

Total Synthesis of Bistratamides G and H from Various Kinds of ΔAla and ΔAbu-Containing Oligopeptides

Yasuchika Yonezawa,* Naoki Tani, and Chung-gi Shin

Laboratory of Organic Chemistry, Faculty of Engineering, Kanagawa University, Rokkakubashi, Kanagawa-ku, Yokohama 221-8686

Received January 11, 2005; E-mail: yonezy01@kanagawa-u.ac.jp

The total synthesis of naturally occurring bistratamides G (**1**) and H (**2**) from various kinds of dehydrooligopeptides is described. First of all, the promising building blocks of **1** and **2**: *N*-{2-[(*S*)-1-(*N*-benzyloxycarbonyl)amino-2-methylpropyl]oxazole (**4**)- and *N*-{2-[(*S*)-1-(*N*-*t*-butoxycarbonyl)amino-2-methylpropyl]thiazol-4-ylcarbonyl}-L-Val-(S)NH_2 (**5**), and methyl (*S*)-2-{1-[*N*-(3-bromo-2-oxopropanoyl)amino-2-methylpropyl]}-5-methyloxazole-4-carboxylate (**6**), as the left- and right-half components of the linear precursor of **1** and **2**, were synthesized. Subsequent thiazolation between **4** or **5** and **6**, respectively, followed by deprotection of both *N*- and *O*-protecting groups of the two formed linear trisheterocyclic peptides. By final macrocyclization using BOP as condensing agent under high-dilution conditions these peptides gave the expected **1** and **2**.

Bistratamides G (**1**) and H (**2**),[1,2] two of many bistratamide-type polyheterocyclic cyclopeptides, isolated recently from the southern Philippines ascidian, *Rissoclinum bistrrum*, exhibit activity in colon tumor HCT-116 cell line assay. The natural products **1** and **2** feature interesting macrocyclic structures, which include various kinds of heterocyclic (thiazole and oxazole) amino acids, (*S*)-2-[1-amino-2-methylpropyl]thiazole-4-carboxylic acid, (*S*)-2-[1-amino-2-methylpropyl]oxazole-4-carboxylic acid, and (*S*)-2-[1-amino-2-methylpropyl]-5-methyloxazole-4-carboxylic acid residues, as shown in Fig. 1.

Various useful synthetic methods for the heterocyclic amino acids have been already reported by a number of investigators.[3] Accordingly, the total synthesis of bistratamide-type dendroamide A (**3**)[4] (Fig. 2) and a few similar natural products has been already achieved by stepwise elongation of the above-mentioned heterocyclic amino acids[5] and by macrocyclization, by three groups of workers.[6–8] Furthermore, interestingly, one of the groups has reported that the metal-templated assembly condensation of the heterocyclic amino acids gave various similar combinatorial trisheterocyclic cyclopeptides together with **3**.[7] The development of a new and general synthetic method of the polyheterocyclic cyclopeptides attracted our attention and prompted us to study the chemical modification and structure-bioactivity relationship.

Recently, we have reported briefly the total synthesis of **1** by a new synthetic method.[9] Herein, we wish to report in detail the total syntheses of both **1** and **2** from various dehydrooligopeptides. That is, the two kinds of desirable straight-chain trisheterocyclic peptides were synthesized from *N*-{2-[(*S*)-1-(*N*-benzyloxycarbonyl)amino-2-methylpropyl]oxazole (**4**)- and *N*-{2-[(*S*)-1-(*N*-*t*-butoxycarbonyl)amino-2-methylpropyl]thiazol-4-ylcarbonyl}-L-Val-(S)NH_2 (**5**), and methyl (*S*)-2-{1-[*N*-(3-bromo-2-oxopropanoyl)]amino-2-methylpropyl}-5-methyloxazole-4-carboxylate (**6**) (Fig. 1). These materials were comparatively readily derived from Δ^1-, Δ^2-, and Δ^3-dehydrodi- and tripeptides.[10] Subsequent macrocyclization of the obtained two kinds of the *N*,*O*-deprotected linear peptides, derived by thiazolation between **4** or **5** and **6** under high-dilution conditions, gave **1** and **2**. This widely applicable synthesis of the polyheterocyclic cyclopeptide is thought to be attributable to a newly developed method for thiazolation[11] and oxazolation from dehydropeptides.[12]

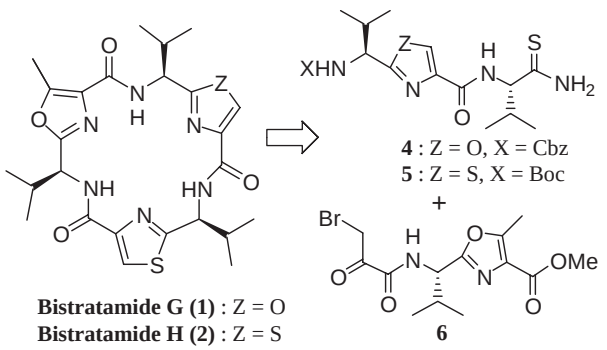


Fig. 1. Retrosynthesis of **1** and **2**.

Results and Discussion

The syntheses of three kinds of building blocks, **4** or **5**, and **6** were accomplished as follows. First of all, to synthesize **4** as the left-half component, the starting Δ^2-dehydrotripeptide[12]

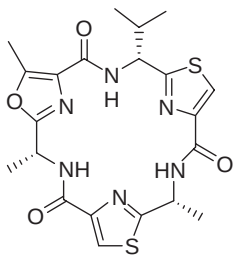


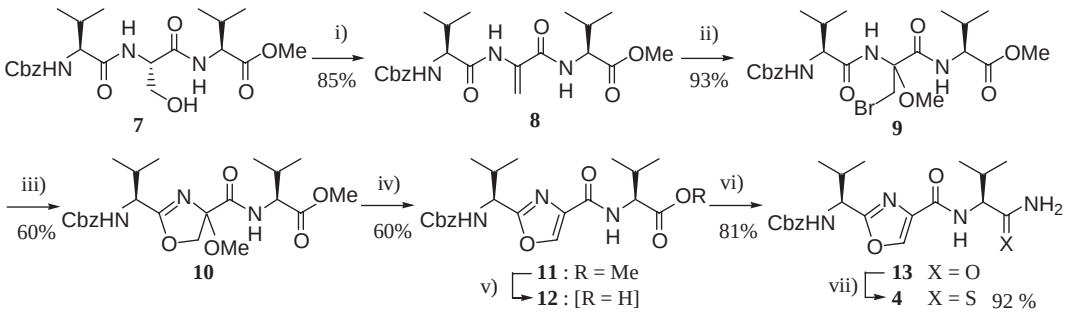
Fig. 2. Dendroamide A (**3**).

Published on the web August 4, 2005; DOI 10.1246/bcsj.78.1492

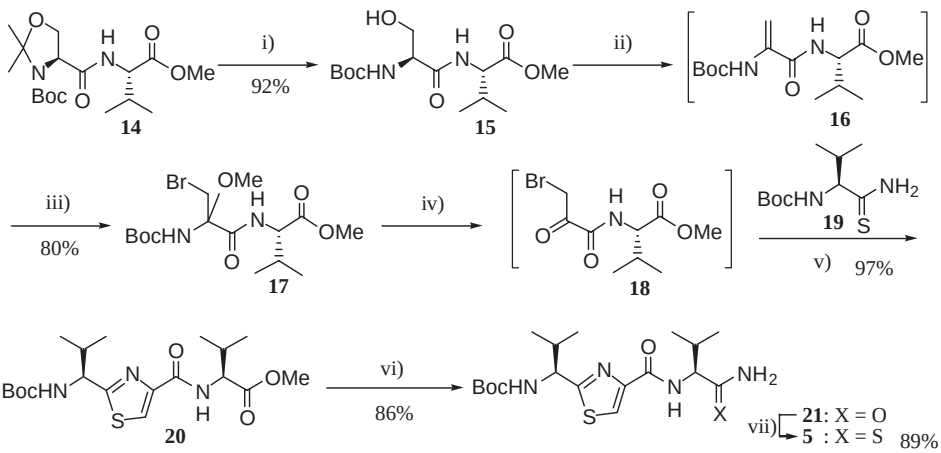
[Cbz-L-Val-ΔAla-L-Val-OMe (**8**). ΔAla = α-dehydroalanine residue. Cbz = benzyloxycarbonyl] was prepared by the usual dehydration of the Ser residue of the authentic Cbz-L-Val-L-Ser-L-Val-OMe (**7**) with methanesulfonyl chloride (Ms-Cl) in the presence of Et_3N and then with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene).[13] Subsequently, the ΔAla residue of **8** was subjected to bromination. However, in the case of bromination of an α-dehydroalanine (ΔAla) residue with NBS (*N*-bromosuccinimide) in $CHCl_3$, it has been already found that various brominated derivatives formed as a mixture. Accordingly, simultaneous bromination and methoxylation of **8** with NBS in MeOH were performed to give the corresponding α-methoxylated β-bromoalanyltripeptide **9**, by the method reported earlier.[14] Then, oxazolination of **9** with Cs_2CO_3 in dioxane at 60 °C proceeded to give the corresponding 4-methoxyoxazoline derivative **10**, the methoxy group of which was β-eliminated with camphorsulfonic acid (CSA) at 70 °C to give the required oxazole dipeptide derivative **11**. After hydrolysis of the methyl ester of **11** with 1 M LiOH, the obtained hydrolysate **12** was amidated with ClCOOEt in the presence of Et_3N and then 28% aq NH_3 (mixed acid anhydride method: MA method) to give the corresponding carboxamide **13**. Finally, thioamidation of **13** with Lawesson's reagent gave the desired thiocarboxamide **4** in 92% yield, as shown in Scheme 1.

