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Regio- and stereoselective synthesis of 2-amino-1-hydroxy-2-aryl ethylphosphonic esters

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Abstract

A highly regio- and diastereoselective synthesis of 2-amino-1-hydroxy-2-aryl ethylphosphonic esters was achieved by opening *trans* 1,2-epoxy-2-aryl ethylphosphonic esters with 28% $NH_{3(aq.)}$ in methanol. © 2000 Published by Elsevier Science Ltd.

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Phosphonic acids with heteroatoms in the α and/or β positions have attracted considerable interest because of their use as inhibitors of proteolytic enzymes, such as renin[1] and human immunodeficiency virus (HIV) protease,[2] as agents affecting the growth of plants[3] or as haptens in the development of catalytic antibodies.[4]

The preparation of β-amino-α-hydroxyalkylphosphonic esters **4** can be accomplished in different ways,[5] but there are only two reports that mention the possibility of obtaining 2-amino-1-hydroxyethylphosphonic acids by the opening of 1,2-epoxyethylphosphonic esters[6] and no papers record the opening of 1,2-epoxy-2-aryl ethylphosphonic esters.

Herein we report a quite general synthetic approach to compounds **4** starting from various types of alkenylphosphonic esters **2**, which are prepared in two ways according to the desired *Z* or *E* stereochemistry (Scheme 1).

Standard Horner–Wittig reaction of the tetraethyl methylenebisphosphonate with aromatic aldehydes carried out in an aqueous two-phase system affords the pure (*E*)-isomers of vinylphosphonates **2** in good yields[7] (Table 1). The same reaction carried out with alkyl or cycloalkyl aldehydes in toluene with sodium hydride also gave the desired (*E*)-isomer of **2**[8] (Table 1).

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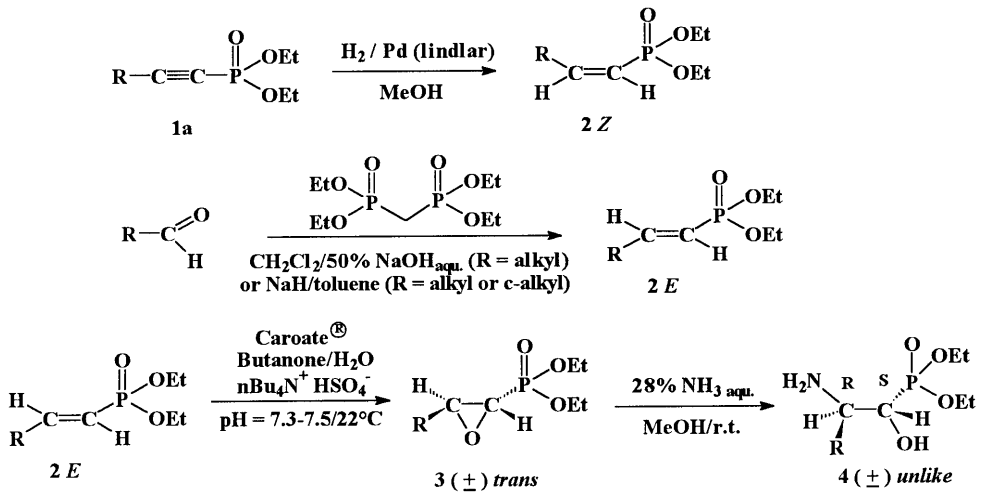

Scheme 1. Preparation of compounds **2**, **3** (Table 1) and **4** (Table 2)

Table 1
Preparation of alkenylphosphonic esters **2** and 1,2-epoxyethylphosphonic esters **3**[a]

	Alkenylphosphonates esters **2**			1,2-Epoxyethylphosphonic esters **3**			
R	Compound	Yield (%)	^{31}P NMR ($CDCl_3$, ppm)	Compound	Yield (%)	^{31}P NMR ($CDCl_3$, ppm)	$^{3}J_{HH}$ (HC-HCP, Hz)
Phenyl	**2a** (*E*)	68	20.1	**3a** (*trans*)	75	17.2	2.4
o-Tolyl	**2b** (*E*)	87	20.0	**3b** (*trans*)	76	17.2	2.5
m-Tolyl	**2c** (*E*)	70	20.2	**3c** (*trans*)	64	17.3	2.3
p-Tolyl	**2d** (*E*)	92	20.6	**3d** (*trans*)	85	17.4	2.3
o-Anisyl	**2e** (*E*)	80	21.1	**3e** (*trans*)	78	18.1	2.4
α-Naphtyl	**2f** (*E*)	83	20.2	**3f** (*trans*)	63	17.2	2.3
Phenyl	**2a** (*Z*)	70	16.5	**3a** (*cis*)	73	17.5	4.6
n-Butyl	**2g** (*Z*)	68	17.7	**3g** (*cis*)	58	19.6	4.5
n-Butyl	**2g** (*E*)	63	19.4	–	–	–	–
c-Hexyl	**2h** (*E*)	58	20.4	–	–	–	–

[a] All alkenylphosphonic esters **2** and 1,2-epoxyethylphosphonic esters **3** were identified satisfactorily by their ^{1}H and ^{13}C NMR and also by comparison with literature data.

