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Rhodium Carbenoid O-H Insertion Reactions With Phenols; A Facile Method for the Synthesis of Trialkyl 2-Aryloxyphosphonoacetates and Their Use in the Preparation of 2-Aryloxy-3-phenylpropanoates.

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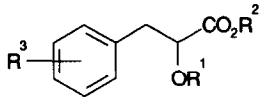
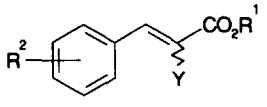
Abstract: A variety of substituted phenols undergo a facile and hitherto unreported rhodium carbenoid mediated O-H insertion reaction with trialkyl 2-diazophosphonoacetates **7** to afford the corresponding trialkyl 2-aryloxyphosphonoacetates **5** in generally good to excellent yield. Phenols containing strongly electron withdrawing groups, bulky *ortho*-substituents or certain *ortho*-heteroatom substituents show reduced or variable yields. Catechol affords a mono-adduct which cyclises to lactone **9**. Aniline inserts preferentially and exclusively over phenol in a competition reaction with **7** to afford an anilinophosphonoacetate **11**. Phenol insertion products **5** are shown to be versatile intermediates in a novel preparation of 2-aryloxy-3-phenylpropenoates **12** by Wadsworth-Emmons reaction with benzaldehydes. Dissolving magnesium metal reduction provides a mild method for the conversion of the propenoates **12** into the corresponding propanoates **13**.

INTRODUCTION

2-Alkoxy- and 2-aryloxy-3-phenylpropanoic acid derivatives **1** have been incorporated into molecules displaying a diverse range of interesting properties. These have included use as sweetening agents,[1] photosensitive materials,[2] liquid crystals[3] and also pharmaceutical applications in molecules displaying antihypertensive,[4] hypolipidemic,[5] hypocholesterolemic activity[6] and antihyperglycaemic activity.[7,8]



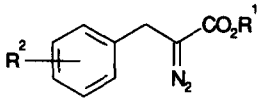


1a R^1 = Alkyl
1b R^1 = Aryl

2a Y = O-Alkyl
2b Y = O-Aryl
2c Y = H, R^1 = Me, R^2 = 4-OCH_2Ph

A variety of synthetic approaches to compounds **1** have been published. For 2-*alkoxy* analogues **1a** these have included reduction of propenoates **2a**,[9] elaboration of acetals,[7] aldol reactions[7] or thermal decomposition of N-acetyl-N-nitrosophenylalanine.[10] More recently we have prepared compounds **1a** *via* rhodium carbenoid

mediated reactions of diazoesters **3** with alcohols.[11] In contrast, published syntheses of 2-*aryloxy*-3-phenylpropanoates **1b** are less diverse, being limited to the benzylation of phenoxyacetic acid[12] or analogues[7] and the nucleophilic displacement of bromide from 2-bromo-3-phenylpropanoates **4a** by phenoxide anions.[5,6] Accordingly, in this paper we wish to describe some of our work leading to a simple and versatile synthesis of compounds **1b**.



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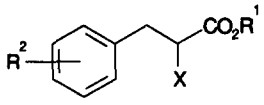
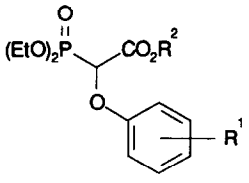


4a X = Br
4b X = Cl, R^1 = Me, R^2 = 4-OCH_2Ph

RESULTS AND DISCUSSION

i) Synthesis of Trialkyl 2-aryloxyphosphonoacetates

In initial attempts to prepare 2-aryloxy-3-phenylpropanoates **1b**, we were attracted to the reaction of the readily available chloride **4b**[13] with phenoxides. Despite literature precedent for similar compounds,[5,6] the reaction of **4b** with sodium phenoxide led only to the formation of E-propenoate **2c**. Phenols would not undergo insertion reactions with carbenoids derived from analogues of **3**[8,11] and alkylation of phenoxyacetic acid derivatives with benzyl halides was not practical for our purposes. As an alternative the preparation of **1b** *via* reduction of the corresponding propenoates **2b** was examined. Previous preparations of such propenoates involved Stobbe-type condensations of aryloxyacetic esters with benzaldehydes which gave variable mixtures of esters, acids and double bond isomers depending upon the conditions chosen.[14] It was reasoned that **2b** should be available *via* Wadsworth-Emmons reaction[15] of the corresponding trialkyl 2-aryloxy-phosphonoacetates **5** with benzaldehydes. Surprisingly, the only previously reported syntheses[16] of **5** involved tedious sequences of halogenation and Arbuzov chemistry upon aryloxyacetates **6**. This process was considered undesirable for the preparation of a wide variety of aryl-substituted analogues of **5**.



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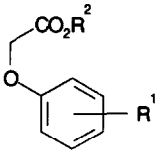

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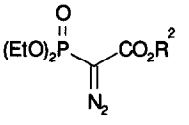
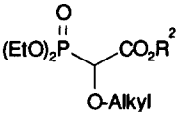


7a R^2 = Et
7b R^2 = Me



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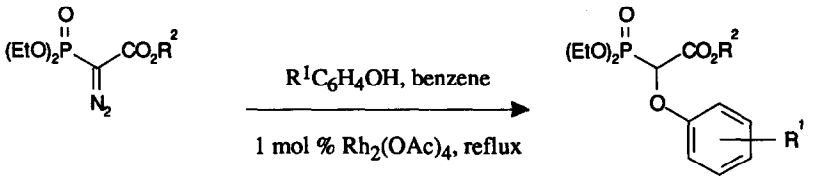
The preparation of trialkyl 2-alkoxyphosphonoacetates **8** by rhodium carbenoid mediated reactions of trialkyl 2-diazophosphonoacetates **7**[17] with alcohols is well documented in the literature.[18] It was felt that a similar process ought to be successful with phenols[19] and we describe here a facile synthesis of **5** which

comprises the first reported[20] rhodium carbenoid mediated O-H insertion reaction of phenols with trialkyl 2-diazophosphonoacetates **7** (Scheme 1, Table 1).



7 **5**

Scheme 1

Table 1. Synthesis of Alkyl 2-Aryloxy-2-diethylphosphonoacetates 5

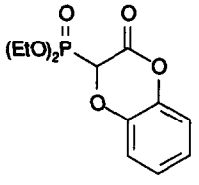
Entry	*Phenol (R^1)*	*Molar Ratio*[i]	*Ester (R^2)*	*Time (h)*	*Yield (%)*[ii]	*b.p. (°C)/mm Hg*[iii]
a	H	1:1	Et	21	66	220/0.05
b	H	2:1	Et	21	86	-
c	H	5:1	Et	21	76	-
d	4-Me	2:1	Et	16	84	225/0.08
e	4-Cl	2:1	Me	14	71	250/0.05
f	4-OMe	2:1	Et	17	69	245/0.05
g	4-OCH_2Ph	2:1	Me	14	71	iv
h	3-CF_3	2:1	Et	22	57	200/0.03[v]
i	4-COMe	2:1	Et	88	44	iv
j	4-CN	2:1	Et	21	<5[vi]	-
k	2-Me	2:1	Et	20	61	250/0.50[vii]
l	2,6-Me_2	2:1	Et	21	0	-
m	3,4-[-(CH=CH)$_2$-]	2:1	Et	24	73	iv
n	2-NO_2	2:1	Et	16	0	-
o	2-OH	2:1	Me	15	83	viii
p	2-NH_2	1:1	Et	15	0	-
q	2-NHCOMe	2:1	Et	24	<5[ix]	-

Notes:- (i) Molar ratio of substituted phenol to diazo compound **7**. (ii) Chromatographed, isolated yields. (iii) Boiling point refers to Kugelrohr distillation, figures quoted are oven temperature (°C) and vacuum pump pressure (mm Hg). (iv) This sample decomposed without distillation at 250°C/0.05mm Hg. (v) Sample crystallised after distillation, m.p. 44-46°C. (vi) See reference 21. (vii) Sample crystallised after distillation, m.p. 41-42°C. (viii) No attempt was made to distil this material, see text of paper. (ix) See reference 22.

In the first series of experiments (entries **a-c**), the ratio of phenol to diazo compound was examined. Clearly the presence of excess phenol is beneficial, though the use of five equivalents of phenol offered no

advantage over the use of two equivalents. In subsequent reactions the latter conditions [two equivalents of the substituted phenol, one equivalent of diazo compound **7**, refluxing benzene, 1% equivalent of $Rh_2(OAc)_4$] were generally adopted. A variety of substituted phenols was examined and in general the yields of adducts **5** were good to excellent (Table 1). However, the yields were dependent upon the nature and position of the substituent. In particular, whilst a moderate electron withdrawing substituent such as 4-acetyl- (entry **i**) gave a useful yield of the desired adduct after prolonged reflux, strongly electron withdrawing substituents such as 4-cyano- (entry **j**) or 2-nitro- (entry **n**) resulted in failure of the reaction. These findings are in accordance with the expected mechanism and reactivity of the highly electrophilic rhodium carbenoid.[20,23] Interestingly, although nitriles are known to react with various diazocarbonyl compounds to afford oxazoles,[24] there was no evidence for the formation of such products from the reaction of diazophosphonoacetate **7** with 4-cyanophenol.

