A Practical, Enantioselective Synthesis of SK&F 104353

Joseph R. Flisak, Kerry J. Gombatz, Monica M. Holmes, Alvydas A. Jarmas, Ivan Lantos,* Wilford L. Mendelson, Vance J. Novack,* James J. Remich, and Lawrence Snyder

SmithKline Beecham Pharmaceuticals, 709 Swedeland Road, P.O. Box 1539, King of Prussia, Pennsylvania 19406-0939

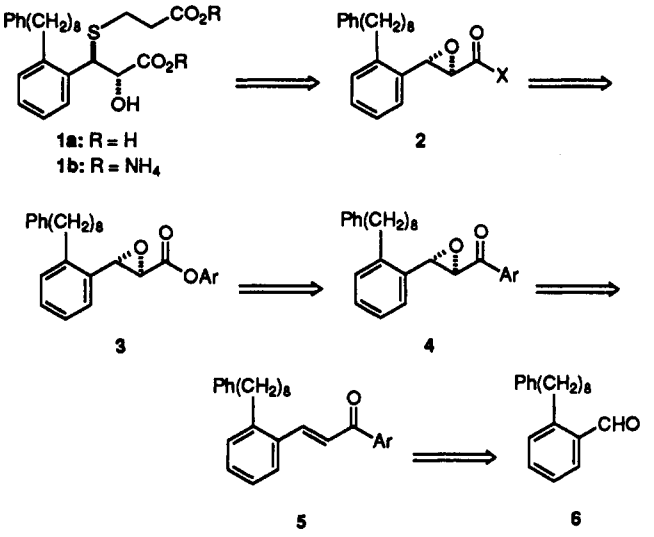
Received June 28, 1993•

A highly efficient and enantioselective (>99.5% ee) synthesis of the title compound has been accomplished. Key steps include (1) epoxidation of unsaturated ketone **7** in the presence of a polyamino acid to afford compound **8** in >95% ee, (2) regioselective Baeyer–Villiger rearrangement of epoxy ketone **8** to afford glycidic ester **9**, and (3) regioselective (35:1) opening of lithium glycidate **13** at C-3 with methyl 3-mercaptopropionate. The approach is economical, and all transformations proceed in high yield and are amenable to large-scale preparation.

The leukotrienes (LTC_4, LTD_4, and LTE_4) are now recognized as possible agents in the pathophysiology of human asthma and other immediate hypersensitivity diseases.[1] A potent and selective leukotriene antagonist, [*R*-(*R**,*S**)]-β-[(2-carboxyethyl)thio]-α-hydroxy-2-(8-phenyloctyl)benzenepropanoic acid (SK&F 104353, **1a**), has been identified as a possible candidate for the treatment of bronchial asthma.[2] While a synthesis of **1a** has been reported,[3] it is somewhat inefficient as it involves a nonregioselective epoxide opening and the separation of enantiomers late in the synthesis. We desired an enantioselective synthesis of **1a** which would surmount these difficulties and provide **1a** in large quantities.[4]

The strategy is shown retrosynthetically in Scheme I. We chose crystalline diammonium salt **1b** as our ultimate target, since **1a** is a viscous oil and difficult to purify on a large scale. An asymmetric epoxide such as **2**, where X is some functionality (–OH or –NHR) capable of directing a regioselective opening at the benzylic position of the epoxide by methyl 3-mercaptopropionate, should provide fairly direct access to **1a/b**. Such epoxides can obviously be readily prepared from aryl glycidic esters (**3**) via hydrolysis or aminolysis. An efficient route to optically active aryl glycidic esters was described in a recent report from these laboratories,[5] which consists of a Julia[6] asymmetric epoxidation of chalcones (**5**) followed by Baeyer–Villiger oxidation of the resulting ketones (**4**). Finally, chalcones such as **5** are available by condensation of an appropriate methyl aryl ketone with aldehyde **6**.

Scheme I



We describe herein the successful implementation of the strategy outlined in Scheme I. In the course of developing this route, we have elaborated the Julia asymmetric epoxidation methodology and the regioselective epoxide opening of a 2,3-epoxy acid (without Lewis acid assistance).

Results and Discussion

Preparation of Asymmetric Epoxide 3. A synthesis of aldehyde **6** has been previously reported.[7] While several methods for converting aldehyde **6** into an optically active epoxide were examined,[8,9] the asymmetric epoxidation

• Abstract published in *Advance ACS Abstracts,* October 1, 1993.

(1) (a) Dahlen, S. E.; Hedqvist, P.; Hammarstrom, S.; Samuelsson, B. *Nature (London)* **1980**, *288*, 484. (b) Peck, M. J.; Piper, P. G.; Williams, T. J. *Prostaglandins* **1981**, *21*, 315. (c) Woodward, D. F.; Weichman, B. M.; Gill, C. A.; Wasserman, M. A. *Prostaglandins* **1983**, *25*, 131. (d) Marom, Z.; Shelhamer, J. H.; Bach, M. K.; Morton, D. R.; Kaliner, M. *Am. Rev. Respir. Dis.* **1982**, *126*, 449.

(2) Mong, S.; Wu, H. L.; Miller, J.; Hall, R. F.; Gleason, J. G.; Crooke, S. T. *Mol. Pharmacol.* **1988**, *32*, 223.

(3) Gleason, J. G.; Hall, R. F.; Perchonock, C. D.; Erhard, K. F.; Frazee, J. S.; Ku, T. W.; Kondrad, K.; McCarthy, M. E.; Mong, S.; Crooke, S. T.; Chi-Rosso, G.; Wasserman, M. A.; Torphy, T. J.; Muccitelli, R. M.; Hay, D. W.; Tucker, S. S.; Vickery-Clark, L. *J. Med. Chem.* **1987**, *30*, 959.

(4) (a) An enantioselective synthesis of SK&F 104353 has recently been reported: Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515. (b) An enantioselective synthesis of the α-methoxy analogue of **1a** has also been reported: Ku, T. W.; Kondrad, K. H.; Gleason, J. G. *J. Org. Chem.* **1989**, *54*, 3487.

(5) Flisak, J. R.; Gombatz, K.; Lantos, I.; Mendelson, W.; Remich, J. R. *Tetrahedron Lett.* **1990**, *31*, 6501.

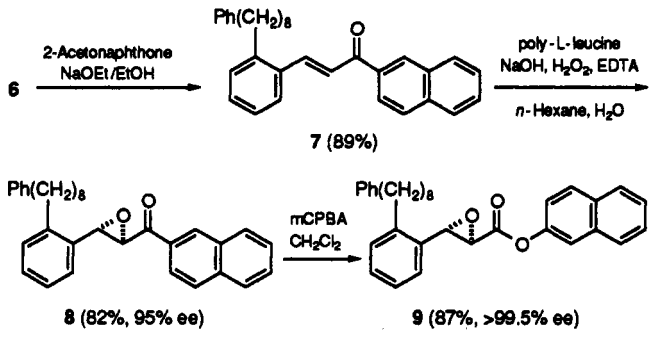
(6) (a) Bezuidenhoudt, B. C. B.; Swanepoel, A.; Augustyn, J. A. N.; Ferreira, D. *Tetrahedron Lett.* **1987**, *28*, 4857. (b) Banfi, S.; Colonna, S.; Molinari, H.; Julia, S.; Guixer, J. *Tetrahedron* **1984**, *40*, 5207. (c) Colonna, S.; Molinari, H.; Banfi, S.; Julia, S.; Masana, J.; Alvarez, A. *Tetrahedron* **1983**, *39*, 1635. (d) Julia, S.; Masana, J.; Rocas, J.; Colonna, S.; Annunziata, R.; Molinari, H. *Ann. Quim.* **1983**, *79*, 102. (e) Julia, S.; Guixer, J.; Masana, J.; Rocas, J.; Colonna, S.; Annuziata, R.; Molinari, H. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1317. (f) Julia, S.; Masana, J.; Vega, J. C. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 929.

(7) Perchonock, C. D.; McCarthy, M. E.; Erhard, K. F.; Gleason, J. G.; Wasserman, M. A.; Muccitelli, R. M.; DeVan, J. F.; Tucker, S. S.; Vickery, L. M.; Kirchner, T.; Weichman, B. M.; Mong, S.; Crooke, S. T.; Newton, J. F. *J. Med. Chem.* **1985**, *28*, 1145.

(8) We examined the elegant asymmetric epoxidation procedure developed by Sharpless: Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. Conversion of aldehyde **6** to the requisite cinnamyl alcohol followed by catalytic asymmetric oxidation [tBuOOH, 5% $Ti(OiPr)_4$, 7.5% (+)-dialkyl tartrate] gave the corresponding epoxy alcohol in 72–80% ee. Unfortunately, this epoxide was a high-boiling oil, which precluded any chance of enriching the optical activity by recrystallization. Due to the modest enantioselectivity and the large number of chemical transformations, this route was abandoned. We thank Ms. Ann M. Tickner for these results.

