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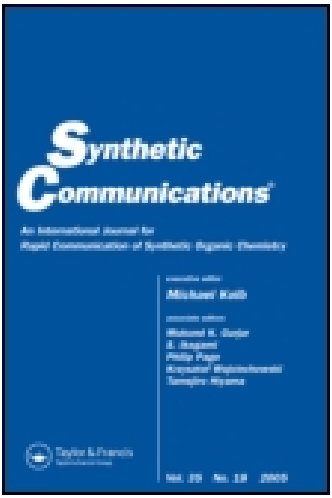

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Synthesis of the First α-Fluoro-Phosphotyrosyl Mimetic

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Synthesis of the First α-Fluoro-Phosphotyrosyl Mimetic

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ABSTRACT

The diastereoselective preparation of (2*S*)-2-fluoro-4-[[bis(1,1-dimethyl-ethoxy)phosphinyl]methyl] benzenepropanoic acid (**5**) is presented as new phosphotyrosyl (pTyr) mimetic suitably protected for incorporation into peptides. Synthesis of **5** utilized electrophilic fluorination under chiral induction provided by the commercially available Evans auxiliary, (*S*)-(+)-4-phenyl-2-oxazolidinone. In order to demonstrate its synthetic utility, analogue **5** was employed to prepare a signal transduction-directed

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tripeptide. The design considerations for this peptide and its preliminary biological evaluation are included.

Key Words: Chiral induction; Enantioselective; Phosphotyrosyl mimetic; Fluorination.

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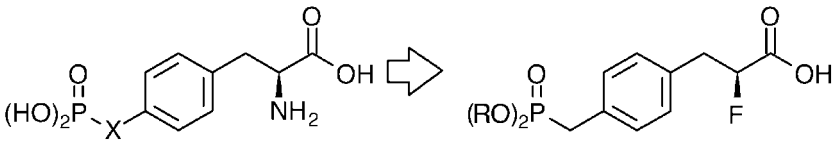
INTRODUCTION

Introduction of fluorine into biologically active molecules has proven to be of widespread value as a means to modify pharmacological activity or to probe physiological mechanisms of action.[1] In the area of cellular signal transduction, phosphotyrosyl residues (pTyr, **1**, Fig. 1) play central roles. To date, fluorination of pTyr surrogates has been limited to the phenylphosphate region of the amino acid side chain; either the phosphoryl-mimicking component or to the aryl ring.[2] An example of the former is provided by F_2Pmp (**2**), wherein the pTyr phosphoryl ester oxygen has been replaced with a difluoromethylene species.[3] This represents a fluorinated variant of the widely used pTyr mimetic, phosphonomethyl phenylalanine (Pmp, **3**).[4–6] In theory, introduction of fluorine substituents at other side chain locations could result in new and potentially useful analogues. Mimetic **4** is a fluorinated des-amino Pmp analogue that can be derived from insertion of a fluorine atom into the α-position of 3-[(4-phosphonomethyl)phenyl]proprionic acid. Conversion of **4** into a more synthetically useful form yields the corresponding bis-Bu^t phosphonic acid ester **5**, which is suitably protected for incorporation of **4** into peptides. Compounds **4** and **5** represent the first pTyr mimetics bearing fluorine substituents outside the phenylphosphate region. The purpose of the current report is to present the synthesis **5** as well as its first application in a signal transduction-related study.



1 pTyr X = O
2 F_2Pmp X = CF_2
3 Pmp X = CH_2

4 R = H
5 R = Bu^t

Figure 1. Structures of pTyr and pTyr mimetics.

