JOC Article

Synthesis of the First Stable Phosphonamide Transition State Analogue

P. de Medina, L. S. Ingrassia,* and M. E. Mulliez

Laboratoire de Synthèse et Physicochimie de Molécules d'Intérêt Biologique, Unité Mixte de Recherche no. 5068 associée au Centre National de la Recherche Scientifique, Université Paul Sabatier, 118 Route de Narbonne, 31062 Toulouse Cedex O4, France

ingrassia_l@hotmail.com

Received February 21, 2003

Three methods were selected for the one-pot synthesis of the fully protected β-fluoroaminophosphonic acids, using the readily accessible N-protected β-fluoroaminals. These were activated by acylation leading, by β-elimination, to a transient *N*-acylimine immediately trapped by reactive forms of dialkyl phosphites. Avoiding basic conditions, the complete or partial deprotection of these N-protected β-fluoroaminophosphonic esters allowed the synthesis of the free amino acids, their esters, and a racemic β-trifluorophosphonamidic acid. The latter, which represents a transition state analogue formed by the bacterial transpeptidase, is perfectly stable at pH 4.7, contrary to the nonfluorinated compounds.

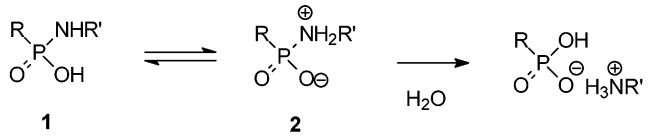
Introduction

Phosphonamides **1** are good analogues of the transition state of the hydrolysis of the peptide bond, so they are often potent inhibitors[1] of peptidases. These compounds are not used[2] as drugs, because they are rather unstable at physiological pHs. This may be attributed to the formation of a transient zwitterion **2** with a good leaving group (ammonium) that is displaced by a water molecule, resulting in an easy hydrolysis overall[3] (Scheme 1).

Conversely, the stability of **1** should be increased by reducing the basicity of the nitrogen. This has been already verified[4] with phosphondiamides bearing two fluorine atoms located in the R group in the α-position relative to phosphorus (R = CHF_2). In this paper, it is established that it is also the case in the β-position, with the trifluoromethyl group. Alanine analogues so formed should be recognized almost as well[5] as the nonfluorinated compounds, since some of them act as antibiotics.[6]

To date two syntheses of these alanine analogues have been described. The first one requires six steps starting from fluorocarboxylic acids.[7,8] The second[9] one is an application of the original Seebach's electrochemical method[10] (later extended by Corcoran and Green[11]) and is straightforward from β-fluoro α-aminocarboxylic acids. However, these in turn must be synthesized in several steps. In addition, in each case,[7−9] the products were not fully characterized.

SCHEME 1



In the search for alternative synthesis of these alanine analogues, we turned to the use of β-fluorinated *N*-acyl hemiaminals **3**, which are now easily prepared.[12] This was initially supported by the following observations: (i) the related *chloro*aminals **3′** were already used for such a functionalization[13] into corresponding phosphonic acid and (ii) the latter relies on the formation of an acylimine,[14] which had already been effected with other *N*-acyl *fluoro*aminals.[14−16] Thus, three methods of synthesis of these fully protected amino acids **4** (part A) were finalized, which made possible the preparation (part B) of free

(1) See inter alia: Rich, D. H. Peptidases Inhibitors In *Comprehensive Medicinal Chemistry*; Sammes P. G., Ed.; Pergamon Press: Oxford, 1990; Vol. II. This has been verified particularly with metallo-proteases but not so much with serine- or cysteine-proteases.

(2) For example, Cbz-$NHCH_2PO(OH)$Phe, one of the most stable, potent inhibitors of carboxypeptidase A displays a half-life of 4 h at pH 6.2 (8 days at pH 7.5): Jacobsen, N. E.; Bartlett, P. A. *J Am. Chem. Soc.* **1981**, *103*, 654.

(3) See inter alia: Benkovic, S. J.; Benkovic, P. A. *J. Am. Chem. Soc.* **1967**, *89*, 4714.

(4) Mulliez, M. *Tetrahedron* **1981**, *37*, 2027.

(5) See for example Krishnamurti, R.; Bellew, D. R.; Prakash, G. K. S. *J. Org. Chem.* **1991**, *56*, 984.

(6) In light of the known activiy of D-Ala-D-Ala analogues, as penicillins or alaphosphaline. See inter alia: Neuhaus, F. C.; Hammes, W. P. *Pharma. Ther.* **1981**, *14*, 265.

(7) Sinitsa, A. D.; Onysko, P. P.; Kim, T. V.; Kiseleva, E. I.; Pirozhenko, V. V. *J. Gen. Chem. U.S.S.R.* **1986**, *52*, 2372.

(8) Flynn, G. A.; Beight, D. W.; Bohme, E. H. W.; Metcalf, B. W. *Tetrahedron Lett.* **1985**, *26*, 285.

(9) Vaubaillon, D.; Giraud, V.; Rabiller, C.; Gruss, U.; Haas, A.; Hägele, G. *Phosphorus, Sulfur Silicon* **1997**, *126*, 177.

(10) Seebach, D.; Charczuk, R.; Gerber, C.; Renaud, P.; Berner, H.; Schneider, H. *Helv. Chim. Acta* **1989**, *72*, 401.

(11) Corcoran, R.; Green, J. *Tetrahedron Lett.* **1990**, *31*, 6827.

(12) Ingrassia, L.; Mulliez, M. *Synthesis* **1999**, *10*, 1731.

(13) Vo Quang, Y.; Carniato, D.; Vo Quang, L.; Le Goffic, F. *Synthesis* **1985**, 62.

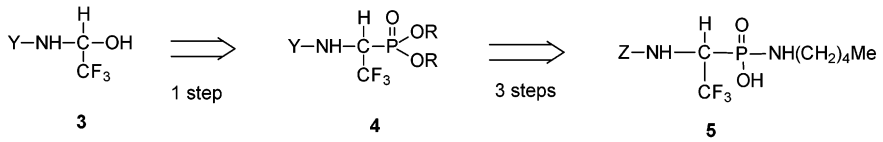
(14) Albrecht, R.; Kresze, G.; Mlakar, B. *Chem. Ber.* **1964**, *97*, 483.

(15) Weygand, F.; Steglich, W.; Lengyel, I.; Fraunberger, F.; Oettmeier, W. *Chem. Ber.* **1966**, *99*, 1944.

(16) Steglich, W.; Burger, K.; Durr, M.; Burgis, E. *Chem. Ber.* **1974**, *107*, 1488.

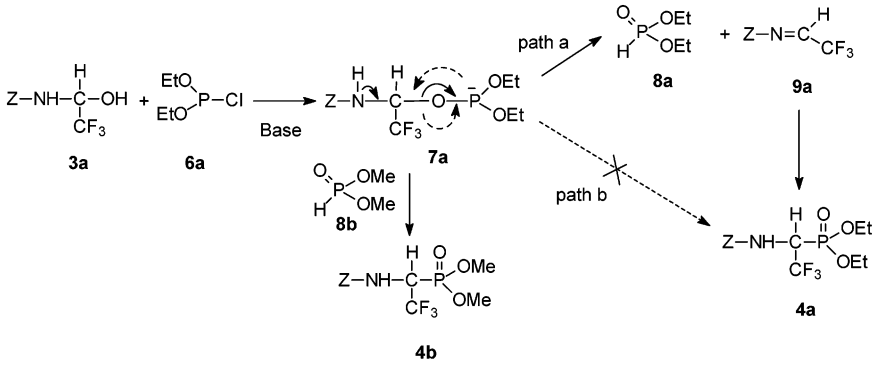
10.1021/jo034229j CCC: $25.00
Published on Web 10/10/2003

SCHEME 2



Y = Acyl group in particular Benzyloxycarbonyl : Z
R = Me, Et, Bn, Ph ...

