Compound **9**·C_6H_6·C_6H_6 crystallizes from CH_2Cl_2–$(CH_2)_6$–C_6H_6 as clear, colorless prisms in the monoclinic space group $P2_1/n$. Unit cell dimensions are as follows: a = 14.642 (2), b = 21.505 (3), and c = 15.777 (2) Å; β = 90.140 (4)°; V = 4978 Å^3; Z = 4. The crystal was examined on a HUBER diffractometer, Mo Kα radiation, at 298 K. The structure was determined by direct methods. Refinement of 317 parameters (3016 reflections with $I > 3\sigma(I)$) has an agreement value, R, currently at 0.14. Only one of the two benzene molecules is complexed.

Compound **9**·$(CH_2)_6$·$(CH_2)_6$ crystallizes from cyclohexane as colorless blades in the monoclinic system $P2_1/n$. Unit cell dimensions are as follows: 14.518 (4), b = 21.242 (5), and c = 15.586 (4) Å; β = 90.21-(1)°; V = 4819 Å^3; Z = 4. The crystal was examined on a modified Picker FACS-1 diffractometer, Mo Kα radiation, at 298 K. The structure was determined by direct methods. Refinement of 257 parameters (2123 reflections with $I > 3\sigma(I)$) has an agreement value, R, currently at 0.13. An uncomplexed, as well as complexed, cyclohexane molecule is present in the crystal.

Compound **10**·CH_2Cl_2·CH_2Cl_2 crystallizes from CH_2Cl_2 as colorless thin blades in the orthorhombic system $Pna2_1$. Unit cell dimensions are as follows: a = 22.847 (4), b = 21.500 (4), and c = 8.865 (2) Å; V = 4355 Å^3; Z = 4. The crystal was examined on a modified Picker FACS-1 diffractometer, Mo Kα radiation, at 295 K. The structure was determined by direct methods. Refinement of 358 parameters (2501 reflections with $F > \sigma(F)$) has an agreement value, R, currently at 0.11. Only one of the two CH_2Cl_2 molecules is involved in host–guest complexation.

Compound **15**·CH_2Cl_2 crystallizes from CH_2Cl_2 as colorless thin platelets in the orthorhombic system $Pnna$. Unit cell dimensions are as follows: a = 8.762 (4), b 20.072 (8), and c = 24.260 (9) Å; V = 4299 Å^3; Z = 4 (eight half molecules related by a twofold axis). The crystal was examined on a modified Picker FACS-1 diffractometer Mo Kα radiation, at 298 K. The structure was determined by heavy-atom methods. Refinement of 151 parameters (1648 reflections with $I > 3\sigma(I)$) has an agreement value, R, currently at 0.10. The propylene bridges are disordered. Full details will be published elsewhere.

Synthesis of Optically Pure α-Amino Acids via Salts of α-Amino-β-propiolactone

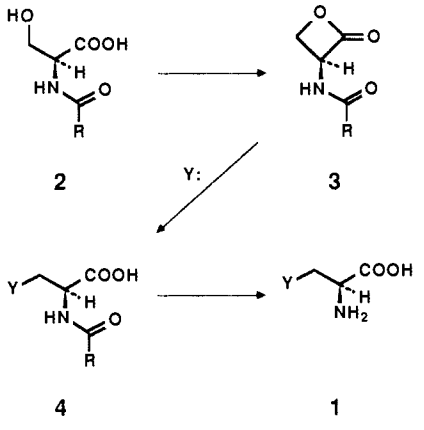
Lee D. Arnold, Robert G. May, and John C. Vederas*

Contribution from the Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2. *Received August 14, 1987*

Abstract: Treatment with trifluoroacetic acid of *N*-(*tert*-butoxycarbonyl)-L-serine β-lactone (**3a**) (available by Mitsunobu cyclization of the corresponding N-protected serine derivative **2**, R = O-*t*-Bu) produces 3-amino-2-oxetanone as its trifluoroacetate salt **5**. Addition of 1 equiv of *p*-toluenesulfonic acid to the reaction mixture affords the corresponding stable tosylate salt **6**, which can be stored indefinitely. The salts **5** and **6** are attacked at the β-carbon by a variety of nucleophiles (e.g., RSH, Me_2S, CF_3COO^-, HPO_4^{2-}, Cl^-, CN^-, pyrazole, N_3^-) to give unprotected, optically pure (2*S*)-α-amino acids **1** in 77–96% isolated yield. The ring openings can be done in a variety of organic solvents (e.g., DMF, trifluoroacetic acid, MeCN) or in water at pH 5.0–5.5, depending on the nucleophile.

The biological importance[1] and synthetic utility[2,3] of α-amino acids **1** continue to stimulate development of new routes to these compounds. Most recent approaches rely on stereospecific construction of one or more bonds to the α-carbon,[4] but several very practical methods attach a side chain to a preexisting chiral

Scheme I



α-amino acid derivative.[5,6] Recently we reported syntheses of amino acids that employ ring-opening of N-protected β-lactones

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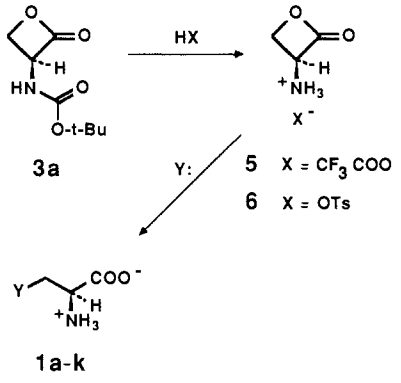
Table I. Reactions of Nucleophiles with (*S*)-3-Amino-2-oxetanone Salts