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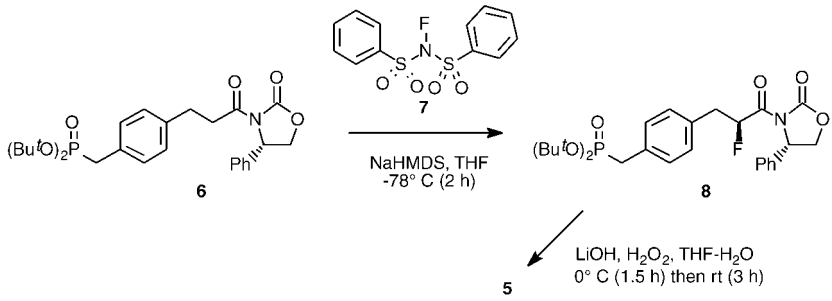
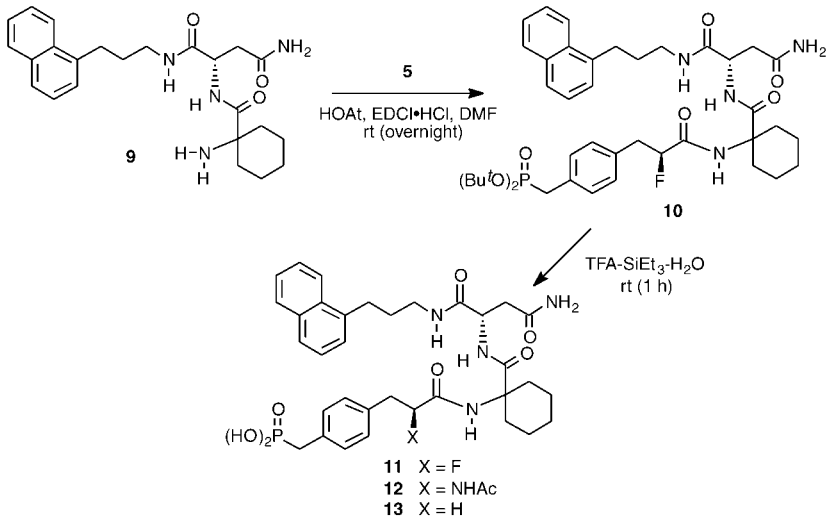
RESULTS AND DISCUSSION

Enantioselective synthesis of α-fluoro phenylproprionic acid has been reported by nucleophilic fluoride displacement of chiral α-sulfonates.[7] However, a more attractive approach is the diastereoselective electrophilic fluorination of an imide enolate derived from an appropriate Evans chiral oxazolidinone auxiliary.[8] Such an approach has been used successfully to prepare α-fluorocarboxylic acids in high enantiopurity.[9] For the synthesis of **5**, the requisite starting chiral imide **6** can be readily prepared from commercially available (*S*)-(+)-4-phenyl-2-oxazolidinone[10] in high yield as previously reported.[11] Treatment of **6** with sodium bis(trimethylsilyl) amide (NaHMDS) in THF at -78°C followed by reaction with *N*-fluorobezenesulfonimide (**7**)[10] gave the (*S*)-α-fluoro analogue **8** in 73% yield without any evidence of the diastereomeric (*R*)-fluoro analogue by ^{1}H-NMR or ^{19}F-NMR (Sch. 1). To complete the synthesis, cleavage of the chiral auxiliary was performed using lithium hydroxide in the presence of hydrogen peroxide to give the desired final product **5** in 96% yield.

Protected analogue **5** represents the first α-fluoro-pTyr mimetic yet reported. Analogue **5** was employed to introduce the α-fluoro-containing pTyr mimetic **4** as a replacement for Pmp (**2**) in the naphthylpropylamide-containing tripeptide **12**, which has been reported previously to exhibit high Grb2 SH2 domain-binding affinity.[12,13] As shown in Sch. 2, coupling of **5** with the naphthylpropylamide-containing dipeptide **9**[13] gave protected **10** in 85% yield using 1-hydroxy-7-azabenzotriazole (HOAt) active ester coupling.[14] TFA-mediated deprotection of **10** gave the desired α-fluoro-containing tripeptide mimetic **11**, which was purified by HPLC. No evidence of epimerization at the α-fluoro center was evident from either the ^{1}H-NMR or the ^{19}F-NMR spectra.



Scheme 1.



Scheme 2.

EXPERIMENTAL

Elemental analyses were obtained from Atlantic Microlab Inc., Norcross, GA, and fast atom bombardment mass spectra (FAB-MS) were acquired with a VG Analytical 7070E mass spectrometer under the control of a VG2035 data system. Where indicated, FAB-MS matrixes used were glycerol or nitrobenzoic acid. ^{1}H-NMR and ^{19}F-NMR data were obtained on a Varian 400 MHz instrument and are reported in ppm relative to TMS or $CFCl_3$, respectively, and referenced to the solvent in which they were run. Solvent was removed by rotary evaporation under reduced pressure, and anhydrous solvents were obtained commercially and used without further drying.

