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An Efficient and Green Method for the Synthesis of *N*-Phosphoramino *o*-Hydroxylphenyl α-Aminophosphonic Monoesters

Jianfeng Zhang, Yadan Wang, Zhanwei Cui, Fei Wang, Zhiwei Miao, and Ruyu Chen

State Key Laboratory of Elemento-Organic Chemistry, Research Institute of Elemento-Organic Chemistry, Nankai University Tianjin, 300071, People's Republic of China

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ABSTRACT: *An efficient and green method to the synthesis of N-protected o-hydroxylphenyl α-aminoalkylphosphonic monoesters is described. It consists of the three-component Mannich-type reaction of phosphoramides, carbonyl compounds (aldehydes or ketones), and 2-chlorobenzo[1,3,2] dioxaphospholes under solvent-free and catalyst-free conditions, followed by hydrolysis.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:596–601, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20483

INTRODUCTION

In recent years, α-aminophosphonic acids, as phosphorous analogues of α-aminocarboxylic acids, have been of great interest owing to their biological activity [1]. α-Aminophosphoryl compounds have been recognized for their high inhibitory activity toward such essential enzymes as renin, 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase, and HIV protease [2]. Also a large number of phosphate-phosphonate derivatives, bearing a P–N–C–P structure were synthesized and their significant herbicidal, antiviral, and fungicidal activities were reported [3].

Among numerous synthetic methods for the preparation of α-aminophosphonic acid derivatives, nucleophilic addition of phosphites to imines catalyzed by Lewis acids such as $InCl_3$ [4], $TaCl_5$–SiO_2 [5], and $Mg(ClO_4)_2$ [6] are common strategies. However, many of these methods utilize toxic organic solvents and in some cases the catalyst is used in stoichiometric amounts. To avoid the disadvantage of using organic solvents, a couple of modifications using montmorillonite clay [7], alumina [8], or $BiNO_3 \cdot 5H_2O$ [9] under solvent-free conditions under microwave irradiation has been reported. Very recently, the direct and solvent-free synthesis of α-aminophosphonates in the presence of catalysts such as Brønsted acids [10], $LiClO_4$ [11], $Mg(ClO_4)_2$ [12], and NBS/CBr_4 [13] has been reported. Ranu and Hajra [14] reported a practical and green alternative for the synthesis of α-aminophosphonates by the condensation of carbonyl compounds (aldehydes and ketones), amines, and neat diethyl phosphite at 75–80°C. We also reported the synthesis of *N*-phosphoramino α-aminophosphonates under solvent-free and catalyst-free conditions [15]. The monoesters of *N*-protected α-aminophosphonic

Corresponding to: Zhiwei Miao; e-mail: miaozhiwei@nankai.edu.cn.
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acid derivatives are the key intermediates for the synthesis of peptides having a phosphonamide linkage. So far, several methods have been developed for the preparation of α-aminoalkylphosphonic monoesters by using PCl_3 [16] or dichlorophosphites [17]. These methods required either irritative acetyl chloride or poisonous benzene as solvent, and so they were not environmentally benign and the yields were low.

To develop more efficient and environment friendly method to prepare structurally diverse α-aminoalkylphosphonic monoesters, we would like to disclose an efficient and green method to the synthesis of *N*-phosphoramino*o*-hydroxyphenyl 1-aminoalkylphosphonic monoesters with high yields.

RESULTS AND DISCUSSION

The Mannich-type reaction of trivalent phosphines has proved facile for the preparation of new types of α-aminoalkanephosphonate compounds [15]. Dialkyl phosphoramidates **1** were allowed to react with 2-chlorobenzo[1,3,2]dioxaphosphole **3** and various substituted aldehydes or ketones at 60°C to afford after hydrolysis the target *N*-phosphoramino 2-hydroxyphenyl α-aminoalkylphosphonic acid monoesters **4a–l** in good yields ranging from 80%–94% (Scheme 1). Aromatic aldehydes were found to produce much better yields than that of ketones (Table 1). The reactions were carried out using a one-pot procedure without solvent and under catalyst-free conditions. The crude products were purified by column chromatography, and their structures were characterized by ^{1}H NMR, ^{31}P NMR, ^{13}C NMR, and HRMS.

