Heteroatom Chemistry
Volume 24, Number 1, 2013

The Kabachnik–Fields and Pudovik Reactions on the Basis of *E,Z*-Citral and Its Imines and (*R,S*)-Citronellal

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Received 25 July 2012; revised 12 October 2012

ABSTRACT: *The Kabachnik–Fields reaction of* E,Z*-citral with diethyl phosphite in the presence of isobutylamine has been found to form α-aminophosphonates. The Pudovik reactions of diethyl phosphite with prenyl imines prepared on the basis of* E,Z*-citral with isobutylamine also allowed us to obtain the same α-aminophosphonates. We have managed to synthesize α-aminophosphonates by the reaction of* O,O*-dialkyl trimethylsilyl phosphites with prenyl imines in the presence of water or diethylamine. α-Aminophosphonates were also synthesized by the reaction of diethyl phosphite with (*R,S*)-citronellal in the presence of alkylamines. α-Aminophosphonates obtained showed bacteriostatic activity against* Staphylococcus aureus *and* Bacillus cereus. © 2012 Wiley Periodicals, Inc. Heteroatom Chem 24:36–42, 2013; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21060

INTRODUCTION

The chemistry of native isoprenoids has intensively been developed in numerous research centers [1–3]. The isoprenoids are of interest from the point of fundamental organic chemistry to develop problems such as chemical behavior, tautomerism, stereochemistry, skeleton structure transformations, and asymmetric synthesis. The importance of these compounds is also related to their practical uses. Owing to the large-scale industrial production of isoprenoids, their importance as an initial material in organic synthesis and the general use of their derivatives in medicine, cosmetics, and perfumery, there exists continuous interest in this field of chemistry of natural compounds. The native isoprenoids and their phosphorylated derivatives such as geranyl pyrophosphate, geranylgeranic acid amides, and methyl ether of farnesylacetic acid have been reported to possess metabolic regulation activity such as antiulcering, gastritis- and wound-healing, lowering blood pressure, antithrombic, and antiplatelet aggregation activities [1, 4, 5]. Phosphorylated isoprenoid derivatives are expected to be a prospective class of nontoxic bioregulators for creating of new drugs [6–11].

The reactions of cyclic isoprenoids with dialkylphosphites, tetraphosphorus decasulfide, and *O,O*-dialkyl dithiophosphoric acids were previously studied [12–16]. Quaternary ammonium polyprenyl phosphates were obtained by the reaction of polyprenols with phosphorus pentoxide in the presence of triethylamine [17]. Over the past few years, we have been involved in developing new synthetic

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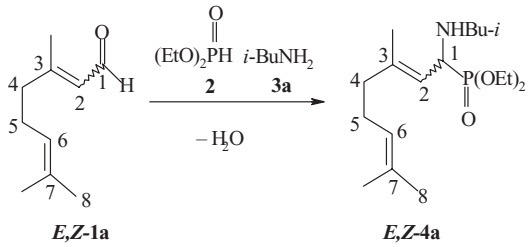
Contract grant sponsor: Russian Foundation for Basic Research.
Contract grant number: 07-03-00617-a.

routes for phosphorylated derivatives of isoprenoids such as racemic β-camphene, (*R*)-(+)-limonene, and (1*S*)-(–)-β-pinene by the reactions with *O,O*-dialkyl dithiophosphoric acids [18, 19], geraniol, and nerol by the reactions with chlorodiethyl phosphite in the presence of triethylamine [20]. Taking into account antimicrobial activity of citral and its derivatives [21–25], we have recently studied reactions of trimethyl phosphite with citral in the presence of acetic acid, triphenyl phosphite with citral in the presence of water, and trimethyl phosphite with citral in the presence of water and triethylamine [26–28]. A convenient method of synthesizing unsaturated α-hydroxyphosphonates was developed on the basis of reaction of dialkyl phosphites with citral in the presence of triethylamine in alcohol solutions [28]. On the basis of our preliminary communication published without experimental details [29], in this article, novel α-aminophosphonates tested for their antibacterial activity are presented by using the Kabachnik–Fields and Pudovik reactions.

RESULTS AND DISCUSSION

The substantial interest in α-aminophosphonates is due to their potential biological activity. The α-aminophosphonate moiety is a versatile and pharmacophoric functional group due to the broad spectrum of biological activity exhibited by substances bearing this structural unit. Some of these compounds are used as herbicides, fungicides, bioantioxidants, and enzyme inhibitors [30–38]. Common methods of synthesizing α-aminophosphonates are usually based on the three-component Kabachnik–Fields reaction of acidic phosphites containing the P—H bond, aldehydes, and primary amines (or other organonitrogen compounds with the labile N—H bond) [39–43]. We deemed it to be necessary to obtain α-aminophosphonates with potential biological activity by using α,β-unsaturated diprenoid aldehydes bearing pharmacophoric prenyl functionalities. Herein we have studied a possibility of α-aminophosphonate synthesis on the basis of citral (the mixture of *E*- and *Z*-isomers 1:1) and its imines and (*R,S*)-citronellal by the Kabachnik–Fields and Pudovik reactions.

