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Catalytic phosphonylation of C = X electrophiles

Presented by Corresponding Member of the NAS of Ukraine O.I. Kolodiazhnyi

A method for the catalytic phosphonylation of C = X electrophiles has been developed. Pyridinium perchlorate is an effective catalyst for the phosphonylation reaction of trialkyl phosphites with various electrophiles C = X (X = O, S, N). The reaction leads to the formation of corresponding α-substituted phosphonates in high yields. The reaction leading to the formation of bisphosphonates represents the highest interest. It was found that the nucleophilic attack of triethyl phosphite on the electron-deficient carbon of the C = X group leads to the formation of betaine, which reacts with pyridinium perchlorate to form alkoxyphosphonium perchlorate and pyridine. Quasiphosphonium salt is unstable and decomposes to form phosphonate, alkene, and perchloric acid, which reacts with pyridine to regenerate pyridinium perchlorate. The intermediate formed from the pyridinium halide decomposes to form alkyl halide. The general strategy of the proposed method for introducing phosphonate groups into a polyprenyl molecule consisted in the sequential treatment of hydroxyl-containing a compound with the Swern reagent with the conversion of the C—OH group into a carbonyl one. Subsequent phosphonylation of the carbonyl-containing intermediate with the reagent $(EtO)_3P/[PyH] + ClO^{4-}$ leads to the formation of hydroxyalkylbisphosphonate. The synthesized prenyl bisphosphonates have a pronounced biological activity. These include, for example, enolpyruvylshikimate-3-phosphate synthase (EPSP), farnesyl protein transferase (FPTase), as well as HIV protease, which are of interest as potential biologically active substances.

Keywords: *phosphonylation, pyridinium perchlorate, bisphosphonates, hydrophosphonates, terpene derivatives.*

Electrophilic reactions are an important type of the conversion of trivalent phosphorus compounds. There are many examples of the catalytic electrophilic activation of organophosphorus compounds that attract the attention of many chemists [1, 2]. Commonly used electrophilic catalysts are Lewis acids, while nucleophilic catalysts are bases. The addition of Lewis acid to a substrate containing a pair of free electrons is accompanied by an increase in the reactivity of the generated complex. Typical examples of the electrophilic asymmetric activation of organophosphorus compounds by chiral Lewis acids are the catalytic phosphonylation of C = X electrophiles (phospha-aldol reaction, phospha-Mannich reaction, and phospha-Michael reaction),

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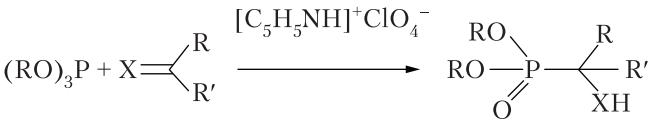


X = O, S, NR

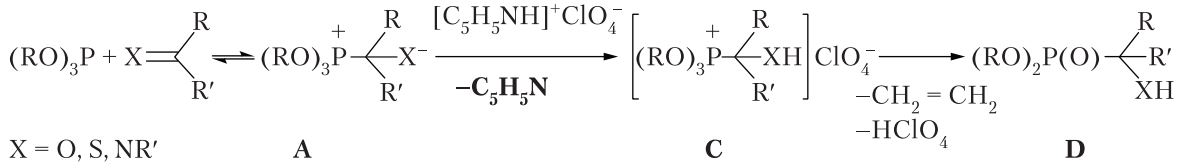
Scheme 1

which proceeds with the formation of functionalized phosphonates such as alpha- and beta-hydroxyphosphonates, aminophosphonates, and hydroxy-bis-phosphonates. The synthesis of functionalized phosphonates has received a lot of attention because of their biological activity [2, 3]. They act as peptide mimics, catalytic antibody haptens, antibiotics and pharmaceuticals, herbicides. and enzyme inhibitors [4].

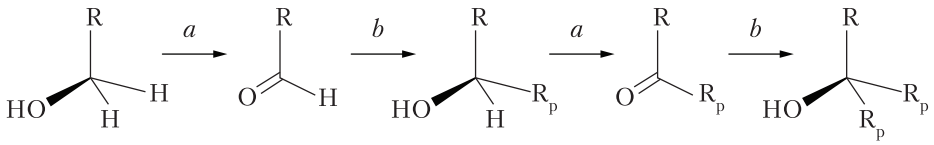
Alpha-hydroxyalkyls (bis-phosphonates), being important pharmaceuticals, are widely used in medical practice and represent a particular interest. Bisphosphonates prevent bone loss and are used to treat osteoporosis and similar diseases. Clinical studies have shown that bisphosphonates reduce the risk of fractures in osteoporosis. The use of bisphosphonates includes the prevention and treatment of osteoporosis, osteitis deformans ("Paget's disease"), bone metastases (with or without hypercalcemia), multiple myeloma, primary hyperparathyroidism, osteogenesis imperfecta, and other diseases that cause bone fragility. The mechanism of action of bisphosphonates is based on their structural analogy with pyrophosphates. The bisphosphonate group mimics the structure of pyrophosphate, thereby inhibiting the activation of enzymes that utilize pyrophosphates. In some cases, the synthesis of bisphosphonates of a certain structure is complex and difficult to overcome. There are two main pathways for the synthesis of α-functionalized phosphonates: the reaction of dialkyl phosphites with unsaturated electrophiles C = X in the presence of Bronsted bases or Lewis acids (the Abramov reaction [5, 6], the Kabachnik–Fields reaction [7, 8] and Pudovik reaction [4, 9]) and the reaction of trialkyl phosphites with aldehydes. However, despite their potential utility, these methods usually suffer from certain disadvantages, such as the low activity of dialkyl phosphites with respect to ketones. The reactions proceed with the formation of various impurities formed under the action of alkaline catalysts (phosphonate-phosphate rearrangement [10, 11], etc.). In addition, Lewis acids used as catalysts are sensitive to moisture and require a special handling and tedious processing.

