Opening of Thiiranes: Preparation of Orthogonal Protected 2-Thioglyceraldehyde

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Treatment of acrolein diethyl acetal sulfide **8** with methanesulfenyl bromide at low temperature results in an efficient thiirane ring opening to a halo disulfide **9**. The bromine in this halo disulfide is easily substituted by silver acetate, sodium azide, sodium iodide, and silver nitrate. Treatment of **9** with tetrabutylammonium acetate yields a novel dehydrohalogenation product **12**. Silica gel converts bromide **9** into a disulfide-substituted version of acrolein **15**. The orthogonal-protected version of 2-thioglyceraldehyde **13** can be deprotected to a useful form of this aldehyde.

Introduction

The introduction of sulfur as a heteroatom in many carbohydrates has shown to be an effective technique for imparting significant biological activity.[1] Their function as enzyme inhibitors, and the antibacterial, antineoplastic, and antiviral activity for a number of sulfur analogues of deoxyribonucleosides is notable.[2,3] It is surprising, given the recent flurry of synthetic activity to prepare derivatives of 4-thio-2-deoxyribose,[3] that a preparation of the simplest member of the thiocarbohydrate family, 2-thioglyceraldehyde, has not been reported in the literature. Nearly 30 years ago, there were, however, a few reports of its use in the literature, one reporting antitumor activity in animal test studies.[4] With respect to the above, and in light of our interest in enzyme-catalyzed reactions in organic chemistry, we required an efficient procedure for the preparation of an orthogonal-protected 2-thioaldehyde derivative.

In this paper, we report an efficient new procedure for the thiirane ring opening, a procedure which directly produces a halo disulfide. The easy transformation of the halo disulfide into a fully protected version of 2-thioglyceraldehyde, and its conversion to a usable form of 2-thioglyceraldehyde, is described. We also report on the preparation of additional analogues, and describe some of the chemistry that we investigated.

Results and Discussion

Our initial strategy, shown in Scheme 1, focused on preparation of this molecule's framework protected as acetal and acetate,[5] with subsequent incorporation of the thiol functionality at position-2, by either Mitsunobu conditions or direct tosylate displacement. Unfortunately, neither of these straightforward procedures produced any reaction when thiolacetic acid, ziram, or triphenylsilanethiol was used in a Mitsunobu reaction[6] with alcohol **2** or their lithium salts were used as nucleophiles for direct tosylate substitution of **3**.

Alternatively, the Mitsunobu-like intermediate suggested in the epoxide to chlorohydrin method of Palumbo et al.[7] was thought to present an alternate approach for introduction of the thiol functionality, as shown in Scheme 2. Unfortunately all attempts to directly replace the triphenylphosphene oxide of presumed intermediate **5**, by a sulfur nucleophile, failed. The use of strong nucleophiles such as lithium benzylmercaptoate resulted in halide substitution only. When either thiolacetic acid with or without triethylamine or triphenylsilanethiol/triethylamine was used as nucleophile, only chlorohydrin **6** was produced. Surprisingly, however, when triphenylsilanethiol was used as a nucleophile without triethylamine, the triphenylsilyl-protected chlorohydrin **7** was formed in high yield, accompanied by triphenylphosphine sulfide.

Electrophilic or nucleophilic thiirane ring opening presents a potentially expedient route to a protected

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(1) Witczak, Z. J. *Curr. Med. Chem.* **1999**, *6*, 165−178.

(2) Zoller, H. *Handbook of Enzyme Inhibitors*; Wiley/VCH: Weinheim, 1999; Part A/1+2, Part B/1+2. Hideya, Y.; Hindsgaul, O.; Palcic, M. M. *J. Am. Chem. Soc.* **1992**, *114*, 5891−5892. Durieux, I.; Martel, M. B.; Got, R. *Glycoconjugate J.* **1990**, *7*, 183−192. Baubichon-Cortay, J.; Broquet, P.; George, P.; Louisot, P. *Glycoconjugate J.* **1989**, *6*, 115−127.