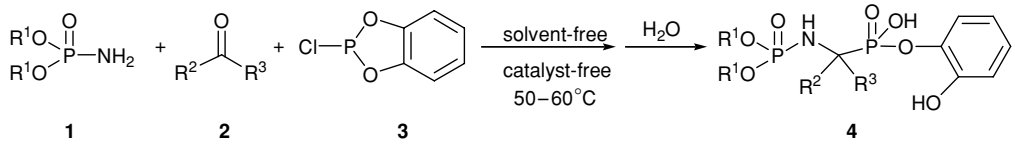
Because the two substituents (R^2, R^3) of the carbonyl compound **2** were different, two isomers were formed in the cases of **4a–j**. Owing to the isomerization phenomenon at the phosphorus center of the phosphonic monoesters group, the products were racemic stereoisomers. There was no stereoselectivity in this reaction. The ^{31}P NMR spectra show that both of the two P atoms appear as doublets due to the P–P splitting, the coupling constants are about 40 Hz. The two signals at ca. $\delta = 8$ and 22 ppm, the first one being attributable to the P-atom of the *N*-phosphoryl group, and the second one to that of the phosphonic monoesters group [15]. In ^{1}H NMR, the CHP protons show obviously quadruple peaks due to the pair of phosphorus atoms coupling with coupling constants of ca. $^2J_{P,CH}$ of 23 and $^3J_{P,CH}$ of 11 Hz.

The possible mechanism of the reactions is shown in Scheme 2, the reactions may occur via two unstable intermediates **5** and **6**. Because the five-membered phosphorus heterocyclic is unstable, intermediates **5** immediately reacted with the created hydrogen chloride to form **6**, which could be observed through tracing the reaction process with ^{31}P NMR spectra (Fig. 1).

In Fig. 1, the ^{31}P NMR spectra tracing the synthesis pathway of **4j**, spectra a exhibits four doublet peaks, corresponding to the existence of intermediate **6** and product **4j**. Peaks 1 and 4 at ca. 41 and 7 ppm belong to intermediate **6** with the phosphoryl chloride group and diethyloxyphosphinyl group [18]; peaks 2 and 3 belong to **4j**. ^{31}P NMR spectra b shows the chemical shift of **4j**, which is formed from **6** by hydrolysis.

To confirm the structure of products **4**, the product **4h** was recrystallized and its structure determined by X-ray diffraction analysis (Fig. 2). Crystallographic data were collected at 113(2) K using a Bruker SMART 1000 CCD diffractometer and Mo Kα radiation ($\lambda = 0.71070$ Å). The structure was solved by direct methods using SHELXS and refined using SHELXL-97 software. Crystal data for **4h**: $C_{17}H_{22}BrNO_7P_2$, $Mr = 494.21$, monoclinic, space group $P2_1/m$, $a = 11.206(4)$, $b = 12.843(4)$, $c = 14.851(5)$ Å, $\alpha = 90$, $\beta = 95.814(5)$, $\gamma = 90°$, $V = 2126.5(13)$ Å^3, $T = 113(2)$ K, $Z = 4$, $D_c = 1.544$ g cm^{-3}, μ(Mo Kα) = 2.121 mm^{-1}, $F(000) = 1008$. Least-squares refinement based on 26,139 reflections with $I > 2\sigma(I)$ (out of 5058 unique reflections) led to final value of $R_1 = 0.0520$ for 4588 observed reflections. The final $wR(F^2)$ was 0.0958 (all data).

Crystallographic data were deposited at Cambridge Crystallographic data Center, 12 Union Road, Cambridge CB2 1EZ, UK and are available from there under the deposition number CCDC 645801.



SCHEME 1 Synthesis of α-aminophosphonic monoesters **4** through phosphoramidates **1**, ketones or aldehydes **2**, and 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphane **3** under solvent-free and catalyst-free conditions.

TABLE 1 Preparation of α-aminophosphonic monoesters **4a–l**

Compounds of **4**	R^1	R^2	R^3	*Yield (%)*[a]
4a	CH_3CH_2	C_6H_5	H	85
4b	CH_3CH_2	4-$MeOC_6H_4$	H	89
4c	$CH_3CH_2CH_2$	4-MeC_6H_4	H	90
4d	$CH_3CH_2CH_2$	C_6H_5	H	92
4e	CH_3CH_2	4-ClC_6H_4	H	88
4f	CH_3CH_2	4-BrC_6H_4	H	94
4g	CH_3CH_2	2-ClC_6H_4	H	93
4h	CH_3CH_2	2-BrC_6H_4	H	94
4i	CH_3CH_2	4-$NO_2C_6H_4$	H	87
4j	CH_3CH_2	3,4-OCH_2O-C_6H_3	H	87
4k	CH_3CH_2	CH_3	CH_3	80
4l	CH_3CH_2	$(CH_2)_4$		81

[a]After purification by column chromatography (1.5 mmol scale).

