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General Method for the Synthesis of High Enantiomeric Purity Chiral Epoxides[1]

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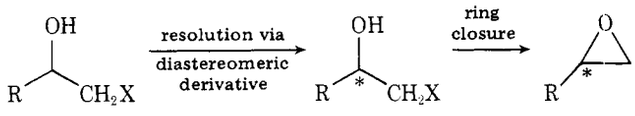
Ring opening of racemic epoxides with thiophenoxide anion affords β-hydroxy sulfides (**3**), which can be resolved by chromatographic separation of their diastereomeric 1-(1-naphthyl)ethylcarbamates (**1** and **2**). Cleavage of either of the carbamate diastereomers with trichlorosilane affords optically pure **3**, which can be converted to the resolved epoxide by S-alkylation followed by treatment with base. Racemic β-hydroxy sulfides are also readily available from the treatment of aldehydes with α-lithioalkyl aryl sulfides.

In view of the large number of stereospecific reactions undergone by epoxides,[2] chiral epoxides of high enantiomeric purity are useful in the synthesis of more complex enantiomerically enriched substances. Because of this utility, many workers have attempted to prepare enantiomerically enriched epoxides. Nevertheless, there are no general synthetic approaches to epoxides of high enantiomeric purity. Two commonly used approaches which warrant mention are asymmetric oxidation and classical resolution.

Numerous asymmetric oxidations of olefins to epoxides have been reported utilizing chiral peracids,[3] chiral phase-transfer catalysts,[4] and chiral transition-metal complexes.[5] Although these are convenient and frequently high yield reactions, the enantiomeric enrichment is often low and not readily predictable. Moreover, the absolute configuration of the predominant enantiomer cannot be reliably assigned from mechanistic considerations.

Alternatively, synthesis of enantiomerically enriched epoxides has been accomplished by optical resolution of an epoxide precursor, generally an alcohol with an appropriate leaving group in the β position, followed by stereospecific epoxide formation (Scheme I).[6] Such approaches can provide epoxides of high enantiomeric purity, but often at considerable expense in time and effort owing to the use of "classical" fractional crystallization techniques for the optical resolutions. Each such resolution is unique, and appropriate resolving agents and conditions must be found by trial and error. Moreover, the enantiomerically pure epoxide precursor has frequently been obtained in low yield since multiple recrystallizations may be necessary to separate the diastereomeric derivatives. These problems can be avoided through the use of multigram LC techniques for the resolution of the epoxide precursor. Our approach to the synthesis of high enantiomeric purity epoxides hinges upon the use of multigram LC.

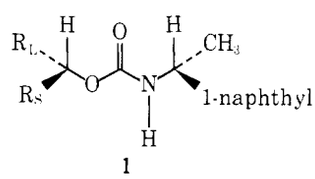
Scheme I



X = Cl, Br, S–*n*-Bu, $N(CH_3)_2$, OAc, OTs, OH

It is known that reaction of enantiomerically pure 1-(1-naphthyl)ethyl isocyanate with a wide variety of racemic secondary alcohols provides diastereomeric carbamate derivatives, **1** and **2**, and that these are frequently separable by liquid chromatography.[7] It is also known that chiral epoxides of high enantiomeric purity can be prepared from resolved β-hydroxy sulfides.[8] If a variety of racemic β-hydroxy sulfides were to prove amenable to resolution using the aforementioned chromatographic approach, a ready, convenient, predictable approach to chiral epoxides of high enantiomeric purity could be realized. Several practical advantages were expected to accrue from this approach.

In nonpolar solvents, diastereomeric carbamates **1** and **2** heavily populate the depicted conformations.[9] The chromatographic separability of the pair appears to derive from the relative ability of R_L and R_S to act in conjunction with the 1-naphthyl group to block the binding of the polar carbonyl



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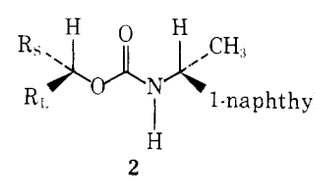

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region of either diastereomer to the adsorbant. Blocking ability may be either steric or electronic in origin, and various groups have been empirically ranked in terms of effectiveness. Thus, chromatographic separability is more or less predictable. A second consequence of the population of these conformations can be observed in the NMR spectra of **1** and **2**. The magnetic anisotropy of the naphthyl ring causes R_S in **1** to be shielded relative to R_S in **2** (the converse is true for R_L). From the observed chemical shift differences and from the

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Table I. Selected NMR and Chromatographic Data for Some Diastereomeric Carbamates

compd	R_L/δ ($CDCl_3$)	R_S/δ ($CDCl_3$)	compd	R_S/δ ($CDCl_3$)	R_L/δ ($CDCl_3$)	α
1a	$CH(CH_3)SPh$/1.27	CH_3/1.21	**2a**	CH_3/1.23	$CH(CH)SPh$/1.27	1.46
1b	CH_2SPh/–	CH_3/1.28	**2b**	CH_3/1.30	CH_2SPh/–	1.25
1c	CH_2SPh/–	CH_3CH_2/0.85	**2c**	CH_3CH_2/0.93	CH_2SPh/–	1.16
1d	Ph/–[a]	CH_2SPh/–	**2d**	CH_2SPh/–	Ph/–[a]	1.30
1e	$CH_3CH_2SCH_2$/–[b]	n-C_8H_{17}/–	**2e**	n-C_8H_{17}/–	$CH_3CH_2SCH_2$/–[b]	1.17
1f[c]	$CH(CH_3)SPh$/1.23	Ph/–	**2f**[c]	Ph/–	$CH(CH_3)SPh$/1.18	1.10
1g[d]	$CH(CH_3)SPh$/1.19	Ph/–	**2g**[d]	Ph/–	$CH(CH_3)SPh$/1.13	1.35
1h[c]	$CH(n$-$C_6H_{13})SPh$/–[a]	C_5H_{11}/–	**2h**[c]	C_5H_{11}/–	$CH(n$-$C_6H_{13})SPh$/–[a]	1.40
1i[d]	$CH(n$-$C_6H_{13})SPh$/–	C_5H_{11}/–	**2i**[d]	C_5H_{11}/–	$CH(n$-$C_6H_{13})SPh$/–[a]	1.25