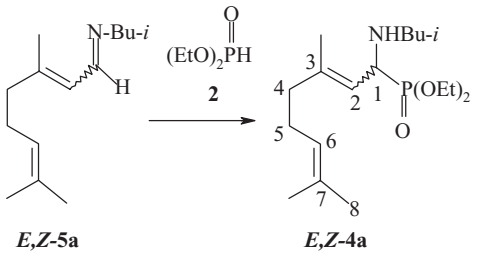
Obviously, the formation of products of α-aminophosphonate structure could be expected by the use of citral in the reaction with dialkyl phosphites and primary amines. Nevertheless, taking into account the presence of a few functional groups in the molecule of citral (the carbonyl group and two C=C bonds), we have not excluded the formation of some by-products by the addition of dialkyl phosphites into the C=C bonds in the accordance with the Pudovik reaction or via the 1,4-addition with the participation of both C=O and C=C bonds likely as previously studied reactions of acidic phosphites with α,β-unsaturated aldehydes [45]. To avoid the formation of undesirable by-products, we have defined the optimal conditions of α-aminophosphonates formation. We have performed the reaction of citral ***E,Z*-1a** with diethyl phosphite **2** in the presence of equimolecular amounts of isobutylamine **3a** under mild conditions (10–15°C). We have shown that this reaction has produced *O,O*-diethyl α-(*N*-isobutylamino)-3,7-dimethylocta-2,6-dienylphosphonates **4a** as the mixture of *E*- and *Z*-isomers with the elimination of water (Scheme 1, method A).



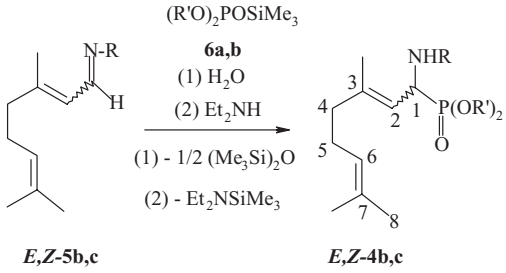
SCHEME 1 Synthesis of α-aminophosphonates ***E,Z*-4a** by the Kabachnik–Fields reaction.

This reaction (Scheme 1) is exothermic. Products ***E,Z*-4a** were formed in high yield (95%) and purified by vacuum distillations. The compounds ***E,Z*-4a** are soluble in common organic solvents. Their structures have been confirmed by evaluation of IR, ^{1}H, ^{13}C, and ^{31}P NMR, mass spectra, and by microanalyses. No individual *E*- and *Z*-isomers of **4a** were separated. It is noteworthy that only the carbonyl group of citral takes part in the reaction with phosphite **2** in the presence of amine **3a**. The both unsaturated C=C bonds of citral remained unchanged as established by IR and ^{1}H spectra (see the Experimental section). Thus, Scheme 1 shows chemospecificity and proceeds with the participation of the carbonyl group of citral and no addition products on the C=C bonds were found in accordance with the Pudovik reaction. The chemospecificity formation of α-aminophosphonates may be explained not only the rather higher reactivity of the carbonyl group than that of the C=C bonds in citral toward phosphite **2**. The spatial hindrance of methyl groups at the C^3 and C^7 carbon atoms could not aver the formation of products of addition of phosphite **2a** into the C=C bonds.

On the other hand, α-aminophosphonates have also been obtained via the interaction of acidic phosphites with imines formed as a result of the condensation of aldehydes with primary amines and



SCHEME 2 Synthesis of α-aminophosphonates ***E,Z*-4a** by the Pudovik reaction.



R = Et (**5b, 4b**), R' = Bu-*i* (**6a, 4b**);
R = Bu (**5c, 4c**), R' = Et (**6b, 4c**)

SCHEME 3 Synthesis of α-aminophosphonates ***E,Z*-4b,c** on the basis of imines ***E,Z*-5b,c**.

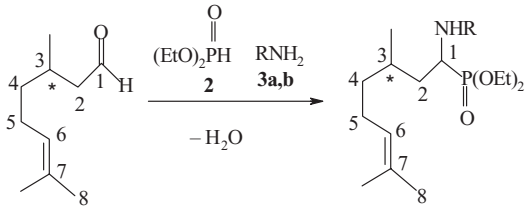
amino acid esters [44, 45]. Chiral Schiff bases were prepared by the condensation of (*S*)-2-hydroxy-3-pinanone and its (*R*)-isomer with glycine ethyl ester [46], aldehydes with MeO-methionine hydrochloride [47], diterpenoid isosteviol [48], and (1*R*)-(–)-myrtenal with aliphatic primary amines [50]. In continuation of a study of prenyl derivative chemistry, we have involved *E,Z*-3,7-dimethylocta-2,6-dienyl *N*-isobutylimines **5a** obtained by the reaction of isobutylamine **3a** with citral ***E,Z*-1a** at –20°C in the interaction with phosphite **2** (Scheme 2, method B).

