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Allylation and Alkylation of Biologically Relevant Nucleophiles by Diallyl Sulfides

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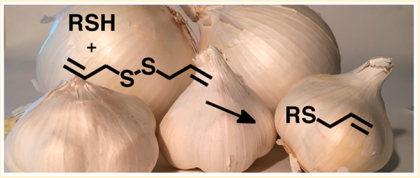
Supporting Information

ABSTRACT: Allyl sulfides are bioactive phytochemicals found in garlic, onion, and other members of the genus *Allium*. Here we showed that diallyl disulfide and diallyl trisulfide can transfer allyl side chains to low molecular weight thiols. Diallyl monosulfide is inert with respect to this allyl transfer reaction. On the other hand, diallyl sulfone, a known metabolite of diallyl monosulfide, alkylates both amines and thiols under physiologically relevant conditions via isomerization to an electrophilic vinyl sulfone.



Diallyl sulfide **1**, diallyl disulfide **2**, and diallyl polysulfides (e.g., **3**) are bioactive phytochemicals found in garlic, onion, chive, and other members of the genus *Allium* (Figure 1).[1−3]

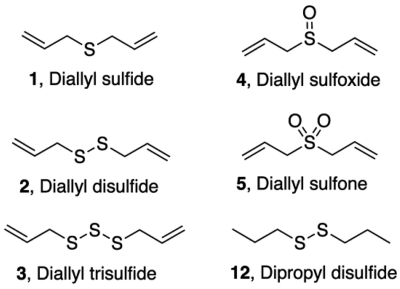
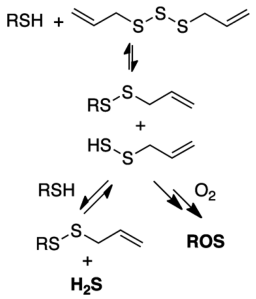


Figure 1. Dietary allyl sulfides and some oxidized metabolites.

These compounds display pleiotropic effects in biological systems. For example, allyl sulfides possess cancer-preventive properties, the ability to kill or arrest the growth of cancer, fungal, and bacterial cells, induce vasorelaxation, and inhibit ADP-induced platelet aggregation.[2,4−9] The biological activities of allyl polysulfides are generally thought to arise from three molecular processes: (i) polysulfide-thiol exchange processes that lead to the modification of cysteine residues on critical target proteins, (ii) thiol-mediated release of persulfide anion (RSS^-) intermediates that produce reactive oxygen species (ROS) via redox-cycling, or (iii) polysulfide exchange reactions that lead to the release of H_2S, which is a known bioactive species and putative endogenous signaling agent (Scheme 1).[5,10−15]

Diallyl sulfides are substantially more bioactive than the corresponding saturated analogs (e.g., **2** versus **12**).[5,16] This is striking because the processes illustrated in Scheme 1 do not imply a central role for the carbon side chains. Thus, it is interesting to consider possible chemical mechanisms by which allyl groups might contribute to the bioactivity of the allyl polysulfide natural products. Along these lines, it may be significant that nucleophilic substitution at carbon in allylic systems is facile.[17]

Scheme 1



The persulfide ($pK_a \sim 6$)[18−20] and hydrogen sulfide ($pK_a = 7$) groups embedded within the allyl polysulfides could provide reasonable leaving groups for such reactions.[21] The transfer of allyl groups from **2** to the thiol residue in glutathione was proposed in 2007, but this supposition was based only upon an apparent release of H_2S from the reaction of **2** and glutathione.[7,22] More recently, LC-MS was used to provide evidence for the generation of *S*-allyl glutathione in this reaction;[22] however, to the best of our knowledge, allyl transfer products arising from the reaction of **2** or **3** with thiols have not been isolated or subjected to rigorous spectroscopic characterization. Thus, we set out to examine whether allyl polysulfides can transfer their allyl groups to biologically relevant nucleophiles such as thiols and amines. In addition, we explored the reactivity of sulfoxide and sulfone metabolites of diallyl sulfide.