CONCLUSION

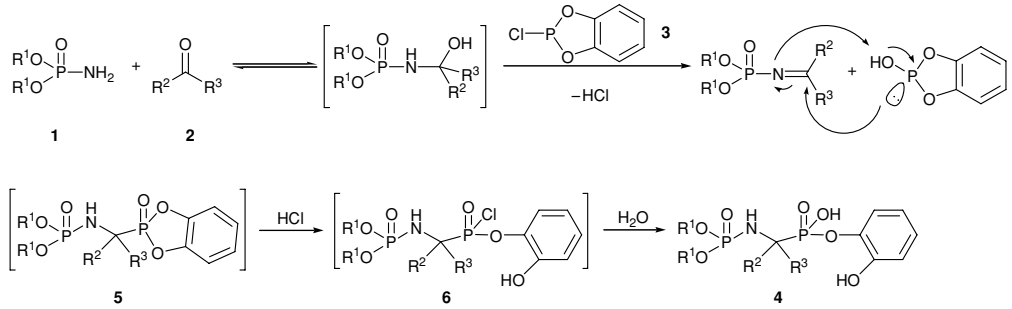
In conclusion, we have developed a convenient and rapid method for the synthesis of various *N*-phosphoramino α-aminoalkylphosphonic monoesters under catalyst-free and solvent-free conditions. The method was successfully applied to substituted aryl aldehydes and also aliphatic ketones. Unfortunately, we failed to get the desired product in the case of aliphatic aldehydes.

EXPERIMENTAL

All melting points were determined on Beijing-Tiker X-4 apparatus without correction. NMR spectra were measured on a Varian AS 400 or a Bruker AC 300 NMR instrument in $CDCl_3$, and chemical shifts were expressed as δ. Coupling constants J are given in hertz. Tetramethyl silane was used as an internal standard for ^1H NMR and 85% H_3PO_4 as an external standard for ^{31}P NMR spectroscopy. HRMS spectra were recorded on GCT-mass micromass spectrometer. IR spectra were recorded on a Equinox55 spectrometer, and band positions were reported in wave numbers (cm^{-1}). X-ray analysis was done on a Bruker SMART 1000 CCD diffractometer. Column chromatography was performed using silica gel H (10–40 μm, Haiyang Chemical Factory of Qingdao, People's Republic of China). The solvent was dried with sodium and redistilled.

General Procedure for the Synthesis of the α-Aminophosphonic Monoesters **4**

A carbonyl compound (1.5 mmol) was added dropwise to a stirred mixture of diethyl (dipropyl) phosphoramidate **1** (1.5 mmol) and 2-chlorobenzo[1,3,2] dioxaphosphole **3** [19] (1.5 mmol, 0.26 g) at 60°C. After stirring for 1–3 min, the mixtures went slimy and the reaction was finished. Then the viscous liquid was dissolved in AcOEt, followed by addition of H_2O (1.5 mmol, 0.03 g). The stirring was continued for additional 30 min, and after that time solvent was evaporated under vacuo. The crude product was purified by flash chromatography on silica gel (AcOEt/petroleum ether 4:1 to AcOEt/MeOH 10:1 as eluent). The obtained results are summarized in Table 1.



SCHEME 2 Possible reaction mechanism for the synthesis of the α-aminophosphonic monoesters **4**.

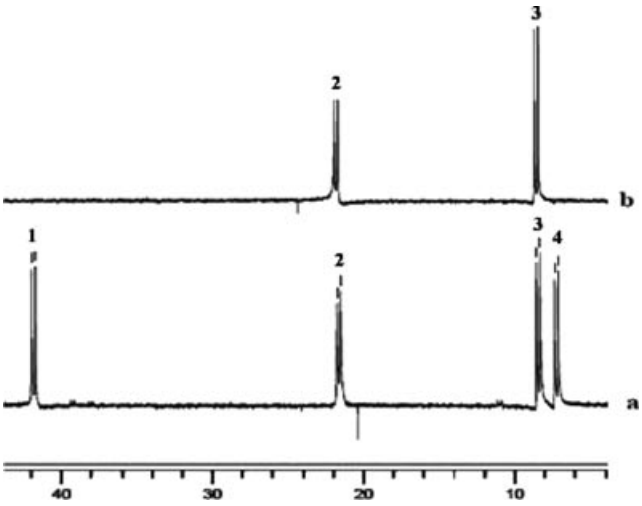


FIGURE 1 ^{31}P NMR spectra tracing the reaction process of **4j**: Spectra a exhibits four doublet peaks, peaks 1 and 4 belong to intermediate **6** with the phosphoryl chloride group and diethyloxyphosphinyl group, peaks 2 and 3 belong to **4j**; spectra b shows the chemical shift of **4j** after absolutely hydrolyzed.

