PIENAAR, ANDRé

A STUDY ON THE REACTION OF HETEROATOM-STABILISED CARBANIONS WITH a,B-UNSATURATED KETONES

PhD UP 1997

A Study on the Reaction of Heteroatom-Stabilised Carbanions with α,β-Unsaturated Ketones

by

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"I'm not trying to prove anything by the way. I'm a scientist and I know what constitutes proof. But the reason I call myself by my childhood name is to remind myself that a scientist must also be absolutely like a child. If he sees a thing, he must say that he sees it, whether it was what he thought he was going to see or not. See first, think later, then test. But always see first. Otherwise you will only see what you were expecting. Most scientist forget that."

So long, and Thanks for All the Fish, Douglas Adams

Acknowledgements

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Summary

The methodology of the addition reactions of a wide range of alkyl- and arylmethylphosphonates to α,β-unsaturated ketones was studied. Reaction conditions were optimised and the conditions determining the nature of the addition, 1,2- vs 1,4-addition, were investigated. This was done in order to ascertain the specific conditions needed to determine the regioselectivity of these reactions.

The 1-hydroxy-alkyl- and 1-hydroxy-arylmethylphosphonates that were obtained, via 1,2-addition, were used as substrates for further transformation reactions. The aromatisation of the hydroxyphosphonates was investigated. Three possible methods were implemented and the feasibility of these reactions in synthetic procedures was studied. The hydroxyphosphonates were transformed to their olefinic counterparts via dehydration under acidic conditions. These dehydration reactions were performed under kinetic as well as thermodynamic conditions and the relative stability of the different isomers was thus determined.

The addition reaction of trimethylsilyl-stabilised carbanions to α,β-unsaturated ketones and saturated ketones was studied in an attempt to implement the Peterson olefination reaction sequence for the preparation of olefins.

In the last chapter the synthetic procedures for the preparation of some substrates, needed during this study are discussed.

Opsomming

Die metodologie van die addisie reaksies van 'n wye reeks alkiel- sowel as arielmetielfosfonate tot α,β-onversadigde ketone was bestudeer. Die reaksie kondisies is verfyn en die spesifieke kondisies vir die verkryging van 1,2- of 1,4-addisie is ondersoek. Hierdie ondersoek is geloods na gelang die spesifieke kondisies daar te stel vir die verkryging van regioselektiwiteit in hierdie addisie reaksies.

Die 1-hidroksie alkiel- and 1-hidroksie arielmetielfosfonate wat verkry was, deur 1,2-addisie, was as substrate gebruik vir die verdere transformasies. Die aromatisering van hierdie hidroksiefosfonate is ondersoek. Drie moontlike prosedures vir hierdie omskakeling is van nader bestudeer ten einde elkeen se toepaslikheid in organiese sintese roetes te bepaal. Die hidroksiefosfonate was na hul onversadigde vorms omgeskakel deur middel van dehidrasie onder suurkondisies. Hierdie reaksies is uitgevoer onder kineties sowel as termodinamiese toestande en sodoende kon die relatiewe stabiliteit van die verskillende isomere bepaal word.

Die addisie reaksie van trimetielsiliel gestabiliseerde anione tot beide α,β-onversadigde sowel as versadigde karboniel verbindings was ondersoek. Hierdie ondersoek was uitgevoer met die oog om die Peterson se olefinasie reaksie te gebruik vir die bereiding van olefienise verbindings.

In die laaste hoofstuk word die verskillende bereidingsmetodes vir sekere substrate, wat gebruik was in hierdie projek bespreek.

List of Abbreviations

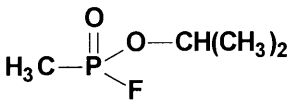
°C	Degrees Celsius
2D	Two dimensional
Aq.	Aqueous
b.p.	Boiling point
CIP	Contact Ion Pairs
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
equiv.	Equivalance
eV	Electron volt
HETCOR	Heteronuclear Shift Correlation
HMPA	Hexamethylphosphoramide
HOMO	Highest Occupied Molecular Orbital
IR	Infra Red
kcals	Kilo Calories
KDA	Potassium diisopropyl amide
KHMDS	Potassium 1,1,1,3,3,3-hexamethyldililazane
LAH	Lithium Aluminium hydride
LDA	Lithium diisopropyl amide
LHMDS	Lithium 1,1,1,3,3,3-hexamethyldililazane
LUMO	Lowest Unoccupied Molecular Orbital
m.p.	Melting Point
MD	Molecular Dynamics
Me	Methyl
mol	Mole
MS	Mass Spectra
n-BuLi	n-Butyllithium
NBS	N-Bromosuccinimide
NMR	Nuclear Magnetic Resonance

NOE	Nuclear Overhauser Effect
Nu	Nucleophile
Ph	Phenyl
ppm	Parts per million
SSIP	Solvent Separated Ion Pair
t-BuLi	tert-Butyllithium
THF	Tetrahydrofuran
TMEDA	N,N,N',N'-Tetramethylethylenediamine
TMSCl	Trimethylchorosilane
TsOH	4-Toluenesulfonic acid
TTFA	Trityl trifluoroacetate

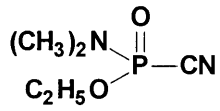
Introduction

1.1 Historic overview

Phosphorus was discovered by Hennig Brand in 1669 when he isolated this product by distilling urine and decomposed its component, $Na(NH_4)HPO_4$. The substance that he obtained glowed in the dark and burst into flames when exposed to air. It was subsequently named "Phosphorus", meaning light bearing. Lethicin was most probably the first organic phosphorus compound to be isolated from brain fat by Vauquelin in 1811, and identified as a phosphorus-containing lipid by Gobly in 1850. The earliest laboratory synthesis of an organic phosphorus compound was reported by Lassaigne in 1820 when he obtained crude alkyl phosphates by reacting alcohols with phosphoric acid. Shrader and Saunders independently discovered the toxic properties of certain phosphate esters on the eve of World War II. This led to the intensive investigation in the chemistry of phosphorus containing organic products as potential insecticides and nerve gases. Of these Sarin (Isopropyl methylphosphonofluoridate) (**1**), Tabun (N,N-dimethylphosphoramisocyanidate) (**2**), Parathion (Diethyl-p-nitrophenyl monothiophosphate) (**3**)[1] as chemical warfare agents and TEPP (tetra-ethyl pyrophosphate) (**4**)[2] as insecticide are well known.



(1)



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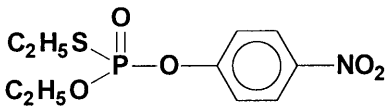
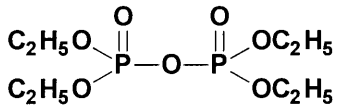


(3)



(4)

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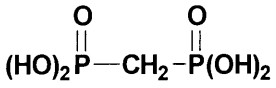
1 J Emsley and D Hall, "*The Chemistry of Phosphorus*", Harper and Row, London, 1976.

2 A L Green, G L Sainsbury, B Saville and M Stansfield, *J. Chem. Soc.*,1958, 1583.

By 1940 it had been clearly established that phosphate esters are the normal constituents in all cells and it is now accepted that they are essential for hereditary processes, growth, development and maintenance of all plants and animals.[3]

The realisation that analogues of naturally occurring phosphates possessed intriguing possibilities for metabolic regulation and perturbation *i.e.* the analogues might be capable of specific or non-specific inhibition of one or more enzymatic process has fuelled the interest in this field of research.[4] Ideally an analogue will contain but one structural variation from the parent substance *e.g.* the presence of a P-C instead of a P-O linkage. Phosphorus carbon bonds are very suitable since they are not easily hydrolysed by enzymes. Examples of analogues are given below.



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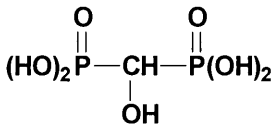

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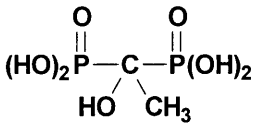

7

Methylenediphosphonic acid (**5**) and hydroxymethylenediphosphonic acid (**6**) have both been found to be of use in the complexation of calcium ions and thereby in the prevention of calcium deposition in living tissue.[5,6] 1-Hydroxyethyl-1,1-diphosphonic acid (**7**) has been investigated extensively for regulation of calcium deposition and transport. The study on the use of these compounds in the treatment of bone disorders is of utmost importance.

Another example of a phosphoric acid that has invaluable medical use is phosphonomycin (**8**).[7] It has been shown to be an effective antibiotic which is bactericidal and inhibits cell-wall synthesis.

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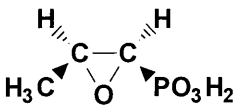
3 D E C Corbridge, "*Phosphorus An outline of its Chemistry, Biochemistry and Technology*" (Fourth Edition), Elsevier, New York , 1990.

4 R Engel, *Chem. Rev.*, **77**, 1977, 349.

5 H Fleisch, R C G Russell and M D Francis, *Science*, **165**, 1969, 1262.

6 M D Francis, R C G Russell and H Fleisch, *Science*, **165**, 1969, 1264.

7 B G Christensen, W J Leanza, T R Beattie and A A Patchett, *Science*, **166**, 1969, 122.



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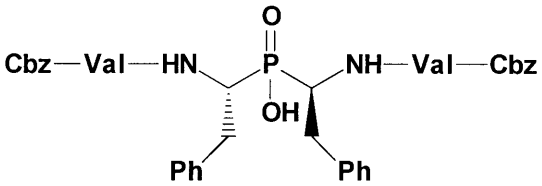
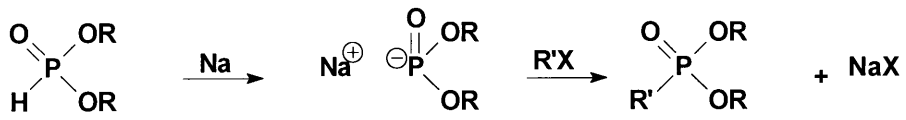


9

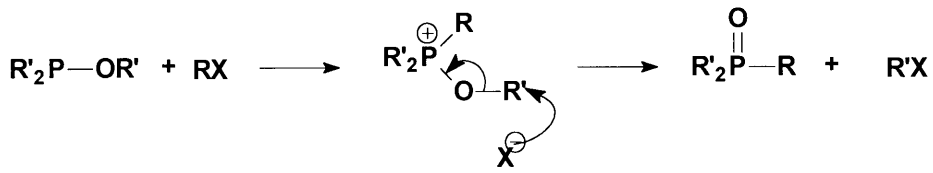
Recently it was shown[8] that phosphinic acid isoteres of hexapeptides (**9**) are powerful inhibitors of HIV protease. This continual interest in phosphorus has led to widespread investigation in the reactions of molecules containing phosphorus.

1.2 Preparation of phosphonates

The Michaelis-Arbuzov reaction, originally discovered by Michaelis in 1898[9] and extensively explored by Arbuzov, is one of the most versatile methods for the formation of carbon-phosphorus bonds. The former involves the reaction of alkali metal derivatives of dialkyl phosphites with alkyl halides, while the Arbuzov reaction involves the treatment of trialkyl phosphites with alkyl halides as shown in Scheme **1**.[10] During the reaction, trivalent phosphorus is converted into a pentavalent phosphorus.



Michaelis reaction



R' = OR, NR_2, SR, alkyl, aryl **X = Cl, Br, I**

Arbuzov reaction

Scheme 1

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8 A Peyman, K Budt, J Spanig, B Stowasser and D Ruppert, *Tetrahedron Lett.*, **33**, 1992, 4549.
9 A K Bhattacharya and G Thyagarajan, *Chem. Rev.*, **81**, 1981, 415.
10 J Boutagy and R Thomas, *Chem. Rev.*, **74**, 1974, 87.

Three probable factors responsible for the wide application of phosphorus derivatives[11] in organic synthesis are:

(i) trivalent phosphorus is highly nucleophilic towards a broad spectrum of electrophiles,
(ii) phosphorus forms strong bonds with oxygen, sulphur, nitrogen, halogens and carbon,
(iii) phosphorus is able to stabilise a negative charge on an adjacent atom.

1.3 Wittig reaction

The olefination of ketones and aldehydes proved troublesome prior to 1950, because chemists had to contend with two isomer problems, that of double bond position and of double bond geometry. Wittig and co-workers then introduced a means for the preparation of alkenes in which positional selectivity, stereoselectivity and chemoselectivity could be obtained depending on the type of ylide, type of carbonyl compound and reaction conditions used.[12] For example, non-stabilised phosphorus ylides (*e.g.* with alkyl groups) react with aldehydes to give mainly *Z* alkenes, except under special conditions. Stabilised ylides with strongly conjugated substituents (*e.g.* COOMe or CN) yield *E* alkenes and semi-stabilised ylides with mild conjugated groups (*e.g.* Ph or allyl) generally give a mixture of *Z*/*E* alkenes.[13]

Pattenden[14] showed the suitability of the Wittig reaction for the unambiguous synthesis of *cis*-polyenes, in particular those with trisubstituted double bonds, since these compounds are not accessible via acetylenic routes. Even though the Wittig reaction has been investigated extensively no general mechanism has been finalised. The most detailed mechanism, Scheme **2**, was proposed by Maryanoff *et. al.*[12] and includes betaines (**10**), oxaphosphetanes (**11**) and zwitterions (**12**) as potential intermediates in the reaction.

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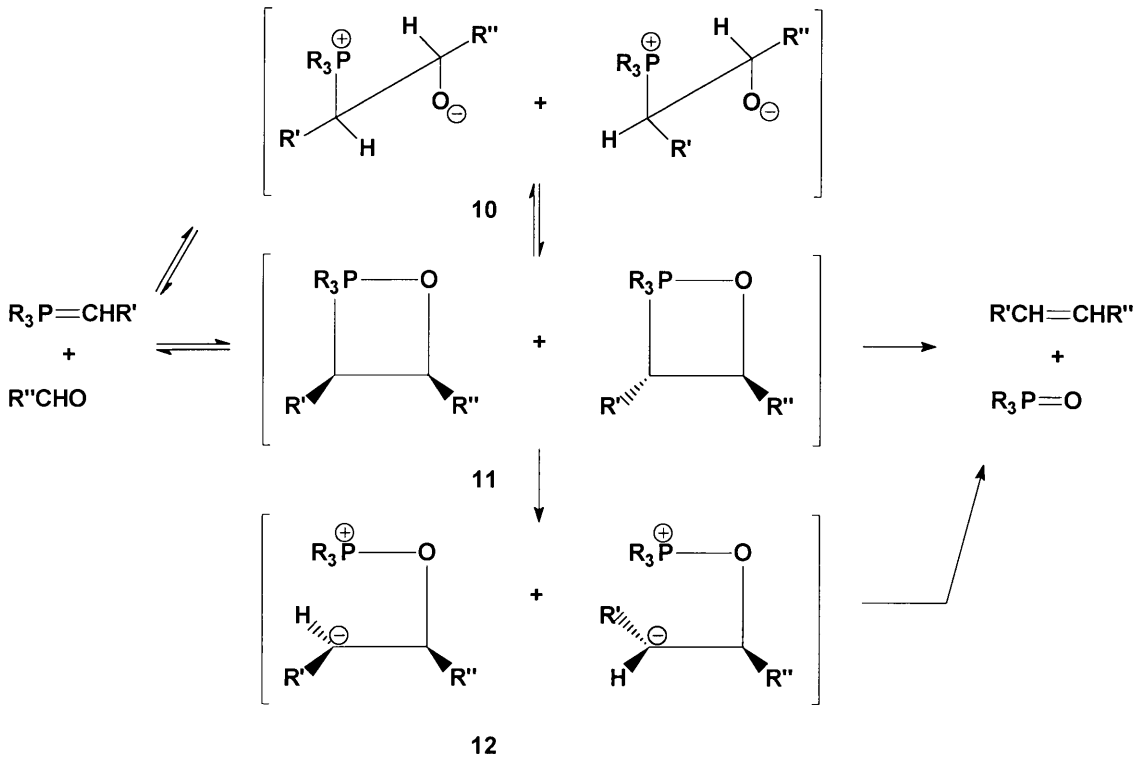
11 J I G Cadogan, "*Introduction: Types of Organophosphorus reagents and their Key reactions*" in "*Organophosphorus reagents in Organic Synthesis*", Academic Press, London, 1979.
12 B E Maryanoff and A B Reitz, *Chem. Rev.*, **89**, 1989, 863.
13 B E Maryanoff, A B Reitz, M S Mutter, R R Inners, H R Almond Jr., R R Whittle and R A Olofson, *J. Am. Chem. Soc.*, **108**, 1986, 7664.
14 G Pattenden and B C L Weeden, *J. Chem. Soc., Chem. Commun.*, 1984, 1968.



Scheme 2

There are, however, several limitations to the Wittig olefin synthesis. In some cases the phosphorane derivatives fail to react[15] and although the stereochemistry of the Wittig reaction can be influenced by the nature of the reactants and reaction conditions,[16] mixtures are often obtained *e.g.* in the preparation of 1,4-diarylbuta-1,3-dienes from *E*-cinnamaldehydes the Wittig reaction yielded a mixture of both possible isomers.[17] This led to the development of several modifications of this reaction.

1.4 Wittig-Horner, Horner-Emmons reaction

These reactions involve the use of organophosphorus compounds which lend themselves to the formation of carbanions. Phosphonates have been reported to invariably have a great preference

15 S V Ley and P R Woodward, *Tetrahedron Lett.*, **28**, 1987, 345.
16 L D Bergelson and M M Shemyakin, *Tetrahedron*, **19**, 1963, 149.
17 R Brettle, D A Dunmur, N J Hindley and C M Marson, *J. Chem. Soc. Perkin Trans. 1*, 1993, 775.

for the formation of *trans* olefins.[18,19] This modification gives rise to the following advantages over the conventional Wittig reaction:

(i) Phosphonate carbanions are much less expensive and more nucleophilic than the corresponding phosphonium ylides. They therefore react with a wider range of aldehydes and ketones under milder conditions.

(ii) The phosphate ion formed from the phosphonates is water soluble and allows much easier separation of the olefin from the reaction mixture.

(iii) The increased reactivity of the phosphonate carbanion, due to its higher nucleophilicity, allows easy alkylation, whereas phosphonium ylides normally do not undergo smooth alkylation. This increased nucleophilicity is attributed to the decreased stabilisation of the negative charge by the valence shell expansion of the phosphorus atom in the phosphonate.

(iv) Phosphonates can be readily prepared via the Michaelis-Arbuzov reaction.

(v) Phosphonates are easier to work with *i.e.* they are less sensitive to atmospheric oxygen and to the nature of the base that is used.[10,20]

There are however large differences in the reactions of stabilised and non-stabilised phosphonates.

1.4.1 Stabilised phosphonates

The first step in the reaction involves the deprotonation of the phosphonate. Phosphonates (**13**) in which the carbanion is stabilised by resonance stabilisation successfully yields olefins as shown in Scheme **3**.

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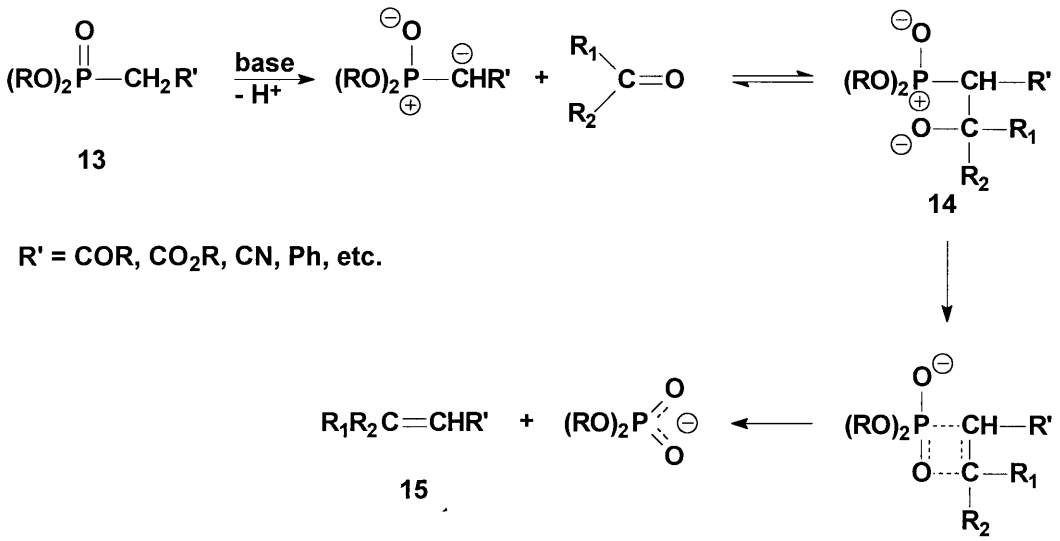
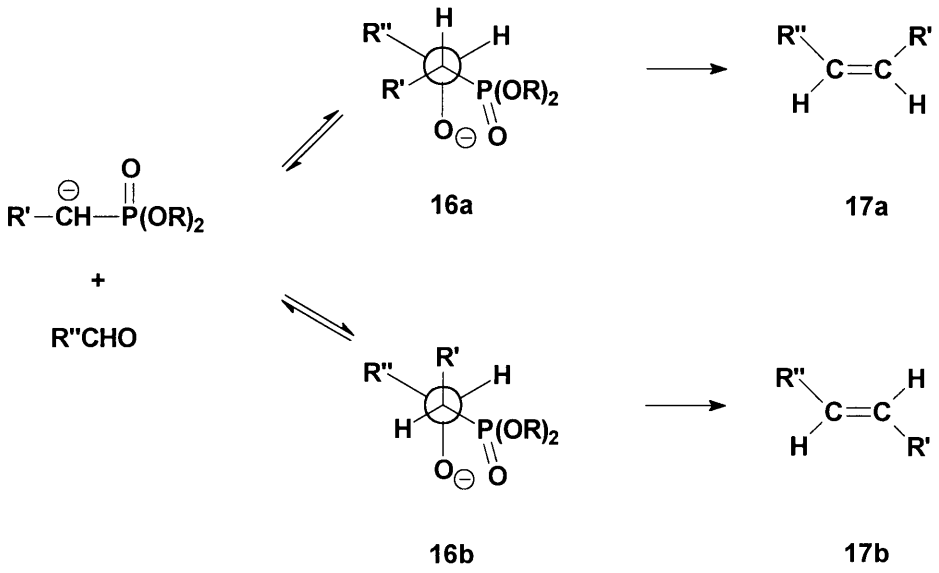
18 L Horner, H Hoffmann, H Whippel and G Klabre, *Chem. Ber.*, **92**, 1959, 2499.
19 D H Wadsworth, O E Shupp, E J Seus and J A Ford, *J. Org. Chem.*, **30**, 1965, 680.
20 W S Wadsworth, Jr. and W D Emmons, *J. Am. Chem. Soc.*, **83**, 1961, 1733.



Scheme 3

The carbanion reacts with the carbonyl compound in a reversible step to form an intermediate oxyanion (betaine) (**14**). The betaine (**14**) then decomposes irreversibly by oxygen transfer to the phosphorus atom to yield the olefin (**15**).[10] The observed stereochemistry of the reactions between stabilised phosphonate carbanions and carbonyl compounds appears to follow the same course as that of the conventional Wittig reaction.

The reaction is also governed at the intermediate level by steric effects. The intermediate oxyanions, formed reversibly, can exist as two diastereoisomers, where the erythro betaine (**16a**) is the precursor for the *cis* olefin (**17a**) via a *cis* elimination, and similarly the threo betaine (**16b**) leads to the *trans* product (**17b**) as shown in Scheme **4**.



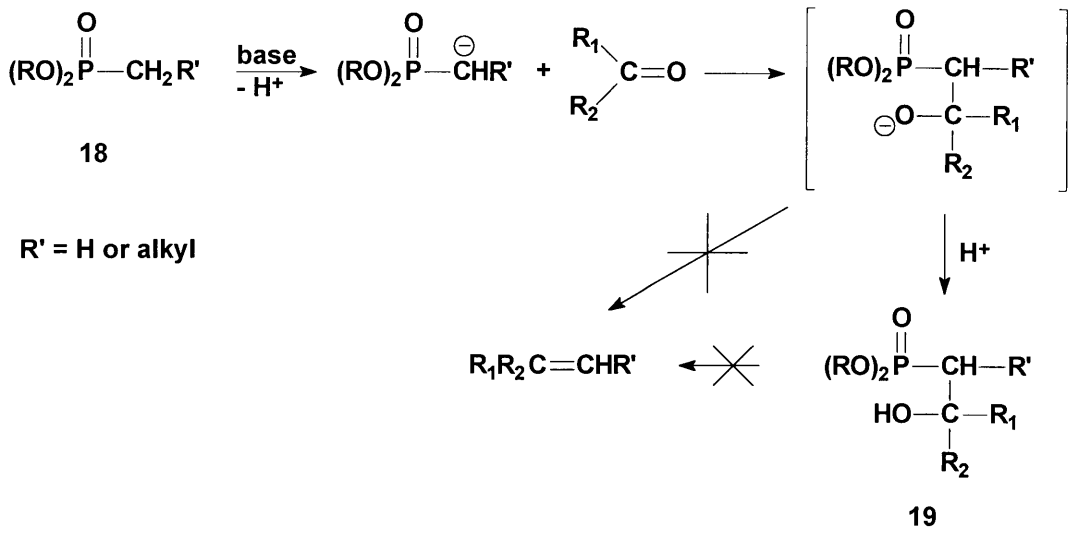
Scheme 4

It has been found that the stereochemistry of the reaction generally favours the *trans* olefin. We can therefore assume that the threo betaine (**16b**) decomposes more rapidly than that of the erythro betaine (**16a**). This would be expected on steric grounds since the erythro betaine is more sterically hindered in the eclipsed conformation and will therefore be formed at a slower rate than the threo betaine. Similarly the threo betaine (**16b**) will decompose faster to the *trans* olefin, because due to less steric hindrance there would be better conjugative stabilisation of the incipient double bond in the transition state. Still *et. al.*[21] have however shown that it is possible to synthesise the more unstable *cis* olefins under specific reaction conditions.

1.4.2 Non-stabilised phosphonates

Phosphonates (**18**) can form non-stabilised carbanions on treatment with base, but in the reaction of these carbanions with aldehydes and ketones the conjugate acid (**19**) of the betaine intermediate is formed instead and can be isolated in high yield (Scheme **5**).

[21] W C Still and C Gennari, *Tetrahedron Lett.*, **24**, 1983, 4405.

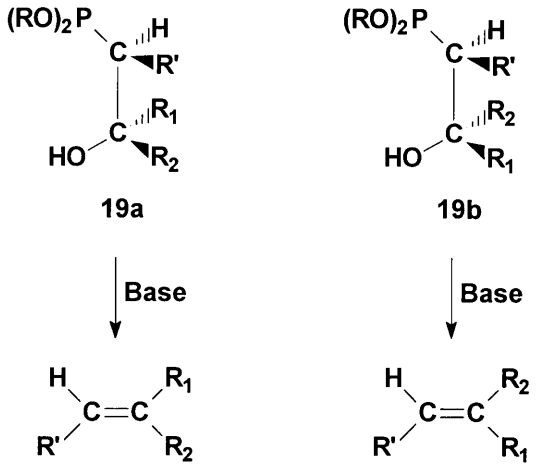


Scheme 5

This change in mechanism of the reaction of non-stabilised phosphonates indicates that considerable negative charge accumulates on the carbon α to the phosphorus atom in the transition state, making Wittig elimination unfavourable.[10] Only under very severe conditions will β-hydroxyalkylphosphonates, without α-stabilising substituents, form alkenes.[22]

A wide range of bases can be used for the deprotonation of non-stabilised phosphonates since the carbanions formed are insensitive to the nature of the cation. The β-hydroxyphosphonate (**19**) can exist in two diastereomeric forms (**19a**) and (**19b**) and each of these decomposes to give a specific olefinic isomer on treatment with base.[19,23,24]

22 E J Corey and G T Kwiatkowski, *J. Am. Chem. Soc.*, **88**, 1966, 5654.
23 L Horner and W Klink, *Tetrahedron Lett.*, 1964, 2467.
24 L Horner and H Winkler, *Tetrahedron Lett.*, 1964, 3265.



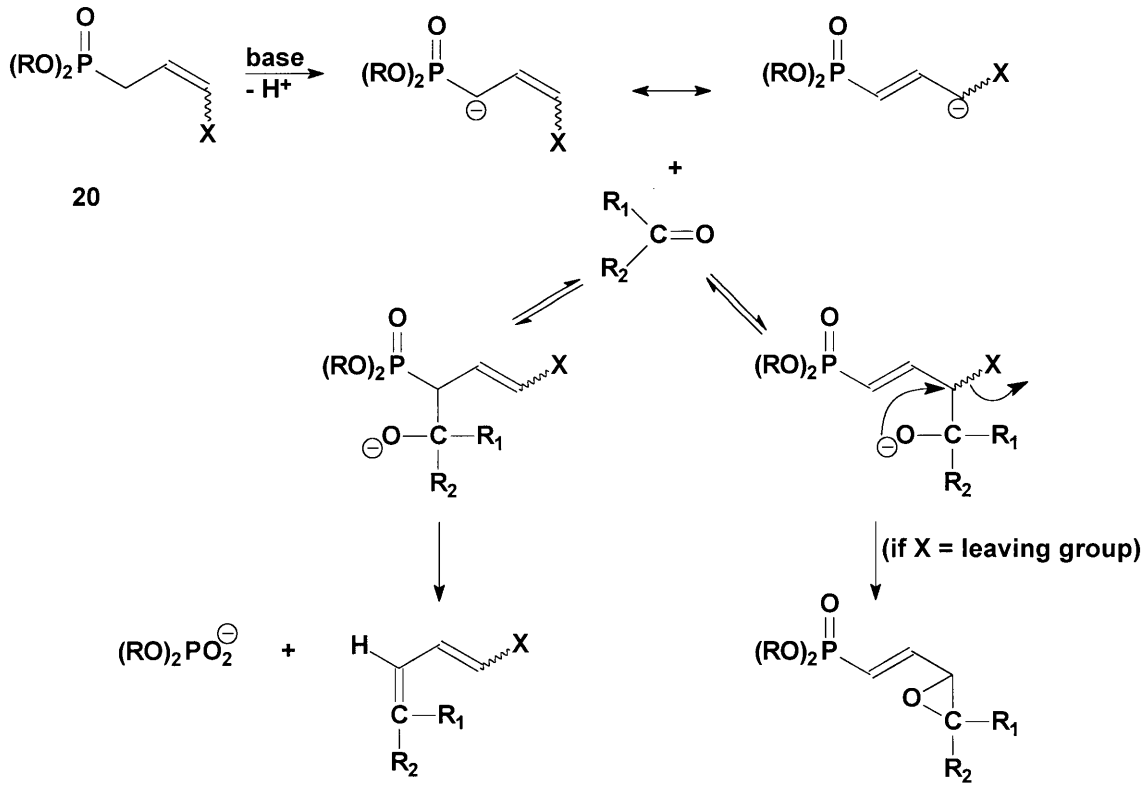
In the absence of α-stabilising groups, the relative steric bulk of the groups R_1 and R_2 and their interaction with R' will often determine the nature of the alkene formed.

The scope and application of the Wittig-Horner reaction has been studied in detail. Trehan *et. al.*[25] reported a modified procedure of the Horner reaction in the synthesis of the highly *cis* selective disubstituted double bonds in *cis*-retinal and 7-*cis*, 9-*cis*, 11-*cis*-retinal. Mead and coworkers[26] reported the successful synthesis of 9-*cis* and 11-*cis* isomers of three trifluoromethylated retinals. The Wadsworth-Emmons reaction is also used to produce streptogram antibiotics.[27] Endless more examples of the application of this reaction in synthetic organic chemistry exist.

1.4.3 Allylic phosphonates

The carbanions derived from allylic phosphonates (**20**) react with carbonyl compounds (Scheme **6**) at either the α- or γ- carbons. As the greatest degree of negative charge resides on the α-carbon, attack at this position predominantly takes place.

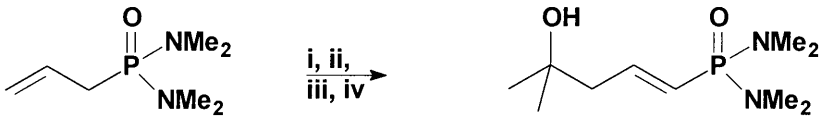
25 A Trehan and R S H Lui, *Tetrahedron Lett.*, **29**, 1988, 419.
26 D Mead, A E Asato, M Denny and R S H Lui, *Tetrahedron Lett.*, **28**, 1987, 259.
27 M Nikaido, R Aslanian, F Scavo, P Helguist, *J. Org. Chem., Chem. Comm.*, **49**, 1984, 4740.



Scheme 6

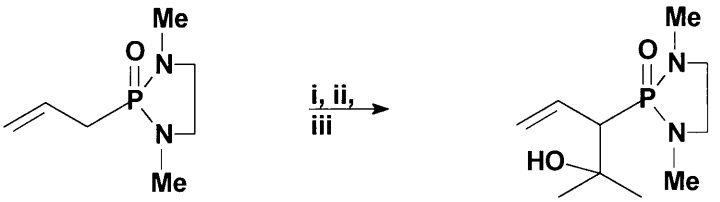
The controlling factor governing the ratio of α- to γ-additions is not clear, but Corey and Cane[28] proposed that these factors are steric in nature. They showed that in the reaction of N,N,N',N'-tetramethylallylphosphonodiamide (**21**) with acetone (Scheme 7) the product of γ-addition (**22**) was exclusively obtained. The course of the reaction could be modified by decreasing the steric bulk of the amide *i.e.* when using N,N'-dimethyl-2-allyl-1,3,2-diazophospholidine 2-oxide (**23**) only the product of α-addition (**24**) was obtained uncontaminated by the γ-addition product.

[28] E J Corey and D E Cane, *J. Org. Chem.*, **34**, 1969,3053.



21 22

i n-BuLi
ii $MgBr_2$
iii Me_2CO
iv H^+



23 24

i n-BuLi
ii Me_2CO
iii H^+

Scheme 7

Davidson *et. al.*[29] confirmed this observation by showing that the course of the reaction could be controlled by the nature of the substituents present on the γ-position of the phosphonate.

Oare *et. al.*[30] also found that the presence of bulky binaphthyl groups on phosphorus made alkylation at C(α) less favoured. Substitution at the β-position of the carbonyl compound, however, retarded the reaction, but had little effect on the selectivity.

29 A H Davidson, C Earnshaw, J I Grayson and S Warren, *J. Chem. Soc. Perkin Trans. 1*, 1977, 1452.

30 D A Oare, M A Henderson, M A Sanner and C H Heathcock, *J. Org. Chem.*, **55**, 1990,157.

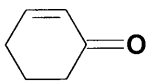
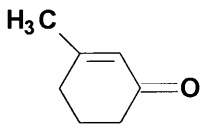
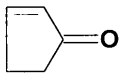
1.5 Addition to α,β-unsaturated ketones

Conjugate additions were first reported by Komnenos in 1883.[31] Conjugate addition refers to the addition of a nucleophile to an unsaturated system in conjugation with an activating group, usually an electron-withdrawing group. Conjugate addition may occur at any site 2n atoms distant from the carbonyl carbon, n = 0, 1, 2.. etc., with n = 1 being by far the most common. This 1,4-addition involving a carbon nucleophile, the so-called Michael addition, is one of the most important carbon-carbon bond formation reactions in synthetic organic transformations.

1.5.1 Regioselectivity of addition reactions

According to quantum chemical calculations,[32] the carbonyl carbon atom carries more charge than the C-3 atom, but the atomic coefficient of the LUMO of the C-3 atom is larger. In Table **1** the LUMO energy levels, carbonyl carbon positive charge q_2 and C_4 coefficient were calculated either by the Hückel method or by an *ab initio* (STO 3 G) one, to take into account the geometric factors for cyclic compounds.

Table 1 Molecular Orbital parameters of cyclic compounds

	Hückel method			***Ab initio* method**		
Ketone	**E_{LUMO} (β units)**	**q_2[a]**	**C_4**	**E_{LUMO} (a.u.)**	**q_2[b]**	**C_4**
	-0.400	+0.43	0.670	0.229	+0.188	0.648
				0.234	+0.187	0.653
	-0.400	+0.43	0.670	0.232	+0.196	0.663

[a] π charge

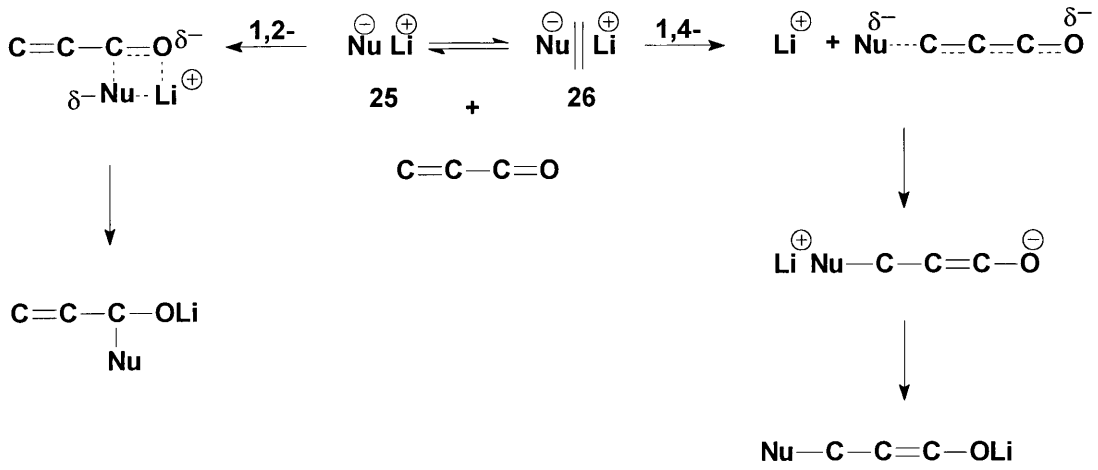
[b] (σ+π) charge

31 P Perlmutter, "*Conjugate Addition Reactions in Organic Synthesis*", Ed J E Baldwin and P D Magnus, Pergamon Press, New York, 1992.

32 M Deschamps and J Seyden-Penne, *Tetrahedron*, **33**, 1977,413.

From the Table it is clear that the carbonyl positive charge, the LUMO energy values and the C4 coefficients are very similar for these cyclic compounds. Therefore, considering only carbonyl carbon q_2 and LUMO characteristics of these enones, the reactivity of these electrophiles towards nucleophilic reagents cannot be predicted. From Klopman-Hudson perturbation theory it follows that addition of nucleophiles to the C=O group is a charge controlled process, whereas conjugate addition is governed by the orbital interaction of the reagents.[33] Thus soft nucleophiles[34] should add to the β-carbon if the additions are under molecular orbital control.[35,36] The course of the reaction is influenced by the electronic and steric effects of the substituents as well as the nucleophilicity of the substrate and the reaction conditions employed.

Cohen introduced a conceptual model to explain and predict the effects the reaction conditions and organolithium structure has on the ratio of 1,2- and 1,4-addition. The key feature of the model (Scheme **6**) is a rapid equilibrium between contact ion pairs (CIP) (**25**) and solvent-separated ion pairs (SSIP) (**26**). (CIP **25**) are assumed to only undergo 1,2-addition whereas (SSIP **26**) only undergo 1,4-addition.



Scheme 6

Conjugate addition is promoted by an increase in the:[31,37, 38, 39, 40, 41, 42, 43, 44, 45, 46]

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33 A N Pudovik, "*Chemistry of Organophosphorus Compounds*", Ed A N Pudovik, MIR Publishers, Moscow, 1989.
34 R G Pearson, *J. Am. Chem. Soc.*, **85**, 1963, 3533.
35 A Loupy and J Seydenne-Penne, *Tetrahedron Lett.*, 1978, 2571.
36 S S Wong, M N Paddon-Row, Y Li and K N Houk, *J. Am. Chem. Soc.*, **112**, 1990, 8679.
37 A Krief, *Tetrahedron*, **36**, 1980, 2531.
38 J Otera, Y Niibo, H Aikawa, *Tetrahedron Lett.*, **28**, 1987, 2147.
39 M Zervos, L Wartski, J Syden-Penne, *Tetrahedron*, **42**, 1986, 4963.

(i) delocalisation of the charge on the nucleophile,

(ii) size (steric hindrance) of the nucleophile,

(iii) solvent polarity *i.e.* addition of HMPA,

(iv) size of the counterions,

(v) temperature of the reaction,

(vi) reaction time.

These conditions, which has been borne out by a study of the addition of sulphur-stabilised carbanions to cycloalkenones,[47] promote the formation of SSIP[48] and would therefore lead to conjugate addition. The most striking prediction of this theory is that low temperatures favour 1,4- over 1,2-addition.

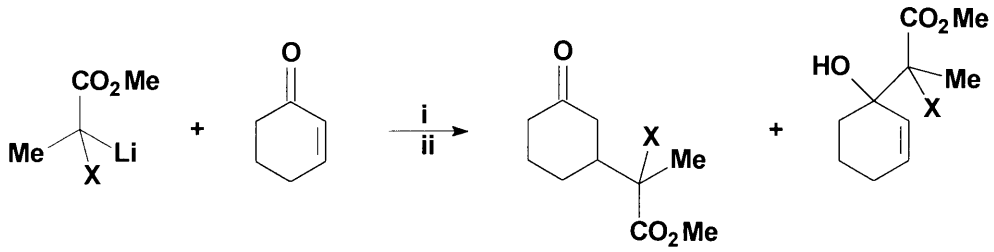
There is ample evidence suggesting that the use of different solvents and counterions can influence regioselectivity.[36] Conjugate addition generally affords more stable products, although 1,2-addition is often faster. Highly resonance stabilised carbanionic nucleophiles tend to favour 1,4-addition. It is believed that carbonyl addition is likely reversible and that the more stable product from conjugate addition will finally predominate under conditions of thermodynamic control.[49,50,51,52] For a highly resonance stabilised carbanion, the frontier orbital interaction is generally more important than electrostatic effects, and thus 1,4- is faster than 1,2-addition. However, Coulombic interactions becomes predominant for localised carbanions, and 1,2-addition is then expected. Although reactions in which conjugate addition is faster than carbonyl

40 D J Ager and M B East, *J. Org. Chem.*, **51**, 1986, 3983.
41 M R Binns, O L Chai, R K Heynes, A A Katsifis, P A Schober and S C Vonwiller, *Tetrahedron Lett.*, **26**, 1985, 1569.
42 S Berrada, P Metzner and R Rakotonirina, *Bull. Soc. Chim. Fr.*, 1984, 881.
43 S K Chung and L B Dunn, *J. Org. Chem.*, **49**, 1984, 935.
44 W Dumont, J Luchetti and A Krief, *J. Chem. Soc., Chem. Commun.*, 1983, 66.
45 M R Binns and R K Haynes, *J. Org. Chem.*, **46**, 1981, 3790.
46 D A Oare and C H Heathcock, *J. Org. Chem.*, **55**, 1990, 157.
47 M R Myers and T Cohen, *J. Org. Chem.*, **54**, 1989, 1290.
48 T M Dolak and T A Bryson, *Tetrahedron Lett.*, 1977, 1961.
49 A G Schultz and Y K Lee, *J. Org. Chem.*, **41**, 1976, 4045.
50 E M Kaiser, P L Knutson and J R McClure, *Tetrahedron Lett.*, 1978, 1747.
51 J Luchetti and A Krief, *Tetrahedron Lett.*, 1978, 2697.
52 G Kyriakakou, M C Roux-Schmitt and J Seyden-Penne, *Tetrahedron*, **31**, 1975, 1883.

addition have been observed in some cases, [32,53] these reactions involve the addition of lithium reagents in solution. It is well-known that lithium reagents are aggregated in solution and that the extent of aggregation depends on the nature of the solvent and the temperature of the reaction.[54,55,56]

1.5.2.1 The effect of temperature

The reversibility of α-hetero-substituted ester (and nitrile) enolates to alkenones has been studied by several groups. Schultz and Lee[49] obtained the following results as shown in Scheme 7, Table 2.



1,4- 1,2-

i THF, 30 min
ii Aq. NH_4Cl

Scheme 7

Table 2 Yields of 1,4- *vs* 1,2-addition at -78°C and room temperature

	-78°C		-78°C to 25°C	
X	**1,4-**	**1,2-**	**1,4-**	**1,2-**
OPh	8	88	84	-
OMe	12	75	62	5
SPh	75	-	86	-
SMe	7	63	85	-
Me	5	88	83	7

53 T Cohen, W D Abraham and M R Myers, *J. Am. Chem. Soc.*, **109**, 1987, 7923.
54 D Seebach, J Gabriel and R Hässig, *Helv. Chim. Acta.*, **67**, 1984, 1083.
55 W Bauer and D Seebach, *Helv. Chim. Acta.*, **67**, 1984, 1972.
56 P Renaud and M A Fox, *J. Am. Chem. Soc.*, **110**, 1988, 5702.

From the Table it is clear that 1,2-addition is favoured at low temperatures. When the reaction mixtures were allowed to warm up to room temperature the yields of 1,4-addition increased. These results clearly prove the reversibility of the addition reactions. Similar results were obtained using α-hetero-substituted acetonitriles.[57] Oare *et. al.*[30] examined the regio- and stereoselectivity in the addition of various enolates to alkenones and observed the following trends:

(i) Increase in the steric bulk in the enolate leads to more conjugate addition,
(ii) *E*-enolates yield more 1,2-addition than do *Z*-enolates,
(iii) Increasing the size of the carbonyl ligand decreases the yield of 1,2-addition,
(iv) Enlarging the size of the β-substituent of the alkenone increases the yield of 1,2-addition,
(v) Softer enolates tend to give more conjugate addition than harder enolates.

Cohen *et. al.*[53] studied the effect of temperature on the regioselectivity of nucleophilic addition of organolithiums stabilised by at least two phenylthio groups to α-enones and came to the conclusion that low temperature favours 1,4- over 1,2-addition. In a further report this dependence on selectivity was confirmed.[47] They also found that less stabilised sulphur-substituted organolithium compounds generally yielded 1,2-addition except when cuprates were used or when HMPA was added.

1.5.2.2 The effect of solvents and variation of the base used

This was illustrated well in the publication of Tanaka *et. al.*[58] where they studied the reaction of (R)-2-crotylphosphonate (**27**) with 2-cyclopentenone to determine the optimal reaction conditions (Scheme **8**).

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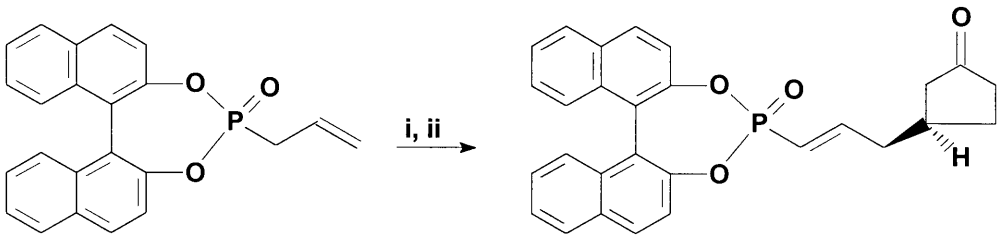
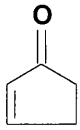
57 N-y Wang, S-s Su and L-y Tsai, *Tetrehedron Lett.*, 1979, 1121.
58 K Tanaka, Y Ohta and K Fuji, *J. Org. Chem.*, **60**, 1995, 8036.



27

i n-BuLi, THF, -78°C

ii 

Scheme 8

The use of different solvents (Table **3**) showed that the inclusion of HMPA and TMEDA (1 equiv.) caused a slight increase in chemical yield but had little effect on selectivity or regiochemistry. DME was found to be an equally effective solvent, but less polar solvents with poorer ligating ability, such as toluene or ether, gave lower yields and diastereoselectivity.

Table 3 Michael addition of the lithiated 27 with 2-cyclopentenone in different solvents

Solvent	Yield	% de
THF	95	91
THF-HMPA	98	92
THF-TMEDA	97	88
DME	93	90
Et_2O	36	58
Toluene	30	70
Toluene-HMPA	40	79

Otera *et. al.*[38] showed that the use of HMPA was crucial for the 1,4-addition reaction of [methoxy(phenylthio)(trimethylsilyl)methyl]lithium to cyclic enones. In an investigation on the addition of [(phenylthio)(trimethylsilyl)methyl]litium to enones Ager *et. al.*[40] found that in both

THF and diethyl ether only 1,2-addition was observed, but in the latter the yields were markedly decreased due to incomplete anion formation. The inclusion of TMEDA only led to a small amount of conjugate addition and 1,2-addition was found to be still the major pathway. By contrast DME led to the 1,4-addition product exclusively. The addition of HMPA in THF promoted conjugate addition in a manner previously observed with other sulphur-containing anions. In a study on the reaction of (*tert*-butylthio)allyl lithium with 2-cyclopentenone Binns *et. al.*[41] observed that HMPA had the same effect on the regioselectivity of the addition reaction.

The reasons for the change in regioselectivity caused by the addition of HMPA are not clear, but a number of possible explanations may be offered.[43] HMPA perhaps makes the addition process reversible due to its cation-solvating ability. It could also be possible that the carbonyl activation by the counterion becomes insignificant in the presence of HMPA, thus making conjugate addition more favourable.[59,60] HMPA could also perturb the HOMO of the nucleophile in some manner favouring conjugate addition.[61] Eliel *et.al.*[62] have observed in their NMR studies that upfield shifts of the phenyl proton and carbon resonances occur when HMPA is added to 2-lithio-2-phenyl-1,3-dithiane complexes. They have suggested that the observed shifts are a result of a contact ion pair in THF *vs* a solvent-separated ion pair in the presence of HMPA.

Other bases than n-BuLi were investigated using THF as solvent and from the results in Table **4** it was clear that lithium was the best counterion with respect to chemical yield and diastereoselectivity.

Table 4 Michael addition of 27 generated with different bases

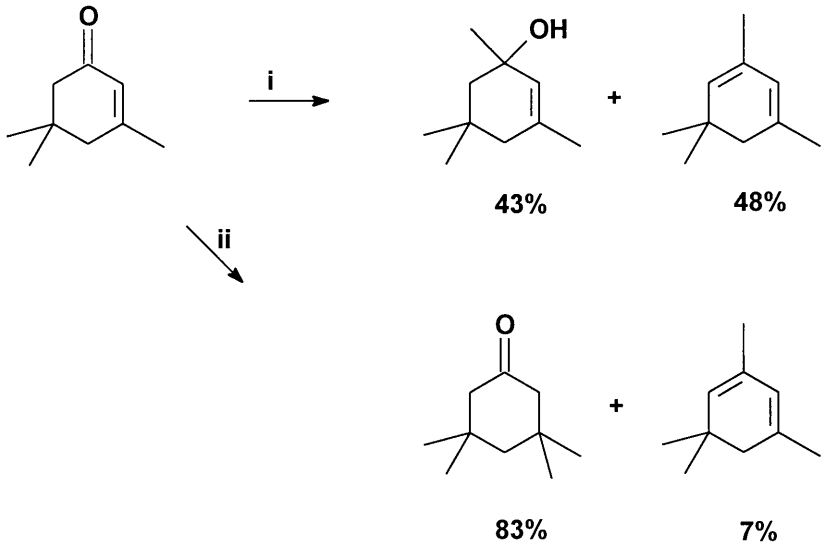
Base	% Yield	% de
LDA	98	91
LHMDS	98	92
$NaCH_2S(O)CH_3$	51	88
KHMDS	67	77
KDA	36	87

59 J M Lefour and A Loupy, *Tetrahedron*, **34**, 1978, 2597.
60 G Kyriadakou, M C Schmitt and J Seyden-Penne, *Tetrahedron*, **31**, 1975, 1883,
61 M El-Bouz and L Wartski, *Tetrahedron Lett.*, **21**, 1980, 2897.
62 A G Abatjoglou, E L Elier and L F Kuyper, *J. Am. Chem. Soc.*, **99**, 1977, 8262.

The counterion of the base can play an important role in the regioselectivity of the addition reaction. The formation of a complex between the metal ion and the carbonyl oxygen of the enone results in an increase of the orbital coefficients at the carbonyl atom compared to the uncomplexed enone. This effect is more pronounced with lithium which leads to 1,2-addition, especially in etheral solvents.[40]

1.5.2.3 The implementation of organocuprates

Reich reported the first organocopper compound in 1923. The first study on the potential of organocopper reagents in synthetic organic chemistry was performed by Henry Gilman's group in 1936.[31] Kharasch's group provided conclusive evidence on the role copper halides play in promoting conjugate addition.[63] They examined the addition of methylmagnesium bromide to isophorone and discovered that, in the absence of any added metal salts, methylmagnesium bromide only gave 1,2-addition products. However, if 1.0 mole per cent of cuprous chloride was added exclusive conjugate addition was obtained in high yield (Scheme **9**).



i CH_3MgBr, Et_2O
ii $CH_3MgBr, CuCl, Et_2O$

Scheme 9

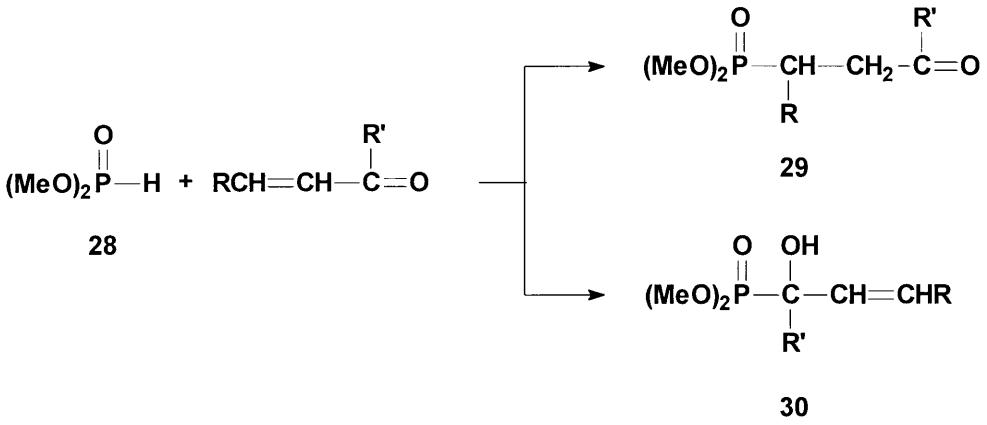
House[64] showed that organocuprates were the reactive species responsible for 1,4-addition to *E*-3-penten-2-one and therefore also the species involved in Kharasch's earlier studies. Much has

63 M S Kharasch and P O Tawney, *J. Am. Chem. Soc.*, **63**, 1941, 2308.
64 H O House, W L Respess and G M Whitesides, *J. Org. Chem.*, **31**, 1966, 3128.

been written on the actual mechanism of organocopper additions but so far attempts to provide concrete evidence have been unsuccessful. House proposed that organocopper reagents add to alkenones via a single electron transfer mechanism.[65,66] He showed that there is a good correlation between the success of many addition reactions and the redox potentials of the reactants, implying that these nucleophiles could act as one-electron reducing agents.

1.5.2.4 The role of phosphites in addition reactions

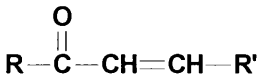
In 1954 A N Pudovik showed that dialkyl phosphites undergo 1,4-addition reactions with α-enones in the presence of alkoxides. Twenty years later B A Arbuzov *et. al.* found that during alkaline catalysis dialkyl phosphites (**28**) can react with α-enones to undergo both 1,4- (**29**) and 1,2-addition reactions (**30**), shown in Scheme **10**.



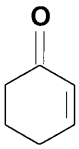
Scheme 10

The reactions of acyclic (**31a-d**) as well as cyclic ketones containing both endo- and exo-cyclic double bonds (**32a-c**) were studied.[33]

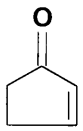
65 H O House, *Acc. Chem. Res.*, **9**, 1976, 59.
66 Y Yamamoto, S Nishii and T Ibuka, *J. Am. Chem. Soc.*, **110**, 1988, 617.



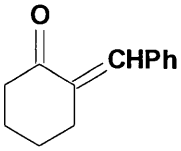
31a R = CH_3, R' = CH_3
31b R = CH_3, R' = Ph
31c R = Ph, R' = Ph
31d R = CH_3, R' =



32a



32b



32c

1.6 The project

Addition to cycloalkenones has, probably, been the most thoroughly studied area in this field in the last twenty years, because with those cyclic conjugate acceptors, often exceptionally high levels of stereoselectivity are possible. Since so many natural products are cyclic, many methods for their synthesis have come to rely on one or more conjugate addition reaction *e.g.* in the area of prostaglandin total synthesis.[31] Attempts to explain and predict the selectivity of the Wittig-Horner reaction has lead to extensive studies in the addition of both stabilised and non-stabilised phosphonates to acyclic enones as well as the stereochemistry of the intermediates formed during these reactions, but cyclic enones and in particular α,β-unsaturated ketones have received very little attention up to this stage.

When commencing this research project, we decided to focus our attention on the addition of localised-, allylic-, and phenyl stabilised phosphonates to cyclic α,β-unsaturated ketones. The reasons for our choice were as follows:

(i) these non-stabilised or weakly stabilised phosphonates carry the potential as reagents for the preparation of conjugated dienes and trienes,

(ii) the hydroxyphosphonates obtained in these reactions carry further synthetic potential, *i.e.* by selective modification of the individual functional groups,

(iii) this as yet unexplored field could lead to a better understanding in the mechanism of these addition reactions,

(iv) the factors governing the regioselectivity of these addition reactions still pose some questions and an investigation into this field could be of great interest,

(v) functionality patterns could be generated that are not accessible or viable via other routes.