The reaction of **7** with 2-naphthol (entry **m**) indicates that the carbenoid will tolerate a larger, bicyclic phenol. Similarly, the phenol may contain one *ortho*-methyl group (entry **k**), but substitution at both *ortho* positions as in 2,6-dimethylphenol (entry **l**) presumably causes too much steric hindrance and the reaction fails, even when conducted at higher temperature in refluxing toluene.[20]



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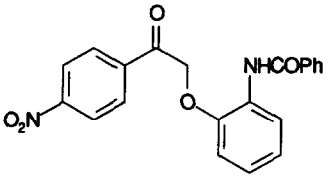

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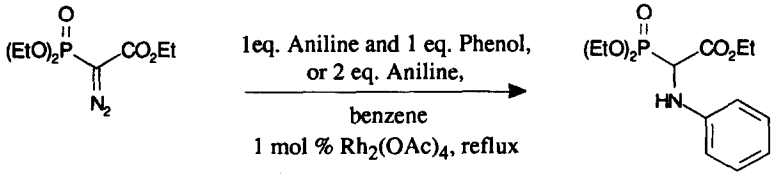
Ortho-heteroatom substituted phenols (entries **o**, **p** and **q**) presented a more confusing picture. Catechol afforded an excellent yield of the expected mono adduct **5o**, but this first-formed hydroxy-ester slowly cyclised to afford the lactone **9**. This cyclisation could be accelerated by treatment with *para*-toluenesulfonic acid in refluxing benzene.[25] Conversely, both 2-amino- and 2-(N-acetylamino)phenol failed to yield the expected adducts. The reason for the failure of these latter two reactions is not known, although it has been suggested[26] that 2-aminophenol fails to react with diazoketones under copper catalysis because it exists as an internal (zwitterionic) salt. These workers found that 2-(N-benzoylamino)phenol behaved as expected, allowing the formation of the aryl ether **10** from α-diazo-4-nitroacetophenone.[26]



7a **11**

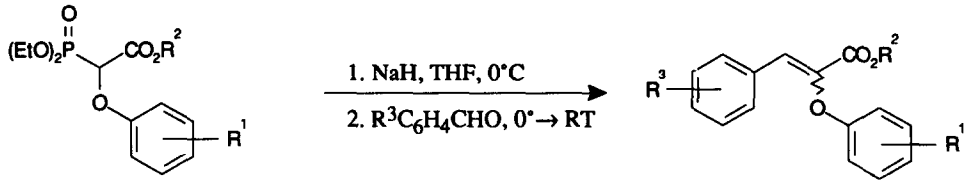
Scheme 2

Finally, and by way of comparison with the failed reaction of 2-aminophenol, a competition experiment in which a mixture of one equivalent each of phenol and aniline was reacted with **7a** (Scheme 2) led

exclusively to the formation of ethyl 2-phenylamino-2-diethylphosphonoacetate **11** in excellent yield (85%). Repetition of this experiment with two equivalents of aniline as the nucleophile rather than a mixture of aniline and phenol gave a similar result (60% yield of **11**). Although anilines are known to react with diazocarbonyl compounds[27] we believe this is the first example of an aniline reacting with **7** and the reaction merits further study. In particular, additional work would be needed to establish whether the apparent yield enhancement in the phenol containing reaction is genuine.

ii) Synthesis of 2-Aryloxy-3-phenylpropanoates

Once a synthetic route to trialkyl 2-aryloxyphosphonoacetates **5** had been established, preparation of the desired target compounds **1b** by a Wadsworth-Emmons olefination and reduction approach was examined. We report here a selection of 2-aryloxy-3-phenylpropanoates prepared in this fashion.



5 **12**

Scheme 3

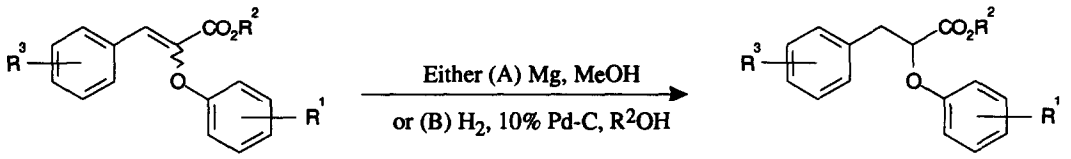
Table 2. Synthesis of 2-Aryloxy-3-phenylpropenoates 12 from Phosphonoacetates 5

Entry	*Precursor*	*R1*	*R2*	*R3*	*Yield (%)*[i]
a	**5a**	H	Et	4-OCH_2Ph	68
b	**5a**	H	Et	2-Cl	86
c	**5m**	3,4-[-$(CH{=}CH)_2$-]	Et	H	72
d	**5g**	4-OCH_2Ph	Me	H	85

Note:- (i) Chromatographed, isolated yields. The products were obtained as a 1:1 mixture of E:Z isomers except for entry **b** which was obtained as a 63:37 Z:E isomer mixture.

For these studies three of the trialkyl 2-aryloxyphosphonoacetates **5** were examined, namely the 2-phenoxy-, 2-(4-benzyloxyphenoxy)- and 2-(2-naphthyloxy)-analogues (**5a**, **5g** and **5m** respectively). Wadsworth-Emmons reaction of these compounds with various benzaldehydes proceeded smoothly at room temperature (Scheme 3, Table 2) to afford the desired olefins **12**. Interestingly, whilst Grell[9] has shown that *2-alkoxy*-phosphonoacetates react with benzaldehyde to give predominantly Z-propenoates, we found that the *2-aryloxy*-derivatives generally gave a 1:1 mixture of E:Z isomers **12**. Presumably these results imply that in the latter case the steric interactions of either the ester or the aryloxy-group with the incoming phenyl group are balanced, hence both diastereoisomeric β-oxyanion (betaine) intermediates are equally favoured.[15] One

exception to this observation was the reaction of **5a** with 2-chlorobenzaldehyde. In this case the product **12b** was isolated as a 63:37 Z:E mixture. Clearly the presence of the additional 2-chloro-substituent re-established the preference for the Z isomer, presumably as a consequence of the now increased steric clash between the chlorophenyl- and ester groups in the transition state.



12 **13**

Scheme 4

Table 3. 2-Aryloxy-3-phenylpropanoic Esters 13

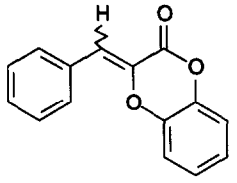
Entry	R^1	R^2	R^3	*Method* [i]	*Yield (%)* [ii]
a	H	Me	4-OCH_2Ph	A	97
b	H	Me	2-Cl	A	57
c	3,4-[-$(CH{=}CH)_2$-]	Et	H	B	74
d	4-OCH_2Ph	Me	H	A	70
e	4-OH	Me	H	B	83

Notes:- (i) (Method A), Magnesium, MeOH; (Method B), Hydrogen, 10% palladium-charcoal, R^2OH. (ii) Chromatographed, isolated yields.

Reduction of 2-aryloxy-3-phenylpropenoates **12** had not previously been reported. However, this was readily achieved in one of two ways (Scheme 4, Table 3). Catalytic hydrogenation over 10% palladium-on-charcoal smoothly reduced the double bond of the 2-naphthyloxy-analogue **12c** to the corresponding propanoate **13c**. The 2-(4-benzyloxyphenoxy)-analogue **12d** was similarly reduced, though this reduction was accompanied by hydrogenolysis of the benzyl ether to afford the free phenol **13e**. Alternatively, reduction of the double bond could also be achieved by means of an electron transfer procedure involving treatment of a methanolic solution of the propenoate **12** with magnesium metal.[28] With this reagent the regioisomeric benzyloxy-substituted propenoates **12a** and **12d** were reduced without debenzylation to afford **13a** and **13d** respectively. Similarly, the 3-(2-chlorophenyl)-analogue **12b** was reduced without loss of the chlorine substituent to afford **13b** in modest yield. In these electron transfer reductions the expected transesterification of the ethyl ester into a methyl ester was observed.

The lactone-phosphonate **9** was also examined as a substrate for the olefination and reduction sequence. This compound reacted with benzaldehyde under Wadsworth-Emmons reaction conditions to afford the expected olefin **14** in modest yield (58%) as a mixture of double bond isomers. Olefin **14** was reduced using catalytic hydrogenation to give the corresponding benzyl-substituted lactone **15** in 76% yield.

