Journal of Medicinal Chemistry

Article

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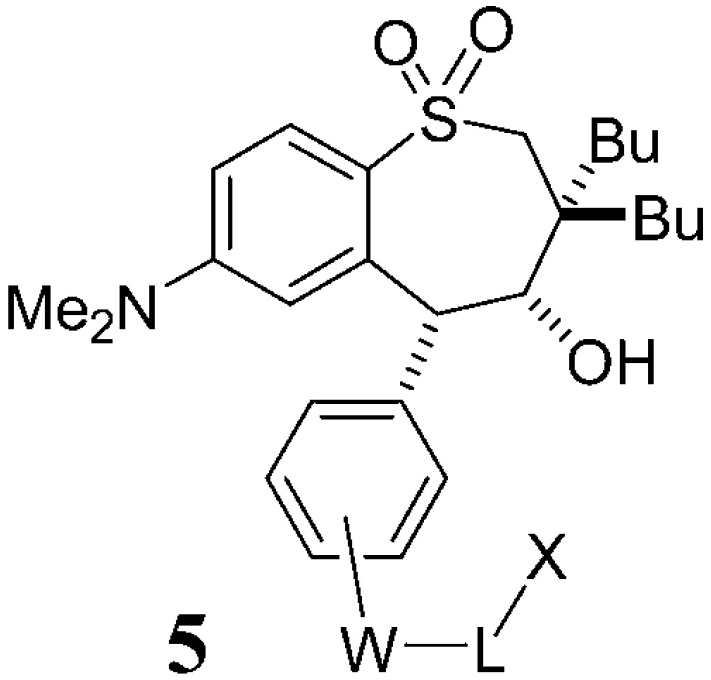
J. Med. Chem., **2005**, 48 (18), 5853-5868• DOI: 10.1021/jm0402162 • Publication Date (Web): 06 August 2005



5

X = polar functionality
L = linker
W = C, NH, O

Journal of Medicinal Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Discovery of Potent, Nonsystemic Apical Sodium-Codependent Bile Acid Transporter Inhibitors (Part 2)

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Received December 14, 2004

In the preceding paper several compounds were reported as potent apical sodium-codependent bile acid transporter (ASBT) inhibitors. Since the primary site for active bile acid reabsorption is via ASBT, which is localized on the luminal surface of the distal ileum, we reasoned that a nonsystemic inhibitor would be desirable to minimize or eliminate potential systemic side effects of an absorbed drug. To ensure bioequivalency and product stability, it was also essential that we identify a nonhygroscopic inhibitor in its most stable crystalline form. A series of benzothiepines were prepared to refine the structure−activity relationship of the substituted phenyl ring at the 5-position of benzothiepine ring and to identify potent, crystalline, nonhygroscopic, and efficacious ASBT inhibitors with low systemic exposure.

Introduction

In the preceding paper,[4] we have demonstrated that inhibiting the reabsorption of bile acid with an apical sodium-codependent bile acid transporter (ASBT) inhibitor should be an effective therapeutic approach to lower the serum LDL cholesterol.[1,2] Since the primary site for active bile acid reabsorption is via ASBT, which is localized on the luminal surface of the distal ileum, we reasoned that a nonsystemic inhibitor would be desirable to minimize or eliminate potential systemic side effects of an absorbed drug.[3]

Our approaches to achieve this goal were to incorporate charged or polar substitutions in the structure of the inhibitors and/or to increase its molecular weight. To introduce a charged or highly polar moiety in the inhibitor without sacrificing its potency was a significant challenge. As articulated in the preceding paper,[4] the core benzothiepine ring structure **1** (Figure 1) will not tolerate any charged substituent, and the phenyl group at the 5-position of the core ring is the only pharmacophoric moiety suitable for this type of structural manipulation. Although the ethylene glycol-linked quaternary ammonium analogue **2** (Figure 1) is a potent ASBT inhibitor, it has the undesirable properties of being a hygroscopic and amorphous solid. To ensure bioequivalency and product stability (e.g., the most stable crystalline form and sufficient shelf storage life), it was essential that we identify a nonhygroscopic inhibitor in its most stable crystalline form. Therefore, the goal of our research was to investigate modifications of the phenyl moiety at the 5-position to maintain or improve potency and, more importantly, to identify a crystalline, nonhygroscopic ASBT inhibitor that has minimal systemic exposure.

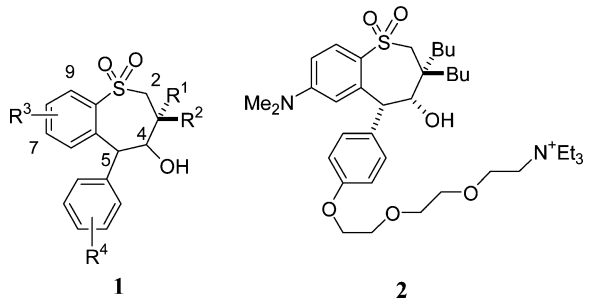

Figure 1. Potent ASBT inhibitor and the corresponding poorly absorbed ASBT inhibitor.

In the preceding article, our laboratories have reported the discovery of potent ASBT inhibitors **1** and **2** and the detailed SAR studies around R^1, R^2, and R^3 of the core ring structure **1**.[4] In this paper we discuss the SAR of the substituted phenyl ring at the 5-position of benzothiepine ring and identify several potent, crystalline, nonhygroscopic, and efficacious ASBT inhibitors with minimal absorption.

Chemistry

The synthetic methods used for the preparation of ASBT inhibitors in this paper are outlined in Scheme 1. In the preceding paper, several linear multistep

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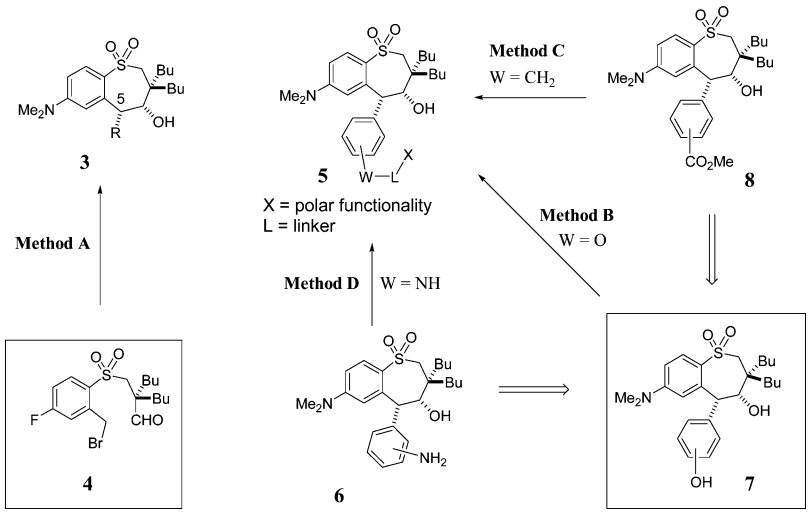
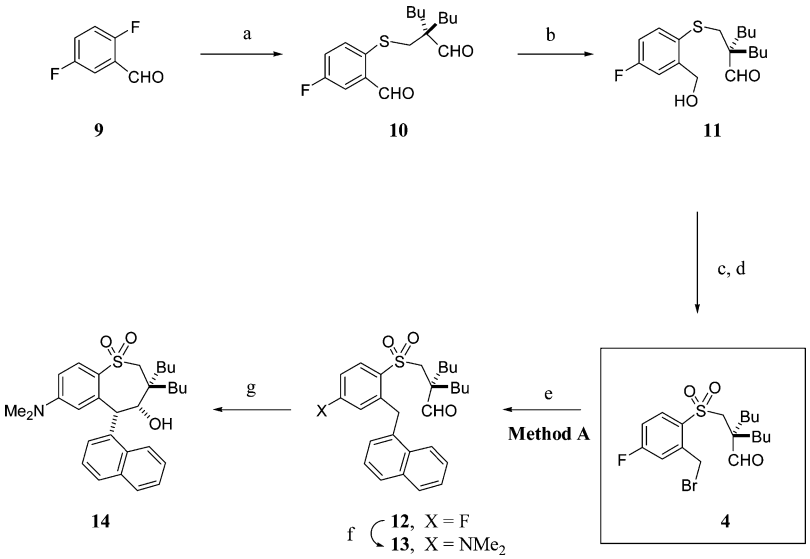
10.1021/jm0402162 CCC: $30.25
Published on Web 08/06/2005

Scheme 1



Scheme 2[a]



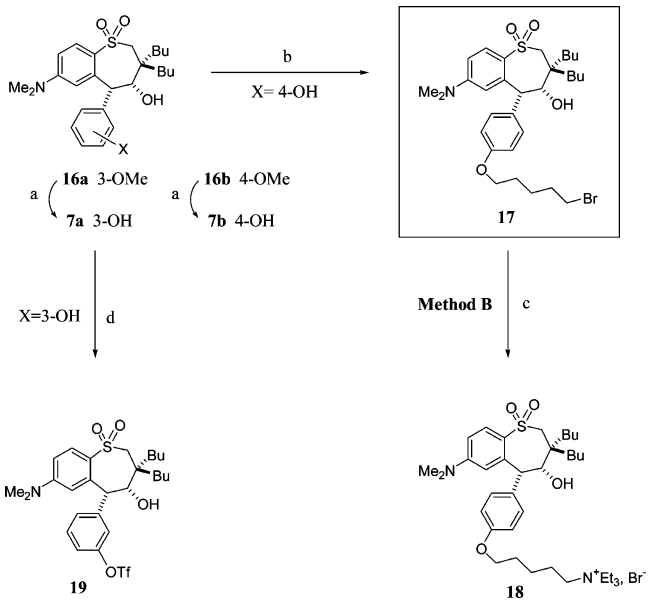
[a] Reagents: (a) Li_2S, DMSO, then $MsOCH_2C(Bu_2)CHO$; (b) DIBAL, THF; (c) Ph_3PBr_2; (d) mCPBA; (e) naphthyl-1-$B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3 (aq), toluene/EtOH; (f) Me_2NH, CH_3CN; (g) KO^{t}Bu, THF.

syntheses were described for the preparation of the benzothiepine ring structure; however, those syntheses were lengthy and required about 2-week average preparation time for each analogue. Since the phenyl ring at the 5-position of the benzothiepine ring was identified as a suitable handle for reducing absorption, a novel efficient synthetic route was developed to provide a versatile starting point for rapid analogue synthesis with various R groups (**3** in Scheme 1). This method (method A) enabled the preparation of potent ASBT inhibitors **3** in 2−3 days from a late-stage key intermediate **4** (see Scheme 2 for details). Compound **5**, which represents three major classes of minimally absorbed ASBT inhibitors (W = N, O, or C), could be obtained via straightforward functionalization of intermediates **6**, **7**, and **8** (Scheme 3, methods D, B and C, respectively). Intermediates **6** and **8** could in turn be prepared from the triflate derivative of **7** via Pd-catalyzed coupling reactions (details in Scheme 4).

Method A. The efficient synthetic method A depicted in Scheme 1 was illustrated in the preparation of naphthalene analogue **14** (Scheme 2). Difluorobenzaldehyde **9** was treated with lithium sulfide, and the resulting lithium phenyl thiolate intermediate was alkylated to give dialdehyde **10**. Selective reduction of the benzaldehyde group with DIBAL gave alcohol **11**, which was subsequently converted to the key bulk intermediate, bromide **4**. Suzuki coupling[5] of **4** with various aryl or heterocyclic boronic acids and subsequent aromatic S_N2 replacement of the resulting intermediate **12** by dimethylamine conveniently gave the benzothiepine precusor **13**. Under basic cyclization conditions aldehyde **13** stereoselectively provided the final product **14** with a cis configuration for the two newly formed stereogenic centers.[6]

Method B. Preparation of ether-linked **5** (Scheme 1, where W = O) was exemplified in the synthesis of **18** (Scheme 3). Demethylation of **16** with boron tribromide gave phenol **7**. 4-Phenol **7b** was treated with a dihalo linker, such as dibromopentane, and NaH in DMF to give a versatile intermediate **17**. Treatment of bromide **17** with various nucleophiles, such as triethylamine, gave triethylammonium analogue **18**. 3-Phenol **7a** was

Scheme 3[a]



[a] Reagents: (a) BBr_3, CH_2Cl_2; (b) $Br(CH_2)_5Br$, NaH, DMF; (c) Et_3N, CH_3CN; (d) Tf_2O, pyridine.

treated with triflic anhydride to provide triflate **19**, which served as a key intermediate in Scheme 4.

Method C. Functionalization of a benzylic linked **5** (Scheme 1, where W = CH_2) was exemplified by the preparation of **23** and **24** (Scheme 4). Triflate **19** was carbonylated to give benzoate **20**,[7] which was reduced to benzyl alcohol **21** and subsequently converted to a versatile bromide intermediate **22**. Treatment of bromide **22** with various nucleophiles such as dimethylamine or trimethylamine gave dimethylamino analogue **23** or trimethylammonium analogue **24**, respectively. Aniline **25**, a precusor for nitrogen-linked analogues, was prepared from triflate **19** via a Pd-catalyzed coupling reaction.[8] Functionalization of aniline linked analogues (method D) is illustrated in Scheme 5.

Method D. Aniline **25** served as a very versatile intermediate for rapid diversification of nitrogen-linked **5** (Scheme 1, where W = NH). For example, aniline **25** could be alkylated to give acid **26** (Scheme 5) or reacted with bromopyridine to yield aminopyridine **27** and its corresponding aminopyridinium **28** or acylated to prepare quaternary ammonium **30**.

To prepare enantiomerically enriched ASBT inhibitors, we have successfully developed an asymmetric synthesis to afford the desired active (*R*,*R*)-enantiomer in good yield (Scheme 6).[6] Alternatively, a racemic mixture from the cyclization of aldehyde **31** was resolved by a simulated flow-bed chiral chromatography, and the undesired (*S*,*S*)-enantiomer could be isomerized to provide additional desired product under the cyclization conditions.

Results and Discussion

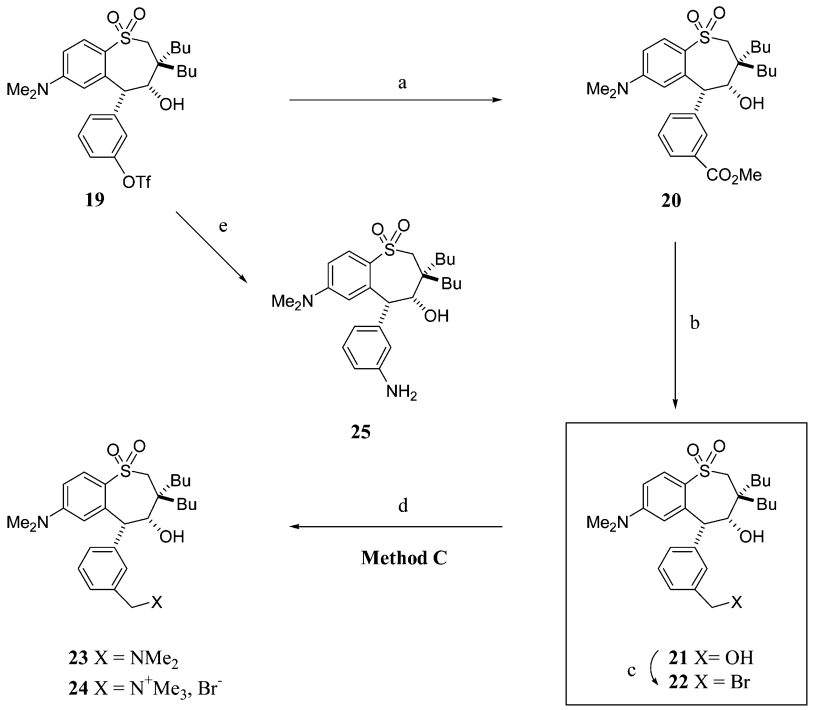
Our research effort can be categorized into three stages. In stage I, the main focus was to establish SAR around the phenyl ring at the 5-position to improve potency and to further identify the optimal position for attachment of the linker and polar functionality. In stage II, the focus was shifted to improving the potency of inhibitors that contained highly polar moieties. In the final stage, our research focused mainly on reducing systemic absorption (while maintaining efficacy) as well as improving solid-state properties such as hygroscopicity, stability, and crystallinity.

Stage I. SAR around the Phenyl Ring. To establish basic SAR around the phenyl ring for a more rigorous future effort, we prepared a series of analogues with emphasis on functionalities that could be tethered with a charged terminal group, functionalities such as ether, amine, thioether, ester, amide, and benzyl. Hydrogen-bonding groups such as hydroxy and methoxy in the 4-position (Table 1, **7b** and **16b**) yielded slightly more potent inhibitors than unsubstituted **32**. The slightly bulkier methylthio group (**33**) decreased the potency by 3-fold, and the bulky hydrophobic *tert*-butyl group (**34**) resulted in much weaker ASBT inhibition. Ester **35**, with an IC_{50} of 41 nM, was 3-fold less potent than **32**, but its acid analogue **36** showed much weaker potency. Benzyl alcohol **37** was equipotent to **32**, but the IC_{50} of the benzylamine **38** dropped to about 1 μM. The benzylamine group, presumably positively charged in the physiological environment, may have induced an unfavorable ionic interaction with the transporter, thus leading to a reduction in potency. A similar SAR trend was also observed in the 3-substitution analogues except that the unfavorable effect was considerably alleviated (**20** vs **35** and **23** vs **38**). Expansion to 3,4-disubstituted phenyl analogues led to slightly less potent inhibitors (**39**−**42**) with an interesting twist that the mixed 3-fluoro-4-methoxyphenyl analogue gave a more potent inhibitor (**42**, IC_{50} = 3.6 nM) than the corresponding difluoro or dimethoxy compounds (**39** and **40**, IC_{50} = 22 and 20 nM, respectively).