The reaction of **2** (0.11 M) with 4-*t*-butylthiophenol **6** (1 equiv) in dry methanol containing triethylamine (1 equiv) at 40 °C for 14 h did not produce isolable amounts of the allyl transfer product **7**. Instead, ^{1}H NMR and mass spectrometric analysis of the crude reaction mixture revealed the expected disulfide exchange and oxidation products **8** (75%) and **9**

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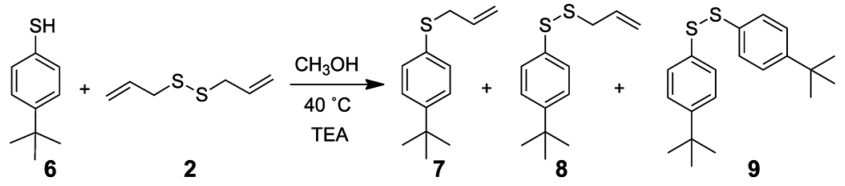
Scheme 2



(20%) alongside just a trace of **7** (Supporting Information S2). However, when **2** was allowed to react with 3 equiv of **6** in methanol containing triethylamine (3 equiv) at 40 °C for 14 h a 14% isolated yield of **7** was obtained (Scheme 2, Table 1). The

Table 1. Allyl Transfer from Compound 2

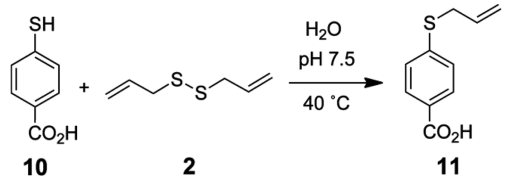
reactants	equiv RSH	solvent	rxn time	product yield
2 + **6**	1	MeOH, TEA, 40 °C	14 h	**7**, trace
2 + **6**	3	MeOH, TEA, 40 °C	14 h	**7**, 14%
2 + **6**	5	MeOH, TEA, 40 °C	2 h	**7**, trace
2 + **6**	5	MeOH, TEA, 40 °C	14 h	**7**, 23%
2 + **6**	5	MeOH, TEA, 40 °C	24 h	**7**, 56%
2 + **6**	5	MeOH, TEA, 40 °C	36 h	**7**, 58%
2 + **6**	10	MeOH, TEA, 40 °C	2 h	**7**, trace
2 + **6**	10	MeOH, TEA, 40 °C	14 h	**7**, 24%
2 + **6**	10	MeOH, TEA, 40 °C	24 h	**7**, 68%
2 + **10**	5	MeOH, TEA, 40 °C	14 h	**11**, 29%
2 + **10**	5	MeOH, TEA, 40 °C	24 h	**11**, 61%
2 + **10**	5	H_2O, pH 7.5, 40 °C	24 h	**11**, 13%
1 + **6**	10	MeOH, TEA, 40 °C	24 h	**7**, 0%
3 + **6**	10	MeOH, TEA, 40 °C	24 h	**7**, 29%
12 + **6**	10	MeOH, TEA, 40 °C	24 h	**13**, 0%

spectral data for **7** isolated from this reaction matched that of authentic material prepared by the reaction of allyl bromide with **2** (Supporting Information S3). The reaction of **2** with 5 equiv of **6** in methanol containing triethylamine (5 equiv) at 40 °C gave a 23% yield of **7** at 14 h and 56% at 24 h (Table 1). The reaction of **2** with 10 equiv of **6** in methanol containing triethylamine (10 equiv) at 40 °C gave a 24% yield of **7** at 14 h and 68% at 24 h. Interestingly, the reaction of **2** with **6** (3 equiv) in tetrahydrofuran (THF) produced **8** (29%) and **9** (71%), but not **7**. Benzylamine and phenol did not react with **2** under these reaction conditions.

Importantly, the allyl transfer reaction also operates in neutral aqueous solution. Specifically, reaction of the water-soluble thiol, 4-carboxythiophenol **10** (5 equiv), with **2** in HEPES buffer (20 mM, pH 7.5, containing 5 mM diethylenetriamine pentaacetic acid to inhibit background autoxidation of the thiol[23]) for 24 h at 40 °C gave the allylated thiol **11** in 13% isolated yield (Scheme 3).

We investigated the analogous reaction of **6** (10 equiv) with other allyl and alkyl sulfides (~0.1 M) in methanol containing triethylamine (10 equiv) at 40 °C for 24 h. Stirring **6** with the

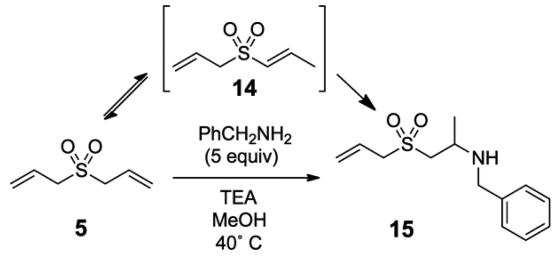
Scheme 3



allyl monosulfide **1** did not produce detectable yields of **7** (for comparison, diallyl disulfide **2** gave a 68% yield of **7** under these conditions). Diallyl trisulfide **3** produced a 29% yield of **7**. Stirring dipropyl disulfide **12** with **6** (10 equiv) under these reaction conditions did not generate any of the alkyl transfer product, 4-(propylthio)-*t*-butylbenzene **13**.

