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A Facile Solution and Solid Phase Synthesis of Phosphotyrosine Mimetic L-4-[DiethylPhosphono(difluoromethyl)]-Phenylalanine (F_2Pmp(EtO)$_2$) Derivatives†

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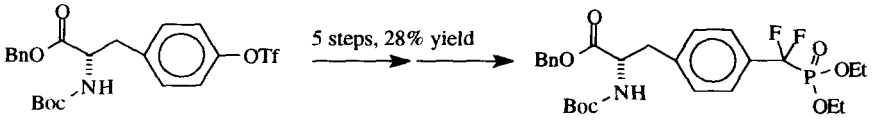
Abstract: The F_2Pmp derivatives were prepared in 80-90% yield from commercially available protected L-4-iodophenylalanine by esterification with diazomethane followed by a CuCl-mediated coupling to (diethylphosphonyl) difluoromethylcadmium bromide. Moreover, treatment of L-4-iodoPhe-containing peptides under the same coupling conditions provided the F_2Pmp-containing peptides in very good yields. © 1997 Elsevier Science Ltd.

INTRODUCTION

Transient phosphorylation of tyrosine residues in proteins, regulated by the interplay of protein tyrosine kinases (PTK) and phosphatases (PTP),[1] plays an important role in signal transduction. Following receptor activation, PTK's phosphorylate tyrosine residues which are used to recruit specific protein partners via interaction with SH2 or PTB domains.[2,3] The critical role of phosphorylated tyrosine in cell growth and metabolism along with the potential of exploiting it to combat various diseases, such as cancer, has generated great interest in synthesizing stable nonhydrolyzable phosphotyrosine mimics. As part of our program to develop small molecule inhibitors of PTP's and SH2 and PTB interactions, we required enzymatically stable, nonhydrolyzable analogs of phosphotyrosine. In particular we wished to prepare difluoro(phosphonomethyl) phenylalanine (F_2Pmp) derivatives which were developed by Burke and coworkers.[4] This derivative, which has a pKa lower than the corresponding nonfluorinated phosphonate analogs, was shown to possess enhanced potency against both SH2 and PTPs.[5]

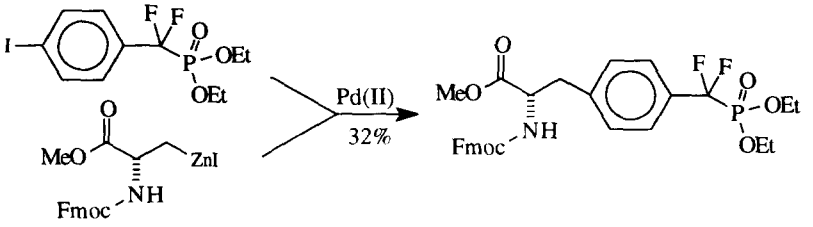
The syntheses of the N-Boc and N-Fmoc derivatives of the title compound were previously described by three groups.[6,7,8] However, the syntheses (schemes 1-3) were somewhat lengthy (5 steps), low yielding (18-



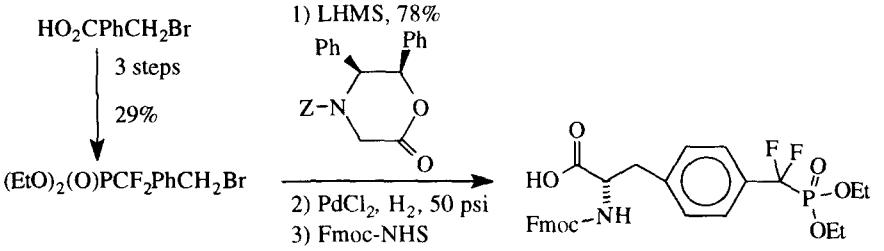
Scheme1. Wrobel's approach

† This manuscript is dedicated to Professor Samuel Danishefsky's excellence as a scientist and educator.

