A New Synthesis of 2-Substituted 6-*endo*-(Methylthio)bicyclo[2.2.1]heptanes. Synthesis and Crystal and Molecular Structure of a Conformationally Restricted Methionine Analogue

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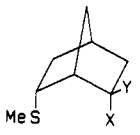
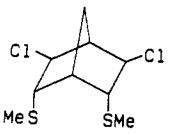
A new and advantageous synthesis of 2-*endo*-substituted-6-*endo*-(methylthio)bicyclo[2.2.1]heptanes, especially suitable for the preparation of such compounds with 2-*endo*-hydroxy and amino substituents, is presented. Also reported is the synthesis of the conformationally restricted methionine analogue (±)-2-*endo*-amino-6-*endo*-(methylthio)bicyclo[2.2.1]heptane-2-*exo*-carboxylic acid and its crystal and molecular structure determined by X-ray crystallographic techniques.

Introduction

The geometric constraint in 2-substituted-6-*endo*-(methylthio)bicyclo[2.2.1]heptanes **1** and **2** has proven advantageous in studies of neighboring group participation in oxidation of thioethers. Electrochemical oxidation of



1a, X = CO_2^-, Y = H; b, X = CH_2OH, Y = H; c, X = $C(Me)_2OH$, Y = H; d, X = CO_2^-, Y = NH_3^+; e, X = $NHCO_2Et$, Y = H; f, X = NH_3^+, Y = CO_2^-; g, X, Y = (=O); h, X = Y = H; i, X = OH, Y = H; j, X = H, Y = OH; k, X = OH, Y = Me; l, X,Y = (=NBn); m, X,Y = ($=NC_6H_{11}$); n, X = NHC_6H_{11}, Y = H; o, X-NHBn, Y = H



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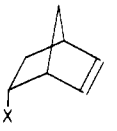
such compounds **1** with 2-*endo*-carboxylate, 2′-hydroxyethyl, or 1′-methylhydroxyethyl groups, i.e. **1a–c**, respectively, in the presence of bromide ion occurs via bromine-catalyzed oxidation of the thioether with neighboring carboxylate or alcohol participation.[1] Neighboring carboxylate participation in the anodic oxidation of the conformationally restricted methionine analogue (±)-2-*exo*-amino-6-*endo*-(methylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid, **1d**, has been reported.[2] Neighboring alcohol and carboxylate participation also results in stabilization of sulfur radical cations in such systems.[3–5] Chemical oxidations occur with neighboring carboxylic acid[6] and alcohol[7,8] participation as well. It is also noteworthy that highly diastereoselective oxidation of the thioether moiety to sulfoxide occurred with *m*-CPBA directed by the alcohol group.[7] Such stereoselectivity was cleverly exploited in the enantioselective synthesis of chiral vinyl sulfoxides which, in turn, are useful in asymmetric Diels–Alder reactions.[9–12]

In most of these compounds there must be 1,6-participation with the formation of a six-membered ring. Since it is well-known for a number of reactions that the effectiveness of neighboring group participation depends on the size of the ring formed and that five-membered-ring formation is often more advantageous than six-membered-ring formation,[13,14] 2-substituted-6-*endo*-(methylthio)bicyclo[2.2.1]heptanes were sought in which the 2-substituent has an electron-rich heteroatom directly attached to C(2). Two such derivatives, **1e**[15] and **2**,[16] were synthesized and studied previously, but an effective general route to such compounds was not found. This paper reports the development of such a route and its application to the synthesis of a number of derivatives including the conformationally constrained methionine analogue **1f**, whose C(2) epimer, i.e. **1d**, had been prepared previously.[2]

Results and Discussion

Because of the difficulties encountered in degrading **1a**, a new synthesis of the bicyclo[2.2.1]heptane system was studied in which the superfluous carbon atom would be omitted from the beginning. The primary goal of this new synthesis is ketone **1g** because it was anticipated that this compound could be readily converted to the compounds of interest. A conceivable intermediate in the syntheses of ketone **1g** is alkene **3a** which in turn is derivable by Diels–Alder reaction of methyl vinyl sulfide with cyclopentadiene. However, vinyl sulfides are not efficient



3a, X = MeS; b, X = $MeSO_2$

dienophiles in Diels–Alder reactions with normal electron demand and, although phenyl vinyl sulfide[17–19] undergoes

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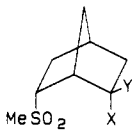
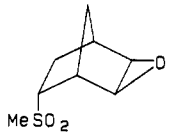
hole-catalyzed Diels–Alder reactions,[20] such reactions with methyl vinyl sulfide and cyclopentadiene were unsuccessful. Vinyl sulfoxides,[21] sulfones,[22] and sulfoximines[23] are useful dienophiles. Since cycloaddition of vinyl sulfoxides is usually accompanied by thermal elimination and the Diels–Alder reaction of methyl vinyl sulfone with cyclopentadiene had already been reported[24] the conversion of the known sulfone **3b** into ketone **1g** was investigated.

There are two concerns with this route. The first is whether the sulfone can be efficiently reduced to the corresponding sulfide because this is an inherently difficult process. Only a few methods have been reported for such reactions.[25,26] To assess the feasibility of reducing a sulfone moiety in this system, known[24] sulfone **4a** was reduced to sulfide **1h** in 17% yield. The low yield is due in part to the volatility of **1h**, X = Y = H, but further efforts to optimize the yield were not made.



4a, X = Y = H
b, X = H, Y = OH
c, X = OH, Y = H
d, X,Y = (=O)
e, X = H, Y = OSitBuMe2

The second concern is whether oxygen can be regioselectively introduced at C(2) in alkene **3b**. To achieve this goal alkene **3b** was selectively epoxidized from the exo direction with *m*-CPBA to give **5** in 86% yield. It was anticipated that hydride reduction of **5** would occur in an S_N2-like fashion[27,28] from the backside of the epoxide ring. Since the backside of C(2) is sterically more hindered than that of C(3), hydride attack should occur preferentially at C(3) to afford C(2)-alcohol **4b**. Treatment of epoxide **5** with LAH gave exclusively tricyclic alcohol **6** in 79% yield.



