Preparation of Benzylic α,α-Difluoronitriles, -tetrazoles, and -sulfonates via Electrophilic Fluorination

Christopher C. Kotoris, Mei-Jin Chen, and Scott D. Taylor*

Department of Chemistry, University of Toronto, Mississauga Campus, 3359 Mississauga Road North, Mississauga, Ontario, Canada L5L 1C6

Received June 17, 1998

Introduction

There are now numerous examples in which the introduction of a fluorine atom(s) significantly alters the biological activity of a given compound.[1] This tactic has been widely used for the development of enzyme inhibitors, especially for enzymes involved in phosphate ester hydrolysis or binding where α-fluorinated phosphonates are used as hydrolytically stable phosphate surrogates.[2] For example, it has been shown that peptides bearing the nonhydrolyzable phosphotyrosine mimetic difluoromethylenephosphonyl phenylalanine (F_2Pmp), **1**, are potent inhibitors of protein tyrosine phosphatases (PTP's) and can be up to 2000 times more potent than the analogous peptide bearing the nonfluorinated analogue (see Figure 1).[3a,b] It has also been shown that certain simple aromatics, such as **2** and **3**, are inhibitors of PTP's, whereas their nonfluorinated counterparts are very poor inhibitors.[4a,b]

As part of our program to create potent and specific nonpeptidyl inhibitors of PTP's,[4b,5] we became interested in developing methodologies for the α-fluorination of various benzyl derivatives.[6a,b] In addition to benzylic α,α-difluoromethylenephosphonates, we were also interested in examining PTP inhibitors that did not bear a dianionic functionality. The reason for this is that, because of the dianionic phosphonate moiety, **1**−**3** are incapable of penetrating the cellular membrane.[4a] Therefore, they are unsuitable for cellular studies and have to be converted to cell-permeable "caged" phosphonate esters, which can be problematic.[7] Consequently, we wish to examine other

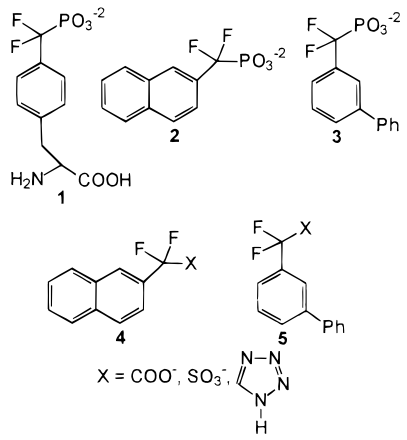


Figure 1.

functionalities that are either more amenable to cellular penetration or more readily converted to caged compounds. However, it was desirable to retain the fluorines because it has been shown that they are essential for potent PTP inhibition.[3−5] Thus, we wished to construct α,α-difluorinated benzylic derivatives in which the phosphate group is replaced with a monoanionic moiety such as a carboxylate, sulfonate, or tetrazole group, anticipating that these moieties may be suitable phosphate biosteres for developing PTP inhibitors and would be more amenable to cellular studies than their phosphonate analogues. To determine if the α,α-difluorocarboxylate, -sulfonate, or -tetrazole moieties are suitable replacements for the difluoromethylenephosphonic acid group, compounds of type **4** or **5** could be constructed and compared with **2** or **3** for inhibition of PTP's.

Benzylic α,α-difluorocarboxylic acids can be readily prepared in good yields from α-keto esters using diethylaminosulfur trifluoride (DAST).[8a] However, to our knowledge, syntheses of benzylic α,α-difluorosulfonates and benzylic α,α-difluorotetrazoles have never been reported. Here we report that these species, as well as benzylic α,α-difluoronitriles, can be prepared via electrophilic fluorination of benzylic carbanions using *N*-fluorobenzenesulfonimide (NFSi).

Results and Discussion

Synthesis of Benzylic α,α-Difluoronitriles and α,α-Difluorotetrazoles. The most common and straightforward approach for constructing tetrazoles is via reaction of nitriles with NaN_3/NH_4Cl in DMF with heating.[9] Thus, we envisioned preparing benzylic α,α-difluorotetrazoles by first synthesizing benzylic α,α-difluoronitriles which would then be converted into the tetrazoles.

Benzylic α,α-difluoronitriles have been prepared in a variety of ways.[8a−f] However, these methodologies either

(1) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley and Sons: New York, 1991.

(2) For some examples of α,α-difluorophosphonates as inhibitors of enzymes other than PTP's, see: Halazy, S.; Ehrhard, A.; Eggenspiller, A.; Berges-Gross, V.; Danzin, C. *Tetrahedron* **1996**, *51*, 177. Blackburn, G. M.; Kent, D. E.; Kolkmann, F. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1119. Hebel, D.; Kirk, K. L.; Kinjo, J.; Kovacs, T.; Lesiak, K.; Balzarini, J.; De Clercq, E.; Torrence, P. F. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 357.

(3) (a) Burke, T. R.; Kole, H. K.; Roller, P. P. *Biochem. Biophys. Res. Commun.* **1994**, *204*, 129. (b) Chen, L.; Wu, L.; Otaka, A.; Smyth, M. S.; Roller, P. R.; Burke, T. R.; den Hertog, J.; Zhang, Z.-Y. *Biochem. Biophys. Res. Commun.* **1995**, *216*, 976.

(4) (a) Kole, K. H.; Smyth, M. S.; Russ, P. L.; Burke, T. R. *Biochem. J.* **1995**, *311*, 1025. (b) Taylor, S. D.; Kotoris, C. C.; Dinaut, A. N.; Wang, Q.; Ramachandran, C.; Huang, H. *Bioorg. Med. Chem.*, in press.

(5) Wang, Q.; Huang, Z.; Ramachandran, C.; Dinaut, A. N.; Taylor, S. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 345.

(6) (a) Taylor, S. D.; Kotoris, C. C.; Dinaut, A. N.; Chen, M.-J. *Tetrahedron* **1998**, *54*, 1691. (b) Taylor, S. D.; Dinaut, A. N.; Thadani, A. T.; Huang, Z. *Tetrahedron Lett.* **1996**, *37*, 8089.

(7) Stankovic, C. J.; Surendram, N.; Lunney, E. A.; Plummer, M. S.; Para, K. S.; Shahripour, A.; Fergus, J. H.; Marks, J. S.; Herrera, R.; Hubbell, S. E.; Humblet, C.; Saltiel, A. R.; Stewart, B. H.; Sawyer, T. K. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1909.

