CHEMISTRY LETTERS, pp. 1909-1910, 1994.

Convenient Synthesis of Dehydrooligopeptides Containing α-Dehydroamino Acid Residue Alone

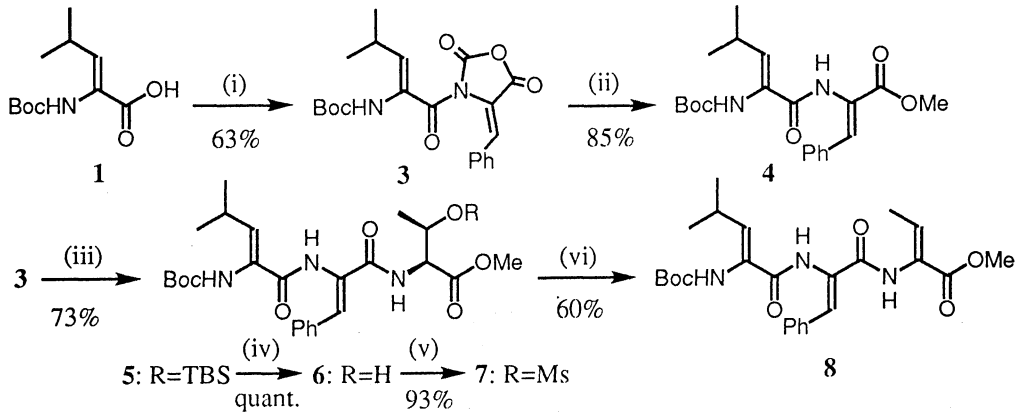
Chung-gi SHIN,* Masao KOSHIMIZU, and Yasuchika YONEZAWA
Laboratory of Organic Chemistry, Faculty of Technology, Kanagawa University,
Kanagawa-ku, Yokohama 221

Convenient synthesis of dehydropeptides containing only α-dehydroamino acid was accomplished by the fragment condensation and β-elimination.

Recently, a number of peptide antibiotics containing α-dehydroamino acid (DHA) residues have been isolated from the culture of various *Streptomyces* strains.[1] Most of them have very attractive macrocyclic structures, but the synthetic study has scarcely been reported. We are much interested in the structure and the functional properties of artificial cyclic dehydropeptide, e.g., as ionophore,[2] as well as the synthesis of the natural product.

In the preceding paper, we (C. S.) have reported the practical synthesis of dehydropolyalanine derivatives by repetition of stepwise elongation of serine derivative and β-elimination.[3] Here, we demonstrate the general synthesis of dehydrooligopeptides composed of various DHA alone.

As a starting material, Boc-ΔLeu-ΔPhe·NCA (**3**) was synthesized by the coupling of *N*-carboxy-α-dehydrophenylalanine anhydride (ΔPhe·NCA: **2**)[4,5] with *N*-*t*-butoxycarbonyl-α-dehydroleucine (Boc-ΔLeu-OH: **1**) in the presence of 4-dimethylaminopyridine (DMAP) by the DCC method.[6] Methanolysis of **3** with MeOH in the presence of *N*-methylmorpholine (NMM) gave Boc-ΔLeu-ΔPhe-OMe (**4**). Similarly, aminolysis of **3** with H-Thr(TBS)-OMe, which was derived by the protection of H-Thr-OMe with *t*-butyldimethylsilyl chloride (TBSCl), gave Boc-ΔLeu-ΔPhe-Thr(TBS)-OMe (**5**). Deprotection of the TBS group with 70% AcOH gave the corresponding *O*-free Thr derivative (**6**). Under sonication, mesylation of **6** with methanesulfonyl chloride (MsCl) and β-elimination with Et_3N proceeded smoothly to give Boc-