(3) Kim, H. O.; Jeong, L. S.; Lee, S. N.; Yoo, S. J.; Moon, H. R.; Kim, K. S.; Chun, M. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, *9*, 1327−1329. Wang, Y.; Inguaggiato, G.; Jasamai, M.; Shah, M.; Hughes, D.; Slater, M.; Simons, C. *Bioorg. Med. Chem.* **1999**, *7*, 481−487. Wirsching, J.; Voss, J. *Eur. J. Org. Chem.* **1938**, *3*, 691−696. Inguaggiato, G. Hughes, D.; De Clercq, E.; Balzarini, J.; Simons, C. *Antiviral Chem. Chemother.* **1999**, *10*, 241−249. Messini, L.; Tiwari, K. N.; Montgomery, J. A.; Secrist, J. A., III. *Nucleosides Nucleotides* **1999**, *18*, 683−685. Jeong, L. S.; Moon, Hyung, R.; Yoo, S. J.; Lee, S. N.; Kim, H.-D.; Chun, M. W. *Nucleosides Nucleotides* **1999**, *18*, 571−572. Inguaggiato, G.; Jasamai, M.; Smith, J. E.; Slater, M.; Simons, C. *Nucleosides Nucleotides* **1999**, *18*, 457−467. Wang, Y.; Inguaggiato, G.; Jasamai, M.; Shah, M.; Hughes, D.; Slater, M.; Simons, C. *Bioorg. Med. Chem.* **1999**, *7*, 481−487. Yoshimura, Y.; Endo, M.; Miura, S.; Sakata, S. *J. Org. Chem.* **1999**, *64*, 7912−7920. Falconer, R. A.; Jablonkai, I.; Toth, I. *Tetrahedron Lett.* **1999**, *40*, 8663−8666.

(4) Stevenes, J. P., and Co., Inc. GB Patent 01,092, 961, 1967; *Chem. Abstr.* **1968**, *68*, 22699, Apple, M. A.; Greenberg, D. M. *Cancer Chemother. Rep.* **1969**, *53*, 195−198. Broome, J. D.; Jeng, M. W. *J. Exp. Med.* **1973**, *138*, 574−592.

(5) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 3791−3793.

(6) Volante, R. P. *Tetrahedron Lett.* **1981**, *22*, 3119−3122. Rollin, P. *Tetrahedron Lett.* **1986**, *27*, 4169−4170. Besson, T.; Neirabeyeh, M. A.; Viaud, M.-C.; Rollin, P. *Synth. Commun.* **1990**, 1631−1639. Gareau, Y.; Brittain, J. *Tetrahedron Lett.* **1993**, *34*, 3363−3366.

(7) Palumbo, G.; Ferreri, C. Caputo, R. *Tetrahedron Lett.* **1983**, *24*, 1307−1310.

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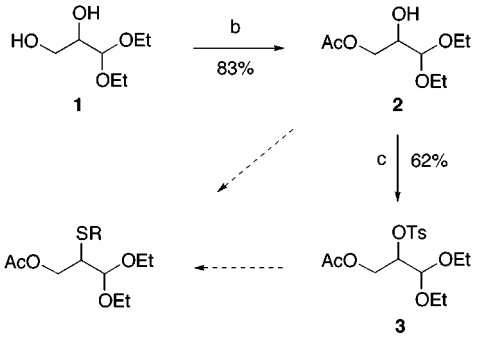
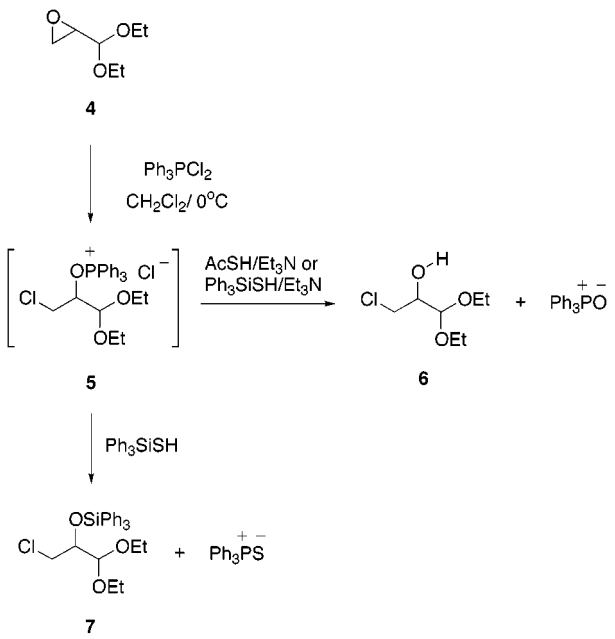
Scheme 1[a]