Finally, the esters **13** were further characterised by hydrolysis with aqueous methanolic sodium hydroxide solution to afford the corresponding carboxylic acids **16**. To our knowledge these acids have not been prepared previously, although the primary amide derivative of **16c** has been reported to be a chlorophyll inhibitor, useful in the manufacture of stained ornamental plants.[29]



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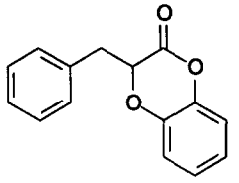

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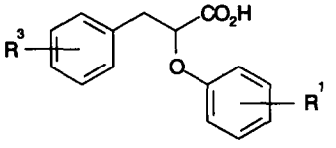

16a $R^1 = H$, $R^3 = 4\text{-}OCH_2Ph$
16b $R^1 = H$, $R^3 = 2\text{-}Cl$
16c $R^1 = 3,4\text{-}[\text{-}(CH{=}CH)_2\text{-}]$, $R^3 = H$
16d $R^1 = 4\text{-}OCH_2Ph$, $R^3 = H$
16e $R^1 = 4\text{-}OH$, $R^3 = H$

SUMMARY

A variety of phenolic compounds have been shown to react with rhodium carbenoids derived from trialkyl 2-diazophosphonoacetates **7** to afford trialkyl 2-aryloxyphosphonoacetates **5** by an O-H insertion reaction. Many phenols gave good to excellent yields, though phenols bearing strongly electron withdrawing groups, bulky *ortho*-substituents, or nitrogenous *ortho*-substituents gave variable or poor results. The reaction of **7** with 2-naphthol suggests that the method may be similarly applicable to polyaromatic phenols. A lactone **9** was the ultimate product derived from the reaction of **7** with catechol. Aniline has been shown to insert preferentially and exclusively over phenol in a competitive insertion reaction with **7a** to afford ethyl 2-phenylamino-2-diethylphosphonoacetate **11**.

The 2-aryloxyphosphonoacetates **5** were shown to be useful precursors in a convenient preparation of 2-aryloxy-3-phenylpropenoates **12** by Wadsworth-Emmons reaction with benzaldehydes. These propenoates were easily reduced, either by catalytic hydrogenation or by means of dissolving magnesium metal in methanol, to afford the corresponding 2-aryloxy-3-phenylpropanoates **13**. Lactone **9** undergoes a similar sequence, and illustrates the versatility of this route in providing a rapid entry into a variety of substituted analogues of **13**. Our results on the biological evaluation of a series of more highly functionalised analogues of **13**, prepared in this manner, will be presented in due course.

EXPERIMENTAL SECTION

General Experimental Details

Melting points were recorded on a Büchi 535 capillary melting point apparatus and are uncorrected. Elemental analyses were performed on a Leeman CEC 440 elemental analyser and all values are within ± 0.4%

of calculated values. Mass spectroscopy was conducted on a Jeol SX 102 mass spectrometer using electron impact (EI), chemical ionisation (CI) with ammonia as the carrier gas, or fast atom bombardment (FAB) in a 3-nitrobenzyl alcohol-sodium acetate (NOBA/Na) matrix. Compounds characterised by high resolution mass measurement were homogeneous by TLC. ^{1}H and ^{13}C NMR spectra were recorded on a Jeol GX 270 NMR spectrometer operating at 270.05 MHz or 67.8 MHz respectively. Spectra were recorded in $CDCl_3$ or DMSO-d_6 solution. Chemical shifts are given in δ (ppm) relative to TMS as internal standard and coupling constants, *J*, are in Hz. IR spectra were recorded on a Perkin-Elmer 298 infra red spectrophotometer. For Kugelrohr distillations a Buchi GKR-51 Kugelrohr oven was employed. Benzene was dried over sodium wire before use. Dry THF was purchased from the Aldrich Chemical Company and used as received. All other reagents and solvents were used without purification.

Ethyl 2-diazo-2-diethylphosphonoacetate **7a** was prepared according to the published procedure[18] and methyl 2-diazo-2-diethylphosphonoacetate **7b** was prepared similarly from methyl 2-diethylphosphonoacetate.

Typical Procedure for the Reaction of Trialkyl 2-Diazophosphonoacetates 7 With Phenols:- Ethyl 2-Phenoxy-2-diethylphosphonoacetate 5a

A mixture of ethyl 2-diazo-2-diethylphosphonoacetate **7a** (2.00 g, 8 mmol), phenol (1.50 g, 16 mmol), rhodium (II) acetate (36 mg, 8 x 10^{-5} mol, 1 mol%) and dry benzene (100 mL) was heated at reflux under a nitrogen atmosphere for 21 h, cooled and concentrated *in vacuo*. The residue was chromatographed on silica gel using ethyl acetate-diethyl ether (1:4 v/v) as eluent to afford the title compound **5a** (2.16 g, 86%) as an oil. Kugelrohr distillation afforded an analytical sample, b.p. 220°C at 0.05 mm Hg. [Found C, 53.05; H, 6.8%; MH^+ (CI) 317.1155. $C_{14}H_{21}O_6P$ requires C, 53.2; H, 6.7%; MH^+ 317.1154]; ν_{max} (film)/cm^{-1} 1751 (CO) and 1265 [$PO(OEt)_2$]; δ_H ($CDCl_3$) 1.28 (3H, t, *J* 7.2, OCH_2CH_3), 1.37 (6H, m, 2 x OCH_2CH_3), 4.30 (6H, m, 3 x OCH_2CH_3), 5.03 (1H, d, *J* 19, POC*H*), 6.93 [2H, m, aromatic *H(2)* and *H(6)*], 7.02 [1H, m, aromatic *H(4)*] and 7.29 [2H, m, aromatic *H(3)* and *H(5)*]; δ_C ($CDCl_3$) 14.1 ($CO_2CH_2CH_3$), 16.4, 16.5 [$PO(OCH_2CH_3)_2$], 62.3 ($CO_2CH_2CH_3$), 64.1 [1C, d, *J* 5.2, $PO(OCH_2CH_3)$], 64.2 [1C, d, *J* 7.2, $PO(OCH_2CH_3)$], 74.5 (1C, d, *J* 157.8, POCH), 115.1 [2C, s, aromatic *C(2)* and *C(6)*], 122.6 [aromatic *C(4)*], 129.7 [2C, s, aromatic *C(3)* and *C(5)*], 157.7 [1C, d, *J* 13.5, aromatic *C(1)*] and 166.5 (*C*O); *m/z* (CI) 317 (MH^+, 100%), 316 (86), 243 (46), 121 (33) and 105 (57).

Ethyl 2-(4-Methylphenoxy)-2-diethylphosphonoacetate 5d

The title compound **5d** was obtained as an oil (84%), b.p. 225°C at 0.08 mm Hg. [Found, C, 54.1; H, 7.2%; M^+ (EI) 330.1229. $C_{15}H_{23}O_6P$ requires C, 54.5; H, 7.0%; M^+ 330.1232]; ν_{max} (film)/cm^{-1} 1755 (CO) and 1270 [$PO(OEt)_2$]; δ_H ($CDCl_3$) 1.28 (3H, t, *J* 7.2, OCH_2CH_3), 1.37 (6H, m, 2 x OCH_2CH_3), 2.28 (3H, s, CH_3), 4.29 (6H, m, 3 x OCH_2CH_3), 5.00 (1H, d, *J* 18.9, POC*H*), 6.82 [2H, m, aromatic *H(2)* and *H(6)*] and 7.07 [2H, m, aromatic *H(3) and H(5)*]; δ_C ($CDCl_3$) 14.1 ($CO_2CH_2CH_3$), 16.3, 16.4 [$PO(OCH_2CH_3)_2$], 20.5 ($ArCH_3$) 62.2 ($CO_2CH_2CH_3$), 64.1 [1C, d, *J* 5.2, $PO(OCH_2CH_3)$], 64.2 [1C, d, *J* 6.2, $PO(OCH_2CH_3)$], 74.8 (1C, d, *J* 157.8, POCH), 115.0 [2C, s, aromatic *C(2)* and *C(6)*], 130.1 [2C, s, aromatic *C(3)* and *C(5)*], 131.9 [aromatic *C(4)*], 155.7 [1C, d, *J* 13.5, aromatic *C(1)*] and 166.6 (*C*O); *m/z* (CI) 348 (MNH_4^+, 100%), 331 (MH^+, 70), 286 (19), 250 (57), 241 (78) and 210 (52).

Methyl 2-(4-Chlorophenoxy)-2-diethylphosphonoacetate **5e**

Methyl 2-diazo-2-diethylphosphonoacetate **7b** and 4-chlorophenol were reacted together by the procedure described above to afford the title compound **5e**, an oil (71%), b.p. 250°C at 0.05 mm Hg. [Found C, 46.15; H, 5.5%; MH^+ (CI) 337.0606. $C_{13}H_{18}ClO_6P$ requires C, 46.4; H, 5.4%; MH^+ 337.0608]; ν_{max} (film)/cm^{-1} 1755 (CO) and 1265 [$PO(OEt)_2$]; δ_H ($CDCl_3$) 1.37 (6H, t, *J* 6.9, 2 x OCH_2CH_3), 3.83 (3H, s, OCH_3), 4.29 (4H, m, 2 x OCH_2CH_3), 5.00 (1H, d, *J* 19, POC*H*), 6.87 [2H, m, aromatic *H(2)* and *H(6)*] and 7.25 [2H, m, aromatic *H(3)* and *H(5)*]; δ_C ($CDCl_3$) 16.3, 16.4 [$PO(OCH_2CH_3)_2$], 53.1 (OCH_3), 64.2, 64.3 [$PO(OCH_2CH_3)_2$], 74.7 (1C, d, *J* 157.8, POCH), 116.5 [2C, s, aromatic *C(2)* and *C(6)*], 127.7 [aromatic *C(4)*], 129.6 [2C, s, aromatic *C(3)* and *C(5)*], 156.2 [1C, d, *J* 13.5, aromatic *C(1)*] and 166.7 (CO); *m/z* (FAB, NOBA/Na) 337 (MH^+).

