A Highly Enantioselective Benzothiepine Synthesis

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A highly enantioselective synthesis of benzothiepine **1a** has been accomplished via an enantioenriched sulfoxide intermediate obtained by asymmetric oxidation with a chiral oxaziridine in 89:11 er. The key step is a thermodynamically controlled asymmetric cyclization reaction that produces two new stereogenic centers. The (4*R*,5*R*) isomer **1a** was obtained in 98:2 er.

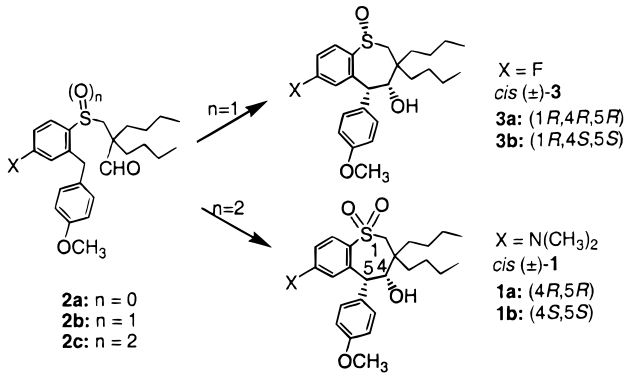
Introduction

Benzothiepines of which **1** (Scheme 1) is representative are potent apical sodium co-dependent bile acid transporter (ASBT) inhibitors useful for the treatment of hypercholesterolemia.[1] Separation of the enantiomers **1a** and **1b** was accomplished initially by liquid chromatography on a chiral stationary phase,[2] and **1a** was found to be the significantly more potent isomer. Since larger quantities of **1a** were required for evaluation in animal models, the development of an enantioselective synthesis seemed very attractive. We now report an efficient enantioselective synthesis of benzothiepines.

During our initial investigation of the synthesis of **1**, we found that cyclization of **2c** (X = NMe_2) with 1.2 equiv of potassium *tert*-butoxide in THF at −10 °C gave only (±)-**1** with the hydroxyl and methoxyphenyl groups in a cis relationship (Scheme 1). The selectivity can be rationalized by invoking potassium ion complexation with the sulfone and alkoxide oxygens, an effect which could only exist in *cis*-(±)-**1** but not in a trans isomer. On the other hand, either oxygen of the achiral sulfone would be capable of directing the ring closure reaction by forming the salt bridge; therefore, no enantioselectivity would be anticipated. If the cyclization were possible with a sulfoxide, a chiral ring closure could be envisioned with an enantioenriched sulfoxide to preferentially provide one enantiomer. To test this hypothesis, (±)-**2b** was prepared by oxidation of **2a** with either 1 equiv of *m*-CPBA or 0.5 equiv of Oxone. Cyclization of (±)-**2b** with potassium *tert*-butoxide in THF at −10 °C yielded only the cis isomers (±)-**3** (Scheme 1). This observation suggests that a chiral sulfoxide (*R*)-**2b** should stereoselectively yield the desired (1*R*,4*R*,5*R*) cyclized product.

Chiral sulfoxides have been extensively used as key intermediates for the enantioselective synthesis of natural products[3] due to their high diastereoselectivity as auxiliaries, yet so far there are no reported examples of asymmetric cyclization utilizing internal chiral sulfoxides. Enantiomerically pure chiral sulfoxides can be readily prepared by enzymatic[4] oxidation using monooxygenases, chemical oxidation using Ti(IV)[5] or Mn(III)[6] complexes, or chiral oxaziridines[7] to convert the prochiral sulfides to the chiral sulfoxides.

Scheme 1



Results and Discussion

We chose to focus on the chemical oxidation of prochiral sulfides by using Sharpless reagents, Davis's oxaziridines, and Jacobsen's catalyst. The aldehyde **4** was selected as a model system to study the asymmetric

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(2) The separation was done on ChiralPak AD column with 10% ethanol/hexane at 1.0 mL/min.

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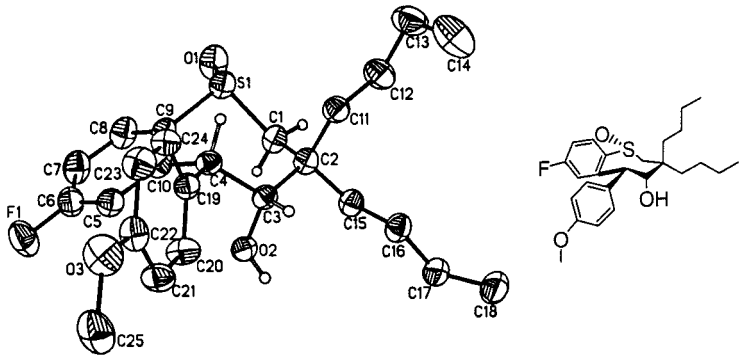
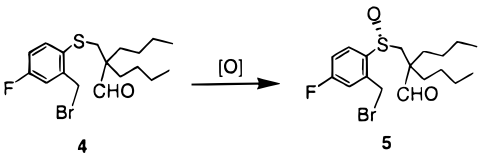


Figure 1. X-ray structure of racemic **3**.