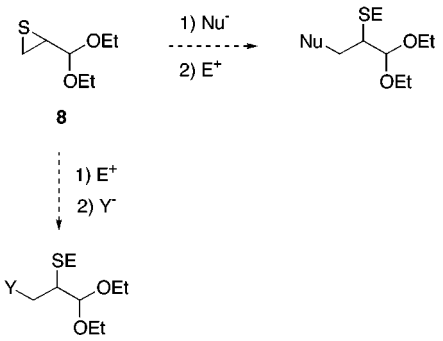


[a] Reagents and conditions: (b) AcCl, collidine, CH_2Cl_2, −78 °C, 3 h; (c) TsCl, DMAP, CH_2Cl_2, rt/5 days.

Scheme 2



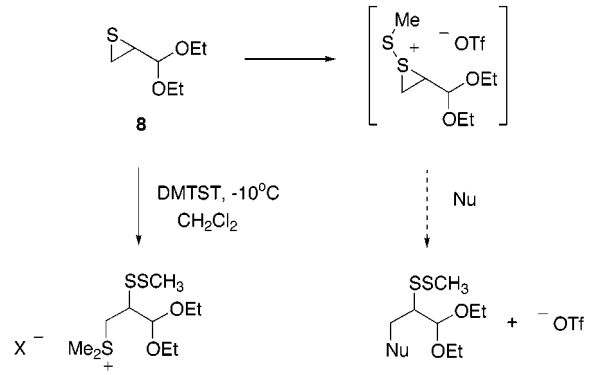
Scheme 3



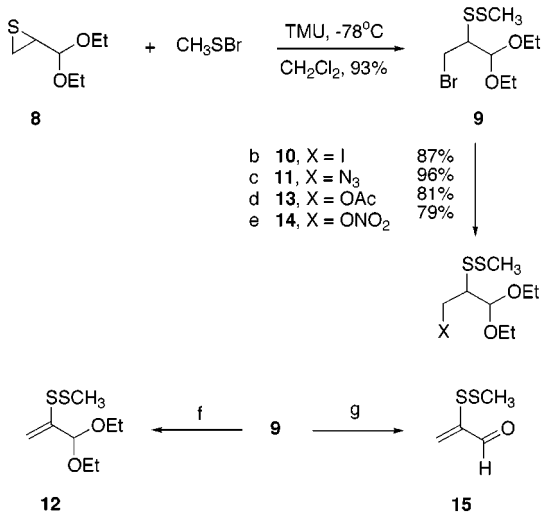
2-thioglyceraldehyde as shown in Scheme 3. Unfortunately, many of the methods that are available are incompatible with an aldehyde or protected aldehyde functional group.[8] Lithium hydroxide and lithium trimethylsilanoate were unreactive nucleophiles toward thiirane **8**, while 2-nitrobenzyl alcohol and phosphate gave only polymerization. Electophilic reagents such as trimethylsilyl acetate and CAN gave respectively, no reaction and polymerization. We were encouraged to find

(8) Iranpoor, N.; Owji, J. *Tetrahedron Lett.* **1991**, *47*, 149−154. Sander, M. *Chem. Rev.* **1966**, *66*, 297−339.

Scheme 4



Scheme 5[a]



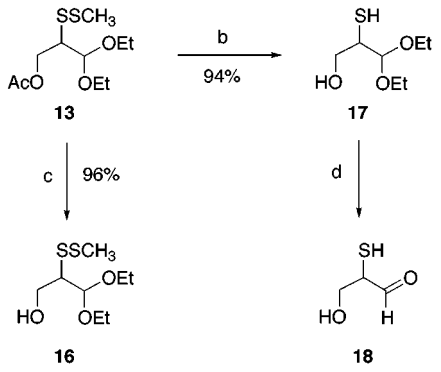
[a] Reagents and conditions: (b) NaI, acetone, reflux, 90 min; (c) NaN_3, DMSO, 17 h; (d) AgOAc, ether, 72 h; (e) $AgNO_3$, ether, 72 h; (f) Bu_4NOAc, THF, reflux, 45 min, quantitative; (g) silica gel.

