Novel Enantioselective Synthesis of α-Methylthreonines and α,β-Dimethylcysteines

Hui Shao, Jaimie K. Rueter, and Murray Goodman*

Department of Chemistry and Biochemistry, University of California−San Diego, La Jolla, California 92093-0343

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Recently, the incorporation of conformationally constrained amino acids into biologically active peptides has emerged as an important route to prepare peptide-based drug molecules.[1] Results have clearly demonstrated that such a strategy can effectively optimize the populations of possible conformations to assist conformational analysis, identify the required pharmacophoric groups to generate potent and receptor-specific ligands, and protect the global molecular structure from metabolic degradation by specific and nonspecific enzymes under physiological conditions.[2] Specifically, it has been shown that incorporation of α-methylated or β-methylated amino acids can be used as an effective probe in an effort to understand local conformations responsible for the bioactivity of a particular peptide.[1a,b] The α-methylation of an amino acid severely restricts rotation around the N−C^{α} (ϕ) and C^{α}−C(O) (φ) bonds along the peptide backbone. On the other hand, β-methylation, by virtue of steric interactions, can strongly affect the populations of side-chain rotamers. The α,β-dimethylated amino acids combine both of the above effects. The four different stereochemical structures obtained by changing the two chiral centers exhibit different conformational preferences. Thus, this approach can provide key information about the conformations responsible for biological recognition.

Despite their potential for generating novel structures, the application of α,β-dimethylated amino acids has not been widely adopted because of difficulties encountered in the preparation of these building blocks. There appears to be no general stereospecific methodology directed at the synthesis of such building blocks. Hruby and co-workers reported the synthesis of α,β-dimethylphenylalanine without stereochemical control at the β-carbon.[3] Most synthetic routes to these unusual amino acids are based on the alkylation of enolates from bislactims, oxazidones, imidazolidinones, or other chiral auxiliaries.[4] Most of these strategies can control the stereochemistry of only one methyl group in each step. Multistep stoichiometric preparation and careful purification of each auxiliary is also required for these syntheses. Recently, we reported the enantioselective synthesis of allothreonines and β-hydroxylvalines using the Sharpless asymmetric dihydroxylation (AD) reaction to generate two chiral centers in one step.[5,6] We now apply this method for catalytic asymmetric synthesis of α,β-dimethylamino acids with high enantiomeric purity at both chiral centers using α-methylthreonine (α,β-dimethylserine) and α,β-dimethylcysteine as examples.

The synthesis of α-methylthreonine analogues begins with the asymmetric dihydroxylation of benzyl tiglate (Scheme 1) in the presence of $(DHQ)_2PHAL$ (AD-mix α) and methanesulfonamide. The reaction proceeds smoothly to yield the (2*R*,3*S*)-diol **1** with excellent optical purity.[7,8] The diol **1** is converted to its 2,3-cyclic sulfite with thionyl chloride and oxidized to the cyclic sulfate **2** in a one-pot reaction. The cyclic sulfate group has been shown to function as an effective leaving group with excellent regioselectivity.[9] Nucleophilic substitution by NaN_3 at the α-carbon of cyclic sulfate **2** occurs with clean inversion of chirality. Acidic hydrolysis provides the desired α-azido ester **3**. Compound **3** readily undergoes catalytic hydrogenation to generate the optically pure (2*S*,3*S*)-α-methylthreonine **4**. The X-ray diffraction analysis of (2*S*,3*S*)-*N*-Boc-α-methylthreonine **5** establishes the correct structure of the final product. In the large-scale synthesis (60 mmol and up), starting from the Sharpless AD reaction, only one silica gel chromatographic purification is necessary to purify **3** before hydrogenation to provide the final product in an 50% overall yield. By changing the Sharpless chiral catalytic ligand to $(DHQD)_2PHAL$ (AD-mix β), the (2*R*,3*R*)-α,β-dimeth-

* To whom correspondence should be addressed.

