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An unusual regiochemistry of reactions of a cyclohexenylphosphonate bearing a β-ethoxycarbonyl group with aldehydes

Ewa Krawczyk *, Krzysztof Owsianik

Center of Molecular and Macromolecular Studies, Polish Academy of Sciences, Department of Heteroorganic Chemistry, Sienkiewicza 112, 90-363 Łódź, Poland

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ABSTRACT

Reactions of lithiated ethyl 6-(dimethoxyphosphoryl)cyclohex-1-enecarboxylate with aliphatic, aromatic, and unsaturated aldehydes were studied and determined to proceed with α or δ regioselectivity. Such an unusual regioselectivity results from the contribution of two allylic carbanions: one, stabilized by the phosphonate moiety and the other stabilized by the carboethoxy group. The course of the reaction depends mainly on the structure of the aldehyde and the reaction conditions. The products of Horner–Wadsworth–Emmons reaction, including an analogue of some retinol metabolites, were formed under kinetic conditions whereas the δ-adducts were obtained as thermodynamic products.

1. Introduction

The chemistry of allylic anions containing α-heteroatom substituents, such as SiR_3, SR, OR, NR_2, $P(O)R_2$ has been intensively investigated over the years.[1] Among these ambident anions, those containing phosphoryl functionality occupy an important position since their reaction with carbonyl compounds constitutes a very useful method in synthetic organic chemistry.[2] Regiochemical control in these reactions is crucial to the application of these methods. Alk-2-enylphosphonic esters being versatile compounds offer their α or γ carbon atom as the nucleophilic center.[2] These phosphonates, activated in α,β, or γ position by an electron withdrawing or donating group, have found wide applications in the synthesis of olefins via the Horner–Wadsworth–Emmons (HWE) reaction.[1,3,4] In this way (*E*,*E*) or (*E*,*Z*) carboalkoxy- and cyano-substituted butadiene[3b,5] and (*E*,*E*)-α,β,γ,δ unsaturated esters[4d] were prepared. On the other hand some reactions of allylic phosphonates, proceeding with γ-regioselectivity, provide easy access to differently substituted cyclic compounds,[2b] including heterocyclic phosphonolactones.[3c]

The synthesis of β-carotenes from retinylphosphonate is an example of utilization of HWE reactions between aldehydes and the acyclic allylic phosphonates containing no additional stabilizing groups.[6] Gerber and Modro examined reactions of non-activated cyclohexen-2-ylphosphonate with various aldehydes and found that 1-[1′-hydroxyalkyl(aryl)]cyclohexen-2-ylphosphonates were formed in most cases.[7] The regioselectivity of these reactions (α- vs γ-addition) was studied and it was established that steric effects of the selected aldehydes exerted an influence on the regiochemical outcome of these condensations.

As a part of our research concerning the synthesis of multifunctional cyclic compounds **1**,[8] we have recently elaborated the regio- and stereo-selective synthesis of new cyclic allylic phosphonates **2**, **3**.[9] Selected model phosphonates were prepared via stereoselective reaction of trimethyl phosphite with cyclohexen-2-yl phosphates **1**. The latter are cyclic Baylis–Hillman adducts (Scheme 1).

The phosphonates **2**, **3** activated by the carboethoxy group in the β position, could be potential substrates for the preparation of *exo*/*endo* unsaturated cyclic compounds by HWE reaction with various aldehydes. Such an unsaturated moiety constitutes a structural part of some metabolites of vitamin A.[10,11] Further development in this area may lead to easy access to biologically important molecules.[11] Thus, we decided to investigate the reaction of a cyclic allylic phosphonate anion derived from **3** with appropriate aldehydes as a possible alternative route to relevant model compounds. We have particularly concentrated on the mechanistic investigations bringing a better understanding on the varied reactivity of multifunctional phosphonate **3**. In this paper, we describe these studies and report the preliminary results.

2. Results and discussion

In the reaction of phosphonate **3** with carbonyl compounds, with respect to the structure of **3**, we could consider the following possible pathways (Scheme 2).

* Corresponding author. E-mail address: ewakrsoj@bilbo.cbmm.lodz.pl (E. Krawczyk).

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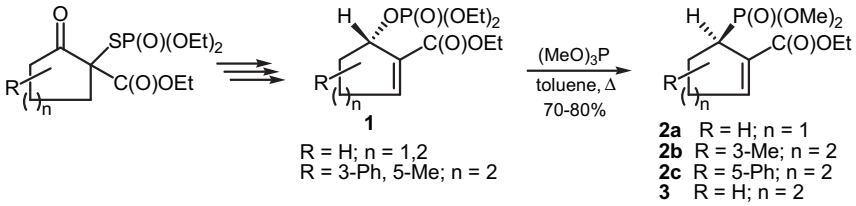
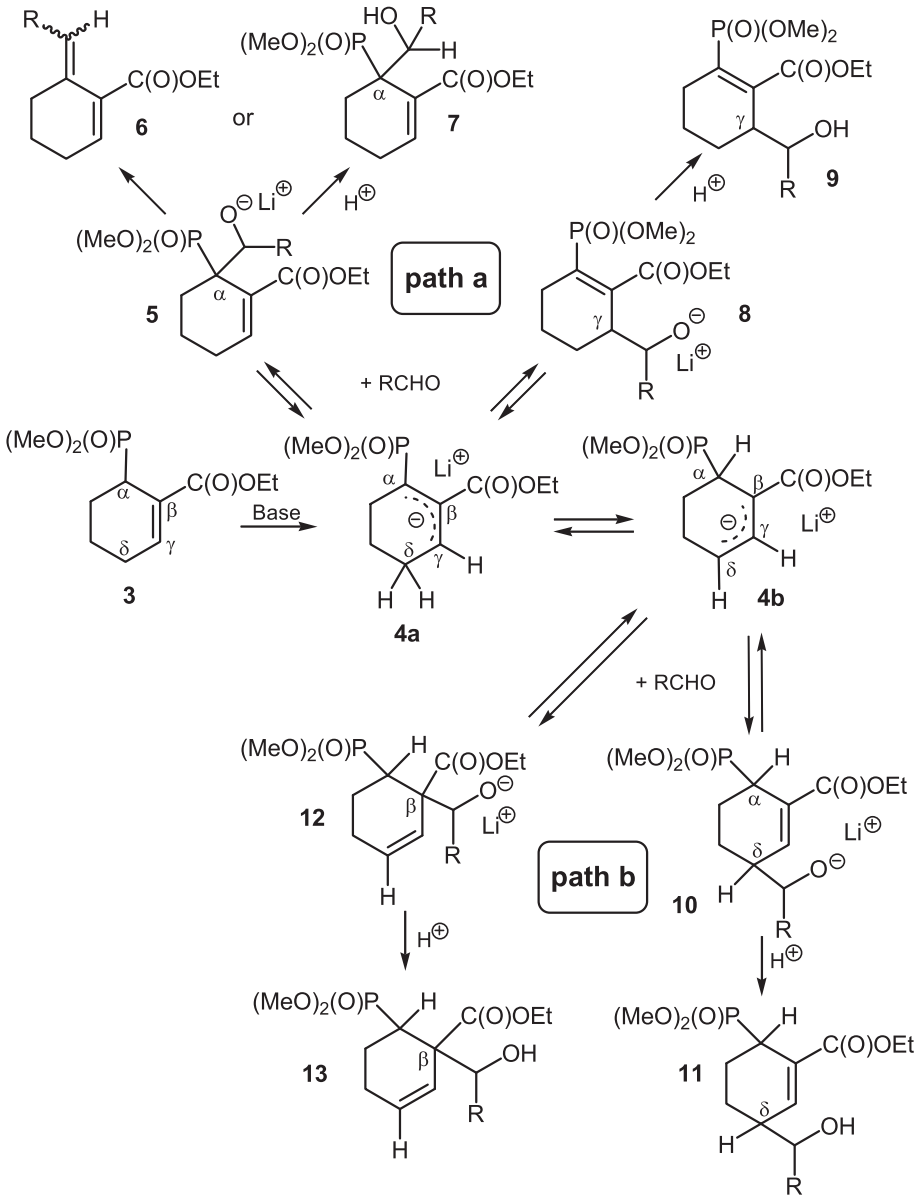


Scheme 1. General synthesis of β-carboethoxy cycloalkenyl phosphonates **2** and **3**.



Scheme 2. Proposed mechanism for the reaction of β-carboethoxy cyclohexenyl phosphonate **3** with aldehydes.

Treatment of the phosphonate **3** with a base should afford the cyclic phosphoryl-stabilized allylic carbanion **4a**, that can react as an ambident species with aldehydes in α-C or γ-C position to give one of two possible intermediates, oxyanion **5** or **8**[12] (Scheme 2, path 'a'). This addition is usually reversible and the corresponding α-adduct **5** is formed as a kinetic, and γ-adduct **8** as a thermodynamic product. Adduct **5** can undergo HWE reaction to give the corresponding diene **6** and phosphate anion or can be simply quenched forming (2-hydroxyalkyl)phosphonate **7**.[13] Similarly the protonation of adduct **8** leads to the final (4-hydroxyalkyl)vinylphosphonate **9**.

The presence of the carboethoxy group at the β-carbon atom of compound **3** also allows deprotonation at the δ position to form an appropriate anion **4b**. In this case the addition of the aldehyde can take place either at the β- or at δ-carbon atom to afford the intermediate adducts **10** and **12** that subsequently form products **11** and **13**, respectively (Scheme 2, path 'b'). We have assumed that equilibrium between **4a** and **4b** could occur by a protonation–deprotonation

sequence and carboanion **4b** would be formed as the thermodynamic isomer.[14] Taking into account the reversibility of the aldehyde addition step, that can proceed by path 'a' or 'b', this reaction can lead to different products. Using different conditions, the reaction can be under kinetic or thermodynamic control. The complex nature of these processes led us to search for a suitable procedure to control their regioselectivity.

