solvent (3 mL). The reaction was completed after 1 h (TLC). Then, it was hydrolyzed with 2-3 drops of water and dried ($MgSO_4$) and the solvent evaporated to give pure compound **23** (520 mg, 97%) as a colorless oil. ^{1}H-NMR: δ 3.73 (s, 6 H, CH_3O), 3.76 (d, 2 H, J = 4.5 Hz, H4H8), 4.85 (s, 2 H, H1H5), 4.92 (s, 2 H, OH), 5.41 (d, 2 H, J = 4.5 Hz, H3H7), 6.82 (m, 8 H), 6.96-7.02 (m, 6 H), 7.28 (t, 4 H). ^{13}C-NMR: δ 156.7, 153.0, 137.5, 129.6, 121.8, 115.6, 114.9, 114.2, 87.9 (C3C7), 82.9 (C4C8), 66.3 (C1C5), 55.7 (CH_3O). IR (KBr): ν 3450 (OH). Anal. Calcd for $C_{32}H_{32}N_2O_6$: C, 71.10; H, 5.97; N, 5.18. Found: C, 71.17; H, 6.08; N, 5.15.

Crystal Structure Determination. A summary of the fundamental crystal data is given in Table III. A crystal of prismatic shape was resin epoxy coated and mounted in a Kappa diffractometer. The cell dimensions were refined by least-squares fitting the values of 25 reflections. The intensities were corrected for Lorentz and polarization effects. Scattering factors for neutral atoms were taken from the *International Tables for X-Ray Crystallography*.[46] The structure was solved by Multan and Fourier methods. An empirical absorption correction[47] was applied at the end of the isotropic refinement. Final refinement with fixed isotropic factors and coordinates for H atoms, except for H4 and H8 whose coordinates were located in a ΔF and refined. Most of the calculations were carried out with the X-ray 80 system.[48]

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Supplementary Material Available: Full spectral data for compounds **2**, **3**, and **4** and tables of X-ray data for **5a** (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Asymmetric Syntheses of All Four Stereoisomers of 2,3-Methanomethionine

Kevin Burgess* and Kwok-Kan Ho

Chemistry Department, Texas A & M University, College Station, Texas 77843

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Asymmetric syntheses of all four stereoisomers of 2,3-methanomethionine ((**Z**)- and (**E**)-**cyclo-Met**) are described. The source of chirality in these reactions is the trifluoromethylsulfonate ester **1b** which reacts with di-*tert*-butyl malonate via direct displacement of trifluoromethylsulfonate followed by lactonization to give 1-(*tert*-butoxycarbonyl)-2-oxo-3-oxabicyclo[3.1.0]hexane (**2**). Conversion of compound **2** into (**Z**)-**cyclo-Met** can be achieved via ring opening of the lactone, Hoffmann rearrangement, mesylation, and displacement with thiomethoxide. A route to (**E**)-**cyclo-Met** was developed using a lipase to effect a critical ester hydrolysis.

Introduction

Substitution of protein amino acids with 2,3-methano analogs ("methanologs")[1] produces peptidomimetics with interesting and potentially valuable properties. First, this modification imposes severe conformational restraints which, in turn, influence the biological properties of these molecules. For instance, substitution of phenylalanine by **cyclo-Phe** gave *tasteless* analogs of aspartame (Asp-PheOMe)[2-4] and peptidomimetics of Leu^5-enkephalin which are opiate *antagonists*.[5-17] Second, proteolytic cleavage is more difficult at sites linking 1-aminocyclopropanecarboxyl fragments than cleavage of normal peptide bonds,[5,18-20] and this enhances the bioavailability of

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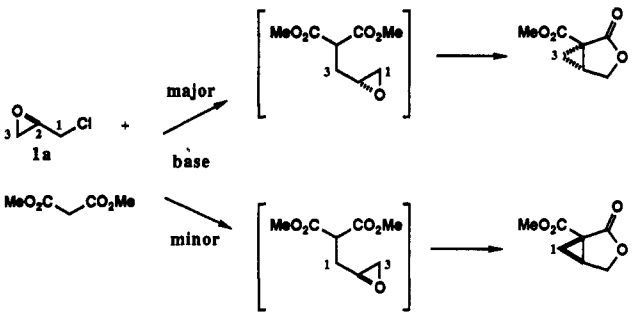
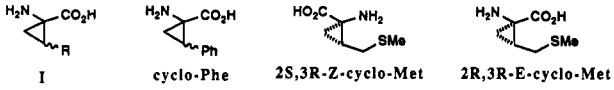
Scheme I. Configuration of Lactone Governed by the Regiochemistry of the First Nucleophilic Attack on the Epoxide 1a



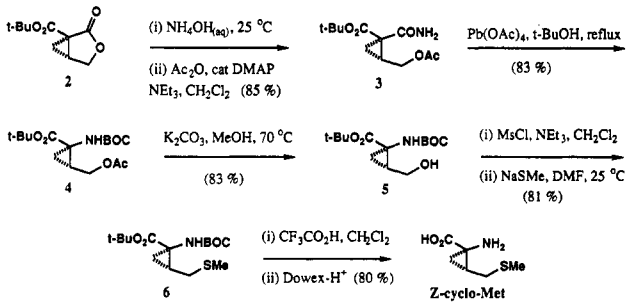
peptidomimetics formed from methanologs. Finally, some cyclopropane-based peptidomimetics of substrates for zinc metalloproteins have been shown to act as suicide enzyme inhibitors via ring cleavage and concomitant alkylation of residues in enzyme active sites.[21,22]



I cyclo-Phe 2S,3R-Z-cyclo-Met 2R,3R-E-cyclo-Met

Limited accessibility of methanologs in optically active form is an obstacle to further investigations of peptidomimetics containing them. Some 3-substituted 2,3-methanoamino acids are naturally occurring (**I** (*E*-isomer in each case): R = Et,[23] Me,[24] and $CH_2NH(C{=}NH)NH_2$[25,26]), but for large-scale work isolation of these compounds from natural sources is impractical; consequently, chemical synthesis seems to be the most attractive approach. Several groups, notably Stammer and co-workers, have prepared 2,3-methanologs of Phe,[27-30] Val,[31] Leu,[31] Tyr,[32,33] Glu[34,35] Met,[36] Pro,[37] Asp,[38] and a number of surrogates for simple nonproteogenic amino acids.[39] Most of the reported syntheses gave *racemic* materials; this is unfortunate because studies of cyclopropane-based peptidomimetics require stereochemically pure compounds. The only 2,3-methanologs of protein amino acids that have been prepared in optically active form are (*E*)- and

Scheme II. Synthesis of (*Z*)-Cyclo-Met



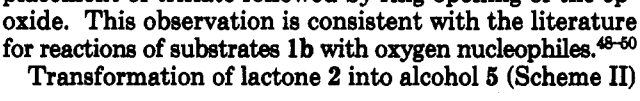
(*Z*)-cyclo-Phe,[30,40,41] although several routes to enantioenriched surrogates of simple nonproteogenic amino acids have been reported.[42-45]

Several retrosynthetic analyses of *functionalized* 2,3-methanologs (i.e., **I**: R ≠ alkyl or aryl) converge to 2,3-methanohomoserine[46,47] derivatives (i.e., **I**: R = CH_2OH). This paper describes preparations of all four stereoisomers of **cyclo-Met** via such intermediates, the first reported asymmetric syntheses of 2,3-methanologs of protein amino acids with a functionalized side chain.