(8) (a) Middleton, W. J.; Bingham, E. M. *J. Org. Chem.* **1980**, *45*, 2883. (b) Bartmann, E.; Krause, J. *J. Fluorine Chem.* **1993**, *61*, 117. (c) Hagele, G.; Haas, A. *J. Fluorine Chem.* **1996**, *76*, 15. (d) Yagupolskii, L. M.; Belinskaya, R. V. *Zh. Obshch. Khim.* **1958**, *28*, 772. (e) Bardin, V. V.; Furin, G. G.; Yakobson, G. G. *Zh. Org. Khim.* **1984**, *20*, 567. (f) Laurent, E.; Marquet, B.; Tardivel, R. *Tetrahedron* **1989**, *45*, 4431.

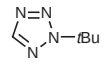
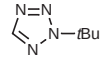
(9) (a) Finnegan, W. G.; Henry, R. A.; Lofquist, R. *J. Am. Chem. Soc.* **1958**, *80*, 3908. (b) Wittenberger, S. J.; Donner, B. G. *J. Org. Chem.* **1993**, *58*, 4139. (c) Thomas, E. W. *Synthesis* **1993**, 767. (d) Duncia, J. V.; Pierce, M. E.; Santella, J. B. *J. Org. Chem.* **1991**, *56*, 2395.

10.1021/jo981163x CCC: $15.00
Published on Web 10/13/1998

require a multistep synthesis or proceed in low yields. These methods also often require uncommon or highly toxic reagents and/or uncommon procedures. Ideally, we wished to develop a method by which benzylic α,α-difluoronitriles could be obtained in a minimum number of steps using readily available and safe reagents. Electrophilic fluorination is rapidly becoming the method of choice for the preparation of fluorinated compounds.[10] We recently reported[6a,b] that benzylic α,α-difluoromethylenephosphonates could be readily prepared in good-to-excellent yield by electrophilic fluorination of benzylic carbanions with NFSi, a relatively cheap and commercially available electrophilic fluorinating agent.[11a−d] Consequently, we reasoned that this approach may be used as a one-step procedure for the synthesis of benzylic α,α-difluoronitriles from benzylnitriles. Our previous studies[6a,b] on the phosphonates and those by other workers using carbon esters as substrates[11c,d] indicate that the yields of fluorinated products are very dependent on the nature of the base and counterion. Thus, we first attempted this reaction by employing commercially available *β*-naphthylacetonitrile (**6**) as a model substrate using different bases and counterions. We initially performed the reaction using a one-step procedure by adding 2.2 equiv of base to a solution of the nitrile in THF at −78 °C followed by the addition of 2.5 equiv of NFSi at −78 °C. With most bases (LDA, KDA, NaHMDS, KHMDS, LiHMDS, and *n*-BuLi) the desired fluorinated product **7** was obtained in low yields (9−16%). However, *t*-BuLi proved to be an exception; this base increased the yield of **7** to 50% (entry 1, Table 1). It is interesting to note that the yield using *t*-BuLi as base was 5 times greater than the yield when *n*-BuLi was used (10% yield). This may be due to the reaction of *n*-BuLi with NFSi which may not occur as readily with the more sterically hindered *t*-BuLi. It is also possible that the poor yields obtained with *n*-BuLi and other bases may be a result of attack of these bases on the nitrile carbon of the α-fluorinated product, although this seems unlikely with the sterically hindered HMDS bases. Because of the possibility that a reaction may also be occurring between NFSi and *t*-BuLi during the one-step fluorination procedure, we examined whether the yield could be improved by performing the reaction in a stepwise fashion using *t*-BuLi as base (1.1 equiv of *t*-BuLi at −78 °C, stirred for 1 h, followed by 1.3 equiv of NFSi, stirred for 2 h, and then repeating the process). However, this did not result in a significant increase in yield. Performing the reaction at −100 °C gave similar yields. We also found that the monofluorinated product **8** could be obtained in a 60% yield using 1.1 equiv of *t*-BuLi and 1.3 equiv of NFSi (entry 2, Table 1).

To examine the scope of this reaction, we attempted the fluorination of a variety of benzylnitriles (entries 3−10, Table 1). Yields of the difluorinated products range from 34 to 56%[12] with the exception of the 4-bromo derivative. Although *t*-BuLi was the best base for the naphthyl and other derivatives (entries 1−8, Table 1), we found that with the 4-nitro and 4-bromo derivatives

Table 1. Electrophilic Fluorination of Benzylic Nitriles and Tetrazoles with NFSi

	substrate		product		
entry	Ar	R	R′	R″	% yield[a]
1	*β*-naphthyl (**6**)	CN	F (**7**)	F	50,[b] 52[c]
2	*β*-naphthyl (**6**)	CN	F (**8**)	H	60[d]
3	α-naphthyl (**9**)	CN	F (**10**)	F	46[b]
4	4-MePh (**11**)	CN	F (**12**)	F	44[b]
5	2-MePh (**13**)	CN	F (**14**)	F	37[b]
6	4-MeOPh (**15**)	CN	F (**16**)	F	34[b]
7	3-MeOPh (**17**)	CN	F (**18**)	F	56[b]
8	3-(Ph)Ph (**19**)	CN	F (**20**)	F	47[b]
9	4-NO_2Ph (**21**)	CN	F (**22**)	F	34,[e] 5[b]
10	4-BrPh (**23**)	CN	F (**24**)	F	19,[f] 0[b]
11	*β*-naphthyl (**25**)		F (**26**)	F	56,[b] 52,[c] 36,[f] 30[g]
12	*β*-naphthyl (**25**)		F (**27**)	H	61[d]

[a] Isolated yields. [b] Performed using a one-step procedure employing 2.2 equiv of *t*-BuLi and 2.5 equiv of NFSi as described in the Experimental Section. [c] Performed using a two-step procedure employing 1.1 equiv of *t*-BuLi and 1.3 equiv of NFSi for each fluorination. [d] Performed using 1.1 equiv of *t*-BuLi and 1.3 equiv of NFSi. [e] Performed using the one-step procedure with NaHMDS as base. [f] Performed using the one-step procedure with LDA as base. [g] Performed using the one-step procedure with *n*-BuLi as base.