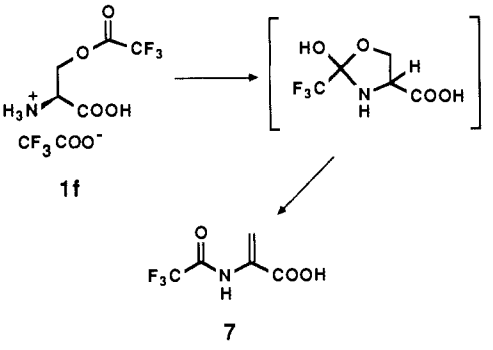
method[a]	reagent (equiv)	conditions	Y	product	yield[b]
A	L-cysteine (3)	pH 5.5, H_2O, 40 min	(*S*)-$^-OOC(H_3N^+)CHCH_2S$–	**1a**	93
A	$H_2NCH_2CH_2SH$·HCl (2)	pH 5.5, H_2O, 35 min	$H_2NCH_2CH_2S$–	**1b**	85[c]
A	LiSH (3)	CH_3CN/THF, 1 h	HS–	**1c**	88
A	$Na_2S_2O_3$ (2)	pH 5.0, H_2O, 1 h	$Na^+{}^-O_3SS$–	**1d**	83
B	Me_2S (4)	TsOH (1.5 equiv), CF_3COOH, 15 min	Me_2S^+–	**1e**	88[d]
C	CF_3COO^-/AG1 (1.3)	CF_3COOH, 16 h	CF_3COO–	**1f**	87[d]
A	K_2HPO_4 (3)	18-crown-6 (1 equiv), DMF, 72 h	H_2PO_4–	**1g**	87
A/C	conc HCl (24–5)	30 min	Cl–	**1h**	92[c]
A	*n*-$Bu_4N^+CN^-$ (1.5)	DMF, –10 °C (0.5 h) → 25 °C (0.5 h)	N≡C–	**1i**	84
B	 (5)	DMF, 2.5 h		**1j**	77
B	NaN_3 (3)	DMF, 1 h	N_3–	**1k**	96

[a] Methods: A, **5** produced and used immediately after removal of trifluoroacetic acid; B, **6** used; C, **5** generated in situ. [b] Isolated yield. [c] Hydrochloride salt. [d] Tosylate salt.

Scheme II



Scheme III



3, derived from N-acylated serines **2**, using nitrogen, oxygen, halogen, sulfur,[6a,b] and carbon[6c] nucleophiles (Scheme I). In the cases studied, the protecting groups on the nitrogen of **4** are readily cleaved to give optically pure **1**. However, certain substituents (e.g., Y = azido) are sensitive to most common deprotection conditions. In the present work, we describe the direct synthesis of some chemically labile, unprotected, optically pure α-amino acids **1** from salts **5** and **6** of α-amino-β-propiolactone (Scheme II). These previously unknown salts are easily accessible in two steps from commercially available *N*-(*tert*-butoxycarbonyl)serine (**2**, R = O-*t*-Bu; BOC = *tert*-butoxycarbonyl).

Results and Discussion

As reported earlier,[6a,c] modified Mitsunobu conditions (Ph_3P, dialkyl azodicarboxylate, –78 °C) readily cyclize BOC-L-serine to the β-lactone **3a** without detectable epimerization. Treatment of **3a** with anhydrous trifluoroacetic acid[7] produces 3-amino-2-oxetanone trifluoroacetate (**5**) in nearly quantitative yield. Removal of excess trifluoroacetic acid and *tert*-butyl trifluoroacetate [bp ~30 °C (60 mm)][8] in vacuo gives material that is best used immediately in subsequent reactions since traces of other salts and residual acid can cause decomposition.[9] However, addition of 1 equiv of *p*-toluenesulfonic acid to the deprotection reaction affords the tosylate salt **6**, which is easily isolated, recrystallized, and stored dry indefinitely.

The unprotected serine β-lactones **5** and **6** eagerly add even poor nucleophiles (e.g., CF_3COO^-)[9] at the β-carbon to form free amino acids **1**, a number of which were previously inaccessible or difficult to prepare (Table I). All known compounds **1** were stereochemically pure based on $[\alpha]_D$ (and HPLC in the case of **1a**). Depending on the nucleophile, the ring openings can be done in THF (with **5**), trifluoroacetic acid, polar aprotic solvents (DMF, MeCN), or even water.

Despite the fact that the 3-amino-2-oxetanone salts hydrolyze quite rapidly (for **6**: $t_{1/2}$ ~ 2.5 h in unbuffered H_2O; $t_{1/2}$ = 10.6 ± 0.5 min in 50 mM potassium phosphate at pH 6.78),[10] good nucleophiles like thiols afford high yields of sulfur-containing amino acids in water if the pH is kept at 5.0–5.5. Reaction of **5** with L-cysteine or β-mercaptoethylamine under these conditions proceeds exclusively by attack of sulfur to give LL-lanthionine (**1a**) and L-thialysine (**1b**),[11,12] respectively. This contrasts the behavior of the protected *N*-benzyloxycarbonyl (Cbz) β-lactone **3** (R = OCH_2Ph), which adds the *nitrogen* of β-mercaptoethylamine in 1:1 acetonitrile/water at pH 5.5.[6a] Presumably, the organic solvent, necessary in the latter reaction to dissolve the N-protected lactone, suppresses thiolate anion formation.

Other sulfur nucleophiles also add to **5**. Reaction of lithium hydrosulfide produces L-cysteine (**1c**) in 88% recrystallized yield, thereby demonstrating the potential to generate expensive D-cysteine from inexpensive D-serine. Ring opening by sodium thiosulfate gives the Bunte salt, (*S*)-sulfo-L-cysteine (**1d**), a metabolic precursor of L-cysteine (**1c**) in certain organisms[13] and a sulfur donor in the biosynthesis of cephalosporin C.[14] Inter-

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(7) The absence of good nucleophiles is essential. Addition of concentrated HCl to **3** produces β-chloroalanine (or its N-acylated derivatives) whereas HBF_4 in water gives L-serine derivatives.[6b]

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(9) In the absence of impurities, **5** is stable for over 1 week in trifluoroacetic acid. However, contamination rapidly leads to formation of *O*-(trifluoroacetyl)-L-serine (**1f**) or its decomposition products (e.g., L-serine). Prolonged exposure (7 days) of **5** to tosylate anion (2 equiv of anhydrous *p*-toluenesulfonic acid, 1.8 equiv of BioRad AG1 anion exchanger in CF_3COOH) generates *O*-tosyl-L-serine, which was isolated in 75% purity (25% serine impurity) as its tosylate salt.

