Hetero-Substituted Methylideneoxazolones. 2,3-Methanohomoserine and -methionine Synthesis†

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The use of hetero-substituted methylideneoxazolones 2–4 in the synthesis of 1-aminocyclopropanecarboxylic acid derivatives is described. The serendipitous formation of bromomethyl spirooxazolones 11 afforded a simple method for the synthesis of both 2,3-methanomethionine (∇Met) diastereomers. A synthesis of (*E*)-2,3-methanohomoserine (14, ∇^EHse) is described which allowed the unequivocal assignment of configurations to the new methionine analogues.

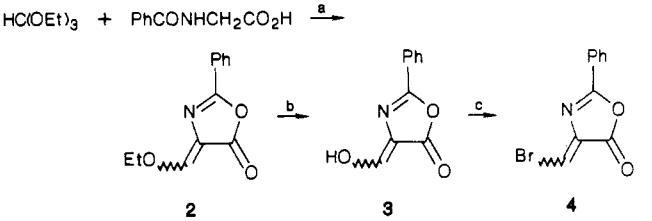
During our studies of substituted 1-aminocyclopropanecarboxylic acids, we chose to investigate the use of 4-(hetero-substituted methylidene)-2-phenyl-5(4*H*)-oxazolones as synthetic intermediates. These compounds were studied in detail some 40 years ago[1] during the penicillin era and were found to show high electrophilic reactivity at the methylidene carbon as might be expected of "vinylogous" esters. It is well known[2] that methylideneoxazolones react with diazomethane to give cyclopropanes, and consequently, we investigated these compounds with the expectation that 2-substituted 1-aminocyclopropanecarboxylic acids might be obtained.

As shown in Scheme I, the β-ethoxy, β-hydroxy, and β-bromo compounds **2–4** could be prepared essentially by the previously described[2] procedures. When **2** was treated with diazomethane, a mixture of products was formed which showed strong δ 2.2 NMR absorption, indicating formation of a predominant amount of β-methyl compound and very little cyclopropane.

Treatment of **3** with oxalyl bromide, in a reaction analogous to that used to make the corresponding chloro compound,[2] gave **4** when carried out in refluxing benzene, since at room temperature a precipitate formed (probably the oxazolone hydrobromide) which was converted into **4** on heating. **4E** was also synthesized by another route through the crystalline dehydroalanine derivative **6**, which was prepared by dehydration[3] of the appropriate serine derivative (Scheme II). This was brominated in the presence of base according to Olsen,[4] and the predominant isomer, **7E**, was crystallized and assigned the *E* configuration by comparison of its ^{1}H NMR spectrum with the published data.[4] Hydrolysis of **7E** gave an oily acid (**8**), which was cyclized directly to the bromo oxazolone **4E** by using a water-soluble carbodiimide (1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride, EDC). The configuration of **4E** was assigned on the basis of the chemical shift position of the vinyl proton (δ 7.25) as compared to that of the known[2] chloro compound (δ 7.20). The first synthesis of **4E** was preferable due to higher yields and ease of operation.

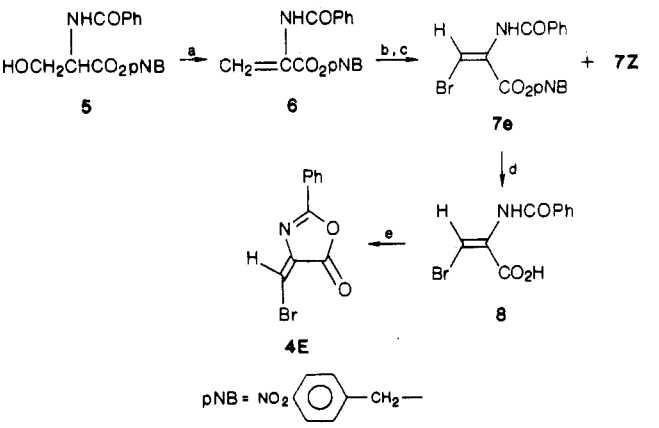
When **4E** was treated with excess diazomethane, a mixture of five compounds (TLC) was formed (Scheme III), and these were readily separated by chromatography. The expected bromocyclopropanes **10** were formed in only 20% yield, along with the methyl insertion product **9**, while the unexpected rearrangement products **11** predominated (43% *Z*/*E*, 3:2). Their structures were confirmed by NMR experiments showing that the bromomethyl protons (δ 3.6–3.8) were coupled directly with the cyclopropane methine proton. This kind of vinyl to allyl group rear-