other bases (entries 9 and 10, Table 1, NaHMDS and LDA, respectively) were more effective than *t*-BuLi. The low yield obtained with the bromo derivative (19%) was due to significant loss of bromine from the aryl ring during the reaction. For inhibition studies, the desired benzylic α,α-difluorotetrazoles **28** and **29** were obtained in quantitative yields by reacting nitriles **7** and **20** with NaN_3 in DMF (Scheme 1), and this reaction did not require any NH_4Cl which is typically employed when converting nitriles to tetrazoles using NaN_3.[9]

In an attempt to increase the overall yields of the benzylic α,α-difluorotetrazoles, we also examined whether it would be possible to obtain the fluorinated tetrazoles by subjecting protected benzyltetrazoles to the fluorination conditions. Thus, electrophilic fluorination was performed on *tert*-butyl-protected[13] tetrazole **25** by employing our one-step procedure using different bases and cations. With the HMDS bases (NaHMDS, KHMDS, and LiHMDS), the desired fluorinated product **26** was ob-

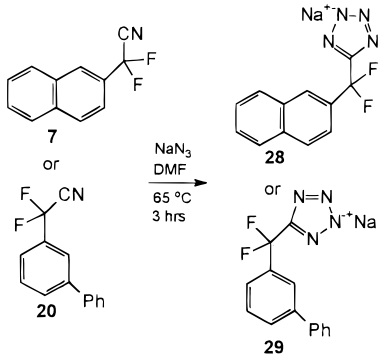
(10) For a review on electrophilic fluorination, see: Rozen, S. *Chem. Rev.* **1996**, *96*, 1717.

(11) For some examples of electrophilic fluorination using NFSi, see: (a) McAtee, J. J.; Schinazi, R. F.; Liotta, D. C. *J. Org. Chem.* **1998**, *63*, 2161. (b) Ender, D.; Potthoff, M.; Raabe, G.; Runsink, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2362. (c) Differding, E.; Ofner, H. *Synlett* **1991**, 187. (d) Differding, E.; Duthaler, R. O.; Kreiger, A.; Ruegg, G. M.; Schmit, C. *Synlett* **1991**, 395.

(12) We also attempted to produce the biphenyl derivative **20** via DAST fluorination of the corresponding α-ketonitrile using the procedure reported by Hagele and Haas.[8c] However, we were unable to obtain any appreciable quantities of **20** in pure form using this procedure.

(13) The *tert*-butyl group is commonly employed as a protecting group for tetrazoles and is removed using acid. For example, see: Tilley, J. W.; Danho, W.; Lovey, K.; Wagner, R.; Swistok, J.; Makofske, R.; Michaelewsky, J.; Triscari, J.; Nelson, D.; Weatherford, S. *J. Med. Chem.* **1991**, *34*, 1125.

Scheme 1

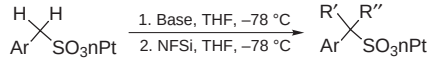


tained in very low yields (3−5%). However, **26** could be obtained in modest-to-reasonable yields using *n*-BuLi, LDA, and *t*-BuLi as bases (entry 11, Table 1), with *t*-BuLi being the most effective.[14] Performing the reaction stepwise using *t*-BuLi did not increase the yield. We also attempted the fluorination reaction using a benzyl protecting group, instead of a *tert*-butyl protecting group, but this was unsuccessful as was the fluorination of unprotected **25** using 3 equiv of base and fluorinating agent. The monofluorinated tetrazole **27** was also obtained in a 61% yield using 1.1 equiv of *t*-BuLi and 1.3 equiv of NFSi (entry 12, Table 1). Because the yield for the fluorination of tetrazole **25** was similar to that obtained for the fluorination of nitrile **6** and because this approach also requires prior protection and eventual deprotection of the tetrazole, it appears that no advantage can be gained (in terms of yield) by fluorinating the protected tetrazoles rather than the nitriles.

Synthesis of Benzylic α,α-Difluorosulfonates. We prepared methyl, ethyl, isopropyl, and neopentyl esters of phenylmethanesulfonate as model substrates for the fluorination of sulfonate esters and subjected them to our electrophilic fluorination conditions. With the methyl, ethyl, and isopropyl ester substrates, only unidentified decomposition products were obtained; this was the case irrespective of the base employed and the manner in which the reaction was carried out (one- or two-step procedure). However, performing the reaction stepwise using *t*-BuLi as base with the neopentyl ester (**30**) as substrate gave the desired difluorinated product (**31**) in good yield (entry 1, Table 2). Performing the reaction in a single step resulted in a dramatic decrease in yield (27%). The results with the methyl, ethyl, and isopropyl esters may be due to competing reactions involving nucleophilic attack of the base at the methylene carbon of the alkoxy group of the ester and loss of the benzylsulfonate moiety (for the methyl or ethyl esters) or removal of the β proton of the alkoxy group followed by elimination of the benzylsulfonate moiety (for the ethyl or isopropyl esters). These side reactions must occur less readily with the neopentyl ester due to lack of a β proton or steric hindrance. Further studies were performed with the neopentyl ester **30** using a variety of bases and counterions. Unlike its nitrile and tetrazole analogues, the fluorination of **30** was not highly dependent upon the base or counterion and reasonable-to-good yields of **31** (63−81%) were obtained using a variety of bases (LDA, KDA, NaHMDS, KHMDS, LiHMDS, and *n*-BuLi), although *t*-BuLi gave the best yields. Higher yields were obtained when the reaction was performed stepwise, with the exception of when NaHMDS was used as base which gave **31** in a higher yield when performed in a single step (77%) as opposed to when performed stepwise (64%). The monofluorinated product **32** could be obtained in an excellent yield using 1.1 equiv of *t*-BuLi and 1.15 equiv of NFSi (entry 2, Table 2).

(14) We also performed the fluorination of the *tert*-butyl-protected α-naphthyltetrazole using t-BuLi as base and obtained yields similar to that obtained with the β isomer.

