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Synthesis of Biologically Active 1-Arylethylphosphonates*

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Abstract—A convenient and inexpensive general preparation method for 1-arylethylphosphonic acids and their esters was developed involving in reduction of the corresponding 1-ethenylphosphonates by ammonium formate in the presence of palladium on carbon. A homogeneous enantioselective hydrogenation of 1-arylethenylphosphonic acids in the presence of chiral ruthenium catalysts provided optically active 1-arylethylphosphonic acids of enantiomeric purity up to 86%. The preliminary data on biological activity testing of the 1-arylethylphosphoic acids synthesized evidence that some among the compounds obtained are low-toxic substances with the properties of immunosuppressors of the central type of action.

1-Arylethylphosphonates are of interest as potential biologically active compounds, primarily as phosphorus analogs of 2-arylpropionic acids that are known as nonsteroid antiphlogistic and analgetic drugs, such as naproxen and ibuprofen which are widely used in the medical practice. It was reported [1] that 1-arylethylphosphonates exhibit negative inotropic and Ca^{2+}-antagonistic activity. In experiments *in vitro* 1-arylethylphosphonic acids inhibit the activity of cyclooxygenase [2]. In experiments *in vivo* it was demonstrated that 1-arylethylphosphonates caused formation in animal organism of antibodies possessing properties of catalysts of stereospecific hydrolysis [3, 4].

1-Arylethylphosphonates find wide synthetic application, in particular, as reagents in Horner reaction that is mentioned in numerous patents (see, e.g., [5–8]).

Although the described synthetic procedures for 1-arylethylphosphonates are numerous most of them are not general, tested on single examples, and often require special experimental technique or inaccessible reagents.

The most traditional methods are reactions of 1-aryl-1-bromoethanes with triethyl phosphite (Arbuzov reaction) [1, 9–11] or with sodium dimethylphosphite (Michaelis–Becker reaction) [12]. The other approach to the synthesis of esters of 1-arylalkylphosphonic acids is based on metallation (effected by sodium amide, butyllithium, or lithium hexamethyldisilazide) followed by alkylation of arylmethylphosphonic acid esters [2, 13]. The preparation of diethyl 1-phenylethylphosphonates and diethyl 1-tolylethylphosphonates by treating a lithium salt of diethyl 1-chloroethylphosphonate with Ph_2CuLi or phenylor tolyllithium in the presence of catalytic amounts of CuI was described [14–16]. Dimethyl 1-phenylethylphosphonate was obtained by addition of dimethylphosphoric acid to β,β-bis(methylsulfonyl)styrene followed by reduction of the product by hydrogen on Raney nickel [17] or to tosylhydrazone of acetophenone with subsequent reduction by sodium borohydride [18]. It was shown by an example of diethyl 1-oxybenzylphosphonate that the hydroxy group could be removed either by substitution with chlorine followed by hydrogenation on Raney nickel or by transformation of it into TsO group and reduction of the latter with sodium borohydride. One more approach to the synthesis of 1-arylethylphosphonates involves in aromatization of the products of 1,4- or 1,2-addition of an α-lithiated derivative of diethyl ethylphosphonate to substituted cyclohexen-2-ones [20]. Chloride of 1-phenylethylphosphonic acid formed by Kinner–Perrin–Clay reaction at partial hydrolysis of a complex obtained from 1-phenyl-1-chloroethane and PCl_3 in the presence of $AlCl_3$ [21].

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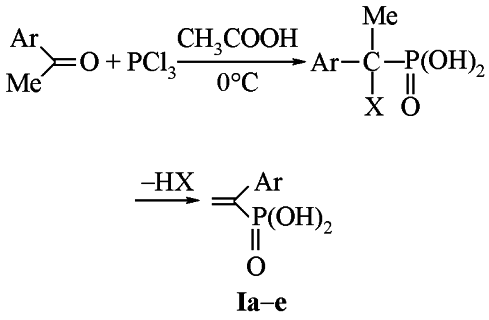
As the most versatile preparation method for 1-arylethylphosphonates would be hydrogenation of the corresponding 1-arylethenylphosphonates that can be obtained by relatively well developed synthetic method (see, for instance, [22]). However this procedure is poorly considered in the literature. The α,β-unsaturated phosphonates are commonly hydrogenated under pressure (3.4–80 at) in the presence of heterogeneous catalysts: palladium (5 or 10%), platinum (5%) or rhodium (5%) on carbon [23–27], but the majority of studies are treating the hydrogenation of 2-substituted ethenylphsphonates. For 1-substituted compounds was the hydrogenation of dimethyl ethenylphosphonate containing a sugar rest in the α-position described [23].

The homogeneous hydrogenation of α,β-unsaturated phosphonates was first performed [28] with diphenyl and diethyl 1- and 2-phenylethenylphosphonates with the use of relatively hard-to-get catalyst, [Pd(O_2PBu_2-*t*)($OPBu_2$-*t*)($HOPBu_2$-*t*)], arising at oxidation of a binuclear complex [(Bu_2-*t*PH)Pd(PBu_2-*t*)]$_2$ [29]. The reduction of α,β-unsaturated phosphonic acids was not described in the literature.

The enantioselective catalytic hydrogenation of 1-substituted ethenylphosphonates seems a convenient approach to the synthesis of optically active 1-substituted ethylphosphonates with an α-C*-stereocenter. This goal is obviously urgent for it is well known that biological activity of chiral compounds can be strongly dependent on the absolute configuration of the chiral center. For instance, the *S*-isomers of α-arylpropionic acids are as a rule more active than *R*-isomers [30]: antiphlogistic activity of the (*S*)-2-(6-methoxy-2-naphthyl)propionic acid is 28 times greater than that of its *R*-isomer [31]. We found in the literature rare examples of enantioselective hydrogenation of α,β-unsaturated phosphonates with a functional group in α-position [32, 33]. The synthesis of optically active 1-arylethylphosphonates up till now was only performed through stereoselective alkylation of functional derivatives of benzylphosphonic acid containing an auxiliary chirality source [34–36], and by stereoselective Arbuzov rearrangement [37].

In the present study was developed a convenient preparative method of the chemoselective reduction of 1-arylethenylphosphonic acids and their esters with ammonium formate [38, 39] in the presence of palladium on carbon, and also was carried out a homogeneous enantioselective hydrogenation of 1-arylethenylphosphonic acids with hydrogen on chiral ruthenium catalyst. We published previously a preliminary communication covering this subject [40].

Apparently the simplest preparation method for 1-arylethenylphosphonic acids is phosphorylation of acetylarenes with phosphorus trichloride in the presence of glacial acetic acid [41–44]. The mechanism of the reaction is still under discussion [45]. The reaction is usually carried out with 23–60 mol% excess of PCl_3 and 2.5–5.25 equiv of glacial acetic acid. Depending on the workup of the reaction mixture the primary products are either 1-chloro- or 1-hydroxybenzylphosphonic acids [41, 42]. To obtain unsaturated acid **I** the reaction mixture is subjected to hydrolysis, 1,1,2,2-tetrachloroethylene is added, and the mixture is boiled with distillation of water [43, 44]. We used this reaction for the synthesis of a series of initial 1-arylethenylphosphonic acids **Ia–f** that were isolated in 60–83% yield (Table 1).



Ia–e

Ar = Ph (**a**), 4-MeC_6H_4 (**b**), 4-PhC_6H_4 (**c**), 4-ClC_6H_4 (**d**), 1-Nf (**e**), 2-Nf (**f**); X = Cl, OH.