Therefore, we have developed a convenient method for the synthesis of bisphosphonates, based on the use of pyridinium perchlorate as a new, effective catalyst for the phosphonylation of C = X electrophiles by trialkyl phosphites (Scheme 1).

Scheme 2 explains the catalytic action of pyridinium perchlorate. The nucleophilic attack of triethyl phosphite on the electron-deficient carbon of the C = X group leads to the formation of betaine A, which reacts with pyridinium perchlorate to form alkoxyphosphonium perchlorate C and pyridine. Salt C is unstable and decomposes to form phosphonate D, alkene, and perchloric acid, which reacts with pyridine to regenerate pyridinium perchlorate. Quasiphosphonium intermediate B, formed from pyridinium halides, decomposes to form EtHlg. Pyridinium perchlorate initiates the reaction of trialkyl phosphites with C = X electrophiles more actively than pyridinium halides. The use of pyridinium perchlorate instead of pyridinium halides significantly increases the reaction rate and increases the yields.



Scheme 2. Possible mechanism of catalysis by pyridinium perchlorate



R = polyprenyl; R_p = $(EtO)_2P(O)$; *a* = $Me_2SO/(COCl)_2/Et_3N$; *b* = $(EtO)_3P/[PyH]^+ClO_4^-$

Scheme 3

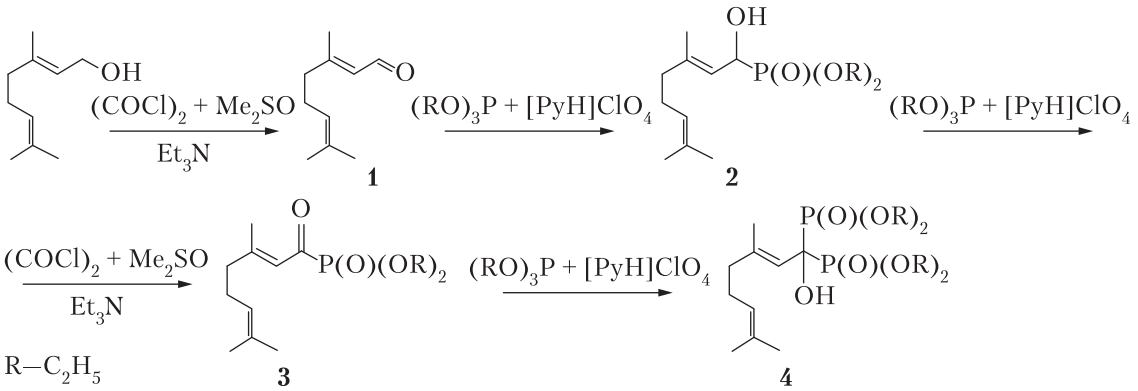
Pyridinium perchlorate can easily be prepared by reacting pyridine with perchloric acid in aqueous solution. It is poorly soluble in water and is easily filtered off as a crystalline substance. After the drying in vacuum desiccator, pyridinium perchlorate is ready to be used.

In all cases, the reactions proceed smoothly in the absence of a solvent or in methylene chloride at room temperature to obtain α-substituted phosphonates without unwanted by-products. Pyridinium perchlorate increases the reaction rate, but is not consumed by the reaction itself. It can be isolated from the reaction mixture and reused; no significant decrease in its activity was observed.

In this regard, in the search for new phosphorus pharmaceuticals, we synthesized bisphosphonate derivatives of terpenes. In accordance with the method previously described by us [2] and based on available natural polyprenols, we oxidized them to the corresponding aldehydes, which were then successively subjected to the phosphonylation by the reaction with dialkyl phosphites and converted to the target hydroxybisphosphonates through the stage of formation of α-ketophosphonates.

The general strategy of our proposed method for introducing phosphonate groups into a polyprenol molecule consists in the sequential treatment of the hydroxyl-containing compound with Swern's reagent (reagent *a*) with the transformation of the C–OH group into a carbonyl one; subsequent phosphonylation of the carbonyl-containing intermediate with $(EtO)_3P/[PyH] + ClO_4^-$, leading to the formation of hydroxyalkylbisphosphonate (Scheme 3).

