acetic anhydride (4.186 g, 41.0 mmol) and 99% formic acid (1.887 g, 41.0 mmol) for 2 h at 55 °C. The solution was cooled to 0 °C and then added slowly to a chilled solution of **1** (7.20 g, 34.1 mmol) in CH_2Cl_2 (40 mL). After 12 h of being stirred at 25 °C the solution was washed with saturated aqueous Na_2CO_3, dried (K_2CO_3), and concentrated to dryness to give an oil (6.83 g), which solidified upon trituration with ethyl acetate. The solid was isolated by filtration and crystallized from 1:1 ethyl acetate–hexanes, giving **3** (4.416 g, 54%) as white needles: mp 140–141 °C; IR 1658, 1638 cm^{-1}; NMR[14] δ 1.27 (s, 3), 1.28 (s, 3), 1.60–2.00 (m, 5), 2.12 (s, 3), 2.65–2.95 (m, 2), 3.25–3.60 (m, 3), 3.70–3.90 (m, 1), 4.60–4.85 (m, 1), 8.27 (s, 1). Anal. Calcd for $C_{12}H_{21}N_3O_2$: C, 60.21; H, 8.85; N, 17.57. Found: C, 60.32; H, 8.96; N, 17.38.

8-Acetyl-2,2-dimethyl-4-formyl-1,4,8-triazaspiro[4.5]decane-1-oxyl (4). To a stirred solution of **3** (2.40 g, 10.0 mmol) in CH_2Cl_2 (60 mL) at −10 °C was added dropwise a solution of 85% MCPBA (2.67 g, 15.0 mmol) in CH_2Cl_2 over 1 h. After 24 h of being stirred at 25 °C, the solution was washed with saturated aqueous $NaHCO_3$, dried (K_2CO_3), and concentrated to dryness to give a red-brown oil (2.209 g). Purification by flash chromatography over silica gel (elution with 1:9 MeOH–ether) gave an orange solid, which was crystallized from 1:1 ethyl acetate–hexanes to give **4** (1.158 g, 45%) as orange-yellow plates: mp 150–151 °C; IR 1667, 1637 cm^{-1}; ESR 3 lines, each showing further splitting, a_N = 14.50 G. Anal. Calcd for $C_{12}H_{20}N_3O_3$: C, 56.66; H, 7.93; N, 16.53. Found: C, 56.78; H, 8.13; N, 16.43.

2,2-Dimethyl-1,4,8-triazaspiro[4.5]decane-1-oxyl (5). Nitroxide **4** (107 mg) was dissolved in a solution of 6 M methanolic KOH (4 mL) and water (1 mL) and stirred at 45 °C for 21 h. The volatiles were removed in vacuo, and the residue was dried (0.05 mm). The residue was triturated with CH_2Cl_2, and the extract was filtered through a column of sand and Celite. The filtrate was dried (K_2CO_3) and then concentrated to dryness, giving 77 mg (100%) of a pale brown solid, mp 95–97 °C. A 20-mg portion was gently sublimed [60 °C (0.05 mm)] to give the analytical sample (12 mg) as a pale yellow powder: mp 109–111 °C (lit.[6] mp 85–87 °C); IR, no C=O; ESR 3 broadened lines, a_N = 14.83 G. Anal. Calcd for $C_9H_{18}N_3O$: C, 58.65; H, 9.85; N, 22.81. Found: C, 58.72; H, 9.96; N, 22.75.

8-Acetyl-2,2,3,3-tetramethyl-1,4,8-triazaspiro[4.5]decane (9). A 250-mL flask was fitted with a Dean–Stark water separator containing anhydrous K_2CO_3 and then was charged with benzene (170 mL), ketone **7** (3.481 g, 24.66 mmol), diamine **6** (2.86 g, 24.7 mmol), and *p*-toluenesulfonic acid monohydrate (20 mg). After a 48-h reflux period with stirring the volatiles were removed in vacuo, giving a thick oil that solidified upon cooling. Trituration with 1:1 ether–hexanes gave a residue, which was collected by filtration giving diamine **9** (5.58 g, 95%) as a white solid, mp 90–95 °C. A 2.00-g portion was sublimed [85 °C (0.2 mm)] to give the analytical sample of **9** (1.84 g) as white needles: mp 100–102 °C; IR 1628 cm^{-1}; NMR[14] δ 1.12 (s, 12), 1.55–1.75 (m, 6), 2.08 (s, 3), 3.45–3.55 (br t, 2), 3.62–3.68 (br t, 2). Anal. Calcd for $C_{13}H_{25}N_3O$: C, 65.22; H, 10.53; N, 17.56. Found: C, 64.92; H, 10.80; N, 17.34.

8-Acetyl-2,2,3,3-tetramethyl-1,4,8-triazaspiro[4.5]decane-1-oxyl (10). To a stirred solution of diamine **9** (1.70 g, 7.11 mmol) in CH_2Cl_2 (75 mL) at −10 °C was added dropwise over 1.5 h a solution of 85% MCPBA (1.90 g, 11.0 mmol) in CH_2Cl_2 (50 mL). The color went from colorless to pale blue to pale green to almost colorless. After the mixture was stirred 24 h at 25 °C, anhydrous K_2CO_3 (5 g) was added. The mixture was stirred for 30 min and then filtered. The filtrate was concentrated to dryness, giving a pale yellow semisolid (3 g). This was dissolved in CH_2Cl_2 and flash chromatographed over silica gel. Elution with 95:5 ether–MeOH gave nitroxide **10** (1.07 g, 59%) as a waxy yellow solid: IR 1632 cm^{-1}; ESR 3 lines, each with further splitting, a_N = 14.75 G.