As we can expect, the interaction of phosphite **2** with imines ***E,Z*-5a** is chemospecific and leads to the same α-aminophosphonates ***E,Z*-4a** in 90% yield. Compounds ***E,Z*-4a** were purified by a subsequent distillation. No vinyl fragments of the unsaturated aldehydes changed under conditions used. It should be noted that physical and spectral data of ***E,Z*-4a** prepared in the Pudovik reaction (Scheme 2) were identical to those of the specimen of ***E,Z*-4a** obtained in the course of the Kabachnik–Fields reaction (Scheme 1). It is considered of interest to compare the rates of the Kabachnik–Fields and Pudovik reactions on the basis of interactions depicted in Schemes 1 and 2. It was found that α-aminophosphonates ***E,Z*-4a** in the Pudovik reaction forms more slowly.

The α,β-unsaturated imines are known to react with dialkyl trimethylsilyl phosphites via one-pot tandem 1,4–1,2-additions. The water treatment of intermediates formed leads to final α-amino-1,3-diphosphonates [45, 51, 52]. In contrast to this data, we have first found that *E,Z*-3,7-dimethylocta-2,6-dienyl *N*-ethylimines **5b** and *E,Z*-3,7-dimethylocta-2,6-dienyl *N*-butylimines **5c** containing the spatially demanding unsaturated C=C bonds react with *O,O*-dialkyl trimethylsilyl phosphites **6a,b** in the presence of equimolar amounts of water at 20°C for 1 h or diethylamine on heating up at 60–70°C for 0.5 h to give α-aminophosphonates ***E,Z*-4b,c** (Scheme 3, method C).

It should be noted that the successful preparation of α-aminophosphonates ***E,Z*-4b,c** is determined by subsequent mixing of reagents. The equimolar amounts of water were added dropwise to imines ***E,Z*-5b** or ***E,Z*-5c**. Silylphosphite **6a** or **6b** was added into the obtained mixture. The reactions in the presence of water were accompanied by intermediate formation of trimethylsilanol that eliminates water leading to bis(trimethylsilyl)oxide in accordance with [53]. In the case of diethylamine, silylphosphite **6b** was added to the mixture of imines ***E,Z*-5c** and diethylamine, resulting in the formation of trimethyl(*N,N'*-diethylamino)silane along with α-aminophosphonates ***E,Z*-4c**. Products ***E,Z*-4b,c** were purified by distillation as well as trimethyl(*N,N'*-diethylamino)silane eliminated. Similar to the reaction of phosphite **2** with imines ***E,Z*-5a** (Scheme 2), the interaction of imines ***E,Z*-5b,c** with silylphosphites **6a,b** proceeds with the participation of the C=N bond (Scheme 3). It was also shown that α-aminophosphonates ***E,Z*-4** may be formed when other proton donor third reagents such as ethanol or acetic acid were involved in the reactions of imines ***E,Z*-5** with silylphosphites **6**.

In continuation of our approach, we have managed to involve (*R,S*)-citronellal in the Kabachnik–Fields reaction. The citronellal seems to be considered as citral hydrated into the C^2=C^3 double bond. Taking into account the spatial hindrance of the C^6=C^7 double bond, the formation of products of α-aminophosphonate structure could be expected by the use (*R,S*)-citronellal. Indeed, the reaction of diethyl phosphite **2** with (*R,S*)-citronellal **7** in the presence of alkylamines **3a,b** yielded *O,O*-dialkyl α-(*N*-alkylamino)-3,7-dimethylocta-6-enylphosphonates **8a,b** (Scheme 4, method A).



SCHEME 4 Synthesis of α-aminophosphonates **8a,b** by the Kabachnik–Fields reaction.

TABLE 1 Antibacterial Activity of α-Aminophosphonates[a]

Compound	Staphylococcus aureus *209 p*	Bacillus cereus *8035*
E,Z-4a	15.6	62.5
8a	15.6	62.5
8b	62.5	125
Nitroxoline	6.25	7.8

[a]Concentration: mg/L in DMSO.

The formation of phosphonates **8a,b** was accompanied by an exothermic effect (up to 40°C). Compounds **8a**,**b** were obtained in 98% yields and purified by means of vacuum distillations. The ^{31}P NMR spectrum of **8b** reveals two signals $\delta = 29.1$ and 31.4 in the ratio 14:1. In the ^{31}P NMR spectrum of **8a**, the ratio of two chemical shifts $\delta = 29.0$ and 29.2 is ~1:1. The observed ^{31}P resonances were assigned to two diastereoisomers of **8a** and **8b** owing to two asymmetrical centers, namely C^1 and C^3 carbon atoms. The ^{1}H NMR spectrum of **8a** shows two doublets of triplets $\delta = 3.72$ and 3.90 ($^3J_{HH} = 7.0$ and 7.3 Hz, $^2J_{PH} = 7.0$ and 15.4 Hz) of the methine protons of the P—CH—CH_2 fragment. The electron impact mass spectra of **8a** and **8b** show the mass peaks *m/e* 347.4 and 333.4 of their molecular ions $[M]^+$, respectively.