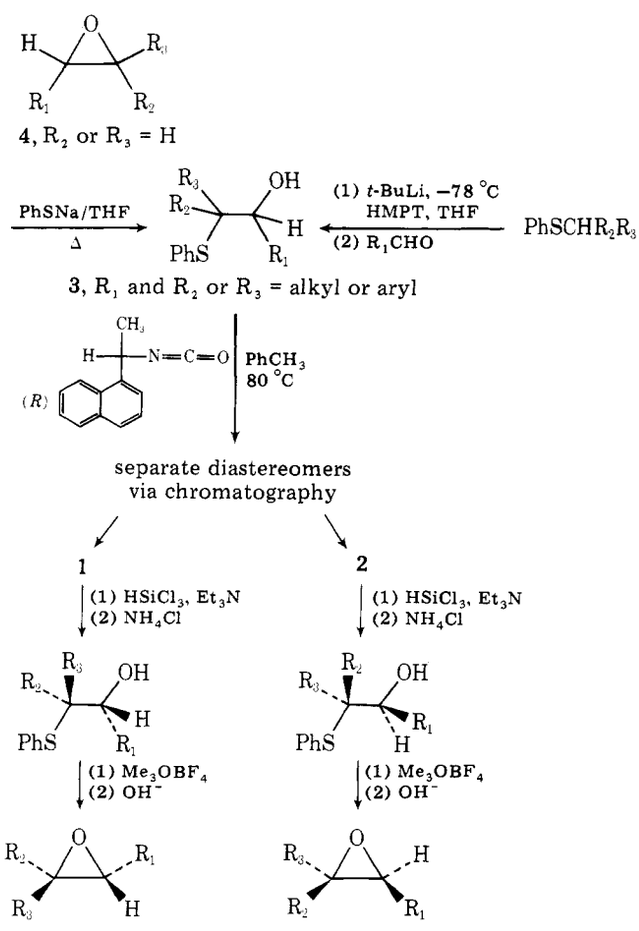
[a] Nonequivalence observed for $NCHCH_3$: **1d**, δ 1.53; **2d**, δ 1.63; **1h**, δ 1.63; **2h**, δ 1.56; **1i**, δ 1.60; **2i**, δ 1.77. [b] No nonequivalence observed. [c] From *erythro*-**3**. [d] From *threo*-**3**.

known configuration of the amine moiety, the absolute configuration at the carbinol center can be determined.[7] Therefore, spectral differences between the diastereomers allow the determination of absolute configuration and diastereomeric purity of the carbamates.

Results and Discussion

Since the aforementioned chromatographic resolution is most applicable to secondary alcohols,[10] we have utilized secondary alcohols bearing various alkyl or aryl substituents, as well as a β-sulfide function, as models to test the proposed approach (Scheme II). Considerable latitude should be possible in the structure of the thiol reagent utilized in synthesis of the β-hydroxy sulfide. In general, the reagent would be picked for availability, compatability with other functional groups or reagents to be used, ability to impart favorable chromatographic properties (separability and detectability), and ease of purification of the product epoxide. Thiophenol is an obvious choice, although substituted thiophenols may prove useful in selected instances.

Scheme II



The requisite β-hydroxy sulfides (**3**) can be obtained in several ways. If the racemic epoxide is available, ring opening with thiophenoxide, *regioselectivity permitting*, is straightforward. Alternatively, reaction of α-thiolithium reagents (derived from alkyl aryl sulfides)[11] with an aldehyde affords erythro–threo mixtures of **3**. These diastereomers are generally separable by chromatography (neutral alumina, 5:1 hexane–methylene chloride), typically with the threo isomer eluting first.[12] An alcohol inversion sequence as described by Corey et al.[14] permits utilization of an otherwise undersired diastereomer and has the effect of increasing the overall yield of the sequence.

Treatment of **3** with enantiomerically pure 1-(1-naphthyl)ethyl isocyanate yields diastereomeric carbamates **1** and **2**, usually in 80–90% yield. These acid-labile carbamates will decompose on silica gel, but they may be chromatographed on either basic or neutral alumina. Table I shows the observed α values (a measure of chromatographic separability) of some diastereomeric β-hydroxy sulfide carbamate derivatives.

On the basis of conformational arguments earlier presented, the absolute configurations of a number of hydroxy sulfides can be correlated with chemical shift differences between diastereomeric carbamates **1** and **2** (Table I). For example, the chemical shift of the methyl group (R_S) in **1a** is upfield relative to its counterpart in the other diastereomer (R_S in **2a**). From this and the known absolute configuration at the nitrogen-bearing center, the absolute configuration at the carbinyl center of the first eluted diastereomer, **1a**, is assigned as *R*. This is also the configuration expected on the basis of elution order if one makes the reasonable assumption that the $CH(CH_3)SC_6H_5$ substituent will be more effective in warding off adsorption than a methyl group.[15] Elution orders of the remaining pairs of diastereomers in Table I may be rationalized on similar grounds. Indeed, elution orders may be considered as auxiliary sources of configuration information.