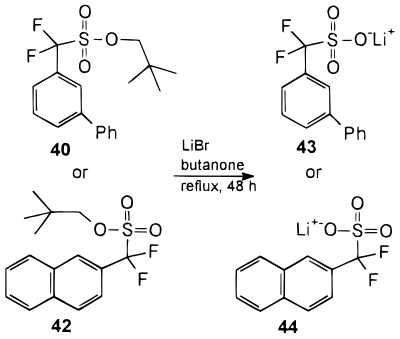
Table 2. Electrophilic Fluorination of Benzylic Sulfonates with NFSi



	substrate	product		
entry	Ar	R′	R″	% yield[a,b]
1	Ph (**30**)	F	F (**31**)	81,[c] 27[d]
2	Ph (**30**)	F	H (**32**)	89[e]
3	4-NO_2Ph (**33**)	F	F (**34**)	86,[f] 11[c]
4	4-BrPh (**35**)	F	F (**36**)	79,[g] 32,[f] 0[c]
5	4-MePh (**37**)	F	F (**38**)	76,[g] 24[c]
6	3-(Ph)Ph (**39**)	F	F (**40**)	59[c]
7	β-naphthyl (**41**)	F	F (**42**)	86[c]

[a] Isolated yields. [b] All reactions were performed stepwise using 1.1 equiv of base and 1.15 equiv of NFSi for each fluorination as described in the Experimental Section, unless noted otherwise. [c] Performed using *t*-BuLi as base. [d] Performed using a one-step procedure employing 2.2 equiv of *t*-BuLi and 2.5 equiv of NFSi. [e] Performed using 1.1 equiv of *t*-BuLi at −78 °C followed by 1.15 equiv of NFSi. [f] Performed using NaHMDS as base. [g] Performed using LDA as base.

Scheme 2



To examine the scope of this reaction, we prepared several neopentyl-protected benzylic sulfonates and subjected these to electrophilic fluorination (Table 2). Good yields of the difluorinated sulfonates were obtained in most instances; however with certain substrates, bases other than *t*-BuLi gave the best yields (nitro, bromo, and 4-methyl derivatives, entries 3, 4, and 5, Table 2). For inhibitor studies, the *m*-biphenyl derivative **40** and naphthyl derivative **42** were readily deprotected to give sulfonic acids **43** and **44** as their lithium salts in excellent yields (88 and 92%, respectively) using LiBr in refluxing butanone (Scheme 2).

Summary

In conclusion, we have demonstrated that benzylic α,α-difluoronitriles, -tetrazoles, and -sulfonates can be prepared by electrophilic fluorination of benzylic carbanions.

Inhibitor studies with **28**, **29**, **43**, and **44** and PTP1B are in progress. The procedures described in this study have the potential to provide novel classes of organofluorides with diverse applications beyond the scope of PTP inhibitors. The benzyltetrazole group is an important biostere for acidic residues in medicinal chemistry,[15] and the α-difluorination of this moiety will provide a potential route for increasing the bioactivity of tetrazole-containing compounds. Sulfotyrosine-bearing peptides have been shown to be inhibitors of PTP's.[16] However, it is possible that benzylic α,α-difluorosulfonates will be more potent PTP inhibitors than benzyl sulfates because there is now considerable evidence that the high affinity of the fluorophosphonates can be attributed to a direct interaction of the fluorines with residues in the active site and is not due to pK_a effects.[3b,17] In addition, the sulfonates may be more amenable to cellular studies than the phosphates. Finally, this tactic can now be extended to the development of inhibitors of enzymes that hydrolyze phenyl sulfates such as aryl sulfatases and steroid sulfatases and proteins that bind tyrosyl sulfates. Recently, there has been considerable interest in the development of steroid sulfatase inhibitors,[18a−d] some of which are estrone sulfonates in which the labile S−O bond in the substrate is replaced by a methylene unit.[18d] Conversion of these compounds to the α,α-difluorosulfonate derivatives may provide a means of increasing the potency of these compounds.

Experimental Section

General. Nitriles **6**, **9**, **11**, **13**, **15**, **17**, **21**, and **23** and other starting materials and reagents were purchased from Aldrich Chemical Co. (Milwaukee, WI) unless stated otherwise. Nitrile **19** was prepared according to a literature procedure.[19] Methyl, ethyl, propyl, and neopentyl (**30**) esters of (phenyl)methanesulfonate were prepared by literature procedures.[20] All NMRs were run in $CDCl_3$ unless stated otherwise. For ^{19}F NMR, chemical shifts are reported in parts per million relative to trifluoroacetic acid (external).

General Procedure for the Preparation of Benzylic α,α-Difluoro- and α-Monofluoronitriles and -tetrazoles. To a solution of the benzylic nitrile or tetrazole in anhydrous THF (approximately 5−10 mL of THF/mmol of nitrile or tetrazole) at −78 °C was added base (2.2 equiv for difluorination, 1.1 equiv for monofluorination) over a period of 2 min. The resulting orange to dark red solution was stirred for 1 h at −78 °C. A solution of NFSi (2.5 equiv for difluorination, 1.3 equiv for monofluorination) in anhydrous THF (approximately 2−4 mL of THF/mmol of NFSi) was added over 2 min, during which time the solution turned from dark red or orange to yellow-brown. After this addition, the solution was stirred for 2−3 h at −78 °C, during which time a precipitate may form. The reaction was quenched with 0.01 N HCl, and the resulting solution (precipitate dissolves) was extracted with $CHCl_3$. The combined organic layers were washed with 5% $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo to give a yellow residue. Purification was achieved using silica gel flash chromatography.

2,2-Difluoro-2-(2-naphthyl)acetonitrile (7). Column chromatography (silica, 8:2 hexane/CH_2Cl_2, $R_f = 0.5$) yielded pure **7** as a white solid in 50% yield using *t*-BuLi as base: mp 33−34 °C; ^1H NMR δ 8.22 (1 H, s), 7.91−8.04 (3 H, m), 7.63−7.70 (3 H, m); ^{19}F NMR δ −6.75; ^{13}C NMR δ 134.77, 132.11, 129.62, 128.86, 128.59, 128.21, 127.89, 127.53, 126.20 (t, $J = 6.3$ Hz), 120.62 (t, $J = 4.1$ Hz), 112.59 (t, $J = 48.3$ Hz), 109.15 (t, $J = 242.8$ Hz); MS *m*/*z* (relative intensity) 203 (100), 177 (64); HRMS calcd for $C_{12}H_7NF_2$ 203.0547, found 203.0555.

2-Fluoro-2-(2-naphthyl)acetonitrile (8). Column chromatography (silica, 8:2 hexane/CH_2Cl_2, $R_f = 0.4$) yielded pure **8** as a white solid in 60% yield using *t*-BuLi as base: mp 54−56 °C; ^1H NMR δ 8.03 (1 H, d, $J = 11.7$ Hz), 7.89−7.96 (3 H, m), 7.55−7.63 (3 H, m), 6.23 (1 H, d, $J = 46.9$ Hz, CHF); ^{19}F NMR δ −91.06 (d, $J = 47.3$ Hz); ^{13}C NMR δ 134.15 (d, $J = 2.2$ Hz), 132.59 (d), 129.51, 128.45 (d, $J = 1.5$ Hz), 128.43 (d, $J = 20.5$ Hz), 127.86, 127.81, 127.14, 123.52 (d, $J = 2.9$ Hz), 115.27 (d, $J = 33.7$ Hz), 80.31 (d, $J = 181.6$ Hz); MS *m*/*z* (relative intensity) 185 (100), 158 (29); HRMS calcd for $C_{12}H_8NF$ 185.0641, found 185.0641.

