at -78 °C, and the mixture was stirred for 0.5 h. TLC showed the disappearance of starting material and the formation of a new spot at R_f = 0.25 (SiO_2, 1:4 ethyl acetate–hexanes, UV). The reaction was quenched at -78 °C with 2 equiv of methyl triflate (methylation product: R_f = 0.54, SiO_2, 1:4 ethyl acetate–hexanes, UV). To this mixture at -23 °C was added a solution of lithium aluminum hydride (1 M in ether, 2 mL) followed by stirring for 0.5 h. Once major spot was detected by TLC (R_f = 0.57, SiO_2 1:4 ethyl acetate–hexanes, phosphomolybdium acid). The reaction was quenched with 15 mL of 10% NH_4Cl and filtered with ether through a layer of Celite 545. The organic layer was separated, and the aqueous layer was extracted three times with 20 mL of ether. The combined organic layers were dried over $MgSO_4$, and the solvent was removed. The residue was quickly chromatographed on SiO_2 (1:10 ethyl acetate–hexanes). Decomposition on SiO_2 limited the yield to 28% (130 mg). This was then dissolved in 5 mL of ether with pyridine (79 mg, 1 mmol) at 0 °C. To this solution was added trifluoroacetic anhydride (210 mg, 1 mmol) followed by stirring for 0.5 h. The milky solution was added to 10 mL of water and extracted with ether (3 × 20 mL). The ether solution was dried over $MgSO_4$ and the solvent removed. The residue was heated in 5 mL of *o*-xylene at 100 °C for 20 min. The reaction solution was added to a mixture of 5 mL of CH_3CN and 5 mL of water at 0 °C. This was oxidized with 2 mL of 0.49 M ammonium cerium nitrate for 0.5 h and extracted with 10 mL of ether and twice with 15 mL of methylene chloride. The combined organic layers were dried over $MgSO_4$ and chromatographed on SiO_2 (1:10 ethyl acetate–hexanes) to give 60% (49 mg) of **12a** as a yellow solid: R_f = 062 (SiO_2, 1:10 ethyl acetate–hexanes, UV); mp 43–44 °C (sublimation) (lit.[26] 45.5 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 6.57 (q, J = 1.5 Hz, 1 H), 6.50 (d, J = 0.9 Hz, 1 H), 3.00 (d hept, J = 0.9, 6.8 Hz, 1 H), 2.01 (d, J = 1.5 Hz, 3 H), 1.10 (d, J = 6.9 Hz, 6 H); IR (CCl_4, cm^{-1}) 2969, 2936, 2877, 1660, 1613, 1241, 914.

Synthesis of 2-Isopropyl-3-*n*-butyl-5-methyl-1,4-benzoquinone (12b). Reaction of 3-isopropyl-4-isopropoxy-3-cyclobutene-1,2-dione (**2c**) with 1.07 equiv of 2-lithiopropene (generated by addition of 2 equiv of *t*-BuLi to a THF solution of 2-bromopropene at -78 °C and stirring for 0.5 h) took place for 0.5 h and then followed the same experimental procedure as the synthesis of thymoquinone, except the reaction was quenched with TFAA after the addition of *n*-BuLi and the product was directly heated and oxidized without purification to give 114 mg (22%) of product **12b** as a yellow oil: R_f = 0.59 (SiO_2, 1:10 ethyl acetate–hexanes, UV); ^1H NMR (300 MHz, $CDCl_3$) δ 6.42 (q, J = 1.2 Hz, 1 H), 2.98 (hept, J = 7.1 Hz, 1 H), 2.47 (t, J = 7.2 Hz, 2 H), 1.98 (d, J = 0.9 Hz, 3 H), 1.37 (m, 3 H), 1.26 (d, J = 6.9 Hz, 6 H), 0.92 (t, J = 6.9 Hz, 3 H); IR (CH_2Cl_2, cm^{-1}) 3687, 3054, 2961, 2933, 2869, 1645, 1602. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.29; H, 9.20. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.29; H, 9.20.

Acknowledgment. This investigation was supported by Grant No. CA40157, awarded by the National Cancer Institute, DHHS. We acknowledge the use of a VG 70-S mass spectrometer purchased through funding from the National Institutes of Health, S10-RR-02478, and a 300-MHz NMR and a 360-MHz NMR purchased through funding from the National Science Foundation, NSF CHE-85-16614 and NSF CHE-8206103, respectively. We thank Professor Harold Moore of U. C. Irvine for sharing his results with us prior to publication.

Registry No. **2c**, 73279-65-9; **4a**, 114094-69-8; **4b**, 114094-70-1; **4c**, 114094-71-2; **5a**, 141462-19-3; **5b**, 141462-20-6; **5c**, 141462-21-7; **5d**, 141462-22-8; **5e**, 141462-23-9; **5f**, 141462-24-0; **5g**, 141462-25-1; **5h**, 141462-26-2; **5i**, 141462-27-3; **6a**, 141462-28-4; **6b**, 141462-29-5; **6c**, 141462-30-8; **6d**, 141462-31-9; **6e**, 141462-32-0; **6f**, 141462-33-1; **6g**, 141462-34-2; **6h**, 141462-35-3; **6i**, 141462-36-4; **7'**, 141462-37-5; **8a**, 141462-38-6; **8b**, 141462-39-7; **8d**, 141462-40-0; **8e**, 141462-41-1; **8f**, 141462-42-2; **8g**, 141462-43-3; **8k**, 141462-44-4; **8l**, 141462-45-5; **9a**, 2397-62-8; **9b**, 22266-99-5; **9c**, 92920-84-8; **9d**, 141462-46-6; **9e**, 80213-82-7; **9f**, 141462-47-7; **9g**, 141462-48-8; **9h**, 141462-49-9; **9i**, 141462-50-2; **9j**, 141462-51-3; **9k**, 141462-52-4; **9l**, 141462-53-5; **12a**, 490-91-5; **12b**, 141462-54-6; diisopropyl squarate, 61699-62-5; isopropylmagnesium chloride, 1068-55-9; PhLi, 591-51-5; 2-lithioanisole, 31600-86-9; 4-lithiotoluene, 2417-95-0; 2-lithiofuran, 2786-02-9; n-BuLi, 109-72-8; 2-bromopropene, 557-93-7.

(26) Zavarin, E.; Anderson, A. B. *J. Org. Chem.* **1955**, *20*, 82.

2-Thioalkyl Penems: An Efficient Synthesis of Sulopenem, a (5*R*,6*S*)-6-(1(*R*)-Hydroxyethyl)-2-[(*cis*-1-oxo-3-thiolanyl)thio]-2-penem Antibacterial

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Received May 8, 1992

A practical synthesis of potent penem antibacterials, CP-70,429 (**1**) (sulopenem) and CP-81,054 (**2**), is described. (L)-Aspartic acid was utilized to generate *both* the (3*S*)- and (3*R*)-thiolanylthio side chains of (5*R*,6*S*)-6-(1-(*R*)-hydroxyethyl)-2-[(*cis*-1-oxo-3-thiolanyl)thio]-2-penem-3-carboxylic acids **1** and **2**. This synthetic pathway provided in high yield enantiopure thioacetate intermediates **15** and **19**. To accommodate the fragile side chain sulfoxide moiety of the targeted β-lactams, standard penem synthetic methodology was modified to facilitate the conversion of **15** and **19** to **1** and **2**. The reactive chloroazetidinone **4b** was utilized to generate key azetidinone trithiocarbonate intermediate **22** which contains the requisite penem side chain. A chemoselective oxalofluoride-based azetidinone N-acylation procedure, which avoids sulfoxide O-acylation, was required for the conversion of **22** to the penem framework.

Introduction

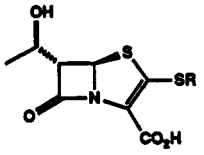
The pioneering synthesis of penems by the Woodward/Ciba group[1] in 1976 along with the Merck discovery[2] of the broad-spectrum carbapenem, thienamycin, from fermentation sources have fueled an intense search, in recent years, for novel therapeutics from the penem and carbapenem families. While a number of candidates

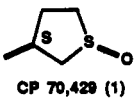
(1) Woodward, R. B. In *Recent Advances in the Chemistry of Beta-Lactam Antibiotics*; Elks, J., Ed.; Special Publication No. 28; Chemical Society: London, 1977; p 167. Ernest, I.; Gosteli, J.; Greengrass, C. W.; Holick, W.; Jackman, D. E.; Pfaendler, H. R.; Woodward, R. B. *J. Am. Chem. Soc.* **1978**, *100*, 8214.

(2) Albers-Schonberg, G.; Arison, B. H.; Hensons, O. D.; Hirshfield, J.; Hoogsteen, K.; Kaczka, E. A.; Rhodes, R. E.; Kahan, J. S.; Kahan, F. M.; Ratcliffe, R. W.; Walton, E.; Ruswinkle, L. J.; Morin, R. B.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 6491.

0022-3263/92/1957-4352$03.00/0

emerged from these discovery efforts, comparatively few have become drugs. The cost of producing these β-lactams certainly has played a significant role in preventing the clinical progression of a number of these compounds. The realization that the commercial potential of penem/carbapenem antibacterials would primarily hinge on the discovery and development of practical syntheses has, in turn, stimulated a widespread search for more efficient routes to these compounds.[3] Herein we wish to report a facile synthesis of CP-70,429 (1) (sulopenem),[4] a broad-spectrum 2-(*cis*-3(*S*)-thio-1(*R*)-thiophane sulfoxide)[5]-containing penem antibacterial which is currently undergoing clinical evaluation. In addition, the synthesis of the diastereomeric penem CP-81,054 (2), containing the enantiomeric thiophane sulfoxide sidechain, is described.



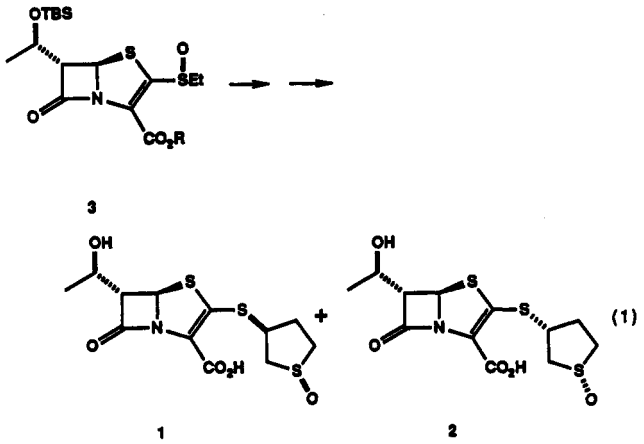


CP 70,429 (1)

2

Results and Discussion

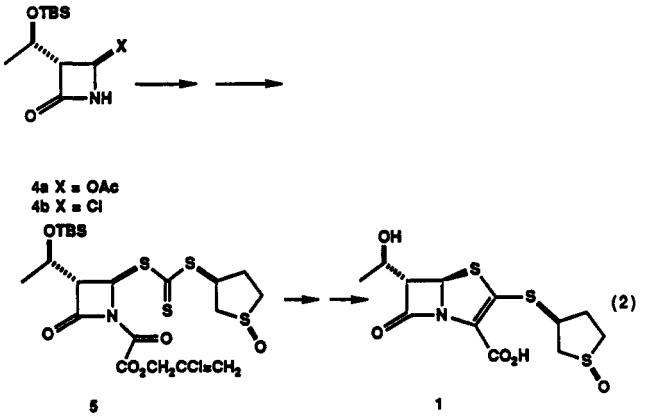
Synthetic Strategy. Treatment of enantiopure penem sulfoxide **3**, reported earlier by DiNinno et al.,[6] with a variety of heterocyclic thiolates provided a convenient access to a number of 3-substituted penem antibacterials including **1** and **2** (eq 1). While this scheme satisfied our



(1)

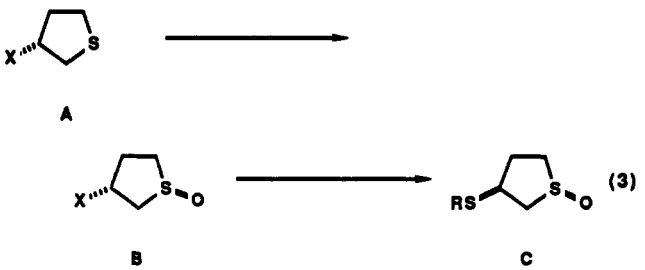
early discovery needs by providing penem analogs, it clearly would not provide a cost effective route to CP-70,429 (1).