SCHEME 3



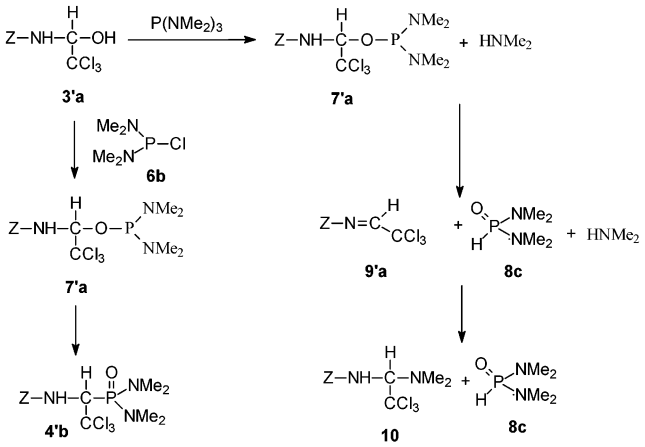
amino acids and particularly a transition state analogue **5** of type **1** (Scheme 2).

Results and Discussion

A. Synthesis of the Fully Protected *β*-Fluoro α-Amino Phosphonic Acids 4. As a rule, the formation of the characteristic P−C bond of nonhalogenated α-aminophosphonic acids results from the addition of nucleophilic phosphorus species to an imine.[17] In the case of *β*-fluorinated compounds, the imine is expected to display an electrophilicity considerably enhanced by the Y-acyl group and the fluorine atoms so that a high sensivity to polymerization was particularly observed with the parent aldehyde fluoral.[14] Therefore, it should be preferably generated in situ. This cannot be realized by simple dehydration,[18] contrary to the common nonfluorinated adducts, such as the "methylol" derivatives,[19] but after selective O-acylation according to the literature.[15−16] On this basis, three methods were selected.

Method A (Scheme 3). The use of chlorophosphite **6a** with hemiaminal **3a** enabled the instantaneous formation of **7a** in the presence of pyridine. This phosphorus tricoordinated intermediate is easily characterized by its downfield ^{31}P NMR signal. Its observed subsequent slower rearrangement into **4a** may result a priori from an either intermolecular (path a, full lines) or intramolecular (path b, dotted lines) process. The latter path must be rejected because of the following: (i) addition to **7a** of dimethylphosphonate **8b** led to significant amounts of the phosphonate dimethylester **4b** and (ii) the rearrangement was considerably accelerated using the triethylamine. Therefore, a *β*-elimination occurs with formation of **8a** and imine **9a**, even if this latter intermediate

SCHEME 4



is not detected by ^{19}F NMR. Then this imine **9a** is combined, as suggested above, extremely rapidly, perhaps (vide infra for comparison with method C) before the proton transfer took place on the nascent reactive anion of **8a**.

The same course of the reaction was also observed with the less favorable, more crowded *β*-tri*chloro* aminal **3′a** (Scheme 4). In the reaction of the latter with hexamethylphosphorus triamide, the involvement of imine **9′a** is also deduced from the formation of phosphite **8c** and aminal **10**. Compound **10** is obtained (Scheme 4) because dimethylamine is a better nucleophile than phosphite **8c**. In contrast, phosphondiamide **4′b** was obtained with the chlorophosphite **6b**. Thus, by analogy, the known[20,21] formation of phosphonic derivatives when using nonhalogenated compounds instead of **3** or **3′** should follow the same intermolecular course.

Nevertheless, although attractive, the generalization of method A is severely limited by the poor stability of

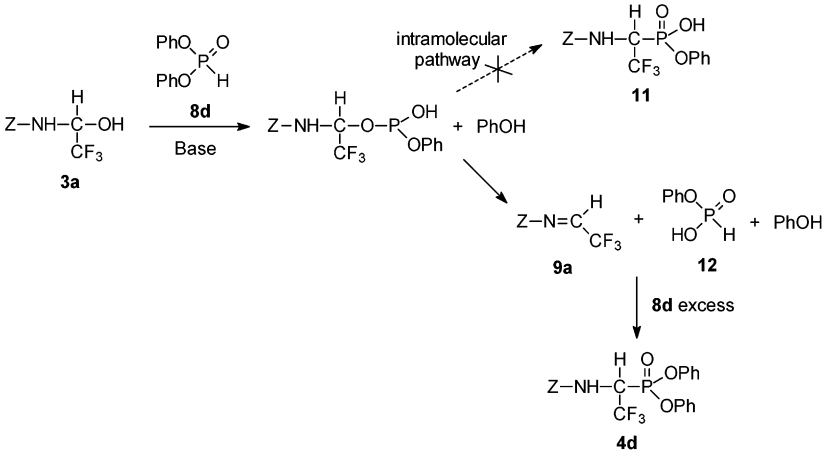
(17) See inter alia: Redmore, D. In *Topics in Phosphorus Chemistry*; Griffith, E. J., Grayson, M., Eds.; Interscience: New York, 1976; Vol. 8, p 515.
(18) With the exception of the *N*-sulfonyl protected hemiaminals: see ref 12.
(19) Einhorn, A. *Justus Liebigs Ann. Chem.* **1905**, *343*, 27.
(20) Ivanov, B. E.; Gorin, Y. A.; Krokhina, *Bull. Acad. Sci. S.S.S.R., Ser. Chim.* **1970**, *11*, 2627.
(21) Scharf, D. J. *J. Org. Chem.* **1976**, *41*, 28.

TABLE 1. Fully Protected β-Halogeno α-Amino Phosphonic Acids Y−NH−CHR−POR′R″ [a]

no.	Y	R	R′	R″	mp °C (recrystallization solvent)	yield % (method)
4a	Z	CF_3	OEt	OEt	54−56 (MeOH−H_2O or DIE−pentane)	55 (A), 72 (C)
4b	Z	CF_3	OMe	OMe	72−74 (Et_2O)	85 (C)
4c	Z	CF_2Cl	OEt	OEt	54−57 (Et_2O−hexane)	70 (C)
4d	Z	CF_3	OPh	OPh	144 (MeOH)	75 (B)
4e$_1$+**4e**$_2$	Z-Ala	CF_3	OPh	OPh	(DIE)	63 (B)
4f$_1$+**4f**$_2$	Z-Ala	CF_3	OiPr	OiPr	(DIE)	88 (Seebach's method[7])
4h$_1$+**4h**$_2$	Z-Ala	CF_3	OMe	OMe	(DIE)	70 (C)
4i	Z	CF_3	H	OH	144−146	77 (C)
4j	Z	CF_3	OBn	OBn	55−57 (MeOH−H_2O)	47 (C)
4k	Z-Gly	CF_3	OEt	OEt	91−93 (Et_2O−hexane)	63 (C)
4l	Z	CF_3	Ph	Ph	227−229 (AcOEt)	51 (A)
4m	$(BnO)_2PO$	CF_3	OEt	OEt	88−90 (DIE)	62 (A)
4a	Z	CCl_3	OEt	OEt	62−63 (MeOH−H_2O)	41 (A)
4b	Z	CCl_3	NMe_2	NMe_2	137−138 (AcOEt)	60 (A)
4c	Z	CCl_3	OPh	OPh	156−159 (MeCN)	73 (B)

[a] Abbreviations: Z, benzyloxycarbonyl; Bn, benzyl; DIE, diisopropyl ether.

SCHEME 5



the requisite chlorophosphites[22] **6**. Moreover, in particular with β-difluorochloroaminal **3b**, a second β-elimination of hydrochloric acid (loss of the C_α-H hydrogen) was observed, resulting in a pronounced decomposition instead of the expected formation of **4c** (Table 1).