Bis(1,1-dimethylethyl) [[4-[(2*S*)-2-fluoro-3-oxo-3-[(4*S*)-2-oxo-4-phenyl-3-oxazolidinyl]propyl]phenyl]methyl]phosphonate (8). To a stirred solution of NaHMDS (8.28 mL, 8.28 mmol) was added dropwise a solution of bis(1,1-dimethylethyl) [[4-[3-oxo-3-[(4*S*)-2-oxo-4-phenyl-3-oxazolidinyl] propyl]phenyl]methyl]phosphonate (**6**)[11] (3.77 g, 7.53 mmol) in THF (40 mL) at −78°C. The solution was stirred at −78°C (0.5 h), *N*-fluorobenzenesulphonimide (**7**) (2.61 g, 8.28 mmol) in THF (25 mL) was added, and the mixture was stirred for additional 2 h at −78°C. The mixture was then warmed to room temperature and stirred overnight. The reaction was quenched by the addition of ice-cooled saturated aqueous NH_4Cl (150 mL),

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extracted with CH_2Cl_2, washed with brine, and dried (Na_2SO_4). Evaporation provided a residue, which was purified by silica gel flash chromatography to provide **8** (2.85 g, 73% yield). ^{1}H-NMR ($CDCl_3$) δ 7.34–7.20 (m, 9H), 6.04 (ddd, 1H, $J = 3.7$ Hz and 8.8 Hz and 49.4 Hz), 5.29 (dd, 1H, $J = 4.2$ Hz and 9.0 Hz), 4.65 (t, 1H, $J = 8.8$ Hz), 4.31 (dd, 1H, J = 3.3 Hz and 8.5 Hz), 3.19 (m, 1H), 3.04 (m, 1H), 2.98 (d, 2H, $J = 21.5$ Hz), 1.39 (s, 18H); ^{19}F-NMR ($CFCl_3$) −190.4; FABMS (+Ve) m/z 520 [MH^+]; Anal. Calcd for $C_{27}H_{35}FNO_6P$: C, 62.41; H, 6.80; N, 2.70. Found: C, 62.64; H, 6.87; N, 2.72.

(2*S*)-2-Fluoro-4-[[bis(1,1-dimethylethoxy)phosphinyl]methyl] benzenepropanoic acid (5). To a solution of **8** (636 mg, 1.22 mmol) in THF-H_2O (v : v, 3 : 1) (18 mL) was added via syringe a solution of aqueous 30% H_2O_2 (0.62 mL, 6.1 mmol) at 0°C over 2 minutes. This was followed by the addition of LiOH (102 mg, 1.44 mmol) in H_2O (2.5 mL). After stirring at 0°C for 1.5 h, the solution was raised to room temperature and stirring was continued (3 h). To the mixture was added sodium sulfite (964 mg, 6.1 mmol) in H_2O (5 mL) followed by 2 N HCl (30 mL). Evaporation of solvent in vacuo provided a residue that was washed using CH_2Cl_2 to remove Evans auxiliary. The aqueous layer was then extracted (EtOAc) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and taken to dryness to provide **5** (440 mg, 96% yield). ^{1}H-NMR ($CDCl_3$) δ 7.20–7.11 (m, 5H), 5.12 (dt, 1H, $J = 5.0$, J = 48.6 Hz), 3.30–3.11 (m, 2H), 2.87 (d, 2H, $J = 21.5$ Hz), 1.30 (s, 18H); ^{19}F-NMR ($CFCl_3$) −189.5; FABMS (−Ve) m/z 373 [M-H].

