# Synthesis of (Racemization Prone) Optically Active Thiols by $S_N2$ Substitution Using Cesium Thiocarboxylates

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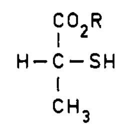
The cesium salt of thioacetic acid is prepared by treatment with cesium carbonate. This salt has a solubility of about 0.7 M in DMF (even higher in $Me_2SO$) at 50 °C. The mesylates of (*R*)-2-octanol, the ethyl ester and *N*,*N*-dimethyl amide of (*R*)-mandelic acid, (*S*)-ethyl lactate, (*S*)-methyl 3-phenyllactate, and (*S*)-diethyl malate underwent clean $S_N2$ substitution in DMF solution. Racemization occurred only in the case of the mesylate of ethyl mandelate when allowed to react in DMF, but complete inversion was achieved on use of absolute ethanol as solvent. Hydrolysis or aminolysis is used to deacylate the thiols (except for aliphatic thioacetates, which are deprotected by treatment with lithium aluminum hydride) to afford 2-mercapto esters or amides. Owing to the sensitivity of the mercapto-bearing carbon, some racemization (0–20% depending on the system) occurs during deprotection. An alternate route to the same materials prepared by the cesium thiocarboxylate method involves treatment of the free alcohol with thioacetic acid in the presence of a twofold amount of the preformed salt from diisopropyl azodicarboxylate (DIAD) and triphenylphosphine. This method works well except for ethyl mandelate and *N*,*N*-dimethylmandelamide. Scale-up of the reaction is difficult, however, owing to the need for a chromatographic separation. Various NMR methods for determining the enantiomeric excesses of the various products are described. Particularly useful for determination of high enantiomeric excesses is an internal calibration method based on the use of $^{13}C$ satellite peaks in the presence of a chiral shift reagent. The enantiomeric excesses of the thiols were determined by conversion to the phosphonodithioates followed by measurement of the *meso*/*d*,*l* ratios obtained from $^{31}P$ NMR spectra. Attempts to hydrolyze 2-acetylthio esters to the free 2-mercapto carboxylic acids lead to 10–40% racemization depending on the compound. A partial solution to this problem was found by use of optically pure *S* bromides obtained from diazotation of (*S*)-alanine, (*S*)-phenylalanine, and (*S*)-valine in the presence of bromide. These bromides, on treatment with cesium thiobenzoate, underwent clean $S_N2$ substitution, and debenzoylation could be brought about without significant racemization.

Phenols and thiophenols,[1] aliphatic thiols,[2] carboxylic acids,[3] and sulfonamides[4] can be converted readily to their corresponding cesium salts on treatment with cesium carbonate. The anions of these salts react often extremely cleanly in $S_N2$ substitutions.[5] A unique application of cesium salts is for the synthesis of macrocycles by anionic nucleophilic ring closure.[3] Cesium salts can also be put to use to solve more prosaic synthetic problems. We have described, for example, synthetic applications for the preparation of alicyclic enantiomerically pure alcohols, including some racemization prone.[6] For example, (*S*)-ethyl lactate could be converted without racemization to the *R* enantiomer by treatment of the mesylate of the (*S*)-lactate with cesium propionate, followed by transacylation to remove the propionyl group.[7] Extensions of this methodology have been described recently.[8]

We describe here a method for the preparation of several optically active thiols, especially ones sensitive to racemization, by use of cesium thiocarboxylates as nucleophiles. Various methods, several quite recent, for the synthesis of optically active thiols have been described,[9-15] but examination reveals restrictions, especially for the synthesis of thiols, that are racemization prone. Indeed syntheses of secondary aliphatic and benzylic thiols that do not racemize readily have been most often described.[9-13,15] Mercapto-bearing carbons adjacent to an electron-withdrawing group like an ester, amide, or nitrile are much more sensitive. Racemization, either complete[15] or partial, in the substitution step[10,14,17b] or by excess nucleophile[16] is a problem commonly encountered. Enantiomeric excesses (ee) or optical purities for such materials are often unknown[12,14,17b] or optical rotations are not reported[9] or are compared in different solvents.[18] The nature of the chemical difficulties is illustrated by the classical synthesis by Owen and Rahman[16] of (*R*)-**1a**,**b** from respectively (*S*)-2-chloropropanoic acid and the tosylate

(1) Piepers, O.; Kellogg, R. M. *J. Chem. Soc., Chem. Commun.* **1978**, 383.
(2) (a) Buter, J.; Kellogg, R. M. *J. Org. Chem.* **1981**, *46*, 4481. (b) Lemaire, M.; Vriesema, B. K.; Kellogg, R. M. *Tetrahedron Lett.* **1985**, *26*, 3499.
(3) (a) Kruizinga, W. H.; Kellogg, R. M. *J. Am. Chem. Soc.* **1981**, *103*, 5183. (b) Talma, A. G.; Jouin, P.; De Vries, J. G.; Troostwijk, C. B.; Werumeus Buning, G. H.; Waninge, J. K.; Visscher, J.; Kellogg, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 3981.
(4) Vriesema, B. K.; Buter, J.; Kellogg, R. M. *J. Org. Chem.* **1984**, *49*, 110.
(5) For a recent review on the use of cesium salts in organic synthesis, see: Klieser, B.; Rossa, L.; Vögtle, F.; *Kontakte (Darmstadt)* **1984**, 3. (b) Also see: Koepp, E.; Vögtle, F. *Synthesis*, in press. (c) Cesium salts have enjoyed long use in solid-phase peptide synthesis: Wang, S. S.; Gisin, B. F.; Winter, D. P.; Makofske, R.; Kulesha, I.; Tzougraki, C.; Meienhofer, J. *J. Org. Chem.* **1977**, *42*, 1286.
(6) (a) Kruizinga, W. H.; Strijtveen, B.; Kellogg, R. M. *J. Org. Chem.* **1981**, *46*, 4321. (b) Application in the synthesis of verrucarol: Trost, B. M.; McDougal, P. G.; Haller, K. T. *J. Am. Chem. Soc.* **1984**, *106*, 383.
(7) Seebach, D.; Hungerbuhler, E.; Schnurrenberger, P.; Weidmann, B.; Zuger, M. *Synthesis* **1982**, 138.
(8) (a) Lerchen, H.-G.; Kunz, H. *Tetrahedron. Lett.* **1985**, *26*, 5257. (b) Huffman, J.; Desai, R. *Synth. Commun.* **1983**, *13*, 553. (c) Torisawa, Y.; Okabe, H.; Ikegami, S. *Chem. Lett.* **1984**, 1555.
(9) Hojo, K.; Yoshino, H.; Mukaiyama, T. *Chem. Lett.* **1977**, 133.
(10) Hojo, K.; Yoshino, H.; Mukaiyama, T. *Chem. Lett.* **1977**, 437.
(11) Damico, J. J.; Schafel, T.; Jackson, D. *Phosphorus Sulfur* **1979**, *7*(3), 301.
(12) Baretta, E.; Cinquini, M.; Colonna, S.; Fornasier, R. *Synthesis* **1974**, 425.
(13) Martin, D. J.; Greco, C. C *J. Org. Chem.* **1968**, *33*, 1275.
(14) Yankeelov, J. A., Jr.; Fok, K.-F.; Carothers, D. J. *J. Org. Chem.* **1978**, *43*, 1623.
(15) (a) Gauthier, J.; Bourdon, F.; Young, R. *Tetrahedron Lett.* **1986**, *27*, 15. (b) See also: Rollins, P. *Synth. Commun.* **1986**, *16*, 611.
(16) Owen, L. N.; Rahman, M. B. *J. Chem. Soc. C* **1971**, 2432.
(17) (a) See, for example, ref 10 for the synthesis of (*R*)-(−)-$C_6H_5CH(CO_2C_2H_5)SCOCH_3$ from ethyl mandelate, with 2-fluoro-*N*-methylpyridinium tosylate. No rotation is reported. (b) For the synthesis of some α-mercapto carboxylic acids of unestablished ee from the corresponding bromides and $Na_2CS_3$, see: Acton, N.; Komotiya, A. *Org. Prep. Proced. Int.* **1982**, *14*, 381. (c) For the synthesis of (*R*)- and (*S*)-2-mercapto-4-methylpentanoic acid with $Na_2CS_3$, see ref 14. The enantiomeric excess of the thiol is not clear and complications with racemization are reported.
(18) See, for example, ref 10 for the synthesis of 2-octanethiol and ref 17b for the synthesis of (*R*)- and (*S*)-2-mercaptopropanoic acids from the corresponding bromides and $Na_2CS_3$.

of (*S*)-ethyl lactate. Optically pure (*R*)-**1a** could only be

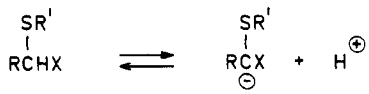


a) R = H
b) R = alkyl

1

obtained under carefully controlled conditions by substitution on the sodium salt of (*S*)-2-chloropropanoic acid with potassium thiobenzoate in boiling acetone, followed by careful deblocking. Excess nucleophile caused racemization, and the benzoyl group was partially lost during reaction. The ester **1b** was not obtained optically pure. To our knowledge, new syntheses of either of these materials in optically pure form have not been reported again in the literature.

