Preparation of gem-difluorinated retrohydroxamic-fosmidomycin

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Dedicated to Professor Manfred Schlosser in honor of his scientific achievements

DOI: http://dx.doi.org/10.3998/ark.5550190.p008.846

Abstract
From several decades, some organophosphorus compounds specifically designed to alter biological systems were introduced on market as agrochemicals (ie glyphosate and glufosinate as herbicides). Nevertheless, it becomes necessary to find new compounds in order to counter plant resistances already observed with glyphosate. Fosmidomicyn and its *N*-acetyl analogues FR-900098 were perceived as starting points for elaboration of new herbicide candidates, targeting the second enzyme of the non-mevalonate pathway in plants, the 1-deoxy-D-xylulose 5-phosphate reductoisomerase (DOXP reductoisomerase or DXR). It is expected that the enhancement of bioactivity compared to the parent compounds, might be reached by insertion of two fluorine atoms close to the phosphonate function. Indeed, the presence of both fluorine atoms could improve the lipophilicity, affect the p*K*a of the phosphonic acid function and then induce better activities. Herein, the synthesis of gem-difluorinated analogues of retrohydroxamic fosmidomycin and FR-900098-ester is reported using a radical addition mediated by a cobaloxime complex.

Keywords: Fosmidomycin, phosphonate, hydroxamic acid, 1-deoxy-D-xylulose 5-phosphate reductoisomerase, DOXP reductoisomerase, DXR

Introduction

The world population is increasing and different estimations from United Nations planned for 2050 a population ranging from 8 to 10.5 billion people. In order to supply sufficient food, the

crop productivity has to urgently increase, and elaboration of powerful and ecocompatible new herbicides in absence of mammalian toxicity appears therefore a crucial issue.

The mevalonate-independent pathway of isoprenoid biosynthesis is widely found in many microorganisms[1-4] as well as in higher plants,[5,6] but it is missing in human, which uses mevalonate pathway for isoprenoid biosynthesis. The unique property of 1-deoxy-D-xylulose 5-phosphate reductoisomerase (DXR), the second enzyme of the DOXP pathway, can therefore be considered as a remarkable and safe target for the discovery of new herbicides. The fosmidomycin **1a** isolated from *Streptomyces lavendulae* in the seventies, has been referenced as an inhibitor of the DXR enzyme,[5,7] as well as *N*-acetyl homologue FR900098 **1b**,[8,9] fosmidomycin and FR900098 retrohydroxamic acids **1c-d**[10,11] and phosphate analogues, namely fosfoxacin **1e**[12] or acetyl analogue **1f**[12] (Figure 1). Fosmidomycin **1a** has been positively evaluated for the treatment of uncomplicated falciparum malaria in combination with clindamycin,[13-15] as well as for its herbicide activities, by use alone in combination with commercial triazine or urea herbicides.[16] Nevertheless, to date and despite these promising results, fosmidomycin has not been reached on the market neither as antimalarial drug nor as herbicide agent.

In the case of the phosphate derivative **1e** and preferentially **1f**, their respective activity clearly revealed stronger than the fosmidomycin on *Synechocystis* DXR.[12] These results could be directly attributed to the phosphate function. However, the intrinsic stability of phosphate group in biological media was questionable and clearly constituted its main drawback for a possible herbicide development. From a bioisostere approach, Van Calenbergh,[17] replaced oxygen atom by a monofluoromethylene group (CHF) and thus, two monofluorinated to FR900098 and to retrohydroxamic-FR900098 analogues were prepared. Both structures displayed that they were, *in vitro*, more potent than fosmidomycin and FR900098 towards *P. Falciparum* strain K1, and the antimalarial activity in an *in vivo* mouse model exceeded those of **1b**.[17]