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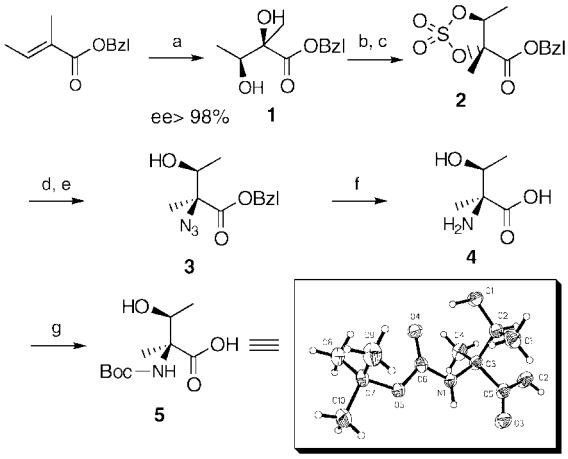
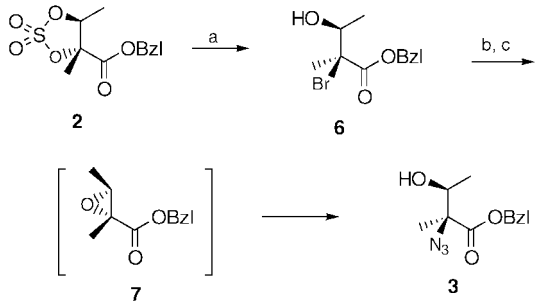
Scheme 1[a]



[a] Key: (a) Sharpless AD, AD-mix-α (91%); (b) $SOCl_2$, DCM; (c) $NaIO_4$, $RuCl_3$ (94%); (d) NaN_3, acetone, H_2O; (e) 20% H_2SO_4, ether (87%); (f) H_2, MeOH, Pd−C (96%); (g) $(Boc)_2O$, BuOH (63%).

Scheme 2[a]



[a] Key: (a) LiBr, acetone, H_2O (93%); (b) NaN_3, acetone, H_2O; (c) 20% H_2SO_4, ether (82%).

ylserine is obtained in a similar manner with a 50% overall yield and 98% enantiomeric excess.

To prepare (2*R*,3*S*)-α-methylthreonine, we first examined the use of LiBr to ring-open the sulfate **2** (Scheme 2), followed by a second nucleophilic displacement with NaN_3 to obtain the desired stereochemistry at the α position.[10] This double-inversion procedure, however, does not result in net retention of configuration, as planned, but instead the epoxide **7** is formed in situ and is then ring opened by the azide anion. The result of this additional displacement with stereochemical inversion is a net inversion of configuration, and the product is identical to compound **3** generated from direct azide displacement of the sulfate. Protection of the alcohol as the *tert*-butyl ether after treatment of the sulfate with LiBr prevents formation of the epoxide, and the stereochemistry of the product is as desired. This reaction, however, proceeds in very low yields as a result of elimination of HBr to form the α,*β*-unsaturated ester, which is a particularly favorable reaction for sterically hindered α carbons. It was hoped that the use of *Z*-2-methylbutenoic acid (angelic acid) as the alkene substrate would allow us to obtain both stereocenters during the AD reaction. (Scheme 3). In this case, the only inversion necessary would occur during the ring opening of the cyclic sulfate with NaN_3. Chiral HPLC analysis of the various intermediates showed a consistent enantiomeric

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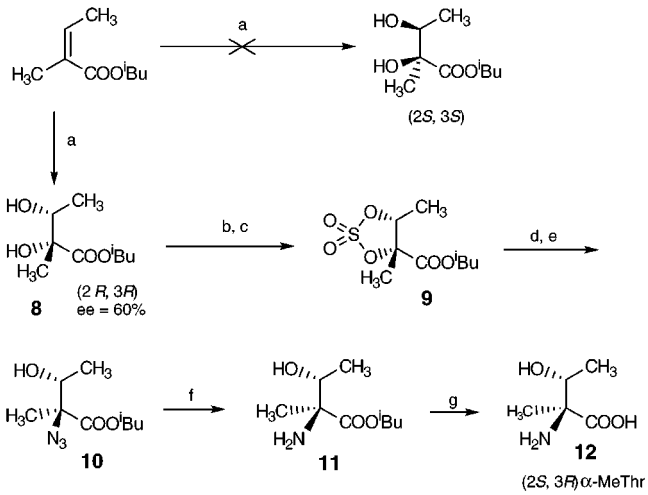
Scheme 3[a]



[a] Key: (a) Sharpless AD, AD-mix-*β* (85%); (b) $SOCl_2$, DCM; (c) KIO_4, $RuCl_3$ (91%); (d) NaN_3, DMF; (e) 20% H_2SO_4, ether (80%); (f) H_2, MeOH, Pd−C (97%); (g) NaOH, MeOH, H_2O (89%).

excess of 60%. This result is consistent with reports that high ee's are not achieved for a variety of *Z* alkenes under similar conditions.[11]