35% yield) and required the use of a large excess (5-15 equiv) of (diethylamino)sulfur trifluoride (DAST). Our

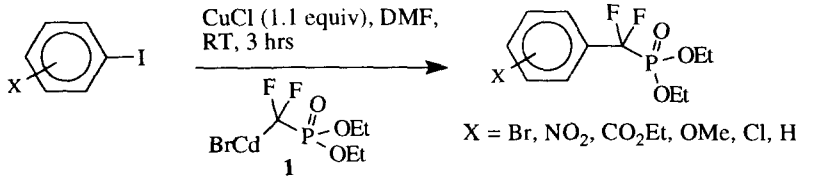


Scheme 2. Burke's approach



Scheme 3. Solas's approach

synthesis of the F_2Pmp derivatives utilized a convenient coupling reaction that was recently described in the literature. Burton[9] reported the formation of α,α-difluorobenzylic phosphonates by a CuCl-promoted coupling of a cadmium derivative[Φ] of diethyl bromodifluoromethylphosphonate (**1**) with aryl iodides (scheme 4). The simplicity and high yielding nature of this reaction prompted us to investigate the feasibility of this reaction for



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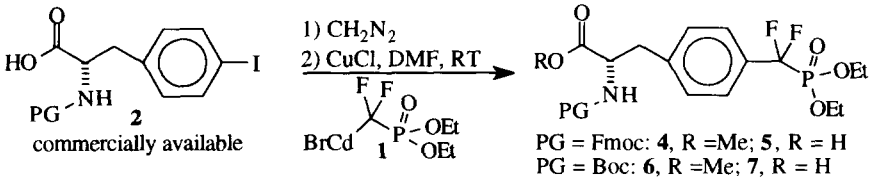
Scheme 4

the preparation of compounds **4**, **5**, **6** and **7** (scheme 5). Herein, we disclose the facile synthesis of these derivatives and the application of the coupling reaction to solid phase synthesis.

RESULTS AND DISCUSSION

N-protected-L-4-iodophenylalanine methyl ester **3** (**3a**, PG=Fmoc; **3b**, PG=Boc) was prepared by treatment of the commercially available N-protected-L-4-iodophenylalanine **2** [Advanced Chemtech] with diazomethane at 0 °C. The Burton protocol, which involved, in our case, treatment of compound **3a** with cadmium reagent **1** (1.7 equiv) in DMF in presence of CuCl (1.1 equiv) for 3-5 hrs, afforded the product in low

[Φ] CAUTION! cadmium metal is highly toxic and a suspected carcinogen.

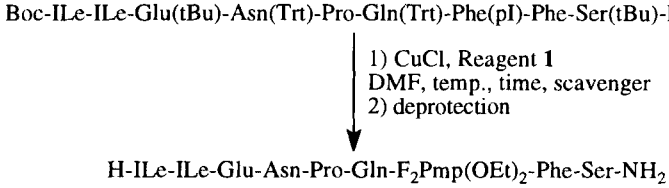


Scheme 5

yield (15-25%) and the majority of starting material was recovered. Heating the reaction mixture (40 °C, 18 hrs) did not improve the outcome. When excess CuCl (3-4 equiv) and reagent **1** (3-5 equiv) were used and the reaction was allowed to stir for 36-40 hrs the product **4** was obtained in 87% yield along with 5% starting material **3a**. The acid **5** was then obtained by LiOH hydrolysis (0 °C) of the methyl ester **4** as described by Burke.[10] Similarly, the Boc-protected F_2Pmp derivative was prepared with the same efficiency. Moreover, the D-4-iodophenylalanine enantiomer is also commercially available which allows access to D-F_2Pmp derivatives. It is noteworthy that product **5** could be used in solid phase synthesis as the diethyl-protected phosphonate derivative or alternately could be hydrolyzed in solution using BSTFA/TMSI to the unprotected phosphonate derivative and used in solid phase synthesis as described by Gordeev.[11]

The exact role that CuCl plays in this coupling reaction[12,13] or the requirement of excess CuCl to drive the reaction to completion is unclear. Burton,[13] in his work on the preparation of 1,1-difluoro-3-alkenphosphonates by CuBr-catalyzed reaction of organozinc phosphonate and allylic halides, suggested that a transmetallation step takes place to afford an organocopper reagent which reacts in an SN2/SN2' fashion with allylic electrophiles. In our case, the second step (the carbon-carbon bond formation step) might involve an oxidative addition/ reductive elimination sequence. The use of excess rather than stoichiometric or catalytic CuCl in coupling reactions has been reported by other groups.[14,15] Piers[14] reported the use of 2-5 equiv of CuCl to effect efficient coupling reactions between two stannane groups and also between stannanes and vinyl halides. The excess CuCl (> 2 equiv) was crucial for the progression of the reaction. They determined that two mmole of copper metal were produced for each mmole of substrate converted to product. As in our case, no apparent explanation for the need of excess CuCl was available.

