New Methods and Reagents in Organic Synthesis. 67.[1] A General Synthesis of Derivatives of Optically Pure 2-(1-Aminoalkyl)thiazole-4-carboxylic Acids

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Preparations of 2-(1-aminoalkyl)thiazole-4-carboxylic acids (thiazole amino acids), important constituents of a series of cytotoxic cyclic peptides from marine organisms, have been conveniently and efficiently achieved as their N- and C-protected derivatives **6** from *N*-Boc or *N*-*Z* α-amino acids **1** in five steps. Esterification of **1** with methyl iodide followed by reduction with lithium chloride–sodium borohydride afforded N-protected amino alcohols **3**. Selective reduction of the α-ester functions of the glutamic acid derivatives (Z-D- and Z-L-Glu(O-*t*-Bu)-OMe and O-*t*-Bu) was also achieved under the above reduction conditions. Dimethyl sulfoxide oxidation, followed by condensation with cysteine methyl ester afforded the thiazolidine derivatives **5**, which were conveniently dehydrogenated with manganese dioxide, called chemical manganese dioxide (CMD) and produced for batteries, to give the desired thiazole amino acid derivatives **6**. The glutamine derivatives (Z-D- and Z-L-(gln)Thz-OMe) were prepared from the corresponding glutamic acid derivatives (Z-D- and Z-L-**6f**). No appreciable racemization was observed in the above conversion, which was proven by HPLC of the 3,5-dinitrobenzoyl derivatives of thiazole amino acids **6** using a chiral column.

In recent years, a series of cytotoxic cyclic peptides containing a thiazole skeleton have been isolated from marine organisms.[3] We have already completed the efficient syntheses of some of these structurally unique and pharmacologically interesting peptides such as dolastatin 3 (its proposed structure and 15 isomers),[4] ascidiacyclamide,[5] patellamides A,[6] B,[7] and C[7] (their proposed and revised structures), and ulithiacyclamide.[5b,8] Schmidt and co-workers similarly accomplished syntheses of dolastatin 3 (its proposed structure and 15 isomers),[9] patellamide B,[10] ulithiacyclamide,[11] and ulicyclamide.[12] Pettit and co-workers[13] reported two reverse isomers of the proposed structure of dolastatin 3, while a simplified analogue of dolastatin 3 was also synthesized by French workers.[14]

Each of these cyclic peptides contains a 2-(1-aminoalkyl)thiazole-4-carboxylic acid (thiazole amino acid) moiety, most of which possess the *R* configuration. Some of the above[9-12] and other[15-17] recent reports disclosed general methods for the preparation of optically active thiazole amino acids using a Hantzsch-type synthesis.[18] However, they suffer from racemization[15,18] or indirect

Scheme I

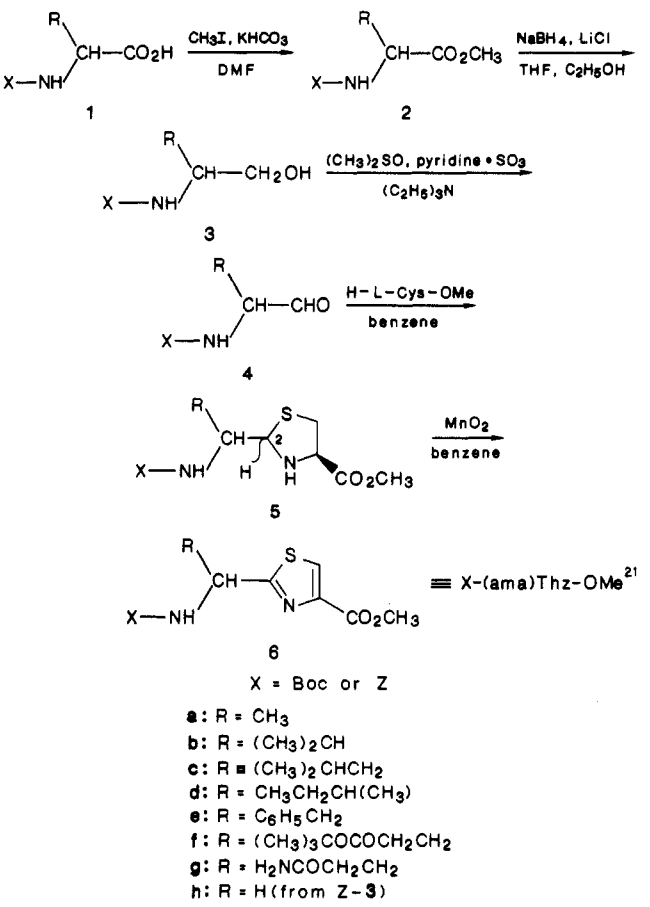

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Table I. Preparation of Thiazole Amino Acid Derivatives