Since our goal was to discover inhibitors with little or no systemic exposure, our mission at this stage was to identify the optimal position to attach moieties that could decrease drug absorption. Representing charged inhibitors with the shortest linker, the benzylammonium analogues (**24**, **43**−**46**) were regarded as very attractive targets (Table 2). Unfortunately, the positively charged terminal diminished their potency to the micromolar range. For example, quaternization of **38** decreased the potency to 6 μM (**43**). The corresponding trimethylammonium **44** also showed very weak inhibition. Presumably, as hypothesized previously, the positive charge near the phenyl ring may have induced an unfavorable ionic interaction with the transporter. The charge-delocalized pyridinium compound (**45**, IC_{50} = 0.85 μM) was almost 7-fold more potent than the corresponding charge-localized trialkyllammonium analogues (**43** and **44**). This unfavorable interaction was alleviated in the 3-substituted series (**44** vs **24** and **45** vs **46**) because each 3-position isomer is about 100-fold more potent than the corresponding 4-substituted isomer. On the other hand, negatively charged benzylsulfonic acid **47** was a very potent ASBT inhibitor with an IC_{50} of 4 nM.

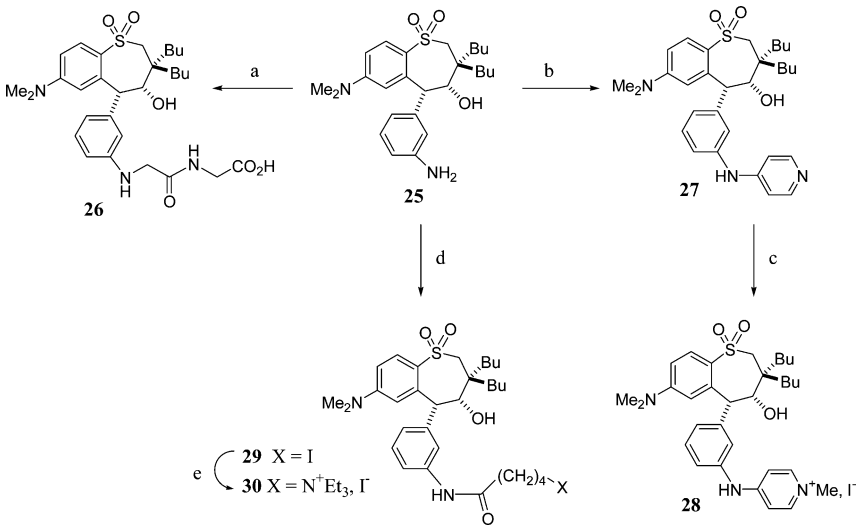
In addition to simple substituted phenyl analogues, other aryl and heterocyclic analogues were also prepared. Bicyclic aryl analogue such as 1-naphthyl (Table 3, **14**, IC_{50} = 620 nM) suffered a 50-fold decrease in potency when compared with **32**. With the less sterically demanding 2-naphthyl analogues, potency was recovered, with the 6-hydroxynaphathlene (**49**, IC_{50} = 17 nM)

Scheme 4[a]



[a] Reagents: (a) CO, $Pd(PPh_3)_4$, MeOH; (b) $LiAlH_4$, THF; (c) Ph_3PBr_2; (d) Me_2NH, CH_3CN; or NMe_3, CH_3CN; (e) $Ph_2C{=}NH$, $Pd(PPh_3)_4$, Cs_2CO_3; then NaOH, $MeOH/H_2O$.

Scheme 5[a]



[a] Reagents: (a) $BrCH_2C(=O)NHCH_2CO2Et$, acetone, then LiOH (aq); (b) 4-Br-pyridine, EtOH; (c) MeI, CH_3CN; (d) $ClC(=O)-(CH_2)_4I$, THF; (e) Et_3N, CH_3CN.

being the most potent analogue. Most heterocycles such as thiophene **50** (IC_{50} = 5 nM) and pyridines (**52**–**54**, IC_{50} = 5–8 nM) were more potent than the phenyl analogue. Among these heterocycles we were especially interested in the pyridine analogues because of greater potency and ease of conversion to its positively charged pyridinium form. Unfortunately, the introduction of a positive charge directly onto the ring resulted in a 30-fold decrease in potency (**55**, IC_{50} = 220 nM).

Conclusion of Stage I Study. Aniline and phenol analogues (**6** and **7** in Scheme 1) were chosen to provide scaffolds in stage II analogue syntheses for reasons of easy synthesis and/or greater potency.

ASBT is more sensitive to the substitution of the phenyl ring at the 4-position than the corresponding 3-position, especially with a positive-charged moiety. Among various substitutions, charge-delocalized pyridinium was better tolerated by ASBT than trialkylammonium. Negative charge, on the other hand, does not have much effect on the potency.

Stage II. Quest of Potent, Highly Polar Inhibitors. To ensure bioequivalency and stability, it was imperative for us to develop an ASBT inhibitor as a nonhygroscopic solid in its most stable crystalline form. Since physical properties of a pure enantiomer are different from those of a racemate, we had to optimize the physical properties of enantiomerically pure inhibitors. Hereon, all analogues discussed in stages II and III were prepared in their more active enantiomeric

Scheme 6

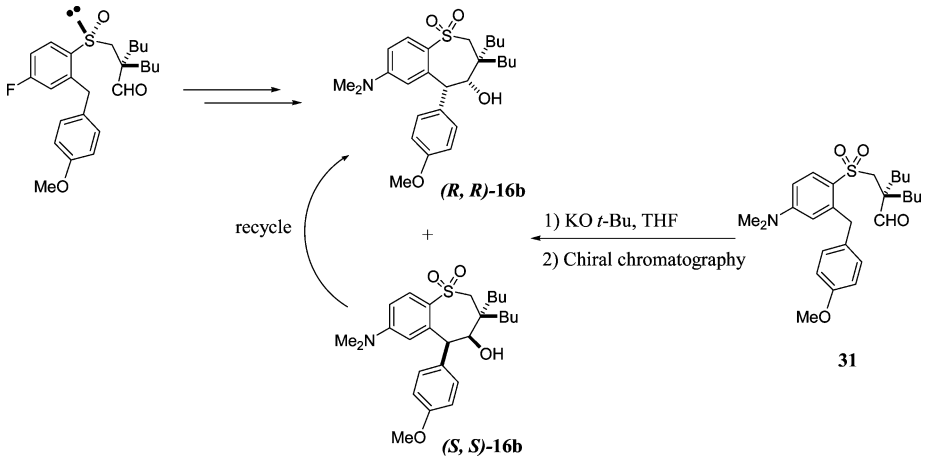
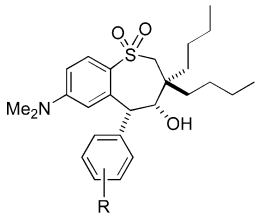


Table 1. SAR of ASBT Inhibition by Substituted Phenyl Analogues



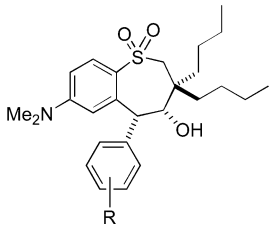
compd	R	IC_{50} (nM)[a]	synthesis[b]
(±)-**32**	4-H	13	ref 4, preparation of **64**
(±)-**7b**	4-OH	2.2	Scheme 3
(±)-**16b**	4-OMe	6.8	ref 4, preparation of **75**
(±)-**33**	4-SMe	42	method A, Scheme 2
(±)-**34**	4-^{t}Bu	1000	method A, Scheme 2
(±)-**35**	4-CO_2Me	41	Scheme 3
(±)-**36**	4-CO_2H	320	NaOH (aq), **35**
(±)-**37**	4-CH_2OH	11	Scheme 3
(±)-**38**	4-CH_2NEt_2	930	method C, Scheme 3
(±)-**7a**	3-OH	7.3	BBr_3, **16a**
(±)-**16a**	3-OMe	11	ref 4, Schemes 1-3
(±)-**20**	3-CO_2Me	7	Scheme 3
(±)-**21**	3-CH_2OH	4.5	Scheme 3
(±)-**23**	3-CH_2NMe_2	47	method C, Scheme 3
(±)-**25**	3-NH_2	2	Scheme 3
(±)-**39**	3-F, 4-F	22	ref 4, Schemes 1−3
(±)-**40**	3-MeO, 4-MeO	20	ref 4, Schemes 1−3
(±)-**41**	3-OH, 4-OH	9.5	BBr_3, **40**
(±)-**42**	3-F, 4-OMe	3.6	ref 4, Schemes 1−3

[a] Taurocholate is transported across the baby hamster kidney cell membrane. [b] Refers to general methods and the scheme in which the synthesis of the exemplified compound was outlined or to reagents and the compound starting material. General methods are detailed in the Experimental Section.

(*R*,*R*)-forms. In general, pure enantiomers exhibited IC_{50} values approximately one-half of those of their corresponding racemates because the (*S*,*S*)-enantiomers were found to be very weak ASBT inhibitors.

We learned from our effort in stage I that the potency of ASBT inhibitors is unfavorably affected by the positive charge around the phenyl ring at the 5-position. In stage II, we further discovered that the potency correlates with the distance between the positive charge and the phenyl ring. An inhibitor bearing a terminal positive charge tethered with a short PEG-linked **57** (Table 4) is 70-fold less potent than the longer PEG-linked **58**. Less polar pentyl ether analogue **18** is 3-fold more potent than equilength ethylene glycol analogue **60**.

Table 2. ASBT Inhibition by Racemic Short-Tailed Phenyl Analogues



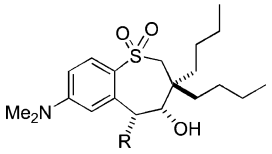
compd	R	IC_{50} (nM)[a]	synthesis[b]
(±)-**38**	4-CH_2NEt_2	930	method C, Scheme 4
(±)-**43**	4-$CH_2N^+Et_3$	5500	method C, Scheme 4
(±)-**44**	4-$CH_2N^+Me_3$	8800	method C, Scheme 4
(±)-**45**	4-CH_2-(N^+)-pyridinium	850	method C, Scheme 4
(±)-**23**	3-CH_2NMe_2	47	method C, Scheme 4
(±)-**24**	3-$CH_2N^+Me_3$	67	method C, Scheme 4
(±)-**46**	3-CH_2-(N^+)-pyridinium	7.5	method C, Scheme 4
(±)-**47**	3-CH_2SO_3H	3.7	method C, Scheme 4

[a] Taurocholate is transported across the baby hamster kidney cell membrane. [b] These compounds were readily prepared from bromide **22** or from the corresponding 4-CH_2Br.

To further probe the tolerance of the ASBT transporter toward the size of inhibitors, several quaternary ammonium groups were attached to inhibitors with various chain lengths. Since inhibitors with a trimethylammonium group (**58**) and a terminal 14-membered heterocyclic ring (**62**) are equipotent, the size of the terminal alkyl group on a long linker seems to have no effect on the potency. Another interesting conclusion is that even though our stage I study suggested that a short-chain terminal positive charge is detrimental for potency, in the stage II study we observed that long-chain inhibitors with positively charged ammonium moieties were actually more potent by at least 8-fold than their corresponding neutral amine analogues (**18** vs **59** and **2** vs **61**). Similarly, pyridinium **64** was about 4-fold more potent than the corresponding neutral pyridine analogue **63**. With shorter linkers, the unfavorable ionic interaction induced by the positively charged fragment dominates; therefore, less potency enhancement was observed (**57** vs **56**). The same SAR trend was also observed in the 3-isomer series (**27**, **28**, **30**, and **66**−**68**).

Several hypotheses were proposed to rationalize the insensitivity of ASBT toward the size of the inhibitor's

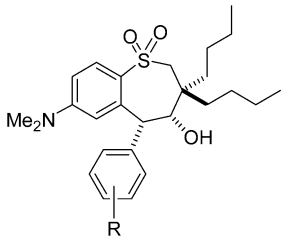
Table 3. ASBT Inhibition by Racemic Non-Phenyl Analogues



compd	R	IC_{50} (nM)[a]	synthesis[b]
(±)-**32**	phenyl	13	ref 4, prep of **64**
(±)-**14c**	1-naphthyl	620	method A, Scheme 2
(±)-**48**	2-(6′-OMe)-naphthyl	75	method A, Scheme 2
(±)-**49**	2-(6′-OH)-naphthyl	17	BBr_3, **48**[c]
(±)-**50**	2-thienyl	30	method A, Scheme 2
(±)-**51**	3-thienyl	5	method A, Scheme 2
(±)-**52**	2-pyridinyl	5	method A, Scheme 2
(±)-**53**	3-pyridinyl	7.5	method A, Scheme 2
(±)-**54**	4-pyridinyl	8	method A, Scheme 2
(±)-**55**	3-[(N^+)-methylpyridinium]	220	MeI, **53**[d]

[a] Taurocholate is transported across the baby hamster kidney cell membrane. [b] Most of these compounds were readily prepared from the key bromide intermediate **4**, as described in Scheme 2, unless indicated otherwise. [c] Treatment of **48** with BBr_3. [d] Treatment of **53** with MeI.

Table 4. ASBT Inhibition by Optically Enriched Long-Tailed Phenyl Analogues



compd	R	IC_{50} (nM)[a]	synthesis[b]
56	4-$OCH_2CH_2NMe_2$	340	method B, Scheme 3
57	4-$OCH_2CH_2N^+Me_3$	260	method B, Scheme 3
58	4-$(OCH_2CH_2)_3N^+Me_3$	4	method B, Scheme 3
59	4-$O(CH_2)_5NEt_2$	16	method B, Scheme 3
18	4-$O(CH_2)_5N^+Et_3$	2	method B, Scheme 3
60	4-$(OCH_2CH_2)_2N^+Et_3$	5.7	method B, Scheme 3
61	4-$(OCH_2CH_2)_3NEt_2$	30	method B, Scheme 3
2	4-$(OCH_2CH_2)_3N^+Et_3$	3	ref 4, prep of **97**
62	see Figure 2	3	method B, Scheme 3
63	see Figure 2	28	method B, Scheme 3
64	see Figure 2	6	EtI, **63**
65	4-$(OCH_2CH_2)_3N(CH_2CH_2OH)_2$	9	method B, Scheme 3
66	3-$OCH_2CH_2NEt_2$	45	method B, Scheme 3
67	3-$OCH_2CH_2N^+Et_3$	7	method B, Scheme 3
68	3-$O(CH_2)_5N^+Et_3$	2	method B, Scheme 3
26	$NHCH_2CONHCH_2CO_2H$	0.3	Scheme 5
27	see Figure 2	52	Scheme 5
28	see Figure 2	2	MeI, **27**
30	3-$NHCO(CH_2)_4N^+Et_3$	0.76	Scheme 5

[a] Taurocholate is transported across the baby hamster kidney cell membrane. [b] Refers to general methods and the scheme in which the synthesis of the exemplified compound was outlined or to the reagent and the compound starting material. Compounds presented here are all enantiomerically enriched, prepared from a enantiomerically enriched starting material derived from a key phenol intermediate **7.** General methods are detailed in the Experimental Section.

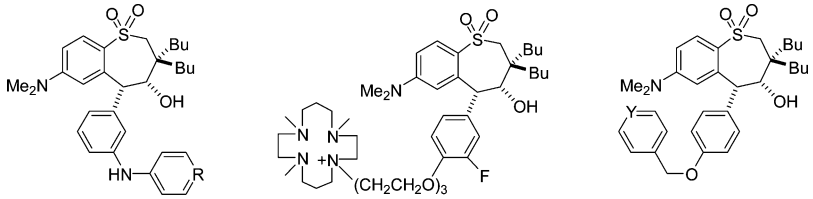
terminal group and its preference for inhibitors with long-tailed positively charged terminal. Our current hypothesis is that while the hydrophobic benzothiepine core structure was docked in the binding pocket of the transporter, at a certain distance away from the phenyl ring, the charged hydrophilic terminal group actually extended outside the ASBT binding pocket into the surface aqueous layer, thus stabilizing the binding of the inhibitor in the transporter. For short linkers, the positive charge might be too close to the transporter and might cause an unfavorable ionic interaction.

Stage III. Physical Properties. The highly charged or polar terminal group that we tethered onto the inhibitors to achieve the potency and low absorption properties has contributed to undesirable hygroscopicity. Not surprisingly, the majority of compounds we just described (Table 4) are noncrystalline and highly hygroscopic and thus were not suitable for development in a solid tablet dosage form. An initial quick-fix approach to prepare a library of anionic salts of an existing quaternized inhibitor (**2**) identified a pamoic acid salt as a crystalline nonhygroscopic solid. Unfortunately the compound was not effective in follow-up animal studies because of poor water solubility. Our focus was thus shifted to optimizing the delicate balance of crystallinity, hygroscopicity, and water solubility by systematically varying the polar terminal group and its linker.

An exhaustive search for the right terminal group finally resulted in the identification of a DABCO quaternary ammonium analogue (Table 5, **69**, $IC_{50} = 1$ nM). This compound was shown to be potent, crystalline, and nonhygroscopic (in a 25°C, 57% humidity chamber). Even though the compound did absorb moisture and gained 12% in weight in the more stringent 40 °C, 80% humidity chamber, it seemed that a suitable quaternary ammonium group with optimized physical properties had been identified. The DABCO quaternary ammonium group was thus introduced to various chain linkers. Not surprisingly, long and floppy hydrophilic ethylene-glycol chains yielded amorphous quaternary ammonium analogues (**70**, **71**), which absorbed significant moisture and rapidly turned into liquids. Compared to C4-linked **69**, longer C5-linked **73**, even though more potent as expected ($IC_{50} = 0.5$ nM), was not crystalline. On the other hand, shorter C3-linked **72** was slightly less potent ($IC_{50} = 4$ nM), but it still gained some weight (7%) in the humidity chamber.