Table 1. Asymmetric Oxidation of Aromatic Sulfide 5



4 **5**

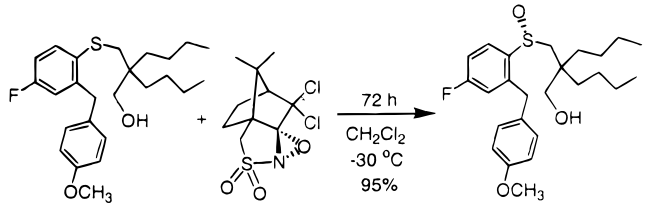
method	temp, °C	(*R*)-**5**/(*S*)-**5**[a]
A. CHP, Ti(Oi-Pr)$_4$/(−)-DET/H_2O (1:2:1)	−25	60/40
B. TBHP, Ti(O*i*-Pr)$_4$/(−)-DET/H_2O (1:2:1)	−25	60/40
C. CHP, Jacobsen's Catalyst, PhI(OAc)$_2$	−25 to rt	60/40
D. (−)-(camphorsulfonyl)oxaziridine	−25	60/40
E. (−)-(dichlorocamphorsulfonyl)oxaziridine	−25	80/20

[a] The enantiomeric ratios were determined by HPLC on (*S*,*S*) Whelk-O 1 with ethanol−hexane (1:9). The absolute configuration of the sulfoxides was derived from the configuration of **1a** and **3**.

oxidation of prochiral aromatic sulfide to the (*R*)- and (*S*)-sulfoxide **5** (Table 1).

Oxidation of **4** at −25 °C with either cumene hydroperoxide (CHP) or *tert*-butyl hydroperoxide (TBHP) in the presence of Ti(O*i*-Pr)$_4$/(−)-DET/H_2O (1:2:1) gave a 60:40 mixture of (*R*)- and (*S*)-sulfoxides (vida infra). Under Jacobsen's conditions, CHP with iodobenzene diacetate in acetonitrile also gave a 60:40 mixture of the sulfoxides **5**. Oxidation with (−)-(camphorsulfonyl)oxaziridine in CH_2Cl_2 was also not very selective (60:40 mixture); however, the corresponding α,α-dichloro derivative under the same conditions gave a much improved 80:20 mixture of **5**. This oxaziridine was selected for further investigation of an enantioselective synthesis of **1a**.

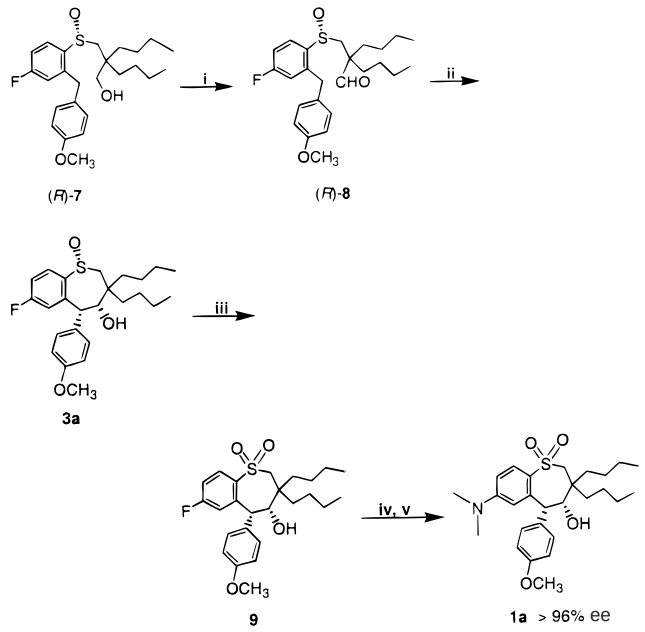
Scheme 2



6 (*R*)-**7** 89:11 er

Oxidation of **6** with (−)-(dichlorocamphorsulfonyl)-oxaziridine and subsequent chromatographic purification gave a 89:11 mixture of (*R*)-**7** and (*S*)-**7** (vida infra) in 95% yield (Scheme 2). Oxidation of the enantioenriched (*R*)-**7** with sulfur trioxide−pyridine gave the aldehydes (*R*)-**8** in 91% yield (Scheme 3). Subsequent cyclization with KO*t*-Bu gave **3a** in 78% yield which was oxidized to **9** with *m*-CPBA in 98% yield. The nucleophilic displacement of fluorine with dimethylamine gave **1a** and

Scheme 3[a]



[a] (i) SO_3·Py, TEA, DMSO, 25 °C (91%); (ii) KO*t*-Bu, THF, −15 °C (78%); (iii) *m*-CPBA, CH_2Cl_2, 0 °C (98%); (iv) $(CH_3)_2NH$, THF, 110 °C (91%); (v) recrystallization in hexane/ethyl acetate (80%).

