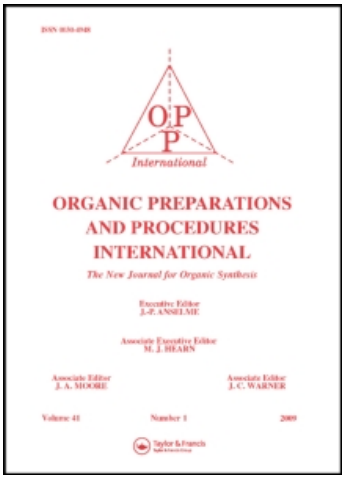

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REGIO- AND STEREOSELECTIVE OXIDATIONS OF THE EXOCYCLIC SULFUR ATOM OF TWO ENDOCYCLIC KETENE DITHIOACETALS

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REGIO- AND STEREOSELECTIVE OXIDATIONS OF THE EXOCYCLIC SULFUR ATOM OF TWO ENDOCYCLIC KETENE DITHIOACETALS

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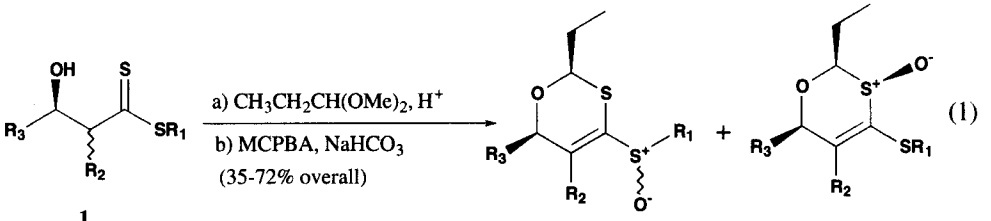
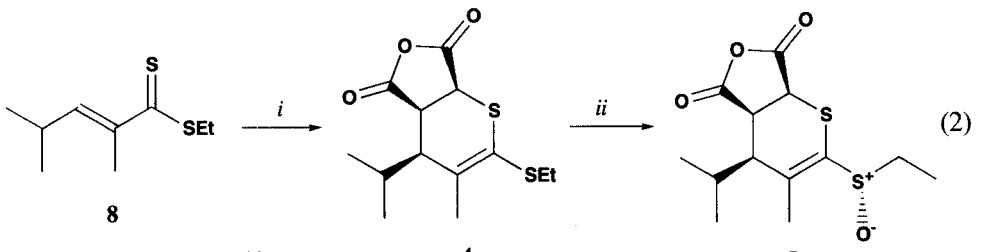
Recent research in our laboratory has demonstrated that β-hydroxydithioesters (**1**) can be acetalized by treatment with acetals such as propanal dimethyl acetal to form substituted 4-alkylthio-Δ^4-1,3-oxathianes,[1] which will undergo oxidation to form mixtures of exocyclic sulfoxides (4-alkanesulfinyl-Δ^4-1,3-oxathianes, **2**) and endocyclic sulfoxides (**3**) with the exocyclic sulfoxides predominating as 75-95% of the mixture (Eq. 1).[2] Among the interesting aspects of this work was the observation that the exocyclic sulfoxides **2** were produced with one epimer of the sulfoxide as 66-80% of the



1 **2** major (2:1 to 4:1 diastereomer ratio) **3** minor

diastereomeric mixture. Previously reported oxidations of sulfide groups which are not part of a ring did not proceed with high stereoselectivity, unless an asymmetric oxidizing agent was employed,[3-5] thus our observation of the stereoselectivity of the oxidations of endocyclic ketene dithioacetals[6] to form sulfoxides like **2** was notable and worth investigating in more detail, with a particular aim of elucidating the configuration of the major diastereomer formed.

