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Synthesis of (*R*)-*N*-[4-[4-(Dibutylamino)-1-hydroxybutyl]phenyl]methanesulfonamide, (*E*)-2-Butenedioate (2:1) Salt (Artilide Fumarate) and the Enantiomers of *N*-[4-[4-(Ethylheptylamino)-1-hydroxybutyl]phenyl]methanesulfonamide, (*E*)-2-Butenedioate (2:1) Salt (Ibutilide Fumarate)

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Abstract: Syntheses of artilide fumarate, its (*S*) enantiomer and the (*R*) and (*S*) enantiomers of ibutilide fumarate were achieved by reduction of the prochiral ketones with (+) and (-)-*B*-chlorodiisopinocampheylborane. Several methods for analyzing the optical purity of these compounds are presented. The absolute configurations were established by a single crystal X-ray crystallographic analysis of (*S*)-*N*-[4-[4-(dibutylamino)-1-hydroxy-4-oxobutyl]phenyl]methanesulfonamide.
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Class III antiarrhythmic agents have been found to be particularly efficacious for controlling re-entrant arrhythmias in the mammalian heart.¹ In humans the re-entrant mechanism has been associated with atrial fibrillation and flutter² and with ventricular tachyarrhythmias and fibrillation.³ The latter arrhythmias play a major role in causing sudden cardiac death which is a leading cause of mortality in the United States.⁴ There has, therefore, been a considerable interest in developing safe Class III agents for treating this largely unmet medical need, and a variety of compounds have now received at least preliminary clinical evaluation.⁵ Most of these achieve the desired electropharmacologic activity by blocking one or more potassium channels in cardiac tissue⁶ which results in a delayed repolarization of the action potential and a resultant prolonged period in which the tissue is refractory to a second, dysrhythmic,

depolarization. At Pharmacia & Upjohn, Inc. we have investigated a series of compounds from which ibutilide fumarate (**17**) was chosen for clinical development.⁷ Unlike other known Class III agents, ibutilide achieves a prolongation of the cardiac action potential by enhancing a slow inward sodium current (I_{Na-s})⁸ which we believe may afford a unique mechanistic advantage.⁹

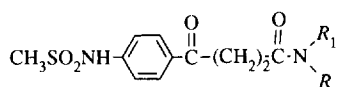
It is now well known that the enantiomers of asymmetric compounds can behave very differently in biological systems. Not only can they show differences in the desired activities, but they can also have different absorption, distribution, metabolism, elimination and toxicity characteristics. One enantiomer, if present, can sometimes have an adverse (or beneficial) effect on these characteristics of the other enantiomer.^{10,11} During the early stages of ibutilide's development, therefore, it became necessary to resolve its asymmetric center so that the behavior of the enantiomers in biological systems could be evaluated. It was found that although the (*R*) enantiomer (**15**, U-82208E) generally appeared to be somewhat more efficacious than the (*S*) enantiomer (**16**, U-82209E), their pharmacology was similar to that of **17** when evaluated on isolated rabbit myocardium¹² and in the conscious dog¹³ and human¹⁴. The enantiomers and racemate had similar pharmacokinetics and pharmacodynamics when administered to dogs¹⁵ and humans¹⁴ and the enantiomers were not interconverted *in vivo*. These results helped to justify our clinical development of the racemate (**17**) for intravenous conversion of atrial fibrillation and flutter to normal sinus rhythm.¹⁶

During ibutilide's development, it was found that it had poor bioavailability after oral administration to humans.¹⁶ A closely related compound (**20**) that had similar pharmacology but better bioavailability was therefore chosen for further evaluation. The enantiomers of **20** were synthesized and the (*R*) enantiomer (**18**, artilide fumarate, U-88943E) was chosen for clinical development. This report describes the synthesis of artilide and its (*S*) enantiomer and the (*R*) and (*S*) enantiomers of ibutilide.

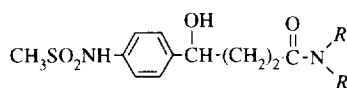
RESULTS AND DISCUSSION

Our approach to the synthesis of the enantiomers of **17** and **20** was based on the work of Brown and coworkers^{17,18} who developed B-chlorodiisopinocampheylborane (DIP-chloride) for the chiral reduction of ketones. Both enantiomers of this reagent could be prepared from readily available starting materials¹⁹ and both were commercially available. It had been shown that high yields of alcohols with excellent optical purity could be obtained by reduction of substituted acetophenones with this reagent. When **1** was reduced with (+)-DIP-chloride at -30 °C and the crude product crystallized to constant rotation, a 47% yield of the (+)-enantiomer (**4**) was obtained. This was reduced with lithium aluminum hydride to give **10** which was isolated as its crystalline hemifumarate salt (**15**). The (-)-enantiomer (**16**)

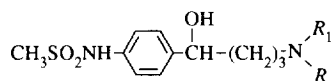
was obtained in a similar manner via the reduction of **1** with (-)-DIP-chloride. Analysis of the chiral purity of **15** and **16** was somewhat problematical since derivatization with commonly used reagents such as α -methoxy- α -(trifluoromethyl)phenylacetic acid^{20,21} appeared to epimerize the alcohol. It was found, however, that the racemate (**12**) would react with (*R*)-1-(1-naphthyl)ethyl isocyanate (**28**) to give a diastereomeric mixture of carbamates (**23**, **22**) that could be separated by reverse phase HPLC. A small amount of the product (**25**) of addition to both the alcohol and the sulfonamide nitrogen was also obtained in this reaction. When the individual enantiomers were allowed to react with **28** it was found that the reaction with **11** to give **22** was faster and gave a better yield of **22** than the corresponding reaction with **10** to give **23**. For routine analysis of chiral purity, we therefore prepared **22** from **11** and the enantiomer **24** from **10**. Using this method it was found that the salts **15** and **16** had greater than 98% optical purity.²²



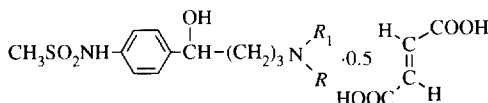
- 1**, $R = -(\text{CH}_2)_6\text{CH}_3$; $R_1 = \text{C}_2\text{H}_5$
2, $R = R_1 = -(\text{CH}_2)_3\text{CH}_3$
3, $R = -(\text{CH}_2)_3\text{CH}_3$, $R_1 = \text{H}$



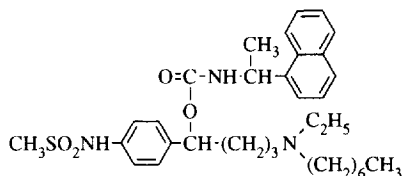
- $R = -(\text{CH}_2)_6\text{CH}_3$; $R_1 = \text{C}_2\text{H}_5$
4 = (*R*)(+); **5** = (*S*)(-)
 $R = R_1 = (\text{CH}_2)_3\text{CH}_3$
6 = (*R*)(+); **7** = (*S*)(-); **8** = (*RS*)
 $R = -(\text{CH}_2)_3\text{CH}_3$; $R_1 = \text{H}$
9 = (*R*)(+)



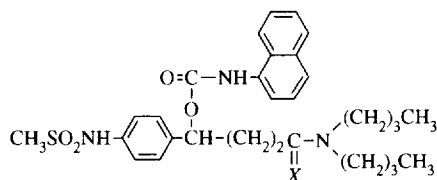
- $R = (\text{CH}_2)_6\text{CH}_3$; $R_1 = \text{C}_2\text{H}_5$
10 = (*R*)(+); **11** = (*S*)(-); **12** = (*RS*)
 $R = R_1 = -(\text{CH}_2)_3\text{CH}_3$
13 = (*RS*)
 $R = (\text{CH}_2)_3\text{CH}_3$; $R_1 = \text{H}$
14 = (*R*)(+)



- $R = (\text{CH}_2)_6\text{CH}_3$; $R_1 = \text{C}_2\text{H}_5$
15 = (*R*)(+); **16** = (*S*)(-); **17** = (*RS*)
 $R = R_1 = (\text{CH}_2)_3\text{CH}_3$
18 = (*R*)(+); **19** = (*S*)(-); **20** = (*RS*)



- 21**, (*R*, *RS*) **22**, (*R*, *S*)
23, (*R*, *R*) **24**, (*S*, *R*)



- 26**, $X = \text{O}$; **27**, $X = \text{H}_2$

A second method for determining the optical purity of these compounds was based on the chiral solvation of **12** with (*R*)-2,2,2-trifluoro-1-(9-anthranyl)ethanol in CDCl_3 .^{23,24} It was found that for the solvate the enantiomeric methine protons on the alcohol substituted carbon were represented by a pair of doublets centered at δ 4.48 and δ 4.55. With the appropriate spin decoupling and signal amplification at least 1% of the enantiomeric impurity in **10** or **11** could be detected by this method.

