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New α-substituted alkylbenzene- and dialkylbenzene-1,2-diphosphonates: side-chain metalation of tetraethyl 4-methyl- and 4,5-dimethylbenzene-1,2-diphosphonates

Sergey N. Tverdomed [a,*], Gerd-Volker Röschenthaler [b,*], Nataliya Kalinovich [b], Enno Lork [b], Alla V. Dogadina [a], Boris I. Ionin [a]

[a] Department of Organic Chemistry, St. Petersburg State Institute of Technology (Technical University), Moskovskii pr. 26, St. Petersburg 190013, Russia
[b] Institute of Inorganic and Physical Chemistry, University of Bremen, Leobener Strasse, D-28334 Bremen, Germany

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ABSTRACT

Carbocyclic 1,2-diphosphonates (**1a**, **1b**) are prepared by the Diels–Alder reaction of classical donor alka-1,3-dienes (isoprene and 2,3-dimethyl-1,3-butadiene) with tetraethyl acetylene bisphosphonate. Their aromatization by the $KMnO_4$–Al_2O_3 system affords 4-methyl and 4,5-dimethylbenzene-1,2-diphosphonates (**2a**, **2b**), used as precursor for the generation of benzyl-type carbanions (**3a**, **3b**) by lithiation with lithium isopropylamide in THF at −80 °C. The carbanions react with electrophilic reagents (chlorotrimethylsilane, *p*-fluorobenzaldehyde, and ethyl trifluoroacetate) in situ to form corresponding α-substituted monoalkyl- and dialkylbenzenediphosphonates in good yields.

1. Introduction

In recent years the synthesis and properties of various toluenephosphonates substituted in the methyl group attracted increased attention. α-Uraciltoluenephosphonate derivatives were considered as prospective AMPA or Kainate receptor antagonists.[1] Corresponding β-aminocarboxylic derivatives in α-position of toluenephosphonates are interesting building blocks in the construction of biologically active phosphopeptides.[2] Toluenephosphonate α-styryl derivatives were examined as prospective electronic luminescence materials[3] and as ligands for asymmetric catalysis.[4] α-Vinyl[5] and α-*O*,*N*,*P* derivatives were used in the synthesis of polydentate ligands,[6] and α-OAlk derivatives as precursors in the synthesis of Zn or Mg-porphyrins containing phenylphosphonate groups, which are interesting materials possessing dielectric properties for recording and saving information.[7] α-Methylenecyclopropyl toluenephosphonate derivatives due to their ability of stabilization of the radical center by the phosphonate group were used as model compounds for the radical isomerization mechanism study of the methylcyclopropyl ring.[8] Till now, only one example has been published concerning the synthesis of α-functionalized *o*-phenylenebisphosphonate alkyl derivatives,[9] although the presence of the rigidly fixed *o*-phenylenebisphosphonate chelating fragment is considered to be promising in pharmacological aspect.[9] This situation is caused by the fact that synthetic approaches to synthesize α-functionalized toluenephosphonates are rather poor. The main method for the preparation of such compounds is either photocatalyzed,[10] or Ni(II),[11] Cu(II),[12] and Pd(II)[13]-catalyzed insertion of the phosphoryl fragment by halide substitution in *p*- and *o*-halotoluenes followed by α-functionalization of the alkyl group,[14] or metal-catalyzed aromatic halide substitution by the phosphonate group in the α-functionalized *p*-halotoluene.[15] Another approach to this class of compounds is based on electrophilic phosphorylation of toluene followed by functionalization at the aromatic methyl group.[16] However, these methods are not suitable for the introduction of two phosphonate groups into the aromatic ring in *ortho*-position to each other, and thus restrict the application of this synthetic strategy.

An alternative approach, allowing a predetermined synthesis of aromatic *o*-diphosphonates is a Diels–Alder ring formation. In the classical mode 'donor diene–acceptor acetylene', this method has been applied to the reactions of acetylenediphosphonate with some activated cyclic dienes, α-pyrone[17] and its derivatives,[18] or 1,3-cyclohexadiene[19] (with fixed cis-configuration).[20] The reaction is accompanied by thermal elimination of low molecular weight compounds (respectively, CO_2 and C_2H_4) resulting in aromatization

* Corresponding authors. Tel.: +49 421 218 2493; fax: +49 421 218 4267 (G.-V.R.).
E-mail addresses: tverd1975@mail.ru (S.N. Tverdomed), gvr@chemie.uni-bremen.de (G.-V. Röschenthaler).

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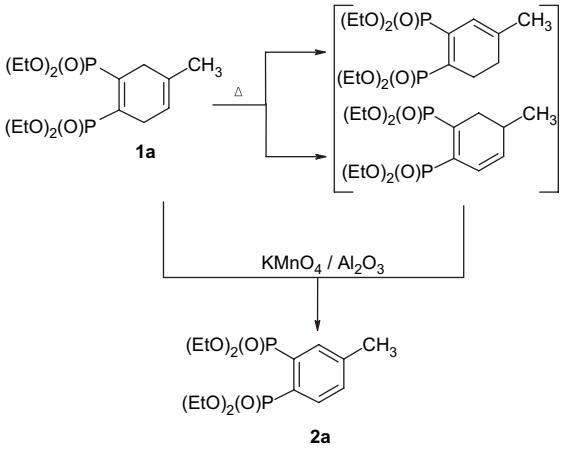
of cyclic 1,2-diphosphonates. In all examples mentioned above, the initial cycloaddition product was not registered, only the aromatic compounds were described. Earlier was reported[21] that tetramethyl acetylenediphosphonate is an active dienophile in Diels–Alder reactions with donor 1,3-alkadienes such as 1,3-butadiene, isoprene, 2,3-dimethyl-1,3-butadiene, and piperylene. In this way, the synthesis of earlier inaccessible tetramethylcyclohexa-1,4-diene-1,2-diphosphonates readily capable to aromatization,[21] was achieved.

Aromatic *o*-diphosphonates containing alkyl substituents in the ring,[22] such as 3-methyl, 4-methyl-, and 4,5-dimethylbenzene-1,2-diphosphonates are a new class of organophosphorus compounds, appropriate for further functionalization. It is known, that the presence of a heteroatom substituent in *ortho*-position of toluene promotes metalation of both the aromatic ring and the alkyl group.[23] Treatment of such benzyl-type organolithium intermediate with an electrophilic reagent in situ leads to formation of polyfunctional α-substituted products.[24] With *meta*- and *para*-isomer the substitution is more complicated and less selective.[25] As far as we know, there are no examples of side-chain metalation of *o*-phenylenebisphosphonate, and only a few and not fully investigated examples are known for toluenephosphonates[26] and phosphates.[27] In this publication we report the successful application of the earlier proposed methodology[22] for the synthesis of *o*-diphosphonates of the toluene and xylene series, which are interesting from the pharmacological point of view,[28] showing the ability of their predetermined functionalization via regioselective metalation at the exocyclic methyl groups leading to various α-alkyl- and α,α-dialkyl-substituted benzene *o*-diphosphonates.

2. Results and discussion

2.1. The Diels–Alder reaction of tetraethyl acetylenediphosphonate with classical donor 1,3-alkadienes

Like tetramethyl acetylenediphosphonate,[22] its tetraethyl analog[29] is an effective dienophile in diene synthesis with such classical 1,3-dienes as isoprene[30] and 2,3-dimethyl-1,3-butadiene.[31] The reaction starts even at room temperature, but the complete conversion of the parent acetylenediphosphonate occurs during heating of the reaction mixture for 5 h at 140–145 °C. The reaction was conducted in a sealed ampoule under dry argon atmosphere with an excess of 1,3-diene as a solvent and catalytic amount of 1,4-hydroquinone as a polymerization inhibitor (Scheme 1). Due to the good solubility of tetraethyl acetylenediphosphonate in excess of the 1,3-diene the reaction mixture is homogenous. This fact and the absence of traces of oxygen resulted in an effective diene synthesis and supression of diene polymerization, thus the yields of carbocyclic diphosphonate ethyl esters **1a**, **1b** are noticeably higher than tetramethyl analogs.[22] Compounds **1a**, **1b** are stable colorless oily liquids. The structures of the synthesized compounds were confirmed by ^{1}H, ^{31}P, ^{13}C NMR spectroscopy, and mass spectrometry. In the ^{1}H NMR spectra typical signals of the methylene ring protons occur at δ 2.8–3.0 and methyl groups at δ≈1.5, for compound **1a** also the signal of the ring olefinic proton is observed at δ 5.2. In the ^{13}C NMR spectra of compounds **1a**, **1b** doublet-doublet signals of the $C_{1,2}$ carbon nuclei in the region of δ 138–139 with spin–spin splitting constants of $^{1}J_{CP}$∼190 Hz and $^{2}J_{CP}$∼3 Hz are typical, as well as dd signals of carbon atoms $C_{4,5}$ and $C_{3,6}$ at δ 110–130 ($^{3}J_{CP}$∼6–7 Hz) and δ 31–35 ($^{2}J_{CP}$∼13–14 Hz). The ^{31}P NMR spectra show signals in the region of δ 17–18. We noted that heating of the carbocyclic diphosphonate **1a** to 230–250 °C leads to the migration of the C_4=C_5 double bond with formation of an isomeric *cyclo*-1,4-, *cyclo*-1,3-, *cyclo*-1,5-dienyldiphosphonates (^{1}H NMR: Me δ 1.53, 1.01, and 1.62; =CH– 5.2, 5.61 and 5.52, 5.34) (Scheme 2).