Method B (Scheme 5). Using diphenyl phosphite **8d** as reactant with hemiaminals **3**, the phosphonic diphenyl esters of type **4** were easily obtained. In this case, the putative three-center intramolecular rearrangement (dotted line, Scheme 5) is also excluded, as no monophenyl ester **11** was formed.

Acid **12** was easily characterized by ^{31}P NMR. The condensation of **12** or phenol on the imine **9a** is avoided by use of a large excess of **8d**. This is not detrimental, because the phosphite **8d** was eliminated with **12** by simple aqueous bicarbonate extractions. Diphenyl esters displaying as a rule a good propensity to crystallization,[4] compound **4d** was easily obtained finally. Similarly with the diasteroisomeric mixture of the hemiaminals **3c**$_1$ and **3c**$_2$, derived from Cbz-alanylamide, the two diastereoisomers **4e**$_1$ and **4e**$_2$ were synthesized, but only one could be separated by crystallization. Nevertheless, each diisopropyl ester **4f**$_1$ and **4f**$_2$ could be obtained in pure form by chromatography on silica gel, after transesterification of the diphenyl esters **4e**$_1$ and **4e**$_2$, using Seebach's titanate method[10] (1.5 equiv, 24 h, at 70 °C, in 2-propanol).

Method C (Scheme 6). Weygand et al.[24] have demonstrated that *O*-trifluoroacetyl derivatives of the hemiaminals **3** (vide infra **13**, Scheme 6) are both stable in pyridine and reactive with alcohols, thiols, and amines. Using diethyl phosphite **8a** alone, no reaction was observed. After addition of several equivalents of triethylamine prone to inducing the formation of imine **9a** by elimination of trifluoroacetate, phosphonate **4a** was formed, but with a low yield (∼20%). This may be attributed to the more rapid polymerization of the imine than its addition to **8a**, because with slow and inverse addition of the activated aminal **13**, the yield was increased to ∼40%. No further improvement, however, was observed in the presence of additional phosphite or triethylamine. With the more basic (pK_a ∼ 13) diazabicycloundecene (DBU) yielding more phosphite anions, only ∼10% of **4a** was detected in the end. Clearly, excessively basic conditions must be avoided. This conclusion is corroborated by the fact that the a priori less

(22) In particular with RNHP(OR′)Cl compounds, if R is a peptide chain, its N-terminal elongation was allowed.

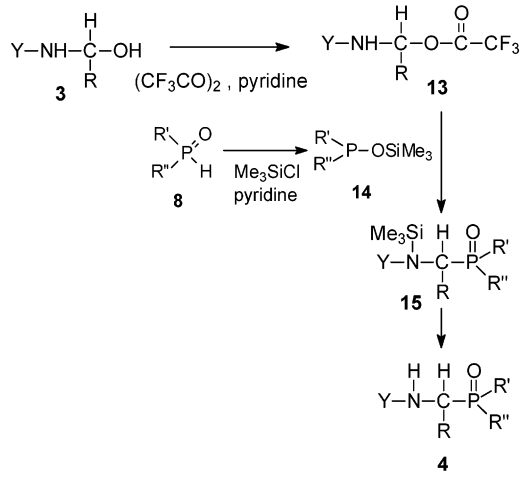
(23) No use for phosphonic esters is indicated in the two misleading following reviews: Siling, M. I.; Laricheva, T. N. *Russ. Chem. Rev.* **1996**, *65*, 279. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999.

(24) Weygand, F.; Steglich, W.; Maierhofer, A.; Fraunberger, F. *Chem. Ber.* **1967**, *100*, 3838.

TABLE 2. Completely or Partially Deprotected β-Trifluorophosphonic Acids

no.	formula	% yield	mp (recryst solvent)
15a	$H_3\overset{+}{N}CHCF_3P(O)(OH)O^-$	quantitative	oil
16a	$H_3\overset{+}{N}CH_2CONHCHCF_3P(O)(OH)O^-$	65	>235 (EtOH)
16b	$H_3\overset{+}{N}CH(Me)CONHCHCF_3P(O)(OH)O^-$	78	>235 (H_2O)
16c	$H_3\overset{+}{N}CH(Me)CONHCHCF_3P(O)(OH)O^-$	69	>235 (EtOH)
17	$H_3\overset{+}{N}CHCF_3P(O)(OEt)_2Cl^-$	60	115−117 ($CHCl_3-Et_2O$) (lit[8] 117−118)
18	Z-NHCHCF$_3$P(O)(OMe)ONa	86	>235
19a	Z-NHCHCF$_3$P(O)(OMe)NH(CH$_2$)$_4$Me	40	110-114 (Et_2O−hexane)
20	Z-NHCHCF$_3$P(O)(ONa)NH(CH$_2$)$_4$Me	51	>235

SCHEME 6



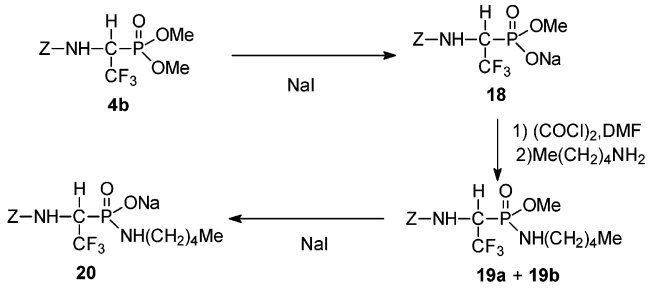
acidic (carboxylic versus phosphonic compounds) trifluoroalanine derivatives are fragile (loss of hydrofluoric acid) in basic conditions.[25] As already performed by Cadogan et al,[26] we turned, therefore, to the addition of silylating reagents, to get the more reactive tricoordinated phosphorus form **14** (effectively detected by ^{31}P NMR) of **8**. In accordance with these expectations, the conversion of **3** into the silylated form **15** of **4** was observed quantitative by ^{31}P and ^{19}F NMR. The desilylation was then readily effected during the aqueous workup. In the case of the more polar acid **4i** soluble in water, the dichloromethane-soluble dicyclohexylammonium salt was intermediately obtained. The acid was finally regenerated after addition of a sulfonic acid resin. As expected, without silylating agents, using hypophosphorus sodium salt in water, hemiaminal **3a** was regenerated instead of **4i**. With the sensitive chlorodifluorohemiaminal **3b** susceptible to loss of hydrochloric acid (vide supra, method A), the compound **4c** was easily synthesized. However, despite these not very basic conditions (pyridine), a 1/1 mixture of **4h$_1$** and **4h$_2$** was obtained starting with each first separated diastereoisomers **3c$_1$** or **3c$_2$**. Here again an extremely reactive imine should be formed, leading to the observed racemization.

Protected compounds **4**, synthesized by the three methods, are assembled in Table 1.

(25) Weygand, F.; Steglich, W.; Oettmeier, W. *Chem. Ber.* **1970**, *103*, 1655.

(26) Afarinkia, K.; Rees, C. W.; Cadogan, J. I. G. *Tetrahedron* **1990**, *46*, 7175.

