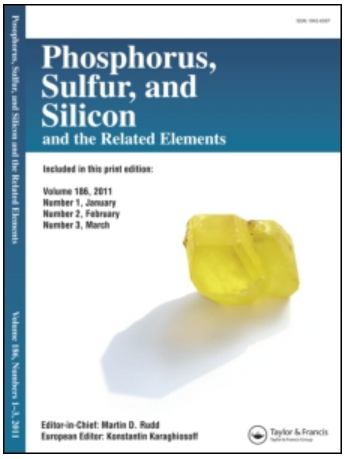

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ONE-POT CONVERSION OF SERINE AND α-METHYLSERINE DERIVATIVES TO THE CORRESPONDING CYSTEINES AND SELENOCYSTINES BY USING CHALCOGENOPHOSPHATE REAGENTS

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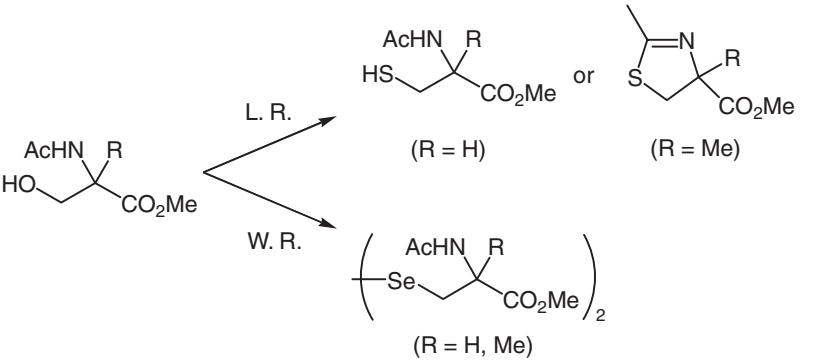
GRAPHICAL ABSTRACT



Abstract *The one-pot reactions of* N*-acetylserine methyl ester and* N*-acetyl-α-methylserine methyl ester with Lawesson's or Woollins' reagent directly produced the corresponding cysteine or selenocysteine derivatives in moderate yields. The transformation would be initiated by phosphorylation of the hydroxy group, rather than chalcogenation of the amide group, and involve the oxazoline as a key intermediate.*

Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.*

Keywords Alcohols; amino acids; selenium; sulfur; thiols

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INTRODUCTION

Chalcogenophosphate reagents, Lawesson's reagent (**1**)[1] and Woollins' reagent (**2**)[2] (Chart 1), are unique organic reagents with the structure of $(ArPX_2)_2$ (**1**, Ar = *p*-$MeOC_6H_4$ and X = S; **2**, Ar = Ph and X = Se), which specifically convert various carbonyl compounds to the corresponding thiocarbonyl[3] and selenocarbonyl[4] compounds, respectively. The reagents are also useful for the syntheses of thiols,[5] sulfides,[6] and selenophenes.[7] These synthetic utilities make the reagents very fascinating because the syntheses are sometimes difficult when other reaction conditions are employed. In this article, we report another useful application of **1** and **2** to a convenient one-pot transformation of *N*-acetylserine methyl ester (**3a**) to cysteine (Cys) and selenocysteine (Sec) derivatives. The reaction conditions were further extended to the synthesis of novel α-methylcysteine (MeCys) and α-methylselenocysteine (MeSec) derivatives.

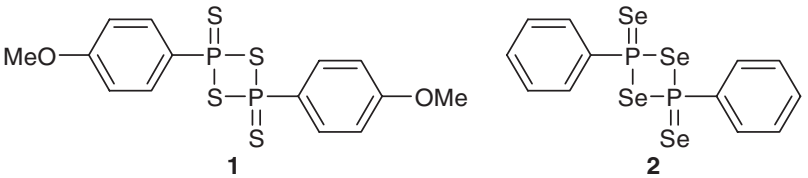
RESULTS AND DISCUSSION

L-Cys derivatives are usually prepared by chemical synthesis from L-serine (L-Ser) by substitution of the β-hydroxy group with a sulfhydryl group through the activated intermediates, such as *O*-sulfonates,[8] β-halogenated alanines,[9] and β-lactones,[10] while in living organisms L-Cys is derived from L-Ser by the *O*-acetylation and subsequent thiolation with a sulfide anion (S^{2-}) or by the sulfur-exchange reaction with L-methionine.[11] On the other hand, L-Sec, the 21st proteinogenic amino acid,[12] is biologically synthesized from L-Ser, which is bound to the Sec-tRNA, either by the direct selenolation with selenophosphate (HPO_3Se^{2-}) or by the sequential phosphorylation and selenolation.[13] In organic synthesis, L-Sec derivatives can be obtained from L-Ser in a few steps through the activation to halides, tosylates, β-lactones, oxazolines, or aziridines.[14] Alternative strategies starting from other natural amino acids have also been developed.[15]

