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Synthesis of a Difluorophosphonomethyl-Containing Phosphatase Inhibitor Designed from the X-ray Structure of a PTP1B-Bound Ligand[1]

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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.
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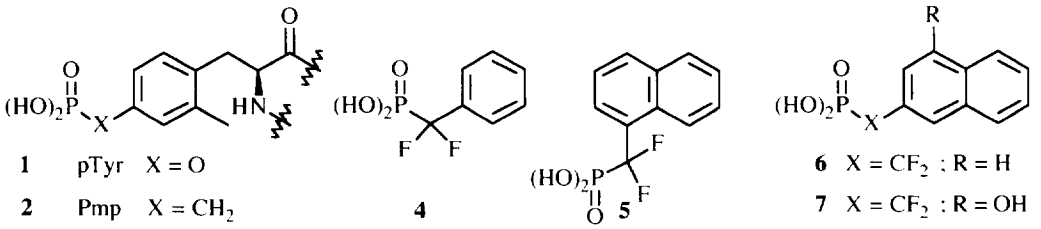
INTRODUCTION

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 (F_2Pmp, **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]



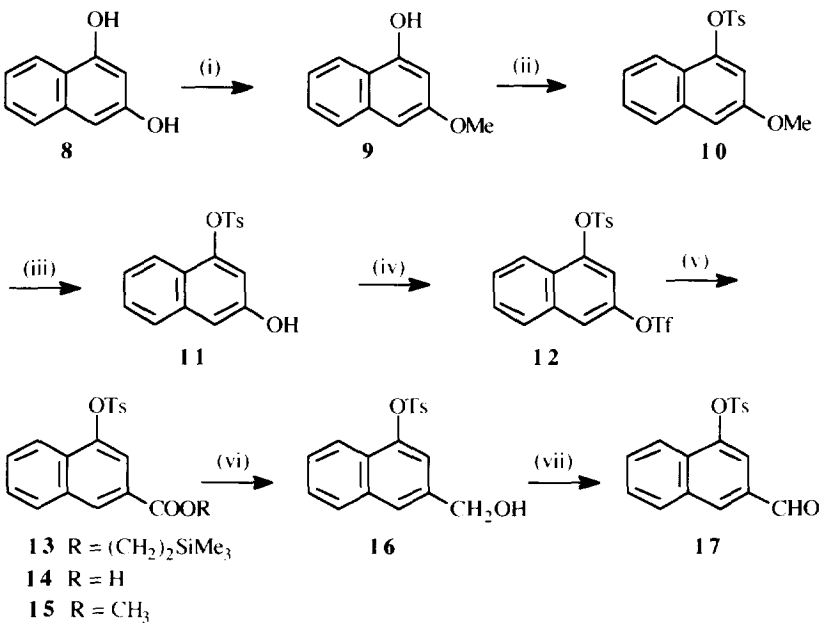
The difluoromethylnaphthylphosphonic acid structure therefore provides a starting nucleus for the development of small molecule PTP inhibitors. To facilitate elaboration of this nucleus into more potent and selective PTP inhibitors, we have examined the binding interactions of 2-difluoromethylnaphthylphosphonic 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 affinity[9] (Ki = 94 μM) relative to it unhydroxylated parent **6**, (Ki = 179 μM).[9] This supports molecular modelling dymanics 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 difluorophosphonate. 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** → **15**, Scheme 1), and the subsequent elaboration of this carbon by addition of phosphonate (**17** → **18**) and fluorine (**20** → **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*-butyldimethylsilyl chloride and tosyl chloride failed, and Bell's method[11] 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 °C[12] 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 BBr_3 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.

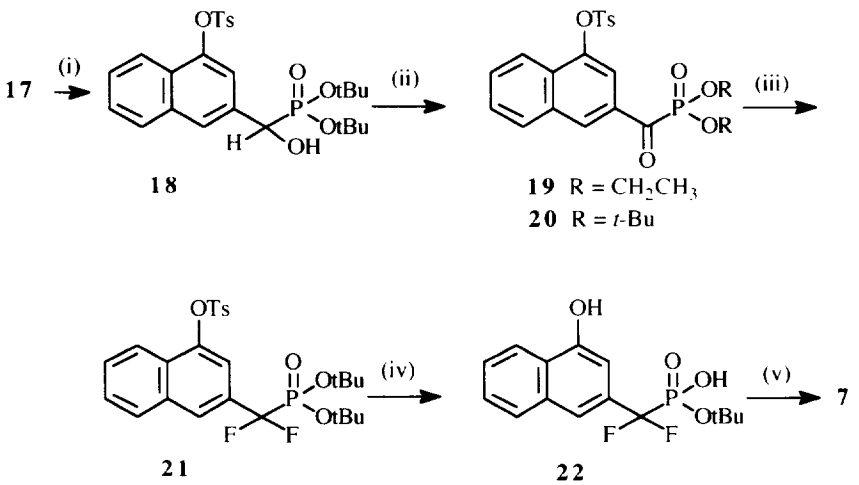


(I) MeOH/HCl; (ii) TsCl, pyridine; (iii) BBr_3, CH_2Cl_2, -78 °C to rt; (iv) Tf_2O; pyridine; (v) ROH, CO, $Pd(OAc)_2$, NEt_3, $Ph_2P(CH_2)_3PPh_2$, DMSO; (vi) $LiAlH_4$, THF; (vii) PCC, CH_2Cl_2;