Results

Pirrung and co-workers have shown[43] that nearly optically pure (*R*)-epichlorohydrin **1a** reacts with dimethyl malonate to give a 1*S*,5*R*-bicyclic lactone with 93.4% ee in 36% yield (Scheme I). The slight loss of stereochemical fidelity observed in this process is a consequence of direct displacement of the chloride competing with attack at the epoxide followed by Payne rearrangement, the latter being the major pathway (Scheme I).

In our syntheses, triflate **1b**[49] was chosen as a starting material because nearly all of the optical activity of **1b** was transferred to product **2** and because both enantiomers of the precursor to **1b** may be purchased or conveniently prepared.[51] This modification of Pirrung's conditions, also using di-*tert*-butyl malonate as shown in eq 1, gave lactone



(eq. 1)

2 in yields of approximately 50%. Reaction of **1b** with the anion of di-*tert*-butyl malonate proceeds via direct displacement of triflate followed by ring opening of the epoxide. This observation is consistent with the literature for reactions of substrates **1b** with oxygen nucleophiles.[48-50]

Transformation of lactone **2** into alcohol **5** (Scheme II)

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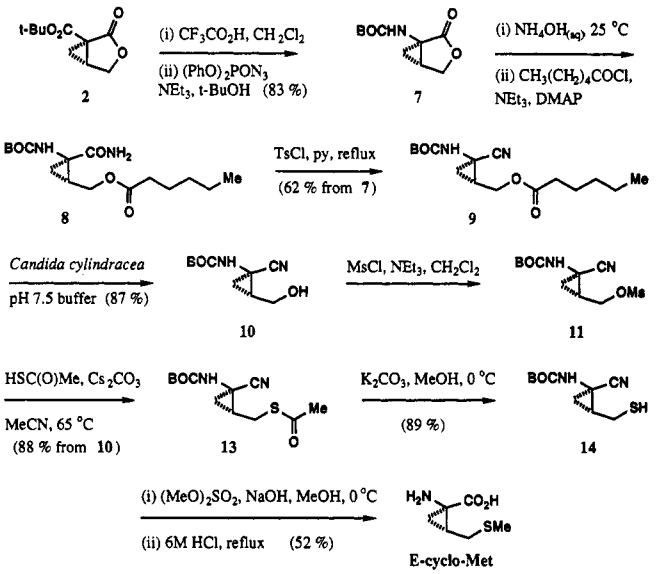
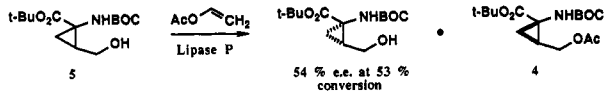
Scheme III. Synthesis of (*E*)-Cyclo-Met



is directly analogous to steps used in a literature preparation of model compounds for investigations of ethene biosynthesis.[43] Mosher's method[52] indicated alcohol **5** had an enantiomeric excess of more than 95% after recrystallization. Mesylation of this alcohol and reaction with thiomethoxide gave **(*Z*)-cyclo-Met** in a fully blocked form. Similar reactions attempted in the corresponding synthesis of **(*E*)-cyclo-Met** were not successful (vide infra).

An alternative to the approach depicted in Scheme II would be to resolve one of the intermediates in the corresponding racemic synthesis; this would be economical since both enantiomers of **(*Z*)-cyclo-Met** are required for future work. Racemic lactone **2** was readily obtained in 61% yield via the reaction of di-*tert*-butyl malonate with (±)-epibromohydrin (see Experimental Section). Several biocatalytic resolutions of racemic intermediates in Scheme II were explored. Enzyme-mediated hydrolysis of racemic **4** or acetylation of racemic **5** was studied by using lipase from *Pseudomonas* AK, *Pseudomonas* K_{10}, *Candida cylindracea*, porcine pancreatic lipase, lipase P, and papain. The best enantiomeric excess was observed for acetylation of alcohol **5** mediated by Amano Lipase P (eq 2), but the enantioselection was below acceptable levels for a practical asymmetric synthesis.

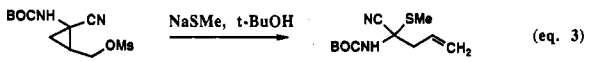


(eq. 2)

Scheme III describes our route to one enantiomer of **(*E*)-cyclo-Met**. The initial step in the synthesis was to introduce the α-amino functionality. Consequently, treatment of **2** with trifluoroacetic acid was used to hydrolyze the *tert*-butyl ester, leaving a carboxylic acid for a Curtius rearrangement with simultaneous protection.[53] The major challenge in this sequence was then encountered: to open lactone **7** and manipulate the products in such a way that the two functionalized tethers will not reform a cyclic system. This was achieved by reacting lactone **7** with aqueous ammonium hydroxide and esterifying the resulting alcohol to give the hexanoate **8**. A long chain ester was deliberately chosen for this step to facilitate deprotection later in the sequence. The amide group of compound **8** was then dehydrated to a nitrile (**9**), thus avoiding ring closure in subsequent steps.

Acidic hydrolysis of ester **9** was inappropriate since the BOC-protecting group also would be removed, and it is necessary to shield the amine during subsequent steps in the synthesis. Unfortunately, hexanoate **9** and the corresponding acetate (prepared by an analogous sequence, not shown) formed a mixture of products when exposed to several of the mildly basic conditions which might otherwise be used to cleave esters. Consequently, hydrolysis mediated by the lipase from *Candida cylindracea* was used to achieve the desired reaction at near neutral pH. Hexanoate **9** reacted more rapidly under these conditions and gave superior yields than the corresponding acetate. Incidentally, there was no evidence for kinetic resolution of **9** at approximately 50% conversion in this enzymatic hydrolysis.

