6,7-Dichloro-1-(ethoxycarbonyl)-3-(methoxycarbonyl)-4-(2-oxo-2-phenylethyl)-1,4,4a,8a-tetrahydroquinoline (8a): mp 164.4–165.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.36 (t, 3 H, J = 7 Hz), 2.9–3.56 (m, 4 H), 3.71 (s, 3 H), 4.31 (q, 2 H, J = 7 Hz), 4.56 (dd, 1 H, J = 6, 6 Hz), 5.87 (d, 1 H, J = 4 Hz), 6.25 (d, 1 H, J = 6 Hz), 7.3–7.6 (m, 3 H), 7.9–8.03 (m, 2 H), 8.15 (s, 1 H). Anal. Calcd for $C_{22}H_{21}O_5NCl_2$: C, 58.67; H, 4.70; N, 3.11. Found: C, 58.69; H, 4.41; N, 2.85.

6,7-Dichloro-1-(ethoxycarbonyl)-3-(methoxycarbonyl)-4-[2-oxo-2-(*p*-methoxyphenyl)ethyl]-1,4,4a,8a-tetrahydroquinoline (8b): oil; ^{1}H NMR ($CDCl_3$) δ 1.36 (t, 3 H, J = 7 Hz), 2.83–3.50 (m, 4 H), 3.72 (s, 3 H), 3.87 (s, 3 H), 4.28 (q, 2 H, J = 7 Hz), 4.55 (dd, 1 H, J = 5, 5 Hz), 5.86 (d, 1 H, J = 4 Hz), 6.28 (d, 1 H, J = 5 Hz), 6.95 (d, 2 H, J = 9 Hz), 7.96 (d, 2 H, J = 9 Hz), 8.27 (s, 1 H).

6,7-Dichloro-1,3-bis(methoxycarbonyl)-4-(1-methyl-2-oxobutyl)-1,4,4a,8a-tetrahydroquinoline (8e). Diastereomerically pure **4e** (initially eluted isomer) gave a single product with **7**: oil; ^{1}H NMR $CDCl_3$) δ 0.96 (d, 3 H, J = 7 Hz), 1.06 (t, 3 H, J = 7 Hz), 2.35–3.30 (m, 5 H), 3.77 (s, 3 H), 3.88 (s, 3 H), 4.75 (dd, 1 H, J = 7, 4 Hz), 5.82 (d, 1 H, J = 5 Hz), 6.10 (d, 1 H, J = 4 Hz), 8.14 (s, 1 H). Anal. Calcd for $C_{18}H_{21}O_5NCl_2$: C, 53.78; H, 2.98; N, 5.29. Found: C, 53.74; H, 3.48; N, 5.26.

6,7-Dichloro-1,3-bis(methoxycarbonyl)-4-(1-methyl-2-oxo-2-phenylethyl)-1,4,4a,8a-tetrahydroquinoline (8f). Diastereomerically pure **4f** (initially eluted isomer) gave a single product with **7**: oil; ^{1}H NMR ($CDCl_3$) δ 1.06 (d, 3 H, J = 7 Hz), 2.76 (dd, 1 H, J = 7, 7 Hz), 3.20 (dd, 1 H, J = 7, 4 Hz), 3.83 (s, 3 H), 3.88 (s, 3 H), 4.4–4.7 (m, 1 H), 4.85 (dd, 1 H, J = 7, 3 Hz), 5.80 (d, 1 H, J = 6 Hz), 5.86 (d, 1 H, J = 3 Hz), 7.3–7.7 (m, 3 H), 8.0–8.3 (m, 3 H).

6,7-Dichloro-1,3-bis(methoxycarbonyl)-4-(1,1-dimethyl-2-oxopropyl)-1,4,4a,8a-tetrahydroquinoline (8g): oil; ^{1}H NMR ($CDCl_3$) δ 1.13 (s, 6 H), 2.22 (s, 3 H), 3.10–3.31 (m, 2 H), 3.75 (s, 3 H), 3.84 (s, 3 H), 4.40 (dd, 1 H, J = 6, 6 Hz), 5.55 (br s, 1 H), 6.46 (d, 1 H, J = 6 Hz), 8.27 (s, 1 H).

6,7-Dichloro-1-[(dimethylamino)carbonyl]-3-(methoxycarbonyl)-4-(1,1-dimethyl-2-oxopropyl)-1,4,4a,8a-tetrahydroquinoline (8i): oil; ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 3 H), 1.15 (s, 3 H), 2.22 (s, 3 H), 2.92 (s, 6 H), 2.90–3.25 (m, 2 H), 3.71 (s, 3 H), 4.25 (ddd, 1 H, J = 6, 6, 1.5 Hz), 5.70 (dd, 1 H, J = 2, 1.5 Hz), 6.28 (d, 1 H, J = 6 Hz), 7.27 (s, 1 H).

Acknowledgment. We are grateful to Chisso, Ltd. for the gift of silyl chlorides and to the Grant-in-Aid for Special Project Research (59104002) administered by the Japanese Ministry of Education, Science, and Culture.

Supplementary Material Available: IR spectral data for **4a–k,m** and **8a–c,e,i–l** and mass spectral data for **4b–k,m** and **8a–c,e,j–l** (3 pages). Ordering information is given on any current masthead page.

Electrophilic Sulfur Transfer Reactions in Organic Synthesis. Preparation of a Diastereomer of the Key Macrocyclic Component of Griseoviridin

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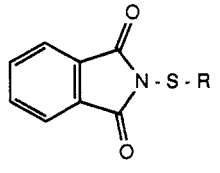
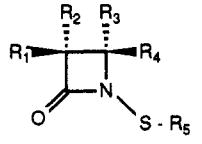
Received July 10, 1986

The utility of electrophilic sulfur transfer reactions was demonstrated by the synthesis of a diastereomer of the key macrocyclic cysteine containing component of griseoviridin. The key step involved direct reaction at the sulfur of *N*-(carbobenzyloxy)-*S*-phthalimido-L-cysteine *tert*-butyl ester with the anion derived from methyl 3-oxa-5(*S*)-[(*tert*-butyldimethylsilyl)oxy]hexanoate.

N-(Alkylthio)- or *N*-(arylthio)phthalimides **1** serves as sulfenyl transfer reagents upon reaction with a variety of heteroatoms[1] and active methylene compounds.[2] We have found this type of electrophilic reaction at sulfur to be especially useful for the preparation of several sulfur-containing molecules of biological interest, including the novel N–S containing β-lactams **2** and **3**.[3] Although related attempts to sulfenylate active methylene compounds often gave mixtures of mono- and bissulfenylated products, we have recently found that anions derived from active methylene compounds **4** react with *S*-phthalimidocysteine derivatives **5** to give the corresponding monosulfenylated products **6** in good yield (eq 1). Since these reactions provide an effective way of transfering an entire cysteine unit to another carbon framework by reaction at sulfur, no racemization of the α-chiral center is expected. This has encouraged us to study the utility of cysteine-based sulfur transfer reactions for the synthesis of other biologically interesting molecules. Herein we report on the successful use of a cysteine-based electrophilic sulfur transfer reaction as the key step in the synthesis of a diastereomer of a primary component (**7**) of griseoviridin (**8**).



