JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 6, 523–530 (1993)

SOLVATION AND METAL ION EFFECTS ON STRUCTURE AND REACTIVITY OF PHOSPHORYL COMPOUNDS.
2. β,γ-SUBSTITUTED ALKYLPHOSPHONIC ESTERS

MARIE-P. BELCIUG, TOM A. MODRO* AND PHILIPPUS L. WESSELS

Centre for Heteroatom Chemistry, Department of Chemistry, University of Pretoria, Pretoria 0002, South Africa

NMR spectroscopic and conformation analyses ware carried out for five dimethyl β,γ-disubstituted propylphosphonates, $YCH_2CHXCH_2PO_3Me_2$, in five solvents and in acetone containing sodium and magnesium ions. Conformational preferences observed for the rotation about the C_1—C_2 bond are determined by the attractive interactions between the oxygen containing substituents X (X = OH, OMe) and the phosphoryl group, and are enhanced by the metal ions, presumably *via* chelation effects. The rotation about the C_2—C_3 bond yields statistical distribution of the rotamers. For Y = benzoyl, there was no evidence for a competition of the carbonyl group for the intramolecular interactions with X or with a metal ion.

INTRODUCTION

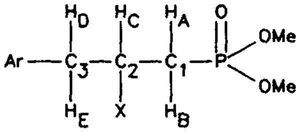
In the first part of this series[1] we reported solvent and alkali metal ion (Na^+, Mg^{2+}) effects on the NMR spectra and conformational preferences for β-substituted β-phenylethylphosphonic esters, $PhCHXCH_2PO_3Me_2$ (**1**, X = OH, OMe, Cl). Conformational analysis was performed using the observed $^3J_{AC}$ and $^3J_{BC}$ vicinal coupling between the protons of the diastereotopic α-methylene group and the chiral group, and the values for the vicinal coupling constants of the individual rotamers calculated according to the approach of Haasnoot *et al.*[2] The analysis revealed strong intramolecular attraction between the phosphoryl group and the oxygen-containing substituent X; the effects were enhanced by the metal ions, indicating some chelating properties of substrates **1** (X = OH, OMe). Weaker effects were found for the analogous carboxylic ester systems (CO_2Et instead of PO_3Me_2 group), suggesting weaker donor properties of the carbonyl group than the phosphoryl group of the phosphonate function.

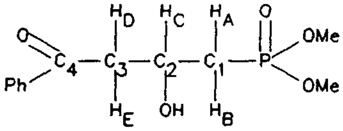
In this work we extended our studies on to two other phosphonic systems: dimethyl β-substituted γ-arylpropylphosphonates (**2**) and dimethyl 2-hydroxy-3-benzoylpropylphosphonate (**3**). Both systems contain *two* pairs of diastereotopic protons (α- and γ-methylene groups), so the conformational analysis could be carried out with respect to the rotation about the C_1—C_2 (more polar section of the molecule) and to the C_2—C_3 (less polar section) bonds. In addition, substrate **3** contains the carbonyl and the phosphoryl groups in the same molecule, identically located with respect to the chiral centre —CHX—, so their relative interactions with substituent X, with solvent and with metal ions could be directly studied.

RESULTS AND DISCUSSION

Substrates

The five phosphonic esters **2a–d** and **3** were synthesized and used for the NMR spectroscopic studies.





2a, AR = Ph; X = OH
b, Ar = Ph; X = OMe
c, Ar = Ph; X = Cl
d, Ar = 3,4-$(MeO)_2C_6H_3$; X = OH

3

---

* Author for correspondence.

0894–3230/93/090523–08$09.00

Received 24 February 1993
Revised 4 May 1993

Racemic alcohols **2a** and **2d** were prepared via β-ketophosphonates as shown in Scheme 1.

$$(MeO)_2P(O){-}CH_3 \xrightarrow{(i),(ii)}$$

$$\begin{tikzcd} (MeO)_2P(O)CH_2Cu \arrow[r, "(iii)"] & (MeO)_2P(O)CH_2C(O)R \arrow[d, "(iv)"] \\ & (MeO)_2P(O)CH_2CH(OH)R \end{tikzcd}$$

(i) BuLi–THF; −60 °C; (ii) CuI; −30 °C;
(iii) RC(O)Cl; (iv) $NaBH_4$–EtOH; 0 °C

Scheme 1

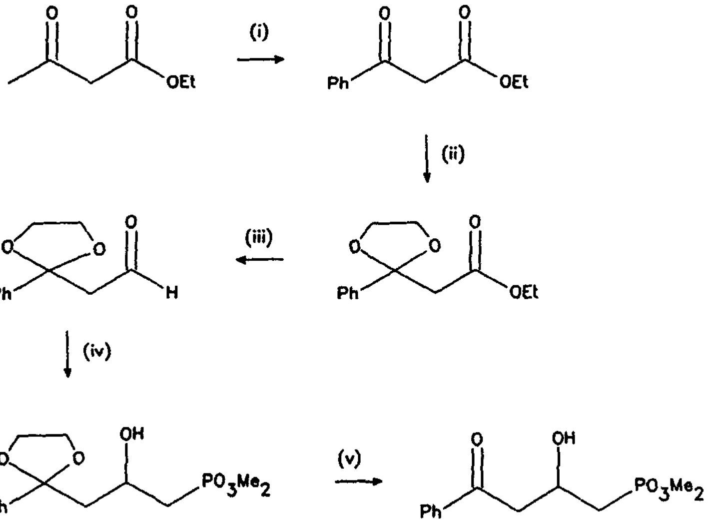
Methyl ether **2b** was prepared by treating **2a** with a large excess of NaH followed by a large excess of MeI in THF–1,2-dimethoxyethane.[3] The chloro derivative **2c** was prepared by treating **2a** with CCl_4–PPh_3, according to Gajda.[4] The synthesis of the ketohydroxyphosphonate **3** is presented in Scheme 2.