2,2,3,3-Tetramethyl-1,4,8-triazaspiro[4.5]decane-1-oxyl (11). Nitroxide **10** (150 mg) was dissolved in a solution of 6 M methanolic KOH (6 mL) and water (1.5 mL) and stirred at 48 °C for 24 h. The volatiles were removed in vacuo, and the residue was dried (0.05 mm) and then triturated with CH_2Cl_2. The extract was filtered through sand and Celite, and the filtrate was dried (K_2CO_3). Removal of the solvent gave nitroxide **11** (106 mg, 85%) as a pale yellow-brown powder, mp 164–166 °C (preheated bath). A 15-mg portion was gently sublimed [75 °C (0.01 mm)] to give the analytical specimen (11 mg) as a pale yellow powder: mp 170–171 °C, IR no C=O; ESR 3 lines, a_N = 14.75 G. Anal. Calcd for $C_{11}H_{22}N_3O$: C, 62.21; H, 10.45; N, 19.80. Found: C, 62.21: H, 10.74; N, 19.60.

8-Acetyl-2,2-dimethyl-1,8-diaza-4-oxaspiro[4.5]decane (12). A 250-mL flask fitted with a Dean–Stark water separator containing anhydrous K_2CO_3 was charged with benzene (150 mL), ketone **7** (10.6 g, 75.0 mmol), 2-amino-2-methylpropan-1-ol (**8**) (6.69 g, 75.0 mmol), and *p*-toluenesulfonic acid monohydrate (40 mg). After a 43-h reflux period the volatiles were removed in vacuo, leaving an oil that solidified upon cooling to give **12** (15.35 g, 97%) as a colorless solid, mp 75–78 °C. Distillation [bp 115–120 °C (0.1 mm)] gave 11.38 g (72%) of **12** as a white solid, mp 77–78 °C, sufficiently pure for the next reaction. The analytical specimen was obtained as a white solid by sublimation [75 °C (0.05 mm)]: mp 80–81 °C; IR 1630 cm^{-1}; NMR[14] δ 1.24 (s, 3), 1.25 (s, 3), 1.55–1.95 (m, 5), 2.10 (s, 3), 3.25–3.56 (m, 3), 3.60 (dd, 2), 4.00–4.10 (m, 1). Anal. Calcd for $C_{11}H_{20}N_2O_2$: C, 62.22; H, 9.50; N, 13.20. Found: C, 62.33; H, 9.80; N, 13.50.

8-Acetyl-2,2-dimethyl-1,8-diaza-4-oxaspiro[4.5]decane-1-oxyl (13). To a stirred solution of amine **12** (2.12 g, 10.0 mmol) in CH_2Cl_2 (60 mL) at −10 °C was added dropwise over 1 h a solution of 85% MCPBA (2.67 g, 15.0 mmol) in CH_2Cl_2 (30 mL). After 12 h of being stirred at 25 °C the mixture was washed with 5% aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated to dryness, giving 1.59 g of crude **13**. Flash chromatography over silica gel and elution with 95:5 ether–MeOH gave nitroxide **13** (1.38 g, 61%) as an orange-yellow solid, mp 92–93 °C. The analytical specimen was obtained as orange-yellow flakes by sublimation [75 °C (0.05 mm)]: mp 93–94 °C; IR 1636 cm^{-1}; ESR 3 lines, a_N = 14.75 G. Anal. Calcd for $C_{11}H_{19}N_2O_3$: C, 58.11; H, 8.43; N, 12.33. Found: C, 58.03; H, 8.65; N, 12.36.

2,2-Dimethyl-1,8-diaza-4-oxaspiro[4.5]decane-1-oxyl (14). Nitroxide **13** (100 mg) was dissolved in a mixture of 6 M methanolic KOH (4 mL) and water (1 mL) and stirred at 47 °C for 22 h. The volatiles were removed in vacuo, and the residue was triturated with CH_2Cl_2. The extract was filtered through sand and Celite and then dried (K_2CO_3). Removal of the solvent gave nitroxide **14** as a pale yellow powder (77 mg, 95%), mp 88–89 °C. Gentle sublimation [60 °C (0.01 mm)] of **14** (17 mg) gave the analytical specimen (14 mg) as pale yellow cubes: mp 90–91 °C; IR no C=O; ESR 3 lines, a_N = 14.63 G. Anal. Calcd for $C_9H_{17}N_2O_2$: C, 58.34; H, 9.25; N, 15.13. Found: C, 58.34; H, 9.32; N, 15.19.

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Registry No. **1**, 113646-66-5; **2**, 811-93-8; **3**, 113646-67-6; **4**, 113646-68-7; **5**, 80028-56-4; **6**, 20485-44-3; **7**, 32161-06-1; **8**, 124-68-5; **9**, 113646-69-8; **10**, 113646-70-1; **11**, 113646-71-2; **12**, 113646-72-3; **13**, 113646-73-4; **14**, 113646-74-5.

