Syntheses of 2-[(1*S*,3*S*)-1-Amino-3-carboxy-3-hydroxypropyl]-thiazole-4-carboxylic Acid and the Tripeptide Skeleton of Nosiheptide Containing the Acid

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The stereoselective synthesis of an amino acid component called Fragment D, *N*,*O*-diprotected 2-[(1*S*, 3*S*)-1-amino-3-carboxy-3-hydroxypropyl]thiazole-4-carboxylic acid of a macrobicyclic peptide antibiotic nosiheptide, was achieved by two routes. The dipeptide, Fragment B-C, 2-[(*Z*)-1-(*N*,*O*-isopropylidene-L-threonylamino)-1-propenyl]thiazole-4-carboxylic acid was also synthesized by the thiazole ring formation from (*Z*)-2-(*N*,*O*-diprotected L-threonylamino)-2-butenethioamide with ethyl bromopyruvate. The coupling of two components by using a condensing agent gave the expected tripeptide **2**, which is an important partial skeleton of the nosiheptide.

Antibiotic nosiheptide (**1**),[1] obtained from the culture of *Streptomyces* (*St.*) *actuosus*, is a macrobicyclic polythiazole-dehydropeptide, as is the antibiotic peptide produced from *St. antibioticus 8466CC*.[2] The peptide (**1**) includes a unique tripeptide substructure (**2**) composed of 2-[(1*S*,3*S*)-1-amino-3-carboxy-3-hydroxypropyl]thiazole-4-carboxylic acid (**3a**) residue called Fragment D and 2-[1-(*N*,*O*-isopropylidene-L-threonyl)amino-(*Z*)-1-propenyl]thiazole-4-carboxylic acid (Fragment B-C: **4**) segment, as shown in Fig. 1. The synthesis of **4** by the thiazole ring forming reaction of *N*-[*N*,*O*-diprotected threonyl(Thr)]-(*Z*)-ΔAbu-thioamide (ΔAbu=2-amino-2-butenoic acid residue) with ethyl bromopyruvate was already communicated[3] (see Scheme 4).

The interesting structure as well as the bioactivity of **1** attracted and prompted us to study the total synthesis and structure-bioactivity relationship. Here, we wish to report the stereoselective syntheses of protected (1*S*, 3*S*)-**3a** and (1*S*,3*R*)-**3b** starting from 5-oxo-L-proline (pyroglutamic acid), and independently from (*Z*,*S*)-2-amino-4,5-dihydroxy-2-pentenoic acid derivative. The practical synthesis of the desired skeleton (**2**) of nosiheptide (**1**) by the coupling of **4** with **3a** is also described.

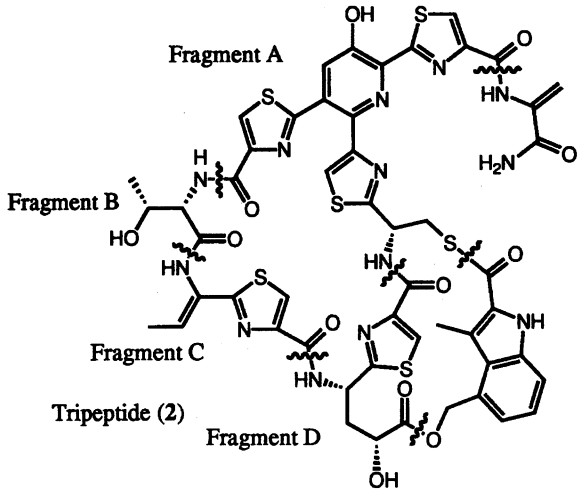


Fig. 1. Nosiheptide (**1**).

Results and Discussion

First of all, we studied the synthesis of **3** from (*S*)-5-hydroxymethyl-2-pyrrolidinone (**5**), which was derived from 5-oxo-L-proline in two steps.[4] In order to introduce hydroxyl group stereoselectively to 3-position of pyrrolidinone ring of **5**, the steric effect of the *O*-substituent group at 5-hydroxymethyl group was thought to be efficient and this was examined in detail. The hydroxyl group was silylated or alkylated with bulky *t*-butyldimethylsilyl (TBS), triphenylmethyl (trityl, Tr), or *t*-butyldiphenylsilyl (TBDPS) chloride in the presences of 4-dimethylaminopyridine (DMAP) and imidazole. Then, the amide group of the formed 5-(*O*-substituted hydroxymethyl)-2-pyrrolidinone intermediate was

also blocked with di-*t*-butyl dicarbonate (Boc_2O) in the presence of both Et_3N and DMAP[4,5] to give the corresponding *N*-Boc-5-[(*O*-TBS)-, (*O*-Tr)-, and (*O*-TBDPS) hydroxymethyl]-2-pyrrolidinones (**6a**, **6b**, and **6c**) in 58—62% yields, respectively.

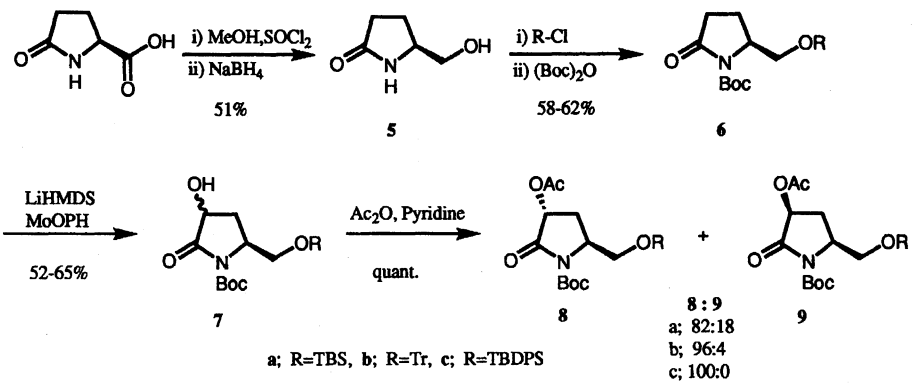
Subsequently, the regioselective and stereoselective hydroxylations of **6a—c** with lithium bis(trimethylsilyl)amide and then MoOPH[6,7] gave the corresponding 3-hydroxypyrrolidinone derivatives (**7a—c**)[7] in 52—65% yields as diastereomeric mixtures. To confirm the configurations and the formation ratios, the formed secondary hydroxyl group of **7** was acylated with Ac_2O in pyridine to give the corresponding 3-acetoxy derivatives (**8** and **9**) almost quantitatively. In the cases of **7a** and **7b**, the ratio of (3*R*,5*S*)-**8a,b** and (3*S*,5*S*)-**9a,b** were found to show high diastereomeric excess in 82 : 18 and 96 : 4, respectively, but the desirable (3*S*,5*S*)-isomers (**9a** and **9b**) were the minor products. In the case of **7c**, only (3*R*,5*S*)-isomer (**8c**) was obtained in an almost quantitative yield, as shown in Scheme 1. The configurations of **8** and **9** could be confirmed in the following way. First, the methoxymethylation of **7c** with chloromethyl methyl ether (MOMCl) gave the corresponding methoxymethoxy derivative (**10b**), which was then reduced with $Me_2S{\cdot}BH_3$ and $(MeO)_3B$ to give the corresponding pyrrolidine derivative.[8] The obtained pyrrolidine was completely identified with the (2*S*,4*R*)-*N*-Boc-2-(TBDPS-oxymethyl)-4-(MOM-oxy)-pyrrolidine,[8] which was derived from *N*-Boc-L-hydroxyproline via (2*S*,4*R*)-*N*-Boc-2-hydroxymethyl-4-(MOM-oxy)pyrrolidine.

Consequently, the inversion of (3*R*)-hydroxyl group of **7c** was successfully inverted in the following way. The S_N2 reaction of (3*R*,5*S*)-**7c** with benzoic acid (BzOH) in the presence of both Ph_3P and diethyl azodicarboxylate (DEAD) proceeded smoothly to give the corresponding (3*S*,5*S*)-benzoyloxy derivative (**10a**). The deprotection of the benzoyl group and the cleavage of the 2-pyrrolidinone ring with NaOEt in EtOH in one-pot gave ethyl (2*S*,4*S*)-4-(*N*-Boc-amino)-2-hydroxy-5-(TBDPS-oxy)-pentanoate (**11a**) in good yield. After protecting the 2-hydroxyl group with MOMCl in the presence of *N*,*N*-diisopropylethylamine [(*i*-Pr)$_2$NEt] to the 2-(methoxymethoxy)pentanoate derivative (**12a**), we deprotected the TBDPS group with *n*-Bu_4NF in AcOH to give the corresponding (2*S*,4*S*)-5-hydroxypentanoate derivative (**13a**) in good yield.

