Allium Chemistry: Synthesis and Sigmatropic Rearrangements of Alk(en)yl 1-Propenyl Disulfide *S*-Oxides from Cut Onion and Garlic[1]

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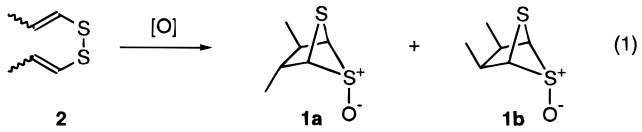
Abstract: Reduction ($LiAlH_4$) of propyl 1-propynyl sulfide (**8**) to (*E*)-1-propenyl propyl sulfide ((*E*)-**10**), C−S cleavage (Li/NH_3) to lithium (*E*)-1-propenethiolate (Li (*E*)-**11**), and reaction with $MeSO_2Cl$ gives (*E*,*E*)-bis(1-propenyl) disulfide ((*E*,*E*)-**2**); *i*-Bu_2AlH reduction of **8** to (*Z*)-**10** and reaction with Li/NH_3 and then $MeSO_2Cl$ gives (*Z*,*Z*)-**2** via Li (*Z*)-**11**. Reaction of $MeSO_2SR$ (R = Me (**12a**), *n*-Pr (**12b**), $CH_2CH{=}CH_2$ (**12c**), CH=CHMe (**12d**)) with K (*E*)-**11** gives (*E*,*Z*)-**2** from (*Z*)-**12d**; Li (*E*,*Z*)-**11** gives alkyl (*E*)- and (*Z*)-1-propenyl disulfides (MeCH=CHSSR, R = Me (**3a**), *n*-Pr (**3b**), $CH_2{=}CHCH_2$ (**3c**)) from **12a**−**c**, respectively. Oxidation at −60 °C of (*E*,*E*)-, (*Z*,*Z*)-, and (*E*,*Z*)-**2** gives (*E*)-1-propenesulfinothioic acid *S*-(*E*)-1-propenyl ester ((*E*,*E*)-**13**, (*E*,*E*)-MeCH=CHS(O)SCH=CHMe) from (*E*,*E*)-**2**, (*Z*,*Z*)-**13** from (*Z*,*Z*)-**2**, and ca. 2:1 (*E*,*Z*)-**13**)/(*Z*,*E*)-**13** from (*E*,*Z*)-**2**. Warming (*Z*,*Z*)-**13** gives (±)-(1α,2α,3*β*,4α,5*β*)-2,3-dimethyl-5,6-dithiabicyclo[2.1.1]hexane 5-oxide (**1a**), *endo*-5-methyl-*exo*-6-methyl-2-oxa-3,7-dithiabicyclo[2.2.1]heptane (**14a**), and *exo*-5-methyl-*endo*-6-methyl-2-oxa-3,7-dithiabicyclo[2.2.1]heptane (**14b**). Warming (*E*,*E*)-**13** gives **14a** and **14b**; (*E*,*Z*)-**13**/(*Z*,*E*)-**13** gives (1α,2α,3α,4α,5*β*)-2,3-dimethyl-5,6-dithiabicyclo-[2.1.1]hexane 5-oxide (**1b**), *exo*-5-methyl-*exo*-6-methyl-2-oxa-3,7-dithiabicyclo[2.2.1]heptane (**14c**), and *endo*-5-methyl-*endo*-6-methyl-2-oxa-3,7-dithiabicyclo[2.2.1]heptane (**14d**). Oxidation of **3a**−**c** gives MeCH=CHSS(O)R (**4**) and MeCH=CHS(O)SR (**5**). At −60 °C, *m*-CPBA (2 equiv) converts (*E*,*E*)-**2** into (*Z*,*Z*)-*d*,*l*-2,3-dimethyl-1,4-butanedithial 1,4-dioxide (**26**) while (*Z*,*Z*)-**2** gives *meso*- and *d*,*l*-**26**. With $NaIO_4$, **4**/**5** (R = Me) gives (*E*)- or (*Z*)-**12a** and $MeCH{=}CHSO_2SMe$ (**6a**); with *m*-CPBA (*Z*)-MeS(O)CHMeCH=S^+−O^- (**25a**) forms. At 85 °C **2** gives 1:1 *cis*- and *trans*-2-mercapto-3,4-dimethyl-2,3-dihydrothiophene (**29**).

Introduction

Zwiebelanes[1,2] (**1a**,**b**)[2] are sulfur-containing flavorants from freshly cut onion (*Allium cepa*), easily synthesized by oxidation of bis(1-propenyl) disulfide, $(MeCH{=}CHS)_2$ (**2**; eq 1).[3] In order to better understand the origin of **1** and other



2 **1a** **1b**

unusual compounds from cut onion,[4] we have examined the low-temperature oxidation with 1 or 2 equiv of oxidant of stereospecifically synthesized geometric isomers of **2**, as well as the related alkyl 1-propenyl disulfides (*E*)- and (*Z*)-MeCH=CHSSR (**3**). Compounds **2** and **3**[5a−e] and *S*-oxides **4**,[2,6a,b,e,i] **5**,[2,6a,b,e] **6**,[2,6c] and **7**[2,6h] are found in extracts and distillates of *Allium* spp. They are thought to account for the insecticidal (as well as insect attracting[6f,g]), larvicidal, nematicidal, antimicrobial, antiasthmatic, or other medicinal properties of these plants, and may make important flavor contributions.[5f,6c,d,h] Structural assignments for **4**−**6** are based primarily on spectroscopic analysis, which in a few cases is open to question. None of these compounds have been previously synthesized. Evidence is presented for facile [3,3]-sigmatropic rearrangement of **2**, its

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(1) Preliminary communications: (a) Bayer, T.; Wagner, H.; Block, E.; Grisoni, S.; Zhao, S. H.; Neszmelyi, A. *J. Am. Chem. Soc.* **1989**, *111*, 3085. (b) Block, E.; Bayer, T. *J. Am. Chem. Soc.* **1990**, *112*, 4584. (c) Block, E.; Zhao, S. H. *Tetrahedron Lett.* **1990**, *31*, 4999. (d) Block, E.; Zhao, S. H. *J. Org. Chem.* **1992**, *57*, 5815.

(2) *Chemical Abstracts* names of compounds not otherwise named in the text: **1a**, (1α,2α,3α,4α,5*β*)-2,3-dimethyl-5,6-dithiabicyclo[2.1.1]hexane 5-oxide; **1b**, (±)-(1α,2α,3*β*,4α,5*β*)-2,3-dimethyl-5,6-dithiabicyclo[2.1.1]-hexane 5-oxide; **4**, alkanesulfinothioic acid *S*-(*E*,*Z*)-1-propenyl ester isomers; (*E*,*Z*)-**4a**, methanesulfinothioic acid *S*-(*E*)-1-propenyl ester; (*E*,*Z*)-**4b**, 1-propanesulfinothioic acid *S*-(*E*,*Z*)-1-propenyl ester; (*E*,*Z*)-**4c**, 2-propene-1-sulfinothioic acid *S*-(*E* or *Z*)-1-propenyl ester; **5**, (*E*)-1-propenesulfinothioic acid *S*-alk(en)yl ester isomers; (*E*)-**5a**, (*E*)-1-propenesulfinothioic acid *S*-methyl ester; (*E*,*Z*)-**5b**, (*E*,*Z*)-1-propenesulfinothioic acid *S*-*n*-propyl ester; (*E*,*Z*)-**5c**, (*E*,*Z*)-1-propenesulfinothioic acid *S*-2-propenyl ester; **6**, (*E*)-1-propenesulfonothioic acid *S*-methyl ester; **7**, 1-propenethiosulfate; K (*E*)-**11**, potassium (*E*)-1-propenethiolate; **12a**, methanesulfonothioic acid *S*-(*E*,*Z*)-1-propenyl ester; **12b**, *n*-propanesulfonothioic acid *S*-(*E*,*Z*)-1-propenyl ester; (*E*,*E*)-**13**, 1-(*E*)-propenesulfinothioic acid *S*-1-(*E*)-propenyl ester; (*Z*,*Z*)-**13**, 1-(*Z*)-propenesulfinothioic acid *S*-1-(*Z*)-propenyl ester; (*E*,*Z*)-**13**, 1-(*E*)-propenesulfinothioic acid *S*-1-(*Z*)-propenyl ester; (*Z*,*E*)-**13**, 1-(*Z*)-propenesulfinothioic acid *S*-1-(*E*)-propenyl ester; **14a**, *endo*-5-methyl-*exo*-6-methyl-2-oxa-3,7-dithiabicyclo[2.2.1]heptane; **14b**, *exo*-5-methyl-*endo*-6-methyl-2-oxa-3,7-dithiabicyclo[2.2.1]heptane; **14c**, *exo*-5-methyl-*exo*-6-methyl-2-oxa-3,7-dithiabicyclo[2.2.1]heptane; **14d**, *endo*-5-methyl-*endo*-6-methyl-2-oxa-3,7-dithiabicyclo[2.2.1]heptane; **15**, *exo*-4-ethyl-2-oxa-3-thiabicyclo-[3.3.0]oct-7-ene; **15a**, *cis*-2-[1′-*tert*-butyldithio)propyl]-4-cyclopentenol; **16**, 2,5-bis-*endo*-dichloro-7-thiabicyclo[2.2.1]heptane; **17a**−**d**, 3,4-dimethyl-2-hydroxy-5-(phenyldithio)thiolanes; **21a**, (2*R*,3*S*/2*S*,3*R*)-2,3-dimethyl-1,4-butanedithial *S*-oxide; **21b**, 2*R*,3*R*/2*S*,3*S*)-2,3-dimethyl-1,4-butanedithial *S*-oxide; **25a**, 2-(methylsulfinyl)propanethial *S*-oxides; **25b**, 2-(*n*-propylsulfinyl)propanethial *S*-oxides; **25c**, 2-(2-propylsulfinyl)propanethial *S*-oxides; **26**, 2,3-dimethyl-1,4-butanedithial 1,4-dioxide; **29a**,**b**, *cis*- and *trans*-2-mercapto-3,4-dimethyl-2,3-dihydrothiophene; **31a**,**b**, *cis*- and *trans*-2-(methylthio)-3,4-dimethyl-2,3-dihydrothiophene.

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(4) For leading references, see refs 1 and 3 in the accompanying paper.[3a]

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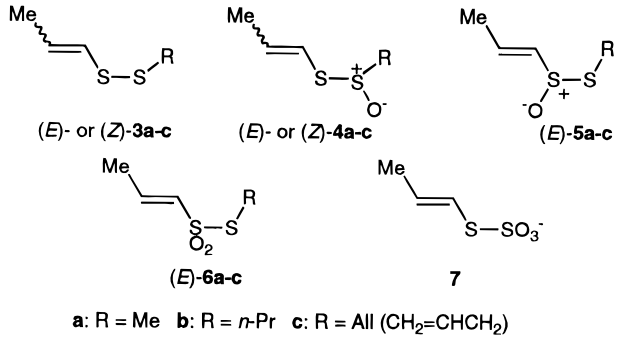
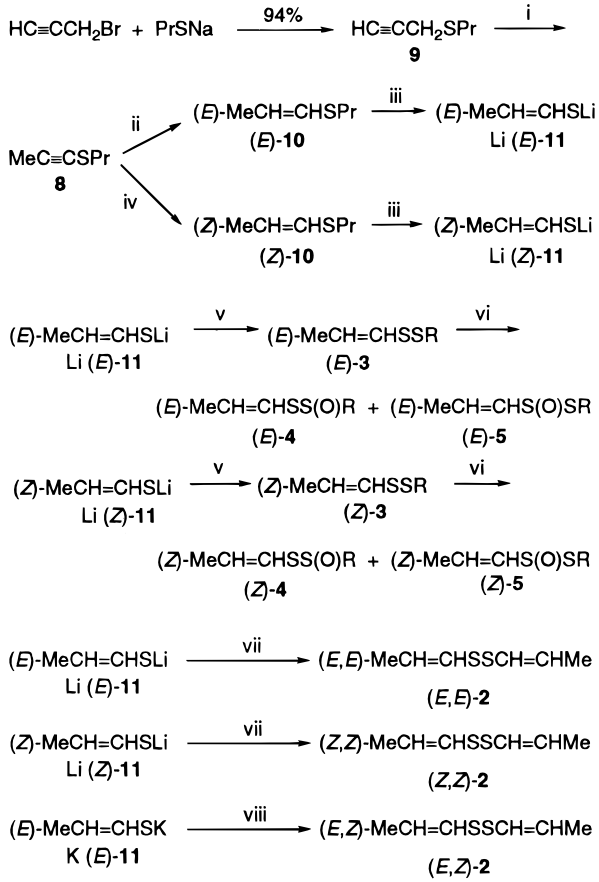


S-oxide, and its *S*,*S*′-dioxide, as well as for related processes involving **4** and the corresponding dioxides of **3**. These studies on the chemistry of **2** and **3** and their *S*-oxides complement our earlier work on the chemistry of 2-propenyl disulfides, CH_2═$CHCH_2SSR$, characteristic of garlic.[7] The work in this and the accompanying paper[3a] more fully defines the extraordinary organosulfur chemistry of plants of the genus *Allium*.[4]

Results and Discussion

A. Stereospecific Synthesis of Isomers of 2 and 3. In order to obtain detailed information on the processes occurring during oxidation of **2** and **3**, individual disulfide isomers were stereospecifically synthesized (Scheme 1) and the course of oxidation was followed using low-temperature NMR. Propyl 1-propynyl sulfide (**8**), available from base-catalyzed isomerization[8] of propyl 2-propynyl sulfide (**9**), was reduced to either (*E*)- or (*Z*)-propenyl propyl sulfide ((*E*)- or (*Z*)-**10**) by known methods.[8c,9a] Cleavage of sulfides **10** (Li/NH_3) with retention of stereochemistry gives lithium thiolates **11** which afford disulfides **3** with the appropriate thiosulfonate **12**. Reaction of Li (*E*)- or (*Z*)-**11** with MsCl gives (*E*,*E*)- or (*Z*,*Z*)-**2**. These reaction conditions were chosen to minimize *E*/*Z* isomerization of the disulfides **2**, a problem encountered with I_2 oxidation of **11**. Reaction of (*E*)-MeCH═CHSK (K (*E*)-**11**)[9b] with (*Z*)-MeCH═$CHSSO_2Me$ ((*Z*)-**12d**)[1d,2] at −78 °C gives (*E*,*Z*)-**2**. Isomers of **2** can also be separated by preparative HPLC. While (*E*,*E*)-**2** and (*Z*,*Z*)-**2** were relatively stable at room temperature, (*E*,*Z*)-**2** on standing underwent disproportionation to a mixture of all three isomers of **2**. Table 1 gives the ^{1}H and ^{13}C NMR methyl group chemical shifts for isomers of **2** and **3a**−**c**. While isomers of **2** have been previously prepared,[10] our syntheses give better stereoselectivity and overall yields than earlier methods.

