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SYNTHETIC POTENTIAL OF CYCLOALKENE-DERIVED PHOSPHONATES

DPhil UP 1992

SYNTHETIC POTENTIAL OF CYCLOALKENE - DERIVED PHOSPHONATES

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Extracts from this work were presented as lectures or posters at conferences and are also published or being prepared for publication:

1. Phosphonic systems: 5. Prototropic equilibria of diethyl alkenylphosphonates, J.P. Gerber, T.A. Modro, C.C.P. Wagener and A.Zwierzak, *Heteroatom Chemistry*, **2**, 1991, 643

2. Phosphonic systems: 9. Solution and solid state structure of R,R (S,S) stereoisomers of the adducts of diethyl (1-cyclohexenyl)methylphosphonate and aldehydes, Kobus P. Gerber, H. Marita Roos and Tomasz A. Modro, *J. Mol. Structure*, in preparation

3. Reactions of diethyl cyclohexenylphosphonates with aldehydes, J.P. Gerber and T.A. Modro, in preparation

Lecture entitled "The Phosphoryl Group, a relative of the Carbonyl?" at the annual Student Symposium of the South African Chemical Institute at Pretoria Technikon, 1991

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by

JACOBUS PETRUS GERBER

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To Charlotte And My Parents

Contents

Summary

The effect of the diethoxy phosphoryl group on an adjacent carbon-carbon double bond was determined for various unsaturated systems and found to be very similar to that of the hydrogen atom. The number of carbon atoms attached to the double bond and allylic hydrogen atoms were found to play the determining role in olefin stabilisation of alkenyl-phosphonates.

The alkylation reactions of 1,2- and 2,3-unsaturated cyclohexenylphosphonates were also investigated. Diethyl cyclohexen-1-ylphosphonate failed to react but both diethyl cyclohexen-2-yl- and cyclohexen-1-ylmethylphosphonate were usually alkylated in the α-position with respect to phosphorus. One example of γ-alkylation was described. Aldehyde addition was also found to occur *via* the α-carbon. Introduction of sterically bulky groups on either the electrophilic carbonyl centre or the α-position on the nucleophile led to diminished yields and to γ-addition being favoured. The latter is a consequence of reversibility of the addition step. Hence, thermodynamic products could be isolated.

The synthetic viability of diene formation from the 2-hydroxy adducts, obtained from the aldehyde addition reactions, was investigated. Although the retro-addition reaction competed with fragmentation to dienes, reasonable to high yields of the latter were obtained. A proton nuclear magnetic resonance spectroscopic study, as well as X-ray crystal structure determinations, of the 2-hydroxyphosphonates were conducted in order to establish the reasons for the observed difference in reactivity between the RR (SS) and RS (SR) diastereoisomers in their fragmentation reactions.

Opsomming

Die invloed van die di-etoksiefosforiel groep op 'n aangrensende koolstof-koolstof dubbel binding is bepaal vir verskeie onversadigde sisteme en is bevind om baie dieselfde te wees as die effek van 'n waterstof atoom. Die aantal koolstof atome gebind aan die dubbel binding en alliliese waterstof atome is bevind om die bepalende rol te speel in olefien stabilisasie van alkenielfosfonate.

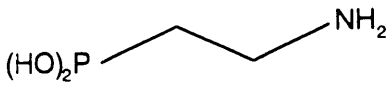
Alkilasie reaksies van 1,2- en 2,3-onversadigde sikloheksenielfosfonate is ook ondersoek. Di-etiel sikloheksen-1-ielfosfonaat het gefaal om te reageer maar beide di-etiel sikloheksen-2-iel- en sikloheksen-1-ielmetielfosfonaat is gewoonlik ge-alkileer in die α-posisie ten opsigte van fosfor. Een voorbeeld van γ-alkilasie is beskryf. Aldehied addisie is ook bevind om plaas te vind *via* die α-koolstof. Toevoeging van groot groepe op of die elektrofiliese karboniel groep of die α-koolstof van die nukleofiel het gelei tot verminderde opbrengste en tot bevoordeling van γ-addisie. Laasgenoemde is 'n gevolg van omkeerbaarheid van die addisie stap. Dus, termodinamiese produkte kon geisoleer word.

Die sintetiese lewensvatbaarheid van diëen formasie van die 2-hidroksie-samestellings, verkry vanaf die aldehied addisie reaksies, is ondersoek. Alhoewel die retro-addisie reaksie gekompeteer het met fragmentasie na diëen, redelik tot goeie opbrengste van laasgenoemde is verkry. 'n Proton kern magnetiese resonans spektroskopiese studie, asook X-straal struktuur determinasies, van die 2-hidroksiefosfonate is uitgevoer om die redes te bepaal vir die waarneembare verskil in reaktiwiteit tussen die RR (SS) en RS (SR) diastereoisomere in hul fragmentasie reaksies.

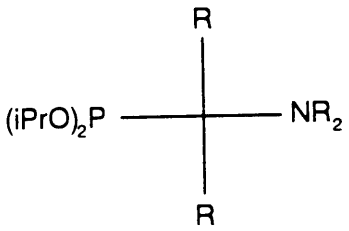
CHAPTER 1
INTRODUCTION

The diverse roles which phosphorus plays in nature are well established. On the one hand, life and its continuation is dependent on phosphorus containing genetic material and energy donors such as adenosine triphosphate.[1] On the other, organophosphorus compounds are being used extensively in the manufacturing of various agents used in chemical warfare[2] and insecticides.[3] Hence, organophosphorus chemistry has attracted considerable interest over the years.

The phosphonic acid class of compounds, as well as their ester derivatives, are no exception. The first example to be isolated from living organisms was 2-aminoethanephosphonic acid[4] (1). In addition, some phosphonic esters, such as diisopropyl α-aminoalkylphosphonates (2),



(1)



(2)

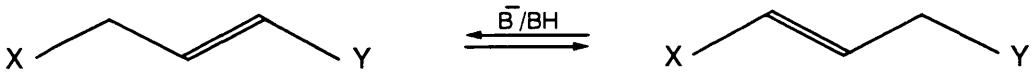
have been found to have excellent selective properties in gold extraction processes.[5] Recently, dialkyl phosphonates and their amides have been shown to have highly active vasodilatory action in human physiology[6] and are among those compounds which show the most promising results in anti-HIV activity.[7] Organophosphorus reagents are also being used more frequently in synthetic organic chemistry.

For these reasons, it was deemed interesting to investigate some reactions of dialkyl phosphonates and to determine their synthetic potential.

(A) Structure and Properties of the Phosphoryl Group

Superficially, one might expect a phosphoryl and carbonyl group to behave similarly. However, this is not the case. A direct comparison is not valid since, in contrast to a carbonyl group with sp^2 hybridised carbon and oxygen atoms and flat configuration, the phosphorus atom of a phosphoryl group has a tetrahedral configuration and sp^3 hybridisation.[8] In addition, the multiple bond of the phosphoryl group consists of d_π-p_π overlap, the bond being formed by 3d-orbitals of phosphorus and 2p-electrons of oxygen, while the double bond of a carbonyl group is formed by 2p-electrons of both atoms.

Much speculation has surrounded the role of a phosphoryl group in the stabilisation of an adjacent double bond.[8] Consider, for example, a prototropic equilibrium where a double bond is situated either α or ß with respect to a substituent X or Y (Scheme 1).

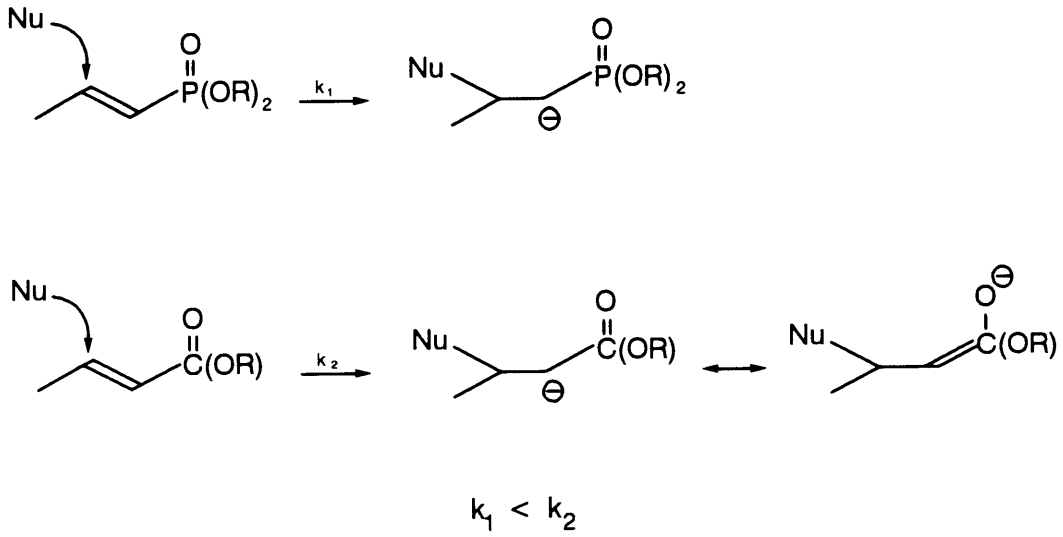


(Scheme 1)

The free energy change for double bond migration in this 1,3-disubstituted propenyl system is related to the effect of substituents X and Y on the stabilities of unsaturated compounds. Hine and co-workers derived the "Double Bond Stabilisation Parameter" as a quantitative measure of these stabilities.[9] Relative to hydrogen, practically all common substituents display a stabilising effect on an adjacent double bond, the alkyl sulphonyl group being one of the few possible exceptions.[10] Unfortunately, very little data is available for phosphonic systems.

Since vinyl compounds of pentavalent phosphorus add nucleophilic reagents less readily at

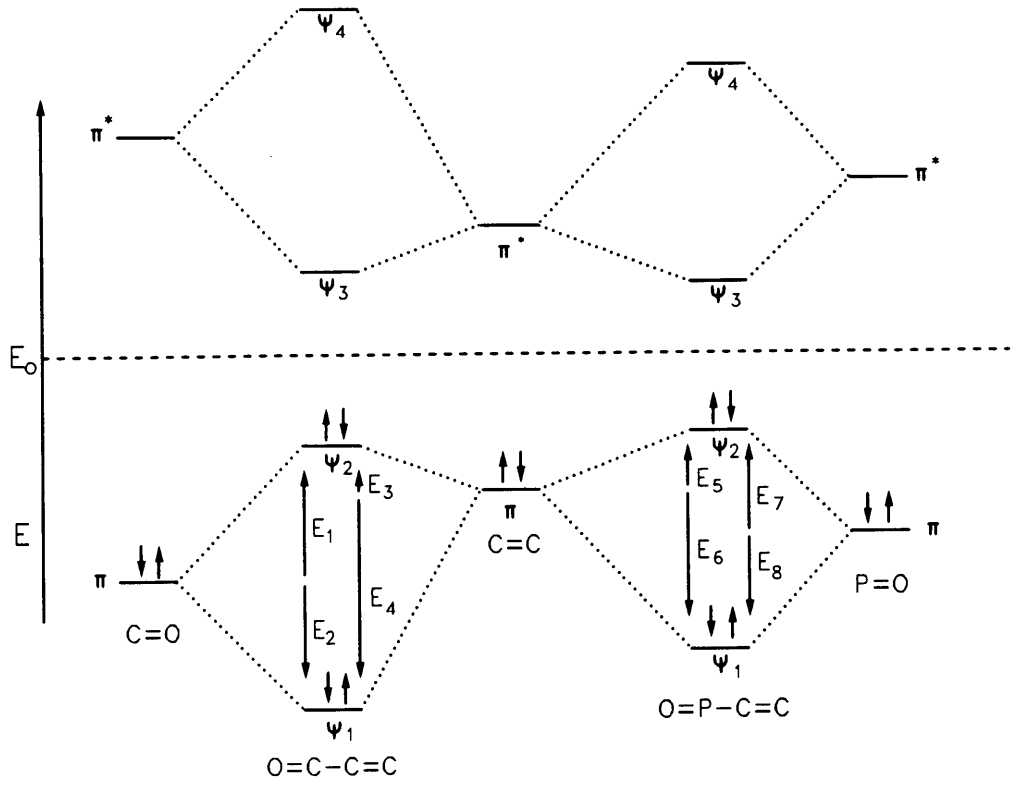
the ß-position than do the corresponding α,ß-unsaturated carbonyl compounds (Scheme 2), the phosphoryl group is proposed to have a weaker polarising effect.[8]



$k_1 < k_2$

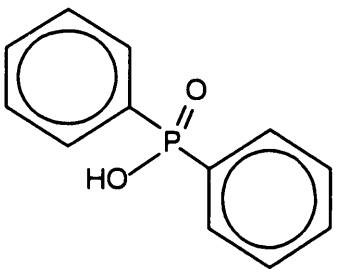
(Scheme 2)

This difference has been ascribed to conjugation which is weaker in the case of the phosphoryl group. This is in accordance with Frontier Orbital Theory[11] which predicts that conjugation should play a lesser role in the stabilisation of unsaturated phosphoryl systems as compared to the corresponding carbonyl systems (fig. 1). The phosphoryl group is expected to be less electronegative than the carbonyl. The bonding orbital of the former (π) and that of the double bond under consideration should, thus, be closer in energy than the bonding orbitals of the carbonyl group and double bond. According to Fleming[11], this implies two medium interactions between the phosphoryl group and adjacent double bond, whereas that of the carbonyl and double bond consists of a strong and a weak interaction to form two new molecular orbitals, ψ_1 and ψ_2. Since a strong and a weak interaction are more effective than two medium interactions, the drop in energy for the carbonyl system (E_2+E_4) should be more than for the phosphoryl system (E_6+E_8). Hence, a carbonyl group should stabilise an adjacent double bond more than a phosphoryl.



(fig. 1)

In agreement with this theoretical description, Jaffé and Freedman found little evidence for resonance between a phosphoryl group and an adjacent aromatic ring in diphenylphosphinic acid[12] (3). The two aryl groups attached to the same phosphorus atom do not form a common conjugated system, as seen from the similar ultraviolet spectra of diphenylphosphinic- and benzenephosphonic acids (4).



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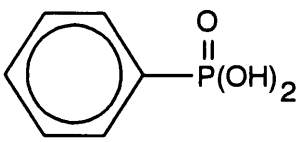
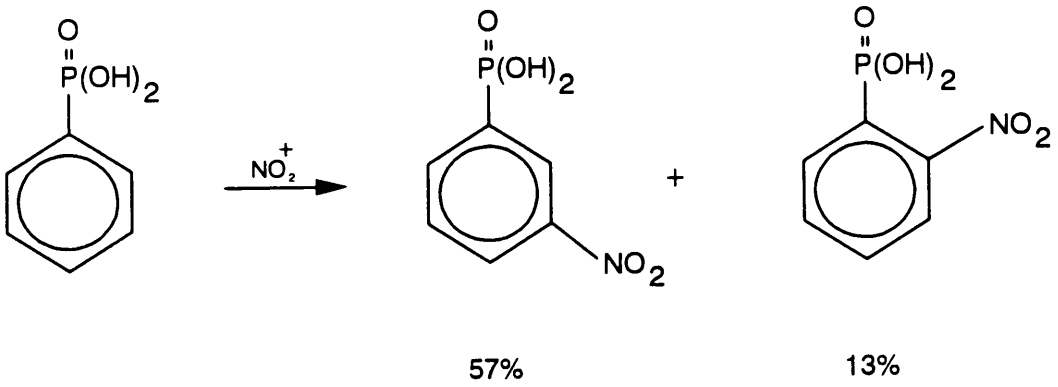


(4)

Although the molar extinction coeficient for the latter is twice that for the former, the general shape of their absorption curves was found to be similar. In addition, the relevant band in the spectra of the mono- and diionic phosphonic acids are similar to that of the neutral molecule. This was also proposed to suggest the absence of conjugation between the phosphoryl group and adjacent aryl rings.[12]

This does not imply the total absence of conjugation in unsaturated phosphonic systems. Chemical reactions are very sensitive to weak interactions, the energy of which, though lower, is still high enough to affect reaction and equilibrium constants markedly. It has been found that the phosphoryl group exerts a *meta*-orientating effect in electrophilic substitution reactions of a benzene ring, analogous to the orientating effect of carboxylic groups.[13] Nitration of phenylphosphonic acid gave rise to *meta* as well as some *ortho* derivatives, with the total absence of *para*-substitution (Scheme 3).



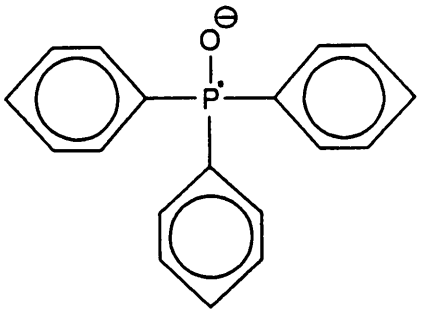
(Scheme 3)

Two proposals have been offered to explain these observations.[8] The first is based on phosphoryl group conjugation with the aromatic ring, analogous to the effect of a nitro group. The second involves the inductive effect, similar to *meta*-orientation caused by the

trifluoromethyl group. The former explanation is favoured, since an inductive effect should influence the *ortho*-position more and make it less susceptible to electrophilic substitution than the *para*-position.[13] However, no *para*-substituted derivatives were observed.

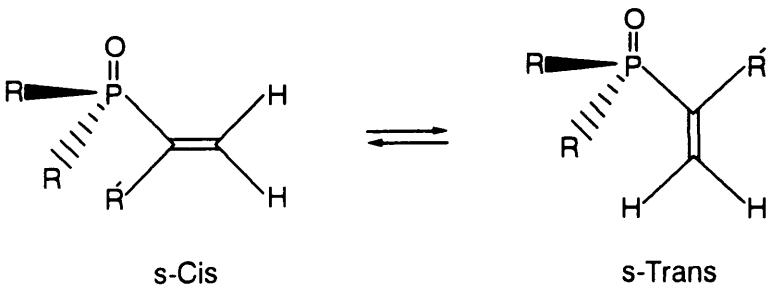
The failure of optical spectral data to confirm conjugation in unsaturated phosphoryl systems could be due to the absence of strong interactions neccessary to bring about changes, which could be observed spectroscopically. Hence, it has been concluded that conjugation is probably too weak to be observed by optical spectroscopic means, though, evidence is provided by more sensitive chemical means.

Radioscopic techniques, such as electronic paramagnetic resonance spectroscopy, have also been used successfully to detect weak conjugative effects in phosphoryl systems.[8] Spectra of the triphenylphosphine oxide radical ion (5) indicate delocalisation of the unpaired electron in all three aromatic rings, the molecule being presented as a single conjugated system.



(5)

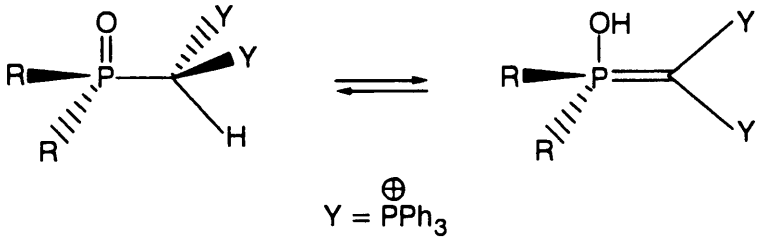
It has been shown that the phosphoryl group and an adjacent double bond are in a planar conformation.[14] Two isomers are possible namely the s-cis and s-trans forms, the latter being preferred (fig. 2).[15]



(fig. 2)

Using Raman spectroscopy, a considerable barrier to rotation about the phosphorus-carbon bond was observed. Increased bond order for this bond was attributed to π-bonding, which would suggest conjugation of the phosphoryl and double bond.

Enolisation of the phosphoryl group has only recently been observed in the solid state[16] (Scheme 4). The strong electron withdrawing character of the two phosphonium groups (Y) renders the C-H acidity higher than that of the P-OH proton. Consequently, proton transfer occurs from the carbon atom to the phosphoryl oxygen. It has also been demonstrated that substitution of the phosphonium groups with less electronegative groups shifts the equilibrium



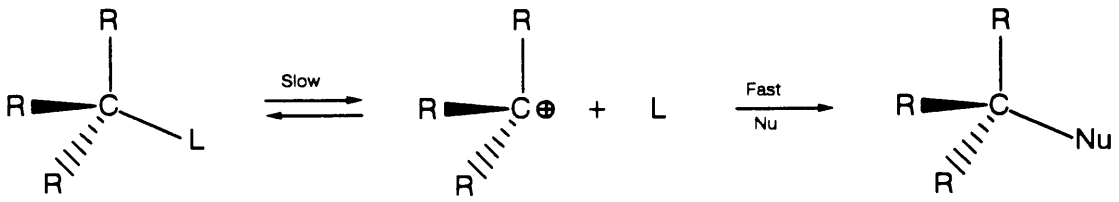
(Scheme 4)

towards the "keto" form. Hence, it was possible to vary the degree of enolisation of the phosphoryl group from 100% to zero.

(B) Reactions of alkenylphosphonic esters

(i) Alkylation

Any species with an unshared electron pair may act as a nucleophile. The rates of S_N1 reactions are independent of the type of nucleophile since it does not participate in the rate determining step[17] (Scheme 5). However, a change in nucleophile may change the product of these substitution reactions.



(Scheme 5)

A number of effects which govern S_N2 reactions have been described in literature.[18,19] It has been suggested that, in terms of equilibria, electrophiles fall into two classes.[20] The first consists of electrophiles which bind strongly to bases which form strong bonds with protons, that is, basic in the usual sense. The other class comprises electrophiles which bind strongly to highly polarisable bases, which often have negligible proton basicity. Nucleophiles have similarly been divided into two categories. Pearson proposed the principle of "hard" and "soft" acids (electrophiles) and bases (nucleophiles) to categorise reactants in nucleophilic substitution reactions.[20] These terms have no bearing on the actual basicity or acidity of a compound. Two criteria were used to classify these acids and bases. It was proposed that "soft" acids will complex readily with bases that are of negligible proton basicity such as

olefins, carbonyl groups and alkyl halides. Another criterion is that an acid which depends strongly on basicity but not on polarisability, as far as rates of nucleophilic substitution reactions are concerned, will depend even less on polarisability in equilibrium binding to bases. Such an acid will therefore be "hard" in nature. Increasing positive oxidation state will also lead to "hard" type of behaviour. In addition, groups attached to the acidic centre will affect the acid class of the compound. Substituents which transfer negative charge to the central atom will increase the "soft" nature of that atom since such transfer of charge is equivalent to a reduction of the oxidation state of the atom under consideration.

Characteristics of "soft" acids are, thus, that the acceptor atom (acid) have a relatively low positive charge density and also high polarisability.[20] Since it has been found experimentally that a complex consisting of the addition of a "soft" base to a "soft" acid have additional stability, it has been proposed that "soft-soft" and "hard-hard" intractions are prefered. Among these "soft" bases are nitriles, phosphites and carbon bases. Characteristic of "soft" bases is their low electronegativity, high polarisability and ease of oxidation. Valence electrons are, thus, held relatively loose. Strong electron withdrawing groups attached to the basic centre under consideration should decrease the basicity of the centre to render it "softer" in nature. Resonance stabilisation by an adjacent group will have a similar effect.

Solvents would necessarily affect the nature of these bases.[20] Due to hydration, water would lower the basicity of highly electronegative anions and make it a "softer" nucleophile. Solvents other than water would have similar effects but lesser in magnitude. Protic solvents would act most like water, whereas aprotic solvents will have a lesser effect. For neutral bases, the influence of the solvent has been found to be small.

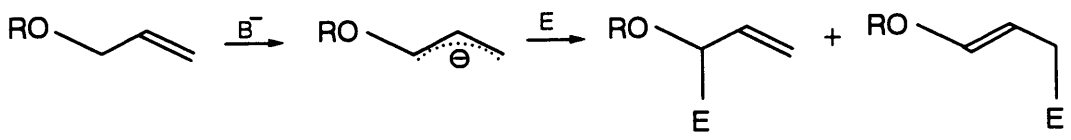
Certain nucleophiles react more rapidly with electrophiles than would have been expected in nucleophilic substitution reactions. Some substrates also show this effect, among them tetra-coordinate phosphorus.[21,22] The common feature in such nucleophiles is the presence of an electronegative atom containing one or more pairs of unshared electrons adjacent to the active centre. Their enhanced reactivity have been ascribed to the "alpha effect", with reference to the pairs of electrons on the alpha atom.[18] It has been proposed that these electrons can stabilise the nucleophile as the transition state complex is formed since the electron density on the nucleophile is depleted in this state. However, some authors propose that the effect is dependent on several factors.[23] The effect has been noted to be associated with reactions exhibiting a large degree of sensitivity to basicity of the attacking nucleophile. The position of the transition state along the reaction coordinate has been described in terms of the pKa of the nucleophile. Thus reactions of nucleophiles with high pKa's have transition states where bond formation has occured to a large extent and *vice versa*. The alpha effect is associated with such a transition state where considerable bond formation is present. Moreover, it has been observed that reactions involving nucleophiles exhibiting the alpha effect are associated with larger equilibrium constants.[23] Reactivity enhancement in substrates has been ascribed to the electronegative atom adjacent to the electrophilic centre which draws electron density away from the latter to render it more positive in character for the incoming nucleophile. Compounds containing a phosphoryl group have both a high net positive charge and a set of empty d-orbitals at the phosphorus atom. π-Bonding from oxygen to the d-orbital on phosphorus reduces the positive character and decreases the susceptibility of the substrate for nucleophiles. When alkyl substitution at phosphorus is replaced by alkoxy groups, π-donation of electrons from oxygen to phosphorus reduces the positive charge density on the latter. Hence, the electrophile becomes "softer" in nature.

The ethylenic bond of an allylic system also activates the adjacent electrophilic centre. This has been attributed to a lowering in activation energy due to stabilisation of the transition state by release of electrons from the double bond to the α-carbon. Hence, allylic compounds undergo substitution reactions much more readily than the analogous saturated compounds.[24] Migration of substituents across the allylic system is well known and a combination of products can be isolated from their reactions. Allylic compounds are very reactive by means of the unimolecular substitution. Bimolecular mechanisms have often not been observed. The reason is due to tautomeric electron release which facilitates departure of the leaving group. The exclusive formation of unrearranged products is usually a reliable indication of substitution by the S_N2 mechanism, since operation of the S_N1 mechanism has been found to afford varying amounts of rearranged products. Reactions of allylic halides with a number of anionic reagents, such as those derived from active methylene compounds and Grignard reagents, frequently appear to involve normal bimolecular substitution.[24] Uncharged nucleophiles have been found to be less discriminating between the α- and γ-carbon atoms of the allylic electrophile. It has been proposed that an anionic nucleophile attacking the α-carbon atom will facilitate separation of the leaving group more than the same reagent attacking the γ-carbon. An uncharged nucleophile would not offer this electrostatic assistance to the departing leaving group.

Nucleophiles with a pair of electrons on more than one atom, or for which canonical forms may be drawn with two or more atoms bearing an unshared electron pair, can obviously react in an ambident fashion. The preferred atom for attack depends on various factors. Where the products are determined by thermodynamic control, the principle product have been proposed to be the one in which the atom of higher basicity has attacked.[17] Kinetically controlled reactions are more complex. In an S_N2 reaction the nucleophile attacks a carbon

atom of a molecule which is "soft" in nature. The more electronegative atom of the ambident nucleophile is the "harder" basic centre in the molecule. Thus, as the character of a reaction changes from S_N1 to S_N2, the ambident nucleophile will more likely attack with its less electronegative atom.[25] However, this is not always the case. The position of attack also depends on the nature of the nucleophile and leaving group. Solvation of the counterion would render the nucleophile more free and, hence, attack by the "harder" centre would be expected to predominate.

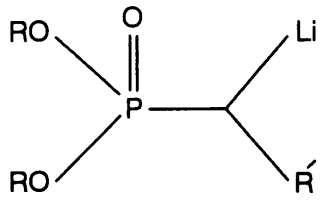
Another effect which governs S_N2 reactions is the freedom of the nucleophile.[17] It has been observed that the rates of bimolecular nucleophilic substitution reactions, involving neutral substrates and anionic nucleophiles in acetone, tend to decrease with increasing concentration of the nucleophilic reagent.[26] This was attributed to ion association of the nucleophilic reagent by consideration of the relative reactivities of the dissociated free anion and ion pair. The rate depression was proposed to be due to common ion repression of the dissociation of the salt. This was demonstrated by a drop in reaction rate when additional counterion was added to solutions of the nucleophiles. Similarly, reaction rates were enhanced by removal of the counterion. The effects of different counterions on alkylation reactions have been found to be less important than steric bulk of groups adjacent to the nucleophilic centre.[24,27] In alkylation reactions of allylic ethers (Scheme 6) the product ratio was found to be



(Scheme 6)

controlled by the size of substituents on the oxygen ligand. The product ratio in these alkylation reactions has been shown to be insensitive to reaction conditions involving a change in solvent or temperature. However, the counterion does have an effect, albeit small.[28] Lithium-carbon bonds are known to have considerable covalent character whereas sodium and potassium form ionic bonds with carbon.[29] Reactivity of these metalated anions decreases as complexation and covalent character of the bonds increase. The effectiveness of solvation of ions decreases from lithium to potassium and will, therefore, counteract the stability order for the ion pair.

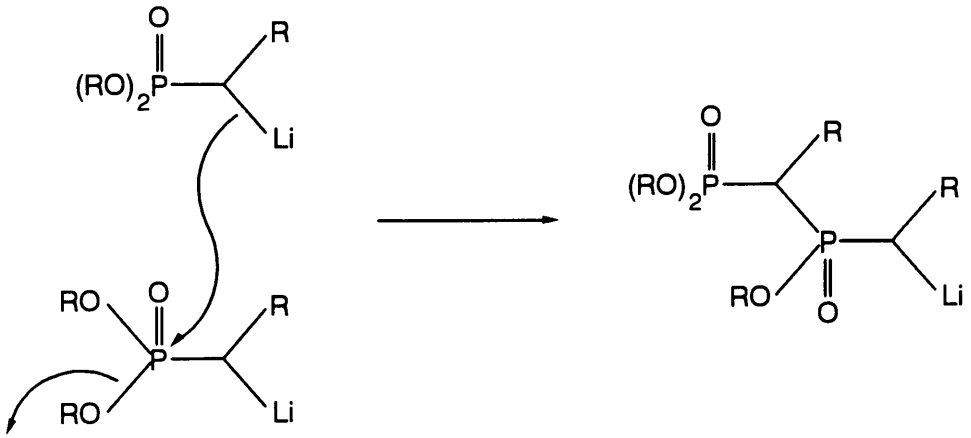
Non-stabilised α-lithiated alkylphosphonates (6) are commonly used as nucleophilic alkylating reagents.[30,31] The strength of their conjugated acids is dependant on the substituents on the



R,Ŕ = Alkyl

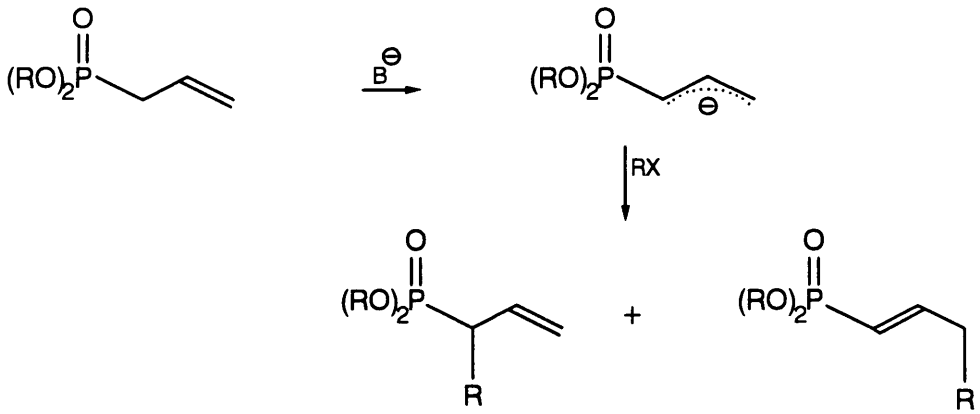
(6)

phosphorus and α-carbon atom. Variation of the alkoxy groups on phosphorus was found to have a lesser effect on the acidity of the α-hydrogen than substituents on the α-carbon.[30] It was shown that acidity of the α-hydrogen can be varied from that of toluene to the acidity order of phenylacetylene, or approximately eight pK_a units. The lithiated carbanions are reactive in the absence of electrophiles and form stable compounds (Scheme 7) via thermal self-condensation reactions which was found to be sterically and electronically controlled.



(Scheme 7)

In alkylations of α,ß-unsaturated alkenylphosphonates the γ-carbon atom competes with the α-position[32] (Scheme 8), although α-addition normally predominates, as with α,ß-unsaturated carbonyl compounds.[17]

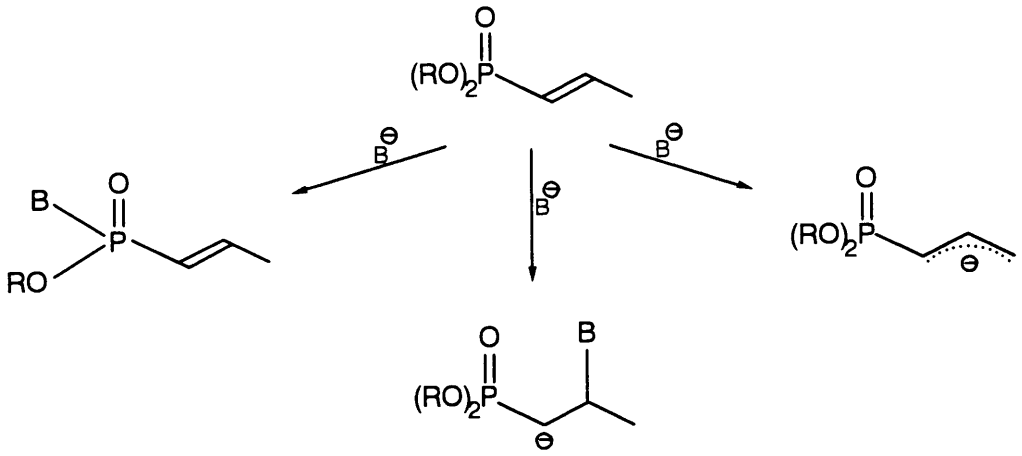


(Scheme 8)

Ab initio calculations have shown that, for propenylphosphonate, the carbon atom α to phosphorus has a higher negative charge than the γ-carbon.[33] This results in higher nucleophilicity of the α-carbon and has been proposed to be the most important factor determining the regioselectivity in alkylation of propenylphosphonates. The degree of

nucleophilicity of the two reaction centres plays a decisive role in the kinetic control of the reaction.[34] However, in thermodynamic controlled reactions, regioselectivity is determined by energy differences between reactants and reaction products. It has been postulated that alkylation of the γ-carbon in these phosphonates is orbital controlled. Hence, a low lying LUMO (lowest unoccupied molecular orbital) of the electrophile will facilitate reaction at the γ-position. This was, indeed, observed experimentally.[33]

In order to abstract a proton from alkenylphosphonates, non-nucleophilic bases should be used since Michael-addition[35] across the double bond and transesterification at phosphorus[36] can compete (Scheme 9).

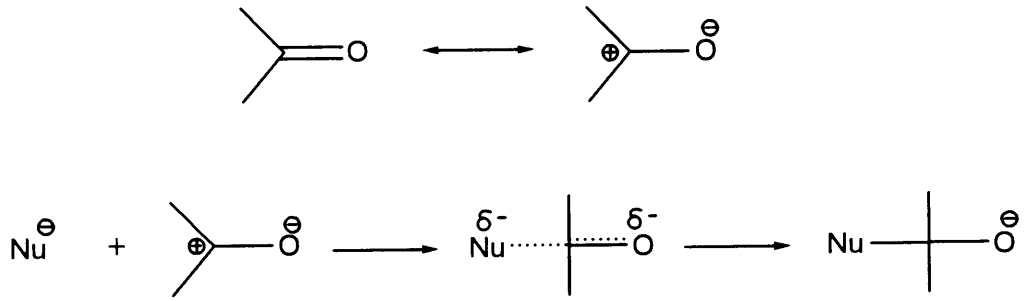


(Scheme 9)

It has been found that the nature of substituents on the double bond affects Michael-addition.[35] Reactions of vinylphosphonates and amines proceed with anti-Markovnikov addition at the multiple bond. Presence of a bulky alkyl substituent at the ß-carbon reduces its electrophilic nature and creates steric hindrance for addition to occur, thus, favouring proton abstraction or reaction at phosphorus.

(ii) Aldehyde addition

Anions of various types can add to aldehydes and ketones in a nucleophilic fashion. It has been proposed that the structure of the carbonyl group which is important in the addition step is the charged form,[18] similar to that of the phosphoryl.[37] This would be expected to present a more electrophilic carbon atom to the incoming nucleophile and one pair of electrons less on carbon as compared to alkyl halides. The equilibrium for the formation of a transition state for nucleophilic addition to a carbonyl group may be represented as in Scheme 10.