Since α-aminophosphonates involve pharmacophoric functionalities, their antibacterial activity was tested against *Staphylococcus aureus 209 p* and *Bacillus cereus 8035* (Table 1). α-Aminophosphonates ***E,Z*-4a** and **8a** were found to be the most active against the Gram-positive bacteria *Staphylococcus aureus* and *Bacillus cereus* with minimum bacteriostatic concentration 15.6 and 62.5 mg/L in DMSO, respectively. Nitroxoline was tested as a standard reference compound to compare the antibacterial activity of α-aminophosphonates obtained.

Thus, the involvement of prenyl aldehydes and their imine derivatives in the phosphorylation reaction serves as a facile method of obtaining unsaturated biologically active α-aminophosphonates.

EXPERIMENTAL

General

All reactions were performed under an atmosphere of dry argon. The solvents were dried prior to use. *E,Z*-Citral and (*R,S*)-citronellal, were purchased from Sigma-Aldrich Chemie Gmbh (Munich, Germany) without further purification. Isobutylamine, isopropylamine, and butylamine were purchased from Acros Organics (Thermo Fisher Scientific, Geel, Belgium) and purified by distillation under KOH prior to use. Diethyl phosphite and dialkyl trimethylsilyl phosphites were prepared in accordance with [54]. The ^{31}P NMR spectra were taken on a Bruker CXP-100 (36.47 MHz) spectrometer (Bruker BioSpin Gmbh, Rheinstetten, Germany) with 85% H_3PO_4 as an external reference. The ^{1}H NMR spectra were recorded at ambient temperature with a Bruker Avance 400 (400 MHz for ^{1}H) and a Bruker Avance 600 (600 MHz) (Bruker BioSpin Gmbh) instruments in $CDCl_3$. Chemical shifts δ are presented in ppm relative to residual resonance of solvent (^{1}H: 7.26 ppm); coupling constants J are given in Hz. The ^{13}C NMR spectra were run with a Bruker Avance-600 spectrometer (100.6 MHz) in $CDCl_3$. Characterization of the multiplicities of signals: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, br = broad. Fourier transform IR spectra were obtained in KBr pellet or in film with a Bruker Vector 22 (Bruker Optik Gmbh, Ettlingen, Germany) (400–4000 cm^{-1}) and expressed in cm^{-1}, δ = the deformation vibration. Mass spectra (EI, 70 eV) were determined on a TRACE MS Finnigan MAT spectrometer (Thermo Finnigan, Bremen, Germany), and mass spectral data were recorded as *m/e*.

Bacteria were cultivated on sabouraited agar. The bacteriostatic activities were evaluated at minimum of the concentration of microorganisms in mg/L that resist growth of bacterial cultures.

*O,O-Diethyl α-(N-isobutylamino)-3,7-dimethylocta-2,6-dienylphosphonates (***E,Z-4a***). Method A.* Isobutylamine **3a** (3.5 g, 47.9 mmol) was added dropwise over 1 h under dry argon to the stirred mixture of diethyl phosphite **2** (5.4 g, 39.1 mmol) and citral ***E,Z*-1a** (6.0, 39.4 mmol) at 10–15°C. After an exothermic period of the reaction had been completed, the stirring of the reaction mixture was continued for 1 h at 20°C. The mixture was evaporated at reduced pressure (0.02 mmHg) at 40°C for 1 h to give crude phosphonates ***E,Z*-4a** (12.8 g, 95%), which were distilled in vacuum; bp 134–136°C (0.02 mmHg), n_D^{20} 1.4680. Found: C, 62.53; H, 10.87; N 3.96; P 8.74. $C_{18}H_{26}NO_3P$

