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Cesium (*Z*)-2-Carbomethoxyethenethiolate: A Reagent for the Preparation of (*Z*)-2-Carbomethoxyethenyl Thioethers Including Selected Cysteine and Homocysteine Derivatives

Jennifer S. O'Donnell,[a] Suneel P. Singh,[a] Thomas A. Metcalf,[a] and Adrian L. Schwan*[a]

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As a means to circumvent the standard and sometimes troubling conjugate addition reaction of thiols to alkyl propiolates, a new reagent, cesium (Z)-2-carbomethoxyethenethiolate, is introduced. The cesium carbonate mediated methanolysis of (Z)-2-carbomethoxyethenyl thiolacetate at low temperature creates cesium (Z)-2-carbomethoxyethenethiolate in solution. For base-insensitive and solvolytically stable electrophiles, efficient substitution can be achieved by direct introduction to the electrophile. The conditions were adapted to accommodate base-sensitive cysteine derivatives, and the use of DMF as a cosolvent permits the isolation of (Z)-2-carbomethoxyethenyl cysteinyl thioethers in high enantiomeric purity (>99:1 *er*) and with good Z/*E* ratios. There was no evidence of carbon substitution reactions.

Introduction

There has been considerable interest in the conjugate addition of thiols to alkynoate esters. The reaction has been used to prepare sulfur heterocycles[1–3] and potential drug candidates,[4] and it also serves as a general tool in organic synthesis.[3,5–10] The addition reaction often gives a mixture of double-bonded isomers and a solvent dependence on the *E*/*Z* ratio of products has been observed[11,12] and explained.[13]

We have been interested in this reaction for eventual access to selected vinylic sulfoxides, which in turn are converted into α,β-unsaturated sulfinyl chlorides.[14] Also, the addition of thiols to methyl propiolate gives thioethers, which after oxidation serve as a general source of alkane- and arenesulfenic acid anions.[15] For the latter reason we had an opportunity to react protected cysteine derivatives with methyl propiolate. Related reactions have been studied in detail previously,[11] with yields varying from 40 to 75%.

Looking to improve on past results, we re-evaluated some of the past chemistry[11] (vide infra) and as a result sought to develop a new protocol for the preparation of carboalkoxyethenyl thioethers, one that creates the vinylic C–S bond at an earlier stage and one that precludes the requirement of a selection of thiols. As many thiols are prepared through manipulation of halides anyway, this was viewed as a useful exercise. The thermodynamically less stable *cis* form of the adduct was targeted on the basis of our needs and the existing ready access to *trans* addition products. Moreover, (*Z*)-2-carboalkoxyethenyl thioethers are useful in the synthesis of β-lactam analogs[16–19] and in the preparation of dienophiles.[10] Given our needs and the established value of (*Z*)-2-carboalkoxyethenyl thioethers,[20] we report herein our study leading to cesium (*Z*)-2-carbomethoxyethenethiolate, which serves to prepare (*Z*)-2-carbomethoxyethenyl thioethers, including some vinylic cysteine and homocysteine derivatives.

Results and Discussion

The conjugate addition of Boc-Cys-OEt (**1a**) to methyl propiolate (MP) parallels closely addition reactions reported by Crisp and Millan,[11] who studied the reactions of Cbz-Cys-OMe with ethyl propiolate (EP) in various solvents. Under neutral conditions, in a variety of solvents, those authors found the desired Michael product and a dehydroalanine derivative, but the *E*/*Z* ratio of the addition products was typically not synthetically useful. Our reactions were done with numerous bases,[21,22] in a variety of solvents,[23] and with varying nitrogen protection (although PG = Boc is detailed here).[24] Analysis of our reaction mixture led to the isolation of Michael adduct **2** (0–68%) in addition to dehydroalanine **3** and bisvinylic thioether **4** (Scheme 1).[25] Those products suggested that the Michael addition could proceed in a satisfactory manner but the immediate desired cysteine/MP adduct was prone to loss of the sulfur group through an elimination reaction from the amino acid. The resulting enethiolate then underwent subsequent Michael addition to unreacted MP.

[a] Department of Chemistry, University of Guelph, Guelph, ON, N1G 2W1, Canada
Fax: +1-519-766-1499
E-mail: schwan@uoguelph.ca
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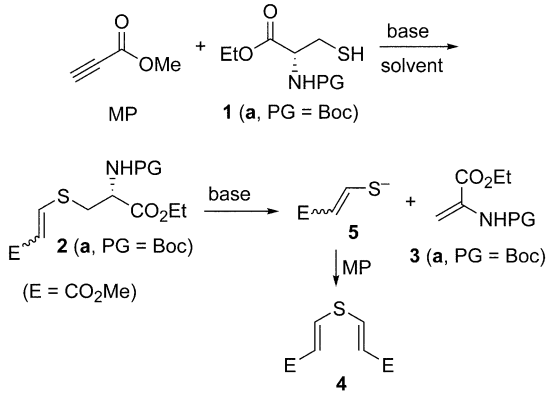
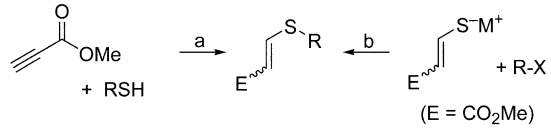


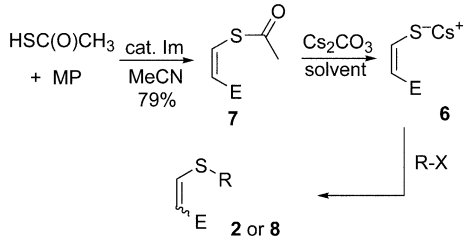
Scheme 1. The sensitivity of direct conjugate addition of MP with protected cysteines.

Although were we able to show that thioether **4** could be treated with alkoxide to recover an equivalent of **5** for alkylation chemistry,[24] the overall plan was viewed as inefficient. Nevertheless, the alkylation chemistry of (ECH=CHS$^-$) prompted us to explore the direct use of (ECH=CHS$^-$) as an enethiolate alternative (Scheme 2, path b) to the problematic conjugate addition reactions (Scheme 2, path a). The use of enethiolates as a source of vinylic thioethers is rare in comparison to the use of thiol addition reactions. As such, only sporadic examples exist in the literature.[10,17,26] As we sought to prepare 2-(*Z*)-carbomethoxyethenyl cysteines from alaninyl halides, and given the base sensitivity of the α-H of amino acids, we decided to pursue the heretofore unknown cesium (*Z*)-carbomethoxyethenethiolate (**6**), as it is recognized that cesium thiolates do not perturb the chirality of selected α-amino acid derivatives.[27–29] Although sodium (*Z*)-carbomethoxyethenethiolate is known,[10,17] its preparation requires aqueous NaOH, which we presumed would have a deleterious effect on the amino acid chemistry.[30]



Scheme 2. Options for the preparation of 2-carboalkoxyethenyl thioethers.

We chose to access the target compound through (*Z*)-2-carbomethoxyethenyl thiolacetate (**7**), a compound that has not been addressed in the primary literature since 1968.[31–34] Targeting the *cis* isomer, we were able to find conditions to effect the addition of thiolacetic acid to MP in good yield and in a >20:1 *Z*/*E* ratio (NMR spectroscopic analysis). Specifically, the use of a catalytic amount of imidazole as the base provided the favorable double bond ratio (Scheme 3). Pure **7** was obtained through flash chromatography in 79% yield on a multigram scale (Scheme 3).[35]



Scheme 3. Formation of cesium (*Z*)-2-carbomethoxyethenethiolate and its general alkylation chemistry.