1



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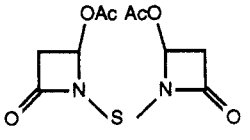

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†Undergraduate research participant.

‡Recipient of an NIH Research Career Development Award, 1983–1988.

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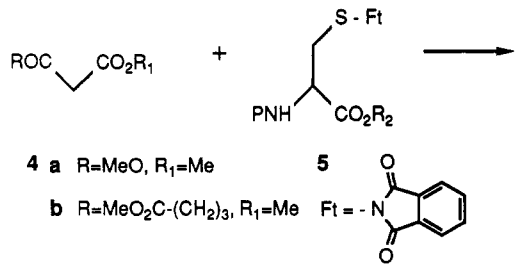
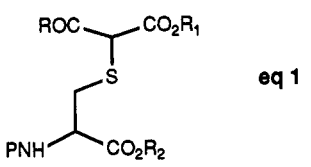


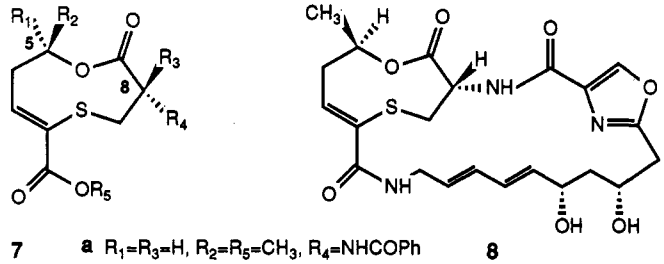
4 **a** R=MeO, R_1=Me **5**

b R=MeO_2C-$(CH_2)_3$, R_1=Me Ft = -



eq 1

6 R_2=tBu, P=Cbz



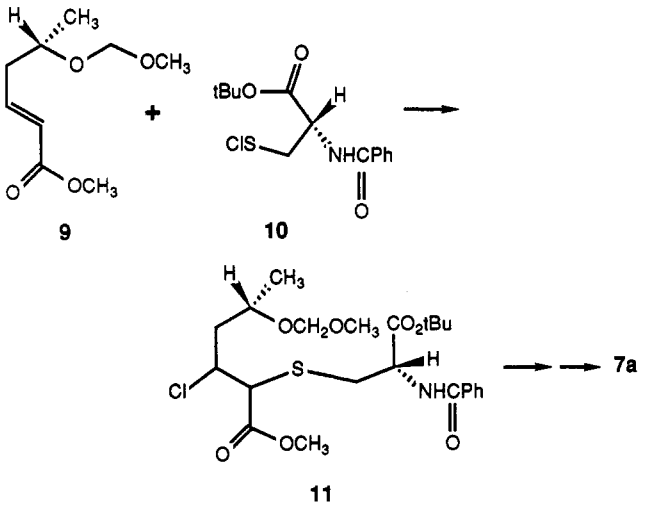
7 **a** R_1=R_3=H, R_2=R_5=CH_3, R_4=NHCOPh **8**

b R_1=R_3=H, R_2=R_5=CH_3, R_4=$NHCO_2CH_2Ph$

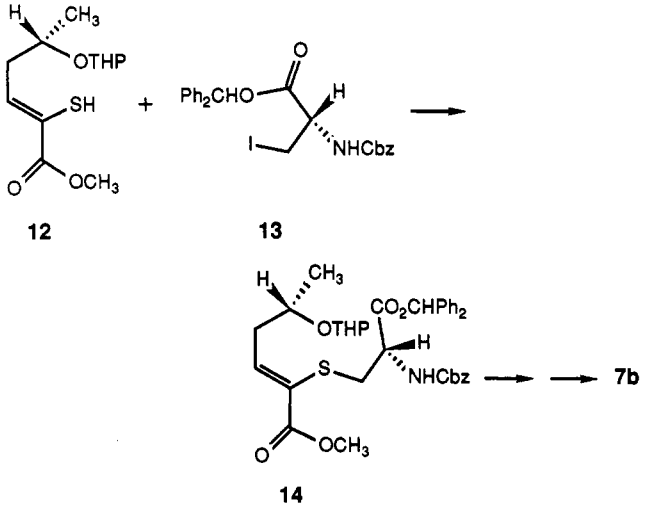
c R_1=R_4=H, R_2=R_5=CH_3, R_3=$NHCO_2CH_2Ph$

Griseoviridin (**8**),[4,5] one of the active compounds in the streptogramin family of antibiotics, has been the subject of synthetic and biological studies for several years. The nine-membered ring heterocyclic component **7** has been previously prepared by two different approaches. Meyers first reported an enantio- and stereospecific synthesis of **7a**, and other optical isomers, which involved an electrophilic addition of sulfenyl chloride **10** to α,β-unsaturated ester **9** (Scheme I).[6] Helquist demonstrated the utility of a nucleophilic reaction of a novel enethiol **12** with a β-iodoalanine derivative **13** for the formation of the cysteine adduct **14** that was subsequently converted to **7b** (Scheme II).[7] Since our approach was to use an intact cysteine residue, we realized that of the two chiral centers in **7**, only the one involved in the lactone linkage would be of concern during the synthesis. Simply starting with the correct optical isomer of cysteine and retaining the configuration throughout would allow control of the second chiral center. Although the cysteine component of griseoviridin is derived from D-cysteine, we decided to start with L-cysteine and maintain the same configuration throughout to prepare **7c**, a diastereomer of **7b**, for potential structure–activity studies. Thus, the basic plan (Scheme III) involved preparation of an optically active β-keto ester **15** and a *S*-phthalimido-L-cysteine derivative **16**, condensation to provide **17**, and eventual elaboration to **7c** by retention of configuration in the cysteine portion and inversion of the remaining chiral center during lactonization.

Scheme I



Scheme II



Results and Discussion

Synthesis of a form of the optically active β-keto ester **15** was readily accomplished by the route shown in Scheme IV. Thus, ethyl acetoacetate was first reduced with bakers' yeast to afford the chiral alcohol **19**[8] in 72% yield (85% ee). Although not optically pure, **19** was enriched enough to eventually allow formation and isolation of the single diastereomer of **7c**. The hydroxy group of **19** was initially protected by conversion to the THP ether **20a** in 97% yield.[9] Saponification then provided the acid **21a** in 60% yield. Subjection of **21a** to the Masamune–Brooks reaction [CDI, $(CH_3O_2CCH_2CO_2^-)_2Mg$][10] gave the desired β-keto ester **15a** in 82% yield.

