_{H,P}$ = 7.0 Hz, 2 H), 7.46 (td, $^3J_{H,H}$ = 5.1 Hz, $^4J_{H,P}$ = 2.9 Hz, 1 H), 8.75 (d, $^3J_{H,H}$ = 5.1 Hz, 2 H) ppm. ^{13}C NMR (100.61 MHz, D_2O): δ = 15.8 (d, $^3J_{C,P}$ = 5.8 Hz), 16.6 (t, $^2J_{C,P}$ = 2.9 Hz), 27.4 (dd, $^1J_{C,P}$ = 133.2 Hz, $^3J_{C,P}$ = 16.1 Hz), 30.1 (dd, $^1J_{C,P}$ = 99.5 Hz, $^3J_{C,P}$ = 17.6 Hz), 60.4 (d, $^2J_{C,P}$ = 5.1 Hz), 122.0 (d, $^4J_{C,P}$ = 2.9 Hz), 156.8 (d, $^3J_{C,P}$ = 12.4 Hz), 168.7 (d, $^1J_{C,P}$ = 172.7 Hz) ppm. HRMS (ESI): calcd. for $C_9H_{17}N_2O_5P_2$ 295.0613; found 295.0601.

Supporting Information (see footnote on the first page of this article): Characterization data and copies of ^{31}P, ^{1}H, and ^{13}C NMR spectra and MS and HRMS spectra for all compounds. Copies of the ^{1}H and ^{13}C NMR spectra.

Acknowledgments

This research was supported in part by a grant from Bayer CropScience and from the Agence Nationale de la Recherche et de la Technologie (ANRT).

[1] For reviews on isoprenoid metabolism, see: a) J. de Ruyck, J. Wouters, C. D. Poulter, *Curr. Enzyme Inhib.* **2011**, *7*, 79–95; b) C. Obiol-Pardo, J. Rubio-Martinez, S. Imperial, *Curr. Med. Chem.* **2011**, *18*, 1325–1338; c) A. J. Wiemer, C.-H. Hsiao, D. F. Wiemer, *Curr. Top. Med. Chem.* **2010**, *10*, 1858–1871; d) D. Ganjewala, S. Kumar, R. Luthra, *Curr. Issues Mol. Biol. (Suppl. 1)* **2009**, *11*, i35–i45; e) N. Singh, G. Cheve, M. A. Avery, C. R. McCurdy, *Curr. Pharm. Des.* **2007**, *13*, 1161–1177; f) P. J. Proteau, *Bioorg. Chem.* **2004**, *32*, 483–493.

[2] For recent papers on the synthesis of fosmidomycin analogues, see: a) C. T. Behrendt, A. Kunfermann, V. Illarionova, A. Matheeussen, M. K. Pein, T. Graewert, J. Kaiser, A. Bacher, W. Eisenreich, B. Illarionov, M. Fischer, L. Maes, M. Groll, T. Kurz, *J. Med. Chem.* **2011**, *54*, 6796–6802; b) M. Andaloussi, M. Lindh, C. Bjoerkelid, S. Suresh, A. Wieckowska, H. Iyer, A. Karlen, M. Larhed, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5403–5407; c) M. Andaloussi, L. M. Henriksson, A. Wieckowska, M. Lindh, C. Bjorkelid, A. M. Larsson, S. Suresh, H. Iyer, B. R. Srinivasa, T. Bergfors, T. Unge, S. L. Mowbray, M. Larhed, T. A. Jones, A. Karlen, *J. Med. Chem.* **2011**, *54*, 4964–4976; d) L. Deng, J. Diao, P. Chen, V. Pujari, Y. Yao, G. Cheng, D. Crick, B. V. V. Prasad, Y. Song, *J. Med. Chem.* **2011**, *54*, 4721–4734.

[3] A. Mac Sweeney, R. Lange, A. D'Arcy, A. Douangamath, J.-P. Surivet, C. Oefner, *J. Biomol. Chem.* **2005**, *345*, 115–127.

