Article

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Discovery of Potent, Nonsystemic Apical Sodium-Codependent Bile Acid Transporter Inhibitors (Part 1)

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Elevated plasma levels of low-density lipoprotein (LDL) cholesterol are a major risk factor for atherosclerosis leading to coronary artery disease (CAD), which remains the main cause of mortality in Western society. We believe that by preventing the reabsorption of bile acids, a minimally absorbed apical sodium-codependent bile acid transporter (ASBT) inhibitor would lower the serum cholesterol without the potential systemic side effects of an absorbed drug. A series of novel benzothiepines (3*R*,3*R*′-2,3,4,5-tetrahydro-5-aryl-1-benzothiepin-4-ol 1,1-dioxides) were synthesized and tested for their ability to inhibit the apical sodium dependent bile acid transport (ASBT)-mediated uptake of [^{14}C]taurocholate (TC) in H14 cells. A 3*R*,4*R*,5*R*/3*S*,4*S*,5*S* racemate was found to have greater potency than the other three possible racemates. Addition of electron-donating groups such as a dimethylamino substituent at the 7 position greatly enhanced potency, and incorporation of a long-chain quaternary ammonium substituent on the 5-phenyl ring was useful in minimizing systemic exposure of this locally active ASBT inhibitor while also increasing water solubility and maintaining potency. The reported results describe the synthesis and SAR development of this benzothiepine class of ASBT inhibitors resulting in an 6000-fold improvement in ASBT inhibition with desired minimal systemic exposure of this locally acting drug candidate.

Introduction

Clinical data strongly indicate that elevated plasma levels of low-density lipoprotein (LDL) cholesterol are a major risk factor for atherosclerosis leading to coronary artery disease (CAD), the number one cause of morbidity and mortality in Western society.[1] The importance of lipid-lowering therapies has been well documented in recent years, leading to revised treatment guidelines in 2001 by the National Cholesterol Education Program (NCEP) of the National Institutes of Health that recommend a more aggressive approach toward hypercholesterolemia.[2]

Results from recent clinical trials involving large patient populations with CAD demonstrate that long-term therapy with cholesterol-lowering agents has a substantial positive impact on survival (lovastatin in ASCAPS; pravastatin in West of Scotland study; simvastatin in 4S study).[3] Also The Program on the Surgical Control of the Hyperlipidemiaa (POSCH) provided solid evidence for the clinical and arteriographic benefits of lipid profile normilization by partial ileal bypass, and longterm followup POSCH data demonstrate that lipid profile normalization decereased overall mortality.[4] Perhaps the most compelling results were the findings from the CARE study (pravastatin), which indicated that a 28% lowering of the plasma LDL cholesterol in patients at risk for heart disease with "normal" total cholesterol levels (~210 mg/dL) decreased their risk of CAD-related morbidity and mortality 24%.[5] Results from the CARE study suggests that therapeutic benefit can be derived from treating patients that have cholesterol levels previously considered to be on the high end of acceptable.

A nonsystemic strategy of lowering cholesterol would complement the existing HMG-CoA reductase inhibitors (statins) and should also reduce the incidence of systemic-related side effects. The bile acid resins are an example of a nonsystemic LDL lowering therapy that have the desired safety profile for treating people with moderately elevated cholesterol, but they are underutilized because of their high dosages and poor palatability. Our studies began with the search for a more potent bile acid sequestrant as an approach to a nonsystemic LDL lowering therapy. When considering ways of improving the in vivo efficiency of bile acid sequestrants, the ileal bile active transporter appeared to be a prime suspect

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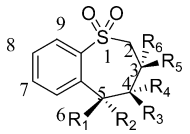


Figure 1. Benzothiepines.

for the commercial products' inefficiency;[6] the active transporter effectively removes the bile acids from the resin via an irreversible sodium-dependent mechanism. Because of this irreversible pathway, we decided to shift our attention to small-molecule apical sodium-codependent bile acid transporter (ASBT) inhibitors, which would offer a more direct route to remove bile acids from the enterohepatic circulation via a nonsystemic mechanism. A palatable, potent, safe, and nonabsorbed ASBT inhibitor would be an improved stand-alone medication over current therapies to lower plasma LDL cholesterol.

In this first of two papers, we will describe our path to a late lead that meets all requirements of a potent, nonsystemic ASBT inhibitor. In part 2, we will describe our strategy toward even more potent, nonsystemic ASBT inhibitors, as well as optimization to acceptable commercial candidates for clinical evaluation.

In Vitro Assay

Identification and selection of lead compounds that inhibit ASBT-mediated bile acid transport were accomplished using a cell-based high-throughput screen. A transfected baby hamster kidney cell line that constitutively expresses human ASBT was established early in the project (H-14) and has provided a high-throughput system to initially evaluate all chemical leads. ASBT inhibitory activity is assessed on the basis of the ability of compounds to inhibit the cellular uptake of 5 μM [^{14}C]taurocholate during a 2 h incubation period. Selectivity is tested in the same assay system using 5 μM [^{14}C]alanine in place of taurocholate to determine the effect on another cellular sodium-dependent cotransporter. All compounds reported in this paper had greater than 100-fold selectivity against the alanine assay.

Synthesis

When we began our search for ASBT inhibitors bile acid analogues in 1990, bile acid oligomers,[7] bile acid dimers,[8] and benzothiazepines[9] were shown to be ASBT inhibitors. The benzothiazepine class represented a new class of inhibitors with improved in vitro activity over the bile acid systems. Recent reports have shown that some benzothiazepine analogues were quite potent in a rat in vivo model.[10] In this paper, we describe the synthesis and pharmacological evaluation of substituted benzothiepines[11] (3*R*,3*R*′-2,3,4,5-tetrahydro-5-aryl-1-benzothiepin-4-ol 1,1-dioxides, Figure 1). By synthetic modification of the benzothiepine ring system, the in vitro potency of our ASBT inhibitors have improved more than 6000-fold as measured in the H-14 cell culture assay system. Since we began our research, a number of interesting inhibitor classes have been developed.[12,13]

We employed various routes in preparing substituted benzothiepines. Detailed synthetic procedures for these transformations are provided in the Experimental Section. One of our initial approaches that we used to incorporate substituents at the 5-phenyl ring (Figure 1, R_1 or R_2 = Ph) is outlined in Scheme 1. Another approach, which integrates substituents on the benzothiepine A ring, is outlined in Scheme 2. Scheme 3 summarizes a method for attaching a positively charged quaternary ammonium group to the benzothiepine backbone. Scheme 4 summarizes methods for incorporating substituents on the 5-phenyl ring and at the 7, 8, and 9 positions. In all methods (Schemes 1−4), a key intermediate is the sulfone aldehyde.[11] The cyclization of this intermediate with KO^{t}Bu occurs with excellent regioselectivity, giving only the cis products as a racemic mixture.

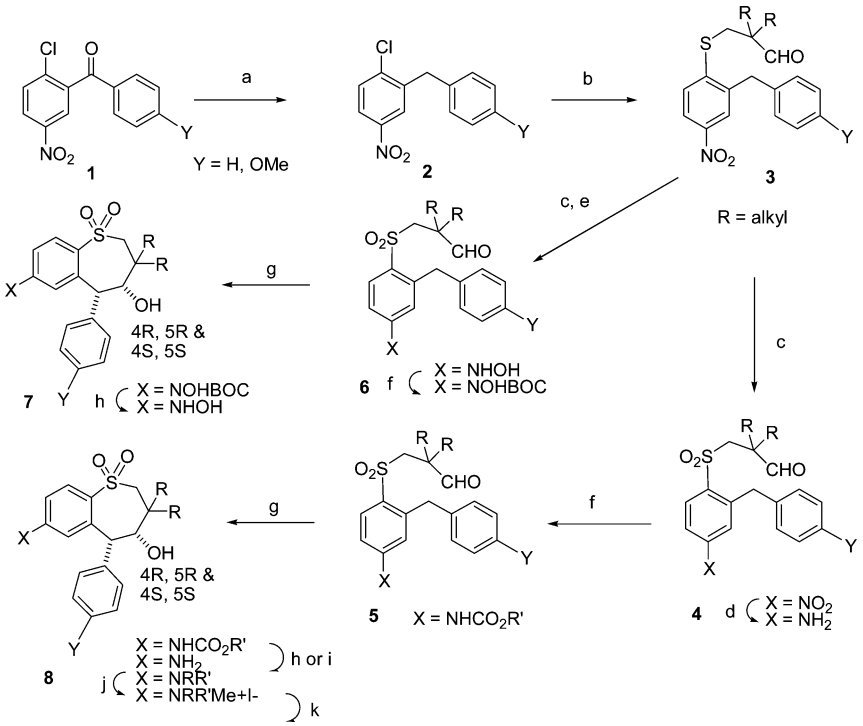
Scheme 1 describes the synthesis of the potent class of 7-amino substituted benzothiepines with further functionalization of the 5-phenyl ring. Benzophenones **1** were treated with triethylsilane/triflic acid to give the diphenylmethanes **2**.[14] Displacement of the chlorine with lithium disulfide,[15] followed by nucleophilic addition of the resulting lithium thiophenoxide intermediates (not shown) to the mesylate aldehydes, gave the sulfide aldehydes **3**. Selective oxidation of the sulfides **3** with mCPBA gave the sulfone intermediates **4** (X = NO_2).[16] Low-pressure catalytic hydrogenation of the nitro group gave the hydroxylamines **6** (X = NHOH), but higher pressures (100 psi) gave completely reduced amine **4** (X = NH_2). Both reduction products were amino-protected as carbamates **5** and **6** (X = NOHBOC). Under cyclization conditions, these amino-protected aldehydes gave stereoselectively the desired benzothiepines **7** (X = NOHBOC) and **8** (X = $NHCO_2R$) with the hydroxyl and aryl groups in a cis relationship. Deprotection conditions gave the free amine **8** (X = NH_2) and hydroxylamine **7** (X = NHOH) products. The free amine products were further substituted at nitrogen via alkylation conditions to give dialkylbenzothiepines and trialkylaminobenzothiepines **8** (X = NRR′, NRR′Me$^+$I$^-$).

Another useful approach that incorporates substituents at the aromatic A ring is outlined in Scheme 2. Phenols **9** were treated with benzoyl chloride/boron trichloride to give the benzophenones **10**.[17] Alkylation of the hydroxy group with a dimethylthiocarbamoyl chloride gave thiocarbamate esters **11**. These esters underwent thermal rearrangement, followed by base hydrolysis, to give the desired thiophenols **12**.[18] Sulfur alkylation and oxidation (as described for compounds **3** and **6**, Scheme 1), followed by catalytic hydrogenation of the benzophenone group, gave the sulfone aldehydes **14**. Cyclization conditions gave stereoselectively the benzothiepines **15** and **16**. In an alternative approach to thiophenols **12**, 4-methoxythiophenol was treated with benzonitrile.[19]

Scheme 3 describes the attachment of positively charged groups to either the 5-phenyl ring or the A ring. Methoxy substituted benzothiepines **17** were treated with BBr_3 to give hydroxybenzothiepines **18**. Alkylation of the hydroxy group gave the iodoalkoxybenzothiepines **19**. Finally, reaction with a tertiary amine gave the trialkylaminobenzothiepines **20**.

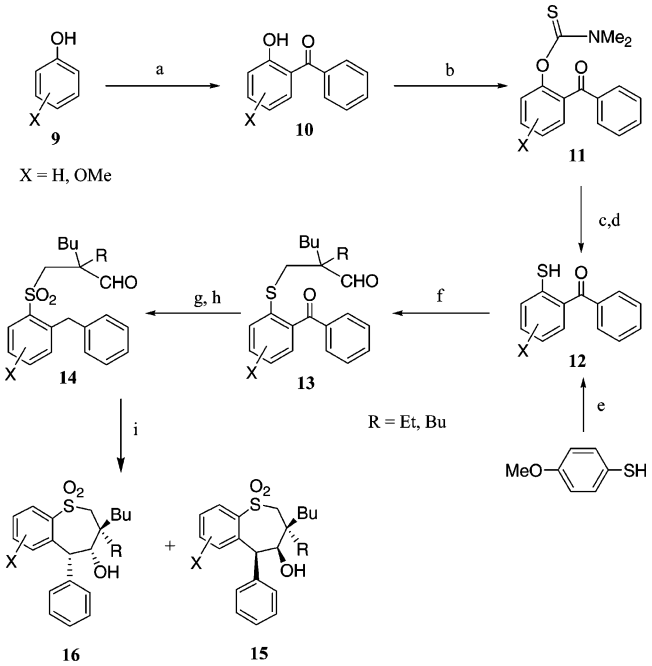
Another useful method for preparing the diphenylmethane intermediate directly from phenols is described in Scheme 4. Phenols **21** were C-benzylated to give diphenylmethanes **22**. Following a similar transformation sequence described for compounds **15** and **16**

Scheme 1[a]



[a] Reagents: (a) Et_3SiH, TfOH, CH_2Cl_2; (b) Li_2S, DMSO, then $MsOCH_2C(R_2)CHO$; (c) mCPBA; (d) 100 psig of H_2, Pd/C; (e) low pressure H_2, Pd/C; (f) K_2CO_3, R′OCOX; (g) KO^{t}Bu, THF; (h) HCl, dioxane; (i) EtSH, BF_3OEt_2, CH_2Cl_2; (j) RCOCl or $MeSO_2Cl$, 4-methylmorpholine; or metal, H_2, RCHO; (k) MeI, CH_3CN.

Scheme 2[a]



[a] Reagents: (a) PhCOCl, BCl_3; (b) NaH, $ClC(S)NMe_2$, DMF; (c) PhOPh, D; (d) KOH, MeOH; (e) BuLi, PhCN, tetramethylethylenediamine; (f) NaH, $MsOCH_2CRR'CHO$; (g) mCPBA; (h) Pd/C, H_2; (i) KO^{t}Bu, THF.

(Scheme 2), these diphenylmethanes **22** were sequentially converted to compounds **23**−**26**.

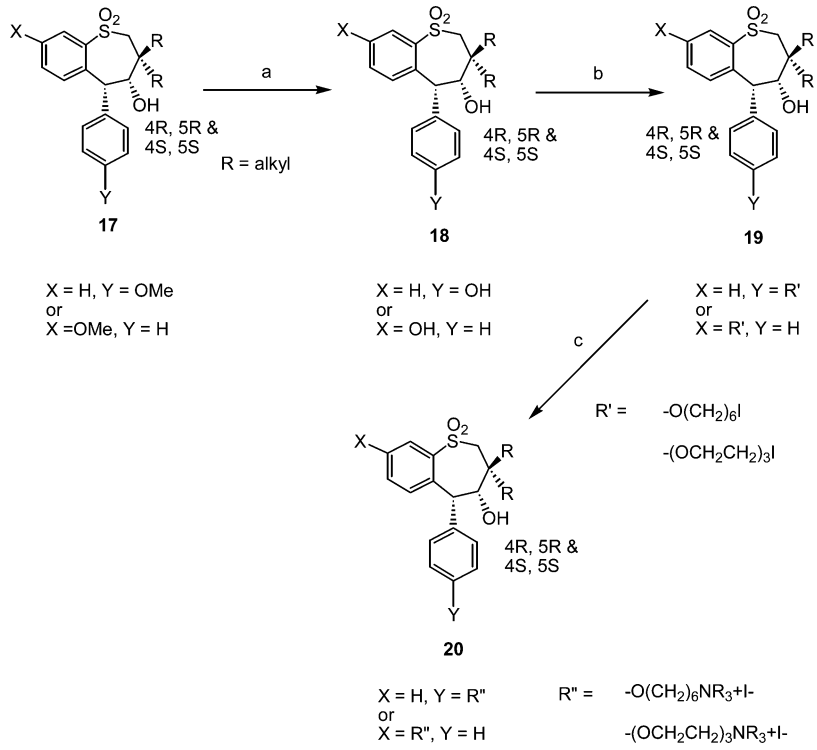
Results and Discussion

In early studies, our primary focus was to increase potency and reduce the number of stereogenic centers. Later, we sought out structural features to limit systemic availability and increase water solubility without decreasing potency. The SAR studies described in this paper include (A) relative stereochemistry at the 3, 4, and 5 positions, (B) aromatic substitution of both phenyl rings, and (C) alkyl substitution at the 3 position.

Our early benzothiepine leads included compounds **34** and **35**. To correlate the relative stereochemistry of positions 3, 4, and 5 with biological activity, we prepared and isolated four isomers as racemates (see Table 1). From this preliminary study, we discovered that optimum in vitro activity occurred when the phenyl, hydroxyl, and ethyl groups are all in the cis configuration (**34a**). Further SAR at the C-3 position will be discussed in a later section. Preliminary in vivo studies with **34a** indicated modest activity, and thus, further modifications were developed to increase potency.