(*Z*)-Isomers of vinylphosphonate esters were obtained by hydrogenation of appropriate alkynylphosphonate **1a** catalyzed by Pd (Lindlar) in MeOH[9] (Table 1).

Phosphonic esters **2***E* and **2***Z* were converted into the corresponding *trans* or *cis* isomers of 1,2-epoxyethylphosphonic esters **3** by the reaction of **2** with dioxirane in a two-phase system according to a previously developed procedure[10] (Table 1). Unfortunately, this method gave no satisfactory results for the (*E*)-isomers of β-alkylsubstituted vinylphosphonates **2g** and **2h**.

Reaction of **3** *trans* with an 84-fold excess of ammonia (28% $NH_{3(aq.)}$) in MeOH[11] gave practically always only one diastereoisomer of the desired product **4**,[12] as established by ^{31}P NMR.

We have observed high regioselectivity (usually about 95%) for compounds **4** as well.[13] The position of the hydroxy group in the α position and the amino group in the β position was confirmed by comparison of chemical shifts and coupling constants in ^{13}C NMR spectra with the data given in the literature for derivatives of compound **4a** and some analogs,[5] and additionally with simulated values by an ACD-CNMR program.

Concerning the diastereoselectivity, the compounds **4**, obtained from the **3** *trans* isomer, are probably the *unlike* diastereoisomers, in agreement with the expected S_N2 opening of the oxirane by NH_3, corroborated by the literature data of compounds **4**.[5]

We have noticed also that the maximum conversion (usually 50–65%) into **4** (Table 2) was reached after about 24 hours, as established by ^{31}P NMR monitoring of the crude reaction mixture. Prolongation of the reaction time because of uncompleted conversion of substrate **3** induces the decomposition of compound **4**, so the reaction should be monitored by ^{31}P NMR and interrupted at the appropriate moment.

Table 2
Preparation of 2-amino-1-hydroxyethylphosphonic esters **4**[a]

4	Reaction time (h)	Conversion (%)	Yield (%)	^{31}P NMR ($CDCl_3$, ppm)	Stereoselectivity (u/l)
a	24	57	42	23.0	100:0
b	23	52	44	23.4	100:0
c	32	54	47	22.8	100:0
d	22	65	59	23.4	98:2
e	23	66	53	23.5/23.8	10:90
f	22	59	53	23.0	100:0

[a] All compounds were identified satisfactorily by their ^1H and ^{13}C NMR (comparing with simulated values of chemical shifts using the ACD-CNMR program), IR and MS FAB (+).

The same procedure was applied toward (*cis*)-1,2-epoxyethylphosphonic esters **3**, but the reaction was very slow (more than 50 hours), not regioselective, and resulted in poor yields.[14]

In conclusion the ammonolysis of *trans* 1,2-epoxyethylphosphonic esters appears to be a valuable synthetic method for the preparation of β-amino-α-hydroxy arylalkylphosphonic derivatives in consideration of its simplicity, applicability and selectivity. The application of this method towards trisubstituted 1,2-epoxyethylphosphonic esters is under investigation.

