Allium Chemistry: Synthesis of 1-[Alk(en)ylsulfinyl]propyl Alk(en)yl Disulfides (Cepaenes), Antithrombotic Flavorants from Homogenates of Onion (*Allium cepa*)

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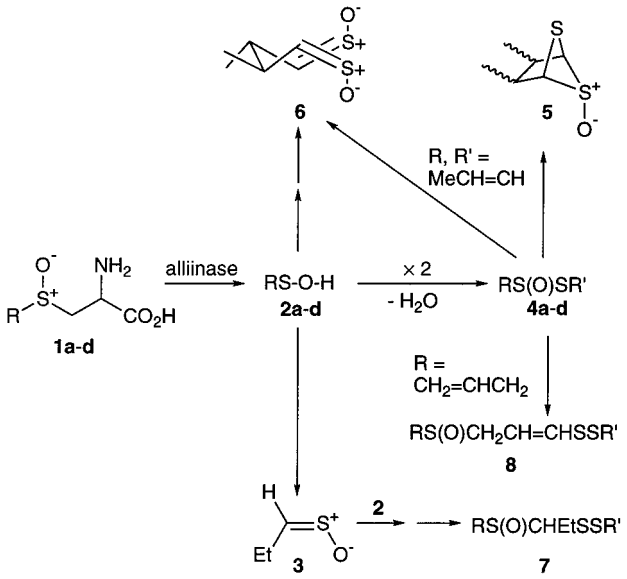
A series of 1-[alk(en)ylsulfinyl]propyl alk(en)yl disulfides (α-sulfinyl disulfides) of structure RS(O)-CHEtSSR′, R, R′ = Me, (*E*,*Z*)-MeCH=CH, *n*-Pr, and CH_2=$CHCH_2$, termed cepaenes, have been synthesized by a variety of routes including oxidation of 1-[alk(en)ylthio]propyl alk(en)yl disulfides, RSCHEtSSR′, termed deoxycepaenes. The cepaenes are identical to compounds isolated from homogenates of onion (*Allium cepa*) and to compounds identified in these homogenates by liquid chromatography/mass spectrometry, while the deoxycepaenes are identical to compounds found in *Allium* distilled oils and in other materials. The antithrombotic activities for several cepaenes are reported.

Keywords: *Allium chemistry; onion (Allium cepa); a-sulfinyl disulfides; cepaenes; antithrombotic compounds*

INTRODUCTION

Folk wisdom has it that raw onion (*Allium cepa*) relieves pain and inflammation, that cough syrups made from chopped onion alleviate symptoms of asthma and other respiratory ailments, and that regular ingestion of onion benefits the cardiovascular system (Block, 1985, 1992). Research on the composition of onion extracts, stimulated by these long-standing beliefs, has led to the discovery of a remarkable variety of organosulfur compounds, some of which possess antiasthmatic, anti-inflammatory, antiallergic, and antithrombotic activity, most likely associated with inhibition of cyclooxygenase (CO) and lipoxygenase (LO) enzymes (Bayer et al., 1988, 1989; Kawakishi and Morimitsu, 1988, 1994; Morimitsu and Kawakishi, 1990, 1991; Block and Bayer, 1990). When an onion is cut, alliinase enzymes act on *S*-alk(en)yl cysteine *S*-oxides **1a**−**d** (Scheme 1) giving sulfenic acids **2a**−**d**, which rearrange to onion lachrymatory factor **3** (LF; C_2H_5CH=S^+−O^-; from **2b**, CH_3CH=CH-SOH) or couple affording thiosulfinates **4**, zwiebelanes **5**, or bissulfine **6**, by processes described elsewhere (Block et al., 1996a−c). Notable among the natural products formed on cutting onion are "cepaenes", a class of structurally related α-sulfinyl disulfides, more precisely 1-[alk(en)ylsulfinyl]propyl alk(en)yl disulfides, RS(O)CHEtSSR′ (**7**), which are potent inhibitors of platelet aggregation and CO and LO enzymes (Kawakishi and Morimitsu, 1988, 1994; Morimitsu and Kawakishi, 1990, 1991; Morimitsu et al., 1992; Bayer et al., 1988, 1989a; Dorsch et al., 1990; Wagner et al., 1990). Cepaenes bear an interesting resemblance to ajoene, CH_2=$CHCH_2S(O)CH_2CH$=$CHSSCH_2CH$=CH_2, and homologs RS(O)CH_2CH=CHSSR′ (**8**), alk(en)yl 3-[alk(en)-ylsulfinyl]prop-1-enyl disulfide antithrombotic substances from extracts of garlic (*Allium sativum*) and wild garlic (ramson; *Allium ursinum*) (Block et al., 1986; Sendl and Wagner, 1991). Until recently (Block and Zhao, 1992), cepaenes have only been available for study in minute quantities through extraction of onion followed by repetitive chromatography.

Scheme 1



R, R': **a** Me; **b** MeCH=CH; **c** *n*-Pr; **d** CH_2=$CHCH_2$

The accompanying paper (Calvey et al., 1997) describes the use of reversed-phase liquid chromatography atmospheric pressure chemical ionization mass spectrometry (LC/APCI-MS) to identify **3**−**8** in CO_2 supercritical fluid extracts of crushed onion, garlic, and ramp (*Allium tricoccum*). Since these LC/MS studies indicate that compounds derived from all four precursor compounds **1a**−**d** are present *in each plant extract*, 16 individual cepaenes and their geometric isomers and diastereomers are possible (Scheme 2). Definitive LC/MS identification of individual components of complex mixtures, such as those from *Allium* extracts, requires retention time and fragmentation patterns of authentic standards. Therefore, to assist in the identification of cepaenes as well as make available samples for determination of antithrombotic activity, we sought stereospecific syntheses of representative cepaenes. We report our results herein.

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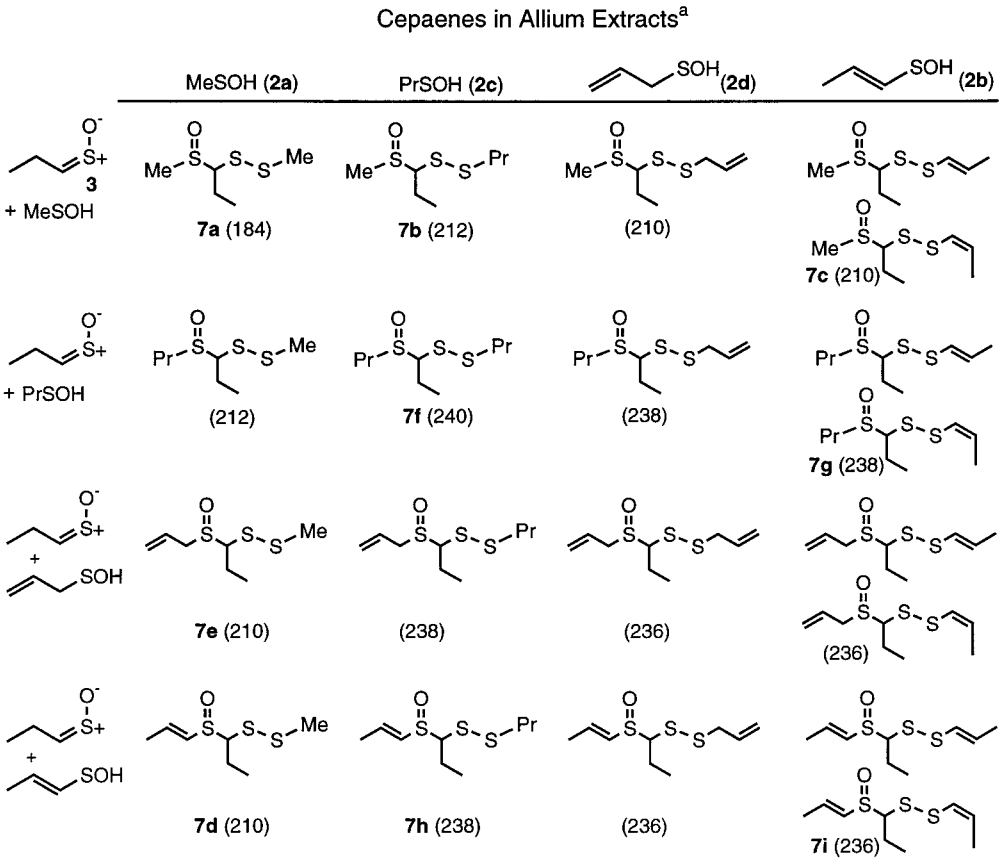
Scheme 2



[a] MW (in parenthesis) follows compound number; only cepaenes synthesized are numbered.

EXPERIMENTAL PROCEDURES

General experimental conditions for syntheses are given elsewhere (Block et al., 1996a).

Caution: Several of the following procedures involve highly odoriferous low molecular weight thiols and related compounds. All operations should be conducted in a well-ventilated hood. Glassware should be rinsed with bleach or alkaline $KMnO_4$ immediately after completion of work.

1-Chloropropanesulfenyl Chloride (14). Dipropyl disulfide (5 g, 33 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 °C under argon. With stirring, SO_2Cl_2 (15.7 g, 116 mmol) in CH_2Cl_2 (20 mL) was added slowly. The mixture was stirred at 0 °C (2 h), warmed to room temperature (3 h), and concentrated in vacuo to afford the known (Tjan et al., 1972) but incompletely characterized **14** as a yellow, pungent oil (9.6 g, 100% yield): ^{1}H NMR δ 5.24 (t, J = 6.9 Hz, 1 H), 2.15 (m, 2 H), 1.13 (t, J = 7.4 Hz, 3 H); ^{13}C NMR δ 71.84, 30.78, 11.27.

1-Chloropropyl Methyl Disulfide (15a). Methanethiol [0.73 g, 15 mmol; measured volumetrically (density 0.9 g/mL)] and then Et_3N (2.1 g, 21 mmol) were added at 0 °C to a solution of **14** (2.0 g, 14 mmol) in tetrahydrofuran (THF) (40 mL), and the mixture was stirred for 30 min at 0 °C and for 1 h at room temperature. The product was washed with 10% aqueous HCl solution (3 × 20 mL), the aqueous layer was extracted with ether (3 × 20 mL), and the combined organic layers were dried and concentrated in vacuo to give **15a**, a yellow oil with pungent odor (1.86 g, 86%): ^{1}H NMR δ 4.97 (t, J = 7.2 Hz, 1 H), 2.54 (s, 1 H), 2.08 (m, 2 H), 1.07 (t, J = 7.8 Hz, 3 H); ^{13}C NMR δ 74.31, 32.03, 24.16, 11.39.

Methyl 1-(Methylthio)propyl Disulfide (9a). *Method 1.* Sodium (0.40 g, 17 mmol) was carefully added to anhydrous MeOH (30 mL) in a 100 mL flask. Methanethiol (0.69 g, 14 mmol) was added all at once. A solution of **15a** (1.50 g, 9.58 mmol) in THF (5 mL) was added dropwise, and the solution was stirred for 16 h at room temperature. The solution was washed with 10% aqueous HCl solution (3 × 20 mL), the aqueous layer was extracted with ether (3 × 20 mL), and the combined organic layers were dried and concentrated in vacuo to give **9a**, a yellow oil (0.98 g, 61% yield): ^{1}H NMR δ 3.67 (dd, J = 8.0, 5.0 Hz, 1 H), 2.43 (s, 3 H), 2.15 (s, 3 H), 2.03 (m, 1 H), 1.83 (m, 1 H), 1.06 (t, J = 7.2 Hz, 3 H); ^{13}C NMR δ 61.14, 28.12, 24.29, 14.61, 11.79; EI-MS m/z (% abundance) 168 (M^+, 0.2), 89 (100), 79 (21), 74 (8), 73 (17), 64 (8), 61 (45).