In our research on the derivatization of Ser and the α-methyl alternate (MeSer), which is a promising chiral building block[16] and has been efficiently obtained by enzymatic synthesis from alanine,[17] we encountered a unique reaction between **3a** and Lawesson's reagent (**1**) (Table 1).

When L-**3a**[18] was reacted with an equimolar amount of **1** in refluxed dioxane for 16 h, *N*-acetyl cysteine methyl ester (**4a**) was directly obtained in up to 51% yield. The yield was decreased by using a small amount of **1** with respect to **3a**. In the reaction mixture, only one major product, which must be converted to **4a** in the workup process, was observed other than the decomposed products of **1** when the reaction was monitored by NMR in deuterated dioxane.

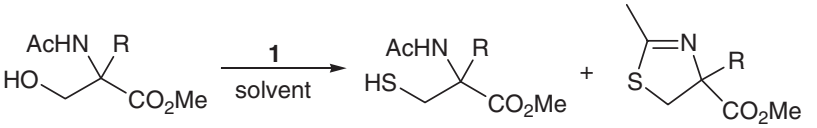
Product **4a** was also obtained by using toluene as a solvent, although the yield was decreased. In the meantime, complete racemization of **4a** was detected, as confirmed by ^1H



1 **2**

Chart 1

Table 1 One-pot conversion of serine derivatives **3a** and **3b** to the corresponding cysteine derivatives by using Lawesson's reagent (**1**)



3a R=H
3b R=Me

4a R=H
4b R=Me

5a R=H
5b R=Me

Reactant	**1** (eq.)	Solvent	Conditions	**4** (%)[a]	**5** (%)[a]
3a	1.0	Dioxane	Reflux, 16 h	51	0
3a	1.0	Dioxane	Reflux, 1.5 h	49	0
3a	0.75	Dioxane	Reflux, 16 h	41	0
3a	0.5	Dioxane	Reflux, 16 h	Trace	0
3a	1.0	Toluene	Reflux, 16 h	33	0
3b	1.0	Dioxane	Reflux, 16 h	0	29
3b	0.75	Dioxane	Reflux, 16 h	0	23
3b	0.75	Dioxane	Reflux, 22 h	0	45
3b	0.5	Dioxane	Reflux, 16 h	0	9
3b	1.0	Toluene	Reflux, 24 h	0	38
6a	0.9	Dioxane	Reflux, 16 h	54	0
6b	0.9	Dioxane	Reflux, 16 h	0	31

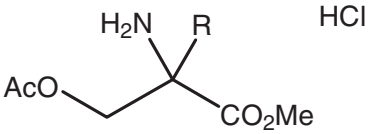
[a]Isolated yields.

NMR for the oxidized disulfide compound, probably due to the high reaction temperature as well as the long reaction time. Product **4a** could be quantitatively led to unprotected Cys by the treatment in refluxed conc. HCl for 6 h.

Similar reaction conditions were subsequently applied for *N*-acetyl-α-methylserine methyl ester (**3b**).[19] In this case, however, *N*-acetyl-α-methylcysteine methyl ester (**4b**) was not obtained. Instead, a thiazoline derivative **5b** was obtained in up to 45% yield. Product **5b** was deprotected to MeCys in good yields ($\sim$80%) by reflux in conc. HCl for 16 h.