The reaction procedure was somewhat simplified: after the hydrolysis the reaction mixture was evaporated in a porcelain evaporating dish, the residue was dissolved in boiling concentrated hydrochloric acid, and the resulting solution was boiled for 3.5–4 h. On cooling the unsaturated acid **Ia, b, d–f** precipitated, it was filtered off and washed on filter with cold benzene.

In the synthesis of acid **Ic** the intermediate saturated adduct 4-$PhC_6H_4CX(CH_3)P(O)(OH)_2$ was insoluble at boiling both in concentrated and diluted hydrochloric acid, and even after prolonged boiling formed only a mixture (~1 : 1) of unsaturated and saturated acids. The presence of the latter is evidenced by ^{1}H NMR spectrum of the separated product: alongside the double doublets of vinyl protons appears a complicated pattern in the resonance region of aromatic protons and a doublet at 1.87 ppm ($^3J_{HP}$ 14.8 Hz) corresponding to a methyl group. The

elimination reaction was completed by dissolving the acid mixture in toluene and boiling with water distillation.

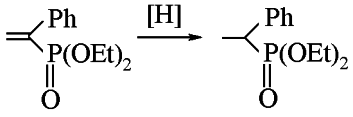
All the acids obtained **Ia–f** were characterized by ^{31}P, ^{1}H (Table 2), ^{13}C NMR, and IR spectra (Table 1). In the $^{31}P\{^{1}H\}$ NMR spectra of the compounds appeared a signal in 14.5–16.0 ppm region characteristic of ethenylphosphonic acids [46]. The assignment of vinyl protons (*cis*-PC=CH and *trans*-PC=CH) in the ^{1}H NMR spectra was done by the values of coupling constants with phosphorus [47] (Table 2). The protons in *cis*-position with respect to phosphorus resonate in the region 6.18–6.57 ppm ($^{3}J_{HP}$ 21.6–22.0 Hz), and the signals from *trans*-protons are observed at 5.88–6.21 ppm ($^{3}J_{HP}$ 44.0–45.1 Hz). The observed upfield shift of these proton signals may be attributed to the shielding by the phenyl ring that according to X-ray diffraction data [48] is not coplanar with the double bond and is situated at an angle of 35° to the latter. This is consistent with the published data [47] on negligible contribution from the magnetic anisotropy of P=O group in the ^{1}H NMR spectra of unsubstituted ethenylphosphonates resulting in small difference in the chemical shifts of the two terminal protons (not exceeding 0.1 ppm).

In the ^{13}C NMR spectra the signal from the vinyl carbon C^{1} in the region 143.7–144.4 ppm is the most characteristic ; the spin-spin coupling constant $^{1}J_{CP}$ amounts to 174.9–176.1 Hz.

In the IR spectra of compounds **Ia–e** a set of absorption bands characteristic of group $P(O)(OH)_2$ vibrations is observed: strong band of the stretching vibrations of P=O bond at 1270–1180 cm^{-1} (commonly two bands presumably from two rotamers [50]); as a rule, prominent bands in the region 1025–985 and 955–930 cm^{-1} belonging to P–O bond vibrations, and a very broad band of OH-vibrations in the region 2725–1600 cm^{-1} with maxima at 2900–2700 s, 2400–2200 m and 1700–1600 w cm^{-1}.

We failed to involve into Conant reaction acetylarenes containing in the ring strong electron-donor substituents: the reaction of 4-methoxyacetophenone with PCL_3 in the presence of glacial acetic acid gave rise to intractable mixture of products. Therefore the synthesis of diethyl 1-(4-methoxyphenyl)ethenylphosphonete (**IIg**) and diethyl 1-(6-methoxy-2-naphthyl)-ethenylphosphonate (**IIh**), and also of diethyl 1-phenylethenylphosphonate (**IIa**) was carried out by palladium-catalyzed hydrophosphorylation of the corresponding terminal acetylenes with diethylphosphorous acid [51].

Looking for a convenient preparative procedure for the synthesis of racemic α-arylethylphosphonic acids and their esters from the respective α-arylethenylphosphonates we tested various hydrogenating agents: sodium borohydride in the presence of $CoCl_2 \cdot 6H_2O$ [52], formamide in the presence of palladium (5%) on carbon, and ammonium formate in the presence of Raney nickel or Pd/C (5%). The selection of the optimum reduction conditions for 1-arylethenylphosphonates was carried out by an example of compound **IIa**. The reaction progress was monitored with ^{31}P NMR spectroscopy by disappearance of the signal from the initial **IIa** at 17.1 ppm, and accumulation of the signal from reaction product diethyl 1-phenylethylphosphonate (**IIIa**) at 30.2 ppm.



IIa **IIIa**

The results presented in Table 3 show that reduction of compound **IIa** with ammonium formate (6 equiv.) in boiling methanol in the presence of 2.8 mol% of Pd/C completed in 3 h affording ester **IIIa** as a single product (run no. *1*). Therewith the catalyst can be filtered off from the reaction mixture and used repeatedly, although with some loss of the catalytic activity (runs nos. *2* and *3*). The use of Raney nickel instead of palladium on carbon resulted in considerable decrease in the reduction rate (run no.4). The systems $NaBH_4/CoCl_2 \cdot 6H_2O$ and $HCONH_2$ in the presence of Pd/C (runs nos. *6* and *5*) were inefficient.

Under the optimal conditions found we carried out reduction of diethyl 1-arylethenylphosphonates **IIg, h** and a series of 1-arylethenylphosphonic acids **Ia–f**. The results obtained are presented in Table 4.

The saturated 1-arylethylphosphonic acids **IVa–c, e, f**) (runs nos. *1*, *2*, *4*, *5*, *7–9*) and diethyl 1-arylphosphonates **IIIa, g, h** (runs nos. *3*, *10–11*) were isolated in 70–88% yield. In none of the above experiments was observed (by ^{31} NMR monitoring) formation of any side product. At acids reduction the reaction rate increased on replacing methanol with water (runs nos. *1*, *2*, *7*, *8*). The latter fact may be due to the adsorption of methanol on the catalyst surface decreasing its catalytic activity. The opportunity of avoiding application of organic solvent obviously improves the environmental quality of the methods.

Table 1. Yields, constants, IR spectra and elemental analyses data of arylethenylphosphoric acids CH_2= C(Ar)P(O)$(OH)_2$ (**Ia**–**f**)

Compd. no.	Ar	Yield, %	mp., °C	IR spectrum ν, cm^{-1}	Found, %		Formula	Calcd., %	
					C	H		C	H
Ia	Ph	83	100–101 (HCl_{aq}), 112-113 (C_6H_6/CH_2Cl_2[a]	2900 br.s, 2300 br.s, 1602, 1492, 1267, 1207, 1170, 1078, 987, 960, 836, 779, 711					
Ib	4-MeC_6H_4	71	120–121 (HCl_{aq})	2800 br.s, 2300 br.s, 1610, 1513, 1259, 1189, 1140, 1016, 958, 935, 823	54.56	5.58	$C_2HnC\wedge P$	54.55	5.59
Ic	4-PhC_6H_4	60	186 (toluene)	2900 br.s, 2350 br.s, 1598, 1486, 1403, 1257, 1213, 1072, 985, 954, 850, 771, 738, 694	64.65	5.09	$C_{14}H_{13}O_3P$	64.62	5.04
Id	4-ClC_6H_4	76	137–139 (HCl_{aq})[c]	2850 br.s, 2300 br.s, 1592, 1492, 1398, 1259, 1189, 1137, 1074, 1008, 952, 933, 846, 835, 752, 728	44.29	3.67	$C_8H_8ClO_3P$	43.96	3.69
Ie	1-Nf	68	133–134 (water)	2800 br.s, 2200 br.s, 1591, 1506, 1205, 1182, 1150, 1093, 1016, 931, 869, 809, 781	61.73	4.72	Cl_2HnO_2P	61.54	4.73
If	2-Nf	71	180–180.5 (water)	2850 br.s, 2250 br.s, 1594, 1506, 1270, 1191, 1097, 1074, 1021, 937, 898, 858, 815, 746	60.89	4.62	Cl_2HnO_2P	61.54	4.73

[a] mp 112113°C. [42]. [b] mp 105°C [44]. [c] mp 141–143°C [43].