Ethyl 2-(4-Methoxyphenoxy)-2-diethylphosphonoacetate **5f**

The title compound **5f** was obtained as an oil (69%), b.p. 245°C at 0.05 mm Hg. [Found M^+ (EI) 346.1178. $C_{15}H_{23}O_7P$ requires M^+ 346.1181]; ν_{max} (film)/cm^{-1} 1755 (CO) and 1270 [$PO(OEt)_2$]; δ_H ($CDCl_3$) 1.29 (3H, t, *J* 7.1, OCH_2CH_3), 1.37 (6H, m, 2 x OCH_2CH_3), 3.76 (3H, s, OCH_3), 4.29 (6H, m, 3 x OCH_2CH_3), 4.93 (1H, d, *J* 18.9, POC*H*), 6.81 (2H, m, Ar*H*) and 6.89 (2H, m, Ar*H*); δ_C ($CDCl_3$) 14.0 ($CO_2CH_2CH_3$), 16.3, 16.4 [$PO(OCH_2CH_3)_2$], 55.6 ($ArOCH_3$), 62.1 ($CO_2CH_2CH_3$), 64.0, 64.1 [$PO(OCH_2CH_3)_2$], 75.7 (1C, d, *J* 157.8, POCH), 114.6 (2C, s, aromatic carbon atoms), 116.6 (2C, s, aromatic carbon atoms), 151.9 [1C, d, *J* 13.5, aromatic *C(1)*], 155.1 [aromatic *C(4)*] and 166.7 (CO); *m/z* (CI) 354 (MNH_4^+, 100%) and 347 (MH^+, 84).

Methyl 2-(4-Benzyloxyphenoxy)-2-diethylphosphonoacetate **5g**

Methyl 2-diazo-2-diethylphosphonoacetate **7b** and 4-benzyloxyphenol were reacted together by the procedure described above to afford the title compound **5g**, a gum (71%). [Found M^+ (EI) 408.1336. $C_{20}H_{25}O_7P$ requires M^+ 408.1338]; ν_{max} (film)/cm^{-1} 1756 (CO) and 1265 [$PO(OEt)_2$]; δ_H ($CDCl_3$) 1.36 (6H, m, 2 x OCH_2CH_3), 3.82 (3H, s, OCH_3), 4.29 (4H, m, 2 x OCH_2CH_3), 4.96 (1H, d, *J* 20.3, POC*H*), 5.00 (2H, s, OCH_2Ph), 6.88 (4H, s, $-OC_6H_4O-$) and 7.40 (5H, m, OC_6H_5); *m/z* (CI) 426 (MNH_4^+, 100%), 4.09 (MH^+, 52) and 348 (11). Attempts to distil this material led only to decomposition of the sample.

Ethyl 2-[3-(Trifluoromethyl)phenoxy]-2-diethylphosphonoacetate **5h**

The title compound **5h** (57%) was purified by chromatography on silica gel using ethyl acetate-diethyl ether (3:17 v/v) as eluent, followed by Kugelrohr distillation, b.p. 200°C at 0.03 mm Hg. The resulting oil subsequently crystallised to afford a white solid, m.p. 44-46°C. [Found C, 46.9; H, 5.4%; M^+ (EI) 384.0951. $C_{15}H_{20}F_3O_6P$ requires C, 46.9; H, 5.25%; M^+ 384.0950]; ν_{max} (film)/cm^{-1} 1750 (CO) and 1265 [$PO(OEt)_2$]; δ_H ($CDCl_3$) 1.29 (3H, t, *J* 7.2, OCH_2CH_3), 1.38 (6H, t, *J* 7.1, 2 x OCH_2CH_3), 4.30 (6H, m, 3 x OCH_2CH_3), 5.05 (1H, d, *J* 18.7, POC*H*), 7.10 (1H, m, Ar*H*), 7.17 (1H, m, Ar*H*), 7.35 (1H, m, Ar*H*) and 7.42 (1H, m, Ar*H*); δ_C ($CDCl_3$) 14.0 ($CO_2CH_2CH_3$), 16.4, 16.5 [$PO(OCH_2CH_3)_2$], 62.5 ($CO_2CH_2CH_3$), 64.2, 64.3 [$PO(OCH_2CH_3)_2$], 74.5 (1C, d, J 158.8, POCH), 112.4 [1C, q, $^3J_{C,F}$ 3.8, aromatic *C(2)*], 118.3 [aromatic *C(6)*], 119.3 [1C, q, $^3J_{C,F}$ 3.8, aromatic *C(4)*], 123.6 (1C, q, $^1J_{C,F}$ 273, $ArCF_3$), 130.3 [aromatic *C(5)*], 132.0 [1C, q, $^2J_{C,F}$ 32.2, aromatic *C(3)*], 157.7 [1C, d, $^3J_{C,P}$ 13.5, aromatic *C(1)*] and 165.9 (CO); *m/z* (CI) 402 (MNH_4^+, 100%) and 385 (MH^+, 50).

Ethyl 2-(4-Acetylphenoxy)-2-diethylphosphonoacetate **5i**

The title compound **5i**, a gum, was obtained in 44% yield after prolonged reaction (88 h) and purification in the usual manner. [Found M^+ (EI) 358.1183. $C_{16}H_{23}O_7P$ requires M^+ 358.1181]; ν_{max} (film)/cm^{-1} 1748 (CO_2Et), 1678 (COMe) and 1265 [$PO(OEt)_2$]; δ_H ($CDCl_3$) 1.35 (9H, m, 3 x OCH_2CH_3), 2.56 (3H, s, $COCH_3$), 4.29 (6H, m, 3 x OCH_2CH_3), 5.11 (1H, d, *J* 18.7, POC*H*), 6.96 [2H, d, *J* 8.8, aromatic *H(2)* and *H(6)*] and 7.94 [2H, d, *J* 8.8, aromatic *H(3)* and *H(5)*]; *m/z* (EI) 358 (M^+, 100%), 343 (87), 285 (48), 155 (25) and 121 (56). An attempt to distil this material led to decomposition of the sample.

Ethyl 2-(2-Methylphenoxy)-2-diethylphosphonoacetate **5k**

The title compound **5k**, (61%), was purified by chromatography on silica gel using ethyl acetate-diethyl ether (3:17 v/v), followed by Kugelrohr distillation, b.p. 250°C at 0.5 mm Hg. The resulting oil subsequently crystallised to afford a white solid, m.p. 41-2°C. [Found C, 54.15; H, 6.65%; M^+ (EI) 330.1229. $C_{15}H_{23}O_6P$ requires C, 54.5; H, 7.0%; M^+ 330.1232]; ν_{max} (film)/cm^{-1} 1750 (CO) and 1265 [$PO(OEt)_2$]; δ_H ($CDCl_3$) 1.28 (3H, t, *J* 7.2, OCH_2CH_3), 1.38 (6H, m, 2 x OCH_2CH_3), 2.33 (3H, s, $ArCH_3$), 4.30 (6H, m, 3 x OCH_2CH_3), 5.04 (1H, d, *J* 18.7, POC*H*), 6.69 [1H, d, *J* 8, aromatic *H(6)*], 6.92 [1H, m, aromatic *H(4)*] and 7.14 (2H, m, aromatic *H(3)* and *H(5)*]; δ_C ($CDCl_3$) 14.4 ($CO_2CH_2CH_3$), 16.7, 16.8 [$PO(OCH_2CH_3)_2$], 62.6 ($CO_2CH_2CH_3$), 64.4, 64.5 [$PO(OCH_2CH_3)_2$], 75.0 (1C, d, *J* 157.8, POCH), 111.8 [aromatic *C(6)*], 122.6 [aromatic *C(4)*], 127.2 [aromatic *C(5)*], 128.0 [aromatic *C(2)*], 131.6 [aromatic *C(3)*], 156.3 [1C, d, *J* 13.5, aromatic *C(1)*] and 167.0 (*CO*); *m/z* (CI) 348 (MNH_4^+, 66%), 331 (MH^+, 100) and 225 (19).

Ethyl 2-Naphthyloxy-2-diethylphosphonoacetate **5m**

The title compound **5m**, a gum (73%), was purified by chromatography on silica gel using ethyl acetate-diethyl ether (3:17 v/v) as eluent. [Found C, 59.0; H, 6.4%; M^+ (EI) 366.1228. $C_{18}H_{23}O_6P$ requires C, 59.0; H, 6.3%; M^+ 366.1232]; ν_{max} (film)/cm^{-1} 1752 (CO) and 1263 [$PO(OEt)_2$]; δ_H ($CDCl_3$) 1.28 (3H, t, *J* 7.1, OCH_2CH_3), 1.39 (6H, t, *J* 7.1, 2 x OCH_2CH_3), 4.33 (6H, m, 3 x OCH_2CH_3), 5.19 (1H, d, *J* 18.7, POC*H*), 7.09 [1H, d, *J* 2.5, Aromatic *H(1)*], 7.25 [1H, dd, J 9.1 and 2.5, aromatic *H(3)*], 7.40 (2H, m, Ar*H*) and 7.73 (3H, m, Ar*H*); δ_C ($CDCl_3$)[30] 14.0 ($CO_2CH_2CH_3$), 16.3, 16.4 [$PO(OCH_2CH_3)_2$], 62.3 ($CO_2CH_2CH_3$), 64.1, 64.2 [$PO(OCH_2CH_3)_2$], 74.5 (1C, d, *J* 157.8, POCH), 107.8 [aromatic *C(1)*][30], 118.4 [aromatic *C(3)*], 124.4 [aromatic *C(6)*], 126.6 [aromatic *C(7)*], 127.0 [aromatic *C(8)*], 127.6 [aromatic *C(5)*], 129.7 [aromatic *C(4a)*], 129.9 [aromatic *C(4)*], 134.0 [aromatic *C(8a)*], 155.5 [1C, d, *J* 13.5, aromatic *C(2)*] and 166.4 (*CO*); *m/z* (CI) 384 (MNH_4^+, 68%), 367 (MH^+, 100), 242 (12), 225 (32), 179 (14), 153 (15), 145 (23), 144 (72) and 115 (20). An attempt to distil this material led only to decomposition of the sample.

