Novel Rearrangements of 2,3-Dimercapto-1-propanol Derivatives: Formation of Dialkyl Sulfide, Dialkyl Disulfide, and 1,2,3-Tris(alkylthio)propane

Chi Wi Ong,* Yi Meen Chou, and Junn Nan Wang

Department of Chemistry, National Sun Yat Sen University, Kaoshiung, Taiwan 804

Received April 29, 1996[⊗]

The base alkylation of 2,3-dimercapto-1-propanol with alkyl halides leads in good yield to 2,3-bis-(alkylthio)-1-propanol and dialkyl sulfide. The reaction of 2,3-bis(alkylthio)-1-propanol with catalytic concentrated sulfuric acid proceeds with rearrangement to give 1,2,3-tris(alkylthio)propane and dialkyl disulfide. The rearrangement reaction takes place through a common intermediate thiaranium intermediate **8**.

Introduction

The chemical compound 2,3-dimercapto-1-propanol is well known for its ability to serve as a ligand for metals.[1] It has been used an antidote for heavy metal poisoning because it forms stable complexes with the mercapto groups and thus facilitates excretion from the body. 2,3-Dimercapto-1-propanol is also effective in reactivating enzymes that have been deactivated by thiol reagents. Recently, 2,3-dimercapto-1-propanol has been found to inhibit transactivation directed by *tat* protein, which is a metal-containing transcriptional transactivating factor in HIV.[2]

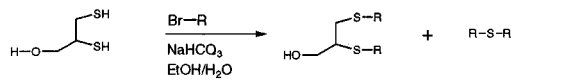
In the course of developing the synthesis of new metal-sequestering agents based on 2,3-dimercapto-1-propanol derivatives, we have uncovered a series of novel rearrangement reactions that lead to the formation of dialkyl sulfide, dialkyl disulfide, and 1,2,3-tris(alkylthio)propane. We report herein a detailed study of these amazingly diverse rearrangement reactions of 2,3-dimercapto-1-propanol with a view of establishing the generality of this process and the influence of substituent on the product distributions. There have been no previous reports on this type of rearrangement, although it has been known that commercially available 2,3-dimercapto-1-propanol contains a minute trace of 1,2,3-tris(alkylthio)propane.[3]

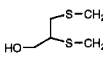
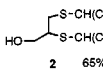
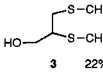
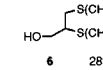
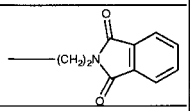
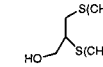
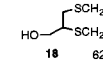
Results and Discussion

The conversion of 2,3-dimercapto-1-propanol to the corresponding *S,S′*-dialkyl derivatives proceeded smoothly upon the addition of alkyl bromide in the presence of sodium bicarbonate and ethanol/water mixture as solvent.[4] In this manner, 2,3-bis(ethylthio)-1-propanol (**1**) and 2,3-bis(isopropyl)-1-propanol **(2**) were obtained as the sole products in good yields. In contrast, the reaction with benzyl bromide was found to give both 2,3-bis-(benzylthio)-1-propanol (**3**) and dibenzyl sulfide (**4**) as the major products (Table 1). The observation of **4** as the major product can be explained by the initial attack of a sulfur atom in **3** with another molecule of benzyl bromide to give the alkylsulfonium intermediate, which then undergoes elimination of dialkyl sulfide and thiaranium intermediate **5**. We noted that the same thiaranium intermediate **5** was formed irrespective of the regioselectivity in S-alkylation (Scheme 1). This was confirmed by reacting pure **3** with benzyl bromide, which was found to give **4** as the major product. When pure **3** was heated with sodium bicarbonate in ethanol/water, only the starting material was recovered. We thus postulate that the reactions with ethyl bromide and isopropyl bromide also must have afforded the corresponding dialkyl sulfides, which were removed during evaporation under vacuo due to their low boiling points. Thus, the reaction with hexyl bromide was found to give 2,3-bis(hexylthio)-1-propanol (**6**) and dihexyl sulfide (**7**).