Table 2. ^{1}H NMR and ^{31}P NMR spectra of arylethenylphosphonic acids CH_2=C(Ar)P(O)$(OH)_2$ (**Ia**–**f**)

Compd. no.	Ar	^{1}H NMR spectrum (CD3OD), δ, ppm (J, Hz)			^{31}P NMR spectrum (CD_2OD), δ, ppm
		trans-PC=CH (d.d, IH)	*cis*-PC=CH (d.d, 1H)	Ar	
Ia	Ph	6.05 ($^2J_{HH}$ 1.6, $^3J_{HP}$ 44.4)	6.23 ($^2J_{HH}$ 1.6, $^3J_{HP}$ 21.6)	7.31-7.41 m(3H), 7.61 m (2H)	15.9[a]
Ib	4-MeC_6H_4[b]	6.03 ($^2J_{HH}$ 1.6, $^3J_{HP}$ 44.4)	6.18 ($^2J_{HH}$ 1.6, $^3J_{HP}$ 22.0)	7.19 a (2H, $^3J_{AB}$ 8.0), 7.51 d.d (2H, $^3J_{AB}$ 8.0)	15.9
Ic	4-PhC_6H_4	6.12 ($^2J_{HH}$ 1.6, $^3J_{HP}$ 44.0)	6.25 ($^2J_{HH}$ 1.6, $^3J_{HP}$ 22.0)	7.36 t (IH, $^3J_{HH}$ 7.2), 7.46 t (2H, $^3J_{HH}$ 7.2), 7.63-7.67 m (4H), 7.71 m (2H)	16.0
Id	4-ClC_6H_4	6.07 ($^2J_{HH}$ 1.5, $^3J_{HP}$ 43.8)	6.24 ($^2J_{HH}$ 1.5, $^3J_{HP}$ 21.6)	7.38 a (2H, $^3J_{AB}$ 8.3), 7.60 d.d (2H, $^3J_{AB}$ 8.3)	15.7
Ie	1-Nf	5.88 ($^2J_{HH}$ 2.2, $^3J_{HP}$ 45.1)	6.57 ($^2J_{HH}$ 2.2, $^3J_{HP}$ 21.9)	7.50 m (4H), 7.88 m (2H), 8.07 m (IH)	14.5
If	2-Nf	6.21 ($^2J_{HH}$ 1.6, $^3J_{HP}$ 44.2)	6.32 ($^2J_{HH}$ 1.6, $^3J_{HP}$ 21.6)	7.51 m (2H), 7.73 m (IH), 7.86-7.90 m (3H), 8.15 s (IH)	15.8

[a] In D_2O. [b] 62.36 s (3H, CH_3).

Table 3. Reduction of diethyl 1-phenylethenylphosphonate **IIa** with various hydrogenating agents

Run no.	Reagent	Solvent	Temperature, °C	Time, h	Yield, % (^{31}P NMR)
1	$HCOONH_4$/Pd–C (6 equiv)/(2.8 mol%)	MeOH	65	3	100
2	$HCOONH_4$/Pd–C (6 equiv)/(4.7 mol%)	MeOH	65	0.3	97
3	$HCOONH_4$/Pd–C[a] (6 equiv)/(4.7 mol%)	MeOH	65	0.3	70
4	$HCOONH_4$/Raney Ni (6 equiv)/(30 mol%)	MeOH	65	1.75	40
5	$HCONH_2$/Pd–C (6 equiv)/(2.8 mol%)	–	65	6.5	<10
6	$NaBH_4/CoCl_2$–$6H_2O$ (2 equiv)/(1 equiv)	EtOH	78	2	20

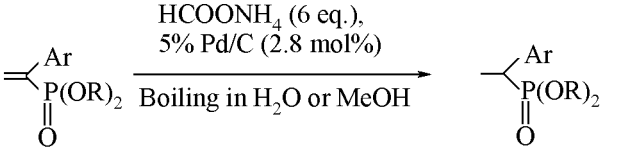
[a] At repeated use of Pd/C.

Table 4. Reduction of 1-arylethenylphosphonic acids **Ia**–**f** and diethyl 1-arylethenylphosphonates **IIa, g, h** by ammonium formate (6 equiv) in the presence of 5% Pd/C (2.8 mol%)

Run no.	No. of initial compound	Solvent	Time, h	Reaction product no.	Yield, %	
					^{31}P NMR	preparative
1	**Ia**	H_2O	2.5	**IVa**	100	–
2	**Ia**	MeOH	4	**IVa**	100	70
3	**IIa**	MeOH	3	**IIIa**	100	87
4	**Ib**	MeOH	4	**IVb**	100	87
5	**Ic**	H_2O + MeOH	4	**IVc**	100	78
6	**Id**	MeOH	4	**IVd + IVa**	50 + 50	–
7	**Ie**	MeOH	5	**IVe**	60	–
8	**Ie**	H_2O	4	**IVe**	100	74
9	**If**	H_2O	4	**IVf**	100	76
10[a]	**IIg**	MeOH	10	**IIIg**	100	88
11[a]	**IIh**	MeOH	10	**IIIh**	100	88

[a] 5% Pd/C (5 mol%), $HCOONH_4$ (7.5 equiv).

Only with poorly soluble in water acid **Ic** is required the use as solvent of a mixture H_2O–MeOH 1 : 1 (run no. 5).



Ia–f, IIa, g, h → **IIIa, g, h, IVa–f**

I, IV$(24), R = H: Ar = Ph (**a**), 4-MeC_6H_4 (**b**), 4-PhC_6H_4 (**c**), 4-ClC_6H_4 (**d**), 1-Nf (**e**), 2-Nf (**f**); **II, III**, R = Et: Ar = Ph (**a**), 4-$MeOC_6H_4$ (**g**), 6-MeO-2-Nf (**h**).

Esters **IIIg, h** containing electron-donor substituents in the ring turned out to be less reactive than unsubstituted analogs (cf. runs nos. *10*, *11* and *3*). In these cases an increased amount was required of reductant $HCOONH_4$ (to 7.5 equiv) and of catalyst Pd/C (to 5 mol%), and the reaction time was prolonged to 10 h instead of 2.5–5 h. The structure of the isolated saturated 1-arylethylphosphonic acids and diethyl 1-arylethylphosphonates was confirmed by spectral data and elemental analyses (Tables 5–7).