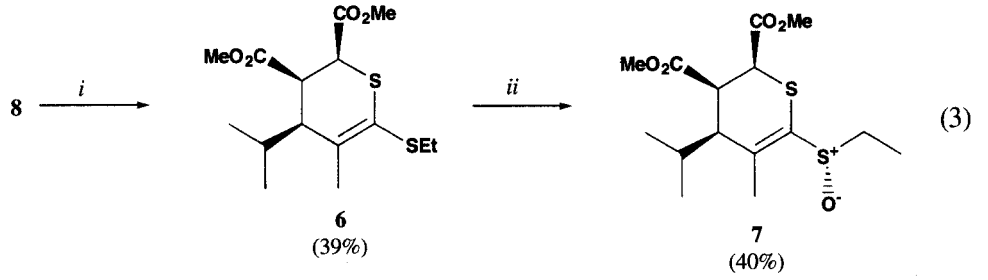
This paper reports that the MCPBA oxidation of the 6-ethylthio-3,4-dihydro-2H-thiopyran **4**, an endocyclic ketene dithioacetal similar to 4-alkylthio-Δ^4-1,3-oxathianes, proceeds with complete regio- *and* stereoselectivity to form the *syn* sulfoxide **5** (Eq. 2), whose structure was proven by X-ray crystallographic analysis.[7] Diester **6** also underwent oxidation with complete stereoselectivity to form the sulfoxide **7**, which was presumed to possess the *syn* geometry by analogy with the oxidation of **4**



8 4 (89%) 5 (81%) (2)

i) maleic anhydride, 110°
ii) MCPBA

(Eq. 3). These results suggest that endocyclic dithioacetals substituted with two *cis* substituents at positions 2 and 3 of the 6-ethylthio-3,4-dihydro-2H-thiopyran system (and positions 2 and 6 of the



6 (39%) 7 (40%) (3)

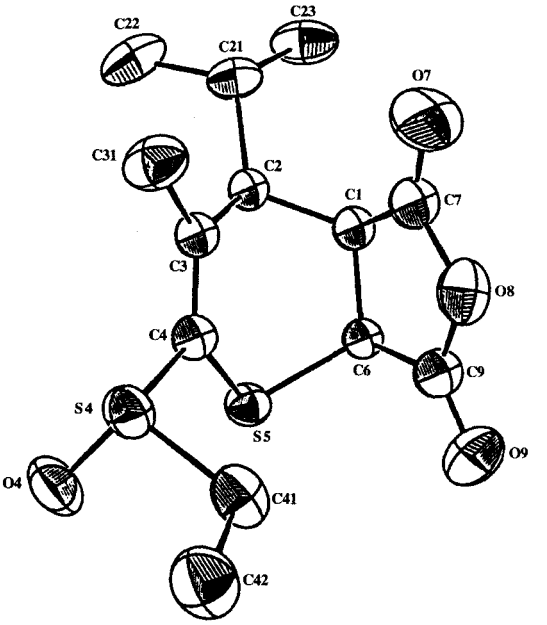
i) dimethyl maleate, 25°, 5 M $LiClO_4$, ether ii) MCPBA

4-alkylthio-Δ^4-1,3-oxathiane ring system) undergo stereoselective oxidations at the exocyclic sulfide group in favor of the *syn* diastereomer,[7] for reasons proposed below.

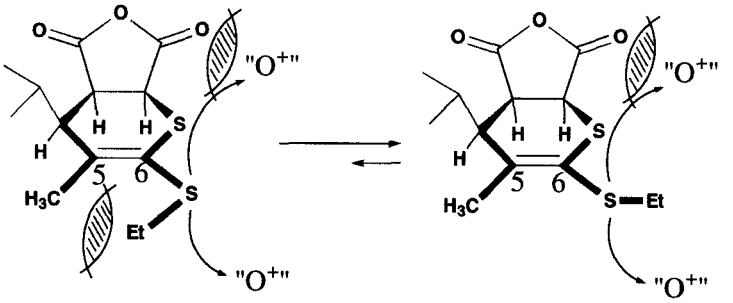
The 6-ethylthio-3,4-dihydro-2H-thiopyran **4** was synthesized by the hetero Diels-Alder reaction between the α,β-unsaturated dithioester **8** and maleic anhydride in refluxing toluene, a cycloaddition precedented by the work of Whitham and coworkers.[8] The reaction of dimethyl maleate and **8** was conducted at room temperature in 5 M lithium perchlorate in ether under mild conditions,[9] and afforded the cycloadduct **6** most cleanly (high temperature conditions led to mixtures of products, possibly due to isomerization of the dimethyl maleate). In both cases, the *endo* stereoselectivity of the cycloadditions, to form the all-*cis* products, was precedented by Whitham's work and indicated by the ^1H NMR coupling constants for **4** and **6**. Treatment of **4** and **6** with approximately one molar equivalent of *meta*-chloroperoxybenzoic acid at -78° in the presence of an excess of sodium bicarbonate yielded the sulfoxides **5** and **7**, respectively, as clean products consisting of single diastereomers, according to the ^1H and ^{13}C NMR analyses of the crude reaction mixtures. The sulfoxide **5** was purified by crystallization and the sulfoxide **7** was purified by chromatography; the latter process resulted in losses due, apparently, to the decomposition of the ketene dithioacetal monoxide on the silica gel column. A single crystal X-ray analysis of the sulfoxide **5** revealed the relative stereochemistry indicated in Eq. 2; an ORTEP drawing of **5** derived from this analysis is shown. The similarities between the NMR data for sulfoxides **5** and **7** suggest that the latter compound also possesses the *syn* geometry, like **5**.