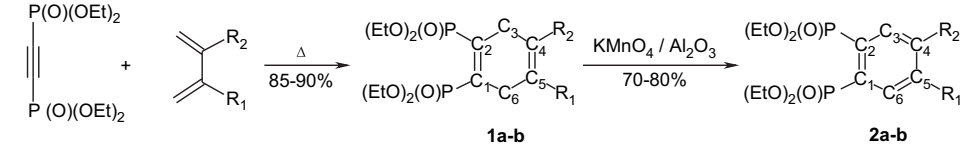


Scheme 2.

We failed to separate the isomers due to their similar boiling points and the sorption characteristics, but further aromatization of the compounds in the mixture afforded one expected *o*-diphosphonate **2a**.

2.2. Synthesis of methyl- and dimethylbenzene-1,2-diphosphonates substituted at alkyl groups

For elaboration of a general procedure for side-chain metalation and functionalization, we have initially investigated tetraethyl 4,5-dimethylbenzene-1,2-diphosphonate **2b**. The benzyl-type carbanion formed upon deprotonation of this compound should be destabilized due to the electron-donor effect of the neighboring methyl group. As for the metalating reagents, we tested *n*-butyllithium (Li^{n}Bu), *tert*-butyllithium (Li^{t}Bu), and lithium diisopropylamide (LDA), which were used in 1 or 2 equiv amounts. For the limitation of a possible nucleophilic attack of these highly basic compounds at the diethylphosphonate groups, the reaction with diphosphonate **2b** was carried out at temperatures below −80 °C in THF for 30 min, then the less reactive electrophile, namely *p*-fluorobenzaldehyde, was added. After acidic hydrolysis, the crude products were studied by ^{31}P and ^{19}F NMR spectroscopy. The results obtained are listed in Table 1, showing the advantage of using LDA instead of other metalating agents. Reduction of the diethylphosphonate groups of compound **2b** observed in the cases of Li^{n}Bu



1a: R_1 = H, R_2 = CH_3 **2a:** R_1 = H, R_2 = CH_3
1b: R_1 = R_2 = CH_3 **2b:** R_1 = R_2 = CH_3

Scheme 1.

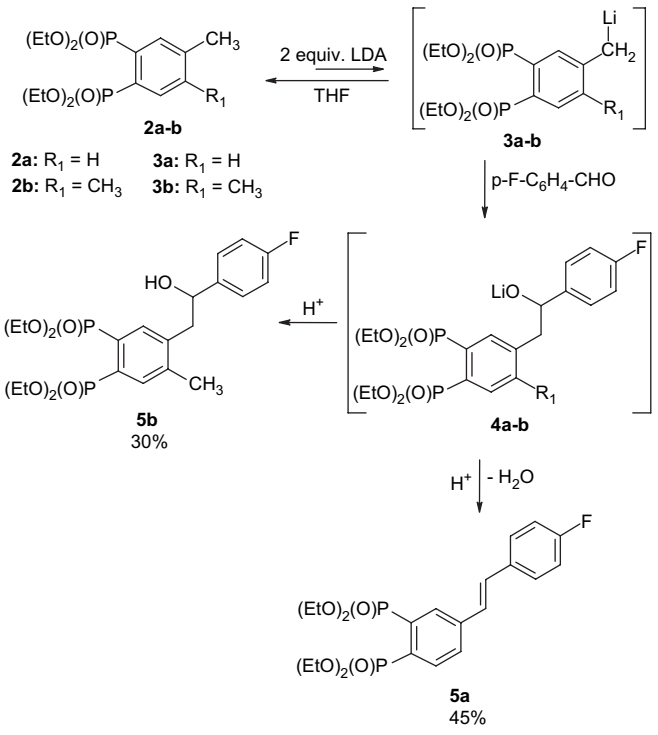
Table 1
Composition of the reaction mixture for metalation of diphosphonate **2b** after treatment with *p*-fluorobenzaldehyde and hydrolysis[a]

Entry	Metalating system	**2b** (%)	**5b** (%)	Others (%)
1	Li^{n}Bu (1 equiv), THF, −90 °C	64	2	34[b]
2	Li^{n}Bu (2 equiv), THF, −90 °C	41	3	56[b]
3	Li^{t}Bu (1 equiv), THF, −100 °C	62	—	28,[c] 10[b]
4	Li^{t}Bu (2 equiv), THF, −100 °C	36	—	52,[c] 12[b]
5	LDA (1 equiv), THF, −80 °C	56	42	2[d]
6	LDA (2 equiv), THF, −80 °C	13	84	3[d]

[a] ^{1}H, ^{31}P, ^{19}F NMR analysis of integral intensity of the corresponding signals.
[b] Not identified mixture of phosphinates and phosphine oxides (^{31}P NMR, $\delta\sim44$–48 and $\delta\sim40$–43).
[c] Diethyl (4-fluorophenyl)(hydroxy)methylphosphonate (^{31}P NMR, δ 22.52 and ^{19}F NMR, δ −115.35).
[d] Phosphonostilbene (^{31}P NMR, δ 22.34 and ^{1}H NMR, δ 6.92).

and Li^{t}Bu is connected with the high nucleophilicity of these reagents,[23] and therefore unlike in the case of toluenephosphonates,[26] they cannot be applied as metalating agents for this class of compounds. Besides, with Li^{t}Bu we observed *ipso*-substitution of one diethylphosphonate group by a ^{t}Bu group with formation of the diethylphosphite anion; the latter reacted with the carbonyl group of *p*-fluorobenzaldehyde affording diethyl (4-fluorphenyl)hydroxymethyl phosphonate as a major product, which was isolated in 30% yield by column chromatography (eluent EtOAc–EtOH 12:1). Its spectral characteristics and constants corresponded completely with the published data.[32] As seen from the data listed in Table 1, the use of 1 equiv of LDA resulted, as seen from ^{13}P and ^{19}F NMR spectra, in the formation of the expected carbinol **5b** in the reaction mixture in 42% yield only, while 56% of the parent compound **2b** was not consumed. This can be explained in a term of deprotonation of compounds **4a**, **4b** by carbanions **3a**, **3b**. Therefore we used 2 equiv of LDA, one for the deprotonation of **2a**, **2b** and the second for deprotonation of the compounds **4a**, **4b** formed (Scheme 3).

The hydrolysis of the carbanion formed and the chromatographic isolation yielded the carbinol **5b** in 30% yield. Under the same reaction conditions carbanion **3a** gave the expected carbinol,



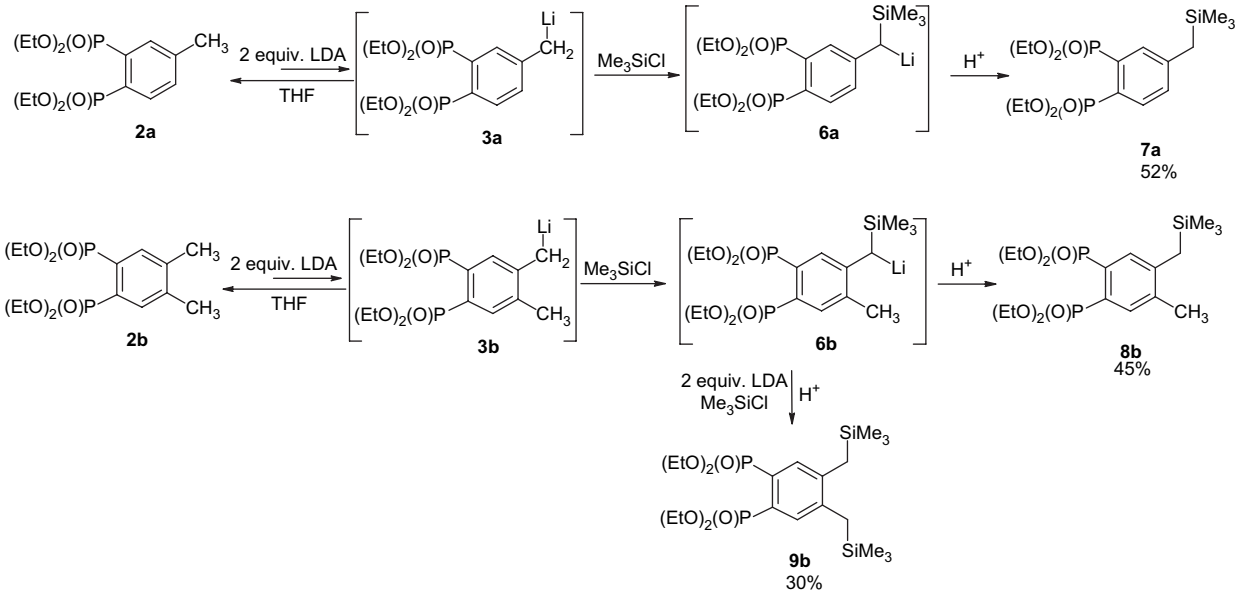
Scheme 3.