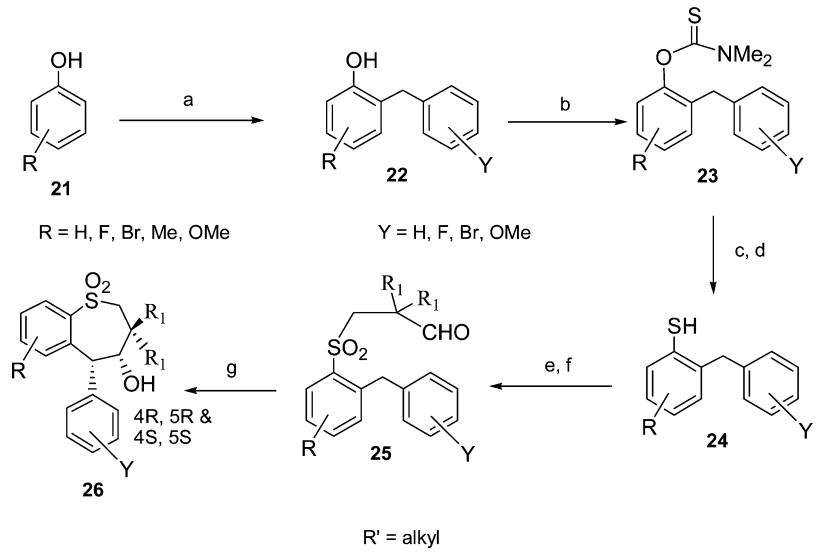
Characterization of 34 and 35. Proton, COSY (correlation spectroscopy), and NOESY (nuclear Overhauser effect spectrometry) NMR experiments and X-ray crystallography were used to assign stereochemistry in compounds **34a**,**b** and **35a**,**b**. Proton NMR easily distinguished the two cis compounds **34a** and **35a** from the trans compounds **34b** and **35b** because the trans compounds exhibit the typical trans three-bond couplings for H4 and H5 and the cis compounds do not. In ^{1}H NMR, compound **34a** exhibits two doublets of triplets (δ = 1.65 and 2.24 ppm) with typical two-bond ($J \approx 14$ Hz) and three-bond coupling constants (J = 4 Hz), indicative of the ring-adjacent methylene protons of the butyl group. These same doublets of triplets exhibit NOESY interactions with H4 and H5, which indicates that H4, H5, and the butyl group are on the same side of the benzothiepine ring. X-ray crystallography data for **34a** (Figure 2) confirms this configuration. Compound **35a** exhibits two doublets of quartets (δ = 1.76

Scheme 3[a]



[a] Reagents: (a) BBr_3 $CHCl_3$; (b) $I(CH_2)_6I$ or $I(CH_2CH_2O)_2CH_2CH_2I$, K_2CO_3, THF; (c) NR_3, CH_3CN.

Scheme 4[a]

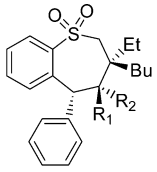


[a] Reagents: (a) NaH, $YPhCH_2X$ (X = Cl, Br); (b) NaH, $ClC(S)NMe_2$, DMF; (c) PhOPh, D; (d) KOH, MeOH; (e) NaH, $MsOCH_2C(R1)_2CHO$; (f) mCPBA; (g) KO^{t}Bu, THF.

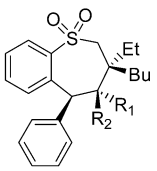
and 2.32 ppm), with typical two-bond ($J = 13.7$ Hz) and three-bond coupling constants ($J = 7.5$ Hz), indicative of the ethyl group's methylene protons. These same doublets of triplets exhibit NOE interactions with H4 and H5, which indicates that H4, H5, and the ethyl group are on the same side of the benzothiepine ring. In the ^{1}H NMR spectrum of compound **35b**, a multiplet ($\delta = 1.70$ ppm, two protons) has a strong COSY interaction with a methyl group triplet ($\delta = 0.91$ ppm), which indicates it must represent the ethyl's methylene. This same multiplet has a strong NOESY interaction with H5, which indicates the ethyl group is on the same side of the benzothiepine ring as H5. Compound **34b**'s stereochemistry was assigned via lack of obvious NMR distinctions and via the process of elimination.

In a search of more potent analogues, we prepared various substituted benzothiepines (see Table 2) that contained the same 3, 4, 5 configuration as compound **34a**. From this SAR study, we found that electron-donating groups in the 7 or 8 position increased in vitro potency, with the 7-substituted dimethylamino analogue being the most potent ($IC_{50} = 0.005$ uM). For comparison the IC_{50} for chenodeoxycholic acid is 50 μM. These results suggest that the dimethylamino group has the right size and electronic properties for optimum activity.

Table 1. Preliminary SAR of Parent Compounds (±)-**34** and (±)-**35**

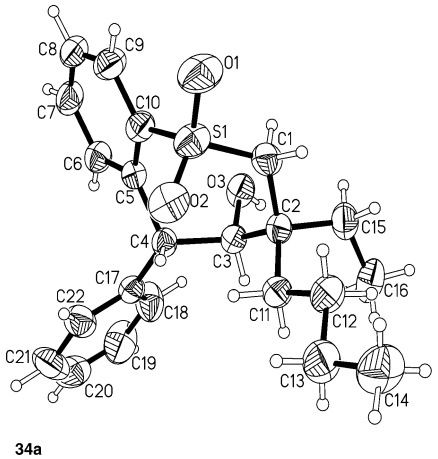


34



35

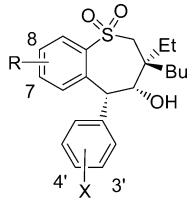
compd	R_1	R_2	IC_{50} (μM)	synthesis
(±)-**34a**	H	OH	0.28	Scheme 2
(±)-**34b**	OH	H	4.8	
(±)-**35a**	H	OH	2	Scheme 2
(±)-**35b**	OH	H	37% at 10 μM	



34a

Figure 2. ORTEP of compound (±)-**34a**.

Table 2. SAR by Substitution on Aromatic Rings of **34**

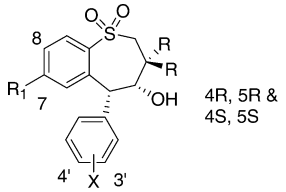


compd	R	X	IC_{50} (μM)	Scheme
34a	7-H	H	0.28	2
36	7-OMe	H	0.055	2
37	8-OH	H	0.09	2, 3
38	8-$OC_{10}H_{19}$	H	16	2, 3
39	7-NH_2	H	0.068	1
40	7-NHOH	H	0.26	1
41	7-N(OH)CO_2-^{t}Bu	H	2.67	1
42	7-$NHCO_2CH_2Ph$	H	0.4	1
43	7-$NHCO_2$-^{t}Bu	H	1.3	1
44	7-NHC_6H_{13}	H	1.67	1
45	7-NMe_2	H	0.005	1
46	7-$NHCOCH_3$	H	0.09	1
47	7-$NHCOC_5H_{11}$	H	0.3	1
48	7-$NHSO_2CH_3$	H	0.6	1
49	7-SMe	4-F	0.019	4
50	7-pyrrolidinyl	4-F	0.059	4
27	7-Br	3'-OMe	0.07	4
28	7-Ph	3'-OMe	0.18	4

The larger alkyl amino groups and electron-withdrawing groups decreased potency.

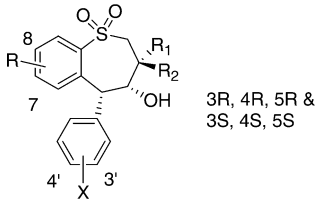
Next we investigated the possibility of replacing the sterogenic center at the C-3 position, which seemed to be critical in the benzothiazepine analogues with a symmetrical diastereotopic dialkyl substitiuent. This study (see Table 3) suggests that the dimethyl analogue is too small to participate in binding the protein's hydrophobic pocket. Furthermore, chain length appears proportional to in vitro potency up to the butyl group. This suggests a size limitation in the hydrophobic pocket. Our results also indicated the Bu, Bu system (IC_{50} = 0.054 μM) is as potent as the unsymmetrical Et, Bu system (IC_{50} = 0.068 uM). Although the Bu, Bu analogue **58** still contains two chiral centers (positions 4 and 5), both are fixed simultaneously by the stereospecific cyclization reaction that is utilized to form the seven-member ring (see Scheme 1).

Table 3. Removal of A Stereogenic Center



compd	R_1	R, R	X	IC_{50} (μM)	Scheme
55	7-NH_2	Me, Me	H	>50	1
56	7-NH_2	Et, Et	H	4	1
57	7-NH_2	Pr, Pr	H	0.23	1
58	7-NH_2	Bu, Bu	H	0.054	1
60	7-Me	pentyl, pentyl	4'-F	0.318	4

Table 4. Comparison of Et, Bu with Bu, Bu and Further SAR

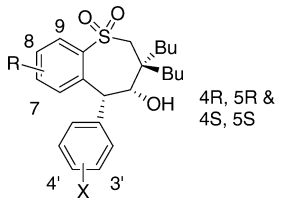


compd	R_1, R_2	R	X	IC_{50} (μM)	Scheme
61	Et, Bu	8-OMe	H	0.12	2
62	Bu, Bu			0.19	2
39	Et, Bu	7-NH_2	H	0.068	1
58	Bu, Bu			0.054	1
45	Et, Bu	7-NMe_2	H	0.005	1
64	Bu, Bu			0.013	1
65	Et, Bu	7-N^+Me_3	H	0.083	1
66	Bu, Bu			0.21	1
67	Et, Bu	7-Me	4'-F	0.021	4
68	Bu, Bu			0.046	4

In general, the Bu, Bu analogues were moderately less potent than the Et, Bu compounds (see Table 4). Although the Et, Bu 7-dimethylamino system was the most potent in this series at 0.005 μM, the Bu, Bu system was also very potent (IC_{50} = 0.013 uM). These results encouraged us to focus on the Bu, Bu system in the further optimization of our ASBT candidate. When the dimethylamino group was alkylated to form the less electron-donating quaternary ammonium salt, the activity was reduced by approximately 15-fold for the Et, Bu system (IC_{50} = 0.083 uM) and 16-fold for the Bu, Bu system (IC_{50} = 0.21 uM).

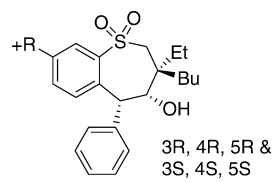
Substituent position and electron-donating properties seem to significantly affect potency of the Bu, Bu series (see Table 5). A dimethylamino group para to the sulfone **76** was almost 20-fold more potent than when the dimethylamino group is placed ortho to the sulfone **81**. Interestingly, we saw a slight increase in potency

Table 5. Further SAR in the Bu, Bu Series

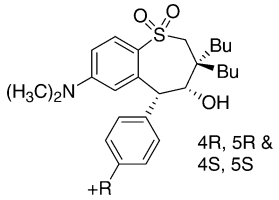


compd	R	X	IC_{50} (μM)	Scheme
64	7-NMe_2	H	0.013	1
73	7-$NHCH_2Ph$	H	1.9	1
74	7-$NHCO_2CH_2Ph$	H	0.6	1
75	7-NMe_2	4'-OMe	0.007	1
76	7-NMe_2	4'-F	0.01	4
80	8-NMe_2	H	0.12	4
81	9-NMe_2	4'-F	0.18	4
88	7-NMe_2, 9-OMe	4'-OMe	0.002	4
89	7-Br	2'-Br	0.55	4
90	7-OMe	4'-F	0.05	4
68	7-Me	4'-F	0.046	4
93	9-F	4'-F	0.18	4

Table 6. Quarternary Ammonium Salts



F



G

compd	R+	IC_{50} (μM)	Scheme
95, **F**	$-O(CH_2)_6N^+Me_3$	21	2, 3
96, **F**	$-(OCH_2CH_2)_3N^+Me_3$	18	2, 3
97, **G**	$-(OCH_2CH_2)_3N^+Et_3$	0.003	1, 3

when the 7-dimethylamino system was further substituted in the 4′ position by a methyl ether group **75** (IC_{50} = 0.007 μM). Enhanced activity was also seen in the 7-dimethylamino system that was further substituted in the 9 position by an electron-donating methoxy **88** (IC_{50} = 0.002 μM). Larger amino groups (7 or 9 position) were less active by about an order of magnitude. In contrast, less electron-donating groups (e.g., Table 5, last four entries) generally led to a decrease in activity that seemed related to the substituent's electron-donating ability and steric properties.

Because the site of action of this drug is located in the distal region of the ileum, limiting systemic exposure was thought to be advantageous. To limit systemic exposure and increase water solubility, we employed a series of analogues containing positively charged quaternary ammonium substrates (see Table 6). When the quaternary ammonium group was placed on a long chain at the 8 position (**95** and **96**), a large decrease in activity was observed. However, the charged group minimally affected potency when attached at the 4′ phenyl position, especially when placed more than four atoms from the phenyl ring. Compound **97** exhibited water solubility and fortunately was as potent (IC_{50} = 0.003 μM) as any of the uncharged analogues. Analogue **97** was shown to have less than 1% of the oral dose of parent compound measurable in the systemic circulation of rat.

Table 7. The 0.24% Cholesterol-Fed Hamster Model [14 Days, 0.2% Dietary Admixture, ~200 (mg/kg)/day][a]

compd	serum total cholesterol (mg/dL)	fecal bile acids (FBA) ((mmol/24 h)/100 g)	24 h fecal weight (g)
control	143 ± 7	6.2 ± 0.8	2.3 ± 0.1
61	126 ± 2[a]	11.9 ± 0.5[a]	2.4 ± 0.04
control	129 ± 9	6.1 ± 0.4	1.7 ± 0.1
39	126 ± 7	8.8 ± 1.1[a]	1.6 ± 0.1
control	135 ± 4	8.0 ± 0.7	2.1 ± 0.2
45	97 ± 5[a]	13.7 ± 0.4[a]	2.1 ± 0.1
control	195 ± 28	8.7 ± 0.6	3.5 ± 0.2
97	141 ± 13[a]	16.2 ± 0.6	3.9 ± 0.3

[a] $P < 0.05$, Students T-test.

In Vivo Efficacy Studies of Benzothiepine Analogues 39, 45, 61, and 97. Our lead ASBT inhibitors were tested in a 14-day cholesterol-fed hamster model. The primary measurements were fecal bile acids (FBA) and serum cholesterol. Table 7 illustrates key results from this study. All compounds chosen for this study were active. For compounds **61** and **39** we believe 200 (mg/kg)/day is not a maximally effective dose because of significant absorption of these compounds in the proximal portion of the small intestine and the lower potency of these compounds (120 and 68 nM, respectively). However we believe this is a maximally effective dose for compounds **45** and **97** because of their markedly increased potency (5 and 3 nM, respectively) and the fact that compound **97** exhibits little, if any, absorption from the GI tract. This study showed significant increases of FBA (140−190%), which is consistent with inhibiting bile acid reabsorption at the apical bile acid transporter site in the ileum. In response to the increased excretion of bile acids, serum cholesterol levels were significantly decreased. One of our earlier leads **61** (IC_{50} = 120 nM) decreased cholesterol in the hamster model by 12% while **45** (IC_{50} = 5 nM) decreased total cholesterol by 28%. Studies with **97** (IC_{50} = 3 nM), which was designed to be minimally absorbed and where chemical complexity was reduced by removal of a chiral center, indicated low systemic exposure and a 28% decrease in total cholesterol in the hamster model. The fact that this is a potent and minimally absorbed drug further supports the hypothesis that inhibition at the ASBT site in the ileum can lead to a decrease in plasma cholesterol.

Conclusions

The benzothiepine class of is one of the most potent classes of inhibitors discovered, and it has been shown in this paper that substituents with appropriate size that donate electron density to the sulfone group have a very positive effect on potency. Our SAR studies have achieved increased potency (6000-fold from early lead) and reduced chirality. We have also found a potent water-soluble racemic analogue with low systemic exposure: **97**. Although analogue **97** is potent and minimally absorbed, its physical properties (hygroscopic and amorphous) are not optimal for a commercial candidate. In our next studies we pursued further fine-tuning the SAR of the substituted phenyl ring at the 5 position of the benzothiepine ring with the goal of identifying a single enantiomer analogue that is a potent, crystalline, nonhygroscopic, and efficacious ASBT inhibitor with low

systemic exposure. These studies are described in part 2 of this series.

Experimental Section

In Vitro Assay of Compounds That Inhibit ASBT-Mediated Uptake of [^{14}C]Taurocholate (TC) in H14 Cells. Baby hamster kidney cells (BHK) transfected with the cDNA of human IBAT (H14 cells) are seeded in 96-well Top-Count tissue culture plates at 60 000 cells/well for assays run within 24 h of seeding, 30 000 cells/well for assays run within 48 h, and 10 000 cells/well for assays run within 72 h.