S-Phthalimidocysteine methyl ester derivative **16a** was prepared by the short sequence shown in Scheme V. Thus, L-cystine (**22**) was first converted to the dimethyl ester **23a**, N-protected with Cbz groups to give **24a** (92% yield),[11a] which was then treated sequentially with sulfuryl chloride and potassium phthalimide to provide **16a** in 61% yield.[12-14]

(4) For the isolation and structural studies of griseoviridin, see: (a) Ehrlich, J.; Coffey, G. L.; Fisher, M. W.; Galbraith, M. M.; Knudsen, M. P.; Sarber, R. W.; Schlingman, A. S.; Smith, R. M.; Weston, J. K. *Antibiot. Ann.* **1954–1955**, 790. (b) Birnbaum, G. I.; Hall, S. R. *J. Am. Chem. Soc.* **1976**, *98*, 1926. (c) Bycroft, B. W.; King, T. J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1996.

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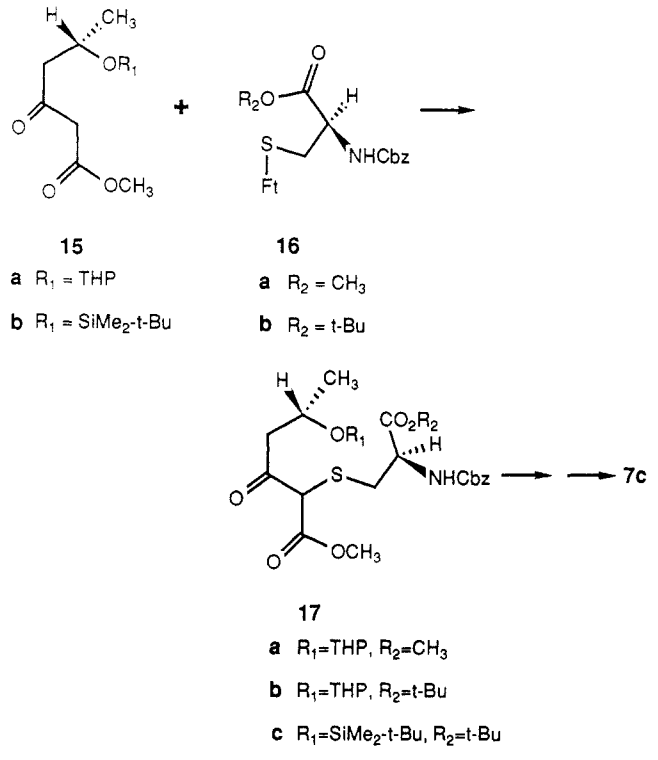
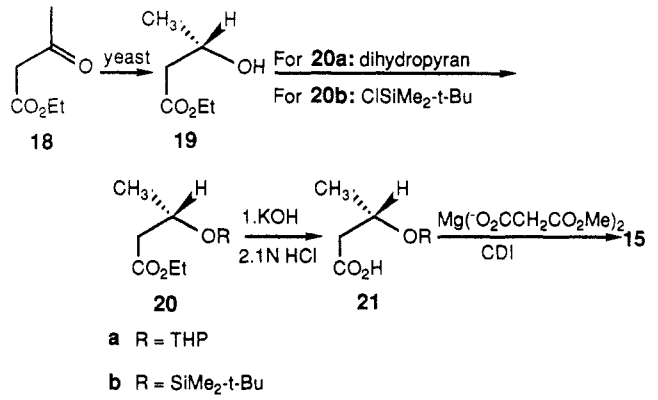
Scheme III



Scheme IV



The key step, which involved condensation of the protected cysteine derivative **16a** and protected β-keto ester **15a** (Scheme III), was accomplished by treating **15a** with sodium hydride and reacting the resulting anion with **16a** in THF for 15 min. The desired product (**17a**) was obtained in 61% yield. No bissulfenylation product was isolated. This successful initial result encouraged us to attempt conversion of **17a**, and variously protected derivatives, to our ultimate target **7c**. Toward this end, two strategies were tested (Scheme VI). The first involved deprotection of **17a**, cyclization of the resulting hydroxy acid **25b** to the lactone **26**, reduction of the keto group, and subsequent dehydration to the desired α,β-unsaturated ester **7**. The second approach involved the same transformations, but in different order (reduction and dehydration followed by hydroxyl deprotection and cyclization).

In the first approach, all attempts to selectively hydrolyze dimethyl ester **17a** to the monoacid **25** failed. However, the differentially protected **17b**, prepared from cystine *tert*-butyl ester by the procedure outlined in Scheme V, was readily converted to **25b** by a simple treatment with moist trifluoroacetic acid, which removed both the *tert*-butyl ester and the THP ether. Several attempts were made to cyclize the hydroxy acid **25b**. Separate reactions with 2,2'-dipyridyl and with DCC/4-(dimethylamino)-pyridine/4-(dimethylamino)pyridine hydrochloride,[16] conditions known to give retention of configuration at the carbinol centers during lactonizations, failed. Use of the Mitsunobu reaction (diethyl azodicarboxylate/triphenylphosphine),[17] which proceeds by hydroxyl activation and therefore inversion at the carbinol center during lactonization, also provided a complex mixture. Since it was possible that the highly acidic methine proton of the β-keto ester portion of **25b** was interfering with these attempted lactonizations, we decided to pursue the alternative sequence of reactions (**17** → **27** → **28** → **7c**, Scheme VI).

In this second approach, β-keto ester **17a** was first reduced with sodium cyanoborohydride to produce the mixture of diastereomeric alcohols **27a**. Attempted dehydration of **27a** by treatment with methanesulfonyl chloride and triethylamine gave a complex mixture of elimination products including compunds with and without the THP ether protecting group on the other secondary alcohol. This problem was circumvented by repeating the synthesis of **17** using a *tert*-butyldimethylsilyl protecting group on the secondary alcohol generated during the original yeast reduction (Schemes IV and III). It should be noted here that chromatographic purification of **17c** removed traces of the other diastereomeric form originally present from the nonenantiospecific yeast reduction to the original β-hydroxy ester **19**. Subsequent reduction of the appropriately protected compound (**17c**) with sodium borohydride afforded a mixture of the desired diastereomeric alcohols **27b** in 58% yield. Although both diastereomers were chromatographically separable, such separation was not necessary since dehydration of either of the separated diastereomers or mixtures of the diastereomers proceeded efficiently. For example, treatment of the diastereomeric mixture **27b** with methanesulfonyl chloride and triethylamine gave the *Z* olefin **28b** exclusively in 73% yield. The TBDMS and *tert*-butyl protecting groups of **28b** were then successively removed by mild acidic hydrolysis[18] to afford **28c** (84% yield) and treatment with anhydrous trifluoroacetic acid provided the penultimate product **28d** (93% yield). Finally, subjection of hydroxy acid **28d** to the Mitsunobu conditions (DEAD/TPP) provided the desired macrocyclic lactone **7c** in 39% yield. Since the Mitsunobu reaction proceeds by inversion of configuration at the carbinol center, this reaction produced the desired diastereomer **7c** (5*R*,8*R*). Comparison of the 300-MHz NMR spectrum of **7c** with that corresponding to the natural diastereomer **7b** (5*R*,8*S*) provided by Professor Helquist, clearly revealed spectral differences and indicated that neither **7b** nor **7c** were contaminated with the other respective diastereomers. With proper choice of optical isomers of starting materials, the procedures described here should allow relatively straightforward syntheses of all the diastereomers of the macrocyclic lactone component of griseoviridin.

