Total Synthesis of Bistratamide G, a Metabolite of the Philippines Ascidian *Lissoclinum bistratum*, from Dehydrotripeptides

Chung-gi Shin,* Chieko Abe, and Yasuchika Yonezawa
Laboratory of Organic Chemistry, Faculty of Engineering, Kanagawa University, Kanagawa-ku, Yokohama 221-8686

(Received March 5, 2004; CL-040251)

Total synthesis of triheterocyclic cyclopeptide bistratamide G, a metabolite from the Philippines ascidian *Lissoclinum bistratum*, was first achieved from two kinds of dehydrotripeptides.

Bistratamide G (**1**),[1,2] one of many bistratamide-type polyheterocyclic cyclopeptides, isolated recently from the southern Philippines ascidian *Lissoclinum bistratum*, shows activity in the human colon tumor HCT-116 cell line assay. The natural **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 useful synthetic methods for the above-mentioned heterocyclic amino acids, and other similar amino acids have been already reported by a number of workers.[3] Accordingly, the total synthesis of bistratamide-type dendroamide A and similar natural products has been also achieved by the stepwise elongation of the above amino acids and then by macrocyclization by four groups of investigators.[4–7] However, though such syntheses have been already reported, for the interesting bioactivities of the polyheterocyclic cyclopeptides, here, a new and general synthetic method for the bistratamides from Δ^2-and Δ^3-dehydrotripeptides[8] has been developed and achieved. In particular, these elongation reactions were carried out without any special condensing agent except for the last macrocyclization

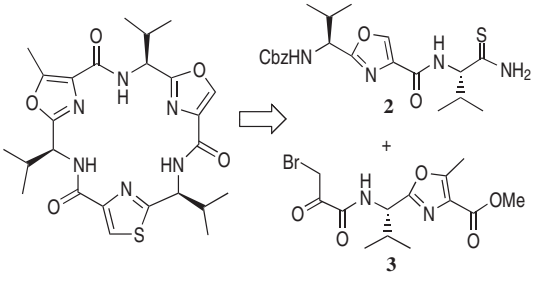
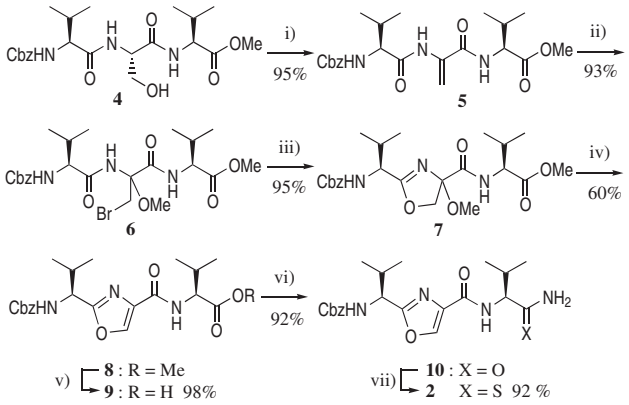


Figure 1. Retrosynthesis of bistratamide G (**1**).

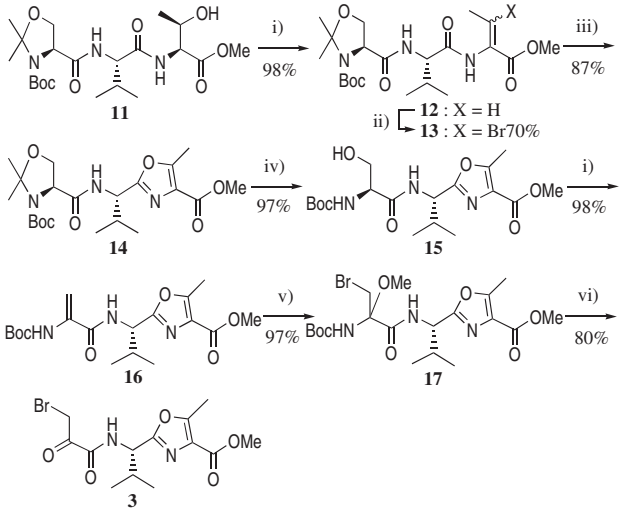
The syntheses of two kinds of building blocks, (*S*)-2-[1-(*N*-Cbzamino)-2-methylpropyl]oxazole-L-valine thioamide (**2**) and methyl (*S*)-2-{1-[*N*-(3-bromo-2-oxopropanoyl)amino]-2-methylpropyl}-5-methyloxazole-4-carboxylate (**3**) as the left- and right-half components of the linear triheterocyclic peptide **18** as the precursor of **1**, respectively, were accomplished as follows. First of all, to synthesize **2**, the starting Δ^2-dehydrotripeptide[8] (Cbz-L-Val-ΔAla-L-Val-OMe (**5**), Cbz = benzyloxycarbonyl, ΔAla = α-dehydroalanine residue) was prepared by the usual dehydration of the Ser residue of Cbz-L-Val-L-Ser-L-Val-OMe (**4**) with methanesulfonyl chloride (MsCl) in the presence of Et_3N and then with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene).[9] Subsequently, according to the method reported previously,[10] simultaneous bromination and methoxylation of **5** with NBS (*N*-bromosuccinimide) in MeOH gave the corresponding α-methoxylated β-bromoalanyltripeptide **6**. Oxazolination of **6** with Cs_2CO_3 in dioxane gave the corresponding 4-methoxyoxazoline derivative **7**, the methoxy group of which was eliminated with camphorsulfonic acid (CSA) to give the expected oxazole derivative **8**. After hydrolysis of the methyl ester of **8** with 1 M LiOH, the obtained hydrolysate **9** was amidated with ClCOOEt in the presence of Et_3N and then with 28% aq. NH_3 to give the corresponding carboxamide **10**. Finally, thiocarbonylation of **10** with Lawesson's reagent gave the required thiocarboxamide **2**, as shown in Scheme 1.