Our reading of previous penem and carbapenem syntheses suggested attractive options for the preparation of penem targets **1** and **2**. We decided to focus our attention on the conversion of enantiopure (3*R*)-4-substituted-3-[(*R*)-1[(*tert*-butyldimethylsilyl)oxy]ethyl]azetidin-2-ones **4** (bearing a leaving group in the 4 position) to the penem skeleton in light of the commercial availability of acetoxyazetidinone **4a**.[7] Our intent was to convert acetoxyazetidinone **4a** to oxalimide **5** containing the CP-70,429 (1) thiophane sulfoxide side chain and utilize the phosphite-mediated cyclization conditions developed independently by workers at Schering[8] and Sankyo[9] to access the penem nucleus (eq 2).



(2)

Side-Chain Synthesis. We were confident that if we could access enantiomerically pure 3-substituted thiophanes A (in which X is a suitable leaving group) we would be able to use the ring substituent to establish the requisite thiophane sulfoxide stereochemistry (eq 3). Several options were already available for obtaining useful thiophane intermediates. (*S*)-3-Hydroxythiophanes had been prepared by Brown[10] et al. via a diisopinocampheylborane-mediated asymmetric hydroboration of 2,3-dihydrothiophene. In addition, enzymatic (horse liver alcohol dehydrogenase) reduction of 3-oxothiophane and oxidation of 3-hydroxythiophane had also been employed for the generation of enantiomerically enriched 3-hydroxythiophane.[11] Recently, an enantioselective asymmetric hydrogenation [BINAP-Ir(I) complex] of 3-oxothiophane has been reported.[12]



(3)

We opted to explore a novel (L)-aspartic acid[7] (**6**) based-approach which we felt would allow us to access *both* thiophane sulfoxide side chains (Scheme I). Sugimura[13]

(3) McCombie, S. W.; Ganguly, A. K. *Medicinal Research Reviews*; John Wiley and Sons: New York, 1988; Vol. 8, p 393. Ernest, I. In *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vol. 2, p 315.

(4) Gootz, T.; Girard, D.; Schelkley, W.; Tensfeldt, T.; Foulds, G.; Kellogg, M.; Stam, J.; Campbell, B.; Jasys, J.; Kelbaugh, P.; Volkmann, R.; Hamanaka, E. *J. Antibiot.* **1990**, *43*, 422. Volkmann, R. A.; Bordner, J.; Foulds, G. H.; Girard, A. E.; Girard, D.; Gootz, T.; Jasys, V. J.; Kelbaugh, P. R.; Kellogg, M. S.; Hamanaka, E. S.; Lindner, D. L.; Nason, D. M.; Retsema, J. A.; Cambell, B. Interscience Conference on Antimicrobial Agents and Chemotherapy; Oct 23–26, 1988; Los Angeles, CA; Paper 220. Volkmann, R. A.; Lindner, D. L. U.S. Pat. 4,794,179, 1988.

(5) We have denoted the 5-membered ring tetrahydrothiophene (thiolane) derivatives mentioned throughout the text as a substituted thiophanes.

(6) DiNinno, F.; Muthard, D. A.; Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron Lett.* **1982**, *23*, 3535.

(7) Kanegafuchi and Takasago Companies. The preparation of azetidinones **4** has been the subject of extensive synthetic investigations. See ref 3 and, in addition: Nakatsuka, T.; Iwata, H.; Tanaka, R.; Imajo, S.; Ishiguro, M. *J. Chem. Soc., Chem. Commun.* **1991**, 662 and references cited therein.

(8) Afonso, A.; Hon, F.; Weinstein, J.; Ganguly, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 6138.

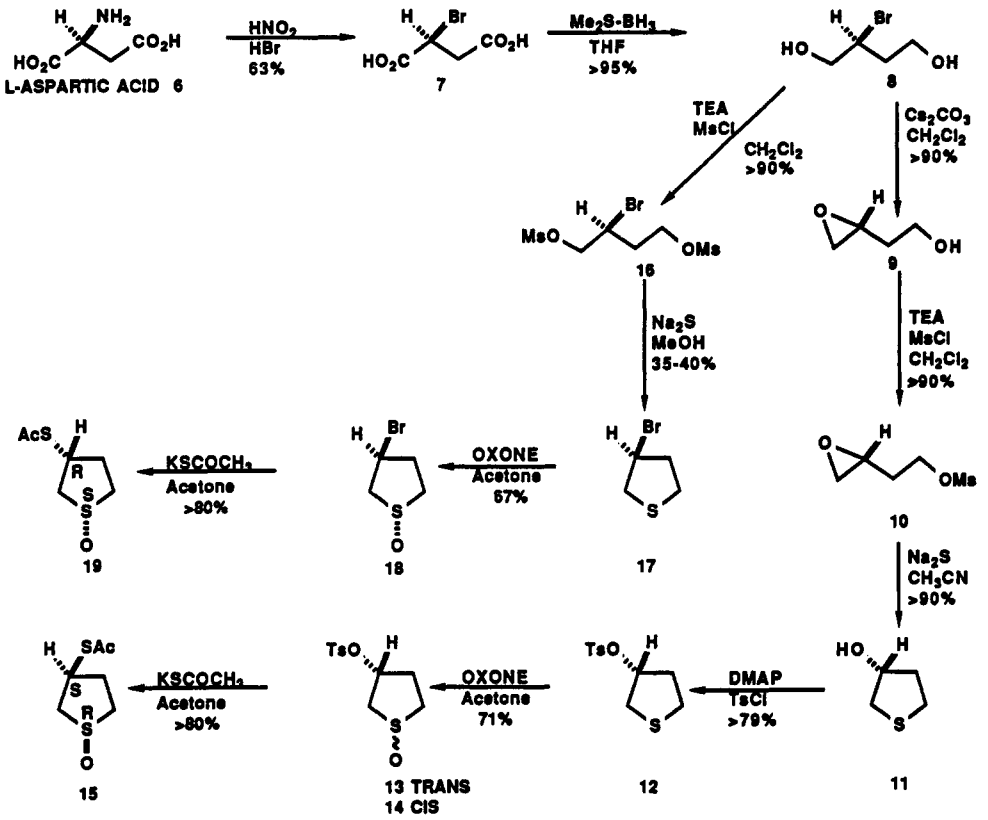
(9) Yoshida, A.; Hayashi, T.; Takeda, N.; Oida, S.; Ohki, E. *Chem. Pharm. Bull.* **1983**, *31*, 768.

(10) Brown, H. C.; Vara Prasad, J. V. N. *J. Am. Chem. Soc.* **1986**, *108*, 2049.

(11) Jones, B. J.; Schwartz, H. M. *Can. J. Chem.* **1981**, *59*, 1574.

(12) Zhang, X.; Mashima, K.; Koyano, K.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Takaya, H. 38th Symposium on Organometallic Chemistry; Oct 25, 1991; Kyoto, Japan.

Scheme I. Side-Chain Synthesis



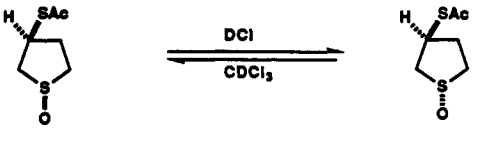
and co-workers previously had converted L-aspartic acid (6) to (*S*)- and (*R*)-mercaptopyrrolidines. We envisioned a similar strategy for the preparation of homochiral (*R*)- and (*S*)-3-mercaptothiophanes required for the synthesis of 1 and 2. Accordingly, diazotization/acid treatment ($NaNO_2/NaBr/H_2SO_4$) of 6 provided the known bromo diacid 7[14] which was allowed to react with diborane to afford bromo diol 8.[13] The isolation of bromo diol 8 and its conversion to epoxide 9[13,15,16] were frustrated by the water solubility of these intermediates. Problems in the diborane reduction workup, however, were obviated by addition of methanol and azeotropic removal of trimethylborate. Additional difficulties in the ensuing epoxide-forming step were circumvented by treatment of diol 8[13] with cesium carbonate in dichloromethane to afford in high yield epoxide 9 (which was not isolated). Following the removal of cesium salts by filtration, the dichloromethane solution containing 9 was then treated directly with Et_3N/mesyl chloride to cleanly afford epoxymesylate 10.[13,16] Sodium sulfide treatment of 10 generated 3-hydroxythiophane (11) (>90% overall yield from 8) which was cleanly converted (DMAP/TsCl) to tosylate 12.[17] *m*-CPBA oxidation of 12 provided mixtures of trans and cis sulfoxides 13 and 14 (ca. 10:1). Potassium peroxymonosulfate (Oxone)[18] oxidation was equally effective in sulfide oxidation and provided a more practical oxidation procedure. The desired trans isomer 13 was produced in 77% yield accompanied by minor amounts of 14.[18] Potassium thioacetate treatment of 13 provided optically pure (1*R*,3*S*)-thioacetate 15 in >80% yield.

To access the other side-chain enantiomer, diol 8 was smoothly converted to bis(mesylate) 16[13] (TEA/MsCl/>90%). The presence of the secondary bromide substituent in 16 raised concerns about regiospecific sulfide addition and episulfide formation during thiophane ring construction. These concerns were justified as bromide 17 was obtained in only 35–40% yield. Fortunately 17 was the only material obtained in appreciable amounts during distillation of the crude reaction mixture. Standard oxidation/thioacetate displacement conditions were employed to generate optically active (1*S*,3*R*)-thioacetate 19.

Thioacetates 15 and 19 and all other products containing the *cis*-3-thio-1-thiophane sulfoxide moiety are susceptible to an acid-catalyzed isomerization (particularly in organic solvents) to yield the undesired trans isomer.[19] As a result, the preparation of 15 and 19 and subsequent reactions (workups) were carefully monitored to ensure the structural integrity of this sidechain.

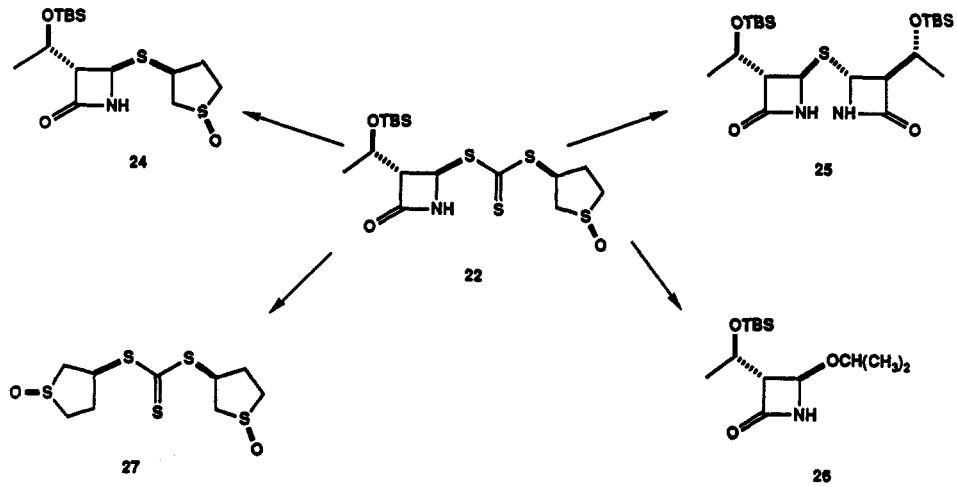
(13) Shibata, T.; Iino, K.; Sugimura, Y. *Heterocycles* **1986**, *24*, 1331.
(14) Walden, P. *Chem. Ber.* **1895**, *28*, 2766. Murakami, T.; Koga, K.; Yamada, S. *Chem. Pharm. Bull.* **1978**, *26*, 307.
(15) Feringa, B. L.; DeLange, B. *Tetrahedron*, **1982**, *44*, 7213. Ikegami, S.; Katsuki, T.; Yamaguchi, M. *Chem. Lett.* **1982**, *1*, 83. Mori, K.; Ikunara, M. *Tetrahedron* **1982**, *40*, 3471. Ladner, W. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1982**, *106*, 1982. Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1982**, *49*, 3707.
(16) Mori, K.; Ikunaka, M. *Tetrahedron* **1984**, *40*, 3471. Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1981**, *46*, 1208.
(17) Urban, F. J.; Breitenbach, R.; Vincent, L. A. *J. Org. Chem.* **1990**, *55*, 3670. R. A. Volkmann U.S. Pat. 4,864,046, 1989.
(18) Quallich, G. J.; Lackey, J. W. *Tetrahedron Lett.* **1990**, *31*, 3685.

