# Optimization of a Tertiary Alcohol Series of Phosphodiesterase-4 (PDE4) Inhibitors: Structure−Activity Relationship Related to PDE4 Inhibition and Human Ether-a-go-go Related Gene Potassium Channel Binding Affinity

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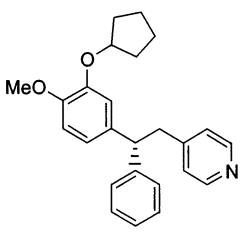
A SAR study on the tertiary alcohol series of phosphodiesterase-4 (PDE4) inhibitors related to **1** is described. In addition to inhibitory potency against PDE4 and the lipopolysaccharide-induced production of TNFα in human whole blood, the binding affinity of these compounds for the human ether-a-go-go related gene (hERG) potassium channel (an in vitro measure for the potential to cause QTc prolongation) was assessed. Four key structural moieties in the molecule were studied, and the impact of the resulting modifications in modulating these activities was evaluated. From these studies, (+)-**3d** (L-869,298) was identified as an optimized structure with respect to PDE4 inhibitory potency, lack of binding affinity to the hERG potassium channel, and pharmacokinetic behavior. (+)-**3d** exhibited good in vivo efficacy in several models of pulmonary function with a wide therapeutic index with respect to emesis and prolongation of the QTc interval.

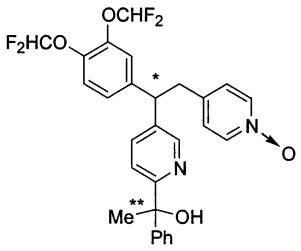
## Introduction

Of the family of phosphodiesterases (PDE) responsible for the hydrolysis of cAMP and cGMP, the cAMP-specific PDE4 isozymes are abundant in inflammatory and immune cells.[1,2] The inhibition of PDE4 not only results in the down-regulation of inflammatory cell activity in vitro[2,3] but also has been found to be generally anti-inflammatory and bronchodilatory in animal models.[3,4] Several selective PDE4 inhibitors have proceeded to the clinic and show promising efficacy for asthma and chronic obstructive pulmonary disease.[5−8] One such compound, CDP-840,[7] was shown to significantly reduce the bronchoconstriction induced by antigen in asthmatic patients but was discontinued in phase IIa.

In previous communications,[9,10] we have described the medicinal chemistry efforts undertaken to improve upon the lead compound CDP-840 with respect to PDE4 inhibitory potency, metabolism issues, and pharmacokinetic properties, culminating in the identification of tertiary alcohol **1**.[11] **1** exhibited excellent in vitro and in vivo profiles and was considered for development. However, while cardiovascular pharmacology studies were carried out, it was observed that iv treatment of anesthetized dogs with **1** resulted in a significant prolongation of the QTc interval. At a dose of 3 mg/kg, a +8.9% prolongation of the QTc interval was observed, with drug plasma levels of 2−5 μM being attained (vide infra; see Table 3). Since prolongation of the QTc interval has been linked to a predisposition of individuals to exhibit ventricular "torsade de pointes" arrhythmia,[12−15] it was imperative to continue our chemistry efforts to identify potent and nonemetic PDE4 inhibitors that were devoid of this ancillary cardiac activity. Herein, we report the SAR studies that we have conducted to address this issue in the tertiary alcohol series of PDE4 inhibitors related to **1**.




**CDP-840**




**1**

## Chemistry

In general, the syntheses of compounds **2**−**4** (Table 1) are analogous to methods that we have previously described[9−11] for the preparation of this class of molecule and are illustrated in Schemes 1−6.

The initial reactions (Schemes 1−3 and 6) involved the addition of an aromatic anion to the requisite aldehyde **5** to provide the racemic secondary alcohols **6**, **13**, **18**, and **26**. The aromatic anions used were those derived from n-BuLi mediated lithium halogen exchange of the bromide at C5 of 2,5-dibromopyridine (Scheme

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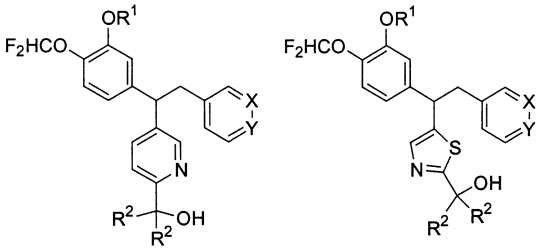
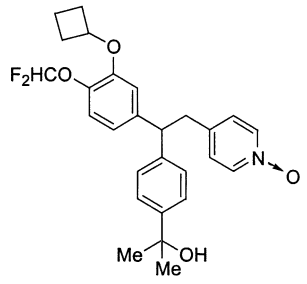


**2** **3**



**4**

1),[16] the pyridyl bromide **12** (Scheme 2), and the aryl bromide **25** (Scheme 6). Alternatively, direct deprotonation at C5 of the 2-(trimethylsilyl)ethoxymethyl (SEM) protected 2-thiazolyl tertiary alcohols **17** (Scheme 3) with n-BuLi provided the corresponding 5-lithiothiazolyl anions.[17]

As shown in Scheme 1, conversion of the racemic alcohols (±)-**6** into the chlorides (±)-**7** with thionyl chloride followed by reaction with the potassium enolate derived from deprotonation of ethyl 4-pyridylacetate with potassium hexamethyldisilylamide (KHMDS) provided intermediate esters (±)-**8** that were hydrolyzed and decarboxylated upon workup to afford racemic triaryls (±)-**9**. Bromopyridine (±)-**9** was functionalized by palladium-catalyzed carbonylation[18] followed by selective oxidation of the monosubstituted pyridine with magnesium monoperoxyphthalate hexahydrate (MMPP) to provide esters (±)-**11**. The racemic tertiary alcohols (±)-**2a**,**b** were then prepared by reaction of (±)-**11** with excess methyl Grignard reagent. Enantiomerically pure inhibitors were obtained by HPLC separation of the racemates using a chiral column. Depending on the compound in question, this separation was accomplished at various stages in the synthesis as dictated by the ease of separation of the two enantiomers on the chiral column. For example, in the case of (±)-**2a**, this separation was carried out on the final product, while in the case of **2b**, the separation was more easily achieved at the stage of (±)-**10b**. It should be noted in this latter case that the more potent enantiomer of **10b** with respect to PDE4 inhibition (data not shown) was carried on to the final product (+)-**2b**.

In a similar fashion, the alcohol (±)-**13** (Scheme 2) was converted into the corresponding chloride (±)-**14** and was then alkylated/decarboxylated as described above to afford the racemic triaryl (±)-**15**. Pyridine oxidation with MMPP, followed by removal of the SEM protecting group with trifluoroacetic acid (TFA) provided (±)-**2c**. Enantiomer separation was realized on the final product using HPLC.

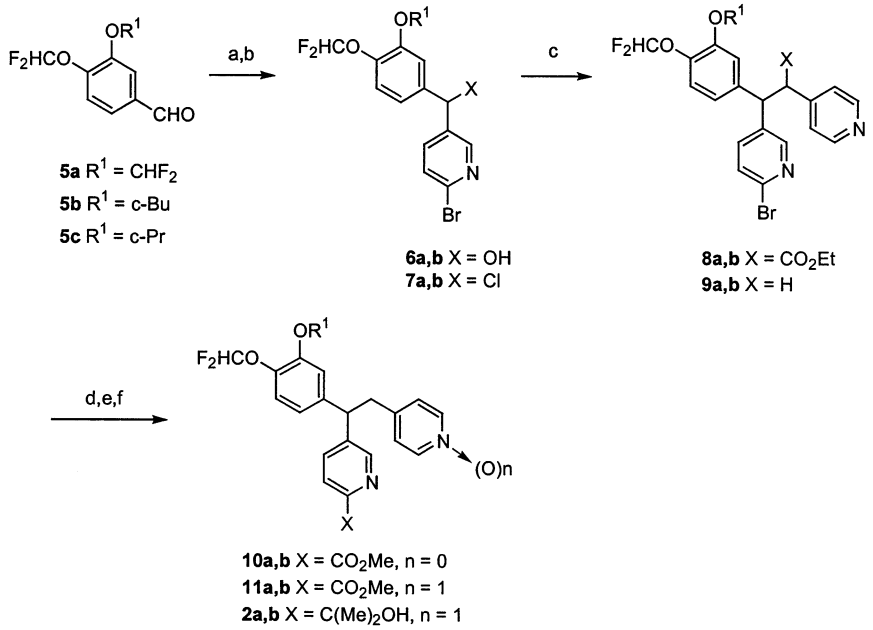
Subjection of the alcohols (±)-**18** (Scheme 3) to a sequence of reactions similar to those described in

**Table 1.** Tertiary Alcohol Phosphodiesterase-4 Inhibitors **2** and **3**

| compd | $R^1$ | $R^2$ | X | Y |
|---|---|---|---|---|
| (+)- and (−)-**2a** | $CHF_2$ | Me | CH | NO |
| (+)-**2b** | c-Bu | Me | CH | NO |
| (+)- and (−)-**2c** | c-Pr | Me | CH | NO |
| (+)- and (−)-**2d** | c-Pr | Me | NO | CH |
| (+)-**2e**[a] | c-Pr | Me | NH | CO |
| (+)-**3a** | c-Bu | Me | CH | NO |
| (±)-**3b** | c-Bu | $CF_3$ | CH | NO |
| (±)-**3c** | c-Pr | $CF_3$ | CH | NO |
| (+)- and (−)-**3d** | c-Pr | $CF_3$ | NO | CH |

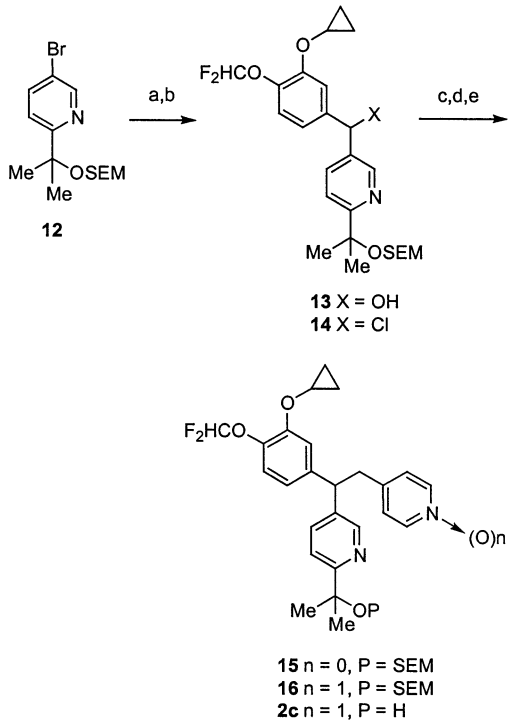
[a] This is the 5-pyridin-2-one.

**Scheme 1**[a]



[a] Reagents: (a) 2,5-dibromopyridine, n-BuLi, $Et_20$, −70 °C, 70−90%; (b) $SOCl_2$, $CH_2Cl_2$; (c) KHMDS, HMPA, ethyl 4-pyridylacetate, THF; LiOH, THF, MeOH, 65 °C; HCl, 91−92% (from **6**); (d) CO(g), $Pd(OAc)_2$, dppf, MeOH, DMF, 50 °C, 91−96%; (e) MMPP, $CH_2Cl_2$, MeOH, 73−77%; (f) MeMgBr, THF, 73−78%.

**Scheme 2**[a]

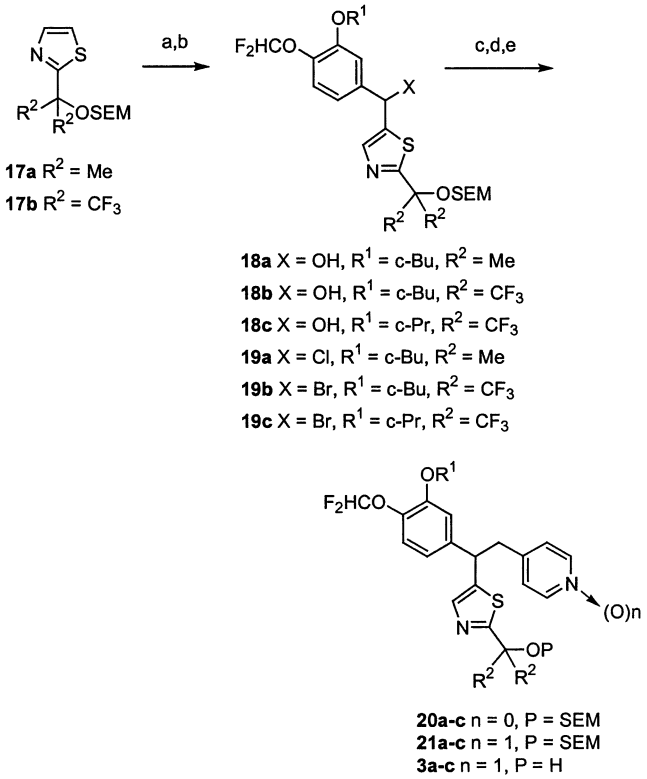



[a] Reagents: (a) n-BuLi, THF, −100 °C; **5c**, 100%; (b) $SOCl_2$, pyridine, PhMe; (c) KHMDS, HMPA, ethyl 4-pyridyl acetate, THF; LiOH, THF, MeOH, 60 °C; HCl, 86% (from **13**); (d) MMPP, $CH_2Cl_2$, MeOH; (e) TFA, $CH_2Cl_2$, 53% (from **15**).

Scheme 2 provided the inhibitors **3a**−**c**. It should be noted that although chloride (±)-**19a** was cleanly alkylated with the anion derived from ethyl 4-pyridylacetate by KHMDS deprotonation, it was observed that the alkylations of the secondary chlorides derived from alcohols (±)-**18b**,**c** with the same anion were rather sluggish. In these examples, a more facile alkylation reaction ensued upon conversion of the alcohols (±)-**18b**,**c** to the more reactive bromides (±)-**19b**,**c**. While both (±)-**3b** and (±)-**3c** were obtained and tested as racemates, (+)-**3a** was obtained enantiomerically pure. In this case, the enantiomers of (±)-**20a** were separated by HPLC and the more potent enantiomer of **20a** with respect to PDE4 inhibition (data not shown) was carried on to the final product (+)-**3a**.