which underwent quantitative dehydration leading to the formation of the corresponding stilbene derivative **5a** (Scheme 3). The ^{1}H NMR spectrum of the crude product showed the presence of the carbinol in 7–8% yield only (^{1}H NMR, $\delta\sim3.16$ and 2.82) and the presence of stilbene **5a** in 82–85%, respectively ($\delta\sim7.05$). The residual carbinol was completely dehydrated in the process of the column chromatography. This fact probably explains the low yield of carbinol **5b**. The metalation of benzenediphosphonates **2a**, **2b** in the presence of 2 equiv of LDA proceeds chemoselectively enough. Products of α,α-diaddition for compound **2a** or α,α′-diaddition for compound **2b** at carbonyl group were not observed.

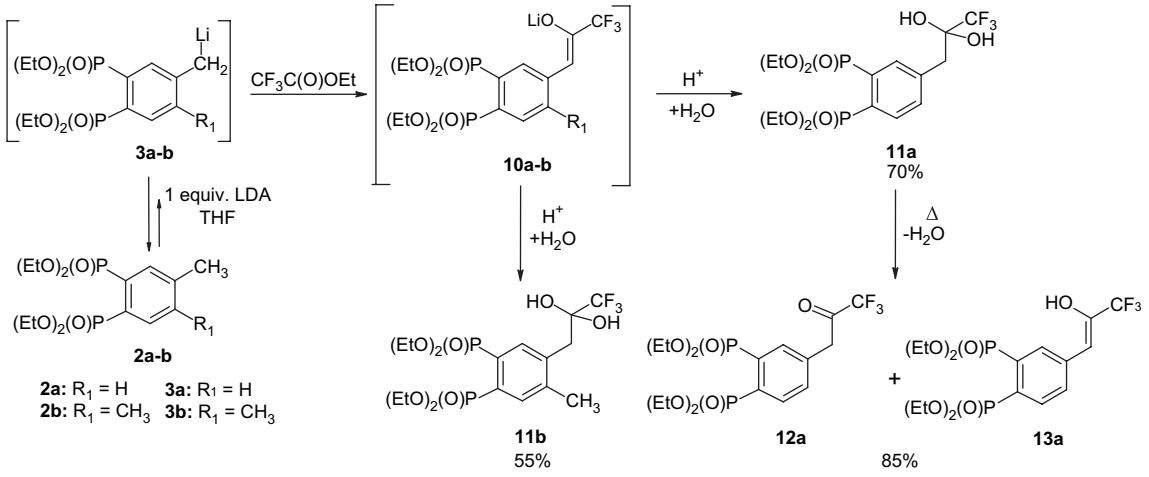
The process of C-metalation is known[33] to obey kinetic control and equilibrium between initial and deprotonated forms of the substrate. The shift of this equilibrium to the desired direction occurs when the generated carbanion reacts with an electrophile and does not react with the parent organometallic compound. It is probable that during the metalation of the diphosphonates **2a**, **2b** this equilibrium is shifted considerably to the parent reagents' side (Scheme 3), as it has been shown by the reaction with bromine as an electrophile, which leads quantitatively to diphosphonates **2a**, **2b** and *N*,*N*-diisopropylhydroxylamine. The attempted reactions of carbanions **3a**, **3b** with weak electrophiles such as benzyl bromide and methyl iodide also failed. Only in the reaction with BzBr, traces (2–3%) of the product of α-substitution (multiplet at δ 2.87) were registered by ^{1}H NMR analysis of the crude product, while the main products were parent diphosphonates **2a**, **2b** with a small content (8–10%) of isomeric benzyl- and methylphosphinates (^{31}P NMR, singlet $\delta\sim45$–48) and phosphine oxides (^{31}P NMR, singlet $\delta\sim39$–42) formed by the permetalation of the corresponding alkyl halides followed by the reduction of diethylphosphonate groups. In a second set of experiments, we studied reactions of lithiated carbanions **3a**, **3b** with chlorotrimethylsilane (Scheme 4). The high reactivity of trimethylsilyl chlorides in reactions with carbanions even at low temperature is well known and is widely used for the characterization of organolithium compounds.[34] Like in the case of the reaction with *p*-fluorobenzaldehyde, this reaction also required for the metalation of diphosphonates (**2a**, **2b**) 2 equiv of LDA per methyl group, when only 1 equiv of LDA was added, the crude product, as follows from ^{31}P NMR analysis, contained a significant fraction of the parent diphosphonates **2a**, **2b**: 48% for **2a** and 63% for **2b**. This probably resulted from the propensity of the α-substituted benzyl carbon to further lithiation on account of the generated carbanion **3a** or **3b**, respectively (Scheme 4). Thus, metalation of diphosphonates **2a**, **2b** using 2 equiv of LDA and the following reactions of the generated carbanions **3a**, **3b** with 1 equiv of Me_3SiCl gave the corresponding mono-α-silylated methyl- and dimethylbenzene-1,2-diphosphonates **7a** and **8b** in tolerable yields (52 and 45%, respectively). The known enhanced activity of chlorotrimethylsilane in reactions with carbanions[34] was confirmed by the reaction of tetraethyl 4,5-dimethylbenzene-1,2-diphosphonate **2b** with 4 equiv of LDA. After the addition of 2 equiv of Me_3SiCl followed by the hydrolysis, the major product was α,α′-disilylated 4,5-dimethylbenzene-1,2-diphosphonate **9b**, which was isolated in 30% yield.

The structure of silylated diphosphonates **7a**, **8b**, **9b** were evidenced by ^{1}H, ^{31}P, ^{13}C NMR spectroscopy, and MS.

In our final experiments, the carbanions **3a**, **3b** generated by using the metalating system based on LDA were tested in the reaction with electrophile such as ethyl trifluoroacetate (Scheme 5). The ^{31}P and ^{19}F NMR analysis of the crude reaction mixtures, showed the presence of parent diphosphonates **2a**, **2b** in 7–10% only, and 90–93% of the desired reaction products. The reaction proceeded with high chemoselectivity affording tetraethyl 4-mono- and 4,5-bis(3,3,3-trifluoro-2,2-dihydroxypropyl)benzene-1,2-diphosphonates **11a**, **11b** formed by the addition of water to the corresponding trifluorobenzoyl derivatives. We found that this



Scheme 4.



Scheme 5.

reaction can be conducted effectively with 1 equiv of LDA per methyl group. With 2 equiv occurred extra tarring of reaction mixture and a decrease in the yield of the target compounds. We explain this fact assuming the initial formation of the benzoyl derivatives in the form of isomeric lithium enolate (Scheme 5) with the α-position not capable to a further metalation. In the process of hydrolysis probably an equilibrium of ketone and enol forms is established whose shift to the ketone is promoted by nucleophilic addition of water at the carbonyl group of the latter, resulting in the formation of the final hydrates **11a**, **11b**, isolated in 70 and 55% yields, respectively. The structures of these compounds were confirmed by X-ray diffraction data (Figs. 1 and 2).[35,36] The principal geometrical parameters of **11a**, **11b** are within the range of standard values.

Compounds **11a**, **11b** were subjected to thermal dehydration in toluene with azeotropic removing of water. With hydrate **11a** this process proceeds smoothly enough, for 15 min at 110 °C. A mixture of ketone **12a** and enol **13a** is formed rather pure (94%, according to ^{31}P, ^{19}F, ^{1}H, ^{13}C NMR, MS-analysis) even without additional purification. As expected, ketone **12a**/enol **13a** ratio depends considerably on the solvent polarity. The ^{19}F, ^{1}H NMR analysis of solutions in DMSO-d_6 and $CDCl_3$ showed a content of the ketone form up to 96 and 85.5%, respectively (^{19}F NMR, δ −79.65, ^{1}H NMR, δ 3.24), while in deuterobenzene the ketoneenol equilibrium falls to ketone/enol ratio 62%:38%. Dehydration of compound **11b** under the same conditions does not lead to the expected products. Even after 2 h in refluxing toluene, using a Dean–Stark trap the reaction mixture contained (^{19}F, ^{1}H NMR) approximately 18% of the parent hydrate **11b**. The products of dehydration under these conditions exerted practically complete thermal destruction, thus analysis by ^{19}F, ^{1}H NMR allowed register of only trace amounts (~5%). In the case of metalation of compound **2b** with 2 or more equiv of LDA and subsequent treatment with 2 equiv of ethyl trifluoroacetate no traces of the product of α,α′-substitution were registered in the crude reaction mixture, thus attesting chemoselectivity of this electrophile.