Scheme I[a]



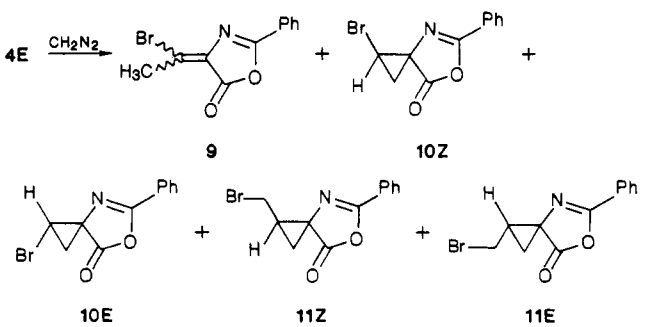
[a] Reagents: (a) Ac_2O; (b) concentrated HCl; (c) $(COBr)_2$/PhH, Δ.

Scheme II[a]



[a] Reagents: (a) EDC, CuCl; (b) Br_2; (c) DBU; (d) NaOH/THF/H_2O; (e) EDC.

Scheme III

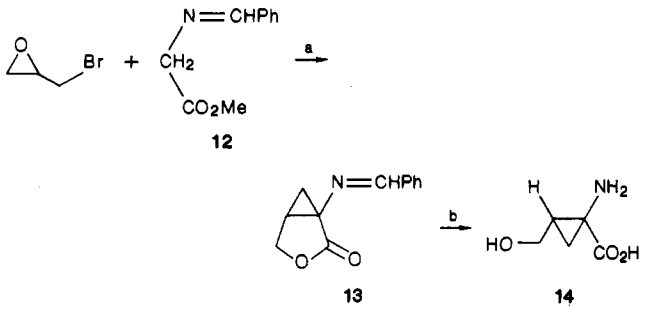


† Cyclopropane-containing amino acids synthesized in our research program have, in the past, been variously named "cyclopropyl-" and "cyclopropane-" amino acids. In the future, we will use the "2,3-methano-" prefix to the amino acid name.

(1) Cornforth, J. W. In *The Chemistry of Penicillin*; Clarke, H. T., Johnson, J. R., Robinson, Sir R., Eds.; Princeton University: Princeton, NJ, 1949; p 743.

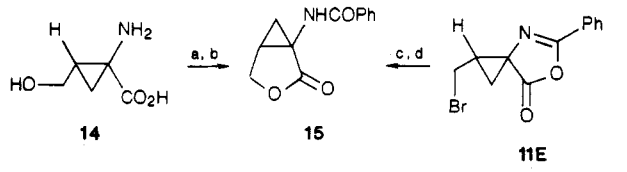
0022-3263/88/1953-0992$01.50/0

Scheme IV[a]



[a] Reagents: (a) LDA, HMPA, THF; (b) HCl, H_2O.

Scheme V[a]

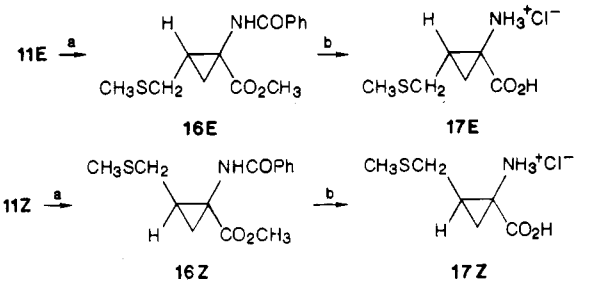


[a] Reagents: (a) PhCOCl, OH^-; (b) H^+, Δ; (c) $KOAc/H_2O$; (d) H^+, Δ.

rangement during cyclopropanation has been previously reported[6] and may occur by migration of the bromine atom to a radical center formed by the spontaneous decomposition of a pyrazoline intermediate.[7] The fact that the analogous (chloromethylidene)oxazolone did not undergo this rearrangement when treated with diazomethane[2] is consistent with the lesser stability of a chlorine vis-à-vis a bromine radical. The formation of the (bromomethyl)cyclopropanes **11** was a welcome surprise because of their obvious potential as 2,3-methanomethionine (∇Met) precursors fitting in well with some concurrent investigations which were also pointed toward the synthesis of this amino acid.