In the ^{31}P NMR spectra of acids **IVa–f** appeared a signal at 27.9–31.3 ppm, and in the spectra of esters **IIIa, g, h** a peak at 29,4–30.6 ppm. In the

Table 5. Yields, constants, IR spectra and elemental analyses data of arylethenylphosphoric acids CH_2= C(Ar)P(O)$(OH)_2$ (**Ia**–**f**)

Compd. no.	Ar	mp, °C or bp, °C (*p*, mm Hg)	IR spectrum *ν*, cm^{-1}	Found, %			Formula	Calcd., %		
				C	H	P		C	H	P
IIIa	Ph	90–92 (0.1)[a]	2981, 2935, 1604, 1494, 1245, 1186, 1054, 1027, 962, 806, 765, 700	Not determined						
IVa	Ph	1516	2850 br, 2300 br, 1602, 1494, 1454, 1247, 1193, 1137, 1006, 931, 767, 696	Not determined						
IVb	4-MeC_6H_4	129–130	2850 br, 2300 br, 1515, 1459, 1243, 1201, 1120, 1051, 1000, 948, 819, 700	53.81	6.64	15.24	$C_9H_{13}O_3P$	54.00	6.55	15.47
IVc	4-PhC_6H_4	215	2900 br, 2350 br, 1486, 1249, 1191, 1133, 1068, 1006, 929, 835, 767, 696	64.13	5.78	–	$Cl_4Hi_5O_3P$	64.12	5.76	–
IVe	1-Nf	181–182	2850 br, 2300 br, 1596, 1511, 1186, 1130, 987, 933, 796, 779	60.96	5.42	13.00	$C_{12}H_{13}O_3P$	61.02	5.55	13.11
IVf	2-Nf	169.5–170	2900 br, 2300 br, 1600, 1508, 1234, 1155, 1101, 1020, 937, 858, 821, 740	60.96	6.08	–	$C_{12}H_{13}O_3P$	61.02	5.55	–
IIg	4-$MeOC_6H_4$	137–141 (0.1	2981, 2937, 1612, 1513, 1249, 1182, 1054, 1025, 964, 838, 800	57.26	8.05	11.12	$C_{13}H_{21}O_4P$	57.35	7.77	11.38
IIIh	6-MeO-2-Nf	Oily substances	2981, 2937, 1606, 1506, 1484, 1392, 1232, 1176, 1054, 1033, 962, 923, 854, 750	322.1330[c]			$C_{17}H_{23}O_4P$	322.1334		

[a] bp103°C (0.4 mm Hg) [15], 159–160°C (15 mm Hg) [13]. [b] mp 151–152°C [11]. [c] HRMS data.

Table 6. ^{1}H NMR and ^{31}P NMR spectra of arylethylphosphonic acids CH_2=C(Ar)P(O)$(OH)_2$ **IVa**–**f**

Compd. no.	Ar	^{1}H NMR spectrum (CD3OD), δ, ppm (J, Hz)			^{31}P NMR spectrum δ, ppm (solvent)
		CH_3 (d.d, 3H)	CH (d.q, 1H)	Ar	
IVa	Ph	1.59 ($^{3}J_{HH}$ 7.6, $^{3}J_{HP}$ 18.0)	3.16 ($^{3}J_{HH}$ 7.6, $^{3}J_{HP}$ 22.6)	7.24 m (2H), 7.32 m (2H), 7.38 m (1H)	31.0 (EtOAc) 30.4 (CD_3OD)
IVb	4-MeC_6H_4[a]	1.56 ($^{3}J_{HH}$ 7.4, $^{3}J_{HP}$ 18.2)	3.14 ($^{3}J_{HH}$ 7.4, $^{3}J_{HP}$ 22.4)	7.14 d (2H, $^{3}J_{AB}$ 8.0), 7.26 d.d (2H, $^{3}J_{AB}$ 8.0)	27.9 (CD_3OD)
IVc	4-PhC_6H_4	1.62 ($^{3}J_{HH}$ 7.1, $^{3}J_{HP}$ 17.8)	3.21 ($^{3}J_{HH}$ 7.1, $^{3}J_{HP}$ 22.8)	7.33 m (1H, $^{3}J_{HH}$ 7.2), 7.41-7.48 m (4H), 7.58 d (2H, $^{3}J_{HH}$ 8.0), 7.61 d (2H, $^{3}J_{HH}$ 7.2)	28.9 (EtOAc)
IVd	4-ClC_6H_4	1.57 ($^{3}J_{HH}$ 7.6, $^{3}J_{HP}$ 18.0)	3.17 ($^{3}J_{HH}$ 7.6, $^{3}J_{HP}$ 22.4)	7.32 d (2H, $^{3}J_{AB}$ 8.4), 7.37 d.d (2H, $^{3}J_{AB}$ 8.4)	29.3 (CD_3OD)
Ve	1-Nf	1.71 ($^{3}J_{HH}$ 7.4, $^{3}J_{HP}$ 17.8)	4.14 ($^{3}J_{HH}$ 7.4, $^{3}J_{HP}$ 22.8)	7.4-7.6 m (3H), 7.7-7.8 m (2H), 7.86 d (1H, $^{3}J_{HH}$ 8.0), 8.19 d (1H, $^{3}J_{HH}$ 8.0)	28.6 (CD_3OD) 31.3 (EtOAc)
IVf	2-Nf	1.69 ($^{3}J_{HH}$ 7.2, $^{3}J_{HP}$ 18.0)	3.35 ($^{3}J_{HH}$ 7.2, $^{3}J_{HP}$ 22.4)	7.42-7.50 m (2H), 7.55 m (1H), 7.80-7.85 m (4H)	29.2 (EtOAc)

[a]

Table 7. ^{1}H NMR and ^{31}P NMR spectra of diethyl 1-arylethylphosphonates $ArCH(CH_3)P(O)(OEt)_2$ (**IIIa**–**c**)

Compd. no.	Ar	^{1}H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz)					^{31}P NMR spectrum, δ, ppm (solvent)
		CH_3 (d.d, 3H)	CH (d.q, 1H)	Ar	OCH_2CH_3		
					CH_2 (m)	CH_3 (t)	
IIIa	Ph	1.57 ($^{3}J_{HH}$ 7.4, $^{3}J_{HP}$ 18.5)	3.17 ($^{3}J_{HH}$ 7.4, $^{3}J_{HP}$ 22.6)	7.20-7.35 m (5H)	3.78 (1H), 3.92 (1H), 4.02 (2H)	1.13 (3H, $^{3}J_{HH}$ 7.1), 1.26 (3H, $^{3}J_{HH}$ 7.1)	30.2 (MeOH) 30.6 (CDC_{13}) 29.4 (Et2O)
IIIg	4-$MeOC_6H_4$[a]	1.53 ($^{3}J_{HH}$ 7.4, $^{3}J_{HP}$ 18.5)	3.11 ($^{3}J_{HH}$ 7.4, $^{3}J_{HP}$ 22.5)	6.85 d (2H, $^{3}J_{AB}$ 8.7), 7.26 d (2H, $^{3}J_{AB}$ 8.7)	3.79 (1H), 3.90 (1H), 4.01 (2H)	1.14 (3H, $^{3}J_{HH}$ 7.0), 1.26 (3H, $^{3}J_{HH}$ 7.0)	30.6 (MeOH)
IIIh	6-MeO-2-Nf[b]	1.61 ($^{3}J_{HH}$ 7.2, $^{3}J_{HP}$ 18.4)	3.30 ($^{3}J_{HH}$ 7.2, ($^{3}J_{HP}$ 22.5)	7.0-7.7 m (6H)	3.76 (1H), 3.93 (1H), 4.04 (2H)	1.06 (3H, $^{3}J_{HH}$ 7.0), 1.22 (3H, $^{3}J_{HH}$ 7.0)	30.0 (MeOH)

[a] 3.78 s (3H, OCH_3). [b] 3.80 s (3H, OCH_3).