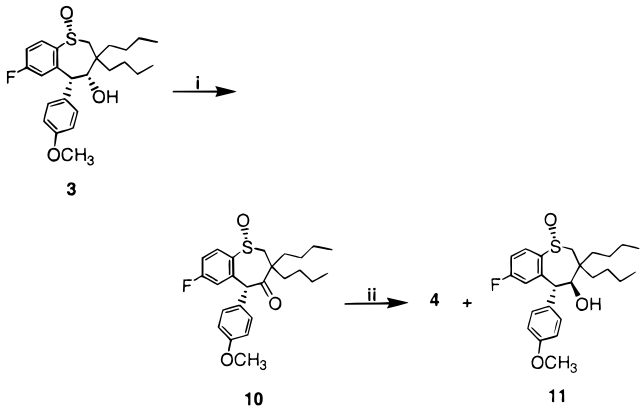
1b in the same 89:11 mixture as observed initially for **7**, thus establishing that the ring-closure reaction is highly enantioselective relative to the enantiomeric purity of the sulfoxide. A single recrystallization provided **1a** in 86% yield with >98:2 er.

The absolute stereochemistries of the sulfoxides **5** (Table 1) and **7** (Scheme 2) can be derived as follows: The X-ray crystal structure of the racemic **3**[8] (Figure 1) shows that the sulfoxide oxygen is cis to the hydroxyl and the methoxyphenyl group, and the possible configuration of the racemic pair **3a** and **3b** (Scheme 1) can only be (1*R*,4*R*,5*R*) and (1*S*,4*S*,5*S*). Since the configuration of **1a** is (4*R*,5*R*) as determined by X-ray,[9] the configuration of C4 and C5 in its precursors **9** and **3a** is also (*R*,*R*), leading to the conclusion that the configuration of sulfoxide sulfur atom in **3a** is *R*. Moreover, since **3a** is generated from the asymmetric oxidation of the sulfide **6**, (*R*)-**7** and (*R*)-**8** are established to be in the *R* configuration as well.

The success of our synthetic strategy relies on the stereocontrolled cyclization of (*R*)-**8** to **3a**, in which the

(8) Racemic **3** was prepared from the cyclization of racemic **8**.
(9) The configuration of **1a** was established from the X-ray structure of corresponding phenol.

Scheme 4[a]



[a] (i) Oxalyl chloride, TEA, DMSO, −78 °C to rt (40%); (ii) $NaBH_4$, CH_3OH, −10 °C to rt.

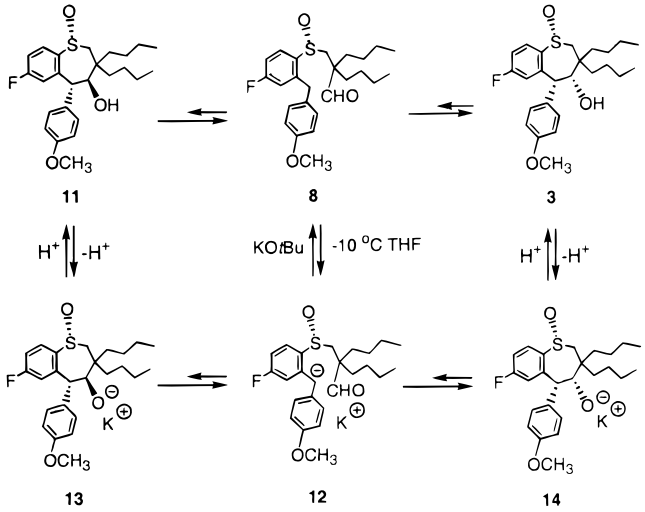
stereochemistry of sulfoxide determines the formation of the two stereogenic centers and yields only one out of the four possible stereoisomers. The first step in elucidating the source of the selectivity is to determine whether the products are kinetically or thermodynamically controlled. Since the cyclization of sulfone **2c** (Scheme 1) at lower temperature (−30 °C) actually gives the trans isomer as a kinetic-controlled product, the formation of the cis isomer is thus suggested to be a thermodynamic-controlled process.[10] It is highly plausible that in the cyclization of sulfoxide the preference for the formation of cis isomer at −10 °C is also the result of a thermodynamic-controlled process.

To gain additional insights into this highly enantioselective cyclization process, we prepared and subjected the presumed thermodynamic-controlled and kinetic-controlled products (**3** and **11**, respectively) to the cyclization conditions at −10 °C. If an equilibrium process is operating at −10 °C, then both materials should give a mixture of same compositions as in the cyclization of **8**. The trans isomer **11** was prepared by Swern oxidation of the cis alcohol **3** to give **10** in 40% yield Scheme 4). The ketone **10** was reduced by $NaBH_4$ to give a 27:73 mixture of both isomers favoring *trans*-**11** in 80% yield.

In the isomerization experiments (Scheme 5), the cis isomer **3**, under the cyclization conditions, after 30 min gave 77% of the cis isomer **3**, 23% of decomposition products, and no trans isomer **11**. On the other hand, *trans*-**11** under the same conditions isomerized to give 75% of *cis*-**3** and 25% of decomposition products. Cyclization of **8** under the same conditions also gave 77% of *cis*-**3**. These experiments establish that the cis isomer is the more thermodynamically stable isomer, and that **3**, **8**, and **11** are in equilibrium.