The ease of the preparation of *S*-phthalimido-substituted cysteine derivatives, **16**, their stability during storage, and efficiency in electrophilic sulfur transfer reactions should make these and related sulfur containing systems

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(17) (a) Kurihara, T.; Nakajima, Y.; Mitsunobu, O. *Tetrahedron Lett.* **1976**, 2455. (b) Mitsunobu, O. *Synthesis* **1981**, 1.
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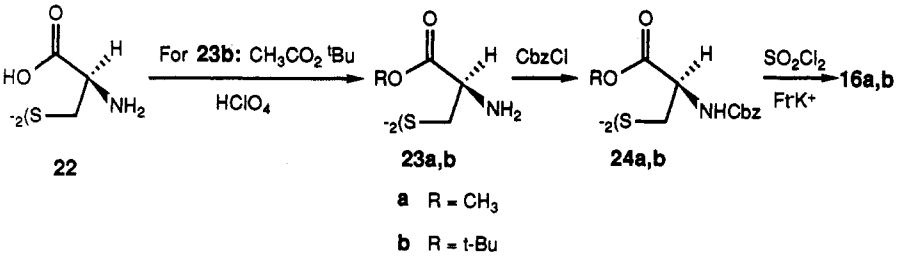
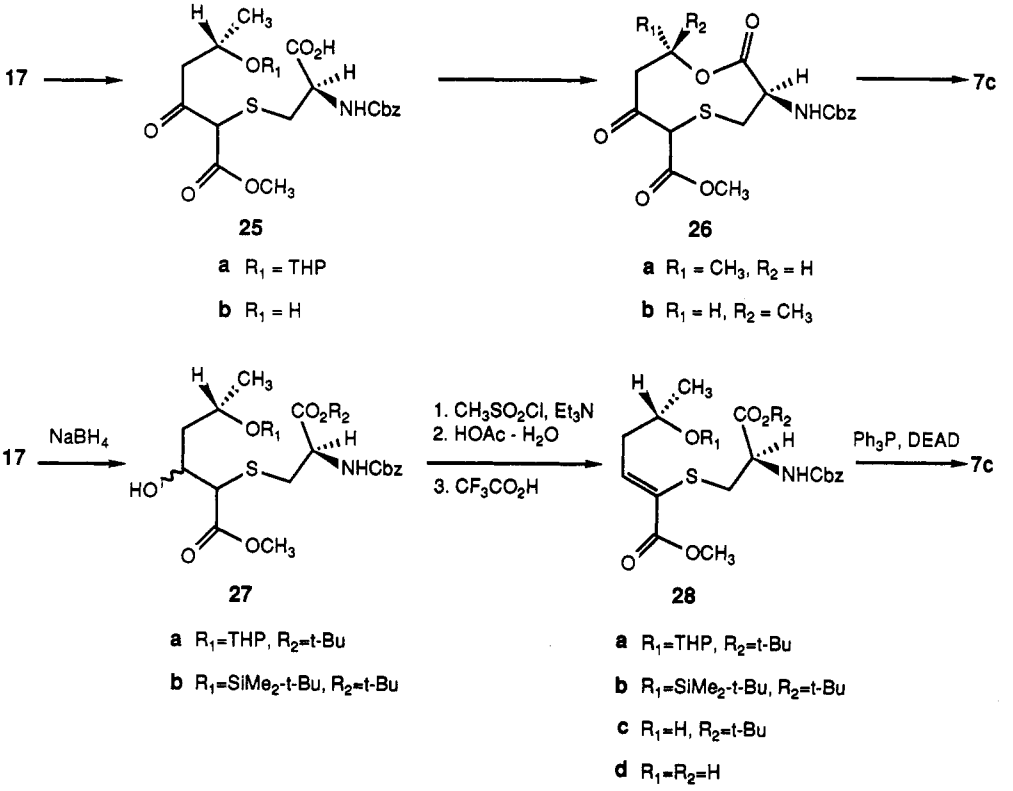
Scheme V



Scheme VI



generally useful synthetic tools.

Experimental Section

Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 727B spectrophotometer. Proton NMR spectra were obtained in deuteriochloroform with tetramethylsilane as an internal standard (unless otherwise indicated) on Varian EM 390, Magnachem A-200, and Nicolet NB 300 NMR spectrometers. Mass spectra were recorded on an AEI MS902 and Dupont DP-1 gas chromatograph mass spectrometer or by Mr. John Occolowitz at Eli Lilly and Co. (FD spectra). Optical rotations were measured with a Rudolf Research Autopol III automatic polarimeter. Elemental analyses were performed by M-H-W Laboratories. All solvents were purified and dried by standard methods. Ether refers to diethyl ether.

(*S*)-(+)-Ethyl 3-hydroxybutanoate (19) was prepared in 72% yield by yeast reduction of ethyl acetoacetate (**18**) using the procedure of Seebach and Sutter:[8] $[\alpha]_D$ +36.9° (*c* 1.35, $CHCl_3$), [lit.[8] $[\alpha]_D$ +37.2° (*c* 1.3, $CHCl_3$)], corresponding to 85% ee. In the literature,[8] further resolution gave enantiomerically pure **19** with $[\alpha]_D$ +43.5°. For our purpose, further resolution was not attempted because eventual preparation and purification of diastereomers made it unnecessary; R_f 0.35 (silica gel, ethyl acetate–hexanes, 3:7); IR (neat) 3450, 2990, 1750 cm^{-1}; ^1H NMR (90 MHz) δ 1.15 (d, 3 H), 1.28 (t, 3 H), 2.43 (d, 2 H), 3.44 (br s, 1 H), 4.16 (m, 1 H), 4.20 (q, 2 H).