(Scheme 10)

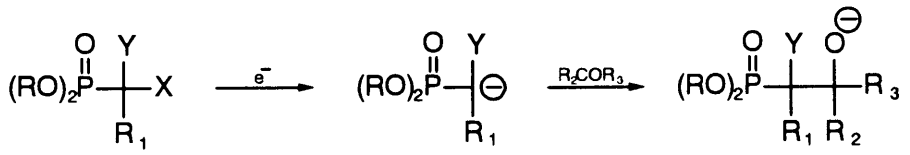
The negative charge on the nucleophile is decreased in the transition state. These changes in charge have been proposed to be responsible for the correlation of nucleophilic reactivity with basicity.[38] Jencks and co-workers found that for a few aldehydes studied, there were no significant difference in sensitivity of nucleophiles towards addition to the carbonyl group.[38] The main contributing factor to the small differences in reactivity is structural features on the aldehyde which induces steric hindrance. The nucleophile is, thus, the determining factor.

Since ionic nucleophiles are usually employed in carbonyl addition reactions, counterions could be expected to play a significant role. The importance of metallic cations in the

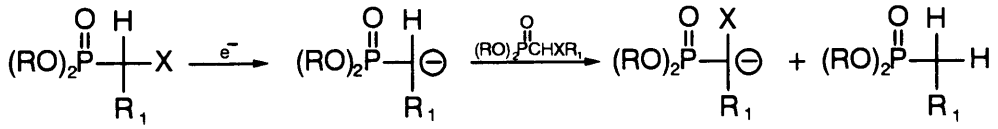
transition state for addition is evident from consideration of their ability to bind to oxyanions. The stability order for metal-oxygen complexes decreases from lithium to potassium.[39] Hence, the former should stabilise the transition state to a larger extent than potassium. Extensive investigations into the effect of metal cations on phosphoryl addition reactions have recently been published.[40] Since it has been shown that addition reactions to carbonyl and phosphoryl groups proceed in analogous fashion,[18] the same rationale can be applied to reactions of the former. Rate accelaration would result if the metal ion interacts stronger with the transition state complex than with ground state molecules. This results from lowering of the free energy of activation for transition state formation. Reversal of the strength of interaction would lead to rate retardation. The absolute effects were proposed to be larger for lithium than for potassium cations due to the higher charge density on the former.[40] If the ground state substrate is neutral, no appreciable interaction with metal cations would be expected although it is conceivable that some degree of association could occur.[41] Hence, metal interaction with the nucleophile and transition state complex will be the determining factors. Buncel *et al*[42] observed that metal cations stabilised the transition state complex to a larger extent than the anionic nucleophile in certain reactions. This is in contrast to the expected results for S_N2 reactions. In the latter, the charge in the transition state is delocalised over the nucleophile, reacting centre and leaving group, leading to weak interaction with metal cations. However, when the charge in the transition state complex is localised, or if effective chelation by the metal ion is possible, stabilisation of the transition state by the metal ion can occur to a greater extent than ground state stabilisation.[42] These effects have been proposed to be dependent on the solvent used, since small charged ions are more easily solvated in polar solvents.[40] Consequently, competition between solvent molecules and reaction intermediates for metal association will result.

Anions derived from phosphonate esters have also been shown to add to carbonyl centres.[43] In general, ketones seem to be less reactive than aldehydes.[44] Steric, rather than electronic effects have been proposed to dominate reactivity of these carbonyl centres. Although most of the earlier examples of the alkylphosphonates contained charge stabilising electron withdrawing groups e.g. cyano, carbonyl or aryl substituents,[45] later studies showed that phosphonates containing hydrogen or alkyl groups have been added successfully to aldehydes and ketones[43].

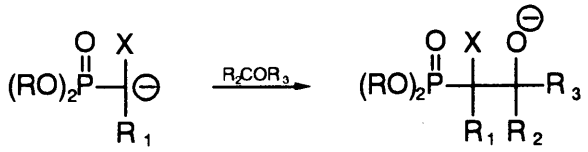
Although organometallic bases, such as alkyllithiums, are normally used for deprotonation, electrochemical means of generating the base *in situ* is now also being employed.[46] In addition, two electron reduction of halophosphonates without α-hydrogens also lead to anion formation (Scheme 11, eqn. 1). In the presence of an α-hydrogen atom, it was shown that the electrogenerated carbanion preferentially deprotonates the substrate (eqn. 2) and this resulting anion adds to the aldehyde (eqn. 3).



eqn. 1



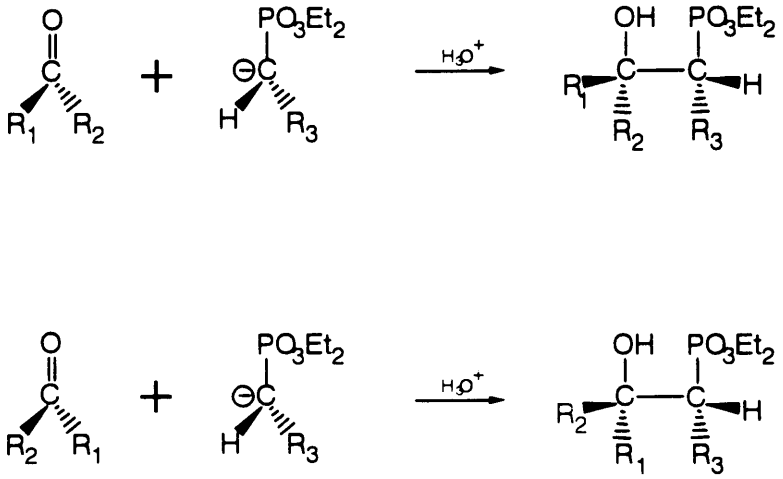
eqn. 2



eqn. 3

(Scheme 11)

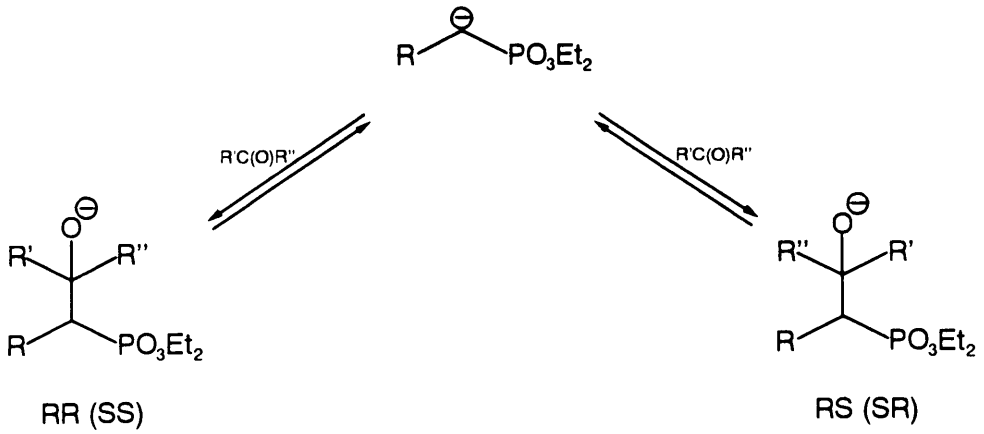
Regardless of the method of generation of the carbanion, most of the addition reactions of α-substituted alkylphosphonate anions to aldehydes or ketones afford two diastereoisomers.[47] Two chiral centres exist in these adducts, one α with respect to phosphorus and the other α to the hydroxyl moiety originating from the carbonyl centre (fig. 3). This is due to the relative spatial approach of the electrophilic centre and phosphonate anion.



(fig. 3)

Selectivity to favour one stereoisomer was found to be dependent upon the steric bulk of the substituents on the electrophile. Thus, when the carbanion derived from diethyl benzylphosphonate was treated with ethylmethyl ketone, Petrova *et al* obtained a mixture of stereoisomers.[47] However, upon treatment of the same phosphonate with 2-chlorocyclohexanone, only the *threo* isomer was observed.

It should be noted that the retro-addition reaction can be a facile process. It has been found that reaction mixtures of alkylphosphonate anions and aldehydes or ketones afforded considerable amounts of unsubstituted phosphonate.[47] Hence, it was postulated that an equilibrium exists between the stereoisomers and parent phosphonate (Scheme 12).

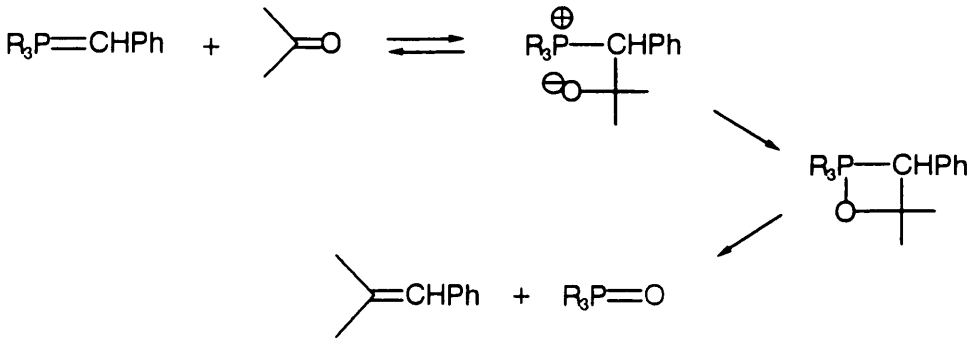


(Scheme 12)

Depending on the thermodynamic or kinetically preferred pathways, prolonged reaction times would alter the ratio of isomers. Where only a single stereoisomer was obtained, it was suggested that kinetically and thermodynamically controlled stereochemistry coincide.

(C) Olefination

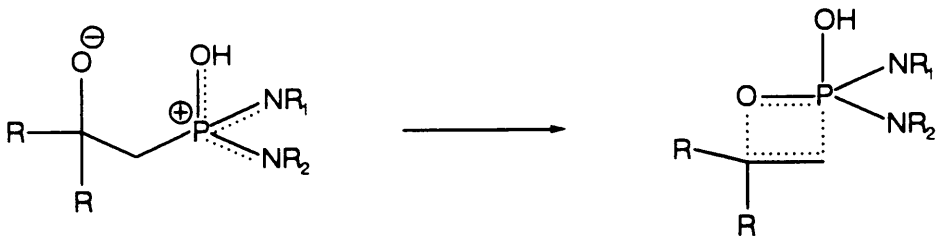
Olefins can be prepared by the well known Wittig reaction involving phosphorus ylides and aldehydes or ketones[48] (Scheme 13). However, a serious limitation of this reaction is the difficulty in controlling olefin geometry. In addition, phosphonium ylides generally do not undergo alkylation and, hence, carbon-skeleton modification is difficult.



(Scheme 13)

A number of variations to the Wittig reaction have been described over the years. The Horner-Wadsworth-Emmons reaction involves addition of stabilised phosphonate carbanions to carbonyl compounds.[49] Isolation of the intermediate hydroxyphosphonates can only be achieved in some rare cases. However, the 2-hydroxyphosphonate adducts of alkyl-phosphonates and carbonyl compounds have been found to be more stable.[50] When a strong electron withdrawing group is present on the carbon α with respect to phosphorus, the sodium and lithium salts have been shown to decompose spontaneously to alkenes even at very low temperatures.[51] Their phosphonic diamides[52] and thiophosphonic analogues[53] have also been used successfully in olefin synthesis. Corey *et al*[53] could not induce olefination from the adducts of non-stabilised alkylphosphonates and carbonyl compounds. However,

the same workers found that 2-hydroxyalkylphosphonic diamides underwent facile thermal decomposition to olefins.[54] The corresponding anionic adducts could not be successfully employed in olefin synthesis. The adducts derived from ketones were found to decompose more rapidly to olefins than those derived from aldehydes. Substitution on the α-carbon also increased the rate of olefination. This was proposed to be consistent with a transition state in which carbon-oxygen and carbon-phosphorus bond breaking are well advanced (fig. 4).

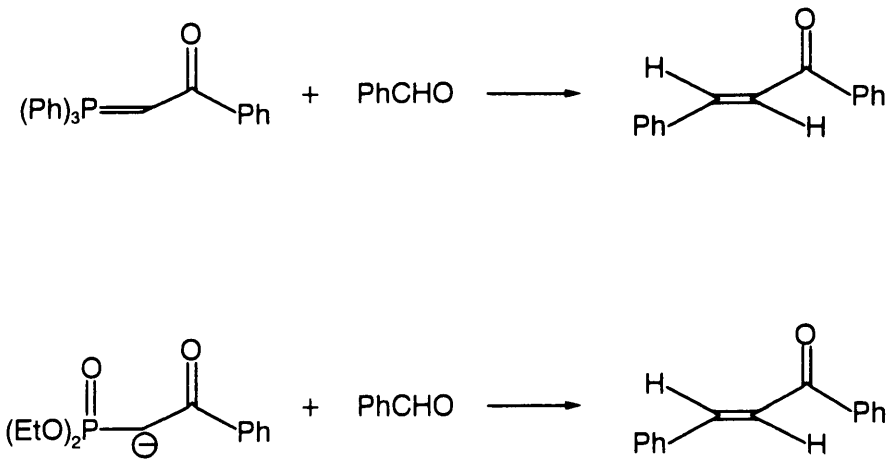


(fig. 4)

The 2-hydroxy adducts of alkylphosphonate esters and carbonyl compounds exhibit contrasting behaviour.[47] Olefin formation was found to occur to the greatest extent for the sodium salts of the adducts. The more stable lithium adducts[39] failed to afford olefins, even at elevated temperatures. Thermal olefination of the neutral 2-hydroxy adducts could not be effected. This was attributed to the low electron density and basicity of the oxygen atom of the phosphoryl group in the esters as compared to the amides. Thus it would be expected that the transfer of the 2-hydroxyl proton to the phosphoryl oxygen atom, as proposed by Corey,[54] would be retarded.

An advantage of using the 2-hydroxyalkylphosphonate esters over the Wittig reaction is their relatively low cost and ease of preparation. In addition, it was shown that, due to their enhanced nucleophilicity, the former reacts with a wider range of ketones and aldehydes,

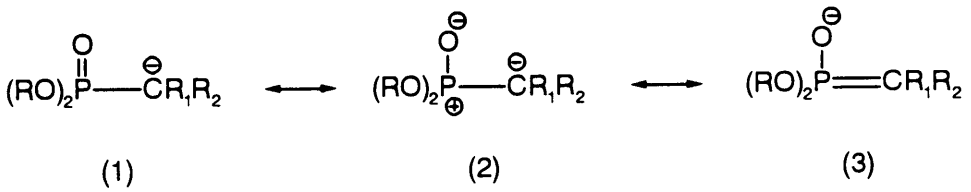
usually under milder conditions. The reaction, for example, of triphenylphenacilidene-phosphorane with benzaldehyde required heating for 30h in boiling THF, whereas that of diethyl phenacylphosphonate and benzaldehyde proceeded exothermally at room temperature and gave comparable yields of olefin (Scheme 14). Another drawback of the Wittig reaction is the need for separation of alkenes and phosphine oxide products which is not a problem with phosphonates which can, as anionic species, be easily removed during an aqueous work-up. In addition, reactions of the latter contain less side products.



(Scheme 14)

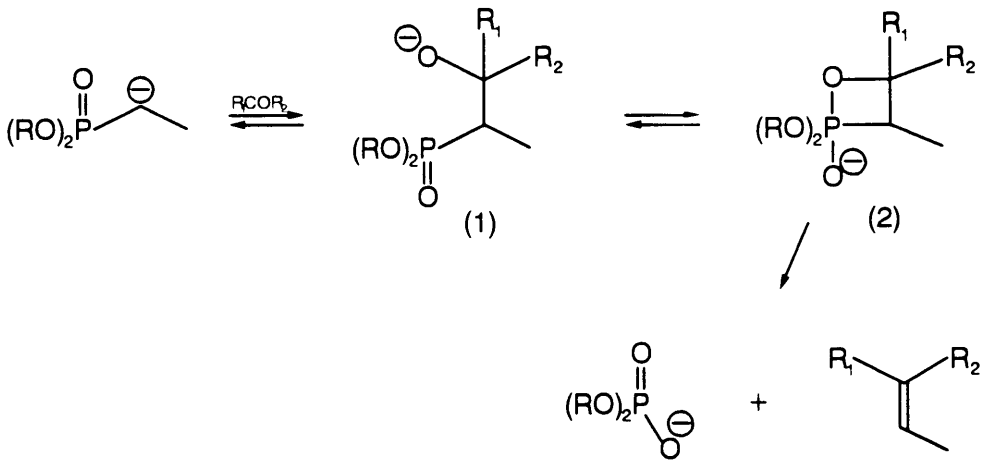
The Wittig-Horner-Emmons reaction,[55] which involves olefination achieved from the reaction of phosphine oxides and aldehydes, also has the disadvantage of requiring rigorous conditions. Hence, only very stable aldehydes or ketones can be used in these reactions. The use of a preformed phosphonate anion circumvent this problem. Moreover, the phosphonate anion can react with alkyl halides to give α-substituted phosphonates which can in turn be treated with base to afford a new anion.[45]

The alkylphosphonate anion has been suggested to exist as a resonance hybrid having three contributing canonical forms (fig. 5). Structures 1 and 3 make use of the availability of



(fig. 5)

empty d-orbitals on phosphorus, similar to the phosphoranes. The first step in the reaction of a phosphonate carbanion with an aldehyde or ketone is the addition of the anion to the carbonyl moiety (Scheme 15). Wadsworth and Emmons[45] suggested that an intermediate 2

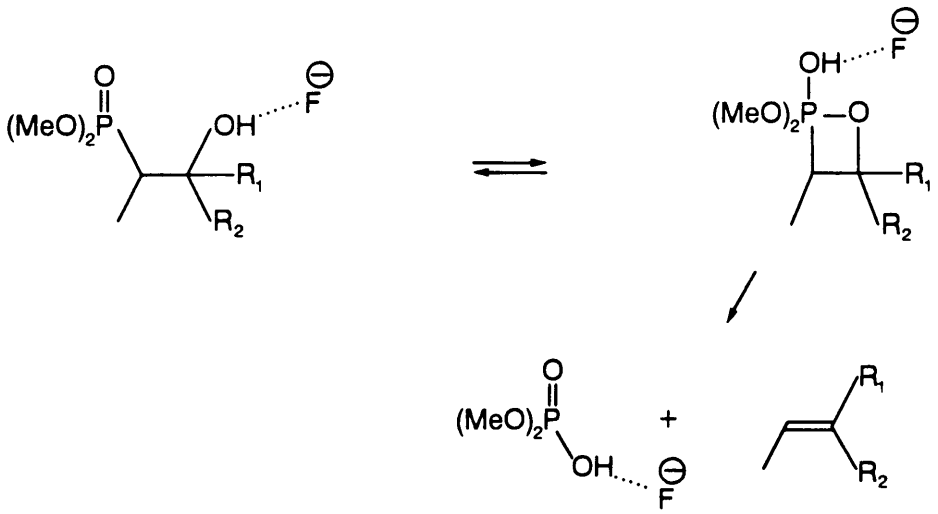


(Scheme 15)

may be involved in the fragmentation reaction, similar to the Wittig reaction.[56,57] The driving force for the reaction was proposed to be provided by the formation of the phosphate anion, which is thermodynamically more stable than the phosphonate carbanion 1 (Scheme 15). The enhanced reactivity of the phosphonate carbanion over a comparable phosphorus ylide has been attributed to the latter having a relatively low degree of charge separation and, hence, being less reactive.[45]

Although Wadsworth and Emmons[45] proposed an intermediate cyclic four-membered system in olefination reactions, evidence for the existence of such a species has been lacking.[58] The need for resonance stabilising α-substituents has been offered as evidence for the build-up of negative charge on the α-carbon in the transition state. In the absence of these stabilising groups, 2-hydroxyphosphonates are isolated and generally do not afford olefins.

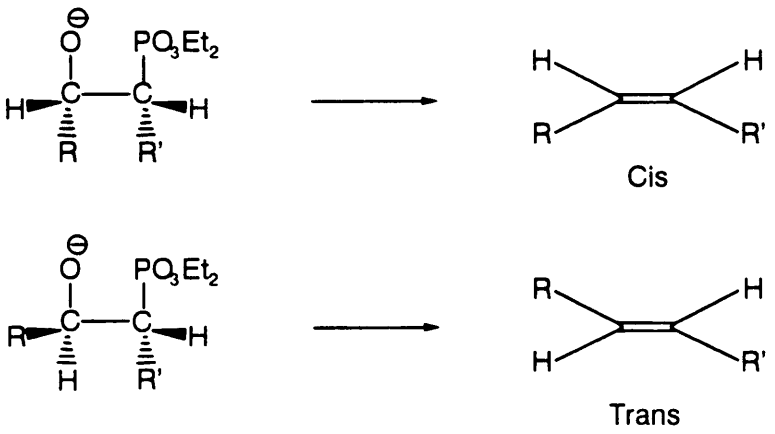
However, not all these alkylphosphonate carbanions necessarily react with carbonyl compounds to give olefins. Where only a hydrogen atom or alkyl group is present on the α-carbon, poor yields of olefins have been obtained upon treatment with ketones.[58] This was ascribed to the intermediate alkoxide requiring activating substituents before decomposition to olefins will occur. Kawashima and co-workers[59] have shown that addition of fluoride ions can induce olefination in these non-activated 2-hydroxyphosphonates, even in the absence of other strong bases. The authors proposed a mechanism in which fluoride ions increase the stability of intermediates and products in the olefination reaction by hydrogen bonding to the appropriate centre (Scheme 16). Hence, the activation energy for formation of the transition state complex is decreased as a result. This was suggested to be the driving force for the reaction.



(Scheme 16)

Ketones have been found to be less reactive towards phosphonate carbanions than aldehydes.[58] This was attributed primarily to steric effects. Electronic effects seem to play a less significant role. With α,ß-unsaturated carbonyl compounds, Michael addition competes with olefination. In the case of ketones the former process have been found to predominate in a number of instances. Imines have also been used successfully in olefination reactions although an excess of base was required to effect decomposition.

As indicated in a previous section, the addition of alkylphosphonate carbanions to carbonyl centres generally affords two diastereoisomers.[47] This would necessarily have a bearing on the stereochemistry of the olefin. Earlier reports have claimed exclusive *trans* stereochemistry for olefins from these reactions.[58] However, later work have shown that *cis* alkenes can also be obtained from the decomposition of 2-hydroxyphosphonates.[61] From Scheme 17 it is evident that each of the specific diastereoisomers can decompose to give either *cis* or *trans* alkenes, analogous to the Wittig reaction. Hence, it was shown that

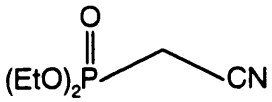


(Scheme 17)

olefination of adducts from the reaction of diethyl benzylphosphonate and ketones, such as ethylmethyl ketone, led to both *cis* and *trans* alkenes.[47] The stereochemistry of the alkene

depends on the relative rates of decomposition of the diastereoisomers. Since the addition step is reversible, the extent of interconversion between the two isomers have also been suggested to have a bearing on stereocontrol. When substituents capable of conjugation with the double bond of the olefin are absent, the steric bulk of groups on the ß-carbon will determine stereochemistry of the olefin due to their interaction with groups on the α-carbon.[58] However, when groups capable of conjugation are present, the alkene in which these groups are *trans* with respect to the double bond usually predominates. This effect has been found to be dependent on the steric bulkiness of the other substituents.

Extensive investigations into the effects governing stereochemistry have been conducted in order to control the outcome of these olefination reactions. Solvent effects have been observed[62] and were proposed to be derived from the extent of betaine reversibility, with reference to the cyclic four-membered transition state described earlier (Scheme 15). The reaction of the diethyl cyanomethylphosphonate carbanion (7) with aromatic aldehydes in



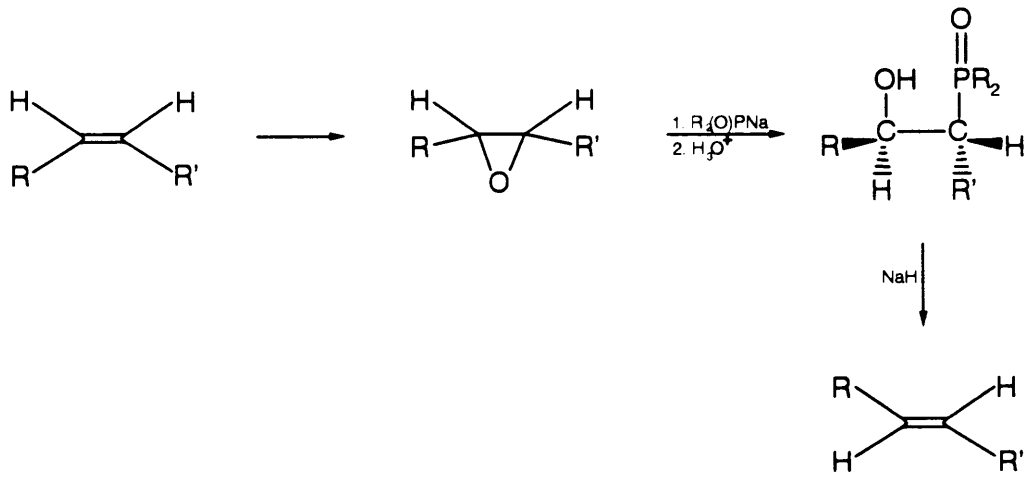
(7)

benzene and tetrahydrofuran (THF) were found to be thermodynamically controlled whereas, in hexamethylphosphorictriamide (HMPT), the reaction can also be kinetically controlled by variation of the proportion and order of added reagents.

Even though the effect of a change in counterion on the stereochemical control of the olefination reaction have been found to be less predictable, some promising results have been

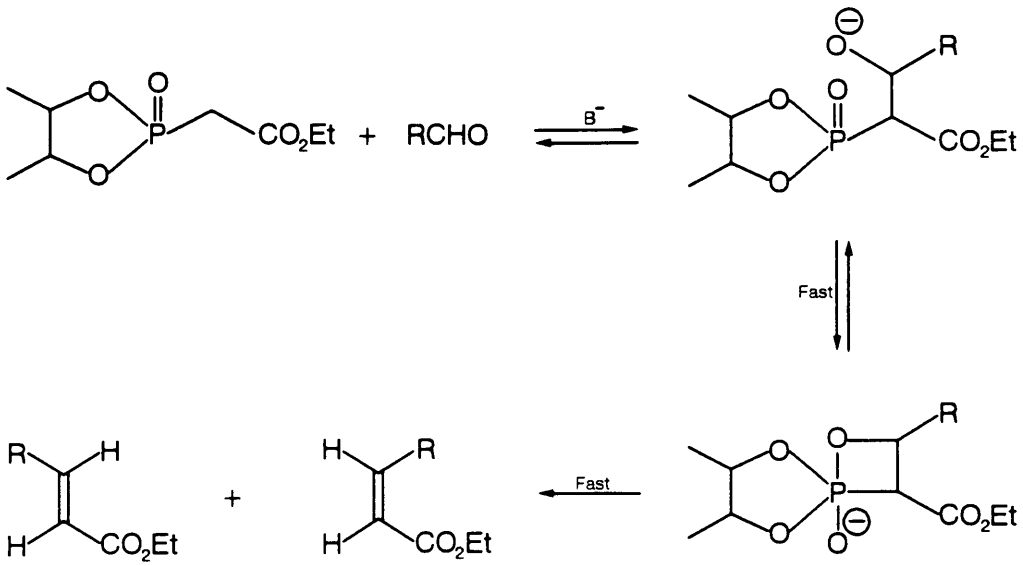
reported.[63,64] A better, though more laborious, approach involves isolation and separation of the diastereoisomeric 2-hydroxyphosphonates. Base catalysed decomposition of the separate stereoisomers would be expected to afford a single alkene. However, a prerequisite is that the 2-hydroxyphosphonate isomeric interconversion should be slow relative to decomposition to olefin.[58]

Since it has often been found that one single stereoisomer of 2-hydroxy-phosphonate is formed exclusively or predominantly,[47] stereocontrol in olefination is assured. This preference for a single stereoisomer have been used advantageously by Whitham and co-workers[65] to interconvert alkene isomers (Scheme 18).



(Scheme 18)

The use of cyclic phosphonate esters have been suggested to control stereochemistry of olefins to favour *cis* alkenes.[66] It was proposed that the use of these phosphonates should lead to more facile formation of the oxaphosphetane intermediate due to release of ring strain in going from the tetrahedral to the trigonal bipyramidal structure (Scheme 19). In addition,

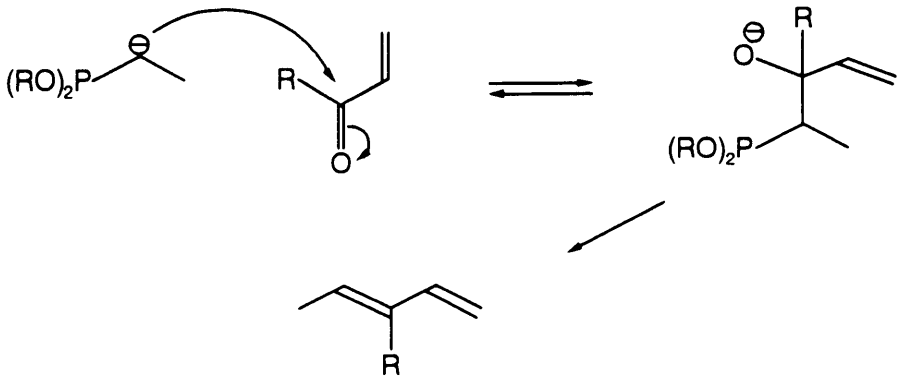


(Scheme 19)

a reduction in rate of reversion to starting phosphonate and carbonyl compound could be anticipated for similar reasons. This was proposed to result in a kinetically controlled reaction and, hence, in a higher proportion of *cis* alkene since this is the kinetic product of the reaction. Experimental results confirmed this prediction in all cases studied.

As discussed earlier, the phosphoryl group is not so effective as the carbonyl in stabilising an adjacent negative charge. Hence, other substituents are required to enhance acidity of the α-hydrogen and stabilisation of the resultant anion. In allylic phosphonates the double bond can stabilise the negative charge upon proton removal. Addition of aldehydes or ketones and subsequent decomposition of the resultant adducts would afford conjugated dienes.[51] In the previous section it was pointed out that both α- and γ-adducts can be obtained from the addition step. However, as expected, Corey and co-workers[51] obtained dienes only from the α-adducts. The method was reported to be superior to both the Reformatsky and the Wittig reaction. Dienes can also be obtained by treatment of saturated alkylphosphonate carbanions with unsaturated ketones or aldehydes[51] (Scheme 20).

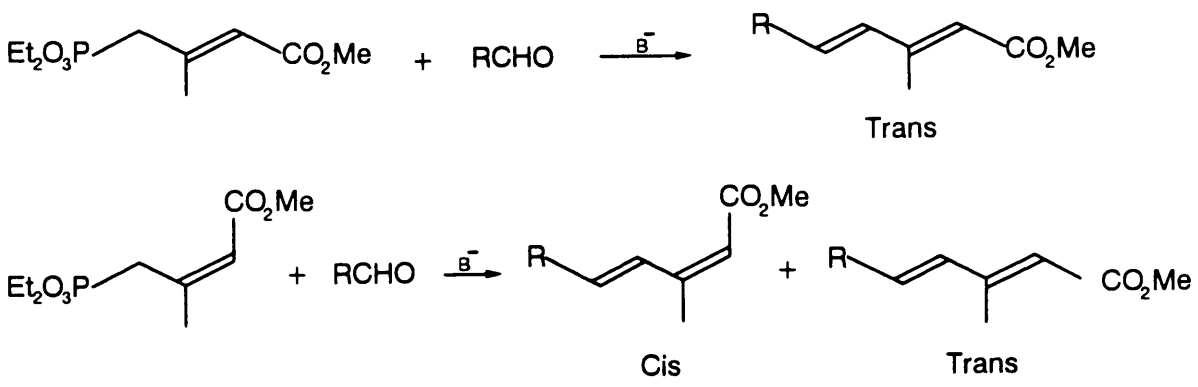
reaction.[51] Dienes can also be obtained by treatment of saturated alkylphosphonate carbanions with unsaturated ketones or aldehydes[51] (Scheme 20).



(Scheme 20)

Unfortunately Michael addition of phosphonate carbanions competes and limits the scope of this procedure. The former process was found to be favoured when proton sources were present in the reaction medium.

Pattenden *et al*[67] investigated the effect of stereochemistry of alkene formation on the geometry of the allylic double bond. *Cis* and *trans* diethyl 3-carbomethoxy-2-methylprop-2-enylphosphonate were condensed with benzaldehyde (Scheme 21). The *trans* ester retained



(Scheme 21)

its stereochemistry to give *trans* products. The *cis* ester, on the other hand, formed mostly *trans* products, due to isomerisation. Uncertainty exists whether this isomerisation of the starting *cis* phosphonate ester proceeds after anion formation.[67]

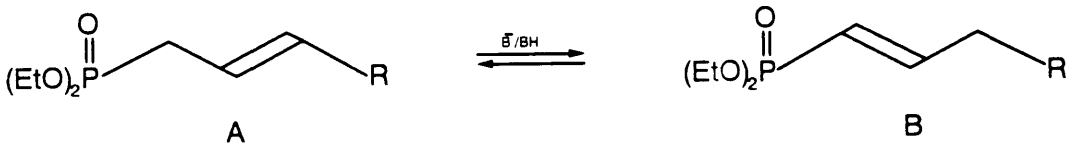
Against this literature background, we decided to extend the investigation of phosphonic esters containing an olefinic function in the phosphonic carbon skeleton. We hoped that the rich chemistry of these systems will lead to some synthetically useful applications, as well as provide additional insight into some fields of organophosphorus chemistry. The results of our investigations are described in the following chapters.

CHAPTER 2

RESULTS AND DISCUSSION

(A) Prototropic Equilibria

Alkenylphosphonic ester carbanions can act as ambident nucleophiles due to isomerisation of the double bond (Scheme 22). The stabilising effect of the phosphonic ester group on an adjacent double bond would, thus, play a significant role in determining the regioselectivity (α- or γ-substitution) of alkylation reactions. Particularly in reversible condensation reactions, the thermodynamically controlled reaction pathway would predominate. Hence it was deemed necessary to investigate the prototropic equilibria of alkenylphosphonate esters.

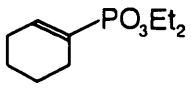


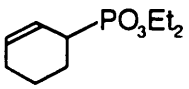
(Scheme 22)

Very little information is available on the stabilising effect of a phosphonic ester group on an adjacent double bond. In the previous chapter mention was made of the "Double Bond Stabilisation Parameter" derived by Hine and co-workers.[9] Practically all common substituents have a stabilising effect on an adjacent double bond. However, the phosphoryl group was not included in this study. The available data suggests that the equilibrium depicted in scheme 22 is dependent on the nature of the substituent R. Thus, when R = hydrogen, isomer B was found to be the exclusive product,[68] whereas, when R = propyl, isomer A represented the thermodynamic product.[69] Since a number of branched chain diethyl alkenylphosphonates were prepared previously in the our laboratory, it was decided to extend the investigation to diethyl cycloalkenylphosphonates.

Both the 1,2- and 2,3-unsaturated isomers of diethyl cyclohexenylphosphonate (8a) and (8b)

as well as diethyl cyclohexylmethylidenephosphonate (9a) and diethyl cyclohexen-1-yl-methylphosphonate (9b) were synthesised.


(8a)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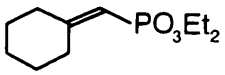
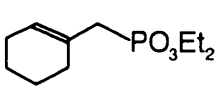

(9a)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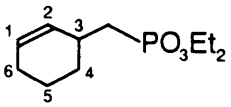
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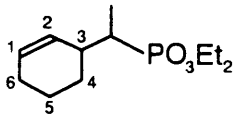
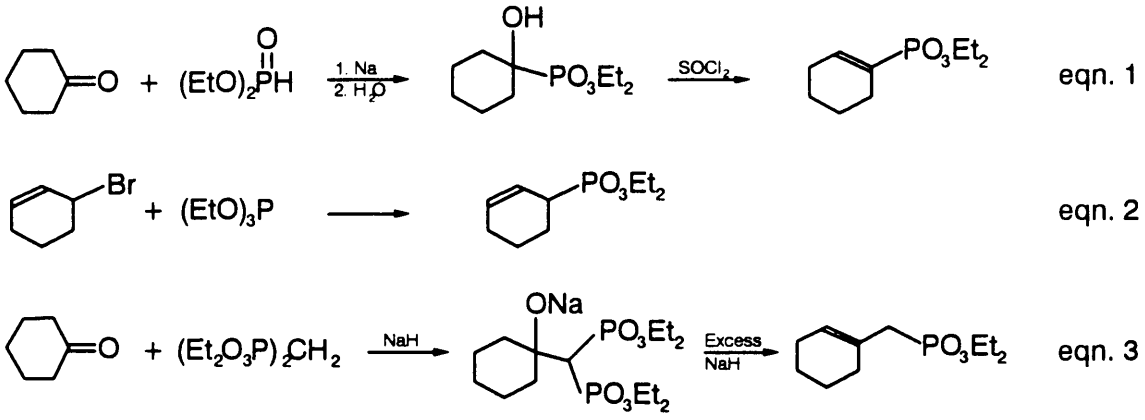
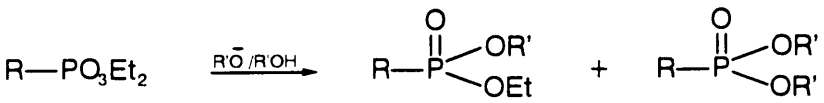

(11)

Compounds (10) and (11) were also prepared from 3-bromocyclohexene and diethyl methyl- and ethylphosphonate, respectively. However, it was found that isomerisation of the double bond could not be effected in these compounds. This is probably due to the protons on carbon 6 of the ring being more acidic than the proton on carbon 3. Hence, there is a lack of driving force for isomerisation to occur and it was consequently decided to concentrate on compounds (8) and (9). Compound (8a) was prepared by reaction of the sodium salt of diethyl phosphite and cyclohexanone. Dehydration of the resultant 1-hydroxyphosphonate afforded the product. Compound (8b) was synthesised from 3-bromocyclohexene and triethyl phosphite, while (9a) was prepared by treatment of sodium tetraethyl methylene-*bis*-phosphonate with cyclohexanone. Upon adding excess sodium hydride to the intermediate 1-hydroxy-*bis*-phosphonate, diethyl cyclohexen-1-ylmethylphosphonate (9b) was obtained as the exclusive product. Reactions leading to products (8a), (8b) and (9a) are presented in scheme 23, equations 1-3, respectively.