Furthermore, to synthesize **5** as the one more left-half component, we prepared the starting Δ^1-dehydrodipeptide [Boc-ΔAla-L-Val-OMe (**16**)] (Boc = *t*-butoxycarbonyl) by consecutive deprotection of *N*-Boc-*N*,*O*-Ip-L-Ser-L-Val-OMe (**14**) (Ip = isopropylidene group), derived from *N*-Boc-*N*,*O*-Ip-L-Ser-OH and H-L-Val-OMe, with a mixture of trifluoroacetic acid (TFA) and $CHCl_3$ (4:96 v/v) and by the usual dehydration of the formed *N*-Boc-L-Ser-L-Val-OMe (**15**), similarly to the case of **8**. Furthermore, similarly to the case of **9**, the methoxy-bromination of **16** gave the corresponding β-bromo-α-methoxylated dipeptide **17**; both Boc and methoxy groups of which were synchronously deprotected and hydrolyzed with TFA and H_2O to give *N*-(3-bromo-2-oxopropanoyl)-L-Val-OMe (**18**). Because of the unstability, without purification, the syrupy **18** was used intact for the next reaction. Subsequent Hantzsch thiazolation between **18** and the authentic *N*-Boc-L-Val-(S)NH_2 (**19**) by successive treatments with $KHCO_3$ in 1,2-dimethoxyethane (DME), with trifluoroacetic anhydride (TFAA) and pyridine, and then with 28% aq NH_3 gave the corresponding thiazoloyl-dipeptide **20**. Similarly to the case of **4**, after the ester hydrolysis of **20** with 1 M LiOH, the successive amidation of the hydrolysate by the MA method and thioamidation of the formed carboxamide **21** with Lawesson's reagent were employed to give the required **5** in 89% yield, as shown in Scheme 2.

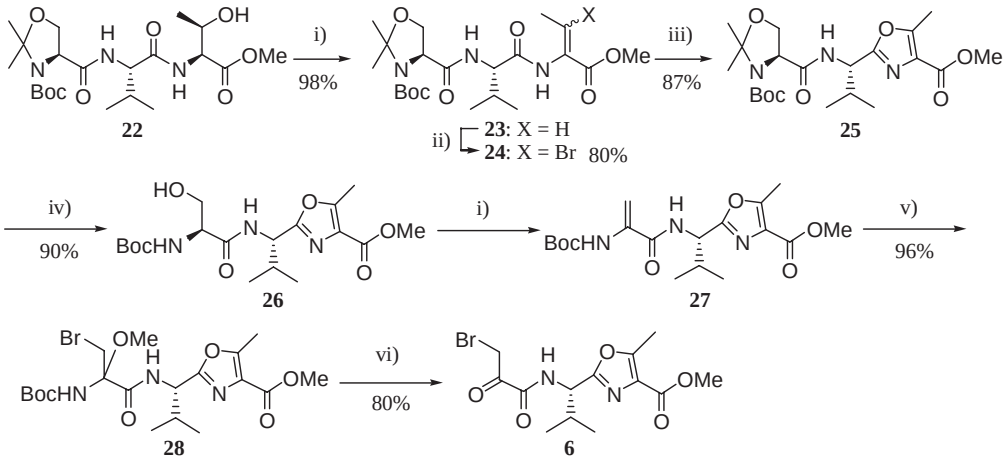
On the other hand, to synthesize **6**, which is the common right-half component of **1** and **2**, firstly, similarly to the case of **8**, *N*-Boc-*N*,*O*-Ip-L-Ser-L-Val-(*Z*)-ΔAbu-OMe (**23**)



Scheme 1. Reagents and conditions: i) MsCl, Et_3N, DBU; ii) NBS, MeOH, rt, 1 h; iii) Cs_2CO_3, dioxane, 60 °C, 6 h; iv) CSA, toluene, 70 °C; v) 1 M LiOH; vi) ClCOOEt, Et_3N, then 28% aq NH_3; vii) Lawesson's reagent.



Scheme 2. Reagents and conditions: i) TFA:$CHCl_3$ (4:96 v/v); ii) MsCl, Et_3N, $CHCl_3$, 0 °C, 1 h, then DBU, rt, 30 min; iii) NBS, MeOH, rt, 1 h; iv) TFA, rt, 30 min, then H_2O, rt, 10 min; v) a) $KHCO_3$, DME, 0 °C, 30 min, 50 °C, overnight, b) TFAA, pyridine, 0 °C, 1 h, c) 28% aq NH_3, 0 °C, 5 min; vi) a) 1 M LiOH, b) ClCOOEt, Et_3N, then 28% aq NH_3; vii) Lawesson's reagent.



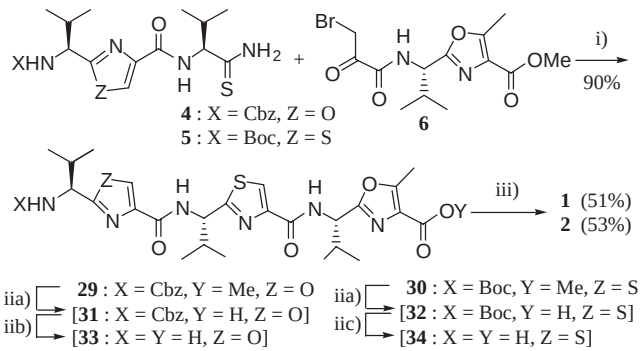
Scheme 3. Reagents and conditions: i) MsCl, Et_3N, $CHCl_3$, 0 °C, 1 h, then DBU, rt, 30 min; ii) NBS, $CHCl_3$, rt, 1 h, Et_3N, rt, 30 min; iii) Cs_2CO_3, dioxane, 60 °C, 6 h; iv) TFA:$CHCl_3$ (4:96 v/v), rt, 5 h; v) NBS, MeOH, rt, 30 min; vi) TFA, rt, 30 min, then H_2O, rt, 10 min.

(ΔAbu = 2-amino-2-butenoic acid) was prepared by the dehydration of the Thr residue of the authentic *N*-Boc-*N*,*O*-Ip-L-Ser-L-Val-L-Thr-OMe (**22**). In the case of the bromination of the ΔAbu residue with NBS, it has been also already found that the formed peptide containing the β-brominated ΔAbu residue was smoothly oxazolated.[15] Accordingly, the bromination of **23** with NBS in $CHCl_3$, in place of MeOH, was carried out to give the corresponding (*E*,*Z*)-Δ^3-dehydrotripeptide **24** containing the ΔAbu(β-Br) residue, which was then oxazolated with Cs_2CO_3[16] at 60 °C to give the required 5-methyloxazole derivative **25**. Secondly, selective deprotection of the Ip group with TFA and $CHCl_3$ (4:96 v/v) was followed by dehydration of the formed *N*-Boc-serinyldipeptide **26**, similarly to the cases of **8** and **23**. That is, repeated consecutive dehydration of the Ser residue of **26** and bromination of the obtained Δ^1-dehydrodipeptide **27** with NBS in MeOH were performed to give the corresponding N-terminal α-methoxylated β-bromoalanyldipeptide derivative **28**. Thirdly, similarly to the case of **18**, deprotection of the Boc group of **28** with TFA and then hydrolysis were employed to give **6** in 80% yield, as shown in Scheme 3. However, because of its lability, without purification, the formed **6** as well was used intact in the next thiazolation with **4** or **5**.

Finally, similarly to the cases of the thiazole ring formation mentioned above, thiazolation between **4** or **5** and **6** gave the desired *N*,*O*-diprotected linear trisheterocyclic peptides **29** and **30**. Then, one pot hydrolysis of the methyl ester of **29** and **30** with 1 M LiOH and deprotection of the Cbz group of the hydrolysates **31** with 10% Pd–C/H_2 and deprotection of the Boc group of **32** with TFA, followed by final macrocyclization of the obtained *N*,*O*-deprotected trisheterocyclic peptides **33** and **34** with BOP[17] and (*i*-Pr)$_2$NEt in DMF under high-dilution conditions (1 mmol/L) at room temperature for 12 h gave the expected **1** and **2** in 51% and 53% yields from **33** and **34**, respectively, as shown in Scheme 4.

The structures of all the new products thus obtained were confirmed by the spectral data (^{1}H and ^{13}C NMR, IR, and specific rotation) and satisfactory elemental analyses.

From the ^{1}H NMR spectra of **29** and **30**, the appearance of the chemical shifts of the oxazole and thiazole ring protons at δ



Scheme 4. Reagents and conditions: i) a) $KHCO_3$, DME, 0 °C, 30 min, 50 °C, overnight, b) TFAA, pyridine, 0 °C, 1 h, c) 28% aq NH_3, 0 °C, 5 min; ii) a) 1 M LiOH, H_2O–dioxane (1:1 v/v), 0 °C, 1 h, rt, 7 h, b) 10% Pd–C, H_2, rt, 3 h, c) TFA, $CHCl_3$, rt, 1 h; iii) BOP, (*i*-Pr)$_2$NEt, DMF, rt, 12 h.

