New syntheses of arylphosphinic acids from the reaction of ethyl diethoxymethylphosphinate with aryl bromides and phenols

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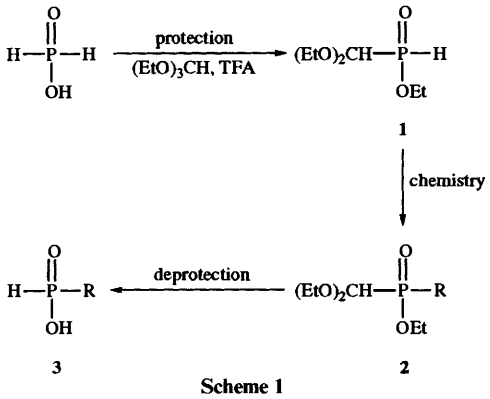
The chemistry of the hypophosphorous acid synthon, ethyl diethoxymethylphosphinate **1** has been further developed to afford efficient new routes to arylphosphinic acids **6** and 2-hydroxyphenylphosphinic acids **10**. In one approach, a palladium(0) catalysed P–H insertion has been used; the second approach utilises a lithium-based ortho rearrangement of aryl phosphonates, readily prepared from the Atherton–Todd reaction of **1** with phenols. In both cases, the phosphinic acids were obtained in a final step by acid deprotection.

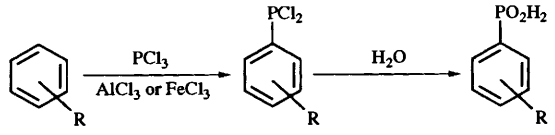
Our interest in the synthesis of functional phosphinic acids [RP(O)(OH)H] has been established for several reasons. These compounds have demonstrated interesting biological activity as close analogues of biologically important carboxylic acids, *e.g.* α- and γ-amino acids.[1,2] In addition, such functional phosphinic acids are readily transformed, *via* oxidation to the corresponding phosphonic acids [1] or through Arbuzov or Michael addition chemistry, into unsymmetrical phosphinic acids [3,4] underlining their utility as important synthetic intermediates. Synthons of hypophosphorous acid,[5,6] such as ethyl diethoxymethylphosphinate **1** have previously been shown to be valuable building blocks for the synthesis of functional aliphatic phosphinic acids.[7] The phosphinate **1** undergoes reactions typical of P–H species—protection of the P–H function as the diethoxymethyl group allows functional group transformations to be performed on the intermediates **2**, and a final deprotection step then regenerates the phosphinic acid functionality, leading to products **3** (Scheme 1).



Scheme 1

As a continuation of our studies into the utility of such reagents, we now report the use of **1** in the synthesis of functional arylphosphinic acids. Two methods are described; a palladium(0)-catalysed coupling with aryl bromides and base-induced rearrangement of phenolic phosphonates.

Existing routes to arylphosphinic acids generally involve the synthesis of the corresponding dichlorophosphine and subsequent aqueous hydrolysis [8] (Scheme 2). The reaction conditions employed together with the difficulty in handling of the intermediates, makes an alternative approach attractive.



Scheme 2

(1) Pd^0-catalysed P–H insertion

We have found that a tetrakis(triphenylphosphine)palladium (0)-catalysed reaction of aryl bromides **4a–g** with ethyl diethoxymethylphosphinate **1** affords arylphosphinate esters **5a–g** in good to excellent yield (Scheme 3). Hydrolysis of the esters with 4 mol dm^{-3} hydrochloric acid afforded the arylphosphinic acids **6a–e** directly.

Similar methodology had been previously employed in the synthesis of arylphosphonic esters,[9] disubstituted phosphinic esters [10] and tertiary phosphine oxides.[11] The diethoxymethyl PH protecting group is sufficiently stable to permit further elaboration of substituents on the aryl ring, prior to acid deprotection, and hence afford a wider range of substituted aryl phosphinic acids. Thus, the nitro **5a**, **b** and cyano **5f**, **g** substituted arylphosphinates can be easily reduced (H_2 over Pd/C) to yield the corresponding amino **5h**, i or aminomethyl **5j**, **k** substituted phosphinates (Scheme 4). Deprotection as described above gives the corresponding phosphinic acids **6f**, **g** and **6h**, **i**, respectively. Such hydrogenolysis in the presence of an unprotected PH function would be thwarted by poisoning of the metal catalyst.

(2) Phosphonate–phosphinate rearrangement

The base-induced rearrangement of phenolic phosphates to give 2-hydroxyphenyl phosphonates has been reported in the literature.[12–16] 2-Hydroxyphenylphosphinic acids **10**, are, however virtually unknown in the literature. An X-ray structure of the parent compound, 2-hydroxyphenylphosphinic acid **10a** was presented in poster form.[17] This compound, a close analogue of salicyclic acid, was prepared [18] *via* coupling of a Grignard reagent derived from a suitably protected 2-bromophenol with a chlorobis(dialkylamino)phosphine and subsequent hydrolysis of the aryl phosphine so formed.

We found that the phenols **7a–d** are readily phosphorylated by **1** under Atherton–Todd conditions, to afford aryl phosphonates **8a–d** in good yield. Treatment of these phosphonates with LDA in tetrahydrofuran at −70 °C gave the rearranged products, 2-hydroxyphenylphosphinates **9a–d**. Hydrolysis of the phosphinates with mineral acid, as above gave the crystalline arylphosphinic acids **10a–d** in high yield (Scheme 5).

The yield obtained for the parent rearranged phosphinate **9a** was disappointing. Attempts to improve this by varying reaction conditions such as choice of base, temperature,

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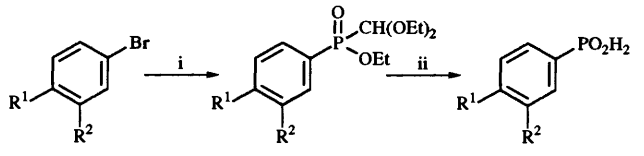
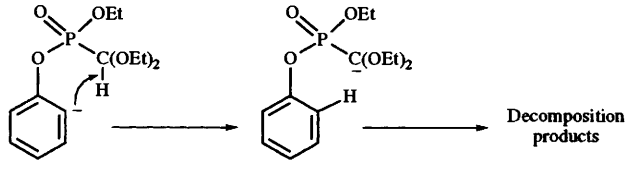


	R^1	R^2		Yield (%)		Yield (%)
a	NO_2	H	**5a**	89	**6a**	88
b	H	NO_2	**5b**	67	**6b**	83
c	NMe_2	H	**5c**	65	**6c**	74
d	Me	H	**5d**	72	**6d**	53
e	Ac	H	**5e**	89	**6e**	65
f	CN	H	**5f**	73		
g	H	CN	**5g**	75		