(Scheme 23)

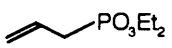
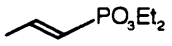
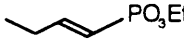
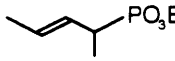
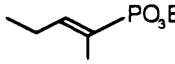
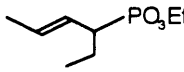
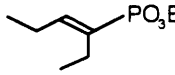
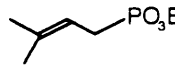
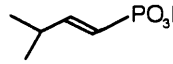
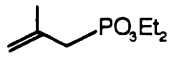
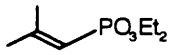
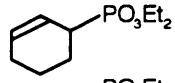
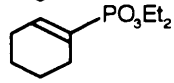
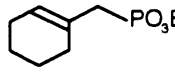
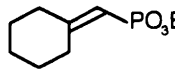
Base-catalysed isomerisation of compounds (8) and (9) was studied by incubation of the substrates in ethanol containing equimolar amounts of sodium ethoxide. The sodium salts of methoxide and *tert*-butoxide resulted in transesterification at the phosphoryl centre (Scheme 24).



(Scheme 24)

An alternative approach involved treatment of the substrates, in dimethoxyethane, with equimolar amounts of sodium hydride, followed by quenching with aq. ammonium chloride solution. The latter procedure gave a mixture which corresponds to the kinetic product of the fast and irreversible protonation of the delocalised allylic carbanion at the α- and γ-carbons. Interestingly enough, both procedures led to a similar composition of the isomeric alkenylphosphonates in the respective reaction mixtures. The progress of the reaction was monitored by ^{1}H and ^{31}P nuclear magnetic resonance spectroscopy. Since the phosphorus atom of a dialkylphosphonate ester group resonates at considerably higher field when it is bonded to a sp^2-hybridised carbon atom than when it is attached to a sp^3-hybridised carbon, the assignment of the ^{31}P chemical shifts was unambiguous. Results, as well as some selected examples from literature and work done previously in our laboratories, are reported in Table 1. For each substrate the proportion of 1,2- and 2,3-unsaturated isomers is given as a percentage of the total mixture. In addition, the number of carbon atoms and diethoxy-phosphoryl groups attached to the double bond, as well as the number of allylic hydrogen atoms, are indicated. The last three columns in the Table refer to the difference in carbon, phosphorus and allylic hydrogen atom substitution on the double bond between the 1,2- and 2,3-unsaturated phosphonates.

Table 1

Compound	% (equil)	No. of[a] C	No. of[a] Allylic H	No. of[a] P	ΔC	ΔH	ΔP[b]
1a 	0	1	2	0	0	1	1
1b 	100	1	3	1			
2a 	81[c]	2	5	0	-1	-3	1
2b 	7[c]	1	2	1			
3a 	29	2	4	0	0	1	1
3b 	71	2	5	1			
4a 	49	2	4	0	0	0	1
4b 	51	2	4	1			
5a 	99	3	8	0	-2	-7	1
5b 	1	1	1	1			
6a 	20	2	5	0	0	1	1
6b 	80	2	6	1			
7a 	5	2	3	0	0	1	1
7b 	95	2	4	1			
8a 	100	3	6	0	-1	-2	1
8b 	0	2	4	1			

a - refers to the number of carbon, allylic hydrogen and phosphorus atoms attached to the double bond

b - refers to the difference between the two isomers in carbon, allylic hydrogen and phosphorus substitution at the double bond

c - material balance consisted of other addition products

For entries 7a and 7b, as well as 8a and 8b (Table 1), the ratio of isomers were the same regardless of the choice of base. For alkoxide bases other than ethoxide, the main product was due to transesterification but the ratio of isomers remained unchanged. The product ratio was also found to be identical, regardless of whether the 1,2- or 2,3-unsaturated isomer was used as starting material. This result was particularly important, since it reassured us that the composition of an equilibrium mixture was, indeed, being determined.

The composition of the equilibrium mixtures shown in Table 1 clearly indicates that the thermodynamic stability of alkenylphosphonate esters is determined by alkyl substitution of the double bond as well as by carbon-hydrogen hyperconjugation (Scheme 25). The role of the diethoxyphosphoryl group is negligible. It is evident from entries 1 and 8 in Table 1 that both 1,2- and 2,3-isomers can predominate, depending on carbon and hydrogen substitution but not on the presence of diethoxyphosphoryl substitution.

(Scheme 25)

Gradual increase in the number of carbon and allylic hydrogen atoms around the double bond shifts the prototropic equilibrium increasingly towards the more substituted isomer. Although it is difficult to evaluate the effect of these two factors independently, they seem to contribute to the overall result to a comparable degree. In system 8 (Table 1), where a total absence of 1,2-unsaturated phosphonate was observed at equilibrium, the cyclic nature of the carbon skeleton can be offered as an explanation. Methylidenecyclohexane is known to isomerise to the more stable 1-methylcyclohexene.[70] This factor is superimposed on the effect of alkyl substitution and hyperconjugation.

Entries 1, 3, 6 and 7 demonstrate that the presence of the phosphoryl group, together with an additional hydrogen atom in the allylic position, are enough to shift the equilibrium strongly in favour of the 1,2-unsaturated isomer. The very high ratio of the isomeric mixture for pair 7 can also be attributed partly to the additional contribution of steric effects operating in the cyclohexenyl system. The preference for 1,2-unsaturation, characteristic of the "0,1,1" structural pattern (refer to the last three columns of Table 1), is to a large extent the result of stabilising hyperconjugative interaction of the single additional allylic hydrogen atom. An analysis of the enthalpies of hydrogenation of several alkenes revealed that the ΔH values for two isomeric alkenes, differing by only one allylic hydrogen atom, can vary from 0,34 $kcalmol^{-1}$ for the isomer with the lower number of hydrogen atoms, to 0,43 $kcalmol^{-1}$ for the isomer with the higher number of allylic hydrogen atoms.[71] This corresponds to an equilibrium constant of approximately two at 25°C. The additional effect of the diethoxyphosphoryl group as an alkene substituent can also contribute to the stability of the 1,2-unsaturated phosphonate. However, its effect is merely weakly stabilising and is best described by entry 4 of Table 1. In this isomeric pair, the only significant structural difference, with respect to the olefinic bond, is the direct presence or absence of a diethoxyphosphoryl group. Although some excess of 1-alkenylphosphonate was observed, the equilibrium constant is not far from unity. Hence, it can be concluded that the diethoxy-phosphoryl group probably resembles the hydrogen atom more closely than any other substituent studied thus far, as far as its effect on an adjacent double bond is concerned.

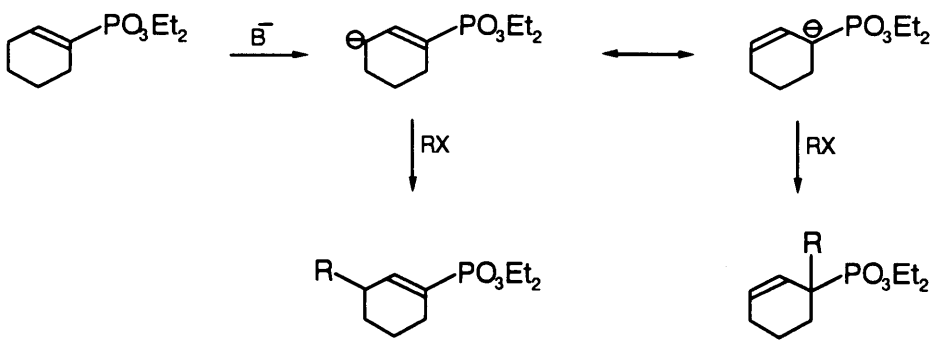
Therefore, it may be expected that in condensation reactions involving carbanions derived from alkenylphosphonate esters, the regioselectivity of thermodynamically controlled products will be determined by structural factors other than the mutual relation between the olefinic group and the dialkoxyphosphoryl substituent.

(B) Reactions of Cyclohexenylphosphonates

(i) Alkylation

Alkylations of alkylphosphonate esters are important since this reaction would lead to extension of the carbon skeleton. Activated phosphonates, such as benzylphosphonate and methylcyanophosphonate, have been used successfully in alkylation reactions. Investigations of allylic systems are limited to propenylphosphonate,[72] although other acyclic analogues[73] have also been studied less extensively. Alkylation was found to occur mostly at the α-position with respect to phosphorus, even though γ-addition is possible. Very little work has been done on cycloalkenylphosphonates. Due to ring congestion, these phosphonate carbanions should be less reactive and, hence, more selective than their acyclic analogues. Self condensation reactions of the type described earlier would not be expected to compete efficiently with alkylation for similar reasons.

Diethyl cyclohexen-1-ylphosphonate was chosen as model compound. Upon deprotonation by an efficient base, such as butyllithium or sodium hydride, a carbanion can result with the negative charge centered at the α- or γ-position with respect to phosphorus (Scheme 26).



(Scheme 26)

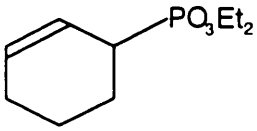
Due to isomerisation of the double bond, the 2,3-unsaturated isomer can be obtained. Hence, regioselectivity of these addition reactions can be investigated. However, only starting

phosphonate was recovered after iodomethane and 1-bromopropane was added to the phosphonate carbanion. This was not due to steric repulsion between the phosphonate and incoming electrophile since quenching of the reaction mixture with D_2O also did not result in deuterium incorporation into the phosphonate. Some effervescence resulted when diethyl cyclohexen-1-ylphosphonate was treated with sodium hydride, which implies that proton abstraction did occur, at least to some extent. Recent results obtained in our laboratory[74] indicate that deprotonation of a γ-hydrogen in the 1,2-unsaturated phosphonate is much less facile than deprotonation of an α-hydrogen in the 2,3-unsaturated system. In the former case, other reactions can occur. It was shown in the previous section that isomerisation to the 2,3-unsaturated phosphonate is not thermodynamically favoured. The absence of products originating from this isomer was, thus, not surprising. However, no obvious reason can be envisaged for the apparent lack of reactivity of the 1,2-unsaturated phosphonate carbanion. It is possible that the immediate concentration of carbanion is low upon addition of the alkyl halide. Reaction between the base and electrophile subsequently occurs and depletes the base concentration. Proton abstraction from the alkyl halide by the phosphonate carbanion is not completely unlikely but deuterium incorporation should then have been observed in the experiment described earlier.

In order to establish whether cycloalkenylphosphonates are reactive enough to be used synthetically, the corresponding diethyl cyclohexen-2-ylphosphonate was prepared as described before. Although base abstraction of the allylic proton α with respect to phosphorus was expected to be more facile, a sterically crowded carbanion would result. In view of the thermodynamic instability of this anion, as compared to the 1,2-unsaturated isomer, enhanced reactivity towards alkyl halides was expected. This was, indeed, the case. Steric factors were found to be less important than suspected and this alkenylphosphonate could be alkylated by various electrophiles. Results are tabulated in Table 2. Yields of isolated products, as well that based upon ^{31} n.m.r. spectra, are reported. Structures of all compounds were determined unambiguously using high resolution proton and ^{31}P n.m.r. spectroscopy, as well as mass spectrometry. Molecular ions were always observed and

molecular fragments confirmed fragmentation patterns. The main fragmentation was found to be cleavage of the carbon-phosphorus bond. Other fragments included the loss of one or two ethylene molecules by McLafferty rearrangement of the phosphonic moiety, similar to patterns described in literature for phosphonates.[75,76] Cleavage of the "new" bond formed between the phosphonate carbanion and the alkyl group of the electrophile was also observed.

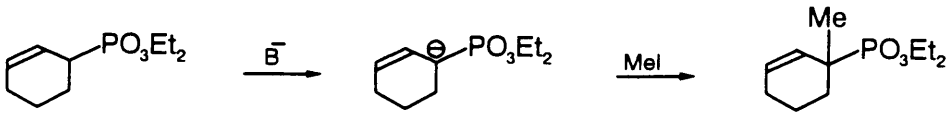
Table 2

Phosphonate	Substrate	Yield (%)	
	Iodomethane	92[a]	99[b]
	1-Bromopropane	89[a]	99[b]
	2-Bromopropane	45[a]	70[b]
	3-Bromopropene	72[a]	80[b]
	Trimethylchlorosilane	34[a]	80[b]

a - isolated yield
b - yield based upon ^{31}P n.m.r. spectra

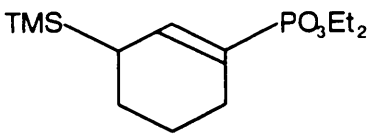
The choice of base was found to be important. Treatment of the phosphonate at low temperature with butyllithium and subsequent addition of the electrophile afforded the adduct. However, the phosphonate, in the presence of sodium hydride, failed to give reaction with alkyl halides, even at elevated temperatures. It is unlikely that this is due to counterion effects since the sodium salt derivative of the phosphonate should be more reactive than the lithium salt.

Contrary to the reaction of diethyl cyclohexen-1-ylphosphonate with iodomethane, the latter was found to react with diethyl cyclohexen-2-ylphosphonate nearly quantitatively. Addition proceeded exclusively at the α-position with respect to phosphorus (Scheme 27).



(Scheme 27)

The effect of an electrophile with increased steric bulk was found to be insignificant as seen from the high yield of adduct obtained from the reaction of 1-bromopropane and cyclohexen-2-ylphosphonate. This seems to indicate that a carbon chain attached to a terminal electrophilic centre does not interfere with the approach of the carbanion. In addition, the effect of the leaving group was negligible since the less reactive alkyl bromide reacted to the same extent as the alkyl iodide. Steric effects did become evident when a secondary alkyl halide was used. The yield of adduct decreased when 2-bromopropane was added to a mixture of diethyl cyclohexen-2-ylphosphonate and butyllithium in THF at low temperature. Material balance consisted of unreacted phosphonate as well as diethyl cyclohexen-1-yl-phosphonate. Hence, it was deemed interesting to investigate the reaction of diethyl cyclohexen-2-ylphosphonate with a tertiary substrate, such as trimethylchlorosilane. Due to steric congestion of the anionic centre and steric bulk of the electrophile, alkylation of the γ-position predominated (12).

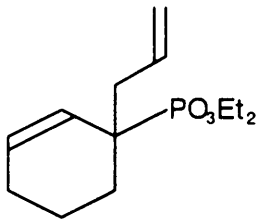


(12)

This was probably due to the enhanced reactivity of the trimethylchlorosilane molecule as opposed to iodomethane. It might also be reasonable to expect a unimolecular substitution mechanism to be operating in the former case due to the instability of the silicon-chlorine

bond.[77] Since the nucleophile does not appear in the rate determining step in S_N1 reactions, it might well be the reason for the relatively unreactive 1,2-unsaturated, α-lithiated form being trapped by trimethylchlorosilane.

In order to extend the study of alkylation reactions of cyclohexen-2-ylphosphonates, the anion derived from the latter was treated with 3-bromopropene. Reaction proceeded to a high extent to afford the product (13). This compound contains an additional unsaturated group

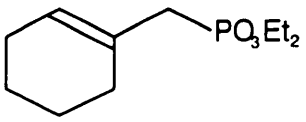


(13)

which is situated in the γ,δ-position with respect to phosphorus. Since ß-allylic protons are present, this molecule could constitute a novel synthon for additional alkylation reactions. These experiments were, however, outside the scope of this study, but they definitely deserve further investigation.

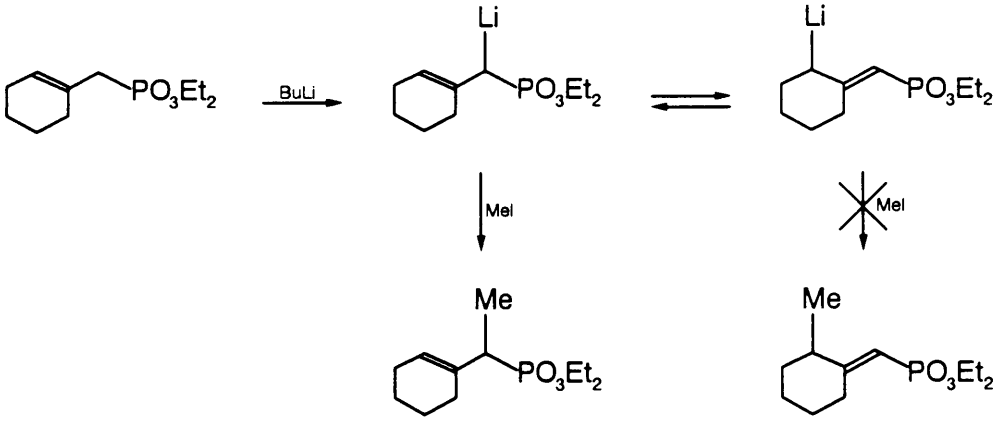
Diethyl cyclohexen-1-ylmethylphosphonate (9b) was also chosen as model compound since, in this compound, the diethoxyphosphoryl group is situated in the ß,γ-position with respect to the olefinic bond, similar as in cyclohexen-2-ylphosphonate. However, an advantage over the latter is its relative thermodynamic stability and uncongested α-carbon atom. Bulky electrophiles should, thus, be able to approach the nucleophilic centre more easily. In addition, competitive isomerisation to the unreactive 1,2-unsaturated isomer should not occur to a large extent. Results of the alkylations of (9b) are summarised in Table 3. Similar analytical techniques were used as before to identify the reaction products.

Table 3

Phosphonate	Substrate	Yield (%)	
	Iodomethane	93[a]	95[b]
	1-Bromopropane	87[a]	99[b]
	2-Bromopropane	65[a]	75[b]
	3-Bromopropene	80[a]	95[b]

a - isolated yield
b - yield based upon ^{31}P n.m.r. spectra

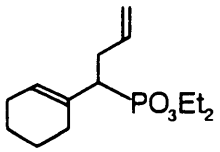
Iodomethane was again used as electrophile to compare the nucleophilicity of diethyl cyclohexen-1-ylmethylphosphonate with its cyclohexen-2-yl analogue. As for reactions of the latter, yields were nearly quantitative and reaction occurred exclusively α with respect to phosphorus (Scheme 28).



(Scheme 28)

1-Bromopropane also afforded α-adduct in high yield. However, the addition reaction was retarded when 2-bromopropane was used as electrophile. Although the yield was higher than for the corresponding 2-cyclohexenyl species, a considerable amount of parent phosphonate was recovered. The lower yield of α-adduct can also be attributed to the lower reactivity of the electrophile, though, it would not be expected to have such a dramatic effect.

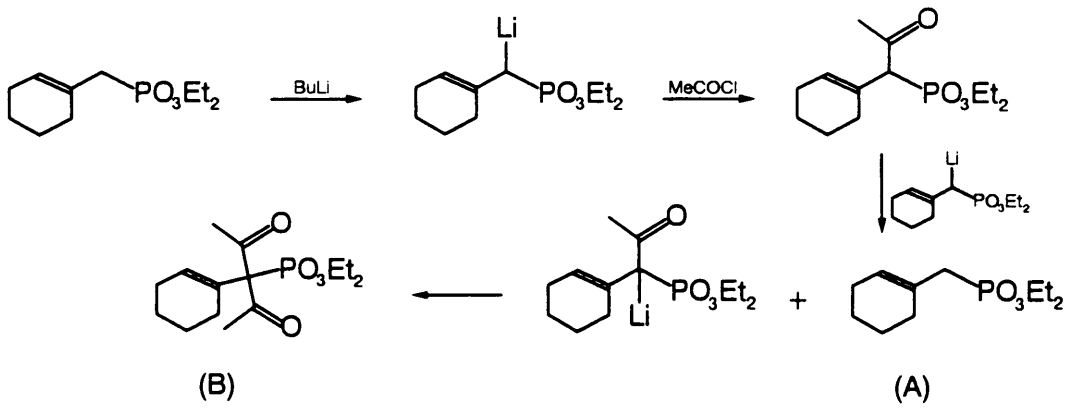
3-Bromopropene again reacted to give the adduct (14) in high yield. The latter compound is interesting in that two reactive allylic centres are present. Hence, treatment of the adduct



(14)

with base could be envisaged to result in competitive abstraction of the proton α, and those ß with respect to phosphorus. Although abstraction of the α-proton would result in an anion which could conjugate with the phosphoryl group, additional substitution at this position renders the proton less acidic. As with the adduct of cyclohexen-2-ylphosphonate and 3-bromopropene, an investigation of the properties of this compound is recommended.

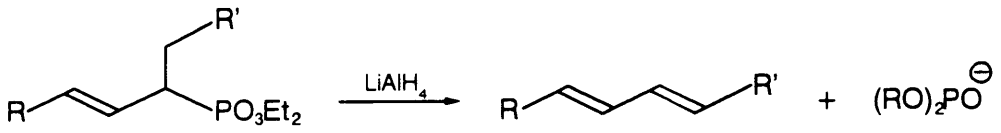
Since alkyl addition proved to be facile, acylation of diethyl cyclohexen-1-ylphosphonate was attempted. Acetyl chloride was selected as electrophile. Due to the planar configuration of the electrophilic centre, approach of the nucleophile should be facilitated relative to alkyl halides. In addition, the carbon-chlorine bond is less stable in acyl chlorides. Upon treatment of the phosphonate carbanion with acetyl chloride, a complex mixture was obtained which consisted mainly of diethyl 1,1'-*bis*-acetylcyclohexen-1-ylmethylphosphonate (B) and unreacted starting material (A) (Scheme 29).



(Scheme 29)

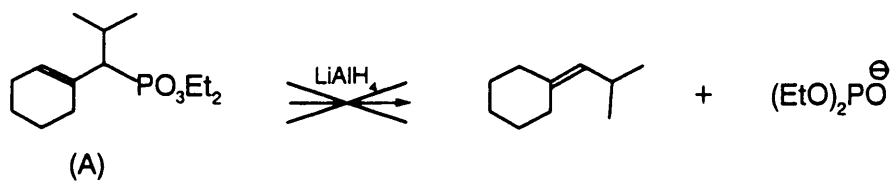
A mechanism is proposed in which acylation of the phosphonate occurs in the α-position. Due to the enhanced acidity of the α-proton on the adduct, proton abstraction by unsubstituted phosphonate carbanion occurs to afford a new carbanion. The latter reacts with a second acetyl chloride molecule to give the disubstituted product.

One of the reasons for the carbon skeleton modification of these cycloalkenylphosphonates was so that a route to substituted olefins could be obtained. Kondo *et al*[32] demonstrated that 2,3-unsaturated acyclic phosphonates could, in the presence of lithium aluminium hydride, decompose to afford *trans* alkenes and phosphonate anions (Scheme 30). This fragmentation could, however, not be repeated by other workers.[74,78]



(Scheme 30)

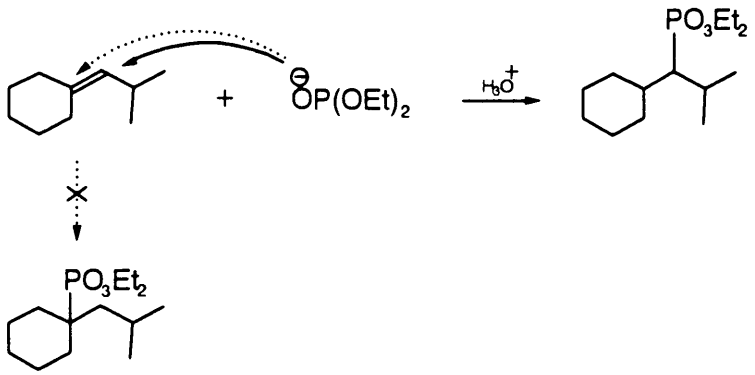
Diethyl cyclohexen-2-ylphosphonate was treated with lithium aluminium hydride as described by Kondo. However, no cyclohexadiene was formed and only starting phosphonate was recovered. Since exclusively *trans* products were obtained by Kondo and co-workers, it was thought possible that specific stereochemical requirements are necessary to effect fragmentation. Hence, diethyl 1-(1'-methylethyl)cyclohexen-1-ylmethylphosphonate(Scheme 31, A) was used as substrate since isomerisation of the double bond and subsequent leaving



(A)

(Scheme 31)

of the phosphoryl moiety should be facilitated in this molecule. In addition, stereochemical requirements should be overcome since restricting structural factors to favour a specific isomer are absent. However, the substrate again failed to afford the expected alkene, even after prolonged reaction times and at elevated temperatures. It is not unlikely that, due to the reactive nature of the phosphite anion, recombination occurs to give the saturated phosphonate (Scheme 32).

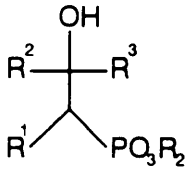


(Scheme 32)

Steric considerations would prevent reverse addition to compete. However, no evidence for these saturated adducts were found and only parent phosphonate was recovered. Due to the failure to effect fragmentation to afford alkenes, this procedure was not further investigated. We have, however, reasons to believe that Kondo's report[32] (a communication, not followed by a full paper) does not constitute a description of a new route to dienes to a degree that had been claimed in the paper.

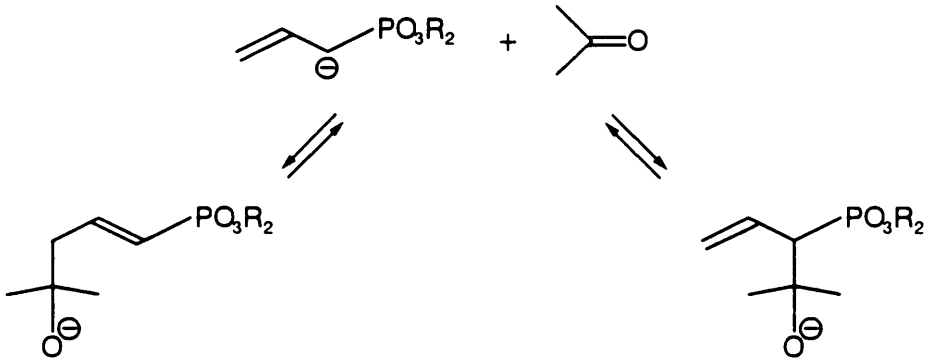
(ii) Aldehyde Addition

As demonstrated in the previous section, cyclohexenylphosphonates can be easily alkylated. Since the substitution reaction is irreversible, kinetically controlled products were mostly observed. In addition, steric effects were shown to play a significant role in these alkylation reactions. Hence, addition of cylohexenylphosphonate ester carbanions to carbonyl centres were attempted in order to establish whether the synthetic usefulness of these phosphonates can be extended. The resultant 2-hydroxyalkenylphosphonates (15) are important precursors of various compounds.



(15)

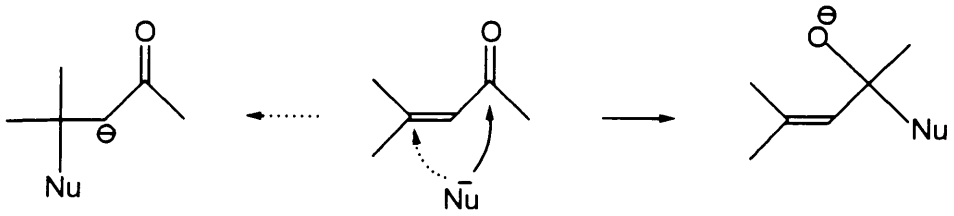
Due to the planar trigonal spatial arrangement of substituents on the electrophilic carbon of aldehydes and ketones, approach of the nucleophile should be facilitated relative to alkyl halides. Moreover, in the former reaction, the addition step is expected to be reversible (Scheme 33). Hence, thermodynamically controlled products should be observed upon prolonged reaction times.



(Scheme 33)

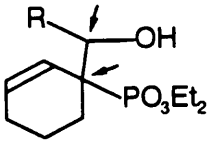
Since alkylation of diethyl cyclohexen-1-ylphosphonate was found to be negligible, reactions of this phosphonate were not attempted. Instead, the 2-cyclohexenyl analogue (8b) was used

as model compound while butyllithium was used as base. In contrast to its reactions with alkyl halides, no adduct was observed upon addition of acetone and cyclohexanone to a mixture of the phosphonate and base in THF. Only parent phosphonate was recovered. This is most probably due to steric effects, although electronic factors can also be operating. Ketones are considerably less electrophilic than alkyl halides. In order to distinguish between these steric and electronic effects, the diethyl 1-cyclohexenylmethylphosphonate carbanion was used as nucleophile. Due to the relatively unhindered α-carbon atom, steric factors would be expected to play a lesser role. However, no reaction with acetone and cyclohexanone was detected. Even mesityl oxide, which can react in a 1,2 as well as a 1,4 fashion (Scheme 34) failed to afford adducts. Thus, it seems as though electronic factors are governing the addition reaction to a larger extent than expected.



(Scheme 34)

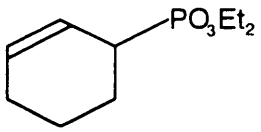
It was, consequently, decided to investigate the addition reactions of diethyl cyclohexen-2-ylphosphonate and aldehydes. The latter should be more electrophilic than ketones and also have a sterically less congested carbonyl carbon. It was, indeed, found that aldehyde addition proceeds to a large extent. In most cases studied, addition occured in the α-position with respect to phosphorus, similar to alkyl halides. A mixture of diastereoisomers was always obtained. As discussed earlier, this is due to two steric courses possible for the approach of the aldehyde and phosphonate carbanion. The resultant adduct (16) contains two



(16)

chiral centres, one α and the other ß with respect to phosphorus. Comparable yield of stereoisomers were usually obtained, athough it was possible to vary the ratio somewhat by the rate of addition of the aldehyde to the phosphonate carbanion. Since no effective probe exists in these molecules to determine their relative stereochemistry, structural assignments were not made to distinguish between the two isomers. Due to the oily nature of the adducts, X-ray structure determinations were impossible. Structures of the adducts were confirmed using high resolution ^{1}H and ^{31}P n.m.r. as well as mass spectrometry. The most common fragmentation pattern involved cleavage of the bond established between the carbanion and the aldehyde moiety in the addition step. Molecular ion peaks were usually observed, although intensities were generally low. Results of the addition reactions are summarised in Table 4.

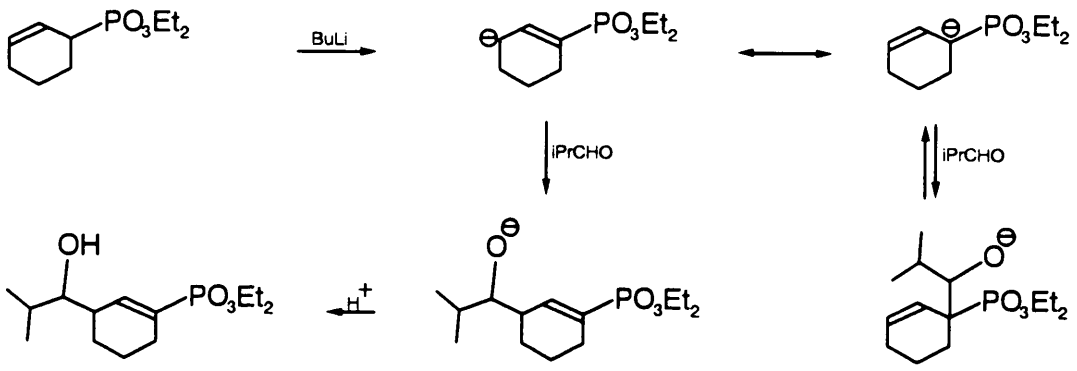
Table 4

Phosphonate	Aldehyde	Yield (%)	
	Acetaldehyde	90[a]	99[b]
	Propionaldehyde	65[a]	90[b]
	Butyraldehyde	80[a]	90[b]
	2-Methylpropionaldehyde	40[a]	50[b]
	Acrolein	71[a]	85[b]
	Benzaldehyde	48[a]	60[b]
	Phenylacetaldehyde	69[a]	95[b]
	3,4,5-Trimethoxybenzaldehyde	39[a]	60[b]
	Cyclohexylcarboxaldehyde	0[a]	0[b]

a - isolated yield
b - yield based upon ^{31}P n.m.r. spectra

Acetaldehyde was chosen as first electrophile due to the relatively low steric bulk on the carbonyl centre. The yield of 2-hydroxyphosphonate was nearly quantitative. This seems to confirm an earlier conclusion that the lack of reactivity of cyclohexenylphosphonates towards ketones is not only determined by steric factors. The exchange of a hydrogen atom for a methyl group at the reactive site of the electrophile would not be expected to have such a dramatic effect.

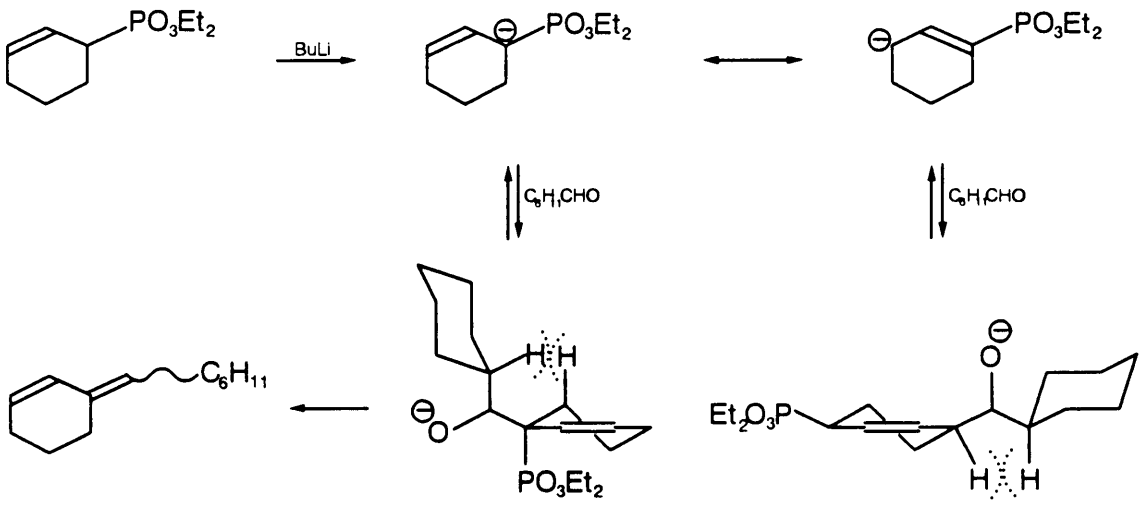
In order to investigate the effect of size of substituents on the carbonyl moiety, propionaldehyde was used as electrophile. Albeit in slightly lower yield than for acetaldehyde, reaction proceeded to a very high extent. This demonstrated that increased chain length of the alkyl substituent of the electrophilic centre does not affect the approach, and subsequent binding, of the nucleophile significantly. This was even more clearly demonstrated by the facile addition of butyraldehyde to diethyl cyclohexen-2-ylphosphonate. Yield of the product obtained from this reaction corresponded to that of propionaldehyde and the same phosphonate. This observation would probably not hold true for very long chains due to random coiling normally associated with the latter. Branching of the side chain on the aldehyde was found to have a dramatic effect as was evident from the significantly decreased yield of adduct obtained from the reaction of cyclohexen-2-ylphosphonate and 2-methylpropionaldehyde. Moreover, in this case, α-addition products were not observed. Isomerisation of the double bond and subsequent γ-addition was found to be the predominant reaction route (Scheme 35). Material balance consisted of both parent and isomerised phosphonate.



(Scheme 35)

It is uncertain whether α-addition did in fact occur initially, though this is probably the case. As a result of the reversibility of α-addition, the thermodynamic product was formed. Reaction with 2-methylpropionaldehyde, therefore, represents the first example in which steric effects of the chosen substrate are responsible for a total change in the regioselectivity of the condensation process.