Method 2. A solution of **15a** (1.0 g, 6.4 mmol) in CH_3CN (5 mL) was added dropwise to a well-stirred solution of AgOTs in CH_3CN (60 mL) under argon at −30 °C. After 30 min, a light yellow precipitate of AgCl appeared. Stirring was continued at this temperature for a total of 6 h, followed by stirring at −5 °C for 4 h. Methanethiol (0.31 g, 6.4 mmol) in CH_3CN (3 mL) was added. The mixture was stirred for 30 min, whereupon a black precipitate appeared. The reaction mixture was diluted with ether (50 mL), filtered, and washed with brine (3 × 30 mL), the aqueous layer was extracted with ether (3 × 20 mL), and the combined organic layers were dried and concentrated in vacuo to give **9a** (0.70 g, 65% yield).

Methyl 1-(Methylsulfinyl)propyl Disulfide (7a). A solution of **9a** (2.23 g, 13.3 mmol) in CH_2Cl_2 (60 mL) was cooled to −78 °C and treated with solid *m*-CPBA (2.70 g, 15.7 mmol) and catalytic anhydrous Na_2CO_3. The mixture was stirred for 1 h at −78 °C and for 6 h at 0 °C. The mixture was washed with cold saturated Na_2CO_3 (3 × 40 mL), the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL), and the combined organic layers were dried (K_2CO_3) and concentrated in vacuo. The crude product was purified by chromatography (CH_2Cl_2/acetone, 9:1) affording **7a**, a yellow liquid with a mild onion-like odor (0.91 g, yield 37%), which by NMR was a 2:1 mixture of diastereomers. Isomers could be separated by reversed-phase HPLC (21 mm RP column, 10 mL/min, 3:7 CH_3CN/H_2O). Major isomer: ^{1}H NMR δ 3.45 (dd, J = 11, 3.3 Hz, 1 H), 2.67 (s, 3 H), 2.40 (s, 3 H), 2.31 (m, 1 H), 1.84 (m, 1 H), 1.10 (t, J = 7.8 Hz, 3 H); ^{13}C NMR δ 75.13, 36.76, 24.86, 19.86, 11.04; HRMS (CI/CH_4) m/z calcd for $C_5H_{13}S_3O$ (MH^+) 185.0129,

found 185.0134. Minor isomer: ^{1}H NMR δ 3.60 (dd, J = 11, 3.3 Hz, 1 H), 2.49 (s, 3 H), 2.44 (s, 3 H), 2.25 (m, 1 H), 1.60 (m, 1 H), 1.15 (t, J = 7.3 Hz, 3 H); ^{13}C NMR δ 73.79, 32.59, 24.60, 18.45, 11.79; IR (ν_{max}) 1046 (vs) cm^{-1}.

1-Chloropropyl Propyl Disulfide (15b). The method for synthesis of **15a** was followed, using PrSH (1.47 g, 20 mmol), Et_3N (3 g, 30 mmol), and **14** (2.88 g, 20 mmol) in THF (50 mL), giving **15b**, a yellow, pungent smelling oil (3.02 g, 82%): ^{1}H NMR δ 4.96 (t, J = 7.2 Hz, 1 H), 2.72 (m, 2 H), 2.13 (m, 2 H), 1.72 (m, 2 H), 1.12 (t, J = 7.8 Hz, 3 H), 1.01 (t, J = 7.8 Hz, 3 H); ^{13}C NMR δ 74.34, 41.59, 32.05, 22.57, 13.09, 11.36.

1-(Methylthio)propyl Propyl Disulfide (9b). Method 2 for the synthesis of **9a** was followed, using a solution of **15b** (0.50 g, 2.70 mmol) in CH_3CN (5 mL), AgOTs (0.75 g, 2.7 mmol) in CH_3CN (30 mL), and then MeSH (0.13 g, 2.70 mmol) in CH_3-CN (3 mL), giving **9b**, a light brown oil (0.39 g, yield, 74%): ^{1}H NMR δ 3.65 (t, J = 6.8 Hz, 1 H), 2.74 (t, J = 8.1 Hz, 2 H), 2.51 (m, 2 H), 2.11 (s, 3 H), 1.81 (m, 2 H), 1.08 (t, J = 7.8 Hz, 3 H), 1.01 (t, J = 7.8 Hz, 3 H); ^{13}C NMR δ 56.35, 41.70, 33.87, 28.29, 22.61, 13.09, 12.25; EI-MS m/z 196 (M$^+$, 0.14%), 122 (12), 117 (3), 89 (71), 74 (16), 73 (14), 59 (9), 58 (8), 45 (64), 43 (32), 41 (100), 39 (32).

1-(Methylsulfinyl)propyl Propyl Disulfide (7b). Oxidation of **9b** (0.30 g, 1.5 mmol) with *m*-CPBA (0.34 g, 2.0 mmol) as described for **7a** gave, after chromatography, **7b** (0.098 g, 31%), a pale yellow oil with a mild onion-like odor: ^{1}H NMR δ 3.50 (dd, J = 11.1 Hz, 3.3 Hz, 1 H), 3.08 (m, 1 H), 2.70 (m, 2 H), 2.45 (s, 3 H), 1.90 (ddq, J = 14.8, 11.0, 7.3 Hz, 2 H), 1.71 (tq, J = 7.5, 7.1 Hz, 1 H), 1.14 (dd, J = 7.2, 6.8 Hz, 3 H), 1.10 (t, J = 7.8 Hz, 3 H); ^{13}C NMR δ 72.91, 52.51, 42.50, 20.03, 16.56, 13.39, 11.14; IR (ν_{max}) 2965 (m), 1455 (m), 1046 (s) cm^{-1} (S=O); HRMS (CI/CH_4) m/z calcd for $C_7H_{17}S_3O$ (MH$^+$) 213.0442, found 213.0454.

1-Chloropropyl (*E*)-1-Propenyl Disulfide [(*E*)-15c]. (*E*)-1-Propenyl propyl sulfide (1.5 g, 13 mmol) was slowly added to a stirred blue solution of lithium (0.16 g, 23 mmol) in liquid NH_3 (15 mL) at −78 °C under argon. Stirring was continued for 45 min, and then NH_3 was pumped away (0.2 mmHg and −50 °C) from the resulting white suspension during 5 h. Ether (30 mL) was added at −55 °C followed by **14** (2.0 g, 14 mmol). The mixture was stirred at −55 °C for 20 h and quenched with water (30 mL). The aqueous layer was extracted with ether (2 × 20 mL), and the combined organic layers were washed with NH_4Cl solution (2 × 30 mL) and brine (3 × 30 mL), dried, and concentrated in vacuo to give **15c** as a yellow oil (1.73 g, 73%): ^{1}H NMR δ 6.17 (d, J = 15 Hz, 1 H), 5.99 (m, 1 H), 4.92 (dd, J = 6, 9 Hz, 1 H), 2.1 (m, 2 H), 1.78 (d, J = 6.6 Hz, 3 H), 1.08 (t, J = 7.2 Hz, 3 H); ^{13}C NMR δ 131.70, 125.15, 72.80, 31.83, 18.19, 11.23; EI-MS m/z 184 (M$^+$, ^{37}Cl, 35%) 182 (M$^+$, ^{35}Cl, 85%), 147 (6%), 106 (100%); HRMS (EI) m/z calcd for $C_6H_{11}S_2Cl$ (M$^+$) 181.9991, found 181.9991; IR (ν_{max}) 2972 (s), 2935 (m), 1653 (m), 1459 (s), 1379 (m), 806 (m), 650 (s) cm^{-1}.

1-Chloropropyl (*Z*)-1-Propenyl Disulfide [(*Z*)-15c]. The synthesis of (*E*)-**15c** was followed. From (*Z*)-1-propenyl propyl sulfide (1.5 g, 13 mmol) (*Z*)-**15c** was obtained as a yellow oil (1.76 g, 74%): ^{1}H NMR δ 6.20 (d, J = 9 Hz, 1 H), 5.76 (m, 1 H), 4.93 (dd, J = 5.7, 7.2 Hz, 1 H), 2.2 (m, 2 H), 1.79 (d, J = 5.6 Hz, 3 H), 1.09 (t, J = 7.2 Hz, 3 H); ^{13}C NMR δ 128.68, 128.19, 73.07, 31.72, 14.25, 11.19; EI-MS m/z 184 (M$^+$, ^{37}Cl, 27%) 182 (M$^+$, ^{35}Cl, 68%), 106 (100%); HRMS (EI) m/z calcd for $C_6H_{11}S_2Cl$ (M$^+$) 181.9991, found 181.9991; IR (ν_{max}) 2969 (s), 2934 (s), 1613 (w), 1454 (s), 1379 (s), 699 (s), 670 (s) cm^{-1}.

1-(Methylthio)propyl (*E*)-1-Propenyl Disulfide [(*E*)-9c]. Method 2 for the synthesis of **9a** was followed, using (*E*)-**15c** (0.30 g, 1.65 mmol), AgOTs (0.92 g, 3.30 mmol), and MeSH (0.16 g, 3.30 mmol). Workup afforded (*E*)-**9c** as a light brown oil (0.174 g, 54%): ^{1}H NMR δ 6.07 (d, J = 15 Hz, 1 H), 5.96 (m, 1 H), 3.70 (dd, J = 8.1, 4.7 Hz, 1 H), 2.22 (s, 3 H), 2.10 (m, 2 H), 1.78 (d, J = 7.8 Hz, 3 H), 1.07 (t, J = 7.2 Hz, 3 H); ^{13}C NMR δ 129.81, 126.27, 60.79, 27.96, 18.24, 14.36, 11.64.

1-(Methylsulfinyl)propyl (*E*)-1-Propenyl Disulfide [(*E*)-7c]. Oxidation of (*E*)-**9c** (0.163 g, 0.84 mmol) with *m*-CPBA (0.174 g, 1.01 mmol) as described for **7a** gave by chromatography two isomers (1:1 by NMR; 0.076 g, 43%). Isomer 1: ^{1}H NMR δ 6.04 (d, J = 15 Hz, 1 H), 5.80 (dq, J = 15.2, 4.7 Hz, 1 H), 3.63 (dd, J = 11.1, 3.3 Hz, 1 H), 2.52 (s, 3 H), 2.29 (dqd, J = 14.7, 7.4, 3.6 Hz, 1 H), 1.79 (d, J = 6.0 Hz, 3 H), 1.60 (ddq, J = 14.5, 10.5, 6.7 Hz, 1 H), 1.17 (dd, J = 7.5, 7.0 Hz, 3 H); ^{13}C NMR δ 133.63, 124.65, 72.93, 32.58, 18.59, 18.37, 12.14; IR (ν_{max}) 2965 (m), 1455 (m), 1044 (s; S=O) cm^{-1}. Isomer 2: ^{1}H NMR δ 6.03 (d, J = 15 Hz, 1 H), 5.82 (dq, J = 14.5, 5.9 Hz, 1 H), 3.49 (dd, J = 11.7, 3.6 Hz, 1 H), 2.72 (s, 3 H), 2.32 (dqd, J = 14.6, 7.3, 3.5 Hz, 1 H), 1.85 (dqd, J = 14.7, 10.7, 7.2 Hz, 1 H), 1.77 (d, J = 5.4 Hz, 3 H), 1.12 (dd, J = 7.6, 7.1 Hz, 3 H); ^{13}C NMR δ 133.84, 125.17, 74.89, 37.39, 20.48, 18.36, 11.29; HRMS (CI/CH_4) m/z calcd for $C_7H_{15}S_3O$ (MH$^+$) 211.0285, found 211.0293.

