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Synthesis of a Difluorophosphonomethyl-Containing Phosphatase Inhibitor Designed from the X-ray Structure of a PTP1B-Bound Ligand¹

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Abstract: Protein-tyrosine phosphatase (PTP) inhibitors are potentially valuable pharmacological tools for studying cellular signal transduction and for therapeutic intervention. Small peptides containing the non-hydrolyzable phosphotyrosyl mimetic difluorophosphonomethyl phenylalanine (F_2Pmp) have been shown to be extremely potent PTP inhibitors, with the fluorines increasing inhibitory potency 1000-fold relative to the unfluorinated species. The high PTP affinity of the phosphonodifluoromethyl pharmacophore has allowed the preparation of small molecule inhibitors containing this moiety, which lack any peptide component. The X-ray structure of one such inhibitor. 2-difluoromethylnaphthylphosphonic acid (**6**) complexed to the catalytic site of PTP1B has recently been solved. Computer assisted molecular modelling of this complex indicates that enhanced binding interactions may result by introduction of hydroxyl functionality onto the naphthalene ring system. Herein is reported the synthesis of one such inhibitor 1,1-difluoro-1-[2-(4-hydroxynaphthalenyl)]methyl]phosphonic acid (**7**), which is prepared in 12 steps from commercially available 1,3-dihydroxynaphthalene. The synthetic approach relies on selective hydroxyl protection and Pd-catalyzed carbonylation to introduce functionality which is subsequently elaborated into the difluorophosphonate structure. The techniques reported herein may be applicable to the preparation of other PTP inhibitors.

INTRODUCTION

The phosphotyrosyl (pTyr) pharmacophore (1), when located on critical signalling proteins, provides a fundamental motif for the activation and integration of many cellular processes. A balance between generation of these pTyr units, by protein-tyrosine kinases (PTKs) and their destruction via protein-tyrosine phosphatases (PTPs), is necessary for normal cellular function. Aberrant patterns of tyrosine phosphorylation resulting in defective signalling, can contribute to several diseases, including cancers and diabetes. As the important role PTPs play both in positive and negative modulation of pTyr-dependent signalling has become more clearly defined, a need has arisen for PTP inhibitors which can function as pharmacological tools, and potentially as therapeutic agents. One approach for the development of PTP inhibitors relies on non-hydrolyzable mimetics of pTyr-containing substrates. Initial work in this area showed that in small peptide substrates, replacement of the pTyr residue with the pTyr mimetic phosphonomethylphenylalanine (Pmp, 2), can result in competitive inhibitors.^{2,3} The Pmp residue contains a methylene unit in place of the normal phosphate ester oxygen.⁴ Subsequent studies have shown that adding two fluorines to the Pmp methylene bridge, giving difluorophosphonomethylphenylalanine (F₂Pmp, 3)⁵ results in a 1000-fold enhancement in PTP inhibitory potency.⁶ This indicates an extremely high affinity of the

difluorophosphonate moiety for the PTP catalytic site; an effect which has been suggested to arise from direct interaction of the fluorines with the enzyme, and not from secondary effects on the phosphonate pKa values.⁷ The binding interaction is of sufficient affinity that small aryl-containing difluorophosphonates, lacking a peptide portion, can also maintain reasonable inhibitory potency.⁸ Structure-activity studies on a series of arylphosphonates showed that the simple phenyl difluorphosphonate **4**, which is a direct simplified analogue of pTyr itself, had little potency, while 1- and 2-substituted naphthyldiflurophosphonates (**5** and **6**, respectively), having the more extended naphthyl ring system, showed good inhibitory potency.⁸