When the reaction conditions were further applied for *O*-acetylserine methyl esters **6a**[20] and **6b** (Chart 2), **4a**, and **5b** were obtained, respectively. The reaction would go through **3a** or **3b** as an initial intermediate because the *O*-acetyl group of **6b** easily migrated to the amino group by the treatment with a base, such as $NaHCO_3$, to produce **3b** in 73% yield.[21]

We subsequently employed Woollins' reagent (**2**) for one-pot synthesis of Sec derivatives from **3a** and **3b** (Table 2). L-**3a** was treated with an equimolar amount of **2** in refluxed benzene for 16 h to give *N,N′*-diacetylselenocystine dimethyl ester (**7a**) in 25% yield. The

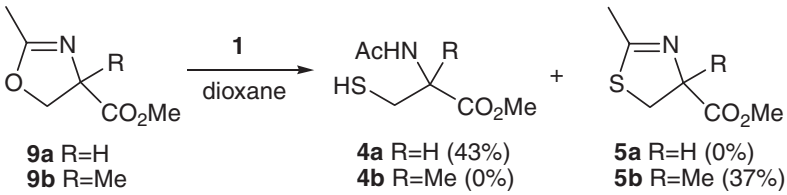


6a R=H
6b R=Me

Chart 2

yield was increased up to 36% when 0.75 mol equivalent of **2** was employed. In this reaction, the primary product would be a selenol (-SeH) but oxidized to the diselenide (**7a**) during the workup process. Partial racemization of **7a** was again observed in the ^{1}H NMR spectrum, which indicated that the diastereomeric excess (d.e.) of **7a** was 24%. Dioxane was also a good solvent. When **3b** was used instead of **3a**, diselenide **7b** was obtained in 45% yield with a small amount of selenazoline **8b** (3%). The yield of **8b** was increased to 12% in refluxed toluene, while the yield of **7b** was decreased to 40%. Major products **7a** and **7b** could be quantitatively hydrolyzed to unprotected Sec[22] and MeSec, respectively, in refluxed conc. HCl for 1–2 h.

As to the mechanism for the conversion of **3** to a cysteine derivative **4** and a selenocystine derivative **7** by chalcogenophosphate reagents **1** and **2**, it should be noted that **4a** and **7a** were not obtained from **3a** when the acetyl group was replaced by Z, Boc, or Fmoc group. This suggested that the *N*-acetyl group is essential for the conversion. Furthermore, oxazolines **9a**[23] (R = H) and **9b** (R = Me), which correspond to the dehydrated products of **3a** and **3b**, also produced **4a** (43%) but not **5a** (0%), and **5b** (37%) but not **4b** (0%), respectively, by the treatment with **1** under the similar reaction conditions to Table 1 (Scheme 1). The transformation reaction from oxazolines to Sec derivatives by using a selenolate reagent was reported previously.[24]

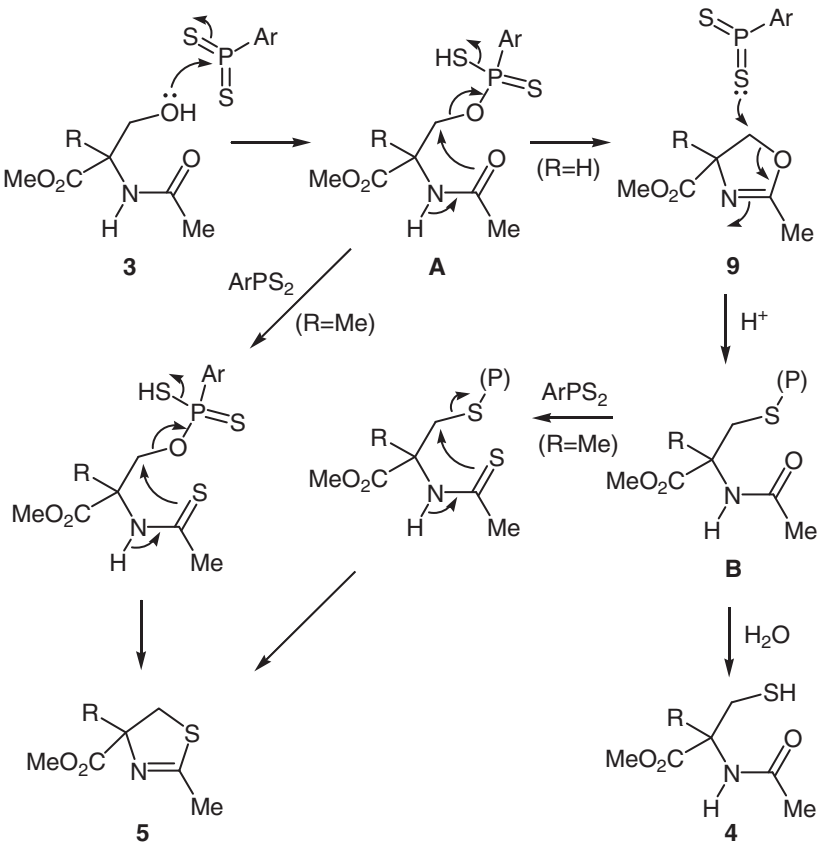


Scheme 1 The reaction of oxazolines **9a** and **9b** with Lawesson's reagent (**1**).