Methyl 2-(2-Hydroxyphenoxy)-2-diethylphosphonoacetate **5o**

The title compound **5o**, an oil (83%), was purified by chromatography on silica gel using ethyl acetate-ether (1:4 v/v) as eluent. [Found M^+ (EI) 318.0865. $C_{13}H_{19}O_7P$ requires M^+ 318.0869]; ν_{max} (film)/cm^{-1} 3210 (OH), 1750 (CO) and 1245 [$PO(OEt)_2$]; δ_H ($CDCl_3$) 1.38 (6H, m, 2 x OCH_2CH_3), 3.87 (3H, s, CO_2CH_3), 4.33 (4H, m, 2 x OCH_2CH_3), 4.77 (1H, d, *J* 19, POC*H*), 6.79 (1H, m, Ar*H*), 6.95-7.15 (3H, m, Ar*H*) and 7.77 (1H, br, exchanges with D_2O, O*H*); *m/z* (FAB, NOBA/Na) 341 (MNa^+), 319 (MH^+), 210 and 121. This compound slowly cyclised to lactone **9**.

Diethyl 3-Oxobenzo-1,4-dioxan-2-phosphonate **9**

A solution of hydroxy-ester **5o** (1.93 g, 6 mmol) and *p*-toluenesulfonic acid monohydrate (1.14 g, 6 mmol) in benzene (200 mL) was heated at reflux, with azeotropic removal of water, for 15 h then cooled and evaporated. The residue was dissolved in dichloromethane (200 mL), washed with saturated sodium bicarbonate solution, dried ($MgSO_4$) and evaporated. The resulting oil was chromatographed on silica gel using ethyl acetate-diethyl ether (1:3 v/v) as eluent to afford the title compound **9** (1.24 g, 72%) as an oil. [Found C, 50.3; H, 5.7%; M^+ (EI) 286.0605. $C_{12}H_{15}O_6P$ requires C, 50.4; H, 5.3%; M^+ 286.0607]; ν_{max} (film)/cm^{-1} 1775 (CO) and 1260 [PO(OEt)$_2$]; δ_H ($CDCl_3$) 1.20 (3H, t, *J* 7, OCH_2CH_3), 1.32 (3H, t, *J* 7, OCH_2CH_3), 4.00-4.40 (4H, m, 2 x OCH_2CH_3), 5.15 (1H, d, *J* 17.3, POC*H*) and 7.09 (4H, m, Ar*H*); δ_C ($CDCl_3$) 16.2 (1C, d, *J* 5.2, OCH_2CH_3), 16.3 (1C, d, *J* 6.2, OCH_2CH_3), 64.1 (1C, d, *J* 6.2, OCH_2CH_3), 64.4 (1C, d, *J* 6.2, OCH_2CH_3), 72.0 (1C, d, *J* 152.6, POCH), 117.2 (2C, s, aromatic CH), 123.6 (aromatic CH), 125.7 (aromatic CH), 140.6 (aromatic quaternary carbon atom), 140.8 (aromatic quaternary carbon atom) and 160.1 (1C, d, *J* 3.1, CO); *m/z* (CI) 304 (MNH_4^+, 100%), 287 (MH^+, 62) and 121 (7).

Competitive Carbenoid Insertion Reaction:- Ethyl 2-Phenylamino-2-diethylphosphonoacetate **11**

A mixture of ethyl 2-diazo-2-diethylphosphonoacetate **7a** (1.25 g, 5 mmol), aniline (0.46 mL, 5 mmol), phenol (0.47 g, 5 mmol), rhodium (II) acetate (22 mg, 5 x 10^{-5} mol) and dry benzene (65 mL) was heated at reflux under an argon atmosphere for 24 h, cooled and concentrated *in vacuo*. The residue was chromatographed on silica gel using ethyl acetate-diethyl ether (1:9 v/v) as eluent to afford the title compound **11** (1.34 g, 85%), m.p. 55-56°C. [Found C, 53.3; H, 7.05; N, 4.6%; M^+ (EI) 315.1238. $C_{14}H_{22}NO_5P$ requires C, 53.3; H, 7.0; N, 4.4%, M^+ 315.1236]; ν_{max} (KBr)/cm^{-1} 3300 (NH), 1745 (CO) and 1240 [PO(OEt)$_2$]; δ_H ($CDCl_3$) 1.25-1.40 (9H, m, 3 x OCH_2CH_3), 4.15-4.30 (6H, m, 3 x OCH_2CH_3), 4.52 [1H, dd, $^3J_{H,NH}$ 9.3 (disappears on shaking the sample with D_2O), $^2J_{H,P}$ 23.1, POC*H*], 4.56 (1H, br, exchanges with D_2O, N*H*), 6.68 [2H, d, *J* 7.5, aromatic *H(2)* and *H(6)*], 6.77 [1H, t, *J* 7.6, aromatic *H(4)*] and 7.19 [2H, dd, *J* 7.5 and 7.6, aromatic *H(3)* and *H(5)*]; δ_C ($CDCl_3$) 14.1 ($CO_2CH_2CH_3$), 16.3 [1C, d, *J* 5.5, P(OCH_2CH_3)], 16.4 [1C, d, *J* 5.4, P(OCH_2CH_3)], 56.5 (1C, d, *J* 148.5, POCH), 62.2 ($CO_2CH_2CH_3$), 63.6 [1C, d, *J* 7.0, P(OCH_2CH_3)], 64.0 [1C, d, *J* 6.64, P(OCH_2CH_3)], 114.0 [2C, s, aromatic *C(2)* and *C(6)*], 119.4 [aromatic *C(4)*], 129.3 [2C, s, aromatic *C(3)* and *C(5)*], 146.2 [1C, d, $^3J_{C,P}$ 11.2, aromatic *C(1)*] and 168.4 (CO); *m/z* (EI) 315 (M^+, 53%), 242 (74), 214 (8), 178 (100), 150 (10), 139 (22), 121 (14), 111 (31) and 104 (99).

Typical Procedure for the Wadsworth-Emmons Condensation of **5** *With Benzaldehydes:- Ethyl 3-(4-Benzyloxyphenyl)-2-phenoxypropenoate* **12a**

A solution of ethyl 2-phenoxy-2-diethylphosphonoacetate **5a** (1.00 g, 3.2 mmol) in dry THF (20 mL) was added slowly to a stirred, ice-cooled suspension of sodium hydride (60% dispersion in mineral oil, 0.14 g, 3.5 mmol) in dry THF (5 mL) under an atmosphere of argon. Stirring was continued at 0°C for 45 min prior to the addition of a solution of 4-benzyloxybenzaldehyde (0.68 g, 3.2 mmol) in dry THF (20 mL). The mixture was stirred and allowed to warm to room temperature over 17 h before being concentrated *in vacuo*, diluted with water (300 mL) and extracted with ethyl acetate (2 x 250 mL). The combined ethyl acetate solutions were washed with water (2 x 400 mL) and brine (400 mL), dried ($MgSO_4$) and evaporated. The crude product was chromatographed on silica gel using hexane-dichloromethane (3:7 v/v) as eluent to afford the title compound **12a** as a wax (0.81 g, 68%), a 1:1 mixture of double bond isomers by ^{1}H NMR

spectroscopy. [Found C, 77.0; H, 5.9%; M^+ (EI) 374.1508. $C_{24}H_{22}O_4$ requires C, 77.0; H, 5.9%; M^+ 374.1518] ν_{max} (film)/cm^{-1} 1725 (CO) and 1640 (C=C); δ_H ($CDCl_3$) Geometric isomerism causes doubling of most peaks, 1.05, 1.18 (combined, 3H, t, *J* 7.1, isomers of OCH_2CH_3), 4.12, 4.18 (combined, 2H, q, *J* 7.1, isomers of OCH_2CH_3), 5.05, 5.08 (combined, 2H, s, OCH_2Ph), 6.73 (0.5H, s, E-olefinic *H*) and 6.80-7.70 (14.5H, m, Z-olefinic *H* and Ar*H*). *m/z* (CI) 392 (MNH_4^+, 100%) and 375 (MH^+, 50).