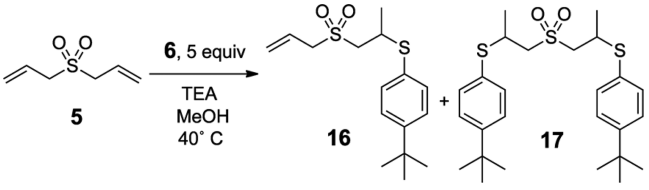
To explore additional pathways by which allyl sulfides might covalently modify biological nucleophiles, we examined the reactivity of two known[4,24] metabolites of **1**, diallyl sulfoxide (**4**) and diallylsulfone (**5**). Compound **4** was prepared in 85% yield by treatment of **1** with oxone (1.1. equiv) in THF/water (1:1) for 1 h (0 °C → 24 °C) and **5** was prepared in 92% yield using a larger excess of oxone (5 equiv) under the same reaction conditions. When the sulfoxide metabolite **4** (0.26 M) was stirred with benzylamine (5 equiv) or the thiophenol derivative **6** (5 equiv) in methanol containing triethylamine (5.5 equiv) at 40 °C for 24 h, no new products were observed. On the other hand, when the sulfone metabolite **5** (0.23 M) was stirred with benzylamine (5 equiv) under these reaction conditions, the alkylation product **15** was generated in 40% yield, with significant amounts of starting material remaining at the end of the reaction (Scheme 4). Similarly, the reaction of the arylmercaptan **6**

Scheme 4



with **5** generated a mixture of **16** and **17** under these reaction conditions (Scheme 5). The products **15**–**17** likely arise via

Scheme 5



base-catalyzed isomerization of the double bond in **5** to yield the electrophilic vinyl sulfone **14**.[25,26] Indeed, we found that stirring of **5** in methanol containing triethylamine (5 equiv) in the absence of benzylamine or the thiophenol **6** gave substantial amounts of the vinyl sulfone derivative **14**, that was detected by diagnostic resonances in the proton NMR at 3.67 and 1.92 ppm (Supporting Information, S12). The yield of the vinyl sulfone observed in our experiment is generally consistent with the

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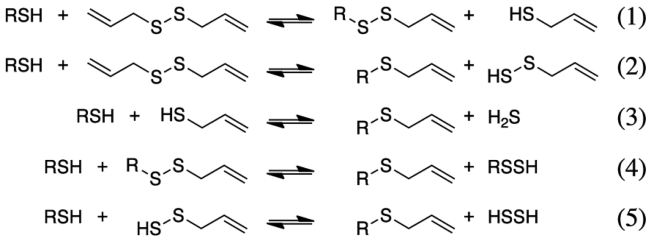
reported 56:44 product ratio of allylsulfone:vinylsulfone resulting from the reflux of methylvinylsulfone in neat triethylamine for 18 h.[26] Finally, we showed that these reactions occur under physiologically relevant conditions. The reaction of **5** with benzylamine in pH 7.5 HEPES buffer produced a 26% yield of **15**, and the reaction of **5** with the aromatic thiol **6** under these conditions provided **16** and **17** in 34% and 8% yields, respectively.

In summary, we characterized several reactions by which the side chains of allyl sulfide natural products might contribute to their bioactivity. We found that **2** and **3** can transfer allyl groups to nucleophilic thiol groups. The aryl thiols used here, with aqueous pK_a values near 7, may be reasonable models for reactive cysteine residues in proteins.[27] The observed allyl transfer reactions involving **2** and **3** required the presence of excess of the thiol. The nucleophilic attack of thiols on the sulfur centers in S−S linkages is fast[28,29] and reactions containing only 1 equiv of thiol rapidly reached a "dead-end" in the disulfide exchange and oxidation products **8** and **9**. On the other hand, when a stoichiometric excess of thiol was present, rapid and reversible sulfur−sulfur exchange equilibria were followed by slower reactions involving nucleophilic attack of aryl thiol on allyl side chains to generate substantial amounts of the allylated product **7**. Our findings with regard to thiol stoichiometry are in line with the recent results of Liang et al.[22] Allyl sulfide **1** is inert with respect to the allyl transfer process. The failure of allyl sulfide **1** to generate **7** in reactions with **6** suggests that thiolate (RS−) is not an effective leaving group in the allyl transfer process, whereas the persulfide (RSS−) or hydrogen sulfide (HS−) leaving groups available in diallyl disulfide and diallyl trisulfide enable nucleophilic substitutions on the allyl side chain. Eqs 1−5 depict reasonable reactions



leading to the transfer of allyl groups from **2** to a thiol residue. Dipropyl disulfide failed to alkylate the aryl thiol **6**, consistent with the higher reactivity of allyl systems compared to propyl systems toward nucleophilic substitution processes.[17] Overall, our results support the possibility that allylation of protein thiol groups could contribute to the bioactivities of allyl disulfides and polysulfides.