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11. *The synthesis of 2-amino-1-hydroxy-2-aryl ethylphosphonic esters—general procedure*
Into a Schlenk flask equipped with magnetic stirrer was introduced 2 mmol of the appropriate *trans* 1,2-epoxy-2-aryl ethylphosphonic ester, 10 ml (0.165 M) of 28% $NH_{3(aq.)}$ and 20 ml of MeOH. The flask was closed tightly and the mixture was stirred intensively at room temperature. The progress of the reaction was monitored by ^{31}P NMR.
After completion of the reaction, NH_3 and methanol were evaporated from the mixture and 10 ml of distilled H_2O was added to the residue. Extraction of the water phase was achieved by adding 10 ml Et_2O, and then by 5×10 ml $CHCl_3$. The combined organic layers were dried with $MgSO_4$, filtered and the solvent was removed under vacuum.
Column chromatography on SilicaGel (70–200 mesh/50 g) using a CH_2Cl_2/AcOEt gradient of 1:1 (150 ml), followed by pure AcOEt (150 ml), and then MeOH/AcOEt (1:4) (200 ml) was used to obtain compound **4**, which was subsequently recrystallized from isopropanol.
12. Solvents and commercially available aldehydes were redistilled prior to use. Tetraethyl methylenebisphosphonate was prepared according to the reported procedure.[15] ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 200.132 and 50.32 MHz, respectively. ^{31}P NMR spectra were recorded at 81.0 MHz in $CDCl_3$. ^{31}P NMR chemical shifts are relative to 85% H_3PO_4. FT-IR spectra were recorded in the form of KBr disks using a Perkin–Elmer 377 spectrometer. Mass spectrometry [FAB (+)] was performed at the University of Montpellier II using a DX300-SX102 spectrometer.
4a: ^1H NMR: δ 1.11 (t, $J=7.1$ Hz, 3H), 1.26 (t, $J=7.1$ Hz, 3H), 2.68 (bs, 3H), 3.80–4.08 (m, 2H), 4.10–4.18 (m, 3H), 4.34 (dd, $J=6.3$ Hz, $J=19.3$ Hz, 1H), 7.25–7.46 (m, aromat., 5H); ^{13}C NMR: δ 16.37 (d, $J=6.1$ Hz), 16.6 (d, $J=5.7$ Hz), 57.49 (d, $J=4.1$ Hz), 62.34 (d, $J=7.2$ Hz), 63.06 (d, $J=7.1$ Hz), 71.88 (d, $J=160.6$ Hz), 127.9, 128.0, 128.36, 128.47, 128.61, 141.21 (d, $J=5.6$ Hz); MS FAB (+)=274.
4b: ^1H NMR: δ 1.09 (t, $J=7.1$ Hz, 3H), 1.28 (t, $J=7.1$ Hz, 3H), 2.39 (s, 3H), 2.90 (bs, 3H), 3.87 (m, 2H), 4.10 (m, 3H), 4.57 (dd, $J=6.7$ Hz, $J=20.5$ Hz, 1H), 7.12–7.58 (m, aromat., 4H); ^{13}C NMR: δ 16.28 (d, $J=5.9$ Hz), 16.52 (d, $J=5.7$ Hz), 19.63, 52.67, 62.33 (d, $J=7.1$ Hz), 63.07 (d, $J=7.0$ Hz), 70.76 (d, $J=162$ Hz), 126.22, 126.89, 127.49, 130.4, 136.3, 138.92; MS FAB (+)=288.
4c: ^1H NMR: δ 1.11 (t, $J=7.1$ Hz, 3H), 1.22 (t, $J=7.1$ Hz, 3H), 2.34 (s, 3H), 3.51 (bs, 3H), 3.66–4.41 (m, 6H), 7.10–7.28 (m, aromat., 4H); ^{13}C NMR: δ 16.36 (d, $J=6.1$ Hz), 16.58 (d, $J=5.7$ Hz), 57.35 (d, $J=4.6$ Hz), 62.44 (d, $J=7.2$ Hz), 63.2 (d, $J=7.2$ Hz), 71.4 (d, $J=162.1$ Hz), 125.03, 128.22, 128.46, 128.8, 138.08, 139.86, MS FAB (+)=288.
4d: ^1H NMR: δ 1.13 (t, $J=7.08$ Hz, 3H), 1.25 (t, $J=7.1$ Hz, 3H), 2.33 (s, 3H), 2.74 (bs, 3H), 3.99 (m, 5H), 4.25 (dd, $J=6.2$ Hz, $J=17.2$ Hz, 1H), 7.14 (d, aromat., 2H, $J=7.9$ Hz); 7.29 (d, aromat., 2H, $J=8.2$ Hz); ^{13}C NMR: δ 16.12 (d, $J=6.1$ Hz), 16.37 (d, $J=5.8$ Hz), 21.04, 56.69, 62.15 (d, $J=7.0$ Hz), 62.70 (d, $J=6.9$ Hz), 71.73 (d, $J=160.7$ Hz), 127.58, 128.78, 136.92, 138.17; MS FAB (+)=288.
4e: ^1H NMR: δ 1.01 (t, $J=7.1$ Hz, 3H), 1.30 (t, $J=7.1$ Hz, 3H), 2.18 (bs, 3H), 3.73 (m, 2H), 3.85 (s, 3H), 4.15 (quin., 2H), 4.33 (dd, $J=4.4$ Hz, $J=6.52$ Hz, 1H), 4.58 (dd, $J=6.6$, $J=26.0$ Hz, 1H), 6.84–7.47 (m, aromat., 4H); ^{13}C NMR: δ 16.03 (d, $J=6.0$ Hz), 16.42 (d, $J=5.6$ Hz), 53.02, 55.3, 61.51(d, $J=7.3$ Hz), 62.83 (d, $J=6.9$ Hz), 69.71 (d, $J=159.2$ Hz), 110.4, 120.54, 127.98, 128.36, 129.16, 156.86; MS FAB (+)=304.
4f: ^1H NMR: δ 0.95 (t, $J=7.0$ Hz, 3H), 1.18 (t, $J=7.0$ Hz, 3H), 3.17 (bs, 3H), 3.7–4.26 (m, 5H), 4.50 (dd, $J=6.0$ Hz, $J=17.9$ Hz, 1H), 7.27–7.88 (m, aromat., 7H); ^{13}C NMR: δ 16.11 (d, $J=5.9$ Hz), 16.38 (d, $J=5.7$ Hz), 57.48 (d, $J=4.4$ Hz), 62.27 (d, $J=7.1$ Hz), 62.83 (d, $J=7.2$ Hz), 71.72 (d, $J=160.9$ Hz), 125.77, 125.86, 126.15, 128.0, 128.4, 133.09 (d, $J=14.2$), 138.96 (d, $J=6.6$ Hz); MS FAB (+)=324.

13. Three phosphorus by-products always accompanied the desired product **4**. Two of them were recognized as di- and monoethylesters of phosphonic acid and one because of very small yield ($\sim$5%) was unidentified.
14. Usually between 7 and 11 phosphorus by-products were observed and the yield of the desired product **4** was about 10%.
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