These results suggest that endocyclic ketene dithioacetals like **4** and **6** (as well as 4-alkylthio-Δ^4-1,3-oxathianes), which possess at least two *cis* substituents on the six-membered ring, undergo

regio- and stereoselective oxidations to favor the formation of the exocyclic sulfoxides having the *syn* geometry. A qualitative conformational analysis of these systems offers a rationale for this stereoselectivity. First, the regioselectivity for the oxidation of the exocyclic sulfide over the endocyclic sulfide group can be attributed to straightforward steric effects. Second, the *cis* substituents of the ring would sterically hinder the approach of the oxidizing agent to the exocyclic sulfide group from a direction which is *cis* to them. Third, the conformations available to the exocyclic sulfoxide group, relative to rotations around the C-S bond emanating from the ring, will be limited by steric hindrances between the ethyl group of the sulfide and the group (methyl in **4** and **6**) attached to C_5. Thus, the "s-*trans*" conformer **9** would be less favored than the "s-*cis*" conformer **10** and, as indicated in **9** and **10**, the preferred "facial" direction of attack (dictated by the *cis* substituents in the ring), along with the preferred "s-*trans*" conformation, leads to the prediction that the oxidation will favor the *syn* diastereomer, as found unambiguously in **5** and as predicted for **7** and **2**.



ORTEP Drawing of Compound **5** (the atom numbers in the drawing do not correspond to the numbering system used in discussions in the text)



9 "s-*trans*"

10 "s-*cis*"

In conclusion, our results lead to the prediction that six-membered rings bearing endocyclic ketene dithioacetal moieties and two or more *cis* substituents will undergo regio- and stereoselective oxidations to form the *syn* exocyclic sulfoxides. In accord with these predictions, the 4-alkylthio-Δ^4-1,3-oxathianes studied earlier, which bear only two *cis* substituents, underwent oxidations with less

stereoselectivity than the 6-ethylthio-3,4-dihydro-2H-thiopyrans studied here, which bore three *cis* substituents. Furthermore, our studies of the oxidations of 4-alkylthio-Δ^4-1,3-oxathianes indicated that the degree of stereoselectivity of the oxidation varied in accordance with the size of the group adjacent to the alkylthio substituent (larger = higher diastereomeric ratio; smaller (H) = lower ratio). This is in accordance with the predicted steric effect of this group upon the conformation of the sulfides (cf. **9** vs. **10**) which, according to our model, dictates the stereoselectivity of the oxidation. Further studies will help to better elucidate this remarkable control over the stereoselective oxidation of an acyclic sulfide.

EXPERIMENTAL SECTION

Reagents were used as purchased without further purification. Tetrahydrofuran (THF) was distilled from sodium-benzophenone, dichloromethane was distilled from calcium hydride, and methanol was distilled from magnesium turnings. All reactions were run under a dry nitrogen atmosphere. Each reaction was worked up by the addition of water followed by extraction into ether, washing of the extracts with saturated sodium chloride, and drying over magnesium sulfate, unless otherwise indicated. Chromatography was done using 230-400 mesh silica gel and the indicated eluents. NMR spectra were measured in solutions in deuterochloroform using tetramethylsilane as an internal standard.

