4-Amino-4,5-dihydrothiophene-2-carboxylic Acid

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Received August 7, 1984

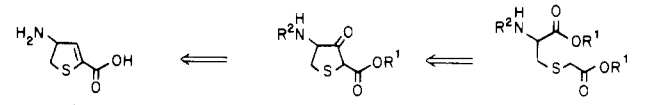
The synthesis of 4-amino-4,5-dihydrothiophene-2-carboxylic acid (1), a compound designed to function as a mechanism-based inhibitor of GABA-T, is described. The key intermediate for the synthesis of racemic 1, as well as the C3-substituted analogues of (*R,S*)-1, compound 3, is prepared by a Dieckmann cyclization of (*R,S*)-*N*-(*tert*-butoxycarbonyl)-*S*-(carbethoxymethyl)cysteine, ethyl ester (2). Reduction of the β-keto ester 3 with $NaBH_4$ produces the β-hydroxy ester, 5, which is dehydrated with $MsCl/Et_3N$ to afford the 4,5-dihydrothiophene, 6. Subsequent removal of the protecting groups yields racemic 1. When optically active 2 was employed, this sequence afforded 1 of varying optical purity. The β-keto ester 3 was shown to be extremely configurationally labile, and its isolation without racemization could not be accomplished. Optically pure 1 (>99% ee) is obtained by performing the Dieckmann cyclization on the N-silylated derivative of 2, compound 20. The reaction of 20 with LDA in THF at −65 °C proceeds via an intramolecular silyl transfer to afford the acetal 22 without any apparent racemization. The judicious choice of desilylation and borohydride reduction conditions allows for the efficient conversion of 22 to 5 without racemization. The conversion of compound 5 generated in this fashion to enantiomerically pure 1 is accomplished in the same manner as that described for the synthesis of racemic 1.

The inhibitory neurotransmitter γ-aminobutyric acid (GABA) is believed to play an important role in the regulation of human brain physiology. Compounds capable of raising brain GABA levels by inhibiting the biosynthetic enzyme GABA transaminase (GABA-T)[1] may prove to be of therapeutic utility and are currently under clinical investigation.[2] This paper details the synthesis of 4-amino-4,5-dihydrothiophene-2-carboxylic acid (1), a compound designed to act as a mechanism-based, irreversible inhibitor of GABA-T.[3]

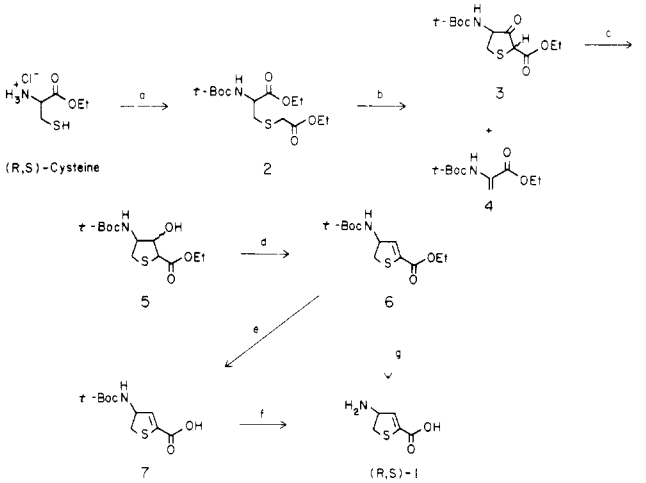
As GABA-T has been shown to abstract only the 4-*pro*-*S*-hydrogen from the substrate GABA,[4] we were interested in the possibility of developing a synthesis of each of the enantiomers of 1 in order to investigate the question of selective inhibition. A retrosynthetic analysis incorporating this consideration (Scheme I) led us to consider cysteine as our starting material. The conversion of the β-keto ester to the α,β-unsaturated acid 1 appeared straightforward. Likewise, there was ample precedent suggesting the practicality of the envisioned Dieckmann cyclization.[5] Before discussing a synthesis of 1 in chiral form, the application of this strategy to a synthesis of racemic 1 and some of its C3-substituted analogues will be outlined.

Synthesis of Racemic 1. The required substrate for the Dieckmann cyclization, (*R,S*)-2, was prepared in a single flask by successive reaction of a solution of (*R,S*)-cysteine ethyl ester with di-*tert*-butyldicarbonate and ethyl bromoacetate, employing triethylamine as base. Cyclization to the β-keto ester 3 was readily effected by addition of 2 to a solution of sodium ethoxide in THF. Compound 3 was obtained following chromatography in

Scheme I



Scheme II[a]



[a] Reagents: (a) $O[CO_2C(CH_3)_3]_2$, Et_3N followed by $BrCH_2CO_2Et$; (b) NaOEt/THF; (c) $NaBH_4$/EtOH; (d) MsCl, Et_3N; (e) LiOH/EtOH; (f) HCl/EtOAc, ion exchange chromatography; (g) TMSI/$CHCl_3$ followed by LiOH/EtOH and ion exchange chromatography.

80–85% yield as a 6/4 mixture of C2 diastereomers. The dehydroamino ester 4 which arises by β-elimination of ethyl 2-mercaptoacetate from the undesired enolate was also isolated in 15% yield (Scheme II). The NMR and IR spectra of 3, as expected for a 5-membered ring, β-keto ester,[6] do not indicate an appreciable amount of enolic material. Reduction of 3 with sodium borohydride gave a mixture of alcohols 5 which was routinely not purified but instead converted to the dihydrothiophene 6 by treatment with mesyl chloride and excess triethylamine. Two different procedures were developed to provide the target compound 1 from 6. Basic hydrolysis of the ester

(1) M. J. Jung, B. Lippert, B. W. Metcalf, P. Bohlen, and P. J. Schechter, *J. Neurochem.*, *29*, 797–802 (1977).

(2) P. J. Schechter, N. F. J. Henkar, J. Grove, N. Harebert, and A. Sjoerdsma, *Neurology*, **34**, 182 (1984); G. P. Tell, P. J. Schechter, J. Koch-Weser, P. Cantinaux, J.-P. Chabannes, and P. A. Lambert, *N. Engl. J. Med.*, **305**, 581–582 (1981).

(3) R. R. Rando, *Biochemistry*, **16**, 4604–4610 (1977); B. W. Metcalf and M. J. Jung, *Mol. Pharmacol.*, **16**, 539–545 (1979); J. P. Burkhart, G. W. Holbert, and B. W. Metcalf, *Tetrahedron Lett.*, 5267 (1984).

(4) M. Bouclier, M. J. Jung, and B. Lippert, *Eur. J. Biochem.*, **98**, 363–368 (1979); G. Burnett, C. Walsh, K. Yonaha, S. Toyama, and S. Soda, *J. Chem. Soc., Chem. Commun.*, 826–828 (1979).

(5) R. B. Woodward and R. H. Eastman, *J. Am. Chem. Soc.*, **68**, 2228(1946). See also J. P. Schaefer and J. J. Bloomfield, Org. *React.* **15**, (1967).

(6) N. J. Leonard, H. S. Gutowsky, W. J. Middleton, and E. M. Peterson, *J. Am. Chem. Soc.* **74**, 4070 (1952).

