168.58 (C-11, s); MS; m/z (relative intensity) 513 (M, 19), 183 (100). Anal. Calcd for $C_{29}H_{28}N_3O_4P$: C, 67.83; H, 5.50; N, 8.18. Found: C, 67.77; H, 5,56; N, 8.04.

1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxo-6-[(triphenylphosphoranylidene)amino]-5-(2-cyanoethenyl)pyrimidine (4b). To a solution of 4.16 g (10 mmol) of **1** in 10 mL of MeCN was added dropwise 0.51 g (10 mmol) of cyanoacetylene **2b** in 10 mL of MeCN. The solution was stirred for 4 days at ambient temperature. Precipitation occurred after addition of ether; recrystallization form CH_2Cl_2/ether gave yellow crystals (0.71 g, 15.2%): mp 206 °C; IR (KBr) 2225 (C≡N), 1640 (CO), 1560 (C=C), 1430 (N=P) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.80 (m, 15 H), 6.87 (d, 1 H, J = 16 Hz), 6.20 (d, 1 H, J = 16 Hz), 3.44 (s, 3 H), 3.31 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 27.60 (C-8, q), 32.09 (C-7, q), 89.11 (C-10, d), 95.75 (C-5, d, J = 2 Hz), 121.06 (C-11, s), 128.20 (C-12, d, J = 107 Hz), 129.51 (C-14, dd, J = 13 Hz), 132.24 (C-13, dd, J = 10 Hz), 133.30 (C-15, dd, J = 3 Hz), 144.57 (C-9, d), 151.67 (C-2, d, J = 1 Hz), 157.14 (C-6, d, J = 10 Hz), 162.26 (C-4, d, J = 1 Hz); high-resolution MS, m/z (relative intensity) for $C_{27}H_{23}N_4O_2P$ found 466.1546 (M, 93.5), calcd 466.1554, 350 (100). Anal. Calcd for $C_{27}H_{23}N_4O_2P$: C, 69.52; H, 4.97; N, 12.01. Found: C, 69.33; H, 5.03; N, 11.83.

1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxo-6-[(triphenylphosphoranylidene)amino]-5-(1,2,2-tricyanoethenyl)pyrimidine (8). A solution of 4.16 g (10 mmol) of **1** and 1.28 g (10 mmol) of TCNE (**5**) in 50 mL of MeCN was stirred 10 min at ambient temperature. Then the mixture was kept at −18 °C for crystallization. After filtration, the crude product obtained was purified by column chromatography (Alox N, activity 1; 10/1 $CHCl_3$/acetone): 2.6 g (50.4%); yellow crystals, mp 222 °C; IR (KBr) 2240 (C≡N), 1710, 1645 (CO), 1520 (C=C), 1440 (N=P) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40–7.84 (m, 15 H), 3.36 (s, 3 H), 3.29 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 28.74 (C-8, q), 32.21 (C-7, q), 90.05 (C-10, s), 95.31 (C-5, d, J = 4 Hz), 112.25, 112.64 (C-16, C-17, s, s), 114.55 114.61 (C-11, s, s, isomer configurations), 126.27 (C-12, d, J = 107 Hz), 129.86 (C-14, dd, J = 13 Hz), 132.92 (C-13, dd, J = 11 Hz), 133.84 (C-15, dd, J = 3 Hz), 134.97 (C-9, s), 151.03 (C-2, s), 158.21 (C-4, s), 158.30 (C-6, d, J = 8 Hz); MS; m/z (relative intensity) 516 (M, 100). Anal. Calcd for $C_{29}H_{21}N_6O_2P$: C, 67.44; H, 4.10; N, 16.27. Found: C, 67.90; H, 4.10; N, 16.41.

Diethyl 1,2,3,4,5,6-Hexahydro-4-methyl-3,5-dioxo-6-[(*N*-methylamino)-(*N*-(triphenylphosphoranylidene)amino)-methylene]-1,2,4-triazine-1,2-dicarboxylate (11). A suspension of 2.05 g (5 mmol) of **1** and 0.87 g (5 mmol) of diethyl azodicarboxylate (**9**) in 30 mL MeCN was heated at reflux for 6 h. After the mixture was cooled, ether was added until precipitation began. Crystallization was finalized at −18 °C; recrystallization from CH_2Cl_2/ether gave 2.7 g (91.9%) of white crystals: mp 179 °C; IR (KBr) 3335 (NH), 1770, 1745, 1700 (CO), 1625, 1590 (C=C), 1430 (N=P) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.22–7.95 (m, 16 H), 3.99 (q, 2 H, J = 7 Hz), 3.61 (q, 2 H, J = 7 Hz), 3.29 (s, 3 H), 3.16 (d, 3 H, J = 10 Hz; s, after H/D exchange), 1.16 (t, 3 H, J = 7 Hz), 0.82 (t, 3 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 14.01 (C-17, q), 14.40 (C-19, q), 27.84 (C-15, q), 31.40 (C-12, q), 60.95 (C-16, t), 62.50 (C-18, t), 106.44 (C-6, d, J = 13 Hz), 128.71 (C-10, dd, J = 14 Hz), 130.04 (C-8, d, J = 100 Hz), 132.40 (C-9, dd, J = 7 Hz), 132.74 (C-11, d), 152.10 (C-13, s), 153.75 (C-14, s), 155.24 (C-3, s), 158.16 (C-7, d, J = 11 Hz), 161.74 (C-5, d, J = 9 Hz); MS, m/z (relative intensity) 589 (M, 0.5), 317 (100). Anal. Calcd for $C_{30}H_{32}N_5O_6P$: C, 61.12; H, 5.47; N, 11.88. Found: C, 60.9; H, 5.7; N, 11.6.

Ethyl 1,2,3,4,6,7-Hexahydro-3,6-dimethyl-2,4,7-trioxo-5-[(triphenylphosphoranylidene)amino]imidazo[5,1-*f*]-[1,2,4]triazine-1-carboxylate (12). **11** (3.66 g, 6.7 mmol) was heated to 160 °C in vacuo (0.2 torr) for 8 h. After the mixture was cooled, the resulting crude melted product was dissolved in CH_2Cl_2 and purified by column chromatography on Alox N (activity 1) with $CHCl_3$/acetone (10/1). The isolated material was recrystallized from CH_2Cl_2/ether: yield, 1.71 g (47%); white crystals, mp 220 °C; IR (KBr) 1810, 1780, 1735 (CO), 1580, 1555 (C=C), 1445 (N=P) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.87 (m, 15 H), 4.27 (q, 2H, J = 7 Hz), 3.18 (s, 3 H), 2.67 (s, 3 H), 1.27 (t, 3 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 14.14 (C-16, q), 24.99 (C-17, q), 25.31 (C-13, q), 62.92 (C-15, t), 81.93 (C-4a, d, J = 26 Hz), 125.10 (C-9, d, J = 101 Hz), 129.20 (C-11, dd, J = 12 Hz), 133.14 (C-10, dd, J = 11 Hz), 133.55 (C-12, d), 149.67 (C-14, s), 156.43 (C-7, s), 161.90 (C-2, s), 167.79 (C-4, s), 177.50 (C-5, d, J = 7 Hz); high-resolution MS, m/z (relative intensity for $C_{28}H_{26}N_5O_5P$ found 543.1667 (M, 52), calcd 543.1666, 262 (100). Anal. Calcd for $C_{28}H_{26}N_5O_5P$: C, 61.87; H, 4.82; N, 12.88. Found: C, 61.59; H, 4.95; N, 12.66.

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Registry No. 1, 99747-54-3; **2a**, 623-47-2; **2b**, 1070-71-9; **4a**, 102587-22-4; **4b**, 102587-23-5; **5**, 670-54-2; **8**, 102587-24-6; **9**, 1972-28-7; **11**, 102587-25-7; **12**, 102587-26-8.

