Dehydrooligopeptides. XIV. Syntheses of 2-[(Z)-1-Amino-1-alken-1-yl]oxazole-4-carboxylic Acid and the Main Common Skeleton of Thiostrepton Peptide Antibiotics, A10255G and J[1)]

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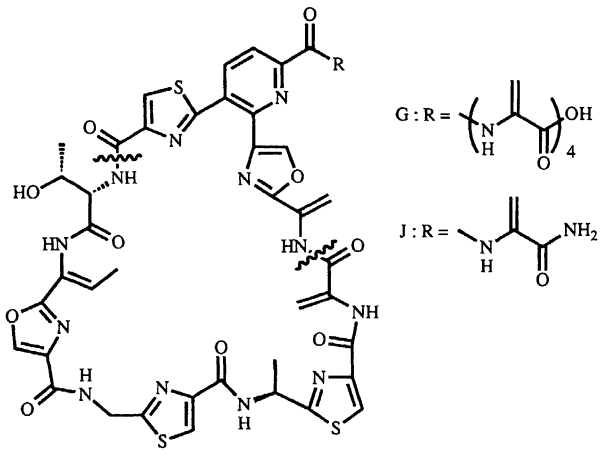
(Received March 13, 1996)

The practical synthesis of a unique dehydropentapeptide (**2**), the common main skeleton of thiostrepton macrocyclic peptide antibiotics, A10255G and J, is described. Peptide **2** is constructed from a novel 2-[(*Z*)-1-amino-1-propen-1-yl]oxazole-4-carboxylic acid, 2-(1-aminomethyl)- and 2-[(*S*)-1-aminoethyl]thiazole-4-carboxylic acid residues, besides L-threonine and dehydroalanine residues at the N- and C-termini, respectively. First, the general syntheses of various 2-[(*Z*)-1-amino-1-alken-1-yl]oxazole-4-carboxylic acid derivatives (**11**) and preparation of N-terminal dehydrodipeptides (**17**) containing the acid (**11a**) were done. Subsequent coupling of **17** with the C-terminal tripeptide comprised of the above two 2-(aminoalkyl)thiazole-4-carboxylic acid moieties (**22**) and (**23**) and serine moiety (**4**), and final β-elimination were tried and gave the desired protected **2** [(**P**)-**2**].

Thiostrepton peptide antibiotics, A10255G and J (**1**),[2)] produced by *Streptomyces gardneri*, are unique macrocyclic polythiazole and -oxazole dehydropeptides. The natural products (**1**) feature a very interesting common main substructure, dehydropentapeptide (**2**), and 2,3-disubstituted pyridine-6-carboxylic acid coupled with polydehydroalanine segments, as illustrated in Fig. 1. Furthermore, the peptide (**2**) consists of a 2-[(*Z*)-1-amino-1-propen-1-yl]oxazole-4-carboxylic acid (**11a**) and two kinds of 2-[(*S*)-1-aminoalkyl]-thiazole-4-carboxylic acids (**22**: R = H and **23**: R = CH_3),



Dehydropentapeptide (**2**)
(**P**)-**2**

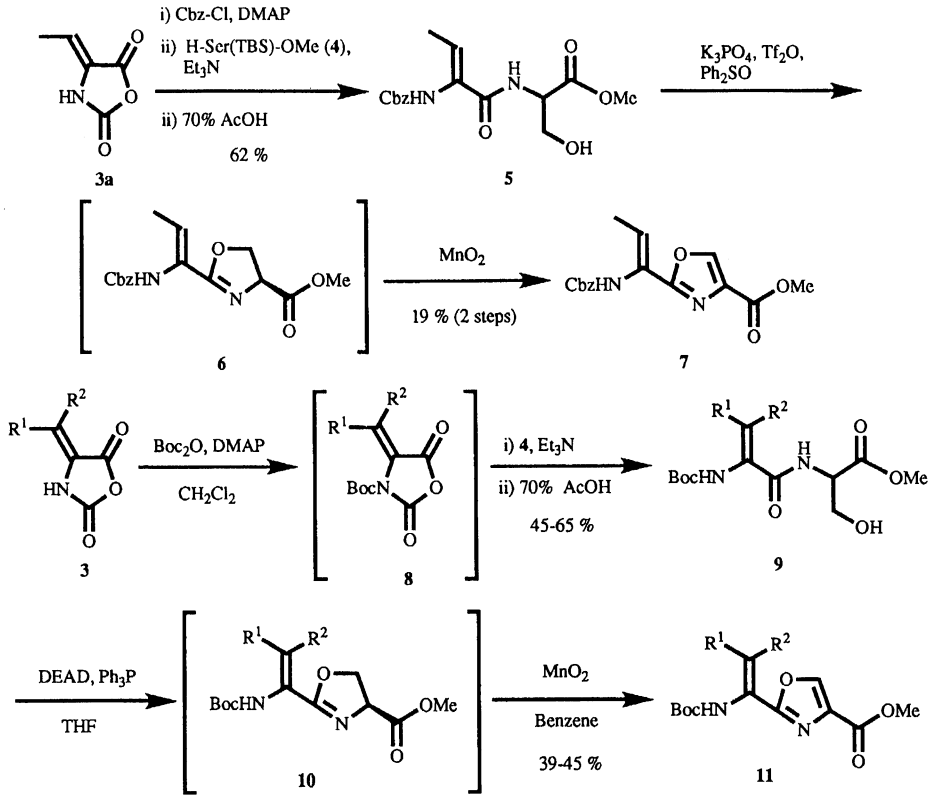
Fig. 1. A10255G and J (**1**).

in addition to L-threonine (Thr) and dehydroalanine (ΔAla) residues at N- and C-termini of **2**, respectively. The peculiar structure as well as the bioactivity of **1** attracted us and prompted us to study the total synthesis and the structure-bioactivity relationship.

More recently, besides the convenient syntheses of a few partial segments of **1**,[3,4)] we have reported briefly on the syntheses of a variety of the related oligodehydroalanines,[5)] dehydropeptides constructed from only α,β-unsaturated α-amino acids [α-dehydroamino acid (DHA, ΔAA)],[6)] 2-[(*Z*)-1-amino-1-alken-1-yl]oxazole-4-carboxylic acids (**11**)[3)] and -thiazole-4-carboxylic acids.[7,8)] Here, we would like to report in detail the general synthesis of **11** (ΔAA: **a**; $R^1 = CH_3$, $R^2 = H$, **b**; $R^1 = R^2 = CH_3$, **c**; $R^1 = (CH_3)_2CH$, $R^2 = H$, **d**; $R^1 = C_6H_5$, $R^2 = H$) starting from *N*-carboxy α-dehydroamino acid anhydride (ΔAA·NCA) (**3**)[9—11)] and preparation of the N-terminal dehydrodipeptides [carboxyl (*C*-) component] (**17**) containing the acid (**11a**). Moreover, after the synthesis of C-terminal tripeptide [amine (*N*-) component] constructed from in turn **22**, **23**, and serine (Ser) residues, the coupling between the *C*- and *N*-components and then β-elimination of the Ser residue were first done to give the desired protected dehydropentapeptide **2** [(**P**)-**2**] of A10255G and J.