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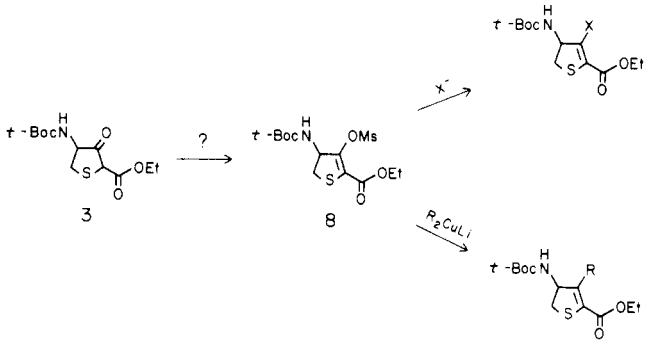
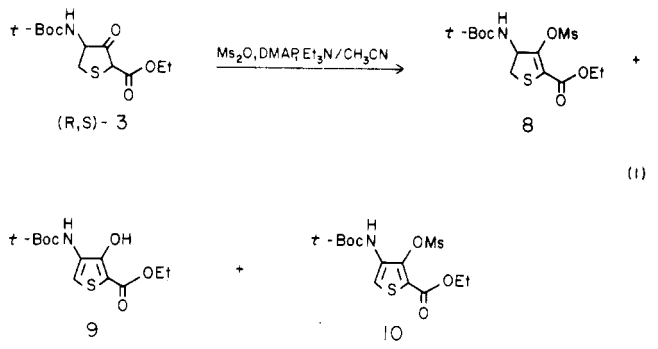
Scheme III



followed by treatment of the isolated acid **7** in ethyl acetate with dry HCl produced the amino acid hydrochloride of **1** along with a 20–30% yield of 2-thiophenecarboxylic acid. Alternatively, the *t*-Boc group of **6** could be removed selectively by using trimethylsilyl iodide, and the resulting amino ester saponified to afford **1**. In both cases analytically pure (*R,S*)-**1** was isolated following ion-exchange chromatography. The former method proceeds in 35–50% from **6**, while the latter method produces **1** in 65–75% yield. The improved yield using trimethylsilyl iodide reflects the smaller amount (<5%) of aromatized side product.

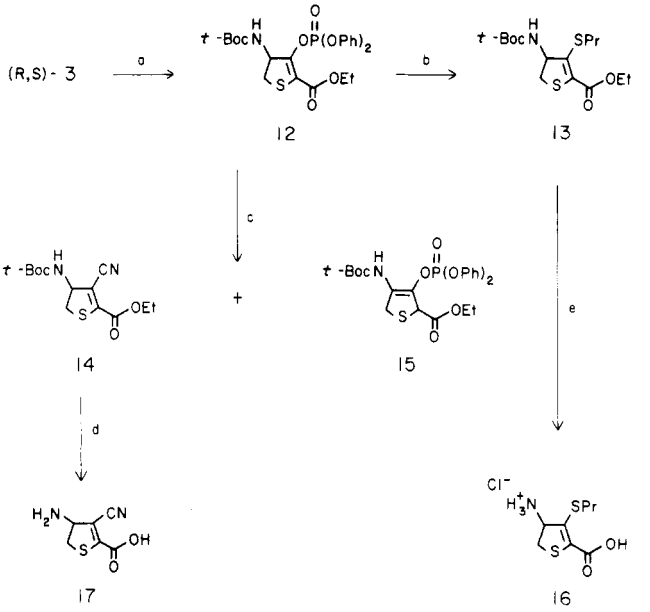
Synthesis of C3-Substituted Analogues of (*R,S*)-1. We next investigated the synthesis of C3-substituted analogues of the dihydrothiophene **1** using (*R,S*)-**3** as our starting material. Since we were interested in compounds containing a halogen or an alkyl group at C3, an intermediate which allowed for the synthesis of both was desired. We felt that the enoate mesylate **8** might serve this purpose (Scheme III). Kowalski has shown that the reaction of enone mesylates derived from cyclic 1,3-diketones with a variety of nucleophiles leads to β-substituted enones in good yield.[7] The reaction of **3**, employing Kowalski's conditions (MsCl, K_2CO_3, CH_2Cl_2), produced a single mesylate which was identified as the aromatic compound **10**. The desired mesylate **8** was synthesized in low yield along with the aromatic compounds **9** and **10** by conducting the reaction in acetonitrile and employing mesyl anhydride (eq 1). The manner in which the undesired



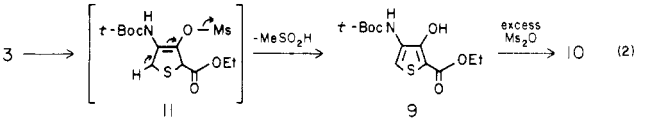
(1)

products **9** and **10** are formed poses an interesting mechanistic question. The aromatic mesylate **10** might arise from **8** by reaction with an additional equivalent of mesylating reagent either at sulfur or nitrogen and subsequent fragmentation. However, the formation of compound **9** suggests that this is not the correct mechanism. In addition, when **6** was treated under similar conditions, no reaction occurred. A more plausible proposal invokes the initial formation of the alternative enol mesylate **11**, followed by a rapid elimination of methanesulfinic acid producing the observed hydroxythiophene **9** (eq 2).

Scheme IV[a]



[a] Reagents: (a) DMAP, Et_3N, diphenyl chlorophosphate/CH_3CN; (b) PrSH, $[(CH_3)_2CH]_2NC_2H_5/CH_3CH$; (c) KCN, 18-crown-6/$CH_3CN$; (d) LiOH/EtOH, HCl/EtOAc, ion exchange chromatography; (e) LiOH/EtOH, HCl/EtOAc.



(2)

Since **8** was not obtained in an acceptable yield, we were encouraged to look for an alternative intermediate which would mimic the chemistry proposed for **8**. Reaction of **3** with tosyl chloride–Et_3N again lead to a mixture of products. However, we were able to obtain an 87% yield of the enoate phosphate **12** upon reaction of **3** with diphenyl chlorophosphate (Scheme IV).[8] All attempts to add halogen nucleophiles (Cl^-, Br^-, I^-) to **12** and **8** under a variety of conditions failed to yield the desired products. The lack of reactivity of **8** and **12** probably reflects the deactivating influence of sulfur in these systems. We did find two reagents which led to the expected products upon reaction with **12**. Propyl mercaptan gave a clean reaction to produce **13** in 82% yield. The reaction of **12** with cyanide ion produced the expected nitrile **14** in 35% yield. Also produced in this latter reaction was the isomeric enol phosphate **15**. Compounds **13** and **14** were converted to the amino acids **16** and **17**, respectively, in a manner similar to that described for **6**.

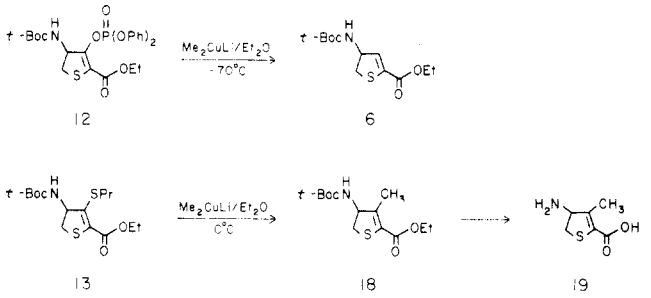
The conversion of enoate phosphates to β-substituted alkyl derivatives using organocuprates has been described by Weiler.[9] The reaction of enoate phosphate **12** with lithium dimethylcuprate occurred rapidly at −70 °C and produced the reduction product **6** containing only 1% of the desired substitution product **18**. This unexpected reduction proved to be only a minor inconvenience since reaction of the sulfide **13** with lithium dimethylcuprate proceeded as expected to afford the methyl-substituted compound **18** (Scheme V).[10] Again conversion of **18** to

(7) C. J. Kowalski and K. W. Fields, *J. Org. Chem.*, **46**, 197 (1981).

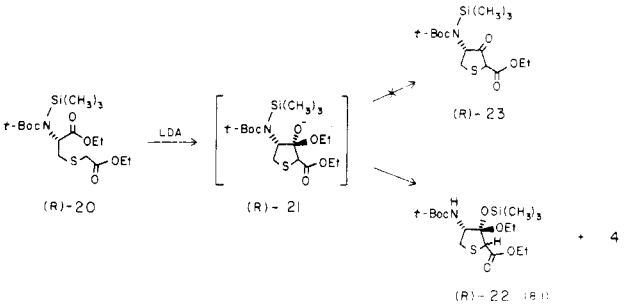
(8) P. A. Bartlett, F. R. Green III, and E. H. Rose, *J. Am. Chem. Soc.*, **100**, 4852 (1978).

(9) F. W. Sum and L. Weiler, *Can. J. Chem.*, **57**, 1431 (1979).

Scheme V

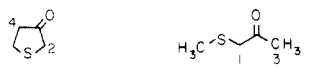


Scheme VI



the amino acid **19** was accomplished in a manner analogous to that described for **6**.