(19) For example, in the course of obtaining a ^1H NMR of *cis*-1,3-thioacetate sulfoxide 15 in $CDCl_3$, isomerization occurred (generating ca. 20% of trans isomer 20 in 30 min), presumably a result of trace amounts of acid present in this solvent. The facility of the acid-mediated stereomutation of 5-membered ring sulfoxides is precedented and most likely results form halide addition to the protonated sulfoxide moiety. See: Sagramora, L.; Garbesi. A.; Fava, A. *Helv. Chim. Acta* **1972**, *55*, 675. Mislow, K.; Simmons, I.; Melillo, J. T.; Ternay, A. L.; *J. Am. Chem. Soc.* **1964**, *86*, 1452. Mislow, K. *Rec. Chem. Progr.* **1967**, *28*, 217.

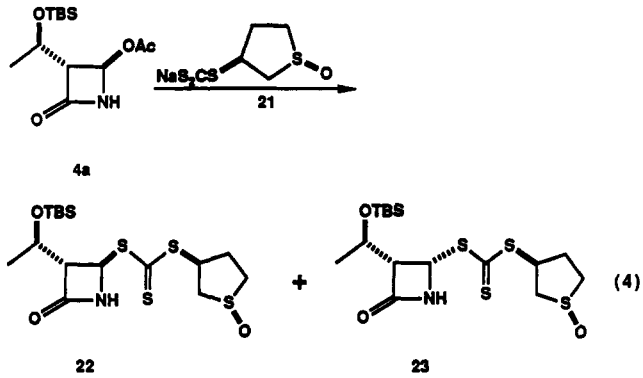


(6)

Scheme II. Azetidinone Trithiocarbonate 22 Stability Study (NaOAC/2-Propanol)



Penem Synthesis. Saponification (NaOEt/EtOH) of thioacetate **15** and trapping of the intermediate thiolate with carbon disulfide (5 equiv) provided sodiotrithiocarbonate **21** which was precipitated as a THF solvate. Condensation of **21** with acetoxyazetidinone **4a** (1.10–1.15 equiv) in *i*-PrOH (−5 to 0 °C) generated in 58% yield the desired azetidinone trithiocarbonate **22** (eq 4). Undesired



cis-substituted azetidinone trithiocarbonate **23** (which typically was not isolated) along with azetidinones **24** and **25** and symmetrical trithiocarbonate **27** were also generated in varying amounts in the condensation and underscored the complexity of this reaction. If reaction temperatures are allowed to exceed 5 °C, **22** loses carbon disulfide to generate azetidinone **24**.

Attempts to improve the overall conversion of **4a** to **22** by manipulating the trithiocarbonate counterion, the solvent, and temperature of this reaction were not successful. Our inability to improve this condensation was due, in part, to the susceptibility of trithiocarbonate **22** to generate a host of byproducts under the reaction conditions. The condensation of **21** with acetoxyazetidinone **4a** is reversible. Trithiocarbonate **22** (desired product) will react with sodium acetate in deuterated 2-propanol. Examination of this sodium acetate reaction by ^{1}H NMR revealed that acetoxyazetidinone **4a** is initially generated under these conditions and that, after 18 h, neither **4a** nor trithiocarbonate **22** is present in this reaction. The same byproducts of the azetidinone trithiocarbonate **22**-forming reaction are now the major products of this sodium acetate reaction as azetidinone **24** (50%), symmetrical trithiocarbonate **27** (25%), and azetidinones **25** (6%), and **26**[20] (3%) are produced (Scheme II).

(20) Furae, M.; Shimazaki; M.; Ohashi, T.; Watanabe, K. Japanese Patent 88222156.

The sodium acetate-mediated degradation of **22** in the NMR stability study suggested that our inability to improve the conversion of acetoxyazetidinone **4a** to trithiocarbonate **22** was tied to the promiscuous acetate leaving group of **4a** and underscored the need for an alternate azetidinone precursor (bearing a different C_4 leaving group). Chloroazetidinone **4b** was selected as an attractive alternative because of its superior reactivity[21] and because the resultant condensation products of **4b** and **21** (trithiocarbonate **22** and sodium chloride) would most likely be compatible. The remarkably stable yet highly reactive chloroazetidione **4b** was prepared as described in the literature.[22] Treatment of sodium trithiocarbonate **21** with chloroazetidinone **4b** in acetone at 0 °C provided the desired trithiocarbonate **22** in >90% yield (Scheme III). As a result, the side products which plagued the acetoxyazetidinone condensation were no longer a significant factor and **22** could be generated in high yield.

Standard acylation conditions (iPr_2NEt/oxalyl chloride **28**[23]/CH_2Cl_2/0 °C) were initially employed to convert trithiocarbonate **22** to oxalimide **5**. Sulfoxide O-acylation, however, was competitive with azetidinone N-acylation under these and a variety of other conditions. Oxalimide **5** was accompanied by trithiocarbonate degradation products including bicyclic trithiocarbonate **29** (produced in ca. 40% yield), a Pummerer byproduct of **22**, and trithiocarbonate **30**, the sulfoxide reduction product of **22**. Both degradation products (**29** and **30**) most likely result from sulfoxide O-acylation. The overall yield of **5** was poor (<10% at −5 °C), demonstrating the need for a chemoselective acylating reagent. Oxalyl fluoride **31** was chosen as a potential solution to this problem and was generated by treatment of chloride **28** with CsF in CH_3CN. The selection of **31** is supported by recent reports[24] describing the reaction selectivity of acyl fluorides and importantly demonstrating acyl fluoride–sulfoxide compatibility. DMSO, for example, reacts violently with chloroformates,

(21) A comparative study examining the effect of leaving groups on the reactivity of 4-substituted azetidin-2-ones is not available; an approximate order of reactivity has been suggested for substituents in the 4-position (Cl > SO_2Ph > OAc > SCSOEt, SCS_2Et > N_3 > OEt > SEt. See: Volkmann, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, Chapter 1.12.

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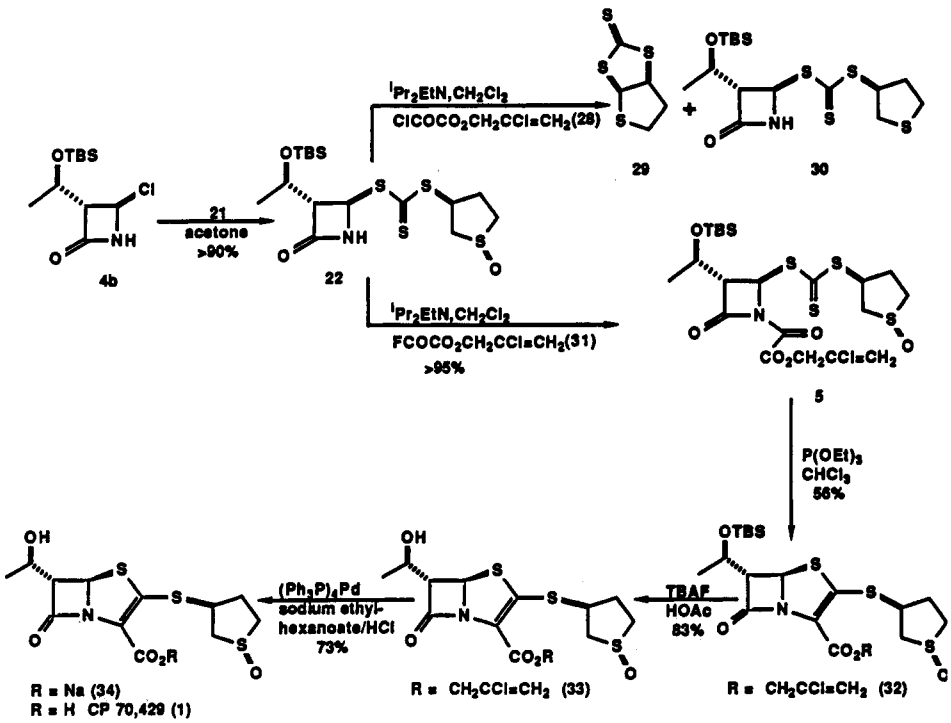
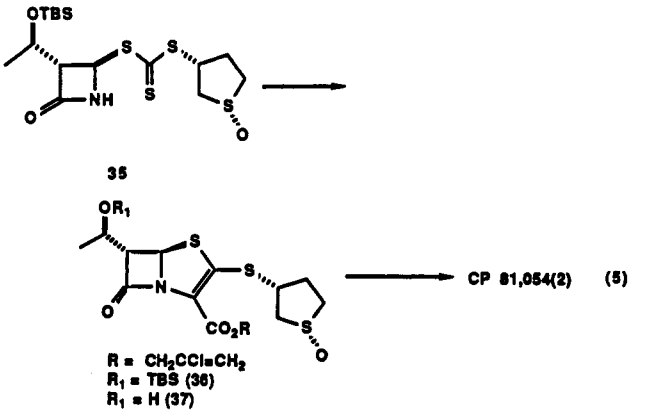
Scheme III



but can be used as a solvent in fluoroformate reactions.[25] In our case, oxalofluoride **31** worked exceedingly well. Dropwise addition of Hunig's base to a CH_2Cl_2 solution (−50 to −60 °C) containing **22** and **31** provided the desired **5** in >95% yield. Remarkably, no byproducts indicative of sulfoxide acylation were isolated.

The key phosphite-mediated conversion[8,9] of **5** to penem **32** was explored next. Accordingly, treatment of **5** with 2.2 equiv of $(EtO)_3P$ in EtOH-free $CHCl_3$ heated to a gentle reflux under a nitrogen atmosphere over an 18-h period provided desired penem **32**[26] in ca. 60% yield.[27] A penem skeleton having the CP-70,429 (**1**) thiophane sulfoxide side chain was now intact, and the conversion of **32** to **1** merely required removal of the alcohol and acid protecting groups. Removal of the *tert*-butyldimethylsilyl moiety was accomplished by TBAF[28] treatment of **32**. Reaction stoichiometry (ca. 10:3:1 HOAc–TBAF–**32**) was crucial to the success of the deprotection as insufficient HOAc results in penem degradation. Alcohol **33** was obtained in 83% yield and was converted to **1** using the palladium(0)-mediated transesterification procedure reported by McCombie and Jeffrey.[29] Accordingly, alcohol **33** was allowed to react with $Ph_3P/(Ph_3P)_4Pd$/sodium hexanoate in CH_2Cl_2 to generate crude sodium salt **34**. An aqueous solution of crude penem sodium salt **34** was subsequently treated with activated charcoal to remove residual palladium impurities retained from the chloroallyl ester deprotection. This purified salt solution was treated with 6 N HCl to yield the crystalline free acid CP-70,429 (**1**). No sulfoxide isomerization was observed in the preparation of **1**.

Chemistry employed in the conversion of thioacetate sulfoxide **15** to CP-70,429 (**1**) was utilized for the conversion of diastereomeric thioacetate sulfoxide **19** to CP-81,054 (**2**) (via intermediates **35**–**37**) (eq 5).



In summary, a practical synthesis of novel thiophane sulfoxide-containing penems **1** and **2** has been achieved. In the process, an asymmetric synthesis of *cis*-3-mercaptothiophane sulfoxides was developed. In addition, synthetic methodology was modified to accommodate the fragile architecture of these targeted penems. Both CP-70,429 (**1**) and diastereomer **2** display an impressive antibacterial profile. Because of its superior stability to renal dehydropeptidase, CP-70,429 (**1**) (sulopenem) was selected for clinical progression. A summary of its biological profile will be published in due course.

