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### STUDIES ON ORGANOPHOSPHORUS COMPOUNDS 54. SYNTHESIS OF 1-HYDROXY-1-ALKYL(ARYL)-2-AMINOETHYLPHOSPHONIC ACIDS AND DERIVATIVES THEREOF

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## STUDIES ON ORGANOPHOSPHORUS COMPOUNDS

### 54. SYNTHESIS OF 1-HYDROXY-1-ALKYL(ARYL)-2-AMINOETHYLPHOSPHONIC ACIDS AND DERIVATIVES THEREOF

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An improved method is developed for the synthesis of 1-hydroxy-1-alkyl(aryl)-2-aminoethylphosphonic acids based on hydrogenation of dialkyl 1-hydroxy-1-alkyl(aryl)-2-nitroethylphosphonates over Raney nickel in acidic medium followed by hydrolysis. The instability of dialkyl 1-hydroxy-1-alkyl(aryl)-2-aminoethylphosphonates was rationalized by the formation of a reactive three-membered ring oxide species as the result of intermolecular interaction. The presence of *p*-toluenesulfonic acid during hydrogenation affords the corresponding ammonium tosylate which can be used directly for the formation of new phosphonopeptides containing a free hydroxyl group.

**Key words:** Phosphonic acid; amino; hydroxy derivative; 1-hydroxy-1-alkyl(aryl)-2-aminoethylphosphonic acids; phosphonopeptides.

## INTRODUCTION

As a phosphorus analogue of isomeric serine, 1-hydroxy-2-amino-ethylphosphonic acid, the unusual aminophosphonic acid containing a hydroxyl group was first isolated from *Acanthamoeba Castellanii*.<sup>1</sup> Biosynthesis of this amino-phosphonic acid has attracted considerable interests very recently.<sup>2,3</sup> Synthesis of various derivatives of this class of potentially bioactive compounds is important for structure-activity investigations. Alkyl substituted derivatives of 1-hydroxy-2-aminoethylphosphonic acid were prepared either by addition of dimethylphosphite to *N*-(2-oxoethyl) phthalimide followed by hydrazinolysis<sup>4</sup> or by aminative cleavage of the ethylene oxide ring of phosphomycin derivatives and subsequent hydrolysis.<sup>5,6</sup> The serious drawback of these methods is associated with the expensive starting materials. Direct hydrogenation of 1-hydroxy-1-alkyl-2-nitroethylphosphonates (**1**) obtained from the nucleophilic addition of nitromethane to acylphosphonates seems to be more practical for the synthesis of 1-hydroxy-1-alkyl(aryl)-2-aminoethylphosphonic acid (**2**). Unfortunately, the scope of application of the method reported by Baranov<sup>7,8</sup> is very limited, especially for the preparation of 1-hydroxy-1-aryl-2-aminoethylphosphonic acids (**2, h–n**). This is probably due to the unstability of the reaction product. Since the basicity of the amino group formed during hydro-

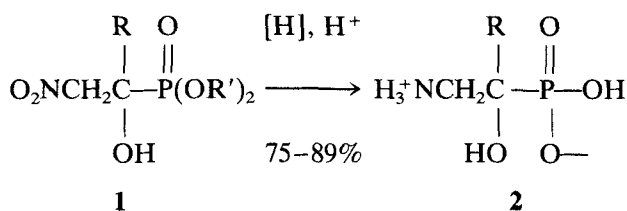
genation is strong enough to initiate the C-P and C-C cleavage of the resultant molecule. Therefore it was necessary to work out an improved method for the synthesis of the title compounds based on the careful examination of the reaction conditions.

In recent years, much attention has been paid on the synthesis of phosphonopeptides<sup>9,10</sup> and the evaluation of their biological activity. In the peptide formation, as a rule, it is usually required to protect either the amino- or phosphono-function during the coupling process. On the other hand, conversion of free aminophosphonic acids to N-protected or P-protected derivatives is generally accomplished by a multistep reaction sequence, due to the specific chemical properties of the molecule under investigation. Synthesis of phosphonopeptides with a free hydroxyl group is a matter of significant interest both from chemical and biological points of view. Since peptidic 1-hydroxy-phosphonates can be regarded as a new class of transition state analog renin inhibitors.<sup>11</sup> These situations encouraged us to devote our efforts to the synthetic study of suitable derivatives of **2** which can be used directly for the synthesis of phosphonopeptides bearing a free hydroxyl group.