Synthesis of (*R*)- and (*S*)-1. Our original proposal to use the Dieckmann product **3** as a key intermediate in a synthesis of the enantiomers of **1** was based upon its ready availability from (*R*)- and (*S*)-cysteine and its assumed stability. It was expected that enolization of **3** would always occur toward the 2-position which is activated both by sulfur and an ester moiety. However, the mechanism proposed to explain the formation of the aromatic mesylate **10** and the isomerization of the enol phosphate **12** to **15** would argue that enolization is facile toward both carbons 2 and 4. Support for the unusually high kinetic acidity of the proton at C4 in a very similar system has recently been published. Carson examined the rate of proton exchange of 3-thiolanone and found that the pyridine-catalyzed exchange in D_2O/Me_2SO occurred three times more rapidly at C4 than C2. In the acyclic model, 1-thiomethyl-2-propanone, exchange at C3 is 2 orders of magnitude slower than at C1 which exhibits an exchange rate similar to that of 3-thiolanone.[11]



In order to assess the success of our synthetic efforts, it was first necessary to develop a method for determining the optical purity of **1**. Application of the GC method developed to separate the enantiomers of γ-vinyl-GABA[12] or NMR experiments with several chiral shift reagents and (*R,S*)-**6** were not successful. The separation of the enantiomers of **1** on an analytical scale was realized by reaction of racemic **1** with *t*-Boc-L-leucine-*N*-hydroxysuccinimide ester, followed by cleavage of the *t*-Boc group to afford a mixture of diastereomeric dipeptides. These diasteromers were cleanly separated on a reverse-phase C-18 column. Using this method, one can detect as little as 0.2% of an enantiomeric impurity in an essentially optically pure sample of **1**. Since the results obtained by this HPLC method were found to correlate well with optical rotation data, observation of the optical rotations of **6** and **1** was used to guide the synthetic work.

Repetition of the synthetic sequence employed to produce racemic **1** using (*R*)-cysteine ethyl ester afforded a 63/37 (*R/S*) mixture of the enantiomers of **1**. On the basis of the earlier discussion, we felt that racemization must be occurring during the Dieckmann cyclization, most reasonably via the β-keto ester **3**. Another possibility would be racemization of **2** before cyclization. However, anion formation adjacent to nitrogen most reasonably would be expected to lead exclusively to the observed β-elimination product **4**. That readdition of ethyl 2-mercaptoacetate to **4** under the Dieckmann reaction conditions does not lead to **3**, and hence racemization was demonstrated in a separate experiment.

We reasoned that the equilibration of the β-keto ester anion **3** could be significantly suppressed by preforming the anion of **2** at low temperature and conducting the reaction at the minimum temperature necessary for product formation. The presence of the acidic NH dictated the use of **2** equiv of base. To test this, (*R*)-**2** was added to a −70 °C solution containing 2.2 equiv of LDA in THF and the dianion allowed to form for 30 min at this temperature. Examination of a reaction aliquot at this point revealed the presence of starting material and **4** but none of the cyclized compound **3**. Upon slow warming, the desired product **3** was observed to form between −40 and −30 °C. When the reaction was further allowed to warm to −15 °C, cooled back to −50 °C, quenched with acetic acid and the product β-keto ester **3** subsequently converted to **1**, an 85/15 (*R/S*) enantiomer ratio was realized. This result appeared to support the proposition that the dianion of **3** is slow to equilibrate (racemize). Further experimentation revealed little correlation between the type of amine base, the method or temperature at which the reaction was quenched, or the solvent employed in this reaction and the observed optical purity of the final product. Although the optical purity of **1** obtained using LDA as base was as high as 92/8, this result was not reproducible.

Because we suspected that the acidic NH of **2**, which dictated the use of 2 equiv of LDA, was facilitating racemization, a silylation procedure to replace the NH of (*R*)-**2** with a trimethylsilyl moiety [bis(trimethylsilyl)acetamide, 120 °C, 6 h; 95% distilled yield of (*R*)-**20**] was developed. The proof of the site of silylation as nitrogen and not oxygen is based upon the reactions of (*R*)-**20** (vide infra) and not the spectral data which are consistent with either structure. That the conditions of the silylation reaction did not notably affect the optical purity of (*R*)-**20** was demonstrated by comparing the optical rotation of (*R*)-**2** with the compound derived from (*R*)-**20** by hydrolysis. When (*R*)-**20** was added to a −65 °C solution containing 1.1 equiv in LDA in THF, the starting material was rapidly consumed, and upon workup three major products were isolated (Scheme VI). As expected, the elimination product **4** was obtained. However, to our surprise, none of the β-keto ester (*R*)-**3**, which would have arisen from hydrolysis of the expected product (*R*)-**23**, was present. The other two products instead were the diastereomeric acetals (*R*)-**22** (8:1 ratio). The formation of (*R*)-**22** most reasonably results from an intramolecular silylation of the initially formed Dieckmann adduct (*R*)-**21**. For this transfer to be facile, the oxygen to which silicon is transferred and the amine substituent should have a cis relationship. Thus we believe (*R*)-**22** to be epimeric at C2. Substitution of the more hindered base, lithium tetra-

(10) G. H. Posner and D. J. Brunelle, *J. Chem. Soc., Chem. Commun.*, 907 (1973).
(11) J. J. Guth, R. L. Gross, and F. W. Carson, *J. Org. Chem.*, **47**, 2666 (1982).
(12) K. D. Haegele, J. Schoun, R. G. Alken, and N. D. Huebert, *J. Chromatogr.*, **274**, 103 (1983).

methylpiperidide, for LDA did not reduce the amount of elimination product **4**. The diastereomeric acetals **22** appeared to offer an ideal solution for the synthesis of optically active **1**, since the trapping of the tetrahedral adduct prevents ketone formation and, therefore, racemization. The enantiomeric purity of (*R*)-**22** was confirmed by treatment of (*R*)-**22** with an aqueous ethanolic potassium fluoride solution to reverse the Dieckmann cyclization and afford optically pure (*R*)-**2** (determined by optical rotation).

Having obtained the optically active, protected Dieckmann product (*R*)-**22**, we now needed a mild method to convert it to the β-keto ester (*R*)-**3**. The production of the retro-Dieckmann product (*R*)-**2** with potassium fluoride under essentially neutral conditions indicated that slightly acidic conditions would be necessary to encourage the collapse of the tetrahedral adduct in the direction of product. Surprisingly, (*R*)-**22** was very resistant to acid (HCl or acetic acid) cleavage, and conditions which afforded **3** also resulted in partial removal of the *t*-BOC group. Reaction of (*R*)-**22** with HF/CH_3CN yielded **3** and again considerable loss of the *t*-BOC group.[13] Buffering of this reaction with pyridine cleanly afforded **3**, which upon conversion to **1** yielded a 53/47 (*R*/*S*) mixture of enantiomers. Having proved the optical purity of (*R*)-**22**, one must conclude that the β-keto ester is an extremely configurationally labile compound with epimerization occurring at near neutral pH. If so, this result may explain the capricious results of the dianion-initiated Dieckmann reaction and suggests that epimerization during workup could have been a major problem.

We continued to investigate the hydrolysis of (*R*)-**22**, incorporating the following considerations: (1) Carson's work on the kinetic acidity of 3-thiolanone showed pyridine to be a more effective catalyst for proton exchange at C4 than C2, and (2) the lability of **3** suggested that the in situ reduction of **3** to **5** would be desirable. With this in mind, we next examined the desilylation of (*R*)-**22** in ethanol, a solvent compatible with a borohydride reduction. The acetal (R)-**22** was not desilylated at an appreciable rate in a 1 M solution of HF in ethanol. Addition of a solution of tetra-*n*-butylammonium fluoride to this reaction resulted in a rapid conversion to (*R*)-**3**, which was subsequently reduced without isolation to (*R*)-**5** by the addition of sodium borohydride. *The enantiomeric purity of* (*R*)-**1** *produced in this manner was routinely greater than 97%.* In this system HF is used to buffer the basic tetraalkylammonium fluoride solution to pH 5–6. The slightly acidic pH prevents the retro-Dieckmann reaction and provides a nonepimerizing medium for the β-keto ester **3**. The solvent may play an important role in preventing racemization. Acetonitrile (dielectric constant = 36.2)/HF rapidly desilylates **22**, whereas in ethanol (dielectric constant = 24.3)/HF desilylation is very slow. Likewise, the more polar solvent would be expected to facilitate enolization and thus epimerization. If sodium borohydride is added before the tetraalkylammonium fluoride reagent, no reaction occurs. Apparently borohydride anion is preferentially complexed by the alkylammonium ion, and no ionized fluoride is available to desilylate **22**.