(10) Hydrolysis rates were determined by observation of the 1820-cm^{-1} carbonyl bond by quantitative FT-IR spectroscopy.

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(13) (a) Kharasch, N.; Arora, A. S. *Phosphorus Sulfur* **1976**, *2*, 1–50. (b) Nakamura, T.; Sato, R. *Biochem. J.* **1963**, *86*, 328–335.

estingly, the tosylate salt **6** condenses quantitatively (by ^1H NMR) with excess dimethyl sulfide in trifluoroacetic acid to produce the dimethyl sulfonium salt of cysteine, which was isolated as the stable ditosylate salt **1e**. This reaction is almost instantaneous, in contrast to the very sluggish condensation of dimethyl sulfide with the N-protected analogues **3** in DMF.

Careful choice of conditions is often helpful in obtaining good yields of free amino acids **1f** → **1k** (Table I). Initial attempts to isolate *O*-(trifluoroacetyl)-L-serine (**1f**) as its trifluoroacetate salt failed due to O → N acyl transfer with concomitant elimination to the *N*-(trifluoroacetyl)dehydroalanine (**7**) in 83% yield (Scheme III). However, addition of 1 equiv of nonvolatile *p*-toluenesulfonic acid allows isolation of the tosylate salt of **1f**. Treatment of **1f** with nucleophiles (e.g., N_3^-) produces exclusively L-serine, and any serine observed in nonaqueous reactions of **5** probably arises in this manner.[9]

Addition of concentrated phosphoric acid to **5** gives only L-serine on aqueous workup, but K_2HPO_4 in DMF with 18-crown-6 generates *O*-phospho-L-serine (**1g**). This biologically important compound[1a,15] is usually synthesized by a protection/deprotection strategy.[16] Chloride is a better nucleophile, and despite its higher water content, concentrated hydrochloric acid effectively converts **5** (or **3a** directly) to β-chloro-L-alanine (**1h**), a suicide substrate for a variety of enzymes.[17] Aqueous potassium cyanide at pH 5 interacts with **5** to provide a 60:40 mixture of L-serine and β-cyanoalanine (**1i**). However, treatment of **5** under anhydrous conditions with tetra-*n*-butylammonium cyanide in DMF[18] gives a good yield of β-cyano-L-alanine (**1i**), a known toxin and enzyme inhibitor.[1a,19,20]

Reactions with nitrogen nucleophiles were done under anhydrous conditions. Thus, pyrazole combines with **6** in DMF to form β-pyrazol-1-yl-L-alanine (**1j**).[21] This suggests that a wide variety of amino acids bearing a heterocyclic ring connected through nitrogen at the β-carbon[1a,22] (e.g., quisqualic acid[5d]) could be synthesized analogously. Under similar conditions sodium azide produces β-azido-L-alanine (**1k**), a mutagenic metabolite isolated from *Salmonella* grown in the presence of azide.[23,24] This labile compound has been chemically inaccessible by other approaches because it cannot survive the conditions usually employed to deprotect amino acid derivatives.

In summary, the previously unreported salts of 3-amino-2-oxetanone are readily accessible and provide a short and practical route to a variety of unprotected, optically pure amino acids **1**, which can often be difficult or tedious to prepare by other means. In most cases the nucleophilic openings of the serine β-lactone can be accomplished with equal facility on either the trifluoroacetate salt **5** or the tosylate salt **6** under similar conditions. Use of **5** is advantageous in "one-pot" conversions of **3a** to the amino acid **1**, whereas **6** is an easily isolable reagent with a long shelf life that can be prepared in multigram quantities and used as needed. Since both enantiomers of serine are relatively inexpensive and L-serine is readily available in isotoptically labeled form, this approach should prove useful for synthesis of sensitive D-amino acids as well as for preparation of the labeled L-isomers.

Experimental Section

Most general precedures and instrumentation have been described previously.[6] Trifluoroacetic acid was dried over P_2O_5, distilled, and stored under argon atmosphere.[9] Anhydrous *p*-toluenesulfonic acid was prepared from the monohydrate by solution in hot benzene with the aid of ethyl acetate, azeotropic removal of water to 50% volume, and crystallization by cooling to 0 °C. The resulting crystals (mp 94–95 °C) were dried in vacuo and stored in a desiccator. Water was processed through a Millipore Milli-Q apparatus and degassed by boiling and cooling under argon atmosphere. Aqueous HCl was prepared free of metal ions from this water and glass-distilled constant-boiling (~110 °C) 5.7 N HCl. Dimthylformamide (DMF) was stirred with BaO (16 h), decanted, and distilled at reduced pressure. Infrared spectroscopic analyses on aqueous solutions of **6** were done on a Nicolet 7199 FT-IR spectrometer with 0.1-mm IR TRANS cells (Kodak, polycrystalline ZnS).[10] Thin-layer chromatography (TLC) of amino acids on silica gel (Merck) usually employed three solvent systems: system A, pH 5.80, 50 mM potassium phosphate buffer/ethanol (30:70); system B, *n*-BuOH/HOAc/H_2O (4:1:1).

(*S*)-3-Amino-2-oxetanone, Trifluoroacetic Acid Salt (5). Typically, BOC-L-serine β-lactone (**3a**)[6a] (187 mg, 1.00 mmol) was treated with distilled CF_3COOH (3.0 mL) at 0–5 °C for 10 min. The solvent was removed in vacuo by bulb-to-bulb distillation at 25 °C (receiving bulb at −78 °C) with the aid of a Kugelrohr apparatus, and the residue of **5** was dissolved in the desired solvent and immediately reacted with a nucleophile. The yield of **5** is quantitative: ^1H NMR (360 MHz, CF_3COOD) δ 5.51 (m, 1 H, C*H*), 4.87 (m, 2 H, CH_2); IR (H_2O solution) 1836 cm^{-1}; IR (CH_3CN solution) 1842 cm^{-1}; FAB^+ MS (glycerol) 88 (MH^+), 289 ($[(MH)_2 \cdot CF_3COO]^+$); R_f ~0.77 (system A, some hydrolysis on plate). Satisfactory elemental analysis could be obtained only on the tosylate salt **6**.