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) 1M LiOH, vi) ClCOOEt, Et_3N, then 28% aq. NH_3, vii) Lawesson's Reagent.

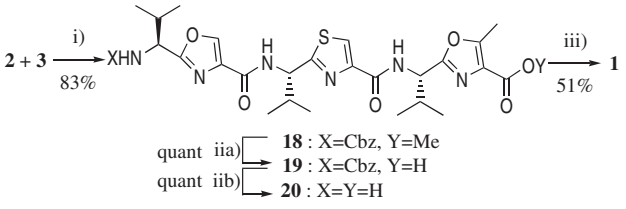
On the other hand, to synthesize **3**, firstly, similarly to the case of **5**, *N*,*O*-isopropylidene (Ip)-*N*-*t*-butoxycarbonyl (Boc)-L-Ser-L-Val-(*Z*)-ΔAbu-OMe (**12**) (ΔAbu = 2-amino-2-butenoic acid) was prepared by the dehydration of the Thr residue of *N*,*O*-Ip-*N*-Boc-L-Ser-L-Val-L-Thr-OMe (**11**).[9] In the case of the bromination of the ΔAbu residue, it has been already reported that the direct oxazolation of the ΔAbu residue-containing peptide with NBS and then with Cs_2CO_3 proceeds smoothly.[9,10] Therefore, the bromination of **12** with NBS in $CHCl_3$, instead of MeOH, was performed to give Δ^3-dehydrotripeptide **13**[8] containing β-Br-ΔAbu residue, which was then oxazolated with Cs_2CO_3 to give the desired 5-methyloxazole derivative **14**. Secondly, selective β-elimination of the Ip group with trifluoroacetic acid (TFA) and $CHCl_3$ (4:96 v/v), followed by dehydration of the formed *N*-Boc-seryldipeptide **15** was carried out, similarly to the cases of **5** and **12**. That is, dehydration of the Ser residue of **15** and bromination of the obtained Δ^2-dehydrodipeptide **16**[8] with NBS in MeOH were carried out consecutively to give the

corresponding α-methoxylated β-bromoalanyldipeptide derivative **17**. Thirdly, deprotection of the Boc group of **17** with TFA and then hydrolysis proceeded smoothly to give **3**, as shown in Scheme 2. However, because of its lability, without purification the formed **3** was used in the next thiazolation with **2**.



Scheme 2. 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.

Finally, thiazolation between the thiocarboxamide group of **2** and the bromoacyl group of **3** by successive treatments with $KHCO_3$ in dimethoxyethane (DME), with trifluoroacetic anhydride (TFAA) and pyridine, and then with 28% aq. NH_3 gave a linear triheterocyclic peptide **18**.[11] Hydrolysis of the ester with 1 M LiOH and deprotection of the Cbz group of the hydrolysate **19** with 10% Pd-C/H_2, followed finally by macrocyclization of the obtained *N*,*O*-deprotected triheterocyclic peptide **20** with BOP and $(i\text{-Pr})_2$NEt in DMF under high-dilution conditions (1 mmol/L) at room temperature for 12 h gave the expected **1**[12] in 51% yield from **20**, 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, ii) a) 1 M LiOH, H_2O-dioxane (1:1 v/v), rt, 30 min, b) 10% Pd-C, H_2, rt, 3 h, iii) BOP, $(i\text{-Pr})_2$NEt, DMF, 12 h.

The structures of all new products thus obtained were confirmed by the ^{1}H and ^{13}C NMR spectral data and the satisfactory results of the elemental analyses. In particular, the chemical and physical constants of the synthetic **1** ($[\alpha]_D^{26}$ −82.3° (*c* 1.00, MeOH)) were fully identical with those of the natural **1** ($[\alpha]_D$ −73.8° (*c* 1.0, MeOH)).