A wide variety of conditions for the conversion of **7** into its cesium enethiolate were evaluated. Cs_2CO_3-mediated methanolysis of the thiolacetate provided some suitability. The mixtures were quenched with *n*BuI as a representative electrophile. Good *E*/*Z* selectivity was observed when the reaction temperature was kept below –10 °C. If the temperature was raised to 50 °C, near-complete isomerization to the *E* isomer was observed. Overall, several representative thioacrylates could be formed, as shown in Table 1.

Table 1. Yields and stereoselectivities of substitution products **2** and **8**.

Entry	RX, temp[a]	Cond.[b]	Prod./ % Yield	*E*/*Z*	*er*[e]
1	*n*BuI, r.t.	A	**8a**/76	1:2.6	–
2	*n*BuI, r.t. (one step)	A	**8a**/73	1:4.2	–
3	*n*BuI	A	**8a**/70	1:16.7	–
4	*n*BuI, r.t. to 50 °C	A	**8a**/56	13.3:1	–
5	BnBr	A	**8b**/83	1:20.7	–
6	3-ClBnBr	A	**8c**/90	1:14.7	–
7	*i*PrI	A	**8d**/0	–	–
8	*c*-C_6H_{11}I	A	**8e**/0	–	–
9	PMBBr	A	**8f**/30	1:5.9	–
10	PMBBr[c]	B	**8f**/92	<1:49[f]	–
11	DPMBr[c]	B	**8g**/40	1:10.9	–
12	BnO_2CCH_2Br	A	**8h**/81	<1:49[f]	–
13	EtO_2CCH_2I	A	**8h**/83	<1:49[f]	–
14	EtO_2CCH_2I	C	**8i**/71	1:8.2	–
15	(*S*)-Bz-homoAla(I)-OMe (**9a**)	A	**8j**/76	1:19.5	>99:1
16	(*S*)-Cbz-homoAla(I)-OMe (**9b**)	A	**8k**/67	1:19.1	>99:1
17	(*R*)-Boc-Ala(I)-OEt (**10a**)	A	**2a**/62	1:25.0	41:59
18	(*R*)-Boc-Ala(I)-OEt[d]	C	**2a**/75	1:8.7	>99:1
19	(*R*)-Cbz-Ala(I)-OEt (**10b**)	A	**2b**/75	1:11.8	46:54
20	(*R*)-Cbz-Ala(I)-OEt[d]	C	**2b**/78	1:6.0	>99:1
21	(*R*)-Bz-Ala(I)-OEt (**10c**)	A	**2c**/75	1:4.7	43:58
22	(*R*)-Bz-Ala(I)-OEt[d]	C	**2c**/76	1:4.3	>99:1
23	(*R*)-Fmoc-Ala(I)-OEt (**10d**)	A	**2d**/52	1:2.4	63:37
24	(*R*)-Fmoc-Ala(I)-OEt	C	**2d**/78	1:6.6	>99:1
25	(*R*)-Fmoc-Ala(Br)-OEt (**10e**)	C	**2d**/81	1:3.6	>99:1

[a] All reactions were performed at –10 °C unless otherwise indicated. [b] Reaction conditions, see Experimental Section. [c] Three equivalents of the electrophile were employed. [d] Reactions were performed at –40 °C. [e] Enantiomeric ratio of the *Z* isomer (only) obtained by chiral HPLC by using a Chiralcel OJ-H column. [f] Minor isomer was not detected.

Typical benzyl bromides reacted effectively with high *Z*/*E* ratios. The reaction of **6** with secondary alkyl iodides did not proceed (Table 1, Entries 7 and 8), but benzhydryl bromide reacted to afford **8g** in low yield. Usually, the elec-

trophile is introduced in MeOH, but if the electrophile is solvolysis prone, THF is an adequate replacement (conditions B). In particular, PMBBr only gave a high yield of thioether when introduced in THF. If MeOH was employed, PMBOMe was clearly evident in the reaction mixture. Product **8f** from this reaction is particularly noteworthy, as this is a useful precursor to α,β-unsaturated sulfinyl chlorides,[14] and the reaction at hand represents a more efficient reaction than through the thiol (Figure 1).

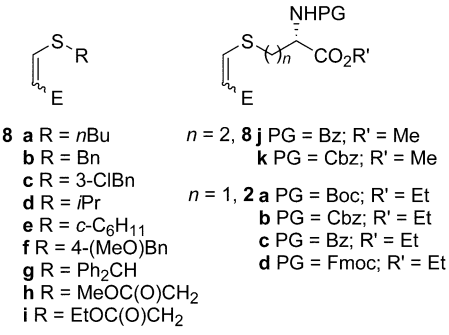
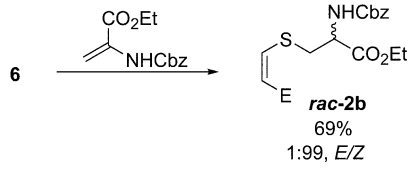


Figure 1. Alkylation products of cesium (*Z*)-2-carbomethoxyethenethiolate.

α-Halo esters are also reactive electrophiles (Table 1, Entries 12 and 13), but transesterification occurred under conditions A. Nevertheless, these two examples were indicative of clean substitution α to the carbonyl group. Moreover, there was no detectable *E* isomer in the mixture. In none of these reactions did we observe any C-alkylation products.

The reaction of **6** with protected homoalaninyl iodides **9** occurred in good yield with high double-bond selectivity and with preservation of chirality of the substrate; no racemization was detected. However, successful application of these conditions to the more-sensitive alaninyl iodides **10** failed. Although good double-bond stereochemistry could be maintained in some cases, there was significant racemization. A control experiment demonstrated that **6** was sufficiently reactive to add to Cbz-Dha-OEt, which resulted the formation of *rac*-**2b** (Scheme 4). Presumably, conditions A induced some elimination of HI from compounds **10** and subsequent conjugate addition produced products of attenuated stereogenicity.



Scheme 4. Reaction of cesium (*Z*)-2-carbomethoxyethenethiolate with a dehydroalanine.

Numerous experiments were performed to improve the outcome of the reactions of **6** with iodides **10**, including the use of substoichiometric amounts of Cs_2CO_3, neutralization methods, and attempts to isolate the cesium enethiolate, but these efforts did not offer any viable solutions. Suitable conditions based on established protocols of Cs_2CO_3 in DMF were eventually found.[27,28] Specifically, **6** is produced as usual in MeOH at –40 °C. That solution is then transferred to a solution of iodide **10** in DMF at –40 °C and stirred for 3 h. Under these conditions, improved yields of the product were obtained and there was no evidence of racemization at the α-position. Strangely, in some cases, the *Z*/*E* double-bond ratio suffered slightly. In the example of **2d**, the yield, the *Z*/*E* ratio, and the α-carbon stereochemistry were all improved, but the electrophilic iodide is clearly superior to the bromide.

These useful reaction conditions prompted us to revisit the reaction of **6** with α-halo esters (Table 1, Entry 14). A good yield and *Z*/*E* ratio were obtained, and the ethyl ester was unperturbed.