2.1. The reaction of phosphonate 3 with aldehydes under standard conditions

First, we examined the reaction of **3** with selected aliphatic, aromatic, and unsaturated aldehydes, according to a general procedure described for acyclic 2-carboethoxy substituted allylphosphonate.[5a] The reaction was performed by addition of an appropriate aldehyde to a THF solution of the lithium phosphonate carbanion at −78 °C. The reaction mixture was stirred at low temperature for 2 h and at room temperature for 10 h and finally quenched with aqueous ammonium chloride.[13] Crude reaction mixtures were analyzed by ^{1}H and ^{31}P NMR spectroscopy. The detailed reaction conditions are given in Table 1.

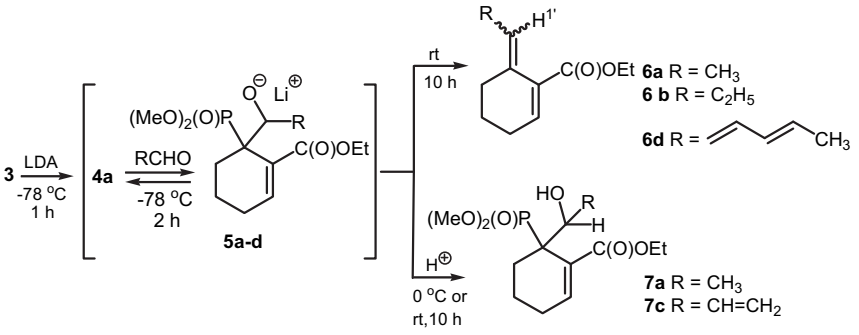
the anion stabilizing polarization of the phosphonyl group.[16] Such a downfield shift ~40 ppm in the ^{31}P NMR spectrum of an anion, compared with its parent compound, is in agreement with delocalization of negative charge in a salt-like structure **4a**.[3c,16,17]

The reactions of phosphonate **3** performed by formation of the carbanion with LDA and addition of simple aliphatic aldehydes proceeded smoothly under the given conditions to give the desired products of the HWE olefination—the corresponding (*E*/*Z*)-ethyl 6-alkylidenecyclohex-1-enecarboxylate **6**. Dienes **6a** (R=CH_3) and **6b** (R=C_2H_5) were obtained in moderate yield and stereoselectivity (Scheme 3, Table 1, entries 1 and 2). When the crude reaction mixture was quenched with water at 0 °C instead of room temperature, the product of the initial addition of acetaldehyde to **4a**, namely compound **7a** (R=CH_3), was isolated (Scheme 3, Table 1, entry 3). The product of the olefination reaction with 2,4-hexadienal **6d** [R=CH_3–(CH=CH)$_2$] was isolated in only 30% yield. The other components of this reaction mixture were the parent phosphonate **3** and unreacted aldehyde (Scheme 3, Table 1, entry 5). In the reaction with acrolein, only the product of addition to **4a** (**7c**, R=–CH_2=CH) was found and isolated in low yield from the reaction mixture at room temperature (Scheme 3, Table 1, entry 4).

Table 1
Reaction of phosphonate **3** with aldehydes according to procedures A and B[a]

Entry	Aldehyde R	Path 'a'		Path 'b' addition product at C_δ	Yield (%)	Ratio of isomers **6** or **7** or **11**
		Addition product at C_α	HWE product			
1	CH_3	—	**6a**	—	41[b]	3:1[c]
2	C_2H_5	—	**6b**	—	45[b]	2:1
3	CH_3[d]	**7a**	—	—	46[e]	2:1
4	CH_2=CH	**7c**	—	—	35[e]	1:1
5	CH_3(CH=CH)$_2$	—	**6d**	—	30[b]	nd
6	C_6H_5	—	—	**11e**	71[e]	2:1[e]
7	C_6H_5[f]	—	—	**11e**	44[e]	1:1[e]
8	$(CH_3)_2$CH	—	—	**11f**	49[e]	1.3:1[e]
9	$(CH_3)_2$CH[g]	—	—	**11f**	41[e]	1:1[e]

[a] Procedure A: base: LDA; procedure B: base: BuLi; conditions: (i) base, THF, −78 °C; (ii) RCHO, THF, −78 °C, 2 h; (iii) rt, 10 h, then NH_4Cl/H_2O.
[b] Yield of isomers mixture after isolation.
[c] After 24 h at rt.
[d] Conditions: (iii) 0 °C, 2 h, then H_2O.
[e] By ^{31}P NMR spectroscopy of crude mixture.
[f] Conditions: (ii), RCHO rt 12 h, then H_2O.
[g] Procedure B.



Scheme 3. Preparation of dienes **6a**,**b**,**d** and α-adducts **7a**,**c** from phosphonate **3**.

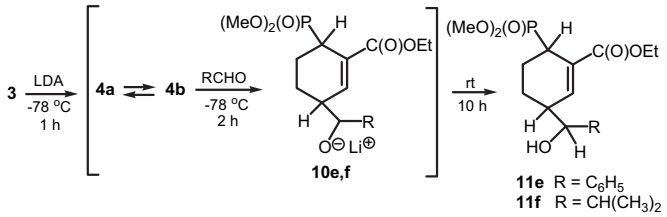
The complete formation of the phosphonate carbanion **4a** from **3**, using lithium diisopropylamide in tetrahydrofuran, was achieved at −78 °C within 1 h. This was proved by quenching the reaction with D_2SO_4, leading to a fully α-deuterated phosphonate **3-d$_1$**.[15] Additionally the structure of lithiated phosphonate **4a** was confirmed by low temperature ^{31}P NMR spectroscopic studies. The ^{31}P NMR signal of lithium phosphonate shifted downfield at −70 °C and indicated

This mixture also contained starting **3** and probably polymerized acrolein.[3a,18]

The structures of all products obtained were confirmed by ^{1}H and ^{31}P NMR spectroscopy and mass spectrometry. The *E*/*Z* ratio of **6a**, **b** was determined by ^{1}H NMR spectroscopy, which indicated that the $H^{1'}$ proton signals of the *E* isomer are observed downfield in comparison to the *Z* isomer.[7,19] Compound **6d** was most likely

formed as a single *E* isomer.[3a] The configuration of the newly formed double bond was not determined due to the complexity of its ^{1}H NMR spectrum. Adducts **7a** and **7c** were obtained as a mixtures of two diastereoisomers formed in a ratio of 2:1 and 1:1, respectively, as determined by ^{31}P NMR spectroscopy.

In contrast, the reactions of lithiated **3** with benzaldehyde and 2-methylpropanal, using LDA or BuLi as a base, afforded δ-addition products **11e** (R=C_6H_5) and **11f** (R=$CH(CH_3)_2$), respectively, in good to moderate yield (Scheme 4, Table 1, entries 6, 8, and 9). The adduct **11e** was stable at room temperature and only partially decomposed to phosphonate **3** and other unidentified compounds when treated with BuLi at low or at ambient temperature (Experimental).



Scheme 4. Preparation of δ-adducts **11e**, **11f** from phosphonate **3**.

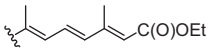
unidentified compounds were the remaining components of the crude reaction mixture (Table 1, entry 7).

2.2. Reaction of phosphonate 3 with aldehydes under modified conditions

Considering the potential synthetic utility of the reactions studied we searched for a method for controlling and improving the regioselectivity. To this end, we extended our studies to examine these reactions under different reaction conditions. The results of these experiments are summarized in Table 2.

Inspection of Table 2 shows that increasing the time (to 10–12 h) at low and at ambient temperature of the reactions of lithiated phosphonate **3** with aliphatic aldehydes like propanal, cyclohexanecarbaldehyde or 2-methylpropanal gave none or only traces of the olefination product (**6f**) (Scheme 5, Table 2, entry 2). Products arising from the self-condensation of aldehydes[20] were the main components of these post-reaction mixtures together with a small amount of phosphonate **3** and other unidentified compounds. Shortening of the time to 4 h at low and room temperature in the reaction with propanal, provided mainly the α-adduct **7b** in 54% yield (Scheme 5, Table 2, entry 1).

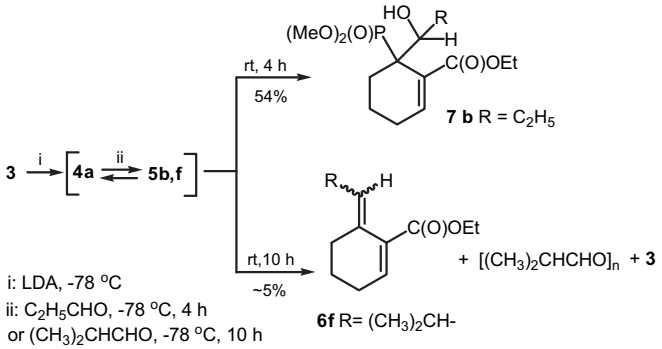
Table 2
Reaction of phosphonate **3** with selected aliphatic and α,β-unsaturated aldehydes and benzaldehyde under modified conditions

Entry	Aldehyde (R)	Conditions[a]	Addition product at C_α or at C_δ	HWE product	Yield[b] (%)	Ratio of isomers **6**, **7** or **11**
1	C_2H_5	**C**[c]	**7b**	—	54	nd
2	$(CH_3)_2CH$	**C**	—	**6f**	~5[e]	nd
3	C_6H_5	**C**	—	**6e**	52	4:1
4	C_6H_5	**D**	—	**6e**	55	5:1
5	$CH_3(CH{=}CH)_2$	**C**[d]		**6d**	35	nd
			11d		30	1.2:1
6		**C**[f]	—	**6g**	78	~20:1

[a] Conditions; **C**: (i) base—LDA, −78 °C, 1 h; (ii) RCHO, −78 °C, 10–12 h, (iii) rt 10–12 h; **D**: (i) NaH, −10–0 °C, 1 h; (ii) RCHO, −40 to −10 °C, 10 h; (iii) 20 °C, 12 h.
[b] Yield of isomers mixture after isolation.
[c] Conditions: (ii) RCHO, −78 °C, 4 h; (iii) rt 4 h.
[d] Conditions: (ii) RCHO, −78 °C, 4 h; (iii) rt 14 h.
[e] Estimated by ^{1}H NMR spectroscopy and GC–MS spectra.
[f] Conditions: (ii) RCHO, −78 °C, 20 h; (iii) rt 20 h.