Summarizing, the synthesis of both (*R*)-**1** and (*S*)-**1** was realized by employing the HF/tetraalkylammonium fluoride hydrolysis of **22** in ethanol to yield **3** which was reduced in situ to the configurationally stable alcohol **5**. Subsequent mesylation/elimination and base hydrolysis affords the *t*-Boc acid **7** in greater than 97% enantiomeric purity. Because the optical purity of the starting cysteine was not determined, one cannot assess to what extent epimerization occurs during this sequence. *To obtain* **1** *of extremely high enantiomeric purity (99.8% or greater), a single recrystallization of* **7** *was performed. The anhydrous HCl cleavage of the t-Boc group followed by anion exchange chromatography afforded enantiomerically pure* **1**.

Generalization of this silyl-transfer reaction by employing external nucleophiles (RLi, RMgX) may provide a novel solution for the synthesis of optically active amino ketones via the readily available amino acids. The synthesis of this important class of synthetic intermediates has been the subject of several recent publications.[14]

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer. All ^1H NMR (90-MHz) spectra were recorded on a Varian Associates Model EM-390 spectrometer. Chemical shifts are reported as parts per million on the δ scale relative to tetramethylsilane as internal standard. Data are presented as follows: chemical shift (multiplicity, integrated intensity, coupling constants, assignment). Unless otherwise noted, the NMR solvent, was $CDCl_3$. Mass spectra were determined on either a Finnigan 3000 or 4600 mass spectrometer.

Tetrahydrofuran (THF) and ether were dried by distillation from $LiAlH_4$. All other solvents were reagent grade and used without further purification. Chromatography refers to purification by flash chromatography on E. Merck Silica gel 60 (230–400 mesh). The eluting solvents are listed in order of the sequence used to elute the product. Unless otherwise noted, all reactions were run under argon, and all workups culminated in washing the organic layer with water and brine, drying over $MgSO_4$, filtering, and concentrating at reduced pressure.

(*R*,*S*)-*N*-(*tert*-Butoxycarbonyl)-*S*-(carbethoxymethyl)cysteine, Ethyl Ester [(*R*,*S*)-2]. To a stirring, ice-cooled solution of 9.0 g (48.5 mmol) of (*R*,*S*)-cysteine ethyl ether hydrochloride and 11.3 g (51.8 mmol) of di-*tert*-butyl dicarbonate in 85 mL of dry CH_2Cl_2 was added 26 mL (186 mmol) of Et_3N over a 10-min period. The cooling bath was removed, and the solution was stirred for an additional 5 h at 25 °C at which point the reaction was again cooled with an ice bath and 7 mL (59.1 mmol) of ethyl bromoacetate was added. After 30 min the cooling bath was removed and stirring was continued for 1 h at 25 °C. Following the removal of the bulk of the solvent under reduced pressure, the reaction was transferred to a separatory funnel with 100 mL of ether. Upon workup 15.8 g of a yellow oil was obtained. Chromatography (25, 35% EtOAc/hexane) afforded 11.54 g (67% yield) of analytically pure (*R*,*S*)-**2** and 2.64 g (16% yield) of the bis-*t*-Boc cysteine ethyl ester: ^1H NMR δ 1.3 (t, 6 H, 2-CH_2CH_3), 1.45 (s, 9 H, *t*-Bu), 3.05 (dd, 2 H, J = 2 and 6 Hz, H-3), 3.25 (s, 2 H, SCH_2CO_2Et), 4.18 (q, 2 H, CH_2CH_3) and 4.20 (q, 2 H, CH_2CH_3), 4.45 (m, 1 H, H-2), 5.5 (br d, 1 H, NH); IR (film) 3360, 1735, 1710, 1510, 1360, 1150, 1050 cm^{-1}; mass spectrum (CI/CH_4), *m*/*e* (relative intensity) 336 (M + 1, 62), 308 (17), 280 (40), 262 (10), 236 (100). Anal. Calcd for $C_{14}H_{25}NO_6S$: C, 50.13; H, 7.51; N, 4.18; S, 9.56. Found: C, 50.15; H, 7.37; N, 4.06; S, 9.52.

Similar results were obtained with the pure (*R*)- and (*S*)-cysteine derivatives. The optical rotations for these compounds were $[\alpha]^{25}_D$ −31.7° (*c* 1.79, EtOH) for (*R*)-**2** and $[\alpha]^{25}_D$ +31.3° (*c* 1.67, EtOH) for (*S*)-**2**.

(*R*,*S*)-Ethyl 4-[(*tert*-Butoxycarbonyl)amino]tetrahydro-3-oxo-2-thiophenecarboxylate [(*R*,*S*)-3]. To a stirring, oil-free suspension of NaH [prepared from 4.87 g (102 mmol) of 50% NaH in oil by washing with 3 × 20 mL of hexane] in 50 mL of THF was added 6 mL (102 mmol) of anhydrous ethanol. Upon cessation of hydrogen evolution, an additional 400 mL of THF was added

(13) R. F. Newton, D. P. Reynolds, M. A. W. Finch, D. R. Kelly, and S. M. Roberts, *Tetrahedron Lett.*, 3981 (1979).

(14) T. F. Buckley III and H. Rapoport, *J. Am. Chem. Soc.*, **103**, 6157 (1983); C. G. Knudsen and H. Rapoport, *J. Org. Chem.*, **48**, 2260 (1983); D. E. McClure, P. K. Lumma, B. H. Arison, J. H. Jones, and J. J. Baldwin, *ibid.*, **48**, 2675 (1983); D. E. McClure, B. H. Arison, J. H. Jones, and J. J. Baldwin, *ibid.*, **46**, 2431 (1981).

followed by the addition of 34 g (102 mmol) of the diester (*R,S*)-**2** in 50 mL of THF over a 4-min period. Thirty minutes later the reaction was quenched by the addition of 10 mL of acetic acid and extracted in a separatory funnel containing ether and water. Upon completion of the workup, 31 g of a golden oil was obtained. Chromatography (15, 35% EtOAc/hexane) gave 24.7 g (84% yield) of (*R,S*)-**3** (6/4 mixture of diastereomers) and 1.5 g (6.9% yield) of **4**. An analytically pure sample was obtained by heating and stirring **3** at 60 °C and 0.05 torr: NMR δ 1.27 (t, 3 H, CH_2CH_3), 1.44 (s, 9 H, *t*-Bu), 2.6–3.6 (m, 2 H, H-5), 4.08 and 4.10 (s, 1 H, H-2), 4.17 and 4.19 (q, 2 H, CH_2CH_3), 4.5 (m, 1 H, H-4), 5.3 (m, 1 H, NH); IR (thin film) 3360, 1765, 1725, 1510, 1380, 1120 cm^{-1}; mass spectrum (EI/70 eV), *m/e* (relative intensity) 290 (M + 1, 1), 234 (10), 173 (4), 128 (5), 57 (100). Anal. Calcd for $C_{12}H_{19}NO_5S$: C, 49.81; H, 6.62; N, 4.86; S, 11.08. Found: C, 49.75; H, 6.66; N, 5.19; S, 10.81.

(*R,S*)-Ethyl 4-[(*tert*-Butoxycarbonyl)amino]-4,5-dihydro-2-thiophenencarboxylate [(*R,S*)-6]. Into a stirring, ice/methanol cooled solution containing 4.12 g (14.3 mmol) of (*R,S*)-**3** in 40 mL of absolute ethanol was added portionwise 380 mg (10 mmol) of $NaBH_4$. After 35 min the reaction was quenched by the addition of 4 mL of acetone. Following the addition of 0.5 mL of acetic acid, the solvent was removed under pressure and the residue was dissolved in EtOAc, washed with half-saturated brine, 2 × 10 mL of water, and brine, dried, and concentrated to afford 4.2 g of the crude alcohol (*R,S*)-**5**.