In the course of this work, the 2,3-bis(alkylthio)-1-propanol prepared above was treated with phenol in the presence of catalytically concentrated sulfuric acid in

Table 1. Base Alkylation of 2,3-Dimercapto-1-propanol with Alkyl Halides To Give 2,3-Bis(alkylthio)-1-propanol and Dialkyl Sulfide



—R		R—S—R
—CH_2CH_3	 **1** 72%	
—$CH(CH_3)_2$	 **2** 65%	
—CH_2Ph	 **3** 22%	$PhCH_2—S—CH_2Ph$ **4** 45%
—$CH_2(CH_2)_4CH_3$	 **6** 28%	$CH_3(CH_2)_5—S—(CH_2)_5CH_3$ **7** 25.8%
	 **15** 44%	
—CH_2COOEt	 **18** 62%	

[⊗] Abstract published in *Advance ACS Abstracts,* October 1, 1996.

(1) Randell, R. V.; Seeler, A. O. *Med. Progr.: BAL N. Eng. J. Med.* **1948**, *239*, 1004.

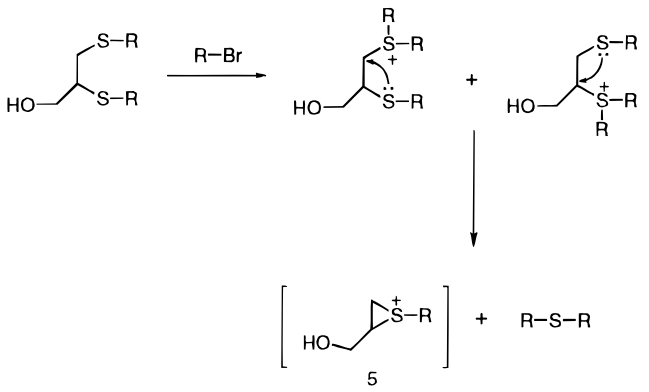
(2) Kubota, S.; El-Farrah, M. A.; Maki, M.; Harada, S.; Hatanaka, M. *AIDS Res. Hum. Retroviruses* **1990**, *6*, 919.

(3) White, L. B.; Torosian, G.; Becker, C. H. *Anal. Chem.* **1974**, *46*, 143.

(4) Ong, C. W.; Yen, F. W.; Chou, Y. M.; Chao, Y. K.; Chen, C. F. *Biorg. Med. Lett.* **1993**, *4*, 607.

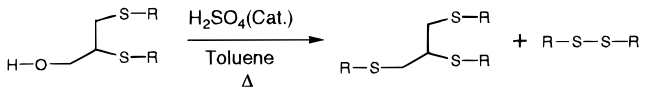
S0022-3263(96)00784-0 CCC: $12.00

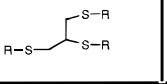
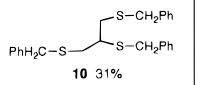
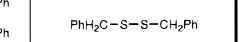
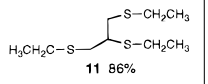
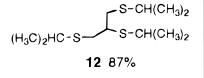
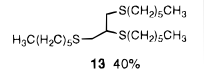
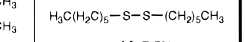
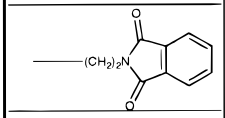
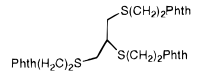
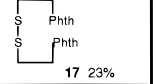
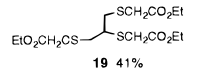
Scheme 1



