Short Communication

Facile Synthesis of C-terminal Δ^2 -Dehydrotripeptides of Antrimycins and CirratiomycinsChung-gi SHIN,* Masahiro IKEDA
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Antrimycins (**1**)^{1~3} and cirratiomycins (**1**)^{4,5} produced by *Streptomyces* (*St.*) *xanthocidicus* MG125-CF1 and *St. cirratus* 248-Sg2, respectively, are the same substances. These are the first linear dehydroheptapeptides containing both three kinds of unusual α -amino acid residues and either an α -dehydrovaline (Δ Val) or α -dehydroisoleucine (Δ Ile) residue, as shown in Fig. 1. Here, we wish to report the facile synthesis of all of the C-terminal Δ^2 -dehydrotripeptide sequences and the configurational determination of the Δ Ile residue of **1**.

According to the methods reported previously,^{6,7} condensation of α -oxoalkanoic acid (**2**; **a**; R = CH₃, **b**; R = CH₃CH₂, 0.50 mol) with benzyl carbamate (0.55 mol) in benzene (800 ml) in the presence of *p*-toluenesulfonic acid (0.10 mol) under reflux for 6 hr gave *N*-benzyloxycarbonyl (Cbz)- α -dehydroamino acid (DHA; **3a**, **b**) in a *ca.* 60% yield.

Subsequent cyclization of **3a**, **b** (30 mmol) thus obtained with SOCl₂ (150 mmol) in acetyl chloride (50 mmol) gave the corresponding *N*-carboxy α -dehydroamino acid anhydride (**4a**: Δ Val-NCA, **4b**: Δ Ile-NCA) in 95% and 90% yields respectively. Particularly, in the case of Δ Ile, **3b** and **4b** obtained were found to be composed of a mixture of (*Z*)- and (*E*)-geometric isomers in a *ca.* 2:3 ratio, as summarized in Table I. However, the repeated recrystallization of **4b** from cyclohexane three times gave only the (*E*)-isomer.

By comparison with the chemical shifts of methylene protons of the ethyl groups of (*E*)- and (*Z*)-isomers of the Δ Ile residue using the available criterion reported previously,^{8~10} the geometric structure of each isomer could be readily confirmed. It is known generally that the γ -proton of the (*E*)-isomer of DHA shifts in to a lower magnetic field than that of the (*Z*)-isomer.¹⁰

Subsequently, one-pot reactions of **4** (10

TABLE I. SYNTHESIS OF Cbz-DHA (**3a**, **b**) AND Δ NCA (**4a**, **b**)

Compd. No.	Yield (%)	mp (°C)	NMR, δ (DMSO- <i>d</i> ₆)	
			CH ₃ CH ₂ - (CH ₃ -)	CH ₃ -
3a	58	171~172	(2.22 s)	1.76 s
3b	60	141~142 ^a	(<i>E</i>) 2.42 q ^b	1.76 s
			(<i>Z</i>) 2.10 q ^b	2.04 s
4a	95	145~146	(2.16 s)	1.96 s
4b	90	69~101 ^a	(<i>E</i>) 2.70 q ^b	1.96 s
			[122 (<i>E</i>)] (<i>Z</i>) 2.26 q ^b	2.24 s

^a Mixture of (*E*) and (*Z*)-isomers (3:2 ratio).

^b *J* = 7.5 Hz.

FIG. 1. Antrimycins and Cirratiomycins.

Abbreviation: Δ^2 , the position number of a double bond of the DHA residue from the *N*-terminus in sequence.