Synthesis of Dihydro-1,4-oxathiins by Rearrangement of 1,3-Oxathiolane Sulfoxides[1]

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A new synthesis of 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxylic acid derivatives by ring expansion of corresponding 1,3-oxathiolane 3-oxides is described. Oxidation of 2-methyl-*N*-phenyl-1,3-oxathiolane-2-acetamide (**7a**) and 2-methyl-1,3-oxathiolane-2-acetic acid methyl ester (**7b**) gave a mixture of cis and trans sulfoxides **8** and **9**, major and minor, respectively. Assignments of the cis and trans sulfoxides were based on the aromatic solvent induced ^1H NMR shifts and the regioselectivity and relative ease of purely thermal reactions of the two isomers. With PTSA as acid catalyst in C_6H_6–DMF at 50 °C both the cis and trans sulfoxides **8a** and **9a** were transformed via sulfenic acid **5a** and thiolsulfinate **10a** to a 5:4:1 mixture of β-hydroxy sulfide **2a**, dihydro-1,4-oxathiin **1a**, and acetoacetanilide **12a** in quantitative yield. This mixture was dehydrated in refluxing benzene with PTSA to obtain the desired 5,6-dihydro-2-methyl-*N*-phenyl-1,4-oxathiin-3-carboxamide (**1a**) in high yield (90%). Similar results were obtained for the cis and trans sulfoxide esters **8b** and **9b**. In the absence of an acid catalyst the cis sulfoxide **8a** at 50 °C underwent a sigmatropic rearrangement to give **5a**, followed by dimerization to **10a**. The cis sulfoxide **8b** rearranged to **10b** even below room temperature. The trans sulfoxides **9** required more drastic conditions (in DMF at 100 °C) for the conversion to isomeric dihydrooxathiin **4** via sulfenic acid **6**. The mechanism of formation of **1a** and **2a** from thiolsulfinate **10a** is also discussed.

We have been interested in the synthesis of 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxylic acid derivatives **1** since compounds of this class[2] show remarkable antifungal activity.[3] A previous synthesis, developed by Kulka

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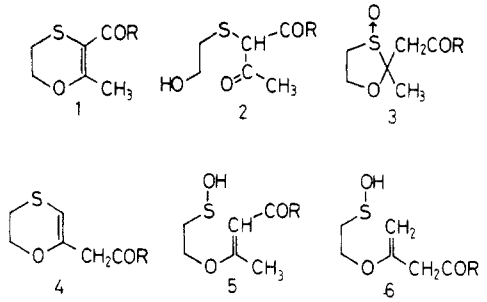
and co-workers,[4] involves the reaction of α-chloroacetoacetanilide or ethyl α-chloroacetoacetate with 2-mercaptoethanol to form intermediate **2** followed by cyclization with loss of water. One disadvantage of this process is the preparation of a α-chloro compound which is inconvenient.

We have developed a new synthesis comprising the preparation and rearrangement of 1,3-oxathiolane sulfoxides **3**. Our synthetic strategy was to avoid use of the α-chloro compound and achieve a ring expansion of 1,3-oxathiolane sulfoxides **3** to the corresponding dihydro-1,4-oxathiins **1**. The ring expansion of penicillin sulfoxides to cephalosporins[5] is now almost classic. Thermal or acid-catalyzed conversion of 1,3-dithiolane monoxide to a dihydro-1,4-dithiin has recently been reported.[6] However, 1,3-oxathiolane sulfoxides **3** had not been prepared or studied. These sulfoxides are interesting because they have the carbonyl-activated hydrogens of the methylene group as well as the unactivated hydrogens of the methyl group. Two sulfoxide stereoisomers would result in pairs of diastereomers because of the adjacent asymmetric carbon. Thus, if the ring opening is a sigmatropic process it is conceivable that two alternative β-eliminations involving hydrogens of methylene group or methyl group would take place depending on the geometry of these groups relative to S→O bond. Accordingly, the formation of two dihydrooxathiins **1** and **4** from their respective intermediates **5** and **6** might be possible.



R = a NHC_6H_5 ; b OCH_3

For our purpose it was desirable that the active hydrogens of the methylene group be involved regioselectively in β-elimination to give the proper sulfenic acid for the formation of the desired dihydrooxathiins **1**. It was also interesting to see if the unactivated methyl hydrogens would undergo β-elimination resulting in the isomeric dihydrooxathiins **4**.

Results and Discussion

Synthesis and Structure of Sulfoxides. The parent

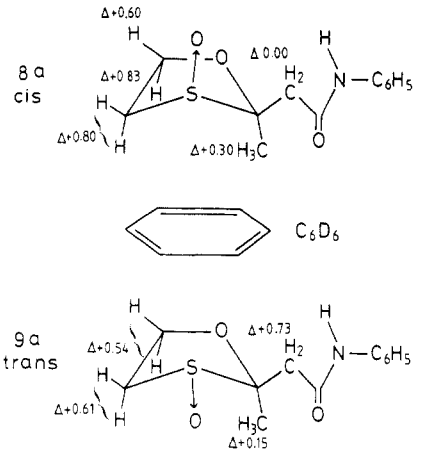
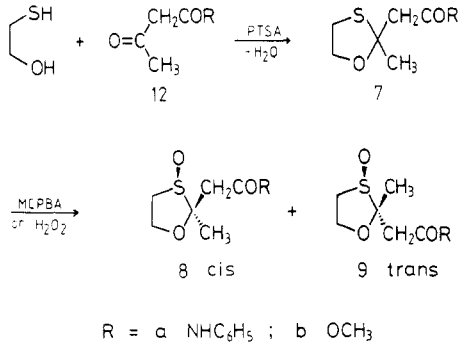


Figure 1. Perspective view of the cis and trans sulfoxides (**8a**, **9a**) and benzene-induced ^1H NMR shifts, $\Delta = \delta(CDCl_3) - \delta(C_6D_6)$.

Scheme I



R = a NHC_6H_5 ; b OCH_3

1,3-oxathiolanes **7** were prepared by the application of the general method for preparation of hemithioketals. The only oxathiolane of this class previously recorded in the literature[7] was the ethyl ester analogue of **7b**. Oxidation of the sulfides with various oxidizing agents gave new sulfoxides in good yields as a mixture of cis and trans isomers **9** and **10** as shown on the Scheme I. We have arbitrarily named the isomers as cis when the sulfoxide oxygen and the CH_2COR group are on the same face of the oxathiolane ring and trans when they are on opposite faces. As these cis and trans sulfoxides are diastereomers and they could be separated from each other by fractional crystallization or preparative TLC.

Assignments of cis and trans isomers were based on their ^1H NMR data and differing chemical properties. Benzene-induced solvent shift values (see Figure 1) provided evidence in support of the cis and trans configuration of S→O bond. This solvent effect is well illustrated with the 2-methyl or 2-methylene protons. Due to the benzene-d_6 associating with the face of the molecules opposite to the one with the sulfoxide oxygen[8] the methyl protons in the cis isomer and the methylene protons in the trans isomer are strongly shielded as a result of the large anisotropy.

Strong evidence for the stereochemistry of the cis and trans sulfoxides was found in the purely thermal reactions of the two isomers. The major isomers readily gave products under mild conditions apparently derived by sigmatropic ring opening to sulfenic acid **5**, involving the activated methylene hydrogens of the side chain. The

(1) A part of this work was presented (a) at the 174th American Chemical Society National Meeting, Chicago, August 28–September 2, 1977 and (b) in Lee, W. S. U.S. Patent 4 152 334, 1979; Can. Patent 1 036 167, 1978; *Chem. Abstr.* **1979**, *90*, 103971e.

(2) A typical compound is 5,6-dihydro-2-methyl-*N*-phenyl-1,4-oxathiin-3-carboxamide (**1a**), which has the common name carboxin[3] and trade name Vitavax and is used as a systemic fungicide for seed treatment.

(3) Marsh, R. W., Ed. *Systemic Fungicides*, 2nd ed.; Longman: New York, 1977; pp 51–60.

(4) Kulka, M.; Thiara, D. S.; Harrison, W. A. U.S. Patent 3 393 202, 1968.

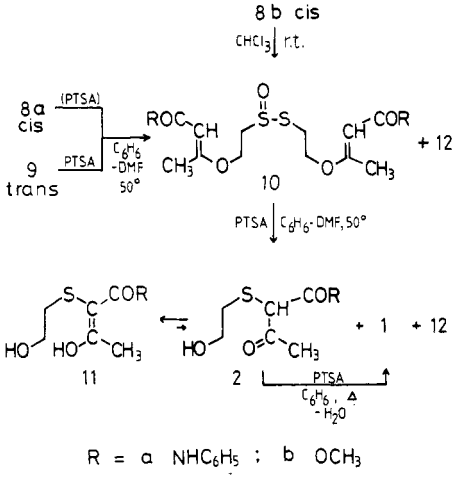
(5) (a) Morin, R. B.; Jackson, B. G.; Mueller, R. A.; Lavagnino, E. R.; Scanlon, W. B.; Andrews, S. L. *J. Am. Chem. Soc.* **1963**, *85*, 1896–1897. (b) Cooper, R. D. G.; Hatfield, L. D.; Spry, D. O. *Acc. Chem. Res.* **1973**, *6*, 32–40.