Reactions of "localised" alkylphosphonates with cyclic enones

2.1 Introduction

The reaction of phosphorus stabilised carbanions with carbonyl compounds represent one of the most important methods in synthetic organic chemistry.[1] However, in recent reviews very few examples of the addition of phosphorus stabilised carbanions to α,β-unsaturated carbonyl compounds could be found. One such example is where the Wadsworth-Emmons reaction of cinnamaldehydes have been employed to prepare 1-aryl-1,3 dienes.[2]

Literature reports show that the reaction of any nucleophile with α,β-unsaturated ketones can follow two routes *i.e.* 1,2- or 1,4-addition, the regioselectivity depending on the nature of the substrates and the reaction conditions employed.[3,4,5,6,7,8,9,10]

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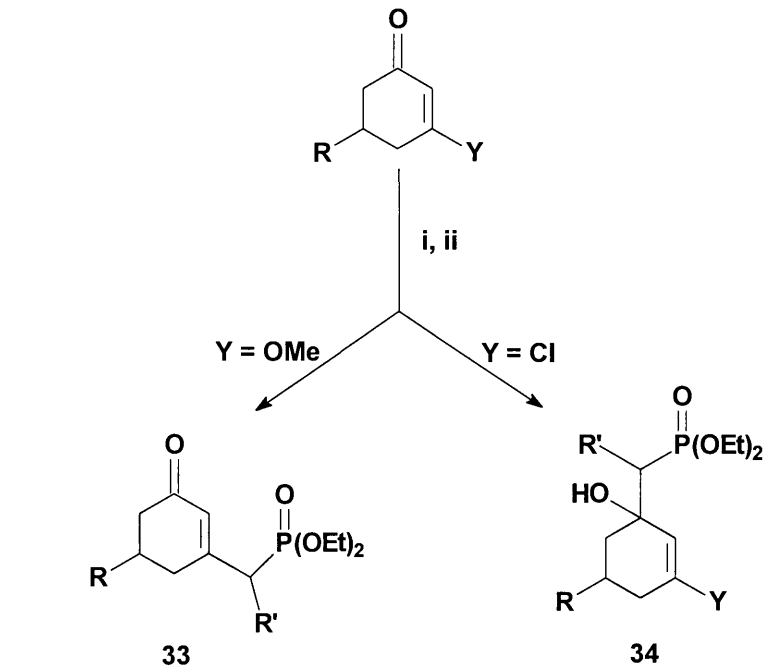
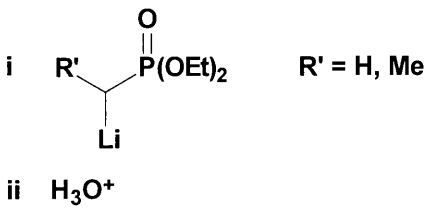
1 J I G Cadogan, *Organophosphorus Reagents in Organic Synthesis*, Academic Press, London, 1979.
2 C Piechuki, *Synthesis*, 1976, 187.
3 W S Wadsworth and W D Emmons, *J. Am. Chem. Soc.*, **83**, 1961, 1733.
4 E D Bergmann and A Solomonovlei, *Tetrahedron*, **27**, 1971, 2675.
5 M Cossentini, B Deschamps, N T Anh and J Seyden-Penne, *Tetrahedron*, **33**, 1977, 409.
6 D H Hua, R Chan-Yu-King, J A McKie and L Myer, *J. Am. Chem. Soc.*, **109**, 1987, 5026.
7 L Duhamel, J Guillemont, Y Le Gallic, G Ple, J M Poirier, Y Ramondec and P Chabardes, *Tetrahedron Lett.*, **31**, 1990, 3129.
8 C Retheford, T S Chou, R M Schelkun and P Knochel, *Tetrahedron Lett.*, **31**, 1990, 1833.
9 E Ohler and E Zbiral, *Synthesis*, 1991,3597.
10 J Zon and E Leja, *Phosphorus, Sulfur Silicon Relat. Elem.*, **71**, 1992, 179.

2.2 Results and Discussion

2.2.1 Nature of the β-substituent

With alkylphosphonates the negative charge is localised and the energy of the HOMO of the nucleophile will therefore be high. The reaction with electrophiles (low energy LUMO) will thus be a charge-controlled process leading mainly to carbonyl addition. However, the nature of the β-substituent on cyclohexenone has been shown to greatly influence the course of the reaction.[8] It was shown in this laboratory in the case of cyclohexenones bearing a β-leaving group that the reaction can occur at the β-carbon (substitution) or at the carbonyl group (addition) depending on the type of β-substituent as depicted in Scheme **11**.[11]



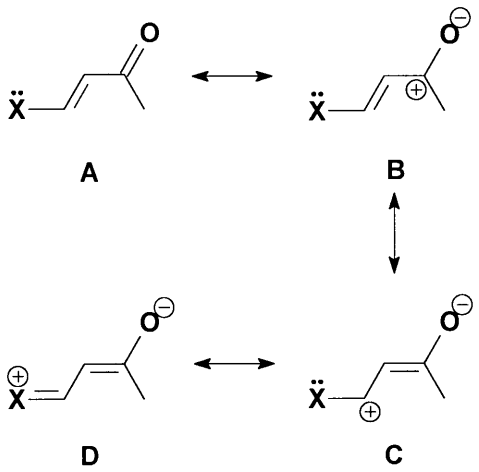


Scheme 11

[11] M J Mphahlele and T A Modro, *J. Org. Chem.*, **60**, 1995, 8236.

Methoxy derivatives reacted with the nucleophiles exclusively at the β-carbon, yielding according to the addition-elimination mechanism, products (**33**). The reaction represents a convenient route to 3-(phosphorylmethyl)cycloalkenones. Retheford *et. al.*[8] showed that the use of 3-iodocyclohexenone can also lead to this addition elimination reaction with suitable nucleophiles.

The reaction with 3-chlorocyclohexenones took a different course and involved the exclusive addition to the carbonyl group. The (2-hydroxyalkyl)phosphonates (**34**), formed during aqueous workup, could be isolated and purified without any signs of decomposition. The rigorous and opposed regioselectivity in the nucleophilic addition of the phosphonate nucleophiles suggest a strong effect of the β-heteroatom on the distribution of the electrophilic reactivity within the α,β-unsaturated system (Scheme **12**).



Scheme 12

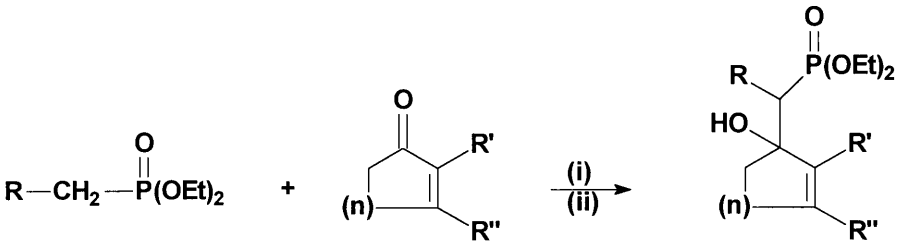
The significant difference in the inductive and resonance components of the electronic effects of the methoxy and chloro substituents (for Cl σ_I = 0.47, and $\sigma_R°$ = -0.21; for OMe σ_I = 0.26 and $\sigma_R°$ = -0.41[12]) should make the contribution of the resonance hybrid **D** much lower for **X** = Cl. The 3-chloro derivatives would therefore display much lower electrophilic reactivity at the β-carbon atom.

12 N S Isaacs, *Physical Organic Chemistry*, Longman Scientific: Burnt Hill, Harlow, 1987, 158.

2.2.2 Reaction conditions

The first step in the Wittig-Horner reaction involves the deprotonation of the alkylphosphonate. In all our experiments n-butyllitium was used, since after deprotonation butane would be formed as side product. Butane is a very weak nucleophile and would therefore not compete with the lithiated phosphonate in the reaction with the α,β-unsaturated ketone. The known affinity of the phosphoryl oxygen for lithium[13] as well as the strength of the carbon-lithium bond should enhance the formation and stability of the lithiated alkylphosphonate derivatives. It was observed in this laboratory[14] that lithium di-isopropylamide (LDA), very frequently used in deprotonation reactions, has a tendency to attack the phosphoryl group to yield the phosphoramide product.

The reaction of lithiated methyl-phosphonic acid diethyl ester (**35a**) and ethyl-phosphonic acid diethyl ester (**35b**) with 2-cyclohexen-1-one (**36a**), 2-methyl-2-cyclohexen-1-one (**36b**), 3-methyl-2-cyclohexen-1-one (**36c**) and 2-methyl-2-cyclopentenone (**36d**) was studied. n-Butyllithium was dissolved in THF and cooled down to -78°C under an inert atmosphere. The phosphonic acid (**35a**) and (**35b**) dissolved in THF was added at -78°C and the reaction mixture was kept at this temperature for 1 hour to ensure that lithiation had been completed. The electrophile was then added at -78°C and the reaction was stirred at this temperature for a further 2 hours before quenching with an aqueous solution of ammonium chloride. In all cases 1,2-addition was exclusively obtained, yielding (2-hydroxyalkyl)phosphonic acid diethyl esters (**37**) upon aqueous workup, as shown in Scheme **13**, Table **5**.



35a, b **36** **37**

(i) nBuLi, -78 °C
(ii) NH_4Cl

n = 1, 2

Scheme 13

[13] E Buncel, E J Dunn, N van Truong R A B Bannard and J G Purdon, *Tetrahedron Lett.*, **31**, 1990, 6513.

[14] H V Garbers and T A Modro, *Heteroatom Chem.*, **1**, 1990, 241.

Table 5 Addition reactions of phosphonic acids (35) with α,β-unsaturated ketones

No.	n	R	R'	R"	% Yield
37a	2	H	H	H	65.5
37b	2	H	H	CH_3	60.6
37c	2	H	CH_3	H	56.0
37d	2	H_3C	H	H	55.7
37e	2	H_3C	H	CH_3	40.6
37f	1	H	CH_3	H	39.1

These tertiary alcohols could be isolated and purified by column chromatography without any sign of decomposition, bearing in mind that at elevated temperatures dehydration would ensue. The course of the reaction could be easily monitored with ^{31}P NMR spectroscopy since the substrate and addition products each have identifiable signals *i.e.* (**35a**) has a phosphorus chemical shift value of 31.02 while the product (**37a**) gave a single peak at δ 30.18.

In the above reactions the substrate could always be observed in the ^{31}P NMR spectra of the crude product. This did not pose much of a problem because this impurity was easily removed with the aid of column chromatography. It was therefore obvious that not one of the above reactions had proceeded to completion under these reaction conditions and that in order to increase the yield of the reaction some modification to this procedure had to be made. A few possible options could have been responsible for this incomplete reaction:

(i) reagents and solvents could contain trace amounts of moisture, causing decomposition of the base and ensuing that lithiation of the nucleophile could not proceed to completion,

(ii) the base used during the lithiation could have decomposed to a certain extent,

(iii) the time allowed for lithiation of the nucleophile could be inadequate and longer reaction times would therefore be needed to ensure complete reaction,

(iv) the 1,2-addition reaction of the nucleophile to the enone could be a reversible process and the ratio in such a case would be rigorously temperature dependant.

A number of experiments were therefore performed in order to isolate the cause for this phenomena that was observed:

(i) Rigorous drying of the THF solvent or distillation of reagents had no effect on the yield of the reaction,

(ii) It was found that an increase in the reaction time from one to two hours had little effect on the yield of the reactions. In the reaction of methyl phosphonic acid diethyl ester with 2-methylcyclohexen-1-one the reaction mixture was allowed to warm up to room temperature and stirred overnight. Only the substrate was isolated after aqueous workup. This shows clearly that the 1,2-addition reaction is reversible and that the rate of the retro-addition is increased by an increase in the reaction temperature.

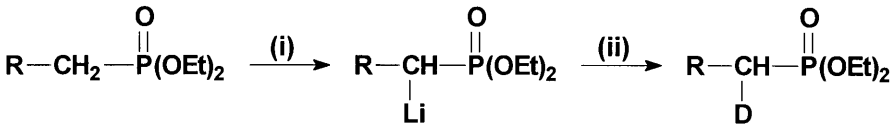
(iii) The amount of base used during these reactions seemed to be of utmost importance. In all the cases studied so far 1.1 molar equivalent of the base was used. It was found that the equilibrium could be pushed over completely, to that of the addition product, by increasing the amount of butyllithium to 2 molar equivalent. With this change the yields of these reactions could be greatly improved *i.e.* with (**37b**) the yield was increased from 40.6% to 60.6%. In the other reactions the increase in yields was less dramatic.

The specific reason for this is not clear at this stage. The first possibility that was considered was that the base had decomposed, but after careful titration this was confirmed not to be the case. The base could also be involved in side reactions, but since no other side products could be isolated this possibility was ruled out. It was found that when Fox *et. al.*[15] studied the reaction of diethyl-methylphosphonate with acetophenones they observed that the yield of the addition reactions could be optimised by using 2 molar equivalents of base for the deprotonation of the nucleophile. Unfortunately no reason was given to explain this trend.

In an attempt to explain this behaviour a number of possible reasons can be put forward. It is known that dianions are much more reactive than their monanionic counterparts.[16] To establish if the dianion was the reactive species involved in the addition reaction it was decided to deprotonate the phosphonate with two mole equivalent of base and quench the reaction with

15 M A Fox, C A Triebel and R Rogers, *Synthetic Commun.*, **12**, 1982, 1055.
16 N S Simpkins, *Sulphones in Organic Synthesis*, Pergaman Press, New York, 1993, 63.

D_2O. From the integration of the ^1H NMR spectra it could be clearly seen that the intensity of the signal of α-CH_2 had decreased by 50% (Scheme **14**) and it was therefore concluded that no dianionic species was formed.



(i) 2 BuLi
(ii) D_2O

Scheme 14

The only other explanation left open is that, since the phosphoryl oxygen has a very high affinity for lithium,[13] that the metal is associated with the phosphoryl group and in doing so preventing the base from approaching the acidic protons α to the phosphorus atom. Thereby 1 mole of the base is rendered unavailable to form the anionic species.

2.2.3 Spectroscopic analysis

Each of the compounds (**37**) was purified and identified by ^1H-, ^{31}P-, ^{13}C- and HETCOR-NMR spectroscopy. IR spectroscopy, MS- and CH analysis were further used to confirm the structures of these compounds. The addition products (**37 a-c, 37f**) contain only one chiral centre, which is situated at the hydroxyl bearing carbon. This will result in two enantiomers and only one signal was observed in the ^{31}P NMR spectrum.

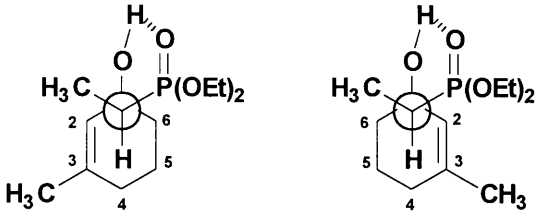
In the case of (**37d**) and (**37e**) two diastereomers were formed since each new compound contains two chiral centres. In the ^{31}P NMR spectra two close signals representing each diastereomer could be observed. Separation of these diastereomers using column chromatography proved troublesome. In both cases we were able to obtain at least one diastereomer pure, but the second fraction from the column always contained trace amounts of the pure diastereomer isolated in the first fraction. The diastereomeric ratio was 2:1 in both cases showing a preference for one isomeric form.

To enable us to assign the relative configuration of each of these diastereomers two assumptions need to be made:

(i) The hydroxyl group is situated close to the phosphoryl substituent due to intramolecular H-bonding. This assumption is valid considering the findings of Belciug *et. al.*[17]

(ii) The H-atom of C_α is situated over the ring system as a result of steric effects.

By employing these assumptions two stereo isomers (**37e**) and (**37e'**) can be drawn as shown below:



37e **37e'**

The torsion angles between C_2, C_6 and the phosphorus atom were used to assign the relative configurations. Literature values[18] for the coupling constants obtained from the Karplus curve give $^3J_{CP} \approx 15$ Hz for $\phi = 180°$ and $^3J_{CP} \approx 5$ Hz for $\phi = 60°$ and these values were used as reference. The $^3J_{CP}$ coupling constants for C_2 were determined for each of these diastereomers (**37e**) and (**37e'**) and were found to be equal to 17.8 Hz and 5.9 Hz respectively. The fact that different coupling constants can be observed not only provides a means for the assignment of the configuration of these diastereomers it also indicates that there is restricted rotation around the C_α-C_1 bond. This restricted rotation is most probably due to the intramolecular H-bonding present between the hydroxyl and phosphoryl group. If free rotation around the C_α-C_1 bond was possible only an average value for the coupling constant would have been obtained. It is therefore clear that when the phosphorus atom is *trans* to C_2 (**37e**) ($\phi = 180°$) a large value for $^3J_{CP}$ was observed. 2D HETCOR experiments were used to determine the C-H correlation since the ^{1}H NMR spectra of each of these compounds were quite complex.

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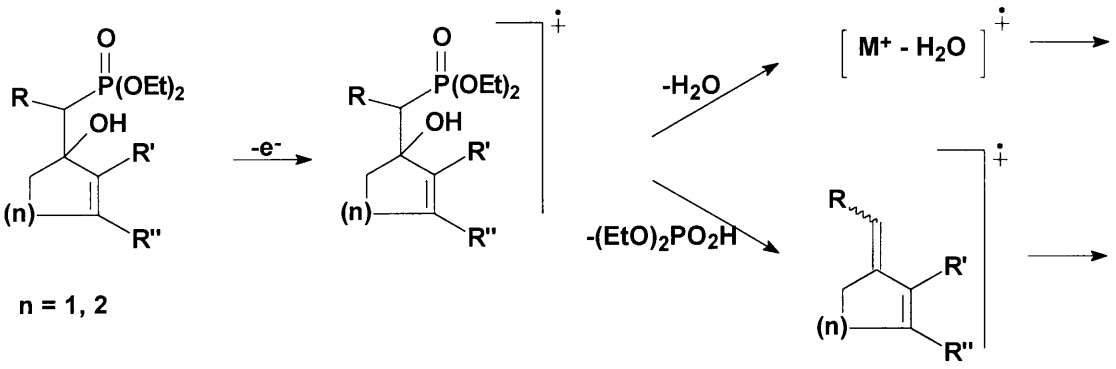
17 M Belciug, A M Modro, T A Modro and P L Wessels, *J. Phys. Org. Chem.*, **5**, 1992, 787.

18 S Berger, S Braun and H Kalinowski, *NMR-Spektroskopie von Nichtmetallen, Band 3 ^{31}P-NMR-Spektroskopie*, Georg Thieme Verlag Stuttgart, New York, 1992, 144.

The IR spectra of (**37a - f**) each gave characteristic signals at ≈ 3400 cm^{-1} for the hydroxyl and ≈ 1200 cm^{-1} for the P=O stretching vibrational frequency.

Considering the MS spectra of these compounds it is noteworthy that it was only possible to observe the M^+ peak in the cases of (**37a**) and (**37c**). The low intensity (≈ 1%) of these signals and the absence of the M^+ peaks for the other compounds clearly indicate that these tertiary alcohols are not thermally very stable. Much stronger signals for (M^+-H_2O) were obtained for all the compounds indicating that the alcohols readily undergo dehydration to form dienes. The elimination of diethyl phosphonate occurred next giving the peak of the expected Wittig product (Scheme **15**) in almost every case. This indicates that this fragment is most stable. In all the fragmentation experiments a signal for PO_3^+ at m/z = 79 could be observed.



Scheme 15

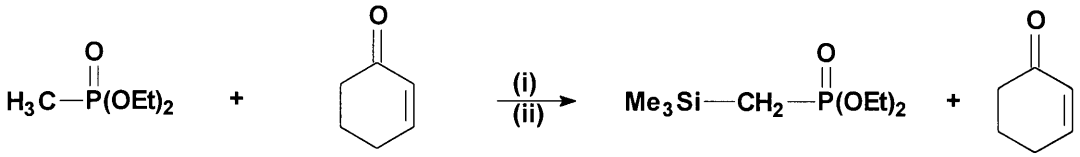
CNH analysis were used to confirm the elemental composition of the compounds.

2.2.4 Regioselectivity

From literature data[19,20,21,22] the use of co-solvents was shown to have a dramatic effect on the regioselectivity of conjugated addition reactions of sulphur containing nucleophiles. The inclusion of the co-solvent HMPA, however, had no effect on the selectivity of the addition

19 M R Binns, O L Chai, R K Heynes, A A Katsifis, P A Schober and S C Vonwiller, *Tetrahedron Lett.*, **26**, 1985, 1569.
20 D J Ager and M B East, *J. Org. Chem.*, **51**, 1986, 3983.
21 J Otera, Y Niibo, H Aikawa, *Tetrahedron Lett.*, **28**, 1987, 2147.
22 K Tanaka, Y Ohta and K Fuji, *J. Org. Chem.*, **60**, 1995, 8036.

reactions of these localised phosphonates and only 1,2-addition was obtained. It was shown[23,24,25,26,27,28] that the use of TMSCl in the reaction mixture greatly enhances the rate of 1,2- as well as 1,4-addition. Trimethylsilanylmethyl-phosphonic acid diethyl ester (**38**) was obtained in the reaction shown in Scheme **16**.



38

(i) nBuLi, -78 ^{0}C, TMEDA, TMSCl
(ii) NH_4Cl

Scheme 16

When the reaction was repeated using TMEDA alone only the alcohol (**37a**) was isolated. No change in the course of the reaction could be obtained at -78°C or by an increase in the reaction temperature to 25°C and keeping it at this temperature overnight in the presence of the co-solvent. Monocuprates were also found to be unsuccessful in forcing 1,4-addition to take place even in the presence of TMEDA.

2.3 Conclusions

It is therefore clear that the addition of "localised" phosphorus stabilised carbanions to α,β-unsaturated ketones is a reversible, and a charge controlled process. Under normal reaction conditions only 1,2-addition would be obtained when no suitable β-leaving group is present on the enone. The most convenient route to obtain conjugate addition to cyclohexenones is by using either iodide or methoxide as substituent in the 3-position of the electrophile in order to change the mechanism of the reaction. From Table **5** it is clear from the yields of the reactions that even when the reaction becomes less favourable, due to the steric hindrance experienced as a result of the methyl group in position 2 of the electrophile, that 1,4-addition still does not occur.

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23 E J Corey, F J Hannon and N W Boaz, *Tetrahedron*, **45**, 1989, 545.
24 Y Horiguchi, S Matsuzawa, E Nakamura and I Kuwajima, *Tetrahedron Lett.*, **27**, 1986, 4025.
25 E J Corey and NW Boaz, *Tetrahedron Lett.*, **26**, 1985, 6015.
26 E Nakamura, S Matsuzawa, Y Horiguchi and I Kuwajima, *Tetrahedron Lett.*, **27**, 1986, 4029.
27 A Alexakis, J Berlan and Y Besace, *Tetrahedron Lett.*, **27**, 1986, 1047.
28 C R Johnson and T J Marren, *Tetrahedron Lett.*, **28**, 1987, 27.

In phosphonate compounds of the type $(EtO)_2P(O)CH_2R$, interaction with the oxygen lone pairs raises the energy of the phosphorus *d* orbitals. These orbitals are therefore no longer good acceptors and cannot stabilise an adjacent negative charge.[5] By replacing the (EtO) functionality with a phenyl group the negative charge should be better delocalised, thus lowering the energy of the HOMO of the nucleophile. This change should lead to conjugate addition more readily since frontier orbitals will play a much larger role in the reaction. A study in the addition reaction of similar phosphorus compounds with only this change in structure should lead to some interesting results.

Reaction of "delocalised" alk-2-enylphosphonates with cyclic enones

3.1 Introduction

The allylcarbanion stabilised by a heteroatom forms an important class of reagents with impressive regioselectivity and can provide access to potential precursors for a wide variety of useful synthetic intermediates. The factors determining the α/γ regioselectivity for the reaction of oxy allylic carbanions with alkyl halides have been well documented.[1,2,3] Carbonyl electrophiles have however received much less attention in the past. It has been demonstrated that alkylation of the carbanion of allyl phosphonic acid diethyl ester (**39**) is highly α-regioselective.[4] Four types of products can be obtained in the reaction of phosphorus stabilised carbanions, derived from allylic phosphonic acids (**39**), with α,β-unsaturated ketones depending on the chemoselectivity of both reagents as shown in Scheme **17**. α-Addition will lead to products (**40a**) and (**40b**) while γ-addition will yield (**40c**) and (**40d**). The reaction is enjoying considerable attention because of its synthetic potential.

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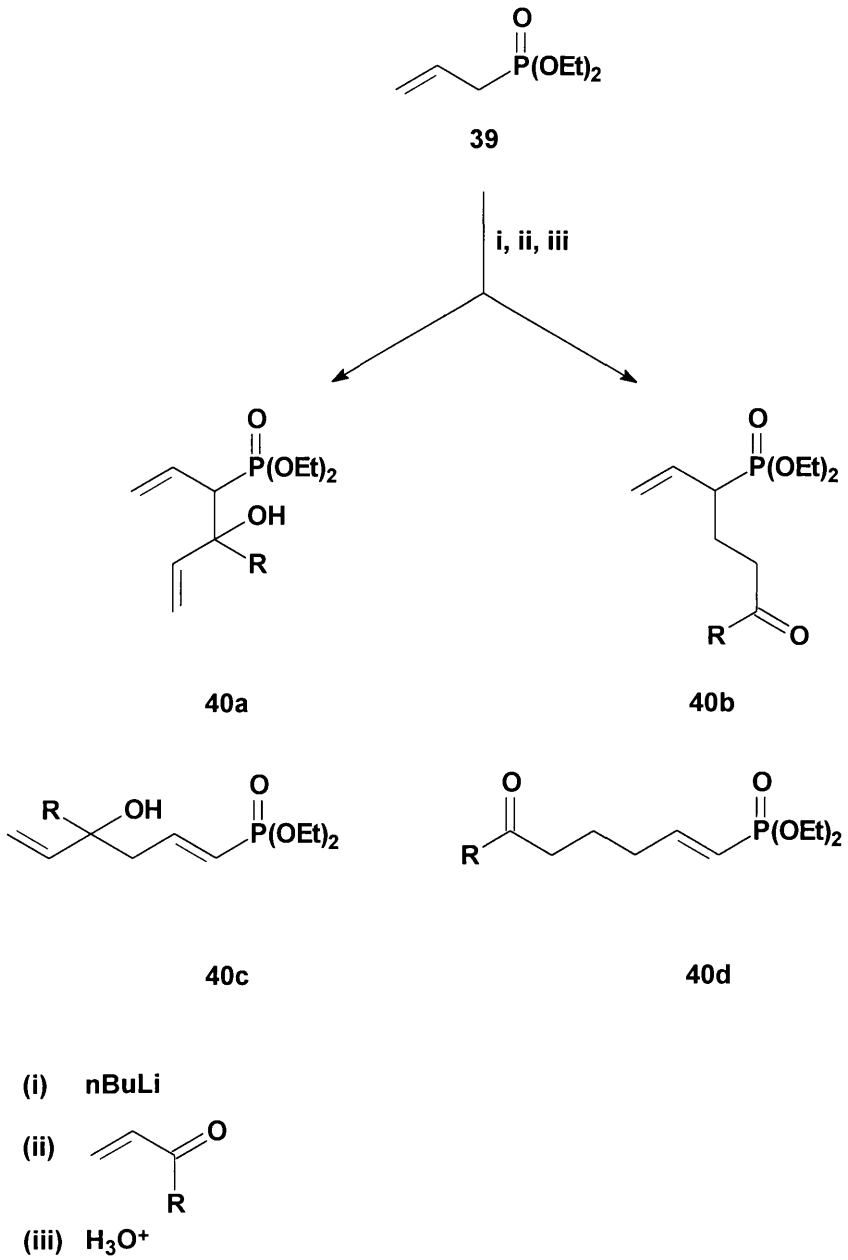
1 S Torii, H Tanaka and Y Tomotaki, *Chem. Lett.*, 1974, 417.
2 D A Evans, G G Andrews and B Buckwalter, *J. Am. Chem. Soc.*, **96**, 1974, 5560.
3 Y Chengye, A Rongyu and Y Jaichang, *Acta Chimica Sinica*, **44**, 1986, 1030.
4 K Kondo, A Negishi and D Tumemoto, *Angew. Chem. Int. Ed. Engl.*, **13**, 1974, 407.



Scheme 17

The reaction of an ambident anion with electrophiles has been shown to be either thermodynamically-[5] or kinetically controlled.[6,7] It is well established that the regioselectivity of a thermodynamically controlled reaction is determined by the energy difference between the two

5 G Lavielle and G Sturtz, *Bull. Soc. Chim. Fr.*, 1970, 1369.
6 R Gompper and H U Wabner, *Angew. Chem. Int. Ed. Engl.*, **15**, 1976, 321.
7 P Atlam, J F Biellmann, S Dube and J J Vicens, *Tetrahedron Lett.*, 1974, 2665.

reaction products. In a kinetically controlled reaction the regioselectivity will however depend on the nucleophilicity of the two reaction centres of the ambident species. Molecular orbital perturbation theory can be used to predict this regioselectivity. The structural parameters of lithiated (**39**) are given, where q_α -0.31843 and q_γ -0.18213 denote the charge density of the carbon atom located on the α- and γ-position from phosphorus and E_{HOMO} -0.21339 is the energy of the highest occupied molecular orbital. These values were obtained using an *ab initio* Gaussian 80 (STO-3G basic set).[8] The higher charge density on the α-position shows that reactions at this site is the result of a charge controlled process while reaction in the γ-position will be orbital controlled.

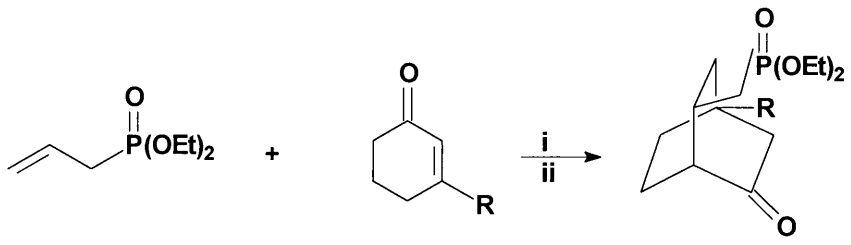
3.2 Results and discussion

3.2.1 Reaction conditions

It was observed that the deprotonation of the allyl-phosphonic acid diethyl ester had to be performed very carefully. The reaction is exothermic and an increase in the temperature during the deprotonation resulted in the isomerisation of the double bond and isolation of vinyl-phosphonic acid diethyl ester. This process was easily followed by ^{31}P NMR spectroscopy since the signal of the vinylic isomer experiences an upfield shift of ≈ 10ppm. The vinylic isomer proved unreactive towards the base and the yields of the addition reaction could be seriously impaired if not enough care was taken. Slow addition rates solved this problem.

In an earlier report[9] it was shown that (**39**) reacts with 2-cyclohexen-1-one (**36a**) and 3-methyl-2-cyclohexen-1-one (**36c**) to form in high yields diethyl (6-oxobicyclo[2.2.2]octan-2-yl)methylphosphonate (**41a**) and diethyl (4-methyl-6-oxobicyclo[2.2.2]octan-2-yl)-methylphosphonate, (**41b**) respectively (Scheme **18**).

8 C Yuan, J Yao and S Li, *Phosphorus, Sulfur and Silicon*, **53**, 1990, 21.
9 AMM Phillips and T A Modro, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1875.



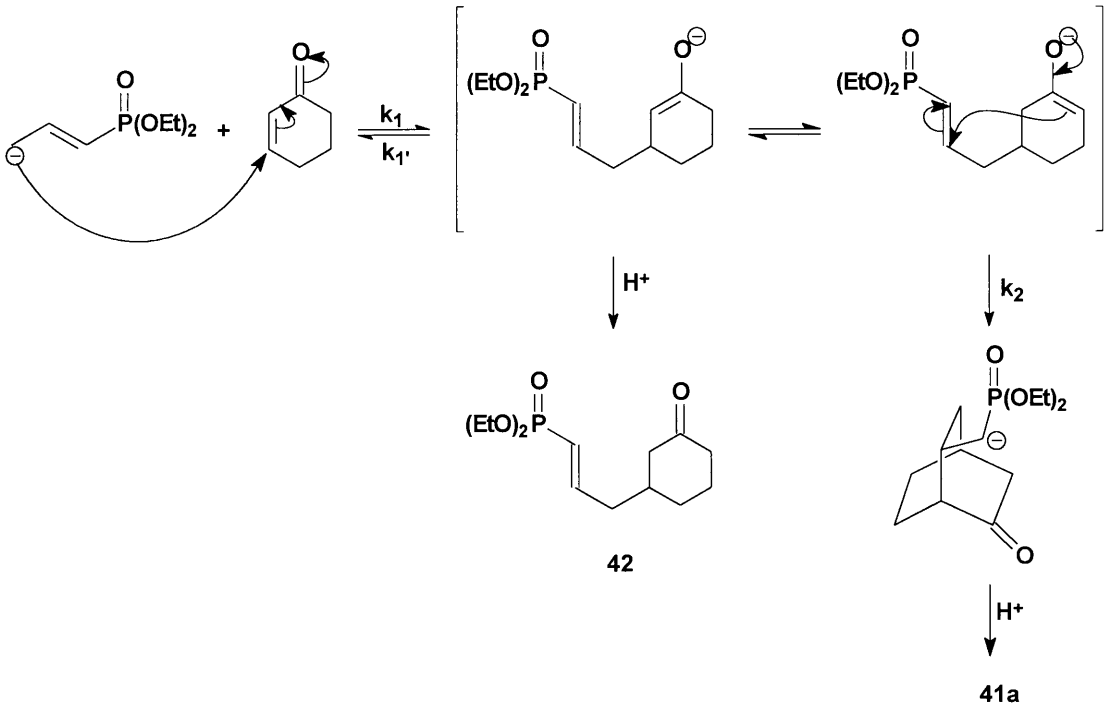
39 **36a, R = H** **41a, R = H**
b, R = Me **b, R = Me**

i **nBuLi**
ii **H_3O^+**

Scheme 18

The nucleophile was lithiated at -78°C and the reaction mixture was stirred at room temperature for 8 hours after the addition of the electrophile. All attempts to repeat the reported yields of the reaction however failed. The addition product (**41a**) could be isolated, but the maximum yield that was obtained was never higher than 15%.

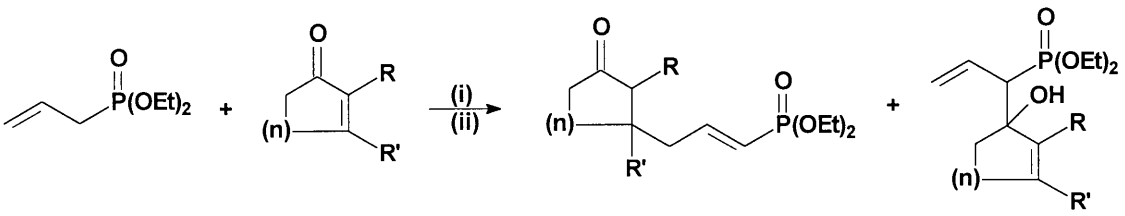
In order to rationalise this low yield we need to consider the mechanism (Scheme **19**) involved more closely.



Scheme 19

1,4-Addition of the nucleophile through the γ-carbon takes place in the first step of the reaction. The first adduct can be isolated at -78°C in the form of (**42**) in high yield by addition of an acid. At room temperature however only (**41**), in very low yield, and the vinylic phosphonate were isolated. This shows that the reaction is reversible. Therefore the rate of addition is faster than the rate of retro-addition at low temperatures implying that $k_1 > k_{1'}$. The rate of the second addition reaction k_2 is unfortunately so small, at -78°C, that no (**41**) could be isolated. When the temperature of the reaction mixture was increased, then all rate constants increased but $k_{1'}$ becomes larger with respect to k_1. The rate constant k_2 leading to the product also becomes larger and a small amount of the intermediate anion was trapped in the second addition reaction. The intermediate was however so short lived that very small yields of the product (**41**) were obtained.

In this project the reaction of lithiated allyl-phosphonic acid diethyl ester (**39**) with α,β-unsaturated ketones (**36 a-d**) was studied in more detail. In the addition reactions of (**39**) it was found that the use of organocuprates was essential in order to obtain reasonable yields. n-Butyllitium was dissolved in THF and cooled down to -78°C under an inert atmosphere. The phosphonate (**39**) dissolved in THF was added very slowly at -78°C and the reaction mixture was kept at this temperature for 1 hour. Copper(I)iodide was added at -78°C and the resulting suspension was stirred for 1 hour. Each of the enones (**36 a-d**) was added at -78°C and the reaction mixture was kept at this temperature for 2 hours before quenching with aqueous ammonium chloride. The results are summarised in Scheme **20** and Table **6**.



39 **36** **42**

(i) nBuLi, CuI
(ii) H_3O^+

Scheme 20

Table 6 Addition reactions of 39 with α,β-unsaturated ketones

No.	n	R	R'	% γ-addition	%α-addition
42a	2	H	H	47.1	0
42b	2	CH_3	H	76.3	0
42c	2	H	CH_3	0	77.5
42d	1	CH_3	H	70.3	0

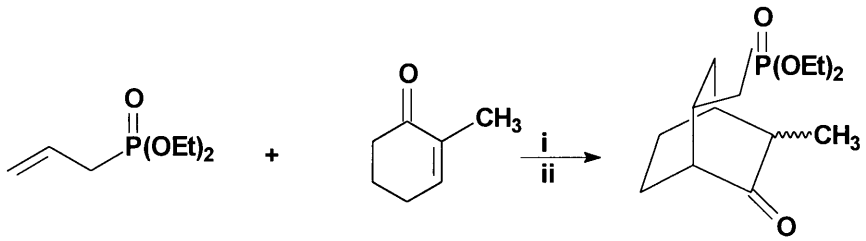
It was found that the reaction of the delocalised carbanion derived from (**39**) with α,β-unsaturated enones was substrate dependant. In the presence of the copper(I) salt conjugate addition to an enone, unsubstituted at β-carbon, occurred exclusively via the γ-carbon atom of the nucleophile. This observation clearly shows that the reaction is fully orbital controlled. The course of the reaction is analogous to that reported for the addition of the optically active allylic phosphonamides,[10] when it was reported that only when the steric bulk of the phosphonamide group was increased could some 1,2-addition be observed. On the other hand, we have found that the substitution of the β-hydrogen in (**42c**) for a methyl group changes the regioselectivity completely with respect to both reagents. The 1,2-adduct by the α-carbon of (**39**) is the exclusive product obtained showing increasing amount of charge control.

Since (**42c**) was the only example where 1,2-addition had taken place it was attempted to force conjugate addition by making use of HMPA as co-solvent. The use of HMPA as co-solvent has been shown to increase the ratio of conjugate addition of sulphur containing nucleophiles.[11,12,13,14] It was found that the inclusion of 2 mole-equivalent of HMPA had no effect on the regioselectivity of the reaction and (**42c**) was the only product that was isolated.

We believed that the reaction of (**39**) and 2-methyl-2-cyclohexen-1-one (**36b, n = 2, R' = H, R = Me**) carries further synthetic potential. The introduction of the methyl group at C_2 was considered advantageous for the stabilisation of the intermediates formed as shown in Scheme **19**. Equilibration of the intermediate to the correct isomeric form to yield the bicyclic product,

10 D H Hua, R Chan-Yu-King, J A McKie and L Myer, *J. Am. Chem. Soc.*, **109**, 1987, 5026.
11 M R Binns, O L Chai, R K Heynes, P A Schober and S C Vonwiller, *Tetrahedron Lett.*, **26**, 1985, 1569.
12 D J Ager and M B East, *J. Org. Chem.*, **51**, 1986, 3983.
13 J Otera, Y Niibo and H Aikawa, *Tetrahedron Lett.*, **28**, 1987, 2147.
14 K Tanaka, Y Ohta and K Fuji, *J. Org. Chem.*, **60**, 1995, 8036.

should now become thermodynamically favourable since the secondary carbon atom C_6 will be able to better stabilise the negative charge than the tertiary carbon C_2. The positive inductive effect experienced from the methyl group will further destabilise one isomer and this should lead to a decrease in the rate of retro-addition at elevated temperatures. The reaction between lithiated (**39**) and (**36b**) was repeated, but this time the reaction mixture was allowed to warm up to room temperature and stirred for 2 hours after addition of the ketone (**36b**). The product, 5-methyl-6-oxo-bicyclo[2.2.2]oct-2-ylmethyl-phosphonic acid diethyl ester (**43**) was obtained with a yield of 70.8% (Scheme **21**).

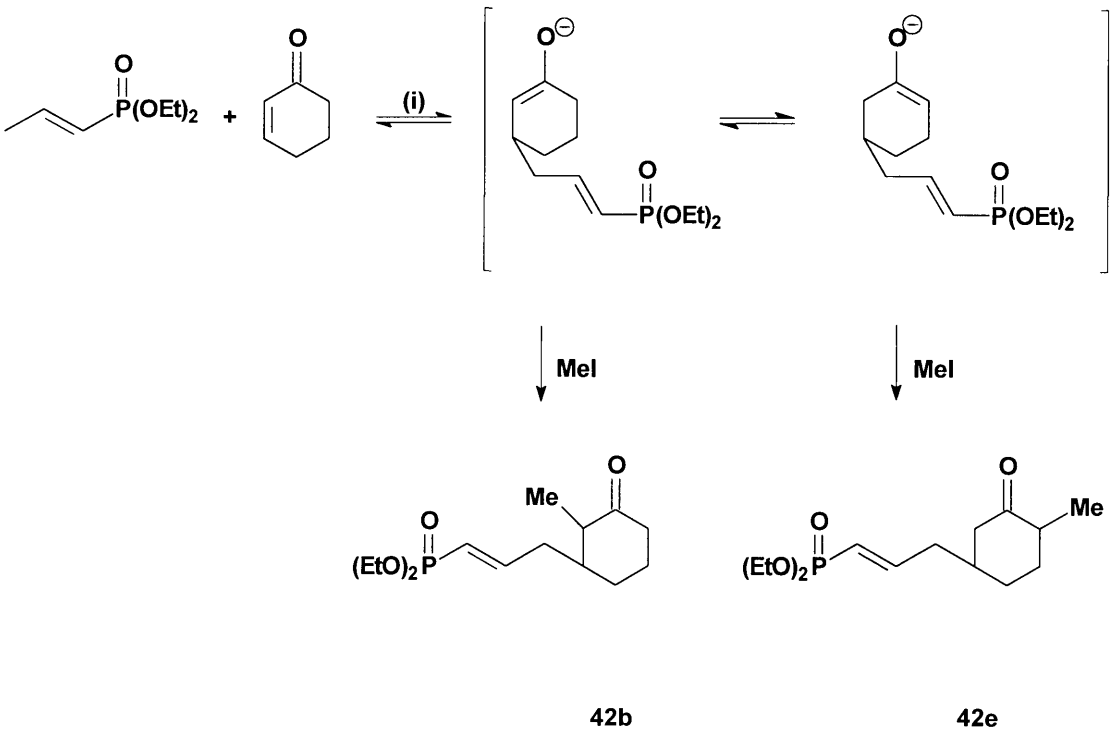


39 **43**

i **nBuLi**
ii **H_3O^+**

Scheme 21

In order to increase the yield of the bicyclic product (**41**), a method had to be devised to stabilise one of the intermediates formed, in an attempt to retard the rate of retro-addition, at elevated temperatures and to promote second cyclisation. Methyl iodide was first employed as an electrophilic reagent expected to trap the first adduct. Two reactions are possible here, as shown in Scheme **22**.



42b **42e**

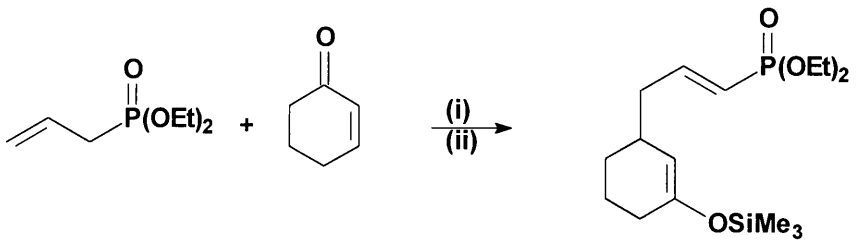
(i) nBuLi, CuI

Scheme 22

Methyl iodide, and later methyl trifluoromethylsulphonate were tested and added to the reaction mixture at -78°C after the carbonyl electrophile was introduced. None of these reagents was able to bring about methylation at C_2 or C_6.

It has been observed that TMSCl (with a polar additive) strongly accelerates the conjugate addition of organocuprates.[15,16,17,18] In this manner it should be possible to trap and isolate the enolate which can then serve as precursor for a variety of other transformations. The trapping of the enolate will also serve to eliminate retro-addition. The reaction was carried out in the normal fashion, but instead of ammonium chloride a quenching solution consisting of trimethylchlorosilane and triethylamine was used. The trimethylsilyl enol ether (**44**) could be isolated and purified by distillation, as shown in Scheme **23**.

15 E Nakamura, S Matsuzawa, Y Horiguchi and I Kuwajima, *Tetrahedron Lett.*, **27**, 1986, 4029.
16 B H Lipshutz, E L Ellsworth, S H Dimock and R A J Smith, *J. Am. Chem. Soc.*, **112**, 1990, 4044.
17 E J Corey and N W Boaz, *Tetrahedron Lett.*, **26**, 1985, 6019.
18 G Stork and J Singh, *J. Am. Chem. Soc.*, **96**, 1974, 6181.



39 **36a** **44**

(i) nBuLi, CuI
(ii) TMSCl, Et_3N

Scheme 23

Due to the low yields that were consistantly obtained and the instability of (**44**) it was decided to abandon any further work in this direction.

3.2.2 Spectroscopic analysis

The compounds discussed in this chapter were isolated and identified by ^{1}H-, ^{31}P-, ^{13}C- and HETCOR-NMR spectroscopy. IR spectroscopy, MS- and CH analysis were also used to unambiguously confirm the structures. The addition product (**42a**) contains only one chiral centre and therefore only one signal in the ^{31}P NMR spectrum was observed for this compound.

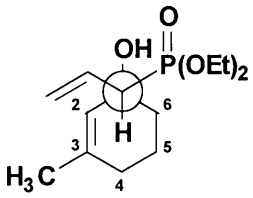
All the other compounds (**41**, **42b-d**, and **43**) contain more than one chiral centre and should therefore display more than one signal in the ^{31}P NMR spectrum. For (**42b**) and (**42d**) the two diastereomers were obtained and could be observed as two close signals in the ^{31}P NMR spectrum. It proved impossible to separate these diastereomers and the diastereomeric ratio of (7:3) for (**42b**) and (10:1) for (**42d**) was obtained respectively from the integration values of the signals in the ^{31}P NMR spectrum.

In both isomers of (**42a, b, d**) the orientation around the double bond is *trans*. This information was gained by a closer look at the $^{3}J_{PC\gamma}$ couplings of the vinylic double bond. Literature values[19] for vinyl-phosphonothioic acid indicate that a carbon atom *trans* to the phosphoryl group will

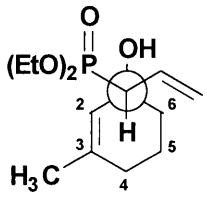
[19] S Berger, S Braun and H Kalinowski, *NMR-Spektroskopie von Nichtmetallen, Band 3, 31P-NMR-Spektroskopie, Georg Thieme Verlag Stuttgart*, New York, 1992, 143.

display a coupling in the region of 25.7 Hz, while the *cis* isomer will result in a coupling constant of 10.1 Hz. The orientation around the double bond $C_\alpha C_\beta$ can be taken as *trans* since the $^3J_{C\gamma P}$ coupling in both isomers has a value of ≈ 22 Hz. Unfortunately, the resolution of the ^1H NMR spectra in the region of H_2 and H_3 in (**42b**) and (**42d**) was not good enough to enable the assignment of the configuration of the individual isomers at these two chiral centres.

In the only reaction where α-addition of the nucleophile was observed (**42c**) we also expect two diastereomers to be formed, but in the ^{31}P NMR spectrum of the crude mixture only one signal was observed. The reaction was therefore stereospecific and analysis of the NMR spectra of this compound proved fruitful. If we make use of the same assumptions as in Chapter **2**, p **30**, then the projections (**42c**) and (**42c'**) represent the most stable conformations of this compound.



42c



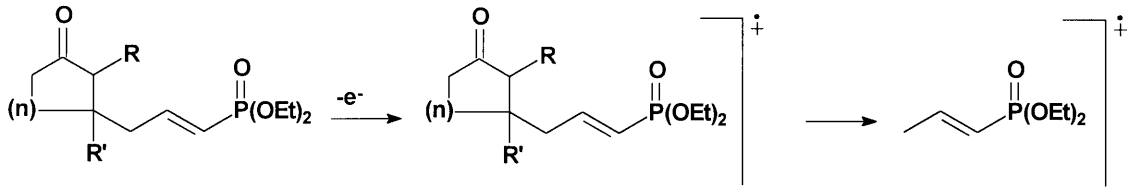
42c'

Considering the ^{13}C NMR spectra we notice that the $^3J_{C6P}$ and $^3J_{C2P}$ coupling constants are equal to 6.0 Hz and 14.4 Hz respectively. This shows clearly that (**42c**) represents the correct structure for this compound since the C_2 atom must be situated *trans* and the C_6 atom *cis* to the phosphorus atom. This seems reasonable if we assume that the methyl group on C_3 plays a role, due to steric interaction in the transition state, making one stereo isomer less favourable.

In compounds (**41**) and (**43**) two diastereomers were again obtained. Unfortunately, it was impossible to separate these diastereomers by using either column chromatography or distillation. This made interpretation of the spectra of the compounds extremely difficult and therefore neither the ^1H nor the ^{13}C NMR spectra of these compounds were useful in gaining more insight into the relative configurations of the individual isomers.

The IR spectra of these compounds gave characteristic signals at ≈ 3400 cm^{-1} for the hydroxyl, ≈ 1700 cm^{-1} for the carbonyl and 1200 cm^{-1} for the P=O stretching vibrational frequencies.

The MS spectra of all these compounds gave the M^+ peak except for (**42c**) where the (M^+-H_2O) peak could be observed. With (**42c**) the next fragmentation resulted in the elimination of diethyl phosphate yielding the peak at m/z 132, corresponding to the fragment expected in the Wittig reaction. A peak at 79 representing the PO_3^+ fragment was also evident. In other compounds, which all contain the ketone functionality, a peak at 179 representing the vinylic phosphonate fragment, resulting from breaking of the C_γ-C_3 bond, (Scheme **24**) gave the parent peak. In these compounds the fragment at 79 was also evident.



Scheme 24

The CNH analysis of the compounds were used as final measure to establish the structure of the individual compounds unambiguously.

3.3 Conclusions

It is clear that steric factors play a major role in determining the regiochemistry of the reactions of allylic phosphonic acid diethyl esters. The reaction can be forced to undergo 1,2-addition by either blocking the β-position with a methyl group or using a suitable leaving group as β-substituent. The reaction was shown to be stereospecific in the case where methyl was used as substituent. Further investigation into the synthetic potential of analogues of (**42c**) should lead to interesting results. The steric effect of different groups, at either the α-,β- or γ-position of the phosphonic acid, should result in differences to the stereo- and regioselectivity. The free acids of (**41**) and (**43**) could be prepared and should lead to crystalline products that will assist in the separation of the isomers and simplify the individual spectra. These spectra can then be used to determine the relative configuration of these molecules.

Reaction of arylmethylphosphonates with 2-cyclohexen-1-ones

4.1 Introduction

Since the aryl group is a weak electron acceptor it should in principle be able to stabilise the negative charge formed after deprotonation of the aryl methyl phosphonic acid esters. Therefore the course of the addition reactions so far studied could change leading to direct olefin formation. It was however found that it was possible to isolate the α-aryl-β-hydroxy-alkylphosponates formed in the addition reaction. This is contradictory to the reaction of fully stabilised carbanions containing additionally CN, COOR or COR functionalities, where the olefinic product was the only product that was obtained.[1] It is known from literature reports[2] that aryl stabilised phosphonic acid derivatives yield a high proportion of *E*-alkenes. *Z*-alkenes can be obtained by stereospecific thermal decomposition of the corresponding β-hydroxy-alkylphosphonamide adducts,[3,4] as well as by the olefination of β-hydroxy-alkylphosphine oxide adducts (as alkali metal salts).[5,6]Petrova and coworkers have shown[4,7,8] that tetramethyldiamides of arylmethylphosphonic acids react after deprotonation with carbonyl compounds to yield (after hydrolysis) β-hydroxy-alkylphosphonamide adducts in high yield, and the pure erythro-diastereoisomers were obtained. An extensive investigation into the reactions of arylmethylphosphonic acid diethyl esters with aldehydes and ketones have been performed over the last couple of years by Petrova *et. al.*[9,10,11] They showed that the reactions of benzylphosphonic acid diethyl esters with ketones are however not stereospecific and that the

1 W S Wadsworth, *Organic Reactions*, **25**, 1977, 78.
2 B E Maryanoff and A B Reits, *Chemical Rev.*,**89**, 1989, 863.
3 E J Corey and G T Kwiatkowski, *J. Am. Chem. Soc.*, **88**, 1966, 5652.
4 J Petrova, M Kirilov and S Momchilova, *Phosphorus and Sulfur*, **17**, 1983, 29.
5 L Horner, H Hoffmann, H G Wippel and G Klahre, *Chem. Ber.*, **92**, 1959, 2499.
6 A D Buss and S Warren, *J. Chem. Soc., Chem. Comm.*, 1981, 100.
7 J Petrova, S Momchilova and M Kirilov, *Phosphorus and Sulfur*, **24**, 1985, 243.
8 S Momchilova, J Petrova and M Kirilov, *Phosphorus and Sulfur*, **35**, 1988, 319.
9 J Petrova, S Momchilova and N G Vassilev, *Phosphorus, Sulfur and Silicon*, **68**, 1992, 45.
10 J Petrova, N G Vassilev and M Kirilov, *Phosphorus, Sulfur and Silicon*, **47**, 1990, 457.
11 J Petrova, M Kirilov and N G Vassilev, *Phosphorus, Sulfur and Silicon*, **85**, 1993, 49.

erythro/threo ratio stays constant irrespective of the reaction time. An increase in temperature influences this ratio in the direction of the more stable isomer, but since the difference in thermodynamic stability is small, the other isomer can always be detected.

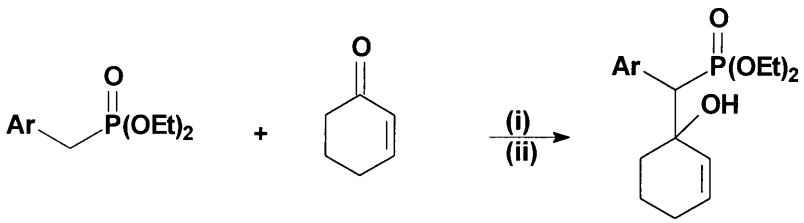
None of these studies involved the addition of phosphonic esters to α,β-unsaturated ketones. Since the aryl functionality serves to delocalise the negative charge of the anion, the energy of the HOMO will be lowered and therefore increased orbital control should prevail, increasing the possibility of conjugate addition.

4.2 Results and discussion

4.2.1 Reaction conditions

The reactions of various arylphosphonic acid diethyl esters (**45**) with 2-cyclohexen-1-ones (**36a-c**) were studied. The anions of arylphosphonic acid diethyl esters were found to be much less reactive than their alkylphosphonic acid diethyl ester (**35**) counterparts, discussed in Chapter **2**. In order to increase the low yields that were obtained, it was decided to decrease the reaction time to 15 minutes as suggested by Petrova *et. al.*[10] This resulted exclusively in the isolation of the substrates. It was found that the use of 2 molar excess of the base was essential to obtain reasonable yields in these addition reactions; *e.g.* when benzylphosphonic acid diethyl ester (**45a**) reacted with 2-cyclohexen-1-one (**36a**), the yield was increased from 24 to 99% by using this large excess of base.

n-Butyllitium was dissolved in THF and to this solution cooled down to -78°C was added the phosphonic ester (**45**) under an inert atmosphere. The reaction mixture was kept at this temperature for 1 hour before the electrophile (**36**) was added. The reaction mixture was stirred for a further 2 hours at this low temperature when it was quenched with an aqueous solution of ammonium chloride. Under these conditions only 1,2-addition resulted as shown in Scheme **25**, Table **7**.

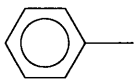
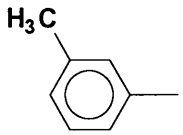
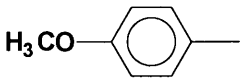
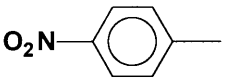
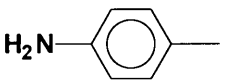
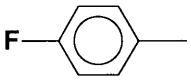


45 36a 46

(i) nBuLi
(ii) H_3O^+

Scheme 25

Table 7 Addition reactions of phosphonic esters (45) to 2-cyclohexen-1-one

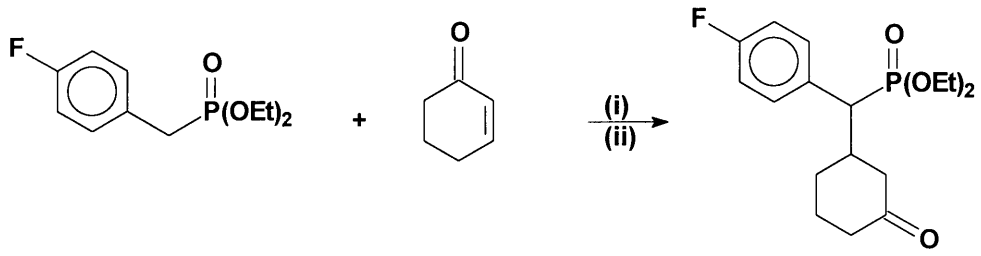
No.	Ar-	%Yield	de
46a		98.7	4:1
46b		55.4	7:3
46c		78.7	4:1
46d		0	
46e		0	
46f		100	5:1

1,2-Addition was the major mode of attack showing that these reactions are charge controlled. In each case two diastereomers were obtained and column chromatography proved successful in

separating these stereoisomers. Not one of the reactions was stereoselective, but in each case there was a preference for one diastereomer.

The anions derived from 4-nitro-benzyl-phosphonic acid diethyl ester (**45d**) and 4-amino-benzyl-phosphonic acid diethyl ester (**45e**) did not show any signs of reactivity towards (**36a**) under these conditions. An increase in the temperature of the reaction mixture and the implementation of organocuprates had no effect, and only the substrates were retrieved.

Only the substrates (**45a**) and (**36a**) were isolated when the temperature of the reaction mixture was increased to room temperature in an attempt to use reaction conditions more suitable for conjugate addition. This shows that the addition reactions of aryl-phosphonic acid diethyl esters are reversible, and that the anion of the substrate is thermodynamically more stable than that of the addition product. In the reaction of 4-fluorobenzylphosphonic acid diethyl ester (**45f**) with (**36a**) the temperature of the reaction was allowed to rise up to -10°C where it was quenched with ammonium chloride. The 1,4-addition product (**47a**) could thus be isolated even though only in small yield (Scheme **26**). When the temperature of the reaction mixture was however raised to room temperature then only the substrates were isolated.



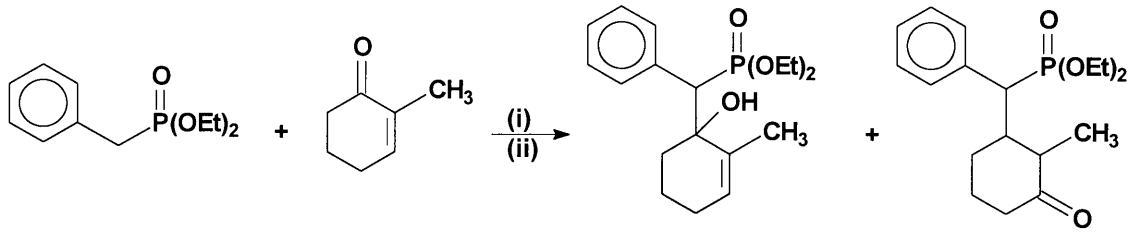
45f **36a** **47a (36%)**

(i) nBuLi
(ii) H_3O^+

Scheme 26

It was decided to investigate the influence steric factors would have on the regioselectivity of the reaction. 2-Methyl-2-cyclohexen-1-one (**36b**) was therefore used as electrophile. The probability of obtaining 1,4-addition has to be increased with the relatively large benzyl-phosphonic acid (**45a**) and the electrophile congested in the region near the carbonyl group. The reaction (Scheme

27) yielded some conjugate addition product (**47b**) (13.2%) but the 1,2-addition (**46g**) (25.6%) was still the major pathway of the reaction.



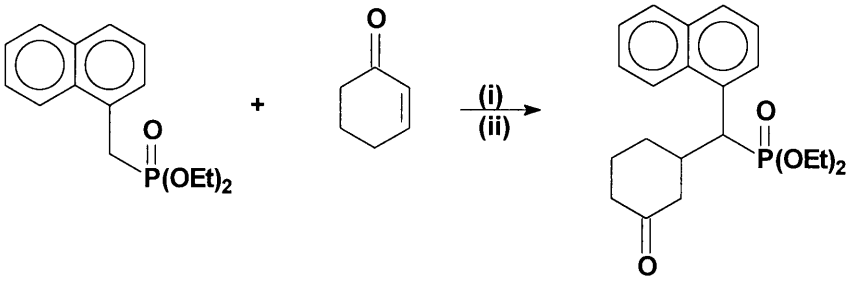
45a **36b** **46g** **47b**

(i) nBuLi
(ii) H_3O^+

Scheme 27

When the reaction was repeated and allowed to warm up to room temperature before quenching, only the substrate (**45a**) was isolated.