entry	amino acid	compd suffix	R	X	isolated yield, % 1→3	3→5	5→6	overall yield, % 1→6
1	D-Ala	**a**	CH_3	Boc	95	84	69	55
2	D-Val	**b**	$(CH_3)_2CH$	Boc	95	87	61	50
3	L-Val	**b**	$(CH_3)_2CH$	Boc	95	88	59	49
4	D-Leu	**c**	$(CH_3)_2CHCH_2$	Boc	96	93	69	62
5	L-Ile	**d**	$CH_3CH_2CH(CH_3)$	Boc	89	92	58	47
6	D-Phe	**e**	$PhCH_2$	Boc	98	84	63	52
7	D-Glu	**f**	t-$BuOCOCH_2CH_2$	Z	67[a]	70	50[b]	23
8	L-Glu	**f**	t-$BuOCOCH_2CH_2$	Z	85[a]	87	50[b]	37
9	Gly	**h**	H	Z		74	29[b]	21[c]

[a] Prepared via Z-Glu(O-*t*-Bu)-O-*t*-Bu. [b] Manganese dioxide prepared by the Goldman procedure[24b] was used. [c] From Z-**3h**.

and/or tedious routes.[9-12,14,16-18] Prior to our synthesis of cytotoxic cyclic peptides,[4-8] we had to establish a new general synthetic method for optically active thiazole amino acids, the details of which are described in this paper.

Obvious building blocks for thiazole amino acids are cysteine and other α-amino acids. The key features of our synthesis are the preparation of N-protected optically active α-amino aldehydes **4**[4,19] and the oxidation of thiazolidine derivatives **5** with manganese dioxide.[4,20]

Commercially available Boc or Z[21] α-amino acids **1** were first converted to the corresponding methyl esters **2** by using methyl iodide in the presence of potassium hydrogen carbonate in dimethylformamide at room temperature. The esterification can also be carried out with (trimethylsilyl)diazomethane[22] in 20% methanol–benzene.[23] The methyl esters **2** were easily reduced with lithium chloride–sodium borohydride (1:1, 2 equiv) in ethanol–tetrahydrofuran to give the amino alcohol derivatives **3**. In the case of the glutamic acid derivative Z-L-**2f**, the methyl ester function was selectively reduced under similar reaction conditions. More conveniently, Z-L-Glu-OH was converted to its di-*tert*-butyl ester, which was selectively reduced with lithium chloride–sodium borohydride to give Z-L-**3f**. Analogously, Z-D-Glu-OH was converted to Z-D-**3f**. Oxidation of the N-protected amino alcohols **3** was conveniently accomplished by the dimethyl sulfoxide oxidation using sulfur trioxide–pyridine complex in the presence of triethylamine, giving the amino aldehyde derivatives **4** without any appreciable racemization.[19] Condensation of **4** with L-cysteine methyl ester smoothly afforded the thiazolidine derivatives **5** as a mixture of C-2 epimers, shown in Scheme I.

Oxidation of the thiazolidines **5** to the thiazoles **6** was most conveniently performed with manganese dioxide, called chemical manganese dioxide (CMD), in the presence or the absence of pyridine in benzene. CMD is industrially produced for batteries and readily commercially available. Its use gives much better results than the use of the usually available activated manganese dioxide (Aldrich). Activated manganese dioxides[24] prepared by the Goldman[24b] and Fatiadi[24c] procedures are also promising. However, these reagents are not readily available and their preparation takes a few days. Sometimes the oxidation efficiency lacks reproducibility. Use of oxidants such as barium manganate,[25] chloranil, trityl perchlorate, nickel peroxide,[26] and ruthenium tetraoxide resulted in failure or lower efficiency of the required oxidation. The glutamine derivatives Z-L- and Z-D-**6g** were conveniently prepared from the glutamic acid derivatives Z-L- and Z-D-**6f**, respectively, by the successive treatment with trifluoroacetic acid, ethyl chlorocarbonate–triethylamine, and ammonium hydroxide. Incidentally, the glycine derivative Z-**6h** was prepared from ethanolamine. As summarized in Table I, each of the overall yields from **1** to **6** is in most cases 50% or more in five steps.