The structures of the new adducts **11e** and **11f** were determined on the basis of detailed spectroscopic analysis: ^{1}H, ^{13}C, ^{31}P NMR, and mass spectrometry. Moreover, double-resonance experiments (COSY), including heteronuclear 2D spectra (HMQC) ultimately confirmed the structure of these derivatives. The formation of γ-addition (vinyl phosphonate) as well as of β-addition adducts was excluded based on ^{1}H and ^{31}P NMR spectroscopic data. The δ-adducts **11e**, **f** were obtained as mixtures of two diastereoisomers, formed in comparable proportions, as determined by ^{31}P NMR spectroscopy. The diastereomeric mixture of **11e** (R=C_6H_5) was separated to individual isomers.

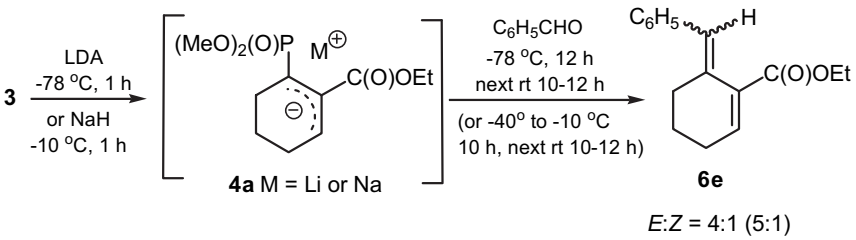
It is evident that the latter reactions (Scheme 4, Table 1, entries 6, 8, and 9) proceed via carbanion **4b** leading to compounds **11e**, **f**. It was of interest to characterize carbanion **4b** by means of ^{31}P NMR spectroscopy. Lithium phosphonate was prepared according to the general procedure at low temperature. Then, after 1 h, this sample was warmed up to ambient temperature and its ^{31}P NMR spectrum was recorded. The ^{31}P chemical shift (30.3 ppm) of this intermediate was close to that of the parent compound **3**. Addition of benzaldehyde to the solution of this anion at room temperature gave the product of δ-addition **11e** in 44% of yield after 12 h of the reaction time. Traces of unreacted phosphonate **3** and some



Scheme 5. Reaction of phosphonate **3** with aliphatic aldehydes under modified conditions.

In this case, prolongation of time under kinetically-controlled conditions, causes a competition between formation of the intermediate α-adduct **5** and self-condensation of enolizable aldehydes. The latter experiment revealed that HWE olefination

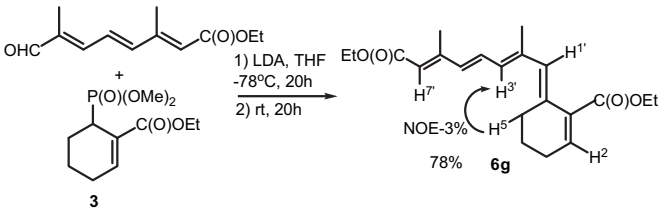
reaction needed more than a few hours at ambient temperature to be complete (Table 2, entry 1 and Table 1, entry 2).



Scheme 6. Synthesis of substituted benzylidene cyclohexene **6e**.

Extension of the reaction time allowed successful HWE olefination reactions with less reactive benzaldehyde, using LDA or sodium hydride as a base (Scheme 6, Table 2, entries 3 and 4).

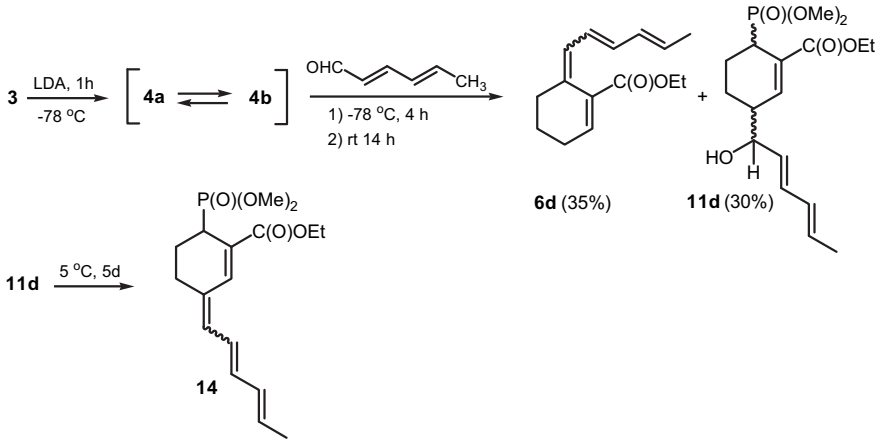
The reaction of lithium phosphonate **4a** with 2,4-hexadienal, performed under the conditions described in Table 1, gave the desired olefination product. However, due to low conversion such a procedure is not synthetically useful. Taking into account that products of the HWE reaction of phosphonate **3** with α,β-unsaturated aldehydes can constitute a building block for the synthesis of polyene-structured natural products,[21] it seemed important searching for suitable conditions to improve the yield of the olefination reaction. Thus, using 2,4-hexadienal, the reaction time was increased. This reaction, performed under the conditions given in Table 2 (entry 5) gave diene **6d** in slightly higher yield (35% after isolation) together with the unexpected δ-addition product **11d**, formed in 30% yield. Adduct **11d** spontaneously converted into



Scheme 8. Synthesis of poliene **6g**.

spectrum, mainly one isomer with traces of a second were detected (Scheme 8; Table 2, entry 6).

Full spectroscopic analysis of **6g**, including $^1H-^1H$ double-resonance was carried out. The *E* geometry of the newly formed



Scheme 7. Reaction of phosphonate **3** with 2,4-hexadienal.

conjugated derivative **14** after 5 days when stored at 5 °C (Scheme 7, Table 2, entry 5).

In turn, utilization of an α,β-unsaturated aldehyde containing a long polyethylene chain, namely (2,6-dimethyl-7-ethoxycarbonyl)-2,4,6-heptatrienal, under the same conditions, did not yield any product. Only unreacted starting materials were found in the crude post-reaction mixture.

It is clear that for condensation with α,β-unsaturated aldehydes, much longer reaction time at low and at room temperature is needed to obtain of HWE reaction product **6** in reasonable yield. Therefore, in the next experiment with (2,6-dimethyl-7-ethoxycarbonyl)-2,4,6-heptatrienal, the adjusted reaction conditions were applied. Prolongation of the reaction time up to 20 h at low and at ambient temperature gave the desired HWE olefination product **6g** in high yield (78%) and stereoselectivity, as concluded on the basis of the ^1H NMR spectrum of the crude reaction mixture. In this double bond was assigned from ^1H NOE experiment. Irradiation of the methylene protons (H^5) of the cyclohexene ring gave an enhancement (~3%) of only one signal (vinyl proton $H^{3'}$). The MNDO calculation of both *E* and *Z* isomers of **6g** confirmed the *E* geometry ($H^{3'}-H^5_{ax}$, $H^{3'}-H^5_{eq}$ 3.4 Å and 3.5 Å, respectively).[22] The derivative **6g** constitutes an analogue of some retinol metabolites such as anhydroretinol (**AR**) or 14-hydroxy-4,14-*retro*-retinol (**14-HRR**).[10]

We have also tested the Bonadies–Scettri[23] procedure, which was earlier successfully adapted by Takacs and co-workers for the synthesis of (*E*,*E*)-α,β,γ,δ unsaturated esters.[4d] From this LiOH-promoted HWE reaction of **3** with both α,β-unsaturated aldehydes, that is, hexadienal and substituted hexatrienal, only starting materials were isolated.

Our investigations revealed that among the possible pathways shown in Scheme 2, the addition of lithiated phosphonate **3** to aldehydes took place exclusively at the α-C and δ-C with respect to phosphorus. Such unusual regiochemistry results from the involvement of two allylic carbanions: **4a**, stabilized by the phosphonate moiety and **4b** stabilized by the carboethoxy group. The formation of carbanion **4a** after removal of the α-proton to phosphorus is kinetically determined. Subsequent reversible reaction of carbanion **4a** with the aldehyde proceeding under kinetic conditions gave the intermediate α-adduct **5**, which collapses to diene **6** and phosphate anion or transposes to 2-hydroxyphosphonate **7** after being quenched with a proton source.

The equilibration of carbanion **4a** to **4b** occurs by a protonation–deprotonation sequence yielding **4b** as the more thermodynamically stable isomer. It is a dominant process at elevated temperature leading exclusively to the δ-substituted conjugated derivatives **11**. The δ-regioselectivity of the reaction with aldehydes containing a bulky substituent could be influenced by steric factors. A similar result was achieved when the phosphonate carbanion was treated with iodomethane to give the product of δ-alkylation's (**2b**) (Experimental).

3. Conclusion

To summarize, we have shown that the course of the reaction of aldehydes with the cyclic allylic phosphonate carbanion, activated in the β-position by a carboethoxy group, depends on the structure of the aldehyde as well as on the reaction conditions. We have established that these conversions are regioselective giving the products via a α- or δ-addition reaction. The unusual δ regioselectivity of some reactions was caused by the presence of the carboethoxy functionality that is responsible for the formation of the appropriate allylic carbanion after removal of the acidic δ hydrogen atom. We have defined the proper HWE reaction conditions to obtain the corresponding substituted polyene (**6g**), an analogue of retinol metabolites.