1-Naphthylmethyl-phosphonic acid diethyl ester (**48**) reacted in an unique fashion. At -78°C neither 1,2- nor 1,4-addition could be observed. When the reaction mixture was allowed to warm up to room temperature and stirred overnight, the product of conjugate addition was exclusively obtained (Scheme **28**). This result is most likely due to the steric bulk of the nucleophile rendering it sterically too hindered to undergo 1,2-addition. The enolate formed in the addition reaction has to be in this case more stable than the anion formed after deprotonation of the substrate since thermodynamic conditions were used to obtain the product.



48 **36a** **47c**

(i) nBuLi
(ii) H_3O^+

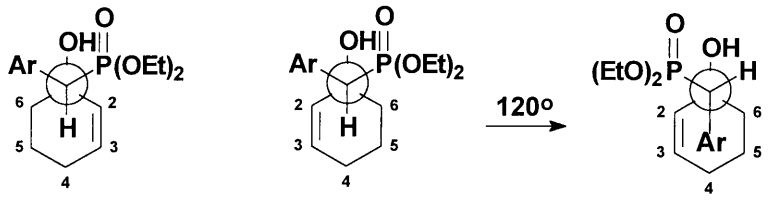
Scheme 28

Steric factors were once again employed to change the course of the reaction of (**48**) described in Scheme **28**. The reaction was repeated using 3-methyl-2-cyclohexen-1-one (**36c**), but no reaction with this electrophile could be detected at -78°C or at room temperature.

4.2.2 Spectroscopic analysis

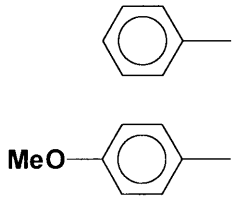
The compounds discussed in this chapter were isolated and identified by ^{1}H-, ^{31}P-, ^{13}C- and HETCOR-NMR spectroscopy. IR spectroscopy and MS analysis were used to confirm the structures of the individual compounds. CH analysis of these compounds proved consistently inaccurate as frequently observed for dialkyl esters of phosphonic acids, the determined content of carbon was usually 1-3% lower than the calculated values and was therefore not used as a means for final confirmation of the structures.

All the compounds discussed in this chapter contain more than one chiral centre and they therefore exist in more than one diastereomeric form. These isomers were separated where possible and were identified individually. (**46a**) and (**46c**) were obtained as two diastereomers and two close signals were observed on the ^{31}P NMR spectrum for each of these compounds. The two isomers could be separated in each case, by using column chromatography, yielding a major and minor fraction. If we make use of the same assumptions as in Chapter **2**, p **30**, then the stereo isomers (**46a, 46a', 46c and 46c'**) represent possible structures for these compounds.



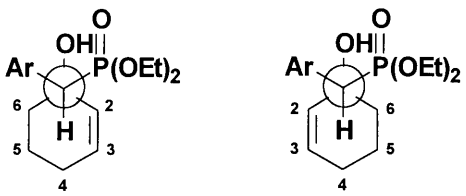
46a, c **46a', c'**

Ar =

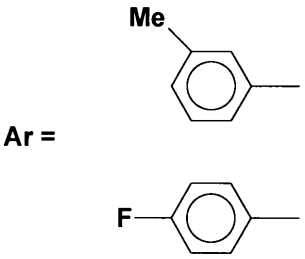


A closer look at the $^{3}J_{CP}$ coupling constants that were observed in the ^{13}C NMR spectrum between the phosphorus atom and C_2 and C_6 shows that the values are respectively equal to ≈ 4.6 and ≈ 11 Hz in both isomers. From this we can deduce that the C_6 atom must be situated *trans* to the phosphorus atom in both isomers of each compound. The major isomer will thus have the structure depicted by (**46a**) and (**46c**) because these isomers will experience the least steric strain in the transition state and will therefore form more readily. The other isomer (**46a'**) and (**46c'**) has to rotate 120° in order to obtain the correct geometric orientation to account for the observed coupling constants. The interaction between the aryl- and cyclohexene rings should render this conformation less suitable to form and it will explain the relative stereoselectivity in the addition reaction noticed in these two reactions.

The reaction of (**45b**) and (**45f**) also yielded two diastereomers in each case and these isomers were separated by column chromatography. The stereoisomers (**46b, 46b', 46f and 46f'**) show the possible structures of the two diastereomers obtained in these reactions.



46b, f **46b', f'**



The $^{3}J_{CP}$ coupling constants of C_6 and C_2 of the major fraction in both cases were found to be equal to ≈ 11.3 and ≈ 4.4 Hz respectively. This shows that, as before, the phosphorus atom must be *trans* to C_6 in these cases and (**46b**) and (**46f**) represents the correct structure. In (**46b'**) and (**46f'**) the C_6 atom is situated *cis* to the phosphorus and indeed gives a coupling equal to ≈ 6.3 Hz in both cases. For (**46b'**) the $^{3}J_{CP}$ coupling to C_2 was found to be equal to 10.0 Hz, confirming the structure. Unfortunately, the $^{3}J_{CP}$ to C_2 in (**46f'**) could not be observed.

With (**46g**) only the $^{3}J_{CP}$ coupling constants of the major isomer, could be obtained. These values were found to be 5.1 and 13.2 Hz for C_6 and C_2 respectively. The carbon atom bearing the methyl substituent will therefore be situated trans to the phosphorus atom and this isomer will thus have a similar structure as that of (**46b'**). More NMR data is necessary to assign the structure of the second isomer.

In the conjugate addition reaction of (**45f**) two diastereomers (**47a**) and (**47a'**) were also obtained, but these could not be separated with the aid of column chromatography. This complicated the assignment of the individual peaks immensely. The $^{3}J_{CP}$ coupling constants for one of the isomers was accurately determined to be 8.2 and 9.4 Hz for C_2 and C_6. These two values are very similar and it is reasonable to assume that free rotation is feasible in this molecule rendering the assignment of the relative configurations of the isomers impossible.

With (**47b**) the two diastereomers could be separated, but the minor isomer always contained impurities complicating the assignment of the NMR spectra. The $^3J_{CP}$ coupling constants of the major fraction was determined as 2.2 Hz and 14.6 Hz for C_6 and C_2 respectively. In this isomer the methyl group, on C_2, will therefore be *trans* to the phosphorus atom.

The reaction of (**48**) yielded the product showing two phosphorus peaks representing the isomers (**47c**) and (**47c'**). The first isomer could be isolated by column chromatography and fractional crystallisation, but the second isomer always contained some traces of the other isomer. The $^3J_{CP}$ of C_6 and C_2 determined for the first isomer was equal to 10.8 and 6.4 Hz respectively. This shows clearly that there is restricted rotation around the C_α-$C_{1'}$ bond of the molecule. The value of the coupling constant between H_α and $H_{1'}$ was determined to be equal to 8.2 Hz. This value should therefore represent the average coupling of all the conformations possible for this compound and can be calculated by means of the Haasnoot equation.[12]

The IR spectra of the condensation products gave the expected characteristic signals at ≈ 3400 cm^{-1} for the hydroxyl, ≈ 1700 cm^{-1} for the carbonyl and ≈ 1200 cm^{-1} for the P=O stretching vibrational frequency.

In the MS spectra of (**46a, b, c, f, g**) no M^+ peak was observed and only the (M^+-H_2O) peak was obtained for all β-hydroxy-alkylphosphonic acid diethyl esters. This shows again that these tertiary alcohols are not very stable compounds. The elimination of diethyl phosphate to yield a fragment representing the expected Wittig product was observed in all cases, but contrary to all the other examples discussed in Chapters **2** and **3**, these signals did not represent the parent peaks of the fragmentation. This shows that the driving force for the Wittig reaction to occur in these substrates is not very strong. In all cases a peak at m/z 79 indicating the PO_3^+ fragment was also observed.

All the carbonyl compounds (**47a-c**) gave in the MS spectra peaks corresponding to their respective M^+ ions. The next fragment that was evident in all the spectra is where the P-C bond broke. This fragment produced the parent peak in each case. From this we can deduce that the substrates of these reactions are thermodynamically more stable than the products of conjugate

[12] C A Haasnoot, F A A M deLeeuw and C Altona, *Tetrahedron*, **36**, 1980, 2783.

addition. This will account for the fact that the conjugate addition does not occur since thermodynamic conditions are needed. A fragment at 81 representing $PO_3H_2^+$ or at 79 representing PO_3^+ was observed in all MS spectra.

4.3 Comparison between NMR, Crystal Structure and Molecular Dynamics data of (47c)

A study of the relevance of the different spectroscopic techniques should yield some interesting results since the data obtained from each of these procedures are related to structure problems in a different medium *i.e.* solution (NMR), solid state (X-ray diffraction) and gas phase (Molecular dynamics).

The molecular dynamics (MD) method known as simulated annealing was used to identify the low energy conformations of (**47c**). This method uses MD calculations to raise the temperature of the molecular system to the plateau phase. This plateau phase is maintained for a certain period of time which allows conformational barriers to be broken in the molecule. Care should be taken to ensure that all barriers are surpassed, by raising the temperature high enough. This plateau phase therefore reproduces the Boltzmann distribution of conformational states.[13] The temperature is then allowed to decrease in the ramp phase. This progressive lowering in the temperature of the system allows the exploration of conformations with decreased energy. Finally the system falls into a global energy minimum or at least a local minimum. Several low energy conformations of (**47c**) could thus be obtained.

The total energy of each sampled conformer consists of kinetic- as well as potential energy. The kinetic energy term arises from the translation of the atoms and the potential energy is due to bond stretching, angle bending and so on. Low energy conformers are better represented by their potential energy and these values are therefore represented on the y-axis of Figures **1-6**. Figure **1** graphically illustrates the simulated annealing cycles. Only the data pertaining to the sampled conformers of the first ten cycles are represented here. In each cycle the final low energy conformer was obtained.

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[13] J P Doucet and J Weber, *Computor-Aided Molecular Design: Theory and Application*, Academic Press Inc., San Diego CA 92101, 197-238.

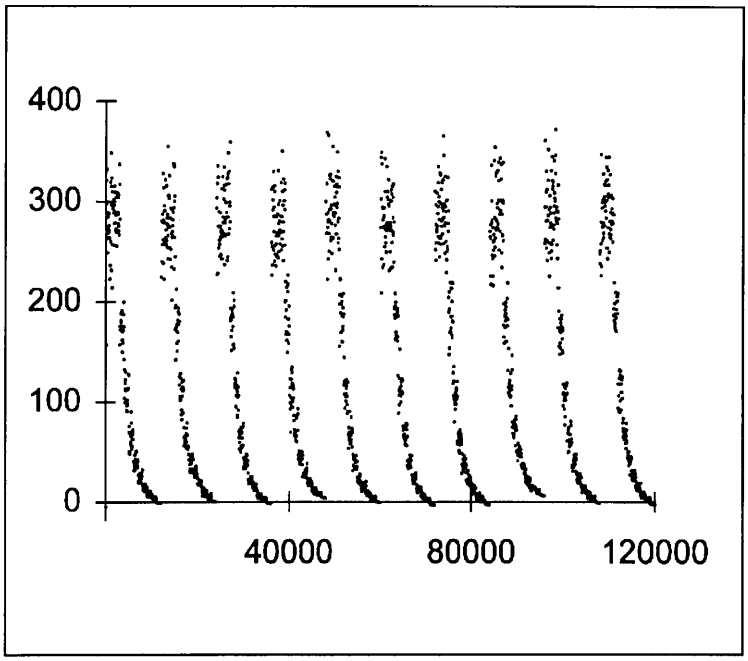

Figure 1 Time (fs) *vs* PE (kcals/mol)

It is essential that the tortional barriers defined by the torsion angles H_{α}-C_{α}-C_1-C_9 and H_{α}-C_{α}-$C_{1'}$-$H_{1'}$ were overcome to make sure that all the conformational space accessible to (**47c**) was searched during the plateau phase. From Figure **2** it is clear that during the simulation when the potential energy was greater than 200 kcals/mol all the torsion angles of H_{α}-C_{α}-C_1-C_9 except those close to 100° were traversed.

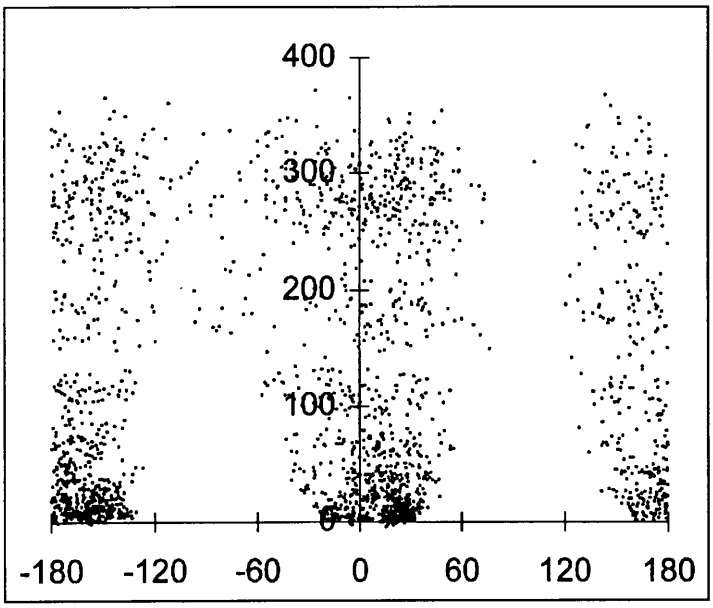

Figure 2 Torsion H_{α}-C_{α}-C_1-C_9 (deg) *vs* PE (kcals/mol)

To identify the reason why no values for the torsion angles equal to 100° were observed, a molecular model of (**47c**) was built where the torsion angle H_{α}-C_{α}-C_1-C_9 was equal to 100°. This model is displayed in Figure **3**.

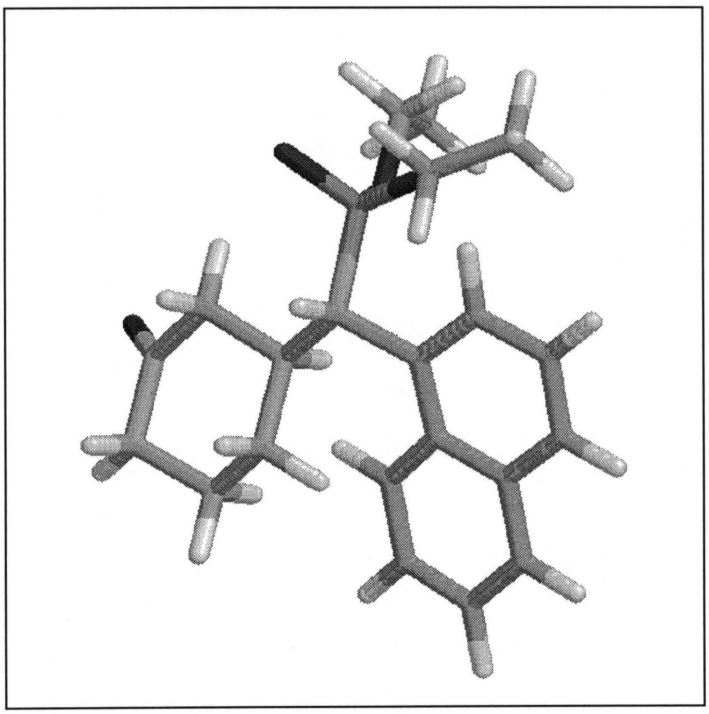

Figure 3 Compound (47c) with the torsion angle H_{α}-C_{α}-C_1-C_9 = 100°

From the figure it can be clearly seen that there is steric repulsion between the hydrogen atoms of the naphthyl and cyclohexanone groups. This torsion angle would therefore be inaccessible to (**47c**).

From Figure **4** it can be seen that all the torsion angles of H_{α}-C_{α}-$C_{1'}$-$H_{1'}$ were successfully traversed during the simulation when the potential energy was greater than 200 kcals/mol. It can therefore be concluded that all conformational barriers defined by both torsion angles were breached and that the plateau phase represents a true Boltzmann distribution of the conformational states.

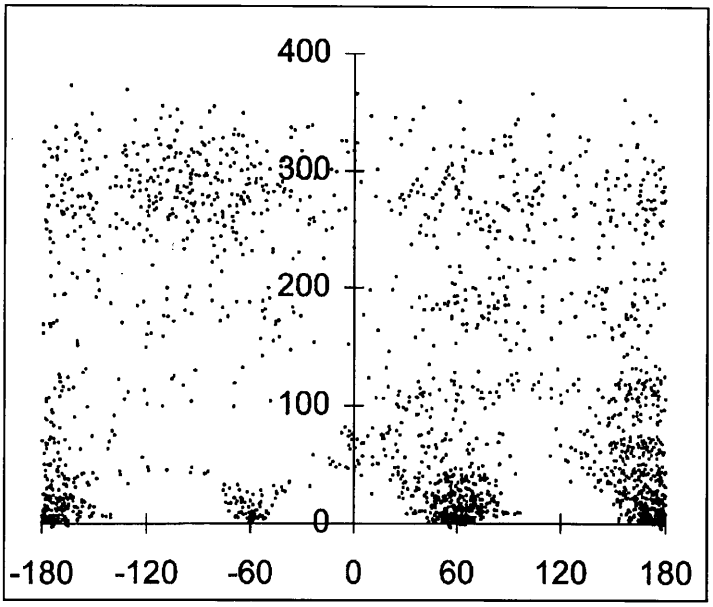

Figure 4 Torsion H_{α}-C_{α}-$C_{1'}$-$H_{1'}$ (deg) *vs* PE (kcals/mol)

In the above figure the convergence of the torsion angles of H_{α}-C_{α}-$C_{1'}$-$H_{1'}$ at 180°, 60° and -60° shows that these conformers must be stabilised by some means. The torsion angle H_{α}-C_{α}-$C_{1'}$-$H_{1'}$ versus the potential energy of the annealed low energy conformers obtained from 50 cycles are summarised in Figure **5**.

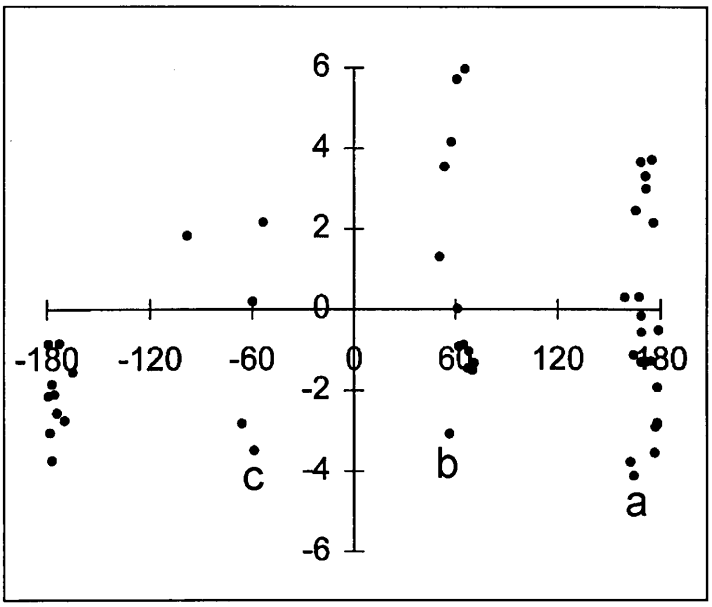

Figure 5 Torsion H_{α}-C_{α}-$C_{1'}$-$H_{1'}$ (deg) *vs* PE (kcals/mol)

It is clear that the population of rotor 180 > rotor 60 ≈ rotor -60. Each of the conformers **b** and **c** shown in Figure **5** was fully minimised using the TRIPOS force field and then used as starting conformers for the annealing experiments, using the same parameters as before, to establish

whether this trend was independent of the starting conformation. The summarised results of these experiments are shown in Figures **6** and **7** respectively.

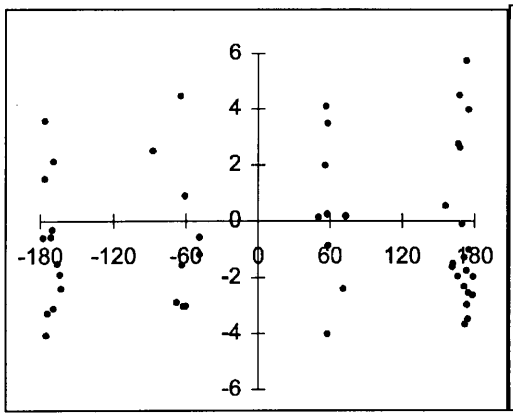

Figure 6Torsion H_{α}-C_{α}-$C_{1'}$-$H_{1'}$ (deg) *vs* PE (kcals/mol)

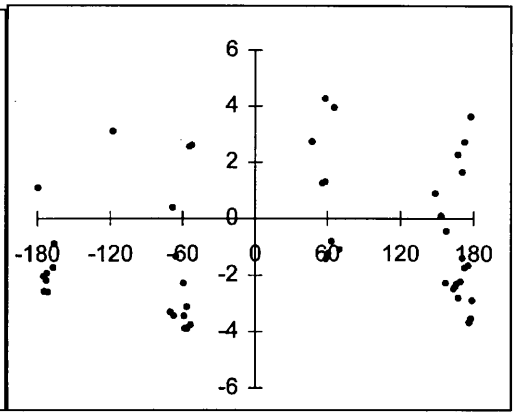

Figure 7 Torsion H_{α}-C_{α}-$C_{1'}$-$H_{1'}$ (deg) *vs* PE (kcals/mol)

From Figures **6** and **7** it is evident that the trend is reproduced and it can be concluded that the conformations are independent of the starting conformation.

The structure that was obtained when conformer **a**, in Figure **5**, also underwent full minimisation is shown in Figure **8**. The similarity of this structure to that of the crystal structure is evident. This shows that even in the gas phase the forces responsible for the formation of the conformer of lowest energy are in operation.

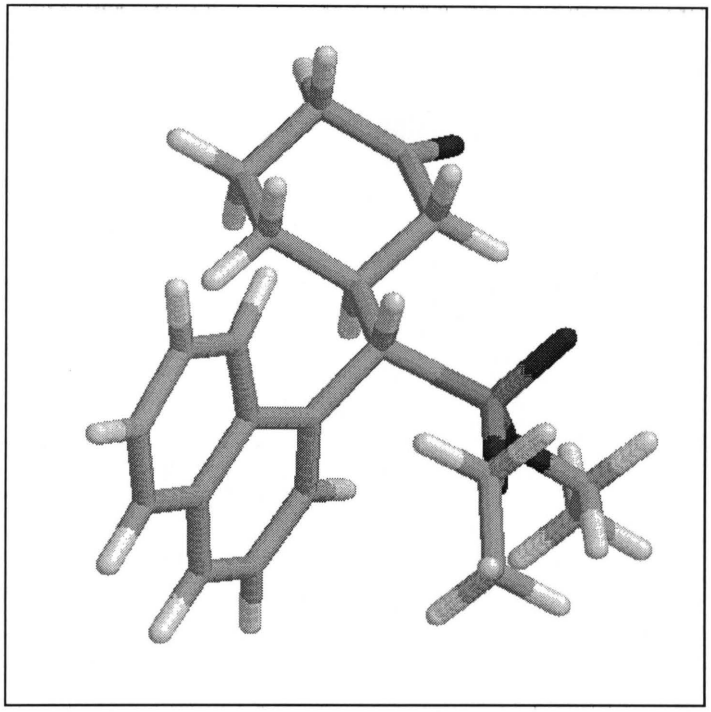

Figure 8 Fully minimised structure of conformer a

If the population distribution of the final annealed rotors are a true reflection of the distribution of the rotors in solution then the theoretically calculated coupling constant between H_α and $H_{1'}$ should compare favourably with that obtained from the experimental data. The Haasnoot equation predicts[12] that the vicinal coupling constant between H_α and $H_{1'}$ is caused by the specific population distribution of the rotors of (**47c**) defined by the torsion angle H_α-C_α-$C_{1'}$-$H_{1'}$ according to the following equation:

$$^3J(H_\alpha H_{1'}) = \chi\text{rotor } 180.{}^3J(\text{torsion rotor } 180) + \chi\text{rotor } 60.{}^3J(\text{torsion rotor } 60) + \chi\text{rotor } (-60).\ {}^3J(\text{torsion rotor } -60)$$

Where χ is the fraction of a given conformer, and ^{3}J(torsion rotor) is a theoretical value of $^3J_{HH}$ coupling constant for an isolated conformer of a given value of the torsion angle.

The theoretical coupling constants were determined by importing the fully minimised conformers into the VICI program. The obtained values are given in Table **8**.

Table 8 The minimised energies, torsion angles and vicinal coupling between H_α and $H_{1'}$.

Conformer	Energy (kcals/mol)	H_α-C_α-$C_{1'}$-$H_{1'}$ (deg)	$J(H_\alpha H_{1'})$ (Hz)
a	-4.61	164.2	13.1
b	-3.36	56.5	3.0
c	-4.08	-58.9	4.1

The population distribution was calculated by using all 150 conformers shown in Figures **5-7**. From these values the vicinal coupling could be calculated as:

$^3J(H_\alpha H_{1'})$ = (90/150) x 13.1 + (33/150) x 3.0 + (27/150) x 4.1

= 9.3 Hz

The theoretical value therefore agrees favourably with that obtained from the ^{1}H NMR spectral data *i.e.* 8.2 Hz. The energy barriers present in the gas and liquid phase were therefore shown to effect the distribution of the different conformers to a similar degree.

The perspective view and atomic numbering of naphthalen-1-yl(3-oxo-cyclohexyl)-methyl-phosphonic acid diethyl ester (**47c**) is given in Figure **9**.

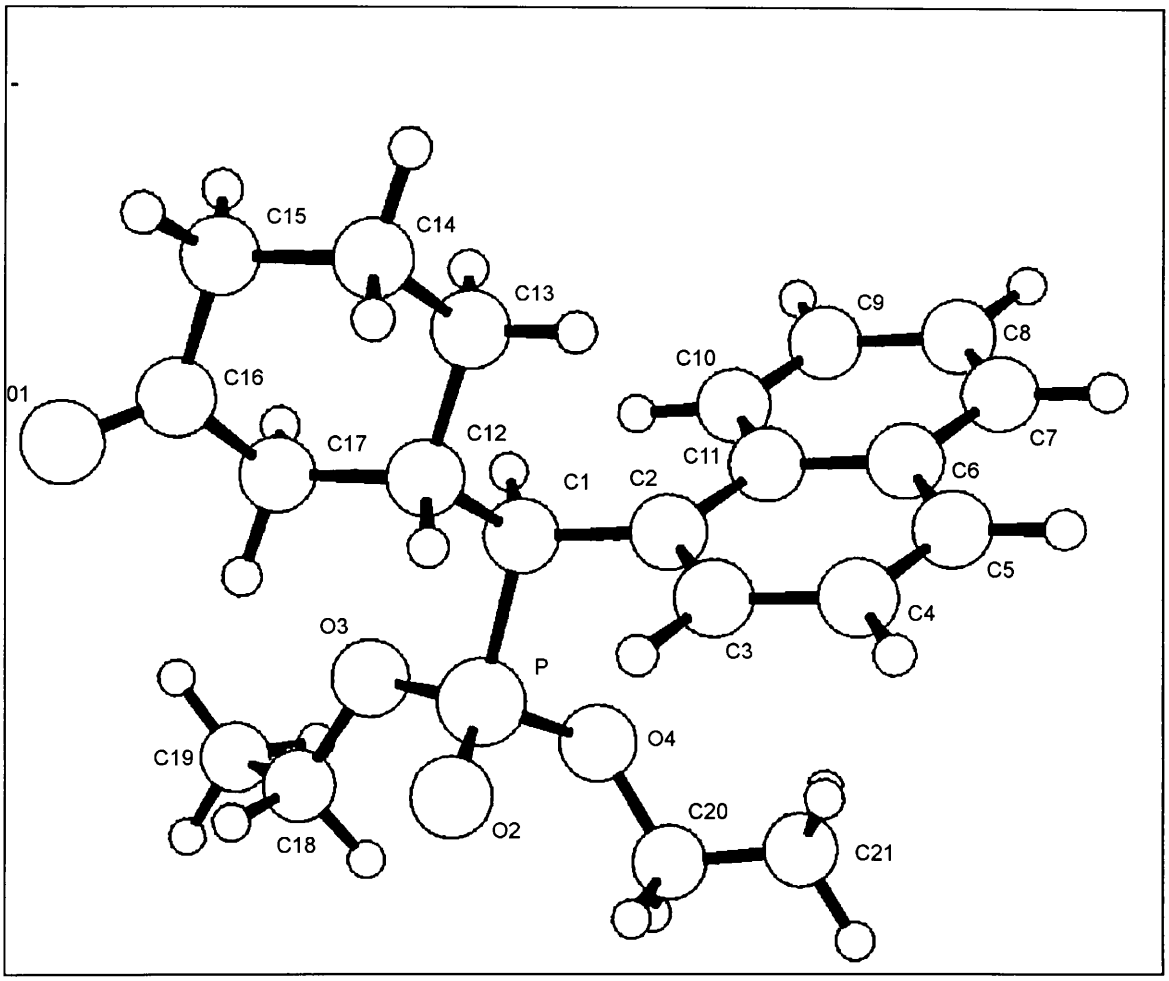

Figure 9 Perspective view with atomic numbering of (47c)

The double bond character of the carbonyl and phosphoryl groups are clearly visible from the bond lengths these functionalities display, *i.e.* 1.194 and 1.456 Å respectively. From Figure **9** it is clear that the two bulky groups (cyclohexanonyl and 1-naphthyl) are orientated in a specific fashion around the C(1) atom, determined by the torsion angle C(12)-C(1)-C(2)-C(3) = 57.1°. Furthermore, it is noted that the two hydrogen atoms at C(1) and C(12) are oriented *trans* to one another. This torsion angle is given by H(1)-C(1)-C(12)-H(12) = 176.3° which is a little higher than the angle of *ca* 164.2° obtained for the conformer **a** from molecular dynamics (Table **8**). This correlation obtained between the solid state data and the value estimated for the gas phase is quite satisfactory.

4.4 Conclusions

From the results obtained in this chapter it is clear that both 1,2- and 1,4-addition reactions of aryl substituted phosphonic acid diethyl esters to α,β-unsaturated ketones are reversible. It was demonstrated that under thermodynamic conditions, which promotes conjugate addition, that 1,4-addition does indeed occur. The anion of the substrate is however relatively stable and in most cases its formation, in a reversable step competes with the formation of the products, leading to diminished yields of condensation. These low yields decrease the synthetic utility of these reactions in the preparation of conjugated products.

Furthermore, we were able to successfully demonstrate the applicability of MD as a useful tool to study these compounds. However, care should be taken not to generalise, since this discussion constitutes only one example where it was attempted to study the correlation between the experimental and theoretical data. More data from different sets of compounds need to be obtained before any general conclusions may be reached with any degree of accuracy.

Aromatisation of the condensation products

5.1 Introduction

Nature has an abundance of natural products containing highly substituted aromatic compounds which possess a wide range of biological activity.[1] Dehydrogenation is frequently the last step in the synthesis of polycyclic aromatic hydrocarbons and their derivatives. In older literature it is observed that sulphur, selenium and platinum metals were predominately used to bring about aromatisation. Although these reagents are still employed in the synthesis of unsubstituted polycyclic aromatic ring systems, they require relatively drastic conditions unsuitable for the synthesis of the more sensitive compounds currently of greatest interest, such as the oxidised metabolites of carcinogenic hydrocarbons.

New milder methods[2] of dehydrogenation, less hampered by these limitations, are generally being preferred to conventional methods. High oxidation potential quinones, such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and chloranil are the best known examples. Others include trityl salts, alkyllithium-N,N,N',N'-tetramethylethylenediamine (TMEDA) complexes, and bromination-dehydrobromination with N-bromosuccinimide (NBS), in addition to various miscellaneous methods. None of these procedures can, however, compete with the high selectivity and efficiency of enzymatic transformations, but recent findings have been encouraging in the last few years.

Metal salt-catalysed aromatisation of substituted cyclohexenones to the corresponding phenols or phenol ethers is a well established procedure.[3,4,5,6] In 1980 Tamura and Yoshimoto reported that

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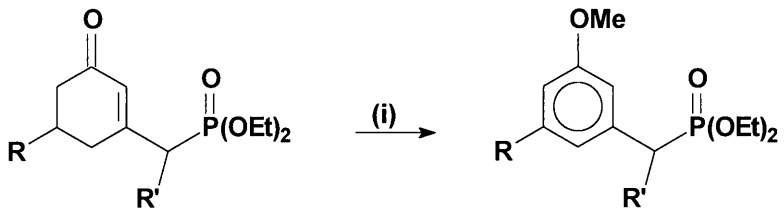
1 A S Kotnis, *Tetrahedron Lett.*, **31**, 1990, 481.
2 P F Fu and R G Harvey, *Chem. Rev.*, **78**, 1978, 317.
3 E M Kosower and G -S Wu, *J. Org. Chem.*, **60**, 1995, 8236.
4 P A Grieco and N Marinovic, *Tetrahedron Lett.*, 1978, 2545.
5 I S Blagbrough, G Pattenden and R A Raphael, *Tetrahedron Lett.*, **23**, 1982, 4843.
6 T Hirao, M Mori and Y Ohshiro, *J. Org. Chem.*, **55**, 1990, 358.

iodine in refluxing methanol can be used effectively to convert cyclohexenones to their corresponding aromatic derivatives.[7] Kotnis[1,8] recently made use of this procedure for the preparation of substituted resorcinols and methoxybenzoates. The only mechanistic suggestion available up to this stage suggest that in the first step of the reaction the 1,4-addition-elimination of methanol to the enol form of the cyclohexadione system occurs.

5.2 Results and discussion

5.2.1 Aromatisation with I_2/MeOH

Some phosphonic acid diethyl esters (**37**) and (**48**) have been subjected to the reaction with I_2 in refluxing methanol. It was observed that the type of aromatic compound that was obtained in this reaction depends on the structure of the substrate. In a recent publication[9] it was demonstrated that δ-ketophosphonates (**48**) yielded the corresponding (3-methoxybenzyl)-phosphonic acid diethyl esters (**49**) as shown in Table **9** (Scheme **29**). The substrate was dissolved in a small amount of methanol. Iodine (2 mole equivalent) was added to this mixture and it was stirred at room temperature until most of the iodine had dissolved. The reaction mixture was then kept at reflux temperature for 90 minutes. Normal aqueous workup afforded the products.



48 **49**

(i) I_2/MeOH

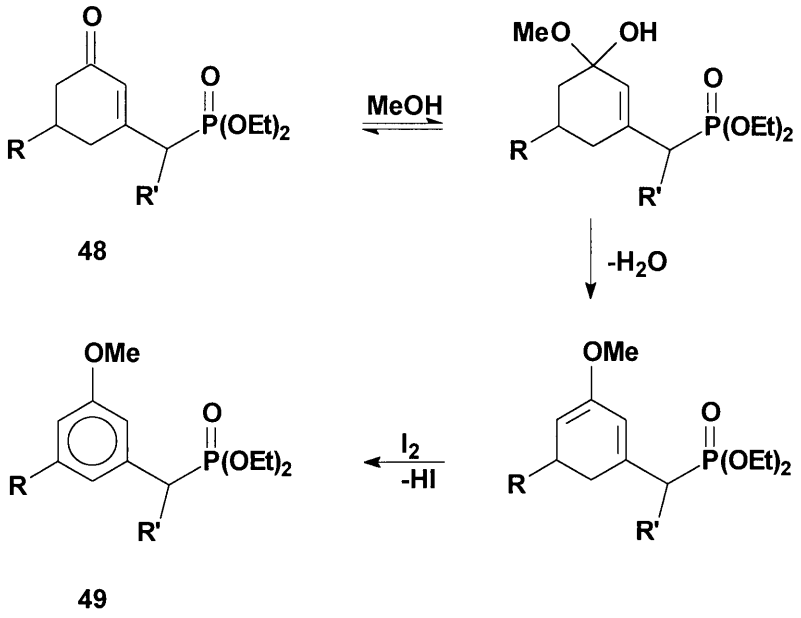
Scheme 29

7 Y Tamura and Y Yoshimoto, *Chem. and Ind.*, 1980, 888.
8 A S Kotnis, *Tetrahedron Lett.*, **32**, 1991, 3441.
9 M J Mphahlele, A Pienaar and T A Modro, *J. Chem. Soc., Perkin Trans. 2*, 1996, 1455.

Table 9 Aromatisation of (48) with I_2 in refluxing MeOH

No.	R	R'	% Yield
49a	H	H	71
49b	H	CH_3	67
49c	CH_3	H	60
49d	CH_3	CH_3	50

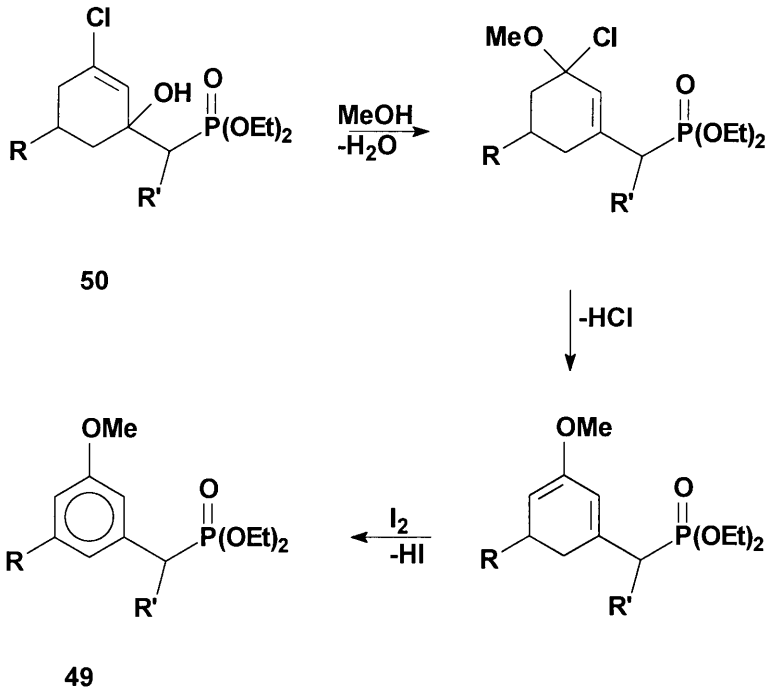
The table shows that good yields were consistently obtained. The mechanism of the reaction is believed to proceed via initial 1,2- (independent of the 1,4-) addition of methanol followed by dehydration and oxidative aromatisation as shown in Scheme **30**.



Scheme 30

The same products (**49a**) and (**49b**) can be obtained[10] from the corresponding 3-chlorocyclohexanols (**50a**) and (**50b**), presumably via the acid-catalysed S_N2'displacement of the allylic alcohol by methanol. Elimination of HCl yields the same cyclohexadiene derivative that was obtained from (**48**). Iodine is active in the last step to promote aromatisation of the product as shown in Table **10** (Scheme **31**).

[10] M J Mphahlele and T A Modro, *J. Org. Chem.*, **60**, 1995, 8236.



50

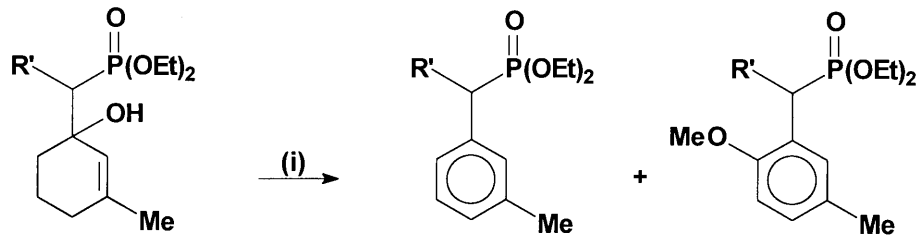
49

Scheme 31

Table 10 Aromatisation of (50) with I_2 in refluxing MeOH

No.	R	R'	% Yield
49a	H	H	71
49b	H	CH_3	67

3-Methyl substituted cyclohexenols (**37b, 37e** and **42c**) reacted with iodine in methanol yielding two types of aromatic products: the expected 3-methyl-benzyl-phosphonic acid derivatives (**51**) as well as their 2-methoxy derivatives (**52**) as depicted in Table **11**, Scheme **32**.



37, 42 51 52

(i) I_2, MeOH

Scheme 32

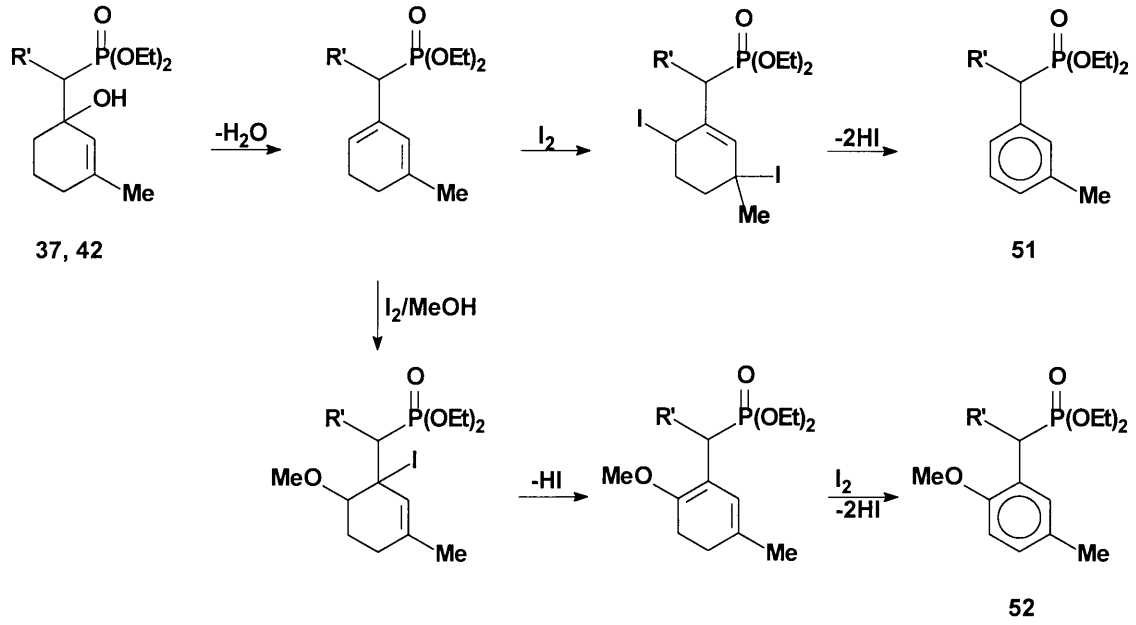
Table 11 Aromatisation of (37b, 37e) and (42c) with I_2 in refluxing MeOH

No	R'	% Yield 51	% Yield 52
51a + 52a	H	11.6	22.4
51b + 52b	CH_3	0	43.2
51c + 52c	$CH{=}CH_2$	8.7	4.8

A mechanism was proposed[9] (Scheme **33**) accounting for both products (**51**) and (**52**), in which the cyclohexadiene, which formed as a result of dehydration, serves as common intermediate. This intermediate either undergoes 1,4-addition of iodine or 1,2-addition of I^+, followed by methoxide. This is followed by the usual aromatisation steps.

As far as 1,4-addition to the diene intermediate is concerned it should be noted that if incorporation of the solvent occurred, then methanol would have to be eliminated for aromatisation to take place. It is however 1,4-addition of iodine, which leads to smooth elimination leading to the final product (**51**) in each case. With the 1,2-addition the situation is more complex since it can involve either the 6,1 or the 2,3 olefinic bond of the intermediate. Each direction yields a vicinal diiodide or the Markovnikov as well as the anti-Markovnikov solvent incorporated products. The observed product (**52**) results from the anti-Markovnikov addition of I^+ - MeO^- species to the 6,1 olefinic bond. The diiodide adduct or the Markovnikov solvent incorporated product would lead, after the respective elimination of HI or MeOH, to the final 6-iodo substituted analogue of (**52**). The anti-Markovnikov orientation of the I^+ - MeO^-

addition can be easily explained by the difference in the substituents present at C_1 and C_6 respectively. Up to 100% of the anti-Markovnikov selectivity has been observed in the addition of ICl and IBr to unsymmetrically substituted alkenes.[11]



Scheme 33

If a bridged iodonium ion structure for the cationic intermediate of the addition to the C_6-C_1 double bond is accepted,[12] then nucleophilic attack of methanol would be expected to occur at the less hindered C_6 centre. The absence of the 6-iodo substituted product could be explained by the known reversibility of the addition of I_2 to alkenes. This will result in an increase in the proportion of the solvent incorporated product containing one strong C-O bond. The absence of the aromatic products derived from the 1,2-addition to the C_2-C_3 double bond of the diene intermediate results most probably from the steric congestion that is experienced by the 1,2,3-trisubstituted benzene derivative.

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11 G H Shmid and D G Garrat, *The Chemistry of Double-Bonded Functional Groups*, Supplement A, Part 2, ed. S Patai, Wiley, New York, 1977, ch. 9.

12 M C Findley, W L Walters and M C Caserio, *J. Org. Chem.*, **36**, 1971, 275.

5.2.2 Aromatisation with pyridinium perbromide

The reaction of 3-(phosphonoalkyl)cyclohexenones (**48**) with the brominating agent, pyridinium perbromide was studied.[9] This reagent, easily prepared from pyridine, Br_2 and 48% HBr,[13] was found to be a convenient brominating agent for phenols, alkenes and ketones.[14] In their work on the total synthesis of diterpenoids, Meyer *et. al.*[15] reported that when a perhydrophenanthrene derivative containing ring C in the enone form was treated with pyridinium perbromide then the ring was converted to a phenolic system fused in the 3,4-positions with the remaining perhydronaphthalene ring. They suggested that the reaction involves the bromination of the enolic form of the enone system at C_2 or C_4, followed by the elimination of HBr leading to the phenolic product. Various products were obtained when the three different substrates of (**48b, 48c, 48d**) were subjected to the same reaction conditions as was reported by Meyer. In a standard reaction pyridinium perbromide was added to a solution of the ketophosphonate in glacial acetic acid. This solution was stirred at room temperature for 1 hour when water was added. Normal aqueous workup afforded the crude reaction mixture which was purified by column chromatography.

The structures of the products obtained proved to be dependent on the nature of the starting materials as shown in Scheme **34**. The reaction products can be devided into four categories: phenols (**53a**), ring brominated phenols (**53c**) and (**53d**), α-C side-chain brominated phenols (**53b**) and (**53f**) and the brominated but unaromatised (**53g**). The isolation and identification of the products (**53**) shed more light on the mechanism and scope of the reaction between cyclic enones and halogenating agents.

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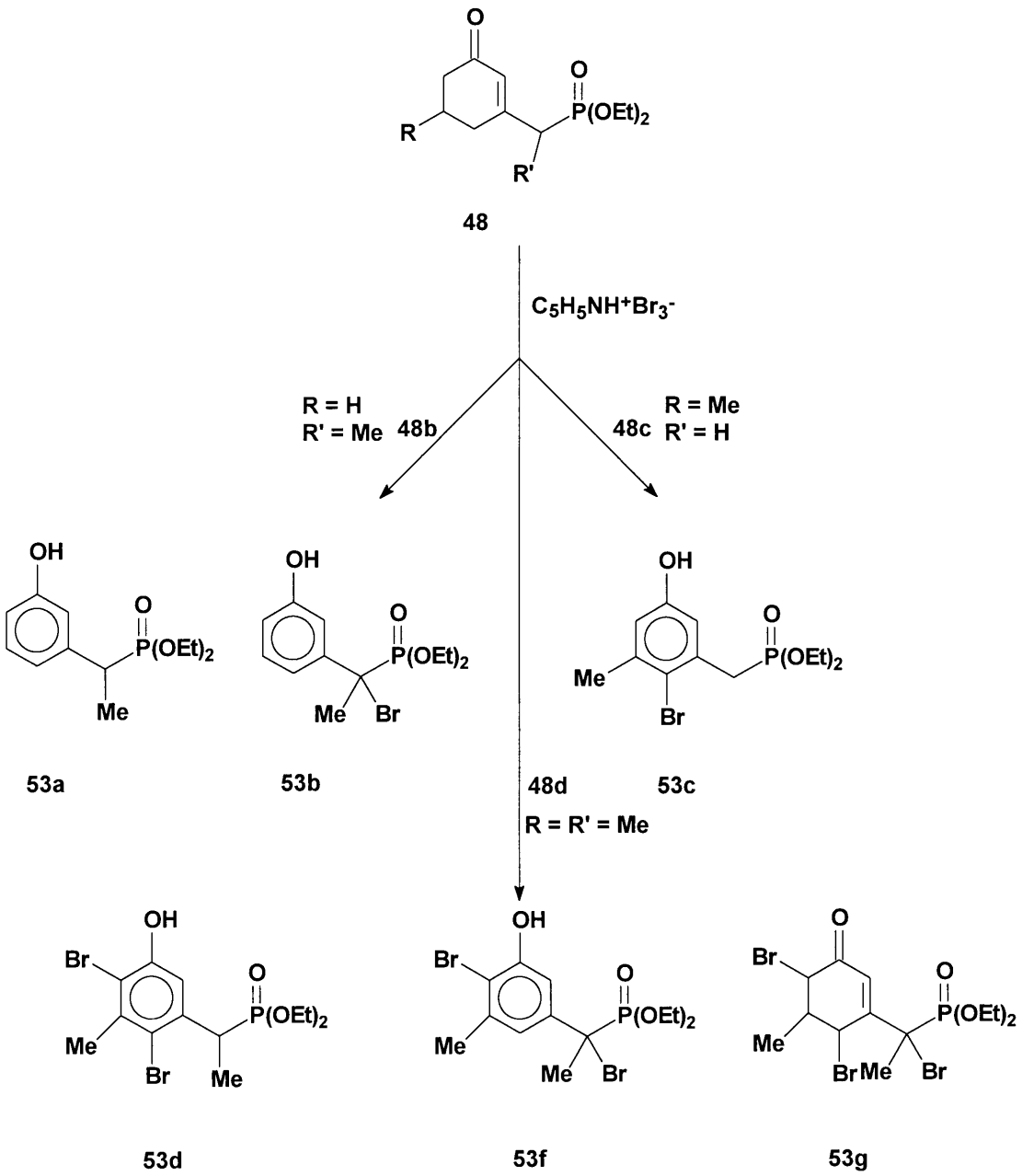
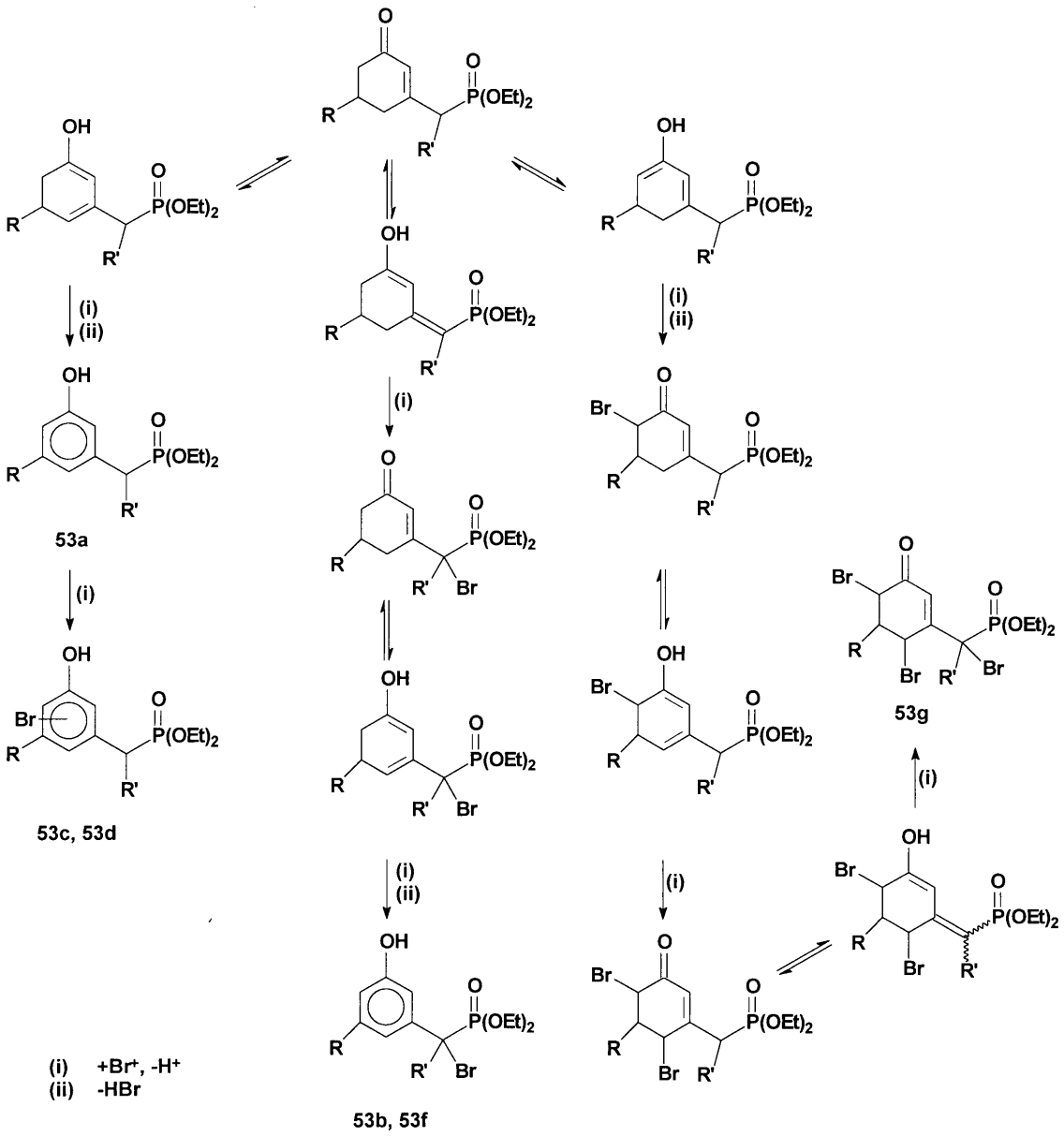
13 L F Fieser and M Fieser, *Reagents for Organic Synthesis*, Wiley, New York, vol. 1, 1967, 967.
14 C Djerassi and C R Scholz, *J. Am. Chem. Soc.*, **70**, 1948, 417.
15 W L Meyer, G B Clemans and R A Manning, *J. Org. Chem.*, **40**, 1975, 3686.



Scheme 34

From these results a general mechanism was proposed[9] for the reaction of (**48**) with pyridinium perbromide. The original Meyer's mechanism applicable to the formation of (**53d**) was used as basis for the mechanism which accounts for all the compounds observed in this work (Scheme **35**).



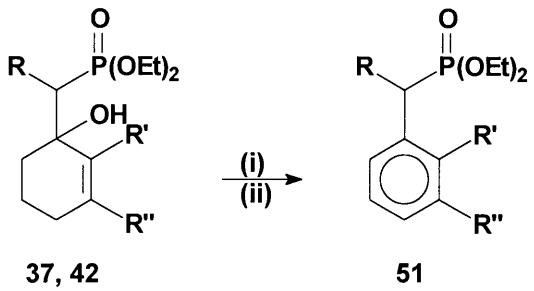
Scheme 35

5.2.3 Aromatisation with Ph_3COH/CF_3CO_2H, $(CF_3CO)_2O$, AcOH

The selectivity and yields of some of the aromatisation reactions discussed in this chapter were found not to be very good. This prompted us to search for an alternative method to bring about the aromatisation of these substrates. The ideal reagent must be inexpensive, react with a wide range of tertiary alcohols and give high yields of the target molecule. Recently Fu and Harvey[16]

[16] P P Fu and R G Harvey, *Tetrahedron Lett.*, **36**, 1974, 3217.

showed that trityl trifluoroacetate (TTFA), generated in situ from triphenylmethanol in trifluoroacetic acid (and a small amount of acid anhydride to mop up any traces of moisture formed), is comparable in reactivity to trityl perchlorate and fluoroborate. The alcohol (**37**) and (**42**) was dissolved in acetic acid containing a mixture of trifluoroacetic acid, trifluoroacetic anhydride and triphenyl methanol. This mixture was kept at reflux temperature overnight. After cooling the mixture was carefully neutralised with NaOH. Normal aqueous workup afforded the respective products. The reaction sequence employed is depicted in Scheme **36**, and results are summarised in Table **12**.

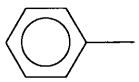
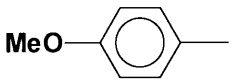
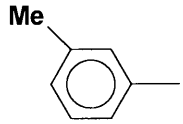
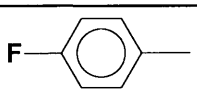


37, 42 **51**

(i) Ph_3COH, CF_3CO_2H, $(CF_3CO)_2O$, AcOH
(ii) reflux, overnight

Scheme 36

Table 12 Aromatisation of (37) and (42)

No	R	R'	R''	% Yield
51a	H	H	CH_3	98.2
51d	H	H	H	86.6
51e	H	CH_3	H	93.2
51f		H	H	81.6
51g		H	H	73.8
51h		H	H	74.9
51i		H	H	88.7

The table shows that under these conditions the tertiary alcohols undergo smooth conversion to their aromatic counterparts. The yields in each case is high and no side products could be detected in the crude products. The product formed as a result of dehydration of the alcohols was the only side product that was occasionally observed. This impurity could be prevented by increasing the reaction time.

5.2.4 Spectroscopic analysis

The compounds discussed in this chapter were isolated and identified by ^{1}H-, ^{31}P- and ^{13}C-NMR spectroscopy. MS-spectra were used to confirm the structures of these compounds. Unfortunately the use of CH analysis proved too inaccurate to be employed as measure for confirmation of the structures of the individual compounds.

The extent of aromatisation was easily followed in the ^{1}H-NMR spectrum where the disappearance of the signals at ≈ 2 ppm (in the aliphatic region) and the appearance of signals at ≈7 ppm (for the aromatic hydrogens) was indicative for the formation of the aromatic analogue of the individual substrates. The differences in the chemical shift values on the ^{31}P NMR spectra were however, not very big. Two signals were observed in the ^{31}P NMR spectra in all cases, one for each diastereomer, *e.g.* compounds (**37e, 42c, 46a, 46b, 46c, 46f**) gave one signal for each diastereomer as illustrated in Figure **10**.