(E)-Ethyl 2,4-Dimethyl-2-pentenedithioate (8).- Ethyl 3-hydroxy-2,4-dimethylpentanedithioate was prepared according to the procedure of Meyers and Walkup;[10] a solution of 2.0 g (15 mmol) of ethyl dithiopropanoate[11] in 75 mL of dry THF was stirred at -78° while 11 mL (16.5 mmol) of a 1.5 M solution of LDA in THF was added dropwise. The solution was stirred at -78° for 30 min, then 1.62 g (22.5 mmol) of freshly-distilled isobutyraldehyde was added. The solution was stirred at -78° for 1 hr, then worked up and chromatographed (90:10 hexanes/ethyl acetate eluent) to yield **ethyl 3-hydroxy-2,4-dimethylpentanedithioate**, a mixture of diastereomers, as a bright yellow oil (1.85 g, 60%). ^{1}H NMR: δ 3.53 (m, 2H), 3.22 (d of q, J = 7.4, 4.4 Hz, 2H), 2.84 (d, J = 2.8 Hz, 0.6 H) / 2.59 (d, J = 7.2 Hz, 0.4 H), 1.33 (t, J = 6.5 Hz, 3H), 1.32 (t, J = 6.5 Hz, 3H), 1.74 (m, 1H), 1.01 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.7 Hz, 3H); ^{13}C NMR δ 244.7, 80.3/79.4, 56.8/56.4, 30.6/30.5, 29.9/29.8, 20.4, 20.1/19.5, 17.6/16.5, 11.8; IR (neat): 3444, 2965, 2930, 2872 cm^{-1}.

This product, which was susceptible to autooxidative decomposition during storage, was immediately used for the next step; 1.80 g (8.7 mmol) of the β-hydroxydithioester was stirred in 15 mL of pyridine (dried over KOH prior to use) at 0°, and 1.6 mL (17 mmol) of phosphorous oxychloride was added. The solution was allowed to warm to room temp with stirring over a 8 hrs period, then ice water (50 mL) was slowly added, and the mixture was extracted with ether (3 x 40 mL). The combined extracts were washed with 10% HCl solution (3 x 30 mL), then with water (2 x 25 mL) and saturated NaCl (1 x 30 mL), then was dried ($MgSO_4$), filtered, concentrated *in vacuo*, and chromatographed (30 g 230-400 mesh silica gel, hexanes eluent) to yield **8** (1.46 g, 89%) as a red-orange oil. ^{1}H NMR: δ 6.44 (d of q, J = 9.4, 1.3 Hz, 1H), 3.20 (q, J = 7.4 Hz, 2H), 2.63 (d of septets, J = 9.3, 7.4 Hz, 1H), 2.13 (d, J = 1.3 Hz, 3H), 1.31 (t, J = 7.4 Hz, 3H), 1.05 (d, J = 7.4 Hz, 6H); ^{13}C NMR: δ 231.6, 141.6, 141.3, 134.5, 30.3, 28.4, 21.9, 17.0, 12.1); IR (neat) 2961, 2925, 2866, 1612 cm^{-1}. Due to the sensitivity of this compound to decomposition, it was carried on to the next steps without further characterization.

(±)-(2S,3S,4S)-6-Ethylthio-4-isopropyl-5-methyl-3,4-dihydro-2H-thiopyran-2,3-dicarboxylic Anhydride (4).- A stirred solution of 0.96 g (5.1 mmol) of the dithioester **8** and 0.56 g (5.7 mmol) maleic anhydride in 15 mL dry toluene was refluxed for 90 minutes, then cooled to room temperature, concentrated *in vacuo*, and chromatographed (30 g 230-400 mesh silica gel, dichoromethane eluent), yielding 1.30 g (89%) of **4** as white crystals, mp. 113-115° (uncorr.); ^{1}H NMR δ 4.18 (d, J = 10.3 Hz, 1H), 4.07 (d of d, J = 10.3, 3.5 Hz, 1H), 2.79 (m, 2H), 2.48 (septet, J = 6.4 Hz, 1H), 2.28 (d of d, J = 10.9, 3.4 Hz, 1H), 2.12 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H), 1.18 (d, J = 6.4 Hz, 3H), 1.03 (d, J = 6.3 Hz, 3H); ^{13}C NMR: δ 171.2, 170.4, 145.1, 127.9, 52.9, 48.4, 47.0, 28.6, 26.1, 23.6, 21.2, 17.8, 15.2.
Anal. Calcd for $C_{13}H_{18}S_2O_3$: C, 54.53; H, 6.34. Found: C, 54.82; H, 6.39