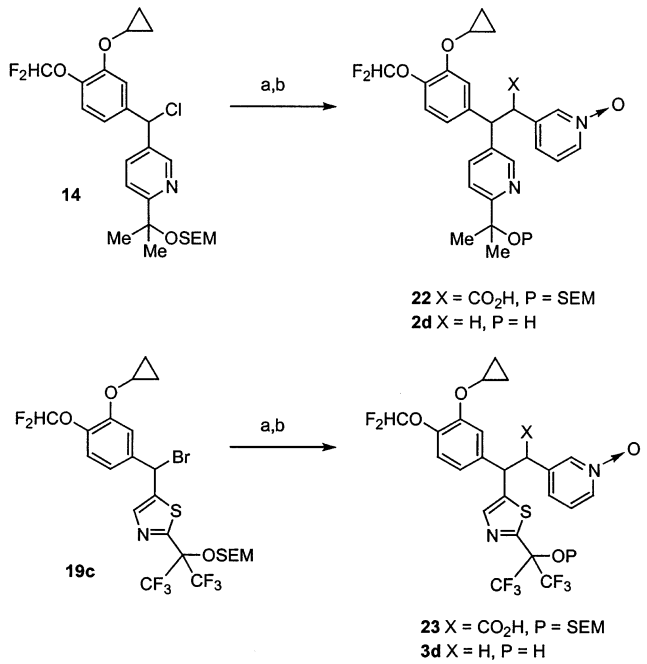
The preparation of the 3-pyridyl *N*-oxides (±)-**2d** and (±)-**3d** (Scheme 4) utilized somewhat modified conditions compared to the 4-pyridyl *N*-oxide series. Since decarboxylation of the acid intermediates in the 3-pyridyl series required harsher conditions than were used in the 4-pyridyl series, we chose to install the 3-pyridine *N*-oxide at an earlier stage to facilitate the decarboxylation process. Although the anion derived from ethyl 3-pyridylacetate *N*-oxide by KHMDS deprotonation cleanly alkylated the pyridyl chloride (±)-**14**, in the thiazole series, the use of the thiazolyl bromide (±)-**19c** rather than the corresponding chloride was required for a successful alkylation reaction. After hydrolysis of the initially formed esters, the acids (±)-**22** and (±)-**23** were decarboxylated in hot DMSO with concomitant removal of the SEM protecting groups. Enantiomer separation was achieved by HPLC on the final product in each case to provide inhibitors (+)-**2d**, (−)-**2d**, (+)-**3d**, and (−)-**3d**.

**Scheme 3**[a]




[a] Reagents: (a) n-BuLi, **5b** or **5c**, $Et_20$, −78°C, 72−94%; (b) $SOCl_2$ or $SOBr_2$, pyr, PhMe; (c) KHMDS (for **19a**,**c**) or NaHMDS (for **19b**), HMPA, ethyl 4-pyridylacetate, THF; LiOH, THF, MeOH, 65 °C; HCl, 20−86% (from **18**); (d) MMPP, $CH_2Cl_2$, MeOH, 48−92%; (e) TFA, $CH_2Cl_2$, 75−85%.

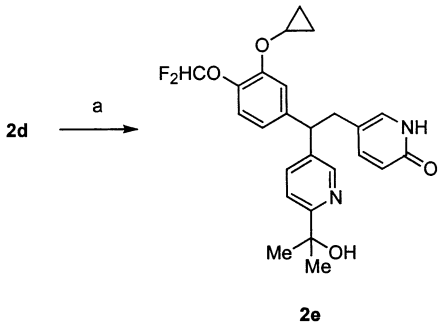
**Scheme 4**[a]




[a] Reagents: (a) KHMDS, HMPA, ethyl 3-pyridylacetate *N*-oxide, THF; LiOH, THF, MeOH, $H_2O$; (b) DMSO, 130 °C, 39−70% (from **14** or **19c**).

The 3-pyridyl *N*-oxide (+)-**2d** was converted to the pyridone (+)-**2e** (Scheme 5), with ~5:1 regioselectivity, by treatment with trifluoroacetic anhydride and triethylamine.[19]

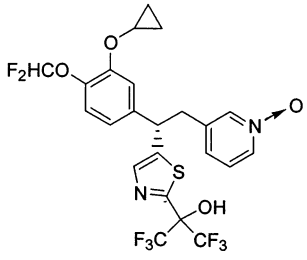
**Scheme 5**[a]



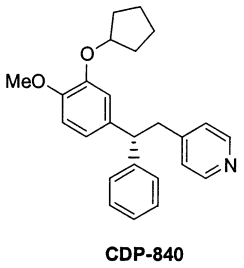

[a] Reagents: (a) TFAA, $Et_3N$, THF, 0−25 °C, 50%.

The synthesis of the inhibitor (±)-**4** is outlined in Scheme 6. According to procedures similar to those described above, the alcohol (±)-**26** was converted into the chloride (±)-**27** and then alkylated/decarboxylated to afford alcohol (±)-**28**. Desilylation occurred simultaneously under the conditions of decarboxylation. $KMnO_4$-mediated oxidation of the benzylic alcohol, followed by esterification of the resulting benzoic acid (±)-**29** provided the ester (±)-**30**. Inhibitor (±)-**4** was obtained by MMPP oxidation of the pyridyl alcohol (±)-**31** obtained upon treatment of (±)-**30** with excess methyl Grignard reagent.

The absolute configuration of (+)-**3d** was assigned as (*S*)-**3d** by X-ray crystallographic analysis.[20] (*S*)-**3d** and




(S)-(+)-3d



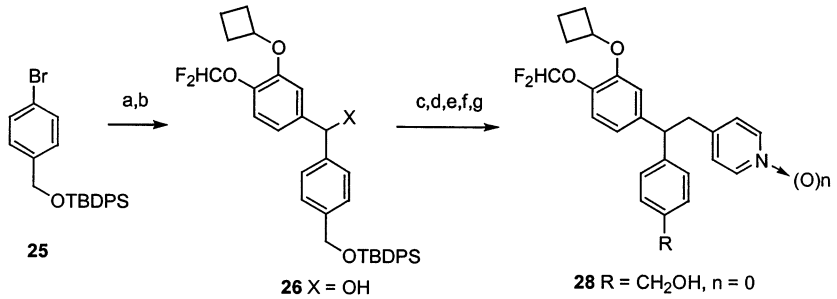

CDP-840

CDP-840 are configured so that when drawn as shown above, the thiazolyl and unsubstituted phenyl moieties, respectively, both project into the page. In the case of CDP-840, this absolute stereochemistry is identified as (*R*) due to the rules of nomenclature. While the absolute configurations of the other more potent enantiomers of resolved inhibitors have not been assigned, we speculate that they are the same as CDP-840 and (*S*)-**3d**.

## In Vitro Studies

Recently, it has been shown that a variety of drugs that exhibit prolongation of the QTc interval tend to preferentially block the voltage-gated potassium ($K^+$) channel encoded by the human ether-a-go-go related gene (hERG).[21−26] The hERG channel is the ion channel implicated in the normal repolarization of the ventricle by the delayed rectifier potassium current $I_{Kr}$.[27−31] MK-499, a methanesulfonanilide class III antiarrhythmic drug that exhibits QTc interval prolongation in dogs,[32] displays good binding affinity for the hERG $K^+$ channel.[22] As a result, a MK-499 displacement binding assay[33] has been developed to rapidly screen compounds for their hERG binding affinity.[15,34−36] Indeed, **1** exhibits a relatively potent binding affinity in this assay ($K_i$ = 1.18 $\mu$M). Owing to the correlation between the prolongation of the QTc interval observed with **1** in vivo in dogs and the potency of **1** in the hERG binding assay, we have taken the binding affinity for the hERG $K^+$ channel as measured in the MK-499 binding assay as an in vitro indicator for the potential for causing QTc interval prolongation. Therefore, our efforts focused on identifying those portions of the molecule that could be modified in such a way to decrease the affinity for the hERG $K^+$ channel while maintaining or improving the inhibitory potency against PDE4. Four moieties of **1**, amenable to modification, were identified for studying this relationship, namely, the tertiary alcohol substituents, the 3-alkoxy substituent of the catechol moiety, the 2,5-disubstituted pyridine bearing the tertiary alcohol, and the 4-pyridyl *N*-oxide. Tertiary alcohols **2**, **3** (Table 1), and **4** were prepared, and the in vitro inhibition of the PDE4A enzyme[37] by these compounds is presented in Table 2. These compounds are essentially nonselective with respect to the inhibition of the PDE4 isozymes (less than a 2-fold difference in the $IC_{50}$ values of inhibition of PDE4A compared to PDE4B, PDE4C, and PDE4D; data not shown), and therefore, only the inhibitory potency against PDE4A was tabulated. Also tabulated is the inhibition of TNFα production in LPS-stimulated human whole blood (HWB)[38] and the binding affinity of the compounds for hERG as measured in the

**Scheme 6**[a]




[a] Reagents: (a) n-BuLi, THF, −78°C; **5b**, 62%; (b) $SOCl_2$, pyr, PhMe; (c) KHMDS, HMPA, ethyl 4-pyridylacetate, THF; LiOH, THF, MeOH, 65 °C; HCl, 41% (three steps); (d) $KMnO_4$, acetone, 72%; (e) $CH_2N_2$, MeOH, 70%; (f) MeMgBr, $CH_2Cl_2$, −78 to 25 °C, 93%; (g) MMPP, $CH_2Cl_2$, MeOH, 61%.

**Table 2.** Biological Data for the Phosphodiesterase-4 Inhibitors[a]

| entry | compd | GST-PDE4A$^{248}$ $IC_{50}$ [b] (nM) | HWB $IC_{50}$ [c] ($\mu$M) | hERG binding $K_i$ [d] ($\mu$M) | rat $t_{1/2}$ [e] (h) |
|---|---|---|---|---|---|
| 1 | **1** | 2.1 ± 0.4 (8) | 0.16 ± 0.04 (15) | 1.18 ± 0.16 (3) | |
| 2 | (−)-**2a** | 35 ± 5 (6) | 0.64 ± 0.11 (17) | 22.7 ± 3.6 (3) | |
| 3 | (+)-**2a** | 520 ± 35 (3) | 9.01 ± 1.82 (5) | 25.4 ± 8.2 (3) | |
| 4 | (+)-**2b** | 1.0 ± 0.1 (5) | 0.12 ± 0.02 (15) | 25.0 ± 3.0 (4) | 1.4 |
| 5 | (+)-**2c** | 1.2 ± 0.3 (3) | 0.06 ± 0.02 (9) | 41.5 ± 13.6 (3) | |
| 6 | (−)-**2c** | 55 ± 17 (3) | 3.52 ± 0.56 (6) | 26.4 ± 3.7 (3) | |
| 7 | (+)-**2d** | 2.1 ± 0.2 (3) | 0.20 ± 0.04 (6) | 42.2 ± 0.2 (3) | |
| 8 | (−)-**2d** | 334 ± 12 (3) | 17.9 ± 5.70 (6) | 44.7 ± 5.9 (3) | |
| 9 | (+)-**2e** | 0.7 ± 0.1 (3) | 0.06 ± 0.02 (9) | 55.9 ± 13.5 (3) | |
| 10 | (±)-**4** | 1.6 ± 0.8 (3) | 0.26 ± 0.04 (9) | 22.4 ± 11.1 (3) | |
| 11 | (+)-**3a** | 0.5 ± 0.2 (3) | 0.09 ± 0.02 (9) | 58.4 ± 1.9 (4) | 1 |
| 12 | (±)-**3b** | 0.8 ± 0.2 (3) | 0.02 ± 0.00 (9) | 38.1 ± 6.2 (3) | 2 |
| 13 | (±)-**3c** | 0.4 ± 0.03 (3) | 0.02 ± 0.00 (6) | 21.0 ± 3.3 (3) | 10 |
| 14 | (+)-**3d** | 0.5 ± 0.1 (4) | 0.09 ± 0.02 (18) | 61.4 ± 15.1 (3) | 5 |
| 15 | (−)-**3d** | 48 ± 13 (3) | 2.64 ± 0.60 (3) | 39.0 ± 1.2 (3) | |
| 16 | CDP-840 | 4.3 ± 0.2 (155) | 16.2 ± 2.3 (12) | | |
| 17 | SB207499 | 38 ± 2 (91) | 18.0 ± 6.1 (18) | | |

[a] For all in vitro assays, each value is reported as the mean ± SEM (*n* value in parentheses). [b] Assayed against the human PDE4A isoform using a construct representing the common region of spliced variants expressed as a GST-fusion protein in Sf9 cells. See ref 37. [c] Inhibition of LPS-induced TNFα production in human whole blood. See ref 38. [d] Displacement binding assay of [$^{35}$S]-radiolabeled MK-499 in membranes derived from HEK 293 cells stably transfected with the hERG gene and expressing the $I_{Kr}$ channel protein. See ref 33. [e] See Experimental Section.

MK-499 binding assay.[33] For selected compounds, the apparent half-life was measured in rats, and these data are also listed. Also tabulated for comparison purposes are the PDE4A inhibitory potencies of CDP-840[7] and SB207499 (Ariflo).[5]

First, it is interesting to note that while the PDE4A inhibitory potency is greatly affected by the absolute configuration of the inhibitor, the $K_i$ for binding to hERG as measured in the MK-499 binding assay is surprisingly[24] unaffected by absolute stereochemistry. For example, consider the four enantiomeric pairs of inhibitors found in entries 2/3, 5/6, 7/8 and 14/15. In each case, one of the enantiomers is at least an order of magnitude more potent in inhibiting PDE4A compared to the alternative enantiomer, but both enantiomers exhibit similar $K_i$ values for hERG binding. In fact, for those enantiomeric pairs where there is a difference in hERG binding, the enantiomer that is the less potent PDE4A inhibitor is the more potent $K^+$ channel binder but by less than 2-fold (entries 5/6 and 14/15). Therefore, for the unresolved inhibitors (±)-**4**, (±)-**3b**, and (±)-**3c** (entries 10, 12, and 13), although the PDE4A inhibitory potency may be somewhat underestimated relative to the active enantiomer, the MK-499 binding activity of the racemate is not expected to be significantly different from that of the active enantiomer. As a result, the racemates were used in these examples for comparison purposes.

