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Dehydrooligopeptides. VII. Convenient Synthesis of Various Dehydrodi- and tripeptide Esters by Using *N*-Carboxy α-Dehydroamino Acid Anhydride[1)]

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The one-pot syntheses of *N*-protected Δ^1- and Δ^2-dehydrodipeptide esters by the coupling of *N*-carboxy α-dehydroamino acid anhydride (ΔNCA) with several kinds of C- or N-protected L-α-amino acids are described. In addition, it was found that a similar coupling of ΔNCA with both C- and N-protected α-amino acids also took place to give Δ^2-dehydrotripeptide derivatives, involving eight kinds of important C-terminal segments of antrimycins and cirratiomycins. The configurational confirmation of the α-dehydroisoleucine residue of the antibiotics is also discussed.

Recently, much attention is being given to the synthesis of dehydrooligopeptides (DHP) from not only pharmacological interests but also regarding its usefulness for asymmetric hydrogenation. Although a number of important results and facts regarding the syntheses and properties of α-dehydroamino acid (DHA) and DHP have been reported by many workers,[2-4)] we also reported a few synthetic methods for DHA and DHP.[5,6)] In particular, the application of *N*-carboxy α-dehydroamino acid anhydride (ΔNCA; **2**), derived from benzyloxycarbonyl (Cbz)-DHA (**1**), to the synthesis of DHP has been briefly reported.[7-10)]

Most recently, some interesting peptide antibiotics, e.g., antrimycins[11-13)] (cirratiomycins)[14)] and lavendomycin,[15,16)] have been discovered and determined structurally. The two kinds of the antibiotics have dehydrohepta- and hexapeptide sequences, containing a dehydrovaline (ΔVal) or a dehydroisoleucine (ΔIle) and a 2-amino-2-butenoic acid (ΔAbu) residue, respectively.

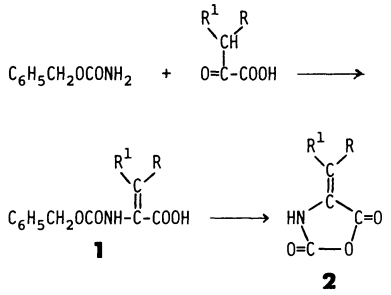
In this paper, we wish to report fully on the synthesis of various kinds of N-protected Δ^1- and Δ^2-dehydrodi- and tripeptide esters,[17)] by a new peptide synthetic method, i.e., the ΔNCA method. Moreover, the synthesis and configuration of all the C-terminal dehydrotripeptide segments of antrimycins are also described.

Results and Discussion

Syntheses of Δ^1- and Δ^2-Dehydrodipeptides. In a preceding paper,[8b)] as is shown in Scheme 1, the synthesis of DHA (**1**) and the corresponding ΔNCA [**2**: **a**; R=R^1=H (ΔAla),[18)] **b**; R=H, R^1=CH$_3$ (ΔAbu), **c**; R=R^1=CH$_3$ (ΔVal), **d**; R=H, R^1=*i*-C$_3$H$_7$ (ΔLeu), **e**; R=H, R^1=C$_6$H$_5$ (ΔPhe)], except for the *N*-carboxy α-dehydroisoleucine anhydride (ΔIle·NCA, **2f**), was reported. Here, according to a previously reported method,[8b,19)] the condensation of 3-methyl-2-oxopentanoic acid with benzyl carbamate was also carried out to give Cbz-α-dehydroisoleucine (**1f**), which was subsequently cyclized to give **2f** in a 90% yield. While the configuration of all the compounds **2** used here except **2f** has a (Z)-geometry, in the case of ΔIle, both the DHA (**1f**) and ΔNCA (**2f**), thus obtained, were found to comprise a mixture of (E)- and (Z)-geometric isomers by ca. a 3:2 ratio. Interestingly, however, it was found that the repeated recrystallization of **2f** from cyclohexane gave only the (E)-isomer.

Generally, by a comparison with the chemical shifts of γ-methylene proton between the (E)- and (Z)-isomers of DHA, the geometry of each isomer could be readily determined. It is well-known that γ-proton of the (E)-isomer of DHA shifts in a lower magnetic field than that of the (Z)-isomer, according to the available criterion reported previously.[20-22)] In the ^{1}H NMR spectrum of **1f** and **2f**, the γ-methylene protons of ethyl groups of (E)-isomer certainly resonate at a lower magnetic field (at δ 2.42 and at δ 2.70) than that of the (Z)-isomer (at δ 2.10 and at δ 2.26): Δδ 0.32 and Δδ 0.44, respectively.