Our data suggested that to achieve this multidimensional balance among potency, water solubility, hygroscopicity, and crystallinity, we needed to replace the long and floppy hydrophilic ethylene glycol linker with an aromatic moiety that would not only provide rigid, hydrophobic backbones but might also provide intermolecular $\pi-\pi$ stacking interactions to stabilize the crystal lattice. Alternatively, shorter all-carbon linkers potentially would pack more easily in the crystalline structure. Results of several benzylic-linked compounds provided strong support for this hypothesis. Benzylic DABCO quaternary ammonium analogue **74** is potent ($IC_{50} = 0.28$ nM), nonhygroscopic (2% weight gain), and crystalline. It also showed efficacy in the rat gavage model. The benzylpyridinium analogue **75**, even though potent and nonhygroscopic, was not crystalline. Besides the benzyl linker, a 4-picolinium linker also led to a very potent, crystalline, and nonhygroscopic ASBT inhibitor (**76**).

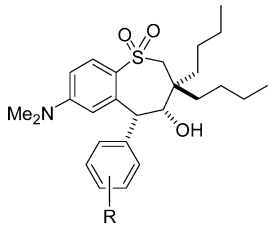
Parallel to our effort in positively charged terminal groups, carboxylic acids were also used to address absorption issues. Short-chain analogue **77** is not as



27 R = N
28 R = N^+CH_3
62
63 Y = N
64 Y = N^+Et

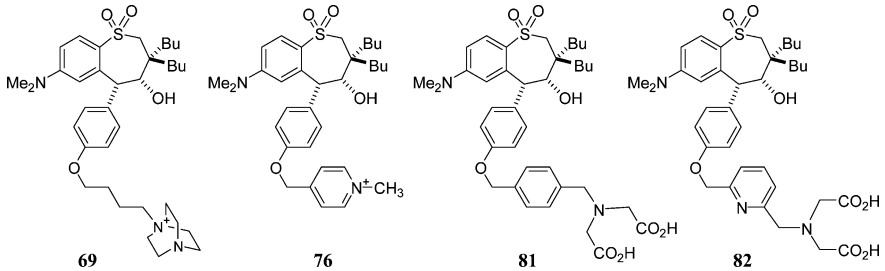
Figure 2. Structures of ASBT inhibitors from Table 4.

Table 5. Physical Properties of Optically Enriched 4-Substituted Analogues[a]



compd	R	IC_{50} (nM)[b]	hygroscp I wt gain (%)[c]	hygroscp II % wt gain (%)[d]	crystallinity[e]
69	$O(CH_2)_4$-(N^+)DB;[f] see Figure 3	1	−1.3	12.33	yes
70	$(OCH_2CH_2)_2$-(N^+)DB	8.5	liquid		no
71	$(OCH_2CH_2)_3$-(N^+)DB	4	liquid		no
72	$O(CH_2)_3$-(N^+)DB	4	3.11	7.4	
73	$O(CH_2)_5$-(N^+)DB	0.5			no
74	$OCH_2C_6H_4(p)CH_2$(N^+)DB	0.28	1.59	2.1	yes
75	$OCH_2C_6H_4(p)CH_2$(N^+)pyridinium	1	0.21	5.4	no
76	see Figure 3	0.75	0.2	2.62	yes
77	OCH_2CO_2H	27	−0.47		no
78	$O(CH_2)_4CO_2H$	8.5			no
79	$OCH_2CONHCH_2CO_2H$	23	1.9	0.59	yes
80	$O(CH_2)_5N(CH_2CO_2H)_2$	2.3	−0.19	2.1	
81	see Figure 3	2			
82	see Figure 3	4	0.72		no

[a] All compounds were prepared using method B in Scheme 3. [b] Taurocholate is transported across the baby hamster kidney cell membrane. [c] % weight gain in a 25 °C, 57% humidity chamber for 2 weeks. [d] % weight gain in a 40 °C, 80% humidity chamber for 2 weeks. [e] Crystallinity as determined by X-ray powder diffraction analysis. [f] (N^+)DB is a DABCO terminal group with the quaternary ammonium attached to the linker (see Figure 3).



69 **76** **81** **82**

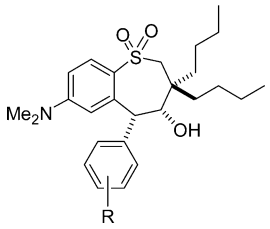
Figure 3. Structures of ASBT inhibitors from Table 5.

potent as the longer chain analogue **78**, but both are not crystalline. A glycine amide linker yielded **79**, which, even though less potent than **78**, is nonhygroscopic and crystalline. Diacid analogues were also found to be potent and nonhygroscopic (**80**−**82**).

Pharmacokinetics and efficacy data of 11 compounds tested in the rat fecal bile acid excretion model were tabulated (Table 6). All five quaternary ammonium ASBT inhibitors (**69**, **72**, **74**−**76**) showed minimal systemic exposure and superior efficacy in preventing bile acid reabsorption than the original PEG-linked lead **2**. Among them, benzylic pyridinium **75** was the most efficacious in this model. It also passed the hygroscopicity test, but disappointingly, it was not crystalline. Of these five quaternary ASBT inhibitors, **74** and **76** have met all the selection criteria and were shown to be potent, crystalline, and nonhygroscopic. They further exhibited low systemic absorption and good in vivo efficacy.

Anionic ASBT inhibitors were also shown to be efficacious and poorly absorbed. Among them, the monoacid of glycine amide **79** demonstrated favorable results in solid-state tests and the efficacy animal model, but a significant amount of the compound was detected in the biles, indicating that it was absorbed and excreted into biles. Monoacid **78** was the most efficacious, but it was not crystalline and showed the highest systemic exposure among all inhibitors tested. In fact, all three monocarboxylic acid analogues (**77**−**79**) showed some extent of systemic exposure (detected either in the

Table 6. Systemic Exposure, Efficacy,[a] and Physical Properties of ASBT Inhibitors



compd	R	C_{max}[b] portal	C_{max}[b] artery	% in bile	efficacy[c]	solid states[d]
69	$O(CH_2)_4$-(N^+)DB;[e] see Figure 3	0	0	0.12	+	no, yes
72	$O(CH_2)_3$-(N^+)DB	0	0	0.21	+	no, ND
74	$OCH_2C_6H_4(p)CH_2$(N^+)DB	0	0	0.11	+	yes, yes
75	$OCH_2C_6H_4(p)CH_2$(N^+)pyridinium	0	0	0.03	++	yes, no
76	see Figure 3	0	0	0.03	+	yes, yes
77	OCH_2CO_2H	0	0.96	15.04	ND	ND, no
78	$O(CH_2)_4CO_2H$	1.1	5.1	3.30	++	ND, no
79	$OCH_2CONHCH_2CO_2H$	0	0	7.14	+	yes, yes
80	$O(CH_2)_5N(CH_2CO_2H)_2$	0	0	0.24	+	yes, ND
81	see Figure 3	0	0	0.12	ND	ND, ND
82	see Figure 3	0	0	0.17	+	ND, no

[a] Fecal bile acid excretion assay in a rat gavage model, comparison dosage at 0.04 mg/kg. [b] Concentration in μg/mL. [c] +, more efficacious than analogue **2** in increasing fecal bile acid excretion; ++, even more effective; ND, not done. [d] Evaluation results in hygroscopicity (40 °C, 80% humidity chamber) and crystallinity tests, respectively: yes, passed; no, failed; ND, not done. Crystallinity of the solid was determined by X-ray powder diffraction analysis. [e] (N^+)DB is a DABCO terminal group with the quaternary ammonium attached to the linker (see Figure 3).

plasma or in the bile excretion), while diacids (**80**−**82**) were poorly absorbed and efficacious.

Conclusion

The hypothesis that a low-systemic ASBT inhibitor would be desirable to minimize or eliminate potential systemic side effects of an absorbed drug has led to the discovery of several potent, crystalline, and nonhygroscopic ASBT inhibitors with minimal systemic absorption. These agents further showed efficacy in the rat models to prevent the reabsorption of bile acids, and some were selected for further clinical trials. Earlier work suggested that 3-substituted analogues are more efficacious than the 4-substituted. Research effort in this area has generated several potent, crystalline inhibitors. Details will be reported when appropriate.

Experimental Section

Hygroscopicity Determination. 25 °C and 57% Humidity Procedure. About 50 mg of substrate was placed in a tared glass vial, and its physical condition was noted. The open vial was placed in a desiccator containing a saturated NaBr solution (hereafter referred to as "humidity chamber"). The humidity chamber was placed in a 25 °C oven. At various time points (typically 1, 2, 3, 7, and 15 days), the vial was removed from the humidity chamber, capped, and placed in a room temperature desiccator containing Drierite for 1 h. The substrate's mass was determined and physical condition noted. The substrate vial was uncapped and returned to the humidity chamber.

Hygroscopicity Determination. 40 °C and 80% Humidity Procedure. About 50 mg of substrate was subjected to the same procedure as described above except that a saturated KBr solution and a 40 °C oven were used.

Crystallinity Determination. X-ray Powder Diffraction (XPD) Analysis. XPD experiments were conducted on an Inel θ/θ diffraction system coupled with a 2 kW normal focus X-ray copper tube (Intel Instruments, France). X-ray scatter data were collected from 0° to 80° 2θ. Samples were run in bulk configuration. Data were collected and analyzed on a computer running Inel's proprietary software. Alternatively, XPD experiments were also conducted on a system comprising a Siemens D5000 diffraction system equipped with a 2 kW normal focus X-ray copper tube (Siemens, Germany). The system was equipped with an autosampler system with a $\theta-\theta$ sample orientation. Data collection and analysis were conducted with a computer running Siemens's proprietary software.

Biology. Taurocholate Uptake Cell Assay. For IC_{50} determination, materials, and methods, please see the preceding paper.[4]

Rat Fecal Bile Acid Excretion Model. Animal Handling and Dosing. Male Wistar rats (Charles River Laboratories) weighing 275−300 g were administered intragastric doses (5, 0.2, and 0.04 mpk) of drug dissolved in aqueous 0.2% (v/v) Tween-80 (2 mL/kg body weight) once a day in the morning for 4 days. Fecal samples were collected on papers during the final 48 h period of the study and analyzed for bile acid content.

Fecal Bile Acid Measurement. Fecal samples from each rat were weighed, and a weight of distilled water equal to 2 times the total weight of feces was added to each sample. Each sample was homogenized, and 1.4 g of the homogenate was diluted with 2.6 mL of butanol/distilled water (2:0.6). The mixture was extracted by incubation for 45 min in a 37 °C water bath and was centrifuged. The concentration of bile acids (μmol/day) was determined using a 96-well enzymatic assay system as described in the preceding paper.[4,9]

Pharmacokinetic Study. Selected compounds were evaluated for systemic exposure in the rat model according to the experimental procedure described for bioavailability assay in the preceding paper.[4]

Chemistry. General. Unless otherwise stated, reactions were carried out under nitrogen and in commercial grade solvents. Solvents were evaporated on a Büchi rotary evaporator at reduced pressure. Silica gel chromatography was performed on either medium pressure liquid chromatography (MPLC) or preparative high-performance liquid chromatography (Waters Associates, Prep-500A or LC-2000), eluting with EtOAc and hexane. Final products were purified by reverse-phase high-performance liquid chromatography (Waters, Delta Prep) and were eluted with acetonitrile and water (each spiked with 0.5% of trifluoroacetic acid). Most new compounds were fully characterized, and structures were assigned spectrally and confirmed by elemental analysis. The purity of the final

products was checked by elemental analyses, and the data were within ±0.4% of the theoretical values. Melting points were determined without correction on a Thomas-Hoover Unimelt apparatus. NMR spectra were obtained on a Varian VXR 300 or 400 MHz spectrometer. High-resolution mass spectra (HRMS) were obtained on a Finnigan MAT 90 or a VG model 250T spectrometer with FAB or EI ionization.

General Synthetic Procedures. Most compounds were prepared using one of the three general procedure sequences described below. For optically enriched final products, an optically enriched starting material was derived from **16b**, which was prepared from **31** followed by a chiral chromatography, as depicted in Scheme 6.

General Method A. (+)-(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-5-(1-naphthyl)-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-Dioxide (14). To a solution of 500 mg (1.19 mmol) of **4** (see procedure described later for each individual compound) in 8 mL of toluene and 5.5 mL of ethanol was added 245 mg (1.43 mmol) of naphthylboronic acid, 300 mg of tetrakis-(triphenylphosphine)palladium (0), and 5.5 mL of a 2 M solution of sodium carbonate in water. This heterogeneous mixture was stirred at 85 °C for 2 h, then cooled to ambient temperature and partitioned between ethyl acetate and water. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification by silica gel chromatography using ethyl acetate/hexanes gave 349 mg (63%) of the intermediate **12** as an oil. Following a similar sequence described in the asymmetric synthesis paper,[6] aldehyde **12** was converted to the title compound **14** as a white solid, mp 200 °C. ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 7.55 Hz, 3H), 0.93 (t, J = 6.85 Hz, 3H), 1.35 (m, 12H), 2.29 (dt, J = 12.3, 2.6 Hz, 1H), 2.66 (s, 6H), 3.15 (ABq, J_{AB} = 48.6, 15 Hz, 2H), 4.39 (d, J = 7.25 Hz, 1H), 5.86 (d, J = 2.4 Hz, 1H), 6.44 (s, 1H), 6.5 (dd, J = 9 Hz, J' = 2.6 Hz, 1H), 7.45 (m, 2H), 7.59 (t, J = 8 Hz, 1H), 7.84 (s, 1H), 7.86 (s, 1H), 7.91 (s, 2H), 7.93 (d,, J = 8.9 Hz, 1H). HRMS (EI) calcd for $C_{30}H_{39}N_1O_3S_1$: 494.2729; found, 494.2709. Anal. Calcd for $C_{30}H_{39}N_1O_3S_1$: C, 72.98; H, 7.96; N, 2.84. Found: C, 72.75; H, 8.17; N, 2.80.

General Method B. (+)-5-{4-[(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydro-1-benzothiepin-5-yl]phenoxy}-*N*,*N*,*N*-triethylpentan-1-aminium Bromide (18). To a stirred solution of pentyl bromide **17** (100 mg, 0.16 mmol; see procedure described later for this specific compound) in acetonitrile (3 mL) was added 166 mg of triethylamine (1.6 mmol). The mixture was stirred at 70 °C for 72 h. The mixture was concentrated in vacuo, and the residue was dissolved in dichloromethane. After addition of ether, the product was precipitated and isolated by filteration to give 80 mg of the title compound **18** as a white solid, mp 134−135 °C. ^{1}H NMR ($CDCl_3$) δ 0.91 (m, 6H), 1.26 (m, 6H), 1.42 (t, J = 6.90 Hz, 9H), 1.63 (m, 8H), 1.90 (m, 4H), 2.22 (m, 1H), 2.83 (s, 6H), 3.08 (m, 2H), 3.44 (m, 2H), 3.53 (m, 6H), 4.03 (m, 2H), 4.10 (m, 1H), 5.49 (s, 1H), 5.99 (s, 1H), 6.52 (d, J = 9 Hz, 1H), 6.91 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 7.8 Hz, 2H), 7.90 (d, J = 9.0 Hz, 1H). HRMS (ES^+) calcd for $C_{37}H_{61}N_2O_4S$ (M^+): 629.4352; found, 629.4346. Anal. Calcd for $C_{37}H_{61}N_2O_4S{\cdot}3H_2O{\cdot}0.5CH_3CN$: C, 58.17; H, 8.83; N, 3.74. Found: C, 57.81; H, 8.50; N, 3.76.

General Method C. (+)-(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-5-{3-[(dimethylamino)methyl]phenyl}-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-Dioxide (23). A solution of bromide **22** in 4 mL of dimethylamine (2.0 M in THF) was sealed in a tube and heated to 55 °C for 30 min, cooled, and evaporated. The resulting mixture was dissolved in ethyl acetate, washed with water, dried ($MgSO_4$), and evaporated. The yellow solid was chromatographed over silica gel to give a white solid, mp 97.6−99.0 °C. ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 6.8 Hz, 6H), 1.07−1.80 (m, 12H), 2.13−2.37 (m, 7H), 2.78 (s, 6H), 3.10 (ABq, J_{AB} = 15.1 Hz, $\Delta\nu$ = 34.6 Hz, 2H), 3.52 (s, 2H), 4.16 (d, 6.8 Hz, 1H), 5.53 (s, 1H), 5.91 (s, 1H), 6.51 (d, 8.9 Hz, 1H), 7.30−7.46 (m, 4H), 7.90 (d, 8.8 Hz, 1H). HRMS (FAB) calcd for $C_{29}H_{44}N_2O_3S$: 501.3151; found, 501.3159. Anal. Calcd for $C_{29}H_{44}N_2O_4S{\cdot}0.6H_2O$: C, 68.09; H, 8.91; N, 5.40. Found: C, 67.85; H, 8.59; N, 5.40.