8.03 and 8.17 and the oxazole ring methyl protons at δ 2.61 each as a singlet in **29**, and two thiazole ring protons at δ 8.03 and 8.07 and the oxazole ring methyl protons at δ 2.62 in **30** supports the formation of the expected linear trisheterocyclic peptides **29** and **30**. Furthermore, it was found that the ^{1}H and ^{13}C NMR spectral data and the specific rotations of the synthetic **1** and **2** were fully identical with the spectral data and rotations of the natural **1** and **2**. Accordingly, the configurational structure of **1** and **2** could be clearly confirmed by the identification of the chemical and physical properties as well as by the satisfactory elemental analysis and MALDI-TOF MS [**1**; Found: *m*/*z* 528.1092 $(M+H)^+$. Calcd for $C_{25}H_{32}N_6O_5S$: 528.2155 $(M+H)^+$. **2**; Found: *m*/*z* 544.1931 $(M+H)^+$. Calcd for $C_{25}H_{32}N_6O_4S_2$: 544.1926 $(M+H)^+$].

In conclusion, it is noteworthy that convenient formation of both the thiazole and oxazole rings in peptides from various dehydrooligopeptides was first developed and resulted in the synthesis of various bistratamide-type natural products. Further investigations of the new syntheses of other heterocyclic cyclopeptides are currently under way in our laboratory.

Experimental

The melting points were measured using a Yamato (Model Mp-21) micro-melting point apparatus, and are uncorrected. The IR spectra were recorded using an EPI-G2 spectrometer in KBr. The ^{1}H and ^{13}C NMR spectra were measured with JEOL EX 200, JNE 500, and 600 spectrometers in $CDCl_3$ or DMSO-d_6 solution with tetramethylsilane used as the internal standard. The specific rotations were measured in a 0.5 dm tube using a JASCO DIP-4 polarimeter in MeOH. The mass spectrometers were obtained by SHIMADZU/KRATOS COMPACT MALDI IV tDE.

Cbz-L-Val-L-Ser-L-Val-OMe (7). The compound **7** was obtained by the coupling of Cbz-L-Val-OH with H-L-Ser-L-Val-OMe by the usual method.

Cbz-L-Val-ΔAla-L-Val-OMe (8). A solution of **7** (1.52 g, 3.37 mmol) in $CHCl_3$ (30 mL) in the presences of Et_3N (0.75 g, 7.41 mmol) and of Ms-Cl (0.66 g, 5.73 mmol) was stirred at 0 °C for 1 h. To the solution was further added, with stirring, DBU (1.04 g, 0.67 mmol) at 0 °C for 30 min and then at room temperature for 1 h. The reaction mixture was diluted with diethyl ether (30 mL) and was washed successively with 10% citric acid (30 mL × 2), saturated aqueous $NaHCO_3$ solution (30 mL × 2), and brine (30 mL × 2) and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave **8** as a colorless syrup. Yield 85% (1.39 g). Without purification, the syrup was used in the next reaction. ^{1}H NMR ($CDCl_3$) δ 0.93 (d, 3H, CHCH_3, $J = 7.2$ Hz), 0.95 (d, 3H, CHCH_3, $J = 6.6$ Hz), 0.96 (d, 3H, CHCH_3, $J = 7.2$ Hz), 0.99 (d, 3H, CHCH_3, $J = 6.6$ Hz), 2.19–2.25 (m, 1H × 2, CH(CH_3)$_2$), 3.77 (s, 3H, $COOCH_3$), 4.13–4.15 (m, 1H, CHCH(CH_3)$_2$), 4.57 (dd, 1H, CHCH(CH_3)$_2$, $J = 4.8$ Hz, $J = 8.4$ Hz), 5.11 (ABq, 2H, Cbz's CH_2, $J = 12.6$ Hz, $J = 23.4$ Hz), 5.36 and 6.52 (each s, 1H × 2, vinyl's H), 6.51 (br d, Cbz's NH, $J = 8.4$ Hz), 6.61 (br s, 1H, NH), 7.31–7.35 (m, 5H, Cbz's Ph), 8.37 (br s, 1H, NH).

Cbz-L-Val-DL-(β-Br-α-MeO)Ala-L-Val-OMe (9). A solution of **8** (1.39 g, 3.20 mmol) and NBS (0.63 g, 3.54 mmol) in THF (20 mL) was stirred at 0 °C for 5 min and continuously in MeOH (30 mL) for 30 min. The reaction mixture was diluted with water (50 mL) and then extracted with EtOAc (50 mL × 2). The combined extracts were washed with saturated aqueous $NaHCO_3$ solution (50 mL × 2) and brine (50 mL × 2) and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a brownish syrup, which was purified on a silica-gel column using a mixture of hexane and EtOAc (3:2 v/v) to give **9** as a colorless syrup. Yield 93% (1.70 g). IR 3356, 2976, 1722, 1689, 1676, 1670, 1527, 1512, 1492, 1483 cm^{-1}. ^{1}H NMR ($CDCl_3$) diastereomer: δ 0.83–0.99 (m, 3H × 4, CH(CH_3)$_2$), 2.18–2.25 (m, 1H × 2, CH(CH_3)$_2$), 3.25 and 3.31 (each s, 3H × 1/2, OCH_3), 3.65–3.70 (m, 1H, $BrCH_2C$), 3.71 and 3.75 (each s, 3H × 1/2, $COOCH_3$), 4.13–4.18 (m, 2H, BrCHC), 4.29–4.35 (m, 1H, CHCH(CH_3)$_2$), 4.42–4.47 (m, 1H, CHCH(CH_3)$_2$), 5.10–5.15 (m, 2H, Cbz's CH_2), 5.37 (br d, 1H, CbzNH, $J = 8.4$ Hz), 7.23 and 7.86 (br d, 1H, NH, $J = 7.8$ Hz), 7.32–7.37 (m, 5H, Cbz's Ph). Found: C, 51.05; H, 6.56; N, 7.35%. Calcd for $C_{23}H_{34}BrN_3O_7$: C, 50.74; H, 6.29; N, 7.72%.

(*RS*,*S*)-2-[1-(*N*-Cbz)Amino]-2-methylpropyl]-4-methoxyoxazole-4-carbonyl-L-Val-OMe (10). A solution of **9** (857 mg, 1.57 mmol) and Cs_2CO_3 (1.28 g, 3.92 mmol) in dioxane (20 mL) was stirred at 60 °C overnight. The reaction mixture was diluted with water (20 mL) and the aqueous solution was extracted with EtOAc (50 mL × 3). The combined extracts were washed with brine (30 mL × 2) and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a brown syrup, which was purified on a silica-gel column using a mixture of hexane and EtOAc (2:3 v/v) to give **10** as a colorless syrup. Yield 60% (438 mg). $[\alpha]_D^{26}$ +11.6° (*c* 1.02, $CHCl_3$). IR 3419, 3336, 2964, 1741, 1735, 1691, 1656, 1535, 1512 cm^{-1}. ^{1}H NMR ($CDCl_3$) diastereomer: δ 0.92, 0.94, 0.96, 0.97, 0.98, 1.01 (d, 3H × 4, CH(CH_3)$_2$, $J = 7.2$ Hz, $J = 7.2$ Hz, $J = 6.6$ Hz, $J = 6.6$ Hz, $J = 6.6$ Hz, $J = 6.6$ Hz), 2.18–2.21 (m, 1H × 2, CH(CH_3)$_2$), 3.25 and 3.31 (each s, 3H × 1/2, OCH_3), 3.71 and 3.75 (each s, 3H × 1/2, $COOCH_3$), 4.29–4.33 (m, 1H, CHCH(CH_3)$_2$), 4.42–4.47 (m, 1H, CHCH(CH_3)$_2$), 4.48–4.56 (m, 2H, oxazoline's CH_2), 5.10–5.15 (m, 2H, Cbz's CH_2), 5.37 (br d, 1H × 1/2, NH, $J = 8.4$ Hz), 7.23 (br d, 1H × 1/2, NH, $J = 7.8$ Hz), 7.24 (br d, 1H × 1/2, NH, $J = 7.8$ Hz), 7.32–7.37 (m, 5H, Cbz's Ph). Found: C, 59.24; H, 6.87; N, 9.38%. Calcd for $C_{23}H_{33}N_3O_7$: C, 59.60; H, 7.18; N, 9.07%.