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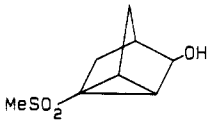

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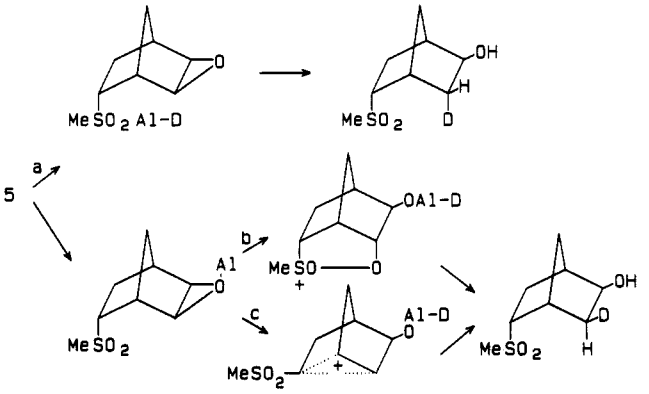
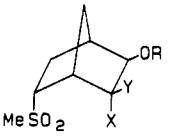
This surprising result suggests that LAH behaves as a base by deprotonating C(6) which then effects backside displacement on C(2) of the epoxide moiety rather than as a hydride donor (the presence of a catalytic amount of base regenerated by LAH cannot be ruled out). However, deprotonation of sulfones by LAH to give α-monoanions and α,α'-dianions has been reported.[29] Treatment of epoxide **5** with lithium triethylborohydride also gave tricyclic alcohol **6**. Reduction of epoxide **5** with a slight excess of DIBALH produced alcohol **7a** as the major product isolated in 40% yield.

Scheme I





7a, R = X = Y = H
b, R = Ac, X = Y = H
c, R = X = H, Y = D

The selective formation of alcohol **7a** suggests that either the sulfone moiety coordinates with the aluminum atom of DIBALH and directs hydride to the backside of C(2), or the aluminum coordinates with the epoxide oxygen and the ring opens with neighboring sulfone participation followed by hydride transfer as shown in Scheme I. Path c shown in the scheme invokes C(6) participation followed by hydride transfer and accounts for the product. However, this pathway is deemed unlikely because opening the coordinated epoxide to generate a cationic center at C(3) with C(5) participation is more favorable than generating a cationic center at C(2) with C(6) participation (path c). The inductively electron-withdrawing $MeSO_2$ group disfavors C(6) participation. It is known[30,31] that either 6-endo or -exo electron-withdrawing substituents disfavor C(6) participation at a cationic center at C(2). The possibility of path a (Scheme I) is supported by the known conversion of sulfones into leaving groups by Lewis acids.[32-34] Neighboring sulfone participation at a cationic center as required by path b (Scheme I) is rare but examples are known[35,36] and particularly relevant is the bromination of 5-*endo*,6-*exo*-bis(phenylsulfonyl)bicyclo[2.2.1]hept-2-ene[36] which occurs apparently with sulfone participation. To distinguish pathway a from b reduction of epoxide **5** with DIBALD was studied. As shown in Scheme I path a leads to 2-*endo*-D whereas path b leads to 2-*exo*-D.

Monodeuterated 3-alcohol was obtained on DIBALD reduction of epoxide **5** in 22% yield. To ascertain the position of the deuterium in this product assignment of resonances in the ^1H NMR spectrum of 3-alcohol **7a** was required. A COSY spectrum and ^1H NMR spectra at 500

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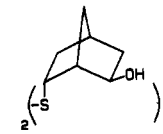
MHz with decoupling were recorded and are included in the supplementary material. In addition, acetate **7b** was prepared and its ^{1}H NMR spectrum measured. The spectra of **7a** and **7b** are similar except that the doublet at δ 3.90 ppm in the spectrum of 3-alcohol **7a** occurs at δ 4.73 ppm in acetate **7b** (and the O–H resonance is absent in the spectrum of **7b**). This allows unequivocal assignment of this resonance of H(3-endo). The COSY spectrum and decoupling experiments on 3-alcohol **7a** reveal that H(3-endo) is strongly coupled (J = 6.8 Hz) to the signal at δ 2.66 ppm which in turn is very strongly coupled (J = 14 Hz) to the resonance at δ 1.26 ppm. This permits assignment of the signals at δ 2.66 and 1.26 ppm to H(2-endo) and H(2-exo), respectively. Long-range W coupling (J = 1.8 Hz) between H(6-exo) and H(2-exo) and greater shift of the signal at δ 1.26 than that at δ 2.66 ppm induced by Eu(fod)$_3$ further support the assignment. In the ^{1}H NMR spectrum of monodeuterated 3-alcohol obtained by reduction of epoxide **5**, the signal at δ 1.26 ppm, due to H(2-exo) is missing and a very large coupling constant (J = 14 Hz) in the signal due to H(2-endo) at δ 2.66 ppm is gone and a small coupling constant (J = 1.8 Hz) is removed from the resonance due to H(6-exo) at δ 3.18 ppm. Thus the deuterium occupies the 2-exo position, i.e. **7c**, is formed in this reaction. This means that path b not path a is predominantly followed in this reaction.

Since the desired regioselective reduction of epoxide **5** to alcohol **4b** could not be accomplished, hydration of alkene **3b** via hydroboration was studied. It was hoped that the electron-withdrawing inductive effect of the sulfone group would favor addition of boron to C(2) and hydrogen to C(3). Hydroboration of alkene **3b** with diborane in THF followed by oxidation with alkaline hydrogen peroxide gave a mixture of 2-*exo*-alcohol **4b** and 3-*exo*-alcohol **7a** in 83% yield in a 5:3 ratio, respectively. Although there is only modest regioselectively in this reaction, this method for preparing **4b** was adopted because the isomeric alcohols could be separated by column chromatography on silica gel. The structural assignment of **4b** is based on its method of synthesis, and ^{1}H NMR spectroscopic analysis which clearly shows that the alcohol group is exo.[37] Initial evidence that the alcohol group is at C(2) and not at C(3) was obtained by the observation that in the ^{1}H NMR spectrum of the epimeric 2-*endo*-alcohol, i.e. **4c**, there is long-range coupling between H-(6-exo) and H(2-exo). Furthermore, the X-ray structure of amino acid **1f** which is derived from **4b**, as outlined below, unequivocally demonstrates that the alcohol group is at C(2).