In general, Entries 18–25 of Table 1 exhibit lower *Z*/*E* ratios in comparison to earlier entries in the Table. The reason may be based on the degree of substitution near the halide-bearing carbon atom. Clearly, the two protecting groups on substrates **10** create a steric impedance, which retards direct substitution of the halide. Few, if any, of the other electrophiles reported herein possess comparable hindrance. It follows then that slower substitution of **6** permits more time for its isomerization, and moreover, the *E* version of **6** may be expected to have less steric demands. The Fmoc and Bz groups offer the lowest *Z*/*E* ratios. The result obtained with the Fmoc group may be due to its large size in relation to the other carbamate-based Cbz and Boc groups. As to the ratio obtained with the benzoyl moiety, the aryl group is two atoms closer to the reaction site than the aryl group in the Cbz moiety, which may add additional steric retardation to the substitution reaction.

With regard to products **2a**–**d**, conditions A and C offer complementary products, depending on one's needs. Conditions A tend to preserve the geometry of the double bond, but clearly the stereochemistry of the amino acid is sacrificed. In contrast, conditions C fully preserve the configuration at the α-carbon while providing a *Z*/*E* ratio that is slighted reduced; in many cases, however, it is still preferable than the ratio obtained under the conditions used for Michael addition.

Conclusions

In this paper we present the new enethiolate reagent cesium (*Z*)-carbomethoxyethenethiolate (**6**). This reagent is conveniently prepared from thiolacetate **7**, which in turn arises from the reaction of thiolacetic acid and methyl propiolate. The *Z* stereochemistry of **6** is maintained at low temperature, and the reagent exhibits sulfur nucleophilicity exclusively with a variety of electrophiles. The compounds prepared have value in the preparation of sulfenate anions[15] and in some cases sulfinyl chlorides.[14]

Most importantly, thiolate **6** reacts with protected alaninyl and homoalaninyl iodides to produce the equivalent of the *Z* Michael addition product of protected cysteine with methyl propiolate. The reaction occurs in good yield

with high double-bond stereoselectivity, all while preserving the integrity of the α-carbon configuration. This is an important achievement given our difficulty and fair yields obtained with base-induced conjugate additions of protected cysteine derivatives. Moreover, the preserved stereogenicity permits further elaboration in target-oriented synthesis.[36–38]

Experimental Section

General: Melting points were determined with a MEL-TEMP melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained with a Bomen FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker model spectrometer at the frequency indicated in $CDCl_3$ unless otherwise noted. Chemical shifts are referenced to $CHCl_3$ or tetramethylsilane and are recorded in parts per million (ppm). Mass spectra (MS) were performed at either the McMaster Regional Centre for Mass Spectrometry, McMaster University, or the WATSPEC Mass Spectrometry Facility, University of Waterloo. Elemental analyses were performed by MHW Laboratories of Pheonix, AZ. Solvents were distilled and dried. Chemicals were purchased from Aldrich unless otherwise specified. All air- and water-sensitive reagents were transferred by oven-dried, nitrogen-purged syringes into flame-dried flasks. Flash chromatography was performed on virgin or recycled 200–450 mesh Type 60 Å silica gel. Analytical thin-layer chromatography (TLC) was performed by using 0.25-mm Merck Kieselgel 60 F_{254} precoated glass-backed silica-gel plates or Silicycle 0.25-mm, extra hard layer, 60 Å F_{254} glass-backed silica-gel plates. HPLC experiments were performed with a Waters 600–2487 (λ = 254 nm) system by using a Chiralcel OJ-H (0.46 × 25 cm) column and *i*PrOH/hexane as the eluent. Optical rotations were measured with a Rudolph Research Autopol III automatic polarimeter in 1-dm tubes.

Sample Reaction of 1a with MP: A solution of (*R*)-Boc-Cys-OEt (**1a**; 1.92 g, 7.72 mmol) was prepared in CH_2Cl_2 (10 mL) and cooled to 0 °C. Methyl propiolate (890 μL, 10.0 mmol) was added, followed by the slow addition of triethylamine (1.18 mL, 8.49 mmol), upon which the solution turned dark brown. The mixture was stirred for 60 min, allowing the ice bath to warm to room temperature. A 5% solution of HCl was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3×), and the combined organic layer washed with H_2O and brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting thioether was isolated by flash chromatography (silica gel, 10% EtOAc/hexanes). Thioether yields were calculated from the thiol. Thioether (**2a**, data presented later) was obtained in 38% yield, accompanied by Boc-Dha-OEt (**3a**)[39] and bisvinylic thioether **4** in variable yields. Data for **4**: M.p. 140–142 °C (MeOH). ^{1}H NMR (400 MHz): δ = 7.70 (d, J = 15.4 Hz, 1 H), 6.09 (d, J = 15.4 Hz, 1 H), 3.77 (s, 3 H) ppm. ^{13}C NMR (100.6 MHz): δ = 164.8, 140.9, 119.0, 51.8 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3002, 2953, 1716, 1582 cm^{-1}. MS (EI): m/z (%) = 202 (100) [M]$^+$, 171 (41), 143 (57), 127 (56), 117 (43), 99 (13), 85 (22), 59 (28), 58 (15). HRMS (EI): calcd. for $C_8H_{10}O_4S$ 202.0300; found 202.0298.

(*Z*)-2-Carbomethoxyethenyl Thiolacetate (7): Methyl propiolate (8.0 mL, 89.4 mmol) in CH_3CN (50 mL) was added dropwise over 2 h to a stirred solution of thiolacetic acid (4.4 mL, 61.8 mmol) and imidazole (210 mg, 3.0 mmol) in CH_3CN (170 mL) at 45 °C. The reaction mixture was stirred overnight at 45 °C. Acetonitrile was removed under vacuum. Pure **7** was obtained by flash chromatography (10% EtOAc/hexanes) in 79% yield. Data for the *Z* isomer: M.p. 51–53 °C (ref.[32] 58–59 °C). ^{1}H NMR (400 MHz): δ = 7.80 (d, J = 10.3 Hz, 1 H), 6.10 (d, J = 10.3 Hz, 1 H), 3.78 (s, 3 H), 2.48 (s, 3 H) ppm. ^{13}C NMR (75.5 MHz): δ = 191.8, 166.5, 137.3, 116.2, 51.7, 30.8 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2849, 1710, 1600, 1359, 1126 cm^{-1}.

General Procedures for the Synthesis of (*Z*)-2-Carbomethoxyethenyl Alkyl Thioethers

Method A: Cs_2CO_3 (1.02 equiv.) was added to a solution of thiolacetate **7** (1 equiv.) dissolved in MeOH (6 mL) at –10 °C, followed by the immediate addition of a solution of RX (1 equiv.) in MeOH (1–2 mL). The reaction mixture was allowed to stir overnight and a 5% solution of HCl was added until the solution was acidic by litmus. CH_2Cl_2 was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3×), and the combined organic layer was washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude thioether, which was purified by flash chromatography through silica gel (EtOAc/hexanes). Thioether yields were calculated from thiolacetate **7**.

Method B: This method mirrors method A, except three equivalents of electrophile were introduced in THF.

Method C: A cooled (–40 or –10 °C) solution of Cs_2CO_3 (1.02 equiv.) in MeOH (6 mL) was added to a cooled (–40 or –10 °C) solution of thiolacetate **7** (1.0 equiv.) in MeOH (6 mL) under a nitrogen atmosphere. The mixture was stirred for 5 min. and added to a cooled solution (–40 or –10 °C) of RX (1.1 equiv.) in DMF (13 mL). The reaction mixture was allowed to stir 3 h, and the volatiles were removed under reduced pressure. The remaining organic layer was added to 10% aqueous citric acid and extracted with diethyl ether (3 × 50 mL). The combined organic layer was washed with H_2O (1 × 20 mL) and brine (2 × 20 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting thioether was purified as per method A.

