

This article was downloaded by:

On: 27 January 2011

Access details: *Access Details: Free Access*

Publisher *Taylor & Francis*

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Organic Preparations and Procedures International

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t902189982>

ENANTIOSELECTIVE SYNTHESIS OF N-Boc AND N-Fmoc PROTECTED DIETHYL 4-PHOSPHONO(DIFLUOROMETHYL)-L-PHENYLALANINE (F₂Pmp)

Mark S. Smyth^a; Terrence R. Burke Jr.^a

^a Laboratory of Medicinal Chemistry, Bldg. 37, Rm 5C06 Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, MD

To cite this Article Smyth, Mark S. and Burke Jr., Terrence R.(1996) 'ENANTIOSELECTIVE SYNTHESIS OF N-Boc AND N-Fmoc PROTECTED DIETHYL 4-PHOSPHONO(DIFLUOROMETHYL)-L-PHENYLALANINE (F₂Pmp)', *Organic Preparations and Procedures International*, 28: 1, 77 – 81

To link to this Article: DOI: 10.1080/00304949609355909

URL: <http://dx.doi.org/10.1080/00304949609355909>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

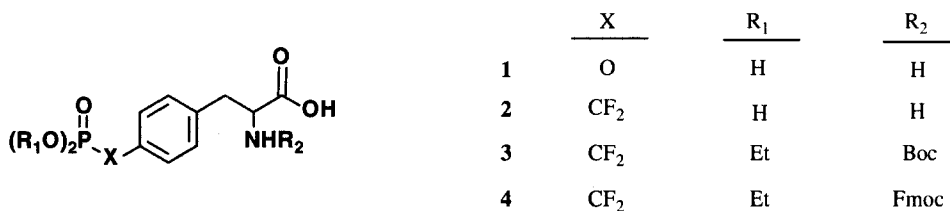
**ENANTIOSELECTIVE SYNTHESIS OF N-Boc AND N-Fmoc PROTECTED DIETHYL 4-
PHOSPHONO(DIFLUOROMETHYL)-L-PHENYLALANINE (F₂Pmp)**

Mark S. Smyth and Terrence R. Burke, Jr.*

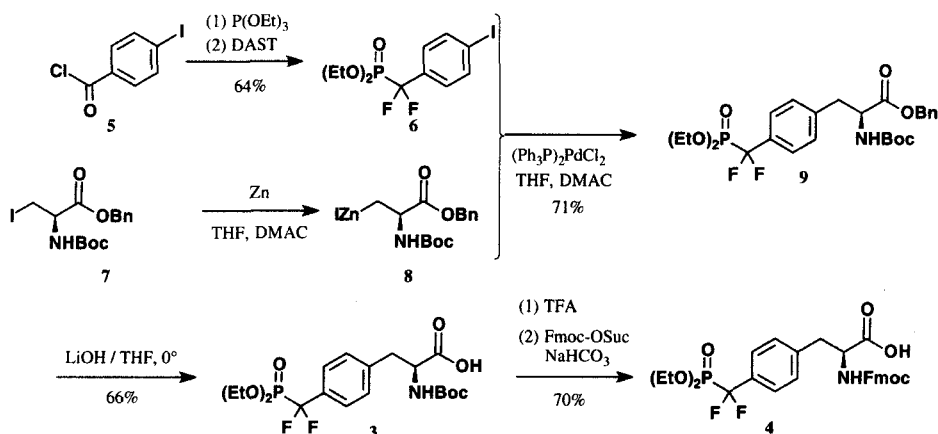
*Laboratory of Medicinal Chemistry, Bldg. 37, Rm 5C06
Developmental Therapeutics Program, Division of Cancer Treatment,
National Cancer Institute, Bethesda, MD 20892*

The phosphotyrosyl (pTyr, **1**) pharmacophore has emerged as a major structural motif in the design of modulators of PTK-dependent cell signaling and the difluorophosphonate analogue, 4-phosphono(difluoromethyl)-l-phenylalanine (F₂Pmp **2**), is an important agent in preparing phosphatase-resistant inhibitors of these pathways.¹⁻³ Synthesis of F₂Pmp-containing peptides has relied on the corresponding ethyl-protected phosphonate. This analogue has been synthesized in its racemic form⁴ in addition to its biologically relevant L-enantiomer as both the N^α-Boc (**3**)^{5,6} and N^α-Fmoc (**4**)⁶ derivatives.

