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[1-Hydroxy-1-(2-hydroxyphenyl)ethyl]phosphonates and -phosphinates: convenient synthesis through intramolecular Abramov reaction and protective activity against influenza A

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ABSTRACT

A combination of intramolecularization and tandem reaction methodologies has been applied to the synthesis of diethylammonium[1-hydroxy-1-(2-hydroxyphenyl)ethyl]phosphonates and -phosphinates, which were found to be unavailable through a standard intermolecular hydrophosphonylation/hydrolysis sequence. A mild hydrolysis of amidophosphites and -phosphonites, bearing 2-acetylphenoxy-fragment and a hydrolytically labile diethylamino-group at the same trivalent phosphorus atom, directly afforded the title compounds. The overall process probably consists of three steps: (i) selective hydrolysis of the P(III)–N bond to generate the hydrophosphoryl-type intermediates; (ii) formation of the strained 2-substituted 3-hydroxy-2-oxo-2,3-dihydro-1,2-benzoxaphospholes through intramolecular Abramov reaction; (iii) hydrolysis of the endocyclic P(IV)–O bond in the 1,2-benzoxaphospholes to give the acyclic products. Being only modestly active in vitro, at high dosage non-toxic water-soluble title α,γ-dihydroxyphosphonates and -phosphinates exhibited beneficial, but short-lasting effect against experimental influenza A infection (H3N2) in mice.

1. Introduction

Ternary α-hydroxyphosphonates and the parent α-hydroxyphosphonic acids have attracted significant attention due to their fascinating biological activity, particularly as enzyme inhibitors,[1] antitumor,[2] antibacterial,[3] and antiviral agents.[4] The most general method for preparation of α-hydroxyphosphonates and related species consists of addition of various hydrophosphoryl compounds to aldehydes and activated ketones (Abramov reaction).[5–7] However, synthesis of quaternary α-hydroxyphosphonates by conventional intermolecular Abramov hydrophosphonylation of less electrophilic unactivated ketones is frequently troublesome. Although hydrophosphonylation of unactivated ketones can be promoted by heating and/or strong base catalysis,[5–7] the same factors favor the competing retro-Abramov reaction[8,9] and phospha-Brook rearrangement,[9,10] thus hampering production of quaternary α-hydroxyphosphonates. These drawbacks stimulated a search of milder methods for hydrophosphonylation of ketones, such as heterogeneous catalysis with basic alumina,[11] alumina impregnated by KF or CsF,[12] impregnated natural phosphates and fluoroapatites,[13] homogeneous catalysis by moderately basic complex of Et_3N with $MgCl_2$[14] or by alkaloid organocatalysts.[15] In 2012, Abramov addition to acetophenones and some aliphatic ketones was found to proceed efficiently at rt in the presence of TMS_2N-supported rare earth complexes with calix[4]-pyrrolyl-ligand[16] or more structurally simple 2-(arylaminomethyl)pyrrolyl-ligand.[17] Intermolecular hydrophosphonylation of acetophenones and even benzophenones was also accomplished using TMS_2N-supported alkaline earth complexes of sterically hindered monoanionic *ortho*-arylamino *N*-arylbenzalimines and β-diaryliminoketones.[18] However, catalytic activity of these complexes was essentially suppressed for aromatic ketones with any substituents in the ortho-position.[17,18]

Over the last 2 decades, the most significant progress in the Abramov phosphonylation have been achieved owing to use of Lewis acid catalysts, which essentially activates both reaction components. Application of chiral Lewis acid catalysts allowed elaboration of highly efficient enantioselective syntheses of ternary α-hydroxyphosphonates from aldehydes.[19] In 2009 Feng et al. reported that $(i\text{-PrO})_4Ti$ can efficiently catalyze Abramov hydrophosphonylation of some acetophenones and aliphatic ketones.[20] Application of aluminum halide complexes with chiral tridentate hydrogenated Schiff bases granted remarkable enantioselectivity in

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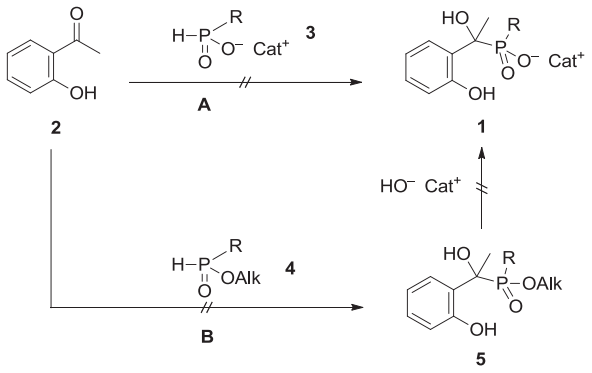
the intermolecular Abramov hydrophosphonylation of some simple ketones under very mild conditions.[21] Nonetheless, a reliable synthesis of multifunctionally substituted quaternary α-hydroxyphosphonates still remains a challenge.

Inspired by enzymatic catalysis intramolecularization of chemical processes,[22] which relies on an artificial pre-organization of the reaction centers into a close proximity to each other, serves as one of the most fruitful and general strategies for synthesis of structurally complex organic compounds.[23] So far, intramolecular Abramov hydrophosphonylation[24] and the mechanistically related Kabachnik–Fields reaction have been sporadically applied for the synthesis of phosphorus heterocycles,[25] but have never been extended to the preparation of acyclic α-hydroxy- or α-aminophosphonates.

In the course of our studies toward novel anti-influenza agents,[26] we were interested in preparation and testing of α,γ-dihydroxyphosphonates and -phosphinates of type **1** (Scheme 1), possessing a quaternary α-hydroxyphosphonate (-phosphinate) scaffold. Herein, we report an expedient synthesis of racemic diethylammonium[1-hydroxy-1-(2-hydroxyphenyl)ethyl] phosphonates and -phosphinates **1a**–**e** through a hydrolytic tandem-type three-steps process, in which the key step proceeds presumably as an intramolecular Abramov addition to an acetophenone moiety. We also disclose the results on in vitro and in vivo evaluation of compounds **1** against influenza A (H3N2).