Earlier work[8] had shown that the base-catalyzed condensation of stabilized anions with epihalohydrins gave (hydroxymethyl)cyclopropanes in good yields. With a view toward the synthesis of 2,3-methanohomoserine (∇Hse) and -methionine (∇Met) derivatives, then, we studied the condensation of a glycine Schiff base derivative with epibromohydrin under various reaction conditions (Scheme IV). Even though our very best procedure gave low yields

Scheme VI[a]



[a] Reagents: (a) CH_3SNa, CH_3OH; (b) HCl/HOAc, Δ.

of the lactone (**13**) derived from the *E* isomer of 2,3-methanohomoserine, it could be hydrolyzed to give ∇Hse (**14**), which was isolated by ion-exchange chromatography. The removal of hexamethylphosphoramide from the product complicated this reaction sequence,[9] but the condensation reaction did not proceed in its absence. Attempts to prepare the desired methionine analogue from this material were unsuccessful, since lactonization complicated our attempts to replace the hydroxyl function by a methylthio group. Lactonization, however, does establish the *E* configuration of the amino acid (**14**), and we were able to tie the hydroxyl (**14**) and bromo (**11**) series of compounds together when the same *N*-benzoyl derivative of ∇^EHse lactone (**15**) was obtained from **14** and the presumed (*E*)-oxazolone (**11E**) as shown in Scheme V.

Finally, when the spirooxazolones **11** were treated separately with sodium methyl mercaptide in dry methanol (Scheme VI), the *N*-benzoyl methyl esters **16E,Z** were formed in acceptable yields. Acidic hydrolysis of these intermediates gave the pure diastereomeric 2,3-methanomethionines **17E,Z** as the hydrochlorides. Even though homoserine lactone can be converted directly into methionine,[10] direct conversion of the lactone **15** with methyl mercaptide anion into a Met derivative did not occur.

Experimental Section

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ^1H NMR spectra were recorded on either a Varian T-60 or Varian EM-390 spectrometer with TMS as an internal standard. Infrared spectra were recorded on a Perkin-Elmer 297 infrared spectrophotometer with polystyrene as the standard.

DL-Serine and hippuric acid were purchased from Sigma Chemical Co. and used without further purification. Triethyl orthoformate, dicyclohexylcarbodiimide (DCC), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDC), oxalyl bromide, 1,4-diazabicyclo[2.2.2]octane (Dabco), Diazald (Aldrich), and *p*-nitrobenzyl bromide were purchased from Aldrich and used without further purification. Benzoyl chloride and methylene chloride were distilled from P_2O_5 and stored over anhydrous calcium chloride; tetrahydrofuran was distilled from potassium metal prior to use, and silica gel 60 was purchased from J. T. Baker Chemical Co. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA.

Thin-layer chromatography was performed on silica gel 60F-254 precoated TLC plates. TLC plates were visualized by using UV light and/or chlorine–tolidine reagent (80 mg of *o*-tolidine dissolved in 15 mL of AcOH, and to this solution was added 0.50 g of KI and the mixture was diluted to 250 mL with H_2O). The following solvent systems were employed: (I) ethyl acetate/hexane (1:2); (II) ether/hexane (1:1); (III) ethyl acetate/hexane (1:5); (IV) chloroform/methanol (1:1); (V) ether/hexane (1:4); (VI) chloroform/methanol/acetic acid (50:10:1); (VII) ether/hexane (4:1);

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(VIII) ether/petroleum ether (1:5).

***N*-Benzoyl-DL-serine *p*-Nitrobenzyl Ester (5).** *N*-Benzoyl-DL-serine (37.0 g, 0.175 mol) was dissolved in EtOAc (600 mL), and to this was added *p*-nitrobenzyl bromide (37.95 g, 0.175 mol), followed by TEA (17.5 g, 0.175 mol). The mixture was refluxed for 48 h and, after cooling, was washed with water (1 × 400 mL) and 5% $NaHCO_3$ (1 × 200 mL). The organic phase was dried (anhydrous Na_2SO_4), and the solvent was removed in vacuo, leaving a pale yellow solid, R_f (III) 0.73, which was crystallized from $CHCl_3$/MeOH (10:1) to give 48.1 g (80%) of the ester **5**: mp 118–119 °C; ^1H NMR (DMSO-d_6) δ 8.50–7.30 (m, 10 H, Ar H and NH), 5.20 (s, 2 H, CH_2), 4.50–4.68 (m, 1 H, CH), 3.81 (d, 2 H, CH_2OH).

Anal. Calcd for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.14. Found: C, 59.17; H, 4.70; N, 8.09.