Experimental Section

General Methods. Reagents, starting materials, and solvents were purchased from common commercial suppliers and were used as received or distilled from the appropriate drying agent. Reactions requiring anhydrous conditions were performed under an atmosphere of nitrogen or argon. Reaction products were purified, when necessary, by chromatography on silica gel (63–200 μm) with the solvent system indicated. Melting points were determined on a Thomas Hoover capillary melting point apparatus and were uncorrected. Infrared spectra were recorded on a Perkin-Elmer 283B spectrophotometer and are reported in cm^{-1}. ^1H spectra were recorded on a Varian VT-300 operating at 300.1 MHz, a

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(27) In addition to 5-thiophane sulfoxide-containing penem **32**, minor amounts (<3%) of the corresponding *S*-ethyl penem were also produced. For a synthesis of this *S*-ethyl penem, see: Leanza, W. J.; DiNinno, F.; Muthard, D. A.; Wilkening, R. R.; Wildonger, K. J.; Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron* **1983**, *39*, 2505.
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Bruker WM-250 operating at 250.1 MHz, or on a Bruker AM-500 operating at 500.1 MHz and are reported in δ units. ^{13}C NMR data were measured on a Varian VT-300 operating at 75.47 MHz, on a Bruker WM-250 equipped with an Aspect 3000 computer operating at 62.9 MHz, or on a Bruker AM-500 operating at 125.76 MHz. Spectra were recorded in $CDCl_3$ with $CHCl_3$ (7.26 ppm for ^1H) or $CDCl_3$ (77.0 ppm for ^{13}C) as an internal standard and in $(CD_3)_2SO$ and D_2O. Mass spectrometry experiments were performed on a Finnigan 4510 mass spectrometer or on a Kratos Concept IS (HR LSIMS) mass spectrometer. The latter instrument was operated at an accelerating potential of 4 kV. Cesium ions were used as the primary ion beam, and the atom gun was operated at 15 kV. Elemental analyses were performed by the Analytical Chemistry Department, Pfizer Central Research.

(*S*)-2-Bromosuccinic Acid (7). To a solution of 1000 g (9.72 mol) of sodium bromide in 2.1 L of 6 N sulfuric acid under nitrogen was added 323.1 g (2.43 mol) of L-aspartic acid, and the resulting solution was cooled to 5 °C. Sodium nitrite (201.4 g, 2.92 mol) was added in portions over a 1.5-h period while the temperature was kept below 10 °C. After the addition was completed, 1 L of distilled water was added, followed by 73.07 g (1.22 mol) of urea. The resulting mixture was poured into a separatory funnel and extracted with 2.5 L of ethyl ether. To the aqueous layer was added 500 g of sodium chloride and the mixture extracted three times with ether (3 × 1.25 L). The combined ether layers were washed with brine and dried (Na_2SO_4) and the solvent evaporated in vacuo to yield 303 g (63%) of diacid 7:[14] mp 185 °C; $[\alpha]_D$ = −73.5° (*c* = 6.0 in ethyl acetate); ^1H NMR (DMSO-d_6, 250.1 MHz) δ 2.83–2.91 (m, 1 H, C*H*H), 2.91–3.11 (m, 1 H, CH*H*), 4.48–4.54 (m, 1 H, CH); ^{13}C NMR (DMSO-d_6 62.90 MHz) δ 39.57, 40.39, 170.03, 170.09.

(*S*)-2-Bromo-1,4-butanediol (8). Under a nitrogen atmosphere, 303.14 g (1.54 mol) of (*S*)-2-bromosuccinic acid (7) was dissolved in 3.2 L of anhydrous tetrahydrofuran and the mixture cooled to −20 °C. To this solution was added dropwise over 90 min a solution of 350.78 g (4.62 mol) of borane–methyl sulfide complex in 438 mL of tetrahydrofuran. The reaction mixture was allowed to warm slowly to 18 °C whereupon the reaction mixture began liberating hydrogen gas and became exothermic. The mixture was cooled using a dry ice/acetone bath, and a constant flow of nitrogen gas was passed over the mixture. After 15 min the cooling bath was removed, and the reaction was allowed to warm to ambient temperature and maintained under a sweep of nitrogen gas for 60 h. One L of methanol was then added slowly. The sweep of nitrogen gas continued for 30 min, and the solvents were then evaporated in vacuo. The residue was taken up in 1 L of methanol, and solvent was evaporated under reduced pressure. This procedure was repeated two more times to yield 282.41 g (100%) of diol 8[13] as an oil: ^1H NMR ($CDCl_3$, 250.1 MHz) δ 2.06–2.16 (m, 2 H, CH_2), 2.83 (bs, 2 H, OH), 3.74–3.91 (m, 4 H, CH_2O), 4.26–4.34 (m, 1 H, CHBr); ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ 37.90, 54.66, 60.04, 67.11.

(*R*)-(2-Hydroxyethyl)oxirane (9) and (*R*)-[2-[(Methanesulfonyl)oxy]ethyl]oxirane (10). A. Employing anhydrous conditions under a nitrogen atmosphere, 20 g (0.118 mol) of (*S*)-2-bromo-1,4-butanediol (8) was dissolved in 400 mL of dry methylene chloride and 69.41 g (0.213 mol) of cesium carbonate was added. The mixture was stirred at room temperature for 40 h and then filtered. The residue was washed with methylene chloride. The combined filtrate and wash liquor were used directly in **B** below. When desired, the solvent could be removed under reduced pressure to yield intermediate (*R*)-(2-hydroxyethyl)oxirane (9)[13] as an oil in virtually quantitative yield: ^1H NMR ($CDCl_3$, 250.1 MHz) δ 1.58–1.66 (m, 1 H, C*H*H), 1.82–1.91 (m, 1 H, CH*H*), 2.49–2.53 (m, 1 H, C*H*HO), 2.71–2.75 (m, 2 H, CH*H*O, OH), 2.99–3.05 (m, 1 H, CHO), 3.71 (t, 2 H, CH_2OH).

B. To a flame-dried flask under a nitrogen atmosphere was added the entire product solution from **A** (about 800 mL) containing **9**, which was then cooled to −25 °C. Triethylamine (21.55 g, 0.213 mol) was added followed by slow addition of 20.34 g (0.178 mol) of methanesulfonyl chloride over 25 min while the reaction temperature was maintained at less than −20 °C. The resulting mixture was allowed to warm to room temperature over 1.5 h and washed with pH 4 phosphate buffer (1 × 50 mL), and the buffer was back-extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were combined with the original organic layer and washed with saturated NaCl (1 × 50 mL) and the brine back-extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were combined with the original organic layer and were dried ($MgSO_4$) and concentrated under reduced pressure to yield 19.62 g (>98%) of mesylate 10[13,16] as an oil: $[\alpha]_D$ = +34.7° (*c* = 0.1 in CH_2Cl_2); ^1H NMR ($CDCl_3$, 250.1 MHz) δ 1.76–1.85 (m, 1 H, CH*H*), 2.02–2.11 (m, 1 H, C*H*H), 2.50–2.52 (m, 1 H, C*H*HO), 2.77–2.80 (m, 1 H, CH*H*O), 2.98–3.04 (m, 1 H, CHO), 2.99 (s, 3 H, CH_3), 4.32 (t, 2 H, CH_2O).

(*R*)-3-Hydroxythiolane (11). Under a nitrogen atmosphere, 19.62 g (0.118 mol) of (*R*)-[2-[(methanesulfonyl)oxy]ethyl]oxirane (10) was dissolved in 600 mL of acetonitrile and 100 mL of water. Sodium sulfide (18.67 g, 0.239 mol) was added, and the reaction mixture was stirred at room temperature for 24 h. The two layers were separated, and the aqueous layer was extracted with methylene chloride (3 × 15 mL). The combined organic layers were washed with 1 N sodium hydroxide. The aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL), salted with NaCl, and extracted with an additional 2 × 100 mL of CH_2Cl_2. All organic layers were combined, washed with 50 mL of 1 N NaOH and 50 mL of saturated NaCl, dried ($MgSO_4$), and concentrated in vacuo to yield 11.05 g of 11 (90% step yield, 90% overall yield from the (*S*)-2-bromo-1,4-butanediol (8)): bp 45 °C (0.2 mm); $[\alpha]_D$ = +13.93° (*c* = 1.4, $CHCl_3$). For the corresponding *S*-isomer, Brown et al.[10] reported $[\alpha]_D^{25}$ = −14.5° (*c* = 1, $CHCl_3$): ^1H NMR ($CDCl_3$, 250.1 MHz) δ 1.70–1.90 (m, 1 H, C*H*H), 2.00–2.18 (m, 2 H, CH*H*, OH), 2.70–2.98 (m, 4 H, CH_2S, CH_2S), 4.50–4.52 (m, 1 H, CHO); ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ 28.29, 38.09, 39.66, 74.48; HRMS (EI) cald for C_4H_8OS 104.0296, found 104.0297.

(*R*)-3-[(*p*-Toluenesulfonyl)oxy]thiolane (12). In a flame-dried flask under a nitrogen atmosphere, 11.03 g (0.106 mol) of (*R*)-3-hydroxythiolane (11) was dissolved in 150 mL of dry methylene chloride and cooled to −5 °C. To this solution were added 25.88 g (0.212 mol) of 4-(dimethylamino)pyridine and 20.19 g (0.106 mol) of *p*-toluenesulfonyl chloride, and the mixture was stirred at room temperature for 60 h. The reaction mixture was then washed with 1 N hydrochloric acid (25 mL), the wash was extracted with methylene chloride (3 × 50 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to provide 34.73 g of crude product. The crude product was passed through a silica gel pad (5-in. diameter, 4-in. deep), eluting with 1:5 ethyl acetate–hexane and then ethyl acetate alone to yield 21.52 g (79%) of tosylate 12 as an oil: $[\alpha]_D$ = +16.76° (*c* = 2.98, $CHCl_3$); ^1H NMR ($CDCl_3$, 250.1 MHz) δ 1.84–1.97 (m, 1 H, C*H*H), 2.20–2.38 (m, 1 H, CH*H*), 2.42 (s, 3 H, CH_3), 2.78–3.00 (m, 4 H, CH_2S, CH_2S), 5.14–5.20 (m, 1 H, CHO) 7.32 (d, *J* = 8.4 Hz, 2 H, ArCH), 7.76 (d, *J* = 8.4 Hz, 2 H, ArCH); ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ 21.70, 28.10, 36.58, 36.58, 83.79, 127.74, 130.03, 133.97, 145.05.

(*R*)-3-[(*p*-Toluenesulfonyl)oxy]thiolane 1(*R*)-Oxide (13). A solution of 46.30 g (0.179 mol) of (*R*)-3-[(toluenesulfonyl)-oxy]thiolane (12) in 600 mL of acetone under a nitrogen atmosphere was cooled to 0 °C. In a separate flask, 61.73 g (0.100 mol) of potassium peroxymonosulfate (Oxone) was stirred in 500 mL of distilled water. This aqueous solution was added to the acetone solution at 0 °C, and the mixture was allowed to warm to room temperature. After 25 min, 75 mL of a 10% (w/v) aqueous sodium sulfite solution was added. Acetone was removed under reduced pressure, 300 mL of ethyl acetate was added, and the aqueous layer was separated. The aqueous layer was extracted again with ethyl acetate (3 × 100 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo to yield 48.57 g of crude product which was purified by silica gel chromatography using 10:10:1 EtOAc–CH_2Cl_2–CH_3OH as eluant to afford 34.67 g (71%) of sulfoxide 13 as a waxy solid: $[\alpha]_D$ = +4.26° (*c* = 3.0, $CHCl_3$); IR (KBr) ν_{max} 1363, 1192, 1179, 1026, 928, 874, 659, 554 cm^{-1}; ^1H NMR ($CDCl_3$, 250.1 MHz) δ 2.41 (s, 3 H, CH_3), 2.59–3.01 (m, 5 H, CH_2, CH_2SO, CHSO), 3.36–3.44 (m, 1 H, CHSO) 5.36–5.41 (m, 1 H, CHO), 7.33 (d, *J* = 8.3 Hz, 2 H, ArCH), 7.72 (d, *J* = 8.3 Hz, 2 H, ArCH); ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ 21.90, 32.56, 50.81, 61.80, 81.90, 127.75, 130.30, 133.31, 145.65, HRMS (EI) calcd for $C_{11}H_{14}O_4S$ 274.0334, found 274.0305.