4. Experimental

4.1. General

^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker AC 200 Spectrometer at 200.13, 50.32 and 81.02 MHz, respectively (using $CDCl_3$ as solvent) unless otherwise noted. When necessary, homonuclear $^{1}H-^{1}H$ correlation (COSY) and heteronuclear $^{1}H-^{13}C$ correlation (HMQC) spectra were obtained for structural assignments. Carbon multiplicities were assigned by DEPT experiments. IR spectra were measured on an Ati Mattson Infinity FT IR 60. GC spectra were performed on a Hewlett–Packard 5890. MS spectra (EI, CI, and HRMS) were recorded on a Finnigan MAT 95 spectrometer. All the reactions were carried out using anhydrous conditions and in an atmosphere of argon. Chromatographic purification was performed on silica gel columns (Merck, Kieselgel 70–230 mesh) with indicated eluent. Chemicals and solvents were obtained from commercial sources and distilled or dried according to standard methods. 2*E*,4*E*,6*E*-2,6-Dimethyl-7-ethoxycarbonyl-2,4,6-heptatrienal[24], and phosphonate **3**[9] were prepared as described.

4.2. Metalations of phosphonate 3

In general, lithiations of phosphonate **3** with lithium diisopropylamide was carried out according to procedure A and C; with butyllithium according to procedure B. Metalation using sodium hydride was performed according to procedure D. The typical procedure A or C, was used in the sets of experiments and represented reactions on scale of 0.25–1 mmol of phosphonate **3**. Variations of these procedures are given with the data of the individual product and in Tables 1 and 2.

*4.2.1. Ethyl 6-deutero-6-(dimethoxyphosphoryl)cyclohex-1-enecarboxylate (**3-d$_1$**).* To a stirred solution of diisopropylamine (30 mg, 0.3 mmol) in THF (1.5 mL) at −78 °C was added butyllithium (0.12 mL, 0.3 mmol, 2.5 M solution in hexane). The mixture was allowed to warm to −20 °C for 30 min, after which was cooled to −78 °C and phosphonate **3** (63 mg, 0.25 mmol) in THF (2 mL) was added dropwise. The light brown solution was stirred at −78 °C for 1 h and quenched by the addition of concentrated D_2SO_4 (25 μL, 0.5 mmol). The resulting colorless mixture was allowed to warm to room temperature, diluted with CH_2Cl_2 (5 mL), washed with water (5 mL), extracted with CH_2Cl_2 (2×3 mL), and dried ($MgSO_4$). The solvent was evaporated in vacuo to give the crude mixture (36 mg). δ_P (81 MHz, $CDCl_3$) 32.5 (10%), 31.8 (7%), 31.5 (83%). Purification of the crude product by preparative chromatography (50% hexane/EtOAc) gave the *title compound* **3-d$_1$** (30 mg, 45%) as yellowish oil; R_f (45% hexane/EtOAc) 0.2; δ_P (81 MHz, $CDCl_3$) 31.5; δ_H (200 MHz $CDCl_3$) 7.03 (1H, t, *J* 3.4 Hz, C=C*H*), 4.20 (2H, q, *J* 7.1 Hz, OC*H*$_2$CH$_3$), 3.71 (3H, t, *J* 10.6 Hz, OC*H*$_3$) 3.70 (3H, t, *J* 10.6 Hz, OC*H*$_3$), 2.30–1.79 (4H, m, C*H*$_2$), 1.72–1.52 (2H, m, C*H*$_2$), 1.28 (3H, t, *J* 7.1 Hz, OCH$_2$C*H*$_3$); δ_D (500 MHz, $CDCl_3$) 3.32 (1D, br s, C(D)-P(O)(OMe)$_2$); *m*/*z* (CI, isobutane) 264 (100, MH^+), 218 (16%).

4.3. Reactions of phosphonate 3 with aldehydes

Procedure A. A solution of phosphonate **3** (262 mg, 1.0 mmol) in THF (3 mL) was added dropwise at −78 °C to THF solution of LDA (1.25 mmol) [freshly prepared from diisopropylamine (0.175 mL, 1.25 mmol) and BuLi (0.78 mL, 1.6 M solution in hexane, 1.25 mmol) in THF (5 mL) at the −20 °C for 30 min]. The mixture was stirred at −78 °C for 1 h before addition of relevant aldehyde (1.0 mmol, freshly distilled) in THF (2 mL). After 2 h, the reaction mixture was allowed to warm to room temperature, stirred for further 10 h and quenched by the addition of saturated aqueous ammonium chloride solution (5 mL), extracted with $CHCl_3$ (3×5 mL), and dried ($MgSO_4$). The solvent was evaporated in vacuo and residue was purified by flash chromatography on silica gel using gradient of EtOAc/petroleum ether as eluent to give the compounds characterized below.

*4.3.1. (Z/E)-Ethyl 6-ethylidenecyclohex-1-enecarboxylate (**6a**).* Color less oil; 73 mg, 41%; R_f (45% EtOAc/hexane) 0.52; ν_{max} (film) 3030, 2920, 2860, 2845, 1710, 1640, 900, 730 cm^{-1}; δ_H (200 MHz, $CDCl_3$) two isomers *E* and *Z* (3:1) 6.90 (1H, dd, *J* 4.1, 4.1 Hz, C=C*H*, *Z*), 6.51 (1H, t, *J* 3.8 Hz, C=C*H*, *E*), 5.95 (1H, q, *J* 9.3 Hz, CH$_3$C*H*=, *E*), 5.36 (1H, q, *J* 9.1 Hz, CH$_3$C*H*=, *Z*), 4.20 (4H, q, *J* 7.1 Hz, OC*H*$_2$CH$_3$), 2.64–2.53 (3H, m, C*H*$_2$), 2.41–2.24 (5H, m, C*H*$_2$), 2.18–1.87 (5H, m, C*H*$_2$, C*H*$_3$CH=, *Z*), 1.64 (3H, d, *J* 9.3 Hz, C*H*$_3$CH=, *E*), 1.59–1.52 (2H, m, C*H*$_2$), 1.31 (6H, br t, *J* 7.1 Hz, OCH$_2$C*H*$_3$); δ_C (50 MHz, $CDCl_3$) 169.0, 166.1, 145.2, 137.8, 132.3, 128.2, 124.9, 122.3, 61.2, 31.5, 28.1, 27.7, 27.1, 24.2, 22.5, 14.8, 14.1, 13.6; *m*/*z* (EI) 180 (25, M^+), 165 (62), 119 (100%); HRMS (EI): M^+, found: 180.1153. $C_{11}H_{16}O_2$ requires 180.1150.

*4.3.2. (Z/E)-Ethyl 6-propylidenecyclohex-1-enecarboxylate (**6b**).* Col orless oil; 87 mg, 45%; R_f (45% EtOAc/hexane) 0.65; ν_{max} (film) 3009, 2890, 2860, 1715, 1646, 1008, 920 cm^{-1}; δ_H (200 MHz, $CDCl_3$) two isomers *E* and *Z* (2:1) 7.05 (1H, t, *J* 4.0 Hz, *H*C=CCOOEt, *Z*), 6.88 (1H, t, *J* 4.7 Hz, *H*C=CCOOEt, *E*), 6.32 (1H, br d, *J* 9.9 Hz, C=C*H*Et, *E*), 5.85 (1H, dt, *J* 2.2, 9.1 Hz, C=C*H*Et, *Z*), 4.17 (2H, q, *J* 7.2 Hz, OC*H*$_2$CH$_3$), 4.14 (2H, q, *J* 7.3 Hz, OC*H*$_2$CH$_3$), 2.25–2.15 (4H, m, CH$_2$), 2.12–2.02 (4H, m, CH$_2$), 1.46 (2H, d, *J* 7.5 Hz, CH$_2$), 1.42 (4H, dd, *J* 7.4, 2.2 Hz, CH$_2$), 1.40–1.33 (2H, m, CH$_2$), 1.25 (3H, t, *J* 7.2 Hz, OCH$_2$C*H*$_3$), 1.14 (3H, t, *J* 7.3 Hz, OCH$_2$C*H*$_3$), 0.97 (3H, t, *J* 7.5 Hz, =CHCH$_2$C*H*$_3$, *E*), 0.95 (3H, t, *J*

7.6 Hz, =CHCH$_2$C*H*$_3$, *Z*); δ_C (50 MHz, $CDCl_3$) 168.8, 165.3, 150.4, 146.2, 141.3, 137.8, 134.3, 131.5, 128.2, 122.3, 60.6, 32.3, 25.9, 25.2, 24.6, 22.5, 21.7, 19.4, 14.5, 13.3, 12.8; *m*/*z* (EI) 194 (33, M^+), 179 (55), 165 (30), 109 (100%); HRMS (EI): M^+, found: 194.1311. $C_{12}H_{18}O_2$ requires 194.1307.

*4.3.3. Ethyl 6-((2E,4E)-hexa-2,4-dienylidene)cyclohex-1-enecarboxylate (**6d**).* Yellow oil; 69 mg, 30%; R_f (40% hexane/EtOAc) 0.59; ν_{max} (film) 2930, 2857, 1737, 1687, 1642, 1449, 1315, 1139 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 6.96 (1H, br d, *J* 14.3 Hz, =CH), 6.37–5.93 (2H, m, =CH), 5.83–5.62 (1H, m, =CH), 5.53–5.48 (1H, m, =CH.), 5.34 (1H, br t, *J* 5.5 Hz, =CH), 4.22 (2H, q, *J* 7.2 Hz, OC*H*$_2$CH$_3$), 2.48–2.14 (4H, m, CH$_2$), 1.78–1.64 (5H, m, CH$_2$, CH$_3$), 1.29 (3H, t, *J* 7.2 Hz, OCH$_2$C*H*$_3$); δ_C (50 MHz, $CDCl_3$) 166.8, 147.6, 144.7, 141.3, 139.4, 137.3, 134.3, 132.4, 128.3, 61.1, 28.6, 26.5, 24.9, 19.3, 14.1; *m*/*z* (CI, isobutane) 233 (20, MH^+), 147 (100), 129 (10%).