The next step in the synthesis of **(*E*)-cyclo-Met** was introduction of the sulfur functionality, but a problem arose. Mesylate **11** was reacted with thiomethoxide under a variety of conditions (e.g., NaSMe in THF, DMF, or *t*-BuOH at a variety of temperatures ranging from 0 to 25 °C) but gave mostly the cyclopropane-cleavage product **12** (eq 3). Failure of the desired transformation was surprising given that synthesis of sulfide **6** via displacement of a mesylate had been successful in the preparation of **(*Z*)-cyclo-Met**. Decreased steric hindrance and increased electrophilicity at the α-carbon of substrate **11** makes this site more susceptible to nucleophilic attack, and this perhaps accounts for these observations. Fortunately, thioacetate displaced mesylate from **11** in an S_N2 sense affording the thioester **13** without formation of significant byproducts (Scheme III). Base-mediated cleavage of this thioacetate gave a good yield of the corresponding thiol, a notable observation since alkaline hydrolyses of ester **9** were impractical. Finally, **(*E*)-cyclo-Met** was obtained via methylation and exhaustive acidic hydrolysis of the intermediate thiol **14**.



11 12 (eq. 3)

Conclusions

The syntheses shown in Schemes II and III were each performed using both enantiomers of **2**; hence, samples of both optical isomers of **(*Z*)**- and **(*E*)-cyclo-Met** were obtained. The enantiomeric excess of the products appears to be limited only by the optical purity of the glycidol triflate (**1b**) used.

Our immediate plans are to form peptidomimetics of the neuropeptide Phe-Met-Arg-Phe-NH_2[54] and of HIV-1 protease substrates containing vulnerable Met-Met linkages. Moreover, we are optimistic that this synthetic approach can be modified for asymmetric syntheses of several other functionalized cyclopropane amino acids.

Experimental Section

General Procedures. Melting points were uncorrected. High-field NMR spectra were recorded on a Bruker AF300 (^1H at 300 MHz, ^{13}C at 75.4 MHz) or a Bruker AC250 (^1H at 250 MHz, ^{13}C at 62.9 MHz), ^1H chemical shifts are reported in δ ppm relative to $CHCl_3$ (7.25 ppm) as internal standard, and ^{13}C chemical shifts are reported in ppm relative to $CHCl_3$ (77.0 ppm) unless specified otherwise. Multiplicities in ^1H NMR are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet, and (m) multiplet.

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The carbon multiplicities are listed as (C) quaternary, (CH) methine, (CH_2) methylene, and (CH_3) methyl assigned via DEPT sequence experiments. Thin-layer chromatography was performed on silica gel 60 F_{254} plates from Whatman. Flash chromatography was performed on SP Silica Gel 60 (230–600 mesh ASTM). Optically active [[(trifluoromethanesulfonyl)oxy]methyl]oxirane (**1b**)[49] was prepared from optically active glycidol purchased from Aldrich. Lipase from *Candida cylindracea* was purchased from Sigma. DMF was stored over 4-Å molecular sieves for 1 week before use, benzene was distilled immediately before use from sodium benzophenone ketyl, pyridine was distilled from KOH pellets, and CH_2Cl_2 and *t*-BuOH were distilled from CaH_2. Other chemicals were purchased from commercial suppliers and used as received.

Assignments of the ^1H NMR of (***Z***)- and (***E***)-**cyclo-Met** are based upon a combination of ^{13}C NMR, DEPT, HETCOR, and difference NOE analyses.

(±)-1-(*tert*-Butoxycarbonyl)-2-oxo-3-oxabicyclo[3.1.0]-hexane (2). Di-*tert*-butyl malonate (9.00 g, 41.61 mmol, 1.00 equiv) was added dropwise to a well-stirred mixture of sodium hydride (2.20 g, 45.77 mmol, 1.10 equiv), tetrabutylammonium iodide (0.15 g, 0.42 mmol, 0.01 equiv), and DMF (166 mL) under nitrogen, and the resulting mixture was stirred at 25 °C for 15 min. The mixture was heated to 80 °C, and epibromohydrin (5.70 g, 41.61 mmol, 1.00 equiv) was added dropwise. After being heated at 80 °C for 12 h, the mixture was poured into H_2O (200 mL) and extracted with diethyl ether (3 × 150 mL). The combined organic layers were dried (anhydrous Na_2SO_4), the solvent was evaporated, and the residue was recrystallized from EtOAc/hexane. Racemic **2** (5.00 g, 61%) was obtained as colorless crystals: R_f 0.35 (20% acetone/hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 4.34 (dd, J = 9.45, 4.78 Hz, 1 H), 4.14 (d, J = 9.38 Hz, 1 H), 2.65 (m, 1 H), 1.99 (dd, J = 7.98, 4.63 Hz, 1 H), 1.48 (s, 9 H), 1.29 (t, J = 5.02 Hz, 1 H).

(1*R*,5*R*)-(−)-1-(*tert*-Butoxycarbonyl)-2-oxo-3-oxabicyclo-[3.1.0]hexane (2). Di-*tert*-butyl malonate (7.49 g, 34.61 mmol, 1.00 equiv) was added dropwise to a well-stirred mixture of sodium hydride (1.99 g, 41.53 mmol, 1.20 equiv) and 15-crown-5 (0.25 mL, 1.25 mmol, 0.03 equiv) in dry benzene (87 mL) at 25 °C under nitrogen. The solution was stirred at 25 °C for 15 min, and (*S*)-(+)-[[(trifluoromethanesulfonyl)oxy]methyl]oxirane (**1b**) (8.56 g, 41.53 mmol, 1.20 equiv, 92% ee) was added via syringe pump (ca. 0.1 mL/min). After the reaction had been stirred for 12 h, the benzene was evaporated under reduced pressure. Water (80 mL) was added to the resulting residue, and the solution was extracted with EtOAc (3 × 80 mL). The combined organic layers were dried, and removal of the solvent gave an oil which was purified by flash chromatography (5%–10% acetone/hexane) to give compound (−)-**2** as colorless crystals (3.27 g, 48%, 91% ee). The enantiomeric excess of this material was determined by a chiral shift experiment using Eu(hfc)$_3$: $[\alpha]^{25}_D$ −105.5° (c = 1.30, CH_2Cl_2).