NMR spectra

In substrates **2** and **3**, the protons H_A, H_B, H_D, H_E and H_C, together with the phosphorus atom, gave rise to ABMPRX spin systems in the ^1H NMR spectra, with protons H_A/H_B corresponding to the AB and protons H_D/H_E to the PR part of the system. The ^1H chemical shifts, and the geminal and vicinal proton-proton coupling constants were obtained from a complete ABM (PRM) sub-spectral analysis of the ^1H NMR spectra.[5] Protons H_A and H_B consistently gave rise to 16 line patterns, except in a few cases where deceptively simple spin systems were observed. For the PRMX system, in almost all cases 12 lines were observed because a four-bond (^1H, ^{31}P) coupling to only one of the $C_\gamma H_2$ protons is observed.

Conformational analysis

The conformational behaviour of phosphonates **2** and **3** was considered in terms of the rotation about the C_1—C_2 and C_2—C_3 bonds. Three stable staggered conformations (X_1, X_2, X_3, or their enantiomeric forms) exist with respect to the former bond (Figure 1), and three analogous conformations (X'_1, X'_2, X'_3) with respect to the rotation about the latter (Figure 2). Using the experimentally measured vicinal coupling constants ($J_{AC}, J_{BC}, J_{DC}, J_{EC}$) and applying the same methodology as before,[1] we determined the populations of the individual conformers in different solvents and in the presence of metal ions. The values of the calculated populations, given in Tables 1 and 2, are significant to only *ca* 5%. The level of the uncertainty is determined by the following factors. First, when calculating the $^3J_{HH}$ values according to Haasnoot *et al.*,[2] dihedral angles of only 60° and 180° were assumed. Second, the



(i) PhC(O)Cl–aq. NaOH; (ii) $HOCH_2CH_2OH$, TsOH–benzene, reflux;
(iii) DIBAL–CH_2Cl_2, −50 °C; (iv) $CH_3PO_3Me_2$ BuLi/THF, −50 °C;
(v) Pyridinium *p*-tosylate/acetone

Scheme 2

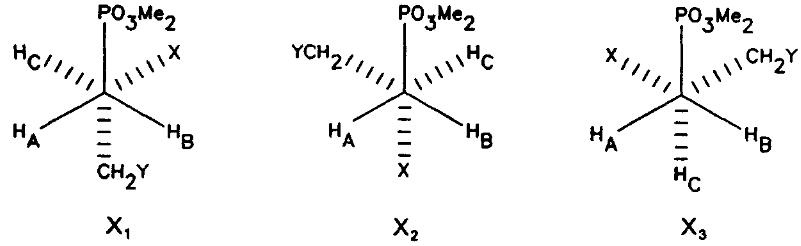


Figure 1. Staggered conformations with respect to the rotation about the C_1—C_2 bond. **2a**, Y = Ph, X = OH; **2b**, Y = Ph, X = OMe; **2c**, Y = Ph, X = Cl; **2d**, Y = 3,4-$(MeO)_2C_6H_3$, Y = OH; **3**, Y = PhC(O), X = OH

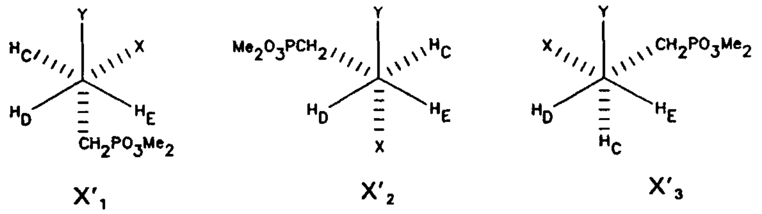


Figure 2. Staggered conformations with respect to the rotation about the C_2—C_3 bond. **2a**, Y = Ph, X = OH; **2b**, Y = Ph, X = OMe; **2c**, Y = Ph, X = Cl; **2d**, Y = 3,4-$(MeO)_2C_6H_3$, X = OH; **3**. Y = PhC(O), X = OH