We found that the sulfone metabolite[4] of allyl sulfide **1** readily alkylates amine and thiol nucleophiles. These reactions likely proceed via base-catalyzed generation of the vinyl sulfone **14**. Reactions of this type could be biologically relevant. For example, vinyl sulfones are electrophilic[30] and have been described as enzyme inactivators.[25,26,31−35] It is possible that one pathway for mechanism-based inactivation of cytochrome P450 2E1 by **1** involves oxidation to **5**, followed by conversion to the vinyl sulfone **14** as the ultimate enzyme inactivator.[4,24]

EXPERIMENTAL SECTION

Materials and Methods. Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. Tetrahydrofuran was distilled under a nitrogen atmosphere over sodium metal with benzophenone ketyl indicator and distilled freshly. Organic solvents were evaporated using either rotary evaporator or by blowing with a stream of nitrogen gas. Column chromatography was performed using 230−400 mesh silica gel as stationary phase. ^{1}H NMR spectra were recorded on either a 500 MHz or a 600 MHz spectrometer with chemical shifts reported in δ ppm. ^{13}C NMR spectra were obtained on the same instruments at 125 and 150 MHz, respectively. ^{1}H NMR chemical shifts (δ) are reported in ppm relative to TMS as internal reference. The ^{13}C NMR spectra employed $CDCl_3$ as an internal reference. FT-IR spectra were obtained on NaCl plates. Melting points were recorded on a Unitemp capillary melting point apparatus.

General Procedure for Allyl Transfer Reactions in Methanol. To a stirred solution of thiol **6** or **10** (1, 3, 5, or 10 equiv) and triethylamine (1, 3, 5, or 10 equiv) in methanol (3 mL) was added polysulfides **1**, **2**, **3**, or **12** (1 equiv) and the mixture heated at 40 °C for 14 or 24 h. Solvent was completely removed *in vacuo* and products purified by column chromatography on silica eluted with mixtures of ethyl acetate−hexanes or methanol−dichloromethane.

General Procedure for Allyl Transfer Reactions in pH 7.5 Buffer. To a stirred solution of thiol **6** or **10** (1, 3, 5, or 10 equiv) in N_2-purged buffer (20 mM HEPES, 5 mM DTPA or 50 mM HEPES, pH 7.5, 100 mM NaCl, 1 mM EDTA, 3 mL) was added polysulfides **1**, **2**, **3** or **12** (1 equiv) and the mixture heated at 40 °C for 14 or 24 h. Solvent was completely removed *in vacuo* and products purified by column chromatography on silica gel eluted with mixture of acetate−hexanes or methanol−dichloromethane.

Synthesis of Authentic Allyl(4-(*tert*-butyl)phenyl)sulfane (7). To a cooled solution of thiol (100 mg, 0.6 mmol) and triethylamine (210 μL, 1.5 mmol) in dry THF (5 mL) was added allyl bromide (123 μL, 1.5 mmol) and the reaction stirred for 30 min at room temperature. Solvent was completely removed *in vacuo* and column chromatography on silica gel eluted with 10% methanol-dichloromethane gave **7** (110 mg, 89% yield) as a colorless oil, R_f = 0.57 (hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32−7.28 (m, 4H), 5.93−5.86 (m, 1H), 5.16−5.06 (m, 2H), 3.53 (d, J = 7.2, 1.2 Hz, 2H), 1.31 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.5, 133.8, 132.3, 129.9, 125.8, 117.5, 37.5, 34.4, 31.2; FT-IR (cm^{-1}) 3074, 2962, 2900, 2861, 1492, 1356, 1121, 916, 824; HRMS (EI-TOF, [M]$^+$) m/z calcd for $C_{13}H_{18}S$: 206.1129, found 206.1135.