(6) (a) Chen, C. H. *Tetrahedron Lett.* **1976**, 25–28. (b) Chen, C. H.; Donatelli, B. A. *J. Org. Chem.* **1976**, *41*, 3053–3054. (c) Janssen, J. W. A. M.; Kwart, H. *J. Org. Chem.* **1977**, *42*, 1530–1533. (d) Hori, M.; Ueda, N.; Shimizu, H.; Kataoka, T. *Tetrahedron Lett.* **1984**, *25*, 757–760.

(7) Djerassi, C.; Gorman, M. *J. Am. Chem. Soc.* **1953**, *75*, 3704–3708.

(8) (a) Ledaal, T. *Tetrahedron Lett.* **1968**, 1683–1688. (b) Cooper, R. D. G.; DeMarco, P. V.; Cheng, J. C.; Jones, N. D. *J. Am. Chem. Soc.* **1969**, *91*, 1408–1415. (c) Andersen, K. K.; Caret, R. L.; Karup-Nielsen, I. *Ibid.* **1974**, *96*, 8026–8032. (d) Whitney, T. A. *Tetrahedron Lett.* **1974**, 2299–2300.

Scheme II



minor isomers required more drastic conditions to give predominantly the products derivable from sulfenic acid **6**, which must have been formed by a sigmatropic rearrangement with the unactivated methyl hydrogens. We thus concluded that the major sulfoxides had the sulfoxide oxygen cis to the amide or ester side chain and that the minor isomers had the corresponding trans relationship.

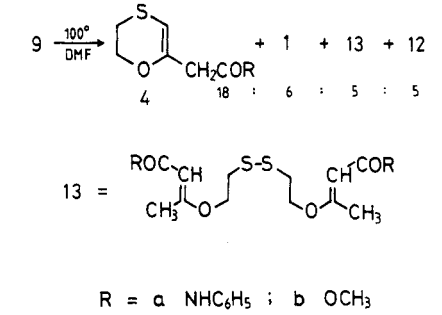
Sulfoxide to Dihydro-1,4-oxathiin Conversion. As shown in Scheme II, in 1:1 C_6H_6–dimethylformamide (DMF) at 50 °C in the presence of *p*-toluenesulfonic acid (PTSA) the cis sulfoxide **8a** was rearranged smoothly to a new thiolsulfinate **10a** and then transformed to a 5:4:1 mixture of β-hydroxy sulfide **2a** as its enol **11a**, dihydrooxathiin **1a**, and actoacetanilide **12a** in quantitative yield. When the solvent was removed[9] and the mixture then dehydrated by azeotropic removal of water in refluxing benzene with PTSA as catalyst, a high yield of the desired dihydrooxathiin **1a** (90%) and β-keto amide **12a** (10%) resulted. Under the same conditions as in the case of the cis isomer, the trans isomer **9a** rearranged to **10a** more slowly to give a similar mixture of **2a**, **1a**, and **12a**. From this mixture was obtained **1a** in a good yield (84%) by the same procedure used for the cis isomer. Likewise, a mixture of cis and trans sulfoxide was converted to **1a** (88%). The formation of **2** was unexpected and its origin will be discussed in detail later.

It was found that even in the absence of acid catalyst in C_6H_6–DMF at 50 °C the cis sulfoxide **8a** was rearranged to **10a** while the trans isomer was recovered unchanged. Surprisingly, cis sulfoxide ester **8b**, under neutral conditions, was rearranged to thiolsulfinate **10b** even below room temperature, whereas its trans isomer **9b** appeared to be of the same order of stability as trans sulfoxide amide **9a**. As expected, under acid catalysis the isolated thiolsulfinates **10a** and **10b** were converted to **1a** and **1b**, respectively, in high yields, by using the same procedure as described above.

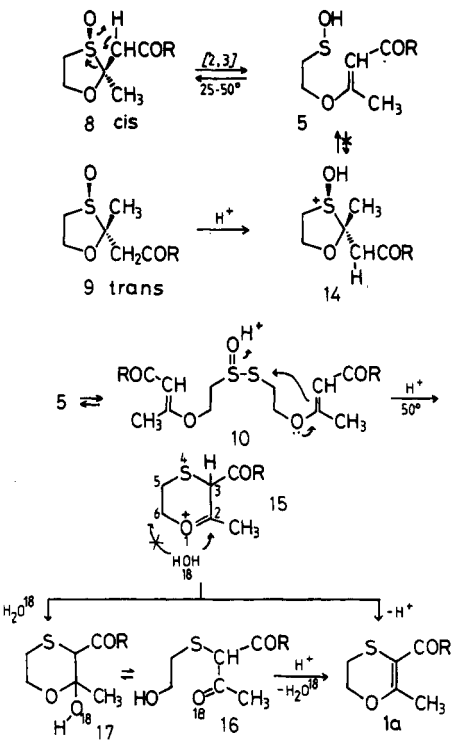
At 100 °C in DMF the trans sulfoxide **9a** reacted slowly to give the isomeric dihydrooxathiin **4a** as the major product. Unexpectedly, dihydrooxathiin **1a** and disulfide **13a** were also formed in addition to the side product **12a** (Scheme III). Similar results were obtained from trans sulfoxide ester **9b**. The structure of **4** was identified by independent synthesis involving the reaction of 4-bromoacetoacetanilide or methyl 4-bromoacetoacetate with 2-

(9) If this mixture, without isolation, was directly refluxed with a Dean–Stark water separator, the conversion of β-hydroxy sulfide **2a** to **1a** was too slow. Furthermore, under prolonged heating the side product acetoacetanilide was dimerized to a 4-pyridone derivative[10] which was difficult to remove and which interferes with crystallization of **1a**.

Scheme III



Scheme IV

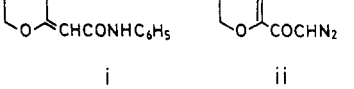


mercaptoethanol to form sulfide, followed by acid-catalyzed dehydration in refluxing benzene.[11] The structure of disulfide **13** was confirmed by its elemental and spectral analysis and by its *m*-chloroperbenzoic acid (MCPBA) oxidation to thiolsulfinate **10**.

Thiolsulfinates. The dimer produced when the cis sulfoxide **8a** was heated in C_6H_6–DMF at 50 °C was a crystalline solid. Its elemental analysis and mass spectrum fitted the empirical formula $C_{24}H_{28}N_2S_2O_5$. Although in the mass spectrum the molecular ion (M^+) at *m/e* 488 was not found it gave characteristic fragments at 253 [M^+ – $C_6H_5NHCOCH{=}C(CH_3)OCH_2CH{=}S$] and 235 [$M^+$ – $C_6H_5NHCOCH{=}C(CH_3)OCH_2CH_2SOH$] resulting from S—S bond cleavage and a proton tranfer from sulfenyl to

(10) Pierce, J. B.; Ariyan, Z. S.; Ovenden, G. S. *J. Med. Chem.* **1982**, *25*, 131–136.

(11) This synthesis was previously reported (Kim, I. K. *Daehan Hwahak Hwoejee* (*Journal of the Korean Chemical Society*) **1981**, *25*, 44–49; *Chem. Abstr.* **1981**, *95*, 24993p) and the structure of product was shown to be i. However, the structure **4** was correct as demonstrated by our unambiguous synthesis involving Wolff rearrangement of diazo ketone ii to **4a** and **4b**. Other supporting evidences for **4** also have been obtained.