[[4-[3-[[1-[[[(1S)-3-amino-1-[[[3-(1-naphthalenyl)propyl]amino]carbonyl]-3-oxopropyl]amino]carbonyl]cyclohexyl]amino]-3-[(2*S*)-2-fluoro] oxopropyl]phenyl]methyl] bis(1,1-dimethylethyl) phosphonate (10). To a solution of **5** (63 mg, 0.169 mmol) and (2*S*)-2-amino-N1-[3-(1-naphthalenyl)-propyl]butanediamide (**9**)[13,15] (65.3 mg, 0.154 mmol) in DMF (4 mL) was added HOAt (0.40 mL, 0.20 mmol) and EDCI · HCl (38.4 mg, 0.20 mmol) at 0°C. The solution was stirred at 0°C (1.5 h) and then at room temperature (24 h). The crude reaction mixture was evaporated in vacuo, and the residue was purified by silica gel flash chromatogaphy to provide **10** (103 mg, 86% yield). ^{1}H-NMR ($CDCl_3$) δ 8.02 (d, 1H, $J = 8.8$ Hz), 7.79 (d, 1H, $J = 8.0$ Hz), 7.65 (t, 1H, $J = 4.8$ Hz), 7.53–7.01 (m, 9H), 7.00 (d, 1H, $J = 8.0$ Hz), 6.59 (d, 1H, $J = 5.5$ Hz), 5.98 (brs, 1H), 5.02 (ddd, 1H, $J = 3.7$ Hz and 7.4 Hz and 49.4 Hz), 4.67 (m, 1H), 3.41 (m, 1H), 3.30 (m, 1H), 3.19–2.83 (m, 7H), 2.42 (dd, 1H, $J = 5.2$ Hz and 15.2 Hz), 2.07–1.47 (m, 10H), 1.38 (s, 18H), 1.29–1.19 (m, 2H); ^{19}F-NMR ($CFCl_3$) −188.1; FABMS (+Ve) m/z 781 [M + H].

([[4-[3-[[1-[[[(1S)-3-Amino-1-[[[3-(1-naphthalenyl)propyl]amino]carbonyl]-3-oxopropyl]amino]carbonyl]cyclohexyl]amino]-3-[(2*S*)-2-fluoro] oxopropyl]phenyl]methyl]phosphonic acid (11). A solution of **11** (103 mg, 0.132 mmol) in a mixture of TFA-TES-H_2O (v : v, 3.7 : 0.1 : 0.2) (4 mL) was

stirred at room temperature (1 h). The solvent was evaporated in vacuo and the residue was purified by HPLC using a Waters Prep LC4000 system having photodiode array detection and binary solvent systems as indicated, where A = 0.1% aqueous TFA and B = 0.1% TFA in acetonitrile. Columns used were either a Vydac C_{18} (10 μm) Peptide and Protein column (20 mm diameter × 250 mm long with a flow of 10 mL/min for preparative work or a 4.6 mm diameter × 250 mm long with a flow of 1.0 mL/min for analytical work). A linear gradient from 10% B to 70% B over 10 minutes provided product retention times of 22.5 minutes on the preparative column and 12.7 minutes on the analytical column. Following liophilization, product **11** was obtained as a white solid (54 mg, 62% yield: 95% purity by HPLC). ^{1}H-NMR ($CDCl_3$) δ 8.16 (s, 1H), 8.03 (m, 1H), 7.82 (dd, 1H, $J = 2.7$ Hz and 6.6 Hz), 7.68 (t, 1H, $J = 4.6$ Hz), 7.46–7.40 (m, 2H), 7.35–7.31 (m, 1H), 7.07 (dd, 2H, $J = 2.2$ Hz and 8.2 Hz), 7.00–6.98 (m, 2H), 6.87 (s, 1H), 5.08 (ddd, 1H, $J = 2.9$ Hz and 9.8 Hz and 49.4 Hz), 4.34 (m, 1H), 3.96 (t, 1H, $J = 6.5$ Hz), 3.12–3.08 (m, 3H), 2.98 (t, 2H, $J = 7.8$ Hz), 2.87 (m, 1H), 2.84 (d, 2H, $J = 21.3$ Hz), 2.59 (dd, 1H, $J = 6.7$ Hz, $J = 16.0$ Hz), 1.95–1.17 (m, 12H); ^{19}F-NMR ($CFCl_3$) −188.2; FABMS (+Ve) m/z 667 [M-H]. Anal. Calcd for $C_{41}H_{46}N_4O_{10} \cdot 2.5H_2O$: C, 57.22; H, 6.59; N, 7.85. Found: C, 57.01; H, 5.91; N, 7.63.

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