SCHEME 7



B. Reactions of the Fully Protected β-Fluoro α-Amino Phosphonic Acids 4. The concomitant cleavage of the N-protecting benzyloxycarbonyl group and the phosphonic alkyl esters using a 40% solution of bromhydric acid in acetic acid is known to be effected in a one-pot procedure.[27] Applied to the fully protected compounds **4**, this enabled the synthesis of the corresponding amino acids, as examplified by **15** (Table 2) in only two reactions, starting from hemiaminals, compared to the known multistep procedures (vide supra). They were easily obtained as either bromohydrates or zwitterions, if necessary, after addition of propylene oxyde. No racemization was observed after dissolving **16b** or **16c** in water. All these amino acids are crystalline, except for **15a** derived from **4a**. Nevertheless, with this latter compound chlorhydrate **17** was isolated as *crystals* following the selective N-deprotection in the presence of cyclohexene and Pd/C 10%.[28] Another type of partial selective deprotection of one function of dimethyl ester **4b** was realized in quasineutral conditions with sodium iodide in acetone[29,30] leading to **18** (Scheme 7). Using the best available method of coupling[31] (DMF, oxalylchloride) with this latter compound and amylamine, the expected (for two chiral centers) mixture of four products formed gave two couples of diastereoisomers **19a** and **19b** easily distinguished by both ^{31}P and ^{19}F NMR. One was selectively crystallized. After deprotection with sodium iodide, under more vigorous conditions, the chirality of the phosphorus was lost

(27) See for example: Mulliez, M. *Bull. Soc. Chim. Fr.* **1985**, 1211.

(28) See for example: Jackson, A. E.; Johnstone, A. W. *Synthesis* **1976**, 685.

(29) Zervas, L.; Dilaris, I. *J. Am. Chem. Soc.* **1955**, *77*, 5354.

(30) See for example: Hirschmann, R.; Yager, K. M.; Taylor, C. M.; Witherington, J.; Sprengeler, P. A.; Philips, B. W.; Moore, W.; Smith, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 8177.

(31) Musiol, H. J.; Grams, F.; Rudolph-Böhner, S.; Moroder, L. *J. Org. Chem.* **1994**, *59*, 6144.

and racemic sodium salt **20** was eventually isolated.[32] In acetate buffer (pH = 4.7) acid **5** is at least partially[33] formed. Either in its salt (**20**) or acid (**5**) form, the product proved to be *indefinitely stable* in this medium. Only a slow hydrolysis ($t_{1/2} \sim 4$ h) was observed at pH ~ 1.5.

Nearly all of the completely or partially deprotected products of Table 2 are expected to be antibiotics. For example, each enantiomer of **15a** has already been proved to be an irreversible inhibitor in vitro of L-alanine racemase[34] (a crucial specific enzyme implicated in bacterial peptidoglycan biosynthesis). Either **16a** or **16b** is the trifluoro analogue of the known antibiotic SR alafosfaline.[35,36] Diastereoisomers **19a** or **19b** and enantiomers of **20** (leading to **5**) are transition state analogues of respectively the formation (with the approximation of an amyl residue in place of a D-alanine one) and the aminolysis of the acylenzyme form of the bacterial transpeptidase. Essential for the reticulation of peptidoglycan, this enzyme is the target of penicillins. With the increasing resistance to the latter, due in particular to the presence of β-lactamases, there is indeed a pressing need for new structurally different antibiotics. Even if our products, which match this requirement, do not display the anticipated bioactivity, the stabilization of transition state analogue **5** is of major importance in light of its generalization to numerous other peptidases.[1] This may also be useful with abzymes or in molecular imprinting.[37]

Experimental Section[38]

Synthesis of the Fully Protected β-Fluoro α-Amino Phosphonic Acids 4. The synthesis of starting hemiaminals **3** have been already described[12] except for the two diastereoisomers **3c₁** and **3c₂** derived from L-alaninamide.[39] Using the general procedure 1 (18 h at 70 °C) they were obtained in a 83% yield after crystallization in dichloroethane: IR 3324, 1654 (broad band); ^{19}F NMR (DMSO-d_6) δ −5.37 (d, J = 8), −5.07 (d, J = 8). Anal. Calcd for $C_{13}H_{15}N_2O_4$: C, 48.75; H, 4.73; N, 8.58. Found: C, 48.70; H, 4.73; N, 8.58. Chromatography of 0.65 g on silica gel with AcOEt−petroleum ether (1:2) as eluant yielded pure **3c1** (0.365 g), **3c2** (0.275 g), and 0.01 g of a mixture of them. **3c1**: mp 153−154 °C; R_f 0.3; $[\alpha]^{25}_D$ + 9.6 (c 5, dioxane); ^{19}F NMR (DMSO-d_6) δ −5.7 (d, J = 8);^{1}H NMR (DMSO-d_6) δ 1.12 (d, 3H, J = 7.12), 4.08 (m, q with addition of D_2O, 1H, J = 7.09), 5.01 (s, 2H), 5.61 (m, q with addition of D_2O, 1H, J = 5.68), 7.34 (br s, 7H), 8.8 (d, 1H, J = 9.3); ^{13}C NMR (DMSO-d_6) δ 17.78, 49.6, 65.25, 70.02 (q, J = 33.9), 123.3 (q, J = 283), 127.6, 128.2, 136.8, 155.5, 173.1. **3c₂**: mp 143−144 °C; R_f 0.23; $[\alpha]^{25}_D$ −22.2 (*c* 5, dioxane); ^{19}F NMR (DMSO-d_6) δ −5.37 (d, J = 8); ^{1}H NMR (DMSO-d_6) δ 1.2 (d, 3H, J = 7.2), 4.05 (m, q with addition of D_2O, 1H, J = 5.7), 5.01 (s, 2H), 5.61 (m, q with addition of D_2O, 1H, J = 5.7), 7.34 (br s, 7H), 8.8 (d, 1H, J = 8.8); ^{13}C NMR (DMSO-d_6) δ 17.98, 49.8, 65.3, 70.02 (q, J = 33.9), 126.3 (q, J = 283), 127.67, 128.2, 136.95, 155.6, 173.2.

Method A. Illustrative Procedure. *N*-Benzyloxycarbonyl α-Amino β-Trifluoro Diethylphosphonate (4a). To a solution of diethyl chlorophosphite **6a** (2.15 g, 13.7 mmol) in dichloroethane (15 mL) were added a solution of hemiaminal **3a** (2.63 g, 10.5 mmol) and triethylamine (1.39 g, 13.7 mmol) in dichloroethane (15 mL) dropwise in 20 min with ice cooling and magnetic stirring. After standing overnight at room temperature, the solution was washed with water, ~10% citric acid solution, ~5% bicarbonate solution (2 × 25 mL of each), the organic layer was dried (Na_2SO_4) and concentrated to dryness, and the product **4a** was crystallized: IR 3211, 1721; ^{19}F NMR (DMSO-d_6) δ 7.35 (pseudo t: dd, J = 8.1); ^{31}P NMR (DMSO-d_6) δ 14.08 (q, J = 8); ^{1}H NMR (DMSO-d_6) δ 1.27 (t, 6H, J = 7.2), 4.11 (m, 4H), 4.8 (m, 1H), 5.14 (s, 2H), 7.37 (s, 5H), 8.6 (d, 1H, J = 8.6); ^{13}C NMR (DMSO-d_6) δ 15.91, 16, 50.3 (dq, J = 156.1, J = 32), 63.1 (d, J = 6.6), 63.4 (d, J = 6.6), 66.4, 123.4 (dq, J = 281, J = 10.2), 127.8, 128, 128.3, 136.44, 156.31 (d, J = 5.9). Anal. Calcd for $C_{14}H_{19}F_3NO_5P$: C, 45.53; H, 5.19; N, 3.79. Found: C 45.51; H, 5.15; N, 3.79.

The use of pyridine and preferably of tetraethylpyrophosphite in place respectively of triethylamine and **6a** allowed the easy observation of **7a** by NMR both of ^{31}P (δ 139.3, q, J = 3.8) and ^{19}F (δ −6.09, dd, J = 3.8, J = 4.5) and its slower conversion into **4a**: 28% after 10 min. At this stage, 1.05 equiv of dimethyl phosphite **8b** was added and the reaction mixture left overnight. NMR analysis (^{31}P, ^{1}H) showed a mixture of **4a** and **4b** (ratio 6:4).