**1** is a potent inhibitor of PDE4A (entry 1), but it also has a fairly high affinity for the hERG channel ($K_i$ = 1.18 $\mu$M). Replacement of the tertiary alcohol phenyl moiety in **1** with a small alkyl group ((−)-**2a**, $R^2$ = Me) resulted in a 15-fold decrease in inhibitory potency against PDE4A (entry 2). However, this was accompanied by a corresponding 20-fold decrease in affinity for hERG. Thus, it appears that a decrease in lipophilicity in this part of the molecule is advantageous in terms of loss of hERG binding affinity but is also detrimental to PDE4A inhibitory potency.

It was known from previous unpublished studies that replacement of the 3-difluoromethoxy moiety with small alkoxy substituents tended to result in more potent PDE4 inhibitors. Thus, while the dimethyl tertiary alcohol moiety of (−)-**2a** was retained, the cyclobutyloxy ((+)-**2b**) and cyclopropyloxy ((+)-**2c**) analogues of (−)-**2a** were prepared (entries 4 and 5). In both cases, and in comparison to (−)-**2a**, a dramatic 30-fold improvement in PDE4A inhibitory potency is observed. In addition, both compounds retain poor binding affinity ($K_i \geq 25$ $\mu$M) for hERG. Thus, in the pyridinedimethylcarbinol series, the ordering of substituents at this position with respect to hERG binding affinity is observed to be $CHF_2 \sim$ c-Bu > c-Pr.

The next area for SAR studies involved replacement of the 4-pyridyl *N*-oxide moiety while maintaining the cyclopropyloxy and dimethyl tertiary alcohol moieties of (+)-**2c**. In the event, preparation of the regioisomeric 3-pyridyl *N*-oxide analogue (+)-**2d** and the pyridone analogue (+)-**2e** provided compounds comparable to (+)-**2c** in inhibiting PDE4A (entries 7 and 9). In addition, both compounds retain a binding affinity to hERG that is similar to (+)-**2c**, suggesting that these substructures are suitable surrogates for the 4-pyridyl *N*-oxide moiety.

The final area for investigation involved replacement of the pyridine ring bearing the dimethyl tertiary alcohol moiety with alternative aromatics (phenyl and thiazolyl). These molecules were prepared in the cyclobutyloxy series (compare with (+)-**2b**, entry 4) and gave rise to the phenyl derivative (±)-**4** (entry 10) and thiazole (+)-**3a** (entry 11). While (±)-**4** is equipotent in hERG binding affinity compared to (+)-**2b**, (+)-**3a** exhibits a further 2-fold decrease in this binding affinity while retaining excellent PDE4A inhibitory potency. The superiority of thiazole (+)-**3a** for lack of hERG binding, compared to both the pyridine ((+)-**2b**) and phenyl ((±)-**4**) containing analogues, may be due to a modulation of the interaction of the tertiary alcohol with the ion channel that is brought about by the change in geometry when the tertiary alcohol is present on a five-membered aromatic ring.

The in vitro profile of (+)-**3a** was deemed to be sufficient for studying its in vivo behavior. Unfortunately, (+)-**3a** displays poor pharmacokinetics in rat, with a $t_{1/2}$ of only approximately 1 h when dosed at 5

**Table 3.** QTc Effects of Phosphodiesterase-4 Inhibitors in Dogs

| compd | hERG binding $K_i$ [a] ($\mu$M) | iv dose [b] (mg/kg) | plasma concn [c] ($\mu$M) | $\Delta$ QTc [d] (%) | HWB $IC_{50}$ [a] ($\mu$M) | ratio[e] plasma concn/$IC_{50}$ |
|---|---|---|---|---|---|---|
| **1**[f] | 1.18 | 3 | 5−2 | +8.9 (6.0, 11.6) | 0.16 | 12.5 |
| (+)-**3a**[g] | 58.4 | 10 | 10−4 | +2.9 (0.6, 5.1) | 0.10 | 40 |
| (+)-**3d**[g] | 61.4 | 10 | 25−19 | +3.0 (1.7, 4.2) | 0.09 | 211 |

[a] See Table 2. [b] Bolus iv dosing (over 2−5 min) as solutions in 60−80% PEG-200. [c] Range of plasma concentrations (±0.2 $\mu$M) measured between 2 and 30 min after dosing by HPLC analysis. Data from $n \geq 2$ dogs. [d] QTc intervals were measured at 15 and 30 min after dosing and recorded at each time point as a percent change from baseline for each dog. These values (range in parentheses) were averaged, and $\Delta$ QTc represents the maximal mean percent change from baseline. See refs 21 and 32. [e] Ratio of the lowest plasma concentration measured over the 30 min recording interval to the $IC_{50}$ for inhibition of LPS-induced TNF$\alpha$ production in human whole blood. [f] $n = 3$ dogs. [g] $n = 2$ dogs.

mg/kg iv, analogous to (+)-**2b** ($t_{1/2}$ = 1.4 h). Since previous studies had shown that replacement of the dimethyl tertiary alcohol moiety with its perfluoro analogue had provided compounds that exhibited improved pharmacokinetic behavior,[9,10] this modification was applied to (+)-**3a** and led to (±)-**3b** (entry 12). While this modification results in a PDE4A inhibitor of similar potency, the binding affinity for hERG is somewhat greater than (+)-**3a**, although the $K_i$ is still in the high micromolar range. Moreover, the $t_{1/2}$ in rats exhibited a moderate increase to 2 h. Since changing the cyclobutyloxy moiety to a cyclopropyloxy moiety had provided a less potent hERG binder in the pyridine series (compare (+)-**2b** and (+)-**2c**, entries 4 and 5), the cyclopropyloxy version of (±)-**3b** and (±)-**3c** (entry 13) was prepared, with the additional expectation that the cyclopropyloxy moiety would be more metabolically stable relative to the cyclobutyloxy analogue and may result in a longer $t_{1/2}$. While both (±)-**3b** and (±)-**3c** exhibit similar PDE4A inhibitory activities, the binding affinity of (±)-**3c** to hERG was surprisingly 2-fold greater than (±)-**3b**. This result is opposite the observations that were made in the pyridine series, but in this thiazole series, we are comparing compounds that bear the bis(trifluoromethyl)carbinol rather than the dimethylcarbinol moiety. However, the rat $t_{1/2}$ for (±)-**3c** is approximately 10 h, a 5-fold increase compared to that for (±)-**3b**. The final optimization involved the preparation of the 3-pyridinyl *N*-oxide analogue of (±)-**3c** ((+)-**3d**, entry 14), a replacement that was expected to be neutral with respect to its PDE4A inhibition and hERG binding properties based on the results obtained in the pyridine series (compare (+)-**2c** and (+)-**2d**, entries 5 and 7). Gratifyingly, (+)-**3d** was found to be a potent PDE4A inhibitor. In addition, (+)-**3d** was the least potent hERG binder in the tertiary alcohol series, exhibiting a 3-fold decrease in binding affinity relative to (±)-**3c**. Furthermore, its $t_{1/2}$ in rats was measured to be 5 h. When compared with (+)-**3a**, (+)-**3d** exhibits a similar in vitro profile combined with improved pharmacokinetics.

## In Vivo Studies

**(A) QTc Effects in Dogs.** Having optimized the series on the basis of decreasing the affinity for the hERG channel, it was imperative to study the correlation of this in vitro binding activity with the effect on the QTc interval in dogs in vivo. The two inhibitors having the weakest hERG binding affinities, (+)-**3a** and (+)-**3d** ($K_i$ = 58.4 and 61.4 $\mu$M, respectively; see Table 2), were examined in a dog ECG model,[21,32] and the data were compared with the results obtained for **1**. The compounds were dosed iv (bolus dosing over 5 min) in chloralose-anesthetized mongrel dogs ($n$ = 2 or 3) at 3−10 mg/kg, and cardiac parameters, including QTc interval measurements, were recorded at 15 and 30 min postdose. The QTc interval measurement for each dog at these time points was compared with each dog's baseline QTc interval to obtain the percent QTc change from baseline for each dog. The values were then averaged at each time point, and the maximal mean percent change from baseline is reported in Table 3 as $\Delta$ QTc.

With a dosage of 3 mg/kg, **1** exhibited a prolongation of the QTc interval ($\Delta$ QTc = +8.9%) at plasma concentrations of 5−2 $\mu$M (Table 3). These plasma concentrations translate to drug levels that are approximately 2- to 4-fold above the $K_i$ for hERG binding ($K_i$ = 1.18 $\mu$M). If one estimates the plasma concentrations that would be required for in vivo efficacy as the human whole blood $IC_{50}$ value for inhibition of LPS-induced TNF$\alpha$ production ($IC_{50}$ = 0.16 $\mu$M), the plasma concentrations achieved in this experiment are 13-fold above this $IC_{50}$ value, giving rise to an approximation of the therapeutic index for QTc interval prolongation of <13.[15,35] In contrast, (+)-**3a** demonstrated a nonsignificant effect ($\Delta$ QTc < +5%) on $\Delta$ QTc (+2.9%) at plasma levels 2-fold higher than those achieved with **1** and that are 5- to 10-fold below the $K_i$ for hERG binding. From a comparison of the plasma concentrations that were attained in this latter experiment with the HWB $IC_{50}$ for (+)-**3a**, the therapeutic index is >40, illustrating the superiority of (+)-**3a** compared to **1** in terms of this undesired ancillary activity. These observations correlate well with the expectation that drug plasma concentrations that exceed the $K_i$ for hERG binding lead to an increased probability for observing prolongation of the QTc interval (as with **1**). A corollary suggests that when two compounds at similar plasma concentrations are compared, the compound with a weaker hERG binding affinity will exhibit a lower potential for causing QTc interval prolongation.

We next studied (+)-**3d**, a compound that has a hERG binding affinity and a HWB $IC_{50}$ for inhibition of TNF$\alpha$ production similar to that of (+)-**3a** (Table 3). Bolus iv administration of (+)-**3d** to dogs also resulted in a nonsignificant prolongation of the QTc interval ($\Delta$ QTc = +3.0%) at plasma levels of 25−19 $\mu$M, approximately 5-fold higher than those observed with (+)-**3a**. Thus, the poor binding affinity of (+)-**3d** for the hERG channel again correlates well with the lack of effect on $\Delta$ QTc at plasma levels 2- to 3-fold below the $K_i$ for hERG binding but with the additional advantage that these plasma levels translate into a therapeutic index of >200.

**Table 4.** In Vivo Comparative Profile of (+)-**3d** with SB207499 (Ariflo), CDP-840, and **1**

| compd | guinea pig[a] (%) (mg/kg) | sheep early (%)/late (%)[b] | squirrel monkey emesis $C_{max}$ [c] ($\mu$M) (mg/kg, range, responders) | squirrel monkey whole blood $IC_{50}$ [d] ($\mu$M) | ratio[e] plasma concn/$IC_{50}$ |
|---|---|---|---|---|---|
| SB207499 | 64 ± 5 (3) | ND | 35 (3, 20−40, $^1/_6$) | 40 ± 14 | 0.9 |
| CDP-840 | 54 ± 3 (1) | $^{39}/_{88}$ | 4 (10, 3−6, $^1/_4$) | 0.60 ± 0.14 | 8.7 |
| **1** | 62 ± 3 (0.3) | $^{33}/_{91}$ | 2.2 (10, 2.1−2.3, $^2/_2$) | 0.11 ± 0.03 | 20 |
| (+)-**3d** | 62 ± 15 (0.01) | $^{68}/_{92}$ | 1.6 (0.5, 1.5−1.7, $^2/_4$) | 0.005 ± 0.002 | 320 |

[a] Mean percent inhibition of ovalbumin-induced bronchoconstriction in conscious guinea pigs dosed ip 30 min prior to challenge reported as ±SEM ($n$ = 4−8). See ref 39. Dose (mg/kg) is shown in parentheses. [b] Mean percent inhibition of early-phase/late-phase antigen-induced bronchoconstriction in Ascaris sensitive sheep ($n$ = 2−4) dosed iv with 0.5 mg/(kg·day) of test compound for 4 days and challenged 2 h postdose on day 4. See ref 40. ND = not determined. [c] In a rising dose (dose-ranging study), the average maximal plasma concentration ($C_{max}$) is achieved after the first po dose in which emesis is observed in at least one monkey in the dosing group ($n \geq 2$). Dose (mg/kg), range of $C_{max}$ in $\mu$M, and number of responders exhibiting emesis are shown in parentheses. [d] Inhibition of LPS-induced TNFα production in squirrel monkey whole blood. This assay was performed according to ref 38 using squirrel monkey whole blood and employing a 4 h incubation after LPS stimulation rather than 24 h. $IC_{50}$ represents the mean ± SEM ($n \geq 3$). [e] Ratio of the $C_{max}$ plasma concentration to the $IC_{50}$ for inhibition of LPS-induced TNFα production in squirrel monkey whole blood.

Thus, optimization of a structural series for lack of in vitro binding affinity to the hERG potassium channel appears to be generally predictive of a decreased potential to cause QTc interval prolongation in vivo. Moreover, by comparing the ratios of the plasma concentrations achieved in these in vivo experiments with the drug concentrations expected for efficacy as measured in an in vitro assay (in this case, HWB $IC_{50}$), we have been able to obtain an approximation of the therapeutic index for QTc prolongation. On the basis of its overall profile, including in vitro potency, pharmacokinetics, and therapeutic index for cardiac safety, (+)-**3d** was selected for efficacy testing in vivo.

**(B) In Vivo Efficacy of (+)-3d.** The in vivo efficacy of (+)-**3d** was tested in several models of pulmonary function, and the results were compared with those of three known PDE4 inhibitors: CDP-840, SB207499, and compound **1** (Table 4).

(+)-**3d** inhibited ovalbumin-induced bronchoconstriction in concious guinea pigs[39] by 62% when administered ip at 0.01 mg/kg (0.5 h pretreatment). (+)-**3d** was also effective for the inhibition of ascaris-induced bronchoconstriction in concious sheep,[40] exhibiting 68% and 92% inhibition of the early-phase and late-phase responses, respectively, at a dose of 0.5 mg/kg iv (4 days of dosing) given 2 h prior to challenge. The results of these studies indicate that the in vivo efficacy of (+)-**3d** is similar or superior to all three comparator compounds as shown in Table 4. Furthermore, dosing of (+)-**3d** in squirrel monkey started inducing emesis at 0.5 mg/kg po, with $C_{max}$ plasma levels of 1.6 $\mu$M being achieved. If one takes into account the potency for inhibition of LPS-induced TNFα production in squirrel monkey whole blood ($IC_{50}$ = 5 nM; see Table 4), an approximation of the emesis window can be made by taking the ratio of these two concentrations. In the case of (+)-**3d**, this ratio is ~300, while for SB207499, CDP-840, and **1**, the same analysis provides ratios of 1, 9, and 20, respectively. Taken together, the data indicate that (+)-**3d** exhibits excellent in vivo efficacy in pulmonary function models while maintaining a large window with respect to emesis.

## Conclusion

In conclusion, we have developed a structure−activity relationship, both for PDE4 inhibition and for binding affinity to the hERG $K^+$ channel, in the tertiary alcohol series of PDE4 inhibitors related to **1**. Modification of four key pharmacophores led to the identification of (+)-**3d** (L-869,298),[41] which exhibits excellent PDE4A inhibitory potency (HWB-TNFα $IC_{50}$ = 0.09 $\mu$M) and poor binding affinity to the hERG $K^+$ channel as measured in the MK-499 binding assay ($K_i$ = 61.4 $\mu$M). This lack of binding affinity was manifested in a no-effect Δ QTc at plasma levels in dogs >200-fold above the PDE4 inhibitory potency in human whole blood. (+)-**3d** was well tolerated in squirrel monkey with an emesis window of >300 and was found to be efficacious in the ovalbumin-induced bronchoconstriction model in guinea pig (62%, 0.01 mg/kg, ip) as well as the ascaris-induced bronchoconstriction model in sheep (68%/92%, early/late, 0.5 mg/kg, iv).

## Experimental Section

**General Chemistry.** NMR spectra were recorded as solutions in acetone-$d_6$, unless stated otherwise, at the field strength indicated and using the solvent as internal standard. $^{13}C$ NMR spectra were acquired with proton decoupling, and peak multiplicities refer to $J_{CF}$. High-resolution mass spectral (HRMS) measurements were made using the FAB or CI techniques at the Biomedical Mass Spectrometry Unit of McGill University, Montréal. Elemental analyses were performed at the Department of Chemistry, Université de Montréal, Montréal. All chemicals and solvents were reagent grade, and all reactions were carried out under a nitrogen atmosphere. Preparative scale HPLC for enantiomer separation was carried out using a CHIRALPAK AD (silica coated with amylose tris(3,5-dimethylphenylcarbamate)) preparative (5 cm × 50 cm) HPLC column from Chiral Technologies. The preparation of aldehydes **5a**−**c** has been described previously.[9−11,41]

**(±)-[3,4-Bis(difluoromethoxy)phenyl](2-bromopyridin-5-yl)methanol ((±)-6a).** To a suspension of 2,5-dibromopyridine (29.8 g, 126 mmol) in ether (750 mL) at −78 °C was added n-BuLi (52.5 mL of a 2.4 M solution in hexane, 126 mmol) dropwise. After the mixture was stirred at this temperature for 45 min, a solution of **5a** (25.0 g, 105 mmol) in ether (150 mL) was added dropwise over 45 min, and then the mixture was stirred for an additional 2 h. The mixture was poured into saturated $NH_4Cl$ (1.5 L), the layers were separated, and the aqueous phase was extracted three times with ethyl acetate. The combined organics were washed successively with 25% $NH_4OAc$ buffer, water, and brine, dried over $MgSO_4$, filtered, and concentrated. The residual brown gum was subjected to flash chromatography (silica gel, hexane/ethyl acetate, 4:1) to provide (±)-**6a** (28.9 g, 70%) as a golden oil. $^1H$ NMR (500 MHz): $\delta$ 5.47 (br s, 1H), 5.99 (s, 1H), 6.96 (t, 1 H, $J$ = 73.8 Hz), 6.99 (t, 1H, $J$ = 74.0 Hz), 7.32 (d, 1H, $J$ = 8.5 Hz), 7.36 (dd, 1H, $J$ = 2.0, 8.5 Hz), 7.48 (s, 1H), 7.55 (d, 1H, $J$ = 8.3 Hz), 7.73 (m, 1H), 8.44 (d, 1H, $J$ = 2.5 Hz).

**(±)-4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[5-(2-bromo)pyridyl]ethyl}pyridine ((±)-9a).** To a solution of

(±)-**6a** (28.9 g, 73.0 mmol) in $CH_2Cl_2$ (340 mL) at room temperature was added $SOCl_2$ (6.92 mL, 94.8 mmol). After 45 min, the mixture was carefully poured into saturated $NaHCO_3$ (700 mL). The layers were separated, and the aqueous phase was extracted with $CH_2Cl_2$. The combined organics were washed with saturated $NaHCO_3$ and brine, dried over $Na_2SO_4$, filtered, and concentrated. The thick yellow oil ((±)-**7a**) was used immediately in the next reaction without further purification. To a solution of ethyl 4-pyridylacetate (31.8 mL, 208 mmol) in THF (830 mL) and HMPA (36.2 mL, 208 mmol) at room temperature was added KHMDS (415 mL of a 0.5 M solution in toluene, 208 mmol) dropwise over 40 min. After being stirred for a further 20 min, a solution of (±)-**7a** (28.7 g, 69.2 mmol) in THF (175 mL) was added dropwise over 15 min. The mixture was stirred at room temperature for 15 h and then poured into saturated $NH_4Cl$ (1.5 L). The layers were separated, and the aqueous phase was extracted twice with ethyl acetate. The combined organics were washed successively with 25% $NH_4OAc$ buffer and brine, dried over $MgSO_4$, filtered, and concentrated to provide crude (±)-**8a**. (±)-**8a** was dissolved in a mixture of THF/MeOH/water (3:1:1, 1 L), and 2 N LiOH (312 mL, 624 mmol) was added. The mixture was heated at 70 °C for 2 h. After the mixture was cooled to room temperature, 2 N HCl (333 mL) was slowly added and the resulting solution was stirred for 1 h. The volatiles were removed on the rotovap, and the residue was partitioned between saturated $NaHCO_3$ and ethyl acetate. The aqueous phase was extracted twice with ethyl acetate. The combined organics were washed with 25% $NH_4OAc$ buffer, water, and brine, dried over $MgSO_4$, filtered, and concentrated. The residual brown gum was subjected to flash chromatography (silica gel, hexane/ethyl acetate, 2:3 to 100% ethyl acetate) to provide (±)-**9a** (31.2 g, 96%, 91% from (±)-**6a**) as a yellow gum. $^1$H NMR (500 MHz): $\delta$ 3.49−3.56 (m, 2H), 4.65 (t, 1H, $J$ = 8.2 Hz), 6.93 (t, 1H, $J$ = 73.8 Hz), 6.94 (t, 1H, $J$ = 73.8 Hz), 7.19 (m, 2H), 7.27 (d, 1H, $J$ = 8.5 Hz), 7.35 (dd, 1H, $J$ = 2.1, 8.5 Hz), 7.42 (d, 1H, $J$ = 1.9 Hz), 7.51 (d, 1H, $J$ = 8.3 Hz), 7.76 (dd, 1H, $J$ = 2.6, 8.2 Hz), 8.37 (m, 1H).

**(±)-4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[5-(2-carbomethoxy)pyridyl]ethyl}pyridine ((±)-10a).** $Pd(OAc)_2$ (429 mg, 1.91 mmol), dppf (2.12 g, 3.82 mmol), $Et_3N$ (8.87 mL, 63.7 mmol), and MeOH (30 mL) were successively added to a solution of (±)-**9a** (15.0 g, 31.8 mmol) in DMF (30 mL). The mixture was purged with vacuum/CO(g) three times and then heated at 50 °C under CO (1 atm, balloon) for 20 h. After the mixture was cooled to room temperature, the volatiles were removed on the rotovap and the residue was poured into water (300 mL). The mixture was extracted three times with ethyl acetate. The combined organics were washed with 25% $NH_4OAc$ buffer, water, and brine, dried over $MgSO_4$, filtered, and concentrated. The residual brown gum was subjected to flash chromatography (silica gel, acetone/toluene, 2:3 to 3:2) to provide (±)-**10a** (13.8 g, 96%) as an orange gum. $^1$H NMR (500 MHz): $\delta$ 3.57 (d, 2H, $J$ = 8.2 Hz), 3.86 (s, 3H), 4.75 (t, 1H, $J$ = 8.3 Hz), 6.94 (t, 1H, $J$ = 73.7 Hz), 6.95 (t, 1H, $J$ = 73.8 Hz), 7.20 (m, 2H), 7.28 (d, 1H, $J$ = 8.5 Hz), 7.37 (dd, 1H, $J$ = 2.1, 8.5 Hz), 7.44 (d, 1H, $J$ = 1.9 Hz), 7.98 (m, 2H), 8.36 (m, 2H), 8.68 (t, 1H, $J$ = 1.5 Hz).

**(±)-4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-[5-(2-carbomethoxy)pyridyl]ethyl}pyridine *N*-Oxide ((±)-11a).** To a solution of (±)-**10a** (2.17 g, 4.82 mmol) in $CH_2Cl_2$/MeOH (9:1, 40 mL) at room temperature was added MMPP (4.77 g, 9.64 mmol). After being stirred for 22 h, the mixture was diluted with ethyl acetate and washed successively with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash chromatography (silica gel, $CHCl_3$/EtOH, 9:1) to provide (±)-**11a** (1.74 g, 77%) as an off-white foam. $^1$H NMR (500 MHz): $\delta$ 3.56 (d, 2H), 3.88 (s, 3H), 4.72 (t, 1H), 6.94 (t, 1H), 6.96 (t, 1H), 7.20 (m, 2H), 7.29 (d, 1H), 7.38 (dd, 1H), 7.45 (d, 1H), 7.94 (d, 2H), 8.00 (s, 2H), 8.69 (s, 1H).

**(±)-4-{2-[3,4-Bis(difluoromethoxy)phenyl]-2-{5-[2-(1-hydroxy-1-methyl)ethyl]pyridyl}ethyl}pyridine *N*-Oxide ((±)-2a).** To a solution of (±)-**11a** (1.74 g, 3.73 mmol) in $CH_2Cl_2$ (40 mL) at −78 °C was added MeMgBr (6.2 mL of a 3 M solution in ether, 18.6 mmol). A thick beige precipitate was observed, and 10 mL of THF was added. After 7 h, 25% $NH_4OAc$ was added and the mixture was warmed to room temperature. The mixture was extracted twice with ethyl acetate. The combined organics were washed successively with water and brine, dried over $MgSO_4$, filtered, and concentrated. The crude material was submitted a second time to the same reaction conditions, and after workup, flash chromatography (silica gel, $CHCl_3$/MeOH, 9:1) provided (±)-**2a** (1.26 g, 73%) as a white foam. $^1$H NMR (500 MHz): $\delta$ 1.44 (s, 6H), 3.50 (m, 2H), 4.56 (t, 1H), 4.59 (s, 1H), 6.92 (t, 1H), 6.96 (t, 1H), 7.20 (m, 2H), 7.27 (d, 1H), 7.35 (dd, 1H), 7.42 (s, 1H), 7.60 (d, 1H), 7.83 (dd, 1H), 7.94 (m, 2H), 8.50 (d, 1H).

**Separation of Enantiomers of (±)-2a.** A solution of (±)-**2a** (1.26 g) in EtOH/hexane (4 mL, 1:1) was injected (1 × 1.26 g) onto a CHIRALPAK AD preparative (5 cm × 50 cm) HPLC column (eluting with hexane/EtOH, 4:1, at 60 mL/min with UV detection at 300 nm). The enantiomers were separated with the faster eluting enantiomer having a retention time of ∼21 min (enantiomer 1) and the slower eluting enantiomer having a retention time of ∼24 min (enantiomer 2). The eluants were concentrated to provide (+)-**2a** (enantiomer 1, 458 mg, 90% ee) as a white foam and (−)-**2a** (enantiomer 2, 173 mg, 86% ee) as a white foam.

**(+)-2a:** $[\alpha]^{25}_D$ +1.2° (*c* 1, $CHCl_3$). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 30.5, 39.9, 48.6, 71.7, 115.48 (t), 115.55 (t), 119.0, 122.1, 122.6, 125.9, 126.5, 135.7, 136.4, 138.0, 138.9, 140.5, 141.3, 142.1, 146.4, 165.2. Anal. ($C_{23}H_{22}N_2O_4F_4$) H, N. C: calcd, 59.23; found, 57.83. CI HRMS ($C_{23}H_{22}N_2O_4F_4K$, M + $K^+$): calcd, 505.1153; found, 505.1154.

**(−)-2a:** $[\alpha]^{25}_D$ −1.3° (*c* 1, $CHCl_3$). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 30.5, 39.9, 48.7, 71.1, 115.4 (t), 115.5 (t), 118.9, 122.1, 122.6, 125.9, 126.4, 135.6, 136.2, 137.9, 138.9, 140.5, 141.3, 142.1, 146.6, 165.2. CI HRMS ($C_{23}H_{23}N_2O_4F_4$, M + $H^+$): calcd, 467.159 55; found, 467.159 40.

**(±)-[(3-Cyclobutyloxy-4-difluoromethoxy)phenyl](2-bromopyridin-5-yl)methanol ((±)-6b).** Following the procedures described for the preparation of (±)-**6a**, but with substitution of the aldehyde **5b** (35.6 g, 147 mmol) for **5a**, (±)-**6b** (53.0 g, 90%) was obtained as a yellow oil. $^1$H NMR (500 MHz): $\delta$ 1.69 (m, 1H), 1.82 (m, 1H), 2.11 (m, 2H), 2.44 (m, 2H), 4.76 (quintet, 1H), 5.38 (br s, 1H), 5.91 (s, 1H), 6.85 (t, 1H), 7.00 (m, 1H), 7.12 (m, 2H), 7.53 (d, 1H), 7.71 (dd, 1H), 8.43 (s, 1H).

**(±)-4-{2-[(3-Cyclobutyloxy-4-difluoromethoxy)phenyl]-2-[5-(2-bromo)pyridyl]ethyl}pyridine ((±)-9b).** Following the procedures described for the preparation of (±)-**9a** but with substitution of the alcohol (±)-**6b** (53.0 g, 133 mmol) for (±)-**6a**, (±)-**9b** (57.9 g, 92%) was obtained as a yellow oil. $^1$H NMR (500 MHz): $\delta$ 1.65 (m, 1H), 1.80 (m, 1H), 2.06 (m, 2H), 2.42 (m, 2H), 3.49 (d, 2H), 4.55 (t, 1H), 4.74 (quintet, 1H), 6.81 (t, 1H), 6.95 (m, 1H), 7.00 (s, 1H), 7.07 (d, 1H), 7.17 (d, 2H), 7.50 (d, 1H), 7.74 (dd, 1H), 8.35 (m, 3H).

**(±)-4-{2-[(3-Cyclobutyloxy-4-difluoromethoxy)phenyl]-2-[5-(2-carbomethoxy)pyridyl]ethyl}pyridine ((±)-10b).** Following the procedures described for the preparation of (±)-**10a** but with substitution of the alcohol (±)-**9b** (57.9 g, 122 mmol) for (±)-**9a**, (±)-**10b** (50.1 g, 91%) was obtained as a yellow oil. $^1$H NMR (500 MHz): $\delta$ 1.66 (m, 1H), 1.80 (m, 1H), 2.07 (m, 2H), 2.41 (m, 2H), 3.53 (d, 2H), 3.86 (s, 3H), 4.66 (t, 1H), 4.75 (quintet, 1H), 6.82 (t, 1H), 6.98 (m, 1H), 7.02 (s, 1H), 7.08 (d, 1H), 7.19 (d, 2H), 7.98 (s, 2H), 8.36 (d, 2H), 8.69 (s, 1H).

**Separation of Enantiomers of (±)-10b.** A solution of (±)-**10b** (50.1 g) in 2-propanol/hexane (165 mL, 1:1) was injected (17 × 2.5−3 g) onto a CHIRALPAK AD preparative (5 cm × 50 cm) HPLC column (eluting with hexane/EtOH, 3:2, at 70 mL/min with UV detection at 300 nm). The enantiomers were separated with the faster eluting enantiomer having a retention time of ∼21 min (enantiomer 1) and the slower eluting enantiomer having a retention time of ∼31 min (enantiomer 2). The eluants were concentrated to provide impure enanti-

omer 1 as a tan gum and chiral **10b** (enantiomer 2, 22.6 g, 96% ee) as a tan gum.

**Chiral 4-{2-[(3-Cyclobutyloxy-4-difluoromethoxy)phenyl]-2-[5-(2-carbomethoxy)pyridyl]ethyl}pyridine *N*-Oxide (Chiral 11b).** Following the procedures described for the preparation of (±)-**11a** but with substitution of the chiral ester **10b** (enantiomer 2, 22.6 g, 50.0 mmol) for (±)-**10a**, chiral **11b** (17.2 g, 73%) was obtained as a yellow oil. $^1$H NMR (500 MHz): $\delta$ 1.65 (m, 1H), 1.80 (m, 1H), 2.08 (m, 2H), 2.42 (m, 2H), 3.55 (d, 2H), 3.87 (s, 3H), 4.63 (t, 1H), 4.77 (quintet, 1H), 6.82 (t, 1H), 6.99 (m, 1H), 7.03 (s, 1H), 7.09 (d, 1H), 7.21 (d, 2H), 7.99 (m, 4H), 8.70 (s, 1H).

**(+)-4-{2-[(3-Cyclobutyloxy-4-difluoromethoxy)phenyl]-2-{5-[2-(1-hydroxy-1-methyl)ethyl]pyridyl}ethyl}pyridine *N*-Oxide ((+)-2b).** Following the procedures described for the preparation of (±)-**2a** but with substitution of the chiral ester **11b** (17.2 g, 36.6 mmol) for (±)-**11a** and with flash chromatography (silica gel) with $CH_2Cl_2$/EtOH (9:1 to 7:3), (+)-**2b** (13.5 g, 78%) was obtained as a white foam. $[\alpha]^{25}_D$ +12.6° (*c* 1, $CHCl_3$). $^1$H NMR (500 MHz): $\delta$ 1.42 (s, 6H), 1.65 (m, 1H), 1.80 (m, 1H), 2.10 (m, 2H), 2.42 (m, 2H), 3.49 (m, 2H), 4.49 (t, 1H), 4.66 (s, 1H), 4.76 (quintet, 1H), 6.81 (t, 1H), 6.97 (m, 1H), 7.00 (s, 1H), 7.06 (d, 1H), 7.20 (d, 2H), 7.56 (d, 1H), 7.81 (dd, 1H), 7.98 (d, 2H), 8.49 (s, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 13.0, 30.3, 30.4, 39.9, 48.9, 71.6, 72.3, 114.1, 115.9 (t), 119.2, 119.8, 122.9, 126.6, 136.8, 137.2, 138.4, 139.1, 140.0, 145.8, 149.2, 164.6. Anal. ($C_{26}H_{28}N_2O_4F_2$) H, N. C: calcd, 66.31; found, 65.75.

**5-Bromo-2-{1-methyl-1-[(2-trimethylsilylethoxy)-methoxy]ethyl}pyridine (12).** To a suspension of 2,5-dibromopyridine (25.5 g, 108 mmol) in toluene (570 mL) at − 78 °C was added n-BuLi (75 mL of a 1.6 M solution in hexane, 120 mmol) dropwise.[9] After the mixture was stirred at this temperature for 30 min, acetone (9.5 mL, 130 mmol) was added dropwise and the mixture was stirred for an additional 40 min. The mixture was poured into saturated $NH_4Cl$ (100 mL), the layers were separated, and the aqueous phase was extracted three times with ethyl acetate. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residual material was subjected to flash chromatography (silica gel, hexane/ethyl acetate, 4:1) to provide 5-bromo-2-(1-hydroxy-1-methyl)ethylpyridine (16.3 g, 70%) as a pale-yellow oil. To this material (16.2 g, 75.2 mmol) in DMF (130 mL) at 0 °C was added solid NaH (4.22 g, 60% in oil, 105.5 mmol) portionwise. After complete addition, the mixture was stirred for 15 min at this temperature and then at room temperature for 1 h. The mixture was recooled to 0 °C, and then 2-(trimethylsilyl)ethoxymethyl chloride (17.2 mL, 97.6 mmol) was slowly added. After being stirred at room temperature for 20 h, the mixture was cooled to 0 °C and poured into ice-cold water (250 mL). The mixture was extracted three times with ethyl acetate. The combined organics were washed three times with water, dried over $MgSO_4$, filtered, and concentrated. The residual material was subjected to flash chromatography (silica gel, hexane/ethyl acetate, 98:2) to provide **12** (25.3 g, 97%) as a colorless liquid. $^1$H NMR (400 MHz): $\delta$ 0.01 (s, 9H), 0.84 (t, 2H), 1.57 (s, 6H), 3.65 (t, 2H), 4.76 (s, 2H), 7.60 (d, 1H), 7.93 (dd, 1H), 8.59 (d, 1H).

**(±)-[(3-Cyclopropyloxy-4-difluoromethoxy)phenyl]{2-[1-methyl-1-(2-trimethylsilylethoxy)methoxy]ethyl-pyridin-5-yl}methanol ((±)-13).** To a solution of **12** (600 mg, 1.74 mmol) in THF (9 mL) at −100 °C was added n-BuLi (1.08 mL of a 1.6 M solution in hexane, 1.74 mmol) dropwise. After the mixture was stirred at this temperature for 20 min, a solution of **5c** (330 mg, 1.45 mmol) in THF (1.5 mL) was added dropwise and the mixture was warmed to −78 °C over 10 min. To the mixture was added saturated $NH_4Cl$ and ethyl acetate. The layers were separated, and the aqueous phase was extracted with ethyl acetate. The combined organics were washed successively with 25% $NH_4OAc$ buffer and brine, dried over $MgSO_4$, filtered, and concentrated. The residual material was subjected to flash chromatography (silica gel, hexane/ethyl acetate, 3:2) to provide (±)-**13** (718 mg, 100%) as a golden oil. $^1$H NMR (400 MHz): $\delta$ 0.00 (s, 9H), 0.71 (m, 2H), 0.81 (m, 2H), 0.86 (t, 2H), 1.54 (s, 6H), 3.66 (t, 2H), 3.90 (m, 1H), 4.71 (s, 2H), 5.14 (d, 1H), 5.92 (d, 1H), 6.77 (t, 1H), 7.02 (dd, 1H), 7.10 (d, 1H), 7.58 (m, 2H), 7.77 (dd, 1H), 8.57 (d, 1H).

**(±)-4-{2-[(3-Cyclopropyloxy-4-difluoromethoxy)phenyl]-2-[-5-(2-(1-methyl-1-[(2-trimethylsilylethoxy)methoxy]-ethyl)pyridyl]ethyl}pyridine ((±)-15).** A solution of (±)-**13** (718 mg, 1.44 mmol) in toluene (5 mL) was added to a room temperature solution of $SOCl_2$ (127 $\mu$L, 1.74 mmol) and pyridine (291 $\mu$L, 3.6 mmol) in toluene (5 mL). After 1 h, the mixture was applied directly to a plug of silica gel and eluted with toluene/ethyl acetate (4:1) and concentrated. The yellow oil ((±)-**14**, 652 mg, 88%) was used immediately in the next reaction. To a solution of ethyl 4-pyridylacetate (628 mg, 3.8 mmol) in THF (14 mL) and HMPA (661 $\mu$L, 3.8 mmol) at 0 °C was added KHMDS (7.6 mL of a 0.5 M solution in toluene, 3.8 mmol) dropwise. After the mixture was stirred for 30 min, a solution of (±)-**14** (652 mg, 1.27 mmol) in THF (4 mL) was added dropwise. The mixture was stirred at room temperature for 15 h and then poured into saturated $NH_4Cl$ and diluted with ethyl acetate. The layers were separated, and the aqueous phase was extracted with ethyl acetate. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved in a mixture of THF/MeOH/water (3:1:1, 28 mL). A 2 N LiOH (5.7 mL, 11.4 mmol) solution was added, and the mixture was heated at 60 °C for 2 h. After the mixture was cooled to room temperature, 2 N HCl (5.7 mL) was slowly added. The volatiles were removed on the rotovap, and the residue was partitioned between 25% $NH_4OAc$ and ethyl acetate. The aqueous phase was extracted with ethyl acetate. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash chromatography (silica gel, hexane/ethyl acetate 1:4 to 100% ethyl acetate) to provide (±)-**15** (710 mg, 98%, 86% from (±)-**13**) as a yellow gum. $^1$H NMR (400 MHz): $\delta$ 0.00 (s, 9H), 0.65 (m, 2H), 0.78 (m, 2H), 0.86 (t, 2H), 1.52 (s, 6H), 3.49 (m, 2H), 3.64 (t, 2H), 3.88 (m, 1H), 4.54 (t, 1H), 4.70 (s, 2H), 6.71 (t, 1H), 6.98 (dd, 1H), 7.05 (d, 1H), 7.19 (m, 2H), 7.45 (d, 1H), 7.54 (d, 1H), 7.80 (dd, 1H), 8.37 (m, 2H), 8.50 (d, 1H).

**(±)-4-{2-[(3-Cyclopropyloxy-4-difluoromethoxy)phenyl]-2-{-5-[2-(1-hydroxy-1-methyl)ethyl]pyridyl}ethyl}pyridine *N*-Oxide ((±)-2c).** Following the procedures described for the preparation of (±)-**11a** but substituting (±)-**15** (710 mg, 1.24 mmol) for (±)-**10a** and carrying out flash chromatography (silica gel) with $CH_2Cl_2$/EtOH (85:15 to 4:1), a mixture of (±)-**15**, (±)-**16**, and bis-*N*-oxide (573 mg) was obtained and used directly in the next reaction. To a solution of this mixture in $CH_2Cl_2$ (10 mL) at 0 °C was added TFA (1 mL). After 30 min, the mixture was warmed to room temperature and stirred for 30 min. The mixture was partitioned between ethyl acetate and 25% $NH_4OAc$. The aqueous phase was extracted twice with ethyl acetate and once with $CH_2Cl_2$. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash chromatography (silica gel, $CH_2Cl_2$/EtOH, 7:3) to provide (±)-**2c** (305 mg, 53% from (±)-**15**) as a colorless foam. $^1$H NMR (500 MHz): $\delta$ 0.71 (m, 2H), 0.82 (m, 2H), 1.47 (s, 6H), 3.53 (m, 2H), 3.92 (m, 1H), 4.55 (t, 1H), 4.71 (br s, 1H), 6.77 (t, 1H), 7.00 (dd, 1H), 7.09 (d, 1H), 7.22 (m, 2H), 7.49 (d, 1H), 7.60 (d, 1H), 7.85 (dd, 1H), 7.99 (m, 2H), 8.54 (d, 1H).

**Separation of Enantiomers of (±)-2c.** A solution of (±)-**2c** (250 mg) in EtOH/hexane (5 mL, 3:7) was injected (1 × 250 mg) onto a CHIRALPAK AD preparative (5 cm × 50 cm) HPLC column (eluting with hexane/EtOH, 7:3, at 80 mL/min with UV detection at 300 nm). The enantiomers were separated with the faster eluting enantiomer having a retention time of ∼25 min (enantiomer 1) and the slower eluting enantiomer having a retention time of ∼40 min (enantiomer 2). The eluants were concentrated to provide (−)-**2c** (enantiomer 1, 100 mg, >99% ee) as a white foam and (+)-**2c** (enantiomer 2, 100 mg, >99% ee) as a white foam.

**(−)-2c:** $[\alpha]^{25}_D$ −10.6° (*c* 1, $CHCl_3$). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 6.1, 6.2, 30.49, 30.53, 40.1, 49.1, 51.6, 71.7, 114.2, 115.8 (t), 118.7, 120.0, 122.7, 126.5, 136.1, 138.6, 138.8, 140.2,

146.7, 150.7, 165.0. FAB HRMS ($C_{25}H_{27}N_2O_4F_2$, M + $H^+$) calcd, 457.193 89; found, 457.193 81.

**(+)-2c:** $[\alpha]^{25}_D$ +8.7° (*c* 1, $CHCl_3$). $^{13}C$ NMR (125 MHz): $\delta$ 6.1, 6.2, 30.49, 30.53, 40.1, 49.1, 51.6, 71.7, 114.2, 115.8 (t), 118.7, 120.0, 122.7, 126.5, 136.1, 138.6, 138.8, 140.2, 146.7, 150.7, 165.0. FAB HRMS ($C_{25}H_{27}N_2O_4F_2$, M + $H^+$) calcd, 457.193 89; found, 457.193 81.

**(±)-3-{2-[(3-Cyclopropyloxy-4-difluoromethoxy)phenyl]-2-{-5-[2-(1-hydroxy-1-methyl)ethyl]pyridyl}ethyl}pyridine *N*-Oxide ((±)-2d).** To a solution of ethyl 3-pyridylacetate *N*-oxide (5.09 g, 28.1 mmol) in THF (100 mL) and HMPA (5 mL, 28.7 mmol) at 0 °C was added KHMDS (60 mL of a 0.5 M solution in toluene, 30 mmol) dropwise. After being stirred at room temperature for 90 min, the mixture was recooled to 0 °C and a solution of (±)-**14** (3.44 g, 6.69 mmol) in THF (30 mL) was added dropwise. The mixture was stirred at 60 °C for 6 h and then poured into saturated $NH_4Cl$ and diluted with ethyl acetate. The layers were separated, and the aqueous phase was extracted with ethyl acetate. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash chromatography (silica gel, $CH_2Cl_2$/EtOH, 99:1 to 95:5) to provide 4.44 g of partially purified ester as a yellow oil. This material was dissolved in a mixture of THF/MeOH/water (3:1:1, 60 mL). A 1.7 N LiOH (12 mL, 20.4 mmol) solution was added, and the mixture was heated at 60 °C for 10.5 h and at room temperature for 15 h. A 2 N HCl (12 mL) solution was slowly added. The volatiles were removed on the rotovap, and the residue was partitioned between water and ethyl acetate. The aqueous phase was extracted three times with ethyl acetate. The combined organics were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated to provide 3.52 g of crude acid (±)-**22**. Crude (±)-**22** was dissolved in DMSO (20 mL) and heated at 130 °C for 4 h. The mixture was poured into water (200 mL) and extracted with $CH_2Cl_2$, and the organics were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated. The residue was subjected to flash chromatography (silica gel, EtOH/ethyl acetate, 1:4 to 1:1) to provide (±)-**2d** (1.22 g, 39% from (±)-**14**) as a white foam. $^1H$ NMR (500 MHz): $\delta$ 0.68 (m, 2H), 0.80 (m, 2H), 1.44 (s, 6H), 3.48 (m, 2H), 3.90 (m, 1H), 4.55 (t, 1H), 4.62 (s, 1H), 6.72 (t, 1H), 7.00 (d, 1H), 7.07 (d, 1H), 7.14 (d, 1H), 7.20 (t, 1H), 7.49 (s, 1H), 7.59 (d, 1H), 7.85 (d, 1H), 7.90 (d, 1H), 8.05 (s, 1H), 8.51 (s, 1H).

**Separation of Enantiomers of (±)-2d.** A solution of (±)-**2d** (1.22 g) in EtOH/hexane (15 mL, 2:3) was injected (3 × 400 g) onto a CHIRALPAK AD preparative (5 cm × 50 cm) HPLC column (eluting with hexane/EtOH, 3:2, at 60 mL/min with UV detection at 270 nm). The enantiomers were separated with the faster eluting enantiomer having a retention time of ∼7.5 min (enantiomer 1) and the slower eluting enantiomer having a retention time of ∼12.5 min (enantiomer 2). The eluants were concentrated to provide (+)-**2d** (enantiomer 1, 463 mg, >99% ee) as a white foam and (−)-**2d** (enantiomer 2, 485 mg, >99% ee) as a white foam.

**(+)-2d:** $[\alpha]^{25}_D$ +24.56° (*c* 1, $CHCl_3$). $^{13}C$ NMR (125 MHz): $\delta$ 6.54, 6.59, 31.1, 38.3, 49.5, 52.3, 72.8, 115.6, 117.7 (t), 119.3, 121.4, 122.8, 126.1, 126.5, 136.6, 137.6, 137.8, 139.5, 140.1, 142.6, 148.3, 151.3, 166.8. FAB HRMS ($C_{25}H_{27}N_2O_4F_2$, M + $H^+$) calcd, 457.193 89; found, 457.193 81.

**(−)-2d:** $[\alpha]^{25}_D$ −26.53° (*c* 1, $CHCl_3$). $^{13}C$ NMR (125 MHz): $\delta$ 6.54, 6.59, 31.1, 38.3, 49.5, 52.3, 72.8, 115.6, 117.7 (t), 119.3, 121.4, 122.8, 126.0, 126.5, 136.6, 137.6, 137.8, 139.5, 140.1, 142.6, 148.3, 151.3, 166.8. FAB HRMS ($C_{25}H_{27}N_2O_4F_2$, M + $H^+$) calcd, 457.193 89; found, 457.193 81.

**(+)-5-{2-[(3-Cyclopropyloxy-4-difluoromethoxy)phenyl]-2-{-5-[2-(1-hydroxy-1-methyl)ethyl]pyridyl}ethyl}pyrid-2-one ((+)-2e).** To a solution of (+)-**2d** (enantiomer 1, 142 mg, 0.31 mmol) and $Et_3N$ (216 $\mu$L, 1.55 mmol) in THF (3 mL) at 0 °C was added TFAA (110 $\mu$L, 0.78 mmol). The mixture was stirred at room temperature for 3 h, 2 N NaOH and MeOH were added, and the mixture was stirred at room temperature for 15 h. The mixture was partitioned between 25% $NH_4OAc$ and ethyl acetate. The aqueous phase was extracted with ethyl acetate. The organics were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated. The crude material was resubjected to the same reaction conditions. After workup, the residue was subjected to flash chromatography (silica gel, EtOH/$CH_2Cl_2$, 3:97 to 1:9) to provide (+)-**2e** (70 mg, 50%) as a white foam. $[\alpha]^{25}_D$ +10.9° (*c* 1, $CHCl_3$). $^1H$ NMR (500 MHz): $\delta$ 0.68 (m, 2H), 0.82 (m, 2H), 1.47 (s, 6H), 3.26 (m, 2H), 3.93 (m, 1H), 4.41 (t, 1H), 4.68 (br s, 1H), 6.30 (d, 1H), 6.76 (t, 1H), 6.99 (dd, 1H), 7.09 (d, 1H), 7.17 (d, 1H), 7.41 (dd, 1H), 7.48 (d, 1H), 7.60 (d, 1H), 7.83 (dd, 1H), 8.519 (d, 1H), 11.50 (br s, 1H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 6.2, 30.5, 37.5, 49.4, 51.5, 71.7, 114.5, 115.9 (t), 117.7, 118.6, 120.0, 120.1, 122.6, 133.2, 136.2, 136.6, 138.5, 140.7, 143.1, 146.8, 150.5, 164.4, 164.7. FAB HRMS ($C_{25}H_{27}N_2O_4F_2$, M + $H^+$) calcd, 457.193 89; found, 457.193 81.

**2-{1-Methyl-1-[(2-trimethylsilylethoxy)methoxy]ethyl}-thiazole (17a).** To a solution of thiazole (2.88 g, 33.8 mmol) in ether (50 mL) at −78 °C was added n-BuLi (21.1 mL of a 1.6 M solution in hexane, 33.8 mmol) dropwise. After the mixture was stirred at this temperature for 20 min, acetone (2.73 mL, 37.2 mmol) was added. After 30 min, the mixture was partitioned between 25% $NH_4OAc$ and ethyl acetate. The aqueous phase was extracted with ethyl acetate. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude alcohol (3.42 g, 23.9 mmol) was dissolved in $CH_2Cl_2$ (25 mL) and diisopropylethylamine (10.4 mL, 59.7 mmol) and cooled to 0 °C. 2-(Trimethylsilyl)ethoxymethyl chloride (4.65 mL, 26.3 mmol) was added. The mixture was stirred at room temperature for 20 h and at reflux for 2 h. A 25% $NH_4OAc$ solution was added, and the mixture was extracted with $CH_2Cl_2$. The organics were washed brine, dried over $MgSO_4$, filtered, and concentrated. The residual material was subjected to flash chromatography (silica gel, hexane/ethyl acetate, 9:1) to provide **17a** (3.28 g, 36%) as a yellow liquid. $^1H$ NMR (500 MHz): $\delta$ 0.01 (s, 9H), 0.87 (t, 2H), 1.65 (s, 6H), 3.67 (t, 2H), 4.79 (s, 2H), 7.51 (d, 1H), 7.69 (d, 1H).

**(±)-[(3-Cyclobutyloxy-4-difluromethoxy)phenyl]{2-[1-methyl-1-(2-trimethylsilylethoxy)methoxy]ethylthiazol-5-yl}methanol ((±)-18a).** To a solution of **17a** (1.72 g, 6.31 mmol) in ether (20 mL) at −78 °C was added n-BuLi (3.94 mL of a 1.6 M solution in hexane, 6.31 mmol) dropwise. After the mixture was stirred at this temperature for 30 min, a solution of **5b** (1.53 g, 6.31 mmol) in ether (4 mL) was added dropwise. After 45 min, 25% $NH_4OAc$ and ethyl acetate were added. The layers were separated, and the aqueous phase was extracted with ethyl acetate. The combined organics were washed successively with 25% $NH_4OAc$ buffer and brine, dried over $MgSO_4$, filtered, and concentrated. The residual material was subjected to flash chromatography (silica gel, hexane/ethyl acetate, 65:35) to provide (±)-**18a** (2.34 g, 72%) as a pale-yellow oil. $^1H$ NMR (500 MHz): $\delta$ 0.01 (s, 9H), 0.87 (dd, 2H), 1.59 (s, 3H), 1.60 (s, 3H), 1.71 (m, 1H), 1.82 (m, 1H), 2.13 (m, 2H), 2.45 (m, 2H), 3.65 (dd, 2H), 4.75 (m, 1H), 4.76 (s, 2H), 5.35 (d, 1H), 6.09 (d, 1H), 6.87 (t, 1H), 7.04 (dd, 1H), 7.12 (m, 2H), 7.47 (s, 1H).

**(±)-4-{2-[(3-Cyclobutyloxy-4-difluromethoxy)phenyl]-2-[5-(2-(1-methyl-1-[(2-trimethylsilylethoxy)methoxy]-ethyl)thiazolyl)]ethyl}pyridine ((±)-20a).** Following the procedures described for the preparation of (±)-**15** but substituting the alcohol (±)-**18a** (2.31 g, 4.48 mmol) for (±)-**13**, (±)-**20a** (2.26 g, 86%) was obtained as a pale-yellow gum. $^1H$ NMR (500 MHz): $\delta$ 0.00 (s, 9H), 0.87 (dd, 2H), 1.58 (s, 3H), 1.59 (s, 3H), 1.69 (m, 1H), 1.81 (m, 1H), 2.04 (m, 1H), 2.12 (m, 1H), 2.35−2.48 (m, 2H), 3.39 (dd, 1H), 3.46 (dd, 1H), 3.63 (dd, 2H), 4.70−4.75 (m, 2H), 4.74 (s, 2H), 6.82 (t, 1H), 6.92 (m, 2H), 7.06 (d, 1H), 7.15 (d, 2H), 7.48 (s, 1H), 8.37 (d, 2H).

**Separation of Enantiomers of (±)-20a.** A solution of (±)-**20a** (2.26 g) in 2-propanol/hexane (28 mL, 1:3.7) was injected (5 × 460 mg) onto a CHIRALPAK AD preparative (5 cm × 50 cm) HPLC column (eluting with hexane/2-propanol, 96:4, at 75 mL/min with UV detection at 280 nm). The enantiomers were separated with the faster eluting enantiomer having a retention time of ∼42 min (enantiomer 1) and the slower eluting enantiomer having a retention time of ∼52 min (enantiomer 2). The eluants were concentrated to provide the

**20a** enantiomer 1 (761 mg, >99% ee) as an off-white gum and the **20a** enantiomer 2 (547 mg, 92% ee) as an off-white gum.

**Chiral 4-{2-[(3-Cyclobutyloxy-4-difluromethoxy)phenyl]-2-[5-(2-(1-methyl-1-[(2-trimethylsilylethoxy)methoxy]-ethyl)thiazolyl)]ethyl}pyridine *N*-Oxide (21a).** Following the procedures described for the preparation of (±)-**11a** but substituting the **20a** enantiomer 1 (750 mg, 1.27 mmol) for (±)-**10a** and carrying out flash chromatography (silica gel) with $CHCl_3$/EtOH (95:5 to 92.5:7.5), chiral **21a** (713 mg, 92%) was obtained as a colorless gum. $^1$H NMR (500 MHz): $\delta$ 0.00 (s, 9H), 0.87 (dd, 2H), 1.58 (s, 3H), 1.59 (s, 3H), 1.68 (m, 1H), 1.82 (m, 1H), 2.04 (m, 1H), 2.14 (m, 1H), 2.38−2.47 (m, 2H), 3.38 (dd, 1H), 3.45 (dd, 1H), 3.64 (dd, 2H), 4.67 (t, 1H), 4.71 (m, 1H), 4.74 (s, 2H), 6.83 (t, 1H), 6.92 (m, 2H), 7.08 (d, 1H), 7.15 (d, 2H), 7.51 (s, 1H), 7.94 (d, 2H).

**(+)-4-{2-[(3-Cyclobutyloxy-4-difluromethoxy)phenyl]-2-[5-(2-(1-hydroxy-1-methyl)ethyl)thiazolyl]ethyl}pyridine *N*-Oxide ((+)-3a).** Following the procedures described for the preparation of (±)-**2c** but substituting chiral **21a** (710 mg, 1.17 mmol) for (±)-**16** and carrying out flash chromatography (silica gel) with $CHCl_3$/EtOH (9:1 to 85:15), (+)-**3a** (473 mg, 85%) was obtained as a white foam. $[\alpha]^{25}_D$ +43.7° (*c* 1.28, $CHCl_3$). $^1$H NMR (500 MHz): $\delta$ 1.51 (s, 3H), 1.52 (s, 3H), 1.68 (m, 1H), 1.81 (m, 1H), 2.04 (m, 1H), 2.13 (m, 1H), 2.38−2.49 (m, 2H), 3.38 (dd, 1H), 3.45 (dd, 1H), 4.66 (t, 1H), 4.75 (quintet, 1H), 4.90 (br s, 1H), 6.83 (t, 1H), 6.93 (m, 2H), 7.08 (d, 1H), 7.17 (d, 2H), 7.47 (s, 1H), 7.97 (d, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 13.1, 30.3, 30.66, 30.74, 41.9, 45.3, 72.3, 73.0, 113.6, 115.9 (t), 119.7, 122.8, 126.6, 138.77, 138.79, 139.1, 139.2, 140.0, 140.8, 149.2, 179.5. FAB HRMS ($C_{24}H_{27}N_2O_4SF_2$, M + $H^+$) calcd, 477.165 78; found, 477.165 96.

**2-{1-Trifluoromethyl-1-[(2-trimethylsilylethoxy)-methoxy]-2,2,2-trifluoroethyl}thiazole (17b).** To a solution of n-BuLi (280 mL of a 1.2 M solution in hexane, 336 mmol) in ether (200 mL) at −78 °C was added a solution of thiazole (25.31 g, 297 mmol) in ether (200 mL) over 50 min. After the mixture was stirred at this temperature for 45 min, hexafluoroacetone was bubbled into the solution for 30 min with the temperature being maintained between −65 and −70 °C. The cooling bath was removed, and the solution was warmed to room temperature. The mixture was partitioned between 25% $NH_4OAc$ and ether. The aqueous phase was acidified to pH 4 with concentrated HCl and then extracted with ether. The combined organics were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated. The crude material was distilled at ∼15 mmHg, collecting the fraction distilling between 40 and 100 °C (78 g). A portion of the pale-yellow liquid (57 g, 227 mmol) so obtained was dissolved in $CH_2Cl_2$ (800 mL) and diisopropylethylamine (80 mL, 459 mmol) and cooled to 0 °C. 2-(Trimethylsilyl)ethoxymethyl chloride (55 mL, 311 mmol) was added over 30 min. After the mixture was stirred at room temperature for 2 days, 25% $NH_4OAc$ was added and the mixture was extracted with $CH_2Cl_2$. The combined organics were washed brine, dried over $Na_2SO_4$, filtered, and concentrated. The residual material was subjected to flash chromatography (silica gel, hexane/ethyl acetate, 9:1) to provide **17b** (86 g, 100%) as a colorless liquid. $^1$H NMR (500 MHz): $\delta$ 0.02 (s, 9H), 0.96 (dd, 2H), 3.35 (dd, 1H), 5.12 (s, 1H), 8.02 (s, 1H).

**(±)-[(3-Cyclobutyloxy-4-difluromethoxy)phenyl]{2-[(1-trifluoromethyl-1-(2-trimethylsilylethoxy)methoxy)-2,2,2-trifluoro]ethylthiazol-5-yl}methanol ((±)-18b).** A solution of **17b** (7.03 g, 18.4 mmol) in ether (30 mL) was added to a −78 °C solution of n-BuLi (7.4 mL of a 2.5 M solution in hexane, 18.5 mmol) in ether (60 mL). After the mixture was stirred at −78 °C for 1 h, this solution was added via cannula to a −78 °C solution of **5b** (3.0 g, 12.4 mmol) in ether (30 mL). After 1 h, saturated $NH_4Cl$ and ethyl acetate were added. The layers were separated, and the aqueous phase was extracted with ethyl acetate. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residual material was subjected to flash chromatography (silica gel, hexane/ethyl acetate, 100:0 to 3:1) to provide (±)-**18b** (6.96 g, 90%) as a pale-yellow oil. $^1$H NMR (400 MHz): $\delta$ 0.01 (s, 9H), 0.93 (dd, 2H), 1.71 (m, 1H), 1.82 (m, 1H), 2.13 (m, 2H), 2.45 (m, 2H), 3.82 (dd, 2H), 4.76 (quintet, 1H), 5.09 (s, 2H), 5.70 (d, 1H), 6.23 (d, 1H), 6.87 (t, 1H), 7.10 (dd, 1H), 7.12 (d, 1H), 7.18 (d, 1H), 7.78 (s, 1H).

**(±)-4-{2-[(3-Cyclobutyloxy-4-difluromethoxy)phenyl]-2-[5-(2-(1-hydroxy-1-trifluoromethyl-2,2,2-trifluoro)ethyl)-thiazolyl]ethyl}pyridine *N*-Oxide ((±)-3b).** A solution of (±)-**18b** (1.98 g, 3.17 mmol) in toluene (20 mL) was added to a room temperature solution of pyridine (700 $\mu$L, 8.65 mmol) and $SOBr_2$ (350 $\mu$L, 4.5 mmol) in toluene (30 mL). After 10 min at room temperature, the mixture was applied directly to a plug of silica gel and eluted with ether and concentrated. The crude bromide (±)-**19b** was used immediately in the next reaction. To a solution of ethyl 4-pyridylacetate (1.62 g, 9.8 mmol) in THF (20 mL) and HMPA (1.8 mL, 10.3 mmol) at room temperature was added NaHMDS (9.5 mL of a 1 M solution in THF, 9.5 mmol) dropwise. After the mixture was stirred for 45 min, the crude bromide (±)-**19b** in THF (10 mL) was added dropwise. The mixture was stirred at room temperature for 15 h and then poured into water and diluted with ethyl acetate. The layers were separated, and the aqueous phase was extracted with ethyl acetate. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved in a mixture of THF/MeOH/water (3:1:1, 32 mL). $LiOH\cdot H_2O$ (3.4 g, 81 mmol) was added, and the mixture was heated at reflux for 4 h. After cooling to room temperature, the mixture was acidified to ∼pH 4−5 with 1 N HCl. The volatiles were removed on the rotovap, and the residue was partitioned between water and ethyl acetate. The aqueous phase was extracted with ethyl acetate. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash chromatography (silica gel, hexane/ethyl acetate 1:1 to 2:3) to provide the pyridine (±)-**20b** (436 mg, 20% from (±)-**18b**) as a yellow gum. To a solution of (±)-**20b** (436 mg, 0.62 mmol) in $CH_2Cl_2$ (10 mL) at 0 °C was added TFA (1 mL). After 1 h, the mixture was partitioned between ethyl acetate and 25% $NH_4OAc$. The aqueous phase was extracted twice with ethyl acetate. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash chromatography (silica gel, toluene/acetone, 7:3) to provide the free alcohol (277 mg, 75%) as a colorless foam. A mixture of this material (203 mg, 0.35 mmol) and MMPP (157 mg, 0.32 mmol) in $CH_2Cl_2$/MeOH (4:1, 10 mL) was stirred at room temperature for 48 h. The mixture was concentrated and partitioned between 1 N NaOH and $CH_2Cl_2$, and the aqueous phase was extracted with $CH_2Cl_2$. The combined organics were concentrated and the residue was subjected to flash chromatography (silica gel, $CH_2Cl_2$/MeOH, 93:7) to provide (±)-**3b** (100 mg, 48%) as a white foam. $^1$H NMR (400 MHz): $\delta$ 1.69 (m, 1H), 1.83 (m, 1H), 2.04 (m, 1H), 2.15 (m, 1H), 3.50 (dd, 1H), 3.59 (dd, 1H), 4.78 (quintet, 1H), 4.84 (t, 1H), 6.87 (t, 1H), 6.99 (dd, 1H), 7.01 (d, 1H), 7.13 (d, 1H), 7.21 (m, 2H), 7.84 (s, 1H), 7.99 (m, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 13.1, 30.3, 41.9, 45.3, 72.4, 113.6, 115.9 (t), 119.8, 121.5 (q), 123.1, 126.6, 138.6, 138.8, 139.0, 139.1, 139.7, 146.2, 149.5, 158.5. Anal. ($C_{24}H_{20}N_2O_4SF_8$) C, N. H: calcd, 3.45; found, 2.62. FAB HRMS ($C_{24}H_{21}N_2O_4SF_8$, M + $H^+$) calcd, 585.109 38; found, 585.109 43.

**(±)-[(3-Cyclopropyloxy-4-difluromethoxy)phenyl]{2-[(1-trifluoromethyl-1-(2-trimethylsilylethoxy)methoxy)-2,2,2-trifluoro]ethylthiazol-5-yl}methanol ((±)-18c).** A solution of **17b** (48.5 g, 127.2 mmol) in ether (100 mL) was added to a −78 °C solution of n-BuLi (80 mL of a 1.58 M solution in hexane, 126.4 mmol) in ether (250 mL), maintaining the temperature between −75 to −77 °C. After being stirred at −78 °C for 90 min, this solution was added via cannula to a −78 °C solution of **5c** (19.0 g, 83.3 mmol) in ether (200 mL). After 2.5 h, saturated $NH_4Cl$ and ethyl acetate were added. The layers were separated, and the aqueous phase was extracted with ethyl acetate. The combined organics were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated. The residual material was subjected to flash chromatography (silica gel, hexane/ethyl acetate, 95:5 to 1:1) to provide (±)-**18c** (47.9 g, 94%) as a pale-yellow oil. $^1$H NMR

(500 MHz): $\delta$ 0.02 (s, 9H), 0.72 (m, 2H), 0.81 (m, 2H), 0.95 (dd, 2H), 3.83 (dd, 2H), 3.91 (m, 1H), 5.10 (s, 2H), 5.77 (d, 1H), 6.28 (d, 1H), 6.80 (t, 1H), 7.12 (d, 1H), 7.17 (d, 1H), 7.60 (s, 1H), 7.80 (s, 1H).

**(±)-4-{2-[(3-Cyclopropyloxy-4-difluromethoxy)phenyl]-2-[5-(2-(1-hydroxy-1-trifluoromethyl-2,2,2-trifluoro)ethyl)-thiazolyl]ethyl}pyridine *N*-Oxide ((±)-3c).** A solution of (±)-**18c** (168 mg, 0.28 mmol) in toluene (2 mL) was added to a 0 °C solution of pyridine (80 $\mu$L, 0.99 mmol) and $SOBr_2$ (60 $\mu$L, 0.77 mmol) in toluene (3 mL). After 1 h at room temperature, the mixture was applied directly to a plug of Celite and eluted with toluene/ethyl acetate (4:1) and concentrated. The crude bromide (±)-**19c** was used immediately in the next reaction. To a solution of ethyl 4-pyridylacetate (170 $\mu$L, 1.11 mmol) in THF (5 mL) and HMPA (200 $\mu$L, 1.15 mmol) at 0 °C was added KHMDS (2.2 mL of a 0.5 M solution in toluene, 1.1 mmol) dropwise. After the mixture was stirred for 30 min, the crude bromide in THF (2 mL) was added dropwise. The mixture was stirred at room temperature for 15 h and then poured into saturated $NH_4Cl$ and diluted with ethyl acetate. The layers were separated, and the aqueous phase was extracted with ethyl acetate. The combined organics were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated. The residue was dissolved in a mixture of THF/MeOH/water (3:1:1, 10 mL). A 1.7 N LiOH (2 mL, 3.4 mmol) solution was added, and the mixture was heated at 60 °C for 2.5 h. After the mixture was cooled to room temperature, 2 N HCl (1.7 mL) was slowly added. The volatiles were removed on the rotovap, and the residue was partitioned between water and ethyl acetate. The aqueous phase was extracted with ethyl acetate. The combined organics were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated. The residue was subjected to flash chromatography (silica gel, hexane/ethyl acetate, 2:3 to 1:4) to provide the pyridine (75 mg, 49% from (±)-**18c**) as a yellow gum. A mixture of this material (97.6 mg, 0.18 mmol) and MMPP (180 mg, 0.36 mmol) in $CH_2Cl_2$/MeOH (10:1, 4.4 mL) was heated at 50 °C for 90 min. After cooling to room temperature, the mixture was immediately subjected to flash chromatography (silica gel, $CH_2Cl_2$/(10% $NH_4OH$ in MeOH), 9:1) to provide (±)-**3c** (68 mg, 68%) as a white foam. $^1$H NMR (500 MHz): $\delta$ 0.63 (m, 1H), 0.71−0.85 (m, 3H), 3.50 (dd, 1H), 3.58 (dd, 1H), 3.89 (m, 1H), 4.85 (dd, 1H), 6.77 (t, 1H), 6.98 (dd, 1H), 7.10 (d, 1H), 7.24 (d, 2H), 7.45 (d, 1H), 7.82 (d, 1H), 8.00 (d, 2H), 8.85 (br s, 1H). $^{13}$C NMR (125 MHz): $\delta$ 6.53, 6.57, 41.6, 45.3, 52.3, 115.5, 117.7 (t), 121.4, 122.8, 122.9 (q), 127.9, 138.7, 139.3, 140.0, 141.4, 141.5, 147.0, 151.5, 160.5. FAB HRMS ($C_{23}H_{19}N_2O_4SF_8$, M + H$^+$) calcd, 571.093 78; found, 571.093 99.