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Removal of *N*-Arylsulfonyl Groups from Hydroxy α-Amino Acids

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Arylsulfonyl substituents are highly effective protecting groups for the amino function of α-amino acids. They are stable to most reaction conditions, provide a strong chromophore, and have been especially useful where the car-

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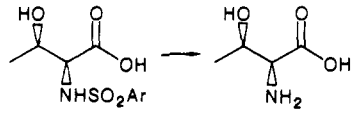
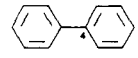
Table I. Reductive Deprotection of *N*-(Arylsulfonyl)threonines



entry	Ar	yield, %		electrochemical reduction		
		Na/NH_3	HBr/HOAc	$E^1_{1/2}$, V	$E^2_{1/2}$, V	yield
1		55	40[a]	−1.88	−2.80	85
2		45	quant	−2.0	−2.65	
3		47	60	−2.0	−2.60	
4		42	79	−1.65	−2.45	
5			quant	−1.50	−2.35	84
6			45[b]	−2.15	−2.75	
7			40[b]	−2.05	−2.55	
8			35[b]	−2.05	−2.70	

[a] A quantitative yield can be obtained in 5 h at 50 °C. [b] These yields have not been optimized.

boxyl group is destined to undergo reaction with an organometallic reagent.[1] Unfortunately, these protecting groups have frequently proved troublesome to remove. A variety of deprotection methods have been used, either hydrolytic[2] or reductive, comprising dissolving metals or complex aluminum hydrides,[3] electrochemical reduction,[4] and a photochemical–borohydride process.[5] No clear comparison has been made among these various methods and with a variety of substrates. Often deprotection has been devised for a specific compound and there is no evidence of its applicability to other structures.[3a,c] For simple α-amino acids, hydrolysis with aqueous hydrobromic acid and reduction with sodium in liquid ammonia have been quite acceptable methods of removal.[1] When other functionality is present, however, such as a β-hydroxyl group, no deprotected amino acid is obtained with aqueous HBr and only a low conversion when sodium in liquid ammonia is used.[1]

In anticipation of the need to remove *N*-arylsulfonyl protecting groups from a number of synthetic hydroxy amino acids, we undertook a comparative investigation of deprotection methods. We sought compatibility with other functionality; thus reductive methods were examined rather than the more drastic hydrolytic processes. Three specific reductive deprotection methods were compared, namely, sodium in liquid ammonia, HBr in acetic acid, and electrolysis. A fourth method, photolysis in the presence of borohydride,[5] was tried but abandoned when it proved ineffective. We also studied a variety of substituted arylsulfonyl groups to determine what role substitution of the phenyl ring played in ease of removal. Although methyl and methoxy substituents might lead to unwanted anion formation in the anticipated reactions with organometallic reagents, they were included since prior sulfonamide anion formation should inhibit this. Threonine was our model amino acid because it is the simplest β-hydroxy-α-amino acid containing two chiral centers. This allows us to determine whether epimerization takes place during any deprotection since this would lead to allothreonine. We also pursued a recent report[6] that described formation of *N*-(*tert*-butoxycarbonyl)-*N*-(tolylsulfonyl)aniline and the hydrolytic removal of the sulfonyl group during alkaline isolation. When applied to *N*-(phenylsulfonyl)threonine, using both catalytic and stoichiometric 4-(dimethylamino)pyridine, this process led only to polymeric products.

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Our results are summarized in Table I. Eight arylsulfonyl derivatives of threonine were used, and they were subjected to the three different reductive deprotection methods. Sodium in liquid ammonia deprotection was applied to only entries 1–4, since the yields were consistently moderate. All reactions were carried out under identical conditions on 100 mg of the derivatized threonine. Sodium was added to a solution of the threonine in refluxing ammonia until a persistent blue color was observed. After quenching with ammonium chloride and evaporation of the ammonia, the residue was dissolved in 1 M phosphoric acid and purified by ion-exchange chromatography. In general this procedure yields from 45% to 55% of product. Maximizing the yield is made difficult by the inability to monitor the reaction, and purification is tedious.

Since hydrobromic acid in acetic acid is not a hydrolytic method of deprotection but rather a reductive one, a difference in ease of cleavage of a variety of arenesulfonamides is reasonable. We initially noticed a dramatic difference in going from *N*-(phenylsulfonyl)threonine (entry 1) to *N*-(*p*-tolylsulfonyl)threonine (entry 2). The phenylsulfonyl group can be removed only to the extent 40% at room temperature in HBr/HOAc, but a *p*-tosyl group can be removed quantitatively under identical conditions. Finding that the presence of just one methyl group made such a dramatic difference, we examined a variety of alkyl-substituted arenesulfonamides as listed in Table I. [(4-Methoxyphenyl)sulfonyl]threonine (entry 7) was added to see if the electron-donating character of the alkyl groups was causing the difference.

Only three of the sulfonyl chlorides (phenyl, 4-methylphenyl, 2,4,6-trimethylphenyl) used to derivatize threonine (entries 1, 2, 6) were commercially available. The remainder were synthesized in good yield by using straightforward procedures.[7] For 2,5-dimethylbenzene-, 4-isopropylbenzene-, and 4-methoxybenzenesulfonyl chlorides, the parent aromatic compound was added dropwise over 2 h to 300 mol % of chlorosulfonic acid and then stirred overnight before isolation. A mixture of all possible sulfonyl chlorides and sulfones was thus obtained, but the major product was always the desired sulfonyl chloride. Using a modified literature procedure,[2b] we synthesized 2,4-dimethylbenzenesulfonyl chloride by addition of chlorosulfonic acid to *m*-xylene at 5–10 °C followed by immediate isolation. 4-Phenylbenzenesulfonyl chloride was obtained from 4-phenylbenzenesulfonic acid, which was synthesized directly from biphenyl.[8]

A simple Schotten–Baumann reaction yields *N*-(phenylsulfonyl)threonine (entry 1) while a mixed benzene-/H_2O, 1/2, solvent system must be used to obtain *N*-(*p*-tolylsulfonyl)threonine (entry 2). Exhaustive studies of solvent composition, time, and temperature led to a 1/1 mixture of THF/H_2O for the highest yields of entries 3–7. (Biphenylylsulfonyl)threonine (entry 8) could only be formed satisfactorily in a 1/1 mixture of CH_3CN/H_2O.