By comparison to monofluoromethylene group, the difluoromethylene group (CF_2) exhibits also steric and electronic properties close to oxygen.[18-21] As a consequence of this equivalence, the p*K*a values of the difluorophosphonate are relatively similar to the phosphate,[19-21] and it might be considered as equivalent to the acidic character of phosphoric group of natural substrate **2**. Moreover, the replacement of phosphate bond ($HO_2P(O)O$-R) by a phosphonate linkage ($HO_2P(O)CF_2$-R) should increase chemical stability towards phosphatase, favouring a better bioavailability.[22] Finally, the DXR inhibitor incorporating difluoromethylene group, could have a higher lipophilic character,[23] allowing potentially a better integration in plants. Therefore, it became obvious that an α,α'-difluorophosphonate group should advantageously replace the phosphate group of **1f**, and preparation of compounds **3** and **4**, analogues to FR-900098 **1b** and parent molecule **1c**, were thus planned to enhance activity of DXR inhibitor for an herbicide application (Figure 1).

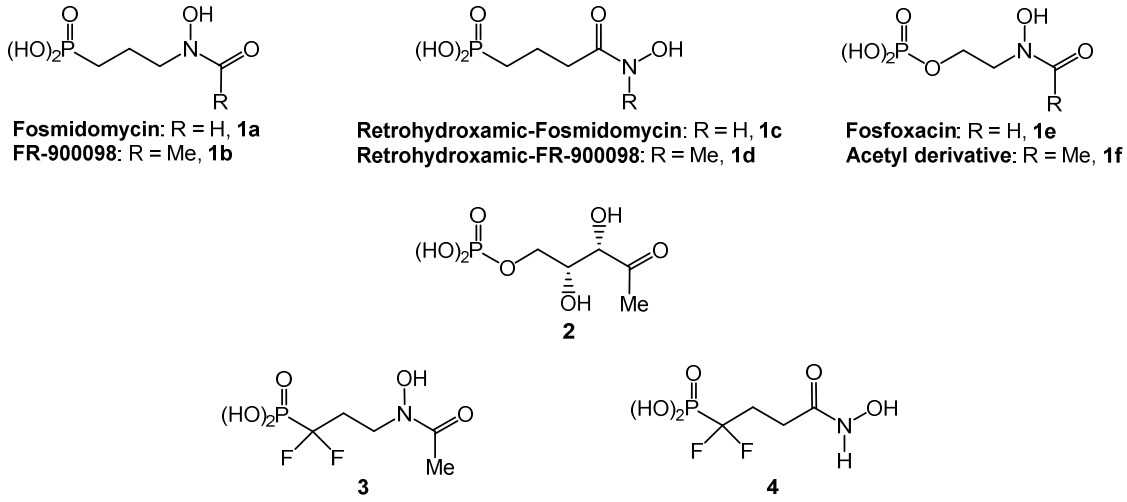
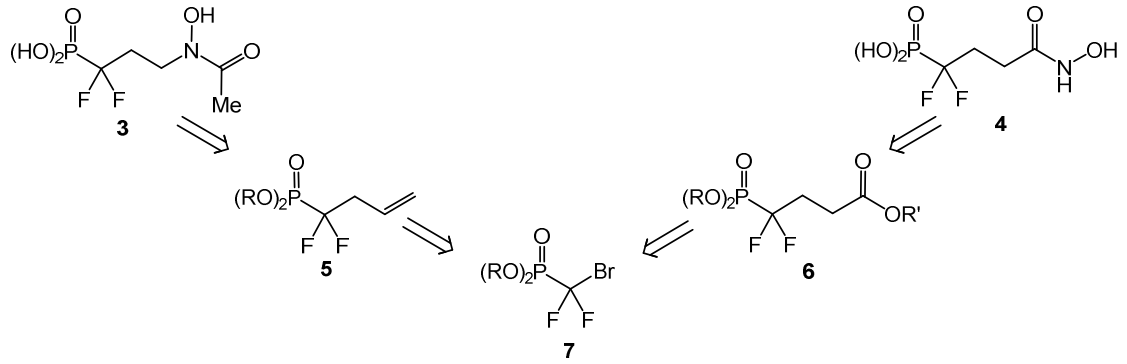


Figure 1. DXR enzyme inhibitors **1a-f** referenced and the natural substrate **2**. Targeted *gem*-difluorophosphonate **3** and retrohydroxamic–fosmidomycin **4** as **1b-c** analogues.