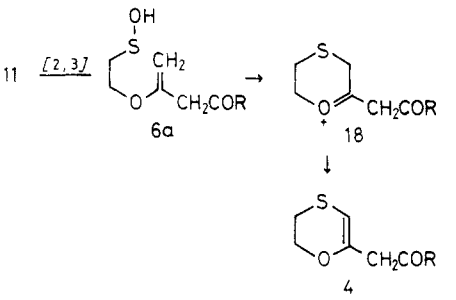
sulfinyl moiety.[12] It gave infrared absorption at 1670 (C=O), 1620 (C=C), 1050 (S→O) cm^{-1}. Its ^1H NMR spectrum had two sharp ^1H singlet at δ 5.08 and 5.13, suggesting that vinyl hydrogens had different environments. These facts are consistent with the thiolsulfinate structure **10a**. Further proof that this was correct was provided by its conversion to dihydrooxathiin **1a** as described previously. The thiolsulfinate **10b** from the cis sulfoxide ester **8b** was a colorless oil. The structure of this was proven by its elemental analysis, its spectral similarity to the thiosulfinate **10a**, and its conversion to dihydrooxathiin **1b**.

Mechanism of Ring Expansion Reaction. Although our attempts to isolate sulfenic acid intermediates were unsuccessful,[13] the isolation of their dimer thiolsulfinates makes the mechanistic pathway from sulfoxide to dihydrooxathiin clearer. In Scheme IV an overall mechanism is summarized. In chloroform at 25 °C or below for **8b** and in C_6H_5–DMF at 50 °C for **8a**, the ring opening of the cis sulfoxides **8** to the sulfenic acids **5** probably occurs by a [2,3] sigmatropic mechanism, whereas the ring opening of the trans sulfoxides **9** to **5** requires acid catalyst and proceeds by stepwise mechanism involving protonated sulfoxide or sulfonium ion **14**.

Unusual mildness of the sigmatropic rearrangement of the cis sulfoxides[15] is attributable to the carbonyl-activated methylene hydrogens. The acidity of these hydrogens lowers the energy required for the rearrangement. Thus, the cis sulfoxide ester rearranges much faster even at a lower temperature than the amide, a fact consistent with the stronger electron withdrawal by the ester carbonyl group. Indeed, the cis sulfoxide ester was rearranged under the unprecedented mild conditions (below room temperature). The facile acid-catalyzed rearrangement of the trans sulfoxides is also due to the active methylene hydrogens capable of regiospecific β-elimination to produce the same sulfenic acids **5a** and **5b** as their cis isomers.

Sulfenic acids **5**, while reversible[16] to sulfoxides **8**, dimerize to thiolsulfinates **10**,[17] producing water equimolar to **10**. Because of an extended conjugated system involving the oxygen lone pair electrons and the α,β-unsaturated carbonyl group in **5**, the double bond is considerably deactivated toward intramolecular addition and, therefore, intermolecular condensation of the sulfenic acid moiety is allowed to take place in competition with the former. The thiolsulfinate is fairly stable under neutral conditions, but in the presence of acid catalyst it cyclizes to the oxonium ion **15** with regeneration of the sulfenic acid which dimerizes again to repeat the process. As shown by the TLC in which thiolsulfinate **10a** appears prior to dihydrooxathiin **1a**, direct cyclization of **5a** to oxonium ion **15** does not occur even in the presence of an acid catalyst,[18] suggesting that the nucleophile component of the sulfenic acid predominates over its electrophilic character for this double bond. Once the thiolsulfinate is formed by dual functioning of the sulfenic acid as S nucleophile/S electrophile,[20] the sulfenyl sulfur atom is now sufficiently electrophilic to undergo an internal S_N2 displacement by the double bond as catalyzed by the acid present as well as assisted by the oxygen lone pairs (see **10** in Scheme IV). The oxonium ion releases the acidic proton to give directly the desired dihydrooxathiins **1**. It also could react with water by addition to C-2 or displacement on C-6 to produce β-hydroxy sulfides **2**. By use of ^{18}O labeling it was found that the addition of water to C-2 was the correct mechanism. The mass spectrum of the β-hydroxy sulfide **2a** produced in the medium containing $H_2{}^{18}O$ showed that carbonyl oxygen was ^{18}O labeled, not the β-hydroxy oxygen, indicating that **16** was formed via **17**. As further proof of this, unlabeled dihydrooxathiin **1a** was obtained, when the ^{18}O-labeled β-hydroxy sulfide **16** was dehydrated. The side product **12a** resulted from the decomposition of the sulfoxides.

Scheme V



In the absence of an acid catalyst the trans sulfoxides **9a** or **9b** required more drastic conditions (in DMF at 100 °C) for the conversion to isomeric dihydrooxathiin **4a** or **4b**. The reaction very likely proceeds initially via sulfenic acids **6** as generated by a sigmatropic rearrangement with the 2-methyl group, followed by cyclization to probable oxonium ion **18** as a precursor of **4**. Unlike the case of sulfenic acid **5**, we found no evidence that **6** formed the corresponding thiolsulfinate. Most likely, the ring closure of **6** to **18** is a self-catalyzed process in which the sulfur atom of **6** changes from a good nucleophile to a relatively weak electrophile to undergo a slow nucleophilic attack by π-electrons of the internal double bond.

The formation of dihydrooxathiin **1** and disulfide **13** was surprising. Probably, at such an elevated temperature, sulfenic acid **6** catalyzed the ring opening of the trans sulfoxide to generate sulfenic acid **5** followed by dimerization to **10** to give **1** as seen in the acid-catalyzed rearrangement in C_6H_6–DMF at 50 °C. The disulfide **13** may have been formed by the disproportionation[21] of **10**.

(12) Block, E.; O'Connor, J. *J. Am. Chem. Soc.* **1974**, *96*, 3921–3929.

(13) Although it has been reported that a sulfenic acid was isolated from a mixture of penicillin sulfoxide ester and sulfenic acid as obtained by refluxing the sulfoxide in ethyl acetate,[14] in our case cis sulfoxide **8a** gave mostly starting material and a small amount (less than 3%) of thiolsulfinate **10a** while the trans isomer **9a** was completely recovered unchanged in refluxing in ethyl acetate for 4 h.

(14) Chou, T. S.; Burgtorf, J. R.; Ellis, A. L.; Lammert, S. R.; Kukolja, S. P. *J. Am. Chem. Soc.* **1974**, *96*, 1609–1610.

(15) The mildest conditions under which a sulfenic acid was generated by sigmatropic rearrangement, to our knowledge, was the case of generating a sulfenic acid from a phthalimidopenicillin sulfoxide ester in refluxing ethyl acetate (77 °C), reported by Chou et al.[14]

(16) This reversibility was confirmed during the acid-catalyzed conversion of the isolated thiolsulfinate **10a** in C_6H_6–DMF at 50 °C to a mixture of **2a**, **1a**, and **12a**: when the reaction was halfway through, the reaction mixture contained sulfoxide **8a** as shown by TLC, HPLC, and ^1H NMR spectrum, indicating that the regenerated sulfenic acid **5a** was transformed to the parent sulfoxide **8a**.

(17) The facile dimerization or dehydration of sulfenic acid to thiolsulfinate is well documented: see (a) Chou, T. S.; Koppel, G. A.; Dorman, D. E.; Paschal, J. W. *J. Am. Chem. Soc.* **1976**, *98*, 7864–7865. (b) Davis, F. A.; Jenkins, R. H., Jr. *Ibid.* **1980**, *102*, 7967–7969.

(18) As an interesting comparison, in the presence of an acid catalyst a sulfenic acid from the penicillin sulfoxide undergoes a nucleophilic attack by the internal double bond on the sulfur atom of the protonated sulfenic acid to give a ring expansion product[19] while under neutral conditions the sulfenic acid adds to the double bond to regenerate the sulfoxide.

(19) (a) Flynn, E. H., Ed. *Cephalosporins and Penicillins–Chemistry and Biology*; Academic Press: New York, 1972; p 670. (b) Gutowski, G. E.; Foster, B. J.; Daniels, C. J. *Tetrahedron Lett.* **1971**, 3433–3436. (c) Kice, J. L. In *Advances in Physical Organic Chemistry*; Gold, V., Bethel, D. Ed.; Academic Press: New York, 1980; Vol. 17, p 73.

(20) (a) Davis, F. A.; Billmers, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 7016–7018. (b) Block, E.; O'Connor, J. *Ibid.* **1974**, *96*, 3929–3944.