that the thioglycoside coupling reagent, DMTST,[9] expediently opened the thiirane without disturbing the acetal protecting group, as shown in Scheme 4. Unfortunately, all attempts to inhibit the incorporation of methyl sulfide from the reagent itself and introduce an alternate nucleophile were unsuccessful. Whereas triphenylsilanthiol was not a competitive nucleophile, stronger nucleophiles such as *p*-methoxybenzene and lithium trimethylsilanoate destroyed the reagent, returning the thiirane unchanged.

We are pleased to report that methanesulfenyl bromide, a reagent easily prepared by treatment of methyl disulfide with bromine, efficiently opens thiirane **8**, producing a versatile brominated disulfide **9**, which can be converted to a fully protected version of 2-thioglyceraldehyde, as shown in Scheme 5. The bromine in **9** can easily be substituted by iodide,[10] azide,[11] nitrate,[12] and acetate.[13] Additionally, hydrogen bromide can be eliminated with tetrabutylammonium acetate to produce a

(9) Dasgupta, F.; Garegg, P. J. *Carbohydrate Res.* **1988**, *177*, c13−c17.
(10) Easton, C. J..; Merrett, M. C. *Tetrahedron* **1997**, *53*, 1151−1156.
(11) Alvarez, S. G.; Alvarez, M. T. *Synthesis* **1997**, 413−414.
(12) Castedo, L.; Marcos, C. F.; Tojo, G. *Synth Commun.* **1995**, *25*, 1729−1739.
(13) Balsamo, A.; Benvenuti, M.; Lapucci, A.; Macchia, B.; Nencetti, S.; Rossello, A.; Macchia, F.; Domiano, P.; Dradi, E. *J. Org. Chem.* **1991**, *56*, 2148−2153. Rosenau, T.; Habicher, W. D. *J. Prakt. Chem./Chem.-Ztg.* **1996**, *338*, 647−653.

Scheme 6[a]



[a] Reagents and conditions: (b) $LiAlH_4$, ether, rt, 15 h; (c) $NaOCH_3/CH_3OH$, rt, 4 h; (d) H_2O, HCl, 50 °C, 4 h.

novel vinyl disulfide **12**. Attempted purification of bromide **9** on silica gel produces predominantly a disulfide version of acrolein **15**, arising from hydrolysis and dehydrohalogenation. An analytical sample of bromide **9** is, however, effectively received by chromatography on Florisil.

The orthogonal-protected 2-thioglyceraldehyde derivative **13** can be deprotected by acetate hydrolysis, giving alcohol **16**, or alternatively the disulfide and acetate can be removed simultaneously at room temperature with lithium aluminum hydride in ether,[14] giving 2-thioglyceraldehyde diethylacetal **17**; Scheme 6. When this reduction is performed in refluxing THF, and to a lesser extent in refluxing ether, an alternate reduction product is formed that appears to incorporate aluminum. Additionally, if the hydride reduction reaction is quenched with water, then acidified, a significant amount of mixed disulfide is formed. The quench is favorably accomplished with cold saturated sodium hydrogen sulfate. Magnesium metal in methanol is also an effective reagent for the acetate hydrolysis and, to a lesser extent, for the disulfide to thiol conversion.[15] This reagent system produces first alcohol **16**, which then forms product **17** contaminated by mixed disulfides. When **17** is heated to 50 °C in water with the pH adjusted to 1, the acetal is quickly cleaved.[16] Although the formation of the aldehyde can be detected by ^{1}H NMR, attempts to isolate this material generates a highly insoluble higher order compound.[17]

For a clean opening of the thiirane ring, we have found that the methanesulfenyl bromide is best prepared with a 3:1 ratio of methyl disulfide and bromine. This reagent can be stored without a noticeable decrease in reactivity for a period of 4 weeks. When a 1:1 ratio is used, bromide **9** is produced along with a product that appears to arise from the direct opening of the thiirane by molecular bromine.[18] Methanesulfenyl bromide, produced as a 1:1 ratio between methyl disulfide and bromine, has been used with silver triflate as a coupling reagent for carbohydrates.[19] When it is preformed, then administered to the thiosugar, a large excess, 6−10 equiv, of the reagent is required to achieve successful coupling. This is in contrast to the procedure where silver triflate is added directly to the carbohydrate and methanesulfenyl bromide, where a slight excess of the reagent is required. We suspect that the equilibrium between methyl disulfide and bromine needs to be pushed forward with the 3:1 ratio, and suspect that for carbohydrate couplings, this ratio may be advantageous.