Table 8. Optimization of conditions for enantioselective reduction of compounds **Ia** and **IIa** (conversion 100%)

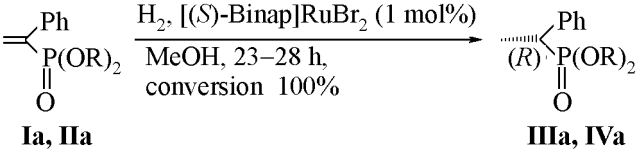
Run no.	No. of initial compound	H_2 pressure, at.	Temperature, °C	Product no. of reaction	Enantiomer excess, %
1	**Ia**	1	20	**IVa**	54
2	**Ia**	1	80	**IVa**	68
3	**Ia**	10	80	**IVa**	73
4	**Ia**	100	80	**IVa**	63
5	**IIa**	80	80	**IIIa**	66

^{1}H NMR spectra of compounds **III** and **IV** instead of two double doublets of vinyl protons characteristic of 1-arylethenylphosphonates appears a double doublet of methyl group in the 1.54–1.71 ppm region ($^3J_{HP}$ 17.8–18.5 Hz) and a double quartet of methine proton ($^2J_{HP}$ 22.4–22.8 Hz). The latter is located in the region 3.11–3.21 ppm in the spectra of phenyl derivatives **IVa–g** and **IIIa, g**, and is shifted downfield in the spectra of 2-naphthyl derivatives **IVf** and **IIIh**, and especially of 1-naphthyl derivative **IVe**. The shift is apparently due to stronger deshielding effected by the naphthalene ring. The presence of a C-stereocenter results in two sets of signals both in the ^{1}H and ^{13}C NMR spectra. In the ^{13}C NMR spectra of phosphonic acids **IV** and diethyl phosphonates **III** the resonance signal from C^1 appears at 34.1–40.8 ppm. The coupling constant $^1J_{CP}$ is considerably smaller than that observed for unsaturated phosphonate **I** and **II** and amounts to 135.0–142.8 Hz. This observation is consistent with the general rule of decreasing of coupling constant $^1J_{CP}$ on going from sp^2- to sp^3-hybridized carbon atom [53].

The conservation of a phosphoryl moiety in compounds **IIIa, g, h** and **IVa–f** is proved by the presence of the corresponding set of absorption bands in the IR spectra. It should be noted that in the IR spectra of saturated phosphonic acids and diethyl phosphonates as well as in the spectra of their unsaturated analogs appears a band in the region 1600–1700 cm^{-1} belonging presumably to the aromatic ring vibrations and frequently erroneously attributed to vibrations of a C=C bond [54].

We did not succeed to carry out chemoselective reduction of acid **Id**: after 4 h of boiling of **Id** solution in methanol in the presence of 6 equiv of $HCOONH_4$ and 2.8 mol% Pd/C (5%) was isolated a mixture of **IVd** and **IVa** products in 1:1 ratio (run no. 6). We failed to avoid dehalogenation also at performing the reaction at room temperature. It should be noted that reductive dehalogenation of aryl halides with ammonium formate in the presence of palladium on carbon is a well known process [55], but a chemoselective reduction of 2-(4-chlorophenyl)-ethenylphosphonic acid without cleavage of C–Cl bond has been reported [38].

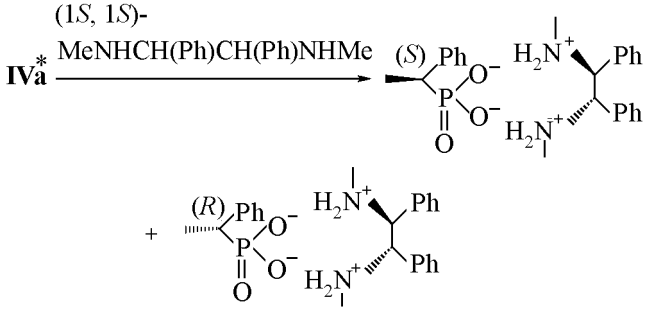
We performed enantioselective hydrogenation of 1-arylethenylphosphonic acids **Ia, b, d, e** with the use of optically active ruthenium catalysts. The preliminary optimization of conditions was carried out by an example of compounds **Ia** and **IIa** and a ruthenium complex of bis(2,2'-diphenylphosphino)-di-1,1'naphthyl [(*S*)-Binap]$RuBr_2$ (1 mol%) in methanol (Table 8).



Ia, IIa **IIIa, IVa**

R = H (**Ia, IVa**), Et (**IIa, IIIa**).

Enantiomer excess with ester **IIIa** was measured by GLC (column Megadex 5). The enantiomers ratio in the product containing (+) and (–) **IVa** was determined from ^{31}P NMR spectra by integral intensities of signals belonging to diastereomeric salts prepared by treating compound IVA with an optically pure diamine. We tested (*S*)-1-phenylethylamine,



Δδ 0.4 ppm

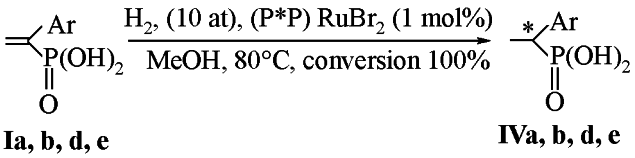
Table 9. Ru(II)-catalyzed enantioselective hydrogenation of 1-arylethenylphosphonic acids **Ia, b, d, e**

Run no.	No. of initial compound	Ar	(P^p)	Reaction product no.	ee, %
1	**Ia**	Ph	(*S*)-Binap	(*R*)-**IVa**	73
2	**Ia**	Ph	(*R*)-MeO-BIPHEP	(*S*)-**IVa**	77
3	**Ia**	Ph	(*R*)-2-furyl-MeO-BIPHEP	(*S*)-**IVa**	24
4	**Ia**	Ph	(*R*,*R*)-Me-DuPHOS	(*R*)-**IVa**	21
5	**Ib**	4-MeC_6H_4	(*S*)-Binap	(*R*)-**IVb**	71
6	**Ib**	4-MeC_6H_4	(*R*)-MeO-BIPHEP	(*S*)-**IVb**	78
7	**Ib**	4-MeC_6H_4	(*R*)-2-furyl-MeO-BIPHEP	(*S*)-**IVb**	25
8	**Ib**	4-MeC_6H_4	(*R*,*R*)-Me-DuPHOS	(*R*)-**IVb**	16
9	**Id**	4-ClC_6H_4	(*S*)-Binap	(*R*)-**IVd**	73
10	**Id**	4-ClC_6H_4	(*R*)-MeO-BIPHEP	(*S*)-**IVd**	86
11	**Id**	4-ClC_6H_4	(*R*)-2-furyl-MeO-BIPHEP	(*S*)-**IVd**	32
12	**Id**	4-ClC_6H_4	(*R*,*R*)-Me-DuPHOS	(*R*)-**IVd**	37
13	**Ie**	1-Nf	(*S*)-Binap	(*R*)-**IVe**	74
14	**Ie**	1-Nf	(*R*)-MeO-BIPHEP	(*S*)-**IVe**	80
15	**Ie**	1-Nf	(*R*)-2-furyl-MeO-BIPHEP	(*S*)-**IVe**	19
16	Ie	1-Nf	(*R*,*R*)-Me-DuPHOS	(*R*)-**IVe**	25

(1*R*,2*R*)-(–)-1,2-cyclohexyldiamine, (1*S*,2*S*)-(–)-1,2-diphenylethylene-1,2-diamine, and (1*S*,2*S*)-(–)-*N*,*N*'-dimethyl-1,2-diphenylethylene-1,2-diamine. As solvent was used $CDCl_3$ or $CDCl_3$ with 4–10% of CD_3OD. The maximum difference between chemical shifts of the signals from two diastereomeric salts (Δδ 0.4 ppm) was observed at the use as diamine of (1*S*,2*S*)-(–)-N,N'-dimethyl-1,2-diphenylethylene-1,2-diamine dissolved in $CDCl_3$ containing 4% of CD_3OD.

