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NEW TOTAL SYNTHESIS OF DENDROAMIDE A FROM DEHYDRODI- AND TRIPEPTIDES

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Abstract — New total synthesis of triheterocyclic cyclopeptide bistratamide-type dendroamide A, isolated from the cyanobacterium *Stigonema dendroideum*, was achieved by various conversions of Δ^1-dehydrodi- and Δ^3-dehydrotripeptides.

A bistratamide-type metabolite, a dendroamide A (**1**),[1] isolated from the cyanobacterium, *Stigonema dendroideum*, exhibits the reverse of multiple drug resistance.[2] The naturally occurring **1** features an interesting macrocyclic structure constituted of three kinds of heterocyclic (thiazole and oxazole) amino acid residues, as shown in Figure 1.

So far, various synthetic methods for the above-mentioned heterocyclic amino acids have been already reported[3] and the total synthesis of **1** has been also achieved by the stepwise elongation of the above amino acids and then macrocyclization.[4-6] On the other hand, in the preceding paper,[7] we have briefly reported new synthetic method for bistratamide G, similar to **1**, from two kinds of dehydrotripeptides. Herein, we would like to report in detail the new total synthesis of **1**, to generalize the convenient synthetic method of various polyheterocyclic cyclopeptides such as bistratamides.

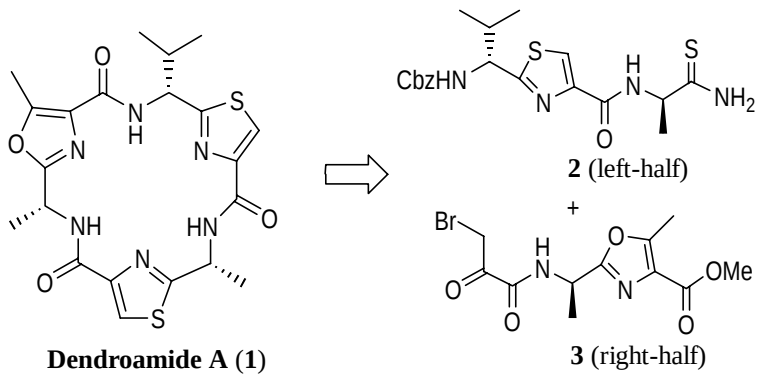
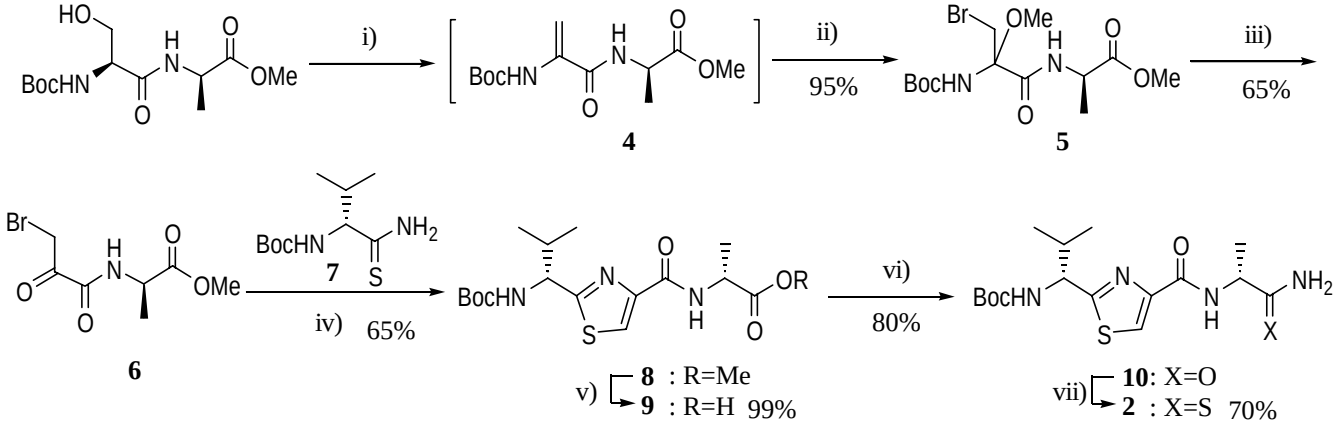