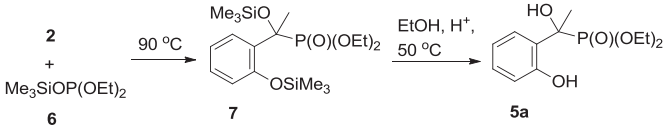
Scheme 1. Initially proposed synthesis of monoanionic [1-hydroxy-1-(2-hydroxyphenyl)ethyl]phosphonates and -phosphinates **1** through intermolecular Abramov hydrophosphonylation.

2. Results and discussion

2.1. Chemistry

At the outset of this work, we considered preparation of racemic compounds **1** using a common intramolecular version of the Abramov reaction as outlined in Scheme 1.

Indeed, a trivial retrosynthetic heterolytic dislocation of P–C and O–H bonds in **1** leads to 2-acetylphenol (**2**) and the salts of hypophosphites (hypophosphonites) **3**. It indicates that intermolecular hydrophosphonylation of **2** as a carbonyl substrate might directly give the desired compounds **1** using **3** as hydrophosphoryl reagents (path **A**).[6,27] According to path **B**, the same carbonyl component **2** and dialkylphosphites or alkylphosphonites **4** could be applied for constructing of α,γ-dihydroxyphosphonates or -phosphinates **5**, but subsequent hydrolysis is required to obtain the target compounds **1**. However, in spite of a formally simple character of both routes **A** and **B**, we encountered severe troubles in each step of the way. In our hands, neither diethylammonium ethylhypophosphite (**3a**) (R=EtO, Cat^+=$Et_2NH_2^+$) nor diethylphosphite (**4a**) (R=AlkO=EtO) reacted with **2** being alone or in the presence of standard basic catalysts like Et_2NH or EtONa[6a,b] at 20–60 °C in different solvents (EtOH, 1,4-dioxane, toluene). As observed by ^{31}P NMR spectra, upon heating of **3a** or **4a** with **2** and EtONa at 80–110 °C a number of reactions took place to give a complex reaction mixture. Our continuous attempts to accomplish selective hydrophosphonylation of **2** by phosphite **4a** using other simple catalysts like basic alumina,[11] KF, and CsF alone or being impregnated on alumina,[12] complex $MgCl_2 \times Et_3N$[14] and (i-PrO)$_4$Ti were also unsuccessful.[20] On the other hand, similarly to the previously reported reactions of substituted in the benzene ring TMS-protected 2-acetylphenols[28] and 2-trifluoroacetylphenols,[29] phosphonylation of **2** with excess trimethylsilyl diethylphosphite (**6**) at 90–100 °C smoothly afforded the bis-silylated quaternary α,γ-dihydroxyphosphonate **7** in 82% yield (Scheme 2). Desilylation of **7** with excess ethanol at 50 °C under slightly acidic conditions gave the dihydroxyphosphonate **5a** quantitatively.

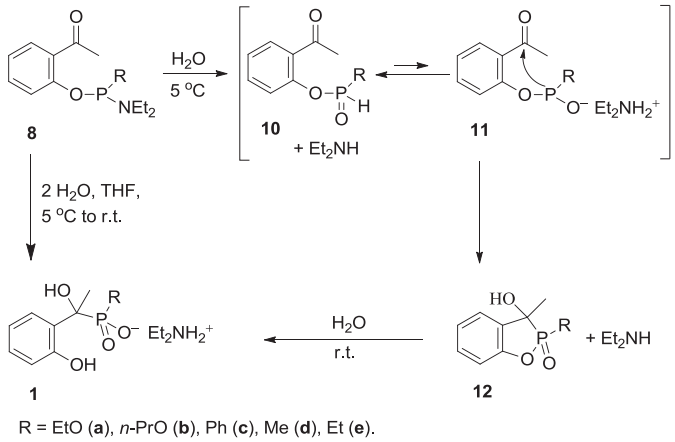


Scheme 2. Synthesis of α,γ-dihydroxyphosphonate **5a** using silylphosphite **6**.

Since water soluble compounds are the most suitable entities for biological studies, we attempted to convert the diester **5a** to some salts of ethyl[1-hydroxy-1-(2-hydroxyphenyl)ethyl] phosphonic acid of type **1** (Scheme 1). So far, only a few examples of selective dealkylation of ternary[30] and quaternary dialkyl α-hydroxyphosphonates to the corresponding salts of alkyl α-hydroxyphosphonic acids using alkali metal iodides have been reported.[31] However, NaI in boiling acetonitrile did not dealkylate the diester **5a**. Upon attempting an alkaline hydrolysis of **5a** at rt, it decomposed to **2** and **4a** (retro-Abramov reaction) similarly to the reported ternary α-hydroxyphosphonate.[32]

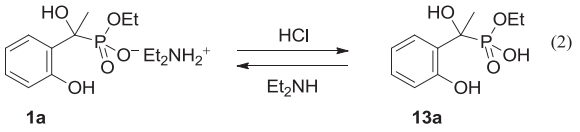
To overcome the troubles derived from the standard intermolecular Abramov reaction (Scheme 1), we designed a synthetic route to **1**, which takes advantage from intramolecularization[22,23] of the key hydrophosphonylation step and a tandem character of the overall process.[33] According to this design, masked hydrophosphoryl or hydrophosphonyl function should be temporary connected to phenolic oxygen of 2-acetylphenoxy-fragment to arrange the reaction centers in propinquity. Upon unmasking, a viable intramolecular Abramov hydrophosphonylation should take place followed by disconnection of phosphonyl function from phenolic oxygen atom. Amidophosphites and amidophosphonites were considered as suitable immediate precursors of hydrophosphoryl and hydrophosphonyl compounds, because the latter could be generated upon a selective hydrolysis of P(III)–N bonds.[34] Appropriate for our purpose amidophosphites and -phosphonites **8**, in which 2-acetyl-phenoxy-fragment and a hydrolytically labile diethylamino-group are located at the same trivalent phosphorus atom, are readily available from **2** (Eq. 1).[35]

