Chiral *N,N*-Disubstituted Trifluoro-3-Amino-2-Propanols Are Potent Inhibitors of Cholesteryl Ester Transfer Protein

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Received January 25, 2002

A novel series of substituted *N*-benzyl-*N*-phenyl-trifluoro-3-amino-2-propanols are described that reversibly inhibit cholesteryl ester transfer protein (CETP). Starting with screening lead **22**, various structural features were explored with respect to inhibition of the CETP-mediated transfer of [^{3}H]cholesterol from high-density cholesterol donor particles to low-density cholesterol acceptor particles. The free hydroxyl group of the propanol was required for high potency, since acylation or alkylation reduced activity. High inhibitory potency was also associated with 3-ether moieties in the aniline ring, and the highest potencies were exhibited by 3-phenoxyaniline analogues. Activity was substantially reduced by oxidation or substitution in the methylene of the benzylic group, implying that the benzyl ring orientation was important for activity. In the benzylic group, substitution at the 3-position was preferred over either the 2- or the 4-positions. Highest potencies were observed with inhibitors in which the 3-benzylic substituent had the potential to adopt an out of plane orientation with respect to the phenyl ring. The best 3-benzylic substituents were OCF_2CF_2H (**42**, IC_{50} 0.14 μM in buffer, 5.6 μM in human serum), cyclopentyl (**39**), 3-*iso*-propoxy (**27**), SCF_3 (**67**), and $C(CF_3)_2OH$ (**36**). Separation of **42** into its enantiomers unexpectedly showed that the minor *R*(+) enantiomer **1a** was 40-fold more potent (IC_{50} 0.02 μM in buffer, 0.6 μM in human serum) than the major *S*(−) enantiomer **1b**, demonstrating that the *R*-chirality at the propanol 2-position is key to high potency in this series. The *R*(+) enantiomer **1a** represents the first reported acyclic CETP inhibitor with submicromolar potency in plasma. A chiral synthesis of **1a** is reported.

Introduction

Epidemiological[1] and clinical[2] studies have demonstrated an inverse relationship between serum high-density cholesterol (HDLc) levels and the incidence of coronary heart disease (CHD). Interventions that raise HDLc have been shown to reduce CHD events,[3,4] whether significant lowering of plasma low-density cholesterol (LDLc) occurs.[5]

Cholesteryl ester transfer protein (CETP) is a plasma carrier glycoprotein that transfers cholesteryl ester (CE) from HDL to very low-density lipoprotein (VLDL) and LDL in exchange for triglyceride (TG).[6−8] There have been several suggestions that CETP plays a proatherogenic role, since CETP lowers cardioprotective HDLc. Thus, inhibiting CETP activity should elevate HDLc and provide a potential therapeutic benefit for patients with CHD.[7−9] There are numerous animal studies that support these hypotheses. For example, transgenic mice expressing simian CETP were observed to develop severe atherosclerosis,[10] rabbits treated with a covalent modifier of CETP[11] had elevated HDLc and exhibited attenuated atherosclerosis,[12] and cholesterol-fed rabbits treated with designed antisense oligodeoxynucleotides also had elevated HDLc and showed significantly reduced aortic lesions.[13] However, the effects of lowering of CETP activity in humans are less clear.[14] On one hand, lowering CETP has been shown to be protective. For example, subjects with a genetic deficiency for CETP had marked hyperalphalipoproteinemia and were protected against atherosclerosis,[15] and analysis for CETP polymorphism in the Framingham Offspring Study identified the Taq 1B−B2 allele in men associated with significantly reduced CETP activity, elevated HDLc, and a reduced risk for CHD.[16] On the other hand, those populations exhibiting hyperalphalipoproteinemia were only protected against atherosclerosis below a certain level of HDLc,[17] and there is evidence to suggest that elevated HDLc levels in certain populations with a common CETP amino polymorphism (Ile405Val) are associated with increased risk for CHD.[18−20] Furthermore, CETP has been suggested to participate in the movement of cholesterol from peripheral cells to the liver for catabolism, a process known as reverse cholesterol transport.[6]

Despite the controversy of the role of CETP in the progression of atherosclerosis, there has been considerable interest in finding inhibitors of CETP. Small molecule CETP inhibitors from a variety of structural classes including sterols, polycyclic natural products, and heterocycles are known.[7] Each class of known

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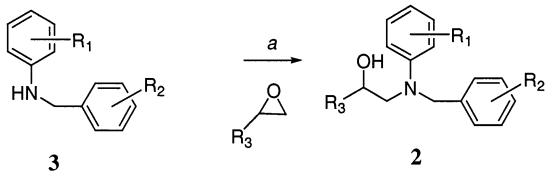
10.1021/jm020038h CCC: $22.00
Published on Web 08/03/2002

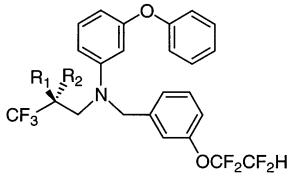
Scheme 1[a]



[a] Reagents: (a) 2-Substituted oxirane, $Yb(CF_3SO_3)_3$, CH_3CN, 50 °C, 2 h. R_1 and R_2 defined in Tables 1−4; $R_3 = CF_3$ or defined in Table 5.

inhibitors appears to require a central core ring for activity. Representative members of these classes typically exhibit modest micromolar IC_{50} values for inhibiting CETP-mediated transfer of ^{3}H-CE from HDL to LDL under buffered assay conditions in vitro.[7] To date, no CETP inhibitor class, either reversible or irreversible, has been described that exhibits submicromolar activity when this CETP-mediated transfer process is assayed in the presence of human plasma.[7] However, recently, a series of tetrahydronaphthalene derivatives have been reported with low nanomolar potency in vitro,[21] and a series of tetrahydoquinoline derivatives have been reported (activity not given).[22]

Herein, we describe the identification *N*,*N*-disubstituted trifluoro-3-amino-2-propanols as an unusually simple class of CETP inhibitors. Subsequent modification of these inhibitors led to the chiral *R*-(+)-trifluoropropanol derivative **1a** having low nanomolar potency in vitro under buffered conditions and submicromolar potency in the presence of human serum. This novel class thus represents the first alicyclic series exhibiting significant inhibitory activity for the CETP system. We also report the contributions of the trifluoromethyl and alcohol moieties to inhibitor potency and significantly extend the structure−activity relationship (SAR) based upon modifications of the benzylic haloalkoxy ether group. The discovery of **1a** was briefly reported in an earlier communication.[23]



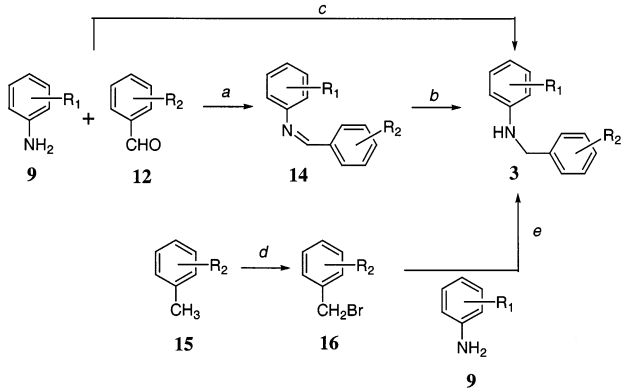
(*R*)-**1a** $R_1 = H$, $R_2 = OH$

(*S*)-**1b** $R_1 = OH$, $R_2 = H$

Chemistry

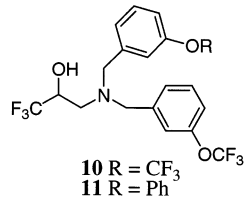
N,*N*-Disubstituted trifluoro-3-amino-2-propanols **2** were readily prepared from the ring-opening reaction of commercially available 2-trifluoromethyloxirane of unspecified enantiomeric composition with the appropriate *N*-benzylaniline **3** (Scheme 1, $R_3 = CF_3$). This reaction proceeded smoothly in the presence of ytterbium(III) triflate in warm acetonitrile. The ytterbium triflate helps the reaction proceed at lower temperature and minimizes the need for large excess quantities of volatile epoxide due to thermal loss. The epoxide ring-opening reaction proceeded with complete regioselectivity, since none of the isomeric 2-amino-3-propanol product was detected. Other *N*,*N*-disubstituted alkanolamines **4**−**8** (Table 5) were prepared similarly from the

Scheme 2[a]

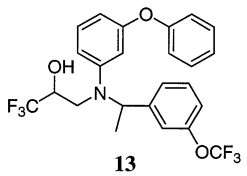


[a] Reagents: (a) Cyclohexane, heat, $-H_2O$. (b) $NaBH_4$, CH_3OH. (c) $NaBH(OAc)_3$, AcOH, DCE, room temperature. (d) NBS, AIBN, CCl_4, heat. (e) Cyclohexane, heat. R_1 and R_2 defined in Tables 1−4.

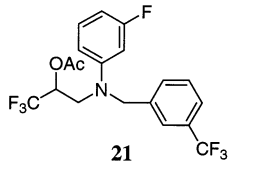
appropriate 2-alkyloxiranes. The required *N*-benzylanilines **3** were conveniently prepared by standard reductive amination or alkylation sequences (Scheme 2). The aniline **9** (or benzylamine in the case of **10** and **11**) was treated with an appropriate benzaldehyde **12** (or ketone in the case of **13**) to generate imine **14**, which was then reduced with sodium borohydride to give the *N*-benzylaniline **3**. Reduction of imine **14** to **3** with ^{3}H-sodium borohydride provided a convenient entry to radiolabeled analogues. Alternatively, direct reductive amination of a mixture of **9** and **12** with sodium triacetoxyborohydride also gave **3**. In cases where the benzaldehyde **12** was difficult to access, radical bromination of a suitable toluene **15** gave the bromomethylbenzene **16**, which could be used to prepare **3** by reaction with an excess of aniline **9**.



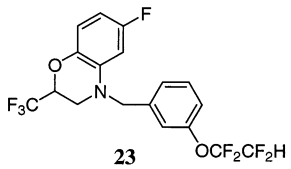
10 $R = CF_3$
11 $R = Ph$



13



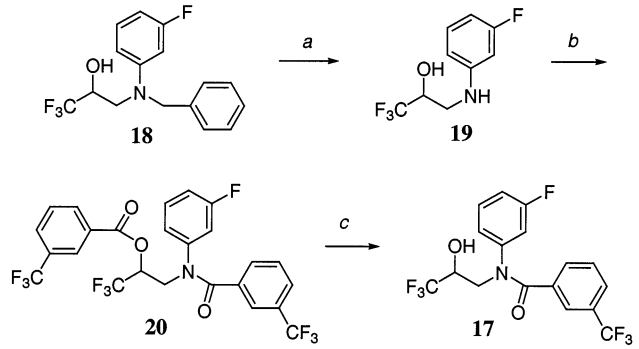
21



23

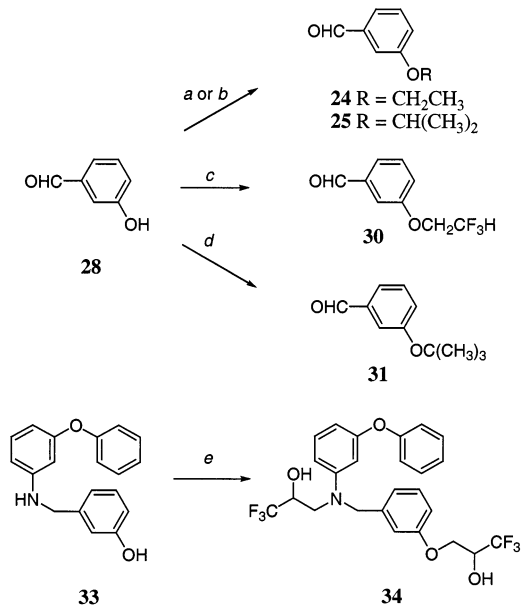
The benzamide **17** was prepared from **18** by treatment with hydrogen over Pd/C to give the secondary amine 19 (Scheme 3). Subsequent treatment of **19** with 3-trifluomethylbenzoyl chloride produced the mixed bis-trifluoromethylbenzoylamide ester **20**, which was hydrolyzed to the benzamide **17** with methanolic ammonia. The acetate **21** was synthesized from **22** (see Table 2) by treatment with acetic anhydride in the presence of triethylamine. Benzoxazine **23** was obtained from 3-[(2,5-difluoro-phenyl)[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol, as prepared by Schemes 1 and 2 (above), by treatment with K_2CO_3 in refluxing dimethylformamide (DMF). Aldehydes **24** and **25**, used in the preparation of **26** and **27** (see Table 4), were synthesized from 3-hydroxy benzaldehyde **28** by

Scheme 3[a]



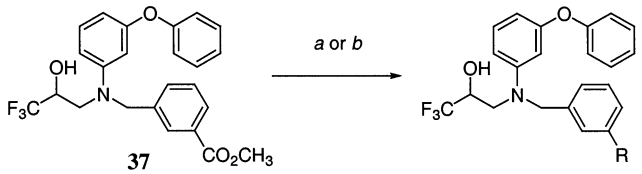
[a] Reagents: (a) H_2, 5% Pd/C, CH_3OH. (b) 3-CF_3PhCOCl, $CHCl_3$. (c) NH_3, CH_3OH.