Summary

In summary we have shown that the methanesulfenyl bromide method of opening thiiranes, is highly successful for the introduction of a sulfur atom next to the aldehyde functional group, as demonstrated here in a synthesis of an orthogonal protected version of the smallest member of the thiosugar family, 2-thioglyceraldehyde. The combined functionality of the α-thioaldehyde is one that has presented itself only a few times in the chemical literature.[20] We suspect that this method will find general applicability in the future, as we have begun to observe success with other thiiranes. We are continuing to investigate the generality of this procedure and will report on that soon. Additionally, we suspect that the differentially substituted molecules we have reported here, will find applicability in synthetic applications. Our own efforts to utilize these materials in enzymatic reactions are underway.

Experimental Section

General Methods. Dichloromethane was distilled from CaH_2. THF and diethyl ether were distilled from sodium metal and benzophenone. Commercially available anhydrous acetone, CH_3OH, and DMSO were used. Molecular sieves (4 Å), obtained as an activated powder (average particle size, 2−3 μm), were further activated overnight, at 120 °C. Reagents of commercial quality were purchased and used without further purification unless otherwise stated. Column chromatography was performed on silica gel 60 Geduran (35−75 μm, EM Science) and Florisil (TLC grade). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 250 and 62.9 MHz, respectively, using TMS and $CDCl_3$ as respective references. Mass spectra were obtained as gc/ms, electrospray and MALDITOF. High-resolution mass spectra were obtained at The Scripps Research Institute and at the Mass Spectrometry Facility in the Department of Chemistry, University of California, Santa Barbara, CA. Elemental analyses were performed in the Chemistry Department at The Scripps Research Institute.

Methanesulfenyl Bromide. Into an oven-dried 5 mL volumetric flask containing 2 mL of anhydrous 1,2-dichloroethane was added bromine (0.9008 g, 5.636 mmol) followed by freshly distilled methyl disulfide (1.5 mL, 1.57 g, 16.66 mmol). The remaining volume was adjusted to 5 mL with more anhydrous 1,2-dichloroethane. The flask was sealed from air and light and then stirred for 4 h. The resultant 2.25 M solution was used immediately, or successfully stored at −30 °C for up to 1 month, without any appreciable change in reactivity.

1-Bromo-3,3-diethoxy-2-(methyldithio)propane (9). Under an atmosphere of argon, thiirane **8**[21] (0.1985 g, 1.223 mmol) was added to a dry 25 mL round-bottom flask containing a

(14) Nishimura, H.; Yamauchi, O.; Takamatsu, H.; *Chem. Pharm. Bull.* **1964**, *12*, 1004. Eliel, E. L.; Rao, V. S.; Smith, S.; Hutchins, R. O. *J. Org. Chem.* **1975**, *40*, 524−526.

(15) Sridhar, M.; Vadivel, S. K.; Bhalerao, U. T. *Synth. Commun.* **1997**, *27*, 1347−1350.

(16) Chou, W.-C.; Chen, L.; Fang, J.-M.; Wong, C.-H. *J. Am. Chem. Soc.* **1994**, *116*, 6191−6194.

(17) 2-Thioglyceraldehyde is listed in the Aldrich Rare Chemicals catalog. Their material behaves identically to our **18**. The elemental analysis is consistent for $C_3H_6O_2S$ (Anal. Calcd for $C_3H_6O_2S$: C, 33.95; H, 5.70. Found: C, 33.92; H, 5.59), and the material is insoluble in $CDCl_3$, acetone-d_6, DMSO-d_6, and D_2O.