(1*R*,2*R*)-(+)-*tert*-Butyl 2-(Acetoxymethyl)-1-carbamoyl-cyclopropane-1-carboxylate (3). (1*R*,5*R*)-(−)-1-(*tert*-Butoxycarbonyl)-2-oxo-3-oxabicyclo[3.1.0]hexane (**2**) (3.05 g, 15.39 mmol, 1.00 equiv) was added to a vigorously stirred 14.8 M ammonium hydroxide solution (154 mL). After the mixture had been stirred overnight at 25 °C, the aqueous ammonium hydroxide was evaporated to dryness. A solution of triethylamine (2.34 g, 23.09 mmol, 1.50 equiv) in CH_2Cl_2 (77 mL) and a catalytic amount of DMAP were added to the residue, followed by dropwise addition of acetic anhydride (2.36 g, 23.09 mmol, 1.50 equiv). After being stirred for 2 h, the solution was evaporated, water (50 mL) was added to the resulting residue, and the solution was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried and evaporated. A yellow oil was obtained which was purified by flash chromatography (10%–30% acetone/hexane) to give (+)-(**3**) (3.35 g, 85%) as colorless crystals: mp 88–89 °C; R_f 0.24 (20% acetone/hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 8.33 (br s, 1 H), 5.74 (br s, 1 H), 4.42 (dd, J = 11.94, 6.01 Hz, 1 H), 4.12 (dd, J = 11.74, 8.56 Hz, 1 H), 2.10 (m, 1 H), 2.04 (s, 3 H), 1.86 (dd, J = 7.87, 4.20 Hz, 1 H), 1.70 (dd, J = 9.38, 4.19 Hz, 1 H), 1.44 (s, 9 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.0 (C), 170.9 (C), 168.9 (C), 82.6 (C), 62.0 (CH_2), 31.8 (C), 30.8 (CH/CH_3), 27.9 (CH/CH_3), 20.9 (CH/CH_3), 19.7 (CH_2); IR ($CHBr_3$) 3484, 3347, 1708, 1670, 1568 cm^{-1}; MS (EI, 70 eV) m/e 258 (0.4, M + 1), 201 (25), 159 (43), 141 (100), 102 (55), 57 (43); $[\alpha]^{25}_D$ +14.5° (c = 1.01, $CHCl_3$). Anal. Calcd for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44. Found: C, 56.16; H, 7.43; N, 5.30.

(1*S*,2*R*)-(−)-*tert*-Butyl 2-(Acetoxymethyl)-1-[*N*-(*tert*-butoxycarbonyl)amino]cyclopropane-1-carboxylate (4). A solution of (1*R*,2*R*)-(+)-*tert*-butyl 2-(acetoxymethyl)-1-carbamoylcyclopropane-1-carboxylate (**3**) (2.44 g, 9.49 mmol, 1.00 equiv) and *t*-BuOH (47 mL) was heated to 70 °C under nitrogen. Lead tetraacetate (8.41 g, 18.97 mmol, 2.00 equiv) was added in one portion, and the mixture was heated at reflux for 2 h. After cooling to 25 °C, Et_2O (30 mL) followed by $NaHCO_3$ (2 g) were added, and the mixture was stirred for 10 min. The mixture was filtered through a short plug of silica, the filtrate was evaporated, and the residue was purified by flash chromatography (10%–20% EtOAc/hexane) to give (−)-(**4**) as colorless crystals (2.61 g, 83%): mp 66–67 °C; R_f 0.46 (20% acetone/hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 5.30 (br s, 1 H), 4.28 (m, 1 H), 4.03 (m, 1 H), 2.07 (s, 3 H), 1.95 (m, 1 H), 1.70 (m, 1 H), 1.43–1.45 (2 overlapped s, 18 H), 1.02 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.2 (C), 171.1 (C), 156.2 (C), 81.5 (C), 79.8 (C), 63.3 (CH_2), 38.8 (C), 28.2 (CH/CH_3), 27.9 (CH/CH_3), 25.5 (CH/CH_3), 21.0 (CH/CH_3), 20.4 (CH_2); IR ($CHBr_3$) 3418, 1727, 1486, 1368, 1243, 1145, 1030 cm^{-1}; MS (EI, 70 eV) m/e 330 (0.1, M + 1), 217 (66), 200 (30), 113 (74), 57 (100); $[\alpha]^{25}_D$ −5.7° (c = 1.31, $CHCl_3$). Anal. Calcd for $C_{16}H_{27}NO_6$: C, 58.34; H, 8.26; N, 4.25. Found: C, 58.43; H, 8.22; N, 4.19.

(1*S*,2*R*)-(−)-*tert*-Butyl 1-[*N*-(*tert*-Butoxycarbonyl)-amino]-2-(hydroxymethyl)cyclopropane-1-carboxylate (5). Potassium carbonate (0.93 g, 6.74 mmol, 2.00 equiv) was added to a well-stirred solution of (−)-**4** (1.11 g, 3.37 mmol, 1.00 equiv) in MeOH (34 mL). After the mixture had been heated at 70 °C for 17 h, the MeOH was evaporated, water (50 mL) was added to the residue, and the resulting solution was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried, and the solvent was evaporated. The crude product was purified by flash chromatography (10%–25% EtOAc/hexane) and recrystallized from EtOAc/hexane to give (−)-**5** as colorless crystals (0.81 g, 83%): mp 106–107 °C; R_f 0.23 (25% EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 5.03 (br s, 1 H), 3.95 (m, 1 H), 3.17 (m, 1 H), 2.22 (m, 1 H), 1.46–1.43 (2 overlapped s, 19 H), 0.70 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.2 (C), 158.1 (C), 81.6 (C), 80.8 (C), 61.6 (CH_2), 38.8 (C), 30.5 (CH/CH_3), 28.2 (CH/CH_3), 27.9 (CH/CH_3), 18.8 (CH_2); IR ($CHBr_3$) 3421, 1708, 1492, 1368, 1290, 1251, 1142 cm^{-1}; MS (EI, 70 eV) m/e 288 (0.04, m + 1), 175 (100), 158 (26), 100 (71), 57 (87); $[\alpha]^{25}_D$ −41.0° (c = 1.25, $CHCl_3$). Anal. Calcd for $C_{14}H_{25}NO_5$: C, 58.52; H, 8.77; N, 4.87. Found: C, 58.74; H, 8.73; N, 4.77. The optical purity was determined by converting the alcohol to the corresponding Mosher's ester using (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid and DCC. A diastereomeric excess of ≥95% was measured by ^{19}F NMR.