Cyclohexylcarboxaldehyde was also used as electrophile, due to its increased bulkiness as compared to 2-methylpropionaldehyde. Although a decreased yield of adduct was expected, it came as a surprise when starting material was recovered as the only phosphorus-containing product. In addition, considerable amounts (34%) of *cis* and *trans* dienes were obtained. These could only be formed from an intermediate 2-hydroxy adduct. Fragmentation of the latter would afford parent phosphonate and diene (Scheme 36). It is evident, however, that the anion of the 2-hydroxyphosphonate is unstable, probably as a result of repulsion between the two alkyl rings and phosphonate moiety.



(Scheme 36)

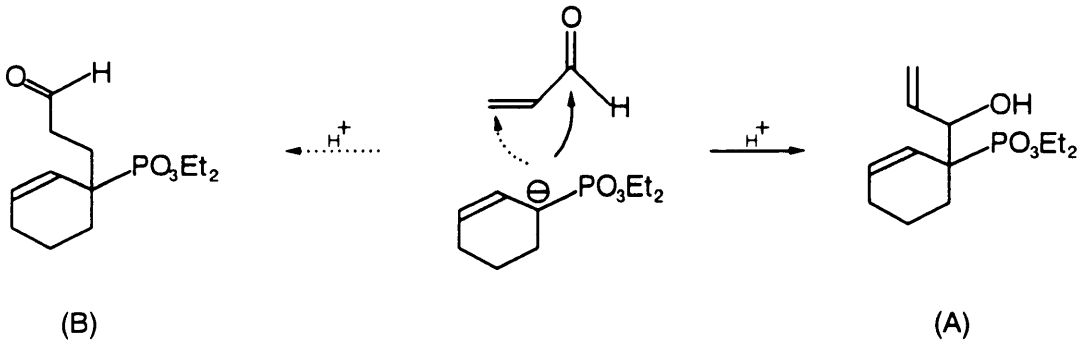
The hypothesis of steric effects was tested by the addition of benzaldehyde to a mixture of cyclohexen-2-ylphosphonate and butyllithium in THF. The corresponding 2-hydroxy-phosphonate (Table 4; entry 6) was obtained in good yield. It is thought possible that, due to the planar geometry of the ring on the carbonyl centre of benzaldehyde, approach of the

nucleophile is facilitated relative to the non-planar cyclohexyl group in cyclohexyl-carboxaldehyde. Insertion of a methylene moiety between the aromatic ring and carbonyl group caused a significant enhancement of adduct formation. The steric bulk of the phenyl ring attached to the carbonyl carbon atom in benzaldehyde is known to be greater than that of a benzyl group.[79] Addition to phenylacetaldehyde proceeded to a similar extent than to the less bulky propionaldehyde. Hence, it can be concluded from results of aldehyde addition reactions that steric effects play a dominant role in determining the reactivity of aldehydes towards cyclohexenylphosphonate ester carbanions.

In order to establish the importance of electronic factors on the addition reaction, 3,4,5-trimethoxybenzaldehyde was used as electrophile. Since three electronegative substituents are present on the aromatic ring and only one is capable of conjugation with the aldehyde moiety, this aldehyde would be expected to be more electrophilic than benzaldehyde. However, reaction of the methoxy substituted aldehyde with cyclohexen-2-ylphosphonate afforded adduct in comparable yield to benzaldehyde. Thus, it seems as though electronic effects on the aldehyde are less important than steric factors.

It was demonstrated earlier that steric bulk of substituents on the carbonyl centre of the electrophile can alter the regiospecificity of addition reactions on the ambident nucleophile. This led to speculation on whether addition reactions to aldehydes proceed regioselectively. Acrolein was regarded as a model electrophile to be used in order to establish the mode of addition of lithiated cyclohexen-2-ylphosphonate. In the previous chapter it was pointed out that phosphoryl containing compounds display "alpha" type of behaviour. Phosphonate carbanions should be somewhat "harder" in nature relative to, e.g. phosphine oxides, since electron donation of the lone pairs on the alkoxy substituents at phosphorus would render the phosphonate moiety more electropositive. Destabilisation of an adjacent negative charge can, thus, be expected. Increased "hardness" of the nucleophile would lead to 1,2-addition at the carbonyl moiety of an α,ß-unsaturated aldehyde since this is the "harder" centre[20] (Scheme 37). In contrast, "softer" nucleophiles would be expected to add to the double bond in a 1,4

fashion.



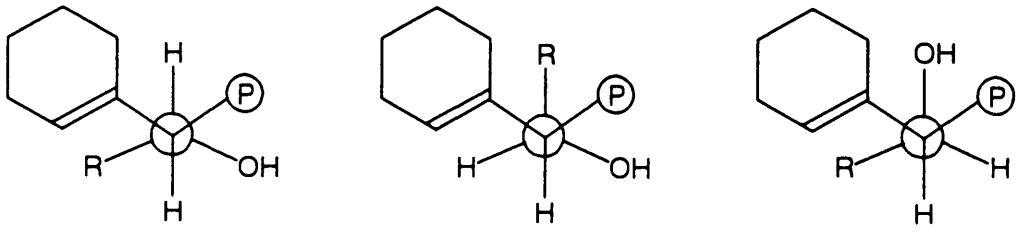
(B) (A)

(Scheme 37)

Upon treatment of diethyl cyclohexen-2-ylphosphonate with butyllithium and addition of acrolein, compound A (Scheme 37) was found to be the predominant product. No 1,4-addition product was observed, even though the terminal end of the double bond is sterically less crowded. It has to be noted, however, that 1,2-addition is common in bimolecular substitution reactions,[24] hence, this may be the determining factor. The result also demonstrated that addition of the phosphonate carbanion to acrolein is a facile process, since the latter reaction proceeded at a higher rate than polymerisation of the electrophile, which is known to occur easily. The resultant adduct can also polymerise, similar to the adduct of propen-2-ylphosphonate and acrolein.[74] However, probably due to the bulk of the 2-hydroxy-cyclohexenylphosphonate, this was not observed and the adduct could be isolated.

In order to extend the investigation of aldehyde addition reactions, diethyl cyclohexen-1-ylmethylphosphonate (9b) was also used as substrate. In the previous section it was demonstrated that alkylation of the latter proceeded to a higher extent than for the sterically more crowded cyclohexen-2-ylphosphonate. Addition to carbonyl centres was, thus, proposed to be facilitated and α-addition with respect to phosphorus was expected to predominate. Indeed, diethyl cyclohexen-1-ylmethylphosphonate could be added to various aldehydes. Addition always occured in the α-position and, as with cyclohexen-2-ylphosphonate, two diastereoisomers were usually obtained. In contrast to adducts of

cyclohexen-2-ylphosphonates, products derived from diethyl cyclohexen-1-ylmethyl-phosphonate contained a structural probe to establish the relative configuration of the isomers. Using the hydrogen atoms α-to phosphorus and α with respect to the hydroxyl group, structural assignments were made possible. In the proton n.m.r. spectrum, a large coupling constant ($\approx$ 10Hz) between these two protons was observed for the one isomer. The latter always resonated at a lower field strength in the ^{31}P n.m.r. spectrum than the isomer with the smaller coupling constant ($\approx$ 4Hz) between the two protons under discussion. Since intramolecular attraction between the phosphoryl and hydroxyl group is known,[80] it follows from inspection of the Newman projections of the most populated conformer that the isomer with the larger coupling constant (*trans* orientation of the vicinal hydrogen atoms) corresponds to the RR or SS pair of enantiomers (fig. 6). By default, the other isomer was denoted as the RS or SR enantiomeric pair.



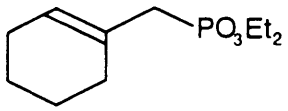
RR(SS) RS(SR) RS(SR)

P = PO_3Et_2

(fig. 6)

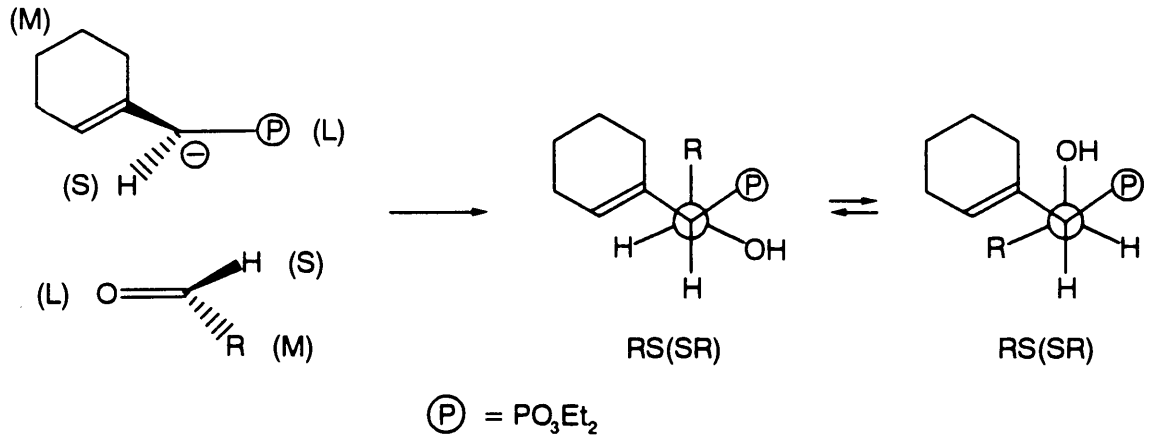
Results of the addition reactions of diethyl cyclohexen-1-ylmethylphosphonate (9b) to aldehydes are summarised in Table 5. Propionaldehyde was demonstrated to add to diethyl cyclohexen-1-ylmethylphosphonate to afford the adduct in a nearly quantitative yield. Steric bulk of substituents on the carbonyl centre of the electrophile was also shown to have a lesser effect on the addition step relative to cyclohexen-2-ylphosphonate. This was evident from a experiment in which 2-methylpropionaldehyde added to the phosphonate carbanion to afford the α-substituted product, contrary to the reaction of the same aldehyde with diethyl cyclohexen-2-ylphosphonate (8b).

Table 5

Phosphonate	Aldehyde	Yield (%)	
	1. Propionaldehyde	85[a]	95[b]
	2. 2-Methylpropionaldehyde	56[a]	75[b]
	3. Acrolein	78[a]	90[b]
	4. Benzaldehyde	85[a]	90[b]
	5. Phenylacetaldehyde	84[a]	95[b]
	6. Cyclohexylcarboxaldehyde	43[a]	70[b]

a - isolated yield
b - yield based upon ^{31}P n.m.r. spectra

In addition, reaction of cyclohexen-1-ylmethylphosphonate and cyclohexylcarboxaldehyde occured and resulted in the formation of the α-substituted phosphonate adduct which was stable enough to be isolated. However, only the RS,SR enantiomeric pair of isomers were obtained, which seems to indicate that steric requirements govern the nucleophilic addition reactions of this aldehyde. Since approach of the reacting centres would involve the sterically least hindered spatial arrangement whereby a large group is situated between two smaller groups (fig. 7), the RS,SR pair would be expected to be the favoured species.

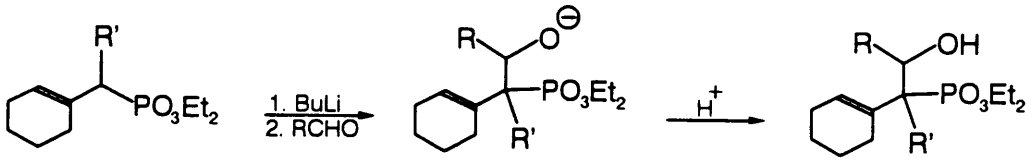


(fig. 7)

From the Newman projections of the RR (SS) and RS (SR) diastereo-isomers (fig. 6), it is evident that the former enantiomeric pair should be more stable since the bulky substituents are more evenly spaced. Thus, it is proposed that the transition state for addition is early and resembles reactants, hence, little bond formation has occured. One would, consequently, expect spatial arrangement of groups in the product to play a lesser role than the relative orientation of reactants in order to attain the transition state.

As for diethyl cyclohexen-2-ylphosphonate, phenylacetaldehyde reacted with the cyclohexen-1-ylmethylphosphonate analogue to afford the 2-hydroxy adduct in high yield. Benzaldehyde also gave the expected product in higher yield than that obtained from the reaction of benzaldehyde and cyclohexen-2-ylphosphonate. This result again indicates the enhancement in reactivity when the nucleophilic centre is less crowded. Diethyl cyclohexen-1-ylmethylphosphonate was also demonstrated to add to acrolein in a regiospecific fashion. The carbon α with respect to phosphorus acted as the nucleophilic centre and addition took place at the carbonyl carbon of the aldehyde. No 1,4-products were observed and polymerisation of the electrophile did not compete.

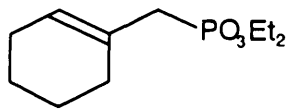
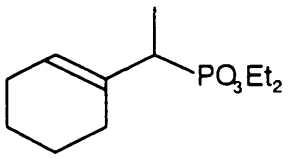
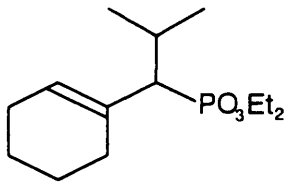
Since diethyl cyclohexen-2-ylphosphonate reacted with alkyl halides and aldehydes to afford a quaternary carbon atom, α with respect to phosphorus, α-disubstituted cyclohexen-1-yl-methylphosphonate derivatives were prepared. These were expected to react more rapidly with aldehydes upon proton abstraction since the α-position is more electron rich (Scheme 38).



(Scheme 38)

From the facile addition of cyclohexen-2-ylphosphonate to various aldehydes, additional crowding of the α-carbon in the cyclohexen-1-ylmethyl analogue was considered to be negligible as long as similar aldehydes were used. Results of the condensation reactions are summarised in Table 6.

Table 6

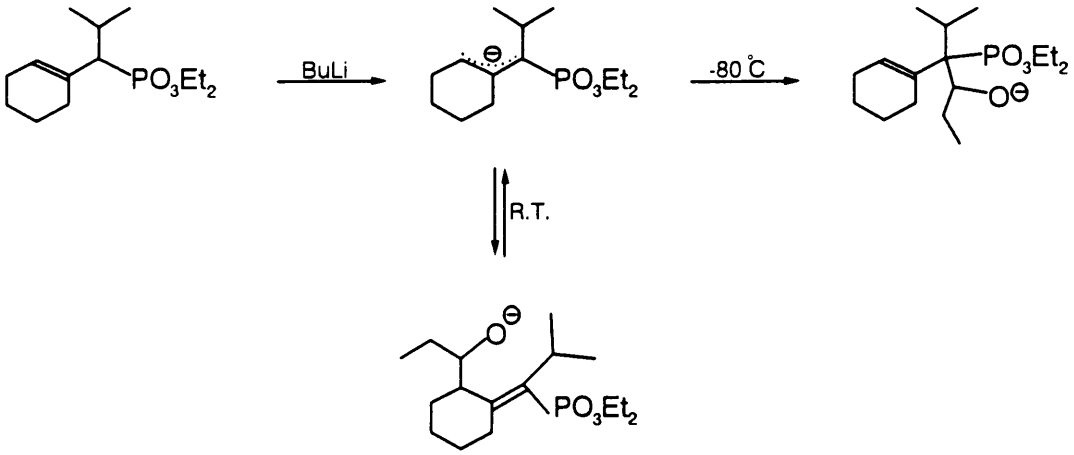
Phosphonate	Aldehyde	Yield (%)	
	Propionaldehyde	85[a]	95[b]
	Benzaldehyde	85[a]	90[b]
	Benzaldehyde	55[a]	70[b]
	Propionaldehyde	30[a]	60[b]
		70[c]	85[c]

a - isolated yield
b - yield based upon ^{31}P n.m.r. spectra
c - work-up at low temperature

Upon treatment of the α-methyl substituted phosphonate with base and subsequent addition of benzaldehyde a fully α-substituted phosphonate resulted. Although the yield of the adduct was somewhat lower than for the α-monosubstituted phosphonate, the two diastereoisomers resulting from this reaction were isolated in comparable amounts. In addition, the yield of adduct was greater than that obtained from the reaction of cyclohexen-2-ylphosphonate and benzaldehyde.

In order to establish the importance of steric congestion *versus* enhanced nucleophilicity of

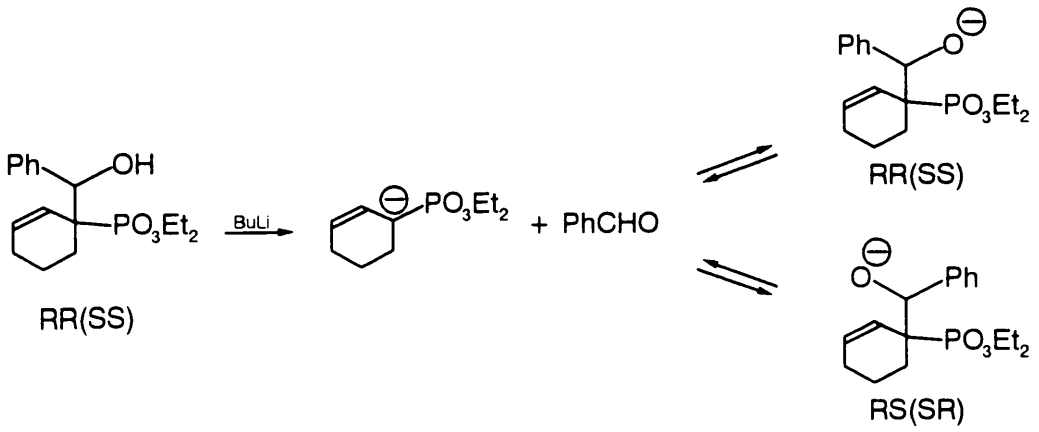
the α-carbon, the α-*iso*-propyl substituted carbanion was treated with propionaldehyde. Usual work-up of the reaction mixture at ambient temperature afforded γ-substituted product as the major component of the reaction mixture (Scheme 39).



(Scheme 39)

However, quenching of the reaction mixture with aqueous ammonium chloride solution at low temperature afforded the α-substituted product. This clearly indicates that α-addition is the kinetic pathway and that it is a reversible process. At elevated temperatures, isomerisation of the olefinic bond and subsequent recombination occurs to give the thermodynamic γ-substituted adduct. The latter step is also reversible, as demonstrated by the observation that parent phosphonate was recovered upon treatment of the γ-adduct with base.

Reversibility of the condensation step is well established.[47] However, although the presence of parent phosphonate gave an indication of reversibility when these adducts were treated with base, recombination should also occur. Hence, the isomeric mixture of adducts of diethyl cyclohexen-2-ylphosphonate and benzaldehyde was separated. Treatment of the RR (SS) enantiomeric pair with butyllithium resulted in the decomposition of the adduct to parent phosphonate (Scheme 40).

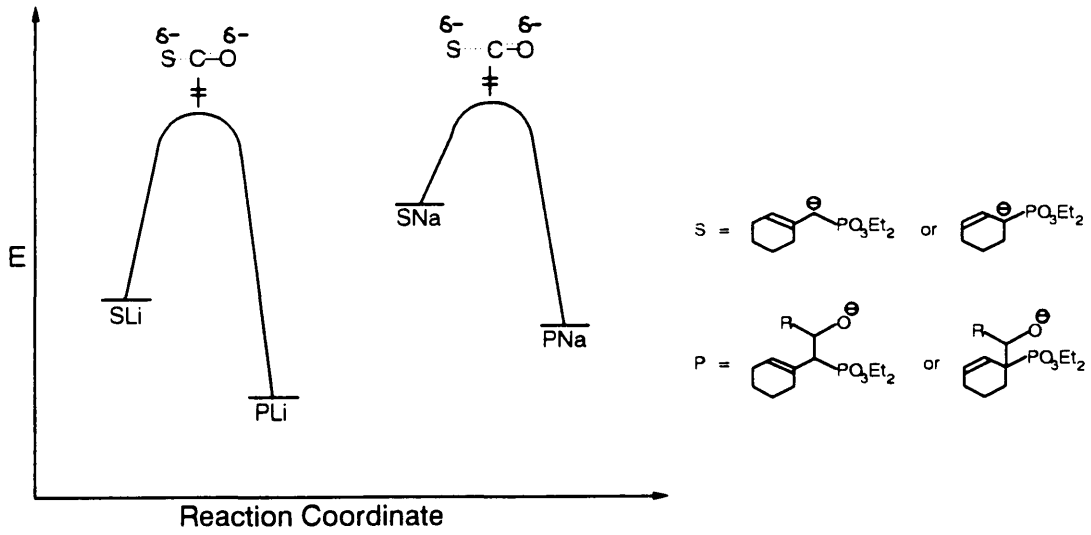


(Scheme 40)

Since the resultant phosphonate carbanion can be approached again by the aldehyde in any spatial orientation, recombination would result in a mixture of diastereoisomers. This was, indeed, observed. Even though a single diastereoisomer was used initially, comparable amounts of both RR (SS) and RS (SR) diastereoisomers were recovered.

It was observed that the use of dimethoxyethane as a solvent, instead of tetrahydrofuran, had a detrimental effect on the addition reaction. This was surprising, since solvation of the metallic counterion would have been expected to be enhanced by the former. A more free and, hence, a more reactive nucleophile would have resulted. In addition, it was found that the use of sodium hydride as base did not effect addition, although some deprotonation was observed. In contrast, the presence of butyllithium resulted in formation of 2-hydroxy adducts between the phosphonates and aldehydes. In the previous paragraph mention was made of the fact that treatment of single diastereoisomers of these adducts with butyllithium, resulted in decomposition and subsequent recombination of the reactants to afford a mixture of diastereoisomers. However, by using sodium hydride in the latter procedure, only parent phosphonate, resulting from the retro-addition reaction, and non-phosphorus containing products were recovered. No recombination products were observed. It is, thus, suggested that the metal counterion plays a very important role in the condensation step. Hence, neither the free phosphonate carbanion, nor its relatively reactive sodium salt can stabilise the transition state for addition. Since lithium cations are known to complex strongly to

carbon and oxygen anions, the former can stabilise the transition state to a larger extent than sodium ions. However, sodium salts of cyclohexenylphosphonates also failed to react with alkyl halides. Stabilisation of the transition state of these substitution reactions by metal counterions should not be very important. An alternative explanation for the difference in reactivity between lithium and sodium salts of the phosphonate carbanions can be forwarded. The sodium salts are closer in energy to the transition state than the lithium salts due to the stability of carbon-lithium bonds.[29] Hence, the transition state for aldehyde addition is earlier in the case of the former (fig. 8) and comparatively little bond formation has occured. Decomposition back to reactants are consequently much more facile.

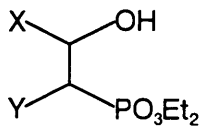


(fig. 8)

In the case of the lithium salts of phosphonate carbanions, the transition state is established later on the reaction coordinate and relatively more bond formation is observed. Recombination to products are, thus, more facile. In addition, the lithium salt of the resultant 2-hydroxyphosphonate should be lower in energy relative to the sodium salt. Hence, stability of products is an additional driving force for condensation reactions of lithium salts of phosphonate carbanions.

(C) Diene formation

In the previous section, mention was made of the potential synthetic value of 2-hydroxy-phosphonate esters derived from the addition of alkenylphosphonates to aldehydes. Probably the most important feature of these adducts is their use as precursors of dienes. Although many literature reports are available on olefination of aromatic systems,[47] relatively few research groups are interested in diene formation from alkenylphosphonates.[51] To the author's knowledge, no work has been done on cycloalkenylphosphonates. A literature survey demonstrated that phosphonate precursors of dienes usually require activating substituents on either of the carbon atoms situated α and ß with respect to the hydroxyl moiety[45,81] (17).

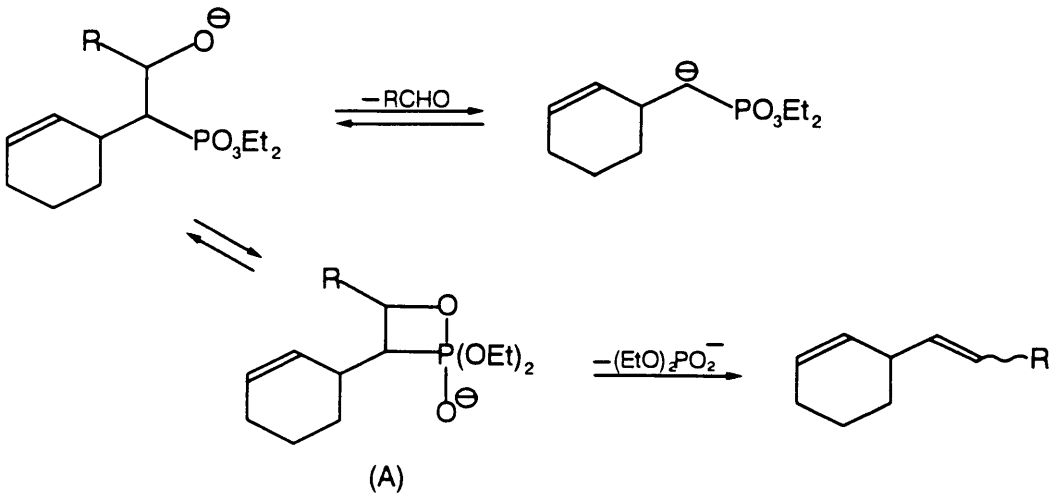


(X,Y = Ar, CN, CO_2Et)

(17)

Reports specify that even the presence of an olefinic bond is not stabilising enough to effect diene formation.[51] Hence, the synthetic potential of the diethyl 2-hydroxycyclohexenyl-phosphonates prepared previously was, subsequently, investigated. It was seen earlier that formation of the 2-hydroxy adducts derived from cyclohexenylphosphonates and aldehydes is under kinetic control. The thermodynamic products were 4-hydroxyphosphonates, but these compounds are not useful as precursors of dienes. Consequently, diastereoisomers of the 2-hydroxy adducts, prepared by kinetically controlled addition, were separated by preparative thin layer chromatography on silica gel. Adducts derived from diethyl cyclohexen-1-ylmethylphosphonate (9b) were initially investigated. Reaction conditions involved treatment of a single diastereoisomer of the 2-hydroxyphosphonate in dimethyl formamide with sodium hydride. As described earlier, the use of butyllithium as base did not result in diene formation. In fragmentation reactions of all the examples studied,

competition between retro-addition and diene formation reactions was observed (Scheme 41).

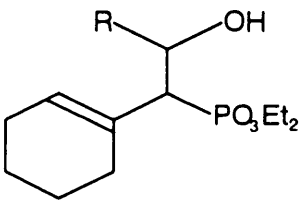


(Scheme 41)

Although conclusive evidence for the existence of the cyclic four-membered oxaphosphetane intermediate, A, is lacking, its intermediacy in this reaction is widely accepted. Some workers have claimed detection of this species in ^{31}P n.m.r. spectra acquired at low temperature.[82] It is, thus, considered valid to regard the oxaphosphetane as intermediate in the fragmentation process. Results of these fragmentation reactions of diethyl 2-hydroxy-cyclohexen-1-ylmethylphosphonates are summarised in Table 7. In all entries, the yield of diene derived from individual RR (SS) and RS (SR) diastereoisomers is reported. Yields are based upon isolated products, as well as on ^{31}P n.m.r. spectra, since volatility of some products led to diminished yield upon isolation of the dienes. Material balance always consisted of parent phosphonate resulting from the retro-addition reaction.

Treatment of the RR(SS)-2-hydroxy adduct of cyclohexen-1-ylmethylphosphonate and propionaldehyde (Table 7; entry 1) with base, afforded a considerably higher yield of the diene than the reaction of the RS (SR) stereoisomer. In the reaction of the latter, retro-addition was found to be more facile. In fragmentation reactions of both stereoisomers of the 2-hydroxy-2-*iso*-propyl derivatives (entry 2), retro-addition was the preferred pathway.

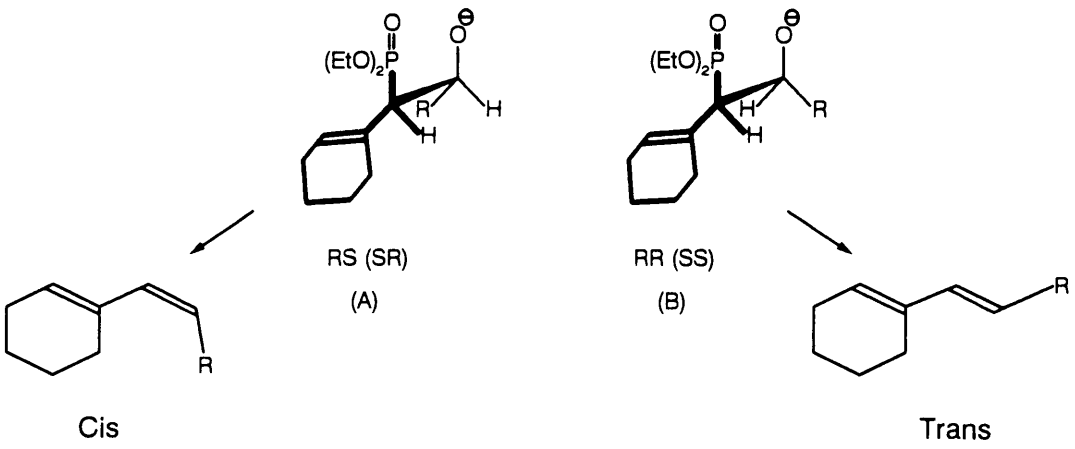
Table 7

Phosphonate	R	RR(SS)[a] Yield (%)		RS(SR)[a] Yield (%)	
	1. Ethyl	56[b]	80[c]	2[b]	5[c]
	2. Iso-propyl	27[b]	35[c]	39[b]	45[c]
	3. Phenyl	52[b]	65[c]	8[b]	15[c]
	4. Benzyl	14[b]	20[c]	0[b]	0[c]

a - relative configuration of the adduct
b - isolated yield
c - yield based upon ^{1}H n.m.r. spectra

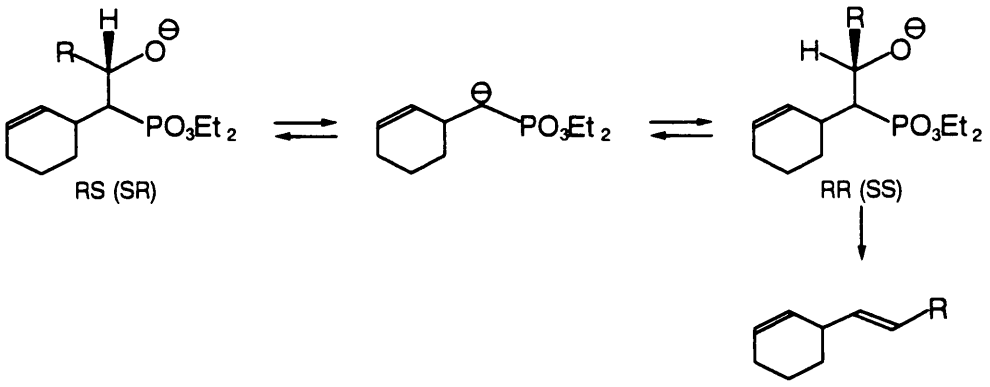
A slightly higher yield of diene was obtained from the RS (SR) pair of enantiomers. However, similar to the fragmentation reaction of the 2-hydroxy-2-ethyl adduct (entry 1), the 2-hydroxy-2-phenyl (entry 3) and 2-hydroxy-2-benzyl (entry 4) derivatives resulted in a higher yield of diene being formed from the RR (SS) than from the RS (SR) diastereo-isomers. For the 2-phenyl substituted 2-hydroxyphosphonate (entry 3), decomposition to afford diene and diethyl phosphate proceeded more efficiently than aldehyde elimination to parent phosphonate.

A surprising observation from the fragmentation reactions of (cyclohexen-1-yl)-2-hydroxy-alkylphosphonates (fig. 9; A and B) was that dienes derived from both stereoisomers of the adducts had the same *trans* configuration. From the three-dimensional projections, it is evident that, in order to attain the cyclic four-membered transition state required for fragmentation to alkene, eclipsing of the alkoxyl and phosphoryl centres is required in both stereoisomers (fig. 9).



(fig. 9)

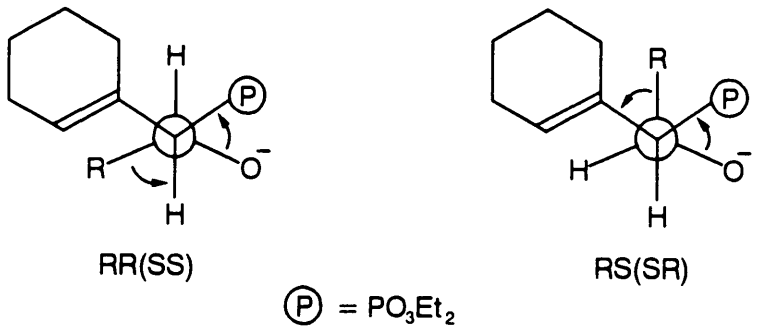
However, once the betaine is formed, collapse of the intermediate would result in *cis* and *trans* alkenes being formed from the RS (SR) and RR (SS) isomers respectively. The vicinal coupling constant between the two protons on the exocyclic double bond in the proton n.m.r. spectra of the dienes clearly indicated *trans* geometry of the products. Moreover, identical spectra were obtained for the dienes derived from both diastereoisomers of the respective 2-hydroxyadducts. This is possibly due to isomerisation of the *cis* alkene once it is formed in the highly basic solution, similar to observations made by Pattenden *et al.*[67] An alternative, and more likely, explanation involves degradation of the RS(SR)-2-hydroxy adduct to parent phosphonate and aldehyde. Subsequent recombination would afford a mixture of two diastereoisomers of which the RR (SS) pair would fragment to *trans* dienes (Scheme 42).



(Scheme 42)

In support of this postulation is the observation that the rate of diene formation from the RR (SS) stereoisomer is usually higher than that of the RS (SR) isomer. However, it was pointed out in the previous section that sodium hydride could not effect the addition of phosphonate to aldehydes. Hence, uncertainty exists about the exact mechanism by which *trans* dienes are formed from *cis* dienes. Additional evidence for the reversibility of the addition reaction is that the yield of the diene was increased significantly (65-80%) when the 2-hydroxy-2-phenyl adduct (Table 7; entry 3) was allowed to react for extended periods of time. Competition from the retro-addition reaction was still evident, though recombination and fragmentation to dienes depleted the source of parent adduct.

In order to determine the reason for the difference in reactivity between the two diastereoisomers of each adduct, a structural analysis of these molecules were conducted. Fragmentation of the adducts to parent phosphonate and aldehydes does not require a specific conformation of groups in the adduct. However, as demonstrated before, phosphate elimination to afford dienes necessitates eclipsing of the alkoxy and phosphoryl moieties. It is evident from inspection of the Newman projections of the 2-hydroxy adducts that this is achieved more easily in the case of stereoisomers with the RR (SS) relative configuration (fig. 10).

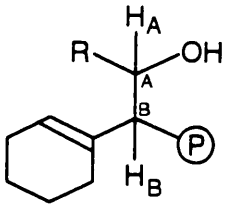


(fig. 10)

Steric congestion between the bulky cyclohexenyl ring and alkyl substituent R would be relieved in the RR (SS) isomer. Mutual attraction between the alkoxyl and phosphoryl

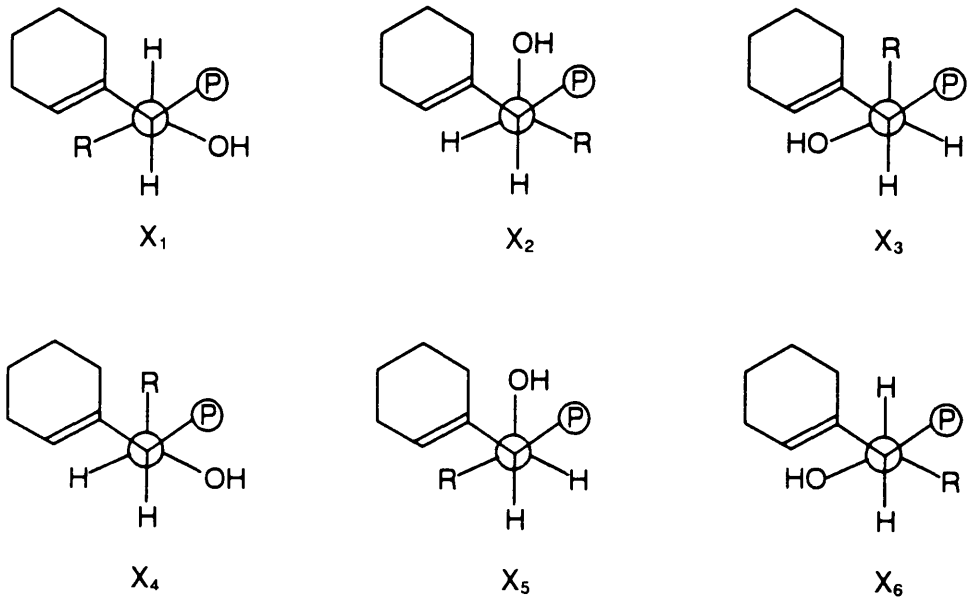
groups are known. Hence, their proximity should not destabilise the conformation. However, eclipsing of the bulky hydrocarbon substituents would be required for phosphate elimination from the RS (SR) pair of enantiomers. The release of steric strain in the RR(SS)-2-hydroxy adducts, as well as the fact that thermodynamically more stable *trans* dienes result directly from their decomposition, are probably the reasons for the enhanced reactivity of these isomers, as demonstrated in Table 7. However, if the transition states for fragmentation to diene and parent phosphonate are early, as described for the latter in the previous section, product stability would not be expected to play a negligible role. The significantly greater yield of diene obtained upon decomposition of the RR(SS)-2-hydroxy-2-phenyl adduct (Table 7; entry 3), as compared to the 2-benzyl analogue (entry 4), gives further evidence that relief of steric congestion is a driving force for betaine formation. The phenyl group is known to be sterically more bulky than the benzyl group.[79] Hence, greater repulsion between the aromatic and cyclohexenyl ring forces the phosphoryl and alkoxyl centres even closer.