Reduction of **2** with (+)-DIP-chloride gave the (+)-alcohol **6**. In this case, however, crystallization from Et_2O gave a mixture of crystals composed of the pure enantiomer (**6**) and the racemate (**8**). Unfortunately, the racemate crystallized more easily than the enantiomer and a simple recrystallization of this mixture did not enhance the enantiomeric purity of **6**. A careful fractional crystallization in which **8** was selectively crystallized from the mixture was successful, however, and a sample of pure **6** was obtained. This recrystallization was facilitated by the fact that the IR spectra of crystals of **6** and **8** in a mineral oil mull were different and small amounts of **8** in a crystalline sample of the mixture could easily be detected. The (*S*) enantiomer (**7**) was prepared in a similar manner using (-)-DIP-chloride for the reduction of **2**. An authentic sample of **8** was prepared by catalytic reduction of **2** with a 10% palladium-on-carbon catalyst. The reaction of **8** with 1-naphthylisocyanate gave the racemic carbamate **26** which could be resolved by HPLC on a Pirkle covalent N-(3,5-dinitrobenzoyl)-D-phenylglycine (DNBPG) column.²⁵ This provided an independent method for evaluating the enantiomeric purity of **6** and **7**. Reduction of **6** and **7** with a solution of lithium aluminum hydride in THF at -10 to -20 °C gave the enantiomeric amines which were converted to their hemifumarate salts **18** and **19**, respectively. The use of a slurry of solid lithium aluminum hydride in THF or higher temperatures for this reduction gave unacceptable levels of impurities that were difficult to remove. A chiral assay for **18** and **19** was based on a method developed by Hsu and Walters²⁶ for ibutilide. The alcohols (**18** and **19**) were allowed to react with 1-naphthyl isocyanate and the resulting carbamates were analyzed on a covalent Pirkle DNBPG column.

Because of the difficulty in obtaining optically pure samples of **6**, alternate procedures for preparing **18** were investigated. In one method it was found that **18** would form a crystalline di-*p*-toluoyl-L-tartrate salt. Although this salt would not crystallize from the racemic mixture (**13**) it could be used to purify **18** that contained at least 10% of the enantiomer (**19**).

A second method for obtaining pure **18** relied on the reduction of **3** with (+)-DIP-chloride. The product **9** could be crystallized to optical purity from EtOAc . Reduction of **9** was carried out with bis(2-methoxyethoxy)aluminum hydride. A non-aqueous work-up was employed to facilitate the isolation of **14** which was soluble in water. This synthesis of **18** was completed by alkylating **14** with *n*-butyl bromide

and sodium bicarbonate in acetonitrile. It is interesting that the use of potassium bicarbonate in this reaction gave large amounts of a biproduct in which both the sulfonamide nitrogen and the secondary amine were alkylated.

With regard to the absolute configuration of the chiral alcohols prepared in this report, Brown and coworkers¹⁷ have shown that the absolute configuration of the alcohols obtained by reduction of a series of substituted acetophenones with (-)-DIP-chloride depends primarily on the bulk of the alkyl substituent adjacent to the ketone. Thus, reduction of acetophenone and butyrophenone gave the (*S*) alcohols with very high optical purity (98% ee). Reduction of isobutyrophenone gave the (*S*) alcohol with 78% ee and reduction of pivalophenone gave the (*R*) alcohol with 79% ee. Based on these observations, if only the steric requirements for the reduction were considered, we would expect the configuration of the alcohol **7** obtained from the reduction of **2** with (-)-DIP-chloride to be (*S*); however, since the influence of the amide and the methanesulfonamide moieties of **2** on the reduction were uncertain, we were not confident in this assignment. The absolute configuration of **7** was therefore determined by a single crystal X-ray analysis which conclusively demonstrated that it had the (*S*) absolute configuration. Based on this result we can confidently make the configurational assignments presented in this report.

EXPERIMENTAL SECTION

General. A 1M solution of LiAlH₄ in THF and (+) or (-)-B-chlorodiisopinocampheylborane [(+) or (-)-DIP-chloride] were obtained from Aldrich Chemical Company, Inc. Analytical thin layer chromatography (TLC) was carried out on Analtech silica gel GF (250 μm) glass plates. Flash chromatography was carried out on Kieselgel 60 (230-400 mesh ASTM silica gel) from E. M. Reagents. Melting points were taken in capillary tubes and are uncorrected. Celite is a filter aid manufactured by Johns-Manville, NY. HPLC analyses of purity for **18** and **19** were carried out on a Brownlee Labs RP-18 Spheri-5, 4.6 mm ID x 25 cm analytical column with a 3 cm RP-18 Spheri-10 guard column using isocratic elution with 22% pH 3 phosphate buffer/78% CH₃CN and a flow rate of 1.5 mL/min and a detector setting of 230 nm. Chiral HPLC analyses were carried out on a 4.6 mm x 25 cm Bakerbond chiral phase DNPG (covalent), 5 μm analytical column supplied by J. T. Baker Chemical Co., Phillipsburg, NJ. Gradients for HPLC separations were generated by a Waters Model 680 Automated Gradient Controller supplied by Waters Associates, Milford, MA.

N-[4-[4-(Butylamino)-1,4-dioxobutyl]phenyl]methanesulfonamide (3). A stirred suspension of 4-[(methylsulfonyl)amino]-γ-oxobenzenebutanoic acid⁷ (80.0 g, 0.294 mol) in THF (2400 mL), under nitrogen, was treated with triethylamine (54.8 mL, 0.392 mol). After 1 h the resulting solution was cooled in an isopropanol-ice bath to -5 °C and treated, dropwise during 15 min, with isobutyl chloroformate (51.2 mL, 0.394 mol). The mixture was stirred in the cold for 90 min and then treated dropwise during 1 h with a solution of n-butylamine (35.2 mL, 0.356 mol) and triethylamine (54.8 mL, 0.392 mol) in THF (700 mL). It was kept in the bath for 90 min and treated with water (500 mL). The mixture was warmed in a hot water bath and the resulting solution was concentrated *in vacuo* to remove THF. The resulting mixture was mixed with EtOAc (700 mL) and the crystalline product was collected by filtration, washed with water and dried to give 68.8 g (71.7%) of **3**, mp 185 °C (dec). An additional 5.6 g of **3**, mp 185 °C (dec) was

obtained by extracting the filtrate with EtOAc. A sample of this material was recrystallized from acetonitrile and had: mp 191-192.5 °C; IR (Nujol) 3380, 3160, 3136, 3084, 3071, 3053, 3024, 3009, 1672, 1638, 1601 cm⁻¹; MS *m/z* (relative intensity) 326 (M⁺, 18.5), 284 (2.5), 254 (48.7), 226 (6.4), 198 (100); ¹H NMR (300 MHz, CDCl₃) δ 0.92 (t, *J* = 7.3 Hz, 3H), 1.36 (m, 2H), 1.49 (m, 2H), 2.59 (t, *J* = 6.6 Hz, 2H), 2.95 (broad s), 3.05 (s, 3H), 3.23 (m, 2H), 3.31 (t, *J* = 6.6 Hz, 2H), 6.48 (broad s, 1H), 7.28 (d, *J* = 8.9 Hz, 2H), 7.95 (d, *J* = 8.8 Hz, 2H). Anal. calcd for C₁₅H₂₂N₂O₄S: C, 55.19; H, 6.79; N, 8.58; S, 9.82. Found: C, 55.02; H, 7.04; N, 8.58; S, 9.73.