2,2-Difluoro-2-(1-naphthyl)acetonitrile (10). Column chromatography (silica, 8:2 hexane/CH_2Cl_2, $R_f = 0.5$) yielded pure **10** as a colorless oil in 46% yield using *t*-BuLi as base: ^1H NMR δ 8.28 (1 H, d, $J = 8.8$ Hz), 7.93−8.07 (3 H, m), 7.48−7.73 (3 H, m); ^{19}F NMR δ −6.73; ^{13}C NMR δ 133.98, 133.63, 129.13, 128.49, 128.08, 126.93, 126.00 (t, $J = 23.4$ Hz), 125.32 (t, $J = 8.1$ Hz), 124.19, 123.36 (t, $J = 2.6$ Hz), 112.76 (t, $J = 48.0$ Hz), 109.68 (t, $J = 243.5$ Hz); MS *m*/*z* (relative intensity) 203 (100), 153 (53); HRMS calcd for $C_{12}H_7NF_2$ 203.0546, found 203.0537.

2,2-Difluoro-2-(4-methylphenyl)acetonitrile (12). Column chromatography (silica, 6.5:3.5 hexane/CH_2Cl_2, $R_f = 0.5$) yielded pure **12** as a colorless oil in 44% yield using *t*-BuLi as base: ^1H NMR δ 7.56 (2 H, d, $J = 8.8$ Hz), 7.34 (2 H, d, $J = 7.4$ Hz), 2.44 (3 H, s, CH_3); ^{19}F NMR δ −6.79; ^{13}C NMR δ 143.18 (t, $J = 2.2$ Hz), 129.81, 128.49 (t, $J = 25.3$ Hz), 125.13 (t, $J = 5.1$ Hz), 112.68 (t, $J = 48.4$ Hz), 109.06 (t, $J = 242.4$ Hz), 21.37; MS *m*/*z* (relative intensity) 167 (99), 91 (100); HRMS calcd for $C_9H_7NF_2$ 167.0547, found 167.0546.

2,2-Difluoro-2-(2-methylphenyl)acetonitrile (14). Column chromatography (silica, 6.5:3.5 hexane/CH_2Cl_2, $R_f = 0.5$) yielded pure **14** as a colorless oil in 37% yield using *t*-BuLi as base: ^1H NMR δ 7.65 (1 H, d, $J = 7.3$ Hz), 7.37−7.49 (1 H, m), 7.33 (2 H, bm), 2.56 (3 H, s, CH_3); ^{19}F NMR δ −9.25; ^{13}C NMR δ 136.72 (bt), 132.45, 132.31 (bt), 129.14 (t, $J = 23.5$ Hz), 126.29, 125.76 (t, $J = 7.7$ Hz), 112.51 (t, $J = 48.4$ Hz), 109.14 (t, $J = 243.9$ Hz), 19.29; MS *m*/*z* (relative intensity) 167 (77), 140 (100); HRMS calcd for $C_9H_7NF_2$ 167.0547, found 167.0545.

2,2-Difluoro-2-(4-methoxyphenyl)acetonitrile (16). Column chromatography (silica, 6.5:3.5 hexane/CH_2Cl_2, $R_f = 0.5$) yielded pure **16** as a colorless oil in 34% yield using *t*-BuLi as base: ^1H NMR δ 7.60 (2 H, d, $J = 8.8$ Hz), 7.01 (2 H, d, $J = 8.8$ Hz), 3.88 (3 H, s, CH_3O); ^{19}F NMR δ −5.30; ^{13}C NMR δ 162.74, 126.99 (t, $J = 5.1$ Hz), 123.33 (t, $J = 25.6$ Hz), 114.51, 112.73 (t, $J = 49.1$ Hz), 109.03 (t, $J = 241.7$ Hz), 55.49; MS *m*/*z* (relative intensity) 183 (100), 157 (84); HRMS calcd for $C_9H_7ONF_2$ 183.0496, found 183.0493.

2,2-Difluoro-2-(3-methoxyphenyl)acetonitrile (18). Column chromatography (silica, 6.5:3.5 hexane/CH_2Cl_2, $R_f = 0.5$)

(15) For some examples of biologically active benzylic tetrazoles, see: Bleisch, T. J.; Ornstein, P. L.; Allen, N. K.; Wright, R. A.; Lodge, D.; Schoepp, D. D. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1161. Kogan, T. P.; Dupre, B.; Keller, K. M.; Scott, I. L.; Bui, H.; Market, R. V.; Beck, P. J.; Vogtus, J. A.; Revelle, B. M.; Scott, D. *J. Med. Chem.* **1995**, *38*, 4976. Al-Khamees, H. A.; Kandil, H. A.; El-Tahir, K. E. H.; Al-Attas, O. S.; Bayomi, S. M. *Sci. Pharm.* **1994**, *62*, 363. Kees, K. L.; Smith, T. M.; McCaleb, M. L.; Prozialeck, D. H.; Cheeseman, R. S.; Christas, J. A.; Patt, W. C.; Steiner, K. E. *J. Med. Chem.* **1992**, *35*, 944. Ornstein, P. L.; Schoepp, D. D.; Arnold, M. B.; Augenstein, N. K.; Lodge, D.; Millar, J. P.; Chambers, J.; Campbell, J.; Paschal, J. W.; Zimmerman, D. M.; Leander, J. D. *J. Med. Chem.* **1992**, *35*, 3547. Musser, J. H.; Kreft, A. F.; Bender, R. H. W.; Kubrak, D. M.; Grimes, D.; Carolson, R. P.; Hand, J. M.; Chang, J. *J. Med. Chem.* **1990**, *33*, 240. Huang, F.-C.; Galemmo, R. A.; Johnson, W. H.; Poli, G. B.; Morrisette, M. M.; Mencel, J. J.; Warus, J. P.; Campbell, H. F.; Nuss, G. W.; Carnathan, G. W.; van Inwegen, R. G. *J. Med. Chem.* **1990**, *33*, 1194. Gapinski, D. M.; Mallet, B. E.; Froelich, L. L.; Jackson, W. T. *J. Med. Chem.* **1990**, *33*, 2798. See also ref 13.