Synthesis of 1,2-Bis(4-(*tert*-butyl)phenyl)disulfane (9). To a solution of hydrogen peroxide (50 μL of 30% hydrogen peroxide) in a 1:1 mixture of diethyl ether and water (4 mL), was added sodium carbonate (38 mg, 0.36 mmol) followed by **6** (50 mg, 0.30 mmol). The resulting mixture was stirred at room temperature for 1 h. The ether layer was separated, washed with DI water, and dried over anhydrous Na2SO4. The solvent was evaporated to yield **9** as a white solid (48 mg, 96%): mp =70−72 °C; R_f = 0.64 (hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, J = 8.4 Hz, 4H), 7.36 (d, J = 8.4 Hz, 4H), 1.33 (s, 18H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.4, 134.0, 127.7, 126.1, 34.5, 31.3; FT-IR (cm^{-1}) 2963, 1493. 1474, 1462, 1387, 1362, 1260, 1120, 1014, 830; HRMS (ESI-TOF, [M]$^+$) m/z calcd for $C_{20}H_{26}S_2$: 330.1476, found 330.1466. Spectral data matched published.[36]

Synthesis of Authentic 4-(Allylthio)benzoic Acid (11). To a cooled solution of thiol **10** (100 mg, 0.65 mmol) and triethylamine (228 μL, 1.62 mmol) in dry THF (5 mL) was added allyl bromide (107 μL, 1.3 mmol) and the mixture stirred for 30 min at room temperature. Solvent was completely removed *in vacuo* and column chromatography on silica gel eluted with 10% methanol−dichloromethane gave **11** (102 mg, 81% yield). As a white solid, R_f = 0.41 (10% methanol/dichloromethane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 5.94−5.86 (m, 1H), 5.29 (dd, J = 17.0, 1.5 Hz, 1H), 5.17 (dd, J = 10.0, 1.0 Hz, 1H), 3.65 (d, J = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 144.7, 132.5, 130.4, 126.8, 118.5, 35.2; FT-IR (cm-1) 3015, 2981, 2553, 1688, 1596, 1418, 1291, 1213, 1082, 905, 754; HRMS (ESI-TOF, [M + H]$^+$) m/z calcd for $C_{10}H_{11}O_2S$: 195.0480, found 195.0486. Spectral data was consistent with published.[37]

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Synthesis of (4-(*tert*-Butyl)phenyl)(propyl)sulfane (13). To a solution of thiol **6** (50 mg, 0.30 mmol) and triethylamine (84 μL, 0.60 mmol) in dry THF (10 mL) at 0−5 °C, was added 1-iodopropane (44 μL, 0.45 mmol) dropwise under an atmosphere of N_2. The resulting mixture was stirred at room temperature for 2 h. The solvent was completely removed *in vacuo*, the residue dissolved in ethyl acetate (10 mL), washed with HC (1 M, 2 × 15 mL) and DI water (1 × 15 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to yield **13** as yellow oil (61 mg, 97% yield). R_f = 0.42 (hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (q, *J* = 16.2, 8.4 Hz, 4H), 2.89 (t, *J* = 7.2 Hz, 2H), 1.66−1.72 (m, 2H), 1.33 (s, 9H), 1.04 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.0, 133.3, 129.3, 125.9, 36.1, 34.4, 31.3, 22.7, 13.5; IR (cm^{-1}) 2954, 2927, 2863, 1496, 1116, 906, 819, 728; HRMS (EI-TOF, $[M]^+$) *m*/*z* calcd for $C_{13}H_{20}S$: 208.1286, found 208.1291.

Synthesis of Diallyl Sulfoxide (4). To a cooled suspension of oxone (5.92 g, 19 mmol) in THF/H2O (1:1) was added diallyl sulfide (2.0 g, 17 mmol) at 0 °C slowly and stirred at room temperature for 1 h. The reaction mixture was filtered and THF evaporated in vacuo. The resulting residue was extracted with dichloromethane (2 × 20 mL), the organic layer dried over Na2SO4, and concentrated to afford crude product. The crude product was purified by column chromatography on silica gel eluted with 40% ethyl acetate/hexanes to give **4** as a colorless oil (1.90 g, 83%). R_f = 0.22 (40% ethyl acetate/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87−5.79 (m, 2H), 5.39 (d, *J* = 10.0 Hz, 2H), 5.33 (d, *J* = 17.0 Hz, 2H), 3.48 (d, *J* = 7.5 Hz, 1H), 3.45 (d, *J* = 7.0 Hz, 1H), 3.35 (d, *J* = 7.5 Hz, 1H), 3.33 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 125.5, 123.5, 53.9; HRMS (ESI-TOF, $[M + Na]^+$) *m*/*z* calcd for $C_6H_{10}OSNa$: 153.0350, found 153.0346. Spectral data was consistent with published.[38]

