of 3-(benzylmercapto)isonicotinonitrile (14): mp 53–54 °C (cyclohexane); IR (KBr) 2220 cm^{-1} (CN); NMR ($CDCl_3$) 8.58 (s, 1 H), 8.42 (d, 1 H), 7.37 (d, 1 H), 7.22 (s, 5 H), 4.22 (s, 2 H).

Anal. Calcd for $C_{13}H_{10}N_2S$: C, 69.00; H, 4.45; N, 12.38. Found: C, 68.84; H, 4.67; N, 12.34.

The more polar material amounted to 0.79 g (12%) of a crystalline solid [mp 170–171 °C (toluene)] which was identified as 3-amino-2-phenylthieno[2,3-c]pyridine (15): NMR ($CDCl_3$) 8.78 (s, 1 H), 8.30 (d, 1 H), 7.76–7.18 (m, 6 H), 4.06 (br, 2 H).

Anal. Calcd for $C_{13}H_{10}N_2S$: C, 69.00; H, 4.45; N, 12.38. Found: C, 68.71; H, 4.70; N, 12.55.

Compound 15 could also be prepared from 3-(benzylmercapto)isonicotinonitrile (14) in the following way. Sodium (50 mg, 2.2 mmol) was dissolved in 25 mL of absolute EtOH under nitrogen at room temperature. To this was added 0.45 g (2.0 mmol) of 14, and the mixture was heated at reflux for 16 h. The mixture was concentrated, and the residue was dissolved in 20 mL of water. The aqueous mixture was extracted three times with a total of 45 mL of CH_2Cl_2. The combined CH_2Cl_2 extracts were dried (Na_2SO_4), filtered, and evaporated, leaving a pale yellow solid. Recrystallization from toluene afforded 0.32 g (71%) of 15, identical in all respects with the material isolated previously.

3-Ethoxyisonicotinonitrile (16). By use of the exact procedure used for the synthesis of 4, 16 was prepared in 83% yield: mp 49–51 °C; IR (KBr) 2225 cm^{-1} (CN); NMR ($CDCl_3$) 8.45 (s, 1 H), 8.34 (d, 1 H), 7.40 (d, 1 H), 4.32 (q, 2 H), 1.48 (t, 3 H).

A sample of this material was converted to its hydrochloride salt (as was done for 6) for analytical purposes; mp 184–186 °C.

Anal. Calcd for $C_8H_8N_2O$·HCl: C, 52.04; H, 4.91; H, 15.18. Found: C, 51.83; H, 4.75; N, 15.03.

3-Ethoxyisonicotinic Acid (17). A mixture of 12.0 g (81 mmol) of 16, 6.48 g (162 mmol) of sodium hydroxide, and 120 mL of absolute EtOH was heated at reflux for 20 h. The mixture was cooled to room temperature and then concentrated, leaving a pale yellow solid. This was dissolved in a minimum amount of water, and the pH was adjusted to 3.0 with 1 N HCl. The mixture was concentrated, and the residue was digested with 500 mL of boiling absolute EtOH, filtered while hot to remove inorganic material, and then concentrated, leaving 13.3 g (98%) of 17 as a white solid: mp 141–144 °C; IR (KBr) 1715 cm^{-1} (carbonyl); NMR (Me_2SO-d_6/D_2O) 8.50 (s, 1 H), 8.30 (d, 1 H), 7.55 (d, 1 H), 4.32 (q, 2 H), 1.21 (t, 3 H). An analytical sample was prepared by recrystallization from ethanol; mp 154–155 °C.

Anal. Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.42; N, 8.38. Found: C, 56.91; H, 5.15; N, 8.48.

Acknowledgment. We are grateful to Mr. Paul R. Kelbaugh for the preparation of 16 and 17 and to Professors D. S. Kemp and D. S. Watt for their helpful suggestions and comments.

Registry No. 1, 68325-15-5; 2, 78790-72-4; 4, 26414-90-4; 5·HCl, 78790-73-5; 6, 78790-74-6; 6·HCl, 78790-75-7; 7, 78790-76-8; 8, 78790-77-9; 8·HCl, 78790-78-0; 9, 78790-79-1; 10, 78790-80-4; 11, 78790-81-5; 12, 78790-82-6; 13, 78790-83-7; 14, 78790-84-8; 15, 78790-85-9; 16, 78790-86-0; 16·HCl, 78790-87-1; 17, 78790-88-2.

Sulfinic Acids and Related Compounds. 13. Unsymmetrical Disulfides Based on Methyl 4-Mercaptobutanesulfinate and 4(*S*)- or 4(*R*)-Mercaptoprolines[1,2]

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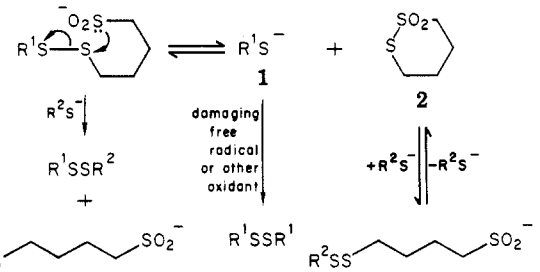
In a study of disulfide–sulfinates containing prolylthio moieties epimeric at C-4, the OH group of N-acetylated 4(*R*)-hydroxy-2(*S*)-pyrrolidinecarboxylic acid ("*trans*-4-hydroxy-L-proline", 3) was converted to an epimeric SH group (11) by replacing a 4-*O*-tosyl group with $PhCH_2S$ (to give 5) and debenzylating. Reaction of 11 as the disodium salt with 1,2-dithiane 1,1-dioxide (2) replaced the H of the SH with $S(CH_2)_4SO_2Na$ to give a disulfide–sulfinate salt (9). Since 9 was unstable in solution, with conversion of disodium 4,4′-trithiobis(butanesulfinate) (22) to the diester 23 as a model, 9 was converted to the disulfide–sulfinic ester 10. Subsidiary peaks in the ^{13}C NMR spectra of *N*-acetyl derivatives were shown to originate from rotamers. Similarly, the epimeric 4(*S*)-hydroxyproline (16) was converted to the 4(*R*)-mercaptoproline epimer (19) of 11, which was converted in turn to the disulfide–sulfinate epimer (21) of the sulfinic ester 10. The two disulfide–sulfinate esters 10 and 21 were stable under ambient conditions and began to disproportionate to the two symmetrical disulfides in refluxing ethyl acetate in 1.5 (21) to ca. 7 h (10). The sulfinic esters 10, 21, and 23 seem likely to serve as biological precursors of sulfinate and thiolate salts, which may be useful for several purposes.

A variety of sulfinate salts containing di- or trisulfide linkages are promising antiradiation drugs.[3] To learn whether chirality might be important in the future design of congeners, study of chiral representatives became desirable; with drugs of the (*S*)-(2-aminoethyl)isothiouronium type, a D enantiomer was twice as protective as the L.[4] If protection against ionizing radiation by di- or trisulfide sulfinates depends upon interactions with enzymes or nucleic acids, chirality might play a key role. Alternatively, protection may involve cyclization of the sulfinate–disulfide (Scheme I),[1] with chirality being unimportant; thus

Scheme I



(1) For paper 12, see: Field, L.; Eswarakrishnan, V. *J. Org. Chem.* **1981**, *46*, 2025.