(2*S*,3*R*)-(−)-*N*-(*tert*-Butoxycarbonyl)-*O*-*tert*-butyl-2,3-methanomethionine (6). (1*S*,2*R*)-(−)-*tert*-Butyl 1-[*N*-(*tert*-butoxycarbonyl)amino]-2-(hydroxymethyl)cyclopropane-1-carboxylate (**5**) (0.36 g, 1.25 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (7 mL) under nitrogen, and the solution was cooled to 0 °C. Triethylamine (0.29 g, 2.50 mmol, 2.00 equiv) was added, followed by dropwise addition of methanesulfonyl chloride (0.25 g, 2.50 mmol, 2.00 equiv). After the solution had been stirred at 0 °C for 5 min and at 25 °C for 1 h, the solvent was evaporated. Water (10 mL) was added to the residue, and the solution was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried, and the solvent was evaporated. The residue was redissolved in DMF (6 mL) under nitrogen and cooled to 25 °C in a water bath, and sodium thiomethoxide (0.22 g, 3.13 mmol, 2.50 equiv) was added in one portion. After the mixture had been stirred in the water bath for 45 min, the mixture was poured into water (15 mL) and the solution was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried and the solvent was evaporated to yield an oil which was purified by flash chromatography (5%–10% EtOAc/hexane) to give (−)-**6** as colorless crystals (0.32 g, 81%): mp 94–95 °C; R_f 0.68 (25% EtOAc/hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 5.16 (br s, 1 H), 2.62 (m, 2 H), 2.14 (s, 3 H), 1.90 (m, 1 H), 1.70 (m, 1 H), 1.44–1.42 (2 overlapped s, 18 H), 0.98 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.4 (C), 156.3 (C), 81.4 (C), 79.9 (C), 40.0 (C), 33.2 (CH_2), 28.3 (CH/CH_3), 28.0 (CH/CH_3), 26.5 (CH/CH_3), 23.2 (CH_2), 15.3 (CH/CH_3); IR ($CHBr_3$) 3418, 1716, 1484, 1367, 1290, 1244, 1143,

1073 cm^{-1}; MS (EI, 70 eV) m/e 318 (0.1, M + 1), 317 (0.02%, M^+), 188 (100); $[\alpha]^{25}_D$ −20.7° (c = 1.15, $CHCl_3$). Anal. Calcd for $C_{15}H_{27}NO_4S$: C, 56.76; H, 8.57; N, 4.41; S, 10.10. Found: C, 56.35; H, 8.31; N, 4.34; S, 9.99.

(2*S*,3*R*)-(−)-2,3-Methanomethionine ((*Z*)-(−)-Cyclo-Met). (2*S*,3*R*)-(−)-*N*-(*tert*-Butoxycarbonyl)-*O*-*tert*-butyl-2,3-methanomethionine (**6**) (0.152 g, 0.477 mmol) was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 °C. Trifluoroacetic acid (0.67 mL) was added dropwise, and the mixture was allowed to warm to 25 °C and was stirred for 1 h. After evaporation of the solvent, the residue was purified by ion-exchange chromatography (Dowex 50×8-100, H^+ form, eluted with 2 M ammonium hydroxide solution) to give a pale yellow solid. This was recrystallized from EtOH to give **(*Z*)-(−)-cyclo-Met** as colorless crystals (0.061 g, 80%): mp 195–196 °C dec; R_f 0.49 (*t*-BuOH/H_2O/acetic acid, 12/5/3); ^1H NMR (250 MHz, D_2O, reference DHO = 4.8 ppm) δ 2.72 (d, J = 7.71 Hz, 2 H), 2.17 (s, 3 H), 1.95 (m, 1 H), 1.59 (dd, J = 9.60, 6.30 Hz, 1 H), 1.13 (dd, J = 7.26, 6.58 Hz, 1 H); ^{13}C NMR (75.4 MHz, D_2O, reference MeOH = 49.9 ppm) δ 175.8 (C), 40.9 (C), 32.0 (CH_2), 24.0 (CH/CH_3), 19.30 (CH_2), 15.1 (CH/CH_3); $[\alpha]^{25}_D$ −22.2° (c = 0.33, H_2O). A sample was purified by HPLC using a C_{18} column (10 × 250 mm, 5 μm, eluted with A: 0.01% TFA in H_2O; B: 0.01% TFA in acetonitrile, 0–10% B in 20 min, detected at 215 nm). After lyophilization of the product fractions, **(*Z*)-cyclo-Met·CF_3COOH** was isolated as colorless crystals: ^1H NMR (300 MHz, D_2O, ref CH_3OH = 3.7 ppm) δ 3.11 (d, J = 7.88 Hz, 2 H, CH_2S), 2.56 (s, 3 H, SCH_3), 2.50 (m, 1 H, cyclopropane CH), 2.15 (dd, J = 9.79, 6.40 Hz, 1 H, *pro-S H* of cyclopropane CH_2), 1.67 (dd, J = 7.77, 6.65 Hz, 1 H, *pro-R H* of cyclopropane CH_2); ^{13}C NMR (300 MHz, D_2O, ref CH_3OH = 49.9 ppm) δ 174.0 (C), 39.7 (C), 31.6 (CH_2), 25.4 (CH/CH_3), 20.2 (CH_2), 15.2 (CH/CH_3); FABMS (glycerol) m/e 162.1 (M + 1), 114.0 (CF_3COOH^+).

The enantiomer was prepared in identical fashion. **(1*S*,5*S*)-(+)-1-(*tert*-Butoxycarbonyl)-2-oxo-3-oxabicyclo[3.1.0]hexane** ((+)-**2**): $[\alpha]^{25}_D$ +104.6° (c = 1.30, CH_2Cl_2). **(1*S*,2*S*)-(−)-*tert*-Butyl 2-(acetoxymethyl)-1-carbamoylcyclopropane-1-carboxylate** ((−)-**3**): $[\alpha]^{25}_D$ −13.9° (c = 1.01, $CHCl_3$). **(1*R*,2*S*)-(+)-*tert*-Butyl 2-(Acetoxymethyl)-1-[*N*-(*tert*-butoxycarbonyl)amino]cyclopropane-1-carboxylate** ((+)-**4**): $[\alpha]^{25}_D$ +5.6° (c = 1.31, $CHCl_3$). **(1*R*,2*S*)-(+)-*tert*-Butyl 1-[*N*-(*tert*-butoxycarbonyl)amino]-2-(hydroxymethyl)-cyclopropane-1-carboxylate** ((+)-**5**): $[\alpha]^{25}_D$ +40.6° (c = 1.25, $CHCl_3$). **(2*R*,2*S*)-(+)-*N*-(*tert*-Butoxycarbonyl)-*O*-*tert*-butyl-2,3-methanomethionine** ((+)-**6**): $[\alpha]^{25}_D$ +21.0° (c = 1.15, $CHCl_3$). **(2*R*,3*S*)-(+)-2,3-Methanomethionine**: $[\alpha]^{25}_D$ +22.2° (c = 0.33, H_2O).