(16) Liotta, A. S.; Kole, H. K.; Fales, H. M.; Roth, J.; Bernier, M. *J. Biol. Chem.* **1994**, *269*, 22996. Desmarais, S.; Jia, Z.; Ramachandran, R. *Arch. Biochem. Biophys.* **1998**, *354*, 225.

(17) Sulfonates are completely ionized at physiological pH. Thus, any increase in inhibitor potency of α,α-difluorosulfonates compared to their nonfluorinated or sulfate counterparts would have to be a result of a direct interaction of the fluorines with residues in the enzyme active site, as appears to be the case with the α-difluorinated phosphonates and PTP's.

(18) For examples, see: (a) Selcer, K. W.; Hegde, P. V.; Li, P.-K. *Cancer Res.* **1997**, *57*, 702. (b) Anderson, C.; Freeman, J.; Lucas, L. H.; Farley, M.; Dalhoumi, H.; Widlanski, T. S. *Biochemistry* **1997**, *36*, 2586. (c) Howarth, N. M.; Purolit, A.; Reed, M. J.; Potter, B. V. L. *Steroids* **1997**, *62*, 346. (d) Li, P. K.; Pillai, R.; Dibbelt, L. *Steroids* **1995**, *60*, 299.

(19) Ruechardt, C.; Grundmeier, M. *Chem. Ber.* **1975**, *108*, 2448.

(20) Mulder, R. J.; van Leusen, A. M.; Strating, J. *Tetrahedron Lett.* **1967**, 3057. Truce, W. E. *Can. J. Chem.* **1969**, *47*, 860. King, J. F.; Durst, T. *J. Am. Chem. Soc.* **1965**, *87*, 5684.

yielded pure **18** as a colorless oil in 56% yield using *t*-BuLi as base: ^{1}H NMR δ 7.41−7.49 (1 H, m), 7.24 (1 H, s), 7.12 (2 H, bm), 3.87 (3 H, s, CH_3O); ^{19}F NMR δ −7.74; ^{13}C NMR δ 160.09, 132.45 (t, J = 24.9 Hz), 130.4, 118.28 (t, J = 1.9 Hz), 117.26 (t, J = 5.5 Hz), 112.51 (t, J = 48.4 Hz), 110.47 (t, J = 5.2 Hz), 108.65 (t, J = 243.2 Hz), 55.42; MS *m*/*z* (relative intensity) 183 (100), 152 (18); HRMS calcd for $C_9H_7ONF_2$ 183.0494, found 183.0487.

2,2-Difluoro-2-(3-phenylphenyl)acetonitrile (20). Column chromatography (silica, 6.5:3.5 hexane/CH_2Cl_2, R_f = 0.5) yielded pure **20** as a colorless oil in 47% yield using *t*-BuLi as base: ^{1}H NMR δ 7.81−7.88 (2 H, m), 7.60−7.65 (4 H, bm), 7.43−7.54 (3 H, m); ^{19}F NMR δ −7.54; ^{13}C NMR δ 142.65, 139.34, 131.84 (t, J = 25.3 Hz), 131.24, 129.73, 129.07, 128.87 (t, J = 7.3 Hz), 128.28, 127.20, 123.87 (t, J = 5.2 Hz), 112.57 (t, J = 48.0 Hz), 108.85 (t, J = 243.5 Hz); MS *m*/*z* (relative intensity) 229 (100), 152 (15); HRMS calcd for $C_{14}H_9NF_2$ 229.0703, found 229.0694.

2,2-Difluoro-2-(4-nitrophenyl)acetonitrile (22). Column chromatography (silica, 6.5:3.5 hexane/CH_2Cl_2, R_f = 0.5) yielded pure **22** as a colorless oil in 34% yield using NaHMDS as base: ^{1}H NMR δ 8.42 (2 H, d, J = 8.8 Hz), 7.91 (2 H, d, J = 8.8 Hz); ^{19}F NMR δ −9.09; ^{13}C NMR δ 150.31, 136.63 (t, J = 25.9 Hz), 126.82 (t, J = 4.8 Hz), 124.53, 111.59 (t, J = 47.0 Hz), 107.45 (t, J = 245.2 Hz); MS *m*/*z* (relative intensity) 198 (54), 152 (100); HRMS calcd for $C_8H_4O_2N_2F_2$ 198.0241, found 198.0241.

2-(4-Bromophenyl)-2,2-difluoroacetonitrile (24). Column chromatography (silica, 6.5:3.5 hexane/CH_2Cl_2, R_f = 0.5) yielded pure **24** as a colorless oil in 19% yield using LDA as base: ^{1}H NMR δ 7.70 (2 H, d, J = 8.8 Hz), 7.55 (2 H, d, J = 7.3 Hz); ^{19}F NMR δ −7.84; ^{13}C NMR δ 132.64, 130.30 (t, J = 25.7 Hz), 127.50 (t, J = 2.9 Hz), 126.84 (t, J = 4.8 Hz), 112.16 (t, J = 48.0 Hz), 108.39 (t, J = 243.5 Hz); MS *m*/*z* (relative intensity) 231 (100), 205 (63); HRMS calcd for $C_8H_4NF_2Br$ 230.9495, found 230.9489.

2-(*tert*-Butyl)-5-[difluoro(2-naphthyl)methyl]-2*H*-1,2,3,4-tetrazole (26). Column chromatography (silica, 6:4 CH_2Cl_2/pentane, R_f = 0.6) yielded pure **26** as a white solid in 56% yield using *t*-BuLi as base: mp 69−71 °C; ^{1}H NMR δ 8.20 (1 H, s), 7.86−7.96 (3 H, m), 7.73 (1 H, d, J = 8.8 Hz), 7.58 (2 H, m), 1.77 (9 H, s, $C(CH_3)_3$); ^{19}F NMR δ −16.10; ^{13}C NMR δ 162.48 (t, J = 34.4 Hz), 134.12, 132.42, 132.12 (t, J = 25.6 Hz), 128.81, 128.63, 127.75, 127.53, 126.79, 125.62 (t, J = 7.0 Hz), 122.41 (t, J = 5.1 Hz), 115.60 (t, J = 242.1 Hz), 65.07, 29.33; MS *m*/*z* (relative intensity) 302 (60), 177 (100); HRMS calcd for $C_{16}H_{16}N_4F_2$ 302.1343, found 302.1347.