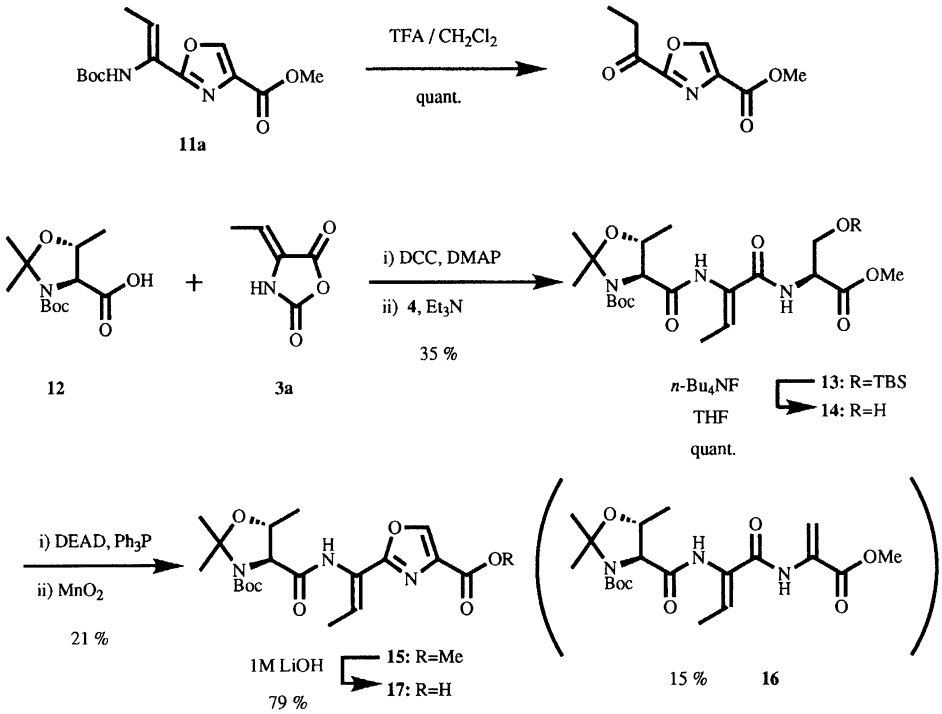
Results and Discussion

Syntheses of 2-[(*Z*)-1-Amino-1-alken-1-yl]oxazole-4-carboxylates (11) and (17). First of all, we studied in detail on the general synthesis of methyl 2-[(*Z*)-1-(Cbz- and Boc)amino-1-alken-1-yl]oxazole-4-carboxylates (**7** and **11**) from the corresponding dehydrodipeptides ΔAA–Ser–OMe (**5** and **9**).



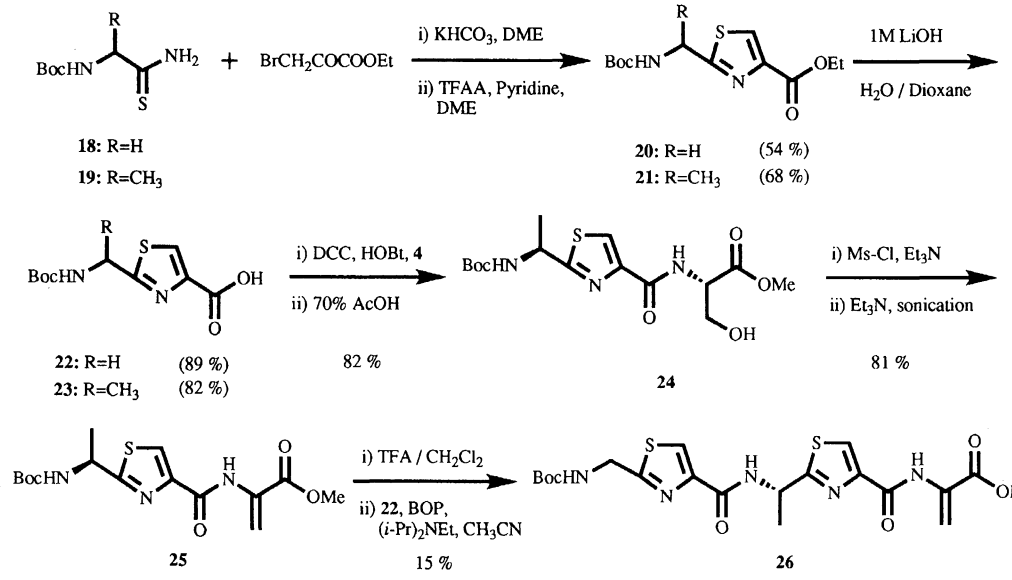
a; R^1=CH_3, R^2=H, **b**; R^1=R^2=CH_3, **c**; R^1=$(CH_3)_2CH$, R^2=H, **d**; R^1=Ph, R^2=H

Scheme 1.

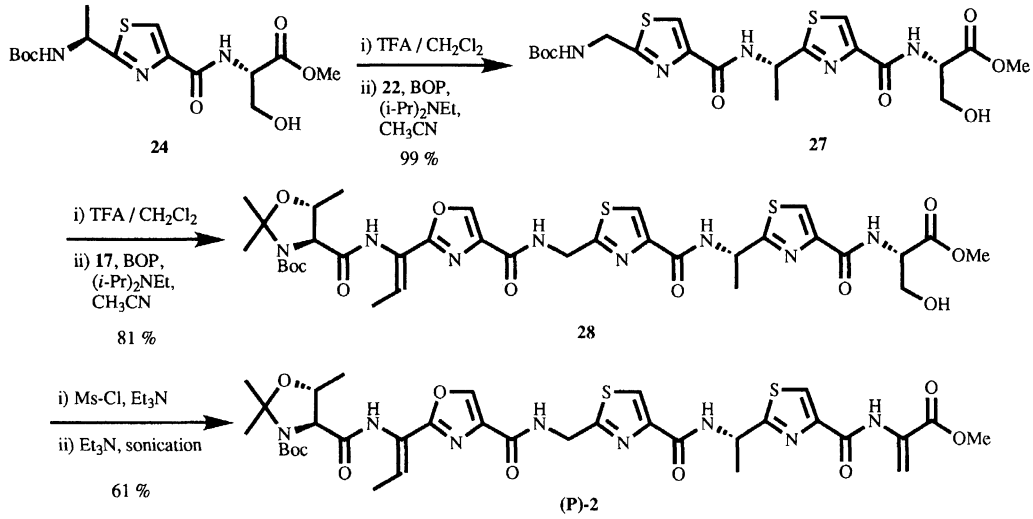


Scheme 2.

N-Protection of (*Z*)-ΔAbu·NCA (**3a**) (Abu = 2-amino-2-butenoic acid) with benzyloxycarbonyl chloride (CbzCl) in the presence of 4-dimethylaminopyridine (DMAP) gave *N*-Cbz–(*Z*)-ΔAbu·NCA, which was immediately coupled with H–Ser(TBS)–OMe (**4**)[5] (TBS=*t*-butyldimethylsilyl) in the presence of Et_3N and then deprotected the TBS group with 70% AcOH to give *N*-Cbz–(*Z*)-ΔAbu–Ser–OMe (**5**) in 62% yield. Subsequently, to form an oxazoline ring by the method



Scheme 3.



Scheme 4.

reported by Yokokawa et al.,[12] cyclization of **5** with trifluoromethanesulfonic anhydride (triflic anhydride, Tf_2O) in the presence of Ph_2SO and K_3PO_4 at −78 °C gave the corresponding 2-[(*Z*)-1-amino-1-propen-1-yl]oxazoline derivative (**6**) as a rather unstable intermediate. Although the intermediate was oxidized in situ with MnO_2, unfortunately, the yield of the obtained oxazole derivative (**7**) was found to be very low (19%) in these two steps.