Scheme 4[a]



[a] Reagents: (a) $(CH_3)_2CHI$, K_2CO_3, *i*-propanol, reflux, 8 h. (b) CH_3CH_2I, $NaOCH_3$, CH_3OH, reflux, 16 h. (c) (i) $NaOCH_3$/MeOH; (ii) $CF_3CH_2OSO_2PhCH_3$, NMP, 90 °C, 24 h. (d) $CCl_3C(NH)OC(CH_3)_3$, $BF_3{\cdot}(CH_3CH_2)_2O$, cyclohexane. (e) 2-Trifluoromethyloxirane, 95 °C, 30 h.

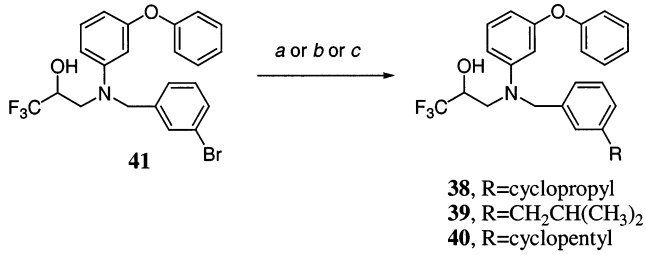
Scheme 5[a]



[a] Reagents: (a) CH_3MgCl, THF, 0 °C, room temperature, 2 h. (b) $CF_3Si(CH_3)_3$, tetrabutylammonium fluoride, toluene, 40 °C, 18 h.

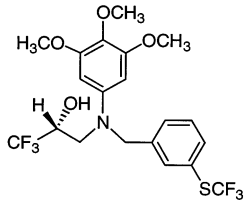
treatment with the alkyl iodides in the presence of base (Scheme 4). For **29,** the aldehyde **30** was prepared similarly, using the more reactive alkyl *p*-toluenesulfonate. To form the 3-*tert*-butyloxybenzaldehyde **31** used in the preparation of **32** (see Table 4), *tert*-butyl-2,2,2-trichloroacetimidate in the presence of BF_3-Et_2O was required (Scheme 4). Epoxide ring opening by both the secondary amino and the phenolic hydroxyl functions of **33** afforded the diol **34** (Scheme 4).

Scheme 6[a]



[a] Reagents: (a) CyclopropylMgBr, $Pd(PPh_3)_4$, THF, reflux. (b) $((CH_3)_2CHCH_2)MgBr$, $Pd(PPh_3)_4$, THF, reflux. (c) Cyclopentyl-MgBr, $Pd(PPh_3)_4$, THF, reflux.

Inhibitors **35** and **36** were prepared from the methyl benzoate **37** either by treatment with excess CH_3MgCl or with excess $CF_3Si(CH_3)_3$ in the presence of tetrabutylammonium fluoride (Scheme 5). The 3-alkyl analogues **38**−**40** were synthesized from the bromo intermediate **41** by reaction with the appropriate alkylmagnesium bromide in the presence of catalyst, $Pd(PPh_3)_4$ (Scheme 6).



Unexpectedly, the potent *N*,*N*-disubstituted trifluoro-3-amino-2-propanol **42** (see Table 4) was shown by analytical chiral chromatography to consist of a 7:1 mixture of enantiomers. Independent chiral gas chromatography (GC) analysis of the corresponding diethylamine adducts confirmed that the commercial 2-trifluoromethyloxirane reagent also contained a 7:1 mixture of the individual *S*(−)- and *R*(+)-enantiomers. The individual enantiomers of **42** were conveniently isolated by standard preparative chiral chromatography. The activity[24] was shown to reside in the minor (+)-isomer, **1a**, which was prepared independently from the reaction of *N*-(3-phenoxyphenyl)-[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amine with the known chiral epoxide, *R*-(+)-2-trifluoromethyloxirane.[25] To confirm the (*R*)-configuration at the chiral carbon in (+)-**1a**, a crystalline analogue **43** was prepared from the reaction of *N*-(3,4,5-trimethoxyphenyl)-[[3-(trifluoromethyl-thio)-phenyl]methyl]amine with *R*-(+)-1,1,1-trifluoro-2,3-epoxypropane, and its structure was determined by X-ray crystallography (Figure 1).

Results and Discussion

An initial chemical lead **22**, identified through screening a combinatorial library, had promising activity (IC_{50} 40 μM) as a CETP inhibitor in a simple buffer assay.[24,26,27] In a similar assay, but in the presence of human serum, which provided the source of the LDL, VLDL, and human CETP, the inhibitory activity (IC_{50} > 200 μM) was markedly reduced.[26,27] The IC_{50} value in human serum is indicative of the inhibitory activity in the target tissue, human blood, when other plasma

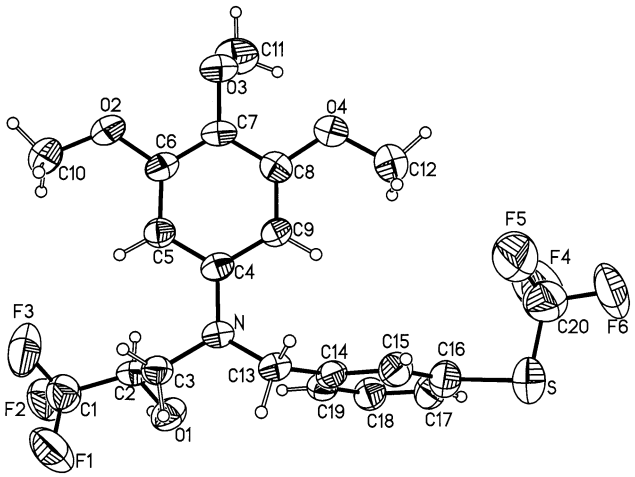
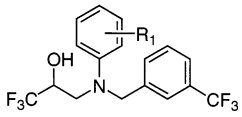


Figure 1. Projection plot of **43** with 30% thermalellipsoids for nonhydrogen atoms confirming the (*R*)-configuration at the C2 alcohol center.

Table 1. Aniline Ring Modifications of *N*-Phenyl-*N*-(3-trifluoromethy)benzyl-trifluoro-3-amino-propanols



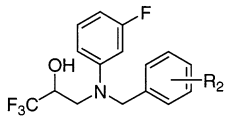
inhibitor	R_1	IC_{50} (μM) in buffer[a]	inhibitor	R_1	IC_{50} (μM) in buffer[a]
22	3-F	37	**47**	H	15
44	3-Cl	12	**48**	2-CH_3	>100
45	3-CF_3	10	**49**	4-CH_3	>100
46	3-CH_3	10			

[a] Ref 24.

lipoproteins are present. We suspect that this value is lower than that in buffer due to nonspecific binding of the inhibitors to nontarget blood proteins. The simplicity of the chemistry needed to prepare **22** suggested that a wide variety of structural modifications could be readily incorporated to explore the SAR within this interesting new class.

As summarized below, several key structural changes provided insights into the SAR and suggested a direction for further modifications. Replacing the aniline 3-F group of **22** with Cl (**44**), CF_3 (**45**), or CH_3 (**46**) increased potency 3−4-fold (Table 1). Removal of the 3-F substituent altogether (**47**) retained the potency, implying that the aniline 3-substituent was open to broad modification. However, substitution in the 2-position with CH_3 (**48**) dramatically reduced activity. Ortho substituents would likely effect the respective orientation of the two phenyl rings, and this in turn may be critical for potency. Moving the CH_3 group to the 4-position (**49**) also reduced activity. Next, keeping the 3-fluoro group in the aniline ring and the trifluoropropanol chain constant, various modifications to the benzylic group were examined. If the benzylic methylene was replaced by CO, as in the benzamide **12**, activity was reduced significantly (buffer IC_{50} > 100 μM). Removal of the benzylic 3-CF_3 group (**50**) or a change to a CH_3 group in either the 3-position (**51**) or the 4-position (**52**) also significantly reduced activity (Table 2), implying that the benzylic 3-substituent was critical for potency. Also, substitution in the benzylic 2-position lowered potency

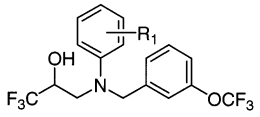
Table 2. Benzyl Ring Modifications of *N*-(3-Fluoro)phenyl-*N*-benzyl-trifluoro-3-amino-propanols



inhibitor	R_2	IC50 (μm) in buffer[a]	inhibitor	R_2	IC50 (μm) in buffer[a]
22	3-CF_3	37	**55**	3-OPh	15
50	H	>100	**56**	4-Ph	20
51	3-CH_3	>100	**57**	3-[(3-CF_3)-OPh	>100
52	4-CH_3	65	**58**	3-OCF_3	12
53	2-CF_3	>100	**59**	3-OCF_2CF_2H	4.5
54	2-CH_3	>100			

[a] Ref 24.

Table 3. Aniline Ring Modifications of *N*-Phenyl-*N*-(3-trifluoromethoxy)benzyl-trifluoro-3-amino-propanols



inhibitor	R_1	IC_{50} (μM) in buffer[a]	IC_{50} (μM) in plasma[a,b]
58	3-F	12	ND
60	3-OCF_3	1.5	46
61	3-OPh	1.0	40
62	4-OPh	25	ND

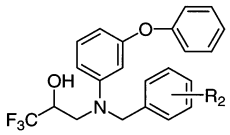
[a] Ref 24. [b] ND, not determined.

(**53** and **54**), possibly for the same reason suggested above for the 2-position in the aniline ring. The benzylic 3-phenoxy (**55**) and 4-phenyl (**56**) analogues were twice as potent as the 3-CF_3 analogue, indicating that larger groups could be accommodated at this position. However, the 3-(3-CF_3-phenoxy) analogue **57** was less potent suggesting that a defined size or steric constraint existed at this position. Other analogues were prepared with various substituents in the benzylic 3-phenoxy ring, but none of these enhanced potency, so the 3-phenoxy approach was not pursued. However, an analogue of **22** with a 3-OCF_3 substituent in the benzylic ring (**58**) was potent, and even more potent was the extended 3-OCF_2CF_2H analogue **59**. Both the acetate **21** (buffer IC_{50} 70 μM) and the constrained benzoxazine analogue **23** (buffer IC_{50} 15 μM) were less potent than their free hydroxyl counterparts (**22** and **59**, respectively) implying that a free hydroxyl group was important for high potency in this series.

A second round of aniline ring modifications was conducted, this time utilizing the more potent inhibitor **58** containing a 3-OCF_3 substituent in the benzylic ring (Table 3). An analogue with a 3-OCF_3 group in the aniline ring (**60**) identified the first low micromolar inhibitor, and more importantly, **60** now exhibited some inhibitory activity in the presence of human serum (IC_{50} 46 μM). Even more potent was the aniline 3-phenoxy analogue **61**. The preferred meta orientation for this aniline 3-phenoxy group was demonstrated by preparing the corresponding 4-positional isomer as in **62**, which exhibited 25-fold lower activity in buffer.