*4.3.4. Ethyl 6-(dimethoxyphosphoryl)-6-(1-hydroxybut-3-enyl)cyclohex-1-enecarboxylate (**7c**).* Colorless oil; 110 mg, 35%; R_f (42% EtOAc/hexane) 0.3; ν_{max} (film) 3380, 2951, 2860, 1702, 1430, 1215, 1118, 1060, 870 cm^{-1}; δ_P (81 MHz, $CDCl_3$) 31.9, 30.1 two diastereoisomers (1:1); δ_H (200 MHz, $CDCl_3$) 7.04 (1H, t, *J* 3.6 Hz, C=C*H*CH$_2$), 6.78–6.54 (3H, m, CH=C*H*$_2$, C*H*=CH$_2$, C=C*H*CH$_2$), 6.42 (1H, d, *J* 17.2 Hz, CH=C*H*$_2$), 6.12 (1H, dd, *J* 10.3, 17.2 Hz, C*H*=CH$_2$), 5.83 (2H, d, *J* 10.3 Hz, CH=C*H*$_2$), 4.34–4.17 (6H, m, OC*H*$_2$Me, C*H*OH), 3.77 (6H, d, *J* 10.8 Hz, OMe), 3.74 (6H, d, *J* 10.8 Hz, OMe), 2.38–2.17 (6H, m, CH$_2$), 2.09–1.93 (2H, br s, CH$_2$), 1.88–1.68 (4H, m, CH$_2$), 1.30 (6H, t, *J* 7.0 Hz, OCH$_2$C*H*$_3$); δ_C (50 MHz, $CDCl_3$) 166.7, 165.3, 141.2, 136.4, 136.3, 128.5, 128.3, 115.5, 114.3, 75.5, 74.2, 60.7, 52.8, 52.6, 46.8 (d, *J* 133.6 Hz) 45.3 (d, *J* 131.2 Hz), 24.9, 23.2, 22.9, 20.1, 17.2, 13.6; *m*/*z* (CI, isobutane) 319 (10, MH^+), 303 (20), 279 (30), 263 (100%).

*4.3.5. Ethyl 6-(dimethoxyphosphoryl)-3-(hydroxy(phenyl)methyl)-cyclohex-1-enecarboxylate (**11e**) [two diastereoisomers (2:1)].* Major isomer separated from the crude mixture by flash chromatography (10% hexane/EtOAc) (170 mg, 46%) as a yellow oil; R_f (50% hexane/EtOAc) 0.19; ν_{max} (film) 3425, 2962, 2871, 1712, 1611, 1606, 1453, 1365, 1261, 1099, 1083, 866, 799; δ_P (81 MHz, $CDCl_3$) 31.4; δ_H (500 MHz, $CDCl_3$) 7.41–7.28 (5H, m, Ph), 7.13 (1H, d, *J* 3.4, Hz, C=CH), 4.71 (1H, d, *J* 5.4 Hz, *H*C(OH)Ph), 4.23 (2H, q, *J* 7.1 Hz, OC*H*$_2$CH$_3$), 3.69 (3H, d, *J* 10.8 Hz, OMe), 3.68 (3H, d, *J* 10.8 Hz, OMe), 3.32 (1H, dd, *J* 24.0, 5.2 Hz, HCP), 2.72 (1H, br s, C*H*CH(OH)Ph), 2.22–2.15 (1H, m, CH$_a$*H*$_b$CH$_2$CHCH=), 2.02 (1H, q, *J* 4.4 Hz, CH$_2$CH$_a$*H*$_b$CHCH=), 1.73–1.67 (1H, m, CH$_a$*H*$_b$CH$_2$CHCH=), 1.64–1.53 (1H, m, CH$_2$CH$_a$*H*$_b$CHCH=), 1.29 (3H, t, *J* 7.1 Hz, OCH$_2$C*H*$_3$); δ_C (125 MHz, $CDCl_3$) 163.9 (*C*OOEt), 142.8 (C-*ipso*-Ar), 144.4 (C=*C*H), 128.0 (Ar), 127.3 (*C*=CH), 126.9 (Ar), 125.7 (Ar), 75.1 (*C*HOH), 60.5 (OC*H*$_2$CH$_3$), 53.2, 53.0 (d, *J* 7.8 Hz, POMe), 43.1 (*C*HCH(OH)), 31.3 (d, *J* 137.6 Hz, CHP), 23.2 (PCH*C*H$_2$), 18.4 (*C*H$_2$CHCH=), 14.1 (OCH$_2$*C*H$_3$); *m*/*z* (CI, isobutane) 369 (100, MH^+), 351 (76), 305 (8), 262 (10%); HRMS (CI, isobutane): MH^+, found: 369.1470. $C_{18}H_{26}O_6P$ requires 369.1467.

Minor isomer separated from the crude mixture by flash chromatography (10% hexane/EtOAc) (92 mg, 25%) as a yellow oil; R_f (50% hexane/EtOAc) 0.17; ν_{max} (film) 3418, 2925, 2851, 1712, 1598, 1560, 1445, 1366, 1259, 1137, 1092, 1075, 966, 697 cm^{-1}; δ_P (81 MHz, $CDCl_3$) 31.6; δ_H (500 MHz, $CDCl_3$) 7.41–7.28 (5H, m, Ph), 7.19 (1H, d, *J* 3.6 Hz, =CH), 5.04 (1H, d, *J* 3.9 Hz, *H*C(OH)Ph), 4.22 (2H, q, *J* 7.1 Hz, OC*H*$_2$CH$_3$), 3.77 (3H, d, *J* 10.8 Hz, OMe), 3.70 (3H, d, *J* 10.8 Hz, OMe), 3.32 (1H, dd, *J* 24.0, 5.1 Hz, HCP), 2.90 (1H, br s, C*H*CH(OH)Ph), 2.23–2.17 (1H, m, CH$_a$*H*$_b$CH$_2$CHCH=), 2.04 (1H, t, *J* 10.0 Hz, CH$_2$CH$_a$*H*$_b$CHCH=), 1.73–1.67 (1H, m, CH$_a$*H*$_b$CH$_2$CHCH=), 1.46–1.41 (1H, m, CH$_2$CH$_a$*H*$_b$CHCH=), 1.29 (3H, t, *J* 7.1 Hz, OCH$_2$C*H*$_3$); δ_C (125 MHz, $CDCl_3$) 164.8 (*C*OOEt), 143.7 (C=*C*H), 141.9 (*ipso*-Ar), 128.0 (Ar), 127.8 (Ar), 127.3 (*C*=CH), 126.5 (Ar), 125.2 (Ar), 124.9 (Ar), 74.1 (*C*HOH), 59.6 (OCH$_2$CH$_3$), 52.3, 51.8 (d, *J* 7.8 Hz, POMe), 42.7 (*C*HCH(OH)), 30.3 (d, *J* 132.0 Hz, CHP), 22.4 (PCH*C*H$_2$), 17.4 (*C*H$_2$CHCH=), 13.2 (OCH$_2$*C*H$_3$); *m*/*z* (CI, isobutane) 369 (100, MH^+), 351 (60), 262 (8), 155 (18%).

*4.3.5.1. Reaction of **11e** with butyllithium.* Butyllithium (0.17 mL of 1.6 M solution in hexane, 0.27 mmol) was added to a stirred solution of the compound **11e** (two diastereoisomers 1:1, 60 mg, 0.16 mmol) in THF (4 mL) at −78 °C. The mixture was allowed to warm to room temperature, stirred for 10 h and quenched by the addition of saturated aqueous ammonium chloride solution (3 mL), extracted with $CHCl_3$ (3×3 mL), and dried ($MgSO_4$). The solvent was evaporated in vacuo to give the crude product (37 mg); *m*/*z* (CI, isobutane) 387 (34), 369 (30, MH^+), 285 (56), 263 (82), 155 (100%).

*4.3.6. Ethyl 6-(dimethoxyphosphoryl)-6-(1-hydroxyethyl)cyclohex-1-enecarboxylate (**7a**). Procedure* A. To THF solution of LDA (0.18 mmol) [freshly prepared from diisopropylamine (0.025 mL, 0.18 mmol) and BuLi (0.078 mL, 2.3 M solution in hexane, 0.18 mmol) in THF (1.5 mL) at the −20 °C for 30 min] at −78 °C was added dropwise a solution of phosphonate **3** (44 mg, 0.17 mmol) in THF (1 mL). The mixture was stirred at −78 °C for 1 h before addition of acetaldehyde (9.5 μL, 0.17 mmol, freshly distilled) in THF (0.5 mL). After 2 h, the reaction mixture was allowed to warm to 0 °C, and quenched by the addition of water (1 mL), extracted with $CHCl_3$ (2×2.5 mL), and dried ($MgSO_4$). The solvent was evaporated in vacuo to give the crude product. Purification by preparative chromatography (50% EtOAc/petroleum ether) gave the *title compound* **7a** (24 mg, 46%) as a colorless oil; R_f (50% hexane/EtOAc) 0.07; ν_{max} (film) 3015, 2929, 2850, 2845, 1708, 1640, 1290, 1285, 1109, 770 cm^{-1}; δ_P (81 MHz, $CDCl_3$) 31.2, 30.6 two diastereoisomers (2:1); δ_H (200 MHz, $CDCl_3$) 7.03 (2H, br q, *J* 4.1 Hz, C=C*H*), 4.24 (2H, q, *J* 7.0 Hz, OC*H*$_2$CH$_3$), 4.23 (2H, q, *J* 7.0 Hz, OC*H*$_2$CH$_3$), 4.17 (1H, br q, *J* 4.4 Hz, C*H*OH), 4.00 (1H, m, C*H*OH), 3.88 (6H, d, *J* 10.6 Hz, OMe), 3.76 (6H, d, *J* 10.7 Hz, OMe), 2.61–2.45 (3H, m, CH$_2$), 2.41–2.20 (4H, m, CH$_2$), 2.11–2.00 (3H, m, CH$_2$), 1.81–1.58 (2H, m, CH$_2$), 1.37 (3H, d, *J* 5.5 Hz, *Me*CHOH), 1.30 (6H, t, *J* 7.0 Hz, OCH$_2$C*H*$_3$), 1.14 (3H, d, *J* 4.4 Hz, *Me*CHOH); δ_C (50 MHz, $CDCl_3$) 167.3, 166.8, 135.5, 133.7, 123.5, 120.8, 71.1, 70.5 (d, *J* 8.6 Hz), 53.0, 62.3, 52.8, 52.5, 43.2 (d, *J* 134.6 Hz), 40.8 (d, *J* 133.2 Hz), 29.4, 25.2, 22.2, 18.9, 14.2, 13.4; *m*/*z* (CI, isobutane) 307 (100, MH^+), 292 (20), 279 (40), 263 (20%); HRMS (EI): M^+, found: 306.1233. $C_{12}H_{18}O_2$ requires 306.1232.