The sensitivity of **1c** or any thiol of general structure **2**, wherein X is an electron-withdrawing group and R is alkyl or aryl, lies for a good part in the acid enhancing properties of the sulfur substituent, relative to oxygen or halogen (eq 1).[19] (Thiols are, of course, often sensitive to

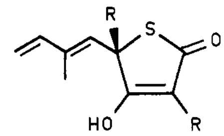


(1)

2

X = electron withdrawing group

oxidation to disulfides; in our experience this problem can almost always be circumvented by use of careful experimental techniques wherein exposure to air is kept to a minimum.) In conjunction with work on chiral macrocyclic ligands for transition metals,[2] we required a practical route to **1** and, more generally, to various examples of **2**. Such compounds are also of interest for the synthesis of certain peptide gap inhibitors[14,20a] and pseudopeptides.[17b] Peptidic thia cyclols are prepared from similar precursors.[20b] There has been recent interest in 1,3-oxathiolanes formed from (racemic) $\alpha$-mercapto acids; these are alkylated via the enolates to provide racemic tertiary thiols.[21] The thiolactonic antibiotics, examples being **3a,b**, contain also segments of an $\alpha$-mercapto acid.[22] Disodium gold(II) thiomalate (**4**) is used extensively for the treatment of arthritic conditions[23a] and isovalthine[23c] (**5**) and tiopronin[23b] (**6**) are of clinical interest.



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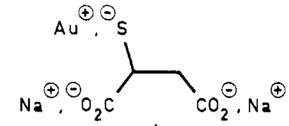

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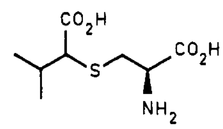
a) R = $CH_3$, thiolactomycin
b) R = $C_2H_5$, thiotetromycin



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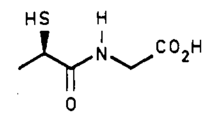

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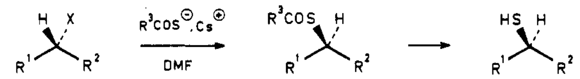
these thiocarboxylates are somewhat hygroscopic it is usually better to prepare them in situ (Experimental Section). Both cesium salts are reasonably soluble in



(2)

DMF (0.5–0.8 M, in the range of 20–50 °C). Reactions are usually carried out in this medium or in $Me_2SO$ although an exception will be mentioned. After removal of the solvent the thiol is freed by aminolysis, by acidic hydrolysis, or in the case of an aliphatic thiol, by treatment with $LiAlH_4$. The procedures are described in the Experimental Section. The crude thiol was virtually pure prior to distillation as judged by $^1H$ NMR spectroscopy. No racemization was observed on using excess nucleophile, in contrast to the action of potassium thioacetate in acetone, as described by Owen and Rahman.[16] Reactions have been run on a scale up to 0.2 mol. Results for the conversions of various compounds are compiled in Table I.

As seen from entries 1–3 and 6, the substitutions, carried out in this case with cesium thioacetate, followed by deacylation, lead to excellent chemical yields of thioacetate and thiol. However, there is clearly, as seen from entries 1–3, some racemization in the deacylation step (see further for the method of ee determination). Note that the amide of entry 4 was formed from starting material that was 48% enantiomerically pure.[25] The conversion of (−)-menthol to (+)-neomenthanethiol (entry 7) proceeded cleanly and in better yields than reported in the literature. Substitution with $NaS_2CN(CH_3)_2$ has been reported in 66% yield[10] and subsequent conversion to neomenthanethiol in, for example, 14%[12] and 45%[24] yields. Our material has the highest rotation ever reported and was shown by NMR methods (see further) to be diastereomerically pure.

Entries 3 and 4 for mandelic acid derivatives represent good tests of the method, owing to the relatively high acidity of the tertiary hydrogens in these derivatives. This consideration is more than theoretical. In DMF substitution by cesium thioacetate on the mesylate of *ethyl mandelate* proceeded in 93% yield, but the product was almost racemic. This problem fortunately could be solved by use of absolute ethanol as solvent. The completely inverted product was obtained in 96% yield. The mesylate of the mandelic acid *dimethyl amide* in contrast did not undergo racemization in DMF.

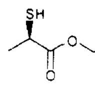
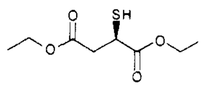
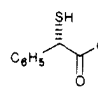
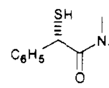
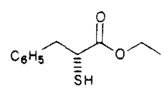
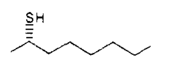
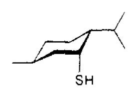
During the course of this work an interesting method was described by Volante[26a] for one-step conversion of

## Results

**A. Substitutions on Acid Derivatives.** The basic strategy followed is given in eq 2. In the first set of investigations chiral alcohols (X is mesylate) were used. The cesium salts of thioacetic acid or thiobenzoic acid ($R^3$ is methyl and phenyl, respectively) are readily obtained by treatment of the acids with cesium carbonate; because

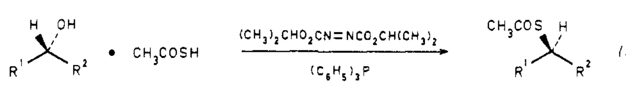
(19) Block, E. *Reactions of Organosulfur Compounds*; Academic: New York, 1978; pp 36–90.
(20) (a) Tourwe, D. *Janssen Chim. Acta* **1985**, *3*, 1. (b) Lucente, G.; Pinnen, F.; Zanetti, G.; Cerrini, S.; Fedeli, W.; Mazza, F. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1499.
(21) Seebach, D.; Naef, R.; Calderati, G. *Tetrahedron* **1984**, *40*, 1313.
(22) (a) Oishi, H.; Noto, T.; Sasaki, M.; Suzuki, K.; Hayashi, T.; Okazaki, H.; Ando, K.; Sawada, M.; *J. Antibiot.* **1982**, *35*, 391, 396, 400, 411. (b) Tsuzuki, K.; Omura, S. *J. Antibiot.* **1983**, *36*, 1589. (c) Wang, C. L.; Salvino, J. M. *Tetrahedron Lett.* **1984**, 5243. (d) Tsuzuki, K.; Akeyoshi, M.; Omura, S.; *Bull. Chem. Soc. Jpn.* **1985**, *58*, 395.
(23) (a) See, for a discussion: Brown, D. H.; Smith, W. E. *Chem. Soc. Rev.* **1980**, *9*, 217. (b) Kleeman, A. *Pharmazeutische Wirkstoffe*; Georg Thieme Verlag: Stuttgart, 1978; p 476. (c) Ohmori, S.; Ubuka, T.; Kuwaki, T.; Horiuchi, K.; Mizuhara, S. *Nature (London)* **1963**, 678.
(24) Van Leusen, D.; Rouwette, P.; Van Leusen, A. M. *J. Org. Chem.* **1981**, *46*, 5159.
(25) Prepared by the method of: Freudenberg, K.; Todd, J.; Seidler, R. *Justus Liebigs Ann. Chem.* **1933**, *199*, 501.

Table I. Synthesis of Thiols from Optically Active Alcohols

| | | acetylthio deriv. | | thiol | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| entry | starting material | yield,[a] % | ee,[b] % | config | | method[c] | yield,[a] % | overall yield,[a] % | [α] | optical purity | ee,[d] % |
| 1 | (S)-ethyl lactate | 95 | 100 | R |  | C | 90 | 86 | $[\alpha]^{22}_D$ 56.1° (c 2, $CHCl_3$) | | 92 |
| 2 | (S)-diethyl malate | 89 | 100 | R |  | C | 90[e] | 81 | $[\alpha]^{20}_{578}$ 31.9° (c 2.1, $CHCl_3$) | 93[f] | 93 |
| 3 | (R)-ethyl mandelate | 96[g] | 98 | S |  | C | 91[h] | 87 | $[\alpha]^{25}_D$ 115° (c 2, 95% EtOH) | 91[i] | 93 |
| 4 | (R)-N,N-dimethylmandelamide[j] | 90 | 48[k] | S |  | C | 98 | 89 | $[\alpha]^{20}_{578}$ 104° (c 1, $CHCl_3$) | | 47[l] |
| 5 | (S)-methyl 3-phenyllactate | 96 | 100 | R |  | B | 95 | 92 | $[\alpha]^{20}_{578}$ −0.65° (c 1.1, $CHCl_3$)[m] | | 79 |
| 6 | (R)-2-octanol | 92 | | S |  | A | 97 | 90 | $[\alpha]^{21}_{546}$ 35.0° (c 2.5, absolute EtOH) | 98[n] | >98 |
| 7 | (−)-menthol | 84[o] | | |  | A | 90 | 76 | $[\alpha]^{20}_D$ 53.2° (c 2, $CHCl_3$) | p | >98 |

