General Synthesis of α,α-Dideuteriated Phosphonic Esters

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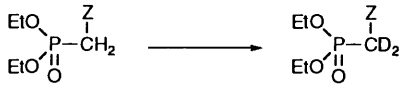
A range of α,α-dideuteriated phosphonic esters has been prepared by deuteriolysis of α-silylated α-phosphonylated carbanions with D_2O as deuterium source. In most cases, incorporation of deuterium is greater than 95% and the yields are good to excellent. The title products are potential tracer compounds in many biological and industrial applications.

α,α-Dideuteriated phosphonic esters form a family of useful compounds in organic synthesis, particularly in Wittig–Horner olefination reactions,[1] and some of these compounds which show biological activity have been described as tracers.[2] In most cited examples the phosphonic residue is bonded to a strongly electron-withdrawing group (Z) (*e.g.*, Z = COR, CO_2R, CN). Incorporation of deuterium is made with D_2O or a deuteriated alcohol (MeOD, EtOD) in the presence of a base (K_2CO_3, MeONa, EtONa, NaH) (Scheme 1). Deuterium-

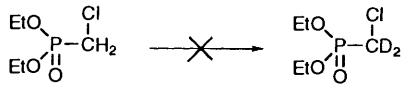


Z = COR, CO_2R, CN

Scheme 1 *Reagents:* Base, D_2O or ROD

incorporation ratios after several successive runs are very variable (16–77%). These methods are subordinated to the presence of an electron-withdrawing substituent (Z) and are totally inadequate for those phosphonates that contain a base-sensitive P–C bond[3] [*e.g.*, Z = F, P(O)(OEt)$_2$]. One should also note the preparation of α-deuteriated phosphonates by the classical Arbuzov reaction of a trialkyl phosphite with a deuteriated halogenoalkane.[4]

We wished to make chloromethyl α,α-dideuterio-phosphonate available in large quantities because of its potential use as a precursor of α-aminoalkylphosphonic acids.[5] Attempted deuteriation of diethyl chloromethylphosphonate by the above mentioned methods was unsatisfactory: the K_2CO_3–D_2O–tetrahydrofuran (THF) system was inactive, whereas reaction with LiOD–D_2O–THF led only to partial deuteriation (≈40%) after 3 h, and furthermore 40% of the product was competitively hydrolysed by the basic reaction medium (Scheme 2). An alternative deuteriation method was obviously needed.

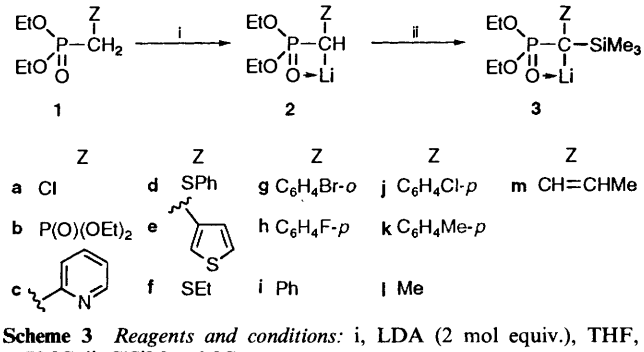


Scheme 2 *Reagents:* K_2CO_3, D_2O, THF or LiOD, D_2O, THF

We have now settled on a new, easy-to-scale-up method that can transform, in a single run, not only chloromethylphosphonate but also α-Z-substituted methylphosphonates, Z being either electron-withdrawing [Cl, P(O)(OEt)$_2$, α-pyridyl, phenylthio, β-thienyl, ethylthio, substituted phenyl] or not (Me, CH=CHMe), into their α,α-dideuterioanalogues, in high yield and with complete incorporation of deuterium, using only D_2O as the cheap deuterium source. Chloro- and fluoro-dideuteriomethylphosphonates could also be prepared in similar yield and deuterium content by a closely related process. A comparison between our method and the published methods of H/D exchange in basic medium will be presented.