requires C, 62.58; H, 10.50; N, 4.05; P, 8.97. IR, ν_{max} (film)/cm^{-1}: 3430 and 3306 (NH), 2960, 2928 and 2870 (CH_3 as, s; CH_2 as, s), 1617 (C=C), 1446 δ (CH_3 as), 1386 δ (CH_3, s), 1245 (P=O), 1057 and 1030 [(P)O—C], 783 (PO_2 as, s). ^{1}H NMR: δ = 0.91 [6H, d, $^3J_{HH}$ = 6.6, $(\underline{CH_3})_2CHCH_2N$] and 0.92 [6H, d, $^3J_{HH}$ = 6.6, $(\underline{CH_3})_2CHCH_2N$]; 1.31 [6H, t, $^3J_{HH}$ = 6.6, $(\underline{CH_3}CH_2O)_2P$] and 1.33 [6H, t, $^3J_{HH}$ = 7.0, $(\underline{CH_3}CH_2O)_2P$]; 1.61 and 1.62 [6H, two s, $(\underline{CH_3})_2C{=}C$] and 1.69 [6H, s, $(\underline{CH_3})_2C{=}C$]; 1.73 (3 H, d, $^4J_{HH}$ 1.5, $\underline{CH_3}C{=}CH$) and 1.80 (3H, d, $^4J_{HH}$ = 1.5, $\underline{CH_3}C{=}CH$); 2.08 [1H, m, $(CH_3)_2\underline{CH}CH_2N$]; 2.11 [4H, m, $\underline{CH_2CH_2}$]; 2.34 [2H, m, $^3J_{HH}$ = 6.2, $(CH_3)_2CH\underline{CH_2}N$] and 2.51 [2H, m, $^3J_{HH}$ 7.0, $(CH_3)_2CH\underline{CH_2}N$]; 3.74 (1H, two dd, $^3J_{HH}$ = 9.9, $^3J_{PH}$ = 12.5, and $^3J_{HH}$ = 2.9, P$\underline{CH}$,]; 4.15 [4H, dq, $^3J_{HH}$ = 7.0 and $^3J_{PH}$ = 19.1, $(\underline{CH_3CH_2}O)_2P$]; 4.18 (1 H, m, PCH—$\underline{CH}{=}C$); 5.11 [1H, m, $(CH_3)_2C{=}\underline{CH}$] and 7.68 [1H, m, $\underline{NH}$]. The ^{13}C NMR (signal form in the ^{13}C {^{1}H}NMR was brought in braces): δ = 16.5 [dq {d}, $^3J_{PC}$ = 4.4, $^1J_{HC}$ = 125.2, $\underline{C}H_3$—CH_2—OP]; 17.6 [q {s}, $^1J_{HC}$ = 125.1, $\underline{C}H_3(CH_3)C{=}C$]; 20.5 and 20.6 [two q {two s}, $^1J_{HC}$ = 124.1 and $^1J_{HC}$ = 125.2, $(CH_3)_2CHCH_2N$]; 23.4 [dq {d}, $^4J_{PC}$ = 2.2, $^1J_{HC}$ = 124.1, PCC=C—$\underline{C}H_3$]; 25.6 [two q {two s}, $^1J_{HC}$ = 121.9, $\underline{C}H_3(CH_3)C{=}C$]; 26.3 and δ_2 26.9 [two dd {two d}, $^4J_{PC}$ = 2.2, $^1J_{HC}$ = 126.2, $PCNHCH_2\underline{C}H(CH_3)_2$]; 28.2 and 28.3 [two t {two s}, $^1J_{HC}$ = 126.2, $(CH_3)_2C{=}C{-}\underline{C}H_2$]; 32.5 [t {s}, $PCC{=}C{-}\underline{C}H_2$]; 53.9 and δ_2 55.0 [two dd {two d}, $^1J_{PC}$ = 20.9, $^1J_{HC}$ = 132.8, P$\underline{C}$H]; 55.8 and 55.9 [two dt {two d}, $^3J_{PC}$ = 15.4, $^3J_{PC}$ = 16.5, $^1J_{HC}$ = 128.4, $PCN\underline{C}H_2$]; 62.3 and 62.6 [two td {two d}, $^2J_{PC}$ = 6.6, $^1J_{HC}$ = 151.5, $PO\underline{C}H_2CH_3$]; 120.2 and 120.7 [two dd {two d}, $^2J_{PC}$ = 6.6, $^1J_{HC}$ = 152.6, P$\underline{C}$CH=C]; 123.8 and 123.9 [two d {two s}, $^1J_{HC}$ = 147.2, $(CH_3)_2C{=}\underline{C}H$]; 131.5 and 131.8 [two s {s}, $(CH_3)_2\underline{C}{=}C$]; 141.2 and 141.5 [two d {d}, $^3J_{PC}$ = 13.2, $PCCH{=}\underline{C}C_2$]. ^{31}P NMR: δ = 24.6. MS (EI), *m/e* (%): 345.3 (3) $[M]^+$, 330.3 (1) $[M - Me]^+$, 316 (1) $[M - Et]^+$, 315.3 (1) $[M - 2Me]^+$, 302.2 (2) $[M - Me_2CH]^+$, 288.2 (1) [M – Bu-*i*]$^+$ and 273.2 [M – NHBu-*i*]$^+$ (4) requires 345.5.