Results and Discussion

It was expected that fluoro analogues of fosmidomycin, and retrohydroxamic fosmidomycin **3** and **4** would be accessible from a same key precursor, the bromodifluoromethylphosphonate **7**. Furthermore, reactions of phosphonate **7** with an appropriate alkene had to afford fluoro intermediates **5** or **6**, which then would be transformed into hydroxamate by modification of the terminal alkene **5** or ester function from **6** (Scheme 1).

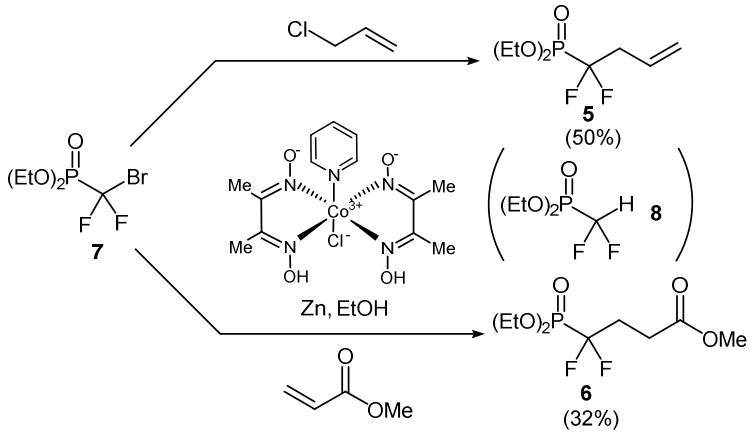


Scheme 1. Retrosynthetic pathway.

In the literature, several strategies were described for the introduction of difluoromethylene group linked to a phosphonate.[18] The most efficient pathway to produce quantitatively **7**, has been to use the Arbusov reaction according to Davisson method, of triethyl phosphite and

difluorodibromomethane.[24] Furthermore, the transformation of bromodifluoromethyl-phosphonate **7** into nucleophilic Grignard or heterocuprate reagents and their reaction with allyl bromide were explored. Unfortunately, none of these reactions were successful to produce allyl difluoromethylphosphonate **5**.

Another strategy developed by Hu,[25] using a bimetallic redox system constituted by cobaloxime(III)/Zn and reported to initiate the radical addition of *per*(poly)fluoroalkyl bromides to electron deficient alkenes, has been used with success producing allyl phosphonate **5**[25] and the phosphonobutyrate **6**[25] in 50% and 32% yields respectively (Scheme 2). Nevertheless, as mentioned by Hu, during the process, difluoromethylphosphonate **8** was formed as major side product, and in the case of **5**, all trials to entirely remove it were unsuccessful. Furthermore, the mixture of **5** and **8** has been used for preparation of *N*-phosphonohydroxamate ester **12**.

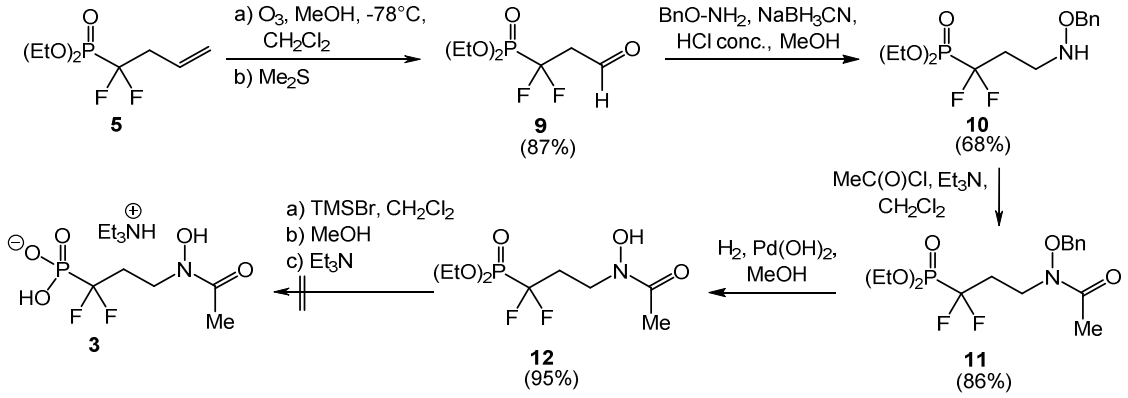


Scheme 2. Preparation of intermediates **5** and **6** by Hu's method.