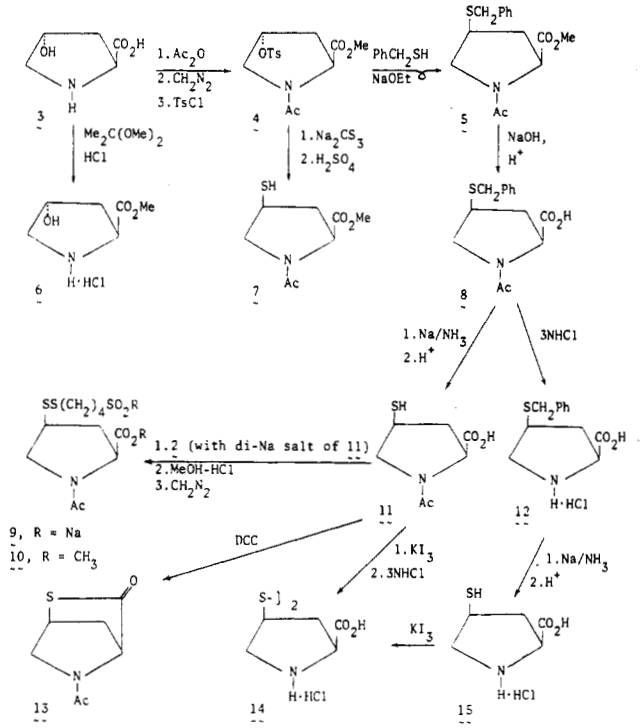
(2) Abstracted from part of the Ph.D. dissertation of V.E., Vanderbilt University, May 1981, which can be consulted for further details.

(3) Srivastava, P. K.; Field, L.; Grenan, M. M. *J. Med. Chem.* **1975**, *18*, 798.

(4) Doherty, D. G.; Shapira, R. *J. Org. Chem.* **1963**, *28*, 1339.

0022-3263/81/1946-4182$01.25/0

Scheme II[a]

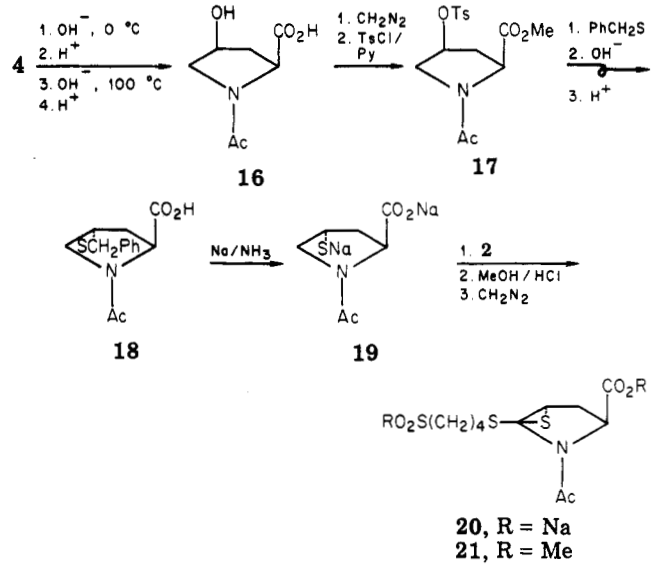


[a] Ts = p-$CH_3C_6H_4SO_2$.

the thiolate **1** may act as a free-radical trap or reducing agent, or the disulfide–sulfinate or the dioxide **2** may act as a thioalkylating agent for an essential SH function (R^2S^- in Scheme I).

4(*R*)-Hydroxy-2(*S*)-pyrrolidinecarboxylic acid ("*trans*-4-hydroxy-L-proline", **3** of Scheme II) was chosen as the chiral framework, with the intent of converting the 4-OH group to epimeric 4-SH groups, partly because **3** is commercially available and of known configuration;[5] replacement of the H of the SH with $S(CH_2)_4SO_2^-$, one of our most promising groups, thus would permit comparison of two epimeric disulfide–sulfinates (if warranted, epimerization of a CO_2H group also may permit later comparison of enantiomers). The hydroxyproline **3** was attractive for other reasons also, however. (1) Penicillamine, $Me_2C(SH)CH(NH_2)CO_2H$, and certain congeners have marked effects on collagen, a principal protein of connective tissue.[6] It also produces immunochemical effects[7] and has been used in treating a number of diseases.[6a] Mercaptoprolines, as possible biotransformation products of the disulfide–sulfinates, thus are of interest as congeners of penicillamine that may produce fewer adverse effects.[8] (2) "*cis*-4-Hydroxy-L-proline" (of which **16** is the *N*-acetyl derivative) decreases secretion of collagen and, when incorporated into collagen, interferes with its conformation.[9] Hence the epimeric 4-mercapto counterparts may show significant effects both on the biosynthesis and properties of collagen. (3) Since the hydroxyproline moiety is present in large amounts in human collagen,[10] mercapto analogues are likely to be well tolerated and biologically significant.

Scheme III[a]



[a] Ts = p-$CH_3C_6H_4SO_2$.

Derivatives of 4(*S*)-Mercaptoproline. Scheme II shows syntheses related to the first of the two epimeric mercaptoprolines needed. The sodium salt **9** at first was the ultimate target for biological use. When the sulfinate **9** proved unattractive because of facile cyclization like that shown in Scheme I, the dimethyl ester **10** was sought instead. The diester **10** should be readily hydrolyzed by esterases to the unstable salt **9**, which by cyclization should expel the *N*-acylmercaptoproline **11**; biological deacylation of **11** then should produce the mercapto-free base corresponding to **15**. Since **10** thus is a possible biological progenitor of congeners of both penicillamine and 4-hydroxyproline, it has attractive possibilities as a related pro-drug,[11] in addition to those as a chiral antiradiation agent. The best synthetic sequence ultimately lay in the conversions **3** → **4** → **5** → **8** → [**11**] → [**9**] → **10**.

For the synthesis of **10**, the 4-tosylate **4** was found to be the most attractive starting material and a sequence developed by Neuberger the best means of obtaining **4**.[12] Neuberger's sequence of acetylation, methylation, and tosylation of **3** in our hands led to **4** in the respective yields of 82–87%, 96–99%, and 76–80% (Scheme II). Two other acetylation procedures were less satisfactory with **3**,[13,14] and an effort to mesylate the *N*-acetyl methyl ester of **3** led only to an unpromising mixture.[15]

In the Neuberger synthesis of **4**, diazomethane is used for methylation (Scheme II).[12] Because of the large amounts of **4** desired, efforts were made to circumvent this use. When these were unpromising, we reverted to diazomethane, but simply with extraction into ether rather than distillation. In the unpromising approaches, methylation of *N*-Ac-**3** with dimethyl sulfite[6a] or methanol–HCl gave yields of 28% and 40%, respectively. Esterification of **3** to **6** with 2,2-dimethoxypropane (Scheme II)[16]