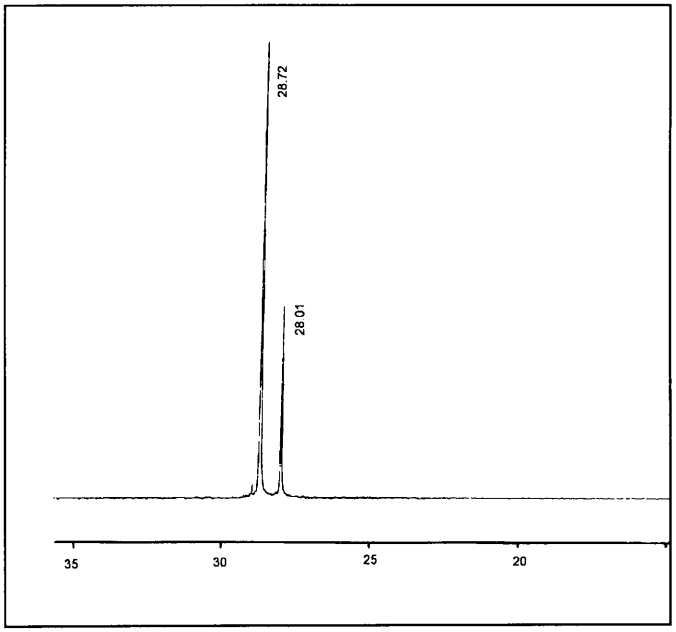


Figure 10 ^{31}P NMR spectrum of (46b, 46b')

Aromatisation of these compounds resulted in the formation of two enantiomers since the chiral centre at the ring was distroyed in the reaction, and this resulted in only one signal being observed in the ^{31}P NMR spectra of these compounds as is demonstrated in Figure **11**. The collapse of the second signal could therefore be used as measure to monitor the course of these reactions.

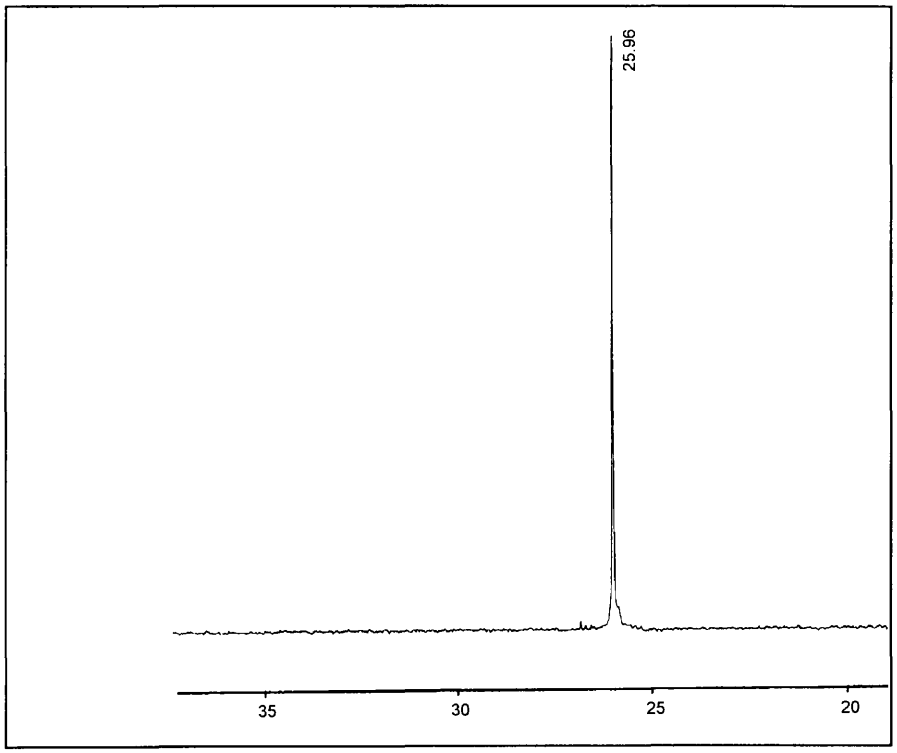


Figure 11 ^{31}P NMR spectrum of (51h)

Some means had to be devised to determine the location of the methoxy substituent in the reactions portrayed in Scheme **32** where the addition of the solvent had occurred. The specific position was obtained in the case of (**52a**) by making use of NOE experiments. In Figure **12** the ^{1}H NMR spectrum of (**52a**) is shown.

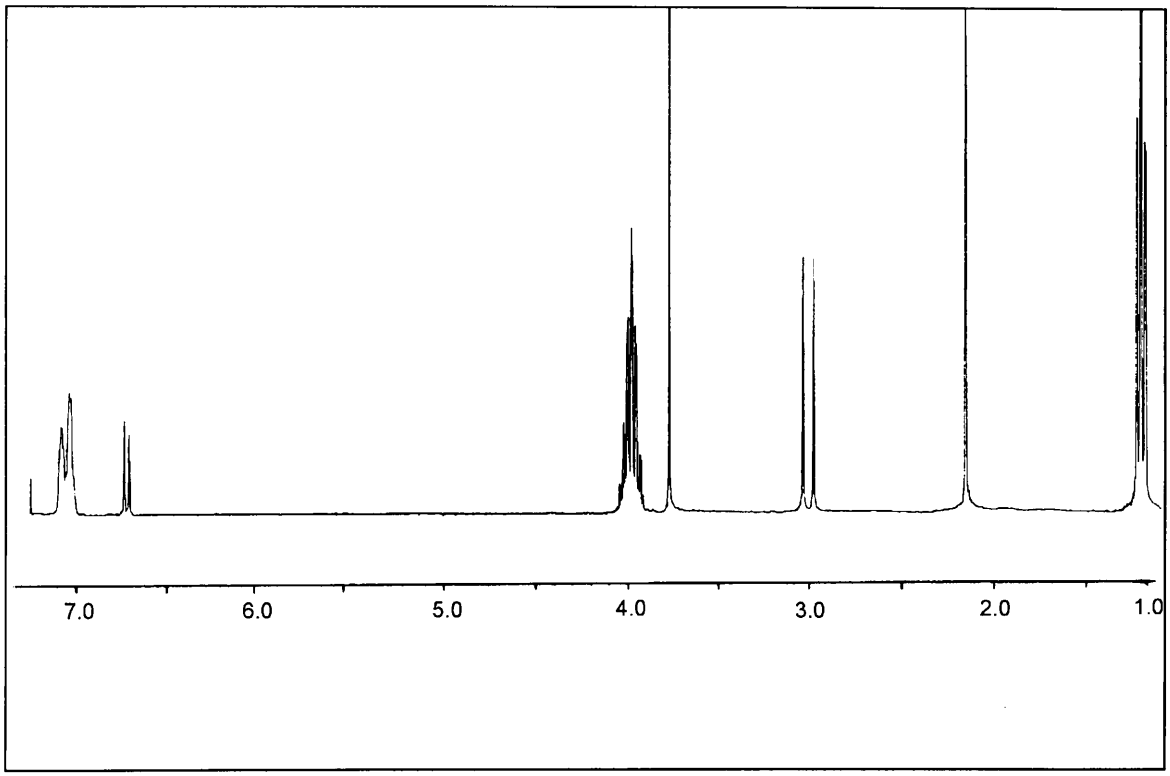


Figure 12 ^{1}H NMR spectrum of (52a)

For example, irradiation of the methoxy signal situated at 3.77 ppm resulted in an NOE effect being observed for only the aromatic hydrogens at C_3 and C_4 as shown in Figure **13**. Since the ring methyl group was unaffected, we could conclude that the methyl and methoxy groups could not be situated close to one another.

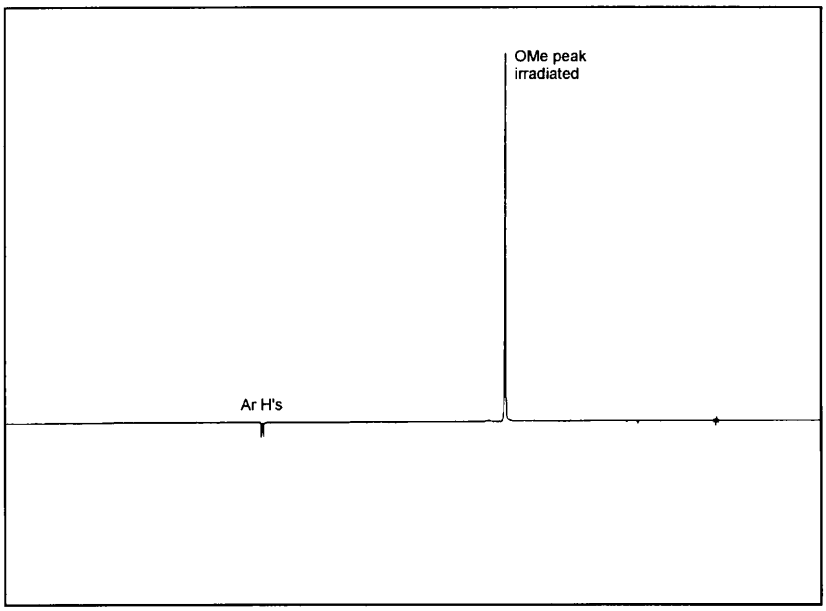


Figure 13 NOE effect of MeO in (52a)

Only the aromatic protons at C_4 and C_6 were affected when the methyl group in (**52a**) was irradiated to confirm the above observation. This effect is illustrated in Figure **14**.

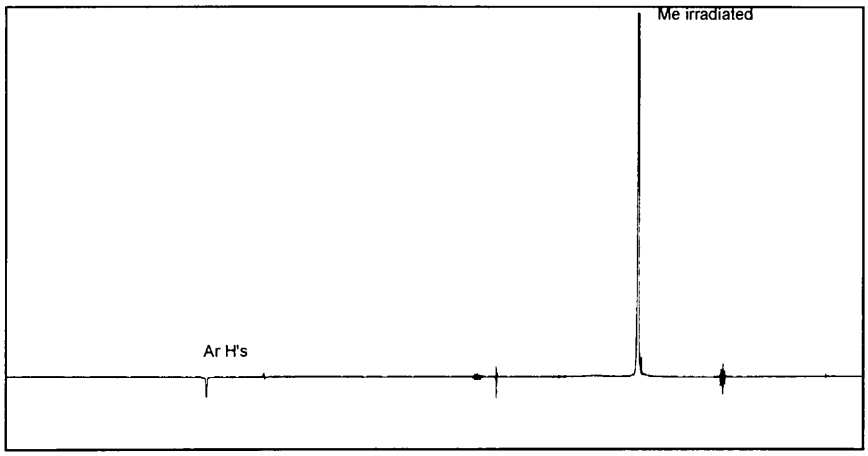


Figure 14 NOE effect of Me in (52a)

The specific structure of (**52a**) was assigned from this information gained from the NOE experiments. The compounds for which inclusion of the solvent had taken place (**52b**) and (**52c**) were assumed to possess analogous structures.

The MS spectra of these compounds gave the following characteristic modes of fragmentation. In all aromatic products either the M^+ or M^++1 peak was observed, each displaying a relatively high intensity. This demonstrates the higher stability of these aromatic derivatives compared to the parent tertiary alcohols where no M^+ peak was observed. The next bond to break was the P-C bond yielding the cyclic fragment of the molecule with no phosphorus component. This peak represented the parent peak in all cases. A fragment at m/z 78 or 81 representing PO_3^+ and $PO_3H_2^+$ respectively was also observed in every spectrum, but the intensity of these peaks was very low.

5.3 Conclusions

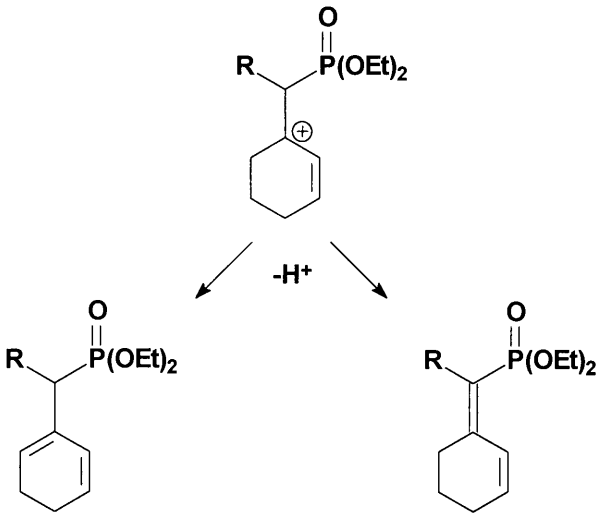
The three different methods studied in this chapter proved useful in achieving aromatisation of the alcohols. It was shown that the iodine in refluxing methanol method, however, can only be used successfully in specific cases, but that it provides a good alternative method for aromatising δ-ketophosphonates as well as 3-chlorocyclohexanols. Its general use is, however, limited in that solvent incorporation is not always desirable. Pyridinium perbromide showed little selectivity and will only be useful in the synthesis of specific target molecules. The last method that was

discussed showed complete selectivity in aromatisation and high yields was obtained in these reactions. This reaction proved to be effective for the conversion of a wide range of cyclic allylic alcohols to their aromatic counterparts.

Transformations of the β-hydroxy-alkylphosphonic esters

6.1 Introduction

The β-hydroxy-alkylphosphonic acid diethyl esters, prepared as described in Chapters **2-4**, are ideal precursors for acid catalysed dehydration leading to conjugated dienes that can undergo further conversions. In the mechanism of this reaction the alcohol is first protonated by the acid. This protonated alcohol then undergoes heterolysis to form the carbocation and water. All the alcohols studied here are tertiary and will therefore readily undergo heterolysis since the tertiary carbocation formed would be very stable. The last step in the reaction involves the removal of a proton, by the conjugate base of the acid, to form the olefinic bond. The orientation of the double bond is determined by the Saytzeff rule[1], and in the case of these β-hydroxy-alkylphosphonic esters the reaction can follow two routes as shown in Scheme **37**.



Scheme 37

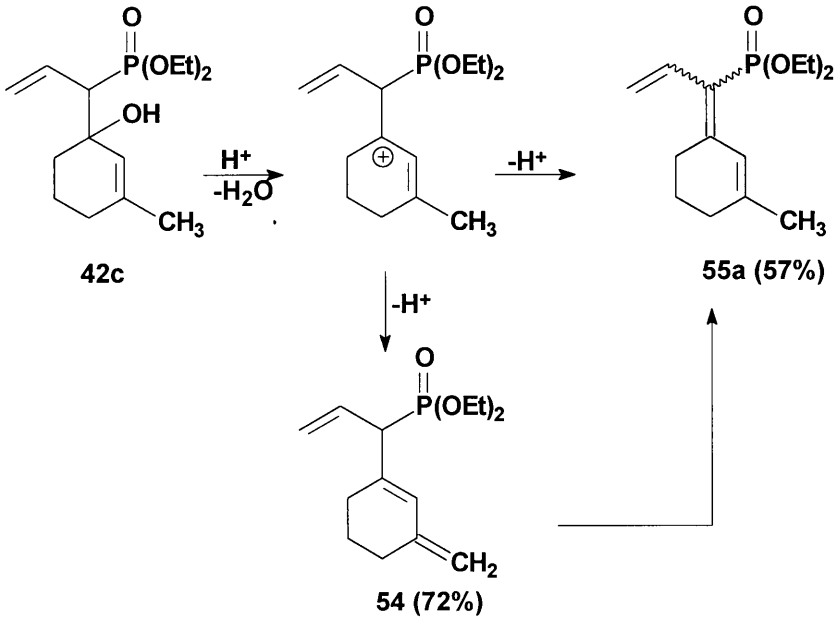
[1] R T Morrison and R N Boyd, *Organic Chemistry, Fourth Ed.*, Allyn and Bacon Inc., London, 1959, 320.

The reaction pathway leading to the endocyclic double bond normally leads to the thermodynamically more stable compound.[2] Therefore, in theory, when the reaction is executed under thermodynamic conditions, it should be possible to convert any kinetic product, formed in the reaction, completely into its isomer, given long enough reaction times.

6.2 Results and discussion

6.2.1 Reaction conditions

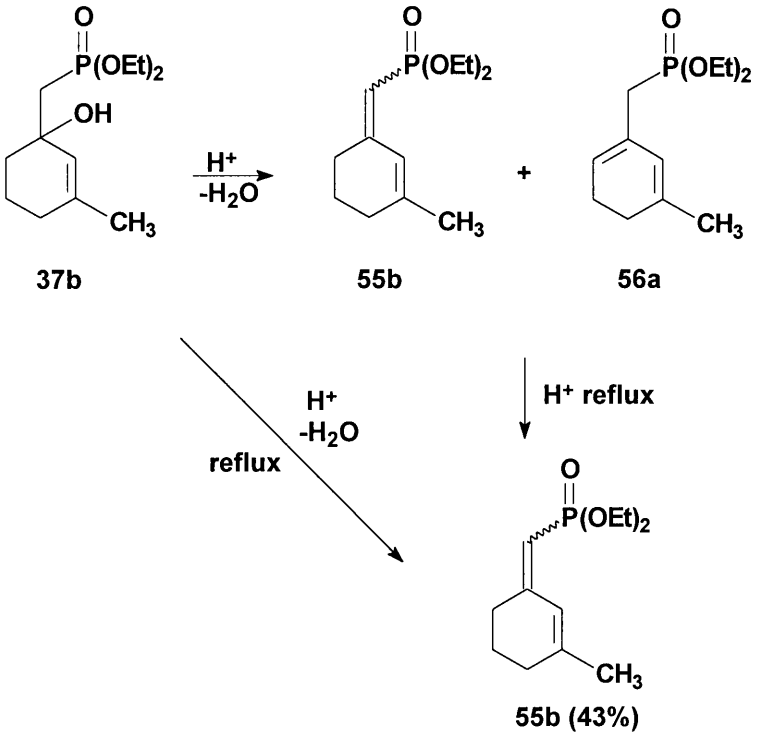
The dehydration reactions of the β-hydroxy-alkylphosphonic acid diethyl esters (**37a-37c, 42c, 46a**) were studied under kinetic as well as thermodynamic conditions. The alcohol (**42c**) was smoothly converted to (**54**) when it was incubated at room temperature in a benzene solution containing a catalytic amount of *p*-toluenesulfonic acid (TsOH) (Scheme **38**). The structure of the allylic phosphonic acid diethyl ester was retained in this reaction. When the reaction of (**42c**) was carried out under reflux, or when the benzene solution of (**54**) was heated under reflux in the presence of TsOH, then the triene (**55a**) was isolated as a 1:1 mixture of two stereoisomers.



Scheme 38

[2] E L Eliel, S H Wilen and L N Mander, *Stereochemistry of Organic compounds*, Wiley, New York, 1994, 737.

No evidence for the deprotonation of the 3-methyl group, leading to the analogue of (**54**), could be observed when (**37b**) was subjected to the same reaction conditions as those employed to prepare the trienes in Scheme **38**. At room temperature a mixture of exocyclic (**55b**) and endocyclic (**56a**) dienes was formed. The (**55b**) isomer (*E*/*Z* ≈ 1.3:1) was the only product obtained when the substrate (**37b**) was treated at reflux temperature or by heating the mixture of (**55b** and **56a**) (Scheme **39**).

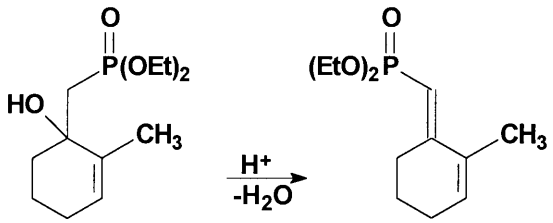


Scheme 39

The product obtained as a result of the endocyclic dehydration (**56a**) was not isolated and fully identified, since it was a minor product in the reaction, but its presence was clearly demonstrated in the ^{31}P NMR spectrum of the crude reaction mixture. The ^{31}P NMR chemical shifts of the vinylic and allylic phosphonic acid diethyl esters have previously been demonstrated to differ by ≈ 10 ppm. While both stereoisomers of (**55b**) give signals typical for vinylic phosphonic acid diethyl esters (δ_P 20.5, 19.3) the signal for (**56a**) (δ_P 27.5) corresponds favourably to the range of the allylic phosphonic acid diethyl esters. The isolation of the vinylic phosphonic acid diethyl ester (**55b**) as the final product provides vital information on the stabilising effect the phosphoryl function has on an adjacent olefinic bond. It is known that methylenecyclohexane is thermodynamically less stable than 1-methylcyclohexene by *ca* 3 kcals/mol (25°C).[2] For the corresponding pair of dienes (1-methylene-2-cyclohexene *vs* 1-methyl-2,6-cyclohexadiene),

combustion measurements showed that the endocylic isomer is more stable by as much as 11 kcals/mol.[3] The fact that (**55b**) is preferred over (**56a**) gives evidence for the considerable stabilising effect of the PO_3Et_2 functionality, situated on the terminal carbon atom of a conjugated diene. This conclusion may not be equally valid for the monoene systems since it was shown[4] that under conditions of prototropic equilibrium, diethyl 1-cyclohexenylmethylphosphonate represents 100% of the equilibrium mixture, with no exocyclic isomer, phosphonomethylene-cyclohexane being detected.

This stabilising effect of the PO_3Et_2 functionality, in the dehydration of alcohols, was confirmed in the reaction of (**37c**), which yielded the exocyclic diene (**55c**) (Scheme **40**) exclusively when the reaction was performed under reflux conditions. In this case however, as a result of steric hindrance introduced by the 2-methyl, only one *E*-stereoisomer was formed.



37c **55c (80%)**

Scheme 40

Dehydration of alcohol (**37a**) took a slightly different course. Conducting the reaction at room temperature resulted in the formation of some of the diene product (**55d**, *E*/*Z* 1:1), but the major product isolated from the reaction mixture proved to be the rearranged allylic alcohol (**57**). When this mixture was treated under reflux, complete dehydration occurred affording a mixture of exocyclic (**55d**, major) and endocyclic dienes (**56b, 56c,** minor, not isolated but identified from the ^{31}P NMR spectrum of the crude mixture) (Scheme **41**).

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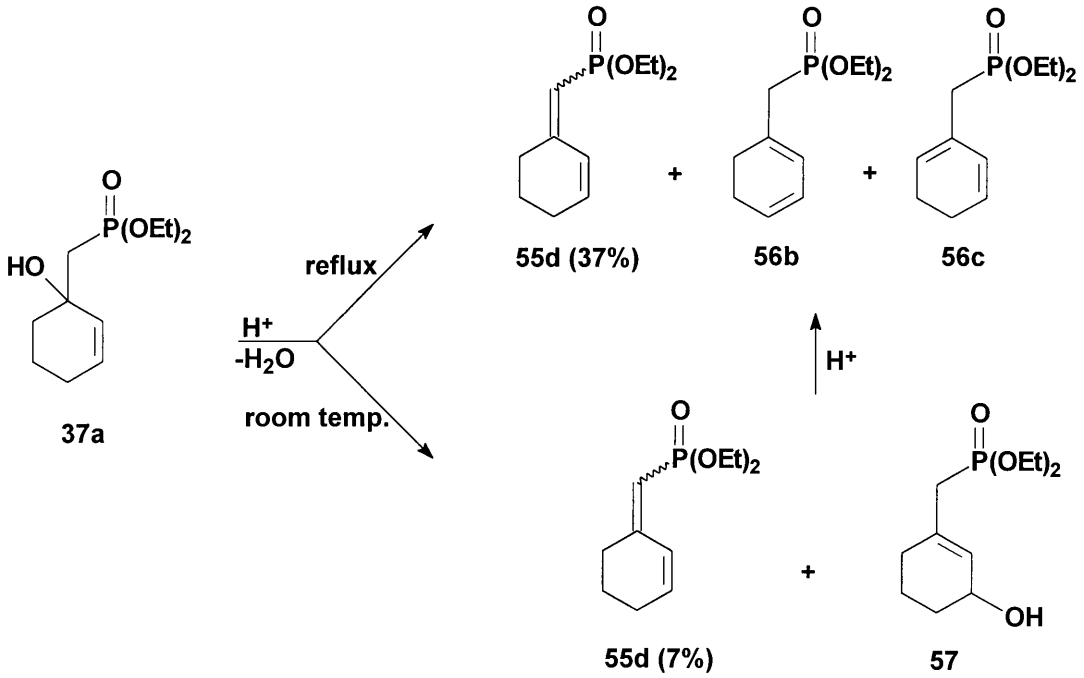
3 O S Pascual and E Almeda, *Philippine At. Energy Comm. [Rept]*, PAEC(D) CH-634, 1993; *Chem. Abstr.*, **60**, 1964, 10521h.

4 J P Gerber, T A Modro, C C P Wagener and A Zwierzak, *Heteroatom Chem.*, **2**, 1991, 643.



Scheme 41

Almost 30 years ago, Corey and Crouse[5] recognised the synthetic potential of the acid catalysed rearrangement of tertiary allylic alcohols of the cyclohex-1-en-3-ol system. Acidic treatment of 3-methyl-3-hydroxy-5-phenyl-pent-1-ene, on the other hand, only gives the dehydration products (isomeric dienes) with no rearranged (primary) alcohol.[6] Öhler and Zbiral[7] investigated the synthetic potential of the rearrangements of α-hydroxyallylic phosphonates to the γ-hydroxyvinylic products (trapped as acetate derivatives).

Warren and coworkers[8] noticed that elimination (dehydration) can interfere with this rearrangement after an extensive study on the stereochemical control in the allylic arrangement of alcohols containing the diphenylphosphinoyl group in the β-position. For the 2-benzylidenecyclohexanone derivatives, the authors observed exclusive elimination products (the olefinic bond not moving away from the phenyl group). 2-Benzylidene-1-(diphenylphosphinoylmethyl)cyclohexanol on the other hand yielded only the (*E*,*E*)-6-benzylidene-1-(diphenylphospinoylmethyl)cyclohexane, *i.e.* the product of the endocyclic

5 E J Corey and D Crouse, *J. Org. Chem.*, **33**, 1968, 298.
6 K Narasaka, H Kusama and Y Hayashi, *Tetrahedron*, **48**, 1992, 2059.
7 E Öhler and E Zbiral, *Chem. Ber.*, **124**, 1991, 175.
8 J Clayden E W Collington, J Elliot, S J Martin, A B McElroy, S Warren and D Waterson, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1849.

dehydration. No product with the exocyclic double bond, in conjugation with the $Ph_2P(O)$ group, could be detected in the latter case. The preferential formation of the exocylic dienes (**55a-55d**) was therefore rather unexpected and possible reasons for this regioselectivity need to be investigated in further detail.

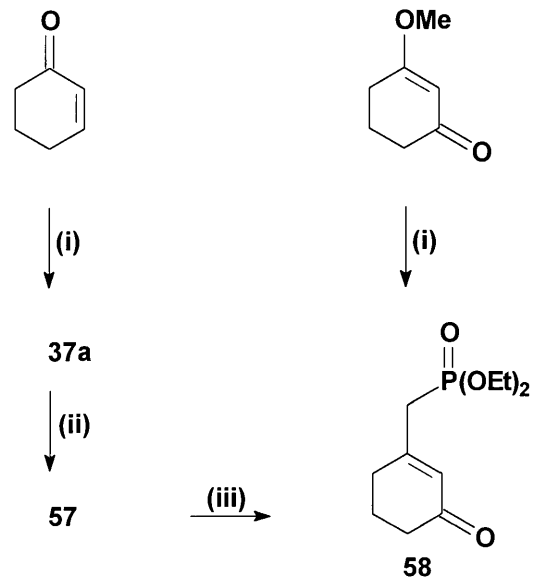
The secondary alcohol (**57**) was isolated and could be oxidised to the corresponding cyclohexanone derivative (**58**). The first method that was employed in an attempt to oxidise the secondary alcohol was by using DMSO and acetic anhydride. This method which is closely related to the "Pfitsner-Moffatt" method[9,10] is used for the oxidation of primary and secondary alcohols to their corresponding carbonyl compounds. Unfortunately this reaction proved unsuccessful and no ketone functionality was obtained.

Manganese dioxide has been considered as a specific reagent for the oxidation of allylic alcohols to allylic aldehydes and ketones.[11] It has been employed in the oxidation of vitamin A_1 and other polyene alcohols.[12,13,14,15,16,17] A large excess of oxidising agent was used in this reaction since it was demonstrated by Henbest[18] and later independently confirmed by Gritter[11] and Evans[19] that the yield of this oxidation reaction is strongly dependent on the quantity of oxidising agent used during the synthesis. The mechanism of this oxidation has not yet been elucidated, but Ball *et. al.*[20] have postulated that the reaction is triphasic, *i.e.* adsorption of the substrate being followed by oxidation and subsequent desorption of the product. The conditions for the reaction discussed here have not been optimised and small changes in the reaction conditions should lead to improved yields. Neutral activated manganese dioxide, prepared according to the method described by Henbest *et. al.*[18] , was added to the alcohol (**57**), dissolved in chloroform. The

9 J D Albright and L Goldman, *J. Org. Chem.*, **30**, 1965, 1107.
10 J D Albright and L Goldman, *J. Am. Chem. Soc.*, **87**,1965, 4214.
11 R J Gritter an T J Wallace, *J. Org. Chem. Soc.*, **24**, 1959, 1051.
12 J Attenburrow, A F B Cameron, J H Chapman, R M Evans, B A Hems, A B A Jansen and T Walker, *J. Chem. Soc.*, 1952, 1094.
13 K R Bharucha, *J. Chem. Soc.*, 1956, 2446.
14 E A Braude and W F Forbes, *J. Chem. Soc.*,1951, 1755.
15 E A Braude and J A Coles, *J. Chem. Soc.*, 1952, 1430.
16 B C Weedon and R J Woods, *J. Chem. Soc.*, 1951, 2687.
17 N L Wendler, H L Slates, N R Trenner and M Tishler, *J. Am. Chem. Soc.*, **73**, 1951, 719.
18 H B Henbest and A Thomas, *J. Chem. Soc.*, 1957, 3032.
19 R M Evans, *Qaurt. Rev.*, 1959, 61.
20 S Ball, T W Goodwin and R A Morton, *Biochem. J.*, **42**, 1948, 516.

mixture was stirred at room temperature for 4 hours. After filtration and evaporation of the solvent the product could be purified by column chromatography.

It was demonstrated earlier that ketone (**58**) can be obtained from the addition-elimination reaction between lithiated methyl-phosphonic acid diethyl ester and 3-methoxycyclohexenone.[21] The preparation of (**58**) via both routes are shown in Scheme **42**. It should however be noted that the relative positions of the C_1 and C_3 atoms in the cyclohexenone skeleton is retained in one and reversed in the other route.

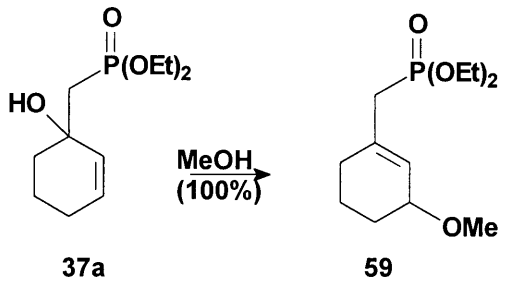


(i) $LiCH_2PO_3Et_2$; H_3O^+
(ii) TsOH
(iii) MnO_2

Scheme 42

Allylic rearrangement, free of any elimination, was observed when the alcohol (**37a**) was heated under reflux in pure methanol, yielding 100% of the corresponding allyl ether (**59**) (Scheme **43**).

[21] M J Maphelele and T A Modro, *J. Org. Chem.*,**60**, 1995, 8236.



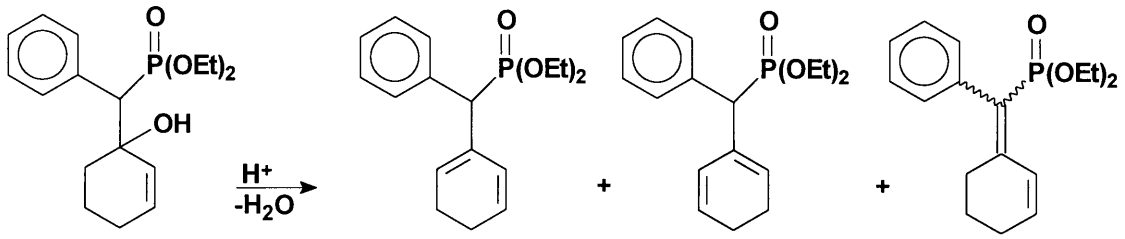
37a 59

Scheme 43

Formation of the rearranged allylic ethers from allylic alcohols and alkanols, as reported by Henbest *et. al.*[22], have been known since 1945. The reactions were performed in the presence of strong acids, the driving force being the formation of a conjugated system of π-bonds. The driving force for the reaction displayed in Scheme **43** could be the higher degree of substitution present at the olefinic bond in the product. This conclusion is supported by the fact that even prolonged refluxing of (**37b**) in methanol resulted in the recovery of the unchanged substrate. It would therefore seem that the steric accessibility of the tertiary *vs* the secondary carbons in the intermediate carbocations, derived from (**37b**) and (**37a**), by the solvent is important for the rearrangement to occur. The reluctance of the substituted sp^2 carbon 3 of (**37b**) to be converted to an sp^3 centre can also be given forward as reason for the lack of reaction observed in this case.

(1-Hydroxy-cyclohex-2-enyl)-phenyl-methylphosphonic acid diethyl ester (**46a**) was used as representative example for the reactions of all aryl-methylphosphonic acid diethyl esters. The reaction was executed at reflux temperature and four products (**55e, 56d, 56e**) were obtained as shown in Scheme **44**. The dehydration products, the endocyclic dienes (**56d**) and (**56e**) were not isolated and fully identified, but their presence could be concluded from the ^{31}P NMR spectra (δ_P 25.48, 26.06). One of the exocyclic dienes (**55e**) was isolated by column chromatography and the full structure of this isomer was determined.

22 I M Henbest, E R H Jones and T C Owen, *J. Chem. Soc.*, 1957, 4909.



46a 56d 56e 55e

Scheme 44

6.2.2 Spectroscopic analysis

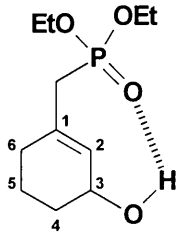
All compounds discussed in this chapter were isolated in pure state and identified by ^{1}H, ^{31}P, ^{13}C and HETCOR NMR spectroscopy. The MS spectra of individual compounds were used to confirm the structure of each compound and IR spectra were recorded when necessary.

Compound (**54**) was obtained as a mixture of two stereoisomers displaying two signals on the ^{31}P NMR spectrum. Unfortunately separation of these isomers proved impossible and the chemical shift values of the mixture is only reported. The characteristic signal of the 3-methyl group in the substrate (singlet at δ_C 23.4, quartet in the ^{1}H-coupled spectra) was absent in the product, and replaced by an additional signal in the olefinic range (δ_C 110.6, triplet in the ^{1}H-coupled spectrum).

The conjugated triene (**55a**) and dienes (**55b, 55e**) were obtained as mixtures of stereoisomers and column chromatography proved successful in the separation of these isomers. The $^{3}J_{CP}$ coupling to C_2 and C_6 was again used to determine the relative orientation around the double bond between C_α and C_1. In (**55a**) and (**55b**) the values obtained for the $^{3}J_{CP}$ coupling to C_2 and C_6 were ≈ 9 and ≈ 20 Hz, respectively. From this we can deduce that the phosphoryl group must be situated trans to C_6, thereby displaying a larger value for $^{3}J_{CP}$, making this the *Z* isomer. The respective values for the $^{3}J_{CP}$ of the *E* isomer (**55a', 55b', 55e'**) were determined as ≈ 6 Hz for C_6 and ≈ 22 Hz for C_2.

In the formation of (**55c**) only one stereoisomer was obtained and the $^{3}J_{CP}$ coupling to C_2 and C_6 was determined to be equal to 23.9 Hz and 6.9 Hz respectively, demonstrating high *E* stereoselectivity in this reaction.

In the reaction of (**37a**) three products were formed *i.e.* (**55d, 55d'**) and (**57**). The two isomers (**55d**) and (**55d'**) were however obtained in very low yields and it was only possible to isolate and record the spectral data of the *E* isomer. The relative configuration of this isomer was confirmed using the $^{3}J_{CP}$ values obtained from the ^{13}C NMR spectrum. The presence of the other isomer can be easily observed on the ^{31}P NMR spectrum of the crude reaction mixture. The structure of compound (**57**) makes intramolecular H-bonding possible, thus restricting the rotation around the C_α-C_1 bond, as shown below.



57

This effect is reflected by the large value of the $^{3}J_{CP}$ to C_6 (31.3 Hz). The molecule is therefore confined to assume the configuration where the phosphorus atom is *trans* to C_6.

This H-bonding effect is no longer present in (**58**) and the absence of $^{3}J_{CP}$ observed for C_6, in the spectrum of this compound as well as the small $^{3}J_{CP}$ value for C_2 (11.1 Hz), confirms that free rotation is possible around the C_α-C_1 bond.

The IR spectra of (**57**) and (**58**) displayed the signals characteristic for the P=O ≈ 1200 cm^{-1}, hydroxyl ≈ 3400 cm^{-1} (**57**) and carbonyl ≈ 1700 cm^{-1} (**58**) groups.

In the MS spectra of (**54**) and (**55a-55d**) the M^+ peak could be observed. The next mode of fragmentation was where the P-C bond broke, eliminating the diethylphosphoric acid and yielding the expected Wittig product. This peak was observed as the base peak in each of these compounds. A peak at m/z 79 representing PO_3^+ was also evident in all spectra. In the spectrum

of (**57**) the intensity of the M^+ peak was very low. Again, as in the case of the tertiary alcohols, a much stronger signal was obtained for the (M^+-H_2O). The Wittig product was observed as the base peak and the peak at 79 was again evident. For (**58**), as expected, a much stronger signal was observed for the M^+ peak. The product where the P-C bond had broken, at m/z 108 was the next mode of fragmentation yielding the base peak. The peak at 79 was again evident.

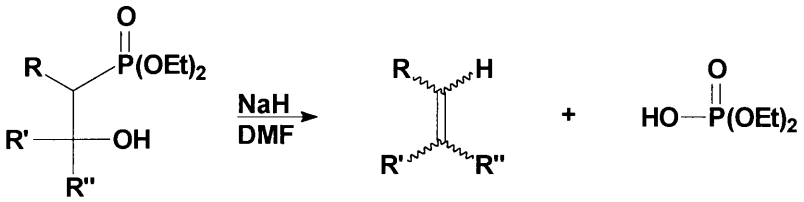
6.3 Conclusions

As expected dehydration of all the tertiary alcohols occurred readily under relatively mild conditions. It was however found that the effect the phosphoryl group exerted on the regioselectivity of the dehydration was pronounced. Exocyclic double bond formation was observed as the thermodynamic product in each case. When cyclic systems, without a group at the 3-position in the ring, were treated with TsOH at ambient temperature rearrangement of the hydroxyl group was observed.

Reactions involving trimethylsilyl-stabilised carbanions

7.1 Wadsworth-Emmons reaction

The Wadsworth-Emmons reaction provides a convenient route for the preparation of olefinic derivatives from β-hydroxy-alkylphosphonic acid diethyl esters. This reaction, shown in Scheme **45**, has found a wide range of application in literature.[1,2,3]



60

Scheme 45

The stereochemistry of the groups R, R' and R" are determined by the nature of the stereochemistry of the β-hydroxy-alkylphosphonate (**60**). However, some difficulties were encountered when this reaction sequence was employed for some of the β-hydroxy-alkylphosphonates prepared thus far.

Treatment of 1-(1-hydroxy-3-methylcyclohex-2-enyl)-allyl-phosphonic acid diethyl ester (**42c**) with sodium hydride in DMF at room temperature for 3 hours yielded the expected olefin (**61**) (Scheme **46**), but removal of the DMF from the newly formed 3-allylidene-1-methyl-cyclohexene (**61**) proved troublesome since the boiling points of the olefin and that of the DMF do not differ sufficiently to promote separation.

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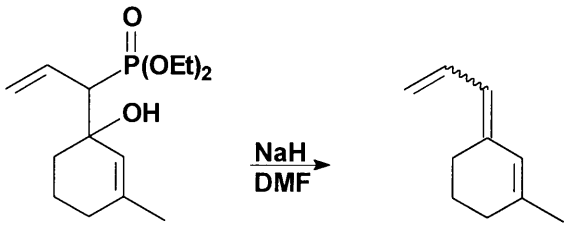
1 J Petrova, N G Vassilev and M Kirilov, *Phosphorus, Sulfur, and Silicon*, **47**, 1990, 457.
2 J Petrova, S Momchilova and N G Vassilev, *Phosphorus, Sulfur, and Silicon*, **68**, 1992, 45.
3 N G Vassilev, J Petrova and M Kirilov, *Phosphorus, Sulfur and Silicon*, **85**, 1993, 49.

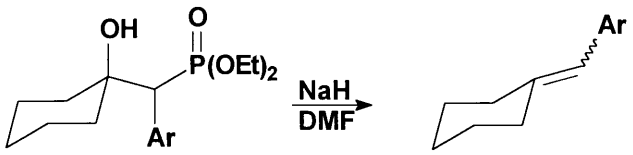


42c 61

Scheme 46

It was therefore decided not to utilise any of the other β-hydroxy-alkylphosphonates, prepared in Chapter **2**, as substrates for this reaction since this problem of isolation would always be encountered.

The β-hydroxy-arylmethylphosphonates described in Chapter **4** should, however, yield olefins with high enough boiling points to facilitate their separation from the solvent mixture. Only the substrates were, however, recovered when (1-hydroxy-cyclohex-2-enyl)-phenyl-methyl-phosphonic acid diethyl ester (**46a**) or (4-fluoro-phenyl)-(1-hydroxy-cyclohex-2-enyl)-methyl-phosphonic acid diethyl ester (**46f**) where subjected to the same reaction conditions. Attempts to change the solvent from DMF to THF or dioxane were also unsuccessful in bringing about any reaction even after prolonged reaction times. To prove that no reaction was indeed taking place the reaction of (**46a**) was repeated. No signs of any diethyl phosphoric acid could be detected in the ^{31}P NMR spectrum of the DMF and water fraction from the reaction mixture. It can therefore be concluded that the Wadsworth-Emmons reaction had failed to proceed to any significant degree with these substrates. These results are contradictory to those obtained by Petrova *et. al.*[3] where they have shown that the Wadsworth-Emmons reaction conditions are effective in converting (1-hydroxy-cyclohexyl)-phenyl-methyl-phosphonic acid diethyl ester (**62**) to cyclohexylidene methyl benzene (**63**) as shown in Scheme **47**.



62 63

Scheme 47

The reason for this discrepancy is not clear at this stage. The only reason that can be put forward to explain this phenomena is that the orientation of the relevant groups are not correct for the Wadsworth-Emmons reaction to take place. In order for elimination of the phosphoryl group to occur, both the phosphoryl and hydroxyl groups have to be co-planar. Steric factors could therefore be responsible for preventing this to occur in some cases, thus giving rise to the stability of the β-hydroxy-arylmethylphosphonates.

The fragmentation pattern of the MS spectra of the aryl-methylphosphonic acid diethyl esters, discussed in Chapter **4**, is in line with these results since the peaks representing the expected Wittig product are either absent or present with very low intensities. This suggests again the low probability for this reaction to occur.

7.2 Peterson olefination reaction

The most frequently used method for the conversion of carbonyl compounds to their corresponding olefinic derivatives involves phosphorus substituted carbanions. This however, does not constitute the only possible route to bring about the desired transformation. Both boron-substituted[4] and sulphur-substituted[5] carbanions have been shown to be effective as olefin-forming reagents.

Another alternative to the Wittig reaction is the Peterson olefination reaction.[6] Silicon is similar to phosphorus since it:

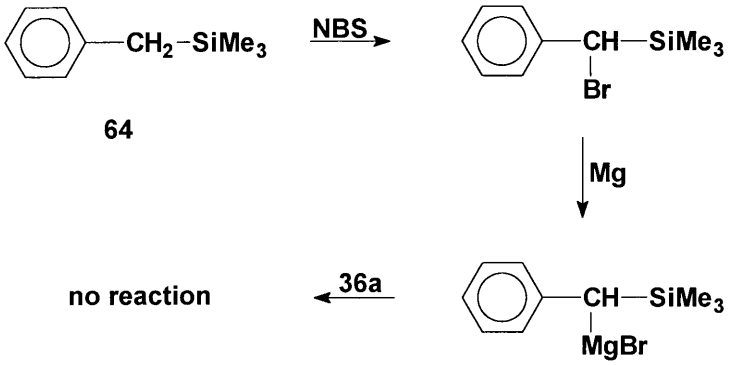
(i) is readily attacked by alkoxides,
(ii) forms strong bonds with oxygen, and
(iii) has *d* orbitals which can conceivably enter into pentacovalent bond formation.[7]

The Peterson olefination has been shown in several cases to be superior to the conventional Wittig reaction due to the higher reactivity of α-silyl carbanions.[8,9] No examples could be

4 G Cainelli, G Dal Bello and G Zubiani, *Tetrahedron Lett.*, 1966, 4315.
5 E J Corey and T Durst, *J. Am. Chem. Soc.*, **88**, 1966, 5656.
6 D J Peterson, *J. Org. Chem.*, **33**, 1968, 780.
7 A G Brook, G E LeGrow and D M MacRae, *Can. J. Chem.*, **45**, 1967, 239.
8 R K Boekman and S M Silver, Tetrahedron Lett., 1973, 3497.

obtained for the addition of silyl carbanions to α,β-unsaturated ketones. Saturated ketone derivatives have, however, been investigated extensively and these reaction procedures were therefore used as models for the reaction of the benzyl trimethylsilane carbanion with 2-cyclohexen-1-one (**36a**).

Two possible methods were investigated for the preparation of the specific β-silylcarbinols. The first method was implemented by Peterson and involves the formation of the Grignard salt of the silane which is then used in the reaction with the carbonyl compound.[6] In their report they showed that the carbinols were obtained in fair yield and that the magnesium alkoxides were not prone to undergo spontaneous elimination. Only the unchanged substrate was obtained when the same reaction sequence (Scheme **48**) was used on (**36a**). The benzyltrimethylsilane (**64**) was dissolved in CCl_4 containing NBS. This mixture was kept at reflux temperature for 3 hours before the product was purified by distillation yielding 56% of a colourless oil. This oil was dissolved in diethyl ether and reacted with magnesium to form the Grignard intermediate. After the addition of the reagent was completed the mixture was refluxed for a further hour to ensure complete reaction. The ketone (**36a**) in diethyl ether was added to the silyl Grignard reagent in diethyl ether. This mixture was refluxed for 4.5 hours. The reaction mixture was then poured onto ice containing ammonium chloride. Aqueous workup, however, showed that no significant reaction had occurred.



Scheme 48

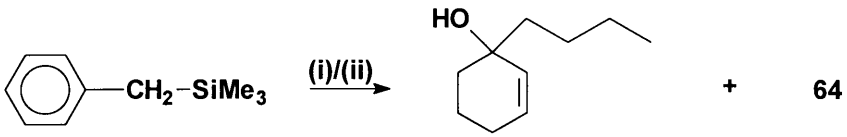
The other method involved the lithiation of the benzyltrimethylsilane (**64**) followed by addition of the α,β-unsaturated ketone (**36a**). Peterson has found[6] that (**64**) was relatively unreactive

---

9 K Shimoji, H Taguchi, K Oshima, H Yamamoto and H Nozaki, *J. Am. Chem. Soc.*, **96**, 1974, 1620.

towards *n*-butyllithium, but that it could be readily metalated by the use of the *n*-BuLi·TMEDA complex. The lithiated complexes thus prepared were then used successfully in the reaction with carbonyl complexes. In our reaction *n*-BuLi was dissolved in THF. To this solution cooled at -78°C was added dropwise with stirring a solution of (**64**) dissolved in THF. The resulting solution was stirred at -78°C for one hour. The electrophile (**36a**) dissolved in THF was added and the mixture was kept at -78°C for an additional two hours before an aqueous solution of ammonium chloride was added. Aqueous workup afforded some products which where then purified and characterised.

The reluctance of the formation of the anionic species of (**64**) with *n*-BuLi alone was confirmed, but it was found that the *n*-BuLi·TMEDA complex was also unable to bring about any significant reaction of (**36a**) to any extent. The only reaction that was observed in both cases involved the 1,2-addition of the butyl group as shown in Scheme **49**, yielding 1-hydroxy-1-butyl-cyclohex-2-ene (**65**).



64 **65**

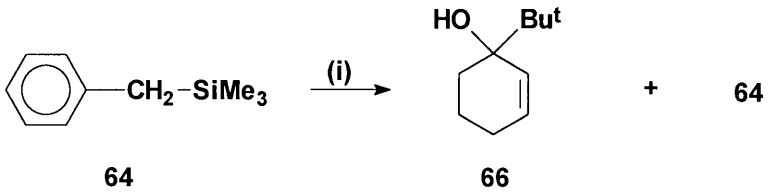
(i) nBuLi, 36a
(ii) nBuLi, TMEDA, 36a

Scheme 49

Chan *et. al.*[10] have shown that lithiation with *n*-BuLi proceeds smoothly in the presence of HMPA. The same procedure, however, proved unsuccessful in bringing about any reaction between (**64**) and (**36a**) and the same reaction sequence as depicted in Scheme **49** was observed.

In order to ensure that lithiation was indeed occurring it was decided to repeat the reaction shown in Scheme **49**, but to use *t*-BuLi in HMPA instead. This reaction proceeded in the similar fashion in that only the addition of the t-butyl group occurred and the product (**66**) was isolated in this reaction as shown in Scheme **50**.

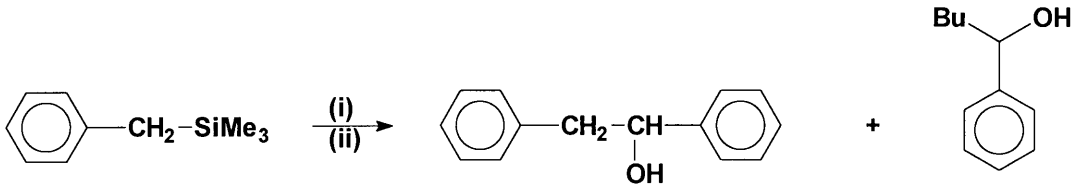
[10] T H Chan, E Chang and E Vinokur, *Tetrahedron Lett.*, **14**, 1970, 1137.



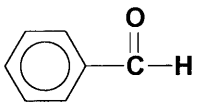
(i) t-BuLi, HMPA, 36a

Scheme 50

The formation of (**66**) and (**65**) instead of the expected condensation of (**64**) with (**36a**) can be a result of a slow lithiation of the silanyl precursor (**64**). In such a case, the base used (*n*-BuLi or *t*-BuLi) would also behave as a nucleophile, reacting according to the addition mechanism with the keto group of (**36a**). It was thus decided to study the reaction of lithiated (**64**) with benzaldehyde. The aldehyde functionality, being a stronger electrophile than (**36a**) should ensure the reaction of any nucleophile formed during the reaction. The reaction and its products are shown in Scheme **51**.



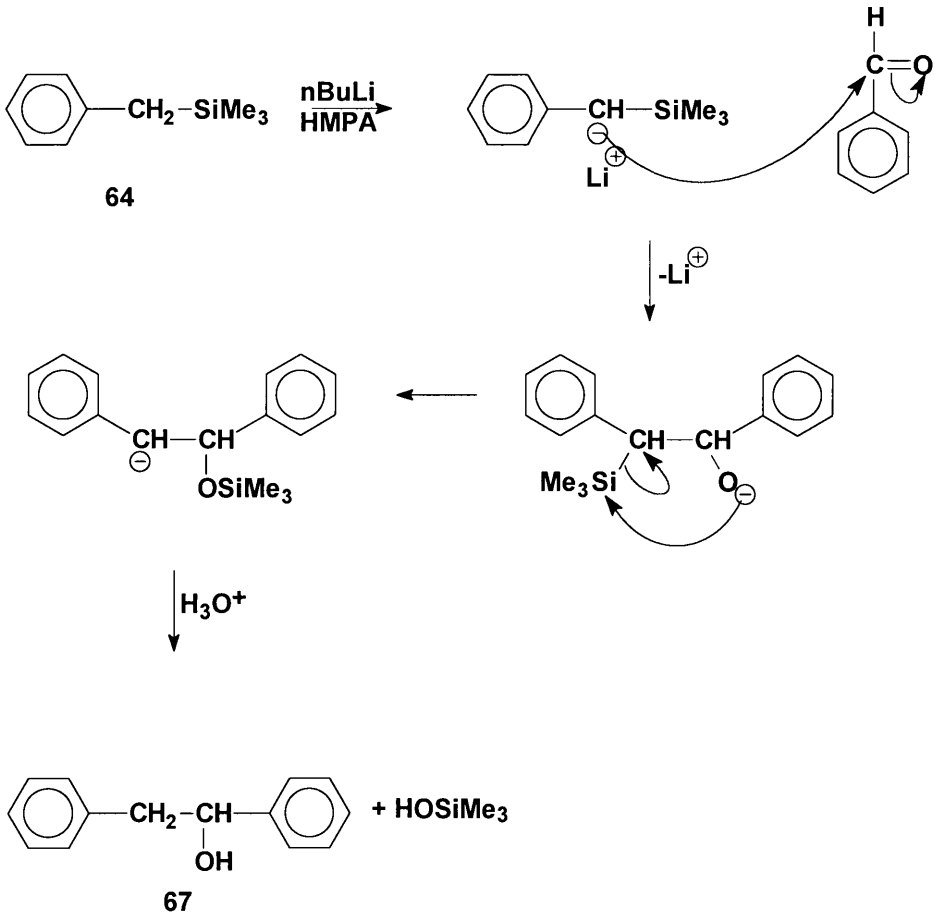
(i) n-BuLi, HMPA

(ii) 

Scheme 51

The major reaction product, was found to be the 1,2-diphenylethanol (**67**), thus the product of the benzylation of benzaldehyde, not stilbene - the expected product of Peterson olefination. The structure of (**67**) was established unambiguously, and because during the workup care was taken to remove all solvents at a temperature not higher than ambient, the alcohol (**67**) did not undergo spontaneous dehydration, driven by the thermodynamic stability of stilbene. No olefinic product was, however, observed in the reaction product. The second alcohol 1-phenylpentanol, resulted from the competitive addition of BuLi to benzaldehyde. This product could not be isolated by

column chromatography pure enough to ensure its unambiguous identification. Formation of (**67**) (instead of stilbene) was a surprising result, and we propose the following mechanism for the observed reaction (Scheme **52**).



Scheme 52

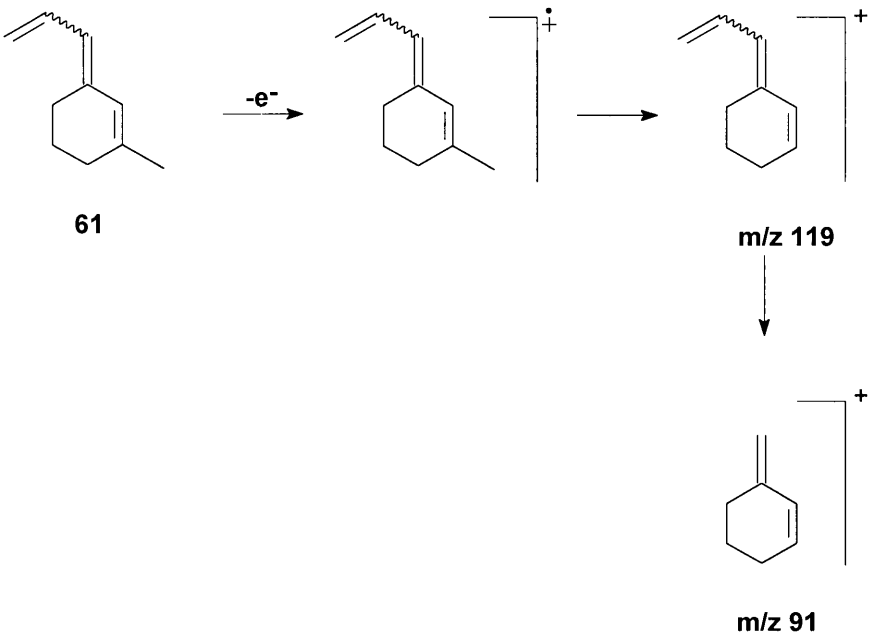
During the reaction deprotonation of the nucleophile occurs in the first step. This is followed by 1,2 attack of the nucleophile on the aldehyde leading to the precursor for the Peterson's reaction. However, before the olefination reaction occurs 1,3 migration of the silicon group takes place, yielding the benzylic carbanion, which on acidic workup affords (**67**) in good yield. This reaction therefore resembles a normal Grignard reaction where metal transfer takes place to the electrophilic oxygen atom. The reaction conditions described have not been varied to a large degree and currently work is being done in our laboratory to investigate the mechanism, scope and limitations of this reaction.

This reaction, however, shows clearly that lithiation does indeed take place in all the reactions and that competitive addition of the base takes place in the cases where (**36a**) is used solely because *n*-BuLi and *t*-BuLi are more nucleophilic that lithiated (**64**).

7.3 Spectroscopic analysis

All compounds discussed in this chapter were isolated, purified and identified by ^{1}H, ^{13}C and HETCOR NMR spectroscopy. The MS spectra of the individual compounds were used to confirm the structure of these compounds unambiguously. The IR spectra of the compounds were recorded when necessary.

The NMR spectra of compound (**61**) were complex and the 2D HETCOR spectra proved essential for the allocation of the signals. In the MS spectra the M^+ peak was evident. The next mode of fragmentation was where the methyl group was lost leaving the peak at m/z 119. The base peak was observed as $C_7H_7^+$ equal to 91 which results from further fragmentation of the C_2-C_3 bond in the molecule as depicted in Scheme **53**.



Scheme 53

The course of the bromination reaction (Scheme **48**) could be easily followed by ^{1}H and ^{13}C NMR spectroscopy, noting the relatively large downfield shifts in the ^{1}H and ^{13}C signals of the α-CH group, *ca* δ_{1H} 2.09 → 4.29 δ_{13C} 27.04 → 43.73 caused by the introduction of the electronegative bromide group at this position. Unfortunately no MS spectrum was recorded of the monobromide species since this intermediate was used in the next step of the reaction to obtain the Grignard salt needed for the reaction with the electrophile.

With compounds (**65**) and (**66**) the absence of the strong signal at 0 ppm, resulting from the three methyl groups present on silicon, as well as the absence of any signals in the aromatic region at about 7 ppm showed that no inclusion of the benzyltrimethylsilane group had occurred in these reactions. The 2D HETCOR experiments proved essential in the assignment of the structures of these compounds. In the MS spectra of these two compounds very small signals were observed for the M^+ peaks at m/z 154. However, large M^+ - H_2O peaks at 136 were observed in both cases showing that the (**65**) and (**66**) readily undergo dehydration. The base peaks in both cases were obtained when the C-C bond, formed in the addition reaction of the base to (**36a**), yielding the fragment at m/z 97 was broken. This bond is therefore so weak that it can cleave even before dehydration has had time to occur. Naturally a peak at 79, resulting from the dehydration of the alcohol, should be evident. This peak was observed in both cases.

The IR spectra of (**65**) and (**66**) gave characteristic signals for the hydroxyl groups at 3600 cm^{-1}.

The formation of (**67**) was deduced from the fact that no evidence of the methyl groups at δ_{1H} 0 of the trimethylsilane function could be detected in the ^{1}H NMR spectrum. However, the strong signal at δ_{13C} 75.27, a doublet, is indicative of the presence of a CH-O bond. The IR spectra gave a strong signal at 3038 cm^{-1} which is characteristic of a hydroxyl group. The MS spectrum of this compound showed the M^+ peak at m/z 198. The next mode of fragmentation involved the elimination of water yielding a peak at 180. All these results together with the correlation obtained from the HETCOR NMR spectrum were used to assign the structure of this compound unambiguously.