(*S*)-3-Amino-2-oxetanone, *p*-Toluenesulfonic Acid Salt (6). BOC-L-serine β-lactone (**3a**)[6a] (600 mg, 3.20 mmol) and anhydrous *p*-toluenesulfonic acid (579 mg, 3.36 mmol) were treated with distilled CF_3COOH (10 mL) at 0–5 °C for 10 min. Removal of solvent in vacuo as above provided a white crystalline residue, which was triturated with dry Et_2O (20 mL) and filtered to yield **6** (806 mg, 97%). This material was analytically pure; however, if desired, recrystallization could be effected from DMF/Et_2O (+25 to −20 °C): mp (~4 °C/min) 135 °C (darkening), 173 °C dec (rapid); $[\alpha]^{25}_D$ −15.9 (±0.1)° (*c* 2.2, DMF); IR (Fluorolube mull) 3040 (s, vbr), 1838 (vs), 1600 (w), 1585 (w), 1550 (m) cm^{-1}; IR (pH 6.8, aqueous solution) 1820 cm^{-1}; IR (DMF solution) 1830 cm^{-1}, ^1H NMR (300 MHz, DMF-d_7) δ 7.66 (d, 2 H, 8.0 Hz, *o*-Ar*H*), 7.15 (d, 2 H, 8.0 Hz, *m*-Ar*H*), 5.53 (dd, 1 H, 4.6 and 6.5 Hz, C*H*), 4.74 (m, 1 H, C*H*HO), 4.68 (m, 1 H, CH*H*O), 3.70 (vbr s, 3 H, NH_3^+), 2.31 (s, 3 H, $ArCH_3$); ^{13}C NMR (75.5 MHz, DMF-d_7) δ 165.84, 145.12, 139.14, 128.67, 126.08, 64.70, 57.45, 20.70; FAB^+ MS (glycerol) 88 ($MH^+ = C_3H_6NO_2$), 180 (MH^+(gly)), 260 (MH^+(TsOH)). Anal. Calcd for $C_{10}H_{13}NO_5S$: C, 46.32; H, 5.05; N, 5.04; S, 12.37. Found: C, 46.44; H, 5.14; N, 5.24; S, 12.41.

L,L-Lanthionine (1a) from 5. To L-cysteine (0.473 g, 3.91 mmol) in degassed H_2O (5 mL) at pH 5.3 was added **5** (produced from 0.244 g (1.30 mmol) of BOC-L-serine β-lactone (**3a**)) in H_2O (5 mL). The mixture was maintained at pH 5.0–5.5 with dropwise addition of 1 N NaOH. After 40 min the pH remained constant, and the material was applied to a column of AG50-X8 resin (80 mL, 3-cm diameter, H^+ form). Elution with a linear gradient of aqueous HCl (0–5 M over 1.5 L) provided chromatographically pure **1a**, which was recovered by removal of solvent in vacuo. This material was recrystallized by suspending in H_2O (2.5 mL), dissolving by addition of concentrated ammonia, cooling to 0 °C, and neutralizing (pH 6) with formic acid. Cooling several hours at 4 °C yielded **1a** (251 mg, 93% overall) as the zwitterion: mp 294–295 °C dec (darkens at 247 °C) (lit.[25] mp 293–295 °C dec); $[\alpha]^{25}_D$ +8.6° (*c* 5.0, 2.4 N NaOH) (lit. $[\alpha]^{22}_D$ +6 (±1)° (*c* 1.0, 1 N NaOH),[26] +7° (*c* 1, 1 N NaOH),[27] +8.4° (*c* 1.0, 1.0 N NaOH),[28] (*c* 1.4,

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(15) For some recent examples, see: (a) Fujisawa, R.; Kuboki, Y.; Sasaki, S. *Arch. Biochem. Biophys.* **1985**, *243*, 619–623. (b) Williams, S. P.; Sykes, B. D.; Bridger, W. A. *Biochemistry* **1985**, *24*, 5527–5531.

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2.4 N NaOH),[29] +8.6° (*c* 5.0, 2.4 N NaOH),[26,30] +9.4° (*c* 1.4, 2.4 N NaOH);[12b,31] IR (KBr disk) 3400 (w, br), 3300–2250 (s, br), 2080 (w), 1608 (s), 1593 (s), 1512 (s), 1389 (s), 1347 (s), 539 (m) cm^{-1}; ^1H NMR (300 MHz, D_2O + DCl) δ 4.45 (dd, 2 H, 7.4 and 4.4 Hz, 2 C*H*), 3.38 (dd, 2 H, 4.4 and 15.0 Hz, 2 C*H*HS), 3.26 (dd, 2 H, 7.4 and 15.0 Hz, 2 CH*H*S); FAB^+ MS (glycerol/HCl) 209 (MH^+), 417 (M_2H^+); R_f 0.33 (system A). Anal. Calcd for $C_6H_{12}N_2O_4$: C, 34.61; H, 5.81; N, 13.45; S, 15.40. Found: C, 34.63; H, 5.84; N, 13.50; S, 15.43. HPLC analysis of **1a** from **5** according to Schuster[32] indicates no detectable *meso*-lanthionine (i.e. <1%) in the sample (t_R = 23.5 (±0.1) min (LL), 24.3 min (meso)).

