



Preparation of alkyl- and aryl-amino[2H₂]methylphosphinic acids

Sylvie Berté-Verrando, François Nief, Carl Patois, Philippe Savignac

► To cite this version:

Sylvie Berté-Verrando, François Nief, Carl Patois, Philippe Savignac. Preparation of alkyl- and aryl-amino[2H₂]methylphosphinic acids. Journal of the Chemical Society, Perkin Transactions 1, 1995, 1 (16), pp.2045-2048. 10.1039/P19950002045 . hal-03166539

HAL Id: hal-03166539

<https://hal.science/hal-03166539>

Submitted on 11 Mar 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Preparation of alkyl- and aryl-amino[$^2\text{H}_2$]methylphosphinic acids

Sylvie Berté-Verrando, François Nief, Carl Patois and Philippe Savignac

Hétéroéléments et Coordination, URA CNRS 1499, DCPH, Ecole Polytechnique

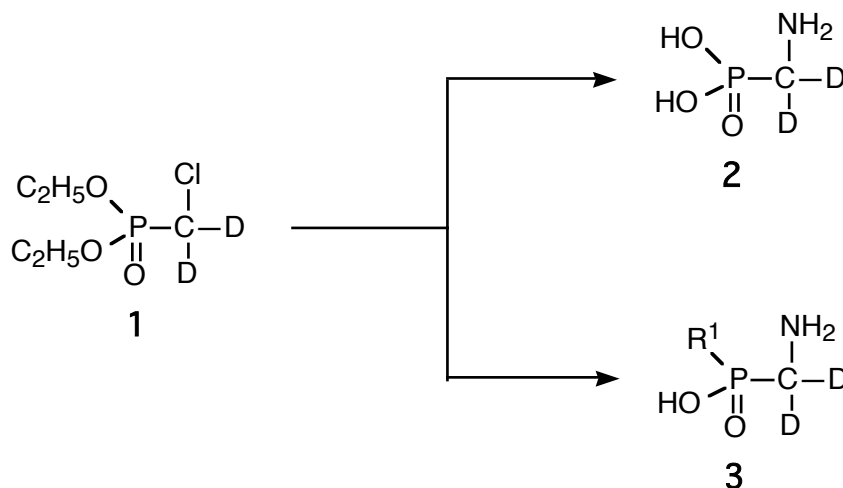
91128 PALAISEAU Cedex, France

α,α -Dideuteriated diethyl chloromethylphosphonate was transformed into α,α -dideuteriated alkyl chloromethylphosphinates after reaction with POCl_3 and Grignard reagents (R^1MgX). α,α -Dideuteriated phenyl chloromethylphosphinate was prepared by deuteriolysis of an α -silylated α -phosphonylated carbanion with D_2O . After conversion into trifluoroethoxyphosphinic esters the α,α -dideuteriated alkyl and phenyl chloromethylphosphinates were transformed into azides and then reduced and hydrogenolised into α,α -dideuteriated alkyl and phenyl aminomethylphosphinic acids.

Since the discovery of 2-aminoethylphosphonic acid (AEP) from protozoa in 1959¹, the number of known natural products containing a P-C bond has been steadily increasing. L-Phosphinothricin, a γ -aminophosphinic acid, is one of the most important members of this class of compounds. It constitutes the N-terminal amino acid of antibiotic tripeptides² produced by several streptomycete and actinomycete strains and exhibits strong herbicidal activity³. The different syntheses of aminophosphinic acids have been described by Maier in 1983⁴, and more recently reviewed by Kukhar and Solodenko⁵.

We recently discovered the usefulness of α,α -dideuteriated diethyl chloromethylphosphonate⁶ **1** in the preparation of α,α -dideuteriated aminomethylphosphonic acid **2**. Since ester **1** is an easily accessible starting material⁷ available in high yield (95%) and with a high deuterium content

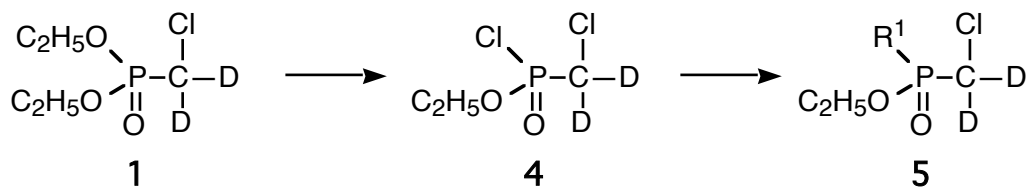
[%D>95] we decided to extend the application of **1** to the preparation of α,α -dideuteriated alkyl and aryl aminomethylphosphinic acids **3** (Scheme1). Consequently, we now describe the preparation of aminomethylphosphinic acids from cheap and readily accessible diethyl chloromethylphosphonate **1**.