The comparison of the results of the metalation–electrophilic substitution of diphosphonates **2a**, **2b** under the same general conditions, showed higher reactivity of the diphosphonate **2a**, probably resulting from resonance stabilization of generated benzyl-type carbanion by phosphonate groups in *para*- and *meta*-positions. The lack of destabilization by the methyl group in *ortho*-position, unlike diphosphonate **2b**, leads to the equilibrium shift to

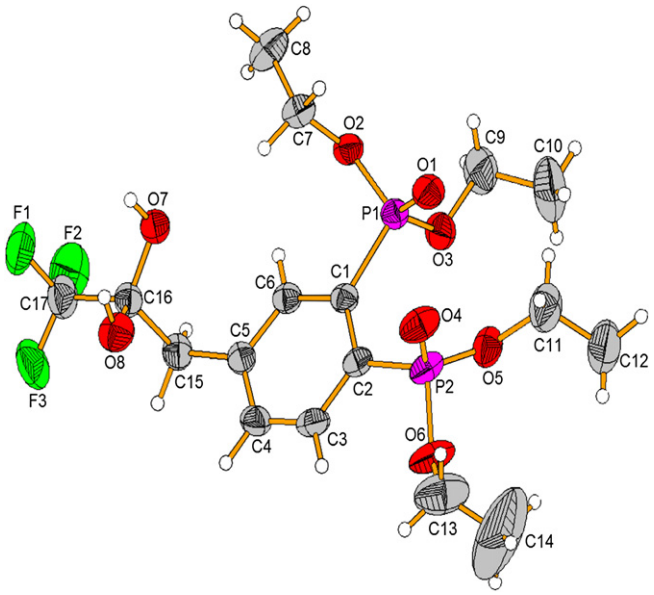


Figure 1. Molecular structure of compound **11a**; bond length in pm, bond angle in ° [C(17)–F(3) 132.3(3), C(17)–C(16) 153.2(3), C(16)–O(7) 138.9(3), C(5)–C(4) 138.0(3), C(1)–P(1) 179.7(2), C(7)–O(2) 146.2(3), C(7)–C(8) 149.1(3), C(13)–C(14) 135.7(6), O(1)–P(1) 147.40(17), O(2)–P(1) 157.8(2); O(7)–C(16)–O(8) 114.8(2), O(8)–C(16)–C(15) 108.1(2), C(4)–C(5)–C(6) 118.1(2), C(4)–C(5)–C(15) 122.0(2), C(6)–C(1)–P(1) 115.6(2), C(2)–C(1)–P(1) 125.4(2), C(3)–C(2)–P(2) 117.6(2), C(4)–C(3)–C(2) 121.8(2), C(7)–O(2)–P(1) 121.7(1), O(1)–P(1)–O(3) 116.13(10), O(1)–P(1)–O(2) 113.81(9), O(3)–P(1)–O(2) 101.6(9)].

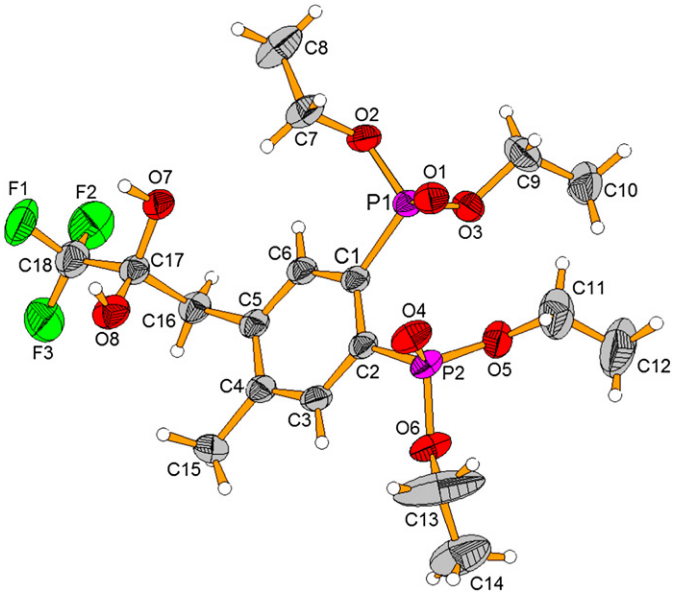


Figure 2. Molecular structure of compound **11b**; bond length in pm, bond angle in ° [C(18)–F(3) 133.4(3), C(4)–C(15) 151.1(3), C(17)–O(8) 139.3(3), C(1)–C(6) 139.9(3), C(1)–P(1) 179.6(2), O(2)–C(7) 145.9(3), C(7)–C(8) 149.2(4), C(2)–C(3) 139.8(3), O(1)–P(1) 146.87(16), P(1)–O(3) 156.3(2); O(8)–C(17)–O(7) 114.4(2), O(2)–C(7)–C(8) 107.6(2), C(6)–C(1)–C(2) 118.5(2), C(6)–C(1)–P(1) 116.5 (2), C(2)–C(1)–P(1) 125.0(2), C(3)–C(2)–P(2) 117.5(2), C(4)–C(3)–C(2) 123.1(2), C(7)–O(2)–P(1) 121.2(2), O(1)–P(1)–O(3) 115.15(9), O(1)–P(1)–O(2) 113.9(9), O(3)–P(1)–O(2) 101.9(9)].

the side of the deprotonated form and higher yield of final reaction products.

3. Summary

In conclusion, we have demonstrated a new methodology for the synthesis of tetraethyl 4-methyl- and 4,5-dimethylbenzene-1,2-diphosphonates functionalized at α-position of alkyl groups based on the following reactions.

(i) Diels–Alder condensation of classical donor 1,3-alkadienes with tetraethyl acetylenediphosphonate; (ii) aromatization of the carbocyclic 1,2-diphosphonates formed; (iii) side-chain metalation of the formed tetraethyl 4-methyl- and 4,5-dimethylbenzene-1,2-diphosphonates; (iv) in situ reaction of the generated benzyl-type carbanions with electrophilic reagents. We improved steps (i) and (ii) as compared with a procedure for the synthesis of related tetramethyl esters earlier proposed by us[22] and prepared a series of earlier unknown carbocyclic and aromatic 1,2-diphosphonates. For steps (iii) and (iv), we revealed experimentally reagents and conditions for effective metalation at methyl groups attached to an aromatic ring and selected appropriate electrophilic reagents for the fixation of the formed carbanions. Using this general strategy we synthesized a series of α-functionalized 4-alkylbenzene-1,2-diphosphonates and α,α′-difunctionalized 4,5-dialkylbenzene-1,2-bisphosphonates, with fluoro- and silicon-containing functional groups, which are prospective as synthones and intermediates for new materials and bioactive compounds.

4. Experimental

4.1. General methods

All reagents were obtained from commercial suppliers and were used without further purification. All solvents used in reactions were freshly distilled from appropriate drying agents before use. THF was distilled from sodium–benzophenone and used immediately. All other reagents were recrystallized or distilled when necessary. Reactions were performed under dry nitrogen atmosphere. Analytical TLC was performed with Merck silica gel 60 F_{254} plates. Visualization was accomplished by UV light or by spraying $Ce(SO_4)_2$ solution in 5% H_2SO_4. Column chromatography was carried out using Merck silica gel 60 (230–400 mesh ASTM). Melting points were determined with an Electrothermal IA9100 Digital Melting Point Apparatus without correction. NMR spectra were obtained on a Bruker DPX-200 spectrometer operating at 200.13 MHz for ^{1}H(TMS), 188.31 MHz for ^{19}F ($CFC1_3$), 80.99 MHz for ^{31}P (H_3PO_4) and 50.32 MHz for ^{13}C (TMS). MS and HRMS spectra were obtained on a Varian MAT CH7A instrument at 70 eV.