General Method D. Individual procedures are described in the preparation of **26**−**30.**

(+)-2-[[[2-(Bromomethyl)-4-fluorophenyl]sulfonyl]-methyl]-2-butylhexanal (4). To a stirred solution of 17.5 g (123 mmol) of 2,5-difluorobenzaldehyde (Aldrich) in 615 mL of DMSO at ambient temperature was added 6.2 g (135 mmol) of lithium sulfide (Aldrich). The dark-red solution was stirred at 75 °C for 1.5 h or until the starting material was completely consumed, and then 34 g (135 mmol) of dibutyl mesylate aldehyde (ref 4) was added at about 50 °C. The reaction mixture was stirred at 75 °C for 3 h or until the reaction was completed. The cooled solution was poured into water and extracted with ethyl acetate. The combined extracts were washed with water several times, dried ($MgSO_4$), and concentrated in vacuo. Silica gel chromatographic purification of the crude product gave 23.6 g (59%) of fluorobenzene dialdehyde **10** as yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.05 Hz, 6H), 1.0−1.4 (m, 8H), 1.5−1.78 (m, 4H), 3.09 (s, 2H), 7.2−7.35 (m, 1H), 7.5−7.6 (m, 2H), 9.43 (s, 1H), 10.50 (d, J = 2.62 Hz, 1H).

To a solution of 22.6 g (69.8 mmol) of the dialdehyde **10** in 650 mL of THF at −60 °C was added 69.8 mL (69.8 mmol) of DIBAL (1 M in THF) via a syringe. The reaction mixture was stirred at −40 °C for 20 h. To the cooled solution at −40 °C was added a sufficient amount of ethyl acetate to quench the excess of DIBAL, followed by 3 N HCl. The mixture was extracted with ethyl acetate, washed with water, dried ($MgSO_4$), and concentrated in vacuo. Silica gel chromatographic purification of the crude product gave 13.5 g (58%) of recovered starting material and 8.1 g (36%) of the desired fluorobenzyl alcohol **11** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.05 Hz, 6H), 1.0−1.4 (m, 8H), 1.5−1.72 (m, 4H), 1.94 (br s, 1H), 3.03 (s, 2H), 4.79 (s, 2H), 6.96 (dt, J = 8.46, 3.02 Hz, 1H), 7.20 (dd, J = 9.47, 2.82 Hz, 1H), 7.42 (dd, J = 8.67, 5.64, 1H), 9.40 (s, 1H).

To a solution of 8.1 g (25 mmol) of benzyl alcohol **11** in 100 mL of DMF at −40 °C was added 47 g (50 mmol) of bromotriphenyphosphonium bromide (Aldrich). The resulting solution was stirred cold for 30 min, then was allowed to warm to 0 °C. To the mixture was added a 10% solution of sodium sulfite and ethyl acetate. The extract was washed a few times with water, dried ($MgSO_4$), and concentrated in vacuo. The mixture was stirred in a small amount of ethyl acetate/hexane mixture (1:4) and filtered through a pad of silica gel, eluting with same solvent mixture. The combined filtrate was concentrated in vacuo to give 9.5 g (98%) of the desired bromide product as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.05 Hz, 6H), 1.0−1.4 (m, 8H), 1.55−1.78 (m, 4H), 3.11 (s, 2H), 4.67 (s, 2H), 7.02 (dt, J = 8.46, 3.02 Hz, 1H), 7.15 (dd, J = 9.47, 2.82 Hz, 1H), 7.46 (dd, J = 8.67, 5.64, 1H), 9.45 (s, 1H).

To a solution of 8.5 g (25 mmol) of sulfide obtained from the previous step in 200 mL of CH_2Cl_2 at 0 °C was added 15.9 g (60 mmol) of mCPBA (Aldrich, 64% peracid). The resulting solution was stirred cold for 10 min, then was stirred at ambient temperature for 5 h. To the mixture was added 10% solution of sodium sulfite and ethyl acetate. The extract was washed several times with saturated Na_2CO_3, dried ($MgSO_4$), and concentrated in vacuo to give 10.2 g (98%) of the desired product **4** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7.05 Hz, 6H), 1.03−1.4 (m, 8H), 1.65−1.82 (m, 2H), 1.90−2.05 (m, 2H), 3.54 (s, 2H), 5.01 (s, 2H), 7.04−7.23 (m, 1H), 7.30 (dd, J = 8.87, 2.42 Hz, 1H), 8.03 (dd, J = 8.86, 5.64, 1H), 9.49 (s, 1H).

(+)-(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-5-(3-hydroxyphenyl)-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-Dioxide (7a). Following a similar procedure as described in the preparation of compound **7b**, **16a** was used to prepare the title compound as a solid. ^{1}H NMR ($CDCl_3$) δ 0.82−0.96 (m, 6H), 1.0−1.7 (m, 13H), 2.2 (td, J = 13.5, 3.6 Hz, 1H), 2.83 (s, 6H), 3.4 (ABq, J_{AB} = 15 Hz, 2H), 4.13 (br s, 1H), 5.48 (s, 1H), 6.08 (d, J = 2.1 Hz, 1H), 6.56 (dd, J = 9.8, 2.1 Hz, 1H), 6.82 (dd, J = 8.1, 2.1 Hz, 1H), 6.99−7.1 (m, 2H), 7.23−7.32 (m, 1H), 7.91 (d, J = 9.6 Hz, 1H). HRMS calcd for $C_{26}H_{38}NO_4S$: 460.2522; found, 460.2516.

(+)-(4*R*,5*R*)-5-(4′-Hydoxyphenyl)-7-(dimethylamino)-tetrahydrobenzothiepine 1,1-Dioxide (7b). To a solution of 47 g (99 mmol) of (dimethylamino)tetrahydrobenzothiepine 1,1-dioxide **16b** in 500 mL of methylene chloride at −10 °C was added dropwise a solution of boron tribromide (297 mL, 1 M in methylene chloride, 297 mmol), and the resulting solution was stirred cold (−5 to 0 °C) for 1 h or until the reaction was complete. The mixture was cooled to −10 °C, and the reaction was slowly quenched with 300 mL of water. The mixture was warmed to 10 °C and further diluted with 300 mL of saturated sodium bicarbonate solution to neutralize the mixture. The aqueous layer was separated and extracted with 300 mL of methylene chloride, and the combined extracts were washed with 200 mL of water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was dissolved in 500 mL of ethyl acetate and stirred with 50 mL of glacial acetic acid for 30 min at ambient temperature. The mixture was washed twice with 200 mL of water and 200 mL of brine, dried over $MgSO_4$, and concentrated in vacuo to give the crude 4-hydroxyphenyl intermediate. The solid residue was recrystallized from methylene chloride to give 37.5 g (82%) of the desired title compound as a white solid. ^{1}H NMR ($CDCl_3$) δ 0.84−0.97 (m, 6H), 1.1−1.5 (m, 10H), 1.57−1.72 (m, 1H), 2.14−2.28 (m, 1H), 2.83 (s, 6H), 3.00 (d, J = 15.3 Hz, 1H), 3.16 (d, J = 15.3 Hz, 1H), 4.11 (s, 2H), 5.48 (s, 1H), 6.02 (d, J = 2.4 Hz, 1H), 6.55 (dd, J = 9, 2.4 Hz, 1H), 6.88 (d, 8,7 Hz, 2H), 7.38 (d, J = 8.7 Hz, 2H), 7.91 (d, J = 9 Hz, 2H).

(+)-(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-5-(1-naphthyl)-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-Dioxide (14). Please see General Method A.

(+)-(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-5-(3-methoxyphenyl)-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-Dioxide (16a). Following a similar procedure as described in the preparation of **75** in the preceding paper,[4] the title compound **16a** was prepared as a white foam. ^{1}H NMR ($CDCl_3$) δ 0.8−0.95 (m, 6H), 1.1−1.68 (m, 13H), 2.2 (td, J = 13.5, 3.6 Hz, 1H), 2.80 (s, 6H), 3.08 (ABq, J_{AB} = 15 Hz, 2H), 3.82 (s, 3H), 4.13 (br s, 1H), 5.48 (s, 1H), 6.04 (m, 1H), 6.53 (dd, J = 8.7, 2.7 Hz, 1H), 6.83 (dd, J = 8.4, 2.1 Hz, 1H), 7.0 (br s, 1H), 7.31 (t, J = 8.1 Hz, 1H), 7.9 (d, J = 9 Hz, 1H). HRMS calcd for $C_{27}H_{40}NO_4S$: 474.2678; found, 474.2692.

(+)-(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-5-{4-[(5-bromopentyl)oxy]phenyl}-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-Dioxide (17). To a stirred solution of 500 mg of phenol **7b** (1.1 mmol) in DMF (5 mL) at −10 °C was added 36 mg of NaH (1.4 mmol). After stirring at −10 °C for 30 min, 1.25 g of 1,5-dibromopentane (5.45 mmol) was added to the reaction mixture and stirred at −10 °C for 30 min and room temperature for 1 h. The reaction was quenched with water in an ice bath, and the sample was extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude was purified on silica gel with 15% ethyl acetate/hexane to afford 470 mg of the title compound **17** as a light-yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.91 (m, 6H), 1.27 (m, 10H), 1.66 (m, 4H), 1.85 (m, 2H), 1.95 (m, 2H), 2.21 (m, 1H), 2.85 (s, 6H), 3.09 (m, 2H), 3.47 (t, J = 6.75 Hz, 2H), 4.01 (t, J = 6.30 Hz, 2H), 4.12 (s, 1H), 5.49 (s, 1H), 6.17 (d, J = 1.8 Hz, 1H), 6.71 (dd, J = 8.70 Hz, 2.40 Hz, 1H), 6.94 (d, J = 8.70 Hz, 2H), 7.41 (d, J = 8.40 Hz, 2H), 7.95 (d, J = 8.70 Hz, 1H).

(+)-5-{4-[(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydro-1-benzothiepin-5-yl]-phenoxy}-*N*,*N*,*N*-triethylpentan-1-aminium Bromide (18). Please see General Method B.

(+)-3-[(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydro-1-benzothiepin-5-yl]-phennyl Trifluoromethanesulfonate (19). A solution of 10.17 g (22.13 mmol) of phenol **7a** in pyridine (42 mL) at 0 °C under N_2 was treated with triflic anhydride (4.1 mL, 24.4 mmol, 1.1 equiv) dropwise. Upon completion of the addition, the bath was removed and the reaction mixture was stirred at room temperature for 21 h. The pyridine was removed in vacuo, and the resulting oil was taken up in water (100 mL) and extracted three times with ethyl acetate (45 mL each). The combined organics were washed with 2 N HCl (100 mL), 10% $CuSO_4$ (100 mL), and brine (100 mL). The combined extracts were dried over $MgSO_4$ and filtered, and volatiles were evaporated. The residue was purified by chromatography on silica gel (25% EtOAc in hexane) to afford the desired title compound **19** as a pale-yellow foam (11.42 g, 87.2%). ^{1}H NMR (CD_3OD) δ 0.85−1.0 (m, 6H), 1.0−1.15 (m, 10H), 1.76 (t, J = 12.6 Hz, 1H), 2.12 (t, J = 13 Hz, 1H), 2.79 (s, 6H), 3.1−3.2 (ABq, 2H), 4.05 (s, 1H), 5.42 (s, 1H), 5.88 (d, J = 2.1 Hz, 1H), 6.59 (dd, J = 8.9, 2.1 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.66 (s, 1H), 7.77 (d, J = 8.9 Hz, 1H).

(+)-Methyl 3-[(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydro-1-benzothiepin-5-yl]benzoate (20). Carbon monoxide gas was purged for 30 min through a solution of 800 mg (1.35 mmol) of triflate **19**, Pd(OAc)2 (30 mg, 0.135 mmol), dppf (150 mg, 0.27 mmol), and Et_3N (273 mg, 2.7 mmol) in 7 mL of anhydrous DMF and 3.5 mL of methanol. The resulting solution was heated at 65 °C under a carbon monoxide atmosphere for 3 h. The mixture was filtered through a pad of Celite, washed with ethyl acetate, poured into a solution of 1 N HCl, extracted twice with ethyl acetate, dried ($MgSO_4$), and evaporated. Silica gel chromatographic purification of the resulting orange solid provided the title compound **20** as a white solid, mp 104.5−106.1 °C. ^{1}H NMR ($CDCl_3$) δ 0.90 (m, 6H), 1.07−1.76 (m, 13H), 2.22 (m, 1H), 2.77 (s, 6H), 3.09 (ABq, J_{AB} = 14.9 Hz, $\Delta\nu$ = 45.5 Hz, 2H), 3.92 (s, 3H), 4.13 (s, 1H), 5.60 (s, 1H), 5.83 (s, 1H), 6.52 (m, 1H), 7.45−7.57 (m, 1H), 7.75 (m, 1H), 8.02 (m, 1H) 8.15 (s,1H). HRMS (FAB) calcd for $C_{28}H_{39}NO_5S$: 502.2627; found, 502.2650. Anal. Calcd for $C_{28}H_{39}NO_5S$: C, 67.04; H, 7.84; N, 2.79. Found: C, 67.52; H, 8.13; N, 2.75.

(+)-(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-5-[3-(hydroxymethyl)phenyl]-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-Dioxide (21). To a solution of 463 mg (0.92 mmol) of ester **20** in 5 mL of THF at 0 °C was added 2.7 mL of lithium aluminum hydride (1 M in THF). The resulting solution was warmed to room temperature and stirred overnight. The reaction was quenched with water, and the solid was filtered and washed with ethyl acetate. The filtrate was washed with brine, dried ($MgSO_4$), evaporated, and purified (SiO_2) to provide the title compound alcohol **21** as a white solid. ^{1}H NMR ($CDCl_3$) δ 0.90 (m, 6H), 1.07−1.76 (m, 13H), 2.23 (m, 1H), 2.79 (s, 6H), 3.00 (ABq, J_{AB} = 15.1 Hz, $\Delta\nu$ = 47.3 Hz, 2H), 4.14 (d, J = 7.1 Hz, 1H), 4.72 (s, 2H), 5.56 (s, 1H), 5.96 (s, 1H), 6.52 (d, J = 8.6 Hz, 1H), 7.32−7.50 (m, 4H), 7.90 (d, 8.8 Hz, 1H). HRMS (FAB) calcd for $C_{27}H_{39}NO_4S$: 474.2678; found, 474.2690.

(+)-(4*R*,5*R*)-5-[3-(Bromomethyl)phenyl]-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-Dioxide (22). To a solution of 395 mg (0.83 mmol) of alcohol **21** in 5 mL of DMF at −40 °C was added triphenylphosphonium dibromide (700 mg, 1.66 mmol) as a solid, and the resulting mixture was stirred at −40 °C for 10 min, warmed to 0 °C, and stirred for 30 min. The reaction was quenched at −40 °C with 10% Na_2SO_3. The mixture was warmed to room temperature, extracted three times with ethyl acetate, dried ($MgSO_4$), filtered through a pad of SiO_2, eluted with 25% ethyl acetate/hexane, and evaporated to give the title compound **22** as a white solid. ^{1}H NMR ($CDCl_3$) δ 0.90−1.0 (m, 6H), 1.0−1.7 (m, 12H), 2.25 (t, J = 15.6 Hz, 1H), 2.82 (s, 6H), 3.1 (ABq, J_{AB} = 15.5 Hz, $\Delta\nu$ = 47.3 Hz, 2H), 4.1−4.2 (m, 1H), 4.55 (dd, J = 13.1, 16.6 Hz, 2H), 5.55 (s, 1H), 5.95 (m, 1H), 6.55 (dd, J = 3, 9.3 Hz, 1H), 7.3−7.45 (m, 3H), 7.6 (s, 1H), 7.92 (d, J = 9.4 Hz, 1H). HRMS (FAB) calcd for $C_{27}H_{38}NO_3SBr$: 536.1834; found, 536.1822.

(+)-(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-5-{3-[(dimethylamino)methyl]phenyl}-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-Dioxide (23). Please see General Method C.

(+)-*N*-{3-[(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydro-1-benzothiepin-5-yl]-benzyl}-*N*,*N*-dimethylmethanaminium Iodide (24). Following a similar procedure as in General Method C, bromide **22** was treated with trimethylamine to give the title compound **24** as a solid. ^{1}H NMR (CD_3OD) δ 0.90 (m, 6H), 1.07−1.61 (m,

12H), 1.84 (m, 1H), 2.18 (m, 1H), 2.79 (s, 6H), 3.13 (m, 10H), 4.12 (s, 1H), 4.57 (s, 2H), 5.46 (s, 1H), 5.88 (s, 1H), 6.61 (d, 6.5 Hz, 1H), 7.60 (m, 2H), 7.69 (m, 1H), 7.79 (d, 8.9 Hz, 1H), 7.87 (m, 1H). HRMS (FAB) calcd for $C_{30}H_{47}N_2O_3SBr$: 515.3307; found, 515.3311.

(+)-(4*R*,5*R*)-5-(3-Aminophenyl)-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-Dioxide (25). To a solution of 11.41 g (19.28 mmol) of the triflate **19**, palladium(II) acetate (433 mg, 1.93 mmol, 10 mol %), racemic BINAP (1.41 g, 2.26 mmol, 12 mol %), and cesium carbonate (8.86 g, 27.2 mmol, 2.0 equiv) in 114 mL of THF was added 6.6 mL (39.4 mmol, 2.0 equiv) of benzophenone imine. The mixture was stirred at reflux for 4 h and filtered through Celite, and the solvent was removed in vacuo providing 19.11 g of the crude imine as a deep-red foam. ^{1}H NMR ($CDOD_3$) δ 0.8−1.45 (m, 16H), 1.6−1.75 (m, 1H), 1.9−2.05 (m, 1H), 2.78 (s, 6H), 2.98−3.15 (ABq, 2H), 3.88 (s, 1H), 5.17 (s, 1H), 5.92 (d, J = 2.2 Hz, 1H), 6.54 (dd, J = 9.1, 2.7 Hz, 1H), 6.74 (d, J = 8.1 Hz, 1H), 6.80 (br s, 1H), 7.0−7.12 (m, 2H), 7.15−7.25 (m, 3H), 7.35−7.52 (m, 7H), 7.52−7.68 (m, 2H), 7.71 (d, J = 7.9 Hz, 1H).