Results and Discussion

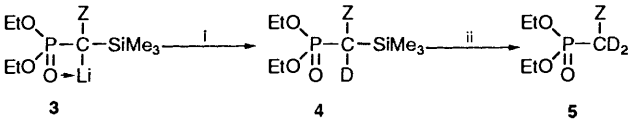
Our method is based upon the formation and reactivity of α-silylated α-phosphonylated carbanions **3**. These carbanions can be quantitatively formed, as we have previously shown,[6] by the reaction of α-Z-substituted methylphosphonates with chlorotrimethylsilane in the presence of 2 mole equivalents of lithium diisopropylamide (LDA) (Scheme 3). Carbanions **3** are



Scheme 3 *Reagents and conditions:* i, LDA (2 mol equiv.), THF, −78 °C; ii, $ClSiMe_3$, 0 °C

remarkably stabilized by the trimethylsilyl group and can be kept at room temperature without rearrangement or decomposition. In order to ensure quantitative formation of carbanions **3** whatever the Z group, phosphonate **1** was treated with 2 mole equivalents of LDA at −78 °C, and the solution was warmed to 0 °C. To carbanion **2** thus formed was then added a slight excess of chlorotrimethylsilane, resulting in quantitative formation of anion **3** in an exothermic ($\Delta T \approx$ 20 °C) reaction. ^{31}P NMR established the quantitative formation of anion **3**: the signal of the α-silylated α-phosphonylated carbanions **3** is ~3 ppm downfield from that of the α-phosphonylated carbanions **2**.

Deuterium was introduced by treatment of α-silylated carbanions **3** with an excess of D_2O at room temperature. Deuteriolysis of carbanion **3** released 1 mole equivalent of LiOD that specifically and cleanly cleaved the C–Si bond of deuterio intermediate **4**, thus incorporating the second deuterium atom of dideuterio product **5** (Scheme 4). The rate of



Scheme 4 *Reagents and conditions:* i, D_2O, THF, 20 °C; ii, LiOD, D_2O, THF, 20 °C

Table 1

Entry	1	C–Si Cleavage conditions	Time *t*/h	Yield (%) of **5**	[%] D in **5**
1	**1a**	LiOD–D_2O–THF	0.5	91	>95
2	**1b**	LiOD–D_2O–THF	1	72	93
3	**1c**	LiOD–D_2O–THF	1	83	>95
4	**1d**	LiOD–D_2O–THF	1	89	>95
5	**1e**	LiOD–D_2O–THF	2	87	>95
6	**1f**	LiOD–D_2O–THF	2	91	>95
7	**1g**	LiOD–D_2O–THF NaOD	8	83	>95
8	**1h**	LiOD–D_2O–THF NaOD	10	94	>95
9	**1i**	LiOD–D_2O–THF NaOD	20	92	>95
10	**1j**	LiOD–D_2O–THF NaOD	20	93	>95
11	**1k**	LiOD–D_2O–THF NaOD	20	96	>95
12	**1l**[a]	EtOD–D_2O, NaOEt–NaOD	5	60	92
13	**1m**	LiOD–D_2O–THF NaOD	3	71	>95

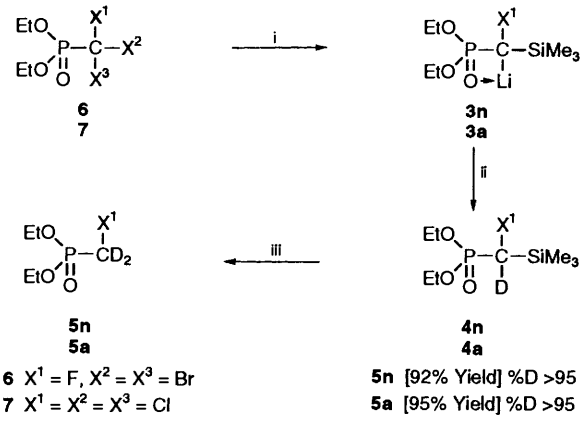
[a] Isolated before treatment.

cleavage of the C–Si bond in intermediate **4** was dependent upon the nature of Z: the stronger the released acid, the faster the cleavage. Reaction times varied from 0.5 to 20 h. Results are summarized in Table 1.