o-Hydroxylphenyl 1-(N-Diethoxyphosphoryl-amino)phenylmethyl Phosphonate **4a**. White solid. mp 156–157°C. δ_P (121 MHz, $CDCl_3$, 85% H_3PO_4): 22.25 (d, $^3J = 40.8$); 8.88 (d, $^3J = 40.8$). δ_H (400 MHz; $CDCl_3$; Me_4Si): 7.74 (br, s, 2H, 2OH), 7.51–6.67 (m, 9 arom. CH), 6.04 (br, s, 1H, NH), 4.59 (dd, $^3J_{PH} = 11.6$, $^2J_{PH} = 22.6$, 1H, CH), 4.18–3.48 (m, 4H, 2OCH_2Me), 1.32 (t, $^3J = 7.0$, 3H, Me), 0.92 (t, $^3J = 7.0$, 3H, Me). δ_C (100 MHz; $CDCl_3$; Me_4Si): 148.66, 139.67, 138.61, 128.88, 128.69, 127.90, 125.45, 121.99, 119.74, 117.66 (12 arom. C), 62.15 (d,$^2J_{PC} = 5.2$, CH_2), 62.05 (d, $^2J_{PC} = 5.2$, CH_2), 54.31 (d, $^1J_{PC} = 155.0$, NCP), 16.52 (d, $^3J_{PC} = 7.2$, Me), 16.41 (d, $^3J_{PC} = 7.2$, Me). IR (KBr): 3432 (NH), 3175 (Ph—OH), 2970 (P—OH), 1260 (N—P=O), 1172 (HO—P=O). HRMS: *m/z* calcd for $C_{17}H_{23}NO_7P_2$ [M – H]$^-$: 414.0877, found: 414.0876.

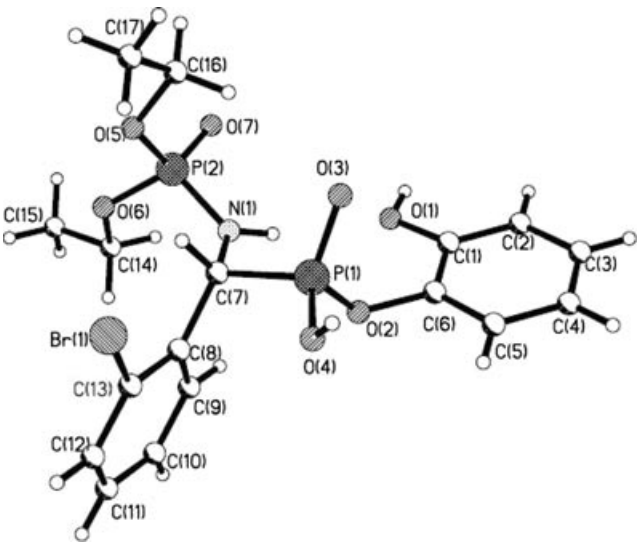


FIGURE 2 X-ray structure of **4h**.

o-Hydroxylphenyl 1-(N-Diethoxyphosphoryl-amino)(4-methoxyphenyl)methyl Phosphonate **4b**. White solid. mp 143–145°C. δ_P (121 MHz, $CDCl_3$, 85% H_3PO_4): 22.62 (d, $^3J = 40.9$); 7.96 (d, $^3J = 40.9$). δ_H (300 MHz; $CDCl_3$; Me_4Si): 8.22 (br, s, 2H, 2OH), 7.43–6.67 (m, 8 arom. CH), 5.95 (br, s, 1H, NH), 4.54 (dd, $^3J_{PH} = 11.7$, $^2J_{PH} = 22.5$, 1H, CH), 4.14–3.51 (*m*, 4H, 2OCH_2Me), 3.77 (s, 3H, OMe), 1.31 (t, $^3J = 6.8$, 3H, Me), 0.97 (t, $^3J = 6.8$, 3H, Me). δ_C (100 MHz; $CDCl_3$; Me_4Si): 147.62, 138.64, 138.54, 129.39, 127.94, 125.97, 121.27, 120.23, 118.21, 114.30 (12 arom. C), 63.70 (d, $^2J_{PC} = 4.8$, CH_2), 63.34 (d, $^2J_{PC} = 4.8$, CH_2), 55.43 (OMe), 52.98 (d, $^1J_{PC} = 159.6$ Hz, NCP), 16.19 (d, $^3J_{PC} = 7.2$ Hz, Me), 15.80 (d, $^3J_{PC} = 7.2$ Hz, Me). IR (KBr): 3440 (NH), 3195 (Ph—OH), 2960 (P—OH), 1263 (N—P=O), 1174 (HO—P=O). HRMS: *m/z* calcd for $C_{18}H_{25}NO_8P_2$ [M – H]$^-$: 444.0983, found: 444.0988.

