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Synthesis of α-Hydroxy(polyprenyl) Bisphosphonates

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Abstract—Bisphosphonates derived from natural terpenes were synthesized by phosphonylation of corresponding aldehydes. The general strategy of introduction of the phosphonate groups into the polyprenol molecule involves successive treatment of a hydroxyl compound by Swern reagent to oxidize the C–OH group into C=O and a $(EtO)_3P/[PyH]^+ClO_4^-$ mixture to phosphylate the resulting carbonyl compound.

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

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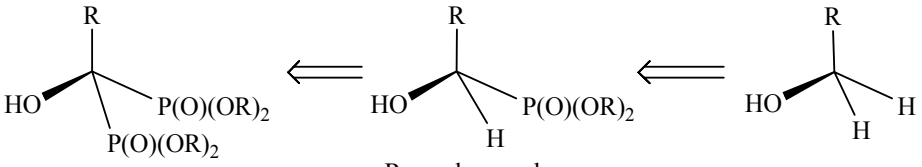
Certain lipophilic phosphorus-containing compounds are used polyfunctional liquid extractants and membrane carriers for rare and trace metals, as well as mineral, amino, and hydroxycarboxylic acids. It was found that the extractants having additional coordination centers, specifically, amino, hydroxy, carboxy, or other functional groups, exhibit enhanced extractive power and selectivity [1]. Aimed at developing new potential membrane and liquid extractants for substrates of various nature, we synthesized bisphosphonate derivatives of terpenes. According to our previously described procedure [2], we took natural polyprenols, and oxidized them to aldehydes, and the latter were first phosphonylated by treatment with diethyl phosphite and then converted into the target hydroxybisphosphonates via α-ketophosphonates (Scheme 1).

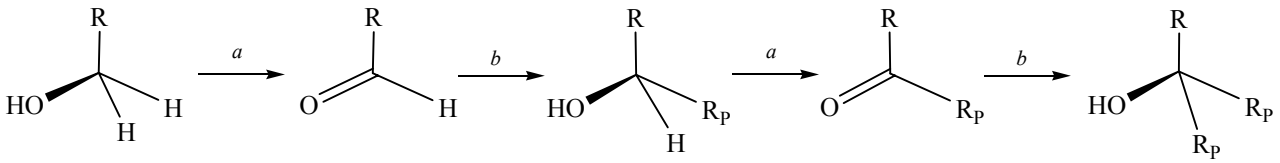
The general strategy of the proposed strategy of introduction of phosphonate groups into the polyprenol molecule involved treatment of a hydroxyl compound by Swern reagent to oxidize the C–OH group into C=O. The carbonyl-containing intermediate was further treated with $(EtO)_3P/[PyH]^+ClO_4^-$ to form hydroxybisphosphonate (Scheme 2).

Scheme 1.



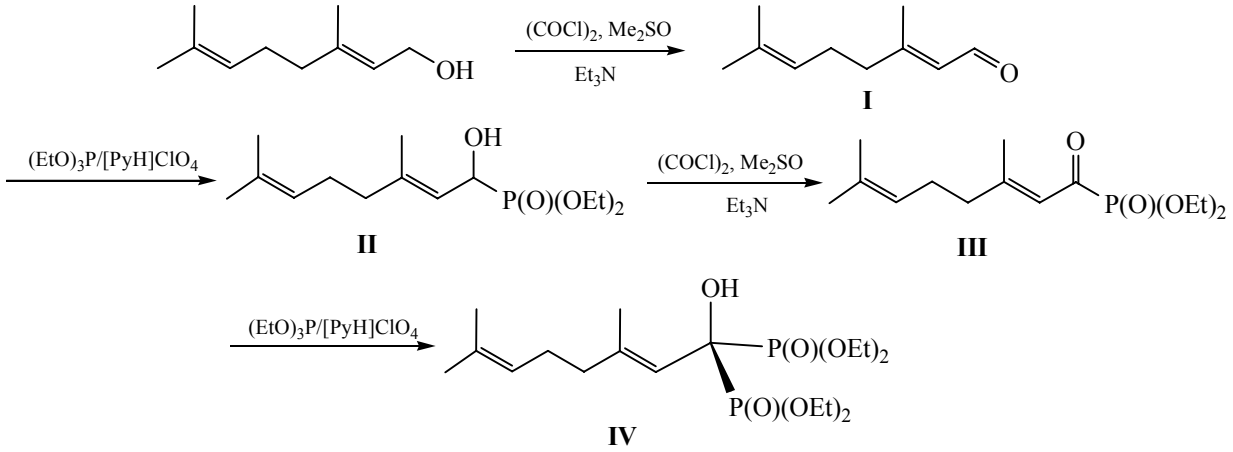
R = polyprenyl.