We were pleased to observe that a mild hydrolysis of **8** directly afforded the desired diethylammonium[1-hydroxy-1-(2-hydroxyphenyl)ethyl]phosphonates and -phosphinates **1** in 54–76% isolated yield (Scheme 3). The hydrolyses of **8** leading to **1** were carried out at 5–8 °C in 10–20 mmol scale, and water-soluble (5–10 mg/mL) microcrystalline products **1a**–**e** were isolated by a simple crystallization from the reaction mixture.



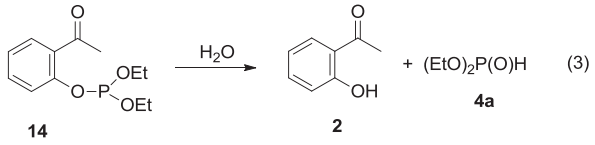
Scheme 3. Tandem hydrolysis of amidophosphites and -phosphonites **8** leading to diethylammonium[1-hydroxy-1-(2-hydroxyphenyl)ethyl]phosphonates and -phosphinates **1**.

The structures of the products **1** were determined by ^{1}H, ^{13}C, ^{31}P NMR, and IR-spectra, the combustion analyses data matched the molecular composition of **1**. In $^{31}P\{^{1}H\}$ NMR spectra (DMSO-d_6) the products **1a** and **1b** exhibit characteristic for acyclic dialkyl α-hydroxyphosphonates singlets at δ_P 23.6 and 22.5 ppm, respectively. The corresponding signal for phenylphosphinate **1c** is observed at δ_P 32.3 ppm, while the resonance signal of the phosphorus nuclei in alkylphosphinates **1d**,**e** is detected in the typical interval δ_P 47.6–42.5 ppm. In ^{1}H NMR (D_2O) spectra of products **1** the most characteristic fragments CH_3–C–P(O) are detected as doublets at δ_H 2.18–2.05 ppm, $^{3}J_{H,P}$=14.2–13.2 Hz. In $^{13}C\{^{1}H\}$ NMR spectra (DMSO-d_6) the fragments CH_3–C(OH)–P(O) reveal a doublet of methyl group at δ_C 24.7–23.3 ppm ($^{2}J_{C,P}$=5.6–4.2 Hz) and a doublet of quaternary carbon at 76.2–74.8 ppm ($^{1}J_{C,P}$=158.8–157.2 Hz). The typical patterns of substituents R at the phosphorus (IV) atom are observed in all the ^{1}H and ^{13}C NMR spectra of **1**. Absence of the coupling to phosphorus nuclei in diethylammonium methylene group signals in ^{1}H and ^{13}C NMR spectra of **1** is evidence of the P–N bond cleavage. The salt **1a** was converted to a free acid **13a** being treated with cold aqueous HCl. Addition of diethylamine to **13a** restored the diethylammonium salt **1a** quantitatively (Eq. 2).



(2)

When amino-derivatives **8** were subjected to hydrolysis at 25 °C, yields of **1** decreased dramatically due to acceleration of competing side processes. According to ^{31}P and ^{1}H NMR spectra, addition of water (4 equiv) to the structurally related to **8** diethyl (2-acetylphenyl)phosphite (**14**)[36] in THF resulted in hydrolysis of the P(III)–OAr bond.[37] The hydrolysis led to consumption of **14** (δ_P 137.7 ppm) after 8 h at rt to form diethylphosphite (**4a**) (δ_P 7.3 ppm, $^{1}J_{PH}$=705 Hz)[38] and **2** (Eq. 3).



(3)

^{31}P NMR monitoring a hydrolysis of amidophosphite **8a** at 5–8 °C in THF revealed a gradual disappearance of the **8a** signal (δ_P 146.3 ppm) with simultaneous rise of a major broadened signal at δ_P 33.3 ppm (ca. 75%), a minor signal at δ_P 12.2 ppm ($^{1}J_{PH}$=620 Hz) (10–15%) and few minute singlets in the interval 24–2 ppm. While the characteristics of the minor signal are analogous to ones of $Et_2N(EtO)P(O)H$ (**15a**),[39] the major signal at δ_P 33.3 ppm should be attributed to 2-ethoxy-3-hydroxy-1,2-benzoxaphosphole **11a** (Scheme 3, R=EtO). Indeed, most of the reported 3-heteroatom-substituted 2-ethoxy-1,2-benzoxaphospholes related to **11a** revealed a phosphorus nuclei resonance within a rather narrow region δ_P 40–33 ppm.[28,35,36,40] After 8 h at 5–8 °C a hydrolysis of **8a** completed. A subsequent stirring of the reaction mixture at 25 °C led to a slow vanishing of the major signal with a synchronized growth of the final product **1a** peak at δ_P 23.9 ppm. Similar tendencies were also observed upon ^{31}P NMR monitoring of amidophosphonites **8c** and **8e** hydrolyses.

Few reported data on reactivity of aminohydrophosphoryl compounds of type $Et_2N(AlkO)P(O)H$ **15**, which could be derived from a minor hydrolysis of P(III)–OAr bond in **8** according to Eq. 3, indicated enhanced reactivity of **15** in addition to ketones compared with dialkylphosphites **4**.[41] However, in our experiments a specially prepared $Et_2N(EtO)P(O)H$ (**15a**)[39] was inert toward **2** at rt and reacted slowly in THF at 50 °C to give a complex mixture of products. Thus, an efficient formation of **1** at rt through a common intermolecular hydrophosphonylation looks very unlikely.