4.2. Typical procedure of the diene synthesis

To a 50 ml ampoule preliminary cooled to −30 °C was given 0.1 mol of tetraethyl acetylenediphosphonate, 0.4 mol of substituted 1,3-butadiene, and 3–5 mg of hydroquinone. Then the ampoule was heated at 140–145 °C for 5 h. After cooling, the reaction completion was verified by NMR spectroscopy on the absence of the acetylenediphosphonate precursor. The excess of 1,3-alkadiene was then distilled off at reduced pressure and the residue was distilled in vacuo.

*4.2.1. Tetraethyl 4-methylcyclohexa-1,4-diene-1,2-diphosphonate (**1a**)*

Bp 148–151 °C (0.1 mmHg). Yield 87%. ^{31}P NMR spectrum, δ ($CDCl_3$): 14.55 s. ^{13}C NMR spectrum, δ ($CDCl_3$): 138.96 (dd, C_1, $^1J_{CP}$ 188.70 Hz, $^2J_{CP}$ 2.5 Hz), 138.74 (dd, C_2, $^1J_{CP}$ 188.23 Hz, $^2J_{CP}$ 3.5 Hz), 129.92 (dd, C_5, $^3J_{CP}$ 7.05 Hz, $^4J_{CP}$ 1.00 Hz), 116.93 (dd, C_4, $^3J_{CP}$ 6.5 Hz, $^4J_{CP}$ 1.0 Hz), 62.45 (d, C_i, $^2J_{CP}$ 4.02 Hz), 35.15 (dd, C_6, $^2J_{CP}$ 14.1 Hz, $^3J_{CP}$ 11.5 Hz), 31.84 (dd, C_3, $^2J_{CP}$ 14.1 Hz, $^3J_{CP}$ 13.6 Hz), 22.70 (s, C_7), 16.50 (d, C_j, $^3J_{CP}$ 4.53 Hz). ^{1}H NMR spectrum, δ ($CDCl_3$): 5.21 (m, 1H), 4.01 (m, 8H), 2.88 (m, 2H), 2.82 (m, 2H), 1.51 (s, 3H), 1.19 (t, 6H, $^3J_{HH}$ 7.2 Hz), 1.18 (t, 6H, $^3J_{HH}$ 7.1 Hz). MS (EI) *m*/*e*=365 (M^+, 100%), 337 (18), 319 (10), 309 (12), 281 (6); HRMS *m*/*e* ($[M-H]^+$) calculated for $C_{15}H_{27}O_6P_2$ 365.32725, found 365.32762.

*4.2.2. Tetraethyl 4,5-dimethylcyclohexa-1,4-diene-1,2-diphosphonate (**1b**)*

Bp 165–169 °C (0.1 mmHg). Yield 85%. ^{31}P NMR spectrum, δ ($CDCl_3$): 14.83 s. ^{13}C NMR spectrum, δ ($CDCl_3$): 139.12 (dd, $C_{1,2}$, $^1J_{CP}$ 191.25 Hz, $^2J_{CP}$ 3.52 Hz), 121.92 (d, $C_{4,5}$, $^3J_{CP}$ 4.02 Hz), 62.47 (d, C_i, $^2J_{CP}$ 3.52 Hz), 37.35 (dd, $C_{3,6}$, $^2J_{CP}$ 13.09 Hz, $^3J_{CP}$ 13.09 Hz), 18.13 (s, $C_{7,8}$), 16.66 (d, C_j, $^3J_{CP}$ 3.02 Hz). ^{1}H NMR spectrum, δ ($CDCl_3$): 4.02 (m, 8H), 2.84 (m, 4H), 1.49 (s, 6H), 1.20 (t, 12H, $^3J_{HH}$ 6.0 Hz). MS (EI) *m*/*e*=379 (M^+, 100%), 351 (14), 333 (11), 305 (10), 249 (45); HRMS *m*/*e* ($[M-H]^+$) calculated for $C_{16}H_{29}O_6P_2$ 379.35334, found 379.35373.

4.3. Typical procedure for the aromatization of carbocyclic diphosphonates

To a solution of 0.05 mol of carbocyclic diphosphonate in 300 ml of acetone under vigorous stirring 0.1 mol of $KMnO_4$–Al_2O_3 (1:1) mixture was added in portions, maintaining temperature of reaction mixture at 0–3 °C. Then stirring was continued for 12 h at room temperature. The final suspension was filtered through a 3–5 mm layer of Celite®, the precipitate was washed carefully with acetone and ether, combined filtrate was evaporated at reduced pressure, residue was distilled in vacuo.

*4.3.1. Tetraethyl 4-methyl-1,2-diphosphonate (**2a**)*

Bp 155–157 °C (0.1 mmHg). Yield 73%. ^{31}P NMR spectrum, δ ($CDCl_3$): 17.63 s, 17.56 s. ^{13}C NMR spectrum, δ ($CDCl_3$): 142.38 (d, C_4, $^3J_{CP}$ 10.57 Hz), 136.44 (dd, C_6, $^2J_{CP}$ 13.09 Hz, $^3J_{CP}$ 10.07 Hz), 135.74 (dd, C_3, $^2J_{CP}$ 13.59 Hz, $^3J_{CP}$ 10.05 Hz), 132.31 (d, C_5, $^3J_{CP}$ 11.07 Hz), 131.75 (dd, C_2, $^1J_{CP}$ 188.23 Hz, $^2J_{CP}$ 11.07 Hz), 128.64 (dd, C_1, $^1J_{CP}$ 191.76 Hz, $^2J_{CP}$ 10.07 Hz), 62.64 (d, C_i, $^2J_{CP}$ 5.54 Hz), 62.54 (d, C_i, $^2J_{CP}$ 5.53 Hz), 21.62 (s, C_7), 16.56 (d, C_j, $^3J_{CP}$ 5.03 Hz). ^{1}H NMR spectrum, δ ($CDCl_3$): 7.85 (dd, 1H, $^3J_{HP}$ 19.96 Hz, $^3J_{HH}$ 7.98 Hz), 7.81 (d, 1H, $^3J_{HP}$ 17.98 Hz), 7.23 (d, 1H, $^3J_{HH}$ 8.01 Hz), 3.99 (m, 8H), 2.24 (s, 3H), 1.17 (t, 6H, $^3J_{HH}$ 8.00 Hz), 1.16 (t, 6H, $^3J_{HH}$ 8.00 Hz). MS (EI) *m*/*e*=364 (M^+, 30%), 319 (100), 291 (27), 255 (29), 227 (80); HRMS *m*/*e* ($[M]^+$) calculated for $C_{15}H_{26}O_6P_2$ 364.12047, found 364.12162, *m*/*e* ($[M-H]^+$) calculated for $C_{15}H_{25}O_6P_2$ 363.11264, found 363.11285.

*4.3.2. Tetraethyl 4,5-dimethyl-1,2-diphosphonate (**2b**)*

Bp 174–177 °C (0.1 mmHg). Yield 78%. ^{31}P NMR spectrum, δ ($CDCl_3$): 17.65 s. ^{13}C NMR spectrum, δ ($CDCl_3$): 140.80 (dd, $C_{4,5}$, $^3J_{CP}$ 11.07 Hz, $^4J_{CP}$ 5.54 Hz), 137.03 (dd, $C_{3,6}$, $^2J_{CP}$ 12.08 Hz, $^3J_{CP}$ 12.08 Hz), 128.63 (dd, $C_{1,2}$, $^1J_{CP}$ 190.25 Hz, $^2J_{CP}$ 10.07 Hz), 62.34 (d, C_i, $^2J_{CP}$ 5.54 Hz), 19.76 (s, $C_{7,8}$), 16.44 (d, C_j, $^3J_{CP}$ 3.02 Hz). ^{1}H NMR spectrum, δ ($CDCl_3$): 7.78 (dd, 2H, $^3J_{HP}$ 10.00 Hz, $^4J_{HP}$ 8.00 Hz), 4.01 (m, 8H), 2.17 (s, 6H), 1.19 (t, 12H, $^3J_{HH}$ 6.00 Hz). MS (EI) *m*/*e*=378 (M^+, 7%), 333 (75), 305 (28), 277 (20), 249 (55), 241 (100); HRMS *m*/*e* ($[M]^+$) calculated for $C_{16}H_{28}O_6P_2$ 378.13612, found 378.13717, *m*/*e* ($[M-H]^+$) calculated for $C_{16}H_{27}O_6P_2$ 377.12829, found 377.12778.