Oxidation of 2-*exo*-alcohol **4b** with Jones' reagent[38] gave ketone **4d** in 61% isolated yield. Reduction of this ketone with DIBALH produced 2-*endo*-alcohol **4c** in 25% isolated yield and alcohol **1i** in 12% yield. Isolation of 2-*endo*-alcohol **4c** in this experiment proved useful in assigning the alcohol moiety to C(2) as delineated above but, because the yield of the desired alcohol **1i** was so low, reduction of the 2-*exo*-alcohol **4b** was studied. Reduction of the alcohol itself was unpromising but its TBDMS derivative **4e** provided 2-*exo*-alcohol **1j** along with 2-*exo*-alcohol **4b** and another compound deduced to be 2-*exo*-hydroxybicyclo[2.2.1]heptane-6-*endo*-thiol. Separation of this mixture was facilitated by selective oxidation of the thiol to the corresponding disulfide with bromine and aqueous potassium bicarbonate. After chromatography on silica gel, 2-*exo*-alcohol **1j** disulfide **8** and 2-*exo*-alcohol **4b** were isolated in 35, 15, and 17% yield, respectively. Swern oxidation[39] of 2-*exo*-alcohol **1j** gave the desired ketone **1g** in 85% yield.



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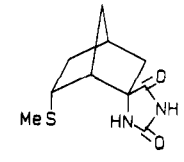
Reduction of ketone **1g** with DIBALH at −70 °C produced 2-*endo*-alcohol **1i** in 66% isolated yield, identical with the material prepared by reduction of ketone **4d** and 2-*exo*-alcohol **1j** in 6% isolated yield, identical with the material prepared as outlined above. Reaction of ketone **1g** with MeMgI gave tertiary alcohol **1k** in 40% isolated yield. The stereochemistry of this alcohol was assigned on the basis of the method of synthesis and the observation of an intramolecular hydrogen bond using IR spectroscopic analysis.

Reductive amination of ketone **1g** could not be effected under standard conditions.[40] However, this ketone reacted with both benzylamine and cyclohexylamine to give the corresponding imines **1l** and **1m**, respectively, in excellent yields. Reduction of the cyclohexylimine with DIBALH afforded *endo*-amine **1n** in 75% overall yield. The structure of the amine was elucidated by ^{1}H NMR spectroscopic analysis using chemical shift and coupling data and in particular the long-range W-coupling of H(2) and H(6) and the shielding of H(3-*endo*) as observed with 2-*endo*-aminobicyclo[2.2.1]heptane. Reduction of the unstable benzylimine **1l** with DIBALH afforded benzylamine **1o** in 52% overall yield.

Ketone **1g** was deemed a reasonable precursor to amino acid **1f** because bicyclo[2.2.1]heptan-2-one has been converted to both isomeric corresponding amino acids via Strecker or Bücherer reactions.[41] However, ketone **1g** proved inert to Strecker reaction conditions even at temperatures up to 135 °C. Under the Bücherer reaction conditions reported to convert bicyclo[2.2.1]heptan-2-one to a mixture of the corresponding hydantoins, ketone **1g** was unreactive. However, at 80 °C hydantoin **9** was formed in 60% isolated yield.



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The preferential formation of hydantoin **9** rather than its epimer may be a result of the anticipated greater thermodynamic stability of hydantoin **9** compared with its epimer. In hydantoin **9** there is less steric repulsion than in its epimer: MeS···NH vs Me···OC, respectively, and there may be an intramolecular hydrogen bond in **9** between NH and S. Hydrolysis of hydantoin **9** provides amino acid **1f** as a solid which on recrystallization yields crystals suitable for X-ray crystallographic analysis. Such analysis unequivocally establishes the structure of **1f** and

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consequently also proves that the alcohol moiety in **4b** the compound from which this amino acid is synthesized, is at C(2) not C(3).

Experimental Section

Reduction of Sulfone 4a. To a solution of sulfone **4a** (348 mg, 2.00 mmol), prepared and purified according to the procedure of Philips and Oku,[24] in dried toluene (8 mL) under an argon atmosphere, was added a 1 M solution of DIBALH in CH_2Cl_2 (6 mL, 6 mmol) by syringe. The CH_2Cl_2 was evaporated by rapidly flowing argon above the warmed solution, and the solution was heated at reflux for 48 h. After cooling to room temperature a few milliliters of EtOH, water, and concd aqueous HCl solution were added sequentially to the reaction mixture. The resulting mixture was extracted with Et_2O (3 × 40 mL), and the extracts were dried (anhyd $MgSO_4$), filtered, and concentrated by distillation of the solvent at atmospheric pressure. The foul-smelling residue was distilled to give a residue of recovered starting material (151 mg) and distillate which was further purified by preparative GC on a 0.25-in. × 6-ft 10% SE-30 on Chromosorb W column at 125 °C. Sulfide **1h** was collected as a colorless oil (27 mg, 17% yield): ^1H NMR (250 MHz) δ 0.82 (1 H, ddd, J = 2.5, 5.3, 10.1 Hz), 1.16–1.52 (5 H, m), 1.85–1.98 (3 H, m), 2.01 (3 H, s, SMe), 2.19 (1 H, br t, J = 4.6 Hz), 2.29 (1 H, br t, J = 3.9 Hz), 3.0 (1 H, m, CHS). Anal. Calcd for $C_8H_{14}S$: C, 67.61; H, 9.86; S, 22.53. Found: C, 67.60; H, 9.94; S, 22.44.

The low yield of sulfide **1h** is ascribable in part to its high volatility.

Epoxide 5. To a stirred solution of alkene **3b** (1.72 g, 0.010 mol) in $CHCl_3$ (40 mL) at 0 °C was added a solution of 85% *m*-CPBA (2.06 g, 0.012 mol) in $CHCl_3$ (30 mL) over 0.5 h. The solution was then warmed to room temperature and stirred overnight. After washing with 10% aqueous NaOH solution (5 × 20 mL) and H_2O (3 × 20 mL), the solution was dried (anhyd $MgSO_4$) and concentrated under reduced pressure to afford pure epoxide **5** (1.62 g, 86% yield): mp 118–120 °C; IR (KBr) 2997, 1329, 1311, 1292, 1133 (SO_2) cm^{-1}; ^1H NMR (250 MHz) δ 0.85 (1 H, d, J = 10 Hz), 1.65 (1 H, br d, J = 10 Hz), 1.81 (1 H, ddd, J = 2.7, 5.5, 12 Hz), 2.02 (1 H, ddd, J = 4.3, 10, 13 Hz), 2.72 (1 H, br m), 2.91 (3 H, s, SO_2Me), 3.07 (1 H, br m), 3.31 (1 H, d, J = 2.7 Hz), 3.39 (1 H, ddd, J = 3.6, 5.5, 10 Hz), 3.65 (1 H, d, J = 3.6 Hz); ^{13}C NMR δ 64.5 (d), 50.1 (d), 47.8 (d), 41.1 (d), 40.1 (SO_2Me, q), 36.9 (d), 27.0 (t), 26.4 (t); MS m/z 188 (53, M$^+$), 108 (87), 79 (100). Anal. Calcd for $C_8H_{12}O_3S$: C, 51.06; H, 6.38. Found: C, 50.94; H, 6.46.