To a stirring, ice-cooled solution of the above alcohol (*R,S*)-**5** and 8.1 mL (58 mmol) of Et_3N in 60 mL of CH_2Cl_2 was added 2.25 mL (29 mmol) of mesyl chloride. The cooling bath was removed, and the reaction was allowed to stir for 2.5 h at 25 °C at which point the mixture was diluted with 150 mL of ether and worked up to afford the crude product. Chromatography (15, 20% EtOAc/hexane) yielded 2.51 g (64% yield) of (*R,S*)-**6** as an oil from which 1.77 g of analytically pure material was crystallized by addition of 5 mL of 2% EtOAc/hexane: mp 75–76.5 °C; NMR δ 1.30 (t, 3 H, CH_2CH_3), 1.45 (s, 9 H, *t*-Bu), 3.05 (dd, 1 H, $J_{4,5}$ = 5 Hz and $J_{5,5'}$ = 12 Hz, H-5), 3.55 (dd, 1 H, $J_{4,5'}$ = 8 Hz, H-5′), 4.20 (q, 2 H, CH_2CH_3), 5.0 (m, 2 H, NH and H-4), 6.45 (d, 1 H, J = 3 Hz, H-3); IR (KBr) 3360, 1690, 1605, 1535, 1365, 1250, 1150, 1070 cm^{-1}. Anal. Calcd for $C_{12}H_{19}NO_4S$: C, 52.73; H, 7.01; N, 5.12; S, 11.73. Found: C, 52.55; H, 6.95; N, 5.13; S, 11.82.

(*R,S*)-4-Amino-4,5-dihydro-2-thiophenecarboxylic Acid [(*R,S*)-1]. To an ice-cooled, stirring solution containing 896 mg (3.28 mmol) of (*R,S*)-**6** in 16 mL of $CHCl_3$ was added 0.54 mL (3.6 mmol) of freshly distilled trimethylsilyl iodide (Cu powder). Five minutes after the addition the cooling bath was removed, and 10 min later the reaction was quenched with 0.5 mL of methanol. The reaction was concentrated, and 15 mL of $CHCl_3$ was added. Removal of the solvent afforded 935 mg of a red-orange crystalline solid. To an ice-cooled, stirring solution of this solid in 20 mL of ethanol was added 10 mL of 1 N LiOH. One hour later the reaction was neutralized with 4 mL of 1 N HCl and, after concentration to a volume of 3–5 mL, adjusted to pH 8–9 with 2 N NH_4OH. The solution was then placed on a BioRad AG 50W-X8 ion-exchange column (H^+ form), and the column was eluted with water to remove the impurities. The purified amino acid was eluted with 2 N NH_4OH, and the eluent concentrated to a volume of 3 or 4 mL. After this solution was cooled to 0 °C, the crystallized amino acid was collected by filtration. The solid was washed with ethanol and ether and dried in vacuo at 40–50 °C to yield 317 mg (64% yield) of analytically pure (*R,S*)-**1** as an off-white crystalline solid: mp 200 °C dec; NMR (CF_3CO_2D/$CDCl_3$) δ 3.53 (dd, 1 H, $J_{4,5}$ = 3 Hz and $J_{5,5'}$ = 13 Hz, H-5), 3.85 (dd, 1 H, $J_{4,5'}$ = 8 Hz, H-5′), 4.95 (m, 1 H, H-4), 6.70 (d, 1 H, J = 3 Hz, H-3), 11.3 (s, 3 H, NH_3^+); IR (KBr) 1625, 1580, 1530, 1360, 1310, 790 cm^{-1}. Anal. Calcd for $C_5H_7NO_2S$: C, 41.37; H, 4.86; N, 9.65; S, 22.09. Found: C, 41.31; H, 4.88; N, 9.70; S, 22.03.

Alternatively racemic **1** was prepared in 48% yield from the *t*-Boc ester (*R,S*)-**6** using the procedure described to obtain enantiomerically pure (*R*)-**1**.

(*R,S*)-Ethyl 4-[(*tert*-Butoxycarbonyl)amino]-4,5-dihydro-3-[(methanesulfonyl)oxy]-2-thiophenencarboxylate [(*R,S*)-8]. To a stirring, ice-cooled solution containing 2.03 g (7.0 mmol) of **3**, 105 mg (0.86 mmol) of 4-(dimethylamino)pyridine, and 1.28 g (7.4 mmol) of methanesulfonic anhydride in 15 mL of acetonitrile was added dropwise 1.1 mL (8.0 mmol) of Et_3N. After 1 h the reaction was diluted with ether and worked up to yield 2.4 g of an oil. Chromatography (20, 35% EtOAc/hexane) afforded 400 mg (20% yield) of the 3-hydroxythiophene **9**, 700 mg (27% yield) of the 3-(mesyloxy)thiophene **10**, and 575 mg (23% yield) of the desired product **8** as a white crystalline solid: NMR δ 1.35 (t, 3 H, CH_2CH_3), 1.50 (s, 9 H, *t*-Bu), 2.9–3.6 (m, 2 H, H-5), 3.30 (s, 3 H SO_2CH_3), 4.25 (q, 2 H, CH_2CH_3), 5.25 (m, 2 H, NH and H-4); IR (KBr) 3320, 1720, 1680, 1640, 1515, 1370, 1320 cm^{-1}, mass spectrum (CI/CH_4), *m/e* (relative intensity) 368 (M + 1, 8), 340 (22), 312 (100), 251 (100), 205 (48). A recrystallized sample (EtOAc/hexane) afforded correct elemental analysis; mp 129–130 °C. Anal. Calcd for $C_{13}H_{21}NO_7S_2$: C, 42.49; H, 5.76; N, 3.81. Found: C, 42.32; H, 5.62; N, 3.60.

The side products **9** and **10** were characterized by their NMR and mass spectrum.

9: NMR δ 1.35 (t, 3 H, CH_2CH_3), 1.50 (s, 9 H, *t*-Bu), 4.35 (q, 2 H, CH_2CH_3), 6.75 (s, 1 H, NH), 7.50 (s, 1 H, H-5), 9.6 (br s, 1 H, ROH); mass spectrum (CI/CH_4), *m/e* (relative intensity) 288 (M + 1, 32), 287 (M^+, 41), 260 (50), 232 (100), 214 (66), 186 (100).

10: NMR δ 1.35 (t, 3 H, CH_2CH_3), 1.50 (s, 9 H, *t*-Bu), 3.40 (s, 3 H, SO_2CH_3), 4.25 (q, 2 H, CH_2CH_3), 7.15 (s, 1 H, NH), 7.70 (s, 1 H, H-5); mass spectrum (70 ev), *m/e* (relative intensity) 365 (M^+, 0.7), 309 (1.2), 265 (3.4), 186 (11), 141 (20), 140 (14), 57 (100).

(*R,S*)-Ethyl 4-[(*tert*-Butoxycarbonyl)amino]-4,5-dihydro-3-[(diphenoxyphosphinyl)oxy]-2-thiophenecarboxylate [(*R,S*)-12]. To a stirring, ice/methanol cooled solution containing 24.7 g (85.5 mmol) of (*R,S*)-**3**, 18.2 mL (88.0 mmol) of diphenyl chlorophosphate, and 430 mg (3.5 mmol) of 4-(dimethylamino)pyridine in 300 mL of acetonitrile was added 14 mL (100 mmol) of Et_3N. The cooling bath was then removed, and the reaction was stirred for 1 h at 25 °C. The reaction was diluted with 500 mL of ether and worked up to afford 46.4 g of a brown oil. Chromatography (20, 25, 35% EtOAc/hexane) produced 40.3 g (87% yield) of **12** as a syrup. An analytical sample was prepared by stirring a portion of this material in vacuo at 60 °C for 1 h: NMR δ 1.15 (t, 3 H, CH_2CH_3), 1.35 (s, 9 H, *t*-Bu), 2.95 (dd, 1 H, $J_{4,5}$ = 6 Hz and $J_{5,5'}$ = 12 Hz, H-5), 3.40 (dd, 1 H, $J_{4,5}$ = 9 Hz, H-5′), 5.20 (m, 1 H, H-4), 5.55 (br d, 1 H, J = 11 Hz, NH), 7.20 (s, 10 H, aromatic); IR (thin film) 3330, 1725, 1640, 1600, 1500, 1180, 1060, 970 cm^{-1}. Anal. Calcd for $C_{24}H_{28}NO_8PS$: C, 55.27; H, 5.41. Found: C, 55.25; H, 5.36.