Table 1. Solvent effects on the conformational behaviour of phosphonates 2 and 3

			Population of rotamers[b]					Population of rotamers[b]		
Substrate (solvent[a])	$^3J_{AC}$ (Hz)	$^3J_{BC}$ (Hz)	X_1	X_2	X_3	$^3J_{DC}$ (Hz)	$^3J_{EC}$ (Hz)	X'_1	X'_2	X'_3
2a (A)	6·5[c]		41	37	22	5·6	6·6	40	31	29
2a (B)	4·4	7·7	54	19	27	6·0	6·6	39	35	26
2a (C)	4·8	7·8	54	24	22	6·0	6·9	42	36	22
2a (D)	3·9	8·4	62	14	24	6·5[c]		36	41	23
2a (E)	3·3	6·3	38	36	26	4·5	6·5	42	18	40
2b (A)	6·0	6·6	43	33	24	5·7	6·2	37	31	32
2b (B)	5·6	6·9	44	32	24	6·2[c]		35	37	28
2b (C)	4·8	7·8	54	25	21	5·9	6·2	35	34	31
2b (D)	6·0[c]		41	28	31	6·0[c]		34	34	32
2b (E)	5·3	7·1	46	29	25	5·9[c]		33	33	34
2c (A)	6·9[c]		40	44	16	4·7	7·7	52	19	29
2c (B)	6·7[c]		39	41	20	5·2	7·8	52	25	23
2c (C)	7·4[c]		45	50	5	5·7	7·3	46	30	24
2c (D)	5·8	6·8	42	31	27	5·0	8·4	58	23	19
2c (E)	5·5	8·1	54	30	16	4·7	8·6	61	20	19
2d (A)	4·3	8·3	60	19	21	6·1	6·3	36	36	28
2d (B)	6·3[c]		36	38	26	6·1	6·4	37	36	27
2d (C)	3·7	8·6	64	13	23	5·9	6·8	41	35	24
2d (D)	4·2	8·3	60	18	22	6·1[c]		34	36	30
2d (E)	6·3[c]		36	38	26	5·6	7·3	47	32	21
3 (A)	4·2	7·3	50	16	34	5·9[c]		33	33	34
3 (B)	4·6	7·8	53	22	25	5·7	6·7	41	30	29
3 (C)	5·6	7·4	48	32	20	5·2[c]		29	23	48
3 (D)	5·3	7·5	49	29	22	6·1[c]		31	36	33
3 (F)	5·0	7·7	52	26	22	6·2[c]		35	37	28

[a] A = CCl_4; B = C_6D_6; C = $CDCl_3$; D = $(CD_3)_2CO$; E = $(CD_3)_2SO$; F = CD_3CN.
[b] ±5%.
[c] Average value for vicinal coupling constants.

Table 2. Effects of metal ions on the conformational behaviour of phosphonates **2** and **3** in acetone-d_6

			Population of rotamers[b]					Population of rotamers[b]		
Substrate (medium[a])	$^3J_{AC}$ (Hz)	$^3J_{BC}$ (Hz)	X_1	X_2	X_3	$^3J_{DC}$ (Hz)	$^3J_{EC}$ (Hz)	X_1'	X_2'	X_3'
2a (A)	3·9	8·4	62	12	24	6·5[c]		36	41	23
2a $(Na)_1$	3·6	9·6	74	14	12	5·9	6·4	37	34	29
2a $(Na)_2$	3·1	9·7	76	8	16	6·0	6·6	39	35	26
2a $(Na)_3$	3·1	9·8	77	8	15	5·9	6·3	42	35	23
2a (Mg)	3·1	8·4	64	5	31	6·4	6·9	40	41	19
2b (A)	6·0[c]		34	35	31	6·0[c]		34	34	32
2b $(Na)_1$	5·4	7·3	48	21	31	6·0[c]		36	33	31
2b $(Na)_2$	5·1	7·4	49	23	28	5·8	5·9	35	32	33
2b $(Na)_3$	5·0	7·8	46	19	27	6·2	4·5	34	33	33
2b (Mg)	5·1	7·8	64	5	31	6·1	4·5	32	37	31
2c (A)	5·8	6·8	42	31	27	5·0	8·4	58	23	19
2c $(Na)_1$	5·5	8·3	45	29	26	4·7	8·6	65	20	15
2c $(Na)_2$	5·1	8·4	48	25	27	4·8	8·7	62	19	19
2c $(Na)_3$	4·9	8·6	42	32	26	4·5	8·7	62	18	20
2c (Mg)	4·6	8·6	47	26	27	4·5	8·8	62	14	24
2d (A)	4·2	8·3	60	18	22	6·1[c]		34	36	30
2d $(Na)_1$	3·8	8·1	60	12	28	6·1	6·3	36	36	28
2d $(Na)_2$	3·5	9·2	70	12	18	6·2	6·4	37	37	26
2d $(Na)_3$	3·3	9·5	74	10	16	6·1	6·4	37	36	27
2d (Mg)	6·4[c]		68	8	24	6·5	6·7	39	41	20
3 (A)	5·3	7·5	49	29	22	6·1[c]		34	36	30
3 $(Na)_1$	3·5	7·9	56	17	27	5·4	6·8	28	29	43
3 $(Na)_2$	4·5	8·2	58	21	21	5·6	7·1	23	31	46
3 $(Na)_3$	4·4	8·4	60	21	19			29	36	30
3 (Mg)	4·4	8·5	64	25	11	5.6[c]		31	29	40

[a] A = acetone-d_6; $(Na)_1$, $(Na)_2$, $(Na)_3$ = acetone-d_6 + NaI, where [NaI]/[substrate] = 1,2,3, respectively; (Mg) = acetone-d_6 + $Mg(ClO_4)_2$, where [$Mg(ClO_4)_2$]/[substrate] = 2.

[b] ±5%.

[c] Average value for vicinal coupling constants.

experimentally determined $^3J_{HH}$ values are accurate only to ±0·1 Hz. Finally, the exact values chosen for the group electronegativities will greatly influence the calculated $^3J_{HH}$ values.