Considering these observations, we proposed the reaction mechanism for the reaction of **3** with **1** (Scheme 2). First, the hydroxy group of **3** reacts with $ArPS_2$, one-half of Lawesson's reagent (**1**), to form a phosphorylated product (**A**).[25] Second, intermediate **A** cyclizes to oxazoline **9** when R = H or react with another $ArPS_2$ to produce the corresponding thioamide and then thiazoline **5b** when R = Me.[26] Third, oxazoline **9** reacts with $ArPS_2$ to yield adduct **B**, which is finally hydrolyzed in the workup process to a Cys derivative. When R = Me, **B** would be converted to thiazoline **5b** via a thioamide derivative. A similar mechanism can be drawn for the reaction of **3** with Woollins' reagent (**2**), but the paths to selenazoline **8** must be significantly narrow.

The alternative path, in which the chalcogenophosphate reagents first react with the amide group of **3** to give thio- or selenoamide and the subsequent cyclization takes place to form thiazoline or selenazoline as an intermediate, may be possible. However, as Lawesson's reagent (**1**) is more reactive toward a hydroxy group than toward a carbonyl group,[27] the path through **A** and **B** would be more feasible.

The transformation of Ser derivatives to the Cys or Sec derivatives by using **1** or **2** reported here has several implications. First, the transformation would be the first example of convenient one-pot organic synthesis of Cys and Sec derivatives from Ser derivatives. Second, the reaction can be considered as an analog to the Cys and Sec biosyntheses.[11,13] It must be possible that a dehydrated intermediate such as oxazoline **9** also intervene in their biological schemes.[28] Third, artificial transformation of the Ser residue at the active site of



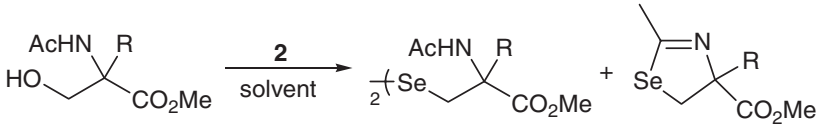
Scheme 2 A plausible mechanism for the reaction between **3** and Lawesson's reagent (**1**).

serine protease subtilisin to Cys and Sec was previously reported.[29] In this transformation, the hydroxy group was initially activated to the sulfonate. The present study suggested that the activation to phosphates is another possibility to obtain such artificial enzymes. Fourth, the MeCys and MeSec derivatives obtained are of interest in the applications to molecular design of antitumor and anti-HIV agents.[30]

CONCLUSION

Lawesson's and Woollins' reagents (**1** and **2**) have been successfully applied to one-pot conversion of Ser and MeSer derivatives to the corresponding Cys and Sec derivatives in moderate yields (Tables 1 and 2). However, since the reaction was carried out under rigorous conditions, racemization at the α-carbon atom was detected in the case of the Ser derivative. It was further suggested that the transformation likely goes through the oxazoline intermediate as shown in Scheme 2. Milder reaction conditions, which would suppress the racemization, are now being sought in our laboratories.

Table 2 One-pot conversion of serine derivatives **3a** and **3b** to the corresponding selenocysteine derivatives by using Woollins' reagent (**2**)



3a R=H
3b R=Me

7a R=H
7b R=Me

8a R=H
8b R=Me

Reactant	**2** (eq.)	Solvent	Conditions	**7** (%)[a]	**8** (%)[a]
3a	1.0	Benzene	Reflux, 16 h	25	0
3a	0.75	Benzene	Reflux, 16 h	36	0
3a	0.5	Benzene	Reflux, 16 h	29	0
3a	0.5	Dioxane	Reflux, 16 h	26	0
3b	0.75	Benzene	Reflux, 24 h	45	3
3b	0.75	Dioxane	Reflux, 24 h	36	1
3b	0.75	Toluene	Reflux, 24 h	40	12

[a]Isolated yields.