Reaction of Epoxide 5 with LAH. To a suspension of epoxide **5** (376 mg, 2.00 mmol) in dry Et_2O (50 mL) was added a solution of LAH (91 mg, 2.4 mmol) at 0 °C over 0.5 h. The reaction mixture was then warmed to room temperature and stirred overnight. Careful addition of H_2O at 0 °C was followed by adjustment of the pH of the solution to ca. 2 by addition of concd aqueous HCl solution. After saturating the aqueous phase with NaCl it was extracted with EtOAc (4 × 30 mL). The extracts were dried (anhyd $MgSO_4$) and concentrated under reduced pressure to an oil (295 mg, 79% yield). Elution of this oil through a short column of silica gel with C_6H_{14}/EtOAc (6:4, 150 mL) gave white crystalline alcohol **6**: mp 96–97 °C (after recrystallization from EtOAc); IR (KBr) 3284 (br, OH), 3009, 2930, 1293 (SO_2), 1181, 1143, 1112, 1084 cm^{-1}; ^1H NMR (250 MHz) δ 1.54–1.84 (3 H, m), 2.05 (2 H, m), 2.17 (3 H, m), 2.89 (3 H, s, SO_2Me), 4.04 (1 H, m); ^{13}C NMR δ 75.7 (d), 44.5 (s), 40.1 (q, SO_2Me), 38.0 (d), 31.5 (t), 30.0 (t), 24.3 (d), 20.2 (d); MS m/z (relative intensity) 188 (6.5, M$^+$), 108 (100), 79 (96). Anal. Calcd for $C_8H_{12}O_3S$: C, 51.06; H, 6.38; S, 17.02. Found: C, 51.25; H, 6.50; S, 17.01.

Reduction of Epoxide 5 with DIBALH. To a solution of epoxide **5** (564 mg, 3.00 mmol) in anhyd CH_2Cl_2 (15 mL) was added a 1 M solution of DIBALH in CH_2Cl_2 (4.5 mL, 4.5 mmol) slowly. The resulting solution was stirred at room temperature for 20 h. The solution was then cooled in an ice–water bath and treated sequentially with EtOH and H_2O and acidified with concd aqueous HCl solution and extracted with EtOAc (4 × 30 mL). The combined extracts were dried (anhyd $MgSO_4$), filtered, concentrated using a rotary evaporator, and chromatographed on silica gel (15 g) eluting with EtOAc to give recovered epoxide **5** (65 mg) and alcohol **7a** (240 mg, 43% yield) identical with that isolated from the hydroboration and oxidation of alkene **3b** (TLC, IR, NMR).

Repetition of this experiment in the same way as above using epoxide **5** (414 mg, 2.20 mmol) dissolved in CH_2Cl_2 (15 mL) and 1 M DIBALH in CH_2Cl_2 (3.3 mL, 3.3 mmol), but stirring for 48 h at room temperature led to a product mixture devoid of starting material and from which alcohol **7a** (154 mg) was isolated in 37% yield.

Reduction of Epoxide 5 with DIBALD. A 1.14 M solution of DIBALD in CH_2Cl_2 (2.0 mL, 2.28 mmol) was added to a stirred solution of epoxide **5** (192 mg, 1.00 mmol) dissolved in CH_2Cl_2 (5 mL) under Ar. The resulting solution was stirred at room temperature for 48 h. The solution was then worked up in the same way as reported for the reduction of epoxide **5** with DIBALH to afford a mixture of unreacted epoxide **5** and alcohol **7c**. These were separated by preparative TLC on silica gel eluting with EtOAc to give pure d_1-alcohol **7c** (35 mg, 22% yield based on consumed epoxide **5**): ^1H NMR δ 1.31 (1 H, ddd, J = 1.3, 2.6, 10 Hz), 1.58 (1 H, ddd, J = 2.5, 5.8, 13 Hz), 1.69–1.98 (3 H, m), 2.33 (1 H, br d, J = 4.8 Hz), 2.65 (1 H, br d, J = 8.1 Hz), 2.73 (1 H, br s), 2.80 (3 H, s, SO_2Me), 3.18 (1 H, ddd, J = 3.7, 5.7, 11 Hz), 3.91 (1 H, br d, J = 6.8 Hz); MS m/z 191 (M$^+$).

Acetylation of Alcohol 7a. To a solution of tertiary alcohol **7a** (190 mg, 1.00 mmol) dissolved in anhyd pyridine (1.0 mL) was added Ac_2O (2 mL). After standing at room temperature for 24 h, cold H_2O (60 mL) was added, and the mixture was extracted with EtOAc (3 × 25 mL). The combined extracts were dried (anhyd $MgSO_4$), filtered, and concentrated by rotary evaporation under reduced pressure to afford a solid. Recrystallization from CH_2Cl_2/C_6H_{14} gave acetate **7b** as colorless needles (200 mg, 86% yield): mp 97–98 °C; IR (KBr) 1725 (C=O), 1299, 1129 (SO_2) cm^{-1}; ^1H NMR (250 MHz) δ 1.31–1.46 (2 H, m), 1.66–1.76 (2 H, m), 1.90–2.02 (4 H, m, s at 1.98, $COCH_3$), 2.49 (1 H, br d, J = 5.1 Hz), 2.68–2.83 (5 H, m, s at 2.80, SO_2Me), 3.20 (1 H, dddd, J = 1.8, 3.8, 5.5, 11 Hz), 4.73 (1 H, dd, J = 1.1, 7.0 Hz); MS (CI methane) m/z 234 (M + 1). Anal. Calcd for $C_{10}H_{16}O_4S$: C, 51.70; H, 6.94. Found: C, 51.63; H, 6.98.