Subjecting all eight *N*-arylsulfonyl derivatives to identical HBr/HOAc deprotection conditions gave a clear indication that the more highly substituted the aryl group, the more easily it could be removed. For entries 5–8, a side product was observed that resulted from bromide displacement of the hydroxyl group of threonine. Subjecting threonine itself to the deprotection conditions yielded a substantial quantity of 2-amino-3-bromobutyric acid. To limit this displacement reaction, the *N*-arylsulfonyl derivative was first dissolved in ethyl acetate and added incrementally to HBr/HOAc containing a large quantity of phenol as a bromine scavenger. When this procedure was used, the (2,4-dimethylphenyl)sulfonyl derivative (entry 5) could be quantitatively deprotected without any bromide displacement of the hydroxyl group. For entries 6–8, the reaction conditions were not optimized.

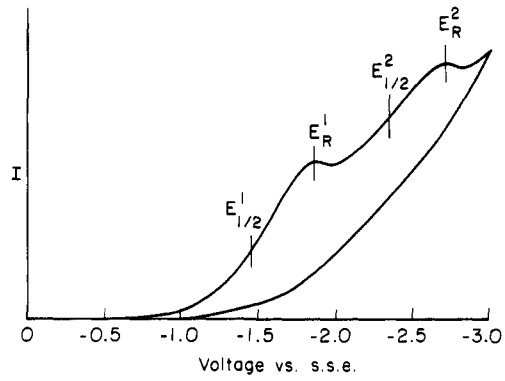

Figure 1. Cyclic voltammogram of *N*-[(2,4-dimethylphenyl)-sulfonyl]threonine in 0.1 M $Et_4N^+Br^-$ in acetonitrile; sweep rate 50 s/in.; abscissa, 0.5 V/in.; Pt cathode and anode; s.s.e. = standard silver electrode, Ag/0.1 M $AgNO_3/CH_3CN$. $E^1_{1/2}$ is the half-wave potential for addition of the first electron; E^1_R is the reduction peak of the first electron; $E^2_{1/2}$ is the half-wave potential for addition of the second electron and is where preparative removal of the sulfonyl group occurs; E^2_R is the reduction peak of the second electron.

Because of the good results reported for electrochemical reductive cleavage of the *N*-arylsulfonyl group[4] and its potential compatibility with the presence of many other functionalities, we applied this method as well to our threonine derivatives. Frequent reference is made to this method, but a clear and precise experimental description could not be found. The basic concepts and operational protocols have recently been well presented,[9] and with this description we developed a convenient and effective procedure.

We began our study by determining the cyclic voltammograms of our derivatives and thus establishing the reduction potentials of the various sulfonamides. Reduction of the sulfonamides is a two-electron process, and two peaks are observed in the voltammogram as illustrated in Figure 1. Table I lists the reduction potentials of all eight compounds. It can clearly be seen that increasing the number of alkyl groups on the benzene ring reduces the potential required to reduce the sulfonyl group. The only apparent deviation is the 2,4,6-trimethyl derivative (entry 6). Undoubtedly the steric bulk of the two *o*-methyl groups leads to a higher energy, and more difficultly achieved, transition state. A (2,4-dimethylphenyl)sulfonyl group, being of lowest reduction potential, appears the most desirable.

Our preparative electrochemistry was done by using the apparatus and system depicted in Figure 2. We performed preparative removal on *N*-(phenylsulfonyl)threonine and *N*-[(2,4-dimethylphenyl)sulfonyl]threonine. These are the derivatives with the highest and lowest reduction potentials, respectively, and thus encompass all our derivatives. A solution of tetraethylammonium bromide in acetonitrile was first preelectrolyzed to remove impurities. Phenol was then added as a proton source to the cathodic chamber, which was again preelectrolyzed to a constant low background level (about 2 mA). Next 100 mg of sample was added to the cathodic solution and was electrolyzed at the

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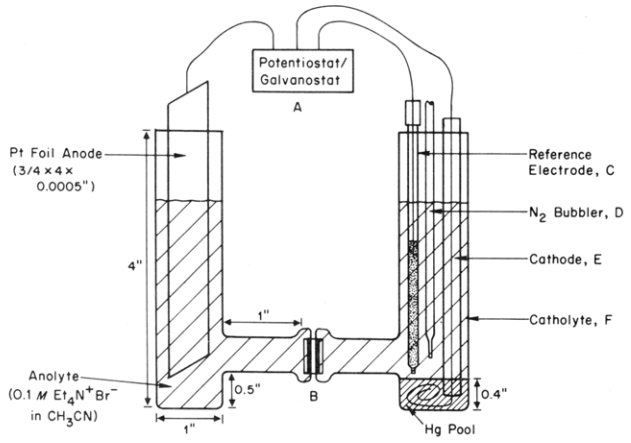