Scheme 2.



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

Scheme 3.



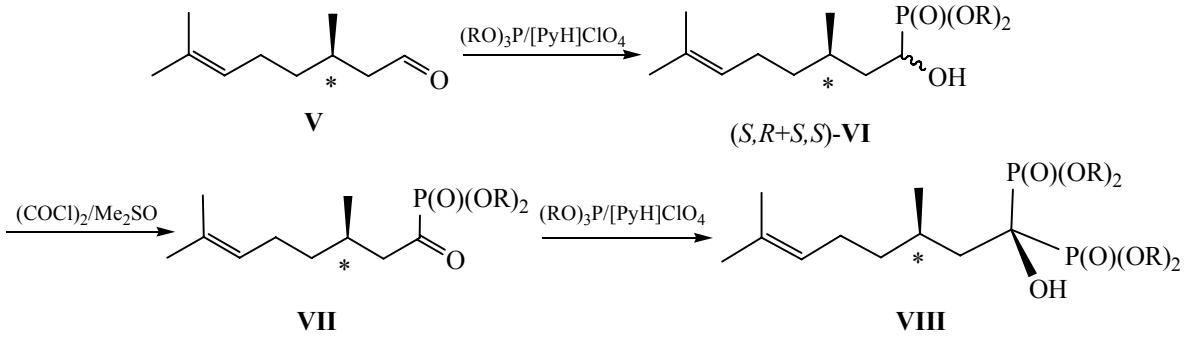
The oxidation of unsaturated popyprenols and also (hydroxyprenyl)phosphonates with Swern reagent [3, 4] proved to be quite a suitable approach in our case, because the reaction proceeded exclusively by the hydroxy group not involving the C=C bond, which was the case with other oxidants. As a result, we could obtain high yield of α-ketophosphonates which were converted into (α-hydroxyisoprenyl)bisphosphonates at the next stage. Reagent *b* reacts with carbonyl compounds to form hydroxyphosphonates in high yields. This reaction with aldehydes readily occurs in methylene chloride or without solvents at temperatures below 0°C and gives rise to corresponding hydroxyphosphonates in nearly quantitative yields. This reagent also readily reacts with α-ketophosphonates. Thus natural geraniol was oxidized Swern oxidation to obtain high yield of geranial (**I**) which was treated with reagent *b* to form hydroxyphosphonate **II** in 80% yield. Vacuum distillation gave compound **II** as a stable colorless oil with a pleasant flower odor. By Swern oxidation the product was converted into α-ketophosphonate **III** (Scheme 3).

Compound **III** was purified by vacuum distillation and isolated as a colorless liquid stable on storage; however, on contact with atmospheric air it immediately hydrolyzed to form, according to ^{1}H and ^{31}P NMR spectra, diethyl phosphite, geranial, and unknown products. At the final stage, α-ketophosphonate was phosphonylated by the same reagent *b* to obtain hydroxybisphosphonate **IV** which was purified by column chromatography on silica gel. The structure of products **III** and **IV** was established by NMR spectroscopy. Thus the δ_P of compound **III** is –2 ppm, which is characteristic of α-ketophosphonates of the similar structure, and the ^{13}C NMR spectrum shows a doublet at 200 ppm ($^{1}J_{CP}$ 150 Hz) from the carbon atom of the α-keto group. The ^{13}C NMR spectrum of bisphosphonate **IV** contains a triplet at 60 ppm ($^{1}J_{CP}$ 130 Hz) from the carbon atom linked to two phosphorus atoms.

