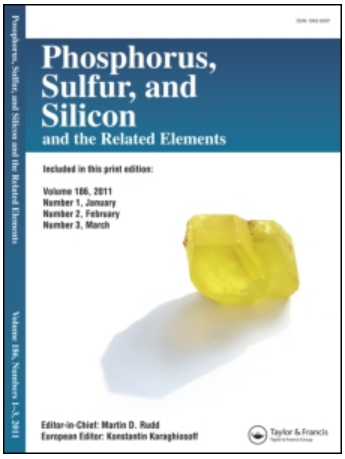

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The Preparation of Dimethyl α-Hydroxyphosphonates and the Chemical Shift Non-Equivalence of Their Diastereotopic Methyl Ester Groups

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Dimethyl α-hydroxyalkyl-, α-hydroxybenzyl-, α-hydroxyfurfuryl-, and α-hydroxy-α-thienylmethyl-phosphonates have been prepared in good yield by the alumina-catalyzed reaction of dimethyl phosphite with the corresponding alkanals, aryl aldehydes (or aryl methyl ketones), furfuraldehyde, and 2- or 3-thiophenecarboxaldehyde, respectively, thus confirming the general utility of this synthetic procedure. The ^{1}H and ^{13}C nmr spectra of the products exhibit characteristic chemical shift non-equivalence of the diastereotopic methyl ester groups, for which a tentative order of non-equivalence is reported and discussed.

Keywords α-Hydroxyphosphonate; benzyl; diastereotopic; furfuryl; NMR; thienyl

INTRODUCTION

α-Hydroxyphosphonates (**3**) are of importance as chemical intermediates,[1,2] complexing agents,[3] and biologically active molecules.[4] Some examples have been shown to act as transition state analogue inhibitors of renin.[5] In addition, the α-hydroxyphosphonate moiety is an important structural feature in nucleoside phosphonates of relevance in various aspects of medicinal chemistry.[6,7] Preparative methods for α-hydroxyphosphonates[8] are generally based on the Abramov reaction,[9] i.e., the base-catalysed addition of dialkyl phosphite (**1**) to a carbonyl compound (**2**) (Scheme 1).

A variety of catalysts has been employed, including an alkoxide or tertiary amine,[10] caesium fluoride,[11] potassium fluoride,[11,12] alumina,[13] potassium fluoride supported on alumina,[14] various solvent-free phosphate supports,[15] lithium bis(trimethylsilyl)amide,[16] quaternary ammonium hydroxide resin,[17] and anhydrous potassium carbonate.[18] The

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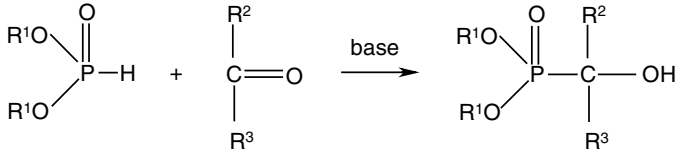
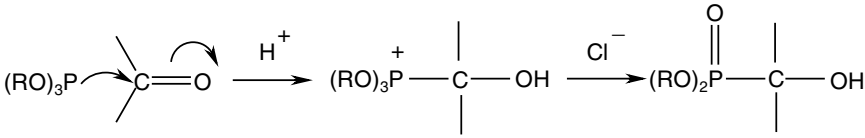


(**1**) (**2**) (**3**)

SCHEME 1

hydrogen chloride-catalyzed addition of trialkyl phosphites to carbonyl compounds has also been reported.[19] Although no reaction mechanism was proposed for this latter synthesis, it can be envisaged that nucleophilic attack of phosphite on the protonated carbonyl compound is involved, followed by dealkylation of the intermediate quasiphosphonium species (**4**) (Scheme 2).



(**4**)

SCHEME 2

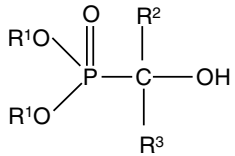
However, the known rapid mono-dealkylation of trialkyl phosphites by hydrogen chloride[20] suggests that the addition of dialkyl phosphite to the carbonyl compound could also be involved.

Surprisingly, there are very few references to the use of alumina as catalyst in the Abramov reaction beyond the original report,[13] although we have found basic alumina (chromatographic grade), in the absence of solvent, to be convenient and efficient in a number of cases.[21] We now report the use of basic alumina in the preparation of a wider range of α-hydroxyphosphonates, and we comment further on the chemical shift non-equivalence of the methyl ester groups in these compounds.[22]

RESULTS AND DISCUSSION

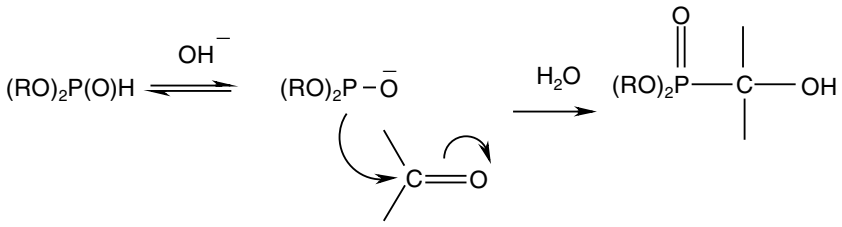
Preparations

Basic alumina was used as a heterogeneous catalyst, in the absence of solvent, for the reaction of dimethyl phosphite with a range of carbonyl compounds (Scheme 1; base = alumina). Products **3a**–**3y** were