o-Hydroxylphenyl 1-(N-Dipropoxyphosphoryl-amino)(4-methylphenyl)methyl Phosphonate **4c**. White solid. mp 134–136°C. δ_P (121 MHz, $CDCl_3$, 85% H_3PO_4): 21.59 (d, $^3J = 41.1$); 8.10 (d, $^3J = 41.1$). δ_H (300 MHz; $CDCl_3$; Me_4Si): 9.75 (br, s, 2H, 2OH), 7.39–6.65 (m, 8 arom. CH), 5.94 (br, s, 1H, NH), 4.56 (dd, $^3J_{PH} = 10.9$, $^2J_{PH} = 21.7$, 1H, CH), 4.13–3.39 (m, 4H, 2OCH_2CH$_2$Me), 2.31 (s, 3H, Ph*Me*), 1.72–1.23 (m, 4H, 2OCH$_2$CH_2Me), 0.93 (t, $^3J = 7.0$, 3H, Me), 0.66 (t, $^3J = 7.0$, 3H, Me). δ_C (75 MHz; $CDCl_3$; Me_4Si): 147.49, 138.40, 138.02, 132.78, 129.35, 127.92, 125.72, 121.11, 119.98, 118.00 (12 arom. C), 68.90 (d, $^2J_{PC} = 5.0$, O*C*H$_2$CH$_2$Me), 68.54 (d, $^2J_{PC} = 5.0$, O*C*H$_2$CH$_2$Me), 53.26 (d, $^1J_{PC} = 159.2$, NCP), 23.50 (d, $^3J_{PC} = 7.5$, OCH$_2$*C*H$_2$Me), 23.16 (d, $^3J_{PC} = 7.5$, OCH$_2$*C*H$_2$Me), 21.13 (Ph*Me*), 9.94 (OCH$_2$CH$_2$*Me*), 9.69 (OCH$_2$CH$_2$*Me*). IR (KBr): 3447 (NH), 3217 (Ph—OH), 2966 (P—OH), 1261 (N—P=O), 1173 (HO—P=O). HRMS: *m/z* calcd for $C_{20}H_{29}NO_7P_2$ [M – H]$^-$: 456.1347, found: 456.1344.

o-Hydroxylphenyl 1-(N-Dipropoxyphosphoryl-amino)phenylmethyl Phosphonate **4d**. White solid. mp 130–132°C. δ_P (121 MHz, $CDCl_3$, 85% H_3PO_4): 21.17 (d, $^3J = 41.1$); 7.96 (d, $^3J = 41.1$). δ_H (300 MHz; $CDCl_3$; Me_4Si): 9.31 (br, s, 2H, 2OH), 7.51–6.66 (m, 9 arom. CH), 6.01 (br, s, 1H, NH), 4.60 (dd, $^3J_{PH} = 11.8$, $^2J_{PH} = 22.7$, 1H, CH), 4.13–3.39 (*m*, 4H,

2OCH_2CH$_2$Me), 1.74–1.23 (*m*, 4H, 2OCH$_2$CH_2Me), 0.92 (t, $^3J = 7.4$, 3H, Me), 0.64 (t, $^3J = 7.4$, 3H, Me). δ_C (100 MHz; $CDCl_3$; Me_4Si): 147.65, 138.54, 136.06, 128.84, 128.46, 128.22, 126.00, 121.23, 120.21, 118.16 (12 arom. C), 69.10 (d, $^2J_{PC} = 5.4$, OCH_2CH$_2$Me), 68.73 (d, $^2J_{PC} = 5.1$, OCH_2CH$_2$Me), 53.67 (d, $^1J_{PC} = 157.6$, NCP), 23.70 (d, $^3J_{PC} = 7.5$, OCH$_2$CH_2Me), 23.33 (d, $^3J_{PC} = 7.7$, OCH$_2$CH_2Me), 10.16 (OCH$_2$CH$_2$*Me*), 9.91 (OCH$_2$CH$_2$*Me*). IR (KBr): 3426 (NH), 3217 (Ph—OH), 2977 (P—OH), 1256 (N—P=O), 1170 (HO—P=O). HRMS: *m/z* calcd for $C_{19}H_{27}NO_7P_2$ [M – H]$^-$: 442.1190, found: 442.1191.