1-(Methylthio)propyl Disulfide (*Z*)-1-Propenyl [(*Z*)-9c]. As in the synthesis of (*E*)-**9c**, (*Z*)-**15c** (0.30 g, 1.65 mmol) was reacted with AgOTs (0.92 g, 3.30 mmol) and then MeSH (0.16 g, 3.30 mmol), affording (*Z*)-**9c** as a light brown oil (0.197 g, 62%): ^{1}H NMR δ 6.16 (d, J = 10.5 Hz, 1 H), 5.74 (m, 1 H), 3.70 (dd, J = 8.1, 4.9 Hz, 1 H), 2.22 (s, 3 H), 2.10 (m, 2 H), 1.77 (d, J = 7.8 Hz, 3 H), 1.09 (t, J = 7.2 Hz, 3 H); ^{13}C NMR δ 129.94, 127.13, 61.39, 28.10, 18.60, 14.59, 11.52.

1-(Methylsulfinyl)propyl (*Z*)-1-Propenyl Disulfide [(*Z*)-7c]. Oxidation of (*Z*)-**9c** (0.154 g, 0.80 mmol) with *m*-CPBA (0.174 g, 1.01 mmol) as described for **7a** gave by chromatography two isomers of (*Z*)-**7c** (1:1 by NMR; 0.068 g, 41%). Isomer 1: ^{1}H NMR δ 6.15 (dq, J = 9.5, 1.5 Hz, 1 H), 5.80 (dq, J = 9.1, 6.5 Hz, 1 H), 3.63 (dd, J = 10.7, 3.8 Hz, 1 H), 2.56 (s, 3 H), 2.32 (dqd, J = 14.4, 7.2, 3.7 Hz, 1 H), 1.79 (dd, J = 6.3, 1.4 Hz, 3 H), 1.58 (ddq, J = 14.7, 10.0, 6.7 Hz, 1 H), 1.21 (t, J = 7.5 Hz, 3 H); ^{13}C NMR δ 129.75, 128.05, 73.30, 32.59, 18.42, 14.51, 11.53; IR (ν_{max}) 2965 (m), 1455 (m), 1044 (s; S=O) cm^{-1}. Isomer 2: ^{1}H NMR δ 6.09 (dq, J = 9.1, 1.6 Hz, 1 H), 5.82 (dq, J = 9.1, 7.2 Hz, 1 H), 3.49 (dd, J = 10.4, 4.0 Hz, 1 H), 2.75 (s, 3 H), 2.34 (dqd, J = 15.2, 6.9, 3.5 Hz, 1 H), 1.90 (ddq, J = 14.7, 10.0, 7.0 Hz, 1 H), 1.80 (dd, J = 6.5, 1.6 Hz, 3 H), 1.12 (dd, J = 7.2, 7.0 Hz, 3 H); ^{13}C NMR δ 129.81, 128.51, 74.77, 37.28, 20.12, 14.23, 11.12.

Bis(1-chloropropyl) Disulfide (17). A solution of KI (2.89g, 17 mmol) in water (50 mL) was added to a stirred solution of **14** (2.53 g, 17 mmol) in CH_2Cl_2 (50 mL) at room temperature. The resultant dark red-purple solution was stirred for 15 min and washed with aqueous $Na_2S_2O_3$ to remove liberated iodine. The organic layer was separated, washed with water (3 × 20 mL), dried, and concentrated in vacuo. The known (Tjan et al., 1972) but incompletely characterized **17** (1.76 g, 47%) was obtained as a pungent smelling dark red oil: ^{1}H NMR δ 5.15 (dd, J = 7.0, 1.8 Hz, 1 H), 5.11 (dd, J = 7.2, 1.8 Hz, 1 H), 2.12 (m, 4 H), 1.13 (t, J = 7.2 Hz, 3 H), 1.09 (t, J = 7.2 Hz, 3 H); ^{13}C NMR δ 73.72, 72.90, 31.96, 31.93, 11.23, 11.17.

(*E*)-4-Ethyl-3,5-dithiaoct-6-ene-2-one [(*E*)-16a]. A solution of (*E*)-1-bromopropene (1.0 g, 8.2 mmol; Hayashi et al., 1986) in THF (28 mL), ether (7 mL), and pentane (7 mL) was cooled to −110 °C, and *tert*-butyllithium (*t*-BuLi) (1.7 M in hexanes, 9.6 mL, 16.4 mmol) was added dropwise, resulting in a pale yellow color. The reaction was stirred for 1 h at −110 °C and was then warmed to −95 °C. Compound **17** (2.15 g, 9.9 mmol) was added dropwise, and the solution was stirred for an additional 1 h. The solution was warmed to −78 °C, and sodium thiolacetate (4 equiv) in 200 mL of THF (also at −78 °C) was added quickly by cannula or large-capacity syringe, stirred for 1 h at −78 °C, and then slowly warmed to −30 °C, at which temperature it was allowed to stir for 1 h. The solution was then warmed quickly to 0 °C and poured into ether (500 mL), washed with saturated aqueous NH_4Cl (200 mL), dried, and concentrated in vacuo. Chromatography (CH_2-Cl_2/hexanes 3:7) gave (*E*)-**16a** as a brown-yellow, pungent oil (1.2 g; 76%): ^{1}H NMR δ 5.97 (dd, J = 15, 1.5 Hz, 1H), 5.86 (dq, J = 15, 5.5 Hz, 1H), 4.58 (t, J = 6.9 Hz, 1 H), 2.34 (s, 3 H), 1.9 (m, 2 H), 1.75 (dd, J = 6.4, 1.9 Hz, 3 H), 1.04 (t, J = 7.4 Hz, 3 H); ^{13}C NMR δ 195.13 (C), 131.82 (CH), 120.63 (CH), 51.84 (CH), 30.42 (CH_3), 29.33 (CH_2), 18.61 (CH_3), 11.73 (CH_3); EIMS m/z 190 (M$^+$, 6%), 117 (13%), 75 (15%), 74 (18%), 73 (8%), 59 (6%), 47 (9%), 40 (100%); IR (ν_{max}) 2970 (m), 1700 (vs), 1440 (m), 1130 (m) cm^{-1}.

(*Z*)-4-Ethyl-3,5-dithiaoct-6-ene-2-one [(*Z*)-16a]. Substitution of (*Z*)-1-bromopropene (Fuller and Walker, 1991) for the *E*-isomer in the procedure for (*E*)-**16a** gave, after chromatog-

raphy, (*Z*)-**16a** (0.85 g; 54%): ^{1}H NMR δ 6.00 (dd, J = 9.5, 1.7 Hz, 1H), 5.75 (dq, J = 9.5, 7 Hz, 1 H), 4.58 (t, J = 7 Hz, 1 H), 2.34 (s, 3 H), 1.9 (m, 2 H), 1.75 (dd, J = 7, 1.7 Hz, 3 H), 1.04 (t, J = 7 Hz, 3 H); ^{13}C NMR δ 195.13 (C), 131.82 (CH), 120.61 (CH), 51.83 (CH), 30.40 (CH_3), 29.33 (CH_2), 14.46 (CH_3), 11.71 (CH_3); EIMS m/z 190 (M^+, 6%), 117 (13%), 75 (15%), 74 (18%), 73 (8%), 59 (6%), 47 (9%), 40 (100%); IR (ν_{max}) 2970 (m), 1700 (vs), 1440 (m), 1130 (m) cm^{-1}.

(*E,Z*)-4-Ethyl-3,5-dithiaoct-6-ene-2-one [(*E,Z*)-16a]. A 100 mL three-neck flask was charged with a solution of bis-(1-propenyl)sulfide (**19**; Trofimov et al., 1986) (2.0 g, 7.5mmol) in ether/hexanes (1:3, 12 mL). A slow stream of HCl gas was introduced through a glass pipet into the reaction mixture, and the progress of the reaction giving 1-chloropropyl (*E,Z*)-1-propenyl sulfide [(*E,Z*)-**18**] was monitored by GC. Sodium thiolacetate (4 equiv) at −78 °C was added dropwise to the (*E,Z*)-**18** solution. The mixture was then warmed to room temperature, stirred for 17 h, and taken into ether, and the organic layer was washed with saturated aqueous NH_4Cl, dried, and concentrated in vacuo, yielding a brown-red oil that was purified by chromatography (CH_2Cl_2/hexanes 3:7) giving (*E,Z*)-**16b** (2.72 g, 80%).

Methyl (*E*)-1-(1-Propenylthio)propyl Disulfide [(*E*)-9d]. A 50 mL three-neck flask was charged with K_2CO_3 (0.58 g, 4.2 mmol) and MeOH (25 mL). The mixture was stirred at room temperature for 30 min and cooled to −55 °C. A solution of (*E*)-**16a** (0.20 g, 1 mmol) in MeOH (5 mL) was added dropwise. When thiolacetate hydrolysis was complete (TLC), $MeSO_2SMe$ (0.63 g, 5 mmol) was added dropwise. The solution was then warmed to room temperature, hexanes were added, and the product was washed with water (5 × 50 mL). The organic layer was separated, dried, and concentrated in vacuo. Chromatography (hexanes) gave (*E*)-**9d**, (0.083 g, 43%) as a pale yellow oil: ^{1}H NMR δ 6.05 (dq, J = 14.5, 2.5 Hz, 1 H), 5.85 (dq, J = 15, 6.5 Hz, 1H), 3.86 (dd, J = 8, 5 Hz, 1 H), 2.48 (s, 3 H), 2.0 (m, 2 H), 1.78 (dd, J = 5.5, 1.5 Hz, 3 H), 1.09 (t, J = 7.4 Hz, 3 H); ^{13}C NMR δ 131.11 (CH), 123.20 (CH), 52.31 (CH), 28.37 (CH_2), 25.19 (CH_3), 18.62 (CH_3), 12.24 (CH_3); EIMS m/z 194 (M^+, 0.3%), 120 (13%), 116 (4%), 115 (56%), 87 (5%), 79 (17%), 74 (17%), 73 (42%), 59 (24%), 46 (14%), 45 (100%).

Methyl (*E*)-1-(1-Propenylsulfinyl)propyl Disulfide [(*E*)-7d]. Oxidation of (*E*)-**9d** (0.083 g, 0.43 mmol) with *m*-CPBA (0.089 g, 0.52 mmol) as described for **7a** gave, after chromatography, (*E*)-**7d** (0.048 g, 53%), a pale yellow oil that was a 2:1 mixture of diastereomers: ^{1}H NMR (of mixture; unadjusted integration) δ 6.45 (m, 6 H), 3.68 (dd, J = 3.5, 10.6 Hz, 1 H), 3.50 (dd, J = 3.3, 10.6 Hz, 2 H), 2.51 (s, 3 H), 2.46 (s, 6 H), 2.22 (m, 3 H), 1.95 (dd, J = 6.2, 1.9 Hz, 9 H), 1.87 (m, 3 H), 1.15 (m, 9 H); ^{13}C NMR (major isomer) δ 138.32 (CH), 131.65 (CH), 75.61 (CH), 24.81 (CH_3), 20.33 (CH_2), 18.04 (CH_3), 11.25 (CH_3); CIMS (NH_3) m/z 421 (2M + H^+, 4%), 228 (M + NH_4^+, 29%), 213 (M + 2, 10%), 211 (MH^+, 62%), 195 (100%), 137 (15%); HRMS (CI/CH_4) m/z calcd for $C_7H_{15}S_3O$ (MH^+) 211.0285, found 211.0286; IR (ν_{max}) 1440 (m), 1035 (vs) cm^{-1}.