The presented observations support a rationalization of events leading to the peculiar formation of **1** from **8** in terms of a domino-type sequential process as outlined in Scheme 3. The initial step consists presumably of the N–P(III) bond hydrolysis with formation of hydrophosphoryl compounds **10** and release of diethylamine. Indeed, hydrolyses of various amidophosphites to give the corresponding hydrophosphoryl compounds proceed rapidly, especially in the presence of acidic catalysts, including ammonium salts.[34] According to the preparation of **8** from **2** and **9** (Eq. 1),[35] starting compounds **8** are ultimately contaminated with small amount of triethylamine hydrochloride. Moreover, the final products **1** possess acidic phenolic hydroxyl and ammonium salt functionalities, which could also serve as catalysts in the hydrolysis of **8**. As generally accepted, the initially formed hydrophosphoryl compounds **10** in the presence of basic amine exist in equilibrium with a very minor, but reactive as nucleophile anionic phosphites (phosphonites) **11**. A proper arrangement of the reaction centers in intramolecular processes could provide 10^4–10^8 times rate acceleration at ambient temperature.[22,42] So, an anionic form **11** would undergo extremely fast cyclization through intramolecular Abramov addition to carbon atom of the carbonyl group to give the five-membered cyclic α-hydroxyphosphonate (-phosphinate) intermediates **12**.[43] Final hydrolysis of the endocyclic P(IV)–O bonds in strained heterocycles **12** to form **1** could proceed rapidly under the mild reaction conditions as reported for a number of 2-substituted-2-oxo-2,3-dihydro-benzo[*d*]oxaphospholes.[28,29,40,44] Thus, intramolecularization of the Abramov hydrophosphonylation as a key stage of three-step tandem process allowed an efficient one-pot preparation of diethylammonium[1-hydroxy-1-(2-hydroxy-phenyl)ethyl]phosphonates and -phosphinates **1**.

2.2. Biological evaluation

The in vitro antiviral activity against influenza A virus strain St. Petersburg/34/72 (H3N2) and cytotoxicity toward Madin–Darby canine kidney (MDCK) cells of diethylammonium[1-hydroxy-1-(2-hydroxyphenyl)ethyl]phosphonates and -phosphinates **1a**–**e** were evaluated similarly to the reported methods.[26,45] In short, MDCK cells in the maintenance medium were pre-treated with each compound at various concentrations followed by infection with 1

or 100 infective doses of influenza A virus (1 virus dose caused 50±3% cells death under the standard experimental conditions) and incubation for 48 h at 37 °C under a 5% CO_2 atmosphere. Anti-influenza A drug rimantadine was also examined as a reference under the same conditions. The inhibition of the virus-induced cytopathic effects for each sample was recorded relative to the cell control and the virus control. The measured effective concentrations for 50%-inhibition of virus-induced cytopathogenicity (EC_{50}) and the cytotoxic concentrations (CC_{50}), which induced 50% damage of MDCK cells, are summarized in Table 1.

In vivo anti-influenza protective activity was tested in the influenza virus A/Aichi/2/68 (H3N2)-infected Balb/c mice of both sexes according to the reported method.[26] In brief, to the groups of mice (10 animals in each group) the tested compounds **1** were SC administered. Each mouse was five-times dosed with 10% of LD_{50}/dose of the tested compounds in saline-DMSO solution (4:1, total 100 μL). Administration of the tested compounds was provided in prophylaxis 24 h and 1 h before infecting, followed by treatment at 24 h, 48 h, and 72 h after infecting. The reference drug Rimantadine was examined under the same conditions. Control group of animals

Table 1
Anti-influenza virus A activity and cytotoxicity of diethylammonium[1-hydroxy-1-(2-hydroxyphenyl)ethyl]phosphonates **1a**,**b** and -phosphinates **1c**–**e** in MDCK cells[a]

Compound	R	Antiviral activity, EC_{50}[b] (μM)		Cytotoxicity, CC_{50}[c] (μM)	Therapeutic index, TI[d]	
		1 Dose	100 Doses		1 Dose	100 Doses
1a	EtO	60	300	7515	125	25
1b	*n*-PrO	47	222	6000	128	27
1c	Ph	45	266	8540	190	32
1d	Me	28	185	10370	368	56
1e	Et	53	316	9230	175	29
Rimantadine		5.0	42	1395	280	33

[a] Virus strain and abbreviations used: influenza virus A: St. Petersburg/34/72 (H3N2); MDCK cells: Madin–Darby canine kidney cells.
[b] Effective concentration (EC_{50}) that required to reduce virus-induced cytopathogenicity by 50% in 48 h experiment.
[c] Cytotoxic concentration (CC_{50}) that caused 50% reduction of MDCK cell viability after 48 h incubation.
[d] TI represents the ratio of CC_{50} to EC_{50}.

As shown in Table 1, all the tested compounds **1** are practically non-toxic for MDCK cells and exhibited moderate antiviral activity against the examined influenza A strain. The most active tested phosphinate **1d** with the smallest substituent R at the phosphorus atom was only 4–5 times less potent in vitro compared to commercial anti-influenza drug Rimantadine. Other tested derivatives **1** revealed lower efficacy as in vitro influenza virus inhibitors. Nevertheless, due to a very low cytotoxicity α,γ-dihydroxyphosphonates **1a**,**b** and -phosphinates **1c**–**e** have comparable with Rimantadine therapeutic index (TI) values. Surprisingly that being tested in vivo compounds **1** revealed a superior to expected protective activity against experimental influenza A infection (Table 2).

was similarly treated five times with the vehicle (100 μL of saline/DMSO 4:1 v/v each dose). The protective efficacies of compounds **1** in mice were evaluated on the basis of the number of survived rodents at the day 8 and 14 post infecting with experimental influenza A infection (Table 2).