The difluoromethylnaphthylphosphonic acid structure therefore provides a starting nucleus for the development of small molecule PTP inhibitors. To facilitate elaboration of this nucleus into more potent and selective PTP inhibitors, we have examined the binding interactions of 2-difluoromethylnaphthylphosphonic acid (6) with the catalytic site of PTP1B, by solving the X-ray structure of the inhibitor enzyme complex.9 Subjecting the resulting X-ray structure to analysis by computer assisted molecular modelling, suggested modifications to the parent inhibitor which could potentially result in enhanced binding interactions with the catalytic site. Several of these modifications called for the addition of hydroxyl groups to the naphthyl ring system in defined locations, which could enter into specific hydrogen bonds with functionality at the catalytic site. One of these "rationally designed" inhibitors is the 4-hydroxy analogue 7. Introduction of a hydroxyl at the 4-position could potentially replace a water molecule situated in the PTP1B•6 complex, allowing new hydrogen bonding interactions with Tyr 46, Lys 120 and Asp 181.9 To date, the only reported preparations of naphthyl difluorphosphonates have been the above mentioned 5 and 6, which lacked other functionality on the naphthyl ring system.^{10,8} Illustrative of possible approaches toward the synthesis of hydroxylated difluoromethylnaphthylphosphonic acids, we herein report the preparation of the 4-hydroxy analogue 7. This compound has recently been shown to exhibit 2-fold enhanced PTP binding affinity⁹ (Ki = 94 μ M) relative to it unhydroxylated parent 6, (Ki = $179 \ \mu M$).⁹ This supports molecular modelling dynanics simulations which show that introduction of the hydroxyl should result in a net increase in binding interactions,⁹ and validates the rationale utilized for the design of 7. The synthetic techniques utilized in the preparation of 7 may be useful for the synthesis of further PTP inhibitors.

SYNTHETIC APPROACH

Although 4-hydroxy target 7 is structurally quite similar to the unsubstituted parent 6, its preparation is significantly more complex. Through retrosynthetic analysis, commercially available 1,3-dihydroxynapthalene 8 was chosen as starting material since it contained both the hydroxyl group at the 1-position and additional functionality at the 3-position which could be transformed into the diffuorophosphonate. The synthetic strategy relied on two key concepts; the introduction at the 3-position of a one carbon unit at the +3 oxidation state through palladium catalyzed carbonylation $(12 \rightarrow 15$, Scheme 1), and the subsequent elaboration of this carbon by addition of phosphonate (17

\rightarrow 18) and fluorine (20 \rightarrow 21) functionalities (Scheme 2).

Selective introduction of the carbonyl functionality at the 3-position required differential protection of hydroxyl functionality. Initial attempts at regioselective protection of 1,3-dihydroxynaphthalene 8 with *tert*-butyl-dimethylsilyl chloride and tosyl chloride failed, and Bell's method¹ was therefore employed to methylate at the less

hindered 3-position, providing 1-hydroxy-3-methoxynaphthalene 9 in 90% yield. The tosyl group was then chosen for protection of the hydroxyl group at the 1-position, due to its stability under strongly acidic conditions. The desired 3-methoxy-1-tosylnaphthalene 10 was obtained in 86% yield by reaction with tosyl chloride, then demethylation of the 3-methoxyl group was achieved in 93% yield using boron tribromide at -78 °C¹² to afford 3-hydroxy-1-tosylnaphthalene 11. It should be noted that a Fries-type rearrangement of the tosyl group, yielding the 2-substituted sulfone, predominated when either the reaction time was prolonged or when BBr₃ was added at a temperature higher than -78 °C. This Lewis acid-catalyzed rearrangement is similar to that recently described using $AlCl_3$.¹³ With a single free hydroxyl at the 3-position now present, activation for carbonylation was achieved by treatment with trifluoromethanesulfonic anhydride, to give 1-tosyl-3-trifluoromethylsulfonylnaphthalene 12 in quantitative yield.



(1) MeOH/HCl; (ii) TsCl, pyridine; (iii) BBr₃, CH₂Cl₂, -78 °C to rt; (iv) Tf₂O; pyridine; (v) ROH, CO, Pd(OAc)₂, NEt₃, Ph₂P(CH₂)₃PPh₂, DMSO; (vi) LiAlH₄, THF; (vii) PCC, CH₂Cl₂;