Solvent effects

NMR spectra of substrates **2** were recorded in five solvents of increasing polarity [CCl_4, C_6D_6, $CDCl_3$, $(CD_3)_2CO$ and $(CD_3)_2SO$], whereas for **3** CD_3CN was used as the most polar solvent instead of DMSO-d_6. The effect of solvent's polarity on the 'polar' and 'nonpolar' sections of the substrate molecule was monitored by examining the NMR spectroscopic characteristics of the two diastereotopic methylene groups. As expected, the group located between the chiral centre and the dimethoxyphosphonyl function (α-CH_AH_B) was more sensitive to solvent effects than the group located at the 'periphery' of the molecule (γ-CH_DH_E). For example, the average solvent-induced change in the chemical shift ($\Delta\delta = \delta_{DMSO} - \delta_{CCl_4}$) for the α-methylene protons in **2a**, **2b** and **2d** is 0·11 ppm, and for **3** 0·06 ppm, whereas the analogous effects on the γ-methylene protons are 0·04 and 0·02 ppm, respectively. The average solvent-induced variations in the vicinal coupling constants J_{AC} and J_{BC} are 1·8 Hz for **2** and 0·9 Hz for **3**; the corresponding effects on the values of J_{DC} and J_{EC} constants are 0·8 and 0·5 Hz, respectively. These results indicate that the changes in the medium affect the conformational equilibria with respect to the rotation about the C_1—C_2 bond to a significantly greater extent than with respect to the C_2—C_3 section. This, in turn, confirms our earlier observation[1] about the intramolecular interactions between the phosphonyl group PO_3Me_2, and the oxygen-containing substituent X (X = OH, OMe). The β-chloro-substituted phosphonate **2c** does not show this selectivity, and hence does not give any evidence for the intramolecular interactions between the PO_3Me_2 and Cl groups.

Solvent effects on substrates **2** and **3** are summarized in Table 1, in which the populations of the individual rotamers in the different solvents (calculated from the observed vicinal coupling constants) are given. Substrates **2a**, **2b** and **2c** can be compared directly with

1, since they represent the derivatives of the latter, in which an additional methylene group has been inserted into the C_β—Ph bond. For the alcohols and methyl ethers (X = OH, OMe), that structural change resulted in a considerable decrease in the selectivity with respect to the rotamers X. For **2a** and **2b**, although the rotamer X_1 is still the most populated, its contribution decreased to an average value of 47%, compared with 71% observed for the corresponding **1**.[1] The preference for the rotamer X_1 was explained by two factors: the attractive interactions between the PO_3Me_2 and the OH (OMe) groups, and by the repulsive (steric) PO_3Me_2–Ph interactions. The greater contributions of rotamers X_2 and X_3 in **2a** and **2b** result from some release of steric repulsions following replacement of phenol by the benzyl substituent. It is known[6] that the steric requirements of the phenyl group are greater than those of benzyl: v_x values for Ph and CH_2Ph are 1·66 and 0·70, respectively. Still, as for **1**, the sum of the populations of rotamers X_1 and X_3 for **2a** and **2b** (*gauche* orientation of the phosphoryl group and the β-oxygen) is more than 70%, pointing at the attractive oxygen–phosphoryl group interactions in the O=P—C—C—OR (R = H, Me) system. The distribution of rotamers for alcohol **2d** was almost identical with that obtained for **2a**, hence substitution of the ring with methoxy group did not alter any intramolecular interactions affecting the rotation about the two C—C bonds. It is interesting that on moving from non-hydrogen-bonding to hydrogen-bonding solvents, the population of rotamer X_1 did not decrease noticeably. This result may suggest that even in a medium capable of breaking the intramolecular P=O···H—O hydrogen bond, the preference for the *gauche* orientation of the PO_3Me_2 and the OH groups is retained due to the previously postulated[1] n(p) → d donor–acceptor interactions involving the β-OR (R = H, Me) group and the phosphoryl centre (Figure 3).

The β-chloro derivative **2c** shows lower selectivity in the rotamers' distribution than the analogous **1**; no evidence for any specific interactions between the phosphoryl group and chlorine atom was obtained, and the populations are in this case probably determined solely by the sum of the non-bonded steric repulsions.

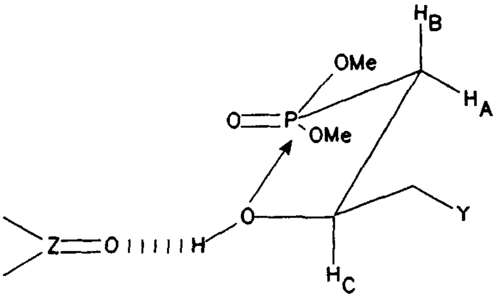


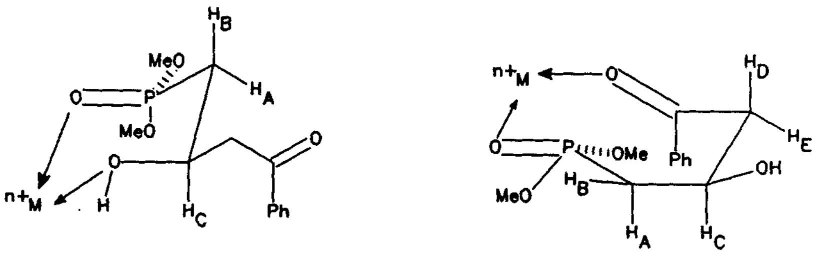
Figure 3. Oxygen–phosphoryl interactions in conformation X_1 for β-hydroxyalkylphosphonates in hydrogen bonding solvents (Z=C or S)

The population of rotamers X′ (rotation about C_2—C_3 bond) corresponds for substrates **2** to a statistical (**2b**) or almost statistical distribution. That result confirmed our expectations that the rotation of the non-polar section of the molecule should not be subject to any specific intramolecular interactions.