On the other hand, instead of the Cbz group, a *t*-butoxycarbonyl (Boc) group was used on the *N*-protecting group of ΔAA·NCA (**3**; ΔAA, **a**; ΔAbu, **b**; ΔVal, **c**; ΔLeu, **d**; ΔPhe). That is, after the preparation of *N*-Boc–ΔAA·NCA (**8a—d**)[7] by the usual acylation of **3** with di-*t*-butyl dicarbonate (Boc_2O), similarly to the case of **5**, the condensation of **8a—d** with **4** and then deprotection of the TBS group gave *N*-Boc–(*Z*)-ΔAA–Ser–OMe (**9a—d**) in 45—65% yields in two steps. According to the method of Galeotti et al.,[13] cyclization of **9a—d** with Ph_3P and diethyl azodicarboxylate (DEAD) in THF gave unstable methyl 2-[(*Z*)-1-(Boc)amino-1-alken-1-yl]-2-oxazoline-4-carboxylates (**10a—d**). Then, without purification, the oxazoline rings were oxidized with MnO_2 in benzene. As a result, the expected **11a—d** were obtained and the yields were found to increase to 39—45% in two steps, as shown in Scheme 1. Unfortunately, however, the yield of the corresponding oxazole derivatives by the oxidation of the oxazoline rings with MnO_2 are generally low. Accordingly, it is necessary to improve the oxidation method using other oxidizing agents.

Furthermore, to synthesize the desired N-terminal dehydrodipeptide, preparation of *N*-Boc-*N*,*O*-isopropylidene-L-Thr–2-[(*Z*)-1-amino-1-propen-1-yl]oxazole-4-carboxylic acid (**17**), the left half of the oligopeptide (**P**)-**2**, after deprotecting the Boc group of **11a**, direct coupling with *N*-Boc-*N*,*O*-isopropylidene-L-Thr–OH (**12**) was planned. Although various deprotections of the Boc group of **11a** was examined, unluckily, the attempts were unsuccessful because of the rapid hydrolytic conversion of 2-[1-(*t*-butoxycarbonylamino)-1-propen-1-yl] group to the undesirable 2-propi-

onyl group almost quantitatively. Accordingly, an alternative method for synthesis of **17** was chosen, as shown in Scheme 2. That is, one-pot coupling[9] of **3a** with **12** by using dicyclohexylcarbodiimide (DCC) in the presence of DMAP and then with **4** in the presence of Et_3N were done to give *N,O*-protected Thr–ΔAbu–Ser(TBS)–OMe (**13**). Subsequent deprotection of the TBS group of **13** with *n*-Bu_4NF gave the corresponding dehydrotripeptide Thr–ΔAbu–Ser–OMe (**14**). Similarly as in the case of **10** from **9**, partial cyclization of **14** with Ph_3P and DEAD followed by oxidation with MnO_2 in benzene gave the expected **15** in 21% yield in two steps. As one of the causes of the low yield of **15**, it was found that undesirable β-elimination occurred by some means to give the corresponding $\Delta^{2,3}$-dehydrotripeptide (**16**).[14]

Finally, ester hydrolysis of **15** with 1 M LiOH (M = mol dm^{-3}) gave the corresponding oxazole-4-carboxylic acid (**17**) in 79% yield.

Syntheses of 2-(1-Aminoalkyl)thiazole-4-carboxylates (22 and 23) and Coupling with N-Terminal Dehydrotripeptide (17). To synthesize the right half of the oligopeptide (**P**)-**2**, first, both *N*-Boc-glycylthioamide [*N*-Boc–Gly-(S)NH_2] (**18**) and *N*-Boc-alanylthioamide [*N*-Boc–L-Ala-(S)NH_2] (**19**) were derived by the thioamidations of the corresponding amides with Lawesson's reagent.[15] Thiazole formations[16] were done by treatment of **18** and **19** with ethyl 3-bromopyruvate in the presence of $KHCO_3$ in dimethoxyethane (DME) followed by oxidation with trifluoroacetic anhydride (TFAA) in the presence of pyridine to give ethyl 2-[1-(Boc)aminomethyl] (**20**)- and 2-[(*S*)-1-(Boc)aminoethyl]thiazole-4-carboxylates (**21**), respectively. Then, the obtained **20** and **21** were hydrolyzed with 1 M LiOH in dioxane to give the corresponding carboxylic acid derivatives (**22** and **23**). Furthermore, coupling of **23** with **4** by using DCC and 1-hydroxy-1*H*-benzotriazole (HOBt), followed by the deprotection of TBS group with 70% AcOH gave 2-[(*S*)-1-(Boc)aminoethyl]thiazole-4-carbonyl-Ser–OMe (**24**) in 82% yield. Subsequent mesylation of the hydroxyl group of **24** with methanesulfonyl chloride (MsCl) in the presence of Et_3N and β-elimination with Et_3N under sonication[5] gave the C-terminal 2-[(*S*)-1-(Boc)aminoethyl]thiazole-4-carbonyl-ΔAla–OMe (**25**) in 81% yield. Next, the deprotection of the Boc group of **25** with trifluoroacetic acid (TFA) in CH_2Cl_2 and then condensation with **22** by using BOP[4,17] as the condensing agent in the presence of *N,N*-diisopropylethylamine [(*i*-Pr)$_2$NEt] in CH_3CN were done. Contrary to the expectation, however, the yield of 2-[2-[(Boc)aminomethyl]thiazole-4-carbonyl-(*S*)-1-aminoethyl]thiazole-4-carbonyl-ΔAla–OMe (**26**) was found to be very low (15%), as shown in Scheme 3. Therefore, the alternate route was examined in the following way.

After deprotection of the Boc group of **24** with TFA, the formed 2-[(*S*)-1-aminoethyl]thiazole-4-carbonyl-Ser–OMe as an intermediate was coupled in situ with **22** to give the corresponding tripeptide (**27**) almost quantitatively. Again, the deprotection of the Boc group of **27** with TFA in CH_2Cl_2, followed by the coupling with N-terminal dehydrodipeptide (**17**) by the BOP method gave the corresponding dehydropentapeptide (**28**) containing a Ser residue at the C-terminus in 81% yield.

Finally, to dehydrate the Ser residue, mesylation of **28** with MsCl in the presence of Et_3N and then β-elimination with Et_3N under sonication was tried smoothly to give the expected N-protected dehydropentapeptide [(**P**)-**2**] in 61% yield, as shown in Scheme 4.

In conclusion, it is worth-noting that the general synthesis of 2-[(*Z*)-1-amino-1-alken-1-yl]oxazole-4-carboxylic acids and the acids (**11**) containing the main skeleton of A10255G and J were accomplished. Moreover, these results will contribute to the total syntheses of the similar thiostrepton macrocyclic peptide antibiotics, such as berninamycin A[18,19] and micrococcin P_1.[20]

Experimental

The melting points were measured using a Yamato (Model Mp-21) micromelting point apparatus, and are uncorrected. The IR spectra were recorded using a Hitachi EPI-G2 spectrometer. The ^{1}H NMR spectra were measured with JEOL EX 90 and FX 200 spectrometers in $CDCl_3$ and DMSO-d_6 with tetramethylsilane as the internal standard. The optical rotations were measured with a DIP-4 polarimeter (Japan Spectroscopic Co., Ltd.).

Starting Materials. The compounds **3a—d** were prepared by the method reported earlier.[9—11]

H–Ser(TBS)–OMe (4). A suspension of Cbz–Ser(TBS)–OMe (6.78 g, 18 mmol) and 10% Pd–C (0.68 g) in EtOH under a H_2 gas stream was stirred at room temperature for 6 h. After removal of Pd–C, the filtrate was concentrated in vacuo to give **4** as a residual colorless syrup, which was used for the next coupling without further purification.