(5) Donohue, J.; Trueblood, K. N. *Acta Crystallogr.* **1952**, *5*, 419.
(6) (a) Sweetman, B. J.; Vestling, M. M.; Ticaric, S. T.; Kelly, P. L.; Field, L.; Merryman, P.; Jaffe, I. A. *J. Med. Chem.* **1971**, *14*, 868. (b) Field, L.; Hanley, W. S.; Kelly, P. L.; Sanders, W. J.; White, J. E.; Jaffe, I. A.; Merryman, P. *Ibid.* **1973**, *16*, 1152. (c) Hanley, W. S.; Snyder, M. E.; Field, L.; Gallo, A. A. *Chem.-Biol. Interact.* **1978**, *21*, 263.
(7) Chen, D.-M.; Di Sabato, G.; Field, L.; Gallo, A. A.; Harshman, S. *Clin. Exp. Immunol.* **1977**, *30*, 317.
(8) Adverse effects are summarized by: Lyle, W. H. "Distamine D-(–)Penicillamine—a Review"; Dista Products Ltd: Liverpool, 1973; pp 22–28.
(9) Uitto, J.; Dehm, P.; Prockop, D. J. *Biochem. Biophys. Acta* **1972**, *278*, 601.
(10) Eastoe, J. E. In "Treatise on Collagen"; Ramachandran, G. N., Ed.; Academic Press: New York, 1967; Vol. 1, p 52.
(11) Higuchi, T.; Stella, V., Eds. "Pro-drugs as Novel Drug Delivery Systems"; American Chemical Society: Washington, DC, 1975.
(12) Neuberger, A. *J. Chem. Soc.* **1945**, 429.
(13) Kolb, J. J.; Toennies, G. *J. Biol. Chem.* **1942**, *144*, 193.
(14) Synge, R. L. M. *Biochem. J.* **1939**, *33*, 1913.
(15) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.
(16) Rachele, J. R. *J. Org. Chem.* **1963**, *28*, 2898.

evidently succeeded (58% yield), but N-acetylation of the 6 was unpromising.

Also explored were routes to 10 via 7 that would be considerably more direct than the sequence of Scheme II eventually used. Reaction of 4 with sodium trithiocarbonate (Scheme II), a method for converting halides to thiols,[17] gave the mercapto ester 7 only in 17% yield (although this result seems susceptible to improvement). Sodium or potassium thioacetate replaced the tosyloxy group of 4 with an acetylthio group only in very low yield, and NMR spectra indicated that the use of thiourea with 4 led not to a thiouronium salt but only to alkene signals, signifying elimination reactions.

In light of the foregoing explorations, the approach to 10 of 3 → 4 → 5 → 8 seemed the best. In this sequence, replacement of the tosylate group of 4 by the benzylthio group gave 5 (Scheme II). Saponification of 5 at 0 °C and acidification then gave the acid 8. The desired inversion evidently occurred rather cleanly in the conversion of 4 to 5, since chromatographically homogeneous 5 of analytical purity was obtained in 69% yield from 4 (and the pure acid 8 in a yield from 4 of 63%). Furthermore, as discussed below, use of the epimeric 4-tosylate of 4 (17 of Scheme III) led to pure 4(*R*)-benzylthio acid 18, epimeric with 8 at C-4, in 47% yield from 17. This acid 18 clearly differed from 8 (melting point, spectra, optical rotation), an improbability unless reasonably clean inversion occurred in the reactions of both 4 and 17. An effort to form the thiolactone 13 from 11 with dicyclohexylcarbodiimide (DCC) led to a new TLC spot, a peak at *m/e* 171 (calculated for the molecular ion of 13, *m/e* 171), and a new peak in the ^{13}C NMR at δ 182; refluxing of the product in EtOAc diminished the TLC spot, and contact with silica gel for 3 h obliterated it, indicating instability.

That racemization did not occur during the conversion of the ester 5 to the acid 8 follows from absence of a 2-CO_2H epimer in 8 (sharp, nearly constant melting point as first isolated in 92% yield from 5; single TLC spot). Furthermore, the ^{13}C NMR peaks for 8 were as expected, with no additional peaks indicating diastereomeric contamination. However, ^1H NMR spectra for *N*-acetyl-4-(*R*)-hydroxyproline (i.e., *N*-Ac-3) at 300 MHz have shown syn–anti rotamerism about the Ac–N bond with a rotamer ratio of 17:83,[18] and peaks for such rotamers appeared also near ^{13}C NMR peaks of the acid 8 (and tosylate 4), although rotameric peaks were not conspicuous in our ^1H NMR spectra; based on ^{13}C peak heights, the ratio of rotamers was about 17:77. The rotameric peaks of 8 appeared as small ancillaries separated only by up to ca. 2 ppm from the large peaks for CH_2, CH_3, and the four ring carbons. That these ancillaries were in fact produced by rotamers and not by diastereomeric contaminants was confirmed in three ways. (1) At 50 °C (our highest feasible temperature), some of the main and ancillary peaks converged to single peaks with shoulders, although they did not quite coalesce. (2) The deacetylated amine salt 12 showed only five cleanly single peaks at δ 62–36. (3) The amine salt 14 showed only four cleanly single peaks at δ 62–36, for the four carbon atoms of the proline ring (this result also confirmed that significant epimerization was improbable elsewhere in the sequence of 8 → 11 → 14).

Since the *N*-acetyl thiol 11 and thiol salt 15 seemed unattractive for biological testing, the conversions involving 11–15 were not pursued extensively. Thus although debenzylation of 8 gave the thiol 11 in 44% yield (single TLC spot), 11 was an easily oxidizable oil difficult to isolate in good yield because of extreme water solubility; under argon, however, 11 in methanol showed no loss of SH from a value of ca. 70% over 9 days, as measured by Ellman's reagent.[19] The amino thiol salt 15 showed 100% thiol content and could be oxidized to 14, but it too was easily oxidized and was inconveniently hygroscopic. It was worth adding that these conversions show that mercaptoproline derivatives can be obtained by deacylation and then debenzylation (8 → 12 → 15 → 14), as well as by the reverse (8 → 11 → 14); hence, the amine function need not be acetylated for effective debenzylation.

The disulfide 9 was sought by reaction of the disodium salt of 11 with 1,2-dithiane 1,1-dioxide (2), an approach we have frequently used for converting SH to $SS(CH_2)_4SO_2Na$.[20] The Ellman reaction became negative, consistent with formation of 9 (Scheme II). However, in about 15 min the typical Ellman color began to reappear, indicating reversion of the 9 to the starting materials by a cyclization like that illustrated in Scheme I.[20] Evidently the formation of 9 is kinetically controlled and the reversion thermodynamically controlled.

The sulfinic ester 10 seemed likely to be considerably more stable and thus more attractive than the salt 9. Methylation of the sulfinic acid with diazomethane seemed plausible, since diazomethane converts a sulfinic acid entirely to the ester, with no formation of the sulfone.[21] The feasibility of such an esterification for 9 was established by the model reaction of eq 1; the diester 23 is of interest

$$2 \xrightarrow{Na_2S} \underset{\mathbf{22}}{[NaO_2S(CH_2)_4S]_2S} \xrightarrow[-NaCl\ (ppt)]{HCl(MeOH)} [HO_2S(CH_2)_4S]_2S \xrightarrow{CH_2N_2} \underset{\mathbf{23}}{[MeO_2S(CH_2)_4S]_2S} \quad (1)$$

per se as a pro-drug variation of the salt 22, a promising antiradiation agent.[3] The ester 23 was obtained in 59% yield (based on Na_2S; used with excess 2 to prepare 22 because 2 is easily removed). The ^1H NMR spectrum of 23 was consistent with the absence of a methyl sulfone.