(±)-*syn*-(2S,3S,4S)-6-Ethanesulfinyl-4-isopropyl-5-methyl-3,4-dihydro-2H-thiopyran-2,3-dicarboxylic Anhydride (5).- A solution of 0.559 g (1.96 mmol) of **4** was stirred in 10 mL dry dichloromethane at -78°, then 1.7 g (20 mmol) of sodium bicarbonate and 0.45 g (~2.1 mmol) of *meta*-chloroperoxybenzoic acid (~85% purity) were added. The mixture was stirred for 4 hrs, then water (25 mL) was added and the mixture was extracted with dichloromethane (3 x 20 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*, and the resulting solid was recrystallized from dichloromethane/hexanes to yield 0.475 g (81%) of **5** as colorless crystals, mp. 195-198° (uncorr.); ^{1}H NMR: δ 4.36 (d, J = 10.1 Hz, 1H), 4.16 (d of d, J = 10.1, 3.7 Hz, 1H), 2.90 (m, 1H), 2.70 (m, 1H), 2.45 (septet, J = 6.3 Hz, 1H), 2.28 (d of d, J = 10.7, 3.2 Hz, 1H), 2.08 (s, 3H), 1.18 (d, J = 6.5 Hz, 3H), 1.17 (t, J = 7.4 Hz, 3H), 1.03 (d, J = 6.2 Hz, 3H). ^{13}C NMR: δ 170.6, 169.9, 151.2, 139.2, 52.5, 48.4, 46.6, 45.7, 25.2, 23.9, 20.9, 17.3, 7.1; IR (dichloromethane solution) 3052, 2983, 1865, 1789.

Crystals of the freshly prepared, air sensitive product **5** were grown by placing a vial containing a solution of 0.039 g of the solid in 2-3 mL ethyl acetate in a sealed jar containing 10 mL of hexanes (under nitrogen), and allowing the system to stand at room temperature in the dark for two days. The solvent was removed from the resulting colorless plates, one of which was mounted on a fiber and subjected to an X-ray crystallographic analysis at room temperature using an Enraf-Nonius CAD-4F system. This analysis resulted in a structural refinement to an R value of 0.0386 (R_w = 0.0400, S = 1.57). An ORTEP drawing of the structure is indicated above; complete listings of the crystallographic parameters for this structure have been deposited in the Cambridge Crystallographic Data Bank.

(±)-(2S,3S,4S) Dimethyl 6-Ethylthio-4-isopropyl-5-methyl-3,4-dihydro-2H-thiopyran-2,3-dicarboxylate (6). A solution of 0.052 g (0.28 mmol) of **8** and 0.10 mL (0.80 mmol) dimethyl maleate was stirred in 2 mL of 5.0 M lithium perchlorate in ether, at room temperature under a nitrogen atmosphere, for 2 d, then it was worked up and chromatographed (20 g 230-400 mesh silica gel, 90:10 hexanes/ethyl acetate eluent) to yield 0.036 g (39%) of **6** as an oil. ^{1}H NMR: δ 4.27 (d, J = 7.0 Hz, 1H), 3.61 (s, 3H), 3.68 (s, 3H), 3.46 (d of d, J = 7.0, 2.8 Hz, 1H), 2.76 (d of q, J = 7.4, 2.3 Hz, 2H), 2.39 (d, J = 3.0 Hz, 1H), 2.38 (septet, J = 6.4 Hz, 1H), 2.07 (s, 3H), 1.21 (t, J = 7.3 Hz, 3H), 1.02 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H). ^{13}C NMR: δ 171.0, 170.2, 139.7, 122.5, 52.5, 51.7, 50.9, 46.9, 45.3, 28.9, 27.5, 22.5, 22.4, 20.6, 14.9. Due to the sensitivity of this compound to autooxidative

decomposition, the next step was carried out without further characterization.