R^1 = Me, R^2 = H, R^3 = Pr^n (**3a**), Bu^n (**3b**), 4-MeC_6H_4 (**3c**), 4-$MeOC_6H_4$ (**3d**), 4-$Me_2CHC_6H_4$ (**3e**), 2,4,6-$Me_3C_6H_2$ (**3f**), 2-HOC_6H_4 (**3g**), 4-ClC_6H_4 (**3h**), 4-FC_6H_4 (**3i**), 3-FC_6H_4 (**3j**), 4-Br-2-HOC_6H_4 (**3k**), 3,4-$(MeO)_2C_6H_3$ (**3l**), 3,4-$CH_2O_2C_6H_3$ (**3m**), 2-$O_2NC_6H_4$ (**3n**), 4-$O_2NC_6H_4$ (**3o**), 1-$C_{10}H_7$ (**3p**), 2-$C_{10}H_7$ (**3q**), 2-C_4H_3O (furyl) (**3r**), 2-C_4H_3S (thienyl) (**3s**), 3-C_4H_3S (thienyl) (**3t**)
R^1 = R^2 = Me, R^3 = Ph (**3u**), 4-MeC_6H_4 (**3v**), 4-BrC_6H_4 (**3w**), 4-FC_6H_4 (**3x**), 2-$O_2NC_6H_4$ (**3y**)

obtained in good yield by extraction of the crude reaction product with dichloromethane, followed by recrystallization from cyclohexane. The mechanism by which alumina acts catalytically in the Abramov reaction has not been studied in detail but it is reasonable to suppose that it functions, together with adsorbed water, as a phase transfer catalyst, providing surface hydroxyl groups for interaction with the dialkyl phosphite (Scheme 3).



SCHEME 3

Structural and NMR studies

Our earlier studies on dimethyl 1-chloromethyl-1-hydroxybenzylphosphonate (**3**, R^1 = Me, R^2 = CH_2Cl, R^3 = Ph) showed that this compound exists as hydrogen-bonded dimers in the solid state, with H-bonding between the phosphoryl oxygen atom of each molecule of the dimer and the hydroxyl hydrogen atom of the other.[22] In each dimeric unit, one molecule of (*S*)-configuration is associated with one of (*R*)-configuration.[22] In other more sterically constrained examples, e.g., diethyl α-hydroxy-*p*-isopropylbenzylphosphonate (**3**, R^1 = Et, R^2 = H, R^3 = 4-$Me_2CHC_6H_4$), intermolecular hydrogen-bonding

TABLE I ^{1}H and ^{13}C nmr Chemical Shifts (ppm) for the Diastereotopic Methoxy Groups in Dimethyl α-Hydroxyalkanephosphonates (3, R^1 = Me, R^2 = H)

	R^3	δ_H (MeO)		$\Delta\delta_H$ (MeO)	δ_C (MeO)		$\Delta\delta_C$ (MeO)
3a	Pr^n	3.81	3.81	0	53.24	53.24	0
3b	Bu^n	3.81	3.81	0	53.29	53.23	0.06

can give rise to the formation of hydrogen-bonded chains rather than dimers.[23] The extent to which such hydrogen-bonding persists in solution and might contribute to some restriction of rotation about the P-C_α bond in α-hydroxyphosphonates is uncertain but the magnetic non-equivalence of the alkyl ester groups is attributed primarily to the presence of the chiral α-carbon atom.[22] Thus, similar non-equivalence is shown by the ester groups of the corresponding dimethyl α-methoxybenzylphosphonates, $(MeO)_2P(O)CHArOMe$, in which neither intra- nor inter-molecular hydrogen-bonding can occur.[22]

^{1}H and ^{13}C nmr chemical shifts for the diastereotopic methyl ester groups in the α-hydroxyphosphonates reported in this paper are shown in Tables I–IV. The differences in chemical shift ($\Delta\delta_H$ or $\Delta\delta_C$) for the two methyl groups are scarcely detectable in the aliphatic series, typified by dimethyl α-hydroxybutyl- and α-hydroxypentylphosphonates (Table I) and $\Delta\delta_H$ values are also quite small in the α-aryl or α-heteroaryl series (Tables II and III), being 0.01–0.05 ppm in all cases except those in which R^2 = H, R^3 = mesityl (**3f**), and R^2 = H, R^3 = 2-furyl (**3r**), for which differences of *ca.* 0.20–0.21 ppm are observed. However, the ^{13}C chemical shifts of the diastereotopic methyl groups in the α-aryl or α-heteroaryl derivatives exhibit slightly greater differences of up to 0.9 ppm, and we have listed the data for these compounds (Tables II and III) in order of decreasing $\Delta\delta_C$ in an attempt to reveal any structurally related trends that might be discernable. ^{1}H and ^{13}C NMR data for six of the α-hydroxybenzylphosphonates (**3c**, **3d**, **3n**, **3o**, **3p**, **3q**) have been reported previously in the course of a study on the asymmetric hydrophosphonylation of aldehydes[16,24] and we have noted that the chemical shift differences recorded for the methyl ester group carbon atoms[16] agree well with those which we have determined for the same compounds (See Table II); and also follow the same order, giving us confidence that the trends reported here, although small, are essentially correct.

The overall pattern is seen more clearly in Figure 1, from which it is evident that the chemical shift for each of the methoxy groups shows a slight but definite trend to higher field as the benzyl substituent groups

TABLE II ^{1}H and ^{13}C nmr Chemical Shifts (ppm) for the Diastereotopic Methoxy Groups in Dimethyl α-Hydroxybenzylphosphonates (3, R^1 = Me, R^2 = H)