With eq 1 as a model, 8 was debenzylated to 11 (Scheme II), the excess sodium was neutralized, and the disalt was converted with 2 to the salt 9, which was promptly precipitated. Acidification and esterification then gave the pure diester 10 in 34–38% yield from 8. The diester 10 proved to be reasonably stable. It showed no change in TLC after at least 2 weeks at ambient conditions, and the disproportionation expected of an unsymmetrical disulfide to symmetrical ones began only after ca. 7 h in refluxing ethyl acetate.

Derivatives of 4(*R*)-Mercaptoproline. Scheme III shows the synthesis of the diester 21, the C-4 epimer of the sulfinate–disulfide 10. The tosylate 4, again the starting material from the commercial hydroxyproline, was converted to 16 (Scheme III) by the method of Neuberger.[12] In Neuberger's synthesis, 4 is saponified to give the carboxylic acid under mild conditions. The corresponding salt then is converted to 16 by using alkali under vigorous conditions with inversion and expulsion of tosylate ion (via the cyclic lactone?); our overall yield of 16 from 4 was 32%. Since saponification of 4 gave no problems (90–94%), the low overall yield presumably finds its cause in competing reactions such as solvolysis and elimination; Neuberger and others have encountered low yields of 16 as well.[12,22] An

(17) Martin, D. J.; Greco, C. C. *J. Org. Chem.* **1968**, *33*, 1275.
(18) Prange, T.; Garbay-Jaurequiberry, C.; Roques, B.; Anteunis, M. *Biochem. Biophys. Res. Commun.* **1974**, *61*, 104.
(19) Ellman, G. L. *Arch. Biochem. Biophys.* **1959**, *82*, 70.
(20) For leading references, see ref 1.
(21) Meek, J. S.; Fowler, J. S. *J. Org. Chem.* **1968**, *33*, 3422.

effort was made to synthesize an *N*-tosyl counterpart of **16** more directly by N-tosylating the hydroxyproline **3**, oxidizing to the 4-oxo compound, and stereoselectively reducing the latter;[23] however, the yields reported could not be achieved.

Once the overall route of Scheme II was at hand, it could be applied in the similar manner of Scheme III to the synthesis of **21** from **16**. After uneventful conversion of the hydroxyproline **16** to the ester tosylate **17**, replacement of tosylate with inversion and subsequent hydrolysis gave **18** (47% from **17**). As with **10**, **18** then was debenzylated and the mixture neutralized only enough to leave the disodium salt **19**. Thioalkylation of the disalt with the dioxide **2**, acidification, and dimethylation as before then gave **21** in overall yields from **18** of 28–46%. This **21** was stable for at least 2 weeks under ambient conditions (TLC). In refluxing ethyl acetate, **21** began to disproportionate after 1.5 h and thus seems considerably less resistant than **10** (7 h) under these conditions.

Experimental Section

Several general procedures were as described earlier.[1] Additionally, ^{13}C NMR spectra were obtained through the kindness of M. Hoch with a JEOL JNM-FX90Q spectrometer operating at 22.5 MHz with Me_4Si as a reference (or DSS in D_2O); where small peaks were seen for rotamers up to ca. 2 ppm from main peaks (**4** and **8**), the δ values reported are for the major peak; at our resolution (JOELCO Model JNM-MH-100), peaks for rotamers were not conspicuous in ^1H NMR spectra. Specific rotations were measured in a 1-dm tube by using a Rudolph Research Autopol III automatic polarimeter. "*trans*-4-Hydroxy-L-proline" (**3**) was purchased from Aldrich Chemical Co. ["99+%, $[\alpha]^{25}$ – 75.3° (*c* 20, H_2O)"]. Distilled liquid NH_3 refers to NH_3 distilled from a blue solution of Na/NH_3 into a flask chilled in dry ice and acetone and equipped with a dry-ice condenser and gas-inlet tube. Diazomethane was prepared from *N*-nitrosomethylurea by extraction into Et_2O without distillation.[24] A positive Ellman test for SH refers to development of a strong yellow color immediately with the usual Ellman conditions described earlier (and used here) for quantitative determinations.[1,19]

Methyl *N*-Acetyl-4(*R*)-(*p*-toluenesulfonyloxy)-pyrrolidine-2(*S*)-carboxylate (4) and Related (Less Promising) Starting Materials. The methyl ester **4** was prepared in overall yields of about 65% by N-acetylation,[22] esterification, and O-tosylation of 4(*R*)-hydroxy-2(*S*)-pyrrolidinecarboxylic acid ("*trans*-4-hydroxy-L-proline", **3**) essentially as described,[12] except that CH_2N_2 was used as an undistilled extract in Et_2O:[24] mp 70–71 °C (lit. mp 60 °C,[12] 71–73 °C[25]); $[\alpha]^{24}_D$ –32.8° (*c* 1.5, MeOH); IR (KBr) 2950, 2900, 2325, 1740 (s), 1630 (s), 1430 (s), 1400 (s), 1340 (s), 1320 (s), 1310 (s), 1280 (m), 1250 (m), 1220 (m), 1190 (s), 1160 (s), 1100 (m), 1080 (m), 1040 (m), 1000 (m), 940 (m), 870 (s), 800 (m), 730 (s), 680 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.9–7.4 (a_2b_2, 4 H), 5.2 (m, 1 H), 4.5 (t, 1 H), 3.9–3.7 (m, 5 H), 2.5 (s, 3 H), 2.4–2.1 (m, 2 H), 2.0 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.91, 169.10 (CO_2Me, COMe), 145.42, 133.40, 130.04, 127.65 (Ph), 78.73 ($CO_2\mathbf{Me}$), 56.85, 53.11, 52.35, 35.40, 21.96, 21.58 ($PhCH_3$, $COCH_3$, and four carbon atoms in the proline ring).

The **4** proved extremely difficult to crystallize initially. Crystallization was best achieved, after completion of the acetylation, esterification, and tosylation,[12] by washing a solution in $CHCl_3$ with 1 N HCl and then H_2O to neutrality, drying (Na_2SO_4), and evaporating to an oil; the oil was kept at ca. 0.5 torr over P_2O_5 overnight and then was rubbed well with Et_2O and allowed to stand under Et_2O at 5 °C overnight; the resulting powder then could be readily crystallized from Et_2O. This procedure was used routinely in preparing **4**, although it may have been unnecessary once seed crystals had been thus obtained since crystallization then was facile.

Anal. Calcd for $C_{15}H_{19}NO_6S$: C, 52.77; H, 5.61; N, 4.10; S, 9.39. Found: C, 52.97; H, 5.69; N, 4.07; S, 9.28.

Earlier efforts to obtain the *N*-acetyl methyl ester of **3** for tosylation were unpromising. Thus dimethyl sulfite (0.13 g, 1.18 mmol) heated with *N*-Ac-3[22] (0.10 g, 0.58 mmol), dry HCl (0.6 g), and MeOH (5 mL) for 20 h gave the *N*-acetyl methyl ester of **3** only in 28% yield. Heating of the *N*-Ac-**3** (0.40 g, 2.31 mmol) with MeOH (5 mL) containing HCl (0.073 g) for 23 h under reflux gave the *N*-acetyl methyl ester of **3** only in 40% yield. In both instances, the ester produced could not be crystallized but had IR and NMR spectra congruent with those of the ester prepared from *N*-Ac-**3** with diazomethane [mp 76–78 °C (lit.[12] mp 78 °C)].