refluxing toluene aimed at synthesizing phenyl ether derivatives. Surprisingly, two totally different products were obtained, and these were characterized as 1,2,3-tris(alkylthio)propane and dialkyl disulfide derivatives. The exact structure of the dialkyl disulfide, in particular, the differentiation from the dialkyl sulfide counterpart, was difficult to ascertain from the ^{1}H NMR. This structure was confirmed by two independent syntheses: (i) dihexyl sulfide from sodium sulfide with hexyl bromide and (ii) dihexyl disulfide from sodium hydrogen sulfide with hexyl bromide, followed by oxidation.[5] Dihexyl sulfide was found to exhibit an ^{1}H NMR signal at δ 2.50 and dihexyl disulfide at δ 2.70 for the methylenethio group. In general, the ^{1}H NMR chemical shifts for the disulfides are at a lower field as compared with the sulfides. The rearrangements of compounds **1**, **2**, **3**, and **6** were summarized in Table 2. To our knowledge, the rearrangement of 2,3-bis(alkylthio)-1-propanol to 1,2,3-tris(alkylthio)propane and dialkyl disulfide is unprecedented. The observed formation of 1,2,3-tris(alkylthio)-propane and dialkyl disulfide is interesting and can be explained by protonation of the sulfur or oxygen atoms. Protonation of the sulfur atom readily eliminates a molecule of alkylmercaptan with the formation of thiaranium intermediate **5** as proposed in Scheme 1, irrespective of which sulfur atom is protonated. The thiaranium intermediate **5** can then undergo further transformation leading to another molecule of alkylmercaptan and acrolein. The alkylmercaptan formed will subsequently lead to the formation of dialkyl disulfide due to oxidation through prolonged reaction time.[5] Alternatively, the protonation of the oxygen atom will readily eliminate a molecule of water with the formation of thiaranium intermediate **8**. Because of the strain in this thiaranium group, it can undergo a ring-opening reaction with the alkyl mercaptan produced by elimination regioselectively at the less substituted position to give 1,2,3-tris(alkylthio)propane (Scheme 2). The ring opening of the thietanium group has also been observed previously.[6,7] A summary of these results is given in Table 2. Ultimately, the ratio of dialkyl disulfide and 1,2,3-tris(alkylthio)propane will be controlled by the ease of disulfide formation. It is known that benzyl mercaptan has a higher pK_a, and it will react slower with electrophiles such as the thiaranium intermediate **8** and thus, favors the formation of disulfide after oxidative self-coupling.[6] This is consistent with the result of 2,3-bis-

Table 2. Reaction of 2,3-Bis(alkylthio)-1-propanol in the Presence of Catalytic Concentrated Sulfuric Acid To Give 1,2,3-Tris(alkylthio)propane and Dialkyl Disulfide[a]



—R		R—S—S—R
—CH_2Ph	 **10** 31%	 **9** 50%
—CH_2CH_3	 **11** 86%	
—$CH(CH_3)_2$	 **12** 87%	
—$CH_2(CH_2)_4CH_3$	 **13** 40%	 **14** 7.5%
	 **16** 56%	 **17** 23%
—CH_2COOEt	 **19** 41%	

[a] The yields of products were based on theoreticel yield.

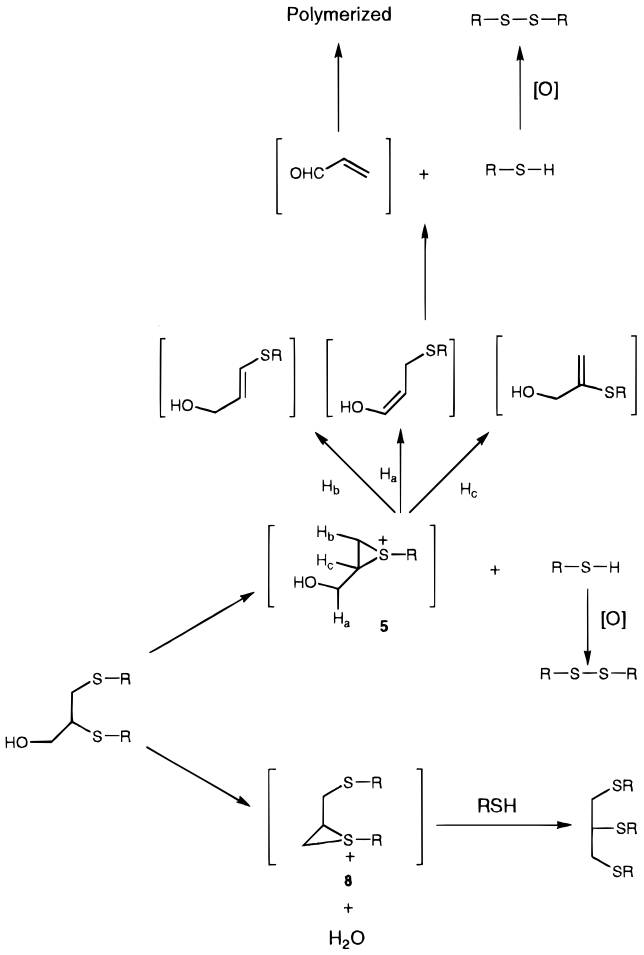
(benzylthio)-1-propanol (**3**), which rearranged under these conditions to give dibenzyl disulfide **9** as the major product (50%), together with 1,2,3-tris(benzylthio)propane **10** (30%). On changing to 2,3-bis(alkylthio)-1-propanol, we observed a decreasing amount of disulfide, and 1,2,3-tris(alkylthio)propane was obtained as the major product. In this manner, **1**, **2**, and **6** gave the corresponding 1,2,3-tris(ethylthio)propane (**11**) (86%), 1,2,3-tris(isopropylthio)propane (**12**) (87%), and 1,2,3-tris(hexylthio)propane (**13**) (40%), in excellent yields. In the case of **6**, some dihexyl disulfide (**14**) (7.5%) was isolated.