We believe that the cyclization reaction occurs as follows: The aldehyde **8** is deprotonated to give a carbanionic intermediate **12**, which can cyclize to either the trans alkoxide **13** or the cis alkoxide **14**; these intermediates are in equilibrium with **12** and can be protonated to products **11** and **3**, respectively. Although both alkoxides **13** and **14** could potentially be formed, the rapidly established equilibrium would shift the product formation to the thermodynamically more stable **14**. Monte Carlo conformational search and energy calculations[11] indicated that potassium ion forms a salt bridge between the alkoxide and sulfoxide oxygens in **14** when they are cis to each other, and that *cis*-**14** is more stable than *trans*-**13** by more than 2 kcal/mol largely due to the electrostatic term.

Scheme 5



Conclusions

We have successfully developed an enantioselective route to synthesize one of the four possible benzothiepine enantiomers of benzothiepines in good ee and yield. This stereoselective cyclization demonstrates the utility of a chiral sulfoxide as a directing group in a cyclization reaction. We have also provided evidence to support our hypothesis that the stereoselective cyclization is directed by the stereochemistry of the sulfoxide and that this is a thermodynamically controlled process.

Experimental Section

General. ^1H NMR spectra were recorded in $CDCl_3$ at 300 or 400 MHz and are reported as chemical shift (multiplicity, coupling constants in hertz, integration) and chemical shifts are reported as δ values in parts per million relative to $CDCl_3$ (δ 7.26). ^{13}C NMR spectra were recorded in $CDCl_3$ at 75 MHz, and chemical shifts are reported as δ values in parts per million relative to $CDCl_3$ (δ 77.00). Mass spectra were recorded in fast atom bombardment (FAB) or electrospray ionization (ESI) mode. Melting points are uncorrected. Analytical HPLC was conducted on 4.6 mm × 250 mm Alltech Altima Silica 5 μ column with hexane/ethyl acetate using UV detection. Chiral HPLC was performed on 4.6 mm × 250 mm ChiralPak AD from Daicel or 4.6 mm × 250 mm (*R*,*R*) Whelk-O 1 column from Regis Technologies with ethanol/hexane using UV detection. Chromatographic purification was done on medium-pressure liquid chromatography (MPLC) or Waters Prep500 using silica gel with hexane/ethyl acetate. X-ray crystallography was done by the X-ray Diffraction Laboratory at the Department of Chemistry in the University of Missouri—St. Louis. All reagents were purchased from Sigma-Aldrich and were used without further purification. All reactions involving air- or moisture-sensitive reagents were conducted under nitrogen.

(±)-2-[[[2-(Bromomethyl)-4-fluorophenyl]sulfinyl]methyl]-2-butylhexanal (5). To a stirred solution of 7.3 g of

(10) Unpublished results.

(11) Monte Carlo conformational search was performed on Macromodel 6.5 with MM3 force field and chloroform as the solvent. Energy calculation was performed on Sybyl 6.5 with Tripos force field and Gasteiger−Huckel charge method.

2-[[[2-(bromomethyl)-4-fluorophenyl]thio]methyl]-2-butylhexanal (4) (20.2 mmol) in 50 mL of CH_2Cl_2 was added 5.2 g of *m*-CPBA (assumed 68% activity, 20.5 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min and at room temperature for 30 min. The mixture was quenched with saturated Na_2SO_3 solution, and the CH_2Cl_2 layer was separated, neutralized with saturated $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated in vacuo. Recrystallization from hexane/ethyl acetate gave 6.8 g of racemic **5** (89%) as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 0.87−0.98 (m, 7H), 1.21−1.39 (m, 8H), 1.76−1.85 (m, 3H), 1.96−2.20 (m, 1H), 3.08 (s, 2H), 4.57−4.70 (ABq, J = 11.10 Hz, 2H), 7.16−7.28 (m, 2H), 8.01 (dd, J = 5.40 Hz, 8.70 Hz, 1H), 9.56 (s, 1H). The structure of **5** was also confirmed by X-ray crystallography. The solid was dissolved in ethanol and chromatographed on (*R*,*R*) Whelk-O 1 with ethanol−hexane (1:9) at 1 mL/min to give 2 peaks at 10.68 min (50%) and 12.08 min (50%).

Oxidation of 4. Method A. 5 (200 mg, 0.55 mmol) was added into the solution of 1.5 mL of Ti(O*i*-Pr)$_4$ (5 mmol), 1.7 mL of (−)-diethyl tartrate (DET) (10 mmol), and 90 μL of H_2O (5 mmol), and the mixture was cooled to −25 °C. Cumene hydroperoxide (CHP, 0.11 mL, 0.60 mmol) was added, and the mixture was stirred for 16 h at −25 °C. TLC indicated the conversion was nearly complete. The mixture was warmed to room temperature, washed with brine, extracted with EtOAc, dried over $MgSO_4$, and concentrated in vacuo. The resulting solid was dissolved in ethanol and chromatographed on (*R*,*R*) Whelk O 1 to give 2 major peaks at 10.58 min (40%) and 11.89 min (60%).