A comprehensive proton n.m.r. spectroscopic study of these 2-hydroxy adducts were conducted in order to establish the conformation of these molecules, since it was evident from the above discussion that conformational effects govern the fragmentation reaction. As described earlier, the relative configuration of each diastereoisomer was determined using the values of the vicinal coupling constant between the two protons on the carbon atoms which are situated α with respect to phosphorus (H_B) and to the hydroxyl group (H_A) (fig. 11).



(fig. 11)

With respect to the rotation about the C_A-C_B bond (fig. 11), three staggered conformations can exist for each diastereoisomer (fig. 12).

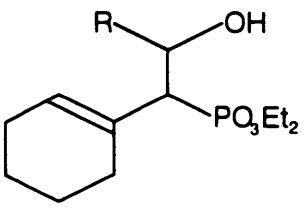


$X_{1\text{-}3}$= RR(SS) $X_{4\text{-}6}$= RS(SR)

(fig. 12)

Table 8 shows that the vicinal coupling constant, ^3J, is large (*ca.* 10Hz) for all RR (SS) stereoisomers, which gives evidence for the anti orientation of the vicinal hydrogens as indicated in X_1 (fig. 12).

Table 8

Phosphonate	R	RR(SS)[a] $\delta^{31}P$	RR(SS)[a] $^3J_{HH}$(Hz)	RS(SR)[a] $\delta^{31}P$	RS(SR)[a] $^3J_{HH}$
	1. Ethyl	30,35	9,6	29,50	4,0
	2. Iso-propyl	30,94	10,0	29,95	3,9
	3. Phenyl	29,46	9,8	27,78	5,1
	4. Benzyl	29,65	9,5	29,21	4,0

a - relative configuration of the adduct

Gauche orientation of the two protons in the RS (SR) isomers was evident from the relatively small coupling constant (*ca.* 4Hz) in the proton n.m.r. spectra. The observed coupling constants are related to the populations, (χ), of the individual rotamers, (X), and to the coupling constants, (^3J_g, ^3J_a), calculated for each rotamer according to equation 1.

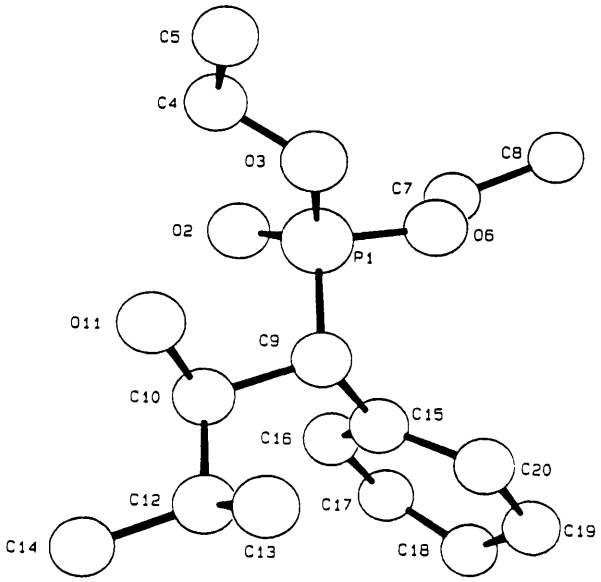
$$^3J_{AB} = \chi_1\ ^3J_a(X_1) + \chi_2\ ^3J_g(X_2) + \chi_3\ ^3J_{g'}(X_3) \qquad \text{eqn. 1}$$

$$^3J_{AB} = \chi_1\ ^3J_a(X_1) + (\chi_2 + \chi_3)\ ^3J_{g(av)} \qquad \text{eqn. 2}$$

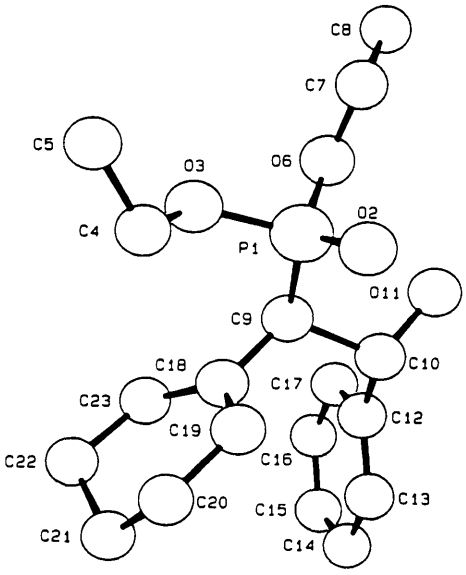
where $^3J_{g(av)} = 0{,}5[^3J_g(X_2) + {}^3J_{g'}(X_3)]$

Since the 2-hydroxy adducts contain only one pair of vicinal hydrogen atoms at the C_A-C_B fragment, eqn. 1 had to be simplified by combining both terms involving the *gauche* orientation of the two atoms under consideration and averaging the two calculated ^3J_g values (eqn. 2). Calculation of the ^3J_g and ^3J_a values was based on the approach by Haasnoot *et al*,[83] using the available group electronegativities.[84] It was found that for the RR (SS) stereoisomer, in $CDCl_3$, the population of rotamer X_1 (fig. 12) is $\approx$95-100 %. It seems feasible that a combination of attractive intramolecular hydrogen bonding between the hydroxy and phosphoryl group, and release of steric repulsion, results in rotamer X_1 representing the sole conformation of the RR(SS)-2-hydroxyphosphonate in solution. Rotamers X_2 and X_3 involve arrangement of the large substituents *gauche* with respect to one another, thus, leading to sterically congested conformations. Even in a protic solvent, such as methanol-d_4, conformer X_1 represents the most stable spatial arrangement of substituents about the C_A-C_B bond. The coupling constant between the two vicinal protons remained virtually unchanged. Hence, limitation of the attractive intramolecular phosphoryl-hydroxyl hydrogen bonding interactions does not affect the rotamer population. For the RS (SR) diastereoisomers, it was found that contribution of rotamer X_6 (fig. 12) was negligible. Since the relative amounts of the *gauche* conformations could not be calculated independently, it is uncertain which form represents the most stable conformer.

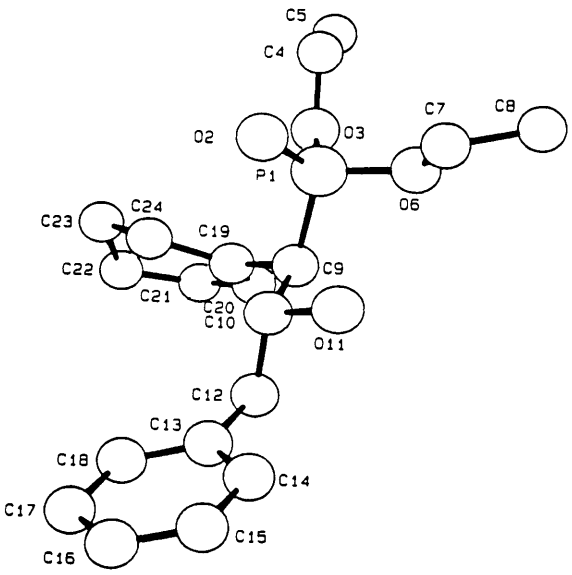
Upon separation of the diastereoisomers of the various 2-hydroxy-(cyclohexen-1-yl)methyl-phosphonates, it was found that the adducts derived from 2-methylpropionaldehyde (fig. 13; 1), benzaldehyde (fig. 13; 2) and phenylacetaldehyde (fig. 13; 3), exhibiting RR (SS) stereochemistry, were crystalline solids. Adducts with the RS (SR) relative configuration were all viscous oils. Recrystallisation of the crystalline adducts, by slow evaporation of their solutions in hexane, afforded colourless crystals on which X-ray diffraction could be performed. The perspective (Ortep[85]) views of the molecules are given in fig. 13.



(1)



(2)



(3)

(fig. 13)

For all three structures, the solid state conformations were almost identical and corresponded to rotamer X_1 (fig. 12) derived from the n.m.r. spectroscopic analysis in solution. Table 9 lists the molecular parameters most related to the conformational analysis in solution.

Table 9

Parameter	1[a]	2[a]	3[a]
Bond distances (Å)			
P-C(9)	1.826(9)	1.810(6)	1.825(6)
C(9)-C(10)	1.552(11)	1.578(9)	1.543(8)
C(9)-C(15)	1.579(12)		
C(9)-C(19)			1.536(8)
C(9)-C(18)		1.489(9)	
C(10)-O(11)	1.430(10)	1.419(7)	1.428(7)
Non-bonded distances (Å)			
O(2)-O(11) intramolecular	3.345	3.398	3.237
O(2)-O(11) intermolecular	2.740	2.745	2.678
O(2)-H(11) intramolecular	3.801	3.727	3.327
O(2)-H(11) intermolecular	1.667	1.823	1.631
P-O(11) intramolecular	2.954	3.006	2.946
P-O(11) intermolecular	4.030	3.878	4.072

a - refers to structures 1,2 and 3 in fig. 13

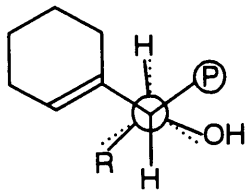
continued on next page

...Table 9 continued

Parameter	1[a]	2[a]	3[a]
Torsion angles (°)			
P-C(9)-C(10)-C(12)	-174(1)	-175(1)	-175(1)
P-C(9)-C(10)-O(11)	-55(1)	-52(1)	-56(1)
P-C(9)-C(10)-H(10)	67(1)	67(1)	65(1)
C(15)-C(9)-C(10)-C(12)	65(1)		
C(19)-C(9)-C(10)-C(12)			62(1)
C(18)-C(9)-C(10)-C(12)		60(1)	
C(15)-C(9)-C(10)-O(11)	-175(1)		
C(19)-C(9)-C(10)-O(11)			-179(1)
C(18)-C(9)-C(10)-O(11)		-177(1)	
C(15)-C(9)-C(10)-H(10)	-54(1)		
C(19)-C(9)-C(10)-H(10)			-58(1)
C(18)-C(9)-C(10)-H(10)		-58(1)	
H(9)-C(9)-C(10)-C(12)	-54(1)	-58(1)	-55(1)
H(9)-C(9)-C(10)-O(11)	65(1)	65(1)	64(1)
H(9)-C(9)-C(10)-H(10)	-173(1)	-176(1)	-175(1)

a - refers to structures 1,2 and 3 in fig. 13

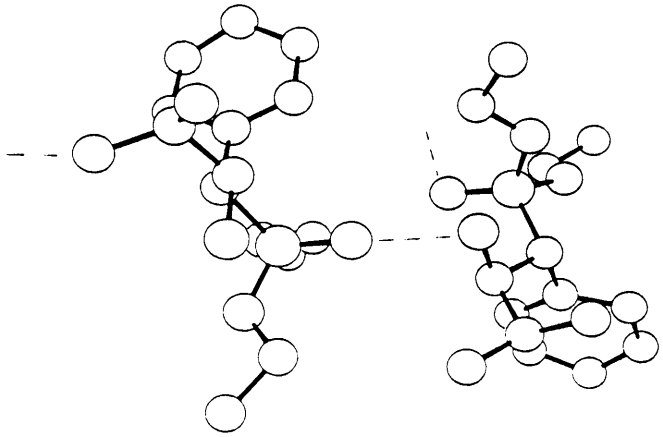
Close inspection of the dihedral angles reveals a slightly distorted staggered conformation in which a reduced torsion angle between the phosphoryl and hydroxyl centres is apparent (fig. 14).



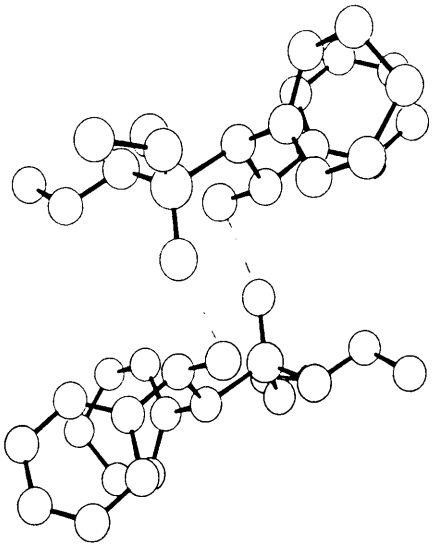
(fig. 14)

This confirmed the postulated attraction between these two groups. The latter is reflected in the enhanced reactivity observed for the RR (SS) stereoisomers of the adducts in diene formation. When substituted into the Karplus equation,[86] the average H_9-C_9-C_{10}-H_{10} (fig. 12) torsion angle affords a vicinal coupling constant of 9,40 Hz, close to the average value of 9,74 Hz observed in solution.

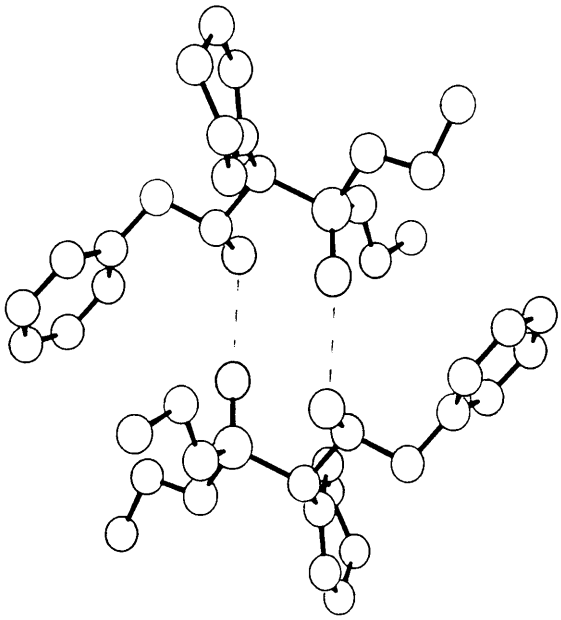
Although there is in all three compounds short intramolecular contact between the hydroxyl oxygen and the phosphorus atom ($\leq$3Å), intermolecular phosphoryl-hydroxyl hydrogen bonding occurs. This results in the large intramolecular distance ($>$3Å) between the phosphoryl oxygen and hydroxyl hydrogen. The corresponding intermolecular distance is exactly as expected for a P=O···H···O-C hydrogen bonded system.[87] The pattern of hydrogen bonding varied from compound to compound but two characteristic arrangements were observed. In the 2-*iso*-propyl substituted adduct, each molecule is involved in intermolecular hydrogen bonding *via* its hydroxyl and phosphoryl groups with two other molecules (fig. 15; 1). This type of arrangement was observed before for some tertiary 2-hydroxyalkylphosphine oxides.[88] For the 2-benzyl and phenyl adducts, intermolecular hydrogen bonding resulted in arrangement of the molecules into centrosymmetric, dimeric structures (fig. 15; 2 and 3), analogous to those observed for the related propen-2-ylphosphonate derivatives.[89] The close intramolecular proximity of the phosphorus atom and hydroxyl oxygen probably results from n(p)→d donation of the non-bonding electrons of oxygen to the empty d-orbitals of phosphorus, similar to that postulated for 2-hydroxy-alkylsulphoxides.[90]



(1)



(2)



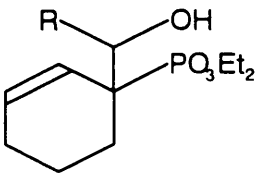
(3)

(fig. 15)

The 2-hydroxy adducts derived from diethyl cyclohexen-2-ylphosphonate were also separated into their respective single diastereoisomers. Except for the one diastereoisomer of diethyl 1-(hydroxyphenylmethyl)cyclohexen-2-ylphosphonate, all compounds were found to be oils. The former crystallised as hair-like needles and could not be employed for X-ray crystal

structure determination. Since vicinal hydrogen atoms on the carbons α to phosphorus and the hydroxyl moiety are absent, n.m.r. spectral analysis could not be used to derive the relative configuration of the adducts. Results of the fragmentation reactions of the adducts are presented in Table 10.

Table 10

Phosphonate	R	RR(SS)[a] Yield (%)	RS(SR)[a] Yield (%)
	1. Ethyl	53[b] 80[c]	37[b] 65[c]
	2. Cyclohexyl	-[d] 20[c]	-[d] 15[c]
	3. Phenyl	47[b] 55[c]	13[b] 20[c]
	4. Benzyl	35[b] 40[c]	51[b] 60[c]

a - relative configuration of the adduct
b - isolated yield
c - yield based upon H n.m.r. spectra
d - not isolated in pure form

From the table of results it is obvious that a preference for phosphate elimination to afford dienes is not limited to a single diastereoisomer. In addition, the difference in yield of diene obtained from the different stereoisomers is generally low. This is evident from the first three entries, in which diene formation was favoured for the RR (SS) diastereoisomer, whereas the last example exhibited enhanced retro-addition reactions to parent phosphonate and aldehyde for this isomer. Instead, a slightly higher yield of diene was obtained from the RS (SR) stereoisomer of the latter adduct.

In the fragmentation reactions of the adducts of cyclohexen-2-ylphosphonate and aldehydes, both *cis* and *trans* alkenes were formed from their respective RS (SR) and RR (SS) diastereo-isomeric precursors. The alkene products allowed confirmation of the previously made assignment of the relative stereochemistry of the 2-hydroxy precursors. In the substituted

dienes, the exocyclic vinylic proton H_A (fig. 16) resonated at considerably higher field in the proton n.m.r. spectrum of the *trans* (fig. 16; A) alkene than of the *cis* (fig. 16; B), as is expected.[91] Hence, it is proposed that the precursor of the *trans* dienes are adducts exhibiting RR (SS) stereo-chemistry, whereas the *cis* alkenes are derived from RS (SR) adducts. The reason for the observation that the endocyclic proton H_B always resonated at lower field strength in the proton n.m.r. spectra of the *cis* dienes than of the *trans*, is somewhat uncertain. However, from inspection of models it seems unlikely that the multiple double bonded system would be planar in Z-dienes. Hence, the expected shielding of the vinylic proton H_B does not occur and this proton resonates at lower field than expected.

(A) (B)

(fig. 16)

The lack of preference of a specific stereoisomer to afford diene was somewhat surprising considering the trend observed for the cyclohexen-1-ylmethyl analogues. However, inspection of the Newman projections of the 2-hydroxy adducts of cyclohexen-2-yl-phosphonate made this apparent anomaly clear (fig. 17).

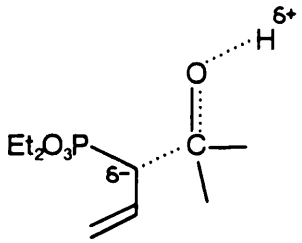
RS(SR) RR(SS)

(fig. 17)

Attraction between the phosphoryl and alkoxyl groups and anti-orientation of the bulky

phosphonate and alkyl substituent R, similar to that observed in the crystal structure of the 1-cyclohexenylmethylphosphonate analogues, were assumed. Rotation, in order to attain the betaine intermediate required for diene formation, would result in relief of steric congestion to a similar extent, irrespective of which stereoisomer is considered. This is due to the fact that eclipsing of the cyclohexenyl ring and alkyl substituent R are observed in either case.

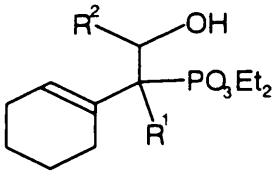
In all the decomposition reactions, effective competition from retro-addition was observed. It was thought likely that the transition states for both phosphate elimination to diene and aldehyde elimination to parent phosphonate were very close in energy. Hence, small structural differences shifted the preferred fragmentation in either direction. Since the transition state for retro-addition involves a build-up of negative charge on the carbon α with respect to phosphorus (fig. 18), it was considered feasible that introduction of an alkyl subsituent in the α position would retard this reaction. Fragmentation to diene would be favoured as a result.



(fig. 18)

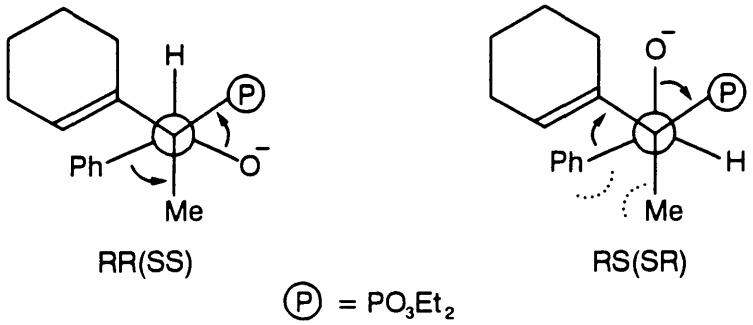
Consequently, the α-methyl and α-*iso*-propyl substituted diethyl cyclohexen-1-ylmethyl-phosphonate derivatives were prepared and reacted with benzaldehyde and propionaladehyde, respectively. Results of the decomposition reactions of these adducts are summarised in Table 11. The yields of diene obtained from fragmentation of the analogous α-unsubstituted adducts are included for comparison.

Table 11

Phosphonate	R^1	R^2	RR(SS)[a] Yield (%)	RS(SR)[a] Yield (%)
	1. Methyl	Phenyl	52[b] 60[c]	14[b] 20[c]
	2. Hydrogen	Phenyl	52[b] 65[c]	8[b] 15[c]
	3. Iso-propyl	Ethyl	50[b] 55[c]	-[d] 45[c]
	4. Hydrogen	Ethyl	56[b] 80[c]	2[b] 5[c]

a - relative configuration of the adduct
b - isolated yield
c - yield based upon H n.m.r. spectra
d - not isolated in pure form

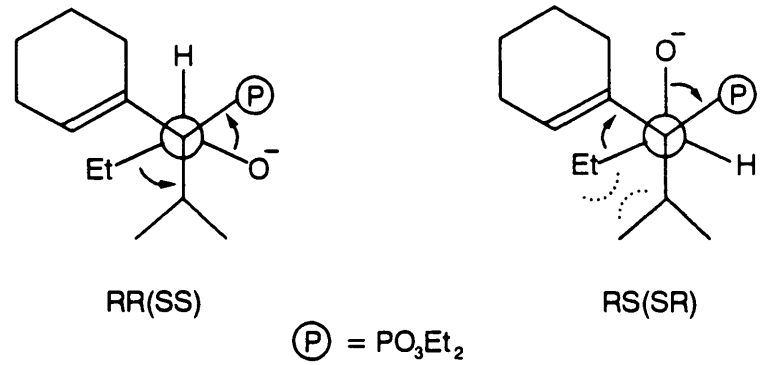
Since a hydrogen atom is absent in the α position with respect to phosphorus, assignment of the relative configuration of the adducts was based upon the relative chemical shifts of the stereoisomers in the ^{31}P n.m.r. spectra. It was observed that the RR(SS)-2-hydroxy adducts of the unsubstituted phosphonates always resonated at a lower field strength in the ^{31}P n.m.r. spectra. The one diastereoisomer of the α-methyl substituted adduct to benzaldehyde (Table 11, entry 1) was crystalline but afforded hair-like needles upon recrystallisation. Hence, X-ray crystal structure determination was not possible. From entry 1, it is evident that introduction of an α-methyl group relative to phosphorus did not have a significant effect on the yield of the diene. It is thought possible that retardation of retro-addition was counterbalanced by structural constraints to effect diene formation. Enhanced steric repulsion between the aromatic ring and methyl group upon formation of the betaine intermediate may be responsible the slightly decreased yield of diene obtained from the RR (SS) pair relative to the unsubstituted analogue (fig. 19). Similar arguments can be used to explain the somewhat higher yield of diene obtained from the RS (SR) stereoisomer relative to its unsubstituted analogue. Increased repulsion between the phenyl ring and methyl group facilitates betaine formation in the α-substituted adduct.



(fig. 19)

As for the unsubstituted analogue, only *trans* alkene was observed in reactions of both diastereoisomers. The conformational assignment was based upon the observation that the ^{13}C n.m.r. signal of the vinylic methyl group was shifted more downfield than anticipated for *cis* alkenes. This is known to be true for systems with a *trans* arrangement of substituents.[91]

A dramatic effect of additional α-substitution was, however, observed for the α-*iso*-propyl derivative (Table 11, entry 3). The yield of diene obtained from the RR (SS) stereoisomer was substantially lower than that obtained from the unsubstituted adduct. In contrast, significantly more diene was formed upon fragmentation of the RS (SR) isomer. Consideration of the Newman projections made the reason for this result apparent (fig. 20).



(fig. 20)

Contrary to the unsubstituted adduct, fragmentation of the RR (SS) *iso*-propyl analogue

would require eclipsing of the ethyl and bulky *iso*-propyl moieties. Hence, diene formation is retarded relative to the unsubstituted 2-hydroxy adduct. In the case of the RS (SR) diastereoisomer, on the other hand, eclipsing of the ethyl and cyclohexenyl ring is accompanied by relief of steric congestion of the ehtl and *iso*-propyl groups. Hence, diene formation is enhanced. This driving force is not available for the unsubstituted adduct and is apparent in the reduced yield of diene obtained from this species. In addition, aldehyde elimination to parent phosphonate is retarded by the presence of the electron donating α-*iso*-propyl group. Consequently, diene formation from the α-substituted adducts is even further facilitated.

In contrast to fragmentation reactions of α-unsubstituted 2-hydroxy adducts, both *cis* and *trans* dienes were obtained from the decomposition reactions of the two diastereoisomers of the α-*iso*-propyl adduct. This gave further evidence for the steric control of the fragmentation reaction.

(D) Conclusions

Prototropic equilibria of diethyl esters of alkenylphosphonates demonstrated that the diethoxy phosphoryl group has a very weakly stabilising effect upon an adjacent double bond. From the results obtained, it seems as though a diethoxy phosphoryl substituent exerts an effect of the same order of magnitude as a hydrogen atom. The latter has been chosen as an arbitrary point of reference by Hine and co-workers[9] in their compilation of "Double Bond Stabilisation Parameters."

Alkylation of cyclohexenylphosphonate carbanions was found to proceed smoothly under very mild conditions. Moreover, alkylation usually occured in a regioselective fashion. Addition in the α-position, with respect to phosphorus, was shown to be the predominant reaction pathway. Steric effects played a significant role. This was demonstrated by the observation that alkylation of diethyl cyclohexen-1-ylmethylphosphonate generally proceeded to a higher extent than its cyclohexen-2-ylphosphonate analogue. An attempt to alkylate the latter using the sterically bulky trimethylchlorosilane as electrophile, resulted in the only example of γ-alkylated product. The synthetic scope of these alkylated adducts as precursors for dienes was found to be limited since a literature report claiming dephosphorylation of such substrates using lithium aluminium hydride was found to be non-reproducible. However, a number of new compounds were synthesised in high yield. In addition, the reactivity and regiospecificity of cyclohexenylphosphonates in alkylation reactions were demonstrated.

From the results obtained in the alkylation reactions, model cyclohexenylphosphonates could be selected with which it was decided to conduct aldehyde condensation reactions. As before, addition usually occured in the α-position with respect to phosphorus. Due to the chirality of the adducts, two diastereoisomers were afforded by the addition reactions. A possible reason for the preferrential formation of RS (SR) diastereoisomers were offered. Although the yields were generally high, steric considerations were found to be important. An advantage of using the sterically crowded cyclohexenylphosphonates was that the

condensation product with acrolein could be isolated. Acyclic analogues were found to polymerise easily due to their reactive nature.[74] The 2-hydroxy adducts obtained from the addition reactions of the phosphonate carbanions to acrolein demonstrated that regioselective attack on the electrophile occurs.

The 2-hydroxyphosphonates acquired from the aldehyde addition reactions were employed in an investigation aiming to establish the factors governing their fragmentation reactions. In contrast to literature reports, it was shown that, even in the absence of any activating groups, 2-hydroxy adducts of cyclohexenylphosphonates can fragment to dienes and phosphate ions. Competition by the reversal of the condensation reaction was found to play a significant role. An alternative fragmentation route involved phosphate elimination to afford dienes. Due to the synthetic potential of the latter reaction, fragmentation of the 2-hydroxy adducts were extensively investigated. For this purpose, X-ray crystal structure determinations were conducted on the RR (SS) diastereoisomers of three adducts. From the results, intramolecular attraction between the phosphoryl and hydroxyl centres was evident. This observation was important, since fragmentation to dienes requires proximity of these functional groups. It was suggested that intramolecular contact between the phosphoryl and hydroxyl centres can be attained more easily in the case of the RR (SS) diastereoisomers, since steric congestion in the parent molecule is relieved relative to the RS (SR) isomer. This argument does not hold for the adducts of cyclohexen-2-ylphosphonates as steric effects are very similar regardless of which stereoisomer is considered.

Trans dienes were obtained from most of the fragmentation reactions. This was in some cases in contrast to expectations, since *cis* alkenes should be observed upon decomposition of the RS (SR) adducts. Subsequent experiments demonstrated that parent phosphonate, resulting from the retro-addition reaction, can recombine with aldehyde to afford RR(SS)-adducts which were then proposed to fragment to *trans* dienes. However, isomerisation of the *cis* alkene upon its formation cannot be excluded. Assuming the presence of an early transition state, the enhanced stability of *trans versus cis* dienes were suggested to be of little

consequence in determining the preferred fragmentation route.

In closing, some interesting observations were made and valuable information was obtained from this study. The exact role of the counterion of the carbanions remains somewhat unclear, although an attempt was made to explain the observed findings. Since a detailed investigation into the effect of counterions was outside the scope of this project, more elaborate research is required in this respect. The double bond stabilising effect of the diethoxy phosphoryl group was established by the prototropic equilibria of alkenyl-phosphonates. However, novel dienyl phosphonates were synthesised by the alkylation of diethyl cyclohexen-2-yl- and cyclohexen-1-ylmethylphosphonate with 3-bromopropene. An investigation of the alkylation of these phosphonates may indicate whether allylic addition α or ß, with respect to phosphorus, is preferred. In addition, a comparative study on the reactivity and factors governing the fragmentation reactions of the acyclic analogues is currently under investigation in our laboratories. The author also suggests that, in view of the insufficient proton n.m.r. spectroscopic data for dienes in literature, a detailed investigation of the spectra of dienes prepared from the 2-hydroxy adducts of diethyl cylohexen-2-ylphosphonate should be considered.

CHAPTER 3

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus no. MFB595010M and are uncorrected.

Mass spectra were recorded on a Varian MAT-212 double focusing direct inlet spectrometer at an ionisation potential of 70 eV.

Infrared spectra were recorded on a Bomem Michelson 100 spectrophotometer.

300 MHz n.m.r. spectra were recorded on a Bruker AC300 spectrometer with T.M.S. as internal standard for ^{1}H n.m.r. spectra and 85% H_3PO_4 as external standard for ^{31}P spectra.

Kieselgel 60 PF_{254} and kieselgel 60 were used for preparative thin layer chromatography (prep. t.l.c.) and column chromatography, respectively.

Micro-distillations were conducted using a Buchi GKR-50 glass tube oven.

All solvents and reagents were distilled before use.

CHAPTER 4

(1) Syntheses

(i) Diethyl 1-hydroxycyclohexylphosphonate[92]

Diethyl phosphite (2,02g; 0,015mol), cyclohexanone (1,42g; 0,015mol) and diethylamine (1,06g; 0,015mol) in ether (10ml) were stirred for 16h at ambient temperature. After all volatiles were evaporated, the mixture was washed with aqueous ammonium chloride solution. Removal of the solvent afforded colourless crystals of diethyl 1-hydroxycyclohexenylphosphonate, m.p. 71,3-72,0°C (lit 52-54°C[93], 72-73°C[94]); ν_{max} ($CHCl_3$) 3100cm^{-1}; ^{1}H n.m.r. ($CDCl_3$) 1,14 (6H; t; J_{HH} 7,1Hz) 1,30-1,80 (8H; m) 3,98 (4H; p; $J_{HH} = J_{HP}$ 7,1Hz) 4,30 (1H; br s), ^{31}P n.m.r. ($CDCl_3$) 26,56 ppm (Found: C, 50,85; H, 8,70. Calc. for $C_{10}H_{21}PO_4$: C, 50,87; H, 9,00%).

(ii) Triethyl phosphite[95]

A well stirred solution of phosphorus trichloride (29,2ml; 0,3mol) and dimethylaniline (127,0ml; 1,0mol), in dry diethyl ether (250ml), was cooled to 0°C and treated with ethanol (58,0ml; 1,0mol). Cooling was maintained for 1h, whereupon the reaction mixture was allowed to warm up to ambient temperature. Stirring was continued for an additional 15h. Subsequent filtration, extraction from water and distillation afforded triethyl phosphite as an oil, b.p. 80°C/20mbar (lit.[96] 57-58°C/16mmHg); ^{1}H n.m.r. ($CDCl_3$) 1,20 (9H; t; J_{HH} 7,0Hz) 3,79 (6H; p; $J_{HH} = J_{HP}$ 7,0Hz) and ^{31}P n.m.r. ($CDCl_3$) 56,61 ppm, identical to an authentic sample.

(iii) 3-Bromocyclohexene[97]

Cyclohexene (6,79g; 0,083mol) and N-bromosuccinimide (11,53g; 0,065mol), in carbon tetrachloride (40ml), were heated under reflux for 2h. After cooling and filtration,

120°C/20mbar (lit.[98] 80-82°C/4mmHg); ^{1}H n.m.r. 1,65 (2H; m) 2,10 (2H; m) 4,81 (1H; br s) 5,79 (1H; m) 5,87 (1H; m).

(iv) Diethyl methylphosphonate[99]

Diethyl phosphite (10,05g; 0,073mol), in a mixture of hexane (40ml) and THF (30ml), were treated with sodium metal (1,67g; 0,073mol). When all the solid material was dissolved, iodomethane (12,36g; 0,087mol) was added dropwise to the solution. The mixture was heated under reflux for 1,5h and stirred at ambient temperature for 14h. Subsequent washing with aq. ammonium chloride solution and distillation of the crude product afforded diethyl methylphosphonate (10,73g; 0,071mol; 96,7%) as an oil, b.p. 86°C/15mbar (lit.[96] 192-194°C); ^{1}H n.m.r. 1,20 (6H; t; J_{HH} 7,1Hz) 1,39 (3H; d; J_{HP} 17,5Hz) 3,98 (4H; p; $J_{HH} = J_{HP}$ 7,1Hz) and ^{31}P n.m.r. ($CDCl_3$) 30,81 ppm.

(v) Diethyl ethylphosphonate[100]

Triethylphosphite (5,06g; 0,030mol) was treated with a catalytic amount of iodoethane (1,00g; 6,41mmol) and heated for 3h. Distillation of the crude product gave diethyl ethylphosphonate (4,90g; 0,030mol; 97,1%) as an oil, b.p. 110°C/20mbar (lit.[100] 86,5-88°C/16mmHg); ^{1}H n.m.r. 0,86 (3H; dt; J_{HP} 20,7Hz; J_{HH} 6,8Hz) 1,01 (6H; t; J_{HH} 7,1Hz) 1,42 (2H; dq; J_{HP} 18,1Hz; J_{HH} 6,8Hz) 3,79 (4H; p; $J_{HH} = J_{HH}$ 7,1Hz) and ^{31}P n.m.r. ($CDCl_3$) 30,81 ppm.

(vi) Diethyl cyclohexen-2-ylmethylphosphonate

Diethyl methylphosphonate (1,90g; 0,012mol) and THF (25ml), under a nitrogen atmosphere, was cooled to -78°C and treated with butyllithium (1,6M in hexane) (9,3ml; 0,015mol). After 30 min., 3-bromocyclohexene (3,10g; 0,019mol) was added to the stirred solution. Cooling was maintained for an additional hour whereupon the reaction mixture was allowed

to warm up to ambient temperature and stirred for 2h. Subsequent washing with aq. ammonium chloride solution, extraction (CH_2Cl_2) and distillation of the impure product, afforded diethyl cyclohexen-2-ylmethylphosphonate (2,59g; 0,011mol; 93,2%) as an oil, b.p. (oven temp.) 115°C/0,3mbar; ^1H n.m.r. 1,23 (6H; t; J_{HH} 7,1Hz) 1,60 (2H; m) 1,95 (1H; m) 2,07 (4H; m) 4,01 (4H; p J_{HH} = J_{HH} 7,1Hz) 5,68 (1H; m) 5,79 (1H; m), ^{31}P n.m.r. ($CDCl_3$) 31,76 ppm and m/e; 232 (16,8%) 151 (48,1%) 137 (100%).