(*S*)-2-[1-(*N*-Cbz)Amino-2-methylpropyl]oxazole-4-carbonyl-L-Val-OMe (11). A solution of **10** (780 mg, 1.68 mmol) and CSA (1.95 mg, 0.84 mmol) in toluene (10 mL) was stirred at 70 °C for 48 h. The reaction mixture was washed with brine (10 mL × 2) and saturated aqueous $NaHCO_3$ solution (10 mL) and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a syrup, which was purified on a silica-gel column using a mixture of hexane and EtOAc (2:3 v/v) to give **11** as a colorless syrup. Yield 60% (438 mg). $[\alpha]_D^{26}$ +11.6° (*c* 1.02, $CHCl_3$). IR 3404, 3317, 2964, 1737, 1726, 1710, 1678, 1597, 1529, 1512, 1502 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.94, 0.97, 1.00, 1.02 (d, 3H × 4, CH(CH_3)$_2$, $J = 6.9$ Hz), 2.21–2.31 (m, 1H × 2, CH(CH_3)$_2$), 3.77 (s, 3H, $COOCH_3$), 4.60–4.69 and 4.85–4.88 (each m, 1H × 2, CHCH(CH_3)$_2$), 5.11–5.17 (m, 2H, Cbz's CH_2), 5.38 (br d, 1H, CbzNH, $J = 9.6$ Hz), 7.31–7.38 (m, 6H, Cbz's Ph and NH), 8.31 (s, 1H, oxazole's ring-H). Found: C, 61.56; H, 7.15; N, 10.09%. Calcd for $C_{22}H_{29}N_3O_6$: C, 61.24; H, 6.77; N, 9.74%.

(*S*)-2-[1-(*N*-Cbz)Amino-2-methylpropyl]oxazole-4-carbonyl-L-Val-OH (12). A solution of **11** (548 mg, 1.27 mmol) and 1 M LiOH (1.9 mL, 1.90 mmol) in a mixture of THF–water (1:1 v/v) (40 mL) was stirred at 0 °C for 30 min and at room temperature for 1 h. The reaction mixture was washed with diethyl ether (50 mL × 2) and the aqueous layer was acidified with citric acid and washed with EtOAc (50 mL × 2) and brine (50 mL × 2), and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a crude **12** as a colorless syrup, which was used intact in the next reaction.

(*S*)-2-[1-(*N*-Cbz)Amino-2-methylpropyl]oxazole-4-carbonyl-L-Val-NH$_2$ (13). A solution of the obtained **12**, Et_3N (141 mg, 1.34 mmol), and ClCOOEt (145 mg, 1.34 mmol) in THF (50 mL) was stirred at 0 °C for 10 min and continuously with 28% NH_3 (10 mL) for 5 min. The reaction mixture was mixed with saturated aqueous NH_4Cl solution (30 mL) and the organic layer was dried over anhydrous Na_2SO_4. Concentration in vacuo gave a yellow syrup, which was purified on a silica-gel column using EtOAc to give a colorless solid. Recrystallization from a mixture of hexane and EtOAc gave **13** as colorless powder. Yield 81% (428 mg). mp 135–136 °C. $[\alpha]_D^{25}$ −6.46° (*c* 0.92, $CHCl_3$). IR 3412, 3317, 2964, 1720, 1708, 1689, 1676, 1664, 1656, 1597, 1529 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.91, 0.95, 1.00, 1.03 (d, 3H × 4, CH(CH_3)$_2$, $J = 7.2$ Hz, $J = 7.2$ Hz, $J = 6.6$ Hz, $J = 6.6$ Hz), 2.17–2.27 (m, 1H × 2, CH(CH_3)$_2$), 4.41–4.44 (m, 1H, CHCH(CH_3)$_2$), 4.83 (dd, 1H, CHCH(CH_3)$_2$, $J = 7.2$ Hz, $J = 9.0$ Hz), 5.10–5.26 (m, 2H, Cbz's CH_2), 5.64 (br d, 1H, CbzNH, $J = 9.6$ Hz), 5.85 and 6.31 (each br d, 1H × 2, NH_2, $J = 13.8$ Hz), 7.32–7.37 (m, 6H, Cbz's

Ph and NH), 8.12 (s, 1H, oxazole's ring-H). Found: C, 60.14; H, 7.04; N, 13.1%. Calcd for $C_{21}H_{28}N_4O_5$: C, 60.56; H, 6.78; N, 13.45%.

***N*-{2-[(*S*)-1-(*N*-Cbz)Amino-2-methylpropyl]oxazol-4-ylcarbonyl}-L-Val-(S)NH_2 (4).** A solution of **13** (963 mg, 2.31 mmol) and Lawesson's reagent (467 mg, 1.15 mmol) in THF (15 mL) was stirred at room temperature overnight. After excess Lawesson's reagent was filtered off, the filtrate was concentrated in vacuo. The obtained syrup was purified on a silica-gel column using a mixture of hexane and EtOAc (1:2 v/v) to give a colorless solid. Recrystallization from a mixture of hexane and EtOAc gave **4** as a colorless powder. Yield 92% (1.00 g). mp 67–68 °C. $[\alpha]_D^{26}$ −64.8° (*c* 0.98, $CHCl_3$). IR 3327, 2968, 1722, 1710, 1691, 1678, 1664, 1546, 1529 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.94 (d, 6H, $CH(CH_3)_2$, $J = 5.4$ Hz), 1.03 (d, 6H, $CH(CH_3)_2$, $J = 6.0$ Hz), 2.20–2.24 and 2.33–2.36 (each m, 1H × 2, $CH(CH_3)_2$), 4.63–4.68 and 4.84–4.87 (m, 1H × 2, $CHCH(CH_3)_2$), 5.11–5.17 (m, 2H, Cbz's CH_2), 5.47 (br d, 1H, CbzNH, $J = 9.0$ Hz), 7.33–7.38 (m, 5H, Cbz's Ph), 7.59 (br d, 1H, NH, $J = 8.4$ Hz), 7.75 and 8.16 (each br s, 1H × 2, NH_2), 8.11 (s, 1H, oxazole's ring-H). Found: C, 58.69; H, 6.21; N, 12.53%. Calcd for $C_{21}H_{28}N_4O_4S$: C, 58.31; H, 6.52; N, 12.95%.

***N*-Boc-*N*,*O*-Ip-L-Ser-L-Val-OMe (14).** The compound **14** was obtained by the coupling of *N*-Boc-*N*,*O*-Ip-L-Ser-OH with H-L-Val-OMe by the usual method.

***N*-Boc-L-Ser-L-Val-OMe (15).** A solution of **14** (1.98 g, 5.53 mmol) in a mixture of TFA and $CHCl_3$ (4:96 v/v) (35 mL) was stirred at room temperature for 3 h. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ solution and the organic layer was washed with brine (10 mL × 2), and dried over anhydrous Na_2SO_4. Concentration in vacuo gave a yellow syrup, which was purified on a silica-gel column using a mixture of hexane and EtOAc (1:2 v/v) to give **15** as a colorless syrup. Yield 92% (1.65 g). $[\alpha]_D^{25}$ −32.6° (*c* 0.78, $CHCl_3$). IR 3417, 3302, 2983, 2949, 1730, 1707, 1676, 1560, 1490 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.00 (s, 3H, $COOCH_3$), 0.91 (d, 3H, $CH(CH_3)_2$, $J =$ 6.6 Hz), 0.95 (d, 3H, $CH(CH_3)_2$, $J = 7.2$ Hz), 1.46 (s, 9H, Boc's *t*-Bu), 2.17–2.26 (m, 1H, $CH(CH_3)_2$), 3.64–3.70 (m, 1H, $CHCHHOH$, $J = 10.2$ Hz), 4.09 (br d, 1H, $CHCHHOH$, $J =$ 10.2 Hz), 4.20 (br s, 1H, OH), 4.49–4.54 (m, 1H, $CHCH_2OH$), 5.63 (br s, 1H, BocNH), 7.13 (br d, 1H, NH, $J = 6.0$ Hz). Found: C, 52.56; H, 8.62; N, 8.48%. Calcd for $C_{14}H_{26}N_2O_6$: C, 52.82; H, 8.23; N, 8.80%.

***N*-Boc-ΔAla-L-Val-OMe (16).** Similarly to the case of **8**, the dehydration of **15** (1.530 g, 4.80 mmol) with Et_3N (1.070 g, 10.56 mmol), Ms-Cl (935 mg, 8.16 mmol), and DBU (1.04 g, 6.71 mmol) in $CHCl_3$ (50 mL) was worked up to give **17** as a colorless syrup, which was used in the next reaction, without purification.

***N*-Boc-DL-(β-Br-α-MeO)Ala-L-Val-OMe (17).** A solution of **16** (1.40 g, 4.66 mmol) and NBS (940 mg, 5.28 mmol) in MeOH (50 mL) was stirred at 0 °C for 30 min. The reaction mixture was poured into water (50 mL) and the resulting solution was extracted with EtOAc (30 mL × 2). The combined extracts were dried over anhydrous Na_2SO_4 and then concentrated in vacuo to give a brown syrup. Purification on a silica-gel column using a mixture of hexane and EtOAc (3:2 v/v) gave **17** as a colorless syrup. Diastereomer. Yield 80% (1.280 g). IR 3307, 2968, 1726, 1709, 1671 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.93 and 0.94 (d, 3H, $CH(CH_3)_2$, $J = 7.2$ Hz), 0.95–1.00 (d, 3H, $CH(CH_3)_2$, $J = 6.6$ Hz), 1.46 (s, 9H, Boc's *t*-Bu), 2.23–2.29 (m, 1H, $CH(CH_3)_2$), 3.29 and 3.32 (each s, 3H, OCH_3), 3.72 and 4.27 (each br d, 1H × 1/2, CH_2Br, $J = 10.8$ Hz), 3.77 and 3.78 (s, 3H, $COOCH_3$), 4.50 and 4.53 (each d, 1H × 1/2, CH_2Br, $J = 13.2$ Hz), 4.51–4.57 (m, 1H, $CHCH(CH_3)_2$), 6.99 and 7.03 (br d, 1H, NH, $J = 8.5$ Hz), 7.37 and 7.39 (each br s, 1H, NH). Found: C, 43.41; H, 6.48; N, 6.47%. Calcd for $C_{15}H_{27}BrN_2O_6$: C, 43.80; H, 6.62; N, 6.81%.