The most informative results were obtained from the conformational analysis of ketohydroxyphosphonate **3**. Rotation about the C_1—C_2 bond yields the distribution of rotamers almost identical with that obtained for other alcohols (**2a**, **2d**). The keto group seems to have no effect on conformational equilibria, hence there is in that system a complete regioselectivity in the intramolecular interactions between the β-OH group and the potential acceptor phosphoryl or carbonyl functions, in favour of the former. In full agreement with that conclusion, the population of rotamers X′ (rotation about C_2—C_3 bond) for **3** follows a statistical distribution, without any evidence for an intramolecular carbonyl–hydroxyl interaction, expected to increase the population of rotamers X'_1 and X'_3.

Metal ion effects

The possibility of an enhancement in the conformational selectivity in phosphonates **2** and **3** via their complexation with metal ions was investigated by recording the ^1H NMR spectra of the substrates in acetone solutions containing Na^+ or Mg^{2+} ions, and comparing them with the results obtained in pure acetone. Conformational analysis, carried out as in previous cases, yielded the distribution of the rotamers (with respect to the rotation about the same two C—C bonds) shown in Table 2. As before,[1] addition of metal ions to the solution of all substrates with an oxygen-containing substituent X resulted in the increase of the selectivity in the rotation about the C_1—C_2 bond in favour of rotamer X_1. This can be taken as an indication of a chelating effect of the O=P—C—C—OR (R = H, Me) fragment of substrates **2** and **3** (and also of **1**[1]), additionally stabilizing the *gauche* orientation of phosphorus and β-oxygen. (As one referee pointed out, chelation can involve one of the POMe groups instead of the phosphoryl group. Our current investigation of the metal ion effects on the ^{17}O NMR spectra of substrates **1**–**3** indicates the involvement of the P=O group in the interaction with metal ions.) The results obtained for the γ-benzoyl derivative **3** deserve separate comment. First, the population of the rotamer X'_1 does not increase on addition of metal ions, so no chelating properties of the O=C—C—C—OR fragment (relative to the analogous ROCCPO moiety) capable of introducing corresponding selectivity to the free rotation



(a) (b)

Figure 4. Proposed models for chelation of metal ions by **3**; (a) rotamer X_1; (b) rotamer X_2'

about the C_2—C_3 bond are indicated. Second, compared with the closely related **2a**, addition of the metal ions to solutions of **3** results in some increase in the combined population of rotamers X_2' and X_3' (from 66% to an average of 72% vs a decrease from 64% to an average of 61% for **2a**). This increase can be attributed to the chelation of a metal ion by the phosphoryl *and* the carbonyl groups in an eight-membered system. A similar complex (in that case seven-membered) was proposed by Sigel and co-workers[7] in their discussion of the coordinating properties of dihydroxyacetone phosphate, with the chelation increasing on the addition of dioxane to aqueous solutions of the reactants. The involvement of the carbonyl and phosphoryl groups in substrate–metal ion interactions should favour the *gauche* orientation of benzoyl and phosphonomethyl fragments; in consequence, the respective rotamers X_2' and X_3' represent the most populated conformations. In conclusion, we propose that the interactions between **3** and the metal ions can be represented by two major structures shown in Figure 4.

In summary, we have demonstrated that polysubstituted alkylphosphonates represent convenient systems for conformational studies and for investigation of the response of the individual functionalities to environmental (solvent, metal ions, etc.) changes. We are currently attempting to support the conclusions of the first two papers of this series by ^{17}O NMR spectroscopic and molecular modelling studies.

EXPERIMENTAL

General. NMR spectra were recorded on a Bruker AC 300 NMR spectrometer at a probe temperature 30 °C. Preparation of the solutions containing the salts were carried out in dry atmosphere in a glove-box. The following solvents were used for NMR spectra analysis: tetrachloromethane (BDH, AnalaR) containing 10% (v/v) cyclohexane-d_{12} (Aldrich, 99.5 atom% D), dried over molecular sieves; benzene-d_6 (Uvasol, Merck); chloroform-d_1 (Uvasol, Merck), dried over molecular sieves; acetone-d_6 (Aldrich, 99·5 atom% D), dried over molecular sieves; dimethyl-d_6 sulphoxide (Uvasol, Merck); and acetonitrile-d_3 (Aldrich, 99·5 atom% D). The concentration of substrates was 0·20 M.

Dimethyl 2-oxo-3-phenylpropylphosphonate. To a stirred mixture of BuLi (1·6 M in hexane, 35·5 ml, 57 mmol) and THF (50 ml) was added dropwise at -60 °C a solution of dimethyl methylphosphonate (7·07 g, 57 mmol) in THF (20 ml), followed after 30 min by the addition of copper(I) iodide (11·9 g, 63 mmol). The solution was warmed to -30 °C, kept for 1 h, cooled to -40 °C and a solution of of phenylacetyl chloride (9·25 g, 60 mmol) in THF (30 ml) was added dropwise. The mixture was stirred at -35 °C for 3 h, left overnight at room temperature, hydrolysed with water (50 ml) and filtered twice through a layer of Celite. After drying ($MgSO_4$) and evaporation of the solvent the product was obtained as a yellow oil; 11·7 g (85%). IR, ν_{max} (CCl_4) (cm^{-1}) 2940 (CH_2), 1717 (C=O), 1252 (P=O), 1038 ($POCH_3$); ^{1}H NMR ($CDCl_3$), δ3.10 (d, 2H, $J = 22·6$ Hz), 3·78 (d, 6H, $J = 11·3$ Hz), 3·89 (s, 2H), 7·20–7·37 (m, 5H); ^{31}P NMR, δ23·0.