(*Z*)-2-Carbomethoxyethenyl Butyl Thioether (8a) (Method A): Thiolacetate **7** (100 mg, 0.625 mmol) in MeOH (5 mL) at –10 °C was treated with Cs_2CO_3 (208 mg, 0.637 mmol), followed by the immediate addition of a solution of *n*BuI (85.3 μL, 0.750 mmol) in MeOH (1 mL). Thioether **8a** (76.5 mg, 70%) was isolated as a pale-yellow oil after flash chromatography (5% EtOAc/hexanes) as a mixture of *E*/*Z* isomers (1:16.7). Data for the *Z* isomer: ^{1}H NMR (400 MHz): δ = 7.70 (d, J = 15.2 Hz, 1 H), 7.11 (d, J = 10.2 Hz, 1 H), 5.85 (d, J = 10.2 Hz, 1 H), 5.75 (d, J = 15.2 Hz, 1 H), 3.74 (s, 3 H), 3.72 (s, 3 H), 2.79 (t, J = 7.4 Hz, 2 H), 2.77 (t, J = 7.4 Hz, 2 H), 1.66 (p, J = 7.4 Hz, 4 H), 1.45 (sextet, J = 7.4 Hz, 4 H), 0.94 (t, J = 7.4 Hz, 3 H), 0.93 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz): δ = 166.7, 150.5, 112.2, 50.8, 35.4, 32.1, 21.3, 13.3 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2961, 2875, 1697, 1581 cm^{-1}. MS (EI): m/z (%) = 174 (100) [M]$^+$, 149 (62), 143 (58), 117 (55), 114 (32), 86 (42), 69 (27), 57 (40). HRMS (EI): calcd. for $C_8H_{14}O_2S$ 174.0715; found 174.0714.

(*Z*)-2-Carbomethoxyethenyl Benzyl Thioether (8b) (Method A): Thiolacetate **7** (120 mg, 0.750 mmol) in MeOH (7 mL) at –10 °C was treated with Cs_2CO_3 (249 mg, 0.765 mmol), followed by the immediate addition of a solution of BnBr (107 μL, 0.900 mmol) in MeOH (3 mL). Thioether **8b** (129 mg, 83%) was isolated as an oil after flash chromatography (5% EtOAc/hexanes) as a mixture of *E*/*Z* isomers (1:20.3). Data for the mixture of isomers: M.p. 47–51 °C. Data for the *Z* isomer:[40] ^{1}H NMR (400 MHz): δ = 7.71 (d, J = 15.1 Hz, 1 H), 7.30 (m, 10 H), 7.06 (d, J = 10.2 Hz, 1 H), 5.83 (d, J = 15.0 Hz, 1 H), 5.82 (d, J = 10.3 Hz, 1 H), 4.00 (s, 2 H), 3.95

(s, 2 H), 3.71 (s, 3 H), 3.70 (s, 3 H) ppm. ^{13}C NMR (100.6 MHz): δ = 166.8, 148.8, 137.0, 128.9, 128.7, 127.4, 113.0, 51.1, 39.3 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3066, 3032, 2951, 2846, 1708, 1585, 1496, 1435, 1312, 1042, 828 cm^{-1}.

(*Z*)-2-Carbomethoxyethenyl 3-Chlorobenzyl Thioether (8c) (Method A): Thiolacetate **7** (120 mg, 0.750 mmol) in MeOH (7 mL) at –10 °C was treated with Cs_2CO_3 (249 mg, 0.765 mmol), followed by the immediate addition of a solution of 3-chlorobenzyl bromide (118 μL, 0.900 mmol) in MeOH (3 mL). Thioether **8c** (165 mg, 90%) was isolated as a pale-yellow oil after flash chromatography (5% EtOAc/hexanes) as a mixture of *E*/*Z* isomers (1:14.6). Data for the *Z* isomer: ^{1}H NMR (400 MHz): δ = 7.33 (s, 1 H), 7.23 (m, 3 H), 7.02 (d, *J* = 10.2 Hz, 1 H), 5.85 (d, *J* = 10.2 Hz, 1 H), 3.93 (s, 2 H), 3.73 (s, 3 H) ppm. ^{13}C NMR (75.5 MHz), δ = 166.8, 148.2, 139.2, 134.5, 130.0, 128.9, 127.6, 127.0, 113.5, 51.2, 38.8 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2952, 1697, 1579, 1224, 1172, 1009, 802 cm^{-1}. MS (EI): *m*/*z* (%) = 242 (49) [M]$^+$, 211 (14), 127 (32), 117 (60), 89 (15). $C_{11}H_{11}ClO_2S$ (242.72): calcd. C 54.46, H 4.53; found C 54.56, H 4.32.

(*Z*)-2-Carbomethoxyethenyl *p*-Methoxybenzyl Thioether (8f) (Method B): Thiolacetate **7** (120 mg, 0.750 mmol) in MeOH (7 mL) at –10 °C was treated with Cs_2CO_3 (249 mg, 0.765 mmol), followed by the immediate addition of a solution of PMBBr (452 mg, 2.25 mmol) in THF (3 mL). Thioether **8f** (164 mg, 92%) was isolated as an oil after flash chromatography (5% EtOAc/hexanes) as the *Z* isomer exclusively (no *E* isomer detected). Data for the *Z* isomer: ^{1}H NMR (400 MHz): δ = 7.24 (d, *J* = 8.7 Hz, 2 H), 7.06 (d, *J* = 10.2 Hz, 1 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 5.81 (d, *J* = 10.2 Hz, 1 H), 3.91 (s, 2 H), 3.78 (s, 3 H), 3.71 (s, 3 H) ppm. ^{13}C NMR (75.5 MHz): δ = 166.8, 158.8, 148.8, 130.0, 128.9, 114.0, 112.8, 55.1, 51.1, 38.7 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3007, 2952, 1698, 1512, 1172, 833 cm^{-1}. $C_{12}H_{14}O_3S$ (238.30): calcd. C 60.53, H 5.88; found C 60.74, H 5.64.

(*Z*)-2-Carbomethoxyethenyl Diphenylmethyl Thioether (8g) (Method B): Thiolacetate **7** (120 mg, 0.750 mmol) in MeOH (7 mL) at –10 °C was treated with Cs_2CO_3 (249 mg, 0.765 mmol), followed by the immediate addition of a solution of DPMBr (185 mg, 2.25 mmol) in THF (3 mL). Thioether **8g** (97.7 mg, 40%) was isolated as a white solid after flash chromatography (5% EtOAc/hexanes) as a mixture of *E*/*Z* isomers (1:10.9). Data for the *Z* isomer: M.p. 109–110 °C (EtOAc/hexanes). ^{1}H NMR (400 MHz): δ = 7.33 (m, 10 H), 6.98 (d, *J* = 10.3 Hz, 1 H), 5.79 (d, *J* = 10.3 Hz, 1 H), 5.42 (s, 1 H), 3.73 (s, 3 H) ppm. ^{13}C NMR (75.5 MHz): δ = 165.6, 145.6, 139.5, 128.9, 128.3, 127.8, 115.1, 55.2, 51.4 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3029, 2951, 1696, 1576, 1438, 1227, 1170, 803 cm^{-1}. MS (EI): *m*/*z* (%) = 284 (2) [M]$^+$, 168 (15), 167 (100), 166 (9), 165 (25), 152 (12). $C_{17}H_{16}O_2S$ (284.37): calcd. C 71.85, H 5.63; found C 72.00, H 5.66.