Table II. HPLC of 3,5-Dinitrobenzoyl Thiazole Amino Acid Derivatives 6 (X = 3,5-Dinitrobenzoyl) Using a Sumipax OA-1000 Column[a]

starting α-amino acid	mobile phase[b]	t_r, min D-form	L-form	ee, %
D-Ala	A	41.96	49.41	>99
D-Val	A	12.89	16.67	>98
L-Val	A	12.89	16.67	>97
D-Leu	A	20.13	22.10	>98
L-Ile	B	16.97[c]	19.41	98.2[d]
D-Phe	A	43.74	49.94	98.8[e]
L-Gln	C	13.85	21.49	98.6
D-Gln	C	13.85	21.49	97.3

[a] Flow rate, 1.5 mL/min; chart speed, 2 mm/min; detection, UV 238 nm. [b] Hexane–1,2-dichloroethane–ethanol (A, 30:6:1; B, 40:8:1; C, 28:14:5). [c] D-allo derivative. [d] Diastereomeric excess. [e] When recrystallized Boc-D-(phe)Thz-OMe (Boc-D-**6e**) was used as starting material, no peak of the L-isomer was detected; hence, ee was 100%.

To confirm the retention of the optical purities of the thiazole amino acid derivatives **6a–e,g** thus obtained, their Boc or Z groups were first removed with trifluoroacetic acid or 25% hydrogen bromide in acetic acid, respectively. Treatment of the N-deprotected products with 3,5-dinitrobenzoyl chloride and triethylamine afforded the 3,5-dinitrobenzoyl derivatives, which were subjected to HPLC using a chiral Sumipax OA-1000 column. For reference, the racemic thiazole amino acids were prepared from racemized amino aldehydes **4** and subjected to HPLC. As shown in Table II, all of the 3,5-dinitrobenzoyl derivatives (**6**, X = 3,5-dinitrobenzoyl) exhibited more than 98% enantiomeric excess. This result revealed that the reaction sequence involving the CMD oxidation and the acidic deprotection proceeded with no or little racemization, though the thiazole amino acids have been reported to

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racemize in acid hydrolysis.[3c]

The method developed here for the preparation of the thiazole amino acids in high enantiomeric purity is a general, convenient, high-yield process suitable for large-scale production. Furthermore, this work establishes the preparation of easily racemizable α-amino aldehyde derivatives and the introduction of chemical manganese dioxide (CMD) for batteries to organic synthesis.

Experimental Section

Melting and boiling points are uncorrected. IR spectra were recorded on a JASCO IRA-2 or IR-810 spectrophotometer using potassium bromide disks or as films. ^{1}H NMR spectra were recorded on a JEOL PMX-60, MH-100, or FX-100 spectrometer in deuteriochloroform using tetramethylsilane as an internal standard. Mass spectra were obtained on a JEOL DX-300 spectrometer. Optical rotations were measured with a JASCO DIP-140 automatic polarimeter. HPLC was carried out with a JASCO Tri Rotar-II high-pressure liquid chromatograph.

Chemicals. Chemical manganese dioxide (CMD) (I.C. sample No. 12) was purchased from the I.C. sample office (Cleveland, OH 44101). Dimethylformamide and dimethyl sulfoxide were dried over molecular sieves (4A). Tetrahydrofuran was distilled from benzophenone ketyl. Silica gel (BW-820 MH or BW-200, purchased from Fuji-Davison) was used for column chromatography.