	R^3	δ_H (MeO)		$\Delta\delta_H$ (MeO)	δ_C (MeO)		$\Delta\delta_C$ (MeO)
3g	2-HOC_6H_4	3.73	3.68	0.05	54.34	53.41	0.93
3n	2-$O_2NC_6H_4$	3.73	3.71	0.02	54.60	53.70	0.90
		(3.74	3.72	0.02	54.48	53.58	0.90)[a]
3o	4-$O_2NC_6H_4$	3.79	3.77	0.02	54.51	53.67	0.84
		(3.78	3.76	0.02	54.42	53.71	0.71)[a]
3k	2-HO-4-BrC_6H_3	3.76	3.74	0.02	54.67	54.03	0.64
3i	4-FC_6H_4	3.75	3.73	0.02	54.10	53.64	0.46
3j	3-FC_6H_4	3.74	3.74	0	54.15	53.71	0.44
3h	4-ClC_6H_4	3.68	3.67	0.01	54.09	53.66	0.43
3p	1-$C_{10}H_7$	3.60	3.51	0.09	53.90	53.57	0.33
		(3.64	3.52	0.12	53.86	53.55	0.31)[a]
3c	4-MeC_6H_4	3.68	3.66	0.02	53.91	53.59	0.32
		(3.70	3.65	0.05	53.82	53.52	0.30)[a]
3q	2-$C_{10}H_7$	3.67	3.64	0.03	53.98	53.67	0.31
		(3.71	3.67	0.04	53.94	53.68	0.26)[a]
3f	2,4,6-$Me_3C_6H_2$	3.73	3.53	0.20	53.61	53.33	0.28
3d	4-$MeOC_6H_4$	3.73	3.70	0.03	53.84	53.58	0.26
		(3.71	3.66	0.05	53.79	53.56	0.23)[a]
3e	4-$Me_2CHC_6H_4$	3.69	3.64	0.05	53.82	53.60	0.22
3m	3,4-$CH_2O_2C_6H_3$	3.71	3.68	0.03	53.64	53.43	0.21
3l	3,4-$(MeO)_2C_6H_3$	3.66	3.72	0.06	53.81	53.68	0.13

[a]Data from Ref. 16 shown for comparison.

vary throughout the series in the order shown in Table II. The trend is greater for the downfield methoxy carbon atom, with a consequent change in chemical shift non-equivalence ($\Delta\delta_C$) throughout the series.

The largest ^{13}C chemical shift differences (0.8–0.9 ppm) were observed for the 2-hydroxybenzyl derivative (**3g**), and for compounds **3n**

TABLE III ^{1}H and ^{13}C nmr Chemical Shifts (ppm) for the Diastereotopic Methoxy Groups in Dimethyl α-Hydroxy-α-heteroarylmethanephosphonates (3, R^1 = Me, R^2 = H)

	R^3	δ_H (MeO)		$\Delta\delta_H$ (MeO)	δ_C (MeO)		$\Delta\delta_C$ (MeO)
3r	2-furyl	3.76	3.97	0.21	53.93	53.29	0.64
3s	2-thienyl	3.73	3.71	0.02	54.11	53.83	0.28
3t	3-thienyl	3.69	3.65	0.04	53.83	53.66	0.17

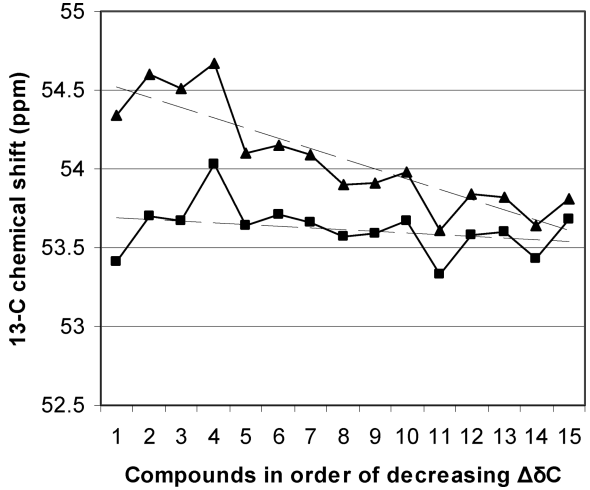


FIGURE 1 Variation in ^{13}C chemical shift of the two diastereotopic methyl ester groups in dimethyl α-hydroxybenzylphosphonates (**3**, R^1 = Me, R^2 = H, R^3 = Ar) in the order listed in Table II: **3g** (1), **3n** (2), **3o** (3), **3k** (4), **3i** (5), **3j** (6), **3h** (7), **3p** (8), **3c** (9), **3q** (10), **3f** (11), **3d** (12), **3e** (13), **3m** (14), **3l** (15). ■ = high field signal; ♦ = low field signal; dotted lines show overall trends.

and **3o** in which a nitro group is present in the 2- or 4-position of the benzyl ring. The ^{13}C chemical shift difference in the 2-hydroxy-4-bromo- (**3k**) derivative is next in order, at 0.64 ppm, followed by the 4-chloro-, and 3- or 4-fluoro-substituted compounds (**3h**, **3i**, **3j**), for which the ^{13}C chemical shift differences observed were 0.43–0.46 ppm. Similar differences in ^{13}C chemical shift (0.43 – 0.46 ppm) were recorded for the methyl ester carbon atoms of the 2-, 3-, and 4-bromo-derivatives.[25] All these compounds, it should be noted, contain one or more

TABLE IV ^1H and ^{13}C nmr Chemical Shifts (ppm) for the Diastereotopic Methoxy Groups in Dimethyl α-Hydroxy-α-methylbenzylphosphonates (3, R^1 = Me, R^2 = Me)

	R^3	δ_H (MeO)		$\Delta\delta_H$ (MeO)	δ_C (MeO)		$\Delta\delta_C$ (MeO)
3w	4-BrC_6H_4	3.77	3.68	0.09	54.03	54.58	0.55
3y	2-$O_2NC_6H_4$	3.73	3.78	0.05	54.18	54.71	0.53
3v	4-MeC_6H_4	3.73	3.63	0.10	53.82	53.42	0.40
3x	4-FC_6H_4	3.75	3.65	0.10	54.25	53.87	0.38
3u	Ph	3.72	3.62	0.10	53.84	54.15	0.31

electronegative substituents bearing lone electron pairs which might be expected to exert a differential screening effect on the diastereotopic methyl ester groups. Nitro groups, with two polarized oxygen atoms, and hydroxyl groups in the 2-position appear to be the most influential.

Compounds in which smaller chemical shift differences ($\Delta\delta_C$ 0.13–0.35 ppm) are observed are the usubstituted dimethyl α-hydroxybenzylphosphonate ($\Delta\delta_C$ 0.35 ppm)[25] and those in which ring substituents bearing lone electron pairs are absent, viz. **3c**, **3e**, and **3f** (which contain electron-donating alkyl groups) or in which oxygen atoms, if present, are in the 3- and/or 4-positions and have alkyl groups attached (**3l**, **3m**).