***N*-Benzoyldehydroalanine *p*-Nitrobenzyl Ester (6).** To a suspension of **5** (8.0 g, 0.023 mol) and CuCl (2.37 g, 0.024 mol) in $CHCl_3$ (240 mL) was added EDC (5.52 g, 0.029 mol) at room temperature. The mixture was stirred at room temperature for 48 h and then washed with water (1 × 200 mL). The organic phase was dried (anhydrous Na_2SO_4) and evaporated in vacuo, leaving a solid, R_f (I) 0.62, which was crystallized from EtOAc/hexane to give 5.90 g (78%) of **6**: mp 136–137 °C; IR (KBr) 3400 (NH), 3065 (=CH), 1710 (C=O), 1600 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 7.80–8.25 (m, 5 H, Ar H and NH), 7.4–7.65 (m, 5 H, Ar H), 6.85 (s, H, =CH), 6.18 (s, 1 H, =CH), 5.2 (s, 2 H, OCH_2).

Anal. Calcd for $C_{17}H_{14}N_2O_5$: C, 62.58; H, 4.32; N, 8.58. Found: C, 62.63; H, 4.35; N, 8.57.

***N*-Benzoyl-3-bromodehydroalanine *p*-Nitrobenzyl Ester (7E).** To an ice-cooled solution of **6** (8 g, 2.5 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise 3.93 g (2.5 mmol) of bromine in dry CH_2Cl_2 (30 mL) under an N_2 atmosphere. After the mixture was stirred at 0 °C for 45 min and at room temperature for 10 min, 2.74 g (2.5 mmol) of Dabco in dry CH_2Cl_2 (20 mL) was added dropwise at 0 °C, and the mixture was stirred at 0 °C for 45 min. After filtration through Celite and solvent removal in vacuo, 8.4 g (88%) of a crude **7E** showing two TLC spots, R_f (I) 0.50 and 0.43, remained. The solid was crystallized from EtOAc/hexane to give 4.2 g (44%) of **7E**: R_f (I) 0.50; mp 153–154 °C; ^1H NMR ($CDCl_3$) δ 8.3–7.3 (m, 10 H, Ar H and NH), 7.20 (s, 1 H, vinyl), 5.35 (s, 2 H, OCH_2).

Anal. Calcd for $C_{17}H_{13}BrN_2O_5$: C, 50.39; H, 3.23; N, 6.91; Br, 19.72. Found: C, 50.25; H, 3.24; N, 6.88; Br, 19.79.

***N*-Benzoyl-3-bromodehydroalanine (8).** To a solution of **7E** (0.918 g, 2.3 mmol) in THF (10 mL) was added 4.54 mL (4.54 mmol) of 1 N NaOH at 0 °C. After the mixture was stirred at room temperature for 5 h, it was concentrated in vacuo and the residue was triturated with water (25 mL). The resulting yellow solid was filtered, and the filtrate was extracted with ether (20 mL). The aqueous layer was acidified to pH 3 with 10% citric acid at room temperature and extracted with EtOAc (2 × 20 mL). An unstable oil, 0.40 g (67%) of **8**, was obtained after the extracts were dried (anhydrous Na_2SO_4) and the solvent was removed: R_f (IV) 0.85; IR (NaCl) 2700–3400 (NH and OH), 1650 (C=O), 1700 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 9.15 (br, s, 1 H, COOH), 8.3–7.3 (m, 6 H, Ar H, vinyl).

2-Phenyl-4-(bromomethylidene)-5(4*H*)-oxazolone (4E). A. From Oxazolone 3. To a suspension of 1.0 g (5.3 mmol) of 2-phenyl-4-(hydroxymethylidene)-5(4*H*)-oxazolone[1,2] (**3**) in benzene (20 mL) was added 1.49 g (6.9 mmol) of oxalyl bromide, and the mixture was refluxed under N_2 for 1 h. After cooling, the solution was evaporated to dryness, and the resulting orange-red solid, showing two components by TLC, R_f (II) 0.84 and 0.55, was purified by crystallization from a mixture of 1:1 ether/hexane to give 0.45 g (34%) of **4E**: R_f (II) 0.83; mp 126–127 °C; ^1H NMR ($CDCl_3$) δ 8.20 (m, 2 H, *o*-ArH), 7.70 (m, 3 H, *m*- and *p*-Ar H), 7.25 (s, 1 H, vinyl).

Anal. Calcd for $C_{10}H_6BrNO_2$: C, 47.65; H, 2.39; N, 5.55; Br, 31.70. Found: C, 47.70; H, 2.44; N, 5.55; Br, 31.61.