Next we decided to explore the applicability of this coupling reaction to the solid phase preparation of F_2Pmp-containing compounds. The previously described syntheses of F_2Pmp moiety are not applicable to solid phase preparation due mainly to the strategic disconnection in the syntheses and the number of steps involved. Our synthesis, on the other hand, owing to the efficiency of coupling and the small number of steps is readily applicable to solid phase synthesis.



Scheme 6

Compound **8** was synthesized, using standard solid phase synthesis protocols, and was treated with CuCl and reagent **1** at RT for 6-7 days (scheme 6) to afford, after cleavage using TFA/TES/H_2O/DCM, the

corresponding product in good yield in addition to small amount of byproducts (**10** and **11**, see Table 1) with higher mass than the phosphorylated peptide. Heating the reaction at 60-70 °C for 14 hours was sufficient to produce high conversion; however, the byproducts (**10** and **11**) were formed in larger quantities. The byproducts **10** (product's mass + 27) and **11** (product's mass + 243) appear to arise from a transfer of ethyl and trityl groups respectively to a different residue in the peptide. We believe that at elevated temperatures, CuCl (a Lewis acid) catalyzes the transfer of acid-labile protecting groups. Hence, we decided to use cation scavengers to retard the formation of the abovementioned byproducts.

Table 1. The Impact of Temperature and Scavengers on the Coupling Reaction

Entry	Time	Temp.	Scavengers	Yield *	S.M.	Product **9**	Byproduct **10**	Byproduct **11**
1	96	25	none	84	50	42	5	3
2	170	25	none	71	17	59	9	15
3	12	45	TES	27	16	23	30	31
4	14	50	none	38	7	36	38	19
5	12	65	A	28	5	26	49	19
6	12	65	A,T	46	9	42	34	16
7	14	65	none	23	8	21	41	30
8	2	75	A,T	82	22	62	4	10
9	2	75	A,T,EMS	94	58	39	2	1

A=Anisole, T=Thioanisole, EMS=Ethyl methyl sulfide, TES=Triethylsilane
Byproduct **10**: product's mass + 28 (Et); Byproduct **11**: product's mass + 243 (Trt)
* yield is based on unconsumed S.M.

When this reaction was conducted at 65 °C for 12-14 hrs in the presence of scavengers (anisole, thioanisole, etc.; see Table 1), the amount of product formed was increased while that of byproducts was reduced (compare entries 6 and 7). However, complete suppression of byproducts was not possible. It appears that the scavengers have no major deleterious effect on the reaction. Inspection of Table 1 shows that, for this specific substrate, temperature and duration of reaction play the biggest role in determining the outcome of the reaction. We found that the best conditions to effect this coupling is to heat the reaction mixture at 75 °C for 2 hrs in the presence of a cocktail of anisole/thioanisole (entry 8). The formation of the requisite product was verified in each case by comparing the retention time and mass spectrum to those of an authentic sample that was prepared on solid phase using the diethyl F_2Pmp derivative **5** (vide supra).

In summary, a facile and efficient synthesis of the title compound derivatives, which has proven to be an effective mimic of phosphotyrosine, is described. The extension of this reaction to solid phase was successful and furnished compounds incorporating the phosphotyrosine mimetic F_2Pmp. We were able to utilize this reaction in the preparation of a library of compounds that incorporate peptidomimetic β-strand templates[16] (not shown). Peptidomimetics of this type have been used to inhibit signal transduction processes involving SH2 domain interactions both at the protein level and in cell culture.[17] This work and other results in this arena will be reported in due course.

ACKNOWLEDGMENTS: We thank Brett Bentley and Dick Shen for conducting HPLC analysis, Jim Dattilo for preparing authentic peptide **9** and Dr. Tomas Vaisar for running the MS analysis.