Scheme 1[a,b]



[a] (i) NaOMe (85%). (ii) $LiAlH_4$ (81%). (iii) Li/NH_3. (iv) DIBAL (75%) or Cu_2Br_2, $LiAlH(OMe)_3$ (73%). (v) $RSSO_2Me$ (**12a**−**c**; 53−63%). (vi) *m*-CPBA, −60 °C (73−82%). (vii) $MeSO_2Cl$ (61−82%). (viii) (*Z*)-MeCH═$CHSSO_2Me$ (**12d**; 60%). [b] R = Me (**3**−**5a**), *n*-Pr (**3**−**5b**), or CH_2═$CHCH_2$ (**3**−**5c**).

B. Monooxidation of 3. Oxidation (*m*-CPBA/−60 °C) of (*E*)-MeCH═CHSSMe ((*E*)-**3a**) gives 2:1 (*E*)-MeCH═CHSS(O)Me ((*E*)-**4a**[2])/(*E*)-MeCH═CHS(O)SMe ((*E*)-**5a**[2]) while (*Z*)-**3a** gives the corresponding (*Z*)-isomers in a 6:1 (*Z*)-**4a**/(*Z*)-**5a** ratio; isomers are separable by preparative TLC or HPLC. Oxidation at sulfur is more difficult next to a (*Z*)- than an (*E*)-1-propenyl group. Similarly, oxidation of (*E*)- or (*Z*)-MeCH═CHSS-*n*-Pr ((*E*)- or (*Z*)-**3b**) gives (*E*)- or (*Z*)-**4b**[2] and (*E*)- or (*Z*)-**5b**,[2] (Scheme 1, R = *n*-Pr) while (*E*)- or (*Z*)-MeCH═CHSSAll ((*E*)- or (*Z*)-**3c**) gives (*E*)- or (*Z*)-**4c**[2] and (*E*)- or (*Z*)-**5c**[2] (Scheme 1, R = All). Preparative TLC of samples containing either (*E*)- or (*Z*)-**4a** leads to the *same* mixture containing 1.7:1 (*E*)-**4a**/(*Z*)-**4a**. A similar (*E*)-**4a**/(*Z*)-**4a** ratio arises when oxidized solutions of either pure (*E*)-**3a** or (*Z*)-**3a** are stored overnight at 25 °C. Individual isomers of (*E*)- and (*Z*)-**5a** are configurationally stable under all conditions examined. The mechanistic significance of these observations will be discussed below.

1-Propenyl thiosulfinates **4a**−**c**/**5a**−**c** have been fully characterized spectroscopically. Data for (*E*)- and (*Z*)-**4a** and **-4b** are in excellent agreement with those published for compounds isolated from cut onion[6a] but differ significantly from some of the data published for isomers of **4** and **5** in crushed garlic.[11] IR spectroscopy confirms the presence of a S(O)S function (1090 cm^{-1} band) while CI-mass spectra (CI-MS) confirm the

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Table 1. ^{1}H (^{13}C) Methyl Group NMR Chemical Shifts in RS(O)$_n$SR′ [a]

R	R′	compd no.	C-3	C-1	*n*	C-1′	C-3′
(*E*)-1-propenyl	Me	**3a**	1.79 (17.9)		0	2.39 (22.0)	
(*Z*)-1-propenyl	Me	**3a**	1.76 (14.3)		0	2.43 (23.0)	
(*E*)-1-propenyl	*n*-Pr	**3b**	1.77 (18.1)		0		
(*Z*)-1-propenyl	*n*-Pr	**3b**	1.75 (14.2)		0		
(*E*)-1-propenyl	allyl	**3c**	1.78 (18.0)		0		
(*E*)-1-propenyl	(*E*)-1-propenyl	**2**	1.78 (18.1)		0		1.78 (18.1)
(*E*)-1-propenyl	(*Z*)-1-propenyl	**2**	1.79 (18.1)		0		1.77 (14.4)
(*Z*)-1-propenyl	(*Z*)-1-propenyl	**2**	1.77 (14.4)		0		1.77 (14.4)
Me	Me			2.99 (42.7)	1	2.67 (14.5)	
(*E*)-1-propenyl	Me	**5a**	1.98 (13.8)		1	2.60 (17.3)	
(*Z*)-1-propenyl	Me	**5a**	1.96		1	2.69	
Me	(*E*)-1-propenyl	**4a**		2.98 (42.1)	1		1.92 (18.9)
Me	(*Z*)-1-propenyl	**4a**		3.04 (42.7)	1		1.86 (15.1)
(*E*)-1-propenyl	*n*-Pr	**5b**	1.94 (17.4)		1		
n-Pr	(*E*)-1-propenyl	**4b**			1		1.90 (15.1)
n-Pr	(*Z*)-1-propenyl	**4b**			1		1.84 (18.9)
(*E*)-1-propenyl	All	**5c**	1.97 (17.5)		1		
All	(*E*)-1-propenyl	**4c**			1		1.89 (19.0)
All	(*Z*)-1-propenyl	**4c**			1		1.84 (15.1)
(*E*)-1-propenyl	(*E*)-1-propenyl	**13**	1.99 (19.5)		1		1.91 (17.9)
(*E*)-1-propenyl	(*Z*)-1-propenyl	**13**	2.10 (19.5)		1		1.84 (15.4)
(*Z*)-1-propenyl	(*E*)-1-propenyl	**13**	1.97 (15.8)		1		1.84 (17.9)
(*Z*)-1-propenyl	(*Z*)-1-propenyl	**13**	1.96		1		1.86
Me	Me			3.29 (48.8)	2	2.68 (18.3)	
(*E*)-1-propenyl	Me	**6a**	2.00 (17.0)		2	2.57 (29.8)	
Me	(*E*)-1-propenyl	**12a**		3.26 (47.9)	2		1.94 (19.0)
Me	(*Z*)-1-propenyl	**12a**		3.23 (48.6)	2		1.87 (15.1)

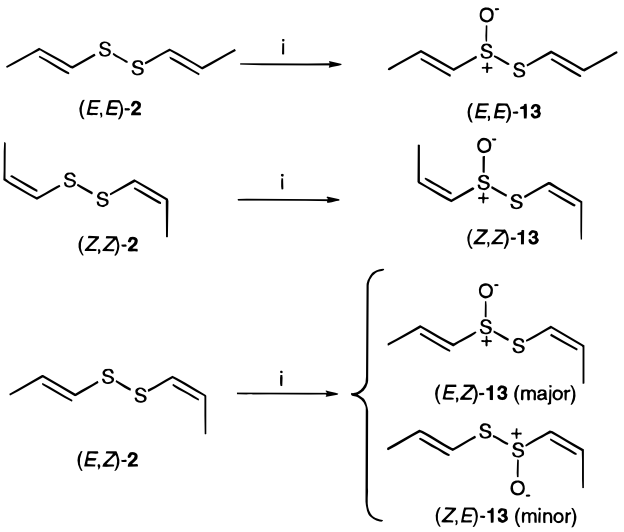
[a] Structure: $C_3-C_2-C_1-S(O)_n-S-C_{1'}-C_{2'}-C_{3'}$.

molecular formulas and EI-MS allow regioisomers to be readily distinguished. The base peak for MeCH═CHSS(O)Me (**4a**) at *m/z* 73 corresponds to MeCH═CHS$^+$ while that for MeCH═CHS(O)SMe (**5a**) at *m/z* 88 corresponds to CH_2═CHCH═S═O$^{\bullet+}$; there are only very small peaks at *m/z* 88 and 73 in **4a** and **5a**, respectively. LC−atmospheric pressure chemical ionization-MS/MS studies (LC−APCI-MS/MS) confirm the identity of synthetic **4a**−**c** and **5a**−**c** with constituents of onion and garlic homogenates.[12] The ^{1}H NMR data in Table 1 indicate that compounds with MeS(O)S− groups show singlets at δ 2.99−3.04 while those with MeSS(O)− groups show singlets at δ 2.60−2.67. The methyls of the (*E*)- and (*Z*)-MeCH═CHSS(O)− groups appear as doublets at δ 1.91−1.93 and 1.86−1.87, respectively, while those of (*E*)-MeCH═CHS(O)S− appear as doublets at δ 1.93−1.99. The regiochemistry of unsymmetrical thiosulfinates also follows from ^{13}C NMR shift data given in Table 1. Thus, MeS(O)S− groups appear at δ_C 42−43 while MeSS(O)− groups appear at δ_C 13−15 ppm.

C. Monooxidation of 2. Oxidation of a pure sample of (*Z*,*Z*)-**2** with $NaIO_4$ in methanol−water at room temperature for 5 h gave *trans*-zwiebelane **1a** in 26% isolated yield, along with minor amounts (1.2%) of *cis*-zwiebelane **1b**; the latter compound may arise by [2,3]-sigmatropic *E*−*Z* isomerization of (*Z*,*Z*)-MeCH═CHS(O)SCH═CHMe (**13**)[2] prior to cyclization (see below). When (*E*,*E*)-**2** was oxidized under identical conditions, **1a** and **1b** could not be detected.

Isomers of **2** at −60 °C were treated with chilled solutions of *m*-CPBA in the presence of dry Na_2CO_3. After 5 min the reaction mixture was analyzed by NMR methods at −60 °C. From the ^{1}H/^{13}C NMR methyl group chemical shift data (Table 1), we conclude that oxidation of individual isomers of **2** gives isomers of thiosulfinates MeCH═CHS(O)SCH═CHMe (**13**)[2] with retention of double bond stereochemistry (Scheme 2). Unsymmetrical disulfide (*E*,*Z*)-**2** gives a 2:1 mixture of (*E*,*Z*)-**13** and (*Z*,*E*)-**13**. Relative rates of oxidation are (*E*,*E*)-**2** > (*E*,*Z*)-**2** > (*Z*,*Z*)-**2**. Structural assignments for (*E*,*Z*)-**13** and (*Z*,*E*)-**13** are based on comparison of the NMR data in Table 1 for thiosulfinates **4a**, **5a**, and **13** as well as the (above) observation that oxidation at sulfur is more difficult next to a (*Z*)- than an (*E*)-1-propenyl group.

Scheme 2[a]



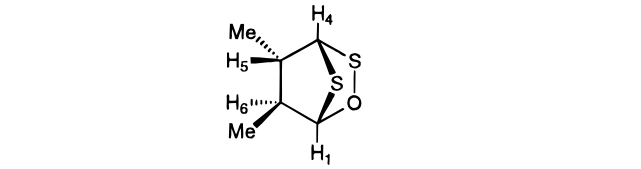
[a] (i) *m*-CPBA, Na_2CO_3, $CDCl_3$, −60 °C.

D. Low-Temperature Rearrangement of Thiosulfinates 13. Solutions of isomers of **13** in NMR tubes containing dioxane as internal standard were kept at −40 °C for 3 h whereby (*Z*,*Z*)-**13** gives *trans*-zwiebelane **1a** along with bicyclic sultenes **14a**[2] (major) and **14b**[2] (minor), (*E*,*E*)-**13** gives only **14a**[2] (major) and **14b**[2] (minor), and (*E*,*Z*)-**13**/(*Z*,*E*)-**13** gives *cis*-zwiebelane **1b** along with bicyclic sultenes **14c**[2] (major) and **14d**[2] (minor) (Schemes 3−6). Thus, the initial products of rearrangement after 3 h at −40 °C are, for (*Z*,*Z*)-**13**, 25:3.3:1

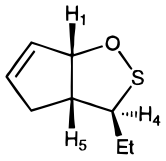
(11) (a) After we pointed out the discrepencies between our NMR data and his, L. Lawson agreed that some of his chemical shift data were in error.[11b] (b) Lawson, L. D. In *Garlic: The Science and Therapeutic Applications of Allium sativum L. and Related Species*; Koch, H. P., Lawson, L. D., Eds.; Williams and Wilkins: Baltimore, MD, 1996; p 56.