Scheme III

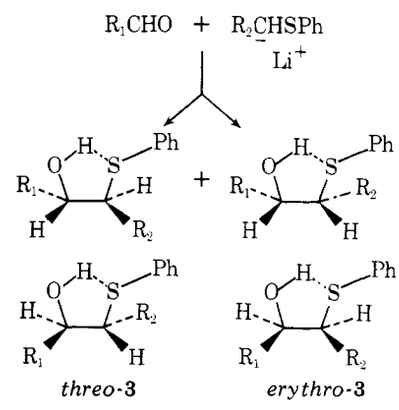


Table II. Optically Active β-Hydroxy Sulfides and Epoxides

hydroxy sulfides[e]				epoxides[f]			
compd	yield, %	$[\alpha]^{25}_D$,[a] deg (c 5, $CHCl_3$)	e.e., %[b]	compd	$[\alpha]^{25}_D$, deg	yield %	optical purity, %
3b	73	−22.1	~95 ± 5	**4b**	+ 14.0 ± 1.0 (c 0.5, Et_2O)	50[c]	100
3c	92	+57.2	95 ± 5	**4c**	+13.5 (c 5, Et_2O)	95	100
3d	65	+21.2	90 ± 5	**4d**	−41.5 (c 5, PhH)	85	88
3e	89	−22.1	85 ± 5	**4e**	+7.5 (c 5, $CHCl_3$)	94	*d*

[a] In this table, all (+)-3 are from low R_f carbamates of (*R*)-(+)-1-(1-naphthyl)ethylamine. [b] Estimated from the NMR determined ratio of the diastereomeric carbamates before silanolysis. Spectral congestion causes these determinations to be less certain than usual. [c] GC yield; due to the volatility of the product, only 5–10% was actually isolated pure. [d] Rotational data not previously reported. By analogy, the e.e is expected to be ~85%. [e] Registry no.: **3b,** 67253-47-8; **3c,** 67210-33-7; **3d,** 67210-34-8; **3e,** 67210-35-9. [f] Registry no.: **4b,** 15448-47-2; **4c,** 3760-95-0; **4d,** 20780-54-5; **4e,** 67210-36-0.

After separation, the carbamates are cleaved by silanolysis,[16] using trichlorosilane and an excess of triethylamine (Scheme II). This reaction retrieves the β-hydroxy sulfides in yields of 80–90%. Subsequent treatment of the resolved β-hydroxy sulfide with trimethyloxonium tetrafluoroborate followed by 10% aqueous NaOH provides optically active epoxide **4** of known absolute configuration. This cyclization sequence, completely stereospecific within the experimental error of the optical purity and enantiomeric excess determinations (Table II), involves S_N2 inversion at the reaction center.

Conclusion

By utilizing the chromatographic separability of diastereomeric carbamates derived from β-hydroxy sulfides, it should be possible to prepare a wide variety of optically active epoxides of high enantiomeric purity and known absolute configuration. Both enantiomers are obtained.

Experimental Section

Melting points were determined on a Büchi apparatus and are uncorrected. NMR spectra were recorded on Varian EM-390 and HR-220 spectrometers at 30 °C. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Mass spectra were obtained on a Varian MAT CH-5 spectrometer. Elemental analyses were performed by M. J. Nemeth and associates, University of Illinois.

General Procedure for the Synthesis of β-Hydroxy Sulfides. A 300 mL three-neck round-bottom flask equipped with an overhead stirrer, addition funnel, N_2 inlet, and reflux condenser was oven-dried and cooled under a stream of dry N_2. Thiophenol (8.0 g, 0.072 mol) in 150 mL of dry tetrahydrofuran was added to the flask, the mixture was cooled in an ice bath, and NaH (4.0 g of a 50% by weight mineral oil dispersion washed with dry pentane to remove the mineral oil) was added in small portions with vigorous stirring. After the evolution of H_2 had ceased, epoxide (0.072 mol) in 50 mL of tetrahydrofuran was added dropwise with stirring at 0 °C. The cold mixture was stirred for 2 h and then heated at reflux for 1–2 h, at which point the suspended matter diasappeared, affording a cloudy solution. Hindred epoxides require longer heating periods, perhaps as much as 10 h. The reaction mixture was cooled in an ice bath and acified with 10% HCl, the THF was removed under vacuum, and the residue was extracted with two 100-mL portions of ether. The ethereal extracts were combined, dried ($MgSO_4$), and concentrated under vacuum to yield crude β-hydroxy sulfide, which was purified either by fractional distillation at reduced pressure or by crystallization.

3-Phenylthio-2-butanol (3a) was a colorless liquid: bp 98–101 °C (0.9 mm); NMR ($CDCl_3$) δ 1.15 (d, *J* = 6.3 Hz, 3H, CH_3CHS), 1.25 (d, *J* = 7.2 Hz, 3 H, CH_3COH), 2.53 (s, 1 H, OH), 3.23 (d of 1, J_d = 4 Hz, J_q = 6.3 Hz, 1 H, CHS), 3.78 (d of q, J_d = 4 Hz, J_q = 7.2 Hz, 1 H, CHOH), 7.1–7.5 (m, 5 H, Ar); IR (neat) 3200–3600, 3080, 3060, 2980, 2940, 2880, 1585, 1480, 1450, 1440, 1380, 1260, 1150, 1000–1100, 910, 750, and 700 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}OS$: C, 65.99; H, 7.74; S, 17.59. Found: C, 66.19; H, 7.90; S, 17.50.

1-Phenythio-2-propanol (3b) was a clear oil: bp 96–99 °C (0.5 mm); NMR ($CDCl_3$) δ 0.92 (t, *J* = 6 Hz, 3 H, CH_3), 1.52 (d of q, *J* = 6 Hz, *J'* = 7 Hz, 2 H, CH_2CH_3), 2.74 and 3.04 (d of AB pattern, J_{AB} = 14 Hz, *J'* = 9 Hz, *J* = 4 Hz, 2 H, SCH_2), 3.1 (broad s, 1 H, OH), 3.6 (m, 1 H, >CH–), 7.0–7.6 (m, 5 H, Ar); IR (neat) 3200–3600, 3080, 2980, 2940, 1590, 1480, 1440, 1380, 1030–1130, 940, 740, and 690 cm^{-1}.

Anal. Calcd for $C_9H_{12}OS$: C, 64.24; H, 7.19; S, 19.06. Found: C, 64.31; H, 7.23; S, 19.23.