(1*R*,5*R*)-(−)-1-[*N*-(*tert*-Butoxycarbonyl)amino]-2-oxo-3-oxabicyclo[3.1.0]hexane (7). A solution of trifluoroacetic acid (7.5 mL) in CH_2Cl_2 (22.5 mL) was added to (−)-**2** (2.48 g, 12.51 mmol, 1.00 equiv) and stirred at 25 °C for 80 min. The solution was evaporated, and the residue was dried under vacuum. The crude carboxylic acid was used without further purification: ^1H NMR (250 MHz, $CDCl_3$) δ 8.81 (br s, 1 H), 4.46 (dd, J = 9.63, 4.78 Hz, 1 H), 4.31 (d, J = 9.60 Hz, 1 H), 2.88 (m, 1 H), 2.14 (dd, J = 8.01, 4.54 Hz, 1 H), 1.56 (t, J = 5.07, 1 H). The acid was redissolved in *t*-BuOH (42 mL) and triethylamine (2.53 g, 25.02 mmol, 2.00 equiv) under nitrogen, diphenylphosphoryl azide (4.13 g, 15.04 mmol, 1.20 equiv) was added, and the solution was refluxed for 17 h. The solvent was evaporated, the residue was redissolved in EtOAc (150 mL), and the solution was filtered. The organic filtrate was washed with saturated NaCl solution (80 mL) and dried, and the solvent was evaporated. The resulting pale yellow solid obtained was purified by flash chromatography (20%–33% acetone/hexane) to give (−)-**7** as colorless crystals (2.21 g, 83%): ^1H NMR (250 MHz, $CDCl_3$) δ 5.29 (br s, 1 H), 4.52 (m, 1 H), 4.14 (d, J = 9.35 Hz, 1 H), 2.42 (m, 1 H), 1.51 (m, 1 H), 1.44 (s, 9 H), 1.21 (m, 1 H); $[\alpha]^{25}_D$ −30.9° (c = 0.43, $CHCl_3$).

(1*R*,2*R*)-(−)-1-[*N*-(*tert*-Butoxycarbonyl)amino]-2-[(hexanoyloxy)methyl]cyclopropane-1-carbonitrile (9). (1*R*,5*R*)-(−)-1-[*N*-[(*tert*-Butoxycarbonyl)amino]-2-oxo-3-oxabicyclo[3.1.0]hexane (**7**) (1.30 g, 6.09 mmol) was added to a vigorously stirred solution of 14.8 M NH_4OH (60 mL). After the mixture had been stirred at 25 °C for 5 h, the NH_4OH was evaporated. The residue was suspended in a solution of CH_2Cl_2 (30 mL) with a catalytic amount of DMAP and triethylamine (0.92 g, 1.27 mL, 9.14 mmol) under nitrogen. The mixture was cooled to 0 °C, and hexanoyl chloride (0.98 g, 0.96 mmol) was added dropwise. After the mixture was stirred at 0 °C for 15 min, the temperature was raised to 25 °C and the mixture was stirred for 3 h. The solvent was evaporated, Et_2O (50 mL) was added to the residue, and the solution was washed with saturated NaCl solution (50 mL), dried, and evaporated. Compound **8** was obtained as a solid and used without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 6.67 (br s, 1 H), 6.03 (br s, 1 H), 5.16 (br s, 1 H), 4.36 (dd, J = 11.68, 6.40 Hz, 1 H), 4.12 (m, 1 H), 2.30 (t, J = 7.4 Hz, 3 H), 1.80–1.16 (s overlapped with m, 17 H), 0.87 (t, J = 6.57 Hz, 3 H). The compound **8** was dissolved in pyridine (20 mL) under nitrogen, and TsCl (1.74 g, 9.14 mmol) was added. After the solution was refluxed for 12 h, a dark brown solution was obtained. The pyridine was evaporated, water (100 mL) was added to the residue, the aqueous layer was extracted with EtOAc (100 + 50 mL), and the combined organic layers were dried and evaporated. The crude product was purified by flash chromatography (5–20% acetone/hexane) to give (−)-**9** (1.18 g, 62%) as an oil: R_f 0.38 (20% acetone/hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 5.09 (br s, 1 H), 4.35 (m, 1 H), 4.07 (m, 1 H), 2.35 (t, J = 7.43 Hz, 2 H), 1.88 (m, 1 H), 1.63–1.31 (s overlapped with m, 17 H), 0.89 (t, J = 6.70 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.5 (C), 154.6 (C), 118.2 (C), 81.4 (C), 63.0 (CH_2), 43.0 (C), 33.9 (CH_2), 31.1 (CH_2), 28.1 (CH/CH_3), 27.0 (CH/CH_3), 24.4 (CH_2), 22.2 (CH_2), 21.2 (CH_2), 13.8 (CH/CH_3); IR (neat) 3352, 2931, 2360, 1739, 1508, 1124, 1101 cm^{-1}; MS (EI, 70 eV) m/e 254 (66, M − 56), 237 (9), 198 (8), 116 (37), 99 (38), 57 (100); $[\alpha]^{25}_D$ −1.4° (c = 1.62, $CHCl_3$). Anal. Calcd for $C_{16}H_{26}N_2O_4$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.13; H, 8.44; N, 9.26.

(1*R*,2*R*)-(+)-1-[*N*-(*tert*-Butoxycarbonyl)amino]-2-(hydroxymethyl)cyclopropane-1-carbonitrile (10). (1*R*,2*R*)-(−)-1-[*N*-(*tert*-Butoxycarbonyl)amino]-2-[(hexanoyloxy)-methyl]cyclopropane-1-carbonitrile (**9**) (1.13 g, 3.64 mmol) was suspended in a vigorously stirred phosphate buffer (pH 7.5, 37 mL) at 25 °C, and lipase from *C. cylindracea* (1.70 g, 1.50 mass equiv) was added. After the mixture had been stirred for 35 h, the enzyme was removed by filtration, water (50 mL) was added to the filtrate, and the resulting solution was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried and evaporated, leaving a residue which was purified by flash chromatography (15–33% acetone/hexane) to give (+)-**10** as colorless crystals (0.57 g, 74%, 91% ee): R_f 0.31 (33% acetone/hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 5.54 (br s, 1 H), 4.02 (dd, J = 11.55, 3.39 Hz, 1 H), 3.51 (t, J = 10.61 Hz, 1 H), 2.51 (br s, 1 H), 1.78 (m, 1 H), 1.45 (s, 10 H), 1.24 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 154.9 (C), 118.8 (C), 81.8 (C), 62.0 (CH_2), 43.5 (C), 31.2 (CH/CH_3), 28.1 (CH/CH_3), 20.5 (CH_2); IR (neat) 3331, 2239, 1704, 1512, 1363, 1281, 1164, 1100, 1037 cm^{-1}; MS (EI, 70 eV) m/e 212 (0.5, M^+), 157 (21), 140 (14), 82 (25), 57 (100); HRMS m/e calcd for $C_{10}H_{16}N_2O_3$ 212.1161, found 212.1154; $[\alpha]^{26}_D$ +2.5° (c = 1.12, $CHCl_3$). The enantiomeric excess of this material was determined via a Eu(fod)$_3$ chiral shift experiment on the corresponding Mosher's ester prepared from (*R*)-(+)-MTPA.