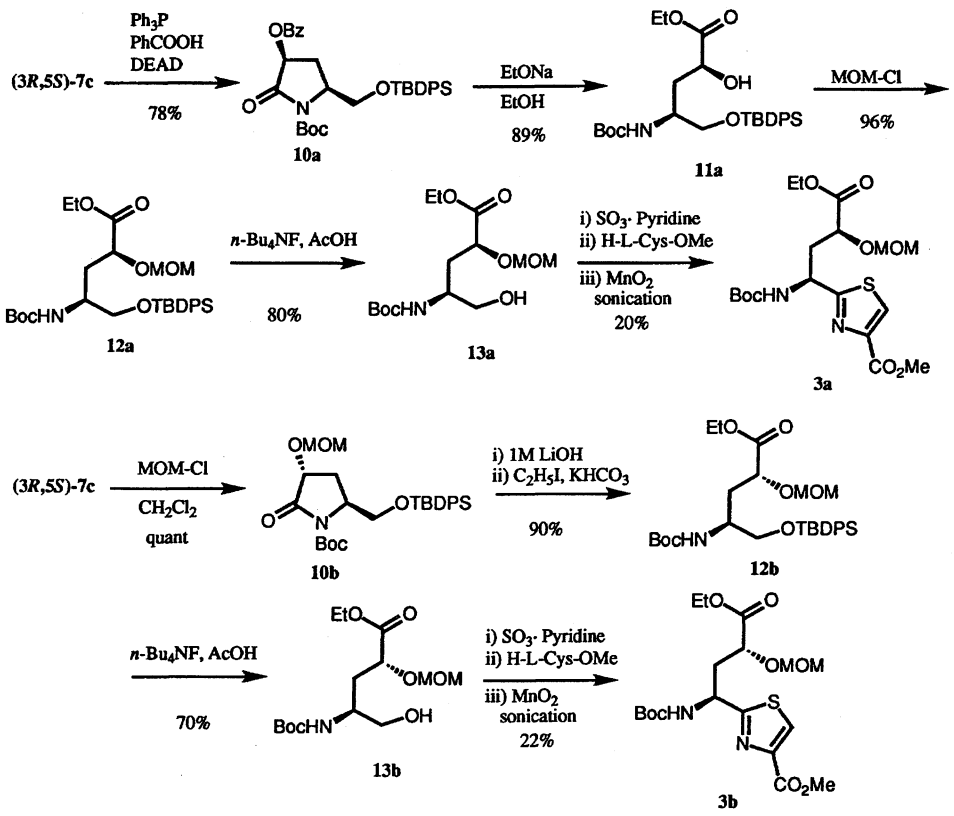
Finally, to construct a thiazole (Thz) ring in **13a**, the oxidation of the hydroxymethyl group with an addition compound pyridine–SO_3 (1/1) in dimethyl sulfoxide (DMSO) in the presence of Et_3N, followed by the cyclization with L-cysteine methyl ester (H–Cys–OMe) in benzene gave the corresponding thiazolidine-4-carboxylate as the intermediate.[9] Without isolation, the immediate oxidation with MnO_2[9] in the presence of pyridine under sonication gave the expected protected (1*S*,3*S*)-**3a**, as shown in Scheme 2. In a similar manner, (1*R*,3*S*)-isomer (**3b**) could be readily synthesized in high yields from **7c**.

Moreover, the independent preparation of (1*S*,3*S*)-**3c** from methyl (4*S*,2*Z*)-2-(benzyloxycarbonyl(Cbz)-amino)-4,5-isopropylidenedioxy-2-pentenoate (**14**) was also accomplished. The compound **14** was derived by the condensation of (*R*)-2,3-*O*-isopropylideneglyceraldehyde with methyl 2-(Cbz-amino)-2-(diethoxyphosphinyl)acetate by the method reported by Schmidt et al.[10] The reduction of **14** with $NiCl_2{\cdot}6H_2O$ and $NaBH_4$ gave the corresponding (2*RS*)-norvaline diastereomers (**15**).[10] Interestingly, the enzymatic separation of the diastereomers by using α-chymotrypsin A (α-CT) in McIlvaine buffer at pH 8[11] gave the corresponding (2*S*, 4*S*)-α-amino acid (**16**) in 43% yield, along with isomeric (2*S*,4*R*)-ester in 40% yield. The configuration of **16** was easily determined by the conversion to the authentic (3*S*,5*S*)-3-(Boc-amino)-5-(hydroxymethyl)oxacyclopentane-2-one,[12,13] while the (2*R*,4*S*)-ester (**15**) was also converted to the corresponding (3*R*,5*S*)-lactone.[12,13] In the case of the mass production of **16** or its diastereoisomer, this enzymatic method was found to be very effective and widely applicable.

Subsequently, the thiazole ring formation was achieved through the thioamide (**18**). Compound **16** was reacted with aqueous ammonia in the presence of *N*-hydroxysuccinimide (HOSu) by the usual dicyclohex-

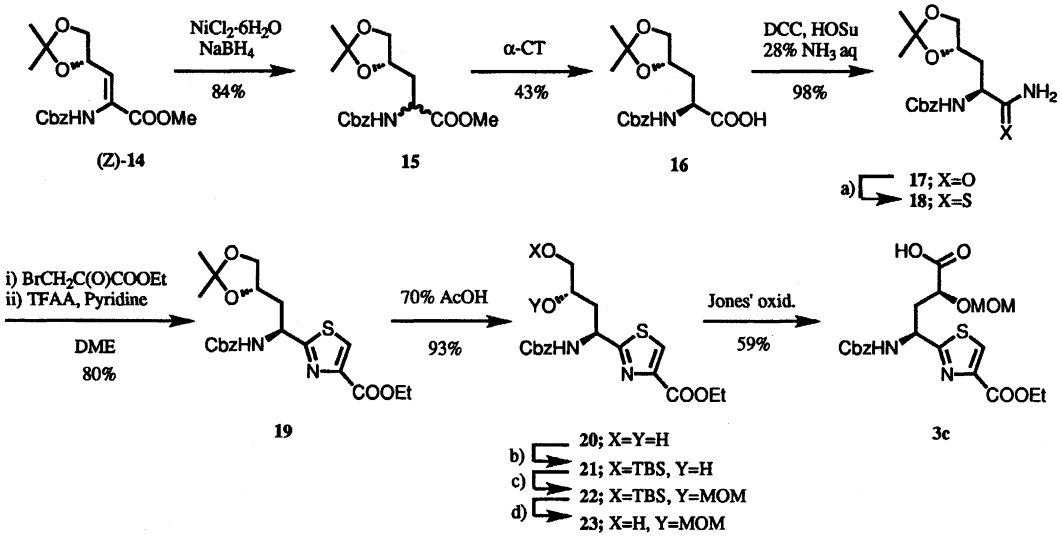


Scheme 1.

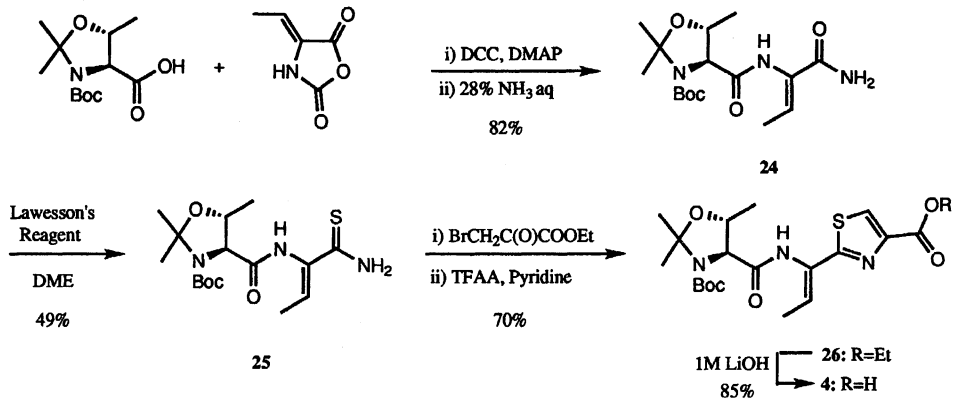


Scheme 2.

ylcarbodiimide (DCC) method giving the corresponding amide (**17**), which was then converted to the expected thioamide (**18**) by Lawesson's reagent.[14] According to the Hantzsch thiazole synthesis,[15] the cyclization of **18** with ethyl bromopyruvate in the presence of pyridine in trifluoroacetic anhydride (TFAA) gave ethyl 2-[(1*S*,3*S*)-1-(Cbz-amino)-3,4-(isopropylidenedioxy)butyl]thiazole-4-carboxylate (**19**). The isopropylidene group was eliminated with 70% AcOH to give the corresponding 3,4-dihydroxy derivative (**20**). Then the selective protection of the primary hydroxyl group with TBSCl in the presence of Et_3N and DMAP in CH_2Cl_2 gave the corresponding 4-(TBS)oxy derivative (**21**). The secondary hydroxyl group of **21** was further blocked with MOMCl in the presence of $(i\text{-Pr})_2NEt$ to the corresponding 3, 4-diprotected derivative (**22**), and the selective elimination of TBS group with n-Bu_4NF in tetrahydrofuran (THF) gave 2-[4-hydroxy-3-(MOM-oxy)butyl]thiazole derivative (**23**), which was finally oxidized with Jones' reagent to give the expected **3c**, as shown in Scheme 3.



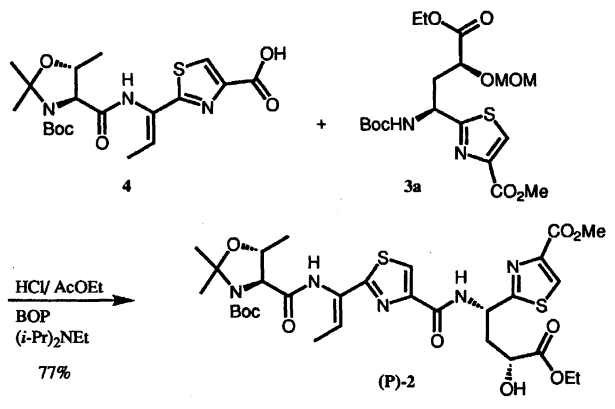
Scheme 3.



Scheme 4.

The synthesis of **4** was examined in detail. The useful one-pot coupling of (*Z*)-*N*-carboxy-2-amino-2-butenoic acid anhydride (ΔAbu·NCA), which was derived by the cyclization of (*Z*)-2-Cbz-amino-2-butenoic acid with $SOCl_2$,[4,5] with *N*-Boc-*N*,*O*-isopropylidene-L-threonine in the presence of DCC and DMAP in THF and then with 28% aqueous ammonia, was achieved to give the *N*-(protected-L-threonyl)-(*Z*)-ΔAbu–NH_2 (**24**). The reaction of **24** with Lawesson's reagent gave the corresponding thioamide (**25**), which was then cyclized with ethyl bromopyruvate to give the corresponding ethyl thiazole-4-carboxylate (**26**). Subsequent ester hydrolysis of **26** with 1 M-LiOH (1 M=1 mol dm^{-3}) gave **4**, as shown in Scheme 4.