(*R,S*)-Ethyl 4-[(*tert*-Butoxycarbonyl)amino]-4,5-dihydro-3-(propylthio)-2-thiophenecarboxylate [(*R,S*)-13]. To a stirring, ice-cooled solution of 15.6 g (30 mmol) of **12** and 3.0 mL (33 mmol) of propanethiol in 100 mL of acetonitrile was added 6.3 mL (36 mmol) of *N,N*-diisopropylethylamine. One hour later the cooling bath was removed, and the reaction was stirred an additional 6 h at 25 °C. Following dilution of the reaction with 200 mL of ether, workup afforded 13.5 g of a slightly yellow solid. Recrystallization of this solid from 40 mL of methanol gave 3.22 g of an analytically pure sample of **13** as white crystals; mp 93–94 °C. The remaining material was chromatographed (15% EtOAc/hexane) to yield an additional 5.27 g of product (total yield 8.49 g or 82%): NMR δ 1.0 (t, 3 H, $SCH_2CH_2CH_3$), 1.1–1.7 (m, 13 H), 2.7–3.2 (m, 3 H), 3.45 (dd, 1 H, $J_{4,5'}$ = 7 Hz and $J_{5,5'}$ = 12 Hz, H-5′), 4.20 (q, 2 H, OCH_2CH_3), 5.15 (m, 1 H, H-4), 5.5 (d, 1 H, J = 10 Hz, NH); IR (KBr) 3350, 1690, 1675, 1530, 1505, 1250, 1220, 1160 cm^{-1}. Anal. Calcd for $C_{15}H_{25}NO_4S_2$: C, 51.85; H, 7.25; N, 4.03; S, 18.45. Found: C, 51.65; H, 7.22; N, 4.21; S, 18.43.

(*R,S*)-4-Amino-4,5-dihydro-3-(propylthio)-2-thiophenecarboxylic Acid, Hydrochloride [(*R,S*)-16]. Hydrolysis of the ester **13** followed by treatment with dry HCl in a manner analogous to that described for the synthesis of (*R*)-**1** afforded the crude yellowish hydrochloride salt of **16**. The HCl deprotection resulted in no detectable aromatization, and recrystallization from acetone gave analytically pure product as a white crystalline solid: mp 160 °C dec; NMR (CD_3OD/$CDCl_3$) δ 1.05 (t, 3 H, CH_3), 1.70 (sextet, 2 H, CH_2CH_3), 2.95 (m, 2 H, SCH_2), 3.45 (dd, 1 H, $J_{4,5}$ = 8 Hz and $J_{5,5'}$ = 13 Hz, H-5), 3.65 (dd, 1 H, $J_{4,5'}$ = 9 Hz, H-5′), 4.9 (m, 5 H, H-4 and exchangeable H). Anal. Calcd for $C_8H_{14}NO_2S_2Cl$: C, 37.57; H, 5.52; N, 5.48; S, 25.07; Cl, 13.86. Found: C, 37.36; H, 5.43; N, 5.22; S, 25.02; Cl, 13.85.

(*R,S*)-Ethyl 4-[(*tert*-Butoxycarbonyl)amino]-4,5-dihydro-3-cyano-2-thiophenecarboxylate [(*R,S*)-14]. To a stirring, ice-cooled solution containing 20.9 g (40 mmol) of **12**, and 400 mg (1.5 mmol) of 18-crown-6 in 120 mL of acetonitrile was

added 3.9 g (60 mmol) of KCN. The cooling bath was removed, and stirring was continued at 25 °C for 3.5 h, at which point the reaction was diluted with 300 mL of ether, washed 3 times with water and once with brine, dried, and concentrated to yield 14.2 g of a brown oil. Chromatography (15, 20% EtOAc/hexane) afforded 1.9 g (9% yield) of the isomeric phosphate **15** and 4.19 g (35% yield) of **14**. Recrystallization of **14** (EtOAc/hexane) produced 3.44 g of **14** as a white crystalline solid: mp 93–94.5 °C; NMR δ 1.30 (t, 3 H, CH_2CH_3), 1.40 (s, 9 H, *t*-Bu), 3.20 (m, 1 H, H-5), 3.60 (m, 1 H, H-5'), 4.30 (q, 2 H, CH_2CH_3), 5.30 (br s, 2 H, NH and H-4); IR (KBr) 3360, 2210, 1710, 1690, 1585, 1520, 1370, 1250, 1160 cm^{-1}. Anal. Calcd for $C_{13}H_{18}N_2O_4S$: C, 52.33; H, 6.08; N, 9.39; S, 10.75. Found: C, 52.02; H, 6.08; N, 9.12; S, 10.85.

Recrystallization of a portion of **15** produced an analytically pure sample as a white crystalline solid: mp 94–95 °C; NMR δ 1.15 (t, 3 H, CH_2CH_3), 1.40 (s, 9 H, *t*-Bu), 4.15 (m, 4 H, CH_2CH_3 and H-5), 4.60 (m, 1 H, H-2), 6.80 (s, 1 H, NH), 7.20 (m, 10 H, aromatic); IR (KBr) 1740, 1505, 1495, 1280, 1230, 1180, 1110, 1010 cm^{-1}; mass spectrum (CI/CH_4), *m/e* (relative intensity) 550 (M + C_2H_5, 30), 522 (M + 1, 15), 521 (M^+, 28) 494 (20), 466 (100), 422 (100), 251 (60). Anal. Calcd for $C_{24}H_{28}NO_8PS$: C, 55.27; H, 5.41; N, 2.68. Found: C, 55.40; H, 5.44; N, 2.70.

(*R,S*)-4-Amino-4,5-dihydro-3-cyano-2-thiophenecarboxylic Acid [(*R,S*)-17]. Hydrolysis of the ester **14** followed by treatment with dry HCl in a manner analgous to that described for the synthesis of (*R*)-**1** yielded the crude hydrochloride salt of **17** which was purified by ion exchange chromatography to afford the free amino acid: mp 209 °C dec; NMR ($CF_3CO_2D/CDCl_3$) δ 3.70 (m, 2 H, H-5), 5.30 (m, 1 H, H-4); IR (KBr) 2215, 1620, 1575, 1510, 1355, 1310 cm^{-1}. Anal. Calcd for $C_6H_6N_2O_2S$: C, 42.34; H, 3.55; N, 16.46; S, 18.84. Found: C, 41.99; H, 3.59; N, 16.65; S, 18.50.

(*R,S*)-Ethyl 4-[(*tert*-Butoxycarbonyl)amino]-4,5-dihydro-3-methyl-2-thiophenecarboxylate [(*R,S*)-18]. A solution of lithium dimethylcuprate was prepared at 20 °C by addition of 81 mL of 1.7 M MeLi·LiBr in ether (140 mmol) to a mechanically stirring solution containing 14.3 g (70 mmol) of CuBr·SMe_2 and 100 mL each of ether and dimethyl sulfide. This stirring solution was cooled to −10 °C, and 2.45 g (7.06 mmol) of **13** was added in 40 mL of ether, after which cooling was maintained with an ice bath (4–5 °C) for 2.5 h. The reaction was cooled to −5 °C, quenched by the careful addition of 50 mL of saturated aqueous NH_4Cl, and stirred vigorously for an additional 15 min. The resulting solution was diluted with ether, washed twice with aqueous NH_4Cl, dried, and concentrated to afford the crude substitution product. Chromatography (20% EtOAc/hexane) afforded 1.51 g (74% yield) of **18** as a white crystalline solid: mp 69–71 °C; NMR δ 1.30 (t, 3 H, CH_2CH_3), 1.45 (s, 9 H, *t*-Bu), 1.15 (s, 3 H, CH_3 at C-3), (dd, 1 H, $J_{4,5}$ = 5 Hz and $J_{5,5'}$ = 12 Hz, H-5), 3.40 (dd, 1 H, $J_{4,5'}$ = 8 Hz, H-5'), 4.25 (q, 2 H, CH_2CH_3), 5.0 (m, 2 H, NH and H-4); IR (KBr) 3360, 1720, 1690, 1620, 1520, 1370, 1250, 1160 cm^{-1}. Anal. Calcd for $C_{13}H_{21}NO_4S$: C, 54.33; H, 7.37; N, 4.87; S, 11.16. Found: C, 54.26; H, 7.44; N, 4.70; S, 11.11.