2-(*tert*-Butyl)-5-[fluoro(2-naphthyl)methyl]-2H-1,2,3,4-tetrazole (27). Column chromatography (silica, 6:4 CH_2Cl_2/pentane, R_f = 0.5) yielded pure **27** as a white solid in 61% yield using *t*-BuLi as base: mp 75−77 °C; ^{1}H NMR δ 8.02 (1 H, s), 7.84−7.93 (3 H, m), 7.72 (1 H, d, J = 1.5 Hz), 7.49−7.54 (2 H, m), 6.93 (1 H, d, J = 45.8 Hz, CHF), 1.76 (9 H, s, $C(CH_3)_3$); ^{19}F NMR δ −93.78 (d, J = 45.7 Hz); ^{13}C NMR δ 163.73 (d, J = 26.4 Hz), 133.54 (d, J = 22.0 Hz), 133.48, 132.81, 128.54, 128.22, 127.64, 126.70, 126.39, 126.38 (d, J = 6.6 Hz), 123.93 (d, J = 5.1 Hz), 86.89 (d, J = 172.8 Hz), 64.36, 29.21; MS *m*/*z* (relative intensity) 284 (50), 56 (100); HRMS calcd for $C_{16}H_{17}N_4F$ 284.1437, found 284.1439.

5-[Difluoro(2-naphthyl)methyl]-2*H*-1,2,3,4-tetrazole (28). A suspension of **7** (100 mg, 0.49 mmol) and NaN_3 (0.035 g, 1.1 equiv) in anhydrous DMF (5 mL) was stirred under argon for 3 h at 65 °C. While still hot the solution was filtered and concentrated in vacuo. The crude product was then HPLC purified, yielding **28** as a white solid (sodium salt) in near quantitative yield: ^{1}H NMR δ CD_3OD) δ 8.07 (1 H, s), 7.89−7.97 (3 H, bm), 7.53−7.66 (3 H, m); ^{19}F NMR δ CD_3OD) δ −10.89; ^{13}C NMR (CD_3OD) δ 161.18 (t, J = 32.6 Hz), 135.41, 135.24 (t, J = 27.1 Hz), 133.91, 129.69, 129.47, 128.74, 128.42, 127.80, 126.37 (t, J = 6.6 Hz), 123.58 (t, J = 4.8 Hz), 119.01 (t, J = 238.4 Hz); negative ion FABMS *m*/*z* (relative intensity) 245 (100).

5-[Difluoro(3-biphenyl)methyl]-2*H*-1,2,3,4-tetrazole (29). Prepared using the same procedure as described for **28** from nitrile **20** in near-quantitative yields: ^{1}H NMR (D_2O) δ 7.38−7.80 (9 H, m); ^{19}F NMR δ D_2O) δ −11.69; ^{13}C NMR (D_2O) δ 161.32 (bt), 141.85, 140.23, 136.85 (t, J = 26.7 Hz), 130.15, 129.93, 129.73, 128.65, 127.66, 125.09 (t, J = 5.9 Hz), 124.40 (t, J = 5.1 Hz), 118.32 (t, J = 239.1 Hz); negative ion FABMS *m*/*z* (relative intensity) 271 (100).

General Procedure for the Preparation of Benzylic α,α-Difluoro- and α-Monofluorosulfonate Esters. To a solution of benzylic sulfonate ester in anhydrous THF (approximately 5 mL of THF/mmol of ester) at −78 °C was added base (1.1 equiv) over a period of 2 min, and the mixture was stirred for 30 min at −78 °C. A solution of NFSi (1.15 equiv) in anhydrous THF (approximately 5 mL of THF mmol NFSi) was added dropwise over 2 min. The mixture was stirred at −78 °C for 1 h, and the process was repeated (1.1 equiv of base, 1.15 equiv of NFSi). The reaction was quenched with water and extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and concentrated, and the desired product was obtained by silica gel chromatography. α-Monofluorinated derivatives can be prepared by omitting the second fluorination step. The α,α-difluorinated products can also be obtained by performing the fluorination in a single step in a manner similar to that described above for the fluorination of the nitriles and tetrazoles; however, the yields tend to be slightly lower compared with the stepwise procedure.

Neopentyl Difluoro(phenyl)methanesulfonate (31). Column chromatography (5:95 EtOAc/hexane, R_f = 0.3) of the crude residue yielded pure **31** as a yellow oil in 81% yield with *t*-BuLi as base: ^{1}H NMR δ 7.72 (2 H, m), 7.55 (3 H, m), 4.11 (2 H, s), 1.01 (9 H, s); ^{19}F NMR δ −24.40 (s); ^{13}C NMR (50 MHz) δ 132.29, 128.63, 127.10, 121.11 (t, J = 283.7 Hz), 83.98, 31.99, 25.80; MS *m*/*z* (relative intensity) 278 (12), 189 (100); HRMS calcd for $C_{12}H_{16}F_2O_3S$ 278.0788, found 278.0780.

Neopentyl Monofluoro(phenyl)methanesulfonate (32). Column chromatography (5:95 EtOAc/hexane, R_f = 0.27) of the crude residue yielded pure **32** as a white solid in 89% yield using *t*-BuLi as base: mp 33−34 °C; ^{1}H NMR δ 7.59 (2 H, m), 7.51 (3 H, m), 6.20 (1 H, d, J = 45.5 Hz), 4.01 (2 H, s), 0.99 (9 H, s); ^{19}F NMR δ −98.67 (d, J = 45.5 Hz); ^{13}C NMR (50 MHz) δ 130.92, 128.68, 127.74, 127.61, 100.50 (d, J = 217.8 Hz), 82.26, 31.88, 25.89; MS *m*/*z* (relative intensity) 109 (100), 55 (27); HRMS calcd for C_7H_6F 109.0453, found 109.0449.

Neopentyl Difluoro(4-nitrophenyl)methanesulfonate (34). Column chromatography (7:93 EtOAc/hexane, R_f = 0.35) of the crude residue yielded pure **34** as a white solid in 86% yield using NaHMDS as base: mp 64−65 °C; ^{1}H NMR δ 8.37 (2 H, d, J = 8.1 Hz), 7.91 (2 H, d, J = 8.1 Hz), 4.19 (2 H, s), 1.03 (9 H, s); ^{19}F NMR δ −25.30; ^{13}C NMR (50 MHz) δ 150.55, 134.18 (t, J = 22.4 Hz), 128.59, 123.75, 120.00 (t, J = 284.6 Hz), 84.83, 32.08, 25.75; MS *m*/*z* (relative intensity) 375 (6), 172 (100); HRMS calcd for $C_7H_4F_2NO_2$ 172.0210, found 172.0219.