Finally, the coupling of **4** with **3a** was carried out by the method communicated previously by us.[3] Namely, to utilize **3a** as the *N*-component, the Boc and MOM groups were eliminated with HCl in EtOAc at 0 °C and the obtained crude deprotected ester was coupled in situ with the *C*-component **4** in CH_3CN by using both (benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate (BOP) as the condensing agent and (*i*-Pr)$_2$NEt at pH 8 at room temperature to give the expected tripeptide [(**P**)-**2**], Fragment B-C-D of **1**, in 77% yield, as shown in Scheme 5.



Scheme 5.

Experimental

Melting points were measured with a Yamato Mp-21 micro-melting point apparatus, and are uncorrected. The IR spectra were recorded with a Hitachi 270-30 spectrometer in KBr. The ^{1}H NMR spectra were measured with JEOL EX 90 and FX 200 spectrometers in $CDCl_3$, DMSO-d_6, and C_6D_6 solution with tetramethylsilane as the internal standard. The specific rotations were measured in a 0.5 dm tube using a JASCO DIP-4 polarimeter in MeOH.

(*S*)-5-Hydroxymethyl-2-pyrrolidinone (5). To a solution of 5-oxo-L-proline (5.00 g, 38.7 mmol) in MeOH (50 ml) was added $SOCl_2$ (3.09 ml, 42.6 mmol) dropwise, with stirring, at −20 °C. After being stirred at −20 °C for 30 min and at room temperature for 1 h, the reaction mixture was concentrated in vacuo to give a residue. This was dissolved in EtOH (70 ml) and then the temperature was reduced by adding $NaBH_4$ (1.61 g, 42.6 mmol) by portions at 0 °C. After being stirred at 0 °C for 30 min and at room temperature for 1.5 h, the resultant solution was acidified with concentrated HCl to pH 3—4 below 0 °C. Evaporation in vacuo gave crude crystals, which were purified on a silica-gel column using a mixture of hexane and EtOAc (10:1 v/v) to give colorless crystals. Recrystallization from acetone gave pure **5** as colorless needles. Yield 51%. Mp 86—87 °C. $[\alpha]_D^{25}$ +33.5° (*c* 0.5, EtOH). IR 3196, 2926, 1662, 1464, 1425 cm^{-1}. ^{1}H NMR δ=1.68—2.47 (m, 4H), 3.30—3.85 (m, 3H), 4.56 (t, 1H, *J*=5.9 Hz, OH), 7.48 (br s, 1H, NH). Found: C, 52.16; H, 7.88; N, 12.17%. Calcd for $C_5H_9NO_2$: C, 52.34; H, 7.77; N, 12.21%.

(*S*)- 1- *t*- Butoxycarbonyl- 5- [(*t*- butyldimethylsiloxy)methyl]-2-pyrrolidinone (6a). To a solution of **5** (1.00 g, 8.64 mmol) in DMF (10 ml) was added, with stirring, TBSCl (1.57 g, 10.42 mmol) and imidazole (1.04 g, 17.36 mmol) for 30 min below 0 °C. After being stirred at 0 °C for 30 min and at room temperature for 6 h, the resulting solution was added to EtOAc (30 ml). This mixture was washed twice with water and then dried over anhydrous Na_2SO_4. Evaporation of EtOAc solution in vacuo gave a crude residue, which was dissolved in CH_2Cl_2 (15 ml). Et_3N (1.34 ml, 9.55 mmol), DMAP (0.21 g, 1.74 mmol), and then Boc_2O (2.07 g, 9.50 mmol) were successively added, with stirring, to the prepared solution. After being stirred at 0 °C for 30 min and at room temperature for 6 h, the reaction mixture was added to $CHCl_3$ (20 ml). This mixture was

washed with 10% citric acid (20 ml) and brine (20 ml), and then dried over anhydrous Na_2SO_4. Evaporation in vacuo gave a residue, which was purified on a silica-gel column using a mixture of hexane and EtOAc (3 : 1 v/v) to give **6a** as a colorless syrup. Yield 60%. $[\alpha]_D^{26}$ −24.1° (*c* 1.31, MeOH). IR 2956, 1791, 1758, 1713, 1371 cm^{-1}. ^1H NMR δ=0.04 (s, 6H), 0.88 (s, 9H), 1.53 (s, 9H), 1.92—2.29 (m, 2H), 2.34—2.96 (m, 2H), 3.68 (dd, 1H, *J*=2.4 and 10.3 Hz), 3.98 (dd, 1H, *J*=3.7 and 10.3 Hz), 4.11—4.21 (m, 1H). Found: C, 58.18; H, 9.39; N, 4.35%. Calcd for $C_{16}H_{31}NO_4Si$: C, 58.32; H, 9.48; N, 4.25%.

(*S*)-1-*t*-Butoxycarbonyl-5-trityloxymethyl-2-pyrrolidinone (6b). Similarly to the case of **6a**, the reaction of **5** (1.00 g, 8.68 mmol) with TrCl (2.66 g, 9.55 mmol) and then protection with Boc_2O (2.07 g, 9.50 mmol) in the presence of Et_3N (1.34 ml, 9.55 mmol) and DMAP (0.21 g, 1.74 mmol) gave crude crystals, which were recrystallized from diisopropyl ether to give **6b** as colorless needles. Yield 62%. Mp 118—119 °C. $[\alpha]_D^{25}$ −34.5° (*c* 0.7, MeOH). IR 2974, 2932, 1785, 1425, 1416, 1368 cm^{-1}. ^1H NMR δ=1.43 (s, 9H), 1.94—2.28 (m, 2H), 2.44—2.87 (m, 2H), 3.10 (dd, 1H, *J*=2.6 Hz), 3.49 (dd, 1H, *J*=4.6 and 9.5 Hz), 4.17—4.38 (m, 1H), 7.18—7.74 (m, 15H). Found: C, 76.29; H, 6.76; N, 3.11%. $C_{29}H_{31}NO_4$: C, 76.12; H, 6.83; N, 3.06%.

(*S*)-1-*t*-Butoxycarbonyl-5-[(*t*-butyldiphenylsiloxy)methyl]-2-pyrrolidinone (6c). Similarly to the case of **6a**, the silylation of **5** (1.00 g, 8.68 mmol) with TBDPSCl (2.23 ml, 10.42 mmol) and then *N*-protection with Boc_2O (2.84 g, 13.02 mmol) in the presence of Et_3N (1.34 ml, 9.55 mmol) and DMAP (0.21 g, 1.74 mmol) gave crude crystals, which were recrystallized from hexane–EtOAc to give **6c** as colorless needles. Yield 58%. Mp 111—113 °C. $[\alpha]_D^{25}$ −33.84° (*c* 0.62, MeOH). IR 2932, 2884, 2854, 1746, 1710, 1311 cm^{-1}. ^1H NMR δ=1.05 (s, 9H), 1.43 (s, 9H), 1.98—2.24 (m, 2H), 2.45—3.84 (m, 2H), 3.69 (dd, 1H, *J*=14.5 and 2.6 Hz), 3.91 (dd, 1H, *J*=4.0 and 14.5 Hz), 4.13—4.31 (m, 1H), 7.34—7.72 (m, 10H). Found: C, 69.01; H, 8.17; N, 3.00%. Calcd for $C_{26}H_{35}NO_4Si$: C, 68.84; H, 7.78; N, 3.09%.

(3*RS*,5*S*)-1-*t*-Butoxycarbonyl-5-[(*t*-butyldimethylsiloxy)methyl]-3-hydroxy-2-pyrrolidinone (7a). To a solution of HMDS (1.91 ml, 8.28 mmol) in THF (5 ml) was added a hexane solution (1.64 M) of *n*-BuLi (1.85 ml, 8.28 mmol) under Ar atmosphere at −78 °C for 30 min and then a solution of **6a** (1.00 g, 2.76 mmol) in THF (5 ml) was added slowly. After being stirred continuously for 30 min, we added MoOPH (1.79 g, 4.14 mmol), with more stirring, to the reaction mixture at −40 °C. After being stirred at −40 °C for 30 min, a saturated aqueous NH_4Cl solution (10 ml) was further added. Evaporation of THF in vacuo gave a residual aqueous solution, which was extracted with EtOAc (20 ml×3). The combined extracts were washed with brine (20 ml) and dried over anhydrous Na_2SO_4. Concentration in vacuo gave a crude syrup, which was purified on a silica-gel column using a mixture of hexane and EtOAc (3 : 2 v/v) to give **7a** as a colorless syrup. Yield 52%. IR 3466, 2932, 2860, 1788, 1722 cm^{-1}. Found: C, 55.75; H, 8.88; N, 4.09%. Calcd for $C_{16}H_{31}NO_5Si$: C, 55.62; H, 9.04; N, 4.05%.

(3*RS*,5*S*)-1-*t*-Butoxycarbonyl-3-hydroxy-5-trityloxymethyl-2-pyrrolidinone (7b). Similarly to the case of **7a**, the reaction of **6b** (1.00 g, 2.19 mmol) with *n*-BuLi (1.33 ml, 6.56 mmol) and then with HMDS (1.37 ml, 6.56 mmol) and MoOPH (0.86 g, 3.28 mmol) gave **7b** as a colorless syrup. Yield 65%. IR 3472, 2980, 1713, 1491, 1452, 1302 cm^{-1}. Found: C, 70.60; H, 6.77; N, 2.85%. Calcd for $C_{31}H_{31}NO_5 \cdot H_2O$: C, 70.86; H, 6.77; N, 2.85%.