(18) Stewart, J. M.; Cordts, H. P. *J. Am. Chem. Soc.* **1952**, *74*, 5880. Epstein, G. Y.; Usov, I. A.; Ivin, S. Z. *Zh. Obshch. Khim.* **1964**, *34*, 1948.

(19) Reference 9.

(20) Bourdon, F.; Ripoll, J.-L.; Vallee, Y. *Tetrahedron Lett.* **1990**, *43*, 6183−6184. Giles, H. G.; Marty, R. A.; De Mayo, P. *Can. J. Chem.* **1976**, *54*, 534. Yoshida, J.-I.; Nakatani, S.; Isoe, S. *J. Org. Chem.* **1993**, *58*, 4855−4865.

magnetic stir-bar and septum. Anhydrous dichloromethane (10 mL) was added followed by 1,1,3,3-tetramethylurea (0.18 mL, 0.175 g, 1.50 mmol) and powdered 4 Å molecular sieves (1.0 g). The solution was cooled to −78 °C, then treated by the dropwise addition of methanesulfenyl bromide (0.66 mL, 1.485 mmol, 2.25 M). The solution was allowed to stir for an additional 25 min at −78 °C, warmed to 0 °C, filtered through a pad of diatomaceous earth, then concentrated at the rotary evaporator. The resulting oil was dissolved in ether (10 mL) and water (15 mL) and then extracted twice with 20 mL of ether. The combined organic layer was then washed twice with water (15 mL), once with brine (10 mL), dried ($MgSO_4$), and concentrated to 0.330 g (93%) of the desired product **9**, as a colorless oil. An analytical sample was obtained by purification on Florisil (5% EtOAc/95% hexane eluent): ^{1}H NMR ($CDCl_3$) δ 4.74 (d, J = 4.4 Hz, 1H), 3.81−3.55 (m, 6H), 3.22−3.16 (m 1H), 2.46 (s, 3H), 1.26 (t, J = 6.9 Hz, 3 H), 1.24 (t, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 102.32, 64.24, 64.12, 57.77, 32.53, 23.71, 15.27, 15.1; mass spectrum $(M)^+$ *m/e* 288/290; HRMS calcd for $C_8H_{17}BrO_2S_2$ $(M)^+$ *m/e* 287.9853, measured 287.9855.

1,1-Diethoxy-3-iodo-2-(methyldithio)-propane (10). Into a dry 25 mL round-bottom flask under argon, was combined the bromide **9** (0.0257 g, 0.0888 mmol), sodium iodide (0.038 g, 0.254 mmol) and 5 mL acetone. This mixture was refluxed 1.5 h, cooled, and concentrated. The oil was diluted with water (10 mL) then extracted twice with 15 mL ether. The organic layer was washed once with water (10 mL), once with brine (10 mL), dried ($MgSO_4$), and concentrated to 0.026 g (87%) of the desired product **10**, as a colorless oil. An analytical sample was obtained by purification on silica gel (3% EtOAc/97% hexane eluent): ^{1}H NMR ($CDCl_3$) δ 4.70 (d, J = 4.4 Hz, 1H), 3.81−3.57 (m, 6H), 3.09−3.02 (m 1H), 2.46 (s, 3H), 1.26 (t, J = 6.9 Hz, 3 H), 1.24 (t, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 103.35, 64.18, 64.12, 57.44, 23.74, 15.30, 15.18, 6.80; mass spectrum $(M)^+$ *m/e* 336; HRMS calcd for $C_8H_{17}IO_2S_2$ $(M)^+$ *m/e* 335.9715, measured 335.9720. Anal. Calcd for $C_8H_{17}IO_2S_2$: C, 28.54; H, 5.10. Found: C, 28.34; H, 5.39.