The more surprising result came upon reduction and saponification of the azido alcohol **10** to give what should have been (2*S*,3*R*)-α-methylthreonine. The optical rotation value was not only predictably low, but it was of the opposite sign from the literature values.[12] Further experiments with the alternate ligand, as well as benzyl angelate, confirmed the low ee's, and opposite absolute configuration for the angelate substrates. These results can be explained by the studying the molecular mechanics model developed by Sharpless to explain the origin of enantioselectivity in these reactions[13] (Figure 1a,b). Figure 1 details the orientation for *trans*-substituted alkenes in the ligand−osmate binding pocket. For clarity, the ligand has been simplified in Figure 1. In the case of the angelates, the alkene hydrogen is replaced by a methyl group, increasing the steric interaction with the ligand. The alkene orients itself in such a way as to keep the one hydrogen atom in the most sterically demanding position, putting the α-methyl at the pseudoequatorial position and the carboxylate at the pseudoaxial position (Figure 1c). This reorientation gives rise to the observed inversion in stereochemistry. Competition between the predicted mechanism and the reorientation mechanism accounts for the low enantiomeric excesses observed. We have investigated numerous methods for inversion of the *β*-C of tiglate-derived diols as a means to synthesize the desired derivative in an enantiomerically pure fashion. However, none of our attempts, including Mitsunobu inversions, have yielded a facile method for accomplishing such a transformation because of the number and nature of the functional groups present and the steric restraints of the methyl groups.

To prepare α,*β*-dimethylcysteine, the azido alcohol **3** (Scheme 4) can be converted to aziridine-2-carboxylic ester **13** under Staudinger reaction conditions with no

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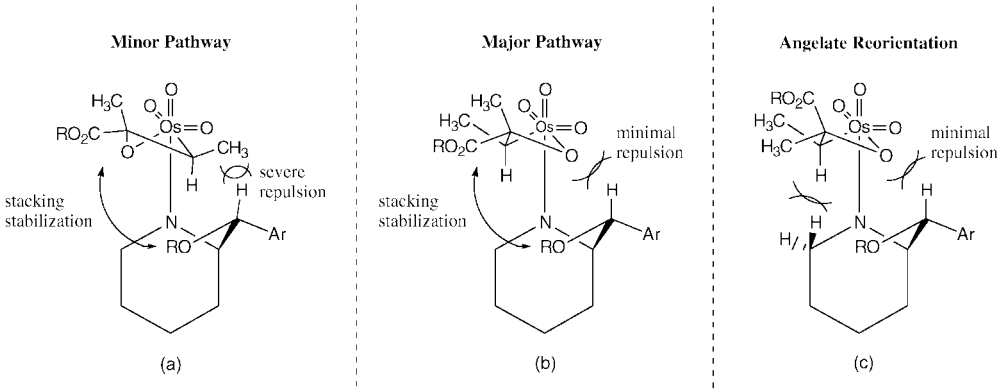
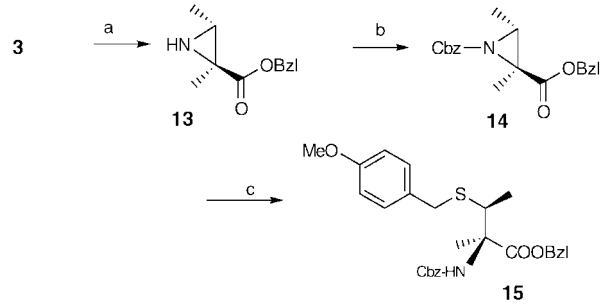


Figure 1. Molecular mechanics model for origin of enantioselectivity: (a) minor pathway for tiglate esters resulting from steric repulsion; (b) major pathway for tiglate esters minimizes steric interactions; (c) orientation of angelate esters to minimize steric interactions gives rise to inversion of stereochemistry.

Scheme 4[a]



[a] Key: (a) PPh_3, MeCN (91%); (b) Cbz-OSu, pyridine (86%); (c) DCM, BF_3-Et_2O, $MeOC_6H_5CH_2SH$ (65%).

loss of enantiomeric purity.[14] The N-unsubstituted aziridine **13** does not undergo ring-opening reaction to provide α,β-dimethylcysteine in the presence of a Lewis acid and a thiol.[14] However, with the aid of boron trifluoride etherate, the activated *N*-(benzyloxycarbonyl)aziridine-2-carboxylic ester **14** reacts with 4-methoxybenzylthiol to give the desired protected α,β-dimethylcysteine **15**.