Scheme 1

The critical carbonylation reaction was next carefully examined. Initial attempts at carbonylation focused on palladium-catalyzed coupling of 12 with carbon monoxide. Using 2-trimethylsilylethyl alcohol as nucleophile in DMSO,¹⁴ ester 13 was obtained in 81% yield. It was our intention to convert 13 into key phosphonate 19 through the intermediacy of the acid chloride. However, treatment of acid 14, obtained in 90 % yield by the reaction of 13 with tetrabutylammonium fluoride, with thionyl chloride followed by addition of triethyl phosphite, gave complicated products.¹⁵ Since we had previously converted aryl aldehydes to difluorophosphonates,^{5,10,16} it was decided to again utilize this approach. This required reduction of ester 13 to the benzylic alcohol 16, followed by oxidation back to the aldehyde. The nature of the ester functionality was therefore no longer critical and accordingly, we designed alternate carbonylation conditions which utilized the inexpensive nucleophile methanol,¹⁷ rather than the expensive 2-trimethylsilylethyl alcohol. Palladium catalyzed coupling of 12 with carbon monoxide in DMSO utilizing methanol as a nucleophile, afforded 3-carbomethoxy-1-tosylnaphthalene 15 in 67 % yield. It should be noted that dimeric material can also be detected if the reaction is run at a higher temperature with a condenser.

To prepare for introduction of the phosphonate functionality, ester 15 was initially reduced to alcohol 16 using LiAlH₄ (73% yield), then re-oxidized (pyridinium chlorochromate) to aldehyde 17 (81% yield).¹⁰ Treatment of 17 with di-*tert*-butyl phosphite using lithium bis(trimethylsilyl)amide as a base at -78 °C gave phosphonate 18 in 80% yield, which was subsequently oxidized to the ketophosphonate 20 in 79% yield using Swern conditions.¹⁶ Introduction of fluorine was achieved at this point according to our previously published method using diethylaminosulfur trifluoride (DAST)¹⁰ to afford globally protected difluorophosphonate 21 in 37-51% yield. Base-catalyzed hydrolysis of 21 resulted in simultaneous de-tosylation and removal of a single *tert*-butyl group, yielding mono-*tert*-butyl-protected 22 in 95 % yield. The synthetic route was finally completed and target 7 obtained in 97% yield by treatment of 22 with trifluoroacetic acid.



(i) (SiMe₃)₂NLi, HP(O)(*tert*-BuO)₂, THF; (ii) (COCl)₂, DMSO, NEt₃, CH₂Cl₂, -78 °C to rt; (iii) DAST, -78 °C to rt; (iv) 0.5 N KOH/THF; (v) 80% TFA

Scheme 2

EXPERIMENTAL

Melting points were determined on a Mel Temp II melting apparatus and are uncorrected. Elemental analyses were obtained from Atlantic Microlab Inc., Norcross, GA. 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 a Bruker AC250 (250 MHz) instrument. Infrared spectral data were acquired on a Perkin-Elmer 1600 series FTIFR instrument. Removal of solvents was performed by rotary evaporation under reduced pressure.

3-Methoxy-1-tosyloxynaphthalene (10). To a stirred solution of 1-hydroxy-3-methoxynaphthalene 9¹¹ (5.66 g, 32.5 mmol) in dry pyridine (8 mL) was added tosyl chloride (12.4 g, 65 mmol, 2.0 equiv.) in one portion at room temperature under argon and the reaction continued at room temperature (20 h). The reaction mixture was carefully quenched with saturated aqueous NaHCO₃ (30 mL), extracted with EtOAc (3 x 50 mL), washed with brine (2 x 10 mL), dried over MgSO₄, and taken to dryness. Purification by silica gel chromatography (hexane:EtOAc, 9:1) afforded **10** as a white solid (9.22 g, 86%): mp 102-103 °C; ¹H NMR (CDCl₃) δ 7.78 (d, 3H, *J* = 8.1 Hz), 7.67 (d, 1H, *J* = 8.1 Hz), 7.41 (ddd, 1H, *J* = 8.1, 6.9, 1.1 Hz), 7.27 (d, 2H, *J* = 8.1 Hz), 7.24 (m, 1H), 7.03 (brd, 1H, J = 2.2 Hz), 6.91 (d, 1H, J = 2.2 Hz), 3.87 (s, 3H), 2.4 (s, 3H); IR (CHCl₃) 2940, 1610, 972 cm⁻¹; FABMS *m/z* 328 (M⁺). Anal. Calcd for C₁₈H₁₆O₄S: C, 65.84; H, 4.91. Found: C, 65.82; H, 4.97.