(12) Calvey, E.; Block, E.; Matusik, J.; White, K. D.; DeOrazio, R.; Sha, D. Manuscript in preparation

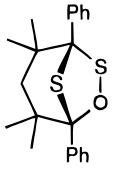
1b/**14a**/**14b**, for (*E*,*E*)-**13**, 4:1 **14a**/**14b**, and for (*E*,*Z*)-**13**/(*Z*,*E*)-**13**, 10:12:1 **1a**/**14c**/**14d**. Compounds **14a**−**d**, which showed neither sulfinyl nor sulfonyl bands in their IR spectra, defied all efforts at chromatographic purification. Structures of **14a**−**d** could be assigned on the basis of their ^{1}H and ^{13}C NMR spectra. In particular, ^{1}H and ^{13}C NMR bands at δ 5.90 (s, 1 H) and 4.84 (d, J = 3 Hz, 1 H) and at δ 100.6 and 82.4, respectively, for **14a**, and at δ 5.88 (s, 1 H) and 4.56 (s, 1 H) and at δ 99.8 and 82.9, respectively, for **14c**, suggest the presence of O−CH_1−S (δ 5.90) and S−CH_4−S (δ 4.84) groups (see structure of **14a** below for numbering). Sultenes **15a**−**c**[2] have been previously reported.[13a−c] Sultene **15a**[13a] shows NMR absorptions at δ_C 95.0 (C-1) and 64.8 (C-4) and δ_H 5.3 (H_1) and 3.3 (H_4), respectively, while **15b**[13b] shows δ_C 113.0 (C-1) and 86.4 (C-5). In **16**,[2] bridgehead protons $H_{1,4}$ appear at δ 3.64, coupled to the vicinal *exo*-protons $H_{2,3x,5,6x}$ with J = 3.4; J = 0 for the corresponding bridgehead proton−vicinal *endo*-proton coupling H_1−H_{6n}/H_4−H_{3n}.[13d] In **14a** protons H_1 (δ 5.90) and H_4 (δ 4.84) have adjacent *endo* (H_6) and *exo* (H_5) protons, as indicated by the respective values of J = 0 and 3.4 Hz. Protons H_5 and H_6 in **14c** must both be *endo* to account for the absence of coupling with the bridgehead protons. Just as sultene **15a** reacts rapidly with 2-methyl-2-propanethiol to give 4-cyclopentenol **15d**,[2] **14a**,**b** react with thiophenol, giving a mixture of isomeric 2-hydroxythiolanes **17a**−**d**.[2,13e]



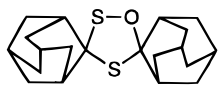
14a



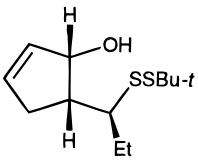
15a



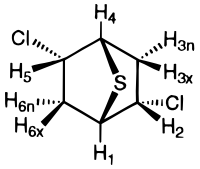
15b



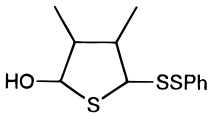
15c



15d



16



17a-d

E. Mechanistic Considerations. While facile rearrangement of (*E*)-1-propenesulfenic acid ((*E*)-MeCH═CHSOH, (*E*)-**19**; from enzymatic cleavage of (*E*)-(+)-*S*-(1-propenyl)-L-cysteine *S*-oxide ((*E*)-**18**); see Scheme 1, accompanying paper[3a]) to onion lachrymatory factor (LF) (*Z*)-propanethial *S*-oxide (EtCH═S^+−O^-, **20**) might be thought to preclude formation of MeCH═CHS(O)SCH═CHMe (**13**), sulfenic acid **19** and related compounds have been trapped with alkynes.[14a−c] The occurrence of thiosulfinates **4** and **5** (MeCH═CHSS(O)R and MeCH═CHS(O)SR) in onion extracts also suggests that **19** can be trapped before it rearranges. Since we have shown that pairs of thiosulfinates RS(O)SR′/R′S(O)SR rapidly scramble, affording mixtures with RS(O)SR/R′S(O)SR′,[14a] formation of **13**/RS(O)SR from **4**/**5** is reasonable. Finally, ab initio (HF/6-31G*) calculations indicate that a 33 kcal/mol activation energy barrier separates the lower homolog of **19**, ethenesulfenic acid (CH_2═CHSOH), from the more stable (by 2.9 kcal/mol) LF (**20**) lower homolog, (*Z*)-ethanethial *S*-oxide ((*Z*)-CH_3-CH═S^+−O^-).[14d] We therefore suggest that isomers of **13** are indeed formed along with the LF **20** when an onion is cut but immediately undergo an unusually facile [3,3]-sigmatropic rearrangement to isomers of 2,3-dimethylbutanedithial *S*-oxide (**21**) (Schemes 3−6). More highly substituted homologs of **13**, where rearrangement is retarded, are known to be stable.[15] Solutions of thiosulfinates (*E*,*E*)-**13**, (*Z*,*Z*)-**13**, and (*E*,*Z*)-**13**/(*Z*,*E*)-**13** in NMR tubes containing dioxane as internal standard were warmed to −15 °C. The disappearance of peaks associated with **13** was followed with time. The so-determined first-order rate constants for disappearance of **13** at −15 °C are 8×10^{-4} s^{-1} for (*E*,*E*)-**13**, 4×10^{-4} s^{-1} for (*E*,*Z*)-**13**/(*Z*,*E*)-**13**, and 3×10^{-4} s^{-1} for (*Z*,*Z*)-**13**. If the ratio of these rate constants, 2.7:1.3:1, is compared to the analogous ratio for Claisen rearrangement of isomeric 1-propenyl 2-butenyl ethers,[16a] it is apparent that the rate ratio for the rearrangement of thiosulfinates is contracted, suggesting a more *advanced* transition state than for the Claisen rearrangement. Activation parameters for rearrangement of (*Z*,*Z*)-**13** at 273 K are E_a = 16 kcal/mol, $\Delta H^{\ddagger}$ = 15.5 kcal/mol, $\Delta S^{\ddagger}$ = −15.3 cal/mol K, and $\Delta G^{\ddagger}$ = 19.5 kcal/mol (see below).

We propose that following oxidation of (*E*,*E*)-**2** with *1* equiv of peracid, in the chairlike transition state for the [3,3]-sigmatropic rearrangement, the thiosulfinate oxygen assumes a pseudoaxial orientation analogous to that favored in 1,2-dithiane 1-oxides[16b] and sultines[16c] and in the sulfoxide thio-Claisen rearrangement.[17] Rearrangement from this transition state gives dithial *S*-oxide ((*Z*)-**21a**),[2] which can assume an appropriate conformation to undergo a very facile intramolecular 1,3-dipolar cycloaddition reaction[18a−c] involving the thial *S*-oxide group as

(13) (a) Block, E.; Wall, A. *J. Org. Chem.* **1987**, *52*, 809. (b) Ishii, A.; Jin, Y.-N.; Hoshino, M.; Nakayama, J. *Heteroatom Chem.* **1995**, *6*, 181. (c) Huisgen, R.; Mioston, G. Unpublished results. (d) Corey, E. J.; Block, E. *J. Org. Chem.* **1966**, *31*, 1663. (e) The stereochemistry is not shown. The stereochemistry at the hydroxy carbon is probably lost since a 4:1 **14a**/**14b** mixture gives a 1:1 mixture (by NMR) of isomers **17a**,**b** on reaction with thiophenol. Similarly, a 12:1 **14c**/**14d** mixture gives a 2.5:1 mixture of isomers **17c**,**d**, different from those obtained with **14a**/**14b**. Isomer **17a** shows an OH stretch in the IR spectrum, a D_2O exchangeable peak at 1.67 ppm (1 H) coupled to a peak at δ 5.29 (1 H, O−CH−S), and other peaks at δ 7.2−7.6 (m), 4.61 (d, 1 H), 2.46 (m, 1 H), 2.08 (m, 1 H), 1.97 (m, 1 H), 1.25 (d, J = 7 Hz, 3 H), 1.17 (d, J = 7 Hz, 3 H). Isomers **17b**−**d** show similar spectra. Mechanistic and full experimental details concerning **17a**−**d** are given elsewhere.[13f] (f) Naganathan, S. Ph.D. Thesis, SUNY−Albany, 1992.

(14) (a) Block, E.; O'Connor, J. *J. Am. Chem. Soc.* **1974**, *96*, 3929. (b) Shelton, J. R.; Davis, K. E. *J. Am. Chem. Soc.* **1967**, *89*, 718. (c) Block, E.; Penn, R. E.; Revelle, L. K. *J. Am. Chem. Soc.* **1979**, *101*, 2200. (d) Turecek, F.; McLafferty, F. W.; Smith, B. J.; Radom, L. *Int. J. Mass Spectrom. Ion Processes* **1990**, *101*, 283. (e) For early interest in the formation of **13**, see Whitaker, J. R. In *Advances in Food Research*; Chichester, C. O., Mrak, E. M., Stewart, G. F., Eds.; Academic Press: New York, 1976; Vol. 22, p 73 ff.

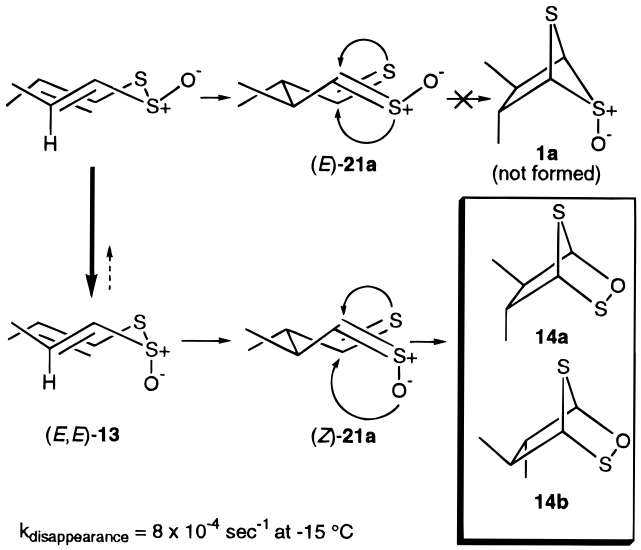
(15) (a) Highly substituted compounds of type R_2C═CRS(O)SCR═CR_2 are isolable at room temperature.[15b−d] (b) Bonini, B. F.; Foresti, E.; Leardini, R.; Maccagnani, G.; Mazzanti, G. *Tetrahedron Lett.* **1984**, *25*, 445. (c) van der Linden, J. B.; Timmermans, J. L.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 91. (d) Oxidation of Me_2C═$CHS(O)_nSCH$═CMe_2, **i**, n = 0, affords **i**, n = 1 and 2, which are moderately stable at 25 °C. We assume that the rate of [3,3]-sigmatropic rearrangement of **i** (n =1) is retarded relative to the rate for **13** by the *gem*-methyl groups.

(16) (a) Vittorelli, P.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1975**, *58*, 1293. (b) Juaristi, E.; Cruz-Sanchez, J. S.; Petsom, A.; Glass, R. S. *Tetrahedron* **1988**, *44*, 5653. (c) Breau, L.; Sharma, N. K.; Butler, I. R.; Durst, T. *Can. J. Chem.* **1991**, *69*, 185.

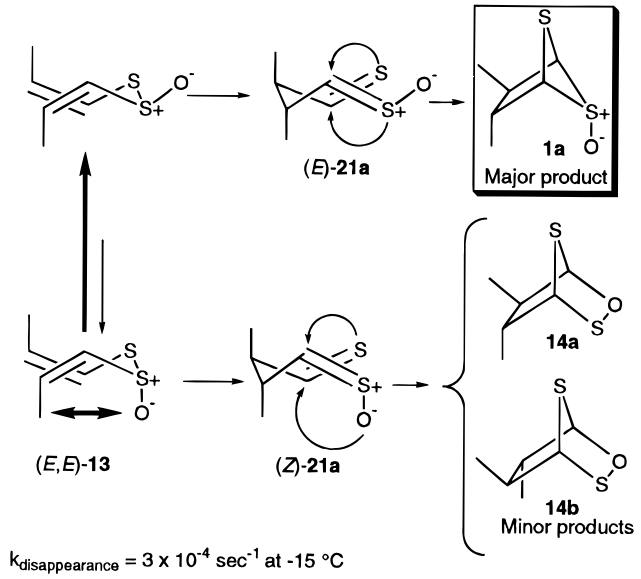
(17) (a) Block, E.; Ahmad, S. *J. Am. Chem. Soc.* **1985**, *107*, 6731. (b) Hwu, J. R.; Anderson, D. A. *Tetrahedron Lett.* **1986**, *27*, 4965. (c) Malherbe, R.; Rist, G.; Bellus, D. *J. Org. Chem.* **1983**, *48*, 860 and references therein.

(18) (a) Block, E.; Bazzi, A. A.; Revelle, L. K. *J. Am. Chem. Soc.* **1980**, *102*, 2490. (b) For analogous intramolecular heterobicyclo[2.2.1]heptane-forming processes involving nitrones, see: Lumma, W. C., Jr. *J. Am. Chem. Soc.* **1969**, *91*, 2820. (c) Hwu, J. R.; Robl, J. A. *J. Chem. Soc., Chem. Commun.* **1986**, 704.

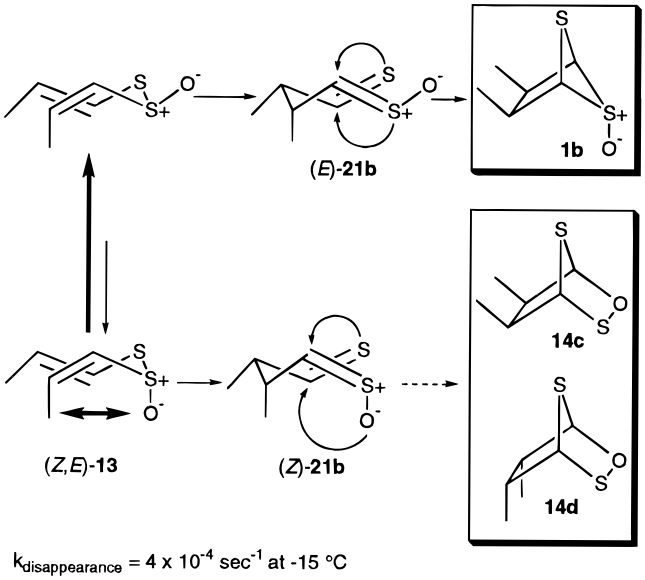
Scheme 3



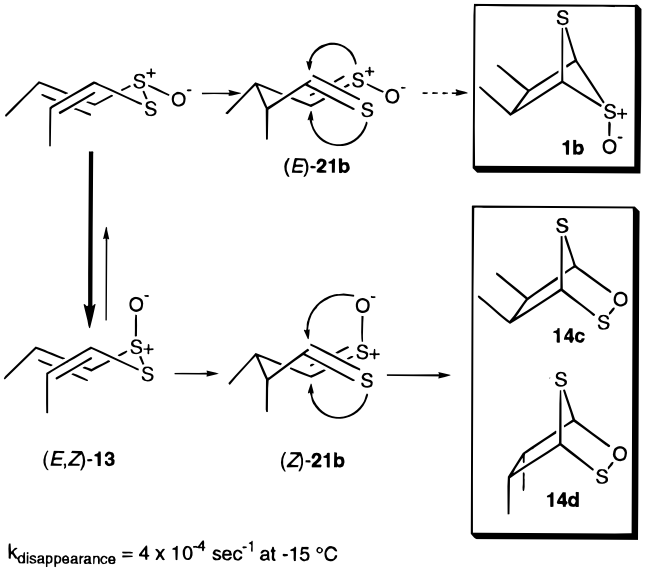
Scheme 4



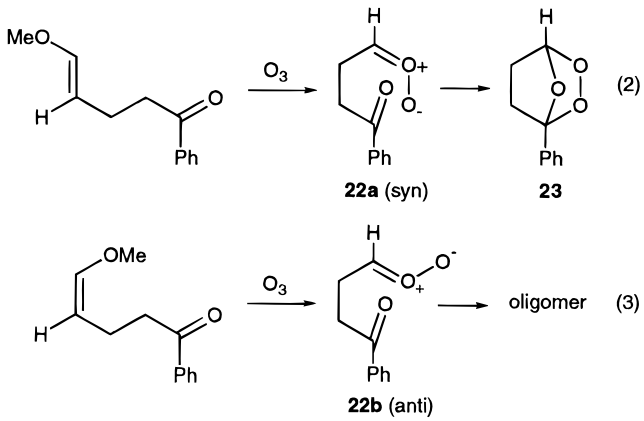
Scheme 5



Scheme 6



a 1,3-dipole[4] and the thial group as a 1,3-dipolarophile,[19a−c] affording **14a**,**b**[2] (Scheme 3). Intermolecular cycloadducts of thiones and thione *S*-oxides are known.[13c] Upon analogous oxidation of (*Z*,*Z*)-**2**, steric effects associated with the *Z* double bonds lead the intermediate to adopt a transition state geometry in which the thiosulfinate oxygen is pseudoequatorial, resulting in the formation of (*E*)-(2*R*,3*S*/2*S*,3*R*)-2,3-dimethyl-1,4-butanedithial *S*-oxide ((*E*)-**21a**), where the geometry of the (*E*)-C=S^+—O^- group favors the intramolecular head-to-tail [2 + 2] process,[20a] yielding **1b** over the sterically now more difficult 1,3-dipolar cycloaddition (Scheme 4). The formation of **14a**,**b** from (*Z*)-**21a** but not from (*E*)-**21a** is analogous to the observation that *syn*-carbonyl oxide **22a** cyclizes to give 1-phenyl-2,3,7-oxabicyclo[2.2.1]heptane (**23**; eq 2) (bridgehead CH, δ 6.22 ppm) whereas *anti*-carbonyl oxide **22b**, because it cannot achieve a suitable conformation for intramolecular cyclization, gives mainly oligomeric material (eq 3).[20b]