The data of Table 2 indicate that compounds **1** revealed a significant anti-influenza A protective activity providing with prolongation the life of animals during the time of the compound administration. Thus, the control mice began to die from day the 2 after the virus infection, and by the day 8 only four from the control ten mice survived. In contrast to that, in the group of mice treated with ethylphosphinate **1e**, a mortality of animals started from the day 6, and by the day 8 seven from ten animals were still alive. In

Table 2
Protective activity against experimental influenza A infection and acute toxicity of α,γ-dihydroxyphosphonate **1a** and -phosphinates **1c**–**e** in mice[a]

Compound	R	No. of infected survivors/total no. of infected mice[b]		Acute toxicity, LD_{50}[c]
		8 Days	14 Days	(mg/kg)
Control (saline/DMSO)		4/10	1/10	ND
1a	EtO	6/10	2/10	3500
1c	Ph	7/10	2/10	4000
1d	Me	7/10	2/10	2000
1e	Et	7/10	3/10	2500
Rimantadine		9/10	7/10	175

[a] Mice were infected intranasally by mouse-adapted influenza virus A/Aichi/2/68 (H3N2).
[b] Mice were dosed daily, totally five times, each time with 10% of LD_{50}. The compounds were administered subcutaneously (SC) in saline/DMSO (4:1, total 100 μL).
[c] Lethal dose (LD_{50}) corresponds to 50% mortality of the animals upon a single dose SC administration in saline/DMSO (4:1, total 200 μL). The toxicity was estimated in the 5 days test.

Prior the experiments on in vivo antiviral activity, the acute toxicities (a median lethal doses LD_{50}) of compounds **1** were roughly estimated in the groups of male mice (four in each group) upon SC administration in increasing single doses from 1000 mg/kg up to 4000 mg/kg (500 mg/kg step). The LD_{50} values indicate a very low acute toxicity of compounds **1** in rodents (Table 2). Moreover, preliminary sub-acute toxicity studies in mice showed no significant toxicity upon 6 days 500 mg/kg/day SC treatment with the phosphonate **1a** and phosphinate **1e**.

mice treated with phenyl- **1c** and methylphosphinate **1d** a survival of rodents by the day 8 was found to be the same, whereas the phosphonate **1a** was slightly less active. However, a considerable anti-influenza effect of substances **1** was observed upon high dosage (10% of LD_{50}) and continuous treatment only. Indeed, while at the day 8 (3 days after the last administration of the tested compounds **1**) an antiviral protective effect in mice was well observed, at the day 14 this effect mostly vanished. In view of the modest in vitro antiviral activity, a substantial in vivo protective

effect could be attributed to some unidentified metabolites of **1**. Anyway, compounds **1** are probably the first α-hydroxyphosphonates (-phosphinates) with the documented considerable anti-influenza activity in vivo. In view of the urgent need in novel anti-influenza pharmaceuticals,[46] the reported herein data inspire a further search of antiviral agents in α-hydroxyphosphonic acid derivatives.

3. Conclusions

A convenient synthesis of diethylammonium[1-hydroxy-1-(2-hydroxyphenyl)ethyl]phosphonates **1a**,**b** and -phosphinates **1c**–**e** by a domino-type hydrolysis of diethylamido(2-acetylphenyl) phosphites **8a**,**b** and -phosphonites **8c**–**e** have been elaborated. Based on the NMR monitoring and model experiments, a reasonable three-step mechanisms involving intramolecular Abramov reaction in the key step have been suggested for formation of compounds **1**. Being very nontoxic, α-hydroxyphosphonates and -phosphinates **1** revealed moderate activity against influenza A virus in vitro, but exhibited a substantial protective potency against experimental influenza A infection in mice.

4. Experimental section

4.1. General procedures

^{1}H, ^{13}C/DEPT, and ^{31}P NMR spectra were recorded on a Bruker Avance-250 spectrometer, operating at 250.1 MHz, 62.9 MHz, and 101.3 MHz, respectively. ^{1}H and ^{13}C NMR chemical shifts were reported relative to TMS. ^{1}H NMR spectra were referenced to the residual peak $CHCl_3$ (7.26 ppm) or to external TMS standard (0 ppm). ^{13}C NMR spectra were referenced to the central peak of $CDCl_3$ (77.0 ppm) and DMSO-d_6 (39.7 ppm) solvents or to external TMS standard (0 ppm). ^{31}P NMR spectra were referenced to 85% H_3PO_4 (external standard, 0 ppm). Abbreviations used in the description of NMR data are as follows: br, broad (or broadened); s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. IR spectra were obtained with a Nicolet-6700 FT-IR instrument in Nujol films or neat films. High resolution electron spray ionization (ESI) mass spectra were recorded using Micromass Platform LCZ-4000, electron impact (EI) HRMS was measured on a MX-1310 mass spectrometer. Microanalyses were performed in the Microanalytical Laboratory of the Arbuzov Institute of Organic and Physical Chemistry (Kazan, Russia). Melting points were measured with a Büchi-510 micro melting point apparatus.