1-Phenylthio-2-butanol (3c) was a clear colorless liquid: bp 109–110 °C (0.6 mm); NMR ($CDCl_3$) δ 0.93 (t, *J* = 7 Hz, 3 H, CH_3), 1.50 (m, 2 H, CH_2CH_3), 2.53 (broad s, 1 H, OH), 2.80 and 3.10 (d of AB pattern, J_{AB} = 12 Hz, *J* = 5 Hz, *J'* = 3 Hz, 2 H, CH_2S), 3.50 (m, 1 H, CHOH), 7.0–7.4 (m, 5 H, Ar); IR (neat) 3200–3600, 3060, 2970, 2930, 2880, 1585, 1480, 1440, 1120, 1070, 740, and 690 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}OS$: C, 65.89; H, 7.74; S, 17.59. Found: C, 66.10; H, 7.72; S, 17.81.

1-Phenyl-2-phenylthioethanol (3d) was obtained as a clear oil: bp 165–169 °C (0.4 mm); NMR ($CDCl_3$) δ 2.90 (broad s, 1 H, OH), 3.00 and 3.10 (d of AB pattern, J_{AB} = 13 Hz, *J* = 9 Hz, *J'* = 4 Hz, 2 H, CH_2S), 4.57 (d of d, *J* = 9 Hz, *J'* = Hz, 1 H, CHOH), 7.2 (m, 10 H, Ar); IR (neat) 3200–3600, 3080, 3040, 2940, 1580, 1500, 1480, 1460, 1450, 1200, 1000–1100, 750, and 700 cm^{-1}; MS (10 eV) *m/e* (relative intensity) 230 (20.81), 124 (100), 107 (18.97).

1-Ethylthio-2-decanol (3e) was a clear colorless liquid: bp 101–103 °C (0.05 mm); NMR ($CDCl_3$) δ 3.5–3.7 (m, 1 H, OCH), 2.3–2.8 (m, 4 H, CH_2SCH_2), 1.2–1.5 (m, 14 H, $(CH_2)_7$), 1.25 (t, 2 H, SCH_2CH_3), 0.87 (t, 3 H, $(CH_2)_7CH_3$); IR (neat) 3200–3600, 2900–2980, 2860, 1440–1470, 1380, 1220–1280, and 1000–1080 cm^{-1}; MS (10 eV) (relative intensity) 218 (3.6), 200 (0.7), 138 (7.1), 76 (100), 61 (5.2).

Anal. Calcd for $C_{12}H_{26}SO$: C, 65.99; H, 12.00; S, 14.68. Found: C, 65.58; H, 11.59; S, 14.55.

7-Phenylthio-6-tridecanol (3h and 3i). This compound was prepared as previously described by Dolak and Bryson.[11] To a solution of phenyl 1-heptyl sulfide (5.0 g, 0.022 mol) and hexamethylphosphoric triamide (10 g, 0.055 mol) in 50 mL of tetrahydrofuran at −78 °C was added dropwise 16 mL of *tert*-butyllithium (1.84 M in pentane). The orange solution thus obtained was stirred at −78 °C for 2 h and 2.0 g (2.5 mL, 0.02 mol) of *n*-hexanal in 100 mL of tetrahydrofuran was allowed to drip into the reaction mixture over a period of 1 h. The reaction mixture was then allowed to warm slowly to room temperature and was poured over 50 g of ice; the organic layer was isolated, and the aqueous layer was extracted twice with 50-mL portions of diethyl ether. The organic layers were combined and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue, a mixture of erythro and threo β-hyroxy sulfide (70%), was chromatographed on neutral alumina with hexane/CH_2Cl_2 (4:1) and afforded two major fractions, the threo and then the erythro isomers.

threo-**3h** (12 g) was a high-boiling clear colorless oil: NMR ($CDCl_3$) δ 0.7–1.0 (t, 6 H, terminal CH_3's), 1.0–1.8 (m, 18 H, CH_2's), 2.3 (broad s, 1 H, OH), 2.8–3.1 (m, 1 H, SCH), 3.45 (m, 1 H, OCH), 7.0–7.5 (m, 5 H, Ar); IR (neat) 3200–3600, 3080, 3060, 2960, 2940, 2860, 1690, 1590, 1480, 1470, 1440, 1380, 1090, 1030, 740, and 690 cm^{-1}; MS (70 eV) *m/e* (relative intensity) 308 (22.38), 208 (100), 110 (74.94), 55 (43.54).

erythro-**3i** (11 g) was obtained as a clear colorless oil: NMR ($CDCl_3$) δ 0.83 (t, 6 H, terminal CH_3's), 1.0–1.9 (m, 18 H, CH_2's), 2.30 (broad s, 1 H, OH), 2.8–3.2 (m, 1 H, SCH), 3.60 (m, 1 H, OCH), 7.0–7.5 (m, 5 H, Ar); IR (neat) 3200–3600, 3080, 3060, 2960, 2930, 2860, 1690, 1580, 1480, 1465, 1435, 1380, 1090, 1020, 740, and 690 cm^{-1}; MS (10 eV) *m/e* (relative intensity) 308 (30.00), 208 (100), 110 (68.72).

1-Phenyl-2-phenylthio-1-propanol (3f and 3 g). This compound was prepared from phenyl ethyl sulfide (15.2 g) and benzaldehyde (11.7 g) by the method used for the preparation of **3h** and **3i.** Distillation, 135–148 °C (0.05 mm), afforded a yellow viscous oil (89%), which was shown by NRM spectroscopy to be a 1:1 erythro–threo mixture. Chromatography of the mixture (neutral alumina, 4:1 hexane–CH_2Cl_2) afforded *threo*-**3f** first and then *erythro*-**3g** as separate 280 nm active bands.

threo-**3f** was, after molecular distillation (100 °C, 0.05 Torr), a clear oil: NMR δ ($CDCl_3$) 7.1–7.5 (m, 10 H, Ar), 4.70 (d, J = 4 Hz, 1 H, CH–O), 3.50 (d of q, J' = 7 Hz, J = 4 Hz, 1 H, CHS), 2.4–2.6 (broad s, 1 H, OH), 1.10 (d, J' = 7 Hz, 3 H, CH_3); IR (neat) 3200–3600, 3070, 3040, 2980, 2940, 2880, 1700, 1590, 1480, 1460, 1380, 1200, 1030, 750, and 700 cm^{-1}.