***S*-(Aminoethyl)-L-cysteine Hydrochloride (1b) from 5.** To 2-aminoethanethiol hydrochloride (201 mg, 1.77 mmol) in degassed H_2O (3.0 mL) was added **5** (produced from BOC-L-serine β-lactone (**3a**) (151 mg, 0.807 mmol)) in H_2O (1.0 mL). The stirred solution was maintained at pH 5.0–5.5 by dropwise addition of 1 N NaOH. When additions of base were no longer required to maintain the pH at 5.5 (~35 min), the mixture was applied to a column of AG50-X8 (80 m, 3-cm diameter, H^+ form) and eluted with a linear gradient (0–2 M over 1.0 L) of aqueous HCl (2 mL/min). Lyophilization of the chromatographically pure fractions yielded 138 mg (85%) of **1b**, which was recrystallized from EtOH/acetone (85% recovery) for elemental analysis: mp 193–194 °C dec (lit. mp 192–192.5 °C,[33] 205–207 °C[34]); $[\alpha]^{25}_D$ +7.2° (*c* 1.0, H_2O) (lit.[33] $[\alpha]_D$ + 7.2° (*c* 1, H_2O)); IR (KBr disk) 3650–2100 (s, br), 2000 (w, br) 1622 (s), 1587 (s), 1516 (s), 1494 (s), 1463 (s), 1427 (s), 1415 (s), 1400 (s), 1348 (s), 1303 (s), 560 (m) cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 4.00 (dd, 1 H, 4.8 and 6.0 Hz, C*H*), 3.27 (t, 2 H, 6.5 Hz, C*H*$_2$NH$_3^+$), 3.16 (dd, 1 H, 4.8 and 14 Hz, CHC*H*HS), 3.14 (d, 6.0 and 14 Hz, CHCH*H*S), 2.94 (td, 1 H, 6.5 and 14 Hz, SC*H*H), 2.92 (td, 1 H, 6.5 and 14.0 Hz, SCH*H*); FAB^+ MS (glycerol/HCl) 165 (MH^+), 329 (M_2H^+); R_f ~0.20 (system A). Anal. Calcd for $C_5H_{13}N_2O_2SCl$: C, 29.92; H, 6.54; N, 13.96; Cl, 17.66; S, 15.97. Found: C, 29.59; H, 6.44; N, 13.98; Cl, 17.40; S, 15.88.

L-Cysteine (1c) from 5. A suspension of LiSH (1.23 M) in THF was produced by bubbling H_2S(g) into THF containing 1.23 M *n*-BuLi at 0 °C. To the suspension of LiSH (2.24 mmol, 1.82 mL of 1.23 M) was added **5** (produced from 210 mg, 1.12 mmol of **3a**) in CH_3CN (1 mL). The mixture was stirred 1 h under Ar and acidified with concentrated HCl (0.15 mL, 1.8 mmol), and solvent was removed in vacuo at 35 °C. The residue was dissolved in H_2O and applied to a column of AG50-X8 (80 mL, 3-cm diameter, H^+ form). Elution with a linear gradient of degassed aqueous HCl (0–2 M over 1 L) provided L-cysteine hydrochloride free of cysteine after removal of solvent in vacuo. This material was isolated as the zwitterion from a minimal amount of EtOH by adjusting to pH 6.5 with concentrated NH_3, cooling to −20 °C, and immediately recrystallizing the precipitate from hot degassed H_2O to yield **1c** (120 mg, 88% overall): mp 240–241 °C dec (lit.[35] mp 240 °C dec); $[\alpha]^{25}_D$ +6.5 (±0.2)° (*c* 2.0, 5 N HCl) (lit.[36] $[\alpha]^{25}_D$ +6.5° (*c* 2, 5 N HCl)); IR (KBr disk) 3600–2650 (s, br), 2542 (m), 2160–1980 (w, br), 1610 (s), 1582 (s), 1519 (s), 1397 (s), 1291 (m), 658 (m), 528 (m), 510 (m), cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 4.31 (dd, 1 H, 4.5 and 5.5 Hz, C*H*), 3.16 (dd, 1 H, 5.5 and 15.0 Hz, C*H*HS), 3.13 (dd, 1 H, 4.5 and 15.0 Hz, CH*H*S); FAB^+ MS (glycerol/HCl) 122 (MH^+), 243 (M_2H^+); R_f 0.45 (system A). Anal. Calcd for $C_3H_7NO_2S$: C, 29.74; H, 5.83; N, 11.56; S, 26.46. Found: C, 29.46; H, 5.85; N, 11.55; S, 26.68.

***S*-Sulfo-L-cysteine, Monosodium Salt Dihydrate (1d).** To $Na_2S_2O_3$ (73.2 mg, 0.463 mmol) in H_2O (1 mL) at pH 5.0 was added **5** (produced from BOC-L-serine β-lactone (**3a**) (43.0 mg, 0.23 mmol)) in H_2O (1 mL). The solution was maintained at pH 5.0 for 1 h, and the solvent was removed in vacuo at 25 °C. The residue was dissolved in H_2O (1.0 mL), applied to a column of Rexyn 102 (1 × 10 cm, H^+ form), and eluted with H_2O (0.25 mL/min). *S*-Sulfo-L-cysteine (R_f 0.81, system A; characteristic brown color with ninhydrin) eluted chromatographically pure as the monosodium salt after 15–20 mL. Lyophilization and recrystallization from H_2O/Et_2O (pH 5) provided 49.7 mg (83%) of **1d** as a white solid: mp 135 °C [foams but remains white (loss of H_2O)], 202–204 °C dec; $[\alpha]^{25}_D$ −83.7 (±0.2)° (*c* 2.5, H_2O) (lit. $[\alpha]^{25}_D$ −86.8° (*c* 4.73, H_2O)[37] for the 1.5 hydrate); IR (KBr disk) 3450 (m, br), 3150 (m, br), 1635 (s, br), 1515 (m), 1400 (m), 1358 (m), 1235 (s), 1217 (s), 1200 (s), 1137 (s), 1030 (s), 636 (s) cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 4.18 (dd, 1 H, 3.7 and 8.0 Hz, C*H*), 3.68 (dd, 1 H, 3.7 and 15.5 Hz, C*H*HSSO$_3^-$), 3.50 (dd, 1 H, 8.0 and 15.5 Hz, CH*H*SO$_3^-$); FAB^- MS (glycerol) 200 ($^-$O$_3$SSCH$_2$CH(NH$_2$)COOH). Anal. Calcd for $C_3H_6NO_5S_2Na\cdot 2H_2O$ (FW 259.2): C, 13.90; H, 3.89; N, 5.40; S, 24.74. Found: C, 14.11; H, 3.85; N, 5.21; S, 24.59.