Hydroboration and Oxidation of Alkene 3b. To a stirred solution of alkene **3b** (2.06 g, 12 mmol) in dry THF (30 mL) was added a 1 M borane–THF solution (15 mL, 15 mmol) over 15 min under Ar and at room temperature. The reaction mixture was stirred at room temperature for 48 h, and then 3 M aqueous NaOH solution (15 mL) was added very cautiously. A 30% aqueous H_2O_2 solution (15 mL) was added to the reaction mixture and stirred overnight. The organic phase was separated, and the aqueous phase was extracted with EtOAc (2 × 40 mL) and then saturated with NaCl and extracted again with EtOAc (2 × 40 mL). After the combined organic phase was dried over anhyd $MgSO_4$, it was concentrated under reduced pressure to afford 2.5 g of colorless oil. This was absorbed on silica gel (15 g) and placed on a column (60 × 3.5 cm) packed with dry silica gel. The column was eluted first with 30% EtOAc/C_6H_{14} (1 L) to remove impurities. Slow elution with EtOAc afforded first solid 2-alcohol **4b** (1.19 g, 52% yield): mp 88.5–90 °C (after recrystallization from EtOAc); IR (KBr) 3500 (OH), 1291, 1132 (SO_2) cm^{-1}; ^1H NMR (500 MHz) δ 1.25 (1 H, br d, J = 9.3 Hz), 1.41 (1 H, ddd, J = 2.7, 4.8, 13 Hz), 1.56 (1 H, ddd, J = 2.7, 5.4, 13 Hz), 1.79–1.92 (3 H, m), 2.44 (2 H, m), 2.67 (1 H, br d, J = 4.0 Hz), 2.84 (3 H, s, SMe), 3.28 (1 H, ddd, J = 4.8, 5.4, 12 Hz), 4.60 (1 H, br d, J = 6.3 Hz); ^{13}C NMR δ 67.7 (d), 61.4 (d), 46.7 (d), 41.3 (q), 40.8 (t), 36.2 (d), 36.2 (t), 29.7 (t); MS (CI, methane) m/z (relative intensity) 190 (M$^+$), 173 (100). Anal. Calcd for $C_8H_{14}O_3S$: C, 50.52; H, 7.41. Found: C, 50.46; H, 7.46.

Further elution with EtOAc gave 3-alcohol **7a** as a colorless oil (707 mg, 31%); mp 68–69 °C (after recrystallization from EtOAc/C_6H_{14}); IR (KBr) 3404 (OH), 1290, 1138 (SO_2) cm^{-1}; ^1H NMR (500 MHz) δ 1.26 (1 H, br d, J = 14 Hz), 1.31 (1 H, br d, J = 10 Hz), 1.57 (1 H, ddd, J = 2.6, 5.7, 13 Hz), 1.83 (1 H, dd, J = 1.8, 10 Hz), 1.93 (1 H, ddd, J = 5.2, 11, 13 Hz), 1.98 (1 H, br s, OH), 2.32 (1 H, d, J = 4.9 Hz), 2.66 (1 H, ddd, J = 2.9, 6.8, 14 Hz), 2.72 (1 H, br s), 2.79 (3 H, s, SO_2Me), 3.18 (1 H, dddd, J = 1.8, 3.7, 6.5, 10 Hz), 3.90 (1 H br d, J = 6.5 Hz); ^{13}C NMR δ 73.0 (d), 62.0 (d), 44.5 (d), 41.1 (q, SO_2Me), 38.3 (d), 36.5 (t), 35.4 (t), 26.1 (t); MS (CI, methane) m/z (relative intensity) 191 (100, M + 1), 173 (50), 111 (38). Anal. Calcd for $C_8H_{14}O_3S$: C, 50.50; H, 7.41. Found: C, 50.65; H. 7.42.

Ketone 4d. To a stirred solution of alcohol **4b** (250 mg, 1.32 mmol) dissolved in acetone (30 mL) and cooled in an ice–water bath was added Jones' reagent[36] dropwise until the yellow color of the reagent persisted. The mixture was then stirred for 3 h below 20 °C, treated with aqueous $NaHSO_3$ solution until the yellow color became green, and extracted with EtOAc (4 × 25 mL). The aqueous layer was saturated with salt and again extracted with EtOAc (2 × 25 mL). The combined extracts were washed with H_2O, dried (anhyd $MgSO_4$), filtered, and concentrated by rotary evaporation to a white solid which was recrystallized from CH_2Cl_2/C_6H_{14} to give ketone **4d** (150 mg, 61% yield): mp 142–143 °C; IR (KBr) 1742 (C=O), 1263, 1132 (SO_2) cm^{-1}; ^1H NMR (250 MHz) δ 1.73–1.91 (2 H, m), 2.06–2.33 (4 H, m), 2.78–2.93 (2 H, m), 2.96 (3 H, s, SO_2Me), 3.64 (1 H, m); MS *m/z* 188 (M^+). Anal. Calcd for $C_8H_{12}O_3S$: C, 51.04; H, 6.42. Found: C, 50.81; H, 6.34.

Reduction of Ketone 4d with DIBALH. A 1 M solution of DIBALH in toluene (5 mL, 5 mmol) was added to a solution of ketone **4d** (188 mg, 1.00 mmol) in dry THF (30 mL). The solution was stirred and heated at 90 °C for 2 d. After cooling in an ice–water bath, EtOH (2 mL), H_2O (20 mL), and concd aqueous HCl were cautiously added sequentially. The mixture was extracted with EtOAc (3 × 25 mL), and the combined extracts dried (anhyd $MgSO_4$), evaporated, and chromatographed on silica gel to give alcohol **1i** (20 mg, 12% yield) and alcohol **4c** (50 mg, 25% yield). Alcohol **1i** was identical (IR, NMR, TLC) with that prepared by reduction of ketone **1g**. Alcohol **4c**: IR (neat) 3465 (OH), 1298, 1123 (SO_2) cm^{-1}; ^1H NMR (250 MHz) δ 1.05 (1 H, ddd, *J* = 3.2, 5.5, 13 Hz), 1.36 (1 H, m), 1.59 (1 H, ddd, *J* = 1.2, 2.5, 10.5 Hz), 1.88–2.28 (3 H, m), 2.40 (1 H, br s), 2.78 (1 H, br s), 3.02 (3 H, s, SO_2Me), 3.55 (1 H, m), 3.80 (1 H, d, *J* = 11.9 Hz), 4.17 (1 H, m); MS (CI, isobutane) *m/z* 193 (M + 3), 192 (M + 2), 191 (M + 1), 173, 121, 111; exact mass calcd for (M + 1) $C_8H_{15}O_3S$ 191.0742, found 191.0750.