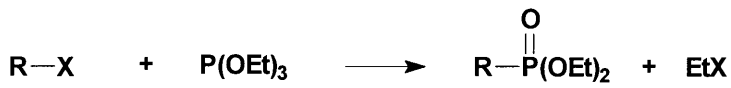
7.4 Conclusions

The reactions studied in this chapter lead to a better understanding of the character of the phosphoryl as well as the silyl groups even though mostly negative results were obtained at this stage of the work. The β-hydroxy-arylmethylphosphonates were shown to be unreactive towards the reaction conditions, employed in the Wadsworth-Emmons reaction for the formation of double bonds. The trimethylsilyl group have been shown to posses radically different characteristics. Unfortunately we were unable to obtain the optimal reaction conditions to bring about the Peterson olefination reaction. The reaction of lithiated (**64**) with aldehydes has however, opened a new field of research. A study into the effect of changing the nature of the aldehyde should lead to interesting results.

Preparation of substrates

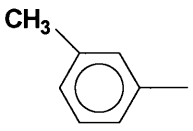
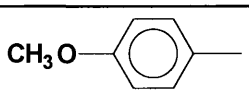
8.1 Synthesis of alkyl- and arylmethylphosphonic acid diethyl esters

All phosphonic acid diethyl esters were prepared using the method introduced by Michaelis-Arbuzov as a general synthetic strategy.[1] In the preparation of the arylmethylphosphonic esters the corresponding aryl halides are less reactive than their alkyl counterparts thus necessitating slightly harsher reaction conditions in order to obtain suitable conversions. In each case triethyl phosphite was slowly added to the corresponding alkyl or arylmethylbromide or chloride. The reaction mixture was then kept at reflux temperature until the evolution of the ethyl halide had ceased. The mixture was then refluxed for a further hour to ensure completion of the reaction. The products were finally purified by fractional distillation. The reaction is displayed in Scheme **54**, and the products are listed in Table **13**.

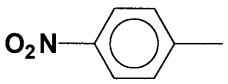
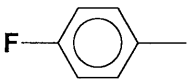
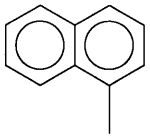


Scheme 54

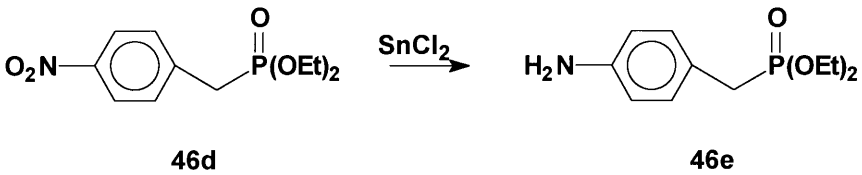
Table 13 The products of the Michaelis-Arbuzov reaction

No.	R	% Yield
39		88.5
35a	CH_3	94.6
46b		88.1
46c		83.3

[1] J Boutagy and R Thomas, *Chem. Rev.*, **74**, 1974, 87.

46d		83.7
46f		80.3
48		95.6

From the results obtained in the experiments described in Chapter **4** it was evident that (**46d**) was readily deprotonated by the base, since a deep red colour was observed after addition of the butyllithium reagent. This anion, however, proved to be too stable to show any significant reactivity towards 2-cyclohexen-1-one (**36a**). It was therefore decided to reduce the nitro- to the amino group in order to decrease the stability of the resulting anion. This however, has the disadvantage of providing another centre where deprotonation is possible. A vast array of reagents have been developed for the reduction of nitro compounds to amines.[2,3,4,5,6] Bellamy *et. al.*[7] have demonstrated that stannous chloride in alcohol or ethyl acetate provides a mild, selective and inexpensive general method for this transformation. 4-Amino-benzyl-phosphonic acid diethyl ester (**46e**) was prepared by the reduction of (**46d**) with $SnCl_2$ yielding 96% of the an orange crystalline material (Scheme **55**).



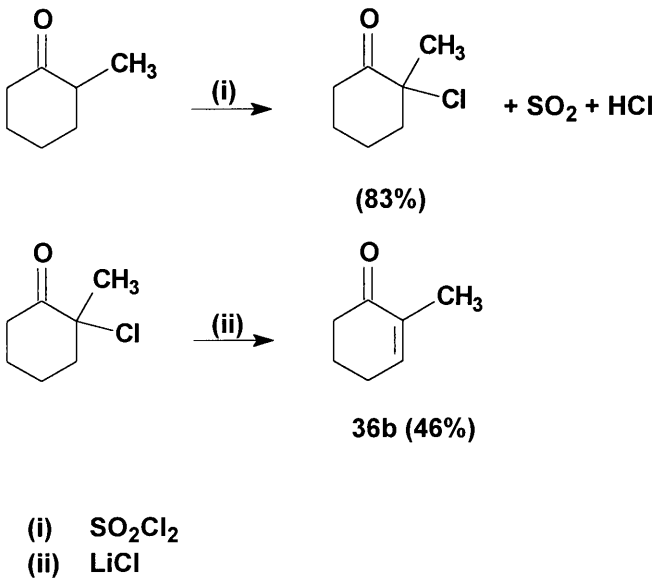
46d **46e**

Scheme 55

2 J George and S Chandrasekaran, *Synth. Comm.*, 1983, 495.
3 F Yuste, M Saldana and F Walls, *Tetrahedron Lett.*, 1982, 147.
4 K F Liou and C H Cheng, *J. Org. Chem.*, **47**, 1982, 3018.
5 A Nose and T Kudo, *Chem. Pharm. Bull.*, **29**, 1981, 1159.
6 J H Babler and S J Sarusi, *Synth. Comm.*, 1981, 925.
7 F D Bellamy and K Ou, *Tetrahedron Lett.*, **25**, 1984, 839.

8.2 Synthesis of 2-Methyl-2-cyclohexen-1-one

2-Methyl-cyclohexen-1-one is available commercially. In this project however, it was prepared from 2-methylcyclohexanone according to a standard procedure described by Warnhoff *et. al.*[8] as shown in Scheme **56**. In the experiment sulfuryl chloride was added to a mixture of 2-methylcyclohexanone dissolved in carbon tetrachloride. The slightly exothermic reaction was controlled by cooling the reaction mixture in a water bath at room temperature. After addition of the chloride the mixture was stirred for an additional 2 hours. Usual aqueous workup and distillation afforded the intermediate monochloro product. The 2-chloro-2-methylcyclohexanone was added to a solution of lithium chloride in DMF. The temperature of this mixture was kept at 100°C for 2 hours. After cooling the mixture was hydrolysed with a 2.5% solution of ether in sulphuric acid. Aqueous workup afforded the crude product which was purified by distillation to give (**36b**).



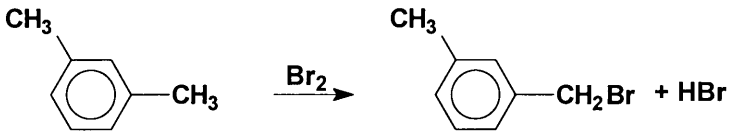
Scheme 56

8.3 Synthesis of precursors for the Arbuzov reaction

1-Bromomethyl-3-methyl-benzene (**68**) needed for the synthesis of (**46b**) was prepared from *m*-xylene according to a standard procedure (Scheme **57**).[9] Bromine was carefully added to *m*-

[8] E W Warnhoff, D G Martin and W S Jones, *Organic Synthesis*,19 , 162.
[9] *Beilst. Handbuch der Org. Chem.*, 4th Ed., Vol **5**, Julius Springer, Berlin, 1922, 365.

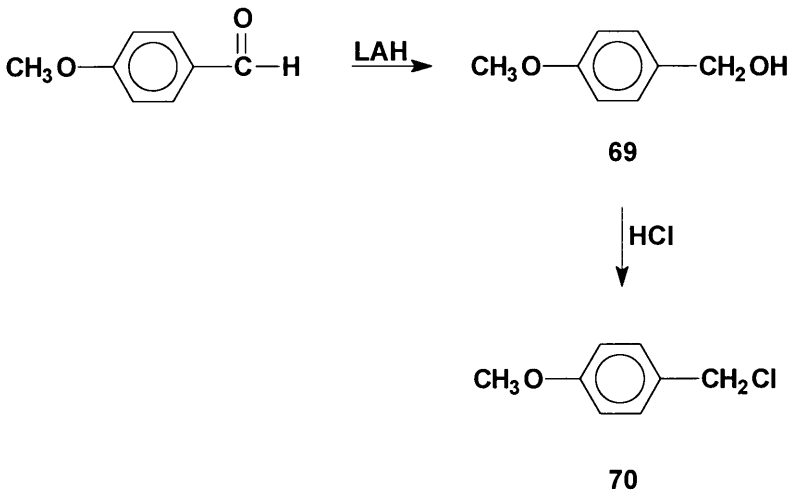
xylene at 130°C. The gas that evolved during the reaction was trapped in an ammonia bath. After the addition of the bromine was complete the reaction mixture was refluxed for a further hour before the product (**68**) was isolated by distillation.



68

Scheme 57

1-Chloromethyl-4-methoxy-benzene however, had to be prepared from 4-methoxy-benzaldehyde. The first step involved the reduction of the aldehyde to give the corresponding alcohol which was then reacted with dry HCl-gas to yield the product (**70**) (Scheme **58**). 4-Methoxy-benzaldehyde was dissolved in dry THF. LAH was added carefully and the mixture was refluxed for 24 hours after the initial spontaneous reaction. The unreacted LAH was deactivated by the addition of dilute sulphuric acid. Aqueous workup afforded the crude product which was isolated by column chromatography. In the second step of the reaction a solution of (**69**) in dry diethyl ether was saturated with HCl gas. This mixture was stoppered and allowed to stand in a refrigerator for 24 hours. The ether and excess HCl was removed under reduced pressure before the product (**70**) was purified by distillation.



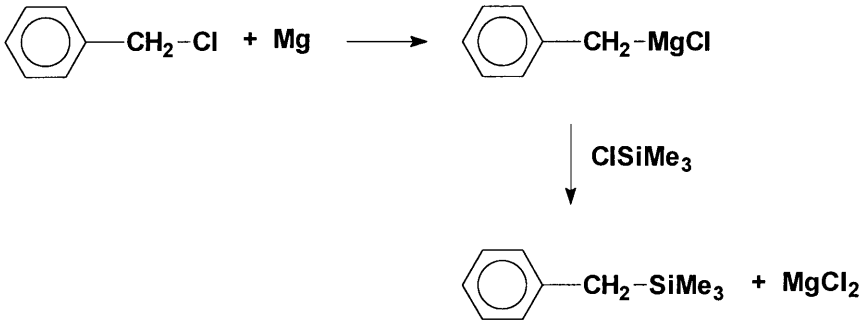
69

70

Scheme 58

8.4 Synthesis of benzyltrimethylsilane

The benzyltrimethylsilane (**64**) was prepared according to a modified procedure introduced by Gilman and Marshall,[10] and implemented by Hauser *et. al.*[11] In the reaction (Scheme **59**) benzyl chloride was treated with magnesium in diethyl ether to afford the Grignard salt. Trimethylchlorosilane was then added and this mixture was stirred at ambient temperature for 60 hours. The mixture was then saturated with carbon dioxide and hydrolysed with hydrochloric acid. Aqueous workup afforded the product which was purified by distillation.



64

Scheme 59

These compounds were isolated, purified and identified by ^{1}H-, ^{31}P-, ^{13}C- NMR spectroscopy and their respective MS spectra were used to confirm the structure of each compound.

10 H Gilman and F J Marshall, *J. Am. Chem. Soc.*, **71**, 1949, 2066.
11 C R Hauser and C R Hance, *J. Am. Chem. Soc.*, **73**, 1952, 5846.

Conclusions and future work

It was demonstrated that the addition of "localized" phosphorus stabilised carbanions to α,β-unsaturated ketones is reversible and that the regioselectivity of the addition reaction is determined by the nature of the β-substituent on the electrophile. It was found that the substrate molecules are thermodynamically more stable than the addition products formed during the reaction. The kinetic product could however, be isolated in each case, provided that a large excess of base was used during the deprotonation stage of the reaction, in order to force the equilibrium of the reaction over in the direction of the desired product. It was furthermore shown that, in contrast to sulfur-stabilised carbanions, that the regioselectivity, 1,2- *vs* 1,4-addition, was insensitive to changes in the solvent medium. The inclusion of HMPA or TMEDA in the reaction mixture showed no detectable increase in the amount of conjugate addition that was obtained.

"Delocalised" alk-2-enylphosphonates were shown to undergo mainly 1,4-addition via the γ-carbon of the nucleophile. These products were obtained under thermodynamic conditions and it is reasonable to assume that 1,2-addition would occur under kinetic conditions. This field was however, not investigated and a study into the conditions needed to obtain the 1,2-addition products will lead to a wide range of 1-hydroxyenylphosphonates that can serve as precursors for further transformations. The inclusion of a methyl group at the 2-position of the electrophile was however, shown to change the course of the addition reaction totally, leading to 1,2-addition via the α-carbon of the nucleophile. This change in the course of the reaction can also be brought about by making use of a suitable leaving group as β-substituent on the electrophile. It could be demonstrated once again that the phosphorus stabilised carbanions were insensitive to the nature of the solvent used. The inclusion of HMPA or TMEDA did not increase the amount of conjugate addition that was obtained in the cases where 1,2-addition was observed in the absence of these co-solvents.

The effect steric congestion at the reactive sites of the nucleophile will have on the course and regioselectivity of the addition reactions have not been investigated. The introduction of bulky substituents, as well as groups that can stabilize a negative charge *e.g.* Ph, CO etc. at the α, β or γ position of the allylic system should lead to some interesting results.

The series of arylmethylphosphonic acid diethyl esters where shown to undergo 1,2 addition. The reactions were shown to be reversible and the anions of the substrate molecules were once again thermodynamically more stable. This complicated the isolation of any conjugate addition product even though, through careful control of the reaction conditions small amounts of the 1,4-addition products could be isolated. The yields of these reactions were low and the products thus obtained were always contaminated with a large excess of the 1,2-addition product.

All the compounds isolated up to this stage were oils except the one diastereomer of the adduct of 1-naphthylmethyl-phosphonic acid diethyl ester (**47c**). Only NMR data were therefore used to assign the relative configurations of the different diastereomers that were isolated by column chromatography. It is however, known that the free acids of phosphonates are to a large degree crystalline materials. The conversion of these esters to their respective free acids, using refluxing HCl, should bring forth crystalline products. X-ray diffraction could then be used as a complementary technique for the confirmation of the relative configuration of these compounds. Preliminary work has been done in this direction with little success. This exercise will lead to an expansion in the series of compounds that can be studied with the aid of molecular dynamics. This will complement the results obtained thus far, making it possible to come to some meaningful conclusions using this relatively new technique. A vast field of research is still open, waiting to be discovered.

Three methods for the aromatisation of the 1-hydroxy alkyl- and 1-hydroxy arylmethylphosphonates were studied. The first method entailed the use of iodine in refluxing methanol. This approach was shown to be very effective in the preparation of the corresponding (3-methoxybenzyl)-phosphonic acid diethyl esters from the corresponding 3-chloro and 3-keto derivatives. In these reactions good yields without the formation of by-products were obtained, but the reaction sequence was shown to be non selective for the conversion of the 1-hydroxy derivatives prepared during the course of this project. Mixtures of products were obtained, which could be readily separated but from a synthetic standpoint the reaction was only of limited use.

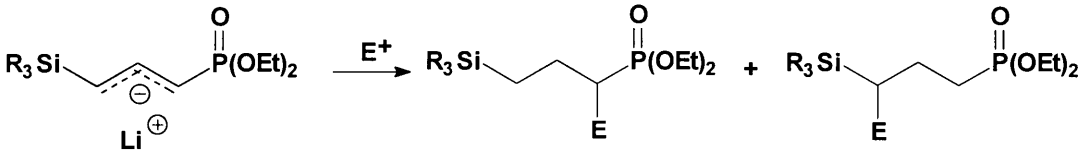
Pyridinium perbromide yielded promising results, but the vast array of different products serves as drawback for the implementation of this reaction in synthetic strategies.

The last method that was studied involved the use of triphenylmethanol, trifluoroacetic acid and acetic anhydride which gave the best results in terms of percentage yield and selectivity. This procedure was employed to a wide range of precursors. The reaction sequence has however, not been optimised and it should be possible to improve on the results that have been obtained up to this stage.

These aromatisation reactions yielded aromatic phosphonates containing an acidic proton situated α to phosphorus. These products can be deprotonated and can therefore be utilised as precursors for addition reactions to aldehyde and ketone functionalities. The addition reactions thus obtained will however, be subjected to much harsher steric requirements. Different modes of attack could therefore be expected and some interesting results should be obtained.

The isolation of the tertiary alcohols automatically leads to a study in the dehydration of these hydroxyphosphonates. From the MS spectral data it was evident that dehydration would readily occur since M^+ peaks of very low intensities were obtained for all the alcohols studied. Interestingly enough, it was found that the phosphonate group exerts a considerable influence on the mode of dehydration. Without any form of stabilisation the endocyclic isomer would be thermodynamically more stable than the exocyclic isomer. Under thermodynamic conditions it was, however, shown that the former represented the major mode of dehydration for all the hydroxyphosphonates.

The anion formed from the lithiation of benzyltrimethylsilane was unable to react with the α,β-unsaturated ketone. It was found that the anion thus formed was not nucleophilic enough. However, with more electrophilic substrates like benzaldehyde good yields of the addition product could be obtained. This observed selectivity difference between phosphonates and silanes could therefore be used effectively in a synthetic strategy. If the starting molecule contains both moieties as shown in Scheme **60**, then in theory it should be possible to abstract the acidic protons and react selectively at the two specific sites by making use of different electrophiles.



Scheme 60

The products obtained in such a sequence can then be used as precursors for other transformation reactions. Changes in the group **R** of the silane could also be investigated as a possible means for increasing the nucleophilic character of this reagent.

Experimental

Solvents and commercially available substrates were purified by conventional methods immediately before use. Reactions involving lithiated reagents were carried out in an atmosphere of dry nitrogen. For column chromatography Merck Kieselgel 60 (0.063 - 0.200 mm) was used as a stationary phase. Mass spectra were recorded on a Varian MAT - 212 double - focusing direct - inlet spectrometer at an ionisation potential of 70 eV. IR spectra were recorded on a Bomen Inc. Michelson 100 spectrometer as solutions in $CHCl_3$. NMR spectra were recorded on a Bruker AC 300 spectrometer for solutions in $CDCl_3$ (Uvasol, Merck). The chemical -shift values are given in δ (ppm) relative to the solvent (^{1}H : 7.24 ppm; ^{13}C : 77.0 ppm). ^{31}P NMR chemical - shift values are given relative to 85 % H_3PO_4 as external standard. Heteronuclear proton - carbon correlation spectra as well as NOE experiments were performed when necessary to assign structures unambiguously. Elemental analysis (C - N - H) were carried out at the Chemistry Department, University of Cape Town.

10.1 Synthesis and characterisation of compounds prepared in Chapter 2

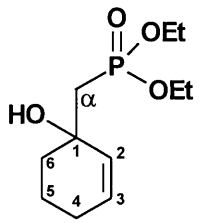
General procedure

Method A: n-Butyllithium (1.1 mol equiv.) (1.6 $mol.dm^{-3}$ solution in hexane) was diluted with THF (*ca* $3cm^3$ per mmol of phosphonate). To this solution cooled at -78°C was added dropwise with stirring a solution of alkyl - phosphonic acid diethyl ester (**35**) (1.0 mol equiv.) dissolved in THF (*ca* $1cm^3$ per mmol of phosphonate) and the solution was stirred at that temperature for 60 min. The electrophile (**36a-d**) (1.2 mol equiv.) dissolved in THF (*ca* $1cm^3$ per mmol of phosphonate) was then added and the reaction mixture stirred at -78°C for 2 hours. Saturated aqueous NH_4Cl was added and the solution allowed to warm up to room temperature. The mixture was then extracted with ether (3 x $20cm^3$). The combined etheral layers were dried ($MgSO_4/Na_2SO_4$), filtered and the solvent removed under reduced pressure. The products were purified and identified as indicated for individual compounds.

Method B: 2 mol equivalents of n-Butyllithium was used instead of 1.1 mol equiv. All addition reactions were carried out using method A except where mentioned.

(37a) 1-Hydroxy-cyclohex-2-enylmethyl-phosphonic acid diethyl ester

Colourless oil purified by column chromatography (EtOAc) Method A 1.783g (54.3%), Method B 1.069g (65.5%).



δ^{1}**H**	1.27	(3H; t; J_{HH} 7.1 Hz; CH_3 of POEt^a)
	1.28	(3H; t; J_{HH} 7.0 Hz; CH_3 of POEt^b)
	1.51 - 1.57	(2H; m; CH_2 on C(5))
	1.70 - 1.78	(2H; m; CH_2 on C(6))
	1.83 - 2.12	(4H; m; CH_2 on C(4), α - CH_2)
	3.91	(1H; s; OH)
	4.05	(4H; m; 2 x CH_2 of POEt)
	5.70	(2H; m; CH on C(2), CH on C(3))
δ^{31}**P**	29.98	
δ^{13}**C**	16.26	(d of q; J_{CP} 6.1 Hz; J_{CH} 129.0 Hz; 2 x CH_3 of POEt)
	18.92	(t; J_{CH} 127.8 Hz; CH_2 on C(5))
	24.72	(t; J_{CH} 125.5 Hz; CH_2 on C(4))
	36.93	(d of t; J_{CP} 14.6 Hz; J_{CH} 130.4 Hz; CH_2 on C(6))
	37.88	(d of t; J_{CP} 139.7 Hz; J_{CH} 130.7 Hz; α - CH_2)
	61.55	(d of t; J_{CP} 6.9 Hz; J_{CH} 148.9 Hz; CH_2 of POEt^a)
	61.64	(d of t; J_{CP} 7.4 Hz; J_{CH} 148.9 Hz; CH_2 of POEt^b)
	67.68	(d; J_{CP} 4.3 Hz; C of C(1))

	129.35	(d; J_{CH} 155.2 Hz; CH on C(3))
	131.98	(d of d; J_{CP} 11.8 Hz; J_{CH} 161.9 Hz; CH on C(2))

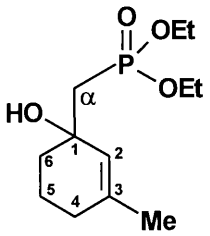
MS	**m/z**	249	(($M^+ + 1$)	<1%)	248	(M^+	1%)
		229	(($M^+ - H_2O$)	92%)	93	($C_7H_9^+$	46%)
		92	($C_7H_8^+$	65%)	91	($C_7H_7^+$	100%)
		79	(PO_3^+	20%)	29	($C_2H_5^+$	56%)
		15	(CH_3^+	7%)			

IR	3436	(s; OH)
	1230	(s; P=O)

Analysis	**C**	**H**
Calculated:	53.22%	8.53%
Found:	52.55%	8.52%

(37b) 1-Hydroxy-3-methyl-cyclohex-2-enylmethyl-phosphonic acid diethyl ester

Colourless oil purified by column chromatography (EtOAc) Method A 0.604g (41.5%), Method B 1.054g (60.6%).



δ^1**H**	1.29	(6H; t; J_{HH} 7.1 Hz; 2 x CH_3 of POEt)
	1.54 - 1.74	(2H; m; CH_2 on C(5))
	1.63	(3H; s; CH_3 on C(3))
	1.75 - 1.92	(4H; m; CH_2 on C(4), CH_2 on C(6))
	1.97	(1H; d of d; J_{HHgem} 16.3 Hz; J_{HP} 16.3 Hz; α - CH^a)
	2.07	(1H; d of d; J_{HHgem} 16.3 Hz; J_{HP} 16.3 Hz; α - CH^b)

	3.82	(1H; s; OH)
	4.05	(2H; d of q; J_{HP} 7.0 Hz; J_{HH} 7.0 Hz; CH_2 of POEt[a])
	4.08	(2H; d of q; J_{HP} 7.0 Hz; J_{HH} 7.0 Hz; CH_2 of POEt[b])
	5.43	(1H; s; CH on C(2))
$\delta^{31}P$	30.18	
$\delta^{13}C$	15.85	(d of q; J_{CP} 6.0 Hz; J_{CH} 127.2 Hz; 2 x CH_3 of POEt)
	18.80	(t; J_{CH} 128.4 Hz; CH_2 on C(5))
	23.07	(q; J_{CH} 126.3 Hz; CH_3 on C(3))
	29.34	(t; J_{CH} 125.5 Hz; CH_2 on C(4))
	36.12	(d of t; J_{CP} 8.6 Hz; J_{CH} 127.7 Hz; CH_2 on C(6))
	37.88	(d of t; J_{CP} 134.0 Hz; J_{CH} 130.0 Hz; α - CH_2)
	61.04	(t; J_{CH} 147.4 Hz; 2 x CH_2 of POEt)
	67.74	(s; C of C(1))
	126.46	(d of d; J_{CP} 12.2 Hz; J_{CH} 157.5 Hz; CH on C(2))
	136.65	(s; C of C(3))

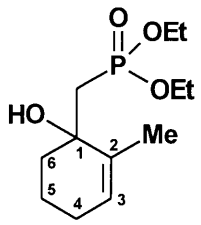
MS	**m/z**	244	($(M^+ - H_2O)$	49%)	243	($C_{12}H_{20}PO_3^+$	84%)
		187	($C_8H_{12}PO_3^+$	97%)	106	($C_8H_{10}^+$	62%)
		105	($C_8H_9^+$	100%)	79	(PO_3^+	21%)
		29	($C_2H_5^+$	20%)			

IR	3436	(s; OH)
	1231	(s; P=O)

Analysis	**C**	**H**
Calculated:	54.95%	8.84%
Found:	54.61%	8.90%

(37c) 1-Hydroxy-2-methyl-cyclohex-2-enylmethyl-phosphonic acid diethyl ester

Colourless oil purified by column chromatography (EtOAc) Method A 0.492g (28.5%), Method B 0.966g (56.0%).



δ^{1}**H**	1.27	(6H; t; 7.0 Hz; 2 x CH_3 of POEt)
	1.32 - 1.70	(3H; m; CH_2 on C(5), CH on C(6))
	1.68	(3H; d; J_{HP} 1.6 Hz; CH_3 on C(2))
	1.80 - 2.00	(3H; m; CH_2 on C(4), CH on C(6))
	1.92	(1H; d of d; J_{HP} 18.5 Hz; J_{HH} 15.5 Hz; α - CH^a)
	2.24	(1H; d of d; J_{HP} 17.4 Hz; J_{HH} 15.5 Hz; α - CH^b)
	3.75	(1H; s; OH)
	4.07	(4H; d of q; J_{HP} 7.2 Hz; J_{HH} 7.2 Hz; CH_2 of POEt)
	5.42	(1H; s; CH on C(3))
δ^{31}**P**	30.60	
δ^{13}**C**	16.02	(d of q; J_{CP} 5.4 Hz; J_{CH} 127.5 Hz; 2 x CH_3 of POEt)
	17.25	(q; J_{CH} 126.0 Hz; CH_3 on C(2))
	19.12	(t; J_{CH} 126.0 Hz; CH_2 on C(5))
	25.00	(t; J_{CH} 126.5 Hz; CH_2 on C(4))
	34.53	(d of t; J_{CP} 134.2 Hz; J_{CH} 130.0 Hz; α - CH_2)
	36.71	(t; J_{CH} 126.3 Hz; CH_2 on C(6))
	61.22	(d of t; J_{CP} 6.5 Hz; J_{CH} 147.6 Hz; CH_2 of $POEt^a$)
	61.52	(d of t; J_{CP} 5.5 Hz; J_{CH} 147.6 Hz; CH_2 of $POEt^b$)
	71.03	(s; C of C(1))
	125.34	(d; J_{CH} 153.0 Hz; CH on C(3))
	136.63	(d; J_{CP} 15.8 Hz; C of C(2))

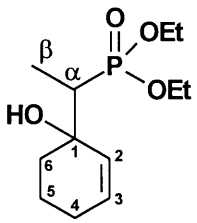
MS	**m/z**	262	(M^+	<1%)	243	((M^+ - H_2O)	84%)
		187	($C_8H_{12}PO_3^+$	77%)	105	($C_8H_9^+$	100%)
		79	(PO_3^+	26%)	29	($C_2H_5^+$	45%)
		15	(CH_3^+	5%)			

IR	3019	(s; OH)
	1221	(s; P=O)

Analysis	**C**	**H**
Calculated:	54.95%	8.84%
Found:	54.79%	9.04%

(37d) 1-(1-Hydroxy-cyclohex-2-enyl)-ethyl-phosphonic acid diethyl ester

Colourless oil purified by column chromatography (EtOAc) 1.761g (55.7%) yielding two isomers.



Isomer (37d) 1.128g (35.7%)

δ^1**H**	1.05	(3H; d of d; J_{HP} 17.4 Hz; J_{HH} 7.3 Hz; β - CH_3)
	1.28	(3H; t; J_{HH} 7.1 Hz; CH_3 of POEt[a])
	1.29	(3H; t; J_{HH} 7.1 Hz; CH_3 of POEt[b])
	1.55 - 1.65	(2H; m; CH_2 on C(5))
	1.77 - 1.83	(2H; m; CH_2 on C(6))
	1.93 - 2.10	(3H; m; CH_2 on C(4), α - CH)
	4.09	(4H; m; 2 x CH_2 of POEt)
	4.36	(1H; s; OH)
	5.42	(1H; d; J_{H2H3} 9.7 Hz; CH on C(2))
	5.88	(1H; d of d; J_{H3H2} 9.7 Hz; J_{H3H4} 5.6 Hz; CH on C(3))

$\delta^{31}P$	33.66	
$\delta^{13}C$	11.01	(d of q; J_{CP} 4.9 Hz; J_{CH} 129.2 Hz; β - CH_3)
	16.33	(d of q; J_{CP} 6.1 Hz; J_{CH} 126.7 Hz; 2 x CH_3 of POEt)
	18.12	(t; J_{CH} 129.8 Hz; CH_2 on C(5))
	24.71	(t; J_{CH} 126.6 Hz; CH_2 on C(4))
	31.65	(d of t; J_{CP} 3.0 Hz; J_{CH} 127.5 Hz; CH_2 on C(6))
	41.80	(d of d; J_{CP} 133.7 Hz; J_{CH} 129.3 Hz; α - CH)
	61.52	(d of t; J_{CP} 7.2 Hz; J_{CH} 147.6 Hz; CH_2 of $POEt^a$)
	61.85	(d of t; J_{CP} 6.3 Hz; J_{CH} 147.6 Hz; CH_2 of $POEt^b$)
	70.52	(s; C of C(1))
	131.10	(d; J_{CH} 156.0 Hz; CH on C(3))
	131.43	(d of d; J_{CP} 14.2 Hz; J_{CH} 156.0 Hz; CH on C(2))

Isomer (37d') 0.632g (20.0%)

$\delta^{1}H$	1.13	(3H; d of d; J_{HP} 18.0 Hz; J_{HH} 7.5 Hz; β - CH_3)
	1.28	(3H; t; J_{HH} 7.0 Hz; CH_3 of $POEt^a$)
	1.29	(3H; t; J_{HH} 7.0 Hz; CH_3 of $POEt^b$)
	1.59 - 1.71	(2H; m; CH_2 on C(5))
	1.79 - 1.91	(2H; m; CH_2 on C(6))
	1.97 - 2.11	(3H; m; CH_2 on C(4), α - CH)
	4.08	(4H; m; 2 x CH_2 of POEt)
	4.39	(1H; s; OH)
	5.80	(2H; m; CH on C(2), CH on C(3))
$\delta^{31}P$	33.56	
$\delta^{13}C$	10.52	(d of q; J_{CP} 4.7 Hz; J_{CH} 129.2 Hz; β -CH_3)
	16.32	(d of q; J_{CP} 5.6 Hz; J_{CH} 126.7 Hz; 2 x CH_3 of POEt)
	18.67	(t; J_{CH} 129.8 Hz; CH_2 on C(5))
	24.84	(t; J_{CH} 126.6 Hz; CH_2 on C(4))

	34.77	(d of t; J_{CP} 10.0 Hz; J_{CH} 127.5 Hz; CH_2 on C(6))
	41.43	(d of d; J_{CP} 133.3 Hz; J_{CH} 129.3 Hz; α - CH)
	61.61	(d of t; J_{CP} 6.8 Hz; J_{CH} 147.6 Hz; CH_2 of POEt[a])
	61.71	(d of t; J_{CP} 7.9 Hz; J_{CH} 147.6 Hz; CH_2 of POEt[b])
	70.25	(s; C of C(1))
	129.82	(d of d; J_{CP} 6.3 Hz; J_{CH} 156.0 Hz; CH on C(2))
	130.96	(d; J_{CH} 156.0 Hz; CH on C(3))

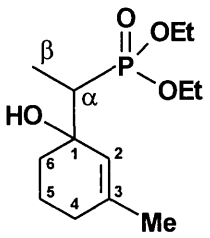
MS	**m/z**	244	($(M^+ - H_2O)$	20%)	243	($C_{12}H_{20}PO_3^+$	68%)
		106	($C_8H_{10}^+$	67%)	105	($C_8H_9^+$	100%)
		91	($C_7H_7^+$	75%)	79	(PO_3^+	30%)
		29	($C_2H_5^+$	29%)	15	(CH_3^+	2%)

IR	3419	(s; OH)
	1219	(s; P=O)

Analysis	**C**	**H**
Calculated:	54.95%	8.84%
Found:	54.74%	9.02%

(37e) 1-(1-Hydroxy-3-methyl-cyclohex-2-enyl)-ethyl-phosphonic acid diethyl ester

Colourless oil purified by column chromatography (EtOAc/EtOH, 9:1) 0.635g (40.6%) yielding two isomers:



Isomer (37e) 0.389g (24.9%)

δ^1**H**	1.04	(3H; d of d; J_{HP} 17.4 Hz; J_{HH} 7.6 Hz; β - CH_3)
	1.29	(3H; t; J_{HH} 7.1 Hz; CH_3 of POEt[a])

	1.30	(3H; t; J_{HH} 7.1 Hz; CH_3 of $POEt^b$)
	1.57 - 1.64	(2H; m; CH_2 on C(5))
	1.66	(3H; s; CH_3 on C(3))
	1.73 - 1.86	(4H; m; CH_2 on C(4), CH_2 on C(6))
	2.06	(1H; d of q; J_{HP} 19.1 Hz; J_{HH} 7.4 Hz; α - CH)
	4.09	(2H; d of q; J_{HP} 7.2 Hz; J_{HH} 7.2 Hz; CH_2 of $POEt^a$)
	4.10	(2H; d of q; J_{HP} 7.2 Hz; J_{HH} 7.2 Hz; CH_2 of $POEt^b$)
	4.32	(1H; s; OH)
	5.16	(1H; s; CH on C(2))
δ^{31}**P**	33.93	
δ^{13}**C**	10.72	(d of q; J_{CP} 5.0 Hz; J_{CH} 133.0 Hz; β - CH_3)
	15.96	(d of q; J_{CP} 5.6 Hz; J_{CH} 127.7 Hz; 2 x CH_3 of POEt)
	18.17	(t; J_{CH} 126.6 Hz; CH_2 on C(5))
	23.34	(q; J_{CH} 125.7 Hz; CH_3 on C(3))
	29.38	(t; J_{CH} 123.8 Hz; CH_2 on C(4))
	30.94	(d of t; J_{CP} 2.9 Hz; J_{CH} 123.1 Hz; CH_2 on C(6))
	41.73	(d of d; J_{CP} 133.4 Hz; J_{CH} 129.0 Hz; α - CH)
	61.08	(d of t; J_{CP} 7.1 Hz; J_{CH} 147.2 Hz; CH_2 of $POEt^a$)
	61.38	(d of t; J_{CP} 6.2 Hz; J_{CH} 147.2 Hz; CH_2 of $POEt^b$)
	70.75	(s; C of C(1))
	125.60	(d of d; J_{CP} 17.8 Hz; J_{CH} 167.6 Hz; CH on C(2))
	138.86	(s; C of C(3))

Isomer (37e') 0.246g (15.7%)

δ^1**H**	1.13	(3H; d of d; J_{HP} 18.0 Hz; J_{HH} 7.3 Hz; β - CH_3)
	1.29	(3H; t; J_{HH} 7.3 Hz; CH_3 of $POEt^a$)
	1.31	(3H; t; J_{HH} 7.3 Hz; CH_3 of $POEt^b$)
	1.58 - 1.70	(2H; m; CH_2 on C(5))
	1.65	(3H; s; CH_3 on C(3))
	1.70 - 1.85	(4H; m; CH_2 on C(4), CH_2 on C(6))

	2.05	(1H; d of q; J_{HP} 19.9 Hz; J_{HH} 7.5 Hz; α - CH)
	4.08	(4H; m; 2 x CH_2 of POEt)
	5.54	(1H; s; CH on C(2))
$\delta^{31}P$	33.76	
$\delta^{13}C$	10.56	(d of q; J_{CP} 4.8 Hz; J_{CH} 129.3 Hz; β - CH_3)
	16.36	(d of q; J_{CP} 5.7 Hz; J_{CH} 131.4 Hz; 2 x CH_3 of POEt)
	19.03	(t; J_{CH} 132.9 Hz; CH_2 on C(5))
	23.92	(q; J_{CH} 126.0 Hz; CH_3 on C(3))
	29.88	(t; J_{CH} 123.4 Hz; CH_2 on C(4))
	34.45	(d of t; J_{CP} 9.8 Hz; J_{CH} 126.3 Hz; CH_2 on C(6))
	41.70	(d of d; J_{CP} 133.1 Hz; J_{CH} 130.6 Hz; α - CH)
	61.54	(d of t; J_{CP} 8.5 Hz; J_{CH} 149.8 Hz; CH_2 of POEt[a])
	61.66	(d of t; J_{CP} 8.6 Hz; J_{CH} 149.8 Hz; CH_2 of POEt[b])
	70.91	(s; C of C(1))
	124.41	(d of d; J_{CP} 5.9 Hz; J_{CH} 156.8 Hz; CH on C(2))
	138.92	(s; C of C(3))

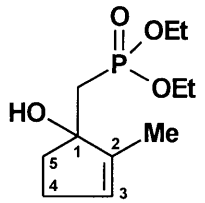
MS	**m/z**	258	($C_{13}H_{23}PO_3^+$	100%)	120	($C_9H_{12}^+$	86%)
		105	($C_8H_9^+$	47%)	79	(PO_3^+	16%)
		29	($C_2H_5^+$	19%)			

IR	3426	(s; OH)
	1219	(s; P=O)

Analysis	**C**	**H**
Calculated:	56.51%	9.12%
Found:	56.40%	9.25%

(37f) 1-Hydroxy-2-methyl-cyclopent-2-enylmethyl-phosphonic acid diethyl ester

Colourless oil purified by column chromatography (EtOAc) 0.645g (39.1%).



δ^{1}**H**	1.31	(3H; t; J_{HH} 7.0 Hz; CH_3 of $POEt^a$)
	1.32	(3H; t; J_{HH} 7.0 Hz; CH_3 of $POEt^b$)
	1.68	(3H; d; J_{HP} 1.7 Hz; CH_3 on C(2))
	1.85	(1H; d of d; J_{HP} 18.7 Hz; J_{HHgem} 15.3 Hz; α - CH^a)
	2.02	(1H; m; CH on C(5))
	2.22	(1H; d of d; J_{HP} 16.7 Hz; J_{HHgem} 15.3 Hz; α - CH^b)
	2.18 - 2.34	(3H; m; CH_2 on C(4), CH on C(5))
	3.89	(1H; s; OH)
	4.08	(2H; d of q; J_{HP} 7.1 Hz; J_{HH} 7.1 Hz; CH_2 of $POEt^a$)
	4.10	(2H; d of q; J_{HP} 7.1 Hz; J_{HH} 7.1 Hz; CH_2 of $POEt^b$)
	5.47	(1H; s; CH on C(3))
δ^{31}**P**	30.71	
δ^{13}**C**	10.83	(q; J_{CH} 123.6 Hz; CH_3 on C(2))
	15.78	(d of q; J_{CP} 5.8 Hz; J_{CH} 125.6 Hz; 2 x CH_3 of POEt)
	28.33	(t; J_{CH} 129.3 Hz; CH_2 on C(4))
	33.94	(d of t; J_{CP} 136.0 Hz; J_{CH} 126.1 Hz; α - CH_2)
	37.93	(t; J_{CH} 130.7 Hz; CH_2 on C(5))
	61.04	(d of t; J_{CP} 6.9 Hz; J_{CH} 147.6 Hz; CH_2 of $POEt^a$)
	61.20	(d of t; J_{CP} 6.3 Hz; J_{CH} 147.6 Hz; CH_2 of $POEt^b$)
	81.80	(d; J_{CP} 4.1 Hz; C of C(1))
	126.96	(d; J_{CH} 160.4 Hz; CH on C(3))

	142.64		(d; J_{CP} 14.0 Hz; C of C(2))				
MS	**m/z**	230	((M^+ - H_2O)	33%)	93	($C_7H_9^+$	56%)
		92	($C_7H_8^+$	100%)	79	(PO_3^+	7%)
		29	($C_2H_5^+$	9%)	15	(CH_3^+	1%)
IR	3019		(s; OH)				
	1221		(s; P=O)				

Analysis	**C**	**H**
Calculated:	53.22%	8.53%
Found:	52.96%	8.81%

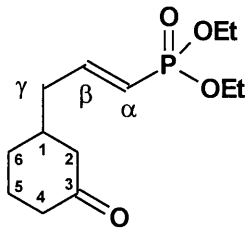
10.2 Synthesis and characterisation of compounds prepared in Chapter 3

General procedure

n-Butyllithium (1.1 mol equiv.) (1.6 $mol.dm^{-3}$ solution in hexane) was diluted with THF (*ca* $3cm^3$ per mmol of phosphonate). To this solution cooled at -78°C was added dropwise with stirring a solution of allyl - phosphonic acid diethyl ester (**39**) (1.0 mol equiv.) dissolved in THF (*ca* $1cm^3$ per mmol of phosphonate) and the solution was stirred at that temperature for 60 min. Copper (I) iodide (0.55 mol equiv.) was then added and the mixture was stirred at -78°C for an additional hour. The electrophile (**36a-d**) (0.75 mol equiv.) dissolved in THF (*ca* $1cm^3$ per mmol of phosphonate) was added and the reaction mixture stirred at -78°C for 60 min. Saturated aqueous NH_4Cl was added and the solution allowed to warm up to room temperature. The solution was stirred until the green colour present in the organic phase had disappeared. The mixture was then extracted with ether (3 x $20cm^3$). The combined etheral layers were dried ($MgSO_4/Na_2SO_4$), filtered and the solvent removed under reduced pressure. The products were purified and identified as indicated for individual compounds.

(42a) 3-(3-Oxo-cyclohexyl)-propenyl-phosphonic acid diethyl ester

Colourless oil purified by column chromatography (EtOAc/$CHCl_3$, 1:5) 0.726g (47.1%).



δ^1**H**	1.27	(3H; t; J_{HH} 8.8 Hz; CH_3 of $POEt^a$)
	1.28	(3H; t; J_{HH} 8.8 Hz; CH_3 of $POEt^b$)
	1.62	(1H; m; CH on C(5))
	1.64 - 2.05	(5H; m; CH_2 on C(6), CH on C(1), CH on C(5), CH on C(4))
	2.22	(2H; d of d; J_{H1H6} 5.6 Hz; J_{H1H2} 5.6 Hz; γ - CH_2)
	2.35	(3H; m; CH_2 on C(2), CH on C(4))
	4.01	(2H; d of q; J_{HP} 7.1 Hz; J_{HH} 7.1 Hz; CH_2 of $POEt^a$)
	4.04	(2H; d of q; J_{HP} 7.1 Hz; J_{HH} 7.1 Hz; CH_2 of $POEt^b$)
	5.64	(1H; d of d of t; J_{HP} 20.7 Hz; $J_{H\alpha H\beta}$ 18.4 Hz; $J_{H\alpha H\gamma}$ 1.2 Hz; α - CH)
	6.66	(1H; d of d of t; J_{HP} 21.6 Hz; $J_{H\beta H\alpha}$ 17.0 Hz; $J_{H\beta H\gamma}$ 6.8 Hz; β - CH)
δ^{31}**P**	18.31	
δ^{13}**C**	15.66	(q; J_{CH} 126.1 Hz; CH_3 on $POEt^a$)
	15.74	(q; J_{CH} 126.1 Hz; CH_3 on $POEt^b$)
	24.26	(t; J_{CH} 127.3 Hz; CH_2 on C(5))
	30.15	(t; J_{CH} 125.0 Hz; CH_2 on C(6))
	37.31	(d; J_{CH} 128.7 Hz; CH on C(1))
	40.31	(d of t; J_{CP} 22.2 Hz; J_{CH} 126.5 Hz; γ - CH_2)
	40.53	(t; J_{CH} 127.7 Hz; CH_2 on C(4))
	46.93	(t; J_{CH} 130.4 Hz; CH_2 on C(2))
	60.98	(t; J_{CH} 147.1 Hz; CH_2 of $POEt^a$)
	61.05	(t; J_{CH} 147.1 Hz; CH_2 of $POEt^b$)
	118.75	(d of d; J_{CP} 186.9 Hz; J_{CH} 156.3 Hz; α - CH)

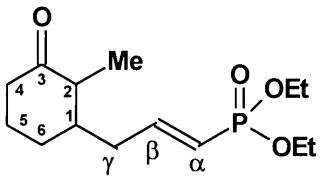
	149.68	(d of d; J_{CP} 8.5 Hz; J_{CH} 156.0 Hz; β - CH)
	209.87	(s; C of C(3))

MS	**m/z**	274	(M^+	2%)	178	($C_7H_{15}PO_3^+$	100%)
		150	($C_5H_{11}PO_3^+$	29%)	122	($C_3H_7PO_3^+$	44%)
		97	($C_6H_9O^+$	18%)	79	(PO_3^+	13%)
		29	($C_2H_5^+$	20%)	15	(CH_3^+	1%)

IR	1708	(s; C=O)
	1251	(s; P=O)

(42b) 3-(2-Methyl-3-oxo-cyclohexyl)-propenyl-phosphonic acid diethyl ester

Colourless oil purified by bulb to bulb distillation (oven temp. 175°C/0.04mmHg) yielding 1.137g (70.3%) of two isomers.



Isomer (42b) 0.830g (51.3%)

δ^1H	1.04	(3H; d; J_{HH} 6.6 Hz; CH_3 on C(2))
	1.28	(3H; t; J_{HH} 7.0 Hz; CH_3 of $POEt^a$)
	1.29	(3H; t; J_{HH} 7.0 Hz; CH_3 of $POEt^b$)
	1.45 - 1.84	(3H; m; CH on C(5), CH on C(6), CH on C(1))
	1.85 - 2.17	(3H; m; CH on C(5), CH on C(6), CH on C(2))
	2.19 - 2.60	(4H; m; CH_2 on C(4), γ - CH_2)
	4.02	(2H; d of q; J_{HP} 7.2 Hz; J_{HH} 7.2 Hz; CH_2 of $POEt^a$)
	4.03	(2H; d of q; J_{HP} 7.2 Hz; J_{HH} 7.2 Hz; CH_2 of $POEt^b$)
	5.69	(1H; d of d; J_{HP} 21.3 Hz; J_{HH} 16.3 Hz; α -CH)
	6.70	(1H; m; β -CH)

δ^{31}P	18.28

$\delta^{13}C$	11.28	(q; J_{CH} 125.2 Hz; CH_3 on C(2))
	15.69	(q; J_{CH} 126.6 Hz; 2 x CH_3 of POEt)
	24.87	(t; J_{CH} 129.6 Hz; CH_2 on C(5))
	29.88	(t; J_{CH} 129.1 Hz; CH_2 on C(6))
	38.09	(d of t; J_{CP} 22.3 Hz; J_{CH} 138.7 Hz; γ - CH_2)
	40.61	(t; J_{CH} 127.8 Hz; CH_2 on C(4))
	44.00	(d; J_{CH} 129.6 Hz; CH on C(1))
	48.73	(d; J_{CH} 119.8 Hz; CH on C(2))
	60.93	(t; J_{CH} 147.5 Hz; 2 x CH_2 of POEt)
	119.14	(d of d; J_{CP} 184.7 Hz; J_{CH} 157.0 Hz; α - CH)
	149.72	(d; J_{CH} 152.1 Hz; β - CH)
	211.19	(s; C of C(3))

Isomer (42b') 0.307g (19.0%)

$\delta^{1}H$	1.00	(3H; d; J_{HH} 7.0 Hz; CH_3 on C(2))
	1.28	(3H; t; J_{HH} 7.0 Hz; CH_3 of $POEt^a$)
	1.29	(3H; t; J_{HH} 7.0 Hz; CH_3 of $POEt^b$)
	1.45 - 1.84	(3H; m; CH on C(5), CH on C(6), CH on C(1))
	1.85 - 2.17	(3H; m; CH on C(5), CH on C(6), CH on C(2))
	2.19 - 2.60	(4H; m; CH_2 on C(4), γ -CH_2)
	4.02	(2H; d of q; J_{HP} 7.2 Hz; J_{HH} 7.2 Hz; CH_2 of $POEt^a$)
	4.03	(2H; d of q; J_{HP} 7.2 Hz; J_{HH} 7.2 Hz; CH_2 of $POEt^b$)
	5.69	(1H; d of d; J_{HP} 21.3 Hz; J_{HH} 16.3 Hz; α - CH)
	6.70	(1H; m; β - CH)
$\delta^{31}P$	18.33	
$\delta^{13}C$	10.91	(q; J_{CH} 125.2 Hz; CH_3 on C(2))
	15.69	(q; J_{CH} 126.6 Hz; 2 x CH_3 of POEt)
	22.79	(t; J_{CH} 129.6 Hz; CH_2 on C(5))
	25.60	(t; J_{CH} 129.1 Hz; CH_2 on C(6))
	33.30	(d of t; J_{CP} 22.0 Hz; J_{CH} 138.7 Hz; γ - CH_2)

	40.84	(t; J_{CH} 127.8 Hz; CH_2 on C(4))
	44.00	(d; J_{CH} 129.6 Hz; CH on C(1))
	47.88	(d; J_{CH} 119.8 Hz; CH on C(2))
	60.93	(t; J_{CH} 147.5 Hz; 2 x CH_2 of POEt)
	118.47	(d of d; J_{CP} 185.5 Hz; J_{CH} 157.0 Hz; α - CH)
	150.47	(d; J_{CH} 152.1 Hz; β - CH)
	211.19	(s; C of C(3))

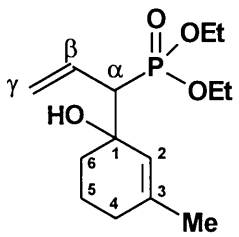
MS	**m/z**	289	($(M^+ + 1)$	2%)	288	(M^+	1%)
		178	($C_7H_{15}PO_3^+$	100%)	110	($C_7H_{10}O^+$	3%)
		79	(PO_3^+	8%)	29	($C_2H_5^+$	19%)
		15	(CH_3^+	1%)			

IR	1706	(s; C=O)
	1236	(s; P=O)

Analysis	**C**	**H**
Calculated:	58.32%	8.74%
Found:	57.75%	8.60%

(42c) 1-(1-Hydroxy-3-methyl-cyclohex-2-enyl)-allyl-phosphonic acid diethyl ester

Colourless oil purified by column chromatography (EtOAc) 1.880g (77.5%).



δ^1**H**	1.28	(3H; t; J_{HH} 7.0 Hz; CH_3 of POEt^a)
	1.30	(3H; t; J_{HH} 7.0 Hz; CH_3 of POEt^b)
	1.57 - 1.64	(2H; m; CH_2 on C(5))

	1.61	(3H; s; CH_3 on C(3))
	1.76 - 1.82	(4H; m; CH_2 on C(4), CH_2 on C(6))
	2.73	(1H; d of d of t; J_{HP} 19.6 Hz; $J_{H\alpha H\beta}$ 9.6 Hz; $J_{H\alpha H\gamma}$ 1.5 Hz; α - CH)
	4.08	(2H; d of q; J_{HP} 7.7 Hz; J_{HH} 7.3 Hz; CH_2 of $POEt^a$)
	4.11	(2H; d of q; J_{HP} 7.7 Hz; J_{HH} 7.3 Hz; CH_2 of $POEt^b$)
	4.25	(1H; s; OH)
	5.13	(2H; m; γ - CH_2)
	5.26	(1H; s; CH on C(2))
	5.59	(1H; m; β - CH)
$\delta^{31}P$	28.83	
$\delta^{13}C$	16.05	(d of q; J_{CP} 5.9 Hz; J_{CH} 125.3 Hz; 2 x CH_3 of POEt)
	18.30	(t; J_{CH} 129.6 Hz; CH_2 on C(5))
	23.37	(q; J_{CH} 125.7 Hz; CH_3 on C(3))
	29.46	(t; J_{CH} 123.4 Hz; CH_2 on C(4))
	32.69	(d of t; J_{CP} 6.0 Hz; J_{CH} 124.6 Hz; CH_2 on C(6))
	53.90	(d of d; J_{CP} 131.4 Hz; J_{CH} 128.7 Hz; α - CH)
	61.79	(t; J_{CH} 151.5 Hz; CH_2 of $POEt^a$)
	61.95	(t; J_{CH} 151.5 Hz; CH_2 of $POEt^b$)
	70.32	(d; J_{CP} 3.0 Hz; C of C(1))
	119.80	(d of t; J_{CP} 12.8 Hz; J_{CH} 156.8 Hz; γ - CH_2)
	126.00	(d of d; J_{CP} 14.4 Hz; J_{CH} 156.9 Hz; CH on C(2))
	130.49	(d of d; J_{CP} 9.5 Hz; J_{CH} 158.2 Hz; β - CH)
	137.86	(s; C of C(3))

MS	**m/z**						
	290	($(M^+ + 1)$	< 1%)	270	($(M^+ - H_2O)$	100%)
	269	($C_{14}H_{22}PO_3^+$	23%)	213	($C_{10}H_{14}PO_3^+$	14%)
	178	($C_7H_{15}PO_3^+$	36%)	150	($C_5H_{11}PO_3^+$	15%)
	132	($C_{10}H_{12}^+$	93%)	131	($C_{10}H_{11}^+$	100%)
	122	($C_3H_7PO_3^+$	42%)	111	($C_7H_{11}O^+$	23%)
	79	(PO_3^+	10%)	29	($C_2H_5^+$	21%)

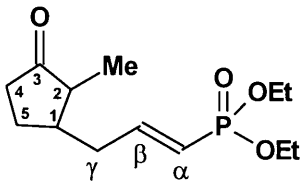
	15	(CH_3^+	2%)

IR	1225	(s; P=O)
	3413	(s; OH)

Analysis	**C**	**H**
Calculated:	58.32%	8.74%
Found:	57.94%	8.94%

(42d) 3-(2-Methyl-3-oxo-cyclopentyl)-propenyl-phosphonic acid diethyl ester

Colourless oil purified by bulb to bulb distillation (oven temp. 175°C/0.35mmHg) 1.176g (76.3%).



Isomer (42d) 0.948g (61.5%)

δ^1**H**	1.01	(3H; d; J_{HH} 5.2 Hz; CH_3 on C(2))
	1.25	(3H; t; J_{HH} 7.2 Hz; CH_3 of POEt[a])
	1.26	(3H; t; J_{HH} 7.2 Hz; CH_3 of POEt[b])
	1.38	(1H; m; CH on C(5))
	1.71	(2H; m; CH on C(1), CH on C(2))
	1.42 - 2.19	(4H; m; CH on C(5), CH_2 on C(4), γ - CH)
	2.51	(1H; m; γ - CH)
	4.01	(4H; d of q; J_{HP} 6.9 Hz; J_{HH} 7.2 Hz; 2 x CH_2 of POEt)
	5.68	(1H; d of d; J_{HP} 23.2 Hz; J_{HH} 17.2 Hz; α - CH)
	6.70	(1H; m; β - CH)

δ^{31}**P**	18.30	

δ^{13}**C**	11.96	(q; J_{CH} 127.5 Hz; CH_3 on C(2))
	15.77	(d of q; J_{CP} 6.1 Hz; J_{CH} 127.0 Hz; 2 x CH_3 of POEt)

	26.32	(t; J_{CH} 130.8 Hz; CH_2 on C(5))
	36.42	(t; J_{CH} 130.8 Hz; CH_2 on C(4))
	38.17	(d of t; J_{CP} 22.2 Hz; J_{CH} 115.1 Hz; γ - CH_2)
	42.99	(d; J_{CH} 128.2 Hz; CH on C(1))
	49.03	(d; J_{CH} 123.0 Hz; CH on C(2))
	61.00	(d of t; J_{CP} 5.0 Hz; J_{CH} 147.1 Hz; 2 x CH_2 of POEt)
	118.69	(d of d; J_{CP} 186.9 Hz; J_{CH} 156.3 Hz; α - CH)
	149.92	(d of d; J_{CP} 4.2 Hz; J_{CH} 155.8 Hz; β - CH)
	218.80	(s; C of C(3))

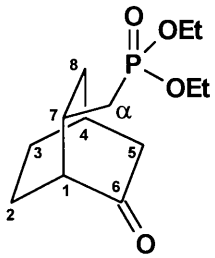
MS	**m/z**	275	(($M^+ + 1$)	82%)	178	($C_7H_{15}PO_3^+$	100%)
		138	($C_9H_{14}O^+$	39%)	122	($C_8H_{10}O^+$	88%)
		111	($C_7H_{11}O^+$	28%)	79	(PO_3^+	38%)
		29	($C_2H_5^+$	66%)	15	(CH_3^+	5%)

IR	1667	(s; C=O)
	1217	(s; P=O)

Analysis	**C**	**H**
Calculated:	56.93%	8.45%
Found:	56.64%	8.56%

(41) 6-Oxo-bicyclo[2.2.2]oct-2-ylmethyl-phosphonic acid diethyl ester

In this case the reaction mixture was allowed to warm up to room temperature where it was stirred for 30 minutes before quenching with aqueous ammonium chloride.The crude yellow oil was purified by bulb to bulb distillation (oven temp. 150°C/0.04mmHg) 0.252g (15.1%).