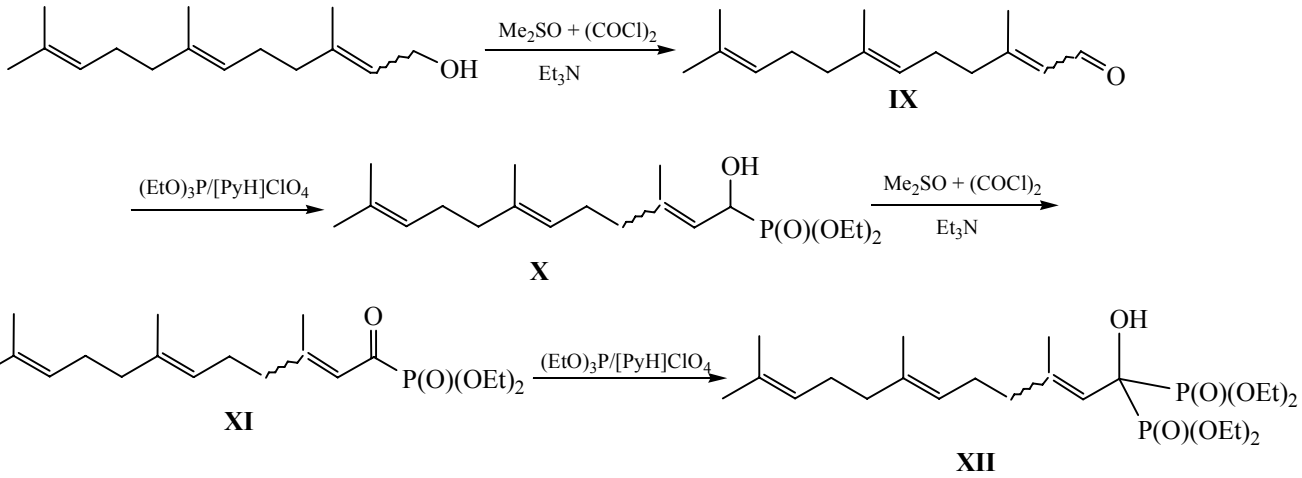
In a similar way, starting with (+)-(*R*)-cintronellal we obtained a chiral bisphosphonate **VIII**. Citronellal was reacted with reagent *b* to obtain hydroxyphosphonate **VI** in quantitative yield. The product was isolated pure by vacuum distillation and oxidized by treatment with Swern reagent to a chiral ketophosphonate **VII** in 70% yield. The signal at –1.96 ppm in the ^{31}P NMR spectrum of compound **VII** is characteristic of α-ketophosphonates. At the final stage, ketophosphonate **VII** was treated with triethyl phosphite in the presence of pyridinium perchlorate in methylene chloride for 24 h at room temperature to obtain a bisphosphonate **VIII** in high yield. The product was purified by column chromatography on silica gel. The ^{1}H NMR spectrum of this compound contains proton signals of ethoxy methyl groups at 1.59 and 1.66 ppm, as well as a triplet at 5.1 ppm ($^{3}J_{HH}$ 7 Hz) from the of the C=CH proton of the 3,7-dimethyloct-6-ene fragment (Scheme 4).

The ^{31}P NMR spectrum of hydroxyphosphonate **VI**, which contains two chiral centers on the α- and γ-carbon atoms shows signals at 26.50 and 26.54 ppm (1 : 1) corresponding to the (*S,R*)- and (*S,S*)-diastereomers of this compound. The two phosphono groups in bisphosphonate **VIII** containing a chiral center on the γ-carbon atom have different magnetic environments, and, therefore, are diasterotopic, and they are represented in the ^{31}P NMR spectrum by two signals at 20.55 and 20.65 ppm.

Scheme 4.



Scheme 5.

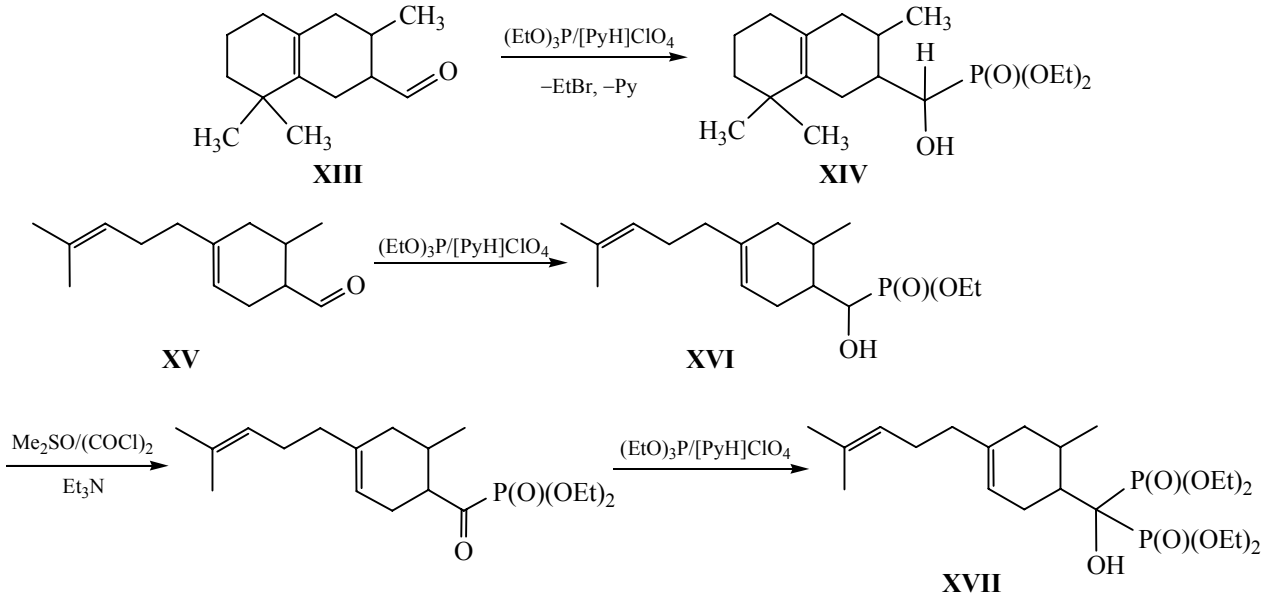


The synthetic strategy described here was also used to phosphonylate the natural sesquiterpene farnesol. The latter was subjected to Swern oxidation to obtain farnesal **IX**. By treatment with reagent *b* the latter aldehyde was converted into hydroxyphosphonate **X** which was purified by vacuum distillation. In view of the fact that the starting farnesol was isolated from natural sources as a mixture of the *cis* and *trans* isomers, hydroxyphosphonate **X**, too, was a mixture of the *cis* and *trans* isomers. Ketophosphonate **XI** is an analog of prenylpyrophosphates which are biologically important compounds [5–7]. Prenylbisphosphonates **III**, **VI**, and **XII** were synthesized for the first time, but some phosphorus-containing terpene derivatives differing in structure from prenylphosphonates and bisphosphonates described in the present work have been previously synthesized and studied. Some of such compounds have been found to exhibit a strongly pronounced biological activity, among them enolpyruvylshikimate-3-phosphate (EPSP) synthase, farnesyl protein transferase (FPT) [7–10], as well as HIV protease [11] (Scheme 5).