Methyl 1-(2-Propenylthio)propyl Disulfide (9e). Method 2 for the synthesis of **9a** was followed, using **15a** (0.30 g, 1.92 mmol), AgOTs (0.53 g, 1.92 mmol), and 2-propenethiol (0.14 g, 1.92 mmol), giving **9e**, a yellow oil (0.28 g, 76%): ^{1}H NMR δ 5.78 (m, 1 H), 5.20 (d, J = 12.0 Hz, 2 H), 3.58 (t, J = 7.0 Hz, 1 H), 3.26 (d, J = 7.2 Hz, 2 H), 2.50 (s, 3 H), 2.18 (m, 1 H), 1.80 (m, 1 H), 1.02 (t, J = 7.8 Hz, 3H); ^{13}C NMR δ 134.36, 117.21, 74.27, 33.44, 31.96, 19.17, 11.41.

Methyl 1-(2-Propenylsulfinyl)propyl Disulfide (7e). Oxidation of **9e** (0.20 g, 1.03 mmol) with *m*-CPBA (0.19 g, 1.10 mmol) as described for **7a** gave, after chromatography, **7e**, a yellow liquid with an onion-like odor (0.072 g, 33%): ^{1}H NMR δ 5.97 (m, 1 H), 5.45 (d, J = 12.3 Hz, 2 H), 3.60 (dd, J = 11.3, 3.7 Hz, 1 H), 3.32 (d, J = 7.8 Hz, 2 H), 2.50 (s, 3 H), 2.35 (m, 1 H), 1.96 (m, 1 H), 1.15 (t, J = 7.8 Hz, 3 H); ^{13}C NMR δ 133.26, 118.48, 69.93, 52.84, 33.96, 19.45, 11.03; IR (ν_{max}) 1044 (s) cm^{-1} (S═O); HRMS (CI/CH_4) m/z calcd for $C_7H_{15}S_3O$ (MH^+) 211.0285, found 211.0297. Analysis by LC/MS indicates that the chromatographed product contains some 2-propenyl 1-(2-propenylsulfinyl)propyl disulfide.

Propyl 1-(Propylthio)propyl Disulfide (9f). Method 2 for the synthesis of **9a** was followed, using a solution of **15b** (0.50 g, 2.70 mmol), AgOTs (0.75 g, 2.7 mmol), and then PrSH (0.21 g, 2.7 mmol), giving **9f**, a pungent smelling yellow liquid (0.47 g, 78%): ^{1}H NMR δ 3.66 (t, J = 7.0 Hz, 1 H), 2.65 (m, 4 H), 1.75 (m, 6 H), 1.06 (t, J = 7.2 Hz, 3 H), 1.01 (t, J = 7.8 Hz, 3 H), 0.98 (t, J = 7.8 Hz, 3 H); ^{13}C NMR δ 53.74, 41.13, 32.20, 29.29, 22.82, 22.47, 13.64, 13.09, 12.18; EI-MS m/z (% abundance) 192 (0.22), 150 (15), 117 (40), 75 (32), 74 (20), 73 (16), 47 (23), 45 (44), 43 (100), 41 (90).

Propyl 1-(Propylsulfinyl)propyl Disulfide (7f). *Method 1.* Oxidation of **9f** (0.30 g, 1.30 mmol) with *m*-CPBA (0.28 g, 1.60 mmol) as described for **7a** gave, after chromatography, two isomers (1:2 by NMR) of **7f** as a pale yellow oil with an onion-like odor (0.106 g, 34%). Minor isomer: ^{1}H NMR δ 3.49 (dd, J = 10.9 Hz, 3.1 Hz, 1 H), 3.12 (dt, J = 13.2, 8.0 Hz, 1 H), 2.74 (t, J = 7.2 Hz, 2 H), 2.71 (dt, J = 12.6, 7.2 Hz, 1 H), 2.37 (dqd, J = 14.7, 7.4, 3.3 Hz, 1 H), 1.95 (ddq, J = 14.6, 10.8, 7.0 Hz, 1 H), 1.91 (tq, J = 7.6, 7.0 Hz, 2 H), 1.72 (tq, J = 7.4, 7.0 Hz, 2 H), 1.14 (t, J = 7.8 Hz, 3 H), 1.11 (t, J = 7.8 Hz, 3 H), 1.01 (dd, J = 7.6, 7.0 Hz, 3 H); ^{13}C NMR δ 72.78, 52.56, 42.50, 22.20, 20.01, 16.49, 13.33, 12.97, 11.08. Major isomer: ^{1}H NMR δ 3.64 (dd, J = 10.9 Hz, 3.2 Hz, 1 H), 2.89 (dt, J = 11.6, 7.1 Hz, 2 H), 2.77 (t, J = 7.2 Hz, 2 H), 2.64 (dt J = 12.6, 7.3 Hz, 1 H), 2.30 (dqd, J = 14.8, 7.4, 3.6 Hz, 1 H), 1.86 (tq, J = 7.2, 7.0 Hz, 2 H), 1.74 (tq, J = 7.2, 7.0 Hz, 2 H), 1.62 (ddq, J = 14.7, 11.5, 7.1 Hz, 1 H), 1.24 (t, J = 7.8 Hz, 3 H), 1.13 (t, J = 7.8 Hz, 3 H), 1.04 (t, J = 7.8 Hz, 3 H); ^{13}C NMR δ 73.89, 48.77, 41.35, 22.22, 19.48, 17.07, 13.55, 13.04, 12.11; IR (ν_{max}) 1046 (s) cm^{-1} (S═O); HRMS (CI/CH_4) m/z calcd for $C_9H_{21}S_3O$ (MH^+) 241.0755, found 241.0760.

Method 2. A solution of PrS(O)SPr (0.10 g, 0.60 mmol) in benzene (10 mL)/water (6 mL) was kept at 60 °C for 36 h. The aqueous layer was extracted with ether (3 × 5 mL), and the combined organic layers were dried and concentrated in vacuo. After purification by column chromatography (CH_2Cl_2/acetone, 9:1), **7f** was obtained as a yellow oil consisting of two isomers (1:1 by NMR; 0.013 g, 9.6%); ^{1}H and ^{13}C NMR and IR spectra were identical to product prepared according to method 1.

(*E*)-1-Propenyl 1-(Propylthio)propyl Disulfide [(*E*)-9g]. Method 2 for the synthesis of **9a** was followed, using (*E*)-**15c** (0.30 g, 1.65 mmol), AgOTs (0.46 g, 1.65 mmol), and PrSH (0.16 g, 1.65 mmol). Workup afforded (*E*)-**9g**, a pungent smelling yellow oil (0.32 g, 87%): ^{1}H NMR δ 6.08 (d, J = 15 Hz, 1 H), 5.95 (m, 1 H), 3.77 (dd, J = 8.0, 4.8 Hz, 1 H), 2.68 (m, 2 H), 2.13 (m, 1 H), 1.81 (d, J = 6.8 Hz, 3 H), 1.67 (m, 3 H), 1.09 (t, J = 7.6 Hz, 3 H), 1.02 (t, J = 7.2 Hz, 3 H); ^{13}C NMR δ 129.65, 126.08, 59.04, 34.11, 28.39, 23.03, 18.28, 13.66, 11.50.

(*E*)-1-Propenyl 1-(Propylsulfinyl)propyl Disulfide [(*E*)-7g]. Oxidation of (*E*)-**9g** (0.30 g, 1.4 mmol) with *m*-CPBA (0.28 g, 1.6 mmol) as described for **7a** gave by chromatography two isomers of (*E*)-**7g**, a light yellow oil (1:2 by NMR; 0.12 g, 39%). Minor isomer: ^{1}H NMR δ 6.08 (d, J = 14.5 Hz, 1 H), 5.80 (m, 1 H), 3.52 (dd, J = 11, 3.9 Hz, 1 H), 3.11 (m, 1 H), 2.70 (m, 1 H), 2.36 (m, 1 H), 1.91 (m, 3 H), 1.80 (d, J = 4.6 Hz, 3 H), 1.16 (t, J = 7.8 Hz, 3 H), 1.10 (t, J = 7.6 Hz, 3 H); ^{13}C NMR δ 133.93, 125.48, 72.49, 52.69, 20.40, 18.34, 16.65, 13.51, 11.19. Major isomer: ^{1}H NMR δ 6.10 (d, J = 14 Hz, 1 H), 5.80 (m, 1 H), 3.68 (dd, J = 11, 3.7 Hz, 1 H), 2.75 (m, 2 H), 2.33 (m, 1 H), 1.95 (m, 3 H), 1.80 (d, J = 4.6 Hz, 3 H), 1.20 (t, J = 7.8 Hz, 3 H), 1.12 (t, J = 7.8 Hz, 3 H); ^{13}C NMR δ 131.81, 125.19, 74.86, 48.92, 19.63, 18.02, 17.65, 13.54, 12.09; IR (ν_{max}) 1049 (s; S═O) cm^{-1}; HRMS (CI/CH_4) m/z calcd for $C_9H_{19}S_3O$ (MH^+) 239.0598, found 239.0603.

(*E*)-1-(1-Propenylthio)propyl Propyl Disulfide [(*E*)-9h]. This compound was prepared according to the procedure given for (*E*)-**9d** using (*E*)-**16a** (0.15g, 0.79 mmol), K_2CO_3 (0.44 g, 3.2 mmol), and $PrSO_2SPr$ (0.72 g, 3.9 mmol), giving (*E*)-**9h** (0.072 g, 41%) as a pale yellow oil: ^{1}H NMR δ 6.05 (dq, J = 14.5, 2.5 Hz, 1 H), 5.85 (dq, J = 15, 6.5 Hz, 1 H), 3.86 (dd, J = 8, 5 Hz, 1 H), 2.75 (t, J = 7 Hz, 2 H), 2.11 (m, 1 H), 1.85 (m, 1 H),1.78 (dd, J = 5.5, 1.5 Hz, 3 H), 1.71 (m, 2 H), 1.07 (t, J = 7.4 Hz, 3 H), 1.00 (t, J = 7.4 Hz, 3 H); ^{13}C NMR δ 131.15 (CH), 122.72 (CH), 60.25 (CH), 41.71 (CH_2), 27.84 (CH_2), 22.67 (CH_2), 18.61 (CH_3), 13.13 (CH_3), 11.63 (CH_3); EIMS m/z 224 (M + 2, 0.05%), 222 (M^+, 0.3%), 115 (100%), 105 (6%), 81 (45%), 74 (12%), 73 (61%), 45 (97%).

(*E*)-1-(1-Propenylsulfinyl)propyl Propyl Disulfide [(*E*)-7h]. Oxidation of (*E*)-**9h** (0.07 g, 0.32 mmol) with *m*-CPBA (0.067 g, 0.39 mmol) as described for **7a** gave (*E*)-**7h** (0.041 g, 53%), a pale yellow oil that was a 2:1 mixture of diastereomers: ^{1}H NMR (of mixture; unadjusted integration) δ 6.5 (m, 6 H), 3.67 (dd, J = 3.3, 10.7 Hz, 1 H), 3.48 (dd, J = 3.3, 10.7 Hz, 2 H), 2.73 (m, 6 H), 2.27 (m, 3 H), 1.96 (d, J = 5.6 Hz, 9 H), 1.88 (m, 3 H), 1.70 (apparent sextet, J = 7 Hz, 6 H), 1.14 (t, J = 7.4 Hz, 9 H), 0.99 (t, 7.4 Hz, 9 H); ^{13}C NMR (major isomer) δ 138.44 (CH), 131.81 (CH), 75.63 (CH), 42.47 (CH_2), 22.31 (CH_2), 20.31 (CH_2), 18.05 (CH_3), 13.04 (CH_3), 11.28 (CH_3); CIMS (NH_3) m/z 477 (2M + H$^+$, 13%), 256 (M + NH_4^+, 31%), 241 (MH^+, 25%), 240 (20%), 239 (MH^+, 100%), 166 (20%), 165 (20%), 149 (91%); HRMS (CI/CH_4) m/z calcd for $C_9H_{19}S_3O$ (MH^+) 239.0598, found 239.0592; IR (ν_{max}) 1440 (m), 1035 (vs) cm^{-1}.