(±)-*syn*-(2S,3S,4S) Dimethyl 6-Ethanesulfinyl-4-isopropyl-5-methyl-3,4-dihydro-2H-thiopyran-2,3-dicarboxylate (7). Using a procedure identical to that used for the preparation of **5**, 0.077 g of **6** was converted to 0.032 g (40%) of **7**, obtained as colorless crystals, mp (uncorr.) 102-111°. ^{1}H NMR: δ 4.26 (d, J = 8.6 Hz, 1H), 3.69 (d of d, J = 8.9, 3.0 Hz, 1H), 3.64 (s, 3H), 3.55 (s, 3H), 3.03 (m, 1H), 2.81 (m, 1H), 2.45 (septet, J = 6.1 Hz, 1H), 2.27 (t, J = 4.1 Hz, 1H), 2.07 (s, 3H), 1.25 (t, J = 7.5 Hz, 3H), 0.98 (d, J = 6.1 Hz, 3H), 0.93 (d, J = 6.1 Hz, 3H). ^{13}C NMR: δ 170.7, 170.2, 145.8, 132.6, 52.7, 52.4, 51.8, 46.4, 46.31, 46.28, 26.3, 23.4, 21.1, 18.1, 7.3; IR (CCl_4 solution): 2966, 2952, 1754, 1743 cm^{-1}. This product was susceptible to autooxidative decomposition upon storage, thus satisfactory analytical data could not be obtained for it.

Acknowledgements.- This research was made possible by grants from the Robert A. Welch Foundation (D-1147 to RDW; B-1202 to SGB), the National Cancer Institute (CA49307 to RDW), and the University of North Texas Research Office (to SGB). The NMR spectrometers used during its course were purchased with the assistance of funds provided by the NSF (#CHE-851404).

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** Author to whom inquiries concerning the X-ray crystallographic analysis of compound **5** should be addressed.

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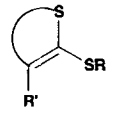
5. For reports of the oxidations of acyclic sulfides by asymmetric oxidizing agents, where a chiral center in the substrate directed the stereoselectivity to afford diastereomer ratios on the order of 2:1 to 3:1, see a) R. Breitschuh and D. Seebach, *Synthesis,* 83 (**1992**); b) S. F. Wnuk, N. K. Dalley and M. J. Robins, *J. Org. Chem.*, **58**, 111(1993).

6. The term "endocyclic ketene dithioacetal" refers to ketene dithioacetals in which the carbon-carbon double bond and one of the two sulfur atoms are all part of a ring. Thus endocyclic ketene dithioacetals possess the general structure **i**, as opposed to non-endocyclic ketene dithioacetals of

general structures **ii**. As discussed in reference 2, endocyclic ketene dithioacetals possess stereo-electronically derived reactivities which are unique from those of non-endocyclic ketene dithioacetals.



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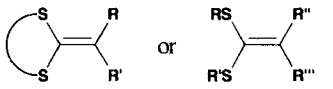
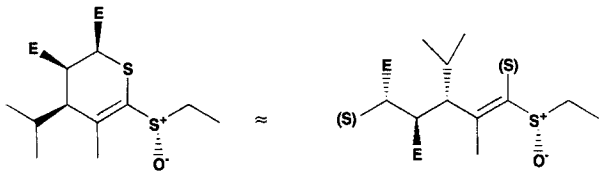


ii

7. The designation of the configuration as *syn* originates from the conventional usage of the *syn/anti* terminology for describing diastereomeric relationships in acyclic systems, and considers the products **5** and **7** to be equivalent to the acyclic system **iii**, where the *syn* relationship between the sulfoxide chiral center and the chiral center closest to it becomes apparent.



iii

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