The methyl ester hydrochloride (**6**) of **3** was prepared, in a procedure based on one of Rachele,[16] by heating a solution of 0.50 g (3.81 mmol) of **3** in a mixture of 50 mL of 2,2-dimethoxypropane, 3.8 mL of concentrated HCl, and 4 mL of MeOH under reflux for 2 h. The mixture was allowed to stand at ca. 25 °C for 24 h (considerable darkening) and then was concentrated at 50–60 °C under reduced pressure. The residue was dissolved in 5 mL of MeOH, and 25 mL of Et_2O was added. Crystalline **6** that separated was removed and dried. Recrystallization from MeOH-Et_2O gave **6** as white needles: 0.40 g (58%); constant mp 171–172 °C; IR (KBr) 3400 (s), 3200–2800 (s, br), 2675 (m), 2600 (m), 2550 (m), 2425 (m), 1740 (s), 1580 (s), 1450 (s), 1410 (m), 1380 (m), 1360 (s), 1320 (s), 1310 (s), 1280 (s), 1240 (s), 1220 (s), 1180 (s), 1080 (s), 1060 (m), 1040 (s), 1030 (s), 980, 950 (s), 920 (m), 900 (s), 860 (m), 780, 740, 700 cm^{-1}; NMR (D_2O) δ 4.8–4.5 (m, 2 H), 3.8 (s, 3 H), 3.6–3.4 (m, 2 H), 2.6–2.1 (m, 2 H).

For the synthesis of methyl *N*-acetyl-4(*S*)-mercaptopyrrolidine-2(*S*)-carboxylate (**7**), the tosylate methyl ester **4** (0.50 g, 1.46 mmol) dissolved in MeOH (1.5 mL) was added at ca. 25 °C under Ar during 5 min to an aqueous solution of sodium trithiocarbonate (33%, 2.14 M, 1.4 mL, 3.00 mmol).[17] The solution was stirred for 4 h at ca. 25 °C and then was washed with $CHCl_3$ (2 × 3 mL) to remove unreacted **4** and any dialkylated trithiocarbonate. The aqueous solution was acidified with H_2SO_4 (6 N) to pH 2 and extracted with $CHCl_3$ (6 × 3 mL). The $CHCl_3$ extract was washed with saturated aqueous $NaHCO_3$ (2 × 10 mL) and H_2O (2 × 5 mL) and then was dried. Evaporation of $CHCl_3$ gave **7** as an oil (50 mg, 17%) that showed a positive Ellman test: NMR ($CDCl_3$) δ 4.6–4.2 (m, 1 H), 3.8 (s with a shoulder, 4 H), 3.6–3.3 (m, 2 H), 3.0–2.6 (m, 1 H), 2.1 (s, 3 H), 2.0–1.9 (m, 1 H), 1.9–1.8 (m, 1 H, SH, peak lost with D_2O).

Methyl *N*-Acetyl-4(*S*)-(benzylthio)pyrrolidine-2(*S*)-carboxylate (5). Phenylmethanethiol (7.66 mL, 65.3 mmol) was added dropwise to a solution of 1.50 g (65.2 mmol) of Na in 26 mL of EtOH. A portion of this solution (12.13 mL, 23.5 mmol) then was added with stirring under Ar during 10 min to **4** (4.00 g, 11.72 mmol) dissolved in EtOH (10 mL). A white solid separated (30 min). The solution was stirred at ca. 25 °C for 20 h. The solid was separated by centrifugation (2.0 g, 88% of $C_7H_7SO_3Na$). The EtOH solution then was evaporated to give an oil. Water was added to this oil, and the suspension was extracted with $CHCl_3$ (5 × 10 mL). The extract then was washed with 5% NaOH (3 × 10 mL) and with H_2O to neutrality. The solution then was dried ($MgSO_4$) and evaporated to an oil. The oil was applied to a silica gel column (200 g, 8 cm in diameter) and was eluted with ca. 450 mL of 50% EtOAc/pentane to remove the first compound, presumably benzyl disulfide (TLC, R_f 0.63, EtOAc). The second compound, **5**, was obtained by elution with 100% EtOAc as a colorless oil that showed only a single spot on TLC (R_f 0.44, EtOAc): 2.36 g (69%); IR (neat) 3650–3200 (m), 3050 (m), 3000 (s), 2950 (s), 2875 (m), 1750–1740 (s), 1660 (s), 1640 (s), 1490 (m), 1450–1400 (s), 1370 (s), 1350 (s), 1250 (s), 1180 (s), 1030 (s), 930 (m), 860, 760, 740 (s), 700 (s) cm^{-1}; NMR ($CDCl_3$) δ 7.25 (s, 5 H), 4.4–4.0 (m, 3 H), 3.7–3.6 (s, with a shoulder, 3 H), 3.4–3.1 (m, 2 H), 2.6–2.3 (m, 1 H), 1.96 (s, 3 H), 1.3–1.1 (m, 2 H).

Anal. Calcd for $C_{15}H_{19}NO_3S$: C, 61.41; H, 6.53; N, 4.78; S, 10.93. Found: C, 61.52; H, 6.69; N, 4.88; S, 10.86.

N-Acetyl-4(*S*)-(benzylthio)pyrrolidine-2(*S*)-carboxylic Acid (8). The *S*-benzyl ester **5** was converted to the acid **8** by dissolving 0.40 g (1.36 mmol) of it in MeOH (1.5 mL), adding 1.37 mL of 1 N aqueous NaOH, and allowing the clear solution to stand

(22) Greenstein, J. P.; Winitz, M. "Chemistry of the Amino Acids"; Wiley: New York, 1961; Vol. 3, pp 2037–2038.
(23) Andreatta, R. H.; Nair, V.; Robertson, A. V.; Simpson, W. R. J. *Aust. J. Chem.* **1967**, *20*, 1493.
(24) Arndt, F. "Organic Syntheses"; Wiley: New York, 1943; Collect. Vol. *II*, p 166, note 3.
(25) Patchett, A. A.; Witkop, B. *J. Am. Chem. Soc.* **1957**, *79*, 185.

at 0 °C for 16 h. The solution then was treated with HCl (1 N, 1.37 mL). MeOH was removed, and the aqueous solution was extracted with $CHCl_3$ (4 × 6 mL). The extract was dried ($MgSO_4$) and evaporated to a semisolid. This semisolid was dissolved in 5% NaOH, washed with CH_2Cl_2, and acidified with 1 N HCl. The white solid **8** was removed by filtration, washed with H_2O, and dried: mp 139–140 °C; 0.35 g (92%). Recrystallization from $CHCl_3$ and Et_2O gave **8** with a TLC R_f of 0.74 (MeOH) and having a constant melting point of 140–141 °C: $[\alpha]^{24}_D$ −45.0° (*c* 1.5, MeOH); IR (KBr) 3600–3300, 3200–2100 (m, br), 1720 (s), 1600 (s), 1590 (s), 1460 (s), 1420 (s), 1360 (m), 1300 (m), 1240 (s), 1210–1200 (m), 1160 (m), 1090, 1070, 1010 (m), 940–920 (m), 890, 780, 740, 720 (s), 680 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.9 (s, 1 H), 7.2 (s, 5 H), 4.4–4.2 (t, 1 H), 3.7 (s with a shoulder, 2 H), 3.6–2.7 (m, 3 H), 2.6–2.2 (m, 1 H), 2.2–1.8 (s with shoulders, 4 H); ^{13}C NMR ($CDCl_3$) δ 172.94, 171.16 (CO_2H, $COCH_3$), 137.84, 128.68, 127.38 (Ph), 58.74, 54.25, 40.81, 36.26, 34.85, 22.01 ($PhCH_2S$, $COCH_3$, four carbons of the proline ring).

Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.02; S, 11.48. Found: C, 60.19; H, 6.24; N, 4.96; S, 11.30.

4(*S*)-(Benzylthio)pyrrolidine-2(*S*)-carboxylic Acid Hydrochloride (12). A solution of **8** (0.40 g, 1.43 mmol) in 3 N HCl (4.5 mL) was heated under reflux for 4 h and then was concentrated to dryness. The residue was dissolved in absolute EtOH, and Et_2O was added. An oil separated from the solution which was shown to be a mixture of the amine hydrochloride **12** and the corresponding ethyl ester by NMR; it showed two spots in TLC. For completion of the hydrolysis, the product again was heated under reflux with 3 N HCl (ca. 1 mL) and H_2O (0.5 mL), and the reaction was monitored by TLC. After 4 h, the solution was concentrated to dryness and kept at ca. 0.1 torr over KOH for 20 h to give the amine hydrochloride **12**: 0.37 g (90%); one spot on TLC, R_f 0.08 (EtOH); mp 94–96 °C; IR (KBr) 3500–3200 (s), 3200–2650 (s), 2550 (s), 2425 (s), 2150–1800 (m), 1720 (s), 1600 (m), 1570 (m), 1480 (m), 1440 (s), 1390 (m), 1350 (m), 1310 (s), 1260 (s), 1210 (s), 1060 (s), 1040–1020 (m), 940 (m), 860, 840, 770, 740 (m), 720 (s), 660 (m) cm^{-1}; ^1H NMR (D_2O) δ 7.4 (s, 5 H), 4.7–4.4 (m, 1 H), 3.9 (s, 2 H), 3.7–3.4 (m, 3 H), 2.9–2.7 (m, 1 H), 2.4–2.2 (m, 1 H); ^{13}C NMR (D_2O) δ 173.36 (CO_2H), 139.61, 130.83, 129.42 (Ph), 61.16, 53.15, 42.26, 37.54, 36.68 (SCH_2 and four carbons in the proline ring); all ^{13}C peaks were single, and there was no indication of the nearby ancillary rotamer peaks seen with the amide **8**.

Anal. Calcd for $C_{12}H_{16}ClNO_2S·0.75H_2O$: C, 50.17; H, 6.14; S, 11.16. Found: C, 50.03; H, 6.28; S, 10.92.

Studies of Derivatives of 4(*S*)-Mercaptopyrrolidine-2-(*S*)-carboxylic Acid (11, 14, and 15). (a) *N*-Acetyl-4(*S*)-mercaptopyrrolidine-2(*S*)-carboxylic Acid (11). The *N*-acetyl *S*-benzyl acid **8** (0.50 g, 1.79 mmol) was added to 50 mL of distilled liquid NH_3 in a flask chilled in dry ice and acetone and equipped with a dry-ice condenser and gas-inlet tube. The mixture was stirred ca. 5 min, and Na (0.17 g, 7.4 mmol) was added portionwise during 2 h. The solution then had attained a faint blue color, which remained for 15 min. Ammonium chloride (0.30 g, 5.61 mmol) then was added slowly, and NH_3 was swept away by using a steady stream of Ar. The white solid residue was rubbed with Et_2O to remove bibenzyl, and the Et_2O solution was decanted. The residue was taken up in 25 mL of MeOH, and dry HCl was passed into the solution until the pH was 1. Precipitated NaCl was separated by centrifugation. Evaporation of the MeOH gave a semisolid which was triturated with $CHCl_3$ (3 × 20 mL). Evaporation of the $CHCl_3$ gave the *N*-acetyl thiol **11** as an oil: 0.15 g (44%); one spot on TLC, R_f 0.68 (MeOH); IR (neat) 3700–3100 (m, br), 3100–2800 (s, br), 2550 (m), 1740 (s), 1660–1600 (s, br), 1440–1400 (s), 1360 (s), 1220–1160 (s, br), 1050 (m), 1030 (s), 1000 (m), 750 (m) cm^{-1}; NMR ($CDCl_3$) δ 4.5–4.2 (m, 1 H), 4.0–3.7 (m, 3 H), 3.5–3.1 (m, 1 H), 2.1 (s with shoulders, 4 H), 1.9–1.8 (d, 1 H, SH, peak lost with D_2O).

(b) Conversion of the Thiols 11 and 15 to the Disulfide 14, 4(*S*),4′(*S*)-Dithiobis[(pyrrolidine)-2(*S*)-carboxylic Acid] Dihydrochloride. The *N*-acetylmercapto acid **11** prepared from Na/NH_3 reduction of **8** (0.50 g, 1.79 mmol) was oxidized in aqueous solution to the disulfide with excess aqueous KI_3. The water solution was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with aqueous sodium thiosulfate and H_2O and dried ($MgSO_4$). Concentration of the $CHCl_3$ solution gave an oil, which was heated under reflux with 3 N HCl (1.3 mL) for 4 h. The solution was concentrated to dryness and kept at 0.1 torr over KOH for 15 h. Compound **14** thus obtained showed a single spot in TLC (0.090 g, 28% from **8**); IR (neat) 3700–3100 (s, br), 3100–2300 (s, br), 1740–1710 (s, br), 1620 (s), 1440–1100 (s, br), 1040 (m), 820 (m), 740 (m) cm^{-1}; ^1H NMR (D_2O δ 4.6–4.4 (m, 1 H), 4.0–3.5 (m, 3 H), 3.0–2.7 (m, 1 H), 2.5–2.2 (m, 1 H); ^{13}C NMR (D_2O) δ 173.41 (CO_2H), 61.60, 53.00, 48.16, 36.19 (four carbons in the ring), no indication of rotameric peaks.

Preparation of the disulfide acid **14** also was achieved by the sequence **12** → **15** → **14**. Thus Na (0.13 g, 5.65 mmol) was added to a solution of the acid **12**·0.75H_2O (0.35 g, 1.22 mmol) in freshly distilled NH_3 (25 mL) during 2 h. The solution was stirred for 1 h more, and NH_3 then was swept away with Ar. The residue was dissolved in 2 mL of MeOH. Methanolic HCl (8 mL, 0.88 M, 7.04 mmol) was added to pH 1 (by moist test paper), and precipitated NaCl was separated by centrifugation. Evaporation of MeOH gave a semisolid. This semisolid was washed once with Et_2O, the residue was dissolved in a minimum of MeOH, and a large amount of Et_2O was added. Precipitated white solid (**15**) was separated by centrifugation and dried: 0.14 g (62%); IR (KBr) 3600–3350 (m), 3300–2900 (s), 2900–2800 (m), 2550 (m), 2100–1900, 1730 (m), 1620–1600 (m), 1400 (s), 1380 (s), 1240 (m), 1210 (m), 1020 cm^{-1}. Compound **15** was quite hygroscopic. Analysis for the thiol content of **15** by the Ellman technique showed 100% of the expected 1 molar equiv; the mercapto acid **15** could be oxidized with excess KI_3 to the disulfide acid **14**; the IR spectrum of this **14** was congruent with that of **14** from the sequence **8** → **11** → **14**, but no attempt was made to purify this **14** further.