***N*-(3-Bromo-2-oxopropanoyl)-L-Val-OMe (18).** A solution of **17** (1.20 g, 2.91 mmol) and TFA (20 mL) in $CHCl_3$ (20 mL) was stirred at room temperature for 30 min. The resulting solution was further stirred with water (20 mL) for 10 min. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ solution (20 mL) and the organic layer was dried over anhydrous Na_2SO_4. Concentration in vacuo gave **18** as a colorless syrup, which was used intact in the next reaction, without purification. ^1H NMR ($CDCl_3$) δ 0.91 (d, 3H, $CH(CH_3)_2$, $J = 7.2$ Hz), 0.94 (d, 3H, $CH(CH_3)_2$, $J = 6.6$ Hz), 2.24–2.37 (m, 1H, $CH(CH_3)_2$), 3.82 (s, 3H, $COOCH_3$), 4.49 (m, 2H, $COCH_2Br$), 5.02 (m, 1H, $CHCH(CH_3)_2$), 7.49 (br s, 1H, NH).

***N*-Boc-L-Val-(S)NH_2 (19).** The compound **19** was obtained by the thioamidation of *N*-Boc-L-Val-NH_2 with Lawesson's reagent by the usual method.

(*S*)-2-[1-(*N*-Boc)Amino-2-methylpropyl]oxazole-4-carbonyl-L-Val-OMe (20). To a solution of **19** (590 mg, 2.54 mmol) in DMF (10 mL) were added, with stirring, K_2CO_3 (2.800 g, 20.32 mmol) and a solution of **18** (1.060 g, 3.80 mmol) in DME (10 mL) at 0 °C. After stirring for overnight at room temperature, the resulting solution was concentrated in vacuo to give a brown syrup, which was dissolved in $CHCl_3$ (20 mL) and washed with water (20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a brown syrup, which was dissolved in DME (10 mL). To the solution were added, with stirring, TFAA (trifluoroacetic anhydride) (704 μL, 5.08 mmol) and pyridine (897 μL, 11.18 mmol) at 0 °C for 30 min. Concentration in vacuo gave a brown syrup, which was further dissolved in EtOAc (30 mL). The resulting solution was washed with brine (20 mL) and stirred with 28% aqueous NH_3 at 0 °C. After stirring for 15 min, the reaction mixture was washed with brine (20 mL × 2) and dried over anhydrous Na_2SO_4. Concentration in vacuo gave a brown syrup, which was purified on a silica-gel column using a mixture of hexane and EtOAc (1:2 v/v) to give **20** as a colorless syrup. Yield 97% (1.02 g). $[\alpha]_D^{25}$ −9.5° (*c* 1.07, $CHCl_3$). IR 3315, 2966, 1743, 1722, 1708, 1691, 1664, 1658, 1546, 1535 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.94 (d, 3H, $CH(CH_3)_2$, $J = 6.6$ Hz), 0.98 (d, 3H, $CH(CH_3)_2$, $J = 7.2$ Hz), 1.00 (d, 3H, $CH(CH_3)_2$, $J = 7.2$ Hz), 1.01 (d, 3H, $CH(CH_3)_2$, $J =$ 6.6 Hz), 1.47 (s, 9H, Boc's *t*-Bu), 2.27–2.40 (m, 1H × 2, $CH(CH_3)_2$), 3.78 (s, 3H, $COOCH_3$), 4.70 (dd, 1H, $CHCH(CH_3)_2$, $J = 5.4$ Hz, $J = 9.0$ Hz), 4.89 (m, 1H, $CHCH(CH_3)_2$), 5.15 (br d, 1H, BocNH, $J = 8.4$ Hz), 7.72 (br d, 1H, NH, $J = 9.0$ Hz), 8.01 (s, 1H, thiazole's ring-H). Found: C, 55.52; H, 7.28; N, 10.48%. Calcd for $C_{19}H_{31}N_3O_5S$: C, 55.18; H, 7.56; N, 10.16%.

(*S*)-2-[1-(*N*-Boc)Amino-2-methylpropyl]oxazole-4-carbonyl-L-Val-NH_2 (21). A solution of **20** (1.05 g, 2.53 mmol) and 1 M LiOH (5 mL, 5.06 mmol) in a mixture of water and dioxane (1:1 v/v) (10 mL) was stirred at 0 °C for 30 min and then at room temperature for 3 h. The resulting solution was washed with diethyl ether (5 mL × 2) and acidified with citric acid and then extracted with EtOAc (10 mL × 2). The combined extracts were washed with brine (10 mL × 2) and dried over anhydrous Na_2SO_4. Concentration in vacuo gave the corresponding free carboxylic acid as a colorless syrup, which was used intact in the next reaction. Similarly to the case of **13**, the amidation of the obtained syrup with Et_3N (281 mg, 2.78 mmol), ClCOOEt (302 mg, 2.78 mmol), and 28% aqueous NH_3 (10 mL) in THF (100 mL) was worked up

to give **21** as a colorless amorphous material. Yield 86% (903 mg). $[\alpha]_D^{25}$ −46.9° (*c* 1.37, $CHCl_3$). IR 3396, 2966, 2933, 1720, 1707, 1689, 1666, 1544, 1533, 1500, 1492 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.92 (d, 3H, $CH(CH_3)_2$, $J = 6.9$ Hz), 1.00 (d, 3H, $CH(CH_3)_2$, $J = 6.9$ Hz), 1.03 (d, 3H, $CH(CH_3)_2$, $J = 6.9$ Hz), 1.05 (d, 3H, $CH(CH_3)_2$, $J = 6.9$ Hz), 1.47 (s, 9H, Boc's *t*-Bu), 2.26–2.32 and 2.37–2.40 (each m, 1H × 2, $CH(CH_3)_2$), 4.46 (dd, 1H, $CHCH(CH_3)_2$, $J = 7.2$ Hz, $J = 9.0$ Hz), 4.87 (dd, 1H, $CHCH(CH_3)_2$, $J = 6.0$ Hz, $J = 9.0$ Hz), 5.22 (br d, 1H, BocNH, $J = 9.0$ Hz), 5.79 and 6.40 (each br s, 1H × 2, NH_2), 7.76 (br d, 1H, NH, $J = 9.0$ Hz), 8.00 (s, 1H, thiazole's ring-H). Found: C, 54.59; H, 7.28; N, 14.41%. Calcd for $C_{18}H_{30}N_4O_4S$: C, 54.25; H, 7.59; N, 14.06%.

***N*-{2-[(*S*)-1-(*N*-Boc)Amino-2-methylpropyl]thiazol-4-ylcarbonyl}-L-Val-(S)NH_2 (5).** Similarly to the case of **4**, the thioamidation of **21** (876 mg, 2.20 mmol) with Lawesson's reagent (490 mg, 1.21 mmol) in DME (30 mL) was worked up to give **5** as a yellow powder. mp 113–114 °C. Yield 89% (811 mg). $[\alpha]_D^{25}$ −54.8° (*c* 0.94, $CHCl_3$). IR 3214, 2966, 1726, 1701, 1689, 1666, 1544, 1528 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.94 (d, 3H, $CH(CH_3)_2$, $J = 6.9$ Hz), 1.03 (d, 3H, $CH(CH_3)_2$, $J = 6.9$ Hz), 1.05 (d, 3H, $CH(CH_3)_2$, $J = 6.9$ Hz), 1.08 (d, 3H, $CH(CH_3)_2$, $J = 6.9$ Hz), 1.51 (s, 9H, Boc's *t*-Bu), 2.38–2.42 (m, 1H × 2, $CH(CH_3)_2$), 4.67–4.69 (m, 1H, $CHCH(CH_3)_2$), 4.89–4.91 (m, 1H, $CHCH(CH_3)_2$), 5.22 (br d, 1H, BocNH, $J = 9.0$ Hz), 7.23 and 8.15 (each br s, 1H × 2, NH_2), 7.53 (br d, 1H, NH, $J = 9.0$ Hz), 8.02 (s, 1H, thiazole's ring-H). Found: C, 52.05; H, 7.14; N, 13.61%. Calcd for $C_{18}H_{30}N_4O_3S_2$: C, 51.99; H, 7.22; N, 13.48%.

***N*-Boc-*N*,*O*-Ip-L-Ser-L-Val-L-Thr-OMe (22).** The compound **22** was obtained by the coupling of *N*-Boc-*N*,*O*-Ip-L-Ser-L-Val-OH with H-L-Thr-OMe by the usual method.