Dimethyl 2-hydroxy-3-phenylpropylphosphonate (2a). $NaBH_4$ (5·14 g, 136 mmol) was added to a stirred solution of the ketophosphonate (11·35 g, 47 mmol) in ethanol (40 ml) at 0 °C and the solution was stirred at room temperature for 2 h. Dilute HCl was added, the mixture was extracted with chloroform (3 x 25 ml) and the combined chloroform solution was washed with water (3 x 30 ml), dried ($MgSO_4$) and evaporated. Compound **2a** was obtained as a pale-yellow oil, 11·0 g (96%). IR, ν_{max} (CCl_4)(cm^{-1}) 3370 (OH), 2939 (CH_2), 1249 (P=O), 1039 ($POCH_3$); ^{1}H NMR ($CDCl_3$), δ1·92 (ddd, 1H, $J = 18·9$, 15·2, 4·8 Hz), 1·97 (ddd, 1H, $J = 16·5$, 15·2, 7·8 Hz), 2·80 (dd, 1H, $J = 13·5$, 6·9 Hz), 2·90 (ddd, 1H, $J = 13·5$, 6·0 2·1 Hz), 3·43 (br s, 1H), 3·72 (d, 3H, $J = 11·0$ Hz), 3·73 (d, 3H, $J = 10·9$ Hz), 4·24 (m, 1H), 7·16–7·35 (m, 5H); ^{13}C NMR, δ31·7 (d, $J = 140·8$ Hz), 44·5 (d, $J = 16·6$ Hz), 52·3 (d, $J = 7·8$ Hz), 52·5 (d, $J = 8·1$ Hz), 67·5 (d, $J = 4·6$ Hz), 126·6 (s), 128·5 (s), 129·4 (s), 137·5 (s); ^{31}P NMR, δ32·0; MS, m/z 244 (M^+, 1%), 226 (29), 153 (100), 121 (22), 109 (40), 91 (80), 65 (24).

Dimethyl 2-methoxy-3-phenylpropylphosphonate (2b). To a solution of **2a** (1·54 g, 6·3 mmol) and iodomethane (3·15 ml, 50 mmol) in THF (10 ml) and DMF (2 ml), NaH (0·32 g, 13·7 mmol) was added and the mixture was heated under reflux for 1 h. Ethyl acetate (50 ml) was added, the excess of NaH was decomposed by the addition of water (50 ml), followed by saturated aqueous NH_4Cl (20 ml). The organic phase was separated, the aqueous phase was extracted with ethyl acetate (40 ml) and the organic solution was washed with water (3 × 15 ml), with saturated aqueous NaCl (3 × 15 ml), dried and evaporated under reduced pressure. Compound **2b** was obtained as a pale-yellow oil, 1·0 g (61%). IR, ν_{max} (CCl_4)(cm^{-1}) 2940 (CH_2) 2820 (OCH_3), 1252 (P=O), 1040 ($POCH_3$); ^{1}H NMR ($CDCl_3$), δ1·92 (ddd, 1H, $J = 18·2$, 15·7, 4·8 Hz), 1·98 (ddd, 1H, $J = 18·0$, 15·7, 7·8 Hz), 2·86 (dd, 1H, $J = 13·8$, 6·2 Hz), 2·93 (ddd, 1H, $J = 13·8$, 5·9, 2·1 Hz), 3·36 (s, 3H), 3·70 (d, 3H, $J = 11·1$ Hz), 3·72 (d, 3H, $J = 10·8$ Hz), 3·80 (m, 1H), 7·20–7·29 (m, 5H); ^{13}C NMR, δ30·1 (d, $J = 140·2$ Hz), 40·8 (d, $J = 12·1$ Hz), 52·0 (d, $J = 6·6$ Hz), 52·5 (d, $J = 6·0$ Hz), 57·2 (s), 77·3 (s), 126·5 (s), 128·4 (s), 129·6 (s), 173·7 (s); ^{31}P NMR, δ32·5; MS, m/z 258 (M^+, < 1%), 226 (100), 167 (87), 153 (8), 135 (14), 109 (18), 65 (24).

Dimethyl 2-chloro-3-phenylpropylphosphonate (2c). A solution of **2a** (2·50 g, 10·2 mmol) and triphenylphosphine (4·03 g, 15·4 mmol) in dry tetrachloromethane (60 ml) was heated under reflux for 20 h. The solvent was evaporated under reduced pressure, the semi-solid residue was extracted with hexane (5 × 40 ml) and the combined extracts were filtered and evaporated. The residue was purified by column chromatography (silica gel, benzene–ethyl acetate, 1 : 1) yielding **2c** as a pale-yellow oil, 1·20 g (45%). IR, ν_{max} (CCl_4)(cm^{-1}) 2940 (CH_2), 1252 (P=O), 1040 ($POCH_3$), 748 (C—Cl); ^{1}H NMR ($CDCl_3$), δ2·13 (dd, 2H, $J = 18·3$, 7·4 Hz), 3·08 (dd, 1H, $J = 13·9$, 7·3 Hz), 3·22 (dd, 1H, $J = 13·9$, 5·7 Hz), 3·75 (d, 3H, $J = 11·0$ Hz), 3·77 (d, 3H, $J = 11·0$ Hz), 4·44 (m, 1H), 7·22–7·35 (m, 5H); ^{13}C NMR, δ33·9 (d, $J = 141·4$ Hz), 45·3 (d, $J = 10·3$ Hz), 52·3 (d, $J = 6·3$ Hz), 52·7 (d, $J = 5·8$ Hz), 56·1 (s), 127·1 (s), 128·5 (s), 129·5 (s), 136·8 (s); ^{31}P NMR, δ29·2; MS, m/z 262 (M^+, < 1%), 226 (76), 117 (100), 109 (24), 91 (45), 79 (22), 65 (16).