[4] a) J. W. Munos, X. Pu, S. O. Mansoorabadi, H. J. Kim, H.-W. Liu, *J. Am. Chem. Soc.* **2009**, *131*, 2048–2049; b) U. Wong, R. J. Cox, *Angew. Chem.* **2007**, *119*, 5014; *Angew. Chem. Int. Ed.* **2007**, *46*, 4926–4929; c) A. Mac Sweeney, R. Lange, R. P. M. Fernandes, H. Schulz, G. E. Dale, A. Douangamath, P. J. Proteau, C. Oefner, *J. Mol. Biol.* **2005**, *345*, 115–127; d) A. Argyrou, J. S. Blanchard, *Biochemistry* **2004**, *43*, 4375–4387; e) K. Reuter, S. Sanderbrand, H. Jomaa, J. Wiesner, I. Steinbrecher, E. Beck, M. Hintz, G. Klebe, M. T. Stubbs, *J. Biol. Chem.* **2002**, *277*, 5378–5384.

[5] For a review on phosphorus-based inhibitors of MMP, see a) A. Veerendhar, R. Reich, E. Breuer, *C. R. Chim.* **2010**, *13*, 1191–1202.

[6] A. Mucha, P. Kafarski, Ł. Berlicki, *J. Med. Chem.* **2011**, *54*, 5955–5980.

[7] Fosmidomycin analogues were docked in the enzyme using the Discovery Studio program, from Accelrys, version 2.0.

[8] a) G. T. Shechkov, I. A. Pevneva, O. A. Meshkova, *Russ. J. Appl. Chem.* **2003**, *76*, 1354–1355; b) A. Kers, I. Kers, J. Stawinski, M. Sobkowski, A. Kraszewski, *Tetrahedron* **1996**, *52*, 9931–9944; c) J. Stawinski, M. Thelin, E. Westman, R. Zain, *J. Org. Chem.* **1990**, *55*, 3503–3506.

[9] a) K. Bravo-Altamirano, Z. Huang, J.-L. Montchamp, *Tetrahedron* **2005**, *61*, 6315–6329; b) K. Bravo-Altamirano, J.-L. Montchamp, *Org. Lett.* **2006**, *8*, 4169–4171; c) K. Bravo-Altamirano, J.-L. Montchamp, *Tetrahedron Lett.* **2007**, *48*, 5755–5759; d) L. Coudray, I. Abrunhosa-Thomas, J.-L. Montchamp, *Tetrahedron Lett.* **2007**, *48*, 6505–6508; e) S. Deprele, J.-L. Montchamp, *J. Am. Chem. Soc.* **2002**, *124*, 9386–9387; f) Q. Xu, L.-B. Han, *Org. Lett.* **2006**, *8*, 2099–2101.

[10] S. Deprele, J.-L. Montchamp, *J. Org. Chem.* **2001**, *66*, 6745–6755.

[11] a) H.-J. Cristau, A. Herve, D. Virieux, *Tetrahedron* **2004**, *60*, 877–884; b) J.-L. Pirat, J. Monbrun, D. Virieux, J.-N. Volle, M. Tillard, H.-J. Cristau, *J. Org. Chem.* **2005**, *70*, 7035–7041.

[12] a) P. Majewska, P. Kafarski, B. Lejczak, *Tetrahedron: Asymmetry* **2006**, *17*, 2870–2875; b) F. Texier-Boullet, A. Foucaud, *Synthesis* **1982**, 165–166; c) F. Texier-Boullet, M. Lequitte, *Tetrahedron Lett.* **1986**, *27*, 3515–3516.

[13] M. Tao, R. Bihovsky, G. J. Wells, J. P. Mallamo, *J. Med. Chem.* **1998**, *41*, 3912–3916.

[14] P. P. Giannousis, P. A. Bartlett, *J. Med. Chem.* **1987**, *30*, 1603–1609.