4.4. General procedure for the generation of benzyl-type carbanions (3a, 3b) and conducting their reactions with electrophilic reagents

To a stirred solution of diphosphonate **2a** (2 g, 5.5 mmol) or **2b** (2.1 g, 5.5 mmol) in 25 ml of THF at −80 °C was added dropwise 2 M solution of lithium diisopropylamide in hexane–THF (5.8 ml, 11.5 mmol). The reaction mixture temperature was increased to −70 °C and the mixture was stirred for 30 min, therewith it became dark-red in color. Then the mixture was again cooled to −80 °C and corresponding electrophilic reagent was added slowly at vigorous stirring. After 2 h at −70 °C the reaction mixture color changed to orange; the mixture was allowed to reach room temperature and was treated with freshly prepared acetate buffer (60 ml). The emulsion formed was extracted with methylene chloride (3×30 ml), combined organic layer was washed with saturated solution of sodium hydrocarbonate (2×50 ml), and dried over Na_2SO_4. Then solvent was removed at reduced pressure and residual crude product was used for analysis by ^{31}P, ^{19}F, and ^{1}H NMR spectroscopy and further purification by column chromatography.

*4.4.1. (E)-Tetraethyl 4-(4-fluorostyryl)benzene-1,2-diphosphonate (**5a**)*

Prepared according to the general procedure from **2a** (2.0 g, 5.5 mmol), 2 M LDA solution (5.8 ml, 11.5 mmol), and *p*-fluorobenzaldehyde (0.7 g, 5.5 mmol). Crude product was purified by column chromatography (EtOAc/EtOH 12:1 as eluent), white crystals (1.16 g, yield 45%, mp 57 °C). R_f (EtOAc/EtOH 12:1) 0.43. ^{31}P NMR spectrum, δ ($CDCl_3$): 22.53 m, 22.43 m. ^{19}F NMR spectrum, δ ($CDCl_3$): −113.77 m. ^{13}C NMR spectrum, δ: 163.26 (d, C_{12}, $^1J_{CF}$ 249.13 Hz), 140.86 (dd, C_4, $^3J_{CP}$ 11.06 Hz, $^4J_{CP}$ 2.01 Hz), 136.35 (dd, C_3, $^2J_{CP}$ 13.08 Hz, $^3J_{CP}$ 10.54 Hz), 133.97 (dd, C_6, $^2J_{CP}$ 13.09 Hz, $^3J_{CP}$ 11.07 Hz), 133.04 (d, $C_{10,14}$, $^3J_{CF}$ 3.52 Hz), 132.51 (dd, C_1, $^1J_{CP}$ 188.23 Hz, $^2J_{CP}$ 11.07 Hz), 131.56 (s, C_7), 130.16 (dd, C_2, $^1J_{CP}$ 191.76 Hz, $^2J_{CP}$ 10.08 Hz), 129.15 (d, C_9, $^4J_{CF}$ 1.51 Hz), 128.92 (d, C_5, $^3J_{CP}$ 8.05 Hz), 126.63 (s, C_8), 116.25 (d, $C_{11,13}$, $^2J_{CF}$ 22.15 Hz), 62.03 (d, C_i, $^2J_{CP}$ 4.04 Hz), 62.91 (d, C_i, $^2J_{CP}$ 4.02 Hz), 16.79 (d, C_j, $^3J_{CP}$ 2.52 Hz), 16.69 (d, C_j, $^3J_{CP}$ 2.58 Hz). ^{1}H NMR spectrum, δ ($CDCl_3$): 8.30 (dd, 1H, $^3J_{HP}$ 14.01 Hz, $^3J_{HH}$ 8.00 Hz), 8.11 (dd, 1H, $^3J_{HP}$ 14.00 Hz, $^4J_{HP}$ 6.05 Hz), 7.67 (dd, 1H, $^3J_{HH}$ 8.00 Hz, $^4J_{HP}$ 2.08 Hz), 7.49 (dd, 2H, $^3J_{HH}$ 10.00 Hz, $^3J_{HF}$ 6.02 Hz), 7.13 (d, 2H, $^3J_{HH}$ 12.34 Hz), 7.05 (AB-system, 2H, $^3J_{HH}$ 19.68 Hz), 4.18 (m, 8H), 1.36 (t, 6H, $^3J_{HH}$ 8.09 Hz), 1.35 (t, 6H, $^3J_{HH}$ 8.05 Hz). MS (EI) *m*/*e*=470 (M^+, 60%), 425 (15), 361 (95), 333 (100), 305 (40), 259 (5); HRMS *m*/*e* ($[M]^+$) calculated for $C_{22}H_{29}FO_6P_2$ 470.14234, found 470.14252.

*4.4.2. Tetraethyl 4-methyl-5-[2-(4-fluorophenyl)-2-hydroxyethyl]benzene-1,2-diphosphonate (**5b**)*

Prepared according to the general procedure from **2b** (2.1 g, 5.5 mmol), 2 M LDA solution (5.8 ml, 11.5 mmol), and *p*-fluorobenzaldehyde (0.7 g, 5.5 mmol). The crude compound was purified by column chromatography (EtOAc/EtOH 10:1 as eluent), colorless oil (0.84 g, yield 30%). R_f (EtOAc/EtOH 10:1) 0.33. ^{31}P NMR spectrum, δ ($CDCl_3$): 18.06 m, 17.88 m. ^{19}F NMR spectrum, δ ($CDCl_3$): −116.57 m. ^{13}C NMR spectrum, δ: 162.42 (d, C_{13}, $^1J_{CF}$ 245.61 Hz), 141.58 (dd, C_5, $^3J_{CP}$ 10.07 Hz, $^4J_{CP}$ 1.48 Hz), 141.15 (dd, C_4, $^3J_{CP}$ 11.07 Hz, $^4J_{CP}$ 1.51 Hz), 140.53 (d, C_{10}, $^4J_{CF}$ 3.02 Hz), 137.36 (dd, $C_{3,6}$, $^2J_{CP}$ 12.08 Hz, $^3J_{CP}$ 12.08 Hz), 129.18 (dd, C_1, $^1J_{CP}$ 190.25 Hz, $^2J_{CP}$ 10.09 Hz), 128.36 (dd, C_2, $^1J_{CP}$ 191.25 Hz, $^2J_{CP}$ 10.57 Hz), 127.94 (d, $C_{11,15}$, $^3J_{CF}$ 8.05 Hz), 115.32 (d, $C_{12,14}$, $^2J_{CF}$ 21.64 Hz), 73.66 (s, C_9), 62.71 (d, C_i, $^2J_{CP}$ 3.52 Hz), 62.64 (d, C_i, $^2J_{CP}$ 3.39 Hz), 43.34 (s, C_8), 20.03 (s, C_7), 16.69 (d, C_j, $^3J_{CP}$ 2.50 Hz), 16.62 (d, C_j, $^3J_{CP}$ 2.53 Hz). ^{1}H NMR spectrum, δ ($CDCl_3$): 7.86 (dd, 1H, $^3J_{HP}$ 13.21 Hz, $^3J_{HH}$ 9.78 Hz), 7.74 (dd, 1H, $^3J_{HP}$ 14.03 Hz, $^4J_{HP}$ 10.00 Hz), 7.15 (dd, 2H, $^3J_{HH}$ 8.08 Hz, $^4J_{HF}$ 3.08 Hz), 6.85 (dd, 2H, $^3J_{HH}$ 10.00 Hz, $^3J_{HF}$ 10.00 Hz), 4.86 (t, 1H, $^3J_{HH}$ 6.24 Hz), 4.04 (m, 8H), 3.13 (dd, 1H, $^2J_{HH}$ 14.05 Hz, $^3J_{HH}$ 8.00 Hz), 2.90 (dd, 1H, $^2J_{HH}$ 14.67 Hz, $^3J_{HH}$ 7.86 Hz), 2.27(s, 3H), 1.27 (t, 12H, $^3J_{HH}$ 7.79 Hz). MS (EI) *m*/*e*=502 (M^+, 100%), 501 ($[M-H]^+$, 20), 487 (10), 378 (35), 365 (10), 247 (15); HRMS *m*/*e* ($[M]^+$) calculated for $C_{23}H_{33}FO_7P_2$ 502.16856, found 502.16596.

*4.4.3. Tetraethyl 4-(trimethylsilylmethyl)benzene-1,2-diphosphonate (**7a**)*

Prepared in accordance with the general procedure from **2a** (2.0 g, 5.5 mmol), 2 M LDA solution (5.8 ml, 11.5 mmol), and chlorotrimethylsilane (0.6 g, 5.5 mmol). Crude product was purified by column chromatography (EtOAc/EtOH 14:1 as eluent), colorless oil (1.24 g, yield 52%). R_f (EtOAc/EtOH 14:1) 0.26. ^{31}P NMR spectrum, δ ($CDCl_3$): 22.34 m, 22.73 m. ^{13}C NMR spectrum, δ ($CDCl_3$): 145.71 (dd, C_4, $^3J_{CP}$ 13.59 Hz, $^4J_{CP}$ 3.02 Hz), 135.70 (dd, C_6, $^2J_{CP}$ 14.09 Hz, $^3J_{CP}$ 9.56 Hz), 135.21 (dd, C_3, $^2J_{CP}$ 14.09 Hz, $^3J_{CP}$ 9.57 Hz), 130.89 (dd, C_5, $^3J_{CP}$ 13.59 Hz, $^4J_{CP}$ 2.52 Hz), 131.08 (dd, C_2, $^1J_{CP}$ 188.24 Hz, $^2J_{CP}$

10.57 Hz), 127.28 (dd, C_1, $^1J_{CP}$ 194.27 Hz, $^2J_{CP}$ 9.56 Hz), 62.61 (d, C_i, $^2J_{CP}$ 6.04 Hz), 62.55 (d, C_i, $^2J_{CP}$ 5.54 Hz), 27.95 (s, C_7), 16.61 (d, C_j, $^3J_{CP}$ 6.54 Hz), −1.73 (s, C_8). ^{1}H NMR spectrum, δ ($CDCl_3$): 7.82 (dd, 1H, $^3J_{HP}$ 20.02 Hz, $^3J_{HH}$ 8.03 Hz), 7.62 (d, 1H, $^3J_{HP}$ 16.00 Hz), 7.05 (d, 1H, $^3J_{HH}$ 8.02 Hz), 4.03 (m, 8H), 2.02 (s, 2H), 1.19 (t, 12H, $^3J_{HH}$ 6.00 Hz), −0.17 (s, 9H). MS (EI) m/e=436 (M^+, 100%), 408 (82), 380 (20), 352 (10), 319 (25), 290 (43); HRMS m/e ($[M]^+$) calculated for $C_{18}H_{34}O_6P_2Si$ 436.15999, found 436.16127.

4.4.4. Tetraethyl 4-methyl-5-(trimethylsilylmethyl)benzene-1,2-diphosphonate (**8b**)

Prepared according to the general procedure from **2b** (2.1 g, 5.5 mmol), 2 M LDA solution (5.8 ml, 11.5 mmol), and chlorotrimethylsilane (0.6 g, 5.5 mmol). Crude product was purified by column chromatography (EtOAc/EtOH 14:1 as eluent), colorless oil (1.13 g, yield 45%). R_f (EtOAc/EtOH 14:1) 0.35. ^{31}P NMR spectrum, δ ($CDCl_3$): 18.66 m, 18.13 m. ^{13}C NMR spectrum, δ ($CDCl_3$): 144.32 (dd, C_5, $^3J_{CP}$ 13.58 Hz, $^4J_{CP}$ 2.52 Hz), 138.87 (dd, C_4, $^3J_{CP}$ 13.59 Hz, $^4J_{CP}$ 3.02 Hz), 137.96 (dd, C_6, $^2J_{CP}$ 14.59 Hz, $^3J_{CP}$ 10.01 Hz), 136.35 (dd, C_3, $^2J_{CP}$ 14.60 Hz, $^3J_{CP}$ 10.07 Hz), 128.52 (dd, C_2, $^1J_{CP}$ 190.75 Hz, $^2J_{CP}$ 10.08 Hz), 126.53 (dd, C_1, $^1J_{CP}$ 193.27 Hz, $^2J_{CP}$ 10.57 Hz), 62.73 (d, C_i, $^2J_{CP}$ 3.21 Hz), 62.61 (d, C_i, $^2J_{CP}$ 3.18 Hz), 24.92 (s, C_8), 20.61 (s, C_7), 16.82 (s, C_j), 16.69 (s, C_j), −0.96 (s, C_9). ^{1}H NMR spectrum, δ ($CDCl_3$): 7.90 (dd, 1H, $^3J_{HP}$ 14.02 Hz, $^4J_{HP}$ 6.01 Hz), 7.73 (dd, 1H, $^3J_{HP}$ 16.00 Hz, $^4J_{HP}$ 6.00 Hz), 4.17 (m, 8H), 2.29 (s, 3H), 2.19 (s, 2H), 1.36 (t, 6H, $^3J_{HH}$ 6.04 Hz), 1.35 (t, 6H, $^3J_{HH}$ 6.02 Hz), 0.01 (s, 9H). MS (EI) m/e=450 (M^+, 100%), 422 (85), 405 (5), 394 (15), 366 (5), 248 (20), 241 (15); HRMS m/e ($[M]^+$) calculated for $C_{19}H_{36}O_6P_2Si$ 450.17564, found 450.17753.

4.4.5. Tetraethyl 4,5-di(trimethylsilylmethyl)benzene-1,2-diphosphonate (**9b**)

Prepared according to the general procedure from **2b** (2.1 g, 5.5 mmol), 2 M LDA solution (11.6 ml, 23.0 mmol), and chlorotrimethylsilane (1.2 g, 11.0 mmol). The crude compound was purified by column chromatography (EtOAc/EtOH 16:1 as eluent), colorless oil (0.87 g, yield 30%). R_f (EtOAc/EtOH 16:1) 0.25. ^{31}P NMR spectrum, δ ($CDCl_3$): 18.69 m. ^{13}C NMR spectrum, δ ($CDCl_3$): 141.99 (dd, $C_{4,5}$, $^3J_{CP}$ 10.11 Hz, $^4J_{CP}$ 4.32 Hz), 136.63 (dd, $C_{3,6}$, $^2J_{CP}$ 12.08 Hz, $^3J_{CP}$ 12.08 Hz), 126.39 (dd, $C_{1,2}$, $^1J_{CP}$ 191.76 Hz, $^2J_{CP}$ 10.08 Hz), 62.63 (d, C_i, $^2J_{CP}$ 5.01 Hz), 25.29 (s, $C_{7,8}$), 16.76 (d, C_j, $^3J_{CP}$ 3.02 Hz), 0.95 (s, $C_{9,10}$). ^{1}H NMR spectrum, δ ($CDCl_3$): 7.69 (dd, 2H, $^3J_{HP}$ 14.01 Hz, $^4J_{HP}$ 10.00 Hz), 4.18 (m, 8H), 2.13 (s, 4H), 1.36 (t, 12H, $^3J_{HH}$ 6.01 Hz), 0.01 (s, 18H). MS (EI) m/e=522 (M^+, 15%), 479 (10), 450 (100), 422 (75), 394 (18), 333 (70), 241 (95); HRMS m/e ($[M]^+$) calculated for $C_{22}H_{44}O_6P_2Si_2$ 522.21517, found 522.21537.

4.4.6. Tetraethyl 4-(3,3,3-trifluoro-2,2-dihydroxy-propyl)benzene-1,2-diphosphonate (**11a**)

Prepared according to the general procedure from **2a** (2.0 g, 5.5 mmol), 2 M LDA solution (2.9 ml, 5.7 mmol), and ethyl trifluoroacetate (0.8 g, 5.6 mmol). Crude product was recrystallized from benzene, colorless crystals (1.84 g, yield 70%, mp 132 °C). ^{31}P NMR spectrum, δ (DMSO-d_6): 17.08 m, 16.83 m. ^{19}F NMR spectrum, δ (DMSO-d_6): −84.00 s. ^{13}C NMR spectrum, δ (DMSO-d_6): 139.90 (d, C_5, $^3J_{CP}$ 10.57 Hz), 138.07 (dd, C_6, $^2J_{CP}$ 13.09 Hz, $^3J_{CP}$ 10.07 Hz), 135.07 (d, C_4, $^3J_{CP}$ 9.56 Hz), 135.01 (dd, C_3, $^2J_{CP}$ 13.59 Hz, $^3J_{CP}$ 9.56 Hz), 131.49 (dd, C_2, $^1J_{CP}$ 187.23 Hz, $^2J_{CP}$ 11.07 Hz), 130.33 (dd, C_1, $^1J_{CP}$ 189.24 Hz, $^2J_{CP}$ 10.57 Hz), 124.81 (q, C_9, $^1J_{CF}$ 289.90 Hz), 93.56 (q, C8, $^2J_{CF}$ 29.69 Hz), 62.79 (d, C_i, $^2J_{CP}$ 6.03 Hz), 62.72 (d, C_i, $^2J_{CP}$ 6.04 Hz), 41.64 (s, C_7), 16.97 (d, C_j, $^3J_{CP}$ 1.51 Hz), 16.87 (d, C_j, $^3J_{CP}$ 1.50 Hz). ^{1}H NMR spectrum, δ (DMSO-d_6): 7.95 (dd, 1H, $^3J_{HP}$ 22.01 Hz, $^3J_{HH}$ 6.02 Hz), 7.89 (d, 1H, $^3J_{HP}$ 20.06 Hz), 7.62 (d, 1H, $^3J_{HH}$ 8.00 Hz), 7.01 (s, 2H), 4.03 (m, 8H), 3.04 (s, 2H), 1.23 (t, 12H, $^3J_{HH}$ 8.04 Hz). MS (EI) m/e=460 ($[M-H_2O]^+$, 5%), 415 (100), 387 (22), 359 (20), 331 (85), 323 (63), 295 (35).