(R)-N-[4-[4-(Ethylheptylamino)-1-hydroxy-4-oxobutyl]phenyl]methane-sulfonamide (4). A stirred solution of 9.0 g (0.028 mol) of (+)-B-chlorodiisopinocampheylborane in 25 mL of THF under nitrogen, was cooled to -30 °C and treated, dropwise over 30 min with 5.00 g (0.0126 mol) of **1** in 50 mL of THF. The mixture was kept at -35 to -30 °C for 45 min when by TLC (5% MeOH-CH₂Cl₂) the reaction was complete. It was mixed with EtOAc (500 mL), treated with diethanolamine (7 mL) and stirred for 1 h (a gummy suspension formed). This mixture was treated with cold water (125 mL); the layers were separated and the aqueous layer was extracted with EtOAc. The extracts were washed with cold water and brine, dried (MgSO₄) and concentrated. The residue was flash chromatographed over silica gel with 3.5% MeOH-CH₂Cl₂ and the product was crystallized from EtOH-hexane to give 3.46 g of a solid. After three recrystallizations 2.34 g (46.6%) of **4** mp 78-81 °C was obtained. A sample was recrystallized from EtOAc-hexane and had: mp 81-83 °C; [α]_D²⁴ + 12 (c 0.5, EtOH); MS *m/z* (relative intensity) 398 (M⁺, 4.4), 170 (100); IR (Nujol) 3239, 3117, 3055, 3031, 3012, 1605 cm⁻¹; UV_{max} (EtOH) 229 nm (ε 14,720), 274 (562), 283 sh (378); ¹H NMR (300 MHz, CDCl₃) δ 0.89 (m, 3H), 1.14 (m, 3H), 1.28 (broad s, 8H), 1.54 (m, 2H), 2.08 (m, 2H), 2.51 (m, 2H), 2.99 (s, 3H), 3.19-3.45 (m, 4H), 4.79 (m, 1H), 4.95 (m, 1H), 6.59 (s, 1H), 7.19 (d, *J* = 8.46 Hz, 2H), 7.36 (d, *J* = 8.43 Hz, 2H). Anal. calcd for C₂₀H₃₄N₂O₄S: C, 60.27; H, 8.60, N, 7.03; S, 8.05. Found: C, 60.53; H, 8.78; N, 7.09; S, 8.07.

The melting point of this enantiomer is lower than that of **5**. Melting points of samples of **4** that had been stored for several days, however, were invariably 90-91 °C, the same as that of **5**. The IR spectra of **4** and **5**, taken in Nujol mull, were also slightly different. When spectra of these compounds were taken in chloroform solution, however, they were identical. These data suggest that the initial crystalline samples of **4** represent a different polymorphic form than that obtained for **5**.

(S)-N-[4-[4-(Ethylheptylamino)-1-hydroxy-4-oxobutyl]phenyl]methane-sulfonamide (5). The reduction of 5.00 g (0.0126 mol) of **1** with (-)-B-chlorodiisopinocampheylborane (9.0 g, 0.028 mol) gave 3.28 g of crude product which after three recrystallizations from EtOAc-hexane yielded 2.8 g (55.8%) of **5**: mp 90-91 °C; [α]_D²⁴ -13 (c 0.68, EtOH); MS *m/z* (relative intensity) 398 (M⁺, 5.9), 170 (100); UV max (EtOH) 229 nm (ε 14,400), 274 (558), 283 sh (373); IR (Nujol) 3284, 3274, 3120, 3058, 3034, 1616 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.89 (m, 3H), 1.14 (m, 3H), 1.28 (broad s, 8H), 1.54 (m, 2H), 2.07 (m, 2H), 2.51 (m, 2H), 2.98 (s, 3H), 3.18-3.44 (m, 4H); 4.78 (m, 1H), 4.90 (m, 1H), 6.89 (s, 1H), 7.19 (d, *J* = 8.39, 2H), 7.35 (d, *J* = 8.41, 2H). Anal. calcd for C₂₀H₃₄N₂O₄S: C, 60.27; H, 8.60; N, 7.03; S, 8.05. Found: C, 60.15; H, 8.58; N, 7.19; S, 8.13.

(R)-N-[4-[4-(Dibutylamino)-1-hydroxy-4-oxobutyl]phenyl] methane-sulfonamide (6). A stirred solution of (+)-B-chlorodiisopinocampheylborane (100 g, 0.312 mol) in THF (278 mL) was cooled, under nitrogen, in a dry ice-acetone bath to -40 °C and treated, during 30 min, with a solution of **2**⁷ (50 g, 0.131 mol) in THF (555 mL); the temperature of the reaction mixture was maintained near -40 °C during the addition. The mixture was kept at -40 °C for 2 h and then treated first with EtOAc (2 L) and then with diethanolamine (80 mL). It was stirred for 1 h, mixed with cold water, and extracted with EtOAc. The extracts were washed with water and brine, dried (Na₂SO₄) and concentrated. The residue was purified by chromatography and crystallized.

A sample of **6** from the chiral reduction was carefully purified by silica gel chromatography with 0-2% MeOH-CH₂Cl₂. A solution of this material (87.6 g) in Et₂O was concentrated on the steam bath to the

cloud point (2200 mL); enough Et₂O was added to give a clear solution which was seeded with the racemate (**8**) and allowed to stand for 24 h. The racemic alcohol (**8**) normally crystallized easily from the mixture. It was removed by filtration and the filtrate was warmed, seeded with the (+) enantiomer (**6**) and allowed to stand for 48 h. The crystalline **6** was then collected by filtration and the filtrate was concentrated to about one-half of its original volume on the steam bath and seeded with the racemate; the crystallization was continued in this manner until no further product was obtained. The progress of the crystallization could be followed by IR; the spectrum of the enantiomer, crystallized in this manner, is very different from that of the racemate and mixtures of the two could easily be detected. The racemate normally crystallized as fine needles while the enantiomer crystallized as large prisms. Since the needles dissolve more readily in warm Et₂O it was sometimes possible to effect a preliminary separation by warming a mixture of crystals in Et₂O and decanting the solution. For this preparation, the first two crops (44.4 g) were impure enantiomer by IR; the third crop was the racemate (3.87 g) and the fourth crop was pure enantiomer (15.97 g). Subsequent crystallization gave 2.48 g of the racemate, 2.23 g of pure enantiomer and 9.5 g of impure enantiomer. Samples of impure enantiomer could be reprocessed as just illustrated. One recrystallization of a sample (27.0 g) of enantiomer that was pure by IR gave 12.2 g of **6**: mp 74-80 °C; $[\alpha]_D^{24} +13$ (c 0.935, EtOH); UV_{max} (EtOH) 229 nm (ϵ 14690), 275 (561), 2.83 (sh, 378); MS *m/z* (relative intensity) 384 (M⁺ 7.8), 200 (6.3), 171 (17.9), 156 (53.9), 128 (100); ¹H NMR (300 MHz, CDCl₃) δ 0.93 (t, *J* = 7.2 Hz, 6H), 1.31 (m, 4H), 1.53 (m, 4H), 2.07 (m, 2H), 2.56 (m, 2H), 2.97 (s, 3H), 3.29 (m, 4H), 4.79 (m, 1H), 4.97 (s, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H); IR (Nujol) 3512, 3155, 1633, 1506 cm⁻¹. Anal. calcd for C₁₉H₃₂N₂O₄S: C, 59.35; H, 8.39; N, 7.28; S, 8.34. Found: C, 59.22; H, 8.62; N, 7.27; S, 8.36.