Sulfur trioxide–pyridine complex (100g), obtained from Aldrich (Lot No. 1113LK), was suspended in carbon tetrachloride (150 mL). After addition of ice–water (1:1) (200 mL), the mixture was shaken violently for 5 min and filtered. The crystals thus obtained were washed with cold water (100 mL) and dried over phosphorus pentoxide in vacuo to give gray white crystals (38 g, 38%). Alternatively, the complex was prepared as followed: To a stirred mixture of pyridine (251 mL, 3.1 mol) and ethanol-free chloroform (800 mL) was added chlorosulfonic acid (100 mL, 1.5 mol) at −5 °C during 1.5 h. The mixture was stirred at −5 °C for 1 h and filtered. The crystals thus obtained were washed with hot ethanol-free chloroform (250 mL × 2) and dried in vacuo to give white crystals (208 g, 87%).

General Procedure for the Preparation of *N*-Boc or *N*-Z α-Amino Acid Methyl Esters 2. (1) With Methyl Iodide. To a solution of the *N*-Boc or *N*-Z α-amino acid 1 (0.25 mol) in dimethylformamide (400 mL) was added pulverized potassium hydrogen carbonate (50 g, 0.5 mol), followed by methyl iodide (25 mL, 0.4 mol). The mixture was stirred at room temperature for 4–5 h. Water (1 L) was added, and the mixture was extracted with ethyl acetate–benzene (1:1) (200 mL × 3). The organic extracts were successively washed with water (200 mL × 2), 5% aqueous sodium sulfite (200 mL) and saturated aqueous sodium chloride (200 mL), and dried over sodium sulfate. Removal of the solvent gave 2, which was used for the next step without further purification.

(2) With (Trimethylsilyl)diazomethane. The *N*-Boc or *N*-Z α-amino acid 1 was esterified as described in our previous paper.[23]

Z-L-Glu(O-*t*-Bu)-O-*t*-Bu. To Z-L-Glu-OH (42 g, 0.15 mol) in methylene chloride (600 mL) was added methanesulfonic acid (10 mL) and isobutylene (300 mL) at −5 °C. The reaction flask was stoppered and the mixture was stirred at room temperature for 30 h. After cooling in an ice bath, the mixture was gradually poured into saturated aqueous sodium hydrogen carbonate (500 mL). The methylene chloride layer was dried over sodium sulfate and filtered. Removal of the solvent gave Z-L-Glu(O-*t*-Bu)-O-*t*-Bu (52 g, 88%) as a colorless oil: IR 3300, 1725, 1520, 1150, 1050 cm^{-1}; NMR δ 1.45 (18 H, s), 1.45–2.6 (4 H, m), 4.3 (1 H, m), 5.15 (2 H, s), 5.49 (1 H, d, J = 9 Hz), 7.42 (5 H, s).

The D-isomer was prepared analogously.

General Procedure for the Preparation of *N*-Boc or *N*-Z Amino Alcohols 3. The α-amino acid methyl ester 2 (0.25 mol) obtained as above was dissolved in tetrahydrofuran (350 mL) under argon, and anhydrous lithium chloride (21.2 g, 0.5 mol) and then sodium borohydride (18.9 g, 0.5 mol) were added. After addition of ethanol (700 mL), the mixture was stirred at room temperature overnight. The mixture was cooled with ice–water, adjusted to pH 4 by the gradual addition of 10% aqueous citric acid (ca. 250 mL), and concentrated in vacuo. Water (700 mL) was added to the residue, which was extracted with methylene chloride (600 mL × 3) and dried over sodium sulfate. Removal of the solvent gave 3, which was purified by recrystallization or distillation.

Boc-D-Ala-ol (Boc-D-3a): mp 52–53 °C (from diethyl ether–hexane); $[\alpha]^{26}_D$ +10.0° (*c* 1, MeOH); IR 3440, 3300, 1675, 1530, 1450, 1365, 1170, 1060 cm^{-1}; NMR δ 1.15 (3 H, d, J = 6 Hz), 1.47 (9 H, s), 3.26 (1 H, br s, disappeared with D_2O), 3.3–4.1 (3 H, m), 4.96 (1 H, d, J = 7 Hz). Anal. Calcd for $C_8H_{17}NO_3$: C, 54.84; H, 9.78; N, 7.99. Found: C, 54.57; H, 9.97; N, 7.83.

Boc-D-Val-ol (Boc-D-3b): bp 98–99 °C (0.45 mm); $[\alpha]^{24}_D$ +16.8° (*c* 1, MeOH); IR 3300, 2950, 1680, 1500, 1390, 1370, 1170, 1020 cm^{-1}; NMR δ 0.91, 0.94 (6 H, dd, J = 7 and 7 Hz), 1.42 (9 H, s), 1.6-2.3 (1 H, m), 2.80 (1 H, br s), 3.10–3.87 (3 H, m), 4.73 (1 H, d, J = 9 Hz).