(*S*)-3-(Acetylthio)thiolane 1(*R*)-Oxide (15). In a flame-dried flask under a nitrogen atmosphere, 31.67 g (0.1156 mol) of (*R*)-3-[(*p*-toluenesulfonyl)oxy]thiolane 1(*R*)-oxide (13) was dissolved in 300 mL of acetone, and 19.81 g (0.1734 mol) of potassium thioacetate was added. This mixture was heated at reflux for 3.5

h and then allowed to stir at room temperature overnight. The crude reaction mixture was filtered, the residue was washed with 500 mL of acetone, and the filtrate and washings were evaporated in vacuo to yield 23.96 g of crude product as an oil. The oil was purified by silica gel flash chromatography using a 19:1 ethyl acetate–methanol solvent mixture as eluant to yield 16.46 g (80%) of thioacetate **15** as an oil which crystallized on standing: mp 51–52 °C; $[\alpha]_D$ = −83.41° (*c* = 0.86, $CHCl_3$); IR (KBr) ν_{max} 1689, 1116, 1025, 627 cm^{-1}; ^1H NMR ($CDCl_3$, 250.1 MHz) δ 2.34 (s, 3 H, CH_3), 2.50–2.59 (m, 2 H, CH_2), 2.63–2.79 (m, 2 H, CHSO, CHSO) 3.02–3.12 (m, 1 H, CHSO), 3.66–3.76 (m, 1 H, CHSO), 3.86–4.00 (m, 1 H, CHS); ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ 30.37, 31.84, 40.73, 53.09, 60.44, 194.97. Anal. Calcd for $C_6H_{10}O_2S_2$: C, 40.43; H, 5.65. Found: C, 40.15; H, 5.53%.

(*S*)-2-Bromo-1,4-bis[(methanesulfonyl)oxy]butane (16). A solution of 70 g (0.414 mol) of (*S*)-2-bromo-1,4-butanediol (**8**) in 1.5 L of methylene chloride was cooled to 0 °C, and 173 mL (1.24 mol) of triethylamine (dried over potassium hydroxide) was added. To this solution was added dropwise, over 80 min, 96 mL (1.24 mol) of methanesulfonyl chloride while the temperature was maintained between 5 and 15 °C. The mixture was then stirred at room temperature for 2.5 h, washed with 2 × 750 mL of water and 1 × 750 mL of brine, and dried ($MgSO_4$) and the solvent evaporated to give an amber oil which was purified by chromatography on a 140-mm × 25-cm silica gel column, eluting with 9:1 chloroform–ethyl acetate. The product fractions were combined and solvent evaporated to give 105 g (97%) of dimesylate **16**[13] as a waxy white solid: $[\alpha]_D$ = +34.49° (*c* = 5, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 2.11–2.18 (m, 1 H, C*H*H), 2.41–2.48 (m, 1 H, CH*H*), 3.05 (s, 3 H, CH_3), 3.09 (s, 3 H, CH_3), 4.28–4.50 (m, 5 H, CHBr, CH_2O, CH_2O); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 34.09, 37.36, 37.77, 45.16, 66.84, 71.41.

(*S*)-3-Bromothiolane (17). To a solution of 97.1 g (0.37 mol) (*S*)-2-bromo-1,4-bis[(methanesulfonyl)oxy]butane (**16**) in 1400 mL of methanol was added over a 1-h period a solution of 98.23 g (0.41 mol) of sodium sulfide nonahydrate in 500 mL of water at 20–26 °C. The mixture was stirred at room temperature for 80 h. The reaction mixture was diluted with 6 L of methylene chloride, and the organic layer was separated and was subsequently washed with 2 × 1 L of H_2O and 1 × 1500 mL of brine and was dried (Na_2SO_4). The solvent was evaporated in vacuo to provide ca. 39.0 g of crude product as a pale yellow oil. The crude oil was distilled in vacuo to yield 26.0 g (38% overall) of bromide **17** (bp 32 °C (0.4 mm)). Alternatively, the crude product (3.0 g) was purified by flash chromatography on silica gel, using 9:1 hexane–ethyl acetate as eluant, to afford 2.03 g (39% overall) of bromide **17**; $[\alpha]_D$ = −104.57° (*c* = 0.53 in $CHCl_3$); ^1H NMR ($CDCl_3$, 250.1 MHz) δ 2.24–2.34 (m, 2 H, CH_2), 2.81–2.89 (m, 1 H, CHS), 2.97–3.08 (m, 2 H, CHS, CHS), 3.23–3.31 (m, 1 H, CHS), 4.44–4.51 (m, 1 H, CHBr); ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ 29.03, 40.62, 40.67, 50.43; HRMS (EI) calcd for C_4H_7BrS 165.9452, found 165.9477.

(*S*)-3-Bromothiolane 1(*S*)-Oxide (18). To a solution of 29.3 g (0.175 mol) of (*S*)-3-bromothiolane (**17**) in 290 mL of acetone cooled to 0 °C was added a solution of 64.68 g (0.105 mol) of potassium peroxymonosulfate (Oxone) in 290 mL of water at 0–5 °C over 1 h, and the resulting mixture was stirred at 0–5 °C for 15 min. A 10% (w/v) solution of sodium bisulfite (50 mL) was added, and the mixture was concentrated under reduced pressure to half its original volume and was extracted with methylene chloride (3 × 500 mL). The organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give crude product which was crystallized from ether–isopropyl ether to yield 14.0 (44%) of **18** a white solid, mp 68–70 °C. The mother liquor was concentrated in vacuo to yield 14.6 g of a white solid which was chromatographed on silica gel using 49:1 ethyl acetate–methanol as eluant to yield an additional 7.3 g (23%) of sulfoxide **18** (combined yield of 67%): mp 68–70 °C; $[\alpha]_D$ = −99.94° (*c* = 5, $CHCl_3$); ^1H NMR ($CDCl_3$, 250.1 MHz) δ 2.40–2.49 (m, 1 H, CH), 2.85–3.03 (m, 2 H, CH, CHSO), 3.20–3.45 (m, 3 H, CH_2SO, CHSO), 4.83–4.90 (m, 1 H, CHBr); ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ 36.85, 45.33, 52.68, 64.74. Anal. Calcd for C_4H_7BrOS: C, 26.24, H, 3.85; S, 17.51. Found: C, 26.47, H, 3.89, S, 17.71.

(*R*)-3-(Acetylthio)thiolane 1(*S*)-Oxide (19). (*S*)-3-Bromothiolane 1(*S*)-oxide (**18**) (24.0 g, 0.131 mol) was treated with potassium thioacetate (22.5 g, 0.197 mol) as described in the conversion of **13** to **15** to give crude product which crystallized upon reaction workup. This material was purified by flash chromatography on silica gel using 49:1 ethyl acetate–methanol as eluant to afford 19.6 g (84%) of thioacetate **19**. A sample was recrystallized from isopropyl ether: mp 57–59 °C; $[\alpha]_D$ = +85.73° (*c* = 1 in $CHCl_3$); ^1H NMR ($CDCl_3$, 250.1 MHz) δ 2.25 (s, 3 H, CH_3), 2.44–2.58 (m, 2 H, CH_2), 2.63.2.72 (m, 2 H, CHSO, CHSO), 2.94–3.03 (m, 1 H, CHSO), 3.59–3.67 (m, 1 H, CHSO), 3.81–3.91 (m, 1 H, CHS); ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ 30.40, 31.84, 40.76, 53.11, 60.46, 195.10. Anal. Calcd for $C_6H_{10}O_2S_2$: C, 40.43, H, 5.65. Found: C, 40.69; H, 5.45.

3(*S*)-[[Mercapto(thiocarbonyl)]thio]thiolane 1(*R*)-Oxide Sodium Salt (21). In a flame-dried flask under a nitrogen atmosphere, a solution of 3.56 g (20 mmol) of 3(*S*)-(acetylthio)-thiolane 1(*R*)-oxide (**15**) in 8 mL of ethanol was cooled to −5 °C. 2 M Sodium ethoxide (9.75 mL, 19.5 mmol) was added, and the mixture was stirred at −5 °C for 30 min and at 0 °C for an additional 30 min. TLC (95:5 EtOAc–MeOH) showed a trace of **15**. The reaction mixture was cooled to −30 °C, 6.0 mL (100 mmol) of carbon disulfide was added, and stirring was continued at −20 °C for 30 min. To this solution was added 100 mL of anhydrous tetrahydrofuran. The resulting mixture was stirred at −20 °C for 30 min and then added dropwise to 800 mL of diethyl ether to afford a bright yellow precipitate. The mixture was filtered, washed with diethyl ether, and dried under a nitrogen atmosphere to give 5.0 g of crude product. This material was placed in 30 mL of tetrahydrofuran, stirred overnight, filtered, and dried under a nitrogen atmosphere to afford 5.38 g (90%) of **21**, solvated with 1.0 molar equiv of tetrahydrofuran: mp 169–171 °C dec; $[\alpha]_D$ = −56° (*c* = 0.01, MeOH); ^1H NMR (D_2O, 300.1 MHz) δ 1.85–1.95 (m, 4 H, CH_2CH_2), 2.39–2.55 (m, 1 H, C*H*H), 2.79–3.27 (m, 4 H, CH*H*, CH_2SO, CHSO), 3.71–3.80 (m, 4 H, OCH_2, OCH_2), 4.04 (dd, *J* = 9.1, 15.1 Hz, 1 H, CHSO), 4.44–4.55 (m, 1 H, CHS); ^{13}C NMR (D_2O, 75.47 MHz) δ 28.04, 33.40, 54.83, 55.00, 61.54, 70.84, 247.29. This material lost tetrahydrofuran on standing and was somewhat hygroscopic and as a result was not fully characterized but was used directly in the next step.

(3*S*,4*R*)-3-[(1*R*)-1-[(Dimethyl-*tert*-butylsilyl)oxy]-ethyl]-4-[[[(1(*R*)-oxo-3(*S*)-thiolanyl)thio]thiocarbonyl]-thio]-2-azetidinone (22) and (3*S*,4*S*)-3-[(1*R*)-1-[(dimethyl-*tert*-butylsilyl)oxy]ethyl]-4-[[[(1(*R*)-oxo-3(*S*)-thiolanyl)-thio]thiocarbonyl]thio]-2-azetidinone (23). To an isopropyl alcohol (20 mL) solution containing (3*R*,4*R*)-4-acetoxy-3-[1(*R*)-[(dimethyl-*tert*-butylsilyl)oxy]ethyl-2-azetidinone (**4a**) (1.87 g, 6.5 mmol) and carbon disulfide (0.15 mL, 2.5 mmol) at 3 °C under a nitrogen atmosphere was added portionwise sodium trithiocarbonate **21** (1.54 g, 5.0 mmol) while the reaction temperature was maintained at 3 °C. After 0.5 h at 3 °C, the reaction was quenched in 40 mL of a saturated ammonium chloride solution and 50 mL of ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with an additional 2 × 25 mL of ethyl acetate. The combined ethyl acetate layers were washed with 2 × 20 mL of H_2O and 2 × 20 mL of 20% $CaCl_2$ and were dried over $MgSO_4$, filtered, and concentrated in vacuo to yield crude product. This material was dissolved in 5 mL of acetone, and 70 mL of isopropyl ether was added dropwise, inducing product crystallization. This suspension was stirred for 1 h, and then 120 mL of petroleum ether was added rapidly with stirring. The resulting solids were collected by filtration and air-dried to give 1.27 g (58%) fo **22**. The mother liquors were chromatographed on silica gel using 9:1 ethyl acetate–methanol as eluant to yield 470 mg of **22** and **23** as a foam, from which an additional 343 mg of **22** and **23** (3:1 **22**:**23**) could be crystallized as described above. Using a Zorbax Sil column (21.2 mm × 25 cm, 7 μm) this mixture was fractionated using hexane–EtOAc–MeOH (50:47.5:2.5) at 20 mL/min to give **22** and **23**. Recrystallization of **22** from 4 mL of acetone by the same procedure gave an analytical sample of azetidinone trithiocarbonate **22**: mp 75–76 °C; $[\alpha]_D$ = +126 (*c* = 0.01, $CHCl_3$); IR (KBr) ν_{max} 2951, 2925, 1764, 1076, 1021, 957, 825, 810 cm^{-1}; ^1H NMR ($CDCl_3$, 500.1 MHz) δ 0.06 (s, 6 H, $SiMe_2$), 0.87 (s, 9 H, tBuSi), 1.30, (d, *J* = 6.3 Hz, 3 H, CH_3CH), 2.71–2.89 (m, 4 H, CH_2, CHSO, CHSO), 3.15–3.24 (m, 2 H, C*H*SO, C*H*CO), 3.72–3.81 (m, 1 H, CHSO), 4.27–4.31 (m, 1 H, CHO), 4.55–4.65 (m, 1 H, CHS), 5.65 (d, *J* = 2.5 Hz, 1 H, CHN), 6.75 (bs, 1 H, NH); ^{13}C NMR ($CDCl_3$, 125.76 MHz) δ −5.15, −4.30, 17.86, 22.38, 25.64, 30.96, 47.76, 52.63, 57.28, 59.18,