Anal. Calcd for $C_{15}H_{16}SO$: C, 73.73; H, 6.60; S, 13.12. Found: C, 73.62; H, 6.54; S, 13.00.

erythro-**3g** was a clear oil: bp 135–140 °C (0.05 mm); NMR δ ($CDCl_3$) 7.1–7.5 (m, 10 H, Ar), 5.99 (d, J = 8 Hz, 1 H, CH–O), 3.23 (d of q, J = 8 Hz, J' = 7 Hz, 1 H, CHS), 1.07 (d, J' = 7 Hz, 3 H, CH_3); IR (neat) 3200–3600, 3070, 3040, 2980, 2940, 2880, 1700, 1590, 1480, 1460, 1380, 1200, 1030, 750, and 700 cm^{-1}; MS (10 eV) *m/e* (relative intensity) 244 (7.33), 200 (8.77), 138 (100), 137 (49.29), 110 (7.74), 107 (14.26).

Anal. Calcd for $C_{15}H_{16}SO$: C, 73.73; H, 6.60; S, 13.12. Found: C, 73.80; H, 6.74; S, 12.34.

General Procedure for the Synthesis of Carbamates. A solution of (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate (0.2 mol) and β-hydroxy sulfide (0.2 mol) in 50 mL of toluene and 1% *N*,*N*-dimethylethanolamine was heated at reflux until the isocyanate band at 2260 cm^{-1} disappeared. The solvent was evaporated, and the carbamates were chromatographed (3–5 g/run) on a 50 mm × 120 cm column of Brinkmann neutral alumina using 2 L/h of 5:1 hexane–CH_2Cl_2 while monitoring continuously at 280 nm using an ISCO UA-5 absorbance monitor. Three fractions were collected: the first peak which was mainly one diastereomer, a middle fraction which resulted from some overlap of the two peaks (this was recycled), and a second peak which was mostly the low R_f diastereomer. The solvent was removed, and in some instances the carbamates could be recrystallized from hexane–CH_2Cl_2.

1-Methyl-2-phenylthiopropyl *N*-[1-(1-naphthyl)ethyl]carbamate 1a was a clear oil: NMR ($CDCl_3$) δ 1.21 (d, 3 H, $OCHCH_3$), 1.27 (d, 3 H, $SCHCH_3$), 3.32 (m, 1 H, SCH), 4.84 (broad d, 1 H, NH), 4.93 (quintet, 1 H, OCH), 5.54 (quintet, 1 H, NCH), 6.82–8.18 (m, 12 H, Ar); IR (neat) 3420, 3080, 2980, 2960, 1690, 1500–1600, 1380, 1200–1260, 1000–1100, 800, 760, and 750 cm^{-1}; MS (70 eV) *m/e* (relative intensity) 379 (0.76), 164 (100), 155 (37.80), 110 (7.14), 77 (5.12), 55 (13.34).

1-Methyl-2-phenylthiopropyl *N*-[1-(1-naphthyl)ethyl]carbamate 2a was a clear oil: NMR ($CDCl_3$) δ 1.23 (d, 3 H, $OCHCH_3$), 1.27 (d, 3 H, $SCHCH_3$), 1.57 (d, 3 H, $NCHCH_3$), 3.32 (m, 1 H, SCH), 4.84 (broad d, 1 H, NH), 4.93 (quintet, 1 H, OCH), 5.57 (quintet, 1 H, NCH), 6.82–8.18 (m, 12 H, Ar); IR (neat) 3420, 3060, 2980, 2940, 1710, 1520, 1480, 1380, 1240, 1160, 800, 780, and 750 cm^{-1}; MS (70 eV) *m/e* (relative intensity) 379 (0.97), 164 (100), 155 (38.42), 110 (7.89), 77 (6.00), 55 (13.56).

1-Methyl-2-phenylthioethyl *N*-[1-(1-naphthyl)ethyl]carbamate 1b was a white solid: mp 63–65 °C; NMR ($CDCl_3$) δ 1.28 (d, 3 H, $OCHCH_3$), 1.59 (d, 3 H, $NCHCH_3$), 2.7–3.3 (m, 2 H, SCH_2), 4.7–5.1 (m, 2 H, NH and OCH), 5.53 (quintet, 1 H, NCH), 6.8–8.2 (m, 12 H, Ar); MS (70 eV) *m/e* (relative intensity) 365 (0.3), 155 (20.0), 151 (17.5), 150 (100), 109 (6.8); IR (KBr) 3340, 3060, 2980, 1690, 1530, 1380, 1250, 1070, 1040, 800, 780, and 730 cm^{-1}.

1-Methyl-2-phenylthioethyl *N*-[1-(1-naphthyl)ethyl]carbamate 2b was a while solid: mp 67–69 °C; NMR ($CDCl_3$) δ 1.30 (d, 3 H, $OCHCH_3$), 1.59 (d, 3 H, $NCHCH_3$), 2.7–3.3 (m, 2 H, SCH_2), 4.7–5.1 (m, 2 H, NH and OCH), 5.53 (quintet, 1 H, NCH), 6.8–8.2 (m, 12 H, Ar); MS (70 eV) *m/e* (relative intensity) 365 (1.0), 155 (36.5), 151 (19.5), 150 (100), 109 (13.4); IR (KBr) 3320, 3080, 2980, 1690, 1540, 1380, 1260, 1240, 1060, 780, 740, and 690 cm^{-1}.