3-Hydroxy-1-tosyloxynaphthalene (11). To a stirred solution of **10** (9.22 g, 28.1 mmol) in dry CH₂Cl₂ (100 mL) at -78 °C under argon was added boron tribromide (7.74 g, 30.9 mmol) dropwise. After 1.5 h the reaction was continued at room temperature (2 h). The reaction mixture was carefully quenched with brine (100 mL), extracted with CH₂Cl₂ (3 x 100 mL), washed with brine (2 x 50 mL), dried (MgSO₄) and taken to dryness. Silica gel chromatography (hexane:EtOAc, 4:1) afforded **11** as a solid (8.19 g, 93%): mp 133-134 °C; ¹H NMR (CDCl₃) δ 7.78 (d, 2H, *J* = 8.3 Hz), 7.75 (d, 1H, *J* = 8.5 Hz), 7.60 (d, 1H, *J* = 8.5 Hz), 7.38 (m, 1H), 7.27 (d, 2H, *J* = 8.3 Hz), 7.05 (brd, 1H, *J* = 2 Hz), 6.94 (d, 1H, *J* = 2 Hz), 2.4 (s, 3H); IR (CHCl₃), 3370, 2926, 1602, 1270 cm⁻¹; FABMS *m*/z 314 (M+). Anal. Calcd for C₁₇H₁₄O₄S: C, 64.95; H, 4.49. Found: C, 65.02; H, 4.51.

1-Tosyloxy-3-trifluoromethylsulfonyloxynaphthalene (12). To a stirred solution of 11 (5 g, 15.9 mmol) in dry pyridine (50 mL) at -20 °C under argon was added trifluoromethanesulfonic anhydride (4.94 g, 17.5 mmol) and the reaction mixture kept at 0 °C (12 h). It was then quenched with brine (20 mL), extracted with Et₂O (3 x 50 mL), washed with brine (2 x 10 mL), dried (MgSO₄) and taken to dryness. Silica gel chromatography (hexane:EtOAc, 9:1) afforded **12** as a crystalline solid (7.1 g, 100%): mp 79-80 °C; ¹H NMR (CDCl₃) δ 7.99 (brd, 1H, J = 7.8 Hz), 7.83 (dd, 1H, J = 7.8, 1.6 Hz), 7.77 (d, 2H, J = 8.3 Hz), 7.65 (d, 1H, J = 2.3 Hz), 7.61-7.5 (m, 2H), 7.3 (d, 2H, J = 8.3 Hz), 7.08 (d, 1H, J = 2.3 Hz); IR (CHCl₃) 3021, 1634, 967 cm⁻¹; FABMS *m/z* 446 (M⁺). Anal. Calcd for C₁₈H₁₃F₃O₆S₂: C, 48.43; H, 2.93. Found: C, 48.18; H, 2.99.

2-(Trimethylsilyl)ethyl 4-tosyloxy-2-naphthoate (13). A mixture of 12 (446 mg, 1 mmol), Pd(OAc)₂ (11.2 mg, 0.05 mmol), and 1,3-bis(diphenylphosphino)propane (21 mg, 0.05 mmol) was prepared at room temperature, then placed under vacuum and recharged with carbon monoxide three times. To this was added 2-(trimethylsilyl)ethyl alcohol (355 mg, 3 mmol), triethylamine (202 mg, 2 mmol) and DMSO (2 mL) and the mixture was stirred at 70 °C under an atmosphere of carbon monoxide (3 h). The reaction mixture was quenched with brine (5 mL), extracted with EtOAc (3 x 10 mL), washed with brine (2 x 5 mL), dried over (MgSO₄) and taken to dryness. Silica gel chromatography (hexane:EtOAc, 4:1) afforded 13 as a white solid (359 mg, 81%): mp 75-76 °C; ¹H NMR (CDCl₃) δ 8.49 (brs, 1H), 7.98-7.9 (m, 2H), 7.8 (d, 2H, J = 8.3 Hz), 7.7 (d, 1H, J = 1.5 Hz), 7.56-7.52 (m, 2H), 7.3 (d, 2H, J = 8.3 Hz), 4.43 (m 2H), 2.42 (s, 3H), 1.14 (m, 2H), 0.05 (s, 9H); IR (CHCl₃) 2989, 2954, 1715, 1520, 1298 cm⁻¹; FABMS *m/z* 442 (M+). Anal. Calcd for C_{2.3}H₂₆O₅SSi: C, 62.42; H, 5.92. Found: C, 62.24; H, 6.0.