(*E*)-1-Propenyl (*E*)-1-(Propenylthio)propyl Disulfide [(*E,E*)-9i]. *Method 1.* Lithium (0.56 g, 80 mmol) was added to liquid NH_3 (50 mL) in a three-neck round-bottom flask at −78 °C. After 15 min, a solution of (*E*)-1-propenyl propyl sulfide (4.64 g, 40 mmol) in THF (30 mL) was added. The NH_3 was removed at −60 °C (0.5 mmHg) using a liquid nitrogen trap until the reaction mixture was almost dry. More THF (80 mL) was added, and the reaction mixture was pumped at −60 °C for another 15 min. Methanesulfonyl chloride (3.66 g, 0.8 equiv, 32 mmol) in THF (5 mL) was added at −65 °C; the resultant white mixture was stirred at −5 °C for 2 h. Cold water (50 mL) was added, and after 30 min, the mixture was extracted with pentane, dried, and concentrated. GC/MS analysis (decane internal standard) showed (*E,E*)-**9i** (27%), (*E,E*)-5,8-diethyl-4,6,7,9-tetrathiadodeca-2,10-diene (18% yield), (*E,E*)-bis(1-propenyl) disulfide, and 2,4,6-triethyl-1,3,5-trithiane. Chromatography (silica gel, hexanes) gave (*E,E*)-**9i** (730 mg; 25%) and (*E,E*)-5,8-diethyl-4,6,7,9-tetrathiadodeca-2,10-diene (250 mg; 9%). (*E,E*)-**9i**: ^{1}H NMR δ 6.15−5.85 (m, 4 H), 3.83 (dd, J = 8.2, 5 Hz, 1 H), 2.1 (m, 1 H), 1.78 (m, 4 H), 1.05 (t, J = 7.3); ^{13}C NMR (APT) δ 131.12 (CH), 129.82 (CH), 126.19 (CH), 120.79 (CH), 59.61 (CH), 27.68 (CH_2), 18.65 (CH_3), 18.12 (CH_3), 11.41 (CH_3); IR (neat, ν_{max}) 2964 (s), 1615 (w), 1442 (s), 936 (s) cm^{-1}; GC/MS (EI) m/z (rel intensity) 220 (M$^+$, 0.2), 146 (4), 115 (66), 45 (100); HRMS (EI) m/z calcd for $C_9H_{16}S_3$ 220.0414, found 220.0434. Minor component: ^{1}H NMR δ 5.75−6.15 (m, 4 H), 3.95−4.03 (m, 2 H), 2.04−2.17 (m, 2 H), 1.70−1.88 (m, 8 H), 1.02−1.11 (m, 6 H); ^{13}C NMR δ 131.01, 130.78, 121.03, 120.68, 60.62, 60.02, 28.04, 27.72, 18.66, 18.62, 11.60, 11.56; GC/MS (EI) m/z (rel intensity) 294 (M$^+$, 0.5), 146 (7), 115 (70), 45 (100).

Method 2. An ether (15 mL) solution of (*E*)-MeCH=CHSPr (3.0 g, 26 mmol) was added slowly to a stirred blue solution of Li (0.32 g, 46 mmol) in NH_3 (20 mL) at −78 °C under argon. The white suspension was stirred for 1 h. Excess NH_3 was removed at −50 °C/0.2 mmHg during 5 h. Ether (30 mL) was added at −50 °C followed by **14** (1.88 g, 13 mmol) in ether (20 mL). The mixture was stirred at −5 °C for 20 h and then quenched with water (30 mL). The aqueous layer was extracted with ether (2 × 20 mL), and the combined organic layers were washed with aqueous NH_4Cl (2 × 30 mL) and brine (3 × 30 mL), dried, and concentrated in vacuo to give (*E,E*)-**9i**, a yellow oil (1.28 g, 45%). The ^{1}H/^{13}C NMR spectra and EI-MS match those of (*E,E*)-**9i** prepared according to method 1.

(*E*)-1-Propenyl (*E*)-1-(Propenylsulfinyl)propyl Disulfide [(*E,E*)-7i]. Oxidation of (*E,E*)-**9i** (0.22 g, 1 mmol) with *m*-CPBA (0.184 g, 1.06 mmol) as described for **7a** gave (*E,E*)-**7i**, a liquid (0.155 g, 64%) consisting of two diastereomers (1:2 by NMR). Pure isomers were obtained by flash chromatography (silica gel, AcOEt/hexanes, 3:7): (minor isomer, less polar) ^{1}H NMR δ 6.48 (dq, J = 15, 7 Hz, 1 H), 6.3 (dq, J = 15, 2 Hz, 1 H), 6.1 (d, J = 15 Hz, 1 H), 6.02 (dq, J = 15, 6 Hz, 1 H), 3.66 (dd, J = 10.5, 3.5 Hz, 1 H), 2.18 (m, 1 H), 1.93 (dd, J = 7, 2 Hz, 3 H), 1.78 (d, J = 6 Hz, 3 H), 1.41 (m, 1 H), 1.13 (t, J = 7.2 Hz, 3 H); ^{13}C NMR δ 138.6, 133.2, 128.32, 125.05, 74.05, 18.74, 18.52, 18.18, 11.73; (major isomer, more polar) ^{1}H NMR δ 6.51 (dq, J = 15, 6 Hz, 1 H), 6.4 (dq, J = 15, 2 Hz, 1 H), 6.05 (d, J = 15 Hz, 1 H), 5.98 (dq, J = 15, 5.5 Hz, 1 H), 3.48 (dd, J = 11, 3.5 Hz, 1 H), 2.22 (m, 1 H), 1.92 (dd, J = 6, 2 Hz, 3 H), 1.85 (m, 1 H), 1.75 (d, J = 5.5 Hz, 3 H), 1.1 (t, J = 7.2 Hz, 3 H); ^{13}C NMR δ 138.3, 133.03, 131.71, 125.38, 74.75, 20.35, 18.16, 17.95, 11.10; MS (EI) m/z 147 (84), 115 (68), 105 (100), 73 (55); HRMS (CI/CH_4) m/z calcd for $C_9H_{17}S_3O$ (MH^+) 237.0442, found 237.0437; IR (ν_{max}) 2965 (m), 1440 (m), 1047 (s; S=O) cm^{-1}.

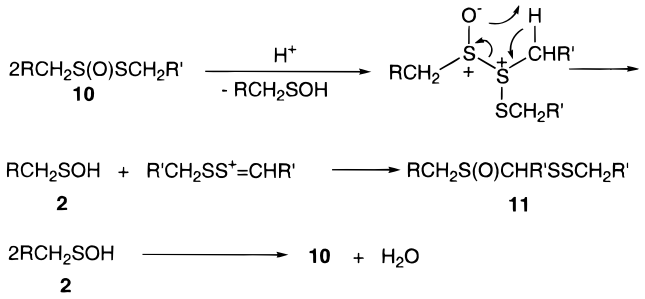
(*E*)-1-Propenyl (*Z*)-1-(1-Propenylthio)propyl Disulfide [(*E,Z*)-9i]. Method 2 for the synthesis of (*E,E*)-**9i** was followed. From the reaction as above involving (*E*)-1-propenyl propyl sulfide (1.5 g, 13 mmol), lithium (0.16 g, 26 mmol) in liquid NH_3 (15 mL), **14** (2.0 g, 11 mmol), and ether (20 mL), followed by chromatography (hexane/EtOAc, 9/1), (*E,Z*)-**9i** was obtained as a yellow oil (1.08 g, 45%) containing ca. 20% (*E,E*)-**9i**: ^{1}H NMR δ 6.10 (m, 2 H), 5.92 (m, 1 H), 5.72 (m, 1 H), 3.86 (dd, J = 4.7, 8.4 Hz, 1 H), 2.1 (m, 2 H), 1.74 (m, 6 H), 1.06 (t, J = 7.2 Hz, 3 H); ^{13}C NMR δ 129.98, 127.08, 126.47, 122.60, 60.02, 27.72, 18.16, 14.79, 11.49; GC/MS (EI) m/z 220 (M$^+$, 44), 205 (100%), 115 (38).

(*E*)-1-Propenyl (*Z*)-1-(1-Propenylsulfinyl)propyl Disulfide [(*E,Z*)-7i]. Oxidation of (*E,Z*)-**9i** (0.20 g, 0.91 mmol) with *m*-CPBA (0.186 g, 1.08 mmol) as described for **7a** gave, after chromatography (9:1 CH_2Cl_2/acetone), (*E,Z*)-**7i**, a pale yellow oil that was a 1:1 mixture of diastereomers (0.084 g, 39%). Isomer 1: ^{1}H NMR δ 6.43 (m, 1 H), 6.20 (m, 1 H), 6.09 (m, 1 H), 5.79 (m, 1 H), 3.57 (dd, J = 4.6, 3.4 Hz, 1 H), 2.33 (m, 1 H), 2.03 (m, 3 H), 1.95 (m, 3 H), 1.76 (d, J = 2.1 Hz, 3 H), 1.16 (t, J = 7.5 Hz, 3 H); ^{13}C NMR δ 140.26, 140.13, 134.25, 129.27, 74.39, 20.35, 18.25, 16.02, 11.21. Isomer 2: ^{1}H NMR δ 6.39 (m, 1 H), 6.17 (m, 1 H), 6.04 (m, 2 H), 3.54 (dd, J = 5.0, 3.5 Hz, 1 H), 2.28 (m, 1 H), 2.01 (m, 3 H), 1.90 (m, 1 H), 1.78 (d, J = 2.9 Hz, 3 H), 1.12 (t, J = 7.3 Hz, 3 H); ^{13}C NMR δ 140.68, 133.38, 128,28, 125.43, 74.33, 20.28, 18.59, 14.46, 11.84; EI-MS m/z 236 (M$^+$, 100%), 220 (28%), 147 (31%); HRMS (CI/CH_4) m/z calcd for $C_9H_{17}S_3O$ (MH^+) 237.0442, found 237.0439; IR (neat, ν_{max}) 1445 (m), 1048 (s) cm^{-1}.