Hydrolysis of the ester **18** followed by treatment with dry HCl afforded the crude hydrochloride of **19** which was purified by ion exchange chromatography (see racemic **1** for procedure) to yield the free amino acid: mp 155–159 °C dec; NMR ($CF_3CO_2D/CDCl_3$) δ 2.4 (s, 3 H, CH_3), 3.35 (dd, 1 H, $J_{4,5}$ = 2 Hz and $J_{5,5'}$ = 12 Hz, H-5), 3.75 (dd, 1 H, $J_{4,5'}$ = 8 Hz, H-5'), 4.75 (m, 1 H, H-4); IR (KBr) 1620, 1560, 1545, 1375, 1320, 790 cm^{-1}. Anal. Calcd for $C_6H_9NO_2S$: C, 45.27; H, 5.70; N, 8.80; S, 20.14. Found: C, 44.88; H, 5.83; N, 8.51; S, 20.10.

HPLC Determination of the Optical Purity of 1. To a stirring solution containing 2.9 mg (20 μmol) of **1** and 0.25 mL of 0.5 M sodium bicarbonate was added 13.2 mg (40 μmol) of *N*-*t*-Boc-L-leucine-*N*-hydroxysuccinimide ester in 0.25 mL of THF. After 30 min the mixture was evaporated to dryness under a stream of dry N_2, and the residue was dissolved in 200 μL of trifluoroacetic acid. Ten minutes later the mixture was again concentrated (N_2) and dissolved in 20 mL of the mobile phase [0.05 M phosphate buffer, pH 7/acetonitrile (95/5)] for HPLC analysis.

A 20-μL aliquot of the above mixture of diastereomeric dipeptides was used for the analysis. The sample was analyzed on a Varian Model 5000 LC using a Lichrosorb RP-18 column (25 cm × 4.6 mm) and a flow rate of 1 mL/min. The effluent is monitored with a Vari-Chrom detector at 210 nm. Under these conditions the diastereomeric derivative of the *R* isomer elutes at 6.7 min and that of the *S* isomer at 15.1 min. The relative optical purity of **1** is determined by the peak area ratio of these two peaks. Unreacted L-leucine and **1** as well as any impurities present in **1** all elute before 5 min.

(*R*)-*N*-(*tert*-Butoxycarbonyl)-*N*-(trimethylsilyl)-*S*-(2-carbethoxyethyl)-L-cysteine, Ethyl Ester [(*R*)-20]. A solution containing 83.2 g (248 mmol) of (*R*)-**2**, 150 mL (600 mmol) of bis(trimethylsilyl)acetamide, and 3 mL (24 mmol) of chlorotrimethylsilane was heated and stirred for 8 h at 130 °C. The reaction was then distilled (bulb-to-bulb) at a pressure of 0.05 torr. The 70–80 °C fraction was discarded, and the 130–140 °C fraction was collected to yield 99.6 g (99% yield) of (*R*)-**20** as a clear, colorless oil: NMR (CCl_4, trimethylsilyl peak assigned δ 0.0) δ 0.0 (s, 9 H, trimethylsilyl), 1.05 (t, 3 H, CH_2CH_3), 1.10 (t, 3 H, CH_2CH_3), 1.20 (s, 9 H, *t*-Bu), 2.85 (s, 2 H, SCH_2CO_2Et), 3.00 (d, 2 H, $J_{2,3}$ = 7 Hz, H-3), 3.55 (t, 1 H, H-2), 3.90 (m, 4 H, 2-CH_2CH_3); IR (thin film) 1735, 1690, 1380, 1360, 1300, 1250, 1160 cm^{-1}. Anal. Calcd for $C_{17}H_{33}NO_6SiS$: C, 50.09; H, 8.16; N, 3.43; S, 7.87. Found: C, 49.97; H, 8.00; N, 3.69; S, 8.00.

In a similar manner 12.5 g (37.3 mmol) of (*S*)-**2** was converted to 14.0 g (92% yield) of (*S*)-**20**.

(*R*)-4-[(*tert*-Butoxycarbonyl)amino]-3-ethoxy-3-[(trimethylsilyl)oxy]-2-tetrahydrothiophenecarboxylic Acid, Ethyl Ether [(*R*)-22]. A solution of lithium tetramethylpiperidide [prepared by the addition of 12 mL of 1.58 M *n*-BuLi (19.1 mmol) to an ice/methanol cooled solution containing 3.55 mL (21 mmol) of 2,2,6,6-tetramethylpiperidine in 25 mL of THF] was added dropwise to a stirring, −65 °C solution containing 7.4 g (18.2 mmol) of (*R*)-**20** in 100 mL of THF. Following the additon, the reaction was maintained at −70 °C for 30 min and then allowed to warm slowly to −38 °C at which point the solution was cooled to −60 °C and quenched with 2 mL of acetic acid. The reaction was diluted with ether, washed with water, 0.5 N HCl, and brine, dried, and concentrated to afforded 6.71 g of an oil. Chromatography (5, 10, 20% EtOAc/hexane) yielded 0.66 g (17% yield) of **4**, 3.83 g (52% yield) of the major diastereomer of (*R*)-**22**, and 0.05 g (7% yield) of the minor diastereomer of (*R*)-**22**. The major diastereomer was characterized by the following: $[\alpha]^{25}_D$ −50.3° (*c* 0.55, EtOH); NMR (CCl_4, trimethylsilyl peak assigned δ 0.0) δ 0.0 (s, 9 H, trimethylsilyl), 1.10 (t, 3 H, CH_2CH_3) 1.15 (t, 3 H, CH_2CH_3), 1.30 (s, 9 H, *t*-Bu), 2.55 (dd, 1 H, $J_{5,5'}$ = 12 Hz and $J_{4,5}$ = 2 Hz, H-5), 3.05 (dd, 1 H, $J_{4,5'}$ = 6 Hz, H-5'), 3.45 (q, 2 H, CH_2CH_3 of acetal), 3.75 (s, 1 H, H-2), 3.95 (m, 3 H, H-4 and CH_2CH_3 of ester), 6.6 (d, 1 H, *J* = 12 Hz, NH); IR (thin film) 3360, 1730, 1715, 1515 cm^{-1}. Anal. Calcd for $C_{17}H_{33}NO_6SiS$: C, 50.09; H, 8.16; N, 3.43; S, 7.87. Found: C, 50.14; H, 8.34; N, 3.38; S, 7.83.

In a similar manner 14.0 g (34.4 mmol) of (*S*)-**20** was converted to 7.53 g (54% yield) of the diastereomeric silyl acetals (*S*)-**22**.

(*R*)-4-[(*tert*-Butoxycarbonyl)amino]-4,5-dihydro-2-thiophenecarboxylic Acid, Ethyl Ester [(*R*)-6]. To a stirring, 25 °C solution containing 37.8 g (93 mmol) of the silyl acetal (*R*)-**22** and 470 mL of a 1 M ethanolic HF solution (prepared by mixing 1 part of 48% aqueous HF with 29 parts of absolute EtOH) was added 93 mL of a 1 M solution of tetra-*n*-butylammonium fluoride in THF. After being stirred for 40 min, the solution was cooled with an ice/methanol bath, and 2.6 g (68 mmol) of $NaBH_4$ was added portionwise at such a rate to maintain the reaction below 0 °C. Following the addition the reaction was stirred for an additional 30 min and then quenched by the addition of 50 mL of acetone. One hour later 6 mL of acetic acid was added, and the reaction was concentrated to a volume of approximately 200 mL. At this point 500 mL of EtOAc was added, and the mixture was washed with 250 mL of 1/3 saturated brine, 2 × 50 mL water, and brine, dried, and concentrated to yield 45.8 g of (*R*)-**5** as a brown oil.