As seen from Table 8, the enantioselectivity of acid **Ia** hydrogenation on [(*S*)-Binap]$RuBr_2$ increased with rising temperature in the range 20–80°C (runs nos.1 and 2), and the dependence on hydrogen pressure between 1 and 100 at has a bell shape with a maximum at 10–20 at (runs nos. 2–4). The maximum selectivity, 73% *ee*, was obtained at 80°C and hydrogen pressure of 10 at (run no. 3). The reactivity of acid **Ia** was higher than that of corresponding diethyl ester **IIa**. Phosphonate **IIa** underwent reduction only under stringent conditions (80°C, 80 at of H_2) affording ester **IIIa** in quantitative yield and enantiomer excess 66%.

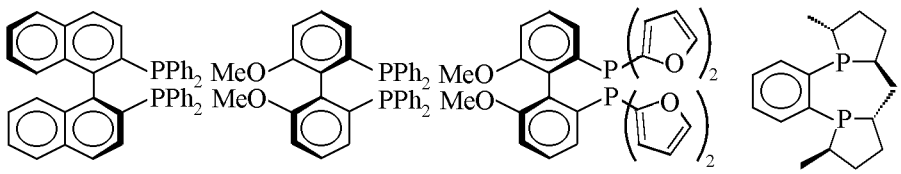
Under the developed optimal conditions we carried out reduction of acids **Ia, b, d, e** with a series of ruthenium catalysts prepared in situ [56] and containing various optically active diphosphine ligands (Table 9).



Ia, b, d, e **IVa, b, d, e**

I, IV, Ar = Ph (**a**), 4-MeC_6H_4 (**b**), 4-ClC_6H_4 (**d**), 1-Nf (**e**).

(P*P):



(*S*)-Binap (*R*)-MeO-BIPHEP (*R*)-2-Furyl-MeO-BIPHEP (*R*,*R*)-Me-DuPHOS

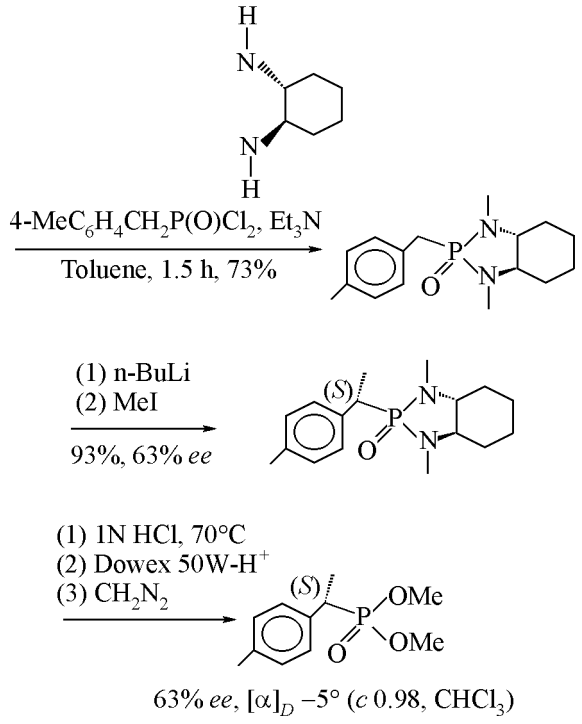
Table 10. The study of biological activity of 1-arylethylphosphonic acids **IVa, c, e, f**

Compounds	Ar	Ld_{50}, mg kg^{-1}	Direction of effect		
			dose, mg kg^{-1}	effect, %	direction of effect
IVa	Ph	700	10	40	Tends to increase the activity
IVc	4-PhC_6H_4	300	10	40	of serotonin system
IVe	1-Nf	500	50	80[a]	Suppression of dopamine system activity
IVf	2-Nf	500	5	60[a]	Increase of serotonin system activity
			10	80[a]	
Trifluoropyrazine			0.5	90	Suppression of dopamine system activity
5-Oxytryptophan			200	100	Increase of serotonin system activity

[a] $p < 0.05$ is valid with respect to intact animals.

The catalysts with ligands (*R,R*)-Me-DuPHOS (runs nos. *4, 8, 12, 16*) and (*R*)-2-furyl-MeO-BIPHEP (runs nos. *3, 7, 11, 15*) furnished saturated 1-arylethylphosphonic acids **IVa, b, d, e** of low enantiomeric purity (ee 16–37 and 19–32% respectively). High enantiomeric purity (ee 71–74%) was obtained with (*S*)-Binap (runs nos. 1, 5, 9, 13). The highest differentiating power demonstrated 6,6'-dimethoxy-2,2'-diphenylphosphinodiphenyl (*R*)-MeO-BIPHEP (77–86%% ee, runs nos. 2, 6, 10, 14).

Assignment of the absolute configuration to compound (*R*)-(**IIIa**) (run no. 1) was done by comparison with the published data [36] of the specific rotation sign of the corresponding (*R*)-dimethyl 1-phenylethylphosphonate obtained by treating the isolated sample of (*R*)-(**IIIa**) with diazomethane. The absolute configuration was assigned to compound (*S*)-(**IIIb**) (run no. 6) was also assigned proceeding from the sign of the specific rotation of the corresponding (*S*)-dimethyl 1-(4-methylphenyl)ethylphosphonate. An authentic sample of (*S*)-dimethyl 1-(4-methylphenyl)ethylphosphonate used for comparison was synthesized along procedure from [36].



It was shown formerly that enantioselective hydrogenation of 2-arylacrylic acids on Ru(II)-catalysts containing atropoisomeric ligands gave rise to compounds with configuration of C^*-stereocenter same as in the applied ligand [57]. We obtained the opposite results. For instance, in hydrogenation of compound **Ia** in the presence of [(*S*)-Binap]$RuBr_2$ prevailed the product (*R*)-(**IVa**).

The results of preliminary testing of 1-arylethylphosphonic acids **IVa, c, e, f** for biological activity are given in Table 10. The data obtained on Ld_{50} show that the acids **IVa, e, f** are low-toxic. In order to reveal the possible antidopaminergic and proserotoninergic activity of compounds **IVa, c, e, f** their interaction with the central effects of L-dioxyphenylalanine (L-DOPA, precursor of dopamine). The results obtained demonstrated that acid **IVe** possesses a pronounced antidopaminergic activity on the par with the known dopaminblockader, trifluoropyrazine. The activity of acid **IVf** is like that of nonselective serotoninmimetics and 5-oxytryptophan. The complete data on the studies of biological activity of 1-arylethylphosphonic acids will be published elsewhere.

EXPERIMENTAL

^1H, ^{13}C, and ^{31}P NMR spectra were registered on spectrometer Varian VXR-400 at operating fre-

quencies 400, 101, and 162 MHz respectively. The chemical shifts are given in δ scale relative to TMS or 85% H_3PO_4. In several cases the chemical shifts were measured relative to the residual protons of the solvents used (3.34 ppm for CD_3OD and 7.25 ppm for $CDCl_3$). IR spectra were recorded on Fourier-transform spectrophotometer IKAR (Joint-Stock Co "Mikrotekh", Russia), resolution 1 cm^{-1}, number of scans 30. Mass spectra were measured on Varian MAT-212 instrument with direct injection of sample into the ion source.

The acute toxicity of 1-arylethylphosphonic acids **IVa, c, e, f** was estimated on male mice of C57B1/6 line. The substances were dispersed in water with added TWEEN-60 and were injected intraperitoneally in doses of 100, 500, and 1000 mg kg^{-1}. The results obtained were treated by procedure of Litchfield and Wilcockson [58]. The experiments on interaction of 1-arylethylphosphonic acids **IVa, c, e, f** with the central effects of L-dioxyphenylalanine were carried out on male rats of Wistar line weighing 220–250 g. The substance studied was dispersed in water containing TWEEN-80, and was injected intraperitoneally simultaneously with L-DOPA (commercial preparation MADOPAR-125, dose 125 mg kg^{-1}). In 60 min was estimated the intensity of stereotypical reactions and the behavior of animals in the test of extrapolation release [59, 60].