Oxidation of unsaturated polyprenols, as well as hydroxyprenylphosphonates, with Swern's reagent [3, 4], in this case turned out to be very convenient, since it proceeded regioselectively only at the hydroxyl group, without affecting the C = C bond, as it happens when using other oxidants. As a result, α-ketophosphonates were obtained in high yields, which were converted into α-hydroxyisoprenylbisphosphonates in the next step. Reagent *b* reacts with carbonyl compounds to form hydroxyphosphonates in high yields. The reaction of tertiary phosphites with aldehydes is easily carried out in methylene chloride or without solvent when cooled below 0 °C and leads to the corresponding hydroxyphosphonates in the almost quantitative yield. The reaction of this mixture with α-ketophosphonates proceeds just as easily. So, starting from

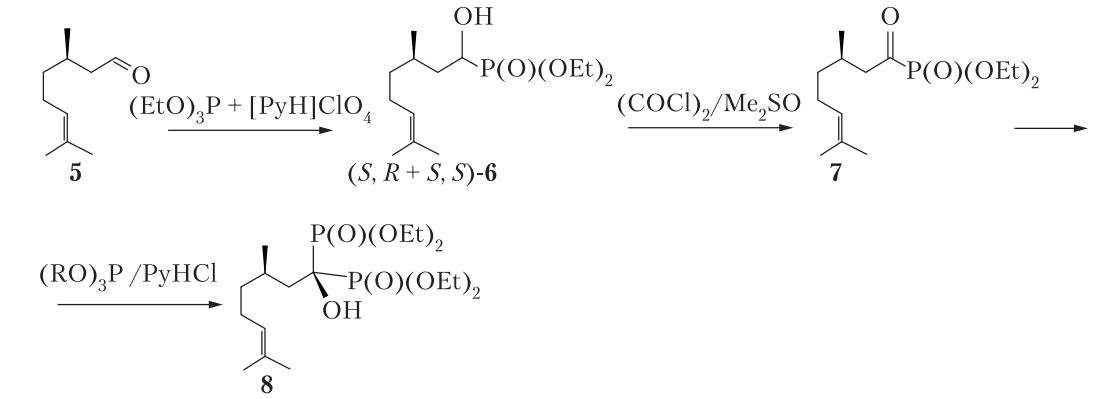


Scheme 4

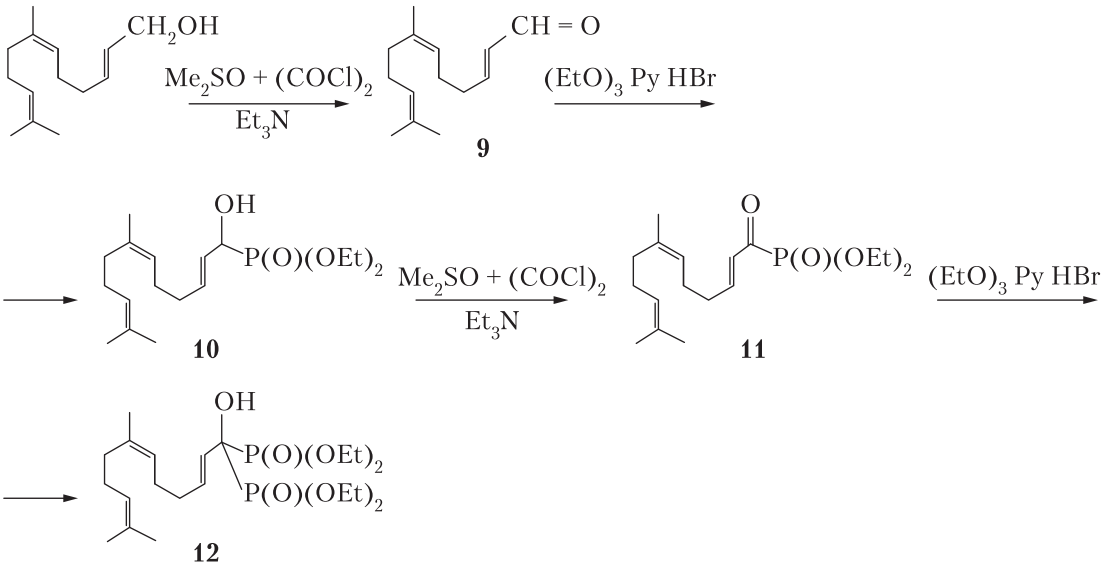
natural geraniol, by oxidation according to Swern in a high yield, geranial **1** was obtained, which by reaction with reactant *b* was converted in the 80 % yield into hydroxyphosphonate **2**. The latter was purified by distillation under vacuo and obtained as a colorless oil with a pleasant floral odor and stable during a storage. Hydroxyphosphonate **2** was converted into α-ketophosphonate **3** by oxidation according to Swern (Scheme 4).