Subsequently, in order to obtain N-protected Δ^1-dehydrodipeptide esters, compounds **2** were subjected to acylation, followed by couplings with L-α-amino acid (AA) esters. After the acylation of **2** with acetyl chloride (Ac-Cl), trifluoroacetic acid anhydride [(Tfa)$_2$O], or di-*t*-butyl carbonate [(Bu^{t}OCO)$_2$O] in the presence of triethylamine or pyridine in tetrahydrofuran (THF) by the usual method, the corresponding *N*-acylated ΔNCA intermediates (**3**, **4**, and **5**), thus



1 **2**

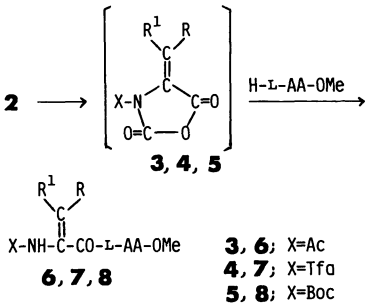
Scheme 1.

formed, were coupled in situ with an appropriate H-L-AA-OMe at room temperature within 1 h to give the desired acyl-Δ^1-(Z, L)-dehydrodipeptide-OMe (**6**, **7**, and **8**) in good yields, respectively, as shown in Scheme 2.

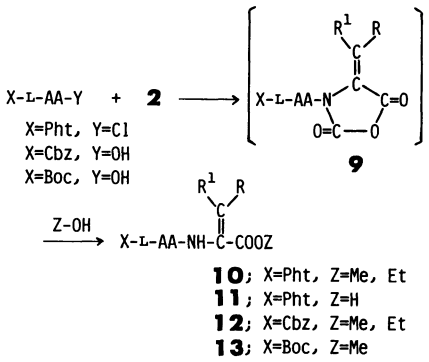
On the other hand, to synthesize Δ^2-dehydrodipeptide esters, which seem to be regio-geometric isomers of **6**—**8**, the ΔNCAs (**2**) were similarly acylated with chloride of phthaloyl(Pht)-L-AA-OH and then the resulting Pht-L-AA-ΔNCA intermediates (**9**) yielded were treated in situ with water, methanol, or ethanol to give Pht-Δ^2-dehydrodipeptide-OH (**10**) and their esters (**11**; Me and Et) in ca. 75% yields, respectively. As a result, the acylation of **2** by the acid chloride method was found to be successful. In addition, it was of much interest to explore whether or not the coupling of **2** with N-protected L-AA-OH could proceed using the other peptide synthetic method.

Attempts at conventional coupling of **2** with Boc- or Cbz-L-AA-OH in the presence of dicyclohexylcarbodiimide (DCC) alone have failed. However, fortunately, it was found that a similar reaction readily took place in the presence of pyridine in addition to DCC at pH 5.5—6.0 to form Boc- and Cbz-L-AA-ΔNCA (**9**). The subsequent treatment of the intermediates (**9**) with methanol or ethanol in one-pot gave the expected Boc- and Cbz-Δ^2-(L, Z)-dehydrodipeptide-OZ (**12** and **13**; Z=Me and Et) in good yields, respectively, as illustrated in Scheme 3.

The yields, physical constants, the ^{1}H NMR spectral data of all the new dehydrodipeptide derivatives



Scheme 2.



Scheme 3.

Table 1. Acyl-Δ^2-Dehydrodipeptide Methyl Esters (**6** and **7**)

Compound[a]	Yield %	Mp θ_m/°C	^{1}H NMR (δ, $CDCl_3$) R-CH=	^{1}H NMR (δ, $CDCl_3$) -NHCHCO- (J/Hz)	$[\alpha]_D^{23}$ (c 1.00°, MeOH)
Ac-ΔAbu-L-Leu-OMe	72	148—150[b]	6.38 q (7.0)	4.45 dt (7.5, 6.0)	−24.3
Ac-ΔAbu-L-Tyr-OMe	79	Syrup	5.77 q (7.0)	4.45 dt (7.5, 7.0)	10.2
Ac-ΔAbu-L-Ser-OMe	65	Syrup	6.44 q (7.0)	4.56 m	7.5
Ac-ΔAbu-L-Pro-OMe	70	118—120[b]	5.50 q (7.0)	4.60 t (7.0)	−22.5
Ac-ΔAbu-L-Met-OMe	70	110—112[b]	6.44 q (7.0)	4.64 dt (7.5, 7.0)	−19.8
Ac-ΔAbu-L-Trp-OMe	65	183—185[b]	6.36 q (7.0)	4.60 m[d]	−2.4
Ac-ΔAbu-L-Glu-OMe (OEt)	75	88—90[c]	6.47 q (7.0)	6.54 dt (7.5, 6.0)	−16.5
Tfa-ΔLeu-L-Phe-OMe	89	103—104[c]	6.19 d (10.0)	4.83 dt (8.0, 5.7)	−15.6
Tfa-ΔPhe-L-Thr-OMe	65	Syrup	7.15—7.29 (+Ph)	4.43 dd (8.5, 3.0)	29.0
Tfa-ΔLeu-L-Orn-OMe (Cbz)	70	Syrup	6.21 d (10.0)	4.58 m	−7.5

a) All compounds were analyzed for C, H, and N, and the results were within ±0.3% of theoretical values. b) Colorless needles from chloroform-diisopropyl ether. c) Colorless needles from hexane. d) Measured in DMSO-d_6.