(21) (a) Koch, P.; Ciuffarin, E.; Fava, A. *J. Am. Chem. Soc.* **1970**, *92*, 5971–5977. (b) Davis, F. A.; Jenkins, R. H., Jr.; Rizvi, S. Q. A.; Yocklovich, S. G. *J. Org. Chem.* **1981**, *46*, 3467–3474.

The ring expansion reaction of the sulfoxides reflects some important aspects from the synthetic as well as mechanistic viewpoints. It is extremely interesting that under the same reaction conditions, i.e., in C_6H_6–DMF at 50 °C with PTSA as catalyst, the cis and trans sulfoxides produced a common sulfenic acid intermediate, followed by dimerization to the thiolsulfinate, and that the reaction eventually ended up with a mixture of products from which high yields of the desired dihydrooxathiins were obtained. The fact that the trans sulfoxides could be converted at will either to dihydrooxathiins 1 or to isomeric dihydrooxathiins 4 by the choice of reaction conditions is also interesting. In addition, the role of DMF is remarkable. It appears that this solvent buffers the PTSA, leaving it sufficiently acidic for the reaction to proceed and minimizing side reactions leading to parent β-keto amide or ester.

Experimental Section

General Procedures. All melting points were obtained with a Electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 735B spectrophotometer. All ^1H NMR spectra were recorded on a Varian Model EM 360 or a Varian Model FT-80 spectrometer with Me_4Si as an internal standard and are reported in δ. Mass spectra were recorded on either a Varian MAT 212 using SS MAT 188 data system or a Hewlet-Packard 5985B. Elemental analysis of new compounds are within 0.4% of the theoretical values, unless otherwise noted.

All chromatographic isolations were accomplished either by high pressure liquid chromatography (HPLC), using μ-Bondapak-phenyl 10 μm (3.9 mm × 30 cm), or by preparative thin-layer chromatography, using Kieselgel GF 254 silica gel. Products isolated by HPLC were detected with a Waters 441 UV absorbance monitor at a wavelength of 254 nm.

Materials. All solvents were freshly distilled and stored under a nitrogen atmosphere. Benzene was purified sufficiently by being shaken with concentrated H_2SO_4 until free from thiophene and predried over Na wire, heated at reflux over Na wire, and distilled at atmospheric pressure. Dimethylformamide (DMF) was predried over $MgSO_4$, distilled under reduced pressure, and stored over 4A molecular sieves. Chloroform was purified by shaking with water to remove the ethanol, drying with $CaCl_2$, and distilling. Methylene chloride was purified with portions of concentrated H_2SO_4, then washed with water, aqueous 5% $NaHCO_3$, and water, then dried with $CaCl_2$, and distilled. Acetoacetanilide and methyl acetoacetate were purchased from Aldrich Chemicals.

Synthesis of 2-Methyl-*N*-phenyl-1,3-oxathiolane-2-acetamide (7a). A solution of acetoacetanilide **12a** (17.72 g, 0.10 mol), 2-mercaptoethanol (8.59 g, 0.11 mol)[22] and *p*-toluenesulfonic acid monohydrate (PTSA) (0.19 g) in anhydrous benzene (40 mL) was refluxed with a Dean–Stark water separator for 5 h. The benzene solution was cooled, washed with sodium bicarbonate solution and with water, dried ($MgSO_4$), and decolorized (charcoal). The solvent was evaporated under reduced pressure to give gummy residue (24.7 g). The residue was crystallized from ethyl acetate–petroleum ether to obtain colorless short needles **7a** (21.4 g, 90.2%): mp 85–87 °C; ^1H NMR (60 MHZ) ($CDCl_3$) δ 1.72 (s, 3, 2-CH_3), 2.92 (s, 2, 2-CH_2), 3.08 (t, 2, 4-CH_2), 4.20 (m, 2, 5-CH_2), 7.00–7.60 (m, 5, Ar H), 8.23 (s, 1, NH); IR (KBr) 1650 (C=O) cm^{-1}. Anal. ($C_{12}H_{15}NO_2S$) C, H, N, S.

Synthesis of 2-Methyl-1,3-oxathiolane-2-acetic Acid Methyl Ester (7b). This compound was prepared by the same procedure as described for **7a**. Thus a solution of methyl acetoacetate (**12b**) (11.61 g, 0.10 mol) and 2-mercaptoethanol (7.81 g, 0.10 mol) in benzene (50 mL) containing 0.95 g of PTSA was refluxed with a Dean–Stark water separator for 3 h. After working up, there was obtained **7b** as a colorless oil (17.36 g, 98.5%): bp 80 °C/7 mmHg; ^1H NMR (60 MHz) ($CDCl_3$) δ 1.73 (s, 3, 2-CH_3), 2.87 (s, 2, 2-CH_2), 3.05 (t, 2, J = 6 Hz, 4-CH_2), 3.67 (s, 3, OCH_3), 4.15 (t, 2, J = 6 Hz, 5-CH_2); IR (NaCl) 1740 (C=O) cm^{-1}. Anal. ($C_7H_{12}O_3S$) C, H, S.

Synthesis of 2-Methyl-*N*-phenyl-1,3-oxathiolane-2-acetamide 3-Oxides (8a and 9a). A solution of 1,3-oxathiolane **7a** (7.12 g, 0.03 mol) in acetic acid (30 mL) was cooled to 15–20 °C in the ice bath, and 35% hydrogen peroxide (6 mL, about 0.06 mol) in water was added dropwise over 30 min while stirring the mixture. Stirring was continued at the same temperature for 1 h 45 min. To the resulting mixture in the same bath was added dropwise 6 N NaOH solution until the mixture reached pH 7. The product was extracted with methylene chloride, and the extract was washed with water and dried (Na_2SO_4). The solvent was evaporated at room temperature under reduced pressure to obtain a white foamy solid residue (7.09 g, 93.3%) as a mixture of cis and trans (ca. 70:30) sulfoxides as determined by NMR spectroscopy (C_6D_6). These isomeric sulfoxides were separated by preparative TLC. Thus 1.0 g of the above mixture was chromatographed on silica gel plates using chloroform–methanol (95:5) as developing solvent (flow rate: **8a** > **9a**) to obtain 0.4968 g of cis isomer (**8a**) and 0.2368 g of trans isomer (**9a**) (recrystallized from ether acetate–petroleum ether).

For **8a**: mp 97–103 °C; ^1H NMR (80 MHz) ($CDCl_3$) δ 1.54 (s, 3, 2-CH_3), 2.88 and 3.12 (AB pattern, 2, J = 14.4 Hz, 2-CH_2), 2.80–3.38 (m, 2, 4-CH_2), 4.09–4.67 (m, 2, 5-CH_2), 6.90–7.58 (m, 5, Ar H), 8.87 (s, 1, NH); ^1H NMR (80 MHz) (C_6D_6) δ 1.23 (s, 3, 2-CH_2), 2.81 and 3.04 (AB pattern, 2, J = 14.4 Hz, 2-CH_2), 2.05–2.27 (m, 2, 4-CH_2), 3.22–4.08 (m, 2, 5-CH_2), 6.73–7.85 (m, 5, Ar H), 9.10 (s, 1, NH); IR (KBr) 1680 (C=O), 1035 (S→O) cm^{-1}. Anal. ($C_{12}H_{15}NO_3S$) C, H, N, S.

For **9a**: mp 121–125 °C dec; ^1H NMR (80 MHz) ($CDCl_3$) δ 1.54 (s, 3, 2-CH_3), 2.94 (s, 2, 2-CH_2), 2.70–3.39 (m, 2, 4-CH_2), 4.27–4.40 (m, 2, 5-CH_2), 7.01–7.50 (m, 5, Ar H), 8.27 (s, 1, NH); ^1H NMR (80 MHz) (C_6D_6) δ 1.39 (s, 3, 2-CH_3), 2.20 (s, 2, 2-CH_3), 2.10–2.80 (m, 2, 2-CH_2), 2.10–2.80 (m, 2, 4-CH_2), 3.54–4.10 (m, 2, 5-CH_2), 6.80–7.45 (m, 6, Ar H, NH); IR (KBr) 1680 (C=O), 1025 (S→O) cm^{-1}. Anal. ($C_{12}H_{15}NO_3S$) C, H, N, S.