(*S*)-Ethyl 3-[(Tetrahydropyranyl)oxy]butanoate (20a). To a solution of the β-hydroxy ester **19** (1.32 g, 10 mmol) in ether (1 mL) were slowly added *p*-toluenesulfonic acid (0.19 g, 1 mmol) and 2,3-dihydropyran (1.26 g, 15 mmol). The mixture was stirred for 2.5 h at 0° C and 0.5 h at room temperature. The ether was added and the solution was shaken vigorously with 10% sodium hydroxide to insure removal of all traces of acid. The solution was dried over $MgSO_4$, the solvent was removed, and the residue was chromatographed to give **20a** (2.09 g, 97%): R_f 0.63 (silica gel, ethyl acetate–hexanes, 3:7); IR (neat) 2960, 1740 cm^{-1}; ^1H NMR (90 MHz) δ 1.23 (t, 6 H), 1.57 (m, br, 6 H), 2.48 (m, 2 H), 3.46 (br, 1 H), 4.10 (m, 4 H), 4.73 (br, 1 H).

(*S*)-Ethyl 3-[(*tert*-Butyldimethylsilyl)oxy]butanoate (20b). To a solution of dimethyl-*tert*-butylsilyl chloride (3.53 g, 23.4 mmol) and imidazole (3.32 g. 48.7 mmol) in DMF (2 mL/g. of **19**) was added the β-hydroxy ester **19** (2.58g, 19.5 mmol). The mixture was stirred for 10 h at room temperature. Ether was added and the solution was washed with distilled water to insure removal of DMF. The solution was dried over $MgSO_4$. The solvent was removed and the residue was chromatographed to give **20b** (4.60 g, 95%): $[\alpha]_D$ +20.1° (*c* 1.27, $CHCl_3$) [No attempt at further resolution was made.]; R_f 0.85 (silica gel, ethyl acetate–hexanes, 3:7); IR (neat) 2880, 1730 cm^{-1}; ^1H NMR (200 MHz) δ 0.04 (s, 3 H), 0.06 (s, 3 H), 0.85 (s, 9 H), 1.22 (m, 6 H), 2.42 (dd, 2 H), 4.12 (q, 2 H), 4.27 (m, 1 H).

(*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]butyric Acid (21b). To ester **20b** (4.56 g, 18.5 mmol) was added 2% methanolic potassium hydroxide solution (60 mL). The mixture was refluxed for 3.5 h, and then MeOH was evaporated to give a yellow solid residue, which was added to distilled water and washed with ether, then acidified with 1 N HCl, extracted with ethyl acetate, dried over $MgSO_4$, evaporated, and chromatographed to give **21b** as an oil (2.90 g, 72%): $[\alpha]_D$ +11.9° (*c* 1.29, $CHCl_3$) [No attempt at

further resolution was made.]; R_f 0.43 (ethyl acetate–hexanes, 3:7); IR (neat) 3400 (br), 2950, 1710 cm^{-1}; ^1H NMR (200 MHz) δ 0.06 (s, 3 H), 0.08 (s, 3 H), 0.87 (s, 9 H), 1.23 (d, 3 H), 2.48 (dd, 2 H), 4.27 (m, 1 H), 10.6 (br s, 1 H).

(*S*)-3-[(Tetrahydropyranyl)oxy]butyric Acid (21a). The same procedure was used as for the preparation of **21b** to provide **21a** in 60% yield as an oil: R_f 0.24 (silica gel, ethyl acetate–hexanes, 3:7); IR (neat) 3550–2850 (br), 1710 cm^{-1}; ^1H NMR (90 MHz) δ 1.21 (d, 3 H), 1.57 (m, br, 6 H), 2.51 (m, 2 H), 3.81 (m, 3 H), 4.95 (br, 1 H).

Methyl 3-Oxo-5(*S*)-[(tetrahydropyranyl)oxy]hexanoate (15a). The carboxylic acid **21a** (1.15 g, 6.0 mmol) was dissolved in freshly distilled THF (10 mL) and 1,1′-carbonyldiimidazole (1.10 g, 6.8 mmol) was added. The reaction mixture was stirred under nitrogen at room temperature for 2 h. In another flask, a heptane solution of dibutylmagnesium (5.43 mL, 3.4 mmol, 0.7 M, Alfa) was added dropwise by syringe into a solution of monomethyl malonate (0.80 g, 6.8 mmol) in THF (10 mL) at −78 °C under nitrogen. The mixture was stirred for 5 min and then warmed to 0 °C over 1 h. The solvent was evaporated to give the magnesium salt as a white solid that was used directly. The solution of the imidazole activated ester of the carboxylic acid was added to the magnesium salt and the reaction was monitored by TLC. After the mixture was stirred under nitrogen at room temperature for 16 h, it was poured into ethyl acetate (60 mL) and washed with 0.5 N HCl until the washings were acidic. The ethyl acetate layer was then washed with a 5% $NaHCO_3$ solution and a saturated NaCl solution, dried over $MgSO_4$, evaporated, and chromatographed to give **15a** as an oil (1.21 g, 82%): R_f 0.28 (silica gel, ethyl acetate–hexanes, 3:7); IR (neat) 2950, 1750, 1710 cm^{-1}; ^1H NMR (90 MHz) δ 1.20 (dd, 3 H), 1.55 (m, br, 6 H), 2.71 (m, 2 H), 3.30 (s, 2 H), 3.51 (d, 2 H), 3.72 (s, 3 H), 4.28 (m, 1 H), 4.68 (br, 1 H); mass spectrum, m/e 244 (M^+).

Methyl 3-Oxo-5(*S*)-[(*tert*-butyldimethylsilyl)oxy]hexanoate (15b). The same procedure was used as for the preparation of **15a** to provide a 76% yield of **15b** as an oil from **21b**: $[\alpha]_D$ +30.8° (c 1.32, $CHCl_3$) [No attempt at further resolution was made.]; R_f 0.70 (silica gel, ethyl acetate–hexanes, 3:7); IR (neat) 2920, 1750, 1720 cm^{-1}; ^1H NMR (200 MHz) δ 0.05 (s, 3 H), 0.07 (s, 3 H), 0.88 (s, 9 H), 1.18 (d, 3 H), 2.67 (dd, 2 H), 3.50 (s, 2 H), 3.74 (s, 3 H), 4.31 (m, 1 H).