Pseudoaxial and pseudoequatorial thiosulfinate oxygen transition state geometries should be favored with (*E*,*Z*)-**13** and (*Z*,*E*)-**13**, respectively. Thus, oxidation of (*E*,*Z*)-**2** could afford comparable amounts of the heterobicyclo[2.1.1]hexane and

(19) (a) Huisgen, R.; Rapp, J. *J. Am. Chem. Soc.* **1987**, *109*, 902. (b) Huisgen, R.; Fisera, L.; Giera, H.; Sustmann, R. *J. Am. Chem. Soc.* **1995**, *117*, 9671. (c) Sustmann, R.; Sicking, W.; Huisgen, R. *J. Am. Chem. Soc.* **1995**, *117*, 9679.

(20) (a) For related examples, see Ishii, A.; Ding, M.-X.; Maeda, K.; Nakayama, J.; Hoshino, M. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 3343. Ishii, A.; Nakayama, J.; Ding, M.; Kotaka, N.; Hoshino, M. *J. Org. Chem.* **1990**, *55*, 2421. (b) Brunnelle, W. H.; Lee, S.-g. *Tetrahedron Lett.* **1994**, 35, 8141. (c) Block, E.; O'Connor, J. *J. Am. Chem. Soc.* **1974**, *96*, 3921.

Table 2. Comparative Activation Parameters for [3,3]-Sigmatropic Rearrangements

compd[a]	E_a (kcal/mol)	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (cal/(mol K))	$\Delta G^{\ddagger}$ (kcal/mol)	ref
(*Z*,*Z*)-**13**	16	15.5	−15.3	19.5	this work
(*Z*,*Z*)-**2**	19	18.3	−24.8	27.5	this work
A		19.3	−4.3		17a
B		25.4	−15.9		15

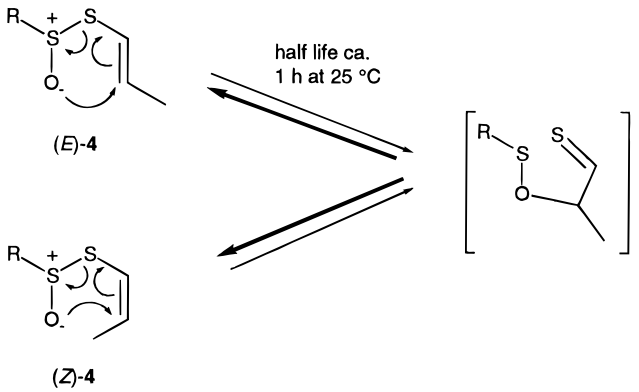
[a] Compound **A** = allyl vinyl sulfoxide, $CH_2{=}CHCH_2S(O)CH{=}CH_2$; compound **B** = 2-butenyl 1-propenyl ether, $MeCH{=}CHCH_2OCH{=}CH$-Me.

heterobicyclo[2.2.1]heptane systems (**1a** and **14c**,**d**, respectively) (Schemes 5 and 6). While there is variation in the type of ring system formed on monooxidation of (*E*,*E*)-, (*E*,*Z*)-, and (*Z*,*Z*)-**2**, there is high stereoselectivity in carbon−carbon bond formation.[3] The low temperature (−15 °C) at which rearrangement of (*Z*,*Z*)-**13** occurs, compared to that for the corresponding 2-butenyl 1-propenyl ether and allyl vinyl sulfoxide (see Table 2), reflects the weakness of the S−S bond (estimated bond energy 46 kcal mol^{-1})[20c] as well as the rate-enhancing effect of the zwitterionic sulfinyl group.[17b]

F. Mechanisms Associated with Natural Occurrence of Zwiebelanes. An enigma arises connecting the mechanism of processes taking place following monooxidation of stereoisomers of **2** to reactions that occur when an onion is cut. We have shown that *trans*-zwiebelane **1a** originates from (*Z*,*Z*)-**13** but not from (*E*,*E*)-**13**. Formation of (*Z*,*Z*)-**13** in onion homogenates is unlikely in that it would require condensation of two molecules of (*Z*)-1-propenesulfenic acid ((*Z*)-**19**). However, since (*Z*)-(+)-*S*-(1-propenyl)-L-cysteine *S*-oxide ((*Z*)-**18**) is not found in onion, and since the barrier to interconversion of (*E*)- to (*Z*)-1-propenesulfenic acid (**19**) is anticipated to be substantial (see part E above),[14d] it is improbable that sufficient quantities of (*Z*)-**19** would be present so that *self-condensation* would be likely. Furthermore, the detection in *Allium* spp. extracts of substantial amounts of (*E*)-MeCH=CHS(O)SR ((*E*)-**5**) *but no Z-isomers* also argues against the formation of significant amounts of (*Z*)-**19** and therefore (*Z*,*Z*)-**13**. In onion extracts, formation of **1a**,**b** might be enzymatically catalyzed with likely altered transition state stereochemistry. Since use of a chiral GC column, which resolves the enantiomers of **1a**, shows **1a** present in extracts of cut onion to be *completely racemic*, this proposal is unlikely. It is possible that **14a**,**b** undergo isomerization to **1a** in an aqueous medium at low pH, similar to sultene **15b**,[13b,21b] although addition of **14a**,**b** to an onion homogenate led to no increase in the concentration of **1a**,**b**. Identification of the alliinase-induced cleavage products from synthetic (*E*)- and (*Z*)-(+)-*S*-(1-propenyl)-L-cysteine *S*-oxide (**18**) under controlled conditions might help resolve this enigma.

G. *E*,*Z*-Isomerization of Mono-α,*β*-Unsaturated Thiosulfinates. All attempts to isolate pure samples of (*E*)- or (*Z*)-**4** (MeCH=CHSS(O)R) from mixtures with **5** (MeCH=CHS(O)-SR) always led to mixtures of (*E*,*Z*)-**4**. Furthermore, stereochemically pure samples of (*E*)-**5**/(*E*)-**4** or (*Z*)-**5**/(*Z*)-**4** were converted during the course of 1 h at 25 °C into (*E*)-**5**/(*E*,*Z*)-**4** or (*Z*)-**5**/(*E*,*Z*)-**4**, respectively.[6i] An equilibrium ratio of 1.6:1 (*E*)-**4**/(*Z*)-**4** was reached after 24 h at 25 °C in $CDCl_3$; the equilibration process was considerably slower in CD_3OD. The

Scheme 7[a]



[a] R = Me, *n*-Pr, $CH_2{=}CHCH_2$.

facile isomerization of isomers of **4**, but not **5** nor precursor disulfides **3**, can be explained by a [2,3]-sigmatropic rearrangement (Scheme 7) analogous to reactions of allylic sulfoxides or thiosulfinates.[22] This process is retarded by hydrogen bonding to the sulfinyl oxygen,[22b] as we observe. Efforts to intercept the thial intermediate with 2,3-dimethyl-1,3-butadiene were unsuccessful. This isomerization explains the surprising observation, noted above in part B, that although only (+)-*S*-(*E*)-1-propenyl-L-cysteine *S*-oxide ((*E*)-**18**) occurs naturally, presumably affording only (*E*)-MeCH=CHSOH ((*E*)-**19**), both (*E*)- and (*Z*)-**4**, but only (*E*)-**5**, are found in *Allium* extracts and distillates. Compound **5** is, of course, incapable of isomerization by the mechanism of Scheme 7.

H. Oxidation of Mono-α,*β*-Unsaturated Thiosulfinates. We examined the oxidation of thiosulfinates MeCH=CHSS(O)R (**4**) and RSS(O)CH=CHMe (**5**) as a route to the corresponding thiosulfonates $MeCH{=}CHSSO_2R$ (**12**)[2] and $RSSO_2CH{=}CHMe$ (**6**),[2] of interest as natural products themselves (e.g., (*E*)-$MeCH{=}CHSO_2SMe$ ((*E*)-**6a**)[2] has been isolated from *Allium grayi*)[6c] as well as synthetic reagents for preparation of α,*β*-unsaturated disulfides. "Nucleophilic" oxidation[23] of (*E*)-**4**/(*E*)-**5** or (*Z*)-**4**/(*Z*)-**5** (MeCH=CHSS(O)R/MeCH=CHS(O)SR) at the sulfinyl sulfur using $NaIO_4$/HOAc gave, respectively, (*E*)-**12**/(*E*)-**6** or (*Z*)-**12**/(*Z*)-**6** ($MeCH{=}CHSSO_2R$/ $MeCH{=}CHSO_2SR$) with no stereoisomerization (Scheme 8). Unlike (*E*)- and (*Z*)-**4**, stereoisomers of **12** were configurationally stable, showing no tendency to undergo *E*/*Z* isomerization. "Electrophilic" oxidation[23] of either (*E*)-**4**/(*E*)-**5** or (*Z*)-**4**/(*Z*)-**5** at the sulfenyl sulfur with *m*-CPBA gave identical 1:1 mixtures of compounds characterized as (*Z*)-2-(alkylsulfinyl)propanethial *S*-oxide (*Z*)-**25** (Scheme 9) (see the Experimental Section for proof of the structure). We presume that initial oxidation of **4**/**5** gives α-disulfoxide **24** (MeCH=CHS(O)S(O)R). While **24** could undergo pseudopericyclic[24a] rearrangement to **25**, the stereochemistry would be expected to be conserved, which is not the case. Therefore, (1) stereochemistry in **24** is lost through [2,3]-sigmatropic rearrangement (Scheme 8) which is more rapid than pseudopericyclic processes, (2) *two* diastereomers of **24** are

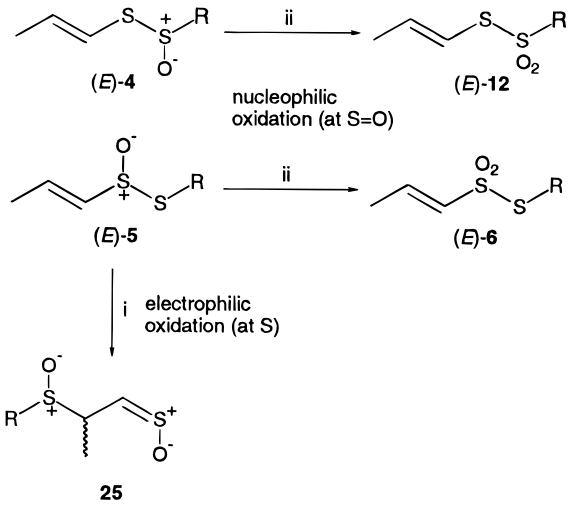
(21) (a) Okuyama, T.; Miyake, K.; Fueno, T.; Yoshimura, T.; Soga, S.; Tsukurimichi, E. *Heteroatom Chem.* **1992**, *3*, 577. (b) On the basis of arguments made in part E, (*E*,*Z*)-**13** (but *not* (*Z*,*E*)-**13**) should result from scrambling[14a] of thiosulfinates (*Z*)-**4** and (*E*)-**5**. Conversion of (*E*,*Z*)-**13** to **14c,d** (Scheme 6) could then be followed by isomerization to **1b** in the aqueous medium, explaining formation of the predominant naturally occurring zwiebelane.

(22) (a) Baldwin, J. E.; Höfle, G.; Choi, S. *J. Am. Chem. Soc.* **1971**, *93*, 2810. (b) Braverman, S. In *The Chemistry of Sulfenic Acids and their Derivatives*; Patai, S., Ed.; Wiley: New York, 1990; Chapter 8 and references therein.

(23) Kim, Y. H.; Takata, T.; Oae, S. *Tetrahedron Lett.* **1978**, *26*, 2305.

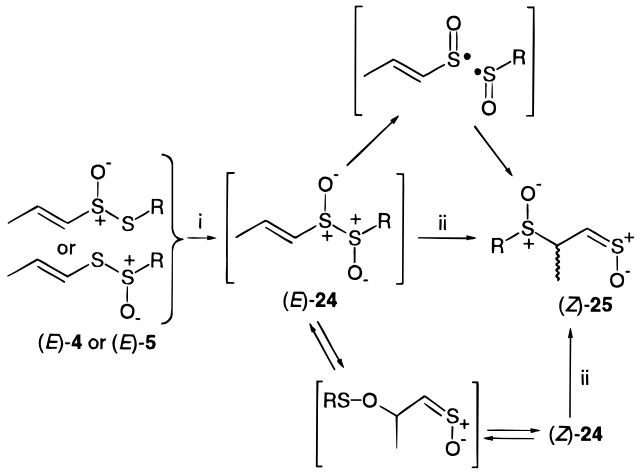
(24) (a) Ross, J. A.; Seiders, R. P.; Lemal, D. M. *J. Am. Chem. Soc.* **1976**, *98*, 4325. (b) Detection of (*Z*,*Z*)-*d*,*l*-**26** and RSO_2SR during electrophilic oxidation of **4**/**5** supports the third possibility ((*Z*,*Z*)-*d*,*l*-**26** and RSO_2SR could arise from dimerization of $MeCH{=}CHSO^{\bullet}$ and $RSO^{\bullet}$, respectively, according to Scheme 11). Scrambling of thiosulfinates **4**/**5** prior to or during oxidation could give **13** and RS(O)SR, which on oxidation would also give (*Z*,*Z*)-*d*,*l*-**26** and RSO_2SR.