63.72, 64.40, 166.15, 222.72. Anal. Calcd for $C_{16}H_{29}NO_3S_4Si$: C, 43.70; H, 6.65, N, 3.19. Found: C, 43.48; H, 6.86; N, 3.08. Trithiocarbonate **23**: mp 119–120.5 °C; $[\alpha]_D$ = −296.3° (*c* = 0.01, $CHCl_3$); ^1H NMR ($CDCl_3$, 300.1 MHz) δ 0.08 (s, 3 H, SiMe), 0.09 (s, 3 H, SiMe), 0.89 (s, 9 H, tBuSi), 1.26 (d, *J* = 6.5 Hz, 3 H, CH_3CH), 2.65–2.76 (m, 3 H, CH_2, CHSO), 2.81–2.88 (m, 1 H, CHSO), 3.12–3.17 (m, 1 H, CHSO), 3.62–3.65 (m, 1 H, CHCO), 3.78 (dd, *J* = 8.8, 14.7 Hz, 1 H, CHSO), 4.32–4.40 (m, 1 H, CHO), 4.50–4.55 (m, 1 H, CHS), 5.88 (d, *J* = 5.2 Hz, 1 H, CHNS), 6.63 (bs, 1 H, NH); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ −4.94, −4.08, 18.00, 22.00, 25.83, 30.74, 47.71, 52.71, 59.69, 59.78, 63.32, 64.80, 166.40, 225.19; HRMS (FAB) M + H calcd for $C_{16}H_{30}NO_3S_4Si$ 440.0877, found 440.0877.

(3*S*,4*R*)-3-[(1*R*)-1-[(Dimethyl-*tert*-butylsilyl)oxy]ethyl]-4-[[[(1(*R*)-oxo-3(*S*)-thiolanyl)thio]thiocarbonyl]thio]-2-azetidinone (22). A suspension of trithiocarbonate **21** as a THF solvate (306 mg, 1 mmol) in acetone at 0 °C under a nitrogen atmosphere was stirred rapidly while chloroazetidinone **4b**[22] (264 mg, 1 mmol) was added in one portion. The mixture was stirred for 30 min and quenched in 1:1 EtOAc–pH 7 phosphate buffer (100 mL). The organic layer was separated and washed with pH 7 phosphate buffer (1 × 50 mL) and brine (1 × 50 mL) and dried over sodium sulfate. The ethyl acetate was removed under reduced pressure, giving 423 mg (96%) of a yellow solid containing trithiocarbonates **22** and **23**. This product [(**22** (97.5%) and **23** (2.5%))] was dissolved in 3 mL of acetone. Isopropyl ether (50 mL) was added dropwise followed by petroleum ether (50 mL). The resultant suspension was stirred overnight and filtered to afford 372 mg (85%) of **22**. An additional 26 mg (6%) of **22** was obtained from the filtrate by repeating this isolation procedure.

Treatment of 22 with Sodium Acetate. Production of (3*S*,4*R*)-3-[(1*R*)-1-[Dimethyl-*tert*-butylsilyl)oxy]ethyl]-4-[(1(*R*)-oxo-3(*S*)-thiolanyl)thio]-2-azetidinone (24), 4,4′-Thiobis[(3*S*,4*R*)-3-[(1*R*)-1-[(dimethyl-*tert*-butylsilyl)oxy]ethyl]-2-azetidinone] (25), (3*S*,4*R*)-3-[(1*R*)-1-[(Dimethyl-*tert*-butylsilyl)oxy]ethyl]-4-(isopropoxy)-2-azetidinone (26), and 3(*S*)-[[[(1(*R*)-Oxo-3(*S*)-thiolanyl)thio]thiocarbonyl]thio]thiolane 1(*R*)-Oxide (27). To an isopropyl alcohol solution (10 mL) containing trithiocarbonate **22** (439 mg, 1 mmol) was added sodium acetate (75 mg, 0.95 mmol). The reaction was allowed to stir for 14 h and was concentrated under reduced pressure. The crude reaction mixture was separated by silica gel chromatography using 1:1 EtOAc–hexane as eluant to afford 52 mg of a mixture of bisazetidinone **25** and azetidinone **26**[20] followed by 9:1 EtOAc–MeOH to afford 211 mg of azetidinone **24** and 74 mg of symmetrical trithiocarbonate **27**. Bisazetidinone **25** and azetidinone **26** were separated on silica gel using 6:1 hexane–EtOAc. Bisazetidinone **25** crystallized as needles from hexane. Azetidinone **24**; mp 123–124.5 °C; $[\alpha]_D$ = +156 (*c* = 0.01, $CHCl_3$); ^1H NMR ($CDCl_3$, 300.1 MHz) δ 0.05 (s, 3 H, SiMe), 0.06 (s, 3 H, SiMe), 0.86 (s, 9 H, tBuSi), 1.21 (d, *J* = 6.3 Hz, 3 H, CH_3CH), 2.56–2.81 (m, 4 H, CH_2, CHSO, CHSO), 3.06–3.11 (m, 2 H, CHSO, CHCO), 3.34–3.40 (m, 1 H, CHS), 3.65–3.72 (m, 1 H, CHSO), 4.20–4.24 (m, 1 H, CHO), 4.88 (d, *J* = 2.1 Hz, 1 H, CHN), 6.96 (bs, 1 H, NH); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ −4.99, −4.29, 17.96, 22.36, 25.74, 33.77, 41.84, 52.87, 53.54, 60.72, 64.77, 66.62, 167.01; HRMS (FAB) M + H calcd for $C_{15}H_{30}NO_3S_2Si$ 364.1429, found 364.1426. Bisazetidinone **25**; mp 129.5–131 °C; $[\alpha]_D$ = +80.4 (*c* = 0.01, $CHCl_3$); ^1H NMR ($CDCl_3$, 300.1 MHz) δ 0.05 (s, 6 H, SiMe), 0.06 (s, 6 H, SiMe), 0.86 (s, 18 H, tBuSi), 3.18 (dd, *J* = 2.1, 4.9 Hz, 2 H, CHCO), 4.18–4.26 (m, 2 H, CHO), 4.86 (d, *J* = 2.1 Hz, 2 H, CHN), 6.79 (bs, 2 H, NH); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ −4.75, −4.37, 18.00, 22.41, 25.80, 52.91, 65.39, 66.79, 166.96; HRMS (FAB) M + H calcd for $C_{22}H_{45}N_2O_4SSi_2$ 489.2639, found 489.2639. Azetidinone **26**:[20] ^1H NMR ($CDCl_3$, 300.1 MHz) δ 0.04 (s, 3 H, SiMe), 0.05 (s, 3 H, SiMe), 0.84 (s, 9 H, tBuSi), 1.16–1.20 (m, 6 H, $CH(CH_3)_2$), 1.22 (d, *J* = 6.3 Hz, 3 H, CH_3CH), 2.98 (dd, 1 H, CHCO), 3.75 (m, *J* = 6.3 Hz, 1 H, $OCH(CH_3)_2$), 4.12–4.16 (m, 1 H, CHO), 5.10 (d, *J* = 2.0 Hz, CHN), 6.19 (bs, 1 H, NH). Trithiocarbonate **27**; mp 184–187 °C $[\alpha]_D$ = −123.5 (*c* = 0.01, 98:2 MeOH–$CHCl_3$); ^1H NMR ($CDCl_3$, 300.1 MHz) δ 2.65–2.86 (m, 8 H, CH_2, CHSO, CHSO), 3.07–3.20 (m, 2 H, CHSO), 3.79 (dd, *J* = 8.8, 14.7 Hz, 2 H, CHSO), 4.47–4.57 (m, 2 H, CHS); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 30.86, 47.81, 52.73, 59.60, 222.14; HRMS (FAB) M + H calcd for $C_9H_{15}O_2S_5$ 314.9668, found 314.9665.

2-Chloroallyl Oxalochloride [[(2-Chloroallyl)oxy]oxalyl Chloride] (28). Oxalyl chloride (130 mL, 1.49 mol) was placed in a dry three-neck flask under N_2 and cooled to 0 °C. With stirring, 2-chloroallyl alcohol (138 g, 1.49 mol) was added dropwise in a manner which maintained the temperature at 0–2 °C and controlled the vigorous evolution of HCl. The reaction mixture was allowed to warm to room temperature and after 16 h at ambient temperature was distilled to yield 214 g (78%) of oxalochloride **28**[23] (bp 82–84 °C (23 mm)): ^1H NMR ($CDCl_3$, 300.1 MHz) δ 4.88 (s, 2 H, OCH_2), 5.53 (m, 1 H, CH), 5.59 (m, 1 H, CH); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 69.42, 117.49, 133.42, 154.83, 160.35.

(3a*S*)-*cis*-Tetrahydrothieno[2,3-*d*]-1,3-dithiole-2-thione (29) and (3*S*,4*R*)-3-[(1*R*)-1-[(Dimethyl-*tert*-butylsilyl)oxy]ethyl]-4-[[(3(*S*)-thiolanylthio)thiocarbonyl]thio]-2-azetidinone (30). To a dichloromethane solution (15 mL) containing azetidinone trithiocarbonate **22** (220 mg, 0.50 mmol) cooled to −5 °C under a nitrogen atmosphere was added *N,N*-diisopropylethylamine (0.096 mL, 0.55 mmol) followed by 2-chloroallyl oxalochloride (**28**) (0.074 mL, 0.55 mmol). The reaction mixture was allowed to stir at −5 °C for 45 min, was then washed with pH 7 phosphate buffer (1 × 20 mL) and brine (1 × 20 mL), and was then dried over $MgSO_4$. The organic solution was filtered and concentrated in vacuo to yield a mixture of products which were chromatographed on silica gel using 50:50 EtOAc–hexane to afford crude bicyclic trithiocarbonate **29** [39 mg (40%)], and azetidinone trithiocarbonate **30** [32 mg, (15%)] along with other minor side products. Bicyclic trithiocarbonate **29** was further purified on silica gel using toluene as eluant to yield a solid; mp 88.5–90 °C; $[\alpha]_D$ = −211.6 (*c* = 0.005, $CHCl_3$); ^1H NMR ($CDCl_3$, 300.1 MHz) δ 2.52–2.73 (m, 2 H, CH_2), 3.09–3.17 (m, 1 H, C*H*HS), 3.43–3.51 (m, 1 H, CH*H*S), 4.73–4.80 (dd, *J* = 5.9, 7.3 Hz, 1 H, CHS), 5.89 (d, *J* = 5.9 Hz, 1 H, CHSS); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 33.17, 35.80, 65.69, 68.17, 224.79; HRMS (EI) calcd for $C_5H_6S_4$ 193.9351, found 193.9349. Azetidonone trithiocarbonate **30**: mp 101–103 °C; $[\alpha]_D$ = +104.3 (*c* = 0.005, $CHCl_3$); ^1H NMR ($CDCl_3$, 300.1 MHz) δ 0.06 (s, 3 H, SiMe), 0.07 (s, 3 H, SiMe), 0.87 (s, 9 H, tBuSi), 1.20 (d, *J* = 6.3 Hz, 3 H, CH_3CHO), 2.09–2.21 (m, 1 H, C*H*H), 2.42–2.52 (m, 1 H, CH*H*), 2.83–2.90 (dd, *J* = 6.4, 11.3 Hz 1 H, CHS), 2.94–2.99 (m 1 H, CHS), 3.20–3.22 (m, 1 H, CHCO), 3.32–3.38 (dd, *J* = 6.1, 11.3 Hz, 1 H, CHS), 4.27–4.32 (m, 1 H, CHO), 4.53–4.62 (m, 1 H, CHS), 5.65 (d, *J* = 2.5 Hz, 1 H, NCHS), 6.57 (bs, 1 H, NH); ^{13}C NMR ($CDCl_3$, 75.47 MHz), δ −5.14, −4.29, 17.91, 22.42, 25.67, 29.60, 35.60, 35.85, 53.38, 57.05, 63.66, 64.44, 165.91, 223.04; HRMS (FAB) M + H calcd for $C_{16}H_{29}NO_2S_4Si$ 424.0924, found 424.0923. Anal. Calcd for $C_{16}H_{29}NO_2S_4Si$: C, 45.35; H, 6.90; N, 3.31. Found: C, 45.36; H, 6.74; N, 3.02.