Method B. Diethyl phosphite **2** (2.9 g, 21.0 mmol) was added dropwise under dry argon to the stirred imines ***E,Z*-5a** (4.3 g, 20.8 mmol) at 20°C, and stirring was continued for 2 h at 20°C. Volatiles were removed under reduced pressure (0.02 mmHg) at 40°C for 1 h to yield crude phosphonates ***E,Z*-4a** (6.5 g, 90%). The residue was distilled in vacuum; bp 140–142°C (0.03 mmHg), n_D^{20} 1.4673. Found: C, 62.56; H, 10.28; N 4.23; P 8.71. $C_{18}H_{26}NO_3P$ requires C, 62.58; H 10.50; N 4.05; P 8.97. ^{31}P NMR: δ = 24.7. MS (EI), *m/e* (%): 345.3 (4) $[M]^+$ requires 345.5.

*O,O-Diisobutyl E,Z-α-(N-ethylamino)-3,7-dimethylocta-2,6-dienylphosphonates (***E,Z-4b***) Method C (in the presence of water).* *O,O*-Diisobutyl trimethylsilyl phosphite **6a** (2.6 g, 9.8 mmol) was added dropwise under dry argon to the stirred mixture of imines ***E,Z*-5b** (1.75 g, 9.8 mmol) and water (0.09 g, 5.0 mmol) at 20°C, and stirring was continued for 1 h at 20°C. The mixture was evaporated at reduced pressure (0.02 mmHg) at 40°C for 1 h to give crude phosphonates ***E,Z*-4b** (3.4 g, 94%), which were distilled in vacuum; bp 140–143°C 0.02 Hg), n_D^{20} 1.4585. Found: C, 63.95; H 11.15; N 3.78; P 7.88. $C_{20}H_{40}NO_3P$ requires C, 64.31; H, 10.79; N, 3.75; P, 8.29. IR, ν_{max} (film)/cm^{-1}: 3421 and 3310 (NH), 2965, and 2876 (CH_3 as, s; CH_2 as, s), 1661 (C=C), 1463 δ (CH_3 as), 1380 and 1374 δ [$(CH_3)_2C$ gem. s], 1248 (P=O), 1049 and 1013 [(P)O—C] and 837 (PO_2 as, s). ^{1}H NMR: δ = 0.90 (3 H, t, $^3J_{HH}$ = 7.0, $\underline{CH_3}CH_2N$) and 0.91 (3H, t, $^3J_{HH}$ = 7.0, $\underline{CH_3}CH_2N$); 0.94 {12H, d, $^3J_{HH}$ 7.0, $[(\underline{CH_3})_2CHCH_2O]_2P$}and 0.95 {12H, d, $^3J_{HH}$ = 7.0, $[(\underline{CH_3})_2CHCH_2O]_2P$}; 1.32 {2H, m, $[(CH_3)_2\underline{CH}CH_2O]_2P$}; 1.58 and 1.60 [6H, two s, $(\underline{CH_3})_2C{=}C$]; 1.65 and 1.68 [6H, two s, $(\underline{CH_3})_2C{=}C$]; 1.69 (3H, d, $^4J_{HH}$ = 3.3, $\underline{CH_3}C{=}CH$) and 1.77 (3H, d, $^4J_{HH}$ = 4.4, $\underline{CH_3}C{=}CH$); 1.93 (4H, m, $^3J_{HH}$ = 6.6, $CH_3\underline{CH_2}N$); 2.08 and 2.11 (3H, two br s, $\underline{CH_3}C{=}C$); 3.60 (1H, dd, $^3J_{HH}$ = 6.6 and $^3J_{PH}$ = 14.0, P$\underline{CH}$); 3.83 {4H, m, $^3J_{HH}$ = 6.2, $[(CH_3)_2CH\underline{CH_2}O]_2P$}; 5.08 (1H, m, PCH—$\underline{CH}{=}C$); 5.93 [1H, m, $(CH_3)_2C{=}\underline{CH}$] and 7.66 (1H, m, $\underline{NH}$). ^{31}P NMR: δ = 24.3. MS (EI), *m/e* (%): 373.4 (1) $[M]^+$, 330.3 (1) $[M - Me_2CH]^+$ and 314.3 (1) $[M - O - Me_2CH]^+$ requires 373.5.