L-Cystine Di-*tert*-butyl Ester (23b). L-Cystine (1.92 g, 8 mmol) was dissolved in aqueous 60% perchloric acid (5.88 g, 35.2 mmol) with stirring in an ice bath. *tert*-Butyl acetate (50 mL) was added and the stirring was continued until a homogeneous solution was obtained (2 h). The mixture was kept at room temperature for 2 days, during which a white solid crystallized out. After cooling at 0 °C for 24 h, the solid was filtered off and washed with ether. A portion of this salt was dissolved in a mixture of ether and aqueous $NaHCO_3$. The organic layer was washed in succession with aqueous $NaHCO_3$ and saturated NaCl solutions, dried, and evaporated to give L-cystine di-*tert*-butyl ester (**23b**) as an oil: IR (neat) 3420, 3340, 2990, 1730 cm^{-1}; ^1H NMR (90 MHz, $(CD_3)_2SO$) δ 1.50 (s, 18 H), 2.10 (br, 4 H), 3.05 (m, 4 H), 3.60 (t, 2 H). [lit.[14] ^1H NMR (the following data is converted from the τ values reported) δ[$(CD_3)_2SO$] 1.38–1.50 (18 H, s, *t*-Bu), 2.8–3.3 (8 H, complex, NH_2 and CH_2), 3.45–3.67 (2 H, t, CH)].

N,N′-Bis(carbobenzyloxy)-L-cystine Dimethyl Ester (24a). Into the mixture of a saturated aqueous $KHCO_3$ solution (30 mL) and $CHCl_3$ (30 mL) in an ice bath were added L-cystine dimethyl ester dihydrochloride (3.40 g, 10 mmol) and carbobenzyloxy chloride (4 mL, 4.78 g, 28 mmol). After shaking the mixture for about 30 min in an ice bath, the water layer was separated and discarded. To the $CHCl_3$ solution was added pyridine (1 mL), and then the solution was washed successively with dilute sulfuric acid, distilled water, and diluted aqueous $KHCO_3$. The solution was dried over $MgSO_4$ and evaporated, and the residue was crystallized from ethyl acetate–hexanes to give **24a** (4.90 g, 92%): mp 68–69 °C (lit.[11a] mp 73–75 °C, lit.[11b] mp 57–61 °C, lit.[11c] oil); R_f 0.40 (silica gel, ethyl acetate–hexanes, 1:1); IR ($CHCl_3$) 3450, 2980, 1720 cm^{-1}; ^1H NMR (90 MHz) δ 3.23 (d, 4 H), 3.82 (s, 6 H), 4.80 (m, 2 H), 5.27 (s, 4 H), 6.10 (d, 2 H), 7.58 (s, 10 H).

N,N′-Bis(carbobenzyloxy)-L-cystine Di-*tert*-butyl Ester (24b). The same procedure as the preparation of **24a** was used. A 76% yield of **24b** was obtained: mp 75.5–76.0 °C; R_f 0.43 (silica gel, ethyl acetate–hexanes, 3:7); ^1H NMR (90 MHz) δ 1.43 (s, 18 H), 3.16 (d, 4 H), 4.54 (m, 2 H), 5.11 (s, 4 H), 5.65 (br, 2 H), 7.36 (s, 10 H). Anal. Calcd for $C_{30}H_{40}O_8N_2S_2$: C 58.05; H, 6.49; N, 4.51. Found: C, 58.19; H, 6.30; N, 4.36.

N-(Carbobenzyloxy)-S-phthalimido-L-cysteine Methyl Ester (16a). The disulfide **24a** (0.54 g, 1.0 mmol) was dissolved in 1,2-dichloroethane (DCE) (3 mL) at 0 °C. Sulfuryl chloride (0.09 mL, 0.15 g, 1.1 mmol) in dichloroethane (DCE, 3mL) was added dropwise. After stirring for 5 min, potassium phthalimide (Ft–K, 0.37 g, 2.0 mmol) was added rapidly. After 10 min at 0 °C and 90 min at room temperature, the mixture was centrifuged. The solvent was evaporated and the residue was chromatographed to give **16a** (0.51g, 61%) as a very thick oil: R_f 0.36 (silica gel, ethyl acetate–hexanes, 1:1); IR (neat) 3390, 3050, 2970, 1720 cm^{-1}; ^1H NMR (90 MHz) δ 3.22 (d, 2 H), 3.55 (s, 3 H), 4.73 (m, 1 H), 5.06 (s, 2 H), 6.30 (br, 1 H), 7.34 (s, 5 H), 7.87 (m, br, 4 H).

N-(Carbobenzyloxy)-S-phthalimido-L-cysteine *tert*-Butyl Ester (16b). The same procedure as for the preparation of **16a** was used to produce **16b** in 72–96% yield as nice white crystals: mp 78–80 °C; R_f 0.25 (silica gel, ethyl acetate–hexanes, 3:7); IR (neat) 3380, 3000, 1720 cm^{-1}; ^1H NMR (90 MHz) δ 1.36 (s, 9 H), 3.21 (d, 2 H), 4.57 (m, 1 H), 5.02 (s, 2 H), 6.16, (br, 1 H), 7.31 (s, 5 H), 7.83 (m, 4 H). Anal. Calcd for $C_{23}H_{24}O_6N_2S$: C, 60.51; H, 5.30; N, 6.14. Found: C, 60.41; H, 5.38, N, 6.10.

Model Sulfur Transfer Reactions. (a) Reaction of dimethyl malonate (**4a**) with *S*-phthalimido-L-cysteine derivative **16b** (**5**, P = Cbz, R_2 = *t*-Bu). Under nitrogen, NaH (115 mg of a 50% oil dispersion, 1.1 equiv) was washed three times with hexanes to remove the oil. THF was added followed by 0.25 mL of dimethyl malonate at room temperature a few minutes later; when hydrogen evolution ceased, **16b** (1 equiv) was added. After stirring for 5 min at room temperature the precipitated sodium phthalimide was removed by filtration. The filtrate was evaporated. The residue was taken up in ethyl acetate and washed with water and brine before drying over $MgSO_4$ and evaporation. The new residue was chromatographed (silica gel, ethyl acetate–hexanes, 1:3) to provide two main fractions. The second was the bissulfenylated product: IR 3420, 3020, 1740, 1720, 1710 (shoulder) cm^{-1}; ^1H ^1H NMR (90 MHz) δ 1.5 (s, 18 H), 3.1 (d, 4 H), 3.8 (s, 6 H), 4.5 (m, 2 H), 5.1 (s, 4 H), 5.8 (br, 2 H), 7.4 (s, 10 H); mass spectrum (FD), m/e 751 (M + 1). The monosulfenylated product **6** (R = OMe, R_1 = Me, P = Cbz, R_2 = *t*-Bu) was obtained in 10% yield. An improved preparation (66%) of **6** was realized by using 2 equiv of NaH during the reaction and adjusting the first aqueous layer of the workup from pH 8 to pH 3.5: IR (neat oil) 3430, 3020, 1735, 1215 cm^{-1}; ^1H NMR (90 MHz) δ 1.5 (s, 9 H), 3.2 (d, 2 H), 3.8 (s, 6 H), 4.3 (s, 1 H), 4.6 (m, 1 H), 5.1 (s, 2 H), 5.7 (m, 1 H), 7.4 (s, 5 H).