Dimethyl 2-oxo-3-(3′,4′-dimethoxyphenyl)propylphosphonate. Prepared from dimethyl methylphosphonate and 3,4-dimethoxyphenylacetyl chloride as described for the phenyl derivative and obtained as a pale-yellow oil (90%). IR, ν_{max} (CCl_4)(cm^{-1}) 2948 (CH_2), 1717 (C=O), 1255 (P=O), 1038 ($POCH_3$); ^{1}H NMR ($CDCl_3$), δ3·05 (d, 2H, $J = 22·6$ Hz), 3·73 (d, 6H, $J = 11·3$ Hz), 3·77 (s, 2H), 3·81 (s, 6H), (6·76–6·80 (m, 3H); ^{31}P NMR, δ 23.0.

Dimethyl 2-hydroxy-3-(3′,4′-dimenthoxyphenyl) propylphosphonate (2d). $NaBH_4$ (0·90 g, 23·8 mmol) was added slowly at 0 °C to a stirred solution of the ketophosphonate (2·50 g, 8·3 mmol) in ethanol (20 ml) and the solution was stirred at room temperature for 2 h. Dilute HCl was added, the mixture was extracted with $CHCl_3$ (3 × 15 ml) and the organic extract was washed with water (3 × 15 ml), dried and evaporated under reduced pressure. Compound **4d** was obtained as a pale-yellow oil, 2·40 g (95%) IR, ν_{max} (CCl_4)(cm^{-1}) 3375 (OH), 2942 (CH_2), 1247 (P=O), 1039 ($POCH_3$); ^{1}H NMR ($CDCl_3$) δ1·91 (ddd, 1H, $J = 18·7$, 15·3, 3·7 Hz), 1·99 (ddd, 1H, 16·4, 15·3, 8·6 Hz), 2·75 (dd, 1H, $J = 13·7$, 6·8 Hz), 2·84 (ddd, 1H, $J = 13·7$, 5·9 Hz), 3·73 (d, 3H, $J = 10·9$ Hz), 3·74 (d, 3H, $J = 10·9$ Hz), 3·85 (s, 3H), 3·87 (s, 3H), 6·73–6·80 (m, 3H); ^{13}C NMR, δ31·8 (d, $J = 139·1$ Hz), 44·1 (d, $J = 16·3$ Hz), 52·4 (d, $J = 6·1$ Hz), 52·7 (d, $J = 6·8$ Hz), 55·9 (s), 67·6 (d, $J = 4·6$ Hz), 111·4 (s), 112·7 (s), 121·5 (s), 130·1 (s), 147.9 (s), 149·0 (s); ^{31}P NMR, δ33·3; MS, m/z 304 (M^+, < 1%), 286 (35), 182 (60), 153 (27), 151 (100), 137 (26), 109 (36), 107 (48), 65 (26).

Ethylene ketal of ethyl 3-oxo-3-phenylpropionate. A mixture containing ethyl 3-oxo-3-phenylpropionate (10·9 g, 56·6 mmol), ethylene glycol (4·22 g 67·9 mmol), *p*-toluenesulphonic acid monohydrate (0·15 g) and benzene (250 ml) was heated under reflux for 52 h with continuous azeotropic removal of water. The cooled mixture was poured into a mixture of diethyl ether (250 ml) and aqueous sodium hydrogencarbonate (100 ml), separated and the organic layer was washed with brine and dried (K_2CO_3). Evaporation of the solvent yielded a mobile yellow oil which was purified by distillation to yield the ketal as a colourless oil, 8·20 g (81%), b.p. 103–105 °C/0·15 Torr. IR, ν_{max} (CCl_4)(cm^{-1}) 2977 (CH_2,CH_3), 2875 (OCH_2CH_2O), 1741 (C=O), 1552 (Ph), 1221 (C—O); ^{1}H NMR ($CDCl_3$), δ1·80 (t, 3H, $J = 7·1$ Hz), 2·89 (s, 2H), 3·65–4·04 (m, 6H), 7·21–7·48 (m, 5H); MS, m/z 159 (19), 149 (100), 105 (86), 87 (10), 77 (59), 51 (31), 29 (16).

Ethylene ketal of 3-oxo-3-phenylpropanal. The above ester (8·96 g, 38 mmol) was dissolved in dry dichloromethane (50 ml) and diisobutylaluminium hydride (DIBAL, 83·6 ml, 1·0 M in hexane, 83·6 mmol) was added with stirring at −78 °C over a period of 1 h. After 90 min the mixture was quenched with methanol (5 ml), warmed to room temperature and diluted with ethyl acetate (200 ml). The solution was washed with saturated aqueous sodium potassium tartrate (200 ml), the aqueous phase was extracted with ethyl acetate (3 × 50 ml) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by bulb-to-bulb distillation (oven temperature 100–120 °C/0·25 Torr), 5·97 g (82%). IR, ν_{max} (CCl_4)(cm^{-1}) 2920 (CH_2), 2830 (OCH_2CH_2), 1880 (C=O), 1563 (Ph), 1231 (H—CO); ^{1}H NMR ($CDCl_3$), δ2·90 (d, 2H, J = 2·9 Hz), 3·79–4·12 (m, 4H), 7·32–7·50 (m, 5H), 9·76 (t, 1H, J = 2·9 Hz); MS, m/z 149 (90), 115 (27), 105 (90) 77 (100), 51 (75).