Methyl [(*Z*)-2-Carbomethoxyethenylsulfanyl]acetate (8h) (Method A): Thiolacetate **7** (100 mg, 0.625 mmol) in MeOH (8 mL) at –10 °C was treated with Cs_2CO_3 (208 mg, 0.637 mmol), followed by the immediate addition of a solution of ethyl 2-iodoacetate (74.0 μL, 0.625 mmol) or benzyl 2-bromoacetate (99.0 μL, 0.625 mmol) in MeOH (2 mL). Transesterified *methyl* ester thioether **8h** (95.9 mg, 81%) was isolated as a pale-yellow oil after flash chromatography (15% EtOAc/hexanes) as the *Z* isomer exclusively (no *E* isomer detected). Data for the *Z* isomer: ^{1}H NMR (400 MHz): δ = 7.23 (d, *J* = 10.1 Hz, 1 H), 5.94 (d, *J* = 10.1 Hz, 1 H), 3.76 (s, 3 H), 3.75 (s, 3 H), 3.44 (s, 2 H) ppm. ^{13}C NMR (75.5 MHz): δ = 169.8, 166.8, 148.1, 113.9, 52.6, 51.3, 36.2 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2953, 1738, 1698, 1582, 1172, 1009, 803 cm^{-1}. MS (EI): *m*/*z* (%) = 190 (40) [M]$^+$, 159 (21), 158 (59), 131 (18), 130 (19), 126 (37), 117 (100), 99 (16), 84 (11), 59 (17). $C_7H_{10}O_4S$ (190.22): calcd. C 44.23, H 5.26; found C 44.40, H 5.09.

Ethyl [(*Z*)-2-Carbomethoxyethenylsulfanyl]acetate (8i) (Method C): A cooled (–10 °C) solution of Cs_2CO_3 (416 mg, 1.27 mmol) in methanol (6 mL) was added to a cooled (–10 °C) solution of thiolacetate **7** (200 mg, 1.25 mmol) in MeOH (6 mL). The mixture was stirred for 5 min and then added to a cooled solution (–10 °C) of RX (148.0 μL, 1.25 mmol) in DMF (13 mL). Thioether **8i** (180 mg, 71%) was obtained as a pale-yellow oil as a mixture of *E*/*Z* isomers (1:8.2). Data for the *Z* isomer: ^{1}H NMR (300 MHz): δ = 7.12 (d, *J* = 10.2 Hz, 1 H), 5.79 (d, *J* = 9.9 Hz, 1 H), 4.06 (q, *J* = 7.2 Hz, 2 H), 3.61 (s, 3 H), 3.30 (s, 2 H), 1.14 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz): δ = 169.1, 166.6, 148.4, 113.9, 61.4, 51.1, 36.3, 13.9 ppm. IR (KBr): $\tilde{\nu}$ = 3433, 2983, 2943, 1734, 1694, 1580, 1219, 1167, 801 cm^{-1}. HRMS (TOF EI+): calcd. for $C_8H_{12}O_4S$ [M]$^+$ 204.0456; found 204.0445.

(*S*)-Bz-homoCys[(*Z*)-2-carbomethoxyethenyl]-OMe (8j) (Method A): Thiolacetate **7** (85.0 mg, 0.531 mmol) in MeOH (5 mL) was treated with Cs_2CO_3 (177 mg, 0.542 mmol), followed by the immediate addition of a solution of Bz-homoAla(I)-OMe (**9a**; 184 mg, 0.531 mmol) in MeOH (2 mL). Thioether **8j** (136 mg, 76%, *er* >99:1) was isolated as a white solid after flash chromatography (30% EtOAc/hexanes, then 50% EtOAc/hexanes) as a mixture of *E*/*Z* isomers (1:19.5). Data for the *Z* isomer: M.p. 102–103 °C. $[\alpha]_D^{25}$ = +43.0 (*c* = 1.05, $CHCl_3$). ^{1}H NMR (400 MHz): δ = 7.82 (d, *J* = 7.2 Hz, 2 H), 7.47 (m, 3 H), 7.06 (d, *J* = 10.2 Hz, 1 H), 7.03 (s, 1 H), 5.87 (d, *J* = 10.2 Hz, 1 H), 4.90 (dt, *J* = 5.1, 7.6 Hz, 1 H), 3.79 (s, 3 H), 3.72 (s, 3 H), 2.86 (m, 2 H), 2.37 (m, 1 H), 2.19 (m, 1 H) ppm. ^{13}C NMR (100.6 MHz): δ = 172.2, 167.2, 166.9, 149.4, 145.9, 133.4, 131.9, 128.6, 127.1, 113.4, 52.8, 51.8, 51.3, 33.4, 31.8, 27.8 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3429, 2952, 1739, 1697, 1666, 1223, 1172, 802 cm^{-1}. MS (EI): *m*/*z* (%) = 337 (3) [M]$^+$, 220 (13), 216 (18), 193 (50), 184 (14), 161 (44), 105 (100), 77 (24). $C_{16}H_{19}NO_5S$ (337.39): calcd. C 56.66, H 5.60; found C 56.86, H 5.57. HPLC (8% *i*PrOH/hexanes, 1 mL min^{-1} flow rate): t_R = 52.6 min.

(*S*)-Cbz-homoCys[(*Z*)-2-carbomethoxyethenyl]-OMe (8k) (Method A): Thiolacetate **7** (594 mg, 3.71 mmol) in MeOH (36 mL) was treated with Cs_2CO_3 (1.23 mg, 3.79 mmol), followed by the immediate addition of a solution of Cbz-homoAla(I)-OMe (**9b**; 1.40 g, 3.71 mmol) in MeOH (12 mL). Thioether **8k** (911 mg, 67%, *er* >99:1) was isolated as an oil after flash chromatography (25% EtOAc/hexanes, then 50% EtOAc/hexanes) as a mixture of *E*/*Z* isomers (1:19.1). Data for the *Z* isomer: $[\alpha]_D^{25}$ = +21.6 (*c* = 1.04, $CHCl_3$). ^{1}H NMR (400 MHz): δ = 7.35 (m, 5 H), 7.01 (d, *J* = 10.2 Hz, 1 H), 5.88 (d, *J* = 10.2 Hz, 1 H), 5.38 (br. d, *J* = 7.6 Hz, 1 H), 5.12 (s, 2 H), 4.48 (dt, *J* = 5.3, 7.6 Hz, 1 H), 3.76 (s, 3 H), 3.74 (s, 3 H), 2.79 (m, 2 H), 2.24 (m, 1 H), 2.04 (m, 1 H) ppm. ^{13}C NMR (75.5 MHz): δ = 172.0, 166.9, 155.9, 149.4, 136.0, 128.5, 128.2, 128.1, 113.3, 67.1, 53.0, 52.6, 51.2, 33.5, 31.6 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3409, 2956, 1742, 1725, 1698, 1218, 1172, 803 cm^{-1}. $C_{17}H_{21}NO_6S$ (367.42): calcd. C 56.61, H 5.72; found C 55.72, H 5.53. HPLC (8% *i*PrOH/hexanes, 1 mL min^{-1} flow rate): t_R = 47.1 min.