1-Azido-3,3-diethoxy-2-(methyldithio)propane (11). Into a dry 25 mL round-bottom flask under argon was combined the bromide **9** (0.156 g, 0.539 mmol) and sodium azide (0.0393 g, 0.6045 mmol) with anhydrous DMSO (8 mL). The mixture was sealed from the air and stirred for a period of 17 h. Water (5 mL) was added, and then the mixture was extracted three times with ether (10 mL). The organic layer was washed twice with water (10 mL) and once with brine (10 mL), dried ($MgSO_4$), and concentrated to 0.130 g (96%) of the desired product **11**, as a colorless oil. An analytical sample was obtained by purification on silica (50% CH_2Cl_2/50% hexane eluent): ^{1}H NMR ($CDCl_3$) δ 4.61 (d, J = 4.8 Hz, 1H), 3.80−3.54 (m, 6H), 3.07−3.02 (m 1H), 2.46 (s, 3H), 1.24 (t, J = 6.9 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 102.32, 64.09, 63.33, 55.27, 50.50, 23.71, 15.10; mass spectrum $(M)^+$ *m/e* 251. Anal. Calcd for $C_8H_{17}N_3O_2S_2$: C, 38.22; H, 6.82; N, 16.72. Found: C, 38.52; H, 6.60; N, 16.57.

3,3-Diethoxy-2-(methyldithio)propene (12). Into a dry 25 mL round-bottom flask under argon was combined the bromide **9** (0.160 g, 0.553 mmol), tetrabutylammonium acetate (0.276 g, 0.914 mmol), and 15 mL of anhydrous THF. The mixture was refluxed for 45 min, cooled, poured into saturated sodium bicarbonate (10 mL), and extracted twice with ether (15 mL). The organic layer was washed twice with water (10 mL) and once with brine (10 mL), dried ($MgSO_4$), and concentrated to 0.115 g (100%) of the desired product **12**, as a colorless oil. An analytical sample was obtained by purification on Florisil (3% EtOAc/97% hexane eluent): ^{1}H NMR ($CDCl_3$) δ 5.69 (s 1H), 5.64 (s 1H), 5.07 (s 1H), 3.69−3.47 (m, 4H), 2.37 (s, 3H), 1.24 (t, J = 6.9 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 111.97, 100.62, 61.59, 21.62, 15.03; mass spectrum $(M)^+$ *m/e* 208. Anal. Calcd for $C_8H_{16}O_2S_2$: C, 46.12; H, 7.74. Found: C, 45.98; H, 7.74.

3,3-Diethoxy-2-(methyldithio)propan-1-ol Acetate (13). Into a dry 25 mL round-bottom flask under argon was combined the bromide **9** (1.60 g, 5.532 mmol), silver acetate (1.351 g, 8.094 mmol), and ether (10 mL). The mixture was stirred under argon for 3 days, allowing the mixture to go completely dry.[22] Ether (20 mL) was added along with activated charcoal. The mixture was filtered through diatomaceous earth and then concentrated to 1.20 g (81%) of the desired product **13**, as a colorless oil. An analytical sample was obtained by purification on silica (15% EtOAc/85% hexane eluent): ^{1}H NMR ($CDCl_3$) δ 4.62 (d, J = 5.1 Hz, 1H), 4.47 (dd, J = 11.7, 5.1 Hz, 1H), 4.32 (dd, J = 11.7, 6.5 Hz, 1H) 3.79−3.50 (m, 4H), 3.23−3.16 (m 1H), 2.43 (s, 3H), 2.09 (s, 3H), 1.24 (t, J = 6.9 Hz, 3 H), 1.22 (t, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.67, 102.07, 63.50, 63.12, 62.71, 54.18, 23.80, 20.80, 15.06; mass spectrum $(M)^+$ *m/e* 268; HRMS calcd for $C_{10}H_{20}O_4S_2$ $(M)^+$ *m/e* 268.0803, measured 268.0800. Anal. Calcd for $C_{10}H_{20}O_4S_2$: C, 44.75; H, 7.51. Found: C, 44.44; H, 7.66.