δ^{1}**H**	1.27	(3H; t; J_{HH} 7.1 Hz; CH_3 of POEt^a)
	1.28	(3H; t; J_{HH} 7.1 Hz; CH_3 of POEt^b)
	1.38 - 1.92	(7H; m; CH on C(8), α - CH_2, CH_2 on C(2), CH_2 on C(3))
	1.96 - 2.26	(5H; m; CH on C(1), CH_2 on C(5), CH on C(4), CH on C(8))
	2.35	(1H; m; CH on C(7))
	4.04	(4H; m; 2 x CH_2 of POEt)
δ^{31}**P**	30.37	
δ^{13}**C**	15.91	(q; J_{CH} 126.9 Hz; CH_3 of POEt^a)
	15.99	(q; J_{CH} 126.9 Hz; CH_3 of POEt^b)
	22.55	(t; J_{CH} 131.2 Hz; CH_2 on C(2))
	22.70	(t; J_{CH} 127.9 Hz; CH_2 on C(3))
	27.49	(d; J_{CH} 136.8 Hz; CH on C(4))
	30.76	(d of d; J_{CP} 3.2 Hz; J_{CH} 126.8 Hz; CH on C(7))
	32.73	(d of d; J_{CP} 132.2 Hz; J_{CH} 128.0 Hz; α - CH_2)
	33.69	(t; J_{CH} 130.8 Hz; CH_2 on C(8))
	44.35	(t; J_{CH} 128.2 Hz; CH_2 on C(5))
	48.33	(d of d; J_{CP} 14.5 Hz; J_{CH} 141.0 Hz; CH on C(1))
	60.97	(t; J_{CH} 147.4 Hz; CH_2 of POEt^a)
	61.16	(t; J_{CH} 147.4 Hz; CH_2 of POEt^b)
	215.68	(s; C of C(6))

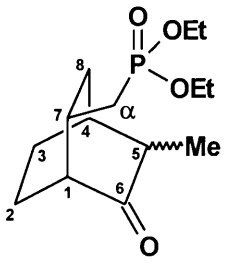
MS	**m/z**	274	(M^+	15%)	246	($C_{11}H_{19}PO_4^+$	100%)
		217	($C_9H_{14}PO_4^+$	93%)	180	($C_7H_{17}PO_3^+$	90%)
		179	($C_7H_{16}PO_3^+$	93%)	152	($C_5H_{13}PO_3^+$	90%)
		138	($C_9H_{14}O^+$	72%)	108	($C_2H_5PO_3^+$	99%)
		97	($C_6H_9O^+$	48%)	79	(PO_3^+	43%)
		29	($C_2H_5^+$	58%)	15	(CH_3^+	4%)

IR	1718	(s; C=O)
	1240	(s; P=O)

Analysis	**C**	**H**
Calculated:	56.92%	8.45%
Found:	56.67%	8.56%

(43) 5-Methyl-6-oxo-bicyclo[2.2.2]oct-2-ylmethyl-phosphonic acid diethyl ester

In this case the reaction mixture was allowed to warm up to room temperature where it was stirred overnight before quenching with aqueous ammonium chloride.The crude yellow oil was purified by bulb to bulb distillation (oven temp. 165°C/0.04mmHg) 1.087g (70.8%).



δ^{1}**H**	1.05	(3H; d; J_{HH} 7.3 Hz; CH_3 on C(5) of isomer B)
	1.09	(3H; d; J_{HH} 7.4 Hz; CH_3 on C(5) of isomer A)
	1.26	(3H; t; J_{HH} 7.1 Hz; CH_3 of $POEt^a$)
	1.27	(3H; t; J_{HH} 7.1 Hz; CH_3 of $POEt^b$)
	1.43 - 1.54	(3H; m; CH on C(2), CH of α - CH_2 , CH on C(3))
	1.62 - 1.99	(6H; m; CH on C(1), CH on C(5), CH on C(4), CH on C(2), CH on C(3), CH of α - CH_2)
	2.10 - 2.15	(2H; m; CH on C(8), CH on C(7))
	2.33	(1H; m; CH on C(8))
	4.03	(4H; m; 2 x CH_2 of POEt)

δ^{31}**P**	30.39	(Isomer A)
	30.55	(Isomer B)

δ^{13}**C**	(Isomer A)	
	13.28	(q; J_{CH} 132.1 Hz; CH_3 on C(5))

	15.74	(d of q; J_{CP} 4.2 Hz; J_{CH} 127.2 Hz; 2 x CH_3 of POEt)
	17.84	(t; J_{CH} 128.9 Hz; CH_2 on C(2))
	22.98	(t; J_{CH} 130.7 Hz; CH_2 on C(3))
	29.05	(t; J_{CH} 129.7 Hz; CH_2 on C(8))
	29.98	(d; J_{CH} 135.9 Hz; CH on C(4))
	33.01	(d; J_{CH} 133.5 Hz; CH on C(7))
	32.80	(d of t; J_{CP} 137.9 Hz; J_{CH} 128.4 Hz; α - CH_2)
	47.01	(d; J_{CH} 126.2 Hz; CH on C(5))
	48.20	(d of d; J_{CP} 14.3 Hz; J_{CH} 127.8 Hz; CH on C(1))
	60.85	(d of t; J_{CP} 5.7 Hz; J_{CH} 146.7 Hz; 2 x CH_2 of POEt)
	218.01	(s; C of C(6))

$\delta^{13}C$ (Isomer B)

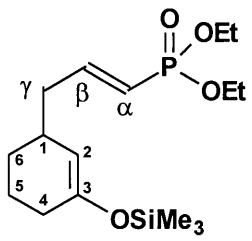
	11.46	(q; J_{CH} 132.1 Hz; CH_3 on C(5))
	15.74	(d of q; J_{CP} 4.2 Hz; J_{CH} 127.2 Hz; 2 x CH_3 of POEt)
	21.73	(t; J_{CH} 128.7 Hz; CH_2 on C(2))
	23.84	(t; J_{CH} 130.6 Hz; CH_2 on C(3))
	31.17	(t; J_{CH} 129.7 Hz; CH_2 on C(8))
	31.83	(d; J_{CH} 138.3 Hz; CH on C(4))
	33.50	(d; J_{CH} 134.7 Hz; CH on C(7))
	35.65	(d of t; J_{CP} 137.9 Hz; J_{CH} 128.4 Hz; α - CH_2)
	46.25	(d; J_{CH} 126.2 Hz; CH on C(5))
	47.78	(d of d; J_{CP} 13.4 Hz; J_{CH} 127.8 Hz; CH on C(1))
	60.85	(d of t; J_{CP} 5.7 Hz; J_{CH} 146.7 Hz; 2 x CH_2 of POEt)
	218.01	(s; C of C(6))

MS	**m/z**	289	((M^+ + 1)	7%)	288	(M^+	20%)
		260	($C_{12}H_{21}PO_4^+$	52%)	231	($C_{10}H_{16}PO_4^+$	25%)
		180	($C_7H_{17}PO_3^+$	78%)	179	($C_7H_{16}PO_3^+$	100%)
		152	($C_5H_{13}PO_3^+$	93%)	138	($C_9H_{14}O^+$	55%)
		97	($C_6H_9O^+$	30%)	79	(PO_3^+	31%)
		29	($C_2H_5^+$	29%)	15	(CH_3^+	<1%)

IR	1714	(s; C=O)
	1240	(s; P=O)

Analysis	**C**	**H**
Calculated:	58.53%	8.42%
Found:	58.26%	8.30%

(44) 3-(3-Trimethylsilane-cyclohex-2-enyl)-propenyl-phosphonic acid diethyl ester



δ^{1}**H**	0.12	(9H; s; 3 x CH_3 of $SiMe_3$)
	1.29	(6H; t; J_{HH} 6.5 Hz; 2 x CH_3 of POEt)
	1.49 - 1.97	(7H; m; CH on C(1), CH_2 on C(6), CH_2 on C(5), CH_2 on C(4))
	2.16	(2H; d of d; $J_{H\gamma H1}$ 7.3 Hz; $J_{H\gamma H\beta}$ 7.3 Hz; γ - CH_2)
	4.02	(2H; d of q; J_{HP} 7.2 Hz; J_{HH} 7.2 Hz; CH_2 of POEt^{a})
	4.04	(2H; d of q; J_{HP} 7.2 Hz; J_{HH} 7.2 Hz; CH_2 of POEt^{b})
	4.70	(1H; d; J_{HH} 1.0 Hz; CH on C(2))
	5.62	(1H; d of d of t; J_{HP} 21.3 Hz; $J_{H\alpha H\beta}$ 17.1 Hz; $J_{H\alpha H\gamma}$ 1.3 Hz; α - CH)
	6.70	(1 H; d of d of t; J_{HP} 21.8 Hz; $J_{H\beta H\alpha}$ 17.1 Hz; $J_{H\beta H\gamma}$ 7.1 Hz; β - CH)
δ^{31}**P**	19.00	
δ^{13}**C**	-0.08	(q; J_{CH} 118.7Hz; CH_3 of $SiMe_3$)
	15.93	(q; J_{CH} 126.9 Hz; CH_3 of POEt^{a})
	16.01	(q; J_{CH} 127.0 Hz; CH_3 of POEt^{b})
	21.09	(t; J_{CH} 126.9 Hz; CH_2 on C(5))
	28.29	(t; J_{CH} 126.8 Hz; CH_2 on C(6))

29.44	(t; J_{CH} 129.1 Hz; CH_2 on C(4))
33.48	(d; J_{CH} 128.4 Hz; CH on C(1))
41.37	(d of t; J_{CP} 21.5 Hz; J_{CH} 127.9 Hz; γ - CH_2)
61.11	(t; J_{CH} 149.2 Hz; CH_2 of $POEt^a$)
61.18	(t; J_{CH} 149.2 Hz; CH_2 of $POEt^b$)
107.30	(d; J_{CH} 152.5 Hz; CH on C(2))
117.96	(d of d; J_{CP} 187.2 Hz; J_{CH} 164.3 Hz; α - CH)
151.02	(s; C of C(3))
151.79	(d of d; J_{CP} 3.6 Hz; J_{CH} 154.8 Hz; β - CH)

10.3 Synthesis and characterisation of compounds prepared in Chapter 4

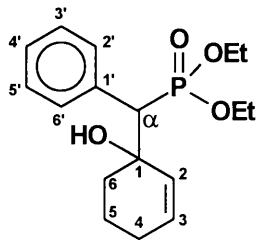
General procedure

n-Butyllithium (2 mol equiv.) (1.6 mol.dm^{-3} solution in hexane) was diluted with THF (*ca* 3cm^3 per mmol of phosphonate). To this solution cooled at -78°C was added dropwise with stirring a solution of aryl-phosphonic acid diethyl ester (**45**) (1.0 mol equiv.) dissolved in THF (*ca* 1cm^3 per mmol of phosphonate) and the solution was stirred at that temperature for 60 min. The electrophile (**36a-c**) (1.2 mol equiv.) dissolved in THF (*ca* 1cm^3 per mmol of phosphonate) was then added and the reaction mixture stirred at -78°C for 2 hours. Saturated aqueous NH_4Cl was added and the solution allowed to warm up to room temperature. The mixture was then extracted with ether (3 x 20cm^3). The combined etheral layers were dried ($MgSO_4$/Na_2SO_4), filtered and the solvent removed under reduced pressure. The products were purified and identified as indicated for individual compounds.

(46a) (1-Hydroxy-cyclohex-2-enyl)-phenyl-methyl-phosphonic acid diethyl ester

Colourless oil purified by column chromatography (EtOAc) yielding two isomers Method A 0.381g (24.5%) Method B 1.420g (98.7%) :

.



Isomer (46a) 1.136g (79.0%)

δ^{1}**H**	0.91	(3H; t; J_{HH} 7.2 Hz; CH_3 of $POEt^a$)
	1.30	(3H; t; J_{HH} 7.1 Hz; CH_3 of $POEt^b$)
	1.50	(2H; m; CH_2 on C(6))
	1.61 - 2.00	(4H; m; CH_2 on C(4), CH_2 on C(5))
	3.27	(1H; d; J_{HP} 23.7 Hz; α - CH)
	3.48	(1H; d of d of t; J_{HP} 9.1 Hz; J_{HH} 7.0 Hz; J_{HH} 7.1 Hz; CH of CH_2 of $POEt^a$)
	3.81	(1H; d of d of t; J_{HP} 8.5 Hz; J_{HH} 10.4 Hz; J_{HH} 7.0 Hz; CH' of CH_2 of $POEt^b$)
	4.08	(2H; m; CH_2 of $POEt^b$)
	4.48	(1H; s; OH)
	5.71	(1H; d of d; J_{H3H4} 6.3 Hz; J_{H3H2} 9.8 Hz; CH on C(3))
	6.00	(1H; d of d; J_{H2H4} 1.9 Hz; J_{H2H3} 10.2 Hz; CH on C(2))
	7.25	(3H; m; CH on C(3'), CH on C(4'), CH on C(5'))
	7.43	(2H; m; CH on C(2'), CH on C(6'))
δ^{31}**P**	28.56	
δ^{13}**C**	15.57	(d of q; J_{CP} 5.4 Hz; J_{CH} 126.2 Hz; CH_3 of $POEt^a$)
	15.90	(d of q; J_{CP} 5.5 Hz; J_{CH} 126.2 Hz; CH_3 of $POEt^b$)
	18.47	(t; J_{CH} 126.7 Hz; CH_2 on C(5))
	24.56	(t; J_{CH} 129.1 Hz; CH_2 on C(4))
	33.87	(d of t; J_{CP} 11.2 Hz; J_{CH} 127.9 Hz; CH_2 on C(6))

	53.54	(d of d; J_{CP} 132.4 Hz; J_{CH} 127.9 Hz; α - CH)
	61.23	(d of t; J_{CP} 7.1 Hz; J_{CH} 147.9 Hz; CH_2 of POEt[a])
	62.85	(d of t; J_{CP} 6.9 Hz; J_{CH} 147.9 Hz; CH_2 of POEt[b])
	71.08	(d; J_{CP} 3.4 Hz; C of C(1))
	127.04	(d; J_{CH} 160.6 Hz; CH on C(4'))
	127.99	(d; J_{CH} 159.2 Hz; CH on C(3'), CH on C(5'))
	128.04	(d; J_{CH} 159.2 Hz; CH on C(3))
	130.38	(d; J_{CH} 159.8 Hz; CH on C(2'))
	130.46	(d; J_{CH} 159.8 Hz; CH on C(6'))
	132.64	(d of d; J_{CP} 4.6 Hz; J_{CH} 173.2 Hz; CH on C(2))
	133.96	(d; J_{CP} 4.8 Hz; C of C(1'))

Isomer (46a') 0.284g (19.7%)

δ^1H	0.95	(3H; t; J_{HH} 7.2 Hz; CH_3 of POEt[a])
	1.22	(3H; t; J_{HH} 7.1 Hz; CH_3 of POEt[b])
	1.50	(2H; m; CH_2 on C(6))
	1.61 - 2.00	(4H; m; CH_2 on C(4), CH_2 on C(5))
	3.22	(1H; d; J_{HP} 22.9 Hz; α - CH)
	3.48	(1H; d of d of t; J_{HP} 9.1 Hz; J_{HH} 7.0 Hz; J_{HH} 7.1 Hz; CH of CH_2 of POEt[a])
	3.81	(1H; d of d of t; J_{HP} 8.5 Hz; J_{HH} 10.4 Hz; J_{HH} 7.0 Hz; CH' of CH_2 of POEt[b])
	4.08	(2H; m; CH_2 of POEt[b])
	4.32	(1H; s; OH)
	5.71	(1H; d of d; J_{H3H4} 6.3 Hz; J_{H3H2} 9.8 Hz; CH on C(3))
	6.00	(1H; d of d; J_{H2H4} 1.9 Hz; J_{H2H3} 10.2 Hz; CH on C(2))
	7.25	(3H; m; CH on C(3'), CH on C(4'), CH on C(5'))
	7.43	(2H; m; CH on C(2'), CH on C(6'))
δ^{31}P	27.85	
δ^{13}C	15.71	(d of q; J_{CP} 6.0 Hz; J_{CH} 126.2 Hz; CH_3 of POEt[a])

	16.03	(d of q; J_{CP} 6.2 Hz; J_{CH} 126.2 Hz; CH_3 of $POEt^b$)
	18.47	(t; J_{CH} 126.7 Hz; CH_2 on C(5))
	24.56	(t; J_{CH} 129.1 Hz; CH_2 on C(4))
	33.87	(d of t; J_{CP} 11.2 Hz; J_{CH} 127.9 Hz; CH_2 on C(6))
	54.77	(d of d; J_{CP} 130.1 Hz; J_{CH} 127.9 Hz; α - CH)
	61.36	(d of t; J_{CP} 6.9 Hz; J_{CH} 147.9 Hz; CH_2 of $POEt^a$)
	63.00	(d of t; J_{CP} 6.8 Hz; J_{CH} 147.9 Hz; CH_2 of $POEt^b$)
	71.08	(d; J_{CP} 3.4 Hz; C of C(1))
	127.04	(d; J_{CH} 160.6 Hz; CH on C(4'))
	127.99	(d; J_{CH} 159.2 Hz; CH on C(3'), CH on C(5'))
	128.04	(d; J_{CH} 159.2 Hz; CH on C(3))
	130.38	(d; J_{CH} 159.8 Hz; CH on C(2'))
	130.46	(d; J_{CH} 159.8 Hz; CH on C(6'))
	132.64	(d of d; J_{CP} 4.6 Hz; J_{CH} 173.2 Hz; CH on C(2))
	133.96	(d; J_{CP} 4.8 Hz; C of C(1'))

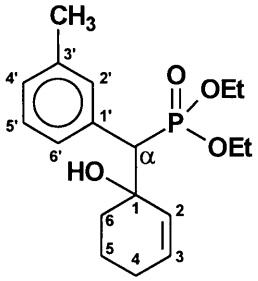
MS	**m/z**	306	($(M^+ - H_2O)$	26%)	228	($C_{11}H_{17}PO_3^+$	100%)
		168	($C_{13}H_{12}^+$	55%)	91	($C_7H_7^+$	51%)
		79	(PO_3^+	7%)	29	($C_2H_5^+$	15%)

IR	3489	(s; OH)
	1231	(s; P=O)

Analysis	**C**	**H**
Calculated:	62.95%	7.77%
Found:	62.92%	7.87%

(46b) (1-Hydroxy-cyclohex-2-enyl)-m-tolyl-methyl-phosphonic acid diethyl ester

Colourless oil purified by column chromatography (EtOAc) yielding two isomers 0.966g (55.4%) :



Isomer (46b) 0.686g (39.3%)

δ^{1}**H**	0.91	(3H; J_{HH} 7.1 Hz; CH_3 of $POEt^a$)
	1.28	(3H; J_{HH} 7.1 Hz; CH_3 of $POEt^b$)
	1.49 - 1.70	(4H; m; CH_2 on C(6), CH_2 on C(5))
	1.83 - 1.99	(2H; m; CH_2 on C(4))
	2.30	(3H; s; CH_3 on C(3'))
	3.23	(1H; d; J_{HP} 23.7 Hz; α - CH)
	3.47	(1H; m; CH of CH_2 of $POEt^a$)
	3.79	(1H; m; CH' of CH_2 of $POEt^a$)
	4.06	(2H; m; CH_2 of $POEt^b$)
	4.51	(1H; s; OH)
	5.70	(1H; d of d; J_{H3H2} 10.2 Hz; J_{H3H4} 3.6 Hz; CH on C(3))
	6.00	(1H; d; J_{HH} 10.2 Hz; CH on C(2))
	7.04	(1H; s; CH on C(2'))
	7.19	(3H; m; CH on C(4'), CH on C(5'), CH on C(6'))
δ^{31}**P**	28.72	
δ^{13}**C**	15.85	(d of q; J_{CP} 6.1 Hz; J_{CH} 125.6 Hz; CH_3 of $POEt^a$)
	16.19	(d of q; J_{CP} 6.0 Hz; J_{CH} 125.6 Hz; CH_3 of $POEt^b$)
	18.66	(t; J_{CH} 130.0 Hz; CH_2 on C(5))
	21.36	(q; J_{CH} 129.8 Hz; CH_3 on C(3'))
	24.73	(t; J_{CH} 127.8 Hz; CH_2 on C(4))

	33.02	(d of t; J_{CP} 11.3 Hz; J_{CH} 129.6 Hz; CH_2 on C(6))
	53.65	(d of d; J_{CP} 131.8 Hz; J_{CH} 128.0 Hz; α - CH)
	61.45	(d of t; J_{CP} 7.8 Hz; J_{CH} 147.6 Hz; CH_2 of $POEt^b$)
	63.18	(d of t; J_{CP} 7.1 Hz; J_{CH} 150.1 Hz; CH_2 of $POEt^a$)
	70.19	(s; C of C(1))
	127.65	(d of d; J_{CP} 6.7 Hz; J_{CH} 160.1 Hz; CH on C(6'))
	127.69	(d; J_{CH} 159.9 Hz; CH on C(4'))
	127.98	(d; J_{CH} 153.8 Hz; CH on C(3))
	128.14	(d; J_{CH} 157.6 Hz; CH on C(5'))
	131.24	(d of d; J_{CP} 7.5 Hz; J_{CH} 156.4 Hz; CH on C(2'))
	132.85	(d of d; J_{CP} 4.4 Hz; J_{CH} 156.4 Hz; CH on C(2))
	137.67	(d; J_{CP} 4.9 Hz; C of C(1'))
	141.55	(s; C of C(3'))

Isomer (46b') (16.1%)

δ^1H	0.96	(3H; J_{HH} 7.0 Hz; CH_3 of $POEt^a$)
	1.30	(3H; J_{HH} 6.9 Hz; CH_3 of $POEt^b$)
	1.49 - 1.66	(4H; m; CH_2 on C(6), CH_2 on C(5))
	1.77 - 1.93	(2H; m; CH_2 on C(4))
	2.30	(3H; s; CH_3 on C(3'))
	3.18	(1H; d; J_{HP} 23.0 Hz; α - CH)
	3.58	(1H; m; CH of CH_2 of $POEt^a$)
	3.82	(1H; m; CH' of CH_2 of $POEt^a$)
	4.06	(2H; m; CH_2 of $POEt^b$)
	4.50	(1H; s; OH)
	5.62	(1H; d; J_{HH} 11.1 Hz; CH on C(2))
	5.75	(1H; m; CH on C(3))
	7.04	(1H; m; CH on C(2'))
	7.19	(3H; m; CH on C(4'), CH on C(5'), CH on C(6'))
δ^{31}P	28.01	

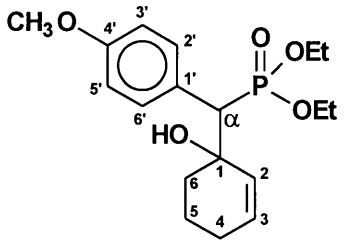
$\delta^{13}C$	15.94	(d of q; J_{CP} 6.0 Hz; J_{CH} 125.6 Hz; CH_3 of $POEt^a$)
	16.27	(d of q; J_{CP} 6.3 Hz; J_{CH} 125.6 Hz; CH_3 of $POEt^b$)
	18.67	(t; J_{CH} 130.0 Hz; CH_2 on C(5))
	21.36	(q; J_{CH} 129.8 Hz; CH_3 on C(3'))
	24.81	(t; J_{CH} 127.8 Hz; CH_2 on C(4))
	36.47	(d of t; J_{CP} 6.3 Hz; J_{CH} 126.2 Hz; CH_2 on C(6))
	54.89	(d of d; J_{CP} 130.5 Hz; J_{CH} 127.4 Hz; α - CH)
	61.58	(d of t; J_{CP} 7.2 Hz; J_{CH} 147.4 Hz; CH_2 of $POEt^a$)
	63.11	(d of t; J_{CP} 7.4 Hz; J_{CH} 147.6 Hz; CH_2 of $POEt^b$)
	71.06	(s; C of C(1))
	127.75	(d; J_{CH} 160.1 Hz; CH on C(6'))
	127.78	(d; J_{CH} 159.9 Hz; CH on C(4'))
	128.20	(d; J_{CH} 157.6 Hz; CH on C(5'))
	130.23	(d of d; J_{CP} 10.0 Hz; J_{CH} 156.4 Hz; CH on C(2'))
	130.60	(t; J_{CH} 153.8 Hz; CH on C(3))
	131.34	(d of d; J_{CP} 4.2 Hz; J_{CH} 156.4 Hz; CH on C(2))
	133.95	(d; J_{CP} 5.5 Hz; C of C(1'))
	137.64	(s; C of C(3'))

MS	**m/z**	320	($(M^+ - H_2O)$	3%)	182	($C_{14}H_{14}$	9%)
		105	($C_8H_9^+$	100%)	79	(PO_3^+	13%)
		29	($C_2H_5^+$	18%)			

IR	3417	(s; OH)
	1209	(s; P=O)

(46c) (1-Hydroxy-cyclohex-2-enyl)-(4-methoxy-phenyl)-methyl-phosphonic acid diethyl ester

Colourless oil purified by column chromatography (EtOAc) yielding two isomers 1.037g (87.7%) :



Isomer (46c) 0.819g (69.3%)

δ^{1}**H**	0.97	(3H; J_{HH} 7.2 Hz; CH_3 of $POEt^a$)
	1.29	(3H; J_{HH} 7.0 Hz; CH_3 of $POEt^b$)
	1.39 - 1.68	(4H; m; CH_2 on C(6), CH_2 on C(5))
	1.75 - 1.99	(2H; m; CH_2 on C(4))
	3.22	(1H; d; J_{HP} 23.8 Hz; α - CH)
	3.52	(1H; m; CH of CH_2 of $POEt^a$)
	3.76	(3H; s; CH_3 of OMe)
	3.82	(1H; m; CH' of CH_2 of $POEt^a$)
	4.03	(2H; m; CH_2 of $POEt^b$)
	4.41	(1H; s; OH)
	5.70	(1H; d of t; J_{H3H2} 10.2 Hz; J_{H3H4} 3.7 Hz; CH on C(3))
	5.96	(1H; d of d; J_{H2H3} 10.2 Hz; J_{H2H4} 1.9 Hz;CH on C(2))
	6.81	(2H; d; J_{HH} 8.6 Hz; CH on C(3'), CH on C(5'))
	7.32	(2H; d of d; J_{HH} 8.6 Hz; J_{HP} 2.0 Hz; CH on C(2'), CH on C(6'))
δ^{31}**P**	28.85	
δ^{13}**C**	15.97	(d of q; J_{CP} 5.2 Hz; J_{CH} 126.0 Hz; CH_3 of $POEt^a$)
	16.18	(d of q; J_{CP} 6.0 Hz; J_{CH} 126.0 Hz; CH_3 of $POEt^b$)
	18.62	(t; J_{CH} 126.1 Hz; CH_2 on C(5))
	24.71	(t; J_{CH} 126.9 Hz; CH_2 on C(4))

	33.89	(d of t; J_{CP} 11.2 Hz; J_{CH} 127.3 Hz; CH_2 on C(6))
	52.81	(d of d; J_{CP} 132.2 Hz; J_{CH} 128.5 Hz; α - CH)
	55.06	(q; J_{CH} 143.7 Hz; CH_3 of OMe)
	61.48	(d of t; J_{CP} 7.3 Hz; J_{CH} 147.5 Hz; CH_2 of $POEt^a$)
	63.06	(d of t; J_{CP} 7.0 Hz; J_{CH} 148.0 Hz; CH_2 of $POEt^b$)
	70.28	(s; C of C(1))
	113.57	(d; J_{CH} 158.9 Hz; CH on C(3'), CH on C(5'))
	125.96	(d; J_{CP} 4.9 Hz; CH on C(1'))
	128.23	(d; J_{CH} 155.1 Hz; CH on C(3))
	131.57	(d of d; J_{CP} 6.9 Hz; J_{CH} 158.8 Hz; CH on C(2'), CH on C(6'))
	132.76	(d of d; J_{CP} 4.6 Hz; J_{CH} 157.8 Hz; CH on C(2))
	158.80	(s; C of C(4'))

Isomer (46c') 0.301g (25.4%)

δ^1**H**	1.20	(3H; J_{HH} 7.2 Hz; CH_3 of $POEt^a$)
	1.28	(3H; J_{HH} 7.2 Hz; CH_3 of $POEt^b$)
	1.49 - 1.66	(4H; m; CH_2 on C(6), CH_2 on C(5))
	1.77 - 1.93	(2H; m; CH_2 on C(4))
	1.98	(3H; s; CH_3 on C(3'))
	3.16	(1H; d; J_{HP} 22.9 Hz; α - CH)
	4.06	(4H; m; 2 x CH_2 of POEt)
	4.31	(1H; s; OH)
	5.70	(1H; m; CH on C(3))
	5.99	(1H; d; J_{HH} 10.2 Hz; CH on C(2))
	7.04	(1H; s; CH on C(2'))
	7.19	(3H; m; CH on C(4'), CH on C(5'), CH on C(6'))
δ^{31}**P**	28.01	
δ^{13}**C**	15.74	(d of q; J_{CP} 5.2 Hz; J_{CH} 125.6 Hz; CH_3 of $POEt^a$)
	15.82	(d of q; J_{CP} 6.0 Hz; J_{CH} 125.6 Hz; CH_3 of $POEt^b$)
	18.26	(t; J_{CH} 130.0 Hz; CH_2 on C(5))

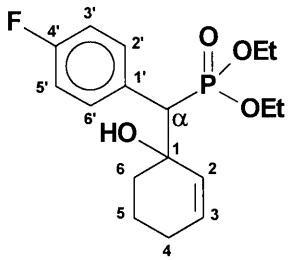
20.39	(q; J_{CH} 129.8 Hz; CH_3 on C(3'))
24.33	(t; J_{CH} 127.8 Hz; CH_2 on C(4))
33.03	(d of t; J_{CP} 6.1 Hz; J_{CH} 126.2 Hz; CH_2 on C(6))
54.42	(d of d; J_{CP} 131.1 Hz; J_{CH} 127.4 Hz; α - CH)
59.74	(d of t; J_{CP} 7.0 Hz; J_{CH} 147.4 Hz; CH_2 of $POEt^a$)
61.06	(d of t; J_{CP} 7.0 Hz; J_{CH} 147.6 Hz; CH_2 of $POEt^b$)
70.69	(s; C of C(1))
127.25	(d; J_{CH} 160.1 Hz; CH on C(6'))
127.35	(d; J_{CH} 159.9 Hz; CH on C(4'))
127.52	(d; J_{CH} 153.8 Hz; CH on C(3))
130.04	(d; J_{CH} 157.6 Hz; CH on C(5'))
130.87	(d of d; J_{CP} 6.8 Hz; J_{CH} 156.4 Hz; CH on C(2'))
132.63	(d of d; J_{CP} 4.2 Hz; J_{CH} 156.4 Hz; CH on C(2))
133.60	(d; J_{CP} 4.9 Hz; C of C(1'))
137.15	(s; C of C(3'))

MS	**m/z**	355	($(M^+ + 1)$	<1%)	336	($(M^+ - H_2O)$	5%)
		199	(C14HO	21%)	21	($C_8H_9O^+$	100%)
		79	(PO_3^+	3%)	29	($C_2H_5^+$	8%)

IR	3436	(s; OH)
	1241	(s; P=O)

(46f) (4-Fluoro-phenyl)-(1-hydroxy-cyclohex-2-enyl)-methyl-phosphonic acid diethyl

Yellow oil prepared by method B. This crude oil was purified by column chromatography using ethyl acetate as eluent yielding 0.714g (100.0%) of a colourless oil containing two isomers.



Isomer A

δ^{1}**H**	0.96	(3H; J_{HH} 7.4 Hz; CH_3 of $POEt^a$)
	1.30	(3H; J_{HH} 7.7 Hz; CH_3 of $POEt^b$)
	1.43 - 1.52	(2H; m; CH_2 on C(5))
	1.63 - 1.97	(4H; m; CH_2 on C(4), CH_2 on C(6))
	2.00	(1H; s; OH)
	3.26	(1H; d; J_{HP} 23.7 Hz; α - CH)
	3.53	(1H; m; CH of CH_2 of $POEt^a$)
	3.84	(1H; m; CH' of CH_2 of $POEt^a$)
	4.08	(2H; m; CH_2 of $POEt^b$)
	5.72	(1H; d of t; J_{H3H2} 10.2 Hz; J_{H3H4} 3.7 Hz; CH on C(3))
	5.99	(1H; d; J_{H2H3} 10.2 Hz; CH on C(2))
	6.97	(2H; d of d; J_{HF} 8.6 Hz; J_{HH} 8.6 Hz; CH on C(3'), CH on C(5'))
	7.40	(2H; m; CH on C(2'), CH on C(6'))
δ^{31}**P**	28.20	(d; J_{PF} 3.8 Hz)
δ^{19}**F**	-115.46	
δ^{13}**C**	15.74	(d of q; J_{CP} 5.3 Hz; J_{CH} 129.9 Hz; CH_3 of $POEt^a$)
	15.98	(d of q; J_{CP} 6.2 Hz; J_{CH} 129.9 Hz; CH_3 of $POEt^b$)
	18.40	(t; J_{CH} 131.2 Hz; CH_2 on C(5))
	24.50	(t; J_{CH} 126.8 Hz; CH_2 on C(4))
	33.81	(d of t; J_{CP} 11.2 Hz; J_{CH} 128.1 Hz; CH_2 on C(6))
	52.67	(d of d; J_{CP} 132.3 Hz; J_{CH} 128.6 Hz; α - CH)
	61.41	(d of t; J_{CP} 7.3 Hz; J_{CH} 147.7 Hz; CH_2 of $POEt^a$)
	62.87	(d of t; J_{CP} 7.5 Hz; J_{CH} 148.5 Hz; CH_2 of $POEt^b$)
	70.98	(s; C of C(1))
	114.80	(d of d; J_{CF} 21.0 Hz; J_{CH} 165.3 Hz; CH on C(3'), CH on C(5'))
	128.21	(d; J_{CH} 155.1 Hz; CH on C(3))
	129.76	(s; C of C(1'))
	131.91	(d; J_{CH} 161.1 Hz; CH on C(2))

	131.97	(d of d; J_{CF} 7.7 Hz; J_{CH} 155.8 Hz; CH on C(6'))
	132.43	(d of d; J_{CF} 4.5 Hz; J_{CH} 155.8 Hz; CH on C(2'))
	161.88	(d; J_{CF} 247.1 Hz; C of C(4'))

Isomer B

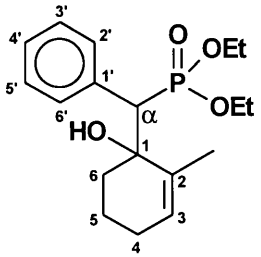
δ^{1}**H**	0.99	(3H; J_{HH} 7.1 Hz; CH_3 of $POEt^a$)
	1.30	(3H; J_{HH} 7.0 Hz; CH_3 of $POEt^b$)
	1.51	(2H; m; CH_2 on C(5))
	1.74 - 2.01	(4H; m; CH_2 on C(4), CH_2 on C(6))
	3.21	(1H; d; J_{HP} 23.0 Hz; α - CH)
	3.61	(1H; m; CH of CH_2 of $POEt^a$)
	3.84	(1H; m; CH' of CH_2 of $POEt^a$)
	4.08	(2H; m; CH_2 of $POEt^b$)
	4.23	(1H; s; OH)
	5.58	(1H; J_{HH} 10.4 Hz; CH on C(2))
	5.79	(1H; m; CH on C(3))
	6.96	(2H; d of d; J_{HF} 8.6 Hz; J_{HH} 8.6 Hz; CH on C(3'), CH on C(5'))
	7.40	(2H; m; CH on C(2'), CH on C(6'))
δ^{31}**P**	27.45	(d; J_{PF} 3.9 Hz)
δ^{19}**F**	-115.57	
δ^{13}**C**	15.61	(d of q; J_{CP} 5.3 Hz; J_{CH} 129.9 Hz; CH_3 of $POEt^a$)
	15.95	(d of q; J_{CP} 6.2 Hz; J_{CH} 129.9 Hz; CH_3 of $POEt^b$)
	18.32	(t; J_{CH} 131.2 Hz; CH_2 on C(5))
	24.44	(t; J_{CH} 126.8 Hz; CH_2 on C(4))
	35.96	(d of t; J_{CP} 6.3 Hz; J_{CH} 128.4 Hz; CH_2 on C(6))
	53.74	(d of d; J_{CP} 132.1 Hz; J_{CH} 127.7 Hz; α - CH)
	61.36	(d of t; J_{CP} 7.3 Hz; J_{CH} 147.7 Hz; CH_2 of $POEt^a$)
	62.66	(d of t; J_{CP} 7.5 Hz; J_{CH} 148.5 Hz; CH_2 of $POEt^b$)
	70.71	(s; C of C(1))

	114.71	(d of d; J_{CF} 21.4 Hz; J_{CH} 165.3 Hz; CH on C(3'), CH on C(5'))
	130.42	(d; J_{CH} 155.1 Hz; CH on C(3))
	128.08	(s; C of C(1'))
	129.80	(d of d; J_{CF} 9.4 Hz; J_{CH} 155.8 Hz; CH on C(6'), CH on C(2'))
	131.86	(d; J_{CH} 161.1 Hz; CH on C(2))
	161.80	(d; J_{CF} 246.4 Hz; C of C(4'))
IR	3440	(s; -OH)
	1219	(s; P=O)

MS	**m/z**	324	($(M^+ - H_2O)$	8%)	246	($C_{11}H_{16}FPO_3^+$	76%)
		187	($C_{13}H_{12}F^+$	12%)	109	($C_7H_6F^+$	100%)
		81	($PO_3H_2^+$	16%)	29	($C_2H_5^+$	16%)

(46g) (1-Hydroxy-2-methyl-cyclohex-2-enyl)-phenyl-methyl-phosphonic acid diethyl ester

Yellow oil prepared by method B but after addition of the electrophile the mixture was allowed to warm up to - 40°C where it was stirred for 2 hours. This crude oil was purified by column chromatography using ethyl acetate: hexane (2:3) as eluent to yield:



Isomer (46g) 0.235g (7.9%)

δ^1**H**	0.87	(3H; t; J_{HH} 7.0 Hz; CH_3 of $POEt^a$)
	1.26	(3H; s; CH_3 on C(2))
	1.29	(3H; t; J_{HH} 7.1 Hz; CH_3 of $POEt^b$)
	1.70	(3H; m; CH on C(6), CH_2 on C(5))
	2.01	(2H; m; CH_2 on C(4))
	2.48	(1H; m; CH on C(6))
	3.49	(1H; d; J_{HP} 22.6 Hz; α - CH)
	3.51	(1H; m; CH of CH_2 of $POEt^a$)

	3.78	(1H; m; CH' of CH_2 of $POEt^a$)
	4.10	(2H; m; CH_2 of $POEt^b$)
	5.41	(1H; m; CH on C(3))
	7.27	(3H; m; CH on C(3'), CH on C(4'), CH on C(5'))
	7.46	(2H; m; CH on C(2'), CH on C(6'))
$\delta^{31}P$	27.16	
$\delta^{13}C$	15.54	(d of q; J_{CP} 5.7 Hz; J_{CH} 126.9 Hz; CH_3 of $POEt^a$)
	15.85	(d of q; J_{CP} 6.4 Hz; J_{CH} 126.9 Hz; CH_3 of $POEt^b$)
	18.49	(q; J_{CH} 126.6 Hz; CH_3 on C(2))
	18.89	(t; J_{CH} 126.7 Hz; CH_2 on C(5))
	24.43	(t; J_{CH} 125.5 Hz; CH_2 on C(4))
	36.28	(t; J_{CH} 128.3 Hz; CH_2 on C(6))
	51.76	(d of d; J_{CP} 131.5 Hz; J_{CH} 128.1 Hz; α - CH)
	60.93	(d of t; J_{CP} 7.2 Hz; J_{CH} 143.4 Hz; CH_2 of $POEt^a$)
	62.76	(d of t; J_{CP} 6.9 Hz; J_{CH} 143.2 Hz; CH_2 of $POEt^b$)
	73.57	(s; C of C(1))
	125.42	(d; J_{CH} 153.5 Hz; CH on C(3))
	127.01	(d; J_{CH} 160.3 Hz; CH on C(4'))
	127.71	(d; J_{CH} 159.2 Hz; CH on C(3'), CH on C(5'))
	131.20	(d of d; J_{CP} 8.1 Hz; J_{CH} 159.8 Hz; CH on C(2'), CH on C(6'))
	133.73	(d; J_{CP} 4.5 Hz; C of C(1'))
	137.83	(d; J_{CP} 9.4 Hz; C of C(2))

MS	**m/z**	320	($(M^+ - H_2O)$	10%)	228	($C_{11}H_{17}PO_3^+$	100%)
		172	($C_7H_8PO_3^+$	66%)	91	($C_7H_7^+$	77%)
		79	(PO_3^+	8%)	29	($C_2H_5^+$	13%)

Isomer (46g') 0.523g (17.6%)

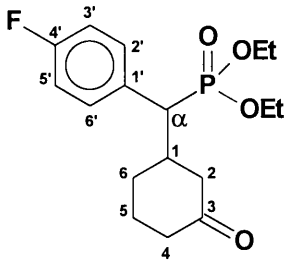
δ^1H	1.10	(3H; t; J_{HH} 7.1 Hz; CH_3 of $POEt^a$)
	1.25	(3H; t; J_{HH} 7.0 Hz; CH_3 of $POEt^b$)

	1.59 - 1.71	(5H; m; CH_3 on C(2), CH_2 on C(5))
	1.82 - 1.92	(2H; m; CH_2 on C(4))
	2.12 - 2.22	(2H; m; CH_2 on C(6))
	3.59	(1H; d; J_{HP} 25.0 Hz; α - CH)
	3.84	(2H; d of q; J_{HP} 7.1 Hz; J_{HH} 7.1 Hz; CH_2 of $POEt^a$)
	4.06	(2H; d of q; J_{HP} 7.1 Hz; J_{HH} 7.0 Hz; CH_2 of $POEt^b$)
	5.45	(1H; m; CH on C(3))
	7.23	(3H; m; CH on C(3'), CH on C(4'), CH on C(5'))
	7.38	(2H; m; CH on C(2'), CH on C(6'))
$\delta^{31}P$	28.69	
$\delta^{13}C$	15.67	(d of q; J_{CP} 7.2 Hz; J_{CH} 129.3 Hz; CH_3 of $POEt^a$)
	15.77	(d of q; J_{CP} 7.0 Hz; J_{CH} 129.3 Hz; CH_3 of $POEt^b$)
	17.90	(q; J_{CH} 128.2 Hz; CH_3 on C(2))
	18.36	(t; J_{CH} 127.7 Hz; CH_2 on C(5))
	24.67	(t; J_{CH} 124.7 Hz; CH_2 on C(4))
	35.14	(d of t; J_{CP} 5.1 Hz; J_{CH} 126.4 Hz; CH_2 on C(6))
	52.88	(d of d; J_{CP} 130.6 Hz; J_{CH} 127.0 Hz; α - CH)
	61.80	(d of t; J_{CP} 6.7 Hz; J_{CH} 147.6 Hz; CH_2 of $POEt^a$)
	62.21	(d of t; J_{CP} 7.0 Hz; J_{CH} 148.1 Hz; CH_2 of $POEt^b$)
	73.57	(s; C of C(1))
	126.75	(d; J_{CH} 160.4 Hz; CH on C(4'))
	127.40	(d; J_{CH} 160.6 Hz; CH on C(3))
	127.52	(d; J_{CH} 160.7 Hz; CH on C(3'), CH on C(5'))
	130.53	(d of d; J_{CP} 6.0 Hz; J_{CH} 158.6 Hz; CH on C(2'), CH on C(6'))
	133.59	(d; J_{CP} 6.8 Hz; C of C(1'))
	135.27	(d; J_{CP} 13.2 Hz; C of C(2))

MS	**m/z**	320	($(M^+ - H_2O)$	10%)	228	($C_{11}H_{17}PO_3^+$	100%)
		172	($C_7H_8PO_3^+$	66%)	91	($C_7H_7^+$	77%)
		79	(PO_3^+	8%)	29	($C_2H_5^+$	13%)

(47a) (4-Fluoro-phenyl)-(3-oxo-cyclohexyl)-methyl-phosphonic acid diethyl ester

Yellow oil prepared by method B but after addition of the electrophile the mixture was allowed to warm up to -10°C. This crude oil was purified by column chromatography using ethyl acetate as eluent yielding 0.242g (36.0%) of a colourless oil containing two isomers.



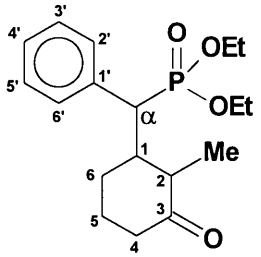
δ^{1}**H**	1.13	(3H; t; J_{HH} 7.2 Hz; CH_3 of $POEt^a$)
	1.19	(3H; t; J_{HH} 7.1 Hz; CH_3 of $POEt^b$)
	1.34 - 1.47	(1H; m; CH on C(6))
	1.86 - 1.92	(2H; m; CH on C(5) CH on C(6))
	2.01 - 2.09	(1H; m; CH on C(5))
	2.22	(1H; m; CH on C(2))
	2.37	(2H; m; CH_2 on C(4))
	2.56	(1H; m; CH on C(1))
	2.80	(1H; m; CH on C(2))
	3.00	(1H; d; J_{HP} 21.4 Hz; α - CH)
	3.52	(1H; m; CH of CH_2 of $POEt^a$)
	3.76	(1H; m; CH' of CH_2 of $POEt^a$)
	3.93	(2H; m; CH_2 of $POEt^b$)
	6.91	(2H; m; CH on C(3'), CH on C(5'))
	7.20	(2H; m; CH on C(2'), CH on C(6'))
δ^{31}**P**	27.09	(d; J_{PF} 3.3 Hz)
	27.16	(d; J_{PF} 4.4 Hz)
δ^{19}**F**	-115.25	(Major)
	-116.44	

$\delta^{13}C$	15.95	(d of q; J_{CP} 5.7 Hz; J_{CH} 127.2 Hz; CH_3 of $POEt^a$)
	16.14	(d of q; J_{CP} 5.9 Hz; J_{CH} 127.2 Hz; CH_3 of $POEt^b$)
	24.58	(t; J_{CH} 127.1 Hz; CH_2 on C(5))
	28.77	(d of t; J_{CP} 9.4 Hz; J_{CH} 125.6 Hz; CH_2 on C(6))
	39.59	(d; J_{CH} 128.8 Hz; CH on C(1))
	40.80	(t; J_{CH} 127.4 Hz; CH_2 on C(4))
	47.14	(d of t; J_{CP} 8.2 Hz; J_{CH} 130.3 Hz; CH_2 on C(2))
	49.24	(d of d; J_{CP} 138.9 Hz; J_{CH} 126.6 Hz; α - CH)
	61.99	(d of t; J_{CP} 6.8 Hz; J_{CH} 147.1 Hz; CH_2 of $POEt^a$)
	62.64	(d of t; J_{CP} 7.2 Hz; J_{CH} 148.9 Hz; CH_2 of $POEt^b$)
	115.26	(d of d; J_{CF} 19.0 Hz; J_{CH} 160.4 Hz; CH on C(3'), CH on C(5'))
	130.33	(d; J_{CP} 23.0 Hz; C of C(1'))
	131.17	(d of d of d; J_{CF} 6.9 Hz; J_{CP} 6.6 Hz; J_{CH} 158.9 Hz; CH on C(2'), CH on C(6'))
	161.88	(d of d; J_{CF} 247.8 Hz; J_{CP} 20.5 Hz; C of C(4'))
	210.25	(s; C of C(3))
IR	1707	(s; C=O)
	1220	(s; P=O)

MS	**m/z**	342	(M^+	2%)	246	($C_{11}H_{16}FPO_3^+$	100%)
		204	($C_{13}H_{13}FO^+$	16%)	109	($C_7H_6F^+$	43%)
		81	($PO_3H_2^+$	5%)	29	($C_2H_5^+$	8%)

(47b) Phenyl-(3-oxo-2-methyl-cyclohexyl)-methyl-phosphonic acid diethyl ester

Yellow oil prepared by method B but after the addition of the electrophile the mixture was allowed to warm up to -40°C where it was stirred for 2 hours. This crude oil was purified by column chromatography using ethyl acetate: hexane (2:3) as eluent to yield 0.391g (13.2%) of a colourless oil.



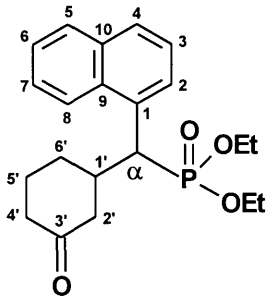
δ^{1}**H**	0.91	(3H; t; J_{HH} 7.0 Hz; CH_3 of $POEt^a$)
	1.11	(3H; d; J_{HP} 6.5 Hz; CH_3 on C(2))
	1.24	(3H; t; J_{HH} 7.1 Hz; CH_3 of $POEt^b$)
	1.46 - 1.55	(2H; m; CH on C(5), CH on C(6))
	1.94 - 2.55	(6H; m; CH on C(1), CH on C(2), CH_2 on C(4), CH on C(5), CH on C(6))
	3.32	(1H; d of d; J_{HP} 26.3 Hz; J_{HH} 3.1 Hz; α - CH)
	3.65	(1H; m; CH of CH_2 of $POEt^a$)
	3.85	(1H; m; CH' of CH_2 of $POEt^a$)
	4.05	(2H; d of q; J_{HP} 7.1 Hz; J_{HH} 7.1 Hz; CH_2 of $POEt^b$)
	7.28	(3H; m; CH on C(3'), CH on C(4'), CH on C(5'))
	7.42	(2H; m; CH on C(2'), CH on C(6'))
δ^{31}**P**	28.61	
δ^{13}**C**	11.94	(q; J_{CH} 126.8 Hz; CH_3 on C(2))
	15.68	(d of q; J_{CP} 5.4 Hz; J_{CH} 128.8 Hz; CH_3 of $POEt^a$)
	15.99	(d of q; J_{CP} 5.4 Hz; J_{CH} 128.8 Hz; CH_3 of $POEt^b$)
	24.81	(t; J_{CH} 130.1 Hz; CH_2 on C(5))
	27.20	(d of t; J_{CP} 2.2 Hz; J_{CH} 128.6 Hz; CH_2 on C(6))
	40.99	(t; J_{CH} 129.1 Hz; CH_2 on C(4))
	44.91	(d of d; J_{CP} 139.5 Hz; J_{CH} 123.3 Hz; α - CH)

	45.24	(d; J_{CH} 129.7 Hz; CH on C(1))
	47.01	(d of d; J_{CP} 14.6 Hz; J_{CH} 129.5 Hz; CH on C(2))
	61.22	(d of t; J_{CP} 7.6 Hz; J_{CH} 146.4 Hz; CH_2 of POEt^a)
	62.27	(d of t; J_{CP} 6.8 Hz; J_{CH} 148.0 Hz; CH_2 of POEt^b)
	127.00	(d; J_{CH} 160.8 Hz; CH on C(4'))
	127.90	(d; J_{CH} 159.8 Hz; CH on C(3'), CH on C(5'))
	130.88	(d; J_{CH} 166.2 Hz; CH on C(2'), CH on C(6'))
	132.17	(d; J_{CP} 4.4 Hz; C of C(1'))

MS	**m/z**	339	($(M^+ + 1)$	1%)	338	(M^+	3%)
		228	($C_{11}H_{17}PO_3^+$	100%)	200	($C_{14}H_{16}O^+$	73%)
		172	($C_7H_8PO_3^+$	63%)	91	($C_7H_7^+$	78%)
		79	(PO_3^+	6%)	29	($C_2H_5^+$	14%)

(47c) Naphthalen-1-yl-3-oxocyclohexyl-methyl-phosphonic acid diethyl ester

Yellow oil prepared by method B but after addition of the electrophile the mixture was allowed to warm up to room temperature. This crude oil was purified by bulb to bulb distillation O.T. 250°C/0.5mmHg yielding 0.242g (36.0%) of a yellow oil containing two isomers.



Isomer (47c) 0.151g (22.5%)

δ^1H	0.71	(3H; t; J_{HH} 7.0 Hz; CH_3 of POEt^a)
	1.25	(3H; t; J_{HH} 7.0 Hz; CH_3 of POEt^b)
	1.29	(1H; m; CH on C(6'))
	1.50	(1H; m; CH on C(5'))
	1.87	(2H; m; CH on C(5'), CH on C(6'))
	2.11 - 2.32	(3H; m; CH on C(2'), CH_2 on C(4'))
	2.68	(1H; m; CH on C(1'))

	2.87	(1H; d of d; J_{HP} 14.2 Hz; J_{HH} 2.0 Hz; CH on C(2'))
	3.28	(1H; m; CH of CH_2 of $POEt^a$)
	3.69	(1H; m; CH' of CH_2 of $POEt^a$)
	3.91	(1H; d of d; J_{HP} 23.6 Hz; J_{HH} 8.2 Hz; α - CH)
	4.05	(2H; m; CH_2 of $POEt^b$)
	7.49	(3H; m; CH on C(6), CH on C(7), CH on C(8))
	7.82	(3H; m; CH on C(2), CH on C(3), CH on C(4))
	8.00	(1H; d; J_{HH} 8.1 Hz; CH on C(5))
$\delta^{31}P$	27.56	
$\delta^{13}C$	15.84	(d of q; J_{CP} 5.2 Hz; J_{CH} 126.9 Hz; CH_3 of $POEt^a$)
	16.29	(d of q; JCP 5.7 Hz; J_{CH} 126.9 Hz; CH_3 of $POEt^b$)
	24.60	(t; J_{CH} 130.4 Hz; CH_2 on C(5'))
	29.24	(d of t; J_{CP} 10.8 Hz; J_{CH} 123.0 Hz; CH_2 on C(6))
	40.85	(t; J_{CH} 128.8 Hz; CH_2 on C(4'))
	41.05	(d; J_{CH} 128.1 Hz; CH on C(1'))
	43.05	(d of d; J_{CP} 138.3 Hz; J_{CH} 127.4 Hz; α - CH)
	49.56	(d of t; J_{CP} 6.4 Hz; J_{CH} 128.6 Hz; CH_2 on C(2'))
	61.40	(d of t; J_{CP} 7.2 Hz; J_{CH} 149.2 Hz; CH_2 of $POEt^a$)
	62.86	(d of t; J_{CP} 7.5 Hz; J_{CH} 149.1 Hz; CH_2 of $POEt^b$)
	122.65	(d; J_{CH} 156.0 Hz; CH on C(5))
	125.19	(d; J_{CH} 159.2 Hz; CH on C(8))
	125.59	(d; J_{CH} 160.6 Hz; CH on C(6))
	126.46	(d; J_{CH} 156.3 Hz; CH on C(7))
	127.01	(d of d; J_{CP} 6.2 Hz; J_{CH} 157.2 Hz; CH on C(2))
	127.89	(d of d; J_{CP} 2.2 Hz; J_{CH} 159.6 Hz; CH on C(3))
	129.14	(d; J_{CH} 159.6 Hz; CH on C(4))
	131.24	(d; J_{CP} 4.6 Hz; C of C(9))
	132.59	(d; J_{CP} 8.5 Hz; C of C(1))
	133.95	(s; C of C(10))
	210.37	(s; C of C(3'))

Isomer (47c') 0.091g (13.5%)

δ^{1}**H**	0.70	(3H; t; J_{HH} 7.0 Hz; CH_3 of $POEt^a$)
	1.24	(3H; t; J_{HH} 7.1 Hz; CH_3 of $POEt^b$)
	1.31 - 1.95	(4H; m; CH_2 on C(5'), CH_2 on C(6'))
	2.11 - 2.32	(3H; m; CH on C(2'), CH_2 on C(4'))
	2.67	(1H; m; CH on C(1'))
	2.88	(1H; d; J_{HP} 16.1 Hz; CH on C(2'))
	3.28	(1H; m; CH of CH_2 of $POEt^a$)
	3.69	(1H; m; CH' of CH_2 of $POEt^a$)
	3.91	(1H; d of d; J_{HP} 23.6 Hz; J_{HH} 8.2 Hz; α - CH)
	4.04	(2H; m; CH_2 of $POEt^b$)
	7.51	(3H; m; CH on C(6), CH on C(7), CH on C(8))
	7.80	(3H; m; CH on C(2), CH on C(3), CH on C(4))
	8.00	(1H; d; J_{HH} 8.1 Hz; CH on C(5))
δ^{31}**P**	27.63	
δ^{13}**C**	15.66	(d of q; J_{CP} 5.2 Hz; J_{CH} 126.9 Hz; CH_3 of $POEt^a$)
	16.11	(d of q; J_{CP} 5.5 Hz; J_{CH} 126.9 Hz; CH_3 of $POEt^b$)
	24.37	(t; J_{CH} 130.4 Hz; CH_2 on C(5'))
	29.04	(d of t; J_{CP} 11.2 Hz; J_{CH} 123.0 Hz; CH_2 on C(6))
	40.85	(d of t; J_{CP} 4.2 Hz; J_{CH} 128.8 Hz; CH_2 on C(4'))
	41.26	(d; J_{CH} 128.1 Hz; CH on C(1'))
	42.84	(d of d; J_{CP} 138.3 Hz; J_{CH} 127.4 Hz; α - CH)
	47.32	(d of t; J_{CP} 5.9 Hz; J_{CH} 128.6 Hz; CH_2 on C(2'))
	61.14	(d of t; J_{CP} 7.2 Hz; J_{CH} 149.2 Hz; CH_2 of $POEt^a$)
	62.60	(d of t; J_{CP} 7.2 Hz; J_{CH} 149.1 Hz; CH_2 of $POEt^b$)
	122.46	(d; J_{CH} 156.0 Hz; CH on C(5))
	124.98	(d; J_{CH} 159.2 Hz; CH on C(8))
	125.39	(d; J_{CH} 160.6 Hz; CH on C(6))
	126.16	(d; J_{CH} 156.3 Hz; CH on C(7))

	126.74	(d of d; J_{CP} 6.2 Hz; J_{CH} 157.2 Hz; CH on C(2))
	127.67	(d; J_{CH} 159.6 Hz; CH on C(3))
	128.91	(d; J_{CH} 159.6 Hz; CH on C(4))
	131.09	(d; J_{CP} 5.0 Hz; C of C(9))
	132.43	(d; J_{CP} 8.5 Hz; C of C(1))
	133.74	(s; C of C(10))
	210.05	(s; C of C(3'))

MS	**m/z**	375	($(M^+ + 1)$	4%)	374	(M^+	16%)
		278	($C_{15}H_{19}PO_3^+$	100%)	141	($C_{11}H_9^+$	77%)
		81	($PO_3H_2^+$	7%)	29	($C_2H_5^+$	8%)

IR	1707	(s; C=O)
	1221	(s; P=O)

10.3.1 Molecular Dynamics

Simulated annealing procedure

The calculations were performed with the default values of the TRIPOS force field[1] (SYBYL program version 6.2 released by TRIPOS Inc., 1699 S Hanley Road, St. Louis, Missouri 63144-2913) running on an INDIGO2 Silicon Graphics Workstation. The electrostatic point charges of the atoms were calculated with the Gasteiger-Hückel method (Gast-Hück command in SYBYL 6.2). All minimisation's were carried out using the Powell method[2] up to a gradient of 0.05 kcals/mol/Å. The default setup for simulated annealing which applied a constant temperature algorythm (NVT command in SYBYL 6.2) based on Berendsen's method[3] and a rate of decreasing the temperature of 0.5 K/fs was used. The thermal bath coupling constant and the integration time step were 5.0 fs and 0.5 fs respectively. Compound (**47c**) was built using the sketch command in SYBYL 6.2 to resemble the conformation found from the crystal structure and then minimised. The minimised structure so obtained was subjected to 50 cycles of

1 W F Gunsteren, *Angew. Chem. Int. Ed. Engl.*, **29**, 1990, 992.

2 M J D Powell, *Restart Procedures for the Conjugate Gradient Method, Mathematical Programming*, **12**, 1977, 3684 - 3690.

3 H J C Berendsen, J P M Postman, W F van Gunsteren, A Dinola and J R Haak, *J. Chem. Phys.*, **81**, 1984, 3684.

simulated annealing using distance dependent relative permittivity and a cut-off radius of 9 Å for non-bonded interactions *in vacuo*. Each cycle which consisted of 12 000 fs was sampled every 50 fs.

Calculation of theoretical coupling constants

Selected minimised structures of compound (**47c**) were imported in the VICI program (PERCH Peak Research software released by R Laatikainen *et. al.* Kuopio University NMR Research Group[4]) with the preservation of the atomic co-ordinates. The torsion H_{α}-C_{α}-$C_{1'}$-$H_{1'}$ was measured and the theoretical coupling constant was calculated by the VICI program which used an improved Karplus relation developed by Haasnoot *et. al.*[5]

10.4 Synthesis and characterisation of compounds prepared in Chapter 5

General procedure

Method A: A solution of the alcohol (1 mol equiv.) and iodine (2 mol equiv.) in methanol (*ca* 30 cm^3 per mmol of alcohol) was heated under reflux in an atmosphere of nitrogen for 90 min. The methanol was evaporated under reduced pressure, the residue dissolved in benzene or ethyl acetate and washed successively with saturated solutions of aqueous $NaHCO_3$ and $Na_2S_2O_3$. The solution was then washed with 5% aqueous NaOH and then with water. After drying ($MgSO_4$/Na_2SO_4), filtering, and evaporation of the solvent under reduced pressure the crude products were purified as shown for each individual compound.