Scheme 1

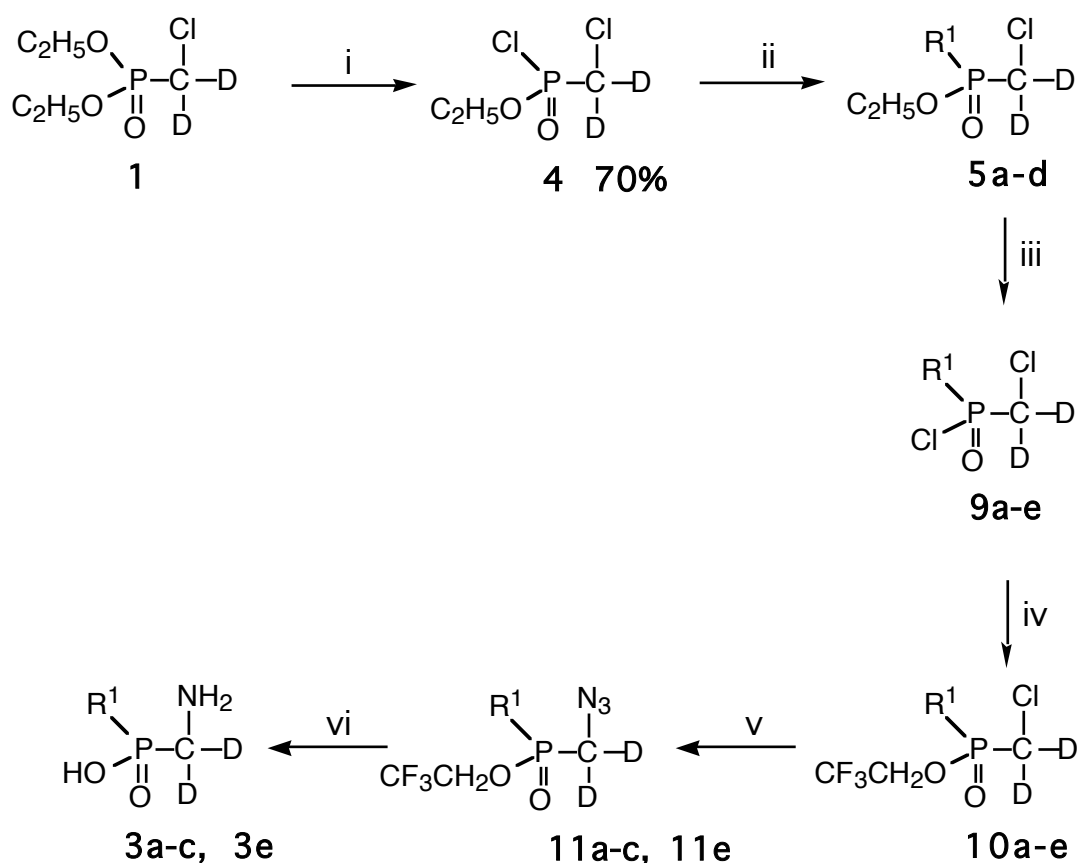
Results and Discussion

For the synthesis of α,α -dideuteriated aminomethylphosphinic acids **3** from **1**, two key steps are needed : a) selective replacement at phosphorus in **1** of only one ethoxy group by an alkyl or aryl group (R¹) in order to obtain chloromethylphosphinates **5** through the intermediate **4** (Scheme 2), and b) selective nucleophilic substitution of the chlorine atom by a precursor of the amino group. The structural and experimental conditions controlling this last step have already been extensively studied in the synthesis of α,α -dideuteriated aminomethylphosphonic esters⁶.



Scheme 2

In the initial stages (Scheme 3) diester **1** was reacted with phosphorus oxychloride in excess at 75-80°C during 4 h; it gave exclusively the monochlorophosphonate **4** in good isolated yield⁸ (70%). Chlorophosphonate **4** can easily be purified since both phosphorus oxychloride in excess and ethyl dichlorophosphate concomitantly formed can be eliminated by distillation.