EXPERIMENTAL

Commercially available organic and inorganic reagents were used without further purification. L-Serine was purchased from Wako Pure Chemical Industries, Ltd. DL-α-methylserine, Lawesson's reagent, and Woollins' reagent were obtained from Sigma-Aldrich, Inc. ^{1}H (500 MHz), ^{13}C (125.8 MHz), and ^{77}Se (95.4 MHz) NMR spectra were measured at 298 K on a Bruker AV500 NMR spectrometer. Gel permeation chromatography was performed on a JAI LC-918 HPLC system. High resolution mass spectra were recorded on a JEOL JMS-T100LP mass spectrometer.

Synthesis of *N*-Acetylcysteine Methyl Ester (4a)[31]

L-**3a**[18] (20.5 mg, 0.13 mmol) and Lawesson's reagent **1** (52 mg, 0.13 mmol) were added in 1,4-dioxane (1.5 mL). After refluxing for 16 h under nitrogen, the mixture was diluted with water and extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by gel permeation chromatography ($CHCl_3$) to give a racemic mixture of **4a** as a white solid (11.5 mg, 51%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (t, $J = 9.0$ Hz, 1H), 2.07 (s, 3H), 3.02 (m, 2H), 3.80 (s, 3H), 4.89 (m, 1H), 6.36 (s, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 23.2, 26.9, 52.9, 53.5, 169.8, 170.6.

Synthesis of 2,4-Dimethyl-4-methoxycarbonylthiazoline (5b)

A racemic mixture of **3b**[19] (21.0 mg, 0.12 mmol) and **1** (37 mg, 0.09 mmol) were added in 1,4-dioxane (1.5 mL). After refluxing for 22 h under nitrogen, the mixture was diluted with water and extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by gel

permeation chromatography ($CHCl_3$) to give a racemic mixture of **5b** as a colorless oil (9.3 mg, 45%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53 (s, 3H), 2.24 (s, 3H), 3.18 (d, $J = 11.4$ Hz, 1H), 3.79 (s, 3H), 3.82 (d, $J = 11.4$ Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 20.4, 24.1, 42.6, 52.9, 84.3, 167.5, 173.9; HRMS (APCI-TOF) *m/z*: calcd for $C_7H_{12}NO_2S$ 174.0589 [M + 1], found 174.0604 [M + 1].

Synthesis of *O*-Acethyl-α-methylserine Methyl Ester Hydrochloride (6b)

To a solution of racemic α-methylserine methyl ester hydrochloride[32] (0.150 g, 0.88 mmol) in AcOH (3 mL), Ac_2O (0.35 mL, 3.7 mmol) was added. After stirring at r.t. for 24 h, the solvent was evaporated under vacuum to give a racemic mixture of **6b** as a white solid (0.185 g, 98%).

Mp: 127–131°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.74 (s, 3H), 2.15 (s, 3H), 3.84 (s, 3H), 4.43 (d, $J = 11.8$ Hz, 1H), 4.50 (d, $J = 11.8$ Hz, 1H), 9.19 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 18.8, 20.8, 53.8, 59.9, 65.6, 169.2, 170.2; HRMS (APCI-TOF) *m/z*: calcd for $C_7H_{14}NO_4$ 176.0923 [M + 1], found 176.0910 [M + 1].

Synthesis of *N,N′*-Diacetylselenocystine Dimethyl Ester (7a)

L-**3a**[18] (19.3 mg, 0.12 mmol) and Woollins' reagent **2** (47 mg, 0.09 mmol) were added in benzene (2 mL). After refluxing for 16 h under nitrogen, the mixture was diluted with water and extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by gel permeation chromatography ($CHCl_3$) to give a diastereomeric mixture of **7a** as a yellow oil (9.5 mg, 36%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.06 (s, 3H), 2.07 (s, 3H), 3.43 (m, 4H), 3.77 (s, 6H), 4.91 (m, 2H), 6.49 (d, $J = 7.0$ Hz, 1H), 6.55 (d, $J = 6.7$ Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 23.2, 31.7, 31.8, 52.6, 52.8, 170.0, 170.2, 171.0, 171.1; ^{77}Se NMR (95.4 MHz, $CDCl_3$) δ 292.9, 295.0; HRMS (APCI-TOF) *m/z*: calcd for $C_{12}H_{21}N_2O_6{}^{80}Se_2$ 448.9730 [M + 1], found 448.9792 [M + 1].

Reaction of 3b with 2

A racemic mixture of **3b**[19] (23.4 mg, 0.13 mmol) and **2** (53 mg, 0.10 mmol) were added in toluene (1.5 mL). After refluxing for 24 h under nitrogen, the mixture was diluted with water and extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by gel permeation chromatography ($CHCl_3$) to give a diastereomeric mixture of **7b** as a slightly yellow solid (12.6 mg, 40%) and a racemic mixture of **8b** as a slightly yellow oil (3.4 mg, 12%).

***N,N′*-Diacetyl-α,α'-dimethylselenocystine dimethyl ester (7b).** Mp: 184–185°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.63 (s, 3H), 1.63 (s, 3H), 2.02 (s, 3H), 2.02 (s, 3H), 3.48 (d, $J = 13.1$ Hz, 1H), 3.52 (d, $J = 13.0$ Hz, 1H), 3.77 (s, 6H), 3.88 (d, $J = 13.0$ Hz, 1H), 3.94 (d, $J = 13.0$ Hz, 1H), 6.57 (s, 1H), 6.60 (s, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 23.7, 23.8, 23.9, 23.9, 36.5, 53.0, 60.8, 60.8, 170.0, 170.1, 173.3, 173.3; ^{77}Se NMR (95.4 MHz, $CDCl_3$) δ 293.7; HRMS (APCI-TOF) *m/z*: calcd for $C_{14}H_{25}N_2O_6{}^{80}Se_2$ 477.0046 [M + 1], found 477.0095 [M + 1].

2,4-Dimethyl-4-methoxycarbonylselenazoline (8b). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55 (s, 3H), 2.33 (s, 3H), 3.38 (d, $J = 10.6$ Hz, 1H), 3.79 (s, 3H), 3.98 (d, $J = 10.6$ Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 23.6, 24.0, 39.1, 52.9, 86.4, 164.7, 173.7; ^{77}Se NMR (95.4 MHz, $CDCl_3$) δ 494.8; HRMS (APCI-TOF) *m/z*: calcd for $C_7H_{12}NO_2{}^{80}Se$ 222.0033 [M + 1], found 222.0056 [M + 1].

Synthesis of α,α'-Dimethylselenocystine Dihydrochloride

A diastereomeric mixture of **7b** (18.1 mg, 0.04 mmol) was dissolved in concentrated HCl (1.5 mL). After refluxing for 2 h, the mixture was lyophilized to give a diastereomeric mixture of α,α'-dimethylselenocystine dihydrochloride as a yellow solid (16.7 mg, quant.).

^{1}H NMR (500 MHz, 1M HCl-D_2O) δ 1.33 (s, 6H), 3.15 (d, $J = 14.3$ Hz, 1H), 3.20 (d, $J = 14.3$ Hz, 1H), 3.37 (d, $J = 14.4$ Hz, 1H), 3.41 (d, $J = 14.4$ Hz, 1H); ^{13}C NMR (125.8 MHz, 1M HCl-D_2O) δ 22.1, 35.2, 60.5, 172.1; ^{77}Se NMR (95.4 MHz, 1M HCl-D_2O) δ 302.9, 304.1; HRMS (APCI-TOF) *m/z*: calcd for $C_8H_{17}N_2O_4{}^{80}Se_2$ 364.9521 [M + 1], found 364.9592 [M + 1].

Synthesis of 2,4-Dimethyl-4-methoxycarbonyloxazoline (9b)

To a suspension of racemic α-methylserine methyl ester hydrochloride (60.0 mg, 0.35 mmol) and Et_3N (75 μL, 0.54 mmol) in CH_2Cl_2 (5 mL), methyl acetimidate hydrochloride (94 mg, 0.86 mmol) were added at 0°C. After refluxing for 19.5 h, the mixture was diluted with water and extracted with CH_2Cl_2. The organic extract was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by gel permeation chromatography ($CHCl_3$) to give a racemic mixture of **9b** as a colorless oil (41.5 mg, 75%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49 (s, 3H), 2.00 (s, 3H), 3.76 (s, 3H), 3.97 (d, $J = 8.7$ Hz, 1H), 4.61 (d, $J = 8.8$ Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.0, 25.3, 52.7, 74.0, 75.9, 166.1, 173.9; HRMS (APCI-TOF) *m/z*: calcd for $C_7H_{12}NO_3$ 158.0817 [M + 1], found 158.0796 [M + 1].

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