After the reaction, a polymeric gum was found at the bottom of the reaction vessel. This can be attributed to the proposed formation of acrolein during the reactions, which undergoes polymerization readily under acidic conditions.

In order to increase the potential of thioethers to serve as ligands for metal ions,[8] we next examined the synthesis of 1,2,3-tris[(2-aminoethyl)thio]propane, using the above methodology. Reaction of 1,2-dimercapto-1-propanol afforded 2,3-bis[(2-phthalimidoethyl)thio]-1-propanol (**15**) in a 44% yield. This was again smoothly rearranged under concentrated sulfuric acid in refluxing toluene to give 1,2,3-tris[(3-phthalimidoethyl)thio]propane (**16**) (56%) and bis(2-phthalimidoethyl) disulfide (**17**) (23%). The versatility was further extended to the synthesis of 2,3-bis[(carbethoxymethyl)thio]-1-propanol (**18**), which again undergoes rearrangement smoothly under acidic conditions to 1,2,3-tris[(carbethoxymethyl)-thio]propane (**19**).

(5) Khurana, J. M.; Sahoo, P. K. *Synth. Commun.* **1992**, *22*, 1691.
(6) Vriesema, B. K.; Lemaire, M.; Buter, J.; Kellog, R. M. *J. Org. Chem.* **1986**, *51*, 5169.
(7) Adams, R. D.; Fallon, S. B. *J. Am. Chem. Soc.* **1994**, *116*, 10540.
(8) Murray, S. G.; Hartley, F. R. *Chem. Rev.* **1981**, 365 and references cited therein.

Scheme 2



In conclusion, we have demonstrated that 2,3-dimercapto-1-propanol derivatives can undergo a wide array of rearrangement reactions. These reactions provide an easy entry to 1,2,3-tris(mercapto)propane derivatives, useful as new metal chelators and of potential therapeutic interest.

Experimental Section

^{1}H NMR spectra were recoded at 300 MHz in chloroform-*d* solutions unless otherwise stated. All column chromatography operations were conducted using Kieselgel 60.

General Procedure for the *S,S′*-Dialkylation of 2,3-Dimercapto-1-propanol. To a solution of 2,3-dimercapto-1-propanol (0.1 M) in a water−ethanol mixture (300 mL:30 mL) was added sodium bicarbonate (0.2 M) and the mixture left to stir at room temperature for 1 h under 1 atm of nitrogen. After this period, the appropriate halide (0.2 M) was added and the mixture refluxed for 3 days. The solution was concentrated to approximately one-third of its volume and extracted with chloroform, dried over magnesium sulfate, and evaporated to dryness. The crude product obtained was chromatographed on a silica gel column to afford the products.

2,3-Bis(ethylthio)-1-propanol (1): colorless oil, 72%; IR ($CHCl_3$) υ = 3500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, J = 7.4 Hz, 6H), 2.60 (m, 4H), 2.77−2.93 (m, 3H), 3.80 (m, 2H); LRMS (EI) *m/z* 180 (M^+), 151, 119, 105; HRMS (EI) M^+ calcd for $C_7H_{16}OS_2$ 180.0643, found 180.0638.

2,3-Bis(isopropylthio)-1-propanol (2): colorless oil, 65%; IR ($CHCl_3$) υ = 3480 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 and 1.33 (dd, J = 2.4 Hz, 12H), 2.90−3.05 (m, 5H), 3.76 (m, 2H); LRMS (EI) *m/z* 208 (M^+), 165, 133; HRMS (EI) M^+ calcd for $C_9H_{20}OS_2$ 208.0955, found 208.0949.