On the basis of the aniline 3-phenoxy analogue **61**, a second round of benzyl ring modifications was carried out (Table 4). Substitution in the benzylic methylene

Table 4. Benzyl Ring Modifications of *N*-(3-Phenoxy)phenyl-*N*-benzyl-trifluoro-3-amino-propanols



inhibitor	R_2	IC_{50} (μm) in buffer[a]	IC_{50} (μm) in plasma[a,b]
61	3-OCF_3	1.0	40
63	4-OCF_3	3.5	120
64	3,4-(OCF_2CF_2O)	12	ND
65	3-OCH_3	15	>200
26	3-OCH_2CH_3	1.6	70
29	3-OCH_2CF_3	1.0	65
66	3-OPh	5.2	70
32	3-O-*t*-Bu	0.66	29
27	3-OPr^i	0.35	21
42	3-OCF_2CF_2H	0.14	5.6
34	3-$OCH_2CH(OH)CF_3$	1.3	62
67	3-SCF_3	0.39	24
38	3-[(2-CH_3)-Pr]	0.54	ND
39	3-cyclopentyl	0.30	ND
40	3-cycloPr	1.0	ND
35	3-$C(CH_3)_2OH$	7.8	ND
36	3-$C(CF_3)_2OH$	0.42	4.9
37	3-CO_2CH_3	16	ND

[a] Ref 24. [b] ND, not determined.

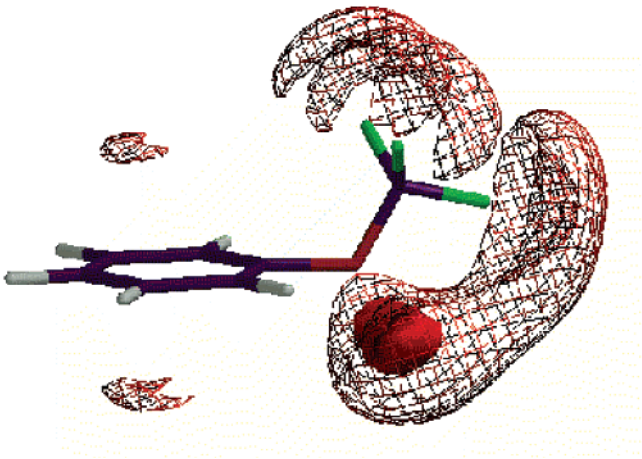
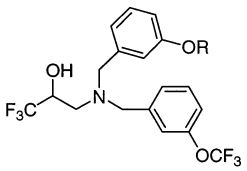


Figure 2. Negative electrostatic potential for $PhOCF_3$ showing electron dense areas out of plane on the ring.[29]

with a methyl group as in **13** voided the activity (buffer IC_{50} > 100 μM) (compare with **17**), again implying that the orientation of the benzyl group to the phenyl ring was important for activity. Moving the benzylic 3-OCF_3 group in **61** to the 4-position as in **63** reduced activity. The fluorinated benzodioxane analogue **64** also had less potency. The 3-CH_3O analogue **65** was 15-fold less potent than **61**, indicating that meta-haloalkoxy groups were preferred for activity. Interestingly, the 3-OCH_2CH_3 and 3-OCH_2CF_3 analogues (**26** and **29**) were more potent than **65** but not more so than **61**. Ab initio calculations with Gaussian 94 predicted that the 3-OCF_3 group is nearly perpendicular (about 90°) to the plane of the phenyl ring in $PhOCF_3$ at the lowest torsional energy conformation (Figure 2).[28,29] This out of plane orientation with respect to the phenyl ring is due to the electron-withdrawing effect of the fluorine atoms, which causes the oxygen to have sp^3 character. This unusual substituent orientation would not be expected in the 3-alkoxy analogues **26**, **29**, and **65**, which would be expected to adopt a more coplanar orientation.[28]

In an effort to explore the contribution of this out-of-plane spatial orientation (Figure 2)[29] to the potency of **61**, additional ether analogues were prepared to replace the 3-OCF_3 group with other nonplanar 3-substituents. Whereas the 3-phenoxy analogue **66** had lower potency than **61**, the more hindered 3-*tert*-butyloxy and 3-*i*-propyloxy analogues **32** and **27** were extremely potent, exhibiting submicromolar buffer IC_{50} values and improved potency vs **61** in the presence of serum. The highest potency, however, was exhibited by the extended 3-(1,1,2,2-tetrafluoroethoxy) analogue **42** (IC_{50} 0.14 μM) with submicromolar potency in buffer and significant low micromolar potency in the presence of human serum (IC_{50} 5.6 μM). Compound **42** therefore represents a more than 250-fold potency increase over the original screening lead **22**.

The presence of a free hydroxyl on the benzylic 3-ether substituent as in **34** did not improve potency vs **61**, and **34** was 10-fold less potent than **42**. Changing the benzylic 3-OCF_3 group to the corresponding thioether SCF_3 analogue **67** improved potency slightly vs **61**, but **67** showed no advantage over **42**. A heteroatom was not required for potency as a linking group at the benzylic 3-position. For example, replacing the oxygen linker from the potent 3-isopropoxy analogue **27** gave the carbon-linked *iso*-butyl analogue **38** with activity comparable to **27**. The related carbocyclic analogue **39** incorporating a cyclopentyl ring also exhibited potency similar to **27** and **38**, but the smaller cyclopropyl system as in **40** had somewhat reduced activity. Heteroaryl replacements were also examined,[30] and of these, the 2-furyl analogue was the most potent (IC_{50} 0.48 μM). Interestingly, the activity of the hindered tertiary alcohol **35** was nearly 8-fold weaker than **61**, but the related bis-trifluoromethyl carbinol **36** had 15-fold higher potency than **35**. Thus, **36** exhibited submicromolar potency in the buffer assay and low micromolar potency (IC_{50} 4.9 μM) comparable to **42** in the serum assay. The intermediate carboxy ester (**37**) had 16-fold lower potency than **61**. Thus, numerous modifications were examined to replace the extended benzylic 3-(1,1,2,2-tetrafluoroethoxy) moiety in **42**, and no functional group was identified that dramatically improved activity at this position.

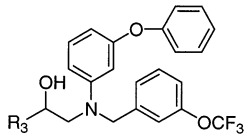


10 R = CF_3
11 R = Ph

Changing the terminal trifluoropropanol moiety in **61** with various aromatic and aliphatic groups did not result in analogues with improved potency (Table 5, **4**−**8**). Also, the *N*,*N*-dibenzyl series was found to be less potent than the *N*-benzyl aniline counterparts. For example, **10** had a buffer IC_{50} of 23 μM as compared with an IC_{50} of 1.5 μM for **60**, and **11** had a buffer IC_{50} of 30 μM as compared to an IC_{50} of 1.0 μM for **61**.

When **42** was analyzed by chiral chromatography, an unexpected 7:1 ratio of enantiomers was observed. The

Table 5. Aminopropanol Chain Modifications in the *N*-(3-Phenoxy)phenyl-*N*-(3-trifluoromethoxy)Benzyl Series



inhibitor	R_3	IC_{50} (μm) in buffer[a]	inhibitor	R_3	IC_{50} (μm) in buffer[a]
61	CF_3	1.0	**6**	4-CF_3Ph	18
4	$CH_2CH_2CH_3$	3.6	**7**	CH_2Ph	>50
5	Ph	>50	**8**	CH=CH_2	>50

[a] Ref 24.

Table 6. CETP Inhibitory Properties of Chiral *N*,*N*-Disubstituted Trifluoro-3-amino-2-propanols

inhibitor	IC_{50} (μM) in buffer[a]	IC_{50} (μM) in plasma[a,b]
1a	0.02	0.6
1b	0.8	20
43	5.0	ND

[a] Ref 24. [b] ND, not determined.

individual enantiomers were obtained by preparative chiral chromatography and analyzed for CETP inhibitory activity. The minor (+)-enantiomer **1a** had an IC_{50} of 0.02 μM while the major (−)-enantiomer **1b** exhibited much less activity (IC_{50} 0.8 μM) (Table 6). The minor (+)-enantiomer **1a** also displayed submicromolar activity (IC_{50} 0.6 μM) in the presence of human serum. Moreover, **1a** could be prepared independently from the known chiral epoxide, *R*-(+)-2-trifluoromethyloxirane,[25] suggesting that the (+)-**1a** enantiomer contained the (*R*)-configuration. Because no unequivocal structural data have been presented for such compounds, we prepared a related crystalline analogue **43** from the same sample of chiral *R*-(+)-2-trifluoromethyloxirane,[25] determined its structure by X-ray analysis (Figure 1), and confirmed that the alcohol configuration in **43** was indeed (*R*). From these data, we concluded that the structure of (+)-**1a** also has the (*R*)-configuration.

More detailed biochemical binding studies comparing the relative affinities and binding properties of **42** and **1a**,**b** have been reported.[24] The results of these efforts demonstrate that inhibitors **42** and **1a** reversibly block both CETP-mediated TG and CE transfer. They associate with HDL and LDL but do not disrupt the structure of these lipoproteins. Their CETP inhibitory activity is highly specific, since they do not inhibit phospholipid transfer protein or lecithin cholesterol acyl transferase. Competition experiments showed that the potent reversible inhibitor **1a** prevented CE binding to CETP and that **1a** bound approximately 5000-fold more efficiently to CETP than CE.

In preliminary animal studies, the potent inhibitors **42** and **1a** provided the first in vivo proof of concept for this class. For example, iv administration of a single dose of **42** at 30 mg/kg inhibited CETP-mediated transfer ex vivo by 50% after 30 min in hCETP transgenic mice (Figure 3) and by 30% after 3 h in cholesterol-fed hamsters (Figure 4). Compound **42** showed similar potency for inhibiting CETP-mediated transfer in cholesterol-fed hamster serum (IC_{50} 12 μM) as in human serum. Surprisingly, administration of a single dose of **1a** at 33 mg/kg inhibited CETP-mediated transfer ex

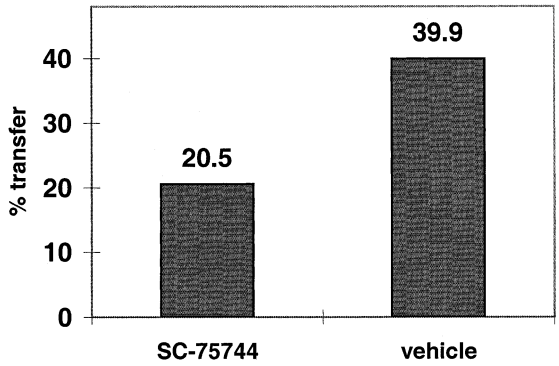


Figure 3. Inhibition of CETP-mediated tranfer ex vivo by **42** at 30 mpk iv after 30 min in hCEPT mouse.

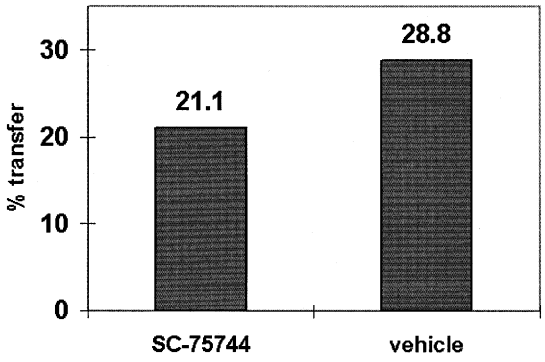


Figure 4. Inhibition of CETP-mediated tranfer ex vivo by **42** at 30 mpk iv after 30 min in hampster.

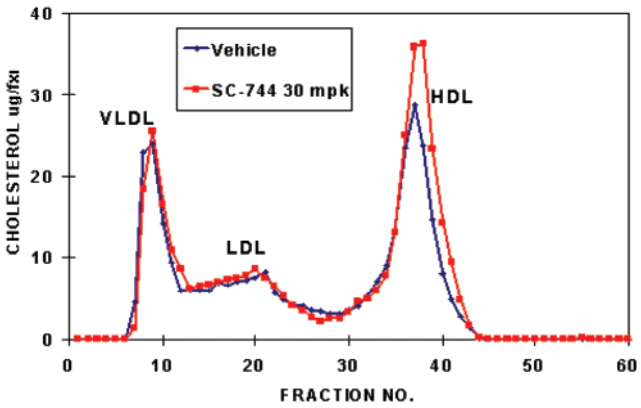


Figure 5. HDL elevation by treatment with **42** in cholesterol-fed hCEPT mice in vivo 30 mpk po, qd, 5 days. Size exclusion chromatography using two Superose 6 columns of a plasma fraction with and without treatment with **42**.

vivo by only 30% after 4 h in cholesterol-fed hamsters. Under these conditions, the observed plasma concentrations of **1a** were more than 10-fold greater than the experimentally determined IC_{50} values for **1a** in either human or hamster serum (IC_{50} 0.6 μM). Thus, the increased in vitro potency of **1a** did not translate into a higher level of ex vivo inhibition of CETP activity. Although compound **42** exhibited a fairly poor oral bioavailability (<10%) in mice, the plasma concentrations 24 h after administration of a single 30 mg/kg dose exceeded the serum IC_{50} levels. Oral dosing of **42** qd for 5 days at 30 mg/kg raised HDLc by 20% in hCETP transgenic mice (Figure 5).

When radiolabeled **42** (with tritium labeling at the benzylic center[24]) was added to human plasma and the plasma was subjected to size exclusion chromatography,

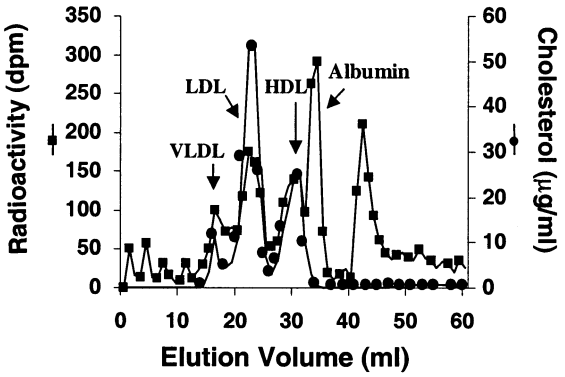


Figure 6. Association of [^{3}H]**42** with plasma lipoproteins and albumin. Size exclusion chromatography on two Superose 6 columns of 0.5 mL of human plasma after the addition of [^{3}H]**42**. The elution positions of VLDL, LDL, HDL, and albumin were determined by chromatographing standards under the same conditions.

the radioactivity was found to elute in five major peaks (Figure 6). The first three peaks coeluted with high molecular weight particles containing cholesterol. These corresponded to the elution positions of VLDL, LDL, and HDL. The elution of the fourth peak was identical to the elution position of albumin. The fifth peak to elute was low molecular weight and probably represented an unbound compound. Approximately 90% of the radioactivity was found in the high molecular weight fractions, and only 10% of the radioactivity was found in the low molecular weight unbound fraction. Similar results were observed using radiolabeled **1a**.

In conclusion, we have discovered chiral *N*,*N*-disubstituted trifluoro-3-amino-2-propanols as a new simple class of potent CETP inhibitors. The most potent inhibitor **1a** also exhibited submicromolar activity in the presence of human serum. In hCETP transgenic mice, **42** showed moderate potency ex vivo in the inhibition of CETP. Similar potencies were observed with hamsters for both **42** and **1a**. Although **42** exhibited poor bioavailability in hCETP transgenic mice, it did raise HDLc moderately after oral dosing qd for 5 days at 30 mg/kg.

Experimental Section

^{1}H NMR, ^{13}C NMR, ^{19}F NMR spectra were collected on a Varian VXR-400 or VXR-300 spectrometer. The samples were dissolved in $CDCl_3$, C_6D_6, or dimethyl sulfoxide (DMSO)-d_6 100 atom % (MSD Isotopes, St. Louis, MO) at a concentration of 0.3−0.7 wt % and placed in 5 mm NMR tubes (Wilmad Glass, Buena, NJ). Mass spectrometry was performed using a SCIEX (Thornhill, Ontario, Canada) API-III mass spectrometer utilizing an electrospray interface. High-resolution mass spectra were obtained by electron impact on a MAT 90 instrument using Electro Calibration with poly(ethylene glycol) (PEG), and samples were dissolved in H_2O/CH_3CN (50:50). UV absorption spectra were taken on a Hewlett-Packard 8451A diode array spectrophotometer. Optical rotation was obtained on a Perkin-Elmer 241 polarimeter using a 1.0 mL microcell and CH_3OH as solvent. All isolated final purified products were routinely analyzed for purity by reverse-phase high-performance liquid chromatography (HPLC) and were generally found to be >95% pure. Yield data on products generated via the general procedures A and C are not optimized (except in some specific cases) since these products were made on a parallel synthesis basis.

Procedure A. Reductive Alkylation of an Amine with a Benzaldehyde. The amine (15 mmol) and the benzaldehyde (15.3 mmol) were dissolved in 60 mL of 1,2-dichloroethane. Acetic acid (16.05 mmol) and solid $NaBH(OAc)_3$ (19.5 mmol) were added. The mixture was stirred at room temperature for 3 h and then acidified with 1 N HCl solution. Alternatively, the amine (15 mmol) and the aldehyde (15 mmol) in cyclohexane were heated to reflux using a Dean−Stark trap to remove water. The recovered resultant imine was stirred with $NaBH_4$ (20 mmol) in methanol for 3 h, and the mixture was acidified with 1 N HCl solution. After the pH was neutralized to 7.5 with 2.5 N NaOH, the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine and water, then dried over anhydrous $MgSO_4$, and concentrated in vacuo to give the desired product as a brown oil, which was examined for purity by reverse phase HPLC analysis.

Procedure B. Alternative Amine Alkylation Procedure. To a solution of toluene (24 mmol) and *N*-bromosuccinimide (24 mmol) in 100 mL of CCl_4 under nitrogen was added 2,2′-azobisisobutyronitrile (4 mmol). The resultant mixture was refluxed for 2 h and then cooled to room temperature and quenched with 300 mL of water. The organic layer was collected, washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo to give a yellow oil. The oil, dissolved in cyclohexane (100 mL), was added dropwise under nitrogen to a solution of the amine (60 mmol) in 500 mL of cyclohexane. The reaction mixture was refluxed overnight and then cooled to room temperature and diluted with water and Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to a dark oil. The crude product was purified by column chromatography on silica eluting with EtOAc/hexane (1:4) to separate the mono- and dialkylated amines and examined for purity by reverse phase HPLC analysis.

Procedure C. Opening of an Epoxide with a Secondary Amine to Give a *β*-Hydroxy Amine. The secondary amine prepared either in procedure A or B (4 mmol) and 2-trifluoromethyloxirane (6 mmol) (TCI America, catalog no. T1557) or another oxirane (6 mmol) were dissolved in 1.5 mL of MeCN. Ytterbium(III) trifluoromethanesulfonate (0.13 g, 0.2 mmol) was added, and the stirred solution was warmed to 50 °C for 2 h (or overnight, if indicated) under an atmosphere of nitrogen. The reaction was quenched with water and extracted with Et_2O. The Et_2O was washed with water and brine and then dried over $MgSO_4$. The crude product was purified by flash column chromatography on silica gel eluting with EtOAc/hexane (1:16 to 1:7) or by semipreparative reverse phase HPLC (if indicated) using C_{18} packing and mobile phase CH_3CN/H_2O (6:4 to 10:0 in 5 min) at a flow rate of 20 mL/min to give the desired product. Purity was checked by reverse phase HPLC analysis.

1-[(3-Phenoxyphenyl)[[3-(trifluoromethoxy)phenyl]-methyl]amino]pentan-2-ol (4). The title compound was prepared from 3-phenoxyaniline and 3-(trifluoromethoxy)-benzaldehyde by procedure A to afford the secondary amine as a yellow oil (MS *m*/*z* M^+ 251), followed by treatment with 2-propyloxirane by procedure C (overnight and purifying product by reverse phase) to give **4** as a light amber oil (yield 51%). HRMS: *m*/*z* $[M + H]^+$ 446.1940 ($C_{25}H_{27}F_3NO_3$ requires 446.1944). Anal. ($C_{25}H_{26}F_3NO_3$) C, H, N.

1-Phenyl-2-[(3-phenoxyphenyl)[[3-(trifluoromethoxy)-phenyl]methyl]amino]ethan-1-ol (5). The title compound was prepared from 3-phenoxyaniline and 3-(trifluoromethyl)-benzaldehyde by procedure A to afford the secondary amine as a yellow oil (MS *m*/*z* M^+ 251), followed by treatment with 2-phenyloxirane by procedure C (overnight and purifying product by reverse phase) to give **5** as a light amber oil (yield 49%). HRMS: *m*/*z* $[M + H]^+$ 480.1792 ($C_{28}H_{25}F_3NO_3$ requires 480.1786). Insufficient material for C, H, and N analysis.

2-[(3-Phenoxyphenyl)[[3-(trifluoromethoxy)phenyl]-methyl]amino]-1-[4-(trifluoromethyl)phenyl]ethan-1-ol (6). To a methylene chloride (40 mL) solution of 4-(trifluoromethyl)styrene (1.50 g, 8.72 mmol) was added *m*-chloroperoxybenzoic acid (4.50 g, 13.0 mmol). The resulting slurry was stirred for 18 h at room temperature under nitrogen. The

reaction mixture was quenched with aqueous sodium hydrogen sulfite (approximately 2 g in 20 mL). Methylene chloride (50 mL) was added, and the mixture was shaken. Insoluble solids were removed by filtration. The organic layer was separated, washed with saturated sodium bicarbonate, dried over $MgSO_4$, and evaporated to give 4-(trifluoromethyl)styrene oxide as a pale yellow oil (1.62 g, 98%).

The title compound was prepared from 3-phenoxyaniline and 3-trifluoro-methoxybenzaldehyde by procedure A to afford the secondary amine as a yellow oil (MS *m/z* M^+ 359.4). To a methylene chloride (5 mL) solution of this amine (1.34 g, 3.7 mmol) and 4-(trifluoromethyl)styrene oxide (0.70 g, 3.7 mmol) was added $Yb(OTf)_3$ (461 mg, 0.74 mmol). The resulting slurry was stirred for 18 h at room temperature under nitrogen. The reaction was quenched with water and extracted with Et_2O. The Et_2O was washed with water and brine and then dried over $MgSO_4$. The crude product, containing a mixture of the two regioisomers, was purified by flash column chromatography on silica gel eluting with 15% EtOAc/hexane. The faster eluting product was isolated and evaporated to an oil. The oil was taken up in EtOH, evaporated, and dried in vacuo for 24 h to give **6** as an amber oil (546 mg, yield 27%). Anal. ($C_{29}H_{23}F_6NO_3$·2EtOH) C, H, N. The second eluting band was also isolated and identified as the unwanted regioisomer.

3-Phenyl-1-[(3-phenoxyphenyl)[[3-(trifluoromethoxy)-phenyl]methyl]amino]propan-2-ol (7). The title compound was prepared from 3-phenoxyaniline and 3-(trifluoromethyl)-benzaldehyde by procedure A to afford the secondary amine as a yellow oil (MS *m/z* M^+ 251), followed by treatment with 2-benzyloxirane by procedure C (overnight and purifying product by reverse phase) to give **7** as a light amber oil (yield 38%). HRMS: *m/z* $[M + H]^+$ 494.1935 ($C_{29}H_{27}F_3NO_3$ requires 494.1944).

1-[(3-Phenoxyphenyl)[[3-(trifluoromethoxy)phenyl]-methyl]amino]but-3-en-2-ol (8). The title compound was prepared from 3-phenoxyphenylaniline and 3-(trifluoromethyl)benzaldehyde by procedure A to afford the secondary amine as a yellow oil (MS *m/z* M^+ 269), which was treated with 2-vinyloxirane by procedure C (overnight and purifying product by reverse phase) to give **8** as an amber oil (yield 38%). HRMS: *m/z* $[M + H]^+$ 430.1621 ($C_{24}H_{23}F_3NO_3$ requires 430.1630).

3-[Bis-[3-(3-trifluoromethoxy)benzyl]amino]-1,1,1-trifluoro-2-propanol (10). The title compound was prepared from 3-(trifluoromethoxy)benzylamine and 3-(trifluoromethoxy)-benzaldehyde by procedure A to afford the secondary amine as a yellow oil (MS *m/z* M^+ 365), followed by treatment with 2-trifluoromethyloxirane by procedure C to give **10** as a light yellow oil (yield 65%). HRMS: *m/z* $[M+H]^+$ 478.1057 ($C_{19}H_{17}F_9NO_3$ requires 478.1064). Anal. ($C_{19}H_{16}F_9NO_3$) C, H, N.

3-[(3-Phenoxybenzyl)[3-(trifluoromethoxy)benzyl]amino]-1,1,1-trifluoro-2-propanol (11). The title compound was prepared from 3-phenoxybenzylamine and 3-(trifluoromethoxy)-benzaldehyde by procedure A to afford the secondary amine as a yellow oil (MS *m/z* M^+ 373), followed by treatment with 2-trifluoromethyloxirane by procedure C to give **11** as yellow oil (61%). HRMS: *m/z* $[M + H]^+$ 486.1475 ($C_{24}H_{22}F_6NO_3$ requires 486.1504). Anal. ($C_{24}H_{21}F_6NO_3$) C, H, N.

3-[(3-Phenoxyphenyl)[1-[3-(trifluoromethoxy)phenyl]-ethyl]amino]-1,1,1-trifluoro-2-propanol (13). The title compound was prepared from 3′-(trifluoromethoxy)acetophenone and 3-phenoxy-aniline following procedure A, and the resulting oil was treated with 2-trifluoromethyloxirane according to procedure C giving **13** as an amber oil (14% yield). HRMS: $[M + H]^+$ 485.1442 ($C_{24}H_{22}F_6NO_3$ requires 485.1426). Anal. ($C_{24}H_{21}F_6NO_3$) C, H, N.

***N*-(3-Fluorophenyl)-*N*-(3,3,3-trifluoro-2-hydroxypropyl)-3-(trifluoromethyl)benzamide (17).** 3-[3-Fluorophenyl(phenylmethyl)amino]-1,1,1-trifluoro-2-propanol (**50**) (2.56 g, 8.2 mmol), prepared below, was dissolved in CH_3OH (30 mL) and hydrogenated over 5% Pd on charcoal for 3 h. The mixture was filtered through Celite, and the solvent and volatiles were removed in vacuo to give 1.8 g (98%) of 3-[(3-fluorophenyl)-amino]-1,1,1-trifluoro-2-propanol **19** as an oil, 99% pure by HPLC analysis. MS: *m/z* $[M + H]^+$ 224.

The oil (446 mg, 2.0 mmol) and Et_3N (544 mg) were dissolved in anhydrous $CHCl_3$ (30 mL) and cooled to 0 °C. 3-Trifluoromethylbenzoyl chloride (1.04 g, 5.0 mmol) dissolved in anhydrous $CHCl_3$ (6 mL) was added over a period of 15 min. The solution was stirred at room temperature. After 14 h, the solution was washed with 5% $NaHCO_3$ solution (2 × 20 mL) and brine (2 × 10 mL) and then dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo gave 3-[3-fluorophenyl[3-(trifluoromethyl)benzoyl]amino]-1,1,1-trifluoro-2-propyl benzoate **20** as an amber oil (832 mg, 73%), which was greater than 95% pure by reverse phase HPLC analysis. HRMS: *m/z* $[M + H]^+$ 568.0968 ($C_{25}H_{16}F_{10}NO_3$ requires 568.0970).

The amber oil (600 mg, 1.06 mmol) was dissolved in CH_3OH and treated with 28% NH_3 solution (122 μL). The solution was stirred at room temperature for 10 h. The reaction was quenched with water and extracted with Et_2O. The Et_2O layer was washed with brine and water and then dried over anhydrous $MgSO_4$. The crude product was purified by flash column chromatography on silica gel eluting with EtOAc/hexane (1:8) to give **17** as a white powder (255 mg, 61%), 97% pure by HPLC analysis. HRMS: *m/z* $[M + H]^+$ 396.0821 ($C_{17}H_{13}F_7NO_2$ requires 396.0854). Anal. ($C_{17}H_{12}F_7NO_2$) C, H, N.

3-[(3-Fluorophenyl)[[3-(trifluoromethyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol Acetate Ester (21). 3-[3-Fluorophenyl[[3-(3-trifluoromethyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol (**22**) (200 mg, 0.52 mmol) prepared below was dissolved in triethylamine (0.6 mL) and acetic anhydride (0.5 mL). The solution was stirred and heated to 80 °C for 1 h. The mixture was cooled and diluted with water (20 mL) and extracted into ether (2 × 40 mL), which was washed with 0.1 N NaOH and water. The ether solution was dried over anhydrous $MgSO_4$. The ether was removed in vacuo giving the required product as an amber oil (191 mg, 87%), 98% pure by HPLC analysis. HRMS: *m/z* $[M + H]^+$ 424.1159 ($C_{19}H_{17}F_7NO_2$ requires 424.1148). Anal. ($C_{19}H_{16}F_7NO_2$) C, H, N.

3-[(3-Fluorophenyl)[[3-(trifluoromethyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol (22). The title compound was prepared from 3-fluoroaniline and 3-(trifluoromethyl)-benzaldehyde by procedure A to afford the secondary amine as a yellow oil (MS *m/z* M^+ 269), followed by treatment with 2-trifluoromethyloxirane by procedure C to give **22** as an amber oil (62% yield). HRMS: *m/z* $[M + H]^+$ 382.1032 ($C_{17}H_{15}F_7NO$ requires 382.1042). Anal. ($C_{17}H_{14}F_7NO$) C, H, N.

6-Fluoro-3,4-dihydro-4-[[(3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]-2-(trifluoromethyl)-2*H*-1,4-benzoxazine (23). 2,5-Difluoroaniline and 3-(1,1,2,2-tetrafluoroethoxy)-benzaldehyde were reacted by procedure A to afford the secondary amine as a yellow oil (MS *m/z* M^+ 335), which was treated with 2-trifluoromethyloxirane by procedure C to give 3-[(2,5-difluorophenyl)[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol as a light yellow oil (1.2 g, 69%). ^1H NMR δ ($CDCl_3$): 2.79 (bs, 1H), 3.30 (dd, 1H), 3.61 (dd, 1H), 4.16 (m, 1H), 4.43 (ABq, 2H), 5.88 (tt, 1H), 6.64 (m, 2H), 7.01 (m, 1H), 7.15 (m, 3H), 7.34 (t, 1H). ^{19}F NMR δ ($CDCl_3$): −137.1 (d, 2F), −128.3 (m, 1F), −117.1 (m, 1F),-88.5 (s, 2F), −79.3 (d, 3F). HRMS: *m/z* $[M + H]^+$ 448.0940 ($C_{18}H_{15}F_9NO_2$ requires 448.1059). Anal. Calcd for $C_{18}H_{14}F_9NO_2$: C, 48.33; H, 3.16; N, 3.13. Found: C, 48.69; H, 3.40; N, 2.90.

To the propanol (500 mg, 1.12 mmol) in DMF (20 mL) was added finely powdered K_2CO_3 (500 mg). The mixture was stirred and heated under reflux at 145 °C for 18 h. The mixture was diluted with water (200 mL) and extracted with diethyl ether (3 × 150 mL). The ether was washed with brine and dried (anhydrous $MgSO_4$). The crude product was purified by flash column chromatography on silica gel eluting with EtOAc/hexane (1:15) to give the desired product as a light yellow oil (48% yield). HRMS: *m/z* $[M + H]^+$ 428.0910 ($C_{18}H_{14}F_8NO_2$ requires 428.0898). Anal. ($C_{18}H_{13}F_8NO_2$) C, H, N.

3-[(3-Phenoxyphenyl)[(3-ethoxyphenyl)methyl]amino]-1,1,1-trifluoro-2-propanol (26). 3-Hydroxybenzaldehyde (**28**)

(1.81 g, 14.8 mmol), sodium methoxide (0.822 g, 15.2 mmol), and ethyl iodide (2.70 g, 17.3 mmol) were refluxed in 25 mL of CH_3OH overnight. Ethyl acetate was added, and the solution was washed with water and dried over $MgSO_4$. Evaporation gave crude 3-ethoxybenzaldehyde (**24**) (1.78 g), which was vacuum-distilled to a pale yellow oil (1.47 g 66%).

The title compound was prepared from 3-ethoxybenzaldehyde (**24**) (420 mg, 2.80 mmol) and 3-phenoxy-aniline (526 mg, 2.84 mmol) by procedure A, and the resulting oil was treated with 2-trifluoromethyloxirane (392 mg, 3.5 mmol) according to procedure C giving **26** as an amber oil (732 mg, 61%). HRMS: *m*/*z* $[M + H]^+$ 432.1770 ($C_{24}H_{25}F_3NO_3$ requires 432.1780). Anal. ($C_{24}H_{24}F_3NO_3$) C, H, N.

3-[(3-Phenoxyphenyl)[[3-(isopropoxy)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol (27). 3-Hydroxybenzaldehyde (5.60 g, 45.9 mmol) and 2-iodopropane (7.86 g, 46.2 mmol) were dissolved in 2-propanol (50 mL). Potassium carbonate (20 g, 145 mmol) was added, and the mixture was heated to reflux for 8 h, at which time thin-layer chromatography (TLC) analysis indicated that the reaction had gone to completion. Water was added to dissolve all solids, and the mixture was extracted with ether (3×). The combined ether layer was washed with water, 2 M NaOH, again with water until clear (4×), and finally with brine. The solution was dried over $MgSO_4$, filtered, and evaporated to give 3-isopropoxybenzaldehyde (**25**) (5.03 g, 67%) as a pale oil. MS: *m*/*z* [M + H] 165.

The title compound was prepared from 3-isopropoxybenzaldehyde (**25**) (780 mg, 4.75 mmol) and 3-phenoxyaniline (881 mg, 4.76 mmol) by procedure A, followed by treatment of the product with 2-trifluoromethyloxirane (764 mg, 6.8 mmol) as in procedure C to give the desired product an amber oil (1.31 g, 62%). HRMS: *m*/*z* $[M + H]^+$ 446.1936 ($C_{25}H_{27}F_3NO_3$ requires 446.1943). Anal. ($C_{25}H_{26}F_3NO_3$) C, H, N.

3-[(3-Phenoxyphenyl)[[3-(2,2,2-trifluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol (29). $NaOCH_3$ (21.61 g, 0.10 mol) in anhydrous CH_3OH was slowly added to 3-hydroxybenzaldehyde (12.22 g, 0.10 mol) in anhydrous CH_3OH (100 mL). The solvent was removed in vacuo. After the flask was purged with N_2, 2,2,2-trifluoroethyl *p*-toluenesulfonate (25.42 g, 0.10 mol) and 100 mL of *N*-methyl pyrrolidine were added. The solution was stirred for 24 h at 90 °C under N_2, quenched with water, and extracted with Et_2O (3×). The combined Et_2O layer was washed with 1 N NaOH (2×), water, and brine, dried over $MgSO_4$, filtered, and evaporated to give 11.72 g of crude product. Chromatography from silica with 5−10% EtOAc in hexane followed by a second chromatography on silica with toluene gave 3-(2,2,2-trifluoroethoxybenzaldehyde) (**30**) (5.24 g, 26%) as a pale oil. ^{19}F NMR δ (C_6D_6): (t, 3F). MS: *m*/*z* [M + H] 205.

The title compound was prepared from 3-(2,2,2-trifluoroethoxybenzaldehyde (**30**) (360 mg, 1.76 mmol) and 3-phenoxyaniline (326 mg, 1.76 mmol) by procedure A, followed by treatment with 2-trifluoromethyloxirane (314 mg, 2.8 mmol) as in procedure C to give **29** as a clear colorless oil (572 mg, 67%). HRMS: *m*/*z* $[M + H]^+$ 486.1498 ($C_{24}H_{22}F_6NO_3$ requires 486.1504). Anal. ($C_{24}H_{21}F_6NO_3$) C, H, N.

3-[[[3-(1,1-Dimethylethoxy)phenyl]methyl](3-phenoxyphenyl)amino]-1,1,1-trifluoro-2-propanol (32). 3-Hydroxybenzaldehyde (**28**) (4.08 g, 33.4 mmol) as slurry in 50 mL of anhydrous CH_2Cl_2 was added to *tert*-butyl-2,2,2-trichloroacetimidate (25.0 g, 114 mmol) in 200 mL of anhydrous cyclohexane with an additional 50 mL of CH_2Cl_2 used in transfer. The mixture was stirred under N_2 until uniform and then, $BF_3 \cdot Et_2O$ (0.50 mL, 4 mmol) was added via syringe and stirring was continued for 1 h. Powdered Na_2CO_3 (50 g, 0.6 mol) was added, and the solution was filtered through a silica gel plug, washing the plug with hexane. The solvent was removed to give crude product 3.54 g (59%) as an amber oil (85% by GC). Chromatography on silica with 6−10% EtOAc in hexane gave 3-*t*-butoxybenzaldehyde (**31**) as a colorless oil (1.88 g, 32%), which was 98% pure by HPLC analysis. MS: *m*/*z* [M + H] 179.

3-*t*-Butoxybenzaldehyde (**31**) (585 mg, 3.27 mmol) and 3-phenoxyaniline (595 mg, 3.21 mmol) by procedure A, followed by treatment of the product with 2-trifluoromethyloxirane (515 mg, 4.6 mmol) as in procedure C to give **32** as an amber oil (823 mg, 56%). HRMS: *m*/*z* $[M + H]^+$ 460.2103 ($C_{26}H_{29}F_3NO_3$ requires 460.2100). Anal. ($C_{26}H_{28}F_3NO_3$) C, H, N.

3-[[(3-Phenoxyphenyl)[3-(3,3,3-trifluoro-2-hydroxy-propoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol (34). 3-Hydroxybenzaldehyde and 3-phenoxyaniline were reacted following procedure A to afford the secondary amine (**33**) as a yellow oil (yield 83%) (MS *m*/*z* M^+ 291). This amine (200 mg, 0.65 mmol) was stirred with 2-trifluoromethyloxirane (522 mg, 3 mmol) for 30 h at 95 °C in a sealed vial to give a dark amber oil, which was purified on silica eluting with ethyl acetate/hexane (1:6) to give **34** as a brown oil (251 mg, 75%). HRMS: *m*/*z* $[M + H]^+$ 516.1638 ($C_{25}H_{24}F_6NO_4$ requires 516.1610). Anal. ($C_{25}H_{23}F_6NO_4$) C, H, N.

α,α-Dimethyl-3-[[(3-phenoxyphenyl)(3,3,3-trifluoro-2-hydroxypropyl)amino]methyl]benzenemethanol (35). To a solution of 3-[[(3-phenoxyphenyl)(3,3,3-trifluoro-2-hydroxypropyl)amino]methyl] benzoic acid, methyl ester (**37**) (218 mg, 0.49 mmol) in 0.7 mL of tetrahydrofuran (THF) at 0 °C was slowly added a 3.0 M THF solution of methylmagnesium chloride (650 μL, 2.0 mmol). The reaction mixture was warmed to room temperature, stirred for 2 h, and then diluted with diethyl ether and quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with dichloromethane, and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluting with 1:4 ethyl acetate:hexane to afford **35** as a light yellow oil (174 mg, 80%). HRMS: *m*/*z* $[M + H]^+$ 446.1938. ($C_{25}H_{27}F_3NO_3$ requires 466.1943). Anal. ($C_{25}H_{26}F_3NO_3 \cdot 0.5H_2O$) C, H, N.

3-[[(3-Phenoxyphenyl)(3,3,3-trifluoro-2-hydroxypropyl)amino]methyl]-α,α-bis(trifluoromethyl)benzenemethanol (36). To a solution of 3-[[(3-phenoxyphenyl)(3,3,3-trifluoro-2-propanol)amino]methyl] benzoic acid, methyl ester (**37**) (331 mg, 0.74 mmol), and trimethyl(trifluoromethyl)silane (423 mg, 3.0 mmol) in 3.0 mL of toluene at room temperature was added a 1.0 M in THF solution of tetrabutylammonium fluoride (150 μL, 0.15 mmol), which had been dried over molecular sieves. The reaction mixture was heated at 40 °C for 18 h. HPLC indicated incomplete reaction; therefore, additional trimethyl(trifluoromethyl)silane (440 μL, 3.0 mmol) and tetrabutylammonium fluoride (150 μL, 0.15 mmol) was added and the reaction mixture was heated to 50 °C in a sealed glass vial. After 2 h, HPLC analysis indicated that no starting material remained. The reaction mixture was quenched with water and extracted with dichloromethane. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified on silica gel eluting with 1:9 ethyl acetate: hexane to afford **36** (46 mg) as a yellow-brown oil. HRMS: *m*/*z* $[M + H]^+$ 554.1385. ($C_{25}H_{21}F_9NO_3$ requires 554.1378). Insufficient material was avaliable for C, H, and N analysis.

3-[[(3-Phenoxyphenyl)(3,3,3-trifluoro-2-hydroxypropyl)amino]methyl]benzoic Acid, Methyl Ester (37). 3-[[(3-Phenoxyphenyl) amino]methyl]benzoic acid, methyl ester was prepared from 3-phenoxyaniline (25.0 g, 135.0 mmol) and 3-(bromomethyl)benzoic acid, methyl ester (8.8 g, 38.4 mmol) as in procedure B to afford the desired trifluoroacetyl (TFA) salt as a yellow oil (10.2 g, 59%). ^1H NMR ($CDCl_3$): δ 8.04 (s, 1H), 8.00 (d, 1H), 7.10−6.92 (m, 7H), 6.84 (t, 1H), 6.47 (d, 1H), 6.22 (s, 1H), 6.08 (d, 1H), 3.72 (d, 2H), 3.48 (s, 3H), 3.30 (bt, 1H). HRMS: *m*/*z* $[M + H]^+$ 334.1442 ($C_{21}H_{19}NO_3$ requires 334.1443). The title compound was prepared from this amine salt (6.2 g, 18.6 mmol) and 2-trifluoromethyloxirane (3.4 g, 30 mmol) by procedure C to give **37** as a pale yellow oil (4.9 g, 79%). HRMS: *m*/*z* $[M + H]^+$ 446.1596 ($C_{24}H_{23}NO_4F_3$ requires 446.1579). Anal. ($C_{24}H_{22}F_3NO_4 \cdot 1.4H_2O$) C, H, N.

3-[[[3-(2-Methylpropyl)phenyl]methyl](3-phenoxyphenyl)amino]-1,1,1-trifluoro-2-propanol (38). A 1.0 M THF solution of 3-{[(3-bromophenyl)methyl](3-phenoxyphenyl)-amino}-1,1,1-trifluoropropan-2-ol (**41**) (0.5 g, 1.0 mmol) (pre-

pared as in **40**) was syringed into a two-neck round-bottom flask containing 2-methylpropylmagnesium bromide (0.33 g, 2.0 mmol) under nitrogen equipped with a stir bar. To the resulting solution was added $Pd(PPh_3)_4$ (57.0 mg, 0.05 mmol). The reaction was allowed to reflux for 18 h at which time TLC indicated desired product. The reaction was cooled, washed with saturated ammonium chloride (2 × 25 mL), dried (anhydrous $MgSO_4$), and concentrated. The crude product was purified by flash column chromatography on silica gel eluting with EtOAc/hexane (1:9) to give **38** as a yellow oil (201 mg, 45%). MS: *m/z* M^+ 443. HRMS: *m/z* $[M + H]^+$ 444.2157 ($C_{26}H_{29}F_3NO_2$ requires 444.2152). Anal. ($C_{26}H_{28}F_3NO_2$) C, H, N.

3-[[(3-Cyclopentylphenyl)methyl](3-phenoxyphenyl)-amino]-1,1,1-trifluoropropan-2-ol (39). The title compound was prepared from 3-phenoxyaniline and 3-cyclopentylbenzaldehyde[31] by procedure A to afford the secondary amine as a yellow oil, followed by treatment with 2-trifluoromethyloxirane by procedure C to give **39** as an amber oil (yield 43%). HRMS: *m/z* $[M + H]^+$ 456.2143 ($C_{27}H_{29}F_3NO_2$ requires 456.2150). Anal. ($C_{27}H_{28}F_3NO_2 \cdot 0.4EtOH$) C, H, N.

3-[[(3-Cyclopropylphenyl)methyl](3-phenoxyphenyl)-amino]-1,1,1-trifluoropropan-2-ol (40). 3-Phenoxyaniline and 3-bromobenzaldehyde were reacted by procedure A to afford the secondary amine as a yellow oil (MS *m/z* M^+ 354), which was treated with 2-trifluoromethyloxirane by procedure C to give 3-[[(3-bromophenyl)methyl]-(3-phenoxyphenyl)amino]-1,1,1-trifluoro-2-propanol (**41**) as an amber oil (yield 63%). HRMS: *m/z* $[M + H]^+$ 466.0598 ($C_{22}H_{20}F_3NO_2Br$ requires 466.0629). A THF (5 mL) solution of cyclopropylmagnesium bromide was prepared from bromocyclopropane (1.45 g, 12.0 mmol) and magnesium (314 mg, 12.9 mmol).[31] To this solution was added 3-[[(3-bromophenyl)methyl](3-phenoxyphenyl)-amino]-1,1,1-trifluoropropan-2-ol (1.4 g, 3.0 mmol) and $Pd(PPh_3)_4$ (0.16 mmol). The resulting solution was refluxed for 18 h under nitrogen, and the reaction mixture was poured into saturated NH_4Cl and extracted with EtOAc. The EtOAc was washed with water and brine and then dried over $MgSO_4$. The crude product was purified by flash column chromatography on silica gel eluting with 15% EtOAc/hexane to give **40** as an amber oil (452 mg, 35%). HRMS: *m/z* $[M + H]^+$ 428.1806 ($C_{25}H_{24}F_3NO_2$ requires 428.1837). Anal. ($C_{25}H_{24}F_3NO_2$) C, H, N.

3-[(3-Phenoxyphenyl)[[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol (42). The title compound was prepared from 3-phenoxyaniline and 3-(1,1,2,2-tetra-fluoroethoxy)benzaldehyde by procedure A to afford (3-phenoxyphenyl)[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amine as a yellow oil (MS *m/z* M^+ 391), followed by treatment with 2-trifluoromethyloxirane by procedure C to give **42** as a light amber oil (yield 63%). HRMS: *m/z* $[M + H]^+$ 504.1425 ($C_{24}H_{21}F_7NO_3$ requires 504.1410). Anal. ($C_{24}H_{20}F_7NO_3$) C, H, N. To separate this compound into its enantiomers, a further preparation of this material was made from 3-phenoxyaniline and 3-(1,1,2,2-tetra-fluoroethoxy)toluene by procedure B to give the secondary amine (MS *m/z* M^+ 391), followed by treatment with 2-trifluoromethyloxirane by procedure C to give **42** as a light amber oil (yield 69%). ^1H NMR, ^{19}F NMR, and HRMS were identical to previously prepared material.

3-[(3-Chlorophenyl)[[3-(trifluoromethyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol (44). The title compound was prepared from 3-chloroaniline and 3-(trifluoromethyl)-benzaldehyde by procedure A to afford the secondary amine as a yellow oil (MS *m/z* M^+ 231), followed by treatment with 2-trifluoromethyloxirane by procedure C to give **25** as an amber oil (54% yield). HRMS: *m/z* $[M + H]^+$ 398.0727 ($C_{17}H_{15}ClF_6NO$ requires 398.0746). Anal. ($C_{17}H_{14}ClF_6NO$) C, H, N.

3-[3-(Trifluoromethyl)phenyl[[3-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol (45). The title compound was prepared from 3-(trifluoromethyl)aniline and 3-(trifluoromethyl)benzaldehyde by procedure A to afford the secondary amine as a brown oil (MS *m/z* M^+ 319), followed by treatment with 2-trifluoromethyloxirane by procedure C to give **26** as an amber oil (66% yield). HRMS: *m/z* $[M + H]^+$ 432.1026 ($C_{18}H_{15}F_9NO$ requires 432.1010). Insufficient material was available for C, H, and N analysis.

3-[3-Methylphenyl[[3-(trifluoromethyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol (46). The title compound was prepared from 3-methylaniline and 3-(trifluoromethyl)-benzaldehyde by procedure A to afford the secondary amine as a brown oil (MS *m/z* M^+ 265), followed by treatment with 2-trifluoromethyloxirane by procedure C to give **46** as a light brown oil (51% yield). HRMS: *m/z* $[M + H]^+$ 378.1254 ($C_{18}H_{18}F_6NO$ requires 378.1288). Anal. ($C_{18}H_{17}F_6NO$) C, H, N.