[a] Isolated yield of pure product. [b] Determined by the $^{13}C$ satellite method, see text. [c] Method of conversion of thioacetate to thiol, see Experimental Section. [d] $^{31}P$ NMR method, see ref 32. [e] Diethyl fumarate (3%) was also isolated. [f] Obtained by comparing the rotation with the rotation of a sample derived from (R)-thiomalic acid of known optical purity as described in the Experimental Section. [g] This reaction was carried out in absolute EtOH; reaction in DMF afforded almost racemic product. [h] The methyl ester was prepared for comparison of optical rotation with the literature value.[38] [i] By comparison with the literature value[38] obtained by extrapolation of a partially enriched sample. [j] Made according to ref 25, $[\alpha]^{20}_{578}$ −85° (c 2, $C_2H_4Cl_2$), corresponding to 48% optical purity; in our hand a sample with $[\alpha]^{20}_{578}$ −177 °C (c 2, $C_2H_4Cl_2$) proved to be optically pure ($^{31}P$ method)[32b] [lit.[25] $[\alpha]^{20}_{578}$ 162° (c 2, $C_2H_4Cl_2$) for the R enantiomer]. [k] With $^1H$ NMR/Eu(hfc)$_3$ experiments it was established that no racemization occurred in the substitution step. [l] This result establishes that the whole reaction sequence is racemization free. [m] The sign and magnitude of this rotation was concentration and wavelength dependent, see Experimental Section. [n] See ref 39; the ee of the thioacetate was not determined. [o] Menthene (5%) was also obtained. [p] Reported values were lower: $[\alpha]_D$ 39° ($CHCl_3$),[12] $[\alpha]^{21}_D$ 47.8° (c 2.01, $CHCl_3$).[24]

alcohols to thioacetates with inversion of configuration by use of a modified Mitsunobu procedure (eq 3).[26b] Equi-



(3)

molar amounts of the hydrazide of the azodicarboxylate and triphenylphosphine oxide are formed in the reaction. No reactions of α-hydroxy acids or derivatives thereof were described, however. Although we feared that esters or other derivatives of α-hydroxy acids would be oxidized to the corresponding keto compounds by the azodicarboxylate,[27] clean substitution, using the preformed salt of diisopropylazodicarboxylate and triphenylphosphine, was found with no detectable oxidation of the alcohol. With (S)-ethyl lactate and (S)-methyl 3-phenyllactate (entries 1 and 5 in Table I) the yields and ee's of the products were virtually identical with those obtained with cesium thioacetate. Disadvantages of the procedure, however, are the exclusive requirement for alcohols as starting materials and the need for a chromatographic separation to obtain pure thioacetate. (S)-Diethyl malate (entry 2) reacted on small scale (10 mmol) cleanly to provide the (acetylthio)malate in 92% yield with no observable elimination. A small amount (3%) of fumarate was observed on treatment at −20 °C of the extraordinarily elimination prone mesylate of diethyl malate with cesium thioacetate.

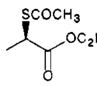
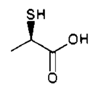
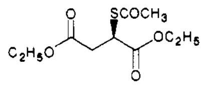
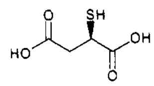
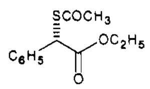
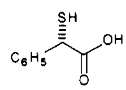
The azo ester method with (R)-ethyl mandelate (entry 3) gave ethyl (acetylthio)mandelate in 93% yield but in an ee of only 69%. We were unable to raise the ee. With the N,N-dimethyl amide of (R)-mandelic acid (entry 4) the reaction was entirely unsatisfactory; only a 20% yield of impure thioacetate could be obtained.

We conclude that the Volante method can be very useful for the preparation on a small scale of thiols from esters of α-hydroxy acids with nearly complete inversion of configuration. In sensitive cases like mandelic acid, some racemization occurs. An advantage of the Volante procedure is that the alcohol need not be activated for reaction in the form of a derivative (true also for the Mukaiyama procedure),[9,10] but there are limitations in scale owing mainly to the need for chromatographic separations.

To assess the cesium thiocarboxylate method better, several qualitative investigations were carried out. 3-Chloro-2-butanone, the mesylate of 3-hydroxy-1-butyl benzyl ether, methyl 2-chloropropionate, and ethyl 2-bromobutanoate (all racemic) reacted quantitatively with cesium thioacetate as judged by $^1H$ NMR spectroscopy on the crude reaction mixtures. The use of cations other than cesium was also examined. A reaction of the mesylate of (S)-ethyl lactate with potassium thioacetate is typical. Substitution was carried out in DMF at an initial concentration of reactants of 0.2 M. However, within minutes a gel formed which made stirring impossible. Dilution to

(26) (a) Volante, R. P. Tetrahedron Lett. 1981, 22, 3119. (b) Review Mitsunobu procedure: Mitsunobu, O. Synthesis 1981, 1.
(27) Yoneda, F.; Suzuki, K.; Nitta, Y. J. Am. Chem. Soc. 1966, 88, 2328.

Table II. Acid Hydrolysis of α-Acetylthio Esters[a]

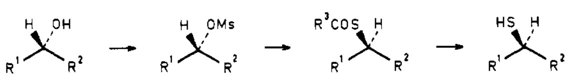
| entry | starting material | product | yield,[b] % | [α] | optical purity | ee,[c] % |
|---|---|---|---|---|---|---|
| 1 |  |  | 70 | $[\alpha]^{25}_{D}$ 51.5° (c 2, EtOAc) | 90[d] | 90 |
| 2 |  |  | 81 | $[\alpha]^{20}_{D}$ 38.0° (c 0.6, EtOH) | 59[e] | 61 |
| 3 |  |  | 85 | $[\alpha]^{25}_{D}$ 112° (c 2, 95% EtOH) | 85[f] | 86 |

[a] For details, see Experimental Section. [b] Yield of pure, isolated compound. [c] Enantiomeric excess of the ester derived from the acid by $^{31}P$ NMR method:[32] entry 1, methyl ester; entry 2, diethyl ester; entry 3, methyl ester. [d] See ref 16. [e] See ref 37. [f] See ref 38.

roughly 0.05 M was necessary to prolongate the reaction. The desired thioacetate eventually was isolated in 80% yield and 100% ee.

In general our experience has been that the cesium salt method described here is experimentally simple and suitable for multigram synthesis chiefly because of the relatively good solubility of the cesium salts. Alcohols can be used readily as source of chiral precursors, and the formation of the mesylates proceeds cleanly and in high yield. However, chlorides and bromides as well as tosylates can also be used with no difficulty. Other thiocarboxylate salts can lead to clean $S_N2$ inversion but the poorer solubility in DMF or $Me_2SO$ increases the experimental difficulties. An application of this methodology in the sparsomycine field will be published separately.[28]

**B. Determination of Enantiomeric Purity and Causes of Racemization.** The reactions described in Table I proceed in stages as shown schematically in eq 4; it is necessary to know the enantiomeric purity at every stage of the reaction. Measurement of the intensities of


(4)

$^{13}C$ satellites in the presence of a chiral shift reagent was useful to measure high ee's of the substitution products. This method, recently described,[29] involves comparison of the $^{13}C$ satellites of the measured absorption for the major enantiomer peak with the intensity of the $^{1}H$ peak for the minor enantiomer. The satellite must not lie under a proton absorption. Since one satellite peak is exactly 0.55% of the main peak, an internal standard is provided. The integration errors become, of course, unavoidably greater as complete enantiomeric purity is approached. However, with this method it has been our experience that the absolute difference between, for example, 97% and 99% enantiomeric purity can be measured readily. The methyl peaks of the thioacetates lie at about δ 2.3 in the $^{1}H$ NMR spectrum free of overlap; these separate cleanly with $Eu(hfc)_3$, and the $^{13}C$ satellite method could be used effectively. In control experiments it was shown on a 60-MHz apparatus that a 5% optical contaminant that had been purposely added could easily be measured by means of this method. No use was made of racemic samples, because these might behave differently than nearly optically pure ones. In the latter case the minor enantiomer can be selectively influenced by the chiral surroundings provided by the major enantiomer.[30]

(28) Colstee, H.; Ottenheijm, H. J. C., personal communication.
(29) See: Jelinski, L. *Chem. Eng. News* **1984**, *62*(45), 26–47.
(30) Williams, T.; Pitcher, R. G.; Bommer, P.; Gutzwiller, J.; Uskokovic, M.; *J. Am. Chem. Soc.* **1969**, *91*, 1871.