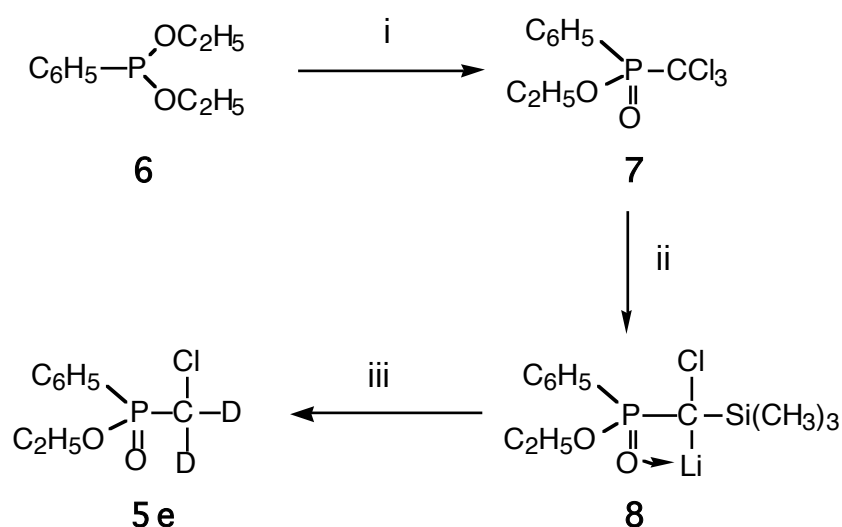
a R¹ = Me b R¹ = Et c R¹ = Pr d R¹ = CH=CH₂ ; e R¹ = Ph

Scheme 3. Reagents and conditions: i, POCl₃ (1.5 mol equiv.), 80°C, 4 h ; ii, R¹MgX (1.5 mol equiv.), THF/diethylether, -78°C ; iii, POCl₃ (1.5 mol equiv.), 0°C ; iv, CF₃CH₂OH, NEt₃, THF, 20°C ; v, NaN₃, DMSO, 90°C ; vi, H₂, EtOH, HCl 12N (3 mol equiv.), Pd/C, 1 at

Chloromethylphosphinates **5 a-d** were obtained by selective substitution of the P-Cl bond with Grignard reagents (R¹MgX). These reactive magnesium derivatives are neither nucleophilic enough to further attack at the phosphorus atom products **5 a-d** nor basic enough to abstract a deuterium of the methylene group. The reaction was run at low temperature in a tetrahydrofuran (THF) / diethyl ether mixture; it worked with any aliphatic Grignard reagents

(saturated or unsaturated) except with $i\text{PrMgCl}$ which not unexpectedly gave rise to an halogen-metal exchange. All products **5 a-c** were obtained in good yields (54-86%) after purification by distillation, except thermally unstable **5d** which was used as such in the following steps.

At the same time a simple and effective protocol for the synthesis of α,α -dideuteriated aryl chloromethylphosphinates has been developed using the aryl trichloromethylphosphinate **7** as starting material. This preparation is very efficient but less general than the previous one since complex mixtures of products were obtained when the substituent at phosphorus (R^1) is an alkyl group. This synthesis is exemplified by the preparation of α,α -dideuteriated O-ethyl phenyl chloromethylphosphinate **5e** (Scheme 4). Diethyl phenyl phosphonite **6** reacted with an excess of CCl_4 in a Michaelis-Arbuzov reaction to give O-ethyl phenyl trichloromethylphosphinate **7** in 85% yield as a crystalline material. Reaction of **7** with two equivalents of BuLi at low temperature in the presence of chlorotrimethylsilane⁷ (as previously described for diethyl trichloromethylphosphonate) yielded an α -lithiated, α -chlorinated, α -silylated stable carbanion **8**. ^{31}P NMR established the quantitative formation of anion **8** [δ (^{31}P) (THF) **8** = + 51.9]. Treatment of carbanion **8** with an excess of D_2O at low temperature afforded **5e** in excellent yield (92%) and with very high deuterium incorporation [%D>95].

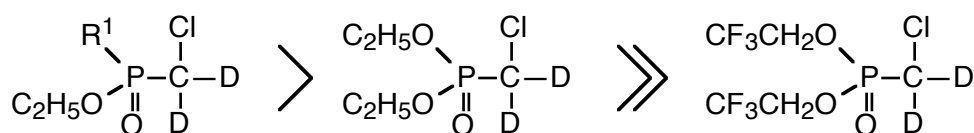


Scheme 4 Reagents and conditions : i, CCl_4 (3 mol equiv.), 80°C ; ii, BuLi (2 mol equiv.), ClSiMe_3 , THF, -80°C ; iii, D_2O , THF, -80°C .

The last key step involves nucleophilic replacement of the chlorine atom by an amine-generating group. In a recent publication we demonstrated the usefulness of sodium azide in dimethyl sulfoxide (DMSO) for this purpose⁶. However, we also showed that replacement of the ethoxy groups at phosphorus by the trifluoroethoxy groups was essential in order to avoid unwanted side reactions such as dealkylation by attack of ethoxy groups.

In the case of chloromethylphosphinic esters **5**, this replacement could be carried out *via* the replacement of the ethoxy group of compounds **5a-d** by chlorine with phosphorus oxychloride (Scheme 3). Chloromethylphosphinic esters **5a-d** being much more reactive than chloromethylphosphonic ester **1** this reaction was best carried out at 0°C. All chloromethylphosphinates **9a-e** were obtained after purification by vacuum distillation (57-71%) except for **9d**.