(vii) Diethyl methyl(cyclohexen-2-yl)methylphosphonate

Diethyl ethylphosphonate (2,89g; 0,017mol) and THF (25ml), under an inert atmosphere, were cooled to -78°C and treated with butyllithium (1,6M in hexane) (12,0ml; 0,019mol). After 30 min., 3-bromocyclohexene (3,36g; 0,021mol) was added to the stirred solution. Cooling was maintained for an additional hour whereupon the reaction mixture was allowed to warm up to ambient temperature and stirred for 2h. Subsequent washing with aq. ammonium chloride solution, extraction (CH_2Cl_2) and distillation of the impure product, afforded two diastereoisomers of diethyl methyl(cyclohexen-2-yl)methylphosphonate (3,97g; 0,016mol; 94,5%) as oils, b.p. (oven temp.) 120°C/0,2mbar; ^1H n.m.r. ($CDCl_3$) 0,91 (3H; dd; J_{HH} 7,2Hz; J_{HP} 1,9Hz) 1,28 (6H; t; J_{HH} 7,1Hz) 1,43 (2H; m) 1,65 (2H; m) 1,84 (4H; m) 2,58 (1H; m) 3,99 (4H; p; J_{HH} = J_{HP} 7,1Hz) 5,33 (1H; d; J_{HH} 9,0Hz) 5,67 (1H; d; J_{HH} 9,0Hz), ^{31}P n.m.r. ($CDCl_3$) 34,62 ppm and ^1H n.m.r. ($CDCl_3$) 1,02 (3H; dd; J_{HH} 7,2Hz; J_{HP} 1,9Hz) 1,28 (6H; t; J_{HH} 7,1Hz) 1,43 (2H; m) 1,65 (2H; m) 1,84 (4H; m) 2,58 (1H; m) 3,99 (4H; p; J_{HH} = J_{HP} 7,1Hz) 5,35 (1H; d; J_{HH} 9,0Hz) 5,68 (1H; d; J_{HH} 9,0Hz), ^{31}P n.m.r. ($CDCl_3$) 34,85 ppm and m/e; M^+ 246 (10,2%) 231 (5,5%) 187 (14,5%) 166 (77,1%) 111 (100,0%) 91 (63,7%).

(viii) Tetraethyl methylene-*bis*-phosphonate[101]

A reaction flask containing diodomethane (68,0g; 0,254mol) and triethyl phosphite (154,0g; 0,927mol), equipped for distillation, was heated (150°C) until the evolution of ethyliodide

ceased (2h). Subsequent distillation of the crude reaction mixture afforded tetraethyl methylene-*bis*-phosphonate (18,4g; 0,064mol; 25.2%) as an oil, b.p. 130-136°C/0.5 mbar (lit. 135-137°C/0,4mmHg); ^{1}H n.m.r. ($CDCl_3$) 1,28 (12H; t; J_{HH} 6,8Hz) 2,38 (2H; dd; J_{HP} 20,8Hz) 4,10 (8H; p; $J_{HH} = J_{HP}$ 6,8Hz) and ^{31}P n.m.r. ($CDCl_3$) 19,85 ppm.

(ix) Diethyl cyclohexen-1-ylphosphonate[103]

Diethyl 1-hydroxycyclohexylphosphonate (1,00g; 4,24mmol), in benzene (5ml), was treated with thionyl chloride (0,67ml; 5,08mmol). The mixture was heated to 60°C and stirred for 4h whereupon aqueous sodium bicarbonate was added. After extraction and evaporation of the solvent, the crude product was distilled to obtain diethyl cyclohexen-1-ylphosphonate (0,67g; 3,07mmol; 72,5%) as an oil, b.p. (oven temp.) 90°C/0,4mbar; ν_{max} ($CHCl_3$) 1634, 1234cm^{-1}; ^{1}H n.m.r. ($CDCl_3$) 1,27 (6H; t; J_{HH} 7,1Hz) 1,60 (4H; m) 2,11 (4H; m) 4,00 (4H; p; $J_{HH} = J_{HP}$ 7,1Hz) 6,76 (1H; m; J_{HP} 22,2Hz), ^{31}P n.m.r ($CDCl_3$) 20,76 ppm and m/e; M^+ 218 (67,6%) 190 (28,8%) 162 (75,8%) 147 (22,4%) 111 (39,7%) 108 (46,3%) 80 (100,0%).

(x) Diethyl cyclohexen-2-ylphosphonate[104]

A reaction flask containing triethyl phosphite (19,83g; 0,119mol) and 3-bromocyclohexene (20,02g; 0,124mol) was equipped for distillation and heated until the evolution of ethyl bromide ceased (2h). Distillation of the crude product afforded diethyl cyclohexen-2-yl-phosphonate (16,97g; 0,078mol; 65,4%) as an oil, b.p. (oven temp.) 100°C/0,4mbar (lit. 86,5-87°C/1mmHg); ν_{max} ($CHCl_3$) 1650cm^{-1}; ^{1}H n.m.r ($CDCl_3$) 1,26 (3H; t; J_{HH} 7,0Hz) 1,27 (3H; t; J_{HH} 7,0Hz) 1,50 (2H; m) 1,84 (2H; m) 1,98 (2H; m) 2,53 (1H; m; J_{HP} 27,1Hz) 4,08 (4H; p; $J_{HH} = J_{HP}$ 7,1Hz) 5,68 (1H; m) 5,85 (1H; m), ^{31}P n.m.r ($CDCl_3$) 30,92 ppm and m/e; M^+ 218 (36,0%) 190 (6,8%) 162 (6,5%) 139 (52,4%) 111 (91,1%) 80 (100,0%).

(xi) Diethyl cyclohexylidenemethylphosphonate

Tetraethyl methylene-*bis*-phosphonate (9,03g; 0,031mol) in dimethoxyethane (85ml) was treated with hexane-washed sodium hydride (0,82g; 0,033mol) and stirred for 1h at ambient temperature, whereupon cyclohexanone (3,33g; 0,034mol) was added. Stirring was continued for an additional 6h. After washing with aqueous ammonium chloride solution, extraction with diethyl ether and evaporation of the solvent, distillation gave diethyl cyclohexylidenemethylphosphonate (4,06g; 0,017mol; 56,4%) as an oil, b.p. (oven temp.) 110°C/0,2mbar; ^{1}H n.m.r ($CDCl_3$) 1,26 (6H; t; J_{HH} 7,1Hz) 1,53 (5H; m) 2,11 (2H; m) 2,52 (2H; m) 3,97 (4H; p; $J_{HH} = J_{HP}$ 7,1Hz) 5,19 (1H; d; J_{HH} 19,8Hz) and ^{31}P n.m.r ($CDCl_3$) 18,76 ppm.

(xii) Diethyl cyclohexen-1-ylmethylphosphonate[45]

Tetraethyl methylene-*bis*-phosphonate (10,60g; 0,036mol) in dimethoxyethane (100ml) was treated with hexane-washed sodium hydride (1,73g; 0,072mol) and stirred for 1h at ambient temperature, whereupon cyclohexanone (3,92g; 0,040mol) was added. Stirring was continued for an additional 16h. After washing with aqueous ammonium chloride solution, extraction with diethyl ether and evaporation of the solvent, distillation gave diethyl cyclohexen-1-ylmethylphosphonate (4,42g; 0,019mol; 52,9%) as an oil b.p. (oven temp.) 110°C/0,2mbar; ν_{max} ($CHCl_3$) 1636cm^{-1}; ^{1}H n.m.r ($CDCl_3$) 1,26 (6H; t; J_{HH} 7,0Hz) 1,53 (4H; m) 1,98 (2H; m) 2,05 (2H; m) 2,43 (2H; d; J_{HP} 21,7Hz) 4,02 (4H; p; $J_{HH} = J_{HP}$ 7,1Hz) 5,56 (1H; br s), ^{31}P n.m.r ($CDCl_3$) 28,76 ppm and m/e; M^+ 232 (25,2%) 218 (35,8%) 204 (11,3%) 189 (17,4%) 175 (15,1%) 139 (53,9%) 111 (90,9%) 93 (66,7%) 80 (100,0%).

(B) Prototropic equilibria

General procedure[69]

The relevant phosphonate (4,59mmol) was treated with a 2,2M solution of sodium ethoxide (4,59mmol) in dry ethanol. The reaction was monitored by ^{31}P n.m.r. spectroscopy. After the equilibrium was established, washing with aq. NH_4Cl solution, extraction (CH_2Cl_2) and evaporation of the solvent afforded isomeric mixtures of which the ^{31}P n.m.r. spectra were recorded. Results are reported in the individual procedures.

(i) Diethyl cyclohexen-1-ylphosphonate

Diethyl 1-cyclohexenylphosphonate afforded a mixture of diethyl cyclohexen-1-ylphosphonate (95%) and diethyl cyclohexen-2-ylphosphonate (5%).

(ii) Diethyl cyclohexen-2-ylphosphonate

Diethyl cyclohexen-2-ylphosphonate afforded a mixture of diethyl cyclohexen-1-ylphosphonate (95%) and diethyl cyclohexen-2-ylphosphonate (5%).

(iii) Diethyl cyclohexen-1-ylmethylphosphonate

Diethyl cyclohexen-1-ylmethylphosphonate afforded exclusively non-isomerised phosphonate.

(iv) Diethyl cyclohexenylmethylidenephosphonate

Diethyl cyclohexenylmethylidenephosphonate afforded exclusively diethyl cyclohexen-1-ylmethylphosphonate.

(v) Diethyl cyclohexen-2-ylmethylphosphonate

Diethyl cyclohexen-2-ylmethylphosphonate afforded exclusively non-isomerised phosphonate.

(vi) Diethyl methyl(cyclohexen-2-yl)methylphosphonate

Diethyl methyl(cyclohexen-2-yl)methylphosphonate afforded exclusively non-isomerised phosphonate.

(3) Addition of cyclohexenylphosphonates to electrophiles

General Procedure[107]

The phosphonate (5mmol) in dry THF, under a nitrogen atmosphere, was cooled to -78°C whereupon a 1,6M solution of butyllithium (6-8,5mmol) was added dropwise. After stirring for 1h, the relevant electrophile (8mmol) was added slowly and stirred continuously at -78°C for 30min. The reaction mixture was allowed to reach ambient temperature, maintaining conditions for 1-16h. Subsequent washing with aqeous ammonium chloride solution, extraction with methylene dichloride, drying and concentration afforded the crude product which was purified by chromatography (silica gel). Properties, as well as spectral and analytical data for each adduct, are reported in the individual syntheses. In all cases, yields of isolated products, as well as that based upon ^{31}P n.m.r. spectra, are reported.

(A) Diethyl cyclohexen-1-ylphosphonate

(i) Iodomethane

Diethyl cyclohexen-1-ylphosphonate (1,03g; 4,72mmol) and butyllithium (3,50ml; 5,60mmol) in dry THF were treated at -78°C with iodomethane (1,07g; 7,56mmol) and stirred at

ambient temperature for 1-4h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which was shown to be diethyl cyclohexen-1-ylphosphonate (0,93g; 4,26mmol; 90,2%), identical (^{31}P, ^{1}H n.m.r. and t.l.c.) to an authentic sample.

(ii) 1-Bromopropane

Diethyl cyclohexen-1-ylphosphonate (1,51g; 6,92mmol) and butyllithium (5,20ml; 8,32mmol) in dry THF were treated at -78°C with 1-bromopropane (1,36g; 11,08mmol) and stirred at ambient temperature for 1-4h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which was shown to be diethyl cyclohexen-1-ylphosphonate (1,43g; 6,56mmol; 94,8%), identical (^{31}P, ^{1}H n.m.r. and t.l.c.) to an authentic sample.

(2) Diethyl cyclohexen-2-ylphosphonate

(i) Iodomethane

Diethyl cyclohexen-2-ylphosphonate (0,50g; 2,30mmol) and butyllithium (1,70ml; 2,72mmol) in dry THF were treated at -78°C with iodomethane (0,52g; 3,66mmol) and stirred at ambient temperature for 1h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which, after chromatography (flash column; 20% ethyl acetate/hexane), yielded diethyl 1-methylcyclohexen-2-ylphosphonate (0,49g; 2,11mmol; 91,7% [99]) as an oil, b.p. (oven temp.) 110°C/0,2mbar; ^{1}H n.m.r. ($CDCl_3$); 1,22 (3H; d; J_{HP} 16,9Hz) 1,28 (6H; t; J_{HH} 7,1Hz) 1,50 (2H; m) 1,83 (1H; m) 1,90 (3H; m) 4,07 (4H; p; $J_{HH} = J_{HP}$ 7,1Hz) 5,57 (1H; m) 5,80 (1H; m), ^{31}P n.m.r. ($CDCl_3$) 33,55 ppm and m/e; M^+ 232 (36,8%) 139 (52,8%) 111 (27,1%) 94 (100%) 79 (34,9%).

(ii) 1-Bromopropane

Diethyl cyclohexen-2-ylphosphonate (1,49g; 6,83mmol) and butyllithium (5,20ml; 8,22mmol) in dry THF were treated at -78°C with 1-bromopropane (1,35g; 10,98mmol) and stirred at ambient temperature for 1h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which, after chromatography (flash column; 20% ethyl acetate/hexane), yielded diethyl 1-propylcyclohexen-2-ylphosphonate (1,58g; 6,08mmol; 89,0% [99]) as an oil, b.p. (oven temp.) 135,0°C/ 0,2mbar; ^1H n.m.r. ($CDCl_3$) 0,86 (3H; t; J_{HH} 7,1Hz) 1,26 (6H; t; J_{HH} 7,1Hz) 1,30 (2H; m) 1,58 (4H; m) 1,95 (4H; m) 4,05 (4H; p; $J_{HH} = J_{HP}$ 7,1Hz) 5,52 (1H; m) 5,89 (1H; m; J_{HP} 14,2; J_{HH} 4,0Hz), ^{31}P n.m.r. ($CDCl_3$) 33,06 ppm and m/e; M^+ 260 (50,9%) 231 (9,9%) 220 (19,7%) 191 (18,8%) 139 (52,7%) 122 (100%) 111 (34,6%) 79 (47,7%).

(iii) 2-Bromopropane

Diethyl cyclohexen-2-ylphosphonate (2,02g; 9,26mmol) and butyllithium (6,90ml; 11,04mmol) in dry THF were treated at -78°C with 2-bromopropane (1,81g; 14,72mmol) and stirred at ambient temperature for 2h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which, after chromatography (column; 20% ethyl acetate/hexane), yielded diethyl 1-(1'-methylethyl)-cyclohexen-2-ylphosphonate (0,45g; 4,17mmol; 45,0% [70]) as an oil, b.p. (oven temp.) 135,0°C/ 0,2 mbar; ^1H n.m.r. ($CDCl_3$) 0,87 (3H; d; J_{HH} 6,9Hz) 1,00 (3H; d; J_{HH} 6,9Hz) 1,26 (6H; t; J_{HH} 7,1Hz) 1,58 (2H; m) 1,93 (4H; m) 2,10 (1H; sept; J_{HH} 6,9Hz; J_{HP} 19,7Hz) 4,05 (4H; p; $J_{HH} = J_{HP}$ 7,1Hz) 5,48 (1H; m) 5,90 (1H; m; J_{HP} 14,3Hz; J_{HH} 4,1Hz), ^{31}P n.m.r. ($CDCl_3$) 32,88 ppm and m/e; M^+ 260 (73,9%) 245 (20,0) 218 (61,3%) 190 (21,7%) 162 (37,8%) 139 (50,5) 122 (100%) 111 (32,5%) 79 (79,3%).

(iv) 3-Bromopropene

Diethyl cyclohexen-2-ylphosphonate (1,00g; 4,59mmol) and butyllithium (3,40ml; 5,44mmol) in dry THF were treated at -78°C with 3-bromopropene (0,90g; 7,44mmol) and stirred at ambient temperature for 2h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which, after chromatography (column; 30% ethyl acetate/hexane), yielded diethyl 1-(propen-2'-yl)cyclohexen-2-ylphosphonate (0,72g; 3,30mmol; 71,9% [80]) as an oil, b.p. decomp. (oven temp.) 140,0°C/0,3 mbar; ^1H n.m.r. ($CDCl_3$) 1,27 (6H; t; J_{HH} 7,1Hz) 1,57 (2H; m) 1,95 (4H; m) 2,40 (2H; m; J_{HH} 6,5Hz) 4,05 (4H; p; $J_{HH} = J_{HP}$ 7,1Hz) 5,00 (2H; d; J 12,6Hz) 5,52 (1H; m) 5,75 (1H; m) 5,90 (1H; m; J_{HH} 4,0Hz; J_{HP} 14,1Hz), ^{31}P n.m.r. ($CDCl_3$) 31,09 ppm and m/e; M^+ 259 (100%) 217 (85,0%) 161 (19,2%) 139 (54,7%) 120 (92,8%) 111 (51,8%) 91 (100%) 79 (98,5%).

(v) Trimethylchlorosilane

Diethyl cyclohexen-2-ylphosphonate (0,99g; 4,54mmol) and butyllithium (3,40ml; 5,44mmol) in dry THF were treated at -78°C with trimethylchlorosilane (0,79g; 7,28mmol) and stirred at ambient temperature for 1h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which, after chromatography (flash column; 20% ethyl acetate/hexane), yielded diethyl 3-trimethylsilylcyclohexen-1-yl-phosphonate (0,44g; 1,52mmol; 33,5% [80]) as an oil, b.p. decomp.; ν_{max} ($CHCl_3$) 1617cm^{-1}, ^1H n.m.r. ($CDCl_3$) 0,01 (9H; s) 1,27 (6H; t; J_{HH} 7,1Hz) 1,45 (2H;m) 1,73 (3H; m) 2,05 (2H; m) 4,05 (4H; p; $J_{HH} = J_{HP}$ 7,1Hz) 6,79 (1H; d; J_{HP} 22,4Hz), ^{31}P n.m.r. ($CDCl_3$) 21,62 ppm, ^{13}C n.m.r. (DEPT) ($CDCl_3$) -3,2 (3xMe) 16,1 (2xMe) 21,5 (CH_2) 22,6 (CH_2) 24,0 (CH_2) 28,3 (CH) 61,0 (2xCH_2) 145,3 (CH) and m/e; 218 (100%) 190 (24,8%) 162 (32,6%) 79 (17,6%).

(vi) Acetaldehyde

Diethyl cyclohexen-2-ylphosphonate (1,46g; 6,70mmol) and butyllithium (7,30ml; 11,68mmol) in dry THF were treated at -78°C with acetaldehyde (0,49g; 11,13mmol) and stirred at ambient temperature for 16h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which, after chromatography (column; 50% ethyl acetate/hexane), yielded two diastereoisomers of diethyl 1-(1'-hydroxyethyl)cyclohexen-2-ylphosphonate (1,58g; 6,03mmol; 90,0% [99]) as oils, b.p. decomp.; ^1H n.m.r. ($CDCl_3$) 1,09 (3H; d; J_{HH} 6,5Hz) 1,27 (6H; t; J_{HH} 7,1Hz) 1,68 (2H; m) 1,96 (4H; m) 4,00 (1H; m; J_{HH} 6,5Hz) 4,07 (4H; p; J_{HH} = J_{HP} 7,1Hz) 5,72 (1H; m) 6,05 (1H; m), ^{31}P n.m.r. ($CDCl_3$) 31,98 ppm, ^{13}C n.m.r. ($CDCl_3$) 16,3 (2xMe; q; J_{CH} 129,6Hz) 18,9 (CH_2; t; J_{CH} 127,4Hz) 22,2 (CH_2; t; J_{CH} 129,5Hz) 23,2 (Me; q; J_{CH} 119,6Hz) 25,1 (CH_2; t; J_{CH} 119,6Hz) 45,9 (C; d; J_{CP} 133,1Hz) 62,2 (2xCH_2; t; J_{CH} 147,8Hz) 70,5 (CH; d; J_{CH} 145,9Hz) 121,9 (CH; d; J_{CH} 159,6Hz) 133,2 (CH; d; J_{CH} 142,2Hz) and ^1H n.m.r. ($CDCl_3$) 1,14 (3H; d; J_{HH} 6,5Hz) 1,27 (6H; t; J_{HH} 7,1Hz) 1,68 (2H; m) 1,96 (4H; m) 3,91 (1H; dq; J_{HH} = J_{HP} 6,5Hz) 4,07 (4H; p; J_{HH} = J_{HP} 7,1Hz) 5,48 (1H; m) 5,93 (1H; m), ^{31}P n.m.r. ($CDCl_3$) 32,44 ppm, ^{13}C n.m.r. ($CDCl_3$) 16,3 (2xMe; q; J_{CH} 129,6Hz) 18,9 (CH_2; t; J_{CH} 127,4Hz) 22,2 (CH_2; t; J_{CH} 129,5Hz) 23,0 (Me; q; J_{CH} 119,6Hz) 25,1 (CH_2; t; J_{CH} 119,6Hz) 45,1 (C; d; J_{CP} 133,7Hz) 62,7 (2xCH_2; t; J_{CH} 147,8Hz) 70,5 (CH; d; J_{CH} 145,9Hz) 124,1 (CH; d; J_{CH} 160,1Hz) 131,4 (CH; d; J_{CH} 150,0Hz) and m/e; M^+ 263 (2,7%) 218 (100%) 190 (23,3%) 162 (52,1%) 79 (25,5%).

(vii) Propionaldehyde

Diethyl cyclohexen-2-ylphosphonate (2,47g; 11,33mmol) and butyllithium (12,20ml; 19,52mmol) in dry THF were treated at -78°C with propionaldehyde (1,05g; 18,09mmol) and stirred at ambient temperature for 16h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which, after chromatography (prep t.l.c. 40% ether/hexane), yielded two diastereoisomers of diethyl

1-(1'-hydroxypropyl)cyclohexen-2-ylphosphonate (2,03g; 7,35mmol; 64,9% [90]) as oils; ν_{max} ($CHCl_3$) 3363cm^{-1}, ^{1}H n.m.r. ($CDCl_3$) 0,95 (3H; t; J_{HH} 7,3Hz) 1,27 (6H; t; J_{HH} 7,1Hz) 1,33-1,80 (4H; m) 1,95 (4H; m) 3,75 (1H; m) 4,10 (4H; p; $J_{HH} = J_{HP}$ 7,1Hz) 5,70 (1H; m) 5,99 (1H; m), ^{31}P n.m.r. ($CDCl_3$) 31,82 ppm, ^{13}C n.m.r. ($CDCl_3$) 11,3 (Me; q; J_{CH} 122,1Hz) 16,4 (2xMe; q; J_{CH} 129,2Hz) 18,9 (CH_2; t; J_{CH} 129,6Hz) 23,3 (CH_2; t; J_{CH} 133,3Hz) 24,5 (CH_2; t; J_{CH} 127,0Hz) 25,0 (CH_2; t; J_{CH} 129,7Hz) 45,9 (C; d; J_{CP} 134,8Hz) 62,0 (2xCH_2; t; J_{CH} 147,9Hz) 76,5 (CH; d; J_{CH} 147,0Hz) 123,5 (CH; d; J_{CH} 159,2Hz) 133,1 (CH; d; J_{CH} 160,5Hz) and ^{1}H n.m.r. ($CDCl_3$) 0,96 (3H; t; J_{HH} 7,3Hz) 1,27 (6H; t; J_{HH} 7,1Hz) 1,33-1,80 (4H; m) 1,95 (4H; m) 3,60 (1H; m) 4,10 (4H; p; $J_{HH} = J_{HP}$ 7,1Hz) 5,53 (1H; m) 5,94 (1H; m), ^{31}P n.m.r. ($CDCl_3$) 32,11 ppm, ^{13}C n.m.r. ($CDCl_3$) 11,4 (Me; q; J_{CH} 122,1Hz) 16,4 (2xMe; q; J_{CH} 129,2Hz) 18,9 (CH_2; t; J_{CH} 129,6Hz) 23,3 (CH_2; t; J_{CH} 133,3Hz) 24,6 (CH_2; t; J_{CH} 125,7Hz) 25,0 (CH_2; t; J_{CH} 129,7Hz) 45,9 (C; d; J_{CP} 134,8Hz) 62,7 (2xCH_2; t; J_{CH} 147,9Hz) 76,5 (CH; d; J_{CH} 147,0Hz) 124,3 (CH; d; J_{CH} 160,5Hz) 131,4 (CH; d; J_{CH} 154,8Hz) and m/e; M^+ 277 (5,9%) 260 (2,8%) 247 (6,2%) 218 (100%) 190 (28,3%) 162 (57,0%) 79 (34,8%).

(viii) <u>Butyraldehyde</u>

Diethyl cyclohexen-2-ylphosphonate (0,51g; 2,34mmol) and butyllithium (2,40ml; 3,84mmol) in dry THF were treated at -78°C with butyraldehyde (0,30g; 4,16mmol) and stirred at ambient temperature for 16h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which, after chromatography (column; 40% ethyl acetate/hexane), yielded two diastereoisomers of diethyl 1-(1'-hydroxybutyl)-cyclohexen-2-ylphosphonate (0,54g; 1,86mmol; 79,5% [90]) as oils; ^{1}H n.m.r. ($CDCl_3$) 0,85 (3H; t; J_{HH} 6,9Hz) 1,27 (6H; t; J_{HH} 7,1Hz) 1,35 (2H; m) 1,54 (2H; m) 1,68 (2H;m) 1,94 (4H; m) 3,66 (1H; m) 4,07 (4H; p; $J_{HH} = J_{HP}$ 7,1Hz) 5,70 (1H; m) 5,99 (1H; m), ^{31}P n.m.r. ($CDCl_3$) 32,07 ppm, ^{13}C n.m.r. ($CDCl_3$) 13,9 (Me; q; J_{CH} 124,4Hz) 16,3 (2xMe; q; J_{CH} 127,1Hz) 18,5 (CH_2; t; J_{CH} 132,9Hz) 19,8 (CH_2; t; J_{CH} 126,2Hz) 23,3 (CH_2; t; J_{CH} 132,1Hz) 25,1 (CH_2; t; J_{CH} 128,1Hz) 34,2 (CH_2; t; J_{CH} 125,7Hz) 45,1 (C; d; J_{CP} 134,3Hz) 62,2

(2xCH_2; t; J_{CH} 147,7Hz) 74,5 (CH; d; J_{CH} 144,7Hz) 123,1 (CH; d; J_{CH} 160,2Hz) 133,1 (CH; d; J_{CH} 164,9Hz) and ^{1}H n.m.r. ($CDCl_3$) 0,86 (3H; t; J_{HH} 6,9Hz) 1,27 (6H; t; J_{HH} 7,1Hz) 1,35 (2H; m) 1,54 (2H; m) 1,68 (2H;m) 1,94 (4H; m) 3,66 (1H; m) 4,07 (4H; p; J_{HH} = J_{HP} 7,1Hz) 5,51 (1H; m) 5,93 (1H; m), ^{31}P n.m.r. ($CDCl_3$) 32,43 ppm, ^{13}C n.m.r. ($CDCl_3$) 13,9 (Me; q; J_{CH} 124,4Hz) 16,3 (2xMe; q; J_{CH} 127,1Hz) 18,9 (CH_2; t; J_{CH} 132,9Hz) 19,9 (CH_2; t; J_{CH} 126,2Hz) 23,3 (CH_2; t; J_{CH} 132,1Hz) 24,4 (CH_2; t; J_{CH} 128,1Hz) 33,8 (CH_2; t; J_{CH} 125,7Hz) 45,1 (C; d; J_{CP} 134,3Hz) 62,9 (2xCH_2; t; J_{CH} 147,7Hz) 74,5 (CH; d; J_{CH} 144,7Hz) 124,3 (CH; d; J_{CH} 164,1Hz) 131,5 (CH; d; J_{CH} 160,0Hz) and m/e; M^+ 291 (4,6%) 247 (6,2) 218 (100%) 190 (23,4%) 162 (41,7%) 79 (25,7%).

(ix) <u>Acrolein</u>

Diethyl cyclohexen-2-ylphosphonate (1,09g; 5,00mmol) and butyllithium (5,30ml; 8,48mmol) in dry THF were treated at -78°C with acrolein (0,43g; 7,67mmol) and stirred at ambient temperature for 16h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which, after chromatography (prep. t.l.c.; diethyl ether), yielded two diastereoisomers of diethyl 1-(1'-hydroxypropen-2'-yl)cyclohexen-2-ylphosphonate (0,97g; 3,54mmol; 70,8% [85]) as oils; ν_{max} ($CHCl_3$) 3395, 1644cm^{-1}, ^{1}H n.m.r. ($CDCl_3$) 1,27 (6H; t; J_{HH} 7,1Hz) 1,55 (2H; m) 1,83 (4H; m) 3,99 (4H; p; J_{HH} = J_{HP} 7,1Hz) 4,12 (1H; m) 5,05 (1H; d; J_{HH} 10,2Hz) 5,15 (1H;t; J_{HH} 10,2Hz) 5,66 (1H; m) 5,91 (1H; m), ^{31}P n.m.r. ($CDCl_3$) 31,29 ppm, ^{13}C n.m.r. ($CDCl_3$) 15,9 (2xMe; q; J_{CH} 126,8Hz) 17,8 (CH_2; t; J_{CH} 124,8Hz) 23,9 (CH_2; t; J_{CH} 129,1Hz) 25,2 (CH_2; t; J_{CH} 129,9Hz) 44,3 (C; d; J_{CP} 137,4Hz) 62,5 (2xCH_2; t; J_{CH} 152,3Hz) 76,3 (CH; d; J_{CH} 151,4Hz) 117.1 (CH_2; t; J_{CH} 155,2Hz) 121,7 (CH; d; J_{CH} 164,4Hz) 132,6 (CH; d; J_{CH} 160,9Hz) 135,9 (CH; d; J_{CH} 155,5Hz) and ^{1}H n.m.r. ($CDCl_3$) 1,27 (6H; t; J_{HH} 7,1Hz) 1,55 (2H; m) 1,83 (4H; m) 3,99 (4H; p; J_{HH} = J_{HP} 7,1Hz) 4,34 (1H; m) 5,05 (1H; d; J_{HH} 10,2Hz) 5,15 (1H; t; J_{HH} 10,2Hz) 5,50 (1H; m) 5,86 (1H; m), ^{31}P n.m.r. ($CDCl_3$) 31,47 ppm, ^{13}C n.m.r. ($CDCl_3$) 15,9 (2xMe; q; J_{CH} 126,8Hz) 18,0 (CH_2; t; J_{CH} 124,8Hz) 23,9 (CH_2; t; J_{CH} 129,1Hz) 25,2 (CH_2; t; J_{CH} 129,9Hz) 44,7 (C; d; J_{CP} 137,4Hz) 62,7 (2xCH_2; t; J_{CH} 152,3Hz) 74,9 (CH; d; J_{CH} 151,2Hz)

115,9 (CH_2; t; J_{CH} 156,8Hz) 123,3 (CH; d; J_{CH} 158,9Hz) 131,4 (CH; d; J_{CH} 156,7Hz) 135,5 (CH; d; J_{CH} 154,8Hz) and m/e; M^+ 275 (0,6%) 257 (1,2%) 218 (100%) 190 (26,2%) 162 (77,7%) 79 (56,6%).

(x) <u>Benzaldehyde</u>

Diethyl cyclohexen-2-ylphosphonate (1,00g; 4,59mmol) and butyllithium (4,90ml; 7,84mmol) in dry THF were treated at -78°C with benzaldehyde (0,77g; 7,26mmol) and stirred at ambient temperature for 16h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which, after chromatography (prep. t.l.c.; 50% diethyl ether/hexane), yielded two diastereoisomers of diethyl 1-(hydroxyphenyl-methyl)cyclohexen-2-ylphosphonate (0,71g; 2,19mmol; 47,7% [60]) of which one was an oil; ν_{max} ($CHCl_3$) 3399, 1600cm^{-1}, ^1H n.m.r. ($CDCl_3$) 1,05 (1H; m) 1,20 (3H; t; J_{HH} 7,1Hz) 1,29 (3H; t;J_{HP} 7,1Hz) 1,55 (2H; m) 1,81 (3H; m) 4,04 (2H; p; J_{HH} = J_{HP} 7,1Hz) 4,14 (2H; p; J_{HH} = J_{HP} 7,1Hz) 4,96 (1H; d; J_{HH} 13,4Hz) 5,70 (1H; m) 5,81 (1H;m) 7,25 (5H; m), ^{31}P n.m.r. ($CDCl_3$) 31,98 ppm, ^{13}C n.m.r. ($CDCl_3$) 16,5 (2xMe; q, J_{CH} 127,1Hz) 18,4 (CH_2; t; J_{CH}128,3Hz) 22,6 (CH_2; t; 128,0Hz) 24,3 (CH_2; t; 129,6Hz) 46,3 (C; d; J_{CP} 130,8Hz) 62,6 (CH_2; t; J_{CH} 148,3Hz) 63,0 (CH_2; t; J_{CH} 148,3Hz) 76,2 (CH; d; J_{CH} 147,5Hz) 124,1 (CH; d; J_{CH} 159,1Hz) 127,1 (CH; d; J_{CH} 153,3Hz) 127,3 (CH; d; J_{CH} 159,9Hz) 127,7 (CH; d; J_{CH} 157,8Hz) 131,6 (CH; d; J_{CH} 157,1Hz) 139,4 (C; s) and the other, colourless crystals (recryst. hexane) m.p. 84,2-84,4°C; ^1H n.m.r. ($CDCl_3$) 0,59 (1H; m) 1,20 (3H; t; J_{HH} 7,1Hz) 1,31 (3H; t; J_{HP} 7,1Hz) 1,40 (2H; m) 1,77 (3H; m) 4,00 (2H; p; J_{HH} = J_{HP} 7,1Hz) 4,11 (2H; p; J_{HH} = J_{HP} 7,1Hz) 4,88 (1H; d; J_{HH} 11,6Hz) 6,05 (2H; s) 7,25 (5H; m), ^{31}P n.m.r. ($CDCl_3$) 32,29 ppm, ^{13}C n.m.r. ($CDCl_3$) 16,1 (2xMe; q, J_{CH} 127,1Hz) 17,3 (CH_2; t; J_{CH}128,3Hz) 24,1 (CH_2; t; 128,0Hz) 25,8 (CH_2; t; 129,6Hz) 46,1 (C; d; J_{CP} 130,7Hz) 62,8 (CH_2; t; J_{CH} 148,3Hz) 76,9 (CH; d; J_{CH} 146,6Hz) 121,4 (CH; d; J_{CH} 162,11Hz) 127,1 (CH; d; J_{CH} 153,3Hz) 127,3 (CH; d; J_{CH} 159,9Hz) 127,7 (CH; d; J_{CH} 157,8Hz) 128,3 (CH; d; J_{CH} 152,8Hz) 139,3 (C; s) and m/e; M^+ 322 (8,5%) 280 (52,7) 218 (8,9%) 189 (18,2%) 170 (19,8%) 105 (32,1%) 91 (100%) 79 (48,6%).

(xi) 3,4,5-Trimethoxybenzaldehyde

Diethyl cyclohexen-2-ylphosphonate (1,49g; 6,83mmol) and butyllithium (7,30ml; 11,68mmol) in dry THF were treated at -78°C with 3,4,5-trimethoxybenzaldehyde (2,10g; 10,55mmol) and stirred at ambient temperature for 16h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which, after chromatography (column; ethyl acetate), yielded two diastereoisomers of diethyl 1-(hydroxy-3,4,5-methoxyphenylmethyl)cyclohexen-2-ylphosphonate (1,11g; 2,66mmol; 39,0% [62]) as oils; ν_{max} ($CHCl_3$) 3600, 3490, 1610cm^{-1}, ^1H n.m.r. ($CDCl_3$) 1,06 (1H; m) 1,20 (3H; t; J_{HH} 7,1Hz) 1,31 (3H; t; $J_{HH} = J_{HP}$ 7,1Hz) 1,43 (2H; m) 1,72 (3H; m) 3,75 (3H; s) 3,77 (6H; s) 4,05 (4H; m; $J_{HH} = J_{HP}$ 7,1Hz) 4,87 (1H; d; J_{HH} 12,3Hz) 5,68 (1H; m) 5,84 (1H; m) 6,52 (2H; s); ^{31}P n.m.r. ($CDCl_3$) 31,89 ppm and ^1H n.m.r. ($CDCl_3$) 0,68 (1H; m) 1,20 (3H; t; J_{HH} 7,1Hz) 1,31 (3H; t; $J_{HH} = J_{HP}$ 7,1Hz) 1,45 (2H; m) 1,72 (3H; m) 3,75 (3H; s) 3,77 (6H; s) 4,05 (4H; m; $J_{HH} = J_{HP}$ 7,1Hz) 4,73 (1H; d; J_{HH} 11,1Hz) 6,05 (2H; s) 6,55 (2H; s); ^{31}P n.m.r. ($CDCl_3$) 32,24 ppm and m/e; M^+ 414 (4,4%) 397 (5,1%) 218 (100%) 190 (25,7%) 162 (37,6%) 79 (24,3%).