## RESULTS AND DISCUSSION

### *Preparation of 1-Hydroxy-1-Alkyl(Aryl)-2-Aminoethylphosphonic Acids*

Compounds **1** are unstable in basic medium,<sup>9</sup> however, catalytic hydrogenation of **1** over Raney-Nickel in acetic acid gives **2** in excellent yield.



	a	b	c	d	e	f	g
R	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	n-C <sub>3</sub> H <sub>7</sub>	n-C <sub>4</sub> H <sub>9</sub>	cyc-C <sub>6</sub> H <sub>11</sub>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	p-FC <sub>6</sub> H <sub>4</sub> H <sub>2</sub>

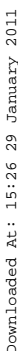
  

	h	i	j	k	l	m	n
R	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub>	C <sub>6</sub> H <sub>5</sub>	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	m-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	p-ClC <sub>6</sub> H <sub>4</sub>	m-FC <sub>6</sub> H <sub>4</sub>	o-FC <sub>6</sub> H <sub>4</sub>

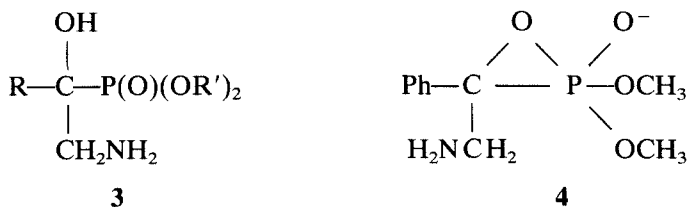
Acetic acid plays an important and interesting role in this reaction. It serves not only as solvent, but also as an accelerator in the hydrogenation process; it also prevents the decomposition of the reaction products. Meanwhile, the use of concentrated acetic acid should be avoided because in such case, the product isolated is usually dark green in color even after treatment with charcoal and multiple recrystallizations. As shown by Atomic Absorption Spectroscopic analysis, the green colored product contains one equivalent atomic weight of nickel. It is rea-

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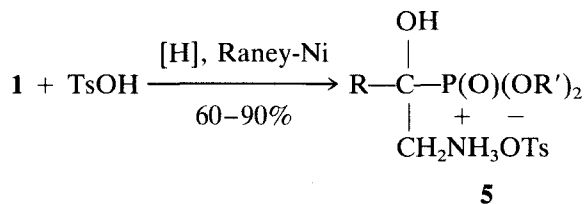
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On the other hand,  $^{31}\text{P}$ -NMR serves as an excellent tool to confirm the acceleration effect of dialkyl 1-hydroxy-1-alkyl(aryl)-2-aminoethylphosphonate (**3**) on the degradation of **1**. A mixture of **3** and **1** in  $\text{CDCl}_3$  was kept at room temperature for 8 hours. In the  $^{31}\text{P}$ -NMR spectrum of this mixture the signals at 16.29 ppm and 22.09 ppm assigned to **1** and **3** respectively disappeared completely, whereas five new signals at 20.51; 10.87; 9.27; 7.56 and  $-0.75$  ppm were observed.

#### *Preparation of Dialkyl 1-Hydroxy-1-Alkyl(Aryl)-2-Aminoethylphosphonate Tosylate*

For the synthesis of phosphonopeptides, one of the functionalities either amino or phosphoryl group should be masked before coupling reaction. However, **3** differs greatly from its free acid **2** in stability. The instability of **3** has been documented<sup>8,9</sup> without any explanation. Our experimental observation suggested that the instability of **3** is associated with the basic property of the amino function which abstracts a proton from the hydroxyl group as the result of an intermolecular interaction. The anion thus formed undergoes cyclization by nucleophilic attack on the phosphorus atom with the formation of the reactive species **4** which is then degraded to a series of by-products. This postulation is well supported by  $^{31}\text{P}$ -NMR. When **3** was kept at ambient temperature for 24 hours, the original signal was replaced by four new peaks at 21.58, 20.83, 20.37 and 7.24 ppm in  $^{31}\text{P}$ -NMR spectrum. It was reported that **3** can be isolated as the salt with picric acid.<sup>7</sup> But picric acid is inconvenient to handle and it is also difficult to remove picrate to generate the free amino-component. In this paper we report a convenient procedure for the preparation of **3** in the form of its tosylate.