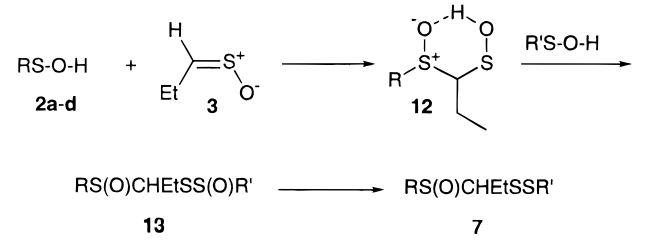
RESULTS AND DISCUSSION

Isolation and Occurrence of Cepaenes and "Deoxycepaenes". In 1988 the isolation of methyl 1-(methylsulfinyl)propyl disulfide [MeS(O)CHEtSSMe, **7a**] from fresh onion extracts was reported. This compound displayed an IC_{50} of 67.6 μmol against an in vitro platelet suspension (Kawakishi and Morimitsu, 1988). It was suggested, without elaboration, that **7**a "is probably formed by the interaction of thiopropanal *S*-oxide and methanesulfenic acid produced in crushed onion". Simultaneously, a paper appeared on the isolation of a series of related compounds of the type MeCH=CHS(O)CHEtSSR, termed "cepaenes", showing interesting biological activity [e.g. for (*E*)-MeCH=CHS(O)CHEtSSPr [(*E*)- **7h**]: IC_{50} = 2.5 μM and 0.8 μM on sheep seminal microsome CO and porcine leucocyte 5-LO, respectively] (Bayer et al., 1988). More recently, it has been shown that mixing onion homogenates with *S*-alk(en)yl-L-cysteine sulfoxides or with other *Allium* species affords various cepaenes (Morimitsu et al., 1992). Oxygen-free analogs of cepaenes, alk(en)yl 1-[alk(en)ylthio]propyl disulfides [RSCHEtSSR′, **9**; termed "deoxycepaenes" by Block and Zhao (1992)], occur rather widely in natural product volatiles. Thus, methyl 1-(methylthio)propyl disulfide (MeSCHEtSSMe; **9a**) occurs in the headspace of meat; syntheses of **9a** and homologs were reported (Dubs and Stüssi, 1978). The compound MeSCHEtSSCH=CHMe (**9c**) is found in *Asafoetida* essential oil (Naimie et al., 1972; Noleau et al., 1991) and *Ferula* species (Dai and Qiu, 1992), while MeCH=CHSCHEtSSCH=CHMe (**9i**) and related compounds occur in distilled oils of onion (Farkas et al., 1992), shallot (*Allium ascalonicum*), Welsh onion (*Allium fistulosum*) (Kuo et al., 1990; Kuo and Ho, 1992a,b), and Chinese chive (*Allium tuberosum*) (Meng et al.,

Scheme 3



Scheme 4



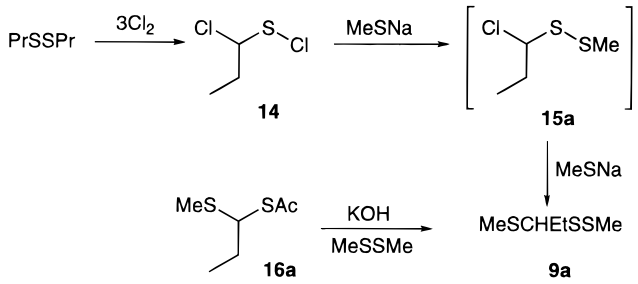
R, R': **a** Me; **b** MeCH=CH; **c** *n*-Pr; **d** CH_2=$CHCH_2$

1996), as well as in volatiles from roasted onion (Tokitomo, 1995).

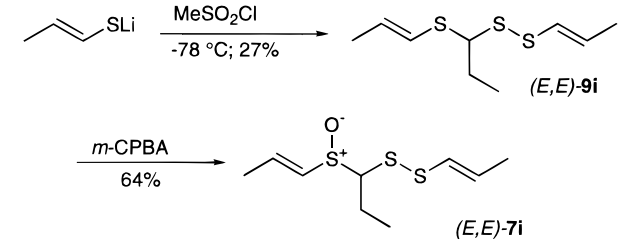
Mechanism of Formation of Cepaenes. In an earlier study we reported the conversion of alkyl alkanethiosulfinates to α-sulfinyl disulfides, $RCH_2S(O)SCH_2R'$ (**10**) → $RCH_2S(O)CHR'SSCH_2R'$ (**11**) (Scheme 3), predicting that compounds such as **11** would possess unusual physiological properties (Block and O'Connor, 1973). There are several difficulties with the application of this mechanism to cepaene formation in onions: (1) In our earlier work, thiosulfinates possessing CH_3S groups afforded α-sulfinyl disulfides more efficiently than those with other RS groups, leading to the expectation that α-sulfinyl disulfides of type **11**, R′ = H (Scheme 3), should be formed from mixtures of thiosulfinates containing **10**, R or R′ = H. In fact, only cepaenes **7** with an *ethyl group* on the carbon between the sulfurs have been found naturally. (2) In our earlier work, the formation of α-sulfinyl disulfides from thiosulfinates was a slow process, requiring prolonged heating. As noted in the accompanying paper (Calvey et al., 1997), cepaene formation/extraction in supercritical CO_2 treatment of onion homogenates is rapid. Because of these problems with the mechanism of Scheme 3, an alternative mechanism is proposed to explain cepaene formation (Scheme 4). We suggest that sulfenic acids **2** add to LF **3**, giving internally hydrogen-bonded α-sulfinylsulfenic acids **12** (it is known that intramolecular hydrogen bonding greatly stabilizes sulfenic acids). The reaction between **2** and **3** is analogous to other reported carbophilic addition reactions of sulfines (Yagami et al., 1980; Block and Aslam, 1985). Intermediate **13** may mediate conversion of **12** to cepaenes **7**.

Synthesis of Cepaenes. *Background.* Refluxing thiosulfinates **10** in benzene/water affords α-sulfinyl disulfides **11** in one step (Scheme 3) (Block and O'Connor, 1973, 1974). Application of this procedure to PrS(O)SPr (**10**, R = R′ = Et) (Block et al., 1986) affords PrS(O)CHEtSSPr [**11**, R = R′ = Et (= **7f**)] in 10% yield as a 1:1 mixture of diastereomers. A more general approach to cepaenes such as **7f** involves selective oxidation of the corresponding deoxycepaene, e.g. PrSCHEtSSPr (**9f**), at the sulfide sulfur. Three syntheses of 1-[alk(en)ylthio]propyl alk(en)yl disulfides (deoxycepaenes; **9**) have been reported. The first (Dubs and Stüssi, 1978) involves treatment of 1-chloropropanesulfenyl chloride, EtCHClSCl (**14**), with excess methanethiolate. Although not mentioned by the authors, 1-chloropropyl methyl disulfide (**15a**; EtCHClSSMe) is a likely intermediate in the latter synthesis. The second synthesis involves hydrolysis of 3-ethyl-2,4-dithiahexan-5-one, MeSCHEtSAc (**16a**), in the presence of a thiosulfenylating agent such as a disulfide (Scheme 5; Dubs and Stüssi, 1978). The nonstereospecific reaction of (*E*,*Z*)-1-propenethiol with 1-(methylthio)-1-propanesulfenyl thiocyanate, MeSCHEtSSCN, is the basis for the third synthesis (Meijer and Vermeer, 1974).

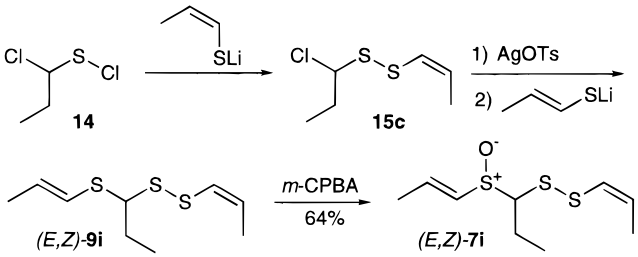
Scheme 5



Scheme 6



Scheme 7



Results. Two-step syntheses of (*E*,*E*)- or (*Z*,*Z*)-1-propenyl 1-(1-propenylsulfinyl)propyl disulfide [(*E*,*E*)- or (*Z*,*Z*)-**7i**] were developed on the basis of the serendipitous finding that low-temperature treatment of lithium (*E*)- or (*Z*)-1-propenethiolate with $MeSO_2Cl$ affords (*E*,*E*)- or (*Z*,*Z*)-1-propenyl 1-(1-propenylthio)-propyl disulfide [(*E*,*E*)- or (*Z*,*Z*)-**9i**], respectively, in 23−27% yields (Scheme 6). The mechanism of this reaction is discussed elsewhere (Block and Zhao, 1992). Oxidation of (*E*,*E*)- or (*Z*,*Z*)-**9i** with *m*-CPBA gives the respective isomers of **7i** in 64% isolated yield. This approach could not be used to prepare (*E*,*Z*)-**7i**, so a lengthier approach was employed, involving sequential treatment of EtCHClSSCH=CHMe-(*Z*) [(*Z*)-**15c**] with silver tosylate in acetonitrile at low temperatures followed by (*E*)-MeCH=CHSLi giving (*E*,*Z*)-**9i** (Scheme 7). If (*E*)-**15c** was substituted for the *Z*-isomer in the above procedure, (*E*,*E*)-**9i** was obtained. Stereoisomeric compounds **15c** were prepared by reaction of EtCHClSCl (**14**) with 1

Table 1. Synthetic Cepaenes and Deoxycepaenes

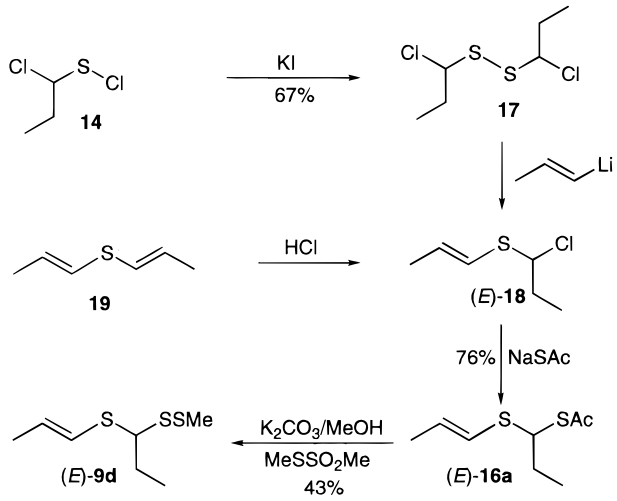
formula	*n*	cepaene/deoxycepaene (compd no.)	nat occ	synth method[p] (yield)[q]	isomer ratio	NMR of CHEt group ^{1}H (*J*, Hz)	^{13}C
$C_5H_{12}S_3O_n$	0	MeSCHEtSSMe (**9a**)	*a*−*c*	A (61%)[r]		3.67 (dd, 8, 5)	61.14
				B (65%)			
	1	MeS(O)CHEtSSMe (**7a**)	*k*, *l*	G (37%)	2:1	3.60 (dd, 11, 3.3)	73.98
						3.45 (dd, 11, 3.3)	75.34
$C_7H_{16}S_3O_n$	0	MeSCHEtSSPr (**9b**)	*d*, *e*	B (74%)[r]		3.65 (t, 6.8)	56.35
	1	MeS(O)CHEtSSPr (**7b**)	*l*	G (31%)	1:1	3.50 (dd, 11, 3.3)	72.91
$C_7H_{14}S_3O_n$	0	MeSCHEtSSCH=CHMe-(*E*) [(*E*)-**9c**]	*b*, *f*−*h*	B (54%)[r,s]		3.70 (dd, 81.1, 4.7)	60.79
	1	MeS(O)CHEtSSCH=CHMe-(*E*) [(*E*)-**7c**]	*l*	G (43%)	1:1	3.63 (dd, 11.1, 3.3)	72.93
						3.49 (dd, 11.7, 3.6)	74.89
	0	MeSCHEtSSCH=CHMe-(*Z*) [(*Z*)-**9c**]	*j*	B (62%)[r,s]		3.70 (dd, 8.1, 4.9)	61.39
	1	MeS(O)CHEtSSCH=CHMe-(*Z*) [(*Z*)-**7c**]	*l*	G (41%)	1:1	3.63 (dd, 10.7, 3.8)	73.30
						3.49 (dd, 10.4, 4.0)	74.77
	0	(*E*)-MeCH=CHSCHEtSSMe [(*E*)-**9d**]	*c*−*e*	C (43%)		3.86 (dd, 8, 5)	52.31
	1	(*E*)-MeCH=CHS(O)CHEtSSMe [(*E*)-**7d**]	*m*	G (53%)	2:1	3.50 (dd, 10.6, 3.3)	75.61
						3.68 (dd, 10.6, 3.5)	
	0	(*Z*)-MeCH=CHSCHEtSSMe [(*Z*)-**9d**]		C (32%)		3.90 (dd, 8.7, 5.4)	52.30
	1	(*Z*)-MeCH=CHS(O)CHEtSSMe [(*Z*)-**7d**]		G (53%)	2:1	3.57 (dd, 10.7, 3.4)	75.14
						3.60 (dd, 10.5, 3.1)	
	0	CH_2=CHCH$_2$SCHEtSSMe (**9e**)		B (76%)[r]		3.58 (t, 7.0)	74.27
	1	CH_2=CHCH$_2$S(O)CHEtSSMe (**7e**)		G (33%)		3.60 (dd, 11.3, 3.7)	69.93
$C_9H_{20}S_3O_n$	0	PrSCHEtSSPr (**9f**)		B (78%)[r]		3.66 (t, 7.0)	53.74
	1	PrS(O)CHEtSSPr (**7f**)		G (34%)	2:1	3.64 (dd, 10.9, 3.2)	73.89
						3.49 (dd, 10.9, 3.1)	72.78
$C_9H_{18}S_3O_n$	0	(*E*)-PrSCHEtSSCH=CHMe [(*E*)-**9g**]	*d*	B (87%)[r]		3.77 (dd, 8.0, 4.8)	59.04
	1	(*E*)-PrS(O)CHEtSSCH=CHMe [(*E*)-**7g**]	*m*	G (39%)	2:1	3.68 (dd, 11, 3.7)	74.86
						3.52 (dd, 11, 3.9)	72.49
	0	(*Z*)-PrSCHEtSSCH=CHMe [(*Z*)-**9g**]		B (87%)[r]		3.77 (dd, 7.8, 4.5)	59.36
	1	(*Z*)-PrS(O)CHEtSSCH=CHMe [(*Z*)-**7g**]	*m*	G (31%)	1:1	3.64 (dd, 10.7, 4.1)	73.00
						3.50 (dd, 11, 3.7)	72.23
	0	(*E*)-MeCH=CHSCHEtSSPr [(*E*)-**9h**]	*d*, *j*	C (41%)		3.86 (dd, 8, 5)	60.25
	1	(*E*)-MeCH=CHS(O)CHEtSSPr [(*E*)-**7h**]	*n*	G (53%)	2:1	3.67 (dd, 10.7, 3.3)	75.63
						3.48 (dd, 10.7, 3.3)	
	0	(*Z*)-MeCH=CHSCHEtSSPr [(*Z*)-**9h**]		C (44%)		3.86 (dd, 8, 5)	60.25
	1	(*Z*)-MeCH=CHS(O)CHEtSSPr [(*Z*)-**7h**]		G (49%)	3:1	3.53 (dd, 10.7, 3.3)	75.28
						3.66 (dd, 10.7, 3.3)	
$C_9H_{16}S_3O_n$	0	(*E*,*E*)-MeCH=CHSCHEtSSCH=CHMe [(*E*,*E*)-**9i**]	*e*, *i*, *j*	D (25%)		3.83 (dd, 8.2, 5)	59.61
				E (45%)			
	1	(*E*,*E*)-MeCH=CHS(O)CHEtSSCH=CHMe [(*E*,*E*)-**7i**]	*n*, *o*	A (50%)	2:1	3.48 (dd, 11, 3.5)	74.75
						3.66 (dd, 10.5, 3.5)	74.05
	0	(*E*,*Z*)-MeCH=CHSCHEtSSCH=CHMe [(*E*,*Z*)-**9i**]	*e*, *i*, *j*	F (45%)		3.86 (dd, 8.4, 4.7)	60.02
	1	(*E*,*Z*)-MeCH=CHS(O)CHEtSSCH=CHMe [(*E*,*Z*)-**7i**]	*n*	G (49%)	1:1	3.57 (dd, 4.6, 3.4)	74.39
						3.54 (dd, 5.0, 3.5)	74.33