o-Hydroxylphenyl 1-(N-Diethoxyphosphoryl-amino)(4-chlorophenyl)methyl Phosphonate **4e**. White solid. mp 162–163°C. δ_P (121 MHz, $CDCl_3$, 85% H_3PO_4): 20.85 (d, $^3J = 39.7$); 7.52 (d, $^3J = 39.7$). δ_H (300 MHz; $CDCl_3$; Me_4Si): 9.27 (br, s, 2H, 2OH), 7.45–6.70 (m, 8 arom. CH), 6.05 (br, s, 1H, NH), 4.57 (dd, $^3J_{PH} = 11.9$, $^2J_{PH} = 21.6$, 1H, CH), 4.16–3.52 (m, 4H, 2OCH_2Me), 1.31 (t, $^3J = 7.0$, 3H, Me), 0.97 (t, $^3J = 7.0$, 3H, Me). δ_C (100 MHz; $CDCl_3$; Me_4Si): 147.58, 138.47, 138.38, 134.51, 129.54, 129.02, 126.24, 121.31, 120.39, 118.37, 117.66 (12 arom. C), 63.87 (d, $^2J_{PC} = 4.3$, CH_2), 63.52 (d, $^2J_{PC} = 4.3$, CH_2), 52.95 (d, $^1J_{PC} = 167.5$, NCP), 16.17 (d, $^3J_{PC} = 7.0$, Me), 15.79 (d, $^3J_{PC} = 7.0$, Me). IR (KBr): 3415 (NH), 3224 (Ph—OH), 2993 (P—OH), 1280 (N—P=O), 1175 (HO—P=O). HRMS: *m/z* calcd for $C_{17}H_{22}ClNO_7P_2$ [M – H]$^-$: 448.0487, found: 448.0482.

o-Hydroxylphenyl 1-(N-Diethoxyphosphoryl-amino)(4-bromophenyl)methyl Phosphonate **4f**. White solid. mp 160–161°C. δ_P (162 MHz, $CDCl_3$, 85% H_3PO_4): 21.24 (d, $^3J = 38.5$); 8.33 (d, $^3J = 38.5$). δ_H (400 MHz; $CDCl_3$; Me_4Si): 9.75 (br, s, 2H, 2OH), 7.42–6.70 (m, 8 arom. CH), 5.96 (br, s, 1H, NH), 4.57 (dd, $^3J_{PH} = 11.0$, $^2J_{PH} = 22.1$, 1H, CH), 4.07–3.45 (m, 4H, 2OCH_2Me), 1.27 (t, $^3J = 7.0$, 3H, Me), 0.97 (t, $^3J = 7.0$, 3H, Me). δ_C (100 MHz; $CDCl_3$; Me_4Si): 147.58, 138.43, 138.32, 135.05, 131.98, 129.85, 126.27, 121.30, 120.40, 118.38 (12 arom. C), 63.88 (d, $^2J_{PC} = 4.9$, CH_2), 63.55 (d, $^2J_{PC} = 4.9$, CH_2), 53.04 (d, $^1J_{PC} = 156.1$, NCP), 16.19 (d, $^3J_{PC} = 7.2$, Me), 15.82 (d, $^3J_{PC} = 7.2$, Me). IR (KBr): 3397 (NH), 3216 (Ph—OH), 2961 (P—OH), 1283 (N—P=O), 1178 (HO—P=O). HRMS: *m/z* calcd for $C_{17}H_{22}BrNO_7P_2$ [M – H]$^-$: 491.9982, found: 491.9976.

o-Hydroxylphenyl 1-(N-Diethoxyphosphoryl-amino)(2-chlorophenyl)methyl Phosphonate **4g**. White solid. mp 149–151°C. δ_P (162 MHz, $CDCl_3$, 85% H_3PO_4): 21.89 (d, $^3J = 42.5$); 8.37 (d, $^3J = 42.5$). δ_H (400 MHz; $CDCl_3$; Me_4Si): 9.97 (br, s, 2H, 2OH), 7.85–6.66 (m, 8 arom. CH), 6.39 (br, s, 1H, NH), 5.28 (dd, $^3J_{PH} = 11.3$, $^2J_{PH} = 22.6$, 1H, CH), 4.21–3.45 (m, 4H, 2OCH_2Me), 1.33 (t, $^3J = 7.0$, 3H, Me), 0.92 (t, $^3J = 7.0$, 3H, Me). δ_C (100 MHz; $CDCl_3$; Me_4Si): 147.35, 138.59, 138.50, 134.53, 133.41, 129.71, 129.46, 127.99, 126.07, 121.29, 120.40, 118.21 (12 arom. C), 64.01 (d, $^2J_{PC} = 5.1$, CH_2), 63.39 (d, $^2J_{PC} = 5.1$, CH_2), 49.23 (d, $^1J_{PC} = 162.1$, NCP), 16.23 (d, $^3J_{PC} = 7.2$, Me), 15.65 (d, $^3J_{PC} = 7.2$, Me). IR (KBr): 3419 (NH), 3240 (Ph—OH), 2975 (P—OH), 1278 (N—P=O), 1180 (HO—P=O). HRMS: *m/z* calcd for $C_{17}H_{22}ClNO_7P_2$ [M – H]$^-$: 448.0487, found: 448.0490.