Isoprenyl ketophosphonate **3** was also purified by distillation in vacuo and isolated as a colorless liquid, stable at a storage. However, upon contact with air moisture, the compound **3** slowly hydrolyzes with the formation of diethyl phosphite, geranial, and other products of unknown structure, as was found by ^{1}H and ^{31}P NMR analysis, At the final stage of the synthesis, α-ketophosphonate was subjected to the phosphonylation with the same reagent *b* to form hydroxybisphosphonate 4, which was purified by chromatography on a silica gel column. The structure of products **3** and **4** was established from the data of the NMR spectra of the purified samples. Thus, the ^{31}P chemical shift of ketophosphonate is at –2 ppm, which is typical of α-ketophosphonates of the corresponding structure, and the ^{13}C NMR spectrum shows a doublet of the carbon atom of the α-keto group at 200 ppm, $^{1}J_{CP}$ 150 Hz. In turn, in the ^{13}C NMR spectrum of bisphosphonate **4**, a triplet of the carbon atom bonded to two phosphorus atoms is detected at 60 ppm, $^{1}J_{CP}$ 130 Hz. In a similar manner, starting from (+)-(*R*)-citronenal, chiral bisphosphonate **8** was obtained. Citronellal was reacted with reagent *b* to obtain hydroxyphosphonate **6** in a very high yield. The product was isolated pure by vacuum distillation and oxidized by treatment with Swern's reagent to a chiral ketophosphonate **7** in the 70 % yield. The signal in the ^{31}P NMR spectrum of this compound at –1.96 ppm responds to the structure of α-ketophosphonates. At the last stage of the synthesis, ketophosphonate 7 by the reaction with triethyl phosphite in the presence of pyridinium perchlorate in methylene chloride for 24 h at room temperature was converted in a high yield into bisphosphonate **8**, which was purified by chromatography on a silica gel column. The ^{1}H NMR spectrum of this compound contains the signals belonging to the ethoxy groups at 1.59 and 1.66 ppm, as well as the triplet of the proton C = CH group of the dimethyl-2,6-octene fragment at 5.1 ppm, $^{3}J_{HN}$ 7 Hz (Scheme 5).

Hydroxyphosphonate **6** bearing two asymmetric centers on the α- and γ-carbon atoms shows signals at 26.50 and 26.54 ppm (1 : 1) corresponding to the presence of the (*S,R*)- and (*S,S*)-diastereomers. Two phosphono groups in bisphosphonate **8** containing a chiral center on the γ-carbon atom have different magnetic environments and, therefore, are diasterotopic. They are represen-

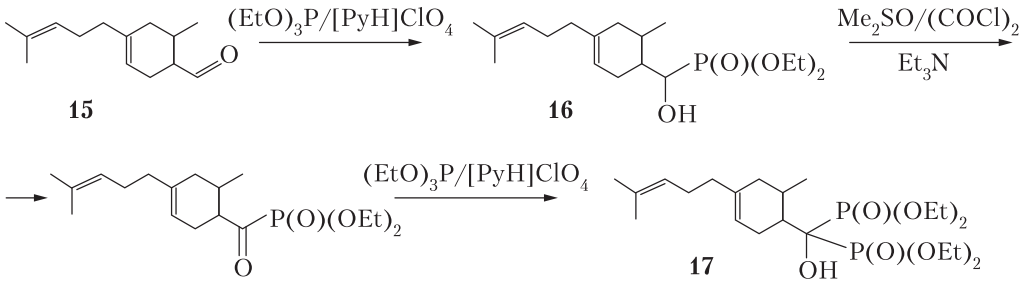


Scheme 5



Scheme 6

ted in the ^{31}P NMR spectrum by two signals at 20.55 and 20.65 ppm. The synthesis strategy described here was also used in the phosphonylation of the natural farnesol. In this case, at first, by Swern's procedure, farnesal **9** was obtained and then converted by the reaction with reagent *b* into the corresponding hydroxyphosphonate **10** purified by the vacuum distillation. Since the original farnesol isolated from natural sources was a mixture of *cis*- and *trans*- isomers, hydroxyphosphonate **10** also consisted of a mixture of *cis*- and *trans*-isomers. Ketophosphonates 11 are analogs of prenyl pyrophosphates, which are of great biological importance [5-7]. The prenyl bisphosphonates synthesized by us (3, 6, and 13) have not been previously described, although some phosphoric terpene derivatives that differ in structure and methods of preparation from the prenyl phosphonates and bisphosphonates discussed here have been synthesized and described, some of which have pronounced biological activity. Some of such compounds have been found to exhibit a strongly pronounced biological activity, among them enolpyruvylshikimate-3-phosphate synthase(EPSP), farnesyl protein transferase (FPTase) ([8, 9], and HIV protease [10] (Scheme 6).