On the day of assay, the cell monolayer is gently washed once with 100 mL of assay buffer (Dulbecco's modified Eagle's medium with 4.5 g/L glucose plus 0.2% (w/v) fatty acid free bovine serum albumin ((FAF)BSA)). To each well 50 mL of a 2-fold concentrate of test compound in assay buffer is added along with 50 mL of 6 mM [^{14}C]taurocholate in assay buffer (final concentration of 3 mM [^{14}C]taurocholate). The cell culture plates are incubated 2 h at 37 °C prior to gentle washing of each well twice with 100 mL of 4 °C Dulbecco's phosphate-buffered saline (PBS) containing 0.2% (w/v) (FAF)-BSA. The wells are then gently washed once with 100 mL of 4 °C PBS without (FAF)BSA. To each 200 mL of liquid, scintillation counting fluid is added. The plates are heat-sealed and shaken for 30 min at room temperature prior to measuring the amount of radioactivity in each well on a Packard Top-Count instrument.

In Vitro Assay of Compounds That Inhibit Uptake of [^{14}C]Alanine. The alanine uptake assay is performed in a fashion identical to that of the taurocholate assay, with the exception that labeled alanine is substituted for the labeled taurocholate.

Bioavailability Assay. Compounds were initially screened for absorption in the rat by comparing iv and oral dosing to calculate % bioavailability. Compounds were solubilized in iv compatible vehicles (saline with pH adjusted to attain clear solutions) and dosed at 2−10 mg per kg of body weight. Sprague Dawley rats were anesthetized with inactin, and the femoral artery and vein were cannulated. Compounds were administered via the femoral vein, and peripheral blood samples were taken via the arterial cannulae at selected time periods up to 8 h. Plasma concentrations of the compounds were determined by quantitative HPLC with UV detection. The lower limit of sensitivities typically ranged from 10 to 100 ng/mL. Clearance and AUC (area under the curve) for the compounds were determined. A second set of rats ($n = 3$ per compound and route) was prepared as described above. An oral dose at 10−20 mpk was administered, and peripheral plasma samples were again administered via the arterial cannulae.

To rank compounds that were typically <1% and to differentiate between these low levels of systemic bioavailability, an alternative method was used. Instead of calculating systematic bioavailabilty using plasma levels from peripheral blood, samples of portal plasma were also obtained. To accomplish this, rats receiving the oral dose were prepared with peripheral and portal access. Cannulae were inserted into both the femoral artery for peripheral access as well as the hepatic portal vein to obtain estimates of the total absorbed drug without first-pass hepatic clearance. In addition, and to add a final method to compare compounds that had low total absorption, the common bile duct was cannulated and total bile flow was collected for the duration of the experiment. The AUC for portal plasma was then obtained to determine % drug absorbed and total biliary excretion as % total dose was also obtained. The fraction absorbed (F) is calculated by

$$F = \frac{\mathrm{AUC_{po}(hepatic\ portal)}}{\mathrm{AUC_{iv}}}$$

Materials and Methods. Animal Handling, Dosing, and Sample Collection. Male golden Syrian hamsters (126−147 g) were obtained from Charles Rivers Laboratories and were single-housed in a constant temperature environment with alternating 12 h light and dark cycles. Hamsters were fed Teklad 7001 rodent meal chow at libitum for 2 weeks before the experimental studies began and the chow was switched to Teklad 7001 rodent meal chow supplemented with 0.24% cholesterol on day 1 of the 14 day experiment. Water was continuously available to the animals. Hamsters were assigned to groups in a manner that normalized each group by pretreatment body weights. Experimental compounds were administered as a 0.2% dietary admixture in the meal chow. On the basis fo average food consumption, the daily dose of compound was calculated to be approximately 200 (mg/kg)/day. Blood samples were collected after the 14 day treatment period by cardiac puncture. Hamsters were anesthetized but not fasted prior to blood collections. Fecal samples were collected during a 48 h period at the end of the study (i.e., days 13−14).

Fecal Bile Acid Measurement.[20] Fecal samples were collected to determine the fecal bile acid (FBA) concentration for each animal. The separate collections from each hamster were weighed and homogenized with distilled water with a Polytron tissue processor (Brinkman Instruments) to generate a homogeneous slurry. Fecal homogenate (1.4 g) was extracted with 2.6 mL of a solution containing tertiary butanol/distilled water in the ratio of 2:0.6 [final concentration of 50% (v/v) tertiary butanol] for 45 min in a 37 °C water bath and subjected to centrifugation for 13 min at 2000g. The concentration of bile acids (mmol/g homogenate) was determined using a 96-well enzymatic assay system.[1,2] Aliquots of the fecal extracts (20 mL) were added to two sets of triplicate wells in a 96-well assay plate. A standardized sodium taurocholate solution and a standardized fecal extract solution (previously made from pooled samples and characterized for its bile acid concentration) were also analyzed for assay quality control. Aliquots of 90 mM sodium taurocholate (20 mL) were serially diluted to generate a standard curve containing 30−540 nmol/well. A 230 mL aliquot of reaction mixture containing 1 M hydrazine hydrate, 0.1 M pyrophosphate, and 0.46 mg/mL NAD was added to each well. Subsequently, a 50 mL aliquot of either 3a-hydroxysteroid dehydrogenase enzyme (HSD, 0.8 units/mL) or assay buffer (0.1 M sodium pyrophosphate) was then added to one each of the two sets of triplicates. Following 60 min of incubation at room temperature, the optical density at 340 nm was measured and the mean of each set of triplicate samples was calculated. The difference in optical density ± HSD enzyme was used to determine the bile acid concentration (mM) of each sample based on the sodium taurocholate standard curve. The bile acid concentration of the extract (mmol/g homogenate), the total weight of the fecal homogenate (g), and the body weight of the hamsters (g) were used to calculate the corresponding FBA concentration in (mmol/day)/kg body weight for each animal. All reagents used for the assay were obtained from Sigma Chemical Co., St. Louis, MO (HSD, catalog no. H-1506; NAD, catalog no. N1636; sodium taurocholate, catalog no. T-4009).

Serum Lipid Measurements.[21] Blood was collected at 14 and 28 days from nonfasted hamsters and put into serum separator tubes. The blood cells were separated from the serum by centrifugation at 2000g for 20 min, and the serum was decanted. Total cholesterol was measured using a Cobas Mira Classic clinical chemistry analyzer (Roche Diagnostic Systems, Indianapolis, IN). This analyzer used the cholesterol oxidase reaction to produce hydrogen peroxide, which was measured colorimetrically. The cholesterol reagent (Roche Diagnostic Systems) was reconstituted according to the package insert. The reagent was calibrated using Roche calibrator serum. Commercial bilevel quality control material was analyzed to verify calibration and reagent performance (QC1, QC2; Bio-Rad Laboratories, Irvine, CA). The cholesterol content of each sample was measured at 500 nm and 37 °C in a calibrated analyzer by mixing 3 mL of sample with 150 mL of cholesterol reagent and 40 mL of water.

The unimate HDL direct cholesterol assay (DHDL, Roche Diagnostics) was based on the absorbance of synthetic polymers and polyanions onto the surface of lipoproteins. The

Table 8. HPLC Gradient

time (min)	solution A (%)	solution B (%)
0	50	50
5	50	50
30	0	100
40	0	100

combined action of polymers, polyanions, and detergent solubilizes cholesterol from HDL but transforms LDL, VLDL, and chylomicrons into detergent-resistant forms. Solubilized cholesterol was oxidized by the sequential enzymatic action of cholesterol esterase and cholesterol oxidase. The H_2O_2 produced in this reaction was reacted with chromogens to form a colored dye. The increase in absorbance at 550 nm was directly proportional to the HDL cholesterol concentration of the sample. The test was performed using a Cobas Mira Classic clinical chemistry analyzer (Roche Diagnostic Systems). The DHDL reagent (Roche Diagnostic Systems) was reconstituted according to the package insert. The reagent was calibrated using Roche HDL direct calibrator. Commercial bilevel quality control material was analyzed to verify calibration and reagent performance (Liquichek lipids control, levels 1 and 2, Bio-Rad Laboratories, Irvine, CA). A 2.4 mL aliquot of serum was analyzed in the presence of 240 mL of reagent 1, 80 mL of reagent 2, and 5 mL of water at 37 °C and 550 nm wavelength.

Triglycerides were hydrolyzed by lipoprotein lipase to glycerol and fatty acids. Glycerol was then phosphorylated to glycerol 3-phosphate by adenosine 5-triphosphate (ATP) in a reaction catalyzed by glycerol kinase (GK). The oxidation of glycerol 3-phosphate was catalyzed by glycerolphosphate oxidase (GPO) to form dihydroxyacetone phosphate and hydrogen peroxide. The hydrogen peroxide reacted with 4-cholorophenol and 4-aminophenazone in the presence of peroxidase to form a quinoneimine complex, which was read at 490−550 nm. The increase in absorbance was proportional to the concentration of triglycerides in the sample. The test was performed using a Cobas Mira Classic clinical chemistry analyzer (Roche Diagnostic Systems). The triglyceride reagent (Roche Diagnostic Systems) was reconstituted according to the package insert. The triglyceride content of each sample was measured at 500 nm at 37 °C in a calibrated analyzer by mixing 4 mL of sample with 300 mL of triglyceride reagent and 40 mL of water.

General Comments. Chemicals were obtained from Aldrich Chemical Co. and were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 300 spectrometer at 300 and 75 MHz, respectively. The ^{1}H chemical shifts are reported in ppm downfield from Me_4Si. The ^{13}C chemical shifts are reported in ppm relative to the center line of $CDCl_3$ (77.0 ppm). Melting points were recorded on a Buchi 510 melting point apparatus and are uncorrected. High-resolution mass spectra were determined by Monsanto Analytical Sciences Center, and microanalyses were performed by Atlantic Microlab Inc. Compound purity was checked by microanalysis. For this manuscript only racemates were evaluated. The following article, part 2 of this series, will describe our research with single enantiomers. Biological data were reported only for compound samples with greater than 95% purity as determined by elemental analysis, HPLC, and/or ^{1}H NMR. HPLC data were obtained on a Spectra Physics 8800 chromatograph using a Beckman Ultrasphere C18 250 mm × 4.6 mm column. HPLC conditions were as follows: detector wavelength = 254 nm; sample size = 10 μL; flow rate = 1.0 mL/min; mobile phase = (A) 0.1% aqueous trifluoroacetic acid, (B) acetonitrile.

The HPLC gradient is shown in Table 8.

(±)-(3*S*,4*R*,5*R*)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1-benzothiepin-4-ol 1,1-Dioxide (34a) and (±)-(3*S*,4*S*,5*S*)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1-benzothiepin-4-ol 1,1-Dioxide (35a). Step 1. (±)-2-Ethyl-2-(methanesulfonyloxymethyl)hexanal (98). To a cold (10 °C) solution of 12.6 g (0.11 mole) of methanesulfonyl chloride and 10.3 g (0.13 mol) of triethylamine was added dropwise 15.8 g of (±)-2-ethyl-2-(hydroxymethyl)hexanal, prepared according to the procedure described in ref 22, while maintaining the reaction temperature below 30 °C. The reaction mixture was stirred at room temperature for 18 h, and the reaction was quenched with dilute HCl and extracted with methylene chloride. The methylene chloride extract was dried over $MgSO_4$ and concentrated in vacuo to give 24.4 g of brown oil **98**. ^{1}H NMR ($CDCl_3$) δ 0.80 (t, J = 7.5 Hz, 3H), 0.82 (t, J = 7.2 Hz, 3H), 1.06−1.28 (m, 5H), 1.48−1.60 (m, 3H), 2.95 (s, 3H), 4.19 (ABq, 2H), 9.38 (s, 1H). HRMS (CI/M + NH_4) calcd for $C_{10}H_{24}O_4SN$: 254.1431; found, 254.1426.

Step 2. 2-((2-Benzoylphenylthio)methyl)-2-ethylhexanal (99). A mixture of 31 g (0.144 mol) of 2-mercaptobenzophenone, 24.4 g (0.1 mol) of 2-ethyl-2-(mesyloxymethyl)-hexanal (**98**), 14.8 g (0.146 mol) of triethylamine, and 80 mL of 2-methoxyethyl ether was held at reflux for 24 h. The reaction mixture was poured into 3 N HCl and extracted with 300 mL of methylene chloride. The methylene chloride layer was washed with 300 mL of 10% NaOH, dried over $MgSO_4$, and concentrated in vacuo to remove 2-methoxyethyl ether. The residue was purified by HPLC (10% EtOAc/hexane) to give 20.5 g (58%) of **99** as an oil.

Step 3. 2-((2-Benzoylphenylsulfonyl)methyl)-2-ethylhexanal (100). To a solution of 9.0 g (0.025 mol) of compound **99** in 100 mL of methylene chloride was added 14.6 g (0.025 mol) of 50−60% MCPBA portionwise. The reaction mixture was stirred at room temperature for 64 h and then was stirred with 200 mL of 1 M potassium carbonate and filtered through Celite. The methylene chloride layer was washed twice with 300 mL of 1 M potassium carbonate, once with 10% sodium hydroxide, and once with brine. The insoluble solid formed during washing was removed by filtration through Celite. The methylene chloride solution was dried and concentrated in vacuo to give 9.2 g (95%) of semisolid. A portion (2.6 g) of this solid was purified by HPLC (10% ethyl acetate/hexane) to give 1.9 g of crystals of **100**, mp 135−136 °C.

Step 4. 2-((2-Phenylmethylphenylsulfonyl)methyl)-2-ethylhexanal (101). A solution of 50 g (0.13 mol) of crude **100** in 250 mL of methylene chloride was divided into two portions and charged to two Fisher−Porter bottles. To each bottle was charged 125 mL of methanol and 5 g of 10% Pd/C. The bottles were pressurized with 70 psi of hydrogen, and the reaction mixture was stirred at room temperature for 7 h before being charged with an additional 5 g of 10% Pd/C. The reaction mixture was again hydrogenated with 70 psi of hydrogen for 7 h. This procedure was repeated one more time, but only 1 g of Pd/C was charged to the reaction mxture. The combined reaction mixture was filtered and concentrated in vacuo to give 46.8 g of **101** as a brown oil.

Step 5. (±)-(3*S*,4*R*,5*R*)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1-benzothiepin-4-ol 1,1-Dioxide (34a) and (±)-(3*S*,4*R*,5*S*)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1-benzothiepin-4-ol 1,1-Dioxide (35a). To a solution of 27.3 g (73.4 mmol) of **101** in 300 mL of anhydrous THF cooled to 2 °C with an ice bath was added 9.7 g (73.4 mmol) of 95% potassium *tert*-butoxide. The reaction mixture was stirred for 20 min, the reaction was quenched with 300 mL of 10% HCl, and the sample was extracted with methylene chloride. The methylene chloride layer was dried over magnesium sulfate and concentrated in vacuo to give 24.7 g of yellow oil. Purification by HPLC (ethyl acetate/hexane) yielded 9.4 g of recovered **101** in the first fraction, 5.5 g (20%) of **35a** in the second fraction, and 6.5 g (24%) of **34a** in the third fraction.

34a: solid; mp 160−161 °C. ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7.6 Hz, 3 H), 0.92 (t, J = 6.8 Hz, 3 H), 1.0−1.56 (m, 6 H), 1.65 (dt, J = 14.0, 4.8 Hz, 1 H), 2.24 (dt, J = 13.6, 3.6 Hz, 1 H), 3.12 (ABq, J = 16.8 Hz, 2 H), 4.21 (d, J = 6.7 Hz, 1 H), 5.60 (s, 1 H), 6.79 (d, J = 7.5, 1 H), 7.30−7.54 (m, 7 H), 8.14 (d, J = 7.5 Hz, 1 H). MS (ES/M + H): 373. HRMS (CI/M + H) calcd for $C_{22}H_{29}O_3S$: 373.1837; found, 373.1839.

35a: solid; mp 179−181 °C. ^{1}H NMR ($CDCl_3$) δ 0.85−0.96 (m, 6 H), 1.15−1.50 (m, 6 H), 1.76 (dq, J = 13.7, 7.5 Hz, 1 H), 2.32 (dq, J = 13.7, 7.5 Hz, 1 H), 3.13 (ABq, J = 15.1 Hz, 2 H), 4.22 (d, J = 6.4 Hz, 1 H), 5.60 (s, 1 H), 6.80 (m, 1 H), 7.30−

7.50 (m, 7 H), 8.10 (m, 1H). Anal. Calcd for $C_{22}H_{29}O_3S$: C, 70.91; H, 7.58; S, 8.61. Found: C, 70.69; H, 7.58; S, 8.55.