Scheme 8[a,b]



[a] R = Me, *n*-Pr, CH_2═$CHCH_2$. [b] (i) *m*-CPBA. (ii) $NaIO_4$, HOAc, H_2O.

Scheme 9[a,b]



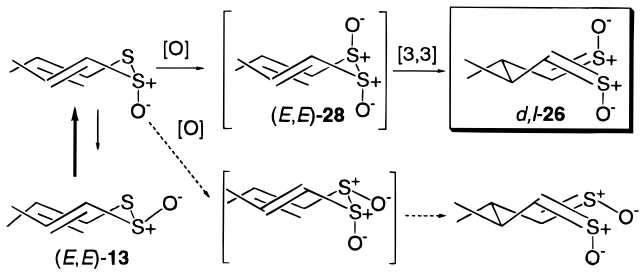
[a] R = Me, *n*-Pr, CH_2═$CHCH_2$. [b] (i) *m*-CPBA. (ii) Concerted 1,3-shift.

formed initially, or (3) conversion of **24** to **25** involves a free radical mechanism (Scheme 9).[24b]

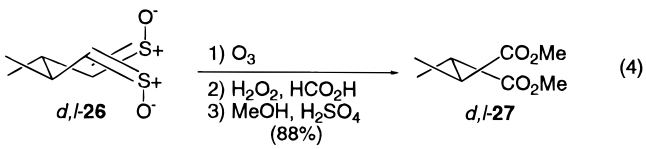
I. Dioxidation of Bis(1-propenyl) Disulfides. Formation of 2,3-Dimethyl-1,4-butanedithial 1,4-Dioxides. In view of the unusual chemistry found on monooxidation of (MeCH═CHS)$_2$ (**2**) to MeCH═CHS(O)SCH═CHMe (**13**) followed by rearrangement of the latter compound, we were interested in examining the reaction of **2** with *2* equiv of oxidant. We find that addition of a chilled CH_2Cl_2 solution of 2.2 equiv of *m*-CPBA to (*E*,*E*)-**2** in CH_2Cl_2 at −60 °C followed by workup gives **26** in 34% yield. Compound **26** is a colorless unstable solid of formula $C_6H_{10}S_2O_2$, showing a single, sharp, strongly UV absorbing peak on HPLC on either normal or C-18 silica gel. Extracts of onion show a strong HPLC peak at the identical retention time (see below). The ^{1}H and ^{13}C NMR spectra (see the Experimental Section) for **26** in $CDCl_3$ and C_6D_6 are similar to those for **20**[25] and **25**, suggesting that **26** is a (*Z*,*Z*)-bissulfine (e.g., $^-$O−S$^+$═CHCHMeCHMeCH═S$^+$−O$^-$). Sequential treatment of synthetic **26** with O_3 (−50 °C), H_2O_2/HCO_2H, and MeOH/H_2SO_4 gave in 88% yield a compound identical by GC−MS and NMR with authentic *d*,*l*-dimethyl 2,3-dimethylsuccinate

(25) Block, E.; Revelle, L. K.; Bazzi, A. A. *Tetrahedron Lett.* **1980**, *21*, 1277.

Scheme 10



(*d*,*l*-**27**) (eq 4) and different from authentic *meso*-**27**,[26] establish-



ing **26** as (*Z*,*Z*)-*d*,*l*-2,3-dimethyl-1,4-butanedithial 1,4-dioxide (*d*,*l*-**26**) (Scheme 10). Dioxidation of (*Z*,*Z*)-**2** and (*E*,*Z*)-**2** affords two different bissulfines, separable by HPLC. On the basis of ^{1}H and ^{13}C NMR analysis of the mixture, (*Z*,*Z*)-*meso*-2,3-dimethyl-1,4-butanedithial 1,4-dioxide (*meso*-**26**) appears to be formed along with *d*,*l*-**26**.

J. Natural Occurrence of 26. Extraction of onion homogenates followed by column chromatography led to isolation of (*Z*,*Z*)-*d*,*l*-**26** with NMR spectra identical to those of synthetic (*Z*,*Z*)-*d*,*l*-**26**. Furthermore, either normal or reversed phase HPLC of onion homogenate extracts showed a strongly UV absorbing peak with retention time identical to that of synthetic (*Z*,*Z*)-*d*,*l*-**26** and different from that of (*Z*,*Z*)-*meso*-**26**. Finally, LC−APCI-MS analysis showed the MS fragmentation of synthetic and natural (*Z*,*Z*)-*d*,*l*-**26** to be superimposable.[12] Bissulfine (*Z*,*Z*)-*d*,*l*-**26** was also found in homogenates of shallot and leek.[27]

K. Mechanistic Considerations Associated with Formation of 26. Compound (*Z*,*Z*)-*d*,*l*-**26**, noteworthy as the first bis(thial *S*-oxide),[28] bears a close relationship to the 2,3-dimethyl-1,4-butanedithial 1-oxides (**21**) postulated as intermediates in the rearrangement of **13**. We therefore propose that following oxidation of (*E*,*E*)-**2** with *2* equiv of peracid, in the chairlike transition state for [3,3]-sigmatropic rearrangement, the vicinal sulfinyl oxygens of (*E*,*E*)-bis(1-propenyl) *vic*-disulfoxide (**28**) can assume an *anti* geometry, suggested by theoretical calculations on an acyclic system to be favorable,[29,30] leading directly to (*Z*,*Z*)-*d*,*l*-**26** (Scheme 10). Compound **28** should undergo a particularly facile [3,3]-sigmatropic (double sulfoxide-accelerated dithio-Claisen) rearrangement due to the weakness of the S−S bond (ca. 36 kcal)[29] and the rate-enhancing effect of the two zwitterionic sulfinyl functions.[17b] The exclusive formation of *d*,*l*-**26** from dioxidation of (*E*,*E*)-**2** is consistent with concerted [3,3]-sigmatropic rearrangement of **28** and with the above

(26) From methylation of *d*,*l*- and *meso*-2,3-dimethylsuccinic acids (Aldrich Chemical Co.).

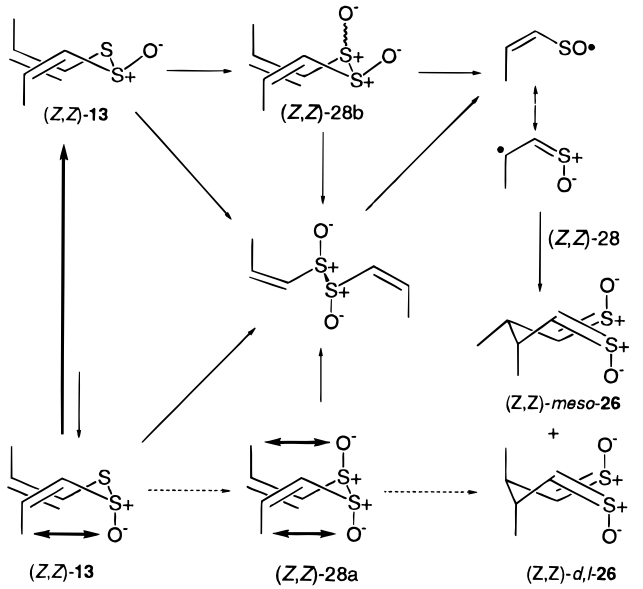
(27) Compound **26** shows moderate in vitro inhibition of 5-lipoxygenase in porcine leucocytes: Wagner, H.; Breu, W. Unpublished results.

(28) Several examples of *bis*(*thione S-oxides*) are known: (a) Nakayama, J.; Mizumura, A.; Yokomori, Y.; Krebs, A.; Schütz, K. *Tetrahedron Lett.* **1995**, *36*, 8583. (b) Zwanenburg, B.; Wagenaar, A.; Thijs, L.; Strating, J. *J. Chem. Soc., Perkins Trans. 1* **1973**, 73.

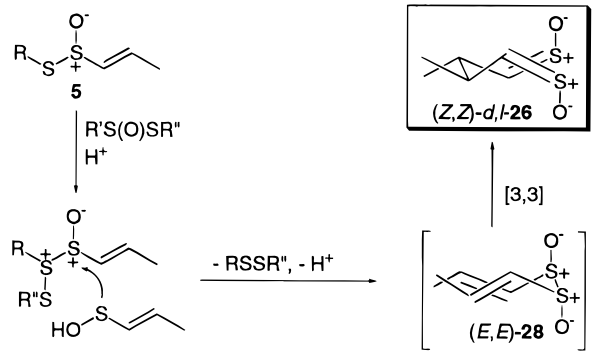
(29) Freeman, F.; Angeletakis, C. N.; Pietro, W. J.; Hehre, W. J. *J. Am. Chem. Soc.* **1982**, *104*, 1161.

(30) (a) Note that *parallel* α-disulfoxides[30b−d] are formed upon oxidation of various bicyclic thiosulfinates, although they appear to be less stable than the corresponding *antiparallel* α-disulfoxides: Folkins, P. L.; Harpp, D. N. *J. Am. Chem. Soc.* **1993**, *115*, 3066. (b) Folkins, P. L.; Harpp, D. N. *J. Am. Chem. Soc.* **1991**, *113*, 8998. (c) Freeman, F.; Lee, C. *J. Org. Chem.* **1988**, *53*, 1263. (d) Freeman, F. *Chem. Rev.* **1984**, *84*, 117.

Scheme 11



Scheme 12



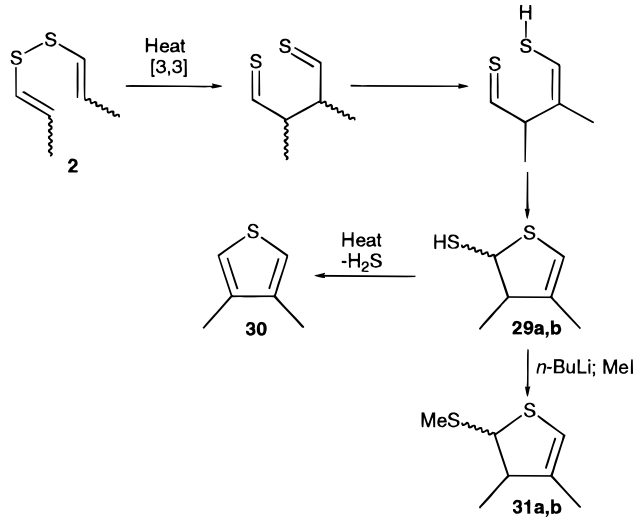
observations on the stereospecificity of products from *monooxidation* of isomers of **2**. On the other hand in the case of (*Z*,*Z*)-**2**, steric considerations suggest that, for the sulfinyl oxygens to be antiperiplanar, the bis(1-propenyl) *vic*-disulfoxide would have to assume an open conformation, unsuitable for a [3,3]-sigmatropic rearrangement. In this case, a homolytic process could occur, giving mixtures of (*Z*,*Z*)-*d*,*l*-**26** and (*Z*,*Z*)-*meso*-**26**, as is observed (Scheme 11).[31] Similar, if not more complex, stereochemical possibilities could occur on dioxidation of (*E*,*Z*)-**2**. Nonantiperiplanar arrangement of the vicinal sulfinyl oxygens might also be possible (e.g., see (*Z*,*Z*)-**28b**, Scheme 11), leading to formation of *E*,*Z*-isomers of *d*,*l*-**26** or *meso*-**26**, as is apparently observed in the cases of dioxidation of (*Z*,*Z*)- and (*E*,*Z*)-**2**.

A possible mechanism for formation of bissulfine **26** in onion extracts is shown in Scheme 12. Acid-catalyzed activation of (*E*)-MeCH═CHS(O)SR ((*E*)-**5**) by alkylsulfenyl transfer from a second molecule of thiosulfinate[32] is followed by nucleophilic attack of (*E*)-MeCH═CHSOH ((*E*)-**19**) at the sulfinyl sulfur of the sulfonium ion intermediate, giving (*E*,*E*)-**28** which then rearranges to (*Z*,*Z*)-*d*,*l*-**26**. Whatever mechanism is actually involved in formation of (*Z*,*Z*)-*d*,*l*-**26** in onion homogenates, it is highly probable that α-disulfoxide (*E*,*E*)-**28** is the immediate precursor.

(31) If the second oxygen is also introduced into an equatorial position and the [3,3]-sigmatropic rearrangement then occurs, the product would be (*E*,*E*)-*d*,*l*-**26**. While this could isomerize to (*Z*,*Z*)-*d*,*l*-**26**, the carbon framework would be unaffected; thus, formation of (*Z*,*Z*)-*meso*-**26** cannot be explained by this mechanism.

(32) Kice, J. L. *Adv. Phys. Org. Chem.* **1980**, *17*, 65.

Scheme 13



L. Pyrolysis of Bis(1-propenyl) Disulfide (2). To complement our study of the [3,3]-sigmatropic rearrangements of MeCH═CHS(O)SCH═CHMe (**13**) and MeCH═CHS(O)S(O)-CH═CHMe (**28**), as well as earlier studies of pyrolysis of bis-(2-propenyl) disulfide,[7] we examined the pyrolysis of isomers of bis(1-propenyl) disulfide (**2**). When a 1% solution of isomers of **2** in benzene is kept at 85 °C for 3 h, GC−MS analysis reveals the formation in over 85% yield of equal amounts of two new compounds, **29a**,**b** (Scheme 13), isomeric with the starting material, as well as ca. 20% of 3,4-dimethylthiophene (**30**), previously observed as the predominant product formed when **2** is heated to 150−200 °C in the presence of $KHSO_4$.[33a] Prolonged heating at higher temperatures results in the conversion of **29a**,**b** to **30**.[33b] Attempts to separate **29a**,**b** by TLC or HPLC were unsuccessful; extensive decomposition occurred under all conditions tried. Compounds **29a** and **29b** could be identified, respectively, as *cis*- and *trans*-2-mercapto-3,4-dimethyl-2,3-dihydrothiophene primarily on the basis of their ^1H and ^{13}C NMR and mass spectra. Methylation of **29a**,**b** affords 1:4 *cis*- and *trans*-2-(methylthio)-3,4-dimethyl-2,3-dihydrothiophene (**31a**/**31b**) (Scheme 13). Compounds **31a**,**b** were stable to storage and could be separated by HPLC on a C-18 column. The basis for assignment of *cis* and *trans* stereochemistry to **31a** and **31b**, respectively, appears in the supporting information.