The effect of sulfur in the thiophene ring (**3s**, **3t**) is less than that of the more electronegative oxygen in furan (**3r**), but with the effect decreasing in the order 2-furyl > 2-thienyl > 3-thienyl, indicating again the significance of substitution in position 2 with an electronegative atom bearing lone pair electrons (Table III).

Within the di-α-substituted series (R^2 = Me, Table IV), the greatest non-equivalence (0.55 and 0.53 ppm) was shown by the 4-bromo- (**3w**) and 2-nitro- (**3y**) derivatives, respectively, and the least by the unsubstituted benzyl compound **3u** (R^2 = Me, R^3 = Ph), for which $\Delta\delta_C = 0.31$. The overall order here does not accord in every detail with that given above for the mono-α-substituted series but it is possible that it is influenced by the steric effect of the additional α-methyl substituent.

CONCLUSIONS

Basic alumina has been confirmed as a useful catalyst in the synthesis of α-hydroxyphosphonates by the Abramov reaction.

A preliminary attempt to correlate chemical shift non-equivalence of the methyl ester groups with the structure of dimethyl α-hydroxyphosphonates indicates that the overall effects are complex and no doubt subject to a variety of contributory factors. Nevertheless, it seems in general that strongly electronegative atoms bearing lone electron pairs, especially in the 2-position are the most influential in generating a differential screening effect on the two methyl ester groups. It is also possible that the influence of aromatic ring currents and the extent to which these are modified by ring substituents, together with stereochemical factors controlling the populations of significant rotamers, are all involved in determining differential through-space screening.

Molecular modelling studies may be helpful in obtaining a clearer insight into the factors involved.

EXPERIMENTAL

Starting materials, solvents, and chromatographic grade basic alumina were obtained commercially. Dichloromethane and cyclohexane were dried and stored over molecular sieves. Other materials were used as supplied. ^{1}H, ^{13}C, and $^{31}P\{^{1}H\}$ NMR spectra were recorded for solutions in $CDCl_3$ on a Bruker AM250 instrument, operating at 250.133 MHz, 62.896 MHz, or 101.256 MHz, respectively. Chemical shifts are reported relative to TMS (internal reference) for ^{1}H and ^{13}C spectra, and 85% phosphoric acid (external reference) for ^{31}P spectra. Microanalysis (for C and H) was carried out on a Carlo Erba 1106 Elemental Analyser.

Preparation of α-Hydroxyphosphonates

Aluminium oxide (basic, chromatographic grade) (40 g) was added gradually to a stirred mixture of dimethyl phosphite (11.0 g, 0.100 mol) and the appropriate carbonyl compound (0.100 mol) at room temperature. The reactants were completely adsorbed on the alumina. After 72 h, the product was extracted with dichloromethane (2 × 200 ml) and the extract was evaporated under reduced pressure to give the crude phosphonic ester, which was either distilled (**3a**, **3b**) or purified by recrystallization from cyclohexane to give the following products.

Dimethyl α-Hydroxybutylphosphonate (3a)

Colorless viscous liquid, b.p. 121–122°C at 0.05 mmHg (yield 86%) (Found: C, 39.49; H, 8.57. Calc. for $C_6H_{15}O_4P$: C, 39.56; H, 8.24%); $\delta_P(CDCl_3)$ 27.75; $\delta_H(CDCl_3)$ 0.95 (CH_3, 3H, t, J_{HCCH} 7.13 Hz), 1.48–1.75 (CH_2CH_2, 4H, m), 3.81 (CH_3O, 3H, d, J_{POCH} 10.40 Hz), 3.81 (CH_3O, 3H, d, J_{POCH} 10.39 Hz), 3.87–3.97 (α-CH, 1H, m), 4.96 (OH, 1H, s); $\delta_C(CDCl_3)$ 13.72 (CH_3, s), 18.91 ($\underline{C}H_2CH_3$, d, J_{PCCC} 13.71 Hz), 33.45 ($CH\underline{C}H_2$, d, J_{PCC} 1.13 Hz), 53.24 (CH_3O x 2, d, J_{POC} 6.89 Hz), 67.11 (α-C, d, J_{PC} 161.65 Hz).

Dimethyl α-Hydroxypentylphosphonate (3b)

Colorless viscous liquid, b.p. 124–126°C at 0.05 mmHg (yield 78%) (Found: C, 42.50; H, 8.67. Calc. for $C_7H_{17}O_4P$: C, 42.85; H, 8.67%); $\delta_P(CDCl_3)$ 27.72; $\delta_H(CDCl_3)$ 0.92 (CH_3, 3H, t, J_{HCCH} 6.99 Hz), 1.21–1.76 [$(CH_2)_3$, 6H, m], 3.81 (CH_3O, 3H, d, J_{POCH} 10.27 Hz), 3.81 (CH_3O, 3H, d, J_{POCH} 10.35 Hz), 3.77–3.94 (α-CH, 1H, m), 5.04 (OH, 1H, s); $\delta_C(CDCl_3)$ 13.95 (CH_3, s), 22.41 ($\underline{C}H_2CH_3$, s), 27.86 ($\underline{C}H_2CH_2CH_3$, d, J_{PCCC} 13.52 Hz), 31.12 ($CH\underline{C}H_2$, s), 53.29 (CH_3O, d, J_{POC} 7.09 Hz), 53.23 (CH_3O, d, J_{POC} 7.00 Hz), 64.44 (α-C, d, J_{PC} 167.31 Hz).