Method B. *tert*-Butyl hydroperoxide (TBHP, 67 μL, 0.60 mmol) was added to the solution of 200 mg of **4** (0.55 mmol) in the Ti(O*i*-Pr)$_4$/(−)-DET/H_2O (1:2:1) solution (same as in method A) at −25 °C and stirred for 16 h at −25 °C. The workup procedure in method A was followed. The crude was dissolved in ethanol and chromatographed on (*R*,*R*) Whelk-O 1 to give 2 peaks at 10.76 min (40%) and 12.17 min (60%).

Method C. Jacobsen's catalyst (18 mg, 0.03 mmol) was added to a solution of 200 mg of **5** (0.55 mmol) in 3 mL of acetonitrile and cooled to −25 °C. CHP (0.11 mL, 0.60 mmol) was then added. The mixture was warmed to room temperature and stirred overnight. PhI(OAc)$_2$ (193 mg, 0.60 mmol) was added into the reaction mixture and stirred overnight. TLC indicated disappearance of **5**. The same workup procedure in method A was followed, and the crude product was chromatographed on (*R*,*R*) Whelk-O 1 to give 2 peaks at 10.69 min (40%) and 12.08 min (60%).

Method D. (−)-(Camphorsulfonyl)oxaziridine (126 mg, 0.55 mmol) was added into a solution of 200 mg of **5** (0.55 mmol) in 20 mL of CH_2Cl_2 at −25 °C. The mixture was stirred at −25 °C overnight, and an aliquot was worked up and chromatographed on (*R*,*R*) Whelk-O 1 to give 2 peaks at 10.47 min (40%) and 11.74 min (60%).

Method E. (−)-(Dichlorocamphorsulfonyl)oxaziridine (165 mg, 0.55 mmol) was added to a solution of 200 mg of **5** (0.55 mmol) in 20 mL of CH_2Cl_2 at −25 °C. The mixture was stirred for 48 h at −25 °C, and an aliquot was worked up and chromatographed on (*R*,*R*) Whelk-O 1 to give 2 peaks at 10.70 min (20%) and 11.74 min (80%).

2-Butyl-2-[[(*R*)-[4-fluoro-2-[(4-methoxyphenyl)methyl]-phenyl]sulfinyl]methyl]-1-hexanol (7). To a stirred solution of 20.00 g (47.78 mmol) of **7** in 1 L of methylene chloride was added 31.50 g of 96% (1*R*) (−)-(8,8-dichloro-10-camphorsulfonyl)oxaziridine (100.34 mmol) at 2 °C. After all the oxaziridine dissolved, the mixture was placed into a −30 °C freezer for 72 h. The solvent was evaporated, and the crude solid was washed with 1 L of hexane. The white solid was filtered off, and the hexane solution was concentrated in vacuo. The crude oil was chromatographed on silica gel column (hexane/ethyl acetate 17:3) to afford 19.00 g (95%) of the product as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.82−0.98 (m, 6H), 1.16−1.32 (m, 12H), 2.30 (d, J = 13.80 Hz, 1H), 2.78 (d, J = 13.50 Hz, 1H), 3.45 (d, J = 12.30 Hz, 1H), 3.69 (d, J = 12.30 Hz, 1H), (s, 3H), 3.97 (d, J = 15.60 Hz, 1H), 4.07 (d, J = 15.90 Hz, 1H), 6.86 (m, 3H), 7.00 (d, J = 8.10 Hz, 2H), 7.20 (m, 1H), 8.02 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 14.17, 14.30, 23.50, 23.69, 25.20, 25.34, 32.78, 35.71, 36.89, 42.47, 55.47, 67.30, 68.06, 114.58, 115.59, 115.88, 117.74, 118.04, 127.27, 127.39, 129.88, 130.27, 138.42, 138.46, 140.60, 140,71, 158.82, 163.01, 166.35. Anal. Calcd for $C_{25}H_{36}O_3SF$: C, 69.09; H, 8.12; S, 7.38. Found: C, 68.90; H, 8.22; S, 7.38.

Enantiomeric excess was determined by chiral HPLC on a (*R*,*R*) Whelk-O 1 column using 5% ethanol hexane as the eluent. It showed to be 78% ee with the first eluting peak as the major product.

(±)-2-Butyl-2-[[[4-fluoro-2-[(4-methoxyphenyl)methyl]-phenyl]sulfinyl]methyl]-1-hexanol (7) was prepared as follows. To a stirred solution of 3.00 g of **6** (7.17 mmol) in a mixture of 5 mL of CH_3OH, 5 mL of THF, and 1 mL of H_2O was added 2.20 g of oxone (3.58 mmol). The mixture was stirred at room-temperature overnight. The solvents were evaporated, and the residue was dissolved in EtOAc, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude was purified on silica gel (hexane/ethyl acetate 9:1) to yield 2.74 g of (±)-**7** (88%). ^{1}H and ^{13}C NMR are identical to that of **7** from the above. HRMS (ES+) calcd of $C_{25}H_{36}O_3SF$ (M + H) 435.2369 found 435.2325.