(b) Reaction of 4b with 16b (5, P = Cbz, R_2 = *t*-Bu). Dimethyl 3-oxopimelate (**4b**) was first prepared in the following manner. Monomethyl malonate (0.96 g, 7.5 mmol) in 5 mL of the THF was added by syringe to a dry round-bottomed flask. The flask was purged with nitrogen, cooled in a dry ice-acetone bath, and maintained under nitrogen while 5.1 mL of 0.7 M dibutylmagnesium (3.6 mmole, Alfa) was added. The mixture was allowed to warm to room temperature over 1 h. The solvent was evaporated and the residual magnesium dimalonate was used directly. Imidazole hydrochloride (200 mg, 1.9 mmol), the sodium salt of monomethyl glutarate (321.5 mg, 1.9 mmol, 100 mol %), and carbonyl diimidazole (340 mg, 2 mmol, 110 mol %) were placed in a dry round-bottomed flask under nitrogen. THF (10 mL) was added and the mixture was stirred for 5 h at room temperature while the salts slowly dissolved. The previously prepared magnesium monomethyl malonate was added and the new mixture was stirred under nitrogen. After 15 h, the resulting suspension was filtered and the liquid phase was evaporated. The residue was partitioned between ether (20 mL) and 0.5 N HCl (20 mL). After separation, the aqueous layer was extracted again with 10 mL of ether. The ether layers were combined and extracted with water and saturated aqueous Na_2CO_3. Drying over $MgSO_4$, filtration, and evaporation gave **4b** in 70.5% as an oil suitable for direct use in the next reaction: IR (neat) 3000, 1740 (br), 1440, 1320 cm^{-1}; ^1H NMR (90 MHz) δ 1.9 (m, 2 H), 2.5 (m, 4 H), 3.5 (s, 2 H), 3.68 (s, 3 H), 3.75 (s, 3 H). Yields of **4b** were substantially lower if imidazole hydrochloride was omitted from the reaction.

Treatment of **4b** with NaH (100 mol % since use of 200 mol % caused saponification problems of the terminal ester during aqueous quenches) in THF, followed by a workup similar to that used for the malonate case, produced **6** (R = $MeO_2C(CH_2)_3$, R_1 = Me, P = Cbz, R_2 = *t*-Bu) in 50% yield (oil) after chromatography: IR (neat) 3200, 2950, 1710, 1210 cm^{-1}; ^1H NMR (90 MHz) δ 1.4 (s, 9 H), 1.6–2.1 (m, 2 H), 2.2–2.8 (m, 4 H), 3.1 (br, 2 H), 3.6 (s, 3 H), 3.75 (s, 3 H), 3.8 (s, 1 H), 4.3 (br, 1 H), 5.1 (s, 2 H), 6.8 (br, 1 H), 7.4 (s, 5 H).

Preparation of 17a. The β-keto ester **15a** (0.10 g, 0.41 mmol) was treated with sodium hydride (0.02 g, 0.42 mmol) in THF (1 mL) at 0 °C. Then the mixture was stirred at room temperature for 30 min and recooled to 0 °C. Compound **16a** (0.17 g, 0.42 mmol) in THF (1 mL) was then added, and the mixture was stirred for 15 min at room temperature. The solvent was evaporated and ethyl acetate was added. The mixture was centrifuged. The clear solution was washed successively with ethyl acetate, distilled water, and a saturated NaCl solution, dried over $MgSO_4$, and chromatographed to give **17a** (0.13 g, 61%) as a very thick oil [All attempts to crystallize **17a** failed.]: R_f 0.21 (ethyl acetate–hexanes, 3:7). IR (neat) 3370, 2960, 1720 cm^{-1}; ^1H NMR (300 MHz) δ 1.10–1.60 (m, 9 H), 3.25–3.35 (d, 2 H), 3.65–3.75 (s, 3 H), 3.75–3.80 (d, 2 H), 3.80–3.85 (s, 3 H), 5.10–5.20 (s, 2 H), 7.34–7.50 (s, 5 H); mass spectrum, *m/e* 511 (M^+) (FD).

Compound 17b was prepared in a similar manner in 51% yield (thick oil) [All attempts to crystallize **17b** failed.]: R_f 0.38 (silica gel, ethyl acetate–hexanes, 3:7); IR (neat) 3350, 2940, 1710 cm^{-1}; ^1H NMR (90 MHz) δ 1.10–1.70 (s, m, 18 H), 3.25–3.35 (d, 2 H), 3.70–3.76 (d, 2 H), 3.76–3.85 (s, 3 H), 5.05–5.20 (s, 2 H), 7.25–7.45 (s, 5 H).

Compound 17c was also prepared in a similar manner in 74% yield (thick oil). All attempts to crystallize **17c** failed: $[\alpha]_D$ +14.7° (*c* 1.30, $CHCl_3$) (The clean singlet at 3.81 ppm in the ^1H NMR spectrum indicated the presence of one diastereomer. The other diastereomer (R_f 0.58) was obtained in impure form.): R_f 0.64 for **17c** (silica gel, ethyl acetate–hexanes, 3:7); IR (neat) 3390, 2950, 1720 cm^{-1}; ^1H NMR (200 MHz) δ 0.04 (s, 3 H), 0.06 (s, 3 H), 0.84 (s, 9 H), 1.19 (d, 3 H), 1.43 (s, 9 H), 2.65 (dd, 2 H), 3.09 (m, 3 H), 3.81 (s, 3 H), 4.27 (m, 2 H), 5.11 (s, 2 H), 5.81 (d, 1 H), 7.35 (s, 5 H); mass spectrum, *m/e* 583 (M^+).