(3*RS*,5*S*)-1-*t*-Butoxycarbonyl-5-[(*t*-butyldiphenylsiloxy)methyl]-3-hydroxy-2-pyrrolidinone (7c). Similarly to the case of **7a**, the reaction of **6c** (1.00 g, 2.22 mmol) with *n*-BuLi (1.34 ml, 6.61 mmol) and then with HMDS (1.39 ml, 6.61 mmol) and MoOPH (1.3 g, 3.31 mmol) gave colorless crystals, which were recrystallized from hexane–EtOAc to give pure **7c** as colorless needles. Yield 58%. Mp 151—152 °C. $[\alpha]_D^{25}$ −11.55° (*c* 1.09, MeOH). IR 3484, 2932, 2854, 1773, 1692, 1332 cm^{-1}. ^1H NMR δ=1.03 (s, 9H), 1.45 (s, 9H), 1.92—2.67 (m, 2H), 3.01 (br s, 1H, OH), 3.65 (dd, 1H, *J*=2.2 and 10.6 Hz), 3.92 (dd, 1H, *J*=3.1 and 10.6 Hz), 4.12—4.29 (m, 1H), 4.74 (dd, 1H, *J*=8.8 and 10.1 Hz), 7.34—7.68 (m, 10H). Found: C, 66.17; H, 7.80; N, 2.91%. Calcd for $C_{26}H_{35}NO_5Si$: C, 66.49; H, 7.51; N, 2.98%.

(3*SR*,5*S*)-3-Acetoxy-1-*t*-butoxycarbonyl-5-[(*t*-butyldimethylsiloxy)methyl]-2-pyrrolidinone (8a and 9a). A solution of **7a** (100 mg, 0.29 mmol) in pyridine (1 ml) and Ac_2O (0.08 ml, 0.87 mmol) was stirred at 40 °C for 1 h. To the reaction mixture was added EtOAc (10 ml) and the resulting solution was washed with 0.5 M-HCl (10 ml) and brine (10 ml) and then dried over anhydrous Na_2SO_4. Evaporation in vacuo gave a residue, which was purified on a silica-gel column using a mixture of hexane and EtOAc (3 : 1 v/v) to give a mixture of **8a** and **9a** as a syrup almost quantitatively in a 82 : 18 ratio. IR 2932, 1770, 1719, 1374, 1311 cm^{-1}. Found: C, 55.58; H, 8.49; N, 3.57%. Calcd for $C_{13}H_{33}NO_6Si$: C, 55.79; H, 8.58; N, 3.61%.

(3*RS*,5*R*)-3-Acetoxy-1-*t*-butoxycarbonyl-5-trityloxymethyl-2-pyrrolidinone (8b and 9b). Similarly to the case of **7a**, the reaction of **7b** (100 mg, 0.21 mmol) with Ac_2O (0.06 ml, 0.63 mmol) in pyridine (1 ml) gave **8b** and **9b** as a syrup almost quantitatively in a 96 : 4 ratio. IR 2974, 1794, 1746, 1719, 1374, 1308 cm^{-1}. Found: C, 70.65; H, 6.67; N, 2.50%. Calcd for $C_{31}H_{33}NO_6 \cdot 1/2H_2O$: C, 70.97; H, 6.53; N, 2.67%.

(3*R*,5*S*)-Acetoxy-1-*t*-butoxycarbonyl-5-[(*t*-butyldiphenylsiloxy)methyl]-2-pyrrolidinone (8c). Similarly to the cases of **8a** and **9a**, the reaction of **7c** (100 mg, 0.21 mmol) with Ac_2O (0.06 ml, 0.63 mmol) in pyridine (1 ml) gave **8c** as a colorless syrup in an almost quantitative yield. $[\alpha]_D^{25}$ +10.07° (*c* 0.44, MeOH). IR 2932, 1797, 1749, 1719, 1374 cm^{-1}. ^1H NMR δ=1.06 (s, 9H), 1.47 (s, 9H), 2.15 (s, 3H, OAc), 1.95—2.63 (m, 2H), 3.62 (dd, 1H, *J*=2.2 and 10.6 Hz), 3.96 (dd, 1H, *J*=2.6 and 10.6 Hz), 4.16—4.31 (m, 1H), 5.84 (dd, 1H, *J*=8.8 and 10.3 Hz), 7.34—7.72 (m, 10H). Found: C, 65.78; H, 7.64; N, 2.53%. Calcd for $C_{28}H_{37}NO_6Si$: C, 65.73; H, 7.29; N, 2.74%.

(3*S*,5*S*)-3-Benzyloxy-1-*t*-butoxycarbonyl-5-*t*-butyldiphenylsiloxymethyl-2-pyrrolidinone (10a). To a solution of **7c** (100 mg, 0.21 mmol) in THF (1 ml) was added, with stirring, successively a solution of Ph_3P (0.17 g, 0.63 mmol) in THF (1 ml) and a solution of benzoic acid (130 mg, 1.05 mmol) in benzene (2 ml) at 0 °C. After being stirred for 8 min, DEAD (0.16 ml, 1.05 mmol) was added to the prepared solution. After being stirred continuously at 0 °C for 5 h, EtOAc (20 ml) was added to the reaction mixture and the organic layer was washed with 10% citric acid (10 ml×2), with saturated aqueous $NaHCO_3$ solution

(10 ml×2), brine (20 ml), and then dried over anhydrous Na_2SO_4. Evaporation in vacuo gave a residue, which was purified on a silica-gel column using a mixture of hexane and EtOAc (5 : 1 v/v) to give colorless crystals. Recrystallization from hexane gave **10a** as colorless needles. Yield 78%. Mp 118—120 °C. $[\alpha]_D^{25}$ −34.41° (*c* 0.27, MeOH). IR 2980, 2932, 1764, 1722, 1281, 1152 cm^{-1}. ^1H NMR δ=1.46 (s, 9H), 1.63 (s, 9H), 2.20—2.71 (m, 2H), 3.81 (dd, 1H, *J*=3.1 and 9.9 Hz), 4.02 (dd, 1H, *J*=5.3 and 9.9 Hz), 4.15—4.36 (m, 1H), 5.58 (dd, 1H, *J*=6.8 and 9.2 Hz), 7.26—8.17 (m, 15H). Found: C, 69.43; H, 6.86; N, 2.56%. Calcd for $C_{33}H_{39}NO_6Si$: C, 69.08; H, 6.85; N, 2.44%.

Ethyl (2*S*,4*S*)-4-*t*-Butoxycarbonylamino-5-*t*-butyldiphenylsiloxy-2-hydroxypentanoate (11a). To a solution of **10a** (1.00 g, 1.78 mmol) in EtOH (30 ml) was added slowly, with stirring, a solution (1.75 M) of EtONa in EtOH (0.5 ml) at 0 °C. The reaction mixture was adjusted to pH 7 with AcOH at room temperature and concentrated in vacuo to give a residue. The residue was purified on a silica-gel column using a mixture of hexane and EtOAc (7 : 2 v/v) to give **11a** as a colorless syrup. Yield 89%. $[\alpha]_D^{25}$ −17.18° (*c* 0.4, MeOH). IR 3424, 3070, 2932, 1719, 1590, 1506 cm^{-1}. 200 MHz ^1H NMR δ=1.07 (s, 9H), 1.30 (t, 3H, *J*=7.0 Hz), 1.44 (s, 9H), 1.69—2.13 (m, 2H), 3.61—3.94 (m, 4H), 4.19—4.29 (m, 3H), 4.96 (br d, 1H, *J*=8.3 Hz, NH), 7.41—7.66 (m, 10H). Found: C, 65.43; H, 8.00; N, 2.71%. Calcd for $C_{28}H_{41}NO_6Si$: C, 65.21; H, 8.01; N, 2.72%.

Ethyl (2*S*,4*S*)-4-*t*-Butoxycarbonylamino-5-*t*-butyldiphenylsiloxy-2-(methoxymethoxy) pentanoate (12a). To a solution of **11a** (330 mg, 0.64 mmol) in CH_2Cl_2 (4 ml) was added slowly, with stirring, MOMCl (0.23 ml, 1.92 mmol), (*i*-Pr)$_2$NEt (0.32 ml, 1.92 mmol) at 0 °C. The prepared mixture was stirred continuously at room temperature for 6 h. The reaction mixture was washed with 10% citric acid (3 ml×3) and brine (3 ml×3), and then dried over anhydrous Na_2SO_4. Evaporation in vacuo gave a residue, which was purified on a silica-gel column using a mixture of hexane and EtOAc (5 : 1 v/v) to give **12a** as a colorless syrup. Yield 96%. $[\alpha]_D^{25}$ −13.80° (*c* 0.44, MeOH). IR 3370, 2938, 2860, 1716, 1590, 1500 cm^{-1}. 200 MHz ^1H NMR δ=1.06 (s, 9H), 1.29 (t, 3H, *J*=7.0 Hz), 1.43 (s, 9H), 1.80—1.98 (m, 2H), 3.37 (s, 3H, OMe), 3.65—4.04 (m, 3H), 4.07—4.24 (m, 3H), 4.62—4.81 (m, 3H, NH, OCH_2O), 7.26—7.70 (m, 10H). Found: C, 64.10; H, 8.12; N, 2.11%. Calcd for $C_{30}H_{45}NO_7Si$: C, 64.37; H, 8.10; N, 2.50%.