Figure 1. Retrosynthesis of **1.**

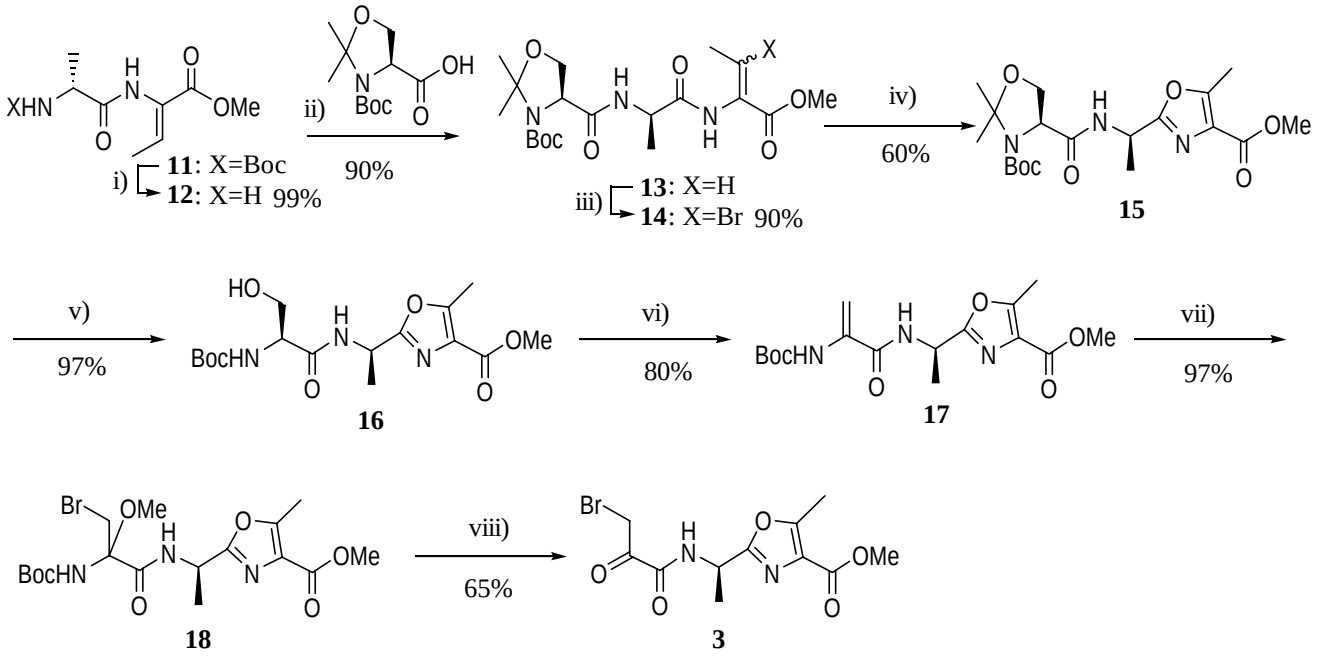
The syntheses of two kinds of building blocks, (*R*)-2-[1-(*N*-Boc)amino-2-methylpropyl]thiazole-4-carbonyl-D-alanine thioamide (**2**) and methyl (*R*)-2-{1-[*N*-(3-bromo-2-oxopropanoyl)amino]ethyl}-5-methyloxzole-4-carboxylate (**3**) as the left- and right-half components of the linear triheterocyclic peptide (**19**) as the precursor of **1**, respectively, were accomplished as follows. First of all, the starting Δ^1-dehydrodipeptide[8] (Boc-ΔAla-D-Ala-OMe) (**4**) was prepared by the usual dehydration of the Ser residue of Boc-L-Ser-D-Ala-OMe. Subsequently, according to the method reported,[9] bromination of an α-dehydroalanine (ΔAla) residue of **4** with NBS in MeOH was performed to give the corresponding *N*-[2-(*N*-Boc)amino-3-bromo-2-methoxy]propanoyl-D-Ala-OMe (**5**). Furthermore, the simultaneous deprotection of the Boc group and hydrolysis of **5** with trifluoroacetic acid (TFA) and H_2O gave the expected (*R*)-*N*-(3-bromo-2-oxopropanoyl)-D-Ala-OMe (**6**). However, in this case, because of its lability, without purification, the formed **6** was submitted intact to the next thiazole ring formation. Thiazolation of **6** with the authentic valine-thiocarboxamide [Boc-D-Val-(S)NH_2] (**7**) with $KHCO_3$ in DME and trifluoroacetic anhydride (TFAA) in pyridine and then with 28% aq. NH_3 gave (*R*)-2-[1-(*N*-Boc)amino-2-(2-methyl)propyl]thiazole-4-carbonyl-D-Ala-OMe (**8**). Ester hydrolysis of **8** with 1 M LiOH, followed by amidation of the formed hydrolysate (**9**) with ClCOOEt in the presence of Et_3N gave the mixed acid anhydride (MA), which was subjected to the treatment of 28% aq. NH_3 to afford the corresponding carboxamide derivative (**10**). Final thioamidation of **10** with Lawesson's reagent was also carried out to give the expected (*R*)-2-[1-(*N*-Boc)amino-2-methylpropyl]thiazole-4-carbonyl-D-Ala-(S)NH_2 (**2**). Compound (**2**) was synthesized as the left-half component of the *N,O*-



Scheme 1. Reagents and conditions: i) MsCl, Et_3N, rt, 1 h, then DBU rt, 2 h, ii) NBS, MeOH, rt, 1 h, iii) TFA, rt, 30 min, then H_2O, rt, 10 min. iv) 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, v) 1M LiOH**,** vi) ClCOOEt, Et_3N, then 28% aq. NH_3, vii) Lawesson's Reagent.

diprotected *N,O*-diprotected linear dendroamide A methyl ester (**19**), as shown in Scheme 3.