[15] K. S. Bharti, S. K. Singh, *Pharmacia Lettre* **2009**, *1*, 39–51.

[16] For reviews on siderophores, see: a) A. du Moulinet d'Hardemare, G. Serratrice, J.-L. Pierre, *Mini-Rev. Org. Chem.* **2010**, *7*, 125–133; b) A. Butler, R. M. Theisen, *Coord. Chem. Rev.* **2010**, *254*, 288–296.

[17] For the pioneering work that was accomplished by Hirao et al., see: a) T. Hirao, T. Masanuga, Y. Ohshiro, T. Agawa, *Tetrahedron Lett.* **1980**, *21*, 3595–3598; b) T. Hirao, T. Masanuga, Y. Ohshiro, T. Agawa, *Synthesis* **1981**, 56; c) T. Hirao, T. Masanuga, N. Yamada, Y. Ohshiro, T. Agawa, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 909–913.

[18] a) J.-L. Pirat, J. Monbrun, D. Virieux, H.-J. Cristau, *Tetrahedron* **2005**, *61*, 7029–7036; b) G. P. Luke, W. C. Shakespeare, *Synth. Commun.* **2002**, *32*, 2951–2957; c) Y. Xu, J. Zhang, *J. Chem. Soc., Chem. Commun.* **1986**, 1606; d) J. Zhang, Y. Xu, G. Huang, H. Guo, *Tetrahedron Lett.* **1988**, *29*, 1955–1958.

[19] P.-A. Jaffrès, N. Bar, D. Villemin, *J. Chem. Soc. Perkin Trans. 1* **1998**, 2083–2089.

[20] a) T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi, K. Hirotsu, *J. Am. Chem. Soc.* **1984**, *106*, 158–163; b) J. M. Brown, P. J. Guiry, *Inorg. Chim. Acta* **1994**, *220*, 249–259; c) M. Rottländer, P. Knochel, *J. Org. Chem.* **1998**, *63*, 203–208.

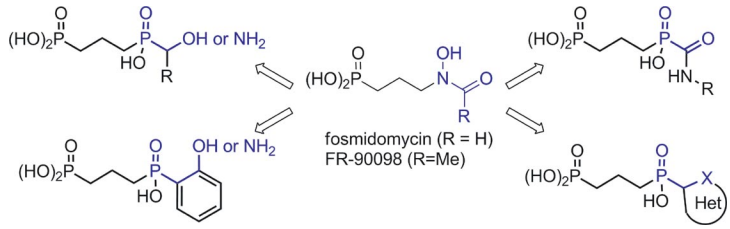
[21] For similar results on activated chloroarenes published, during the course of our study, by J.-L. Montchamp, see: E. L. Deal, C. Petit, J.-L. Montchamp, *Org. Lett.* **2011**, *13*, 3270–3273.

[22] a) P. Shahgaldian, A. W. Coleman, V. I. Kalchenko, *Tetrahedron Lett.* **2001**, *42*, 577–579; b) M. C. Allen, W. Fuhrer, B. Tuck, R. Wade, J. M. Wood, *J. Med. Chem.* **1989**, *32*, 1652–1661; c) M. Morr, C. Kakoschke, L. Ernst, *Tetrahedron Lett.* **2001**, *42*, 8841–8843.

[23] A. Baceiredo, G. Bertrand, P. Mazerolles, J.-P. Majoral, *J. Chem. Soc., Chem. Commun.* **1981**, 1197–1198.

Received: February 22, 2012
Published Online: ■

EurJOC European Journal of Organic Chemistry



Fosmidomycin (**1a**) and FR-90098 are potent inhibitors of 1-deoxy-D-xylulose-5-phosphate reductoisomerase (DXR). The replacement of the hydroxamic acid by functionalized phosphinic acids led to four types of targets which could act as analogues of fosmidomycin.

Keywords: Synthetic methods / Natural products / Enzymes / Inhibitors / Phosphorus / Palladium / Arylation