Ethyl (2*S*, 4*S*)- 4- *t*- Butoxycarbonylamino- 5- hydroxy-2-(methoxymethoxy)pentanoate (13a). To a solution of **12a** (250 mg, 0.47 mmol) in THF (2 ml) was added a solution (1 M) of *n*-Bu$_4$NF in THF (0.88 ml) and AcOH (0.88 ml) at 0 °C. The prepared solution was stirred continuously at room temperature for 8 h. Evaporation in vacuo gave a residue, which was purified on a silica-gel column using a mixture of hexane and EtOAc (1 : 1 v/v) to give **13a** as a colorless syrup. Yield 80%. Mp 86—87 °C. $[\alpha]_D^{25}$ −21.56° (*c* 0.4, MeOH). IR 3394, 2974, 1695, 1524 cm^{-1}. 200 MHz ^1H NMR δ=1.29 (t, 3H, *J*=7.0 Hz), 1.44 (s, 9H), 1.86—2.01 (m, 2H), 2.33 (br s, 1H, OH), 3.40 (s, 3H, OMe), 3.61—4.01 (m, 3H), 4.09—4.33 (m, 3H), 4.71 (s, 2H, OCH_2O), 4.92 (br d, 1H, *J*=8.4 Hz, NH). Found: C, 52.21; H, 8.37; N, 4.79%. Calcd for $C_{14}H_{27}NO_7$: C, 52.33; H, 8.47; N, 4.36%.

Methyl 2- [(1*S*, 3*S*)- 1- *t*- Butoxycarbonylamino-3-ethoxycarbonyl- 3- (methoxymethoxy)propyl]thiazole-4-carboxylate (3a). To a solution of **13a** (43 mg, 0.13 mmol) in CH_2Cl_2 (2 ml) was added dropwise, with stirring, Et_3N (0.15 ml, 1.04 mmol) and a solution of SO_3·pyridine complex (59 mg, 0.39 mmol) in DMSO (2 ml) at −10 °C. After being stirred at −10 °C for 2 h, diethyl ether (1 ml) and chilled EtOAc (3 ml) were added to the prepared mixture. The reaction mixture was washed with 10% citric acid (3 ml×3) and brine (3 ml×3), and then dried over anhydrous Na_2SO_4. Evaporation in vacuo gave a crude residue, which was dissolved in benzene (2 ml). To the benzene solution was added a solution of L-Cys–OMe (35 mg, 0.26 mmol) in benzene (1.5 ml). The resulting solution was stirred at room temperature overnight. MnO_2 (283 mg) and pyridine (10 μl) were further added, with stirring, to the prepared mixture under sonication. After removal of MnO_2, the filtrate was concentrated in vacuo to give a residue, which was purified on a silica-gel column using a mixture of hexane and EtOAc (3 : 1 v/v) to give **3a** as a yellow syrup. Yield 20%. $[\alpha]_D^{25}$ −7.00° (*c* 0.22, MeOH). IR 3364, 2974, 1725, 1506 cm^{-1}. ^1H NMR δ=1.27 (t, 3H, *J*=7.0 Hz), 1.43 (s, 9H), 2.26—2.59 (m, 2H), 3.40 (s, 3H, OMe), 3.94 (s, 3H, COOMe), 4.04—4.32 (m, 3H), 4.69 (s, 2H, OCH_2O), 5.26—5.51 (m, 1H), 5.61 (br d, 1H, *J*=7.9 Hz, NH), 8.11 (s, 1H, Thz–H-5). Found: C, 49.93; H, 6.63; N, 6.25%. Calcd for $C_{18}H_{28}N_2O_8S$: C, 49.99; H, 6.53; N, 6.45%.

(3*R*,5*S*)-1-*t*-Butoxycarbonyl-5-[(*t*-butyldiphenylsiloxy)methyl]- 3- methoxymethoxy- 2- pyrrolidinone (10b). To a solution of **7c** (1.0 g, 2.13 mmol) in CH_2Cl_2 (5 ml) was added slowly, with stirring, MOMCl (0.48 ml, 6.39 mmol) and *N*,*N*-diisopropylethylamine (1.09 ml, 6.39 mmol) at 0 °C. After being stirred at room temperature for 8 h, diethyl ether (2 ml) was added to the reaction mixture and the resulting solution was washed with 10% citric acid (5 ml×3), with brine (5 ml×3), and then dried over anhydrous Na_2SO_4. Evaporation in vacuo gave a residue, which was purified on a silica-gel column using a mixture of hexane and EtOAc (3 : 1 v/v) to give **10b** as a colorless syrup. $[\alpha]_D^{25}$ +21.28° (*c* 0.34, MeOH). IR 2932, 1791, 1761, 1716, 1371 cm^{-1}. ^1H NMR δ=1.05 (s, 9H), 1.47 (s, 9H), 2.04—2.46 (m, 2H), 3.41 (s, 3H, OMe), 3.63 (dd, 1H, *J*=12.8 and 2.2 Hz), 3.95 (dd, 1H, *J*=4.0 and 12.8 Hz), 4.09—4.27 (m, 1H), 4.79—4.90 (m, 1H), 4.74 and 4.98 (ABq, 2H, *J*=6.6 Hz, OCH_2O), 7.35—7.67 (m, 10H). Found: C, 65.15; H, 7.94; N, 2.63%. Calcd for $C_{28}H_{39}NO_6Si$: C, 65.47; H, 7.65; N, 2.73%.

Ethyl (2*R*,4*S*)-4-*t*-Butoxycarbonylamino-5-*t*-butyldiphenylsiloxy- 2- (methoxymethoxy) pentanoate (12b). To a solution of **10b** (1.09 g, 2.13 mmol) in dioxane (10 ml) was added, with stirring, 1 M-LiOH (2.8 ml) at 0 °C. The reaction mixture was poured into water (50 ml) and then extracted with diethyl ether (10 ml×2). The aqueous layer was acidified with 10% citric acid to pH 3—4 and extracted with EtOAc (20 ml×3). The combined extracts were washed with brine (20 ml×3) and dried over anhydrous Na_2SO_4. Evaporation in vacuo gave a residue, which was dissolved in DMF (8 ml). To the solution was added, with stirring, $KHCO_3$ (0.43 g, 4.26 mmol) and EtI (0.51 ml, 6.39 mmol) at 0 °C. After being stirred at 0 °C for 30 min and at room temperature for a while, the reaction mixture was poured into water (50 ml). The aqueous solution was extracted with EtOAc (10 ml×2) and the com-

bined extracts were washed with brine and then dried over anhydrous Na_2SO_4. Evaporation in vacuo gave a residue, which was purified on a silica-gel column using a mixture of hexane and EtOAc (5 : 2 v/v) to give **12b** as a colorless syrup. Yield 90%. $[\alpha]_D^{25}$ −9.74° (*c* 0.52, MeOH). IR 3400, 2932, 2860, 1716, 1503 cm^{-1}. ^1H NMR δ=1.08 (s, 9H), 1.28 (t, 3H, *J*=7.0 Hz), 1.42 (s, 9H), 2.00—2.23 (m, 2H), 3.36 (s, 3H, OMe), 3.72—4.06 (m, 3H), 4.13—4.32 (m, 3H, *J*=7.03 Hz), 4.59—4.86 (m, 3H, NH, OCH_2O), 7.31—7.72 (m, 10H). Found: C, 64.59; H, 8.16; N, 2.35%. Calcd for $C_{30}H_{45}NO_7Si$: C, 64.37; H, 8.10; N, 2.50%.

Ethyl (2*R*, 4*S*)-4-*t*-Butoxycarbonylamino-5-hydroxy-2-(methoxymethoxy)pentanoate (13b). Similarly to the case of **12a**, the reaction of **12b** (250 mg, 0.47 mmol) with *n*-Bu_4NF and AcOH gave **13b** as a colorless syrup. Yield 70%. $[\alpha]_D^{25}$ +10.24° (*c* 0.66, MeOH). IR 3376, 2974, 1695, 1524 cm^{-1}. ^1H NMR δ=1.29 (t, 3H, *J*=7.0 Hz), 1.43 (s, 9H), 1.92—2.10 (m, 2H), 2.39 (br s, 1H, OH), 3.39 (s, 3H, OMe), 3.62—3.90 (m, 3H), 4.09—4.33 (m, 3H, *J*=7.0 Hz), 4.69 (s, 2H, OCH_2O), 5.14 (br d, 1H, *J*=7.7 Hz, NH). Found: C, 52.54; H, 8.22; N, 4.25%. Calcd for $C_{14}H_{27}NO_7$: C, 52.33; H, 8.47; N, 4.36%.

Methyl 2-[(1*R*, 3*S*)-1-*t*-Butoxycarbonylamino-3-ethoxycarbonyl-3-(methoxymethoxy)propyl]thiazole-4-carboxylate (3b). Similarly to the case of **3a**, the reaction of **13b** (312 mg, 0.97 mmol) with L-Cys–OMe (262 mg, 0.26 mmol) and then MnO_2 (2 g) gave **3b** as a yellow syrup. Yield 22%. $[\alpha]_D^{25}$ −12.38° (*c* 0.43, MeOH). IR 3358, 2980, 1725, 1503 cm^{-1}. ^1H NMR δ=1.27 (t, 3H, *J*=7.0 Hz), 1.42 (s, 9H), 2.26—2.59 (m, 2H), 3.40 (s, 3H, OMe), 3.94 (s, 3H, COOMe), 4.04—4.32 (m, 3H), 4.69 (s, 2H, OCH_2O), 5.10—5.34 (m, 1H), 5.59 (br d, 1H, *J*=6.8 Hz, NH), 8.11 (s, 1H, Thz–H-5). Found: C, 50.25; H, 6.56; N, 6.28%. Calcd for $C_{18}H_{28}N_2O_8S$: C, 49.99; H, 6.53; N, 6.48%.