Method B: The alcohol (1 mol equiv.) was added to a solution of acetic acid (*ca* 10 cm^3 per mmol of alcohol) containing trifluoroacetic acid (*ca* 1.2 cm^3 per mmol of alcohol), trifluoroacetic anhydride (2 mol equiv.) and triphenyl methanol (1.1 mol equiv.). This mixture was refluxed overnight. After cooling the mixture was neutralised with sodium hydroxide and

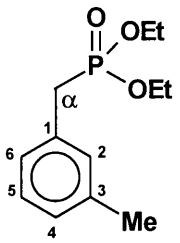
4 R Laaitikainen, M Niemitz, J Sundelin and T Hassinien, Kuopio University NMR Research Group, Department of Chemistry, University of Kuopio, P.O. Box 1627, SF-70211, Kuopio, Finland.

5 C A Haasnoot, F A A M deLeeuw and C Altona, *Tetrahedron*, **36**, 1980, 2783.

extracted with chloroform (3 x 20cm^3). The combined chloroform layers were dried ($MgSO_4/Na_2SO_4$), filtered and the solvent removed under reduced pressure to yield crude brown oils. These oils were purified by column chromatography using ethyl acetate/hexane (2:3) as eluent to afford the individual compounds.

(51a) 3-Methyl-benzyl-phosphonic acid diethyl ester

Colourless oil prepared by method A, purified by column chromatography (EtOAc) 0.058g (11.6%). Method B afforded the same product 0.368g (98.2%).



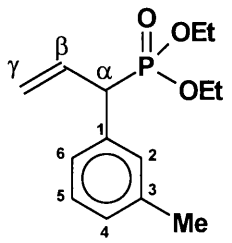
δ^1**H**	1.21	(6H; t; J_{HH} 7.0 Hz; 2 x CH_3 of POEt)
	2.30	(3H; s; CH_3 on C(3))
	3.08	(2H; d; J_{HP} 21.6 Hz; α - CH_2)
	3.96	(2H; d of q; J_{HP} 6.6 Hz; J_{HH} 6.6 Hz; CH_2 of POEt^a)
	4.01	(2H; d of q; J_{HP} 6.6 Hz; J_{HH} 6.6 Hz; CH_2 of POEt^b)
	7.04	(3H; m; CH on C(2), CH on C(4), CH on C(6))
	7.18	(1H; d of d; J_{HH} 7.4 Hz; CH on C(5))
δ^{31}**P**	27.30	
δ^{13}**C**	16.34	(d of q; J_{CP} 5.7 Hz; J_{CH} 126.9 Hz; 2 x CH_3 of POEt)
	21.33	(q; J_{CH} 124.9 Hz; CH_3 on C(3))
	33.65	(d of t; J_{CP} 138.1 Hz; J_{CH} 127.5 Hz; α - CH_2)
	62.08	(d of t; J_{CP} 6.6 Hz; J_{CH} 145.2 Hz; 2 x CH_2 of POEt)
	126.73	(d; J_{CH} 159.3 Hz; CH on C(4))
	126.83	(d; J_{CH} 159.3 Hz; CH on C(5))
	127.61	(d of d; J_{CP} 3.7 Hz; J_{CH} 158.3 Hz; CH on C(6))

	128.37	(d; J_{CH} 159.2 Hz; CH on C(2))
	130.53	(d; J_{CP} 6.4 Hz; C of C(1))
	138.06	(s; C of C(3))

MS	**m/z**	243	(($M^+ + 1$)	6%)	242	(M^+	40%)
		105	($C_8H_9^+$	100%)	79	(PO_3^+	11%)
		29	($C_2H_5^+$	12%)			

(51c) 1-m-Tolyl-allyl-phosphonic acid diethyl ester

Colourless oil prepared by method A, purified by column chromatography (EtOAc) 0.040g (8.7%).



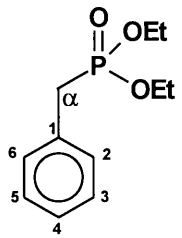
δ^1**H**	1.25	(6H; t; J_{HH} 7.1 Hz; 2 x CH_3 of POEt)
	2.31	(3H; s; CH_3 on C(3))
	3.95	(1H; m; α - CH)
	4.04	(2H; d of q; J_{HP} 6.9 Hz; J_{HH} 6.9 Hz; CH_2 of $POEt^a$)
	4.07	(2H; d of q; J_{HP} 6.9 Hz; J_{HH} 6.9 Hz; CH_2 of $POEt^b$)
	5.21	(2H; m; γ - CH_2)
	6.16	(1H; m; β - CH)
	7.14	(4H; m; CH on C(4), CH on C(5), CH on C(2), CH on C(6))
δ^{31}**P**	25.74	
δ^{13}**C**	16.01	(d of q; J_{CP} 6.6 Hz; J_{CH} 127.2 Hz; CH_3 of $POEt^a$)
	16.15	(d of q; J_{CP} 6.4 Hz; J_{CH} 127.2 Hz; CH_3 of $POEt^b$)
	21.23	(q; J_{CH} 129.0 Hz; CH_3 on C(3))

	49.69	(d of d; J_{CP} 137.0 Hz; J_{CH} 131.7 Hz; α - CH)
	62.61	(d of t; J_{CP} 6.6 Hz; J_{CH} 147.8 Hz; CH_2 of $POEt^a$)
	62.86	(d of t; J_{CP} 6.8 Hz; J_{CH} 147.8 Hz; CH_2 of $POEt^b$)
	118.74	(d of t; J_{CP} 13.2 Hz; J_{CH} 157.9 Hz; γ - CH_2)
	125.84	(d; J_{CH} 158.9 Hz; CH on C(4))
	127.88	(d; J_{CH} 159.5 Hz; CH on C(5))
	127.91	(d; J_{CH} 159.8 Hz; β - CH)
	128.35	(d; J_{CH} 159.8 Hz; CH on C(6))
	129.52	(d; J_{CH} 159.7 Hz; CH on C(2))
	132.88	(d of d; J_{CP} 8.8 Hz; J_{CH} 159.0 Hz; β-CH)
	135.14	(s; C of C(1))
	138.07	(s; C of C(3))

MS	**m/z**	269	($(M^+ + 1)$	84%)	213	($C_{10}H_{14}PO_3^+$	100%)
		131	($C_{10}H_{11}^+$	100%)	117	($C_9H_9^+$	35%)
		105	($C_8H_9^+$	13%)	79	(PO_3^+	5%)
		77	($C_6H_5^+$	12%)	29	($C_2H_5^+$	11%)
		15	(CH_3^+	1%)			

(51d) Benzyl-phosphonic acid diethyl ester

Colourless oil prepared by method B 0.316g (86.6%).



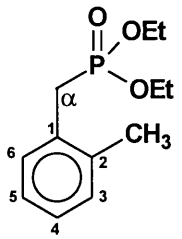
δ^1H	1.18	(3H; t; J_{HH} 7.1 Hz; CH_3 of $POEt^a$)
	1.19	(3H; t; J_{HH} 7.1 Hz; CH_3 of $POEt^b$)
	3.11	(2H; d; J_{HP} 21.6 Hz; α - CH_2)
	3.97	(4H; d of q; J_{HP} 7.2 Hz; J_{HH} 7.1 Hz; 2 x CH_2 of POEt)
	7.22	(5H; m; CH on C(2), CH on C(3), CH on C(4), CH on C(5), CH on C(6))

$\delta^{31}P$	27.19	
$\delta^{13}C$	15.70	(d of q; J_{CP} 5.7 Hz; J_{CH} 127.1 Hz; 2 x CH_3 of POEt)
	33.05	(d of t; J_{CP} 138.3 Hz; J_{CH} 127.7 Hz; α - CH_2)
	61.65	(d of t; J_{CP} 6.9 Hz; J_{CH} 146.7 Hz; 2 x CH_2 of POEt)
	126.29	(d of d; J_{CP} 3.3 Hz; J_{CH} 163.5 Hz; CH on C(4))
	127.90	(d of d; J_{CP} 2.8 Hz; J_{CH} 160.1 Hz; CH on C(3), CH on C(5))
	129.22	(d of d; J_{CP} 6.4 Hz; J_{CH} 158.6 Hz; CH on C(2), CH on C(6))
	130.94	(d; J_{CP} 9.2 Hz; C of C(1))

MS	**m/z**	229	((M^+ + 1)	13%)	228	(M^+	83%)
		172	($C_7H_9PO_3^+$	77%)	91	($C_7H_7^+$	100%)
		79	(PO_3^+	4%)	29	($C_2H_5^+$	17%)

(51e) 2-Methyl-benzyl-phosphonic acid diethyl ester

Colourless oil prepared by method B 0.345g (93.2%).



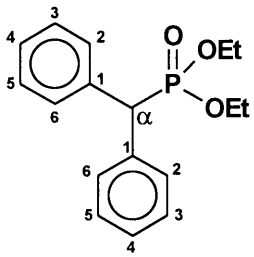
$\delta^{1}H$	1.20	(6H; t; J_{HH} 7.0 Hz; 2 x CH_3 of POEt)
	2.35	(3H; d; J_{HP} 1.6 Hz; CH_3 on C(2))
	3.15	(2H; d; J_{HP} 22.0 Hz; α - CH_2)
	3.94	(4H; d of q; J_{HP} 7.3 Hz; J_{HH} 7.0 Hz; 2 x CH_3 of POEt)
	7.11	(3H; m; CH on C(3), CH on C(4), CH on C(5))
	7.23	(1H; m; CH on C(6))
$\delta^{31}P$	27.59	
$\delta^{13}C$	15.86	(d of q; J_{CP} 6.0 Hz; J_{CH} 123.8Hz; 2 x CH_3 of POEt)

	19.42	(q; J_{CH} 126.6 Hz; CH_3 on C(2))
	30.55	(d of t; J_{CP} 138.6 Hz; J_{CH} 129.6 Hz; α - CH_2)
	61.76	(d of t; J_{CP} 6.9 Hz; J_{CH} 147.5 Hz; CH_2 of POET)
	125.54	(d of d; J_{CP} 3.6 Hz; J_{CH} 161.1 Hz; CH on C(4))
	126.63	(d of d; J_{CP} 3.8 Hz; J_{CH} 159.8 Hz; CH on C(5))
	129.51	(d; J_{CP} 9.8 Hz; C of C(1))
	129.98	(d of d; J_{CP} 3.1 Hz; J_{CH} 159.3 Hz; CH on C(3))
	130.19	(d of d; J_{CP} 5.7 Hz; J_{CH} 159.3 Hz; CH on C(6))
	136.52	(d; J_{CP} 6.9 Hz; C of C(2))

MS	**m/z**	243	((M^+ + 1)	12%)	242	(M^+	66%)
		186	($C_8H_{11}PO_3^+$	62%)	104	($C_8H_8^+$	100%)
		91	($C_7H_7^+$	32%)	79	(PO_3^+	23%)
		29	($C_2H_5^+$	29%)	15	(CH_3^+	4%)

(51f) Benzhydryl-phosphonic acid diethyl ester

Colourless oil prepared by method B 0.157g (81.6%).

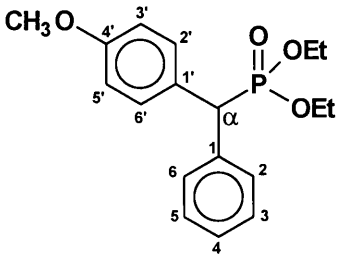


δ^1H	1.05	(6H; t; J_{HH} 7.1 Hz; 2 x CH_3 of POEt)
	3.91	(4H; d of q; J_{HP} 7.4 Hz; J_{HH} 7.1 Hz; 2 x CH_2 of POEt)
	4.39	(1H; d; J_{HP} 25.1 Hz; α - CH)
	7.17	(2H; d of d; J_{HH} 7.2 Hz; 2 x CH on C(4))
	7.25	(4H; d of d; J_{HH} 7.2 Hz; 2 x CH on C(3), 2 x CH on C(5))
	7.49	(4H; d; J_{HH} 7.1 Hz; 2 x CH on C(2), 2 x CH on C(6))
δ^{31}P	25.68	
δ^{13}C	16.00	(d of q; J_{CP} 5.4 Hz; J_{CH} 125.2 Hz; 2 x CH_3 of POEt)

	51.14	(d of d; J_{CP} 138.3 Hz; J_{CH} 124.5 Hz; α - CH)
	62.41	(d of t; J_{CP} 7.0 Hz; J_{CH} 147.7 Hz; 2 x CH_2 of POEt)
	62.46	(t; J_{CH} 147.7 Hz; CH_2 of $POEt^b$)
	126.89	(d; J_{CH} 170.5 Hz; 2 x CH on C(4))
	128.34	(d; J_{CH} 161.2 Hz; 2 x CH on C(3), 2 x CH on C(5))
	129.21	(d; J_{CH} 153.5 Hz; 2 x CH on C(2))
	129.31	(d; J_{CH} 153.5 Hz; 2 x CH on C(6))
	136.69	(d; J_{CP} 5.2 Hz; 2 x C of C(1))

(51g) (4-Methoxy-phenyl)-phenyl-methyl-phosphonic acid diethyl ester

Colourless oil prepared by method B 0.140g (73.8%).



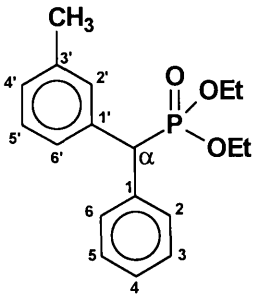
δ^1**H**	1.05	(3H; t; J_{HH} 7.1 Hz; CH_3 of $POEt^a$)
	1.06	(3H; t; J_{HH} 7.1 Hz; CH_3 of $POEt^b$)
	3.69	(3H; s; CH_3 of OMe)
	3.80	(2H; m; CH_2 of $POEt^a$)
	3.92	(2H; m; CH_2 of $POEt^b$)
	4.34	(1H; d; J_{HP} 25.3 Hz; α - CH)
	6.79	(2H; d; J_{HH} 6.8 Hz; CH on C(3'), CH on C(5'))
	7.17	(1H; d; J_{HH} 8.1 Hz; CH on C(4))
	7.24	(2H; d of d; J_{HH} 7.5 Hz; CH on C(3), CH on C(5))
	7.40	(2H; d; J_{HH} 6.9 Hz; CH on C(2'), CH on C(6'))
	7.46	(2H; d; J_{HH} 7.0 Hz; CH on C(2), CH on C(6))
δ^{31}**P**	25.98	
δ^{13}**C**	16.03	(d of q; J_{CP} 3.2 Hz; J_{CH} 126.2 Hz; 2 x CH_3 of POEt)

	50.13	(d of d; J_{CP} 138.6 Hz; J_{CH} 124.3 Hz; α - CH)
	54.91	(q; J_{CH} 143.7 Hz; CH_3 of OMe)
	62.38	(d of t; J_{CP} 5.4 Hz; J_{CH} 147.8 Hz; 2 x CH_2 of POEt)
	113.75	(d; J_{CH} 159.2 Hz; CH on C(3'), CH on C(5'))
	126.79	(d; J_{CH} 161.1 Hz; CH on C(4))
	128.28	(d; J_{CH} 152.4 Hz; CH on C(3), CH on C(5))
	128.65	(d; J_{CP} 5.2 Hz; C of C(1'))
	129.13	(d of d; J_{CP} 7.8 Hz; J_{CH} 153.2 Hz; CH on C(2), CH on C(6))
	130.27	(d of d; J_{CP} 8.1 Hz; J_{CH} 150.1 Hz; CH on C(2'), CH on C(6'))
	137.01	(s; C of C(1))
	158.49	(s; C of C(4'))

MS	**m/z**	335	(($M^+ + 1$)	4%)	334	(M^+	16%)
		197	($C_{14}H_{13}O^+$	100%)	79	(PO_3^+	<1%)
		29	($C_2H_5^+$	6%)			

(51h) Phenyl-m-tolyl-methyl-phosphonic acid diethyl ester

Colourless oil prepared by method B 0.205g (74.9%).



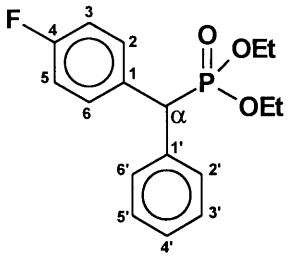
δ^1**H**	1.09	(3H; t; J_{HH} 7.0 Hz; CH_3 of $POEt^a$)
	1.10	(3H; t; J_{HH} 7.0 Hz; CH_3 of $POEt^b$)
	2.30	(3H; s; CH_3 on C(3'))
	3.82	(2H; m; CH_2 of $POEt^a$)
	3.96	(2H; m; CH_2 of $POEt^b$)
	4.37	(1H; d; J_{HP} 25.1 Hz; α - CH)
	7.03	(1H; d; J_{HH} 7.4 Hz; CH on C(4'))

	7.23	(6H; m; CH on C(2'), CH on C(5'), CH on C(6'), CH on C(3), CH on C(4), CH on C(5))
	7.51	(2H; d; J_{HH} 7.1 Hz; CH on C(2), CH on C(6))
$\delta^{31}P$	25.87	
$\delta^{13}C$	15.82	(d of q; J_{CP} 5.7 Hz; J_{CH} 127.9 Hz; 2 x CH_3 of POEt)
	21.04	(q; J_{CH} 126.3 Hz; CH_3 on C(3'))
	50.88	(d of d; J_{CP} 138.4 Hz; J_{CH} 124.3 Hz; α - CH)
	62.33	(d of t; J_{CP} 6.9 Hz; J_{CH} 147.7Hz; 2 x CH_2 of POEt)
	126.14	(d of d; J_{CP} 7.8 Hz; J_{CH} 166.3 Hz; CH on C(6'))
	126.72	(d; J_{CH} 160.6 Hz; CH on C(4))
	127.55	(d; J_{CH} 158.4Hz; CH on C(4'))
	128.06	(d; J_{CH} 159.5Hz; CH on C(5'))
	128.16	(d; J_{CH} 161.6Hz; CH on C(3), CH on C(5))
	129.11	(d of d; J_{CP} 8.0 Hz; J_{CH} 160.8 Hz; CH on C(2), CH on C(6))
	129.82	(d of d; J_{CP} 8.3 Hz; J_{CH} 164.1 Hz; CH on C(2'))
	136.30	(d; J_{CP} 5.2 Hz; C of C(1))
	136.55	(d; J_{CP} 5.2 Hz; C of C(1'))
	137.72	(s; C of C(3'))

MS	**m/z**	319	(($M^+ + 1$)	13%)	318	(M^+	50%)
		181	($C_{14}H_{13}^+$	100%)	166	($C_{13}H_{10}^+$	67%)
		79	(PO_3^+	<1%)			

(51i) (4-Fluoro-phenyl)-phenyl-methyl-phosphonic acid diethyl ester

Colourless oil prepared by method B 0.360g (88.7%).

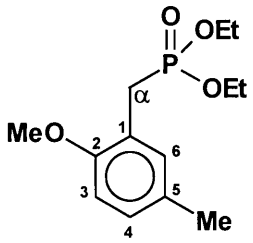


δ^{1}**H**	1.08	(3H; t; J_{HH} 7.3 Hz; CH_3 of $POEt^a$)
	1.10	(3H; t; J_{HH} 7.2 Hz; CH_3 of $POEt^b$)
	3.80	(2H; m; CH_2 of $POEt^a$)
	3.95	(2H; m; CH_2 of $POEt^b$)
	4.38	(1H; d; J_{HP} 25.2 Hz; α - CH)
	6.97	(2H; d of d; J_{HF} 8.7 Hz; J_{HH} 8.7 Hz; CH on C(3), CH on C(5))
	7.24	(3H; m; CH on C(3'), CH on C(4'), CH on C(5'))
	7.47	(4H; m; CH on C(2), CH on C(2'), CH on C(6), CH on C(6'))
δ^{31}**P**	25.39	(d; J_{PF} 2.8 Hz)
δ^{19}**F**	-115.79	
δ^{13}**C**	16.00	(d of q; J_{CP} 4.5 Hz; J_{CH} 127.0 Hz; 2 x CH_3 of POEt)
	30.24	(d of d; J_{CP} 139.1 Hz; J_{CH} 124.5 Hz; α - CH)
	62.38	(d of t; J_{CP} 6.7 Hz; J_{CH} 150.0 Hz; CH_2 of $POEt^a$)
	62.54	(d of t; J_{CP} 7.4 Hz; J_{CH} 150.0 Hz; CH_2 of $POEt^b$)
	115.19	(d of d; J_{CF} 21.4 Hz; J_{CH} 163.1 Hz; CH on C(3), CH on C(5))
	126.52	(d; J_{CF} 11.0 Hz; C of C(1))
	127.05	(d; J_{CH} 154.4 Hz; CH on C(4'))
	128.44	(d; J_{CH} 160.7 Hz; CH on C(3'), CH on C(5'))
	129.18	(d of d; J_{CP} 7.8 Hz; J_{CH} 159.9 Hz; CH on C(2'), CH on C(6'))
	130.85	(d of d of d; J_{CF} 8.0 Hz; J_{CP} 8.0 Hz; J_{CH} 160.6 Hz; CH on C(2), CH on C(6))

	136.54	(d; J_{CP} 5.2 Hz; C of C(1'))					
	161.78	(d; J_{CF} 247.4 Hz; C of C(4))					
MS	**m/z**	322	(M^+	15%)	185	($C_{13}H_{10}F^+$	100%)
		109	($C_7H_5F^+$	35%)	81	($PO_3H_2^+$	14%)
		29	($C_2H_5^+$	12%)			

(52a) 2-Methoxy-5-methyl-benzyl-phosphonic acid diethyl ester

Colourless oil prepared by method A, purified by column chromatography (EtOAc) 0.126g (22.4%).



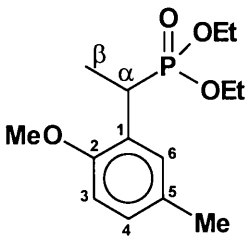
δ^1**H**	1.20	(3H; t; J_{HH} 7.3 Hz; CH_3 of $POEt^a$)
	1.21	(3H; t; J_{HH} 7.3 Hz; CH_3 of $POEt^b$)
	2.16	(3H; s; CH_3 on C(5))
	3.02	(2H; d; J_{HP} 21.1 Hz; α - CH_2)
	3.77	(3H; s; CH_3 of OMe)
	3.97	(2H; d of q; J_{HP} 7.2 Hz; J_{HH} 7.2 Hz; CH_2 of $POEt^a$)
	3.97	(2H; d of q; J_{HP} 7.2 Hz; J_{HH} 7.2 Hz; CH_2 of $POEt^b$)
	6.72	(1H; d; J_{HH} 8.1 Hz; CH on C(3))
	7.05	(2H; m; CH on C(4), CH on C(6))
δ^{31}**P**	27.74	
δ^{13}**C**	16.22	(d of q; J_{CP} 2.3 Hz; J_{CH} 125.4 Hz; 2 x CH_3 of POEt)
	21.14	(q; J_{CH} 127.1 Hz; CH_3 on C(5))
	32.51	(d of t; J_{CP} 139.3 Hz; J_{CH} 127.1 Hz; α - CH_2)

	55.10	(q; J_{CH} 143.5 Hz; CH_3 of OMe)
	61.92	(d of t; J_{CP} 5.4 Hz; J_{CH} 149.5 Hz; 2 x CH_2 of POEt)
	109.78	(d; J_{CH} 156.7 Hz; CH on C(3))
	127.43	(d; J_{CH} 157.4 Hz; CH on C(6))
	127.75	(d; J_{CH} 157.9 Hz; CH on C(4))
	131.83	(d; J_{CP} 6.3 Hz; C of C(1))
	137.87	(s; C of C(5))
	149.52	(s; C of C(2))

MS	**m/z**	273	(($M^+ + 1$)	6%)	272	(M^+	40%)
		136	($C_9H_{12}O^+$	44%)	91	($C_7H_7^+$	35%)
		79	(PO_3^+	4%)	29	($C_2H_5^+$	22%)

(52b) 1-(2-Methoxy-5-methyl-phenyl)-ethyl-phosphonic acid diethyl ester

Colourless oil prepared by method A, purified by column chromatography (EtOAc) 0.129g (43.2%).



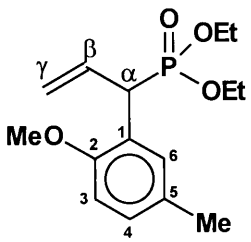
δ^1**H**	1.11	(3H; t; J_{HH} 7.0 Hz; CH_3 of $POEt^a$)
	1.25	(3H; t; J_{HH} 7.0 Hz; CH_3 of $POEt^b$)
	1.53	(3H; d of d; J_{HP} 18.5 Hz; J_{HH} 7.5 Hz; β - CH_3)
	2.31	(3H; s; CH_3 on C(5))
	3.10	(1H; d of q; J_{HP} 22.6 Hz; J_{HH} 7.5 Hz; α - CH)
	3.77 - 3.88	(2H; m; CH_2 of $POEt^a$)
	3.78	(3H; s; CH_3 of OMe)
	4.00	(2H; m; CH_2 of $POEt^b$)
	6.74	(1H; d; J_{HH} 8.2 Hz; CH on C(3))

	7.12	(2H; m; CH on C(4), CH on C(6))
δ^{31}P	30.56	
δ^{13}C	15.62	(d of q; J_{CP} 15.9 Hz; J_{CH} 129.8 Hz; β - CH_3)
	16.21	(d of q; J_{CP} 5.1 Hz; J_{CH} 129.6 Hz; 2 x CH_3 of POEt)
	21.35	(q; J_{CH} 126.3 Hz; CH_3 on C(5))
	38.29	(d of d; J_{CP} 137.9 Hz; J_{CH} 130.2 Hz; α - CH)
	55.22	(q; J_{CH} 143.7 Hz; CH_3 of OMe)
	61.78	(d of t; J_{CP} 6.6 Hz; J_{CH} 143.8 Hz; CH_2 of POEt^a)
	62.31	(d of t; J_{CP} 7.0 Hz; J_{CH} 143.8 Hz; CH_2 of POEt^b)
	109.74	(d; J_{CH} 156.4 Hz; CH on C(3))
	127.71	(d; J_{CH} 159.8 Hz; CH on C(6))
	128.19	(d; J_{CH} 159.2 Hz; CH on C(4))
	135.88	(s; C of C(5))
	137.76	(d; J_{CP} 6.9 Hz; C of C(1))
	149.70	(s; C of C(2))

MS	**m/z**	287	((M^+ + 1)	6%)	286	(M^+	40%)
		149	($C_{10}H_{13}O^+$	100%)	134	($C_9H_{10}O^+$	8%)
		119	($C_9H_{11}^+$	15%)	79	(PO_3^+	3%)
		29	($C_2H_5^+$	3%)			

(52c) 1-(2-Methoxy-5-methyl-phenyl)-allyl-phosphonic acid diethyl ester

Colourless oil prepared by method A, purified by column chromatography (EtOAc) 0.022g (4.8%).



δ^{1}**H**	1.11	(6H; t; J_{HH} 7.2 Hz; 2 x CH_3 of POEt)
	2.17	(3H; s; CH_3 on C(5))
	3.77	(1H; m; α -CH)
	3.78	(3H; s; CH_3 of OMe)
	4.03	(4H; d of q; J_{HP} 7.2 Hz; J_{HH} 7.2 Hz; 2 x CH_2 of POEt)
	5.21	(2H; m; γ - CH_2)
	6.16	(1H; m; β - CH)
	6.75	(1H; d; J_{HH} 8.3 Hz; CH on C(3))
	7.14	(2H; m; CH on C(4), CH on C(6))
δ^{31}**P**	26.10	
δ^{13}**C**	16.01	(d of q; J_{CP} 6.6 Hz; J_{CH} 127.2 Hz; CH_3 of POEt^a)
	16.15	(d of q; J_{CP} 6.4 Hz; J_{CH} 127.2 Hz; CH_3 of POEt^b)
	20.74	(q; J_{CH} 129.0 Hz; CH_3 on C(5))
	48.76	(d of d; J_{CP} 138.0 Hz; J_{CH} 133.2 Hz; α - CH)
	55.12	(q; J_{CH} 143.6 Hz; CH_3 of OMe)
	62.61	(d of t; J_{CP} 6.6 Hz; J_{CH} 147.8 Hz; CH_2 of POEt^a)
	62.86	(d of t; J_{CP} 6.8 Hz; J_{CH} 147.8 Hz; CH_2 of POEt^b)
	109.85	(d; J_{CH} 157.1 Hz; CH on C(3))
	118.45	(d of t; J_{CP} 13.9 Hz; J_{CH} 157.9 Hz; γ - CH_2)
	127.16	(d; J_{CH} 159.8 Hz; CH on C(4))
	128.34	(d; J_{CH} 159.8 Hz; β - CH)
	131.10	(d; J_{CH} 159.7 Hz; CH on C(6))
	133.15	(d of d; J_{CP} 8.5 Hz; J_{CH} 159.0 Hz; β-CH)
	135.04	(s; C of C(1))
	138.07	(s; C of C(5))
	174.67	(s; C of C(2))

10.5 Synthesis and characterisation of compounds prepared in Chapter 6

General procedure for the Dehydration of Tertiary Alcohols under Kinetic conditions

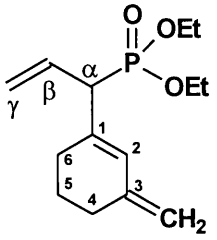
The alcohol (1 mol equiv.) was dissolved in benzene (*ca* 4cm^3 per mmol of alcohol) containing TsOH (0.08 mol equiv.). This mixture was stirred at room temperature for 24 hours. The mixture was then washed with an aqueous solution of $NaHCO_3$ and then with water. The organic layer was dried $MgSO_4$/Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude products were purified as shown for each individual compound.

General procedure for the Dehydration of Tertiary Alcohols under Thermodynamic conditions

The alcohol (1 mol equiv.) was dissolved in benzene (*ca* 4cm^3 per mmol of alcohol) containing TsOH (0.08 mol equiv.). This mixture was refluxed for 7 hours. The mixture was then washed with an aqueous solution of $NaHCO_3$ and then with water. The organic layer was dried $MgSO_4$/Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude products were purified as shown for each individual compound.

(54) 1-(3-Methylene-cyclohex-1-enyl)-allyl-phosphonic acid diethyl ester

A colourless oil was obtained 0.888g (72.1%) which needed no further purification.



δ^1**H**	1.18	(6H; m; 2 x CH_3 of POEt)
	1.61	(2H; m; CH_2 on C(5))
	1.98 - 2.21	(4H; m; CH_2 on C(4), CH_2 on C(6))

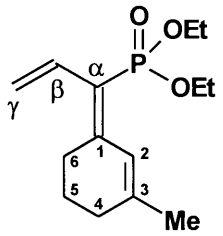
	3.18	(1H; d of d; J_{HP} 25.1 Hz; $J_{H\alpha H\beta}$ 8.2 Hz; α - CH)
	3.99	(4H; m; 2 x CH_2 of POEt)
	4.64	(1H; s; CH of CH_2 on C(3))
	4.66	(1H; s; CH' of CH_2 on C(3))
	5.18	(2H; m; γ - CH_2)
	5.88	(1H; m; β - CH)
	6.06	(1H; s; CH on C(2))
$\delta^{31}P$	25.58	
	25.54	
$\delta^{13}C$	16.33	(d of q; J_{CP} 5.6 Hz; J_{CH} 127.8 Hz; 2 x CH_3 of POEt)
	23.05	(t; J_{CH} 128.4 Hz; CH_2 on C(5))
	28.28	(t; J_{CH} 132.4 Hz; CH_2 on C(6))
	30.02	(t; J_{CH} 132.5 Hz; CH_2 on C(4))
	51.39	(d of d; J_{CP} 135.8 Hz; J_{CH} 131.3 Hz; α - CH)
	62.26	(d of t; J_{CP} 6.9 Hz; J_{CH} 145.9 Hz; 2 x CH_2 of POEt)
	110.58	(t; J_{CH} 156.1 Hz; CH_2 on C(3))
	118.53	(t; J_{CH} 157.5 Hz; γ - CH_2)
	126.84	(d of d; J_{CP} 12.9 Hz; J_{CH} 148.5 Hz; CH on C(2))
	128.76	(d of d; J_{CP} 12.1 Hz; J_{CH} 148.5 Hz; β - CH)
	136.08	(s; C of C(3))
	142.93	(s; C of C(1))

MS	**m/z**	270	(M^+	13%)	133	($C_{10}H_{13}^+$	13%)
		131	($C_{10}H_{11}^+$	100%)	91	($C_7H_7^+$	37%)
		79	(PO_3^+	9%)	29	($C_2H_5^+$	21%)
		15	(CH_3^+	3%)			

Analysis	**C**	**H**
Calculated:	62.21%	8.58%
Found:	62.89%	8.56%

(55a) *Z*-1-(3-Methyl-cyclohex-2-enylidene)-allyl-phosphonic acid diethyl ester

Colourless oil purified by column chromatography (EtOAc) 0.157g (28.6%).



δ^{1}**H**	1.28	(6H; t; J_{HH} 7.1 Hz; 2 x CH_3 of POEt)
	1.69	(2H; d of d of d of d; J_{H5H4} 6.0 Hz; J_{H5H6} 5.4 Hz; CH_2 on C(5))
	1.84	(3H; s; CH_3 on C(3))
	2.07	(2H; d of d; J_{HH} 6.0 Hz; CH_2 on C(4))
	2.45	(2H; m; CH_2 on C(6))
	4.02	(4H; m; 2 x CH_2 of POEt)
	5.26	(1H; d of d of d; J_{HH} 15.1 Hz;$J_{H\gamma H\beta}$ 14.6 Hz; J_{HP} 2.2 Hz; γ - CH_a)
	5.27	(1H; d of d of d; J_{HH} 15.1 Hz; $J_{H\gamma H\beta}$ 9.4 Hz; J_{HP} 2.2 Hz; γ - CH_b)
	6.39	(1H; m; β - CH)
	7.14	(1H; m; CH on C(2))
δ^{31}**P**	19.35	
δ^{13}**C**	16.23	(d of q; J_{CP} 6.6 Hz; J_{CH} 127.1 Hz; 2 x CH_3 of POEt)
	22.54	(t; J_{CH} 128.0 Hz; CH_2 on C(5))
	24.88	(q; J_{CH} 122.4 Hz; CH_3 on C(3))
	28.38	(d of t; J_{CP}16.5 Hz; J_{CH} 126.5 Hz; CH_2 on C(6))
	30.69	(t; J_{CH} 124.5 Hz; CH_2 on C(4))
	61.24	(d of t; J_{CP} 4.9 Hz; J_{CH} 144.7 Hz; 2 x CH_2 of POEt)
	118.96	(d of t; J_{CP} 8.2 Hz; J_{CH} 158.0 Hz; γ - CH_2)
	123.24	(d of d; J_{CP} 8.3 Hz; J_{CH} 156.4 Hz; CH on C(2))
	132.95	(d of d; J_{CP} 9.7 Hz; J_{CH} 156.9 Hz; β - CH)
	146.46	(s; C of C(3))

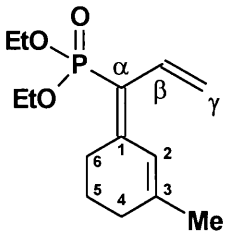
	152.04	(d; J_{CP} 9.6 Hz; α - C)
	152.05	(d; J_{CP} 9.6 Hz; C of C(1))

MS	**m/z**	271	($(M^+ + 1)$	4%)	270	(M^+	17%)
		213	($C_{10}H_{14}PO_3^+$	6%)	132	($C_{10}H_{12}^+$	100%)
		105	($C_8H_9^+$	25%)	91	($C_7H_7^+$	93%)
		79	(PO_3^+	13%)	29	($C_2H_5^+$	15%)
		15	(CH_3^+	1%)			

Analysis	**C**	**H**
Calculated:	62.21%	8.58%
Found:	61.99	8.35%

(55a') ***E*-1-(3-Methyl-cyclohex-2-enylidene)-allyl-phosphonic acid diethyl ester**

Colourless oil purified by column chromatography (EtOAc) 0.154g (28.1%).



δ^1**H**	1.26	(6H; t; J_{HH} 7.1 Hz; 2 x CH_3 of POEt)
	1.71	(2H; d of d of d of d; J_{H5H4} 6.2 Hz; J_{H5H6} 5.7 Hz; CH_2 on C(5))
	1.79	(3H; s; CH_3 on C(3))
	2.05	(2H; d of d; J_{HH} 6.1 Hz; CH_2 on C(4))
	2.74	(2H; m; CH_2 on C(6))
	4.02	(4H; m; 2 x CH_2 of POEt)
	5.26	(1H; d of d of d; J_{HH} 16.4 Hz; $J_{H\gamma H\beta}$ 16.7 Hz; J_{HP} 2.2 Hz; γ - CH_a)
	5.27	(1H; d of d of d; J_{HH} 16.7 Hz; $J_{H\gamma H\beta}$ 9.4 Hz; J_{HP} 2.2 Hz; γ - CH_b)
	6.39	(1H; m; β - CH)
	7.14	(1H; m; CH on C(2))

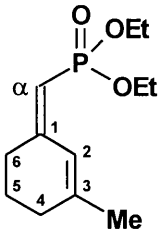
$\delta^{31}P$	20.08	
$\delta^{13}C$	16.25	(d of q; J_{CP} 6.9 Hz; J_{CH} 127.0 Hz; 2 x CH_3 of POEt)
	22.66	(t; J_{CH} 128.3 Hz; CH_2 on C(5))
	24.63	(q; J_{CH} 125.5 Hz; CH_3 on C(3))
	28.41	(d of t; J_{CP} 6.6 Hz; J_{CH} 128.8 Hz; CH_2 on C(6))
	30.83	(t; J_{CH} 124.9 Hz; CH_2 on C(4))
	61.24	(d of t; J_{CP} 5.7 Hz; J_{CH} 144.6 Hz; 2 x CH_2 of POEt)
	61.28	(t; J_{CH} 144.6 Hz; CH_2 of POEt[b])
	120.05	(d of t; J_{CP} 9.4 Hz; J_{CH} 158.0 Hz; γ - CH_2)
	122.70	(d of d; J_{CP} 20.7 Hz; J_{CH} 133.1 Hz; CH on C(2))
	132.68	(d of d; J_{CP} 9.6 Hz; J_{CH} 156.1 Hz; β - CH)
	143.58	(d; J_{CP} 10.3 Hz; C of C(1))
	146.55	(s; C of C(3))
	151.48	(d; J_{CP} 11.8 Hz; α - C)

MS	**m/z**	271	($(M^+ + 1)$	7%)	270	(M^+	34%)
		213	($C_{10}H_{14}PO_3^+$	43%)	131	($C_{10}H_{11}^+$	100%)
		105	($C_8H_9^+$	12%)	79	(PO_3^+	7%)
		29	($C_2H_5^+$	13%)	15	(CH_3^+	<1%)

Analysis	**C**	**H**
Calculated:	62.21%	8.58%
Found:	62.14	8.58%

(55b) *Z*-3-Methyl-cyclohex-2-enylidenemethyl-phosphonic acid diethyl ester

Colourless oil purified by column chromatography (EtOAc) 0.289g (18.5%).



δ^{1}**H**	1.25	(6H; t; J_{HH} 7.1 Hz; 2 x CH_3 of POEt)
	1.69	(2H; d of d of d of d; J_{HH} 6.1 Hz; CH_2 on C(5))
	1.79	(3H; s; CH_3 on C(3))
	2.05	(2H; d of d; J_{HH} 6.0 Hz; CH_2 on C(4))
	2.29	(2H; m; CH_2 on C(6))
	3.99	(4H; d of q; J_{HP} 7.2 Hz; J_{HH} 7.2 Hz; 2 x CH_2 of POEt)
	5.03	(1H; d; J_{HP} 17.6 Hz; α - CH)
	6.80	(1H; s; CH on C(2))
δ^{31}**P**	19.29	
δ^{13}**C**	15.88	(d of q; J_{CP} 6.4 Hz; J_{CH} 126.9 Hz; 2 x CH_3 of POEt)
	22.17	(t; J_{CH} 128.5 Hz; CH_2 on C(5))
	24.07	(q; J_{CH} 126.3 Hz; CH_3 on C(3))
	30.33	(t; J_{CH} 126.3 Hz; CH_2 on C(4))
	32.90	(d of t; J_{CP} 22.5 Hz; J_{CH} 128.4 Hz; CH_2 on C(6))
	60.67	(d of t; J_{CP} 5.4 Hz; J_{CH} 146.6 Hz; 2 x CH_2 of POEt)
	105.83	(d of d; J_{CP} 187.8 Hz; J_{CH} 154.2 Hz; α - CH)
	121.29	(d of d; J_{CP} 9.1 Hz; J_{CH} 158.0 Hz; CH on C(2))
	147.08	(s; C of C(3))
	156.33	(d; J_{CP} 5.1 Hz; C of C(1))

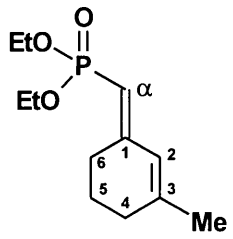
MS	**m/z**	245	((M^+ + 1)	10%)	244	(M^+	30%)
		187	($C_8H_{12}PO_3^+$	30%)	106	($C_8H_{10}^+$	58%)

105	($C_8H_9^+$	100%)	91	($C_7H_7^+$	58%)
79	(PO_3^+	39%)	29	($C_2H_5^+$	33%)
15	(CH_3^+	4%)			

Analysis	**C**	**H**
Calculated:	56.93%	8.45%
Found:	56.64%	8.56%

(55b') ***E*-3-Methyl-cyclohex-2-enylidenemethyl-phosphonic acid diethyl ester**

Colourless oil purified by column chromatography (EtOAc) 0.393g (24.4%).



δ^1**H**	1.25	(6H; t; J_{HH} 7.1 Hz; 2 x CH_3 of POEt)
	1.68	(2H; m; CH_2 on C(5))
	1.76	(3H; s; CH_3 on C(3))
	2.03	(2H; d of d; J_{HH} 6.0 Hz; CH_2 on C(4))
	2.64	(2H; m; CH_2 on C(6))
	3.97	(4H; d of q; J_{HP} 7.1 Hz; J_{HH} 7.1 Hz; 2 x CH_2 of POEt)
	5.11	(1H; d; J_{HP} 18.2 Hz; α - CH)
	5.86	(1H; s; CH on C(2))
δ^{31}**P**	20.49	
δ^{13}**C**	15.85	(d of q; J_{CP} 6.1 Hz; J_{CH} 126.9 Hz; 2 x CH_3 of POEt)
	21.79	(t; J_{CH} 128.6 Hz; CH_2 on C(5))
	23.66	(q; J_{CH} 126.3 Hz; CH_3 on C(3))
	26.69	(d of t; J_{CP} 6.3 Hz; J_{CH} 126.6 Hz; CH_2 on C(6))

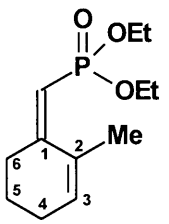
	29.94	(t; J_{CH} 123.7 Hz; CH_2 on C(4))
	60.59	(d of t; J_{CP} 4.4 Hz; J_{CH} 146.8 Hz; 2 x CH_2 of POEt)
	60.63	(t; J_{CH} 146.8 Hz; CH_2 of $POEt^b$)
	107.29	(d of d; J_{CP} 193.0 Hz; J_{CH} 151.6 Hz; α - CH)
	125.82	(d of d; J_{CP} 27.7 Hz; J_{CH} 155.8 Hz; CH on C(2))
	146.33	(s; C of C(3))
	156.93	(d; J_{CP} 8.2 Hz; C of C(1))

MS	**m/z**	245	((M^+ + 1)	16%)	244	(M^+	61%)
		187	($C_8H_{12}PO_3^+$	37%)	106	($C_8H_{10}^+$	87%)
		105	($C_8H_9^+$	100%) 91	($C_7H_7^+$	71%)	
		79	(PO_3^+	33%)	29	($C_2H_5^+$	43%)
		15	(CH_3^+	6%)			

Analysis	**C**	**H**
Calculated:	56.93%	8.45%
Found:	56.64%	8.56%

(55c) 2-Methyl-cyclohex-2-enylidenemethyl-phosphonic acid diethyl ester

Colourless oil purified by column chromatography (EtOAc) 0.074g (79.5%).



δ^1**H**	1.27	(6H; t; J_{HH} 7.1 Hz; 2 x CH_3 of POEt)
	1.68	(2H; d of d of d of d; J_{HH} 6.3 Hz; CH_2 on C(5))
	1.78	(3H; s; CH_3 on C(2))
	2.14	(2H; m; CH_2 on C(4))
	2.74	(2H; m; CH_2 on C(6))
	4.04	(4H; d of q; J_{HP} 7.3 Hz; J_{HH} 7.1 Hz; 2 x CH_2 of POEt)

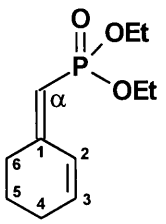
	5.38	(1H; d; J_{HP} 17.0 Hz; α - CH)
	5.98	(1H; m; CH on C(3))
$\delta^{31}P$	20.88	
$\delta^{13}C$	16.20	(d of q; J_{CP} 6.0 Hz; J_{CH} 126.1 Hz; 2 x CH_3 of POEt)
	19.60	(q; J_{CH} 126.6 Hz; CH_3 on C(2))
	22.39	(t; J_{CH} 147.1 Hz; CH_2 on C(5))
	26.01	(t; J_{CH} 128.4 Hz; CH_2 on C(4))
	28.63	(d of t; J_{CP} 6.9 Hz; J_{CH} 135.3 Hz; CH_2 on C(6))
	61.17	(d of t; J_{CP} 5.4 Hz; J_{CH} 146.9 Hz; 2 x CH_2 of POEt)
	107.41	(d of d; J_{CP} 192.7 Hz; J_{CH} 153.7 Hz; α - CH)
	132.56	(d; J_{CP} 23.9 Hz; C of C(2))
	134.99	(d; J_{CH} 159.2 Hz; CH on C(3))
	157.86	(d; J_{CP} 8.8 Hz; C of C(1))

MS	**m/z**	244	(M^+	4%)	91	($C_7H_7^+$	31%)
		79	(PO_3^+	19%)	29	($C_2H_5^+$	17%)
		15	(CH_3^+	4%)			

Analysis	**C**	**H**
Calculated:	59.02%	8.61%
Found:	59.19%	8.59%

(55d) Cyclohex-2-enylidenemethyl-phosphonic acid diethyl ester

Colourless oil purified by column chromatography (EtOAc) 0.073g (7.4%).



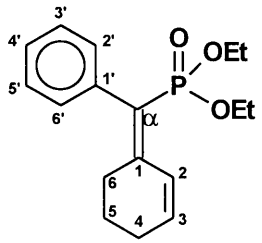
δ^{1}**H**	1.28	(6H; t; J_{HH} 7.1 Hz; 2 x CH_3 of POEt)
	1.73	(2H; d of d of d of d; J_{HH} 5.1 Hz; CH_2 on C(5))
	2.15	(2H; m; CH_2 on C(6))
	2.39	(2H; m; CH_2 on C(4))
	4.05	(4H; d of q; J_{HP} 7.3 Hz; J_{HH} 7.3 Hz; 2 x CH_3 of POEt)
	5.18	(1H; d; J_{HP} 17.5 Hz; α - CH)
	6.16	(1H; m; CH on C(3))
	7.02	(1H; d; J_{HH} 10.2 Hz; CH on C(2))
δ^{31}**P**	18.49	
δ^{13}**C**	16.31	(d of q; J_{CP} 6.6 Hz; J_{CH} 126.5 Hz; 2 x CH_3 of POEt)
	22.48	(t; J_{CH} 124.4 Hz; CH_2 on C(5))
	25.64	(t; J_{CH} 126.9 Hz; CH_2 on C(4))
	33.73	(d of t; J_{CP} 22.3 Hz; J_{CH} 128.2 Hz; CH_2 on C(6))
	61.25	(d of t; J_{CP} 5.1 Hz; J_{CH} 144.5 Hz; 2 x CH_2 of POEt)
	109.22	(d of d; J_{CP} 186.8 Hz; J_{CH} 154.9 Hz; α - CH)
	125.65	(d of d; J_{CP} 8.8 Hz; J_{CH} 157.6 Hz; CH on C(2))
	137.48	(d; J_{CH} 157.5 Hz; CH on C(3))
	155.89	(s; C of C(1))

MS	**m/z**	231	(($M^+ + 1$)	11%)	230	(M^+	43%)
		201	($C_9H_{14}PO_3^+$	22%)	173	($C_7H_{10}PO_3^+$	49%)
		93	($C_7H_9^+$	38%)	92	($C_7H_8^+$	92%)
		91	($C_7H_7^+$	100%)	79	(PO_3^+	28%)
		29	($C_2H_5^+$	42%)	15	(CH_3^+	6%)

Analysis	**C**	**H**
Calculated:	57.38%	8.32%
Found:	58.01%	8.46%

(55e) Cyclohex-2-enylidene-phenyl-methyl-phosphonic acid diethyl ester

Colourless oil purified by column chromatography (EtOAc) 0.084g (40.8%).

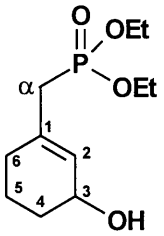


δ^{1}**H**	1.13	(6H; J_{HH} 7.0 Hz; 2 x CH_3 of POEt)
	1.75	(2H; d of d of d of d; J_{HH} 5.9 Hz; CH_2 on C(5))
	2.12	(2H; m; CH_2 on C(6))
	2.95	(2H; m; CH_2 on C(4))
	3.95	(4H; d of q; J_{HP} 7.1 Hz; J_{HH} 7.0 Hz; 2 x CH_2 of POEt)
	5.85	(1H; d; J_{HH} 10.2 Hz; CH on C(2))
	5.94	(1H; m; CH on C(3))
	7.10	(2H; d; J_{HH} 6.4 Hz; CH on C(2'), CH on C(6'))
	7.21	(3H; m; CH on C(3'), CH on C(4'), CH on C(5'))
δ^{31}**P**	18.17	
δ^{13}**C**	16.07	(d of q; J_{CP} 6.8 Hz; J_{CH} 126.9 Hz; 2 x CH_3 of POEt)
	22.38	(t; J_{CH} 126.0 Hz; CH_2 on C(5))
	25.63	(t; J_{CH} 127.2 Hz; CH_2 on C(4))
	28.53	(d of t; J_{CP} 6.4 Hz; J_{CH} 129.4 Hz; CH_2 on C(6))
	61.44	(d of t; J_{CP} 5.8 Hz; J_{CH} 144.7 Hz; 2 x CH_2 of POEt)
	126.78	(d; J_{CH} 160.2 Hz; CH on C(4'))
	127.04	(d of d; J_{CP} 20.5 Hz; J_{CH} 161.2 Hz; CH on C(2))
	127.45	(d; J_{CP} ; α - C)
	127.80	(d; J_{CH} 160.1 Hz; CH on C(3'))
	127.90	(d; J_{CH} 160.1 Hz; CH on C(5'))
	130.22	(d; J_{CH} 160.3 Hz; CH on C(2'))
	130.28	(d; J_{CH} 160.1 Hz; CH on C(6'))

	137.72	(d; J_{CP} 9.6 Hz; C of C(1'))					
	150.73	(d; J_{CP} 12.8 Hz; C of C(1))					
MS	**m/z**	307	($(M^+ + 1)$	21%)	306	(M^+	31%)
		168	($C_{13}H_{12}^+$	100%)	79	(PO_3^+	2%)
		29	($C_2H_5^+$	13%)			

(57) 3-Hydroxy-cyclohex-1-enylmethyl-phosphonic acid diethyl ester

Colourless oil purified by column chromatography (EtOAc) 0.482g (45.0%).



δ^1**H**	1.24	(6H; t; J_{HH} 7.0 Hz; 2 x CH_3 of POEt)
	1.52	(2H; m; CH_2 on C(6))
	1.70	(2H; m; CH_2 on C(5))
	2.05	(2H; m; CH_2 on C(4))
	2.46	(2H; m; α - CH_2)
	3.93	(1H; m; CH on C(3))
	4.01	(4H; m; 2 x CH_2 of POEt)
	5.59	(1H; s; CH on C(2))
δ^{31}**P**	27.89	
δ^{13}**C**	16.35	(d of q; J_{CP} 5.9 Hz; J_{CH} 125.6 Hz; 2 x CH_3 of POEt)
	19.30	(d of t; J_{CP} 19.4 Hz; J_{CH} 128.6 Hz; CH_2 on C(5))
	28.65	(d of t; J_{CP} 31.3 Hz; J_{CH} 128.3 Hz; CH_2 on C(6))
	29.52	(t; J_{CH} 127.1 Hz; CH_2 on C(4))
	35.17	(d of t; J_{CP} 137.2 Hz; J_{CH} 130.3 Hz; α - CH_2)

	61.79	(d of t; J_{CP} 6.8 Hz; J_{CH} 147.2 Hz; 2 x CH_2 of POEt)
	70.73	(d; J_{CH} 140.7 Hz; CH on C(3))
	127.85	(d of d; J_{CP} 11.4 Hz; J_{CH} 158.0 Hz; CH on C(2))
	132.45	(d; J_{CP} 10.5 Hz; C of C(1))

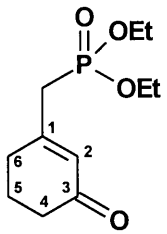
MS	**m/z**	248	(M^+	<1%)	230	((M^+-H_2O)	40%)
		229	($C_{11}H_{18}PO_3^+$	76%)	201	($C_9H_{14}PO_3^+$	33%)
		173	($C_7H_{10}PO_3^+$	92%)	91	($C_7H_7^+$	100%)
		29	($C_2H_5^+$	26%)	15	(CH_3^+	3%)

Analysis	**C**	**H**
Calculated:	53.22%	8.53%
Found:	53.38%	8.41%

Oxidation of 3-Hydroxy-cyclohex-1-enylmethyl-phosphonic acid diethyl ester

3 - Hydroxy - cyclohex - 1 - enylmethyl - phosphonic acid diethyl ester 0.208g (0.839mmol) was dissolved in 30cm^3 chloroform. Neutral activated manganese dioxide, prepared just prior to the reaction according to the method of Henbest *et. al.*[4] 2.949g (33.9mmol) was added and the mixture stirred for 4 hours at room temperature. The mixture was filtered through celite and the solvent removed under reduced pressure to yield a crude yellow oil. This oil was purified by column chromatography using ethyl acetate as eluent. The silica gel used for the separation was deactivated first by pouring wet ether containing 1% acetic acid and then allowing the ether to evaporate. A colourless oil 0.087g (42.2%) was obtained.

(58) 3-Oxo-cyclohex-1-enylmethyl-phosphonic acid diethyl ester



δ^1**H**	1.22	(6H; t; J_{HH} 7.1 Hz; 2 x CH_3 of POEt)
	1.91	(2H; t of t; J_{HH} 6.0 Hz; CH_2 on C(5))

	2.26	(2H; t; J_{HH} 6.0 Hz; CH_2 on C(4))
	2.38	(2H; d of t; J_{HP} 3.8 Hz; J_{HH} 5.7 Hz; CH_2 on C(6))
	2.66	(2H; d; J_{HP} 23.6 Hz; α - CH_2)
	4.01	(4H; d of q; J_{HP} 7.4 Hz; J_{HH} 7.4 Hz; 2 x CH_2 of POEt)
	5.85	(1H; d; J_{HP} 4.9 Hz; CH on C(2))
$\delta^{31}P$	24.22	
$\delta^{13}C$	16.27	(d of q; J_{CP} 6.1 Hz; J_{CH} 126.5 Hz; 2 x CH_3 of POEt)
	22.39	(t; J_{CH} 129.4 Hz; CH_2 on C(5))
	30.31	(t; J_{CH} 128.1 Hz; CH_2 on C(6))
	36.05	(d of t; J_{CP} 134.9 Hz; J_{CH} 127.5 Hz; α - CH_2)
	36.80	(t; J_{CH} 127.8 Hz; CH_2 on C(4))
	62.19	(d of t; J_{CP} 6.6 Hz; J_{CH} 150.6 Hz; 2 x CH_2 of POEt)
	129.19	(d of d; J_{CP} 11.1 Hz; J_{CH} 161.7 Hz; CH on C(2))
	155.95	(d; J_{CP} 11.0 Hz; C of C(1))
	198.80	(s; C of C(3))

MS	**m/z**	246	(M^+	19%)	189	($C_7H_{10}PO_4^+$	26%)
		108	($C_7H_8O^+$	100%)	79	(PO_3^+	22%)
		29	($C_2H_5^+$	11%)	15	(CH_3^+	1%)

IR	1667	(s; C=O)
	1257	(s; P=O)

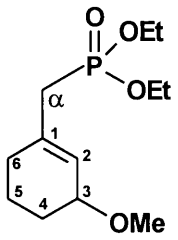
Analysis	**C**	**H**
Calculated:	53.65%	7.78%
Found:	53.79%	7.54%

Rearrangement of Tertiary Alcohols

1 - Hydroxy - cyclohex - 2 - enylmethyl phosphonic acid diethyl ester 0.437g (1.76 mmol) was dissolved in methanol (30ml). This mixture was kept at reflux temperature for 3 hours, cooled

and the solvent removed under reduced pressure. The residue was dissolved in chloroform, dried (Na_2SO_4), filtered and the solvent removed under reduced pressure to yield, *3 - methoxy - cyclohex - 1 - enylmethyl - phosphonic acid diethyl ester* 0.479g (100%) as a yellow oil.