EXPERIMENTAL

General. All solution phase reactions were run in flame-dried glassware under an inert atmosphere. THF, MeOH and DMF were freshly distilled. DMF was dried over 4 Å molecular sieves (4 Å MS, beads, 4-8 mesh) overnight, distilled at reduced pressure, and stored over 4 Å MS. Cadmium metal [CAUTION! cadmium metal is highly toxic and a suspected carcinogen] was washed with 2N HCl (1X), deionized water (3X) and acetone (3X) and dried under high vacuum for 4-6 hrs. The resultant clumps were crushed into a powder under inert atmosphere then dried for an additional 16 hrs. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity 500 spectrometer, and the $CHCl_3$ peaks at δ 7.26 ppm (^{1}H NMR) and 77.23 ppm (^{13}C NMR) served as an internal standard. ^{19}F NMR was measured on a Bruker AC200. The mass spectra were obtained using a Fisons VG Quattro spectrometer. Optical rotation was measured on a JASCO DIP 370. Flash column chromatography[18] was done using Merck's silica gel 60. Analytical thin layer chromatography was done on silica gel 60 F254. Melting points (mp) are uncorrected and were recorded using an electrothermal digital melting point apparatus model IA9100.

Peptide synthesis: Peptide **8** was prepared by standard SPPS using Fmoc strategy; [polystyrene resin with PAL linker, side chains were protected as follows Glu (OBut), Asn (Trt), Gln (Trt), Ser (But), mixture of amino acid-HBTU-HOBt-NMM (5:5:5:10 equiv) in DMF was used for couplings. Deprotection of Fmoc was accomplished by treatment with 25% piperidine in DMF for 9 min.]. The last amino acid was incorporated as Boc-protected. Dry resin (10-30μmol) was than mixed with CuCl (35 equiv) and DMF solution of reagent **1**(50-60 equiv) and shaken or stirred in sealed vial at temperature stated. For the reactions conducted in the presence of scavengers, 5% anisole, 5% thioanisole, 5% triethylsilane and 40% ethyl methyl sulfide were used.

Cleavage of peptides from resin: Peptides from PAL-PS were cleaved by treatment with TFA-H_2O-TES-DCM (85:5:5:5) for 90 min. followed by precipitation from Et_2O.

H-Ile-Ile-Glu-Asn-Pro-Gln-Phe(pI)-Phe-Ser-NH$_2$: retention time = 17.33 min (Vydac C8, 10 mic., 4.6x250 mm; eluent 1: H_2O with 0.1%TFA, eluent 2: CH_3CN with 0.1%TFA; gradient 15-45% of eluent 2 over 30 minutes at a flow rate of 1mL/min). MS (ES$^+$) 1219.7 (M+H), 629.4 (M+H+K), 621.6 (M+H+Na).

H-Ile-Ile-Glu-Asn-Pro-Gln-F2Pmp(OEt)$_2$-Phe-Ser-NH$_2$ (9):retention time = 18.31min. MS (ES$^+$) 1280.7 (M+H), 659.3 (M+H+K), 651.6 (M+H+Na), 640.7 (M+2H). Amino acid analysis of HCl hydrolysate (Numbers in parentheses are expected values) : Asp 1.01 (1), Glu 2.08 (2), Ile 1.78 (2), Phe 1.01 (1), Pro 1.24 (1) and Ser 0.88 (1).

Byproduct 10: retention time = 19.45 min. MS (ES$^+$) 1307.7 (M+H), 665.6 (M+H+Na), 654.7 (M+2H). Daughter ions of **10**, peak 655 : 1203.5, 1056.1, 837.4, 723.9, 529.3, 470.8, 356.6, 305.8, 227.3, 199.1, 119.8, 86.0

Byproduct 11: retention time = 20.45. MS (ES$^+$) 773.12 (M+H+Na), 762.1 (M+2H). Daughter ions of **11**, peak 762 : 1280.1, 244.1

Methyl N-Fmoc-L-4-iodophenylalanine (3a): N-Fmoc-L-4-iodophenylalanine (0.5 g, 1.0 mmol) was dissolved in MeOH/THF (1:1, 8mL total), cooled to 0 °C and an ethereal solution of diazomethane was added until the yellow color persisted. Nitrogen gas was bubbled through solution and the solvents evaporated to leave behind a white solid that was purified by flash column chromatography on silica gel using 30% EtOAc/hexanes