All the manipulations with trivalent phosphorus compounds were conducted under atmosphere of argon. THF, diethyl ether, and toluene were distilled from Na/benzophenone under nitrogen. Trimethylsilyl diethylphosphite (**6**)[47] and amidophosphites (-phosphonites) **8** were prepared according to the reported methods.[35]

Biological evaluations were carried out similarly to the previously described procedures.[26,45]

4.2. General procedure for the synthesis diethylammonium salts of [1-hydroxy-1-(2-hydroxyphenyl)ethyl]phosphonic 1a,b and -phosphinic acids 1c–e by hydrolysis of diethylamido(2-acetylphenyl)phosphites and -phosphonites 8

To a cold (5 °C) solution of amidophosphite (-phosphonite) **8** (10.0 mmol) in dry deaerated THF (30 mL) a solution of water (0.72 mL, 720 mg, 40 mmol) in deaerated THF (5 mL) was added dropwise. After stirring at 5–8 °C for 6–8 h until starting **8** consumed (^{31}P NMR monitoring), the reaction mixture was allowed to warm to ambient temperature (22–25 °C) and stirred for 1 day (22–24 h). The reaction mixture was diluted with dry toluene (50 mL) and evaporated. The oily residue was treated with dry diethyl ether (30 mL) and crystallized at −25 °C. The resulted solid **1** was collected by filtration through a glass sinter. Recrystallization from di-*iso*-propyl ether and dichloromethane afforded analytically pure colorless microcrystalline products **1**.

*4.2.1. Diethylammonium ethyl[1-hydroxy-1-(2-hydroxyphenyl)ethyl] phosphonate (**1a**).* Yield 1.99 g (62%), mp=110–112 °C (decomp.). ^{1}H NMR (D_2O): δ 7.67–6.98 (m, 4H, ArH), 4.01 (dq, $^{3}J_{H,P}=^{3}J_{H,H}$=7.2 Hz, 2H, POCH_2CH$_3$), 3.08 (q, *J*=7.1 Hz, 4H, NCH_2CH$_3$), 2.15 (d, $^{3}J_{H,P}$=13.4 Hz, 3H, CH_3CP), 1.43 (t, *J*=7.1 Hz, 6H, NCH$_2$CH_3), 1.28 (br t, *J*=7.2 Hz, 3H, OCH$_2$CH_3). ^{13}C{^{1}H}/DEPT NMR (DMSO-d_6): δ 158.7 (d, *J*=3.6 Hz, C_{Ar}), 133.4 (d, *J*=2.2 Hz, C_{Ar}), 130.5 (d, *J*=4.7 Hz, C_{Ar}H), 130.1 (br s, C_{Ar}H), 122.6 (br s, C_{Ar}H), 121.0 (d, *J*=1.0 Hz, C_{Ar}H), 74.8 (d, *J*=158.8 Hz, HOCP), 64.3 (d, *J*=5.4 Hz, POCH$_2$), 47.9 (s, NCH$_2$), 24.7 (d, *J*=4.2 Hz, CH$_3$CP), 18.3 (d, *J*=5.8 Hz, POCH$_2$CH$_3$), 13.9 (s, NCH$_2$CH$_3$). ^{31}P{^{1}H} NMR (DMSO-d_6): δ 23.6. IR (Nujol): ν 3305 (O–H), 3190–3080 (O–H), 2780–2420 (N^+–H), 1178 (P=O), 1055 (P–OAlk) cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{10}H_{16}O_5P$ [MH^+–Et_2NH]: 247.0730; found: 247.0727. Anal. Calcd for $C_{14}H_{26}NO_5P$: C, 52.66; H, 8.21; N, 4.39; P, 9.70. Found: C, 52.60; H, 8.25; N, 4.27; P, 9.98.

*4.2.2. Diethylammonium n-propyl[1-hydroxy-1-(2-hydroxyphenyl) ethyl]phosphonate (**1b**).* Yield 1.795 g (54%), mp=107–109 °C (decomp.). ^{1}H NMR (D_2O): δ 7.64–7.01 (m, 4H, ArH), 3.96 (dt, $^{3}J_{H,P}=^{3}J_{H,H}$=7.0 Hz, 2H, POCH_2CH$_2$CH$_3$), 3.05 (q, *J*=7.2 Hz, 4H, NCH_2CH$_3$), 2.12 (d, $^{3}J_{H,P}$=13.2 Hz, 3H, CH_3CP), 1.68–1.54 (m, 2H, POCH$_2$CH_2CH$_3$), 1.41 (t, *J*=7.2 Hz, 6H, NCH$_2$CH_3), 0.96 (t, *J*=6.8 Hz, 3H, POCH$_2$CH$_2$CH_3). ^{31}P{^{1}H} NMR (DMSO-d_6): δ 22.5. IR (Nujol): ν 3308 (O–H), 3194–3085 (O–H), 2790–2410 (N^+–H), 1175 (P=O), 1057 (P–OAlk) cm^{-1}. Anal. Calcd for $C_{15}H_{28}NO_5P$: C, 54.05; H, 8.47; N, 4.20; P, 9.29. Found: C, 53.81; H, 8.77; N, 3.93; P, 9.12.

*4.2.3. Diethylammonium[1-hydroxy-1-(2-hydroxyphenyl)ethyl]phenylphosphinate (**1c**).* Yield 2.68 g (76%), mp=166–167 °C (decomp.). ^{1}H NMR (D_2O): δ 7.94–6.97 (m, 9H, ArH), 3.01 (q, *J*=7.1 Hz, 4H, NCH_2CH$_3$), 2.18 (d, $^{3}J_{H,P}$=14.2 Hz, 3H, CH_3CP), 1.42 (t, *J*=7.1 Hz, 6H, NCH$_2$CH_3). ^{13}C{^{1}H}/DEPT NMR (DMSO-d_6): δ 158.5 (d, *J*=3.8 Hz, C_{Ar}), 133.8 (d, *J*=3.0 Hz, C_{Ar}), 132.2 (d, *J*=2.8 Hz, C_{Ph}H), 131.6 (d, *J*=133.8 Hz, C_{Ph}), 131.2 (d, *J*=9.8 Hz, 2C_{Ph}H), 130.2 (d, *J*=4.2 Hz, C_{Ar}H), 130.0 (br s, C_{Ar}H), 128.4 (d, *J*=12.5 Hz, 2C_{Ph}H), 122.3 (br s, C_{Ar}H), 120.2 (d, *J*=1.6 Hz, C_{Ar}H), 76.2 (d, *J*=157.2 Hz, HOCP), 47.6 (s, NCH$_2$), 23.8 (d, *J*=5.6 Hz, CH$_3$CP), 13.5 (s, NCH$_2$CH$_3$). ^{31}P{^{1}H} NMR (DMSO-d_6): δ 32.3. IR (Nujol): ν 3302 (O–H), 3200–3080 (O–H), 2775–2415 (N^+–H), 1154 (P=O) cm^{-1}. Anal. Calcd for $C_{18}H_{26}NO_4P$: C, 61.53; H, 7.46; N, 3.99; P, 8.81. Found: C, 61.36; H, 7.44; N, 3.73; P, 8.77.