***N*-Boc-*N*,*O*-Ip-L-Ser-L-Val-(*Z*)-ΔAbu-OMe (23).** Similarly to the cases of **8** and **16**, the dehydration of **22** (3.12 g, 6.79 mmol) of Et_3N (1.51 g, 14.94 mmol), Ms-Cl (1.32 g, 11.54 mmol), and DBU (1.46 g, 9.50 mmol) in $CHCl_3$ (30 mL) was worked up to give **23** as a colorless powder. Yield 98% (2.94 g). mp 124–125 °C. $[\alpha]_D^{26}$ −74.1° (*c* 1.02, $CHCl_3$). IR 3327, 2968, 1722, 1710, 1691, 1678, 1664, 1546, 1529 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.98 and 1.01 (d, 3H × 2, $CH(CH_3)_2$, $J = 6.6$ Hz), 1.43–1.60 (m, 15H, Ip's CH_3 × 2, Boc's *t*-Bu), 1.81 (d, 3H, ΔAbu's CH_3, $J = 7.2$ Hz), 2.43–2.47 (m, 1H, $CH(CH_3)_2$), 3.74 (s, 3H, $COOCH_3$), 4.11–4.46 (m, 4H, $-OCH_2$, NCH × 2), 6.82 (br q, 1H, olefin's H, $J = 7.2$ Hz), 6.98 (br s, 1H, NH), 8.98 (br s, 1H, NH). Found: C, 57.51; H, 7.64; N, 9.28%. Calcd for $C_{21}H_{35}N_3O_7$: C, 57.13; H, 7.99; N, 9.52%.

***N*-Boc-*N*,*O*-Ip-L-Ser-L-Val-(*Z*)-ΔAbu(β-Br)-OMe (24).** A solution of **23** (2.89 g, 6.55 mmol) and NBS (1.28 g, 7.20 mmol) in $CHCl_3$ (30 mL) was stirred at room temperature for 3 h. The resulting solution was further stirred with Et_3N (0.73 g, 7.21 mmol) at 0 °C for 30 min and then at room temperature for 5 h. The reaction mixture was diluted with diethyl ether (20 mL) and washed successively with 10% citric acid (20 mL × 2), saturated $NaHCO_3$ (20 mL × 2), and brine (20 mL × 2), and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a brown syrup, which was purified on a silica-gel column using a mixture of hexane and EtOAc (1:1 v/v) to give **24** as colorless crystals. Yield 80% (2.73 g). mp 124–125 °C. IR 3327, 2975, 1765, 1726, 1701, 1695, 1664, 1529, 1500 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.92–1.00 (m, 3H × 2, $CH(CH_3)_2$), 1.53 and 1.65 (each s, 3H × 2, Ip's CH_3), 1.49 (s, 9H, Boc's *t*-Bu), 2.41 (s, 3H × 1/2, ΔAbu's CH_3), 2.47–2.49 (m, 1H, $CH(CH_3)_2$), 2.59 (s, 3H × 1/2, ΔAbu's CH_3), 3.77 (s, 3H, $COOCH_3$), 4.14–4.16 and 4.22–4.26 (each m, 1H × 2, OCH_2), 4.40–4.45 (m, 1H, $CHCH(CH_3)_2$), 4.54–4.58 (m, 1H × 2, CHNH and CHN*H*), 7.88 (br s, 1H, NH), 8.27 (br s, 1H, NH). Found: C, 48.07; H, 6.17; N, 7.75%. Calcd for $C_{21}H_{34}BrN_3O_7$: C, 48.47; H, 6.56; N, 8.07%.

Methyl (*S*)-2-[1-(*N*-Boc-*N*,*O*-Ip-L-Ser)Amino-2-methylpropyl]-5-methyl-oxazole-4-carboxylate (25). A solution of **24** (1.45 g, 2.79 mmol) and Cs_2CO_3 (2.27 g, 6.95 mmol) in dioxane (30 mL) was stirred at 60 °C overnight. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (50 mL × 3). The combined extracts were washed with brine (30 mL × 2) and dried over anhydrous Na_2SO_4. Concentration in vacuo gave a brown syrup, which was purified on a silica-gel column using a mixture of hexane and EtOAc (3:2 v/v) to give **25** as a colorless syrup. Yield 87% (1.07 g). $[\alpha]_D^{26}$ −85.4° (*c* 1.08, $CHCl_3$). IR 3233, 2980, 1756, 1708, 1691, 1678, 1546, 1529 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.91 and 0.95 (d, 3H × 2, $CH(CH_3)_2$, $J = 6.6$ Hz), 1.38–1.76 (m, 15H, Ip's CH_3 × 2, Boc's *t*-Bu), 2.25–2.28 (m, 1H, $CH(CH_3)_2$), 2.60 (s, 3H, oxazole's ring-CH_3), 3.88–4.55 (m, 3H, OCH_2 and NC*H*CH_2O), 3.89 (s, 3H, $COOCH_3$), 5.07 (dd, 1H, $CHCH(CH_3)_2$, $J = 6.6$ Hz, $J = 9.0$ Hz), 7.50 (br s, 1H, NH). Found: C, 57.63; H, 7.28; N, 9.14%. Calcd for $C_{21}H_{33}N_3O_7$: C, 57.39; H, 7.57; N, 9.56%.

Methyl (*S*)-2-[1-(*N*-Boc-L-Ser)Amino-2-methylpropyl]-5-methyloxazole-4-carboxylate (26). A solution of **25** (2.35 g, 5.35 mmol) in a mixture of TFA and $CHCl_3$ (4:96 v/v) (200 mL) was stirred at room temperature for 2 h. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ solution (150 mL) and the organic layer was washed with brine (100 mL × 2) and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residual substance, which was purified on a silica-gel column using a mixture of hexane and EtOAc to give **26** as a colorless powder. Yield 90% (1.92 g). mp 153–154 °C. $[\alpha]_D^{26}$ −64.8° (*c* 0.98, $CHCl_3$). IR 3327, 2968, 1722, 1710, 1691, 1678, 1664, 1529 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.91 and 0.95 (d, 3H × 2, $CH(CH_3)_2$, $J = 6.6$ Hz), 1.61 (s, 9H, Boc's *t*-Bu), 2.25–2.28 (m, 1H, $CH(CH_3)_2$), 2.60 (s, 3H, oxazole's ring-CH_3), 3.67 (br d, 1H, $CHCH_2OH$, $J = 7.0$ Hz), 3.89 (s, 3H, $COOCH_3$), 4.10 (br d, 2H, $CHCH_2O$, $J = 7.0$ Hz), 4.30 (br s, 1H, OH), 5.23 (dd, 1H, $CHCH(CH_3)_2$, $J = 6.6$ Hz, $J = 9.0$ Hz), 6.85 (br s, 1H, BocNH), 7.50 (br s, 1H, NH). Found: C, 54.54; H, 7.71; N, 10.13%. Calcd for $C_{18}H_{29}N_3O_7$: C, 54.12; H, 7.32; N, 10.52%.

Methyl (*S*)-2-[1-(*N*-Boc-ΔAla)Amino-2-methylpropyl]-5-methyloxazole-4-carboxylate (27). Similarly to the case of **23**, the dehydration of **26** (532 mg, 1.33 mmol) with Et_3N (228 mg, 2.26 mmol), Ms-Cl (228 mg, 2.00 mmol), and DBU (287 mg, 1.86 mmol) in $CHCl_3$ (10 mL) was worked up to give **27** as a crude syrup, which was intact used in the next reaction. ^1H NMR ($CDCl_3$) δ 0.93 and 0.99 (d, 3H × 2, $CH(CH_3)_2$, $J = 7.8$ Hz), 1.48 (s, 9H, Boc's *t*-Bu), 2.26–2.31 (m, 1H, $CH(CH_3)_2$), 2.63 (s, 3H, oxazole's ring-CH_3), 3.92 (s, 3H, $COOCH_3$), 5.09 (dd, 1H, $CHCH(CH_3)_2$, $J = 4.6$ Hz, $J = 8.4$ Hz), 5.18 and 6.06 (each s, 1H × 2, vinyl's H), 6.73 (br d, 1H, NH, $J = 8.4$ Hz), 7.24 (br s, 1H, BocNH).

Methyl (*S*)-2-{1-[*N*-Boc-DL-(β-Br-α-MeO)Ala]Amino-2-methylpropyl}-5-methyloxazole-4-carboxylate (28). Similarly to the case of **9**, the bromination of **27** (508 mg, 1.33 mmol) with NBS (267 mg, 1.50 mmol) in THF (20 mL) and MeOH (30 mL) was worked up to give **28** as a yellow syrup. Yield 96% (630 mg). IR 3327, 2972, 1722, 1710, 1691, 1483 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.95 and 1.00 (d, 3H × 2, $CH(CH_3)_2$, $J = 7.2$ Hz), 1.45 (s, 9H, Boc's *t*-Bu), 2.26–2.33 (m, 1H, $CH(CH_3)_2$), 2.61 and 2.77 (each

s, 3H, oxazole's ring-CH_3), 3.33 and 3.49 (each s, 3H, OCH_3), 3.67 and 4.13 (each br d, 1H × 2, CH_2Br, $J = 10.8$ Hz), 3.91 (s, 3H, $COOCH_3$), 5.02 (dd, 1H, C*H*CH$(CH_3)_2$, $J = 6.6$ Hz, $J = 9.6$ Hz), 5.98 (br s, 1H, BocNH), 7.13 (br d, 1H, NH, $J = 9.6$ Hz). Found: C, 46.68; H, 6.48; N, 8.18%. Calcd for $C_{19}H_{30}BrN_3O_7$: C, 46.36; H, 6.14; N, 8.53%.