3-[Phenyl[[3-(trifluoromethyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol (47). The title compound was prepared from 3-(trifluoromethyl)aniline and 3-(trifluoromethyl)benzaldehyde by procedure A to afford the secondary amine as a yellow oil (MS *m/z* M^+ 251), followed by treatment with 2-trifluoromethyloxirane by procedure C to give **47** as a light amber oil (63% yield). HRMS: *m/z* $[M + H]^+$ 364.1122 ($C_{17}H_{16}F_6NO$ requires 364.1136). Anal. ($C_{17}H_{15}F_6NO$) C, H, N.

3-[2-Methylphenyl[[3-(trifluoromethyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol (48). The title compound was prepared from 3-methylaniline and 3-(trifluoromethyl)-benzaldehyde by procedure A to afford the secondary amine as a dark brown oil (MS *m/z* M^+ 265), followed by treatment with 2-trifluoromethyloxirane by procedure C to give **48** as a brown oil (42% yield). HRMS: *m/z* $[M + H]^+$ 378.1254 ($C_{18}H_{18}F_6NO$ requires 378.1288). Anal. ($C_{18}H_{17}F_6NO$) C, H, N.

3-[4-Methylphenyl[[3-(trifluoromethyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol (49). The title compound was prepared from 3-methylaniline and 3-(trifluoromethyl)-benzaldehyde by procedure A to afford the secondary amine as a yellow oil (MS *m/z* M^+ 265), followed by treatment with 2-trifluoromethyloxirane by procedure C to give **49** as an amber oil (48% yield). HRMS: *m/z* $[M + H]^+$ 378.1267 ($C_{18}H_{18}F_6NO$ requires 378.1288). Anal. ($C_{18}H_{17}F_6NO$) C, H, N.

3-[(3-Fluorophenyl)[(phenyl)methyl]amino]-1,1,1-trifluoro-2-propanol (50). The title compound was prepared from 3-fluoroaniline and benzaldehyde by procedure A to afford the secondary amine as a brown oil (MS *m/z* M^+ 201), followed by treatment with 2-trifluoromethyloxirane by procedure C to give **50** as a yellow oil (44% yield). HRMS: *m/z* $[M + H]^+$ 314.1178 ($C_{16}H_{16}F_4NO$ requires 314.1168). Insufficient material was available for C, H, and N analysis.

3-[(3-Fluorophenyl)[[3-methylphenyl]methyl]amino]-1,1,1-trifluoro-2-propanol (51). The title compound was prepared from 3-fluoroaniline and 3-methylbenzaldehyde by procedure A to afford the secondary amine as a yellow oil (MS *m/z* M^+ 215), followed by treatment with 2-trifluoromethyloxirane by procedure C to give **51** as a light yellow oil (32% yield). HRMS: *m/z* $[M + H]^+$ 328.1300 ($C_{17}H_{18}F_4NO$ requires 328.1325). Anal. ($C_{17}H_{17}F_4NO$) C, H, N.

3-[(3-Fluorophenyl)[[4-methylphenyl]methyl]amino]-1,1,1-trifluoro-2-propanol (52). The title compound was prepared from 3-fluoroaniline and 4-methylbenzaldehyde by procedure A to afford the secondary amine as a yellow oil (MS *m/z* M^+ 215), followed by treatment with 2-trifluoromethyloxirane by procedure C to give **52** as an amber oil (44% yield). HRMS: *m/z* $[M + H]^+$ 328.1333 ($C_{17}H_{18}F_4NO$ requires 328.1325). Anal. ($C_{17}H_{17}F_4NO$) C, H, N.

3-[(3-Fluorophenyl)[[2-(trifluoromethyl)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol (53). The title compound was prepared from 3-fluoroaniline and 2-(trifluoromethyl)-benzaldehyde by procedure A to afford the secondary amine as a yellow oil (MS *m/z* M^+ 269), followed by treatment with 2-trifluoromethyloxirane by procedure C to give **53** as a brown oil (37% yield). HRMS: *m/z* $[M + H]^+$ 382.1053 ($C_{17}H_{15}F_7NO$ requires 382.1042). Anal. ($C_{17}H_{14}F_7NO$) C, H, N.

3-[(3-Fluorophenyl)[[2-methylphenyl]methyl]amino]-1,1,1-trifluoro-2-propanol (54). The title compound was prepared from 3-fluoroaniline and 2-methylbenzaldehyde by procedure A to afford the secondary amine as a dark yellow oil (MS *m/z* M^+ 215), followed by treatment with 2-trifluoromethyloxirane by procedure C to give **54** as a yellow oil (44%

yield). HRMS: *m/z* $[M + H]^+$ 328.1353 ($C_{17}H_{18}F_4NO$ requires 328.1325). Anal. ($C_{17}H_{17}F_4NO$) C, H, N.

3-[(3-Fluorophenyl)[[3-(phenoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol (55). The title compound was prepared from 3-fluoroaniline and 3-(phenoxy)benzaldehyde by procedure A to afford the secondary amine as a yellow oil (MS *m/z* M^+ 293), followed by treatment with 2-trifluoromethyloxirane by procedure C to give **55** as an amber oil. HRMS: *m/z* $[M + H]^+$ 406.1418 ($C_{22}H_{20}F_4NO_2$ requires 406.1430). Anal. ($C_{22}H_{19}F_4NO_2$) C, H, N.

3-[(3-Fluorophenyl)[[4-(phenyl)phenyl] methyl]amino]-1,1,1-trifluoro-2-propanol (56). The title compound was prepared from 3-fluoroaniline and 4-phenylbenzaldehyde by procedure A to afford the secondary amine as an amber oil, followed by treatment with 2-trifluoromethyloxirane by procedure C to give **56** as a brown oil (yield 41%). HRMS: *m/z* $[M + H]^+$ 390.1468 ($C_{22}H_{20}F_4NO$ requires 390.1481). Anal. ($C_{22}H_{19}F_4NO$) C, H, N.

3-[(3-Fluorophenyl)[[3-(3-trifluoromethylphenoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol (57). The title compound was prepared from 3-fluoroaniline and 3-(3-trifluoromethylphenoxy)benzaldehyde by procedure A to afford the secondary amine as a yellow oil (MS *m/z* M^+ 361), followed by treatment with 2-trifluoromethyloxirane by procedure C to give **57** as a brown oil (40% yield). HRMS: *m/z* $[M + H]^+$ 474.1338 ($C_{23}H_{19}F_7NO_2$ requires 474.1305). Anal. ($C_{23}H_{18}F_7NO_2$) C, H, N.

3-[(3-Fluorophenyl)[[3-(trifluoromethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol (58). The title compound was prepared from 3-fluoroaniline and 3-(trifluoromethoxy)benzaldehyde by procedure A to afford the secondary amine as a yellow oil (MS *m/z* M^+ 285), followed by treatment with 2-trifluoromethyloxirane by procedure C to give **58** as a light yellow oil (yield 52%). HRMS: *m/z* $[M + H]^+$ 398.0987 ($C_{17}H_{15}F_7NO_2$ requires 398.0991). Anal. ($C_{17}H_{14}F_7NO_2$) C, H, N.

3-[(3-Fluorophenyl)[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol (59). The title compound was prepared from 3-fluoroaniline and 3-(1,1,2,2-tetrafluoroethoxy)benzaldehyde by procedure A to afford the secondary amine as a yellow oil (MS *m/z* M^+ 317), followed by treatment with 2-trifluoromethyloxirane by procedure C to give **59** as a light yellow oil (61% yield). HRMS: *m/z* $[M + H]^+$ 430.1042 ($C_{18}H_{16}F_8NO_2$ requires 430.1053). Anal. ($C_{18}H_{15}F_8NO_2$) C, H, N.

3-[(3-Trifluoromethoxy)phenyl[[3-(trifluoromethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol (60). The title compound was prepared from 3-trifluoromethoxyaniline and 3-(trifluoromethoxy)benzaldehyde by procedure A to afford the secondary amine as a yellow oil (MS *m/z* M^+ 351), followed by treatment with 2-trifluoromethyloxirane by procedure C to give **60** as a light yellow oil (yield 43%). HRMS: *m/z* $[M + H]^+$ 464.0898 ($C_{18}H_{15}F_9NO_3$ requires 464.0909). Anal. ($C_{18}H_{14}F_9NO_3$) C, H, N.

3-[(3-Phenoxyphenyl)[[3-(trifluoromethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol (61). The title compound was prepared from 3-phenoxyaniline and 3-(trifluoromethoxy)benzaldehyde by procedure A to afford the secondary amine as a yellow oil (MS *m/z* M^+ 359), followed by treatment with 2-trifluoromethyloxirane by procedure C to give **61** as a light amber oil (yield 37%). HRMS: *m/z* $[M + H]^+$ 472.1342 ($C_{23}H_{20}F_6NO_3$ requires 472.1347). Anal. ($C_{23}H_{19}F_6NO_3$) C, H, N.

3-[(4-Phenoxyphenyl)[[3-(trifluoromethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propan-ol (62). The title compound was prepared from 4-phenoxyaniline and 3-(trifluoromethoxy)benzaldehyde by procedure A to afford the secondary amine as a yellow oil (MS *m/z* M^+ 359), followed by treatment with 2-trifluoromethyloxirane by procedure C to give **62** as a light amber oil (42%). HRMS: *m/z* $[M + H]^+$ 472.1334 ($C_{23}H_{20}F_6NO_3$ requires 472.1347). Anal. ($C_{23}H_{19}F_6NO_3$) C, H, N.

3-[(3-Phenoxyphenyl)[[4-(trifluoromethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propan-ol (63). The title compound was prepared from 3-phenoxyaniline and 4-(trifluoromethoxy)benzaldehyde by procedure A to afford the secondary amine as a yellow oil (MS *m/z* M^+ 359), followed by treatment with 2-trifluoromethyloxirane by procedure C to give **63** as a light amber oil (42%). HRMS: *m/z* $[M + H]^+$ 472.1344 ($C_{23}H_{20}F_6NO_3$ requires 472.1347). Anal. ($C_{23}H_{19}F_6NO_3$) C, H, N.

3-[(3-Phenoxyphenyl)[(2,2,3,3-tetrafluoro-2,3-dihydro-1,4-benzodioxin-6-yl)methyl]amino]-1,1,1-trifluoro-2-propanol (64). The title compound was prepared from 3-phenoxyaniline and 2,2,3,3-tetrafluorobenzo-1,4-dioxin-6-carbaldehyde by procedure A to afford the secondary amine as a yellow oil (MS *m/z* M^+ 236), followed by treatment with 2-trifluoromethyloxirane by procedure C to give **64** as a light amber oil (44%). HRMS: *m/z* $[M + H]^+$ 527.1925 ($C_{24}H_{19}F_7NO_4$ requires 527.1906). Anal. ($C_{24}H_{18}F_7NO_4$) C, H, N.

3-[(3-Phenoxyphenyl)[[3-(methoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol (65). The title compound was prepared from 3-methoxybenzaldehyde and 3-phenoxy-aniline following procedure A, and the resulting oil was reacted with 2-trifluoromethyloxirane according to procedure C giving **65** as an amber oil (50%). HRMS: *m/z* $[M + H]^+$ 417.1548 ($C_{23}H_{23}F_3NO_3$ requires 417.1552). Anal. ($C_{23}H_{22}NF_3O_3$) C, H, N.

3-[(3-Phenoxyphenyl)[[3-phenoxyphenyl]methyl]amino]-1,1,1-trifluoro-2-propanol (66). The title compound was prepared from 3-phenoxyaniline and 3-phenoxybenzaldehyde by procedure A to afford the secondary amine as a brown oil (MS *m/z* M^+ 367), followed by treatment with 2-trifluoromethyloxirane by procedure C to give **66** as a brown oil (yield 39%). HRMS: *m/z* $[M + H]^+$ 480.1772 ($C_{28}H_{25}F_3NO_3$ requires 480.1788). Anal. ($C_{28}H_{24}F_3NO_3$) C, H, N.