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 $LiAlH_4$ (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) $(SiMe_3)_2NLi$, $HP(O)(tert\text{-}BuO)_2$, THF; (ii) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -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 **9**[11] (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 $NaHCO_3$ (30 mL), extracted with EtOAc (3 x 50 mL), washed with brine (2 x 10 mL), dried over $MgSO_4$, 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 ($CDCl_3$) 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 ($CHCl_3$) 2940, 1610, 972 cm^{-1}; FABMS *m/z* 328 (M^+). Anal. Calcd for $C_{18}H_{16}O_4S$: 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 CH_2Cl_2 (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 CH_2Cl_2 (3 x 100 mL), washed with brine (2 x 50 mL), dried ($MgSO_4$) and taken to dryness. Silica gel chromatography (hexane:EtOAc, 4:1) afforded **11** as a solid (8.19 g, 93%): mp 133-134 °C; ^{1}H NMR ($CDCl_3$) 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), 7.23 (m, 1H), 7.05 (brd, 1H, J = 2 Hz), 6.94 (d, 1H, J = 2 Hz), 2.4 (s, 3H); IR ($CHCl_3$), 3370, 2926, 1602, 1270 cm^{-1}; FABMS m/z 314 (M+). Anal. Calcd for $C_{17}H_{14}O_4S$: 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 Et_2O (3 x 50 mL), washed with brine (2 x 10 mL), dried ($MgSO_4$) 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; ^{1}H NMR ($CDCl_3$) 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 ($CHCl_3$) 3021, 1634, 967 cm^{-1}; FABMS m/z 446 (M+). Anal. Calcd for $C_{18}H_{13}F_3O_6S_2$: 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 ($MgSO_4$) and taken to dryness. Silica gel chromatography (hexane:EtOAc, 4:1) afforded **13** as a white solid (359 mg, 81%): mp 75-76 °C; ^{1}H NMR ($CDCl_3$) 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 ($CHCl_3$) 2989, 2954, 1715, 1520, 1298 cm^{-1}; FABMS m/z 442 (M+). Anal. Calcd for $C_{23}H_{26}O_5SSi$: 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 ($MgSO_4$) and taken to dryness. Silica gel chromatography (hexane:EtOAc, 9:1) afforded **14** as a solid (1.27 g, 86%): mp 204-205 °C; ^{1}H NMR ($CDCl_3$) 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 ($CHCl_3$) 3600-2750 (br), 1731, 1520, 987 cm^{-1}; FABMS m/z 342 (M+). Anal. Calcd for $C_{18}H_{14}O_5S$: 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 ($MgSO_4$) 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; ^{1}H NMR ($CDCl_3$) 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), 3.94 (s, 3H), 2.42 (s, 3H); IR ($CHCl_3$) 3020, 2954, 1716, 1438, 1372 cm^{-1}; FABMS *m/z* 356 (M+). Anal. Calcd for $C_{19}H_{16}O_5S$: 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 $LiAlH_4$ (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 ($MgSO_4$) 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 ($CDCl_3$) 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 ($CHCl_3$) 3450, 2947, 1602, 907 cm^{-1}; FABMS *m/z* 328 (M+). Anal. Calcd for $C_{18}H_{16}O_4S$: 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 CH_2Cl_2 (30 mL) was added dropwise via cannula at room temperature under argon to a solution of pyridinium chlorochromate in CH_2Cl_2 (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 ($CDCl_3$) 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 ($CHCl_3$) 3018, 1697, 1215, 765 cm^{-1}; FABMS *m/z* 326 (M+). Anal. Calcd for $C_{18}H_{14}O_4S$: 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 ($MgSO_4$) and taken to dryness. Silica gel chromatography ($CHCl_3$:MeOH, 99:1) afforded **18** as a crystalline solid (2.4 g, 80%): mp 145-146 °C; ^1H NMR ($CDCl_3$) 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 ($CHCl_3$) 3283, 2982, 1580, 918 cm^{-1}; FABMS *m/z* 520 (M+). Anal. Calcd for $C_{26}H_{33}O_7PS$: 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 CH_2Cl_2 (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 CH_2Cl_2 (15 mL) was added, followed after 30 min by Et_3N (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 ($MgSO_4$) and taken to dryness. Silica gel chromatography ($CHCl_3$:MeOH, 99:1) afforded **20** as a colorless oil (1.84 g, 79%): ^1H NMR ($CDCl_3$) 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 $C_{26}H_{31}O_7PS{\bullet}2H_2O$: 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 $NaHCO_3$ (10 mL), extracted with EtOAc (3 x 15 mL), washed with saturated $NaHCO_3$ (2 x 5 mL), dried ($MgSO_4$) 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 ($CDCl_3$) 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 $C_{26}H_{31}F_2O_6PS$: 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 H_2O (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 ($MgSO_4$) and taken to dryness. Silica gel chromatography ($CHCl_3$:MeOH, 9:1) afforded **22** as a crystalline solid (121 mg, 95%): mp 118-119 °C; ^1H NMR ($CDCl_3$) 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); IR ($CHCl_3$) 3430 (br), 2982, 1571, 932 cm^{-1}; FABMS *m/z* 330 $(M)^+$. Anal.Calcd for $C_{15}H_{17}O_4F_2P \cdot 2^3/_4H_2O$: 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 C_{18} 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 ($CDCl_3$) 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); ^{19}F NMR ($CFCl_3$) δ -112.3 (d, *J* = 110.2 Hz); IR ($CHCl_3$) 3359 (br), 2991, 925 cm-1; FABMS *m/z* 274 $(M-H)^+$; HRMS Calcd. for $C_{11}H_9F_2O_4P$, 273.0128 $(M-H)^+$; Found, 273.0124.

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