(S)-N-[4-[4-(Dibutylamino)-1-hydroxy-4-oxobutyl]phenyl]methane-sulfonamide (7). A stirred solution of (-)-B-chlorodiiisopinocampheylborane (25 g, 0.078 mol) in THF (85 mL) was cooled, under nitrogen, in a bath at -35 to -40 °C and treated, dropwise during 1.5 h, with a solution of **2**⁷ (13.4 g, 0.035 mol) in THF (140 mL); the initial yellow solution became colorless after 30 min, when by TLC (5% MeOH-CH₂Cl₂) the reaction was complete. The bath was allowed to warm to -20 °C and the mixture was treated with EtOAc (140 mL). It was then poured into a mixture of EtOAc (700 mL) and diethanolamine (18.2 mL) and stirred for 30 min at ambient temperature. This mixture was washed with cold water; the aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried (MgSO₄) and concentrated *in vacuo*. The oily residue was washed twice with a mixture of Et₂O and pentane to remove α -pinene and the residue (12.3 g) was chromatographed on silica gel (600 mL) with 2.5% MeOH-CH₂Cl₂ to give 8.37 g of product. This was crystallized from *tert*-butyl methyl ether to give 2.22 g of **7**: mp 70-71 °C; $[\alpha]_D^{24} -13$ (c 0.834, EtOH). The IR and mass spectra were identical to those of **6**. Anal. calcd for C₁₉H₃₂N₂O₄S: C, 59.34; H, 8.39; N, 7.29; S, 8.34. Found: C, 59.36; H, 8.39; N, 7.27; S, 8.23.

Slow recrystallization of this material from *tert*-butyl methyl ether at ambient temperature gave crystals that were used for the X-ray study: mp 71-72 °C; $[\alpha]_D^{25} -15.3^\circ$ (c 1, EtOH).

N-[4-[4-(Dibutylamino)-1-hydroxy-4-oxobutyl]phenyl]methanesulfonamide (8). A suspension of **2**⁷ (5.0 g, 0.013 mol) and 10% palladium-on-carbon catalyst (0.6 g) in EtOH (150 mL) was hydrogenated on a Parr apparatus at an initial pressure of 359 kPa for 4 h and 45 min. The catalyst was removed by filtration through Celite and the filtrate was concentrated *in vacuo*. A solution of the residue in EtOAc was filtered through Celite and concentrated. The residue was crystallized from *tert*-butyl methyl ether to give 3.80 g, mp 80-81 °C and 0.453 g, mp 79-80 °C of **8**. The analytical sample had: mp 80-81 °C; MS *m/z* (relative intensity) 384 (M⁺, 5.3), 367 (0.7), 200 (6.2), 171 (18.7), 156 (57.5), 128 (100); ¹H NMR (300 MHz, CDCl₃) δ 0.93 (t, *J* = 7.25 Hz, 6H), 1.31 (m, 4H), 1.52 (m, 4H), 2.07 (m, 2H), 2.51 (m, 2H), 2.98 (s, 3H), 3.20 (m, 2H), 3.33 (m, 2H), 4.77 (m, 1H), 4.97 (d, *J* = 3.94 Hz, 1H), 6.88 (s, 1H), 7.20 (d, *J* = 8.43 Hz, 2H), 7.35 (d, *J* = 8.45 Hz, 2H); IR (Nujol) 3328, 3199, 1594, 1514 cm⁻¹. Anal. calcd for C₁₉H₃₂N₂O₄S: C, 59.34; H, 8.39; N, 7.29; S, 8.34. Found: C, 59.43; H, 8.37; N, 7.30; S, 8.33.

Preparation of the 1-naphthylcarbamate (26) of 8. A stirred solution of 0.43 g (1.12 mmol) of **8** in acetonitrile (40 mL) was treated, dropwise, during 1 min with a solution of 1-naphthylisocyanate (0.20 g, 1.18 mmol) in acetonitrile (2 mL). The mixture was kept at ambient temperature for 3 h and quenched with methanol. This mixture was concentrated and the residue was chromatographed under pressure on silica gel (200 mL) with 2.5% MeOH-CH₂Cl₂. The product (**26**) amounted to 0.38 g: ¹H NMR (300 MHz, CDCl₃) δ 0.89 (m, 6H), 1.27 (m, 4H), 1.49 (m, 4H), 2.3 (m, 4H), 2.96 (s, 3H), 3.16 (m, 2H), 3.31 (m, 2H), 5.78 (m, 1H), 7.26 (m, 6H), 7.5 (m, 5H), 7.87 (m, 3H).

Analysis of the chiral purity of 6 and 7. A solution of the hydroxy amide (**6** or **7**, 0.011 g) in acetonitrile (2 mL), in a capped vial, was treated with 1-naphthylisocyanate (0.016 g) in acetonitrile (1 mL) and allowed to stand with occasional shaking at ambient temperature for 1 h. The mixture was concentrated *in vacuo*, treated with a little MeOH and concentrated. The HPLC assay was carried out on a covalent Pirkle DNBPG column at a flow rate of 0.7 mL/min with a detection setting of 230 nm. A programmed gradient was used: 85% hexane/15% EtOH for 5 min, a gradient from 85% hexane/15% EtOH to 75% hexane/25% EtOH over 20 min with gradient curve number three, 75% hexane/25% EtOH for 1 min and return to the initial conditions with gradient curve number eleven. Under these conditions, the carbamates of enantiomers **6** and **7** had retention times (t_R) of 24.9 min and 27.15 min respectively.

(R)-N-[4-[4-(Butylamino)-1-hydroxy-4-oxobutyl]phenyl]methane-sulfonamide (9). A stirred solution of (+)-B-chlorodiisopinocampheylborane (57.0 g, 0.178 mol) in THF (450 mL), under nitrogen, was cooled to -35 °C in an EtOH-Dry Ice bath and treated during 65 min with a suspension of **3** (23.1 g, 0.0708 mol) in THF (240 mL). The mixture was kept at -30 to -35 °C for 2 h, treated with additional (+)-B-chlorodiisopinocampheylborane (5.0 g, 0.0156 mol) and kept at -30 °C for one additional hour. It was then poured into a solution of diethanolamine (42 mL) in EtOAc (1 L) and stirred for 45 min. This mixture was washed with water and the aqueous layer was extracted with EtOAc; the combined organic solution was washed with brine, dried (MgSO₄) and concentrated. Chromatography of the residue on silica gel with 5% MeOH-CH₂Cl₂ gave 21.3 g of crude product which was recrystallized three times from EtOAc to give 10.8 g (46.4%) of **9**: mp 120-122 °C; [α]_D²⁴ +14 (c 0.83, EtOH); IR (Nujol) 3366, 3212, 3112, 3054, 3013, 1642, 1613 cm⁻¹; MS *m/z* (relative intensity) 328 (M⁺, 6.5), 310 (2.4), 200 (8.3), 115 (100); ¹H NMR (300 MHz, CDCl₃) δ 0.92 (t, *J* = 7.2 Hz, 3H), 1.35 (m, 2H), 1.48 (m, 2H), 1.99 (m, 2H), 2.31 (m, 2H), 2.96 (s, 3H), 3.22 (t, *J* = 7.0 Hz, 2H), 4.69 (m, 1H), 7.18 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H). Anal. calcd for C₁₅H₂₄N₂O₄S: C, 54.85; H, 7.36; N, 8.53; S, 9.76. Found: C, 54.55; H, 7.37; N, 8.46; S, 9.63.