Similarly with the hemiaminal **3′a**, the product **4′a** was obtained: IR 3218, 1719; ^{31}P NMR ($CDCl_3$) δ 13.8; ^{1}H NMR ($CDCl_3$) δ 1.28 (m, 6H), 4.16 (m, 4H), 4.92 (dd, 1H, J = 19, J = 11), 5.16 (s, 2H), 5.75 (br s, 1H), 7.35 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 16.3 (d, J = 5.84), 63.81, (d, J = 6.83), 63.85 (d, J = 6.83), 63.96 (d, J = 159.4), 67.92, 97.34 (d, J = 14.91), 128.32, 128.42, 128.57, 155.73 (d, J = 6.04). Anal. Calcd for $C_{14}H_{19}Cl_3NO_3P$: C, 40.16; H, 4.57; N, 3.35. Found: C, 40.01; H, 4.47; N, 3.20.

Similarly with hemiaminal **3′a** and phosphite **6b,** the product **4′b** was obtained: IR 3163, 1706. ^{31}P NMR ($CDCl_3$) δ 25.5; ^{1}H NMR ($CDCl_3$) δ 2.57, 2.68 (2d, 12H, J = 9.75), 4.8 (dd, 1H, J = 12.24, J = 8), 5.15 (s, 2H), 7.23 (s, 5H); ^{13}C NMR δ 36.25 (d, J = 2.62), 37.23 (d, J = 2.62), 62.09 (d, J = 124.3), 67.64, 99.44 (d, J = 11.9) 128.09, 128.29, 128.5, 136, 155.71 (d, J = 6.65). Anal. Calcd for $C_{14}H_{21}Cl_3N_3O_3P$: C, 40.35; H, 5.08; N, 10.08. Found: C, 40.17; H, 5.04; N, 9.79. With hexamethylphosphorus triamide in place of phosphite **6b**, ^{31}P NMR showed the exclusive formation of **8c** (δ 21.8, J(undecoupled)= 570) (lit[40] δ 21.5, J = 568) after 30 min of vigorous stirring with an excess of carbon tetrachloride. A ~5% bicarbonate solution was then added. After decantation and extractions with dichloromethane, the cumulated organic extracts were dried (Na_2SO_4) and concentrated to dryness, giving the aminal **10** as an oil: ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 6H), 5.12 (d, 1H, J = 7.5), 5.13 (s, 2H), 5.5 (br s, 1H), 7.31 (s, 5H). Similarly with hemiaminal **3a** in place of **3′a**, the only phosphorus compound **8c** was formed in less than 3 h.

Similarly with hemiaminal **3a** and chlorodiphenyl phosphite **6c**, the product **4e** was obtained: IR 3168, 1705; ^{19}F NMR

(32) Theoretically, two additional more simple one-pot syntheses of **5** (i.e. **20**) may be envisaged using the P−H compound **4i**: first by electrophilic amination and the second one after silylation with bissilylacetamide (BSA) according to the literature (see, for example: Hata, T.; Yamamoto, I.; Sekine, M. *Chem. Lett.* **1976**, 601). The silylated phosphorous intermediate compound formed should react in a Staudinger reaction with amyl azide and eventually lead, after hydrolysis, to **5**. In fact, the initial Staudinger reaction is followed by a cyclization expelling the N-silylated amylamine. This was not unexpected in light of the known participation of the amide group in the hydrolysis of N-acyl α-amino phosphonic monoesters: Rahil, J.; Pratt, R. F. *J. Chem. Soc., Perkin Trans. 2* **1991**, 947. Moreover, the heterocycles formed, as for phosphorous heterocycles in general and in particular the related phosphoxazolones (ref 30), remain resistant to aminolysis.

(33) The literature values for pK_a of comparable phosphonamidic acids are rather conflicting from ~7 (Crunden, E. W.; Hudson, R. F. *Chem. Ind. (London)* **1962**, 613) to ~3 (Suarez, A. I.; Lin, J; Thompson, C. M. *Tetrahedron* **1996**, *52*, 6117).

(34) Wang, E. A.; Walsh, C. *Biochemistry* **1981**, *20*, 7539.

(35) Allen, J. G.; Atherton, F. R.; Hall, M. J.; Hassal, C. H., Holmes, S. W.; Lambert, R. W.; Nisbet, L. L.; Ringrose, P. S. *Nature* **1978**, *272*, 56.

(36) Hassal, C. H. *Actual. Chim. Ther.* **1985**, *12*, 193.

(37) Wulf, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1812.

(38) More details are available in L.S.I.'s thesis, Toulouse, Dec 2000.

(39) Chen, S. T.; Wu, S. H.; Wang, K. T. *Synthesis* **1989**, 37.

(40) ^{31}P Nuclear Magnetic Resonance In *Topics in Phosphorus Chemistry*; Crutchfield, M. M., Dungan, C. H., Mark, V., Van Wazer, J., Graysson, M., Griffith, J., Eds.; J. Wiley, New York: 1967; p 673.

(DMSO-d_6) δ 10.58 (dd, J = 9, J = 2.7); ^{31}P NMR (DMSO-d_6) δ 25.05 (q, J = 2.7); ^{1}H NMR (DMSO-d_6) δ 4.95 (qAB, 2H, J_{AB} 12.4), 5.63 (m, 1H), 7−8.8 (15 H), 8.74 (d, 1H, J = 10.2); ^{13}C NMR (DMSO-d_6) δ 52.28 (dq, J = 73, J = 37), 65.89, 127.01−136.44 (m), 156.2 (d, J = 4.5). Anal. Calcd for $C_{22}H_{19}F_3NO_3P$: C, 60.97; H, 4.42; N, 3.23. Found: C, 60.64; H, 4.38; N, 3.32.

Similarly with $(BnO)_2P(O)NHCHCF_3OH$ **3c**, the product **4m** was obtained in less than 30 min: IR 3157, 1289; ^{19}F NMR ($CDCl_3$) δ 4.8 (pseudo t: dd, J = 7.1); ^{31}P NMR ($CDCl_3$) δ 6.9 (d, J = 20.28), 13.79 (dq, J = 20.43, J = 7); ^{1}H NMR ($CDCl_3$) δ 1.26 (m, 6H), 4.14 (m, 6H), 5.04 (d, J = 7.14, 2H), 7.31 (s, 10H); ^{13}C NMR δ 16.28 (d, J = 5.7), 16.23 (d, J = 5.7), 53.82 (dq, J = 156.6, J = 37.8), 63.9 (d, J = 6.9), 63.8 (d, J = 6.9), 68.45 (d, J = 4.5), 68.50 (d, J = 4.5), 123.54 (ddd, J = 281, J = 9.8, J = 3.1), 128.54−127.6 (5s), 135.89, 136.04. Anal. Calcd for $C_{20}H_{26}F_3NO_6P_2$: C, 48.49; H, 5.29; N, 2.83. Found: C, 48.76; H, 5.37; N, 2.81.

Method B. Illustrative Procedure. *N*-Benzyloxycarbonyl α-Amino *β*-Trifluoro Diphenylphosphonate (4d). A solution of hemiaminal **3a**, diphenyl phosphite **8d** (5.6 g, 23.9 mmol, 6 equiv), and triethylamine (0.53 g, 5.2 mmol, 1.3 equiv) in dioxane (7 mL) was kept at room temperature until completion of the reaction (1.5 h by ^{19}F NMR; the ^{31}P NMR spectrum showed two new products in 1/1 ratio δ 5.1 (**4d**) and −2 (coupled: d, J = 636, **12**). The reaction mixture was concentrated to dryness, taken up in dichloromethane (60 mL), and treated as above (method A). IR 3270, 1727; ^{19}F NMR ($CDCl_3$) δ 5.71 (pseudo t: dd, J = 7.9); ^{31}P NMR ($CDCl_3$) δ 5.1 (q, J = 7.3); ^{1}H NMR ($CDCl_3$) δ 5.16 (2H), 6 (m, 1H), 7.2 (mf, 11H), 7.13 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 51.11 (dq, J = 162.5, J = 32.5), 66.7, 123.16 (q, J = 294.1), 120.2−130 (m: 9 signals incorporating two d δ 120.2, 120.3, J = 3.7), 149.1 (d, J = 9.3), 149.42 (d, J = 9.3), 156.28 (d, J = 6.2). Anal. Calcd for $C_{22}H_{19}F_3NO_5P$: C, 56.78; H, 4.12; N, 3.01. Found :C, 56.48; H, 4.09; N, 2.94.