(1*R*,2*R*)-(+)-1-[*N*-(*tert*-Butoxycarbonyl)amino]-2-[(acetylthio)methyl]cyclopropane-1-carbonitrile (13). Methanesulfonyl chloride (0.326 g, 2.849 mmol, 1.20 equiv) was added dropwise to a solution of (+)-**10** (0.504 g, 2.375 mmol) and triethylamine (0.228 g, 2.849 mmol, 1.20 equiv) in CH_2Cl_2 (12 mL) at 0 °C under nitrogen. After the addition, the reaction mixture was warmed to 25 °C and stirred for 30 min. The CH_2Cl_2 was evaporated, water (20 mL) was added to the residue, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried and evaporated. Mesylate **11** was obtained as an oil and used without further purification: ^1H NMR (250 MHz, $CDCl_3$) δ 5.42 (br s, 1 H), 4.50 (dd, J = 11.59, 5.92 Hz, 1 H), 4.16 (dd, J = 11.36, 8.76 Hz, 1 H), 3.09 (s, 3 H), 1.93 (m, 1 H), 1.81 (m, 1 H), 1.59 (m, 1 H), 1.46 (s, 9 H). The mesylate **11** was dissolved in acetonitrile (12 mL), cesium carbonate (0.845, g, 2.593 mmol, 1.10 equiv) was added followed by thioacetic acid (0.197 g, 2.593 mmol, 1.10 equiv), and the mixture was heated at 65 °C for 15 min. After the mixture was cooled to 25 °C, water (20 mL) was added and the resulting solution was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried and evaporated, leaving a residue which was purified by flash chromatography (10–20% acetone/hexane) to give (+)-**13** as an oil (0.561 g, 88% from (+)-**10**): R_f 0.55 (33% acetone/

hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.04 (br s, 1 H), 3.07 (br s, 2 H), 2.36 (s, 3 H), 1.74 (m, 1 H), 1.47 (br s, 10 H), 1.36 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 195.2 (C), 154.4 (C), 118.4 (C), 81.5 (C), 43.8 (C), 30.5 (CH/CH_3), 29.7 (CH_2), 28.6 (CH/CH_3), 28.2 (CH/CH_3), 23.7 (CH_2); IR (neat) 3370, 2924, 2854, 2361, 2344, 1648, 1137 cm^{-1}; MS (EI, 70 eV) m/e 271 (0.9, M + 1), 214 (70), 172 (33), 155 (64), 95 (97), 57 (100); $[\alpha]^{25}_D$ +16.0° (c = 1.12, $CHCl_3$). Anal. Calcd for $C_{12}H_{18}N_2O_3S$: C, 53.31; H, 6.71; N, 10.36; S, 11.86. Found: C, 52.98; H, 6.64; N, 10.41; S, 11.56.

2-[*N*-(*tert*-Butoxycarbonyl)amino]-2-(methylthio)pent-4-ene-1-nitrile (12). Sodium thiomethoxide (0.0032 g, 0.046 mmol, 1.00 equiv) was added to a solution of the mesylate 11 (0.0133 g, 0.0458 mmol) in *t*-BuOH (0.2 mL) under nitrogen at 25 °C. After the mixture had been stirred for 30 min, the solvent was evaporated, and the residue was purified by flash chromatography (5% acetone/hexane) to give 12 (0.0048 g, 43%) as a colorless oil: R_f 0.26 (10% acetone/hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.83 (m, 1 H), 5.28 (m, 2 H), 4.89 (br s, 1 H), 2.92 (d, J = 7.09 Hz, 2 H), 2.41 (s, 3 H), 1.47 (s, 9 H); HRMS m/e calcd for $C_{11}H_{18}N_2O_2S$ 242.1089, found 242.1089.

(1*R*,2*R*)-(+)-1-[*N*-(*tert*-Butoxycarbonyl)amino]-2-(mercaptomethyl)cyclopropane-1-carbonitrile (14). Potassium carbonate (0.529 g, 3.832 mmol) was added to a solution of (+)-13 (0.518 g, 1.915 mmol) in MeOH (10 mL) at 0 °C. After the mixture had been stirred at 0 °C for 30 min, the MeOH was evaporated, water (20 mL) was added to the residue, and the solution was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried and evaporated, leaving a residue which was purified by flash chromatography (15–30% acetone/hexane) to give (+)-14 as colorless crystals (0.338 g, 89%): R_f 0.20 (20% acetone/hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.46 (br s, 1 H), 3.64 (m, 1 H), 3.04 (d, J = 10.8 Hz, 1 H), 2.28 (m, 1 H), 1.42 (s overlapped with m, 12 H); ^{13}C NMR (62 MHz, $CDCl_3$) δ 155.3 (C), 102.6 (C), 80.2 (C), 46.5 (C), 30.9 (CH_2), 28.2 (CH/CH_3), 27.4 (CH/CH_3), 19.0 (CH_2); IR ($CHBr_3$) 3422, 3020, 2361, 1701, 1613, 1142 cm^{-1}; MS (EI, 70 eV) m/e 229 (1, M + 1), 228 (0.9, M$^+$), 172 (95), 127 (100), 57 (62); $[\alpha]^{26}_D$ +24.1° (c = 1.115, $CHCl_3$). Anal. Calcd for $C_{10}H_{16}N_2O_2S$: C, 52.61; H, 7.06. Found: C, 52.19; H, 6.81.