2,3-Bis(benzylthio)-1-propanol (3): colorless oil, 22%; IR ($CHCl_3$) υ = 3500, 3100, 2850 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.59 (d, J = 8.6 Hz, 2H), 2.75 (m, 1H), 3.61 (s, 2H), 3.68 (s, 2H), 3.70 (m, 2H), 7.23−7.27 (m, 10H); LRMS (EI) *m/z* 304 (M^+), 213, 122, 91; HRMS (EI) $(M - 1)^+$ calcd for $C_{17}H_{19}OS_2$ 303.0877, found 303.0881.

Dibenzyl sulfide (4): light yellow oil, 45%; IR ($CHCl_3$) υ = 3100, 2880 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.58 (s, 4H), 7.22−7.31 (m, 10H); LRMS (EI) *m/z* 214 (M^+), 123, 91; HRMS (EI) (M^+) calcd for $C_{14}H_{14}S$ 214.0816, found 214.0812.

2,3-Bis(hexylthio)-1-propanol (6): light yellow oil, 28%; IR ($CHCl_3$) υ = 3500, 2900, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 6.8 Hz, 6H), 1.25−1.50 (m, 12H), 1.59 (m, 4H), 2.50−3.00 (m, 7H), 3.75 (qq, J = 5 Hz, 2H); LRMS (EI) *m/z* 292 (M^+), 207, 175; HRMS (EI) (M^+) calcd for $C_{15}H_{32}OS_2$ 292.1895, found 292.1897. Anal. Calcd for $C_{15}H_{32}OS_2$ C, 61.64; H, 10.96. Found: C, 61.38; H, 10.93.

Dihexyl sulfide (7): light yellow oil, 25.8%; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 6.7 Hz, 6H), 1.25−1.50 (m, 12H), 1.59 (m, 4H), 2.50 (t, J = 7.5 Hz, 4H); LRMS (EI) *m/z* 202 (M^+), 117, 85; HRMS (EI) (M^+) calcd for $C_{12}H_{26}S$ 202.1755, found 202.1913.

Reactions of 2,3-Bis(thio-derivative)-1-propanol with Concentrated Sulfuric Acid in Refluxing Toluene. To a solution of the 2,3-bis(thio-derivative)-1-propanol in toluene was added a few drops of concentrated sulfuric acid and the mixture refluxed under azeotropic conditions overnight. Toluene was then removed under reduced pressure and the crude product treated with dilute NaOH followed by extraction with $CHCl_3$. The crude product obtained was then chromatographically separated.

Dibenzyl disulfide (9): light yellow oil, 50%; IR ($CHCl_3$) υ = 3100, 2880 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.58 (s, 4H), 7.22−7.31 (m, 10H); LRMS (EI) *m/z* 246 (M^+), 123, 91; HRMS (EI) (M^+) calcd for $C_{14}H_{14}S_2$ 246.0537, found 246.0542.

1,2,3-Tris(benzylthio)propane (10): yellow oil, 31%; IR ($CHCl_3$) υ = 3100, 2850 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.50−3.00 (m, 5H), 3.62 (s, 4H), 3.74 (s, 2H), 7.22−7.42 (m, 15H); LRMS (EI) *m/z* 319 (M^+ = 410), 195, 91; HRMS (EI) $(M)^+$ calcd for $C_{24}H_{26}S_3$ 410.1196, found 410.1179.

1,2,3-Tris(ethylthio)propane (11): light yellow oil, 86%; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 9H), 2.57 (q, J = 7.2 Hz, 4H), 2.90 (m, 5H); ^{13}C NMR δ 14.2, 15.0, 25.0, 27.1, 36.2, 45.8; LRMS (EI) *m/z* 224 (M^+), 195, 163; HRMS (EI) (M^+) calcd for $C_9H_{20}S_3$ 224.0727, found 224.0725.

1,2,3-Tris(isopropylthio)propane (12): yellow oil, 87%; IR ($CHCl_3$) υ = 2880 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (m, 18H), 2.80−3.20 (m, 8H), LRMS (EI) *m/z* 266 (M^+), 223, 191, 137, 89; HRMS (EI) (M^+) calcd for $C_{12}H_{26}S_3$ 266.1197, found 266.1196.