By comparison of reactions between phosphorus esters and phosphorus oxychloride reported in Scheme 3 it appears that reactivity of phosphorus esters increases with increasing electron density at oxygen of the alkoxy substituent at phosphorus : we verified that bis(trifluoroethyl) chloromethylphosphonate was completely inert towards phosphorus oxychloride (Scheme 5).



Scheme 5

Chloromethylphosphinates **9a-e** were straightforwardly transformed into trifluoroethyl esters **10a-e** in good yields (75-95%) by reaction with trifluoroethanol in THF at room temperature in the presence of triethylamine. All these esters **10a-e** were then reacted with sodium azide in DMSO at 90°C. Reaction times were variable, the longest being with **10e** (R¹=phenyl ; 7h). Yields are generally good (72-84%) and very few side products are detected (< 8% as gauged by ³¹P NMR). So obtained azides **11a-c** and **11e** were used without purification in the final step ; unfortunately **10d** (R¹ = CH=CH₂) was polymerised in the reaction conditions.

These crude azidomethylphosphinates **11a-c** and **11e** were then subjected to reduction Pd/C catalyzed under 1 atm H₂ pressure in the presence of 12 N hydrochloric acid. Hydrogenolysis of the ester function and reduction of the azido into amino group occurred simultaneously at room temperature. After filtration of the ethanolic solution and neutralisation of the hydrochloric acid by addition of propylene oxide, α,α -dideuteriated aminomethylphosphinic acids **3a-c** and **3e** were obtained as precipitates (43-60%). The deuterium content [%D>95%] was fully conserved throughout this multistep synthesis, as verified by the absence of the methylene protons in ¹H NMR spectra

Conclusion

We have herein described the first synthesis of α,α -dideuteriated aminomethylphosphinic acids **3** by nucleophilic amination of chloromethylphosphinates. This multistep synthesis uses easily accessible starting materials with high deuterium incorporation. Every step only makes use of commercial reagents and can easily be scaled up. It is interesting to note that this preparation confirms the advantage of the trifluoroethoxy group over the ethoxy substituent at phosphorus⁶ in the nucleophilic amination of chloromethylphosphinic esters. Only substitution of chlorine was observed and no dealkylated products were detected with R(CF₃CH₂O)P(O)CH₂Cl, whereas with R(EtO)P(O)CH₂Cl the dealkylation and amination are competitive processes.

Experimental

³¹P NMR and ¹H NMR spectra were recorded on a Bruker AC 200 spectrometer with 85% H₃PO₄ as external standard (positive chemical shifts are downfield of this reference) for ³¹P NMR and CDCl₃ as internal standard for ¹H NMR; ²H NMR spectra were recorded on a Bruker AM 400 spectrometer with CDCl₃ 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 Buchi 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 O-Ethyl Chloromethylchlorophosphonate **4*** (Scheme 3). - In a 100 cm³ pear-shaped flask were introduced α,α -dideuteriated diethyl chloromethyl phosphonate **1** (18,8 g, 100 mmol) and phosphorus oxychloride (23g, 150 mmol). The reaction mixture was heated for 4h at 80°C then purified by distillation under reduced pressure after fitting a short column (8 cm fractionating column equipped with a condenser).

Compound **4** (70%), b.p. (0,2 mmHg) 62-69°C ; δ_P (CDCl₃) +30,5 ; δ_H (CDCl₃) 1,43 (t, ³J_{H-H} 7, OCH₂Me), 4,36 (dq, ³J_{P-H} 10 and ³J_{H-H} 7, OCH₂Me); δ_C (CDCl₃) 15.95 (d, ³J_{P-C} 7, OCH₂Me, 38.40 (dp, ¹J_{P-C} 143.6, P-CD₂), 65.22 (d, ²J_{P-C} 8 OCH₂Me)

*α,α -Dideuteriated O-Ethyl P-Alkylchloromethylphosphinates **5a-5d*** (Scheme 4). -To a stirred mixture of **4** (8,95 g, 50 mmol) in THF / ether (1/1) (200 cm³) cooled to -78°C was added dropwise over the period of a few minutes a solution of a commercial alkyl magnesium chloride (55 mmol) in THF (previously standardized before use by titration). The reaction mixture was allowed to warm to room temperature then treated with a 5N hydrochloric acid until acidic pH. The aqueous phase was extracted with CH₂Cl₂ (3 x 50 cm³), the organic layer was dried (MgSO₄), and the solvents were evaporated off under reduced pressure. The crude products were purified by bulb-to- bulb distillation.