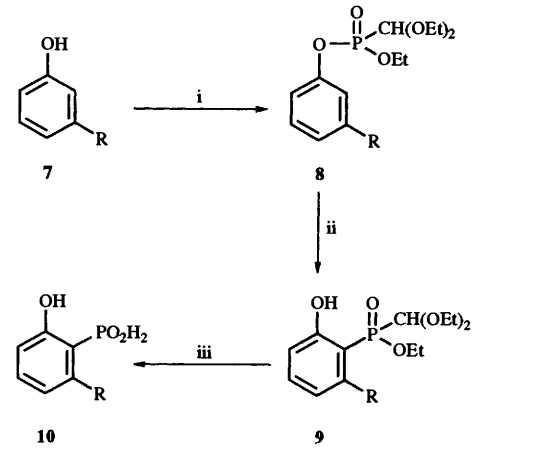
Scheme 3 *Reagents and conditions:* i, $(EtO)_2CHP[(O)OEt]H$ **1**, $[Pd(PPh_3)_4]$ 1–10 h, 90–100 °C; ii, 4 mol dm^{-3} HCl

sequence of addition did not improve the process. The corresponding phosphate–phosphonate rearrangement proceeds in much higher yield.[12] One reason for the low yield obtained for **9a** could be competing deprotonation of the acetal C–H proton by the *ortho* lithium species, leading to decomposition products (see below).



Direct deprotonation of the acetal C–H by LDA can comfortably be ruled out, on the basis of earlier results with alkyl phosphinates.[7] To try and prove this hypothesis, a deuterium quench experiment was performed. Generation of the anion of **8a** with LDA at −70 °C followed by an immediate quench with deuterioacetic acid, gave a product identical with **8a**, except with a greatly reduced signal in the ^1H NMR spectrum corresponding to the acetal C–H.

With a second *ortho*-directing group, as in **8b–d**, where the lithium would be expected to be more strongly coordinated, this process is suppressed in favour of the rearrangement, resulting in higher yields for phosphinates **9b–d**. The regiochemistry shown for the rearranged products **9b–d** was established by NMR experiments on the corresponding acids (see Tables 1 and 2). With the P–H functionality protected as the diethoxymethyl group, it was possible to reduce the chloro



7	R	Yield (%) **8**	Yield (%) **9**	Yield (%) **10**
a	H	90	15	90
b	F	74	78	90
c	Cl	77	63	50
d	Br	78	52	77

Scheme 5 *Reagents and conditions:* i, compound **1** Et_3N, CCl_4; ii, LDA, THF, −70 °C; iii, 4 mol dm^{-3} HCl, 90–100 °C

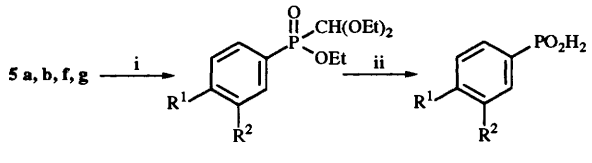
substituent in phosphinate **9c** (H_2/Pd-C) to give **9a** in high yield, thus circumventing the poor yield previously obtained.

(3) 2-Naphthol derivatives

We were interested to study the regioselectivity of the rearrangement of 2-naphthol-derived phosphonates which, at the time of this work, was unknown in the literature. Phosphorylation of 2-naphthol with **1** gave the phosphonate **11** which, on treatment with LDA, gave a 2:1 mixture of phosphinates **12** and **13**, again in a rather poor yield of 27% (Scheme 6). Subsequently, a similar study has been published, reporting the analogous phosphate–phosphonate rearrangement.[19] The authors obtained a similar 2:1 ratio of isomers, although only the major isomer was characterised.

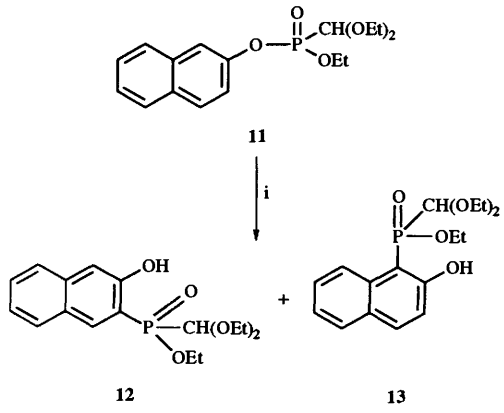
Conclusions

We have demonstrated that ethyl diethoxymethylphosphinate **1** may be successfully employed to prepare substituted arylphospinic acids. This broadening of the utility of such hypophosphorous acid synthons, which are stable and easily prepared, underlines their key role in synthetic organophosphorus chemistry.



	R^1	R^2		R^1	R^2	Yield (%)		R^1	R^2	Yield (%)
a	NO_2	H	**h**	NH_2	H	70	**f**	NH_2	H	75
b	H	NO_2	**i**	H	NH_2	92	**g**	H	NH_2	76
f	CN	H	**j**	CH_2NH_2	H	75	**h**	CH_2NH_2	H	90
g	H	CN	**k**	H	CH_2NH_2	90	**i**	H	CH_2NH_2	79

Scheme 4 *Reagents and conditions:* i, Pd–C, H_2 EtOH; ii, 4 mol dm^{-3} HCl, 90–100 °C



Scheme 6 *Reagents and conditions:* i, LDA, THF, −70 °C

Experimental

All compounds for which analytical and spectroscopic data are quoted were homogeneous by TLC and ^{31}P NMR. TLC was carried out on Merck high performance silica gel $60F_{254}$ pre-coated glass plates (10 × 5 cm). Products were visualised by UV light or by spraying with aqueous alkaline potassium permanganate. Preparative chromatography was performed on silica gel 60 (70–230 mesh ASTM) (Merck). Solvents were routinely dried before use using procedures described in *The Purification of Laboratory Chemicals*, D. D. Perrin and W. L. F. Armarego, Pergamon Press. Melting points were carried out on a Büchi type S apparatus and are uncorrected. ^1H NMR spectra were recorded on a Bruker AC400 spectrometer operating at 400.13 MHz or a JEOL FX-90Q spectrometer operating at 89.55 MHz. Referenced internally to Me_4Si (for $CDCl_3$ solutions) and externally to sodium (trimethylsilyl)propionate (for D_2O solutions). ^{13}C NMR spectra were recorded on the above instruments operating at 100.614 and 22.49 MHz, respectively (and referenced internally to $^{13}CDCl_3$) as were ^{31}P NMR spectra operating at 161.91 and 36.21 MHz, respectively (and referenced externally to H_3PO_4 for both $CDCl_3$ and D_2O solutions). ^{19}F NMR spectra were obtained on the JEOL FX-90Q instrument operating at 84.25 MHz (and referenced externally to $CFCl_3$). *J* Values are given in Hz. IR spectra were measured on a Perkin-Elmer 881 grating spectrophotometer as thin films or Nujol mulls. Only significant absorptions are quoted. Microanalyses were obtained by Instrumentation, Research and Consultancy Services, University of Manchester. Physical analytical data for the arylphosphinic acids **6** and **10** are summarised in Table 3.

Table 1 400 MHz spectroscopic data (δ_H) for phosphinic acids 10 a–d $\delta_H([^2H_6]$-DMSO)

Compound	3-H	4-H	5-H	6-H	P-H
10a	6.87 (m)	7.40 (dt)	6.92 (dt)	7.5 (ddd)	7.53 (d)
10b	6.72 (m)	7.44 (dt)	6.69 (m)	—	7.73 (d)
10c	6.84 (dd)	7.42 (t)	6.96 (dd)	—	7.78 (d)
10d	6.86 (dd)	7.33 (t)	7.13 (ddd)	—	7.69 (d)

Ethyl diethoxymethyl(4-nitrophenyl)phosphinate 5a

A mixture of ethyl diethoxymethylphosphinate **1** (3.9 g, 20 mmol), 4-bromonitrobenzene **4a** (4.0 g, 20 mmol), dry triethylamine (4.0 g, 40 mmol), toluene (15 cm^3) and tetrakis(triphenylphosphine)palladium(0) (2.3 g, 2 mmol) was sealed in a thick-walled tube under argon. The mixture was heated at 90 °C for 1 h during which time the reaction mixture became clear and then deposited a precipitate (of triethylamine hydrobromide). The reaction mixture was poured onto ethyl acetate (50 cm^3), filtered, and evaporated to afford an oil. Purification by column chromatography over silica gel with diethyl ether as eluent afforded compound **5a** (5.7 g, 89%) as an oil; ν_{max}(thin film)/cm^{-1} 1600 (Ar), 1520, 1350 (NO_2), 1440 (ArP), 1240 (PO) and 1060 (POAlk); $\delta_H(CDCl_3$, 90 MHz), 8.4–7.95 (4 H, m, ArH), 4.85 (1 H, d, *J* 7.2, PCH), 4.4–4.0 (2 H, m, $POCH_2$), 4.0–3.5 (4 H, m, CH_2 × 2) and 1.3 (9 H, m, CH_3 × 3); $\delta_P(CDCl_3$, 36 MHz) 28.8.

Ethyl diethoxymethyl(3-nitrophenyl)phosphinate 5b

This compound was similarly prepared from **1** (2.0 g, 10 mmol) and 3-nitrobromobenzene **4b** (2.0 g, 10 mmol) with heating at 90 °C for 6 h. Purification by column chromatography over silica gel eluting with diethyl ether afforded compound **5b** (2.1 g, 67%) as an oil; ν_{max}(thin film)/cm^{-1} 1600 (Ar), 1530, 1350 (NO_2), 1230 (PO) and 1060 (POAlk); $\delta_H(CDCl_3$, 90 MHz) 8.8–8.25 (3 H, m, ArH), 7.95–7.6 (1 H, m, ArH), 4.9 (1 H, d, *J* 7.2, PCH), 4.5–3.5 (6 H, m, CH_2 × 3) and 1.3 (9 H, m, CH_3 × 3); $\delta_P(CDCl_3$, 36 MHz) 28.3.

Ethyl diethoxymethyl(4-*N*-*N*-dimethylaminophenyl) phosphinate 5c

This compound was similarly prepared from **1** (3.9 g, 20 mmol) and 4-bromo-*N*,*N*-dimethylaniline **4c** (4.1 g, 20 mmol) with heating at 100 °C for 10 h. Purification by column chromatography over silica gel eluting with ethyl acetate–diethyl ether (1 : 1) afforded compound **5c** (4.1 g, 65%) as an oil; ν_{max}(thin film)/cm^{-1} 1600 (Ar), 1440, 1230 and 1040; $\delta_H(CDCl_3$, 90 MHz), 7.7 (2 H, m, ArH), 6.7 (2 H, dd, ArH), 4.75 (1 H, d, *J* 7.2, PCH), 4.4–3.4 (6 H, m, CH_2 × 3), 3.0 (6 H, s, NCH_3 × 2) and 1.3 (9 H, m, CH_3 × 3); $\delta_P(CDCl_3$, 36 MHz) 32.8.

Table 2 100 MHz spectroscopic data (δ_C) for phosphinic acids **10a–d**

	Chemical shift $\delta_C([^2H_6]$-DMSO)						Carbon–phosphorus coupling constant (*J*/Hz) [Carbon-fluorine (*J*/Hz)]					
Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-1P	C-2P	C-3P	C-4P	C-5P	C-6P
10a	118.32 (d)	159.92 (d)	116.02 (s)	134.07 (s)	119.03 (d)	131.59 (d)	128.8	4.82	7.75	—	12.98	7.85
10b	104.83 (dd)	162.21 (dd)	112.92 (dd)	135.54 (d)	105.81 (dd)	163.54 (d)	121.24 [21.33]	7.74 [1.61]	6.94 [3.12]	— [11.26]	5.23 [22.03]	— [246.80]
10c	113.27 (d)	163.30 (d)	116.34 (d)	135.21 (s)	120.57 (d)	135.68 (d)	125.9	3.01	7.44	—	6.13	3.32
10d	114.67 (d)	163.53 (s)	116.93 (d)	135.44 (s)	124.01 (d)	124.52 (d)	127.2	—	7.34	—	7.24	4.95

Table 3 Physical analytical data for aryl phosphinic acids **6a–i**, **10a–d**

Compd.	Mp (*T*/°C) (Lit.)	Found (%) (Required) C	H	N	P	^{31}P NMR δ(solvent)	J_{PH}/Hz
6a	175–177 (134)[21]	38.55 (38.50)	3.40 3.25	7.30 7.50	16.40 (16.55)	13.7 ([$^2H_6$-]DMSO)	562.0
6b	163–168	38.45 (38.50)	3.00 3.25	7.30 7.50	16.20 (16.55)	13.0 ($^2H_6$]-DMSO)	572.5
6c	152–154 (162)[22]	51.40 (51.90)	6.35 6.55	7.45 7.55	17.0 (16.75)	16.1 (D_2O)	563.0
6d	102–103 (104)[23]	53.70 (53.85)	5.60 5.81		19.8 (19.85)	18.5 (D_2O–NaOD)	523.9
6e	115–118	52.00 (52.2)	4.80 4.95		16.55 (16.80)	20.3 (D_2O)	570.0
6f	171–174 (169)[24]	45.70 (45.85)	5.10 5.15	8.80 8.90	19.50 (19.70)	17.4 (D_2O)	540.0
6g	240–244	45.65 (45.85)	5.0 5.15	8.80 8.90	19.70 (19.70)	19.9 (D_2O–DCl)	577.0
6h	> 250	48.90 (49.15)	5.80 5.90	8.20	18.1 (18.1)	17.8 (D_2O)	529.2
6i	> 250	48.90 (49.15)	5.70 5.90	8.00 8.20	18.3 (18.1)	17.7 (D_2O)	530.0
10a	128–132	45.5 (45.6)	4.3 4.45		19.6 (19.6)	22.3 (D_2O)	590.0
10b	105	41.15 (40.49)	3.3 3.45		17.6 (17.6)	14.5–14.4 (D_2O)	591.0
10c	112	37.05 (37.4)	2.9 3.15		16.2 (16.1)	18.5 (D_2O)	591.0
10d	122–125	30.25 (30.4)	2.6 2.55		13.15 (13.1)	13.4 (D_2O–NaOD)	556.5

Ethyl diethoxymethyl(4-methylphenyl)phosphinate 5d
This compound was similarly prepared from **1** (3.9 g, 20 mmol) and 4-bromotoluene **4d** (3.4 g, 20 mmol), with heating at 100 °C for 1 h. Purification by column chromatography over silica gel eluting with diethyl ether afforded compound **5d** (4.1 g, 72%) as an oil; ν_{max}(thin film)/cm^{-1} 1605 (Ar), 1405, 1240 (PO), and 1060 (POAlk); δ_H($CDCl_3$, 90 MHz), 7.8 (2 H, m, ArH), 7.4 (2 H, m, ArH), 4.8 (1 H, d, *J* 7.2, PCH), 4.5–3.5 (6 H, m, CH_2 × 3), 2.45 (3 H, s, $ArCH_3$) and 1.3 (9 H, m, CH_3 × 3); δ_P($CDCl_3$, 36 MHz) 31.6.

Ethyl 4-acetylphenyl(diethoxymethyl)phosphinate 5e
This compound was similarly prepared from **1** (3.9 g, 20 mmol) and 4-bromoacetophenone **4e** (4.0 g, 20 mmol), with heating at 100 °C for 1 h. Purification by column chromatography over silica gel eluting with ethyl acetate–diethyl ether (1 : 1) afforded compound **5e** (5.6 g, 89%) as an oil; ν_{max}(thin film)/cm^{-1} 1700 (CO), 1440 (ArP), 1260, (PO) and 1060 (POAlk); δ_H($CDCl_3$, 90 MHz), 8.2–7.8 (4 H, m, ArH), 4.8 (1 H, d, *J* 7.2, PCH), 4.45–3.75 (6 H, m, CH_2 × 3), 2.6 (3 H, s, $COCH_3$) and 1.5–1.1 (9 H, m, CH_3 × 3); δ_P($CDCl_3$, 36 MHz) 30.3.

Ethyl 4-cyanophenyl(diethoxymethyl)phosphinate 5f
This compound was similarly prepared from **1** (3.9 g, 20 mmol) and 4-bromobenzonitrile **4f** (3.7 g, 20 mmol) with heating at 90 °C for 1 h. Purification by column chromatography over silica gel eluting with diethyl ether afforded compound **5f** (4.4 g, 75%) as an oil; ν_{max}(thin film)/cm^{-1} 2240, (CN), 1400, 1230, (PO) and 1060 (POAlk); δ_H($CDCl_3$, 90 MHz) 8.2–7.7 (4 H, m, ArH), 4.9 (1 H, d, *J* 7.2, PCH), 4.5–3.5 (6 H, m, CH_2 × 3) and 1.35 (9 H, m, CH_3 × 3); δ_P($CDCl_3$, 36 MHz) 26.3.

Ethyl 3-cyanophenyl(diethoxymethyl)phosphinate 5g
This compound was similarly prepared from **1** (3.9 g, 20 mmol) and 3-bromobenzonitrile **4f** (3.7 g, 20 mmol) with heating at 100 °C for 1 h. Purification by column chromatography over silica gel eluting with diethyl ether afforded compound **5g** (4.3 g, 73%) as an oil; ν_{max}(thin film)/cm^{-1} 2240, (CN), 1240, (PO) and 1060 (POAlk); δ_H($CDCl_3$, 90 MHz), 8.0–7.6 (4 H, m, ArH), 4.9 (1 H, d, *J* 7.2, PCH), 4.5–3.6 (6 H, m, CH_2 × 3) and 1.3 (9 H, m, CH_3 × 3); δ_P($CDCl_3$, 36 MHz) 28.5.

Ethyl 4-aminomethylphenyl(diethoxymethyl)phosphinate 5j
A solution of the nitrile **5f** (0.6 g, 2 mmol) in ethanol (25 cm^3) and chloroform (1 cm^3) was reduced over 5% Pd/C (0.2 g) with hydrogen at 40 psi at 45 °C. After 24 h, filtration and evaporation of the solvents afforded the crude product as the hydrochloride. The salt was dissolved in THF, treated with triethylamine, filtered and evaporated to an oil. Purification by column chromatography over silica gel eluting with 5% methanol in chloroform afforded compound **5j** (450 mg, 75%) as a colourless oil; ν_{max}(thin film)/cm^{-1} 3400br (NH_2), 1600, 1220 and 1060 (POAlk); δ_H($CDCl_3$, 90 MHz) 7.9–7.6 (4 H, m, ArH), 6.7 (2 H, br s, NH_2), 4.75 (1 H, d, *J* 7.6, PCH), 4.2 (2 H, s, $ArCH_2$), 4.3–4.0 (2 H, m, CH_2OP), 4.0–3.5 (4 H, m, CH_2 × 2) and 1.2 (9 H, m, CH_3 × 3); δ_P($CDCl_3$, 36 MHz) 30.9.

Ethyl 3-aminomethylphenyl(diethoxymethyl)phosphinate 5k
This compound was similarly prepared as described above, with reduction of the nitrile **5g** for 30 h. The crude product was purified by column chromatography eluting with 5% methanol in chloroform to yield recovered starting material **5g** (2.8 g, 68%) and then the desired compound **5k** (1.2 g, 29%) as a colourless oil; ν_{max}(thin film)/cm^{-1} 3350br (NH_2), 1230 and 1060 (POAlk); δ_H($CDCl_3$, 90 MHz), 8.0–7.3 (4 H, m, ArH), 5.25 (2 H, br s, NH_2), 4.8 (1 H, d, *J* 7.5, PCH), 3.95 (2 H, s $ArCH_2$), 4.4–3.5 (6 H, m, CH_2 × 3) and 1.2 (9 H, m, CH_3 × 3); δ_P($CDCl_3$, 36 MHz) 31.2.

Ethyl 4-aminophenyl(diethoxymethyl)phosphinate 5h
A solution of compound **5a** (1.6 g, 5 mmol) in absolute ethanol (25 cm^3) was reduced over 5% Pd–C (0.2 g) with hydrogen at 40 psi. After 24 h, the reaction mixture was filtered and con-

centrated. Purification by column chromatography over silica gel eluting with 10% methanol in ethyl acetate afforded compound **5h** as a viscous oil (1.0 g, 70%); ν_{max}(thin film)/cm^{-1} 3350br (NH_2), 1640, 1600, 1440, 1220 and 1060 (POAlk); δ_H($CDCl_3$, 90 MHz), 7.7–7.2 (2 H, m, ArH), 6.6 (2 H, dd, ArH), 4.7 (1 H, d, *J* 7.6, (PCH), 4.2–3.5 (8 H, m, CH_2 × 3 and NH_2) and 1.2 (9 H, m, CH_3 × 3); δ_P($CDCl_3$, 36 MHz) 32.4.

Ethyl 3-aminophenyl(diethoxymethyl)phosphinate 5i
This compound was similarly prepared as described above, compound **5b** (1.5 g, 4.7 mmol) being reduced to a colourless solid (1.2 g, 92%), mp 82 °C; ν_{max}(thin film)/cm^{-1} 3370br (NH_2), 1635, 1600, 1440, 1230 and 1060 (POAlk); δ_H($CDCl_3$, 90 MHz), 7.3–7.0 (3 H, m, ArH), 6.9–6.7 (1 H, m, ArH), 4.75 (1 H, d, *J* 7.2, PCH), 4.4–3.5 (8 H, m, CH_2 × 3 and NH_2) and 1.25 (9 H, m, CH_3 × 3); δ_P($CDCl_3$, 36 MHz) 31.6.

4-Nitrophenylphosphinic acid 6a
A solution of **5a** (0.3 g, 0.95 mmol) in 4 mol dm^{-3} hydrochloric acid (20 cm^3) was heated at 100 °C for 4 h and then evaporated to afford an oil which upon co-evaporation with water gave a solid. Recrystallisation from ethanol yielded compound **6a** (0.15 g, 88%) as yellow crystals; ν_{max}(Nujol)/cm^{-1} 2420 (PH), 1540, 1350 (NO_2), 1200 and 1080; δ_H[$(CD_3)_2SO$ 90 MHz], 9.0 (1 H, br s, POH), 8.4–8.2 (2 H, m, ArH), 8.15–7.8 (2 H, m, ArH) and 7.6 (1 H, d, *J* 562, PH).

3-Nitrophenylphosphinic acid 6b
This compound was similarly prepared from **5b** (1.0 g, 3.2 mmol) by treatment with 4 mol dm^{-3} hydrochloric acid (25 cm^3), to give a yellow solid (0.50 g, 83%); ν_{max}(Nujol)/cm^{-1} 2380 (PH), 1530 and 1350 (NO_2); δ_H[$(CD_3)_2SO$, 90 MHz], 7.9 (1 H, br s, POH), 8.6–7.4 (4 H, m, ArH) and 7.6 (1 H, d, *J* 572, PH).

4-*N*,*N*-Dimethylaminophenylphosphinic acid 6c
A solution of **5c** (3.2 g, 10.2 mmol) in 4 mol dm^{-3} hydrochloric acid (30 cm^3) and ethanol (30 cm^3) was heated for 3 h and then evaporated to yield an oil. This was partitioned between water and ether. The aqueous phase was separated, concentrated and purified by passage down an ion-exchange column (Dowex 50-W H^+ form) eluting with water. Evaporation of appropriate fractions afforded compound **6c** (1.4 g, 74%) as a colourless solid; ν_{max}(Nujol)/cm^{-1} 2380 (PH), 1600; δ_H(D_2O, 90 MHz), 8.3–7.8 (4 H, m, ArH), 7.8 (1 H, d, *J* 563, PH) and 3.5 (6 H, s, NCH_3 × 2).

4-Methylphenylphosphinic acid 6d
A solution of **5d** (3.6 g, 12.6 mmol) in 4 mol dm^{-3} hydrochloric acid (30 cm^3) and ethanol (20 cm^3) was heated at reflux for 6 h. Evaporation of solvents and co-evaporation with water (4 ×) afforded a crude solid, which was recrystallised [EtOAc–light petroleum (bp 60–80 °C), 1:5] to afford compound **6d** (1.0 g, 53%) as a colourless solid; ν_{max}(Nujol)/cm^{-1} 2420 (PH), 1600 and 1460; δ_H(D_2O/NaOD, 90 MHz), 7.6–7.0 (4 H, m, ArH), 7.3 (1 H, d, *J* 524, PH) and 2.2 (3 H, s, CH_3).

4-Acetylphenylphosphinic acid 6e
This compound was similarly prepared from **5e** (0.5 g, 1.6 mmol), 4 mol dm^{-3} hydrochloric acid (10 cm^3) and ethanol (3 cm^3). Recrystallisation (toluene) afforded compound **6e** (0.2 g, 65%) as white crystals; ν_{max}(Nujol)/cm^{-1} 2400 (PH), 1660, 1600 and 1250; δ_H(D_2O, 90 MHz) 7.9–7.3 (4 H, m, ArH), 7.5 (1 H, d, *J* 570, PH) and 2.4 (3 H, s, CH_3).

4-Aminophenylphosphinic acid 6f
A solution of **5h** (1.8 g, 6.2 mmol) in 4 mol dm^{-3} hydrochloric acid (25 cm^3) was heated at 100 °C for 6 h. Evaporation and co-evaporation with water (2 ×) afforded the crude product hydrochloride salt. The salt was dissolved in ethanol and propylene oxide added dropwise to the solution. The resultant precipitate was filtered off to afford the compound **6f** (1.2 g, 75%) as a colourless solid; ν_{max}(Nujol)/cm^{-1} 3400br (NH_2) and 2375 (PH); δ_H(D_2O, 90 MHz) 8.7–7.8 (4 H, m, ArH) and 7.8 (1 H, d, *J* 540, PH).

3-Aminophenylphosphinic acid 6g
Similarly, the phosphinate **5i** (2.2 g, 7.6 mmol) afforded compound **6g** (0.9 g, 76%); ν_{max}(Nujol)/cm^{-1} 3950br (NH_2) and 2375 (PH); δ_H(D_2O–DCl, 90 MHz), 7.9–7.4 (4 H, m, Ar-H) and 7.25 (1 H, d, *J* 577, PH).

4-Aminomethylphenylphosphinic acid 6h
A solution of **5j** (0.4 g, 1.3 mmol) in 4 mol dm^{-3} hydrochloric acid (20 cm^3) was heated to 100 °C for 6 h. Evaporation of the solvent and co-evaporation of the residue with water (4 ×) afforded the crude product which was purified by ion-exchange chromatography (Dowex 50-W H^+ form) with water as eluent. Compound **6h** was isolated as a white powder (0.2 g, 90%); ν_{max}(Nujol)/cm^{-1} 3440, 3400br (NH_2) and 2360 (PH); δ_H(D_2O, 90 MHz), 7.8–7.3 (4 H, m, ArH), 7.28 (1 H, d, *J* 592.2, PH) and 4.2 (2 H, s, CH_2).

3-Aminomethylphenylphosphinic acid 6i
Similarly, compound **5k** (1.4 g, 4.6 mmol) afforded compound **6i** (0.5 g, 79%); ν_{max}(Nujol)/cm^{-1} 3350, 3280br (NH_2) and 2360 (PH); δ_H(D_2O, 90 MHz), 7.8–7.2 (4 H, m, ArH), 7.28 (1 H, d, *J* 530, PH) and 4.15 (2 H, s, CH_2).

Ethyl diethoxymethyl(phenyl)phosphonate 8a
A solution of the phenol **7a** (1.9 g, 20 mmol) and **1** (3.9 g, 20 mmol) in carbon tetrachloride (50 cm^3) was cooled to 0 °C under argon after which dry triethylamine (2.0 g, 20 mmol) was added dropwise to it over 10 min. After being warmed to 23 °C and stirred for 0.5 h, the mixture was filtered. The filtrate was washed with cold 1 mol dm^{-3} hydrochloric acid, 1 mol dm^{-3} aqueous sodium hydroxide and brine, dried ($MgSO_4$) and evaporated to yield the crude product as an oil. Purification by distillation on a wiped-wall distillation unit at 80 °C/0.1 mmHg afforded compound **8a** (5.1 g, 90%) as a clear oil; ν_{max}(thin film)/cm^{-1} 1590, 1500, 1260, 1200 and 1060; δ_H($CDCl_3$, 90 MHz) 7.3 (5 H, m, ArH), 4.95 (1 H, d, *J* 7.2, CHP), 4.5–4.2 (2 H, m, CH_2), 4.0–3.8 (4 H, m, CH_2 × 2) and 1.3 (9 H, m, CH_3 × 3); δ_P($CDCl_3$, 36 MHz) 10.5.

Ethyl diethoxymethyl(3-fluorophenyl)phosphate 8b
This compound was similarly prepared from 3-fluorophenol **7b** (5.6 g, 50 mmol) and **1** (9.8 g, 50 mmol). Distillation on a wiped-wall distillation unit at 90 °C/0.1 mmHg gave compound **8b** (11.4 g, 74%); ν_{max}(thin film)/cm^{-1} 1260, 1240, 1100 and 1040; δ_H($CDCl_3$, 90 MHz) 7.5–6.8 (4 H, m, ArH), 4.95 (1 H, d, *J* 7.2 CHP), 4.55–4.2 (2 H, m, CH_2), 4.1–3.8 (4 H, m, CH_2 × 2) and 1.3 (9 H, m, CH_3 × 3); δ_C($CDCl_3$, 22.5 MHz) 165.0 (d, $J_{C\text{-}3,F}$ 245.8, C-3), 154.1 (dd, $J_{C\text{-}1,P}$ 8.2, $J_{C\text{-}1,F}$ 11.0, C-1), 132.8 (d, *J* 22.0, C-4), 110.5 (dd, $J_{C\text{-}2,P}$ 4.1, $J_{C\text{-}2,F}$ 24.7, C-2), 101.0 (d, $J_{C,P}$ 210.1, PCH), 66.5 (d, $J_{C,P}$ 5.5, $POCH_2$) 65.7 (d, $J_{C,P}$ 6.9, $PCHOCH_2$), 18.3 (d, $J_{C,P}$ 5.5, $POCH_2CH_3$) and 17.0 (s, CH_3); δ_P($CDCl_3$, 36 MHz) 10.6; δ_F($CDCl_3$, 84 MHz) −111.2.

Ethyl 3-chlorophenyl(diethoxymethyl)phosphate 8c
Similarly, 3-chlorophenol **7c** (12.8 g, 0.1 mol) and **1** (19.6 g, 0.1 mol) gave compound **8c** (24.8 g, 77%) after distillation at 100 °C/0.1 mm; 1 mm; ν_{max}(thin film)/cm^{-1} 1590, 1260, 1210, 1050 and 780; δ_H($CDCl_3$, 90 MHz) 7.4–7.1 (4 H, m, ArH),

4.95 (1 H, d, *J* 7.2, PCH), 4.5–4.2 (2 H, m, CH_2), 4.1–3.8 (4 H, m, CH_2 × 2) and 1.3 (9 H, m, CH_3 × 3); δ_P($CDCl_3$, 36 MHz) 10.6.

Ethyl 3-bromophenyl(diethoxymethyl)phosphonate 8d

Similarly, 3-bromophenol **7d** (8.6 g, 50 mmol) and **1** (9.8 g, 50 mmol) gave compound **8d** (21.7 g, 78%) as a clear oil after distillation at 100 °C/0.1 mmHg; ν_{max}(thin film)/cm^{-1}, 1250, 1210, 1050 and 710; δ_H($CDCl_3$, 90 MHz) 7.6–7.2 (4 H, m, ArH), 4.95 (1 H, d, *J* 7.2, PCH), 4.6–4.2 (2 H, m, CH_2), 4.1–3.8 (4 H, m, CH_2 × 2) and 1.3 (9 H, m, CH_3 × 3); δ_P($CDCl_3$, 36 MHz) 10.6.

Ethyl diethoxymethyl(2-hydroxyphenyl)phosphinate 9a

A solution of lithium diisopropylamide (10 mmol) in dry tetrahydrofuran (10 cm^3) was added dropwise to a solution of compound **8a** (2.9 g, 10 mmol) in THF (20 cm^3) at −70 °C under argon. The reaction mixture was stirred at −70 °C for 1 h and then allowed to warm to room temperature. The reaction mixture was poured into saturated aqueous ammonium chloride (50 cm^3). The organic phase was washed with water, dried ($MgSO_4$) and evaporated to afford a crude product, purification of which by column chromatography over silica gel eluting with light petroleum–diethyl ether (1:1) afforded compound **9a** (0.43 g, 15%) as a colourless solid, mp 110–111 °C; ν_{max}(Nujol)/cm^{-1} 3000 (OH), 1440 (ArP), 1200 (PO) and 1040 (P-OAlk); δ_H($CDCl_3$, 90 MHz) 10.41 (1 H, br s, OH), 7.6–7.2 (2 H, m, ArH), 7.1–6.8 (2 H, m, ArH), 4.85 (1 H, d, *J* 7.5, PCH), 4.4–4.0 (2 H, m, CH_2), 4.0–3.8 (4 H, m, CH_2 × 2) and 1.3 (9 H, m, CH_3 × 3); δ_C($CDCl_3$, 22.5 MHz) 163.3 (d, $J_{C\text{-}2,P}$ 5.5 C-2), 135.3 (d, $J_{C\text{-}4,P}$ 2.7, C-4), 132.5 (d, $J_{C\text{-}6,P}$ 6.9, C-6), 119.2 (d, $J_{C\text{-}5,P}$ 12.4, C-5), 117.8 (d, $J_{C\text{-}3,P}$ 8.2, C-3), 108.6 (d, $J_{C\text{-}1,P}$ 119.4, C-1), 101.2 (d, $J_{C,P}$ 160.6, PCH), 66.0–65.4 (dd, $PCHOCH_2$ × 2), 62.2 (d, $J_{C,P}$ 6.1, $POCH_2$), 16.45 (d, $J_{C,P}$ 5.5, CH_3) and 15.1 (s, CH_3) δ_P($CDCl_3$, 36 MHz) 37.9 (Found: C, 54.55; H, 7.5; P, 10.95. $C_{13}H_{21}O_5P$ requires C, 54.15; H, 7.35; P, 10.75).

Ethyl diethoxymethyl(2-fluoro-6-hydroxyphenyl)phosphinate 9b

Similarly, **8b** (6.1 g, 20 mmol) gave a crude product which was purified by column chromatography eluting with light petroleum–diethyl ether (1:1) to afford compound **9b** (4.8 g, 78%) as an oil; ν_{max}(Nujol)/cm^{-1} 3100 (OH), 1580, 1450 (ArP), 1140 (PO), 1080 and 1040; δ_H($CDCl_3$, 90 MHz) 11.2 (1 H, s, OH), 7.6–7.2 (1 H, m, ArH), 6.8–6.4 (2 H, m, ArH), 5.0 (1 H, dd, $J_{C,P}$ 7.2 $J_{C,F}$ 2.0, PCH), 4.4–3.7 (6 H, m, CH_2 × 3) and 1.3 (9 H, m, CH_3 × 3); δ_C($CDCl_3$, 22.5 MHz) 164.9 (d, $J_{C\text{-}6,F}$ 10.5, C-6), 163.2 (d, $J_{C\text{-}2,F}$ 248.5, C-2), 136.1 (d, $J_{C\text{-}4,F}$ 11.0, C-4), 113.9 (dd, $J_{C\text{-}5,P}$ 8.2, $J_{C\text{-}5,F}$ 2.7, C-5), 105.5 (dd, $J_{C\text{-}3,P}$ 6.9, $J_{C\text{-}3,F}$ 23.3, C-3), 100.0 (dd, $J_{C,P}$ 166.1, $J_{C,F}$ 4.1, PCH), 98.0 (dd, $J_{C\text{-}1,P}$ 114.0, $J_{C\text{-}1,F}$ 23.3, C-1), 64.8 (dd, CH_2), 62.6 (d, *J* 8.2, CH_2), 16.2 (d, *J* 6.8, CH_3) and 15.0 (d, *J* 8.0, CH_3); δ_P($CDCl_3$, 36 MHz) 37.4 (d, $J_{P,F}$ 3.9); δ_F($CDCl_3$, 84 MHz) −103.7 (Found: C, 50.9; H, 6.9; P, 10.1. $C_{13}H_{20}FO_5P$ requires C, 51.0; H, 6.6; P, 10.1).

Ethyl 2-chloro-6-hydroxyphenyl(diethoxymethyl)phosphinate 9c

Similarly, **8c** (6.4 g, 20 mmol) gave a crude product which was purified by column chromatography eluting with light petroleum–diethyl ether (1:1) to afford compound **9c** (4.0 g, 63%) as a clear oil; ν_{max}(thin film)/cm^{-1} 3000 (OH), 1580, 1440, 1200, 1060 and 780; δ_H($CDCl_3$, 90 MHz) 11.95 (1 H, s, OH), 7.6–6.7 (3 H, m, ArH), 5.25 (1 H, d, *J* 7.0, PCH), 4.2–3.7 (6 H, m, CH_2 × 3) and 1.3 (9 H, m, CH_3 × 3); δ_P($CDCl_3$, 36 MHz) 39.7.

Ethyl 2-bromo-6-hydroxyphenyl(diethoxymethyl)phosphinate 9d

Similarly, **8d** (7.3 g, 20 mmol) gave a crude product which was purified by column chromatography over silica gel eluting with light petroleum–diethyl ether (2:1) to afford compound **9d** (3.8 g, 52%) as a low-melting waxy solid; ν_{max}(thin film)/cm^{-1} 3100 (OH), 1580, 1440, 1200 and 1050; δ_H($CDCl_3$, 90 MHz) 11.95 (1 H, s, OH), 7.5–6.8 (3 H, m, ArH), 5.5 (1 H, d, *J* 10.0, PCH), 4.4–3.5 (6 H, m, CH_2 × 3), 1.3 (6 H, 2 × t, CH_3 × 2) and 1.0 (3 H, t, *J* 7.0, CH_3); δ_P($CDCl_3$, 36 MHz) 40.1 (Found: C, 42.75; H, 5.4; P, 8.45. $C_{13}H_{20}BrO_5P$ requires C, 42.50; H, 5.50; P, 8.45).

Reduction of 9c by catalytic hydrogenation

A mixture of **9c** (200 mg, 0.62 mmol) and 10% palladium-on-carbon (50 mg) in absolute ethanol (10 cm^3) was hydrogenated at 40 °C for 24 h. Filtration and evaporation afforded an oil that was purified by column chromatography over silica gel with light petroleum–diethyl ether (1:1) to afford compound **9a** (125 mg, 70%), identical in all respects with that obtained previously.

2-Hydroxyphenylphosphinic acid 10a

Compound **9a** (1.0 g, 3.5 mmol) was dissolved in absolute ethanol (12.5 cm^3) and 4 mol dm^{-3} hydrochloric was added to the solution. The mixture was heated at 100 °C for 3 h and then evaporated to afford an oil that was co-evaporated with water (4 × 25 cm) and absolute ethanol (4 × 25 cm^3). The resulting oil crystallised on storage and was recrystallised from ethyl acetate to give compound **10a** (0.49 g, 90%) as white needles; ν_{max}(Nujol)/cm^{-1} 3100 (OH), 2410 (PH), 1600 and 1440; δ_H[$(CD_3)_2SO$, 400 MHz] 7.53 (1 H, d, J_{PH} 560.2, PH), 7.50 (1 H, ddd, J_{6P} 9.2, $J_{5,6}$ 7.5, $J_{4,6}$ 1.7, 6-H), 7.40 (1 H, dt, $J_{4,5}$ 7.5, $J_{4,6}$ 1.7, 4-H), 6.92 (1 H, dt, $J_{5,6}$ 7.5, *J* 2.0, 5-H) and 6.87 (1 H, m, 3-H).