Synthesis of Diallyl Sulfone (5). To a cooled suspension of oxone (26.9 g, 87 mmol) in THF/H2O (1:1) was added diallyl sulfide (2.0 g, 17 mmol) at 0 °C slowly and the resulting mixture stirred at room temperature for 1 h. The reaction mixture was filtered and THF was evaporated in vacuo. The resulting residue was extracted with dichloromethane (2 × 20 mL), the organic layer dried over Na2SO4, and concentrated to afford the sulfone **5** as a colorless oil (2.3 g, 92% yield). R_f = 0.58 (40% ethyl acetate/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93−5.85 (m, 2H), 5.48 (d, *J* = 10.0 Hz, 2H), 5.41 (d, *J* = 17.5 Hz, 2H), 3.68 (d, *J* = 7.5 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 124.9, 124.8, 55.9; IR (cm^{-1}) 3090, 3027, 2979, 2919, 1640, 1426, 1318, 1290, 1132, 937, 869; HRMS (EI-TOF, $[M]^+$) *m*/*z* calcd for $C_6H_{10}O_2S$: 146.0402, found 146.0406. Spectral data was consistent with published.[38]

Synthesis of 1-(Allylsulfonyl)-*N*-benzylpropan-2-amine (15) in Methanol. To a stirred solution of diallyl sulfone **5** (100 mg, 0.68 mmol) and triethylamine (520 μL, 3.76 mmol) in methanol (3 mL) was added benzylamine (373 μL, 3.42 mmol) and the reaction heated at 40 °C for 14 h. The solvent completely removed by blowing with a stream of nitrogen gas and column chromatography on silica gel eluted with 70% ethyl acetate−hexanes gave **15** as a colorless oil (69 mg, 40% yield). Spectral data provided below.

Synthesis of 1-(Allylsulfonyl)-*N*-benzylpropan-2-amine (15) in pH 7.5 Buffer. To a stirred solution of diallyl sulfone **5** (50 mg, 0.34 mmol) in buffer (50 mM HEPES, pH 7.5, 100 mM NaCl, 1 mM EDTA, 2 mL) was added benzylamine (186 μL, 1.71 mmol) and the mixture heated at 40 °C for 24 h. The solvent was completely removed by blowing stream of nitrogen gas on the mixture. The residue was dissolved in ethyl acetate and washed with H_2O and brine. The organic layer evaporated *in vacuo* and column chromatography on silica gel eluted with 70% ethyl acetate−hexanes gave **15** as a colorless oil (23 mg, 26% yield). R_f = 0.19 (50% ethyl acetate/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.33 (m, 4H), 7.31−7.26 (m, 1H), 5.96−5.88 (m, 1H), 5.47 (d, *J* = 10.0 Hz, 1H), 5.38 (d, *J* = 17.5 Hz, 1H), 3.91−3.83 (m, 2H), 3.78−3.71 (m, 2H), 3.46−3.33 (m, 1H), 3.15 (dd, *J* = 14.5, 8.0 Hz, 1H), 2.94 (dd, *J* = 14.5, 4.0 Hz, 1H), 1.29 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.7, 128.5, 128.1, 127.1, 125.1, 124.6, 58.9, 57.2, 51.0, 47.9, 20.6; FT-IR (cm^{-1}) 3620, 2965, 2923, 1485, 1389, 1305, 1110, 835; HRMS (ESI-TOF, $[M + H]^+$) *m*/*z* calcd for $C_{13}H_{19}NO_2S$: 254.1215, found 254.1219.

Synthesis of (4-(*tert*-Butyl)phenyl)(1-(vinylsulfonyl)propan-2-yl)sulfane (16) and (Sulfonylbis(propane-1,2-diyl))bis((4-(*tert*-butyl)phenyl)sulfane) (17) in Methanol. To a stirred solution of diallyl sulfone **5** (100 mg, 0.68 mmol) and triethylamine (520 μL, 3.76 mmol) in methanol (3 mL) was added thiol **6** (589 μL, 3.42 mmol) and the mixture heated at 40 °C for 14 h. The solvent was completely removed by blowing a stream of nitrogen gas on the mixture and the products **16** and **17** were isolated by column chromatography on silica gel eluted with 20% ethyl acetate−hexanes) as colorless oils, in 43% yield (92 mg) and 19% yield (62 mg), respectively. Spectral data below.