***N*-Cbz–(*Z*)-ΔAbu–L-Ser–OMe (5).** To a chilled solution of **3a** (0.65 g, 4.76 mmol) in CH_2Cl_2 (20 ml) in the presence of DMAP (0.058 g, 0.476 mmol) was added, with stirring, CbzCl (0.838 ml, 5.24 mmol) under cooling for 6 h. A solution of **4** [derived from Cbz–Ser(TBS)–OMe (1.92 g, 5.24 mmol)] and Et_3N (0.791 ml, 5.24 mmol) in CH_2Cl_2 (10 ml) was added to the resulting solution and then stirred at 0 °C for 6 h. After concentration in vacuo, the obtained residual syrup was dissolved in 70% AcOH (20 ml) and then stirred at room temperature for 12 h. Concentration in vacuo gave a residue, which was purified on a silica-gel column using EtOAc to give **5** as a colorless syrup. Yield 62%. $[\alpha]_D^{25}$ +6.96° (*c* 1.0, MeOH). IR (KBr) 3910, 3886, 3364, 2950, 2260, 1989, 1887, 1740, 1677, 1641, 1518 cm^{-1}. ^{1}H NMR δ = 1.70 (d, 3H, CH_3, J = 7.0 Hz), 3.14 (br s, 1H, OH), 3.72 (s, 3H, CH_3), 3.80—4.00 (m, 2H, β-H), 4.57—4.66 (m, 1H, α-H), 5.10 (s, 2H, CH_2), 6.35 (q, 1H, CH=, J = 7.0 Hz), 7.02 (br s, 1H, NH), 7.02—7.22 (m, 1H, NH), 7.32 (s, 5H, Ph). Found: C, 57.26; H, 6.29; N, 7.99%. Calcd for $C_{16}H_{20}N_2O_6$: C, 57.13; H, 5.99; N, 8.33%.

Methyl 2-[(*Z*)-1-(*N*-Benzyloxycarbonylamino)-1-propenyl]-oxazole-4-carboxylate (7). To a solution of Ph_2SO (0.247 g, 1.2 mmol) in CH_2Cl_2 (30 ml) was added, drop by drop, with stirring, a solution of Tf_2O (0.142 ml, 0.914 mmol) in CH_2Cl_2 (3 ml) at −78 °C for 30 min under an Ar gas stream. To the resulting mixture was added, with stirring, a solution of K_2PO_3 (1.294 g, 6.1 mmol) and **5** (0.205 g, 0.61 mmol) in CH_2Cl_2 (5 ml) for 30 min. The resultant mixture was stirred continuously for 20 min at room temperature and added to water (30 ml). The aqueous solution was extracted three times with CH_2Cl_2 (20 ml × 3) and the combined extracts were concentrated in vacuo to give a crude syrup. The residue obtained

was dissolved in benzene (30 ml) and then MnO_2 (0.518 g, 6.1 mmol) was added to the resulting solution at room temperature. After this was stirred for 48 h, MnO_2 was filtered off. 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 (1 : 1 v/v) to give pale yellow crystals. Recrystallization from hexane–EtOAc gave **7** as pale yellow needles. Yield 19%. Mp 135.5—137.0 °C. IR 3586, 3298, 2254, 1725, 1701, 1572, 1518 cm^{-1}. ^1H NMR $\delta = 1.87$ (d, 3H, CH_3, $J = 7.3$ Hz), 3.91 (s, 3H, CH_3), 5.16 (s, 2H, CH_2), 6.40 (br s, 1H, NH), 6.63 (q, 1H, CH=, $J = 7.3$ Hz), 7.34 (s, 5H, Ph), 8.13 (s, 1H, ring-H). Found: C, 60.90; H, 5.19; N, 8.80%. Calcd for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.10; N, 8.86%.

***N*-Boc–(*Z*)-ΔAbu–L-Ser–OMe (9a).** To a solution of **3a** (1.00 g, 7.87 mmol) in CH_2Cl_2 (20 ml) were added, with stirring, Boc_2O (2.06 g, 11.80 mmol) and DMAP (0.19 g, 1.57 mmol) at 0 °C for 6 h. A solution of H–Ser(TBS)–OMe (**4**) [made from Cbz–Ser(TBS)–OMe (2.02 g, 8.65 mmol)] and Et_3N (1.7 ml, 11.80 mmol) in CH_2Cl_2 (80 ml) was added to the resulting solution. After this was stirred at 0 °C for 2 h, the reaction mixture was dissolved in diethyl ether (30 ml) and then washed successively with brine (20 ml), saturated aqueous $NaHCO_3$ solution (20 ml), and 10 % citric acid (20 ml), and finally dried over anhydrous Na_2SO_4. Evaporation in vacuo gave a crude residue, which was stirred with 70% AcOH at room temperature. Concentration in vacuo gave a residue, which was purified on a silica-gel column using EtOAc gave **9a** as a colorless syrup. Yield 54%. $[\alpha]_D^{25}$ +6.6° (*c* 1.80, MeOH). IR 3364, 2974, 1707, 1641 cm^{-1}. ^1H NMR $\delta = 1.45$ (s, 9H, Boc), 1.87 (s, 3H, CH_3), 3.77 (s, 3H, $COOCH_3$), 3.94—3.98 (m, 3H, CH_2 and OH), 4.59—4.75 (m, 1H, α-H), 6.25 (br s, 1H, NH), 6.47 (q, 1H, CH=, $J = 7.5$ Hz), 7.03 (br d, 1H, NH, $J = 7.5$ Hz). Found: C, 49.66; H, 7.27; N, 8.52%. Calcd for $C_{13}H_{22}N_2O_6 \cdot 0.5H_2O$: C, 50.15; H, 7.45; N, 8.99%.

***N*-Boc–ΔVal–L-Ser–OMe (9b).** Similarly to the case of **9a**, the coupling of **3b** with **5** was done to give **9b** as colorless needles. Yield 45%. Mp 114—115 °C. $[\alpha]_D^{25}$ +6.24° (*c* 0.75, MeOH). IR 3268, 2974, 1695, 1509 cm^{-1}. ^1H NMR $\delta = 1.44$ (s, 9H, Boc), 1.79 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 3.79 (s, 3H, CH_3), 3.80—4.30 (m, 4H, α-H, β-H, and OH), 6.19 (br s, 1H, NH), 6.93 (d, 1H, NH, $J = 7.7$ Hz). Found: C, 52.89; H, 7.71; N, 8.81%. Calcd for $C_{14}H_{24}N_2O_6$: C, 53.16; H, 7.65; N, 8.85%.

***N*-Boc–(*Z*)-ΔLeu–L-Ser–OMe (9c).** Similarly to the case of **9a**, the coupling of **3c** with **5** was done to give **9c** as colorless needles. Yield 65%. Mp 69—70 °C. $[\alpha]_D^{25}$ +11.11° (*c* 0.38, MeOH). IR 3316, 2962, 1704, 1638 cm^{-1}. ^1H NMR $\delta = 1.04$ (s×2, 6H, $(CH_3)_2$). 1.40 (s, 9H, Boc), 2.40—2.80 (m, 1H, γ-H), 3.40—3.60 (br s, 1H, OH), 3.80 (s, 3H, CH_3), 3.80—4.20 (m, 3H, α-H and β-H), 6.18 (br s, 1H, NH), 6.24 (d, 1H, CH=, $J = 9.2$ Hz), 7.02 (br d, 1H, NH, $J = 6.6$ Hz). Found: C, 54.37; H, 8.14; N, 8.43%. Calcd for $C_{15}H_{26}N_2O_6$: C, 54.53; H, 7.93; N, 8.48%.