1-Ethyl-2-phenylthioethyl *N*-[1-(1-naphthyl)ethyl]carbamate 1c was a white solid: mp 71–73 °C; NMR ($CDCl_3$) δ 0.85 (t, 3 H, CH_2CH_3), 1.94 (d, 3 H, $NCHCH_3$), 1.4–1.8 (m, CH_2CH_3), 2.73–3.18 (m, 2 H, SCH_2), 4.84 (m, 1 H, OCH), 4.95 (broad d, 1 H, NH), 5.59 (quintet, 1 H, NCH), 6.8–8.2 (m, 11 H, Ar); MS (70 eV) *m/e* (relative intensity) 379 (0.2), 164 (100), 155 (19.3), 110 (12.1); IR (KBr) 3380, 3120, 3060, 2980, 1680, 1540, 1250, 1050, 780, 750, and 700 cm^{-1}.

1-Ethyl-2-phenylthioethyl *N*-[1-(1-naphthyl)ethyl]carbamate 2c was a white solid: mp 97–98 °C; NMR ($CDCl_3$) δ 0.93 (t, 3 H, CH_2CH_3), 1.58 (d, 3 H, $NCHCH_3$), 1.4–1.8 (m, CH_2CH_3), 2.73–3.18 (m, 2 H, SCH_2), 4.84 (m, 1 H, OCH), 4.95 (broad d, 1 H, NH) 5.59 (quintet, 1 H, NCH), 6.8–8.2 (m, 12 H, Ar); MS (70 eV) *m/e* (relative intensity) 379 (0.6), 164 (100), 155 (47.9), 110 (24.6); IR (KBr) 3380, 3080, 2980, 2940, 2880, 1690, 1545, 1390, 1370, 1250, 1050, 780, and 750 cm^{-1}.

1-Phenyl-2-phenylthioethyl *N*-[1-(1-napthyl)ethyl]carbamate 1d was a white solid: NMR ($CDCl_3$) δ 1.53 (d, J = 7.0 Hz, 3 H, CH_3), 3.23 (m, 2 H, SCH_2), 4.37 (broad s, 1 H, NH), 5.47 (quintet, J = 7.0 Hz, 1 H, CHNH), 5.77 (d of d, J = 6.0 Hz, J' = 11.0 Hz, CHOH), 7.0–8.2 (m, 17 H, Ar); IR (KBr) 3420, 3340, 3060, 2980, 2940, 1720, 1600, 1590, 1500–1550, 1400, 1380, 1200–1250, 1000–1100, 800, 780, 740, and 700 cm^{-1}; MS (70 eV) *m/e* (relative intensity) 427 (0.38), 318 (1.08), 212 (100), 155 (53.04), 109 (3.97).

1-Phenyl-2-phenylthioethyl *N*-[1-(1-naphthyl)ethyl]carbamate 2d was a white solid: NMR ($CDCl_3$) δ 1.63 (d, J = 7.0 Hz, 3 H, CH_3), 3.18 and 3.23 (d of AB pattern, J_{AB} = 12.0 Hz, J = 9.0 Hz, J' = 6.0 Hz, 2 H, CH_2S), 5.05 (broad s, 1 H, NH), 5.50 (quintet, J = 7.0 Hz, 1 H, $CHCH_3$), 5.77 (d of d, J = 9.0 Hz, J' = 6.0 Hz, 1 H, –CHOH–), 6.9–8.2 (m, 17 H, Ar); IR (KBr) 3420, 3080, 2980, 2930, 1720, 1600, 1585, 1500–1550, 1450, 1440, 1400, 1380, 1210–1260, 1020–1100, 800, 780, 740, and 700 cm^{-1}; MS (70 eV) *m/e* (relative intensity) 427 (0.13), 318 (0.29), 212 (100), 155 (70.39).

1-Octyl-2-ethylthioethyl *N*-[1-(1-naphthyl)ethyl]carbamate 1e was a clear colorless oil: NMR ($CDCl_3$) δ 0.87 (t, 3 H, $(CH_2)_6CH_3$), 1.1–1.7 (m, 15 H, $(CH_2)_6$ and SCH_2CH_3), 1.63 (d, 3 H, $NCHCH_3$), 2.4–2.8 (m, 4 H, CH_2SCH_2), 4.86 (quintet, 1 H, OCH), 5.00 (broad d, 1 H, NH), 5.63 (pent, 1 H, NCH), 7.2–8.2 (m, 7 H, Ar); MS (70 eV) *m/e* (relative intensity) 415 (0.16), 215 (15.53), 200 (100), 171 (34.5), 155 (59.0); IR (neat) 3420, 2960, 2940, 2860, 1710, 1510, 1450, 1390, 1370, 1310, 1210–1270, 1060, 800, and 780 cm^{-1}.

1-Octyl-2-ethylthioethyl *N*-[1-(1-naphthyl)ethyl]carbamate 2e was a clear colorless oil: NMR ($CDCl_3$) δ 0.87 (t, 3 H, $(CH_2)_6CH_3$), 1.1–1.7 (m, 15 H, $(CH_2)_6$ and SCH_2CH_3), 1.63 (d, 3 H, $NCHCH_3$), 2.4–2.8 (m, 4 H, CH_2SCH_2), 4.86 (quintet, 1 H, OCH), 5.00 (broad d, 1 H, NH), 5.63 (pent, 1 H, NCH), 7.2–8.2 (m, 7 H, Ar); MS (70 eV) *m/e* (relative intensity) 415 (0.8), 215 (16.1), 200 (100), 171 (36.7), 155 (51.6); IR (neat) 3420, 2960, 2940, 2860, 1710, 1510, 1450, 1390, 1370, 1310, 1210–1270, 1060, 800, and 780 cm^{-1}.