*4.3.7. Ethyl 6-(dimethoxyphosphoryl)-3-(1-hydroxy-2-methylpropyl)cyclohex-1-enecarboxylate (**11f**). Procedure* A. Yellow oil; 153 mg, 46%; R_f (40% hexane/EtOAc) 0.17; ν_{max} (film) 2959, 2924, 2851, 1718, 1463, 1260, 1156, 1074, 801 cm^{-1}; δ_P (81 MHz, $CDCl_3$) 31.5, 31.2 two diastereoisomers (1.3:1); δ_H (500 MHz, $CDCl_3$) 7.04 (1H, br s, =CH), 6.88–6.85 (1H, m, =CH), 4.23 (2×2H, q, *J* 7.1 Hz, OC*H*$_2$CH$_3$), 4.09 (1H, m, CHC*H*OH), 3.79 (1H, br s, CHC*H*OH), 3.75 (6H, d, *J* 10.7 Hz, OMe), 3.69 (6H, d, *J* 10.7 Hz, OMe), 3.48 (1H, br d, *J* 21.2, HCP), 3.33 (1H, br d, *J* 21.2 Hz, HCP), 2.96–2.52 (4H, m, Me$_2$C*H*, CH$_2$), 2.46 (1H, t, *J* 6.5 Hz, CH$_2$C*H*CHOH), 2.26–2.01 (3H, m, CH$_2$, CH$_2$C*H*CHOH), 1.82–1.38 (4H, m, CH$_2$), 1.30 (3H, t, *J* 7.1 Hz, OCH$_2$C*H*$_3$), 1.20 (3H, t, *J* 7.1 Hz, OCH$_2$C*H*$_3$), 0.97 (3H, d, *J* 7.1 Hz, *Me*CH), 0.93 (3H, d, *J* 6.8 Hz, *Me*CH), 0.92 (3H, d, *J* 7.1 Hz, *Me*CH), 0.87 (3H, d, *J* 6.8 Hz, *Me*CH); δ_C (50 MHz, $CDCl_3$) 165.0, 164.1, 145.3, 142.2, 128.5, 128.3, 127.3, 80.0, 78.8, 60.7, 53.8, 53.6, 32.3 (d, *J* 137.0 Hz), 30.8 (d, *J* 132.0 Hz), 30.3, 29.9, 24.9, 23.2, 21.9, 21.5, 20.1, 19.4, 16.6; *m*/*z* (EI) 334 (18, M^+), 263 (100%); HRMS (CI, isobutane): MH^+, found: 335.1550. $C_{15}H_{29}O_6P$ requires 335.1545.

Procedure B. A BuLi (0.26 mL of 1.6 M solution in hexane, 0.42 mmol) was added to a stirred solution of the phosphonate **3** (72 mg, 0.27 mmol) in THF (4 mL) at −78 °C. The mixture was stirred at −78 °C for 1 h before addition of 2-methylpropanal (20 mg,

0.27 mmol, freshly distilled) in THF (1 mL). After 2 h, the reaction mixture was allowed to warm to room temperature, stirred for further 10 h, and quenched by the addition of saturated aqueous ammonium chloride solution (3 mL), extracted with $CHCl_3$ (3×3 mL), and dried ($MgSO_4$). The solvent was evaporated in vacuo to give the crude product, which was purified by flash chromatography (20% petroleum ether/EtOAc) to give *the title compound* **11f** (37 mg, 41%) as a yellow oil; R_f (50% hexane/EtOAc) 0.09; δ_P (81 MHz, $CDCl_3$) 32.0, 31.2 two isomers (1:1); δ_H (200 MHz, $CDCl_3$) 7.10–6.70 (2H, m, =C*H*), 4.21 (4H, q, *J* 7.1 Hz, O*CH*$_2$CH$_3$), 4.30–4.10 (2H, m, CHC*H*OH), 3.80 (6H, d, *J* 10.1 Hz, OMe), 3.70 (6H, d, *J* 10.1 Hz, OMe), 3.42–3.38 (2H, m, HCP), 2.70–2.60 (3H, m, C*H*CHOH, Me$_2$C*H*), 2.50–2.20 (4H, m, C*H*$_2$, C*H*CHOH), 1.90–1.30 (5H, m, CH$_2$), 1.24 (6H, t, *J* 7.1 Hz, OCH$_2$C*H*$_3$), 0.93 (3H, d, *J* 7.1 Hz, *Me*CH), 0.91 (3H, d, *J* 6.3 Hz, *Me*CH), 0.88 (3H, d, *J* 6.3 Hz, *Me*CH), 0.87 (3H, d, *J* 7.1 Hz, *Me*CH); *m*/*z* (CI, isobutane) 335 (8, M^+), 275 (15), 263 (100%).

4.4. Reaction of phosphonate 3 with aldehydes

Procedure C. A solution of phosphonate **3** (65 mg, 0.25 mmol) in THF (1 mL) was added dropwise at −78 °C to THF solution of LDA (0.3 mmol) [freshly prepared from diisopropylamine (0.042 mL, 0.3 mmol) and BuLi (0.13 mL, 2.3 M solution in hexane, 0.3 mmol) in THF (2 mL) at the −20 °C for 30 min]. The mixture was stirred at −78 °C for 1 h before addition of relevant aldehyde (0.25 mmol, freshly distilled) in THF (1 mL). After 10 h of the stirring at −78 °C, the reaction mixture was allowed to warm to room temperature, stirred for further 10 h, and quenched by the addition of saturated aqueous ammonium chloride solution (2 mL), extracted with $CHCl_3$ (3×2 mL), and dried ($MgSO_4$). The solvent was evaporated in vacuo. The crude mixture was chromatographed (silica gel, hexane/EtOAc) to give following products.

*4.4.1. (Z/E)-Ethyl 6-(2-methylpropylidene)cyclohex-1-enecarboxylate (**6f**).* Yellow oil; 2.6 mg, 5%; R_f (50% hexane/EtOAc) 0.76; δ_H (200 MHz, $CDCl_3$) 7.09 (1H, t, *J* 6.6 Hz, =C*H*COOEt), 5.89 (1H, d, *J* 6.6 Hz, =C*H*CHMe$_2$), 4.22 (2H, q, *J* 7.2 Hz, O*CH*$_2$CH$_3$), 2.58 (1H, septet, *J* 6.6 Hz, Me$_2$C*H*), 2.28–2.23 (2H, m, CH$_2$), 2.02 (2H, dd, *J* 3.0, 3.9 Hz, CH$_2$), 1.40 (2H, m, CH$_2$), 1.34 (3H, t, *J* 7.2 Hz, OCH$_2$C*H*$_3$), 0.93 (6H, d, *J* 6.6 Hz, *Me*CH); *m*/*z* (CI, isobutane) 209 (4, MH^+) 208 (10), 206 (25), 205 (100), 183 (30), 159 (45%) [GC–MS; column: DB-1, 30 m, 50 (3)-10/min–250 (10), mass peak: retention time 16′32″, relative abundance: 50%].

*4.4.2. Ethyl 6-(dimethoxyphosphoryl)-6-(1-hydroxypropyl)cyclohex-1-enecarboxylate (**7b**).* A solution of phosphonate **3** (42 mg, 0.16 mmol) in THF (1 mL) was added dropwise at −78 °C to THF solution of LDA (0.2 mmol) [freshly prepared from diisopropylamine (0.028 mL, 0.2 mmol) and BuLi (0.09 mL, 2.3 M solution in hexane, 0.2 mmol) in THF (1 mL) at the −20 °C for 30 min]. The mixture was stirred at −78 °C for 1 h before addition of propionaldehyde (10 mg, 0.17 mmol, freshly distilled) in THF (0.3 mL). After 4 h the reaction mixture was allowed to warm to room temperature, stirred for further 4 h and quenched by the addition of water (1 mL), extracted with Et_2O (3×1 mL), and dried ($MgSO_4$). The solvent was evaporated in vacuo to give the crude product, which was purified by preparative chromatography (40% petroleum ether/EtOAc) to give *the titled compound* **7b** as colorless oil (28 mg, 54%); R_f (50% hexane/EtOAc) 0.08; ν_{max} 3315, 2940, 2755, 1706, 1648, 1257, 1118, 1080, 945 cm^{-1}; δ_P (81 MHz, $CDCl_3$) 31.5; δ_H (200 MHz, $CDCl_3$) 7.05 (1H, t, *J* 3.1 Hz, C=C*H*), 4.24 (2H, q, *J* 7.1 Hz, O*CH*$_2$CH$_3$), 4.17–3.91 (1H, m, C*H*OH), 3.76 (3H, d, *J* 10.7 Hz, OMe), 3.73 (3H, d, *J* 10.7 Hz, OMe), 2.54–2.02 (4H. m, CH$_2$), 1.80–1.38 (4H, m, CH$_2$, CH$_3$C*H*$_2$CH=), 1.32 (3H, t, *J* 7.1 Hz, OCH$_2$C*H*$_3$), 1.12 (3H, t, *J* 7.2 Hz, C*H*$_3$CH$_2$CH); δ_C (50 MHz, $CDCl_3$) 167.1, 134.1, 121.8, 72.1 (d, *J* 9.0 Hz), 62.4, 53.0, 51.8, 42.8 (d, *J* 133.4 Hz), 27.8, 24.5, 22.8, 18.9, 13.8, 12.1; *m*/*z* (CI, isobutane) 321 (18, MH^+), 291 (100), 279 (60), 275 (95), 205 (32%); HRMS (EI): M^+, found: 320.1389. $C_{14}H_{25}O_6P$ requires 320.1390.