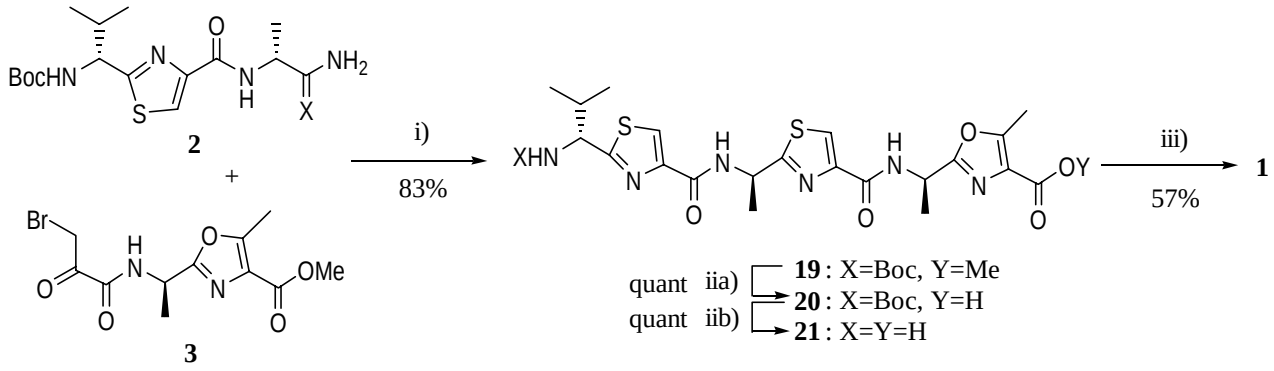
On the other hand, to synthesize the right-half component (**3**), firstly, deprotection of the Boc group of the authentic Δ^2-dehydrodipeptide[8] [Boc-D-Ala-(*Z*)-ΔAbu-OMe (ΔAbu=2-amino-2-butenoic acid residue)] (**11**) with TFA gave H-D-Ala-(*Z*)-ΔAbu-OMe (**12**). Without isolation, the formed **12** was *in situ* coupled with the authentic *N*-Boc-*N*,*O*-isopropylidene (Ip)-D-Ser-OH by using BOP[10] as the condensing agent to give the corresponding Δ^3-dehydrotripeptide derivative (**13**).[8] Subsequently, in this case, bromination of the ΔAbu residue with NBS in $CHCl_3$, in place of MeOH, was carried out to give *N*-Boc-*N*,*O*-Ip-D-Ala-(*Z*)-ΔAbu(β-Br)-OMe (**14**). Secondly, the desirable oxazolation of **14** with Cs_2CO_3[11] in dioxane at 60 °C proceeded to give the corresponding 5-methyloxazole derivative (**15**), by the method reported previously.[12] Subsequent deprotection of the Ip group of **15** with a mixture of TFA and $CHCl_3$ (4 : 96 v/v), followed by usual dehydration of the formed *N*-Boc-seryldipeptide derivative (**16**) gave (*R*)-*N*-Boc-Δ^1-dehydroalanyldipeptide (**17**).[8] Thirdly, similarly to the cases of **5** and **6**, the bromination of the ΔAla residue of **17** in MeOH was worked up to give the corresponding (3-bromo-2-methoxy)propanoyl derivative (**18**), the Boc and MeO groups of which were then deprotected and hydrolyzed to give methyl (*R*)-2-[1-*N*-(3-bromo-2-oxopropanoyl)aminoethyl]-5-methyl-



Scheme 2. Reagents and conditions: i) TFA rt, 30 min ii) BOP, rt, 6 h iii) NBS, $CHCl_3$, rt, 1 h, Et_3N, rt, 30 min, iv) Cs_2CO_3, dioxane, 60 °C, 6 h, v) TFA:$CHCl_3$ (4:96 v/v), rt, 5 h, vi) MsCl, Et_3N, $CHCl_3$, 0 °C, 1 h, then DBU, rt, 30 min, vii) NBS, MeOH, rt, 30 min, viii) TFA, rt, 30 min, then H_2O, rt, 10 min.

oxazole-4-carboxylate (**3**) as the right-half component, as shown in Scheme 2. Since the obtained compound (**3**) was also found to be slightly unstable, it was used intact for the next reaction, without purification.

Finally, similarly to the case of **8**, thiazolation between **2** and **3** was tried successfully to give **19** in 83% yield. Subsequently, consecutive one-pot ester hydrolysis of **19** with 1 M LiOH, *N*-deprotection of the hydrolysate (**20**) with TFA, followed by macrocyclization of both the formed N- and O-termini free linear dendroamide A (**21**), with BOP and $(i\text{-Pr})_2$NEt in DMF under high-dilution conditions (1 mmol/L) gave the desired **1** as colorless crystals in 57% yield, as shown in Scheme 3.



Scheme 3. Reagents and conditions: i) $KHCO_3$, 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), rt, 30 min, b) TFA, rt, 3 h, iii) BOP, $(i\text{-Pr})_2$NEt, DMF, rt, 12 h.

The structures of all new products thus obtained were confirmed by the ^{1}H NMR and ^{13}C NMR spectral data and the satisfactory results of the elemental analyses. From the ^{1}H NMR spectrum of **19**, the appearance of the chemical shifts of two thiazole ring protons at δ 8.05 and 8.06 as a singlet and the oxazole ring methyl protons at δ 2.62 as a singlet supports the formation of the expected linear dendroamide A. In particular, the chemical and physical constants of the synthetic **1** [mp 145-146 °C, $[\alpha]_D^{25}$ +69.1° (*c* 0.33, $CHCl_3$), MALDI-TOF MS (489.99)] were fully identical with those of the natural **1** ($[\alpha]_D^{25}$ +40.5°)[1] and the alternative synthetic **1** [mp 146-148 °C, $[\alpha]_D^{25}$ +66.9° (*c* 0.70, $CHCl_3$)].[4-6]

In conclusion, it is worth noting that formation of both the thiazole and oxazole rings from various dehydropeptides for the synthesis of bistratamide-type natural products was newly developed and generalized. Further investigations of the new syntheses of other polyheterocyclic 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 spectrophotometer 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 MS spectra were obtained by SHIMAZU/KRATOS COMPACT MALDI IV tDE.