Alternative Synthesis of 101. Step 1. 2-Mercaptodiphenylmethane (102). To a 500 mL flask was charged 16 g (0.4 mol) of 60% sodium hydride oil dispersion. The sodium hydride was washed twice with 50 mL of hexane. To the reaction flask was charged 100 mL of DMF. To this mixture was added a solution of 55.2 g (0.3 mol) of 2-hydroxydiphenylmethane in 2000 mL of DMF in 1 h while the temperature was maintained below 30 °C by an ice−water bath. After complete addition of the reagent, the mixture was stirred at room temperature for 30 min, then cooled with an ice bath. To the reaction mixture was added 49.4 g (0.4 mol) of dimethylthiocarbamoyl chloride at once. The ice bath was removed, and the reaction mixture was stirred at room temperature for 18 h before being poured into 300 mL of water. The organic was extracted into 500 mL of toluene. The toluene layer was washed successively with 10% sodium hydroxide and brine and was concentrated in vacuo to give 78.6 g of a yellow oil, which was 95% pure dimethyl *O*-2-benzylphenylthiocarbamate. This oil was heated at 280−300 °C in a Kugelrohhr pot under house vacuum for 30 min. The residue was Kugelrohr distilled at 1 Torr (180−280 °C). The distillate (56.3 g) was crystallized from methanol to give 37.3 g (46%) of the rearranged product dimethyl *S*-2-benzylphenylthiocarbamate as a yellow solid. A mixture of 57 g (0.21 mol) of this yellow solid, 30 g of potassium hydroxide, and 150 mL of methanol was stirred overnight and then was concentrated in vacuo. The residue was diluted with 200 mL of water and extracted with ether. The aqueous layer was made acidic with concentrated HCl. The oily suspension was extracted into ether. The ether extract was dried over magnesium sulfate and concentrated in vacuo. The residue was crystallized from hexane to give 37.1 g (88%) of compound **102** as a yellow solid.

Step 2. (±)-2-((2-Phenylmethylphenylthio)methyl)-2-ethylhexanal (103). A mixture of 60 g (0.3 mol) of compound **102**, 70 g (0.3 mol) of **98**, 32.4 g (0.32 mol) of triethylamine, and 120 mL of 2-methoxyethyl ether was held at reflux for 6 h and concentrated in vacuo. The residue was triturated with 500 mL of water and 30 mL of concentrated HCl. The mixture was extracted into 400 mL of ether. The ether layer was washed successively with brine, 10% sodium hydroxide, and brine and was dried over magnesium sulfate and concentrated in vacuo. The residue (98.3 g) was purified by HPLC with 2−5% ethyl acetate/hexane as eluent to give **103** as a yellow syrup.

Step 3. (±)-2-((2-Phenylmethylphenylsulfonyl)methyl)-2-ethylhexanal (101). To a solution of 72.8 g (0.21 mol) of **103** from step 2 in 1 L of CH_2Cl_2 cooled to 10 °C was added 132 g of 50−60% MCPBA in 40 min. The reaction mixture was stirred for 2 h. An additional 13 g of 50−60% MCPBA was added to the reaction mixture. The reaction mixture was stirred for 2 h and filtered through Celite. The CH_2Cl_2 solution was washed twice with 1 L of 1 M potassium carbonate and then with 1 L of brine. The CH_2Cl_2 layer was dried ($MgSO_4$) and concentrated to give 76 g of compound **101** as a thick oil.

(±)-(3*S*,4*S*,5*R*)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1-benzothiepin-4-ol 1,1-Dioxide (34b) and (±)-(3*S*,4*R*,5*S*)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1-benzothiepin-4-ol 1,1-Dioxide (35b). Step 1. (±)-3-Butyl-3-ethyl-2,3-dihydro-5-phenylbenzothiepine (A). Compound **A** was prepared according to the procedure described in ref 11.

Step 2. (±)-(3*S*,4*S*,5*R*)-3-Butyl-3-ethyl-4,5-oxo-2,3,4,5-tetrahydro-5-phenyl-1-benzothiepine 1,1-Dioxide (B) and (±)-(3*S*,4*R*,5*S*)-3-Butyl-3-ethyl-4,5-oxo-2,3,4,5-tetrahydro-5-phenyl-1-benzothiepine 1,1-Dioxide (C). To a solution of 1.3 g (4.03 mmol) sulfide olefin **A** from step 1 in 25 mL of CH_2Cl_2 was added 5.0 g of 50−60% MCPBA portionwise. After being stirred overnight, the reaction mixture was heated to reflux for 3 h. The mixture was filtered, and the filtrate was washed with 10% potassium carbonate (3 × 50 mL) and brine (50 mL). The CH_2Cl_2 layer was dried ($MgSO_4$), filtered, and concentrated to 1.37 g of yellow oil. Purification by preparative HPLC eluting with EtOAc/hexanes gave a mixture of **B** and **C** (0.65 g) as a crystalline product. Trituration with hexanes gave pure **B** (0.142 g) as a white crystalline solid. The hexane filtrate was concentrated in vacuo to give a mixture of 30% **B** and 70% **C**.

B: ^{1}H NMR ($CDCl_3$) δ 0.67 (m, 3H), 0.85−1.15 (m, 6H), 1.60 (m, 1H), 1.75 (m, 1H), 3.29 (s, 1H), 3.42 (q_{AB}, J_{AB} = 12.0 Hz, $\Delta\nu$ = 24.0 Hz, 2H), 7.24 (m, 5H), 7.57 (d, J = 7.2 Hz, 1H), 7.59 (s, J = 7.2 Hz, 1H), 7.66 (d, 1H), 8.02 (d, 1H). MS (EI): 370.

C: ^{1}H NMR ($CDCl_3$) δ 0.67 (m, 3H), 0.90−1.00 (m, 3H), 1.25−1.50 (m, 4), 1.74 (m, 1H), 3.30 (s, 1H), 3.40 (q_{AB}, J_{AB} = 12.0 Hz, $\Delta\nu$ = 24.0 Hz, 2H), 7.24 (m, 5H), 7.57 (d, J = 7.2 Hz, 1H), 7.59 (s, J = 7.2 Hz, 1H), 7.66 (d, 1H), 8.02 (d, 1H). MS (EI): 370.

Step 3. (±)-(3*S*,4*S*,5*R*)-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1-benzothiepin-4-ol 1,1-Dioxide (34b) and (±)-(3*S*,4*S*,5*S*)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1-benzothiepin-4-ol 1,1-Dioxide (35b). A mixture of 30% **B** and 70% **C** (0.15 g, 0.40 mmol) was dissolved in methanol (15 mL) in a 3 oz. Fischer−Porter bottle. A 10% Pd/C (0.10 g) sample was added to the bottle, and it was pressurized to 70 psig of H_2. After 5 h, the reaction mixture was filtered and concentrated in vacuo. Purification by preparative HPLC eluting with EtOAc/hexanes gave isolation of **34b** and **35b**.

34b: ^{1}H NMR ($CDCl_3$) δ 0.83 (t, J = 7.8 Hz, 3H), 0.88 (t, J = 7.8 Hz, 3H), 1.29 (m, 6H), 1.64 (m, 2H), 1.75 (d, J = 4.7 Hz, 1H), 3.38 (ABq, J = 15.5 Hz, 2H), 4.42 (dd, J = 9.7, 3.9 Hz, 1H), 5.03 (d, J = 9.7 Hz, 1H), 7.10 (d, J = 7.8 Hz, 1H), 7.37−7.43 (m, 7H), 8.08 (d, J = 7.8 Hz, 1H). MS (EI): 372.

35b: ^{1}H NMR ($CDCl_3$) δ 0.78 (t, J = 6.6 Hz, 3H), 0.91 (t, J = 6.6 Hz, 3H), 1.06−1.35 (m, 6H), 1.70 (m, 2H), 1.80 (d, J = 3.9 Hz, 1H), 3.40 (ABq, J = 15.5 Hz, 2H), 4.42 (dd, J = 9.3, 3.9 Hz, 1H), 5.04 (d, J = 9.3 Hz, 1H), 7.10 (d, J = 6.9 Hz, 1H), 7.33−7.44 (m, 7H), 8.05 (d, J = 6.9 Hz, 1H). MS (EI): 372.

(±)-(3*S*,4*R*,5*R*)-3-Butyl-3-ethyl-5-(3-methoxyphenyl)-2,3,4,5-tetrahydro-7-bromobenzothiepin-4-ol 1,1-Dioxide (27). Alkylation of 4-bromophenol with 3-methoxybenzyl chloride according to the procedure described in ref 23 gave 4-bromo-2-(3′-methoxybenzyl)phenol: mp 95.4−96.8 °C. ^{1}H NMR (CD_3OD) δ 3.64 (s, 3H), 3.85 (s, 2H), 6.67−6.78 (m, 4H), 7.05−7.17 (m, 3H). MS (EI/M+): 293. This material was converted to compound **27**, mp 102−106 °C, and its (±)-(3*S*,4*S*,5*S*)-diastereomer, mp 97−101.5 °C, by a procedure similar to the one for **34a** described from synthesis of **102** above. The diastereomers were separated by HPLC (ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$) δ 0.9−1.1 (m, 6 H), 1.1−1.8 (m, 7 H), 2.28 (br t, J = 13.8 Hz, 1 H), 3.21 (ABq, J = 15.7 Hz, 2 H), 3.92 (s, 3H), 4.28 (d, J = 7 Hz, 1 H), 5.58 (s, 1 H), 7.00 (d, J = 8 Hz, 1 H), 7.10 (s, 2 H), 7.16 (d, J = 8 Hz, 1 H), 7.46 (t, J = 8 Hz, 1 H), 7.62 (d, J = 8 Hz, 1 H), 8.04 (d, J = 8 Hz, 1 H). MS (CI/M + H): 481. Anal. Calcd for $C_{23}H_{29}BrO_4S$: C, 57.38; H, 6.07; S, 6.60. Found: C, 57.11; H, 6.01; S, 6.53.

(±)-(3*S*,4*R*,5*R*)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(3-methoxyphenyl)-7-phenyl-1-benzothiepin-4-ol 1,1-Dioxide (28). To a mixture of 0.6 g (1.25 mmol) of **27** of 60 mL of toluene and 25 mL of ethanol was added 0.18 g (1.55 mmol) of phenylboronic acid followed by a solution of 0.38 g (2.7 mmol) of potassium carbonate in 1 mL of water. To the above mixture was added 0.1 g (0.087 mmol) of tetrakis(triphenylphosphinyl)-palladium. The reaction mixture was stirred and heated at 90 °C for 1 h. To the above mixture was add another equal portion of phenylboronic acid, potassium carbonate solution, and tetrakis(triphenylphosphinyl)palladium. The mixture was held at 90 °C for 4 h and cooled. The reaction mixture was diluted with 100 mL of water and extracted with methylene chloride (4 × 50 mL). The methylene chloride extracts were washed with 10% sodium hydroxide (2 × 50 mL), dried over $MgSO_4$, and concentrated in a vacuum to give 0.6 g of solid. Purification with HPLC on silica gel (4:1 hexane/EtOAc) gave 0.4 g of a white solid **28**, mp 212−214 °C. ^{1}H NMR ($CDCl_3$) δ 0.9−1.1 (m, 6 H), 1.1−1.9 (m, 7 H), 2.28 (br t, J = 13.8 Hz, 1 H), 3.14 (ABq, J = 15.7 Hz, 2 H), 3.92 (s, 3H), 4.16 (d, J = 7 Hz, 1 H), 5.62 (s, 1 H), 7.00 (d, J = 8 Hz, 1 H), 7.16 (d, J = 8 Hz, 1 H), 7.24 (d, J = 8 Hz, 1 H), 7.4−7.5 (m, 7H), 7.66 (d, J

= 8 Hz, 1 H), 8.25 (d, J = 8 Hz, 1 H). MS (CI/M + H): 479. HRMS (CI/M + H) calcd for $C_{29}H_{35}O_4S$: 479.2262; found, 479.2256.

(±)-(3*S*,4*R*,5*R*)-7-Methoxy-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1-benzothiepin-4-ol 1,1-Dioxide (36). Step 1. 2-Mercapto-5-methoxybenzophenone (104). Amounts of 66.2 g of 4-methoxythiophenol, 360 mL of 2.5 N *n*-butyllithium, and 105 g of tetramethylethylenediamine were combined with 400 mL of cyclohexane. The mixture was cooled to 0 °C, and a solution of 66.7 g of benzonitrile in 200 mL of cyclohexane was added. The reaction mixture was stirred at 0 °C for 3 and 1 h at room temperature. A solution of 600 mL of 6 N sulfuric acid was added, and the mixture was heated to 60 °C for 2 h. The organic phase was separated, and the aqueous phase was neutralized with 10% aqueous NaOH. Extraction with ethyl ether gave 73.2 g of brown oil, which was Kugelrohr distilled to remove 4-methoxythiophenol and gave 43.86 g of crude **104** as a brown oil.

Step2. 2-((2-Benzoyl-4-methoxyphenylthio)methyl)-2-ethylhexanal (105). Reaction of 10 g (0.04 mol) of crude **104** with 4.8 g (0.02 mol) of mesylate **98** and 3.2 mL (0.23 mol) of triethylamine in 50 mL of diglyme according to the procedure for the preparation of **99** gave 10.5 g of crude product, which was purified by HPLC (5% ethyl acetate/hexane) to give 1.7 g (22%) of **105**.

Step 3. 2-((2-Benzoyl-4-methoxyphenylsulfonyl)methyl)-2-ethylhexanal (106). A solution of 1.2 g (3.1 mmol) of **105** in 25 mL of methylene chloride was reacted with 2.0 g (6.2 mmol) of 50−60% MCPBA according to the procedure for **100**, giving 1.16 g (90%) of **106** as a yellow oil.

Step 4. 2-((2-Phenylmethyl-4-methoxyphenylsulfonyl)-methyl)-2-ethylhexanal (107). Hydrogenation of 1.1 g of **106**, according to the procedure for intermediate **101** from step 4 of **34a**, gave **107** as a yellow oil (1.1 g).

Step 5. (±)-(3*S*,4*R*,5*R*)-7-Methoxy-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1-benzothiepin-4-ol 1,1-Dioxide (36). A solution of 1.1 g of **107**, 0.36 g of potassium *tert*-butoxide, and 25 mL of anhydrous THF was held at reflux for 2 h and worked up as for compound **34a** to give 1.07 g of a crude product, which was purified by HPLC to give 40 mg of the (±)-(3*S*,4*S*,5*S*)-diastereomer as crystals, mp 153−154 °C and 90 mg (8%) of the (±)-(3*S*,4*R*,5*R*)-diastereomer of **36**, mp 136−140 °C. ^{1}H NMR ($CDCl_3$) δ 0.9−1.1 (m, 6 H), 1.1−1.8 (m, 7 H), 2.22 (br t, J = 13.8 Hz, 1 H), 3.10 (ABq, J = 15.7 Hz, 2 H), 3.66 (s, 3H), 4.20 (s, 1 H), 5.52 (s, 1 H), 6.30 (d, J = 2 Hz, 1 H), 6.81 (dd, J = 8, J = 2 Hz, 1 H), 7.3−7.5 (m, 5 H), 8.05 (d, J = 8 Hz, 1 H). Anal. Calcd for $C_{23}H_{30}O_4S$: C, 67.94; H, 7.46; S, 6.98. Found: C, 68.08; H, 7.61; S, 8.01.

(±)-(3*S*,4*R*,5*R*)-8-Hydroxy-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1-benzothiepin-4-ol 1,1-Dioxide (37). Reaction of **61** with BBr_3 according to the procedure described in ref 24 gave compound **37**. The resulting residue was concentrated in vacuo, and the desired product was collected as a white solid, mp 226.5−228.5 °C. HPLC: t_R = 17.7 min. ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7.6 Hz, 3H), 0.92 (t, J = 7.6 Hz, 3H), 1.14 (m, 1H), 1.26−1.64 (m, 6H), 2.22 (br t, J = 10.0 Hz, 1H), 3.12 (ABq, 2H), 4.17 (s, 1H), 5.26 (br s, 1H), 5.51 (s, 1H), 6.65 (d, J = 8.8 Hz, 1H), 6.86 (dd, J = 8.8, 2.8 Hz, 1H), 7.35 (d, J = 6.8 Hz, 1H), 7.42 (t, J = 7.6 Hz, 2H), 7.48 (d, J = 7.2 Hz, 2H), 7.61 (d, J = 2.8 Hz, 1H). MS (CI/M + Li): 395. HRMS (CI/M + H) calcd for $C_{22}H_{29}O_4S$: 389.1787; found, 389.1778. Anal. Calcd for $C_{22}H_{28}O_4S$: C, 68.01; H, 7.26. Found: C, 67.01; H, 7.28.

(±)-(3*S*,4*R*,5*R*)-8-(1-Decyloxy)-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1-benzothiepin-4-ol 1,1-Dioxide (38). Compound **37** was reacted with K_2CO_3 and 1-iododecane, according to the procedure described in ref 25 to give compound **38**. Purification via preparative HPLC (eluting with EtOAc/hexane) gave the isolated product as a colorless oil, **38**. HPLC: t_R = 31.0 min. ^{1}H NMR ($CDCl_3$) δ 0.82−0.91 (m, 9H), 1.14−1.32 (m, 19H), 1.35−1.49 (m, 3H), 1.66−1.74 (m, 3H), 2.27 (m, 1H), 3.08 (ABq, 2H), 3.92 (t, J = 6.4 Hz, 2H), 4.14 (d, J = 6.8 Hz, 1H), 5.47 (s, 1H), 6.63 (d, J = 8.8 Hz, 1H), 6.85 (dd, J = 8.4, 2.4 Hz, 1H), 7.30 (t, J = 7.2 Hz, 1H), 7.37 (t, J = 7.6 Hz, 2H), 7.44 (d, J = 7.2 Hz, 1H), 7.60 (d, J = 2.8 Hz, 1H). MS (FAB/M + Li): 535. HRMS (ESI/M + H) calcd for $C_{32}H_{49}O_4S$: 529.3352; found, 529.3305. Anal. Calcd for $C_{32}H_{48}O_4S$: C, 72.68; H, 9.15; S, 6.06. Found: C, 71.27; H, 8.84; S, 5.35.

(±)-(3*S*,4*R*,5*R*)-7-Amino-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1-benzothiepin-4-ol 1,1-Dioxide (39). Compound **42** (1.91 g, 3.66 mmol) and CH_2Cl_2 (5.0 mL) were combined in a 100 mL round-bottom flask. The flask was purged with N_2 and fitted with a magnetic stirrer. Ethanethiol (6.80 g, 109 mmol) and boron trifluoride etherate (5.20 g, 36.6 mmol) were added. After 96 h, water (50 mL) was added. After 10 min, the mixture was extracted with $CHCl_3$ (3×). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to give compound **39** as a white solid (1.50 g). ^{1}H NMR (CD_2Cl_2) δ 0.85 (t, J = 7.5 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H), 1.05−1.20 (m, 1H), 1.25−1.68 (m, 6H), 2.19 (m, 1H), 3.07 (ABq, 2H), 4.15 (s, 1H), 5.49 (s, 1H), 5.99 (d, J = 1.8 Hz, 1H), 6.56 (dd, J = 8.7, 2.4 Hz, 1H), 7.34−7.50 (m, 6H), 7.81 (d, J = 8.4 Hz, 1H). MS (CI/M + H): 388. HRMS (M + H) calcd for $C_{22}H_{30}O_3SN$: 388.1946; found, 388.1963. Anal. Calcd for $C_{22}H_{29}O_3SN$: C, 68.19; H, 7.54; N, 3.61; S, 8.27. Found: C, 67.14; H, 7.44; N, 3.48; S, 8.12.

(±)-(3*S*,4*R*,5*R*)-7-Hydroxyamino-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1-benzothiepin-4-ol 1,1-Dioxide (40). Compound **41** (0.050 g, 0.099 mmol) and 4 N HCl in dioxane (0.50 mL/2.0 mmol) were combined in a 4 mL vial. The vial was purged with N_2 and fitted with a magnetic stirrer. After 30 min, a solution of NaOAc (0.27 g, 2.0 mmol) in water (1.0 mL) and ethyl ether (1.0 mL) was added to the reaction vial. After an additional 10 min, additional ethyl ether was added, and the mixture was washed with water (6×). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to give compound **40** (0.0397 g, 99%). ^{1}H NMR ($CDCl_3$) δ 0.83 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 7.5 Hz, 3H), 1.05−1.20 (m, 1H), 1.22−1.65 (m, 6H), 1.18 (m, 1H), 3.08 (br q, 2H), 4.13 (s, 1H), 5.46 (s, 1H), 6.12 (s, 1H), 6.79 (s, 1H), 7.30−7.43 (m, 6H), 7.86 (s, 1H). Anal. Calcd for $C_{22}H_{29}NO_4S$: C, 65.48; H, 7.24; N, 3.47: S, 7.95. Found: C, 64.98; H, 7.15; N, 3.25; S, 7.65.

(±)-[(3*S*,4*R*,5*R*)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-5-phenyl-1-benzothiepin-7-yl]hydroxycarbamic Acid 1,1-Dimethylethyl Ester (41). Step 1. 2-((2-Phenylmethyl-4-hydroxyaminophenylsulfonyl)methyl)-2-ethylhexanal (113). Intermediate **110** (from step 3 of the synthesis of **42**) (0.50 g, 1.2 mmol), ethanol (7.50 mL), and 10% Pd/C (0.050 g) were combined in a 25 mL round-bottom flask. The flask was purged with N_2. Hydrogen gas was bubbled through the reaction mixture for 30 min. The reaction mixture was purged with N_2, filtered through Celite washing with ethanol and then ethyl ether, and concentrated in vacuo. The resulting residue was dissolved in ethyl ether, dried (Na_2SO_4), filtered, and concentrated in vacuo to give compound **113**. ^{1}H NMR ($CDCl_3$) δ 0.76 (t, J = 7.5 Hz, 3H), 0.87 (t, J = 7.2 Hz, 3H), 0.94−1.15 (m, 2H), 1.16−1.29 (m, 2H), 1.49−2.10 (m, 4H), 2.97 (s, 2H), 4.41 (s, 2H), 6.77 (s, 1H), 6.92 (d, J = 9.0 Hz, 1H), 7.16−7.34 (m, 6H), 7.87 (d, J = 8.4 Hz, 1H), 9.35 (s, 1H).

Step 2. 2-((2-Phenylmethyl-4-hydroxycarboxybutylaminophenylsulfonyl)methyl)-2-ethylhexanal (114). Compound **113** (8.50 g, 0.0211 mol, step 1) and di-*tert*-butyl dicarbonate (4.80 g, 0.0220 mol) were combined in a 100 mL round-bottom flask. The flask was purged with N_2 and fitted with a magnetic stirrer. THF (25.0 mL) was added, and the mixture was heated to 60 °C. After 6 h, the reaction mixture was cooled to room temperature, and additional di-*tert*-butyl dicarbonate (1.43 g, 0.0066 mol) was added. The mixture was heated to 60 °C. After 16 h, the reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was dissolved in EtOAc (40.0 mL) and washed with aqueous 1% HCl (2 × 25 mL) and aqueous 5% $NaHCO_3$ (2 × 25 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography on silica gel eluting with 10% EtOAc/hexanes and concentrated

in vacuo gave **114** (4.11 g, 39%). ^{1}H NMR ($CDCl_3$) δ 0.76 (t, J = 7.2 Hz, 3H), 0.87 (t, J = 7.2 Hz, 3H), 0.93−1.17 (m, 2H), 1.20−1.28 (m, 2H), 1.52 (s, 9H), 1.59−1.98 (m, 4H), 2.95 (s, 2H), 4.51 (s, 2H), 7.13−7.31 (m, 5H), 7.40 (s, 1H), 7.56 (d, J = 8.7 Hz, 1H), 8.01 (d, J = 8.7 Hz, 1H), 9.35 (s, 1H). MS (FAB/M − BOC): 401.

Step 3. [(±)-(3*S*,4*R*,5*R*)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-5-phenyl-1-benzothiepin-7-yl]-hydroxycarbamic Acid, 1,1-Dimethylethyl Ester (41). Compound **114** (1.00 g, 1.98 mmol) was reacted with KO^{t}Bu by a procedure similar to that used for compound **34a**, step 5. Purification by preparative HPLC eluting with 20% EtOAc/hexanes and concentration in vacuo gave separation of **41** (0.195 g, 20%) from its (3α,4α,5α)-diastereomer. HPLC: t_R = 21.2 min. ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 7.5 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H), 1.02−1.20 (m, 1H), 1.23−1.75 (m, 6H), 1.37 (s, 9H), 2.19 (m, 1H), 3.09 (ABq, 2H), 4.15 (s, 1H), 5.55 (s, 1H), 6.90 (s, 1H), 7.30−7.46 (m, 6H), 8.01 (d, J = 8.7 Hz, 1H). HRMS (FAB/M + H) calcd for $C_{27}H_{38}NO_6S$: 504.2420; found, 504.2428.

(±)-[(3*S*,4*R*,5*R*)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-5-phenyl-1-benzothiepin-7-yl]carbamic Acid, Phenylmethyl Ester (42). Step 1. 2-Chloro-5-nitrodiphenylmethane (108). 2-Chloro-5-nitrobenzophenone (45.0 g, 0.172 mol) and CH_2Cl_2 (345.0 mL) were combined in a 3 L round-bottom flask. The reaction flask was purged with N_2 and fitted with an addition funnel and magnetic stirrer. The solution was cooled with ice bath. A solution of trifluoromethane sulfonic acid (51.62 g, 0.3440 mol) in CH_2Cl_2 (345.0 mL) was added dropwise to the reaction flask via the addition funnel. After 5 min, a solution of triethylsilane (30.0 g, 0.258 mol) in CH_2Cl_2 (345.0 mL) was added dropwise to the reaction flask via the addition funnel. After an additional 5 min, a second solution of trifluoromethane sulfonic acid (51.62 g, 0.3440 mol) in CH_2Cl_2 (345.0 mL) was added dropwise to the reaction flask via the addition funnel. After an additional 5 min, a solution of triethylsilane (30.0 g, 0.258 mol) in CH_2Cl_2 (345.0 mL) was added dropwise to the reaction flask via the addition funnel. After the mixture was allowed to warm to room temperature overnight, the reaction mixture was slowly poured into cold saturated aqueous $NaHCO_3$ (1600 mL). After the mixture was stirred for 30 min, the layers were separated. The aqueous layer was extracted with additional CH_2Cl_2 (2 × 500 mL). All organic layers were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. Crystallization from hexane gave the desired **108** (39.00 g, 92%). ^{1}H NMR ($CDCl_3$) δ 4.19 (s, 2H), 7.20 (d, J = 8.1 Hz, 1H), 7.23−7.35 (m, 4H), 7.54 (d, J = 9.3 Hz, 1H), 8.03 (m, 2H). MS (CI/M + H): 248.

Step 2. 2-((2-Phenylmethyl-4-nitrophenylthio)methyl)-2-ethylhexanal (109). Compound **108** (38.70 g, 0.156 mol), lithium sulfide (7.18 g, 0.156 mol), and DMSO (1500 mL) were combined in a dry 2 L round-bottom flask. The reaction flask was purged with N_2, equipped with magnetic stirrer and condenser, and heated to 75 °C. After 15 h, the reaction mixture was cooled to room temperature. A solution of compound **98** (step 1 of the synthesis of **34a**) (51.7 g, 0.219 mol) in DMSO (90 mL) was added, and the flask was heated to 80 °C. After 48 h, the reaction mixture was cooled to room temperature. Additional **98** (14.75 g, 0.0624 mol) in DMSO (20 mL) was added, and the flask was heated to 80 °C. After 63 h, the reaction mixture was cooled to room temperature and slowly added to 5% aqueous acetic acid (1900 mL). The resulting mixture was divided into two portions, and each was extracted with ethyl ether (4 × 700 mL). Organic extracts were combined, dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting oil was redissolved in ethyl ether, washed with water, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by preparative HPLC eluting with 5% EtOAc/hexanes and concentrated in vacuo gave compound **109** (40.22 g, 67%). ^{1}H NMR ($CDCl_3$) δ 0.82 (t, J = 10.5 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H), 1.03−1.23 (m, 2H), 1.24−1.35 (m, 2H), 1.62−1.77 (m, 4H), 3.16 (s, 2H), 4.10 (s, 2H), 7.10−7.35 (m, 5H), 7.42 (d, J = 8.7 Hz, 1H), 7.90 (d, J = 2.4 Hz, 1H), 8.06 (dd, J = 8.7, 2.4 Hz, 1H), 9.44 (s, 1H). %). MS (CI/M + H): 386.

Step 3. 2-((2-Phenylmethyl-4-nitrophenylsulfonyl)methyl)-2-ethylhexanal (110). Compound **109** (52.30 g, 0.136 mol) and $CHCl_3$ (1000 mL) were combined in a 2 L round-bottom flask. The flask was purged with N_2, fitted with a magnetic stirrer, and cooled with an ice bath. mCPBA (72.20 g, 0.2719 mol) was added slowly, and the reaction mixture was allowed to warm to room temperature. After 18 h, the reaction mixture was cooled with an ice bath and filtered. The filtrate was washed with 10% aqueous K_2CO_3 (900 mL), and the aqueous washes were extracted with $CHCl_3$ (3 × 250 mL). All $CHCl_3$ layers were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by precipitation from ethanol and then crystallization from ethyl ether and concentrated in vacuo gave **110** (31.80 g, 56%). The mother liquor was concentrated in vacuo and purified by preparative HPLC eluting with 10% EtOAc/hexanes to give additional **110** (5.66 g, 10%). Combined yield: 66%. ^{1}H NMR ($CDCl_3$) δ 0.81 (t, J = 7.5 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H), 0.96−1.20 (m, 2H), 1.22−1.35 (m, 2H), 1.57−2.00 (m, 4H), 3.08 (ABq, 2H), 4.61 (s, 2H), 7.18 (d, J = 6.9 Hz, 1H), 7.26−7.37 (m, 4H), 8.12 (d, J = 1.5 Hz, 1H), 8.23 (d, J = 2.1 Hz, 1H), 9.36 (s, 1H). MS (CI/M + H): 418.

Step 4. 2-((2-Phenylmethyl-4-aminophenylsulfonyl)-methyl)-2-ethylhexanal (111). Compound **110** (5.80 g, 0.0139 mol) and ethanol (180 mL) were combined in a Parr reactor. Under a N_2 atmosphere, 10% Pd/C (0.58 g) was added. The reactor was subjected to 100 psig of H_2 and heated to 55 °C. After 17 h, the reactor was cooled to room temperature, and the reaction mixture was filtered through Celite and concentrated until nearly dry to give a solution of the compound **111**. Note: The product will polymerize if concentrated to dryness. ^{1}H NMR ($CDCl_3$) δ 0.82 (t, J = 7.5 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H), 1.00−1.20 (m, 2H), 1.25−1.35 (m, 2H), 1.55−1.95 (m, 4H), 3.04 (ABq, 2H), 4.45 (s, 2H), 6.48 (d, J = 1.8 Hz, 1H), 6.63 (dd, J = 8.7, 2.1 Hz, 1H), 6.95−7.60 (m, 5H), 7.85 (d, J = 8.7 Hz, 1H), 9.40 (s, 1H). MS (CI/M + H): 388.

Step 5. 2-((2-Phenylmethyl-4-carboxybenzylaminophenylsulfonyl)methyl)-2-ethylhexanal (112). A solution of compound **111** (5.38 g, 0.0139 mol) in $PhCH_3$ (17.4 g) and additional $PhCH_3$ (30 mL) were combined in a 500 mL round-bottom flask. The reaction flask was purged with N_2 and fitted with a magnetic stirrer. Potassium carbonate (4.23 g, 0.0306 mol) and additional $PhCH_3$ (20 mL) were added. A solution of benzyl chloroformate (5.0 g, 0.29 mol) in $PhCH_3$ (25 mL) was added. After 17 h, the reaction flask was heated to 50 °C. After an additional 1.5 h, more K_2CO_3 (0.96 g, 0.0069 mol) and benzyl chloroformate (1.20 g, 0.007 03 mol) were added. After 4 h more, the reaction mixture was allowed to cool to room temperature, and it was washed with water and 10% aqueous K_2CO_3. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. Crystallization from $PhCH_3$/hexanes and concentrated in vacuo gave the desired product **112** plus a minor amount of benzyl chloroformate (7.49 g). ^{1}H NMR ($CDCl_3$) δ 0.77 (t, J = 7.5 Hz, 3H), 0.87 (t, J = 7.2 Hz, 3H), 0.95−1.20 (m, 2H), 1.22−1.30 (m, 2H), 1.52−1.93 (m, 4H), 3.00 (ABq, 2H), 4.47 (s, 2H), 5.19 (s, 2H), 6.92 (s, 1H), 7.17−7.40 (m, 10H), 7.54 (dd, J = 9.0, 2.1 Hz, 1H), 7.96 (d, J = 9.7 Hz, 1H).

Step 6. (±)-[(3*S*,4*R*,5*R*)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-5-phenyl-1-benzothiepin-7-yl]-carbamic Acid, Phenylmethyl Ester (42) Compound **112** (7.49 g, 0.0144 mol) was reacted with KO^{t}Bu by a procedure similar to that used for compound **34a**, step 5. Purification by preparative HPLC eluting with 15% EtOAc/hexanes and concentrated in vacuo gave separation of compound **42** (2.05 g, 27%) from its (3α,4α,5α)-diastereomer. ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 6.9 Hz, 3H), 1.05−1.20 (m, 1H), 1.25−1.70 (m, 6H), 2.20 (m, 1H), 3.11 (ABq, 2H), 4.17 (s, 1H), 5.10 (s, 2H), 5.53 (s, 1H), 6.48 (d, J = 2.10 Hz, 1H), 6.78 (s, 1H), 7.28−7.48 (m, 10H), 7.68 (dd, J = 8.4, 1.2 Hz, 1H), 8.03 (d, J = 8.7 Hz, 1H). HRMS (CI/M + H) calcd for $C_{30}H_{36}O_5SN$: 522.2314; found, 522.2287. Anal. Calcd for $C_{30}H_{35}O_5SN$: C, 69.07; H, 6.76; N, 2.68; S, 6.15. Found: C, 66.18; H, 6.60; N, 2.56; S, 5.83.