The thioacetates of entries 1, 2, and 5 were demonstrated to be at least 99.5% enantiomerically pure; no measureable amount of enantiomeric contaminant could be detected. The thioacetate derived from ethyl mandelate contained about 1% of the *R* enantiomer. The starting amide of entry 4 had an ee of 48%. With the aid of $Eu(hfc)_3$ the ee of the thioacetate derived from this alcohol was shown to be the same. Substitution with cesium thioacetate therefore proceeds with complete inversion.

The thiols derived from deacetylation of the thioacetates in our hands were unsuitable for determination of ee either by addition of shift reagent or conversion to a Mosher[31] derivative. Instability of the thiols and unclean reactions were encountered. To solve these problems a method for determination of ee's of thiols by conversion to the phosphonodithioates, as shown in eq 5, has been recently described by us.[32] The ee is obtained, following the equation of Horeau,[33] from the *meso*/*d,l* ratio as measured by $^{31}P$ NMR spectroscopy. The $^{31}P$ absorptions for the *d,l* and (two) *meso* isomers are very well separated. $^{31}P$ NMR data will be published separately.[43]

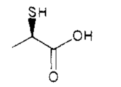
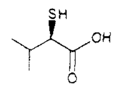
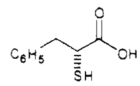
$$2\,RSH + CH_3P(=O)Cl_2 \xrightarrow{2(C_2H_5)_3N} CH_3P(=O)(SR)_2 \quad (5)$$

As seen from Table I, deacylation, for the case of sensitive thiols, is always attended by some racemization although in most cases (entries 1–4) the amount is not great. For racemization-sensitive materials we were unable to avoid this problem entirely. The sensitivity of the 3-phenyllactate system (entry 5) is particularly surprising. Deprotection with 3% HCl in $CH_3OH$ or $C_2H_5OH$ can lead, depending on the thioacetate, to 7–8% racemization and aminolysis with 1 N $NH_3$ to 7–21% racemization. No improvement was found with, for example, 2% HCl in 1:1 dioxane/$H_2O$, $C_2H_5OH$ with Dowex 50W X8 (acidic form), $C_2H_5OH$ with 3% 4-toluenesulfonic acid, or aminolysis with 4-chloroaniline.[34] $Ti(OR)_4$ (R is methyl or ethyl depending on the ester) was also ineffective.[7]

Even greater problems were encountered on attempts to hydrolyze the esters to the free acids. Results are given in Table II. Best results were obtained by acid-catalyzed hydrolysis (HCl in $H_2O$/dioxane), which led, dependent

(31) Dale, J. A.; Duff, D. L.; Mosher, H. S. *J. Org. Chem.* **1968**, *33*, 3245.
(32) (a) Feringa, B. L.; Smaardijk, A. A.; Wynberg, H.; Strijtveen, B.; Kellogg, R. M.; *Tetrahedron Lett.* **1986**, *27*, 997. (b) See also: Feringa, B. L.; Smaardijk, A. A.; Wynberg, H. *J. Am. Chem. Soc.* **1985**, *107*, 4798.
(33) Vigneron, J. P.; Dhaenens, M.; Horeau, A. *Tetrahedron* **1973**, *29*, 1055.
(34) Fuchs, G. *Acta Chem. Scand.* **1965**, *19*, 1490.

**Table III. α-Mercapto Carboxylic Acids from α-Bromo Carboxylic Acids**

| | | thio- | α-mercaptocarboxylic acid | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| entry | bromide[a] | benzoate yield, % | config | | method | yield,[b] % | overall yield, % | [α] | optical purity, % | ee,[c] % |
| 1 | (*S*)-2-bromopropanoic acid[d] | 85 | *R* |  | D<br>E | 60<br>76 | 64 | $[\alpha]^{23}_D$ 56.4° (*c* 4, EtOAc) | 98[f] | >98[e] |
| 2 | (*S*)-2-bromoisovaleric acid | 95 | *R* |  | D<br>E | 48<br>71 | 67 | $[\alpha]^{20}_D$ 23.3° (*c* 0.68, $Et_2O$) | *g* | >98[e] |
| 3 | (*S*)-2-bromo-3-phenylpropanoic acid | 75 | *R* |  | D | 52 | 39 | $[\alpha]^{20}_D$ −9.5° (*c* 1, MeOH) | *h* | 93[i] |

[a] α-Bromo acids were prepared by diazotization of the corresponding amino acids.[36] [b] Yield of pure, isolated material. [c] This is the enantiomeric excess of the methyl ester of the acids, which reflects the enantiomeric excess as determined by the $^{31}P$ NMR method[32] of the acid. [d] This compound can be made optically pure only with extreme care; the α-chloroacid is more readily handled. [e] This establishes that starting material was also optically pure. [f] Literature[16] $[\alpha]^{25}_D$ 57.1° (*c* 6.9, EtOAc). [g] Literature[40] $[\alpha]^{20}_D$ 13.7° (*c* 3, ether). [h] Literature[17b] $[\alpha]^{25}_D$ −7.84° (*c* 1, MeOH). [i] Prepared from bromide with $[\alpha]^{22}_D$ −10.2° (*c* 1, MeOH): rotation of −10.0° (*c* 1, MeOH)[17b] for the *S* enantiomer and +11.2° (*c* 1, MeOH)[17b] for the *R* enantiomer have been reported. This implies that our starting bromide was not entirely optically pure.

on the compound, to 10–40% racemization. Various other approaches, not detailed here, led to unsatisfactory results. Similar problems were encountered by Owen and Rahman.[16]

**C. Substitutions on Derivatives of Free Acids.** Problems of racemization during deprotection of the carboxyl group would be alleviated if substitution could be carried out on suitable derivatives of the free acids.[16] The free acids are less racemization prone than esters or other acid derivatives (amino acid esters often racemize readily whereas the free amino acids are optically stable). The limitation in this approach is that suitable methods for the selective activation of hydroxyl groups of α-hydroxy *acids* are not available. Mesylation of α-hydroxy acids, for example, leads to anhydride formation and other complications.[3a] (We have, however, recently discovered a single-step method for substitution of α-hydroxy acids by thio acids with in some cases *retention* of configuration. This method will appear separately.[35])

A route to α-substituted acids capable of substitution is via diazotization of α-amino acids in the presence of bromide.[36] By this means certain α-bromo acids can be obtained optically pure, although considerable experimental care is required. As mentioned, Owen and Rahman[16] substituted the *sodium salt* of 2-chloropropanoic acid with potassium thiocarboxylates in acetone. Racemization occurs readily under these conditions, and some free thiol is formed during the reaction. We found that with cesium thiobenzoate, chosen because the substitution products are usually crystalline, in DMF 2-bromo *acids* were cleanly substituted in excellent yield without encumbrance from any detectable racemization or debenzoylation. Results are given in Table III. In independent experiments it was established that recrystallization of the crude thiobenzoates led to no measurable optical enrichment. Debenzoylation was readily accomplished without racemization by aminolysis (see Experimental Section). Enantiomeric excesses of the free thio acids were established by esterification followed by application of the $^{31}P$ NMR method.[32]

For those cases in which optically pure 2-bromo acids are available, this method provides a clean entry to the corresponding inverted thiols with high enantiomeric excess.

(35) Strijtveen, B.; Kellogg, R. M., manuscript in preparation.

(36) For example: Freudenberg, K.; Markert, L. *Chem. Ber.* **1927**, *60*, 2447.

## Experimental Section

**General Remarks.** All solvents and reagents were purified and dried where necessary according to standard procedures. Melting points (uncorrected) were determined on a Mettler FP-2 melting point apparatus, equipped with a Mettler FP-21 microscope. Infrared spectra were recorded on a Perkin-Elmer 257 grating spectrometer. $^1H$ NMR spectra were recorded in $CDCl_3$ on a Hitachi Perkin-Elmer R-24B NMR spectrometer (at 60 MHz) or on a Nicolet NT-200 spectrometer (at 200 MHz). Chemical shifts in $^1H$ NMR are denoted in δ units (ppm) relative to tetramethylsilane ($Me_4Si$) as an internal standard at δ = 0. $^{13}C$ NMR spectra were recorded in $CDCl_3$ on a Varian XL-100 (at 25.16 MHz) or on a Nicolet NT200 (at 50.32 MHz) spectrometer. Chemical shifts are denoted in δ units (ppm) relative to $\delta_{CDCl_3}$ = 76.9. $^{19}F$ NMR spectra were recorded on a Varian XL-100 (at 94.1 MHz) or on a Nicolet NT-200 (at 188.2 MHz) spectrometer. Chemical shifts are denoted in δ units (ppm relative to $CFCl_3$ as an internal standard at δ = 0). $^{31}P$ NMR spectra were recorded on a Nicolet NT-200 (at 81.0 MHz) spectrometer. Chemical shift values are given in hertz with 85% $H_3PO_4$ (δ = 0.0) as an external standard. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet.

