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Silver-Mediated Allylic Disulfide Rearrangement for Conjugation of Thiols in Protic Media

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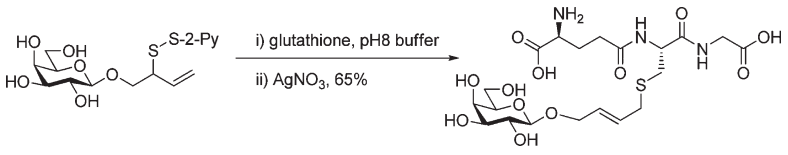
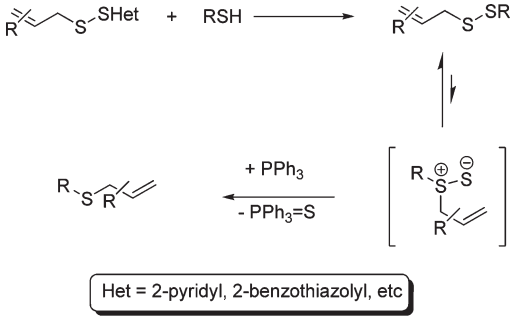


Alkyl and aryl allyl disulfides are induced to undergo the desulfurative allylic rearrangement by silver nitrate in protic solvents at room temperature, thereby removing the necessity for the use of phosphines as thiophilic reagents. The silver-mediated reaction functions at ambient temperature in protic solvents and in the absence of protecting groups

Introduction

Allylic disulfides, readily formed by the well-known reaction between a thiol and a sulfenyl transfer reagent,[1] may be converted into the more permanent alkyl allyl thioethers by the desulfurative allylic disulfide rearrangement. We have studied this reaction extensively over the past several years, during the course of which we have demonstrated that it is accelerated in polar solvents and that it may be applied to the functionalization of peptidyl thiols in protic media at room temperature.[2] This reaction proceeds through an unfavorable equilibrium, the result of a reversible 2,3-sigmatropic rearrangement, with a transient allylic thiosulfoxide from which an atom of sulfur is excised by triphenylphosphine and

SCHEME 1. Phosphine-Mediated Allylic Disulfide Rearrangement



which drives the equilibrium in the forward direction (Scheme 1).[3] Recent computational work has provided strong support for this mechanism, in particular for the rate-determining step being the desulfurization of the transient thiosulfoxide by the phosphine and, in line with our initial postulate, for the acceleration in protic media being due to the stabilization of the thiosulfoxide.[4]

Although in this reaction the phosphine can be replaced by morpholine in some instances, typically with a reduction in the *E*/*Z* selectivity of the final product, and can be dispensed with altogether in methanol at reflux, the optimum conditions, which result in excellent *E*/*Z* selectivity for disubstituted olefin formation, require the use of stoichiometric

(1) (a) Chalker, J. M.; Bernardes, G. J. L.; Lin, Y. A.; Davis, B. G. *Chem. Asian J.* **2009**, *4*, 630–640. (b) Hackenberger, C. P. R.; Schwarzer, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 10030–10047. (c) Hermanson, G. T. *Bioconjugate Techniques*; Academic Press: San Diego, 1996. (d) Lundblad, R. L. *Chemical Reagents for Protein Modification*, 3rd ed.; CRC Press: Boca Raton, 2005.

(2) (a) Crich, D.; Krishnamurthy, V.; Hutton, T. K. *J. Am. Chem. Soc.* **2006**, *128*, 2544–2545. (b) Crich, D.; Brebion, F.; Krishnamurthy, V. *Org. Lett.* **2006**, *8*, 3593–3596. (c) Crich, D.; Krishnamurthy, V.; Brebion, F.; Karatholuvhu, M.; Subramanian, V.; Hutton, T. K. *J. Am. Chem. Soc.* **2007**, *129*, 10282–10294. (d) Crich, D.; Yang, F. *J. Org. Chem.* **2008**, *73*, 7017–7027.

(3) For the early work on this rearrangement, see: (a) Höfle, G.; Baldwin, J. E. *J. Am. Chem. Soc.* **1971**, *93*, 6307–6308. (b) Baechler, R. D.; Hummel, J. D.; Mislow, K. *J. Am. Chem. Soc.* **1973**, *95*, 4442–4444. (c) Moore, C. G.; Trego, G. R. *Tetrahedron* **1962**, *18*, 205–218. (d) Evans, M. B.; Higgins, G. M. C.; Moore, C. G.; Porter, M.; Saville, B.; Smith, J. F.; Trego, B. R.; Watson, A. A. *Chem. Ind.* **1960**, 897. (e) Pilgram, K.; Phillips, D. D.; Korte, F. *J. Org. Chem.* **1964**, *29*, 1844–1847. (f) Block, E.; Iyer, R.; Grisoni, S.; Saha, C.; Belman, S.; Lossing, F. P. *J. Am. Chem. Soc.* **1988**, *110*, 7813–7827. (g) Braverman, S.; Cherkinsky, M. *Top. Curr. Chem.* **2007**, *275*, 67–102.

(4) Li, Z.; Wang, C.; Fu, Y.; Guo, Q.-X.; Liu, L. *J. Org. Chem.* **2008**, *73*, 6127–6136.