Similarly with hemiaminal **3′a**, the product **4′c** was obtained (exothermic reaction and crystallization in the reaction mixture after a few minutes; **12** was characterized by ^{31}P NMR in the filtrate): IR 3314, 1724; ^{31}P NMR (DMSO-d_6) δ 6.59 (coupled: d, J = 20.7); ^{1}H NMR (DMSO-d_6) δ 5.18 (s, 2H), 5.34 (dd, 1H, J = 20.6, J = 10.5), 6.7−7.3 (mf, 15H), 9.31 (dd, 1H, J = 10.5, J = 1.9); ^{13}C NMR (DMSO-d_6) δ 70.45 (d, J = 165.21), 72.44, 102.43 (d, J = 17.93), 125.83−155.63 (m), 162.16 (d, J = 6.45). Anal. Calcd for $C_{22}H_{19}Cl_3NO_5$: C, 51.33; H, 3.72; N, 2.72. Found :C, 51.20; H, 3.66; N, 2.77.

Similarly with the two diastereoisomers $\mathbf{3c_1}$ and $\mathbf{3c_2}$, products $\mathbf{4e_1}$ and $\mathbf{4e_2}$ were obtained (reaction over in less than 15 min): R_f (AcOEt/petroleum ether 1:3) 0.3, 0.24; ^{19}F NMR (dioxane) δ 7.55 (pseudo t: dd, J = 8.4), 7.04 (pseudo t: dd, J = 8.4); ^{31}P NMR (dioxane) δ 6.2 (m: two overlapping q). Anal. Calcd for $C_{25}H_{24}N_2O_6P$: C, 55.98; H, 4.51; N, 5.22. Found: C, 55.56; H, 4.50; N, 5.07. By crystallization in MeOH (4 g), 0.53 g yielded 0.175 g (66%) of a single diasteroisomer as white crystals: mp 135−137 °C; R_f 0.3; IR 3297, 1691, 1670; ^{19}F NMR (DMSO-d_6) δ 8.54 (dd, J = 8.6); ^{31}P NMR (DMSO-d_6) + 7.45 (q, J = 7.2); ^{1}H NMR (DMSO-d_6) δ 1.25 (d, 3H, J = 7.2), 4.37 (dq, 1H), 5.03 (s, 2H), 5.62 (m, 1H), 7.08−7.64 (m, 16H), 9.4 (d, 1H, J = 8.6); ^{13}C NMR (DMSO-d_6) 17.97, 48.64 (dq, J = 163.2, J = 32,5), 49.6, 65.28, 123.1 (dq, J = 282.1, J = 10.6), 115.1−130 (m, 9 signals), 136.9, 149.1 (d, J = 9.5), 149.2 (d, J = 13), 155.65, 173.99. Attemped preparative chromatography with the same eluant as for the analytical chromatography proved ineffective.

Following Seebach's method (1.5 equiv of titanate, 24 h, at 70 °C, in 2-propanol), the preceding esters $\mathbf{4e_1}$ and $\mathbf{4e_2}$ are transesterified into $\mathbf{4f_1}$ and $\mathbf{4f_2}$ without reaction on the urethane N-protecting group.[43] Anal. Calcd for $C_{19}H_{28}F_3N_2O_6P$: C, 48.72; H, 5.98; N, 6.03. Found: C, 48.76; H, 5.89; N, 5.69. Chromatography on silica gel with AcOEt/petroleum ether/acetic acid (10/40/1) as eluant yielded pure $\mathbf{4f_1}$ (0.2 g), $\mathbf{4f_2}$ (0.21 g), and 0.05 g of a mixture of them. $\mathbf{4f_1}$: mp 112 °C; R_f 0.36; $[\alpha]^{25}_D$ + 17° (c = 5, dioxane); ^{19}F NMR ($CDCl_3$) δ 6.75 (pseudo t: dd, J = 8.2); ^{31}P NMR ($CDCl_3$) δ 10.55 (q, J = 6.3); ^{1}H NMR ($CDCl_3$) δ 1.3 (m, 15H), 4.87 (m, 4H), 5.06 (s, 2H), 5.42 (d, 1H, J = 8.9), 7.29 (s, 5H), 7.52 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 18.9, 23.6 (d, J = 5.5), 24.24 (d, J = 3), 48.24 (dq, J = 160.2, J = 32.3); 50.21, 66.92, 73.5, 73.6, 122.59 (dq, J = 7.9, J = 281.1), 128.1, 128.3, 128.5, 136.23, 155.76, 173.01 (d, J = 5.7). $\mathbf{4f_2}$: mp 135 °C; R_f 0.26; $[\alpha]^{25}_D$ −32 (c = 5, dioxane); ^{19}F NMR ($CDCl_3$) δ 6.85 (pseudo t: dd, J = 8.1); ^{31}P NMR ($CDCl_3$) δ 10.55 (q, J = 6.2); ^{1}H NMR ($CDCl_3$) δ 1.29 (m, 15H), 4.3−4.89 (m, 4H), 5.08 (s, 2H), 5.4 (d, 1H, J = 9.2), 7.28 (s, 5H), 7.6 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 18.92, 23.5 (d, J = 5.7), 24.1 (d, J = 4.1), 48.12 (dq, J = 158.1, J = 31.3), 50.12, 66.8, 73.4, 73.52, 122.67 (dq, J = 7.8 J = 284.4), 128, 128.3, 128.6, 136.3, 155.7, 173.11 (d, J = 5.7).

Method C. Illustrative Procedure. *N*-Benzyloxycarbonyl α-Amino *β*-Trifluoro Diethylphosphonate (4a). Under magnetical stirring, the pale yellow solution resulting from the addition of trifluoroaceticanhydride (1 g, 4.7 mmol) to a pyridine (10 mL) solution of the hemiaminal **3a** (0.63 g, 4 mmol) was added dropwise in a few minutes to a dichloromethane (8 mL) solution of the phosphite **8a** (1.15 g, 8.3 mmol) followed by addition of trimethylchlorosilane (2.17 g, 20 mmol). After completion of the reaction (less than 30 min), the mixture was concentrated to dryness and the residue was taken up in dichloromethane and treated as above (method A).

Similarly with the hemiaminal **3a** and the phosphite **8b**, the product **4b** was obtained: IR 3210, 1725; ^{19}F NMR (DMSO-d_6) δ 7.4 (pseudo t: dd, J = 7.9); ^{31}P NMR (DMSO-d_6) δ 16.77 (q, J = 7.8); ^{1}H NMR (DMSO-d_6) δ 3.75 (d, 3H, J = 10.5) 4.85 (m, 1H), 5.15 (s, 2H), 7.38 (s, 5H), 8.66 (d, 1H, J = 8.66); ^{13}C NMR (DMSO-d_6) δ 55.63 (d, J = 6.5), 53.82 (d, J = 6.45), 49.8 (dq, J = 156, J = 32), 66.5, 123.31 (dq, J = 281, J = 10), 127.86, 128, 128.31, 136.32, 156.2 (d, J = 6.1). Anal. Calcd for $C_{12}H_{15}F_3NO_5P$: C, 42.24; H, 4.43; N, 4.10. Found: C, 42.03; H, 4.27; N, 3.98.