*4.4.3. Ethyl 6-(dimethoxyphosphoryl)-3-((2E,4E)-1-hydroxyhexa-2,4-dienyl)cyclohex-1-enecarboxylate (**11d**).* A solution of phosphonate **3** (112 mg, 0.43 mmol) in THF (4 mL) was added dropwise at −78 °C to THF solution of LDA (0.54 mmol) [freshly prepared from diisopropylamine (0.075 mL, 0.54 mmol) and BuLi (0.23 mL, 2.3 M solution in hexane, 0.54 mmol) in THF (4 mL) at the −20 °C for 30 min]. The mixture was stirred at −78 °C for 1 h before addition of 2,4-hexadienal (40 mg, 0.41 mmol, freshly distilled) in THF (2 mL). After 4 h the reaction mixture was allowed to warm to room temperature, stirred for further 14 h and quenched by the addition of water (3 mL), extracted with $CHCl_3$ (3×5 mL), and dried ($MgSO_4$). The solvent was evaporated in vacuo and crude mixture was chromatographed (silica gel, 50% petroleum ether/EtOAc, EtOAc) to give products: **6d** (33 mg, 35%) as yellowish oil; R_f (40% hexane/EtOAc) 0.59, and *the titled compound* **11d** (44 mg, 30%) as yellow oil; R_f (40% hexane/EtOAc) 0.07; ν_{max} (film) 3409, 2957, 2871, 1714, 1678, 1646, 1450, 1252, 1186, 1054 cm^{-1}; δ_P (81 MHz $CDCl_3$) 30.6, 30.9, (two diastereoisomers, 1.2:1); δ_H (500 MHz, $CDCl_3$) 7.05 (1H, d, *J* 3.8 Hz, C*H*CCOOEt,), 7.02 (1H, dd, *J* 4.2, 4.2 Hz, C*H*CCOOEt), 6.30 (2H, dd, *J* 10.0, 15.1 Hz, MeCH=CHC*H*=), 6.04 (2H, br t, *J* 10.0 Hz, MeCH=C*H*CH=), 5.79–5.65 (3H, m, 2×MeC*H*=CH, MeCH=CHCH=C*H*), 5.54 (1H, dd, *J* 6.3, 15.1 Hz, MeCH=CHCH=C*H*), 4.36 (1H, t, *J* 6.3 Hz, C*H*OH), 4.21 (4H, q, *J* 7.1 Hz, O*CH*$_2$CH$_3$), 4.13 (1H, t, *J* 7.1 Hz, C*H*OH), 3.78 (3H, d, *J* 10.8 Hz, OMe), 3.76 (3H, d, *J* 11.1 Hz, OMe), 3.74 (3H, d, *J* 10.8 Hz, OMe), 3.71 (3H, d, *J* 11.1 Hz, OMe), 3.32 (2H, br d, *J* 20.1 Hz, HCP), 2.62–2.48 (1H, m, C*H*CHOH), 2.38–2.18 (5H, m, CHC*H*$_2$CH$_2$, PCHC*H*$_2$CH$_2$, C*H*CHOH), 2.09–1.85 (2H, m, CHC*H*$_a$H$_b$CH$_2$, PCHC*H*$_a$H$_b$CH$_2$), 1.74 (2×3H, d, *J* 6.2 Hz, *Me*CH=), 1.80–1.50 (2H, m, PCHCH$_a$*H*$_b$CH$_2$, CHCH$_a$*H*$_b$CH$_2$), 1.29 (6H, t, *J* 7.1 Hz, OCH$_2$C*H*$_3$); δ_C (50 MHz, $CDCl_3$) 168.2, 143.0 (d, *J* 15.9 Hz), 141.9 (d, *J* 11.3 Hz), 139.4, 137.6, 137.3, 133.4, 132.9, 132.2, 124.2, 78.7, 78.1, 61.2, 61.0, 52.8 (d, *J* 7.0 Hz), 52.9 (d, *J* 7.0 Hz), 46.4, 45.7, 34.0 (d, *J* 133.5 Hz), 31.6 (d, *J* 138.3 Hz), 22.6, 17.9, 17.2, 14.0, 13.6; *m*/*z* (CI, isobutane) 359 (10, MH^+), 341 (100%).

*4.4.4. Ethyl 6-(dimethoxyphosphoryl)-3-((2E,4E)-hexa-2,4-dienylidene) cyclohex-1-enecarboxylate (**14**).* Yellow oil; 27 mg, 20%; R_f (40% hexane/EtOAc) 0.09; ν_{max} (film) 2952, 2791, 1722, 1688, 1642, 1480, 1371, 1242, 1186, 1045 cm^{-1}; δ_P (81 MHz, $CDCl_3$) 28.6; δ_H (200 MHz, $CDCl_3$) 6.74 (1H, s, CH), 6.29 (1H, dd, *J* 10.6, 15.1 Hz, CH), 6.07–6.00 (1H, m, CH), 5.98–5.68 (2H, m, CH), 5.55 (1H, dd, *J* 15.1, 6.0 Hz, C*H*Me), 4.21 (2H, q, *J* 7.1 Hz, O*CH*$_2$CH$_3$), 3.77 (3H, d, *J* 10.8 Hz, OMe), 3.73 (3H, d, *J* 10.8 Hz, OMe), 3.36 (1H, dd, *J* 4.5, 25.3 Hz, HCP), 2.88–2.78 (1H, br s, CH$_2$), 2.58–2.51 (1H, m, CH$_2$), 2.09–1.85 (1H, m, CH$_2$), 1.74 (3H, d, *J* 6.0 Hz, C*H*$_3$CH), 1.58–1.38 (1H, m, CH$_2$), 1.29 (3H, t, *J* 7.0 Hz, OCH$_2$C*H*$_3$); δ_C (51 MHz, $CDCl_3$) 166.8, 144.7, 141.9 (d, *J* 11.5 Hz), 136.4, 133.4, 132.9, 132.2, 128.3, 61.4, 52.8 (d, *J* 11.0 Hz), 52.5 (d, *J* 11.0 Hz), 38.5 (d, *J* 141.4 Hz), 29.7, 28.5, 24.9, 23.8, 14.2; *m*/*z* (CI, isobutane) 341 (100, MH^+), 679 (18%, 2×(M−H)); HRMS (CI, isobutane): MH^+, found: 341.1512. $C_{17}H_{26}O_5P$ requires 341.1518.

*4.4.5. (E)-ethyl 6-((2E,4E,6E)-8-ethoxy-2,6-dimethyl-8-oxoocta-2,4,6-trienylidene)cyclohex-1-enecarboxylate **(6g)**.* A solution of phosphonate **3** (61 mg, 0.23 mmol) in THF (4 mL) was added dropwise at −78 °C to THF solution of LDA (0.28 mmol) [freshly prepared from diisopropylamine (0.040 mL, 0.28 mmol) and BuLi (0.12 mL, 2.3 M solution in hexane, 0.28 mmol) in THF (4 mL) at the −20 °C for 30 min]. The mixture was stirred at −78 °C for 1 h before addition of (2,6-dimethyl-7-ethoxycarbonyl)-2,4,6-heptatrienal (42 mg, 0.2 mmol) in THF (2 mL). After 20 h at −78 °C the reaction mixture was allowed to warm to room temperature, stirred for further 20 h and quenched by the addition of water (3 mL), extracted with $CHCl_3$ (3×5 mL), and dried ($MgSO_4$). The solvent was evaporated in vacuo and crude mixture was chromatographed (silica gel, 10% EtOAc/

petroleum ether) to give *the titled compound* **6g** (53.6 mg, 78%) as a yellow semisolid; R_f (50% hexane/EtOAc) 0.66; ν_{max} (Nujol) 2956, 2910, 2788, 1728, 1638, 1448, 1280, 1191, 1032 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 6.90 (1H, dd, *J* 11.4, 15.0 Hz, CH=C*H*CH=), 6.64 (1H, t, *J* 3.9 Hz, *H*C=CCOOEt), 6.41 (1H, s, C=C*H*CMe), 6.25 (1H, d, *J* 15.0 Hz, =CMeC*H*=CH–CH), 6.13 (1H, d, *J* 11.4 Hz, *H*C=CMe), 5.77 (1H, s, C(Me)=C*H*COOEt), 4.25 (2H, q, *J* 7.1 Hz, OCH_2CH$_3$), 4.17 (2H, q, *J* 7.0 Hz, OCH_2CH$_3$), 2.60 (2H, t, *J* 5.6 Hz, HC=CCH_2), 2.34 (3H, s, C(*Me*)=CHCOOEt), 2.30–2.26 (2H, m, C=CHCH_2), 1.99 (3H, s, HC=C*Me*), 1.74–1.67 (2H, m, CH_2CH$_2$C=), 1.33 (3H, t, *J* 7.1 Hz, OCH$_2$CH_3), 1.28 (3H, t, *J* 7.0 Hz, OCH$_2$CH_3); δ_C (50 MHz, $CDCl_3$) 167.9, 167.2 (2×COOEt), 152.6, 138.6 (2×HC=*C*), 138.0, 135.3 (2×HC=C), 133.7, 132.3 (2×HC=*C*), 131.1, 130.7, 130.3, 118.8 (4×HC=C), 60.7, 59.7 (2×OCH$_2$CH$_3$), 27.5, 25.9, 22.1, (3×CH$_2$), 18.1, 13.8 (2×CH$_3$), 14.3, 14.2 (2×OCH$_2$CH$_3$); *m*/*z* (CI, isobutane) 345 (44, MH^+), 299 (100), 253 (40%); HRMS (CI, isobutane): MH^+, found: 345.2049. $C_{21}H_{29}O_4$ requires: 345.2065.