3-[(3-Phenoxyphenyl)[[3-(trifluoromethylthio)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol (67). The title compound was prepared from 3-trifluoromethylthiobenzaldehyde and 3-phenoxyaniline by procedure A to afford the secondary amine as a yellow oil (MS *m/z* M^+ 375), followed by treatment of this product with 2-trifluoromethyloxirane as in procedure C to give **67** as an amber oil (yield 57%). HRMS: *m/z* $[M + H]^+$ 488.1116 ($C_{23}H_{20}F_6NO_2S$ requires 488.1119). Anal. ($C_{23}H_{19}F_6NO_2S$) C, H, N.

Separation of 3-[(3-Phenoxyphenyl)[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol (42) into Its Enantiomers. On a Chiralpak AD HPLC column, using mobile phase 2-propanol/hexane (1:9) and UV absorption detection at 250 nm, was injected 3-[(3-phenoxyphenyl)[[3-(1,1,2,2-tetrafluoroethoxy)phenyl], methyl]amino]-1,1,1-trifluoro-2-propanol **(42)** (12.2 g, 24 mmol). Two peaks were observed at 6.36 and 8.43 min. Collection of the compound eluting at 8.43 min gave (2*R*)-3-[(3-phenoxyphenyl)[[3-(1,1,2,2-tetrafluoro-ethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol (**1a**) (1.4 g, 11%); $[\alpha]_{589} = +16.8°$ (*c* 0.125 g/dL, CH_3CN), $[\alpha]_{365} = +84.0°$ (*c* 0.125 g/dL, CH_3CN). ^1H NMR and ^{19}F NMR were identical to **42**. HRMS: *m/z* $[M + H]^+$ 504.1388 ($C_{24}H_{21}F_7NO_3$ requires 504.1410). Anal. ($C_{24}H_{20}F_7NO_3$) C, H, N.

Collection of the compound eluting at 6.36 min gave (2*S*)-3-[(3-phenoxyphenyl)[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol **(1b)** (10.5 g, 86%); $[\alpha]_{589} = -17.0°$ (*c* 0.125 g/dL, CH_3CN), $[\alpha]_{365} = -85.7°$ (*c* 0.125 g/dL, CH_3CN). ^1H NMR and ^{19}F NMR were identical to **42**. HRMS: *m/z* $[M + H]^+$ 504.1431 ($C_{24}H_{21}F_7NO_3$ requires 504.1410). Anal. ($C_{24}H_{20}F_7NO_3$) C, H, N.

***R*-(+)-2-Trifluoromethyloxirane.**[25] (+)-DIP-Cl (1.2 kg, 3.74 mol) was transferred to a 5 L three neck flask containing 5 L of ether under nitrogen. Anhydrous ether (5 L) was added, and the mixture was stirred until the solids dissolved and the temperature equilibrated to 0 °C. 3-Bromotrifluoroacetone (326 mL, 3.14 mol) was added, and the reaction was stirred for 72 h, while maintaining the temperature between −4 and 5 °C. The reaction was followed with ^{19}F NMR by removing an aliquot (20 μL), quenching with anhydrous methanol (0.6 mL), and referencing to external D_2O. The reduction was 68% complete at 48 h. The ether was removed under vacuum (100

to 0.1 Torr), leaving a pale, viscous oil. A 5 L three neck flask equipped with a stirrer, dropping funnel, and short-path distillation head with chilled receiver was charged with the 50% (w/w) NaOH and heated to 40 °C. With external heat removed, the mixture was added dropwise to the NaOH, with the rate controlled to maintain the pot temperature below 65 °C. Stirring broke up a yellow-orange solid byproduct. The product epoxide formed immediately, distilling over with a head temperature of 32−42 °C to give a colorless liquid (145 g, 43%). ^{1}H NMR δ (C_6D_6): 2.50 (m, 1H, CF_3CH), 2.15 (dd, 1H, J = 2.10, 5.01 Hz), 1.75 (m, 1H). ^{19}F NMR δ (C_6D_6): −75.4 (d, J = 4.7 Hz).

Chiral GC Analysis of 2-Trifluoromethyloxirane Diethylamine Adducts. Chiral GC/MS analysis was performed on the diethylamine adduct from *R*-(+)-2-trifluoromethyloxirane using a γ-cyclodextrin column: 4 drops of epoxide and 4 drops of diethylamine were heated briefly in a sealed vial, diluted with MTBE, and analyzed. Two peaks were found as follows: 10.97 and 11.11 min (ratio 1:230; 99% ee). M + H$^+$ calcd, 186; found, 186, both peaks. Commercially available 2-trifluoromethyloxirane from TCI lot OGH01 gave two peaks, 10.96 and 11.12 min (ratio 8.5:1; 79% ee).

(2*R*)-3-[(3-Phenoxyphenyl)[[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol (1a). The title compound was prepared from 3-phenoxyaniline and 3-(1,1,2,2-tetrafluoroethoxy)toluene by procedure B to afford the secondary amine as a yellow oil (MS *m*/*z* M$^+$ 391), followed by treatment with *R*-(+)-2-trifluoromethyloxirane by procedure C to give **1a** as an light amber oil (yield 66%). ^{1}H NMR and ^{19}F NMR were identical to **42**. $[\alpha]_{589}/[\alpha]_{365}$ were the same as observed above. HRMS: *m*/*z* [M + H]$^+$ 504.1431 ($C_{24}H_{21}O_3NF_7$ requires 504.1410). Anal. ($C_{24}H_{20}F_7NO_3$) C, H, N.

(2*R*,+)-1,1,1-Trifluoro-3-[(3,4,5-trimethoxyphenyl)[[(3-trifluoromethylthio)phenyl]methyl]amino]propan-2-ol (43). The title compound was prepared from 3,4,5-trimethoxyaniline and 3-(trifluoromethylthio)benzaldehyde by procedure A to afford the secondary amine as a brown oil (MS *m*/*z* M$^+$ 285), followed by treatment with (*R*+)-2-trifluoromethyloxirane by procedure C to give **43** as an oil, which was triturated with hexanes to give a white solid. The precipitate was isolated by filtration and dried in vacuo to give the desired product as white crystals; mp 88.9−89.1 (yield 52%); [α] ($CHCl_3$) +26.8 at 589 nm; mp 88.9−89.1. HRMS: *m*/*z* [M + H]$^+$ 486.1158 ($C_{20}H_{22}F_6NO_4S$ requires 486.1174). Anal. ($C_{20}H_{21}F_6NO_4S$) C, H, N. Chiral HPLC: 97.59% at 250 nm (Chiralpak-AD normal phase column, heptane/2-propanol).

Inhibition of CETP Ex Vivo. Inhibition of CETP activity with either compound **42** or **1a** was determined by administering the compound to an animal by intravenous injection, measuring the amount of transfer of tritium-labeled CE ([^{3}H]CE) from HDL to VLDL and LDL particles, and comparing this amount of transfer with the amount of transfer observed in control animals.

Male golden Syrian hamsters were maintained on a diet of chow containing 0.24% cholesterol for at least 2 weeks prior to the study. For animals receiving intravenous dosing immediately before the experiment, animals were anesthetized with pentobarbital. Anesthesia was maintained throughout the experiment. In-dwelling catheters were inserted into the jugular vein and carotid artery. At the start of the experiment, all animals received 0.2 mL of a solution containing [^{3}H]CE-HDL into the jugular vein. [^{3}H]CE-HDL is a preparation of human HDL containing [^{3}H]CE and was prepared according to the method of Glenn et al.[33] Test compound was dissolved as a 80 mM stock solution in vehicle (2% ethanol:98% PEG 400, Sigma Chemical Company, St. Louis, MO) and administered either by bolus injection or by continuous infusion. Two minutes after the [^{3}H]CE-HDL dose was administered, animals received 0.1 mL of the test solution injected into the jugular vein. Control animals received 0.1 mL of the intravenous vehicle solution without test compound. After 5 min, the first blood samples (0.5 mL) were taken from the carotid artery and collected in standard microtainer tubes containing ethylenediamine tetraacetic acid. Saline (0.5 mL) was injected to flush the catheter and replace blood volume. Subsequent blood samples were taken at 2 and 4 h by the same method. Blood samples were mixed well and kept on ice until the completion of the experiment. Plasma was obtained by centrifugation of the blood samples at 4 °C. The plasma (50 μL) was treated with 5 μL of precipitating reagent (dextran sulfate, 10 g/L; 0.5 M magnesium chloride) to remove VLDL/LDL. After the plasma was centrifuged, the resulting supernatant (25 μL) containing the HDL was analyzed for radioactivity using a liquid scintillation counter.

The percentage of [^{3}H]CE transferred from HDL to LDL and VLDL (% transfer) was calculated based on the total radioactivity in equivalent plasma samples before precipitation. Typically, the amount of transfer from HDL to LDL and VLDL in control animals was 20−35% after 4 h. The PEG vehicle was determined to have no effect on CETP activity in this model.

Alternatively, inhibition of CETP activity by a test compound was determined by administering the compound to mice that have been selected for expression of human CETP (hCETP) by transgenic manipulation (hCETP mice). Test compounds were administered by intravenous injection, and the amount of transfer of [^{3}H]CE from HDL to VLDL and LDL particles was determined and compared to the amount of transfer observed in control animals. C57Bl/6 mice that were homozygous for the hCETP gene were maintained on a high fat chow diet, such as TD 88051, as described by Nishina et al. (*J. Lipid Res.* **1990**, *31*, 859−869) for at least 2 weeks prior to the study. Mice received an intravenous bolus injection of test compound in 10% ethanol and 90% PEG. Control animals received the vehicle solution without test compound by oral gavage or by an intravenous bolus injection. At the start of the experiment, all animals received 0.05 mL of a solution containing [^{3}H]CE-HDL into the tail vein. [^{3}H]CE-HDL is a preparation of human HDL containing [^{3}H]CE and was prepared according to the method of Glenn et al.[33] After 30 min, the animals were exsanguinated and blood was collected in standard microtainer tubes containing ethylenediamine tetraacetic acid. Blood samples were mixed well and kept on ice until the completion of the experiment. Plasma was obtained by centrifugation of the blood samples at 4 °C. The plasma was separated and analyzed by gel filtration chromatography, and the relative proportion of [^{3}H]CE in the VLDL, LDL, and HDL regions was determined.

The percentage of [^{3}H]CE transferred from HDL to LDL and VLDL (% transfer) was calculated based on the total radioactivity in equivalent plasma samples before precipitation. Typically, the amount of transfer from HDL to LDL and VLDL in control animals was 20−35 after 30 min. The PEG was determined to have no effect on CETP activity in this model.

Effect of 42 on VLDLc, LDLc, and HDLc In Vivo. A strain of C57bl mouse was made to transgenically express human CETP. Plasma concentrations of hCETP ranged from 2 to 20 μg/mL. The hCETP mice were made hypercholesterolemic by feeding cholesterol- and fat-supplemented chow for a minimum of 2 weeks, as described above. Test compounds were administered orally in selected aqueous- or oil-based vehicles for up to 1 week. The animals were sacrificed. Serum was obtained and analyzed by size exclusion chromatography (see below) for the relative abundance of VLDLc, LDLc, and HDLc.

Binding of [^{3}H]-Labeled 42 With Plasma Lipoproteins and Albumin. [^{3}H]**42**[24] (33 000 dpm in 20 μL of 16% DMSO) was mixed with 0.5 mL of human plasma. The mixture was then subjected to size exclusion chromatography using two Superose 6 columns and TSE buffer as eluant. One milliliter fractions were collected and analyzed for cholesterol to locate the lipoproteins[32] or for liquid scintillation counting to locate [^{3}H]SC-75744. The elution positions of VLDL, LDL, HDL, and albumin were determined by chromatographing standards[32] under the same conditions.

Acknowledgment. We thank Shengtian Yang, Claude R. Jones, and John Likos for NMR assistance and James Doom and Gary Mappes for mass spectral analysis. We also thank Anne Daiss for elemental analysis. We are grateful to Brad McKinnis for chiral chromatography analysis and radiolabel synthesis. This paper is dedicated to Prof. Herbert C. Brown on the occasion of his 90th birthday.

Supporting Information Available: Details of the X-ray structure for **43**. These materials are available free of charge via the Internet at http://pubs.acs.org.

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JM020038H