*4.2.4. Diethylammonium methyl[1-hydroxy-1-(2-hydroxyphenyl) ethyl]phosphinate (**1d**).* Yield 1.70 g (59%), mp=126–128 °C (decomp.). ^{1}H NMR (D_2O): δ 7.69–7.00 (m, 4H, ArH), 2.99 (q, *J*=7.1 Hz, 4H, NCH_2CH$_3$), 2.06 (d, $^{3}J_{H,P}$=13.6 Hz, 3H, CH_3CP), 1.44 (t, *J*=7.1 Hz, 6H, NCH$_2$CH_3), 1.38 (d, $^{2}J_{H,P}$=17.6 Hz, 3H, CH_3P). ^{13}C{^{1}H}/DEPT NMR (DMSO-d_6): δ 157.9 (d, *J*=3.9 Hz, C_{Ar}), 133.1 (d, *J*=2.4 Hz, C_{Ar}), 130.6 (d, *J*=4.7 Hz, C_{Ar}H), 130.0 (br s, C_{Ar}H), 122.2 (br s, C_{Ar}H), 120.6 (d, *J*=1.4 Hz, C_{Ar}H), 75.4 (d, *J*=156.5 Hz, HOCP), 47.6 (s, NCH$_2$), 23.5 (d, *J*=4.8 Hz, CH$_3$CP), 13.8 (s, NCH$_2$CH$_3$), 12.30 (d, *J*=148.6 Hz, CH$_3$P). ^{31}P{^{1}H} NMR (DMSO-d_6): δ 42.5. IR (Nujol): ν 3286 (O–H), 3185–3070 (O–H), 2790–2425 (N^+–H), 1148 (P=O) cm^{-1}. Anal. Calcd for $C_{13}H_{24}NO_4P$: C, 53.97; H, 8.36; N, 4.84; P, 10.71. Found: C, 53.76; H, 7.62; N, 4.65; P, 10.79.

*4.2.5. Diethylammonium ethyl[1-hydroxy-1-(2-hydroxyphenyl)ethyl] phosphinate (**1e**).* Yield 2.22 g (73%), mp=159–160 °C (decomp.). ^{1}H NMR (D_2O): δ 7.66–6.95 (m, 4H, ArH), 3.03 (q, *J*=7.1 Hz, 4H,

NCH_2CH_3), 2.05 (d, $^3J_{H,P}$=13.8 Hz, 3H, CH_3CP), 1.68 (dq, $^2J_{H,P}$=17.8 Hz, $^3J_{H,H}$=7.2 Hz, 2H, PCH_2CH_3), 1.42 (t, J=7.1 Hz, 6H, NCH_2CH_3), 1.14 (dt, $^3J_{H,P}$=18.6 Hz, $^3J_{H,H}$=7.2 Hz, 3H, PCH_2CH_3). $^{13}C\{^1H\}$/DEPT NMR (DMSO-d_6): δ 158.1 (d, J=3.8 Hz, C_{Ar}), 133.0 (d, J=2.2 Hz, C_{Ar}), 130.8 (d, J=4.6 Hz, $C_{Ar}H$), 130.2 (br s, $C_{Ar}H$), 122.5 (br s, $C_{Ar}H$), 120.4 (d, J=1.6 Hz, $C_{Ar}H$), 75.6 (d, J=156.2 Hz, HOCP), 47.5 (s, NCH_2), 23.3 (d, J=5.1 Hz, CH_3CP), 18.7 (d, J=145.8 Hz, CH_3CH_2P), 13.6 (s, NCH_2CH_3), 6.8 (d, J=6.6 Hz, CH_3CH_2P). $^{31}P\{^1H\}$ NMR (DMSO-d_6): δ 47.6. IR (Nujol): ν 3282 (O–H), 3190–3075 (O–H), 2790–2420 (N^+–H), 1144 (P=O) cm^{-1}. Anal. Calcd for $C_{14}H_{26}NO_4P$: C, 55.43; H, 8.64; N, 4.62; P, 10.21. Found: C, 55.15; H, 8.83; N, 4.28; P, 10.32.

4.3. Synthesis of diethyl[1-hydroxy-1-(2-hydroxyphenyl) ethyl]phosphonate (5a)

*4.3.1. Diethyl[1-trimethylsiloxy-1-(2-trimethylsiloxyphenyl)ethyl] phosphonate (**7**).* 2-Acetylphenol (**2**) (1.08 g, 7.94 mmol) and trimethylsilyl diethylphosphite (**6**) (6.835 g, 32.5 mmol) were placed into an argon-filled Teflon screw-cup 25 mL round-bottom reactor, and the reaction mixture was stirred for 4 h at 90–100 °C. The reaction mixture was fractionated by vacuum distillation, and subsequent distillation afforded the bis-silylated product **7** (2.72 g, 82%) as a colorless mobile oil, bp=119–122 (0.02 mmHg). ^1H NMR ($CDCl_3$): δ 7.41–7.23 (m, 2H, ArH), 7.05–6.88 (m, 2H, ArH), 4.05–3.80 (m, 4H, $2OCH_2CH_3$), 1.85 (d, $^3J_{H,P}$=14.6 Hz, 3H, CH_3CP), 1.25 (br t, J=7.0 Hz, 3H, OCH_2CH_3), 1.21 (br t, J=7.0 Hz, 3H, OCH_2CH_3), 0.38 [s, 9H, $(CH_3)_3SiO$], 0.25 [s, 9H, $(CH_3)_3SiO$]. $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 23.4. IR (film): ν 1198 (P=O), 1055 (P–OAlk), 1016 (C–OSi) cm^{-1}. HRMS (EI): m/z calcd for $C_{18}H_{35}O_5PSi_2$ [M^+]: 418.1761; found: 418.1752.