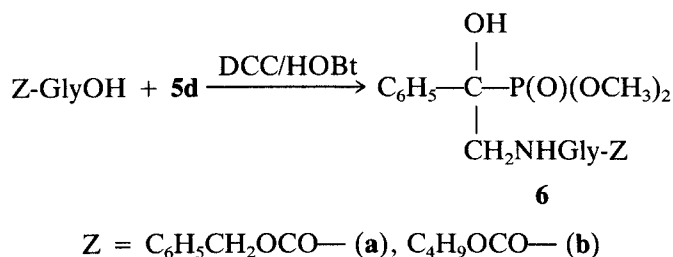
	a	b	c	d	e
R	$\text{CH}_3$	$\text{n-C}_3\text{H}_7$	$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2$	$\text{C}_6\text{H}_5$	$\text{p-CH}_3\text{C}_6\text{H}_4$
R'	$\text{i-C}_3\text{H}_7$	$\text{C}_2\text{H}_5$	$\text{CH}_3$	$\text{CH}_3$	$\text{C}_2\text{H}_5$

	f	g	h	i	j
R	m-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	p-ClC <sub>6</sub> H <sub>4</sub>	m-FC <sub>6</sub> H <sub>4</sub>	m-FC <sub>6</sub> H <sub>4</sub>	m-FC <sub>6</sub> H <sub>4</sub>
R'	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	i-C <sub>3</sub> H <sub>7</sub>

Hydrogenation proceeds smoothly in the presence of p-toluenesulfonic acid in ethanol. The tosylate of 1-hydroxy-1-alkyl(aryl)-2-aminoethylphosphonates (**5**) were isolated as a crystalline solid in good yield. They can be used directly in phosphonopeptide synthesis. By treating a dichloromethane solution of **5** with 10% K<sub>2</sub>CO<sub>3</sub>, an unstable **3** was isolate which decomposed completely after standing for 24 hours at room temperature.

### Synthesis of Phosphonopeptides Containing a Free Hydroxyl Group

New phosphono-peptides containing a free hydroxyl group namely dimethyl 1-hydroxy-1-phenyl-2-N-(N'-benzoxycarbonylglycyl) aminoethylphosphonate (**6a**) and dimethyl-1-hydroxy-1-phenyl-2-N-(N'-t-butoxycarbonylglycyl)-aminoethylphosphonate (**6b**) are prepared by coupling N-substituted glycine with **5d** employing the dicyclohexylcarbodiimide /N-hydroxybenzotriazole (DCC/HOBt) method.



The mixed anhydride method, which is very popular in peptide formation, can not be used in the coupling reaction. In the synthesis of this type of phosphonopeptides, any operation with alkaline washing should be avoided in order not to form reactive species related to **4**.

### EXPERIMENTAL

Melting points are uncorrected. <sup>1</sup>H-NMR are recorded on a Varian EM-360A (60MHz) apparatus. D<sub>2</sub>O or D<sub>2</sub>O/NaOD is used as solvent and TMS as external standard. <sup>31</sup>P-NMR are taken on a FX-90Q (90MHz) spectrometer employing CDCl<sub>3</sub> as solvent and 85% H<sub>3</sub>PO<sub>4</sub> as external standard. <sup>19</sup>F-NMR are measured on a Varian EM-360L (60MHz) spectrometer TFA as external standard. IR are taken from a Perkin-Elmer-983G spectrophotometer (KCl or KBr disc). Compounds **1** are synthesized by an improved method developed in our laboratory. 10% Pd/C is prepared from PdCl<sub>2</sub> according to conventional method, Raney-Nickel is prepared by digesting aluminum with sodium hydroxide from Al/Ni alloy. Z-Gly-OH, Boc-Gly-OH, DCC and HOBt are purchased from the Experimental Laboratories, Shanghai Institute of Biochemistry, Academia Sinica, and used as received.