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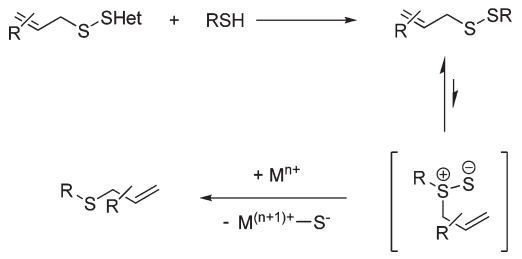
SCHEME 2. Proposed Metal-Mediated Allylic Disulfide Rearrangement



phosphine,[2] a common feature with the Staudinger ligation.[5] In our continuing study of this desulfurative allylic rearrangement, we have investigated alternative means of promoting the desulfurization step, retaining the high E/Z selectivity featured by the original variant. We initially considered the development of water-soluble phosphines, as has been achieved for the traceless Staudinger ligation,[6] so as to be able to accelerate the reaction in aqueous media but ultimately opted to search for a completely phosphine-free system. Along these lines we conceived that thiophilic metal species would bind preferentially to and excise sulfur from the more nucleophilic thiosulfoxide rather than from the allylic disulfide (Scheme 2), and we report here on the reduction of this concept to practice.[7]

Results and Discussion

We set out to screen a number of commonly available, potentially thiophilic salts for the rearrangement of a model system under protic conditions at room temperature. To this end a model diallyl disulfide **5** was prepared as outlined in Scheme 3 beginning from 3,4-dihydroxybutene.[8] Thus, the diol was readily converted to the cyclic thiocarbonate **1** with thiophosgene, and this latter was subjected to the Newman−Kwart[9] rearrangement to give the thiolcarbonate **2** in excellent yield. In contrast to the somewhat complex purely thermal process, the tetrakis(triphenylphosphino)-palladium(0) catalyzed rearrangement took place efficiently and in high yield in ethanol at reflux.[10−13] Cleavage of the cyclic thiolcarbonate **2** was best achieved by reduction with lithium aluminum hydride and was followed by immediate conversion of the resulting mercapto alcohol to the requisite pyridyl disulfide **3** by exposure to 2,2′-dipyridyl disulfide. Finally, the sulfenyl donor **3** was allowed to react with a protected L-cysteine derivative **4** to give the model disulfide **5** in 55% yield (Scheme 3).

SCHEME 3. Preparation of a Model System

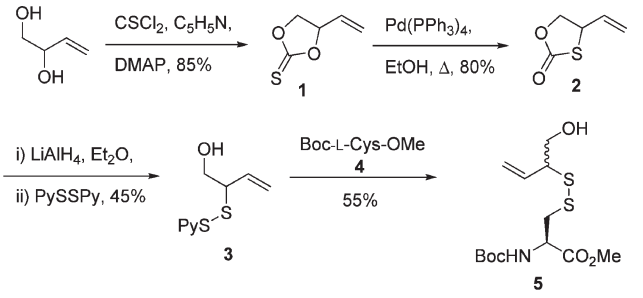
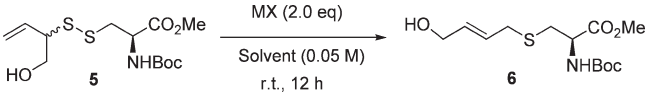


TABLE 1. Screening of Potentially Thiophilic Metal Salts



MX	CD_3CN (%)[a,b]	CD_3OD (%)[a,b]
$CoCl_2$	< 5	< 5
$NiCl_2$	< 5	< 5
CuCl	25	55
$Fe(NH_4)_2(SO_4)_2$	< 5	< 5
$AgNO_3$[c]	38	72

[a]Yields refer to isolated material. [b]As determined by ^{1}H NMR spectroscopy, the balance of the material is largely made up of unreacted substrate; [c]The $AgNO_3$-mediated reaction was also conducted in DMF and in ethanol, resulting in isolated yields of 70% and 68%, respectively, of **6** after 12 h.

With a model system in hand, screening experiments were conducted in both deuterioacetonitrile and deuteriomethanol at room temperature with monitoring by NMR spectroscopy and final chromatographic isolation of the products, leading to the results outlined in Table 1.

Among the salts screened, silver nitrate was the clear favorite, bringing about the desired rearrangement of the model system in high yield, with excellent *trans*-selectivity, in a matter of hours at room temperature. Silver salts were therefore adopted as the reagents of choice and applied to the conjugation of a number of systems as set out in Table 2.[14] Where available the yields for the same reactions previously obtained by the phosphine-mediated rearrangement are also presented in Table 2 for ease of comparison. Although the yields presented in Table 2 for the rearrangement mediated by silver nitrate are, with one exception, slightly lower than their counterparts for the phosphine-mediated rearrangement, it must be realized that the latter, for the most part, required more forcing conditions. Thus, entries 1 and 2 of

(5) (a) Lin, F. L.; Hoyt, H. M.; van Halbeek, H.; Bergman, R. G.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2005**, *127*, 2686–2695. (b) Soellner, M. B.; Nilsson, B. L.; Raines, R. T. *J. Am. Chem. Soc.* **2006**, *128*, 8820–8828. (c) Köhn, M.; Breinbauer, R. *Angew. Chem., Int. Ed.* **2004**, *43*, 3106–3116.