B. From Bromodehydroalanine 8. To a solution of **8** (0.30 g, 1.10 mmol) in CH_3CN (5 mL) was added EDC (0.23 g, 1.10 mmol). The mixture was stirred at room temperature for 3 h and evaporated to dryness. The semisolid residue was partitioned between water (70 mL) and EtOAc (25 mL). The organic layer was separated, dried (anhydrous Na_2SO_4), and evaporated in vacuo. The residue was triturated with a 1:1 mixture of ether/hexane and filtered through silica gel. The filtrate was evaporated in vacuo to give 0.20 g (71%) of light-yellow crystals of **4E**: R_f (II) 0.83; mp 126–128 °C.

Addition of Diazomethane to 2-Phenyl-4-(bromomethylidene)-5(4*H*)-oxazolone (4E). Into a suspension of 7.20 g (28.6 mmol) of **4E** in 20 mL of ether was distilled 3 g (71 mmol) of CH_2N_2 in 200 mL of ether (prepared from Diazald), dissolving **4E** as it reacted. After the reaction mixture was allowed to stand overnight, anhydrous $CaCl_2$ pellets were added to it and it was filtered and concentrated in vacuo to 7.66 g of orange oil, R_f (VIII) 0.80, 0.69, 0.63, 0.52, 0.46, 0.36. A $CHCl_3$ solution of the oil was filtered through 11 g of silica gel (230–400 mesh) with 150 mL of $CHCl_3$ as eluant. The $CHCl_3$ was removed in vacuo to give 7.46 g of oil. The mixture of compounds was then purified by column chromatography [400 g of silica gel (Whatman K6GF; 5–20 μm); 90-mm-diameter column, petroleum ether/THF (50:1) eluant; 100 mL/min flow rate; 100 mL/fraction] using air pressure to push eluant through the column. Fractions 9–11 contained **9**, fractions 13–19 contained **10Z**, fractions 17–30 contained **11Z**, fractions 26–37 contained **10E**, and fractions 34–60 contained **11E**. Fractions 9 and 10 were combined to give 0.31 g (4.1%) of **9** as a white solid: mp 87–89 °C; R_f (VIII) 0.80; NMR ($CDCl_3$) δ 8.1 (m, 2 H, *o*-Ar H), 7.5 (m, 3 H, *m*- and *p*-Ar H), 3.0 (s, 3 H, H_3CC=C).

Anal. Calcd for $C_{11}H_8NO_2Br$: C, 49.65; H, 3.03; N, 5.26; Br, 30.03. Found: C, 49.68; H, 3.04; N, 5.22; Br, 30.10.

Fractions 14 and 15 were combined to give 1.28 g (17%) of **10Z** as a white solid: mp 105–108 °C; R_f (V) 0.63; NMR ($CDCl_3$) δ 8.1 (m, 2 H, *o*-ArH), 7.5 (m, 3 H, *m*- and *p*-Ar H), 3.7 (t, 1 H, ∇-CH), 2.3 (m, 2 H, ∇-CH_2).

Anal. Calcd for $C_{11}H_8NO_2Br$: C, 49.65; H, 3.03; N, 5.26; Br, 30.03. Found: C, 49.51; H, 3.05; N, 5.25; Br, 29.99.

Fractions 20–25 were combined to give 2.05 g (26%) of **11Z** as a white solid: mp 70–72 °C; R_f (V) 0.52; NMR ($CDCl_3$) δ 8.0 (m, 2 H, *o*-Ar H), 7.5 (m, 3 H, *m*- and *p*-Ar H), 3.65 (dd, 2 H, CH_2Br), 2.5 (m, 1 H, ∇-CH), 2.1–1.7 (m, 2 H, ∇-CH_2).

Anal. Calcd for $C_{12}H_{10}NO_2Br$: C, 51.45; H, 3.60; N, 5.00; Br, 28.53. Found: C, 51.41; H, 3.61; N, 4.97; Br, 28.47.

Fractions 31–33 were combined to give 0.31 g (4.1%) of **10E** as a white solid: mp 128–135 °C; R_f (V) 0.46; NMR ($CDCl_3$) δ 7.95 (m, 2 H, *o*-Ar H), 7.5 (m, 3 H, *m*- and *p*-Ar H), 3.9 (t, 1 H, ∇-CH), 2.45 (t, 1 H, ∇-CH_2), 2.15 (t, 1 H, ∇-CH_2).