Neopentyl Difluoro(4-bromophenyl)methanesulfonate (36). Column chromatography (5:95 EtOAc/hexane, R_f = 0.5) of the crude residue yielded pure **36** as a pale yellow solid in 79% yield using LDA as base: mp 46−46.5 °C; ^{1}H NMR δ 7.65 (2 H, d, J = 8.8 Hz), 7.56 (2 H, d, J = 8.8 Hz), 4.13 (2 H, s), 1.01 (9 H, s); ^{19}F NMR δ −24.70; ^{13}C NMR (50 MHz) δ 132.09, 128.68 (t, J = 6.0 Hz), 127.41, 120.79 (t, J = 283.7 Hz), 84.18, 32.07, 25.80; MS *m*/*z* (relative intensity) 205 (100), 126 (70); HRMS calcd for $C_7H_4F_2Br$ 204.9464, found 204.9458.

Neopentyl Difluoro(4-methylphenyl)methanesulfonate (38). Column chromatography (1:4 CH_2Cl_2/hexane, R_f = 0.25) of the crude residue yielded pure **38** as a white solid in 76% yield using LDA as base: mp 43−43.5 °C; ^{1}H NMR δ 7.60 (2 H, d, J = 8.1 Hz), 7.31 (2 H, d, J = 8.1 Hz), 4.11 (2 H, s), 2.42 (3 H, s), 1.02 (9 H, s); ^{19}F NMR δ −23.96; ^{13}C NMR δ 143.08, 129.45, 127.05 (t, J = 5.5 Hz), 121.51 (t, J = 283.6 Hz), 83.98, 32.08, 25.91, 21.34; MS *m*/*z* (relative intensity) 141 (100), 142 (17); HRMS calcd for $C_8H_7F_2$ 141.0516, found 141.0514.

Neopentyl Difluoro(3-phenylphenyl)methanesulfonate (40). Column chromatography (5:95 EtOAc/hexane, R_f = 0.4) of the crude material yielded pure **40** as a colorless oil in 59% yield using *t*-BuLi as base: ^{1}H NMR δ 7.45−7.94 (9 H, m), 4.17 (2 H, s) 1.04 (9 H, s); ^{19}F NMR δ −24.15; ^{13}C NMR δ 142.15, 139.76, 130.94, 129.08, 128.94, 128.03, 127.21, 125.86, 125.77, 121.17 (t, J = 283.7 Hz), 84.05, 32.03, 25.86; MS *m*/*z* (relative intensity) 203 (100), 204 (23), 354 (9); HRMS calcd for $C_{18}H_{20}F_2O_3S$ 354.1101, found 354.1104.

Neopentyl Difluoro(2-naphthyl)methanesulfonate (42). Column chromatography (5:95 EtOAc/hexane, R_f = 0.5) of the crude residue yielded pure **42** as a white solid in 86% yield using *t*-BuLi as base: mp 55−55.5 °C; ^{1}H NMR δ 8.26 (1 H, s), 7.77−7.99 (3 H, m), 7.72−7.75 (1 H, m), 7.58−7.63 (2 H, m), 4.18 (2

H, s), 1.03 (9 H, s); ^{19}F NMR δ −23.63; ^{13}C NMR δ 135.02, 132.38, 128.94, 128.72, 128.37, 128.14, 127.83, 127.14, 122.66, 121.44 (t, J = 283.7 Hz), 83.98, 31.99, 25.84; MS m/z (relative intensity) 328 (5), 177 (100); HRMS calcd for $C_{16}H_{18}F_2O_3S$ 328.0945, found 328.0941.

Lithium Difluoro(3-phenylphenyl)methanesulfonate (43). A solution of **40** (200 mg, 0.56 mmol, 1.0 equiv) and LiBr (53 mg, 0.62 mmol, 1.1 equiv) in butanone (5 mL) was refluxed for 48 h. The solution was evaporated to dryness, and water (10 mL) was poured in. The solution was washed with CH_2Cl_2 (3 × 15 mL), and the aqueous layer was lyophilized. The crude residue was purified by HPLC to give the pure **43** as a white solid in 88% yield: mp 174−175 °C; ^{1}H NMR (D_2O) δ 7.71 (1 H, s), 7.52 (1 H, d, J = 5.9 Hz), 7.07−7.17 (4 H, m), 6.86−6.93 (3 H, m); ^{19}F NMR (D_2O) δ −24.74; ^{13}C NMR (D_2O) δ 156.03, 154.65, 146.81 (t, J = 22.9 Hz), 144.73, 144.06, 142.93, 141.97, 140.78, 140.11, 135.71 (t, J = 276.4 Hz); negative ion FABMS m/z (relative intensity) 283 (100).

Lithium Difluoro(2-naphthyl)methanesulfonate (44). **44** was prepared from **42** in the same manner as described for **43**. HPLC purification of the crude residue yielded pure **44** as a white solid in 92% yield: mp 263−265 °C; ^{1}H NMR (D_2O) δ 7.89 (1 H, s), 7.48 (1 H, d, J = 7.3 Hz), 7.27 (2 H, t, J = 8.8 Hz), 7.04 (1 H, d, J = 5.9 Hz), 6.78 (2 H, m); ^{19}F NMR (D_2O) δ −24.25; ^{13}C NMR (D_2O) δ 149.32, 147.26, 143.82, 143.51, 143.09, 142.86, 142.64, 142.49, 142.35, 142.18, 138.20, 136.03 (t, J = 276.8 Hz); negative ion FABMS m/z (relative intensity) 257 (100).

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada and Merck Frosst Canada for financial support.

Supporting Information Available: ^{1}H, ^{13}C, ^{19}F (when applicable) NMR spectra for compounds **7**, **8**, **10**, **12**, **14**, **16**, **18**, **20**, **22**, **24**−**29**, and **31**−**44**, HPLC procedures and chromatograms for **28**, **29**, **43**, and **44**, procedures for the synthesis of tetrazole **25** and sulfonate esters **33**, **35**, **37**, **39**, and **41** (88 pages). This material is contained in libraries on microfiche, immediately following this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO981163X