***N*-Boc–(*Z*)-ΔPhe–L-Ser–OMe (9d).** Similarly to the case of **9a**, the coupling of **3d** with **5** was done to give **9d** as a pale yellow syrup. Yield 60%. $[\alpha]_D^{25}$ +23.45° (*c* 0.87, MeOH). IR 3352, 2974, 1713, 1629 cm^{-1}. ^1H NMR $\delta = 1.44$ (s, 9H, Boc), 3.80 (s, 3H, CH_3), 3.85—4.73 (m, 4H, α-H, β-H, and OH), 6.39 (br s, 1H, NH), 7.50 (m, 7H, CH=, Ph-H, and NH). Found: C, 58.99; H, 6.77; N, 7.30%. Calcd for $C_{18}H_{24}N_2O_6$: C, 59.33; H, 6.64; N, 7.69%.

Methyl 2-[(*Z*)-1-(*N*-*t*-Butoxycarbonylamino)-1-propen-1-yl]-oxazole-4-carboxylate (11a). To a solution of **9a** (0.87 g, 2.88 mmol) in THF (20 ml) were added, with stirring, DEAD (0.64 ml, 4.32 mmol) and Ph_3P (1.08 g, 4.32 mmol) at room temperature. After this was stirred for 10 min, the reaction mixture was concentrated in vacuo to give a residue. The residual substance was dissolved in benzene (50 ml). MnO_2 (10 g) was added slowly and the resulting solution was stirred at room temperature for 48 h. After removal of MnO_2, the filtrate was concentrated in vacuo to give a crude residue, which was purified on a silica-gel column using a mixture of hexane and EtOAc (1 : 1 v/v) to give colorless crystals. Recrystallization from hexane-EtOAc gave **11a** as colorless needles. Yield 40%. Mp 131—132 °C. IR 2926, 1731, 1670, 1645 cm $^{-1}$. ^1H NMR $\delta = 1.47$ (s, 9H, Boc), 1.87 (d, 3H, CH_3, $J = 7.3$ Hz), 2.92 (s, 3H, CH_3), 6.25 (br s, 1H, NH), 6.56 (q, 1H, CH=, $J = 7.3$ Hz), 8.15 (s, 1H, ring-H). Found: C, 55.37; H, 6.55; N, 10.14%. Calcd for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43; N, 9.92%.

Methyl 2-[1-(*N*-*t*-Butoxycarbonylamino)-2-methyl-1-propen-1-yl]oxazole-4-carboxylate (11b). Similarly to the case of **11a**, the cyclization and then oxidation of **9b** was done to give **11b** as colorless needles. Yield 39%. Mp 86—87 °C. IR 2962, 1731, 1662 cm^{-1}. ^1H NMR $\delta = 1.42$ (s, 9H, Boc), 1.94 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 5.94 (br s, 1H, NH), 8.18 (s, 1H, ring-H). Found: C, 57.01; H, 6.85; N, 9.48%. Calcd for $C_{14}H_{20}N_2O_5$: C, 56.74; H, 6.80; N, 9.45%.

Methyl 2-[(*Z*)-1-(*N*-*t*-Butoxycarbonylamino)-3-methyl-1-butene-1-yl]oxazole-4-carboxylate (11c). Similarly to the case of **11a**, the cyclization and then oxidation of **8c** was done to give **11c** as colorless needles. Yield 45%. Mp 105—106 °C. IR 2968, 1731, 1660 cm^{-1}. ^1H NMR $\delta = 1.09$ (s×2, 6H, $(CH_3)_2$), 1.45 (s, 9H, Boc), 2.77 (m, 1H, γ-H), 3.92 (s, 3H, CH_3), 6.03 (br s, 1H, NH), 6.33 (d, 1H, CH=, $J = 10.1$ Hz), 8.16 (s, 1H, ring-H). Found: C, 58.27; H, 7.20; N, 9.05%. Calcd for $C_{15}H_{22}N_2O_5$: C, 58.05; H, 7.15; N, 9.03%.

Methyl 2-[(*Z*)-1-(*N*-*t*-Butoxycarbonyl)amino-1-(2-phenyl)ethenyl]oxazole-4-carboxylate (11d). Similarly to the case of **11a**, the cyclization and then oxidation of **9d** was done to give **11d** as colorless needles. Yield 41%. Mp 195—196 °C. IR 2974, 1725, 1644, 1630 cm^{-1}. ^1H NMR $\delta = 1.38$ (s, 9H, Boc), 3.93 (s, 3H, CH_3), 6.45 (br s, 1H, NH), 7.17—7.68 (m, 6H, Ph-H and CH=), 8.15 (s, 1H, ring-H). Found: C, 63.03; H, 5.91; N, 8.17%. Calcd for $C_{18}H_{20}N_2O_5$: C, 62.78; H, 5.85; N, 8.14%.

Methyl 2-Propionyloxazole-4-carboxylate. A solution of **11a** (20 mg, 0.07 mmol) in TFA and CH_2Cl_2 (10 ml, 1 : 1 v/v) was stirred at room temperature for 30 min. Concentration in vacuo, followed by the azeotropic distillation with toluene three times, gave a residue, which was dissolved in EtOAc (20 ml). The resulting solution was washed with brine, dried over anhydrous Na_2SO_4, and then concentrated in vacuo. Recrystallization from hexane–EtOAc gave pale yellow powders. Yield 85%. Mp 99—100 °C. IR 3448, 3124, 3070, 2260, 1989, 1956, 1941, 1731, 1710, 1614 cm^{-1}. ^1H NMR $\delta = 1.32$ (t, 3H, CH_3, $J = 7.3$ Hz), 3.28 (d, 2H, CH_2, $J = 7.3$ Hz), 3.97 (s, 3H, CH_3), 8.37 (s, 1H, ring-H). Found: C, 52.44; H, 5.02; N, 7.78%. Calcd for $C_8H_9NO_4$: C, 52.46; H, 4.95; N, 7.65%.

***N*-*t*-Butoxycarbonyl-*N*,*O*-isopropylidene-L-threonyl–(*Z*)-ΔAbu–L-Ser(TBS)–OMe (13) and *N*-*t*-Butoxycarbonyl-*N*,*O*-isopropylidene-L-threonyl–(*Z*)-ΔAbu–L-Ser–OMe (14).** A solution of *N*-Boc-*N*,*O*-isopropylidene–Thr–OH (**12**) (4.79 g, 18 mmol) and DCC (3.81 g, 18 mmol) in CH_2Cl_2 (100 ml) was stirred at 0 °C for 10 min. To the resulting solution was added, with stirring, **3a** (2.13 g, 18 mmol) and DMAP (0.41 g, 3.4 mmol). After stirring for 4 h, **4** [made from Cbz–Ser(TBS)–OMe (6.78 g, 18 mmol)] and Et_3N (2.59 ml, 18 mmol) were added, with stirring, to the resultant solution at 0 °C for 24 h. *N*,*N*′-Dicyclohexylurea deposited was filtered off and the filtrate was washed successively with brine (20 ml), saturated aqueous $NaHCO_3$ solution (20 ml), and 10% citric acid (20 ml), and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residue, which was purified on a silica-gel

column using a mixture of EtOAc and hexane (1 : 1 v/v) to give **13** as a colorless syrup. While the syrup (**13**) obtained was dissolved in THF (40 ml) and the resulting solution was stirred with *n*-Bu_4NF (16.08 ml, 11.0 mmol) at 0 °C for 30 min. Concentration in vacuo gave a residue, which was purified on a silica-gel column using EtOAc to give colorless crystals. Recrystallization from hexane-EtOAc gave **14** as colorless needles.