L-Cysteine Dimethylsulfonium, Bis(*p*-toluenesulfonic acid) Salt (1e). To (*S*)-3-amino-2-oxetanone *p*-toluenesulfonic acid salt (**6**) (100 mg, 0.386 mmol) and anhydrous *p*-toluenesulfonic acid (99.6 mg, 0.579 mmol) in trifluoroacetic acid (3.0 mL) was added dimethyl sulfide (113 μL, 1.54 mmol). After 15 min the solvent was removed in vacuo. The syrupy residue was dissolved in MeOH (5 mL), and **1e** crystallized as shiny white needles (168 mg, 88%) following addition of Et_2O (20 mL) and cooling to −20 °C: mp 141–142 °C dec; $[\alpha]^{25}_D$ +11.8 (±0.4)° (*c* 0.96, DMF); IR (MeOH cast) 3483 (m), 2930 (m, vbr), 1742 (m), 1193 (vs), 815 (m), 682 (m), 567 (s), cm^{-1}; ^1H NMR (300 MHz, MeOH-d_4) δ 7.70 (d, 4 H, 8 Hz, *o*-Ar*H*), 7.24 (d, 4 H, 8 Hz, *m*-Ar*H*), 4.65 (dd, 1 H, 5.8 and 8.2 Hz, C*H*), 3.95 (dd, 1 H, 8.2 and 13.8 Hz, C*H*HS), 3.81 (dd, 1 H, 5.8 and 13.8 Hz, CH*H*S), 3.07 (s, 3 H, S(C*H*$_3$)CH$_3$), 3.06 (s, 3 H, S(CH$_3$)C*H*$_3$), 2.36 (s, 6 H, ArC*H*$_3$); EI MS 172.0195 (TsOH), 62.0207 (Me_2S); FAB^+ MS (glycerol) 150 (100%, $Me_2S^+CH_2CH(NH_2)COOH$); R_f ~0.08 (system A). Anal. Calcd for $C_{19}H_{27}NO_8S_3$: C, 46.23; H, 5.51; N, 2.84; S, 19.48. Found: C, 46.15; H, 5.49; N, 2.91; S, 19.55.

***O*-(Trifluoroacetyl)-L-serine, *p*-Toluenesulfonic Acid Salt (1f).** BOC-L-serine β-lactone (**3a**) (106 mg, 0.566 mmol) and AG1-X8 resin (240 mg, ~0.8 meq, CF_3COO^- form, dried in vacuo at 64 °C) were treated with distilled trifluoroacetic acid (4 mL), and the mixture was stirred 16 h under Ar. The resin was removed by filtration and washed with CF_3COOH (2 × 1 mL). *p*-Toluenesulfonic acid (97.5 mg, 0.566 mmol) was added to the combined filtrate and washing, and trifluoroacetic acid was removed by bulb-to-bulb distillation in vacuo. The white solid residue was triturated with dry Et_2O (5 mL), filtered, and washed well with ether to yield **1f** (178.5 mg, 87%): mp 181.5–182.0 °C (darkens at 178 °C); $[\alpha]^{25}_D$ +10.0 (±0.4)° (*c* 0.45, DMF); IR (KBr disk) 3420 (m, vbr), 3300–2400 (s, vbr), 1799 (s), 1754 (s), 1621 (w), 1600 (w), 1532 (m), 1345 (w), 1229 (m), 1194 (s), 1156 (vs), 1129 (m), 1041 (s), 1014 (s), 812 (m), 691 (s), cm^{-1}; ^1H NMR (400 MHz, DMF-d_7) δ 9.15 (br s, ~4 H, COO*H*, N*H*$_3^+$), 7.66 (d, 2 H, 8.0 Hz, *o*-Ar*H*), 7.14 (d, 2 H, 8.0 Hz, *m*-Ar*H*), 5.14 (dd, 1 H, 2.4 and 12.3 Hz, C*H*HO), 5.01 (dd, 1 H, 4.6 and 12.3 Hz, CH*H*O), 4.88 (br m, 1 H, C*H*), 2.30 (s, 3 H, ArC*H*$_3$); ^{19}F NMR (376.5 MHz, DMF-d_7) δ −75.5 (s, C*F*$_3$COO); EI MS 172.0195 (TsOH), 156.0274 ((M − CO_2H) = $C_4H_5NO_2F_3$); FAB^+ MS (glycerol) 202 (MH^+ = $CF_3COOCH_2CH(NH_3^+)COOH$), 374 ($MH^+$·TsOH), 294 ($MH^+$·gly); R_f ~0.68 (system A, some hydrolysis on plate). Anal. Calcd for $C_{12}H_{14}NO_7SF_3$: C, 38.61; H, 3.78; N, 3.75. Found: C, 38.96; H, 3.93; N, 3.99.

2-[*N*-(Trifluoroacetyl)amino]propenoic Acid (7). BOC-L-serine β-lactone (**3a**) (144 mg, 0.769 mmol) was dissolved in distilled trifluoroacetic acid, and the solution was allowed to stand 16 days under Ar. Bulb-to-bulb distillation in vacuo at 25 °C (0.1 Torr) first removed the trifluoroacetic acid and subsequently caused the sublimation of a white solid, which was collected in a clean chilled receiving bulb. The last third of **7** sublimate was obtained on warming to 45 °C to give a total of 117 mg (83%) of **7**. ^1H NMR on the pot residue indicated it was primarily *O*-(trifluoroacetyl)serine (**1f**). For **7**: mp 126–128 °C; IR (CH_3CN cast) 3380 (m), 3400–2200 (mult, br, w), 1744 (m), 1702 (vs), 1638 (w), 1552 (s), 1445 (s), 1300 (m), 1213 (s), 1188 (m), 1164 (s), 910 (m) cm^{-1}; ^1H NMR (300 MHz, CD_3CN) δ 8.72 (br s, ~1 H, N*H*), 6.46 (s, 1 H, (*E*)-C*H*H), 6.11 (s, 1 H, (*Z*)-CH*H*); EI MS 183.0134 (183.0144 calcd); CI MS (NH_3) 201 (M + NH_4^+); R_f ~0.87 (system B; UV active, pink-brown with ninhydrin). Anal. Calcd for $C_5H_4NO_3F_3$: C, 32.80; H, 2.20 N, 7.65. Found: C, 32.52; H, 2.18; N, 7.62.