(2*R*,3*R*)-(+)-2,3-Methanomethionine-trifluoroacetic Acid ((*E*)-(+)-cyclo-Met). A solution of dimethyl sulfate (0.456 g, 3.614 mmol, 2.50 equiv) in 50% $NaOH_{(aq)}$ (0.289 mL, 2.5 equiv) was added dropwise to a solution of (+)-14 (0.330 g, 1.445 mmol, 1.00 equiv) in MeOH (7.3 mL) at 0 °C under nitrogen. After the reaction had been stirred at 0 °C for 30 min, water (20 mL) was added, and the solution was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried and the solvent was evaporated, leaving a residue which was purified by flash chromatography (10–20% acetone/hexane) to give (1*R*,2*R*)-1-[*N*-(*tert*-butoxycarbonyl)amino]-2-[(methylthio)methyl]cyclopropane-1-carbonitrile as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.19 (br s, 1 H), 2.90 (dd, J = 13.73, 6.29 Hz, 1 H), 2.51 (dd, J = 13.58, 8.16 Hz, 1 H), 2.19 (s, 3 H), 1.71 (m, 1 H), 1.46 (s, 10 H), 1.32 (m, 1 H). The (1*R*,2*R*)-1-[*N*-(*tert*-butoxycarbonyl)amino]-2-[(methylthio)methyl]cyclopropane-1-carbonitrile was dissolved in 6 M HCl (13 mL) and heated to reflux for 19 h. After the solution had been cooled to 25 °C, water (10 mL) was added and the solution was lyophilized. The lyophilized residue was purified by ion-exchange chromatography on a Dowex 50 × 8-100 column (H^+ form, eluted with 2 M NH_4OH). After lyophilization of the product fractions, **(*E*)-(+)-cyclo-Met** was obtained (0.105 g, 52%). A sample of the ion-exchanged product was further purified by HPLC on a C_{18} column (10 × 250 mm, 5 μm, eluted with A: 0.01% TFA in H_2O; B: 0.01% TFA in acetonitrile, 0–10% B in 20 min, detected at 215 nm) to give colorless crystals: R_f 0.62 (14.8 M ammonium hydroxide-/H_2O/1-propanol (1/4/12)); ^{1}H NMR (300 MHz, D_2O, ref CH_3OH = 3.70 ppm) δ 3.28 (dd, J = 13.95, 6.53 Hz, 1 H, H of CH_2S), 3.13 (dd, J = 13.95, 8.36 Hz, 1 H, H of CH_2S), 2.51 (s, 3 H, SCH_3), 2.36 (m, 1 H, cyclopropane CH), 1.97 (d, J = 9.80 Hz, 2 H, cyclopropane CH_2); ^{13}C NMR (75.4 MHz, D_2O, ref CH_3OH = 49.9 ppm) δ 172.6 (C), 39.5 (C), 31.4 (CH_2), 28.0 (CH/CH_3), 20.4 (CH_2), 15.2 (CH, CH_3); FABMS (glycerol) m/e 162.1 (M + 1), 114.0 (CF_3COOH^+); $[\alpha]^{26}_D$ +19.0° (c = 0.29, H_2O).

The enantiomer was prepared in identical fashion. **(1*S*,5*S*)-(+)-1-[*N*-(*tert*-Butoxycarbonyl)amino]-2-oxo-3-oxabicyclo[3.1.0]hexane** ((+)-7: $[\alpha]^{24}_D$ +31.5° (c = 0.43, $CHCl_3$). **(1*S*,2*S*)-(+)-1-[*N*-(*tert*-Butoxycarbonyl)amino]-2-(hexanoyloxy)methyl]cyclopropane-1-carbonitrile** ((+)-9): $[\alpha]^{25}_D$ +1.4° (c = 1.62, $CHCl_3$). **(1*S*,2*S*)-(-)-1-[*N*-(*tert*-Butoxycarbonyl)amino]-2-(hydroxymethyl)cyclopropane-1-carbonitrile** ((-)-10): $[\alpha]^{25}_D$ -2.8° (c = 1.12, $CHCl_3$). **(1*S*,2*S*)-(-)-1-[*N*-(*tert*-Butoxycarbonyl)amino]-2-[(acetylthio)methyl]-cyclopropane-1-carbonitrile** ((-)-13): $[\alpha]^{25}_D$ -16.1° (c = 1.12, $CHCl_3$). **(1*S*,2*S*)-(-)-1-[*N*-(*tert*-Butoxycarbonyl)amino]-2-(mercaptomethyl)cyclopropane-1-carbonitrile** ((-)-14): $[\alpha]^{25}_D$ -25.0° (c = 1.12, $CHCl_3$). **(2*S*,3*S*)-(-)-2,3-Methanomethionine-trifluoroacetic acid:** $[\alpha]^{25}_D$ -18.9° (c = 0.29, H_2O).

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Registry No. (*S*)-(+)-**1b**, 74748-75-7; (*R*)-(-)-**1b**, 143169-39-5; (±)-**2**, 143122-73-0; (1*R*,5*R*)-**2**, 143169-40-8; (1*R*,5*R*)-**2** (free acid), 143169-57-7; (1*S*,5*S*)-**2**, 143169-41-9; (1*R*,2*R*)-**3**, 143122-74-1; (1*S*,2*S*)-**3**, 143169-42-0; (1*S*,2*R*)-**4**, 143122-75-2; (1*R*,2*S*)-**4**, 143169-43-1; (1*S*,2*R*)-**5**, 143122-76-3; (1*R*,2*S*)-**5**, 143234-52-0; (2*S*,3*R*)-**6**, 143122-77-4; (2*R*,3*S*)-**6**, 143169-44-2; (1*R*,5*R*)-**7**, 143169-45-3; (1*S*,5*S*)-**7**, 143169-46-4; (1*R*,2*R*)-**8**, 143122-78-5; (1*R*,2*R*)-**9**, 143122-79-6; (1*S*,2*S*)-**9**, 143169-47-5; (1*R*,2*R*)-**10**, 143122-80-9; (1*S*,2*S*)-**10**, 143169-48-6; (1*R*,2*R*)-**11**, 143122-81-0; **12**, 143122-82-1; (1*R*,2*R*)-**13**, 143122-83-2; (1*S*,2*S*)-**13**, 143169-49-7; (1*R*,2*R*)-**14**, 143122-84-3; (1*R*,2*R*)-**14** (*S*-methyl derivative), 143122-85-4; (1*S*,2*S*)-**14**, 143169-50-0; $CH_2(COOBu\text{-}t)_2$, 541-16-2; $CH_3(CH_2)_4COCl$, 142-61-0; (2*S*,3*R*)-*Z*-cyclo-Met, 143169-51-1; (2*R*,3*S*)-*Z*-cyclo-Met, 143169-52-2; (2*R*,3*R*)-*E*-cyclo-Met, 143169-54-4; (2*S*,3*S*)-*E*-cyclo-Met, 143169-56-6; epibromohydrin, 3132-64-7.

Supplementary Material Available: ^{1}H and/or ^{13}C NMR spectra of **10**, **12**, **14**, **(*Z*)-cyclo-Met**, and **(*E*)-cyclo-Met** (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.