2-Butyl-2-[[(*R*)-[4-fluoro-2-[(4-methoxyphenyl)methyl]-phenyl]sulfinyl]methyl]-1-hexanal (8). 7 (78% ee, 19.00 g, 43.72 mmol) and 20.96 g of sulfur trioxide−pyridine (131.16 mmol) were added to a solution of 13.27 g of triethylamine (131.16 mmol) in 200 mL of DMSO at room temperature. The mixture was stirred at room temperature for 48 h. H_2O (500 mL) was added to the mixture and stirred vigorously. The mixture was then extracted with 500 mL of EtOAc twice. The EtOAc layer was separated, dried over $MgSO_4$, and concentrated in vacuo. The crude oil was filtered through 500 mL of silica gel using hexane/ethyl acetate (17:3) to give 17.30 g (91%) of the product as a light orange oil: ^{1}H NMR ($CDCl_3$) δ 0.85−0.95 (m, 6H), 1.11−1.17 (m, 4H), 1.21−1.39 (m, 4H), 1.59−1.76 (m, 4H), 1.89−1.99 (m, 1H), 2.57 (d, J = 14.10 Hz, 1H), 2.91 (d, J = 13.80 Hz, 1H), 3.97 (d, J = 15.90 Hz, 1H), 4,12 (d, J = 15.90 Hz, 1H), 6.86 (m, 3H), 7.03 (d, J = 8.4 Hz, 2H), 7.19 (td, J = 8.4 Hz, 2.4 Hz, 1H), 8.02 (dd, J = 8.7 Hz, 5.7 Hz, 1H), 9.49 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.03, 14.12, 23.33, 23.36, 25.78, 26.03, 32.48, 33.33, 36.84, 52.26, 55.50, 60.84, 114.51, 115.51, 115.80, 117.49, 117.78, 127.20, 127.32, 130.03, 130.54, 139.44, 139.47, 140.93, 141.04, 158.78, 163.00, 166.34, 204.27.

(±)-2-Butyl-2-[[4-fluoro-2-[(4-methoxyphenyl)methyl]-phenyl]sulfinyl]methyl]-1-hexanal (8) was also prepared from the oxidation of (±)-**7** by sulfur trioxide−pyridine and triethylamine in DMSO. Yield: 81%. ^{1}H and ^{13}C NMR are identical to those of **8** from the above.

(1*R*,4*R*,5*R*)-3,3-Dibutyl-7-fluoro-2,3,4,5-tetrahydro-5-(4-methoxyphenyl)-1-benzothiepin-4-ol 1-Oxide (3). To a stirred solution of 17.30 g of **8** (39.99 mmol) in 300 mL of THF at −15 °C was added 47.99 mL of 1.0 M KO*t*-Bu in THF (1.2 equiv) under N_2. The solution was stirred at −15 °C for 4 h. The solution was then quenched with 100 mL of H_2O and neutralized with 4 mL of concentrated HCl solution at 0 °C. The THF layer was separated, dried over $MgSO_4$, and concentrated in vacuo. The product was purified by silica gel chromatography (hexane/ethyl acetate 17:3) to give 13.44 g (78%) of the product as a white solid: mp 166−167 °C. ^{1}H NMR ($CDCl_3$) δ 0.87−0.97 (m, 6H), 1.16−1.32 (m, 4H), 1.34−1.48 (m, 4H), 1.50−1.69 (m, 4H), 1.86−1.96 (m, 1H), 2.88 (d, J = 13 Hz, 1H), 3.00 (d, J = 13 Hz, 1H), 3.85 (s, 3H), 4.00 (s, 1H), (s, 1H), 6.52 (dd, J = 9.9 Hz, 2.4 Hz, 1H), 6.94 (d, J = 9 Hz, 2H), 7.13 (td, J = 8.4 Hz, 2.4 Hz, 1H), (d, J = 8.7 Hz, 2H), 7.82 (dd, J = 8.7 Hz, 5.7 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 14.21, 23.40, 23.56, 24.52, 25.21, 32.00, 35.53, 45.09, 46.76, 55.55, 59.68, 74.68, 114.62, 114.96, 115.25, 118.35, 118.67, 124.83, 124.94, 129.95, 133.79, 138.46, 138.56, 140.36, 159.12, 162.54, 165.85. HRMS (ES+) calcd for $C_{25}H_{34}O_3SF$ (M+H) 433.2213 found 433.2246. Anal. Calcd for $C_{25}H_{33}O_3SF$: C, 69.41; H, 7.69. Found: C, 69.29; H, 7.66.

***rel*-(1*R*,4*R*,5*R*)-3,3-Dibutyl-7-fluoro-2,3,4,5-tetrahydro-5-(4-methoxyphenyl)-1-benzothiepin-4-ol 1-oxide (±)-3** was also prepared from the cyclization of (±)-**8** by KO*t*-Bu in THF at −10 °C. Yield: 77%. ^{1}H and ^{13}C NMR are identical to those of **4** from the above.