(6) Tam, A.; Soellner, M. B.; Raines, R. T. *J. Am. Chem. Soc.* **2007**, *129*, 11421–11430.

(7) We note that the analogous deselenative allylic selenosulfide rearrangement of *S*-alkyl *Se*-allyl seleno sulfides proceeds in some cases in the absence of phosphine[2] and has been recently applied to the allylation of a protein. Chaulker, J. M.; Lin, Y. A.; Boutureira, O.; Davis, B. G. *Chem. Commun.* **2009**, 3714–3716.

(8) Although 3,4-dihydroxybutene is available commercially, it may be obtained more economically by hydrolysis of the much cheaper 4-vinyl-1,3-dioxolan-2-one.

(9) Zonta, C.; De Lucchi, O.; Vollicelli, R.; Cotarca, L. *Top. Curr. Chem.* **2007**, *275*, 131–162.

(10) Metal-catalyzed [3,3]-sigmatropic rearrangements of a variety of allylic thionoesters have been described in the literature previously. See, for example: (a) Overman, L. E.; Roberts, S. W.; Sneddon, H. F. *Org. Lett.* **2008**, *10*, 1485–1488. (b) Gais, H.-J.; Böhme, A. *J. Org. Chem.* **2002**, *67*, 1153–1161, and references therein.

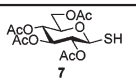
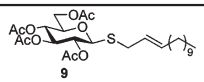
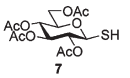
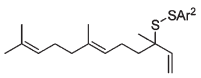
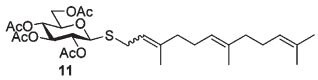
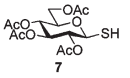
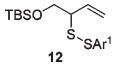
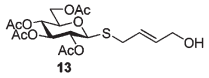
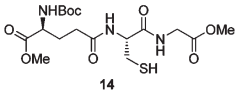
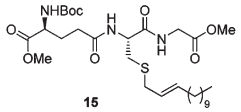
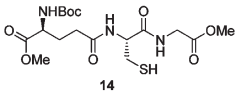
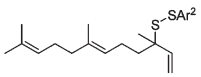
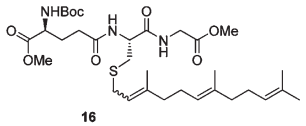
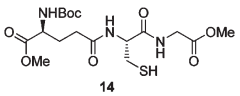
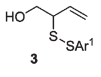
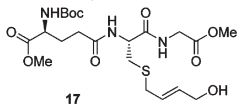
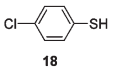
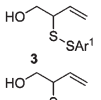
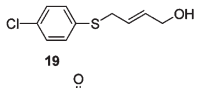
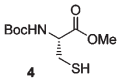
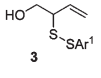
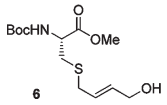
(11) No attempt was made to develop an asymmetric version of this reaction in view of the destruction of the stereogenic center in the subsequent application.

(12) The photochemical [1,3]-rearrangement of allylic thiocarbamates is also a known reaction: Sakamoto, M.; Yoshiaki, M.; Takahashi, M.; Fujita, T.; Watanabe, S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 373–377.

(13) For a recent palladium-catalyzed variant on the aromatic Newman−Kwart reaction, see: Harvey, J. N.; Jover, J.; Lloyd-Jones, G. C.; Moseley, J. D.; Murray, P.; Renny, J. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7612–7615.

(14) For a collection of reviews on reactions promoted and/or catalyzed by the coinage metals, see: Lipshutz, B., H.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 2793–2795, and the reviews immediately following this editorial.

TABLE 2. Silver-Promoted Desulfurative Allylic Disulfide Rearrangement in Methanol

Entry	Thiol	Allylic Partner[a]	Product	$AgNO_3$-Mediated Yield[b]	PPh_3-Mediated Yield
1	 **7**	 **8**	 **9**	62%	73%[c]
2	 **7**	 **10**	 **11**	50%[d] *E*:*Z* = 1.5:1	66%[c] *E*:*Z* = 1.8:1
3	 **7**	 **12**	 **13**	67%[e]	-[f]
4	 **14**	 **8**	 **15**	61%	70%[g]
5	 **14**	 **10**	 **16**	60% *E*:*Z* = 1.5:1	70%[c] *E*:*Z* = 1.7:1
6	 **14**	 **3**	 **17**	65%	37%
7	 **18**	 **3**	 **19**	51%	0%
8	 **4**	 **3**	 **6**	56%[h]	67%[h]

[a] Ar^1 = 2-pyridyl, Ar^2 = 2-benzothiazolyl. [b] Unless otherwise stated, all reactions were conducted for 16 h at room temperature in MeOH with 0.05 M thiol and 2.2 equiv of $AgNO_3$. [c] Conducted with 0.05 M substrate and 3 equiv of PPh_3 in benzene at reflux. [d] Et_3N (1.2 equiv) was added to accelerate disulfide formation, and rearrangement was complete in 2 days. [e] Rearrangement complete in 24 h. [f] In the attempted reaction with PPh_3 a complex reaction mixture was obtained that did not contain a significant quantity of the anticipated product. [g] $Ph_2P(4\text{-}C_6H_4NMe_2)$ was used as the thiophile. [h] The lower yield observed here as compared to that reported in Table 1 reflects the incorporation of the sulfenyl transfer step in Table 2.