Dimethyl α-Hydroxy-4-methylbenzylphosphonate (3c)

White crystalline solid, m.p 98°C (yield 68%); $\delta_P(CDCl_3)$ 23.88; $\delta_H(CDCl_3)$ 2.34 (4-CH_3, 3H, d, $^7J_{PH}$ 1.79 Hz), 3.68 (CH_3O, 3H, d, J_{POCH} 10.45 Hz), 3.66 (CH_3O, 3H, d, J_{POCH} 10.28 Hz), 4.88 (OH, 1H, dd, J_{HCOH} 5.59 Hz, J_{PCOH} 5.86 Hz), 4.98 (α-CH, 1H, dd, J_{PCH} 10.88 Hz, J_{HOCH} 5.59 Hz), 7.16–7.39 (4H, arom); $\delta_C(CDCl_3)$ 21.19 (4-CH_3, d, $^6J_{PC}$ 1.07 Hz), 53.59 (CH_3O, d, J_{POC} 7.29 Hz), 53.91 (CH_3O, d, J_{POC} 7.04 Hz), 70.37 (α-C, d, J_{PC} 160.71 Hz), 124.22–144.02 (arom).

Dimethyl α-Hydroxy-4-methoxybenzylphosphonate (3d)

White crystalline solid, m.p. 72°C (yield 72%) (Found: C, 48.80; H, 6.21. Calc. for $C_{10}H_{15}O_5P$: C, 48.78; H, 6.09%); $\delta_P(CDCl_3)$ 23.98; $\delta_H(CDCl_3)$ 3.73 (CH_3OP, 3H, d, J_{POCH} 10.38 Hz), 3.70 (CH_3OP, 3H, d, J_{POCH} 10.22 Hz), 3.85(-$C_6H_4OC\underline{H}_3$-4, 3H, s), 5.04 (α-CH, 1H, d, J_{PCH} 10.69 Hz), 5.31 (OH, 1H, br), 6.91–7.48 (4H, arom); $\delta_C(CDCl_3)$ 53.58 (CH_3OP, d, J_{POC} 7.36 Hz), 53.84 (CH_3OP, d, J_{POC} 6.98 Hz), 55.20 (-$C_6H_4O\underline{C}H_3$-4, s), 69.95 (α-C, d, J_{PC} 162.91 Hz), 113.73–128.87 (arom).

Dimethyl α-Hydroxy-4-isopropylbenzylphosphonate (3e)

White crystalline solid, m.p. 69°C (yield 75%) (Found: C, 56.29; H, 6.85. Calc. for $C_{12}H_{19}O_4P$: C, 55.81; H, 7.36%); $\delta_P(CDCl_3)$ 23.87; $\delta_H(CDCl_3)$ 1.23($\underline{Me}_2CH$, 6H, d, J_{HCCH} 6.95 Hz), 2.89 ($Me_2C\underline{H}$, 1H, septet, J_{HCCH} 6.90 Hz), 3.69 (CH_3O, 3H, d, J_{POCH} 10.39 Hz), 3.64 (CH_3O, 3H, d, J_{POCH} 10.34 Hz), 5.00 (α-CH, 1H, d, J_{PCH} 10.94 Hz), 7.18–7.41 (4H, arom); $\delta_C(CDCl_3)$ 23.94 ($\underline{Me}_2CH$, s), 33.84 ($Me_2\underline{C}H$, s), 53.82 (CH_3O, d, J_{POC} 6.79 Hz), 53.60 (CH_3O, d, J_{POC} 6.98 Hz), 70.44 (α-C, d, J_{PC} 161.09 Hz), 126.44–148.90 (arom).

Dimethyl α-Hydroxy-2,4,6-trimethylbenzylphosphonate (3f)

White crystalline solid, m.p. 115°C (yield 78%); $\delta_P(CDCl_3)$ 26.10; $\delta_H(CDCl_3)$ 2.24 (4-CH_3, 3H, s), 2.45 (2,6-Me_2, 6H, s), 3.73 (CH_3O, 3H, d, J_{POCH} 10.62 Hz), 3.53 (CH_3O, 3H, d, J_{POCH} 10.37 Hz), 4.80 (OH, 1H, s), 5.48 (α-CH, 1H, d, J_{PCH} 15.55 Hz), 6.82–7.27 (2H, arom); $\delta_C(CDCl_3)$ 20.96 (4-CH_3, s), 21.01 (2,6-Me_2, s), 53.33 (CH_3O, d, J_{POC} 6.90 Hz), 53.61(CH_3O, d, J_{POC} 6.9 Hz), 68.26 (α-C, d, J_{PC} 162.16 Hz), 129.61–137.49 (arom).

Dimethyl α-Hydroxy-2-hydroxybenzylphosphonate (3g)

Very light green crystalline solid, m.p. 90°C (yield 80%) (Found: C, 46.29; H, 4.85. Calc. for $C_9H_{13}O_5P$: C, 46.55; H, 5.60%); $\delta_P(CDCl_3)$ 24.34; $\delta_H(CDCl_3)$ 3.73 (CH_3O, 3H, d, J_{POCH} 10.45 Hz), 3.68 (CH_3O, 3H, d, J_{POCH} 10.89 Hz), 5.01 (OH, 1H, br), 5.12 (α-CH, 1H, d, J_{PCH} 12.24 Hz),

7.00–7.53 (4H, arom); $\delta_C(CDCl_3)$ 53.41 (CH_3O, d, J_{POC} 6.86 Hz), 54.34 (CH_3O, d, J_{POC} 7.29 Hz), 69.86 (α-C, d, J_{PC} 162.91 Hz); 117.87–129.85 (arom).

Dimethyl α-Hydroxy-4-chlorobenzylphosphonate (3h)

White crystalline solid, m.p. 68°C (yield 75%) (Found: C, 43.41; H, 4.80. Calc.for $C_9H_{12}ClO_4P$: C, 43.11; H, 4.80%); $\delta_P(CDCl_3)$ 23.08; $\delta_H(CDCl_3)$ 3.68 (CH_3O, 3H, d, J_{POCH} 10.58 Hz), 3.67 (CH_3O, 3H, d, J_{POCH} 10.33 Hz), 5.16 (α-CH, 1H, d, J_{PCH} 11.43 Hz), 7.27–7.42 (4H, arom); $\delta_C(CDCl_3)$ 53.66 (CH_3O, d, J_{POC} 7.61 Hz), 54.09 (CH_3O, d, J_{POC} 6.91 Hz), 69.82 (α-C, d, J_{PC} 161.53 Hz), 128.38–136.32 (arom).