Methyl (*S*)-2-[1-(3-Bromo-2-oxopropanoyl)amino-2-methylpropyl]-5-methyloxazole-4-carboxylate (6). Similarly to the case of **18**, the hydrolysis of **28** (4.56 g, 9.26 mmol) with TFA (50 mL) in $CHCl_3$ (50 mL) was worked up for 1 h to give **6** as a colorless syrup. Because of the unstability, the obtained **6** was used intact in the next reaction. Yield 80% (2.67 g). ^{1}H NMR ($CDCl_3$) δ 0.93 (d, 3H, CH(C*H*$_3$)$_2$, $J = 7.2$ Hz), 0.97 (d, 3H, CH(C*H*$_3$)$_2$, $J = 6.6$ Hz), 2.24–2.37 (m, 1H, C*H*$(CH_3)_2$), 2.67 (s, 3H, oxazole's ring-CH_3), 3.67 (s, 3H, $COOCH_3$), 4.49 (q, 2H, CH_2Br, $J = 13.7$ Hz), 5.02 (dd, 1H, C*H*CH$(CH_3)_2$, $J = 6.6$ Hz, $J = 9.6$ Hz), 7.49 (br d, 1H, NH, $J = 9.6$ Hz).

Methyl (*S*,*S*,*S*)-2-{1-[2-(1-{2-[1-(*N*-Cbz)Amino-2-methylpropyl]oxazole-4-carbonylamino}-2-methylpropyl)thiazole-4-carbonylamino]-2-methylpropyl}-5-methyloxazole-4-carboxylate (29). Similarly to the case of **20**, the thiazolation of **4** (0.80 g, 1.84 mmol) in DME (20 mL) with **6** (1.66 g, 4.60 mmol) in DME (20 mL) in the presence of $KHCO_3$ (1.47 g, 14.72 mmol) was worked up to give a brown syrup, which was purified on a silica-gel column using a mixture of hexane and EtOAc (2:1 v/v) to give **29** as a colorless powder. Yield 90% (1.15 g). mp 71–72 °C. $[\alpha]_D^{26}$ +4.2° (*c* 0.93, $CHCl_3$). IR 3404, 3323, 2964, 1718, 1676, 1670, 1612, 1541, 1533, 1498 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.91 (d, 3H, CH(C*H*$_3$)$_2$, $J = 6.6$ Hz), 0.93 (d, 3H, CH(C*H*$_3$)$_2$, $J = 6.6$ Hz), 0.95 (d, 3H, CH(C*H*$_3$)$_2$, $J = 7.2$ Hz), 0.97 (d, 3H, CH(C*H*$_3$)$_2$, $J = 7.2$ Hz), 0.99 (d, 3H, CH(C*H*$_3$)$_2$, $J = 7.2$ Hz), 1.12 (d, 3H, CH(C*H*$_3$)$_2$, $J = 7.2$ Hz), 2.23–2.25, 2.35–2.37, and 2.56–2.62 (each m, 1H × 3, C*H*$(CH_3)_2$), 2.61 (s, 3H, oxazole's ring-CH_3), 3.91 (s, 3H, $COOCH_3$), 4.83–4.88 (m, 1H, C*H*CH$(CH_3)_2$), 5.13 (ABq, 2H, Cbz's CH_2, $J = 13.8$ Hz, $J = 21.0$ Hz), 5.17–5.20 and 5.32–5.38 (each m, 1H × 2, C*H*CH$(CH_3)_2$), 5.52 (br s, 1H, NH, $J = 9.6$ Hz), 7.33–7.36 (m, 5H, Cbz's Ph), 7.45 and 7.85 (each br d, 1H × 2, NH, $J = 9.6$ Hz), 8.03 (s, 1H, oxazole's ring-H), 8.17 (s, 1H, thiazole's ring-H). Found: C, 58.38; H, 6.23; N, 12.48%. Calcd for $C_{34}H_{42}N_6O_8S$: C, 58.77; H, 6.09; N, 12.19%.

Methyl (*S*,*S*,*S*)-2-{1-[2-(1-{2-[1-(*N*-Boc)Amino-2-methylpropyl]thiazole-4-carbonylamino}-2-methylpropyl)thiazole-4-carbonylamino]-2-methylpropyl}-5-methyloxazole-4-carboxylate (30). Similarly to the case of **29**, the thiazolation of **5** (356 mg, 0.86 mmol) in DME (10 mL) with **6** (931 mg, 2.58 mmol) in DME (20 mL) in the presence of $KHCO_3$ (688 mg, 6.88 mmol) was worked up to give a brown syrup, which was purified on a silica-gel column using a mixture of hexane and EtOAc (3:1 v/v) to give **32** as a colorless syrup. Yield 92% (529 mg). $[\alpha]_D^{26}$ −12.6° (*c* 0.95, $CHCl_3$). IR 3402, 2974, 2933, 1720, 1656, 1544 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.95 (d, 3H, CH(C*H*$_3$)$_2$, $J = 7.2$ Hz), 0.98 (d, 3H, CH(C*H*$_3$)$_2$, $J = 6.6$ Hz), 1.02 (d, 3H, CH(C*H*$_3$)$_2$, $J = 6.6$ Hz), 1.04 (d, 3H, CH(C*H*$_3$)$_2$, $J = 7.2$ Hz), 1.06 (d, 3H, CH(C*H*$_3$)$_2$, $J = 7.2$ Hz), 1.07 (d, 3H, CH(C*H*$_3$)$_2$, $J = 6.6$ Hz), 1.46 (s, 9H, Boc's *t*-Bu), 2.34–2.40 (m, 1H × 2, C*H*$(CH_3)_2$), 2.60–2.65 (m, 1H, C*H*$(CH_3)_2$), 2.62 (s, 3H, oxazole's ring-CH_3), 3.91 (s, 3H, $COOCH_3$), 4.91 (br s, 1H, BocNH), 5.18 (dd, 1H × 2, C*H*CH$(CH_3)_2$, $J = 7.2$ Hz, $J = 9.0$ Hz), 5.37 (dd, 1H, C*H*CH$(CH_3)_2$, $J = 6.0$ Hz, $J = 9.0$ Hz), 7.79 (br d, 1H, NH, $J = 9.0$ Hz), 7.81 (br d, 1H, NH, $J = 9.0$ Hz), 8.03 and 8.07 (each s, 1H × 2, thiazole's ring-H). Found: C, 55.27; H, 6.35; N, 12.57%. Calcd for $C_{31}H_{44}N_6O_7S_2$: C, 55.01; H, 6.55; N, 12.42%.

Bistratamide G (1). A solution of **29** (458 mg, 0.66 mmol) and 1 M LiOH (2 mL) in a mixture of THF and water (1:1 v/v) (40 mL) at 0 °C was stirred for 1 h and then at room temperature for 7 h. The resultant solution was washed with diethyl ether (20 mL) and the aqueous solution was acidified with citric acid. The resulting solution was extracted with EtOAc (50 mL × 2) and the combined extracts were washed with brine (30 mL × 2) and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave (*S*,*S*,*S*)-2-{1-[2-(1-{2-[1-(*N*-Cbz)amino-2-methylpropyl]oxazole-4-carbonylamino}-2-methylpropyl)thiazole-4-carbonylamino]-2-methylpropyl}-5-methyloxazole-4-carboxylic acid (**31**) as a colorless syrup, which was dissolved in MeOH (50 mL). The solution was stirred with 10% Pd–C under H_2 gas stream at room temperature for 4 h. The reaction mixture was concentrated in vacuo to give (*S*,*S*,*S*)-2-[1-(2-{1-[2-(1-amino-2-methylpropyl)oxazole-4-carbonylamino]-2-methylpropyl}thiazole-4-carbonylamino)-2-methylpropyl]-5-methyloxazole-4-carboxylic acid (**33**) as a colorless syrup. To the solution of **33** (350 mg, 0.64 mmol) in dry DMF (458 mL) was slowly added, with stirring, a solution of BOP (42.4 mg, 0.96 mmol) and (*i*-Pr)$_2$NEt (16.5 mg, 1.28 mmol) in dry DMF (20 mL) at 0 °C for 1 h. After stirring at room temperature overnight, the reaction mixture was mixed with water (458 mL) and extracted with EtOAc (50 mL × 3). The combined extracts were washed with brine (30 mL × 2) and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a brown syrup, which was purified on a silica gel column using a mixture of hexane and EtOAc (1:3 v/v) to give **1** as colorless crystals. Yield 51% (178 mg). mp 85–86 °C. $[\alpha]_D^{26}$ −82.3° (*c* 1.00, MeOH). IR 3396, 2964, 1685, 1676, 1597, 1533, 1508 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 0.79 (d, 3H, CH(C*H*$_3$)$_2$, $J = 6.6$ Hz), 0.80 (d, 3H, CH(C*H*$_3$)$_2$, $J = 6.6$ Hz), 0.83 (d, 3H, CH(C*H*$_3$)$_2$, $J = 7.2$ Hz), 0.84 (d, 3H, CH(C*H*$_3$)$_2$, $J = 7.2$ Hz), 0.86 (d, 3H, CH(C*H*$_3$)$_2$, $J = 7.2$ Hz), 0.87 (d, 3H, CH(C*H*$_3$)$_2$, $J = 7.2$ Hz), 2.04–2.09, 2.11–2.14, and 2.17–2.21 (each m, 1H × 3, C*H*$(CH_3)_2$), 2.46 (s, 3H, oxazole's ring-CH_3), 4.91 (dd, 1H, C*H*CH$(CH_3)_2$, $J = 4.2$ Hz, $J = 7.2$ Hz), 4.97 (dd, 1H, C*H*CH$(CH_3)_2$, $J = 6.0$ Hz, $J = 9.0$ Hz), 5.28 (dd, 1H, C*H*CH$(CH_3)_2$, $J = 6.0$ Hz, $J = 9.0$ Hz), 8.20 (br d, 1H, NH, $J = 7.2$ Hz), 8.22 (br d, 1H, NH, $J = 9.0$ Hz), 8.23 (s, 1H, oxazole's ring-H), 8.36 (br d, 1H, NH, $J = 9.0$ Hz), 8.68 (s, 1H, thiazole's ring-H). ^{13}C NMR (DMSO-d_6) δ 11.1, 18.03, 18.05, 18.l, 18.2, 18.3, 18.6, 32.6, 32.9, 34.6, 52.1, 52.7, 54.8, 125.2, 128.0, 134.5, 143.0, 147.9, 152.9, 158.4, 159.3, 160.3, 160.6, 163.2, 168.3. MALDI-TOFMS Found: *m*/*z* 528.l092 ($M + H^+$). Calcd for $C_{25}H_{32}N_6O_5S$: 528.2155 ($M + H^+$).