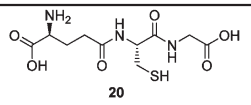
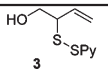
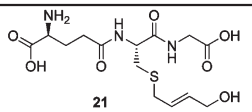
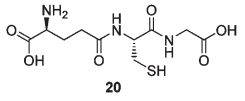
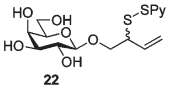
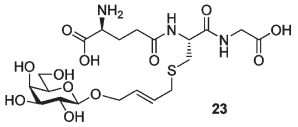
Table 2 report yields for reactions conducted with triphenylphosphine in benzene at reflux, as no rearrangement was observed at room temperature. In distinct contrast, the same rearrangements were effected at room temperature with silver nitrate. With the siloxylated allylic disulfide **12**,[14,15] sulfenyl transfer to the anomeric thiol **7** with subsequent silver-mediated desulfurative rearrangement was again successful, albeit with concomitant cleavage of the silyl ether group (Table 2, entry 3). When this same reaction was attempted in methanol at room temperature in the presence of triphenylphosphine rather than silver nitrate, a complex mixture was observed that did not contain the anticipated product (Table 2, entry 3). The failure of Table 2, entry 3 under the phosphine-mediated conditions is likely due to reduced nucleophilicity of the sulfur bound to the anomeric carbon, on which we have previously remarked,[2] and the electron-withdrawing silyl ether moiety that destabilizes the partial positive charge on the allylic framework in the thiosulfoxide. Both of these factors reduce the equilibrium concentration of the thiosulfoxide, thereby retarding the desulfurization step, and so permit the onset of other deleterious processes including disulfide scrambling. Clearly, in view of Table 2, entry 3, silver nitrate is a more effective desulfurization reagent than triphenylphosphine and enables the combination of these factors to be overcome. This same retarding effect of the homoallylic oxygen on the phosphine-mediated rearrangement is apparent from a comparison of the yields in entries 4 and 6 of Table 2 when both reactions were conducted in methanol at room temperature.

Entry 7 of Table 2 is particularly interesting as we had previously found that allyl aryl disulfides do not undergo the phosphine-mediated desulfurative allylic rearrangement owing to the more facile nature of the direct attack of the phosphine on the disulfide bond itself. Indeed, the simple heating of the disulfide formed from **3** and **18** with triphenyl phosphine resulted in none of the desired product **19**. Clearly, the silver-mediated protocol reported here overcomes this problem and results in a good yield of the rearranged allylic sulfide **19**. As noted previously, the allyl aryl disulfides can also be inducted to undergo desulfurative allylic rearrangement by simple heating to reflux in methanol, but the yields in such cases are only modest.[2] Finally, Table 2, entry 8, is the preparative-scale run of the initial screening reaction. The somewhat lower yield reported for the preparative-scale reaction reflects the two-step nature of the process as opposed to the use of an isolated disulfide in

(15) Obtained by silylation of **3** under standard conditions with *tert*-butyldimethylsilyl chloride in 80% yield.

(16) For all disubstituted alkenes, only the *E*-isomers were observed and isolated.

TABLE 3. Silver-Promoted Desulfurative Allylic Disulfide Rearrangement in Aqueous Buffer[a]

Entry	Thiol	Allylic Partner	Product	$AgNO_3$-Mediated Yield
1	 **20**	 **3**	 **21**	85%
2	 **20**	 **22**	 **23**	65%

[a]Disulfide formation: Tris buffer (0.2 M, pH 8), MeCN, and THF (2:1:1), 12−16 h. Rearrangement: $AgNO_3$ (2.2 equiv), Tris buffer, and acetonitrile, 24 h.

the screening reactions. In general and with the exception of entries 2 and 5 in which trisubstituted olefins were formed, the silver-mediated reaction presented in Table 2 took place with excellent *E*-selectivity on a par with that obtained in the phosphine-mediated reactions.[16]

The applicability of the silver-mediated reaction under aqueous conditions is demonstrated by the examples of Table 3. In particular, entry 2 of Table 3 shows how this chemistry may be applied to the formation of glycoconjugates in the complete absence of protecting groups. Once again, excellent *E*-selectivity was observed under these conditions.[16]

Conclusion

We demonstrate a new variant on the desulfurative allylic disulfide rearrangement in which the key desulfurization of the transient thiosulfoxide intermediate is achieved through the use of silver nitrate rather than a triarylphosphine. This metal-mediated process enables the desulfurative allylic rearrangement of aryl allyl disulfides, something that could not be achieved with phosphines owing to the more facile disulfide cleavage reaction. Reactions take place at room temperature, give excellent *E*-selectivity for the formation of disubstituted alkenes, and are conducted in protic media, including aqueous mixtures with organic solvents.