0022-3263/93/1958-6247$04.00/0 © 1993 American Chemical Society

Scheme II



developed by Julia emerged as the method of choice.[6] Julia has reported an enantioselective epoxidation of substituted benzylidine acetophenones (5 to 4, Scheme I) which employs a triphasic system consisting of NaOH/aqueous H_2O_2, an organic solvent, and a polyamino acid. Despite the variable yields and optical purities achieved by Julia, we were attracted to this procedure as the reaction conditions are mild, enantioselectivities can often be exceedingly high, and the procedure is operationally simple. Furthermore, substrates such as 3 are readily accessible from 4 via Baeyer–Villiger oxidation.[5] Therefore, it ultimately became necessary to prepare an unsaturated aryl ketone such as 5.

In choosing a specific substrate 5, we considered the very practical problem of designing intermediates which were easy to isolate and purify (i.e., crystalline). Toward this goal, we selected Ar = 2-naphthyl.[10] This unsaturated ketone (7, Scheme II) was prepared by condensing aldehyde 6 with inexpensive 2-acetonaphthone in the presence of sodium ethoxide. The product crystallized directly from the reaction mixture and was isolated in 89% yield by simple filtration.

The asymmetric epoxidation of 7 was evaluated with a number of commercial polyamino acids, and we concluded that poly-L-leucine[11] consistently gave the highest yields and enantioselectivities. Unfortunately, commercial poly-L-leucine is extremely expensive. However, this polymer can be readily prepared by polymerization of L-leucine-*N*-carboxyanhydride (leucine-NCA).[12,13] While there are a number of published methods for effecting this polymerization,[14] we found that a solid-state procedure was the most convenient and reliable.[15] Freshly prepared leucine-NCA was placed in large trays to a depth of 6–8 cm, and then the trays were left at ambient temperature in a humidity chamber at 70–75% relative humidity. The progress of the polymerization was conveniently monitored by IR, as the two carbonyl stretches for leucine-NCA (1780, 1830 cm^{-1}) were eventually displaced by an amide carbonyl stretch (1655 cm^{-1}, indicative of an α-helix conformation). Typically, the polymerization was complete in 5–10 days. While poly-L-leucine from this procedure could be characterized by many of the usual analytical techniques (^1H NMR, IR, elemental analysis), we have not yet developed a satisfactory method to measure molecular weight distribution. Poly-L-leucine is stable and inert; consequently, no special precautions were taken when handling or storing this material.

Optimal conditions for the asymmetric epoxidation of 7 varied somewhat from those reported by Julia. Typically, unsaturated ketone 7 was combined with a nearly equal weight of poly-L-leucine in a mixture of n-hexane/water containing approximately 12 molar equiv of sodium hydroxide. This slurry was stirred at ambient temperature for 24 h and then treated with EDTA[16] (2.5 mol %) followed by 20 equiv of 30% aqueous hydrogen peroxide. Additional base and hydrogen peroxide were added if the reaction did not go to completion within 20 h. We were surprised that hexane was the solvent of choice for this reaction, since Julia reported low asymmetric inductions in hexane. Cyclohexane and carbon tetrachloride also performed well under our reaction conditions, whereas little or no reactivity was encountered in dichloromethane, 1,2-dichloroethane, and toluene.[17] During the 24-h stir period prior to addition of hydrogen peroxide, the polymer swells and apparently adopts a more reactive physical state. When poly-L-leucine was subjected to this preactivation period, epoxidations were typically complete within 20–24 h of the hydrogen peroxide addition. In contrast, the reaction required 72 h to go to completion if hydrogen peroxide was added at the outset. Such lengthy reaction times were disadvantageous because hydrogen peroxide, which decomposed under the basic reaction conditions, had to be constantly replenished. The addition of EDTA to the reaction mixture served further to control this decomposition process. When the reaction was deemed complete, poly-L-leucine was removed by filtration and washed with a small amount of solvent to remove residual product. In contrast to Julia's results, we have found that the reisolated polymer is entirely reusable. Thus, the same poly-L-leucine was used in six consecutive asymmetric epoxidations (7 to 8), and we observed no erosion in either yield or enantioselectivity!

According to the above procedure, naphthyl ketone 7 was routinely converted to epoxy ketone 8 in good yield (72–82%) and with high asymmetric induction (94–96% ee). Enantiomeric purity was ascertained by chiral HPLC analysis and comparison to the racemic compound, which was prepared by oxidation of 7 with basic hydrogen

(9) Optically active epoxides can also be prepared via an asymmetric Darzens condensation: (a) Pridgen, L. N.; Abdel-Magid, A.; Lantos, I. *Tetrahedron Lett.*. 1989, *30*, 5539. (b) Abdel-Magid, A.; Pridgen, L. N.; Eggleston, D. S.; Lantos, I. *J. Am. Chem. Soc.* 1986, *108*, 4595. The optically active bromohydrins from this procedure were treated with ammonium hydroxide to provide direct access to epoxy amides (2, X = NH_2) with high enantioselectivity. However, this chemistry was not economically competitive with alternate routes under consideration. We thank Dr. Lendon N. Pridgen and Ms. Susan Shilcrat for these results.

(10) Compound 5 was obtained as a high-boiling oil with Ar = *p*-bromophenyl or *p*-tolyl, while a very low-melting solid was obtained with Ar = *p*-methoxyphenyl.

(11) Commercial polyamino acids were purchased from Sigma Chemical Co., St. Louis, MO. Of the several types of poly-L-leucine available from Sigma, that which was purchased as mol wt 3000–15 000 gave the most satisfactory results.

(12) Leucine-NCA can be prepared by several methods. In preparing leucine-NCA from L-leucine and phosgene in THF, it was important that the THF be free of peroxides: (a) Blacklock, T. J.; Shuman, R. F.; Butcher, J. W.; Shearin, W. E., Jr.: Budavari, J.; Grenda, V. J. *J. Org. Chem.* 1988, *53*, 836. (b) Katakai, R.; Iizuka, Y. *J. Org. Chem.* 1985, *50*, 715. (c) Daly, W. H.; Poche, D. *Tetrahedron Lett.* 1988, *29*, 5859.

(13) Satisfactory poly-L-leucine could not be prepared unless the leucine-NCA was relatively pure. The purity of leucine-NCA was monitored by chlorine assay (<0.8%) and melting point (73–78 °C).

(14) (a) Katchalski, E.; Sela, M. In *Advances in Protein Chemistry*; Afinsen, C.B., Jr., Anson, M. L., Bailey, K., Edsall, J. T., Eds.; Academic Press: New York, 1958; Vol. 13, pp 243–492. (b) Korshak, V. V.; Rogozhin, S. V.; Davankov, V. A.; Davidovich, Yu.A.; Makarova, T. A. *Russ. Chem. Rev.* 1965, *34*, 329. (c) Bamford, C. H.; Block, H. In *Comprehensive Chemical Kinetics*; Bamford, C. H., Tipper, C. F. H., Eds.; Elsevier Sci. Publ.: Amsterdam, 1976; Vol. 15, Chapter 8, pp 583–637.

(15) Shionoya, G.; Furukawa, T.; Akamatsu, A. (Ajinomoto Co., Inc.) Japan. Kokai Patent 74 38,995.

(16) EDTA = ethylenediaminetetraacetic acid, disodium salt dihydrate.

(17) The sluggish manner in which compound 7 epoxidized in toluene was unexpected, as this was a common solvent in Julia's work.[6a] At this time, we do not have an explanation for this difference in results.

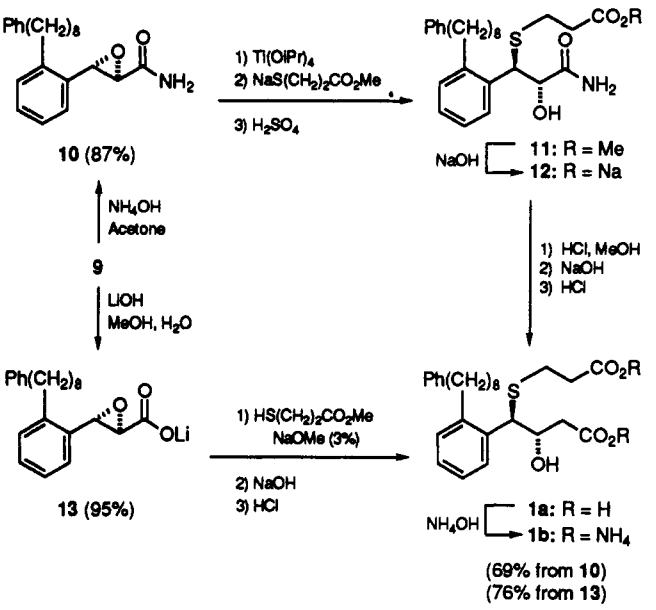
peroxide under phase-transfer conditions. The 2*R*-*trans* configuration was assigned to the epoxide based upon prior results,[5] as well as the successful conversion of **8** to **1b** (vide infra). Due to the 2-naphthyl substituent, compound **8** was crystalline and available in 95–98% ee from a single crystallization.[18]

Treatment of **8** with 1.3 equiv of *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane at reflux temperature resulted in a smooth Baeyer–Villiger oxidation to produce 2-naphthyl glycidic ester **9** in 87% yield. The oxidation was regioselective, as we were unable to detect any byproducts from migration of the epoxide moiety. Once again, crystallinity was imparted by the 2-naphthyl substituent, which enabled us to enhance the optical purity of our product. Thus, ester **9** was isolated in >99.5% ee by crystallization during workup.[19] Optical purity was again measured by chiral HPLC comparison to the racemate, prepared by Baeyer–Villiger oxidation of the racemic epoxy ketone. With compound **9** in hand, it was now necessary to open the epoxide regioselectively with an appropriate thiol.

Regioselective Cleavage of the Epoxide. On the basis of the results on the methyl glycidic ester,[3] we did not anticipate that methyl 3-mercaptopropionate would add selectively to the benzylic position of glycidic ester **9**. Sharpless has reported regioselective C-3 openings of 2,3-epoxy acids and amides mediated by titanium tetraisopropoxide.[20] Unfortunately, while a glycidic acid route would have provided fairly direct access to the final product, it proved unfeasible because the chiral epoxy acid derived from **9** underwent facile decarboxylation. Therefore, we considered the option of using a glycidic amide, although this would introduce additional steps to ultimately convert the amide to an acid. Toward this end, glycidic ester **9** was treated with aqueous ammonium hydroxide in acetone to afford epoxy amide **10** (Scheme III) in 87% yield. The amide was crystalline, which facilitated large-scale purifications.

The sodium salt of methyl 3-mercaptopropionate (2.2 equiv) reacted with glycidic amide **10** in the presence of titanium tetraisopropoxide (2.5 equiv) to afford amide/ester **11** in 95% yield. While a single isomer was evident by ^{1}H NMR (400 MHz),[21] structure **11** was not proven definitively until the final conversion of **11** to **1b**. Unfortunately, **11** was a low-melting solid, and numerous attempts to crystallize it directly from the unpurified reaction mixture met with failure. This became problematic because the excess thiol (required for optimal yields in the epoxide opening) was not easily removed, and conversion of unpurified **11** to **1b** afforded final product

Scheme III



of low purity. Consequently, we had to proceed rather circuitously.

Treatment of **11** with sodium hydroxide afforded monosodium salt **12**, which could be extracted into organic solvents and isolated as a noncrystalline solid; excess thiol from the epoxide opening remained in the aqueous layer, presumably as the sodium salt of 3-mercaptopropionic acid. Surprisingly, we were unable to find a suitable procedure for direct hydrolysis of **12** to **1a**. Instead, compound **12** was converted to a dimethyl ester (HCl, MeOH, H_2O), which was then hydrolyzed to **1a** (1. NaOH; 2. HCl). Diacid **1a** was a viscous oil and difficult to purify. In order to avoid large-scale chromatographies, unpurified **1a** was converted directly to diammonium salt **1b** (NH_4-OH, H_2O, acetone), which was isolated as a crystalline monohydrate in 69% yield from **10**. HPLC analysis indicated an optical purity of >99.5% ee for this material.[22] The structure of **1b** (particularly the 2*S*,3*R*-configuration) was proven definitively by correlation to a single-crystal X-ray structure (vide infra). Thus, starting with *o*-tolualdehyde, SK&F 104353 was obtained as a diammonium salt (**1b**) in 29% overall yield. The longest linear sequence was 10 steps.

However, despite the success of the glycidic amide route, we were dissatisfied with the number of transformations required to convert **9** to **1a**, and the glycidic acid option was reconsidered in the hope of developing a more efficient route. While the glycidic acid obtained from **9** was unstable, we reasoned that it might be possible to isolate a stable carboxylate salt. Treatment of glycidic ester **9** with NaOH afforded the corresponding sodium carboxylate as an oil, which proved difficult to isolate. However, a highly crystalline lithium salt (**13**) was obtained in excellent yield (95%) upon hydrolysis of **9** with LiOH. Compound **13** was extremely stable at pH > 7 and surprisingly nonhygroscopic.

To our knowledge, the Sharpless methodology[20] has never been applied to a carboxylate salt. In fact, reaction of **13** with the lithium salt of methyl 3-mercaptopropionate

(18) The unsaturated ketones in ref 10 were also converted to 2*R*-*trans* epoxides, **4**, under typical reaction conditions. Compound **4** with Ar = *p*-bromophenyl was obtained as a crystalline product (93% ee unpurified, 99% ee after one recrystallization, mp 58–59 °C, 70% yield). A high-boiling oil was obtained for compound **4** with Ar = *p*-tolyl (95% ee, 80% yield). Compound **4** with Ar = *p*-methoxyphenyl was obtained as a very low-melting solid which could not be recrystallized (97% ee, 60% yield).

(19) Compounds **4** with Ar = *p*-tolyl and *p*-methoxyphenyl (see ref 18) also underwent regioselective Baeyer–Villiger oxidations to produce **3** with Ar = *p*-tolyl (99% ee, 69% yield) and Ar = *p*-methoxyphenyl (% ee not available, 84% yield), respectively. Baeyer–Villiger oxidation of compound **4** with Ar = *p*-bromophenyl was not regioselective, as evidenced by isolation of 15–20% of 1-[2-(8-phenyloctyl)phenyl]-1-(formyloxy)-1-[(4-bromobenzyl)oxy]methane.

(20) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560.

(21) Prior to ^{1}H NMR analysis, unpurified **11** was slurried several times with hexane in order to remove excess thiol. An authentic sample of the undesired regioisomer was not prepared.

(22) The optical purity of **1b** was measured by direct comparison to a sample of racemic **1a**, which was kindly provided to us by Karl Erhard. The synthesis of racemic **1a** has been reported.[3]

in the presence of titanium tetraisopropoxide gave low yields and significant amounts of byproducts. In the absence of titanium tetraisopropoxide, most 2,3-epoxy acids are attacked preferentially at C-2 by amines and thiolates.[20,23] Nevertheless, ammonia reportedly adds with modest selectivity (~3:1) to the C-3 carbon of *trans*-phenylglycidic acid,[24] while the same reaction proceeds with high C-3 selectivity (~30:1) on the corresponding *cis* isomer.[25] Presumably, it is the ammonium salt of phenylglycidic acid which is undergoing nucleophilic cleavage by ammonia in these examples.

Despite the modest regioselectivity reported for the addition of ammonia to *trans*-phenylglycidic acid in the absence of a Lewis acid, we examined compound **13** and discovered that this particular glycidic acid reacted with methyl 3-mercaptopropionate with exceptionally high selectivity at the C-3 carbon. In the presence of 3% sodium methoxide, methyl 3-mercaptopropionate (1.25 equiv) added smoothly to the benzylic position of **13** under mild conditions (THF, 5 °C, 4 h). In situ hydrolysis of the methyl ester (1. NaOH; 2. HCl) afforded diacid **1a** directly. The regioselectivity of the epoxide opening, prior to methyl ester hydrolysis, was determined by quenching with ethereal diazomethane. HPLC comparison of the resulting dimethyl esters to an authentic mixture of regioisomers[3] indicated that the thiol addition had proceeded with 35:1 regioselection! This level of control, which did not require the addition of a Lewis acid, could also be achieved with other bases such as sodium hydride, lithium hydride, and n-butyllithium.[26] As in the previous procedure, diacid **1a** was conveniently purified by treatment with ammonium hydroxide, which afforded diammonium salt **1b** as a monohydrate in 76% overall yield from **13**. HPLC analysis indicated an optical purity of >99.5% ee for this material.[22] The synthesis of **1b** via this chemistry was significantly more efficient than that via glycidic amide **10**, as evidenced by a higher overall yield from *o*-tolualdehyde (35%) and a reduction in the longest linear sequence to eight steps.

The relative and absolute stereochemistry of **1b** was proven by correlation to the bis(4-iodo-α-methylbenzylamine) salt.[27] An X-ray structure was available on the bis(4-iodo-α-methylbenzylamine) salt, which served to confirm the 2*S*,3*R* configuration of SK&F 104353.[28] In order to prove the stereochemistry of **1b**, both diammonium salt **1b** and the bis(4-iodo-α-methylbenzylamine) salt were converted to SK&F 104353 free acid (**1a**). The samples of **1a** prepared in this manner were compared analytically (^{1}H/^{13}C NMR, IR, chiral HPLC) and were found to be identical.

Experimental Section

Unless otherwise noted, reagents were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran, if used as a reaction solvent, was dried over 4A molecular sieves. All other solvents were obtained from commercial suppliers as reagent grade and were used without further purification. All nonaqueous reactions were performed under an atmosphere of dry nitrogen.

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were recorded on Jeol GX 270, Bruker WM 360, or Bruker AM 400 spectrometers. Chemical shifts are reported in ppm (δ) downfield from tetramethylsilane. IR spectra were recorded on a Perkin-Elmer Model 283 infrared spectrophotometer. FT-IR spectra were obtained on a Nicolet 6000 FT infrared spectrometer. Optical rotations were recorded at 25 °C on a Perkin-Elmer 241 MC polarimeter. Combustion analyses were run on a Perkin-Elmer 240 °C elemental analyzer.

(*E*)-1-(2-Naphthalenyl)-3-[2-(8-phenyloctyl)phenyl]-2-propen-1-one (7). Ethanol (95%, 3.53 L) was cooled to 5 °C and treated with 36.8 g (1.16 mol) of sodium metal over a 30-min period. During the addition of sodium metal, the reaction temperature rose to approximately 25 °C. The resulting solution of sodium ethoxide was cooled to 10–15 °C and treated with 115.6 g (0.68 mol) of 2-acetonaphthone. After the solution was stirred for 5 min, 200.0 g (92% purity, 0.625 mol) of 2-(8-phenyloctyl)benzaldehyde (**6**) was added in one portion. The reaction mixture was allowed to warm to ambient temperature and then stirred for 18 h. A yellow precipitate was deposited during this period. The reaction was treated with 350 mL of ice–water, cooled to 10–15 °C for 1 h, and filtered. The filter cake was washed with 400 mL of 50% aqueous ethanol and air dried for 12 h. The yellow solid was pulverized and dried for an additional 20 h in vacuo (0.5 mmHg) at ambient temperature to afford 261 g (95% purity, 89% yield) of unsaturated ketone **7**: mp 41.0–42.5 °C; FT-IR (KBr) 1658, 1597, 1467, 1325, 1185, 1124, 1016, 970, 763 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.55 (d, 1 H, J = 1.2 Hz), 8.21 (d, 1 H, J = 15.5 Hz), 8.11–7.12 (m, 15 H), 7.62 (d, 1 H, J = 15.6 Hz), 2.75 (t, 2 H, J = 7.7 Hz), 2.57 (t, 2 H, J = 7.7 Hz), 1.59 (b, 4 H), 1.29 (b, 8 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 190.2, 143.3, 142.9, 142.4, 135.6, 135.5, 133.5, 132.6, 130.2, 130.1, 129.9, 129.5, 128.5, 128.3, 128.1, 127.8, 126.7, 126.6, 126.3, 125.5, 124.5, 123.3, 35.9, 33.4, 31.7, 31.4, 29.4, 29.4, 29.3, 29.2. Anal. Calcd for $C_{33}H_{34}O$: C, 88.74; H, 7.67. Found: C, 88.84; H, 7.68.

Poly-L-leucine. L-Leucine-*N*-carboxyanhydride (672 g, 4.27 mol, mp 73–75 °C, Cl = 0.59%) was placed in a 4-L wide-mouth bottle and covered with a paper towel. The height of the solid in the bottle was 6–8 cm. The bottle was placed in a HOTPACK temperature humidity chamber (Model 317532) set at 25 °C and 70% relative humidity. The polymerization was monitored by IR (disappearance of carbonyl stretches at 1780 and 1830 cm^{-1}) and was complete in 9 days. This afforded 500 g of poly-L-leucine, which was stored in a closed bottle at ambient temperature: mp >250 °C; water content (Karl Fischer) = 1.35%; FT-IR (KBr) 3300, 3062, 2958, 2938, 1655 (s), 1583, 1554, 1469, 1406, 1386, 722, 709 cm^{-1}; ^{1}H NMR (CF_3CO_2D, 400 MHz) δ 4.80–4.70 (bs, 1 H), 1.78–1.65 (m, 3 H), 1.01 (two doublets, 6 H, J = 15.4 Hz). Anal. Calcd: dependent upon polymer chain length. Found: C, 60.86; H, 9.47; N, 11.69.

(2*R*-*trans*)-(2-Naphthalenyl) [3-[2-(8-Phenyloctyl)phenyl]oxiranyl]methanone (8). A stirred solution of 255 g (6.375 mol) of sodium hydroxide in 650 mL of water at 14–18 °C was treated sequentially with 215 g of poly-L-leucine, 4.0 L of n-hexane, and 250 g (95% purity, 0.531 mol) of unsaturated ketone **7**. The heterogeneous mixture was stirred at ambient temperature for 16 h and then cooled to 10–15 °C. EDTA[16] (5.0 g) was added, followed by 1.126 L (10.93 mol) of 30% hydrogen peroxide at such a rate that the reaction temperature did not exceed 25 °C. The hydrogen peroxide was added below the surface of the reaction mixture by means of a polypropylene tube attached to the dropping funnel. This addition required approximately 2 h, and then the reaction was stirred for 20 h at ambient temperature. A solution of 5.0 g (0.125 mol) of sodium hydroxide in 150 mL (1.45 mol) of 30% hydrogen peroxide was then added and the reaction stirred at 20–24 °C for an additional 5 h. The reaction mixture was treated with 300 mL of ethyl acetate and filtered. The filter cake (consisting of poly-L-leucine and some product) was first washed with 500 mL of ethyl acetate and then slurried in 1.5 L of hot (40–55 °C) ethyl acetate for 20 min and refiltered. [Note: If desired, the isolated poly-L-leucine can be reused after air-drying for several hours on a Buchner funnel.] The combined

(23) (a) Liwschitz, Y.; Rabinsohn, Y.; Perera, D. *J. Chem. Soc.* **1962**, 1116. (b) Harada, K.; Oh-Hashi, *J. Bull. Chem. Soc. Jpn.* **1966**, *39*, 2311.
(24) Harada, K. *J. Org. Chem.* **1966**, *31*, 1407.
(25) Harada, K.; Nakajima, Y. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2911.
(26) The high regioselectivity in this particular reaction is most likely a result of either electronic factors or a chelating effect of the lithium cation. An explanation for the results is still under investigation in these laboratories.
(27) We thank Ms. Susan Shilcrat (SmithKline Beecham Pharmaceuticals) for a sample of this salt.
(28) The X-ray structure of the bis((*R*)-4-iodo-α-methylbenzylamine) salt of SK&F 104353 was obtained by Dr. Drake Eggleston (SmithKline Beecham Pharmaceuticals).

filtrates were washed with three 500-mL portions of water and 1 L of brine, dried over 300 g of magnesium sulfate, filtered, and concentrated in vacuo (14 mmHg) at 30–40 °C to afford a white solid. This material was recrystallized from 1.9 L of 95:5 hexane/toluene to afford 200 g (82%) of epoxy ketone 8. Analysis by HPLC indicated 95.3% ee. An analytical sample of high optical purity (>99.8% ee) was prepared by two recrystallizations from 2-propanol: HPLC (Daicel Chiralpak OP(+), methanol, 0.8 mL/min) t_R(2*R-trans* isomer) = 12.1 min, t_R(2*S-trans* isomer) = 18.8 min; mp 61–62 °C; $[\alpha]_D$ +21.40° (*c* 1.0, THF); FT-IR (KBr) 2923, 2850, 1674, 1403, 1281, 1223, 763, 754, 746, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.59 (d, 1 H, J = 1.3 Hz), 8.10–7.12 (m, 15 H), 4.36 (d, 1 H, J = 1.9 Hz), 4.33 (d, 1 H, J = 1.9 Hz), 2.66 (m, 2 H), 2.50 (t, 2 H, J = 7.7 Hz), 1.60–1.42 (m, 4 H), 1.19–1.02 (m, 8 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 193.1, 142.9, 141.5, 136.0, 133.6, 133.0, 132.5, 130.5, 129.7, 129.4, 129.1, 128.9, 128.5, 128.4, 128.2, 127.9, 127.1, 126.5, 125.6, 124.3, 123.7, 60.5, 57.7, 35.8, 32.7, 31.2, 29.4, 29.2, 29.1. Anal. Calcd for $C_{33}H_{34}O_2$: C, 85.67; H, 7.40. Found: C, 85.60; H, 7.30.

(*trans*)-(2-Naphthalenyl) [3-[2-(8-Phenyloctyl)phenyl]-oxiranyl]methanone. Authentic Mixture of Enantiomers. A mixture of 10.0 g (22.4 mmol) of unsaturated ketone 7, 11.0 g (0.27 mol) of sodium hydroxide, 0.21 g (0.56 mmol) of EDTA, 0.9 g (2.23 mmol) of Aliquat 336, 11 mL of water, and 100 mL of toluene was cooled to 5–10 °C. While the mixture was stirred vigorously, 15 mL (0.48 mol) of 30% hydrogen peroxide was added over a 20-min period. The reaction was allowed to warm to ambient temperature and stirred for 5 days. HPLC analysis indicated approximately 50% conversion to product. The reaction was diluted with 100 mL of diethyl ether and washed with water. The organic layer was then washed with brine, dried over magnesium sulfate, and concentrated in vacuo to a solid residue. Recrystallization from 250 mL of hexane and 20 mL of diethyl ether afforded 4.05 g (39%) of the desired racemate: HPLC (Daicel Chiralpak OP(+), methanol, 0.8 mL/min) t_R(2*R-trans* isomer) = 12.1 min, t_R(2*S-trans* isomer) = 18.8 min; mp 75.5–77.0 °C; FT-IR (KBr) 2932, 2857, 1674, 1404, 1282, 1224, 762, 752, 746, 693 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.59 (d, 1 H, J = 1.0 Hz), 8.10–7.13 (m, 15 H), 4.37 (d, 1 H, J = 1.9 Hz), 4.34 (d, 1 H, J = 1.9 Hz), 2.66 (m, 2 H), 2.51 (t, 2 H, J = 7.7 Hz), 1.60–1.41 (m, 4 H), 1.28–1.04 (m, 8 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 193.0, 142.8, 141.4, 136.0, 133.5, 133.0, 132.4, 130.4, 129.7, 129.3, 129.0, 128.9, 128.5, 128.3, 128.2, 127.9, 127.1, 126.4, 125.5, 124.3, 123.7, 60.5, 57.7, 35.9, 32.7, 31.2, 29.4, 29.2, 29.1. Anal. Calcd for $C_{33}H_{34}O_2$: C, 85.67; H, 7.40. Found: C, 85.50; H, 7.48.

(2*R-trans*)-(2-Naphthalenyl) 3-[2-(8-Phenyloctyl)phenyl]oxiranecarboxylate (9). A stirred solution of 1.0 kg (2.16 mol) of epoxy ketone 8 in 6.25 L of dichloromethane at ambient temperature was treated with 587 g (2.81 mol) of 82.4% *m*-chloroperoxybenzoic acid.[29] The reaction mixture was warmed to reflux, maintained at this temperature for 5 h, and then cooled to ambient temperature. In order to destroy excess oxidant, 54 g (0.65 mol) of cyclohexene was added and the reaction stirred for an additional 30 min. The reaction mixture was filtered to remove precipitated *m*-chlorobenzoic acid, and the filter cake was washed with 900 mL of dichloromethane. The filtrate was returned to the reaction flask, and the flask was fitted with a distillation head. As dichloromethane was removed by distillation at 1 atm, 2-propanol was added in order to maintain a constant volume. The distillation was stopped when the head temperature had reached 76–78 °C, and a total of 8 L of 2-propanol had been added. While still hot, the solution was treated with 1 L of toluene and then allowed to cool to ambient temperature. The mixture was further cooled for 12 h at 0 °C. The resulting white solid was isolated by filtration, washed with 1 L of cold (0 °C) 2-propanol/toluene (9:1), and dried in vacuo (1–3 mmHg) at ambient temperature to afford 902 g (87%) of epoxy ester 9. Analysis by HPLC indicated >99.5% ee: HPLC (Daicel Chiralcel OJ, 50:50 hexane/2-propanol, 1.5 mL/min) t_R(2*S-trans* isomer) = 32.4 min, t_R(2*R-trans* isomer) = 55.6 min; mp 81.0–81.5 °C; $[\alpha]_D$ −90.6° (*c* 1.0, $CHCl_3$), $[\alpha]_{546}$ −109.9° (*c* 1.0, $CHCl_3$); FT-IR (KBr) 2920, 2849, 1762, 1469, 1250, 1183, 900, 746 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84 (m, 3 H), 7.64 (d, 1 H, J = 2.2 Hz), 7.50 (m, 2 H), 7.21 (m, 10 H), 4.46 (d, 1 H, J = 1.7 Hz), 3.67 (d, 1 H, J = 1.7 Hz), 2.78 (m, 2 H), 2.52 (m, 2 H), 1.66 (m, 2 H), 1.54 (m, 3 H), 1.30 (m, 7 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.1, 147.8, 142.8, 141.4, 133.6, 132.5, 131.6, 129.7, 129.4, 128.7, 128.3, 128.2, 127.8, 127.7, 126.8, 126.4, 126.0, 125.5, 124.4, 120.4, 118.3, 56.6, 56.2, 35.9, 32.9, 31.4, 31.2, 29.6, 29.5, 29.4, 29.3. Anal. Calcd for $C_{33}H_{34}O_3$: C, 82.80; H, 7.16. Found: C, 82.88; H, 7.34.

(*trans*)-(2-Naphthalenyl) 3-[2-(8-Phenyloctyl)phenyl]oxiranecarboxylate. Authentic Mixture of Enantiomers. A solution of 0.75 g (1.62 mmol) of *trans*-(2-naphthalenyl) [3-[2-(8-phenyloctyl)phenyl]oxiranyl]methanone in 9 mL of dichloromethane at ambient temperature was treated with 0.85 g (4.2 mmol) of 85% *m*-chloroperoxybenzoic acid. The resulting solution was then refluxed for 4.5 h. After being cooled to ambient temperature, the reaction was filtered to remove *m*-chlorobenzoic acid. The organic layer was concentrated in vacuo to afford a solid. Recrystallization from hot absolute ethanol gave 0.5 g (65%) of the desired racemate: HPLC (Daicel Chiralcel OJ, 50:50 hexane/2-propanol, 1.5 mL/min) t_R(2*S-trans* isomer) = 32.4 min, t_R(2*R-trans* isomer) = 55.6 min; mp 67–68 °C; FT-IR (KBr) 2921, 2850, 1762, 1469, 1250, 1184, 900, 747 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.85 (m, 3 H), 7.65 (d, 1 H, J = 2.3 Hz), 7.50 (m, 2 H), 7.25 (m, 10 H), 4.46 (d, 1 H, J = 1.7 Hz), 3.68 (d, 1 H, J = 1.7 Hz), 2.79 (m, 2 H), 2.54 (m, 2 H), 1.67 (m, 2 H), 1.56 (m, 3 H), 1.31 (m, 7 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.1, 147.9, 142.8, 141.4, 133.7, 132.6, 131.7, 129.6, 129.4, 128.7, 128.3, 128.2, 127.8, 127.7, 126.8, 126.4, 126.0, 125.5, 124.4, 120.4, 118.3, 56.6, 56.2, 35.9, 32.9, 31.4, 31.2, 29.6, 29.5, 29.3. Anal. Calcd for $C_{33}H_{34}O_3$: C, 82.80; H, 7.16. Found: C, 82.43; H, 7.22.

(2*R-trans*)-3-[2-(8-Phenyloctyl)phenyl]oxiranecarboxamide (10). A stirred solution of 40 g (83.7 mmol) of ester 9 in 400 mL of acetone was treated at ambient temperature with 80 mL of aqueous 28–30% ammonium hydroxide. A solid precipitate formed in the flask. After being stirred briefly at ambient temperature, the reaction mixture was heated to reflux for 20 min and then cooled back to ambient temperature. The majority of the acetone was removed in vacuo, and the residue was diluted with 800 mL of toluene. The toluene layer was washed sequentially with three 500-mL portions of aqueous 10% sodium hydroxide, 500 mL of water, and 500 mL of brine. Toluene was then removed in vacuo to produce 29.5 g of a solid. Recrystallization of this material from 360 mL of 9:1 hexane/dichloromethane gave 25.7 g (99.4% purity, 87% yield) of the desired amide: mp 81.5–82.5 °C; $[\alpha]_D$ +14.2° (*c* 1.0, CH_2Cl_2), $[\alpha]_{546}$ +16.7° (*c* 1.0, CH_2Cl_2); IR ($CHCl_3$) 2920, 2845, 1685, 1560 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28–7.15 (m, 9 H), 6.20 (s, 1 H), 5.88 (s, 1 H), 4.11 (d, 1 H, J = 2.0 Hz), 3.37 (d, 1 H, J = 2.0 Hz), 2.70 (m, 2 H), 2.58 (m, 2 H), 1.61–1.56 (m, 4 H), 1.32 (m, 8 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3, 142.8, 141.3, 132.7, 129.2, 128.5, 128.3, 128.2, 126.2, 125.5, 124.2, 58.0, 56.9, 35.9, 32.6, 31.5, 30.9, 29.4, 29.4, 29.3, 29.2. Anal. Calcd for $C_{23}H_{29}NO_2$: C, 78.59; H, 8.32; N, 3.99. Found: C, 78.42; H, 8.24; N, 3.99.

[*S*-(*R,*S**)]-α-Hydroxy-β-[[2-(methoxycarbonyl)ethyl]thio]-2-(8-phenyloctyl)benzenepropanamide (11).** A stirred suspension of 9.6 g (0.24 mol, 60% suspension in mineral oil) of sodium hydride in 280 mL of dichloromethane was cooled to −5 °C and treated with 27.0 mL (0.24 mol) of methyl 3-mercaptopropionate over a 5-min period. (CAUTION: Hydrogen gas is evolved and should be properly vented). This solution was stirred at −5 °C for 30 min after addition of the thiol. In a separate flask, a solution of 40.0 g (0.11 mol) of amide 10 in 120 mL of dichloromethane at ambient temperature was treated with 84.8 mL (0.28 mol) of titanium(IV) isopropoxide. This solution was stirred at ambient temperature for 10 min and then added over 20 min to the cold (−5 °C) solution of the sodium thiolate. The reaction mixture was stirred at −5 °C for 90 min and then diluted with 400 mL of cold (5 °C) ethyl acetate and quenched over 15 min with 400 mL of aqueous 10% sulfuric acid. The quenched reaction was allowed to warm to ambient temperature over 90

(29) Typically, the *m*-CPBA utilized in this reaction was anhydrous (80–85% *m*-CPBA, 15–20% *m*-chlorobenzoic acid). However, identical results were obtained with wet *m*-CPBA (70% *m*-CPBA). Although not specifically tried with compound 8, the commercially available form of *m*-CPBA (i.e., 50–60% *m*-CPBA) gave excellent results on other epoxidized chalcone substrates.

(30) This compound, which was kindly provided to us by Mr. Matthew Sienko (SmithKline Beecham Pharmaceuticals), was prepared by a Darzen's condensation of 6 with methyl chloroacetate (NaOMe, MeOH, CH_2Cl_2, 0 °C).[3]

min with stirring. The contents of the flask were transferred to a separatory funnel, the layers were separated, and the aqueous phase was extracted with two 200-mL portions of ethyl acetate. The combined organic extracts were concentrated in vacuo at 40 °C to afford 80.0 g (61.9% assay, 95% yield) of the desired compound as a viscous oil, which was used without further purification in the next step.

In order to prepare an analytical sample, the crude oil (from another run) was slurried in hexanes and the hexanes removed by decantation. The residue was then purified further by flash chromatography (silica gel, 1:1 ethyl acetate/petroleum ether). After the desired fractions were concentrated, the residual oil was triturated with hexanes to produce a solid. The product was filtered, washed with hexanes, and dried in vacuo at ambient temperature: mp 41.5–42.5 °C; FT-IR (KBr) 3600–3100, 3477, 3100–3000, 3000–2800, 1728, 1668, 1604, 1571, 1368, 1223, 1204, 1157, 751, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.57 (d, 1 H, J = 7.6 Hz), 7.30–7.09 (m, 8 H), 6.43 (s, 1 H), 5.42 (s, 1 H), 4.70 (d, 1 H, J = 4.2 Hz), 4.54 (d, 1 H, J = 4.3 Hz), 3.70 (s, 3 H), 2.91–2.68 (m, 4 H), 2.66–2.53 (m, 4 H), 1.62–1.60 (m, 4 H), 1.34 (s, 8 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 173.3, 172.5, 143.0, 141.2, 134.9, 129.7, 128.5, 128.4, 128.3, 127.8, 125.8, 125.6, 72.6, 52.0, 47.4, 36.0, 34.0, 33.0, 31.5, 30.9, 29.7, 29.5, 29.3, 26.3, 22.6. Anal. Calcd for $C_{27}H_{37}NO_4S$: C, 68.75; H, 7.91; N, 2.97; S, 6.80. Found: C, 68.49; H, 8.05; N, 2.97; S, 6.84.

[*R*-(*R,*S**)]-β-[(2-Carboxyethyl)thio]-α-hydroxy-2-(8-phenyloctyl)benzenepropanamide, Sodium Salt (12).** A solution of 80.0 g (61.9% assay, 0.105 mol) of 11 in 500 mL of absolute methanol was cooled to 5–10 °C and treated with 155 mL (0.39 mol) of 2.5 N aqueous sodium hydroxide over a 10-min period. During the addition of base, which was exothermic, the internal reaction temperature was allowed to rise to 20–25 °C. The reaction was then stirred at ambient temperature for 16 h. Deionized water (500 mL) was added, and the resulting reaction mixture was concentrated in vacuo at 40 °C to remove methanol. The aqueous concentrate was transferred to a separatory funnel and extracted with 400 mL of ethyl acetate. The aqueous phase was treated with solid sodium chloride until saturated and then extracted with two portions (1 × 400 mL, 1 × 200 mL) of ethyl acetate. The combined organic extracts were concentrated in vacuo at 40 °C to afford 85.0 g of a viscous oil. This oil (which retained solvent) was used directly in the next step without further purification.

An analytical sample was synthesized by hydrolysis of the analytical sample prepared for 11. Thus, 9.8 g (20.8 mmol) of analytical sample 11 in 30 mL of absolute methanol was treated with 9.8 mL (24.5 mmol) of 2.5 N aqueous sodium hydroxide, as above. Workup was as described above, except the combined ethyl acetate extracts were dried over anhydrous sodium sulfate prior to the removal of solvent. After an unsuccessful attempt to crystallize the unpurified product from absolute ethanol, the solution was reconcentrated to dryness. The unpurified product was dissolved in 100 mL of dichloromethane. This solution was slowly treated with approximately 170 mL of hexane to produce a precipitate. The white solid was filtered, slurried in 100 mL of hexane, refiltered, and dried in vacuo at ambient temperature to afford 7.0 g (70%) of monosodium salt 12: mp 172–173 °C; FT-IR (KBr) 3600–3100, 3100–3000, 3000–2750, 1663, 1630, 1604, 1572, 1424, 1301, 1277, 1076, 745, 700 cm^{-1}; ^1H NMR (DMSO-d_6, 270 MHz) δ 7.66 (m, 1 H), 7.66–7.02 (m, 8 H), 4.47 (d, 1 H, J = 4.4 Hz), 4.36 (d, 1 H, J = 4.4 Hz), 3.40 (bs, 3 H), 2.75–2.65 (m, 2 H), 2.61–2.51 (m, 4 H), 2.21–2.06 (m, 2 H), 1.56 (m, 4 H), 1.31 (s, 8 H); ^{13}C NMR (DMSO-d_6, 68 MHz) δ 175.1, 174.3, 142.3, 140.4, 137.4, 129.3, 128.6, 128.2, 128.2, 126.3, 125.5, 125.0, 72.8, 45.7, 38.1, 35.1, 32.4, 31.0, 30.3, 29.2, 28.9, 28.8, 28.7, 27.9. Anal. Calcd for $C_{26}H_{34}NO_4SNa$: C, 65.11; H, 7.15; N, 2.92; S, 6.69. Found: C, 64.50; H, 7.06; N, 2.98; S, 6.31.

[*R*-(*R,*S**)]-β-[(2-Carboxyethyl)thio]-α-hydroxy-2-(8-phenyloctyl)benzenepropanoic Acid, Diammonium Salt (1b). From 12.** A solution of 85.0 g of unpurified 12 in 1.0 L of methanol at ambient temperature was treated with 480 mL of aqueous 25% hydrochloric acid. This solution was then heated at reflux temperature for 20 h. After the solution was cooled to 5–10 °C, 50 g of sodium hydroxide was added in a single portion. A 10–15 °C exotherm was observed. After the reaction had cooled back to 5–10 °C, another 50-g portion of sodium hydroxide was added. Again, an exotherm was observed, and the reaction was cooled back to 5–10 °C. Finally, a third 50-g portion of sodium hydroxide was added. After this addition, the reaction was permitted to reach ambient temperature and stirred for 2 h. Deionized water (500 mL) was added, and the resulting reaction mixture was concentrated in vacuo at 40 °C to remove methanol. The aqueous concentrate was extracted with four 500-mL portions of ethyl acetate. These ethyl acetate extracts were discarded. The aqueous phase was then treated with 500 mL of fresh ethyl acetate, and while it was stirred vigorously, the pH was adjusted to 2.0 by the addition of concentrated hydrochloric acid. The layers were separated, and the aqueous phase was extracted with another 200 mL of ethyl acetate. The last two ethyl acetate extracts were combined, washed with 250-mL of aqueous 20% sodium chloride, and concentrated in vacuo at 40 °C to afford 55.0 g of a viscous oil. This material was redissolved in 400 mL of anhydrous acetone. While the solution was stirred at ambient temperature, the pH was adjusted to 8.5 by the dropwise addition of concentrated (28–30%) aqueous ammonium hydroxide over a 30–45-min period. The product was allowed to slowly precipitate at ambient temperature over a 30-min period and then at 0–5 °C for 1 h. The resulting white solid was isolated by filtration under nitrogen, washed with two 75-mL portions of cold 20:1 acetone/deionized water, and dried in vacuo at ambient temperature to afford 62.5 g of unpurified product. This material was recrystallized by suspending the solid in 400 mL of acetone at ambient temperature and slowly adding just enough deionized water to completely dissolve the solid. A total of 55 mL of water was required. The solution was cooled, without stirring, to −5 to 0 °C for 24 h. The white crystalline product was isolated by filtration under nitrogen, washed with two 50-mL portions of cold 20:1 acetone/deionized water, and dried in vacuo at ambient temperature to afford 39.3 g (69% from 10) of diammonium salt 1b as a monohydrate: mp 91–96 °C (presumably dehydration); water content (Karl Fischer) = 3.50% (theory is 3.53% for monohydrate); $[\alpha]_D$ −47.1° (*c* 1.0, H_2O); FT-IR (KBr) 3600–2800, 3100–2800, 3000–2800, 1570, 1399, 1097, 767, 749, 698 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.63 (m, 1 H), 7.28–6.98 (m, 8 H), 4.49 (d, 1 H, J = 3.2 Hz), 3.96 (d, 1 H, J = 3.3 Hz), 2.91–2.84 (m, 1 H), 2.65–2.41 (m, 5 H), 2.30–2.14 (m, 2 H), 1.54 (m, 4 H), 1.29 (s, 8 H); ^{13}C NMR (DMSO-d_6, 67.8 MHz) δ 174.2, 174.2, 142.4, 140.5, 138.0, 130.1, 128.4, 128.2, 128.2, 126.0, 125.5, 124.8, 73.5, 46.4, 36.7, 35.2, 32.4, 31.1, 30.6, 29.3, 29.0, 28.9, 28.7, 27.4. Anal. Calcd for $C_{26}H_{40}N_2O_5S \cdot H_2O$: C, 61.15; H, 8.27; N, 5.49; S, 6.28. Found: C, 61.19; H, 8.25; N, 5.39; S, 6.39.

(2*R-trans*)-3-[2-(8-Phenyloctyl)phenyl]oxiranecarboxylic Acid, Lithium Salt (13). A stirred suspension of 100 g (209 mmol) of ester 9 in 600 mL of absolute methanol at ambient temperature was treated with a solution of 26.3 g (626 mmol) of lithium hydroxide monohydrate in 150 mL of deionized water. The addition was performed over a 10-min period. During the addition of base, the ester dissolved and there was an exotherm to approximately 34 °C. After 60 min at 25–34 °C, 1 L of hot (65 °C) deionized water was added at a constant rate over a 5-min period. The resulting mixture was warmed to 60–65 °C to produce a clear brown homogeneous solution and then allowed to cool slowly to ambient temperature. The mixture was cooled to 0–5 °C for 15 h and the solid product isolated by filtration. The filter cake was washed with three 100-mL portions of cold (0–5 °C) 3:1 deionized water/methanol and dried in vacuo (2–5 mmHg) at 40 °C to afford 71.3 g (95%) of the desired product. An analytical sample was prepared by recrystallization from aqueous methanol: mp 176.0–178.5 °C; $[\alpha]_D$ −33.9° (*c* 1.0, CH_3OH); FT-IR (KBr) 3600–3100, 3100–3000, 3000–2800, 1615, 1446, 1312, 765, 752, 735, 695 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.28–7.04 (m, 9 H), 3.86 (d, 1 H, J = 2.1 Hz), 2.88 (d, 1 H, J = 2.0 Hz), 2.71–2.50 (m, 4 H), 1.54–1.52 (m, 4 H), 1.26 (s, 8 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 170.0, 142.3, 140.5, 135.6, 128.9, 128.2, 128.2, 127.3, 125.9, 125.5, 124.0, 60.1, 53.6, 35.2, 32.0, 31.0, 30.5, 28.9, 28.7. Anal. Calcd for $C_{23}H_{27}O_3Li$: C, 77.08; H, 7.59. Found: C, 77.25; H, 7.85.

(*R,*S**)-Methyl α-Hydroxy-β-[[2-(methoxycarbonyl)ethyl]thio]-2-(8-phenyloctyl)benzenepropanoate (Desired Regioisomer) and (*S**,*S**)-Methyl β-Hydroxy-α-[[2-(methoxycarbonyl)ethyl]thio]-2-(8-phenyloctyl)benzenepropanoate (Undesired Regioisomer). Authentic Samples.**[3] A

solution of 2.35 g (6.42 mmol) of (±-*trans*)-methyl 3-[2-(8-phenyloctyl)phenyl]oxiranecarboxylate[30] in 57 mL of anhydrous methanol and 1.14 mL (8.18 mmol) of triethylamine was prepared. While the solution was stirred at ambient temperature, a solution of 1.32 g (10.98 mmol) of methyl 3-mercaptopropionate in 15 mL of anhydrous methanol and 2.8 mL (20.09 mmol) of triethylamine was added over a 20-min period. After 20 h at ambient temperature, an additional 0.38 g (3.16 mmol) of methyl 3-mercaptopropionate and 0.44 mL (3.16 mmol) of triethylamine was added. After 4 h of additional stirring, another 0.38 g (3.16 mmol) of methyl 3-mercaptopropionate and 0.44 mL (3.16 mmol) of triethylamine was added. The reaction mixture was then stirred for a total of 48 h at ambient temperature (some unreacted glycidic ester remained). The reaction mixture was concentrated in vacuo at 40 °C to remove most of the methanol. The oily residue was redissolved in 50 mL of ethyl acetate, and 25 mL of deionized water was added. While the mixture was stirred vigorously, the pH was adjusted to 2.5 by the addition of 1 N aqueous hydrochloric acid. The layers were separated, and the aqueous layer was extracted with 25 mL of ethyl acetate. The combined extracts were washed with two 25-mL portions of aqueous 15% sodium chloride, dried over sodium sulfate, filtered, and concentrated in vacuo at 40 °C. The residue was placed under high vacuum at ambient temperature to afford 3.88 g of a clear oil. ^{1}H NMR analysis indicated two isomeric products in a ratio of approximately 2:1 (desired to undesired regioisomer). The mixture was purified by chromatography on silica gel GF (80:20 hexanes/ethyl acetate). The regioisomers were then separated by chromatography on neutral alumina GF (80:20 hexanes/ethyl acetate).

Desired regioisomer: HPLC (Ultrasphere ODS 5 μm, 80:20:0.1 acetonitrile/water/acetic acid, 1.0 mL/min, UV detection at 210 nm) t_R = 8.9 min; FT-IR (neat film) 3484, 3100–3000, 3000–2800, 1741, 1603, 1584, 1247, 1219, 1173, 750, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.60 (m, 1 H), 7.30–7.11 (m, 8 H), 4.60 (d, 1 H, J = 5.1 Hz), 4.54 (d, 1 H, J = 4.8 Hz), 3.65 (s, 3 H), 3.64 (s, 3 H), 2.81–2.75 (m, 2 H), 2.71–2.51 (m, 6 H), 1.61–1.56 (m, 4 H), 1.33 (s, 8 H); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 172.3, 172.0, 142.8, 140.6, 134.6, 129.5, 128.7, 128.3, 127.8, 126.1, 125.5, 73.0, 52.3, 51.8, 47.9, 35.9, 34.3, 32.5, 31.5, 31.3, 29.7, 29.5, 29.3, 26.7. Anal. Calcd for $C_{28}H_{38}O_5S$: C, 69.10; H, 7.87; S, 6.59. Found: C, 69.28; H, 7.79; S, 6.21.

Undesired regioisomer: HPLC (Ultrasphere ODS 5 μm, 80:20:0.1 acetonitrile/water/acetic acid, 1.0 mL/min, UV detection at 210 nm) t_R = 8.1 min; FT-IR (neat film) 3497, 3100–3000, 3000–2800, 1740, 1604, 1583, 1260–1140, 766, 750, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.42 (m, 1 H), 7.30–7.13 (m, 8 H), 5.26 (d, 1 H, J = 8.8 Hz), 3.79 (s, 3 H), 3.63 (d, 1 H, J = 8.8 Hz), 3.63 (s, 3 H), 2.81–2.57 (m, 6 H), 2.45–2.38 (m, 2 H), 1.59 (m, 4 H), 1.33 (s, 8 H); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 172.5, 171.7, 142.8, 140.9, 137.8, 129.5, 128.4, 128.2, 128.2, 126.3, 125.8, 125.5, 70.2, 53.3, 52.6, 52.6, 51.8, 35.9, 34.1, 32.7, 31.6, 31.5, 29.6, 29.4, 29.3, 27.4. Anal. Calcd for $C_{28}H_{38}O_5S$: C, 69.10; H, 7.87; S, 6.59. Found: C, 69.29; H, 8.02; S, 6.62.

[*R*-(*R,*S**)]-β-[(2-Carboxyethyl)thio]-α-hydroxy-2-(8-phenyloctyl)benzenepropanoic Acid, Diammonium Salt (1b). From 13.** A stirred suspension of 100.0 g (279 mmol) of lithium carboxylate **13** and 38.6 mL (348 mmol) of methyl 3-mercaptopropionate in 700 mL of tetrahydrofuran was cooled to 0 °C and then treated with 1.95 g (9 mmol) of 25% sodium methoxide in methanol. The reaction mixture was allowed to warm to 5–10 °C and stirred for 4 h. A small sample was removed at this time, treated with ethereal diazomethane, and analyzed by HPLC (Ultrasphere ODS 5 μm, 80:20:0.1 acetonitrile/water/acetic acid, 1.0 mL/min, UV detection at 210 nm). This analysis of the dimethyl esters indicated a >35:1 selectivity for addition of the thiol to the 3-position of **13**. After 4 h at 5–10 °C, the reaction was quenched with 250 mL (625 mmol) of 2.5 N aqueous sodium hydroxide over a period of 10 min. The reaction temperature rose to approximately 20 °C during the quench. Stirring was then continued at 20 °C for an additional 30 min. The pH was adjusted to 2.5 by the addition of 200 mL of 6 N aqueous hydrochloric acid, and the layers were separated. The aqueous layer was washed with 200 mL of ethyl acetate, and this ethyl acetate extract was held separately. The tetrahydrofuran and ethyl acetate layers were each washed separately with 150 mL of aqueous 10% sodium chloride. The tetrahydrofuran extract was concentrated in vacuo to near dryness, combined with the ethyl acetate extract, and concentrated again in vacuo to afford 161.0 g of a yellow viscous oil. This material was redissolved in 1.05 L of anhydrous acetone. While the solution was stirred at ambient temperature, the pH was slowly adjusted to approximately 6.4–6.6 by the addition of concentrated (28–30%) ammonium hydroxide. The product was allowed to slowly precipitate at ambient temperature over a 30-min period, while the pH was maintained at 6.4–6.6 with concentrated ammonium hydroxide. After 30 min, concentrated ammonium hydroxide was added to adjust the pH to a final value of 8.4. A total of approximately 60 mL of concentrated ammonium hydroxide was used. The mixture was then cooled to 0 °C for 16 h. The resulting white solid was isolated by filtration under nitrogen, washed with two 200-mL portions of cold (0 °C) 20:1 acetone/deionized water, and dried in vacuo at ambient temperature to afford 139.0 g of unpurified product. This material was recrystallized by suspending the solid in 675 mL of acetone at ambient temperature and slowly adding just enough deionized water to completely dissolve the solid. A total of 132 mL of water was required. The hazy solution was filtered into a clean flask, and while it was stirred at ambient temperature, an additional 250 mL of acetone was added over a 30-min period. The product was allowed to crystallize for 60 min at ambient temperature and then stored at 0 °C for 16 h. The white crystalline solid was isolated by filtration under nitrogen, washed with three 200-mL portions of cold (0 °C) 20:1 acetone/deionized water, and dried in vacuo at ambient temperature to afford 108 g (76%) of diammonium salt **1b** as a monohydrate: Analysis by HPLC indicated >99.5% ee (Daicel Chiralcel OD, 90:10:0.1 hexane/2-propanol/trifluoroacetic acid, 2.0 mL/min, UV detection at 215 nm) t_R(2*R*,3*S* isomer) = 7.03 min, t_R(2*S*,3*R* isomer) = 11.74 min; mp 91–96 °C (presumably dehydration); water content (Karl Fischer) = 3.62% (theory is 3.53% for monohydrate); $[\alpha]_D$ −47.6° (*c* 1.0, H_2O); FT-IR (KBr) 3600–2800, 3100–3000, 3000–2800, 1567, 1387, 1097, 767, 749, 698 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.63 (m, 1 H), 7.28–6.98 (m, 8 H), 4.49 (d, 1 H, J = 3.3 Hz), 3.95 (d, 1 H, J = 3.3 Hz), 2.91–2.84 (m, 1 H), 2.65–2.41 (m, 5 H), 2.30–2.14 (m, 2 H), 1.54 (m, 4 H), 1.30 (s, 8 H); ^{13}C NMR (DMSO-d_6, 67.8 MHz) δ 174.27 (2 carbons), 142.3, 140.5, 138.0, 130.1, 128.4, 128.2, 128.2, 126.0, 125.5, 124.8, 73.5, 46.4, 36.8, 35.2, 32.4, 31.1, 30.6, 29.3, 29.0, 28.9, 28.7, 27.4. Anal. Calcd for $C_{26}H_{40}N_2O_5S{\cdot}H_2O$: C, 61.15; H, 8.27; N, 5.49; S, 6.28. Found: C, 61.19; H, 8.36; N, 5.52; S, 6.28.

[*R*-(*R,*S**)]-β-[(2-Carboxyethyl)thio]-α-hydroxy-2-(8-phenyloctyl)benzenepropanoic Acid. From Diammonium Salt 1b.** A suspension of 200 mg (0.39 mmol) of diammonium salt **1b** in 5 mL of ethyl acetate was treated with 4 mL of 0.5 N HCl. After the suspension was stirred for 5 min, the layers were separated and the aqueous layer was extracted with 4 mL of ethyl acetate. The organic layers were combined, washed with 2 × 4 mL of 6 N HCl and 3 × 5 mL of water, dried over sodium sulfate, and concentrated under vacuum to afford 172 mg (96% yield) of **1a** as an oil: chiral HPLC (Bakerbond Chiralcel OD, 96.5:3.5:0.1 hexane/2-propanol/ trifluoroacetic acid, 2.0 mL/min, UV detection at 215 nm), t_R (2*R*,3*S* isomer) = 6.7 min (0.1%), t_R (2*S*,3*R* isomer) = 8.6 min (99.9%); FT-IR (neat film) 3025, 2990, 2925, 2875, 2850, 1715, 1530, 1495, 1475, 1450, 1380, 1255, 1140, 1095, 1005, 910, 850, 745, 710, 700, 685 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.58 (d, 1 H, J = 6.9 Hz), 7.29–7.14 (m, 8 H), 4.63 (d, 1 H, J = 4.8 Hz), 4.58 (br s, 1 H), 2.82–2.59 (m, 8 H), 1.60 (br s, 4 H), 1.34 (br s, 8 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.9, 176.4, 142.9, 141.0, 134.3, 129.7, 128.6, 128.4, 128.2, 128.0, 126.2, 125.6, 72.9, 47.2, 36.0, 34.3, 32.6, 31.5, 31.2, 29.7, 29.5, 29.3, 26.2.

[*R*-(*R,*S**)]-β-[(2-Carboxyethyl)thio]-α-hydroxy-2-(8-phenyloctyl)benzenepropanoic Acid. From the Bis((*R*)-4-iodo-α-methylbenzylamine) Salt.** A suspension of 175 mg (0.18 mmol) of bis((*R*)-4-iodo-α-methylbenzylamine) salt of SK&F 104353 in 5 mL of ethyl acetate was treated with 4 mL of 0.5 N HCl. After the suspension was stirred for 5 min, the layers were separated and the aqueous layer was extracted again with 3 mL of ethyl acetate. The organic layers were combined, washed with 2 × 4 mL of 6 N HCl and 3 × 4 mL of water, dried over sodium sulfate, and concentrated under vacuum to afford 77 mg (87% yield) of **1a** as an oil: chiral HPLC (Bakerbond Chiralcel OD, 96.5:3.5:0.1 hexane/2-propanol/trifluoroacetic acid, 2 mL/min,

UV detection at 215 nm), t_R (2*R*,3*S* isomer) = 6.4 min (2.1%), t_R (2*S*,3*R* isomer) = 8.6 min (97.9%); FT-IR (neat film) 3020, 2990, 2025, 2870, 2850, 1715, 1530, 1495, 1475, 1455, 1380, 1245, 1140, 1095, 1000, 925, 845, 750, 710, 700, 685 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.58 (d, 1 H, J = 7.2 Hz), 7.29–7.13 (m, 8 H), 4.63 (d, 1 H, J = 4.8 Hz), 4.58 (d, 1 H, J = 4.3 Hz), 2.81–2.56 (m, 8 H), 1.59 (br s, 4 H), 1.34 (br s, 8 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.8, 176.3, 142.9, 141.0, 134.4, 129.7, 128.6, 128.4, 128.2, 128.0, 126.2, 125.6, 72.9, 47.2, 36.0, 34.3, 32.6, 31.5, 31.2, 29.7, 29.5, 29.3, 26.2.

Acknowledgment. We are indebted to members of the Analytical Chemistry and Physical & Structural Chemistry Departments for much of the analytical data: E. Reich for combustion analyses and optical rotations, R. Butts for optical rotations, D. Staiger and P. Offen for NMR spectra, G. Zuber for FT-IR spectra, and T. Last and Ted Chen for chiral assays. We also thank Ken Kopple and Professors T. Cohen, L. Overman, and the late P. Gassman for helpful discussions.