Dimethyl 4,4′-Trithiobis(butanesulfinate) (23). Disodium 4,4′-trithiobis(butanesulfinate) (**22**) was prepared from **2** (2.5 g, 16.42 mmol) and $Na_2S·9H_2O$ (1.9 g, 7.91 mmol) essentially as described (but without purification by reprecipitation).[1] The salt **22** was dissolved in 10 mL of MeOH and acidified with MeOH–HCl (0.844 M, 21 mL, 17.7 mmol). The methanolic solution was separated from NaCl (centrifugation) and esterified with an ethereal solution of CH_2N_2 to give a faintly yellow solution. Excess CH_2N_2 was destroyed by adding 2 drops of AcOH. Evaporation of the solvent gave an oily residue, which was taken up in $CHCl_3$, washed once with H_2O, and dried (Na_2SO_4). Evaporation of $CHCl_3$ gave a semisolid, which was chromatographed on 150 g of silica gel in an 8-cm-diameter column by using 50% EtOAc–pentane. The diester **23** (R_f 0.37, 1:1 EtOAc–pentane) was obtained as a colorless oil: 1.7 g (59% based on Na_2S); n^{25}_D 1.5575; IR (neat) 3700–3300, 2950 (s), 1730 (m), 1630–1600, 1440 (s), 1400 (s), 1280 (m), 1230 (m), 1140–1100 (s), 990–970 (s), 750–740 (s), 690–680 (s) cm^{-1};[26] NMR ($CDCl_3$) δ 3.8 (s, 3 H), 3.0–2.6 (m, 4 H), 2.0–1.7 (m, 4 H).

Anal. Calcd for $C_{10}H_{22}O_4S_5$: C, 32.76; H, 6.05; S, 43.73. Found: C, 32.80; H, 6.15; S, 43.85.

Methyl 4-[[*N*-Acetyl-2(*S*)-(methoxycarbonyl)-4(*S*)-pyrrolidinyl]dithio]butanesulfinate (10) and the Corresponding Disodium Salt (9). The *N*-acetyl *S*-benzyl acid **8** (0.41 g, 1.47 mmol) was added to 25 mL of freshly distilled liquid NH_3 in a flask chilled and equipped as before. The mixture was stirred for ca. 15 min, and Na wire (0.1006 g, 4.38 mmol, i.e., 3 equiv) was added in six portions over 2 h. The solution was stirred for 15 min more (remained blue), and NH_3 was swept away with Ar. The residue was dissolved in 5 mL of MeOH. MeOH–HCl (0.738 mL of a 1.99 M solution, 1.47 mmol) was then added to the solution. The disodium salt of **11** (71% SH by Ellman analysis) in MeOH thus remaining was cooled to 0 °C. To this solution was added the dioxide **2** (0.44 g, 2.89 mmol) dissolved in 6 mL of MeOH during 10 min to give the disulfide sulfinate salt **9**. After the addition, a 10-μL sample was tested for SH by Ellman's analysis. There was no absorbance initially, but the typical yellow color developed after 15 min, reflecting a slow reversion of **9** to **2** and the disalt of **11**. The reaction mixture therefore was stirred for only 5 min after addition of **2** had been completed, and Et_2O was added. Precipitated **9** was separated by centrifugation, washed with Me_2CO, and dried. This white solid was dissolved in a minimum of MeOH (3 mL, without removing the residue of NaCl

(26) Reported values for alkyl arenesulfinates are 1153–1099 and 990–889 cm^{-1} (Field, L.; Hoelzel, C. B.; Locke, J. M. *J. Am. Chem. Soc.* **1962**, *84*, 847).

from the acidification) and acidified to pH 1 by using MeOH–HCl (2 mL of a 1.99 M solution, 3.98 mmol). This solution was treated with an excess of an ethereal solution of CH_2N_2. Excess CH_2N_2 was destroyed by using AcOH. The NaCl produced by the two treatments with HCl was then separated by centrifugation. Evaporation of the solvent gave a semisolid, which was taken up in $CHCl_3$, washed once with H_2O, and dried (Na_2SO_4). $CHCl_3$ was evaporated to leave an oil (0.56 g, 103%). The oil (0.15 g) was applied to a preparative thin-layer plate by using $CHCl_3$, and the plate was developed with 4:1 EtOAc–Me_2CO. Extraction of the band with R_f 0.29 yielded 50 mg (34% based on **8**) of **10** as an oil: $[\alpha]^{26}_D$ +4.4° (*c* 1.9, MeOH); IR (neat) 3700–3300 (m), 3050–2800 (m), 1740–1730 (s), 1640 (s), 1420–1400 (s), 1350, 1260, 1190 (s), 1170, 1110 (s), 1020, 990–970 (s), 860 (m), 830, 740 (s), 700–680 cm^{-1};[26] NMR ($CDCl_3$) δ 4.4–4.1 (m, 1 H), 4.0–3.8 (m, 1 H), 3.7 (s with a shoulder, 7 H), 3.5–3.1 (m, 2 H), 2.8–2.3 (m, 5 H), 2.0 (s, 3 H), 1.9–1.5 (m, 4 H).

Anal. Calcd for $C_{13}H_{23}NO_5S_3$: C, 42.25; H, 6.27; N, 3.79; S, 26.03. Found: C, 42.44; H, 6.33; N, 3.71; S, 25.67.

On the larger scale of 4.0 g of **8**, the overall yield of **10** was 2.0 g (38%); this **10** had IR and NMR spectra congruent with the analytical sample. The sulfinate ester **10** showed no change by TLC after at least 2 weeks in a stoppered container under ambient conditions. Only after 7 h in refluxing EtOAc (1.5 mL) did 20 mg of **10** first show a change on TLC from the original single spot (R_f 0.14, EtOAc) to three spots (R_f 0.04, 0.14, and 0.19).

Methyl *N*-Acetyl-4(*S*)-(*p*-toluenesulfonyloxy)-pyrrolidine-2(*S*)-carboxylate (17). *N*-Acetyl-4(*S*)-hydroxypyrrolidine-2(*S*)-carboxylic acid (**16**, "*N*-acetyl-*cis*-4-hydroxy-L-proline", "N-acetylallohydroxy-L-proline") was prepared from compound **4** in a yield of 32% from **4** essentially as described:[12] mp 144–145 °C (lit.[12] mp 144–145 °C). The acid **16** (0.20 g, 1.15 mmol) was dissolved in 5 mL of 4:1 dioxane–MeOH and treated with an excess of an ethereal solution of CH_2N_2. Excess CH_2N_2 was destroyed by using AcOH. The mixture then was evaporated to dryness in vacuo. Traces of dioxane were removed completely by drying in a desiccator over P_2O_5. The oily methyl ester of **16** obtained could not be crystallized; hence, a 0.30-g (1.60 mmol) sample was dissolved in dry pyridine, the solution was cooled to 0 °C, and *p*-toluenesulfonyl chloride (0.33 g, 1.73 mmol) in pyridine (1.1 mL) was added. The solution was kept at 0 °C for 3 days. HCl (2 M, 9.8 mL) then was added, and the solution was cooled to 0 °C. The **17** that precipitated was separated, dried (0.31 g, 79% from **16**), and recrystallized from EtOAc–Et_2O: constant mp 142–143 °C; $[\alpha]^{24}_D$ –33.6° (*c* 1.6, MeOH); IR (KBr) 3400 (m), 3000 (m), 2950 (m), 2875 (m), 1740 (s), 1640–1620 (s), 1590 (s), 1460 (s), 1430 (s), 1410 (s, d), 1360 (s), 1340 (s), 1290 (m), 1210 (s), 1180 (s), 1170–1160 (s), 1090 (s), 1040 (s), 1010 (m), 980 (m), 970 (s), 960 (s), 900 (s), 860 (m), 840 (s), 810 (m), 760, 700 (s), 650 (m) cm^{-1}; NMR ($CDCl_3$) δ 7.8–7.2 (q, a_2b_2, 4 H), 5.2–5.0 (m, 1 H), 4.7–4.4 (m, 1 H), 3.8–3.6 (m, 5 H), 2.7–2.6 (m, 1 H), 2.5 (s, 3 H), 2.4–2.2 (m, 1 H), 2.0 (s with shoulder, 3 H).

