2-[4-(triethylsiloxy)-4-(trifluoromethyl)-2,5-cyclohexadienylidene]propionate (6) in 10 mL of 10% water–90% tetrahydrofuran. The resulting mixture was heated at 70 °C for 1 h, allowed to cool to room temperature, and filtered. The filter cake was washed with tetrahydrofuran. Concentration of the combined filtrates gave a residue, which was poured into 20 mL of 1 N HCl. The aqueous mixture was extracted with three 10-mL portions of diethyl ether. Combination, drying ($MgSO_4$), and concentration of the organic layers gave a residue, which was purified by PTLC (two 2-mm plates eluted with 50% dichloromethane–50% petroleum ether) to give 97 mg (65% yield) of ethyl 2-[4-(trifluoromethyl)phenyl]propionate (7) as a colorless liquid: ^1H NMR ($CDCl_3$) δ 1.21 (t, 3 H, J = 8 Hz), 1.51 (d, 3 H, J = 7 Hz), 3.78 (q, 1 H, J = 7 Hz), 4.12 (m, 2 H), 7.42 (d, 2 H, J = 8 Hz), 7.59 (d, 2 H, J = 8 Hz); ^{19}F NMR ($CDCl_3$) δ -63.0 (s); high-resolution mass spectrum calcd for $C_{12}H_{13}F_3O_2$ 246.0876, found 246.0873.

The following compounds (12a,b) were prepared by similar procedures.

Ethyl 2-[4-(perfluorohexyl)phenyl]propionate (12a): 91% yield; pale yellow oil; ^1H NMR ($CDCl_3$) δ 1.23 (t, 3 H, J = 7 Hz), 1.53 (d, 3 H, J = 8 Hz), 3.78 (q, 2 H, J = 7 Hz), 4.15 (m, 1 H), 7.45 (d, 2 H, J = 9 Hz), 7.75 (d, 2 H, J = 9 Hz); ^{19}F NMR ($CDCl_3$) δ -80.99 (t), -110.66 (m), -122.00 (br s); -122.25 (br s), -123.30 (br s), -126.48 (m); IR (neat) 2985, 1737, 1617, 1240, 1146, 1019, 837, 807, 745, 695 cm^{-1}; high-resolution mass spectrum calcd for $C_{17}H_{13}O_2F_{13}$ 496.0708, found 496.0713.

Ethyl 2-[4-(perfluorooctyl)phenyl]propionate (12b): 85% yield; pale yellow oil; ^1H ($CDCl_3$) δ 1.22 (t, 3 H, J = 7 Hz), 1.53 (d, 3 H, J = 8 Hz), 3.78 (q, 1 H, J = 7 Hz), 4.15 (m, 2 H), 7.45 (d, 2 H, J = 10 Hz), 7.56 (d, 2 H, J = 10 Hz); ^{19}F NMR ($CDCl_3$) δ -81.33 (t), -111.09 (m), -121.64 (br s), -122.43 (br s), -123.28 (br s), -126.62 (br s); IR (neat) 2985, 2938, 1737, 1616, 1421, 1369, 1298, 1209, 1151, 1026, 705, 656, 561 cm^{-1}; high-resolution mass spectrum calcd for $C_{19}H_{13}O_2F_{17}$ 596.0644, found 596.0610.

2-[4-(Trifluoromethyl)phenyl]propionic Acid (8). A mixture of 1.0 g (4.0 mmol) of ethyl 2-[4-(trifluoromethyl)-phenyl]propionate (7), 5 mL of 1 N sodium hydroxide, and 5 mL of ethanol was heated at reflux for 1 h and poured into 30 mL of 1 N HCl. The resulting aqueous mixture was extracted with three 10-mL portions of dichloromethane. Combination, drying ($MgSO_4$), and concentration of the organic layers afforded 0.86 g (95% yield) of 2-[4-(trifluoromethyl)phenyl]propionic acid (8) as a white solid. An analytical sample was obtained by recrystallization from hexane: mp 56–58 °C; ^1H NMR ($CDCl_3$) δ 1.53 (d, 3 H, J = 9 Hz), 3.81 (q, 1 H, J = 9 Hz), 7.44 (d, 2 H, J = 11 Hz), 7.60 (d, 2 H, J = 11 Hz); ^{13}C NMR ($CDCl_3$) δ 18.0 (o), 45.2 (o), 125.6 (o), 125.6 (o), 128.1 (o), 130.0 (o), 143.5 (e), 179.9 (e); ^{19}F NMR ($CDCl_3$) δ -63.2 (s); IR (KBr) 2963, 1712, 1619, 1419, 1327, 1264, 1232, 1166, 1124, 1072, 1019, 843 cm^{-1}; high-resolution mass spectrum calcd for $C_{10}H_9O_2F_3$ 218.0555, found 218.0556. Anal. Calcd C, 55.06; H, 4.16. Found: C, 55.05; H, 4.16.

The following compounds (13a,b) were prepared by similar procedures.

2-[4-(Perfluorohexyl)phenyl]propionic acid (13a): 95% yield; white solid; mp 61–62 °C (dichloromethane); ^1H NMR ($CDCl_3$) δ 1.55 (d, 3 H, J = 7 Hz), 3.83 (q, 1 H, J = 7 Hz), 7.47 (d, 2 H, J = 8 Hz), 7.56 (d, 2 H, J = 8 Hz); ^{13}C NMR ($CDCl_3$) δ 17.6 (o), 44.7 (o), 126.7 (o), 126.8 (o), 126.9 (o), 127.5 (o), 143.3 (e), 179.1 (e); ^{19}F NMR ($CDCl_3$) δ -81.25 (t), -111.10 (m), -122.00 (br s), -122.30 (br s), -123.20 (br s), -126.50 (br s); IR (neat) 2925, 1710, 1620, 1520, 1460, 1420, 1360, 1290, 1220, 1200, 1140, 795, 565, 536 cm^{-1}; high-resolution mass spectrum calcd for $C_{15}H_9O_2F_{13}$ 468.0395, found 468.0433. Anal. Calcd: C, 38.48; H, 1.94. Found: C, 38.70; H, 1.89.

2-[4-(Perfluorooctyl)phenyl]propionic acid (13b): 94% yield; white solid; mp 89–90 °C (dichloromethane–methanol); ^1H NMR ($CDCl_3$) δ 1.55 (d, 3 H, J = 7 Hz), 3.82 (q, 1 H, J = 7 Hz), 7.47 (d, 2 H, J = 9 Hz), 7.57 (d, 2 H, J = 9 Hz); ^{13}C NMR ($CDCl_3$) δ 18.1 (o), 45.2 (o), 127.2 (o), 127.3 (o), 127.4 (o), 143.8 (e), 179.3 (e); ^{19}F NMR ($CDCl_3$) δ -81.36 (t), -111.17 (m), -121.56 (br s), -122.51 (m), -123.48 (br s), -126.72 (br s); IR (neat) 2990, 2940, 1690, 1418, 1300, 1225, 1195, 1140, 860, 805, 560 cm^{-1}; high-resolution mass spectrum calcd for $C_{17}H_9O_2F_{17}$ 568.0331, found 568.0331. Anal. Calcd: C, 35.93; H, 1.60. Found: C, 36.32; H, 1.56.

Registry No. 4, 120120-28-7; 6, 134904-84-0; 7, 134904-85-1; 8, 134904-86-2; 9a, 114934-90-6; 9b, 114934-91-7; 10a, 134904-87-3; 10b, 134904-88-4; 11a, 134904-89-5; 11b, 134904-90-8; 12a, 134904-91-9; 12b, 134904-92-0; 13a, 134904-93-1; 13b, 134904-94-2; $C_6F_{13}I$, 355-43-1; $C_8F_{17}I$, 507-63-1; $(EtO)_2POCH(Me)CO_2Et$, 3699-66-9; 1,4-benzoquinone, 106-51-4.

Supplementary Material Available: ^1H NMR data for compounds 6, 7, 9a, 9b, 10a, 10b, 11a, 11b, 12a, and 12b (10 pages). Ordering information is given on any current masthead page.

S–S Bond Formation Reaction Using Bis(1-methyl-1*H*-tetrazol-5-yl) Disulfide

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Received March 8, 1991

Bis(1-methyl-1*H*-tetrazol-5-yl) disulfide 1 displays extraordinarily high reactivity to nucleophiles, and its reaction with thiols gives disulfides and 1-methyl-1*H*-tetrazole 5-thiol (NMTT).[1] 1 was also found to be a useful reagent for the geometrical isomerization of *Z* olefins to *E* ones in nonpolar solvents.[2] During the isomerization reaction, 1 is considered to dissociate thermally and generate the tetrazolylthio radical (TetS•), which leads to thermal isomerization in a manner similar to the isomerization by iodine.[3] The disulfide–thiol exchange reaction between 1 and dithiothreitol (DTT) was reported to give cyclic disulfide 3 and NMTT via the hypothetical intermediate 2 by intramolecular second disulfide formation as shown in Scheme I.

Our interest was focused on the formation of the unsymmetrical disulfide bond using 1 because the new S–S bond formation is a very significant class of reactions[4] in the synthesis of biologically active compounds,[5] such as atrial natriuretic peptides (ANP).[6] We tried to isolate acyclic A corresponding to the hypothetical intermediate 2 and examine the character of A. Described herein is the application of 1 to the preparation of versatile monotetrazolyl disulfides A, which were found to be useful for the synthesis of unsymmetrical disulfides B as well as symmetrical ones C possessing groups sensitive to other disulfide-forming reagents, such as iodine (Scheme II).

Preparation of Mixed Disulfides 6. Disulfide 1 was prepared in high yield by two-phase oxidation (CH_2Cl_2–H_2O) with $KHCO_3$–Br_2,[7] because 1 decomposed gradually on dissolution in H_2O. The usual oxidation method using $FeCl_3$ or other reagents in an aqueous solution gave mod-

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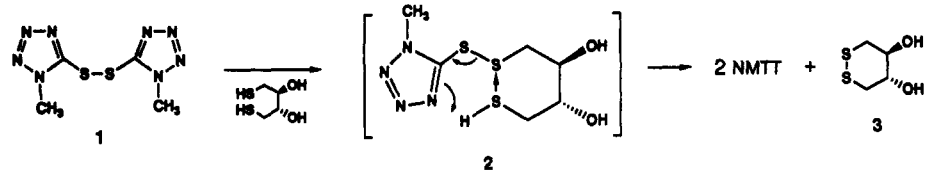
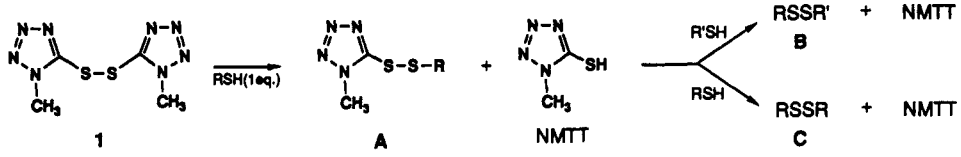
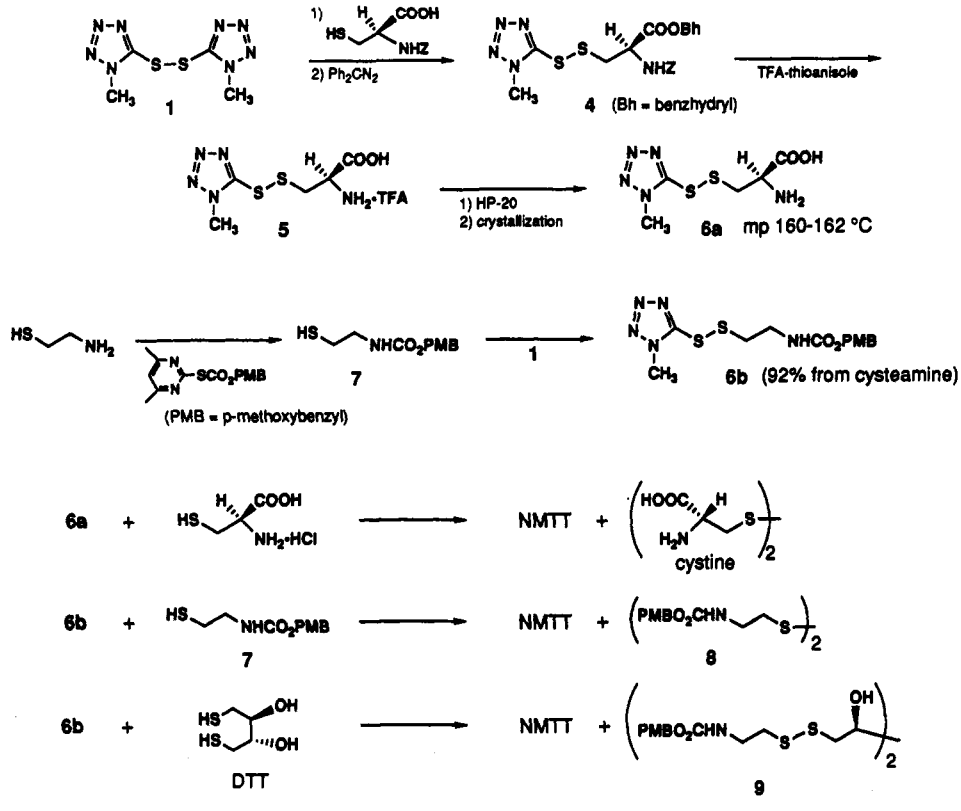
Scheme I



Scheme II



Scheme III



erate results, and repeated crystallization was needed to remove impure substances.[1]

Although the reaction of 1 with 1 equiv of cysteine hydrochloride proceeded smoothly, isolation of the product was very difficult. Therefore, *N*-carbobenzoxy cysteine was chosen as a thiol, and the mixed disulfide obtained was treated with diphenyldiazomethane. Purification by SiO_2 chromatography gave the pure benzhydryl ester 4, the structure of which was characterized after the transformation into **6a** by the usual deprotection procedure. Deprotection of the amino group accompanied by deprotection of the benzhydryl ester group was accomplished with TFA–thioanisole at 40 °C, and the resulting TFA–amine salt 5 was purified by passage through HP-20 resin (eluted with water), which gave pure monotetrazolyl disulfide **6a** as colorless flakes in 34.7% overall yield (Scheme III).

As a second example of a monotetrazolyl disulfide, a cysteamine derivative **6b** was also synthesized as shown in Scheme III. The NMTT group of these compounds is stable only under acidic conditions. After treatment with acids, such as trifluoroacetic acid, no decomposition product was observed on TLC.

Decomposition of mono- and bistetrazolyl disulfides in aqueous media depended on pH. NMTT-disulfide 1 decomposes gradually ($\tau_{1/2}$ ca. 40 h at 25 °C) in dilute sulfuric acid (pH 1.25). At pH 7.39, however, 1 decomposes rapidly (within 30 s at 25 °C).[1] Monotetrazolyl disulfide **6a**, which was stable ($\tau_{1/2}$ > 1 h at 20 °C) at pH 1.25, decomposes gradually ($\tau_{1/2}$ 16.3 min at 20 °C) in phosphate buffer solution (pH 6.80).[8] Although the rate of decomposition of these disulfides was found to be high in a neutral aqueous solution, their reactions with thiols preceded the decomposition and gave the thiol–disulfide exchange products in high yields.

Thiol–Disulfide Exchange Reaction of 6 with Thiols. ^1H NMR spectroscopy showed that the exchange reaction between **6a** and cysteine hydrochloride (1 equiv) proceeded rapidly and quantitatively in D_2O (Scheme III). UV measurements showed that the reaction in phosphate buffer solution (pH 6.8, 0.5×10^{-4} M/L each) ended within

(8) The half-life time was determined by Guggenheim method using UV spectrometer.

30 s at 20 °C and gave NMTT and cystine quantitatively. Isolation of NMTT and cystine by preparative experiment confirmed this reaction. Thus, **6a** should be a useful reagent for the introduction of cysteine[9] without any deprotection procedure.

Reaction of mixed disulfide **6b** with *N*-[[(*p*-methoxybenzyl)oxy]carbonyl]cysteamine furnished *N*-[[(*p*-methoxybenzyl)oxy]carbonyl]cysteamine disulfide quantitatively (Scheme III). On the other hand, reaction of **6b** with 0.5 equiv of DTT afforded NMTT and the new mixed disulfide **9**; no cyclic C_2-symmetrical disulfide **3** was produced. This result shows that disulfide formation easily occurs in the cyclic transient compound **2** where both groups involved are positioned very closely and that the aliphatic disulfides are more stable than the bistetrazolyl or monotetrazolyl disulfides.

The iodine oxidation of thiol peptides, though a very general method, might unfavorably iodinate or oxidize some amino acids such as tyrosine, histidine, and tryptophan.[10] Another problem is the stability of the sulfide groups in methionine toward the iodine oxidation because of the possibility of sulfoxide formation. As acid-sensitive amino-protecting groups are partially or completely removed by hydrogen iodide produced during the iodine oxidation, the reaction has to be carried out in basic media.[11]

Although the autoxidation of thiols using bases or heavy metals as catalysts also gives disulfides, the reaction proceeds sluggishly and nonstoichiometrically with some side reactions occurring frequently.[12] Clearly, selective preparation of unsymmetrical disulfides is very difficult by iodine oxidation or autoxidation of a mixture of two different thiols.

The use of NMTT disulfide for the S–S bond formation reaction has the advantage, as described above, of the reaction proceeding rapidly and stoichiometrically and being able to be carried out under neutral or acidic condition without undesirable side reactions. The extremely high reactivity of monotetrazolyl disulfides to thiols and relatively high stability in an aqueous solution is expected to make it possible to synthesize unsymmetrical or symmetrical cystine peptides in polar solvents such as water by using a stoichiometric amount of NMTT disulfide. Moreover, it is noteworthy that NMTT produced as a byproduct from the disulfide formation can be easily removed from the reaction mixture by utilizing its high solubility in water, especially alkaline solution.

In conclusion, NMTT disulfide **1** is an excellent reagent for the S–S bond formation[13] and gives stoichiometrically unsymmetrical disulfides including intramolecular ones under mild reaction conditions in an aqueous solution. **1** is a useful oxidative reagent for thiols possessing groups sensitive to other disulfide-forming reagents, such as halogen or metallic compounds. However, note that the use of **1** on olefinic compounds at a high temperature causes isomerization of *Z* olefins to *E* ones.

Experimental Section

Reactions using anhydrous solvents (dried over type 4A molecular sieves) were carried out in a nitrogen atmosphere. Melting points are not corrected. Organic extracts were dried over anhydrous magnesium sulfate. Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained on a Varian XL-200 NMR spectrometer with tetramethylsilane as an internal reference. Ultraviolet (UV) spectra were recorded on a Hitachi 323 spectrometer.

Preparation of Cysteinyl 1-Methyl-1*H*-tetrazol-5-yl Disulfide (6a). Bis(1-methyl-1*H*-tetrazol-5-yl) Disulfide (1). To a solution of 1-methyl-1*H*-tetrazole 5-thiol (NMTT), 24.0 g (0.206 mol) in a mixture of 260 mL of 10% aqueous $KHCO_3$ and 300 mL of CH_2Cl_2, was added a solution of bromine (5.30 mL, 0.103 mol) in 20 mL of CH_2Cl_2 over 20 min at 0 °C. CH_2Cl_2 solution was separated and washed with H_2O, dried, and concentrated in vacuo. The residue was crystallized from a mixture of acetone and ether (4:1), giving 14.4 g (60.0%) of **1** as colorless prisms: mp 113–114 °C.[1]

Cysteinyl 1-Methyl-1*H*-tetrazol-5-yl Disulfide (6a). To a solution of disulfide **1** (3.45 g, 15 mmol) in 30 mL of THF was added a solution of *N*-carbobenzoxycysteine[14] (3.83 g, 15 mmol) in 30 mL of THF at rt. After the solution was stirred for 30 min, 4.37 g (15 mmol × 1.5) of diphenyldiazomethane was added to the mixture. When nitrogen gas evolution ceased, the reaction mixture was concentrated in vacuo and the residue was purified by SiO_2 column chromatography (Merck Lobar C, eluted with toluene–AcOEt (5%)) and gave 4.2 g (52.3% from **1**) of mixed disulfide benzhydryl ester **4**: colorless foam; ^{1}H NMR ($CDCl_3$) δ 3.50 (m, 2 H), 3.82 (s, 3 H), 4.82 (m, 1 H), 5.07 (s, 2 H), 6.15 (d, *J* = 8 Hz, 1 H), 6.88 (s, 1 H), 7.17–7.43 (m, 15 H). To a solution of **4** (4.2 g) in 15 mL of thioanisole was added 60 mL of trifluoroacetic acid (TFA), and the mixture was stirred for 2.5 h at 40 °C. Concentration in vacuo and trituration with ether gave salt **5** as a colorless powder, which was dissolved in H_2O and passed through HP-20 resin (100 mL) by elution with H_2O.

Fractions containing the desired product were collected and concentrated to 20–30 mL, giving 1.21 g (65.6% from **4**) of **6a** as colorless flakes: mp 160–162 °C; ^{1}H NMR (D_2O–DCl) δ 3.95, 4.12 (ABq, d, *J* = 15.5, 7.0 Hz, 2 H), 4.56 (s, 3 H), 5.02 (dd, *J* = 5.0, 7.0 Hz, 1 H). Anal. Calcd for $C_5H_9N_5O_2S_2$: C, 25.52; H, 3.86; N, 29.77; S, 27.25. Found: C, 25.31; H, 3.79; N, 29.64; S, 27.18.

***N*-[[(*p*-Methoxybenzyl)oxy]carbonyl]cysteamine (7).** A solution of cysteamine (3.09 g, 40 mmol) and *p*-methoxybenzyl *S*-(4,6-dimethylpyrimidin-2-yl) thiocarbonate (6.09 g, 20 mmol) in 60 mL of AcOEt was stirred for 2 h at 20 °C. The resulting colorless crystals were removed by filtration, and the filtrate was concentrated in vacuo. Purification by SiO_2 chromatography (SiO_2 40 g, eluted with *n*-hexane–AcOEt (25%)) gave 4.7 g (97.9%) of **7** as colorless prisms: mp 40 °C; ^{1}H NMR ($CDCl_3$) δ 1.32 (t, *J* = 9.0 Hz, 1 H), 2.64 (td, *J* = 6.0, 8.0 Hz, 2 H), 3.35 (q, *J* = 6 Hz, 2 H), 3.79 (s, 3 H), 5.03 (s, 2 H), 5.17 (br s, 1 H), 6.80–7.40 (m, 4 H). Anal. Calcd for $C_{11}H_{15}NO_3S$: C, 54.74; H, 6.28; N, 5.81. Found: C, 54.60; H, 6.25; N, 5.77.

2-[[[(*p*-Methoxybenzyl)oxy]carbonyl]amino]ethyl 1-Methyl-1*H*-tetrazol-5-yl Disulfide (6b). To a solution of **1** (460 mg, 2 mmol) in 20 mL of THF was added thiol **7** (482 mg, 2 mmol) at 20 °C, and the mixture was stirred for 15 min then partitioned between AcOEt and 5% aqueous $NaHCO_3$. AcOEt solution was washed with H_2O, dried, and concentrated in vacuo. Chromatographic separation (SiO_2, Merck Lobar B; eluted with toluene–AcOEt (10%)) gave 670 mg (94.2%) of **6b** as a colorless oil. As this product was contaminated with several organic solvents, the samples were dissolved in benzene and concentrated in vacuo. By repeating the procedures, peaks assignable to the organic solvents except benzene were removed in the ^{1}H NMR spectrum: ^{1}H NMR ($CDCl_3$) δ 3.03 (t, *J* = 6.0 Hz, 2 H), 3.56 (q, *J* = 6.0 Hz, 2 H), 3.77 (s, 3 H), 4.00 (s, 3 H), 5.01 (s, 2 H), 5.82 (br s, 1 H), 6.75–7.37 (m, 4.24 H, contains 0.04 mol of benzene). Anal. Calcd for $C_{13}H_{17}N_5O_3S_2 \cdot 0.04C_6H_6$: C, 44.34; H. 4.86; N, 19.53; S, 17.88. Found: C, 44.30; H, 4.84; N, 19.47; S, 17.56.

^{1}H NMR Measurements of the Exchange Reaction between 6a and Cysteine Hydrochloride. To a solution of cysteine hydrochloride (8.8 mg, 0.05 mmol) in 0.5 mL of D_2O was added 11.7 mg (0.05 mmol) of **6a** at rt, and the ^{1}H NMR spectrum of the resulting solution was measured immediately at 37 °C. The

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signals of cystine were observed in place of signals of cysteine hydrochloride, and the signals of **6a** had disappeared. Cysteine hydrochloride: ^{1}H NMR δ 3.65 (d, J = 5.0 Hz, 2 H), 4.84 (t, J = 5.0 Hz, 1 H). Cystine hydrochloride: ^{1}H NMR δ 3.81 (d ABq, A-part, J = 7.5, 16.0 Hz, 1 H), 3.93 (d ABq, B-part, J = 5.0, 16.0 Hz, 1 H), 5.00 (dd, J = 5.0, 7.5 Hz, 1 H). The scale-up experiment also gave cystine quantitatively as a colorless powder.

UV Measurements of the Exchange Reaction between 6a and Cysteine Hydrochloride. A solution of cysteine hydrochloride in a phosphate buffer solution, pH 6.8 (0.05 mmol/L, 2.00 mL), was shaken in a cell with a solution of **6a** (0.05 mmol/L, 2.00 mL) in the same buffer solution at 20 °C, and the mixture was quenched immediately with a phosphate buffer solution (pH 2.0). The UV spectrum of the resulting solution was measured in a rapid-scan mode with a Hitachi 320 UV spectrometer. The absorption of **6a** (end absorption) disappeared, and the absorption of NMTT (λ_{max} 235 nm) was observed quantitatively.

Thiol–Disulfide Exchange Reaction between 7 and 6b. To a solution of disulfide **6b** (355 mg, 1 mmol) in 5 mL of THF was added a solution of thiol **7** (241 mg, 1 mmol) in 2 mL of THF, and the mixture was partitioned between AcOEt and 5% aqueous $NaHCO_3$. The organic solution was washed with H_2O, dried, and concentrated in vacuo. Chromatographic purification (SiO_2 30 g, eluted with CH_2Cl_2–AcOEt (10%)) gave 457 mg (95.0%) of disulfide **8** as colorless flakes: mp 122–123 °C; ^{1}H NMR ($CDCl_3$) δ 2.76 (t, J = 6.0 Hz, 4 H), 3.46 (q, J = 6.0 Hz, 4 H), 3.78 (s, 6 H), 5.02 (s, 4 H), 5.25 (br s, 2 H), 6.75–7.40 (m, 8 H). Anal. Calcd for $C_{22}H_{28}N_2O_6S_2$: C, 54.97; H, 5.88; N, 5.83; S, 13.34. Found: C, 54.99; H, 5.80; N, 5.91; S, 13.37.

Thiol–Disulfide Exchange Reaction between Dithiothreitol (DTT) and 6b. To a solution of **6b** (105 mg, 0.296 mmol) in 5 mL of THF was added 22.8 mg (0.296 mmol × 0.5) of dithiothreitol at rt, and the reaction mixture was partitioned between AcOEt and 5% aqueous $NaHCO_3$. The organic solution was washed with H_2O, dried, and concentrated in vacuo. Crystallization of the residue from ether gave 90.5 mg (96.7%) of **9** as colorless plates: mp 102–103 °C; ^{1}H NMR ($CDCl_3$) δ 2.83 (t, J = 6.2 Hz, 4 H), 2.93 (m, 6 H), 3.52 (q, J = 6.2 Hz, 4 H), 3.81 (s, 6 H), 3.91 (td, J = 6.2, 7.0 Hz, 2 H), 5.03 (s, 4 H), 5.17 (t, J = 6.2 Hz, 2 H), 6.84–6.95 (m, 4 H), 7.20–7.35 (m, 4 H); IR (Nujol) 3350, 1683, 1536, 1031 cm^{-1}. Anal. Calcd for $C_{26}H_{36}N_2O_8S_4$: C, 49.35; H, 5.73; N, 4.43; S, 20.26. Found: C, 49.15; H, 5.72; N, 4.42; S, 20.16.

Enzymatic Resolution of 2-Substituted Oxiranemethanols, a Class of Synthetically Useful Building Blocks Bearing a Chiral Quaternary Center†

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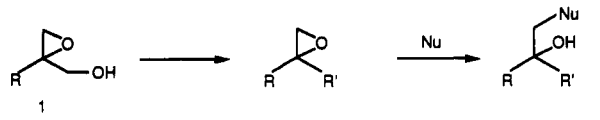
Received February 21, 1991 (Revised Manuscript Received May 31, 1991)

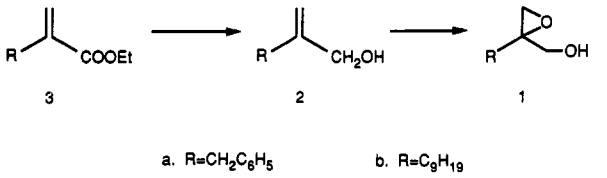
2-Substituted oxiranemethanols **1** can be considered synthetically useful building blocks bearing a quaternary carbon constituted by an oxirane ring. The fact that epoxides are versatile and important intermediates in organic synthesis is well-documented.[1] In the case of 2-substituted oxiranemethanols, the heterocyclic ring can be opened by a variety of reagents, so that synthetic applications can be summarized in Scheme I. Chiral epoxides can be prepared either by the Sharpless asymmetric epoxidation of allylic alcohols[2] or by enzymatic resolution of epoxy esters.[3] We wish to report here that enantiomerically pure oxiranemethanols of type **1** can be obtained by the enzymatic transesterification procedure developed by Wong[4] that we have successfully applied to the resolution of a few 2-methylalkanols.[5] *Pseudomonas fluorescens* lipase (PFL, Fluka, Switzerland) was used as the biocatalyst in an organic solvent, and vinyl acetate was the acyl donor. A few examples of preparation of chiral **1** are already available by the Sharpless asymmetric epoxidation of the proper allylic alcohol **2**.[6] A general access to these methylene alcohols is still lacking,[7] and for the purpose of our work we relied upon a recently described preparation of α-alkylated acrylic esters of type **3**.[8]

These esters could be reduced to the corresponding allylic alcohols **2** with diisobutylaluminum hydride (2 equiv in THF, −30 °C) and further epoxidized to oxiranemethanols by the vanadium acetylacetonate/*tert*-butyl

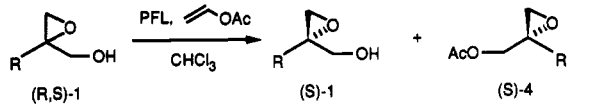
Scheme I



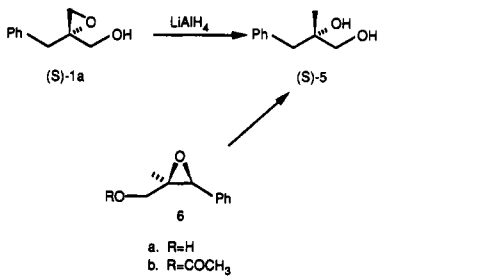
Scheme II



Scheme III



Scheme IV



†This work is dedicated to the memory of Professor Alberto Fiecchi, deceased on January 24, 1991.

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(3) Among many examples of enzymatic resolution of epoxyesters, see: Ladner, W. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1984**, *106*, 7250. Sabbioni, G.; Jones, J. B. *J. Org. Chem.* **1987**, *52*, 4565. Mohr, P.; Rosslein, L.; Tamm, C. *Helv. Chim. Acta* **1987**, *70*, 142. Bianchi, D.; Cabri, W.; Cesti, P.; Francalanci, F.; Rama, F. *Tetrahedron Lett.* **1988**, *29*, 2455. Marples, B. A.; Rogers-Evans, M. *Tetrahedron Lett.* **1989**, *30*, 261.

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(5) (a) Ferraboschi, P.; Grisenti, P.; Santaniello, E. *Synlett* **1990**, 545. (b) Ferraboschi, P.; Grisenti, P.; Manzocchi, A.; Santaniello, E. *J. Org. Chem.* **1990**, *55*, 6214. (c) Santaniello, E.; Ferraboschi, P.; Grisenti, P. *Tetrahedron Lett.* **1990**, *31*, 5657. Note that in the last paper, in the second scheme at p 5659 the stereochemistry of the products has to be reversed. For the corresponding correction, see: *Ibid.* **1991**, *32*(4), 430.

(6) Pfenninger, A. *Synthesis* **1986**, 89.

(7) The method of preparation of the methylene alcohols of type **1** according to Barluenga et al. gave low yields for our compounds **1a** and **1b**. See: Barluenga, J.; Concellon, J. M.; Fernandez-Simon, J. L.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1988**, 536.

(8) Kirschleger, B.; Queignec, R. *Synthesis* **1986**, 926.

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