Boc-L-Ser-D-Ala-OMe. The dipeptide was derived from Boc-L-Ser-OH and H-D-Ala-OMe by the usual coupling method. Colorless syrup. $[\alpha]_D^{24}$ +12.8° (*c* 1.0, MeOH). IR 3331, 1722, 1679, 1529 cm^{-1}. ^1H NMR δ 1.39 (d, 3H, Ala's CH_3, *J*=7.0 Hz), 1.45 (s, 9H, Boc's *t*-Bu), 3.35 (bs, 1H, OH), 3.64 (br m, 1H, Ser's β-H), 3.71 (s, 3H, COOMe), 4.04 (br m, 1H, Ser's β-H), 4.17 (br m, 1H, Ser's α-H), 4.53 (bq, 1H, Ala's α-H, *J*=7.0 Hz, *J*=6.5 Hz,), 5.65 (bd, 1H, 1H, Ala's NH, *J*=7.5 Hz), 7.24 (bs, 1H, Ser's NH) *Anal*. Calcd for $C_{12}H_{22}N_2O_6$: C, 49.65; H, 7.64; N, 9.65. Found: C, 49.45; H, 7.73; N, 9.78.

***(RS)-N*-[2-(*N*-*t*-Butoxycarbonyl)amino-3-bromo-2-methoxy]propanoyl-D-Ala-OMe (5)**. The dehydration of Boc-L-Ser-D-Ala-OMe (1.53 g, 5.27 mmol), with Et_3N (1.61 mL, 11.59 mmol), Ms-Cl (10.69 mL, 8.96 mmol) and DBU (1.10 mL, 7.38 mmol) in $CHCl_3$ (50 mL) gave Boc-ΔAla-D-Ala-OMe (**4**), which was intact brominated with NBS (1.03 g, 5.80 mmol) in MeOH (50 mL) to give **5** as a slightly unstable colorless crystals. Yield 95% (1.28 g). IR 3408, 3358, 2978, 1749, 1724, 1664, 1483 cm^{-1}. ^1H NMR δ 1.45 (s, 9H, Boc's *t*-Bu), 1.47 (d, 3H, Ala's CH_3, *J* = 7.0 Hz), 3.31 (s, 3H, OCH_3), 3.66 (d, 1H, BrCHH_aC (OCH_3), *J* = 6.5 Hz), 3.77 (s, 3H, $COOCH_3$), 4.22 (br d, 1H, BrCHH_bC (OCH_3), *J* = 6.5 Hz), 4.57-4.63 (m, 1H, Ala's α-H), 6.09 (s, 1H × 2/3, Boc's NH), 6.15 (br s, 1H × 1/3, Boc's NH), 7.03 (br d, 1H × 2/3, NH, *J* = 7.5 Hz), 7.11 (br d, 1H × 1/3, NH, *J* = 8.5 Hz). *Anal*. Calcd for $C_{13}H_{23}N_2O_6Br$: C, 40.74; H, 6.05; N, 7.31. Found: C, 40.42; H, 5.83; N, 6.98.

***N*-(3-Bromo-2-oxopropanoyl)-D-Ala-OMe (6)**. The simultaneous deprotection and hydrolysis of **5** (960 mg, 2.50 mmol) with TFA (20 mL) and then water (20 mL) gave **6** as an unsatable yellow syrup, which was immediately used to the next reaction, without purification. Yield 65% (410 mg).

(*R*)-2-[1-(*N*-*t*-Butoxycarbonyl)amino-2-methylpropyl]thiazole-4-carbonyl-D-Ala-OMe (8). To a solution of Boc-D-Val-(S)NH_2 (**7**) (1.89 g, 8.14 mmol) in DME (20 mL) was added, with stirring, $KHCO_3$ (6.52 g, 65.12 mmol) and a solution of **6** (5.11 g, 20.35 mmol) in DME (20 mL) at 0 °C. After stirring at rt overnight, the resulting solution was concentrated *in vacuo* to give a brown syrup, which was dissolved in $CHCl_3$ (30 mL) and washed with water (30 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 (30 mL). To the solution were added, with stirring, TFAA (2.26 mL) and pyridine (2.88 mL, 35.82 mmol) at 0 °C for 30 min. Concentration in vacuo gave a brown syrup, which was further dissolved in EtOAc (50 mL). The resulting solution was stirred with 28% aqueous NH_3 (10 mL) at 0 °C. After stirring for 15 min, the

reaction mixture was 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 (2 : 1 v/v) to give **8** as a colorless syrup. Yield 70% (2.20 g). $[\alpha]_D^{26}$ +17.6° (*c* 1.09, $CHCl_3$). IR 3323, 2972, 2933, 1743, 1708, 1664, 1658, 1546 cm^{-1}. ^1H NMR δ 0.93, 0.99 (d, 6H, 2(C*H*$_3$)$_2$CH, *J* = 6.5 Hz), 1.46 (s, 9H, Boc's *t*-Bu), 1.53 (d, 3H, Ala's CH_3, *J* = 7.0 Hz), 2.35-2.39 (m, 1H, (CH$_3$)$_2$C*H*), 3.77 (s, 3H, COOCH_3), 4.78 (dq, 1H, Ala's α-H, *J* = 6.0 Hz, *J* = 7.5 Hz), 4.86 (dd, 1H, NHC*H*, *J* = 6.0 Hz, *J* = 7.5 Hz), 5.21 (br d, 1H, N*H*CH, *J* = 7.5 Hz), 7.74 (d, 1H, NH, *J* = 7.5 Hz), 8.01 (s, 1H, thiazole ring-H). *Anal*. Calcd for $C_{17}H_{27}N_3O_5S$: C, 52.97; H, 7.06; N, 10.90. Found: C, 52.85; H, 7.27; N, 10.53.