Elemental analyses were performed in the microanalytical department of the laboratory.

**General Methods for the Deacylation of Thiocarboxylates.** All these reactions were carried out in an atmosphere of dry, oxygen-free nitrogen.

**Method A.** Simple thiols no containing other sensitive functional groups were obtained by reduction of the thioacetate, with excess $LiAlH_4$ in diethyl ether, followed by acidic workup.

**Method B.** α-Mercapto carboxylates were obtained by stirring 10 mmol of the corresponding thioacetate with 40 mL of 1 N $NH_3$ for 5 h. After cautious acidification with 4 N HCl, the product was extracted with ether (4 × 20 mL), dried ($MgSO_4$), evaporated, and distilled.

**Method C.** α-Mercapto carboxylates were obtained by stirring 10 mmol of the corresponding α-acetylthio compound with 20 mL of 3% HCl/ROH (16.5 mmol) for 18 h. After evaporation of the solvent and volatiles, a nearly quantitative yield of α-mercapto carboxylate remained, which was purified by Kugelrohr distillation.

**Method D.** α-Mercapto carboxylic acids were obtained by stirring of the corresponding α-benzoylthio compound (10 mmol) with 40 mL of 1 N $NH_3$ for 3.5 h. Workup as described in method B.

**Method E.** α-Mercapto carboxylic acids were obtained by treatment of the corresponding α-acetylthio compound (10 mmol) for 24 h or the corresponding α-benzoylthio compound (10 mmol) for 48 h with 4-chloroaniline (11 mmol) in 10 mL benzene as described by Fuchs.[34] We used a modified workup procedure. After the reaction, the solution was set aside at 10 °C for 3 h, and the precipitate was filtered off. After evaporation of the filtrate, the residue was subjected to short-column chromatography (silica gel 60, $CH_2Cl_2$) to remove the excess 4-chloroaniline ($R_f$ 0.9). The almost pure $\alpha$-mercapto carboxylic acid ($R_f$ ~0.1) was purified by distillation under vacuum.

**Determination of the Enantiomeric Excesses (ee).** The ee's of starting materials, intermediates, and products were determined as follows.

**Alcohols**: by comparison with the literature values and/or by the $^{31}P$ NMR method recently described by Feringa et al.[32b]

**$\alpha$-Bromo acids**: by comparison of optical rotations with the literature values and/or by extrapolation from the ee of the resulting thiols as determined by the $^{31}P$ NMR method recently described by us.[32a]

**Thioacetates**: by comparison of optical rotations with the literature values and/or by $^1H$ NMR experiments with Eu(hfc)$_3$. [This latter method was used for a rough estimation of the ee (up to 95%) or for an accurate estimation (up to 99% ee) for samples with an ee higher than 95% by the $^{13}C$ satellite method described in the text.]

**Thiols**: by comparison of optical rotations with the literature values, by Mosher's method,[31] and/or by the $^{31}P$ NMR method recently described by us.[32a]

**Preparation of the Cesium Salts.** Cesium thioacetate was made by addition of $Cs_2CO_3$ to a solution of 10% excess of freshly distilled thioacetic acid in methanol. The solvent was stripped off. The residue was triturated (decanted) three times with dry acetone and again evaporated. The resulting white powder can be stored for several weeks in a desiccator under nitrogen but is very hygroscopic and not easily handled.

A better method is to prepare the salt in situ in methanol as described above and after evaporation to dissolve the solid in DMF or another appropriate solvent.

Cesium thiobenzoate was prepared in the same way from freshly distilled thiobenzoic acid [100 °C (15 torr)]. After evaporation of methanol the remaining solid was triturated (decanted) several times with dry acetone and again evaporated to dryness. The resulting white powder is hygroscopic but can be handled as such and stored for months in a desiccator under nitrogen.

**Esters of carboxylic acids** were prepared in a refluxing solution of the acid in a 1:1 mixture of benzene and the appropriate alcohol to which a little Dowex 50 WX 8 was added. Water was removed by azeotropic distillation overnight with aid of a Soxhlet apparatus filled with molecular sieves. After normal workup a quantitative yield of the ester was obtained.

**Mesylates** were prepared from their corresponding alcohols by adding, dropwise over 20–25 min, a solution of mesyl chloride (11.45 g, 100 mmol) in 100 mL of ether to a stirred solution of 50 mmol of the alcohol and $(C_2H_5)_3N$ (20 mL, 150 mmol) in 200 mL of ether at −30 to −20 °C. After being stirred for another 20 min at −20 °C the reaction was worked up by adding the amount 1 N HCl necessary to make the solution acidic. The ether layer was extracted with 2 × 50 mL of cold water and then brine, dried ($MgSO_4$), and then evaporated. A nearly quantitative yield of colorless mesylate remained, which can be used without further purification.

**$S_N2$ substitutions with cesium thiocarboxylates** were carried out by stirring 1.05 equiv of the Cs salt dissolved in the minimal amount of solvent (DMF or $Me_2SO$) with 1 equiv of the substrate during 20 h at room temperature unless otherwise noted. Hereafter a threefold amount of ether was added, and DMF was removed by repeated washing with small amounts of water.

**Azodicarboxylate, Triphenylphosphine, and Thioacetic Acid Approach.** Volante's method[26] for the synthesis of chiral thioacetates was used with a slight modification. After evaporation of the solvent, the products were dissolved in the minimum amount of hexane, filtered, and set aside at −20 °C overnight to precipitate most of the triphenylphosphine oxide formed. After filtration and evaporation of the solvent, the product was subjected to chromatography.

**Ethyl (*R*)-2-(Acetylthio)propionate.** Treatment of the mesylate of (*S*)-ethyl lactate (200 mmol, 39.2 g) with $CsSCOCH_3$ (210 mmol, 42.6 g) in 400 mL of DMF overnight gave normal workup the crude product, 33.4 g (190 mmol, 95% yield), as a colorless oil: bp 50 °C (7 torr); $[\alpha]^{20}_{578}$ +137.5° (*c*, 3, $CHCl_3$); $^1H$ NMR $\delta$ 1.22 (t, 3 H), 1.46 (d, 3 H), 2.28 (s, 3 H), 4.06 (q, 2 H), and 4.10 (q, 1 H); $^{13}C$ NMR $\delta$ 193.32 (s), 171.46 (s), 61.21 (t), 40.66 (d), 29.75 (q), 17.33 (q), and 13.67 (q); mass spectrum, exact mass *m/e* calculated for $C_7H_{14}O_3S$ 176.051, found 176.052. Starting from (*S*)-ethyl lactate (50 mmol) Volante's method gave the same results in all respects, including rotation. These samples were shown to be optically pure by the $^{13}C$ satellite/Eu(hfc)$_3$ method.

**Ethyl (*R*)-2-Mercaptopropionate.** The above thioacetate (10 mmol, 1.76 g) was stirred with 20 mL of 3% $C_2H_5OH/HCl$ (method C) overnight to afford after evaporation of the solvent and distillation the thiol, 1.21 g (9 mmol, 90% yield), as a clear oil: bp 75 °C (15 torr); $[\alpha]^{22}_D$ 56.1° (*c* 2, $CHCl_3$); ee 92% ($^{31}P$ method); $^1H$ NMR $\delta$ 1.28 (t, 3 H), 1.52 (d, 3 H), 2.13 (d, 1 H), 3.5 (m, 1 H), and 4.17 (q, 2 H); $^{13}C$ NMR: $\delta$ 173.40 (s), 61.11 (t), 35.47 (d), 20.86 (q), and 13.77 (q); mass spectrum, exact mass *m/e* calculated for $C_5H_{10}O_2S$ 134.040, found 134.041.

The same compound was made by stirring the thioacetate (10 mmol, 1.76 g) with 40 mL of 1 N $NH_3$ (method A). Normal workup and distillation gave the thiol, 1.07 g (8 mmol, 80% yield): $[\alpha]^{23}_D$ 53.7 (*c* 3, $CHCl_3$); ee 88% ($^{31}P$ method). From these data it was calculated that enantiomerically pure thiol must have $[\alpha]^{23}_D$ +61.0° (*c* 3, $CHCl_3$).

Optically pure thiol was made by esterification of optically pure (*R*)-2-mercaptopropanoic acid obtained from optically pure (*S*)-2-bromopropanoic acid (see text, part C); $[\alpha]^{22}_D$ +60.5° (*c* 3, $CHCl_3$); ee ≥98% ($^{31}P$ method). This value is in excellent agreement with the value calculated above from optically enriched samples.