Individual isomers of **2** were heated in benzene. HPLC analysis during the reaction showed that all three isomers gave the same mixture of **29a**/**29b** and that *no isomerization from one isomer of 2 to another occurred under the pyrolysis conditions*. The relative rates of reaction of the three isomers of **2** were found to be *E*,*Z* > *E*,*E* > *Z*,*Z*. For (*Z*,*Z*)-**2**, activation parameters at 373 K are $E_a = 19$ kcal/mol, $\Delta H^{\ddagger} = 18.3$ kcal/mol, $\Delta S^{\ddagger} = -24.8$ cal/mol K, and $\Delta G^{\ddagger} = 27.5$ kcal/mol. On the basis of the above studies, we suggest that **29a**,**b** are formed via a concerted dithio-Claisen [3,3]-sigmatropic rearrangement[34,35] from **2** (estimated S−S bond energy 60 kcal/mol) followed by thioenolization and intramolecular addition of SH to CH═S (Scheme 13) similar to known cyclizations involving 1,4-diketones.[36] The absence of interconversion of isomers of **2** under the reaction conditions precludes a homolytic route to

(33) (a) Boelens, H.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 141. (b) Pyrolysis of **2** at 100−110 °C affords **30** as the major product.

(34) Campbell, M. M.; Evgenios, D. M. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2866.

(35) Larsson, F. C. V.; Brandsma, L.; Lawesson, S.-O. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 258.

(36) March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley & Sons: New York, 1985; p 791.

29a,**b**. Pyrolysis of bis(2-methyl-1-propenyl) disulfide, which is unable to undergo thioenolization after dithio-Claisen rearrangement, led to a complex mixture with no major product. Attempted intramolecular addition of the SH group of **29a**,**b** to the double bond under either free radical-catalyzed (UV irradiation; thermolysis in the presence of AIBN) or acid-catalyzed conditions were unsuccessful, leading instead to formation of thiophene **30**. We believe that thiophene **30**, one of the significant contributors to the aroma of garlic, leek,[37a] and cooked or fried onions,[37] is formed in these plants from **29a**,**b** by loss of H_2S. These previously unknown compounds may play an important role in the characteristic odor and flavor of onions and other alliaceous plants. We have used compounds **29a**,**b** as starting materials for the synthesis of 2-(alkyldithio)-3,4-dimethylthiophenes,[38a] postulated to occur in distilled oils of scallions (*Allium fistulosum* L. var. Caespitosum) and Welsh onions (*Allium fistulosum* L. var. Maichuon).[38b,c]

Experimental Section

(*E*)-1-Propenyl Propyl Sulfide ((*E*)-10).[10b] Propyl 1-propynyl sulfide (**8**; 57 g, 0.5 mol), prepared by refluxing propyl 2-propynyl sulfide (**9**) in NaOMe/MeOH for 36 h, was added all at once to a stirred suspension of $LiAlH_4$ (19 g, 0.5 mol) in THF (500 mL) at 0 °C. The gray suspension was heated at reflux for 18 h, cooled to 25 °C, and quenched by slow addition to a vigorously stirred mixture of 2 N NaOH (500 mL) and pentane (1 L) at 0 °C. The aqueous layer was extracted with pentane (4 × 250 mL), and the combined extracts were dried, concentrated, and distilled to yield 47 g (81%) of (*E*)-**10**: bp 58 °C, 18 mmHg (lit.[10b] bp 34.5 °C, 15 mmHg); ^{1}H NMR δ 5.91 (dq, J = 15.5, 2 Hz, 1H), 5.64 (dq, J = 15.5, 7 Hz, 1 H), 2.60 (t, J = 8 Hz, 2 H), 1.73 (dd, J = 7, 2 Hz, 3 H), 1.66 (sextet, J = 8 Hz, 2 H), 0.98 (t, J = 8 Hz, 3 H); ^{13}C NMR δ 125.59, 123.72, 34.89, 22.88, 18.49, 13.34; IR (ν_{max}) 3015 (m), 2962 (s), 2873 (s), 1623 (m), 1448 (m), 1377 (m), 1335 (m), 1290 (m), 1235 (m), 936 (s), 783 (m) cm^{-1}; EI-MS *m/z* (rel intens) 116 (M$^+$, 39), 87 (22), 74 (100), 73 (25), 71 (13), 59 (20). The *E*/*Z* ratio was 49:1 as determined by GC.

(*Z*)-1-Propenyl Propyl Sulfide ((*Z*)-10).[10b] To a solution of **8** (22.8 g, 0.2 mol) in pentane (200 mL) at −4 °C under argon was slowly added DIBAL (1 M in 350 mL of CH_2Cl_2, 0.35 mol) via cannula during 1 h. The solution was stirred at 25 °C for 22 h when GC analysis indicated completion of the reaction. The mixture was then added slowly to ice cold NaOH (1 L, 3 M) with vigorous stirring. After extraction with ether, drying, and concentration, (*Z*)-**10** (17.5 g, 75%, *cis*:*trans* > 99:1), a clear colorless oil, was obtained by distillation (bp 55 °C at 18 mmHg): ^{1}H NMR δ 5.89 (dq, J = 9, 2 Hz, 1 H), 5.70 (dq, J = 9, 7 Hz, 1 H), 2.62 (t, J = 7 Hz, 2 H), 1.68 (dd, J = 7, 2 Hz, 3 H), 1.62 (sextet, J = 7 Hz, 2 H), 0.97 (t, J = 7 Hz); ^{13}C NMR δ 125.94, 123.44, 35.71, 23.57, 14.41, 13.10; IR (ν_{max}) 3020 (m), 2962 (s), 2932 (m), 2873 (m), 1613 (m), 1456 (m), 1379 (m), 1334 (s), 1292 (m), 1240 (m), 935 (m), 755 (m), 662 (s) cm^{-1}; EI-MS *m/z* (rel intens) 118 (M$^+$ + 2, 2), 116 (M$^+$, 45), 87 (25), 75 (8), 74 (100), 73 (28), 72 (8), 71 (12), 59 (20). GC analysis of the freshly prepared sample shows no *E*-isomer. At 0 °C (*Z*)-**10** undergoes slow isomerization and becomes a 1:1 *E*/*Z* mixture in about 6 weeks.

General Procedure for the Synthesis of Alkyl 1-Propenyl Disulfides (3). In a 1 L 3-necked round-bottom flask at −78 °C, NH_3 (200 mL) was condensed. Small pieces of Li metal (1.4 g, 0.2 mol) were added. After all the Li had dissolved, THF (50 mL) was added to the blue solution followed by dropwise addition of a solution of **10** in THF (11.6 g, 0.1 mol in 50 mL). When the addition was complete, more **10** was added dropwise to discharge the blue color. The pale yellow solution was warmed to −30 °C, and NH_3 was evaporated under reduced pressure. The milky white residue was diluted with THF (50 mL), and a solution of the corresponding thiosulfonate (0.2 mol) in THF (50 mL) was added rapidly. After the addition was complete the mixture was allowed to warm slowly to 25 °C. The mixture was poured into cold saturated aqueous NH_4Cl and hexanes, and the aqueous layer was separated and extracted with hexanes. Organic layers were combined, dried, and concentrated, yielding the crude disulfide which was purified by distillation under reduced pressure or by preparative reversed phase HPLC.

Methyl (*E*)-1-Propenyl Disulfide ((*E*)-3a).[39] The above procedure was followed using $MeSO_2SMe$ (**12a**; 25.2 g, 0.2 mol). Bulb-to-bulb distillation at 55 °C, 17 mmHg, yielded 7.57 g (63%) of pure disulfide: ^{1}H NMR δ 6.10−5.90 (m, 2 H), 2.39 (s, 3 H), 1.79 (d, J = 6.6 Hz, 3 H); ^{13}C NMR δ 130.05, 124.30, 21.98, 17.94; IR (ν_{max}) 3011 (m), 2912 (s), 2849 (m), 1431 (s), 1376 (m), 1306 (m), 1232 (m), 935 (s) cm^{-1}; EI-MS *m/z* (rel intens) 122 (M$^+$ + 2, 5), 120 (M$^+$, 41), 87 (4), 80 (12), 75 (16), 73 (12), 72 (24), 71 (13), 47 (23), 45 (100).

Methyl (*Z*)-1-Propenyl Disulfide ((*Z*)-3a).[39] The above procedure was followed except that after the blue color faded solid NH_4Cl (8 g, 0.15 mol) was added followed by $MeSO_2SMe$ (**12a**; 7 g, 55.6 mmol), with half the indicated amounts of the other reagents. Distillation gave 3.2 g (53%) of a pale yellow oil: bp 69−70 °C, 30 mmHg; ^{1}H NMR δ 6.13 (dq, J = 8, 2 Hz, 1 H), 5.77 (dq, J = 8, 7 Hz, 1 H), 2.43 (s, 3 H), 1.76 (dd, J = 7, 2 Hz, 3 H); ^{13}C NMR δ 128.87, 128.00, 23.03, 14.33; IR (ν_{max}) 2973 (m), 2913 (s), 2850 (m), 1611 (m), 1430 (m), 1378 (m), 1326 (s), 1306 (m), 1140 (m), 1068 (m), 953 (m), 931 (m), 754 (m) cm^{-1}; EI-MS *m/z* (rel intens) 122 (M$^+$ + 2, 10), 120 (M$^+$, 100), 105 (5), 87 (10), 80 (25), 75 (37), 74 (21), 73 (27), 72 (56).

(*E*,*E*)-Bis(1-propenyl) Disulfide ((*E*,*E*)-2). A solution of (*E*)-**10** (4.64 g, 40 mmol) in 30 mL of ether was added slowly to a blue solution of Li (0.56 g, 80 mmol) in 40 mL of NH_3 at −78 °C under Ar. A white suspension was obtained. Excess NH_3 was removed below −60 °C under a 0.2 mmHg vacuum using a liquid N_2 trap. More ether (40 mL) was added at −78 °C, MsCl (9.1 g, 80 mmol, 2 equiv) in ether (40 mL) was added at −78 °C, and the mixture was stirred at 5 °C during 1 h and then quenched with water and extracted with pentane. The organic layer was washed with $NaHCO_3$, dried, and concentrated to give (*E*,*E*)-**2** (2.4 g, 82%): ^{1}H NMR δ 5.85−6.10 (AB d, J = 15.5, 6.6 Hz, 4 H), 1.78 (dd, J = 6.7, 1.2 Hz, 6 H); ^{13}C NMR δ 130.49, 124.47, 18.06; GC−MS (EI) *m/z* 148 (M$^+$ + 2, 1), 146 (M$^+$, 14), 113 (7), 73 (18), 71 (15), 45 (100). Spectroscopic data for (*E*,*E*)-**2** agree well with published values.[10,39]

(*Z*,*Z*)-Bis(1-propenyl) Disulfide ((*Z*,*Z*)-2).[39] As in the synthesis of (*E*,*E*)-**2**, (*Z*)-**10** (4.87 g, 0.042 mol) in dry Et_2O (30 mL) was added to Li (0.58 g, 0.084 mol) dissolved in liquid NH_3. After the addition, NH_3 was removed at 0.025 mmHg (at −70 °C) from the now white suspension. Ether (40 mL) was added followed by a solution of MsCl (7.0 mL, 10.4 g, 0.091 mol) in ether (30 mL). The mixture was stirred for 10 min at the same temperature. After quenching with water (10 mL), the mixture was rapidly warmed to 25 °C and diluted with pentane (100 mL). Layers were separated, and the aqueous layer was extracted with pentane (100 mL). Combined organic layers were dried ($MgSO_4$), filtered, and concentrated, and the residue was immediately purified by flash column chromatography (silica gel, hexanes) to yield 1.88 g (61%) of a yellow oil: ^{1}H NMR δ 6.12 (qd, J = 9.3, 1.6 Hz, 2 H), 5.76 (qd, J = 9.6, 6.8 Hz, 2 H), 1.77 (dd, J = 6.8, 1.6 Hz, 6 H); ^{13}C δ 128.72, 128.06, 14.35; GC−MS (EI) same as that for (*E*,*E*)-**3**.

(*E*)-1-Propenyl Thiobenzoate. (*E*)-1-Bromopropene[40] (10 mmol, 1.2 g, 856 μL) in the Trapp mixture (42 mL of THF/ether/pentane, 4:1:1) was treated with 2 equiv of *t*-BuLi (1.7 M in pentane) at −110 °C for 1 h. Styrene sulfide[41] (2.04 g, 15 mmol) in THF (10 mL) was added at −78 °C, and the mixture was stirred at that temperature for 2.5 h. Benzoyl chloride (15 mmol) was added by a syringe, and the mixture was stirred for 1 h at −78 °C. After extraction with ether and washing with aqueous $NaHCO_3$, the title compound (1.24 g, 70% yield)

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was isolated by chromatography on silica gel (CH_2Cl_2/hexane, 1:9) as a colorless, low melting solid: ^{1}H NMR δ 7.95 (m, 2 H), 7.57 (m, 1 H), 7.46 (m, 2 H), 6.62 (dq, J = 15.6, 2 Hz, 1 H), 6.03 (dq, J = 15.6, 6.6 Hz, 1 H), 1.91 (dd, J = 6.6, 2 Hz, 3 H); ^{13}C NMR δ 189.90, 136.66, 133.44, 132.03, 128.59, 127.11, 116.70, 18.88; GC−MS (EI) *m/z* 178 (M^+, 4.1), 105 (100), 77 (69.4), 51 (34.2). Hydrolysis conditions to prepare (*E*)-MeCH═CHSK are as follows: (*E*)-1-propenyl thiobenzoate (160 mg, 0.9 mmol) was added at −60 °C to a suspension of K_2CO_3 (350 mg, 2.5 mmol) in 15 mL of dry MeOH, prepared by stirring at 20 °C for 4 h. The mixture was warmed to 0 °C during 2 h.