Bistratamide H (2). Similarly to the case of **1**, the ester hydrolysis of **30** (371 mg, 0.55 mmol) with 1 M LiOH (0.90 mL) in MeOH (20 mL) was worked up to give (*S*,*S*,*S*)-2-{1-[2-(1-{2-[1-(*N*-Boc)amino-2-methylpropyl]thiazole-4-carbonylamino}-2-methylpropyl)thiazole-4-carbonylamino]-2-methylpropyl}-5-methyloxazole-4-carboxylic acid (**32**) as colorless crystals. To deprotect the Boc group, we stirred a solution of **32** (327 mg, 0.49 mmol) and TFA (10 mL) in $CHCl_3$ (15 mL) at room temperature for 1 h. Concentration of the resulting solution in vacuo gave (*S*,*S*,*S*)-2-[1-(2-{1-[2-(1-amino-2-methylpropyl)thiazole-4-carbonylamino]-2-methylpropyl}thiazole-4-carbonylamino)-2-methylpropyl]-5-methyloxazole-4-carboxylic acid (**34**) as colorless crystals. The cyclization of **34** (350 mg, 0.62 mmol) was also similarly worked up to give **2** as colorless crystals. Yield 53% (217 mg). mp 199–200 °C. Yield 53% (217 mg). $[\alpha]_D^{25}$ −92.5° (*c* 1.00, MeOH). IR 3390, 2955, 1670, 1530, 1505, 1490 cm^{-1}. ^{1}H NMR (DMSO-

d_6) δ 0.91 (d, 3H, CH(CH_3)$_2$, $J = 7.2$ Hz), 0.94 (d, 3H, CH(CH_3)$_2$, $J = 7.2$ Hz), 0.95 (d, 3H, CH(CH_3)$_2$, $J = 7.2$ Hz), 0.97 (d, 3H, CH(CH_3)$_2$, $J = 7.2$ Hz), 0.99 (d, 3H, CH(CH_3)$_2$, $J = 7.2$ Hz), 1.00 (d, 3H, CH(CH_3)$_2$, $J = 7.2$ Hz), 2.16–2.28 (m, 1H × 3, CH(CH$_3$)$_2$), 2.59 (s, 3H, oxazole's ring-CH$_3$), 5.07 (dd, 1H, CHCH(CH$_3$)$_2$, $J = 4.8$ Hz, $J = 8.4$ Hz), 5.35 (dd, 1H, CHCH(CH$_3$)$_2$, $J = 5.4$ Hz, $J = 8.4$ Hz), 5.46 (dd, 1H, CHCH(CH$_3$)$_2$, $J = 6.6$ Hz, $J = 9.5$ Hz), 8.32 and 8.34 (each s, 1H × 2, thiazole's ring-H), 8.34 (br d, 1H, NH, $J = 9.5$ Hz), 8.49 (br d, 1H, NH, $J = 8.4$ Hz), 8.52 (br d, 1H, NH, $J = 8.4$ Hz). ^{13}C NMR (DMSO-d_6) δ 11.2, 17.9, 18.0, 18.1, 18.2, 18.4, 18.8, 32.7, 34.3, 34.5, 52.2, 54.5, 54.7, 124.7, 125.2, 127.8, 147.8, 148.3, 153.2, 158.9, 159.4, 159.6, 160.4, 168.4, 168.9. MALDI-TOFMS Found: m/z 544.1931 ($M + H^+$). Calcd for $C_{25}H_{32}N_6O_4S_2$: 544.1926 ($M + H^+$).

This work was supported in part by a Grant-in-Aid for Scientific Research No. 14550829 from the Ministry of Education, Culture, Sports, Science and Technology and by a "High-Tech Research Project" from the Ministry of Education, Culture, Sports, Science and Technology.

References

1 D. J. Faulkner, *J. Nat. Prod. Rep.*, **19**, 1 (2002).

2 L. J. Perez and D. J. Faulkner, *J. Nat. Prod.*, **66**, 247 (2003).

3 a) D. L. Evans, D. K. Minster, U. Jordis, S. M. Hecht, A. L. Mazzu, and A. I. Meyers, *J. Org. Chem.*, **44**, 497 (1979). b) C. W. Holzapfel and G. R. Pettit, *J. Org. Chem.*, **50**, 2323 (1985). c) R. Houssain, M. Lohez, J.-L. Bernier, and J.-P. Henichart, *J. Org. Chem.*, **50**, 2787 (1985). d) R. C. Kelly, I. Gebhard, and N. Wicnienski, *J. Org. Chem.*, **51**, 4590 (1986). e) Y. Yamada, M. Shiobata, T. Sugiura, S. Kata, and T. Shioiri, *J. Org. Chem.*, **52**, 1252 (1987). f) C. W. Holzapfel, M. W. Brendankemp, and J. Vanzyl, *Synth. Commun.*, **20**, 2235 (1990). g) M. North and G. Pattenden, *Tetrahedron*, **46**, 8267 (1990). h) P. Wipf and C. P. Miller, *J. Org. Chem.*, **58**, 3604 (1993). i) E. Anguilar and A. I. Meyers, *Tetrahedron Lett.*, **35**, 2473 (1994). j) P. Wipf, C. P. Miller, S. Venkatraman, and P. C. Fritch, *Tetrahedron Lett.*, **36**, 6395 (1995). k) P. Larfargue, P. Guenot, and J.-P. Lellouche, *Synlett*, **1995**, 171. l) A. I. Meyers and F. X. Tavares, *J. Org. Chem.*, **61**, 8207 (1996). m) D. R. Williams, P. D. Lowder, T.-G. Gu, and D. A. Brooks, *Tetrahedron Lett.*, **38**, 331 (1997).

4 J. Ogino, R. E. Moore, G. M. Patterson, and C. D. Smith, *J. Nat. Prod.*, **59**, 581 (1996).

5 A. Vertram and G. Pattenden, *Synlett*, **2000**, 1519; **2001**, 1873.

6 Z. Xiz and C. D. Smith, *J. Org. Chem.*, **66**, 3459 (2001).

7 A. Vertram and G. Pattenden, *Heterocycles*, **58**, 521 (2002).

8 a) S. L. You and J. W. Kelly, *J. Org. Chem.*, **68**, 9606 (2003). b) S. L. You and J. W. Kelly, *Chem.—Eur. J.*, **10**, 71 (2004).

9 C. Shin, C. Abe, and Y. Yonezawa, *Chem. Lett.*, **33**, 664 (2004).

10 In this paper, the symbols Δ^1, Δ^2, and Δ^3 indicate the position number of the α-dehydroamino acid residue from the N-terminus in sequence.

11 a) T. Suzuki, A. Nagasaki, K. Okumura, and C. Shin, *Heterocycles*, **55**, 835 (2001). b) A. Nagasaki, Y. Adachi, Y. Yonezawa, and C. Shin, *Heterocycles*, **60**, 321 (2003).

12 H. Saito, T. Yamada, K. Okumura, Y. Yonezawa, and C. Shin, *Chem. Lett.*, **2002**, 1098.

13 T. Yamada, K. Okumura, Y. Yonezawa, and C. Shin, *Chem. Lett.*, **2001**, 102.

14 C. Shin, Y. Sato, and J. Yoshimura, *Bull. Chem. Soc. Jpn.*, **49**, 1909 (1976).

15 N. Endoh, K. Tsuboi, R. Kim, Y. Yonezawa, and C. Shin, *Heterocycles*, **60**, 1567 (2003).

16 J. Das, J. A. Reid, D. R. Kronenthal, J. Singh, P. Pansegrau, and R. H. Mueller, *Tetrahedron Lett.*, **33**, 7835 (1992).

17 BOP = Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate.