SYNTHESIS OF *N,N'*-UNSYMMETRICAL DIACYLCYSTINES AND CYSTINE-CONTAINING DIPEPTIDES†

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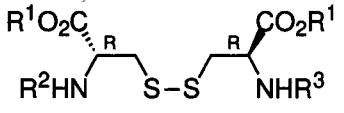
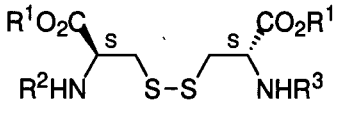
Abstract - *N,N'*-Unsymmetrical diacylcystines ((RR)-**1** and (SS)-**1**) were prepared in good yields by three-step reaction sequences starting from cystine diethyl esters ((RR)-**5** and (SS)-**5**). The key step reaction for diacylcystine synthesis, cleavage of diacylcystine diethyl esters ((RR)-**2** and (SS)-**2**) proceeded with no detectable racemization of the products ((RR)-**1** and (SS)-**1**). Cystine-containing dipeptides ((RRS)-**3**, (RRR)-**3**, and (SSR)-**3**) were also prepared in high yields and in high optical purity.

In recent years, considerable chemical and medicinal interest has been focused on derivatives of diacylcystines and cystine-containing peptides.[1] For the preparation of cystine moiety, the disulfide bond forming reactions from cysteinyl residues have been frequently employed.[2] However, the reactions often involved formation of symmetrical disulfides and a tedious work-up for separation of the desired one from side products. On the other hand, treatment of unsymmetrical cystine derivatives under basic conditions was known to cause elimination and dismutation of the disulfides, and result in racemization and decomposition of the products, and disproportionation to symmetrical disulfides.[3] Synthetic approaches to cystine derivatives (**1** and **3**) bearing free carboxylic acids from their esters (**2** and **4**) have been scarcely investigated.



RR



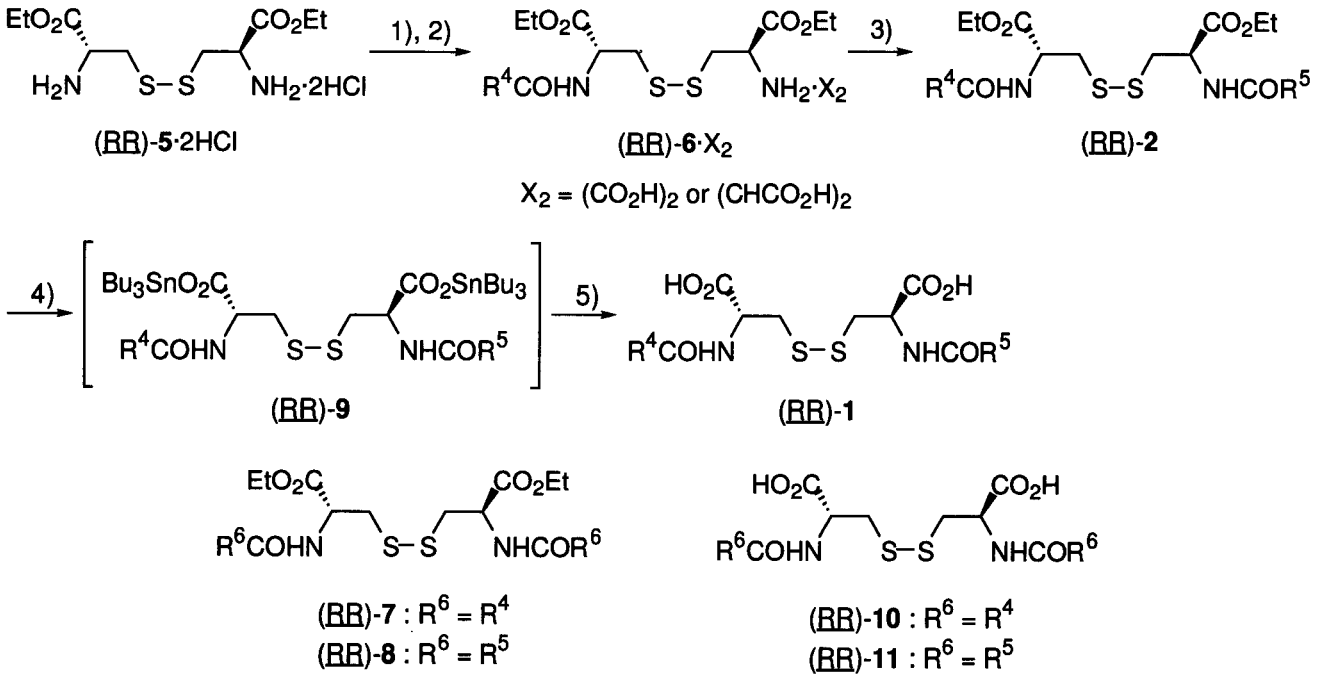
SS

1 : R^1 = H, R^2, R^3 = acyl
2 : R^1 = Et, R^2, R^3 = acyl
1, 2 : $R^2 \neq R^3$

3 : R^1 = H, R^2 = acyl, R^3 = *N*-protected amino acid moiety
4 : R^1 = Et, R^2 = acyl, R^3 = *N*-protected amino acid moiety
5 : R^1 = Et, $R^2 = R^3$ = H

Scheme 1

During the course of our continuing works to search for pharmaceutically significant compounds starting from amino acids,[4] we required a general method for the preparation of *N,N'*-unsymmetrical diacylcystines (**1**) and cystine-containing dipeptides (**3**) with *N*-protected amino acids. We felt that cleavage of their ester derivatives (**2** and **4**) under neutral reaction conditions would provide a more efficient synthesis of **1** and **3**. Here, we describe a new synthetic approach involving monoacylation of cystine diethyl ester (**5**), followed by preparation of *N,N'*-unsymmetrical diacylcystine diester (**2** and **4**) and cleavage of esters with bis(tri-*n*-butyltin)oxide (BBTO)[5] to provide *N,N'*-unsymmetrical diacylcystines (**1** and **3**).



(RR)-**5**·2HCl → (RR)-**6**·X_2 → (RR)-**2**

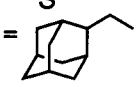
X_2 = $(CO_2H)_2$ or $(CHCO_2H)_2$

(RR)-**9** → (RR)-**1**

(RR)-**7** : $R^6 = R^4$
(RR)-**8** : $R^6 = R^5$

(RR)-**10** : $R^6 = R^4$
(RR)-**11** : $R^6 = R^5$

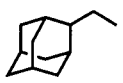
(RR)-**1**, (RR)-**2**, (RR)-**9**

a) R^4 = $PhCH_2CH_2$ R^5 = Ph
b) R^4 = $^tBuCH_2$ R^5 = 
c) R^4 = ^tBu R^5 = 

(RR)-**6**, (RR)-**7**, (RR)-**10**

a) R^4 = $PhCH_2CH_2$
b) R^4 = $^tBuCH_2$
c) R^4 = ^tBu
d) R^4 = ^tBuO

(RR)-**8**, (RR)-**11**

a) R^5 = Ph
b) R^5 = 
c) R^5 = 

1) R^4COCl or $(R^4CO)_2O$, DIPEA (3.3 eq) / CH_2Cl_2 2) Oxalic acid or Fumaric acid
3) R^5COCl, DIPEA (1.1eq) / CH_2Cl_2 4) BBTO / Toluene at 100 °C
5) 10% KF solution and then 5% citric acid solution

Scheme 2

Table 1. Preparation of Monoacylcystine Diethyl Ester ((RR)-6 and (SS)-6)

product	X_2 [a]	yield (%)	$[\alpha]_D^{25}$ (*c* 0.2, MeOH)	mp (℃)
(RR)-**6a**	F	38	-69.5°	118-119
(SS)-**6a**	F	38	+69.9°	118-119
(RR)-**6b**	F	42	-91.7°	104-106
(SS)-**6b**	F	40	+90.8°	103-105
(RR)-**6c**	O	45	-112.5°	129-130
(SS)-**6c**	O	42	+112.7°	129-130
(RR)-**6d**	F	44	-61.5°	121-122
(SS)-**6d**	F	40	+60.4°	120-122

[a] X = F, Fumaric acid. X = O, Oxalic acid.

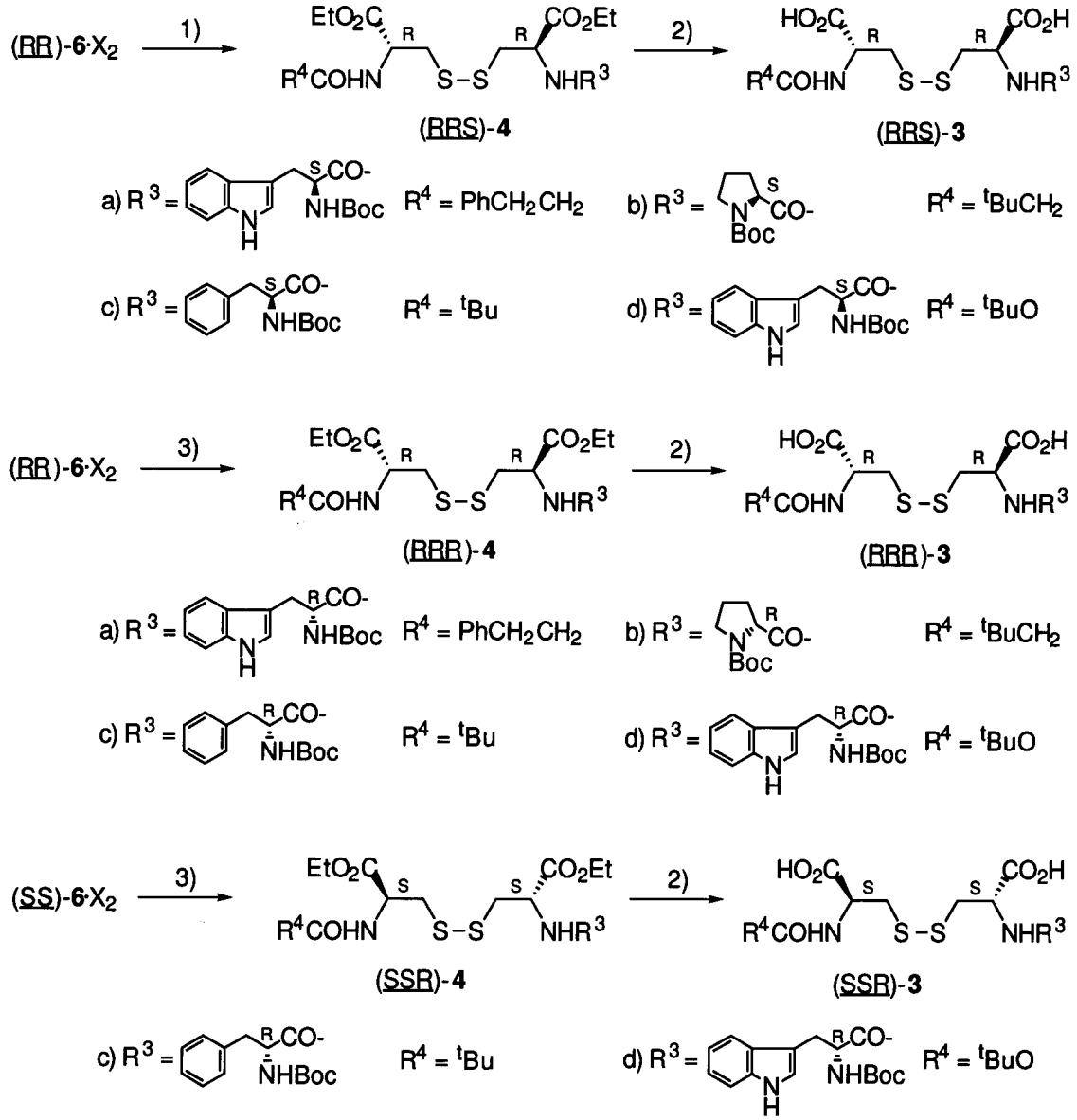
Initially, we investigated the preparation of *N,N'*-unsymmetrical diacyl-L-cystine ((RR)-**1**) from L-cystine diethyl ester ((RR)-**5**) dihydrochloride[6] as shown in Scheme 2. The first-step acylation of (RR)-**5**·2HCl with 1.2 equimolar amounts of acyl chloride (R^4COCl) in the presence of 3.3 equimolar amounts of *N,N'*-diisopropylethylamine (DIPEA) gave a mixture of monoacyl-L-cystine diethyl ester ((RR)-**6**) and symmetrical diacylcystine diethyl ester ((RR)-**7**). After a conventional work-up and subsequent treatment of oxalic acid or fumaric acid, (RR)-**6** was obtained as crystalline salts in 38-45% yields. Monoacyl derivative ((SS)-**6**) was also obtained from D-cystine diethyl ester ((SS)-**5**) under similar conditions. The results are summarized in Table 1. The second-step acylation of (RR)-**6a**·fumarate with benzoyl chloride using 3.2 equimolar amounts of DIPEA gave *N,N'*-unsymmetrical diacyl-L-cystine diethyl ester ((RR)-**2a**) together with a small amount of contaminants, (RR)-**7a** and (RR)-**8a** ((RR)-**2a**:contaminants = 19:1). To avoid disproportionation of the resulting diacylcystine diethyl ester, the acylation was carried out in the presence of equimolar amounts of DIPEA at -78 ℃. The acylation of (RR)-**6a**·fumarate with benzoyl chloride (1.05

Table 2. Preparation and Cleavage of *N,N'*-Unsymmetrical Diacylcystine Diethyl Ester ((RR)-2 and (SS)-2)

product	yield (%)	$[\alpha]_D^{25}$ [a]	mp (℃)	product	yield (%)	$[\alpha]_D^{25}$ [b]	mp (℃)
(RR)-**2a**	81	+53.1°	122-124	(RR)-**1a**	92	-168.2°	170-172 [c]
(SS)-**2a**	85	-53.2°	121-124	(SS)-**1a**	91	+169.4°	170-172 [c]
(RR)-**2b**	80	+51.8°	132-134	(RR)-**1b**	90	-207.5°	184-186
(SS)-**2b**	78	-51.0°	132-134	(SS)-**1b**	91	+210.0°	184-186
(RR)-**2c**	54	+54.0°	111-112	(RR)-**1c**	97	+146.1°	159-161 [c]

[a] *c* 0.2, $CHCl_3$. [b] *c* 0.2, MeOH. [c] 2Dicyclohexylamine (DCHA) salt.

eq.) gave a mixture of (RR)-**2a** and two contaminants (97:3) in 95% yield. Recrystallization of the mixture with AcOEt-Et_2O gave colorless crystals ((RR)-**2a**) in 81% (>99% ee) yield.[7] Similarly, *N,N'*-unsymmetrical diacyl-L-cystine diethyl ester ((RR)-**2b,c**) and D-cystine isomer ((SS)-**2a,b**) were obtained from the corresponding monoacyl derivatives ((RR)-**6b,c** and (SS)-**6a,b**) in good yields. The results are demonstrated in Table 2. Conversion of (RR)-**2** into (RR)-**1** was carried out by use of BBTO in toluene at 100 ℃. The reaction smoothly proceeded to give the intermediary cystine tributyltin ester ((RR)-**9**). By treatment of (RR)-**9** with 10% potassium fluoride (KF) solution, (RR)-**1** was obtained without racemization and dismutation of the product in high yield and in high optical purity.[8] Similarly, *N,N'*-unsymmetrical diacyl-D-cystine ((SS)-**1**) was prepared from (SS)-**2** by cleavage of its ethyl ester with BBTO. The results are summarized in Table 2.



1) *N*-Boc-L-amino acid, HOBT, EDC, CH_2Cl_2
2) BBTO / Toluene at 100 °C, 10% KF solution and then 5% citric acid solution
3) *N*-Boc-D-amino acid, HOBT, EDC, CH_2Cl_2

Scheme 3

Preparation of cystine-containing peptides ((RRS)-**3**) was carried out through the sequence of reactions outlined in Scheme 3. Condensation of (RR)-**6** with *N*-Boc-L-amino acids in the presence of 1-hydroxybenzotriazole (HOBT) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) hydrochloride gave dipeptide diethyl esters ((RRS)-**4**) in 90-95% (>99% de) yields. Conversion of (RRS)-**4** into their tributyltin ester with BBTO in toluene, followed by treatment with 10% KF solution gave (RRS)-**3** in good yields and in high optical purity (>99% de). Similarly, treatment of epimers ((RRR)-**4**) and diastereoisomers ((SSR)-**4**) of (RRS)-**4** with BBTO gave also the corresponding cystine-containing dipeptides ((RRR)-**3** and (SSR)-**3**) in good yields and in high optical purity. The results for preparation and cleavage of cystine-dipeptides diethyl esters ((RRS)-**4**, (RRR)-**4**, and (SSR)-**4**) are summarized in Table 3.

Table 3. Preparation and Cleavage of Cystine-dipeptides Diethyl Ester ((RRS)-4, (RRR)-4, and (SSR)-4)

product	yield (%)	$[\alpha]_D^{25}$ [a]	product	yield (%)	$[\alpha]_D^{25}$ [b]	mp (°C) [c]
(RRS)-**4a**	91	+1.9°	(RRS)-**3a**	82	-105.2°	126-127
(RRR)-**4a**	92	+23.0°	(RRR)-**3a**	84	-93.3°	193-194
(RRS)-**4b**	95	-15.5°	(RRS)-**3b**	93	-213.6°	176-177 [d]
(RRR)-**4b**	95	+94.8°	(RRR)-**3b**	91	-121.0°	198-200
(RRS)-**4c**	92	+23.9°	(RRS)-**3c**	90	+24.0° [a]	145-147
(RRR)-**4c**	92	+43.6°	(RRR)-**3c**	88	+54.8° [a]	155-156
(SSR)-**4c**	91	-23.8°	(SSR)-**3c**	88	-24.3° [a]	145-147
(RRS)-**4d**	92	-79.5° [b]	(RRS)-**3d**	77	-108.0°	127-129
(RRR)-**4d**	90	-64.5° [b]	(RRR)-**3d**	81	-86.0°	179-181
(SSR)-**4d**	91	+80.2° [b]	(SSR)-**3d**	82	+110.2°	128-129

[a] *c* 0.2, $CHCl_3$. [b] *c* 0.2, MeOH. [c] 2DCHA salt. [d] Free carboxylic acid.

EXPERIMENTAL

All melting points were taken in open capillary tubes on a melting point apparatus (Büchi 535) without correction. IR spectra were taken with an Analect RFX-65 spectrophotometer. ^{1}H-NMR spectra were measured with a Gemini (Varian, 300 MHz) spectrometer with tetramethylsilane (TMS) as an internal standard. The MS spectra, atmospheric pressure chemical ionization mass spectra (APCI-MS) and electrospray ionization mass spectra (ESI-MS) were obtained with a SSQ7000C (Finnigan MAT Inc.) and an INCOS50 (Finnigan MAT Inc.) spectrometers. Optical rotation were measured on a Horiba SEPA-200 digital polarimeter. Chiral high-performance liquid chromatographic (HPLC) analysis was done with a Hitachi 638-30 (UV detection). Elemental analysis were obtained by using a Perkin-Elmer 2400, a

Yanagimoto MT-3 or a YEW ion chromato IC-7000. In general, reactions were carried out in dry solvents under argon atmosphere unless otherwise mentioned.

Preparation of *N*-Monoacylcystine Diethyl Esters ((RR)-6 and (SS)-6)

N-Monoacylcystine diethyl esters ((RR)-**6** and (SS)-**6**) were prepared by acylation of cystine diethyl esters ((RR)-**5** and (SS)-**5**) dihydrochloride with the corresponding acid chlorides in CH_2Cl_2 in the presence of DIPEA. The general procedure is exemplified by the preparation of *N*-(2,2-dimethyl)propanoyl-L-cystine diethyl ester ((RR)-**6c**) oxalate. A solution of 2,2-dimethylpropanoyl chloride (1.57 g, 13.0 mmol) in CH_2Cl_2 (15 mL) was added to a stirred solution of (RR)-**5**·2HCl (4.0 g,10.8 mmol) and DIPEA (4.62 g, 35.7 mmol) in CH_2Cl_2 (150 mL) at -30 ℃. After being stirred for 30 min at the same temperature, the reaction was quenched by adding H_2O (50 mL). The aqueous layer was separated and adjusted to pH 2 with 10% HCl solution and extracted with AcOEt. (The AcOEt layer gave 1.7 g (34%) of *N*,*N*-bis(2,2-dimethylpropanoyl)-L-cystine diethyl ester ((RR)-**7c**)). The acidic aqueous layer was adjusted to pH 6 with sat. $NaHCO_3$ solution and extracted with AcOEt. The organic layer was dried over Na_2SO_4. Then, a solution of oxalic acid (486 mg, 5.40 mmol) in MeOH (15 mL) was added to the organic layer. Evaporation of the solvent and recrystallization of the residue from AcOEt-Et_2O gave 2.30 g (45%, >99% ee) of (RR)-**6c**·oxalate as colorless needles, mp 129-130 ℃. IR (Nujol) cm^{-1}: 3445, 3217, 1732, 1724, 1703, 1661, 1624. APCI-MS *m/z*: 381 (MH^+). ^{1}H-NMR (DMSO-d_6) δ: 1.12 (9H, s), 1.18, 1.24 (6H, each t, *J* = 7.1 Hz), 3.03-3.24 (4H, m), 4.09, 4.19 (4H, each q, *J* = 7.1 Hz), 4.15 (1H, m), 4.50 (1H, m), 6.75 (4H, br, D_2O-exchangeable), 7.90 (1H, quasi d, D_2O-exchangeable). *Anal.* Calcd for $C_{15}H_{28}N_2O_5S_2\cdot C_2H_2O_4$: C, 43.39; H, 6.43; N, 5.95; S, 13.65. Found: C, 43.23; H, 6.39; N, 5.81; S, 13.79. Chiral HPLC analysis was carried out under the following conditions: column, Opti-Pak CE (ID 3.9 x 150 mm); eluent, MeOH/aq.$HClO_4$ (pH 2)(3/17), 1.0 mL/min; detector, 210 nm; retention time, (SS)-**6c** (13 min), (RR)-**6c** (28 min).

N-(3-Phenyl)propanoyl-L-cystine Diethyl Ester ((RR)-6a)

This compound was obtained from (RR)-**5**·2HCl and 3-phenylpropanoyl chloride. Treatment of (RR)-**6a** with fumaric acid gave (RR)-**6a**·fumarate in 38% yield.[9] mp 118-119 ℃. IR (Nujol) cm^{-1}: 3329, 1743, 1658, 1615. APCI-MS *m/z*: 429 (MH^+). ^{1}H-NMR (DMSO-d_6) δ: 1.19, 1.21 (6H, each t, *J* = 7.1 Hz), 2.44 (2H, m), 2.82 (2H, quasi t), 2.90-3.14 (4H, m), 3.69 (1H, quasi t), 4.10, 4.12 (4H, each q, *J* = 7.1 Hz), 4.54 (1H, m), 6.60 (2H, s), 7.14-7.30 (5H, m), 8.45 (1H, quasi d, D_2O-exchangeable). *Anal.* Calcd for $C_{19}H_{28}N_2O_5S_2\cdot C_4H_4O_4$: C, 50.72; H, 5.92; N, 5.14; S, 11.77. Found: C, 50.49; H, 5.87; N, 5.07; S, 11.87.

N-(3-Phenyl)propanoyl-D-cystine Diethyl Ester ((SS)-6a)

This compound was obtained from (SS)-**5**·2HCl and 3-phenylpropanoyl chloride. Treatment of (SS)-**6a** with fumaric acid gave (SS)-**6a**·fumarate in 38% yield.[9] mp 118-119 ℃. IR (Nujol) cm^{-1}: 3325, 1744, 1657, 1614. APCI-MS *m/z*: 429 (MH^+). ^{1}H-NMR (DMSO-d_6) δ: 1.18, 1.21 (6H, each t, *J* = 7.1 Hz), 2.44 (2H, m), 2.28 (2H, quasi t), 2.90-3.14 (4H, m), 3.66 (1H, quasi t), 4.10, 4.12 (4H, each q, *J* = 7.1

Hz), 4.54 (1H, m), 6.60 (2H, s), 7.14-7.30 (5H, m), 8.44 (1H, quasi d, D_2O-exchangeable). *Anal.* Calcd for $C_{19}H_{28}N_2O_5S_2 \cdot C_4H_4O_4$: C, 50.72; H, 5.92; N, 5.14; S, 11.77. Found: C, 50.45; H, 5.62; N, 4.94; S, 11.84.

N-(3,3-Dimethyl)butyryl-L-cystine Diethyl Ester ((RR)-6b)

This compound was obtained from (RR)-**5**·2HCl and 3,3-dimethylbutyryl chloride. Treatment of (RR)-**6b** with fumaric acid gave (RR)-**6b**·fumarate in 42% (>99% ee) yield. mp 104-106 ℃. IR (Nujol) cm^{-1}: 3300, 1743, 1651. APCI-MS *m/z*: 395 (MH^+). ^{1}H-NMR (DMSO-d_6) δ: 0.97 (9H, s), 1.19, 1.21 (6H, each t, J = 7.1 Hz), 2.01 (2H, s), 2.90-3.16 (4H, m), 3.67 (1H, quasi t), 4.10, 4.12 (4H, each q, J = 7.1 Hz), 4.53 (1H, m), 6.60 (2H, s), 8.27 (1H, quasi d, D_2O-exchangeable). *Anal.* Calcd for $C_{16}H_{30}N_2O_5S_2 \cdot C_4H_4O_4$: C, 47.04; H, 6.71; N, 5.49; S, 12.56. Found: C, 46.99; H, 6.67; N, 5.40; S, 12.71. Chiral HPLC analysis was carried out under the following conditions: column, Opti-Pak CE (ID 3.9 x 150 mm); eluent, MeOH/ aq. $HClO_4$ (pH 2)(3/17), 1.2 mL/min; detector, 210 nm; retention time, (SS)-**6b** (25 min), (RR)-**6b** (54 min).

N-(3,3-Dimethyl)butyryl-D-cystine Diethyl Ester ((SS)-6b)

This compound was obtained from (SS)-**5**·2HCl and 3,3-dimethylbutyryl chloride. Treatment of (SS)-**6b** with fumaric acid gave (SS)-**6b**·fumarate in 40% (>99% ee) yield. mp 103-105 ℃. IR (Nujol) cm^{-1}: 3296, 1743, 1651. APCI-MS *m/z*: 395 (MH^+). ^{1}H-NMR (DMSO-d_6) δ: 0.96 (9H, s), 1.19, 1.21 (6H, each t, J = 7.1 Hz), 2.01 (2H, s), 2.90-3.16 (4H, m), 3.67 (1H, quasi t), 4.10, 4.12 (4H, each q, J = 7.1 Hz), 4.52 (1H, m), 6.61 (2H, s), 8.27 (1H, quasi d, D_2O-exchangeable). *Anal.* Calcd for $C_{16}H_{30}N_2O_5S_2 \cdot C_4H_4O_4$: C, 47.04; H, 6.71; N, 5.49; S, 12.56. Found : C, 46.84; H, 6.66; N, 5.41; S, 12.67.

N-(2,2-Dimethyl)propanoyl-D-cystine Diethyl Ester ((SS)-6c)

This compound was obtained from (SS)-**5**·2HCl and 2,2-dimethylpropanoyl chloride. Treatment of (SS)-**6c** with oxalic acid gave (SS)-**6c**·oxalate in 42% (>99% ee) yield. mp 129-130 ℃. IR (Nujol) cm^{-1}: 3445, 3217, 1724, 1703, 1661, 1624. APCI-MS *m/z*: 381 (MH^+). ^{1}H-NMR (DMSO-d_6) δ: 1.12 (9H, s), 1.18, 1.24 (6H, each t, J = 7.1 Hz), 3.03-3.25 (4H, m), 4.09, 4.19 (4H, each q, J = 7.1 Hz), 4.15 (1H, m), 4.50 (1H, m), 6.75 (4H, br, D_2O-exchageable), 7.91 (1H, br d, D_2O-exchangeable). *Anal.* Calcd for $C_{15}H_{28}N_2O_5S_2 \cdot C_2H_2O_4$: C, 43.39; H, 6.43; N, 5.95; S, 13.56. Found: C, 43.56; H, 6.42; N, 5.83; S, 13.60.

N-tert-Butoxycarbonyl-L-cystine Diethyl Ester ((RR)-6d)

This compound was obtained from ((RR)-**5**·2HCl and Boc_2O. Treatment of (RR)-**6d** with fumaric acid gave (RR)-**6d**·fumarate in 44% yield.[10] mp 121-122 ℃. IR (Nujol) cm^{-1}: 3377, 1746, 1693, 1655, 1618. APCI-MS *m/z*: 397 (MH^+). ^{1}H-NMR (DMSO-d_6) δ: 1.19, 1.21 (6H, each t, J = 7.1 Hz), 1.39 (9H, s), 2.94 (2H, m), 3.01-3.12 (2H, m), 3.69 (1H, quasi t), 4.06-4.16 (4H, m), 4.24 (1H, m), 6.60 (2H, s), 7.37 (1H, quasi d, D_2O-exchangeable). *Anal.* Calcd for $C_{15}H_{28}N_2O_6S_2 \cdot C_4H_4O_4$: C, 44.52; H, 6.29; N, 5.46; S, 12.51. Found: C, 44.38; H, 6.22; N, 5.53; S, 12.59.

N-*tert*-Butoxycarbonyl-D-cystine Diethyl Ester ((SS)-6d)

This compound was obtained from (SS)-**5**·2HCl and Boc_2O. Treatment of (SS)-**6d** with fumaric acid gave (SS)-**6d**·fumarate in 40% yield.[10] mp 120-122 ℃. IR (Nujol) cm^{-1}: 3376, 1746, 1692, 1655, 1617. APCI-MS *m/z*: 397 (MH^+). ^{1}H-NMR (DMSO-d_6) δ :1.19,1.21 (6H, each t, *J* = 7.1 Hz), 1.39 (9H, s), 2.94 (2H, m), 3.01-3.12 (2H, m), 3.69 (1H, quasi t), 4.06-4.16 (4H, m), 4.24 (1H, m), 6.60 (2H, s), 7.35 (1H, quasi d, D_2O-exchageable). *Anal.* Calcd for $C_{15}H_{28}N_2O_6S_2 \cdot C_4H_4O_4$: C, 44.52; H, 6.29; N, 5.46; S, 12.51. Found: C, 44.46; H, 6.28; N, 5.32, S, 12.74.

Preparation of *N,N'*-Unsymmetrical Diacylcystine Diethyl Esters ((RR)-2 and (SS)-2)

N,N'-Unsymmetrical diacylcystine diethyl esters ((RR)-**2** and (SS)-**2**) were prepared from monoacylcystine diethyl esters ((RR)-**6** and (SS)-**6**) with the corresponding acid chloride in CH_2Cl_2 in the presence of equimolar amounts of DIPEA. The general procedure is exemplified by the preparation of *N*-3-phenylpropanoyl-*N'*-benzoyl-L-cystine diethyl ester ((RR)-**2a**). A solution of DIPEA (166 mg, 1.29 mmol) in CH_2Cl_2 (0.5 mL) was added to a stirred suspension of (RR)-**6a**·fumarate (700 mg, 1.29 mmol) and benzoyl chloride (190 mg, 1.35 mmol) in CH_2Cl_2 (25 mL) at -78 °C. After being stirred for 30 min at -78 °C, the reaction was quenched by adding H_2O. The organic layer was washed with H_2O, and dried over Na_2SO_4. Evaporation of the solvent and recrystallization of the residue with AcOEt-Et_2O gave 554 mg (81%, >99% ee) of (RR)-**2a**, mp 122-124 °C. IR (Nujol) cm^{-1}: 3325, 1751, 1741, 1651, 1635. APCI-MS *m/z*: 533 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 1.26, 1.32 (6H, each t, *J* = 7.1 Hz), 2.54 (2H, m), 2.95 (2H, quasi t), 3.13 (1H, m), 3.21-3.35 (3H, m), 4.19 (2H, quasi q), 4.27 (2H, q, *J* = 7.1 Hz), 4.84 (1H, m), 5.03 (1H, m), 6.47 (1H, quasi d, D_2O-exchangeable), 7.07 (1H, quasi d, D_2O-exchangeable), 7.15-7.30 (5H, m), 7.41-7.56 (3H, m), 7.85 (2H, m). *Anal.* Cacld for $C_{26}H_{32}N_2O_6S_2$: C, 58.63; H, 6.06; N, 5.26; S, 12.05. Found: C, 58.41; H, 6.01; N, 5.22; S, 12.17. HPLC analysis was carried out under the following conditions: column, L-column ODS (ID 4.6 x 150 mm); eluent, MeCN/H_2O (1/1), 1.0 mL/min; detector, 225 nm; retention time, (RR)-**8a** (9 min), (RR)-**2a** (12 min), (RR)-**7a** (16 min). Chiral HPLC analysis was carried out under the following conditions: column, CHIRALCEL OD-RH (ID 4.6 x 150 mm); eluent, MeCN/H_2O (9/11), 0.5 mL/min; detector, 225 nm; retention time, (SS)-**2a** (26 min), (RR)-**2a** (29 min).

N-3-Phenylpropanoyl-*N'*-benzoyl-D-cystine Diethyl Ester ((SS)-2a)

This compound was obtained from (SS)-**6a**·fumarate and benzoyl chloride in 85% (>99% ee) yield. mp 121-124 ℃. IR (Nujol) cm^{-1}: 3326, 1751, 1741, 1650, 1635. APCI-MS *m/z*: 533 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 1.26, 1.32 (6H, each t, *J* = 7.1 Hz), 2.54 (2H, m), 2.94 (2H, quasi t), 3.13(1H, m), 3.21-3.35 (3H, m), 3.30 (2H, m), 4.19 (2H, quasi q), 4.27 (2H, q, *J* = 7.1 Hz), 4.87 (1H, m), 5.03 (1H, m), 6.46 (1H, quasi d, D_2O-exchangeable), 7.07 (1H, quasi d, D_2O-exchangeable), 7.15-7.30 (5H, m), 7.41-7.56 (3H, m), 7.84 (2H, m). *Anal.* Calcd for $C_{26}H_{32}N_2O_6S_2$: C, 58.63; H, 6.06; N, 5.26; S, 12.05. Found: C, 58.64; H, 5.81; N, 5.22; S, 12.29.

N-(3,3-Dimethyl)butyryl-*N'*-thenoyl-L-cystine Diethyl Ester ((RR)-2b)

This compound was obtained from (RR)-**6b**·fumarate and thenoyl chloride in 80% (>99% ee) yield. mp

132-134 ℃. IR (Nujol) cm^{-1}: 3309, 1725, 1650, 1632. APCI-MS *m/z*: 505 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 1.04 (9H, s), 1.28, 1.32 (6H, each t, *J* = 7.1 Hz), 2.12 (2H, s), 3.23 (2H, quasi q), 3.32 (2H, quasi d), 4.20, 4.27 (4H, each quasi q), 4.85 (1H, m), 5.01 (1H, m), 6.36 (1H, d, *J* = 7.3 Hz, D_2O-exchangeable), 6.98 (1H, d, *J* = 7.3 Hz, D_2O-exchangeable), 7.10 (1H, dd, *J* = 3.7, 4.9 Hz), 7.52 (1H, dd, *J* = 1.1, 4.9 Hz), 7.63 (1H, dd, *J* = 1.1, 3.7 Hz). *Anal.* Calcd for $C_{21}H_{32}N_2O_6S_3$: C, 49.98; H, 6.34; N, 5.55; S, 19.06. Found: C, 50.15; H, 6.32; N, 5.43; S, 19.29. HPLC analysis was carried out under the following conditions: column, L-column ODS (ID 4.6 x 150 mm); eluent, MeCN/H_2O (1/1), 1.0 mL/min; detector, 225 nm; retention time, (RR)-**8b** (8 min), (RR)-**2b** (10 min), (RR)-**7b** (13 min). Chiral HPLC analysis was carried out under the following conditions: column, CHIRALCEL OD-RH (ID 4.6 x 150 mm); eluent, MeCN/H_2O/MeOH (3/5/2), 0.5 mL/min; detector, 250 nm; retention time, (SS)-**2b** (28 min), (RR)-**2b** (31 min).

N-(3,3-Dimethyl)butyryl-*N'*-thenoyl-L-cystine Diethyl Ester ((SS)-2b)

This compound was obtained from (SS)-**6b**·fumarate and thenoyl chloride in 78% (>99% ee) yield. mp 132-134 ℃. IR (Nujol) cm^{-1}: 3310, 1725, 1651, 1633. APCI-MS *m/z* 505 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 1.04 (9H, s), 1.28, 1.32 (6H, each t, *J* = 7.1 Hz), 2.12 (2H, s), 3.23 (2H, quasi q), 3.32 (2H, quasi d), 4.20, 4.27 (4H, each quasi q), 4.85 (1H, m), 5.01 (1H, m), 6.35 (1H, d, *J* = 7.2 Hz, D_2O-exchangeable), 6.97 (1H, d, *J* = 7.2 Hz, D_2O-exchangeable), 7.10 (1H, dd, *J* = 3.7, 4.9 Hz), 7.52 (1H, dd, *J* = 1.1, 4.9 Hz), 7.63 (1H, dd, *J* = 1.1, 3.7 Hz). *Anal.* Calcd for $C_{21}H_{32}N_2O_6S_3$: C, 49.98; H, 6.34; N, 5.55; S, 19.06. Found: C, 49.83; H, 6.35; N, 5.49; S, 19.04.

N-(2,2-Dimethyl)propanoyl-*N'*-(2-adamantyl)acetyl-L-cystine Diethyl Ester ((RR)-2c)

This compound was obtained from (SS)-**6c**·oxalate and 2-adamantylacetyl chloride in 54% yield.[11] mp 111-112 ℃. IR (Nujol) cm^{-1}: 3336, 3314, 1745, 1699, 1639. APCI-MS *m/z*: 557 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 1.23 (9H, s), 1.29, 1.30 (6H, each t, *J* = 7.1 Hz), 1.57 (2H, m), 1.69-1.92 (12H, m), 2.26 (1H, m), 2.39-2.43 (2H, m), 3.16-3.29 (4H, m), 4.17-4.27 (4H, quasi d), 4.77-4.87 (2H, m), 6.44 (1H, d, *J* = 7.3 Hz, D_2O-exchangeable), 6.48 (1H, d, *J* = 7.3 Hz, D_2O-exchangeable). *Anal.* Calcd for $C_{27}H_{44}N_2O_6S_2$: C, 58.24; H, 7.97; N, 5.03; S, 11.52. Found: C, 58.21; H, 8.00; N, 4.97; S, 11.72. HPLC analysis was carried out under the following conditions: column, L-column ODS (ID 4.6 x 150 mm); eluent, MeCN/H_2O (13/7), 1.0 mL/min; detector, 210 nm; retention time, (RR)-**7c** (4 min), (RR)-**2c** (10 min), (RR)-**8c** (31 min).

Preparation of *N,N'*-Unsymmetrical Diacylcystine ((RR)-1 and (SS)-1)

N,N'-Unsymmetrical diacylcystines ((RR)-**1** and (SS)-**1**) were prepared by treatment of cystine esters ((RR)-**2** and (SS)-**2**) with BBTO in toluene. The general procedure is exemplified by preparation of *N*-3-phenylpropanoyl-*N'*-benzoyl-L-cystine ((RR)-**1a**). A solution of (RR)-**2a** (450 mg, 0.85 mmol) and BBTO (5.04 g, 8.45 mmol) in toluene (40 mL) was stirred for 15 h at 100 °C. The solvent was removed and the oily residue was dissolved in AcOEt (40 mL). 10% KF solution (40 mL) was added to the AcOEt solution and the mixture was stirred for 1 h at rt. The resulting insoluble organotin fluoride was removed by

filtration. The aqueous layer was separated from the filtrate and adjusted to pH 3 with 5% citric acid solution and extracted with AcOEt. The organic layer was washed with sat.$(NH_4)_2SO_4$ solution and dried over Na_2SO_4. Evaporation of the AcOEt gave 373 mg (92%, >99% ee) of (RR)-**1a** as a foam. IR (Nujol) cm^{-1}: 3288, 1723, 1683, 1603. ESI-MS *m/z*: 475 (M^+-H). ^{1}H-NMR (DMSO-d_6) δ: 2.40 (2H, m), 2.78 (2H, m), 2.92 (1H, m), 3.07-3.20(2H, m), 3.26 (1H, m), 4.52 (1H, m), 4.65(1H, m), 7.12-7.28 (5H, m), 7.49-7.59 (3H, m), 7.87 (2H, m), 8.32 (1H, d, *J* = 7.9 Hz, D_2O-exchageable), 8.80 (1H, d, *J* = 8.1 Hz, D_2O-exchangeable), 12.90 (2H, br, D_2O-exchangeable). HPLC analysis was carried out under the following conditions: column, L-column ODS (ID 4.6 x 150 mm); eluent, MeCN/ 20mM NaH_2PO_4 (pH 3)(3/7), 1.0 mL/min; detector, 225 nm; retention time, (RR)-**11a** (6 min), (RR)-**1a** (13 min), (RR)-**10a** (22 min). Chiral HPLC analysis was carried out under the following conditions: column, CHIRALCEL OJ-R (ID 4.6 x 150 mm); eluent, MeCN/ 0.5M $NaClO_4$ (pH 2)(3/7), 0.5 mL/min; detector, 225 nm; retention time, (SS)-**1a** (10 min), (RR)-**1a** (11 min). Treatment of (RR)-**1a** with dicyclohexylamine (DCHA) gave (RR)-**1a**·2DCHA in a quantitative yield, mp 170-172 °C. *Anal.* Calcd for $C_{22}H_{24}N_2O_6S_2 \cdot 2C_{12}H_{23}N \cdot 0.5H_2O$: C, 65.14; H, 8.44; N, 6.61; S, 7.56. Found: C, 65.26; H, 8.31; N, 6.40; S, 7.55.

N-3-Phenylpropanoyl-*N* '-benzoyl-D-cystine ((SS)-1a)

This compound was obtained by treatment of (SS)-**2a** with BBTO in 91% (>99% ee) yield as a foam. IR (Nujol) cm^{-1}: 3304, 1725, 1633, 1604. ESI-MS *m/z*: 475 (M^+-H). ^{1}H-NMR (DMSO-d_6) δ: 2.40 (2H, m), 2.79 (2H, m), 2.92 (1H, m), 3.07-3.20 (2H, m), 3.26 (1H, m), 4.52 (1H, m), 4.69 (1H, m), 7.12-7.28 (5H, m), 7.45-7.59 (3H, m), 7.87 (2H, m), 8.32 (1H, d, *J* = 7.9 Hz, D_2O-exchageable), 8.80 (1H, d, *J* = 8.1 Hz, D_2O-exchangeable), 12.90 (2H, br, D_2O-exchangeable). Treatment of (SS)-**1a** with DCHA gave (SS)-**1a**·2DCHA in a quantitative yield, mp 170-172 °C. *Anal.* Calcd for $C_{22}H_{26}N_2O_6S_2 \cdot 2C_{12}H_{23}N \cdot H_2O$: C, 64.45; H, 8.47; N, 6.54; S,7.48. Found: C, 64.64; H, 8.33; N, 6.47; S, 7.64.

N-(3,3-Dimethyl)butyryl-*N* '-thenoyl-L-cystine ((RR)-1b)

This compound was obtained by treatment of (RR)-**2b** with BBTO in 90% (>99% ee) yield. mp 184-186 °C. IR (Nujol) cm^{-1}: 3382, 3324, 1749, 1716, 1618. ESI-MS *m/z*: 447 (M^+-H). ^{1}H-NMR (DMSO-d_6) δ: 0.94 (9H, s), 1.99 (2H, s), 2.92 (1H, m), 3.12-3.28 (3H, m), 4.48 (1H, m), 4.65 (1H, m), 7.16 (1H, dd, *J* = 3.9, 5.0 Hz), 7.79 (1H, dd, *J* =1.1, 5.0 Hz), 7.82 (1H, dd, *J* = 1.1, 3.9 Hz), 8.12 (1H, d, *J* = 7.9 Hz, D_2O-exchangeable), 8.81 (1H, d, *J* = 8.1 Hz, D_2O-exchangeable), 12.90 (2H, br, D_2O-exchangeable). *Anal.* Calcd for $C_{17}H_{24}N_2O_6S_3$: C, 45.52; H, 5.39; N, 6.25; S, 21.44. Found: C, 45.68; H, 5.30; N, 6.19; S, 21.43. HPLC analysis was carried out under the following conditions: column, L-column ODS (ID 4.6 x 150 mm); eluent, MeCN/ 20mM NaH_2PO_4 (pH 3)(1/3), 1.0 mL/min; detector, 250 nm; retention time, (RR)-**11b** (10 min), (RR)-**1b** (17 min), (RR)-**10b** (29 min). Chiral HPLC analysis was carried out under the following conditions: column, Chirobiotic T (ID 4.6 x 250 mm); eluent, MeOH/triethylamine/AcOH (100/1/1), 1.0 mL/min; detector, 250 nm; retention time, (RR)-**1b** (6 min), (SS)-**1b** (10 min).

N-(3,3-Dimethyl)butyryl-*N* '-thenoyl-D-cystine((SS)-1b)

This compound was obtained by treatment of (SS)-**2b** with BBTO in 91% (>99% ee) yield. mp 184-186

°C. IR (Nujol) cm^{-1}: 3382, 3323, 1749, 1715, 1617. ESI-MS *m/z*: 447 (M^+-H). ^{1}H-NMR (DMSO-d_6) δ: 0.94 (9H, s), 1.99 (2H, s), 2.92 (1H, m), 3.12-3.28(3H, m), 4.48 (1H, m), 4.65 (1H, m), 7.16 (1H, dd, *J* = 3.9, 5.0 Hz), 7.79 (1H, dd, *J* = 1.1, 5.0 Hz), 7.83 (1H, dd, *J* = 1.1, 3.9 Hz), 8.12 (1H, d, *J* = 7.9 Hz, D_2O-exchangeable), 8.81 (1H, d, *J* = 8.1 Hz, D_2O-exchangeable), 12.90 (2H, br, D_2O-exchangeable). *Anal.* Calcd for $C_{17}H_{24}N_2O_6S_3$: C, 45.52; H, 5.39; N, 6.25; S, 21.44. Found: C, 45.74; H, 5.37; N, 6.08; S, 21.49.

N-(2,2-Dimethyl)propanoyl-N'-(2-adamantyl)acetyl-L-cystine ((RR)-1c)

This compound was obtained by treatment of (RR)-**2c** with BBTO in 97% yield as a foam.[11] IR (Nujol) cm^{-1}: 3328, 1727, 1628. ESI-MS *m/z*: 499 (M^+-H). ^{1}H-NMR (DMSO-d_6) δ: 1.11 (9H, s), 1.46 (2H, m), 1.62-1.93 (12H, m), 2.26 (2H, m), 2.89 (1H, m), 3.02 (1H, m), 3.08-3.19 (2H, m), 4.41-4.51 (2H, m), 7.69 (1H, d, *J* = 7.9 Hz, D_2O-exchangeable), 8.22 (1H, d, *J* = 8.1 Hz, D_2O-exchangeable), 12.76 (2H, br, D_2O-exchangeable). HPLC analysis was carried out under the following conditions: column, L-column ODS (ID 4.6 x 150 mm); eluent, MeCN/ 20mM NaH_2PO_4 (pH 3)(1/1), 1.0 mL/min; detector, 210 nm; retention time, (RR)-**10c** (2 min), (RR)-**1c** (4 min), (RR)-**11c** (15 min). Treatment of (RR)-**1c** with DCHA gave (RR)-**1c**·2DCHA in a quantitative yield. mp 159-161 °C. *Anal.* Calcd for $C_{23}H_{36}N_2O_6S_2 \cdot 2C_{12}H_{23}N_2 \cdot 0.5H_2O$: C, 64.71; H, 9.59; N, 6.42; S, 7.35. Found: C, 64.90; H, 9.76; N, 6.34; S, 7.42.

Preparation of N-Acylcystine-dipeptide Diethyl Esters ((RRS)-4, (RRR)-4, and (SSR)-4)

N-Acylcystine-dipeptide diethyl esters ((RRS)-**4**, (RRR)-**4**, and (SSR)-**4**) were prepared from monoacylcystine diethyl esters ((RR)-**6** and (SS)-**6**) and the corresponding *N*-(*tert*-butoxycarbonyl)amino acids in CH_2Cl_2 in the presence of HOBT and EDC. The general procedure is exemplified by the preparation of *N*-(2,2-dimethyl)propanoyl-*N'*-(*tert* -butoxycarbonyl)-L-phenylalanyl-L-cystine diethyl ester ((RRS)-**4c**): HOBT (191 mg, 1.41 mmol) and EDC·HCl (270 mg, 1.41 mmol) were added to a stirred solution of *N*-(*tert* -butoxycarbonyl)-L-phenylalanine (374 mg, 1.41 mmol) in CH_2Cl_2 (38 mL) under ice-cooling. After 30 mim, (RR)-**6c**·oxalate (600 mg, 1.28 mmol) was added followed by addition of a solution of triethylamine (260 mg, 2.56 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The whole was stirred for 2 h at 0-2 °C and poured into crushed ice and extracted with AcOEt. The organic layer was washed with 10% citric acid solution, H_2O, sat. $NaHCO_3$ solution, and brine, and dried. Removal of the solvent gave a crude product, which was purified by column chromatography on silica gel (x 10). Elution of AcOEt : hexane (1:2) gave 740 mg (92%, >99% de) of (RRS)-**4c** as a foam. IR (neat) cm^{-1}: 3342, 1739, 1665, 1605. APCI-MS *m/z*: 628 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 1.23 (9H, s), 1.28, 1.30 (6H, each t, *J* = 7.1 Hz), 1.39 (9H, s), 2.99-3.22 (6H, m), 4.15-4.26 (4H, m), 4.43 (1H, quasi d), 4.74-4.82 (2H, m), 5.20 (1H, quasi d, D_2O-exchangeable), 6.55, 6.87 (2H, each quasi d, D_2O-exchangeable), 7.20-7.33 (5H, m). HPLC analysis was carried out under the following conditions: column, L-column ODS (ID 4.6 x 150 mm); eluent, MeCN/H_2O (11/9), 1.0 mL/min; detector, 210 nm; retention time, (RRR)-**4c** (13 min), (RRS)-**4c** and (SSR)-**4c** (14 min). Chiral HPLC analysis was carried out under the following conditions: column, CHIRALCEL OD-RH (ID 4.6 x 150 mm); eluent, MeCN/H_2O (9/11), 0.5 mL/min; detector, 210 nm; retention time, (SSR)-**4c** (23 min), (RRS)-**4c** (25 min).

_N_-3-Phenylpropanoyl-_N'_-(_tert_-butoxycarbonyl)-L-tryptophanyl-L-cystine Diethyl Ester ((RRS)-4a)

This compound was obtained from (RR)-**6a**·fumarate and _N_-(_tert_-butoxycarbonyl)-L-tryptophane in 91% (>99% de) yield as a foam. IR (Nujol) cm^{-1}: 3314, 1735, 1655. APCI-MS _m/z_: 715 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 1.25, 1.26 (6H, each t, J = 7.1 Hz), 1.42 (9H, s), 2.54-2.61 (2H, m), 2.95-3.04 (6H, m), 3.20 (1H, m), 3.36 (1H, m), 4.10-4.22 (4H, m), 4.53 (1H, m), 4.70-4.82 (2H, m), 5.21 (1H, quasi d, D_2O-exchangeable), 6.35, 6.78 (2H, each br, D_2O-exchangeable), 7.08-7.36 (9H, m), 7.64 (1H, quasi d), 8.46 (1H, s, D_2O-exchangeable). HPLC analysis was carried out under the following conditions: column, L-column ODS (ID 4.6 x 150 mm); eluent, MeCN/H_2O (1/1), 1.0 mL/min; detector, 220 nm; retention time, (RRR)-**4a** (24 min), (RRS)-**4a** (26 min).

_N_-3-Phenylprpanoyl-_N'_-(_tert_-butoxycarbonyl)-D-tryptophanyl-L-cystine Diethyl Ester ((RRR)-4a)

This compound was obtained from (RR)-**6a**·fumarate and _N_-(_tert_-butoxycarbonyl)-D-tryptophane in 92% (>99% de) yield as a foam. IR (Nujol) cm^{-1}: 3289, 1735, 1655. APCI-MS _m/z_: 715 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 1.23, 1.28 (6H, each t, J = 7.1 Hz), 1.42 (9H, s), 2.56-2.62 (2H, m), 2.72 (1H, m) 2.86-3.05 (5H, m), 3.17 (1H, m), 3.30 (1H, m), 4.13, 4.20 (4H, each quasi q), 4.50 (1H, m), 4.70 (1H, m), 4.78 (1H, m), 5.18 (1H, br, D_2O-exchangeable), 6.42 (1H, d, J = 7.3 Hz, D_2O-exchangeable), 6.50 (H, d, J = 7.7 Hz, D_2O-exchangeable), 7.06-7.37 (9H, m), 7.64 (1H, quasi d), 8.44 (1H, s, D_2O-exchangeable).

_N_-(3,3-Dimethyl)butyryl-_N'_-(_tert_-butoxycarbonyl)-L-prolinyl-L-cystine Diethyl Ester ((RRS)-4b)

This compound was obtained from (RR)-**6b**·fumarate and _N_-(_tert_-butoxycarbonyl)-L-proline in 95% (>99% de) yield as a foam. IR (neat) cm^{-1}: 3310, 1743,1699, 1672. APCI-MS _m/z_: 592 (MH^+). ^{1}H-NMR ($CDCl_3$) δ : 1.06 (9H, s), 1.30 (6H, t, J = 7.1 Hz), 1.47 (9H, s), 1.90 (2H, m), 2.02-2.38 (2H, m), 2.14 (2H, s), 3.10-3.28 (4H, m), 3.32-3.56 (2H, m), 4.22 (4H, quasi q), 4.30 (1H, m), 4.76-4.87 (2H, m), 6.34 (1H, br, D_2O-exchangeable), 6.88, 7.36 (1H, each br, D_2O-exchangeable, rotamer was observed). Chiral HPLC analysis was carried out under the following conditions: column, CHIRALCEL OD-RH (ID 4.6 x 150 mm); eluent, MeCN/H_2O (2/3), 0.5 mL/min; detector, 210 nm; retention time, (RRR)-**4b** (17 min), (RRS)-**4b** (21 min).

_N_-(3,3-Dimethyl)butyryl-_N'_-(_tert_-butoxycarbonyl)-D-prolinyl-L-cystine Diethyl Ester ((RRR)-4b)

This compound was obtained from (RR)-**6b**·fumarate and _N_-(_tert_-butoxycarbonyl)-D-proline in 95% (>99% de) yield as a foam. IR (neat) cm^{-1}: 3312, 1743, 1699, 1673. APCI-MS _m/z_: 592 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 1.06 (9H, s), 1.29 (6H, t, J = 7.1 Hz), 1.48 (9H, s), 1.91 (2H, m), 2.10-2.40 (2H, m), 2.14 (2H, s), 3.15 (2H, d, J = 5.5 Hz), 3.23 (2H, m), 3.30-3.48 (2H, m), 4.22 (4H, quasi q), 4.32 (1H, m), 4.76-4.90 (2H, m), 6.45 (1H, br, D_2O-exchangeable), 6.91, 7.61 (1H, each br, D_2O-exchangeable, rotamer was observed).

_N_-(2,2-Dimethyl)propanoyl-_N'_-(*tert*-butoxycarbonyl)-D-phenylalanyl-L-cystine Diethyl Ester ((RRR)-4c)

This compound was obtained from (RR)-**6c**·oxalate and _N_-(*tert*-butoxycarbonyl)-D-phenylalanine in 92% (>99% de) yield as a foam. IR (neat) cm^{-1}: 3344, 1738, 1663, 1604. APCI-MS *m/z*: 628 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 1.23 (9H, s), 1.28, 1.30 (6H, each t, *J* = 7.1 Hz), 1.40 (9H, s), 2.98-3.26 (6H, m), 4.14-4.27 (4H, m), 4.41 (1H, m), 4.74-4.82 (2H, m), 5.03 (1H, m, D_2O-exchangeable), 6.53, 6.77 (2H, each quasi d, D_2O-exchangeable), 7.20-7.33 (5H, m).

_N_-(2,2-Dimethyl)propanoyl-_N'_-(*tert*-butoxycarbonyl)-L-phenylalanyl-D-cystine Diethyl Ester ((SSR)-4c)

This compound was obtained from (SS)-**6c**·oxalate and _N_-(*tert*-butoxycarbonyl)-L-phenylalanine in 91% (>99% de) yield as a foam. IR (neat) cm^{-1}: 3341, 1739, 1665, 1604. ACPI-MS *m/z*: 628 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 1.23 (9H, s), 1.28, 1.30 (6H, each t, *J* = 7.1 Hz), 1.39 (9H, s), 2.98-3.22 (6H, m), 4.15-4.26 (4H, m), 4.42 (1H, m), 4.74-4.82 (2H, m), 5.21 (1H, m, D_2O-exchangeable), 6.55, 6.87 (2H, each quasi d, D_2O-exchangeable), 7.19-7.33 (5H, m).

_N_-(*tert*-Butoxycarbonyl)-_N'_-(*tert*-butoxycarbonyl)-L-tryptophanyl-L-cystine Diethyl Ester ((RRS)-4d)

This compound was obtained from (RR)-**6d**·fumarate and _N_-(*tert*-butoxycarbonyl)-L-tryptophane in 92% (>99% de) yield as a foam. IR (Nujol) cm^{-1}: 3331, 1697. APCI-MS *m/z*: 683 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 1.26, 1.27 (6H, each t, *J* = 7.1 Hz), 1.43 (9H, s), 1.46 (9H, s), 2.92-3.23 (5H, m), 3.39 (1H, m), 4.09-4.23 (4H, m), 4.52 (1H, m), 4.74 (1H, m), 5.22 (1H, m, D_2O-exchangeable), 5.36 (1H, br d, D_2O-exchangeable), 6.73 (1H, d, *J* = 7.3 Hz, D_2O-exchangeable), 7.09-7.21 (3H, m), 7.36 (1H, quasi d), 7.65 (1H, quasi d), 8.53 (1H, s, D_2O-exchangeable). Chiral HPLC analysis was carried out under the following conditions: column, CHIRALCEL OJ-R (ID 4.6 x 150 mm); eluent, MeCN/H_2O (9/11), 0.5 mL/min; detector, 220 nm; retention time, (RRS)-**4d** (18 min), (RRR)-**4d** (20 min), (SSR)-**4d** (23 min).

_N_-(*tert*-Butoxycarbonyl)-_N'_-(*tert*-butoxycarbonyl)-D-tryptophanyl-L-cystine Diethyl Ester ((RRR)-4d)

This compound was obtained from (RR)-**6d**·fumarate and _N_-(*tert*-butoxycarbonyl)-D-tryptophane in 90% (>99% de) yield as a foam. IR (Nujol) cm^{-1}: 3331, 1694. APCI-MS *m/z*: 683 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 1.24, 1.29 (6H, each t, *J* = 7.1 Hz), 1.43 (9H, s), 1.47 (9H, s), 2.76 (1H, m), 2.90-3.10 (3H, m), 3.18 (1H, m), 3.32 (1H, m), 4.09-4.25 (4H, m), 4.52 (1H, m), 4.72 (1H, m), 5.21 (1H, m, D_2O-exchangeable), 5.38 (1H, br d, D_2O-exchangeable), 6.44 (1H, d, *J* = 7.1 Hz, D_2O-exchangeable), 7.09-7.22 (3H, m), 7.37 (1H, quasi d), 7.66 (1H, quasi d), 8.54 (1H, s, D_2O-exchangeable).

_N_-(*tert*-Butoxycarbonyl)-_N'_-(*tert*-butoxycarbonyl)-L-tryptophanyl-D-cystine Diethyl Ester ((SSR)-4d)

This compound was obtained from (SS)-**6d**·fumarate and _N_-(*tert*-butoxycarbonyl)-L-tryptophane in 91%

(>99% de) yield as a foam. IR (Nujol) cm^{-1}: 3325, 1694. APCI-MS *m/z*: 683 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 1.26, 1.27 (6H, each t, J = 7.1 Hz), 1.43 (9H, s), 1.46 (9H, s), 2.92-3.23 (5H, m), 3.40 (1H, m), 4.09-4.23 (4H, m), 4.52 (1H, m), 4.75 (1H, m), 5.22 (1H, m, D_2O-exchangeable), 5.36 (1H, br d, D_2O-exchangeable), 6.73 (1H, d, J = 7.3 Hz, D_2O-exchangeable), 7.09-7.22 (3H, m), 7.36 (1H, quasi d), 7.65 (1H, quasi d), 8.54 (1H, s, D_2O-exchangeable).

Preparation of *N*-Acylcystine-dipeptide ((RRS)-3, (RRR)-3, and (SSR)-3)

N-Acylcystine-dipeptides ((RRS)-**3**,(RRR)-**3**, and (SSR)-**3**) were prepared by cleavage of *N*-acylcystine-dipeptide diethyl esters ((RRS)-**4**, (RRR)-**4**, and (SSR)-**4**) with BBTO under similar conditions used for preparation of *N,N'*-unsymmetrical diacylcystine ((RR)-**1** and (SS)-**1**). The general procedure is exemplified by the preparation of *N*-(2,2-dimethyl)propanoyl-*N'*-(*tert*-butoxycarbonyl)-L-phenylalanyl-L-cystine ((RRS)-**3c**): BBTO (5.70 g, 9.56 mmol) was added to a solution of (RRS)-**4c** (600 mg, 0.96 mmol) in toluene (45 mL) and the mixture was stirred for 15 h at 100 ℃. The solvent was removed under reduced pressure and AcOEt (50 mL) was added to the residue. 10% KF solution (50 mL) was added to the AcOEt solution and the mixture was stirred for 30 min at rt. The resulting insoluble organotin fluoride was removed by filtration. The aqueous layer was separated from the filtrate and washed with AcOEt, and adjusted to pH 3 with 5% citric acid solution, and extracted with AcOEt. The organic layer was washed with brine, and dried. Evaporation of the AcOEt gave 491 mg (90%, >99% de) of (RRS)-**3c** as a foam. IR (Nujol) cm^{-1}: 3324, 1724, 1647. ESI-MS *m/z*: 570 (M^+-H). ^{1}H-NMR (DMSO-d_6) δ: 1.11 (9H, s), 1.21, 1.28 (9H, br s, s, rotamer was observed), 2.72 (1H, m), 2.92-3.08 (3H, m), 3.16-3.25 (2H, m), 4.19 (1H, m), 4.44-4.54 (2H, m), 6.42, 6.86 (1H, br d, d, J = 8.8 Hz, D_2O-exchangeable, rotamer was observed), 7.15-7.34 (5H, m), 7.68 (1H, br d, D_2O-exchangeable), 8.27, 8.38 (1H, d, br d, J = 7.5 Hz, D_2O-exchangeable, rotamer was observed), 12.80 (2H, br, D_2O-exchangeable). HPLC analysis was carried out under the following conditions: column, TSKgel Octyl-80Ts (ID 4.6 x 150 mm); eluent, MeOH/ 20mM NaH_2PO_4 (pH 3)(11/9), 1.0 mL/min; detector, 210 nm; retention time, (RRS)-**3c** and (SSR)-**3c** (19 min), (RRR)-**3c** (22 min). Chiral HPLC analysis was carried out under the following conditions: column, CHIRALCEL OJ-R (ID 4.6 x 150 mm); eluent, MeCN/ 0.5M $NaClO_4$ (pH 2)(1/3), 0.5 mL/min; detector, 210 nm; retention time, (RRS)-**3c** (27 min), (SSR)-**3c** (30 min). (RRS)-**3c**·2DCHA: mp 145-147 ℃. *Anal.* Calcd for $C_{25}H_{37}N_3O_8S_2 \cdot 2C_{12}H_{23}N \cdot H_2O$: C, 61.80; H, 9.00; N, 7.35; S, 6.73. Found: C, 61.75; H, 8.83; N, 7.26; S, 6.67.

***N*-3-Phenylpropanoyl-*N'*-(*tert*-butoxycarbonyl)-L-tryptophanyl-L-cystine ((RRS)-3a)**

This compound was obtained from (RRS)-**4a** in 82% (>99% de) yield as a foam. IR (Nujol) cm^{-1}: 3307, 1722, 1651. ESI-MS *m/z*: 657 (M^+-H). ^{1}H-NMR (DMSO-d_6) δ: 1.13, 1.28 (9H, each s, rotamer was observed), 2.43 (2H, m), 2.78-3.20 (8H, m), 4.25 (1H, m), 4.47-4.58 (2H, m), 6.72 (1H, d, J = 8.6 Hz, D_2O-exchangeable), 6.97 (1H, m), 7.05 (1H, m), 7.12-7.35 (7H, m), 7.59 (1H, quasi d), 8.28-8.35 (2H, m, D_2O-exchangeable), 10.80 (1H, s, D_2O-exchangeable), 12.90 (2H, br, D_2O-exchangeable). Chiral HPLC analysis was carried out under the following conditions: column, CHIRALCEL OJ-R (ID 4.6 x 150 mm); eluent, MeCN/ 0.5M $NaClO_4$ (pH 2)(7/13), 0.5 mL/min; detector, 220 nm; retention time, (RRS)-**3a**

(17 min), (RRR)-**3a** (24 min). (RRS)-**3a**·2DCHA : mp 126-127 ℃. *Anal.* Calcd for $C_{31}H_{38}N_4O_8S_2 \cdot 2C_{12}H_{23}N \cdot 1.5H_2O$: C, 63.01; H, 8.36; N, 8.02; S, 6.12. Found: C, 62.91; H, 8.20; N, 7.91; S, 6.36.

N-3-Phenylpropanoyl-N '-(*tert*-butoxycarbonyl)-D-tryptophanyl-L-cystine ((RRR)-3a)

This compound was obtained from (RRR)-**4a** in 84% (>99% de) yield as a foam. IR (Nujol) cm^{-1}: 3313, 1724, 1655. ESI-MS *m/z*: 657 (M^+-H). ^{1}H-NMR (DMSO-d_6) δ: 1.13, 1.29 (9H, each s, rotamer was observed), 2.43 (2H, m), 2.78-3.20 (8H, m), 4.25 (1H, m), 4.47-4.58 (2H, m), 6.71 (1H, d, J = 8.6 Hz, D_2O-exchangeable), 6.96 (1H, m), 7.05 (1H, m), 7.11-7.28 (6H, m), 7.31 (1H, quasi d), 7.62 (1H, quasi d), 8.31 (1H, d, J = 7.9 Hz, D_2O-exchangeable), 8.40 (1H, d, J = 7.7 Hz, D_2O-exchangeable), 10.78 (1H, s, D_2O-exchangeable), 12.92 (2H, br, D_2O-exchangeable). (RRR)-**3a**·2DCHA: mp 193-194 ℃. *Anal.* Calcd for $C_{31}H_{38}N_4O_8S_2 \cdot 2C_{12}H_{23}N \cdot 0.5H_2O$: C, 64.11; H, 8.31; N, 8.16; S, 6.22. Found: C, 64.12; H, 8.33; N, 8.07; S, 6.27.

N-(3,3-Dimethyl)butyryl-N '-(*tert*-butoxycarbonyl)-L-prolinyl-L-cystine ((RRS)-3b)

This compound was obtained from (RRS)-**4b** in 93% (>99% de) yield as colorless crystals. mp 176-177 ℃ (decomp). IR (Nujol) cm^{-1}: 3370, 3313, 1732, 1641. ESI-MS *m/z*: 534 (M^+-H). ^{1}H-NMR (DMSO-d_6) δ: 0.96 (9H, s), 1.33, 1.40 (9H, each s, rotamer was observed), 1.68-1.82 (3H, m), 1.85-2.20 (1H, m), 2.00 (2H, s), 2.86-3.01 (2H, m), 3.11-3.20 (2H, m), 3.20-3.45 (2H, m), 4.05-4.18 (1H, m), 4.43-4.55 (2H, m), 8.10, 8.17 (1H, br d, d, J = 8.2 Hz, D_2O-exchangeable, rotamer was observed), 8.12 (1H, d, J = 7.7 Hz, D_2O-exchangeable), 12.82 (2H, br, D_2O-exchangeable). *Anal.* Calcd for $C_{22}H_{37}N_3O_8S_2$: C, 49.33; H, 6.96; N, 7.84; S, 11.97. Found: C, 49.27; H, 6.90; N, 7.72; S, 11.73. Chiral HPLC analysis was carried out under the following conditions: column, CHIRALCEL OD-RH (ID 4.6 x 150 mm); eluent, MeCN/ 0.5M $NaClO_4$ (pH 2)(1/3), 0.5 mL/min; detector, 210 nm; retention time, (RRR)-**3b** (14 min), (RRS)-**3b** (17 min).

N-(3,3-Dimethyl)butyryl-N '-(*tert*-butoxycarbonyl)-D-prolinyl-L-cystine ((RRR)-3b)

This compound was obtained from (RRR)-**4b** in 91% (>99% de) yield as a foam. IR (Nujol) cm^{-1}: 3321, 1733, 1652. ESI-MS *m/z*: 534 (M^+-H). ^{1}H-NMR (DMSO-d_6) δ: 0.96 (9H, s), 1.33, 1.39 (9H, each s, rotamer was observed), 1.65-1.90 (3H, m), 1.95-2.18 (1H, m), 2.00 (2H, s), 2.86-3.01 (2H, m), 3.10-3.18 (2H, m), 3.20-3.42 (2H, m), 4.07-4.19 (1H, m), 4.41-4.57 (2H, m), 8.12 (1H, d, J = 7.7 Hz, D_2O-exchangeable), 8.15, 8.22 (1H, br d, d, J = 8.1 Hz, D_2O-exchangeable, rotamer was observed), 12.80 (2H, br, D_2O-exchangeable). (RRR)-**3b**·2DCHA: mp 198-200 ℃. *Anal.* Calcd for $C_{22}H_{37}N_3O_8S_2 \cdot 2C_{12}H_{23}N \cdot 0.5H_2O$: C, 60.89; H, 9.33; N, 7.72; S, 7.07. Found: C, 61.19; H, 9.32; N, 7.43; S, 6.93.