(*E*)-1-Propenyl (*Z*)-1-Propenyl Disulfide ((*E*,*Z*)-2). A solution of K_2CO_3 (350 mg, 2.5 mmol) in dry MeOH (15 mL) was stirred at 25 °C for 0.5 h. (*E*)-1-Propenyl thiobenzoate (160 mg, 0.9 mmol) was added to the resultant suspension at −60 °C. The mixture was allowed to warm to 0 °C during 2 h. Analysis by TLC showed complete disappearance of starting material (5% EtOAc in hexanes). The reaction was cooled to −78 °C, and (*Z*)-1-propenyl methanesulfonothioate ((*Z*)-**5**; 155 mg, 1.02 mmol) in THF (2 mL) was added via syringe. The reaction mixture was warmed to −50 °C during 30 min and quenched with aqueous NH_4Cl. Extraction with pentane afforded the crude product which was purified by column chromatography (silica gel, hexanes) to give (*E*,*Z*)-**2** as a pale yellow liquid (79 mg, 60%; purity >90% by GC): ^{1}H NMR ($CDCl_3$) δ 5.95−6.15 (m, 3 H), 5.77 (m, 1 H), 1.71 (dd, J = 6.4, 1.1 Hz, 3 H), 1.70 (dd, J = 6.9, 1.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 130.7, 128.5, 124.8, 127.9, 18.1, 14.4; GC−MS (EI) same as that for (*Z*,*Z*)-**3**.

Oxidation of Alkyl 1-Propenyl Disulfides 3 and Thiosulfinates 4/5. NMR Experiments. Crude disulfide was purified by preparative HPLC (C-18, 4:1 MeOH/water). To a solution of the disulfide (or thiosulfinate) containing 5 μL of an internal standard, usually dioxane (0.0586 mmol) or anisole (0.0461 mmol), in $CDCl_3$ at −60 °C was added a solution of *m*-CPBA also at −60 °C. After stirring for 5 min, a portion of the reaction mixture was transferred into an NMR tube at −60 °C using a cooled pipet. The tube was introduced into the probe at −52 °C. Analysis at various temperatures was obtained by gradually warming the probe.

Monooxidation of Methyl (*E*)-1-Propenyl Disulfide ((*E*)-3a). Methanesulfinothioic Acid (*E*,*Z*)-*S*-1-Propenyl Ester (4a) and (*E*)-1-Propenesulfinothioic Acid *S*-Methyl Ester (5a). A solution of disulfide (*E*)-**3a** (330 mg, 2.75 mmol) in CH_2Cl_2 (20 mL) containing anisole (0.184 mmol) as internal NMR standard was cooled to −78 °C and treated with a cold solution of *m*-CPBA (475 mg, 2.75 mmol) in CH_2Cl_2 (5 mL). The reaction was stirred at −78 °C for 30 min and then warmed to −10 °C during 1 h. Solid anhydrous K_2CO_3 was added, and the reaction mixture was filtered. NMR analysis at temperatures ≤0 °C indicated a 3:1 (*E*)-**4a**/(*E*)-**5a** mixture and an 82% combined yield of thiosulfinates. Concentration and purification by PCTLC using 1:4 ethyl acetate/hexanes as eluent yielded 98 mg (26%) of (*E*)-**5a** and 201 mg (54%) of (*E*)- and (*Z*)-**4a**[3a] (1.6:1 *E*/*Z*) with the following spectral data: (*E*)-**4a**[3a] (major): ^{1}H NMR δ 6.32−6.47 (m, 2 H), 2.98 (s, 3 H), 1.92 (dd, J = 6, 1 Hz, 3 H); ^{13}C NMR δ 137.30 (S*C*H═), 116.84 (Me*C*H═), 42.14 (*C*H_3S(O)), 15.16 (*C*H_3CH═); UV (hexanes) λ (log ϵ_{max}) 220 (4.12), 264 (3.69). (*E*)-**5a** (minor): ^{1}H NMR δ 6.30−6.62 (m, 2 H), 2.60 (s, 3 H), 1.98 (dd, J = 6, 1 Hz, 3 H); ^{13}C NMR 135.78, 132.94, 17.32, 13.76; IR (neat, ν_{max}) 2970 (m), 2920 (m), 1627 (m), 1438 (m), 1329 (m), 1309 (m), 1290 (m), 1129 (m), 1095 (s), 1074 (s), 949 (m) cm^{-1}; UV (hexanes) λ (log ϵ_{max}) 208 (4.10), 266 (3.67); CI-MS (CH_4) *m/z* (rel intens) 139 (M^+H + 2, 18), 137 (M^+H, 100), 120 (53), 113 (21), 105 (27), 88 (50). (*Z*)-**4a**[3a] (minor): ^{1}H NMR δ 6.32−6.47 (m, 2 H), 3.04 (s, 3 H), 1.86 (dd, J = 6, 1.5 Hz, 3 H); ^{13}C NMR δ 144.08 (S*C*H═), 115.71 (Me*C*H═), 42.66 (*C*H_3S(O)), 18.91 (*C*H_3CH═); UV (hexanes) λ (log ϵ_{max}) 216 (4.17), 266 (3.68). **4a**: IR (neat, ν_{max}) 3003 (m), 2912 (m), 1440 (m), 1416 (m), 1332 (m), 1087 (s), 944 (m), 673 (m) cm^{-1}; EI-MS *m/z* (rel intens) 138 (M^+ + 2, 2), 136 (M^+, 15), 73 (100), 45 (95); CI-MS (CH_4) *m/z* (rel intens) 139 (M^+H + 2, 15), 137 (M^+H, 100), 120 (22), 113 (25), 105 (7); HRMS calcd for $C_4H_8OS_2$, 136.0017, found 136.0047.

Monooxidation of Methyl (*Z*)-1-Propenyl Disulfide ((*Z*)-3a). Methanesulfinothioic Acid (*E*,*Z*)-*S*-1-Propenyl Ester (4a) and (*Z*)-1-Propenesulfinothioic Acid *S*-Methyl Ester (5a). A stirred solution of disulfide (*Z*)-**3a** (360 mg, 3 mmol) in CH_2Cl_2 (10 mL) was cooled to −60 °C and treated with a cold solution of *m*-CPBA (570 mg, 3.3 mmol) in CH_2Cl_2 (5 mL). The reaction was warmed to room temperature during 2 h. Solid anhydrous K_2CO_3 was added, and the reaction mixture was filtered through Celite and rapidly concentrated in vacuo without warming. Analysis of the crude concentrate by ^{1}H NMR showed a 6:1 (*Z*)-**4a**/(*Z*)-**5a** mixture as indicated by δ 6.32−6.47 (m, 2H), 3.04 (s, 3H), 1.86 (dd, J = 6, 1.5 Hz, 3H) ((*Z*)-**4a**, major) and δ 6.52−6.20 (m), 2.69 (s), 1.97 (dd). Concentration and purification by PCTLC using 1:9 EtOAc/hexanes as eluent yielded 256 mg (63%) of (*E*)- and (*Z*)-**4a**[3a] (1.6:1 *E*/*Z*) with spectroscopic properties identical to those of the mixture obtained from oxidation of (*E*)-**3a**. Compound (*Z*)-**5a**, estimated by NMR to be originally present in ca. 10% yield, could not be isolated following chromatography in this reaction or in repetitions of this reaction on twice the scale.

Low-Temperature Monooxidation of Isomers of 2 (NMR Study). A solution of **2** in $CDCl_3$ (1 mL) cooled to −60 °C containing anhydrous Na_2CO_3 (1 equiv) was treated with a solution of *m*-CPBA in $CDCl_3$ (1 equiv in 0.5 mL), also cooled to −60 °C. After 5 min the reaction mixture was transferred to an NMR tube cooled to −60 °C using a cold pipet. The NMR probe was cooled to the required temperature, and then the sample was introduced for analysis. Spectra were recorded at −30 to −40 °C; the progress of each oxidation was followed with time. Oxidation of (*E*,*E*)-**2** gives a product with ^{1}H NMR δ 6.65−6.30 (m, 4 H), 1.99 (d, J = 6.3 Hz, 3 H), 1.91 (d, J = 5 Hz, 3 H) and ^{13}C NMR δ 145.37, 136.37, 130.67, 115.61, 19.45, 17.91. Oxidation of (*Z*,*Z*)-**2** gives a product with ^{1}H NMR δ 6.6−6.0 (m, 4 H), 1.96 (d, J = 6.3 Hz, 3 H), 1.86 (d, J = 6.3 Hz, 3 H). Oxidation of (*E*,*Z*)-**2** gives a mixture of two products (minor product indicated by asterisk) with ^{1}H NMR δ 6.65−6.20 (m, 4 H), 2.10 (d, J = 5 Hz), 1.97* (d, J = 7 Hz), 1.92* (d, J = 5 Hz), 1.84 (d, J = 7 Hz) and ^{13}C NMR δ 145.65, 137.52*, 136.44*, 134.96, 131.16, 117.01, 115.42*, 19.48, 17.90*, 15.75*, 15.42. The relative rate of oxidation is (*E*,*E*)-**2** > (*E*,*Z*)-**2** > (*Z*,*Z*)-**2**. The above data are consistent with products being (*E*,*E*)-**13** from (*E*,*E*)-**2**, (*Z*,*Z*)-**13** from (*Z*,*Z*)-**2**, and a 3:1 (*E*,*Z*)-**13**/(*Z*,*E*)-**13** mixture from (*E*,*Z*)-**2** (see Scheme 2 for structures; composition based on integration of the methyl doublets).

Room Temperature Oxidation of (*Z*,*Z*)-2. (±)-(1α,2α,3*β*,4α,5*β*)- and (1α,2α,3α,4α,5*β*)-2,3-Dimethyl-5,6-dithiabicyclo[2.1.1]hexane 5-Oxide (1a and 1b). A solution of (*Z*,*Z*)-**2** (1.2 g, 8.2 mmol) in MeOH (13 mL) was added to a MeOH/water (2:1; 216 mL) solution of $NaIO_4$ (6.4 g, 30 mmol) at 25 °C. After 5 h, the yellow reaction mixture was filtered through Celite which was then washed well with MeOH. The yellow filtrate was concentrated on a rotary evaporator (bath temperature 36 °C). The remaining aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated until about 1 mL of solution remained. This was *immediately* purified by flash column chromatography (20% EtOAc/hexanes), yielding **1a**[3] as a colorless oil (350 mg, 26%) which solidifies when cooled. Fractions containing **1b**[3] were also obtained (1.2%, NMR yield).

Rearrangement of Thiosulfinates 13. Upon warming to −15 °C in the NMR probe, (*E*,*E*)-**13**, (*E*,*Z*)-**13**/(*Z*,*E*)-**13**, and (*Z*,*Z*)-**13** rearranged with half-lifes of ca. 15, 30, and 40 min, respectively. Rate constants for disappearance of (*Z*,*Z*)-**13**, monitored by integrating the methyl group ^{1}H NMR signals, were determined at −25, −15, −9, and 0 °C as 0.4 × 10^{-4}, 3.0 × 10^{-4}, 4.3 × 10^{-4}, and 12.2 × 10^{-4} s^{-1}, respectively. A plot of ln k vs 1/T gave activation parameters at 273 K: E_a = 16 kcal/mol, $\Delta H^{\ddagger}$ = 15.5 kcal/mol, $\Delta S^{\ddagger}$ = −15.3 cal/mol K, and $\Delta G^{\ddagger}$ = 19.5 kcal/mol.

For analytical purposes, a solution of mixed isomers of **2** in CH_2Cl_2 was treated at −40 °C with dry Na_2CO_3 (1 equiv) and peracetic acid (35% in HOAc, 1 equiv) and the solution was warmed to room temperature during 2.5 h and rapidly worked up as above. Analysis by ^{1}H NMR spectroscopy showed peaks in the δ 4.0−5.0 ppm region at 4.12 (s), 4.21/4.25 (dd), 4.56 (s), 4.58 (s), 4.83 (d), and 4.90 (d). If it is assumed that the 4.12 and 4.21/4.25 peaks correspond to two protons each and the remaining peaks in this region to a single proton, from the integrated areas the relative amounts of the $C_6H_{10}S_2O$ isomers is as follows: **1a**, 10; **1b**, 6; **14a**, 10; **14b**, 2; **14c**, 11; **14d**, 1.

For preparative purposes, solutions of individual isomers of **2** (75 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) were treated with stirring at −40 °C with anhydrous Na_2CO_3 (1 equiv) followed by peracetic acid (35% in HOAc, 1 equiv) for 3 h and then warmed to 0 °C. The product was

poured into cold, saturated $NaHCO_3$ solution, and the organic layer was separated and extracted with an equal volume of CH_2Cl_2. The combined organic layers were dried and concentrated in vacuo and dissolved in $CDCl_3$ for analysis by NMR. The major product from oxidation of (*E*,*E*)-**2**, **14a**, showed the following: ^{1}H NMR δ 5.90 (s, 1 H), 4.84 (d, J = 3 Hz, 1 H), 2.01 (m, 1 H), 1.75 (m, 1 H), 1.24 (d, J = 7 Hz, 3 H), 1.01 (d, J = 7 Hz) and small peaks at δ 4.60 (s) and 0.97 (d), attributed to isomer **14b**; ^{13}C NMR δ 100.64, 82.43, 47.59, 42.96, 18.97, 15.09; IR (neat, ν_{max}) 2960 (m), 2917 (m), 1146 (m), 917 (m) cm^{-1}. The **14a**/**14b** ratio was 4:1 from NMR analysis; an identical **14a**/**14b** ratio was obtained by substituting *m*-CPBA for peracetic acid. Oxidation of (*Z*,*Z*)-**2** under the above conditions gave a mixture of **1a** (major product), as indicated by the 4.21/4.25 doublet of doublets, among other characteristic peaks,[3] along with the above peaks for **14a** (lesser product) and **14b** (trace) in a **1a**/**14a**/**14b** ratio of 25:3.3:1. Oxidation of (*E*,*Z*)-**2** under the above conditions gave a mixture of **1b**, as indicated by the δ 4.12 singlet among other characteristic peaks,[3] along with a compound identified as **14c**: ^{1}H NMR δ 5.88 (s, 1 H), 4.56 (d, 1 H), 2.24 (m, 2 H), 2.08 (m, 2 H), 1.10 (d, J = 7 Hz, 3 H), 0.89 (d, J = 7 Hz) and a small peak at 4.91 (d) attributed to **14d**; ^{13}C NMR δ 99.81, 82.94, 43.34, 31.32, 14.60, 13.73. The **1b**/**14c**/**14d** ratio was 10:12:1 from NMR analysis. Compounds **14a**−**d** defied all efforts at chromatographic purification (silica gel, C-18 silica gel, alumina, Florisil, polyacrylamide gel).