Synthesis of 2-Methyl-1,3-oxathiolane-2-acetic Acid Methyl Ester, 3-Oxides (8b and 9b). These compounds were prepared by the same procedure as described for **8a** and **9a**. To a stirred solution of 1,3-oxathiolane **7b** (3.52 g, 0.02 mol) in acetic acid (20 mL) at 10–15 °C was added 35% hydrogen peroxide (4 mL, about 0.04 mol) in water dropwise over 10 min. Stirring was continued at the same temperature for 1 h. The resulting reaction mixture was place in the salt–ice bath at −3 to 3 °C and diluted with ice-cold chloroform (150 mL). After workup there was obtained a mixture of cis and trans (ca. 3:2) isomeric sulfoxides **8b** and **9b** (by NMR spectrum in C_6D_6) as a colorless oil (3.80 g, 99%): ^1H NMR (60 MHz) ($CDCl_3$) δ 1.53 (s, 3, 2-CH_3), 2.95–3.53 (m, 4, 2-CH_2, 4-CH_2), 3.73 (s, 1.2, OCH_3),[a] 3.77 (s, 1.8, OCH_3),[b] 4.07–4.80 (m, 2, 5-CH_2), a/b = trans/cis = 2/3; ^1H NMR (60 MHz) (C_6D_6) δ 1.25 (s, 1.8, 2-CH_3),[b] 1.45 (s, 1.2, 2-CH_3),[a] 2.45 (s, 0.8, 2-CH_2),[a] 2.12–2.80 (m, 2, 4-CH_2), 2.80 and 3.12 (AB pattern, 1.2, 2-CH_2),[b] 3.22 (s, 1.2, OCH_3),[a] 3.32 (s, 1.8, OCH_3),[b] 3.30–4.25 (m 2, 5-CH_2), a/b = trans/cis = 2/3.

Synthesis of 5,6-Dihydro-2-methyl-*N*-phenyl-1,4-oxathiin-3-carboxamide (1a). Method A. From Cis Sulfoxide 8a. A solution of cis sulfoxide **8a** (0.500 g, 1.97 mmol) in 1:1 C_6H_6–DMF (20 mL) containing PTSA (3.8 mg) was placed in the water bath at 50 °C and allowed to stir for 24 h. The solvent was thoroughly evaporated to give an oily residue (0.514 g) as a 5:4:1 mixture of β-hydroxy sulfide **2a**, dihydrooxathiin **1a**, and acetoacetanilide **12a** as shown by NMR spectrum. This residue was dissolved in benzene (20 mL) containing PTSA (3.8 mg) and the solution refluxed with Dean–Stark water trap for 2.5 h. After removing the solvent, a gummy solid residue (0.456 g) as a 9:1 mixture of dihydrooxathiin **1a** and acetoacetanilide **12a** was dissolved in methylene chloride (25 mL), and the solution was washed with 0.5 N NaOH solution and then with water and dried (Na_2SO_4). The solvent was evaporated to obtain a crystalline solid (0.421 g, 90%). This compound had identical NMR and IR spectra with those of the compound prepared by the previously known method.[4]

Method B. From Trans Sulfoxide 9a. A solution of trans sulfoxide **9a** (0.500 g, 1.97 mmol) in 1:1 C_6H_6–DMF containing PTSA (3.8 mg) was placed in the water bath at 50 °C and allowed

(22) Use of 2-mercaptoethanol in 10% excess is recommended to prevent or minimize the formation of 4-pyridone derivatives[10] from acetoacetanilide.

to stir for 72 h. The solvent was evaporated to give an oily residue (0.530 g) as a 5:3:1 mixture of β-hydroxy sulfide **2a**, dihydrooxathiin **1a**, and acetoacetanilide **12a** (by NMR spectrum). This residue was dissolved in benzene (20 mL) containing PTSA (3.8 mg), and the solution was refluxed with a Dean–Stark water trap for 2.5 h. After removing the solvent, the gummy solid residue (0.424 g) as a 9:1 mixture of dihydrooxathiin **1a** and acetoacetanilide **12a** (NMR spectrum) was dissolved in methylene chloride (25 mL), and the solution was washed with 0.5 N NaOH solution and then with water and dried (Na_2SO_4). The solvent was evaporated to obtain a crystalline solid (0.390 g, 84%); NMR and IR spectra of the compound were identical with those obtained in the preceding experiment.

Method C. From the Thiolsulfinate 10a. To a stirred solution of thiolsulfinate **10a** (0.50 g, 1.0 mmol) in 1:1 C_6H_6–DMF (20 mL) was added PTSA (4 mg). The reaction mixture was placed in the water bath at 50 °C and allowed to stir for 19 h. The solvent was evaporated to give an oily residue (0.53 g), which was a 13:5:1 mixture of dihydrooxathiin **1a**, β-hydroxy sulfide **2a**, and acetoacetanilide **12a** as shown by the NMR spectrum. This residue was dissolved in benzene (20 mL) containing PTSA (3.8 mg) and the solution was refluxed with a Dean–Stark water trap for 2.5 h. After removing the solvent, a gummy solid residue (0.471 g) as a 95:5 mixture of dihydrooxathiin **1a** and acetoacetanilide **12a** (NMR spectrum) was dissolved in methylene chloride (25 mL), and the solution was washed with 0.5 N NaOH solution and then with water and dried (Na_2SO_4). The solvent was evaporated to obtain a crystalline solid (0.457 g, 95%). This product had identical NMR and IR spectra with those of the compound obtained in the preceding experiment.

Synthesis of 5,6-Dihydro-2-methyl-1,4-oxathiin-3-carboxylic Acid Methyl Ester (1b). Method A. From a Mixture of Cis and Trans Sulfoxide 8b and 9b. A solution of a mixture of cis and trans (ca. 3:2) isomeric sulfoxides (**8b** and **9b**) (0.500 g, 2.6 mmol) in 1:1 C_6H_6–DMF (20 mL) containing PTSA (5.0 mg) was placed in the water bath at 50 °C and allowed to stir for 60 h. The solvent was evaporated to give an oily residue (0.434 g). This residue was dissolved in benzene (20 mL) containing PTSA (5.0 mg), and the solution was refluxed with a Dean–Stark water trap for 2.5 h. After workup there was obtained a crystalline solid (0.411 g, 90%). Recrystallization from ethyl acetate–petroleum ether gave **1b** as colorless needles: mp 58–60 °C; ^{1}H NMR (60 MHz) ($CDCl_3$) δ 2.27 (s, 3, CH_3), 2.88 (t, 2, CH_2S), 3.70 (s, 3, OCH_3), 4.30 (t, 2, CH_2O); IR (KBr) 1700 (C=O), 1580 (C=C) cm^{-1}. Anal. ($C_7H_{10}O_3S$) C, H, S.

Method B. From the Thiolsulfinate 10b. To a stirred solution of thiolsulfinate **10b** (0.10 g, 0.2 mmol) in 1:1 C_6H_6–DMF (5 mL) was added PTSA (1 mg). The reaction mixture was placed in the water bath at 50 °C and allowed to stir for 94 h. The solvent was evaporated to give an oily residue (0.10 g). This residue was dissolved in benzene (10 mL) containing PTSA (0.6 mg), and the solution was refluxed on a Dean–Stark water trap for 2 h. After workup there was obtained a crystalline solid (82 mg, 85%), which had identical NMR and IR spectra with those of the compound obtained in the preceding experiment.