Boc-L-Val-ol (Boc-L-3b): bp 97.5–99 °C (0.3–0.35 mm); $[\alpha]^{23}_D$ −16.7° (*c* 1, MeOH). Anal. Calcd for $C_{10}H_{21}NO_3$: C, 59.09; H, 10.41; N, 6.89. Found: C, 58.50; H, 10.61; N, 6.88.

Boc-D-Leu-ol (Boc-D-3c): bp 127 °C (0.8 mm); $[\alpha]^{24}_D$ +28.3° (*c* 1, MeOH); IR 3300, 2950, 1680, 1520, 1400, 1360, 1240, 1180, 1060 cm^{-1}; NMR δ 0.97 (6 H, d, J = 6 Hz), 1.50 (9 H, s), 1.2–2.0 (3 H, m), 3.47–4.0 (4 H, m, 1 H disappeared with D_2O), 4.83–5.57 (1 H, br d). Anal. Calcd for $C_{11}H_{23}NO_3$: C, 60.78; H, 10.69; N, 6.45. Found: C, 60.70; H, 11.05; N, 6.40.

Boc-L-Ile-ol (Boc-L-3d): bp 121–126 °C (0.6 mm); $[\alpha]^{26}_D$ +15.7° (*c* 1, MeOH); IR 3350, 2975, 1690, 1510, 1460, 1390, 1370, 1250, 1180, 1080, 1050, 1030 cm^{-1}; NMR δ 0.7–1.8 (9 H, m), 1.47 (9 H, s), 2.97 (1 H, br s, disappeared with D_2O), 3.3–3.9 (3 H, m), 4.72–5.10 (1 H, br d, J = 8 Hz). Anal. Calcd for $C_{11}H_{23}NO_3$: C, 60.78; H, 10.69; N, 6.45. Found: C, 60.56; H, 10.83; N, 6.34.

Boc-D-Phe-ol (Boc-D-3e): mp 96–97 °C (from ethyl acetate–hexane); $[\alpha]^{23}_D$ +28.3° (*c* 1, MeOH); IR 3380, 1680, 1525, 1440, 1390, 1365 cm^{-1}; NMR δ 1.43 (9 H, s), 2.40 (1 H, br s, disappeared with D_2O), 2.86 (2 H, d, J = 6 Hz), 3.5–4.1 (3 H, m), 4.78 (1 H, br), 7.28 (5 H, s). Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.81; H, 8.42; N, 5.48.

Z-L- and Z-D-Glu(O-*t*-Bu)-ol (Z-L- and Z-D-3f): colorless oil; IR 3280, 1700, 1520, 1240, 1150, 1060 cm^{-1}; NMR δ 1.41 (9 H, s), 1.41–2.20 (4 H, m), 3.07–3.9 (4 H, m), 5.07 (2 H, s), 5.43 (1 H, d, J = 8 Hz), 7.31 (5 H, s).

Z-Gly-ol (Z-3h). To ethanolamine (7.2 mL, 0.12 mol) in benzene (20 mL) was added benzyloxycarbonyl chloride (7.14 mL, 0.05 mol) in benzene (40 mL) within 20 min at 10 °C. The mixture was stirred at room temperature for 0.5 h, successively washed with water (50 mL × 2) and saturated aqueous sodium chloride (50 mL), dried over sodium sulfate, and concentrated to give **3g** (9.25 g, 95%) as colorless crystals, mp 60–62 °C (from ethyl acetate–hexane).

General Procedure for the Preparation of *N*-Boc or *N*-Z α-Amino Aldehydes 4. To a solution of 3 (0.1 mol) and triethylamine (30.4 g, 0.3 mol) in methylene chloride (300 mL) cooled to −10 °C was added in one portion sulfur trioxide–pyridine complex (47.7 g, 0.3 mol) in dimethyl sulfoxide (300 mL). The mixture was stirred vigorously for 10 min at 10–20 °C, poured into ice-saturated aqueous sodium chloride (900 mL), and extracted with cooled diethyl ether (400 mL × 1, 200 mL × 2). The organic extracts were washed with cooled 10% aqueous citric acid (200 mL) and cooled saturated aqueous sodium chloride (200 mL × 2), dried over sodium sulfate, and concentrated in vacuo to give 4, which was used for the next step without further purification.