(*R*)-Boc-Cys[(*Z*)-2-carbomethoxyethenyl]-OEt (2a) (Method C): A cooled (–40 °C) solution of Cs_2CO_3 (416 mg, 1.27 mmol) in MeOH (6 mL) was added to a cooled (–40 °C) solution of thiolacetate **7** (200 mg, 1.25 mmol) in MeOH (6 mL). The mixture was stirred for 5 min and then added to a cooled solution (–40 °C) of Boc-Ala(I)-OEt (**10a**; 471 mg, 1.37 mmol) in DMF (13 mL). Workup and purification gave thioether **2a** (320 mg, 77%, *er* >99:1) as an oil as a mixture of *E*/*Z* isomers (1:8.7). Data for the *Z* isomer: $[\alpha]_D^{25}$ = +50.5 (*c* = 0.80, CH_2Cl_2). ^{1}H NMR (400 MHz): δ = 7.02 (d, *J* = 10.1 Hz,

1 H), 5.85 (d, J = 10.1 Hz, 1 H), 5.39 (br. d, J = 6.4 Hz, 1 H), 4.60 (m 1 H), 4.23 (q, J = 7.1 Hz, 2 H), 3.74 (s, 3 H), 3.29 (br. m, 2 H), 1.45 (s, 9 H), 1.28 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100.6 MHz), δ = 169.9, 165.4, 154.9, 146.3, 114.8, 80.4, 62.1, 53.1, 51.4, 35.2, 28.2, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 3432, 2987, 1747, 1718, 1690 cm^{-1}. MS (TOF CI+): m/z (%) = 334.1 (0.6) [M + H]$^+$, 278.1 (20). 277.1 (16), 260.1 (39), 234.1 (100), 228.0 (59), 216.0 (77), 160.0 (78). $C_{14}H_{23}NO_6S$ (333.40): calcd. C 50.47, H 6.90; found C 50.60, H 6.88. HPLC (8% iPrOH/hexanes, 1 mL min^{-1} flow rate): t_R = 17.3 min. Data for the E isomer: ^{1}H NMR (400 MHz): δ = 7.51 (d, J = 15.3 Hz, 1 H), 5.79 (d, J = 15.3 Hz, 1 H), 5.34 (br. d, J = 6.4 Hz, 1 H), 4.58 (m 1 H), 4.16 (q, J = 6.3 Hz, 2 H), 3.64 (s, 3 H), 3.34 (ABX, J_{AX} = 4.7 Hz, J_{BX} = 4.8 Hz, J_{AB} = 14.1 Hz, 2 H), 1.38 (s, 9 H), 1.24 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100.6 MHz): δ = 169.9, 165.4, 154.9, 146.3, 80.4, 62.2, 53.1, 51.4, 35.2, 28.2, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 3367, 2979, 1716, 1584, 1524, 1255, 1165 cm^{-1}. MS (ES+): m/z (%) = 356.1 (21) [M + Na]$^+$, 351.2 (66) [M + NH$_4$]$^+$, 334.1 (8) [M + H]$^+$, 278.0 (15), 234.0 (32), 219.9 (20), 202.9 (7). HRMS (TOF ESI+): calcd. for $C_{14}H_{27}NO_2S$ [M + NH$_4$]$^+$ 351.1590; found 351.1590. HPLC (8% iPrOH/hexanes, 1 mL min^{-1} flow rate): t_R = 10.9 min.

(*R*)-Cbz-Cys[(*Z*)-2-carbomethoxyethenyl]-OEt (2b) (Method C): A cooled (–40 °C) solution of Cs_2CO_3 (416 mg, 1.27 mmol) in MeOH (6 mL) was added to a cooled (–40 °C) solution of thiolacetate **7** (200 mg, 1.25 mmol) in MeOH (6 mL). The mixture was stirred for 5 min and then added to a cooled solution (–40 °C) of Cbz-Ala(I)-OEt (**10b**; 518 mg, 1.37 mmol) in DMF (13 mL). Workup and purification gave thioether **2b** (360 mg, 78%, *er* >99:1) as a white solid as a mixture of *E*/*Z* isomers (1:5.4). The isomeric mixture was separated by careful flash chromatography (15% EtOAc/hexanes). Data for the Z isomer: $[\alpha]_D^{25}$ = +65.0 (c = 0.96, CH_2Cl_2). M.p. 76–77 °C. ^{1}H NMR (400 MHz): δ = 7.35 (m, 5 H), 6.95 (d, J = 10.1 Hz, 1 H), 5.78 (d, J = 10.1 Hz, 1 H), 5.65 (br. d, J = 6.6 Hz, 1 H), 5.12 (AB$_q$, J = 12.2 Hz, 2 H), 4.66 (m, 1 H), 4.23 (q, J = 7.2 Hz, 2 H), 3.73 (s, 3 H), 3.30 (d, J = 4.4 Hz, 2 H), 1.29 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz), δ = 169.7, 166.8, 155.6, 149.7, 136.1, 128.5, 128.3, 128.1, 113.5, 67.1, 62.2, 54.4, 51.3, 38.3, 14.1 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3425, 3035, 2952, 1748, 1719, 1701, 805, 602 cm^{-1}. MS (TOF CI+): m/z (%) = 368.1 (49) [M + H]$^+$, 324.1 (61), 277.1 (43), 260.0 (100), 243.1 (49), 228.0 (94), 216.0 (90), 183.1 (55), 117.0 (70), 108.1 (60), 91.0 (87). $C_{17}H_{21}NO_6S$ (367.42): calcd. C 55.61, H 5.72; found C 55.38, H 5.52. HPLC (8% iPrOH/hexanes, 1 mL min^{-1} flow rate): t_R = 48.9 min. Data for the E isomer: M.p. 58–59 °C. ^{1}H NMR (400 MHz): δ = 7.55 (d, J = 15.2 Hz, 1 H), 7.33–7.29 (m, 5 H), 5.84 (d, J = 15.2 Hz, 1 H), 5.65 (br. d, J = 6.0 Hz, 1 H), 5.13 (AB$_q$, J = 12.1 Hz, 2 H), 4.66 (m, 1 H), 4.23 (q, J = 7.1 Hz, 2 H), 3.67 (s, 3 H), 3.31 (ABX, J_{AX} = 4.7 Hz, J_{BX} = 4.8 Hz, J_{AB} = 14.0 Hz, 2 H), 1.27 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100.6 MHz): δ = 168.3, 164.1, 154.2, 144.8, 134.6, 127.2, 127.0, 126.8, 113.7, 66.0, 61.1, 52.2, 50.2, 23.8, 12.7 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3325, 1728, 1713, 1693, 1583, 1274, 1167 cm^{-1}. MS (ESI+): m/z (%) = 390.2 (100) [M + Na]$^+$, 385.2 (7) [M + NH$_4$]$^+$, 242.5 (56). HRMS (TOF ESI+): calcd. for $C_{17}H_{25}N_2O_6S$ [M + NH$_4$]$^+$ 385.1433; found 385.1454. HPLC (8% iPrOH/hexanes, 1 mL min^{-1} flow rate): t_R = 23.5 min.