(4*R*,5*R*)-3,3-Dibutyl-7-fluoro-2,3,4,5-tetrahydro-5-(4-methoxyphenyl)-1-benzothiepin-4-ol 1,1-Dioxide (9). To a stirred solution of 13.44 g (31.07 mmol) of **3** in 150 mL of CH_2Cl_2 was added 9.46 g of *m*-CPBA (assumed 68% activity, 37.28 mmol) at 0 °C. After stirring at 0 °C for 2 h, the mixture was allowed to warm to room temperature and stirred for 4 h. Saturated aqueous Na_2SO_3 (50 mL) was added to the mixture and stirred for 30 min. The solution was then neutralized with 50 mL of saturated $NaHCO_3$ solution. The methylene chloride layer was separated, dried over $MgSO_4$, and concentrated in vacuo to give 13.00 g (97%) of the product as a white solid: mp 159−160 °C. ^{1}H NMR ($CDCl_3$) δ 0.89−0.95 (m, 6H), 1.09−1.42 (m, 12H), 2.21 (m, 1H), 3.08 (d, J = 15.6 Hz, 1H), 3.19 (d, J = 15.6 Hz, 1H), 3.87 (s, 3H), 4.18 (s, 1H), (s, 1H), 6.54 (dd, J = 10.2 Hz, 2.4 Hz, 1H), 6.96−7.07 (m, 3H), 7.40 (d, J = 8.1 Hz, 2H), 8.11 (dd, J = Hz, 5.85 Hz, 1H).^{13}C NMR ($CDCl_3$) δ 14.18, 14.24, 23.39, 24.61, 25.15, 29.96, 35.39, 44.37, 46.23, 55.55, 56.91, 113.90, 114.19, 114.78, 119.24, 119.56, 129.94, 130.10, 134.25, 135.99, 136.05, 143.56, 143.66, 159.17. HRMS (ES+) calcd for $C_{25}H_{34}O_4SF$ (M + H) 449.2162 found 449.2184.

(4*R*,5*R*)-3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-(4-methoxyphenyl)-1-benzothiepin-4-ol 1,1-Dioxide (1a). To a solution of 13.00 g (28.98 mmol) of **9** in 73 mL of 2.0 M of dimethylamine in THF (146 mmol) in a Parr reactor was added ca. 20 mL of neat dimethylamine. The mixture was sealed and stirred at 110 °C overnight and cooled to ambient temperature. The excess dimethylamine and THF were evaporated. The crude oil was dissolved in 200 mL of EtOAc and washed with 100 mL of water, dried over $MgSO_4$, and concentrated in vacuo. Purification on a silica gel column using hexane/ethyl acetate (4:1) gave 12.43 g (91%) of the product as a white solid: mp 134−135 °C. ^{1}H NMR ($CDCl_3$) δ 0.87−0.93 (m, 6H), 1.10 (m, 12H), 2.17−2.25 (m, 1H), 2.81 (s, 6H), 2.99 (d, J = 15.3 Hz, 1H), 3.15 (d, J = 15.3 Hz, 1H), 3.84 (s, 3H), 4.11 (d, J = 7.5 Hz, 1H), 5.49 (s, 1H), 5.99 (d, J = 2.4 Hz, 1H), 6.51 (dd, J = 8.7 Hz, 2.4 Hz, 1H), (d, J = 8.7 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 8.7 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 14.24, 14.30, 23.45, 23.47, 24.69, 25.19, 30.04, 35.61, 39.97, 44.36, 46.52, 55.53, 57.69, 76.67, 108.84, 114.28, 114.81, 126.23, 129.45, 130.28, 135.28, 139.94, 153.34, 158.75. HRMS (ES+) calcd for $C_{27}H_{40}NO_4S$ (M + H) 474.2678 found 474.2684. Anal. Calcd for $C_{27}H_{39}NO_4S$: C, 68.46; H, 8.30; N, 2.96. Found: 68.54; H, 8.29; N, 2.98. The product was determined to have 89:11 er by chiral HPLC on a ChiralPak AD column using 5% ethanol/hexane as the eluent. Recrystallization of this solid from hexane/ethyl acetate gave 1.7 g of the racemic product. The remaining solution was concentrated to give 10.6 g of the enantioenriched product as a white solid. Enantiomeric ratio of this solid was determined by chiral HPLC to be 98:2 with the first eluting peak as the major product.