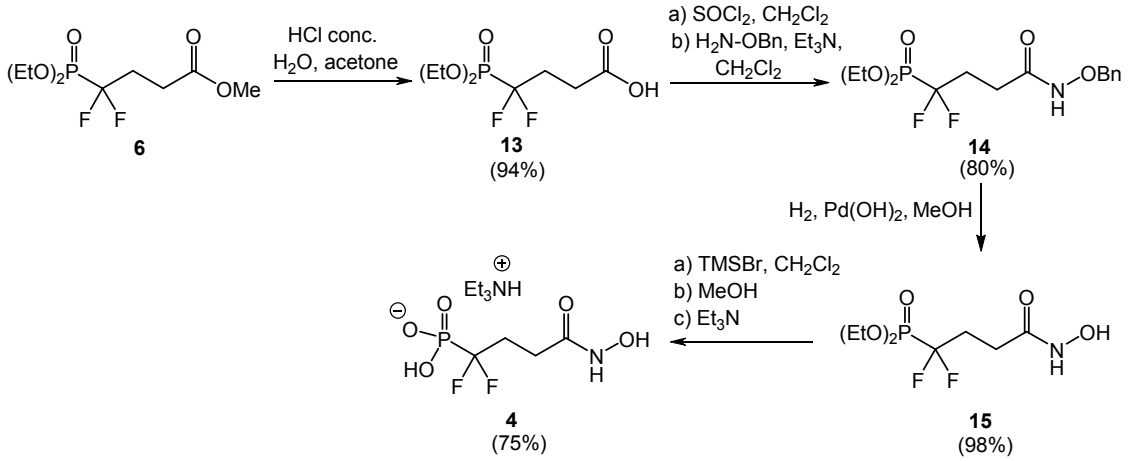
The preparation of *N*-phosphonohydroxamate ester **12** was accomplished through an ozonolysis of the alkene **5** applying the Chambers's procedure.[26] Due to its low stability, aldehyde **9** had to be promptly used for the next step, and its transformation by a reductive amination, using sodium cyanoborohydride in acidic conditions,[27] afforded the *O*-benzylhydroxylamino phosphonate **10** in 68% yield. Finally, the acylation was performed in dichloromethane using acetyl chloride and triethylamine as a base. Difluoromethyl hydroxamate **11** was obtained in 86% yield. The benzyl group was cleaved using hydrogen and palladium hydroxide as catalyst, giving the difluoromethylphosphonate **12** analogue of FR-900098-ester (95% yield). The hydrolysis of the phosphonate ester using trimethylsilyl bromide,[28,29] followed by methanolysis at room temperature, did not afford pure phosphonic acid **3**. Otherwise, another attempt by acidolysis of **12** and neutralization, followed by *N*-acetylation also revealed not convincing for a clean access to phosphonic acid **3** (Scheme 3).

Contrary to **3**, the synthesis of the difluorofosmidomycin analogue **4** has been achieved without difficulty. Firstly, the hydrolysis of the ester **6** under acidic conditions produced the corresponding carboxylic acid **13** in nearly quantitative yield. After chlorination and reaction

with *O*-benzylhydroxylamine, the protected hydroxamic acid **14**, was isolated in 80% yield. From compound **14,** benzyl group was removed quantitatively by hydrogenolysis to give **15**. The final step of the synthesis was the deprotection of the corresponding phosphonate into phosphonic acid **4** (75% yield), using 10 equivalents of trimethylsilyl bromide followed by a methanolysis at room temperature (Scheme 4).



Scheme 3. Synthesis of *gem*-difluoro **12**, analogue of FR-900098-ester.