o-Hydroxylphenyl 1-(N-Diethoxyphosphoryl-amino)(2-bromophenyl)methyl Phosphonate **4h**. White solid. mp 162–164°C. δ_P (121 MHz, $CDCl_3$, 85% H_3PO_4): 21.87 (d, $^3J = 44.8$); 7.74 (d, $^3J = 44.8$). δ_H (300 MHz; $CDCl_3$; Me_4Si): 7.67 (br, s, 2H, 2OH), 7.43–6.60 (m, 8 arom. CH), 5.89 (br, s, 1H, NH), 5.17 (dd, $^3J_{PH} = 11.7$, $^2J_{PH} = 22.6$, 1H, CH), 4.31–3.48 (*m*, 4H, 2OCH_2Me), 1.19 (t, $^3J = 6.8$, 3H, Me), 0.83 (t, $^3J = 6.8$, 3H, Me). δ_C (75 MHz; $CDCl_3$; Me_4Si): 147.34, 139.51, 138.50, 133.53, 132.52, 129.46, 128.17, 125.60, 124.18, 121.33, 120.17, 117.85 (12 arom. C), 63.01 (d, $^2J_{PC} = 5.1$, CH_2), 62.37 (d, $^2J_{PC} = 5.1$, CH_2), 49.03 (d, $^1J_{PC} = 157.1$, NCP), 16.33 (d, $^3J_{PC} = 7.3$, Me), 15.75 (d, $^3J_{PC} = 7.3$, Me). IR (KBr): 3405 (NH), 3144 (Ph—OH), 2987 (P—OH), 1280 (N—P=O), 1171 (HO—P=O). HRMS: *m/z* calcd for $C_{17}H_{22}BrNO_7P_2$ [M – H]$^-$: 491.9982, found: 491.9976.

o-Hydroxylphenyl 1-(N-Diethoxyphosphoryl-amino)(4-nitrophenyl)methyl Phosphonate **4i**. White solid. mp 146–147°C. δ_P (162 MHz, $CDCl_3$, 85% H_3PO_4): 19.56 (d, $^3J = 37.4$); 7.70 (d, $^3J = 37.4$). δ_H (300 MHz; $CDCl_3$; Me_4Si): 10.22 (br, s, 2H, 2OH), 8.09–6.69 (m, 8 arom. CH), 6.10 (br, s, 1H, NH), 4.77 (dd, $^3J_{PH} = 11.4$, $^2J_{PH} = 24.2$, 1H, CH), , 4.11–3.65 (m, 4H, 2OCH_2Me), 1.23 (t, $^3J = 7.0$, 3H, Me), 0.96 (t, $^3J = 7.0$, 3H, Me). δ_C (100 MHz; $CDCl_3$; Me_4Si): 147.84, 147.52, 143.35, 138.16, 129.11, 126.51, 123.78, 121.29, 120.48, 118.26 (12 arom. C), 64.05 (d, $^2J_{PC} = 5.4$, CH_2), 63.81 (d, $^2J_{PC} = 5.4$, CH_2), 53.29 (d, $^1J_{PC} = 156.0$, NCP), 16.09 (d, $^3J_{PC} = 7.1$, Me), 15.85 (d, $^3J_{PC} = 7.1$, Me). IR (KBr): 3400 (NH), 3112 (Ph—OH), 2953 (P—OH), 1284 (N—P=O), 1183 (HO—P=O). HRMS: *m/z* calcd for $C_{17}H_{22}N_2O_9P_2$ [M – H]$^-$: 459.0728, found: 459.0730.

o-Hydroxylphenyl 1-(N-Diethoxyphosphoryl-amino) anisylmethyl Phosphonate **4j**. White solid. mp 155–157°C. δ_P (162 MHz, $CDCl_3$, 85% H_3PO_4): 21.69 (d, $^3J = 39.1$); 8.48 (d, $^3J = 39.1$). δ_H (400 MHz; $CDCl_3$; Me_4Si): 9.61 (br, s, 2H, 2OH), 7.02–6.66 (m,