Ethyl 3-(2-Chlorophenyl)-2-phenoxypropenoate ***12b***

Ethyl 2-phenoxy-2-diethylphosphonoacetate **5a** was reacted with 2-chlorobenzaldehyde in a manner similar to that described above. ^{1}H NMR analysis of the crude reaction mixture containing product **12b** indicated a Z:E isomer ratio of 63:37. The crude product was chromatographed on silica gel using hexane-dichloromethane (3:2 v/v) as eluent to afford the individual isomers:-

Z-isomer ***(Z-12b)***: An oil (55%). [Found M^+ (EI) 302.071. $C_{17}H_{15}ClO_3$ requires M^+ 302.071]; ν_{max} (film)/cm^{-1} 1727 (CO) and 1641 (C=C); δ_H ($CDCl_3$) 1.19 (3H, t, *J* 7.1, OCH_2CH_3), 4.22 (2H, q, *J* 7.1, OCH_2CH_3), 6.90-7.50 (8H, m, Ar*H*), 7.74 (1H, s, olefinic *H*) and 7.96 (1H, m, Ar*H*); δ_C ($CDCl_3$) 14.0 (OCH_2CH_3), 61.6 (OCH_2CH_3), 115.6 [2C, s, phenoxy *C(2)* and *C(6)*], 122.1 [phenoxy *C(4)*], 122.8 (*C*H), 126.9 (*C*H), 129.6 [3C, br s, phenoxy *C(3), C(5)* and chlorophenyl *(CH)*], 130.2 (*C*H), 130.6 [chlorophenyl *C(1)*], 130.8 (*C*H), 134.6 [chlorophenyl *C(2)*], 141.5 (olefinic *C*OPh), 156.5 [phenoxy *C(1)*] and 163.4 (*C*O); *m/z* (FAB, NOBA-Na) 325 (MNa^+), 303 (MH^+), 267 (MH^+–*HCl*) and 257 (MH^+–*EtOH*).

E-isomer ***(E-12b)***: An oil (31%). [Found M^+ (EI) 302.0709. $C_{17}H_{15}ClO_3$ requires M^+ 302.071]; ν_{max} (film)/cm^{-1} 1730 (CO) and 1641 (C=C); δ_H ($CDCl_3$) 0.97 (3H, t, *J* 7.1, OCH_2CH_3), 4.04 (2H, q, *J* 7.1, OCH_2CH_3), 6.74 (1H, s, olefinic *H*) and 7.05-7.40 (9H, m, Ar*H*); δ_C ($CDCl_3$) 13.5 (OCH_2CH_3), 61.3 (OCH_2CH_3), 117.6 [2C, s, phenoxy *C(2)* and *C(6)*], 121.6 [phenoxy *C(4)*], 123.5 (*C*H), 126.2 (*C*H), 129.1 [2C, br s, 2 x chlorophenyl *(CH)*], 129.7 [2C, s, phenoxy *C(3)* and *C(5)*], 130.5 (*C*H), 132.7 [chlorophenyl *C(1)*], 133.4 [chlorophenyl *C(2)*], 144.6 (olefinic *C*OPh), 156.4 [phenoxy *C(1)*] and 162.7 (*C*O); *m/z* (FAB, NOBA-Na) 325 (MNa^+), 303 (MH^+), 267 (MH^+–*HCl*) and 257 (MH^+–*EtOH*).

Ethyl 2-(2-Naphthyloxy)-3-phenylpropenoate ***12c***

Ethyl 2-naphthyloxy-2-diethylphosphonoacetate **5m** was reacted with benzaldehyde in a manner similar to that described above. The crude product was purified by chromatography on silica gel using hexane-dichloromethane (1:3 v/v) to afford the title compound **12c** as a gum (72%), a 1:1 mixture of double bond isomers by ^{1}H NMR spectroscopy. [Found M^+ (EI) 318.1263. $C_{21}H_{18}O_3$ requires M^+ 318.1256]; ν_{max} (film)/cm^{-1} 1725 (CO) and 1625 (C=C); δ_H ($CDCl_3$) Geometric isomerism causes doubling of most peaks, 1.01, 1.16 (combined, 3H, t, *J* 7.1, isomers of OCH_2CH_3), 4.05-4.22 (combined, 2H, q, *J* 7.1, isomers of OCH_2CH_3), 6.82 (0.5H, s, E-olefinic *H*) and 7.20-7.90 (12.5H, s, Z-olefinic *H* and Ar*H*); *m/z* (CI) 336 (MH_4^+, 100%), 319 (MH^+), 318 (16), 194 (42) and 177 (29).

Methyl 2-(4-Benzyloxyphenoxy)-3-phenylpropenoate ***12d***

Methyl 2-(4-benzyloxyphenoxy)-2-diethylphosphonoacetate **5g** was reacted with benzaldehyde in a manner similar to that described above. The crude product was purified by chromatography on silica gel using hexane-dichloromethane (1:4 v/v) as eluent to afford the title compound **12d** as an oil (85%), a 1:1 mixture of double bond isomers by ^{1}H NMR spectroscopy. [Found M^+ (EI) 360.1362. $C_{23}H_{20}O_4$ requires M^+

360.1362]; ν_{max} (film)/cm^{-1} 1727 (CO) and 1640 (C=C); δ_H ($CDCl_3$) Geometric isomerism causes doubling of most peaks, 3.63 and 3.70 (combined, 3H, s, isomers of OCH_3), 4.95 and 4.99 (combined, 2H, s, isomers of OCH_2Ph), 6.52 (0.5H, s, E-olefinic *H*) and 6.95-7.85 (14.5H, m, Z-olefinic *H* and Ar*H*); *m/z* (CI) 378 (MNH_4^+, 100%), 348 (44), 331 (23) and 260 (12).

Typical Procedure for Reduction of Propenoates **12** *(Method A):- Methyl 3-(4-Benzyloxyphenyl)-2-phenoxypropanoate* **13a**

Magnesium turnings (0.50 g, 21 mmol) was added to a stirred solution of **12a** (0.77 g, 2 mmol) and iodine (*ca* 20 mg) in methanol (50 mL) at room temperature. Stirring was continued at room temperature until evolution of hydrogen commenced and then a futher portion of magnesium (2.00 g, 83 mmol) was added. The reaction flask was fitted with a reflux condenser, immersed in a cold water bath and left to stir for 20 h, by which time all the magnesium had dissolved. The reaction mixture was concentrated *in vacuo*, the residue diluted with water (300 mL) and stirred vigorously during the addition of sufficient concentrated hydrochloric acid to give a final pH value of pH 2 *when all the solid had dissolved.* The mixture was extracted with ethyl acetate (2 x 200 mL), the combined ethyl acetate solutions were washed with water (400 mL) and brine (400 mL), dried ($MgSO_4$) and evaporated to afford the title compound **13a**, a gum, (0.70 g, 97%) which was used in the next stage without purification. [Found C, 75.9; H, 6.0%; M^+ (EI) 362.1514. $C_{23}H_{22}O_4$ requires C, 76.2; H, 6.1%; M^+ 362.1518]; ν_{max} (film)/cm^{-1} 1750 (CO); δ_H ($CDCl_3$) 3.16 (2H, m, $ArCH_2CH$), 3.69 (3H, s, OCH_3), 4.77 (1H, dd, *J* 5.5 and 7.4, $ArCH_2CH$), 5.03 (2H, s, OCH_2Ph) and 6.80-7.40 (14H, m, Ar*H*); δ_C ($CDCl_3$) 38.3 ($ArCH_2CH$), 52.3 (OCH_3), 69.9 (OCH_2Ph), 77.9 ($ArCH_2CH$), 114.8 (2C, s, aromatic *C*H), 115.2 (2C, s, aromatic *C*H), 121.7 [2-phenoxy *C(4)*], 127.5 (2C, s, aromatic *C*H), 127.9 [benzyloxy-group, aromatic *C(4)*], 128.5 (2C, s, aromatic *C*H), 129.5 (2C, s, aromatic *C*H), 130.5 (2C, s, aromatic *C*H), 130.6 [3-aryl *C(1)*], 137.0 [benzyloxy-group, aromatic *C(1)*], 157.7 (aromatic *C*-O), 157.8 (aromatic *C*-O), and 171.8 (*C*O); *m/z* (CI) 380 (MNH_4^+, 100%), 362 (MH^+, 4), 288 (34) and 269 (7).

Methyl 3-(2-Chlorophenyl)-2-phenoxypropanoate **13b**

The propenoate **12b** was reduced by Method A (above), followed by chromatography on silica gel using ethyl acetate-hexane (1:3 v/v) as eluent to afford the title compound **13b** as an oil (57%). [Found M^+ (EI) 290.0709. $C_{16}H_{15}ClO_3$ requires M^+ 290.071]; ν_{max} (film)/cm^{-1} 1750 (CO); δ_H ($CDCl_3$) 3.34 (1H, dd, *J* 13.8 and 8.3, $ArCH_aHCH$), 3.42 (1H, dd, *J* 13.8 and 5.2, $ArCHH_bCH$), 3.72 (3H, s, OCH_3), 4.92 (1H, dd, *J* 8.3 and 5.2, $ArCH_2CH$), 6.81 [2H, d, *J* 8.8, phenoxy *H(2)* and *H(6)*], 6.94 (1H, m, Ar*H*) and 7.15-7.40 (6H, m, Ar*H*); δ_C ($CDCl_3$) 36.9 ($ArCH_2CH$), 52.3 (OCH_3), 76.0 ($ArCH_2CH$), 115.3 [2C, s, phenoxy *C(2)* and *C(6)*], 121.8 [phenoxy *C(4)*], 126.8 [chlorophenyl *C(6)*], 128.5 [2C, s, chlorophenyl *C(4)* and *C(5)*], 129.5 [2C, s, phenoxy *C(3)* and *C(5)*], 132.0 [chlorophenyl *C(3)*], 133.9 [chlorophenyl *C(2)*], 134.2 [chlorophenyl *C(1)*], 157.7 [phenoxy *C(1)*] and 171.5 (*C*O); *m/z* (CI) 308 (MNH_4^+, 100%), 290 (MH^+, 4) and 216 (27).