[a] Dubs and Stüssi (1978). [b] Meng et al. (1996). [c] Kuo et al. (1990). [d] Kuo and Ho (1992a). [e] Farkas et al. (1992). [f] Noleau et al. (1991). [g] Dai and Qiu (1992). [h] Naimie et al. (1972). [i] Tokitomo (1995). [j] Kuo and Ho (1992b). [k] Kawakishi and Morimitsu (1988). [l] Morimitsu and Kawakishi (1990). [m] Morimitsu et al. (1992). [n] Bayer et al. (1989). [o] Bayer et al. (1988). [p] Methods of preparations: A, MeSNa plus EtCHClSSR; B, RSH + EtCHClSSR′ + AgOTs; C, (*E*)- or (*Z*)-MeCH=CHSCHEtSAc/K_2CO_3 + RSO_2SR; D, MeCH=CHSLi + MsCl; E, 2MeCH=CHSLi + EtCHClSCl; F, EtCHClSSR + MeCH=CHSLi; G, oxidation with *m*-CPBA. [q] Unless otherwise indicated, yields are after chromatographic purification. [r] Crude yields; products used directly for subsequent step. [s] Earlier nonstereospecific synthesis: Meijer and Vermeer (1974). [t] Chemical Abstracts Service names (provided by the author): methyl 1-(methylthio)propyl disulfide (**9a**); methyl 1-(methylsulfinyl)propyl disulfide (**7a**); 1-(methylthio)propyl propyl disulfide (**9b**); 1-(methylsulfinyl)propyl disulfide (**7b**); 1-(methylthio)propyl (*E*,*Z*)-1-propenyl disulfide [(*E*,*Z*)-**9c**]; 1-(methylsulfinyl)propyl (*E*,*Z*)-1-propenyl disulfide [*E*,*Z*)-**7c**]; methyl (*E*,*Z*)-1-(1-propenylthio)propyl disulfide [(*E*,*Z*)-**9d**]; methyl (*E*,*Z*)-1-(1-propenylsulfinyl)propyl disulfide [(*E*,*Z*)-**7d**]; methyl 1-(2-propenylthio)propyl disulfide (**9e**); methyl 1-(2-propenylsulfinyl)propyl disulfide (**7e**); propyl 1-(propylthio)propyl disulfide (**9f**); propyl 1-(propylsulfinyl)propyl disulfide (**7f**); (*E*,*Z*)-1-propenyl 1-(propylthio)propyl disulfide [(*E*,*Z*)-**9g**]; (*E*,*Z*)-1-propenyl 1-(propylsulfinyl)propyl disulfide [(*E*,*Z*)-**7g**]; (*E*,*Z*)-1-propenyl (*E*)-1-(propenylthio)propyl disulfide [(*E*,*E*)- or (*E*,*Z*)-**9h**]; (*E*,*Z*)-1-(1-propenylsulfinyl)propyl propyl disulfide [(*E*,*Z*)-**7h**]; (*E*,*E*)- or (*E*,*Z*)-1-propenyl (*E*)-1-(propenylthio)propyl disulfide [(*E*,*E*)- or (*E*,*Z*)-**9i**]; (*E*,*E*)- or (*E*,*Z*)-1-propenyl (*E*)-1-(propenylsulfinyl)propyl disulfide [(*E*,*Z*)-**7i**].

equiv of lithium (*E*)- or (*Z*)-1-propenethiolate (Block et al., 1996b). Silver tosylate presumably converts α-chlorodisulfides into α-tosylatodisulfides (not isolated), which undergo nucleophilic displacement more rapidly at carbon than at disulfide sulfur. The technique of chloride activation by silver tosylate proved particularly useful with saturated thiols, which are even more nucleophilic in the anionic form than the delocalized 1-propenethiolate, especially toward the activated S−S bond in a 1-propenyl disulfide. Reaction at low temperature of α-tosylatodisulfides with the less nucleophilic thiol, rather than more nucleophilic thiolate, affords deoxycepaenes, in most cases with minimal contamination by the dimeric disulfides formed as side products in the Dubs and Stüssi (1978) procedure.

Several deoxycepaenes were prepared by base-induced cleavage of 1-[alk(en)ylthio]propyl thioacetates (RSCHEtSAc, **16**) in the presence of thiosulfonates (RSO_2SR') as sulfenylating agents (Scheme 8). Thus, (*E*)- and (*Z*)-1-(propenylthio)propyl thioacetate [(*E*,*Z*)-MeCH=CHSCHEtSAc [(*E*,*Z*)-**16a**] were prepared by treatment of bis(1-chloropropyl) disulfide (**17**; from reaction of **14** with KI (Tjan et al., 1972)] with (*E*)- and (*Z*)-1-propenyllithium at low temperature to give 1-chloropropyl (*E*)- and (*Z*)-1-propenyl sulfide [(*E*,*Z*)-**18**]; this step was followed by displacement of the α-chloro group with thioacetate. Compound (*E*,*Z*)-**18** can also be prepared nonstereospecifically by addition of 1 equiv of HCl to bis(1-propenyl) sulfide (**19**) (Trofimov et al., 1986). The various deoxycepaenes prepared are sum-

Scheme 8



marized in Table 1 along with their conversion to the corresponding cepaenes. All cepaenes and deoxycepaenes were fully characterized by spectroscopic methods. Deoxycepaenes readily disproportionate to symmetrical disulfides (Dubs and Stüssi, 1978). Thus, crude compounds were immediately oxidized to the cepaenes, less prone to disproportionate, and easier to purify by chromatography, due to their polarity.

Properties of Cepaenes and Deoxycepaenes, Including Biological Activity. Table 1 summarizes the nomenclature, methods of synthesis, yields, and isomer mix for each of the cepaenes and deoxycepaenes prepared, along with chemical shift information for the unique carbon (and attached hydrogen) bonded to two sulfurs. The accompanying paper (Calvey et al., 1997) gives MS/MS fragmentation data for MH^+ of **7a**,**c**,**d**,**g**−**i**. Cepaenes are light yellow oils with onion-like odors. As evaluated by "expert flavorists", cepaene **7i** has a slight fresh onion and fruity-melon-like flavor with a taste threshold of 10 ppb, while deoxycepaene **9i** has a green onion, tropical fruit, slightly rubbery flavor with a taste threshold of 5 ppb. Deoxycepaenes have in their ^{1}H NMR spectra a characteristic doublet of doublets (sometimes seen as an apparent triplet) for the SC**H**EtSS center generally found at δ 3.6−3.9, J = 5, 8 Hz; in cepaenes this signal appears at δ 3.5−3.7, J = 3−4, 10−11 Hz. The ^{13}C NMR shifts of the S**C**HEtSS carbon appear at δ 52−61 (deoxycepaenes) and δ 72−76 (cepaenes). In deoxycepaenes, the sulfide MeS ^{1}H (^{13}C) NMR signals appear at ca. δ 2.1−2.2 (24−28); in cepaenes, MeS(O) groups appear at δ 2.5−2.7 (33−37); in both cepaenes or deoxycepaenes, disulfide MeSS groups appear at δ 2.4−2.5 (25−28). All cepaenes display a characteristic S=O band in the IR at 1035−1049 cm^{-1}. There is good agreement between our spectroscopic data for synthetic cepaenes and published data for natural cepaenes.

Several synthetic cepaenes were tested for antithrombotic activity. The ID_{50} (substrate concentration necessary to reduce by 50% the extent of platelet aggregation induced by agonist ADP or collagen compared to the control) of these compounds was determined in vitro using human platelet suspensions. A series of synthetic cepaenes **7** inhibited aggregation induced by 10 μM ADP to the following extent [data given as compound number (μM ID_{50})]: **7a** (68), (*E*,*Z*)-**7d** (141), **7f** (147), (*E*,*Z*)-**7h** (95), (*E*,*E*)-**7i** (125, 173; separable diastereomers), (*Z*,*Z*)-**7i** (104). Analogous data for aggregration induced by collagen (2 μg/mL PRP): (*E*,*E*)-**7i** (26, 22; separable diastereomers), (*Z*,*Z*)-**7i** (19). For collagen, average response of two different blood donors is given. The experimental procedure is given elsewhere (Block et al., 1986). These values, revealing a higher degree of antithrombotic activity than found by us for ajoene from garlic [**8**, R = R′ = allyl; μM ID_{50} 213/166 (ADP) and 243/196 (collagen); (E)-/(Z)-ajoene) (Block et al, 1986)], are in good agreement with published data (Morimitsu and Kawakishi, 1990; Kawakishi and Morimitsu, 1994).