Ethylene ketal of dimethyl 2-hydroxy-3-oxo-4-phenylbutylphosphonate. BuLi (18·8 ml, 1·6 *M* solution in hexane, 30·1 mmol) was added dropwise with stirring at −50 °C to a solution dimethyl methylphosphonate (3·11 g, 25·1 mmol) in dry THF (50 ml). After stirring for 1 h at −50 °C the aldehyde described above (3·21 g, 16·7 mmol) dissolved in THF (50 ml) was added dropwise over a period of 2 h. After a further 5 h at −50 °C, the mixture was left overnight at room temperature, hydrolysed with a minimum volume of concentrated aqueous NH_4Cl and chloroform (50 ml)was added. The mixture was filtered through a layer of Celite and the chloroform layer was washed with water (3 × 25 ml), dried and evaporated under reduced pressure. The product was obtained as a pale-yellow oil, 4·25 g (81%). IR, ν_{max} (CCl_4)(cm^{-1}) 3474 (OH), 2953 (CH_2), 2893 (OCH_2CH_2O), 1551 (Ph), 1234 (P=O), 1045 ($POCH_3$); ^{1}H NMR ($CDCl_3$), δ1·95 (ddd, 1H, J = 18·2, 15·4, 5·5 Hz), 1·99 (ddd, 1H, J = 17·9, 15·4, 7·6 Hz), 2·13 (ddd, 1H, J = 18·6, 14·9, 8·5 Hz), 2·18 (ddd, 1H, J = 18·0, 14·9, 3·1 Hz), 3·69 (d, 3H, J = 10·8 Hz), 3·71 (d, 3H, J = 10·8 Hz), 3·68–4·06 (m, 5H), 4·28–4·31 (m, 1H), 7·28–7·43 (m, 5H); ^{13}C NMR, δ33·0 (d, J = 139·5 Hz), 47·2 (d, J = 13·4 Hz), 52·2 (d, J = 6·1 Hz), 52·5 (d, J = 6·0 Hz), 63·3 (d, J = 2·8 Hz), 64·1 (s), 64·5 (s), 125·5 (s), 128·4 (s), 141·6 (s); ^{31}P NMR, δ32·4; MS, m/z 153 (15), 149 (100), 109 (16), 105 (99), 77 (46), 51 (10), 43 (13).

Dimethyl 2-hydroxy-3-benzoylpropylphosphonate (3). A solution of the ketal described above (0·52 g, 1·6 mmol) and pyridinium *p*-toluenesulphonate (0·79 g, 3·1 mmol) in acetone (50 ml) was heated under reflux for 80 h and the solvent was evaporated under reduced pressure. Aqueous $NaHCO_3$ was added and the mixture was extracted with ethyl acetate (2 × 15 ml). The combined organic extracts were washed with saturated aqueous NaCl, dried and evaporated under reduced pressure. Compound **3** was obtained as a pale-yellow oil, 0·33 g (73%). IR, ν_{max}(CCl_4)(cm^{-1}) 3386 (OH), 2954 (CH_2), 1726 (C=O), 1597 (Ph), 1236 (P=O), 1045 ($POCH_3$); ^{1}H NMR ($CDCl_3$), δ2·10 (ddd, 1H, J = 17·9, 15·3, 7·4 Hz), 2·20 (ddd, 1H, J = 18·3, 15·3, 5·6 Hz), 3·33 (d, 2H, J = 5·2 Hz), 3·76 (d, 3H, J = 11·0 Hz), 3·79 (d, 3H, J = 10·9 Hz), 4·62 (dddd, 1H, J = 12·3, 7·4, 5·6, 5·2 Hz), 7·14–7·31 (m, 5H); ^{13}C NMR, δ32·0 (d, J = 138·9 Hz), 45·4 (d, J = 11·6 Hz), 52·5 (d, J = 6·3 Hz), 52·6 (d, J = 6·2 Hz), 63·5 (s), 128·1 (s), 128·7 (s), 140·2 (s), 198·8 (s); ^{31}P NMR, δ32·0; MS, m/z 167 (20), 153 (62), 149 (67), 124 (44), 109 (30), 105 (74), 77 (100), 51 (36).

ACKNOWLEDGEMENTS

Financial assistance from the University of Pretoria and the Foundation for Research Development is gratefully acknowledged.

REFERENCES

1. M. P. Belciug, A. M. Modro, T. A. Modro and P. L. Wessels, *J. Phys. Org. Chem.* 5, 787 (1992).
2. C. A. Haasnoot, F. A. A. M. de Leeuw and C. Altona, *Tetrahedron* 36, 2783 (1980).
3. B. A. Stoochnoff and N. L. Benoiton, *Tetrahedron Lett.* 21 (1973).
4. T. Gajda, *Synthesis*, 717 (1990).
5. R. K. Harris, *Nuclear Magnetic Resonance Spectroscopy*. Longman Scientific, Burnt Mill (1986).
6. (a) M. Charton, *J. Am. Chem. Soc.* 97, 3691 (1975); (b) N. S. Isaacs, *Physical Organic Chemistry*, p. 298. Longman, New York (1987).
7. (a) S. S. Massoud and H. Sigel, *Inorg. Chem.* **27**, 1447 (1988); (b) H. Sigel, *Am. Chem. Soc. Symp. Ser.* No. **402**, 159 (1989); (c) G. Liang, D. Chen, M. Bastian and H. Sigel, *J. Am. Chem. Soc.* **114**, 7780 (1992).