Synthesis of *S*-[2-[[1-Methyl-3-oxo-3-(phenylamino)-1-propenyl]oxy]ethyl] 2-[[1-Methyl-3-oxo-3-(phenylamino)-1-propenyl]oxy]ethanethiosulfinate (10a). A solution of cis sulfoxide **8a** (10.0 g, 39 mmol) in 1:1 C_6H_6–DMF (100 mL–100 mL) was allowed to stir in the water bath at 50 °C for 5 h. The solvent was evaporated to obtain a colorless oily residue. This was dissolved in methylene chloride (50 mL), washed with cold water, and dried (Na_2SO_4). The solvent was removed to give a colorless oily residue (8.77 g), which was an 85:15 mixture of thiolsulfinate **10a** and cis sulfoxide **8a** by NMR spectroscopy and TLC. Crystallization from methylene chloride–cyclohexane gave **10a** as a white solid (5.74 g, 59.6%): mp 137–138 °C; ^{1}NMR (60 MHz) ($CDCl_3$) δ 2.38 (s, 6, CH_3), 3.47 (t, 2, J = 5.5 Hz, CH_2S), 3.52 (t, 2, J = 5.5 Hz, CH_2S), 4.07 (t, 2, J = 5.5 Hz, CH_2O), 4.25 (t, 2, J = 5.5 Hz, CH_2O), 5.12 (s, 1, olefinic CH), 5.17 (s, 1, olefinic CH), 7.00–7.80 (m, 12, Ar H, NH); IR (KBr) 1670 (C=O), 1080 (S→O) cm^{-1}; mass spectrum (20 eV), m/e (relative intensity) 488 (M^+, not observed), 253 (5.4, M^+ –S =$CHCH_2OC(CH_3)$=$CHCONHC_6H_5$), 235 (9.4, M^+ – $HOSCH_2CH_2OC(CH_3)$=$CHCONHC_6H_5$), 177 (17.6, $CH_3CO^+CH_2CONHC_6H_5$), 160 (14.6, CH_3C^+=$CHCONHC_6H_5$), 143 (15.4, S=$CHCH_2O$ $C(CH_3)$=$CHCO^+$), 93 (100, $C_6H_5NH_2^+$). Anal. ($C_{24}H_{28}N_2O_5S_2$) C, H, N, S.

Synthesis of Methyl 5,14-Dimethyl-3-oxo-2,6,13-trioxa-9,10-dithiahexadeca-4,14-dien-16-oate 9-Oxide (10b). A mixture of cis and trans sulfoxides **8b** and **9b** (1.2 g, 6.24 mmol) was allowed to stand for 10 days at 0–2 °C. From the resulting reaction mixture, the products were separated by preparative TLC using 7:3 (v/v) benzene–ethyl acetate as eluant. The second band (R_f 0.2) was **9b**. The first band (R_f 0.6) was extracted with chloroform to give **10b** as a colorless oily liquid (0.46 g, 20%).

For **9b**: mp 27–29 °C; ^{1}H NMR (60 MHz) ($CDCl_3$) δ 1.53 (s, 3, 2-CH_3), 2.95 (s, 2, 2-CH_2), 2.78–3.50 (m, 2, 4-CH_2) 3.72 (s, 3, OCH_3), 4.30–4.50 (m, 2, 2-CH_2); ^{1}H NMR (60 MHz) (C_6D_6) δ 1.50 (s, 3, 2-CH_3), 2.57 (s, 2, 2-CH_2), 2.45–3.03 (m, 2, 4-CH_2), 3.32 (s, 3, OCH_3), 3.65–4.30 (m, 2, 5-CH_2); IR (NaCl) 1740 (C=O), 1050 (S→O) cm^{-1}.

For **10b**: ^{1}H NMR (60 MHz) ($CDCl_3$) δ 2.32 (s, 6, CH_3), 3.48 (t, 2, J = 6 Hz, CH_2S), 3.50 (t, 2, J = 6 Hz, CH_2S), 3.70 (s, 6, OCH_3), 4.11 (t, 2, J = 6 Hz, CH_2O), 4.28 (t, 2, J = 6 Hz, CH_2O), 5.07 (s, 1, olefinic CH), 5.12 (s, 1, olefinic CH): IR (NaCl) 1710 (C=O), 1050 (S→O) cm^{-1}; mass spectrum (20 eV), m/e (relative intensity) 366 (M^+, not observed), 192 (4.4, M^+ – S=$CHCH_2OC(CH_3)$=$CHCO_2CH_3$), 174 (16.1, M^+ – $HOSCH_2CH_2OC(CH_3)$=$CHCO_2CH_3$), 116 (33.1, $CH_3CO^+CH_2CO_2CH_3$), 59 (100, $CO_2CH_3^+$). Anal. ($C_{14}H_{22}O_7S_2$) C, H, S.

Reaction of Thiolsulfinate 10a with $H_2{}^{18}O$. To a stirred solution of thiolsulfinate **10a** (600 mg, 1.23 mmol) in 1:1 C_6H_6–DMF (30 mL) was added PTSA (12 mg) and 97.4% $H_2{}^{18}O$ (0.25 mL, 12.3 mmol) in water. The reaction mixture was placed in the water bath at 50 °C and allowed to stir for 20 h. The solvent was removed to give a light brown oily residue. This was dissolved in methylene chloride (50 mL), washed with cold water, and dried (Na_2SO_4). Evaporation of the solvent gave a oily residue (555 mg), which was a 3:1 mixture of β-hydroxy sulfide **17** and acetoacetanilide **12a** as determined by NMR spectrum. These compounds were separated by preparative TLC using 7:3 (v/v) benzene–ethyl acetate as eluant. The second band (R_f 0.3) was extracted with chloroform to give a white crystalline solid (43 mg), which was identical with authentic acetoacetanilide **12a** containing no ^{18}O isotope (by mass spectrum). The first band (R_f 0.45) was extracted with chloroform to obtain a oily residue (281 mg). This product was β-hydroxy sulfide **16** containing ^{18}O isotope (by NMR and mass spectra). A solution of **16** (150 mg, 0.6 mmol) and PTSA (5.6 mg) in anhydrous benzene was refluxed with a Dean–Stark water separator for 3.5 h. After workup there was obtained a crystalline solid (146 mg). This product was 5,6-dihydro-2-methyl-*N*-phenyl-1,4-oxathiin-3-acetamide (**1a**) containing no ^{18}O isotope (by mass spectrum).

For **16**: mass spectrum (20 eV), m/e (relative intensity) 255 [3.5, $M^+(^{18}O)$], 253 [6.9, $M^+(^{16}O)$], 179 [0.7, $M^+(^{18}O)$–SCH_2CH_2O], 177 [1.3, M^+ (^{16}O) – SCH_2CH_2O], 135 [1.3, $M^+(^{18}O)$ – $CONHC_6H_5$], 133 [3.0, $M^+(^{16}O)$ – $CONHC_6H_5$], 93 [100, $C_6H_5NH_3^+$].

Reaction of 9a in DMF at 100 °C. A solution of trans sulfoxide **9a** (0.500 g, 2.60 mmol) in DMF (12.5 mL) was heated at 100 °C while stirring for 4 days. The solvent was removed to give an oily residue, which was dissolved in methylene chloride, washed with cold water, and dried (Na_2SO_4). Evaporation of the solvent gave a dark brown oily residue (0.364 g), as a 18:6:5:5 mixture of respectively isomeric dihydro-1,4-oxathiin **4a**, dihydro-1,4-oxathiin **1a**, disulfide **13a**, and acetoacetanilide **12a** as determined by NMR spectrum and HPLC. These were separated by preparative TLC using 7:3 (v/v) benzene–ethyl acetate as eluant. The first band (R_f 0.8), the second band (R_f 0.7), and the fourth band (R_f 0.4) were respectively extracted with the mixture of chloroform and methanol (1:1) to give **1a** (62 mg), **4a** (75 mg), and **12a** (46 mg). The third band (R_f 0.6) was extracted with a 1:1 mixture of acetone and methanol to give disulfide **13a** (38 mg).

For **4a**: mp 152–155 °C; ^{1}H NMR (60 MHz) ($CDCl_3$) δ 2.98 (t, 2, J = 4.5 Hz, 5-CH_2), 3.17 (s, 2, CH_2CO), 4.45 (t, 2, J = 4.5 Hz, 6-CH_2), 5.20 (s, 1, olefinic CH), 7.07–7.67 (m, 5, Ar H), 7.93 (s, 1, NH); IR (KBr) 1660 (C=O) cm^{-1}; mass spectrum (25 eV), m/e (relative intensity) 235 (100, M^+), 115 (55.1, M^+ – $CONHC_6H_5$), 93 (14.7, $C_6H_5NH_3^+$). Anal. ($C_{12}H_{13}NO_2S$) C, H, N, S.