Scheme 4. Synthesis of *gem*-difluorinated retrohydroxamic acid triethylammonium salt **4**.

Conclusions

In conclusion, using difluorobromomethylphosphonate as a key building block, we performed an efficient synthesis of new gem-difluorinated analogues of retrohydroxamic fosmidomycin and retrohydroxamic-FR-900098-ester **4** and **12**. Both fluorinated fosmidomycin analogues **4** and **12** were not active on the biological tests for determination of herbicide activity.

Acknowledgements

This research was supported by a Grant from Bayer CropScience and the CNRS.

Experimental Section

General. All air and/or water sensitive reactions were carried out under nitrogen atmosphere. The solvents were dried using standard methods, distilled and stored under nitrogen. Reactions were monitored by ^{31}P NMR using DMSO–d_6 as internal references. Purifications by column chromatography were performed on silica gel (Merck 60 AC. 35–70μm).
Unless otherwise specified, NMR spectra were recorded on a BRUKER Ultra shield 400 plus instrument at 161.99 MHz for ^{31}P, 376.50 MHz for ^{19}F, 400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C. The spectrometer used for low and high resolution mass spectra was electrospray ionization (ESI) WATERS Micromass Q-Tof spectrometer with as internal reference H_3PO_4 (0.1 % in water/acetonitrile, 1:1).
The diethyl (bromodifluoromethyl)phosphonate **7**, was prepared according to procedure described by Davisson.[24] The diethyl 1,1-difluoro-3-butenylphosphonate **5**[25,30,31] and methyl 4-(diethoxyphosphinyl)-4,4-difluorobutyrate **6**[25] were synthesized using procedure reported by Hu.[25] Diethyl (1,1-difluoro-3-oxopropyl)phosphonate **9**[26] was accessible applying Chambers's procedure.[26]

Diethyl (3-(benzyloxyamino)-1,1-difluoropropyl)phosphonate 10. In a 500 mL two-necked flask were introduced diethyl 1,1-difluoro-3-oxopropylphosphonate **9** (3.0 g, 13 mmol), *O*-benzyl-hydroxylamine (1.6 g, 13 mmol) and methanol (10 mL). The reaction mixture was stirred for 1h at room temperature. After addition of methanol (190 mL) the mixture was treated portionwise with sodium cyanoborohydride (2.45 g, 39 mmol) over 30 min. Then, aqueous hydrochloric acid (13 mL, 37%) was added over 40 min under ice cooling. The mixture was allowed to warm up to room temperature and sodium cyanoborohydride (0.57 g, 9.1 mmol) was added. The reaction mixture was stirred at room temperature over 2 h. The solution was concentrated and treated with aqueous potassium hydroxide (10%) until *p*H basic. The product was extracted with ethyl acetate (3 × 150 mL), the organic layers were combined, dried over $MgSO_4$ and concentrated under vacuum. A purification by column chromatography on silica gel with heptane/EtOAc/EtOH as eluent (100:0:0 to 60:36:4) gave **10** as a yellow liquid (3.0 g, 68%). ^{31}P NMR ($CDCl_3$): δ 6.90 (t, *J* 107.5 Hz). ^{19}F NMR ($CDCl_3$): δ –111.08 (d, *J* 107.9 Hz). ^{1}H NMR ($CDCl_3$): δ 1.39 (t, 6H, *J* 7.0 Hz, CH_3), 2.30-2.46 (m, 2H, CH_2), 3.24 (t, 2H, *J* 7.2 Hz, CH_2), 4.24–4.33 (m, 4H, P(O)OCH_2), 4.71 (s, 2H, $PhCH_2$), 5.69 (broad s, 1H, NH), 7.28–7.34 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 16.4 (d, *J* 5.1 Hz, CH_3, 2 C), 32.2 (td, *J* 20.5 Hz and 14.6 Hz, CH_2, 1 C), 44.4 (q, *J* 5.4 Hz, NCH_2, 1 C), 64.5 (d, *J* 6.6 Hz, P(O)OCH_2, 2 C), 76.2 (s, $PhCH_2$, 1 C), 120.5 (td, *J* 259.8 Hz and 215.9 Hz, CF_2, 1C), 127.9 (s, CHar, 1 C), 128.4 (s, CHar, 2 C),

128.4 (s, CHar, 2 C), 137.7 (s, Car, 1 C). HRMS (*m/z*) calcd for $C_{14}H_{23}F_2NO_4P$: 338.1333. Found: 338.1327.