(*R*)-Bz-Cys[(*Z*)-2-carbomethoxyethenyl]-OEt (2c) (Method C): A cooled (–40 °C) solution of Cs_2CO_3 (204 mg, 0.625 mmol) in MeOH (2.5 mL) was added to a cooled (–40 °C) solution of thiolacetate **7** (100 mg, 0.625 mmol) in MeOH (2.5 mL). The mixture was stirred for 5 min and then added to a cooled solution (–40 °C) of Bz-Ala(I)-OEt (**10c**; 238 mg, 0.687 mmol) in DMF (6 mL). Workup and purification gave thioether **2c** (160 mg, 76%, *er* >99:1) as a white solid as a mixture of *E*/*Z* isomers (1:4.3). The isomeric mixture was separated by flash chromatography (10% EtOAc/hexanes, then 15% EtOAc/hexanes). Data for the Z isomer: $[\alpha]_D^{25}$ = +83.5 (c = 0.96, CH_2Cl_2). M.p. 91–92 °C. ^{1}H NMR (400 MHz): δ = 7.80 (m, 2 H), 7.51 (m, 3 H), 7.10 (br. d, J = 6.6 Hz, 1 H), 7.03 (d, J = 10.1 Hz, 1 H), 5.81 (d, J = 10.1 Hz, 1 H), 5.06 (dt, J = 4.3, 6.6 Hz, 1 H), 4.28 (q, J = 6.6 Hz, 2 H), 3.72 (s, 3 H), 3.45 (ABX, J_{AX} = 4.7 Hz, J_{BX} = 4.0 Hz, J_{AB} = 14.3 Hz, 2 H), 1.32 (t, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz), δ = 169.9, 167.2, 149.9, 133.4, 132.1, 128.7, 127.1, 113.5, 62.4, 53.3, 51.4, 38.1, 14.2 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3426, 3032, 2952, 1737, 1698, 1665, 804 cm^{-1}. MS (EI): m/z (%) = 337 (14) [M]$^+$, 216 (59), 143 (14), 105 (100), 77 (30). $C_{16}H_{19}NO_5S$ (337.39): calcd. C 57.00, H 5.63; found C 56.90, H 5.67. HPLC (8% iPrOH/hexanes, 1 mL min^{-1} flow rate): t_R = 52.1 min. Data for the E isomer: M.p. 84–85 °C. ^{1}H NMR (400 MHz): δ = 7.78–7.76 (m, 2 H), 7.55 (d, J = 15.3 Hz, 1 H), 7.52–7.48 (m, 1 H), 7.44–7.40 (m, 2 H), 6.98 (br. d, J = 5.7 Hz, 1 H), 5.86 (d, J = 15.3 Hz, 1 H), 5.06 (dt, J = 4.3, 6.7 Hz, 1 H), 4.26 (q, J = 7.1 Hz, 2 H), 3.61 (s, 3 H), 3.56–3.34 (ABX, J_{AX} = 4.6 Hz, J_{BX} = 4.2 Hz, J_{AB} = 14.1 Hz, 2 H), 1.31 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100.6 MHz): δ = 169.8, 167.1, 165.2, 146.2, 133.3, 132.0, 128.6, 127.1, 115.2, 62.5, 52.4, 51.4, 34.8, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 3339, 2951, 1701, 1580, 1523, 1219, 1169 cm^{-1}. MS (ES+): m/z (%) = 360.1, (42) [M + Na]$^+$, 338.1 (100) [M + H]$^+$, 306.1 (11), 242 (18). HRMS (TOF ESI+): calcd. for $C_{16}H_{20}NO_6S$ [M + H]$^+$ 338.1062; found 338.1053. HPLC (8% iPrOH/hexanes, 1 mL min^{-1} flow rate): t_R = 42.5 min.

(*R*)-Fmoc-Cys[(*Z*)-2-carbomethoxyethenyl]-OEt (2d) (Method C): A cooled (–10 °C) solution of Cs_2CO_3 (204 mg, 0.625 mmol) in MeOH (2.5 mL) was added to a cooled (–10 °C) solution of thiolacetate **7** (100 mg, 0.625 mmol) in MeOH (2.5 mL) under a nitrogen atmosphere. The mixture was stirred for 5 min and then added to a cooled solution (–10 °C) of Fmoc-Ala(I)-OEt (**10d**; 319 mg, 0.687 mmol) or Fmoc-Ala(Br)-OEt (**10e**; 274 mg, 0.656 mmol) in DMF (6 mL). Workup and purification gave thioether **2d** (222 mg, 78% from **10d**; 231 mg, 81% from **10e**; *er* >99:1) as a white solid as a mixture of *E*/*Z* isomers (1:6.6 from **10d**; 1:3.6 from **10e**). The isomeric mixture was separated by flash chromatography (10% EtOAc/hexanes). It should be noted that the reaction was not complete after 3 h when the experiment was performed at –40 °C. Data for the Z isomer: $[\alpha]_D^{25}$ = +29.7 (c = 0.8, CH_2Cl_2). ^{1}H NMR (400 MHz): δ = 7.74 (d, J = 7.4 Hz, 2 H), 7.57 (d, J = 7.4 Hz, 2 H), 7.38 (t, J = 7.4 Hz, 2 H), 7.30 (t, J = 7.4 Hz, 2 H), 6.96 (d, J = 10.1 Hz, 1 H), 5.81 (d, J = 10.1 Hz, 1 H), 5.80 (br. s, 1 H), 4.67 (m, 1 H), 4.40 (m, 2 H), 4.21 (m, 3 H), 3.71 (s, 3 H), 3.27 (br. d, J = 4.5 Hz, 2 H), 1.27 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz), δ = 169.6, 166.7, 155.5, 149.4, 143.5, 141.1, 127.6, 127.0, 124.9, 119.9, 113.5, 67.0, 62.1, 54.2, 51.2, 46.9, 38.2, 14.0 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3417, 1723, 1698, 1172 cm^{-1}. MS (CI, NH$_3$): m/z (%) = 473 (100) [M + NH$_4$]$^+$, 456 (11), 372 (13), 277 (19), 234 (20), 179 (16), 178 (20). HRMS (EI). calcd. for $C_{24}H_{25}NO_6S$ [M]$^+$ 455.1404; found 455.1412. HPLC (30% iPrOH/hexanes, 0.7 mL min^{-1} flow rate): t_R = 49.6 min. Data for the E isomer: ^{1}H NMR (400 MHz): δ = 7.74 (d, J = 7.5 Hz, 2 H), 7.59–7.55 (m, 3 H), 7.38 (t, J = 7.4 Hz, 2 H), 7.32–7.27 (m, 2 H), 5.86 (d, J = 15.3 Hz, 1 H), 5.65 (d, J = 7.2 Hz, 1 H), 4.68 (m, 1 H), 4.45–4.32 (m, 2 H), 4.26–4.19 (m, 3 H), 3.62 (s, 3 H), 3.42–3.24 (ABX, J_{AX} = 4.6 Hz, J_{BX} = 4.7 Hz, J_{AB} = 14.0 Hz, 2 H), 1.30 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100.6 MHz): δ = 169.6, 165.3, 155.5, 146.0, 143.6, 141.2, 127.7, 127.0, 125.0, 119.9, 115.0, 67.3, 62.4, 53.4, 51.4, 47.0, 34.9, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 3325, 1710, 1583, 1268, 1167 cm^{-1}. MS (ESI+): m/z (%) = 478.1 (100) [M + Na]$^+$, 473.1 (54) [M + NH$_4$]$^+$, 456.1 (9) [M + H]$^+$, 449.4 (44), 425.2 (37), 390.1 (57), 385.1 (45), 368.2 (14), 192.1 (10), 102.1 (13).