**(*R*)-2-(Benzoylthio)propanoic acid** was prepared by treatment of (*S*)-2-bromopropanoic acid ($[\alpha]^{20}_D$ −26.1° (neat); lit.[41] $[\alpha]^{20}_D$ −26.7° (neat)) (9.0 g, 59 mmol) with cesium thiobenzoate (16.7 g, 62 mmol) in 125 mL of DMF. After workup a thick oil was obtained. Crystallization from cyclohexane afforded product as white needles, 10.5 g (50 mmol, 85% yield): mp 62.5–63 °C (lit.[16] mp 62–63 °C); $[\alpha]^{23}_D$ +102.0° (*c* 3.5, $CHCl_3$) [lit.[16] $[\alpha]$ +102.8° (*c* 3.4, $CHCl_3$)]; $^1H$ NMR $\delta$ 1.6 (d, 3 H), 4.3 (q, 1 H), 7.3–8.0 (m, 5 H), and 11.0 (s, 1 H). Anal. Calcd for $C_{10}H_{10}O_3S$: C, 57.13; H, 4.79; S, 15.25. Found: C, 57.13; H, 4.85; S, 15.10.

**(*R*)-2-Mercaptopropanoic acid [(*R*)-thiolactic acid]** was obtained by treatment of the thiobenzoate (5.25 g, 25 mmol) with 100 mL of 1 N $NH_3$ (method D) to give after workup and distillation the thiol, 1.59 g (15 mmol, 60% yield), as a clear oil: bp 100 °C (4 torr); $^1H$ NMR $\delta$ 1.5 (d, 3 H), 2.2 (d, 1 H), 3.5 (m, 1 H), and 11.5 (s, 1 H); $[\alpha]^{23}_D$ +56.3° (*c* 4, $C_2H_5O_2CCH_3$) [lit.[16] $[\alpha]^{25}_D$ +57.1° (*c* 6.9, $C_2H_5O_2CCH_3$)]; optical purity 98%.

Treatment of the thiobenzoate (5.25 g, 25 mmol) with 4-chloroaniline (27.5 mmol, 3.51 g) at room temperature in 25 mL of benzene (method E) gave after workup and distillation the thiol, 2.0 g (18.8 mmol, 76% yield) as a clear oil: $[\alpha]^{23}_D$ +56.4° (*c* 5, $C_2H_5O_2CCH_3$); optical purity 98%. Esterification of this sample afforded ethyl 2-mercaptopropionate, $[\alpha]^{22}_D$ +60.5° (*c* 3, $CHCl_3$), which was shown to be enantiomerically pure (>98% ee) by the $^{31}P$ method.[32a] This means that the sample of thiol was also optically pure. Acid hydrolysis of the thioacetate (1.76 g, 10 mmol) in 1 N HCl solution at 70 °C for 16 h afforded after saturation of the water layer with salt and extraction with ether the same thiol, 0.74 g (7 mmol, 70% yield): $[\alpha]^{25}_D$ +51.5° (*c* 2, $C_2H_5O_2CCH_3$); optical purity 90%.

**Diethyl (*R*)-2-(Acetylthio)succinate.** Treatment of the mesylate of (*S*)-diethyl malate (40 mmol, 10.6 g) with cesium thioacetate 42 mmol, 8.74 g) in 100 mL of DMF or $Me_2SO$ for 5 days at −20 °C gave, as judged by $^1H$ NMR spectroscopy, 94% thioacetate and 3% elimination product (diethyl fumarate) which was sublimed at 80 °C (0.1 torr). The residue was distilled and gave, after a small forerun, the thioacetate, 8.83 g (35.5 mmol, yield 89%), bp 110 °C (0.05 torr), as a colorless oil: $[\alpha]^{22}_{578}$ +73.6° (*c* 2.7, $CHCl_3$); $^1H$ NMR $\delta$ 1.63 (t, 6 H), 2.27 (s, 3 H), 2.6–3.4 (m, 2 H), 4.13 (q, 2 H), 4.20 (q, 2 H), and 4.5 (t, 1 H); $^{13}C$ NMR $\delta$ 192.36 (s), 169.72 (s), 169.57 (s), 61.36 (t), 60.37 (t), 40.69 (d), 36.18 (t), 29.47 (q), 13.56 (q), and $\delta$ 13.43 (q); mass spectrum, exact mass *m/e* calcd for $C_{10}H_{16}O_5S$ 248.072, found 248.071.

Volante's procedure gave, starting from (*S*)-diethyl malate (30-mmol scale), when carried out at −10 to 0 °C, 90% thioacetate, which was in all respects the same as the sample derived above. No elimination product was detected by $^1H$ NMR. Both samples of thioacetate were shown to be optically pure by the $^{13}C$ satellite/Eu(hfc)$_3$ method as described in the text.

**Diethyl (*R*)-2-mercaptosuccinate** was obtained by esterification of (*R*)-thiomalic acid (100 mmol, 15 g) of 60% e.e. to give after distillation the diethyl ester, 2.04 g (9.9 mmol, 9.9% yield), bp 80 °C (0.3 torr), as a clear oil: $[\alpha]^{20}_{578}$ +20.6° (*c* 2.5, $CHCl_3$), ee 61% ($^{31}P$ method); $^1H$ NMR $\delta$ 1.25 (t, 3 H), 1.27 (t, 3 H), 2.17 (d, 1 H), 2.4–3.2 (m, 2 H), 3.5–3.85 (m, 1 H), 4.1 (q, 2 H), and 4.14 (q, 2 H); $^{13}C$ NMR $\delta$ 171.91 (s), 169.92 (s), 61.31 (t), 60.56 (t), 39.51 (d), 35.87 (t), 13.76 (q), and 13.63 (q); mass spectrum, exact mass *m/e* calcd for $C_8H_{14}O_4S$ 206.061, found 206.060. The same compound was prepared by treatment of diethyl 2-(acetylthio)succinate (10 mmol, 2.48 g) with 3% $C_2H_5OH/HCl$ (20 mL) (method C) to give after distillation diethyl 2-mercaptosuccinate, 1.85 g (9 mmol, 90% yield) as a clear oil, $[\alpha]^{20}_{578}$ +31.9° (c 2, $CHCl_3$) (93% optical purity). Treatment of diethyl 2-(acetylthio)succinate (15 mmol, 1.24 g) with 60 mL of 1 N $NH_3$ (method B) gave after distillation, the same thiol, 0.7 g (3.3 mmol, 65% yield), $[\alpha]^{20}_{578}$ 22.3° (*c* 2.6, $CHCl_3$) (65% optical purity).

**(*R*)-2-Mercaptosuccinic Acid [(*R*)-Thiomalic Acid].** Acid hydrolysis (20 mL of 6 N HCl, 1:1 $H_2O$/dioxane, reflux 8 h) of diethyl (*R*)-2-(acetylthio)succinate (10 mmol, 2.48 g) afforded, after evaporation of the solvent and azeotropic removal of water with benzene, a white powder; this was purified by crystallization from benzene/ethyl acetate (2:1) to give white crystals of thiomalic acid, 1.28 g (8.1 mmol, 81% yield), mp 143–145 °C (lit.[37] 145 °C for a sample with 64% ee), $[\alpha]^{20}_D$ +38.0° (*c* 0.6 EtOH). The highest rotation reported in the literature for thiomalic acid that has been repeatedly recrystallized is $[\alpha]^{17}_D$ +64.4° ($C_2H_5OH$).[37] If this material is enantiomerically pure, then our thiomalic acid would have an optical purity of 59%.

Esterification of the sample of thiomalic acid that we prepared afforded the diethyl ester which showed an ee of 61% by the $^{31}P$ method. This is indeed in good agreement with the optical purity as determined by rotation. Because it is known[37] that thiomalic acid has a eutectic near 60% ee, no attempts were made to improve the optical purity by further recrystallization.

**(*S*)-Ethyl 2-(Acetylthio)-2-phenylacetate.** Treatment of the mesylate of (*R*)-ethyl mandelate (12.9 g, 50 mmol) with cesium thioacetate (52 mmol, 10.82 g) in 60 mL of $C_2H_5OH$ gave after evaporation of the solvent, dissolution in ether, filtration, and again evaporation the thioacetate, 11.4 g (48 mmol, 96% yield); $[\alpha]^{20}_{578}$ +223° (*c* 1.0, $CHCl_3$), bp 110 °C (0.7 torr). By the $^{13}C$ satellite/Eu(hfc)$_3$ method this sample was shown to have ee 98%. When the reaction was carried out in DMF almost complete racemization was observed.

Volante's method gave from (*R*)-ethyl mandelate (10 mmol) a 78% yield of the thioacetate, $[\alpha]^{20}_{578}$ +153° (*c* 1.0, $CHCl_3$), optical purity 69%. With Eu(hfc)$_3$ two peaks were obtained for the tertiary proton in the 60-MHz $^1H$ NMR spectrum in a ratio of 1:6.5 (ee 73%), which confirms that optical purity measurement; $^1H$ NMR $\delta$ 1.2 (t, 3 H), 2.28 (s, 3 H), 4.1 (q, 2 H), 5.25 (s, 1 H), and 7.26 (m, 5 H).