General Procedure for the Condensation of *N*-Boc or *N*-Z α-Amino Aldehydes 4 with Cysteine Methyl Ester. Preparation of Thiazolidines 5. To a stirred solution of 4 (0.2 mol) in benzene (240 mL) was added 1 M solution of H-L-Cys-OMe in benzene (240 mL). The mixture was stirred overnight at room temperature. The concentrated residue was purified by column chromatography on silica gel using ethyl acetate–hexane (1:4–1:2) as an eluent to give the thiazolidine 5, which was used for the next step. The NMR and thin-layer chromatography reveal 5 is a mixture of C-2 epimers.

General Procedure for the Manganese Dioxide (CMD) Oxidation of 5. Preparation of Methyl 2-[1-((*tert*-Butyloxycarbonyl)amino)alkyl]- or 2-[1-((Benzyloxycarbonyl)amino)alkyl]thiazole-4-carboxylates 6. To CMD (391 g, 4.5 mol) suspended in benzene (1.2 L) containing pyridine (18 mL) was added the thiazolidine 5 (0.18 mol) in benzene (600 mL) at

55 °C. The mixture was stirred at 55 °C for 2–4 h. After filtration, the insoluble material was washed with benzene. The organic layer was concentrated in vacuo, and the residue was purified by recrystallization from diethyl ether–hexane or by column chromatography on silica gel using either benzene–diethyl ether (9:1) or ethyl acetate–hexane (5:2–4:1) as an eluent to give the thiazole amino acid **6**.

Boc-D-(ala)Thz-OMe (Boc-D-6a): mp 101–103 °C; $[\alpha]^{23}_D$ +28.5° (*c* 0.5, MeOH); IR 3370, 3100, 2975, 1720, 1685, 1495, 1235, 1160 cm^{-1}; NMR δ 1.45 (9 H, s), 1.63 (3 H, d, *J* = 7 Hz), 3.97 (3 H, s), 4.97–5.47 (2 H, m), 8.17 (1 H, s). Anal. Calcd for $C_{12}H_{18}N_2O_4S$: C, 50.34; H, 6.34; N, 9.78. Found: C, 50.60; H, 6.56; N, 9.66.

Boc-D-(val)Thz-OMe (Boc-D-6b): mp 122–123 °C; $[\alpha]^{24}_D$ +27.0° (*c* 1, MeOH); IR 3300, 3100, 2950, 1720, 1700, 1480, 1360, 1230 cm^{-1}; NMR δ 0.93, 1.01 (6 H, dd, *J* = 7 and 7 Hz), 1.46 (9 H, s), 2.1–2.8 (1 H, m), 4.00 (3 H, s), 4.95 (1 H, dd, *J* = 6 and 9 Hz), 5.42 (1 H, br d, *J* = 9 Hz), 8.18 (1 H, s). Anal. Calcd for $C_{14}H_{22}N_2O_4S$: C, 53.48; H, 7.05; N, 8.91. Found: C, 53.60; H, 7.30; N, 8.82.

Boc-L-(val)Thz-OMe (Boc-L-6b): mp 122–124 °C; $[\alpha]^{24}_D$ −26.0° (*c* 1, MeOH). Anal. Calcd for $C_{14}H_{22}N_2O_4S$: C, 53.48; H, 7.05; N, 8.91. Found: C, 53.41; H, 7.17; N, 8.95.

Boc-D-(leu)Thz-OMe (Boc-D-6c): mp 56–58 °C (from pentane); $[\alpha]^{24}_D$ +22.5° (*c* 1, MeOH); IR 3425, 3300, 2950, 1720, 1690, 1525, 1250 cm^{-1}; NMR δ 1.02 (6 H, d, *J* = 6 Hz), 1.47 (s), 1.47–2.07 (m) (12 H), 4.00 (3 H, s), 4.97–5.3 (1 H, m), 5.46 (1 H, br d, *J* = 8 Hz), 8.2 (1 H, s); MS, calcd for $C_{15}H_{24}N_2O_4S$ 328.14568, found 328.14556.