Figure 2. Preparative electrochemical cell. A: Princeton Applied Research Model 173 potentiostat/galvanostat, equipped with a Model 176 current follower. B: Fisher-Porter Solv-Seal joint, 9 mm, with Teflon sleeve and neoprene O-ring seals, fitted with medium-porosity glass frit positioned with Teflon rings. C: IBM Model 8635246 electrode, Ag/0.1 M $AgNO_3/CH_3CN$, with Vycor tip. D: N_2 bubbler, 5.75-in. disposable Pasteur pipet, used for stirring with vigorous N_2 stream. E: cathode; 18-gauge Cu wire, contained unsealed in glass tube. F: catholyte; 0.1 M $Et_4N^+Br^-$ in CH_3CN, 100 mg of *N*-(arylsulfonyl)threonine, and 300 mol % phenol.

proper $E^2_{1/2}$, as determined by voltametry, at a current of about 20 mA. Reaction was judged complete when the current returned to the background level. After isolation and ion-exchange chromatography, threonine was obtained in 85% yield. We found through trial and error that the reaction would only take place in CH_3CN with a Hg pool cathode and phenol as a proton source. A Pt cathode proved ineffective, as did acetic acid as a source of protons.

Thus we have demonstrated a variety of methods that can be used to deprotect *N*-arylsulfonyl groups in hydroxy amino acids that will probably also be compatible with other functionalities. Knowing that a (2,4-dimethylphenyl)sulfonyl group is most easily removed will allow its use in planning a synthetic strategy. With this array of removal methods, the advantages of arylsulfonyl protection for amines can be incorporated into a synthesis with confidence of ultimate deprotection. The possibility also exists for selective removal of one sulfonyl group in the presence of another, depending on the aryl substitution pattern.

Experimental Section

General. Acetonitrile was distilled from CaH_2 immediately prior to use. NMR spectra are reported in ppm (δ) downfield from Me_4Si (^1H). All nonaqueous reactions were carried out under an inert (N_2) atmosphere, and all stirring was done magnetically. Temperatures refer to bath temperatures. Organic solutions were dried over Na_2SO_4 and then evaporated with a Berkeley rotary evaporator (water aspirator) followed by static evaporation with an oil pump. Melting points (Pyrex capillary) were determined on a Büchi melting point apparatus and are uncorrected.

Tetraethylammonium bromide was recrystallized four times from $CHCl_3/CCl_4$ and dried until totally solvent free. Preparative electrochemistry was done by using a Princeton Applied Research Model 173 potentiostat/galvanostat equipped with a Model 179 digital coulometer. Cyclic voltammograms were determined with the above equipment and a PAR Model 175 universal programmer and a Hewlett-Packard Model 7004B X-Y recorder. Elemental analyses and mass spectra were obtained from the Analytical Laboratory, College of Chemistry, University of California, Berkeley.

4-Isopropylbenzenesulfonyl Chloride, 2,5-Dimethylbenzenesulfonyl Chloride, and 4-Methoxybenzenesulfonyl Chloride.[7] To 300 mol % of chlorosulfonic acid at room temperature was added dropwise over 2 h 50 mL of cumene (0.36 mol), *p*-xylene (0.41 mol), or anisole (0.46 mol). The reaction mixture was then stirred for an additional 18 h before being poured onto 300 mL of ice and extracted with EtOAc (3 × 400 mL). The organic phases were combined, dried, and evaporated to yield a viscous yellow oil, which was flash chromatographed (5% EtOAc/hexanes) to yield a clear oil in all cases.

4-Isopropylbenzenesulfonyl chloride: 32.4 g, 0.15 mol, 41% yield; ^1H NMR (250 MHz, $CDCl_3$) δ 1.3 (d, 6 H, J = 6.94 Hz), 3.0 (q, 1 H, J = 6.90 Hz), 7.5 (d, 2 H, J = 8.44 Hz), 7.9 (d, 2 H, J = 8.61 Hz); IR (neat) 2980, 2950, 2900, 1600, 1470, 1430, 1360 (br), 1160 (br), 1090, 1060, 850, 780 cm^{-1}.

2,5-Dimethylbenzenesulfonyl chloride: 39 g, 0.19 mol, 47% yield; ^1H NMR (250 MHz, $CDCl_3$) δ 1.5 (s, 3 H), 1.8 (s, 3 H), 6.4 (d, 1 H), 6.6 (d, 1 H), 7.0 (s, 1 H); IR (neat) 2950, 1500, 1450, 1360, 1300, 1160, 900, 840, 710 cm^{-1}.

4-Methoxybenzenesulfonyl chloride: 49 g, 0.24 mol, 52% yield; ^1H NMR (250 MHz, $CDCl_3$) δ 3.8 (s, 3 H), 6.9 (d, 2 H, J = 9.05 Hz), 7.9 (d, 2 H, J = 9.04 Hz).

2,4-Dimethylbenzenesulfonyl Chloride.[2b] *m*-Xylene (86 mL, 75 g, 0.7 mol) was cooled to −10 °C, and $ClSO_3H$ (142 mL, 250 g, 2.14 mol) was added dropwise over a period of 2 h. The reaction temperature was kept between 10 and 15 °C to prevent solidification. After addition was complete, the reaction mixture was slowly poured onto 300 mL of crushed ice and extracted with EtOAc (3 × 400 mL). The organic phases were combined, dried, and evaporated to yield a yellow oil. Flash chromatography with 5% EtOAc/hexanes yielded 78 g (0.38 mol, 54%) of a clear oil, which crystallized upon cooling to −78 °C: mp 30 °C (lit.[2b] mp 34 °C); ^1H NMR (250 MHz, $CDCl_3$) δ 2.4 (s, 3 H), 2.7 (s, 1 H), 7.2 (d, 1 H), 7.2 (s, 1 H), 7.9 (d, 1 H); IR (neat) 2950, 1610, 1360, 1160, 1050, 840, 660 cm^{-1}.