4.4.7. Tetraethyl 4-methyl-5-(3,3,3-trifluoro-2,2-dihydroxy-propyl)benzene-1,2-diphosphonate (**11b**)

Prepared according to the general procedure from **2b** (2.1 g, 5.5 mmol), 2 M LDA solution (2.9 ml, 5.7 mmol), and ethyl trifluoroacetate (0.80 g, 5.6 mmol). Crude product was purified by recrystallization from 1,4-dioxane–H_2O 2:1, colorless crystals (1.50 g, yield 55%, mp 188 °C). ^{31}P NMR spectrum, δ (DMSO-d_6): 17.34 m, 17.25 m. ^{19}F NMR, δ (DMSO-d_6): −84.70 s. ^{13}C NMR spectrum, δ (DMSO-d_6): 143.17 (d, C_5, $^3J_{CP}$ 9.56 Hz), 139.18 (dd, C_3, $^2J_{CP}$ 12.08 Hz, $^3J_{CP}$ 12.08 Hz), 138.34 (d, C_4, $^3J_{CP}$ 10.07 Hz), 137.12 (dd, C_6, $^2J_{CP}$ 12.58 Hz, $^3J_{CP}$ 12.58 Hz), 130.12 (dd, C_1, $^1J_{CP}$ 188.74 Hz, $^2J_{CP}$ 11.07 Hz), 128.42 (dd, C_2, $^1J_{CP}$ 190.25 Hz, $^2J_{CP}$ 10.67 Hz), 124.93 (q, C_{10}, $^1J_{CF}$ 290.40 Hz), 94.00 (q, C_9, $^2J_{CF}$ 30.70 Hz), 62.65 (d, C_i, $^2J_{CP}$ 4.03 Hz), 38.05 (s, C_8), 20.59 (s, C_7), 16.96 (s, C_j), 16.86 (s, C_j). ^{1}H NMR spectrum, δ (DMSO-d_6): 7.97 (dd, 1H, $^3J_{HP}$ 16.04 Hz, $^4J_{HP}$ 6.01 Hz), 7.77 (dd, 1H, $^3J_{HP}$ 15.21 Hz, $^4J_{HP}$ 5.45 Hz), 6.94 (s, 2H), 4.01 (m, 8H), 3.04 (s, 2H), 2.39 (s, 3H), 1.24 (t, 12H, $^3J_{HH}$ 6.24 Hz). MS (EI) m/e=474 ($[M-H_2O]^+$, 5%), 429 (100), 401 (25), 365 (30), 345 (65), 337 (95), 327 (20), 309 (38), 282 (8).

4.4.8. Tetraethyl 4-(3,3,3-trifluoro-2-oxopropyl)benzene-1,2-diphosphonate (**12a**) and tetraethyl 4-(E,Z)-(3,3,3-trifluoro-2-hydroxyprop-1-enyl)benzene-1,2-diphosphonate (**13a**)

Prepared by dehydration of **11a** (1.3 g) at reflux in anhydrous toluene (20 ml) with a Dean–Stark trap for 15 min. To the cooled solution at room temperature was added 2.0 g of anhydrous silica gel (60 Å) and mixture was stirred at room temperature for 1 h. The suspension was filtered; the filtrate was evaporated at reduced pressure. The residual colorless oil (1.06 g, yield 85%) consisted of practically pure ketone **12a** and enol **13a** mixture in molar ratio 96:4 (DMSO), 85.5:14.5 (chloroform), and 62:38 (benzene).

*4.4.8.1. Compound **12a**.* ^{31}P NMR spectrum, δ (DMSO-d_6): 16.36 m, 16.26 m. ^{19}F NMR spectrum, δ (DMSO-d_6): −79.65 s. ^{13}C NMR spectrum, δ (DMSO-d_6): 187.88 (q, C_8, $^2J_{CF}$ 35.23 Hz), 138.29 (d, C_4, $^3J_{CP}$ 13.08 Hz), 137.03 (dd, C_6, $^2J_{CP}$ 13.09 Hz, $^3J_{CP}$ 11.07 Hz), 135.85 (dd, C_3, $^2J_{CP}$ 13.09 Hz, $^3J_{CP}$ 10.07 Hz), 134.70 (d, C_5, $^3J_{CP}$ 10.29 Hz), 133.71 (dd, C_2, $^1J_{CP}$ 187.73 Hz, $^2J_{CP}$ 10.57 Hz), 132.53 (dd, C_1, $^1J_{CP}$ 190.26 Hz, $^2J_{CP}$ 10.07 Hz), 116.13 (q, C_9, $^1J_{CF}$ 292.92 Hz), 62.69 (d, C_i, $^2J_{CP}$ 7.12 Hz), 62.48 (d, C_i, $^2J_{CP}$ 6.85 Hz), 42.01 (s, C_7), 16.47 (d, C_j, $^3J_{CP}$ 1.01 Hz), 16.37 (d, C_j, $^3J_{CP}$ 1.06 Hz). ^{1}H NMR spectrum, δ (DMSO-d_6): 8.15 (dd, 1H, $^3J_{HP}$ 20.06 Hz, $^3J_{HH}$ 8.02 Hz), 8.08 (dd, 1H, $^3J_{HP}$ 18.54 Hz, $^4J_{HP}$ 2.02 Hz), 6.80 (dd, 1H, $^3J_{HH}$ 8.02 Hz, $^4J_{HP}$ 2.01 Hz), 4.07 (m, 8H), 3.24 (s, 2H), 1.10(t, 6H, $^3J_{HH}$ 7.23 Hz), 1.09 (t, 6H, $^3J_{HH}$ 7.14 Hz). MS (EI) m/e=460 (M^+, 10%), 415 (100), 387 (20), 359 (18), 331 (65), 323 (70), 295 (30); HRMS m/e ($[M]^+$) calculated for $C_{17}H_{25}F_3O_7P_2$ 460.10276, found 460.10067, m/e ($[M-H]^+$) calculated for $C_{17}H_{24}F_3O_7P_2$ 459.09494, found 459.09448.

*4.4.8.2. Compound **13a**.* ^{31}P NMR spectrum, δ (C_6D_6): 16.87 m, 16.70 m. ^{19}F NMR spectrum, δ (C_6D_6): −71.90 s. ^{13}C NMR spectrum, δ (C_6D_6): 144.15 (q, C_8, $^2J_{CF}$ 32.72 Hz), 138.07 (d, C_4, $^3J_{CP}$ 14.11 Hz), 136.53 (d, C_5, $^3J_{CP}$ 9.56 Hz), 135.92 (dd, C_3, $^2J_{CP}$ 14.18 Hz, $^3J_{CP}$ 9.68 Hz), 134.87 (dd, C_6, $^2J_{CP}$ 13.99 Hz, $^3J_{CP}$ 10.01 Hz), 134.16 (dd, C_2, $^1J_{CP}$ 189.74 Hz, $^2J_{CP}$ 10.07 Hz), 132.45 (dd, C_1, $^1J_{CP}$ 188.74 Hz, $^2J_{CP}$ 11.58 Hz), 114.72 (q, C_9, $^1J_{CF}$ 286.88 Hz), 104.58 (m, C_7), 62.78 (d, C_i, $^2J_{CP}$ 6.89 Hz), 62.73 (d, C_i, $^2J_{CP}$ 7.03 Hz), 16.33 (d, C_j, $^3J_{CP}$ 1.12 Hz), 16.30 (d, C_j, $^3J_{CP}$ 1.08 Hz). ^{1}H NMR spectrum, δ (C_6D_6): 11.50 (s, 1H), 9.07 (dd, 1H, $^3J_{HP}$ 14.04 Hz, $^3J_{HH}$ 6.01 Hz), 8.24 (dd, 1H, $^3J_{HP}$ 19.00 Hz, $^4J_{HP}$ 2.02 Hz), 7.59 (dd, 1H, $^3J_{HH}$ 8.00 Hz, $^4J_{HP}$ 2.09 Hz), 5.94(s, 1H), 4.04 (m, 8H), 1.07(t, 12H, $^3J_{HH}$ 7.89 Hz). MS (EI) m/e=460 (M^+, 10%), 415 (100), 387 (20), 359 (18), 331 (65), 323 (70), 295 (30); HRMS m/e ($[M]^+$) calculated for $C_{17}H_{25}F_3O_7P_2$ 460.10276, found 460.10067, m/e ($[M-H]^+$) calculated for $C_{17}H_{24}F_3O_7P_2$ 459.09494, found 459.09448.

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35. CCDC 669742 contains the supplementary crystallographic data of compound **11a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
36. CCDC 669741 contains the supplementary crystallographic data of compound **11b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.