Boc-L-(ile)Thz-OMe (Boc-L-6d): colorless oil; $[\alpha]^{22}_D$ −22.7° (*c* 1, MeOH); IR 3325, 3000, 2960, 1700, 1490, 1240, 1060 cm^{-1}; NMR δ 0.58–1.43 (8 H, m), 1.50 (9 H, s), 1.9–2.4 (1 H, m), 4.17 (3 H, s), 5.00 (1 H, dd, *J* = 5 and 8 Hz), 5.33 (1 H, br d, *J* = 8 Hz), 8.23 (1 H, s). Anal. Calcd for $C_{15}H_{24}N_2O_4S$: C, 54.86; H, 7.37; N, 8.53. Found: C, 54.39; H, 7.27; N, 8.26. MS, calcd for $C_{15}H_{24}N_2O_4S$ 328.14568, found 328.14695.

Boc-D-(phe)Thz-OMe (Boc-D-6e): mp 103–105 °C; $[\alpha]^{22}_D$ −8.8° (*c* 1, MeOH); IR 3380, 1730, 1695 cm^{-1}; NMR δ 1.40 (9 H, s), 3.33 (2 H, m), 3.99 (3 H, s), 5.1–5.5 (2 H, m), 7.32 (5 H, m), 8.06 (1 H, s). Anal. Calcd for $C_{18}H_{22}N_2O_4S$: C, 59.64; H, 6.12; N, 7.73. Found: C, 59.58; H, 5.78; N, 7.82.

Z-L-[glu(O-*t*-Bu)]Thz-OMe (Z-L-6f): analogously prepared by the use of Goldman's manganese dioxide;[24b] mp 83–85 °C; $[\alpha]^{23}_D$ −13.7° (*c* 1, MeOH); IR 3400, 3260, 1720, 1685, 1650 cm^{-1}; NMR δ 1.40 (9 H, s), 2–2.6 (4 H, m), 3.88 (3 H, s), 5–5.37 (1 H, m), 5.0 (2 H, s), 6.17 (1 H, d, *J* = 8 Hz), 7.33 (5 H, s), 8.07 (1 H, s). MS, calcd for $C_{21}H_{26}N_2O_6S$ 434.1513, found 434.1508.

Z-D-[glu(O-*t*-Bu)]Thz-OMe (Z-D-6f): mp 83–85 °C; $[\alpha]^{23}_D$ +14.3° (*c* 1, MeOH). Anal. Calcd for $C_{21}H_{26}N_2O_6S$: C, 58.04; H, 6.04; N, 6.45. Found: C, 57.77; H, 5.99; N, 6.23.

Z-(gly)Thz-OMe (Z-6h): analogously prepared by the use of Goldman's manganese dioxide:[24b] mp 95–97 °C (from ethyl acetate–hexane); IR 3290, 1720, 1705 cm^{-1}; NMR δ 3.93 (3 H, s), 4.73 (2 H, d, *J* = 6 Hz), 5.15 (2 H, s), 6.03 (1 H, br t, *J* = 6 Hz), 7.33 (5 H, s), 8.12 (1 H, s). Anal. Calcd for $C_{14}H_{14}N_2O_4S$: C, 54.88; H, 4.62; N, 9.15. Found: C, 55.28; H, 4.51; N, 9.06.