Scheme 7

We used the proposed procedure as the basis for the preparation of hydroxyphosphonates **14** and **16**, which are also derivatives of natural terpenes. Hydroxyphosphonate **14** was successfully distilled under high vacuum and then isolated as a crystalline substance; its monocyclic analog **16** was also purified by the vacuum distillation. By Swern's treatment, hydroxyphosphonate **14** was converted into ketophosphonate, the formation of which was recorded using the ^{31}P NMR spectrum (δ_P –2 ppm), and then, without special purification, the latter was reacted with triethyl phosphite in the presence of pyridine. Bisphosphonate 17 was isolated and purified by column chromatography on silica gel in a low yield (about 25 %) (Scheme 7).

Thus, we have developed a relatively simple method for the synthesis of α-hydroxy-bisphosphonates, derivatives of terpenes, which are of interest as potential biologically active substances [11, 12]. We will carry out research in this direction in the future.

Experimental Part. The NMR spectra were registered on a Varian VXR-300 spectrometer at 300 (^{1}H), 60 (^{13}C), and 126.16 (^{31}P) MHz relative to Me4Si (^{1}H, ^{13}C) or 85 % H_3PO_4 (^{31}P). Solvents were preliminarily distilled in an inert atmosphere: diethyl ether, hexane heptane, benzene, and carbon tetrachloride over phosphorus pentoxide, methanol and triethylamine over sodium, and ethyl acetate over calcium chloride. Reagents, silica gel and TLC plates (Poligram SIL G/UV 254) were purchased from Fluka and Acros. Geraniol, farnesol, and (+)-(R)-citronellal were purchased from Merck.

***Diethyl[(2E)-1-hydroxy-3,7-dimethylocta-2,6-dienyl]phosphonate* (2).** Pyridinium perchlorate (1 g, mol) was added to a cold (0 °C) solution of geranial (0.3 g, 0.02 mol) and triethyl phosphite (3.1 g, mol), and the reaction mixture was stirred for 2 h at room temperature, after which it was filtered, diluted with diethyl ether, and filtered again to remove pyridinium perchlorate (~0.009 mol). The solvent was removed by the evaporation, and the residue was distilled in vacuum. Yield 80 %, bp 135 °C (0.08 mmHg).

^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.28 t (3H, CH_3, J_{HH} 7), 1.29 t (3H, CH_3, J_{HH} 7), 1.61 s (3H, CH_3), 1.69 s (3H, CH_3), 2.1 br.s (4H, CH_2), 4.12 m (4H, OCH_2) 4.52 d.d (1H, PCH, J_{HH} 9, J_{HP} 9), 5.12 br.s (1H, CH=C), 5.36 br.s (1H, CH=C).

^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 16.4, 17.0, 17.6, 25.60, 26.7, 37.90, 37.9, 61.7, 61.8, 65.1, 66.1, 119.1, 124.0, 131.7, 138.8.

^{31}P NMR spectrum ($CDCl_3$): 24.19 ppm.

***Diethyl[(2E)-3,7-dimethyl-1-oxoocta-2,6-dienyl)-phosphonate* (3).** A solution of 2 ml of DMSO in 4 ml of methylene chloride and a solution of 2.8 g of hydroxyphosphonate **2** in 8 ml of methylene chloride were added in succession to a solution of 1 ml of oxalyl chloride in 20 ml

of dry methylene chloride at –60 °C. After 15 min, 7 ml of triethylamine was added at –50 °C. The reaction mixture was stirred for 5 min, heated to room temperature, and diluted with 50 ml of ice water. The aqueous layer was separated and extracted with methylene chloride (2 × 20 ml). The combined organic layers were dried over $MgSO_4$, the solvent was evaporated, and the residue was distilled in vacuum. Yield 70 %, bp 115 °C (0.08 mmHg).

^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.87 m (3H, CH_3), 1.24 s (3H, CH_3C=), 1.29 s (3H, CH_3C=), 1.31 t (6H, CH_3CH_2O, J_{HH} 7), 1.6 m (2H, CH_2), 2.0 m (2H, CH_2), 2.29 m (2H, CH_2), 4.1 m (4H, CH_2O), 5.33 m (=CH–C=O).

^{31}P NMR spectrum ($CDCl_3$): δ_P 1.2 ppm.

Found P, %: 10.76. $C_{14}H_{25}O_4P$. Calculated P, %: 10.74.

***Tetraethyl[(2E)-1-hydroxy-3,7-dimethylocta-2,6-dienylidene]bisphosphonate* (4)**. Pyridinium perchlorate (0.3 g, 3 mmol) was added to a cold (0 °C) solution of 0.5 g (3 mmol) of triethyl phosphite and 0.7 g (2.5 mmol) of ketophosphonate **3** in 3 ml of methylene chloride, and the mixture was left to stand for 24 h at room temperature. The precipitate that formed was filtered off, the solvent was evaporated, and the residue was chromatographed on a column of silica gel, eluent ethyl acetate–hexane, 1 : 1. Yield 65 %, oil.