The convergent method of Smyth and Burke⁶ has proven to be a valuable route for the preparation of **3** and **4**, and has come to be used by a number of investigators. However, the lack of detailed experimental conditions in the original communication has hindered its duplication. Additionally, uncontrolled exothermic reactions have occurred during the scaleup of the fluorination reaction using diethylaminosulfur trifluoride (DAST). Although L-F₂Pmp continues to increase in importance, there has as yet been no full experimental procedure reported for its preparation. We therefore present herein the detailed preparation of ethyl-protected F₂Pmp as both its N^α-Boc (**3**) and N^α-Fmoc (**4**) derivatives. The synthesis of (L)-**4** by direct conversion from (L)-**3**, differs from our original procedure, which carried the N^α-Fmoc protection through the entire reaction sequence,⁶ and is identical to the procedure we previously reported for the racemic compound.⁴ Subsequent to our work, a similar conversion of (L)-**3** to (L)-**4** has also been reported.⁷



At the heart of the synthesis is the Pd²⁺-mediated coupling of the aryl iodide **6** and the organozinc reagent **8** formed from iodoalanine analogue **7**. This is analogous to the reported preparation of a protected L-Pmp derivative,⁸ which itself relied on the work of Jackson.⁹ Arbuzov reaction of triethyl phosphite with commercially available 4-iodobenzoyl chloride **5** gave the crude keto-phosphonate as a clear yellow liquid which was fluorinated using DAST (neat, 5 equivalents) then purified chromatographically to provide difluorophosphonate **6** (64% from the acid chloride). On scaleup, the DAST fluorination can become uncontrollably exothermic when run neat.¹⁰ Previously reported organozinc reagent **8**^{11,12} is prepared from compound **7**, which is derived from commercially available *N*^α-Boc L-serine benzyl ester.¹¹ Treatment of a 0.5 M solution of **7** in THF-*N,N*-dimethylacetamide (DMAC) (1:1) with acid-washed zinc dust (1 equivalent) at 65° (1 hr) provided the organozinc compound **8**, to which was then added a mixture of difluorophosphonate **6**, 1.0 M in THF-DMAC, and (Ph₃P)₂PdCl₂ (5 mol %) and the reaction stirred at 65° for 4-5 hrs. Workup afforded coupled product **9** in 71% as a colorless syrup. The only detected side products were the dehalogenated *N*^α-Boc L-alanine benzyl ester and the bis aryl compound resulting from homo-coupling of the aryl iodide (15-20%). It should also be noted that the coupling reaction failed when an aryl bromide was used. Treatment of **9** with 0.2 N LiOH (~2 equivalents) in THF at 0° gave final product **3** as a white foam in 66% yield. Conversion to the corresponding *N*^α-Fmoc protected analogue **4** was achieved by initial treatment with trifluoroacetic acid (TFA), followed by reaction with 9-fluorenylmethyl succinimidyl carbonate (Fmoc-OSuc) and NaHCO₃ in aqueous dioxane. Chromatographic purification gave final **7** in 70% yield as a white foam.



EXPERIMENTAL SECTION

Removal of solvents was performed by rotary evaporation under reduced pressure. Melting points were determined on a Mel Temp II melting point apparatus and are uncorrected. Fast atom bombardment mass spectra (FABMS) were acquired with a VG Analytical 7070E mass spectrometer under the control of a VG 2035 data system. ¹H NMR data were obtained on Bruker AC250 (250 MHz) instrument.

Diethyl 4-Iodo-phosphono(difluoromethyl)benzene (6).- To 4-iodobenzoyl chloride **8** (20.0 g, 75 mmol) in anhydrous toluene (36 mL) at room temperature under argon was added dropwise via syringe, triethyl phosphite (12.7 mL, 75 mmol). An exothermic reaction occurs which was controlled by the rate of addition. The cloudy yellow solution was stirred (3 hrs) then solvent was removed under vacuum. The residual clear yellow liquid was placed under high vacuum to provide crude intermediate diethyl 4-iodobenzoylphosphonate quantitatively in sufficient purity for further use. To the ketophosphonate under argon at -78° was added slowly via syringe DAST (50 mL, 375 mmol). After swirling by hand to dislodge the stir bar and dissolve starting material, the clear yellow solution was stirred at 0° (2 hrs). The mixture was diluted with CHCl₃ (25 mL) and slowly added to a suspension of NaHCO₃ (70 g) in ice-cold H₂O (200 mL). The mixture was stirred briefly, then extracted with CHCl₃ (2 x 50 mL), dried (MgSO₄) and taken to dryness and purified by silica gel chromatography (hexanes / EtOAc; 3:1) to provide product **9** as a clear yellow oil (18.6 g, 64%). ¹H NMR (CDCl₃) δ 7.79 (d, 2H, *J* = 8.0 Hz), 7.33 (d, 2H, *J* = 7.9 Hz), 4.31-4.08 (m, 4H), 1.30 (t, 6H, *J* = 7.1 Hz); FABMS (NBA matrix) *m/z* 391 (MH⁺).