**(*S*)-Methyl 2-Mercapto-2-phenylacetate.** Transesterification of the above ethyl ester to the methyl ester was necessary for comparison with optical rotations reported in the literature. Treatment of (*S*)-ethyl 2-(acetylthio)-2-phenylacetate (10 mmol, 2.38 g) with 3% $CH_3OH/HCl$ (Method C) afforded after distillation the methyl ester, 1.78 g (9.1 mmol, 91% yield), as a colorless oil: bp 130 °C (2 torr); $[\alpha]^{25}_D$ +115° (*c* 2, $C_2H_5OH$ 95%) [lit.[38] $[\alpha]^{25}_D$ +126.0° (*c* 1.4, 95% $C_2H_5OH$)]; optical purity 91% (by rotation) and 93% (by $^{31}P$ NMR); $^1H$ NMR $\delta$ 2.5 (d, 1 H), 3.67 (s, 3 H), 4.71 (d, 1 H), and 7.3 (m, 5 H). Esterification of a sample of (*S*)-2-mercapto-2-phenylacetic acid with an ee of 85% (see later) afforded a sample of the methyl ester, $[\alpha]^{25}_D$ +107.2° (95% $C_2H_5OH$), optical purity 85%. This was confirmed by the $^{31}P$ NMR method, which gave an ee of 86%.

**(*S*)-2-Mercapto-2-phenylacetic Acid [(*S*)-Thiomandelic Acid].** During acid hydrolysis of ethyl 2-(acetylthio)-2-phenylacetate (40 mmol, 9.52 g) in 50 mL of concentrated HCl (ambient temperature, 4 days) the acid precipitated and was filtered off (5.3 g). From the filtrate another 1.1 g of acid could be obtained by extraction with ether, total yield 6.4 g (30 mmol, 75% yield); recrystallization from benzene–hexane (1:3) gave the acid as white needles: mp 88.5–90 °C (lit.[37] mp 88–88.5 °C for a sample with 80% optical purity); $[\alpha]^{25}_D$ +112.2° (*c* 2, 95% EtOH, [lit.[37] $[\alpha]^{25}_D$ −132.4° (95% EtOH) for the *R* enantiomer]; optical purity 85%. Attempts to improve the optical purity by recrystallization were unsuccessful.

The methyl ester derived from this sample showed ee 86% as established by the $^{31}P$ NMR method, confirming the optical purity of its acid precursor.

The $^1H$ NMR spectrum is reported in ref 38.

**(*S*)-*N*,*N*-Dimethyl-2-(acetylthio)-2-phenylacetamide** was prepared by treating the mesylate of (*R*)-*N*,*N*-dimethylmandelamide[25] (10 mmol, 2.57 g), $[\alpha]^{20}_{578}$ −85° (*c* 2, tetrachloroethene) (optical purity 48%),[32b] with $CsSCOCH_3$ (10.5 mmol, 2.18 g) in 20 mL of DMF, which gave the thioacetate, 2.13 g (9 mmol, 90% yield), as a thick, colorless oil, which slowly crystallized: $[\alpha]^{20}_{578}$ +173° (*c* 1.5, $CHCl_3$), ee 48% as determined by the Eu(hfc$_3$/$^1H$ NMR shift experiments on the tertiary proton: $^1H$ NMR $\delta$ 2.2 (s, 3 H), 2.91 and 2.95 (2 × s, 6 H), 5.6 (s, 1 H), and 7.1 (m, 5 H); $^{13}C$ NMR $\delta$ 194.81 (s), 168.73 (s) [136.09, 128.83, 128.08, $C_6H_5$], 50.33 (d), 3 7.47 (q), 36.17 (q), and 29.71 (q) mass spectrum, exact mass *m/e* calcd for $C_{12}H_{15}O_2NS$ 237.082, found 237.080. Anal. Calcd for $C_{12}H_{15}O_2NS$: 60.79; H, 6.38; S, 13.52. Found: C, 60.68; H, 6.31; S, 13.39.

**(*S*)-*N*,*N*-Dimethylthiomandelamide.** (*S*)-*N*,*N*-Dimethyl-2-(acetylthio)-2-phenylacetamide (5 mmol, 1.19 g) was treated with 3% HCl/MeOH (method C). After evaporation of the solvent and volatiles in vacuo, the thiol, 0.97 g (4.95 mmol, 98% yield), was obtained as a clear oil, $[\alpha]^{20}_{578}$ +104° (*c* 1, $CHCl_3$), ee 47% ($^{31}P$ method); $^1H$ NMR $\delta$ 2.67 (d, 1 H), 2.89 (s, 6 H(!)), 4.87 (d, 1 H), and 7.13 (m, 5 H); mass spectrum, exact mass *m/e* calcd for $C_{10}H_{13}ONS$ 195.072, found 195.071.

For this compound the $CON(CH_3)_2$ group gives by coincidence a singlet ($\delta$ 2.89) in the 60-MHz $^1H$ NMR spectrum.

**(*R*)-2-(Benzoylthio)-3-methylbutanoic acid** was prepared by treatment of (*S*)-2-bromoisovaleric acid (18.1 g, 100 mmol) $[\alpha]^{20}_D$ −22.4° (*c* 4, benzene) [lit.[42] $[\alpha]^{20}_D$ −22.4° (*c* 4, benzene)], with CsSCOPh (28.4 g, 105 mmol) in 175 mL of DMF to give after recrystallization from hexane the thiobenzoate, 22.4 g (94 mmol, 94% yield): mp 91.8–92.4°; $[\alpha]^{21}_{578}$ +83.3° (*c* 1, $CHCl_3$); $^1H$ NMR $\delta$ 1.1 (d, 3 H), 2.3 (m, 1 H), 4.3 (d, 1 H), 7.1–7.9 (m, 5 H), and 11.4 (s, 1 H); $^{13}C$ NMR $\delta$ 189.99 (s), 177.58 (s) [136.0, 133.63, 128.507, 127.25, $C_6H_5$], 52.79 (d), 30.20 (d), 20.28 (q), and 19.47 (q); mass spectrum, exact mass calcd for $C_{12}H_{14}O_3S$ *m/e* 238.066, found 238.064. Anal. Calcd for $C_{12}H_{14}O_3S$: C, 60.48; H, 5.92; S, 13.45. Found: C, 60.23; H, 6.01; S, 13.40.

**(*R*)-2-Mercapto-3-methylbutanoic acid** was prepared by treatment of (*R*)-2-(benzoylthio)-3-methylbutanoic acid (10 mmol, 2.38 g) with 4-chloroaniline (method E) as described for the synthesis of (*R*)-thiolactic acid to give the acid, 0.95 g (7.1 mmol, 71% yield): mp 35 °C (lit.[40] mp 35 °C); $[\alpha]^{20}_D$ +23.3° (*c* 0.68, ether) [lit.[40] $[\alpha]^{20}_D$ +13.7°, c 3, ether).

The same compound was prepared by treatment of the thiobenzoate (20 mmol, 4.76 g) with 1 N $NH_3$ (80 mL) (method D) to give the acid, 1.3 g (9.9 mmol, 48%), in all respects the same as the acid obtained above. This yield has not been optimized.

The methyl ester derived from these samples proved to be enantiomerically pure by the $^{31}P$ NMR method. This implies that its acid precursor also must have been enantiomerically pure. The acid has the following: $^1H$ NMR $\delta$ 1.1 (dd, 6 H), 2.05 (m, 1 H), 2.10 (d, 1 H), 3.1 (dd, 1 H), and 11.4 (s, 1 H); $^{13}C$ NMR $\delta$ 178.81 (s), 48.48 (d), 32.41 (d), 20.51 (q), and 19.03 (q). Anal. Calcd for $C_5H_{10}O_2S$: C, 44.75; H, 7.51; S, 23.89. Found: C, 44.61; H, 7.36; S, 23.68.

**(*R*)-Methyl 2-(acetylthio)-3-phenylpropionate** was prepared by treatment of the mesylate of commercially available and enantiomerically pure (*S*)-3-phenyllactic acid methyl ester (2.58 g, 10 mmol) with $CsSCOCH_3$ (10.5 mmol, 2.18 g) in 20 mL of DMF to give the thioacetate, 2.26 g (9.6 mmol, 96% yield), as a clear oil, $[\alpha]^{20}_{578}$ +63.6° (*c* 2, $CHCl_3$). *No* elimination product was detected; $^1H$ NMR $\delta$ 2.28 (s, 3 H), 2.7–3.45 (m, 2 H), 3.6 (s, 3 H), and 4.3 (t, 1 H); mass spectrum, exact mass *m/e* calcd for $C_{12}H_{14}O_3S$ 238.085, found 238.083. Anal. Calcd for $C_{12}H_{14}O_3S$: C, 60.48; H, 5.92; S, 13.45. Found: C, 60.29; H, 5.83; S, 13.32.