Diethyl (3-(*N*-(benzyloxy)acetamido)-1,1-difluoropropyl)phosphonate 11. In a 100 mL two-necked flask were introduced diethyl (3-(benzyloxyamino)-1,1-difluoropropyl)phosphonate **10** (1.2 g, 3.6 mmol), triethylamine (0.58 mL, 4.2 mmol) and CH_2Cl_2 (30 mL). The reaction mixture was cooled to 0°C and acetyl chloride (0.30 mL, 4.2 mmol) was added dropwise. The mixture was stirred overnight at room temperature. Then, water (20 mL) was poured on and the reaction mixture was extracted with CH_2Cl_2 (2 × 50 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under vacuum. Purification by column chromatography on silica gel with as eluent a mixture of heptane/EtOAc/EtOH (100:0:0 to 50:45:5) gave **11** (1.2 g, 86%). ^{31}P NMR ($CDCl_3$): δ 6.51 (t, *J* 107.0 Hz). ^{19}F NMR ($CDCl_3$): δ –112.34 (d, *J* 106.7 Hz). ^{1}H NMR ($CDCl_3$): δ 1.39 (t, 6H, $^3J_{HH}$ 7.0 Hz, CH_3), 2.10 (s, 3H, CH_3), 2.40–2.47 (m, 2H, CH_2), 3.93 (t, 2H, $^3J_{HH}$ 7.5 Hz, NCH_2), 4.24–4.33 (m, 4H, OCH_2), 4.85 (s, 2H, $PhCH_2$), 7.35–7.43 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 16.4 (d, *J* 5.9 Hz, CH_3, 2 C), 20.6 (s, CH_3, 1 C), 30.8 (q, *J* 18.3 Hz, CH_2, 1 C), 38.5 (s, CH_2, 1 C), 64.6 (d, *J* 6.6 Hz, OCH_2, 2 C), 76.5 (s, $PhCH_2$, 1 C), 119.8 (td, *J* 259.8 Hz and 215.9 Hz, CF_2, 1 C), 128.8 (s, CHar, 2 C), 129.1 (s, CHar, 1 C), 129.3 (s, CHar, 2 C), 134.2 (s, Car, 1 C), 172.0 (s, C(O), 1 C). HRMS (*m/z*) calcd for $C_{16}H_{25}F_2NO_5P$: 380.1438. Found: 380.1448.

Diethyl (1,1-difluoro-3-(*N*-hydroxyacetamido)propyl)phosphonate 12. In a Schlenck tube under nitrogen were introduced palladium dihydroxide on charcoal (150 mg, 10%) and **11** (1.5 g, 4.0 mmol) in degassed ethanol (100 mL). The reaction mixture was stirred vigorously under a hydrogen atmosphere at room temperature for 12 h. The reaction mixture was filtered on a celite pad and the filtrate was concentrated under vacuum to afford **12** as yellow liquid (1.1 g, 95%). ^{31}P NMR (CD_3OD): δ 5.17 (t, *J* 108.0 Hz). ^{19}F NMR (CD_3OD): δ –114.98 (d, *J* 107.9 Hz). ^{1}H NMR (CD_3OD): δ 1.39 (td, 6H, *J* 7.1 Hz and 0.5 Hz, CH_3), 2.10 (s, 3H, CH_3), 2.35–2.45 (m, 2H, CH_2), 3.87 (t, 2H, *J* 7.7 Hz, NCH_2), 4.26–4.34 (m, 4H, OCH_2). ^{13}C NMR (CD_3OD): δ 14.9 (d, *J* 5.1 Hz, CH_3, 2 C), 18.5 (s, CH_3, 1 C), 30.3 (td, *J* 20.5 Hz and 14.6 Hz, CH_2, 1 C), 40.2 (q, *J* 5.8 Hz, NCH_2, 1 C), 64.6 (d, *J* 7.3 Hz, OCH_2, 2 C), 119.4 (td, *J* 259.1 Hz and 218.8 Hz, CF_2, 1 C), 172.2 (s, C(O), 1 C). HRMS (*m/z*) calcd for $C_9H_{19}F_2NO_5P$: 290.0969, found: 290.0974.