Methanol was boiled and distilled over magnesium methylate. Ammonium formate of "pure" grade was dried in a vacuum-desiccator over P_2O_5.

1-Acetylnaphthalene was prepared and purified by the known procedures [61].

Palladium on carbon (5% of Pd). A mixture of 0.167 g of palladium(II) chloride, 0.4 ml of concn hydrochloric acid, and 1 ml of water was heated on a water bath till homogeneous solution formed (about 30 min). The solution obtained was fast added dropwise while vigorous stirring to a hot (80°C) dispersion of 1.9 g of carbon in 24.5 ml of water, and then dropwise was added 0.5 ml of 37% formalin. The mixture was stirred for 30 min, then cooled, and 30% solution of potassium hydroxide was added till weakly alkaline reaction against litmus. Another 30 min the mixture was maintained at 60°C with intermittent stirring, and then 2 h more at room temperature. The catalyst was filtered off and washed with water till negative reaction for OH ions against phenolphthalein, dried in air and then in a desiccator over potassium hydroxide.

1-Phenylethenylphosphonic acid (Ia). Into a round-bottom flask filled with argon equipped with a reflux condenser, dropping funnel, and connected to supply of dry argon was charged 23.3 ml (0.2 mol) of acetophenone. At cooling on an ice bath and while vigorous stirring to the flask was slowly added dropwise 24 ml (0.275 mol) of freshly distilled PCl_3. The reaction mixture was stirred for 1 h at room temperature, then it was again cooled, and slowly (within 30 min) was added dropwise 34.35 ml (0.6 mol) of glacial acetic acid. Then the reaction mixture was left overnight.

The solution obtained was poured on 700 g of ice and left for 24 h. Then it was evaporated in a porcelain evaporating dish at 90–92°C till small volume. The residue was dissolved in 50 ml of boiling concn HCl, and the solution was boiled for 3.5 h. The crystals that precipitated on cooling were filtered off and washed with cold benzene. We obtained 30.59 g (83%) of acid **Ia**. ^{13}C NMR spectrum (CD_3OD, δ, ppm): 129.0 d (2CH arom, $^3J_{CP}$ 5.7 Hz), 129.4 s (CH arom), 129.58 d (CH_2=C, $^2J_{CP}$ 7.5 Hz), 129.61 s (2CH arom), 139.1 d (C arom, $^2J_{CP}$ 12.4 Hz), 144.6 d (C–P, $^1J_{CP}$ 174.9 Hz).

1-(4-Methylphenyl)ethenylphosphonic acid (Ib) was prepared in a similar way from 7.38 g (55 mmol) of 4-methylacetophenone, 6.5 ml (74 mmol) of PCl_3, and 9.4 ml (164 mmol) of glacial CH_3COOH. We obtained 7.7 g (71%) of acid **Ib**. ^{13}C NMR spectrum (CD_3OD, δ, ppm): 21.6 s (CH_3), 128.7, 128.8, 128.85, 130.2 s (2CH arom), 136.0 d (C arom, $^2J_{CP}$ 12.2 Hz), 139.2 s (C arom), 144.0 d (C–P, $^1J_{CP}$ 175.3 Hz).

1-(4-Diphenyl)ethenylphosphonic acid (Ic) was prepared in a similar way from 4.4 g (22.4 mmol) of 4-acetyldiphenyl, 3.14 ml (36 mmol) of PCl_3, and 4.5 ml (78.6 mmol) of glacial CH_3COOH without cooling of the reaction mixture in the course of reaction. To the residue obtained after evaporation was added 150 ml of toluene, and the solution obtained was boiled for 10 h while distilling off the forming water. The precipitate separated on cooling was filtered off. Yield 3.5 g (60%).

1-(4-Chlorophenyl)ethenylphosphonic acid (Ib) was prepared in a similar way from 10.4 ml (80.2 mmol) of 4-chloroacetophenone, 9.6 ml (110 mmol) of PCl_3, and 13.6 ml (237.6 mmol) of glacial CH_3COOH. We obtained 13.3 g (76%) of acid **Id**. ^{13}C NMR spectrum (CD_3OD, δ, ppm): 129.7 s (2CH arom), 129.9 d (CH_2=C, $^2J_{CP}$ 7.4 Hz), 130.5 d (2CH arom, $^3J_{CP}$ 5.9 Hz), 135.3 s (C arom), 137.9 d (C arom, $^2J_{CP}$ 12.3 Hz), 143.7 d (C–P, $^1J_{CP}$ 175.3 Hz).

1-(1-Naphthyl)ethenylphosphonic acid (Ie) was prepared in a similar way from 9.16 g (54 mmol) of 1-acetylnaphthalene, 6.4 ml (73 mmol) of PCl_3, and 9.4 ml (169 mmol) of glacial CH_3COOH. The residue obtained by evaporation was recrystallized from water and washed on filter with cold benzene. We obtained 8.6 g (68%) of acid **Ie**. ^{13}C NMR spectrum (CD_3OD, δ, ppm): 126.2 d (CH arom, J_{CP} 2.0 Hz), 127.1 s (CH arom), 127.2 s (CH arom), 127.4 s (CH arom), 127.9 d (CH arom, J_{CP} 4.0 Hz), 129.3 d (CH arom, J_{CP} 3.0 Hz), 129.4 s (CH arom), 132.7 d (CH_2=C, $^2J_{CP}$ 8.1 Hz), 133.4 d (C arom, J_{CP} 4.4 Hz), 135.6 s (C arom), 137.2 d (C arom, $^2J_{CP}$ 10.1 Hz), 143.9 d (C–P, $^1J_{CP}$ 176.1 Hz).

1-(2-Naphthyl)ethenylphosphonic acid (Ie) was prepared in a similar way from 9.2 g (54 mmol) of 2-acetylnaphthalene, 7 ml (80 mmol) of PCl_3, and 10.0 ml (175 mmol) of glacial CH_3COOH. The boiling with HCl continued for 4 h. The residue obtained by evaporation was recrystallized from water and washed on filter with cold benzene. We obtained 9 g (71%) of acid **If**. ^{13}C NMR spectrum (CD_3OD, δ, ppm): 126.7 d (CH arom, J_{CP} 5.6 Hz), 127.6 (CH arom), 128.1 d (CH arom, J_{CP} 5.7 Hz), 128.8 s (CH arom), 129.2 s (CH arom), 129.6 s (CH arom), 129.9 d (*C*H_2=C, $^2J_{CP}$ 7.9 Hz), 134.6 s (C arom), 134.9 s (C arom), 136.4 s (C arom), 144.4 d (C–P, $^1J_{CP}$ 174.9 Hz).

Diethyl 1-phenylethylphosphonate (IIIa). A mixture of 1.2 g (5 mmol) of compound **IIa**, 1.91 g (30 mmol, 6 equiv) of $HCOONH_4$, 0.29 g of 5% Pd/C (2.7 mol% of Pd) in 70 ml of anhydrous MeOH was boiled for 3 h in a flow of dry argon. The catalyst was separated by filtration of the reaction mixture through a thin bed of silica gel. The filtrate was evaporated in a vacuum, the residue was extracted with Et_2O. The ether extract was washed with small portion of water, dried on $MgSO_4$, filtered, and evaporated. The residue was distilled under reduced pressure in a flow of argon. We obtained 1.05 g (87%) of phosphonate **IIIa**. ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.2 d (CH_3, J_{CP} 5.2 Hz), 15.9 d (CH_3, J_{CP} 5.7 Hz), 16.1 d (CH_3, J_{CP} 6.1 Hz), 61.6 d (CH_2, $^2J_{CP}$ 7.0 Hz), 62.1 d (CH_2, $^2J_{CP}$ 6.9 Hz), 38.1 d (CH– P, $^1J_{CP}$ 137.7 Hz), 126.7 s (CH arom), 128.3, 128.4, 128.5, 128.6, 137.6 d (C arom, $^2J_{CP}$ 7.0 Hz).