**(±)-3-{2-[(3-Cyclopropyloxy-4-difluromethoxy)phenyl]-2-[5-(2-(1-hydroxy-1-trifluoromethyl-2,2,2-trifluoro)ethyl)-thiazolyl]ethyl}pyridine *N*-Oxide ((±)-3d).** To a solution of ethyl 3-pyridylacetate *N*-oxide (146 g, 805.8 mmol) in THF (4 L) and HMPA (145 mL, 833.4 mmol) at 0 °C was added KHMDS (1.6 L of a 0.5 M solution in toluene, 800 mmol) via an addition funnel, maintaining the temperature at less than 7 °C. After being stirred at room temperature for 2 h, the mixture was recooled to 0 °C and a solution of (±)-**19c** (prepared as described above from 109.5 g, 179.2 mmol of alcohol (±)-**18c**) in THF (300 mL) was added, maintaining the temperature at less than 5 °C. After the addition was complete, the mixture was stirred at room temperature for 15 h and then poured into saturated $NH_4Cl$ (12 L) and diluted with ethyl acetate. The layers were separated, and the aqueous phase was extracted three times with ethyl acetate. The combined organics were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated. The residue was subjected to flash chromatography (silica gel, $CH_2Cl_2$/EtOH, 99:1 to 96:4) to provide the intermediate ester as a red foam (87.4 g, 63%). This material was dissolved in a mixture of THF/MeOH/water (3:1:1, 1 L). A 1.7 N LiOH (220 mL, 374 mmol) solution was added, and the mixture was heated at 60 °C for 4 h and at room temperature for 15 h. Then 2 N HCl (200 mL) was slowly added. The volatiles were removed on the rotovap, and the residue was partitioned between brine and ethyl acetate. The aqueous phase was extracted twice with ethyl acetate. The combined organics were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated to provide 90.4 g of crude acid (±)-**23** as a yellow foam. A portion of crude (±)-**23** (65.1 g) was dissolved in DMSO (600 mL) and heated at 130 °C for 2.5 h. The mixture was poured into water (3 L) and brine (600 mL) and extracted four times with $CH_2Cl_2$. The combined organics were washed three times with water, dried over $Na_2SO_4$, filtered, and concentrated. The residue was subjected to flash chromatography (silica gel, $CH_2Cl_2$/(10% $NH_4OH$ in MeOH), 95:5 to 9:1) to provide (±)-**3d** (34.8 g, 70% from (±)-**19c**) as a yellow foam. $^1$H NMR (500 MHz): $\delta$ 0.63 (m, 1H), 0.71−0.85 (m, 3H), 3.48 (dd, 1H), 3.57 (dd, 1H), 3.90 (m, 1H), 4.90 (dd, 1H), 6.79 (t, 1H), 7.01 (dd, 1H), 7.13 (m, 2H), 7.23 (t, 1H), 7.49 (s, 1H), 7.87 (s, 1H), 7.95 (d, 1H), 8.10 (s, 1H), 8.42 (br s, 1H).

**Separation of Enantiomers of (±)-3d.** A solution of (±)-**3d** (33 g) in EtOH/hexane (500 mL, 1:1) was injected (33 × 1 g) onto a CHIRALPAK AD preparative (5 cm × 50 cm) HPLC column (eluting with hexane/EtOH, 9:1, at 70 mL/min with UV detection at 290−293 nm). The enantiomers were separated with the faster eluting enantiomer having a retention time of ∼14 min (enantiomer 1) and the slower eluting enantiomer having a retention time of ∼24 min (enantiomer 2). The eluants were concentrated to provide (+)-**3d** (enantiomer 1, 13.5 g, >99% ee) as a yellow foam and (−)-**3d** (enantiomer 2, 2.69 g, 92% ee) as a yellow foam.

**(+)-3d** (enantiomer 1, 13.5 g) was recrystallized from EtOH (13 mL) and water (5 mL) to provide (+)-**3d** (5.34 g) as colorless crystals, mp 158−160 °C. Recrystallization of the mother liquors provided an additional 5.27 g of (+)-**3d**. $[\alpha]^{25}_D$ +60.56° (*c* 1, $CHCl_3$). $^{13}$C NMR (125 MHz): $\delta$ 6.5, 6.6, 39.8, 45.3, 52.3, 115.6, 117.6 (t), 121.3, 122.83, 122.84 (q), 126.6, 127.5, 137.9, 139.4, 140.0, 140.2, 141.2, 141.5, 147.0, 151.4, 160.5. Anal. ($C_{23}H_{18}N_2O_4F_8S$) C, N. H: calcd, 3.18; found, 2.02. FAB HRMS ($C_{23}H_{19}N_2O_4F_8S$, M + H$^+$) calcd, 571.093 78; found, 571.093 50.

**(−)-3d:** $[\alpha]^{25}_D$ −56.03° (*c* 1, $CHCl_3$). $^{13}$C NMR (125 MHz): $\delta$ 6.5, 6.6, 39.9, 45.3, 52.3, 115.6, 117.6 (t), 121.3, 122.85, 122.86 (q), 126.7, 127.5, 138.0, 139.5, 140.0, 140.2, 141.3, 141.5, 147.0, 151.5, 160.5. FAB HRMS ($C_{23}H_{19}N_2O_4F_8S$, M + H$^+$) calcd, 571.093 78; found, 571.093 86.

**(±)-[(3-Cyclobutyloxy-4-difluoromethoxy)phenyl][4-(1-*tert*-butyldiphenylsilyloxymethyl)phenyl]methanol ((±)-26).** To a solution of 4-bromo-2-(*tert*-butyldiphenylsilyloxymethyl)benzene[41] (**25**, 8.53 g, 20.0 mmol) in THF (20 mL) at −78 °C was added n-BuLi (12.5 mL of a 1.6 M solution in hexane, 20.0 mmol) dropwise. After the mixture was stirred at this temperature for 30 min, a solution of **5b** (4.05 g, 16.7 mmol) in THF (10 mL) was added dropwise and then stirred for 2.5 h. The mixture was partitioned between 25% $NH_4OAc$ and ethyl acetate, the layers were separated, and the aqueous phase was extracted with ethyl acetate. The combined organics were washed successively with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash chromatography (silica gel, hexane/ethyl acetate, 85:15 to 4:1) to provide (±)-**26** (6.12 g, 62%) as an amber gum. $^1$H NMR (500 MHz): $\delta$ 1.07 (s, 9H), 1.70 (m, 1H), 1.82 (m, 1H), 2.12 (m, 2H), 2.44 (m, 2H), 4.53 (quintet, 1H), 4.69 (s, 2H), 4.92 (d, 1H), 5.80 (d, 1H), 6.83 (t, 1H), 6.99 (m, 1H), 7.08 (m, 2H), 7.34 (d, 2H), 7.40−7.50 (m, 8H), 7.71 (m, 4H).

**(±)-4-{2-[3-Cyclobutyloxy-4-difluoromethoxy)phenyl]-2-[4-(1-hydroxymethyl)phenyl]ethyl}pyridine ((±)-28).** A solution of (±)-**26** (6.12 g, 10.4 mmol) in toluene (10 mL) was added to a room temperature solution of $SOCl_2$ (0.91 mL, 12.5 mmol) and pyridine (2.10 mL, 26.0 mmol) in toluene (10 mL). After 25 min, the mixture was filtered and washed with toluene and the filtrates were concentrated to provide crude (±)-**27** as an amber oil that was used immediately in the next reaction without further purification. To a solution of ethyl 4-pyridylacetate (4.8 mL, 31.2 mmol) in THF (50 mL) and HMPA (5.4 mL, 31.2 mmol) at room temperature was added KHMDS (62.4 mL of a 0.5 M solution in toluene, 31.2 mmol) dropwise over 10 min. After the mixture was stirred for a further 20 min, a solution of (±)-**27** in THF (25 mL) was added dropwise over 15 min. The mixture was stirred at room

temperature for 15 h and then poured into saturated $NH_4Cl$ (1.5 L). The layers were separated, and the aqueous phase was extracted two times with ethyl acetate. The combined organics were washed successively with 25% $NH_4OAc$ buffer and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved in a mixture of THF/MeOH/water (3:1:1, 100 mL). LiOH (2.49 g, 104 mmol) was added, and the mixture was heated at 70 °C for 4 h. After the mixture was cooled to room temperature, 1 N HCl (105 mL) was slowly added and the resulting solution was stirred for 20 min. The volatiles were removed on the rotovap, and the residue was partitioned between water and ethyl acetate. The aqueous phase was extracted twice with ethyl acetate. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash chromatography (silica gel, hexane/ethyl acetate, 1:1 to 100% ethyl acetate) to provide (±)-**28** (1.80 g, 41% from (±)-**26**) as an orange gum. $^1$H NMR (500 MHz): $\delta$ 1.66 (m, 1H), 1.80 (m, 1H), 2.00−2.12 (m, 2H), 2.40 (m, 2H), 3.42 (m, 2H), 4.20 (br s, 1H), 4.42 (t, 1H), 4.55 (s, 2H), 4.71 (quintet, 1H), 6.80 (t, 1H), 6.90 (dd, 1H), 6.94 (s, 1H), 7.02 (d, 1H), 7.14 (d, 2H), 7.26 (d, 2H), 7.33 (d, 2H), 8.33 (d, 2H).

**(±)-4-{2-[3-Cyclobutyloxy-4-difluoromethoxy)phenyl]-2-[4-(1-carbomethoxy)phenyl]ethyl}pyridine ((±)-30).** To a solution of (±)-**28** (1.36 g, 3.20 mmol) in acetone (20 mL) at 0 °C was added $KMnO_4$ (2.52 g, 16 mmol), and the mixture was stirred at room temperature for 2 h. After the mixture was recooled to 0 °C, 10% $Na_2S_2O_3$ was added and the resulting mixture was filtered through Celite and washed with acetone. Water was added to the filtrate, and the mixture was extracted twice with ethyl acetate. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated to provide crude (±)-**29** (1.01 g, 72%) as a white solid. A portion of this material (206 mg, 0.47 mmol) was suspended in MeOH (3 mL) at room temperature, and a solution of $CH_2N_2$ in ether was added until the starting material was consumed. The mixture was concentrated and the residue was subjected to flash chromatography (silica gel, hexane/ethyl acetate, 1:4 to 100% ethyl acetate) to provide (±)-**30** (150 mg, 70%) as an oil. $^1$H NMR (500 MHz): $\delta$ 1.65 (m, 1H), 1.80 (m, 1H), 2.09 (m, 2H), 2.40 (m, 2H), 3.48 (m, 2H), 3.83 (s, 3H), 4.55 (t, 1H), 4.73 (quintet, 1H), 6.80 (t, 1H), 6.95 (m, 2H), 7.05 (d, 1H), 7.15 (d, 2H), 7.51 (d, 2H), 7.90 (d, 2H), 8.34 (d, 2H).

**(±)-4-{2-[(3-Cyclobutyloxy-4-difluoromethoxy)phenyl]-2-{4-[1-(1-hydroxy-1-methyl)ethyl]phenyl}pyridine *N*-Oxide ((±)-4).** To a solution of (±)-**30** (150 mg, 0.33 mmol) in $CH_2Cl_2$ (5 mL) at −78 °C was added MeMgBr (550 $\mu$L of a 3 M solution in ether, 1.65 mmol). The mixture was slowly warmed to room temperature over 1 h and then stirred at this temperature for 1 h. A 25% $NH_4OAc$ solution was added, and the mixture was extracted twice with ethyl acetate. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude alcohol (±)-**31** (140 mg, 93%) was used as such in the subsequent reaction. To a solution of (±)-**31** (140 mg, 0.31 mmol) in $CH_2Cl_2$/MeOH (10:1, 4.4 mL) at room temperature was added MMPP (153 mg, 0.31 mmol). After being stirred for 2.5 h, the mixture was partitioned between ethyl acetate and saturated $NaHCO_3$. The aqueous phase was extracted with ethyl acetate. The combined organics were washed with saturated $NaHCO_3$, water, and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash chromatography (silica gel, $CH_2Cl_2$/EtOH, 95:5 to 85:15) to provide (±)-**4** (89 mg, 61%) as a white foam. $^1$H NMR (500 MHz): $\delta$ 1.45 (s, 6H), 1.65 (m, 1H), 1.80 (m, 1H), 2.10 (m, 2H), 2.40 (m, 2H), 3.42 (d, 2H), 4.01 (br s, 1H), 4.36 (t, 1H), 4.74 (quintet, 1H), 6.80 (t, 1H), 6.94 (m, 2H), 7.03 (d, 1H), 7.15 (d, 2H), 7.30 (d, 2H), 7.43 (d, 2H), 7.92 (d, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 13.0, 30.4, 31.66, 31.71, 40.5, 51.5, 72.2, 114.1, 116.0 (t), 119.8, 122.7, 124.8, 126.5, 127.4, 138.7, 139.6, 140.6, 141.7, 147.9, 149.0. Anal. ($C_{27}H_{29}NO_4F_2$) C, H, N.

**Measurement of Rat $t_{1/2}$.** Male Sprague−Dawley rats (two to four) were starved overnight and then dosed intravenously in the jugular vein with compounds dissolved in 60% PEG 200/water at a dose of 5 mg/kg in a dose volume of 1 mL/1 kg body weight. Blood was taken from the jugular vein at 0, 5, 15, and 30 min and at 1, 2, 4, 6, 8, and 24 h after dosing. The blood was centrifuged, and the plasma was collected. To 100 $\mu$L of each plasma sample was added an equal volume of acetonitrile to precipitate protein. After centrifugation, an aliquot of the supernatant was subjected to reverse-phase HPLC analysis. The parent compound was quantitated from the area of the pertinent peak relative to standard curves obtained by spiking rat plasma with varying concentrations of the compound. The $t_{1/2}$ was calculated from the analysis of the averaged plasma concentrations observed from 5 min to 24 h.

**Supporting Information Available:** Full details of the X-ray structural analysis of (*S*)-(+)-**3d** (five tables and ORTEP drawing). This material is available free of charge via the Internet at http://pubs.acs.org.

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