(±)-[(3*S*,4*R*,5*R*)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-5-phenyl-1-benzothiepin-7-yl]-carbamic Acid 1,1-Dimethylethyl Ester (43). Step 1. 2-((2-Phenylmethyl-4-carboxybenzylaminophenylsulfonyl)-methyl)2-ethylhexanal (115). Compound **111** (from step 5 of the synthesis of **42**) (0.47 g, 1.2 mmol) was reacted with di-*tert*-butyl dicarbonate according to the procedure for intermediate **114** (step 2 of the synthesis of **41**). Purification by preparative HPLC eluting with 15% EtOAc/hexanes and concentrated in vacuo gave compound **115** (0.19 g, 32%). ^{1}H NMR ($CDCl_3$) δ 0.76 (t, J = 7.5 Hz, 3H), 0.86 (t, J = 7.2 Hz, 3H), 0.95−1.16 (m, 2H), 1.20−1.29 (m, 2H), 1.49 (s, 9H), 1.55−1.90 (m, 4H), 2.97 (ABq, 2H), 4.46 (s, 2H), 6.74 (s, 1H), 7.15−7.32 (m, 6H), 7.54 (dd, J = 8.7, 2.1 Hz, 1H), 7.94 (d, J = 8.7 Hz, 1H), 9.33 (s, 1H). MS (FAB/M + Li): 494.2.

Step 2. [(±)-(3*S*,4*R*,5*R*)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-5-phenyl-1-benzothiepin-7-yl]-carbamic Acid 1,1-Dimethylethyl Ester (43). Compound **115** (0.142 g, 0.290 mmol) was reacted with KO^{t}Bu by a procedure similar to that used for compound **34a**, step 5. Purification by preparative HPLC eluting with 15% EtOAc/hexanes and concentrated in vacuo gave separation of the desired product **43** (0.0533 g, 38%) from its (3α,4α,5α)-diastereomer, mp 140.0−150.0 °C. HPLC: t_R = 23.7 min. ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 7.5 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H), 1.05−1.20 (m, 1H), 1.22−1.65 (m, 6H), 1.44 (s, 9H), 2.19 (m, 1H), 3.09 (ABq, 2H), 4.15 (s, 1H), 5.52 (s, 1H), 6.31 (d, J = 1.8 Hz, 1H), 6.60 (s, 1H), 7.34−7.48 (m, 5H), 7.80 (d, J = 8.7 Hz, 1H), 8.02 (d, J = 8.7 Hz, 1H). MS (FAB/M + Li): 494. HRMS (FAB/M + NH_4) calcd for $C_{27}H_{41}N_2O_5S$: 505.2736; found, 505.2731.

(±)-(3*S*,4*R*,5*R*)-7-(1-Hexylamino)-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1-benzothiepin-4-ol 1,1-Dioxide (44). Compound **39** (0.10 g, 0.26 mmol), $Ru_3(CO)_{12}$ (0.010 g, 0.0078 mmol), hexanal (0.052 g, 0.52 mmol), and ethanol (50.0 mL) were combined in a Parr reactor. The reactor was purged with H_2 and fitted with an overhead stirrer. The reactor was loaded with 540 psig of H_2. An amount of 60 psig of CO/H_2 was added, and the reactor was heated to 125 °C. After 18 h, the reactor was cooled to room temperature, and its contents were filtered and concentrated in vacuo. Purification by preparative HPLC eluting with 15% EtOAc/hexanes and concentrated in vacuo gave compound **44** (0.0757 g, 62%), mp 154.0−160.0 °C. ^{1}H NMR ($CDCl_3$) δ 0.82−0.93 (m, 9H), 1.20−1.64 (m, 15H), 2.20 (m, 1H), 3.10 (m, 4H), 4.17 (s, 1H), 5.50 (br s, 1H), 6.37 (br s, 1H), 6.98 (br s, 1H), 7.33−7.48 (m, 5H), 7.95 (br s, 1H). MS (CI/M + H): 472. HRMS (FAB/M + H) calcd for $C_{28}H_{42}NO_3S$: 472.2885; found, 472.2866. Anal. Calcd for $C_{28}H_{41}O_3SN$: C, 71.30; H, 8.76; N, 2.79; S, 6.80. Found: C, 70.16; H, 8.82; N, 2.88; S, 6.60.

(±)-(3*S*,4*R*,5*R*)-7-(Dimethylamino)-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1-benzothiepin-4-ol 1,1-Dioxide (45). Compound **39** (0.200 g, 0.516 mmol), methanol (4.0 mL), THF (3.0 mL), aqueous 37% formaldehyde (0.400 mL/5.34 mmol), and a solution of Raney nickel (0.200 g) in ethanol (0.200 mL) were combined in a 1 oz. Fischer−Porter bottle. The bottle was purged with N_2, loaded to 40 psig of H_2, and heated to 40 °C. After 2 h, the reaction mixture was allowed to cool to room temperature, filtered through Celite washing with ethyl ether, and concentrated in vacuo. The residue was redissolved in ethyl ether, washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to give compound **45** (0.200 g, 93%). ^{1}H NMR ($CDCl_3$) δ 0.83 (t, J = 7.5 Hz, 3H), 0.89 (t, J = 7.5 Hz, 3H), 1.04−1.17 (m, 1H), 1.23−1.65 (m, 6H), 2.20 (m, 1H), 2.77 (s, 6H), 3.06 (ABq, 2H), 4.14 (d, J = 7.8 Hz, 1H), 5.53 (s, 1H), 5.91 (d, J = 2.4 Hz, 1H), 6.49 (dd, J = 9.0, 2.7 Hz, 1H), 7.29−7.41 (m, 5H), 7.49 (d, J = 7.2 Hz, 1H), 7.88 (d, J = 9.0, 1H). MS (FAB/M + Li): 422. HRMS (M+) calcd for $C_{24}H_{33}O_3SN$: 415.2181; found, 415.2187; C, 69.36; H, 8.0; N, 3.37; S, 7.1. Found: C, 69.21; H, 8.08; N, 3.28; S, 7.58.

General Procedure for Preparation of Compounds 46−48. In a typical procedure, compound **39** (0.194 mmol) and CH_2Cl_2 (4.0 mL) were combined in a 25 mL round-bottom flask. The reaction flask was purged with N_2 and fitted with a magnetic stirrer. A solution of 4-methylmorpholine (0.029 g, 0.29 mmol) in CH_2Cl_2 (1.5 mL) was added, and the mixture was cooled with an ice bath. A solution of acyl or mesyl chloride (actual reagent used for each analogue given below) (0.29 mmol) in CH_2Cl_2 (1.5 mL) was added, and the reaction mixture was allowed to warm to room temperature. After 17 h, additional acyl or mesyl chloride (0.013 g, 0.097 mmol) and 4-methylmorpholine (0.010 g, 0.099 mmol) in CH_2Cl_2 (1.0 mL) was added. After an additional 1 h, the reaction mixture was diluted with ethyl ether and washed with water. The aqueous wash was extracted with ethyl ether (2×). All organic layers were combined, washed with aqueous 10% K_2CO_3 and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by precipitation from ethyl ether/hexanes gave the desired amide **46**, **47**, or **48**.

***N*-[(±)-(3*S*,4*R*,5*R*)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-5-phenyl-1-benzothiepin-7-yl]acetamide (46).** Reagent: acetyl chloride. Yield: 90%. Mp 148.0 °C. HPLC: t_R = 12.9 min. ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 7.5 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H), 1.05−1.15 (m, 1H), 1.23−1.69 (m, 6H), 1.77 (d, J = 6.6 Hz, 1H), 2.04 (s, 3H), 2.20 (m, 1H), 3.12 (ABq, 2H), 4.17 (d, J = 6.9 Hz, 1H), 5.52 (s, 1H), 6.70 (s, 1H), 7.33−7.52 (m, 6H), 7.74 (d, J = 8.1 Hz, 1H), 8.00 (d, J = 8.7 Hz, 1H). HRMS (FAB/M + NH_4) calcd for $C_{24}H_{35}O_4SN_2$: 447.2318; found, 447.2304. Anal. Calcd for $C_{24}H_{31}O_4SN$: C, 67.10; H, 7.27; N, 3.26; S, 7.46. Found: C, 65.51; H, 7.24; N, 3.13; S, 7.11.

***N*-[(±)-(3*S*,4*R*,5*R*)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-5-phenyl-1-benzothiepin-7-yl]hexanamide (47).** Reagent: hexanoyl chloride. Yield = 84%. Mp 152.0 °C. HPLC: t_R = 23.3 min. ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 6.6 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H), 1.02−1.18 (m, 1H), 1.20−1.68 (m, 14H), 1.73 (d, J = 6.6 Hz, 1H), 2.15 (m, 1H), 2.23 (t, J = 7.8 Hz, 3H), 3.11 (ABq, 2H), 4.16 (d, J = 6.3 Hz, 1H), 5.53 (s, 1H), 6.64 (d, J = 1.5 Hz, 1H), 7.31−7.48 (m, 6H), 7.85 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 8.7 Hz, 1H). HRMS (FAB/M + NH_4) calcd for $C_{28}H_{43}N_2O_4S$: 503.2944; found, 503.2931. Anal. Calcd for $C_{28}H_{39}O_4SN$: C, 69.24; H, 8.09; N, 2.88; S, 6.60. Found: C, 68.24; H, 8.02; N, 2.84; S, 6.50.

***N*-[(±)-(3*S*,4*R*,5*R*)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-5-phenyl-1-benzothiepin-7-yl]-methanesulfonamide (48).** Reagent: methanesulfonyl chloride. Yield = 33%. Mp 265.0 °C. HPLC: t_R = 14.3 min. ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 7.5 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H), 1.09−1.22 (m, 1H), 1.25−1.65 (m, 6H), 2.25 (m, 1H), 2.84 (s, 3H), 3.08 (s, 2H), 4.09 (s, 2H), 5.49 (s, 1H), 6.52 (d, J = 2.1 Hz, 1H), 7.25−7.31 (m, 2H), 7.38 (t, J = 7.2 Hz, 2H), 7.50 (d, J = 7.2 Hz, 2H), 7.93 (d, J = 8.7 Hz, 1H), 9.10 (s, 1H). MS (FAB/M + Li): 472. HRMS (FAB/M + NH_4) calcd for $C_{23}H_{35}N_2O_5S_2$: 483.1987; found, 483.1976. RP-HPLC: 5−90% MeOH/H_2O/0.1% TFA, 96.7% pure; 5−90% CH_3CN/H_2O/0.1% TFA, 97.1% pure; average, 96.9%.

(±)-(3*S*,4*R*,5*R*)-3-Butyl-3-ethyl-5-(4-fluorophenyl)-2,3,4,5-tetrahydro-7-(methylthio)-1-benzothiepin-4-ol 1,1-Dioxide (49). Step 1. (±)-(3*S*,4*R*,5*R*)-3-Butyl-3-ethyl-5-(4-fluorophenyl)-2,3,4,5-tetrahydro-7-fluoro-benzothiepin-4-ol 1,1-Dioxide (Intermediate 69). Alkylation of 4-fluorophenol with 4-fluorobenzyl chloride according to the procedure described in ref 23 gave 4-fluoro-2-(4′-fluorobenzyl)phenol. This material was converted to compound **69** by a procedure similar to that described for compound **34a**, mp 134.5−139 °C, and its (±)-(3*S*,4*S*,5*S*)-diastereomer, mp 228−230 °C. HPLC (ethyl acetate/hexane) gave separation of the diastereomers. ^{13}C NMR ($CDCl_3$) δ 6.63, 13.77, 13.84, 23.0, 24.7, 27.6, 29.0, 44.1, 46.1, 56.4, 75.5, 113.3 (d, J = 22.1 Hz), 115.7 (d, J = 21.4 Hz), 118.7 (d, J = 24.0 Hz), 129.3 (d, J = 9.55 Hz), 130.4 (d, J = 8.0 Hz), 135.6 (d, J = 3.1 Hz), 138.1 (d, J = 3.4 Hz), 143.4 (d, J = 7.3 Hz), 161.8 (d, J = 246.4 Hz), 165.1 (d, J = 254.0 Hz).

Step 2. A mixture of 0.68 g (1.66 mmol) of intermediate **69**, 0.2 g (5 mmol) of sodium methanethiolate, and 15 mL of anhydrous DMF was stirred at room temperature for 16 days. The reaction mixture was diluted with ether and washed with water and brine and dried over $MgSO_4$. The ether solution was concentrated in vacuo. The residue was purified by HPLC (20%

ethyl acetate in hexanes). The first fraction was impure (±)-(3*S*,4*S*,5*S*)-diastereomer. The second fraction was compound **49**, mp 185−186.5 °C. ^{1}H NMR ($CDCl_3$) δ 0.88−1.04 (m, 6 H), 1.1−1.8 (m, 7 H), 2.26 (br t, J = 12.0 Hz, 1 H), 2.38 (s, 3 H), 3.18 (ABq, J = 15.1 Hz, 2 H), 4.20 (d, J = 6 Hz, 1 H), 5.58 (s, 1 H), 6.62 (s, 1 H), 7.14−7.26 (m, 3 H), 7.5−7.6 (m, 2 H), 8.04 (d, J = 9 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 162.99 (d, J = 246.5 Hz), 147.66, 140.08 (d, J = 1.2 Hz), 139.17 (d, J = 3.4 Hz), 136.75, 131.63 (d, J = 8 Hz), 129.04, 128.47, 116.93 (d, J = 21.2 Hz), 76.91, 57.76, 47.16, 45.22, 30.21, 28.95, 25.91, 24.25, 15.54, 15.10, 7.98. GC−MS (CI/M + H): 437.

(±)-(3*S*,4*R*,5*R*)-3-Butyl-3-ethyl-5-(4-fluorophenyl)-2,3,4,5-tetrahydro-7-(1-pyrrolidinyl)-1-benzothiepin-4-ol 1,1-Dioxide (50). The amine is pyrrolidine. A mixture of 0.53 g (1.30 mmol) of intermediate **69** (from step 1 of synthesis of **49**) and 50 equiv of amine was held at reflux for 2 h. The reaction mixture was diluted with ether, washed with water and brine, and dried over $MgSO_4$. The ether solution was concentrated in vacuo. The residue was crystallized from ether/hexanes to give compound **50**, mp 174.5−177 °C. ^{1}H NMR ($CDCl_3$) δ 0.8−1.0 (m, 6 H), 1.1−1.8 (m, 11 H), 2.26 (br t, J = 12.6 Hz, 1 H), 2.9−3.2 (m, 6 H), 3.81 (d, J = 7 Hz, 2 H), 4.11 (d, J = 7.2 Hz, 1 H), 5.46 (s, 1 H), 5.82 (s, 1 H), 6.04 (d, J = 7.8, 1 H), 7.18 (t, J = 7.8 Hz, 2 H), 7.58 (t, J = 6.6 Hz, 2 H), 7.74 (d, J = 7.8 Hz, 1 H). ^{13}C NMR (acetone-d_6) δ 6.4, 13.5, 14.8, 23.2, 24.8, 25.0, 27.8, 44.1, 46.5, 47.0, 57.1, 75.8, 108.0, 114.5, 115.2 (d, J = 21.2 Hz), 126.3, 128.2, 130.9 (d, J = 8 Hz), 140.4 (d, J = 3.4 Hz), 141.0, 150.5, 161.7 (d, J = 243.8 Hz). MS (CI/M + H): 460.

General Procedure for Compounds 55−60. In a typical procedure, 0.100 mol of 2-alkyl-2-(hydroxymethyl)alkanal, prepared by reaction of formaldehyde with 2-alkylalkanal, according to the procedure described in ref 22, was added dropwise to a cold (10 °C) solution of 12.6 g (0.11 mol) of methanesulfonyl chloride and 10.3 g (0.13 mol) of triethylamine while maintaining the reaction temperature below 30 °C. The reaction mixture was stirred at room temperature for 18 h, the reaction was quenched with dilute HCl, and the sample was extracted with methylene chloride. The methylene chloride extract was dried over $MgSO_4$ and concentrated in vacuo to give the 2-alkyl-2-(methanesulfonylmethyl)alkanal as a brown oil. This brown oil was used in the synthesis of compounds **55**−**58** by a procedure similar to the one described for compound **34a** above. See each compound below for purification methods and specific alkanal used.

(±)-(4*R*,5*R*)-7-Amino-3,3-dimethyl-2,3,4,5-tetrahydro-5-phenyl-1-benzothiepin-4-ol 1,1-Dioxide (55). The reagent was 2-methylpropanal. The residue was concentrated in vacuo, and the desired product was recrystallized from EtOAc/CH_2Cl_2/hexane as a white solid, mp 185−186 °C. ^{1}H NMR ($CDCl_3$) δ 1.12 (s, 3H), 1.49 (s, 3H), 3.14 (q_{ab}, J_{ab}= 15, 81.9 Hz, 2H), 3.28 (d, J = 15 Hz, 1H), 4.00 (s, 1H), 5.30 (s, 1H), 5.51 (s, 1H), 5.97 (s, 1H), 6.56 (dd, J = 6.5, 2.1 Hz), 7.31−7.52 (m, 5H), 7.89 (d, J = 8.4 Hz, 1H). MS (FAB/M + H): 332. HRMS (EI) calcd for $C_{18}H_{21}NO_3S$: 331.1242; found, 331.1232.