Typical Procedure for Reduction of Propenoates **12** *(Method B):- Ethyl 2-(2-Naphthyloxy)-3-phenylpropanoate* **13c**

A solution of propenoate **12c** (0.30 g, 0.94 mmol) in ethanol (50 mL) was hydrogenated over 10% palladium on charcoal (0.09 g) at 30 psi in a Parr hydrogenation apparatus for 20 h. The catalyst was filtered off, the solvent evaporated and the residue chromatographed on silica gel using hexane-

dichloromethane (3:7 v/v) as eluent to afford the title compound **13c** as an oil, (0.22 g, 74%). [Found M^+ (EI) 320.1411. $C_{21}H_{20}O_3$ requires M^+ 320.1412]; ν_{max} (film)/cm^{-1} 1755 and 1735 (CO); δ_H ($CDCl_3$) 1.17 (3H, t, *J* 7.1, OCH_2CH_3), 3.30 (2H, m, $PhCH_2CH$), 4.15 (2H, m, OCH_2CH_3), 4.94 (1H, dd, *J* 5.5 and 7.7, $PhCH_2CH$), 7.02 (1H, d, *J* 2.5, Ar*H*) and 7.15-7.80 (1H, m, Ar*H*); *m/z* (EI) 320 (M^+, 100%), 247 (9), 177 (30), 144 (64), 135 (44), 127 (21), 115 (48), 105 (28), and 91 (24).

Methyl 2-(4-Benzyloxyphenoxy)-3-phenylpropanoate 13d

The propenoate **12d** was reduced by Method A (above), followed by chromatography on silica gel using ethyl acetate-hexane (1:4 v/v) as eluent to afford the title compound **13d** as a gum (70%). [Found C, 76.0; H, 6.1%; M^+ (EI) 362.1507. $C_{23}H_{22}O_4$ requires C, 76.2; H, 6.1%; M^+ 362.1518]; ν_{max} (film)/cm^{-1} 1745, 1725 (CO); δ_H ($CDCl_3$) 3.20 (2H, m, $PhCH_2CH$), 3.71 (3H, s, OCH_3), 4.69 (1H, dd, *J* 7.1 and 5.7, $PhCH_2CH$), 4.97 (2H, s, OCH_2Ph), 6.74 (2H, d, *J* 9.2, OAr*H*), 6.83 (2H, d, *J* 9.2, OAr*H*) and 7.20-7.45 (10H, m, Ar*H*); δ_C ($CDCl_3$) 39.2 ($PhCH_2CH$), 52.2 (OCH_3), 70.5 (OCH_2Ph), 79.0 ($PhCH_2CH$), 115.7, 116.7 [2 x 2C, s, phenoxy *C(2), C(3), C(5)* and *C(6)*], 126.9 [3-phenyl *C(4)*], 127.4 (2C, s, benzyloxy-group, aromatic *C*H), 127.9 [benzyloxy-group, aromatic *C(4)*], 128.4 (2C, s, aromatic *C*H), 128.5 (2C, s, aromatic *C*H), 129.4 (2C, s, aromatic *C*H), 136.4 (aromatic *C*-CH_2), 137.1 (aromatic *C*-CH_2), 152.1 (aromatic *C*-O), 153.8 (aromatic *C*-O) and 171.9 (*C*O); *m/z* (CI) 380 (MNH_4^+, 100%) and 362 (M^+, 27).

Methyl 2-(4-Hydroxyphenoxy)-3-phenylpropanoate 13e

The propenoate **12d** was reduced by Method B (above), followed by chromatography on silica gel using methanol-dichloromethane (1:19 v/v) as eluent to afford the title compound **13e** as a gum (83%). [Found M^+ (EI) 272.1048. $C_{16}H_{16}O_4$ requires M^+ 272.1049]; ν_{max} (film)/cm^{-1} 3420 (OH) and 1738 (CO); δ_H ($CDCl_3$) 3.20 (2H, m, $PhCH_2CH$), 3.70 (3H, s, OCH_3), 4.69 (1H, dd, *J* 4.4 and 7.4, $PhCH_2CH$), 5.19 (1H, s, exchanges with D_2O, O*H*), 6.66 (4H, s, Ar*H*) and 7.28 (5H, s, Ar*H*); δ_C ($CDCl_3$) 39.1 ($PhCH_2CH$), 52.3 (OCH_3), 79.1 ($PhCH_2CH$), 116.0, 116.9 [2 x 2C, s, phenoxy *C(2), C(3), C(5)* and *C(6)*], 126.9 [phenyl *C(4)*], 128.4, 129.4 [2 x 2C, s, phenyl *C(2), C(3), C(5)* and *C(6)*], 136.3 [phenyl *C(1)*], 150.5, 151.7 [phenoxy *C(1)* and *C(4)*] and 172.2 (*C*O); *m/z* (EI) 272 (M^+, 85%), 213 (12), 163 (43), 147 (4), 135 (23), 131 (48), 121 (100), 110 (64), 109 (47) and 91 (68).

2-Benzylidene-3-oxobenzo-1,4-dioxan 14

Diethyl 3-oxobenzo-1,4-dioxan-2-phosphonate **9** was reacted with benzaldehyde in a manner similar to that described previously. The crude product was purified by chromatography on silica gel using dichloromethane-hexane (1:1 v/v) as eluent to afford the title compound **14** (58%) as a mixture of double bond isomers whose ratio was not determined, m.p. 79-81°C. [Found M^+ (EI) 238.0618. $C_{15}H_{10}O_3$ requires M^+ 238.063]; ν_{max} (KBr)/cm^{-1} 1747 (CO) and 1627 (C=C); δ_H ($CDCl_3$) 6.90-7.90 (10H, complex series of multiplets, all hydrogen atoms); *m/z* (CI) 256 (MNH_4^+, 100%), 238 (M^+, 10) and 210 (4).

2-Benzyl-3-oxobenzo-1,4-dioxan 15

The benzylidene-lactone **14** was reduced by Method B (above), using 1,4-dioxan as solvent. The resulting mixture was chromatographed on silica gel using dichloromethane-hexane (1:1 v/v) as eluent to afford the title compound **15** as an oil (76%). [Found M^+ (EI) 240.0782. $C_{15}H_{12}O_3$ requires M^+ 240.0787];

ν_{max} (film)/cm^{-1} 1775 (CO); δ_H ($CDCl_3$) 3.19 (1H, dd, *J* 14.6 and 8.8, PhC*H*$_a$HCH), 3.34 (1H, dd, *J* 14.6 and 3.9, PhCH*H*$_b$CH), 4.80 (1H, dd, *J* 8.8 and 3.9, $PhCH_2CH$), 7.05 (4H, m, Ar*H*) and 7.29 (5H, m, Ar*H*); δ_C ($CDCl_3$) 36.5 ($PhCH_2CH$), 75.6 ($PhCH_2CH$), 117.1, 117.6, 123.2, 125.4 (aromatic *C*H), 127.2 [phenyl *C(4)*], 128.5, 129.6 [2 x 2C, s, phenyl *C(2), C(3), C(5)* and *C(6)*], 135.4 [phenyl *C(1)*], 141.1, 141.6 (2 x aromatic *C*-O) and 164.4 (*C*O); *m/z* (CI) 276 [$(M+H_2O)NH_4^+$, 100%], 258 (MNH_4^+, 42) and 240 (M^+, 3).