Anal. Calcd. For C₁₁H₁₄F₂IO₃P: C, 33.87; H, 3.62. Found: C, 34.05; H, 3.67

N^α-Boc 4-[(Diethyl phosphono(difluoromethyl))-L-phenylalanine Benzyl Ester (9).- To a solution of N^α-Boc 3-iodo-L-alanine benzyl ester **7**¹¹ (404 mg, 1.0 mmol) in anhydrous THF (1.0 mL) and anhydrous DMAC (1.0 mL) at room temperature under argon was added acid washed zinc dust (65 mg, 1.0 mmol). The solution was warmed to 65 - 70° (higher temperatures result in less pure product) and stirred (1 hr). To this was then added rapidly a mixture of diethyl 4-iodo-phosphono(difluoromethyl)benzene **6** (195 mg, 0.5 mmol) and (PPh₃)₂PdCl₂ (18 mg, 0.5 equivalents) in 1 mL THF:DMAC (1:1) and the mixture was stirred at 65 - 70° (5 hrs). The mixture was cooled to 0°, diluted with saturated NH₄Cl (10 mL), extracted with EtOAc (2 x 10 mL), and the combined extracts were dried (MgSO₄) and taken to dryness. The residue was placed under high vacuum to remove residual DMAC, providing crude product (719 mg). Purification by silica gel chromatography (gradient elution with hexanes / EtOAc; 3:1, 1:1, 0:1) afforded pure **9** as a viscous yellow syrup¹³ (193 mg, 71%). The reaction was run on a 50 mmol scale¹⁴ (reaction times were increased by approximately 2.5-fold) to provide **9** in 26% yield. ¹H NMR (CDCl₃) δ 7.42 (d, 2H, *J* = 7.7 Hz), 7.33-7.20 (m, 5H), 7.05 (d, 2H, *J* = 7.8 Hz), 5.11 (d, 1H, *J* = 12.1 Hz), 5.02 (d, 1H, *J* = 12.1 Hz), 4.92 (br d, 1H, *J* = 12.1 Hz), 4.63-4.52 (m, 1H), 4.19-4.01 (m, 4H), 3.15-2.99 (m, 2H), 1.35 (s, 9H), 1.22 (t, 6H, *J* = 7.3 Hz).

Anal. Calcd. For C₂₆H₃₄F₂NO₇P: C, 57.67; H, 6.33; N, 2.59. Found: C, 57.91; H, 6.25; N, 2.40

N^α-Boc 4-[(Diethyl phosphono(difluoromethyl))-L-phenylalanine (3).- To a stirred solution of **9** (497 mg, 0.92 mmol) in THF (9 mL) at 0° was added 0.2 N LiOH (1.8 mmol) dropwise and the mixture then stirred at 0° (20 min). The mixture was then diluted with H₂O (10 mL) and washed with EtOAc (20 mL). The aqueous layer was cooled to 0° and acidified with ice-cold 0.2 N HCl (~15 mL) and extracted with EtOAc (3 x 20 mL). The combined EtOAc layers were washed with brine (15 mL), dried (MgSO₄), taken to dryness and placed under high vacuum. The resulting residue (324 mg) was triturated with anhydrous ether (5 mL), cooled to 0° and a precipitate removed by filtration. The

filtrate was taken to dryness to yield **3** as a white foam^{13, 15} (275 mg, 66%). $[\alpha]_D^{24} = +8.06^\circ$ (c 1.08, MeOH); lit.⁵ $[\alpha]_D^{25} = +7.96^\circ$ (c 1.08, MeOH). ¹H NMR (CDCl₃) δ 7.47 (d, 2H, $J = 7.8$ Hz), 7.22 (d, 2H, $J = 7.8$ Hz), 5.03 (d, 1H, $J = 7.9$ Hz), 4.61-4.48 (m, 1H), 4.20-3.99 (m, 4H), 3.22-3.02 (m, 2H), 1.35 (s, 9H), 1.24 (t, 3H, $J = 7.0$ Hz), 1.23 (t, 3H, $J = 7.2$ Hz).