Z-L-(gln)Thz-OMe (Z-L-6g). Z-L-[glu(O-*t*-Bu)]Thz-OMe (Z-L-6f) (2.1 g, 4.8 mmol) was dissolved in trifluoroacetic acid (20 mL). The mixture was stirred at room temperature for 2 h and concentrated in vacuo. Benzene (30 mL) was added to the residue, and evaporated in vacuo. This workup using benzene was repeated three times. The residual carboxylic acid was dissolved in tetrahydrofuran (30 mL) and cooled to −15 °C. Triethylamine (1.69 mL, 12.1 mmol) and ethyl chlorocarbonate (1.16 mL, 12.1 mmol) were successively added. After the mixture was stirred at −15 °C for 0.5 h, concentrated ammonium hydroxide (5 mL) in tetrahydrofuran (30 mL) was added, and the mixture was stirred at −15 °C for 0.5 h and then at room temperature for 0.5 h. Chloroform (250 mL) was added, and the mixture was washed with 5% aqueous sodium hydrogen carbonate. The organic layer was dried over magnesium sulfate and concentrated in vacuo. The residue was crystallized by the addition of ethyl acetate. Filtration gave **Z-L-6g** (1.07 g, 59%) as colorless crystals: mp 157–160 °C; $[\alpha]^{23}_D$ −18.9° (*c* 1, DMF); IR 3400, 3260, 3080, 1720, 1685, 1650, 1525, 1230 cm^{-1}; NMR δ 1.9–2.65 (4 H, m), 3.93 (3 H, s), 4.8–5.3 (2 H, m), 5.10 (2 H, m), 7.32 (5 H, s), 8.13 (1 H, s). Anal. Calcd for $C_{17}H_{19}N_3O_5S$: C, 54.09; H, 5.08; N, 11.14. Found: C, 53.90; H, 4.98; N, 11.30.

Z-D-(gln)Thz-OMe (Z-D-6g): analogously prepared from Z-D-6f: mp 158–160 °C (from methanol); $[\alpha]^{23}_D$ +19.4° (*c* 1, DMF). Anal. Calcd for $C_{17}H_{19}N_3O_5S$: C, 54.09; H, 5.08; N, 11.14. Found: C, 53.65; H, 4.87; N, 10.88.

Determination of Optical Purities of Thiazole Amino Acids 6. (1) Preparation of Optically Active 3,5-Dinitrobenzoyl Derivatives 6 (X = 3,5-Dinitrobenzoyl). Boc-(ama)Thz-OMe (Boc-**6a–e**) (0.1 mmol) was dissolved in trifluoroacetic acid (1 mL), and the mixture was allowed to react at room temperature for 15 min. Trifluoroacetic acid was removed in vacuo, and the residue dissolved in methylene chloride (20 mL) was washed with saturated aqueous sodium hydrogen carbonate (10 mL) and dried over sodium sulfate. Concentration in vacuo gave H-(ama)Thz-OMe, which was dissolved in tetrahydrofuran (2 mL). Triethylamine (12 mg, 0.12 mmol) and then 3,5-dinitrobenzoyl chloride (28 mg, 0.12 mmol) was added, and the mixture was stirred at room temperature for 2–3 h. Ethyl acetate (30 mL) was added, and the mixture was successively washed with 5% aqueous hydrochloric acid (10 mL), water (10 mL), and saturated aqueous sodium chloride (10 mL) and dried over sodium sulfate. A part of the concentrated residue was purified by preparative thin-layer chromatography using silica gel (Merck Art 5744, 0.5 mm, 20 × 20 cm, benzene–diethyl ether (4:1–3:1)), giving the *N*-3,5-dinitrobenzoyl derivative **6** (X = 3,5-dinitrobenzoyl).

In the case of Z-D- and Z-L-(gln)Thz-OMe (Z-D- and Z-L-**6g**), deprotection of the Z group was carried out with 25% hydrogen bromide in acetic acid at room temperature.[27] After neutralization, the 3,5-dinitrobenzoylation was accomplished as above.

(2) Preparation of Racemic 3,5-Dinitrobenzoyl Derivatives 6 (X = 3,5-Dinitrobenzoyl) of Thiazole Amino Acids. Optically active Boc α-amino aldehydes Boc-D- or Boc-L-**4** were respectively racemized by adsorption on a column of silica gel (BW-820 MH) in ethyl acetate–hexane (1:3) during 2–3 days. Racemic Boc α-amino aldehydes Boc-D- and Boc-L-**4** thus obtained were respectively converted to the 3,5-dinitrobenzoyl derivatives as described as above.

(3) HPLC Analysis. Each 3,5-dinitrobenzoyl derivative (1 mg) was dissolved in 1,2-dichloroethane (1 mL), and 1–2 μL of them was subjected to HPLC using a chiral Sumipax OA-1000 column (i.d. 4.6 × 250 mm, purchased from Sumitomo Chemicals Co. Ltd.). The results are summarized in Table II.

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(27) Cf.: Ben-Ishai, D.; Berger, A. *J. Org. Chem.* **1952**, *17*, 1564. Ben-Ishai, D. *J. Org. Chem.* **1954**, *19*, 62.