The proposed procedure was also used to prepare hydroxyphosphonates **XIV** and **XVI**, which, too, are derivatives of natural terpenes. Hydroxyphosphonate **XIV** could be distilled in high vacuum and then isolated as crystals; its monocyclic analog **XVI** was also purified by vacuum distillation. By Swern oxidation compound **XVI** was converted into a ketophosphonate whose formation was detected by ^{31}P NMR spectroscopy (δ_P –2 ppm). Without special purification, this phosphonate was reacted with triethyl phosphite in the presence of pyridine to obtain bisphosphonate **XVII** isolated in low yield (~25%) by column chromatography on silica gel (Scheme 6).

Thus, we have developed a fairly simple method of synthesis of α-hydroxybisphosphonates derived from terpenes, which present interest as potential biologically active compounds, as well as liquid and

Scheme 6.



membrane extractants for substrates of natural and synthetic origin. Research in this field will be described in subsequent publications.

EXPERIMENTAL

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 Me_4Si (^{1}H, ^{13}C) or 85%-ной H_3PO_4 (^{31}P). Solvents were preliminarily distilled in ab 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, Acros, and Sinbias (Donetsk, Ukraine). Geraniol (**I**), farnesol (**IX**), and (+)-(*R*)-citronellal (**V**) were purchased from Merck.

Diethyl [(2*E*)-1-hydroxy-3,7-dimethylocta-2,6-dienyl]phosphonate (II). Pyridinium perchlorate (1 g, 0.01 mol) was added to a cold (0°C) solution of geranial (0.3 g, 0.02 mol) and triethyl phosphite (3.1 g, 0.02 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 evaporation, abd the residue was distilled in a 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 [15].

Diethyl [(2*E*)-3,7-dimethyl-1-oxoocta-2,6-dienyl)-phosphonate (III). A solution of 2 mL of DMSO in 4 mL of methylene chloride and a solution of 2.8 g of hydroxyphosphonate **IIa** 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 −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 a 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 [(2*E*)-1-hydroxy-3,7-dimethylocta-2,6-dienylidene]bisphosphonate (IV). 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 **III** 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)-(6*E*)-1-hydroxy-3,7-dimethylocta-2,6-dienyl]phosphonate (VI). 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 a 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): (*Sp*,*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; (*Rp*,*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 [(6*E*)-3,7-dimethyl-1-oxooct-6-enyl]phosphonate (VII). A solution of 0.9 mL of DMSO in 2 mL of methylene chloride and a solution of 1.4 g of hydroxyphosphonate **VI** 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 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 a 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 [(6*E*)-1-hydroxy-3,7-dimethylocta-6-enylidene]bisphosphonate (VIII). 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 **VII** 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, $C\underline{H}_3CH_2$, *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 [(2*E*,6*E*)-1-hydroxy-3,7,11-trimethyldodeca-2,6,10-trienyl]phosphonate (X). 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 perchlorate. The solvent was evaporated, and the residue was distilled in a 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. $C_{17}H_{31}O_4P$. Calculated P, %: 9.37.

Dimethyl [(2*E*,6*E*)-3,7,11-trimethyl-1-oxododeca-2,6,10-trienyl]phosphonate (XI). A solution of

0.9 mL of DMSO in 2 mL of methylene chloride and a solution of 1.4 g of hydroxyphosphonate **X** 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 extracter 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 a 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 [(2*E*,6*E*)-1-hydroxy-3,7,11-trimethyldodeca-2,6,10-trienylidene]bisphosphonate (XII). Pyridinium perchlorate (3 mmol) was added to a cold (0°C) solution of 3 mmol of trimethyl phosphite and 2.5 mmol of ketophosphonate **XI** 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 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 (1H, CH=). NMR spectrum ^{31}P ($CDCl_3$), δ_P 23 ppm. 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 (XIV) was prepared similarly to compound **XI**. 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 (XVI). Pyridinium perchlorate (0.5 g, 0.005 mol) was added to a cold (0°C) solution of aldehyde **XV** (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 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-methylpent-3-enyl)cyclohex-3-en-1-yl]methylene]bisphosphonate (XVII) was prepared similarly to compound **XII**. 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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