1,2,3-Tris(hexylthio)propane (13): yellow oil, 37.2%; IR ($CHCl_3$) υ = 2950 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.6 Hz, 9H), 1.25−1.50 (m, 18H), 1.59 (m, 6H), 2.55 (m, 6H), 2.88 (m, 5H); LRMS (EI) *m/z* 392 (M^+), 307, 275, 131; HRMS (EI) (M^+) calcd for $C_{21}H_{44}S_3$ 392.2605, found 392.2596. Anal. Calcd for $C_{21}H_{44}S_3$: C, 64.29; H, 11.22. Found: C, 64.28; H, 11.27.

Dihexyl disulfide (14): light yellow oil, 7.5%; IR ($CHCl_3$) υ = 2950 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 6.7 Hz, 6H), 1.25−1.50 (m, 12H), 1.67 (m, 4H), 2.68 (t, J = 7.5 Hz, 4H); LRMS (EI) *m/z* 234 (M^+), 150, 117, 85; HRMS (EI) (M^+) calcd for $C_{12}H_{26}S_2$ 234.1476, found 234.1482.

2,3-Bis[(2-phthalimidoethyl)thio]-1-propanol (15): light yellow oil, 44%; IR ($CHCl_3$) υ = 3500, 1770, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.80−3.10 (m, 7H), 3.90 (m, 6H), 7.72 (m, 4H), 7.83 (m, 4H); LRMS (FAB) *m/z* 470 (M^+), 296, 263, 174, 160; HRMS (FAB) (M^+) calcd for $C_{23}H_{22}N_2O_5S_2$ 470.0970, found 470.0968.

1,2,3-Tris[(2-phthalimidoethyl)thio]propane (16): yellow oil, 56%; IR ($CHCl_3$) υ = 1774, 1708 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.00 (m, 10H), 3.23 (m, 1H), 3.97 (m, 6H), 7.73 (m, 6H), 7.86 (m, 6H); LRMS (FAB) *m/z* 659 (M^+), 485, 452, 206; HRMS (FAB) (M^+) calcd for $C_{33}H_{29}N_3O_6S_3$ 659.1218, found 659.1218.

Bis(2-phthalimidoethyl) disulfide (17): yellow oil, 23%; IR ($CHCl_3$) υ = 1775, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.04 (t, J = 7 Hz, 2H), 4.04 (t, J = 7 Hz, 4H), 7.74 (m, 4H), 7.85 (m, 4H); LRMS (EI) *m/z* 412 (M^+), 206; HRMS (FAB) (M^+) calcd for $C_{20}H_{16}N_2O_4S_2$ 412.0552, found 412.0548.

2,3-Bis[(carbethoxymethyl)thio]-1-propanol (18): colorless oil, 62%; IR ($CHCl_3$) υ = 3500, 2900, 1750 cm^{-1}; ^{1}H NMR

($CDCl_3$) δ 1.26 (t, J = 7.5 Hz, 6H), 2.94 (d, J = 5 Hz, 2H), 3.10 (m, 1H), 3.24 (s, 2H), 3.30 (s, 2H), 3.75 (m, 2H), 4.14 (q, J = 7.2 Hz, 4H); LRMS (EI) m/z 296 (M^+), 279, 223, 177. Anal. Calcd for $C_{11}H_{20}O_5S_2$: C, 44.59; H, 6.76. Found: C, 44.54; H, 6.87.

1,2,3-Tris[(carbethoxymethyl)thio]propane (19): colorless oil, 41%; IR ($CHCl_3$) υ = 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (t, J = 7.2 Hz, 9H), 3.10 (m, 4H), 3.34 (m, 7H), 4.23 (q, J = 7.2 Hz, 6H); LRMS (EI) m/z 398 (M^+), 278, 238, 160.

Acknowledgment. We would like to thank the National Science Council of Taiwan for the research grant studentship grant to Y.M.C. (Ph.D.) and J.N.W. (M.Sc.). We thank National Tsing Hua University for assistance in obtaining the high-resolution mass spectra.

Supporting Information Available: Copies of proton NMR spectra of compounds **1**−**4**, **6**, **7**, and **9**−**19** (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO960784S