*4.4.6. (E/Z)-Ethyl 6-benzylidenecyclohex-1-enecarboxylate (**6e**).* To solution of carbanion **4a** (0.16 mmol) in THF (0.5 mL) [freshly prepared from phosphonate **3** (43 mg, 0.16 mmol) and LDA (0.24 mmol) at −78 °C and measured by ^{31}P NMR at −70 °C (subchapter 4.7.)] benzaldehyde (13 mg, 0.12 mmol) in THF (0.5 mL) was added at −78 °C via cannula, under argon atmosphere. After 12 h at −78 °C and 10 h at room temperature, the reaction mixture was quenched with water (0.5 mL), extracted with $CHCl_3$ (2×0.5 mL), dried ($MgSO_4$), and evaporated in vacuo to give crude product, which was purified by flash chromatography (30% EtOAc/hexane) to give **6e** (15 mg, 52%) as yellow semisolid; R_f (50% hexane/EtOAc) 0.6; δ_H (200 MHz, $CDCl_3$) two isomers *E* and *Z* (4:1), 7.36–7.29 (10H, m, Ph), 7.16 (1H, br s, C=C*H*, *Z*), 7.10 (1H, d, *J* 4.1 Hz, C=C*H*, *E*), 6.70 (1H, br s, *H*(Ph)C=C, *E*), 6.55 (1H, d, *J* 5.6 Hz, *H*(Ph)C=C, *Z*), 4.36 (2H, q, *J* 6.9 Hz, OCH_2CH$_3$, *E*), 4.22 (2H, q, *J* 6.8 Hz, OCH_2CH$_3$, *Z*), 2.98 (1H, br s, CH$_2$, *E*), 2.86 (1H, t, *J* 7.8 Hz, CH$_2$, *Z*), 2.83–2.73 (4H, m, CH$_2$, *E*, and *Z*), 2.54–2.31 (4H, m, CH$_2$, *E*, and *Z*), 2.26–1.82 (2H, m, CH$_2$, *Z*), 1.32 (3H, t, *J* 6.9 Hz, OCH$_2$CH_3, *E*), 1.22 (3H, t, *J* 6.9 Hz, OCH$_2$CH_3, *Z*); *m*/*z* (EI) 242 (14, M^+), 213 (74), 101 (100%).

4.5. Reaction of phosphonate 3 with benzaldehyde

*4.5.1. (E/Z)-Ethyl 6-benzylidenecyclohex-1-enecarboxylate (**6e**). Procedure* D. To a mixture of sodium hydride (14 mg, 0.57 mmol, 60% dispersion in oil, freshly washed with dry hexane) in THF (10 mL) at −10 °C was added a solution of phosphonate **3** (59 mg, 0.23 mmol) in THF (5 mL). The mixture was stirred at −5 °C to 0 °C for 1 h before addition of benzaldehyde (22 mg, 0.21 mmol, freshly distilled) at −40 °C. The mixture was stirred at −40 °C to −10 °C for 10 h and was allowed to warm to room temperature, stirred for further 12 h and quenched by the adsorption on silica gel (10 mL). Elution with hexane (100 mL), 50% hexane/EtOAc (150 mL) and evaporation of the solvent gave the brown oil. Purification of the crude product by preparative chromatography gave *the titled compound* **6e** (26 mg, 52%) as a yellow semisolid; R_f (50% hexane/EtOAc) 0.66; ν_{max} (Nujol) 2952, 2850, 1710, 1606, 1560, 1445, 1236, 1137, 1093, 732, 697 cm^{-1}; δ_H (500 MHz, $CDCl_3$) two isomers *E* and *Z* (5:1), 7.42–7.28 (10H, m, Ph), 7.23 (1H, br s, C*H*=CCOOEt, *E*), 7.20–7.18 (1H, m, C*H*=CCOOEt, *Z*), 6.68 (1H, br s, *H*(Ph)C=C, *E*), 6.58 (1H, br s, *H*(Ph)C=C, *Z*), 4.32 (2H, q, *J* 7.0 Hz, OCH_2CH$_3$, *E*), 4.28 (2H, q, *J* 7.1 Hz, OCH_2CH$_3$, *Z*), 2.95 (1H, m, CH_aH$_b$C=C, *E*), 2.84 (2H, dd, *J* 5.8, 6.8 Hz, =CHCH_2, Z), 2.73 (3H, br d, *J* 4.1 Hz, CH_2C=C, =CHCH_2, *E*), 2.55 (1H, t, *J* 6.5 Hz, CH_aH$_b$C=C, *Z*), 2.50 (1H, m, CH$_a$*H*$_b$C=C, *Z*), 1.86–1.56 (4H, m, CH$_2$CH_2CH$_2$, *E*, and *Z*) 1.39 (3H, t, *J* 7.0 Hz, OCH$_2$CH_3, *E*), 1.32 (3H, t, *J* 7.1 Hz, OCH$_2$CH_3, *Z*); δ_C (50 MHz, $CDCl_3$) 167.9, 167.1, 142.4, 139.8, 137.7, 136.7, 136.1, 133.7, 133.4, 129.3, 128.3, 128.1, 127.5, 127.3, 126.7, 126.6, 60.9, 60.8, 35.1, 31.6, 29.2, 27.2, 26.5, 26.3, 14.3, 14.2; *m*/*z* (CI, isobutane) 243 (44, MH^+), 227 (20), 91 (100%); HRMS (EI): M^+, found: 242.1302. $C_{16}H_{18}O_2$ requires 242.1307.

4.6. Ethyl 6-(dimethoxyphosphoryl)-3-methylcyclohex-1-enecarboxylate (2b)[9]

A solution of phosphonate **3** (38 mg, 0.14 mmol) in THF (2 mL) was added dropwise at −78 °C to THF solution of LDA (0.18 mmol) [freshly prepared from diisopropylamine (0.025 mL, 0.18 mmol) and BuLi (0.11 mL, 1.6 M solution in hexane, 0.18 mmol) in THF (3 mL) at the −20 °C for 30 min]. The mixture was stirred at −78 °C for 1 h before the addition of methyl iodide (0.2 mL, 0.3 mmol, freshly distilled). After 0.5 h at −78 °C the reaction mixture was warmed to room temperature and stirred for further 1 h, quenched by the addition of saturated aqueous ammonium chloride solution (3 mL), extracted with $CHCl_3$ (3×2 mL), and dried ($MgSO_4$). The solvent was evaporated in vacuo and the crude product was purified by column chromatography (silica gel, 70% EtOAc/petroleum ether) to give the *titled compound* **2b** (19 mg, 50%) as a yellow oil; R_f (50% hexane/EtOAc) 0.17; δ_P (81 MHz, $CDCl_3$) 32.6; δ_H (200 MHz, $CDCl_3$) 7.04 (1H, br s, =C*H*), 4.23 (2H, q, *J* 7.1 Hz, OCH_2CH$_3$), 3.75 (3H, d, *J* 10.7 Hz, OMe), 3.69 (3H, d, *J* 10.7 Hz, OMe), 3.33 (1H, br d, *J* 24.6, HCP), 2.43–2.31 (1H, m, MeC*H*), 2.21–2.06 (2H, m, CH$_2$), 1.82–1.55 (2H, m, CH$_2$), 1.30 (3H, t, *J* 7.1 Hz, OCH$_2$CH_3), 1.07 (3H, d, *J* 6.6 Hz, *Me*CH); *m*/*z* (EI) 276 (15, M^+), 233 (15), 127 (100%).

4.7. Low-temperature ^{31}P NMR measurements

^{31}P NMR spectra were recorded on a Bruker DRX 500 Spectrometer at 202.45 MHz. There were obtained with proton decoupling and referenced to the external H_3PO_4. In experiments 5 mm NMR tubes were used sealed with rubber septa. LDA was directly prepared in NMR tube under argon at −70 °C (acetone/dry ice) and phosphonate **3** was added by a syringe. The spectra of phosphonate carbanion were measured at low temperatures (−70 °C) or in independent experiment at room temperature.

*4.7.1. Reaction of phosphonate carbanion **4b** with benzaldehyde.* To solution of carbanion **4b** (0.16 mmol) in THF (0.5 mL) [freshly prepared from phosphonate **3** (30 mg, 0.11 mmol) and LDA (0.15 mmol) at −78 °C for 1 h, slowly warmed to room temperature and measured by ^{31}P NMR at 20 °C], benzaldehyde (9.6 mg, 0.10 mmol) in THF (0.2 mL) was added, via cannula, under argon atmosphere. After 10 h at room temperature, the reaction mixture was quenched by the addition of water (0.5 mL), extracted with $CHCl_3$ (2×0.5 mL), dried ($MgSO_4$), and evaporated in vacuo to give crude product, which was purified by preparative chromatography (50% EtOAc/hexane) to give **11e** (15 mg; 42%), R_f (50% hexane/EtOAc) 0.17; δ_P (200 MHz, $CDCl_3$) 30.3, 30.1; *m*/*z* (CI, isobutane) 369 (64, MH^+), 351 (56), 305 (50), 263 (42%).

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.01.016.

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