13: Yield 35%. $[\alpha]_D^{26}$ −124.6° (*c* 0.35, MeOH). IR 3334, 3274, 2938, 2860, 1755, 1677, 1653, 1539, 1518 cm^{-1}. ^1H NMR δ = 0.07 (s, 6H, $CH_3\times2$), 0.84 (s, 9H, $CH_3\times3$), 1.41 (d, 3H, CH_3, J = 5.5 Hz), 1.45 (s, 9H, Boc), 1.61 (s, 6H, $(CH_3)_2C$), 1.76 (d, 3H, CH_3, J = 7.0 Hz), 3.73 (s, 3H, CH_3), 3.81—4.39 (m, 4H, α-H, β-H×2), 4.56—4.73 (m, 1H, α-H), 6.51 (q, 1H, CH=, J = 7.0 Hz), 6.98 (br d, 1H, NH, J = 7.3 Hz), 7.44 (br s, 1H, NH). Found: C, 56.13; H, 8.56; N, 7.49%. Calcd for $C_{26}H_{47}N_3O_8Si$: C, 55.99; H, 8.49; N, 7.54%.

14: Yield quant. Mp 158—159 °C. $[\alpha]_D^{26}$ +20.57° (*c* 0.70, MeOH). IR 3448, 3238, 2938, 1746, 1668, 1536 cm^{-1}. ^1H NMR δ = 1.45 (d, 3H, CH_3, J = 5.7 Hz), 1.46 (s, 9H, Boc), 1.61 (s, 6H, $(CH_3)_2C$), 1.73 (d, 3H, CH_3, J = 7.0 Hz), 2.01 (br s, 1H, OH), 3.76 (s, 3H, CH_3), 3.84—4.43 (m, 4H, α-H and β-H×2), 4.58—4.70 (m, 1H, α-H), 6.86 (q, 1H, CH=, J = 7.0 Hz), 7.35 (br d, 1H, NH, J = 4.8 Hz), 7.64 (br s, 1H, NH). Found: C, 53.76; H, 7.49; N, 9.25%. Calcd for $C_{20}H_{33}N_8O_3$: C, 54.17; H, 7.50; N, 9.48%.

Methyl 2-[(*Z*)-1-(*N*-*t*-Butoxycarbonyl-*N*,*O*-isopropylidene-L-threonylamin)-1-propen-1-yl]oxazole-4-carboxylate (15) and *N*-*t*-Butoxycarbonyl-*N*,*O*-isopropylidene-L-threonyl–(*Z*)-ΔAbu–ΔAla–OMe (16). To a solution of **14** (1.50 g, 3.37 mmol) in THF (30 ml) were added, with stirring, DEAD (0.797 ml, 5.06 mmol) and Ph_3P (1.328 g, 5.06 mmol) at 0 °C. After stirring for 10 min, the reaction mixture was concentrated in vacuo to give a residue, which was dissolved in benzene (50 ml). The benzene solution was stirred with MnO_2 (15 g) at room temperature for 72 h and then MnO_2 was filtered off. The filtrate was concentrated in vacuo to give a residual syrup. The syrup obtained was chromatographed on a silica-gel column using a mixture of hexane and EtOAc (1 : 2 v/v) to give **15** as colorless syrup and colorless crystals. The crystals were recrystallized from a hexane–EtOAc to give **16** as colorless needles.

15: Yield 21%. $[\alpha]_D^{26}$ −1.33° (*c* 0.75, MeOH). IR 3472, 2152, 1689 cm^{-1}. ^1H NMR δ = 1.46 (s, 9H, Boc), 1.49 (d, 3H, CH_3, J = 5.1 Hz), 1.66 (s, 6H, $(CH_3)_2C$), 1.91 (d, 3H, CH_3, J = 7.3 Hz), 3.89 (s, 3H, CH_3), 3.96—4.31 (m, 2H, α-H and β-H), 6.70 (q, 1H, CH=, J = 7.3 Hz), 7.73 (br s, 1H, NH), 8.14 (s, 1H, ring-H). Found: C, 56.99; H, 7.03; N, 9.71%. Calcd for $C_{20}H_{29}N_3O_7$: C, 56.73; H, 6.90; N, 9.92%.

16: Yield 15%. Mp 162—164 °C. $[\alpha]_D^{25}$ −2.4° (*c* 1.0, MeOH). IR 3778, 3358, 3256, 2980, 2260, 1737, 1680, 1650, 1542, 1509 cm^{-1}. ^1H NMR δ = 1.44 (s, 9H, Boc), 1.45 (d, 3H, CH_3, J = 6.0 Hz), 1.61 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 1.80 (d, 3H, CH_3, J = 7.0 Hz), 3.83 (s, 3H, CH_3), 3.94 (d, 1H, α-H, J = 3.9 Hz), 4.32—4.47 (m, 1H, β-H), 5.91 (d, 1H, vinyl-H, J = 0.9 Hz), 6.52 (s, 1H, vinyl-H), 6.62 (q, 1H, CH=, J = 7.0 Hz), 7.45 (br s, 1H, NH), 8.40 (br s, 1H, NH). Found: C, 56.50; H, 7.48; N, 9.84%. Calcd for $C_{20}H_{31}N_3O_7$: C, 56.46; H, 7.34; N, 9.88%.

2-[(*Z*)-1-(*N*-*t*-Butoxycarbonyl-*N*,*O*-isopropylidene-L-threonyl)amino-1-propen-1-yl]oxazole-4-carboxylic Acid (17). A solution of **15** (0.299 g, 0.70 mmol) in H_2O–dioxane (10 ml; 1 : 1 v/v) was stirred with 1 M LiOH (1.05 ml) at 0 °C for overnight. The reaction mixture was washed with diethyl ether (5 ml) and the aqueous layer was acidified to pH 3 with 10% citric acid and then extracted with EtOAc (30 ml). The organic layer was washed with brine (10 ml) and dried over anhydrous Na_2SO_4. Concentration in vacuo gave crude crystals, which were recrystallized from hexane–EtOAc to give **17** as colorless needles. Yield 79%. Mp 91—92 °C. $[\alpha]_D^{26}$ −5.0° (*c* 0.36, MeOH). IR 3442, 2255, 1665 cm^{-1}. ^1H NMR δ = 1.16—1.27 (m, 3H, CH_3), 1.26 (s, 9H, Boc), 1.41 (s×2, 3H×2, $CH_3\times2$), 1.69 (d, 3H, CH_3, J = 7.3 Hz), 3.80—4.30 (m, 2H, α-H and β-H), 6.43 (q, 1H, CH=, J = 7.3 Hz), 8.58 (s, 1H, ring-H), 9.69 (br s, 1H, NH), 12.80 (br s, 1H, COOH). Found: C, 51.99; H, 6.77; N, 9.27%. Calcd for $C_{19}H_{27}N_3O_7\cdot1.5H_2O$: C, 52.29; H, 6.93; N, 9.63%.