(R)-N-[4-[4-(Ethylheptylamino)-1-hydroxybutyl]phenyl] methane-sulfonamide (10). An ice cold stirred suspension of LiAlH₄ (0.23 g, 6.0 mmol) in THF (4 mL), under nitrogen, was treated, dropwise during 25 min, with a solution of **4** (1.2 g, 3.0 mmol) in THF (12 mL). The mixture was kept in the ice bath for 30 min and then treated cautiously with a saturated solution of potassium sodium tartrate (8 mL). It was stirred for 20 min and then extracted with EtOAc. The extracts were washed with water and brine, dried (MgSO₄) and concentrated. Flash chromatography of the residue on silica gel with 10% MeOH-CHCl₃ gave the product which was partitioned between saturated aqueous NaHCO₃ and Et₂O. The ether extract was washed with water and brine, dried (MgSO₄) and concentrated to give 0.67 g of **10**, an oil: [α]_D²⁴ +18 (c 0.546, EtOH); HRMS calcd for C₂₀H₃₆N₂O₃S *m/z* 384.2447 (M⁺), found *m/z* 384.2445; UV_{max} (EtOH) 229 nm (ε, 14,000), 274 (565), 283 sh (388); ¹H NMR (300 MHz, CDCl₃) δ 0.89 (m, 3H), 1.09 (t, *J* = 7.09, 3H), 1.29 (broad s, 8H), 1.53 (m, 2H), 1.69 (broad s, 3H), 1.96 (m, 1H), 2.33-2.77 (m, 6H), 2.94 (s, 3H), 4.60 (m, 1H), 7.17 (d, *J* = 8.40 Hz, 2H), 7.37 (d, *J* = 8.43 Hz, 2H).

(S)-N-[4-[4-(Ethylheptylamino)-1-hydroxybutyl]phenyl] methane-sulfonamide (11). Reduction of **5** (1.2 g, 3.0 mmol) with LiAlH₄ (0.27 g, 7.1 mmol) gave 0.715 g of **11**, an oil: [α]_D²⁴ -18 (c 0.352, EtOH); HRMS calcd for C₂₀H₃₆N₂O₃S *m/z* 384.2447 (M⁺), found 384.2444; UV_{max} (EtOH) 230 nm (ε, 13,820), 274 (561), 283 sh (379). The ¹H NMR spectrum was identical to that of **10**.

Reaction of 12 with (R)-1-(1-naphthyl)ethylisocyanate 28; HPLC analysis of the diastereomeric mixture 21. A solution of **12**⁷ (0.50 g, 1.3 mmol) in 1-methyl-2-pyrrolidinone (5 mL) was cooled to -10 °C under nitrogen, and treated portionwise during 2 h with a solution of **28** (0.301 g, 1.53 mmol) in CH₂Cl₂ (4 mL). The mixture was maintained at -10 °C for 3 h and at -15 °C for 18 h; the reaction was complete by TLC (15% MeOH-CH₂Cl₃). It was then diluted with Et₂O, washed repeatedly with water and then brine, dried (MgSO₄) and concentrated. The residue was flash chromatographed over silica gel with 10% MeOH-CHCl₃. The first product eluted from the column amounted to 0.20 g of the diastereomeric product **25**: FAB MS *m/z* 779 (M+H)⁺. The second product eluted amounted to 0.44 g of the diastereomeric mixture **21**: FAB MS *m/z* 582 (M+H)⁺. This was analyzed by HPLC on a Brownlee Labs 3 cm RP-18 Spheri-10 guard column and two RP-18 Spheri-5, 4.6 mm ID x 24 cm analytical columns in series using isocratic elution with 17% of a 10% solution of CH₃CN in pH 3 phosphate buffer and 83% of a 90% solution of CH₃CN in pH 3 phosphate buffer. The flow rate was 1.5 mL/min and the detector was set at 225 nm. Two peaks with retention times (*t_R*) of 65.7 and 69 min and integrals of 52.2 and 47.8%, respectively were obtained. The resolution (*R_s*) for this separation was 1.47 and the separation factor (α) was 1.05.

Reaction of 10 with (R)-1-(1-naphthyl)ethyl isocyanate (28). A solution of **10** (0.133 g, 0.345 mmol) in 1-methyl-2-pyrrolidinone (0.7 mL) was cooled to -10 °C, under nitrogen, and treated portionwise during 50 min with a solution of 0.085 g (0.43 mol) of **28** in CH₂Cl₂ (1 mL). The mixture was kept at -8 to -10 °C for 4 h and diluted with Et₂O. Flash chromatography of the crude product gave 7.9 mg of **25**: HR FAB MS calcd for C₄₆H₅₉N₄O₅S *m/z* 779.4206 (M+H)⁺, found *m/z* 779.4223 and 59 mg of **23**: [α]_D²⁴ +17 (c 0.419, EtOH); FAB MS *m/z* (relative intensity) 582[(M+H)⁺, 41.4], 496 (6.0), 383 (10.9), 367 (100), 156 (57.8), 144 (27.5); HR FAB MS calcd for C₃₃H₄₈N₃O₄S *m/z* 582.3365 (M+H)⁺, found 582.3387; ¹H NMR (300 MHz, CDCl₃) δ 0.86-0.98 (m, 6H), 1.24 (broad s, 8H), 1.38 (broad s, 5H), 1.60 (d, *J* = 6.66 Hz, 3H), 1.79 (m, 1H), 2.32-2.51 (m, 6H), 2.80 (s, 1H), 2.98 (s, 2H), 5.20 (m, 0.5H), 5.62 (m, 2H), 6.49 (m, 0.5H), 6.80 (m, 0.5H), 7.15 (m, 1H), 7.26 (m, 3H), 7.51 (m, 4H), 7.79 (d, *J* = 7.70 Hz, 1H), 7.88 (m, 1H), 8.12 (d, *J* = 8.73 Hz, 1H). By HPLC this material was greater than 99% of one enantiomer (**23**), *t_R* = 70.2 min.

Reaction of 11 with (R)-1-(1-naphthyl)ethyl isocyanate (28). A solution of **11** (0.10 g, 0.26 mmol) in 1-methyl-2-pyrrolidinone (0.6 mL) was cooled to -10 °C under nitrogen, and treated with a solution of **28** (0.072 g, 0.37 mmol) in CH₂Cl₂ (1 mL), portionwise during 50 min. The mixture was kept at -8 °C for 1 h and at -5 °C for 1 h and then diluted with Et₂O. The crude product was flash chromatographed on silica gel to give a small amount of **25**: HR FAB MS calcd for C₄₆H₅₉N₄O₅S *m/z* 779.4206 (M+H)⁺, found 779.4223 and 0.0866 g of **22**: [α]_D²⁴ -8 (c 0.418, EtOH); FAB MS *m/z* (relative intensity) 582[(M+H)⁺, 63.4], 383 (6.6), 367 (100), 144 (25.3); HR FAB MS calcd for C₃₃H₄₈N₃O₄S *m/z* 582.3365 (M+H)⁺, found 582.3387; ¹H NMR (300 MHz, CDCl₃) δ 0.87-1.01 (m, 6H), 1.27-1.87 (m, 17H), 2.0-2.3 (m), 2.37-2.52 (m, 4H), 2.94 (s, 3H), 5.18 (m, 0.5H), 5.60 (m, 1.5H), 7.09-7.28 (m, 5H), 7.45 (m, 4H), 7.75-7.85 (m, 2H), 7.97-8.16 (m, 1H). By HPLC this material was greater than 97% of one enantiomer (**22**), *t_R* = 64.8 min.