4-Phenylbenzenesulfonic Acid.[8] To 30.8 g (0.2 mol) of biphenyl in 170 mL of $CHCl_3$ was added dropwise over 1 h a solution of 16.4 mL (28.8 g, 0.25 mol) of $ClSO_3H$ in 25 mL of $CHCl_3$. The reaction mixture was stirred for an additional 0.5 h. Product began to precipitate after 15 min and was later collected and washed with $CHCl_3$ before being dried under vacuum: yield, 32 g, 0.14 mol, 68%; mp 117–119 °C (lit.[8] mp 138 °C); ^1H NMR (250 MHz, acetone-d_6) δ 7.4 (m, 3 H), 7.7 (m, 4 H), 7.9 (m, 2 H).

4-Phenylbenzenesulfonyl Chloride. A solution of 3 g (12.8 mmol) of 4-biphenylsulfonic acid in 50 mL of phenylphosphonic dichloride was heated at 90 °C for 24 h. Cooling to room temperature, pouring onto ice, and stirring for 20 min led to a white precipitate, which was collected by vacuum filtration and yielded the sulfonyl chloride quantitatively: mp 142–143 °C (lit.[10] mp 115 °C); ^1H NMR (250 MHz, acetone-d_6) δ 7.7 (m, 4 H), 7.9 (m, 3 H), 8.0 (d, 1 H), 8.1 (d, 1 H); IR (KBr pellet) 1600, 1460, 1380, 1160, 1080, 1020, 950, 760, 700 cm^{-1}.

***N*-(Phenylsulfonyl)threonine.** L-Threonine (23.8 g, 0.2 mol) was dissolved in 150 mL of H_2O, to this solution were added 47.4 g (0.45 mol) of Na_2CO_3 and 42.4 g (30.63 mL, 0.24 mol) of benzenesulfonyl chloride, and the mixture was stirred for 18 h. After addition of H_2O to dissolve the solids, the aqueous phase was extracted with EtOAc (2 × 100 mL). Acidification to pH 1 (concentrated H_3PO_4) led to crystallization, which was completed by cooling at 5 °C overnight. The yield of *N*-(phenylsulfonyl)-threonine was 23.6 g, 0.13 mol, 65%: mp 145–147 °C; ^1H NMR (250 MHz, acetone-d_6) δ 1.1 (d, 3 H), 3.9 (s, 1 H, br), 3.9 (m, 1 H), 4.1 (m, 1 H), 7.7 (m, 3 H), 7.9 (m, 2 H). Anal. Calcd for $C_{10}H_{13}NO_5S$: C, 46.3; H, 5.1; N, 5.4. Found: C, 46.2; H, 5.1; N, 5.3.

***N*-(*p*-Tolylsulfonyl)threonine.** to 23.8 g (0.2 mol) of L-threonine in 200 mL of H_2O was added 47.4 g (0.45 mol) of Na_2CO_3 with stirring until dissolved, followed by a solution of 40.0 g (0.22 mol) of *p*-toluenesulfonyl chloride in 100 mL of benzene. The reaction mixture was stirred at room temperature overnight. Water was added, and the aqueous phase was washed with benzene (100 mL) before acidification to pH 1 (concentrated H_3PO_4) and refrigeration to facilitate crystallization. The yield of (*p*-tolylsulfonyl)threonine was 39 g, 0.15 mol, 73%: mp 100–102 °C; ^1H NMR (250 MHz, acetone-d_6) δ 1.1 (d, 3 H, J = 6.36 Hz),

(10) Gebauer-Fülnegg, E.; Riesz, E.; Ilse, S. *Monatsh. Chem.* **1928**, *49*, 46.

2.4 (s, 3 H), 3.8 (dd, 1 H, J = 3.02, 9.28 Hz), 4.3 (m, 1 H, J = 3.0, 6.33 Hz), 6.4 (d, 1 H, J = 9.30 Hz), 7.3 (d, 2 H, J = 8.1 Hz), 7.7 (d, 2 H, J = 8.25 Hz). Anal. Calcd for $C_{11}H_{15}NO_5S \cdot {}^1/_2H_2O$: C, 46.8; H, 5.7; N, 5.0. Found: C, 46.9; H, 5.6; N, 4.9.

General Procedure for *N*-(Arylsulfonyl)threonine Formation. This process is suitable for [(4-isopropylphenyl)-, [(2,5-dimethylphenyl)-, [(2,4-dimethylphenyl)-, [(2,4,6-trimethylphenyl)-, and [(4-methoxyphenyl)sulfonyl]threonine. To 500 mg (4.2 mmol) of L-threonine in 40 mL of THF/H_2O, 1/1, were added 1.3 g (10.5 mmol) of Na_2CO_3 and 5.40 mmol of the appropriate arenesulfonyl chloride. The reaction mixture was stirred at room temperature for 18 h, after which it was washed with benzene (1 × 30 mL). The aqueous phase was then acidified to pH 1 (concentrated H_3PO_4) and extracted with EtOAc (3 × 30 mL), which was dried and evaporated to yield the product. Samples for elemental analysis were recrystallized from EtOAc/hexanes.