(xii) Phenylacetaldehyde

Diethyl cyclohexen-2-ylphosphonate (3,00g; 13,76mmol) and butyllithium (13,50ml; 21,60mmol) in dry THF were treated at -78°C with phenylacetaldehyde (2,64g; 22,00mmol) and stirred at ambient temperature for 16h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which, after chromatography (prep. t.l.c.; 40% diethyl ether/hexane), yielded two diastereoisomers of diethyl 1-(1'-hydroxy-2'-phenylethyl)cyclohexen-2-ylphosphonate (3,21g; 9,49mmol; 69,0% [95]) as oils, ^1H n.m.r. ($CDCl_3$) 1,28 (6H; t; J_{HH} 7,1Hz) 1,60 - 2,10 (6H; m) 3.01 (1H; d; J_{HP} 13,9Hz) 3,98 (1H; m) 4.03 (1H; m) 4,07 (4H; p; $J_{HH} = J_{HP}$ 7,1Hz) 5.81 (1H; m) 6,10 (1H; m) 7,22 (5H; m), ^{31}P n.m.r. ($CDCl_3$) 31,44 ppm, ^{13}C n.m.r. ($CDCl_3$) 16,3 (2xMe; q; J_{CH} 129,9Hz) 18,6 (CH_2; t; J_{CH} 134,2Hz) 23,2 (CH_2; t; J_{CH} 127,7Hz) 24,5 (CH_2; t; J_{CH}

129,1Hz) 38,6 (CH_2; t; J_{CH} 127,1Hz) 45,7 (C; d; J_{CP} 136,3Hz) 62,2 (2xCH_2; t; J_{CH} 147,9Hz) 76,0 (CH; d; J_{CH} 152,7Hz) 123,1 (CH; d; J_{CH} 156,2Hz) 128,0 (CH; d; J_{CH} 159,1Hz) 128,1 (CH; d; J_{CH} 160,0Hz) 129,1 (CH; d; J_{CH} 156,8Hz) 133,2 (CH; d; J_{CH} 160,4Hz) 139,8 (C; s) and ^{1}H n.m.r. ($CDCl_3$) 1,28 (3H; t; J_{HH} 7,1Hz) 1,31 (3H; t; J_{HH} 7,1Hz) 1,60 - 2,10 (6H; m) 2,62 (1H; dd; J_{HH} 10,3Hz, J_{HH} 13,8Hz) 2,86 (1H; d; J_{HP} 13,8Hz) 4.02 (1H; m) 4,07 (4H; p; J_{HH} = J_{HP} 7,1Hz) 5.62 (1H; m) 6,06 (1H; m) 7,21 (5H; m), ^{31}P n.m.r. ($CDCl_3$) 31,88 ppm, ^{13}C n.m.r. ($CDCl_3$) 16,3 (2xMe; q; J_{CH} 129,9Hz) 18,9 (CH_2; t; J_{CH} 134,2Hz) 23,2 (CH_2; t; J_{CH} 127,7Hz) 24,3 (CH_2; t; J_{CH} 129,1Hz) 38,3 (CH_2; t; J_{CH} 127,1Hz) 45,7 (C; d; J_{CP} 136,3Hz) 62,7 (2xCH_2; t; J_{CH} 147,8Hz) 76,0 (CH; d; J_{CH} 152,7Hz) 123,9 (CH; d; J_{CH} 144,1Hz) 125,9 (CH; d; J_{CH} 159,1Hz) 128,0 (CH; d; J_{CH} 160,0Hz) 129,1 (CH; d; J_{CH} 156,8Hz) 132,0 (CH; d; J_{CH} 160,4Hz) 139,8 (C; s) and m/e; 247 (17,1%) 218 (100%) 190 (24,7%) 162 (41,9%) 91 (63,6%) 79 (35,7%).

(xiii) <u>Cyclohexylcarboxaldehyde</u>

Diethyl cyclohexen-2-ylphosphonate (0,50g; 2,30mmol) and butyllithium (2,40ml; 3,84mmol) in dry THF were treated at -78°C with cyclohexylcarboxaldehyde (0,41g; 3,66mmol) and stirred at ambient temperature for 16h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded a mixture of products. Chromatography (column; hexane and ethyl acetate) gave diethyl cyclohexen-2-ylphosphonate (0,26g; 1,19mmol; 51,8%), identical (^{31}P, ^{1}H n.m.r. and t.l.c.) to an authentic sample, as well as *trans* 3-cyclohexylmethylidenenecyclohexene (19,5%); ^{1}H n.m.r. ($CDCl_3$) 1,29 (6H; m) 1,66 (6H; m) 2,10 (2H; m) 2,20 (1H; m) 2,35 (2H; m) 5,08 (1H; d; J_{HH} 10,0Hz) 5,63 (1H; dt; J_{HH} 10,0Hz; J_{HH} 4,2Hz) 5,98 (1H; dt; J_{HH} 10,0Hz; J_{HH} 2,0Hz) and *cis* 3-cyclohexyl-methylidenecyclohexene (13,9%); ^{1}H n.m.r. ($CDCl_3$) 1,29 (6H; m) 1,66 (6H; m) 2,10 (2H; m) 2,15 (1H; m) 2,22 (2H; m) 4,93 (1H; d; J_{HH} 10,0Hz) 5,77 (1H; ddt; J_{HH} 10,0Hz; J_{HH} 4,0Hz; J_{HH} 1,9Hz) 6,39 (1H; dt; J_{HH} 10,1Hz; J_{HH} 2,0Hz).

(xiv) 2-Methylpropionaldehyde

Diethyl cyclohexen-2-ylphosphonate (1,98g; 9,08mmol) and butyllithium (9,70ml; 15,52mmol) in dry THF were treated at -78°C with 2-methylpropionaldehyde (1,09g; 15,13mmol) and stirred at ambient temperature for 16h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which, after chromatography (column; 50% ethyl acetate/hexane), yielded two diastereo-isomers of diethyl 3-(1'-hydroxy-2'-methylpropyl)cyclohexen-1-ylphosphonate (1,05g; 3,61mmol; 39,8% [50]) as oils; ν_{max} ($CHCl_3$) 3336, 1631cm^{-1}, ^{1}H n.m.r. ($CDCl_3$) 0,85 (3H, d, J_{HH} 6,8Hz) 0,87 (3H, d, J_{HH} 6,8Hz) 1,25 6H, t, J_{HH} 7,1Hz) 1,5-2,3 (8H; m) 3,26 (1H, dd, J_{HH} 6,8Hz; J_{HH} 5,0Hz) 4,00 (4H, p, J_{HH} = J_{HP} 7,1Hz) 6,57 (1H, d, J_{HH} 21,6Hz), ^{31}P n.m.r.($CDCl_3$) 20,91 ppm, ^{13}C n.m.r. ($CDCl_3$) 16,2 (2xMe; q; J_{CH} 127,1Hz) 19,4 (2xMe; q; J_{CH} 137,6Hz) 21,0 (CH_2; t; J_{CH} 131,0Hz) 21,5 (CH_2; t; J_{CH} 131,0Hz) 24,3 (CH_2; t; J_{CH} 129,5Hz) 29,9 (CH; d; J_{CH} 125,1Hz) 39,6 (CH; d; J_{CH} 123,1Hz) 61,5 (2xCH_2; t; J_{CH} 146,3Hz) 78,6 (CH; d; J_{CH} 138,5Hz) 129,5 (C; d; J_{CP} 174,7Hz) 145,4 (CH; d; J_{CH} 157,4Hz) and ^{1}H n.m.r. ($CDCl_3$) 0,86 (3H, d, J_{HH} 6,9Hz) 0,92 (3H, d, J_{HH} 6,9Hz) 1,25 (6H, t, J_{HH}7,1Hz) 1,5-2,3 (8H; m) 3,08 (1H, dd, J_{HH} = J_{HH} 5,7Hz) 4,00 (4H, p, J_{HH} = J_{HP} 7,1Hz) 6,84 (1H, d, J_{HH} 23,6Hz), ^{31}P n.m.r. ($CDCl_3$) 21,20 ppm, ^{13}C n.m.r. ($CDCl_3$) 16,2 (2xMe; q; J_{CH} 127,1Hz) 19,4 (2xMe; q; J_{CH} 137,6Hz) 21,0 (CH_2; t; J_{CH} 131,0Hz) 24,3 (CH_2; t; J_{CH} 129,5Hz) 30,6 (CH; d; J_{CH} 125,1Hz) 39,6 (CH; d; J_{CH} 123,1Hz) 65,1 (CH_2; t; J_{CH} 147,3Hz) 78,6 (CH; d; J_{CH} 138,5Hz) 128,6 (C; d; J_{CP} 174,7Hz) 144,1 (CH; d; J_{CH} 160,5Hz) and m/e M^+ 290 (9,1%) 275 (18,2%) 218 (100,0%) 190 (16,9%) 178 (83,3%) 162 (24,8%) 138 (30,1%) 79 (31,3%).

(xv) Acetone

Diethyl cyclohexen-2-ylphosphonate (0,52g; 2,38mmol) and butyllithium (2,50ml; 4,00mmol) in dry THF were treated at -78°C with acetone (0,24g; 4,14mmol) and stirred at ambient temperature for 16h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and

concentration, the reaction mixture afforded an oil which was shown to be diethyl cyclohexen-2-ylphosphonate (0,44g; 2,02mmol; 84,9%), identical (^{31}P, ^{1}H n.m.r. and t.l.c.) to an authentic sample.

(xvi) Cyclohexanone

Diethyl cyclohexen-2-ylphosphonate (0,50g; 2,30mmol) and butyllithium (2,40ml; 3,84mmol) in dry THF were treated at -78°C with cyclohexanone (0,35g; 3,57mmol) and stirred at ambient temperature for 16h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which was shown to be diethyl cyclohexen-2-ylphosphonate (0,44g; 2,02mmol; 87,8%), identical (^{31}P, ^{1}H n.m.r. and t.l.c.) to an authentic sample.

(3) Diethyl cyclohexen-1-ylmethylphosphonate

(i) Iodomethane

Diethyl cyclohexen-1-ylmethylphosphonate (1,01g; 4,35mmol) and butyllithium (3,30ml; 5,28mmol) in dry THF were treated at -78°C with iodomethane (0,75g; 5,29mmol) and stirred at ambient temperature for 1h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which, after chromatography (column; 30% ethyl acetate/hexane), yielded diethyl 1-methylcyclohexen-1-ylmethylphosphonate (1,00g; 4,06mmol; 93,4% [95]) as an oil, b.p. (oven temp.) 120°C/0,2mbar; ^{1}H n.m.r. ($CDCl_3$) 1,21 (3H; dd; J_{HH} 7,6Hz; J_{HP} 18,5Hz) 1,27 (6H; t; J_{HH} 7,1Hz) 1,54 (4H; m) 2,01 (4H; m) 2,45 (1H; dq; J_{HH} 7,4Hz; J_{HP} 22,9Hz) 4,02 (4H; p; $J_{HH} = J_{HP}$ 7,1Hz) 5,59 (1H; br s), ^{31}P n.m.r. ($CDCl_3$) 31,74 ppm and m/e; M^+ 246 (47,8%) 231 (12,0%) 138 (29,5%) 108 (100%) 93 (22,0%) 79 (33,4%).

(ii) 1-Bromopropane

Diethyl cyclohexen-1-ylmethylphosphonate (1,01g; 4,35mmol) and butyllithium (3,30ml; 5,28mmol) in dry THF were treated at -78°C with 1-bromopropane (0,65g; 5,29mmol) and stirred at ambient temperature for 1h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which, after chromatography (column; 30% ethyl acetate/hexane), yielded diethyl 1-propylcyclohexen-1-ylmethylphosphonate (1,04g; 3,79mmol; 87,2% [99]) as an oil, b.p. (oven temp.) 130°C/0,2mbar; ^{1}H n.m.r. ($CDCl_3$) 0,81 (3H; t; J_{HH} 7,1Hz) 1,24 (6H; t; J_{HH} 7,1Hz) 1,25 (2H; m) 1,58 (6H; m) 1,95 (4H; m) 2,34 (1H; dt; J_{HH} 7,1Hz; J_{HP} 22,8Hz) 3,98 (4H; p; J_{HH} = J_{HP} 7,1Hz) 5,53 (1H; br s), ^{31}P n.m.r. ($CDCl_3$) 31,18 ppm and m/e; M^+ 274 (96,2%) 232 (75,4%) 136 (100%) 107 (66,0%) 95 (47,1%) 79 (44,7%).

(iii) 3-Bromopropene

Diethyl cyclohexen-1-ylmethylphosphonate (1,00g; 4,31mmol) and butyllithium (3,20ml; 5,12mmol) in dry THF were treated at -78°C with 3-bromopropene (0,63g; 5,21mmol) and stirred at ambient temperature for 1h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which, after chromatography (column; 30% ethyl acetate/hexane), yielded diethyl 1-(propen-2'-yl)-cyclohexen-1-ylmethylphosphonate (0,94g; 3,45mmol; 80,2% [95]) as an oil, b.p. (oven temp.) 130°C/0,2mbar; ^{1}H n.m.r. ($CDCl_3$) 1,21 (3H; t; J_{HH} 7,1Hz) 1,22 (3H; t; J_{HH} 7,1Hz) 1,48 (4H; m) 1,95 (4H; m) 2,40 (3H; m) 4,00 (4H; p; J_{HH} = J_{HP} 7,1Hz) 4,88 (1H; d; J_{HHc} 10,0Hz) 4,94 (1H; d; J_{HHt} 17,0Hz) 5,53 (1H; br s) 5,61 (1H; m), ^{31}P n.m.r. ($CDCl_3$) 30,05 ppm, ^{13}C n.m.r. ($CDCl_3$) 16,2 (2xMe; q; J_{CH} 127,1Hz) 22,0 (CH_2; t; J_{CH} 127,8Hz) 22,7 (CH_2; t; J_{CH} 127,5Hz) 25,3 (CH_2; t; J_{CH} 121,9Hz) 27,4 (CH_2; t; J_{CH} 128,0Hz) 31,6 (CH_2; t; J_{CH} 128,1Hz) 45,6 (CH; dd; J_{CH} = J_{CP} 130,3Hz) 61,3 (2xCH_2; t J_{CH} 147,0Hz) 115,9 (CH_2; t; J_{CH} 157,7Hz) 126,6 (CH; d; J_{CH} 154,0Hz) 131,5 (C; s) 135,8 (CH; d; J_{CH} 152,1Hz) and m/e; M^+ 272 (22,1%) 231 (26,3%) 134 (100%) 91 (42,3%) 79 (19,5%).

(iv) 2-Bromopropane

Diethyl cyclohexen-1-ylmethylphosphonate (2,53g; 10,90mmol) and butyllithium (8,0ml; 12,80mmol) in dry THF were treated at -78°C with 2-bromopropane (2,12g; 17,24mmol) and stirred at ambient temperature for 2h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which, after chromatography (column; methylene dichloride), yielded diethyl 1-(1'-methylethyl)-cyclohexen-1-ylmethylphosphonate (1,93g; 7,04mmol; 64,6% [77]) as an oil, b.p. (oven temp.) 140°C/0,4mbar; ^1H n.m.r. ($CDCl_3$) 0,82 (3H; d; J_{HH} 6,4Hz) 1,02 (3H; d; J_{HH} 6,4Hz) 1,20 (3H; t; J_{HH} 7,1Hz) 1,21 (3H; t; J_{HH} 7,1Hz) 1,50 (4H; m) 1,98 (5H; m) 3,97 (4H; p; $J_{HH} = J_{HP}$ 7,1Hz) 5,53 (1H; br s), ^{31}P n.m.r. ($CDCl_3$) 30,67 ppm and m/e; M^+ 274 (31,6%) 259 (4,7%) 231 (82,5%) 203 (40,9%) 175 (48,9%) 136 (90,1%) 93 (90,9%) 81 (91,4%) 41 (100,0%).

(v) Propionaldehyde

Diethyl cyclohexen-1-ylmethylphosphonate (2,00g; 8,62mmol) and butyllithium (9,20ml; 14,72mmol) in dry THF were treated at -78°C with propionaldehyde (0,80g; 13,79mmol) and stirred at ambient temperature for 16h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which, after chromatography (prep. t.l.c.; 40% diethyl ether/ hexane), yielded two diastereoisomers of diethyl 1-(1'-hydroxypropyl)cyclohexen-1-ylmethylphosphonate (2,12g; 7,31mmol; 84,8% [95]) as oils; ν_{max} ($CHCl_3$) 3591, 3421, 1669cm^{-1}, ^1H n.m.r. ($CDCl_3$) 0,87 (3H; t; J_{HH} 7,3Hz) 1,25 (6H; t; J_{HH} 7,1Hz) 1,57 (6H; m) 2,00 (4H; m) 2,36 (1H; dd; J_{HH} 4,0Hz; J_{HP} 24,5Hz) 3,90 (1H; m) 4,01 (4H; p; $J_{HH} = J_{HP}$ 7,1Hz) 5,72 (1H; br s), ^{31}P n.m.r. ($CDCl_3$) 29,50 ppm, ^{13}C n.m.r. ($CDCl_3$) 9,5 (Me; q; J_{CH} 125,3Hz) 16,3 (2xMe; q; J_{CH} 127,1Hz) 22,0 (CH_2; t; J_{CH} 127,7Hz) 22,8 (CH_2; t; J_{CH} 127,6Hz) 25,2 (CH_2; t; J_{CH} 124,3Hz) 27,8 (CH_2; t; J_{CH} 126,2Hz) 28,6 (CH_2; t; J_{CH} 125,7Hz) 52,6 (CH; dd; $J_{CH} = J_{CP}$ 129,6Hz) 61,9 (2xCH_2; t; J_{CH} 145,3Hz) 62,6 (2xCH_2; t; J_{CH} 145,3Hz) 71,2 (CH; d; J_{CH} 146,0Hz) 127,4 (CH; d; J_{CH} 152,7Hz) 131,4

(C; s) and ^{1}H n.m.r. ($CDCl_3$) 0,92 (3H; t; J_{HH} 7,3Hz) 1,28 (6H; t; J_{HH} 7,1Hz) 1,57 (6H; m) 2,00 (4H; m) 2,39 (1H; dd; J_{HH} 9,6Hz; J_{HP} 20,4Hz) 3,89 (1H; m) 4,01 (4H; p; J_{HH} = J_{HP} 7,1Hz) 5,58 (1H; br s), ^{31}P n.m.r. ($CDCl_3$) 30,35 ppm, ^{13}C n.m.r. ($CDCl_3$) 10,3 (Me; q; J_{CH} 125,3Hz) 16,4 (2xMe; q; J_{CH} 127,1Hz) 21,9 (CH_2; t; J_{CH} 127,7Hz) 22,9 (CH_2; t; J_{CH} 127,6Hz) 25,5 (CH_2; t; J_{CH} 124,3Hz) 27,7 (CH_2; t; J_{CH} 126,2Hz) 29,9 (CH_2; t; J_{CH} 125,7Hz) 51,7 (CH; dd; J_{CH} = J_{CP} 129,6Hz) 61,5 (2xCH_2; t; J_{CH} 145,3Hz) 62,9 (2xCH_2; t; J_{CH} 145,3Hz) 71,4 (CH; d; J_{CH} 146,0Hz) 128,6 (CH; d; J_{CH} 152,7Hz) 130,0 (C; s) and m/e; M^+ 291 (10,8%) 273 (52,2%) 232 (17,7%) 204 (45,7%) 176 (61,7%) 135 (100%) 94 (58,9%).

(vi) <u>Acrolein</u>

Diethyl cyclohexen-1-ylmethylphosphonate (1,48g; 6,38mmol) and butyllithium (6,80ml; 10,88mmol) in dry THF were treated at -78°C with acrolein (0,59g; 10,53mmol) and stirred at ambient temperature for 16h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which, after chromatography (prep. t.l.c.; diethyl ether), yielded two diastereoisomers of diethyl 1-(1'-hydroxypropen-2'-yl)cyclohexen-1-ylmethylphosphonate (1,43g; 4,96mmol; 77,8% [90]) as oils; ^{1}H n.m.r. ($CDCl_3$) 1,28 (6H; t; J_{HH} 7,1Hz) 1,48 (4H; m) 1,96 (4H; m) 2,43 (1H; dd; J_{HH} 5,0Hz; J_{HP} 23,6Hz) 4,05 (4H; p; J_{HH} = J_{HP} 7,1Hz) 4,53 (1H; m) 5,11 (1H; d; J_{HH} 8,9Hz) 5,31 (1H; d; J_{HH} 16,9Hz) 5,63 (1H; br s) 5,75 (1H; ddd; J_{HHt} 16,8Hz; J_{HHc} 10,6Hz; J_{HH} 5,9Hz), ^{31}P n.m.r. ($CDCl_3$) 28,06 ppm, ^{13}C n.m.r. ($CDCl_3$) 16,1 (2xMe; q; J_{CH} 127,4Hz) 21,6 (CH_2; t; J_{CH} 127,5Hz) 22,6 (CH_2; t; J_{CH} 127,6Hz) 25,2 (CH_2; t; J_{CH} 127,7Hz) 29,4 (CH_2; t; J_{CH} 126,1Hz) 52,5 (CH; dd; J_{CH} = J_{CP} 128,1Hz) 61,5 (CH_2; t; J_{CH} 144,8) 62,6 (CH_2; t; J_{CH} 144,8Hz) 70,8 (CH; d; J_{CH} 152,2Hz) 115,4 (CH_2; t; J_{CH} 158,2Hz) 127,9 (CH; d; J_{CH} 159,6Hz) 130,6 (C; s) 138,1 (CH; J_{CH} 155,1Hz) and ^{1}H n.m.r. ($CDCl_3$) 1,25 (6H; t; J_{HH} 7,1Hz) 1,48 (4H; m) 1,96 (4H; m) 2,41 (1H; dd; J_{HH} 9,6Hz; J_{HP} 20,2Hz) 4,03 (4H; p; J_{HH} = J_{HP} 7,1Hz) 4,40 (1H; m) 5,06 (1H; d; J_{HH} 8,9Hz) 5,25 (1H; d; J_{HH} 17,1Hz) 5,60 (1H; br s) 5,75 (1H; ddd; J_{HHt} 16,8Hz; J_{HHc} 10,6Hz; J_{HH} 6,2Hz), ^{31}P n.m.r. ($CDCl_3$) 29,30 ppm, ^{13}C n.m.r. ($CDCl_3$) 16,0 (2xMe; q; J_{CH} 127,4Hz) 21,6 (CH_2; t; J_{CH} 127,5Hz) 22,5 (CH_2; t;

J_{CH} 127,6Hz) 25,2 (CH_2; t; J_{CH} 127,7Hz) 28,6 (CH_2; t; J_{CH} 126,6Hz) 52,5 (CH; dd; J_{CH} = J_{CP} 128,4Hz) 61,9 (CH_2; t; J_{CH} 144,8) 62,4 (CH_2; t; J_{CH} 144,8Hz) 71,2 (CH; d; J_{CH} 146,5Hz) 115,4 (CH_2; t; J_{CH} 158,2Hz) 127,5 (CH; d; J_{CH} 153,6Hz) 130,6 (C; s) 138,1 (CH; J_{CH} 155,3Hz) and m/e; M^+ 289 (10,6%) 271 (47,9%) 232 (9,5%) 204 (9,0%) 176 (15,6%) 133 (100%) 91 (25,8%).

(vii) <u>2-Methylpropionaldehyde</u>

Diethyl cyclohexen-1-ylmethylphosphonate (2,54g; 0,011mmol) and butyllithium (12,1ml; 0,019mmol) in dry THF were treated at -78°C with 2-methylpropionaldehyde (1,24g; 0,017mmol) and stirred at ambient temperature for 16h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which, after chromatography (prep. t.l.c.; 40% diethyl ether/hexane), yielded two diastereoisomers of diethyl 1-(1'-hydroxy-2'-methylpropyl)cyclohexen-1-ylmethyl-phosphonate (1,85g; 6,08mmol; 55,3% [75]) of which the RS (SR) stereoisomer was an oil; ^1H n.m.r. ($CDCl_3$) 0,81 (3H; d; J_{HH} 6,7Hz) 0,92 (3H; d; J_{HH} 6,7Hz) 1,21 (3H; t; J_{HH} 7,1Hz) 1,24 (3H; t; J_{HH} 7,1Hz) 1,53 (4H; m) 1,74 (1H; ddq; J_{HH} = J_{HH} = J_{HP} 7,1Hz) 2,05 (4H; m) 2,53 (1H; dd; J_{HH} 3,9Hz; J_{HP} 25,2Hz) 3,62 (1H; dd; J_{HH} 4,3Hz; J_{HH} 6,5Hz) 4,02 (4H; m; J_{HH} = J_{HP} 7,1Hz) 5,74 (1H; br s), ^{31}P n.m.r. ($CDCl_3$) 29,95 ppm, ^{13}C n.m.r. ($CDCl_3$) 13,8 (2xMe; q; J_{CH} 124,6Hz) 16,4 (2xMe; q; J_{CH} 126,2Hz) 21,2 (CH_2; t; J_{CH} 126,2Hz) 22,0 (CH_2; t; J_{CH} 122,9Hz) 25,5 (CH_2; t; J_{CH} 125,5Hz) 28,8 (CH_2; t; J_{CH} 125,3Hz) 29,2 (CH; d; J_{CH} 134,9Hz) 50,7 (CH; dd; J_{CH} = J_{CP} 130,4Hz) 61,9 (CH_2; t; J_{CH} 149,2Hz) 62,4 (CH_2; t; J_{CH} 149,2Hz) 73,5 (CH; d; J_{CH} 144,0Hz) 127,5 (CH; d; J_{CH} 149,3Hz) 131,2 (C; s) and the RR (SS) stereoisomer colourless crystals (recryst. from hexane), m.p. 97,0-97,2°C; ^1H n.m.r. ($CDCl_3$) 0,77 (3H; d; J_{HH} 6,7Hz) 0,93 (3H; d; J_{HH} 6,7Hz) 1,25 (6H; t; J_{HH} 7,1Hz) 1,54 (4H; m) 1,71 (1H; ddq; J_{HH} = J_{HH} 2,2Hz; J_{HP} 6,8Hz) 1,98 (4H; m) 2,53 (1H; dd; J_{HH} 10,0Hz; J_{HP} 21,0Hz) 3,84 (1H; ddd; J_{HH} = J_{HH} 2,5Hz; J_{HH} 10,4Hz) 4,04 (4H; m; J_{HH} = J_{HP} 7,1Hz) 5,56 (1H; br s), ^{31}P n.m.r. ($CDCl_3$) 30,94 ppm and m/e; M^+ 304 (2,2%) 261 (15,4%) 243 (3,2%) 232 (100,0%) 204 (20,6%) 176 (23,2%) 91 (47,4%) 79 (24,1%).

(viii) Cyclohexylcarboxaldehyde

Diethyl cyclohexen-1-ylmethylphosphonate (1,93g; 8,31mmol) and butyllithium (8,90ml; 14,24mmol) in dry THF were treated at -78°C with cyclohexylcarboxaldehyde (1,50g; 13,38mmol) and stirred at ambient temperature for 16h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which, after chromatography (prep. t.l.c.; 50% ether/ hexane), yielded RS (SR)-diethyl 1-(1'-hydroxy-2'-cyclohexylmethyl)cyclohexen-1-ylmethylphosphonate (1,23g; 3,57mmol; 43,0% [70]) as an oil; ^1H n.m.r. ($CDCl_3$) 0,92 (2H;m) 1,01 (4H; m) 1,20 (3H; t; J_{HH} 7,1Hz) 1,23 (3H; t; J_{HH} 7,1Hz) 1,52 (9H; m) 1,97 (5H; m) 2,51 (1H; dd; J_{HH} 4,0Hz; J_{HP} 25,2Hz) 3,66 (1H; dd; J_{HH} 4,1Hz; J_{HH} 6,4Hz) 4,00 (4H; p; $J_{HH} = J_{HP}$ 7,1Hz) 5,74 (1H; br s), ^{31}P n.m.r. ($CDCl_3$) 30,09 ppm, ^{13}C n.m.r. ($CDCl_3$) 16,2 (2xMe; q; J_{CH} 127,1Hz) 22,9 (CH_2; t; J_{CH} 131,7Hz) 23,6 (CH_2; t; J_{CH} 127,4Hz) 24,2-26,4 (4xCH_2; m) 28,3 (CH_2; t; J_{CH} 126,6Hz) 29,7 (CH_2; t; J_{CH} 122,7Hz) 40,2 (CH; d; J_{CH} 125,5Hz) 47,9 (CH; dd; $J_{CH} = J_{CP}$ 129,7Hz) 61,3 (CH_2; t; J_{CH} 147,5Hz) 62,8 (CH_2; t; J_{CH} 147,5Hz) 74,1 (CH; d; J_{CH} 142,0Hz) 128,1 (CH; d; J_{CH} 154,4Hz) 130,4 (C; s) and m/e; M^+ 343 (6,9%) 314 (11,8%) 231 (86,5%) 218 (93,5%) 162 (45,7%) 93 (79,0%) 79 (100%).

(ix) Phenylacetaldehyde

Diethyl cyclohexen-1-ylmethylphosphonate (2,51g; 10,82mmol) and butyllithium (11,00ml; 17,60mmol) in dry THF were treated at -78°C with phenylacetaldehyde (2,07g; 17,24mmol) and stirred at ambient temperature for 16h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which, after chromatography (prep t.l.c.; 50% diethyl ether/hexane), yielded two diastereoisomers of diethyl 1-(1'-hydroxy-2'-phenylethyl)cyclohexen-1-ylmethylphosphonate (3,19g; 9,06mmol; 83,7% [95]) of which the RS (SR) isomer was an oil; ν_{max} ($CHCl_3$) 3571, 3413, 1672, 1608cm^{-1}, ^1H n.m.r. ($CDCl_3$) 1,26 (3H; t; J_{HH} 7,1Hz) 1,27 (3H; t; J_{HH} 7,1Hz) 1,61 (4H; m) 2,09 (4H; m) 2,42 (1H; dd; J_{HH} 4,0Hz; J_{HP} 24,3Hz) 2,84 (2H; d; J_{HH} 6,6Hz) 4,08 (4H; p;

J_{HH} = J_{HP} 7,1Hz) 4,34 (1H; ddt; J_{HH} = J_{HH} 6,3Hz; J_{HP} 4,1Hz) 5,81 (1H; br s) 7,22 (5H; m), ^{31}P n.m.r. ($CDCl_3$) 29,21 ppm, ^{13}C n.m.r. ($CDCl_3$) 16,3 (2xMe; q; J_{CH} 126,2Hz) 22,0 (CH_2; t; J_{CH} 126,8Hz) 22,9 (CH_2; t; J_{CH} 126,7Hz) 25,6 (CH_2; t; J_{CH} 126,3Hz) 29,7 (CH_2; t; J_{CH} 128,5Hz) 40,8 (CH_2; t; J_{CH} 127,2Hz) 50,2 (CH; dd; J_{CH} = J_{CP} 127,6Hz) 61,7 (CH_2; t; J_{CH} 146,3Hz) 62,7 (CH_2; t; J_{CH} 146,3Hz) 71,1 (CH; d; J_{CH} 144,3Hz) 126,2 (CH; d; J_{CH} 159,0Hz) 128,2 (2xCH; d; J_{CH} 151,4Hz) 129,0 (CH; d; J_{CH} 145,9Hz) 129,3 (2xCH; d; J_{CH} 156,3Hz) 130,0 (C; s) 138,5 (C; s) and the RR (SS) stereoisomer colourless crystals (recryst. from hexane), m.p. 90,7-90,9°C; ^{1}H n.m.r. ($CDCl_3$) 1,27 (6H; t; J_{HH} 7,1Hz) 1,57 (4H; m) 2,04 (4H; m) 2,47 (1H; dd; J_{HH} 9,5Hz; J_{HP} 21,1Hz) 2,54 (1H; dd; J_{HH} 8,8Hz; J_{HH} 14,4Hz) 2,93 (1H; dd; J_{HH} 2,7Hz; J_{HH} 13,9Hz) 4,05 (4H; m; J_{HH} = J_{HP} 7,1Hz) 4,21 (1H; ddt; J_{HH} 2,8; J_{HH} 9,5Hz; J_{HP} 2,8Hz) 5,67 (1H; br s) 7,22 (5H; m), ^{31}P n.m.r. ($CDCl_3$) 29,65 ppm and m/e M^+ 352 (2,5%) 261 (6,4%) 232 (100%) 197 (15,4%) 176 (15,0%) 91 (64,7%).

(x) <u>Benzaldehyde</u>

Diethyl cyclohexen-1-ylmethylphosphonate (2,50g; 0,011mol) and butyllithium (12,0ml; 0,019mol) in dry THF were treated at -78°C with benzaldehyde (1,90g; 0,018mol) and stirred at ambient temperature for 16h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which, after chromatography (prep t.l.c.; 50% diethyl ether/hexane), yielded two diastereoisomers of diethyl 1-(hydroxyphenylmethyl)cyclohexen-1-ylmethylphosphonate (3,15g; 9,32mmol; 84,7% [90]) of which the RS (SR) stereoisomer was an oil; ^{1}H n.m.r. ($CDCl_3$) 1,12 (3H; t; J_{HH} 7,1Hz) 1,16 (3H; t; J_{HH} 7,1Hz) 1,40 (4H; m) 1,95 (4H; m) 2,56 (1H; dd; J_{HH} 5,1Hz; J_{HP} 23,2Hz) 3,92 (4H; m) 5,14 (1H; dd; J_{HH} = J_{HP} 5,3Hz) 5,79 (1H; br s) 7,22 (5H; m), ^{31}P n.m.r. ($CDCl_3$) 27,78 ppm, ^{13}C n.m.r. ($CDCl_3$) 16,1 (2xMe; q; J_{CH} 126,9Hz) 21,7 (CH_2; t; J_{CH} 127,7Hz) 22,8 (CH_2; t; J_{CH} 127,8Hz) 25,4 (CH_2; t; J_{CH} 126,7Hz) 30,1 (CH_2; t; J_{CH} 125,6Hz) 53,0 (CH; dd; J_{CH} = J_{CP} 127,0Hz) 61,3 (CH_2; t; 147,7Hz) 62,8 (CH_2; t; J_{CH} 147,7Hz) 71,8 (CH; d; J_{CH} 147,2Hz) 126,2 (2xCH; d; J_{CH} 158,3Hz) 127,0 (CH; d; J_{CH} 159,8Hz) 127,5 (2xCH; d; J_{CH} 159,5Hz) 128,9 (CH; d; J_{CH} 154,0Hz) 129,1 (C; s) 141,4 (C;

s) and the RR (SS) stereoisomer colourless crystals (recryst. from hexane), m.p. 92,4-92,7°C; ^{1}H n.m.r. ($CDCl_3$) 1,23 (3H; t; J_{HH} 7,1Hz) 1,26 (3H; t; J_{HH} 7,1Hz) 1,43 (2H; m) 1,80 (6H; m) 2,61 (1H; dd; J_{HH} 9,8Hz; J_{HP} 19,6Hz) 4,02 (2H; p; J_{HH} = J_{HP} 7,1Hz) 4,06 (2H; p; J_{HH} = J_{HP} 7,1Hz) 4,92 (1H; dd; J_{HH} = J_{HP} 9,7Hz) 5,56 (1H; br s) 7,20 (5H; m), ^{31}P n.m.r. ($CDCl_3$) 29,46 ppm, ^{13}C n.m.r. ($CDCl_3$) 14,6 (2xMe; q; J_{CH} 126,4Hz) 21,5 (CH_2; t; J_{CH} 127,7Hz) 22,4 (CH_2; t; J_{CH} 128,0Hz) 25,1 (CH_2; t; J_{CH} 126,6Hz) 29,5 (CH_2; t; J_{CH} 129,3Hz) 53,7 (CH; dd; J_{CH} = J_{CP} 127,4Hz) 61,9 (CH_2; t; 147,7Hz) 62,2 (CH_2; t; J_{CH} 147,7Hz) 73,9 (CH; d; J_{CH} 148,0Hz) 126,5 (2xCH; d; J_{CH} 148,2Hz) 127,1 (CH; d; J_{CH} 153,3Hz) 127,4 (2xCH; d; J_{CH} 153,6Hz) 127,6 (CH; d; J_{CH} 148,8Hz) 130,5 (C; s) 142,0 (C; s) and m/e; M^+ 338 (3,0%) 321 (29,9%) 308 (100,0%) 260 (28,3%) 232 (63,7%) 190 (83,9%) 169 (94,2%) 107 (94,1%) 93 (81,7%) 83 (96,6%).