Silyl Ether 4e. A solution of alcohol **4b** (950 mg, 5.00 mmol), *tert*-butyldimethylsilyl chloride (905 mg, 6.00 mmol), and imidazole (850 mg, 12.5 mmol) dissolved in anhyd $HCONMe_2$ (4 mL) was stirred and heated at 40 °C overnight following the general procedure of Corey and Venkateshwarlu.[42] The mixture was stirred and heated at 40 °C overnight. The mixture was then chromatographed on a silica gel column and elution with EtOAc/C_6H_{14} (4:6) gave silyl ether **4e** (1.4 g, 93% yield) as a white solid: mp 38 °C; IR (KBr) 1293, 1146, 1130 (SO_2) cm^{-1}; ^1H NMR (250 MHz) δ 0.07 (6 H, s, SiMe), 0.89 (9 H, s, tBu), 1.22 (1 H, br d, *J* = 9.9 Hz), 1.41 (1 H, br d, *J* = 13 Hz), 1.58 (1 H, ddd, *J* = 2.6, 5.2, 13 Hz), 1.80–1.96 (3 H, m), 2.40 (1 H, br s), 2.59 (1 H, br s), 2.83 (3 H, s, SO_2Me), 3.23 (1 H, ddd, *J* = 4.8, 4.9, 11 Hz), 4.57 (1 H, br d, *J* = 6.2 Hz). Anal. Calcd for $C_{14}H_{28}O_3SiS$: C, 55.26; H, 9.21. Found: C, 55.42; H, 9.12.

Reduction of Silyl Ether 4e. To a solution of silyl ether **4e** (3.01 g, 10.0 mmol) dissolved in benzene (45 mL) was added a 1.5 M solution of DIBALH in toluene (40 mL, 60 mmol). The solution was stirred and heated in a bath maintained at 90 °C for 3 d. After cooling in an ice–water bath, EtOH (5 mL), H_2O (25 mL), and sufficient cold, dilute HCl solution to make a clear solution were added sequentially. The solution was extracted with EtOAc (3 × 50 mL), and the combined extracts were dried (anhyd $MgSO_4$), filtered, and concentrated by rotary evaporation to a yellow oil. ^1H NMR spectroscopic analysis of this oil showed that in addition to the absorption peaks ascribable to alcohol **4b** and alcohol **1j** there were the following absorptions δ 1.41 (d, *J* = 3.1 Hz), 3.2 (m), and 4.6 (br d, *J* = 6.8 Hz) which were surmised to be due to 2-*exo*-hydroxybicyclo[2.2.1]heptane-6-*endo*-thiol. Since this presumed thiol and alcohol **1j** were not separable on silica gel chromatography, the mixture was selectively oxidized. The yellow oil was dissolved in CH_2Cl_2 and a 10% aqueous solution of $KHCO_3$ (10 mL) added. To this well-stirred mixture was added a solution of Br_2 (1 mL) in CH_2Cl_2 (50 mL) dropwise until the color of Br_2 persisted. The organic layer was then separated and the aqueous layer extracted with EtOAc (2 × 50 mL). The combined organic extracts were dried (anhyd $MgSO_4$), filtered, concentrated by rotary evaporation to a yellow oil which was chromatographed on silica gel eluting with 30% EtOAc in C_6H_{14} to afford alcohol **1j**, X = H and Y = OH (1.10 g, 35% yield): IR (neat) 3363 (OH) cm^{-1}; ^1H NMR (250 MHz) δ 0.70 (1 H, ddd, *J* = 2.7, 5.0, 12.6 Hz), 1.23 (1 H, m), 1.33 (1 H, m), 1.68–1.77 (2 H, m), 1.96 (1 H, m), 2.05 (3 H, s, SMe), 2.24–2.31 (2 H, m), 2.98 (1 H, ddd, *J* = 4.6, 4.7, 11.2 Hz), 4.36 (1 H, br d, *J* = 6.9 Hz, CHO); ^{13}C NMR δ 69.3 (CO), 46.9 (d), 44.0 (d), 42.2 (t), 36.2 (t), 36.0 (d), 35.3 (t), 15.2 (CS); MS *m/z* exact mass calcd for $C_8H_{14}OS$ 158.0765, found 158.0752. Elution with 80% EtOAc in C_6H_{14} gave disulfide **8** (120 mg, 15% yield): mp 155 °C; IR (KBr) 3306 (OH) cm^{-1}; ^1H NMR (250 MHz) δ 0.74 (1 H, ddd, *J* = 2.7, 5.4, 13 Hz), 1.24–1.42 (2 H, m), 1.66–1.80 (3 H, m), 1.95 (1 H, m), 2.30 (1 H, br s), 2.50 (1 H, br s), 3.34 (1 H, ddd, *J* = 4.3, 5.3, 11.5 Hz, CHO), 4.45 (1 H, br d, *J* = 6.9 Hz); MS *m/z* 288 (M + 2); 287 (M + 1), 286 (M^+). Anal. Calcd for $C_{14}H_{22}O_2S_2$: C, 58.71; H, 7.80. S, 22.38. Found: C, 58.74; H, 7.80; S, 22.34. Elution with pure EtOAc yielded alcohol **4b** (300 mg, 17% yield).

Ketone 1g. A solution of freshly dried DMSO (343 mg, 4.40 mmol) in dried CH_2Cl_2 (4 mL) was added over 15 min to a solution of oxalyl chloride (280 mg, 2.20 mmol) dissolved in dried CH_2Cl_2 (5 mL), stirred, and cooled at −78 °C.[39] After stirring for an additional 5 min, a solution of alcohol **1j** (316 mg, 2.00 mmol) dissolved in dried CH_2Cl_2 was added dropwise over 10 min. After stirring an additional 15 min at −78 °C, Et_3N (1.4 mL, 10 mmol) was added. The reaction mixture was allowed to warm to room temperature, concentrated by rotary evaporation, and chromatographed on a silica gel column eluting with EtOAc/C_6H_{14} (3:7) to afford ketone **1g** (270 mg, 85% yield): IR (neat), 1744 (C=O), cm^{-1}; ^1H NMR (250 MHz) δ 1.21 (1 H, ddd, *J* = 2.6, 4.5, 13 Hz), 1.71 (1 H, m), 1.82–1.91 (2 H, m), 2.06–2.17 (4 H, m, with s at 2.12 SMe), 2.33 (1 H, m), 2.70 (1 H, br s), 2.82 (1 H, br s), 3.32 (1 H, ddd, *J* = 4.5, 4.5, 11 Hz); ^{13}C NMR δ 213.3 (CO), 53.8 (d), 44.2 (t), 41.5 (d), 37.4 (t), 35.5 (t), 34.6 (d), 14.5 (SMe); MS *m/z* exact mass calcd for $C_8H_{12}SO$ 156.0609, found 156.0618.