2-Chloroallyl Oxalofluoride [[(2-Chloroallyl)oxy])oxalyl Fluoride] (31). Cesium fluoride (167 g, 1.1 mol) was placed in a 1-L single-neck flask and gently heated under high vacuum with a flame until the solid became free flowing. The flask was allowed to cool to room temperature, the vacuum was broken with nitrogen, and anhydrous acetonitrile (183 mL) was added. This mixture was cooled to −20 °C, and 2-chloroallyl oxalochloride (**28**) (183 g, 1.0 mol) was added dropwise over a 30-min period under a nitrogen atmosphere. The mixture was allowed to slowly warm to room temperature and was stirred at ambient temperature for 16 h. Byproduct cesium chloride was removed by filtration and was washed with acetonitrile. The filtrate and wash were combined and concentrated in vacuo and the residue distilled at reduced pressure to yield 129 g (77%) of oxalofluoride **31** (bp 62–64 °C (22 mm)): ^1H NMR ($CDCl_3$, 500.1 MHz) δ 4.92 (s, 2 H, OCH_2), 5.55–5.63 (m, 2 H, $=CH_2$); ^{13}C NMR ($CDCl_3$, 125.76 MHz) δ 69.10, 117.43, 133.23, 145.88 (*J* = 374.5 Hz), 152.64 (*J* = 88.0 Hz); IR ($CHCl_3$) 1770, 1870 cm^{-1}; HRMS (EI) calcd for $C_3H_4ClFO_3$ 165.9833, found 165.9843.

(3*S*,4*R*)-*N*-[[(2-Chloroallyl)oxy]oxalyl]-3-[1(*R*)-[(dimethyl-*tert*-butylsilyl)oxy]ethyl]-4-[[[(1(*R*)-oxo-3(*S*)-thiolanyl)thio]thiocarbonyl]thio]-2-azetidinone (5). In a flame-dried, three-neck flask equipped with a dropping funnel and low-temperature thermometer under a nitrogen atmosphere containing a solution of trithiocarbonate **22** (2.63 g, 6.0 mmol) in 30 mL of dry methylene chloride (passed through neutral alumina) cooled to −55 °C was added *N,N*-diisopropylethylamine (1.26 mL, 7.2 mmol) followed by 2-chloroallyl oxalofluoride (**31**) (0.93 mL, 7.2 mmol). Addition occurred as fast as possible while the internal reaction temperature was maintained between −50

and −55 °C. The reaction was stirred for 15 min and was quenched with 45 mL of H_2O and was allowed to warm to 0 °C at which time additional CH_2Cl_2 (60 mL) was added. The organic layer was separated, washed with H_2O (1 × 45 mL), pH 7 phosphate buffer (1 × 60 mL), and saturated brine (1 × 50 mL), and dried over $MgSO_4$. The organic extract was filtered and concentrated in vacuo to yield 3.45 g (98%) of **5**, as a yellow foam, which was used directly in the next step: ^{1}H NMR ($CDCl_3$, 500.1 MHz) δ 0.01 (s, 3 H, SiMe), 0.07 (s, 3 H, SiMe), 0.84 (s, 9 H, tBu), 1.21 (d, J = 6.2 Hz, 3 H, CH_3), 2.65–2.89 (m, 4 H, CH_2, CHSO, CHSO), 3.11–3.16 (m, 1 H, CHSO), 3.58 (dd, J = 2.0, 3.0 Hz, 1 H, CHCO), 3.75 (d, J = 8.9, 14.9 Hz, 1 H, CHSO), 4.35 (m, 1 H, CHO), 4.58–4.63 (m, 1 H, CHS), 4.81 (s, 2 H, CH_2), 5.44 (d, J = 1.3 Hz, 1 H, =CH_2), 5.53 (m, 1 H, =CH_2), 6.67 (d, J = 3.0 Hz, 1 H, NCHS); ^{13}C NMR ($CDCl_3$, 125.76 MHz) δ −5.34, −4.30, 17.71, 21.92, 25.52, 30.89, 47.69, 52.64, 58.84, 59.22, 64.37, 65.76, 67.82, 116.61, 133.74, 153.69, 158.40, 163.13, 217.44; HRMS (FAB) M + H calcd for $C_{21}H_{33}ClNO_6S_4Si$ 586.0669, found 586.0666.

2-Chloroallyl (5*R*,6*S*)-6-[1(*R*)-[(Dimethyl-*tert*-butylsilyl)oxy]ethyl]-2-[(1(*R*)-oxo-3(*S*)-thiolanyl)thio]-2-penem-3-carboxylate (32). Under a nitrogen atmosphere, a solution of oxalimide **5** (3.45 g, 5.9 mmol) in 240 mL of ethanol-free chloroform was heated to a gentle reflux, and a solution of triethyl phosphite (2.46 mL, 14.4 mmol) in 10 mL of ethanol-free chloroform was added dropwise via syringe pump over a 24-h period. The reaction was heated at a gentle reflux for an additional 10 h and was then cooled to room temperature and concentrated in vacuo. The residue was dissolved in 5 mL of ethyl acetate and allowed to stir. Isopropyl ether (200 mL) was added dropwise to this solution as crystallization began. Finally, petroleum ether (75 mL) was added, the mixture was filtered, and the solids were air dried to afford 1.76 g (56%) of penem **32**: mp 140–141 °C; $[\alpha]_D$ = +36.78 (c = 0.5, $CHCl_3$); IR (KBr) ν_{max} 1768, 1679, 1493, 1330 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250.1 MHz) δ 0.07 (s, 6 H, $SiMe_2$), 0.87 (s, 9 H, tBuSi), 1.24 (d, J = 6.3 Hz, 3 H, CH_3), 2.63–2.85 (m, 4 H, CH_2, CHSO, CHSO), 3.10–3.14 (m, 1 H, CHSO), 3.61–3.68 (m, 1 H, CHS), 3.71 (dd, J = 1.5, 4.6 Hz, 1 H, CHCO), 3.94 (dd, J = 8.4, 14.3 Hz, 1 H, CHSO), 4.22–4.27 (m, 1 H, CHO), 4.65 (d, J = 14.2 Hz, 1 H, CO_2CH), 4.84 (d, J = 14.2 Hz, 1 H, CO_2CH), 5.38 (m, 1 H, =CH_2), 5.64 (m, 1 H, =CH_2), 5.68 (d, J = 1.5 Hz, 1 H, NCHS); ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ −5.10, −4.29, 17.96, 22.53, 25.71, 33.29, 46.82, 52.77, 61.35, 64.15, 65.05, 65.82, 71.98, 114.44, 114.44, 117.90, 134.84, 158.72, 172.05. Anal. Calcd for $C_{21}H_{32}ClNO_5S_3Si$: C, 46.89, H, 5.99; N, 2.60. Found: C, 46.75, H, 5.86; N, 2.57.

2-Chloroallyl (5*R*,6*S*)-6-(1(*R*)-Hydroxyethyl)-2-[(1(*R*)-oxo-3(*S*)-thiolanyl)thio]-2-penem-3-carboxylate (33). Under a nitrogen atmosphere penem **32** (2.13 g, 3.96 mmol) was dissolved in 2.4 mL (42.4 mmol) of glacial acetic acid. To this stirred reaction was added 2 mL of THF followed by 10.1 mL (10.1 mmol) of 1 M tetrabutylammonium fluoride in tetrahydrofuran. The resulting solution was stirred for 16 h at room temperature and was then diluted with 85 mL of ethyl acetate and 30 mL of water. The pH of the aqueous solution was adjusted to 6.4 with potassium acetate, the layers were separated, and the organic layer was washed with 3 × 25 mL of water. The aqueous layers were combined and back-washed with 3 × 25 mL CH_2Cl_2. The combined organic layers (ethyl acetate and CH_2Cl_2) were dried over Na_2SO_4, filtered, and concentrated in vacuo to yield 1.39 g (83%) of alcohol **33** as a white crystalline solid: mp 177–178 °C; $[\alpha]_D$ = +45.28° (c = 0.25 in DMSO); IR (KBr) ν_{max} 1780, 1673, 1484, 1320, 1119, 1014 cm^{-1}; ^{1}H NMR (DMSO-d_6, 250.1 MHz) δ 1.17 (d, J = 6.3 Hz, 3 H, Me), 2.41–3.03 (m, 5 H, CH_2, CH_2SO, CHSO), 3.71 (dd, J = 9.0, 14.4 Hz, 1 H, CHSO), 3.86 (dd, J = 1.4, 5.9 Hz, 1 H, CHCO), 3.92–4.04 (m, 2 H, CHO, CHS), 4.70 (d, J = 14.2 Hz, 1 H, CO_2CH_2), 4.84 (d, J = 14.2 Hz, 1 H, CO_2CH_2), 5.24 (d, J = 4.7 Hz, 1 H, OH), 5.48 (m, 1 H, =CH_2), 5.72 (d, J = 1.4 Hz, 1 H, NCHS), 5.79 (d, J = 1.3 Hz, 1 H, =CH_2); ^{13}C NMR (DMSO-d_6, 62.90 MHz) δ 21.40, 33.37, 46.38, 52.10, 60.29, 63.74, 64.74, 65.05, 71.32, 115.11, 115.42, 134.90, 155.62, 158.24, 173.58. Anal. Calcd for $C_{15}H_{18}ClNO_5S_3$: C, 42.50; H, 4.28; N, 3.30; S, 22.69. Found: C, 42.81; H, 4.09, N, 3.18; S, 22.80.

Sodium (5*R*,6*S*)-6-(1(*R*)-Hydroxyethyl)-2[(1(*R*)-oxo-3-(*S*)-thiolanyl)thio]-2-penem-3-carboxylate (34). A flame-dried flask wrapped in aluminum foil under a nitrogen atmosphere was charged with chloroallyl ester **33** (3.60 g, 8.5 mmol) in 115 mL of degassed CH_2Cl_2, followed by triphenylphosphine (0.72 g, 2.75 mmol), sodium 2-ethylhexanoate (6.72 mL of 1.39 M in ethyl acetate, 9.34 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.72 g, 0.62 mmol). The reaction was stirred at room temperature for 50 min. An additional 72 mg each of triphenylphosphine and tetrakis(triphenylphosphine)palladium(0) were added, and the reaction was stirred at room temperature for an additional 20 min. Ethyl acetate (150 mL) was added to the reaction mixture over a 15-min period. The reaction mixture was filtered, and the solids were air dried to yield 4.07 g of crude sodium salt **34**. This solid was taken up in 70 mL of water, treated with activated carbon, and filtered and the filtrate freeze-dried to yield 2.63 g of sodium salt **34**.