1-Phenyl-2-phenylthio propyl *N*-[1-(1-naphthyl)ethyl]carbamate 1f was a clear oil: NMR ($CDCl_3$) 7.0–8.3 (m, 17 H, Ar), 5.70 (d, 1 H, OCH), 5.56 (quintet, 1 H, NCH), 4.96 (broad d, J = 7 Hz, 1 H, NH), 3.5 (m, 1 H, SCH), 1.64 (d, J = 7 Hz, 3 H, $NCCH_3$), 1.23 (d, J = 6 Hz, 3 H, $SCCH_3$); IR (neat) 3420, 3080, 2980, 2940, 1740, 1600, 1585, 1480–1540, 1450, 1380, 1200–1260, 1000–1100, 800, 780, 750, and 700 cm^{-1}; MS (70 eV) *m/e* (relative intensity) 441 (0.2), 226 (35.0), 155 (100), 138 (49.3), 137 (57.2), 77 (74.8), 127 (27.3), 57 (14.0), 43 (28.8).

1-Phenyl-2-phenythiopropyl *N*-[1-(1-napthyl)ethyl]carbamate 2f was a clear oil: NMR ($CDCl_3$) δ 8.0–7.1 (m, 17 H, Ar), 5.71 (d, J = 7 Hz, 1 H, OCH), 5.57 (quintet, J = 7 Hz, 1 H, NCH), 4.91 (broad d, 1 H, NH), 3.36 (m, 1 H, OCH), 1.64 (d, J = 7 Hz, 3 H, $NCCH_3$), 1.18 (broad peak sharpened to a doublet on warming to 70 °C at 90 MHz, 3 H, $SCCH_3$); MS (70 eV) *m/e* (relative intensity) 441 (0.2), 226 (46.5), 155 (100), 138 (21.9), 137 (38.2), 77 (23.2), 127 (17.1), 57 (38.9), 43 (28.7); IR (neat) 3420, 3080, 2980, 1740, 1600, (17.1), 57 (38.9), 43 (28.7); IR (neat) 3420, 3080, 2980, 2940, 1740, 1600, 1585, 1480–1540, 1450, 1380, 1200–1260, 1000–1100, 800, 780, 750, and 700 cm^{-1}.

1-Phenyl-2-phenylthiopropyl *N*-[1-(1-naphthyl)ethyl]carbamate 1g was a clear oil: NMR ($CDCl_3$) δ 7.0–8.5 (m, 17 H, Ar), 5.90 (d, J = 7 Hz, 1 H, OCH), 5.73 (quintet, J = 7 Hz, 1 H, NCH), 5.15 (broad d, J = 7 Hz, 1 H, NH), 3.5–3.7 (m, 1 H, SCH), 1.67 (d, J = 7 Hz, 3 H, $NCCH_3$), 1.19 (broad d, 3 H, $SCCH_3$); MS (70 eV) *m/e* (relative intensity) 441 (0.2), 226 (57.4), 155 (100), 150 (25.6), 138 (22.6), 137 (38.4), 110 (5.8), 77 (17.9); IR (neat) 3420, 3060, 2980, 2940, 2880, 1730, 1600, 1580, 1470–1550, 1450, 1400, 1380, 1300–1350, 1200–1260, 1000–1110, 800, 780, 750, and 700 cm^{-1}.

1-Phenyl-2-phenylthiopropyl *N*-[1-(1-naphthyl)ethyl]carbamate 2 g was a clear oil: NMR ($CDCl_3$) δ 7.0–8.5 (m, 17 H, Ar), 6.01 (d, J = 5 Hz, 1 H, OCH), 5.26 (broad d, J = 7 Hz, 1 H, NH), 5.20 (quintet, J = 7 Hz, 1 H, NCH), 3.5–3.7 (m, 1 H, SCH), 1.62 (d, J = 7 Hz, 3 H, $NCCH_3$), 1.13 (d, J = 7 Hz, 3 H, $SCHCH_3$); MS (70 eV) 441 (0.2), 226 (97.0), 155 (100), 150 (7.2), 138 (65.6), 137 (82.8), 110 (11.5), 77 (21.5); IR (neat) 3420, 3060, 2980, 2940, 2880, 1730, 1600, 1580, 1470–1550, 1450, 1400, 1380, 1300–1350, 1200–1260, 1000–1110, 800, 780, 750, and 700 cm^{-1}.

1-Pentyl-2-phenylthiooctyl *N*-[1-(naphthyl)ethyl]carbamate 1 h was a white solid: mp 78–81 °C, NMR ($CDCl_3$) δ 7.2–8.5 (m, 12 H, Ar), 5.80 (quintet, 1 H, NCH), 5.0–5.3 (m, 2 H, NH and OCH), 3.2–3.5 (m, 1 H, SCH), 1.63 (d, 3 H, $NCCH_3$), 1.0–1.8 (m, 19 H, CH_2's), 0.8–1.0 (m, 6 H, terminal CH_3's); MS (70 eV) 505 (0.5), 290 (58.5), 155 (100), 110 (48.9); IR (KBr) 3360, 3060, 2960, 2940, 2880, 1690, 1520, 1390, 1370, 1320, 1240, 1070, 1030, 800, 780, 750, and 690 cm^{-1}.

1-Pentyl-2-phenylthiooctyl *N*-[1-(naphthyl)ethyl]carbamate 2h was a clear oil: (NMR ($CDCl_3$) δ 7.2–8.5 (m, 12 H, Ar), 5.80 (quintet, 1 H, NCH), 5.0–5.3 (m, 2 H, NH and OCH), 3.2–3.5 (m, 1 H, SCH), 1.56 (d, 3 H, $NCCH_3$), 1.0–1.8 (m, 19 H, CH_2's), 0.8–1.0 (m, 6 H, terminal CH_3's); MS (70 eV) *m/e* (relative intensity) 505 (0.1), 290 (46.8), 155 (100), 110 (36.4); IR (neat) 3420, 3060, 2980, 2940, 2880, 1725, 1480–1550, 1450, 1400, 1380, 1320, 1240, 1060, 800, 780, 750, and 690 cm^{-1}.