***O*-Phospho-L-serine (1g).** K_2HPO_4 (0.446 g, 3.28 mmol, dried 4 h at 130 °C) and 18-crown-6 ether (0.867 g, 3.28 mmol) were stirred 16 h in anhydrous DMF (10 mL). BOC-L-serine β-lactone (**3a**) (169 mg, 0.902 mmol) was deprotected to **5** and added as a solution in DMF (3 mL). The mixture was stirred 3 days, diluted with H_2O (to 50 mL), and applied to a column of AG1-X8 (80 mL, 3-cm diameter, OH^- form). Elution (2 mL/min) with a linear gradient (0–3 M over 1.0 L) of formic acid afforded *O*-phospho-L-serine (**1g**) (145.6 mg) in 87% yield after lyophilization: mp 170–171 °C dec (lit.[16] mp 175–176 °C dec); $[\alpha]^{25}_D$ +7.2° (*c* 1.0, H_2O) (lit.[16] $[\alpha]^{25}_D$ +7.2° (*c* 1.0, H_2O)); IR (KBr disk) 3420 (w, br), 3180 (w), 2700 (w), 2400–2260 (w), 1620 (w), 1560 (m), 1260 (m), 1089 (s), 1045 (s), 1000 (s), 970 (s), 740 (m), 810 (m) cm^{-1}; ^1H NMR (300 MHz, D_2O + DCl) δ 4.37–4.27 (m, 2 H, C*H*C*H*H),

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4.26–4.16 (m, 1 H, CH*H*); ^{31}P NMR (161.96 MHz, D_2O + DCl) −0.45 (br s); FAB$^+$ MS (glycerol/HCl) 186 (MH^+), 371 (M_2H^+), R_f 0.43 (system A). Anal. Calcd for $C_3H_8NO_6P$: C, 19.47; H, 4.35; N, 7.57. Found: C, 19.27; H, 4.29; N, 7.82.

β-Chloro-L-alanine (1h). Concentrated HCl (1.0 mL, ~12 mmol) was added to **5** produced from BOC-L-serine β-lactone (**3a**) (92.0 mg, 0.492 mmol). After 5 min H_2O (5 mL) was added, and the solvent was removed in vacuo at 35 °C. The residue was redissolved in H_2O (5 mL), and again the solvent was removed. Recrystallization of the solid residue from MeOH/Et_2O yields 78.5 mg (92%) of β-chloro-L-alanine (**1h**) as its hydrochloride salt. Since literature reports that the hydrochloride has "no distinct mp" and $[\alpha]_D$ is "close to zero",[30] the material was converted to the free base for complete characterization. Hence, the hydrochloride was dissolved in a minimal amount of H_2O, 1 equiv of 2 N LiOH was added, and **1h** (56.5 mg, 93% recovery) was obtained by addition of excess EtOH with cooling to −10 °C. A nearly identical yield of the hydrochloride of **1h** was also obtained simply by addition of concentrated HCl to BOC-L-serine β-lactone (**3a**) (1.0 mL/100 mg).

For 1h (Hydrochloride) from 5: $[\alpha]^{25}_D$ +0.80° (*c* 1.0, H_2O); IR (KBr disk) 3720–2200 (vs, br), 1980 (m), 1960 (m), 1745 (vs), 1600 (s), 1500 (vs), 1410 (s), 1350 (s), 1230 (s), 1200 (s), 1150 (m), 1070 (m), 890 (m), 850 (s), 790 (s), 680 (s) cm^{-1}; ^{1}H NMR (80 MHz, D_2O) δ 4.60–4.44 (m, 1 H, C*H*), 4.25–4.07 (m, 2 H, CH_2Cl); FAB$^+$ MS (glycerol) 124 (MH^+); R_f 0.76 (system A). Anal. Calcd for $C_3H_7NO_2Cl_2$: C, 22.52; H, 4.42; N, 8.75. Found: C, 22.09; H, 4.48; N, 8.63.

For Free Base 1h: mp 156–157 °C (lit.[38] mp 160 °C); $[\alpha]^{25}_D$ −15.8° (*c* 1.0, H_2O) (lit.[30] $[\alpha]^{20}_D$ −15.5° (*c* 1, H_2O), −15° (*c* 9.9, H_2O)[26]); IR (KBr disk) 3660–2160 (m, multg, br), 2080 (w), 1630 (s), 1600 (s), 1390 (s), 1300 (s), 860 (s), 640 (s), 540 (s), 450 (s) cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 4.62 (dd, 1 H, 3.25 and 4.5 Hz, C*H*), 4.21 (dd, 1 H, 4.5 and 13.0 Hz, C*H*HCl), 4.10 (dd, 1 H, 3.25 and 13.0 Hz, CH*H*Cl); FAB$^+$ MS (glycerol) 124 (MH^+). Anal. Calcd for $C_3H_6NO_2Cl$: C, 29.16; H, 4.90; N, 11.34; Cl, 28.69. Found: C, 28.99; H, 4.95; N, 11.08; Cl, 28.51.