#### 1-Hydroxy-1-alkyl-2-aminoethylphosphonic acid, **2**.

General procedure, **Method A**: To a stirred solution of **1** (0.02 mol) in 50 mL of ethanol and 10 mL of glacial acetic acid, is added 1 g of Raney-Ni washed thoroughly with ethanol. The mixture is then hydrogenated at r.t. (18–22°C) and atmospheric pressure until the absorption of hydrogen ceased. The catalyst is filtered off and washed thoroughly with ethanol. The filtrate and washings are combined and

the solvent is removed on a rotatory evaporator. The residue is refluxed with 40 mL of 8 N hydrochloric acid at 100°C for 8 h. After being cooled, the solution is extracted with benzene (10 mL) and the aqueous solution is then evaporated to dryness. After that, the resultant solid or syrupy material is dissolved in a minimum amount of methanol, to this solution propylene oxide is added with stirring until precipitation occurred. The products are collected by filtration and recrystallized from EtOH/H<sub>2</sub>O.

**1-Hydroxy-1-methyl-2-aminoethylphosphonic acid, 2a.** 75% yield, mp. 242–243°C (dec.) (Literature<sup>5</sup> 240–243°C). IR ( $\nu$ , cm<sup>-1</sup>): 3700–2000 (NH, OH), 1130 (P=O), 900 (P—O—H). <sup>1</sup>H-NMR ( $\delta$ , ppm): 1.19 (d, 3H, J = 12 Hz); 2.55–3.08 (m, 2H).

**2b.** 81% yield, mp. 242–244°C (dec.) (Literature<sup>8</sup> 235–236°C). IR ( $\nu$ , cm<sup>-1</sup>): 3700–2000 (OH, NH), 1135 (P=O), 919 (P—O—H). <sup>1</sup>H-NMR ( $\delta$ , ppm): 0.60–1.25 (m, 3H); 1.4–2.1 (m, 2H); 2.6–3.3 (m, 2H).

**2c.** 80% yield, mp. 240–241°C (dec.) (Literature<sup>8</sup> 231–232°C). IR ( $\nu$ , cm<sup>-1</sup>): 3100–2000 (NH, OH), 1120 (P=O), 918 (P—O—H). <sup>1</sup>H-NMR ( $\delta$ , ppm): 0.6–1.0 (t, 3H, J = 6Hz); 1.0–1.9 (m, 4H); 2.7 (d, 2H, J = 12Hz).

**2d.** 85% yield, mp. 234–235°C (dec.) (Literature<sup>8</sup> 230–231°C). IR ( $\nu$ , cm<sup>-1</sup>): 3700–2000 (NH, OH), 1125 (P=O), 918 (P—O—H). <sup>1</sup>H-NMR ( $\delta$ , ppm): 0.8–2.0 (m, 9H); 2.6–3.1 (m, 2H).

**2e.** 78% yield, mp. 236–237°C (dec.). Calculated for C<sub>8</sub>H<sub>18</sub>NO<sub>4</sub>P · H<sub>2</sub>O (241.0), C 39.83; H 8.30; N 5.81 (%). Found C 40.23; H 8.14; N 5.84 (%). IR ( $\nu$ , cm<sup>-1</sup>): 3700–2000 (NH, OH), 1127 (P=O), 904 (P—O—H). <sup>1</sup>H-NMR ( $\delta$ , ppm): 0.5–2.1 (m, 11H); 2.4–3.3 (m, 2H).

**2f.** 76% yield, mp. 240–242°C (dec.) (Literature<sup>8</sup> 238–239°C). IR ( $\nu$ , cm<sup>-1</sup>): 3600–2000 (NH, OH), 1105 (P=O), 905 (P—O—H). <sup>1</sup>H-NMR ( $\delta$ , ppm): 2.3–3.1 (m, 4H); 7.2 (s, 5H).

**2g.** 75% yield, mp. 239–240°C (dec.). Calculated for C<sub>9</sub>H<sub>13</sub>FNO<sub>4</sub>P (249.0), C 43.37; H 5.22; N 5.62 (%). Found C 42.79; H 5.17; N 5.46 (%). IR ( $\nu$ , cm<sup>-1</sup>): 3700–2150 (NH, OH), 1151 (P=O), 983 (C—F), 908 (P—O—H). <sup>1</sup>H-NMR ( $\delta$ , ppm): 2.0–2.7 (d, 2H, J = 14); 2.7–3.1 (m, 2H); 6.7–7.5 (m, 4H). <sup>19</sup>F-NMR: 37.5 ppm.

**2h.** 78% yield, mp. 246–247°C (dec.). Calculated for C<sub>10</sub>H<sub>14</sub>NO<sub>4</sub>P · H<sub>2</sub>O (263.0), C 45.63; H 6.84; N 5.32 (%). Found C 46.09; H 6.89; N 5.33 (%). IR ( $\nu$ , cm<sup>-1</sup>): 3700–2000 (NH, OH), 1133 (P=O), 918 (P—O—H). <sup>1</sup>H-NMR ( $\delta$ , ppm): 1.5–2.3 (m, 2H); 2.3–3.1 (m, 4H); 7.0–7.7 (m, 5H).

**2i.** 82%, mp. 231–232°C (dec.) (Literature<sup>8</sup> 226–227°C). Calculated for C<sub>8</sub>H<sub>12</sub>NO<sub>4</sub>P (217.0), C 44.20; H 5.58; N 6.45 (%). Found C 43.89; H 5.57; N 6.27 (%). IR ( $\nu$ , cm<sup>-1</sup>): 3700–2000 (NH, OH), 1140 (P=O), 905 (P—O—H). <sup>1</sup>H-NMR (TFA/TMS,  $\delta$ , ppm): 3.4 (m, 2H); 6.5–6.8 (m, 8H).

**2j.** 82% yield, mp. 225–226°C (dec.). Calculated for C<sub>9</sub>H<sub>14</sub>NO<sub>4</sub>P · H<sub>2</sub>O (249.2) C 43.37; H 6.48; N 5.62 (%). Found C 43.45; H 6.65; N 5.53 (%). IR ( $\nu$ , cm<sup>-1</sup>): 3700–2000 (NH, OH), 1138 (P=O), 900 (P—O—H). <sup>1</sup>H-NMR ( $\delta$ , ppm): 2.07 (s, 3H); 3.05 (d, 2H, J = 6Hz).

**2k.** 70% yield, mp. 218–220°C (dec.). Calculated for C<sub>9</sub>H<sub>14</sub>NO<sub>4</sub>P (231.2). C 43.37; H 6.48; N 5.62 (%). Found C 43.68; H 6.71; N 5.40 (%). IR ( $\nu$ , cm<sup>-1</sup>): 3700–1950 (NH, OH), 1151 (P=O), 909 (P—O—H). <sup>1</sup>H-NMR ( $\delta$ , ppm): 2.2 (s, 3H); 3.2 (d, 2H, J = 6Hz); 7.2 (m, 4H).

**2l.** 80% yield, mp. 235–236°C (dec.). Calculated for C<sub>8</sub>H<sub>11</sub>ClNO<sub>4</sub>P (251.6). C 38.18; H 4.42; N 5.56 (%). Found C 38.20; H 4.80; N 5.05 (%). IR ( $\nu$ , cm<sup>-1</sup>): 3700–2000 (NH, OH), 1487 (C—Cl), 1049 (P=O), 908 (P—O—H). <sup>1</sup>H-NMR ( $\delta$ , ppm): 3.5 (m, 2H, CH<sub>2</sub>N), 7.8 (m, 4H).

**2m.** 89% yield, mp. 237–238°C (dec.). Calculated for C<sub>8</sub>H<sub>11</sub>FNO<sub>4</sub>P (235.0). C 40.86; H 4.68; N 5.96 (%). Found: C 40.89; H 4.58; N 5.84 (%). IR ( $\nu$ , cm<sup>-1</sup>): 3700–1900 (NH, OH), 1143 (P=O), 1100 (C—F), 918 (P—O—H). <sup>1</sup>H-NMR ( $\delta$ , ppm): 2.99–3.65 (m, 2H); 6.64–7.50 (m, 4H). <sup>19</sup>F-NMR: 34.09 ppm.

**2n.** 84% yield, mp. 247–248°C (dec.). Calculated for C<sub>8</sub>H<sub>11</sub>FNO<sub>4</sub>P (235.0) C 40.86; H 4.68; N 5.96 (%). Found: C 40.17; H 4.86; N 5.72 (%). IR ( $\nu$ , cm<sup>-1</sup>): 3700–2000 (NH, OH), 1211 (P=O), 1132 (C—F), 907 (P—O—H). <sup>1</sup>H-NMR ( $\delta$ , ppm): 3.2 (d, 2H, J = 6Hz); 6.5–7.7 (m, 4H). <sup>19</sup>F-NMR: 29.5 ppm.