Into an ice-cooled, stirring solution containing the crude alcohol (*R*)-**5**, 390 mL of CH_2Cl_2, and 52 mL (372 mmol) of Et_3N was added 14.3 mL (186 mmol) of mesyl chloride. The reaction was stirred an additional 20 min at 0 °C and then 5 h at 25 °C. The mixture was diluted with 1.1 L of ether, washed with 300 mL of H_2O, 70 mL of 0.5 N HCl, and brine, dried, and concentrated to produce 33.6 g of a brown crystalline mass. Chromatography (10, 15, 20% EtOAc/hexanes) afforded 20.6 g (81% yield) of (*R*)-**6**:

mp 89–90.5 °C, $[\alpha]^{25}_D$ −128.1° (c 0.49, EtOH). Anal. Calcd for $C_{12}H_{19}NO_4S$: C, 52.73; H, 7.01; N, 5.12; S, 11.73. Found: C, 52.50; H, 7.08; N, 4.89; S, 11.79.

In a similar experiment (S)-6 was prepared from the silyl acetal (S)-22 in 74% yield: mp 88–90 °C; $[\alpha]^{25}_D$ +122.8° (c 0.50, EtOH).

(R)-4-[(*tert*-Butoxycarbonyl)amino]-4,5-dihydro-2-thiophenecarboxylic Acid [(R)-7]. To a stirring, ice-cooled solution containing 20.5 g (75 mmol) of (R)-6 in 240 mL of EtOH was added 100 mL of 1 N LiOH. After being stirred for 1 h the reaction was neutralized with 10 mL of 6 N HCl and the bulk of the EtOH was removed in vacuo. The mixture was diluted with 250 mL each of EtOAc and ether and 30 mL of 2 N HCl, and the organic phase was washed with 2 × 30 mL water and brine, dried, and concentrated to afford 18.0 g (98% yield) of (R)-7 as a white crystalline solid. This material was shown to be a 98.7/1.3 mixture of R/S isomers. Recrystallization (85 mL of EtOAc/95 mL of hexane) produced 11.24 g of (R)-7 containing no detectable S isomer: mp 147 °C dec; $[\alpha]^{25}_D$ −140.8° (c 0.50, EtOH); NMR δ 1.50 (s, 9 H, *t*-Bu), 3.15 (dd, 1 H, $J_{4,5}$ = 5 Hz and $J_{5,5'}$ = 12 Hz, H-5), 3.65 (dd, 1 H, $J_{4,5'}$ = 12 Hz, H-5'), 5.15 (m, 2 H, H-4 and NH), 6.60 (d, 1 H, $J_{3,4}$ = 3 Hz, H-3), 11.0 (s, 1 H, CO_2H); IR (KBr) 3360, 1700, 1515, 1370, 1250, 1160 cm^{-1}. Anal. Calcd for $C_{10}H_{15}NO_4S$: C, 48.96; H, 6.16; N, 5.71; S, 13.07. Found: C, 48.75; H, 6.16; N, 5.66; S, 12.99.

In a similar experiment (S)-7 was prepared from (S)-6 in 95% yield and shown to be 99.1/0.9 mixture of S/R isomers by HPLC. After recrystallization this sample contained no detectable R isomer: mp 133 °C dec; $[\alpha]^{25}_D$ +141.3° (c 1.05, EtOH). Anal. Calcd: as above. Found: C, 48.84; H, 6.26; N, 5.46; S, 13.10.

(R)-4-Amino-4,5-dihydro-2-thiophenecarboxylic Acid [(R)-1]. Dry HCl gas was bubbled into an ice-cooled, stirring solution containing 11.15 g (45.5 mmol) of the recrystallized acid (R)-7 in 400 mL of EtOAc for 4 min. The cooling bath was removed, and stirring was continued for 2 h at which point the reaction was filtered, and the collected solid was washed with EtOAc and ether to produce 6.4 g of the crude hydrochloride of (R)-1. The filtrate was concentrated to 100 mL in volume and extracted with water, and the aqueous phase was then back-extracted with 3 × 70 mL of ether. The combined organic extracts were dried and concentrated to yield 1.55 (27% yield) of thiophene-2-carboxylic acid. The aqueous wash was combined with the 6.4 g of filtered solid, adjusted to pH 8–9 with NH_4OH, and purified by ion exchange chromatography to afford 4.41 g (63% yield) of analytically pure (R)-1 as a white crystalline solid: mp 202 °C dec; $[\alpha]^{25}_D$ −145.9° (c 0.5, 0.1 N NaOH). HPLC analysis showed no detectable S isomer. Anal. Calcd for $C_5H_7NO_2S$: C, 41.37; H, 4.86; N, 9.65; S, 22.09. Found: C, 41.12; H, 4.86; N, 9.41; S, 22.04.

Employing the same procedure described for the synthesis of (R)-1 with the exception that the product in the filtrate was not recovered, 1.2 g (4.9 mmol) of (S)-7 was converted to 325 mg (46% yield) of (S)-1: mp 203 °C dec; $[\alpha]^{25}_D$ +143.7° (c 0.5, 0.1 N NaOH). HPLC analysis detected 0.2% of the R isomer. Anal. Calcd: as above. Found: C, 41.53; H, 4.86; N, 9.58; S, 22.01.

Acknowledgment. We are indebted to Mr. Edward Huber for providing the optical rotation data and to Mrs. Charlene Mercer for preparing the manuscript.

Synthesis and Reactions of Tetranitroethylene[1]

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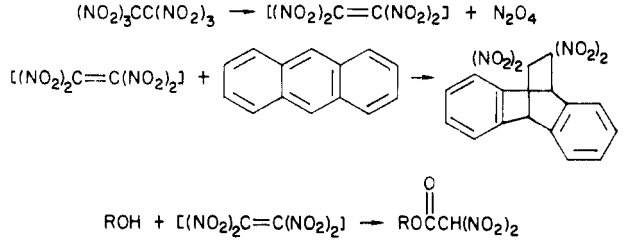
Received December 18, 1984

Tetranitroethylene was isolated in 50% yield by flash vacuum pyrolysis of hexanitroethane. Critical for the isolation is a trap temperature such that dinitrogen tetraoxide is not condensed. Tetranitroethylene reacted quantitatively with anthracene to give 11,11,12,12-tetranitro-9,10-dihydro-9,10-ethanoanthracene, and competition experiments with anthracene showed that tetranitroethylene is at least an order of magnitude more reactive than tetracyanoethylene. Tetranitroethylene reacted with cyclopentadiene to give 5,5,6,6-tetranitronorbornene and with ethanol to give ethyl dinitroacetate. Acetylenes and olefins reacted with tetranitroethylene to give 3-nitroisoxazoles and 3-nitro-2-isoxazolines, respectively.

The isolation of tetranitroethylene, expected to be an exceptionally powerful dienophile and electron acceptor, has not been reported. Previously, we found that heating hexanitroethane in refluxing benzene in the presence of a diene or an anthracene derivative gave the products that would be expected from the Diels–Alder reactions of these compounds with tetranitroethylene.[2] The products were



rationalized on the basis of the extrusion of dinitrogen tetroxide from hexanitroethane to give tetranitroethylene, as an unstable intermediate, which reacts in situ with these reagents. Similarly, heating hexanitroethane with alcohols gave alkyl dinitroacetates,[3] explainable by the addition of the alcohols to tetranitroethylene followed by loss of the labile nitro groups adjacent to the resulting ether.

Thermolysis of this anthracene adduct of tetranitroethylene resulted in another extrusion of dinitrogen tetroxide to give the corresponding *vic*-dinitro olefin,[4] a stable compound, providing additional evidence for the course of the hexanitroethane reactions. Nevertheless, the existence of tetranitroethylene as a discrete intermediate is not proved by this evidence, and mechanisms involving stepwise reactions of hexanitroethane π complexes or pentanitroethyl radicals are not rigorously excluded.

Heating hexanitroethane in the absence of a trapping agent has been reported to give only simple gaseous decomposition products.[5] The reaction of the ambident NO_2

(1) This work was supported by the U.S. Army Research Office.
(2) Griffin, T. S.; Baum, K. *J. Org. Chem.* **1980**, *45*, 2880.
(3) Tzeng, D.; Baum, K. *J. Org. Chem.* **1983**, *48*, 5384.
(4) Baum, K.; Griffin, T. S. *J. Org. Chem.* **1981**, *46*, 4811.

0022-3263/85/1950-2736$01.50/0