(*R*)-2-(1-*t*-Butoxycarbonylamino-2-methylpropyl)thiazole-4-carbonyl-D-Ala-NH_2 (10). To a solution of **8** (230 mg, 0.59 mmol) in water-dioxane (100 mL, 1 : 1 v/v) was added, with stirring, 1 M LiOH (12 mL) for 30 min under cooling. After stirring for 6 h at rt, the reaction mixture was washed with ether (50 mL × 2) and acidified to pH 00 with citric acid and then extracted with EtOAc (100 mL x 2). The combined extracts were washed with brine (100 mL × 2) and dried over anhydrous $NaSO_4$ and then concentrated *in vacuo* to give free acid (**9**) as a colorless syrup. Without purification, to a chilled solution of the obtained **9** in THF (100 mL) were added**,** with stirring, Et_3N (0.84 mL, 6.05 mmol) and ClCOOEt (0.57 mL, 6.07 mmol). After stirring for 20 min at rt, to the resultant solution was added 28% aqueous NH_3 (10 mL) and the whole was further stirred for 10 min. The reaction mixture was mixed with saturated NH_4Cl aqueous 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 colorless amorphous. Recrystallization from EtOAc-hexane gave **10** as colorless crystals. Yield 86% (175 mg). $[\alpha]_D^{26}$ +59.2° (*c* 0.97, $CHCl_3$). IR 3396, 3325, 2974, 2933, 1707, 1689, 1656, 1544 cm^{-1}. ^1H NMR δ 0.98 (d, 3H, C*H*$_3$CHCH$_3$, *J* = 6.5 Hz), 0.98 (d, 3H, CH$_3$CHC*H*$_3$, *J* = 7.0 Hz), 1.46 (s, 9H, Boc's *t*-Bu), 1.51 (d, 3H, Ala's CH_3, *J* = 7.0 Hz), 2.34-2.38 (m, 1H, (CH$_3$)$_2$C*H*), 4.70-4.76 (m, 1H, Ala's α-H), 4.83-4.86 (m, 1H, NHC*H*), 5.33 (br d, 1H, N*H*CH, *J* = 8.5 Hz), 6.04 and 6.77 (br d, 2H, 2 x NH, *J* = 8.2 Hz), 7.77 (br d, 1H, NH, *J* = 8.2 Hz), 8.01 (s, 1H, thiazole's ring-H). *Anal*. Calcd for $C_{16}H_{26}N_4O_4S$: C, 51.87; H, 7.07; N, 15.12. Found: C, 51.78; H, 7.21; N, 14.97.

(*R*)-2-(1-*t*-Butoxycarbonylamino-2-methylpropyl)thiazole-4-carbonyl-D-Ala-(S)NH_2 (2). To a solution of **10** (158 mg, 4.26 mmol) in DME (30 mL) was added, with stirring, Lawesson's reagent (95 mg, 0.23 mmol) at rt. After stirring overnight, the insoluble reagent was filtered off and the filtrate was concentrated *in vacuo* to give a brown syrup. The obtained syrup was purified on a silica gel column using a mixture of hexane and EtOAc (1 : 2 v/v) to give colorless crystals, which were recrystallized from

hexane-EtOAc (1 : 1 v/v) to give **2** as a colorless powder. Yield 72% (118 mg). mp 84.5-85.5 °C. $[\alpha]_D^{26}$ +70.0° (*c* 0.92, $CHCl_3$). IR 3419, 2974, 1689, 1654, 1544, 1481 cm^{-1}. ^1H NMR δ 0.94, 1.00 (d, 6H, 2(CH_3)$_2$CH, *J* = 6.7 Hz), 1.46 (s, 9H, *t*-Bu), 1.62 (d, 3H, Ala's CH_3, *J* = 6.7 Hz), 2.53-2.38 (m, 1H, (CH_3)$_2$CH), 4.82-4.89 (m, 1H, NHC*H*), 5.03-5.11 (dq, 1H, Ala's α-H, *J* = 6.7 Hz, *J* = 7.5 Hz), 5.24 (br d, 1H, N*H*CH, *J* = 8.0 Hz), 7.91 and 8.59 (br s, 1H × 2, NH_2), 8.12 (br d, 1H, NH, *J* = 7.5 Hz). *Anal*. Calcd for $C_{16}H_{26}N_4O_3S_2$: C, 49.72; H, 6.78; N, 14.49. Found: C, 49.79; H, 7.06; N, 13.81.