To a solution of 19.1 g of the above crude imine in CH_3OH (200 mL) was added sodium acetate (6.33 g, 77.2 mmol) and hydroxylamine hydrochloride (4.02 g, 57.9 mmol). After the mixture was stirred for 1 h, 1 N NaOH (100 mL) was added and the mix was extracted with CH_2Cl_2 (2 × 100 mL, 1 × 50 mL). The combined organics were washed with brine (100 mL), dried over $MgSO_4$, and filtered, and the solvent was evaporated. The residue was purified by chromatography on silica gel (50% EtOAc in hexane) to afford the desired amino compound **25** as a white solid (8.64 g, 97.9%), mp 142−143 °C. ^{1}H NMR ($CDCl_3$) δ 0.92 (m, 6H), 1.25 (m, 12H), 2.23 (dt,, J = 12.3, 2.6 Hz, 1H), 2.83 (s, 6H), 3.10 (ABq, J_{AB} = 48.6 Hz, J' = 15 Hz, 2H), 4.14 (br s, 1H), 4.40 (br, 2H), 5.45 (s, 1H), 6.08 (d, J = 2.4 Hz, 1H), 6.51 (dd, J = 9, 2.6 Hz, 1H), 6.71 (br d, J = 7.8 Hz, 1H), 6.88 (br s, 1H), 6.97 (br d, J = 7.7 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.90 (d, J = 8.9 Hz, 1H). HRMS (EI) calcd for $C_{26}H_{38}N_2O_3S_1$: 459.2681; found, 459.2664.

(+)-*N*-{3-[(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydro-1-benzothiepin-5-yl]-phenyl}glycylglycine (26). To a solution of 141 mg (0.78 mmol) of *N*-(choloracetyl)glycine ethyl ester and 300 mg (0.65 mmol) of **25** in 10 mL of acetone were added 108 mg (0.78 mmol) of potassium carbonate and 20 mg of tetrabutylammonium iodide, and the resulting mixture was stirred at reflux for 6 days. During the heating period, more chloroacetyl (25 mg, and 60 mg) and potassium carbonate (50 mg) were added. The mixture was evaporated and partitioned between ethyl acetate and water. The combined organic layer was dried and concentrated in vacuo to give 205 mg of the ester precursor. HRMS (EI, M + H) calcd for $C_{32}H_{47}N_3O_6S_1$: 602.3264; found, 602.3279.

To a solution of 170 mg (0.28 mmol) of the ester obtained above in 3 mL of THF and 3 mL of water was added 35 mg of lithium hydroxide monohydrate, and the resulting solution was stirred at 45 °C for 1 h. The reaction mixture was stirred at room termperature for 2 h and acidified with 1 N hydrochloric acid until the solution turned cloudy. The mixture was extracted with ethyl acetate and washed with water, dried, and concentrated in vacuo to give 100 mg of the title compound **26** as a white solid. ^{1}H NMR ($CDCl_3$) δ 0.90 (m, 6H), 1.15−1.62 (m, 12H), 2.19 (m, 1H), 2.78 (s, 6H), 3.07 (ABq, J_{AB} = 15.0 Hz, $\Delta\nu$ = 44.6 Hz, 2H), 3.82 (s, 3H), 3.98 (s, 2H), 4.13 (s, 1H), 5.39 (s, 1H), 6.07 (s, 1H), 6.49 (d, J = 7.5 Hz, 1H), 6.56 (d, J = 8.0 Hz, 1H), 6.95 (s, 1H), 7.19 (s, 1H), 7.24 (m, 1H), 7.85 (d, J = 8.9 Hz, 1H). HRMS (ES) calcd for $C_{30}H_{43}N_3O_6S$: 574.2950; found, 574.2940. Anal. Calcd for $C_{30}H_{43}N_3O_6S\cdot 0.6H_2O$: C, 61.64; H, 7.62; N, 7.19. Found: C, 61.59; H, 7.41; N, 6.84.

(+)-(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-5-[3-(4-pyridinylamino)phenyl]-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-Dioxide (27). A solution of 600 mg (1.31 mmol) of **25** and 300 mg (1.54 mmol) of 4-bromopyridine hydrochloride salt in 4 mL of absolute ethanol was stirred at 58 °C for 45 h, and the volatiles were evaporated. The residue was dissolved in ethyl acetate, washed with aqueous sodium bicarbonate, dried, and concentrated in vacuo, and the desired product was purified by silica gel chromatography (0−10% ethanol/dichloromethane) to yield 660 mg (91% yield) of pyridine **27** as an off-white solid, mp 147−150 °C. ^{1}H NMR ($CDCl_3$) δ 0.84−0.94 (m, 6H), 1.11−1.52 (mm, 10H), 1.62 (br t, J = 13 Hz, 1H), 2.22 (br t, J = 13 Hz, 1H), 2.81 (s, 6H), 3.07 (q_{ab}, J = 15.3, 45.3 Hz, 2H), 4.12−4.14 (m, 1H), 5.50 (s, 1H), 5.98 (d, J = 2.7 Hz, 1H), 6.47 (br s, 1H), 6.51 (dd, J = 2.7, 9.0 Hz, 1H), 6.80 (d, J = 6.3 Hz, 2H), 7.18 (dd, J = 1.2, 8.4 Hz, 1H), 7.26−7.43 (m, 3H), 7.89 (d, J = 9.0 Hz, 1H), 8.21 (d, J = 5.7 Hz, 2H). HRMS (EI) calcd for $C_{31}H_{42}N_3O_3S$: 536.2947; found, 536.2939. Anal. Calcd for $(C_{31}H_{42}N_3O_3S\cdot 0.5H_2O\cdot 0.3C_4H_8O_2$: C, 67.71; H, 7.83; N, 7.35. Found: C, 67.68; H, 7.87; N, 7.34.

(+)-4-({3-[(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydro-1-benzothiepin-5-yl]-phenyl}amino)-1-methylpyridinium Iodide (28). A solution of 240 mg (0.45 mmol) of **27** and 29 μL (0.47 mmol) of iodomethane in 4 mL of acetonitrile was stirred at room temperature for 48 h, and solid was collected by filtration and triturated with diethyl ether to yield the desired product **28** as a colorless solid, mp 258−262 °C. ^{1}H NMR ($CDCl_3$) δ 0.78−0.87 (m, 6H), 0.97−1.46 (mm, 10H), 1.57 (br t, J = 11 Hz, 1H), 2.12 (br t, J = 11 Hz, 1H), 2.75 (s, 6H), 3.02 (s, 2H), 3.97 (s, 3H), 4.04 (d, J = 7.5 Hz, 1H), 5.38 (s, 1H) 5.85 (d, J = 2.1 Hz, 1H), 6.42 (dd, J = 2.4, 8.7 Hz, 1H), 7.12−7.55 (mm, 7H), 7.77 (d, J = 8.7 Hz, 1H), 8.00 (d, J = 6.9 Hz, 2H), 10.47 (s, 1H). HRMS (FAB) calcd for $C_{32}H_{44}N_3O_3S$: 550.3103; found, 550.3088. Anal. Calcd for $(C_{32}H_{44}N_3O_3S\cdot 0.25H_2O$: C, 56.34; H, 6.57; N, 6.15. Found: C, 56.35; H, 6.37; N, 6.13.

(+)-5-({3-[(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydro-1-benzothiepin-5-yl]-phenyl}amino)-*N*,*N*,*N*-triethyl-5-oxo-1-pentanaminium Trifluoroacetate (30). Aniline **25** was acylated with 5-chlorovalery chloride, and the resulting chloride **29** was treated with triethylamine as in General Method B to provide the desired title compound **30** as a solid. ^{1}H NMR ($CDCl_3$) δ 0.80−0.96 (m, 6H), 0.99−1.54 (m, 21 H), 1.59−1.84 (m, 4H), 2.09−2.24 (m, 1H), 2.45−2.58 (m, 2H), 2.81 (s, 6H), 3.09 (ABq, J_{AB} = 15.6 Hz, ΔV=18.5 Hz, 2H), 3.13−3.31 (m, 8H), 4.16 (s, 1H), 5.44 (s, 1H), 6.08 (d, J = 1.8 Hz, 1H), 6.57 (dd, J = 9.3 and 2.7 Hz, 1H), 7.24 (t, J = 7.5 Hz, 1H), 7.34 (t, J = 8.4 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.74 (s, 1H), 7.88 (d, J = 9.0 Hz, 1H), 9.22 (s, 1H). HRMS (FAB^+) calcd for $C_{37}H_{60}N_3O_4S$: 642.4304; found, 642.4343.

(+)-(4*R*,5*R*)-5-(4′-Methylthiophenyl)-7-(dimethylamino)-tetrahydrobenzothiepine 1,1-dioxide (33). Following a similar procedure as in General Method A, the title compound **33** was prepared from 4-methylthiophenylboronic acid and **4** as a solid. ^{1}H NMR ($CDCl_3$) δ 0.8−1.0 (m, 6H), 1.0−1.72 (m, 13H), 1.55−1.7 (m, 1H), 2.13−2.25 (m, 1H), 2.51 (s, 3H), 2.82 (s, 6H), 3.00 (d, J = 15.1 Hz, 1H), 3.16 (d, J = 15.1 Hz, 1H), 4.10 (s, 1H), 5.50 (s, 1H), 6.0−6.2 (m,1H), 6.6−6.75 (m, 1H), 7.25 (d, J = 7.9 Hz, 1H), 7.43 (d, J = 8 Hz, 1H), 7.9 (d, J = 7.5 Hz, 1H). MS (ESI): *m/z* 490 (M + H, 100).

(+)-(4*R*,5*R*)-5-(4′-*tert*-Butylphenyl)-7-(dimethylamino)-tetrahydrobenzothiepine 1,1-Dioxide (34). Following a similar procedure as in General Method A, the title compound **34** was prepared from 4-*tert*-butyphenylboronic acid and **4** as a white solid, mp 195.5−196 °C. ^{1}H NMR ($CDCl_3$) δ 0.90 (m, 6H), 1.33 (s, 9H), 1.40 (m, 12H), 2.25 (br t, J = 12.3 Hz, 1H), 2.77 (s, 6H), 3.06 (ABq, J_{AB} = 46 Hz, J' = 15 Hz, 2H), 4.15 (s, 1H), 5.50 (s, 1H), 5.95 (d, J = 2.4 Hz, 1H), 6.47 (dd, J = 9, 2.6 Hz, 1H), 7.40 (s, 4H), 7.89 (d, J = 8.9 Hz, 1H). HRMS (EI) calcd for $C_{30}H_{45}N1O_3S$: 500.3198; found, 500.3189.

(+)-Methyl 4-[(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydro-1-benzothiepin-5-yl]benzoate (35). Following a similar procedure as in the preparation of ester **20**, the title compound **35** was prepared from **7b** as a solid, mp 219.3−220.1 °C. ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 6.6 Hz, 6H), 1.07−1.80 (m, 12H), 2.19 (m, 1H), 2.80 (s, 6H), 3.10 (ABq, J_{AB} = 14.9 Hz, $\Delta\nu$ = 46.8 Hz, 2H), 3.94 (s, 3H), 4.12 (s, 1H), 5.60 (s, 1H), 5.97 (d, J = 2.2 Hz,

1H), 6.76 (d, J = 6.8 Hz, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.94 (d, J = 8.9 Hz, 1H), 8.09 (d, J = 8.3 Hz, 2H). HRMS (FAB) calcd for $C_{28}H_{39}NO_5S$: 502.2627; found, 502.2619. Anal. Calcd for $C_{28}H_{39}NO_5S$: C, 67.04; H, 7.84; N, 2.79. Found: C, 67.07; H, 7.99; N, 2.79.

(+)-4-[(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydro-1-benzothiepin-5-yl]benzoic Acid (36). Ester **35** was hydrolyzed with LiOH as described in the preparation of **26** to provide the title compound **36** as a solid. ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 6.6 Hz, 6H), 1.07−1.80 (m, 12H), 2.21 (m, 1H), 2.80 (s, 6H), 3.10 (ABq, J_{AB} = 15.1 Hz, $\Delta\nu$ = 48.9 Hz, 2H), 4.13 (s, 1H), 5.63(s, 1H), 5.89 (s, 1H), 6.56 (d, J = 8.8 Hz, 1H), 7.65 (d, J = 7.9 Hz, 2H), 7.92 (d, J = 8.9 Hz, 1H), 8.16 (d, J = 8.1 Hz, 2H). HRMS (FAB) calcd for $C_{27}H_{37}NO_5S$: 488.2471; found, 488.2474. Anal. Calcd for $C_{27}H_{37}NO_5S$: C, 66.50; H, 7.65; N, 2.87. Found: C, 66.42; H, 7.75; N, 2.82.

(+)-(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-5-[4-(hydroxymethyl)phenyl]-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-Dioxide (37). Following a similar procedure as in the preparation of alcohol **21**, the title compound **37** was prepared from **35** as a solid. ^{1}H NMR ($CDCl_3$) δ 0.90 (m, 6H), 1.07−1.72 (m, 13H), 2.22 (m, 1H), 2.80 (s, 6H), 3.08 (ABq, J_{AB} = 15.1 Hz, $\Delta\nu$ = 42.04 Hz, 2H), 4.12 (d, J = 5.0 Hz, 1H), 4.75 (s, 2H), 5.54 (s, 1H), 5.98 (s, 1H), 6.53 (d, J = 6.8 Hz, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 7.9 Hz, 2H), 7.90 (d, J = 8.8 Hz, 1H). HRMS (FAB) calcd for $C_{27}H_{39}NO_4S$: 474.2678; found, 474.2655. Anal. Calcd for $C_{27}H_{39}NO_4S$: C, 68.46; H, 8.30; N, 2.96. Found: C, 68.67; H, 8.53; N, 2.88.

(+)-(4*R*,5*R*)-3,3-Dibutyl-5-{4-[(diethylamino)methyl]-phenyl}-7-(dimethylamino)-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-Dioxide (38). Following a similar procedure as in General Method C, the title compound **38** was prepared from the corresponding benzyl bromide and diethylamine as a colorless solid, mp 119−120 °C. ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7.2 Hz, 6H), 1.09 (t, J = 6.9 Hz, 6H), 1.15−1.75 (mm, 12H), 2.24 (br t, J = 7.5 Hz, 1H), 2.55−2.69 (m, 4H), 2.78 (s, 6H), 3.08 (q_{ab}, J = 15.3, 45.0 Hz, 2H), 3.68 (br s, 2H), 4.14 (d, J = 7.5 Hz, 1H), 5.53 (s, 1H), 5.90 (d, J = 2.4 Hz, 1H), 6.51 (dd, J = 6.6, 2.4 Hz, 1H), 7.42 (q_{ab}, J = 7.8, 13.2 Hz, 4H), 7.89 (d, J = 8.7 Hz, 1H). HRMS (FAB) calcd for $C_{31}H_{49}N_2O_3S$: 529.3464; found, 529.3380. Anal. Calcd for $C_{31}H_{48}N_2O_3S\cdot0.3C_2O_2F_3H$: C, 67.41; H, 8.64; N, 4.97. Found: C, 67.39; H, 8.86; N, 4.81.

(+)-(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-5-(3,4-difluorophenyl)-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-Dioxide (39). Following a similar procedure as described in the preparation of **75** in the preceding paper,[4] the title compound **39** was prepared as a solid, mp 183.8−183.9 °C. ^{1}H NMR ($CDCl_3$) δ 0.91(m, 6H), 1.03−1.52 (m, 11H), 1.62 (m, 1H), 2.19 (m, 1H), 2.85 (s, 6H), 3.07 (ABq, J_{AB} = 15 Hz, $\Delta\nu$ = 55.9 Hz, 2H), 4.05 (s, 1H), 5.50 (s, 1H), 5.95 (s, 1H), 6.60 (d, J = 8.9 Hz, 1H), 7.20 (m, 2H), 7.41 (m, 1H), 7.97 (d, J = 8.7, 1H). HRMS (FAB) calcd for $C_{26}H_{35}F_2O_3S$: 480.2384; found, 480.2391. Anal. Calcd for $C_{26}H_{35}F_2O_3S$: C, 65.11; H,7.36; N, 2.92. Found: C, 65.21; H, 7.52; N, 2.81.

(+)-(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-5-(3,4-dimethoxyphenyl)-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-Dioxide(40). Following a similar procedure as described in the preparation of **75** in the preceding paper,[4] 3,4-dimethoxybenzene was used to prepare the title compound **40** as a solid, mp 158−159 °C. ^{1}H NMR ($CDCl_3$) δ 0.84−0.94 (m, 6H), 1.02−1.72 (mm, 12H), 2.19 (dt, J = 12.0, 3.0 Hz, 1H), 2.82, (s, 6H), 3.06 (q_{ab}, J = 12.0, 48.0 Hz, 2H), 3.87 (s, 3H), 3.91 (s, 3H), 4.12 (br d, J = 6.0 Hz, 1H), 5.45 (s, 1H), 6.04 (d, J = 2.4 Hz, 1H), 6.52 (dd, J = 9.0, 2.4 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.97 (br s, 1H), 7.10 (br d, J = 8.4, Hz, 1H), 7.90 (d, J = 9.0 Hz, 1H). HRMS (FAB) calcd for $C_{28}H_{42}NO_5S$: 504.2784; found, 504.2765. Anal. Calcd for $C_{28}H_{41}NO_5S$: C, 66.77; H, 8.20; N, 2.78. Found: C, 67.11; H, 8.22; N, 2.76.