Alcohol 1i. To a stirred solution of ketone **1g** (300 mg, 1.92 mmol) in THF (10 mL) cooled in a dry ice–acetone bath, was added a 1 M solution of DIBALH in THF (4 mL, 4 mmol). The solution was stirred at −78 °C for 2 h, allowed to warm to room temperature, and stirred at room temperature for 1 h. The reaction mixture was worked up in the same way as in reduction of ketone **4d** with DIBALH to give a yellow oil which was purified by preparative TLC on silica gel eluting with 30% EtOAc/C_6H_{14}. The fraction of R_f = 0.5 was extracted to afford alcohol **1i** (200 mg, 66% yield): IR (neat) 3426 (OH) cm^{-1}; ^1H NMR (250 MHz) δ 1.05 (1 H, ddd, *J* = 3.2, 5.0, 12.9 MHz), 1.17–1.33 (3 H, m), 1.42 (1 H, m), 2.13–2.30 (5 H, m with s at δ 2.21, SMe), 2.53 (1 H, br s), 3.21 (1 H, m, CHO), 5.26 (1 H, br s, OH); ^{13}C NMR δ 77.1 (CO), 45.6 (d), 42.2 (d), 40.3 (t), 38.2 (t), 38.1 (t), 37.1 (d), 15.8 (SMe); MS *m/z* exact mass calcd for $C_8H_{14}OS$ 158.0765, found 158.0748. Another chromatography fraction was extracted to give alcohol **1j** (20 mg, 6% yield) identical (TLC, IR, ^1H NMR) with that prepared by the reduction of silyl ether **4e** with DIBALH.

Alcohol 1k. A 3 M solution of MeMgI in THF (2 mL, 6 mmol) was added to a stirred solution of ketone **1g** (400 mg, 2.50 mmol) in THF (20 mL) cooled in a dry ice–acetone bath. It was allowed to come to room temperature and was stirred overnight. It was then placed in an ice–water bath and cold 2 M aqueous H_2SO_4 solution added dropwise until a clear solution was obtained. The solution was extracted with EtOAc (3 × 50 mL). The extracts were combined, dried (anhyd $MgSO_4$), filtered, and concentrated by rotary evaporation to a yellow oil which was purified by preparative TLC on silica gel eluting with 30% EtOAc in C_6H_{14}. The fraction of R_f = 0.55 was extracted to give alcohol **1k** (178 mg, 40% yield): IR (neat) 3405 (OH) cm^{-1}; ^1H NMR (250 MHz) δ 1.09–1.37 (6 H, m with s at δ 1.25, MeC), 1.65 (1 H, m), 1.78 (1 H, m), 2.21 (6 H, m with s at δ 2.18, SMe), 3.21 (1 H, m), 5.26 (1 H, br s, OH); ^{13}C NMR δ 80.4 (CO), 48.0 (t), 47.8 (d), 46.2 (d), 38.8 (t), 36.9 (d), 36.5 (t), 30.9 (MeC), 15.8 (SMe); MS *m/z* exact mass calcd for $C_9H_{16}OS$ 172.0921, found 172.0909.

Measurement of O–H stretching frequencies of **1k** in CCl_4 (percent transmittance in parentheses): neat, neat, 3413; 0.56 M, 3409 (2); 56 mM, 3422 (27); 9.3 mM, 3423 (72); 2.6 mM, 3423 (90) cm^{-1}.

***N*-Cyclohexylimine 1m.** A solution of ketone **1g** (178 mg, 1.14 mmol) in cyclohexylamine (2 mL) was heated in the presence of molecular sieves (3 Å) at 120–130 °C until all the ketone reacted as monitored by IR spectroscopy. The solution was cooled to room temperature under Ar and immediately placed on a silica gel

(42) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

column (20 × 2.5 cm). Elution with 1:1 EtOAc/C_6H_{14} removed traces of impurities and subsequent elution with EtOAc afforded pure *N*-cyclohexylimine **1m** (248 mg, 92% yield) as a colorless oil: IR (neat) 1683 (N=C), cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (1 H, m), 1.11–1.80 (12 H, m), 1.88 (1 H, m), 2.07 (3 H, s, SMe), 2.08–2.21 (2 H, m), 2.51 (1 H, br s), 2.81 (1 H, br s), 3.05 (1 H, m), 3.18 (1 H, m); ^{13}C NMR δ 172.0 (s, C=N), 61.0, 50.8, 45.1, 44.4, 43.9, 42.2, 39.1, 37.9, 37.0, 35.6, 35.4, 34.8, 34.1, 33.9, 33.6, 33.3, 25.6, 25.0, 24.9, 24.8, 14.8; MS *m/z* exact mass calcd for $C_{14}H_{23}NS$ 237.1551, found 237.1541.

***N*-Cyclohexylamine 1n.** Pure *N*-cyclohexylimine **1m** (248 mg, 1.05 mmol) was dissolved in dry benzene (20 mL) and then a 1.5 M solution of DIBALH in toluene (4 mL, 6 mmol) was added with caution and the resulting solution was stirred and heated at 80 °C under Ar overnight. To the cooled reaction mixture was added NaF (1g, 24 mmol) and then diluted with dry benzene (60 mL). H_2O (0.3 mL, 18 mmol) was added, the reaction mixture was stirred at room temperature for at least 0.5 h, and then it was filtered. The solid residue was washed with $CHCl_3$ (30–40 mL). The combined organic layers were concentrated under reduced pressure to afford an oily residue which was distilled at 135–140 °C/100 μm to give *N*-cyclohexylamine **1n** (205 mg, 75% overall yield) as a colorless oil: IR (neat) 3299 (NH) cm^{-1}; ^1H NMR (500 MHz) δ 0.86 (1 H, ddd, *J* = 2.8, 6.2, 13 Hz), 0.96 (1 H, m), 1.05–1.29 (5 H, m), 1.34 (1 H, d, *J* = 9.9 Hz), 1.42 (1 H, d, *J* = 9.9 Hz), 1.59 (1 H, d, *J* = 13 Hz), 1.68–1.71 (2 H, m), 1.79 (1 H, br d, *J* = 13 Hz), 1.91 (1 H, br d, *J* = 13 Hz), 2.11 (3 H, s, SMe), 2.17–2.53 (3 H, m), 2.53 (1 H, br s), 2.56 (1 H, m), 3.11 (1 H, m, H_6), 3.34 (1 H, m, H_2); ^{13}C NMR δ 58.0, 54.6, 46.9, 41.7, 40.3, 39.4, 38.3, 36.6, 33.5, 32.2, 26.1, 25.1, 24.8, 16.8; MS (CI, isobutane) *m/z* (relative intensity) 240 (100, M + 1), 192 (95); exact mass calcd for (M + 1) $C_{14}H_{25}SN$ 240.1786, found 240.1723.