Dimethyl α-Hydroxy-4-fluorobenzylphosphonate (3i)

White crystalline solid, m.p. 98°C (yield 82%) (Found: C, 46.33; H, 5.16. Calc. for $C_9H_{12}FO_4P$: C, 46.15; H, 5.12%); $\delta_P(CDCl_3)$ 23.19 (d, $^6J_{FP}$ 6.71 Hz); $\delta_H(CDCl_3)$ 3.75 (CH_3O, 3H, d, J_{POCH} 10.59 Hz), 3.73 (CH_3O, 3H, d, J_{POCH} 13.38 Hz), 5.45 (α-CH, 1H, d, J_{PCH} 10.50 Hz), 5.47 (OH, 1H, s), 7.01–7.74 (4H, arom); $\delta_C(CDCl_3)$ 53.64 (CH_3O, d, J_{POC} 7.23 Hz), 54.10 (CH_3O, d, J_{POC} 7.11 Hz), 63.41 (α-C, d, J_{PC} 161.27 Hz), 114.82–162.00 (arom).

Dimethyl α-Hydroxy-3-fluorobenzylphosphonate (3j)

White crystalline solid, m.p. 97°C (yield 82%) (Found: C, 46.05; H, 5.06. Calc. for $C_9H_{12}FO_4P$: 46.15; H. 5.12%); $\delta_P(CDCl_3)$ 28.48 (d, $^5J_{FP}$ 4.97 Hz); $\delta_H(CDCl_3)$ 3.74 (CH_3O x 2, 6H, d, J_{POCH} 10.07 Hz), 5.06 (α-CH, 1H, d, J_{PCH} 11.96 Hz), 5.52 (OH, 1H, s), 6.93–7.34 (4H, arom); $\delta_C(CDCl_3)$ 53.71 (CH_3O, d, J_{POC} 7.49 Hz), 54.15 (CH_3O, d, J_{POC} 1.89 Hz), 64.87 (α-C, dd, J_{PC} 164.92 Hz, $^4J_{FC}$ 1.89 Hz), 113.85–164.76 (arom).

Dimethyl α-Hydroxy-2-hydroxy-4-bromobenzylphosphonate (3k)

Very light green crystalline solid, m.p. 95°C (yield 78%) (Found: C, 34.79; H, 3.63. Calc. for $C_9H_{12}BrO_5P$: C, 34.83; H, 3.87%); $\delta_P(CDCl_3)$ 23.4; $\delta_H(CDCl_3)$ 3.76 (CH_3O, 3H, d, J_{POCH} 10.48 Hz), 3.74 (CH_3O, 3H, d, J_{POCH} 10.53 Hz), 4.72 (OH, 1H, br); 5.15 (α-CH, 1H, d, J_{PCH} 12.57 Hz), 6.89–7.68 (3H, arom); $\delta_P(CDCl_3)$ 54.03 (CH_3O, d, J_{POC} 7.42 Hz), 54.67 (CH_3O, d, J_{POC} 7.17 Hz), 68.98 (α-C, d, J_{PC} 163.09 Hz), 111.37–160.53 (arom).

Dimethyl α-Hydroxy-3,4-dimethoxybenzylphosphonate (3l)

Off-white crystalline solid, m.p. 124°C (yield 92%); $\delta_P(CDCl_3)$ 23.77; $\delta_H(CDCl_3)$ 3.72 (CH_3OP, 3H, d, J_{POCH} 10.45 Hz), 3.66 (CH_3OP, 3H, d, J_{POCH} 10.33 Hz), 3.89 (3-CH_3O, 3H, s), 3.88 (4-CH_3O, 3H, s), 4.99 (α-CH,

1H, d, J_{PCH} 10.48 Hz), 6.83–7.48 (3H, arom); $\delta_C(CDCl_3)$ 53.68 (CH_3OP, d, J_{POC} 7.55 Hz), 53.81(CH_3OP, d, J_{POC} 6.98 Hz), 55.87 (3-CH_3O, s), 55.92 (4-CH_3O, s), 70.23 (α-C, d, J_{PC} 161.78 Hz), 108.97–148.94 (arom).

Dimethyl α-Hydroxypiperonylphosphonate (3m)

White crystalline solid, m.p. 104.5°C (yield 84%); $\delta_P(CDCl_3)$ 23.4; $\delta_H(CDCl_3)$ 3.71 (CH_3O, 3H, d, J_{POCH} 10.58 Hz), 3.68 (CH_3O, 3H, d, J_{POCH} 10.32 Hz), 4.95 (α-CH, 1H, d, J_{PCH} 10.87 Hz), 5.24 (OH, 1H, s), 5.94 (O-CH_2-O, 2H, s), 6.74–7.42 (3H, arom); $\delta_C(CDCl_3)$ 53.64 (CH_3O, d, J_{POC} 7.36 Hz), 53.43 (CH_3O, d, J_{POC} 7.17 Hz), 70.23 (α-C, d, J_{PC} 162.85 Hz), 101.13 (O-CH_2-O), 129.61–137.47 (arom).

Dimethyl α-Hydroxy-2-nitrobenzylphosphonate (3n)

Light green crystalline solid, m.p. 166.5°C (yield 87%) (Found: C, 41.84; H, 4.17; N, 5.23. Calc. for $C_9H_{12}NO_6P$: C, 41.3; H, 4.59; N. 5.36%); $\delta_P(CDCl_3)$ 22.18; $\delta_H(CDCl_3)$ 3.73 (CH_3O, 3H, d, J_{POCH} 10.53 Hz), 3.71 (CH_3O, 3H, d, J_{POCH} 10.63 Hz); 5.57 (OH, 1H, br), 6.29 (α-CH, 1H, d, J_{PCH} 14.19 Hz), 7.29–8.03 (4H, arom); $\delta_C(CDCl_3)$ 53.70 (CH_3O, d, J_{POC} 6.92 Hz), 54.60 (CH_3O, d, J_{POC} 7.49 Hz), 65.45 (α-C, d, J_{PC} 162.03 Hz), 124.66–147.52 (arom).