(±)-(4*R*,5*R*)-7-Amino-3,3-diethyl-2,3,4,5-tetrahydro-5-phenyl-1-benzothiepin-4-ol 1,1-Dioxide (56). The reagent was 2-ethylbutanal. The residue was concentrated in vacuo, and the desired product was isolated via preparative HPLC (eluting with EtOAc/hexane) as a white solid, mp 245.8−246.8 °C. ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 6 Hz, 3H), 0.92 (t, J = 6 Hz, 3H), 1.36 (m, 1H), 1.54 (m, 1H), 1.71 (m, 1H), 2.28 (m, 1H), 3.09 (q_{AB}, J_{AB} = 15.0 Hz, $\Delta\nu$ = 42.4 Hz, 2H), 3.97 (bs, 2H), 4.15 (d, J = 8 Hz, 1H), 5.49 (s, 1H), 5.95 (s, 1H), 6.54 (d, J = 1H), 7.29−7.53 (m, 6H), 7.88 (d, J = 8.2 Hz, 1H). HRMS (ES/M + H) calcd for $C_{20}H_{26}NO_3S$: 360.1633; found, 360.1632. Anal. Calcd for $C_{20}H_{25}NO_3S$: C, 66.82; H, 7.01; N, 3.90. Found C, 66.54; H, 7.20; N, 3.69.

(±)-(4*R*,5*R*)-7-Amino-3,3-dipropyl-2,3,4,5-tetrahydro-5-phenyl-1-benzothiepin-4-ol 1,1-Dioxide (57). The reagent was 2-propylpentanal. The residue was concentrated in vacuo, and the desired product was isolated via preparative HPLC (eluting with EtOAc/hexane) as a white solid. ^{1}H NMR ($CDCl_3$) δ 0.85−0.95 (m, 6H), 1.42−1.80 (m, 4H), 1.92−1.98 (m, 1H), 2.13−2.21 (m, 1H), 3.09 (d, J = 15.3 Hz, 2H), 3.45 (t, J = 6.6 Hz, 1H), 3.70 (t, J = 6.6 Hz, 1H), 4.15 (m, 2H), 5.50 (s, 1H), 5.94 (s, 1H), 6.73 (dd, J = 8.4, 2.4 Hz, 1H), 7.32−7.48 (m, 6H), 7.86 (d, J = 9.0 Hz, 1H). MS (FAB/M + H): 388.

(±)-(4*R*,5*R*)-7-Amino-3,3-dibutyl-2,3,4,5-tetrahydro-5-phenyl-1-benzothiepin-4-ol 1,1-Dioxide (58). The reagent was 2-butylhexanal. The residue was concentrated in vacuo, and the desired product was isolated via preparative HPLC (eluting with EtOAc/hexane) as a white solid, mp 93.4−94.6 °C. ^{1}H NMR ($CDCl_3$) δ 0.92 (m, 6H), 1.03−1.70 (m, 12H), 2.21 (m, 1H), 3.09 (q_{AB}, J_{AB} = 18.0 Hz, $\Delta\nu$ = 37.8 Hz, 2H), 3.96 (bs, 2H), 4.14 (d, J = 7.4 Hz), 5.51 (s, 1H), 5.94 (s, 1H), 6.56 (d, J = 8.7 Hz, 1H), 7.41−7.53 (m, 6H), 7.87 (d, J = 8.4 Hz, 1H). HRMS (ES+) calcd for $C_{24}H_{34}NO_3S$: 416.2259; found, 416.2261. Anal. Calcd for $C_{24}H_{33}NO_3S\cdot 0.2H_2O$: C, 68.77; H, 8.03; N, 3.34. Found: C, 68.83; H, 8.33; N, 3.01.

(±)-(4*R*,5*R*)-7-Methyl-3,3-dipentyl-2,3,4,5-tetrahydro-5-(4-fluorophenyl)-1-benzothiepin-4-ol 1,1-Dioxide (60). The reagent was 2-pentylheptanal. Alkylation of 4-methylphenol with 4-fluorobenzyl chloride according to the procedure described in *J. Chem. Soc*. **1958**, 2431 gave 4-methyl-2-(4′-fluorobenzyl)phenol. ^{1}H NMR ($CDCl_3$) δ 2.25 (s, 3H), 3.92 (s, 2H), 6.68 (d, J = 8.0 Hz, 1H), 6.90−6.94 (m, 4H), 7.17 (d, J = 5.2 Hz, 1H), 7.19 (d, J = 6.0 Hz, 1H). MS (EI/M+): 216. HRMS (EI/M+) calcd for $C_{14}H_{13}FO$: 216.0950; found, 216.0941. This phenol and the 2-pentylheptanal were employed in a procedure similar to the one for compounds **55**−**58** described above to give compound **60**. The residue was concentrated in vacuo, and the desired product was isolated via preparative HPLC (eluting with EtOAc/hexane) as a white solid **60**: mp 85−87°C. HPLC: t_R = 35.1 min. ^{1}H NMR ($CDCl_3$) δ 0.85−1.05(m, 6H), 1.10−1.95 (m, 15H), 2.28 (dt, J = 13.2, 3.3 Hz, 1H), 2.35 (s, 3H), 3.12 (ABq, 2H), 4.18 (d, J = 6.9 Hz, 1H), 5.54 (s, 1H), 6.68 (s, 1H), 7.18−7.26 (m, 3H), 7.50 (t, J = 6.9 Hz, 2H), 8.0 (d, J = 2.7 Hz, 1H). MS (CI/M + H): 461. HRMS (CI/M + NH_4) calcd for $C_{27}H_{41}FNO_3S$: 478.2791; found, 478.2794.

(±)-(3*S*,4*R*,5*R*)-8-Methoxy-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1-benzothiepin-4-ol 1,1-Dioxide (61). The substitution of 3-methoxythiophenol for 4-methoxythiophenol in the procedure for compound **36**, steps 1−5, gave **61**. The desired product was isolated via preparative HPLC (eluting with EtOAc/hexane) as a white solid, mp 125.5−126.5 °C. HPLC: t_R = 24.1 min. ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H), 1.10−1.66 (m, 7H), 2.23 (dt, J = 13.2, 3.3 Hz, 1H), 3.12 (ABq, 2H), 3.83 (s, 3H), 4.18 (d, J = 6.9 Hz, 1H), 5.54 (s, 1H), 6.68 (d, J = 8.7 Hz, 1H), 6.91 (dd, J = 8.7, 3.0 Hz, 1H), 7.34 (t, J = 6.9 Hz, 1H), 7.42 (t, J = 6.9 Hz, 2H), 7.47 (t, J = 7.2 Hz, 2H), 7.66 (d, J = 2.7 Hz, 1H). MS (CI/M + H): 403. HRMS (CI/M + H) calcd for $C_{23}H_{31}O_4S$: 403.1943; found, 403.1939.

(±)-(4*R*,5*R*)-8-Methoxy-3,3-dibutyl-2,3,4,5-tetrahydro-5-phenyl-1-benzothiepin-4-ol 1,1-Dioxide (62). Compound **62** was prepared by a similar procedure to that described for **61**, substituting 2-butylhexanal for 2-ethylhexanal. The resulting residue was concentrated in vacuo, and the desired product **62** was isolated via preparative HPLC (eluting with EtOAc/hexane) as a white foam. ^{1}H NMR ($CDCl_3$) δ 0.82−0.98 (m, 6H), 1.1−1.65 (m, 12H), 2.25 (td, J = 15, 3 Hz, 1H), 3.12 (ABq, J_{AB} = 16.5 Hz, 2H), 3.83 (s, 3H), 4.18 (d, J = 7.5 Hz, 1H), 5.3 (s, 1H), 6.68 (d, J = 8.4 Hz, 1H), 6.92 (dd, J = 8.4, 3 Hz, 1H), 7.3−7.5 (m, 5H), 7.66 (d, J = 3 Hz, 1H). HRMS calcd for $C_{25}H_{35}O_4S$: 431.2256; found, 431.2281.

(±)-(4*R*,5*R*)-7-(Dimethylamino)-3,3-dibutyl-2,3,4,5-tetrahydro-5-phenyl-1-benzothiepin-4-ol 1,1-Dioxide (64). Compound **64** was prepared by a similar procedure to that described for **45**, substituting 2-butylhexanal for 2-ethylhexanal. The resulting residue was concentrated in vacuo, and the desired product was isolated via preparative HPLC (eluting with EtOAc/hexane) as a white solid, mp 161.5−162.2 °C. ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 6.3 Hz, 6H), 1.05−1.54 (m, 11H), 1.63 (m, 1H), 2.24 (m, 1H), 2.78 (s, 6H), 3.05 (q_{AB}, J_{AB} = 15 Hz, $\Delta\nu$ = 46.7 Hz, 2H), 4.18 (m, 1H), 5.53 (s, 1H), 5.93 (s, 1H), 6.94 (d, J = 8.5 Hz, 1H), 7.27−7.42 (m, 3H), 7.45 (d, J = 8.3

Hz, 2H), 7.87 (d, J = 8.7 Hz, 1H). HRMS (ES+) calcd for $C_{26}H_{38}NO_3S$: 444.2572; found, 444.2563.

(±)-(3*S*,4*R*,5*R*)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-*N*,*N*,*N*-trimethyl-5-phenyl-1-benzothiepin-7-aminium Iodide 1,1-Dioxide (65). Reaction of compound **45** with MeI in CH_3CN, according to the procedure described in *Tetrahedron* **1993**, *49* (46), 10733−10738, gave **65**. The residue was concentrated in vacuo, and the desired product was recrystallized from acetonitrile/ethyl ether as a yellow solid, mp 120−124 °C. ^{1}H NMR (CD_3OD) δ 0.83 (t, J = 8.2 Hz, 3H), 0.9 (t, J = 8.2 Hz, 3H), 1.04−1.6 (m, 6H), 1.78 (br t, J = 14.4 Hz, 1H), 2.07 (br t, J = 14.4 Hz, 1H), 3.18 (q, J = 16.8 Hz, 2H), 3.46 (s,9H), 4.16 (s, 1H), 5.46 (s, 1H), 7.06 (s, 1H), 7.33−7.55 (m, 5H), 7.95 (d, J = 7.5 Hz, 1H), 8.2 (d, J = 7.5 Hz, 1H). HRMS (M+) calcd for $C_{25}H_{36}NO_3S$: 430.2416; found, 430.2417.

(±)-(4*R*,5*R*)-3,3-Dibutyl-2,3,4,5-tetrahydro-4-hydroxy-*N*,*N*,*N*-trimethyl-5-phenyl-1-benzothiepin-7-aminium Iodide 1,1-Dioxide (66). Compound **66** was prepared by a similar procedure to that described for **65**, substituting 2-butylhexanal for 2-ethylhexanal. The resulting residue was concentrated in vacuo, and the desired product was isolated via preparative HPLC (eluting with EtOAc/hexane) as a white solid **66**, mp 146.5−148.0 °C. ^{1}H NMR (CD_3OD) δ 0.91 (m, 6H), 1.02−1.55 (m, 11H), 1.88 (m, 1H), 2.12 (m, 1H), 3.15−3.35 (m, 2H), 3.49 (s, 9H), 4.20 (s, 1H), 5.51 (s, 1H), 7.10 (s, 1H), 7.37−7.59 (m, 5H), 8.01 (d, J = 8.7 Hz, 1H), 8.24 (d, J = 8.4 Hz, 1H). HRMS (FAB/M+) calcd for $C_{27}H_{40}NO_3S$: 458.2729; found, 458.2743.

(±)-(3S,4*R*,5*R*)-7-Methyl-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-(4-fluorophenyl)-1-benzothiepin-4-ol 1,1-Dioxide (67). Compound **67** was prepared by a procedure similar to that described for **60**, substituting 2-ethylhexanal for 2-pentylheptanal. The resulting residue was concentrated in vacuo, and the desired product was isolated via preparative HPLC (eluting with EtOAc/hexane) as a white solid, mp 164−165 °C. HPLC: t_R = 26.4 min. ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 7.5 Hz, 3H), 0.95 (t, J = 7.2 Hz, 3H), 1.10−1.80 (m, 7H), 2.28 (dt, J = 13.2, 3.3 Hz, 1H), 2.35 (s, 3H), 3.12 (ABq, 2H), 4.18 (d, J = 6.9 Hz, 1H), 5.54 (s, 1H), 6.68 (s, 1H), 7.18−7.26 (m, 3H), 7.50 (t, J = 6.9 Hz, 2H), 8.10 (d, J = 2.7 Hz, 1H). MS (CI/M + H): 405. HRMS (CI/M + NH_4) calcd for $C_{23}H_{33}NFO_3S$: 422.2165; found, 422.2142.

(±)-(4*R*,5*R*)-7-Methyl-3,3-dibutyl-2,3,4,5-tetrahydro-5-(4-fluorophenyl)-1-benzothiepin-4-ol 1,1-Dioxide (68). Compound **68** was prepared by a procedure similar to that described for **60**, substituting 2-butylhexanal for 2-pentylheptanal. The residue was concentrated in vacuo, and the desired product was isolated via preparative HPLC (eluting with EtOAc/hexane) as a white solid, mp 145−147 °C. HPLC: t_R = 31.5min. ^{1}H NMR ($CDCl_3$) δ 0.85−1.05 (m, 6H), 1.15−1.80 (m, 11H), 2.28 (dt, J = 13.2, 3.3 Hz, 1H), 2.35 (s, 3H), 3.12 (ABq, 2H), 4.18 (d, J = 6.9 Hz, 1H), 5.54 (s, 1H), 6.68 (s, 1H), 7.18−7.26 (m, 3H), 7.50 (t, J = 6.9 Hz, 2H), 8.10 (d, J = 2.7 Hz, 1H). MS (CI/M + H): 433. HRMS (CI/M + NH_4) calcd for $C_{25}H_{37}NFO_3S$: 450.2478; found, 450.2471.

(±)-(4*R*,5*R*)-7-(Phenylmethylamino)-3,3-dibutyl-2,3,4,5-tetrahydro-5-phenyl-1-benzothiepin-4-ol 1,1-Dioxide (73). Compound **73** was prepared by a procedure similar to that described for **45**, substituting benzaldehyde for formaldehyde and substituting 2-butylhexanal for 2-ethylhexanal. The residue was concentrated in vacuo, and the desired product was isolated via preparative HPLC (eluting with EtOAc/hexane) as a white solid, mp 86.8−88.1 °C. ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 6 Hz, 6H), 0.98−1.66 (m, 12H), 2.16 (m, 1H), 3.04 (q_{AB}, J_{AB} = 15 Hz, $\Delta\nu$ = 41.3 Hz, 2H), 4.08 (s, 1H), 4.12 (s, 1H), 5.44 (s, 1H), 5.84 (s, 1H), 6.42 (d, J = 9 Hz, 1H), 7.12 (d, J = 7.8 Hz, 2H), 7.16−7.26 (m, 10H), 7.83 (d, J = 8.3 Hz, 1H). HRMS (ES+/M + H) calcd for $C_{31}H_{40}NO_3S$: 506.2729; found, 506.2714.

[(±)-(4*R*,5*R*)-3,3-Dibutyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-5-phenyl-1-benzothiepin-7-yl]carbamic Acid, Phenylmethyl Ester (74) Compound **74** was prepared by a similar procedure to that described for **42**, substituting 2-butylhexanal for 2-ethylhexanal. The residue was concentrated in vacuo, and the desired product was isolated via preparative HPLC (eluting with EtOAc/hexane) as a white solid, mp 95.5−97.6 °C. ^{1}H NMR ($CDCl_3$) δ 0.91 (m, 6H), 1.02−1.52 (m, 12H), 1.63 (m, 1H), 2.23 (m, 1H), 3.12 (q_{AB}, J_{AB} = 18.0 Hz, $\Delta\nu$ = 36.1 Hz, 2H), 4.18 (d, J = 7.0 Hz, 1H), 5.13 (s, 1H), 5.53 (s, 1H), 6.43 (s, 1H), 6.65 (s, 1H), 7.29−7.52 (m, 10H), 7.74 (d, J = 8.7 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H). HRMS (ES+/M + H) calcd for $C_{32}H_{40}NO_5S$: 550.2627; found, 550.2643.