1-Pentyl-2-phenylthiooctyl *N*-[1-(napthyl)ethyl]carbamate

1i was a clear oil: NMR ($CDCl_3$) δ 7.2–8.5 (m, 12 H, Ar), 5.73 (quintet, 1 H, NCH), 4.7–5.1 (m, 2 H, NH and OCH), 3.5 (m, 1 H, SCH), 1.63 (d, 3 H, $NCCH_3$), 1.0–1.8 (m, 19 H, CH_2's), 0.8 (m, 6 H, terminal CH_3's); IR (neat) 3420, 3200–3400, 3070, 2920, 2880, 1715, 1650, 1450–1570, 1390, 1250, 1210, 1000–1150, 800, and 780 cm^{-1}; MS *m/e* 505.

1-Pentyl-2-phenylthiooctyl *N*-[1-(naphthyl)ethyl]carbamate 2i was a clear oil: NMR ($CDCl_3$) δ 7.2–7.5 (m, 12 H, Ar), 5.73 (quintet, 1 H, NCH), 4.7–5.1 (m, 2 H, NH and OCH), 3.5 (m, 1 H, SCH), 1.53 (d, 3 H, $NCCH_3$), 1.0–1.8 (m, 19 H, CH_2's) 0.8 (m, 6 H, terminal CH_3's); IR (neat) 3420, 3200–3400, 3070, 2920, 2880, 1715, 1650, 1450–1570, 1390, 1250, 1210, 1000–1150, 800, and 780 cm^{-1}; MS *m/e* 505.

General Procedure for the Hydrolysis of Carbamates. In a dry 100 mL three-neck flask (equipped with an overhead stirrer, reflux condenser, N_2 inlet, and separatory funnel) was placed 20 mmol of carbamate, 5.1 mL (30 mmol) of triethylamine, and 50 mL of CH_2Cl_2. Trichlorosilane (1.7 mL, 20 mmol) in 10 mL of CH_2Cl_2 was added to the above solution with stirring, and the mixture was then refluxed overnight. The reaction mixture was extracted once with NH_4Cl (saturated) solution, the organic layer was dried ($MgSO_4$), and the solvent was removed under reduced pressure. Chromatography of the residue on neutral alumina with 4:1 hexane–CH_2CL_2 provided pure, optically active β-hydroxy sulfides in quantitative yield.

General Procedure for Synthesis of Optically Active Expoxides from 3. To a stirred solution of 0.01 mol of **3** in 20 mL of CH_2Cl_2 under N_2 was added 1.4 g (0.011 mol) of trimethyloxonium fluoroborate. The mixture was stirred fro 1–2 h until all of the salt dissolved. A condenser was placed on the reaction vessel, and aqueous NaOH (20 mL, 10%) was then added. The mixture was stirred vigorously, and the appearance of epoxide was monitored by GC. When the reaction was over (usually 0.5–2 h), the organic layer was isolated and dried ($MgSO_4$) and the solvent was removed by distillation. The mixture of sulfide and epoxide was purified by either liquid chromatography or preparative GC (15% SE-30 or 15% Carbowax on Chromosorb W).

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Registry No.—**1a,** 67210-23-5; **1b,** 67210-24-6; **1c,** 67210-25-7; **1d,** 67210-26-8; **1e,** 67210-27-9; **1f,** 67210-28-0; **1g,** 67253-42-3; **1h,** 67314-18-5; **1i,** 67210-29-1; **2b,** 67210-30-4; **2c,** 67210-31-5; **2d,** 67210-32-6; **2e,** 67238-06-6; **2f,** 67253-43-4; **2g,** 67253-44-5; **2h,** 67253-45-6; **2i,** 67253-46-7; **3a,** 67210-37-1; **3b,** 67253-48-9; **3c,** 67210-38-2; **3d,** 67210-39-3; **3e,** 67210-40-6; **3f,** 67210-41-7; **3g,** 67210-42-8; **3h,** 67210-43-9; **3i,** 67210-44-0; **4a,** 3266-23-7; **4b,** 16033-71-9; **4c,** 55555-96-9; **4d,** 67253-49-0; **4e,** 67210-45-1; thiophenol, 108-98-5; phenyl 1-heptyl sulfide, 13910-15-1; *n*-hexanal, 66-25-1; phenyl ethyl sulfide, 622-38-8; benzaldehyde, 100-52-7; (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate, 42340-98-7.

References and Notes

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(10) The separation relies on carbinyl hydrogen bonding to populate the conformations depicted in **1** and **2.** Similar optical resolution of tertiary alcohols will depend upon the conformational behavior of the resultant carbamates and cannot be generalized from the present model.
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(12) The elution order of the diastereomers may be rationalized by considering the stereochemical disposition of the substituents during intramolecular hydrogen bonding of the hydroxyl to the sulfur (Scheme III). In such a conformation, the threo isomer has these substituents anti to one another; the erythro isomer has them syn to one another. Thus, the threo isomer is expected to be the most mobile chromatographically, not only on the "warding off" basis advanced for the carbamates[8] but also on the grounds that repulsion between the substituents would cause the erythro isomer to spend relatively less time in the intramolecularly hydrogen bonded form and to hence be relatively more polar toward the absorbent. This argument is similar to one proposed to explain the GC separability of certain diols.[13]
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(15) In the conformations depicted (**1** and **2**), diastereomer **2a** has both effective "warding off" groups, the naphthyl and the $CH(CH_3)SC_6H_5$, on the same face, leaving the other face of the diastereomer relatively accessible to the adsorbent. However, neither face of **1a** is as readily accessible. Hence, **1a** is expected to elute before **2a.** Note that phenyl is more "protective" than $-CH_2SC_6H_5$ in **1d** and **2d** and that $-CH_2SCH_2CH_3$ is more "protective" than n-C_8H_{17}. The steric and electronic composition of a substituent *near the point of attachment* is more important then "remote" structure for relatively nonpolar substituents. Remote polar binding sites would certainly be expected to influence chromatographic behavior. It is evident that such simple concepts could provide a rational basis for engineering chromatographic separability into diastereomeric carbamates.
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