With compounds **4a–f** (entries 1–6), C–Si bond cleavage was rapidly and cleanly carried out with released LiOD; with compounds **4g–k** (entries 7–11), cleavage was slower, but could be accelerated by the addition of Na metal (2 mol equiv.) to the reaction mixture; with compound **4m** (entry 13), Na metal (2 mol equiv.) was added and the reaction mixture required heating to 45 °C. Compound **4l** (entry 12) was unreactive under the above conditions and was therefore isolated and treated in a further step with NaOEt–NaOD in a D_2O–EtOD mixture; cleavage was complete after 5 h at room temperature. Compound **5l** was thus the only compound that could not be obtained in a one-pot procedure. Compounds **5a–m** were isolated after acidic treatment, except for the pyridyl compound **5c**, extraction and bulb-to-bulb distillation in a Kugelrohr apparatus.

For phosphonates **1a–m**, we used LDA as metallating reagent; with compound **1b** [Z = P(O)$(OEt)_2$] (entry 2) however, when using this base the incorporation of deuterium was only 62 ± 1%. We could overcome this difficulty and raise the deuterium content to 93% by replacing LDA by lithium 2,2,6,6-tetramethylpiperidide (LiTMP). We suggest the following tentative explanation of this phenomenon. Of all α-silylated α-phosphonylated carbanions of type **3** we prepared, compound **3b** [Z = P(O)$(OEt)_2$] is the most stable and deuteriolysis was so slow that this anion could still be observed by ^{31}P NMR spectroscopy even after addition of D_2O to the reaction mixture [$\delta(^{31}P)$ (THF) **3b** = 42.07]. Presumably, the lower D incorporation in compound **5b** in the case of LDA is due to a phenomenon similar to that pointed out by Seebach.[7] A proton is transferred to carbanion **3** by diisopropylamine, which in turn is deuteriated in a concerted mechanism. Most probably, direct deuteriation and concerted proton transfer are competing reactions for all carbanions **3**, but in the case of compound **3b**, which is the most sterically hindered, protonation by diisopropylamine is no more a minor reaction. Association between anion **3b** and the amine would clearly be less favoured with the more sterically hindered 2,2,6,6-tetramethylpiperidine, thus reducing the concerted proton-transfer pathway, and dramatically increasing D incorporation.

Dideuteriofluoromethylphosphonate **5n** could not be made from the protonated analogue **1n**: in fact, metallation of diethyl fluoromethylphosphonate yielded a carbanion **2n** that was unstable, despite the presence of excess of LDA. Yet this difficulty could be overcome by using a slightly different reaction scheme with diethyl dibromofluoromethylphosphonate[8] **6** as precursor (Scheme 5). Action of 2 mole equivalents of



Scheme 5 *Reagents and conditions:* i, BuLi (2 mol equiv.), THF, −78 °C; $ClSiMe_3$; ii, D_2O, **3a** or EtOD, **3n**, THF, −78 °C; iii, LiOD, D_2O or EtOLi, EtOD, 0 °C

BuLi in the presence of Me_3SiCl resulted in Br–Li exchange and concomitant coupling with the $SiMe_3$ group, thus affording anion **3n**. Subsequent treatment of anion **3n** at −78 °C by excess of EtOD released EtOLi that selectively and instantaneously cleaved the C–Si bond of intermediate **4n**, yielding compound **5n** which was isolated after acidic treatment (Scheme 5).

Likewise, compound **5a** (Z = Cl) could also be obtained by action of 2 mole equivalents of BuLi on diethyl trichloromethylphosphonate[9] **7** followed by silylation and deuteriolysis in the usual way. The yield and %D were also excellent (Scheme 5), and thus this method is interesting as an alternative route to compound **5a** because diethyl trichloromethylphosphonate **7** has just recently been made commercially available.