Fractions 38–60 were combined to give 1.94 g (25%) of **11E** as a white solid: mp 101–102 °C; R_f (V) 0.36; NMR ($CDCl_3$) δ 7.95 (m, 2 H, *o*-Ar H), 7.5 (m, 3 H, *m*- and *p*-Ar H), 3.73 (dd, 2 H, CH_2Br), 2.7 (m, 1 H, ∇-CH), 2.17 (dd, 1 H, ∇-CH_2), 1.77 (dd, 1 H, ∇-CH_2).

Anal. Calcd for $C_{12}H_{10}NO_2Br$: C, 51.45; H, 3.60; N, 5.00; Br, 28.53. Found: C, 51.54; H, 3.77; N, 4.96; Br, 28.45.

***N*-Benzylidene-2,3-methanohomoserine γ-Lactone (13).** A 2-L round-bottom flask fitted with a septum was flame dried under N_2, and 8.70 mL (62 mmol) of diisopropylamine was injected via syringe. Dry THF (200 mL) was injected, and the solution was cooled to −20 °C in a CO_2/2-propanol bath, followed by injection of 5.54 mL (56.4 mmol) of 10.2 M *n*-BuLi/hexane. The solution was stirred for 30 min at −20 to 0 °C and then cooled to −80 °C. A solution of 10.00 g (56.4 mmol) of **12**[11] in 200 mL of dry THF under N_2 was transferred via syringe to the LDA solution, and the reaction mixture was stirred at −80 °C for 60 min. To the enolate were added 9.8 mL (56 mmol) of hexamethylphosphoramide and a solution of 7.74 g (56.4 mmol) of epibromohydrin in 250 mL of dry THF. The mixture was stirred at −80 °C for 60 min and allowed to warm to room temperature over a 5.5-h period. Another equivalent of LDA was prepared as before and transferred via syringe to the 2-L reaction flask, which had been cooled to −80 °C. The reaction mixture was stirred for 22 h while warming to room temperature, then concentrated in vacuo to ca. 500 mL, and partitioned between EtOAc (100 mL) and cold saturated NH_4Cl (100 mL). The layers were separated, and the organic phase was extracted with cold saturated NH_4Cl (2 × 100 mL). The EtOAc solution was dried (anhydrous $MgSO_4$),

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filtered, and concentrated in vacuo to give 11.16 g of a semisolid residue. Trituration of the crude product with 100 mL of ether gave a yellow solid, which was filtered and dried in vacuo to weigh 2.21 g (19%); mp 97.5–104.5 °C. The filtrate was concentrated in vacuo to give 8.14 g of red-brown oil, which was triturated with 100 mL of ether to give 0.54 g (5%) of yellow solid; mp 99–106 °C. The combined solids were recrystallized twice from methanol to give 0.93 g (8%) of **13**: mp 106.5–107.5 °C; NMR ($CDCl_3$) δ 9.2 (s, 1 H, N=CH), 7.8 (m, 2 H, *o*-Ar H), 7.5 (m, 3 H, *m*- and *p*-Ar H), 4.3 (dd, 2 H, CH_2O), 2.5 (m, 1 H, ▽-H), 1.8 (dd, 1 H, ▽-H), 1.4 (t, 1 H, ▽-H).

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.51; H, 5.52; N, 6.96.

(*E*)-2,3-Methanohomoserine (14). The preceding procedure for the synthesis of **13** was repeated, the crude product (orange solid) was treated with 60 mL of 1 N HCl, and the mixture was stirred at room temperature for 3 h. The brown solution was extracted with CH_2Cl_2 (4 × 25 mL), and the combined extracts were back-washed with 25 mL of H_2O. The combined aqueous solutions were applied to an ion-exchange column [450 mL of Dowex-50 (H^+), 2.5 × 23 cm column, 4 mL/min flow rate]. The column was washed with 225 mL of 1 N HCl followed by 400 mL of H_2O. The amino acid was then eluted from the column with 3 N NH_4OH, and the ninhydrin-positive fractions were combined, treated with charcoal, filtered, and concentrated in vacuo to 6.72 g of an orange solid. The solid was triturated with ether (2 × 40 mL), and the sticky insolubles were then triturated with 30 mL of hot methanol, during which a yellow precipitate formed. After cooling of the mixture, the solid was filtered and washed with cold methanol (2 × 20 mL) to give 1.20 g (16%) of solid white **14**: mp 206 °C dec; NMR (D_2O) δ 4.1 (d, 2 H, CH_2O), 2.14–1.60 (m, 3 H, ▽-H). The analytical sample was recrystallized from H_2O/EtOH; mp 207–208 °C.

Anal. Calcd for $C_5H_9NO_3$: C, 45.80; H, 6.92; N, 10.68. Found: C, 45.86; H, 6.94; N, 10.72.