Synthesis of (4-(*tert*-Butyl)phenyl)(1-(vinylsulfonyl)propan-2-yl)sulfane (16) and (Sulfonylbis(propane-1,2-diyl))bis((4-(*tert*-butyl)phenyl)sulfane) (17) in pH 7.5 Buffer. To a solution of diallyl sulfone **5** (50 mg, 0.34 mmol) in buffer (50 mM HEPES, pH 7.5, 100 mM NaCl, 1 mM EDTA, 2 mL) was added thiol **6** (294 μL, 1.71 mmol) and the mixture heated at 40 °C for 24 h. The solvent was completely removed by blowing on the mixture with a stream of nitrogen gas. The residue was mixed with ethyl acetate (3 mL) and the resulting cloudy mixture washed with H_2O (2 × 1.5 mL) and brine to remove buffer salts. The organic layer was evaporated *in vacuo* and products **16** and **17** isolated by column chromatography on silica gel eluted with 20% ethyl acetate−hexanes as colorless oils in 34% yield (36 mg) and 8% yield (13 mg), respectively. (**16**) R_f = 0.15 (10% ethyl acetate/hexanes); Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.34 (m, 4H), 5.82−5.74 (m, 1H), 5.37 (dd, *J* = 10.5, 1.0 Hz, 1H), 5.28 (dd, *J* = 17.0, 1.0 Hz, 1H), 3.71−3.61 (m, 3H), 3.32 (dd, *J* = 10.5, 1.0 Hz, 1H), 2.97 (dd, *J* = 15.0, 10.0 Hz, 1H), 1.53 (d, *J* = 6.5 Hz, 3H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6, 133.1, 129.0, 126.3, 124.8, 124.7, 59.0, 56.8, 37.4, 34.61, 31.2, 20.7; FT-IR (cm^{-1}) 2962, 2923, 2865, 1491, 1391, 1310, 1129, 827; HRMS (ESI-TOF, $[M + Na]^+$) *m*/*z* calcd for $C_{16}H_{24}O_2S_2Na$: 335.1115, found 335.1109.

(**17**) R_f = 0.29 (10% ethyl acetate/hexanes); Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.31 (m, 8H), 3.66−3.61 (m, 2H), 3.28 (td, *J* = 13.5, 3.5 Hz, 2H), 3.04 (dd, *J* = 14.0, 9.5 Hz, 1H), 2.94 (dd, *J* = 14.0, 9.5 Hz, 1H), 1.46 (d, *J* = 5.0 Hz, 6H), 1.31 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6, 151.5, 133.1, 132.9, 128.8, 128.7, 126.3, 60.2, 59.9, 37.2, 37.1, 34.6, 34.5, 31.1, 20.6, 20.5; FT-IR (cm^{-1}) 2961, 2926, 2860, 1490, 1456, 1394, 1264, 1128, 828; HRMS (ESI-TOF, $[M + Na]^+$) *m*/*z* calcd for $C_{26}H_{38}O_2S_3Na$: 501.1932, found 501.1929.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02517.