In conclusion, a convenient and general synthetic method for the various bistratamide-type metabolites has been efficiently developed.

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

References and Notes

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 For examples: a) D. A. Evans, J. R. Gege, and J. L. Leightow, *J. Am. Chem. Soc.*, **114**, 9434 (1992). b) S. K. Chattopadhyay, J. Kempson, A. McNeil, G. Pattenden, M. Reader, D. E. Rippon, and D. Waite, *J. Chem. Soc., Perkin Trans. 1*, **2000**, 2415. c) P. Wipf and C. P. Miller, *Tetrahedron Lett.*, **33**, 907 (1992). d) Y. Hamada, M. Shibata, T. Sugiura, S. Kata, and T. Shioiri, *J. Org. Chem.*, **52**, 1252 (1987).
4 C. D. Smith and Z. Xia, *J. Org. Chem.*, **66**, 3459 (2001).
5 A. Bertram and G. Pattenden, *Heterocycles*, **58**, 521 (2002).
6 a) S. L. You and J. W. Kelly, *J. Org. Chem.*, **68**, 9506 (2003). b) S. L. You and J. W. Kelly, *Chem.—Eur. J.*, **10**, 71 (2004).
7 S. V. Downing, E. Aguilar, and A. I. Meyers, *J. Org. Chem.*, **64**, 826 (1999).
8 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.
9 a) T. Kayano, Y. Yonezawa, and C. Shin, *Chem. Lett.*, **33**, 72 (2004). b) H. Saito, T. Yamada, K. Okumura, Y. Yonezawa, and C. Shin, *Chem. Lett.*, **2002**, 1098.
10 N. Endoh, K. Tsuboi, R. Kim, Y. Yonezawa, and C. Shin, *Heterocycles*, **60**, 1567 (2003).
11 **18**: Colorless solid. mp 71.0–71.5 °C. $[\alpha]_D^{26}$ +4.2° (*c* 0.93, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz) $\delta = 0.91$ (d, 3H, $J = 6.6$ Hz), 0.93 (d, 3H, $J = 6.6$ Hz), 0.95 (d, 3H, $J = 7.2$ Hz), 0.97 (d, 3H, $J = 7.2$ Hz), 0.99 (d, 3H, $J = 7.2$ Hz), 1.12 (d, 3H, $J = 7.2$ Hz), 2.23–2.25, 2.35–2.37 and 2.56–2.62 (each m, 1H × 3), 2.61 (s, 3H), 3.91 (s, 3H), 4.84–4.88 (m, 1H), 5.08–5.14 (m, 2H), 5.17–5.20, 5.32–5.38, and 5.49–5.52 (each m, 1H × 3), 7.33–7.36 (m, 5H), 7.45 and 7.85 (each br d, 1H × 2, $J = 9.6$ Hz), 8.03 (s, 1H), 8.17 (s, 1H). Found: C, 58.83; H, 6.23; N, 12.48%. Calcd for $C_{34}H_{42}N_6O_8S$: C, 58.77; H, 6.09; N, 12.19%.
12 **1**: Colorless solid. mp 85.0–85.5 °C. $[\alpha]_D^{26}$ −82.3° (*c* 1.00, MeOH). IR (KBr) 3396, 2964, 1685, 1676, 1597, 1533, 1508 cm^{-1}. ^{1}H NMR (DMSO-d_6, 600 MHz) $\delta = 0.79$ (d, 3H, $J = 6.6$ Hz), 0.80 (d, 3H, $J = 6.6$ Hz), 0.83 (d, 3H, $J = 7.2$ Hz), 0.84 (d, 3H, $J = 7.2$ Hz), 0.86 (d, 3H, $J = 7.2$ Hz), 0.87 (d, 3H, $J = 7.2$ Hz), 2.04–2.09 (m, 1H), 2.11–2.14 (m, 1H), 2.17–2.21 (m, 1H), 2.46 (s, 3H), 4.91 (dd, 1H, $J = 7.2$, 4.2 Hz), 4.97 (dd, 1H, $J = 9.0$, 6.0 Hz), 5.28 (dd, 1H, $J = 9.0$, 6.0 Hz), 8.20 (br d, 1H, $J = 7.2$ Hz), 8.22 (br d, 1H, $J = 9.0$ Hz), 8.23 (s, 1H), 8.36 (br d, 1H, $J = 9.0$ Hz), 8.68 (s, 1H). ^{13}C NMR (DMSO-d_6, 150 MHz) $\delta = 11.1$, 18.0, 18.1, 18.1, 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 528.10 ($M + H^+$). Calcd for $C_{25}H_{32}N_6O_5S$: 528.63 ($M + H^+$).

Published on the web (Advance View) June 5, 2004; DOI 10.1246/cl.2004.664