Experimental Section

4-Vinyl-1,3-dioxolane-2-thione (1). To a stirred solution of but-3-ene-1,2-diol (10.0 g, 113.5 mmol) in dichloromethane (200 mL) under a nitrogen atmosphere was added pyridine (19.8 g, 250 mmol) followed by DMAP (1.39 g, 11.4 mmol) at 0 °C. Thiophosgene (14.4 g, 124.8 mmol) dissolved in dichloromethane (100 mL) then was added dropwise over a period of 2 h. The reaction mixture was stirred at room temperature for 3 h and then diluted with 1.0 M HCl (100 mL). The organic part was separated and washed with saturated NaCl (100 mL), dried over sodium sulfate, and evaporated to dryness. The crude product was purified by column chromatography using EtOAc/hexanes as eluent to give 4-vinyl-1,3-dioxolane-2-thione (**1**) as a dark yellow liquid (12.5 g, 85%). IR (neat): 1709 cm^{-1}. ^1H NMR (500 MHz): 5.95 (ddd, J = 17.0, J = 10.5, J = 7.0 Hz, 1H), 5.56 (d, J = 17.0 Hz, 1H), 5.51 (d, J = 10.5 Hz, 1H), 5.34 (m, 1H), 4.78 (t, J = 8.5 Hz, 1H), 4.36 (t, J = 8.5 Hz, 1H). ^{13}C NMR (125 MHz): δ 191.7, 131.2, 122.8, 82.7, 73.1. HREIMS: calcd for $C_5H_6O_2S$ $[M]^+$ 130.0089, found 130.0064.

4-Vinyl-1,3-oxathiolan-2-one (2). To a stirred solution of 4-vinyl-1,3-dioxolane-2-thione (**1**) (5.08 g, 39.1 mmol) in degassed ethanol (150 mL) (0.26 M) was added $Pd(PPh_3)_4$ (904 mg, 0.78 mmol). The reaction mixture was stirred at 75 °C for 1 h, after which the dark brown mixture was cooled to room temperature, solvents were evaporated, and the product was purified by column chromatography using EtOAc/hexanes as eluent to give 4-vinyl-1,3-oxathiolan-2-one (**2**) as a colorless oil (4.0 g, 80%). IR (neat): 1738 cm^{-1}. ^1H NMR (500 MHz): δ 5.89 (ddd, J = 17.0, J = 10.0, J = 7.0 Hz, 1H), 5.41 (d, J = 17.0 Hz, 1H), 5.29 (d, J = 10.0 Hz, 1H), 4.55 (m, 2H), 4.20 (m, 1H). ^{13}C NMR (125 MHz): δ 172.8, 133.2, 120.4, 72.7, 51.6. HREIMS: calcd for $C_5H_6O_2S$ $[M]^+$ 130.0089, found 130.0089.

2-(Pyridin-2-yldisulfanyl)-but-3-en-1-ol (3). To a stirred solution of 4-vinyl-1,3-oxathiolan-2-one (**2**) (2.0 g, 15.4 mmol) in dry ether (15 mL) cooled to 0 °C was added $LiAlH_4$ (584 mg, 15.4 mmol). The reaction mixture was stirred at the same temperature for 30 min and then at room temperature for 2 h before ethyl acetate (5 mL) was added, followed by the sequential addition of 1.0 M HCl (10.0 mL) and MeOH (10.0 mL). The reaction mixture was stirred at room temperature for 30 min and then filtered through a pad of Celite with washing of the filter pad with MeOH (10.0 mL) and 1.0 M HCl (5.0 mL). The filtrate and washings were transferred to a solution of 2,2′-dipyridyl disulfide (3.0 g, 13.6 mmol) in MeOH (10.0 mL). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 1 h before the solvents were evaporated and the crude reaction mixture was dissolved in EtOAc (100 mL) and washed with saturated bicarbonate solution (50 mL). The ethyl acetate portion was further washed with brine solution (50 mL), dried over sodium sulfate, filtered, and evaporated to dryness. The crude product was purified by column chromatography on silica gel using EtOAc/toluene as eluent to give 2-(pyridin-2-yldisulfanyl)-but-3-en-1-ol (**3**) as a colorless liquid (1.47 g, 45% for two steps). ^1H NMR (400 MHz): δ 8.48 (dd, J = 1.5 Hz, J = 4.8 Hz, 1H), 7.56 (m, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.14 (dd, J = 7.2 Hz, J = 4.8 Hz, 1H), 5.94 (m, 1H), 5.88 (m, 1H), 5.24 (dd, J = 16.5 Hz, J = 9.3 Hz, 2H), 3.79 (m, 1H), 3.62 (m, 2H). ^{13}C NMR (125 MHz): δ 159.2, 150.0, 137.1, 134.3, 122.2, 121.8, 118.6, 61.4, 56.6. ESIHRMS: calcd for $C_9H_{11}NOS_2Na$ $[M + Na]^+$ 236.0180, found 236.0191.

Methyl 2-*tert*-Butoxycarbonylamino-3-(1-hydroxymethylallyldisulfanyl)propionate (5). To a stirred solution of 2-(pyridin-2-yldisulfanyl)-but-3-en-1-ol (**3**) (160 mg, 0.75 mmol) in methanol (6.0 mL) was added a solution of *N*-Boc-L-Cys-OMe (**4**) (176 mg, 0.75 mmol) in methanol (1.5 mL). The reaction mixture was stirred at room temperature under N_2 atmosphere for 4 h before the solvents were removed and the crude product was purified by column chromatography on silica gel using EtOAc/hexanes as eluent to give methyl 2-*tert*-butoxycarbonylamino-3-(1-hydroxymethylallyldisulfanyl)propionate (**5**) as a thick oil (139 mg, 55%). ^1H NMR (500 MHz): δ 5.81−5.78 (m, 1H), 5.38 (d, J = 8.0 Hz, 1H), 5.35−5.26 (m, 2H), 4.64−4.62 (m, 1H), 3.94 (d, J = 6.5 Hz, 2H), 3.80 (s, 3H), 3.57−3.49 (m, 1H),

3.22−3.11 (m, 2H), 2.23 (br s, 1H), 1.42 (s, 9H), ^{13}C NMR (125 MHz): δ 171.7, 155.6, 134.8, 134.7, 119.7, 119.6, 80.9, 63.6, 57.2, 56.7, 53.5, 53.2, 42.0, 41.8, 28.8. ESIHRMS: calcd for $C_{13}H_{23}NO_5S_2Na$ $[M + Na]^+$ 360.0915, found 360.0933.

General Procedure for Silver Nitrate Promoted Rearrangement of Allylic Disulfides. Thiol (1.0 equiv) was added to a stirred solution of disulfide in methanol (0.05 M) at room temperature. The reaction mixture was stirred at room temperature under a nitrogen atmosphere until complete disulfide exchange was visible on TLC (usually less than 1 h). The reaction mixture was then treated with silver nitrate (2.0 equiv) and stirred in the dark for 16 h. After completion of the reaction (monitored by ESI mass spectrometry), NaCl (10 equiv) was added, and the reaction mixture was stirred for 3−4 h. The reaction mixture was diluted with methanol and centrifuged to remove the black precipitate. The solvent was then concentrated to afford the crude product, which was purified by column chromatography on silica gel to give the rearranged product.

(*E*)-*N*-*tert*-Butoxycarbonyl-*S*-(4-hydroxybut-2-enyl)-L-cysteine Methyl Ester (6). Following the general procedure for the silver nitrate promoted rearrangement of allylic disulfides compound **6** was prepared in 72% yield as an oil. $[\alpha]^{23}_D$ 23.5 (c = 1.0). ^{1}H NMR (500 MHz): δ 5.80 (dd, J = 15.0, J = 5.0 Hz, 1H), 5.68 (dd, J = 15.0, J = 6.0 Hz, 1H), 5.28 (d, J = 7.5 Hz, 1H), 4.51 (d, J = 8.0 Hz, 1H), 4.15 (d, J = 5.5 Hz, 2H), 3.78 (s, 3H), 3.17 (d, J = 7.0 Hz, 2H), 2.84 (dd, J = 14.0, J = 5.5 Hz, 2H), 1.90 (br s, 1H), 1.46 (s, 9H). ^{13}C NMR (125 MHz): δ 172.0, 156.0, 133.3, 127.7, 80.7, 63.2, 53.6, 52.8, 34.3, 33.3, 28.5. ESIHRMS: calcd for $C_{13}H_{23}NO_5SNa$ $[M + Na]^+$ 328.1195, found 328.1183.

2-(2-(Tridec-1-en-3-yl)disulfanyl)pyridine (8). Compound **8** was prepared according to literature procedure and had spectral data in agreement with the literature.[2c]

Tridec-2-enyl-(tetra-*O*-acetyl-1-thio-β-D-glucopyranoside) (9). Following the general procedure for the silver nitrate promoted rearrangement of allylic disulfides, compound **9** was prepared in 62% yield. Its spectral data was consistent with that reported in the literature.[2c]

3,7,11-Trimethyl-dodeca-2,6,10-trienyl Tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (11). To a stirred solution of 2-(1,5,9-trimethyl-1-vinyldeca-4,8-dienyldisulfanyl)benzothiazole[2b] (**10**) (78 mg, 0.19 mmol) in methanol (3.0 mL) was added triethylamine (27 μL, 0.19 mmol) followed by 1-thio-β-D-glucose tetraacetate (**7**) (54 mg, 0.16 mmol). After 1 h, silver nitrate (58 mg, 0.34 mmol) was added, and the reaction mixture was stirred under a N_2 atmosphere in the dark for 36 h. After following the general workup procedure the crude product was purified by column chromatography to give the title product (**11**) in 50% yield with spectral data consistent with that reported in the literature.[2b]

1-*tert*-Butyldimethylsilyloxy-2-(pyridin-2-yldisulfanyl)but-3-ene (12). To a stirred solution of 2-(pyridin-2-yldisulfanyl)but-3-en-1-ol (**3**) (1.0 g, 4.69 mmol) in DMF (10.0 mL) under a nitrogen atmosphere was added imidazole (319 mg, 4.69 mmol) followed by *tert*-butyldimethylsilyl chloride (716 mg, 4.69 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 10 h. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with water (100 mL). The organic part was washed with saturated NaCl solution (50 mL), dried over sodium sulfate, and evaporated to dryness. The crude product was purified by column chromatography on silica gel using EtOAc/hexanes as eluent to give the title product (**12**) as an oil (1.20 g, 80%). ^{1}H NMR (500 MHz): δ 8.44 (ddd, J = 5.0, J = 2.0, J = 1.0 Hz, 1H), 7.56 (m, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.14 (dd, J = 7.2, J = 4.8 Hz, 1H), 5.94 (m, 1H), 5.88 (m, 1H), 5.24 (dd, J = 16.5, J = 9.3 Hz, 2H), 3.79 (m, 1H), 3.62 (m, 2H), 0.90 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (125 MHz): δ 161.2, 149.5, 137.1, 134.5, 120.6, 119.8, 119.2, 64.7, 57.1, 26.1, 18.6, −5.1. ESIHRMS: calcd for $C_{15}H_{25}NOS_2SiNa$ $[M + Na]^+$ 350.1045, found 350.1042.

***S*-4-Hydroxybut-2-enyl 2,3,4,6-Tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (13).** To a stirred solution of 1-*tert*-butyldimethylsilyloxy-2-(pyridin-2-yldisulfanyl)-but-3-ene (**12**) (115 mg, 0.35 mmol) in MeOH (2.0 mL) was added 1-thio-β-D-glucose tetraacetate (100 mg, 0.29 mmol) under a nitrogen atmosphere. The yellow-colored solution was stirred at room temperature for 1 h before the solvents were removed, and the crude reaction mixture was purified by column chromatography on silica gel to give the mixed disulfide. The mixed disulfide (78 mg, 0.13 mmol) was dissolved in MeOH (2.0 mL), and silver nitrate (46 mg, 0.27 mmol) was added. The reaction mixture was stirred at room temperature under a N_2 atmosphere in the dark for 16 h before NaCl (75 mg, 1.3 mmol) was added, and the solution was stirred for 3−4 h, diluted with MeOH (10.0 mL), and centrifuged. The supernatant were evaporated to give the crude product, which was purified by column chromatography on silica gel using EtOAc/hexanes as eluent to give **13** (45 mg, 67%). $[\alpha]^{23}_D$ −49.5 (c = 1.0). ^{1}H NMR (500 MHz): δ 5.78 (dt, J = 15.5, J = 5.0, 1H), 5.71 (dtd, J = 15.5, J = 6.5, J = 1.0 Hz, 1H), 5.22 (t, J = 9.6 Hz, 1H), 5.07 (t, J = 9.6, 1H), 5.06 (t, J = 9.6 Hz, 1H), 4.50 (d, J = 10.0 Hz, 1H), 4.24 (dd, J = 12.0, J = 5.0 Hz, 1H), 4.18−4.10 (m, 2H), 4.15 (dd, J = 12.0, J = 2.0 Hz, 1H), 3.68 (ddd, J = 9.5, J = 5.0, J = 2.0, 1H), 3.38 (dd, J = 13.5, J = 7.5, 1H), 3.26 (ddd, J = 13.5, J = 6.0, J = 1.0 Hz, 1H), 2.09 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H), 1.77 (br s, 1H). ^{13}C NMR (125 MHz): δ 170.9, 170.5, 169.7, 169.6, 133.0, 127.2, 82.2, 76.0, 74.1, 70.2, 68.6, 63.0, 62.4, 31.6, 20.9, 20.9, 20.8, 20.8. ESIHRMS: calcd for $C_{18}H_{26}O_{10}SNa$ $[M + Na]^+$ 457.1144, found 457.1138.

***N*-*tert*-Butoxycarbonyl-*S*-(tridec-2-enyl)glutathione Dimethyl Ester (15)[2b].** Following the general procedure for the silver nitrate promoted rearrangement of allylic disulfides, compound **15** was prepared in 61% yield. Its spectral data were consistent with that reported in the literature.[2b]

***N*-*tert*-Butoxycarbonyl-*S*-(3,7,11-trimethyldodeca-2,6,10-trienyl)-glutathione Dimethyl Ester (16).** To a stirred solution of 2-(1,5,9-trimethyl-1-vinyl-deca-4,8-dienyldisulfanyl)-benzothiazole (**10**) (120 mg, 0.30 mmol) in methanol (5.0 mL) was added triethylamine (38 μL, 0.27 mmol) followed by Boc-(α-OMe)-γ-L-Glu-L-Cys-Gly-OMe[2a] (**14**) (100 mg, 0.23 mmol). After 1 h, silver nitrate (78 mg, 0.46 mmol) was added, and the reaction mixture was stirred under a N_2 atmosphere in the dark for 16 h. After following the general workup procedure, the crude product was purified by column chromatography on silica gel to give the title product in 60% yield with spectral data consistent with the literature.[2b]

***N*-*tert*-Butoxycarbonyl-*S*-(4-hydroxybut-2-enyl)glutathione Dimethyl Ester (17).** Following the general procedure for the silver nitrate promoted rearrangement of allylic disulfides, a stirred solution of 2-(pyridin-2-yldisulfanyl)-but-3-en-1-ol (**3**) (70 mg, 0.25 mmol) in methanol (5.0 mL) was treated with Boc-(α-OMe)-γ-L-Glu-L-Cys-Gly-OMe[2a] (**14**) (108 mg, 0.25 mmol). The reaction mixture was stirred under a N_2 atmosphere for 12 h before silver nitrate (85 mg, 0.50 mmol) was added, and the mixture was stirred in the dark for 16 h before the general workup procedure was applied. The crude product was purified by column chromatography on silica gel using $CHCl_3$/MeOH as eluent to give the title product (**17**) in 65% yield. $[\alpha]^{23}_D$ −2.0 (c 0.85). ^{1}H NMR (400 MHz): δ 7.16 (br s, 1H), 6.92 (d, J = 7.6 Hz, 1H), 5.87−5.80 (m, 1H), 5.72−5.65 (m, 1H), 5.38 (d, J = 7.6 Hz, 1H), 4.64−4.59 (m, 1H), 4.37 (br s, 1H), 4.12 (br s, 2H), 4.03 (d, J = 5.6 Hz, 2H), 3.74 (s, 3H), 3.73 (s, 3H), 3.27 (br s, 1H), 3.19 (d, J = 7.2 Hz, 2H), 2.90−2.86 (m, 1H), 2.80−2.76 (m, 1H), 2.36−2.33 (m, 2H), 2.18 (m, 1H), 1.95−1.89 (m, 1H), 1.42 (s, 9H). ^{13}C NMR (100 MHz): δ 173.1, 172.6, 170.9, 170.3, 156.1, 133.4, 128.4, 80.6, 63.1, 53.0, 52.9, 52.7, 41.5, 34.5, 33.0, 32.4, 29.0, 28.6. ESIHRMS: calcd for $C_{21}H_{35}N_3O_9SNa$ $[M + Na]^+$ 528.19920, found 528.2016.

(*E*)-4-(4-Chlorophenylsulfanyl)but-2-en-1-ol (19). Following the general procedure for the silver nitrate promoted rearrangement of allylic disulfides, compound **19** was prepared in 51% yield. Its spectral data were consistent with that reported in the literature.[2c]

(*E*)-*S*-(4-Hydroxybut-2-enyl)glutathione (21). Glutathione (**20**) (29 mg, 0.09 mmol) was dissolved in 2 mL of Tris buffer (0.2 M, pH 8), and the resulting solution was treated with 2-(pyridin-2-yldisulfanyl)but-3-en-1-ol (**3**) (75 mg, 0.28 mmol) dissolved in 2.0 mL of CH_3CN/THF (1:1). The reaction mixture was stirred at room temperature for 12 h, after which excess disulfide and liberated pyridinethiol were removed by washing with *tert*-butyl methyl ether (5 mL). The residue was dissolved in water (3 mL) and treated with silver nitrate (2.2 equiv). The yellow suspension was allowed to stir for 24 h and then treated with 3 mL of 5% diluted HCl and centrifuged. The supernatant was injected into a reversed-phase HPLC system for purification using a gradient of 100% B to 50% B developed over 50 min (A, 0.1% TFA/CH_3CN; B, 0.1% TFA/H_2O; column, Varian Microsorb C_{18} 250 mm × 21.4 mm; flow rate, 10 mL/min; UV detection, 215 nm). Lyophilization of the fraction eluting at 19 min afforded the rearranged glutathione **21** in 85% yield as a white foam. $[\alpha]^{23}_D$ −23.2 (*c* 0.8, CH_3OH). ^{1}H NMR (500 MHz, CD_3OD): δ 5.80−5.74 (m, 1H), 5.69−5.64 (m, 1H), 4.53 (dd, J = 11.5, J = 6.0 Hz, 1H), 4.06 (d, J = 5.0 Hz, 2H), 3.97 (d, J = 8.0 Hz, 2H), 3.61 (t, J = 8.5 Hz, 1H), 3.18 (d, J = 8.0 Hz, 2H), 2.99 (dd, J = 17.5, J = 6.0 Hz, 1H), 2.70 (dd, J = 17.0, J = 11.5 Hz, 1H), 2.57−2.50 (m, 2H), 2.48−2.03 (m, 2H). ^{13}C NMR (125 MHz, CD_3OD): δ 173.9, 172.7, 172.4, 170.4, 132.8, 126.9, 61.8, 54.2, 53.2, 40.7, 33.2, 32.1, 31.7, 26.6. ESIHRMS: calcd for $C_{14}H_{23}N_3O_7SNa$ $[M + Na]^+$ 400.1154, found 400.1150.

S-[4-(β-D-Galactopyranosyloxy)but-2-enyl]glutathione (23). Glutathione (11 mg, 0.03 mmol) was dissolved in 0.5 mL of Tris buffer (0.2M, pH 8) to which 2-(2-pyridyldisulfanyl)-3-enyl β-D-galactopyranoside[2d] (**22**) (37.5 mg, 0.10 mmol) dissolved in 0.5 mL of CH_3CN was added. The reaction mixture was stirred at room temperature for 16 h before the excess disulfide and liberated pyridinethiol were removed by washing with *tert*-butyl methyl ether (5 mL). The residue was dissolved in water (3 mL) and treated with silver nitrate (2.2 equiv). The yellow suspension was allowed to stir for 24 h and then was treated with 3 mL of 5% diluted HCl and centrifuged. The supernatant was injected into a reversed-phase HPLC system for purification to give the product in 65% yield, whose spectral data were consistent with the literature.[2d]

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Supporting Information Available: Copies of the ^{1}H and ^{13}C NMR spectra of compounds **1**−**3**, **5**, **6**, **9**, **11**−**13**, **15**−**17**, **19**, **21**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.