Dimethyl α-Hydroxy-4-nitrobenzylphosphonate (3o)

Off-white crystalline solid, m.p. 101°C (yield 88%) (Found: C, 40.96; H, 4.88; N, 5.83. Calc. for $C_9H_{12}NO_6P$: C, 41.37; H, 4.59; N, 5.36%); $\delta_P(CDCl_3)$ 21.88; $\delta_H(CDCl_3)$ 3.79 (CH_3O, 3H, d, J_{POCH} 10.44 Hz), 3.77 (CH_3O, 3H, d, J_{POCH} 10.76 Hz); 5.24 (α-CH, 1H, d, J_{PCH} 12.56 Hz); 7.28–8.43 (4H, arom); $\delta_C(CDCl_3)$ 53.67 (CH_3O, d, J_{POC} 4.97 Hz), 54.51 (CH_3O, d, J_{POC} 7.29 Hz), 69.91(α-C, d, J_{PC} 159.19 Hz), 123.44–147.63 (arom).

Dimethyl α-Hydroxy-α-(1-naphthyl)methanephosphonate (3p)

White crystalline solid, m.p. 139°C (yield 84%) (Found: C, 59.01; H, 5.36. Calc. for $C_{13}H_{15}O_4P$: C, 58.64; H, 5.63%); δ_P ($CDCl_3$) 23.68; $\delta_H(CDCl_3)$ 3.60 (CH_3O, 3H, d, J_{POCH} 10.46 Hz), 3.51 (CH_3O, 3H, d, J_{POCH} 10.31 Hz), 4.99 (OH, 1H, dd, J_{PCOH} 9.89 Hz, J_{HCOH} 5.98 Hz), 5.36 (α-CH, 1H, dd, J_{PCH} 11.74 Hz, J_{HOCH} 5,32 Hz), 7.42–8.07 (7H, arom); $\delta_C(CDCl_3)$ 53.57 (CH_3O, d, J_{POC} 7.61 Hz), 53.90 (CH_3O, d, J_{POC} 7.04 Hz), 67.03 (α-C, d, J_{PC} 162.28 Hz), 123.40–136.68 (arom).

Dimethyl α-Hydroxy-α-(2-naphthyl)methanephosphonate (3q)

White crystalline solid, m.p. 129°C (yield 82%) (Found: C, 59.31; H. 5.29. Calc. for $C_{13}H_{15}O_4P$: C, 58.64; H, 5.63%); $\delta_P(CDCl_3)$ 23.59; $\delta_H(CDCl_3)$ 3.67 (CH_3O, 3H, d, J_{POCH} 10.45 Hz), 3.64 (CH_3O, 3H, d, J_{POCH} 10.33 Hz), 5.05 (OH, 1H, s), 5.22 (α-CH, 1H, d, J_{PCH} 11.42 Hz), 7.24–7.93

(7H, arom); $\delta_C(CDCl_3)$ 53.67 (CH_3O, d, J_{POC} 7.36 Hz), 53.98 (CH_3O, d, J_{POC} 7.11 Hz), 70.72 (α-C, d, J_{PC} 160.39 Hz), 124.84–135.14 (arom).

Dimethyl α-Hydroxyfurfurylphosphonate (3r)

Brown crystalline solid, m.p. 45°C (yield 78%); $\delta_P(CDCl_3)$ 21.67; $\delta_H(CDCl_3)$ 3.76 (CH_3O, 3H, d, J_{POCH} 10.61 Hz), 3.97 (CH_3O, 3H, d, J_{POCH} 10.46 Hz), 5.06 (α-CH, 1H, dd, J_{PCH} 13.73 Hz, J_{HOCH} 7.19 Hz), 5.56 (OH, 1H, dd, J_{PCOH} 7.50 Hz, J_{HCOH} 7.50 Hz), 6.35–7.42 (3H, arom); $\delta_C(CDCl_3)$ 53.29 (CH_3O, d, J_{POC} 6.79 Hz), 53.93 (CH_3O, d, J_{POC} 7.40 Hz), 64.21 (α-C, d, J_{PC} 168.57 Hz), 140.17 (C-2, s), 142.81 (C-5, d, J_{PCCOC} 2.07 Hz), 110.75 (C-3, d, J_{PCCC} 1.64 Hz), 109.35 (C-4, d, J_{PCCCC} 6.60 Hz).

Dimethyl α-Hydroxy-α-(2-thienyl)methanephosphonate (3s)

Yellow crystalline solid, m.p. 82°C (yield 86%) (Found: C, 37.36; H, 4.72. Calc. for $C_7H_{11}O_4PS$: C, 37.83; H, 4.95%); $\delta_P(CDCl_3)$ 21.94; $\delta_H(CDCl_3)$ 3.73 (CH_3O, 3H, d, J_{POCH} 10.41 Hz), 3.71 (CH_3O, 3H, d, J_{POCH} 10.39 Hz), 5.27 (α-CH, 1H, d, J_{PCH} 12.14 Hz), 5.52 (OH, 1H, s), 6.97–7.30 (3H, arom); $\delta_C(CDCl_3)$ 53.83 (CH_3O, d, J_{POC} 7.29 Hz), 54.11 (CH_3O, d, J_{POC} 7.39 Hz), 66.55 (α-C, d, J_{PC} 168.57 Hz), 125.76–139.62 (arom).