(+)-4-[(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydro-1-benzothiepin-5-yl]-1,2-benzenediol (41). A solution of 5-(3′,4′-dimethoxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine 1,1-dioxide (1.0 g, 2.0 mmol) in CH_2Cl_2 (8 mL) at −78 °C under N_2 was treated with BBr_3 (11.9 mL of a 1.0 M solution in CH_2Cl_2, 11.9 mmol, 6.0 equiv) and stirred at −78 °C for 30 min, then at 0 °C for 1 h. The mixture was carefully quenched by the addition of H_2O (25 mL) at −20 °C and was diluted with 1 N HCl (25 mL), stirred for 30 min at 25 °C, and extracted with EtOAc (4 × 50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 × 50 mL) and saturated aqueous NaCl (50 mL) and were dried ($MgSO_4$) and concentrated to give a pale-green oil. The oil was dissolved in CH_2Cl_2 (5 mL) and allowed to stand at 25 °C overnight, during which time a white solid crystallized. The solid was collected (30% Et_2O/hexane wash) to give the title compound **41** (0.91 g, 97%) as a white crystalline solid. ^{1}H NMR ($CDCl_3$) δ 0.89−0.94 (m, 6H), 1.15−1.51 (br m, 10H), 1.82 (m, 1H), 2.09 (m, 1H), 2.82 (s, 6H), 3.19 (ABq, J_{AB} = 14.9 Hz, J = 22.3 Hz, 2H), 4.08 (s, 1H), 5.17 (s, 1H), 6.20 (d, J = 2.6 Hz, 1H), 6.56 (dd, J = 8.9, 2.6 Hz, 1H), 6.81 (s, 1H), 6.90 (br s, 2H), 7.74 (d, J = 8.9 Hz, 1H). HRMS calcd for $C_{26}H_{37}NO_5S$: 476.2461; found, 476.2458.

(+)-(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-5-(3-fluoro-4-methxoyphenyl)-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-Dioxide (42). Following a similar procedure as described in the preparation of **75** in the preceding paper,[4] 3-fluoro-4-methoxybenzene was used to prepare the title compound **42** as a solid, mp 202−202.5 °C. ^{1}H NMR ($CDCl_3$) δ 0.87−0.95 (m, 6H), 1.04−1.70 (mm, 12H), 2.20 (dt, J = 15.0, 2.4 Hz, 1H), 2.83 (s, 6H), 3.06 (q_{ab}, J_{ab}= 15, 54.0 Hz, 2H), 3.92 (s, 3H), 4.06 (d, J = 7.5 Hz, 1H), 5.46 (s, 1H), 5.98 (d, J = 2.4 Hz, 1H), 6.53 (dd, J = 2.4, 9.0 Hz, 1H), 6.99 (t, J = 8.4 Hz, 1H), 7.17 (br d, J = 8.4 Hz, 1H), 7.24 (dd, J = 2.1, 12.0 Hz, 1H), 7.90 (d, J = 9.0 Hz, 1H). ^{19}F NMR ($CDCl_3$) δ −135.35 (dd, J = 12.9, 9.6 Hz). HRMS (EI) calcd for $C_{27}H_{39}NO_4SF$: 492.2584; found, 492.2597. Anal. Calcd for $C_{27}H_{38}NO_4SF$: C, 66.27; H, 7.84; N, 2.81. Found: C, 66.25; H, 7.98; N, 2.80.

(+)-*N*-{4-[(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydro-1-benzothiepin-5-yl]-benzyl}-*N*,*N*-diethylethanaminium Iodide (43). Following a similar procedure as in General Method C, the title compound **43** was prepared from the corresponding benzyl bromide as an off-white solid, mp 212−212.5 °C. ^{1}H NMR ($CDCl_3$) δ 0.72−0.82 (m, 6H), 0.88−1.51 (mm, 12H), 2.07 (br t, J = 12.3 Hz, 1H), 2.58 (br s, 9H), 2.66 (s, 6H), 2.97 (q_{ab}, J = 6.3, 21.6 Hz, 2H), 3.22−3.36 (m, 6H), 3.92 (s, 1H), 4.48−4.60 (m, 2H), 5.34 (s, 1H), 5.73 (s, 1H), 6.41 (d, J = 7.2 Hz, 1H), 7.42 (d, J = 8.1 Hz, 2H), 7.53 (d, J = 7.5 Hz, 2H), 7.72 (d, J = 8.7 Hz, 1H). HRMS (FAB) calcd for $C_{33}H_{53}N_2O_3S$: 557.3777; found, 557.3745. Anal. Calcd for $C_{33}H_{53}IN_2O_3S$: C, 57.88; H, 7.80; N, 4.08. Found: C, 57.99; H, 8.03; N, 4.21.

(+)-{4-[(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydro-1-benzothiepin-5-yl]-phenyle}-*N*,*N*,*N*-trimethylmethanaminium Iodide (44). Following a similar procedure as in General Method C, the title compound **44** was prepared from the corresponding benzyl bromide as an off-white solid, mp 217−218 °C. ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.2 Hz, 6H), 1.0−1.60 (mm, 12H), 1.69 (br s, 1H), 2.22 (t, J = 12.3 Hz, 1H), 2.77 (s, 6H), 3.06 (q_{ab}, J = 15.3, 43.8 Hz, 2H), 3.44 (s, 9H), 4.08 (s, 1H), 5.00 (q_{ab}, J = 12.6, 37.2 Hz, 2H), 5.55 (s, 1H), 5.77 (d, J = 2.4 Hz, 1H), 6.50 (dd, J = 9.0, 2.4 Hz, 1H), 7.67 (q_{ab}, J = 8.4, 9.0 Hz, 4H), 7.86 (d, J = 8.7 Hz, 1H). HRMS (FAB) calcd for $C_{30}H_{47}N_2O_3S$: 515.3307; found, 515.3283. Anal. Calcd for $C_{30}H_{47}IN_2O_3S$: C, 56.07; H, 7.37; N, 4.36. Found: C, 56.06; H, 7.41; N, 4.32.

(+)-1-{4-[(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydro-1-benzothiepin-5-yl]-benzyl}pyridinium Bromide (45). Following a similar procedure as in General Method C, the title compound **45** was prepared from the corresponding benzyl bromide as a solid, mp 170.2−171.8 °C. ^{1}H NMR ($CDCl_3$) δ 0.90 (m, 6H), 1.01−1.79 (m, 13H), 2.14 (m, 1H), 2.75 (s, 6H), 3.12 (m, 2H), 4.04 (s, 1H), 5.40 (s, 1H), 5.88 (m, 2H), 6.59 (d, J = 8.9 Hz, 1H), 7.62 (m, 4H), 7.76 (d, J = 8.9 Hz, 1H), 8.15 (m, 2H), 8.63 (t, J = 8.7 Hz, 1H), 9.10 (d, J = 5.6 Hz, 2H). HRMS (FAB) calcd for $C_{32}H_{43}N_2O_3S^+$: 535.2994; found, 535.2986. Anal. Calcd for $C_{32}H_{43}N_2O_3SBr\cdot1.6H_2O$: C, 59.64; H, 7.23; N, 4.35. Found: C, 59.63; H, 7.04; N, 4.27.

(+)-1-{3-[(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydro-1-benzothiepin-5-yl]-benzyl}pyridinium Bromide (46). Following a similar procedure as in General Method C, the title compound **46** was prepared from the corresponding benzyl bromide **22** as a solid. ^{1}H NMR (CD_3OD) δ 0.90 (m, 6H), 1.01−1.61 (m, 11H), 1.68 (m, 1H), 2.14 (m, 1H), 2.73 (s, 6H), 3.13 (m, 2H), 4.07 (s, 1H), 5.40 (s, 1H), 5.85 (m, 3H), 6.58 (d, J = 8.6 Hz, 1H), 7.53 (m, 3H), 7.77 (m, 2H), 8.13 (m, 2H), 8.62 (m, 1H), 9.10 (m, 2H). HRMS (FAB) calcd for $C_{32}H_{43}N_2O_3S^+$: 535.2994; found, 535.2985.

(+)-{3-[(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydro-1-benzothiepin-5-yl]-phenyl}methanesulfonic Acid (47). Following a similar procedure as in General Method C, bromide **22** was reacted with sodium sulfite to give the title compound **47** as a solid: ^{1}H NMR (CD_3OD) δ 0.93 (m, 6H), 1.08−1.61 (m, 11H), 1.83 (m, 1H), 2.14 (m, 1H), 3.05 (s, 6H), 3.19 (s, 2H), 4.13 (m, 3H), 5.41 (s, 1H), 6.75 (s, 1H), 7.18−7.49 (m, 4H), 7.77 (s, 1H), 8.03 (d, J = 8.6 Hz, 1H). HRMS (FAB) calcd for $C_{27}H_{39}NO_6S$: 538.2297; found, 538.2379.

(+)-(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-5-(6-methoxy-2-naphthyl)-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-Dioxide (48). Following a similar procedure as in General Method A, the title compound **48** was prepared from **4** (Scheme 2) as a white solid, mp 185 °C. ^{1}H NMR ($CDCl_3$) δ 0.87 (m, 6H), 1.35 (m, 12H), 2.22 (dt, J = 12.3, 2.6 Hz, 1H), 2.71 (s, 6H), 3.21 (ABq, J_{AB} = 48.6 Hz, J' = 15 Hz, 2H), 3.93 (s, 3H), 4.23 (d, J = 7.25 Hz, 1H), 5.67, (s, 1H), 6.00 (d, J = 2.4 Hz, 1H), 6.50 (dd, J = 9, 2.6 Hz, 1H), 7.17 (m, 2H), 7.58 (br d, J = 8 Hz, 1H), 7.75 (m, 2H), 7.86 (br s, 1H), 7.91 (d,, J = 8.9 Hz, 1H). HRMS (EI) calcd for $C_{31}H_{41}N_1O_4S_1$: 523.2756; found, 523.2740.

(+)-(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-5-(6-hydroxy-2-naphthyl)-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-Dioxide (49). Following a similar procedure as in General Method A, the title compound **49** was prepared from **4** (Scheme 2) as a white solid, mp 139 °C. ^{1}H NMR ($CDCl_3$) δ 0.88 (m, 6H), 1.35 (m, 12H), 2.23 (dt, J = 12.3, 2.6 Hz, 1H), 2.72 (s, 6H), 3.10 (ABq, J_{AB} = 48.6 Hz, J' = 15 Hz, 2H), 4.22 (br s, 1H), 5.08 (br s, 1H), 5.66 (s, 1H), 6.04 (d, J = 2.4 Hz, 1H), 6.56 (dd, J = 9, 2.6 Hz, 1H), 7.12 (dd, J = 8.85, 2.4 Hz, 1H), 7.15 (m, 1H), 7.58 (d, J = 9 Hz, 1H), 7.73 (m, 2H), 7.85 (s, 1H), 7.93 (d, J = 8.9 Hz, 1H). HRMS (EI) calcd for $C_{30}H_{39}N_1O_4S_1$: 509.2600; found, 509.2581.

(+)-(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-5-(2-thienyl)-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-Dioxide (50). Following a similar procedure as in General Method A, the title compound **50** was prepared from **4** (Scheme 2) as a white foam. ^{1}H NMR ($CDCl_3$) δ 0.8−1.0 (m, 6H), 1.0−1.73 (m, 11H), 2.23 (td, J = 13.5, 4.2 Hz, 1H), 2.88 (s, 6H), 3.1 (ABq, J_{AB} = 15.1 Hz, 2H), 4.18 (s, 1H), 5.81 (s, 1H), 6.39 (br s, 1H), 6.67−6.78 (m, 1H), 7.03−7.12 (m, 1H), 7.13−7.19 (m, 1H), 7.28−7.35 (m, 1H), 7.94 (d, J = 9 Hz, 1H). HRMS calcd for $C_{24}H_{36}NO_3S_2$: 450.2137; found, 450.2129.

(+)-(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-5-(3-thienyl)-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-Dioxide (51). Following a similar procedure as in General Method A, the title compound **51** was prepared from **4** (Scheme 2) as a white solid, mp 73 °C. ^{1}H NMR ($CDCl_3$) δ 0.91 (m, 6H), 1.40 (m, 12H), 2.21 (dt, J = 12.3, 2.6 Hz, 1H), 2.82 (s, 6H), 3.05 06 (ABq, J_{AB} = 48.6 Hz, J' = 15 Hz, 2H), 4.09 (d, J = 6.4 Hz, 1H), 5.61 (s, 1H), 5.99 (d, J = 2.4 Hz, 1H), 6.53 (dd, J = 9, 2.6 Hz, 1H), 7.17 (dd,, J = 4.8, 1.4 Hz, 1H), 7.35 (m, 2H), 7.88 (d,, J = 8.9 Hz, 1H). HRMS (EI) calcd for $C_{24}H_{35}N_1O_3S_2$: 450.2137; found, 450.2153. Anal. Calcd for $C_{24}H_{35}N_1O_3S_2$: C, 64.10; H, 7.85; N, 3.11. Found: C, 63.97; H, 8.09; N, 2.99.

(+)-(4*R*,5*S*)-3,3-Dibutyl-7-(dimethylamino)-5-(2-pyridinyl)-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-Dioxide (52). Following a similar procedure as in General Method A, the title compound **52** was prepared from **4** (Scheme 2) as a white solid. ^{1}H NMR ($CDCl_3$) δ 0.8−1.0 (m, 6H), 1.0−1.72 (m, 12H), 2.32 (t, J = 11.3 Hz, 1H), 2.76 (s, 6H), 3.1−3.25 (m, 2H), 3.9 (br m, 1H), 4.2 (s, 1H), 5.47 (s,1H), 5.6 (d, J = 2.4 Hz, 1H), 6.5 (dd, J = 8.86, 2.4 Hz, 1H), 7.25−7.37 (m, 2H), 7.73 (dt, J = 7.7, 1.6 Hz, 1H), 7.89 (d, J = 8.85 Hz, 1H), 8.68 (d, J = 4.2 Hz, 1H). MS (ESI): *m/z* 445 (M + H, 100).

(+)-(4*R*,5*S*)-3,3-Dibutyl-7-(dimethylamino)-5-(3-pyridinyl)-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-Dioxide (53). Following a similar procedure as in General Method A, the title compound **53** was prepared from **4** (Scheme 2) as a solid. ^{1}H NMR ($CDCl_3$) δ 0.8−1.0 (m, 6H), 1.0−1.72 (m, 11H), 2.15−2.30 (m, 1H), 2.81 (s, 6H), 3.07 (d, J = 15.1 Hz, 1H), 3.18 (d, J = 15.3 Hz, 1H), 4.07 (d, J = 7.1 Hz, 1H), 5.57 (s, 1H), 5.93 (s, 1H), 5.81 (d, J = 2.4 Hz, 1H), 6.53 (dd, J = 2.6, 9.1 Hz, 1H), 7.37 (dd, J = 4.8, 7.9 Hz, 1H), 7.83−7.97 [m (with δ at 7.92, J = 8.9), 2H], 8.58 (dd, J = 1.4, 4.6 Hz, 1H), 8.78 (d, J = 1.6 Hz, 1H). MS (ESI): *m/z* 445 (M + H).

(+)-(4*R*,5*S*)-3,3-Dibutyl-7-(dimethylamino)-5-(4-pyridinyl)-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-Dioxide (54). Following a similar procedure as in General Method A, the title compound **54** was prepared from **4** (Scheme 2) as a solid. ^{1}H NMR ($CDCl_3$) δ 0.8−1.0 (m, 6H), 1.0−1.68 (m, ??H), 2.2 (t, J = 9.9 Hz, 1H), 2.82 (s, 6H), 2.99 (d, J = 15.3 Hz, 1H), 3.19 (d, J = 15.3 Hz, 1H), 4.06 (d, J = 7.9 Hz, 1H), 5.6 (s, 1H), 5.73 (d, J = 2.4 Hz, 1H), 6.56 (dd, J = 8.86, 2.4 Hz, 1H), 7.64 (d, J = 6.1 Hz, 1H), 7.92 (d, J = 8.85 Hz, 1H), 8.68 (d, J = 6.1 Hz, 1H). MS (ESI): *m/z* 445 (M + H, 100).

(+)-3-[(4*R*,5*S*)-3,3-Dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydro-1-benzothiepin-5-yl]-1-methylpyridinium Iodide (55). Pyridine **53** was treated with methyl iodide to give the title compound **55** as a solid. ^{1}H NMR ($CDCl_3$) δ 0.85−0.95 (m, 6H), 1.0−1.7 (m, 11H), 2.05−2.2 (m, 1H), 2.86 (s, 6H), 3.15 (s, 2H), 4.06 (d, J = 7.1 Hz, 1H), 4.30 (d, J = 7.2 Hz, 1H), 4.83 (s, 3H), 5.51 (s, 1H), 5.71 (s,1H), 6.55 (dd, J = 2.2, 8.9 Hz, 1H), 7.80 (d, J = 8.9 Hz, 1H), 8.02 (dd, J = 6.1, 7.9 Hz, 1H), 8.46 (d, J = 8.2 Hz, 1H), 9.86 (s, 1H). HRMS (FAB) calcd for $C_{26}H_{39}N_2O_3S$: 459.2681; found, 459.2700.