***rel*-(1*R*,5*R*)-3,3-Dibutyl-7-fluoro-2,3-dihydro-5-(4-methoxyphenyl)-1-benzothiepin-4-(5*H*)-one 1-Oxide (10).** To a stirred solution of 0.46 mL of DMSO (6.48 mmol) in 1.0 mL of CH_2Cl_2 was added 2.4 mL of 2.0 M oxalyl chloride in CH_2Cl_2 solution dropwise at −78 °C in a dry ice−acetone bath. The mixture was stirred at −78 °C for 30 min. To the mixture was added 1.4 g of (±)-**8** (3.24 mmol) in 10 mL of CH_2Cl_2 dropwise, and the resulting mixture was stirred at −78 °C for 2 h. To the stirred mixture was added 1.8 mL of triethylamine (12.96 mmol), and the mixture was stirred at −78 °C for 30 min. The dry ice−acetone bath was removed, and the mixture was stirred for 1 h. The mixture was quenched with H_2O at 0 °C and extracted with 100 mL of CH_2Cl_2. The extracts were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/ethyl acetate 95: 5) to afford 0.56 g of **10** (40%) as a colorless oil: ^{1}H NMR δ 0.77 (t, J = 7.0 Hz, 3H), 0.86 (t, J = 7.2 Hz, 3H), 1.07−1.15 (m, 2H), 1.21−1.32 (m, 5H), 1.47−1.62 (m, 3H), 1.90−1.98 (m, 1H), 2,46−2.53 (m, 1H), 3.05 (d, J = Hz, 1H), 3.35 (d, J = 12.8 Hz, 1H), 3.82 (s, 3H), 5.73 (s, 1H), 6.88 (dd, J = 2.4 Hz, 9.2 Hz, 1H), 6.92 (d, J = 12.0 Hz, 2H), 7.11 (td, J = 2.5 Hz, 8.3 Hz, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.78 (dd, J = 5.4 Hz, 8.6 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 13.84, 14.13, 23.25, 23.39, 25.59, 26.66, 33.82, 34.28, 52.48, 55.51, 56.61, 66.72, 114.35, 114.86, 115.19, 115.38, 115.68, 125.46, 125.58, 126.44, 131.14, 138.66, 138.76, 139.06, 159.60, 163.19, 166.52, 206.72. HRMS (ES+) calcd for $C_{25}H_{32}O_3SF$ (M + H) 431.2056 found 431.2031.

***rel*-(1*R*,4*S*,5*R*)-3,3-Dibutyl-7-fluoro-2,3,4,5-tetrahydro-5-(4-methoxyphenyl)-1-benzothiepin-4-ol 1-Oxide (11).** To a stirred solution of 0.51 g of **10** (1.18 mmol) in 10 mL of CH_3-OH was added 45 mg of $NaBH_4$ (1.18 mmol) at −20 °C in a dry ice−acetone bath. The mixture was stirred at −20 °C for 30 min and then slowly warmed to room temperature and stirred for another 1 h. The mixture was quenched with H_2O at 0 °C, and CH_3OH was evaporated. The mixture was extracted with EtOAc, and the extracts were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give 0.5 g of the mixture of 3% **10**, 27% of **3**, and 70% of **11** (by ^{1}H NMR). The mixture was chromatographed on silica gel (hexane/ethyl acetate 17:3) to yield 0.12 g of **3** and 0.32 g of **11**: ^{1}H NMR ($CDCl_3$) δ 0.83 (t, J = 7.2 Hz, 3H), 0.99 (t, J = 7.2 Hz, 3H), 1.16−1.24 (m, 4H), 1.28−1.46 (m, 4H), 1.51−1.75 (m, 4H), 1.98−2.06 (m, 1H), 3.02−0.09 (m, 2H), 3.83 (s, 3H), 3.90 (d, J = 9.2 Hz, 1H), 4.50 (d, J = 9.6 Hz, 1H), 6.75 (dd, J = 2.2 Hz, 10.6 Hz, 1H), 7.00 (d, J = 8.8 Hz, 2H), 7.08 (td, J = 2.4 Hz, 8.2 Hz, 1H), 7.24 (d, J = 3.2 Hz, 2H), 7.79 (dd, J = 5.6 Hz, 8.8 Hz, 1H). A satisfactory analytical result was not obtained due to instability of **11**.

Isomerization of 3 and 11. To a stirred solution of 100 mg of **3** (0.23 mmol) in 3 mL of THF was added 0.25 mL of 1.0 M KO*t*-Bu in THF (0.25 mmol) at −10 °C. The mixture was stirred at −10 °C for 30 min, and an aliquot was quickly transferred into a vial cooled at −10 °C in a dry ice−acetone bath. The aliquot was quenched with H_2O and extracted with ether. The ether layer was subject to HPLC equipped with a Alltech Silica column (ethanol/hexane 2:98 at 1.0 mL/min) and gave **3** at 16.98 min (76.8%). The whole mixture was quenched with H_2O, treated with saturated NH_4Cl solution, extracted with EtOAc, dried over $MgSO_4$, and concentrated in vacuo. ^{1}H NMR ($CDCl_3$) showed the major component to be **3**, some decomposition products, a small amount of **8**, and no **11**. To a stirred solution of 100 mg of **11** (0.23 mmol) in 3 mL of THF was added 0.25 mL of 1.0 M KO*t*-Bu in THF (0.25 mmol) at −10 °C. The mixture was stirred at −10 °C for 30 min, and an aliquot was quickly transferred into a vial cooled at −10 °C in a dry ice−acetone bath. The aliquot was quenched with H_2O, extracted with ether, and analyzed by HPLC and gave **3** at 16.20 min (74.8%). The mixture was quenched with H_2O, treated with saturated NH_4Cl solution, extracted with EtOAc, dried over $MgSO_4$, and concentrated in vacuo. ^{1}H NMR ($CDCl_3$) showed the major component to be **3**, some decomposition products, a small amount of **8**, and no **11**.

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Supporting Information Available: One full-scale NMR spectrum of each new compound; X-ray crystallographic data ORTEP diagrams. This material is available free of charge via the Internet at http://pubs.acs.org.

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