(xi) Acetone

Diethyl cyclohexen-1-ylmethylphosphonate (0,73g; 3,15mmol) and butyllithium (3,30ml; 5,28mmol) in dry THF were treated at -78°C with acetone (0,30g; 5,17mmol) and stirred at ambient temperature for 2-16h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which was shown to be diethyl cyclohexen-1-ylmethylphosphonate (0,69g; 2,97mmol; 94,4%), identical (^{31}P, ^{1}H n.m.r. and t.l.c.) to an authentic sample.

(xii) Mesityl oxide

Diethyl cyclohexen-1-ylmethylphosphonate (1,00g; 4,31mmol) and butyllithium (4,60ml; 7,36mmol) in dry THF were treated at -78°C with mesityl oxide (0,67g; 6,83mmol) and stirred at ambient temperature for 16h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which was shown to be diethyl cyclohexen-1-ylmethylphosphonate (0,97g; 4,18mmol; 96,9%), identical (^{31}P, ^{1}H n.m.r. and t.l.c.) to an authentic sample.

(xiii) Cyclohexanone

Diethyl cyclohexen-1-ylmethylphosphonate (0,52g; 2,24mmol) and butyllithium (2,40ml; 3,84mmol) in dry THF were treated at -78°C with cyclohexanone (0,35g; 3,57mmol) and stirred at ambient temperature for 16h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which was shown to be diethyl cyclohexen-1-ylmethylphosphonate (0,50g; 2,15mmol; 96,0%), identical (^{31}P, ^{1}H n.m.r. and t.l.c.) to an authentic sample.

(xiv) Acetyl chloride

Diethyl cyclohexen-1-ylmethylphosphonate (2,03g; 8,75mmol) and butyllithium (6,6ml; 10,50mmol) in dry THF were treated at -78°C with acetyl chloride (1,10g; 14,00mmol) and stirred at ambient temperature for 4h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which, after chromatography (column; methylene chloride), yielded diethyl 1,1'-*bis*-acetylcyclohexen-1-ylmethylphosphonate (1,34g; 4,24mmol; 48,4% [60]) as an oil; ν_{max} ($CHCl_3$) 1758, 1720, 1637cm^{-1}, ^{1}H n.m.r. ($CDCl_3$) 1,22 (6H, t, J_{HH} 6,9Hz) 1,54 (4H; m) 1,92 (3H; s) 2,01 (4H; m) 2,11 (3H, s) 3,98 (4H, p, $J_{HH} = J_{HP}$ 6,8Hz) 5,54 (1H; br s), ^{31}P n.m.r.($CDCl_3$) 15,07 ppm, ^{13}C n.m.r. ($CDCl_3$) 16,0 (2xMe; q; J_{CH} 127,4Hz) 20,8 (2xMe; q; J_{CH} 130,1Hz) 20,9 (CH_2; t; J_{CH} 128,3Hz) 22,6 (CH_2; t; J_{CH} 127,6Hz) 25,2 (CH_2; t; J_{CH} 126,9Hz) 28,8 (CH_2; J_{CH} 127,1Hz) 61,5 (2xCH_2; t; J_{CH} 147,1Hz) 122,0 (C; d; J_{CP} 171,4Hz) 128,2 (CH; d; J_{CH} 155,5Hz) 157,7 (C; s) 148,6 (C; s) and m/e; 301 (1,1%) 286 (10,5%) 259 (4,9%) 232 (100,0%) 204 (94,4%) 176 (35,3%) 151 (15,9%) 93 (31,5%).

(4) Diethyl methyl(cyclohexen-1-yl)methylphosphonate

(i) Benzaldehyde

Diethyl methyl(cyclohexen-1-yl)methylphosphonate (1,56g; 6,31mmol) and butyllithium (6,5ml; 10,40mmol) in dry THF were treated at -78°C with benzaldehyde (1,07g; 10,10mmol) and stirred at ambient temperature for 16h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which, after chromatography (prep t.l.c.; 50% diethyl ether/hexane), yielded two diastereoisomers of diethyl 1-methyl-1-(hydroxyphenylmethyl)cyclohexen-1-ylmethyl-phosphonate (1,12g; 3,18mmol; 50,4% [70]) of which one was crystalline, m.p. 113,1-113,4°C; ^{1}H n.m.r. ($CDCl_3$) 1,06 (3H; d; J_{HH} 17,1Hz) 1,18 (3H; t; J_{HH} 7,1Hz) 1,22 (3H; t; J_{HH} 7,1Hz) 1,41 (4H; m) 1,95 (4H; m) 3,98 (2H; p; $J_{HH} = J_{HP}$ 7,1Hz) 4,05 (2H; p; $J_{HH} = J_{HP}$ 7,1Hz) 5,28 (1H; d; J_{HH} 7,6Hz) 5,64 (1H; br s) 7,20 (5H; m), ^{31}P n.m.r. ($CDCl_3$) 29,51 ppm, ^{13}C n.m.r. ($CDCl_3$) 12,1 (Me; q; J_{CH} 129,5Hz) 16,2 (2xMe; q; J_{CH} 126,7Hz) 21,7 (CH_2; t; J_{CH} 127,5Hz) 22,9 (CH_2; t; J_{CH} 126,9Hz) 25,6 (CH_2; t; J_{CH} 125,9Hz) 26,6 (CH_2; t; J_{CH} 126,1Hz) 51,1 (C; d; J_{CP} 133,1Hz) 61,9 (2xCH_2; t; J_{CH} 147,7Hz) 74,8 (CH; d; J_{CH} 147,6Hz) 126,2 (CH; d; J_{CH} 141,0Hz) 126,4 (CH; d; J_{CH} 159,2Hz) 126,8 (2xCH; d; J_{CH} 158,9Hz) 127,6 (2xCH; d; J_{CH} 158,2Hz) 133,9 (C; s) 140,1 (C; s) and the other an oil; ^{1}H n.m.r. ($CDCl_3$) 1,08 (3H; d; J_{HH} 16,3Hz) 1,16 (3H; t; J_{HH} 7,1Hz) 1,19 (3H; t; J_{HH} 7,1Hz) 1,52 (4H; m) 2,09 (4H; m) 4,00 (4H; m) 5,00 (1H; d; J_{HH} 5,4Hz) 6,06 (1H; br s) 7,24 (5H; m), ^{31}P n.m.r. ($CDCl_3$) 30,87 ppm, ^{13}C n.m.r. ($CDCl_3$) 13,9 (Me; q; J_{CH} 124,4Hz) 16,2 (2xMe; q; J_{CH} 125,8Hz) 21,6 (CH_2; t; J_{CH} 123,5Hz) 22,5 (CH_2; t; J_{CH} 123,4Hz) 26,0 (CH_2; t; J_{CH} 125,3Hz) 27,5 (CH_2; t; J_{CH} 125,2Hz) 49,5 (C; d; J_{CP} 132,7Hz) 61,3 (CH_2; t; J_{CH} 142,7Hz) 63,1 (CH_2; t; J_{CH} 142,7Hz) 76,6 (CH; d; J_{CH} 146,9Hz) 127,0 (2xCH; d; J_{CH} 159,5Hz) 127,5 (CH; d; J_{CH} 159,6Hz) 127,7 (CH; d; J_{CH} 159,9Hz) 128,4 (2xCH; d; J_{CH} 158,6Hz) 132,1 (C; s) 139,2 (C; s) and m/e; 260 (33,4%) 246 (69,7%) 232 (12,3%) 122 (31,2%) 105 (100,0%) 91 (40,6%).

(5) Diethyl 1-(2'-methylethyl)cyclohexen-1-ylmethylphosphonate

(i) Propionaldehyde

Procedure A

Diethyl 1-(2'-methylethyl)cyclohexen-1ylmethylphosphonate (1,38g; 5,02mmol) and butyllithium (5,5ml; 8,78mmol) in dry THF were treated at -78°C with propionaldehyde (0,47g; 8,03mmol) and stirred at ambient temperature for 16h. After washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration, the reaction mixture afforded an oil which, after chromatography (column; methylene dichloride), yielded two diastereoisomers of diethyl 1-[2'-(1'-hydroxypropyl)cylohexylidenyl)]-2-methylpropylphosphonate (1,15g; 3,47mmol; 69,1% [85]) as oils; ν_{max} ($CHCl_3$) 3601, 3403, 1587cm^{-1}, ^1H n.m.r. ($CDCl_3$) 0,94 (3H; t; J_{HH} 7,3Hz) 1,13 (3H; d; J_{HH} 7,0Hz) 1,15 (3H; d; J_{HH} 7,0Hz) 1,26 (6H; t; J_{HH} 7,1Hz) 1,30-2,00 (12H; m) 3,09 (1H; m) 4,00 (4H; p; $J_{HH} = J_{HP}$ 7,1Hz), ^{31}P n.m.r. ($CDCl_3$) 22,11 ppm, ^{13}C n.m.r. ($CDCl_3$) 10,8 (2xMe; q; J_{CH} 122,3Hz) 16,1 (2xMe; q; J_{CH} 127,0Hz) 20,9 (CH_2; t; J_{CH} 126,3Hz) 22,6 (CH_2; t; J_{CH} 126,3Hz) 27,8 (CH_2; t; J_{CH} 123,7Hz) 28,5 (CH_2; t; J_{CH} 122,8Hz) 29,3 (CH; d; J_{CH} 121,8) 46,3 (CH; d; J_{CH} 128,1Hz) 60,5 (2xCH_2; t; J_{CH} 142,3Hz) 71,1 (CH; d; J_{CH} 139,4Hz) 129,2 (C; d; J_{CP} 164,9Hz) 158,2 (C; s) and ^1H n.m.r. ($CDCl_3$) 0,96 (3H; t; J_{HH} 7,3Hz) 1,14 (3H; d; J_{HH} 7,0Hz) 1,16 (3H; d; J_{HH} 7,0Hz) 1,25 (6H; t; J_{HH} 7,1Hz) 1,30-2,00 (12H; m) 3,17 (1H; m) 4,00 (4H; p; $J_{HH} = J_{HP}$ 7,1Hz), ^{31}P n.m.r. ($CDCl_3$) 22,23 ppm, ^{13}C n.m.r. ($CDCl_3$) 10,5 (2xMe; q; J_{CH} 127,3Hz) 16,1 (2xMe; q; J_{CH} 127,0Hz) 20,9 (CH_2; t; J_{CH} 126,3Hz) 22,6 (CH_2; t; J_{CH} 126,3Hz) 27,8 (CH_2; t; J_{CH} 123,7Hz) 28,5 (CH_2; t; J_{CH} 122,8Hz) 29,3 (CH; d; J_{CH} 121,8) 46,3 (CH; d; J_{CH} 128,1Hz) 60,5 (2xCH_2; t; J_{CH} 142,3Hz) 71,1 (CH; d; J_{CH} 139,4Hz) 127,1 (C; d; J_{CP} 159,1Hz) 157,4 (C; s) and m/e; 317 (1,0%) 303 (6,7%) 274 (81,1%) 231 (46,7%) 203 (54,7%) 161 (27,0%) 133 (54,7%) 119 (50,2%) 93 (85,3%) 81 (84,1%) 41 (100,0%).

Procedure B

Diethyl 1-(2'-methylethyl)cyclohexen-1-ylmethylphosphonate (0,20g; 0,73mmol) and butyllithium (0,7ml; 1,12mmol) in dry THF were treated at -78°C with propionaldehyde (0,07g; 1,21mmol) and stirred at this temperature for 6h. After quenching of the reaction mixture at -78°C, washing (aq. NH_4Cl), extraction (methylene dichloride) and concentration afforded an oil which, after chromatography (prep t.l.c.; 50% diethyl ether/hexane), yielded two diastereoisomers of diethyl 1-(1'-hydroxypropyl)-1-(1''-methylethyl)cyclohexen-1-yl-methylphosphonate (0,08g; 0,24mmol; 32,9% [60]) as oils; ^{1}H n.m.r. ($CDCl_3$) 1,02 (3H; d; J_{HH} 6,9Hz) 1,11 (3H; t; J_{HH} 7,3Hz) 1,19 (3H; d; J_{HH} 6,9Hz) 1,25 (3H; t; J_{HH} 7,1Hz) 1,27 (3H; t; J_{HH} 7,1Hz) 1,55 (5H; m) 1,71 (1H; dq; J_{HH} 7,3Hz; J_{HH} 6,8Hz) 2,01 (4H; m) 2,42 (1H; dq; J_{HH} 7,3Hz; J_{HH} 6,7Hz) 3,85 (1H; m) 4,00 (4H; m) 5,79 (1H; br s), ^{31}P n.m.r. ($CDCl_3$) 33,80 ppm and ^{1}H n.m.r. ($CDCl_3$) 0,98 (3H; d; J_{HH} 6,9Hz) 1,00 (3H; t; J_{HH} 7,3Hz) 1,23 (3H; d; J_{HH} 6,9Hz) 1,27 (3H; t; J_{HH} 7,1Hz) 1,30 (3H; t; J_{HH} 7,1Hz) 1,53 (5H; m) 1,76 (1H; dq; J_{HH} 6,8Hz; J_{HH} 7,3Hz) 2,02 (4H; m) 2,28 (1H; dq; J_{HH} 6,7Hz; J_{HH} 7,3Hz) 3,87 (1H; m) 4,10 (4H; m) 5,50 (1H; br s), ^{31}P n.m.r. ($CDCl_3$) 34,53 ppm, ^{13}C n.m.r. ($CDCl_3$) 12,1 (Me; q; J_{CH} 125,7Hz) 16,4 (2xMe; q; J_{CH} 126,9Hz) 18,9 (2xMe; q; J_{CH} 126,0Hz) 19,7 (CH_2; t; J_{CH} 126,1Hz) 22,2 (CH_2; t; J_{CH} 128,7Hz) 23,4 (CH_2; t; J_{CH} 127,6Hz) 25,9 (CH_2; t; J_{CH} 125,1Hz) 27,9 (CH_2; t; J_{CH} 127,2Hz) 31,4 (CH; d; J_{CH} 129,7) 53,2 (C; d; J_{CP} 130,1Hz) 61,1 (CH_2; t; J_{CH} 147,3Hz) 61,9 (CH_2; t; J_{CH} 147,3Hz) 75,1 (CH; d; J_{CH} 145,9Hz) 125,8 (CH; d; J_{CH} 149,1Hz) 134,0 (C; s) and m/e; M^+ 314 (51,1%) 299 (13,9%) 274 (40,9%) 259 (56,3%) 232 (67,9%) 176 (80,1%) 161 (86,7%) 93 (91,8%) 55 (95,4%) 41 (100,0%).

(D) Dephosphorylation of 2-hydroxyalkylphosphonates

General procedure[107]

The phosphonate (5mmol) in dry dimethyl formamide (17ml) was treated with sodium hydride (hexane washed) (6mmol). The reaction mixture was stirred for 4-20h at ambient

temperature, whereupon aqueous ammonium chloride was added and the mixture extracted with hexane/diethyl ether. Purification by chromatography (column; hexane) afforded the pure product. Spectral data are given in the individual syntheses.

(i) Diethyl 1-(1'-hydroxypropyl)cyclohexen-2-ylphosphonate

RR(SS)-diethyl 1-(1'-hydroxypropyl)cyclohexen-2-ylphosphonate (0,431g; 1,56mmol) and sodium hydride (0,045g; 1,87mmol) afforded *trans* 3-propylidenecyclohexene (0,100g; 0,82mmol; 52,5% [80]) as an oil, ^{1}H n.m.r. ($CDCl_3$) 0,99 (3H; t; J_{HH} 7,6Hz) 1,69 (2H; m) 2,12 (4H; m) 2,32 (2H; m) 5,22 (1H; t; J_{HH} 7,4Hz) 5,68 (1H; dt; J_{HH} 4,0Hz; J_{HH} 9,9Hz) 6,01 (1H; dd; J_{HH} 9,8Hz; J_{HH} 1,6Hz).

RR(SS)-diethyl 1-(1'-hydroxypropyl)cyclohexen-2-ylphosphonate (0,601g; 2,17mmol) and sodium hydride (0,079g; 2.63mmol) afforded *cis* 3-propylidenecyclohexene (0,097g; 0,079mmol; 36,6% [65]) as an oil, ^{1}H n.m.r. ($CDCl_3$) 0,99 (3H; t; J_{HH} 7,6Hz) 1,69 (2H; m) 2,12 (4H; m) 2,32 (2H; m) 5,09 (1H; t; J_{HH} 7,4Hz) 5,79 (1H; ddt; J_{HH} 10,1Hz; J_{HH} 4,2Hz; J_{HH} 1,5Hz) 6,39 (1H; ddt; J_{HH} 10,2Hz; J_{HH} 2,0Hz; J_{HH} 0,9Hz).

(ii) Diethyl 1-(hydroxyphenylmethyl)cyclohexen-2-ylphosphonate

RR(SS)-diethyl1-(hydroxyphenylmethyl)cyclohexen-2-ylphosphonate(1,397g;4,31mmol)and sodium hydride (0,156g; 5,20mmol) afforded *trans* 3-benzylidenecyclohexene (0,347g; 2,04mmol; 47,3% [55]) as an oil, ^{1}H n.m.r. ($CDCl_3$) 1,71 (2H; dt; J_{HH} = J_{HH} 6,3Hz) 2,18 (2H; m) 2,65 (2H; m) 5,90 (1H; dt; J_{HH} 9,7Hz; J_{HH} 4,2Hz) 6,21 (1H; dt; J_{HH} 9,8Hz; J_{HH} 2,0Hz) 6,26 (1H; s) 7,27 (5H; m), ^{13}C n.m.r. ($CDCl_3$) 25,5 (CH_2; t; J_{CH} 126,9Hz) 26,8 (CH_2; t; J_{CH} 131,3Hz) 31,6 (CH_2; t; J_{CH} 127,9Hz) 126,1 (CH; d; J_{CH} 160,5Hz) 126,2 (CH; d; J_{CH} 150,5Hz) 128,0 (2xCH; d; J_{CH} 159,2) 129,0 (2xCH; d; J_{CH} 152,7Hz) 130,1 (CH; d; J_{CH} 150,8Hz) 132,8 (C; s) 137,8 (C; s).

RS(SR)-diethyl1-(hydroxyphenylmethyl)cyclohexen-2-ylphosphonate(1,071g;3,30mmol)and sodium hydride (0,095g; 3,96mmol) afforded *cis* 3-benzylidenecyclohexene (0,073g; 0,43mmol; 13,0% [20]) as an oil, ^{1}H n.m.r. ($CDCl_3$) 1,81 (2H; dt; J_{HH} = J_{HH} 6,3Hz) 2,19 (2H; m) 2,42 (2H; m) 5,99 (1H; dt; J_{HH} 10,3Hz; J_{HH} 1,8Hz) 6,19 (1H; s) 6,70 (1H; dt; J_{HH} 10,3Hz; J_{HH} 0,8Hz) 7,26 (5H; m), ^{13}C n.m.r. ($CDCl_3$) 25,3 (CH_2; t; J_{CH} 126,9Hz) 25,7 (CH_2; t; J_{CH} 131,3Hz) 32,4 (CH_2; t; J_{CH} 127,9Hz) 124,4 (CH; d; J_{CH} 141,4Hz) 125,5 (CH; d; J_{CH} 157,2Hz) 126,1 (CH; d; J_{CH} 150,5Hz) 128,0 (2xCH; d; J_{CH} 159,2) 129,0 (2xCH; d; J_{CH} 152,7Hz) 132,9 (C; s) 137,2 (C; s).

(iii) <u>Diethyl 1-(1'-hydroxy-2'-phenylethyl)cyclohexen-2-ylphosphonate</u>

RR(SS)-diethyl 1-(1'-hydroxy-2'-phenylethyl)cyclohexen-2-ylphosphonate (2,497g; 7,38mmol) and sodium hydride (0,213g; 8,88mmol) afforded *trans* 3-(2-phenylethylidene)cyclohexene (0,473g; 2,57mmol; 34,8% [40]) as an oil, ^{1}H n.m.r. ($CDCl_3$) 1,77 (2H; dt; J_{HH} = J_{HH} 6,3Hz) 2,19 (2H; m) 2,46 (2H; t; J_{CH} 5,7Hz) 3,49 (2H; d; J_{CH} 7,5Hz) 5,46 (1H; t; J_{HH} 7,5Hz) 5,78 (1H; dt; J_{CH} 9,8Hz; J_{CH} 4,1Hz) 6,12 (1H; d; J_{HH} 9,9Hz) 7,23 (5H; m), ^{13}C n.m.r. ($CDCl_3$) 22,8 (CH_2; t; J_{CH} 127,7Hz) 25,3 (CH_2; t; J_{CH} 122,3Hz) 31,9 (CH_2; t; J_{CH} 126,3Hz) 125,1 (CH; d; J_{CH} 154,3Hz) 125,8 (CH; d; J_{CH} 160,1Hz) 128,0 (2xCH; d; J_{CH} 163,5Hz) 128,2 (2xCH; d; J_{CH} 160,1Hz) 131,0 (CH; d; J_{CH} 154,0Hz) 135,5 (C; s) 140,9 (C; s).

RS(SR)-diethyl 1-(1'-hydroxy-2'-phenylethyl)cyclohexen-2-ylphosphonate (2,510g; 7,42mmol) and sodium hydride (0,214g; 8,92mmol) afforded *cis* 3-(2-phenylethylidene)cyclohexene (0,698g; 3,79mmol; 51,1% [60]) as an oil, ^{1}H n.m.r. ($CDCl_3$) 1,77 (2H; dt; J_{HH} = J_{HH} 6,3Hz) 2,19 (2H; m) 2,36 (2H; t; J_{CH} 6,4Hz) 3,49 (2H; d; J_{CH} 7,5Hz) 5,32 (1H; dt; J_{CH} 7,6Hz; J_{HH} 1,0Hz) 5,93 (1H; ddt; J_{CH} 9,2Hz; J_{CH} 4,1Hz; J_{CH} 1,8Hz) 6,58 (1H; d; J_{HH} 9,2Hz) 7,23 (5H; m), ^{13}C n.m.r. ($CDCl_3$) 22,8 (CH_2; t; J_{CH} 127,7Hz) 25,3 (CH_2; t; J_{CH} 122,3Hz) 31,9 (CH_2; t; J_{CH} 126,3Hz) 124,2 (CH; d; J_{CH} 154,7Hz) 125,8 (CH; d; J_{CH} 160,1Hz) 128,0 (2xCH; d; J_{CH} 163,5Hz) 128,2 (2xCH; d; J_{CH} 160,1Hz) 130,6 (CH; d; J_{CH} 153,8Hz) 135,5

(C; s) 140,9 (C; s).

(iv) Diethyl 1-(1'-hydroxypropyl)cyclohexen-1-ylphosphonate

RR(SS)-diethyl 1-(1'-hydroxypropyl)cyclohexen-1-ylphosphonate (0,989g; 3,41mmol) and sodium hydride (0,098g; 4,08mmol) afforded *trans* 1-buten-1-ylcyclohexene (0,261g; 1,92mmol; 56,2% [80]) as an oil, ^{1}H n.m.r. ($CDCl_3$) 0,99 (2H; dt; J_{HH} 7,5Hz) 1,60 (4H; m) 2,08 (4H; m) 5,57 (1H; dt; J_{CH} 15,7Hz; J_{CH} 6,6Hz) 5,62 (1H; br s) 6,01 (1H; d; J_{HH} 15,7Hz), ^{13}C n.m.r. ($CDCl_3$) 14,0 (Me; q; J_{CH} 125,9Hz) 22,6 (CH_2; t; J_{CH} 127,7Hz) 24,2 (CH_2; t; J_{CH} 120,1Hz) 24,6 (CH_2; t; J_{CH} 128,5Hz) 25,8 (CH_2; t; J_{CH} 127,9Hz) 29,7 (CH_2; t; J_{CH} 146,0Hz) 126,9 (CH; d; J_{CH} 152,9Hz) 128,2 (CH; d; J_{CH} 148,7Hz) 132,5 (CH; d; J_{CH} 152,7Hz) 135,7 (C; s).

RS(SR)-diethyl 1-(1'-hydroxypropyl)cyclohexen-1-ylphosphonate (1,695g; 5,84mmol) and sodium hydride (0,168g; 7,00mmol) afforded *trans* 1-buten-1-ylcyclohexene (0,015g; 0,11mmol; 1,9% [5]) as an oil, identical (^{1}H n.m.r.) to an authentic sample.

(v) Diethyl 1-(1'-hydroxy-2'-methylpropyl)cyclohexen-1-ylphosphonate

RR(SS)-diethyl 1-(1'-hydroxy-2'-methylpropyl)cyclohexen-1-ylphosphonate (3,003g; 9,87mmol) and sodium hydride (0,284g; 11,85mmol) afforded *trans* 1-(3-methylbuten-1-yl)cyclohexene (0,406g; 2,70mmol; 27,4% [35]) as an oil, ^{1}H, n.m.r. ($CDCl_3$) 1,00 (6H; d; J_{CH} 6,7Hz) 1,64 (4H; m) 2,10 (4H; m) 2,30 (1H; dq; J_{CH} 13,4Hz; J_{CH} 6,7Hz) 5,50 (1H; dd; J_{CH} 15,8Hz; J_{CH} 6,9Hz) 5,65 (1H; br s) 5,98 (1H; d; J_{CH} 15,8Hz), ^{13}C n.m.r. ($CDCl_3$) 22,6 (2xMe; q; J_{CH} 125,6Hz) 22,7 (CH_2; t; J_{CH} 127,7Hz) 24,3 (CH_2; t; J_{CH} 125,9Hz) 24,6 (CH_2; t; J_{CH} 126,5Hz) 25,8 (CH_2; t; J_{CH} 126,5Hz) 31,2 (CH; d; J_{CH} 125,3Hz) 127,2 (CH; d; J_{CH} 152,4Hz) 130,4 (CH; d; J_{CH} 146,7Hz) 133,7 (CH; d; J_{CH} 147,3Hz) 135,6 (C; s).

RS(SR)-diethyl 1-(1'-hydroxy-2'-methylpropyl)cyclohexen-1-ylphosphonate (2,499g;

8,22mmol) and sodium hydride (0,237g; 9,88mmol) afforded *trans* 1-(3-methylbuten-1-yl)cyclohexene (0,475g; 3,16mmol; 38,5% [45]) as an oil, identical (^{1}H n.m.r.) to an authentic sample.

(vi) Diethyl 1-(hydroxyphenylmethyl)cyclohexen-1-ylphosphonate

RR(SS)-diethyl1-(hydroxyphenylmethyl)cyclohexen-1-ylphosphonate(1,593g;4,71mmol)and sodium hydride (0,136g; 5,67mmol) afforded *trans* 1-phenyl-2-cyclohexen-1-ylethylene (0,449g; 2,44mmol; 51,8% [65]) as an oil, ^{1}H, n.m.r. ($CDCl_3$) 1,71 (4H; m) 2,22 (4H; m) 2,31 (2H; m) 5,93 (1H; t; J_{CH} 4,0Hz) 6,47 (1H; d; J_{CH} 16,2Hz) 6,81 (1H; d; J_{CH} 16,1Hz) 7,21 (1H; d; J_{CH} 7,8Hz) 7,32 (2H; dd; J_{CH} = J_{CH} 7,8Hz) 7,42 (2H; d; J_{CH} 7,8Hz).

RS(SR)-diethyl1-(hydroxyphenylmethyl)cyclohexen-1-ylphosphonate(1,436g;4,25mmol)and sodium hydride (0,122g; 5,08mmol) afforded *trans* 1-phenyl-2-cyclohexen-1-ylethylene (0,059g; 0,32mmol; 7,5% [15]) as an oil, identical (^{1}H n.m.r.) to an authentic sample.

(vii) Diethyl 1-(1'-hydroxy-2'-phenylethyl)cyclohexen-1-ylphosphonate

RR(SS)-diethyl 1-(1'-hydroxy-2'-phenylethyl)cyclohexen-1-ylphosphonate (1,014g; 2,88mmol) and sodium hydride (0,083g; 3,46mmol) afforded *trans* 1-cyclohexen-1-yl-3-phenylpropene (0,081g; 0,41mmol; 14,2% [20]) as an oil, ^{1}H, n.m.r. ($CDCl_3$) 1,63 (4H; m) 2,14 (4H; m) 3,43 (2H; d; J_{CH} 6,9Hz) 5,70 (1H; dt; J_{CH} 15,2Hz; J_{CH} 7,0Hz) 6,12 (1H; d; J_{CH} 15,6Hz) 7,23 (5H; m).

RS(SR)-diethyl 1-(1'-hydroxy-2'-phenylethyl)cyclohexen-1-ylphosphonate (1,333g; 3,79mmol) and sodium hydride (0,109g; 4,54mmol) afforded diethyl cyclohexen-1-ylmethylphosphonate (0,717g; 3,09mmol; 81,5%), as well as diethyl cyclohexylidenemethylphosphonate (0,112g; 0,48mmol; 12,7%), identical (^{1}H, ^{31}P n.m.r.) to authentic samples.

(viii) Diethyl 1-methyl-1-(hydroxyphenylmethyl)cyclohexen-1-ylphosphonate

RR(SS)-diethyl 1-methyl-1-(hydroxyphenylmethyl)cyclohexen-1-ylphosphonate (1,389g; 3,94mmol) and sodium hydride (0,114g; 4,75mmol) afforded *trans* 1-phenyl-2-cyclohexen-1-ylpropene (0,41g; 2,07mmol; 52,4% [60]) as an oil, ^{1}H, n.m.r. ($CDCl_3$) 1,65 (2H; m) 1,75 (2H; m) 2,00 (3H; s) 2,22 (2H; m) 2,34 (2H; m) 6,03 (1H; t; J_{CH} 4,0Hz) 6,59 (1H; s) 7,29 (5H; m), ^{13}C n.m.r. ($CDCl_3$) 15,1 (Me; q; J_{CH} 126,4Hz) 22,4 (CH_2; t; J_{CH} 127,7Hz) 22,7 (CH_2; t; J_{CH} 124,5Hz) 23,2 (CH_2; t; J_{CH} 127,5Hz) 26,2 (CH_2; t; J_{CH} 124,9Hz) 122,9 (C; s) 125,1 (2xCH; d; J_{CH} 147,1Hz) 128,0 (2xCH; d; J_{CH} 152,3Hz) 129,4 (CH; d; J_{CH} 158,3Hz) 137,9 (C; s) 139,1 (C; s).

RS(SR)-diethyl 1-methyl-1-(hydroxyphenylmethyl)cyclohexen-1-ylphosphonate (0,997g; 2,83mmol) and sodium hydride (0,082g; 3,42mmol) afforded *trans* 1-phenyl-2-cyclohexen-1-ylpropene (0,081g; 0,41mmol; 14,4% [20]) as an oil, identical (^{1}H n.m.r.) to an authentic sample.

(ix) Diethyl 1-(1'-hydroxypropyl)-1-(1''-methylethyl)cyclohexen-1-ylphosphonate

RR(SS)-diethyll-(1'-hydroxypropyl)-1-(1''-methylethyl)cyclohexen-1-ylphosphonate (0,015g; 0,045mmol) and sodium hydride (0,002g; 0,083mmol) afforded *trans* 1-(2-methylhexen-3-yl)-cyclohexene (0,004g; 0,022mmol; 49,9% [55]) as an oil, ^{1}H, n.m.r. ($CDCl_3$) 0,96 (3H; t; J_{CH} 7,3Hz) 1,03 (3H; d; J_{CH} 6,9Hz) 1,07 (3H; d; J_{CH} 6,9Hz) 1,58 (4H; m) 2,09 (6H; m) 2,75 (1H; dq; J_{CH} = J_{CH} 7,0Hz) 5,08; t; J_{CH} 7,2Hz) 5,40 (1H; br s).

RS(SR)-diethyll-(1'-hydroxypropyl)-1-(1''-methylethyl)cyclohexen-1-ylphosphonate (0,011g; 0,033mmol) and sodium hydride (0,001g; 0,042mmol) afforded *cis* 1-(2-methylhexen-3-yl)-cyclohexene [45%] which was not isolated in pure form; ^{1}H, n.m.r. ($CDCl_3$) 0,89 (3H; d; J_{CH} 6,8Hz) 0,91 (3H; t; J_{CH} 7,3Hz) 0,94 (3H; d; J_{CH} 6,9Hz) 1,58 (4H; m) 2,00 (6H; m) 2,22 (1H; dq; J_{CH} = J_{CH} 6,8Hz) 5,04; dt; J_{CH} 7,2Hz; J_{CH} 1,0Hz) 5,26 (1H; br s).

(E) Crystal structure determination

Colourless crystals of the substrates were obtained by slow evaporation of their solutions in hexane. Diethyl 1-(1'-hydroxy-2'-methylpropyl)cyclohexen-1-ylphosphonate (fig. 13; 1) crystallised in the space group C2/c, while diethyl 1-(hydroxyphenylmethyl)cyclohexen-1-yl- (fig. 13; 2) and 1-(1'-hydroxy-2'-phenylethyl)cyclohexen-1-ylphosphonate (fig. 13; 3) crystallised in P1. All diffraction measurements were performed at room temperature and the data collected with an Enraf-Nonius CAD4 diffractometer using monochromated Mo-K_α (λ = 0,7107Å) radiation. The lattice constants were obtained from a least squares fit of 25 centered reflections in the ranges $6° < \theta < 13°$, $18° < \theta \leq 20°$ and $13° < \theta \leq 16°$ for 1,2 and 3, respectively. Data were corrected for Lorentz and polarisation effects. Absorption corrections were applied for 2 and 3. Intensity checks were conducted every hour and an orientation control every 200 reflections. Three standard reflections were used to check orientation and crystal stability at regular intervals. The decay during data collection was 2,3%, 0,8% and 7,8% (corrected) for 1,2, and 3, respectively. The structures were solved by direct methods and refined anisotropically using a full matrix method ($1/\sigma^2$F-weights) using SHELX76.[108] All hydrogen atoms, except the experimentally located and refined hydroxyl hydrogen (H_{11}) of 2 and 3, were placed in calculated positions and were included in the refinement with a common isotropic temperature factor that converged to U = 0,310(16) Å^2, 0,175(7) Å^2 and 0,262(5) Å^2 for 1,2 and 3, respectively. The following bond distances were refined in a fixed mode: in 1, the C-O and C-C bond distances of the PO_3Et_2 groups. In 3, the same bond distances were fixed, as well as the C(22)-C(23) bond in the cyclohexene ring. In 2, the same bond distances were fixed as in 1, with the exception of the C(4)-C(5) bond. The C-C and C-O distances of the PO_3Et_2 groups were constrained to 1,500(1) Å and 1,420(1) Å, respectively. The C(22)-C(23) bond was constrained to 1,500(1)Å. This was necessary, since the very high thermal motions of these atoms resulted in unrealistic bond lengths. Crystallographic data acquisition and refinement details of compounds 1,2 and 3 are recorded in Table 12.

Table 12

Compound	1	2	3
Emperical formula	$C_{15}H_{29}O_4P$	$C_{18}H_{27}O_4P$	$C_{19}H_{29}O_4P$
Molecular weight ($g.mol^{-1}$)	304	338	352
Crystal dimension (mm)	0,55x0,22x0,35	0,18x0,47x0,75	0,20x0,20x0,32
Space group	C2/c	P1	P1
Cell dimensions			
a (Å)	19,433(2)	9,074(1)	8,106(1)
b (Å)	9,564(3)	10,446(1)	11,943(1)
c (Å)	19,778(3)	11,062(2)	12,103(2)
α (°)		109,47(1)	116,63(1)
β (°)	101,70(1)	103,87(1)	99,91(1)
γ (°)		103,87(1)	94,91(1)
Z	8	2	2
Volume ($Å^3$)	3599,5	993,6	1016,2
D(calc) ($g.cm^{-3}$)	1,12	1,20	1,15
μ (cm^{-1})	1,25	1,24	1,15
T (°C)	26	21	24
F(000)	1328	364	380
Scan type (ω:2θ)	1 : 1	1 : 1	1 : 1
Scan range (θ°)	$3 \leq \theta \leq 27$	$3 \leq \theta \leq 30$	$3 \leq \theta \leq 27$
hkl-indices			
h	0:24	-12:0	-10:10
k	0:12	-14:14	0:15
l	-25:25	-15:15	-15:15
Maximum scan speed (variable, $deg.min^{-1}$)	max 3,30	max 5,49	max 5,49
Max. scan time (sec)	60	60	60

Compound	1	2	3
Scan angle (ω+0,34tanθ)°	0,56	0,63	0,52
Aperture size (mm)	1,3x4,0	1,3x4,0	1,3x4,0
Reflections collected	4255	5424	4417
EAC correction factor (Max)	none	0,998	0,997
EAC correction factor (Min)	none	0,640	0,963
EAC correction factor (Av)		0,823	0,981
Unique reflections used	1472($>2\sigma(1)$)	2812($>4\sigma(1)$)	1996($>4\sigma(1)$)
R_{int}	0,0481	0,0000	0,0000
Parameters refined	194	218	227
Max. positional shift/esd	0,171	0,274	0,198
Residual e^- dens. (eÅ^3) Max	0,46	0,76	0,40
Residual e^- dens. (eÅ^3) Min	-0,45	-0,84	-0,32
R	0,1235	0,1313	0,0922
R_w	0,0635	0,1013	0,0761

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