(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-5-{4-[2-(dimethylamino)ethoxy]phenyl}-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-Dioxide (56). Following a similar procedure as in General Method B, the title compound **56** was prepared from the corresponding iodoethyl ether and dimethylamine as a white solid, mp 155−158 °C. ^{1}H NMR ($CDCl_3$) δ 0.89 (m, 6H), 1.0−1.74 (m, 11H), 2.18 (br t, J = 13.1 Hz, 1H), 2.34 (s, 6H), 2.72 (t, J = 7.1 Hz, 8H), 2.8 (s, 6H), 3.05 (q, J = 20.0 Hz, 2H), 4.08 (m, 3H), 5.45 (s, 1H), 5.93 (s,1H), 6.46 (d, J = 7.5 Hz, 1H), 6.9 (d, J = 7.5 Hz, 2H), 7.35 (d, J = 7.5 Hz, 2H), 7.85 (d, J = 7.5 Hz, 1H). HRMS (MH^+) calcd for $C_{30}H_{47}N_2O_4S$: 531.3257; found, 531.3191.

2-{4-[(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydro-1-benzothiepin-5-yl]-phenoxy}-*N*,*N*,*N*-trimethylethanaminium Iodide (57). Following a similar procedure as in General Method B, the title compound **57** was prepared from the corresponding iodoethyl ether and trimethylamine as a yellow solid. ^{1}H NMR (CD_3OD) δ 0.88 (m, 6H), 0.96−1.5 (m, 10H), 1.7 (brt, J = 10.99 Hz, 1H), 2.05 (brt, J = 10.99 Hz, 1H), 2.74 (s, 6H), 3.06 (q, J = 13.3 Hz, 2H), 3.25 (s, 9H), 3.8 (s, 2H), 3.98 (s, 1H), 4.46 (s, 2H), 5.25 (s, 1H), 5.99 (s, 1H), 6.5 (d, J = 9.99 Hz, 1H), 7.0 (d, J = 9.99 Hz, 2H), 7.4 (d, J = 9.99 Hz, 2H), 7.66 (d, J = 9.99 Hz, 1H). MS (ESI) calcd for $C_{31}H_{49}N_2O_4S$: 545.81; found, 545.2.

2-[2-(2-{4-[(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydro-1-benzothiepin-5-yl]-phenoxy}ethoxy)ethoxy]-*N*,*N*,*N*-trimethylethanaminium Iodide (58). Following a similar procedure as in General Method B, the title compound **58** was prepared from the corresponding iodoethylene ether and trimethylamine as a solid. ^{1}H NMR ($CDCl_3$) δ 0.90 (q,6H), 1.05−1.65 (m,12H), 2.2 (t,1H), 2.8 (s,6H), 2.95 (q,2H), 3.45 (s,9H), 3.7 (s,4H), 3.8 (m,2H), 3.9 (m,2H), 4.0 (m,2H), 4.1 (m,3H), 5.45 (s,1H), 5.95 (s,1H), 6.5 (d,1H), 6.9 (d,2H), 7.4 (d,2H), 7.85 (d,1H). ^{13}C NMR ($CDCl_3$) δ 13.998, 14.086, 23.196, 23.253, 24.482, 24.983, 29.891, 35.398, 39.817, 44.168, 46.334, 55.016, 57.527, 65.200, 65.905, 67.521, 69.816, 70.446, 70.484, 76.329, 108.592, 114.528, 114.778, 125.998, 129.135, 130.220, 135.583, 139.808, 153.125, 157.559. HRMS (FAB) calcd for $C_{35}H_{57}N_2O_6S$: 633.3932. Found: 633.3973.

(4*R-cis*)-3,3-Dibutyl-5-[4-[[5-(diethylamino)pentyl]oxy]-phenyl]-7-(dimethylamino)-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-Dioxide (59). Following a similar procedure as in General Method B, the title compound **59** was prepared from the corresponding bromopentyl ether **17** and dimethylamine as a yellow foamy solid. ^{1}H NMR ($CDCl_3$) δ 0.89 (m, 6H), 1.20−1.47 (m, 12H), 1.53−1.67 (m, 4H), 1.76−1.90 (m, 8H), 2.21 (m, 1H), 2.74−2.92 (m, 12H), 3.07 (ABq, 2H), 4.00 (t, J = 6.3 Hz, 2H), 4.10 (d, J = 7.8 Hz, 1H), 5.48 (s, 1H), 6.00 (d, J = 2.4 Hz, 1H), 6.51 (dd, J = 9.2 Hz, 2.6 Hz, 1H), 6.92 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 9.0 Hz, 1H).

2-(2-{4-[(4R,5R)-3,3-Dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydro-1-benzothiepin-5-yl]-phenoxy}ethoxy)-*N,N,N*-triethylethanaminium Bromide (60). Following a similar procedure as in General Method B, the title compound **60** was prepared from the corresponding bromoethylene ether and trimethylamine as an off-white solid, mp 193−195 °C. ^{1}H NMR ($CDCl_3$) δ 0.82−0.92 (m, 6H), 1.02−1.52 (mm, 11H), 1.37 (t, J = 7.2 Hz, 9H), 1.60 (br t, J = 14 Hz, 1H), 1.98 (br t, J = 14 Hz, 1H), 2.81 (s, 6H), 3.04 (q_{ab}, J = 15.3, 42.4 Hz, 2H), 3.56 (q, J = 7.2 Hz, 6H), 3.79−3.86 (m, 2H), 3.89−3.94 (m, 2H), 4.04−4.15 (mm, 5H), 5.45 (s, 1H), 6.00 (d, J = 1.8 Hz, 1H), 6.45 (dd, J = 2.1, 8.8 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 8.7 Hz, 2H), 7.87 (d, J = 8.7 Hz, 1H). HRMS (FAB) calcd for $C_{36}H_{59}N_2O_5S$: 631.4145; found, 631.4140. Anal. Calcd for $C_{36}H_{59}N_2O_5SBr\cdot 1.0CH_2Cl_3$: C, 55.77; H, 7.71; N, 3.51. Found: C, 55.85; H, 8.94; N, 3.49.

(4*R*,5*R*)-3,3-Dibutyl-5-[4-(2-{2-[2-(diethylamino)ethoxy]-ethoxy}ethoxy)phenyl]-7-(dimethylamino)-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-Dioxide (61). Following a similar procedure as in General Method B, the title compound **61** was prepared from the corresponding iodoethylene ether and dimethylamine as a light-yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.91 (m, 6H), 1.05 (t, J = 7.0 Hz, 6H), 1.25 (m, 12H), 2.19 (dt, J = 12.3, 2.6 Hz, 1H), 2.62 (q, J = 7.05 Hz, 4H), 2.71 (t, J = 6.25 Hz, 2H), 2.81 (s, 6H), 3.06 (ABq, J_{AB} = 48.6 Hz, J' = 15 Hz, 2H), 3.65 (m, 4H), 3.74 (m, 2H), 3.88 (t, J = 4.4 Hz, 2H), 4.12 (m, 3H), 5.47 (s, 1H), 5.97 (d, J = 2.4 Hz, 1H), 6.50 (dd, J = 9 Hz, J' = 2.6 Hz, 1H), 6.89 (d, J = 8.9 Hz, 2H), 7.39 (d, J = 8.5 Hz, 2H), 7.88 (d,, J = 8.9 Hz, 1H). HRMS (EI) calcd for $C_{36}H_{58}N_2O_6S_1$: 647.4094; found, 647.4065.

1-{2-[2-(2-{4-[(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydro-1-benzothiepin-5-yl]-2-fluorophenoxy}ethoxy)ethoxy]ethyl}-1,4,8,11-tetramethyl-4,8,11-triaza-1-azoniacyclotetradecane Iodide (62). Following a similar procedure as in General Method B, the title compound **62** was prepared from the corresponding iodoethylene ether and the corresponding amine as a white solid. ^{1}H NMR ($CDCl_3$) δ 0.9 (m, 6H), 0.98−1.9 (m, 15H), 1.94 (s, 2H), 2.04 (m, 9H), 2.25−2.6 (m, 9H), 2.8 (m, 7H), 3.05 (q, J = 17.5 Hz, 2H), 3.3 (s, 2H), 3.65−4.25 (m, 16H), 5.4 (s, 1H), 5.93 (s, 1H), 6.5 (d, J = 7.5 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 7.3 (d, J = 13.5 Hz, 1H), 7.85 (d, J = 7.5 Hz, 1H). MS (ESI) calcd for $C_{46}H_{79}FN_5O_6S$: 849.23; found, 849.4.

(4*R-cis*)-4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]-1-methylpyridine (63). Following a similar procedure as in the preparation of **17**, the title compound **63** was prepared from phenol **7b** and 4-picolyl chloride as a colorless solid, mp 102−107 °C. ^{1}H NMR ($CDCl_3$) δ 0.84−0.92 (m, 6H), 1.02−1.50 (mm, 11H), 1.71 (br t, J = 13 Hz, 1H), 2.19 (br t, J = 13 Hz, 1H), 2.79 (s, 6H), 3.05 (q_{ab}, J = 15, 51.3 Hz, 2H), 4.11 (d, J = 8.1 Hz, 1H), 5.23 (s, 2H), 5.49 (s, 1H), 5.91 (d, J = 2.4 Hz, 1H), 6.50 (dd, J = 2.4, 9.0 Hz, 1H), 6.99 (d, J = 8.7 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 6.0 Hz, 2H), 7.89 (d, J = 9.0 Hz, 1H), 8.67 (dd, J = 1.5, 6.3 Hz, 2H). HRMS (ESI) calcd for $C_{32}H_{42}N_2O_4S$: 550.2865; found, 550.2863. Anal. Calcd for $(C_{32}H_{42}N_2O_4S\cdot 0.25CH_2Cl_2$: C, 67.71; H, 7.48; N, 4.89. Found: C, 67.81; H, 7.32; N, 4.73.

4-({4-[(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydro-1-benzothiepin-5-yl]-phenoxy}methyl)-1-ethylpyridinium Trifluoroacetate (64). Following a similar procedure as in General Method B, pyridine **63** was treated with ethyl iodide to give the title compound **64** as an off-white solid, mp 145−148 °C. ^{1}H NMR ($CDCl_3$) δ 0.60−0.68 (m, 6H), 0.77−1.30 (mm, 12H), 1.44 (t, J = 7.2 Hz, 3H), 1.90 (br t, J = 15 Hz, 1H), 2.56 (s, 6H), 2.84 (q, J = 15 Hz, 2H), 3.80 (s, 1H), 4.55 (q, J = 7.2 Hz, 2H), 5.11 (s, 1H), 5.16 (s, 2H), 5.72 (d, J = 2.4 Hz, 1H), 6,24 (dd, J = 2.7, 8.8 Hz, 1H), 6.08 (d, J = 8.7 Hz, 2H), 7.24 (d, J = 9.0 Hz, 2H), 7.56 (d, J = 9.0 Hz, 1H), 7.96 (d, J = 6.6 Hz, 2H), 8.99 (d, J = 6.6 Hz, 2H). HRMS (EI) calcd for $C_{34}H_{47}N_2O_4S$: 579.3257; found, 579.3259. Anal. Calcd for $(C_{36}H_{47}N_2O_6S_1F_3\cdot 1.35TFA\cdot 0.6H_2O$: C, 59.20; H, 6.70; N, 3.76. Found: C, 59.18; H, 6.70; N, 3.86.

(4*R*,5*R*)-5-{4-[2-(2-{2-[Bis(2-hydroxyethyl)amino]ethoxy}-ethoxy)ethoxy]phenyl}-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-Dioxide Hydrochloride (65). Following a similar procedure as in General Method B, the title compound **65** was prepared from the corresponding chloroethylene ether and the corresponding amine as a white amorphous solid. ^{1}H NMR ($CDCl_3$) δ 0.87−0.93 (m, 6H), 1.18−1.51 (m, 10H), 1.61−1.68 (m, 1H), 2.16−2.24 (m, 1H), 2.81 (s, 6H), 2.83−2.97 (m, 6H), 2.99 (d, J = 15.1 Hz, 1H), 3.14 (d, J = 14.9 Hz, 1H), 3.66−3.74 (m, 10H), 3.87 (t, J = 4.8 Hz, 2H), 4.09−4.13 (m, 1H), 4.17 (t, J = 4.8 Hz, 1H), 5.48 (s, 1H), 5.99 (d, J = 2.4 Hz, 1H), 6.50 (dd, J = 9.0, 2.5 Hz, 1H), 6.95 (d, J = 8.7 Hz, 2H), 7.40 (d, J = 8.5 Hz, 2H), 7.89 (d, J = 8.9 Hz, 1H). HRMS (EI) calcd for $C_{36}H_{59}N_2O_8S$: 679.3992; found, 679.4037.

(4*R*,5*R*)-3,3-Dibutyl-5-{3-[2-(diethylamino)ethoxy]phenyl}-7-(dimethylamino)-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-Dioxide (66). Following a similar procedure as in General Method B, the title compound **66** was prepared from the corresponding iodoethyl ether and the diethylamine as a white solid, mp 105−109 °C. ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 6.7 Hz, 6H), 1.09−1.68 (m, 17H), 2.13 (br t, J = 13.1 Hz, 1H), 2.6−2.8 (m, 10H), 2.85−3.1 (m, 4H), 4.04 (m, 3H), 5.34 (s, 1H), 5.86 (s, 1H), 6.35 (d, J = 7.5 Hz, 1H), 6.7 (d, J = 7.5 Hz, 1H), 6.88 (s, 1H), 6.99 (d, J = 7.5 Hz, 1H), 7.15 (t, J = 7.5 Hz, 1H), 7.7 (d, J = 7.5 Hz, 1H). HRMS (MH^+) calcd for $C_{30}H_{47}N_2O_4S$: 531.3257; found, 531.3202.

2-{3-[(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydro-1-benzothiepin-5-yl]phenoxy}-*N,N,N*-triethylethanaminium Iodide (67). Following a similar procedure as in General Method B, the title compound **67** was prepared from the corresponding iodoethyl ether and the triethylamine as a yellow solid, mp 150−152 °C. ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 8.25 Hz, 6H), 0.95−1.85 (m, 20H), 2.09 (br t, J = 13.1 Hz, 1H), 2.79 (s, 6H), 3.10 (s, 2H), 3.48 (m, 6H), 3.8−4.08 (m, 2H), 4.19 (s, 1H), 4.36−4.88 (m, 2H), 5.38 (s, 1H), 5.84 (s,1H), 6.45 (d, J = 7.5 Hz, 1H), 6.84(d, J = 7.5 Hz, 1H), 7.05 (d, J = 7.5 Hz, 1H), 7.27 (m, 2H), 7.85 (d, J = 7.5 Hz, 1H). HRMS calcd for $C_{34}H_{55}N_2O_4S$: 587.3883; found, 587.3878. Anal. Calcd for $C_{34}H_{55}N_2O_4SI$: C, 57.13; H, 7.76; N, 3.92; S, 4.49; I, 17.75. Found: C, 59.42; H, 8.20; N, 4.17; S, 4.64; I, 18.84.

5-{3-[(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydro-1-benzothiepin-5-yl]phenoxy}-*N,N,N*-triethylpentan-1-aminium Trifluoroacetate (68). Following a similar procedure as in General Method B, the title compound **68** was prepared from the corresponding bromopentyl ether and the triethylamine as a solid. ^{1}H NMR ($CDCl_3$) δ 0.84−1.00 (m, 6H), 1.04−1.92 (m, 27H), 2.13−2.27 (m, 1H), 2.81 (s, 6H), 3.08 (ABq, J_{AB} = 15.3 Hz, ΔV=36.2 Hz, 2H), 3.12 (t, J = 6.6 Hz, 2H), 3.29 (q, J = 7.8 Hz, 6H), 3.96 (t, J = 6.0 Hz, 2H), 4.15 (s, 1H), 5.48 (s, 1H), 6.01 (d, J = 2.1 Hz, 1H), 6.51 (dd, J = 9.3 and 2.4 Hz, 1H), 6.84 (dd, J = 7.8 and 1.8 Hz, 1H), 6.94 (s, 1H), 7.17 (d, J = 7.5 Hz, 1H), 7.34 (t, J = 8.4 Hz, 1H), 7.88 (d, J = 9.0 Hz, 1H). HRMS (FAB^+) calcd for $C_{37}H_{61}N_2O_4S$: 629.4352; found, 629.4343.

(4*R-cis*)-1-[4-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]-phenoxy]butyl]-4-aza-1-azoniabicyclo[2.2.2]octane Methanesulfonate (Salt) (69). Following a similar procedure as in General Method B, the title compound **69** was prepared from the corresponding methanesulfonyl butyl ether and DABCO

as a white solid, mp 248−251 °C. ^{1}H NMR ($CDCl_3$) δ 0.91 (m, 6H), 1.14−1.47 (m, 14H), 1.63 (m, 1H), 1.96 (m, 4H), 2.21 (m, 1H), 2.77 (s, 3H), 2.82 (s, 3H), 3.07 (ABq, 2H), 3.26 (t, J = 7.1 Hz, 6H), 3.60 (m, 8H), 4.08 (m, 3H), 5.47 (s, 1H), 5.99 (d, J = 2.4 Hz, 1H), 6.51 (dd, J = 8.9 Hz, 2.6 Hz, 1H), 6.91 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.89 (d, J = 9.0 Hz, 1H).