6-Fluoro-(2-hydroxyphenyl)phosphinic acid 10b

Similarly, **9b** (1.0 g, 3.3 mmol) gave a product which was recrystallised from toluene to afford compound **10b** (520 mg, 90%) as colourless needles; ν_{max}(Nujol)/cm^{-1} 3100 (OH), 2420 (PH), 1590, 1440 and 1100 (CF); δ_H[$(CD_3)_2SO$, 400 MHz] 7.73 (1 H, d, J_{PH} 591.0, PH), 7.44 (1 H, dt, *J* 8.25, 7.16, 4-H), 6.72 (1 H, m, H-3) and 6.69 (1 H, m, 5-H).

6-Chloro(2-hydroxyphenyl)phosphinic acid 10c

Similarly, **9c** (1.0 g, 3.1 mmol) gave a product which was recrystallised from toluene–light petroleum (1:3) to afford compound **10c** (300 mg, 50%) as a white solid; ν_{max}(Nujol)/cm^{-1} 3000 (OH), 2400 (PH), 1600, 1400 and 780 (CCl); δ_H-[$(CD_3)_2SO$, 400 MHz] 10.4 (1 H, br s, OH), 7.78 (1 H, d, J_{PH} 597.1, PH), 7.42 (1 H, t, *J* 8.2, 4-H), 6.96 (1 H, dd, *J* 8.35, 4.05, 5-H) and 6.84 (1 H, dd, *J* 7.85, 4.55, 3-H).

6-Bromo-(2-hydroxyphenyl)phosphinic acid 10d

Similarly, **9d** (2.0 g, 5.5 mmol), gave a product which was recrystallised from toluene–light petroleum (3:1) to afford compound **10d** (1.0 g, 77%) as a white solid; ν_{max}(Nujol)/cm^{-1} 3200 (OH), 2420 (PH), 1590 and 1440; δ_H[$(CD_3)_2SO$, 400 MHz] 8.0 (1 H, br s, OH), 7.69 (1 H, d, J_{PH} 597.8, PH), 7.33 (1 H, t, *J* 8.15, 4-H), 7.13 (1 H, ddd, *J* 7.85, 4.5, 0.6, 5-H) and 6.86 (1 H, dd, *J* 8.35, 4.0, 3-H).

Ethyl diethoxymethyl(2-naphthyl)phosphonate 11

2-Naphthol (14.4 g, 0.1 mol) and **1** (19.6 g, 0.1 mol) were dissolved in a mixture of dry THF–CCl_4 (1:5) (100 cm^3) at room temperature. Dry triethylamine (10.0 g, 0.1 mol) was added dropwise to the mixture the internal temperature of which was maintained at < 30 °C by means of an ice-bath. The mixture was then stirred at room temperature for 4 h, filtered and the filtrate washed with cold 1 mol dm^{-3} hydrochloric acid, 1 mol dm^{-3} aqueous sodium hydroxide and water and dried ($MgSO_4$). Evaporation followed by distillation on a wiped-wall distillation unit at 140 °C/0.1 mmHg afforded compound **11** (26.4 g, 78%) as a clear oil; ν_{max}(thin film)/cm^{-1} 1600/1510 (Ar),

1280 (PO), 1210 and 1060; δ_H($CDCl_3$, 90 MHz) 7.9–7.7 (4 H, m, Ar), 7.6–7.3 (3 H, m, Ar), 4.95 (1 H, d, *J* 7.2, PCH), 4.5–4.2 (2 H, m, CH_2), 4.1–3.6 (4 H, m, CH_2 × 2) and 1.25 (9 H, m, CH_3 × 3); δ_P($CDCl_3$, 36 MHz) 10.8.

LDA-induced rearrangement of 11

A solution of lithium diisopropylamide (10 mmol) in dry tetrahydrofuran (THF) (10 cm^3) was added dropwise to a solution of compound **11** (3.4 g, 10 mmol) in THF (40 cm^3) at −70 °C under argon. The reaction mixture was stirred at −70 °C for 1 h and then at room temperature for 1 h. The reaction mixture was poured into saturated aqueous ammonium chloride (50 cm^3) and extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$) and evaporated to give the crude product as an oil. Purification by column chromatography over silica gel eluting with light petroleum–diethyl ether (3:1) afforded ethyl diethoxymethyl(2-hydroxy-1-naphthyl)phosphinate **13** (0.3 g, 9%) as an oil; δ_H($CDCl_3$, 90 MHz) 13.1 (1 H, s, OH), 8.4–7.5 (6 H, m, Ar), 5.5 (1 H, d, *J* 10.8, PCH), 4.8–3.6 (6 H, m, CH_2 × 3) and 1.3 (9 H, m, CH_3 × 3); δ_C($CDCl_3$, 22.5 MHz) (quaternary carbons) 169.5 (d, $J_{C\text{-}2,P}$ 4.3, C-2), 137.3 (d, $J_{C\text{-}8,P}$ 9.5, C-8), 132.0 (d, $J_{C\text{-}4,P}$ 11.0, C-4) and 102.5 (d, $J_{C\text{-}1,P}$ 117.0, C-1); δ_P($CDCl_3$, 36 MHz) 42.6. Additionally obtained was ethyl diethoxymethyl(2-hydroxy-3-naphthyl)phosphinate **12** (0.6 g, 18%) as a white solid, mp 108–112 °C; δ_H($CDCl_3$, 90 MHz) 10.7 (1 H, s, OH), 8.4–7.8 (6 H, m, Ar), 5.2 (1 H, d, *J* 7.9, PCH), 4.8–3.8 (6 H, m, CH_2 × 3) and 1.3 (9 H, m, CH_3 × 3); δ_C($CDCl_3$, 22.5 MHz) (quaternary c) 158.2 (d, $J_{C\text{-}2,P}$ 5.5, C-2), 138.4 (d, $J_{C\text{-}8,P}$ 2.0, C-8), 127.9 (d, $J_{C\text{-}4,P}$ 13.0, C-4) and 113.0 (d, $J_{C\text{-}3,P}$ 116.7, C-3); δ_P($CDCl_3$, 36 MHz) 36.3.

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