Reduction of 17c to 27b. The ketone **17c** (1.21 g, 2.0 mmol) was dissolved in methanol (1 mL), and sodium borohydride (0.02 g, 0.5 mmol) was added at 0 °C. The cooling bath was removed and the mixture was stirred for 15 min. Distilled water was added and the solution was brought to pH 6–8 by addition of solid $NaHCO_3$. The mixture was then extracted with ether, dried over $MgSO_4$, evaporated, and chromatographed to give the two diastereomers (at the new chiral center) of **27b** in a ratio of about 1:1 (the total yield was 0.70 g, 58%). Both diastereomers were oils. Diastereomer 1: $[\alpha]_D$ −11.8° (*c* 1.04, $CHCl_3$); R_f 0.47 (silica gel, ethyl acetate–hexanes, 3:7); IR ($CDCl_3$) 3400 (br), 2950, 1720 cm^{-1}; ^1H NMR (200 MHz) δ 0.06 (s, 3 H), 0.08 (s, 3 H), 0.87 (s, 9 H), 1.19 (d, 3 H), 1.45 (s, 9 H), 1.75 (m, 2 H), 3.12 (m, 2 H), 3.32 (m, 1 H), 3.74 (s, 3 H), 4.16 (m, 2 H), 4.53 (m, 1 H), 5.14 (s, 2 H), 5.84 (m, 1 H), 7.35 (s, 5 H). Diastereomer 2: $[\alpha]_D$ −11.2° (*c* 1.03, $CHCl_3$); R_f 0.40 (silica gel, ethyl acetate–hexanes, 3:7); IR ($CDCl_3$) 3400 (br), 2950, 1720 cm^{-1}; ^1H NMR (200 MHz) δ 0.08 (s, 3 H), 0.10 (s, 3 H), 0.88 (s, 9 H), 1.21 (d, 3 H), 1.46 (s, 9 H), 1.96 (m, 2 H), 3.09 (m, 2 H), 3.33 (m, 1 H), 3.74 (s, 3 H), 4.06 (m, 1 H), 4.21 (m, 1 H), 4.51 (m, 1 H), 5.13 (s, 2 H), 5.70 (m, 1 H), 7.35 (s, 5 H).

Dehydration of 27b to 28b. To the mixture of two diastereomers of α-thio-β-hydroxy ester **27b** (0.774 g, 1.32 mmol) in CH_2Cl_2 (15 mL) in an ice bath were added triethylamine (0.334 g, 3.31 mmol) and methanesulfonyl chloride (0.166 g, 1.45 mmol). The reaction mixture was stirred at room temperature for 25 min; then distilled water was added. The solution was extracted with CH_2Cl_2, dried over $MgSO_4$, and evaporated and the residue was chromatographed to give **28b** (0.544 g, 73%) as an oil: $[\alpha]_D$ +19.5° (*c* 1.30, $CHCl_3$); R_f 0.65 (silica gel, ethyl acetate–hexanes, 3:7); IR (neat) 3390, 2950, 1720 cm^{-1}; ^1H NMR (200 MHz) δ 0.02 (s, 3 H), 0.04 (s, 3 H), 0.84 (s, 9 H), 1.13 (d, 3 H), 1.44 (s, 9 H), 2.51 (m, 1 H), 3.12 (dd, 2 H), 3.35 (dd, 1 H), 3.70 (s, 3 H), 3.87 (m, 1 H), 4.29 (m, 1 H), 4.99 (s, 2 H), 5.45 (d, 1 H), 7.09 (t, 1 H), 7.26 (m, 5 H).

Deprotection of 28b to 28c. To compound **28b** (0.504 g, 0.89 mmol) were added acetic acid (5 mL) and distilled water (1 mL). The mixture was stirred at room temperature for 23 h. More distilled water was added and the solution was brought to pH 6–8 with solid $NaHCO_3$, then extracted with ether, dried over $MgSO_4$, and evaporated, and the residue was chromatographed to give **28c** (0.340 g, 84%) as an oil: $[\alpha]_D$ +97.9° (*c* 1.02, $CHCl_3$); R_f 0.27, (silica gel, ethyl acetate–hexanes, 3:7); IR (neat) 3360 (br), 2980, 1720 cm^{-1}; ^1H NMR (200 MHz) δ 1.27 (d, 3 H), 1.50 (s, 9 H), 2.39 (m, 1 H), 3.01 (dd, 2 H), 3.47 (dd, 1 H), 3.76 (s, 3 H), 4.00 (m, 1 H), 4.53 (m, 1 H), 5.10 (s, 2 H), 5.94 (d, 1 H), 7.26 (t, 1 H), 7.37 (m, 5 H); mass spectrum, *m/e* 454 (M^+ + 1).

Deprotection of 28c to 28d. To **28c** (0.240 g, 0.53 mmol) was added trifluoroacetic acid (3 mL). The mixture was stirred for 55 min. The solvent was evaporated. To the residue were added 5% aqueous $NaHCO_3$ (6 mL) and ether. The layers were separated and the ether layer was extracted with two more 4-mL portions of 5% $NaHCO_3$. The combined aqueous layers were acidified to pH 4–5 by dropwise addition, with swirling, of 1 N HCl and then extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, evaporated, and chromatographed to give **28d** (0.195 g, 93%) as an oil: $[\alpha]_D$ +21.1° (*c* 1.29, $CHCl_3$); R_f 0.03 (silica gel, ethyl acetate–hexanes, 1:1); IR (neat) 3650–2800 (br), 1780, 1720 cm^{-1}; ^1H NMR (200 MHz) δ 1.37 (d, 3 H), 2.84 (m, 2 H), 3.29 (d, 2 H), 3.81 (s, 3 H), 4.58 (m, 1 H), 5.13 (s, 2 H), 5.21 (m, 1 H), 5.85 (d, 1 H), 7.07 (t, 1 H), 7.37, (m, 5 H), 9.36 (br s, 1 H); mass spectrum, *m/e* 379 ($M^+ - H_2O$).

Cyclization of Hydroxy Acid 28d to Lactone 7c. To a stirred mixture of hydroxy acid **28d** (0.128 g, 0.32 mmol) and triphenylphosphine (0.127 g, 0.49 mmol) in benzene (15 mL) was added by syringe diethyl azodicarboxylate (0.076 mL, 0.085 g, 0.49 mmol) at room temperature. After the solution was stirred for 2 days at room temperature, the white precipitate was removed by filtration and the solvent was evaporated. The residue was chromatographed to give **7c** (0.048 g, 39%): mp 115.0–115.5 °C (after recrystallization from CH_2Cl_2–hexanes); R_f 0.56 (silica gel, ethyl acetate–hexanes, 1:1); IR ($CDCl_3$) 3330, 2990, 1720, 1250, 1060 cm^{-1}; ^1H NMR (300 MHz) δ 1.42 (d, 3 H), 2.38 (m, 1 H), 3.00 (dd, 1 H), 3.15 (d, 1 H), 3.38 (dd, 1 H), 4.60 (m, 1 H), 5.12 (dd, 2 H, m, 1 H), 5.76 (d, 1 H, NH), 7.39 (m, 5 H), 7.49 (dd, 1 H); mass spectrum, *m/e* 379 (M^+), 288 ($M^+ - C_6H_5CH_2$).

Acknowledgment. We gratefully acknowledge support from the national Institutes of Health (NIH) and Eli Lilly and Co. as well as a Reilly Fellowship for Li Liu. Mrs. Kathleen Peterson recorded the 300-MHz NMR spectra on an instrument provided by grants from NIH and the University of Notre Dame. Structure drawings were produced with ChemDraw by S. Rubenstein. We are especially grateful for discussions with Professor Paul Helquist.