*O,O-Diethyl E,Z-α-(N-butylamino)-3,7-dimethylocta-2,6-dienylphosphonates (***E,Z-4c***). (Method C in the presence of water). These* were obtained similarly. Yield: 85%; bp 147–149°C (0.02 mmHg). Found: C, 62.64; H, 10.77; N, 3.88; P, 8.68. $C_{18}H_{26}NO_3P$ requires C, 62.58; H, 10.50; N, 4.05; P, 8.97%. ^{1}H NMR: δ = 0.90 (3H, t, $^3J_{HH}$ = 7.3, $\underline{CH_3}CH_2CH_2CH_2N$); 1.61 and 1.63 [6H, two s, $(\underline{CH_3})_2C{=}C$]; 1.69 and 1.70 [6H, two s, $(\underline{CH_3})_2C{=}C$]; 1.71 and 1.72 (3H, two d, $^4J_{HH}$ = 1.1, $\underline{CH_3}C{=}CH$); 1.79 and 1.80 (3H, two d, $^4J_{HH}$ = 1.1 and $^4J_{HH}$ = 1.5, $\underline{CH_3}C{=}CH$); 2.12 (4H, m, $CH_3\underline{CH_2}\underline{CH_2}CH_2N$); 2.48 (2H, t, $^3J_{HH}$ = 7.0, $CH_2\underline{CH_2}N$) and 2.50 (2H, t, $^3J_{HH}$ = 7.0, $CH_2\underline{CH_2}N$); 2.65 (2H, m, $^3J_{HH}$ = 7.3, $CH\underline{CH_2}N$); 3.74 (1H, dd, $^3J_{HH}$ = 9.9 and $^3J_{PH}$ = 17.2, P$\underline{CH}$); 4.05 (4H, m, $^3J_{HH}$ = 7.3, $(CH_3\underline{CH_2}O)_2P$); 5.05 (1H, m, PCH—$\underline{CH}{=}C$); 5.09 [1H, m, $(CH_3)_2C{=}\underline{CH}$] and 7.79 (1H, m, $\underline{NH}$). ^{31}P NMR: δ = 24.6.

Method C (in the presence of diethylamine). Diethylamine (1.0 g, 13.7 mmol) was added dropwise under dry argon to the stirred imines ***E,Z*-5c** (2.8 g, 13.5 mmol) at 20°C. Silyl phosphite **6b**

(2.8 g, 13.3 mmol) was added dropwise with stirring to the mixture obtained at 20°C. The stirred mixture was heated for 0.5 h at 60–70°C, than cooled and evaporated at reduced pressure (0.06 mmHg) at 40°C for 1 h with use of a trap cooled by liquid nitrogen. Product ***E,Z*-4d** (3.4 g, 74%) was isolated from the residue by vacuum distillation; bp 156–158°C (0.04 mmHg). Found: C, 62.33; H, 10.26; N, 4.36; P, 9.19. $C_{18}H_{26}NO_3P$ requires C, 62.58; H, 10.50; N, 4.05; P, 8.98. ^{31}P NMR: δ = 24.4. Distillation of the contents of the liquid nitrogen trap gave trimethyl(*N,N*′-diethylamino)silane (1.7 g, 89%); bp 126–128°C, n_D^{20} 1.4096 [53]: bp 126.8–127.1°C (738 mmHg), n_D^{20} 1.4109.

*O,O-Diethyl α-(N-isobutylamino)-3,7-dimethyl-octa-6-enylphosphonates (***8a***).* Isobutylamine **3a** (3.2 g, 43.8 mmol) was added dropwise under dry argon to the stirred mixture of diethyl phosphite **2** (5.0 g, 36.2 mmol) and (*R,S*)-citronellal **7** (5.6 g, 36.3 mmol) at 20°C. After an exothermic period of the reaction had been completed, the stirring of the reaction mixture was continued for 2 h at 20°C. The mixture was evaporated at reduced pressure (0.5 mmHg) at 40°C for 1 h and at 0.02 mmHg at 40°C for 1 h to give crude phosphonates **8a** (12.3 g, 98%), which were distilled in vacuum; bp 77–80°C (0.02 mmHg), n_D^{20} 1.4590. Found: C, 62.59; H, 11.09; N, 4.23; P, 8.51. $C_{18}H_{38}NO_3P$ requires C, 62.22; H, 11.02; N, 4.03; P, 8.91. IR, ν_{max} (film)/cm^{-1}: 3383 and 3323 (NH), 2957, 2927, and 2871 (CH_3 as, s; CH_2 as, s), 1463 δ (CH_3 as), 1383 δ (CH_3 s), 1242 (P=O), 1057 and 1029 [(P)O—C], 786 (PO_2 as, s). ^{1}H NMR: δ = 0.92 [6H, d, $^3J_{HH}$ = 7.0, $(\underline{CH_3})_2CHCH_2N$] and 0.93 [6H, d, $^3J_{HH}$ = 6.6, $(\underline{CH_3})_2CHCH_2N$]; 1.04 [3H, d, $^3J_{HH}$ = 7.0, $\underline{CH_3}CH(CH_2)_2$]; 1.25, 1.28, and 1.34 [6H, three t, $^3J_{HH}$ = 7.0, $(\underline{CH_3}CH_2O)_2P$]; 1.61 [3H, s, $\underline{CH_3}C{=}CH$]; 1.69 [3H, d, $^4J_{HH}$ = 1.5, $\underline{CH_3}C{=}CH$]; 1.70–1.76 [2H, m, $^3J_{HH}$ = 6.6, C=C—$CH_2\underline{CH_2}$]; 1.97–2.08 [2H, m, $^3J_{HH}$ = 6.6, C=C—$\underline{CH_2}CH_2$]; 2.48–2.56 and 2.63–2.66 [2H, two m, $^3J_{HH}$ = 6.6, NCH—$\underline{CH_2}CH$]; 2.75 [2H, d, $^3J_{HH}$ = 7.0, $N\underline{CH_2}CH(CH_3)_3$]; 3.72 [1H, dt, $^3J_{HH}$ = 7.0, $^2J_{PH}$ = 7.0, $P\underline{CH}CH_2$] and 3.90 [1 H, dt, $^3J_{HH}$ = 7.3, $^2J_{PH}$ = 15.4, $P\underline{CH}CH_2$]; 4.16 [4H, two dq, $^3J_{HH}$ = 7.3, $^3J_{PH}$ = 2.2 and $^3J_{HH}$ = 7.0, $^3J_{PH}$ = 2.2, $(CH_3\underline{CH_2}O)_2P$]; 5.09 [1H, three t, $^3J_{HH}$ = 7.0, $^4J_{HH}$ = 1.5, $(CH_3)_2C{=}\underline{CH}{-}CH_2$]; 8.53 [1H, br m, $\underline{NH}$]. The ^{13}C NMR (signal form in the ^{13}C {^{1}H}NMR was brought in braces): δ = 56.2 [td {d}, $^3J_{PC}$ = 15.0, $^1J_{HC}$ = 138.3, $PON\underline{C}H_2$]; 61.6 and 61.8 [two td {two d}, $^2J_{PC}$ = 7.7, $^1J_{HC}$ = 142.7, $PO\underline{C}H_2CH_3$]; 63.3 and 63.8 [two dd {two d}, $^1J_{PC}$ = 20.0, $^1J_{HC}$ = 147.1, $P\underline{C}H$], 124.5 and 124.8 [two d {two s}, $^1J_{HC}$ = 147.2, $C{=}\underline{C}^6H$]; 130.7 and 130.0 [two s {two s}, $PCC{=}\underline{C}^7C_2$]. ^{31}P NMR: δ = 29.0 and 29.2 in ratio 1:1. MS (EI), *m/e* (%): 347.4 $[M]^+$ (6); 304.3 $[M - Me_2CH]^+$ (10); 276.3 $[M - Bu\text{-}i - N]^+$ (14) requires 347.5.