(±)-(4*R*,5*R*)-3,3-Dibutyl-3−2,3,4,5-tetrahydro-5-(4-methoxyphenyl)-7-(dimethylamino)-1-benzothiepin-4-ol 1,1-Dioxide (75). 2-Chloro-5-nitro-4′-methoxybenzophenone was prepared according to the procedure described in *Chem. Pharm. Bull*. **1997**, *45* (9), 1470−1474. This material was converted to compound **75** by a procedure similar to that described for **45**, substituting 2-butylhexanal for 2-ethylhexanal. The residue was concentrated in vacuo, and the desired product was isolated via preparative HPLC (eluting with EtOAc/hexane) as a white solid. ^{1}H NMR ($CDCl_3$) δ 0.90 (m, 6H), 1.05−1.45 (m, 10H), 1.63 (m, 1H), 2.21 (m, 1H), 2.80 (s, 6H), 3.06 (q_{AB}, J_{AB} = 16.2 Hz, $\Delta\nu$ = 45.0 Hz, 2H), 3.83 (s, 3H), 4.10 (d, J = 7.5 Hz, 1H), 5.46 (s, 1H), 5.98 (d, J = 0.9 Hz, 1H), 6.50 (d, J = 8.7 Hz, 1H), 6.94 (d, J = 8.7 Hz, 2H), 7.42 (d, J = 8.7 Hz, 2H), 7.87 (d, J = 8.7 Hz, 1H). HRMS (FAB+/M + H) calcd for $C_{27}H_{40}NO_4S$: 474.2678; found, 474.2675. Anal. Calcd for $C_{27}H_{39}NO_4S$: C, 68.48; H, 8.30; N, 2.96. Found C, 68.89; H, 8.41; N, 2.86.

(±)-(4*R*,5*R*)-3,3-Dibutyl-3−2,3,4,5-tetrahydro-5-(4-fluorophenyl)-7-(dimethylamino)-1-benzothiepin-4-ol 1,1-Dioxide (76). Compound **70** was reacted with $HNMe_2$ by a procedure similar to that described for **50**, to give compound **76**. The residue was concentrated in vacuo, and the desired product was isolated via preparative HPLC (eluting with EtOAc/hexane) as a white solid, mp 170.5−171.0 °C. ^{1}H NMR ($CDCl_3$) δ 0.95−1.02 (m, 6H), 1.15−1.58 (m, 10H), 1.74 (m, 1H), 2.29 (m, 1H), 2.90 (s, 6H), 3.16 (q_{AB}, J_{AB} = 14.4 Hz, $\Delta\nu$ = 51.0 Hz, 2H), 4.19 (d, J = 8.7 Hz, 1H), 5.62 (s, 1H), 5.98 (s, 1H), 6.60 (d, J = 8.7 Hz, 1H), 7.17 (d, J = 7.5 Hz, 1H), 7.20 (d, J = 7.5 Hz, 1H), 7.58 (m, 2H), 7.99 (d, J = 8.7 Hz, 1H). MS (EI): 461.

(±)-(4*R*,5*R*)-3,3-Dibutyl-3−2,3,4,5-tetrahydro-5-phenyl-8-(dimethylamino)-1-benzothiepin-4-ol 1,1-Dioxide (80). The phenol was 3-fluorophenol. Benzyl chloride was used, and the amine was dimethylamine. Alkylation of a substituted phenol with a substituted benzyl chloride, according to the procedure described in ref 23 gave a substituted diphenylmethane. With this diphenylmethane and with substitution of 2-butylhexanal for 2-ethylhexanal, compound **80** was prepared by a procedure similar to that described for **50**. The residue was concentrated in vacuo, and the desired product was isolated via preparative HPLC (eluting with EtOAc/hexane) as a white solid. ^{1}H NMR ($CDCl_3$) δ 0.91 (m, 6H), 1.07−1.78 (m, 11H), 2.24 (m, 1H), 2.98 (s, 6H), 3.11 (q_{AB}, J = 15.3 Hz, $\Delta\nu$ = 37.6 Hz, 2H), 4.14 (d, J = 6.6 Hz, 1H), 5.49 (s, 1H), 6.60 (d, J = 8.7 Hz, 1H), 6.76 (m, 1H), 7.30−7.56 (m, 7H). HRMS (FAB/M + H) calcd for $C_{26}H_{38}NO_3S$: 444.2572; found, 444.2565.

(±)-(4*R*,5*R*)-3,3-Dibutyl-3-2,3,4,5-tetrahydro-5-(4-fluorophenyl)-9-(dimethylamino)-1-benzothiepin-4-ol 1,1-Dioxide (81). Compound **93** was reacted with dimethylamine, using a procedure similar to that for compound **50**, to give compound **81**. The residue was concentrated in vacuo, and the desired product was isolated via recrystallization from ethyl ether/hexane as a colorless solid, mp 159.0−160.0 °C. ^{1}H NMR ($CDCl_3$) δ 0.86−0.94 (m, 6H), 1.12−1.62 (m, 11H), 2.30 (m, 1H), 3.00 (m, 8H), 4.08 (d, J = 7.8 Hz, 1H), 5.70 (s, 1H), 6.29 (d, J = 7.8 Hz, 1H), 6.88 (d, J = 7.8 Hz, 1H), 7.01 (d, J = 8.1 Hz, 1H), 7.04 (d, J = 8.1 Hz, 1H), 7.15 (t, J = 7.9 Hz, 1H), 7.43 (m, 2H). MS (EI): 461. Anal. Calcd for $C_{26}H_{36}FNO_3S$: C, 67.65; H, 7.86; N, 3.03. Found: C, 67.16; H, 7.91; N, 3.02.

(±)-(4*R*,5*R*)-3,3-Dibutyl-3−2,3,4,5-tetrahydro-5-(4-methoxyphenyl)-7-(dimethylamino)-9-methoxy-1-benzothiepin-4-ol 1,1-Dioxide (88). The phenol was 2 methoxy-4-fluorophenol, benzyl chloride was used, and the 4-methoxybenzyl chloride amine was dimethylamine. Alkylation of a substituted

phenol with a substituted benzyl chloride, according to the procedure described in ref 23, gave a substituted diphenylmethane. Using this diphenylmethane and substituting 2-butylhexanal for 2-ethylhexanal, compound **88** was prepared by a procedure similar to that described for **50**. The residue was concentrated in vacuo, and the desired product was isolated via preparative HPLC (eluting with EtOAc/hexane) as a white solid. ^{1}H NMR ($CDCl_3$) δ 0.87−0.91 (m, 6H), 1.10−1.63 (m, 11H), 2.80 (s, 6H), 3.18 (q_{AB}, J_{AB} = 15.0 Hz, $\Delta\nu$ = 40.5 Hz, 2H), 3.82 (s, 3H), 3.88 (s, 3H), 4.08 (s, 1H), 5.65 (s, 1H), 6.12 (s, 1H), 6.90 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 9.0 Hz, 1H). MS for $C_{28}H_{41}O_5NS$: 516.4. RP-HPLC: 5−90% MeOH/H_2O/0.1% TFA, 91.5% pure; 5−90% CH_3CN/H_2O/0.1% TFA, 92.4% pure; average, 92.0%. HRMS (ESI/M + H) calcd for $C_{28}H_{42}NO_5S$: 504.2785; found, 504.2778.

General Procedure for Compounds 89, 90, and 93. Alkylation of a substituted phenol with a substituted benzyl chloride, according to the procedure described in ref 23 gave a substituted diphenylmethane. With this diphenylmethane and with substitution of 2-butylhexanal for 2-ethylhexanal, compounds **89**, **90**, and **93** were prepared by a procedure similar to that described for **34a**. See each compound below for purification methods and specific phenol and benzyl chloride used.

(±)-(4*R*,5*R*)-3,3-Dibutyl-3-2,3,4,5-tetrahydro-5-(2-bromophenyl)-7-bromo-1-benzothiepin-4-ol 1,1-Dioxide (89). The phenol was 4-bromophenol, and benzyl chloride was 2-bromobenzyl chloride. The residue was concentrated in vacuo, and the desired product was isolated via preparative HPLC (eluting with EtOAc/hexane) as a white solid. ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7.2 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H), 1.08 (m, 1H), 1.20−1.47 (m, 9H), 1.70 (m, 1H), 2.20 (m, 1H), 3.14 (q_{AB}, J_{AB} = 15.6 Hz, $\Delta\nu$ = 45.6 Hz, 2H), 4.15 (d, J = 6.0 Hz, 1H), 5.99 (s, 1H), 6.81 (s, 1H), 7.24−7.28 (m, 2H), 7.49 (t, J = 8.0 Hz), 7.55 (dd, J = 8.4, 2.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 7.6 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H). HRMS (CI/M + H) calcd for $C_{24}H_{31}O_3SBr_2$: 557.0361; found, 557.0352. Anal. Calcd for $C_{24}H_{30}O_3SBr_2$: C, 51.63; H, 5.42; S, 5.74; Br, 28.62. Found: C, 51.10; H, 5.47; S, 5.61; Br, 29.10.

(±)-(4*R*,5*R*)-3,3-Dibutyl-3−2,3,4,5-tetrahydro-5-(4-fluorophenyl)-7-methoxy-1-benzothiepin-4-ol 1,1-Dioxide (90). The phenol was 4-methoxyphenolbenzyl chloride, and 4-fluorobenzyl chloride was used. The residue was concentrated in vacuo, and the desired product was isolated via preparative HPLC (eluting with EtOAc/hexane) as a white solid, mp 167−170°C. HPLC: t_R = 30.5 min. ^{1}H NMR ($CDCl_3$) δ 0.85−1.05 (m, 6H), 1.15−1.80 (m, 11H), 2.28 (dt, J = 13.2, 3.3 Hz, 1H), 3.75 (s, 3H), 3.12 (ABq, 2H), 4.21 (s, 1H), 5.56 (s, 1H), 6.88 (dd, J = 7 Hz, 2.6 Hz, 1H), 7.18 (t, J = 7.0 Hz, 1H), 7.51 (t, J = 6.9 Hz, 2H), 8.09 (d, J = 2.7 Hz, 1H). MS (CI/M + H): 449. HRMS (CI/M + NH_4) calcd for $C_{25}H_{37}FO_4SN$: 466.2427; found, 466.2417. Anal. Calcd for $C_{25}H_{33}FO_4S$: C, 66.94; H, 7.40; S, 7.14. Found: C, 65.35; H, 7.06; S, 7.04.

(±)-(4*R*,5*R*)-3,3-Dibutyl-3−2,3,4,5-tetrahydro-5-(4-fluorophenyl)-9-fluoro-1-benzothiepin-4-ol 1,1-Dioxide (93). The phenol was 4-fluorophenol, and the benzyl chloride was 4-fluorobenzyl chloride. The residue was concentrated in vacuo, the desired product was isolated via preparative HPLC (eluting with EtOAc/hexane) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 0.86−0.96 (m, 6H), 1.10−1.62 (m, 11H), 2.16 (m, 1H), 3.25 (q_{AB}, J_{AB} = 15.0 Hz, $\Delta\nu$ = 58.3 Hz, 2H), 4.13 (s, 1H), 5.65 (s, 1H), 6.56 (d, J = 5.1 Hz, 1H), 7.00−7.10 (m, 3H), 7.32 (m, 1H), 7.53 (m, 1H). MS (EI) for $C_{24}H_{30}F_2O_3S$: 436. Anal. Calcd for $C_{24}H_{30}F_2O_3S$: C, 66.03; H, 6.92; S, 8.70. Found: C, 65.93; H, 7.01; S, 7.53.

6-[[(±)-(3*S*,5*R*)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-5-phenyl-1-benzothiepin-8-yl]oxy]-*N*,*N*,*N*-trimethyl-1-hexanaminium Iodide (95). Compound **37** was reacted with K_2CO_3 and 1,6-diiodohexane according to the procedure described in *Org. Synth.* **1955**, *3* (Collective Vol.), 140, to give (4β,5β)-3-butyl-3-ethyl-4-hydroxy-8-(6′-iodohexyloxy)-5-phenyl-2,3,4,5-tetrahydrobenzothiepine 1,1-dioxide, which was reacted with trimethylamine, using a procedure similar to that described for **50**, to give compound **95**. The residue was concentrated in vacuo, and the desired product was isolated by precipitation from CH_3CN/ethyl ether as a white solid. ^{1}H NMR ($CDCl_3$) δ 0.89 (m, 6H), 1.12 (m, 1H), 1.23−1.80 (m, 14H), 2.18 (m, 1H), 3.10 (ABq, 2H), 3.33 (s, 9H), 3.46 (m, 2H), 3.99 (br s, 2H), 4.16 (s, 1H), 5.44 (s, 1H), 6.64 (d, J = 7.8 Hz, 1H), 6.85 (m, 1H), 7.32 (d, J = 6.0 Hz, 1H), 7.39 (t, J = 6.6 Hz, 2H), 7.46 (m, 2H), 7.58 (s, 1H). MS (FAB/M + H): 530.2.

2-[2-[2-[[(±)-(3*S*,4*R*,5*R*)-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-5-phenyl-1-benzothiepin-8-yl]oxy]ethoxy]ethoxy]-*N*,*N*,*N*-trimethylethanaminium Iodide (96). Compound **37** was reacted with K_2CO_3 and 1,2-bis(2-iodoethoxy)ethane and then trimethylamine, using a procedure similar to that described for **95**, to give compound **96**. The residue was concentrated in vacuo, and the desired product was isolated by precipitation from CH_3CN/ethyl ether as a white solid, mp 101.0−105.0 °C. HPLC: t_R = 8.1 min. ^{1}H NMR ($CDCl_3$) δ 0.80 (t, J = 7.2 Hz, 3H), 0.85 (t, J = 6.9 Hz, 3H), 1.06 (m, 2H), 1.20−1.40 (m, 3H), 1.45−1.65 (m, 2H), 2.12 (br t, J = 12.6 Hz, 1H), 2.31 (d, J = 6.3 Hz, 1H), 3.10 (ABq, 2H), 3.30 (s, 9H), 3.62 (s, 4H), 3.76 (m, 4H), 3.88 (br s, 2H), 4.09 (br t, J = 3.9 Hz, 2H), 4.14 (br d, J = 6.0 Hz, 1H), 5.36 (s, 1H), 6.63 (d, J = 8.7 Hz, 1H), 6.86 (dd, J = 8.7, 3.0 Hz, 1H), 7.28 (d, J = 7.2 Hz, 1H), 7.35 (t, J = 7.2 Hz, 2H), 7.46 (d, J = 7.2 Hz, 2H), 7.56 (d, J = 2.7 Hz, 1H). MS (ES/M+): 562.2. HRMS (ES/M+) calcd for $C_{31}H_{48}O_6SN$: 562.3187; found, 562.3202. Anal. Calcd for $C_{31}H_{48}O_6SNI$: C, 53.99; H, 7.01; N, 2.03. Found: C, 53.00; H, 6.97; N, 2.39.

***N*-[2-[2-[2-[4-[(±)-(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]ethoxy]ethoxy]ethoxy]-*N*,*N*,*N*-triethylaminium Iodide (97).** Compound **75** was reacted with BBr_3, using a procedure similar to that described for **37**, to give (4β,5β)-3,3-dibutyl-4-hydroxy-7-dimethylamino-5-(4′-hydroxyphenyl)-2,3,4,5-tetrahydrobenzothiepine 1,1-dioxide **124**. ^{1}H NMR ($CDCl_3$) δ 0.90 (m, 6H), 1.04−1.18 (m, 1H), 1.20−1.46 (m, 9H), 1.63 (m, 1H), 2.19 (m, 1H), 3.07 (ABq, J = 14.7 Hz, $\Delta\nu$ = 44.1 Hz, 2 H), 3.66−3.79 (m, 5H), 3.87 (m, 2H), 4.06−4.18 (m, 3H), 5.46 (s, 1H), 5.98 (d, J = 3.0 Hz, 1H), 6.49 (dd, J = 9.9, 2.7 Hz, 1H), 6.95 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.1 Hz, 2H), 7.87 (d, J = 9.3 Hz, 1H). MS (CI/M + Li): 749. Compound **124** was reacted with K_2CO_3 and 1,2-bis(2-iodoethoxy)ethane and then triethylamine, using a procedure similar to that described for **95**, to give compound **97**. The residue was concentrated in vacuo, and the desired product was isolated by precipitation from CH_3CN/ethyl ether as a white solid, mp 131−133 °C. ^{1}H NMR ($CDCl_3$) δ 0.81−0.95 (m, 6H), 1.0−1.7 (m, 20H), 2.17 (br t, J = 13.1 Hz, 1H), 2.78 (s, 6H), 3.03 (q, J = 20 Hz, 2H), 3.5 (q, J = 7.5 Hz, 6H), 3.7 (s, 6H), 3.81 (t, J = 5.0 Hz, 2H), 3.97 (t, J = 5.0 Hz, 2H), 4.04 (d, J = 7.5 Hz, 1H), 4.1 (t, J = 5.0 Hz, 2H), 5.42 (s, 1H), 5.89 (d, J = 5.2 Hz, 1H), 6.45 (d, J = 7.5 Hz, 1H), 6.86 (d, J = 7.5 Hz, 2H), 7.35 (d, J = 7.5 Hz, 2H), 7.8 (d, J = 7.5 Hz, 1H). HRMS (M − I) calcd for $C_{38}H_{63}N_2O_6S$: 675.4407; found, 675.4368. Anal. Calcd for $C_{38}H_{63}N_2O_6SI$: C, 56.85. H, 7.91. N, 3.49. I, 15.80. Found: C, 55.74. H, 7.83. N, 3.47. I, 15.49.

Supporting Information Available: X-ray crystallographic information for **34a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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