N-(2,2-Dimethyl)propanoyl-N'-(*tert*-butoxycarbonyl)-D-phenylalanyl-L-cystine ((RRR)-3c)

This compound was obtained from (RRR)-**4c** in 88% (>99% de) yield as a foam. IR (Nujol) cm^{-1}: 3324, 1725, 1647. ESI-MS *m/z*: 570 (M^+-H). ^{1}H-NMR (DMSO-d_6) δ: 1.10 (9H, s), 1.22, 1.28 (9H, br s, s, rotamer was observed), 2.72 (1H, m), 2.86-3.08 (3H, m), 3.12-3.22 (2H, m), 4.23 (1H, m), 4.43-4.58

(2H, m), 6.42, 6.84 (1H, br d, d, J = 8.8 Hz, D_2O-exchangeable, rotamer was observed), 7.15-7.32 (5H, m), 7.69 (1H, br d, D_2O-exchangeable), 8.39, 8.45 (1H, d, br d, J = 8.2 Hz, D_2O-exchangeable, rotamer was observed), 12.90 (2H, br, D_2O-exchangeable). (RRR)-**3c**·2DCHA : mp 155-156 ℃. *Anal.* Calcd for $C_{25}H_{37}N_3O_8S_2 \cdot 2C_{12}H_{23}N \cdot H_2O$: C, 61.80; H, 9.00; N, 7.35; S, 6.73. Found: C, 61.94; H, 8.97; N ,7.32; S, 6.53.

N-(2,2-Dimethyl)propanoyl-N'-(*tert*-butoxycarbonyl)-D-phenylalanyl-D-cystine ((SSR)-3c)

This compound was obtained from (SSR)-**4c** in 88% (>99% de) yield as a foam. IR (Nujol) cm^{-1}: 3225, 1724, 1647. ESI-MS *m/z*: 570 (M^+-H). ^{1}H-NMR (DMSO-d_6) δ: 1.11 (9H, s), 1.22, 1.28 (9H, br s, s, rotamer was observed), 2.72 (1H, m), 2.92-3.09 (3H, m), 3.15-3.24 (2H, m), 4.19 (1H, m), 4.44-4.54 (2H, m), 6.40, 6.86 (1H, br d, d, J = 8.8 Hz, D_2O-exchangeable, rotamer was observed), 7.15-7.35 (5H, m) 7.70 (1H, d, D_2O-exchangeable), 8.28, 8.39 (1H, d, br d, J = 7.7 Hz, D_2O-exchangeable, rotamer was observed), 12.80 (2H, br, D_2O-exchangeable). (SSR)-**3c**·2DCHA : mp 145-147 °C. *Anal.* Calcd for $C_{25}H_{37}N_3O_8S_2 \cdot 2C_{12}H_{23}N \cdot H_2O$: C, 61.80; H, 9.00, N, 7.35; S, 6.73. Found: C, 61.85; H, 8.88; N, 7.24; S, 6.78.

N-(*tert*-Butoxycarbonyl)-N'-(*tert*-butoxycarbonyl)-L-tryptophanyl-L-cystine ((RRS)-3d)

This compound was obtained from (RRS)-**4d** in 77% (>99% de) yield as a foam. IR (Nujol) cm^{-1}: 3330, 1745, 1721, 1695. ESI-MS *m/z*: 625 (M^+-H). ^{1}H-NMR (DMSO-d_6) δ: 1.14, 1.29 (9H, each s, rotamer was observed), 1.38 (9H, s), 2.84-3.04 (3H, m), 3.06-3.24 (3H, m), 4.09-4.28 (2H, m), 4.56 (1H, m), 6.21, 6.69 (1H, br d, d, J = 8.4 Hz, D_2O-exchangeable, rotamer was observed), 6.97 (1H, m), 7.06 (1H, m), 7.13 (1H, s), 6.84, 7.19 (1H, br d, d, J = 8.6 Hz, D_2O-exchangeable, rotamer was observed), 7.32 (1H, quasi d), 7.59 (1H, quasi d), 8.28 (1H, d, J = 8.1 Hz, D_2O-exchangeable), 10.80 (1H, s, D_2O-exchangeable), 12.90 (2H, br, D_2O-exchangeable). Chiral HPLC analysis was carried out under the following conditions: 1) column, Chirobiotic T (ID 4.6 x 250 mm); eluent, MeOH/triethylamine/AcOH (100/1/1), 1.0 mL/min; detector, 280 nm; retention time, (RRS)-**3d** (4 min), (SSR)-**3d** (12 min). 2) column, CHIRALCEL OJ-R (ID 4.6 x 150 mm); eluent, MeCN/ 0.5M $NaClO_4$ (pH 2)(3/7), 0.5 mL/min; detector, 220 nm; retention time, (RRS)-**3d** (22 min), (RRR)-**3d** (27 min). (RRS)-**3d**·2DCHA : mp 127-129 °C. *Anal.* Calcd for $C_{27}H_{38}N_4O_9S_2 \cdot 2C_{12}H_{23}N \cdot H_2O$: C, 60.81; H, 8.60; N, 8.34; S, 6.37. Found: C, 60.98; H, 8.56; N, 8.49; S, 6.49.

N-(*tert*-Butoxycarbonyl)-N'-(*tert*-butoxycarbonyl)-D-tryptophanyl-L-cystine ((RRR)-3d)

This compound was obtained from (RRR)-**4d** in 81% (>99% de) yield as a foam. IR (Nujol) cm^{-1}: 3329, 1745, 1720, 1695. ESI-MS *m/z*: 625 (M^+-H). ^{1}H-NMR (DMSO-d_6) δ: 1.13, 1.29 (9H, each s, rotamer was observed), 1.38 (9H, s), 2.84-3.02 (3H, m), 3.04-3.22 (3H, m), 4.09-4.30 (2H, m), 4.54 (1H, m), 6.19, 6.69 (1H, br d, d, J = 8.6 Hz, D_2O-exchangeable, rotamer was observed), 6.97 (1H, m), 7.05 (1H, m), 7.13 (1H, s), 6.82, 7.19 (1H, br d, d, J = 8.4 Hz, D_2O-exchangeable, rotamer was observed), 7.32 (1H, quasi d), 7.61 (1H, quasi d), 8.38 (1H, d, J = 7.9 Hz, D_2O-exchangeable), 10.78 (1H, s, D_2O-

exchangeable), 12.90 (2H, br, D_2O-exchangeable). (RRR)-**3d**·2DCHA : mp 179-181 °C. *Anal.* Calcd for $C_{27}H_{38}N_4O_9S_2 \cdot 2C_{12}H_{23}N$: C, 61.91; H, 8.56; N, 8.49; S, 6.48. Found: C, 61.81; H, 8.52; N, 8.32; S, 6.54.

***N*-(*tert*-Butoxycarbonyl)-*N'*-(*tert*-butoxycarbonyl)-D-tryptophanyl-D-cystine ((SSR)-3d)** This compound was obtained from (SSR)-**4d** in 82% (>99% de) yield as a foam. IR (Nujol) cm^{-1}: 3324, 1745, 1720, 1697. ESI-MS *m/z*: 625 (M^+-H). ^{1}H-NMR (DMSO-d_6) δ: 1.14, 1.29 (9H, each s, rotamer was observed), 1.38 (9H, s), 2.84-3.04 (3H, m), 3.06-3.23 (3H, m), 4.09-4.28 (2H, m), 4.55 (1H, m), 6.20, 6.69 (1H, br d, d, J = 8.4 Hz, D_2O-exchangeable, rotamer was observed), 6.97 (1H, m), 7.06 (1H, m), 7.13 (1H, s), 6.83, 7.19 (1H, br d, d, J = 8.6 Hz, D_2O-exchangeable, rotamer was observed), 7.32 (1H, quasi d), 7.59 (1H, quasi d), 8.28 (1H, d, J = 8.1 Hz, D_2O-exchangeable), 10.80 (1H, s, D_2O-exchangeable), 12.79 (2H, br, D_2O-exchangeable). (SSR)-**3d**·2DCHA : mp 128-129 °C. *Anal.* Calcd for $C_{27}H_{38}N_4O_9S_2 \cdot 2C_{12}H_{23}N \cdot H_2O$: C, 60.81; H, 8.60; N, 8.34; S, 6.37. Found: C, 60.88; H, 8.53; N, 8.44; S, 6.29.

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† This paper is dedicated to Prof. Teruaki Mukaiyama on the occasion of his 73rd birthday.

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7. HPLC analysis of crystals showed contamination of a trace amounts (0.5-1.0%) of (RR)-**7a** and (RR)-**8a**. Crystals were used for the next step without further purification.
8. HPLC analysis of product showed contamination of a trace amounts (0.5-1.0%) of (RR)-**10a** and (RR)-**11a** based on contaminants of esters ((RR)-**7a** and (RR)-**8a**).
9. Although not determined precisely, the optical purity of the fumarates ((RR)-**6a** and (SS)-**6a**) is presumed to be high, since the diethyl esters ((RR)-**2a** and (SS)-**2a**) obtained from (RR)-**6a** and (SS)-**6a** showed by chiral HPLC analysis to be >99% ee.
10. The optical purity of the fumarates ((RR)-**6d** and (SS)-**6d**) is presumed to be high. The cystine-containing dipeptide diethyl esters ((RRS)-**3d**, (RRR)-**3d**, and (SSR)-**3d**) prepared from (RR)-**6d** and (SS)-**6d** showed by chiral HPLC analysis to be >99% de.
11. The optical purity of (RR)-**2c** and (SS)-**2c** is presumed to be high. The preparation and cleavage conditions for (RR)-**2c** and (SS)-**2c** were as mild as those used for other optical active (RR)-**2** and (SS)-**2**.

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