^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Block, E. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1135−1178.
(2) Münchberg, U.; Anwar, A.; Mecklenburg, S.; Jacob, C. *Org. Biomol. Chem.* **2007**, *5*, 1505−1518.
(3) Block, E. *Garlic and the other alliums: the lore and the science*; Royal Society of Chemistry: Cambridge, 2009.
(4) Brady, J. F.; Ishizaki, H.; Fukuto, J. M.; Lin, M. C.; Fadel, A.; Gapac, J. M.; Yang, C. S. *Chem. Res. Toxicol.* **1991**, *4*, 642−647.
(5) Munday, R.; Munday, J. S.; Munday, C. M. *Free Radical Biol. Med.* **2003**, *34*, 1200−1211.
(6) Munday, R.; Munday, C. M. *Methods Enzymol.* **2004**, *382*, 449−456.
(7) Benavides, G. A.; Squadrito, G. L.; Mills, R. W.; Patel, R. P.; Darley-Usmar, V. M.; Doeller, J. E.; Kraus, D. W.; Isbell, T. S.; Patel, T. P. *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 17977−17982.
(8) Truong, D.; Hindmarsh, W.; O'Brien, D. J. *Chem.-Biol. Interact.* **2009**, *180*, 79−80.
(9) Chan, K. C.; Hsu, C. C.; Yin, M. C. *Thromb. Res.* **2002**, *108*, 317−322.
(10) Chatterji, T.; Gates, K. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 535−538.
(11) Chatterji, T.; Gates, K. S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1349−1352.
(12) Chatterji, T.; Keerthi, K.; Gates, K. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3921−3924.
(13) Mitra, K.; Kim, W.; Daniels, J. S.; Gates, K. S. *J. Am. Chem. Soc.* **1997**, *119*, 11691−11692.
(14) Hoffman, M.; Rajapakse, A.; Shen, X.; Gates, K. S. *Chem. Res. Toxicol.* **2012**, *25*, 1609−1615.
(15) Zhao, Y.; Biggs, T. D.; Xian, M. *Chem. Commun.* **2014**, *50*, 11788−11805.
(16) Sparnins, V. L.; Barany, G.; Wattenberg, L. W. *Carcinogenesis* **1988**, *9*, 131−134.
(17) Streitwieser, A. *Chem. Rev.* **1956**, *56*, 571−752.
(18) Everett, S. A.; Folkes, L. K.; Wardman, P.; Asmus, K.-D. *Free Radical Res.* **1994**, *20*, 387−400.
(19) Park, C.-M.; Weerasinghe, L.; Day, J. J.; Fukuto, J. M.; Xian, M. *Mol. BioSyst.* **2015**, *11*, 1775−1785.
(20) Pan, J.; Carroll, K. S. *ACS Chem. Biol.* **2013**, *8*, 1110−1116.
(21) Parsons, Z. D.; Gates, K. S. *Abstracts of Papers 244th ACS National Meeting & Exposition* August 2012, pp 19−23.
(22) Liang, D.; Wu, H.; Wong, M. W.; Huang, D. *Org. Lett.* **2015**, *17*, 4196−4199.
(23) Misra, H. P. *J. Biol. Chem.* **1974**, *249*, 2151−2155.
(24) Jin, L.; Baillie, T. A. *Chem. Res. Toxicol.* **1997**, *10*, 318−327.
(25) Meadows, D. C.; Gervay-Hague, J. *Med. Res. Rev.* **2006**, *26*, 793−814.
(26) O'Connor, D. E.; Lyness, W. I. *J. Am. Chem. Soc.* **1964**, *86*, 3840−3846.
(27) Semenow-Garwood, D. *J. Org. Chem.* **1972**, *37*, 3797−3803.
(28) Guo, W.; Pleasants, J.; Rabenstein, D. L. *J. Org. Chem.* **1990**, *55*, 373−376.
(29) Keire, D. A.; Strauss, E.; Guo, W.; Noszal, B.; Rabenstein, D. L. *J. Org. Chem.* **1992**, *57*, 123−127.
(30) Forristal, I.; Lawson, K.; Rayner, C. *Sulfur Lett.* **2003**, *26*, 89−94.
(31) Liu, S.; Hanzlik, R. P. *J. Med. Chem.* **1992**, *35*, 1067.
(32) Morales-Sanfrutos, J.; Lopez-Jaramillo, J.; Ortega-Muñoz, M.; Megia-Fernandez, A.; Perez-Balderas, F.; Hernandez-Mateo, F.; Santoyo-Gonzalez, F. *Org. Biomol. Chem.* **2010**, *8*, 667−675.
(33) Liu, S.; Zhou, B.; Yang, H.; He, Y.; JIang, Z. X.; Kumar, W.; Wu, L.; Zhang, Z. Y. *J. Am. Chem. Soc.* **2008**, *130*, 8251−8260.
(34) Li, H.; O'Donoghue, A. J.; van der Linden, W. A.; Xie, S. C.; Yoo, E.; Foe, I. T.; Tilley, L.; Craik, C. S.; da Fonseca, P. C. A.; Bogyo, M. *Nature* **2016**, *530*, 233−236.
(35) Vinyl sulfonium ions display similar properties, see: (a) Qu, W.; Catcott, K. C.; Zhang, K.; Liu, S.; Guo, J. J.; Ma, J.; Pablo, M.; Glick, J.; Xiu, Y.; Kenton, N.; Ma, X.; Duclos, R. I. J.; Zhou, Z. S. *J. Am. Chem. Soc.* **2016**, *138*, 2877−2880. (b) Zhao, G.; Zhou, Z. S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2331−2335.
(36) Frei, R.; Courant, T.; Wodrich, M. D.; Waser, J. *Chem. - Eur. J.* **2015**, *21*, 2662−2668.
(37) Wrobel, J.; Green, D.; Jetter, J.; Kao, W.; Rogers, J.; Pérez, M. C.; Hardenburg, J.; Deecher, D. C.; López, F. J.; Arey, B. J.; Shen, E. S. *Bioorg. Med. Chem.* **2002**, *10*, 639−656.
(38) Bahrami, K.; Khodaei, M. M.; Arabi, M. S. *J. Org. Chem.* **2010**, *75*, 6208−6213.

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