For **13a**: ^{1}H NMR (60 MHz) ($CDCl_3$) δ 2.40 (s, 6, CH_3), 3.02 (t, 4, J = 6.5 Hz, CH_2S), 4.05 (t, 4, J = 6.5 Hz, CH_2O), 5.13 (s,

2, olefinic CH), 7.10–7.60 (m, 10, Ar H), 7.63 (s, 2, NH); IR (KBr) 1680 (C=O), 1610 (C=C) cm^{-1}; mass spectrum (20 eV), *m/e* (relative intensity) 472 (1.9, M^+), 236 (37.1, $C_6H_5NHCOCH{=}C(CH_3)OCH_2CH_2S^+$), 117 (100, $HSCH_2CH_2OC(CH_3){=}CH^+$), 93 (96.9, $C_6H_5NH_3^+$). Anal. ($C_{24}H_{28}N_2S_2O_4$) C, H, N, S.

Oxidation of Disulfide 13a to Thiolsulfinate 10a. To an ice-cooled solution of disulfide **13a** (10 mg, 0.02 mmol), obtained from the previous experiment, in chloroform (4 mL) was added a cold solution of MCPBA (80%, 4.6 mg, 0.02 mmol) in chloroform (2 mL). The reaction mixture was stirred at ice-bath temperature for 3 min and poured into ice-cold saturated sodium bicarbonate solution (5 mL). The organic layer was separated, washed with ice-cold water twice, and dried (Na_2SO_4). Evaporation of the solvent gave thiolsulfinate **10a** as an oily residue (9 mg), identical in NMR and IR spectra with the compound prepared by the previous method.

Reaction of Trans Sulfoxide 9b in DMF at 100 °C. A solution of trans sulfoxide **9b** (0.500 g, 2.60 mmol) in DMF (0.25 mL) was heated at 100 °C while stirring for 7 days. The solvent was removed to give an oily residue, which was dissolved in methylene chloride, washed with cold water, and dried (Na_2SO_4). Evaporation of the solvent gave a brown oily residue (316 mg), which was approximately a 5:3:1:1 mixture of respectively isomeric dihydro-1,4-oxathiin **4b**, dihydro-1,4-oxathiin **1b**, disulfide **13b**, and trans sulfoxide **9b** as determined by NMR. These were separated by preparative TLC using 9:9:2 (v/v) methylene chloride–hexane–ethyl acetate as eluant. The first band (R_f 0.8), the second (R_f 0.7), the third (R_f 0.5), and the fourth (R_f 0.3) were respectively extracted with a 1:1 mixture of chloroform and methanol to give **1b** (90 mg), **4b** (148 mg), **13b** (33 mg), and **9b** (11 mg).

For **4b**: bp 93–95 °C (10 mmHg); ^1H NMR (60 MHz) ($CDCl_3$) δ 2.93 (t, J = 4.5 Hz, 5-CH_2), 3.07 (s, 2, CH_2CO), 3.70 (s, 3, OCH_3), 4.30 (t, 2, J = 4.5 Hz, 6-CH_2), 5.05 (s, 1, olefinic CH); IR (NaCl) 1740 (C=O) cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 174 (74.8, M^+), 115 (94.0, $M^+ - CO_2CH_3$), 101 (94.5, $M^+ - CH_2CO_2CH_3$). Anal. ($C_7H_{10}O_3S$) C, H, S.

For **13b**: ^1H NMR (60 MHz) ($CDCl_3$) δ 2.30 (s, 6, CH_3), 3.00 (t, 4, J = 6 Hz, CH_2S), 3.67 (s, 6, OCH_3), 4.07 (t, 4, J = 6 Hz, CH_2O), 5.07 (s, 2, olefinic CH). Anal. ($C_{14}H_{22}O_6S_2$) C, H, S.

Oxidation of Disulfide 13b to Thiolsulfinate 10b. To a solution of disulfide **13b** (7 mg, 0.02 mmol), obtained from the foregoing experiment, in chloroform-*d* (0.4 mL) was added a solution of MCPBA (80%, 4.6 mg, 0.02 mmol) in chloroform-*d* (0.2 mL). The reaction mixture was shaken at 34 °C for 5 min and poured into ice-cold saturated sodium bicarbonate solution (5 mL). The organic layer was separated, washed with ice-cold water, and dried (Na_2SO_4). Evaporation of the solvent gave thiolsulfinate **10b** as an oily residue (6 mg), identical in NMR spectrum with that of the compound prepared by the previous method.

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Registry No. **1a**, 5234-68-4; **1b**, 102437-87-6; **2a**, 56537-72-5; **4a**, 102437-90-1; **4b**, 102437-92-3; **7a**, 67980-06-7; **7b**, 80563-95-7; **8a**, 68563-70-2; **8b**, 102437-84-3; **9a**, 68563-71-3; **9b**, 102437-85-4; **10a**, 102437-86-5; **10b**, 102437-88-7; **12a**, 102-01-2; **12b**, 105-45-3; **13a**, 102437-91-2; **13b**, 102437-93-4; **16**, 102437-94-5; **17**, 102437-89-8.

Synthetic Approach to Versatile Chiral Molecules Containing a Fluorine Atom

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Studies of the synthetic tools for the preparation of chiral monofluorinated compounds, involving microbial asymmetric reduction, are described. The preparation and utility of such chiral monofluorinated compounds are reported.

Our studies of the synthetic utility of fluoro olefins have focused on the use of an extremely versatile building block in the preparations of α-fluorinated ketones, a group of compounds which reflect increasing interest in the molecular design concerning the biological activities.[1-4] However, no general stereocontrolled synthetic approach to chiral monofluorinated synthons, for a key process to achieve the above purpose, has been reported except a few approaches to a suicide inactivator.[5-8]

In our previous paper, we have reported that microbial transformation can be a useful synthetic technique for preparing optically active fluorinated compounds.[9-15]

As part of our continuing interest in preparing versatile chiral synthons in fluorine chemistry,[12-15] we now report the use of microorganisms to prepare chiral fluorinated synthons.[16-22]

(1) Filler, R.; Kobayashi, Y. *Biomedicinal Aspects of Fluorine Chemistry*; Kodansha and Elsevier Biomedical: Amsterdam, 1983.
(2) Smith, F. A. *Handbook of Experimental Pharmacology*; Springer-Verlog: Berlin, 1970; Vol. XX. Part 2, p 166.
(3) Ishikawa, N. *Kagaku To Seibutsu* **1984**, *22*, 93.
(4) Quistad, G. B.; Cerf, D. C.; Schooley, D. A.; Staal, G. B. *Nature (London)* **1981**, *289*, 176.
(5) Tsushima, T. *Kagaku To Seibutsu* **1982**, *20*, 770.
(6) Souda, K.; Tanizawa, K.; Esaki, N. *Kagaku* **1980**, *35*, 97 and references cited therein.
(7) Johnson, M.; Marcotte, P.; Donovan, J.; Walsh, C. *Biochemistry* **1977**, *18*, 1729.
(8) Metcalf, B. W.; Bey, P.; Danzin, C.; Jung, M. J.; Casora, P.; Vevert, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 2551.
(9) Kitazume, T.; Ishikawa, N. *Chem. Lett.* **1983**, 237.
(10) Kitazume, T.; Yamazaki, T.; Ishikawa, N. *Nippon Kagaku Kaishi* **1983**, 1363.
(11) Kitazume, T.; Ishikawa, N.*Chem. Lett.* **1984**, 587.
(12) Kitazume, T.; Sato, T.; Ishikawa, N. *Chem. Lett.* **1984**, 1811.
(13) Kitazume, T.; Ishikawa, N. *Chem. Lett.* **1984**, 1815.
(14) Kitazume, T.; Ishikawa, N. *J. Fluorine Chem.* **1985**, *29*, 431.
(15) Kitazume, T.; Sato, T. *J. Fluorine Chem.* **1985**, *30*, 189.
(16) Bucciarelli, M.; Forni, A.; Moretti, I.; Torre, G. *J. Chem. Soc., Chem. Commun.* **1983**, 897.
(17) Bucciarelli, M.; Forni, A.; Moretti, I.; Torre, G. J. *J. Chem. Soc., Chem. Commun.* **1983**, 897.
(18) Retey, R.; Robinson, J. A. *Stereospecificity in Organic Chemistry and Enzymology*; Verlag Chemie: Basel, 1982, and references cited therein.
(19) Yamada, H.; Shimizu, S.; Tani, Y.; Hino, T. *Enzyme Engineering*; Plenum Press: New York, 1980; Vol. 5, p 405.

0022-3263/86/1951-2795$01.50/0