4-Diethoxyphosphinyl-4,4-difluorobutanoic acid 13. In a 100 mL two-necked flask were introduced methyl 4-(diethoxyphosphinyl)-4,4-difluorobutyrate **6** (4.5 g, 16.4 mmol) and acetone (40 mL), followed by a slow addition of hydrochloric acid solution (22 mL, 6 M). The resulting mixture was stirred under reflux for 45 min. The acetone was removed under vacuum and the product was extracted with diethyl ether (3 × 100 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under vacuum to give **13** as a colorless liquid (4.0 g, 94%). ^{31}P NMR (101.25 MHz, $CDCl_3$): δ 6.47 (t, *J* 107.9 Hz). ^{19}F NMR (235.33 MHz, MeOD): δ – 114.01 (d, *J* 108.2 Hz). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.38 (t, 6H, *J* 7.1 Hz, CH_3), 2.32–2.69 (m, 4H, CH_2CH_2), 4.22–4.34 (m, 4H, OCH_2), 8.64 (broad s, 1H, OH). ^{13}C NMR ($CDCl_3$): δ 16.3 (d, *J* 5.9 Hz, CH_3, 2 C), 25.8 (q, *J* 5.1 Hz, CH_2, 1 C), 29.2 (td, *J* 21.2 Hz and 16.0 Hz, CH_2, 1 C), 64.9 (d, J

6.6 Hz, CH_2, 2 C), 119.8 (td, J 259.8 Hz and 217.4 Hz, CF_2, 1 C), 175.96 (s, C(O), 1 C). HRMS (*m/z*) calcd for $C_8H_{16}F_2O_5P$: 261.0703, found: 261.0722.

Diethyl (4-(benzyloxyamino)-1,1-difluoro-4-oxobutyl)phosphonate 14. In a 250 mL two-necked flask were introduced 4-diethylphosphonyl-4,4-difluorobutyric acid (**13**, 4.0 g, 15.4 mmol) and CH_2Cl_2 (100 mL). The mixture was cooled at 0 °C and thionyl chloride (2.25 mL, 30.8 mmol) was slowly added. The resulting mixture was stirred at room temperature for 4 h, then concentrated under vacuum and evaporated twice with dry toluene (2 × 20 mL). The acyl chloride was used directly without further purification. In a 250 mL two-necked flask were successively introduced *O*-benzyl hydroxylamine (2.27 g, 18.4 mmol), CH_2Cl_2 (150 mL) and triethylamine (2.6 mL, 18.7 mmol). A solution of 4-diethoxyphosphinyl-4,4-difluorobutyric acid chloride (15.4 mmol) in CH_2Cl_2 (50 mL) was added dropwise. The mixture was stirred at room temperature overnight. Then, water (100 mL) was poured on and the product was extracted with CH_2Cl_2 (3 × 150 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography on silica gel with as eluent a mixture of heptane/EtOAc/EtOH (100:0:0 to 40:54:6) affording **14** as yellow liquid (4.5 g, 80%). ^{31}P NMR (CD_3OD): δ 5.34 (t, *J* 109.0 Hz). ^{19}F NMR (CD_3OD): δ –115.66 (d, *J* 109.2 Hz). ^{1}H NMR (CD_3OD): δ 1.38 (t, 6H, *J* 7.1 Hz, CH_3), 2.30-2.50 (m, 4H, CH_2CH_2), 4.24–4.34 (m, 4H, OCH_2), 4.84 (s, 2H, $PhCH_2$), 7.35–7.45 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 16.4 (d, *J* 5.1 Hz, CH_3, 2 C), 24.9 (s, CH_2, 1 C), 29.7 (q, *J* 19.0 Hz, CH_2, 1 C), 64.7 (s, OCH_2, 2 C), 78.1 (s, $PhCH_2$, 1 C), 120.1 (td, J 259.8 Hz and 215.9 Hz, CF_2, 1 C), 128.5 (s, CHar, 2 C), 128.6 (s, CHar, 1 C), 129.1 (s, CHar, 2 C), 135.4 (s, Car, 1 C), 168.9 (s, C(O), 1 C). HRMS (*m/z*) calcd for $C_{15}H_{23}F_2NO_5P$: 366.1282. Found: 366.1281.