Similarly with the hemiaminal **3b** and the phosphite **8a**, the product **4c** was obtained: IR 3198, 1719; ^{19}F NMR ($CDCl_3$) δ 13.06 (m); ^{31}P NMR ($CDCl_3$) δ 19.4 (m); ^{1}H NMR δ 1.31 (m, 6H), 4.11 (m, 4H), 4.8 (m, 1H), 5.17 (s, 2H), 7.33 (br s, 6H); ^{13}C NMR ($CDCl_3$) δ 16.21 (d, J = 5.7), 55.9 (dt, J = 155.6, J = 29.9), 63.94 (d, J = 4.2), 67.92, 126.7 (dt, J = 10.1, J = 296), 128.2, 128.5, 128.6, 135.6, 155.65 (d, J = 6.35). Anal. Calcd for $C_{14}H_{19}ClF_2NO_5P$: C, 43.59; H, 4.96; N, 3.63. Found: C, 43.3; H, 4.94; N, 3.57.

Similarly with the two diastereoisomers $\mathbf{3c_1}$ and $\mathbf{3c_2}$ or with a single diasteroisomer, products $\mathbf{4h_1}$ and $\mathbf{4h_2}$ were obtained (reaction over in 3 h): ^{19}F NMR (CH_2Cl_2) δ 6.02 (pseudo t: dd, J = 8.2), 6.42 (pseudo t: dd, J = 8.2); ^{31}P NMR (CH_2Cl_2) δ 5.27 (q, J = 8.2), 5.69 (q, J = 8.2). The attempted selective crystallization of either $\mathbf{4h_1}$ or $\mathbf{4h_2}$ in MeOH or Et_2O−hexane mixtures proved to be unsuccessful and accompanied by the slow degradation of the products.

With the hemiaminal **3a** and the ammonium salt of hypophosphorous acid in situ silylated in the presence of hexamethyldisilazane[41,42] (1 equiv) and trimethylchlorosilane (2 equiv), the compound **4i** was formed. The extraction procedure was modified: the residue of the reaction mixture was first treated with a ∼10% citric acid solution and extracted with chloroform. To the aqueous layer was added DCHA (8 equiv), and the dicyclohexylammonium salts of both the compound **4i** and trifluoroacetic acid were extracted with chloroform (five times). After neutralization with Amberlyst 15 resin, the insoluble material (the dicyclohexylammonium resin and product **4i**) was filtered after 2 h and taken up in water. After filtration and concentration to dryness, NMR-pure product **4i** was obtained: IR, 3291, 2454, 1704; ^{19}F NMR (DMSO-d_6) δ

(41) Issleib, K.; Mögelin, W.; Balzuweit, A. *Z. Anorg. Allg. Chem.* **1985**, *530*, 16.
(42) Boyd, E. A.; Ragan A. C.; James, K. *Tetrahedron Lett.* **1992**, *33*, 813.
(43) Shapiro, G.; Marzi, M. *J. Org. Chem.* **1997**, *62*, 7096.

7.99 (pseudo t: dd, $J = 7.5$); ^{31}P NMR (DMSO-d_6) δ 15.57 (q, $J = 7.5$; undecoupled: dm, $J = 575.6$); ^{1}H NMR (DMSO-d_6) δ 4.53 (m), 5.13 (s, 2H), 7.07 (dm, $J = 575.5$), 7.37 (s, 5H), 8.45 (d, 1H, $J = 6.9$), 10.37 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 52.73 (dq, $J = 113.2$, $J = 30.1$), 66.37, 124.01 (dq, $J = 8.3$, $J = 282.2$), 127.2, 127.59, 128.33, 136.28, 156.31 (d, $J = 5.89$).

Similarly with the hemiaminal **3a** and dibenzyl phosphite, the product **4j** was obtained: IR 3314, 1710; ^{19}F NMR (DMSO-d_6) δ 7.23 (pseudo t: dd, $J = 7.6$); ^{31}P NMR (DMSO-d_6) δ 15.15 (q, J 7.66); ^{1}H NMR (DMSO-d_6) δ 5.14 (m, 7H), 7.37 (s, 15H), 8.77 (d, $J = 9.4$); ^{13}C NMR (DMSO-d_6) d 50.5 (dq, $J = 156.3$, $J = 32.1$), 66.53, 68.06 (d, $J = 6.5$), 68.24 (d, $J = 6.5$), 126.22 (dq, $J = 10.4$, $J = 276$), 127.7−128.4 (m: 15 signals), 135.7 (d, $J = 1.2$), 135.8 (d, $J = 1.2$), 136.21, 156.33 (d, $J = 6.2$). Anal. Calcd for $C_{24}H_{23}F_3NO_5P$: C, 58.42; H, 4.70; N, 2.84. Found: C, 58.34; H, 4.61; N, 2.60.

Similarly with the phosphite **8** and the hemiaminal derived from benzyloxycarbonylglycinamide, the compound **4k** was obtained: ^{19}F NMR (DMSO-d_6) δ 5.88 (pseudo t: dd, $J = 7.3$); ^{31}P NMR (DMSO-d_6) δ 12.6 (q, $J = 7.3$); ^{1}H NMR (DMSO-d_6) δ 1.24 (t, 3H, $J = 7.1$), 3.8 (d, 2H, $J = 6.4$), 4.12 (dq, 4H, $J = 8.3$), 5.03 (s, 2H), 5.11 (m, 1H), 7.34 (s, 5H), 7.45 (m, 1H), 9.0 (d, 1H, $J = 9$); ^{13}C NMR (DMSO-d_6) δ 16.02 (d, $J = 5.5$),16.12 (d, $J = 5.5$), 42.84, 47.11 (dq, $J = 156$, $J = 31$), 63.12 (d, $J = 6.8$), 63.6 (d, $J = 6.8$), 65.38, 126.8 (dq, $J = 10.1$), $J = 282$), 127.6, 127.7, 128.3, 136.9, 156.41, 170.03 (d, $J = 4.8$). Anal. Calcd for $C_{16}H_{22}F_3N_5O_6P$: C, 45.08; H, 5.20. N, 6.57. Found: C, 44.75; H, 5.21; N, 6.39.

Complete Acid Deprotection. Illustrative Procedure. *β*-Trifluoro α-Amino Phosphonic Acid 15. To compound **4a** (0.37 g, 1 mmol) was added a ∼40% HBr/AcOH solution (7 g). Immediatly a gas (CO_2) evolved. After 24 h the reaction mixture was concentrated to dryness. After dissolution of the residue in water (20 mL), extractions with chloroform (3 × 15 mL), concentration of the aqueous layer, and dissolution in ethanol (4 mL), propylene oxide (2 mL) was added and an immediate precipitation of **15** took place. The product was filtered and dried in the presence of P_2O_5: ^{19}F NMR δ 9.5 (pseudo t: dd, $J = 7.6$): ^{31}P NMR (D_2O) δ 5.45 (q, $J = 7.2$); ^{13}C NMR (D_2O) δ 53.02 (dq, $J = 126$, $J = 30.2$), 125.2 (q, $J = 279$). Anal. Calcd for $C_2H_5F_3NO_3P$: C, 13.42; H, 2.81; N, 7.82. Found: C, 13.71; H, 2.75; N, 6.54.

Similarly with compound **4k**, the product **16a** was obtained: IR 3508, 3293, 1670; ^{19}F NMR (D_2O) δ 8.5 (pseudo t: dd, $J = 6.9$); ^{31}P NMR (D_2O) δ 6.75 (q, $J = 6.6$); ^{1}H NMR (DMSO-d_6) δ 3.9 (d, s with D_2O, 2H, $J = 6.9$), 4.5 (m, q with D_2O, 1H, $J = 8.1$), 9.13 (m, 1H); ^{13}C NMR (D_2O) δ 43.12, 52.2 (dq, $J = 170.2$, $J = 31.0$), 126.3 (dq, $J = 5$, $J = 276$), 169.9 (d, $J = 5.2$). Anal. Calcd for $C_4H_8F_3N_2OP\cdot 2H_2O$: C, 17.66; H, 4.44. N, 10.29. Found: C, 17.91; H, 4.12; N, 10.37.