Diethyl 1-(4-methoxyphenyl)ethylphosphonate (IIIg) was prepared similarly by reduction of 0.72 g (2.7 mmol) of compound **IIg** with ammonium formate (1.27 g, 20.1 mmol, 7.5 equiv) in 40 ml of anhydrous MeOH in the presence of 0.28 g of 5% Pd/C (4.9 mol% of Pd). Reaction time was 10 h. Yield 0.64 g (88%). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.0 d (CH_3, J_{CP} 4.6 Hz), 15.7 d (CH_3, J_{CP} 5.9 Hz), 15.8 d (CH_3, J_{CP} 5.5 Hz), 36.7 d (CH–P, $^1J_{CP}$ 138.5 Hz), 54.4 s (CH_3O), 61.2 d (CH_2, $^2J_{CP}$ 7.2 Hz), 61.8 d (CH_2, $^2J_{CP}$ 6.4 Hz), 113.1 s (2CH arom), 129.0 d (2CH arom, $^3J_{CP}$ 6.1 Hz), 131.3 d (C arom, $^2J_{CP}$ 9.2 Hz), 158.0 s (C–OMe).

Diethyl 1-(6-methoxy-2-naphthyl)ethylphosphonate (IIIh) was prepared similarly by reduction of 0.72 g (2.5 mmol) of compound **IIh** with ammonium formate (1.06 g, 16.8 mmol, 7.5 equiv) in 34 ml of anhydrous MeOH in the presence of 0.24 g of 5% Pd/C (5 mol% of Pd). Reaction time was 10 h. The catalyst was separated by filtration of the reaction mixture through a thin bed of silica gel. The filtrate was evaporated in a vacuum, the residue was extracted with Et_2O. The ether extract was washed with small portion of water, dried on $MgSO_4$, filtered, and evaporated. The residue was thick red-brown oily substance. Yield 0.64 g (88%). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.3 d (CH_3, J_{CP} 4.5 Hz), 16.0 d (CH_3, J_{CP} 5.4 Hz), 16.1 d (CH_3, J_{CP} 5.7 Hz), 37.9 d (CH–P, $^1J_{CP}$ 138.0 Hz), 54.8 s (CH_3O), 61.6 d (CH_2, $^2J_{CP}$ 7.1 Hz), 62.1 d (CH_2, $^2J_{CP}$ 6.9 Hz), 105.1 s (CH arom), 118.6 s (CH arom), 126.5 s (CH arom), 126.8, 127.0, 128.3, 128.9 s (CH arom), 132.0, 133.3 s (C arom), 157.3 s (C–OMe).

1-Phenylethylphosphonic acid (IVa). A mixture of 0.92 g (5 mmol) of compound **Ia**, 1.90 g (30 mmol) of ammonium formate, and 0.3 g of 5% Pd/C (2.8 mol% of Pd) in 70 ml of anhydrous MeOH was boiled for 4 h in a flow of dry argon. The catalyst was removed by filtration through a thin bed of silica gel, methanol was distilled off on rotary evaporator. The residue was acidified with a small amount of conc. HCl and extracted with EtOAc. The organic extracts were dried on $MgSO_4$, filtered therefrom, and evaporated. The residue (yellowish oily substance) was recrystallized from a mixture benzene…petroleum ether. We obtained 0.65 g (70%) of acid **IVa**. ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 14.7 d (CH_3), 37.6 d (CH–P, $^1J_{CP}$ 140.7 Hz), 127.2 s (CH arom), 128.4 s (2CH arom), 128.6 d (2 CH arom), 136.6 d (C arom, $^2J_{CP}$ 6.4 Hz).

1-(4-Methylphenyl)ethylphosphonic acid (IVb) was prepared similarly by reduction of 0.99 g (5 mmol) of compound **Ib** with ammonium formate (1.9 g, 30 mmol) in 70 ml of anhydrous MeOH in the presence of 0.3 g of 5% Pd/C. Yield 0.87 g (87%). ^{13}C NMR spectrum (CD_3OD, δ, ppm): 16.3 s *C*H_3CH), 21.1 s (CH_3Ar), 39.9 d (CH–P, $^1J_{CP}$

142.8 Hz), 129.5 d (2CH arom), 129.9 s (2CH arom), 132.8 d (C arom, $^2J_{CP}$ 13.0 Hz), 137.3 s (Me–C arom).

1-(4-Diphenyl)ethylphosphonic acid (IVc) was prepared similarly by reduction of 1.3 g (5 mmol) of compound **Ic** with ammonium formate (1.89 g, 30 mmol) in 100 ml of water in the presence of 0.30 g of 5% Pd/C. The compound obtained was recrystallized from ethyl acetate. Yield 0.8 g (61%).

1-(1-Naphthyl)ethylphosphonic acid (IVe) was obtained similarly by reduction of 1.22 g (5.2 mmol) of compound **Ie** with ammonium formate (1.98 g, 31 mmol) in 40 ml of water in the presence of 0.31 g of 5% Pd/C. Yield 0.91 g (74%). ^{13}C NMR spectrum (CD_3OD, δ, ppm): 17.3 d (CH_3, $^2J_{CP}$ 4.4 Hz), 34.1 d (CH–P, $^1J_{CP}$ 135.0 Hz), 124.6 s (CH arom), 126.4, 126.45, 126.6, 126.7, 127.0 s (CH arom), 128.2 s (CH arom), 129.8 s (CH arom), 133.3 d (C arom, J_{CP} 7.1 Hz), 135.4 s (C arom), 137.0 d (C arom, J_{CP} 6.2 Hz).

1-(2-Naphthyl)ethylphosphonic acid (IVf) was obtained similarly by reduction of 1 g (4.27 mmol) of compound **If** with ammonium formate (1.62 g, 25.7 mmol) in 60 ml of water in the presence of 0.273 g of 5% Pd/C. Yield 0.7 g (69%). ^{13}C NMR spectrum (CD_3OD, δ, ppm): 16.6 d (CH_3, $^2J_{CP}$ 4.3 Hz), 40.8 d (CH–P, $^1J_{CP}$ 136.1 Hz), 126.9 s (CH arom), 127.2 s (CH arom), 128.41, 128.46, 128.5, 128.8 s (CH arom), 129.0 s (CH arom), 134.2 d (C arom, J_{CP} 1.8 Hz), 135.2 d (C arom, J_{CP} 2.2 Hz), 138.4 d (C arom, $^2J_{CP}$ 8.0 Hz).

General procedure for enantioselective hydrogenation. Into a flask of 50 ml capacity was charged 7 mg (0.012 mmol) of (*R*)-MeO-BIPHEP and 3.2 mg (0.01 mmol) of (COD)Ru[η^3-$(CH_2)_2CCH_3$]. Anhydrous acetone (5 ml) was added dropwise, and then 122 μl of 0.18 M solution of HBr in methanol. The reaction mixture was stirred at room temperature for 30 min. The solvent was distilled off in a vacuum. To the orange solid residue of the catalyst under argon atmosphere was added 2 ml of methanol and 1 mmol of acid **I**. The reaction flask was placed into a steel pressure reactor of 500 ml capacity, and hydrogen was supplied to the reactor to the desired pressure. The reaction mixture was always maintained till 100% conversion.

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