β-Cyano-L-alanine (1i) from 5. A solution of **5** (prepared from 79.0 mg, 0.422 mmol of BOC-L-serine β-lactone (**3a**)) in DMF (2 mL) was added dropwise to tetra-*n*-butylammonium cyanide (170 mg, 0.633 mmol) in DMF (3 mL) at −10 °C over 10 min. The solution was stirred 30 min at −10 °C and allowed to warm to 25 °C over 30 min. The solvent was removed in vacuo at 25 °C to yield an orange syrup, which was dissolved in H_2O (1 mL) and applied to a column of AG11 A8 (30 g, 1 × 40 cm). Elution with H_2O (0.4 mL/min) and lyophilization of the fractions, which produced the characteristic blue-gree color with ninhydrin spray reagent, provided 40.3 mg (84%) of **1i** free of salts. For an improved melting point, this solid was precipitated from pH 6.0 H_2O by addition of dioxane and dried in vacuo over P_2O_5 (34.5 mg, 72% yield after two precipitations): mp 213–216 °C dec (first precipitation) 217–218 °C (second precipitation) (lit.[39] mp 206, 208–209, 218–218.5 °C); $[\alpha]^{25}_D$ −2.9° (*c* 1.4, 1 N HOAc) (lit.[39] $[\alpha]^{25}_D$ −2.9° (*c* 1.4, 1 N HOAc)); IR (KBr disk) 3420 (m, br), 3020 (s, br), 2225 (w), 1630 (vs, br), 1610 (s), 1575 (m), 1528 (s), 1417 (s), 1330 (s), 1160 (w), 1070 (w), 880 (w) cm^{-1}; ^{1}H NMR (200 MHz, D_2O) δ 4.10 (t, 1 H, 5.8 Hz, C*H*), 3.08 (d, 2 H, 5.8 Hz, CH_2CN); FAB$^+$ MS (glycerol/HCl) 115 (MH^+), 229 (M_2H^+), 343 (M_3H^+); R_f ~0.65 (system A, characteristic blue-green color with ninhydrin).

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β-Pyrazol-1-yl-L-alanine (1j). (*S*)-3-Amino-2-oxetanone salt **6** (100 mg, 0.385 mmol) was added to pyrazole (131 mg, 1.93 mmol) in distilled DMF (3.0 mL), and the mixture was stirred at 25 °C for 2.5 h. The solvent was removed in vacuo at 25 °C, and the residue was dissolved in H_2O (3 mL) and applied to a column of AG50-X8 (1 × 10 cm, H^+ form). The resin was washed with H_2O (30 mL) and eluted with a gradient of aqueous NH_4OH (0–0.25 N over 70 mL and then 100 mL of 0.25 N NH_4OH). The product emerged chromatographically pure with 0.25 N NH_4OH and was lyophilized (2×) and dried in vacuo over P_2O_5 to yield 77% (46.2 mg) of **1j** (mp 234–236 °C dec). For an improved melting point this material could be recrystallized from H_2O/EtOH: mp 241–243 °C (lit. mp 236–238 °C dec,[40] 243 °C dec[41]); $[\alpha]^{25}_D$ −72 (±1)° (*c* 0.54, H_2O) (lit. $[\alpha]^{25}_D$ −78° (*c* 3.4, H_2O),[40] −72.0° (*c* 1.0, H_2O)[41]); IR (KBr disk) 3700–2200 (m, vbr), 1617 (s), 1580 (s), 1485 (m), 1395 (m), 767 (m) cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 7.65 (d, 1 H, 2 Hz, Ar*H*H′H″), 7.61 (d, 1 H, 2 Hz, ArHH′*H*″), 6.38 (t, 1 H, 2 Hz, ArH*H*′H″), 4.66 (d, 2 H, 5 Hz, CH_2N), 4.18 (t, 1 H, 5 Hz, C*H*); FAB$^+$ MS (glycerol/HCl) 156 (MH^+), 311 (M_2H^+); R_f 0.67 (solvent A; characteristic blue-purple color with ninhydrin).

β-Azido-L-alanine (1k). A solution of **6** (53.0 mg, 0.204 mmol) in DMF (1 mL) was added to NaN_3 (14.6 mg, 0.225 mmol) in DMF (5 mL), and the mixture was stirred 3.5 h. The solvent was removed in vacuo at 25 °C. The residue was dissolved in H_2O (0.3 mL) and applied to a column of Bio-Rad Ion Retardation Resin Ag11 A8 (15 g, 1 × 20 cm) and eluted with H_2O (0.3 mL/min). Fractions containing amino acid were pooled and lyophilized to yield 25.6 mg (96%) of pure β-azido-L-alanine. For the optimum melting point this material was recrystallized by dissolving in a minimal volume of H_2O at 40 °C, adding MeOH (3 vol) and acetone (until cloudy), and cooling to −20 °C:[23,42] mp 174–175 °C dec; $[\alpha]^{25}_D$ +37.2 (±0.5)° (*c* 0.5, H_2O); IR (KBr disk) 3420 (m, br), 3070 (s, br), 2113 (s), 1600 (vs, br), 1440 (s) cm^{-1}; ^{1}H NMR (300 MHz, MeOD-d_4 δ 3.63 (dd, 1 H, 4.5 and 12 Hz, C*H*HN$_3$), 3.53 (dd, 1 H, 7.2 and 12 Hz, CH*H*N$_3$), 3.37 (dd, 1 H, 4.5 and 7.2 Hz, C*H*); ^{1}H NMR (300 MHz, D_2O) δ 3.93 (dd, 1 H, 5.0 and 17.5 Hz, C*H*HN$_3$), 3.92 (m, 1 H, C*H*), 3.84 (dd, 1 H, 7.0 and 17.5 Hz, CH*H*N$_3$); EI MS: 131.0570 (MH^+, calcd 131.0570 for $C_3H_7N_4O_2$), 88.0400 (MH^+ − HN_3), 85.0515 (M − CO_2H), 74.0245 (base peak, M − CH_2N_3); FAB$^+$ MS (glycerol) 131 (MH^+); R_f 0.80 (system A; UV active; brown-purple with ninhydrin).

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Registry No. 1a, 922-55-4; **1b**, 4099-35-8; **1c**, 52-90-4; **1d**, 7381-67-1; **1e**, 112839-91-5; **1f**, 112839-92-6; **1g**, 407-41-0; **1h** (free base), 2731-73-9; **1h**·HCl, 51887-89-9; **1i**, 6232-19-5; **1j**, 2734-48-7; **1k**, 105661-40-3; **3a**, 98541-64-1; **5**, 112839-94-8; **6**, 112839-95-9; **7**, 675-00-3; H-Cys-OH, 52-90-4; $H_2NCH_2CH_2SH$·HCl, 156-57-0; pyrazole, 288-13-1.

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(42) Recrystallization from hot methanol[23] causes partial decomposition of **1k**.