Ethyl 2-[(*N*-*t*-Butoxycarbonyl)aminomethyl]thiazole-4-carboxylate (20). To a solution of **18** (8.63 g, 45.0 mmol) in DME (100 ml) was added, with stirring, $KHCO_3$ (36.31 g, 0.36 mmol) under an Ar gas stream at room temperature. After stirring for 5 min, ethyl 3-bromopyruvate (17.07 ml, 0.136 mmol) was added to the resulting suspension and then stirred for 10 min. A solution of TFAA (25.09 ml, 0.18 mmol) and pyridine (31.46 ml, 0.39 mmol) in DME (70 ml) was further added to the above obtained solution at −10 °C. After this was stirred for 30 min, the solvent was evaporated in vacuo to give a residue, which was dissolved in $CHCl_3$ (100 ml). The resulting solution was washed with brine (60 ml) and dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residue, which was purified on a silica-gel column using a mixture of hexane and EtOAc to give colorless crystals. Recrystallization from hexane–EtOAc (1 : 1 v/v) gave **20** as colorless needles. Yield 54%. Mp 101—102 °C. IR 3456, 3088, 2986, 2932, 2314, 1722, 1506 cm^{-1}. ^1H NMR δ = 1.40 (t, 3H, CH_3, J = 7.0 Hz), 1.47 (s, 9H, Boc), 4.42 (q, 2H, CH_2, J = 7.0 Hz), 4.65 (d, 2H, CH_2, J = 6.4 Hz), 5.15—5.50 (m, 1H, NH), 8.12 (s, 1H, ring-H). Found: C, 50.33; H, 6.22; N, 9.70%. Calcd for $C_{12}H_{18}N_2O_4S$: C, 50.33; H, 6.34; N, 9.78%.

Ethyl 2-[(*S*)-1-(*N*-*t*-Butoxycarbonyl)aminoethyl]thiazole-4-carboxylate (21). Similarly to the case of **20**, the thiazolation of **19** was done to give **21** as colorless needles. Yield 68%. Mp 87—88 °C. $[\alpha]_D^{26}$ −43.2°(*c* 0.67, CH_2Cl_2). IR 3382, 3118, 2986, 2938, 1722, 1689, 1515 cm^{-1}. ^1H NMR δ = 1.40 (t, 3H, CH_3, J = 7.0 Hz), 1.44 (s, 9H, Boc), 1.62 (d, 3H, CH_3, J = 6.8 Hz), 4.42 (q, 2H, CH_2, J = 7.0 Hz), 4.90—5.35 (m, 2H, NH and α-H), 8.08 (s, 1H, ring-H). Found: 51.95; H, 6.88; N, 9.27%. Calcd for $C_{13}H_{20}N_2O_4S$: C, 51.98; H, 6.71; N, 9.33%.

2-[(*N*-*t*-Butoxycarbonyl)aminomethyl]thiazole-4-carboxylic Acid (22). Similarly to the case of **17**, the ester hydrolysis of **20** was done to give **22** as colorless needles. Yield 89%. Mp 180—181 °C. IR 3448, 3370, 3106, 2980, 1725, 1707, 1705, 1780, 1515 cm^{-1}. ^1H NMR δ = 1.41 (s, 9H, Boc), 4.46 (d, 2H, CH_2, J = 6.2 Hz), 7.81 (t, 1H, NH, J = 6.2 Hz), 8.34 (s, 1H, ring-H), 12.80 (br s, 1H, COOH). Found: C, 46.52; H, 5.28; N, 10.86%. Calcd for $C_{10}H_{14}N_2O_4S$: C, 46.50; H, 5.46; N, 10.85%.

2-[(*S*)-1-(*N*-*t*-Butoxycarbonyl)aminoethyl]thiazole-4-carboxylic Acid (23). Similarly to the case of **17**, the ester hydrolysis of **21** was done to give **23** as colorless needles. Yield 82%. Mp 128—129 °C. $[\alpha]_D^{26}$ −31.9° (*c* 0.85, MeOH). IR 3376, 3106, 2974, 2626, 1965, 1518 cm^{-1}. ^1H NMR δ = 1.40 (s, 9H, Boc), 1.45 (d, 3H, CH_3, J = 8.6 Hz), 4.70—5.01 (m, 1H, α-H), 7.81 (br d, 1H, NH, J = 7.5 Hz), 8.32 (s, 1H, ring-H), 12.87 (br s, 1H, COOH). Found: C, 48.41; H, 6.06; N, 10.32%. Calcd for $C_{11}H_{16}N_2O_4S$: C, 48.52; H, 5.92; N, 10.29%.

2-[(*S*)-1-(*N*-*t*-Butoxycarbonyl)aminoethyl]thiazole-4-carbonyl–L-Ser–OMe (24). To a solution of **4** [derived from Cbz–Ser(TBS)–OMe (10.37 g, 28 mmol)] in DMF (50 ml) were added, with stirring, a solution of **23** (3.49 g, 13 mmol) and HOBt (2.60 g, 19 mmol) in DMF (40 ml) and then DCC (3.18 g, 15 mmol)

at 0 °C. After this was stirred for 3 h, the resulting solution was stirred continuously at room temperature overnight. *N,N'*-Dicyclohexylurea deposited was filtered off, the filtrate was poured into water (100 ml) and was extracted with EtOAc (100 ml). The organic layer was washed successively with brine (30 ml), saturated aqueous $NaHCO_3$ solution (30 ml), and 10% citric acid (30 ml), and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residue, which was stirred with 70% AcOH (60 ml) at room temperature for 12 h. The reaction mixture was again concentrated in vacuo to give a residue, which was purified on a silica-gel column using EtOAc to give colorless crystals. Recrystallization from hexane–EtOAc gave **24** as colorless needles. Yield 82%. Mp 142—143 °C. $[\alpha]_D^{26}$ −7.2° (*c* 0.50, MeOH). IR 3454, 3400, 3346, 3121, 2986, 2932, 1740, 1692, 1665, 1551, 1515 cm^{-1}. ^1H NMR δ = 1.46 (s, 9H, Boc), 1.59 (d, 3H, CH_3, J = 6.8 Hz), 2.90 (br s, 1H, OH), 3.82 (s, 3H, CH_3), 4.01—4.12 (m, 2H, CH_2, β-H), 4.76—5.11 (m, 3H, NH and α-H×2), 8.04 (s, 1H, ring-H), 8.12 (br d, 1H, NH, J = 7.5 Hz). Found: C, 48.21; H, 6.15; N, 11.07%. Calcd for $C_{15}H_{23}N_3O_6S$: C, 48.25; H, 6.21; N, 11.25%.

2-[(*S*)-1-(*N-t*-Butoxycarbonyl)aminoethyl]thiazole-4-carbonyl–ΔAla–OMe (25). To a solution of **24** (0.983 g, 2.54 mmol) in CH_2Cl_2 (10 ml) were added Et_3N (0.39 ml, 2.77 mmol) and MsCl (0.214 ml, 2.77 mmol) under sonication at 0 °C for 30 min. Et_3N (0.389 ml, 2.77 mmol) was further added to the resultant solution. The reaction mixture was diluted with diethyl ether (10 ml) and then washed successively with brine (10 ml), saturated aqueous $NaHCO_3$ solution (10 ml), and 10% citric acid (10 ml), and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave crude crystals, which were recrystallized from hexane-EtOAc to give **25** as colorless needles. Yield 81%. Mp 120—121 °C. $[\alpha]_D^{26}$ +54.55° (*c* 0.11, MeOH). IR 3454, 3400, 3346, 3124, 2986, 2832, 1740, 1692, 1665, 1551, 1515 cm^{-1}. ^1H NMR δ = 1.44 (s, 9H, Boc), 1.62 (d, 3H, CH_3, J = 6.6 Hz), 3.88 (s, 3H, CH_3), 4.98—5.29 (m, 2H, NH and α-H), 5.79 (d, 1H, vinyl-H, J = 1.5 Hz), 6.57 (s, 1H, vinyl-H), 8.05 (s, 1H, ring-H), 9.63 (br s, 1H, NH). Found: 49.25; H, 5.78; N, 11.53%. Calcd for $C_{15}H_{21}N_3O_5S \cdot 0.5H_2O$: C, 49.45; H, 6.09; N, 11.54%.