(*R,Z*)-2-(3-*t*-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-4-carbonyl-D-Ala-ΔAbu-OMe (13). A solution of H-D-Thr-OMe (93 mg, 3.24 mmol) and TFA (20 mL) in $CHCl_3$ (20 mL) was stirred at rt for 30 min and then concentrated *in vacuo* togive a residual syrup, which was dissolved in a solution of *N*-Boc-*N,O*-Ip-L-Ser-OH (67 mg, 2.73 mmol), BOP (132 mg, 2.98 mmol), and (*i*-Pr)$_2$NEt (0.92 mL, 5.40 mmol) in DMF (15 mL). The resulting solution was stirred for 30 min under cooling and at rt overnight. The reaction mixture was added to water (20 mL) and the aqueous solution was extracted with EtOAc (30 mL × 3). The combined extracts were washed with brine (20 mL × 2) and dried over anhydrous $NaSO_4$. 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 colorless crystals. Recrystallization from a hexane-EtOAc gave **13** as colorless crystals. Yield 92% (103 mg). mp149-150 °C $[\alpha]_D^{26}$ –18.3° (*c* 0.59, $CHCl_3$). IR 3446, 3273, 2980, 1726, 1708, 1654, 1647, 1527, 1440 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.32, 1.35 (s, 9H, Boc's *t*-Bu), 1.43,1.46 and 1.49 (s, 6H, Isop's CH_3 × 2), 1.59 (d, 3H, CHC*H*$_3$, *J* = 6.7 Hz), 1.71 (d, 3H, ΔAbu's CH_3, *J* =7.2 Hz), 3.69 (s, 3H, $COOCH_3$), 3.81-4.57 (m, 4H, OCH_2, NCH × 2), 6.62 (br q, 1H, olefin's H, *J* =7.2 Hz),8.00, 8.25 (br d, 1H × 2/3, 1H × 1/3, NH, *J* = 5.4 Hz), 9.16, 9.42 (br s, 1H × 1/3, 1H × 2/3, NH). *Anal*. Calcd for $C_{14}H_{31}N_3O_5$: C, 55.05; H,10.23; N, 13.76. Found: C, 55.08; H, 10.31; N, 13.71.

Methyl (*R,R,Z*)-2-[(3-*t*-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-4-carbonyl-D-alanyl]amino-3-bromo-2-butenoate (14). A solution of **13** (112 mg, 2.70 mmol) and NBS (53 mg, 2.97 mmol) in $CHCl_3$ (20 mL) was stirred at rt for 30 min. To the resulting solution was added, with stirring, Et_3N (0.41 mL, 2.95 mmol). After stirring for 30 min under cooling and then for 30 min at rt, the reaction mixture was mixed with ether (20 mL) and washed successively with 10% citric acid (20 mL x 2), saturated aqueous $NaHCO_3$ solution (20 mL × 2), and brine (20 mL × 2), and finally dried over anhydrous $NaSO_4$. 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 colorless crystals. Recrystallization from a hexane-EtOAc gave **14** as colorless crystals. Yield 75% (100 mg). mp 112.5-113.5 °C. $[\alpha]_D^{25}$ –22.9° (*c* 0.96, $CHCl_3$). IR 3462, 3369, 2983, 1726, 1701, 1695, 1664, 1529, 1500 cm^{-1}. ^1H NMR

($CDCl_3$) δ 1.47 (s, 9H, Boc's *t*-Bu), 1.43 (d, 3H, Ala's CH_3, *J* = 7.2 Hz), 1.53 and 1.61 (each s, 3H × 2, Isop's CH_3 × 2), 2.34 (s, 3H, ΔAbu(Br)'s CH_3), 3.79 (s, 3H, $COOCH_3$), 4.11-4.48 (m, 4H, OCH_2, NCH × 2), 6.76 and 7.02 (br s, 1H × 1/3, 1H × 2/3, NH), 8.45 and 8.59 (br s, 1H × 2/3, 1H × 1/3, NH). *Anal*. Calcd for $C_{19}H_{30}N_3O_7Br$: C, 46.35; H, 6.14; N, 8.53. Found: C, 46.71; H, 6.45; N, 8.21.

Methyl (*R,R*)-2-[1-(3-*t*-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-4-carbonyl]aminoethyl-5-methyloxazole-4-carboxylate (15) A suspension of **14** (0.95 g, 1.92 mmol) and Cs_2CO_3 (127 mg, 2.24 mmol) in dioxane (20 mL) was stirred at 60 °C overnight. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (50 mL × 3). The combined extracts were washed with brine (30 mL x 2) and dried over anhydrous $NaSO_4$. 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 **15** as a colorless syrup. Yield 65% (51 mg). $[\alpha]_D^{26}$ –40.2° (*c* 0.92, $CHCl_3$). IR 2980, 1708, 1691, 1678, 1546, 1529 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.20 (s, 9H, Boc's *t*-Bu), 1.37 and 1.50 (each s, 3H × 2, Isop's CH_3 × 2), 1.40 (d, 3H, CHC*H*$_3$, *J* = 6.0 Hz), 2.52 (s, 3H, oxazole's ring-CH_3), 3.74 (s, 3H, $COOCH_3$), 4.03-4.07 and 4.18-4.28 (each m, 1H × 2, OCH_2), 5.00 (dq, 1H, C*H*CH_3), *J* = 6.6, *J* = 7.5 Hz), 8.48 and 8.55 (br d, 1H × 1/3, 1H × 2/3, N*H*, *J* = 7.5 Hz). *Anal*. Calcd for $C_{19}H_{29}N_3O_7$: C, 55.46; H, 7.10; N, 10.21. Found: C, 55.10; H, 7.27; N, 10.56.