Methyl (4*S*, 2*Z*)-2-Benzyloxycarbonylamino-4,5-isopropylidenedioxy-2-pentenoate (14). To a solution of 1,2 : 5,6-di-*O*-isopropylidene-D-mannitol (2.75 g, 10.5 mmol) in 5% aqueous $NaHCO_3$ solution (15 ml) was added dropwise a solution of $NaIO_4$ (2.56 g, 12.0 mmol) in water (13 ml) under cooling; the resulting solution was stirred for 1 h. A solution of methyl (*N*-Cbz-amino)-2-diethoxyphosphorylacetate (3.25 g, 10.0 mmol) in CH_2Cl_2 (30 ml) was added, with stirring, to the above solution under cooling. To the resulting solution was added aqueous 6 M-K_2CO_3 solution (13 ml) and tetrabutylammonium bromide (TBAB) (200 mg, 0.62 mmol) and the resultant solution was stirred at room temperature for 4 h. The aqueous layer of the reaction mixture was extracted with CH_2Cl_2 (20 ml×3), the combined extracts were washed with brine (20 ml×3) and dried over anhydrous Na_2SO_4. Evaporation in vacuo gave a residue, which was chromatographed on a silica-gel column using a mixture of hexane and EtOAc (5 : 1 v/v) to give (*Z*)- and (*E*)-isomers of **14** as colorless crystals and a syrup in 9 : 1 ratio. Yield 87%.

(*Z*)-Isomer: Colorless prisms from hexane and AcOEt. Mp 84—86 °C. $[\alpha]_D^{17}$ −4.83° (*c* 0.60, $CHCl_3$) [Lit,[9]) $[\alpha]_D^{26}$ −1.30° (*c* 0.30, $CHCl_3$)]. IR 3310, 2986, 1728, 1668, 1506 cm^{-1}. 200 MHz ^1H NMR δ=1.37 (s, 3H), 1.45 (s, 3H, COOMe), 3.78 (s, 3H), 3.83 (dd, 1H, *J*=6.3 and 8.3 Hz), 4.31 (dd, 1H, *J*=6.6 and 8.3 Hz), 4.83 (ddd, 1H, *J*=6.3, 6.6, and 8.3 Hz), 5.13 (s, 2H), 6.45 (d, 1H, *J*=8.3 Hz, CH=), 6.67 (br s, 1H, NH), 7.36 (s, 5H). Found: C, 61.17; H, 6.44; N, 4.34%. Calcd for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31; N, 4.18%.

(*E*)-Isomer: Syrup. $[\alpha]_D^{25}$ +14.68° (*c* 0.10, MeOH). 200 MHz ^1H NMR δ=1.40 (s, 3H), 1.45 (s, 3H), 3.66 (dd, 1H, *J*=7.1 and 8.3 Hz), 3.84 (s, 3H, COOMe), 4.26 (dd, 1H, *J*=6.3 and 8.3 Hz), 5.15 (s, 2H), 5.35 (ddd, 1H, *J*=6.3, 7.1, and 8.3 Hz), 6.92 (br s, 1H, NH), 7.02 (d, 1H, *J*=8.3 Hz, CH=), 7.37 (s, 5H). Found: C, 61.25; H, 6.39; N, 4.52%. Calcd for $C_{17}H_{21}NO_6$: C, 60.88; H, 6.31; N, 4.18%.

Methyl (2*RS*,4*S*)-2-Benzyloxycarbonylamino-4,5-(isopropylidenedioxy)pentanoate (15). To a solution of **14** (4.85 g, 14.5 mmol) in MeOH (30 ml) was added $NiCl_2 \cdot 6H_2O$ (690 mg, 2.9 mmol) and $NaBH_4$ (600 mg, 16.0 mmol) under cooling. After being stirred at room temperature for 1 h, saturated aqueous NH_4Cl solution (30 ml) was added to the reaction mixture and the resulting solution was extracted with EtOAc (15 ml×3). The combined extracts were washed with brine (20 ml×3) and dried over anhydrous Na_2SO_4. Evaporation in vacuo gave a residue, which was purified on a silica-gel column using a mixture of hexane and EtOAc (4 : 1 v/v) to give **15** as a colorless syrup. Yield 84% in 1 : 1 diastereometric ratio. IR 3346, 2986, 1725, 1530 cm^{-1}. Found: C, 60.65; H, 6.72; N, 4.44%. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.56%.

(2*S*, 4*S*)-2-Benzyloxycarbonylamino-4,5-(isopropylidenedioxy)pentanoic Acid (16). A solution (10 ml) of **15** (340 mg, 1.0 mmol) and α-CT (150 mg) in McIlvaine buffer (pH 8) in the presence of $CaCl_2$ (10 μg) was incubated, with shaking, at 35 °C for 20 h. The reaction mixture was acidified slightly with 10% citric acid (1 ml) and was extracted with ethyl acetate (20 ml). The organic extract was washed with a saturated aqueous $NaHCO_3$ solution (15 ml×3) and with brine (10 ml×3) and then dried over anhydrous Na_2SO_4. Evaporation in vacuo gave methyl ester of (2*S*,4*R*)-diasteromer of **15** as colorless syrup in a 45% yield. On the other hand, the aqueous layer was acidified with 10% citric acid (45 ml) and extracted with EtOAc (15 ml×3). The combined extracts were washed with brine (10 ml×3) and dried over anhydrous Na_2SO_4. Evaporation in vacuo gave colorless crystals, which were recrystallized from EtOAc–hexane to give **16** as colorless needles. Yield 43% (d.e. 93%). Mp 109—110 °C. $[\alpha]_D^{25}$ −22.67° (*c* 1.0, $CHCl_3$). IR 3328, 2986, 1728, 1527 cm^{-1}. 200 MHz ^1H NMR δ=1.34 and 1.42 (s×2, 6H), 1.97—2.15 (m, 2H), 3.57 (dd, 1H, *J*=6.8 and 8.3 Hz), 4.09 (dd, 1H, *J*=5.9 and 8.3 Hz), 4.19—4.29 (m, 1H), 4.51—4.61 (m, 1H), 5.13 (s, 2H), 5.96 (d, 1H, *J*=7.7 Hz, NH), 7.35 (s, 5H), 9.57 (br s, 1H, COOH). Found: C, 59.23; H, 6.66; N, 4.25%. Calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33%.

(2*S*, 4*S*)-2-Benzyloxycarbonylamino-4,5-(isopropylidenedioxy)pentanamide (17). To a solution of **16** (1.87 g, 5.74 mmol) in CH_2Cl_2 (20 ml) was added slowly a solution of DCC (1.20 g, 5.80 mmol) in CH_2Cl_2 (10 ml) at 0 °C. After stirring for 30 min, HOSu (670 mg, 5.80 mmol) was added to the resulting mixture. After being stirred at room temperature for a while, dicyclohexyl urea (DCU) which deposited was filtered off. The filtrate was concentrated in vacuo to give a residue, which was dissolved in EtOAc (20 ml). The resulting solution was treated with 28% NH_4OH (0.76 ml) and stirred continuously for 30 min. The reaction mixture was washed with brine (15 ml×3) and dried over anhydrous Na_2SO_4. Evaporation in vacuo gave colorless crystals, which were recrystallized from hexane–EtOAc

to give **17** as colorless needles. Yield 98%. Mp 106—107 °C. $[\alpha]_D^{26}$ −12.26° (*c* 0.89, MeOH). IR 3382, 3316, 3184, 2980, 1677, 1530 cm^{-1}. 200 MHz ^1H NMR δ=1.34 and 1.41 (s×2, 6H), 1.80—2.14 (m, 2H), 3.53 (dd, 1H, *J*=7.3 and 8.3 Hz), 4.08 (dd, 1H, *J*=5.9 and 8.3 Hz), 4.18—4.42 (m, 2H), 5.13 (s, 2H), 6.17 (br d, 1H, *J*=6.2 Hz, NH), 6.51 (br s, 2H, $CONH_2$), 7.35 (s, 5H). Found: C, 59.95; H, 7.04; N, 8.29%. Calcd for $C_{16}H_{22}N_2O_5$: C, 59.62; H, 6.88; N, 8.69%.

(2*S*, 4*S*)-2-Benzyloxycarbonylamino-4, 5-(isopropylidenedioxy)pentanethioamide (18). A solution of **17** (1.67 g, 5.18 mmol) and Lawesson's reagent (1.05 g, 2.59 mmol) in 1,2-dimethoxyethane (25 ml) was stirred at 0 °C overnight. The reaction mixture was concentrated in vacuo to give a residue, which was purified on a silica-gel column using a mixture of hexane and EtOAc (1.7 : 1 v/v) to give **18** as a colorless syrup. Yield 65%. $[\alpha]_D^{26}$ −5.92° (*c* 0.35, MeOH). IR 3316, 3208, 2986, 2932, 1707, 1629, 1509 cm^{-1}. 200 MHz ^1H NMR δ=1.33 and 1.42 (s×2, 6H), 1.89—2.46 (m, 2H), 3.51—3.58 (dd, 1H, *J*=7.1 and 8.3 Hz), 4.04—4.12 (dd, 1H, *J*=6.34 and 8.3 Hz), 4.21—4.39 (m, 1H), 4.74—4.82 (m, 1H), 5.13 (s, 2H), 6.31 (br d, 1H, *J*=7.3 Hz, NH), 7.36 (s, 5H), 7.74 and 7.96 (br s×2, 2H, $CSNH_2$). Found: C, 56.90; H, 6.86; N, 7.82%. Calcd for $C_{16}H_{22}N_2O_4S$: C, 56.79; H, 6.55; N, 8.28%.

Ethyl 2-[(1*S*, 3*S*)-Benzyloxycarbonylamino-3, 4-(isopropylidenedioxy)butyl]thiazole-4-carboxylate (19). To a suspension of **18** (1.03 g, 3.05 mmol) and $KHCO_3$ (2.45 g, 24.4 mmol) in 1,2-dimethoxyethane (15 ml) was added dropwise ethyl bromopyruvate (1.15 ml, 9.15 mmol) under Ar atmosphere at 0 °C. After being stirred for 10 min, a solution of TFAA (1.70 ml, 12.2 mmol) and pyridine (1.95 ml, 24.4 mmol) in 1,2-dimethoxyethane (15 ml) was added dropwise, with stirring, to the resultant solution. After being stirred for 2 h, the reaction mixture was concentrated in vacuo to give a residue, which was dissolved in EtOAc (30 ml) and then washed with brine (20 ml×3), dried over anhydrous Na_2SO_4. Evaporation in vacuo gave a residual syrup, which was purified on a silica-gel column using a mixture of hexane and EtOAc (3 : 2 v/v) to give **19** as a yellow syrup. Yield 80%. $[\alpha]_D^{25}$ −11.8° (*c* 0.11, MeOH). IR 3316, 2980, 1722, 1530 cm^{-1}. 200 MHz ^1H NMR δ=1.39 (t, 3H, *J*=6.8 Hz), 1.28 and 1.42 (s×2, 6H), 2.08—2.52 (m, 2H), 3.51—4.12 (m, 3H), 4.41 (q, 2H, *J*=6.8 Hz), 5.15 (s, 2H), 5.33—5.42 (m, 1H), 6.53 (br d, 1H, *J*=8.3 Hz, NH), 7.36 (s, 5H), 8.08 (s, 1H, Thz–H-5). Found: C, 57.82; H, 5.98; N, 6.65%. Calcd for $C_{21}H_{26}N_2O_6S$: C, 58.05; H, 6.03; N, 6.45%.

Ethyl 2-[(1*S*,3*S*)-1-Benzyloxycarbonylamino-3,4-dihydroxybutyl]thiazole-4-carboxylate (20). A solution of **19** (660 mg, 1.52 mmol) in 70% AcOH (4 ml) was stirred at room temperature overnight and the reaction mixture was concentrated in vacuo to give a residue. The residue was dissolved in benzene and then azeotropic distillation was done three times. The residual crystals obtained were recrystallized from benzene–hexane to give **20** as colorless needles. Yield 93%. $[\alpha]_D^{25}$ −19.14° (*c* 0.43, MeOH). Mp 138—139 °C. IR 3286, 3058, 2986, 2938, 2878, 1725, 1698, 1548, 1518, 1500 cm^{-1}. 200 MHz ^1H NMR δ=1.37 (t, 3H, *J*=7.33 Hz), 1.98—2.18 (m, 2H), 2.64 (br s, 1H, OH), 3.47—3.65 (m, 3H, OH), 3.76—3.90 (m, 1H), 4.38 (q, 2H, *J*=7.3 Hz), 5.12 (s, 2H), 5.31—5.41 (m, 1H), 6.44 (br d, 1H, *J*=8.3 Hz, NH), 7.34 (s, 5H), 8.06 (s, 1H, Thz–H-5). Found: C, 54.89; H, 5.65; N, 6.84%. Calcd for $C_{18}H_{22}N_2O_6S$: C, 54.81; H, 5.62; N, 7.10%.

Ethyl 2-[(1*S*,3*S*)-1-Benzyloxycarbonylamino-4-*t*-butyldimethylsiloxy-3-hydroxybutyl]thiazole-4-carboxylate (21). To a solution of **20** (556 mg, 1.4 mmol) in CH_2Cl_2 (4 ml) was added, with stirring, Et_3N (0.26 ml, 1.82 mmol), TBSCl (253 mg, 1.68 mmol), and DMAP (14 mg, 0.11 mmol) at 0 °C. After being stirred at 0 °C for 30 min, diethyl ether (4 ml) and then EtOAc (10 ml) was added at room temperature, and the mixed organic solution was washed successively with 10% citric acid (10 ml×3), a saturated aqueous $NaHCO_3$ solution (10 ml×3), and brine (10 ml×3) and then dried over anhydrous Na_2SO_4. Evaporation in vacuo gave a residual syrup, which was purified on a silica-gel column using a mixture of hexane and EtOAc (2 : 1 v/v) to give **21** as a colorless syrup. Yield 95%. $[\alpha]_D^{24}$ −14.04° (*c* 0.85, MeOH). IR 3340, 2932, 2860, 1722, 1503 cm^{-1}. 200 MHz ^1H NMR δ=0.01 (s, 6H), 0.83 (s, 9H), 1.35 (t, 3H, *J*=7.1 Hz), 1.78—2.21 (m, 2H), 2.90 (br s, 1H, OH), 3.35—3.70 (m, 3H), 4.37 (q, 2H, *J*=7.0 Hz), 5.10 (s, 2H), 5.25—5.45 (m, 1H), 6.65 (br d, 1H, *J*=7.5 Hz, NH), 7.30 (s, 5H), 8.03 (s, 1H, Thz–H-5). Found: C, 56.64; H, 6.96; N, 5.31%. Calcd for $C_{24}H_{36}N_2O_6SSi$: C, 56.67; H, 7.13; N, 5.51%.

Ethyl 2-[(1*S*,3*S*)-1-Benzyloxycarbonylamino-4-*t*-butyldimethylsiloxy-3-(methoxymethoxy)butyl]thiazole-4-carboxylate (22). To a solution of **21** (670 mg, 1.31 mmol) in CH_2Cl_2 (7 ml) was added slowly, dropwise, $(i\text{-Pr})_2NEt$ (0.66 ml, 3.94 mmol) and MOMCl (0.30 ml, 3.94 mmol) at 0 °C. After being stirred at 0 °C for 10 min and at room temperature for 8 h, diethyl ether (5 ml) and EtOAc (10 ml) were further added, and the organic resulting solution was washed successively with 10% citric acid (10 ml×3), saturated aqueous $NaHCO_3$ solution (10 ml×3), brine (10 ml×3), and then dried over anhydrous Na_2SO_4. Evaporation in vacuo gave a residual syrup, which was purified on a silica-gel column using a mixture of hexane and EtOAc (2 : 1 v/v) to give **22** as a colorless syrup. Yield 98%. $[\alpha]_D^{25}$ −13.92° (*c* 0.35, MeOH). IR 3670, 2944, 2866, 1716, 1536 cm^{-1}. 200 MHz ^1H NMR δ=0.03 (s, 6H), 0.87 (s, 9H), 1.39 (t, 3H, *J*=6.8 Hz), 2.11—2.36 (m, 2H), 3.34 (s, 3H, OMe), 3.52—3.72 (m, 3H), 4.40 (q, 2H, *J*=6.8 Hz), 4.61 and 4.71 (ABq, 2H, *J*=6.3 Hz, OCH_2O), 5.12 (s, 2H), 5.21—5.39 (m, 1H), 6.29 (br d, 1H, *J*=6.8 Hz, NH), 7.35 (s, 5H), 8.07 (s, 1H, Thz–H-5). Found: C, 56.60; H, 7.33; N, 4.89%. Calcd for $C_{26}H_{40}N_2O_7SSi$: C, 56.50; H, 7.29; N, 5.07%.

Ethyl 2-[(1*S*,3*S*)-1-Benzyloxycarbonylamino-4-hydroxy-3-(methoxymethoxy)butyl]thiazole-4-carboxylate (23). To a solution of **22** (670 mg, 1.21 mmol) in THF (7 ml) was added, with stirring, a solution (1.53 ml) of *n*-Bu_4NF in THF (1 M) at 0 °C. After being stirred at 0 °C for 10 min and at room temperature for 2 h, the reaction mixture was evaporated in vacuo to give a residual syrup. The residue was purified on a silica-gel column using a mixture of hexane and EtOAc (1 : 2 v/v) to give **23** as colorless syrup. Yield 97%. $[\alpha]_D^{25}$ −14.70° (*c* 0.57, MeOH). IR 3340, 2938, 1719, 1536 cm^{-1}. 200 MHz ^1H NMR δ=1.39 (t, 3H, *J*=6.8 Hz), 2.18—2.30 (m, 2H), 3.39 (s, 3H, Me), 3.56 (s, 2H), 3.61—3.76 (m, 2H, OH), 4.40 (q, 2H, *J*=6.8 Hz), 4.55 and 4.72 (ABq, 2H, *J*=6.8 Hz, OCH_2O), 5.12 (s, 2H), 5.29—5.44 (m, 1H), 6.11 (br d, 1H, *J*=8.8 Hz, NH), 7.35 (s, 5H), 8.07 (s, 1H, Thz–H-5). Found: C, 54.91; H,

5.76; N, 6.46%. Calcd for $C_{20}H_{26}N_2O_7S$: C, 54.78; H, 5.98; N, 6.39%.

Ethyl 2-[(1*S*,3*S*)-1-Benzyloxycarbonylamino-3-carboxy-3-(methoxymethoxy)propyl]thiazole-4-carboxylate (3c). To a solution of **23** (473 mg, 1.08 mmol) in acetone (20 ml), Jones' reagent (1.42 ml) was added, with stirring at 0 °C. After being stirred for 6 h, the reaction mixture was neutralized with a saturated aqueous $NaHCO_3$ solution and the deposited material was filtered off. The filtrate was concentrated in vacuo to half volume, and extracted with ethyl acetate (5 ml). The aqueous layer was acidified with 10% citric acid and extracted three times with EtOAc (10 ml×3). The combined extracts were washed twice with brine (15 ml×2) and dried over anhydrous Na_2SO_4. Evaporation in vacuo gave **3c** as a colorless syrup. Yield 59%. $[\alpha]_D^{25}$ −40.09° (*c* 0.60, MeOH). IR 3496, 3316, 2974, 1725, 1530 cm^{-1}. 200 MHz ^1H NMR δ=1.27 (t, 3H, *J*=6.8 Hz), 2.39 (m, 2H), 3.23 (s, 3H, OMe), 4.21—4.34 (m, 3H), 4.52 and 4.63 (d×2, 2H, J_{AB}=6.4 Hz, OCH_2O), 5.01 (s, 2H), 5.21—5.40 (m, 1H), 6.35 (br d, 1H, *J*=8.3 Hz, NH), 7.22 (s, 5H), 7.99 (s, 1H, Thz-H-5), 8.96 (br s, 1H, COOH). Found: C, 53.23; H, 5.17; N, 5.96%. Calcd for $C_{20}H_{24}N_2O_8S$: C, 53.09; H, 5.35; N, 6.19%.