**Method B:** The procedure is similar with that described for method A except that instead of Raney-Ni, 10% Pd/C in glacial acid (30 mL) is used. After the hydrogenation, the catalyst is filtered off, the filtrate is directly refluxed with equal volume of concentrated hydrochloric acid for 8 h. After work up, **2a** and **2i** are obtained in 80% and 89% yields, respectively.

**Dialkyl 1-hydroxy-1-alkyl-2-aminoethylphosphonate tosylates, 5.** General procedure: 0.01 mol of **1** and 1.9 g of p-toluenesulfonic acid monohydrate are dissolved in 20–30 mL of ethanol, 0.5 g of Raney-Ni added and the mixture stirred. The resultant mixture is then hydrogenated at 20–25°C at atmospheric pressure until the absorption of hydrogen ceased (12–24 h). The catalyst is then filtered off and washed thoroughly with ethanol. The filtrate and washings are combined and evaporated on a rotatory evaporator. The solid or syrupy products thus obtained are triturated with diethyl ether until solidification occurred. The product is collected and recrystallized from ether/ethanol.

**5a.** 68% yield, mp. 72–74°C. Calculated for  $C_{16}H_{30}NO_7PS$  (411.5), C 46.69; H 7.36; N 3.40 (%). Found C 45.98; H 7.67; N 3.25 (%). IR ( $\nu$ ,  $cm^{-1}$ ): 3700–2000 (N—H, O—H), 1210 (P=O), 1000 (P—O—C), 680 (S—O).  $^1H$ -NMR ( $\delta$ , ppm): 1.2 (d, 12H,  $J$  = 12 Hz); 1.4 (d, 3H,  $J$  = 15 Hz); 2.2 (s, 3H); 3.1 (d, 2H,  $J$  = 9 Hz); 4.2–5.0 (m, 2H, inv. in  $H_2O$ ); 7.2 (d, 2H,  $J$  = 7 Hz); 7.6 (d, 2H,  $J$  = 7 Hz).

**5b.** 60% yield, mp. 113–114°C. Calculated for  $C_{16}H_{30}NO_7PS$  (411.5). C 46.69; H 7.36; N 3.40 (%). Found C 46.37; H 7.38; N 3.31 (%). IR ( $\nu$ ,  $cm^{-1}$ ): 3700–2000, 1200, 1030, 680.  $^1H$ -NMR ( $\delta$ , ppm): 0.82 (t, 3H,  $J$  = 6 Hz); 1.0–2.0 (m, 10 H); 2.22 (s, 3H); 3.10 (d, 2H,  $J$  = 12 Hz); 3.85–4.37 (m, 4H); 7.20 (d, 2H,  $J$  = 8 Hz); 7.55 (d, 2H,  $J$  = 8 Hz).

**5c.** 87% yield, mp. 134–135°C. Calculated for  $C_{19}H_{28}NO_7PS$  (446.0). C 51.12; H 6.28; N 3.14 (%). Found C 50.64; H 6.23; N 3.07 (%). IR ( $\nu$ ,  $cm^{-1}$ ): 3700–2000, 1210, 1030, 680.  $^1H$ -NMR ( $\delta$ , ppm): 1.45–2.13 (m, 2H); 2.00 (s, 3H); 2.27 (t, 2H); 2.84 (d, 1H,  $J$  = 6 Hz); 3.10 (s, 1H); 3.57 (d, 6H,  $J$  = 11 Hz); 6.95 (s, 7H); 7.30 (d, 2H,  $J$  = 8).

**5d.** 90% yield, 154–155°C. Calculated for  $C_{17}H_{24}NO_7PS$  (417.0) C 48.92; H 5.76; N 3.36 (%). Found C 48.62; H 5.39; N 3.03 (%). IR ( $\nu$ ,  $cm^{-1}$ ): 3500–2000, 1180, 1025, 675.  $^1H$ -NMR ( $\delta$ , ppm): 2.12 (s, 3H); 3.2–3.6 (q, 8H); 6.9–7.5 (m, 9H).