Methyl (*R,R*)-2-[1-*N*-(*t*-Butoxycarbonyl-L-seryl)aminoethyl]-5-methyloxazole-4-carboxylate (16). A solution of **15** (1.60 g, 3.88 mmol) in a mixture of TFA and $CHCl_3$ (200 mL, 4 : 96 v/v) was stirred at rt for 1 h. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ solution (100 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 yellow syrup, which was purified on a silica gel column using a mixture of hexane and EtOAc (1 : 5 v/v) to give colorless powder. Recrystallization from a hexane-EtOAc gave **16** as colorless powder. Yield 78% (112 mg). mp153-154 °C. $[\alpha]_D^{26}$ +3.6° (*c* 0.97, $CHCl_3$). IR 3424, 3298, 2987, 1756, 1705, 1689, 1564 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.45 (s, 9H, Boc's *t*-Bu), 1.57 (d, 3H, C*H*$_3$CH$_2$, *J* = 7.2 Hz), 2.60 (s, 3H, oxazole ring-CH_3), 3.72 (br d, 1H, OH, *J* = 6.6 Hz), 3.90 (s, 3H, $COOCH_3$), 4.02-4.20 (m, 3H, Ser's α-H, Ser's β-H), 5.23 (dq, 1H, Ala's α-H, *J* = 6.6 Hz, *J* = 7.2 Hz), 5.74 (br s, 1H, BocNH), 7.07 (br s, 1H, NH). *Anal*. Calcd for $C_{16}H_{25}N_3O_7$: C, 51.74; H, 6.78; N, 11.31. Found: C, 51.81; H, 6.65; N, 11.52.

Methyl 2-[1-(*N*-*t*-Butoxycarbonyl-2-propenoyl)aminoethyl]-5-methyloxazole-4-carboxylate (17). To a solution of **16** (105 mg, 9.13 mmol) in $CHCl_3$ (50 mL) were added, with stirring, Et_3N (0.46 mL, 20.09 mmol) and MsCl (0.26 mL, 15.52 mmol) under cooling. After stirring at rt for 1 h, DBU (0.63

mL, 12.78 mmol) was added to the resulting solution under cooling. The resultant solution was further stirred for 30 min under cooling and at rt overnight. The reaction mixture was diluted with ether (50 mL) and washed successively with 10% citric acid (30 mL), saturated aqueous $NaHCO_3$ solution (30 mL × 2) and brine (30 mL × 2) and finally dried over anhydrous $NaSO_4$. Concentration *in vacuo* gave a brown syrup, which was purified on a silica gel column using EtOAc gave **17** as an amorphous material. Yield 86% (0.86 g). Without purification, the product (**17**) was used intact for the next reaction.

Methyl (*SR,R*)-2-{*N*-[2-(*N*-*t*-Butoxycarbonyl-3-bromo-2-methoxy)propanoyl]aminoethyl}-5-methyloxazole-4-carboxylate (18). A solution of **17** (1.67 g, 0.61 mmol) and NBS (117 mg, 0.65 mmol) in MeOH (50 mL) was stirred for 4 h under cooling. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL × 2). The combined extracts were washed with saturated aqueous $NaHCO_3$ solution (50 mL × 2), brine (50 mL × 2) and then dried over anhydrous $NaSO_4$. 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 **18** as colorless syrup (diastereomer). Yield 75% (971 mg) IR 3329, 2980, 1735, 1724, 1710, 1691, 1678, 1529, 1483 cm^{-1}. ^1H NMR δ 1.42 and 1.43 (s, 9H, Boc's *t*-Bu), 1.61 and 1.62 (d, 3H, CHCH_3, *J*=7.5 Hz), 2.61 (s, 3H, oxazole's ring CH_3), 3.30 and 3.31 (s, 3H, OCH_3), 3.68 and 3.69 (d, 1H, BrCHH_aC(OMe), *J* = 10.5 Hz), 3.90 (s, 3H, $COOCH_3$), 4.11 (br d, 1H, BrCHH_bC(OMe), *J* = 10.5 Hz), 5.24-5.30 (m, 1H, NHC*H*CH_3), 5.94 (br, 1H, BocNH), 7.13 (br d, 1H, N*H*CH, *J* = 9.0 Hz). *Anal*. Calcd for $C_{17}H_{26}N_3O_7Br$: C, 43.98; H, 5.64; N, 9.05. Found: C, 43.57; H, 5.32; N, 9.36.

Methyl (*R*)-2-[1-*N*-(3-Bromo-2-oxopropanoyl)aminoethyl]-5-methyloxazole-4-carboxylate (3). A solution of **18** (357 mg, 0.77 mmol) and TFA (100 mL) in $CHCl_3$ (100 mL) was stirred at rt for 3 h. The resulting solution was mixed with water (50 mL) and further stirred for 10 min. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ solution (50 mL) and the organic layer was dried over anhydrous $NaSO_4$. Concentration *in vacuo* at 0 ^oC gave **2** as a colorless syrup, which was used to the next reaction without isolation, because of the unstability.

Methyl (*R,R,R*)-2-(2-{2-[1-(*N*-*t*-Butoxycarbonyl)aminoethyl-2-methylpropyl]thiazole-4-carbonyl}-aminoethyl}thiazole-4-carbonyl)aminoethyl-5-methyloxazole-4-carboxylate (19). To a chilled solution of **2** (52 mg, 0.13 mmol) in DME (10 mL) were added, with stirring, $KHCO_3$ (104 mg, 1.04 mmol) and then a solution of **3** (357 mg, 0.77 mmol) in DME (20 mL). After stirring overnight, the reaction solution was concentrated *in vacuo* to give a brown syrup, which was dissolved in $CHCl_3$ (30 mL). The resulting solution was washed with water (20 mL) and dried over anhydrous Na_2SO_4.