Methanesulfonothioic Acid (*Z*)-*S*-1-Propenyl Ester ((*Z*)-12a). In a 250 mL three-necked round-bottomed flask with a dry ice condenser and argon bubbler, NH_3 (50 mL) was condensed at −78 °C. Lithium (0.14 g, 20 mmol) was added in small portions, giving a blue solution. After 10 min, (*Z*)-**10** (1.14g, 10 mmol) in 30 mL of freshly distilled THF was added slowly via an addition funnel. The blue color disappeared immediately, and NH_3 was removed at −40 °C under vacuum (1 mmHg) using a liquid N_2 trap during 2 h. More THF (100 mL) was added via syringe. The reaction mixture was transferred into a dry ice cooled jacketed addition funnel, and added dropwise, during a period of 30 min, to a solution of MsCl (23 g, 0.2 mol) in THF (50 mL) with vigorous stirring. After completion of addition, the solution was stirred for 5 min at −78 °C, then quenched with water (100 mL), warmed to 0 °C, extracted with ether, and washed with $NaHCO_3$ (3 × 100 mL) and water and the organic layer dried and concentrated. Excess **2** and MsCl were removed under vacuum using a Vigreaux column (30 °C, 0.2mmHg), and the residue was chromatographed on silica gel (CH_2Cl_2/hexanes, 2:3) to give (*Z*)-**15a** (510 mg, 34%): ^{1}H NMR δ 6.33 (m, 2 H), 3.23 (s, 3 H), 1.87 (d, J = 5.1 Hz, 3 H); ^{13}C NMR δ 139.36 (CH), 116.87 (CH), 48.57 (CH_3), 15.14 (CH_3); IR (ν_{max}) 2968 (m), 1314 (s), 1131 (s) cm^{-1}; UV (hexanes) λ_{max} 258, 210 nm; GC−MS (EI) *m/z* (rel intens) 152 (M^+, 6), 73 (24), 72 (26), 45 (100).

Methanesulfonothioic Acid (*E*)-*S*-1-Propenyl Ester ((*E*)-12a). Using (*E*)-**10** as in the procedure for the synthesis of (*Z*)-**12a**, (*E*)-**12a** was obtained in 22% yield: ^{1}H NMR δ 6.38 (m, 2 H), 3.26 (s, 3 H), 1.94 (d, J = 4.8 Hz, 3 H); ^{13}C NMR δ 145.09, 116.59, 47.87, 19.02; CI-MS (EI) *m/z* same as that for the *Z*-isomer; HRMS calcd for $C_4H_8O_2S_2$ 151.9966, found 151.9958.

Methanesulfonothioic Acid (*E*,*Z*)-*S*-1-Propenyl Ester ((*E*,*Z*)-12a). To a solution of (*E*,*Z*)-**4a** (443 mg, 3.26 mmol) in 7:4 HOAc/water (11 mL) and THF (3 mL) was added $NaIO_4$ (1.05 g, 4.9 mmol). The mixture was stirred at 25 °C for 12 h whereupon the brown solution was poured into a 1:1 water/CH_2Cl_2 mixture (100 mL). Solid Na_2CO_3 was added to the stirred mixture until the evolution of CO_2 ceased. The pink organic layer was separated, and the aqueous layer was extracted once with CH_2Cl_2 (25 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ followed by 10% aqueous sodium thiosulfate solution, dried, concentrated, and purified by PCTLC to yield (*E*,*Z*)-**12a** as a yellow oil (332 mg, 67%).

(*E*)-1-Propenesulfonothioic Acid *S*-Methyl Ester ((*E*)-6a, "Allygrin"). To a solution of (*E*)-**4a** (77 mg, 0.57 mmol) in a minimum amount of THF were added 5 mL of acetic acid and 3 mL of water followed by sodium periodate (320 g, 1.5 mmol), and the reaction mixture was stirred for 12h. The brownish solution was poured into 50 mL of a 1:1 water/CH_2Cl_2 mixture, and solid Na_2CO_3 was added to the stirred mixture until the evolution of CO_2 ceased. The pink organic layer was separated, and the aqueous layer was extracted once with 25 mL of CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$ followed by 10% aqueous sodium thiosulfate solution, dried, concentrated, and purified by PCTLC, giving (*E*)-**6a** (49 mg, 57%), a yellow oil: ^{1}H NMR δ 6.87 (dq, J = 15, 7 Hz, 1 H), 6.47 (dq, J = 15, 1.5 Hz, 1 H), 2.57 (s, 3 H), 2.00 (dd, J = 7, 1.5 Hz, 1 H); ^{13}C NMR 142.9, 133.4, 29.8, 17.0; IR (ν_{max}) 2925 (m), 1634 (m), 1438 (m), 1329 (s), 1290 (m), 1127 (s), 945 (m) cm^{-1}; CI-MS *m/z* (rel intens) 155 (M^+ + H + 2, 3), 153 (M^+ + H, 13), 105 (25), 89 (40), 73 (100). Spectroscopic data for synthetic and natural[6c] (*E*)-**16a** are in good agreement.

(*Z*)-2-(Methylsulfinyl)propanethial *S*-Oxides (25a). To a stirred solution of (*E*,*Z*)-**4a** in CH_2Cl_2 (77 mg, 0.57 mmol, 3 mL) at −50 °C was added a solution of *m*-CPBA (108 mg, 0.63 mmol) in CH_2Cl_2 (3 mL) also cooled to −50 °C. The reaction mixture was allowed to warm to −20 °C over 2 h, filtered through anhydrous K_2CO_3, and concentrated. Rapid chromatography through silica gel using 1:20 acetone/CH_2Cl_2 as eluent yielded 27 mg (31%) of a 1:1 mixture of the two diastereoisomers, which could be further separated by TLC (ethyl acetate/hexanes). The yield of sulfinylsulfines as determined by NMR is 63%. Isomer A: ^{1}H NMR δ 8.27 (d, J = 8 Hz, 1 H), 5.87 (m, 1 H), 2.68 (s, 3 H), 1.60 (d, J = 7 Hz, 3 H); ^{1}H NMR (C_6D_6) δ 7.19 (d, J = 7.8 Hz, 1 H), 5.63 (m, 1 H), 1.98 (s, 3 H), 1.07 (d, J = 6.2 Hz, 3 H); ^{13}C NMR δ 174.92, 67.80, 44.55, 20.98. Isomer B: ^{1}H NMR δ 8.44 (d, J = 8 Hz, 1 H), 5.87 (m, 1 H), 2.69 (s, 3 H), 1.57 (d, J = 7 Hz, 3 H); ^{1}H NMR (C_6D_6) δ 7.62 (d, J = 7.8 Hz, 1 H), 5.63 (m, 1 H), 1.94 (s, 3 H), 1.03 (d, J = 6.2 Hz, 3 H); ^{13}C NMR δ 175.92, 68.51, 44.62, 20.65. Both isomers, IR (ν_{max}) 1135 (s) cm^{-1}; CI-MS (CH_4) *m/z* (rel intens) 154 (M^+ + 2), 152 (M^+). Analysis by ^{1}H NMR spectroscopy of a sample of **25a** in $CDCl_3$ containing D_2O showed no evidence of deuterium incorporation. In an experiment in which an excess of *m*-CPBA was used, a product was formed having ^{1}H NMR δ 8.39 (d, J = 8.5 Hz, 1 H), 6.19 (dq, J = 6.2, 8.5 Hz, 1 H), 3.09 (s, 3 H), 1.65 (d, J = 6.2 Hz, 3 H). This product, thought to be (*Z*)-**25a**, decomposed on attempted chromatography.

Similar oxidation of (*E*)-**5a** gave the identical 1:1 **25a** mixture in 52% yield. Compound **25a** could also be prepared by *m*-CPBA oxidation of **3a** in CH_2Cl_2 (or less effectively, $CHCl_3$) at −20 °C for 1.5 h. In addition to the major product **25a**, traces of (*E*,*Z*)-**12a** and $MeSO_2SMe$ were detected. When the oxidation of **3a** was run in CH_2Cl_2 at 20 °C, the major products were (*E*,*Z*)-**12a** and $MeSO_2SMe$, with minor amounts of **25a** and **26**. When the oxidation of **3a** was run in ether at −20 °C for 75 min, the major product was (*E*,*Z*)-**12a**, with only trace amounts of **25a**.

Bisoxidation of (*E*,*E*)-Bis(1-propenyl) Disulfide (2) to (*Z*,*Z*)-*d*,*l*-26. Disulfide **2** (75 mg, 0.5 mmol) was dissolved in CH_2Cl_2 (2 mL) and cooled to −60 °C, and *m*-CPBA (200 mg, 1.16 mmol) in CH_2Cl_2 (2 mL), also cooled to −60 °C, was added dropwise. The reaction mixture was warmed to 0 °C over 2 h, and poured into cold saturated aqueous Na_2CO_3. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the organic layers were combined, dried (anhydrous K_2CO_3), concentrated, and analyzed by NMR. The resulting **26**, purified by rapid chromatography (silica gel, 1:20 acetone/CH_2Cl_2), was a colorless solid (decomposition point 48 °C); ^{1}H NMR ($CDCl_3$) δ 8.09 (d, J = 9.6 Hz, 2 H), 3.73 (m, 2 H), 1.24 (d, J = 6.5 Hz, 6 H); ^{1}H NMR (C_6D_6) δ 7.06 (d, J = 9.6 Hz, 2 H), 3.3 (m, 2 H), 0.60 (d, J = 6.3 Hz, 6 H); ^{13}C NMR δ 179.56, 36.11, 17.34; IR (neat) 1120 (s), 1103 (s), cm^{-1}; FD-MS indicated the parent ion at *m/z* 178; HRMS calcd for $C_6H_{10}S_2O_2$ 178.0122, found 178.0121. Under LC−APCI-MS conditions (C-18 column, MeCN/water) synthetic *d*,*l*-**26** showed *m/z* 179 (MH^+, 100%); under daughter ion analysis conditions fragment ions were seen at *m/z* 160, 112, 96, 80, 68, and 41, along with a *m/z* 178 parent ion.

(*Z*,*Z*)-*d*,*l*-2,3-Dimethyl-1,4-butanedithial 1,4-Dioxide (*d*,*l*-26) from Onion. Onion bulbs were peeled, homogenized at 25 °C, chilled to 4 °C, and at this temperature rapidly filtered through cheesecloth, extracted with CH_2Cl_2, centrifuged, dried ($MgSO_4$), and concentrated in vacuo. The concentrate was subjected to column chromatography (silica gel, 100:1 CH_2Cl_2/acetone), affording a mixture of **26** and **1a**. Although **26** is not readily separated from **1a**, from its NMR spectra, **26** can be characterized as an isomer of 2,3-dimethyl-1,4-butanedithial 1,4-dioxide.

***cis*- and *trans*-2-Mercapto-3,4-dimethyl-2,3-dihydrothiophene (29a,b).** A solution of mixed isomers of **2** in benzene (1% solution)

was kept at 85 °C for 1 h. Analysis of the reaction mixture by GC and GC−MS indicated disappearance of starting material and formation of two compounds isomeric with **2** (85%) along with ca. 20% of 3,4-dimethylthiophene (**30**; identified by its mass spectrum). Benzene was removed in vacuo, and $CDCl_3$ was added for NMR analysis. **29a**: ^{1}H NMR δ 5.77 (s, 1 H), 4.87 (dd, 1 H), 2.89 (dq, 1 H), 1.99 (d, J = 8.24 Hz, 1 H), 1.76 (s, 3 H), 1.17 (d, J = 6.67 Hz, 3 H); ^{13}C NMR δ 135.6, 117.5, 57.9, 49.6, 15.95, 12.25; GC−MS (EI) (retention time 11.1 min) *m/z* 148 (M + 2, 2%), 146 (M^+, 25%), 113 (100%), 111 (95%), 97 (78%), 79 (41%), 45 (96%). **29b**: ^{1}H NMR δ 5.65 (s, 1 H), 4.28 (dd, 1 H), 2.70 (dq, 1 H), 2.37 (d, J = 7.27 Hz, 1 H), 1.75 (s, 3 H), 1.10 (d, J = 6.78, 3 H); ^{13}C NMR δ 135.2, 115.4, 54.4, 53.8, 15.9, 12.3; GC−MS (retention time 9.5 min) *m/z* 148 (M + 2, 3%), 146 (M^+, 25%), 113 (100%), 111 (80%), 97 (66%), 79 (40%), 45 (93%). Pyrolysis of pure samples of (*E*,*E*)-**2**, (*E*,*Z*)-**2**, and (*Z*,*Z*)-**2** led to identical mixtures of **29a** and **29b**, with the order of reaction being (*E*,*Z*)-**2** > (*E*,*E*)-**2** > (*Z*,*Z*)-**2**. Pyrolysis of **2** at 100−110 °C affords **30** as the major product.

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Supporting Information Available: Text describing the general experimental conditions, HPLC isolation of isomers of **2**, synthesis of (*E*)- and (*Z*)-**3b**, (*E*)-**3c**, (*E*,*Z*)-**4b**,**c**, (*E*)-**5b**,**c**, **10**, **11**, (*Z*)-**12b**, (*Z*)-**25b**,**c**, and **31a**,**b**, bisoxidation of (*Z*,*Z*)- and (*E*,*Z*)-**2**, natural occurrence of **1a**,**b** and *d*,*l*-**26**, and ozonolysis of *d*,*l*-**26** (8 pages). This material is contained in many libraries on microfiche, immediately following this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering instructions and Internet access instructions.

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