Compound **5a** (82%), b.p. (20 mmHg) 150-155°C ; δ_P (CDCl₃) +48,2 ; δ_H (CDCl₃) 1,35 (t, ³J_{H-H} 7, OCH₂Me), 1,60 (d, ²J_{P-H} 15 , P-Me), 4,07 (dq, ³J_{P-H} = ³J_{H-H} = 7, OCH₂Me) ; δ_C (CDCl₃) 11.1 (d, ¹J_{P-C} 102, P-Me), 15.9 (d, ³J_{P-C} 5.9, OCH₂Me), 34.7 (dp, ²J_{P-C} 96.5 and ¹J_{C-D} 23.2, P-CD₂), 60.9 (d, ²J_{P-C} 6, OCH₂Me). HRMS: (Found: M⁺, 158, 02329. Calc. for C₄H₈D₂35ClO₂P: M, 158, 02324).

Compound **5b** (60%), b.p. (20 mmHg) 160-165°C ; δ_P (CDCl₃) +50,6 ; δ_H (CDCl₃) 1,15 (dt, ³J_{P-H} 19 and ³J_{H-H} 7, P-CH₂Me), 1,29 (t, ³J_{H-H} 7, OCH₂Me), 1,85 (dq, ²J_{P-H} 15,4 and ³J_{H-H} 7,7, P-CH₂Me), 4,10 (dq, ³J_{P-H} = ³J_{H-H} = 7, OCH₂Me).

Compound **5c** (54%), b.p. (20 mmHg) 165-170°C ; δ_P (CDCl₃) +49,2 ; δ_H (CDCl₃) 1,15 (t, $^3J_{H-H}$ 7, P-(CH₂)₂Me), 1,30 (t, $^3J_{H-H}$ 7, OCH₂Me), 1,34-1,90 (m, P-(CH₂)₂Me), 4,10 (dq, $^3J_{P-H} = ^3J_{H-H} = 7$, OCH₂Me).

Compound **5d** (76%), δ_P (CDCl₃) +33,2 ; δ_H (CDCl₃) 1,35 (t, $^3J_{H-H}$ 7, OCH₂Me), 4,10 (dq, $^3J_{P-H} = ^3J_{H-H} = 7$, OCH₂Me), 6,16-6,57 (m, CH=CH₂).

O-Ethyl P-Phenylrichloromethylphosphinate 7 (Scheme 5). -A 1000 cm³ round-bottomed flask fitted with a mechanical stirrer, a thermometer and a reflux condenser was charged with CCl₄ (46.2g, 300 mmol). To CCl₄ heated on reflux was added dropwise Diethyl Phenyl Phosphonite **6** (19, 8 g, 100 mmol). After complete addition the reaction mixture was heated for 2h then cooled to room temperature and the excess of CCl₄ evaporated off under reduced pressure. The crude product was purified by addition of hexane in which **7** spontaneously crystallized.

Compound **7** (85%), m.p. 89-90°C (from hexane/ether) 70/30 ; δ_P (CDCl₃) +24,5 ; δ_H (CDCl₃) 1,41 (t, $^3J_{H-H}$ 7, OCH₂Me), 4,46 (dq, $^3J_{P-H} = ^3J_{H-H} = 7$, OCH₂Me), 7,55 (m, C₆H₅) and 8,02 (m, 2H, C₆H₅) ; δ_C (CDCl₃) 17,0 (d, $^3J_{P-C}$ 5, OCH₂Me) 65,5 (d, $^2J_{P-C}$ 6,5, OCH₂Me), 93,5 (d, $^1J_{P-C}$ 105, CCl₃), 123,8 (d, $^1J_{P-C}$ 150, C_{ipso} C₆H₅), 128,7 (d, $^3J_{P-C}$ 13,9, C_{méta} C₆H₅), 134,4 (d, $^4J_{P-C}$ 2,4, C_{para} C₆H₅), 135,0 (d, $^2J_{P-C}$ 9,7, C_{ortho} C₆H₅).

α,α -Dideuteriated O-Ethyl P-Phenylchloromethylphosphinate 5e (Scheme 5). -To a stirred mixture of BuLi (1.6 mol / dm³ in hexane ; 132 cm³, 210 mmol) and THF (270 cm³) cooled to -80°C was added a mixture of **7** (28.7g, 100 mmol) and chlorotrimethylsilane (11.40g, 105 mmol) in THF (100 cm³). The reaction mixture was stirred at -80°C for 15 min, D₂O (50 cm³) was added at -78°C, and the mixture was allowed to warm to 0°C. When deuteriolysis was complete (30 min at 0°C) the reaction mixture was treated with 2N hydrochloric acid until acidic pH. The aqueous phase was extracted with CH₂Cl₂ (3 x 50 cm³), the organic layer was dried (MgSO₄), and the solvents were evaporated off under reduced pressure. and the crude product was purified by bulb-to-bulb distillation.