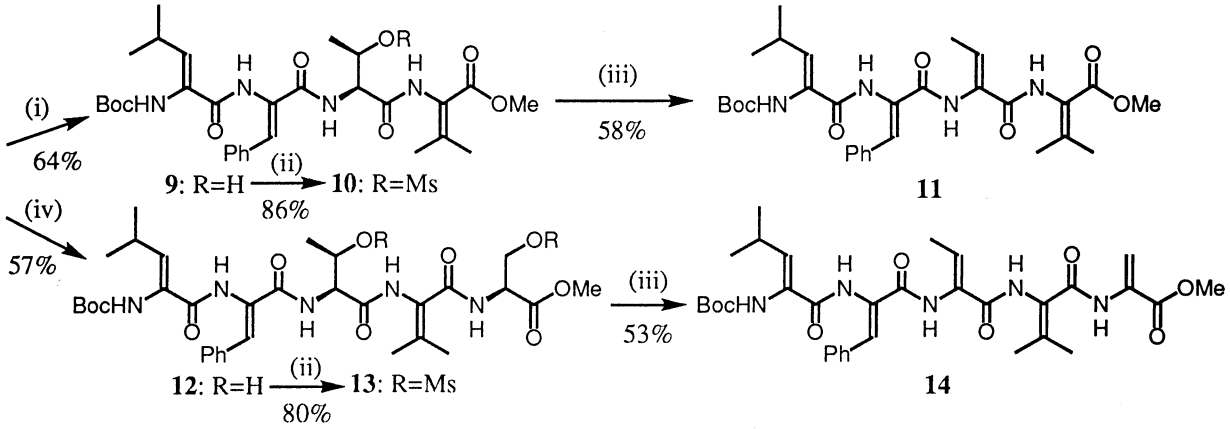


(i) ΔPhe·NCA **2**, DCC, DMAP, CH_2Cl_2, r.t., 24 h, (ii) MeOH, NMM, 60 °C, 2 h, (iii) H-Thr(TBS)-OMe, NMM, THF, 70 °C, 24 h, (iv) 70% AcOH, r.t., 12 h, (v) MsCl, Et_3N, CH_2Cl_2, sonication, 35 °C, 30 min, (vi) Et_3N, CH_2Cl_2, sonication, 35 °C, 30 min.

Scheme 1.

ΔLeu-ΔPhe-ΔAbu-OMe (**8**) (ΔAbu=2-amino-2-butenoic acid), as shown in Scheme 1.

To further elongate the peptide bond, the similar reaction of **3** with H-Thr-ΔVal-OMe[7] gave the corresponding Thr derivative (**9**), which was treated with MsCl. Subsequent β-elimination of the methanesulfonate group of the Thr(Ms) derivative (**10**) was done by using DBU[6] under sonication to give Boc-ΔLeu-ΔPhe-ΔAbu-ΔVal-OMe (**11**). In addition, the similar coupling of **3** with H-Thr-ΔVal-Ser-OMe[7] yielded Boc-ΔLeu-ΔPhe-Thr-ΔVal-Ser-OMe (**12**). The mesylation of **12** and subsequent β-elimination gave the expected Boc-ΔLeu-ΔPhe-ΔAbu-ΔVal-ΔAla-OMe (**14**), as shown in Scheme 2. The structures of all of the new products thus obtained were confirmed by the ^{1}H NMR spectral data and the satisfactory results of elemental analyses (Table 1).



(i) H-Thr-ΔVal-OMe, NMM, THF, 70 °C, 48 h, (ii) MsCl, Et_3N, CH_2Cl_2, sonication, 35 °C, 30 min, (iii) DBU, DMSO, sonication, 35 °C, 1 h, (iv) H-Thr-ΔVal-Ser-OMe, NMM, THF, 70 °C, 48 h.

Scheme 2.

Table 1. The elemental analyses and ^{1}H NMR data of **4, 8, 11, 14**

Compd. No.	Mp / °C	^{1}H NMR (δ), olefin-H (J_{Hz}) in $CDCl_3$ -ΔLeu-	-ΔPhe-[e]	-ΔAbu-	-ΔVal- (CH_3)	-ΔAla-
4 [a]	79 - 80	6.45d (9.9)	7.27-7.58m	—	—	—
8 [b]	181 - 182	6.17d (11.4)	7.33-7.51m	6.85q (7.0)	—	—
11 [c]	200 - 201	6.02d (9.9)	7.23s	6.80q (7.0)	1.86s, 2.07s	—
14 [d]	191 - 192	6.27d (9.9)	7.19-7.39m	6.81q (7.5)	1.85s, 2.09s	5.84s, 6.47s

a) Found: C, 64.76; H, 7.41; N, 7.04%. Calcd for $C_{21}H_{28}N_2O_5$: C, 64.93; H, 7.27; N, 7.21%.
b) Found: C, 63.85; H, 7.05; N, 8.97%. Calcd for $C_{25}H_{33}N_3O_6$: C, 63.68; H, 7.05; N, 8.91%.
c) Found: C, 62.98; H, 7.04; N, 9.71%. Calcd for $C_{30}H_{40}N_4O_7$: C, 63.36; H, 7.09; N, 9.85%.
d) Found: C, 60.21; H, 6.93; N, 10.55%. Calcd for $C_{33}H_{43}N_5O_8 \cdot H_2O$: C, 60.44; H, 6.92 ; N, 10.68%.
e) Olefin-H + Ph-H.

References

1) For example, M. Debono, R. M. Molloy, J. L. Occolowitz, J. W. Paschal, A. H. Hunt, K. H. Michel, and J. W. Martin, *J. Org. Chem.*, **57**, 5200 (1992).
2) S. Kimura, E. Ozeki, and Y. Imanishi, *Biopolymers*, **28**, 1235 (1989).
3) C. Shin, K. Okumura, A. Ito, and Y. Nakamura, *Chem. Lett.*, **1994**, 1301.
4) C. Shin, Y. Yonezawa, and J. Yoshimura, *Chem. Lett.*, **1981**, 1635.
5) C. Shin, S. Honda, K. Morooka, and Y. Yonezawa, *Bull. Chem. Soc. Jpn.*, **66**, 1844 (1993).
6) DCC= *N, N'*-Dicyclohexylcarbodiimide. DBU= 1, 8-Diazabicyclo [5.4.0] undeca-5-ene.
7) C. Shin, Y. Yonezawa, and M. Ikeda, *Bull. Chem. Soc. Jpn.*, **59**, 3573 (1986).

(Received June 23, 1994)