^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.27 t (6H, *J* 7), 1.28 t (6H, *J* 7), 1.6 s 1.63 s (3H), 1.8 m (3H), 2.0 m (4H, CH_2), 4.21 m (8H, OCH_2), 4.8 m (1H, CH=), 5.1 t (1H, CH=, J_{HH} 7).

^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (*J*, Hz): 16.21, 16.41, 17.59, 17.81, 25.61, 26.87, 36.9, 60.93, 64.53, 67.83, 71.13, 115.5, 124.03, 131.67, 139.77.

^{31}P NMR spectrum ($CDCl_3$): δ_P 23.3 ppm.

Found, %: C 50.45; H 8.41; P 14.50. $C_{18}H_{36}O_7P_2$. Calculated, %: C 50.70; H 8.51; P 14.53

***Diethyl[(S_P/R,R/R_P)-(6E)-1-hydroxy-3,7-di-methylocta-2,6-dienyl]phosphonate* (6)**. Pyridinium perchlorate (~0.75 g, 0.005 mol) was added to a cold (0 °C) solution of citronellal (1.5 g, 0.01 mol) and triethyl phosphite (1.6 g, 0.01 mol). The reaction mixture was stirred for 2 h at room temperature, filtered, diluted with diethyl ether, filtered to remove pyridinium perchlorate, the solvent was evaporated, and the residue was distilled in vacuum. Yield 80 %, bp 145–150 °C (0.08 mmHg).

Mixture of the (S_P/*R*,R_P/*R*) diastereomers. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.96 d (3H, CH_3, *J* 7), 1.29 t (3H, CH_3, *J* 7), 1.30 t (3H, CH_3, *J* 7), 1.58 s (3H, CH_3), 1.65 s (3H, CH_3), 1.83 m (2H, CH_2), 1.96 m (2H, CH_2), 3.82 m (1H, CH), 4.09 m (4H, OCH_2), 5.07 t (1H, CH=C, *J* 7), 5.7 br.s (1H, OH).

^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (*J*, Hz): (S_P,*R*) 16.45, 16.49, 17.6, 20.25, 25.19, 25.52, 25.65, 28.30 d (*J* 12), 35.75, 38.11, 62.51 d (*J* 7.5), 62.64 d (*J* 6), 65.59 d (*J* 158), 124.70, 131.09; (R_P, *R*) 16.45, 16.49, 18.35, 20.25, 25.19, 25.52, 25.65, 29.0 d (*J* 12), 37.80, 38.56, 62.51 d (*J* 7.5), 62.64 d (*J* 6), 66.06 d (*J* 157), 124.72, 131.13.

^{31}P NMR spectrum ($CDCl_3$): δ_P, ppm: 26.50, 26.54.

Found P, %: 10.69. $C_{14}H_{29}O_4P$. Calculated P, %: 10.59.

***Diethyl[(6E)-3,7-dimethyl-1-oxooct-6-enyl]phosphonate* (7).** A solution of 0.9 ml of DMSO in 2 ml of methylene chloride and a solution of 1.4 g of hydroxyphosphonate **6** in 4 ml of methylene stirred and a solution of 0.5 ml of oxalyl chloride in 10 ml of dry methylene chloride were added in succession to a solution of 0.5 ml of oxalyl chloride in 10 ml of dry methylene chloride at –60 °C. After 15 min, 3.5 ml of triethylamine was added at –50 °C. The mixture was

stirred for 5 min, heated to room temperature, and diluted with 35 ml of ice water. The aqueous layer was separated and extracted with methylene chloride (2 × 10 ml). The combined organic layers were dried over $MgSO_4$, the solvent was evaporated, and the residue was distilled in vacuum. Yield 70 %, mp 115 °C (0.08 mmHg).

^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.87 m (3H, CH_3), 0.91 d (CH_3CH, *J* 7), 1.37 t (CH_3CH_2, *J* 7), 1.58 s (3H, CH_3C=), 1.66 s (3H, CH_3C=), 1.97 m (2H, CH_2), 2.14 m (2H, CH_2), 2.6–2.8 m (2H, CH_2C=O), 4.21 m (4H, OCH_2), 6.06 t (2H, CH=C, *J* 6.5).

^{31}P NMR spectrum ($CDCl_3$): δ_P 1.96 ppm.

Found P, %: 10.76. $C_{14}H_{27}O_4P$. Calculated P, %: 10.67.

***Tetraethyl[(6E)-1-hydroxy-3,7-dimethylocta-6-enylidene]bisphosphonate* (8).** Pyridinium perchlorate (0.3 g, 3 mmol) was added to a cold (0 °C) solution of 0.5 g (3 mmol) of triethyl phosphite and 0.7 g (2.5 mmol) of ketophosphonate **7** in 3 ml of methylene chloride, and the mixture was left to stand overnight at room temperature. The precipitate was filtered off, the solvent was evaporated, and the residue was chromatographed on a column of silica gel. Yield 65 %, oil.

^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.02 d (3H, *J* 4), 1.34 t (12H, CH_3CH_2, *J* 7), 1.59 s (3H, CH_3C=), 1.66 s (3H, CH_3C=), 2.0 m (4H, CH_2), 4.23 m (8H, OCH_2), 5.1 t (CHC=, *J* 7).

^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 20.55, 20.65.

Found, %: C 50.45; H 8.41; P 14.50. $C_{18}H_{38}O_7P_2$. Calculated, %: C 50.46; H 8.94; P 14.46.

***Dimethyl[(2E,6E)-1-hydroxy-3,7,11-trimethyl-dodeca-2,6,10-trienyl]phosphonate* (10).** Pyridinium perchlorate (0.5 g, ~0.005 mol) was added to a cold (0 °C) solution of farnesal (2.2 g, 0.01 mol) and trimethyl phosphite (1.3 g, 0.01 mol). The reaction mixture was stirred for 2 h at room temperature and then filtered, diluted with diethyl ether, and filtered again to separate ~0.0049 mol of pyridinium per- chlorate. The solvent was evaporated, and the residue was distilled in vacuum. Yield 90 %, oil.

^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.59 s (3H, CH_3C=), 1.66 s (3H, CH_3C=), 1.69 d (3H, CH_3CH, J_{HH} 1.5), 1.71 (3H, CH_3CH, J_{HH} 1.5), 2.09 m (6H, CH_2), 2.25 m (2H, CH_2), 3.78 d (3H, CH_3O, J_{HP} 10), 3.8 d (3H, CH_3O, J_{HP} 10), 4.5 br.s (1H, OH), 4.7 t (1H, PCH, J_{HP} 10), 5.09 br.s (1H, CH=C), 5.35 br.s (2H, CH=C).

^{31}P NMR spectrum ($CDCl_3$): δ_P 26.05 ppm.

Found P, % 9.39. $C_{17}H_31O_4P$. Calculated P, %: 9.37.

***Dimethyl[(2E,6E)-3,7,11-trimethyl-1-oxododeca-2,6,10-trienyl]phosphonate* (11).** A solution of 0.9 ml of DMSO in 2 ml of methylene chloride and a solution of 1.4 g of hydroxyphosphonate **10** in 4 ml of methylene chloride were added in succession to a solution of 0.5 ml of oxalyl chloride in 10 ml of dry methylene chloride at –60 °C. After 15 min, 3.5 ml of triethylamine was added –50 °C. The reaction mixture was stirred for 5 min, heated to room temperature, and diluted with 35 ml of ice water. The aqueous layer was separated and extracted with methylene chloride (2 × 10 ml). The combined organic solutions were dried over $MgSO_4$, the solvent was evaporated, and the residue was distilled in vacuum. Yield 60 %, bp 145 °C (0.1 mmHg).

^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.6 s (3H, CH_3C=), 1.66 s (3H, CH_3C=), 1.69 d (3H, CH_3C=, *J* 1.5), 1.71 (3H, CH_3C=, *J* 1.5), 2.1 m (6H, CH_2), 2.25 m (2H, CH_2), 3.75 d (3H, CH_3O, J_{HP} 10), 3.8 d (3H, CH_3O, J_{HP} 10), 5.1 br.s (1H, CH=C), 5.5 br.s (2H, CH=C).

^{31}P NMR spectrum ($CDCl_3$): δ_P 0.98 ppm.

Found, %: C 62.38; H 8.89; P 9.45. $C_{17}H_{29}O_4P$. Calculated, %: C 62.18; H 8.90; P 9.43.

Tetramethyl[(2E,6E)-1-hydroxy-3,7,11-trimethyldodeca-2,6,10-trienylidene]bisphosphonate (12). Pyridinium perchlorate (3 mmol) was added to a cold (0 °C) solution of 3 mmol of trimethyl phosphite and 2.5 mmol of ketophosphonate **11** in 3 ml of methylene chloride, and the mixture was left to stand for 24 h at room temperature. The precipitate that formed was filtered off, the solvent was evaporated, and the residue was chromatographed on a column with silica gel (eluent hexane–ethyl acetate, 3 : 1). Yield 65 %, oil.

^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.6 s (3H, CH_3), 1.69 s (3H, CH_3), 1.8 d.d (3H, J_{HP} 8, J_{HH} 7), 2.0 m (4H, CH_2), 3,75 d (3H, CH_3O, J_{HP} 10), 3.8 d (3H, CH_3O, J_{HP} 10), 4.8 m (2H, CH=), 5.1 m.

Found P, %: 14.60. $C_{18}H_{34}O_7P_2$. Calculated P, %: 14.60.

***Diethyl[(hydroxy)(3,8,8-trimethyl-1,2,3,4,5,6,7,8-octahydronaphtalen-2-yl)methyl]phosphonate* (14)** was prepared similarly to compound **11**. Yield 80 %, bp 190 °C (0.1 mmHg), mp 107–110 °C (hexane).