***N*-[(4-Isopropylphenyl)sulfonyl]threonine:** 800 mg, 2.65 mmol, 63% yield; mp 128 °C dec; ^{1}H NMR (250 MHz, acetone-d_6) δ 1.1 (d, 3 H, J = 6.35 Hz), 1.2 (d, 6 H, J = 6.91 Hz), 3.0 (m, 1 H), 3.8 (d, 1 H, J = 3.05 Hz), 4.1 (m, 1 H), 7.4 (d, 2 H, J = 8.36 Hz), 7.8 (d, 2 H, J = 8.44 Hz). Anal. Calcd for $C_{13}H_{19}NO_5S$: C, 51.8; H, 6.3; N, 4.6. Found: C, 51.8; H, 6.3; N, 4.6.

***N*-[(2,5-Dimethylphenyl)sulfonyl]threonine:** clear oil, 804 mg, 2.9 mmol, 69% yield; ^{1}H NMR (250 MHz, acetone-d_6) δ 1.1 (d, 3 H), 2.3 (s, 3 H), 2.6 (s, 3 H), 3.8 (d, 1 H), 4.1 (m, 1 H), 6.4 (d, 1 H), 6.6 (s, 1 H, br), 7.2 (m, 2 H), 7.9 (s, 1 H); mass spectrum calcd for $C_{12}H_{17}NO_5S$ m/e 287.3280, found 243.0564 ($M^+ - C_2H_4O$), 242.0845 ($M^+ - CHO_2$).

***N*-[(2,4-Dimethylphenyl)sulfonyl]threonine:** 880 mg, 3.06 mmol, 73% yield; mp 132–133 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 1.1 (d, 3 H), 2.3 (s, 3 H), 2.6 (s, 3 H), 3.2 (s, 1 H, br), 3.8 (d, 1 H, J = 3.07 Hz), 4.1 (m, 1 H), 7.1 (d, 1 H, J = 8.3 Hz), 7.2 (s, 1 H), 7.8 (d, 1 H, J = 7.98 Hz). Anal. Calcd for $C_{12}H_{17}NO_5S$: C, 50.2; H, 6.0; N, 4.9. Found: C, 50.0; H, 6.0; N, 4.9.

***N*-[(2,4,6-Trimethylphenyl)sulfonyl]threonine:** 684 mg, 2.27 mmol, 54% yield; mp 165–167 °C dec; ^{1}H NMR (250 MHz, acetone-d_6) δ 1.1 (d, 3 H, J = 6.35 Hz), 2.3 (s, 3 H), 2.6 (s, 6 H), 3.7 (d, 1 H), 4.2 (m, 1 H), 6.2 (d, 1 H, J = 9.37 Hz), 7.0 (s, 2 H). Anal. Calcd for $C_{13}H_{19}NO_5S$: C, 51.8; H, 6.4; N, 4.6. Found: C, 51.8; H, 6.5; N, 4.4.

***N*-[(4-Methoxyphenyl)sulfonyl]threonine:** 600 mg, 2.07 mmol, 50% yield; mp 139–141 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 1.1 (d, 3 H, J = 6.33 Hz), 3.9 (s, 3 H), 3.9 (d, 1 H), 4.2 (m, 1 H), 5.3 (s, 1 H, br), 6.2 (d, 1 H, J = 9.41 Hz), 7.1 (d, 2 H, J = 8.79 Hz), 7.9 (d, 2 H, J = 8.78 Hz). Anal. Calcd for $C_{11}H_{15}NO_6S$: C, 45.7; H, 5.2; N, 4.8. Found: C, 45.7; H, 5.3; N, 4.8.

***N*-[(4-Phenylphenyl)sulfonyl]threonine.** To 500 mg (4.2 mmol) of L-threonine in 40 mL of CH_3CN/H_2O, 1/1, were added 1.3 g (10.5 mmol) of Na_2CO_3 and 1.24 g (5.0 mmol) of 4-biphenylsulfonyl chloride. The reaction mixture was stirred at room temperature for 48 h, the CH_3CN was evaporated, and 10 mL of 2 N NaOH was added. After being washed with benzene (1 × 30 mL), the aqueous phase was acidified to pH 1 (concentrated H_3PO_4) and extracted with EtOAc (3 × 30 mL) which was dried and evaporated to yield 500 mg, 1.48 mmol, 36% of product: mp 184–185 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 1.2 (d, 3 H), 3.9 (d, 1 H), 4.1 (m, 1 H), 6.6 (m, 1 H), 6.7 (s, 1 H), 7.5 (m, 3 H), 7.7 (d, 2 H), 7.9 (d, 2 H), 8.0 (m, 2 H). Anal. Calcd for $C_{16}H_{17}NO_5S$: C, 57.3; H, 5.1; N, 4.2. Found: C, 57.6; H, 4.9; N, 4.5.

Na/NH_3 Removal of *N*-Arylsulfonyl Groups from Threonine. This process was applied to entries 1–4, Table I. To 100 mg of *N*-(arylsulfonyl)threonine in 10 mL of refluxing NH_3 was added Na till a persistent blue color was observed for 10 min. Ammonium chloride was then added to the reaction mixture until the blue color disappeared; the NH_3 then was allowed to evaporate. The residue was dissolved in 5 mL of 1 M H_3PO_4 and washed with EtOAc (1 × 5 mL) before being applied to an ion-exchange column (Dowex 50W-X8, 200–400 mesh, hydrogen form). Salts were eluted with H_2O, and threonine was eluted with 2% NH_3/H_2O, with ninhydrin monitoring of the elution. Evaporation gave pure threonine: ^{1}H NMR (250 MHz, D_2O) δ 1.2 (d, 3 H, J = 6.57 Hz), 3.5 (d, 1 H, J = 4.89 Hz), 4.2 (m, 1 H).