**(*R*)-Methyl 2-mercapto-3-phenylpropionate** was prepared by treatment of (*R*)-methyl-2-(acetylthio)-3-phenylpropionate (5 mmol, 1.19 g) with 1 N $NH_3$ (20 mL) (method B) to give, after normal workup, the thiol, 0.92 g (4.7 mmol, 95% yield), as a clear oil: bp 100–105 °C (2 torr), $^1H$ NMR $\delta$ 2.07 (d, 1 H), 2.7–3.5 (m, 2 H), 3.4–3.85 (m, 1 H), 3.6 (s, 3 H), and 7.1 (s, 5 H, br); $[\alpha]^{20}_{578}$

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−0.65° (c 1.1, $CHCl_3$). The sign and magnitude of the rotation of this sample are concentration and wavelength dependent:

| λ, nm | $[\alpha]^{20}$ (c 1.1) | $[\alpha]^{20}$ (c 0.8) |
|---|---|---|
| 578 | −0.65° | +0.4° |
| 546 | −0.10° | +1.12° |
| 436 | +6.05° | +8.0° |
| 365 | +24.4° | +29.5° |

The ee of this sample was established by the $^{31}P$ NMR method to be 79%.

The same methyl ester was prepared by esterification of (R)-2-mercapto-3-phenyllactic acid (see below), in 98% yield, bp 100–105 °C (2 torr). This was shown by the $^{31}P$ NMR method to have an ee of 93%.

**(R)-2-(Benzoylthio)-3-phenylpropanoic acid** was prepared by treatment of (S)-2-bromo-3-phenylpropanoic acid[17b] (2.29 g, 10 mmol), $[\alpha]^{22}_D$ −10.2° (c 1, MeOH) [lit.[17b] $[\alpha]^{25}_D$ −10.0° (c 1, MeOH)], with $CsSCOC_6H_5$ (10.5 mmol, 2.97 g) in 15 mL of DMF, to give after crystallization from petroleum ether, (bp 60–80 °C, the acid, 2.14 g (7.5 mmol, 75% yield): mp 103–104 °C; $[\alpha]^{20}_{578}$ +3.2° (c 0.5, $CHCl_3$); $^1H$ NMR δ 2.8–3.6 (m, 2 H), 4.6 (t, 1 H), 7.17 (s, 5 H), 7.1–8.0 (m, 5 H), and 11.4 (s, 1 H); $^{13}C$ NMR δ 189.67 (s), 176.72 (s) [136.79, 135.92, 133.75, 129.03, 128.57, 128.43, 127.32, 127.0, 2 × $C_6H_5$], 46.99 (d), and 37.43 (t); mass spectrum, exact mass m/e calcd for $C_{16}H_{14}O_3S$ 286.066, found 286.067. Anal. Calcd for $C_{16}H_{14}O_3S$: C, 67.11; H, 4.93; S, 11.20. Found: C, 66.96; H, 5.01; S, 11.12.

**(R)-2-Mercapto-3-phenylpropanoic acid** was prepared by treatment of (R)-2-(benzoylthio)-3-phenylpropanoic acid (5 mmol, 1.43 g) with 1 N $NH_3$ (20 mL) (method D) to give the acid, 0.47 g (2.6 mmol, 52% yield), after chromatography (silica gel 60, $CH_2Cl_2$ and distillation), $[\alpha]^{20}_D$ −9.5° (c 1, MeOH) [lit.[17b] $[\alpha]^{25}_D$ −7.84° (c 1, MeOH)]. The $^1H$ NMR spectrum was in accord with that described in ref 17b.

The methyl ester prepared from this sample had an ee of 93% ($^{31}P$ method). This implies that the optical purity of the starting material, (S)-2-bromo-3-phenylpropanoic acid, also must have been only 93% (see experiment with (R)-methyl 2-mercapto-3-phenylpropionate).

**(S)-(+)-2-Octanethiol** was prepared by treatment of the mesylate of (R)-(−)-2-octanol[39] (2.08 g, 10 mmol), $[\alpha]^{20}_D$ −9.9° (neat) (optically pure), with $CsSCOCH_3$ (2.18 g, 10.5 mmol) in 20 mL of DMF at 40 °C for 18 h to give a 92% yield of the thioacetate, which was reduced with excess $LiAlH_4$ to give the thiol, 1.31 g (9 mmol, total yield 90%), which had, after distillation, bp 65–70 °C (15 torr) [lit.[26] bp 65–70 °C (15 torr)], $[\alpha]^{21}_{546}$ 35.0° (c 2.5, absolute EtOH) [lit.[39] $[\alpha]_{546}$ 35.7° (c 5.1, absolute EtOH)]. This sample was enantiomerically pure as established by the $^{31}P$ NMR method.

**(+)-Neomenthanethiol** was prepared by treatment of the mesylate of (−)-menthol (20 mmol, 4.68 g) with $CsSCOCH_3$ (21 mmol, 4.36 g) in 25 mL of DMF at 55 °C for 20 h to give a 89% yield of (+)-neomenthyl thioacetate together with 5% menthene, which distilled at 70–100 °C (10 torr). The residue (84%) was almost pure substitution product: $^1H$ NMR δ 0.6–2.1 (m, 8 H), 2.28 (s, 3 H), and 4.02 (m, 1 H). No rotation was taken, because of small amounts of impurities still present. Reduction with $LiAlH_4$ afforded the crude thiol in 95% yield. After a small forerun, pure thiol (2.45 g, 15 mmol, total yield 76%) distilled at 110 °C (9 torr), $[\alpha]^{20}_D$ +53.2° (c 2, $CHCl_3$) [lit.[24] $[\alpha]^{27}_D$ +47.8° (c 2.06, $CHCl_3$), lit.[12] $[\alpha]^{25}_D$ +39.0° ($CHCl_3$)]. Our material proved to be optically ($^{31}P$ method) and diastereomerically ($^{13}C$, $^{31}P$ NMR) pure: $^1H$ NMR δ 0.6–2.1 (m, 9 H) and 3.45 (m, 1 H); $^{13}C$ NMR δ [one diastereomer] 48.14, 43.93, 40.04, 35.18, 30.20, 25.83, 24.07, 22.05, 20.76, and 20.26.

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**Registry No.** Cesium thioacetate, 56827-86-2; cesium thiobenzoate, 89664-67-5; ethyl (R)-2-(acetylthio)propionate, 78560-77-7; (S)-ethyl lactate, 687-47-8; ethyl (R)-2-mercaptopropionate, 103616-07-5; (R)-2-(benzoylthio)propanoic acid, 33179-02-1; (S)-2-bromopropanoic acid, 32644-15-8; (R)-2-mercaptopropanoic acid, 33178-96-0; diethyl (R)-(acetylthio)succinate, 89373-38-6; (S)-diethyl malate, 691-84-9; diethyl (R)-2-mercaptosuccinate, 103499-56-5; (R)-2-mercaptosuccinic acid, 20182-99-4; (S)-ethyl 2-(acetylthio)-2-phenylacetate, 103499-53-2; (R)-ethyl mandelate, 10606-72-1; (S)-ethyl 2-mercapto-2-phenylacetate, 103499-57-6; (S)-methyl 2-mercapto-2-phenylacetate, 103499-60-1; (S)-2-mercapto-2-phenylacetic acid, 103616-08-6; (S)-N,N-dimethyl-2-(acetylthio)-2-phenylacetamide, 103499-54-3; (R)-N,N-dimethylmandelamide, 97315-03-2; (S)-N,N-dimethylthiomandelamide, 103499-58-7; (R)-(2-benzoylthio)-3-methylbutanoic acid, 103499-61-2; (S)-2-bromoisovaleric acid, 26782-75-2; (R)-2-mercapto-3-methylbutanoic acid, 39801-53-1; (R)-methyl 2-mercapto-3-methylbutanoate, 103499-62-3; (R)-methyl 2-(acetylthio)-3-phenylpropionate, 103499-55-4; (S)-methyl 3-phenyllactate, 13673-95-5; (R)-methyl 2-mercapto-3-phenylpropionate, 103499-59-8; (R)-2-(benzoylthio)-3-phenylpropanoic acid, 103499-63-4; (S)-2-bromo-3-phenylpropanoic acid, 35016-63-8; (R)-2-mercapto-3-phenylpropanoic acid, 84800-12-4; (S)-2-octyl thioacetate, 62258-08-6; (R)-2-octanol, 5978-70-1; (S)-2-octanethiol, 50764-49-3; (+)-neomenthyl thioacetate, 103532-45-2; (−)-menthol, 2216-51-5; (+)-neomenthanethiol, 53273-24-8.

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