to afford pure product (0.52 g, 98%). mp: 137-138.5 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.78 (2H, d, J = 7.0 Hz), 7.60 (2H, d, J = 8.0 Hz), 7.57 (2H, t, J = 6.0 Hz), 7.42 (2H, t, J = 7.0 Hz), 7.33 (2H, t, J = 7.0 Hz), 6.81 (2H, d, J = 8.0 Hz), 5.24 (1H, d, J = 8.0 Hz), 4.64 (1H, m), 4.48 (1H, dd, J = 10.5, 7.0 Hz), 4.37 (1H, dd, J = 11.0, 7.0 Hz), 4.21 (1H, t, J = 7.0 Hz), 3.74 (3H, s), 3.09 (1H, dd, J = 13.5, 6.5 Hz), 3.02 (1H, dd, J = 13.5, 6.5 Hz), [the 3.09 and 3.02 signals are parts of an AB quartet pattern; iiII IIii]. ^{13}C NMR ($CDCl_3$) δ 171.8, 155.6, 144.0, 143.8, 141.5, 137.8, 135.6, 131.5, 127.9, 127.3, 125.2, 125.1, 120.2, 92.9, 67.1, 54.7, 52.7, 47.3, 37.9. IR ($CDCl_3$) cm^{-1} 3434, 3067, 2984, 2958, 2906, 1743, 1723, 1513, 1477, 1385, 1350, 1214, 1099, 925. MS (ES^+) 550.3 (M+Na), 528.3 (M+H).

Methyl N-Boc-L-4-iodophenylalanine (3b): Treatment of N-Boc-L-4-iodophenylalanine as above afforded the pure product. mp: 77-78 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.61 (2H, d, J = 8.0 Hz), 6.87 (2H, d, J = 8.0 Hz), 4.98 (1H, d, J = 8.0 Hz), 4.57 (1H, m), 3.71 (3H, s), 3.07 (1H, dd, J = 13.5, 5.5 Hz), 2.97 (1H, dd, J = 13.5, 5.5 Hz), [the 3.07 and 2.97 signals are parts of an AB quartet pattern; iiII IIii], 1.41 (9H, s). ^{13}C NMR ($CDCl_3$) δ 172.2, 155.2, 137.8, 135.9, 131.5, 92.7, 80.3, 54.4, 52.6, 38.1, 28.5. IR ($CDCl_3$) cm^{-1} 3437, 2984, 2956, 2937, 2904, 1744, 1711, 1488, 1384, 1167, 1101, 909. MS (ES^+) 428.1 (M+Na), 406.1 (M+H).

Methyl N-Fmoc-L-4-[diethylphosphono(difluoromethyl)]-phenylalanine (4): The coupling reaction, performed as described by Burton[9] with slight modification, was conducted as follows: To acid-washed cadmium metal (0.63 g, 5.5 mmol, gray powder, -100 mesh) in dry DMF (5.0 mL, distilled under vaccum then stored over 4Å MS) under nitrogen was added diethyl bromodifluoromethylphosphonate (0.89 mL, 5.0 mmol) dropwise over 5 min (slightly exothermic reaction). The reaction was stirred at room temperature for 3 hrs and allowed to stand for 30 min. An aliquot (2.5 mL, 2.5 mmol) of the above solution was added to a flame-dried round-bottomed flask followed by addition of CuCl (0.38 g, 3.8 mmol) and N-Fmoc-L-4-iodophenylalanine methyl ester (0.5 g, 0.95 mmol) and the reaction was stirred at room temperature for 18 hrs. A second aliquot (1.5 mL, 1.5 mmol) of the cadmium reagent **1** was then added and the reaction allowed to stir an additional 18 hrs. Ether (100.0 mL) was added and the mixture was filtered through celite and the solids were washed with additional amounts of ether. The combined ether layers were washed with sat. NH_4Cl solution (60.0 mL) and water (60.0 mL) and dried over Na_2SO_4. Flash chromatography using 45% EtOAc/Hexanes afforded the pure product (0.49 g, 87% yield) in addition to recovered iodo compound (25 mg).$[\alpha]_D^{24}$ =+28.0° (c 1.08, $CHCl_3$); lit.[6] $[\alpha]_D^{24}$ =+21.4° (c 1.05, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.77 (2H, d, J = 8.0 Hz), 7.57 (2H, d, J = 7.0 Hz), 7.54 (2H, d, J = 7.5 Hz), 7.41 (2H, t, J = 7.0 Hz), 7.32 (2H, m), 7.17 (2H, d, J = 8.0 Hz), 5.26 (1H, d, J = 8.0 Hz), 4.69 (1H, m), 4.45 (1H, dd, J = 11.0, 7.5 Hz), 4.38 (1H, dd, J = 11.0, 7.0 Hz), 4.22 (3H, m), 4.14 (2H, m), 3.74 (3H, s), 3.18 (1H, dd, J = 13.5, 5.5 Hz), 3.12 (1H, dd, J = 13.5, 5.5 Hz) [the 3.18 and 3.12 signals are parts of an AB quartet pattern; iiII IIii], 1.30 (6H, dt, J = 7.0, 1.5 Hz). ^{13}C NMR ($CDCl_3$) δ 171.7, 155.6, 143.9, 143.8, 141.4, 140.0, 131.5 (td, J = 23.0, 14.0 Hz), 129.5, 127.9, 127.2, 126.6, 125.2, 125.1, 120.1, 118.1 (td, J = 265.0, 219.0 Hz), 67.1, 65.0, 54.8, 52.6, 47.3,