Similarly with compound **4f$_1$**, the product **16b** was obtained and crystallized directly in a minimal amount of water: IR 3304, 1678; $[\alpha]^{25}_D + 63°$ ($c = 4$, H_2O) with no change after 8 h; ^{19}F NMR (D_2O) δ 7.15 (pseudo t: dd, $J = 7.24$); ^{31}P NMR (D_2O) δ 6.4 (q, $J = 7.2$); ^{1}H NMR (CF_3COOH, C_6D_6 ext) δ 1.9 (d, 3H, $J = 7.4$), 4.72 (m, 1H), 5.31 (m, 1H), 8.86 (m, 1H); ^{13}C NMR (CF_3COOH, C_6D_6 ext) δ 16.4, 52.06 (dq, $J = 150.3$, $J = 34.2$), 52.23, 122.7 (dq, $J = 7.7$, $J = 280.5$), 172.51 (d, $J = 5$). Anal. Calcd for $C_5H_{10}F_3N_2O_4P$: C, 24.01; H, 4.03; N, 11.20. Found: C, 23.93; H, 3.73; N, 11.00.

Similarly with compound **4f$_2$**, the product **16c** was obtained and crystallized directly in ethanol, without addition of propylene oxide. $[\alpha]^{25}_D -36°$ ($c = 4$, H_2O) with no change after 8 h; ^{19}F NMR (D_2O) δ 7.75 (pseudo t: dd, $J = 7.4$); ^{31}P NMR (D_2O) δ 6.85 (q, $J = 7.5$). Anal. Calcd for $C_5H_{10}F_3N_2O_4P\cdot H_2O$: C, 22.30; H, 4.50; N, 10.45. Found: C, 22.14; H, 4.40; N, 10.08.

Selective N-Deprotection. *β*-Trifluoro α-Amino Diethyl Phosphonate Hydrochloride 17. The free base was prepared according to the literature[28] (reflux during 1 h), and the salt was formed by addition of excess dry gaseous hydrochloric acid: IR 3404; ^{19}F NMR ($CDCl_3$) δ 8.33 (pseudo t: dd, $J = 7.2$); ^{31}P NMR ($CDCl_3$) δ 12.6 (q, $J = 7.5$); ^{1}H NMR ($CDCl_3$) δ 1.36 (t, 6H, $J = 7.1$), 4.35 (m, 4H), 4.87 (m, 1H), 8.94 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 16.02 (d, $J = 5.6$), 48.4 (dq, $J = 148.1$, $J = 31.4$), 63.8 (d, $J = 5.9$), 123.03 (dq, $J = 10.2$, $J = 281.5$). Anal. Calcd for $C_6H_{13}F_3NO_3P$.HCl: C, 26.53; H, 5.20; N, 5.16. Found: C, 26.03; H, 5.14; N, 5.02.

Selective Partial P-Deprotection. Illustrative Procedure. *N*-Benzyloxycarboxyl *β*-Trifluoro α-Amino Monomethylphosphonate Sodium Salt (18). A stirred mixture of compound **4b** (0.43 g, 1.25 mmol), sodium iodide (0.19 g, 1 equiv), and acetone (3 g) was heated at reflux. A clear solution was observed after 5 min and a white precipitate appeared after 45 min. The reaction mixture was then cooled at 4 °C and the product was filtered off, rinsed with cooled acetone, and dried in the presence of P_2O_5: IR 3450, 3328, 1719; ^{19}F NMR (DMSO-d_6) δ 13.7 (pseudo t: dd $J = 5.3$); ^{31}P NMR (DMSO-d_6) δ 5.5 (q, $J = 5.2$); ^{1}H NMR (DMSO-d_6) δ 3.4 (d, 3H, $J = 10.3$), 4.1 (m, 1H), 5.08 (s, 2H), 7.15 (m, 1H), 7.36 (s, 5H); ^{13}C NMR (DMSO-d_6) d 49.9 (dq $J = 158$, $J = 30$), 51.3 (d, $J = 5.8$), 65.8, 122.4 (q, $J = 279$), 127.7, 128, 128.3, 136.7, 158.2. Anal. Calcd for $C_{11}H_{12}F_3NNaO_5P\cdot 0.5H_2O$: C, 36.88; H, 3.66; N, 3.91. Found: C, 37.26; H, 3.83; N, 3.90.

Similarly with compound **19a**, the product **20** was obtained after 8 h of heating: IR 3244, 1723; ^{19}F NMR (DMSO-d_6 + D_2O) δ 12.05 (pseudo t: dd, $J = 5.9$); ^{31}P NMR (DMSO-d_6 + D_2O) δ 7.9 (q, $J = 5.98$); ^{1}H NMR (DMSO-d_6) δ 0.8 (m, 3H), 1.2 (m, 6H), 2.7 (m, 2H), 3.9 (m, 1H), 5.05 (s, 2H), 6.57 m (1H), 7.34 (s, 5H); ^{13}C NMR (DMSO-d_6 + D_2O) δ 13.7, 21.7, 28.3, 31.4 (d, $J = 5.6$), 41.1, 51.5 (dq, $J = 157.2$, $J = 30.1$ Hz), 65.8, 120.02 (dq, $J = 7$, $J = 280.3$) 127.3, 128, 128.3, 136.4, 156.4 (d, $J = 5.94$). Anal. Calcd for $C_{15}H_{21}F_3N_2NaO_4P\cdot 1.5\ H_2O$: C, 41.77; H, 5.61; N, 6.49. Found: C, 41.78; H, 5.37; N, 6.21.

Pentylamide of *N*-Benzyloxycarbonyl *β*-Trifluoro α-Amino Monomethylphosphonate (19a). To a cooled (4 °C) dichloromethane (10 g) solution of monoester **18** (0.33 g, 0.95 mmol) and DMF (0.04 g, 0.55 mmol) was added oxalyl chloride (0.26 g, 1.9 mmol). After 30 min, the ^{31}P NMR spectrum showed only two quadruplets at δ 27.3 and 26.1. The mixture was concentrated nearly to dryness and pentylamine (0.17 g, 1.9 mmol) was added. Two hours later only two quadruplets at δ 20.6 and 18.8 were detected. Dilution with dichloromethane (40 g) and treatment as usual resulted in the isolation of 0.28 g of oil (80% yield of **19a** and **19b**). After standing overnight at 4 °C in a mixture of diethyl ether (2 g) and hexane (1 g), 0.14 g of **19a** crystallized: ^{31}P NMR ($CDCl_3$) δ 20.2 (q, $J = 5.98$); ^{1}H NMR ($CDCl_3$) δ 0.74−0.94 (m, 3H), 1.1−1.63 (m, 6H), 2.8 (m, d with irradiation at 1.5, 2H, $J = 8.65$), 3.7 (d, 3H, $J = 10.9$), 4.71 (m, 1H), 5.15 (s, 2H), 5.8 (m, 1H), 7.33 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 13.99, 22.3, 28.7, 31.6 (d, $J = 5.4$), 41.2, 50.9 (dq, $J = 160.1$, $J = 31.3$); 51.8 (d, $J = 5.8$), 67.8, 123.1 (dq, $J = 7.2$, $J = 279.56$), 128.1, 128.3, 128.6, 135.8, 156.1 (d, $J = 6.3$). Anal. Calcd for $C_{16}H_{24}F_3N_2O_4P$: C, 48.49; H, 6.10; N, 7.07. Found: C, 48.23; H, 5.87; N, 6.89.

JO034229J