(59) 3-Methoxy-cyclohex-1-enylmethyl-phosphonic acid diethyl ester



δ^1**H**	1.27	(6H; t; J_{HH} 7.2 Hz; 2 x CH_3 of POEt)
	1.55	(2H; m; CH_2 on C(5))
	1.72	(2H; m; CH_2 on C(6))
	2.08	(2H; m; CH_2 on C(4))
	2.45	(1H;d of d; J_{HP} 22.0 Hz; J_{HH} 14.9 Hz; CH^a of α - CH_2)
	2.51	(1H;d of d; J_{HP} 22.0 Hz; J_{HH} 14.9 Hz; CH^b of α - CH_2)
	3.31	(3H; s; CH_3 of OMe)
	3.72	(1H; m; CH on C(3))
	4.05	(4H; d of q; J_{HP} 7.2 Hz; J_{HH} 7.2 Hz; 2 x CH_2 of POEt)
	5.68	(1H; m; CH on C(2))
δ^{31}**P**	27.69	
δ^{13}**C**	15.84	(d of q; J_{CP} 5.5 Hz; J_{CH} 127.7 Hz; 2 x CH_3 of POEt)
	18.74	(t; J_{CH} 128.3 Hz; CH_2 on C(5))
	26.76	(t; J_{CH} 127.3 Hz; CH_2 on C(6))
	29.10	(t; J_{CH} 125.9 Hz; CH_2 on C(4))
	34.64	(d of t; J_{CP} 137.2 Hz; J_{CH} 131.2 Hz; α - CH_2)
	55.07	(q; J_{CH} 140.4 Hz; CH_3 of OMe)
	61.30	(d of t; J_{CP} 6.3 Hz; J_{CH} 147.3 Hz; 2 x CH_2 of POEt)
	73.83	(d; J_{CH} 141.4 Hz; CH on C(3))
	126.27	(d of d; J_{CP} 12.5 Hz; J_{CH} 153.4 Hz; CH on C(2))

	132.40	(d; J_{CP} 10.3 Hz; C of C(1))

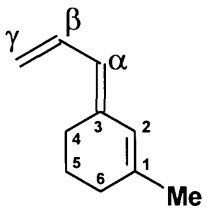
MS	**m/z**	246	($(M^+ - 15)$	<1%)	229	($C_{11}H_{18}PO_3^+$	70%)
		173	($C_7H_{10}PO_3^+$	61%)	124	($C_8H_{12}O^+$	100%)
		91	($C_7H_7^+$	66%)	79	(PO_3^+	11%)
		29	($C_2H_5^+$	14%)			

Analysis	**C**	**H**
Calculated:	55.16%	8.49%
Found:	52.76%	9.01%

10.6 Synthesis and characterisation of compounds prepared in Chapter 7

(61) 3-Allylidene-1-methyl-cyclohexene

1-(1-Hydroxy-cyclohex-2-enyl)-allyl phosphonic acid diethyl ester (1 mol equiv.) was dissolved in DMF. To this solution was added NaH (2 mol equiv.) and the resulting solution was stirred at room temperature for 3 hours. Water was carefully added and the DMF was removed under reduced pressure. This mixture was extracted with ether (3 x 20cm^3). The combined etheral layers were washed with water, dried ($MgSO_4$/Na_2SO_4), filtered and the solvent removed under reduced pressure to yield a brown oil. The yield of the reaction was low since the boiling points of the DMF and product were too close.



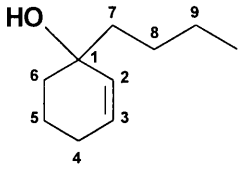
δ^1**H**	1.70	(2H; t; J_{HH} 6.3 Hz; CH_2 on C(6))
	1.75	(3H; s; CH_3 on C(1))
	2.03	(2H; t; J_{HH} 6.2 Hz; CH_2 on C(4))
	2.37	(2H; m; CH_2 on C(5))

	4.97	(1H; d of d; $J_{H\gamma H\beta}$ 10.1 Hz; $J_{H\gamma H\alpha}$ 1.6 Hz; γ - CH)
	5.09	(1H; d of d; $J_{H\gamma H\beta}$ 16.6 Hz; $J_{H\gamma H\alpha}$ 1.6 Hz; γ - CH)
	5.76	(1H; d; J_{HH} 11.3 Hz; α - CH)
	5.84	(1H; s; CH on C(2))
	6.61	(1H; d of d of d; $J_{H\beta H\gamma}$ 16.9 Hz; $J_{H\beta H\gamma}$ 10.7 Hz; $J_{H\beta H\alpha}$ 10.6 Hz; β - CH)
$\delta^{13}C$	22.53	(t; J_{CH} 127.7 Hz; CH_2 on C(4))
	23.96	(q; J_{CH} 126.0 Hz; CH_3 on C(1))
	24.32	(q; J_{CH} 126.0 Hz; CH_3 on C(1))
	24.83	(t; J_{CH} 127.5 Hz; CH_2 on C(5))
	29.63	(t; J_{CH} 124.7 Hz; CH_2 on C(6))
	30.64	(t; J_{CH} 124.2 Hz; CH_2 on C(5))
	30.75	(t; J_{CH} 124.2 Hz; CH_2 on C(6))
	36.92	(t; J_{CH} 126.1 Hz; CH_2 on C(4))
	114.87	(t; J_{CH} 159.5 Hz; γ - CH_2)
	124.35	(d; J_{CH} 150.3 Hz; α - CH)
	126.53	(d; J_{CH} 160.3 Hz; CH on C(2))
	126.65	(d; J_{CH} 160.3 Hz; CH on C(2))
	128.06	(s; C of C(1))
	132.97	(d; J_{CH} 150.8 Hz; β - CH)
	149.68	(s; C of C(3))

MS	**m/z**	135	($(M + 1)^+$	10%)	134	(M^+	75%)
		119	($C_9H_{11}^+$	61%)	105	($C_8H_9^+$	38%)
		91	($C_7H_7^+$	100%)	29	($C_2H_5^+$	4%)

(65) 1-Hydroxy-1-butyl-2-cyclohexene

This product was obtained from the addition of lithiated benzyltrimethylsilane (**64**) to (**36a**). The addition was performed according to the standard procedure (Method A) used in Chapter **2**, where (**64**) was used instead of the phosphonate. After removal of the solvent a yellow oil was obtained that was purified by bulb to bulb distillation, 65°C/2mmHg, yielding 1.015g (63.0%) of a colourless oil.



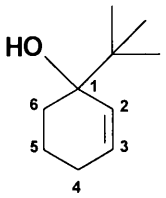
δ^{1}**H**	0.88	(3H; t; J_{HH} 7.0 Hz; CH_3 on C(9))
	1.29	(4H; m; CH_2 on C(8), CH_2 on C(9))
	1.48	(2H; m; CH_2 on C(7))
	1.63	(4H; m; CH_2 on C(5), CH_2 on C(6))
	1.96	(2H; m; CH_2 on C(4))
	5.58	(1H; d; J_{H2H3} 10.0 Hz; CH on C(2))
	5.76	(1H; d of t; J_{H3H2} 10.0 Hz; J_{H3H4} 3.8 Hz; CH on C(3))
δ^{13}**C**	13.92	(q; J_{CH} 124.4 Hz; CH_3 on C(9))
	18.96	(t; J_{CH} 127.0 Hz; CH_2 on C(5))
	23.16	(t; J_{CH} 127.4 Hz; CH_2 on C(9))
	25.12	(t; J_{CH} 126.0 Hz; CH_2 on C(4))
	25.59	(t; J_{CH} 124.0 Hz; CH_2 on C(8))
	35.31	(t; J_{CH} 127.8 Hz; CH_2 on C(6))
	41.97	(t; J_{CH} 123.6 Hz; CH_2 on C(7))
	69.53	(s; C of C(1))
	129.40	(d; J_{CH} 156.9 Hz; CH on C(3))
	132.87	(d; J_{CH} 157.7 Hz; CH on C(2))

MS	**m/z**	154	(M^+	3%)	136	((M^+ - H_2O)	47%)
		97	($C_6H_9O^+$	100%)	79	($C_6H_7^+$	64%)
		57	($C_4H_9^+$	42%)			

IR 3621 (s; OH)

(66) 1-Hydroxy-*t*-butyl-2-cyclohexene

This product was obtained from the addition of lithiated benzyltrimethylsilane (**64**) to (**36a**). The addition was performed according to the standard procedure (Method A) used in Chapter **2**, where (**64**) was used instead of the phosphonate. In this case t-BuLi was used as lithiating agent in the first step of the reaction. A yellow oil was obtained that was purified by bulb to bulb distillation, 75°C/0.8mmHg, yielding 0.444g (60%) of a colourless oil.



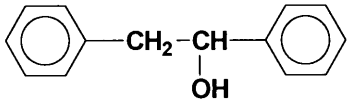
δ^1**H**	0.96	(9H; s; 3 x CH_3 of Bu^t)
	1.69	(4H; m; CH_2 on C(5), CH_2 on C(6))
	2.02	(2H; m; CH_2 on C(4))
	5.86	(2H; m; CH on C(2), CH on C(3))
δ^{13}**C**	19.00	(t; J_{CH} 128.6 Hz; CH_2 on C(5))
	24.90	(q; J_{CH} 125.0 Hz; 3 x CH_3 of Bu^t)
	25.18	(t; J_{CH} 127.0 Hz; CH_2 on C(4))
	30.56	(t; J_{CH} 126.3 Hz; CH_2 on C(6))
	87.04	(s; C of C(1))
	129.65	(d; J_{CH} 141.6 Hz; CH on C(3))
	131.46	(d; J_{CH} 141.6 Hz; CH on C(2))

MS	**m/z**	154	(M^+	<1%)	136	((M^+ - H_2O)	28%)
		97	($C_6H_9O^+$	100%)	79	($C_6H_7^+$	62%)
		57	($C_4H_9^+$	55%)			

IR 3600 (s; OH)

(67) 1,2-Diphenylethanol

This product was obtained from the addition of lithiated benzyltrimethylsilane (**64**) to benzaldehyde. The addition was performed according to the standard procedure (Method A) used in Chapter **2**, where (**64**) was used instead of the phosphonate. A yellow oil was obtained that was purified by column chromatography using ethyl acetate/hexane (1:3) as eluent to yield 0.653g (68.2%) of a yellow crystalline material m.p. 66.6-67°C.



δ^1**H**	1.34	(1H; s; OH)
	1.67	(2H; d; J_{HH} 6.6 Hz; CH_2)
	3.48	(1H; t; J_{HH} 6.6 Hz; CH)
	5.99	(10H; m; Ar H's)

δ^{13}**C**	45.65	(t; J_{CH} 127.8 Hz; CH_2)
	74.98	(d; J_{CH} 143.7 Hz; CH)
	125.84	(d; J_{CH} 158.0 Hz; Ar H's)
	126.28	(d; J_{CH} 159.9 Hz; Ar H's)
	127.30	(d; J_{CH} 159.5 Hz; Ar H's)
	128.14	(d; J_{CH} 159.1 Hz; Ar H's)
	128.20	(d; J_{CH} 159.1 Hz; Ar H's)
	129.41	(d; J_{CH} 157.5 Hz; Ar H's)
	138.04	(s; C of C-CH_2)
	143.83	(s; C of C-CHOH)

MS	**m/z**	198	(M^+	3%)	180	((M^+ - H_2O)	8%)
		105	($C_8H_9^+$	37%)	91	($C_7H_7^+$	100%)
		77	($C_6H_5^+$	49%)			

IR 3038 (s; OH)

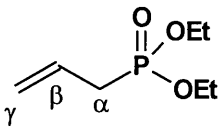
10.7 Synthesis and characterisation of substrates used during this study

General Procedure for the preparation of non-aromatic Phosphonates

Triethylphosphite (1 mol equiv.) reacted with the corresponding bromoalkane (4 mol equiv.) according to a standard procedure[6] to give the following phosphonates.

(39) Allyl-phosphonic acid diethyl ester

Purified by distillation yielding a colourless oil 18.582g (88.5%) b.p. 58°C/0.3mmHg (lit.[7] b.p. 97-98°C/16mmHg).



δ^{1}**H**	1.29	(6H; t; J_{HH} 6.4Hz; 2 x CH_3 of POEt)
	2.58	(2H; d of d; J_{HP} 21.9 Hz; J_{HH} 7.3 Hz; α - CH_2)
	4.08	(4H; d of q; J_{HP} 7.2 Hz; J_{HH} 7.2 Hz; 2 x CH_2 of POEt)
	5.19	(2H; m; γ - CH_2)
	5.77	(1H; m; β - CH)
δ^{31}**P**	27.68	
δ^{13}**C**	15.98	(q; J_{CH} 127.0 Hz; CH_3 of POEt[a])
	16.05	(q; J_{CH} 127.0 Hz; CH_3 of POEt[b])
	31.39	(d of t; J_{CP} 139.3 Hz; J_{CH} 127.4 Hz; α - CH_2)
	61.42	(t; J_{CH} 149.7 Hz; CH_2 of POEt[a])
	61.51	(t; J_{CH} 149.7 Hz; CH_2 of POEt[b])
	119.4	(d of t; J_{CP} 14.3 Hz; J_{CH} 156.9 Hz; γ - CH_2)
	127.2	(d of d; J_{CP} 11.2 Hz; J_{CH} 157.7 Hz; β - CH)

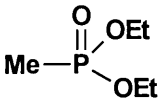
6 M H Bride, W A W Cummings and W J Pickles, *J. Appl. Chem.*, **11**, 1961, 352.

7 R S Edmundson, *Dictionary of Organophosphorus Compounds*, Chapman and Hall, London, 1988, 721.

MS	**m/z**	178	(M^+	8%)	109	($C_2H_6PO_3^+$	100%)
		81	($H_2PO_3^+$	75%)	41	($C_3H_5^+$	54%)
		29	($C_2H_5^+$	42%)			

(35a) Methyl-phosphonic acid diethyl ester

Purified by distillation yielding a colourless oil 18.987g (94.6%) b.p. 97-99°C/12mmHg (lit.[8] b.p.52-53°C/1mmHg).



δ^1**H**	1.26	(3H; t; J_{HH} 7.0 Hz; CH_3 of POEt[a])
	1.27	(3H; t; J_{HH} 7.1 Hz; CH_3 of POEt[b])
	1.41	(3H; d of d; J_{HP} 17.5 Hz; J_{HH} 3.9 Hz; α - CH_3)
	4.04	(4H; m; 2 x CH_2 of POEt)
δ^{31}**P**	31.04	
δ^{13}**C**	9.66	(d of q; J_{CP} 144.1 Hz; J_{CH} 132.8 Hz; α - CH_3)
	14.93	(q; J_{HH} 127.0 Hz; 2 x CH_3 of POEt)
	59.80	(t; J_{HH} 148.3 Hz; 2 x CH_2 of POEt)

MS	**m/z**	153	((M^+ + 1)	3%)	152	(M^+	3%)
		108	($C_2H_5PO_3^+$	26%)	97	($CH_6PO_3^+$	100%)
		79	(PO_3^+	98%)	29	($C_2H_5^+$	15%)
		15	(CH_3^+	10%)			

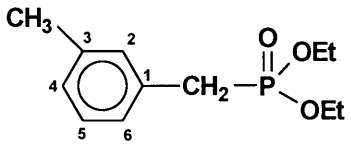
[8] R S Edmundson, *Dictionary of Organophosphorus Compounds*, Chapman and Hall, London, 1988, 235.

General Procedure for the preparation of aromatic Phosphonates

Triethylphosphite (1 mol equiv.) reacted with the corresponding bromoalkane (1 mol equiv.) according to a standard procedure[9] to give the following phosphonates.

(46b) 3-Methyl-benzyl-phosphonic acid diethyl ester

Purified by column chromatography yielding 8.810g (88.1%) of a colourless oil (lit.[10] b.p.126-127°C/0.7 mmHg).



δ^{1}**H**	1.21	(6H; t; J_{HH} 7.0 Hz; 2 x CH_3 of POEt)
	2.29	(3H; s; CH_3 on C(3))
	3.07	(2H; d; J_{HP} 21.6 Hz; α - CH_2)
	3.95	(4H; d of q; J_{HP} 7.0 Hz; J_{HH} 7.0 Hz; 2 x CH_2 of POEt)
	7.02	(3H; m; CH on C(2), CH on C(4), CH on C(5))
	7.17	(1H; m; CH on C(6))
δ^{31}**P**	27.20	
δ^{13}**C**	15.85	(d of q; J_{CP} 6.0 Hz; J_{CH} 125.4 Hz; 2 x CH_3 of POEt)
	20.79	(q; J_{CH} 126.3 Hz; CH_3 on C(3))
	33.18	(d of t; J_{CP} 138.0 Hz; J_{CH} 130.9 Hz; α - CH_2)
	61.52	(d of t; J_{CP} 7.1 Hz; J_{CH} 145.2 Hz; 2 x CH_2 of POEt)
	126.33	(d of d; J_{CP} 6.4 Hz; J_{CH} 159.3 Hz; CH on C(6))
	127.10	(d; J_{CH} 158.1 Hz; CH on C(4))
	127.85	(d; J_{CH} 159.5 Hz; CH on C(5))
	130.06	(d of d; J_{CP} 6.5 Hz; J_{CH} 156.3 Hz; CH on C(2))
	130.99	(d; J_{CP} 9.5 Hz; C of C(1))
	137.49	(s; C of C(3))

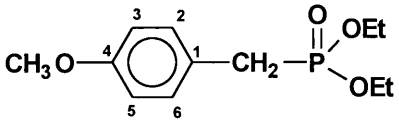
9 M Fedoryński *et. al.*, *J. Org. Chem.*, 43, 1978, 4682.

10 R S Edmundson, *Dictionary of Organophosphorus Compounds*, Chapman and Hall, London, 1988, 555.

MS	**m/z**	243	($(M^+ + 1)$	11%)	242	(M^+	66%)
		105	($C_8H_9^+$	97%)	79	(PO_3^+	27%)
		29	($C_2H_5^+$	30%)			

(46c) 4-Methoxy-benzyl-phosphonic acid diethyl ester

Purified by distillation yielding a colourless oil 8.937g (83.3%) b.p. 135 - 138°C/0.4mmHg (lit.[11] b.p. 125 - 128°C/0.21mmHg).



δ^1H	1.19	(3H; t; J_{HH} 7.1 Hz; CH_3 of POEt[a])
	1.21	(3H; t; J_{HH} 7.1 Hz; CH_3 of POEt[b])
	3.03	(2H; d; J_{HP} 21.1 Hz; α - CH_2)
	3.73	(3H; s; CH_3 of OMe)
	3.95	(4H; d of q; J_{HP} 7.3 Hz; J_{HH} 7.1 Hz; 2 x CH_2 of POEt)
	6.69	(2H; d; J_{HH} 7.7 Hz; CH on C(3), CH on C(5))
	7.16	(2H; d; J_{HH} 8.4 Hz; CH on C(2), CH on C(6))
δ^{31}P	27.37	
δ^{13}C	15.92	(d of q; J_{CP} 6.2 Hz; J_{CH} 125.4 Hz; 2 x CH_3 of POEt)
	32.28	(d of t; J_{CP} 138.6 Hz; J_{CH} 131.3 Hz; α - CH_2)
	54.69	(q; J_{CH} 143.6 Hz; CH_3 of OMe)
	61.51	(d of t; J_{CP} 6.7 Hz; J_{CH} 148.1 Hz; 2 x CH_2 of POEt)
	113.52	(d; J_{CH} 163.0 Hz; CH on C(3), CH on C(5))
	123.00	(d; J_{CP} 8.5 Hz; C of C(1))
	130.23	(d; J_{CH} 157.9 Hz; CH on C(2), CH on C(6))
	158.15	(s; C of C(4))

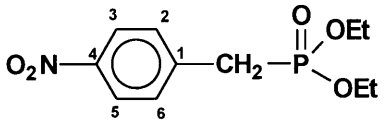
MS	**m/z**	259	($(M^+ + 1)$	11%)	258	(M^+	78%)

[11] R S Edmundson, *Dictionary of Organophosphorus Compounds*, Chapman and Hall, London, 1988, 527.

	121	($C_8H_9O^+$	100%)	79	(PO_3^+	3%)
	29	($C_2H_5^+$	16%)			

(46d) 4-Nitro-benzyl-phosphonic acid diethyl ester

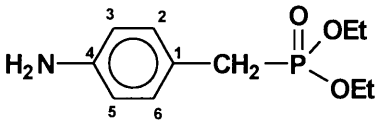
Purified by column chromatography (EtOAc) yielding 14.257g (83.7%) of a colourless oil.



δ^1**H**	1.21	(6H; t; J_{HH} 7.2 Hz; 2 x CH_3 of POEt)
	3.19	(2H; d; J_{HP} 22.4 Hz; α - CH_2)
	4.00	(4H; d of q; J_{HP} 7.4 Hz; J_{HH} 7.2 Hz; 2 x CH_2 of POEt)
	7.41	(1H; d; J_{HP} 2.3 Hz; CH on C(2))
	7.44	(1H; d; J_{HP} 2.4 Hz; CH on C(6))
	8.10	(1H; s; CH on C(3))
	8.13	(1H; s; CH on C(5))
δ^{31}**P**	24.69	
δ^{13}**C**	15.82	(d of q; J_{CP} 5.3 Hz; J_{CH} 127.9 Hz; 2 x CH_3 of POEt)
	33.31	(d of t; J_{CP} 137.0 Hz; J_{CH} 131.3 Hz; α - CH_2)
	61.88	(d of t; J_{CP} 7.0 Hz; J_{CH} 147.8 Hz; 2 x CH_2 of POEt)
	123.07	(d; J_{CH} 168.4 Hz; CH on C(2), CH on C(6))
	130.17	(d; J_{CH} 163.9 Hz; CH on C(3))
	130.25	(d; J_{CH} 163.9 Hz; CH on C(5))
	139.47	(d; J_{CP} 9.2 Hz; C of C(1))
	146.49	(s; CH on C(4))

MS	**m/z**	274	(($M^+ + 1$)	9%)	273	(M^+	30%)
		137	($C_4H_{10}PO_3^+$	42%)	136	($C_7H_6NO_2^+$	34%)
		109	($C_2H_6PO_3^+$	100%)	90	($C_7H_6^+$	61%)
		79	(PO_3^+	6%)	29	($C_2H_5^+$	51%)

(46e) Reduction of 4-Nitro-benzyl-phosphonic acid diethyl ester



4 - Nitro - benzyl - phosphonic acid diethyl ester 8.577g (31.4 mmol) reacted with tin(II)chloride according to a standard procedure[12] to give 7.320g (95.9%) of an orange crystalline material, m.p. 86.8-88.6°C.

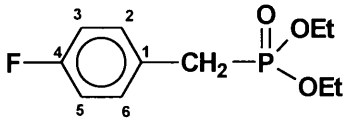
δ^{1}**H**	1.21	(6H; t; J_{HH} 7.1 Hz; 2 x CH_3 of POEt)
	3.00	(2H; d; J_{HP} 20.9 Hz; α - CH_2)
	3.96	(4H; d of q; J_{HP} 7.2 Hz; J_{HH} 7.1 Hz; 2 x CH_2 of POEt)
	6.60	(2H; d; J_{HP} 8.5 Hz; CH on C(3), CH on C(5))
	7.04	(2H; d of d; J_{HP} 2.5 Hz; J_{HH} 8.5 Hz; CH on C(2), CH on C(6))
δ^{31}**P**	27.93	
δ^{13}**C**	15.96	(d of q; J_{CP} 5.9 Hz; J_{CH} 126.1 Hz; 2 x CH_3 of POEt)
	32.26	(d of t; J_{CP} 139.0 Hz; J_{CH} 127.3 Hz; α - CH_2)
	61.74	(d of t; J_{CP} 6.7 Hz; J_{CH} 148.4 Hz; 2 x CH_2 of POEt)
	114.97	(d; J_{CH} 157.4 Hz; CH on C(3), CH on C(5))
	120.10	(s; C of C(1))
	130.15	(d of d; J_{CP} 6.6 Hz; J_{CH} 156.7 Hz; CH on C(2), CH on C(6))
	145.17	(s; C of C(4))

MS	**m/z**	244	($(M^+ + 1)$	5%)	243	(M^+	32%)
		106	($C_7H_8N^+$	100%)	79	(PO_3^+	5%)
		29	($C_2H_5^+$	6%)			

[12] F D Bellamy and K Ou, *Tetrahedron Lett.*, **25**, 1984, 839.

(46f) 4-Fluoro-benzyl-phosphonic acid diethyl ester

Purified by distillation yielding a colourless oil 13.714g (80.3%) b.p. 118 -119°C/1.5mmHg (lit.[13] b.p. 105°C/0.65mmHg).



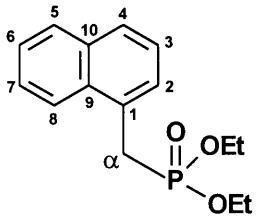
δ^{1}**H**	1.21	(6H; t; J_{HH} 7.1 Hz; 2 x CH_3 of POEt)
	3.07	(2H; d; J_{HP} 21.4 Hz; α - CH)
	3.97	(4H; d of q; J_{HP} 7.0 Hz; J_{HH} 7.1 Hz; 2 x CH_2 of POEt)
	6.96	(2H; d of d; J_{HP} 8.6 Hz; J_{HH} 8.6 Hz; CH on C(3), CH on C(5))
	7.23	(2H; m; CH on C(2), CH on C(6))
δ^{31}**P**	26.66	(d; J_{HF} 5.1 Hz)
δ^{19}**F**	-115.01	
δ^{13}**C**	15.94	(d of q; J_{CP} 6.0 Hz; J_{CH} 126.1 Hz; 2 x CH_3 of POEt)
	32.51	(d of t; J_{CP} 139.2 Hz; J_{CH} 129.5 Hz; α - CH_2)
	61.69	(d of t; J_{CP} 6.7 Hz; J_{CH} 147.4 Hz; 2 x CH_2 of POEt)
	114.96	(d of d of d; J_{CF} 21.5 Hz; J_{CP} 2.6 Hz; J_{CH} 162.2 Hz; CH on C(3), CH on C(5))
	127.11	(d; J_{CP} 12.1 Hz; C of C(1))
	130.89	(d of d of d; J_{CF} 7.2 Hz; J_{CP} 7.2 Hz; J_{CH} 158.7 Hz; CH on C(2), CH on C(6))
	161.51	(d of d; J_{CF} 245.3 Hz; J_{CP} 3.8 Hz; C of C(4))

MS	**m/z**	246	(M^+	10%)	109	($C_7H_6F^+$	100%)
		81	($PO_3H_2^+$	14%)	29	($C_2H_5^+$	9%)

13 R S Edmundson, *Dictionary of Organophosphorus Compounds*, Chapman and Hall, London, 1988, 439.

(48) Naphthalen-1-ylmethyl-phosphonic acid diethyl ester

Purified by distillation yielding a colourless oil 22.642g (95.6%) b.p. 179°C/1.5mmHg (lit.[14] b.p. 205-206°C/5mmHg.



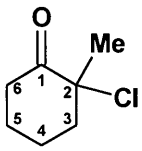
δ^{1}**H**	1.13	(6H; t; J_{HH} 7.1 Hz; 2 x CH_3 of POEt)
	3.62	(2H; d; J_{HP} 22.0 Hz; α - CH_2)
	3.90	(4H; m; 2 x CH_2 of POEt)
	7.49	(4H; m; CH on C(2), CH on C(3), CH on C(6), CH on C(7))
	7.75	(1H; d; J_{HH} 8.1 Hz; CH on C(5))
	7.82	(1H; d; J_{HH} 7.8 Hz; CH on C(4))
	8.09	(1H; d; J_{HH} 8.5 Hz; CH on C(8))
δ^{31}**P**	26.80	
δ^{13}**C**	15.95	(d of q; J_{CP} 6.0 Hz; J_{CH} 127.1 Hz; 2 x CH_3 of POEt)
	30.50	(d of t; J_{CP} 138.9 Hz; J_{CH} 129.0 Hz; α - CH_2)
	61.75	(d of t; J_{CP} 6.9 Hz; J_{CH} 144.1 Hz; 2 x CH_2 of POEt)
	124.10	(d; J_{CH} 158.1 Hz; CH on C(5))
	125.01	(d of d; J_{CP} 4.0 Hz; J_{CH} 159.9 Hz; CH on C(8))
	125.38	(d; J_{CH} 159.6 Hz; CH on C(8))
	125.69	(d; J_{CH} 159.9 Hz; CH on C(7))
	127.37	(d of d; J_{CP} 4.1 Hz; J_{CH} 157.7 Hz; CH on C(3))
	127.80	(d; J_{CP} 9.8 Hz; C of C(1))
	128.11	(d of d; J_{CP} 7.5 Hz; J_{CH} 152.2 Hz; CH on C(2))
	128.25	(d; J_{CH} 152.2 Hz; CH on C(4))
	131.74	(d; J_{CP} 5.1 Hz; C of C(9))
	133.57	(d; J_{CP} 2.6 Hz; C of C(10))

14 R S Edmundson, *Dictionary of Organophosphorus Compounds*, Chapman and Hall, London, 1988, 617.

MS	**m/z**	279	($(M^+ + 1)$	2%)	278	(M^+	68%)
		141	($C_{11}H_9^+$	100%)	81	($PO_3H_2^+$	12%)
		29	($C_2H_5^+$	12%)			

(62) Synthesis of 2-Chloro-2-methylcyclohexanone

2 - Methylcyclohexanone 111.998g (1.00 mol) reacted with sulfuryl chloride 90cm^3 (1.11 mol) according to a standard procedure[15] to yield after distillation 121.757g (82.8%) b.p. 88 - 90°C/13mmHg (lit.[15] b.p. 94 - 96°C/27mmHg) of a colourless oil.



δ^1**H**	1.56	(3H; s; CH_3 on C(2))
	1.64	(2H; m; CH on C(4), CH on C(5))
	1.80	(1H; m; CH on C(6))
	1.96	(1H; m; CH on C(4))
	2.03	(1H; m; CH on C(5))
	2.24	(1H; m; CH on C(6))
	2.29	(1H; m; CH on C(3))
	2.98	(1H; d of d of d of d; $J_{H3H3'}$ 12.8 Hz; J_{H3H4} 12.8 Hz; $J_{H3H4'}$ 6.1 Hz; J_{H3H5} 1.6 Hz; CH on C(3))
δ^{13}**C**	21.15	(t; J_{CH} 128.3 Hz; CH_2 on C(4))
	26.32	(q; J_{CH} 129.5 Hz; CH_3 on C(2))
	26.75	(t; J_{CH} 127.7 Hz; CH_2 on C(5))
	36.62	(t; J_{CH} 130.3 Hz; CH_2 on C(3))
	42.66	(t; J_{CH} 129.2 Hz; CH_2 on C(6))
	70.21	(s; C of C(2))
	206.37	(s; C of C(1))

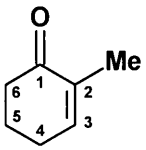
[15] E W Warnhoff, D G Martin and W S Johnson, Organic Synthesis, 19 , 162.

MS	**m/z**	149	($(M^+ + 2)$	<1%)	148	($(M^+ + 1)$	100%)
		147	(M^+	1%)	111	($C_7H_{11}O^+$	10%)
		69	($C_4H_5O^+$	71%)	56	($C_3H_4O^+$	100%)
		15	(CH_3^+	2%)			

IR 1720 (s; C=O)

(63) Synthesis of 2-Methyl-cyclohex-2-enone

2 - Chloro - 2 - methylcyclohexanone 56.163g (0.382 mol) reacted with DMF 125cm^3 (1.62 mol) in the presence of lithium chloride 13.008g (0.310 mol) according to a standard procedure[15] to give 19.165g (45.6%) of a colourless oil after distillation b.p. 80 - 83°C/13mmHg (lit.[15] b.p. 83 - 85.5°C/35mmHg).



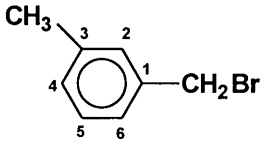
δ^1**H**	1.72	(3H; s; CH_3 on C(2))
	1.93	(2H; d of d of d of d; J_{H5H4} 4.3 Hz; J_{H5H6} 3.1 Hz; CH_2 on C(5))
	2.29	(2H; d of d of d; J_{H4H3} 3.5 Hz; J_{H4H5} 4.1 Hz; CH_2 on C(4))
	2.39	(2H; d of d; J_{H6H5} 3.4 Hz; CH_2 on C(6))
	6.70	(1H; d of d of d of d; J_{H3H4} 4.1 Hz; J_{H3H5} 1.2 Hz; CH on C(3))
δ^{13}**C**	14.69	(q; J_{CH} 127.4 Hz; CH_3 on C(2))
	22.32	(t; J_{CH} 128.8 Hz; CH_2 on C(5))
	24.94	(t; J_{CH} 127.4 Hz; CH_2 on C(4))
	37.19	(t; J_{CH} 127.5 Hz; CH_2 on C(6))
	134.32	(s; C of C(2))
	144.16	(d; J_{CH} 154.3 Hz; CH on C(3))
	197.86	(s; C of C(1))

MS	**m/z**	111	($(M^+ + 1)$	<1%)	110	(M^+	100%)
		82	($C_5H_6O^+$	100%)	67	($C_4H_3O^+$	24%)

		54	($C_3H_2O^+$	94%)	15	(CH_3^+	2%)
IR	1663		(s; C=O)				

(64) Synthesis of 1-Bromomethyl-3-methyl-benzene

m - Xylene 49.980g (472 mmol) reacted with bromine 83.019g (519 mmol) according to a standard procedure to give after distillation 75.970g (87.0%) of a colourless oil b.p. 58 - 61°C/0.5mmHg).



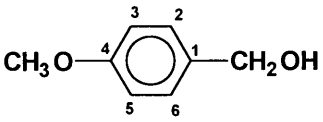
δ^1**H**	2.35	(3H; s; CH_3 on C(3))
	4.46	(2H; s; CH_2 on C(1))
	7.10	(1H; d; J_{HH} 7.1 Hz; CH on C(6))
	7.20	(3H; m; CH on C(2), CH on C (4), CH on C(5))
δ^{13}**C**	21.20	(q; J_{CH} 127.0 Hz; CH_3 on C(3))
	33.62	(t; J_{CH} 152.6 Hz; CH_2 on C(1))
	126.00	(d; J_{CH} 159.2 Hz; CH on C(6))
	128.58	(d; J_{CH} 159.9 Hz; CH on C(4))
	129.11	(d; J_{CH} 158.5 Hz; CH on C(2))
	129.64	(d; J_{CH} 155.8 Hz; CH on C(5))
	137.61	(s; C of C(3))
	138.36	(s; C of C(1))

MS	**m/z**	186	((M^+ + 2)	46%)	184	(M^+	47%)
		105	($C_8H_9^+$	51%)	79	($C_6H_7^+$	100%)

(65) Synthesis of (4-Methoxy-phenyl)-methanol

4 - Methoxy - benzaldehyde 29.500g (246 mmol) was dissolved in 100 cm^3 dry THF. Lithium aluminium anhydride 9.342g (246 mmol) was added carefully and after the initial spontaneous reaction, the reaction mixture was kept at reflux temperature for 24 hours. Aqueous sulphuric

acid was added and after all unreacted anhydride had reacted, the mixture was extracted with (3 x 20 cm^3) portions of ether. The combined etheral layers were dried over Na_2SO_4 , filtered and the solvent removed under reduced pressure to yield a colourless oil. This oil was purified by column chromatography (EtOAc) to give 14.753g (49.2%) of the alcohol.

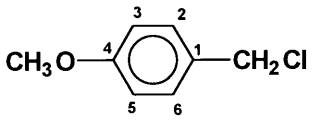


δ^1**H**	2.50	(1H; s; OH)
	3.77	(3H; s; CH_3 of OMe)
	4.56	(2H; s; CH_2 on C(1))
	6.86	(2H; d; J_{HH} 8.6 Hz; CH on C(3), CH on C(5))
	7.25	(2H; d; J_{HH} 8.6 Hz; CH on C(2), CH on C(6))
δ^{13}**C**	54.84	(q; J_{CH} 143.8 Hz; CH_3 of OMe)
	64.04	(t; J_{CH} 144.3 Hz; CH_2 on C(1))
	113.48	(d; J_{CH} 158.7 Hz; CH on C(3), CH on C(5))
	128.23	(d; J_{CH} 153.4 Hz; CH on C(2), CH on CH on C(6))
	132.97	(s; C of C(1))
	158.64	(s; C of C(4))

MS	**m/z**	139	($(M^+ + 1)$	9%)	138	(M^+	100%)
		121	($C_8H_9O^+$	66%)	109	($C_7H_7O^+$	86%)
		77	($C_6H_5^+$	55%)	15	(CH_3^+	3%)

(66) Synthesis of 1-Chloromethyl-4-methoxy-benzene

(4 - Methoxy - phenyl) - methanol 7.136g (58.5 mmol) reacted with dry hydrogen chloride gas according to a standard procedure[16] to give 6.210g (75.8%) of a colourless oil after distillation b.p. 71 - 72°C/0.95mmHg lit.[16] b.p. 101 - 103°C/8 - 10mmHg.



16 R L Shriner and C L Hull, *J. Org. Chem.*, **10**, 1945, 228.

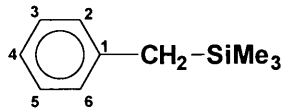
δ^1**H**	3.80	(3H; s; CH_3 of OMe)
	4.56	(2H; s; CH_2 on C(1))
	6.87	(2H; d; J_{HH} 8.7 Hz; CH on C(3), CH on C(5))
	7.30	(2H; d; J_{HH} 8.7 Hz; CH on C(2), CH on C(6))

δ^{13}**C**	46.07	(t; J_{CH} 151.1 Hz; CH_2 on C(1))
	54.97	(q; J_{CH} 143.9 Hz; CH_3 of OMe)
	113.90	(d; J_{CH} 159.9 Hz; CH on C(3), CH on C(5))
	129.49	(s; C of C(1))
	129.83	(d; J_{CH} 158.0 Hz; CH on C(2), CH on C(6))
	159.49	(s; C of C(4))

MS	**m/z**	158	($(M^+ + 2)$	14%)	156	(M^+	42%)
		121	($C_8H_9O^+$	100%)	91	($C_7H_7^+$	20%)
		77	($C_6H_5^+$	41%)	15	(CH_3^+	3%)

(64) Synthesis of Benzyltrimethylsilane

Benzylchloride 23.159g (0.185 mol) reacted with magnesium 5.005g (0.209 mol) in 130 cm^3 diethyl ether. To this solution was added trimethylchlorosilane 10.010g (0.0927 mol) dissolved in 50 cm^3 diethyl ether. After 60 hours the mixture was saturated with carbon dioxide gas and hydrolysed with 40 cm^3 of ice cold 3N HCl. The ether phase was washed with sodium carbonate, until free from phenylacetic acid. The resulting mixture was dried MgSO4, filtered and the solvent removed under reduced pressure to yield a yellow oil. This oil was purified by distillation yielding 13.000g (85.5%), b.p.88-89°C/15mmHg Lit[17] b.p. 95°C/34mmHg of a colourless oil.



δ^1**H**	0.00	(9H; s; 3 x CH_3 of $SiMe_3$)
	2.09	(2H; s; CH_2)
	7.00	(2H; d; J_{HH} 7.5 Hz; CH on C(2), CH on C(6))

[17] C R Hauser and C R Hance, *J. Am. Chem. Soc.*, **73**, 1952, 5846.

	7.08	(1H; d; J_{HH} 7.5 Hz; CH on C(4))
	7.22	(2H; d of d; J_{HH} 7.5 Hz; CH on C(3), CH on C(5))
$\delta^{13}C$	-1.93	(q; J_{CH} 118.8 Hz; 3 x CH_3 of $SiMe_3$)
	27.04	(t; J_{CH} 119.9 Hz; CH_2)
	123.86	(d; J_{CH} 160.4 Hz; CH on C(4))
	128.02	(d; J_{CH} 159.2 Hz; CH on C(2), CH on C(6))
	128.10	(d; J_{CH} 159.2 Hz; CH on C(3), CH on C(5))
	140.43	(s; C of C(1))

MS	**m/z**	164	(M^+	73%)	149	($C_9H_{13}Si^+$	50%)
		121	($C_7H_9Si^+$	61%)	73	($SiMe_3^+$	100%)

Appendix 1

Crystallographic Data acquisition and refinement details of compound (47c)

Empirical formula	$C_{21}H_{27}PO_4$
Molecular weight	374.42
Crystal dimension, mm	0.21 x 0.22 x 0.24
Space group	P_2, (no 4)
Cell dimensions	
a, Å	8.454(2)
b, Å	10.443(2)
c, Å	11.922(2)
α, °	90
β, °	104.03(2)
γ, °	90
Z	2
Volume, $Å^3$	1021(1)
D(calc), $g.cm^{-3}$	1.20
μ, cm^{-1}	1.15
Radiation (λ, Å)	M_oK_α, 0.7107
T, °C	22
F(000)	378.0
Scan type (ω:2θ)	1:1
Scan Range (θ °)	$3 \leq \theta \leq 30$
Zone collected:	
h	-11, +11
k	-14, 0
l	0, +16
Max. scan speed ($deg.min^{-1}$)	5.48
Max. scan time, sec.	60

Scan angle ($\omega + 0.34 \tan \theta$)°	0.63
Aperture size (mm)	1.3 x 4.0
Reflections collected	2738
Decay, %	3 (uncorrected)
EAC correction factor: Maximum Minimum Average	 1.000 0.798 0.887
Unique reflections used ($> 3\sigma(I)$)	1952
R_{int}	0.014
Parameters refined	241
Max. positional shift/esd	0.37
Residual electron density ($eÅ^3$): Maximum Minimum	 +0.26 -0.23
$U_{iso}(H)$, $Å^2$	0.107(4)
R	0.054
R_w	0.032

Table 14 Fractional atomic coordinates ($x10^4$) and equivalent thermal factors ($x10^3 Å^2$)

Atom	x/a	y/b	z/c	U_{eq}
P	258(1)	2636	3300(1)	57(1)
C(1)	2213(4)	2711(5)	2921(3)	48(1)
C(2)	1931(5)	3273(5)	1705(3)	51(1)
C(3)	1039(5)	2600(6)	779(3)	64(1)
C(4)	747(6)	3081(5)	-355(4)	72(1)
C(5)	1356(6)	4232(5)	-569(4)	67(1)
C(6)	2289(5)	4954(4)	348(4)	57(1)
C(7)	2943(6)	6160(5)	134(4)	74(1)
C(8)	3806(7)	6886(5)	1012(5)	91(2)
C(9)	4054(7)	6440(6)	2169(5)	91(2)
C(10)	3437(6)	5308(5)	2407(4)	71(1)
C(11)	2566(5)	4507(5)	1508(4)	52(1)
C(12)	3050(5)	1375(4)	2982(3)	48(1)
C(13)	4655(5)	1493(5)	2600(4)	65(1)
C(14)	5521(6)	206(5)	2660(5)	84(2)
C(15)	5953(5)	-295(5)	3910(4)	82(2)
C(16)	4481(6)	-337(5)	4393(4)	63(1)
O(1)	4153(4)	-1255(4)	4889(3)	94(1)
C(17)	3426(5)	846(5)	4247(3)	59(1)
O(2)	-792(4)	1566(3)	2818(3)	70(1)
O(3)	788(3)	2695(4)	4651(2)	75(1)
C(18)	-424(6)	2463(9)	5318(4)	133(3)
C(19)	69(7)	2829(10)	6426(4)	167(3)
O(4)	-527(4)	4008(3)	2975(3)	82(1)
C(20)	-2154(7)	4213(7)	2303(6)	125(2)
C(21)	-2254(9)	4877(8)	1289(6)	156(3)

Table 15 Bond lengths (Å)

P-C(1)	1.817(3)	P-O(2)	1.456(3)
P-O(3)	1.565(3)	P-O(4)	1.588(4)
C(1)-C(2)	1.529(5)	C(1)-C(12)	1.558(6)
C(2)-C(3)	1.370(5)	C(2)-C(11)	1.438(5)
C(3)-C(4)	1.406(5)	C(4)-C(5)	1.356(6)
C(5)-C(6)	1.402(5)	C(6)-C(7)	1.424(5)
C(6)-C(11)	1.423(5)	C(7)-C(8)	1.354(6)
C(8)-C(9)	1.422(6)	C(9)-C(10)	1.351(6)
C(10)-C(11)	1.417(5)	C(12)-C(13)	1.537(5)
C(12)-C(17)	1.565(5)	C(13)-C(14)	1.524(6)
C(14)-C(15)	1.537(6)	C(15)-C(16)	1.494(6)
C(16)-O(1)	1.194(5)	C(16)-C(17)	1.508(6)
O(3)-C(18)	1.461(5)	C(18)-C(19)	1.341(6)
O(4)-C(20)	1.430(6)	C(20)-C(21)	1.378(7)

Table 16 Valence angles(°)

C(1)-P-O(2)	116.1(2)	C(1)-P-O(3)	101.8(2)
O(2)-P-O(3)	115.6(2)	C(1)-P-O(4)	104.6(2)
O2)-P-O(4)	114.7(2)	O(3)-P-O(4)	102.4(2)
P-C(1)-C(2)	108.1(3)	P-C(1)-C(12)	112.3(3)
C(2)-C(1)-C(12)	110.6(3)	C(1)-C(2)C(3)	119.8(4)
C(1)-C(2)-C(11)	121.4(4)	C(3)-C(2)-C(11)	118.8(4)
C(2)-C(3)-C(4)	121.7(5)	C(3)-C(4)-C(5)	120.7(5)
C(4)-C(5)-C(6)	119.8(4)	C(5)-C(6)-C(7)	120.3(4)
C(5)-C(6)-C(11)	120.7(4)	C(7)-C(6)-C(11)	119.0(4)
C(6)-C(7)-C(8)	121.0(5)	C(7)-C(8)-C(9)	119.5(5)
C(8)-C(9)-C(10)	121.1(5)	C(9)-C(10)-C(11)	121.0(5)
C(2)-C(11)-C(6)	118.2(4)	C(2)-C(11)-C(10)	123.5(4)
C(6)-C(11)-C(10)	118.3(4)	C(1)-C(12)-C(13)	109.7(3)
C(1)-C(12)-C(17)	110.2(3)	C(13)-C(12)-C(17)	109.0(3)
C(12)-C(13)-C(14)	111.3(4)	C(13)-C(14)-C(15)	110.2(4)
C(14)-C(15)-C(16)	111.0(4)	C(15)-C(16)-O(1)	122.0(5)
C(15)-C(16)-C(17)	117.2(4)	O(1)-C(16)-C(17)	120.9(5)
C(12)-C(17)-C(16)	112.1(4)	P-O(3)-C(18)	119.3(2)
O(3)-C(18)-C(19)	113.4(5)	P-O(4)-C(20)	124.1(4)
O(4)-C(20)-C(21)	114.4(6)		

Table 17 Anisotropic thermal factors (x 10^3 $Å^2$)

Atom	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
P	58(1)	65(1)	48(1)	-5(1)	14(1)	2(1)
C(1)	51(2)	51(2)	43(2)	5(3)	11(2)	-3(3)
C(2)	54(3)	53(3)	42(2)	1(2)	7(2)	0(2)
C(3)	77(3)	61(3)	53(2)	-1(3)	12(2)	-5(3)
C(4)	91(4)	76(4)	44(3)	-10(3)	9(2)	-9(3)
C(5)	80(3)	75(4)	43(3)	4(3)	10(2)	5(3)
C(6)	67(3)	48(3)	57(3)	5(2)	17(2)	8(2)
C(7)	86(4)	63(4)	72(3)	21(3)	20(3)	10(3)
C(8)	121(5)	51(3)	92(4)	11(3)	10(4)	-15(3)
C(9)	126(5)	64(4)	72(4)	-1(3)	1(4)	-27(4)
C(10)	84(4)	50(3)	66(3)	8(3)	-8(3)	-7(3)
C(11)	54(3)	49(3)	52(3)	0(2)	11(2)	8(2)
C(12)	54(3)	44(3)	48(2)	3(2)	14(2)	-2(2)
C(13)	65(3)	62(3)	74(3)	15(3)	28(3)	7(3)
C(14)	72(4)	80(4)	114(4)	10(4)	50(3)	12(3)
C(15)	59(3)	73(4)	117(4)	27(3)	23(3)	12(3)
C(16)	64(3)	63(3)	55(3)	4(3)	0(2)	-5(3)
O(1)	84(3)	83(3)	112(3)	48(3)	21(2)	7(2)
C(17)	71(3)	51(3)	53(3)	8(2)	14(2)	6(3)
O(2)	64(2)	76(2)	69(2)	-9(2)	15(2)	-15(2)
O(3)	68(2)	109(3)	52(2)	-12(2)	22(1)	-2(3)
C(18)	84(4)	250(10)	75(4)	-44(6)	38(3)	-20(6)
C(19)	111(5)	339(12)	55(4)	-7(7)	31(4)	-2(8)
O(4)	73(3)	77(3)	94(3)	0(2)	20(2)	13(2)
C(20)	93(5)	110(6)	163(7)	45(6)	16(5)	27(5)
C(21)	149(7)	174(9)	123(7)	24(6)	-8(5)	47(6)

Table 18 Coordinates of the hydrogen atoms (x10^4)

Atom	x/a	y/b	z/c	U
H(1)	3028(4)	3311(5)	3541(3)	107(4)
H(3)	550(5)	1676(6)	923(3)	107(4)
H(4)	28(6)	2528(5)	-1063(4)	107(4)
H(5)	1124(6)	4592(5)	-1442(4)	107(4)
H(7)	2747(6)	6503(5)	-744(4)	107(4)
H(8)	4302(7)	7796(5)	836(5)	107(4)
H(9)	4748(7)	7018(6)	2869(5)	107(4)
H(10)	3612(6)	5006(5)	3295(4)	107(4)
H(12)	2236(5)	726(4)	2414(3)	107(4)
H(13A)	5444(5)	2164(5)	3160(4)	107(4)
H(13B)	4392(5)	1841(5)	1721(4)	107(4)
H(14A)	4729(6)	-472(5)	2111(5)	107(4)
H(14B)	6625(6)	320(5)	2366(5)	107(4)
H(15A)	6852(5)	330(5)	4437(4)	107(4)
H(15B)	6451(5)	-1248(5)	3921(4)	107(4)
H(17A)	2289(5)	611(5)	4460(3)	107(4)
H(17B)	4050(5)	1577(5)	4830(3)	107(4)
H(18A)	-684(6)	1449(9)	5296(4)	107(4)
H(18B)	-1521(6)	2982(9)	4919(4)	107(4)
H(19A)	-794(7)	2814(10)	6961(4)	107(4)
H(19B)	6(7)	3743(10)	5993(4)	107(4)
H(19C)	1285(7)	2686(10)	6959(4)	107(4)
H(20A)	-2805(7)	4751(7)	2822(6)	107(4)
H(20B)	-2729(7)	3292(7)	2092(6)	107(4)
H(21A)	-3453(9)	5174(8)	813(6)	107(4)
H(21B)	-1661(9)	4358(8)	722(6)	107(4)
H(21C)	-1539(9)	5710(8)	1626(6)	107(4)

Table 19 Torsion angles

Plane	Angle	Plane	Angle
O(2)-P-C(1)-H(1)	-160.3(4)	C(1)-C(12)-C(13)-H(13A)	59.2(5)
O(2)-P-C(1)-C(2)	79.4(4)	C(1)-C(12)-C(13)-H(13B)	-60.3(5)
O(2)-P-C(1)-C(12)	-42.9(4)	C(1)-C(12)-C(13)-C(14)	179.4(4)
O(3)-P-C(1)-H(1)	-33.9(4)	H(12)-C(12)-C(13)-H(13A)	178.5(5)
O(3)-P-C(1)-C(2)	-154.2(3)	H(12)-C(12)-C(13)-H(13B)	59.1(6)
O(3)-P-C(1)-C(12)	83.4(4)	H(12)-C(12)-C(13)-C(14)	-61.3(6)
O(4)-P-C(1)-H(1)	72.3(4)	C(17)-C(12)-C(13)-H(13A)	-61.6(5)
O(4)-P-C(1)-C(2)	-48.0(4)	C(17)-C(12)-C(13)-H(13B)	178.9(4)
O(4)-P-C(1)-C(12)	-170.3(3)	C(17)-C(12)-C(13)-C(14)	58.6(5)
C(1)-P-O(3)-C(18)	-170.7(4)	C(1)-C(12)-C(17)-C(16)	-170.6(4)
O(2)-P-O(3)-C(18)	-44.0(5)	C(1)-C(12)-C(17)-H(17A)	69.1(5)
O(4)-P-O(3)-C(18)	81.3(4)	C(1)-C(12)-C(17)-H(17B)	-50.1(5)
C(1)-P-O(4)-C(20)	130.6(5)	H(12)-C(12)-C(17)-C(16)	70.0(6)
O(2)-P-O(4)-C(20)	2.4(5)	H(12)-C(12)-C(17)-H(17A)	-50.3(6)
O(3)-P-O(4)-C(20)	-123.6(5)	H(12)-C(12)-C(17)-H(17B)	-169.5(5)
P-C(1)-C(2)-C(3)	-66.3(5)	C(13)-C(12)-C(17)-C(16)	-50.0(5)
P-C(1)-C(2)-C(11)	112.9(4)	C(13)-C(12)-C(17)-H(17A)	-170.4(4)
H(1)-C(1)-C(2)-C(3)	174.6(5)	C(13)-C(12)-C(17)-H(17B)	70.4(5)
H(1)-C(1)-C(2)-C(11)	-6.3(7)	C(12)-C(13)-C(14)-H(14A)	58.8(6)
C(12)-C(1)-C(2)-C(3)	57.1(6)	C(12)-C(13)-C(14)-H(14B)	178.6(5)
C(12)-C(1)-C(2)-C(11)	-123.8(5)	C(12)-C(13)-C(14)-C(15)	-61.3(6)
P-C(1)-C(12)-H(12)	57.4(4)	H(13A)-C(13)-C(14)-H(14A)	179.1(6)
P-C(1)-C(12)-C(13)	177.4(3)	H(13)-C(13)-C(14)-H(14B)	-61.1(7)
P-C(1)-C(12)-C(17)	-62.5(4)	H(13A)-C(13)-C(14)-C(15)	59.0(6)
H(1)-C(1)-C(12)-H(12)	176.3(4)	H(13B)-C(13)-C(14)-H(14A)	-61.5(7)
H(1)-C(1)-C(12)-C(13)	-63.6(5)	H(13B)-C(13)-C(14)-H(14B)	58.3(7)
H(1)-C(1)-C(12)-C(17)	56.5(5)	H(13B)-C(13)-C(14)-C(15)	178.4(5)
C(2)-C(1)-C(12)-H(12)	-63.5(5)	C(13)-C(14)-C(15)-H(15A)	-66.3(6)
C(2)-C(1)-C(12)-C(13)	56.6(5)	C(13)-C(14)-C(15)-H(15B)	174.2(5)

C(2)-C(1)-C(12)-C(17)	176.6(4)	C(13)-C(14)-C(15)-C(16)	54.0(6)
C(1)-C(2)-C(3)-H(3)	-0.3(7)	H(14A)-C(14)-C(15)-H(15A)	173.6(6)
C(1)-C(2)-C(3)-C(4)	179.9(4)	H(14A)-C(14)-C(15)-H(15B)	54.1(7)
C(11)-C(2)-C(3)-H(3)	-179.4(5)	H(14A)-C(14)-C(15)-C(16)	-66.1(7)
C(11)-C(2)-C(3)-C(4)	0.7(7)	H(14B)-C(14)-C(15)-H(15A)	53.8(7)
C(1)-C(2)-C(11)-C(6)	178.5(4)	H(14B)-C(14)-C(15)-H(15B)	-65.7(7)
C(1)-C(2)-C(11)-C(10)	-2.2(7)	H(14B)-C(14)-C(15)-C(16)	174.1(5)
C(3)-C(2)-C(11)-C(6)	-2.4(6)	C(14)-C(15)-C(16)-O(1)	132.5(5)
C(3)-C(2)-C(11)-C(10)	177.0(5)	C(14)-C(15)-C(16)-C(17)	-48.6(6)
C(2)-C(3)-C(4)-H(4)	-179.4(5)	H(15A)-C(15)-C(16)-O(1)	-107.3(6)
C(2)-C(3)-C(4)-C(5)	0.5(8)	H(15A)-C(15)-C(16)-C(17)	71.6(7)
H(3)-C(3)-C(4)-H(4)	0.7(8)	H(15B)-C(15)-C(16)-O(1)	12.3(8)
H(3)-C(3)-C(4)-C(5)	-179.4(5)	H(15B)-C(15)-C(16)-C(17)	-168.8(5)
C(3)-C(4)-C(5)-H(5)	-180.0(5)	C(15)-C(16)-C(17)-C(12)	47.2(6)
C(3)-C(4)-C(5)-C(6)	0.1(8)	C(15)-C(16)-C(17)-H(17A)	167.6(5)
H(4)-C(4)-C(5)-H(5)	-0.1(8)	C(15)-C(16)-C(17)-H(17B)	-73.2(6)
H(4)-C(4)-C(5)-C(6)	180.0(5)	O(1)-C(16)-C(17)-C(12)	-133.9(5)
C(4)-C(5)-C(6)-C(7)	179.6(5)	O(1)-C(16)-C(17)-H(17A)	-13.5(6)
C(4)-C(5)-C(6)-C(11)	-1.9(7)	O(1)-C(16)-C(17)-H(17B)	105.7(5)
H(5)-C(5)-C(6)-C(7)	-0.3(8)	P-O(3)-C(18)-H(18A)	74.3(6)
H(5)-C(5)-C(6)-C(11)	178.2(5)	P-O(3)-C(18)-H(18B)	-44.5(7)
C(5)-C(6)-C(7)-H(7)	-2.0(8)	P-O(3)-C(18)-C(19)	-165.3(5)
C(5)-C(6)-C(7)-C(8)	178.1(5)	P-O(3)-C(18)-H(19B)	-126.9(5)
C(11)-C(6)-C(7)-H(7)	179.5(5)	O(3)-C(18)-C(19)-H(19A)	172.0(7)
C(11)-C(6)-C(7)-C(8)	0.5(8)	O(3)-C(18)-C(19)-H(19B)	65.6(6)
C(5)-C(6)-C(11)-C(2)	3.0(7)	O(3)-C(18)-C(19)-H(19C)	-40.8(11)
C(5)-C(6)-C(11)-C(10)	-176.4(5)	H(18A)-C(18)-C(19)-H(19A)	-67.6(10)
C(7)-C(6)-C(11)-C(2)	-178.5(5)	H(18A)-C(18)-C(19)-H(19B)	-174.0(8)
C(7)-C(6)-C(11)-C(10)	2.2(7)	H(18A)-C(18)-C(19)H(19C)	79.7(11)
C(6)-C(7)-C(8)-H(8)	179.6(6)	H(18B)-C(18)-C(19)-H(19A)	51.3(11)
C(6)-C(7)-C(8)-C(9)	-0.5(9)	H(18B)-C(18)-C(19)-H(19B)	-55.2(7)

H(7)-C(7)-C(8)-H(8)	-0.4(9)	H(18B)-C(18)-C(19)H(19C)	-161.5(8)
H(7)-C(7)-C(8)-C(9)	179.5(6)	P-O(4)-C(20)-H(20A)	120.2(6)
C(7)-C(8)-C(9)-H(9)	179.8(6)	P-O(4)-C(20)-H(20B)	1.6(7)
C(7)-C(8)-C(9)-C(10)	-0.3(9)	P-O(4)-C(20)-C(21)	-119.4(6)
H(8)-C(8)-C(9)-H(9)	-0.3(10)	O(4)-C(20)-C(21)-H(21A)	-171.3(7)
H(8)-C(8)-C(9)-C(10)	179.6(6)	O(4)-C(20)-C(21)-H(21B)	61.8(9)
C(8)-C(9)-C(10)-H(10)	178.1(6)	O(4)-C(20)-C(21)-H(21C)	-53.5(8)
C(8)-C(9)-C(10)-C(11)	2.1(9)	H(20A)-C(20)-C(21)-H(21A)	-50.8(11)
H(9)-C(9)-C(10)-H(10)	1.9(9)	H(20A)-C(20)-C(21)-H(21B)	-177.7(8)
H(9)-C(9)-C(10)-C(11)	-178.0(6)	H(20A)-C(20)-C(21)-H(21C)	67.0(9)
C(9)-C(10)-C(11)-C(2)	177.7(5)	H(20B)-C(20)-C(21)-H(21A)	67.8(11)
C(9)-C(10)-C(11)-C(6)	-3.0(7)	H(20B)-C(20)-C(21)-H(21B)	-59.2(10)
H(10)-C(10)-C(11)-C(2)	-2.2(8)	H(20B)-C(20)-C(21)-H(21C)	-174.5(8)
H(10)-C(10)-C(11)-C(6)	177.2(5)		