Cleavage of *N*-[(2,4-Dimethylphenyl)sulfonyl]threonine with HBr/HOAc. These conditions are maximized for this derivative only, but can be used as a general procedure. To 1 g (10.6 mmol) of phenol in 10 mL of 32% HBr/HOAc in a flask with a glass stopper was added in three portions over 3 h a solution of 100 mg (0.35 mmol) of *N*-[(2,4-dimethylphenyl)sulfonyl]-threonine in 3 mL of EtOAc. After addition was complete, the reaction mixture was stirred for an additional 15 h at room temperature, then it was cooled to 0 °C, and H_2O (10 mL) was added. The aqueous phas was washed with EtOAc (2 × 15 mL) before being evaporated to dryness in vacuo to yield threonine hydrobromide quantitatively: ^{1}H NMR (250 MHz, D_2O) δ 1.2 (d, 3 H), 3.9 (d, 1 H), 4.3 (m, 1 H). When EtOAc and incremental addition were not used, a mixture of threonine and 2-amino-3-bromobutyric acid hydrobromide was obtained: ^{1}H NMR (250 MHz, D_2O) δ 1.3 (d, 3 H), 4.2 (d, 1 H), 5.4 (m, 1 H).

Sample Preparation for Cyclic Voltammograms.[4a] In general a sample was prepared in 20 mL of CH_3CN that was 0.1 M in $Et_4N^+Br^-$ and 0.01 M in *N*-(arylsulfonyl)threonine. This was transferred to a PAR cyclic voltammogram cell equipped with Pt microelectrodes as cathode and anode and a Ag/Ag^+, $AgNO_3$ reference electrode. Standard conditions used a sweep rate of 100 mV/s at 100 mA and 50 s/in. and swept from 0 to −3 or 3.3 V, depending on the compound. A sample voltammogram is shown in Figure 1.

Preparative Electrochemical Deprotection.[4a] Using the electrode placement indicated in Figure 2, a Hg pool as cathode, and Pt foil as anode, we electrolyzed 40 mL of 0.1 M $Et_4N^+Br^-$ in CH_3CN at −3 V until the background current was less than 2 mA. Phenol (300 mol %) was added to the cathodic chamber, and the system was again electrolyzed to a background of less than 2 mA. *N*-(Arylsulfonyl)threonine (100 mg) was next added to the cathodic chamber and the electrolysis carried out at the appropriate $E^2_{1/2}$. Typically current would increase to 18–20 mA and remain there until reaction was nearly complete. A slow return to 2 mA was then observed. About 120% of the necessary number of coulombs was used. The cathodic solution was then evaporated to dryness in vacuo, and the solid residue was dissolved in 3 mL of 1 M H_3PO_4 and washed with $CHCl_3$. The aqueous phase was then loaded onto an ion-exchange column (Dowex 50W-X8, 20–50 mesh, hydrogen form), salts were eluted with H_2O, and threonine was eluted with 2% NH_3/H_2O, with ninhydrin monitoring of the elution. Yields are given in Table I.

Registry No. *i*-PrPh, 98-82-8; *p*-$Me_2C_6H_4$, 106-42-3; PhOMe, 100-66-3; *m*-$Me_2C_6H_4$, 108-38-3; Ph_2, 92-52-4; *p*-(*i*-Pr)$C_6H_4SO_2Cl$, 54997-90-9; 2,5-$Me_2C_6H_3SO_2Cl$, 19040-62-1; *p*-$MeOC_6H_4SO_2Cl$, 98-68-0; 2,4-$Me_2C_6H_3SO_2Cl$, 609-60-9; *p*-$PhC_6H_4SO_3H$, 2113-68-0; *p*-$PhC_6H_4SO_2Cl$, 1623-93-4; $PhSO_2Cl$, 98-09-9; *p*-$MeC_6H_4SO_2Cl$, 98-59-9; $PhSO_2$-Thr-OH, 93474-55-6; *p*-$MeC_6H_4SO_2$-Thr-OH, 34235-88-6; *p*-(*i*-Pr)$C_6H_4SO_2$-Thr-OH, 113793-27-4; 2,5-$Me_2C_6H_3SO_2$-Thr-OH, 113793-28-5; 2,4-$Me_2C_6H_3SO_2$-Thr-OH, 113793-29-6; 2,4,6-$Me_3C_6H_2SO_2$-Thr-OH, 113793-30-9; *p*-$MeOC_6H_4SO_2$-Thr-OH, 113793-31-0; *p*-$PhC_6H_4SO_2$-Thr-OH, 113793-32-1; 2,4,6-$Me_3C_6H_2SO_2Cl$, 773-64-8; H-Thr-OH, 72-19-5.

Improved, Stereospecific Synthesis of Highly Substituted Butyrolactones via Dyotropic Rearrangement

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Butyrolactones (dihydro-2(3*H*)-furanones) comprise a very important and ubiquitous structural moiety throughout all of organic chemistry, being well-represented in both natural and unnatural molecular families.[1] Many of these substances exhibit important and potentially very useful pharmacological activity,[2] often as a direct result

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