*4.3.2. Diethyl[1-hydroxy-1-(2-hydroxyphenyl)ethyl]phosphonate (**5a**).* To a solution of **7** (2.58 g, 6.16 mmol) in anhydrous ethanol (20 mL) one drop of acetyl chloride (ca. 8 mg, 0.1 mmol) was added, and the reaction mixture was stirred for 2 h at 50 °C under argon. The reaction mixture was evaporated; the residue was dissolved in a new portion of ethanol (20 mL), evaporated again and subjected to vacuumization for 2 days at 0.2 mmHg to give the title compound **5a** (1.70 g, quantitative yield) as a colorless viscous oil. ^1H NMR ($CDCl_3$): δ 12.45 (br s, 1H, OH), 7.45–7.24 (m, 2H, ArH), 7.03–6.82 (m, 2H, ArH), 4.08–3.78 (m, 5H, $2OCH_2CH_3$+OH), 1.91 (d, $^3J_{H,P}$=14.8 Hz, 3H, CH_3CP), 1.29 (br t, J=7.0 Hz, 3H, OCH_2CH_3), 1.20 (t, J=7.0 Hz, 3H, OCH_2CH_3). $^{13}C\{^1H\}$/DEPT NMR ($CDCl_3$): δ 158.2 (d, J=4.3 Hz, C_{Ar}), 130.3 (d, J=3.0 Hz, C_{Ar}), 129.0 (d, J=4.8 Hz, $C_{Ar}H$), 128.1 (d, J=3.6 Hz, $C_{Ar}H$), 121.5 (d, J=1.2 Hz, $C_{Ar}H$), 118.4 (d, J=2.0 Hz, $C_{Ar}H$), 75.7 (d, J=161.6 Hz, HOCP), 63.8 (d, J=7.1 Hz, $POCH_2$), 62.7 (d, J=7.1 Hz, $POCH_2$), 24.8 (d, J=2.3 Hz, CH_3CP), 16.3 (d, J=5.2 Hz, $POCH_2CH_3$), 16.1 (d, J=5.6 Hz, $POCH_2CH_3$). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 24.1. IR (film): ν 3340–3120 (O–H), 1188 (P=O), 1052 (P–OAlk) cm^{-1}. HRMS (ESI): m/z calcd for $C_{12}H_{20}O_5P$ [MH^+]: 275.1043; found: 275.1036. Anal. Calcd for $C_{12}H_{19}O_5P$: C, 52.55; H, 6.98; P, 11.29. Found: C, 52.31; H, 7.16; P, 10.98.

4.4. Interconversion of diethylammonium phosphonate 1a and free acid 13a

*4.4.1. Ethyl[1-hydroxy-1-(2-hydroxyphenyl)ethyl]phosphonic acid (**13a**).* A cold (5 °C) solution of diethylammonium phosphonate **1a** (285.0 mg, 0.895 mmol) in chloroform (30 mL) was shacked with a cold 0.2 M aqueous hydrochloric acid (10 mL). The organic layer was separated, and the aqueous phase was additionally extracted with chloroform (2×10 mL). The combined organic extract was dried over anhydrous $MgSO_4$, filtered, and evaporated to give the title acid **13a** (212.5 mg, 96.5%) as a colorless sticky oil. ^1H NMR (D_2O): δ 7.65–6.93 (m, 4H, ArH), 4.04 (dq, $^3J_{H,P}$=$^3J_{H,H}$=7.1 Hz, 2H, $POCH_2CH_3$), 2.18 (d, $^3J_{H,P}$=13.7 Hz, 3H, CH_3CP), 1.29 (t, J=7.1 Hz, 3H, OCH_2CH_3). $^{13}C\{^1H\}$/DEPT NMR (D_2O): δ 159.2 (d, J=3.8 Hz, C_{Ar}), 132.1 (d, J=2.4 Hz, C_{Ar}), 130.2 (d, J=4.3 Hz, $C_{Ar}H$), 129.7 (br s, $C_{Ar}H$), 121.9 (br s, $C_{Ar}H$), 120.6 (d, J=1.5 Hz, $C_{Ar}H$), 75.6 (d, J=160.3 Hz, HOCP), 63.6 (d, J=5.8 Hz, $POCH_2$), 24.9 (d, J=4.8 Hz, CH_3CP), 18.6 (d, J=5.5 Hz, $POCH_2CH_3$). $^{31}P\{^1H\}$ NMR (D_2O): δ 22.3. HRMS (ESI): m/z calcd for $C_{10}H_{16}O_5P$ [MH^+]: 247.0730; found: 247.0724. Anal. Calcd for $C_{10}H_{15}O_5P$: C, 48.78; H, 6.14. Found: C, 48.41; H, 6.49.

*4.4.2. Diethylammonium ethyl[1-hydroxy-1-(2-hydroxyphenyl)ethyl] phosphonate (**1a**).* A solution of acid **13a** (124 mg, 0.504 mmol) in diethyl ether (5 mL) was treated with diethylamine (70 μL, 50 mg, 0.68 mmol). Evaporation followed by vacuumization afforded diethylammonium salt **1a** (161 mg, quantitative yield) as a colorless solid. For characterization of **1a**, see above.

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