3,3-Diethoxy-2-(methyldithio)propan-1-ol Nitrate (14). Into a dry 25 mL round-bottom flask under argon were combined the bromide **9** (0.0407 g, 0.1407 mmol), acetone (3 mL), water (0.25 mL), and silver nitrate (0.0294 g, 0.173 mmol). The mixture was stirred under argon for a period of 3 days, concentrated, and then diluted with ether (20 mL). The ether layer was treated with $MgSO_4$ and then activated charcoal. After filtration through diatomaceous earth and concentration, 0.030 g (80%) of the desired product **14** was obtained, as a colorless oil. An analytical sample was obtained by purification on silica (25% EtOAc/75% hexane eluent: ^{1}H NMR ($CDCl_3$) δ 4.89 (dd, J = 11.7, 5.8 Hz, 1H), 4.70 (dd, J = 11.7, 7.1 Hz, 1H), 4.64 (d, J = 4.4 Hz, 1H), 3.80−3.47 (m, 4H), 3.27−3.20 (m 1H), 2.46 (s, 3H), 1.24 (t, J = 6.9 Hz, 3 H), 1.23 (t, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 102.29, 71.12, 64.42, 63.68, 62.71, 53.06, 15.09; mass spectrum $(M)^+$ *m/e* 271; HRMS calcd for $C_8H_{17}NO_5S_2$ $(M)^+$ *m/e* 271.0548, measured 271.0544. Anal. Calcd for $C_8H_{17}NO_5S_2$: C, 35.41; H, 6.31; N, 5.16. Found: C, 35.60; H, 6.51; N, 4.78.

3,3-Diethoxy-2-(methyldithio)-propan-1-ol (16). Into a dry 25 mL round-bottom flask under argon were combined acetate **13** (0.2005 g, 0.747 mmol) and 10 mL of dry methanol. Two drops of a 25% solution of $NaOCH_3/CH_3OH$ were added, and the resultant mixture was stirred for 4 h at room temperature. The volatiles were removed, and then ether (10 mL) and $NaHSO_4$ (10 mL, saturated) were added. The resultant was extracted twice with ether (15 mL). The organic layer was washed twice with water (10 mL), once with brine (10 mL), dried ($MgSO_4$) and concentrated to 0.162 g (96%) of the desired product **16**, as a colorless oil. An analytical sample was obtained by purification on silica (30% EtOAc/70% hexane eluent): ^{1}H NMR ($CDCl_3$) δ 4.69 (d, J = 5.5 Hz, 1H), 3.94 (m, 2H), 3.84−3.56 (m, 4H), 3.13−3.07 (m 1H), 2.75 (m, 1H), 2.45 (s, 3H), 1.25 (t, J = 6.9 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 103.85, 64.50, 63.00, 61.88, 55.74, 24.00, 15.24; mass spectrum $(M)^+$ *m/e* 226; HRMS calcd for $C_8H_{18}O_3S_2$ $(M + Na)^+$ *m/e* 249.0590, measured 249.0591.

3,3-Diethoxy-2-mercaptopropan-1-ol (17). Into a dry 25 mL round-bottom flask under argon was combined acetate **13** (0.043 g, 0.160 mmol) and 8 mL of anhydrous ether. The mixture was cooled to −10 °C in an ice/methanol bath and then treated with lithium aluminum hydride (0.026 g, 0.685 mmol). After being stirred at room temperature overnight, the mixture was returned to −10 °C and quenched by the dropwise addition of $NaHSO_4$ (2 mL, saturated). The resultant mixture was extracted twice with ether (15 mL). The organic layer was washed twice with water (10 mL), dried ($MgSO_4$), and concentrated to 0.027 g (94%) of the desired product **17**, as a colorless oil. An analytical sample (17) was obtained by purification on Florisil (10% EtOAc/90% hexane eluent): ^{1}H NMR ($CDCl_3$) δ 4.57 (d, J = 5.1 Hz, 1H), 3.87−3.45 (m, 6H), 3.12−3.03 (m 1H), 2.75 (m, 1H), 1.74 (d, J = 9.1 Hz, 1H), 1.25 (t, J = 6.9 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 105.82, 64.68, 64.21, 63.27, 43.86, 15.27, 15.18; mass spectrum for the disulfide (M

(21) Pederson, R. L.; Liu, K. K. C.; Rutan, J. F.; Chen, L.; Wong, C.-H. *J. Org. Chem.* **1990**, *55*, 4897−4901.

(22) When the reaction volume was not allowed to decrease by evaporation of the ether, the starting material was returned unchanged.

+ Na)$^+$ *m/e* 381; HRMS calcd for $C_{14}H_{30}O_6S_2$ (M + Na)$^+$ *m/e* 381.1376, measured 381.1390.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **9**−**14**, **16**, and **17** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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