4-Tosyloxy-2-naphthoic acid (14). To a stirred solution of 13 (1.9 g, 4.3 mmol) in THF (15 mL) at 0 °C under argon was added tetrabutylammoniumfluoride (1 M, 8.6 mL) and the reaction continued at room temperature (12 h). The reaction mixture was quenched with 0.5 N HCl (to pH 5-6), extracted with EtOAc (3 x 30 mL), washed with brine (2 x 10 mL), dried (MgSO₄) and taken to dryness. Silica gel chromatography (hexane:EtOAc, 9:1) afforded 14 as a solid (1.27 g, 86%): mp 204-205 °C; ¹H NMR (CDCl₃) δ 8.59 (br s, 1H), 8.03-7.94 (m, 2H), 7.81 (d, 2H, J = 8.3 Hz), 7.75 (brd, 1H, J = 1.2 Hz), 7.62-7.56 (m, 2H), 7.32 (d, 2H, J = 8.3 Hz), 2.44 (s, 3H); IR (CHCl₃) 3600-2750 (br), 1731, 1520, 987 cm⁻¹; FABMS *m*/z 342 (M+). Anal. Calcd for C₁₈H₁₄O₅S: C, 63.15; H, 4.12. Found: C, 63.42; H, 4.07.

Methyl 4-tosyloxy-2-naphthoate (15). A mixture of 12 (4.72 g, 10.6 mmol), $Pd(OAc)_2$ (119 mg, 0.53 mmol), and 1,3-bis(diphenylphosphino)propane (218.6 mg, 0.53 mmol) was prepared at room temperature, then placed under vacuum and recharged with carbon monoxide three times. To this was added methanol (6.79 g, 212 mmol), triethylamine (2.36 g, 23.2 mmol) and DMSO (15 mL) and the mixture was stirred at 70 °C under an atmosphere of carbon monoxide. (3 h). The reaction mixture was quenched with brine (30 mL), extracted with EtOAc (3 x 50 mL), washed with brine (2 x 10 mL), dried (MgSO₄) and taken to dryness. Silica gel chromatography (hexane:EtOAc, 4:1) afforded 15 as a white solid (2.54 g, 67%): mp 119-120 °C; ¹H NMR (CDCl₃) δ 8.5 (br s, 1H), 7.96-7.9 (m, 2H), 7.79 (d, 2H, J = 8.3 Hz), 7.75 (d, 1H, J = 1.4 Hz), 7.56-7.52 (m, 2H), 7.29 (d, 2H, J = 8.3 Hz)

8.3 Hz), 3.94 (s, 3H), 2.42 (s, 3H); IR (CHCl₃) 3020, 2954, 1716, 1438, 1372 cm⁻¹; FABMS m/z 356 (M⁺). Anal. Calcd for C₁₉H₁₆O₅S: C, 64.05; H, 4.53. Found: C, 63.81; H, 4.62.

1-Tosyloxy-3-hydroxymethylnaphthalene (16). A solution of 15 (7.72 g, 21.7 mmol) in THF (30 mL) was added dropwise via cannula to a suspension of LiAlH₄ (2.47 g, 65 mmol) in THF (15 mL) at 0 °C under argon. The reaction mixture was stirred at room temperature (3 h) then quenched at 0 °C with 1 N HCl (30 mL) and extracted with ether (3 x 100 mL), washed with brine (2 x 20 mL), dried (MgSO₄) and taken to dryness. Silica gel chromatography (hexane:EtOAc, 4:1) afforded 16 as a white solid (5.2 g, 73%): mp 129-130 °C; ¹H NMR (CDCl₃) δ 7.84 (d, 1H, *J* = 8.3 Hz), 7.78 (d, 2H, *J* = 8.3 Hz), 7.71 (brs, 1H), 7.48-7.36 (m, 3H), 7.27 (d, 2H, *J* = 8.3 Hz), 7.24 (brs, 1H), 4.79 (s, 2H), 2.41 (s, 3H); IR (CHCl₃) 3450, 2947, 1602, 907 cm⁻¹; FABMS *m*/z 328 (M+). Anal. Calcd for C₁₈H₁₆O₄S: C, 65.84; H, 4.91. Found: C, 65.69; H, 5.00.