7 arom. CH), 5.91 (d, $^2J_{HH'} = 4.5$, 2H, OCH_2O), 5.84 (br, s, 1H, NH), 4.52 (dd, $^3J_{PH} = 12.1$, $^2J_{PH} = 22.6$, 1H, CH), 4.12–3.62 (m, 4H, $2CH_2$), 1.27 (t, $^3J = 7.0$, 3H, Me), 1.01 (t, $^3J = 7.0$, 3H, Me). δ_C (100 MHz; $CDCl_3$; Me_4Si): 148.02, 147.86, 147.63, 147.59, 129.67, 126.02, 121.89, 121.25, 120.22, 118.24, 108.66, 108.57 (12 arom. C), 101.41 (OCH_2O), 63.76 (d, $^2J_{PC} = 5.3$, CH_2), 63.44 (d, $^2J_{PC} = 4.8$, CH_2), 53.34 (d, $^1J_{PC} = 159.4$, NCP), 16.19 (d, $^3J_{PC} = 7.0$, Me), 15.86 (d, $^3J_{PC} = 7.3$, Me). IR (KBr): 3441 (NH), 3223 (Ph—OH), 2995 (P—OH), 1244 (N—P=O), 1167 (HO—P=O). HRMS: *m/z* calcd for $C_{18}H_{23}NO_9P_2$ [M – H]$^-$: 458.0775, found: 458.0773.

o-Hydroxylphenyl 1-(N-Diethoxyphosphoryl-amino)(dimethyl)methyl Phosphonate **4k**. Colorless oil. δ_P (162 MHz, $CDCl_3$, 85% H_3PO_4): 27.52 (d, $^3J = 25.0$); 7.25 (d, $^3J = 25.0$). δ_H (400 MHz; $CDCl_3$; Me_4Si): 10.06 (br, s, 2H, 2OH), 7.20–6.76 (m, 4 arom. CH), 4.56 (br, s, 1H, NH), 4.10–3.97 (m, 4H, $2OCH_2Me$), 1.57 (s, 3H, Me), 1.53 (s, 3H, Me), 1.25 (t, 6H, $^3J = 7.0$, $2OCH_2Me$); δ_C (75 MHz; $CDCl_3$; Me_4Si): 147.66, 138.63, 125.51, 120.86, 119.75, 117.91 (6 arom. C), 63.38 (d, $^2J_{PC} = 5.5$, $2CH_2$), 51.61 (d, $^1J_{PC} = 161.0$, NCP), 23.73 (d, $^2J_{PC} = 7.0$, 2Me), 15.98 (d, $^3J_{PC} = 7.2$, $2OCH_2\mathit{Me}$). IR (KBr): 3250 (NH), 3121 (Ph—OH), 2993 (P—OH), 1269 (N—P=O), 1193 (HO—P=O). HRMS: *m/z* calcd for $C_{13}H_{23}NO_7P_2$ [M – H]$^-$: 366.0877, found: 366.0873.

o-Hydroxylphenyl 1-(N-Diethoxyphosphoryl-amino)cyclopentylmethyl Phosphonate **4l**. Colorless oil. δ_P (162 MHz, $CDCl_3$, 85% H_3PO_4): 22.03 (d, $^3J = 38.6$); 8.63 (d, $^3J = 38.6$). δ_H (400 MHz; $CDCl_3$; Me_4Si): 9.82 (br, s, 2H, 2OH), 7.26–6.71 (m, 4 arom. CH), 4.23–3.38 (m, 4H, $2OC\mathit{H}_2Me$), 3.68 (br, 1H, NH), 2.13–1.75 (m, 8H, $4CH_2$), 1.28–1.15 (m, 6H, 2Me); δ_C (100 MHz; $CDCl_3$; Me_4Si): 148.08, 139.03, 125.59, 120.88, 119.81, 118.29 (6 arom. C), 63.78 (d, $^2J_{PC} = 4.9$, $2OCH_2Me$), 61.33 (d, $^1J_{PC} = 162.2$, NCP), 35.65 ($2CH_2$), 23.99 (d, $^2J_{PC} = 11.9$, $2CH_2$), 16.19 (d, $^3J_{PC} = 6.8$, $2OCH_2\mathit{Me}$). IR (KBr): 3250 (NH), 3193 (Ph—OH), 2971 (P—OH), 1271 (N—P=O), 1200 (HO—P=O). HRMS: *m/z* calcd for $C_{15}H_{25}NO_7P_2$ [M – H]$^-$: 392.1033, found: 392.1035.

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