38.1, 16.5. ^{19}F NMR ($CDCl_3$) δ -109.6 (d, J = 116.0 Hz). IR ($CDCl_3$) cm^{-1} 3431, 3070, 2990, 2959, 2904, 1749, 1721, 1600, 1509, 1451, 1385, 1351, 1267, 1213, 1066, 914. MS (ES^+) 610.3 (M+Na), 588.4 (M+H).

Methyl N-Boc-L-4-[diethylphosphono(difluoromethyl)]-phenylalanine (6): Compound (**6**) was prepared following the procedure described above for the preparation of **4**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.54 (2H, d, J = 8.0 Hz), 7.22 (2H, d, J = 7.5 Hz), 4.98 (1H, d, J = 7.5 Hz), 4.59 (1H, m), 4.22 (4H, m), 3.71 (3H, s), 3.17 (1H, dd, J = 13.5, 5.5 Hz), 3.07 (1H, dd, J = 13.5, 5.5 Hz) [the 3.17 and 3.07 signals are parts of an AB quartet pattern; iiII IIii], 1.42 (9H, s), 1.30 (6H, m). ^{13}C NMR ($CDCl_3$) δ 172.2, 155.2, 139.3, 131.5 (td, J = 23.0, 14.0 Hz), 129.6, 126.6, 118.2 (td, J = 263.0, 220.0 Hz), 80.3, 65.0, 54.4, 52.6, 38.4, 28.5, 16.6. ^{19}F NMR ($CDCl_3$) δ -109.6 (d, J = 117.0 Hz). IR ($CDCl_3$) cm^{-1} 3440, 2992, 2937, 1745, 1715, 1502, 1473, 1368, 1265, 1167, 1025. MS (ES^+) 488.3 (M+Na), 466.4 (M+H).

N-Fmoc-L-4-[diethylphosphono(difluoromethyl)]-phenylalanine (5): To compound **4** (0.070 g, 0.12 mmol) in THF (1.5 mL) at 0 °C was added 0.2N LiOHaq (1.2 mL, 0.24 mmol) and the reaction was stirred for 40 min. The reaction was added to a biphase of 0.2N HCl/ EtOAc (1:1, 40 mL total), the aqueous layer was extracted with EtOAc (30 mL) and the combined EtOAc layer was dried over $MgSO_4$. Filtration and solvent evaporation left behind the product (0.055g, 80%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.61 (1H, br s), 7.76 (2H, d, J = 7.5 Hz), 7.56 (2H, d, J = 7.5 Hz), 7.51 (2H, d, J = 7.5 Hz), 7.39 (2H, t, J = 7.5 Hz), 7.30 (2H, m), 7.21 (2H, d, J = 8.0 Hz), 5.54 (1H, d, J = 8.0 Hz), 4.69 (1H, m), 4.45 (1H, dd, J = 10.5, 7.0 Hz), 4.35 (1H, dd, J = 10.5, 7.0 Hz), 4.21 (5H, m), 3.21 (2H, m), 1.28 (6H, m). MS (ES^+) 596.2 (M+Na), 574.2 (M+H).

N-Boc-L-4-[diethylphosphono(difluoromethyl)]-phenylalanine (7): Compound **7** was prepared following the procedure described above for the preparation of **5.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.53 (2H, d, J = 7.5 Hz), 7.27 (2H, d, J = 7.5 Hz), 5.12 (1H, br s), 4.98 (1H, br s), 4.64 (1H, br s), 4.22 (4H, m), 3.22 (1H, dd, J = 13.0, 5.5 Hz), 3.13 (1H, dd, J = 13.0, 5.5 Hz), 1.42 (9H, s), 1.30 (6H, m). MS (ES^-) 450.2 (M-H).

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