***N*-Benzoyl-(*E*)-2,3-methanohomoserine γ-Lactone (15). A. From (*E*)-2,3-Methanohomoserine.** A solution of 0.50 g (3.3 mmol) of **14** in 2 mL of 2 N NaOH was cooled in an ice bath, and 1.6 g (11.4 mmol) of benzoyl chloride and 6 mL of 2 N NaOH were added over 45 min. The reaction mixture was allowed to warm to room temperature and was stirred for 24 h with 2 mL of 2 N NaOH being added to keep the pH above 9. The solution was cooled in an ice bath and acidified to pH 2 with 2 N HCl, and the precipitate was filtered. The filtrate was extracted with ether (2 × 2 mL), causing a white solid to precipitate, and after cooling to 0 °C, the solid was filtered, washed with cold water, combined with precipitate above, and dried over P_2O_5 to give 0.19 g (54%) of the intermediate hydroxy acid: mp 235–236 °C; R_f (VI) 0.35; NMR (CD_3OD) δ 7.85 (m, 2 H, *o*-Ar H), 7.5 (m, 3 H, *m*- and *p*-Ar H), 3.85 (d, 2 H, CH_2O), 2.0–1.6 (m, 2 H, ▽-H), 1.37 (dd, 1 H, ▽-H); IR (Nujol) 3400 (OH), 3270 (NH), 1700 (acid C=O), 1625 cm^{-1} (amide C=O). The hydroxy acid obtained above was added to 3 mL of H_2O containing 3 drops of 0.1 N HCl, and the mixture was heated to reflux. After 4.5 h, the lactonization was complete (TLC). The mixture was kept at 5 °C overnight and filtered, and the resulting solid was dried in vacuo over P_2O_5 to give 0.08 g of **15** as a white solid, mp 240 °C, spectroscopically identical with that in part B.

B. From the (*E*)-Bromomethyl Oxazolone 11E. To a solution of **11E** (400 mg, 1.42 mmol) in THF (3.5 mL) was added 1.5 mL of 10% K_2CO_3 solution, and the reaction mixture was allowed to stand at room temperature. When hydrolysis was complete (TLC), the suspension was cooled in an ice bath, adjusted to pH 1 with 4 N HCl, and refluxed overnight. The solvent was removed under reduced pressure, and the residue was extracted with AcOEt (2 × 20 mL). The combined organic extracts were washed with water (3 × 30 mL), dried (anhydrous $MgSO_4$), and evaporated under reduced pressure to give 200 mg (70%) of the lactone **15**. Recrystallization from CH_2Cl_2/petroleum ether gave the title compound (90 mg, 29%): mp 235–236 °C; NMR (CD_2Cl_2/DMSO) δ 9.25 (br s, 1 H, NH), 7.90 (m, 2 H, *o*-Ar H), 7.5 (m, 3 H, *m*- and *p*-Ar H), 4.6 (m, 1 H, CH_2O), 4.2 (d, 1 H, CH_2O), 2.35 (m, 1 H, ▽-H), 1.75 (m, 1 H, ▽-H), 1.25 (m, 1 H, ▽-H); IR (KBr) 3260 (NH), 1760 (lactone C=O), 1640 cm^{-1} (amide C=O).

Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.18; H, 5.14; N, 6.41.

***N*-Benzoyl-(*E*)-2,3-methanomethionine Methyl Ester (16E).** Into a flask, under an N_2 atmosphere, containing 95 mg (4.1 mmol) of sodium metal was distilled (from Mg) 15 mL of MeOH. A stream of methyl mercaptan (dried through a $CaCl_2$ tube) was bubbled into the methanol solution for ca. 20 min, and the solution was transferred *through a needle* to another flask containing 600 mg (2.1 mmol) of **11E**. The reaction mixture was heated in an oil bath at 50 °C for 3.5 h and evaporated in vacuo, the solid residue was dissolved in CH_2Cl_2 (20 mL), and the solution was washed with water (3 × 15 mL). The combined aqueous washings were extracted with CH_2Cl_2 (10 mL), and the combined CH_2Cl_2 solution was dried (anhydrous $MgSO_4$) and concentrated in vacuo to give 360 mg of crude product, which was recrystallized from EtOH/Et_2O to give 320 mg (53%) of **16E**: R_f (VII) 0.55; mp 122.5–123.5 °C; ^1H NMR ($CDCl_3$) δ 7.8 (m, 2 H, *o*-Ar H), 7.45 (m, 3 H, Ar H), 7.0 (br, 1 H, NH), 3.7 (s, 3 H, CO_2CH_3), 2.85 (d, 2 H, CH_2S), 2.15 (s, 3 H, CH_3S), 2.0–1.2 (m, 3 H, ▽-H).

Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.21; H, 6.09; N, 5.02; S, 11.46. Found: C, 59.75; H, 6.08; N, 4.93; S, 11.38.

***N*-Benzoyl-(*Z*)-2,3-methanomethionine Methyl Ester (16Z).** The above procedure was repeated with 600 mg (2.1 mmol) of **11Z**, and the crude product was recrystallized from EtOH/Et_2O to give 136 mg (22.5%) of **16Z**: mp 112.5–113.5 °C; R_f (VII) 0.46; ^1H NMR ($CDCl_3$) δ 7.85 (m, 3 H, *o*-Ar H and NH), 7.4 (m, 3 H, *m*- and *p*-Ar H), 3.65 (s, 3 H, CO_2CH_3), 2.65 (m, 2 H, CH_2S), 2.15 (s, 3 H, CH_3S), 2.0–1.6 (m, 2 H, ▽-H), 1.2 (m, 1 H, ▽-H).

Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.21; H, 6.09; N, 5.02; S, 11.46. Found: C, 60.16; H, 6.14; N, 5.01; S, 11.49.

(*E*)-2,3-Methanomethionine Hydrochloride (17E). A solution of 315 mg (1.13 mmol) of **16E** in 16.6 mL of 1:1 glacial acetic acid and concentrated HCl in a 100-mL round-bottom flask was refluxed under N_2 for 9 h. The reaction mixture was evaporated in vacuo, 50 mL of H_2O was added, and the aqueous solution was extracted with ether (3 × 30 mL) to remove benzoic acid. The aqueous phase was evaporated in vacuo, the residue was dissolved in 1 mL of 0.2 N AcOH, and the solution was passed through a Bio-Gel P-2 column (200–400 mesh, 2 × 100 cm, 0.2 N AcOH eluant, 10 mL/min flow rate). The ninhydrin-positive fractions were combined and lyophilized to give 80 mg (36%) of **17E**, which was recrystallized from EtOH/Et_2O: mp 137–140 °C; R_f (VI) 0.47; ^1H NMR (D_2O) δ 3–2.7 (m, 2 H, CH, CH_2S), 2.15 (s, 3 H, CH_3S), 1.8–1.5 (m, 3 H, ▽-H).

Anal. Calcd for $C_6H_{12}NO_2SCl$: C, 36.45; H, 6.12; N, 7.08; S, 16.21. Found: C, 36.53; H, 6.00; N, 7.00; S, 16.13.

(*Z*)-2,3-Methanomethionine Hydrochloride (17Z). A solution of 276 mg (0.99 mmol) of **16Z** in 13 mL of concentrated HCl/acetic acid (1:1) in a 50-mL round-bottom flask was refluxed under N_2 for 13 h and worked up by the procedure used for **17E**, giving 80 mg (40%) of **17Z**, which was recrystallized from EtOH/Et_2O: mp 184–192 °C dec; ^1H NMR (D_2O) δ 3.05–2.75 (m, 2 H, CH_2S), 2.2 (s, 3 H, CH_3S), 1.9–1.7 (m, 2 H, ▽-H), 1.5–1.2 (m, 1 H, ▽-H).

Anal. Calcd for $C_6H_2NO_2SCl \cdot {}^1/_5EtOH$: C, 34.85; H, 6.28; N, 6.71; S, 15.34. Found: C, 34.34; H, 5.90; N, 6.56; S, 14.89.

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Registry No. **3**, 65037-88-9; **4E**, 112575-25-4; **5**, 112575-26-5; **6**, 112575-27-6; **7E**, 112575-28-7; **8**, 112575-29-8; **9**, 112575-30-1; **10E**, 112575-31-2; **10Z**, 112575-32-3; **11E**, 112575-33-4; **11Z**, 112575-24-3; **12**, 66646-88-6; **13**, 112575-34-5; **14**, 112575-35-6; **14** (*N*-benzoyl derivative), 112575-40-3; **15**, 112575-36-7; **16E**, 112575-37-8; **16Z**, 112575-41-4; **17E**, 112575-38-9; **17Z**, 112575-39-0; *p*-$BrCH_2C_6H_4NO_2$, 100-11-8; PhCOCl, 98-88-4; epibromohydrin, 3132-64-7.