Dimethyl α-Hydroxy-α-(3-thienyl)methanephosphonate (3t)

Light yellow crystalline solid, m.p. 72°C (yield 98%) (Found: C, 37.36; H, 4.72. Calc. for $C_7H_{11}O_4PS$: C, 37.83; H, 4.95%); $\delta_P(CDCl_3)$ 23.19; $\delta_H(CDCl_3)$ 3.69 (CH_3O, 3H, d, J_{POCH} 9.62 Hz), 3.65 (CH_3O, 3H, d, J_{POCH} 9.56 Hz), 5.12 (α-CH, 1H, d, J_{PCH} 11.20 Hz, J_{HOCH} 6.49 Hz), 5.35 (OH, 1H, dd, J_{PCOH} 8.23 Hz, J_{HCOH} 6.52 Hz), 7.16–7.41 (3H, arom); $\delta_C(CDCl_3)$ 53.66 (CH_3O, d, J_{POC} 6.98 Hz), 53.83 (CH_3O, d, J_{POC} 7.63 Hz), 66.98 (α-C, d, J_{PC} 162.90 Hz), 122.97–137.63 (arom).

Dimethyl α-Hydroxy-α-methylbenzylphosphonate (3u)

White crystalline solid, m.p. 130°C (yield 52%) (Found: C, 52.37; H, 6.52. Calc. for $C_{10}H_{15}O_4P$: C, 52.17; H, 6.52%); $\delta_P(CDCl_3)$ 26.02; $\delta_H(CDCl_3)$ 1.83 (α-CH_3, 3H, d, J_{PCCH} 15.63 Hz), 3.72 (CH_3O, 3H, d, J_{POCH} 10.18 Hz), 3.62 (CH_3O, 3H, d, J_{POCH} 10.26 Hz), 7.23–7.64 (5H, arom); $\delta_C(CDCl_3)$ 25.81 (α-CH_3, d, J_{PCC} 3.89 Hz), 53.84 (CH_3O, d, J_{POC} 7.67 Hz), 54.15 (CH_3O, d, J_{POC} 7.36 Hz), 73.73 (α-C, d, J_{PC} 159.57 Hz), 125.84–141.12 (arom).

Dimethyl α-Hydroxy-α-methyl-4-methylbenzylphosphonate (3v)

White crystalline solid, m.p. 150°C (yield 52%) (Found: C, 54.06; H, 6.15. Calc. for $C_{11}H_{17}O_4P$: C, 54.09; H, 6.96%); $\delta_P(CDCl_3)$ 26.25; $\delta_H(CDCl_3)$ 1.81 (α-CH_3, 3H, d, J_{PCCH} 15.70 Hz), 2.34 (4-CH_3, 3H, d,

$^{7}J_{PH}$ 1.54 Hz), 3.73 (CH_3O, 3H, d, J_{POCH} 10.18 Hz), 3.63 (CH_3O, 3H, d, J_{POCH} 10.23 Hz), 4.27 (OH, 1H, d, J_{PCOH} 5.01 Hz), 7.15–7.51 (4H, arom); $\delta_C(CDCl_3)$ 21.04 (4-CH_3, s,), 25.80 (α-CH_3, d, J_{PCC} 4.40 Hz), 53.82 (CH_3O, d, J_{POC} 7.61 Hz), 53.42 (CH_3O, d, J_{POC} 7.61 Hz), 73.64 (α-C, d, J_{PC} 159.33 Hz), 125.71–128.01 (arom).

Dimethyl α-Hydroxy-α-methyl-4-bromobenzylphosphonate (3w)

White crystalline solid, m.p. 60°C (yield 66%); $\delta_P(CDCl_3)$ 25.28; $\delta_H(CDCl_3)$ 1.81 (α-CH_3, 3H, d, J_{PCCH} 15.88 Hz), 3.77 (CH_3O, 3H, d, J_{POCH} 10.27 Hz), 3.68 (CH_3O, 3H, d, J_{POCH} 10.39 Hz), 6.45 (OH, 1H, s), 7.29–7.83 (4H, arom); $\delta_C(CDCl_3)$ 25.63 (α-CH_3, s), 54.03 (CH_3O, d, J_{POC} 7.80 Hz), 54.58 (CH_3O, d, J_{POC} 7.61 Hz), 73.41 (α-C, d, J_{PC} 159.83 Hz), 121.74–140.03 (arom).

Dimethyl α-Hydroxy-α-methyl-4-fluorobenzylphosphonate (3x)

White crystalline solid, m.p. 181.5°C (yield 85%) (Found: C, 48.35; H, 5.59. Calc. for $C_{10}H_{14}FO_4P$: C, 48.38; H, 5.64%); $\delta_P(CDCl_3)$ 25.78 (d, $^{6}J_{FP}$ 4.51 Hz); $\delta_H(CDCl_3)$ 1.82 (α-CH_3, 3H, d, J_{PCCH} 15.60 Hz), 3.75 (CH_3O, 3H, d, J_{POCH} 10.10 Hz), 3.65 (CH_3O, 3H, d, J_{POCH} 10.22 Hz), 4.28 (OH, 1H, d, $^{7}J_{HF}$ 4.23 Hz), 7.04–7.58 (4H, arom); $\delta_C(CDCl_3)$, 25.91 (α-CH_3, d, J_{PCC} 4.21 Hz), 53.87 (CH_3O, d, J_{POC} 7.74 Hz), 54.25 (CH_3O, d, J_{POC} 7.80 Hz), 73.40 (α-C, d, J_{PC} 160.40 Hz), 114.72–136.82 (arom).

Dimethyl α-Hydroxy-α-methyl-2-nitrobenzylphosphonate (3y)

White crystalline solid, m.p. 110°C (yield 62%); $\delta_P(CDCl_3)$ 23.98; $\delta_H(CDCl_3)$ 1.91 (α-CH_3, 3H, d, J_{PCCH} 15.57 Hz), 3.73 (CH_3O, 3H, d, J_{POCH} 10.22 Hz), 3.78 (CH_3O, 3H, d, J_{POCH} 10.39 Hz), 5.25 (OH, 1H, s), 7.27–8.12 (4H, arom); $\delta_C(CDCl_3)$ 27.11 (α-CH_3, s), 54.18 (CH_3O, d, J_{POC} 7.67 Hz), 54.71 (CH_3O, d, J_{POC} 7.42 Hz), 74.92 (α-C, d, J_{PC} 162.47 Hz), 123.98–138.04 (arom).

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