TABLE II. SYNTHESIS OF Δ^2 -DEHYDRO-TRYPEPTIDES (6 AND 7)

Compd. No.	Yield (%)	mp (°C)	NMR, δ (CDCl ₃) CH ₃ CH ₂ - (CH ₃ -)	[α] _D ²⁵ (c 1.0) ^a
6a	66	149~150	(2.04 s) 1.72 s	-26.8°
6b	40	156~157	(2.06 s) 1.76 s	-26.4°
6c	30	170~171	(2.04 s) 1.76 s	-24.7°
6d	30	185~186	(2.04 s) 1.74 s	-27.4°
7a	65	159~161 ^b	(E) 2.40 q 1.72 s (Z) 2.10 q 2.04 s	-31.6°
7b	54	175~176 ^b	(E) 2.44 q 1.76 s (Z) 2.08 q 2.04 s	-26.2°
7c	34	178~179 ^b	(E) 2.40 q 1.76 s (Z) 2.08 q 2.04 s	-27.0°
7d	39	186~187 ^b	(E) 2.42 q 1.76 s (Z) 2.08 q 2.04 s	-29.0°

^a Recorded in MeOH.^b Mixture of (E) and (Z)-isomers (3:2 ratio).

mmol) with an appropriate Boc-(L)- α -amino acid (AA: Ala, But, norVal, Leu; 11 mmol) and then with H-(L)-Ser-OMe (11 mmol) in the presence of dicyclohexylcarbodiimide (DCC; 11 mmol) and a small amount of pyridine in THF (3 ml) gave the expected Δ^2 -dehydrotripeptide methyl ester (6 and 7) via Boc-AA- Δ NCA (5) formed as an intermediate.¹¹⁾ As a result, in the case of 4b, even if the pure (E)-isomer was used, it was found that geometric isomerization took place to give a 3:2 mixture of the (Z)- and (E)-isomers of 7. Subsequent deprotection of 7a with LiOH/CF₃COOH was further performed to give a geometric mixture

of H-Ala- Δ Ile-Ser-OH [8: *E*- Δ Ile; δ 1.11 (3H, t, $J=7.5$ Hz, -CH₂CH₃), 1.85 (3H, s, -CH₃) and 2.45 (2H, q, -CH₂CH₃). *Z*- Δ Ile; δ 1.06 (t, $J=7.5$ Hz), 2.06 s and 2.23 q] in a 65% yield. The ¹H-NMR spectra of the *E*-isomers of both 7 and 8 thus obtained were found to be very similar to that of the C-terminal dehydrotripeptide segment of antrimycins³⁾ and cirratomycins.⁵⁾ Consequently, the natural products (1) containing a Δ Ile residue could be unambiguously determined to be (*E*)-isomers.

In conclusion, it is noteworthy that not only the synthesis of all the C-terminal Δ^2 -dehydrotripeptides of 1 but also configurational confirmation of the DHA residue could be readily carried out.

REFERENCES

- 1) N. Shimada, K. Morimoto, H. Naganawa, T. Takita, M. Hamada, K. Maeda, T. Takeuchi and H. Umezawa, *J. Antibiot.*, **34**, 1613 (1981).
- 2) K. Morimoto, N. Shimada, H. Naganawa, T. Takita and H. Umezawa, *J. Antibiot.*, **34**, 1615 (1981).
- 3) K. Morimoto, N. Shimada, H. Naganawa, T. Takita, H. Umezawa and H. Kambara, *J. Antibiot.*, **35**, 378 (1982).
- 4) T. Shiroza, N. Ebisawa, K. Furihata, T. Endo, H. Seto and N. Ōtake, *Agric. Biol. Chem.*, **46**, 865 (1982).
- 5) T. Shiroza, N. Ebisawa, K. Furihata, T. Endo, H. Seto and N. Ōtake, *Agric. Biol. Chem.*, **46**, 1891 (1982).
- 6) C. Shin, Y. Yonezawa and J. Yoshimura, *Chem. Lett.*, 1635 (1981).
- 7) C. Shin, Y. Yonezawa and T. Yamada, *Chem.*

- Pharm. Bull.*, **32**, 3934 (1984).
- 8) A. Srinivasan, K. D. Richards and R. K. Olsen, *Tetrahedron Lett.*, 891 (1976).
- 9) D. Hoppe and R. Hollmann, *Chem. Ber.*, **109**, 3062 (1976).
- 10) C. Shin, M. Hayakawa, T. Suzuki, A. Ohtsuka and J. Yoshimura, *Bull. Chem. Soc. Jpn.*, **51**, 550 (1978).
- 11) C. Shin, T. Yamada and Y. Yonezawa, *Tetrahedron Lett.*, **24**, 2175 (1983).
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