HRMS (TOF ESI+): calcd. for $C_{24}H_{26}NO_6S$ $[M + H]^+$ 456.1481; found 456.1502. HPLC (30% *i*PrOH/hexanes, 0.7 mL min^{-1} flow rate): t_R = 27.2 min.

Supporting Information (see footnote on the first page of this article): Preparation of the amino acid based electrophiles.

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[1] A. A. Esmaili, M. Ghereghloo, M. R. Islami, H. R. Bijanzadeh, *Tetrahedron* **2003**, *59*, 4785–4788.
[2] V. A. Bakulev, V. S. Berseneva, N. P. Belskaia, Y. Y. Morzherin, A. Zaitsev, W. Dehaen, I. Luyten, S. Toppet, *Org. Biomol. Chem.* **2003**, *1*, 134–139.
[3] M. Journet, A. Rouillard, D. Cai, R. D. Larsen, *J. Org. Chem.* **1997**, *62*, 8630–8631.
[4] M. Mitsukuchi, T. Ikemoto, M. Taguchi, S. Higuchi, S. Abe, H. Yasui, K. Hatayama, K. Sota, *Chem. Pharm. Bull.* **1989**, *37*, 3286–3293.
[5] N. Maezaki, S. Yagi, R. Yoshigami, J. Maeda, T. Suzuki, S. Ohsawa, K. Tsukamoto, T. Tanaka, *J. Org. Chem.* **2003**, *68*, 5550–5558.
[6] Y. V. Bilokin, A. Melman, V. Niddam, B. Benhamu, M. D. Bachi, *Tetrahedron* **2000**, *56*, 3425–3437.
[7] J. Zhang, S. Saito, T. Koizumi, *J. Org. Chem.* **1998**, *63*, 9375–9384.
[8] L. N. Sobenina, A. P. Demenev, A. b. I. Mikhaleva, V. N. Elokhina, A. G. Mal′kina, O. g. A. Tarasova, I. A. Ushakov, B. A. Trofimov, *Synthesis* **2001**, 293–299.
[9] Y. Arai, Y. Hayashi, M. Yamamoto, H. Takayema, T. Koizumi, *J. Chem. Soc. Perkin Trans. 1* **1988**, 3133–3140.
[10] O. De Lucchi, M. Buso, G. Modena, *Tetrahedron Lett.* **1987**, *28*, 107–110.
[11] G. T. Crisp, M. J. Millan, *Tetrahedron* **1998**, *54*, 637–648.
[12] P. D. Halphen, T. C. Owen, *J. Org. Chem.* **1973**, *38*, 3507–3510.
[13] M. E. Jung, K. R. Buszek, *J. Am. Chem. Soc.* **1988**, *110*, 3965–3969.
[14] A. L. Schwan, R. R. Strickler, Y. Lear, M. L. Kalin, T. E. Rietveld, T.-J. Xiang, D. Brillon, *J. Org. Chem.* **1998**, *63*, 7825–7832.
[15] J. S. O'Donnell, A. L. Schwan, *Tetrahedron Lett.* **2003**, *44*, 6293–6296.
[16] H. R. Pfaendler, J. Gosteli, R. B. Woodward, *J. Am. Chem. Soc.* **1980**, *102*, 2039–2043.
[17] H. R. Pfaendler, J. Gosteli, R. B. Woodward, *J. Am. Chem. Soc.* **1979**, *101*, 6306–6310.
[18] P. H. Crackett, C. W. Greengrass, R. J. Stoodley, *Tetrahedron Lett.* **1986**, *27*, 1301–1304.
[19] N. D. Pearson, T. C. Smale, R. Southgate, *Tetrahedron Lett.* **1995**, *36*, 4493–4496.
[20] Under IUPAC nomenclature, the targets (products) of this chemistry are known as methyl (2*Z*)-3-(alkylsulfanyl)prop-2-enoates.
[21] N. D. Smith, M. Goodman, *Org. Lett.* **2003**, *5*, 1035–1037.
[22] C. Dugave, A. Menez, *J. Org. Chem.* **1996**, *61*, 6067–6070.
[23] O. Arjona, R. Medel, J. Rojas, A. M. Costa, J. Vilarrasa, *Tetrahedron Lett.* **2003**, *44*, 6369–6373.
[24] J. S. O'Donnell, PhD Thesis, University of Guelph, **2005**.
[25] M. Hashemi, M. Akhbari, S. Arianfar, *J. Sulfur Chem.* **2004**, *25*, 95–99.
[26] For more examples of ethenethiolate chemistry, see: a) M. Ochiai, M. Hirobe, K. Miyamoto, *J. Am. Chem. Soc.* **2006**, *128*, 9046–9047; b) A. L. Schwan, M. D. Refvik, *Synlett* **1998**, 96–98; c) V. A. Potapov, N. K. Gusarova, B. A. Trofimov, S. V. Amosova, A. S. Kashik, *Sulfur Lett.* **1985**, *3*, 151–154; d) K. Kpegba, P. Metzner, *Tetrahedron Lett.* **1990**, *31*, 1853–1856; e) E. Block, S.-H. Zhao, *J. Org. Chem.* **1992**, *57*, 5815–5817; f) S. V. Amosova, G. M. Gavrilova, A. V. Afonin, *Russ. J. Org. Chem.* **2005**, *41*,402–405.
[27] H. Shao, S. H. H. Wang, C.-W. Lee, G. Oesapay, M. Goodman, *J. Chem. Soc.* **1995**, *60*, 2956–2957.
[28] C. Dugave, A. Menez, *Tetrahedron: Asymmetry* **1997**, *8*, 1453–1465.
[29] R. N. Salvatore, R. A. Smith, A. K. Nischwitz, T. Gavin, *Tetrahedron Lett.* **2005**, *46*, 8931–8935.
[30] Silver (*Z*)-carbomethoxyethenethiolate is also known, but its preparation also requires hydroxide. M. Giffard, I. Léauté, *J. Chem. Res. (S)* **1990**, 320–321.
[31] L. N. Owen, M. U. S. Sultanbawa, *J. Chem. Soc.* **1949**, 3109–3113.
[32] W. H. Mueller, *J. Org. Chem.* **1966**, *31*, 3075–3079.
[33] G. Dallas, J. W. Lown, J. C. N. Ma, *J. Chem. Soc. C* **1968**, 2510–2514.
[34] D. T. Witiak, M. C. Lu, *J. Org. Chem.* **1968**, *33*, 4451–4454.
[35] The separability of 7 from its *E* isomer is important, as in our experience, the chromatographic separation of *E*/*Z* isomers of alkyl carbomethoxyethenyl thioethers can be challenging.
[36] X. Moreau, J.-M. Campagne, *J. Org. Chem.* **2003**, *68*, 5346–5350.
[37] C. P. Sar, J. Jeko, P. Fajer, K. Hideg, *Synthesis* **1999**, 1039–1045.
[38] G. T. Crisp, M. J. Millan, *Tetrahedron* **1998**, *54*, 649–666.
[39] J. L. Adams, T. M. Chen, B. W. Metcalf, *J. Org. Chem.* **1985**, *50*, 2730–2736.
[40] U. Koelle, C. Rietmann, J. Tjoe, T. Wagner, U. Englert, *Organometallics* **1995**, *14*, 703–713.

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