Concentration *in vacuo* gave a brown syrup, which was dissolved in DMF and cooled at about 0 °C. To the solution were added TFAA (0.36 mL, 0.26 mmol) and pyridine (0.46 mL, 0.57 mmol) and stirred for 30 min under cooling. Reaction mixture was concentrated *in vacuo* to give a brown syrup, which was dissolved in EtOAc (30 mL) and washed with brine (20 mL). The resulting solution was stirred with 28% aqueous NH_3 (19 mL) under cooling for 20 min and washed with brine (20 mL × 2) and then dried over anhydrous $NaSO_4$. Concentration *in vacuo* gave a brown syrup, which was purified on a silica gel column using a mixture of hexane and EtOAc (1 : 4 v/v) to give **19** as colorless syrup. Yield 83% (691 mg). $[\alpha]_D^{27}$ +14.6° (*c* 0.92, $CHCl_3$). IR 3402, 2974, 2933, 1720, 1656, 1544 cm^{-1}. ^1H NMR δ 0.93 (d, 3H, Val's CH_3, *J*=5.0 Hz), 0.99 (d, 3H, Val's CH_3, *J* = 6.5 Hz), 1.45 (s, 9H, Boc' *t*-Bu), 1.69 (d, 3H, CHC*H*$_3$, *J* = 7.0 Hz), 1.77 (d, 3H, CHC*H*$_3$, *J* = 7.0 Hz), 2.34-2.38 (m, 1H, $(CH_3)_2$C*H*), 2.62 (s, 3H, oxazole's ring-CH_3), 3.90 (s, 3H, $COOCH_3$), 4.85-4.88 (m, 1H, NHC*H*), 5.19 (d, 1H, N*H*CH, *J* = 7.0 Hz), 5.46 (dq, 1H, CH_3C*H*, *J*=5.0 Hz, *J* = 7.0 Hz), 5.57 (dq, 1H, CH_3C*H*, *J* = 5.0 Hz, *J* = 7.0 Hz), 7.76 (br d, 1H, NH, *J* = 7.0 Hz), 7.81 (br d, 1H, NH, *J* = 7.0 Hz), 8.05 (s, 1H, thiazole's ring-H), 8.06 (s, 1H, thiazole's ring-H). *Anal*. Calcd for $C_{27}H_{36}N_6O_7S_2$: C, 52.24; H, 5.85; N, 13.54. Found: C, 52.46; H, 5.65; N, 13.35.

Dendroamide A (1). A solution of **19** (371 mg, 0.60 mmol) and 1 M LiOH (0.90 mL) in MeOH (20 mL) was stirred under cooling for 1 h and at rt overnight. The reaction solution was diluted with water (20 mL), washed with ether (20 mL) and acidified with citric acid and then extracted with EtOAc (50 mL × 2). The combined extracts were washed with brine (30 mL × 2), dried over anhydrous $NaSO_4$ and concentrated *in vacuo* to give the hydrolyzed product (**20**) as colorless crystals. Without purification, the obtained crystals were dissolved in $CHCl_3$ (15 mL) and mixed with TFA (10 mL) and then the whole was stirred for 1 h at rt. The reaction mixture was concentrated *in vacuo* to give the deprotected linear dendroamide A (**21**) as colorless crystals, which used to the next reaction, without purification. The obtained crystals (350 mg, 0.58 mmol) was dissolved in dry DMF (560 mL) and cooled at 0 °C. To the resultant solution was added dropwise a solution of BOP (380 mg, 0.86 mmol) and *N,N'*-diisopropylethylamine (0.21 mL, 1.16 mmol) in dry DMF (20 mL). After stirring for 1 h under cooling and 48 h at rt, the reaction mixture was diluted with water (580 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 (1 : 3 v/v) to give **1** as colorless crystals. Yield 57% (220 mg). mp 145-146 °C (recrystallization from hexane and EtOAc). $[\alpha]_D^{26}$ +69.1° (*c* 0.33, $CHCl_3$). IR 3404, 1670, 1544, 1510, 1477 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.98 (d, 3H, CH_3CHC*H*$_3$, *J* = 6.9 Hz), 1.08 (d, 3H, C*H*$_3$CHCH_3, *J* = 6.9 Hz), 1.71 (d, 3H, CHC*H*$_3$, *J* = 6.9 Hz), 1.73 (d, 3H, CHC*H*$_3$, *J* = 6.9 Hz), 2.29-2.41

(m, 1H, C*H*(CH_3)$_2$), 2.68 (s, 3H, oxazole ring-CH_3), 5.21 (dq, 1H, C*H*CH_3, *J* = 6.5 Hz, *J* = 6.9 Hz), 5.31 (dd, 1H, C*H*CH(CH_3)$_2$, *J* = 4.9 Hz, *J* = 8.0 Hz), 5.72 (dq, 1H, C*H*CH_3, *J* = 6.9 Hz, *J* = 8.0 Hz), 8.14 (s, 1H, thiazole ring-H), 8.15 (s, 1H, thiazole ring-H), 8.49 (br d, 1H, NH, *J* = 8.0 Hz), 8.55 (br d, 1H, NH, *J* = 8.0 Hz), 8.65 (br d, 1H, NH, *J* = 6.5 Hz). ^{13}C NMR($CDCl_3$) δ 11.6, 18.3, 18.4, 20.9, 24.9, 35.1, 44.3, 47.0, 55.9, 123.6, 123.8, 128.4, 148.8, 153.8, 159.5, 159.8, 160.5, 161.7, 168.2, 171.1. MALDI-TOF MS: Found 489.99, Calcd 488.59. *Anal*. Calcd for $C_{21}H_{24}N_6O_4S_2$: C, 51.62; H, 4.95; N, 17.29. Found: C, 51.46; H, 4.85: N, 17.37.

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