2-[(*S*)-1-[2-[(*N-t*-Butoxycarbonyl)aminomethyl]thiazole-4-carbonylamino]ethyl]thiazole-4-carbonyl–ΔAla–OMe (26). A solution of **25** (0.427 g, 1.14 mmol) in a mixture of TFA (5 ml) and CH_2Cl_2 (5 ml) was stirred at room temperature for 30 min and then concentrated in vacuo. The obtained residue was dissolved in CH_3CN (10 ml) and to the resulting solution were added, with stirring, $(i\text{-}Pr)_2NEt$ (0.489 g, 2.85 mmol), **22** (0.353 g, 1.25 mmol) and BOP (0.556 g, 1.25 mmol) at 0 °C. After this was stirred for 30 min, the reaction mixture was stirred continuously overnight at room temperature. Concentration in vacuo gave a residue, which was dissolved in EtOAc (20 ml). The resultant solution was washed successively with brine (10 ml), saturated aqueous $NaHCO_3$ solution (10 ml), and 10% citric acid (10 ml), and then dried over anhydrous Na_2SO_4. Concentration 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 colorless crystals. Recrystallization from hexane–EtOAc gave **26** as colorless needles. Yield 15%. MP 131—132 °C. $[\alpha]_D^{26}$ +2.96° (*c* 0.20, MeOH). IR 3370, 3100, 2980, 2260, 1725, 1668, 1641, 1539, 1500 cm^{-1}. ^1H NMR δ = 1.47 (s, 9H, Boc), 1.77 (d, 3H, CH_3, J = 6.8 Hz), 3.91 (s, 3H, CH_3), 4.62 (d, 2H, CH_2, J = 6.4 Hz), 5.30—5.50 (m, 2H, NH and α-H), 6.00 (d, 1H, vinyl-H, J = 1.5 Hz), 6.79 (s, 1H, vinyl-H), 8.00—8.20 (m, 1H, NH), 8.09 (s, 1H, ring-H), 8.12 (s, 1H, ring-H), 9.70 (br s, 1H, NH). Found: C, 48.65; H, 5.10; N, 14.13%. Calcd for $C_{20}H_{25}N_5O_6S_2$: C, 48.47; H, 5.09; N, 14.13%.

2-[(*S*)-1-[2-[(*N-t*-Butoxycarbonyl)aminomethyl]thiazole-4-carbonylamino]ethyl]thiazole-4-carbonyl–L-Ser–OMe (27). Similarly to the case of **26**, the coupling of **24** with **22** was done to give **27** as colorless needles. Yield 99%. Mp 133—134 °C. $[\alpha]_D^{26}$ +23.84° (*c* 1.98, MeOH). IR 3404, 3212, 2980, 2260, 1725, 1668, 1641, 1539, 1500 cm^{-1}. ^1H NMR δ = 1.45 (s, 9H, Boc), 1.71 (d, 3H, CH_3, J = 7.0 Hz), 3.81 (s, 3H, CH_3), 3.98 (br s, 1H, OH), 3.92—4.15 (m, 2H, β-H), 4.57 (d, 2H, CH_2, J = 6.4 Hz), 4.70—4.95 (m, 1H, α-H), 5.30—5.82 (m, 2H, NH and α-H), 8.05 (s, 1H, ring-H), 8.07 (s, 1H, ring-H), 8.15—8.35 (m, 2H, NH×2). Found: C, 46.75; H, 5.25; N, 13.72%. Calcd for $C_{20}H_{27}N_5O_7S_2$: C, 46.77; H, 5.59; N, 14.13%.

2-[(*S*)-1-[2-[2-[(*Z*)-1-(*N-t*-Butoxycarbonyl-*N,O*-isopropylidene)-L-threonylamino)-1-propen-1-yl]oxazole-4-carbonylaminomethyl]thiazole-4-carbonylamino]ethyl]thiazole-4-carbonyl–L-Ser–OMe (28). Similarly to the case of **26**, the coupling of **27** (0.309 g, 0.56 mmol) with **17** (0.229 g, 0.56 mmol) was done to give **27** as colorless needles. Yield 81%. Mp 126—127 °C. $[\alpha]_D^{26}$ −8.33° (*c* 0.36, MeOH). IR 3412, 2980, 1671, 1596, 1539 cm^{-1}. ^1H NMR δ = 1.41 (s, 9H, Boc), 1.45 (d, 3H, CH_3, J = 4.9 Hz), 1.62 (s×2, 3H×2, $(CH_3)_2C$), 1.74 (d, 3H, CH_3, J = 6.7 Hz), 1.86 (d, 3H, CH_3, J = 7.0 Hz), 3.51 (br s, 1H, OH), 3.79 (s, 3H, CH_3), 4.10—4.36 (m, 4H, α-H and β-H), 4.82—4.85 (m, 1H, α-H), 4.89 (d, 2H, CH_2, J = 5.5 Hz), 5.50—5.56 (m, 1H, α-H), 6.62 (q, 1H, CH=, J = 7.0 Hz), 7.74 (br s, 1H, NH), 7.85 (br t, 1H, NH, J = 5.5 Hz), 8.07 (s, 1H, ring-H), 8.10 (s, 1H, ring-H), 8.14 (s, 1H, ring-H), 8.20—8.22 (m, 2H, NH×2). Found: C, 48.88; H, 5.35; N, 13.39%. Calcd for $C_{34}H_{44}N_8O_{11}S_2 \cdot 2H_2O$: C, 48.56; H, 5.39; N, 13.33%.

2-[(*S*)-1-[2-[2-[(*Z*)-1-(*N-t*-Butoxycarbonyl-*N,O*-isopropylidene-L-threonyl)amino-1-propenyl]oxazole-4-carbonylaminomethyl]thiazole-4-carbonylamino]ethyl]thiazole-4-carbonyl–ΔAla–OMe [(P)-2]. Similarly to the case of **25**, the β-elimination of **28** (0.036 g, 0.04 mmol) with MsCl (3.8 μml, 0.05 mmol) and Et_3N (13.7 μml, 0.10 mmol) was done to give (**P**)-**2** as colorless needles. Yield 61%. Mp 130—131 °C. $[\alpha]_D^{25}$ +2.50° (*c* 0.40, MeOH). IR 3370, 2980, 1680, 1596, 1536 cm^{-1}. ^1H NMR δ = 1.37 (d, 3H, CH_3, J = 6.7 Hz), 1.50 (s, 9H, Boc), 1.55 (s, 6H, $(CH_3)_2C$), 1.73 (d, 3H, CH_3, J = 7.0 Hz), 1.81 (d, 3H, CH_3, J = 7.4 Hz), 3.82 (s, 3H, CH_3), 3.92 (d, 1H, α-H, J = 6.7 Hz), 4.25—4.35 (m, 1H, β-H), 4.48 (d, 2H, CH_2, J = 6.2 Hz), 5.48—5.54 (m, 1H, α-H), 5.93 (d, 1H, vinyl-H, J = 1.3 Hz), 6.56 (s, 1H, vinyl-H), 6.71 (q, 1H, CH=, J = 7.4 Hz), 7.50 (br s, 1H, NH), 7.63—7.65 (m, 1H, NH), 8.02—8.04 (m, 3H, ring-H×2 and NH), 8.08 (s, 1H, ring-H), 9.65 (br s, 1H, NH). Found: C, 51.82; H, 5.33; N, 13.85%. Calcd for $C_{34}H_{42}N_8O_{10}S_2$: C, 51.89; H, 5.38; N, 14.24%.

This work was supported in part by Grant-in-Aid for Scientific Research No. 06640703 from the Ministry of Education, Science and Culture.

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