1-Tosyloxy-3-formylnaphthalene (17). A solution of 16 (5.2 g, 15.7 mmol) in CH₂Cl₂ (30 mL) was added dropwise via cannula at room temperature under argon to a solution of pyridinium chlorochromate in CH₂Cl₂ (10.2 g, 47.2 mmol) and the reaction continued at room temperature (2 h). It was then diluted with ether, filtered through a pad of celite and taken to dryness. Silica gel chromatography (hexane:EtOAc, 4:1) afforded 17 as a solid (4.2 g, 81.2%): mp 129-130 °C;; ¹H NMR (CDCl₃) δ 10.1 (s, 1H), 8.25 (brs, 1H), 8.07-7.97 (M, 2H), 7.81 (d, 2H, *J* = 8.3 Hz), 7.65-7.59 (m, 2H), 7.56 (d, 1H, *J* = 1.4 Hz), 7.33 (d, 2H, *J* = 8.3 Hz), 2.45 (s, 3H); IR (CHCl₃) 3018, 1697, 1215, 765 cm⁻¹; FABMS *m/z* 326 (M⁺). Anal. Calcd for C₁₈H₁₄O₄S: C, 66.24; H, 4.32. Found: C, 66.32; H, 6.41.

Bis(tert-butyl) [1-hydroxy-1-[2-(4-tosyloxynaphthalenyl)]methyl]phosphonate (18). To di-*tert*-butyl phosphite (1.23 g, 6.23 mmol) in THF (35 mL) at -78 °C under argon was added (TMS)₂NLi (1.0 M, 6.33 mL) and the reaction mixture stirred at -78 °C (30 min). A solution of 17 (1.88 g, 5.8 mmol) in THF (15 mL) was added via cannula and stirring continued at -78 °C (3 h). The reaction mixture was quenched by addition of 1N HCl (8 mL) at -78 °C, then extracted with EtOAc (3 x 70 mL), washed with brine (2 x 10 mL), dried (MgSO₄) and taken to dryness. Silica gel chromatography (CHCl₃:MeOH, 99:1) afforded 18 as a crystalline solid (2.4 g, 80%): mp 145-146 °C; ¹H NMR (CDCl₃) δ 7.81-7.76 (m, 4H), 7.25 (d, 2H, *J* = 8.3 Hz), 4.93 (d, 1H, *J* =10.3 Hz), 2.39 (s, 3H), 1.44 (s, 9H), 1.38 (s, 9H); IR (CHCl₃) 3283, 2982, 1580, 918 cm⁻¹; FABMS *m/z* 520 (M+). Anal. Calcd for C₂₆H₃₃O₇PS: C, 59.99; H, 6.39. Found: C, 60.07; H, 6.41.

Bis(tert-butyl) [1-oxo-1-[2-(4-tosyloxynaphthalenyl)]methyl]phosphonate (20). To a solution of oxalyl chloride (2.0 M, 4.57 ml, 9.14 mmol) in CH₂Cl₂ (30 mL) at -78 °C under argon was added DMSO (1.43 g, 18.3 mmol, 4 equiv.). After 10 min, 18 (2.4 g, 4.57 mmol) in CH₂Cl₂ (15 mL) was added, followed after 30 min by Et₃N (4.62 g, 45.5 mmol). The dry ice-acetone bath was then removed and the reaction mixture was stirred at room temperature (1 h) then quenched at -78 °C with 1N HCl (8 mL). The mixture was extracted with EtOAc (3 x 70 mL), washed with brine (2 x 10 mL), dried (MgSO₄) and taken to dryness. Silica gel chromatography (CHCl₃:MeOH, 99:1) afforded 20 as a colorless oil (1.84 g, 79%): ¹H NMR (CDCl₃) δ 9.04 (brs, 1H), 8.0-7.96 (m, 2H), 7.8 (d, 2H, *J* = 8.3 Hz), 7.75 (d, 1H, *J* = 1 Hz)7.62 -7.53 (m, 2H), 7.29 (d, 2H, *J* = 8.3 Hz), 2.41 (s, 3H), 1.54 (s, 18H); IR (film) 2981, 1736, 1655, 1397, 922 cm⁻¹; FABMS *m/z* 518 (M+). Anal. Calcd for C₂₆H₃₁O₇PS•2H₂O: C, 56.32; H, 6.32. Found: C, 56.03; H, 6.23.