*O,O-Diethyl α-(N-isopropylamino)-3,7-dimethyl-octa-6-enylphosphonates (***8b***).* These were obtained similarly. Yield: 98%; bp 63–65°C (0.02 mmHg), n_D^{20} 1.4560. Found: C, 61.37; H, 10.57; N, 3.84; P, 8.90. $C_{17}H_{36}NO_3P$ requires C, 61.23; H, 10.86; N, 4.20; P, 9.29. IR, ν_{max} (film)/cm^{-1}: 3399 and 3310 (NH), 2966, 2928, and 2870 (CH_3 as, s; CH_2 as, s), 1638 (C=C), 1456 δ (CH_3 as), 1379 δ (CH_3 s), 1240 (P=O), 1055 and 1036 [(P)O—C], 783 (PO_2 as, s). ^{1}H NMR: δ = 0.91 [3H, d, $^3J_{HH}$ = 6.6, $\underline{CH_3}CH$] and 0.95 [3H, d, $^3J_{HH}$ = 6.6, $\underline{CH_3}CH$]; 1.03 [6H, d, $^3J_{HH}$ = 5.9, $(\underline{CH_3})_2CHN$] and 1.07 [6H, d, $^3J_{HH}$ = 6.2, $(\underline{CH_3})_2CHN$]; 1.24–1.30 and 1.36–1.41 [1H, two m, $(CH_3)_2\underline{CH}N$, $CH_3\underline{CH}$]; 1.34 [4H, t, $^3J_{HH}$ = 7.0, $(\underline{CH_3}CH_2O)_2P$]; 1.62 [3H, s, $(CH_3)\underline{CH_3}C{=}CH$] and 1.69 [3H, s, $(\underline{CH_3})CH_3C{=}CH$]; 1.48–1.54 and 1.71–1.79 [2H, two m, C=C—$CH_2\underline{CH_2}$]; 1.91–2.10 [2H, m, C=C—$\underline{CH_2}CH_2$]; 2.92–2.98 and 3.09–3.14 [2H, two m, PCH—$\underline{CH_2}CH$]; 3.72 and 3.96 (1H, two m, $P\underline{CH}CH_2$); 4.15 [4H, two dq, $^3J_{HH}$ = 7.3, $^3J_{PH}$ = 15.4, $(\underline{CH_3}CH_2O)_2P$]; 5.11 [1H, m, $(CH_3)_2C{=}\underline{CH}{-}CH_2$]; 8.51 [1H, br m, $\underline{NH}$]. ^{31}P NMR: δ = 28.7. MS (EI), *m/e* (%): 333.4 $[M]^+$ (5) requires 333.5.

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