Diethyl (1,1-difluoro-4-(hydroxyamino)-4-oxobutyl)phosphonate 15. Proceeding as for **12**, compound **15** was obtained from **14** as yellow liquid (1.1g, 98%). ^{31}P NMR ($CDCl_3$): δ 6.51 (t, J 108.0 Hz). ^{19}F NMR ($CDCl_3$): δ –111.86 (d, J 107.9 Hz). ^{1}H NMR ($CDCl_3$): δ 1.31 (t, 6H, J 7.0 Hz, CH_3), 2.2–2.5 (m, 4H, CH_2-CH_2), 4.15–4.25 (m, 4H, OCH_2), 8.70 (broad s, 0.8H), 9.87 (broad s, 0.8H). ^{13}C NMR ($CDCl_3$): δ 16.3 (d, *J* 5.1 Hz, CH_3, 2 C), 24.5 (CH_2, 1 C), 29.7 (q, *J* 19.3 Hz, CH_2, 1 C), 65.0 (d, *J* 6.6 Hz, OCH_2, 2 C), 120.1 (td, *J* 259.8 Hz and 216.6 Hz, CF_2, 1 C), 169.4 (s, C(O), 1 C). HRMS (*m/z*) calcd for $C_8H_{17}F_2NO_5P$: 276.0812. Found: 276.0809.

Triethylammonium (1,1-difluoro-4-(hydroxyamino)-4-oxobutyl)phosphonate 4. In a 50 mL three-necked flask were introduced **15** (1 mmol) and CH_2Cl_2 (10 mL). The mixture was stirred in an ice bath (T = 0°C) and trimethylsilylbromide (1.3 mL, 10 mmol) was added. The reaction mixture was stirred at room temperature for 14 h and concentrated to dryness under vacuum. Methanol (10 mL) was added and the resulting mixture was stirred at room temperature for 2 h and then concentrated under vacuum. The crude was dissolved in methanol (10 mL) and triethylamine (1.4 mL, 10 mmol) was added slowly. The solvent was removed under vacuum. The crude was dissolved in water (50 mL) and the suspension filtered off. The aqueous layer was washed with chloroform (3 × 50 mL). After concentration under vacuum, the salt **4** was obtained as a colorless gum (240 mg, 75%). ^{31}P NMR (D_2O): δ 4.75 (t, *J* 95.1 Hz); ^{19}F NMR (D_2O): δ –113.50 (d, *J* 95.2 Hz). ^{1}H NMR (D_2O): δ 1.14 (t, 9H, *J* 7.3 Hz, CH_3), 2.1-2.3 (m, 2H, CH_2), 2.46

(t, 2H, *J* 7.3 Hz, $CH_2C(O)$), 3.06 (q, *J* 7.3 Hz, 6H, $^5CH_2$). ^{13}C NMR (D_2O): δ 8.2 (s, CH_3, 3 C), 27.1 (q, *J* 5.4 Hz, $CH_2C(O)$, 1 C), 29.4 (td, *J* 21.2 Hz, and 14.6 Hz, CH_2, 1 C), 46.6 (s, NCH_2, 3 C), 122.0 (td, J 257.6 Hz and 196.9 Hz, CF_2, 1 C), 178.8 (s, C(O), 1 C). HRMS (*m/z*) calcd for $C_4H_9F_2NO_5P$: 220.0186. Found 220.0191.

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