Assay for the enantiomeric purity of 10 and 11 by the chiral solvating method.^{23,24} In the ¹H NMR (300 MHz, CDCl₃) spectrum of **12** the hydroxy methine proton is represented by an apparent doublet centered at δ 4.6 while in the corresponding spectrum of **12** plus an equimolar amount of (R)-2,2,2-trifluoro-1-(9-anthranil) ethanol this proton is represented by a pair of doublets centered at δ 4.48 and δ 4.55. In subsequent experiments, these doublets were shown to represent the corresponding protons of the enantiomers **11** and **10**, respectively. This difference in chemical shifts for the complexes formed between the two enantiomers of **12** and the chiral reagent can serve as a means for measuring the optical purity of the enantiomers. Thus irradiation of the signal at δ 1.64 for the methylene protons adjacent to the hydroxy methine proton of **12** resolved the pair of doublets into a pair of sharp singlets at δ 4.49 and δ 4.54. In a similar manner the spectra of **11** and **10** gave singlets at about δ 4.52 and δ 4.58, respectively. When a pure sample of **11** was mixed with 2.2% and 5.3% of **10** the impurity peak in the ¹H NMR spectra of the mixture was found to integrate for 2.4% and 5.9% of the total absorption. Similarly, a mixture of **10** with 4.0% of **11** gave a signal that integrated for 3.0% of the total absorption.

(R)-N-[4-[4-(Butylamino)-1-hydroxybutyl]phenyl]methanesulfonamide 14. A solution of **9** (3.285 g, 0.01 mol) in dry THF (90 mL) was added, dropwise during 1 h directly into a well stirred solution of 3.4 M sodium bis(2-methoxyethoxy)aluminum hydride in toluene (11 mL, 37.4 mmol) in THF (25 mL) under nitrogen at ambient temperature. The reaction mixture warmed slightly during the addition, a clear, colorless solution resulted. The mixture was kept at ambient temperature for 17 h 20 min, cooled in an ice bath and treated with 6M H₂SO₄ (5.61 mL, 33.7 mmol) during 12 min with vigorous stirring; the ice bath was removed after the initial vigorous reaction that resulted from the first few drops of acid. This mixture was stirred for 38 min and then treated, dropwise, with MeOH (37.5 mL). The resulting mixture was stirred for 3 h and filtered through Celite. The granular solid was washed three times with a total of 500 mL of warm 10% MeOH-CH₂Cl₂; the combined filtrate was concentrated *in vacuo*. The residue was mixed with a little absolute EtOH and concentrated. A solution of this residue in CH₂Cl₂ was filtered through a small pad of Magnisol C and concentrated. The residue was crystallized from EtOAc-*tert*-butyl methyl ether to give in two crops 2.75 g (87.6%) of **14**, mp 108-110 °C. A sample was recrystallized from EtOAc and had: mp 108.5-110.5 °C; [α]_D²⁴ +21 (c 0.999, EtOH); UV_{max} (EtOH) 230 nm (ϵ 13,600), 258 (736), 274 (sh 591), 283 (sh 402); IR (Nujol) 3308, 3110, 3053, 1608 cm⁻¹; MS *m/z* (relative intensity) 314 (M⁺, 5.7), 253 (55.7), 235 (32.4), 184 (33.3), 162 (68.7), 144 (29.4), 86 (100); ¹H NMR (300 MHz, CDCl₃) δ 0.92 (t, *J* = 7.3 Hz, 3H), 1.39 (m, 2H), 1.52 (m, 3H), 1.75 (m, 2H), 1.96 (m, 1H), 2.64 (m, 3H), 2.82 (m, 1H), 2.96 (s, 3H), 4.64 (m, 1H), 4.9 (broad s), 7.15 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H). Anal. calcd for C₁₅H₂₆N₂O₃S: C, 57.30; H, 8.34; N, 8.91; S, 10.20. Found: C, 57.28; H, 8.36; N, 8.85; S, 10.05.

(R)-N-[4-[4-(Ethylheptylamino)-1-hydroxybutyl]phenyl] methane-sulfonamide, (E)-2-butenedioate (2:1) salt (15). A solution of **10** (15.3 g, 0.0398 mol) in absolute EtOH (153 mL) was treated with a solution of fumaric acid (2.31 g, 0.0199 mol) in absolute EtOH (153 mL). The resulting solution was concentrated and the oily residue was dissolved in acetone and concentrated. This residue was dissolved in warm acetone and allowed to crystallize. A solution of the crystals in hot acetone (150 mL) was filtered through Celite, concentrated to 100 mL and crystallized to give 6.4 g, mp 101-108 °C of the salt that contained 3.6% acetone. This was dried *in vacuo* at 60 °C for 20 h to give **15**: mp 105-106.5 °C; [α]_D²⁴ +15 (c 0.892, EtOH); MS *m/z* (relative intensity) 384 (M⁺, 11.5), 305 (30.8), 299 (50.2), 156 (100); IR (Nujol) 3323, 3088, 1614, 1571 cm⁻¹; UV_{max} (EtOH) 228 nm (ϵ 16860), 267 (890), 283 sh (566); ¹H NMR (300 MHz, CDCl₃) δ 0.87 (m, 3H), 1.17 (t, *J* = 7.09 Hz, 3H), 1.28 (m, 8H), 1.58 (m, 2H), 1.72 (broad s, 4H), 2.81-2.97 (m, 6H), 2.89 (s, 3H), 4.62 (broad s, 1H), 6.47 (s, 1H), 7.17 (d, *J* = 8.43 Hz, 2H), 7.25 (d, *J* = 8.44 Hz, 2H). Anal. calcd for C₂₂H₃₈N₂O₅S: C, 59.70; H, 8.65; N, 6.33; S, 7.24. Found: C, 59.77; H, 8.88; N, 6.33; S, 7.43.

A sample of **15** (0.051 g) was mixed with a little saturated NaHCO₃ and extracted with CH₂Cl₂. The extract was dried (Na₂SO₄) and concentrated. A solution of the residue (0.034 g) in 1-methyl-2-pyrrolidone (0.25 mL) was cooled, under nitrogen to -10 °C and treated, portionwise during 45 min with a solution of (S)-1-(1-naphthyl)ethyl isocyanate (0.028 g, 0.142 mmol) in CH₂Cl₂ (0.8 mL). The mixture was kept at -5 °C for 2 h and diluted with Et₂O. The solution was washed three times with water and then brine, dried (MgSO₄) and concentrated. By HPLC, the crude residue contained greater than 98% of **24**, *t*_R = 63.3 min.

(S)-N-[4-[4-(Ethylheptylamino)-1-hydroxybutyl]phenyl] methane-sulfonamide, (E)-2-butenedioate (2:1) salt (16). The salt prepared from 25.8 g (0.0670 mol) of **11** and 3.77 g (0.0325 mol) of fumaric acid was crystallized from acetone to give **16**: mp 105-106.5 °C; [α]_D²⁵ -16 (c 0.783, EtOH), UV_{max} (EtOH) 228 nm (ϵ 16840), 267 (885), 283 sh (571). The IR and ¹H NMR spectra were identical to those of **15**. Anal. calcd for C₂₂H₃₈N₂O₅S: C, 59.70; H, 8.65; N, 6.33; S, 7.25. Found: C, 59.42; H, 8.67; N, 6.33; S, 6.78.

A sample of **16** (0.051 g) was mixed with a little saturated NaHCO₃ and extracted with CH₂Cl₂. The extract was dried (Na₂SO₄) and concentrated. A solution of the residue (0.043 g) in 1-methyl-2-

pyrrolidinone (0.3 mL) was cooled, under nitrogen, to $-10\text{ }^{\circ}\text{C}$ and treated portionwise during 50 min with a solution of 0.031 g (0.157 mmol) of (*R*)-1-(1-naphthyl)ethyl isocyanate in CH_2Cl_2 (0.5 mL). The mixture was kept at -10 to $-5\text{ }^{\circ}\text{C}$ for 3 h and mixed with Et_2O . The solution was washed four times with water and then with brine, dried (MgSO_4) and concentrated. By HPLC the crude residue contained greater than 98% of **22** $t_{\text{R}} = 63$ min.

(*R*)-N-[4-[4-(Dibutylamino)-1-hydroxybutyl]phenyl]methanesulfonamide, (*E*)-2-butenedioate (2:1) salt (18) by lithium aluminum hydride reduction of 6. A stirred solution of 1M LiAlH_4 in THF (600 mL) was mixed with THF (600 mL) at $0\text{ }^{\circ}\text{C}$, under nitrogen, cooled to $-20\text{ }^{\circ}\text{C}$, (bath temperature $-40\text{ }^{\circ}\text{C}$) and treated dropwise with a solution of **6** (97.0 g, 0.252 mol) in THF (1000 mL) during 1 h 15 min. This mixture was kept at $-10\text{ }^{\circ}\text{C}$ for 1 h and then treated, cautiously at first, with a saturated solution of potassium sodium tartrate (620 mL); the bath was maintained at $-20\text{ }^{\circ}\text{C}$ during this addition. The mixture was kept at ambient temperature for 1 h; the THF solution was decanted and combined with subsequent EtOAc extracts. The aqueous layer was extracted thoroughly with EtOAc. The organic solutions were washed with water and brine, dried (MgSO_4) and concentrated *in vacuo* to give 97.7 g of crude product. This was combined with fumaric acid (15.3 g, 0.132 mol), dissolved in acetone and crystallized to give 78.1 g, mp $169\text{--}171\text{ }^{\circ}\text{C}$ and 10.6 g, mp $168.5\text{--}171\text{ }^{\circ}\text{C}$ of **18** (82.1% yield). This material was pure by HPLC and had a chiral purity of greater than 98% by the HPLC method. Recrystallization of the first crop from acetone gave 64.1 g of **18**: mp $169.5\text{--}170.5\text{ }^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{24} +16$ (c 0.956, EtOH).

(*S*)-N-[4-[4-(Dibutylamino)-1-hydroxybutyl]phenyl]methanesulfonamide, (*E*)-2-butenedioate (2:1) salt (19). A stirred solution of a 1M solution of LiAlH_4 in THF (20.7 mL, 0.02 mol) in THF (20.7 mL), under nitrogen, was cooled in an ice bath and treated dropwise, during 40 min, with a solution of **7** (3.8 g, 0.01 mol, 98.3% pure by chiral HPLC) in 40 ml of THF. The mixture was stirred for 1 h and quenched by the cautious addition of 21 mL of saturated potassium sodium tartrate solution. This mixture was stirred for 15 min in the cold and 15 min at ambient temperature; it was extracted with four portions of EtOAc. The EtOAc extracts were washed with water and then with brine, dried (MgSO_4) and concentrated to give the crude product. This was chromatographed, under pressure, over 700 mL of silica gel with 10% $\text{MeOH}/\text{CHCl}_3$ to give 3.5 g of product which was combined with 0.5 equivalents of fumaric acid (0.548 g, 0.00473 mol) in EtOH and crystallized to give 2.58 g (60%) of **19**: mp $168.5\text{--}169\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{24} -15$ (c 0.828, EtOH). The chiral purity was 95.6% by the chiral HPLC assay; the IR, NMR and mass spectra were identical to those of **18**. Anal. calcd for $\text{C}_{21}\text{H}_{36}\text{N}_2\text{O}_5\text{S}$: C, 58.85; H, 8.47; N, 6.54; S, 7.48. Found: C, 58.55; H, 8.37; N, 6.43; S, 7.47.

Preparation of the 1-naphthylcarbamate (27) of N-[4-[4-(dibutylamino)-1-hydroxybutyl]phenyl]methane-sulfamide (13). To a stirred mixture of **13**⁷ (0.3 g, 0.8 mmol) in acetonitrile (30 mL) was added during 30 sec a solution of 1-naphthylisocyanate (0.3 mL, 2.1 mmol) in acetonitrile (10 mL) and then acetic acid (0.15 mL). The mixture was stirred at ambient temperature for 1 h, quenched with MeOH and after 5 min concentrated *in vacuo*. The residue was chromatographed, under pressure, over 50 mL of silica gel with 0.7% HOAc/10% $\text{MeOH}/\text{CHCl}_3$ to give 0.10 g of the acetic acid salt of **27** which had: FAB MS m/z (relative intensity) 540 [(M+H)⁺, 64.9], 496 (6.3), 353 (100), 142 (51.8); ¹H NMR (300 MHz, CDCl_3) δ 0.91 (m, 6H), 1.32 (m, 4H), 1.57 (m, 4H), 1.85 (m, 2H), 2.02 (s), 2.90 (m, 4H), 2.96 (s, 3H), 3.0 (m, 1H), 5.76 (m, 1H), 7.19-8.06 (m, 13H).

Analysis of the chiral purity of 18 and 19. A mixture of the fumaric acid salt (**18** or **19**, 10 mg) in acetonitrile (2 mL) was treated with three drops of 1-naphthylisocyanate and one drop of acetic acid and stirred for 1 h. The mixture was concentrated, treated with a little MeOH, allowed to stand for 5 min and concentrated. The residue was analyzed by HPLC on a covalent Pirkle DNBPG column at a flow rate of 1 ml/min and a detector setting of 230 nm using isocratic elution with 35% EtOH/0.05% TFA/0.05% TEA/hexane. Under these conditions, the carbamates **18** and **19** had retention times (t_{R}) of 15.3 and 17.0 min, respectively.

(R)-N-[4-[4-(Dibutylamino)-1-hydroxybutyl]phenyl]methanesulfonamide, Di-*p*-toluoyl-L-tartrate (1:1) salt. A sample of **18** was dissolved in a mixture of Et₂O and saturated aqueous NaHCO₃. The ether solution was washed with brine, dried (MgSO₄) and concentrated *in vacuo* to give the free base. A sample of this material (2.03 g, 5.48 mmol) was dissolved in Et₂O and added to a solution of di-*p*-toluoyl-L-tartaric acid (2.22 g, 5.48 mmol) in acetonitrile. The salt crystallized to give 3.61 g, mp 137-137.5 °C (dec). An analytical sample was prepared by dissolving some of this material in warm acetone, adding water until saturated and crystallizing: mp 140-140.5 °C (dec); [α]_D²⁴ -57 (c 0.995, EtOH); UV_{max} (EtOH) 235 nm (ε 40,930), 270 (sh, 2490), 281 (sh, 1660); IR (Nujol) 3399, 3126, 2661, 2565, 1733, 1718, 1667, 1614 cm⁻¹; MS *m/z* (relative intensity) 370 (M⁺, 1.3), 327 (16.1), 291 (5.9), 200 (4.2), 142 (100), 119 (34.7), 100 (46.5), 91 (37.3); ¹H NMR [300 MHz, (CD₃)₂SO] δ 0.83 (t, *J* = 7.16 Hz, 6H), 1.21 (m, 4H), 1.51 (m, 8H), 2.37 (s, 6H), 2.9 (m, 9H), 4.49 (m, 1H), 5.64 (s, 2H), 7.24 (m, 8H), 7.86 (d, *J* = 8.06 Hz, 4H), 9.71 (s, 1H). Anal. calcd for C₃₉H₅₂N₂O₁₁S: C, 61.89; H, 6.92; N, 3.70; S, 4.24. Found: C, 61.52; H, 6.92; N, 3.65; S, 4.16.

Enhancing the Chiral Purity of 18 by Forming the Di-*p*-toluoyl-L-tartrate (1:1) salt. A sample of **18** (free base) that had been prepared from **6** without enhancing its chiral purity (about 90% (+) enantiomer by HPLC analysis) was dissolved in a mixture of Et₂O and saturated NaHCO₃. The Et₂O solution was washed with brine, dried (MgSO₄) and concentrated to give 2.16 g (5.83 mmol). A solution of this material in acetonitrile was treated with 2.36 g (5.83 mmol) of di-*p*-toluoyl-L-tartaric acid and the salt was crystallized from CH₃CN-EtOAc to give 3.72 g, mp 135.5-137.5 °C (dec). This was recrystallized twice from acetone-water to give 2.14 g of the salt: mp 140-140.5 °C (dec); [α]_D²⁴ -57 (c 1.009, EtOH). The IR spectrum was identical to that of the authentic sample.

The salt was dissolved in warm acetone, mixed with dilute NaHCO₃ and extracted with Et₂O. The extracts were washed with brine, dried (MgSO₄) and concentrated to give 1.00 g (0.00270 mol) of the base. This was mixed with fumaric acid (0.157 g, 0.00135 mol), dissolved in acetone (85 mL) and crystallized to give 1.052 g of **18**; mp 169-170.5 °C; [α]_D²⁴ +16 (c 1.038, EtOH). The IR was identical to that of an authentic sample. The sample was pure (+) enantiomer by HPLC analysis.

(R)-N-[4-[4-(Dibutylamino)-1-hydroxybutyl]phenyl]methanesulfonamide, (E)-2-butenedioate (2:1) salt 18 by alkylation of 14 with butylbromide. A mechanically stirred mixture of **14** (3.14 g, 0.01 mol), *n*-butylbromide (1.93 mL, 0.018 mol), sodium bicarbonate (2.10 g, 0.025 mol) and acetonitrile (100 mL) was warmed in an oil bath at 95 °C (gentle reflux), under nitrogen for 21 h. It was then concentrated *in vacuo*; the residue was mixed with dilute NaHCO₃ (45 mL) and extracted four times with 90 mL portions of Et₂O. To remove residual **14**, the extracts were each washed four times with 45 mL portions of water and then with brine; they were combined, dried (MgSO₄) and concentrated to give 3.38 g (0.00913 mol) of crude product. This was dissolved in acetone (25 mL), mixed with a solution of fumaric acid (0.528 g, 0.00455 mol) in acetone (50 mL) and crystallized to give in two crops 3.19 g (74.6%) of the salt, mp 167-169 °C. It was dissolved in absolute EtOH and crystallized from EtOH-acetone twice to give 2.12 g of **18**: mp 168.5-170.5 °C; [α]_D²⁴ +16 (c 0.991, EtOH); UV_{max} (EtOH) 228 nm (ε 16470), 267 (879), 283 (sh 544); IR (Nujol) 3324, 1597 cm⁻¹; MS *m/z* (relative intensity) 370 (M⁺, 11.3), 327 (62.7), 291 (20.8), 142 (100); ¹H NMR [300 MHz, (CD₃)₂SO] δ 0.88 (t, *J* = 7.2 Hz, 6H), 1.27 (m, 4H), 1.40 (m, 5H), 1.58 (m, 3H), 2.51 (m, 6H), 2.95 (s, 3H), 4.50 (m, 1H), 6.51 (s, 1H), 7.16 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 9.66 (broad s). Anal. calcd for C₂₁H₃₆N₂O₅S, C, 58.85; H, 8.47; N, 6.54; S, 7.48. Found: C, 58.72; H, 8.70; N, 6.55; S, 7.48.

X-ray Structure Determination of 7. C₁₉H₃₂N₂O₄S, formula wt. = 384.5; monoclinic; space group P2₁2₁2₁; Z = 4; *a* = 5.382(2), *b* = 10.326(7), *c* = 39.083(8) Å, V = 2172(1) Å³; calculated density = 1.18 g cm⁻³, absorption coefficient μ = 1.43 mm⁻¹. Intensity data were collected on a clear thick plate 0.06 x 0.36 x 0.48 mm mounted on a glass fiber on a Siemens P2₁ diffractometer. Graphite monochromatized CuKα radiation was used, (λ(CuKα) = 1.5418 Å), with 2θ max = 130°. Intensity data were measured at low temperature [153(2)°K], using θ/2θ scans with scan widths ≥3.2° and a scan rate of 2°/min. The total time

spent counting background, half at each end of the scan, was equal to the time spent scanning. Of 2024 unique reflections measured, 1741 had intensities $> 3\sigma$. Ten reflections periodically monitored showed no trend towards deterioration; $\sigma^2(I)$ was approximated by $\sigma^2(I)$ from counting statistics $+ (0.07I)^2$, where the coefficient of I was calculated from the variations in intensities of the monitored reflections. Cell parameters were determined by least squares fit of $K\alpha_1$ 2 θ values ($\lambda K\alpha_1=1.5402$) for 25 high 2 θ reflections.²⁷ An L_p correction appropriate for a monochromator with 50% perfect character was applied, and the data were corrected for absorption.²⁸ A data collection had previously been done on a crystal having weaker intensities, and in this case the data was collected as though the crystal were monoclinic ($\pm h, k, l$), and then the data collection was repeated in another quadrant, ($+h, k, -l$). A systemic difference in intensities was observed, with h, k, l and $h, k, -l$ reflections uniformly less intense than the equivalent $-h, k, -l$ and $-h, k, l$ reflections. The refinement on data from this crystal resulted in very small B_{11} values, and for some atoms B_{11} refined to negative values, a physical impossibility. Preliminary scans on the crystal used for the final data collection showed similar systematic differences; the data was collected in only one octant, however, and the B_{11} values in the final refinement were reasonable.

The structure was solved by direct methods, using DIREC.²⁹ Least squares refinement included coordinates for all atoms and anisotropic thermal parameters for nonhydrogen atoms. The function minimized in the refinement was $\sum \omega (F_o^2 - F_c^2)^2$, where weights ω were $1/\sigma^2(F_o^2)$ and F_c^2 was as defined by Larson.³⁰ In the final refinement anomalous dispersion factors³¹ were included; in the final cycle all shifts were $\leq 0.2\sigma$. The absolute configuration was determined to be (*S*) by the method of Bijvoet,³² comparing accurate measurements of 12 reflections which were very strongly influenced by anomalous dispersion, each one measured at all accessible symmetry related positions (40 Friedel pairs). All twelve comparisons indicated unequivocally that the (*S*) enantiomer is the correct one. The final agreement index *R* was 0.093 for 2020 reflections, (4 intense reflections were given zero weight in the refinement) and 0.086 for the 1745 reflections having $F_o^2 \geq 3\sigma$. The standard deviation of fit was 2.9. Atomic form factors were from Doyle and Turner,³³ and, for hydrogen, from Stewart, Davidson & Simpson.³⁴ The CRYM system of computer programs was used.²⁹

There are two intermolecular hydrogen bonds: between the secondary amine and the carbonyl oxygen related by $1-x, y+0.5, 1.5-z$, with N - O distance 2.783(7)Å; and between the hydroxyl and one of the sulfone oxygens related by $-x, y+0.5, 1.5-z$, with O - O distance 2.815(7)Å. In the latter hydrogen bond the hydrogen was found to be approximately midway between the oxygens, 1.55 Å from the hydroxyl oxygen and 1.28 Å from the sulfone oxygen. The atomic coordinates and thermal parameters are deposited at the Cambridge Crystallographic Data Centre.

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