Anal. Calcd for $C_{15}H_{19}NO_6S$: C, 52.77; H, 5.61. Found: C, 52.75; H, 5.85.

***N*-Acetyl-4(*R*)-(benzylthio)pyrrolidine-2(*S*)-carboxylic Acid (18).** In the general manner used for **5**, Na (0.25 g, 10.9 mmol) was dissolved in MeOH (5 mL), and phenylmethanethiol (1.29 mL, 11.0 mmol) was added. This solution (2 mL, 3.49 mmol) was added to **17** (0.40 g, 1.17 mmol) dissolved in MeOH (5 mL), and the solution was stirred at ca. 25 °C for 72 h. At this time, the spot corresponding to the starting tosylate **17** had disappeared. Solid was separated, MeOH was evaporated, H_2O was added to the oil, and the suspension was extracted with $CHCl_3$ (3 × 10 mL). The $CHCl_3$ extract was washed with 5% NaOH (2 × 5 mL) and H_2O, dried ($MgSO_4$), and evaporated. The residual oil was applied to ca. 20 g of silica gel in a column 4 cm in diameter and was eluted with 50% EtOAc/pentane. The product, the methyl ester of **18**, was obtained as colorless oil: 0.18 g (52%); TLC R_f 0.33 (1:1 EtOAc/pentane); NMR ($CDCl_3$) δ 7.3 (s, 5 H), 4.6–4.4 (m, 1 H), 3.8–3.6 (m, 6 H), 3.6–3.2 (m, 2 H), 2.3–2.1 (m, 2 H), 2.0 (s, 3 H); the IR spectrum was virtually congruent with that of **5**, except for weaker bands at 1250, 760, and 740 cm^{-1} and for a new band at 810 (w) cm^{-1}.

The methyl ester of **18** was converted to **18**, much as **5** was converted to **8**, by dissolving 0.070 g (0.239 mmol) in MeOH (1 mL) and adding 0.24 mL of 1 N NaOH. The solution was kept at 0 °C for 24 h, acidified with 0.48 mL of 1 N HCl, and kept at 0 °C for 48 h. Precipitated **18** was removed, washed with H_2O, and dried: 0.060 g (90% from the methyl ester); mp 161–162 °C; $[\alpha]^{24}_D$ –26.2° (*c* 1.2, MeOH); the IR spectrum was virtually congruent with that of the diastereomer **8** except for changes in relative intensities of several bands; NMR (MeOH-d_4) δ 7.4–7.2 (s, 5 H), 4.6–4.4 (m, 1 H), 3.9–3.6 (m, 3 H), 3.5–3.2 (MeOH overlapped expected m, 2 H peak), 2.4–2.1 (m, 2 H), 2.0 (s, 3 H).

Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; S, 11.48. Found: C, 60.10; H, 6.24; S, 11.51.

Methyl 4-[[*N*-Acetyl-2(*S*)-(methoxycarbonyl)-4(*R*)-pyrrolidinyl]dithio]butanesulfinate (21) and the Corresponding Disodium Salt (20). The *N*-acetyl *S*-benzyl acid **18** was converted to the disodium salt (**20**) and diester (**21**) of the sulfinate–disulfide exactly as described for the conversion of the epimeric **8** to the disalt **9** and diester **10**, except for quantities of reagents. Thus **18** (0.30 g, 1.07 mmol) reduced with 0.074 g (3.22 mmol, 3.00 equiv) of sodium in liquid NH_3 (30 mL) gave residue which was dissolved in 4 mL of MeOH. Addition of MeOH–HCl (1.1 mL of a 0.97 M solution, 1.07 mmol) then gave the disodium salt **19** (65% SH by Ellman analysis), which was allowed to react with 0.33 g (2.17 mmol) of **2** in 3.9 mL of MeOH. As with **9**, a 10-μL sample then produced no absorbance with Ellman's reagent at first but did so after 15 min (about the time frame seen with **9**). Precipitation 5 min after the addition by using Et_2O, acidification of the resulting **20** in 3 mL of MeOH with 3 mL of 0.97 M MeOH–HCl (2.9 equiv), and esterification with excess CH_2N_2 gave 0.40 g (101%) of crude **21**. Preparative TLC of 0.25 g of this oil, with development with EtOAc, gave **21** as a colorless viscous oil: 70 mg (28% of **21** based on **18**); R_f 0.26 (EtOAc); $[\alpha]^{24}_D$ –31.2° (*c* 1.3, MeOH); NMR ($CDCl_3$) δ 4.8–4.4 (m, 1 H), 4.2–3.9 (m, 1 H), 3.9–3.7 (m, 7 H), 3.7–3.4 (m, 2 H), 2.9–2.6 (m, 3 H), 2.5–2.2 (m, 2 H), 2.1–2.0 (s with shoulder, 4 H), 1.9–1.7 (m, 3 H); the IR spectrum of **21** was congruent with that of **10**, except for much weaker bands at 860 and 740 cm^{-1} for **21**.[26]

Anal. Calcd for $C_{13}H_{23}NO_5S_3$: C, 42.25; H, 6.27; N, 3.79; S, 26.03. Found: C, 42.37; H, 6.38; N, 3.81; S, 25.80.

In a large-scale preparation of **21** from **18** (3.29 g, 11.8 mmol), the overall yield of **21** was 2.0 g (46%; identical in spectra and TLC with the above **21**). Under the conditions given for **10**, TLC showed no change of the **21** under ambient conditions after at least 2 weeks; in refluxing EtOAc (2 mL), **21** (40 mg) showed a change from a single TLC spot (R_f 0.28, EtOAc) to three spots (including R_f 0.28) after only 1.5 h.

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Registry No. **2**, 18321-15-8; **3**, 51-35-4; **3** *N*-acetyl, 33996-33-7; **3** *N*-acetyl methyl ester, 67943-19-5; **4**, 57750-51-3; **5**, 78854-22-5; **6**, 40216-83-9; **7**, 78804-92-9; **8**, 78854-23-6; **9**, 78804-93-0; **10**, 78804-94-1; **11**, 78854-24-7; **11**·2Na, 78854-25-8; **12**, 78854-26-9; **14**, 78804-95-2; **15**, 78854-27-0; **16**, 66267-44-5; **16** methyl ester, 78804-96-3; **17**, 78804-97-4; **18**, 78854-28-1; **18** methyl ester, 78854-29-2; **19**, 78854-30-5; **20**, 78804-98-5; **21**, 78804-99-6; **22**, 56527-86-7; **23**, 78805-00-2; phenylmethanethiol, 100-53-8.