Compound **5e** (92%), b.p. (20mmHg) 225-230°C; δ_P (CDCl₃) +34,5 ; δ_H (CDCl₃) 1,35 (t, $^3J_{H-H}$ 7, OCH₂Me), 4,14 (m, $^3J_{P-H} = ^3J_{H-H} = 7$, OCH₂Me), 7,57 (m, C₆H₅) and 7,84 (m, C₆H₅) ; δ_C (CDCl₃) 15.9 (d, $^3J_{P-C}$ 5.4, OCH₂Me), 35.5 (dp, $^1J_{P-C}$ 105, P-CD₂), 61.37 (d, $^2J_{P-C}$ 5.8, OCH₂CH₃), 127.18 (d, $^1J_{P-C}$ 136, C_{ipso} C₆H₅) 128.30 (d, $^3J_{P-C}$ 12.6, C_{meta} C₆H₅), 131.70 (d, $^2J_{P-C}$ 10.2, C_{ortho} C₆H₅), 132.25 (s, C_{para} C₆H₅) ; δ_D (H₂O/C₃D₆O) 3,05 (br s, CD₂) ; HRMS: (Found: M⁺, 220, 03894. Calc.for C₉H₁₀D₂35ClO₂P: M, 220, 03889) .

*α,α -Dideuteriated P-Alkylchloromethylchlorophosphinates **9a-9e*** (Scheme 6). -In a 100 cm³ pear-shaped flask containing phosphorus oxychloride (23g, 150 mmol) cooled to 0°C was added dropwise over a few minutes compound **5** (100 mmol). The reaction mixture was allowed to warm slowly to room temperature then purified by distillation under reduced pressure after fitting a short column (8 cm fractionating column equipped with a condenser) .

Compound **9a** (71%), b.p. (0,2 mmHg) 69°C ; δ_P (CDCl₃) +57,5 ; δ_H (CDCl₃) 2,10 (d, $^2J_{P-H}$ 14, P-Me).

Compound **9b** (50%), b.p. (0,2 mmHg) 72°C ; δ_P (CDCl₃) +63,7 ; δ_H (CDCl₃) 1,32 (dt, $^3J_{P-H}$ 23 and $^3J_{H-H}$ 7, P-CH₂Me), 2,35 (dq, $^2J_{P-H}$ 15,4 and $^3J_{H-H}$ 7,7, P-CH₂Me).

Compound **9c** (57%), b.p. (0,2 mmHg) 75°C ; δ_P (CDCl₃) +61,8 ; δ_H (CDCl₃) 1,10 (t, $^3J_{H-H}$ 7, P-(CH₂)₂Me), 1,65-2,35 (m, P-(CH₂)₂Me).

Compound **9d** (61%), δ_P (CDCl₃) +42,7 ; δ_H (CDCl₃) 6,25-6,74 (m, CH=CH₂).

Compound **9e** (61%), b.p. (20 mmHg) 200-210°C ; δ_P (CDCl₃) +46,1 ; δ_H (CDCl₃) 7,63 (m, C₆H₅) and 7,94 (m, C₆H₅).

*α,α -Dideuteriated O-Trifluoroethyl P-Alkylchloromethylphosphinates **10a-10e*** (Scheme 8). -

To a solution of compound **9** (100 mmol) in THF (400 cm³) were successively added at room temperature under stirring, trifluoroethanol (10,5g,105 mmol) in THF (100 cm³) and dropwise over a few minutes , triethylamine (10.6g, 105mmol) in THF (50 cm³). After the addition was complete, the resulting mixture was stirred at room temperature for 2 h. The organic salts were removed by suction filtration, and the filter cake washed with THF. The solvent was removed under reduced pressure and the residue was dissolved in ether and filtered to remove

insoluble triethylamine hydrochloride. Solvent was evaporated off under reduced pressure and the crude product was purified by bulb-to-bulb distillation.

Compound **10a** (75%), b.p. (20 mmHg) 150-155°C ; δ_P (CDCl₃) +52,8 ; δ_H (CDCl₃) 1,74 (d, ²J_{P-H} 15, P-Me), 4,37 (m, OCH₂CF₃).

Compound **10b** (90%), b.p. (20 mmHg) 160-165°C ; δ_P (CDCl₃) +55,6 ; δ_H (CDCl₃) 1,21 (dt, ³J_{P-H} 20 and ³J_{H-H} 7, P-CH₂Me); 2,00 (dq, ²J_{P-H} 15,7 and ³J_{H-H} 7,8, P-CH₂Me), 4,38 (m, OCH₂CF₃).

Compound **10c** (87%), b.p. (20 mmHg) 165-170°C ; δ_P (CDCl₃) +61,8 ; δ_H (CDCl₃) 1,07 (t, ³J_{H-H} 7, P-(CH₂)₂Me), 1,56-2,05 (m, P-(CH₂)₂Me), 4,35 (m, OCH₂CF₃).