It should be pointed out that the stereospecific and regioselective ring-opening reactions of aziridine intermediates with a wide variety of nucleophiles, including organometallic reagents, have been extensively studied in recent years.[15] As a result of recent advances, the aziridine-2-carboxylic esters described here and further modified aziridine structures are appealing synthons for the preparation of novel heterocyclic α,β-dimethylated amino acids.

Experimental Section

General Methods. NMR spectra were recorded in $CDCl_3$ (or indicated specifically) at 300 MHz (^1H) and 75 MHz (^{13}C) using tetramethylsilane as the internal standard. The IR spectra were obtained using a Nicolet FT-IR instrument. Optical rotations were recorded at 20 °C using a Perkin-Elmer 241 polarimeter. Column and thin-layer chromatographies were carried out on silica gel (230−400 mesh ASTM) with the indicated solvent system. Microanalyses were provided by Desert Analytics, Tucson, AZ. Mass spectra were measured at UCR Mass Spectrometry Facility. All the asymmetric ligands were purchased from Aldrich Co.

Benzyl (2*R*,3*S*)-2,3-Dihydroxy-2-methylbutyrate (1). To a stirred solution of AD-mix α (42 g) and methanesulfonamide (0.3 g, 30 mmol) in *tert*-butyl alcohol (150 mL) and water (150 mL) at 4 °C was added benzyl tiglate (5.71 g, 30 mmol). The reaction was stirred at 4 °C until the alkene was consumed (ca. 2 days). Sodium sulfite (45 g) was added as a solid, and the mixture was stirred for 30 min. Diethyl ether (600 mL) was added, the mixture was washed with water (2 × 50 mL), and the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The pure product (6.11 g, 91%) was obtained as a colorless oil by silica gel chromatography with hexanes−ethyl acetate (70:30 v/v). The enantiomeric excess (>98%) was determined using chiral column liquid chromatography: $[\alpha]^{20}_D = -1.15$ (*c* 4.68, $CHCl_3$); IR (neat) 3488 (broad, OH), 3092, 3065, 3034, 2984, 2940, 1729 (C=O) cm^{-1}; ^1H NMR δ 1.23 (d, $J = 6.3$ Hz, 3H), 1.34 (s, 3H), 2.65 (d, $J = 7.8$ Hz, 1H), 3.70 (s, 1H), 4.00 (m, 1H), 5.24 (s, 2H), 7.37 (s, 5H); ^{13}C NMR 16.3, 21.5, 67.5, 71.2, 71.9, 127.0 (m), 135.2, 176.0 ppm. FAB-MS MH^+ 225, MNH_4^+ 242; HRMS MH^+ calcd for $C_{12}H_{17}O_4$ 225.1127, found 225.1128 (0.5 ppm). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.16; H, 7.12.

Cyclic Sulfate (2). To a stirred solution of **1** (2.14 g, 9.5 mmol) in methylene chloride (20 mL) at 0 °C was added thionyl chloride (1.88 mL, 24 mmol) dropwise. The solution was warmed to 40 °C and stirred while the HCl evolved was swept away by a stream of nitrogen. After 2.5 h, the solution was concentrated under reduced pressure to remove excess $SOCl_2$ and solvent. The crude cyclic sulfite was dried in vacuo for 2 h and dissolved in a mixture of water (30 mL), CH_3CN (20 mL), and CCl_4 (20 mL). $NaIO_4$ (3.98 g, 18.6 mmol) and $RuCl_3$ hydrate (23 mg, 0.11 mmol) were added, and the solution was vigorously stirred for 3 h at ca. 40 °C, until the cyclic sulfite was totally consumed. Ethyl ether (250 mL) was added to the cooled mixture, and the organic layer was removed. It was necessary to add a small amount of activated carbon (10 mg) to the organic layer in order to remove the brown color. The organic layer was then dried ($MgSO_4$) and concentrated under reduced pressure. The pure cyclic sulfate (2.53 g, 94%) was isolated as a colorless oil by silica gel chromatography with hexanes−ethyl acetate (85:15 v/v): $[\alpha]^{20}_D = -6.9$ (*c* 4.84, $CHCl_3$); IR (neat) 3091, 3066, 3038, 3000, 2980, 1745 (C=O), 1387 (sulfate), 1219 (sulfate) cm^{-1}; ^1H NMR δ 1.61 (d, $J = 6.3$ Hz, 3H), 1.73 (s, 3H), 5.25 (q, $J = 6.5$ Hz, 1H), 5.30 (s, 2H), 7.41 (s, 5H); ^{13}C NMR 14.4, 18.0, 68.6, 82.6, 89.1, 128.0 (m), 134.1, 167.4 ppm. FAB-MS MNH_4^+ 304; HRMS MNH_4^+ calcd for $C_{12}H_{18}O_6NS$ 304.0855, found 304.0837. Anal. Calcd for $C_{12}H_{14}O_6S$: C, 50.34; H, 4.93. Found: C, 50.42; H, 5.00.

Benzyl (2*S*,3*S*)-2-Azido-3-hydroxy-2-methylbutyrate (3). To a stirred solution of cyclic sulfate **2** (6.93 g, 24.2 mmol) in

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acetone (50 mL) and water (5 mL) was added sodium azide (3.94 g, 60.6 mmol) as a solid. The mixture was heated to 50 °C for 4 h until **2** was consumed. The mixture was concentrated under reduced pressure. Ethyl ether (300 mL) and water (10 mL) were added, and the solution was chilled to 0 °C followed by addition of 20% H_2SO_4 aqueous solution (30 mL) dropwise. The solution was stirred vigorously at 20 °C for 48 h. The organic layer was collected and concentrated. The pure product (5.27 g, 87%) was isolated as a colorless oil by silica gel chromatography with hexanes−ethyl acetate (75:25 v/v). $[\alpha]^{20}_D = -78$ (*c* 2.8, $CHCl_3$); IR (neat) 3436 (OH), 3037, 2979, 2113 (N_3), 1738 (C=O) cm^{-1}; ^1H NMR δ 1.18 (d, $J = 6.3$ Hz, 3H), 1.60 (s, 3H), 4.00 (q, $J = 6.3$ Hz, 1H), 5.26 (s, 2H), 7.40 (s, 5H); ^{13}C NMR 17.6, 18.1, 67.6, 70.3, 71.2, 128.0 (m), 134.8, 171.5 ppm; FAB-MS MNH_4^+ 267; HRMS MNH_4^+ calcd for $C_{12}H_{19}O_3N_4$ 267.1457, found 267.1442. Anal. Calcd for $C_{12}H_{15}O_3N_3$: C, 57.82; H, 6.07; N, 16.85. Found: C, 57.97; H, 6.11; N, 16.77.

(2*S*,3*S*) 2-Methylthreonine (4). A solution of **3** (3.10 g, 12.45 mmol) and a small amount of Pd−carbon in methanol (100 mL) was pressurized with 45 psi H_2 for 12 h. The Pd−carbon solid was removed through filtration, and the product was concentrated under reduced pressure. The crude product was dissolved in H_2O (30 mL) and purified by Amberlite IR-120 (plus) ion-exchange resin with water and then 1 N aqueous NH_3 to give **4** as a white solid (1.59 g, 96%): mp 265−267 °C (dec); $[\alpha]^{20}_D = +11.7$ (*c* 1.35, H_2O); ^1H NMR (360 MHz, DMSO-d_6) δ 1.01 (d, $J = 6.1$ Hz, 3H), 1.21 (s, 3H), 3.74 (q, $J = 6.1$ Hz, 1H); FAB-MS MNH_4^+ 151. Anal. Calcd for $C_5H_{11}O_3N$: C, 45.11; H, 8.27; N, 10.5. Found: C, 45.27; H, 8.33, N, 10.2.

***N*-(*tert*-Butyloxycarbonyl)-(2*S*,3*S*)-2-methylthreonine (5).** Compound **4** (2.0 g, 1.5 mmol) was dissolved in *n*-butanol (20 mL) followed by addition of $(Boc)_2O$ (3.33 g, 15.3 mmol). The solution was stirred vigorously for 24 h. After removal of the solvent under reduced pressure, the pure product (2.20 g, 63%) was crystallized by adding hexane (20 mL) in ethyl acetate (2 mL) at 0 °C. The single crystal of **5** was obtained from ethyl acetate solution at 20 °C: mp 138−141 °C; $[\alpha]^{20}_D = +10.0$ (*c* 1.22, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$) δ 1.18 (d, $J = 6.1$ Hz, 3H), 1.45 (s, 9H), 1.59 (s, 3H), 4.23 (q, $J = 6.5$ Hz, 1H); FAB-MS MH^+ 234. Anal. Calcd for $C_{10}H_{19}O_5N$: C, 51.50; H, 8.15; N, 6.01. Found: C, 51.65; H, 8.23; N, 6.05.

Benzyl (2*S*,3*S*)-2-Bromo-3-hydroxy-2-methylbutyrate (6). To a stirred solution of cyclic sulfate **2** (4.0 g, 13.9 mmol) in DMF (60 mL) was added solid lithium bromide (1.33 g, 15.3 mmol). The mixture was heated at 50 °C for 3 h until **2** was consumed. The mixture was concentrated under reduced pressure. Ethyl ether (400 mL) and water (10 mL) were added, and the solution was chilled to 0 °C followed by addition of 20% H_2SO_4 aqueous solution (30 mL) dropwise. The solution was stirred vigorously at 20 °C for 48 h. The organic layer was collected and concentrated. The pure product (3.71 g, 93%) as a colorless oil was isolated by silica gel chromatography with hexanes−ethyl acetate (70:30 v/v): $[\alpha]^{20}_D = +12.5$ (*c* 1.27, $CHCl_3$); IR (neat) 3450 (OH), 3091, 3065, 3034, 2983, 2935, 1734 (C=O) cm^{-1}; ^1H NMR (300 MHz) δ 1.35 (d, $J = 6.6$ Hz, 3H), 1.89 (s, 3H), 4.36 (q, $J = 6.3$ Hz, 1H), 5.25 (m, 2H), 7.38 (s, 5H); FAB-MS MH^+ 287; HRMS MH^+ calcd for $C_{12}H_{16}O_3Br$ 287.0283, found 287.0283. Anal. Calcd for $C_{12}H_{15}O_3Br$: C, 50.35; H, 5.24. Found: C, 50.53; H, 5.30.

Isobutyl (2*R*,3*R*)-2,3-Dihydroxy-2-methylbutyrate (8). Compound **8** was obtained using the same procedure as described for **1** with AD-mix β. The pure product (4.8 g, 85%) was obtained as a colorless oil by silica gel chromatography with hexanes−ethyl acetate (70:30 v/v): $[\alpha]^{20}_D = -6.6$ (*c* 1.42, $CHCl_3$); IR (neat) 3449 (OH), 2964, 1725 (C=O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.96 (d, $J = 6.8$ Hz, 6H), 1.17 (d, $J = 6.6$ Hz, 3H), 1.45 (s, 3H), 1.99 (m, 1H), 3.83 (q, $J = 6.4$ Hz, 1H), 3.99 (m, 2H); ^{13}C NMR 17.5, 18.8, 22.3, 27.5, 72.0, 72.1, 77.2, 175.6 ppm; FAB-MS MH^+ 191, MNa^+ 213. Anal. Calcd for $C_9H_{18}O_4$: C, 56.84; H, 9.47. Found: C, 56.57; H, 9.40.

Cyclic Sulfate 9. To a stirred solution of **8** (2.30 g, 12.1 mmol) in methylene chloride (20 mL) at 0 °C was added thionyl chloride (1.88 mL, 24.0 mmol) dropwise. The solution was warmed to 40 °C and stirred while the HCl evolved was swept away by a stream of nitrogen. After 2.5 h, the solution was concentrated under reduced pressure to remove excess $SOCl_2$ and solvent. The crude cyclic sulfite was dried in vacuo for 2 h and dissolved in a mixture of water (30 mL), CH_3CN (20 mL), and CCl_4 (20 mL). $NaIO_4$ (3.98 g, 18.6 mmol) and $RuCl_3$ hydrate (23 mg, 0.11 mmol) were added, and the solution was vigorously stirred for 3 h at ca. 40 °C until the cyclic sulfite was totally consumed. Ethyl ether (250 mL) was added to the cooled mixture, and the organic layer was removed. It was necessary to add a small amount of activated carbon (10 mg) to the organic layer in order to remove the brown color. The organic layer was then dried ($MgSO_4$) and concentrated under reduced pressure. The pure cyclic sulfate (2.77 g, 91%) was isolated as a colorless oil by silica gel chromatography with hexanes−ethyl acetate (85:15 v/v): $[\alpha]^{20}_D = -9.1$ (*c* 2.64, $CHCl_3$); IR (neat) 2695, 1742 (C=O), 1380 (sulfate) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.97 (d, $J = 6.4$ Hz, 6H), 1.49 (d, $J = 6.4$ Hz, 3H), 1.77 (s, 3H), 2.01 (m, 1H), 4.03 (m, 2H), 4.87 (d, $J = 6.4$ Hz, 1H); ^{13}C NMR 14.5, 18.8, 21.3, 27.6, 73.0, 84.5, 90.7, 167.0 ppm; FAB-MS MH^+ 253, MNa^+ 275. Anal. Calcd for $C_9H_{16}O_6S$: C, 42.86; H, 6.35. Found: C, 42.46; H, 6.11.

Isobutyl (2*S*,3*R*)-2-Azido-3-hydroxy-2-methylbutyrate (10). To a stirred solution of **9** (0.80 g, 3.17 mmol) in DMF (15 mL) was added sodium azide (260 mg, 4 mmol) as a solid. The mixture was stirred at room temperature for 4 h and then heated at 50 °C for ca. 3 h until **9** was consumed. The mixture was concentrated under reduced pressure. Ethyl ether (100 mL) and water (3 mL) were added, and the solution was chilled to 0 °C followed by addition of 20% H_2SO_4 aqueous solution (5 mL) dropwise. The solution was stirred vigorously at 20 °C for 48 h. The organic layer was collected and concentrated. The pure product (545 mg, 80%) was isolated as a colorless oil by silica gel chromatography with hexanes−ethyl acetate (75:25 v/v): $[\alpha]^{20}_D = -43.6$ (*c* 3.40, $CHCl_3$); IR (neat) 3502 (OH), 2113 (N_3), 1731 (C=O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.97 (d, $J = 6.4$ Hz, 3H), 1.23 (d, $J = 6.4$ Hz, 3H), 1.45 (s, 3H), 2.01 (m, 1H), 2.19 (d, $J = 7.6$ Hz, 3H), 4.00 (m, 3H); FAB-MS MH^+ 215, MNa^+ 238. Anal. Calcd for $C_9H_{17}O_3N_3$: C, 50.23; H, 7.96; N, 19.53. Found: C, 50.20; H, 7.77; N, 19.76.

Isobutyl (2*S*,3*R*)-2-Methylthreoninate (11). Compound **11** was obtained from **10** by the same procedure as described for **4**: yield 98%; $[\alpha]^{20}_D = -8.1$ (*c* 1.11, CH_3OH); ^1H NMR (200 MHz, $CHCl_3$) δ 0.95 (d, $J = 6.8$ Hz, 3H), 1.16 (d, $J = 6.4$ Hz, 3H), 1.26 (s, 3H), 1.98 (m, 4H), 3.92 (m, 3H); FAB-MS MH^+ 190, MNa^+ 212. Anal. Calcd for $C_9H_{19}O_3N$: C, 56.14; H, 10.05; N, 7.40. Found: C, 56.48; H, 810.00; N,7.11.

(2*S*,3*R*)-2-Methylthreonine (12). A solution of **11** (116.3 mg, 0.88 mmol) was dissolved in methanol (2 mL) and cooled to 0 °C. Sodium hydroxide (1 N, 1.76 mL, 1.76 mmol) was added dropwise. The solution was brought to room temperature and stirred for 3 h. The solvent was removed, and the resulting solid was purified via ion-exchange chromatography to give the product (104.6 mg, 89.4%) as a white solid: $[\alpha]^{20}_D = +10.5$ (*c* 2.09, H_2O); ^1H NMR (360 MHz, D_2O) δ 1.20 (d, $J = 6.1$ Hz, 3H), 1.35 (s, 3H), 4.13 (d, $J = 6.1$ Hz, 1H); FAB-MS MH^+ 134.

Benzyl (2*S*,3*R*)-2,3-Dimethylaziridine-2-carboxylate (13). To a stirred solution of azido alcohol **3** (2.40 g, 9.64 mmol) in acetonitrile (45 mL) was added PPh_3 (5.05 g, 19.3 mmol) as a solid. The mixture was stirred at 20 °C for 1 h and then refluxed for 4 h until **3** was consumed. After removal of the solvent, the pure product (1.88 g, 91%) was isolated by silica gel chromatography with hexanes−ethyl acetate (70:30 v/v): $[\alpha]^{20}_D = +57$ (*c* 1.4, $CHCl_3$); IR (neat) 3291 (NH), 3092, 3071, 3035, 3005, 2963, 2937, 1723 (C=O) cm^{-1}; ^1H NMR δ 1.11 (d, $J = 5.7$ Hz, 3H), 1.33 (s, 3H), 2.28 (q, $J = 5.7$ Hz, 1H), 5.09 (m, 2H), 7.28 (s, 5H); ^{13}C NMR 13.1, 13.3, 37.7, 38.3, 66.8, 127.0 (m), 135.1, 174.2 ppm; FAB-MS MH^+ 206; HRMS MH^+ calcd for $C_{12}H_{16}O_2N$ 206.1181, found 206.1189. Anal. Calcd for $C_{12}H_{15}O_2N$: C, 70.22; H, 7.36; N, 6.82. Found: C, 70.18; H, 7.34; N, 6.56.

Benzyl (2*S*,3*R*)-*N*-(Benzyloxycarbonyl)-2,3-dimethylaziridine-2-carboxylate (14). To a stirred solution of aziridine **13** (1.00 g, 4.88 mmol) in pyridine (20 mL) were added solid *N*-[(benzyloxycarbonyl)oxy]succinimide (Cbz-OSu) (2.43 g, 9.76 mmol) and 4-(dimethylamino)pyridine (DMAP) (89 mg, 0.73 mmol). The mixture was stirred at 4 °C for 24 h. After removal of the solvent, the pure product (1.44 g, 86%) was isolated by silica gel chromatography with hexanes−ethyl acetate (90:10 v/v): $[\alpha]^{20}_D = +19.4$ (*c* 1.22, $CHCl_3$); IR (neat) 3291 (NH), 3092, 3071, 3035, 3005, 2963, 2937, 1723 (C=O) cm^{-1}; ^1H NMR δ 1.33 (d, $J = 5.7$ Hz, 3H), 1.54 (s, 3H), 3.13 (q, $J = 5.7$ Hz, 1H), 5.14

(m, 4H), 7.36 (m, 10H); ^{13}C NMR 13.1, 13.6, 42.9, 44.8, 67.2, 67.6, 127.0 (m), 135.0, 135.6, 160.2, 169.73 ppm; FAB-MS MH^+ 340; HRMS MH^+ calcd for $C_{20}H_{22}O_4N$ 340.1552, found 340.1549. Anal. Calcd for $C_{20}H_{21}O_4N$: C, 70.80; H, 6.19; N,4.13. Found: C, 70.98; H, 6.24; N, 4.10.

Benzyl (2*R*,3*S*)-*N*-(Benzyloxycarbonyl)-2,3-dimethyl-*S*-(4-methoxybenzyl)cysteinate (15). To a stirred solution of **14** (1.40 g, 4.12 mmol) and 4-methoxybenzylthiol (2.54 g, 16.47 mmol) in dry methylene chloride (20 mL) at 0 °C was added anhydrous boron trifluoride diethyl etherate (BF_3·$O(Et)_2$) (1.52 mL, 12.35 mmol) dropwise. The mixture was stirred at 0 °C for 2 days, and then the reaction was quenched by addition of aqueous NH_4Cl solution. Diethyl ether (200 mL) was added, the mixture was washed by saturated $NaHCO_3$ solution (2 × 50 mL), and the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The pure product (1.31 g, 65%, 97% ee) was obtained as a colorless oil by silica gel chromatography with hexanes−ethyl acetate (80:20 v/v): $[\alpha]^{20}_D = -18.4$ (*c* 1.53, $CHCl_3$); ^{1}H NMR δ 1.26 (d, $J = 6.9$ Hz, 3H), 1.67 (s, 3H), 3.08 (q, $J = 6.6$ Hz, 1H), 3.63 (d, $J = 1.8$ Hz, 2H), 3.77 (s, 3H), 5.03 (s, 2H), 5.16 (m, 2H), 5.71 (s, 1H, NH), 6.81 (d, $J = 8.7$ Hz, 2H), 7.16 (d, $J = 8.4$ Hz, 2H), 7.33 (m, 10H); ^{13}C NMR 20.8, 20.9, 36.1, 45.8, 55.1, 62.9, 66.1, 67.0, 113 (m), 129 (m), 134.8, 135.8, 154.4, 171.5 ppm; FAB-MS MH^+ 494; HRMS MH^+ calcd for $C_{28}H_{32}O_5NS$ 494.2001, found 494.1996. Anal. Calcd for $C_{28}H_{31}O_5NS$: C, 68.15; H, 6.29; N, 2.84. Found: C, 68.33; H, 6.35; N, 2.88.

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Supporting Information Available: X-ray crystallographic data for compound **5**, (2*S*,3*S*)-Boc-α-methylthreonine (9 pages). This material is contained in 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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