***N*-Benzylamine 1o.** A solution of ketone **1g** (156 mg, 1.00 mmol) in dried and distilled $BnNH_2$ (5 mL) was heated in the presence of molecular sieves (3 Å) at 140 °C for 4 h. The excess $BnNH_2$ was then distilled off under reduced pressure and the residue dissolved in dry benzene (10 mL). A 1.5 M solution of DIBALH in toluene (2 mL, 3.0 mmol) was added with caution, and the resulting solution was stirred and heated at 80 °C under Ar overnight. The reaction mixture was then cooled in an ice–water bath, and NaF (500 mg, 12 mmol) was added followed by the addition of H_2O (10 mL). The mixture was stirred for 0.5 h, filtered, and extracted with EtOAc (3 × 20 mL). The combined extracts were dried (anhyd $MgSO_4$), filtered, and concentrated. The residue was distilled from bulb-to-bulb (140 °C/0.1 mm) to afford a colorless liquid (320 mg). A portion (45 mg) of this material was further purified by preparative TLC on silica gel to give **1o** (18 mg, 52% yield) as a colorless oil: IR (neat) 3302 (NH) cm^{-1}; ^1H NMR δ 0.98 (1 H, ddd, *J* = 2.5, 5.8, 12 Hz), 1.22–1.30 (1 H, m), 1.36–1.49 (2 H, m), 2.11–2.31 (5 H, m, s at 2.18, SCH_3), 2.50 (1 H, br s), 2.67 (1 H, br s), 3.14–3.29 (2 H, m) 3.74 (1 H, d, *J* = 13 Hz), 3.96 (1 H, d, *J* = 13 Hz), 7.20–7.40 (5 H, m, ArH); MS (CI, methane) *m/z* 248 (M + 1); exact mass calcd for $C_{15}H_{21}NS$ 247.139, found 247.140.

Hydantoin 9. To a solution of $(NH_4)_2CO_3$ (1.6 g, 17 mmol) in 1 M aqueous KCN solution (4 mL, 4 mmol) and H_2O (6 mL) was added a solution of ketone **1g** (430 mg, 2.75 mmol) in MeOH (3 mL), and the resulting cloudy solution was repeatedly degassed and sealed in a high-pressure flask and then heated with stirring at 80 °C for 2 d. The reaction mixture was then cooled and extracted with EtOAc (3 × 50 mL). The organic phase was dried (anhyd $MgSO_4$) and evaporated under reduced pressure to afford a solid residue which was crystallized from EtOAc to give hydantoin **9** (330 mg, 60% yield): mp 187–188 °C (after recrystallization from EtOAc); IR (KBr) 3180, 3039 (br) (NH), 1769, 1712 (CO), cm^{-1}; ^1H NMR (250 MHz) δ 1.13 (1 H, ddd, *J* = 2.6, 7.0, 12 Hz), 1.35–1.48 (2 H, m), 2.11 (3 H, s, SMe), 2.23–2.40 (3 H, m), 2.51–2.58 (2 H, m), 3.23 (1 H, ddd, *J* = 3.3, 6.6, 11 Hz), 7.75 (1 H, br s), 9.09 (1 H, br s); ^{13}C NMR δ 178.4 (CO), 156.1 (CO), 68.7 (s), 46.8 (d), 46.4 (d), 42.5 (t), 37.3 (t), 36.3 (t), 35.8 (d), 15.4 (q, SCH_3); MS *m/z* 226 (M^+); exact mass calcd for $C_{10}H_{14}N_2O_2S$ 226.0776, found 226.0761.

Unreacted ketone **1g** (50 mg, 12% yield) was isolated from the mother liquor after evaporation and chromatography on a preparative TLC plate eluting with 30% EtOAc in C_6H_{14}.

Amino Acid 1f. A mixture of hydantoin **9** (226 mg, 1.00 mmol) and $Ba(OH)_2$ (855 mg, 5.00 mmol) in H_2O (30 mL) was heated in an autoclave at about 120 °C overnight. The reaction mixture was then diluted with H_2O to about 100 mL and boiled. Dry ice was added in small pieces and with great caution until no more turbidity was noticeable. The mixture was filtered and lyophilized. The white solid residue (230 mg) was dissolved in the minimum amount of deionized H_2O (~25 mL), and then the pH of the solution was adjusted to about 6.5 by the addition of dilute aqueous H_2SO_4. The resulting white precipitate was removed and the aqueous phase lyophilized to afford pure amino acid **1f** (171 mg, 85% yield): mp 180 °C dec (after recrystallization from MeOH/EtOAc); IR (KBr) 3440 (br), 3200–2995 (NH_3^+), 1631 (CO_2^-), 1376 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 1.01 (1 H, ddd, *J* = 2.4, 7.5, 13 Hz), 1.37 (1 H, br s), 1.39 (1 H, br s), 1.94 (1 H, d, *J* = 17 Hz), 2.05 (3 H, s, SMe), 2.11–2.18 (1 H, m), 2.27–2.33 (2 H, m), 2.59 (1 H, br s), 3.26 (1 H, ddd, *J* = 3.3, 7.4, 15 Hz); MS (CI, CH_4) *m/z* (relative intensity) 202 (100, M + 1), 156 (31); exact mass calcd for $C_9H_{15}NO_2S$ 201.0824, found 201.0842.

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Supplementary Material Available: General Experimental Section, ORTEP drawings of amino acid **1f** and the packing of the molecule in the unit cell, tables of crystal data, description of data collection, structure solution, and refinement, final atomic positional and thermal parameters, bond length, bond angle, and selected torsion angle data, COSY spectrum and ^1H NMR spectra at 500 MHz with decoupling of 3-alcohol **7a**, and ^1H NMR spectra at 250 MHz of compounds **1f,g,i–k,m–o**, **4c**, **7c**, and **9** (32 pages); structure factors for amino acid **1f** (6 pages). Ordering information is given on any current masthead page.