Compound **10d** (91%), δ_P (CDCl₃) +37,6 ; δ_H (CDCl₃) 4,36 (m, OCH₂CF₃), 6,12-6,63 (m, CH=CH₂).

Compound **10e** (95%), b.p. (20 mmHg) 195-200°C ; δ_P (CDCl₃) +38,3 ; δ_H (CDCl₃) 4,43 (m, OCH₂CF₃), 7,82 (m, C₆H₅) and 7,88 (m, C₆H₅); δ_C (CDCl₃) 36.2 (dp, ¹J_{P-C} 104.1, P-CD₂), 34.1 (dt, ²J_{C-F} 38 and ²J_{C-P} 6, OCH₂CF₃), 123 (dq, ¹J_{C-F} 277.7 and ³J_{P-C} 8.7, OCH₂CF₃), 126.6 (d, ¹J_{P-C} 123.9, C_{ipso} C₆H₅) 129.15 (d, ³J_{P-C} 13.4, C_{méta} C₆H₅), 132.2 (d, ²J_{P-C} 10.5, C_{ortho} C₆H₅), 134.05 (s, C_{para} C₆H₅) HRMS: (Found M⁺, 274, 01077. Calc.for C₉H₇D₂F₃35ClO₂P: M, 274, 01062).

α,α-Dideuteriated O-Trifluoroethyl P-Alkylazidomethylphosphinates 11a-11c, 11e (Scheme 9). -A mixture of compounds **10** (50 mmol) and sodium azide (75 mmol) in DMSO (165 cm³) was heated under stirring at 90-95°C during 3h. After cooling the reaction was treated with water (165 cm³) and extracted with ether (3x80 cm³). The organic layer was dried (MgSO₄), and the solvents were evaporated off under reduced pressure. Azides were controled before use but never purified by distillation.

Compound **11a** (72%), δ_P (CDCl₃) +52,8 ; δ_H (CDCl₃) 1,63 (d, ²J_{P-H} 14, P-CH₃) ; 4,40 (m, OCH₂CF₃).

Compound **11b** (84%), δ_P (CDCl₃) +56,5 ; δ_H (CDCl₃) 1,23 (dt, ³J_{P-H} 19 and ³J_{H-H} 7, P-CH₂Me), 1,93 (dq, ²J_{P-H} 16 and ³J_{H-H} 8, P-CH₂Me), 4,42 (m, OCH₂CF₃).

Compound **11c** (80%), δ_P (CDCl₃) +63,1 ; δ_H (CDCl₃) 1,08 (t, $^3J_{H-H}$ 7, P-(CH₂)₂Me), 1,60-2,98 (m, P-(CH₂)₂Me), 4,41 (m, OCH₂CF₃).

Compound **11e** (84%), δ_P (CDCl₃) +39,4 ; δ_H (CDCl₃) 4,34 (m, OCH₂CF₃), 7,60 (m, C₆H₅) and 7,85 (m, C₆H₅).

*α,α -Dideuteriated P-Alkylaminomethylphosphinic Acids **3a-3c 3e*** (Scheme 10). -In a 1000 cm³ vessel were introduced compound **11** (50 mmol) in ethanol (95%) (200 cm³), Pd/C (10%) (1.50g), and 12N hydrochloric acid (12.5 cm³). Under atmospheric pressure of H₂ the reaction mixture was stirred at room temperature for 24 h. The catalyst was removed by suction filtration over celite, and the filter cake washed with hot water. The solvents were evaporated off under reduced pressure. The crude product was dissolved in ethanol (95%), then after addition of propylene oxide acids **3** spontaneously precipitated.

Compound **3a** (60%), m.p. > 260°C ; δ_P (D₂O) +32,3 ; δ_H (D₂O) 1,26 (d, $^2J_{P-H}$ 14, P-Me) ; δ_C (D₂O/C₃D₆O) 16,12 (d, $^1J_{P-C}$ 97,5, P-CH₃), 39,1 (dp, $^1J_{P-C}$ 91,1 and $^1J_{C-D}$ 20,7, P-CD₂) ; δ_D (H₂O/C₃D₆O) 2,90 (br s, CD₂); HRMS: (Found: M⁺, 111,0419. Calc. for C₂H₆D₂PNO₂: M, 111,0418).