(5*R*,6*S*)-6-(1-(*R*)-1-Hydroxyethyl)-2-[(1(*R*)-oxo-3(*S*)-thiolanyl)thio]-2-penem-3-carboxylic Acid (1). Sodium salt **34** (2.63 g) was dissolved in 8 mL of distilled H_2O. The solution was cooled to 0–5 °C. The pH was adjusted to 2.45 with 1 N HCl inducing crystallization of the free acid. This suspension was stirred at 0–5 °C for 45 min and filtered. The resultant crystals were washed with a small amount of H_2O and air dried to yield 2.16 g (73%) of CP-70,429 (**1**) as a white crystalline solid: mp 135 °C dec; $[\alpha]_D$ = +366.01° (c = 1, dimethyl sulfoxide); IR (KBr) ν_{max} 1784, 1680, 1504, 1388, 1294, 997 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500.1 MHz) δ 1.16 (d, J = 6.3 Hz, 3 H, CH_3), 2.35–2.43 (m, 1 H, C*H*H), 2.62–2.74 (m, 2 H, C*H*H, CHSO), 2.81–2.88 (m, 1 H, CHSO), 2.98–3.02 (m, 1 H, CHSO), 3.74–3.77 (m, 1 H, CHSO), 3.79–3.81 (m, 1 H, CHCO), 3.85–3.91 (m, 1 H, CHS), 3.97–3.99 (m, 1 H, CHO), 5.21 (bs, 1 H, OH), 5.72 (d, J = 1.4 Hz, NCHS); ^{13}C NMR ($CDCl_3$, 125.76 HMz), δ 21.52, 33.48, 46.27, 52.19, 60.55, 63.96, 64.32, 71.11, 117.80, 151.53, 160.88, 173.36. Anal. Calcd for $C_{12}H_{15}NO_5S_3$: C, 41.25; H, 4.33; N, 4.01. Found: C, 40.98; H, 4.22; N, 3.99.

(3*S*,4*R*)-3-[1(*R*)-[(Dimethyl-*tert*-butylsilyl)oxy]ethyl]-4-[[[(1(*S*)-oxothiolanyl)thio]thiocarbonyl]thio]-2-azetidinone (35). Sodium metal (2.23 g, 0.097 mol) was suspended in 340 mL of dry isopropyl alcohol. This mixture was refluxed for 2.5 h at which point a clear solution was obtained which was then cooled to room temperature. Under a nitrogen atmosphere, thioacetate **19** (18.1 g, 0.102 mol) was dissolved in 260 mL of dry isopropyl alcohol and cooled to 0 °C. With stirring the freshly prepared sodium isopropoxide solution was added over a 17-min period to the thioacetate solution while the temperature was maintained at 0–2 °C. After being stirred for an additional 30 min at 0 °C, the mixture was chilled to −30 °C and carbon disulfide (23.3 g, 18.4 ml, 0.306 mol) in 50 mL of isopropyl alcohol was added. The resulting yellow suspension was warmed to 0 °C and stirred for an additional 10 min, thus producing 3(*R*)-[[mercapto(thiocarbonyl)]thio]thiolane 1(*S*)-oxide sodium salt. To this suspension was added dropwise a solution of (3*R*,4*R*)-4-acetoxy-3-[1(*R*)-[(dimethyl-*tert*-butylsilyl)oxy]ethyl]-2-azetidinone (**4a**) (32.1 g, 0.112 mol) while the temperature was maintained at 0–3 °C. After being stirred, at 0–2 °C for an additional 20 min, the reaction mixture was poured into 900 mL of saturated NH_4Cl and 900 mL of ethyl acetate and diluted with an additional 2250 mL of ethyl acetate. The organic layer was separated, washed sequentially with 1 × 900 mL of H_2O, 1 × 900 mL of 20% $CaCl_2$, 1 × 900 mL of H_2O, 1 × 900 mL of 20% $CaCl_2$, and 2 × 900 mL of saturated NaCl and was dried (Na_2SO_4), filtered, and stripped in vacuo to yield crude product as a solid. This material was twice recrystallized by dissolving it in 50–60 mL of acetone, with crystallization induced by the slow addition, with stirring, of 500 mL of isopropyl ether to yield 26.49 g (62%) of purified trithiocarbonate **35**: mp 90–94 °C dec; $[\alpha]_D$ = +315.05° (c = 1, $CHCl_3$); IR (KBr) ν_{max} 1766, 1075, 1018, 824, 809 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250.1 MHz) δ 0.04 (s, 3 H, SiMe), 0.04 (s, 3 H, SiMe), 0.84 (s, 9 H, tBuSi), 1.17 (d, J = 6.2 Hz, 3 H, CH_3), 2.64–2.69 (m, 3 H, CH_2, CHSO), 2.81–2.89 (m, 1 H, CHSO), 3.11–3.20 (m, 2 H, CHSO, CHCO), 3.75 (dd, J = 9.0, 14.9 Hz, 1 H, CHSO), 4.23–4.28 (m, 1 H, CHO), 4.49–4.54 (m, 1 H, CHS), 5.61 (d, J = 2.2 Hz, 1 H, NCHS), 6.74 (bs, 1 H, NH); ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ −5.10, −4.26, 17.91, 22.40, 25.69, 30.67, 47.84, 52.62, 57.31, 59.45, 63.88, 64.48, 166.55, 222.57; HRMS (EI) calcd for $C_{16}H_{29}NO_3S_4Si$ 439.0799, found 439.0843.

2-Chloroallyl (5*R*,6*S*)-6-[1(*R*)-[(Dimethyl-*tert*-butylsilyl)oxy]ethyl]-2-[(1(*S*)-oxo-3(*R*)-thiolanyl)thio]-2-penem-3-carboxylate (36). (3*S*,4*R*)-3-[1(*R*)-[(Dimethyl-*tert*-butylsilyl)oxy]ethyl]-4-1(*S*)-oxo[[[(3(*R*)-thiolanyl)thio]thiocarbonyl]-

thio]-2-azetidinone (35) (26.4 g, 60.1 mmol) was treated with 2-chloroallyl oxalofluoride (31) (13.0 g, 78.3 mmol) and *N,N*-diisopropylethylamine (13.6 mL, 78.3 mmol) in 300 mL of dry methylene chloride at −60 °C as described in the preparation of oxalimide 5 to afford 33.2 g of intermediate oxalimide which was converted (according to the procedure described for the conversion of 5 to penem 32) to 11.3 g of crude penem. Crude product was tritrated with 200 mL of diisopropyl ether to afford, after filtration, 9.8 g (50.4%) of penem 36; mp 122–125 °C dec; $[\alpha]_D$ = +158.13° (c = 1, $CHCl_3$); IR (KBr) ν_{max} 1784, 1681, 1492, 1324, 1198, 1117 cm^{-1}; ^1H NMR ($CDCl_3$, 250.1 MHz) δ 0.03 (s, 6 H, Me_2Si), 0.83 (s, 9 H, tBuSi), 1.20 (d, J = 6.3 Hz, 3 H, CH_3), 2.64–2.78 (m, 4 H, CH_2, CHSO, CHSO), 3.08–3.10 (m, 1 H, CHSO), 3.61–3.82 (m, 3 H, CHS, CHSO, CHCO), 4.21–4.23 (m, 1 H, CHO), 4.61 (d, J = 14.1 H, 1 H, $CHCO_2$), 4.79 (d, J = 14.1 Hz, 1 H, $CHCO_2$), 5.34 (d, J = 1.9 Hz, 1 H, $=CH_2$), 5.61 (m, 2 H, $=CH_2$ NCHS); ^{13}C NMR (DMSO-d_6, 62.90 MHz) δ −5.44, −4.54, 17.54, 21.64, 25.52, 32.98, 46.44, 51.99, 60.52, 64.08, 64.56, 65.13, 70.89, 115.09, 115.58, 134.84, 155.22, 158.23, 173.07; HRMS (EI) calcd for $C_{17}H_{23}ClNO_5S_3Si$ (*p*-tBu) 480.0426, found 480.0451.

2-Chloroallyl (5*R*,6*S*)-6-(1(*R*)-Hydroxyethyl)-2-[(1(*S*)-oxo-3(*R*)-thiolanyl)thio]-2-penem-3-carboxylate (37). Employing the procedure utilized for the conversion of 32 to 33, 2-chloroallyl (5*R*,6*S*)-6-[1(*R*)-[(Dimethyl-*tert*-butylsilyl)oxy]-ethyl]-2-[(1(*S*)-oxo-3(*R*)-thiolanyl)thio]-2-penem-3-carboxylate (36) (6.0 g, 11.2 mmol) was converted to 4.0 g (84%) of 37; mp 156–158 °C dec; $[\alpha]_D$ = +186.7 (c = 0.35 in DMSO); IR (KBr) ν_{max} 3184, 1765, 1684, 1490, 1319, 1200, 1123, 994 cm^{-1}; ^1H NMR (DMSO-d_6, 250.1 MHz) δ 1.18 (d, J = 6.3 Hz, 3 H, CH_3), 2.38–3.00 (m, 5 H, CH_2, CH_2SO, CHSO), 3.66 (dd, J = 14.6, 8.9 Hz, 1 H, CHSO), 3.85–4.01 (m, 3 H, CHO, CHCO, CHS), 4.69 (d, J = 14.1 Hz, 1 H, $CHCO_2$), 4.64 (d, J = 14.1 Hz, 1 H, $CHCO_2$), 5.22 (d, J = 4.6 Hz, 1 H, OH), 5.46 (m, 1 H, =CH), 5.71 (d, J = 1.6 Hz, 1 H, NCHS), 5.77 (d, J = 1.2 Hz, 1 H, =CH); ^{13}C NMR (DMSO-d_6, 62.90 MHz) δ 21.39, 32.93, 46.35, 51.95, 60.50, 63.72, 64.71, 65.07, 71.36, 115.17, 115.17, 134.90, 155.30, 158.22, 173.60. Anal. Calcd for $C_{15}H_{18}ClNO_5S_3$: C, 42.49; H, 4.28; N, 3.30. Found: C, 42.48; H, 4.35; N, 3.24.

(5*R*,6*S*)-6-(1(*R*)-1-Hydroxyethyl)-2-[(1(*S*)-oxo-3(*R*)-thiolanyl)thio]-2-penem-3-carboxylic Acid (2). As described in the conversion of 33 to 34, 2-chloroallyl (5*R*,6*S*)-6-(1(*R*)-hydroxyethyl-2-[(1(*S*)-oxo-3(*R*)-thiolanyl)thio]-2-penem-3-carboxylate (37) (4.24 g, 10 mmol) was converted to its corresponding sodium salt, mp 120–123 °C dec; $[\alpha]_D$ = +115.29 (c = 0.21, DMSO). The sodium salt was treated with 3 N HCl as described in the conversion of 34 to 1 to afford 2.6 g (75%) of CP-81,032 (2): mp 185–187 °C dec; $[\alpha]_D$ = +128.67 (c = 1, DMSO); IR (KBr) ν_{max} 3472, 3434, 1778, 1747, 1502, 1299, 1232, 991 cm^{-1}; ^1H NMR (DMSO-d_6, 250.1 MHz) δ 1.14 (d, J = 6.3 Hz, 3 H, CH_3), 2.34–3.02 (m, 5 H, CH_2, CH_2SO, CHSO), 3.66 (dd, J = 14.6, 8.8 Hz, 1 H, CHSO), 3.78–4.01 (m, 3 H, CHO, CHCO, SCH), 5.19 (bs, 1 H, OH), 5.70 (s, 1 H, NCHS); ^{13}C NMR (DMSO-d_6, 62.90 MHz) δ 21.40, 33.07, 46.19, 52.00, 60.60, 63.85, 64.17, 71.09, 117.87, 151.10, 160.66, 173.15. Anal. Calcd for $C_{12}H_{15}NO_6S_3$: C, 41.24; H, 4.33; N, 4.01. Found: C, 41.14; H, 4.33; N, 3.97.

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Supplementary Material Available: ^{13}C or ^1H NMR spectrum of each compound (32 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

New Macrolide Antibiotics: Synthesis of a 14-Membered Azalide

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The first example of a 14-membered azalide antibiotic (5) has been prepared. The key steps are sequential oxidative cleavage processes converting furanone 12 to aldehyde 14 and the subsequent reductive rearrangement of oxime 15 to amine 20.

Introduction

The erythromycin family of antibiotics has been known for 40 years.[1] Erythromycin A has provided effective and, above all, safe antibiotic therapy for much of that time. However, the last few years have seen something of a macrolide renaissance, ostensibly as a result of the emergence of a number of new semisynthetic erythromycin A derivatives—particularly clarithromycin[2,4] (2) and azithromycin (3).[3,4] Each of these addresses some of the shortcomings of the parent—notably poor oral bioavailability[5] as a result of acid instability, together with the

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(4) Clarithromycin (Biaxin) received FDA approval on Oct. 31, 1991. Azithromycin (Zithromax) initially received FDA approval on Nov 1, 1991.

(5) This can be allayed to some extent by using enterically coated formulations or 2′-ester prodrugs.

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