Bis(tert-butyl) [1,1-difluoro-1-[2-(4-tosyloxynaphthalenyl)] methyl]phosphonate (21). To 20 (103.6 mg, 0.2 mmol) at -78 °C under argon was added diethylaminosulfur trifluoride (161.2 mg, 1 mmol). After addition, the dry ice bath was removed and the reaction mixture kept at room temperature overnight. The mixture was re-cooled to -78 °C, and added to saturated NaHCO₃ (10 mL), extracted with EtOAc (3 x 15 mL), washed with saturated NaHCO₃ (2 x 5 mL), dried (MgSO₄) and taken to dryness. Silica gel chromatography (hexane:EtOAc, 1:1) afforded 21 as an oil which crystallized (54.7 mg, 51%): mp 118-119 °C; ¹H NMR (CDCl₃) δ 8.0 (brs, 1H), 7.96-7.92 (m, 1H), 7.88-7.86 (m, 1H), 7.79 (d, 2H, J = 8.3 Hz), 7.56-7.46 (m, 2H), 7.34 (brs, 1H), 7.29 (d, 2H, J = 8.3 Hz), 2.42 (s, 3H), 1.48 (s, 18H); IR (film) 2982, 1584, 918 cm⁻¹; FABMS *m/z* 540 (M+). Anal. Calcd for C₂₆H₃₁F₂O₆PS: C, 57.78; H, 5.74. Found: C, 57.61; H, 5.8.

(Tert-butyl) [1,1-difluoro-1-[2-(4-hydroxynaphthalenyl)]methyl]phosphonate (22). To a solution of compound 21 (207.7 mg, 0.39 mmol) in THF (2 mL) at room temperature under argon was added KOH (108 mg, 1.9 mmol) in H₂O (3.8 mL) and the mixture then stirred at reflux (1 h). The mixture was cooled to 0 °C, diluted with EtOAc (10 mL), quenched with 0.5 N HCl (4 mL), extracted with EtOAc (3 x 20 mL), washed with brine (2 x 5 mL), dried (MgSO₄) and taken to dryness. Silica gel chromatography (CHCl₃:MeOH, 9:1) afforded 22 as a crystalline solid (121 mg, 95%): mp 118-119 °C; ¹H NMR (CDCl₃) δ 8.20-8.15 (m, 1H), 7.89 -7.79 (m, 1H), 7.59 (br s, 1H), 7.47-7.44 (m, 2H), 7.07 (brs, 1H), 1.38 (s, 9H); 1R (CHCl₃) 3430 (br), 2982, 1571, 932 cm⁻¹; FABMS *m*/*z* 330 (M)⁺. Anal.Calcd for C₁₅H₁₇O₄F₂P[•]2³/₄H₂O: C, 47.43; H, 5.93. Found: C, 47.42; H, 6.03.

[1,1-Difluoro-1-[2-(4-hydroxynaphthalenyl)]methyl]phosphonic acid (7). To compound 22 (28.7 mg, 0.09 mmol) was added 80% trifluoroacetic acid (2 mL) and the mixture stirred at room temperature (2 h). Trifluoroacetic acid was removed under high vacuum, and the resulting residue was purified by hplc (Vydac C₁₈ peptide and protein semi-prep column; A = 0.05% aqueous TFA, B = 0.5% TFA in acetonitrile; linear gradient, 0% B to 5% B over 20 minutes) then refiltered to obtain 7 as a yellow solid (23 mg, 97 %): ¹H NMR (CDCl₃) δ 8.22-8.15 (m, 1H), 7.85-7.82 (m, 1H), 7.61 (brs, 1H), 7.49-7.46 (m, 2H), 7.06 (brs, 1H); ¹⁹F NMR (CFCl₃) δ -112.3

(d, J = 110.2 Hz); IR (CHCl₃) 3359 (br), 2991, 925 cm-1; FABMS m/z 274 (M-H)+; HRMS Calcd. for C₁₁H₉F₂O₄P, 273.0128 (M-H)+; Found, 273.0124.

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