Compound **3b** (50%), m.p. > 260°C ; δ_P (D₂O) +36,5 ; δ_H (D₂O) 0,94 (dt, $^3J_{P-H}$ 18 and $^3J_{H-H}$ 7, P-CH₂Me), 2,00 (dq, $^2J_{P-H}$ 15,5 and $^3J_{H-H}$ 7,7, P-CH₂Me) ; δ_C (H₂O/C₃D₆O) 6,5 (d, $^2J_{P-C}$ 6, P-CH₂Me), 22,8 (d, $^1J_{P-C}$ 97,9, P-CH₂Me), 37,3 (dp, $^1J_{P-C}$ 86,6 and $^1J_{C-D}$ 20,7, P-CD₂) ; δ_D (H₂O/C₃D₆O) 2,90 (br s, CD₂). HRMS: (Found M⁺, 125,0575. Calc. for C₃H₈D₂PNO₂: (M, 125,0574).

Compound **3c** (43%), m.p. > 260°C ; δ_P (D₂O) +34,7 ; δ_H (D₂O) 0,86 (t, $^3J_{H-H}$ 7, P-(CH₂)₂Me), 1,35-2,15 (m, P-(CH₂)₂Me) ; δ_C (H₂O/C₃D₆O) 15,18 (d, $^2J_{P-C}$ 21,5, P-CH₂-CH₂-CH₃), 15,28 (s, P-CH₂-CH₂-CH₃), 31,25 (d, $^1J_{P-C}$ 96,5, P-CH₂-CH₂-CH₃), 37,05 (dp, $^1J_{P-C}$ 98 and $^1J_{C-D}$ 20,7, P-CD₂) ; δ_D (H₂O/C₃D₆O) 2,87 (br s, CD₂).

HRMS: (Found M⁺, 139,0731. Calc. for C₄H₁₀D₂PNO₂: (M, 139,0731).

Compound **3e** (43%), m.p. > 260°C ; δ_P (D₂O) +27,9 ; δ_H (D₂O) 7,56 (m, C₆H₅) and 7,74 (m, C₆H₅) ; δ_C (H₂O/C₃D₆O) 37,1 (dp, $^1J_{P-C}$ 98 and $^1J_{C-D}$ 20,7, P-CD₂), 128,9 (d, $^3J_{P-C}$ 12,2, C_{méta} C₆H₅), 131,4 (d, $^2J_{P-C}$ 9,3, C_{ortho} C₆H₅), 132,2 (s, C_{para} C₆H₅), 133,6 (d, $^1J_{P-C}$ 125,3,

C_{ipso} C₆H₅) ; δ_D (H₂O/C₃D₆O) 3,05 (br s, CD₂); HRMS: (Found: M⁺, 173,0575. Calc. for C₇H₈D₂PNO₂ : M, 173,0574).

Acknowledgements.

We thank Dr.J.P.Morizur (Universite Paris VI, ERS 72 CNRS) for the HRMS measurements.

References

- 1 (a) M.Horiguchi and M.Kandatsu, *Nature.*, 1959, **184**, 901; (b) Reviews: *The Role of Phosphonates in Living Systems*, R.L.Hilderbrand, Ed; CRC Press; Boca Raton, FL, 1983; (c) T.Hori, M.Horiguchi and A.Hayashi, *Biochemistry of Natural C-P Compounds*; Maruzen, Kyoto Branch Publishing Service; Kyoto, Japan 1984.
- 2 (a) E. Bayer, K.H.Gugel, K.Haegeler, H.Hagenmeier, S.Jessipow, W.A.Koenig and H.Zaehner, *Helv.Chim.Acta.*, 1972,**55**,224; (b) Y.Kondo, T.Shomura, Y.Ogawa, T.Tsuruoka, H.Watanabe, K. Totsukawa, T.Suzuki, C.Moriyama, J.Yoshida, S.Inouye and T.Niida, *Sci.Rep.Meiji Seika Kaisha*, 1973, 13, 34; (c) S.Omura, K.Hinotozawa, N.Imamura and M.Murata, *J.Antibiot.*, 1984, **37**, 939.
- 3 K.Weissermel, H.J.Kleiner, M.Finke and U.H.Felcht, *Angew.Chem., Int.Ed.,Engl.*, 1981, **20**, 223.
- 4 L.Maier, *Phosphorus and Sulfur*, 1983, **14**, 295.
- 5 V.P Kukhar and V.A.Solodenko, *Russian Chem.Rev.*, 1987, **56**, 589.
- 6 S.Berte-Verrando, F.Nief, C.Patois and P.Savignac, *Phosphorus, Sulfur, and Silicon and the Related Elements*, in the press.
- 7 (a) M.P.Teulade and P.Savignac, *J.Organomet.Chem.*, 1988, **338**, 295. (b) S.Berte-Verrando, F.Nief, C.Patois and P.Savignac, *J.Chem.Soc.Perkin Trans.I*, 1994, 821.
- 8 X.Morise, P.Savignac, J.C Guillemin and J.M.Denis, *Synthetic.Commun.*, 1991, **21**, 793.