(*Z*)-2-(*N*-*t*-Butoxycarbonyl-*N*,*O*-isopropylidene-L-threonyl)amino-2-butenamide (24). To a stirred solution of *N*-Boc-*N*,*O*-isopropylidene-L-threonine (2.03 g, 7.86 mmol) and DCC (1.80 g, 8.72 mmol) in THF (20 ml) at 0 °C for 30 min was added (*Z*)-ΔAbu·NCA (100 mg, 7.90 mmol) and DMAP (100 mg, 0.82 mmol). The resulting solution was further stirred at 0 °C for 1 h and at room temperature for 3 h. After removal of the deposited DCU, the filtrate was concentrated in vacuo to give a residue, which was dissolved in EtOAc (50 ml). To the resulting solution was added concentrated aqueous NH_4OH solution (6 ml) at 0 °C. After being stirred for 30 min, the reaction mixture was washed with brine (20 ml×2) and dried over anhydrous Na_2SO_4. Evaporation in vacuo gave residual crystals, which were recrystallized from hexane–$CHCl_3$ to give **24** as colorless needles. Yield 82%. Mp 87—89 °C. $[\alpha]_D^{25}$ −42.7° (*c* 1.80, MeOH). IR 3454, 3372, 3370, 3274, 1677, 1650, 1527, 1410 cm^{-1}. ^1H NMR (DMSO-d_6, 70 °C) δ=1.33 (d, 3H, *J*=5.9 Hz), 1.39 (s, 9H), 1.51 and 1.52 (s×2, 6H), 1.63 (d, 3H, *J*=7.3 Hz, =CHC*H*$_3$), 3.90—4.25 (m, 2H), 6.43 (q, 1H, *J*=7.3 Hz, =C*H*CH$_3$), 6.91 (br s, 2H, NH_2), 9.13 (br s, 1H, NH). Found: C, 45.80; H, 6.37; N, 9.54%. Calcd for $C_{16}H_{27}N_3O_5$·$CHCl_3$: C, 45.31; H, 6.26; N, 9.32%.

(*Z*)-2-(*N*-*t*-Butoxycarbonyl-*N*,*O*-isopropylidene-L-threonyl)amino-2-butenethioamide (25). A solution of **24** (200 mg, 0.59 mmol) and Lawesson's reagent (120 mg, 0.30 mmol) in 1,2-dimethoxyethane (3 ml) was stirred at room temperature for 5 h. The reaction mixture was concentrated in vacuo to give a residue, which was purified on a silica-gel column using a mixture of hexane and EtOAc (2:1 v/v) to give yellow crystals. Recrystallization from hexane–EtOAc gave **25** as yellow powder. Yield 49%. Mp 153—155 °C. $[\alpha]_D^{26}$ −41.5° (*c* 1.20, MeOH). IR 3310, 3208, 2980, 1677, 1515, 1476, 1371 cm^{-1}. ^1H NMR (C_6D_6, 70 °C) δ=1.25 (d, 3H, *J*=8.1 Hz), 1.32 (s, 9H), 1.50 (d, 3H, *J*=7.7 Hz, =CHC*H*$_3$), 1.60 and 1.66 (s×2, 6H), 3.68 (d, 1H, *J*=6.2 Hz), 4.33 (dq, 1H, *J*=6.2 and 8.1 Hz), 6.80—8.00 (m, 4H, NH_2, NH, =C*H*CH$_3$). Found: C, 53.84; H, 7.64; N, 11.56%. Calcd for $C_{16}H_{27}N_3O_4S$: C, 53.76; H, 7.61; N, 11.76%.

Ethyl 2-[(*Z*)-1-(*N*-*t*-Butoxycarbonyl-*N*,*O*-isopropylidene-L-threonyl)amino-1-propenyl]thiazole-4-carboxylate (26). To a stirred solution of **25** (82 mg, 0.23 mmol) and $KHCO_3$ (185 mg, 1.85 mmol) in 1,2-dimethoxyethane (3 ml) under Ar atmosphere at room temperature for 5 min was added ethyl bromopyruvate (140 mg, 0.72 mmol) at 0 °C for 3 min, and then a solution of TFA (30 μl, 0.92 mmol) and pyridine (160 μl, 1.98 mmol) in 1,2-dimethoxyethane (1 ml) was added. After being stirred at room temperature for 1 h, the reaction mixture was concentrated in vacuo to give a residue, which was dissolved in $CHCl_3$ (20 ml) and washed with water (5 ml×2). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a residue. The obtained residue was purified on a silica-gel column using a mixture of hexane and EtOAc (4:1 v/v) to give **26** as a colorless amorphous solid. Yield 70%. $[\alpha]_D^{24}$ −9.5° (*c* 1.01, MeOH). IR 3274, 1698, 1536 cm^{-1}. ^1H NMR δ=1.35 (d, 3H, *J*=7.3 Hz), 1.45 (s and t, 12H, *J*=7.0 Hz), 1.67 (s, 6H), 1.89 (d, 3H, *J*=7.3 Hz, =CHC*H*$_3$), 4.01 (d, 1H, *J*=7.7 Hz), 4.34 (dq, 1H, *J*=7.3 and 7.7 Hz), 4.38 (q, 2H, *J*=7.0 Hz), 6.54 (q, 1H, *J*=7.3 Hz, =C*H*CH$_3$), 7.84 (br s, 1H, NH), 8.04 (s, 1H, Thz-H-5). Found: C, 55.62; H, 6.73; N, 9.21%. Calcd for $C_{21}H_{31}N_3O_6S$: C, 55.61; H, 6.89; N, 9.23%.

2-[(*Z*)-1-(*N*-Butoxycarbonyl-*N*,*O*-isopropylidene-L-threonyl)amino-1-propenyl]thiazole-4-carboxylic Acid (4). A solution of **26** (200 mg, 0.50 ml) in MeOH (20 ml) and 1 M-LiOH (5 ml) was stirred at 0 °C for 3 h. To the reaction mixture was added saturated aqueous $NaHCO_3$ solution (20 ml). After removal of MeOH in vacuo, the residual aqueous layer was washed with diethyl ether (5 ml×3) and acidified with 10% citric acid to pH 3—4. The crystals which deposited were washed with water and recrystallized from EtOAc to give **4** as colorless powder. Yield 73%. Mp 111—113 °C. $[\alpha]_D^{25}$ −8.3° (*c* 0.75, MeOH). IR 3424, 1698, 1515, 1404 cm^{-1}. ^1H NMR δ=1.46 (s, 9H), 1.49 (d, 3H, *J*=6.4 Hz), 1.65 (s, 6H), 1.88 (d, 3H, *J*=7.0 Hz, =CHC*H*$_3$), 4.05 (d, 1H, *J*=7.5 Hz), 4.38 (dq, 1H, *J*=6.4 and 7.5 Hz), 6.57 (q, 1H, *J*=7.5 Hz, =C*H*CH$_3$), 8.00 (br s, 1H, NH), 8.11 (s, 1H, Thz-H-5), 8.54 (br s, 1H, COOH). Found: C, 53.46; H, 6.45; N, 9.50%. Calcd for $C_{19}H_{27}N_3O_6S$: C, 53.63; H, 6.40; N, 9.88%.

Synthesis of the Tripeptide [(P)-2]. A solution of **3a** (23 mg, 0.053 mmol) in EtOAc (2 ml) saturated with dry HCl gas was stirred at 0 °C for 1 h. Concentration in vacuo gave a residue, which was dissolved together with **4** (23.5 mg, 0.053 mmol) in CH_3CN (0.5 ml). To the resulting solution was added BOP (23.3 mg, 0.053 mmol). This solution was made basic to pH 9 with *N*,*N*-diisopropylethylamine. Concentration of the reaction mixture in vacuo gave crystals, which were recrystallized from EtOAc–hexane to give **2** as colorless powder. Mp 97—98 °C. Yield 77%. $[\alpha]_D^{25}$ +2.65° (*c* 1.63, MeOH). IR 3304, 2926, 2848, 1707, 1539 cm^{-1}. ^1H NMR δ=1.25 (t, 3H, *J*=7.3 Hz), 1.40 (s, 9H), 1.44 (d, 3H, *J*=6.1 Hz), 1.63 (s, 6H), 1.84 (d, 3H, *J*=7.0 Hz), 2.30—2.36 (m, 1H), 2.78—2.82 (m, 1H), 3.92 (s, 3H), 4.00—4.03 (m, 2H), 4.19 (q, 2H, *J*=7.3 Hz), 4.27—4.32 (m, 1H), 4.39 (br s, 1H, OH), 5.77—5.80 (m, 1H), 6.52 (q, 1H, *J*=7.0 Hz, =CH), 7.74 (br s, 1H, NH), 8.01 and 8.09 (s×2, 2H, 2×Thz-H), 8.87 (br s, 1H, NH). Found: C, 52.50; H, 6.06; N, 8.99%. Calcd for $C_{30}H_{41}N_5O_{10}S_2$: C, 51.79; H, 5.94; N, 10.06%.

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