**5e.** 72% yield, mp. 126–127°C. Calculated for  $C_{20}H_{30}NO_7PS$  (459.5) C 52.28; H 6.58; N 3.05 (%). Found C 52.24; H 6.56; N 3.04 (%). IR ( $\nu$ ,  $cm^{-1}$ ): 3700–2000, 1215, 1030, 680.  $^1H$ -NMR ( $\delta$ , ppm): 0.8–1.2 (m, 6H, 2CH<sub>3</sub>); 2.13 (s, 3H, CH<sub>3</sub>Ar); 3.3–4.1 (m, 6H, 2CH<sub>2</sub>O + CH<sub>2</sub>N); 6.9–7.65 (m, 8H<sub>arom</sub>).

**5f.** 70% yield, mp. 139–140°C. Calculated for  $C_{20}H_{30}NO_7PS$  (459.5) C 52.28; H 6.58; N 3.05 (%). Found C 52.78; H 6.39; N 3.04 (%). IR ( $\nu$ ,  $cm^{-1}$ ): 3700–2000, 1220, 1030, 685.  $^1H$ -NMR ( $\delta$ , ppm): 0.85–1.25 (m, 6H, 2CH<sub>3</sub>); 2.20 (s, 3H, CH<sub>3</sub>Ar); 3.56 (d, 2H,  $J$  = 8 Hz, CH<sub>2</sub>N); 3.8–4.1 (m, 4H, 2CH<sub>2</sub>O); 7.1–7.6 (m, 8H<sub>arom</sub>).

**5g.** 83% yield, mp. 160.5–162°C. Calculated for  $C_{19}H_{27}ClNO_7PS$  (480.0) C 47.50; H 5.68; N 2.92; Cl 7.39 (%). Found C 46.99; H 5.48; N 2.90; Cl 7.37 (%). IR ( $\nu$ ,  $cm^{-1}$ ): 3700–2000, 1210, 1030, 680.  $^1H$ -NMR ( $\delta$ , ppm): 1.00–1.35 (m, 6H); 2.27 (s, 3H); 3.50–4.27 (m, 6H, 2CH<sub>2</sub>O + CH<sub>2</sub>N); 7.05–7.80 (m, 8H<sub>arom</sub>).

**5h.** 96% yield, mp. 149–150°C. Calculated for  $C_{17}H_{23}FNO_7PS$  (435.4) C 46.89; H 5.33; N 3.22 (%). Found C 46.56; H 5.37; N 3.08 (%). IR ( $\nu$ ,  $cm^{-1}$ ): 3700–2000, 1210, 1060, 1030, 680.  $^1H$ -NMR ( $\delta$ , ppm): 2.25 (s, 3H); 3.18–3.94 (m, 8H, CH<sub>2</sub>N + 2CH<sub>3</sub>OP); 6.78–7.78 (m, 8H<sub>arom</sub>).  $^{19}F$ -NMR ( $D_2O/TFA$ ,  $\delta$ ): 35.0 ppm.

**5i.** 92% yield, mp. 137–138°C. Calculated for  $C_{19}H_{27}FNO_7PS$  (463.0) C 49.24; H 5.83; N 3.02 (%). Found C 49.63; H 5.81; N 3.00 (%). IR ( $\nu$ ,  $cm^{-1}$ ): 3500–2000, 1210, 1060, 1030, 680.  $^1H$ -NMR ( $\delta$ , ppm): 0.85–1.48 (m, 6H); 2.35 (s, 3H); 3.33–4.36 (m, 6H, 2CH<sub>2</sub>O + CH<sub>2</sub>N); 6.93–7.90 (m, 8H<sub>arom</sub>).  $^{19}F$ -NMR ( $D_2O/TFA$ ,  $\delta$ ): 35.0 ppm.

**5j.** 84% yield, mp 144–145°C. Calculated for  $C_{21}H_{31}FNO_7PS$  (491.4) C 51.32; H 6.31; N 2.85 (%). Found C 51.51; H 5.71; N 2.74 (%). IR ( $\nu$ ,  $cm^{-1}$ ): 3700–2000, 1210, 1030, 1010, 680.  $^1H$ -NMR ( $\delta$ , ppm): 0.7–1.5 (m, 12H); 2.2 (s, 3H); 3.5 (d, 2H, CH<sub>2</sub>N,  $J$  = 6 Hz); 6.8–7.8 (m, 8H<sub>arom</sub>).  $^{19}F$ -NMR ( $D_2O/TFA$ ,  $\delta$ ): 35.5 ppm.