1-[2-(2-{4-[(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydro-1-benzothiepin-5-yl]-phenoxy}ethoxy)ethyl]-1-azoniabicyclo[2.2.2]octane Bromide (70). Following a similar procedure as in General Method B, the title compound **70** was prepared from the corresponding bromoethylene ether and DABCO as a white solid, mp 161−162.5 °C. ^{1}H NMR ($CDCl_3$) δ 0.90 (m, 6H), 1.27 (m, 6H), 1.44 (m, 12H), 2.03 (m, 6H, 2.22 (m, 2H), 3.07 (m, 2H), 3.88 (m, 10H), 4.09 (m, 3H), 4.15 (m, 2H), 5.50 (s, 1H), 5.97 (d, J = 2.40 Hz, 1H), 6.52 (dd, J = 8.70 Hz, 2.70 Hz, 1H), 6.91 (d, J = 8.70 Hz, 2H), 7.44 (d, J = 8.40 Hz, 2H), 7.91 (d, J = 8.70 Hz, 1H). HRMS (ES$^+$) calcd for $C_{37}H_{57}N_2O_5S$ (M^+): 641.3988; found, 641.4005. Anal. Calcd for ($C_{37}H_{57}N_2O_5SBr$·8.72H_2O: C, 50.56; H, 8.53; N, 3.18. Found: C, 50.47; H, 6.84; N, 3.21.

1-{2-[2-(2-{4-[(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydro-1-benzothiepin-5-yl]phenoxy}ethoxy)ethoxy]ethyl}-4-aza-1-azoniabicyclo-[2.2.2]octane Chloride (71). Following a similar procedure as in General Method B, the title compound **71** was prepared from the corresponding chloroethylene ether and DABCO as a solid, mp 146−148 °C. ^{1}H NMR ($CDCl_3$) δ 0.89 (m, 6H), 1.11−1.49 (m, 13H), 1.62 (m, 1H), 2.80 (s, 6H), 3.04 (m, 2H), 3.16 (m, 8H), 3.72 (m, 10H), 3.85 (m, 4H), 4.14 (m, 2H), 5.46 (s, 1H), 5.96 (d, J = 2.00 Hz, 1H), 6.50 (dd, J = 9.20 Hz, 2.40 Hz, 1H), 6.92 (d, J = 8.80 Hz, 2H), 7.42 (d, J = 8.40 Hz, 2H), 7.88 (d, J = 8.80 Hz, 1H). HRMS (ES$^+$) calcd for $C_{38}H_{60}N_3O_6S$ (M^+): 686.4203; found, 686.4216.

(4*R-cis*)-1-[3-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]-phenoxy]propyl]-4-aza-1-azoniabicyclo[2.2.2]octane Methanesulfonate (Salt) (72). Following a similar procedure as in General Method B, the title compound **72** was prepared from the corresponding methanesulfonyl propy ether and DABCO as a white solid, mp (dec) 230−235 °C. ^{1}H NMR ($CDCl_3$) δ 0.86−0.95 (m, 6H), 1.04−1.52 (m, 10H), 1.57−1.70 (m, 1H), 2.12−2.25 (m, 3H), 2.28−2.39 (m, 2H), 2.83 (s, 6H), 3.04 (s, 3H), 3.09 (AB_q, J_{AB} = 15.6 Hz, J = 42.2 Hz, 2H), 3.22−3.32 (m, 6H), 3.56−3.66 (m, 6H), 3.73−3.83 (m, 2H), 4.06−4.17 9m, 3H), 5.47 (s, 1H), 5.97 (s, 1H), 6.51 (d, J = 8.6 Hz, 1H), 6.90(d, J = 8.6 Hz, 2H), 7.41 (d, J = 8.7 Hz, 2H), 7.89 (d, J = 8.9 Hz, 1H). MS (ES$^+$): *m/z* 612.4. HRMS (ES$^+$) calcd for $C_{35}H_{54}N_3O_4S^+$: 612.3835; found, 612.3840.

1-(5-{4-[(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-4-hydroxy-1,1-dioxido-2,3,4,5-tetrahydro-1-benzothiepin-5-yl]-phenoxy}pentyl)-4-aza-1-azoniabicyclo[2.2.2]octane Chloride (73). Following a similar procedure as in General Method B, the title compound **73** was prepared from the corresponding chloropentyl ether and DABCO as a white solid, mp 178.5−180 °C. ^{1}H NMR ($CDCl_3$) δ 0.91 (m, 6H), 1.25 (m, 14H), 1.89 (m, 4H), 2.15 (m, 1H), 2.82 (s, 6H), 3.07 (m, 2H), 3.27 (t, J = 7.35 Hz, 6H), 3.67 (t, J = 7.65 Hz, 8H), 4.00 (t, J = 6.00 Hz, 2H), 4.098 (m, 1H), 5.48 (s, 1H), 5.99 (d, J = 2.40 Hz, 1H), 6.51 (dd, J = 9.00 Hz, 2.70 Hz, 1H), 6.90 (d, J = 8.70 Hz, 2H), 7.40 (d, J = 8.70 Hz, 2H), 7.89 (d, J = 8.70 Hz, 1H). HRMS (ES$^+$) calcd for $C_{37}H_{58}N_3O_4S$: 640.4148; found, 640.4163. Anal. Calcd for ($C_{37}H_{58}N_3O_4SCl$·4.9H_2O: C, 58.11; H, 8.93; N, 5.49. Found: C, 58.08; H, 8.635; N, 5.84.

(4*R-cis*)-1-[[4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]-phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo-[2.2.2]octane Chloride Salt (74). Following a similar procedure as in General Method B, the title compound **74** was prepared from the corresponding chloromethyl benzyl ether and DABCO as a white solid, mp 223−230 °C (dec); ^{1}H NMR ($CDCl_3$) δ 0.89 (m, 6H), 1.27−1.52 (br m, 10H), 1.63 (m, 1H), 2.20 (m, 1H), 2.81 (s, 6H), 3.06 (ABq, J_{AB} = 15.1 Hz, J = 43.3 Hz, 2H), 3.16 (s, 6H), 3.76 (s, 6H), 4.11 (d, J = 7.7 Hz, 1H), 5.09 (s, 2H), 5.14 (s, 2H), 5.48 (s, 1H), 5.96 (s, 1H), 6.49 (d, J = 8.9 Hz, 1H), 6.99 (d, J = 8.0 Hz, 2H), 7.26 (m, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 7.4 Hz, 2H), 7.68 (d, J = 7.4 Hz, 2H), 7.87 (d, J = 8.9 Hz, 1H). HRMS calcd for $C_{40}H_{56}N_3O_4S$: 674.3992; found, 674.4005. Anal. Calcd for $C_{40}H_{56}N_3O_4S$: ′ C, 67.62; H, 7.95; N, 5.92; S, 4.51. Found: C, 67.48; H, 8.32; N, 5.85; S, 4.60.

(4*R-cis*)-1-[[4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]-phenoxy]methyl]phenyl]methyl]pyridinium Chloride Salt (75). Following a similar procedure as in General Method B, the title compound **75** was prepared from the corresponding chloromethyl benzyl ether and pyridine as a yellow solid, mp 154−156 °C. ^{1}H NMR ($CDCl_3$) δ 0.83 (m, 6H), 1.06−1.44 (br m, 10H), 1.60 (m, 1H), 2.13 (m, 1H), 2.71 (s, 6H), 3.02 (ABq, J_{AB} = 15.1 Hz, J = 28.4 Hz, 2H), 4.09 (s, 1H), 5.00 (s, 2H), 5.38 (s, 1H), 5.91 (d, J = 2.4 Hz, 1H), 6.26 (s, 2H), 6.41 (dd, J = 8.9, 2.4 Hz, 1H), 6.91 (d, J = 8.7 Hz, 2H), 7.26 (m, 1H), 7.40 (d, J = 7.7 Hz, 4H), 7.73 (d, J = 7.9 Hz, 2H), 7.78 (d, J = 8.9 Hz, 2H), 7.93 (t, J = 6.8 Hz, 1H), 8.34 (t, J = 7.7 Hz, 1H), 8.58 (br s, 1H), 9.69 (d, J = 5.8 Hz, 2H). HRMS calcd for $C_{39}H_{49}N_2O_4S$: 641.3413; found, 641.3425.

(4*R-cis*)-4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]-1-methylpyridinium Trifluoroacetate Salt (76). Following a similar procedure as in General Method B, pyridine **63** was treated with methyl iodide, ionic-exchanged to a trifluoroacetate salt, to give the title compound **76** as a colorless solid, mp 96−99 °C. ^{1}H NMR ($CDCl_3$) δ 0.85−0.95 (m, 6H), 1.03−1.52 (m, 10H), 1.57−1.70 (m, 1H), 2.12−2.27 (m, 1H), 2.84 (s, 6H), 3.09 (ABq, J_{AB} = 15.0, 27.9 Hz, 2H), 4.11 (s, 1H), 4.46 (s, 3H), 5.37 (s, 2H), 5.50 (s, 1H), 6.07 (d, J = 2.4 Hz, 1H), 6.61 (dd, J = 2.5, 8.7 Hz, 1H), 7.02 (d, J = 8.7 Hz, 2H), 7.48 (d, J = 7.2 Hz, 2H), 7.90 (d, J = 8.7 Hz, 1H), 8.14 (d, J = 6.3 Hz, 2H), 8.80 (d, J = 6.6 Hz, 2H). HRMS calcd for $C_{33}H_{45}N_2O_4S$: 565.3100; found, 565.3125.

(4*R-cis*)-5-[[5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]-phenoxy]acetic Acid (77). Following a similar procedure as in the preparation of **17**, the title compound **77** was prepared from its corresponding phenol **7b** and chloroacetate as a white solid, mp 119−123 °C. ^{1}H NMR ($CDCl_3$) δ 0.89−0.94 (m, 6H), 1.19−1.43 (m, 10H), 1.61−1.65 (m, 1H), 2.17−2.21 (m, 1H), 2.85 (s, 6H), 3.02 (d, J = 15.1 Hz, 1H), 3.17 (t, J = 14.9 Hz, 1H), 4.12 (s, 1H), 4.72 (s, 2H), 5.51 (s, 1H), 6.17 (s, 1H), 6.74 (d, J = 9.1 Hz, 1H), 6.99 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 7.97 (d, J = 8.7 Hz, 1H). HRMS calcd for $C_{28}H_{40}NO_6S$: 518.2576; found, 518.2569.

(4*R-cis*)-5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]pentanoic Acid (78). Following a similar procedure as in the preparation of **17**, the title compound **78** was prepared from its corresponding phenol **7b** and appropriate halide as a white foam, mp 76−79 °C. ^{1}H NMR ($CDCl_3$) δ 0.90 (m, 6H), 1.10−1.46 (br m, 10H), 1.62 (m, 1H), 1.87 (m, 4H), 2.20 (m, 1H), 2.45 (m, 2H), 2.81 (s, 6H), 3.05 (ABq, J_{AB} = 15.1 Hz, J = 49.7 Hz, 2H), 4.00 (s, 2H), 4.09 (s, 1H), 5.45 (s, 1H), 5.99 (d, J = 2.4 Hz, 1H), 6.48 (dd, J = 8.9, 2.4 Hz, 1H), 6.91 (d, J = 8.7 Hz, 2H), 7.39 (m, 5H), 7.39 (d, J = 8.3 Hz, 2H), 7.84 (d, J = 8.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 14.3, 21.6, 23.4, 24.6, 25.2, 28.8, 30.0, 33.8, 35.6, 40.0, 44.4, 46.5, 57.6, 67.6, 76.7, 76.9, 108.8, 114.8, 114.9, 126.1, 129.3, 130.3, 135.3, 140.0, 153.3, 158.1, 179.4. HRMS calcd for $C_{31}H_{45}NO_6S$: 560.3046; found, 560.3043.

(4*R-cis*)-*N*-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]-phenoxyacetyl]glycine (79). Following a similar procedure as in the preparation of **26**, the glycine ester intermediate was prepared from phenol **7b** as a white foam. ^{1}H NMR ($CDCl_3$) δ 0.86−0.98 (m, 6H), 1.04−1.56 (m, 13H), 1.58−1.71 (m, 1H), 2.14−2.29 (m, 1H), 2.73 (s, 6H), 3.08 (AB_q, J_{AB} = 15.3 Hz, J = 48.9 Hz, 2H), 4.06−4.19 (m, 6H), 4.25 (q, J = 7.0 Hz, 2H), 4.57 (s, 2H), 5.50 (s, 1H), 5.98 (s, 1H), 6.56 (d, J = 8.6 Hz, 1H),

6.98 (d, J = 8.5 Hz, 2H), 7.17 (s, 1H), 7.47 (d, J = 8.3 Hz, 2H), 7.91 (d, J = 8.7 Hz, 1H).

A solution of 7.3 g (12.1 mmol) of the above glycine ester and 1.5 g of LiOH monohydrate (36.3 mmol) in 60 mL of THF and 60 mL of water was heated to 45 °C for 2 h. The resulting solution was cooled to ambient temperature, acidified with 1 N HCl, and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by recrystallization from ethyl acetate gave 5.45 g (78%) of the desired title compound **79** as a white crystalline solid, mp 149−150 °C. ^{1}H NMR (CD_3-OD) δ 0.88−0.98 (m, 6H), 1.06−1.56 (m, 10H), 1.70−1.84 (m, 1H), 2.06−2.20 (m, 1H), 2.79 (s, 6H), 3.11 (AB_q, J_{AB} = 15.3 Hz, J = 21.6 Hz, 2H), 4.01 (s, 2H), 4.07 (s, 1H), 4.61 (s, 2H), 5.31 (s, 1H), 6.04 (s, 1H), 6.57 (d, J = 9.0 Hz, 1H), 7.08 (d, J = 7.8 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), 7.76 (d, J = 9.0 Hz, 1H), 8.42 (m, 1H). HRMS (ES^+) calcd for $C_{30}H_{42}N_2O_7S$: 575.2712; found, 575.2790. Anal. Calcd for $C_{30}H_{42}N_2O_7S$: C, 62.69; H, 7.37; N, 4.87. Found: C, 62.87; H, 7.56; N, 4.87.

(4*R*-*cis*)-*N*-(Carboxymethyl)-*N*-[5-[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]pentyl]glycine (80). Following a similar procedure as in the preparation of **17**, a diester intermediate of diacid **80** was prepared. The mixture of the diester and 2.7 g (64.3 mmol) of LiOH in THF (75 mL) and water (50 mL) was stirred at 40 °C for 18 h. The reaction mixture was acidified with 1% HCl and extracted with dichloromethane. The residue was triturated with hexane and filtered to give 8.9 g (93%) of the desired title compound **80** as a solid, mp 148−162 °C. ^{1}H NMR (CD_3OD) δ 0.92 (t, 6H), 1.1−1.9 (m, 31H), 2.15 (t, 1H),2.8(s, 6H), 3.15 (ABq, 2H), 3.75(m, 1H), 4.1 (m, 6H), 5.3 (s, 1H), 6.1 (s, 1H), 6.6 (d, 1H), 7.0(d, 2H), 7.4 (d, 2H), 7.8 (d, 1H); MS (M + H): *m/z* 661. Anal. Calcd for $C_{35}H_{52}N_2O_8S\cdot1.5H_2O$: C,61.11; H,8.06; N,4.07; S,4.66. Found: C,61.00; H,7.72; N,3.89; S,4.47.

(4*R*-*cis*)-*N*-(Carboxymethyl)-*N*-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-glycine (81). Following a similar procedure as in General Method B, the benzyl diester intermediate of diacid **81** was prepared from chloromethyl benzyl ether and iminodiacetate as a solid. ^{1}H NMR ($CDCl_3$) δ 0.90 (q, 6H), 1.05−1.65 (m, 17H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.55 (s, 4H), 3.95 (s, 2H), 4.1−4.2 (m, 5H), 5.05 (s, 2H), 5.42 (s, 1H), 5.95 (s, 1H), 6.5 (d, 1H), 7.0 (d, 2H), 7.4 (s, 6H), 7.8 (d, 1H).

A solution of 0.863 g (1.15 mmol) of the above benzyl diester and 0.232 g (5.52 mmol) of LiOH in 30 mL of THF and 30 mL of water was stirred at 40 °C under N_2 for 4 h. The reaction mixture was diluted with ether and washed with 1% HCl. The aqueous layer was extracted twice with ether, and the combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give the desired title compound **81** as a solid, mp 175 °C. ^{1}H NMR (THF-d_8) δ 0.95 (q, 6H), 1.05−1.65 (m, 11H), 2.22 (t, 1H), 2.8 (s, 6H), 3.0 (t, 2H), 3.5 (s, 4H), 3.9 (s, 2H), 4.1 (d, 1H), 5.1 (s, 2H), 5.4 (s, 1H), 6.05 (s, 1H), 6.5 (d, 1H), 7.0 (d, 2H), 7.4 (m, 6H), 7.78 (d, 1H). HRMS calcd for $C_{38}H_{50}N_2O_8S$: 695.3366; found 695.3359. Anal. Calcd for $C_{38}H_{50}N_2O_8S$: C, 65.68; H, 7.25; N, 4.03; S, 4.61. Found: C, 64.95; H, 7.32; N, 3.94; S, 4.62.

(4*R*-*cis*)-*N*-(Carboxymethyl)-*N*-[[6-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]-2-pyridinyl]methyl]-glycine (82). Following a similar procedure as in the preparation of **81**, the title compound **82** was prepared as a white solid (0.44 g, 90%), mp 153−155 °C. ^{1}H NMR ($CDCl_3$) δ 0.84−0.95 (m, 6H), 1.02−1.5 (m, 10H), 1.56−1.66 (m, 1H), 2.14−2.24 (m, 1H), 2.80 (s, 6H), 3.10 (ABq, 2H), 3.90 (m, 3H), 4.05 (s, 1H), 4.40 (s, 2H), 5.20 (s, 2H), 5.50 (s, 1H), 5.97 (s, 1H), 6.50 (d, 1H), 7.02 (d, 2H), 7.3 (d, 1H), 7.42 (d, 2H), 7.58 (d, 1H), 7.8−7.9 (m, 2H). HRMS calcd for $C_{37}H_{49}N_3O_8S$: 696.3319; found, 696.3331.

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JM0402162