Typical Procedure for the Hydrolysis of Esters 13:- 3-(4-Benzyloxyphenyl)-2-phenoxypropanoic Acid 16a

A mixture of the ester **13a** (0.70 g, 1.9 mmol), aqueous sodium hydroxide solution (10% w/v, 10 mL) and methanol (10 mL) was stirred at room temperature for 5 h, concentrated *in vacuo* and diluted with water (300 mL). The solution was acidified to pH 2 with dilute hydrochloric acid then extracted with ethyl acetate (2 x 250 mL). The combined organic solutions were washed with brine, dried ($MgSO_4$) and evaporated. The residual solid was crystallised from dichloromethane-hexane to afford the title compound **16a** (0.47 g, 70 %), m.p. 117-8°C. [Found C, 75.9; H, 5.9%; M$^+$ (EI) 348.1360. $C_{22}H_{20}O_4$ requires C, 75.8; H, 5.8%; M$^+$ 348.1362); ν_{max} (KBr)/cm^{-1} 3200-2500 (COOH) and 1710 (CO); δ_H ($CDCl_3$) 3.22 (2H, d, *J* 6.1, $ArCH_2CH$), 4.00 (1H, br, exchanges with D_2O, COO*H*), 4.81 (1H, t, *J* 6.1, $ArCH_2CH$), 5.02 (2H, s, OCH_2Ph), 6.80-7.00 (5H, m, Ar*H*) and 7.15-7.45 (9H, m, Ar*H*); δ_C ($CDCl_3$) 38.0 ($ArCH_2CH$), 70.0 (OCH_2Ar), 77.5 ($ArCH_2CH$), 114.9, 115.4 [2 x 2C, s, phenoxy *C(2) and C(6)* together with 3-phenyl *C(3)* and *C(5)*], 122.1 [phenoxy *C(4)*], 127.5 (2C, s, aromatic *C*H), 128.0 [benzyloxy-group, aromatic *C(4)*], 128.3 [3-phenyl *C(1)*], 128.6 (2C, s, aromatic *C*H), 129.7 (2C, s, aromatic *C*H), 130.6 (2C, s, aromatic *C*H), 137.0 [benzyloxy-group, aromatic *C(1)*], 157.4 (aromatic *C*-O), 157.9 (aromatic *C*-O) and 176.4 (*C*O); *m/z* (EI) 348 (M^+, 19%), 255 (4), 197 (36) and 91 ($PhCH_2^+$, 100).

3-(2-Chlorophenyl)-2-phenoxypropanoic Acid 16b

Ester **13b** was hydrolysed by the method described above to afford the title compound **16b** (59%) as a gum. [Found M$^+$ (EI) 276.0541. $C_{15}H_{13}ClO_3$ requires M$^+$ 272.0553]; ν_{max} (film)/cm^{-1} 3500-2500 (COOH) and 1720 (CO); δ_H ($CDCl_3$) 3.33 (1H, dd, *J* 14.0 and 8.8, ArC*H*$_a$HCH), 3.52 (1H, dd, *J* 14.0 and 4.7, ArCH*H*$_b$CH), 4.94 (1H, dd, *J* 8.8 and 4.7, $ArCH_2CH$), 6.81 (2H, d, *J* 8.8, Ar*H*), 6.95 (1H, t, *J* 7.5, Ar*H*), 7.10-7.40 (6H, m, Ar*H*) and 7.60 (1H, br, exchanges with D_2O, COO*H*); δ_C ($CDCl_3$) 36.8 ($ArCH_2CH$), 75.6 ($ArCH_2CH$), 115.3 [2C, s, phenoxy *C(2)* and *C(6)*], 122.1 [phenoxy *C(4)*], 126.8, 128.7, 129.5 [chlorophenyl *C(4), C(5),* and *C(6)*], 129.6 [2C, s, phenoxy *C(3)* and *C(5)*], 132.1 [chlorophenyl *C(3)*], 133.7 [chlorophenyl *C(2)*], 134.2 [chlorophenyl *C(1)*], 157.5 [phenoxy *C(1)*] and 176.5 (*C*O); *m/z* (CI) 294 (MNH_4^+, 100%), 277 (MH^+, 2) and 232 (6).

2-(2-Naphthyloxy)-3-phenylpropanoic Acid 16c

Ester **13c** was hydrolysed by the method described above to afford the title compound **16c** (85%), m.p. 109-110°C (dichloromethane-hexane). [Found C, 77.8; H, 5.3%; M$^+$ (EI) 292.1099. $C_{19}H_{16}O_3$ requires C, 78.1; H, 5.5%; M$^+$ 292.1100]; ν_{max} (KBr)/cm^{-1} 3000-2700 (COOH) and 1700 (CO); δ_H ($CDCl_3$) 3.33 (2H, d, *J* 5.9, $PhCH_2CH$), 5.01 (1H, t, *J* 5.9, $PhCH_2CH$), 5.10 (1H, br, exchanges with D_2O, COO*H*), 7.05 [1H, d, *J* 2.5, naphthyl *H(1)*], 7.13 (1H, dd, *J* 2.5 and 9, naphthyl *H(3)*] and 7.15-7.80 (10H, complex); δ_C ($CDCl_3$)[30] 38.8 ($PhCH_2CH$), 77.3 ($PhCH_2CH$), 108.1 [naphthyl *C(1)*], 118.8 [naphthyl *C(3)*], 124.3 [naphthyl *C(6)*],

126.6 [naphthyl *C(7)*], 127.0 [phenyl *C(4)*], 127.2 [naphthyl *C(8)*], 127.7 [naphthyl *C(5)*], 128.6 [2C, s, phenyl *C(2)* and *C(6)*], 129.5 [3C, br s, phenyl *C(3)* and *C(5)* together with naphthyl *C(4a)*], 129.9 [naphthyl *C(4)*], 134.1 [naphthyl *C(8a)*], 136.0 [phenyl *C(1)*], 155.3 [naphthyl *C(2)*] and 176.4 (*C*O); *m/z* (CI) 310 (MNH_4^+, 100%), 293 (MH^+, 25) and 144 (13).

2-(4-Benzyloxyphenoxy)-3-phenylpropanoic Acid **16d**

Ester **13d** was hydrolysed by the method described above to afford the title compound **16d** (73%), m.p. 107-109°C (dichloromethane-hexane). [Found C, 75.7; H, 5.8%; M^+ (EI) 348.1362. $C_{22}H_{20}O_4$ requires C, 75.8; H, 5.8%; M^+ 348.1362]; ν_{max} (KBr)/cm^{-1} 3300-2500 (COOH) and 1700 (CO); δ_H ($CDCl_3$) 3.24 (2H, m, PhCH_2CH), 4.72 (1H, t, *J* 5.2, PhCH$_2$C*H*), 4.96 (2H, s, OCH_2Ph), 6.74 (2H, d, *J* 9.2, phenoxy Ar*H*), 6.83 (2H, d, *J* 9.2, phenoxy Ar*H*), 7.15-7.45 (10H, m, Ar*H*) and 7.50 (1H, br, exchanges with D_2O, COO*H*); δ_C ($CDCl_3$) 38.8 (PhCH$_2$CH), 70.6 (OCH$_2$Ph), 78.8 (PhCH$_2$CH), 115.8, 117.0 [2 x 2C, s, phenoxy *C(2), C(3), C(5)* and *C(6)*], 127.0 [3-phenyl *C(4)*], 127.4 (2C, s, benzyloxy-group, aromatic *C*H), 127.9 [benzyloxy-group, aromatic *C(4)*], 128.5 (2C, s, aromatic *C*H), 128.6 (2C, s, aromatic *C*H), 129.5 (2C, s, aromatic *C*H), 136.2 (aromatic *C*-CH$_2$), 137.0 (aromatic *C*-CH$_2$), 151.8 (aromatic *C*-O), 154.0 (aromatic *C*-O) and 176.4 (*C*O); *m/z* (CI) 366 (MNH_4^+, 100%), 348 [(MNH_4^+–H_2O), 11], 304 (3) and 279 (3).

2-(4-Hydroxyphenoxy)-3-phenylpropanoic Acid **16e**

Ester **13e** was hydrolysed by the method described above to afford the title compound **16e** (70%), m.p. 140-141°C (dichloromethane-hexane). [Found C, 69.7; H, 5.4%; M^+ (EI) 258.0893. $C_{15}H_{14}O_4$ requires C, 69.8; H, 5.5%; M^+ 258.0892]; ν_{max} (KBr)/cm^{-1} 3450 (OH), 3200-2500 (COOH) and 1715 (CO); δ_H ($CDCl_3$) 3.22 (2H, m, PhCH_2CH), 4.62 (1H, dd, *J* 7.4 and 5.0, PhCH$_2$C*H*), 4.75 (1H, br, exchanges with D_2O, O*H*), 6.68 (4H, s, phenoxy Ar*H*), 7.25 (5H, m, Ar*H*) and 8.00 (1H, br, exchanges with D_2O, COO*H*); δ_C (DMSO-d_6) 38.1 (PhCH$_2$CH), 77.5 (PhCH$_2$CH), 115.3, 116.1 [2 x 2C, s, phenoxy *C(2), C(3), C(5)* and *C(6)*], 126.4 [phenyl *C(4)*], 128.1 [2C, s, phenyl *C(2)* and *C(6)*], 129.3 [2C, s, phenyl *C(3)* and *C(5)*], 136.9 [phenyl *C(1)*], 150.3, 151.6 [phenoxy *C(1)* and *C(4)*] and 172.2 (*C*O); *m/z* (CI) 276 (MNH_4^+, 83%), 258 [(MNH_4^+–H_2O), 100], 213 (17), 166 (8), 149 (30), 131 (15) and 110 (45).

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21. Starting material **7a** was recovered in 87% yield and 4-cyanophenol was recovered in 95% yield from this reaction. ^{1}H NMR analysis of the crude reaction mixture showed evidence of traces of a phosphorus

coupled doublet at δ 5.09 (1H, d, *J* 18.7, POC*H*) expected of the insertion product, but there was insufficient material to allow isolation.

22. This reaction appeared to give rise to a complex mixture of products. ^{1}H NMR analysis of the crude reaction mixture showed evidence of traces of a phosphorus coupled doublet at δ 4.80 (1H, d, *J* 18.6, POC*H*) expected of the insertion product, but there was insufficient material to allow isolation.
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