N^o-Fmoc 4-[(Diethyl phosphono(difluoromethyl))-L-phenylalanine (4).- A solution of **3** (824 mg, 1.83 mmol) in 90% TFA (5 mL) was stirred at room temperature (1 hr) then TFA was removed under high vacuum. The residue was treated with H₂O (10 mL) and evaporated under high vacuum, then taken up in dioxane (25 mL). Fmoc-OSuc (613 mg, 1.83 mmol) was added, followed by a solution of NaHCO₃ (922 mg, 11.0 mmol) in H₂O (10 mL) and the mixture was stirred at room temperature (2¹/₂ hrs). The mixture was partitioned between ice-cold 0.2 N HCl (100 mL) and EtOAc (2 x 100 mL); the combined organic layers were washed with ice-cold 0.2 N HCl (100 mL), dried (MgSO₄) then taken to dryness to provide crude **4** as a syrup. Purification by silica gel chromatography (CHCl₃ followed by EtOAc) gave pure **4** as a foam^{15, 16} (730 mg, 70%). $[\alpha]_D^{24} = +41.6^\circ$ (c 1.10, CHCl₃); lit.¹⁶ $[\alpha]_D^{25} = +42.0^\circ$ (c 1.0, MeOH). ¹H NMR (CDCl₃) δ 7.68 (d, 2H, $J = 7.4$ Hz), 7.48 (d, 2H, $J = 7.2$ Hz), 7.43 (d, 2H, $J = 8.1$ Hz), 7.32 (t, 2H, $J = 7.3$ Hz), 7.22 (t, 2H, $J = 7.2$ Hz), 7.13 (d, 2H, $J = 7.7$ Hz), 5.40 (br d, 1H, $J = 7$ Hz), 4.66-4.56 (m, 1H), 4.48-4.24 (m, 2H), 4.16-3.98 (m, 5H), 3.12 (d, 2H, $J = 5$ Hz), 1.21 (t, 3H, $J = 7$ Hz), 1.18 (t, 3H, $J = 7$ Hz).

REFERENCES

1. T. R. Burke, Jr., M. S. Smyth, A. Otaka, M. Nomizu, P. P. Roller, G. Wolf, R. Case and S. E. Shoelson, *Biochemistry*, **33**, 6490 (1994).
2. T. Gilmer, M. Rodriquez, S. Jordan, R. Crosby, K. Alligood, M. Green, M. Kimery, C. Wagner, D. Kinder, P. Charifson, A. M. Hassell, D. Willard, M. Luther, D. Rusnak, D. D. Sternbach, M. Mehrotra, M. Peel, L. Shampine, R. Davis, J. Robbins, I. R. Patel, D. Kassel, W. Burkhardt, M. Moyer, T. Bradshaw and J. Berman, *J. Biol. Chem.*, **269**, 31711 (1994).
3. T. R. Burke, Jr., H. K. Kole and P. P. Roller, *Biochem. Biophys. Res. Commun.*, **204**, 129 (1994).
4. T. R. Burke, Jr., M. S. Smyth, A. Otaka and P. P. Roller, *Tetrahedron Lett.*, **34**, 4125 (1993).
5. J. Wrobel and A. Dietrich, *ibid.*, **34**, 3543 (1993).
6. M. S. Smyth and T. R. Burke, Jr., *ibid.*, **35**, 551 (1994).
7. M. F. Gordeev, D. V. Patel, P. L. Barker and E. M. Gordon, *ibid.*, **35**, 7585 (1994).
8. R. L. Dow and B. M. Bechle, *Synlett*, 293 (1994).
9. R. F. W. Jackson, M. J. Wythes and A. Wood *Tetrahedron Lett.*, **43**, 5941 (1989).
10. W. J. Middleton, *Chemical and Engineering News*, pp 43 (May 21, 1979).

N-Boc AND N-Fmoc PROTECTED DIETHYL 4-PHOSPHONO(DIFLUOROMETHYL)-L-PHENYLALANINE (F₂Pmp)

11. R. F. W. Jackson, N. Wishart, A. Wood, K. James and M. J. Wythes, *J. Org. Chem.*, **57**, 3397 (1992).
12. M. J. Dunn, R. F. W. Jackson, J. Pietruszka, N. Wishart, D. Ellis and M. J. Wythes, *Synlett*, 499 (1993).
13. Previously characterized in reference 5.
14. Work was performed under NCI contract N01-CM-277674.
15. Previously characterized as the racemate in reference 4.
16. Previously characterized in reference 7.

(Received August 16, 1995; in revised form October 4, 1995)