ACKNOWLEDGMENT

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Supporting Information Available: Synthetic procedures for (*Z*)-**9d**, (*E*,*Z*)-**9d**, (*Z*)-**7d**, (*E*,*Z*)-**7d**, (*Z*)-**9h**, (*E*,*Z*)-**9h**, (*Z*)-**7h**, (*E*,*Z*)-**7h**, (*Z*)-**9g**, and (*Z*)-**7g** (3 pages). Ordering information is given on any current masthead page.

LITERATURE CITED

Bayer, T.; Wagner, H.; Wray, V.; Dorsch, W. Inhibitors of Cyclo-oxygenase and Lipoxygenase in Onions. *Lancet* **1988**, 906.

Bayer, T.; Breu, W.; Seligmann, O.; Wray, V.; Wagner, H. Biologically Active Thiosulphinates and α-Sulphinyldisulfides from *Allium cepa*. *Phytochemistry* **1989a**, *28*, 2373−2377.

Bayer, T.; Wagner, H.; Block, E.; Grisoni, S.; Zhao, S. H.; Neszmelyi, A. Zwiebelanes: Novel 2,3-Dimethyl-5,6-dithiabicyclo[2.1.1]hexanes from Onion. *J. Am. Chem. Soc.* **1989b**, *111*, 3085−3086.

Block, E. The Chemistry of Garlic and Onions. *Sci. Am.* **1985**, *252*, 114−119.

Block, E. The Organosulfur Chemistry of the Genus *Allium*—Implications for Organic Sulfur Chemistry. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1135−1178.

Block, E.; Aslam, M. Serendipitous Synthesis of Alkyl Trimethylsilyldithioformates by Trapping of Bis(trimethylsilyl)-thione with Alkanesulfenic Acids. Synthesis of Bis- and Tris-(trimethylsilyl)methanethiols. *Tetrahedron Lett.* **1985**, *26*, 2259−2262.

Block, E.; Bayer, T. (*Z*,*Z*)-*d*,*l*-2,3-Dimethyl-1,4-butanedithial 1,4-Dioxide: A Novel Biologically Active Organosulfur Compound from Onion. Formation of *vic*-Disulfoxides in Onion Extracts. *J. Am. Chem. Soc.* **1990**, *112*, 4584−4585.

Block, E.; O'Connor, J. The Chemistry of Alkyl Thiosulfinate Esters. V. A Novel Synthesis of α-Heteroatom Substituted Disulfides. *J. Am. Chem. Soc.* **1973**, *95*, 5048−5051.

Block, E.; O'Connor, J. The Chemistry of Alkyl Thiosulfinate Esters. VII. Mechanistic Studies and Synthetic Applications. *J. Am. Chem. Soc.* **1974**, *96*, 3929−3944.

Block, E.; Zhao, S.-H. *Allium* Chemistry: Simple Syntheses of Antithrombotic "Cepaenes" from Onion and "Deoxycepaenes" from Oil of Shallot by Reaction of 1-Propenethiolate with Sulfonyl Halides. *J. Org. Chem.* **1992**, *57*, 5815−5817.

Block, E.; Ahmad, S.; Catalfamo, J.; Jain, M. K.; Apitz-Castro, R. Antithrombotic Organosulfur Compounds from Garlic: Structural, Mechanistic and Synthetic Studies. *J. Am. Chem. Soc.* **1986**, *108*, 7045−7055.

Block, E.; Thiruvazhi, M.; Toscano, P. J.; Bayer, T.; Grisoni, S.; Zhao, S.-H. *Allium* Chemistry: Structure, Synthesis, Natural Occurrence in Onion (*Allium cepa*), and Reactions of 2,3-Dimethyl-5,6-dithiabicyclo[2.1.1]hexane *S*-Oxides. *J. Am. Chem. Soc.* **1996a**, *118*, 2790−2798.

Block, E.; Bayer, T.; Naganathan, S.; Zhao, S.-H. *Allium* Chemistry: Synthesis and Sigmatropic Rearrangements of Alk(en)yl 1-Propenyl Disulfide *S*-Oxides from Cut Onion and Garlic. *J. Am. Chem. Soc.* **1996b**, *118*, 2799−2810.

Block, E.; Gillies, J. Z.; Gillies, C. W.; Bazzi, A. A.; Putman, D.; Revelle, L. K.; Wall, A.; Wang, D.; Zhang, X. *Allium* Chemistry: Microwave Spectroscopic Identification, Mech-

anism of Formation, Synthesis, and Reactions of (*E*,*Z*)-Propanethial *S*-Oxide, the Lachrymatory Factor of the Onion (*Allium cepa*). *J. Am. Chem. Soc.* **1996c**, *118*, 7492−7501.

Calvey, E. M.; Matusik, J. E.; White, K. D.; DeOrazio, R.; Sha, D.; Block, E. *Allium* Chemistry: Supercritical Fluid Extraction and LC-APCI-MS of Thiosulfinates and Related Compounds from Homogenates of Garlic, Onion and Ramp. Identification in Garlic and Ramp and Synthesis of 1-Propanesulfinothioic Acid *S*-Allyl Ester. *J. Agric. Food Chem.* **1997**, *45*, 4406−4413.

Dai, B.; Qiu, C. Comparison of Constituents of Essential Oils from Two Species of Ferula in Chinese Traditional Drugs by GC-MS. *Yaowu Fenxi Zazhi* **1992**, *12*, 285−288; *Chem. Abstr.* **1993**, *118*, 45561e.

Dorsch, W.; Schneider, E.; Bayer, T.; Breu, W.; Wagner, H. Anti-Inflammatory Effects of Onions: Inhibition of Chemotaxis of Human Polymorphonuclear Leukocytes by Thiosulfinates and Cepaenes. *Int. Arch. Allergy Appl. Immunol.* **1990**, *92*, 39−42.

Dubs, P.; Stussi, R. Investigation of the Head-Space of Roasted Meat. II. Synthesis of Substituted 2,4,5-Trithiahexanes. *Helv. Chim. Acta* **1978**, *61*, 2351−2359.

Farkas, P.; Hradsky, P.; Kovac, M. Novel Flavor Components Identified in the Steam Distillate of Onion (*Allium cepa*). *Z. Lebensm.-Unters. Forsch.* **1992**, *195*, 459−462.

Fuller, C. E.; Walker, D. G. An Improved Synthesis of Isomerically Pure *cis*-1-Bromopropene. *J. Org. Chem.* **1991**, *56*, 4066−4067.

Hayashi, T.; Konishi, M.; Okamoto, Y.; Kabeta, K.; Kumata, M. Asymmetric Synthesis Catalyzed by Chiral Ferrocenylphosphine-Transition-Metal Complexes. 3. Preparation of Optically Active Allylsilanes by Palladium-Catalyzed Asymmetric Grignard Cross-Coupling. *J. Org. Chem.* **1986**, *51*, 3772−3781.

Kawakishi, S.; Morimitsu, Y. New Inhibitor of Platelet Aggregation in Onion Oil. *Lancet* **1988**, 330.

Kawakishi, S.; Morimitsu, Y. Sulfur Chemistry of Onions and Inhibitory Factors of the Arachidonic Acid Cascade. In *Food Phytochemicals for Cancer Prevention*; ACS Symposium Series 546; Huang, M.-T., Osawa, T., Ho, C.-T., Rosen, R. T., Eds.; American Chemical Society: Washington DC, 1994; pp 84−96.

Kuo, M.-C.; Ho, C. T. Volatile Constituents of the Distilled Oils of Welsh Onions (*Allium fistulosum* L. Variety Maichuon) and Scallions (*Allium fistulosum* L. Variety Caespitosum). *J. Agric. Food Chem.* **1992a**, *40*, 111−117.

Kuo, M.-C.; Ho, C. T. Volatile Constituents of the Solvent Extracts of Welsh Onions (*Allium fistulosum* L. Variety Maichuon) and Scallions (*Allium fistulosum* L. Variety Caespitosum). *J. Agric. Food Chem.* **1992b**, *40*, 1906−1910.

Kuo, M.-C.; Chien, M.; Ho, C. T. Novel Polysulfides Identified in the Volatile Components from Welsh Onions (*Allium fistulosum* L. Variety Maichuon) and Scallions (*Allium fistulosum* L. Variety Caespitosum). *J. Agric. Food Chem.* **1990**, *38*, 1378−1381.

Meijer, J.; Vermeer, P. Synthesis of 1-(Methylthio)propyl Propenyl Disulfide and *sec*-Butyl 3-(Methylthio)allyl Disulfide, Two Pesticides from Asafoetida. *Recl. Trav. Chim Pays-Bas* **1974**, *93*, 242.

Meng, Z.; Wang, Y.; Cao, Y.; Ji, J. Study on Volatile Compounds of *Allium tuberosum*. *Zhongguo Yaoke Daxue Xuebao* **1996**, *27*, 139−140; *Chem. Abstr.* **1996**, *125*, 326880s.

Morimitsu, Y.; Kawakishi, S. Inhibitors of Platelet Aggregation from Onion. *Phytochemistry* **1990**, *29*, 3435−3439.

Morimitsu, Y.; Kawakishi, S. Optical Resolution of 1-(Methylsulfinyl)propyl Alk(en)yl Disulfides, Inhibitors of Platelet Aggregation Isolated from Onion. *Agric. Biol. Chem.* **1991**, *55*, 889−890.

Morimitsu, Y.; Morioka, Y.; Kawakishi, S. Inhibitors of Platelet Aggregation Generated from Mixtures of Allium Species and/or *S*-Alk(en)yl-L-Cysteine Sulfoxides. *J. Agric. Food Chem.* **1992**, *40*, 368−372.

Naimie, H.; Samek, Z.; Dolejs, L.; Rehacek, Z. About the Volatile Components of Asafoetida; Two New Natural Sulfur Compounds with Pesticidal Activity. *Collect. Czech. Chem. Commun.* **1972**, *37*, 1166−1177.

Noleau, I.; Hubert, R.; Peyroux, A. S. Volatile Compounds in Leek and Asafoetida. *J. Essent. Oil. Res.* **1991**, *3*, 241−256.

Sendl, A.; Wagner, H. Isolation and Identification of Homologues of Ajoene and Alliin from Bulb-Extracts of *Allium ursinum*. *Planta Med.* **1991**, *57*, 361−362.

Tjan, S. B.; Haakman, J. C.; Teunis, C. J.; Peer, H. G. Synthesis of 3,5-Dialkyl-1,2,4-trithiolanes. Assignment of Configuration and Conformational Analysis by PMR. *Tetrahedron* **1972**, *28*, 3489−3500.

Tokitomo, Y. Flavor Constituents of Roasted Onions of Different Cultivars, and Comparison of Their Aroma Patterns. *Nippon Shokuhin Kagaku Kogaku Kaishi* **1995**, *42*, 1003−1011; *Chem. Abstr.* **1996**, *124*, 115785f.

Trofimov, B. A.; Amosova, S. V.; Musorin, G. K.; Kalabin, G. A.; Nosyreva, V. V.; Al'pert, M. L. Di(1-propenyl) Sulfide from Diallyl Sulfide via Prototropic Isomerization in Superbase Systems. *Sulfur Lett.* **1986**, *4*, 67−72.

Wagner, H.; Dorsch, W.; Bayer, T.; Breu, W.; Willer, F. Antiasthmatic Effects of Onions: Inhibition of 5-Lipoxygenase and Cyclooxygenase in vitro by Thiosulfinates and "Cepaenes". *Prostaglandins, Leukotrienes Essent. Fatty Acids* **1990**, *39*, 59−62.

Yagami, M.; Kawakishi, S.; Namiki, M. Identification of Intermediates in the Formation of Onion Flavor. *Agric. Biol. Chem.* **1980**, *44*, 2533−2538.

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