**Diethyl 1-hydroxy-1-(*m*-fluorophenyl)-2-aminoethyl-phosphonate (3i).** A suspension of **5i** (0.5g) in  $CH_2Cl_2$  (30 mL) is quickly treated with 10 mL 10%  $K_2CO_3$  solution. The organic layer is separated and the aqueous layer is extracted with  $CH_2Cl_2$  (3  $\times$  10 mL). The combined  $CH_2Cl_2$  solution is dried over anhydrous sodium sulfate. After removal of the solvent in vacuum, the  $^{31}P$ -NMR and  $^1H$ -NMR of the oily product thus obtained are immediately recorded.  $^1H$ -NMR ( $CDCl_3/TMS$ ,  $\delta$ , ppm): 1.10–1.60 (t, 6H,  $J$  = 6 Hz); 2.6–3.7 (br, 4H, CH<sub>2</sub>N, NH<sub>2</sub>); 3.8–4.5 (m, 4H, 2CH<sub>2</sub>O); 5.30 (s, 1H, OH); 6.8–7.7 (m, 4H<sub>arom</sub>).  $^{31}P$ -NMR ( $CDCl_3/85\% H_3PO_4$ ,  $\delta$ ): 22.09 ppm. After standing for one day, its  $^{31}P$ -NMR spectrum showed several signals at 21.58, 20.83, 20.39 and 7.24 ppm.

**Dimethyl 1-hydroxy-1-phenyl-2-*N'*-(*benzoxycarbonyl*glycyl)-aminoethylphosphonate, 6a.** A suspension of Cbz-glycine (0.15 g 0.72 mmol), HOBT (0.14 g, 1 mmol) and DCC (0.15 g, 0.72 mmol) in 5 mL of  $CH_2Cl_2$  are stirred at r.t. for 4 h. then cooled to  $-5^\circ C$  with an ice-salt bath. At that temp. **5d** (0.3 g, 0.72 mmol) is added followed by dropwise addition of triethylamine (0.72 mmol). The temperature is maintained at  $0-5^\circ C$  for 2 h. and then raised to r.t. ( $20^\circ C$ ) for 12 h. Finally 20 mL of ethylacetate is added and the undissolved materials are filtered off. After evaporation of the solvents under reduced pressure the product is separated by chromatography on a silica TLC plate; yield 50% of **6a**, a white powder, m.p. 170–172°C. Calculated for  $C_{26}H_{23}N_2O_7P$  (436.4). P 7.10 (%); Found P 6.70 (%). IR ( $\nu$ ,  $cm^{-1}$ ): 3400, 1695, 1200, 1020.  $^1H$ -NMR ( $CDCl_3/TMS$ ,  $\delta$ , ppm): 3.25–3.85 (m, 10H 2OCH<sub>3</sub> + 2NCH<sub>2</sub>); 5.05 (s, 2H, CH<sub>2</sub>Ph); 7.35 (m, 10H<sub>arom</sub>).

**Dimethyl 1-hydroxy-1-phenyl-2-*N'*-(*t*-butoxycarbonyl)glycyl) amino ethylphosphonate, 6b.** Boc-glycine (0.13 g, 0.74 mmol) is coupled with **5d** in a similar manner as described above. After work-up, **6b** is obtained in 86% yield as a colorless crystalline solid, mp. 157–158°C. Calculated for  $C_{17}H_{27}N_2O_7P$



(402.4). C 50.74; H 6.78; N 6.96; P 7.70 (%). Found C 50.75; H 6.57; N 6.91; P 7.40 (%). IR ( $\nu$ ,  $\text{cm}^{-1}$ ): 3422, 3254, 1684, 1202, 1174, 1031.  $^1\text{H}$ -NMR ( $\text{CDCl}_3/\text{TMS}$ ,  $\delta$ , ppm): 1.26 [s, 9H,  $(\text{CH}_3)_3\text{C}$ ]; 3.24–3.90 (m, 10H,  $2\text{NCH}_2 + 2\text{CH}_2\text{O}$ ); 4.40 (br, 2H,  $2\text{CONH}$ ); 6.90–7.60 (m,  $5\text{H}_{\text{arom}}$ ). Ms (EI, 70 eV); 403 ( $\text{M} + 1$ , 11.72%); 293 (10.23%); 237 (44.89%); 216 (90.48%); 193 (24.47%); 105 (100%); 80 (50.28%).

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