The currently described method was compared with the published methods consisting of H/D exchange in basic medium with D_2O as deuterium source; we chose the K_2CO_3–D_2O–THF and LiOD–D_2O–THF systems. Results are summarized in Table 2. Those phosphonates **1** of which the methylene protons are not acidic enough (Z = Me and Z = CH=CHMe) were not tested, neither were those which are rapidly decomposed in basic aqueous medium [Z = P(O)-$(OEt)_2$ and Z = F]. With the K_2CO_3–D_2O–THF system, only compound **1c** (entry 2) gave satisfactory results; the other phosphonates were not reactive enough [0 < %D < 25], and with the LiOD–D_2O–THF system, only compound **1j** (entry 6) gave a satisfactory result; competition between hydrolysis and deuterium incorporation was observed (Table 2). The LiOD–D_2O–THF system proved to be more efficient in terms of D incorporation, yet competition between hydrolysis and

Table 2[a]

Entry	1	Yield (%)[b] of 5	[% D][b] in 5	Yield (%)[c] of 5	[% D][c] in 5
1	**1a**	90	0	60	40
2	**1c**	95	100	30	100
3	**1d**	69	25	32	100
4	**1f**	91	0	60	45
5	**1i**	94	13	65	100
6	**1j**	95	12	75	100

[a] Reactions performed using 20 mmol substrate. [b] K_2CO_3 (2 g), D_2O (10 cm^3), THF (20 cm^3), 60 °C, 3 h. [c] Li (0.150 g), D_2O (10 cm^3), THF (20 cm^3), 60 °C, 3 h.

deuterium incorporation was observed, resulting in only poor to fair yields [30 < yield % < 75]. These comparison experiments clearly underscore the wider applicability and efficiency of the method here reported.

Conclusions.—In summary, our deuterium incorporation method in phosphonic esters has several advantages: in all but one example it is a one-pot procedure, it uses only cheap D_2O as the deuterium source, it can easily be scaled up (up to 1 mol), incorporation of deuterium and chemical yields are good to excellent, and the reaction conditions are mild enough to preserve functionality at phosphorus. Chemical yields and deuterium incorporation are always better than those obtained by previously reported methods.

Experimental

^{31}P NMR and ^1H NMR spectra were recorded on a Bruker AC200 spectrometer, with 85% H_3PO_4 as external standard (positive chemical shifts are downfield of this reference) for ^{31}P NMR and $CDCl_3$ as internal standard for ^1H NMR; ^2H NMR spectra were recorded on a Bruker AM400 spectrometer with $CDCl_3$ as internal standard; coupling constants are quoted in Hz. High-resolution mass spectra (HRMS) were recorded on VG ZAB-HSQ or Bruker CMS 47X ICR FT mass spectrometers. All reactions, including deuteriolysis, were carried out under an inert atmosphere and scrupulously anhydrous conditions. A Büchi GKR-50 apparatus with three flasks was used for distillation. The flask containing the crude product was in the upper part of the oven, and the collecting flask just outside.

α,α-Dideuteriated Diethyl Phosphonates **5a**, **5c–5f** (*Schemes* 3 *and* 4).—To a stirred mixture of BuLi (1.6 mol dm^{-3} in hexane; 66 cm^3, 105 mmol) and THF (65 cm^3) cooled to −70 °C was added a solution of diisopropylamine (11.5 g, 118 mmol) in THF (30 cm^3). The reaction mixture was allowed to warm to −10 °C and was maintained at that temperature for 10 min. Then it was cooled to −78 °C and a solution of compound **1** (50 mmol) in THF (30 cm^3) was added dropwise over the period of a few minutes. The reaction mixture was allowed to warm to 0 °C, and a solution of chlorotrimethylsilane (6 g, 55 mmol) in THF (20 cm^3) was added. The reaction was exothermic (~15–20 °C increase in temperature). After 30 min, D_2O (30 cm^3) was added at room temperature with vigorous stirring of the mixture. When deuteriolysis was complete (see Table 1) the reaction mixture was treated with 5 mol dm^{-3} hydrochloric acid (except for **5c**). The aqueous phase was extracted with CH_2Cl_2 (3 × 50 cm^3), the organic layer was dried ($MgSO_4$), and the solvents were evaporated off under reduced pressure. The crude product was purified by bulb-to-bulb distillation.

Compound **5a** (8.6 g, 91%), b.p. (16 mmHg) 160–165 °C; $\delta_H(CDCl_3)$ 1.36 (t, $^3J_{HH}$ 7, OCH_2Me) and 4.20 (dq, $^3J_{PH}$ = $^3J_{HH}$ = 7, OCH_2Me); $\delta_D(CDCl_3)$ 3.37 (br s, CD_2); $\delta_P(CDCl_3)$ +18.9; HRMS: (Found: M^+, 188.0364. Calc. for $C_5H_{10}{}^{35}ClD_2O_3P$: M, 188.0333).

Compound **5c** (9.6 g, 83%), b.p. (16 mmHg) 230–240 °C; $\delta_H(CDCl_3)$ 1.23 (t, $^3J_{HH}$ 7, OCH_2Me), 4.04 (dq, $^3J_{PH}$ = $^3J_{HH}$ = 7, OCH_2Me), 7.15 (1 H, m), 7.37 (1 H, m), 7.60 (1 H, m) and 8.50 (1 H, m); $\delta_D(CDCl_3)$ 3.18 (d, $^2J_{PD}$ 3, CD_2); $\delta_P(CDCl_3)$ +25.4; HRMS: (Found: M^+, 231.0993. Calc. for $C_{10}H_{14}D_2NO_3P$: M, 231.0993).

Compound **5d** (11.6 g, 89%), b.p. (16 mmHg), 240–250 °C; $\delta_H(CDCl_3)$ 1.31 (t, $^3J_{HH}$ 7, OCH_2Me), 4.14 (dq, $^3J_{PH}$ = $^3J_{HH}$ = 7, OCH_2Me), 7.27 (3 H, m) and 7.42 (2 H, m); $\delta_D(CDCl_3)$ 3.10 (br s, CD_2); $\delta_P(CDCl_3)$ +23.5; HRMS: (Found: M^+, 262.0788. Calc. for $C_{11}H_{15}D_2O_3PS$: M, 262.0762).

Compound **5e** (10.2 g, 87%), b.p. (16 mmHg), 215–220 °C; $\delta_H(CDCl_3)$ 1.25 (t, $^3J_{HH}$ 7, OCH_2Me), 4.03 (dq, $^3J_{PH}$ = $^3J_{HH}$ = 7, OCH_2Me), 7.08 (1 H, m), 7.16 (1 H, m) and 7.27 (1 H, m); $\delta_D(CDCl_3)$ 3.10 (br s, CD_2); $\delta_P(CDCl_3)$ +26.4; HRMS: (Found: M^+, 236.0606. Calc. for $C_9H_{13}D_2O_3PS$: M, 236.0605).

Compound **5f** (9.7 g, 91%), b.p. (16 mmHg) 190–200 °C; $\delta_H(CDCl_3)$ 1.26 (t, $^3J_{HH}$ 7, SCH_2Me), 1.33 (t, $^3J_{HH}$ 7, OCH_2Me), 2.73 (q, $^3J_{HH}$ 7, SCH_2Me) and 4.16 (dq, $^3J_{PH}$ = $^3J_{HH}$ = 7, OCH_2Me); $\delta_D(CDCl_3)$ 2.54 (d, $^2J_{PD}$ 1.5, CD_2); $\delta_P(CDCl_3)$ +25.2; HRMS: (Found: M^+, 214.0762. Calc. for $C_7H_{15}D_2O_3PS$: M, 214.0762).

Tetraethyl Dideuteriomethylenebisphosphonate **5b** (*Schemes* 3 *and* 4).—Experimental conditions were the same as those described above except that 2,2,6,6-tetramethylpiperidine (16.2 g, 115 mmol) was used instead of diisopropylamine. Compound **5b** (10 g, 72%), b.p. (16 mmHg) 220–230 °C; $\delta_H(CDCl_3)$ 1.35 (t, $^3J_{HH}$ 7, OCH_2Me) and 4.18 (dq, $^3J_{PH}$ = $^3J_{HH}$ = 7, OCH_2Me); $\delta_D(CDCl_3)$ 2.29 (br s, CD_2); $\delta_P(CDCl_3)$ +20.0; HRMS: (Found: M^+, 290.1020. Calc. for $C_9H_{20}D_2O_6P_2$: M, 290.1017).

α,α-Dideuteriated Diethyl Phosphonates **5g–5k** (*Schemes* 3 *and* 4).—Experimental conditions were the same as those described above except that, after addition of D_2O (30 cm^3), Na metal (2.3 g, 100 mmol) was added at room temperature to the reaction mixture. When deuteriolysis was complete (see Table 1) the reaction mixture was treated with 5 mol dm^{-3} hydrochloric acid as above.

Compound **5g** (12.8 g, 83%), b.p. (16 mmHg) 240–245 °C; $\delta_H(CDCl_3)$ 1.25 (t, $^3J_{HH}$ 7, OCH_2Me), 4.05 (dq, $^3J_{PH}$ = $^3J_{HH}$ = 7, OCH_2Me), 7.10 (1 H, m), 7.27 (1 H, m), 7.44 (1 H, m) and 7.54 (1 H, m); $\delta_D(CDCl_3)$ 3.27 (br s, CD_2); $\delta_P(CDCl_3)$ +25.7.

Compound **5h** (11.6 g, 94%), b.p. (16 mmHg) 200–210 °C; $\delta_H(CDCl_3)$ 1.25 (t, $^3J_{HH}$ 7, OCH_2Me), 4.02 (dq, $^3J_{PH}$ = $^3J_{HH}$ = 7, OCH_2Me), 7.01 (2 H, m) and 7.27 (2 H, m); $\delta_D(CDCl_3)$ 3.02 (br s, CD_2); $\delta_P(CDCl_3)$ +26.7; HRMS: (Found: M^+, 248.0968. Calc. for $C_{11}H_{14}D_2FO_3P$: M, 248.0947).

Compound **5i** (10.6 g, 92%), b.p. (16 mmHg) 210–220 °C; $\delta_H(CDCl_3)$ 1.21 (t, $^3J_{HH}$ 7, OCH_2Me), 3.98 (dq, $^3J_{PH}$ = $^3J_{HH}$ = 7, OCH_2Me) and 7.27 (br s, Ph); $\delta_D(CDCl_3)$ 2.94 (d, $^2J_{PD}$ 3, CD_2); $\delta_P(CDCl_3)$ +27.1; HRMS: (Found: M^+, 230.1079. Calc. for $C_{11}H_{15}D_2O_3P$: (M, 230.1050).

Compound **5j** (12.3 g, 93%), b.p. (16 mmHg) 240–245 °C; $\delta_H(CDCl_3)$ 1.26 (t, $^3J_{HH}$ 7, OCH_2Me), 4.03 (dq, $^3J_{PH}$ = $^3J_{HH}$ = 7, OCH_2Me) and 7.26 (m, C_6H_4); $\delta_D(CDCl_3)$ 2.63 (d, $^2J_{PD}$ 3, CD_2); $\delta_P(CDCl_3)$ +26.3.

Compound **5k** (11.7 g, 96%), b.p. (16 mmHg) 220–225 °C; $\delta_H(CDCl_3)$ 1.25 (t, $^3J_{HH}$ 7, OCH_2Me), 2.32 (d, J 2.5, *p*-Me), 4.01 (dq, $^3J_{PH}$ = $^3J_{HH}$ = 7, OCH_2Me) and 7.10 (m, C_6H_4); $\delta_D(CDCl_3)$ 2.94 (d, $^2J_{PD}$ 2.5, CD_2); $\delta_P(CDCl_3)$ +27.3.

Diethyl 1,1-*Dideuteriobut-2-enylphosphonate* **5m** (*Schemes* 3 *and* 4).—Experimental conditions were the same as those described above except that, after addition of D_2O (30 cm^3), Na metal (2.3 g, 100 mmol) was added to the reaction mixture,

which was then heated at 45 °C for 3 h. Compound **5m** (6.9 g, 71%), b.p. (16 mmHg) 170–175 °C; $\delta_H(CDCl_3)$ 1.30 (t, $^3J_{HH}$ 7, OCH_2Me), 1.69 (t, $^3J_{HH}$ 6, $CHMe$), 4.08 (dq, $^3J_{PH} = {}^3J_{HH} = 7$, OCH_2Me), 5.44 (m, =CH) and 5.58 (m, =CH); $\delta_D(CDCl_3)$ 2.43 (br s, CD_2); $\delta_P(CDCl_3)$ +28.7.

Diethyl 1,1-*Dideuterioethylphosphonate* **5l** (*Schemes* 3 *and* 4).—Experimental conditions were the same as those described above except that, after addition of D_2O (30 cm^3), the aqueous phase was extracted with CH_2Cl_2 (3 × 50 cm^3), the organic layer was dried ($MgSO_4$) and the solvent was evaporated off under reduced pressure. The crude product was dissolved in a mixture of D_2O (20 cm^3) and EtOD (20 cm^3), and Na metal (2 g, 87 mmol) was added at room temperature. When deuteriolysis was complete (see Table 1), water was added (30 cm^3), the aqueous phase was extracted with CH_2Cl_2 (3 × 50 cm^3), the organic layer was dried ($MgSO_4$), and the solvent was evaporated off under reduced pressure. The crude product was purified by bulb-to-bulb distillation. Compound **5l** (5 g, 60%), b.p. (16 mmHg) 130–145 °C; $\delta_H(CDCl_3)$ 1.11 (d, $^3J_{PH}$ 20, Me), 1.29 (t, $^3J_{HH}$ 7, OCH_2Me) and 4.10 (dq, $^3J_{PH} = {}^3J_{HH} = 7$, OCH_2Me); $\delta_D(CDCl_3)$ 1.60 (br s, CD_2); $\delta_P(CDCl_3)$ +34.0.

Diethyl Dideuteriofluoromethylphosphonate **5n** (*Scheme* 5).—To a stirred mixture of BuLi (1.6 mol dm^{-3} in hexane; 66 cm^3, 105 mmol) and THF (65 cm^3) cooled to −78 °C was added a mixture of dibromide **6** (16.4 g, 50 mmol) and chlorotrimethylsilane (6 g, 55 mmol) in THF (50 cm^3). The reaction mixture was stirred at −78 °C for 5 min, ethan[^{2}H]ol (30 cm^3) was added at −78 °C, and the mixture was allowed to warm to 0 °C. When deuteriolysis was complete (10 min at 0 °C) the reaction mixture was poured into a beaker containing a stirred mixture of 2 mol dm^{-3} hydrochloric acid (30 cm^3), an equal volume of crushed ice, and dichloromethane (50 cm^3). The aqueous phase was extracted with CH_2Cl_2 (2 × 50 cm^3). The combined organic extracts were dried ($MgSO_4$), the solvents were evaporated off under reduced pressure, and the crude product was purified by bulb-to-bulb distillation. Compound **5n** (7.9 g, 92%), b.p. (16 mmHg) 155–160 °C; $\delta_H(CDCl_3)$ 1.34 (t, $^3J_{HH}$ 7, OCH_2Me) and 4.19 (dq, $^3J_{PH} = {}^3J_{HH} = 7$, OCH_2Me); $\delta_D(CDCl_3)$ 4.54 ($^2J_{FD}$ 7, CD_2); $\delta_P(CDCl_3)$ +16.7 (d, $^2J_{PF}$ 63.7); HRMS: [Found: ($M^+ - 1$), 171.0577. Calc. for $C_5H_9D_2FO_3P$: (M − 1), 171.0550].

Diethyl Chlorodideuteriomethylphosphonate **5a** (*Scheme* 5).—To a stirred mixture of BuLi (1.6 mol dm^{-3} in hexane; 66 cm^3, 105 mmol) and THF (65 cm^3) cooled to −78 °C was added a mixture of trichloride **7** (12.7 g, 50 mmol) and chlorotrimethylsilane (6 g, 55 mmol) in THF (50 cm^3). The reaction mixture was stirred at −78 °C for 5 min, D_2O (30 cm^3) was added at −78 °C, and the mixture was allowed to warm to 0 °C. When deuteriolysis was complete (10 min at 0 °C) the reaction mixture was treated with 5 mol dm^{-3} hydrochloric acid (20 cm^3). The aqueous phase was extracted with CH_2Cl_2 (3 × 50 cm^3) and the organic layer was dried ($MgSO_4$), the solvents were evaporated off under reduced pressure and the crude product was purified by bulb-to-bulb distillation (9 g, 95%).

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