^{1}H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 0.957 d (3H, CH_3C, *J* 6), 0.975 s (6H, CH_3), 1.34 t (6H, CH_3CH_2O, *J* 7), 1.43 m (2H, CH_2), 1.6 m (4H, CH_2), 1.8 m (2H, CH_2), 1.9 m (1H, CH), 2.0 m (1H, CH), 2.19 m (2H, CH_2), 2.91 m (1H, OH), 4.2 m (5H, CH_2O + PCH).

^{31}P NMR spectrum ($CDCl_3$): δ_P 24.0 ppm.

***Diethyl[(hydroxy)[6-methyl-4-(4-methylpent-3-enyl)cyclohex-3-en-1-yl]]methylphosphonate* (16).** Pyridinium perchlorate (0.5 g, 0.005 mol) was added to a cold (0 °C) solution of aldehyde **15** (0.01 mol) and triethyl phosphite (1.6 g, 0.01 mol) in 5 ml of methylene chloride. The reaction mixture was stirred for a few hours (under TLC control) and then filtered, diluted with diethyl ether, and filtered again to separate ~0.0049 mol of pyridinium perchlorate. The solvent was evaporated, and the residue was purified first by the vacuum distillation and then by column chromatography on silica gel (eluent ethyl acetate-hexane, 1 : 3). Yield 80 %. Colorless oil, bp 180 °C (0.08 mmHg).

^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.99 d (3H, CH_3, *J* 6), 1.33 t (6H, CH_3CH_2, *J* 7), 1.6 s (3H, CH_3), 1.87 s (3H, CH_3), 1.91–2.22 m (10H, CH_2 + CH), 3.51 br.s (OH), 4.17 m (5H, OCH_2 + PCH, *J* 7, *J* 8), 6.28 s (1H, CH=C), 5.32 m (2H, CH=C).

^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (*J*, Hz): 8.87, 16.28, 17.3, 25.4, 25.78, 27.01, 27.08, 29.96, 32.15, 33.69 d (*J* 150), 42.8, 61.81 d (*J* 6), 120.6, 123.9, 130.8, 135.59.

^{31}P NMR spectrum ($CDCl_3$): δ 26.6 ppm.

Found, %: C 62.68; H 9.65; P 8.88. $C_{18}H_{33}O_4P$. Calculated, %: C 62.77; H 9.66; P 8.99.

***Tetraethyl[(hydroxy)[6-methyl-4-(4-methyl-pent-3-enyl)cyclohex-3-en-1-yl]methylene]bisphosphonate* (17)** was prepared similarly to compound **12**. Yield 25 %, oil, purified by column chromatography.

^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.15 d (3H, CH_3, *J* 6), 1.3 t (3H, CH_3, *J* 7), 1.32 t (3H, CH_3, *J* 7),1.6 m (6H, CH_3), 2.0–2.5 m (6H, CH_2), 4.4 m (4H, OCH_2), 5.2 m (1H, CH=), 5.4 m (1H, CH=).

^{31}P NMR spectrum ($CDCl_3$): δ_P 23.0 ppm.

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КАТАЛІТИЧНЕ ФОСФОНІЛЮВАННЯ C=X ЕЛЕКТРОФІЛІВ

Розроблено метод каталітичного фосфонілювання електрофілів C = X. Реакція призводить до утворення відповідних α-заміщених фосфонатів з високими виходами. Особливий інтерес становить реакція з утворенням бісфосфонатів. Встановлено, що нуклеофільна атака триетилфосфіту на електронодефіцитний вуглець групи C = X спричиняє утворення бетаїну, який реагує з перхлоратом піридинію з утворенням перхлорату алкоксифосфонію і піридину. Квазіфосфонієва сіль нестабільна і розкладається з утворенням фосфонату, алкену і хлорної кислоти, яка реагує з піридином, регенеруючи перхлорат піридинію. Інтермедіат, що утворюється з галогеніду піридинію, розкладається з утворенням галоїдного алкілу. Загальна стратегія пропонованого методу введення фосфонатних груп у молекулу поліпренолів полягала в послідовній обробці гідроксилвмісної сполуки реагентом Шверна з перетворенням C–OH групи в карбонільну; подальше фосфонілювання карбонілвмісного интермедіату реагентом $(EtO)_3P/[PyH]^+ClO_4^-$ призводить до утворення гідроксибісфосфонату. Синтезовані бісфосфонати мають виражену біологічну активність. До них, наприклад, належать синтаза енолпірувілшикімат-3-фосфату (EPSP), фарнезол-протеїнтрансфераза (FPTase), а також ВІД-протеаза. Таким чином, нами розроблений порівняно простий метод синтезу α-гідроксибісфосфонатів — похідних терпенів, які становлять інтерес як потенційні біологічно активні речовини.

Ключові слова: *фосфонілювання, перхлорат піридинію, бісфосфонати, гідроксифосфонати, похідні терпену.*