(**6—8** and **10—13**) are summarized in Tables 1—3. In the ^{1}H NMR spectra, no characteristic differences could be observed between the olefin proton signals of the two types of Δ^1- and Δ^2-dehydrodipeptide esters.

From the above results, the possibility of consecutive reactions of **2** with N-protected AA-OH and then H-AA-OZ (Z=Me and Et) instead of alcohols is expected. Furthermore, similar couplings of **2** with appropriate peptides are also anticipated.

Synthesis of Δ^2-Dehydrotripeptides. So far, it has been difficult to synthesize Δ^2-dehydrotripeptide esters, containing a DHA residue in center, by the conventional coupling of Δ^1- or Δ^2-dehydrodipeptide with

Table 2. Boc-Δ^1-Dehydrodipeptide Methyl Esters (**8**)

Compound[a]	Yield %	Mp[b] θ_m/°C	^{1}H NMR (δ, $CDCl_3$) -CH=	^{1}H NMR (δ, $CDCl_3$) -NHC$\underline{H}$CO- (J/Hz)	$[\alpha]_D^{23}$ (c 1.00°)[d]
Boc-ΔPhe-Gly-OMe	70	156—157	7.14 s	4.14 d (8.0)	—
Boc-ΔPhe-L-Leu-OMe	75	99—101	7.12 s	4.68 dt (8.0, 8.0)	−41.8
Boc-ΔPhe-L-Phe-OMe	65	127—128	7.04 s	4.90 dt (6.0, 7.0)	−3.6
Boc-ΔLeu-L-Ser-OMe	60	Syrup	6.25 d (10.0)	4.66 dt (3.5, 7.0)	−11.9
Boc-ΔnVal-L-Tyr-OMe[c]	70	Syrup	6.39 t (7.0)	4.80 dt (7.0, 8.0)	−11.7

a) All compounds were analyzed for C, H, and N, and the results were within ±0.3% of theoretical values. b) Colorless needles from chloroform-diisopropyl ether. c) nVal is normal valine residue. d) Measured in methanol.

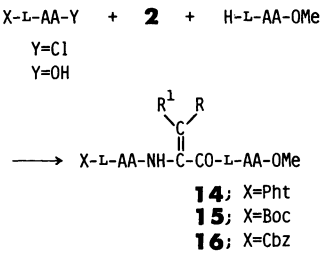
Table 3. *N*-Blocked-Δ^2-Dehydrodipeptide Derivatives (**10**, **11**, **12**, and **13**)

Compound[a]	Yield %	Mp θ_m/°C	^{1}H NMR (δ, $CDCl_3$) R-CH=	^{1}H NMR (δ, $CDCl_3$) -NHC$\underline{H}$CO- (J/Hz)	$[\alpha]_D^{24}$ (c 1.00°, MeOH)
Pht-DL-Phe-ΔnVal-OH	73[b]	148—150[d]	6.76 t (7.0)	5.20 dt[h] (8.0, 5.5)	—
Pht-Gly-ΔPhe-OMe	86[b]	160—161[e]	7.46—7.26 m (+Ph)	4.43 s	—
Pht-L-Ala-ΔAbu-OEt	85[b]	133—135[d]	6.76 q (7.0)	5.06 q (7.0)	0.9
Cbz-L-Ala-ΔAbu-OMe	52[c]	137—138[f]	6.76 q (7.0)	4.43 m	−10.5 (c 0.65)
Cbz-Gly-ΔAbu-OEt	13[b] 74[c]	Syrup	7.02 q (7.0)	3.87 d (6.0)	—
Cbz-Gly-ΔPhe-OMe	82[c]	107—108[f]	7.25—7.53 m (+Ph)	3.91 d (7.0)	—
Boc-L-Ala-ΔAbu-OMe	55	116—117[g]	6.80 q (7.0)	4.40 m	−25.7
Boc-L-Val-ΔAbu-OMe	63	110—111[g]	6.82 q (7.0)	4.10 m	−25.4
Boc-L-Leu-ΔAbu-OMe	58	Syrup	6.64 q (7.0)	4.18 m	−19.2
Boc-L-Phe-ΔAbu-OMe	75	96—98[f]	6.73 q (7.0)	4.58 dt (8.0, 7.0)	−15.0
Boc-Gly-ΔAbu-OMe	51	103—104[g]	6.84 q (7.0)	3.98 d (6.0)	—
Boc-L-Leu-ΔPhe-OMe	76	91—93[g]	7.24—7.50 m (+Ph)	4.28 m	41.5
Boc-L-Phe-ΔPhe-OMe	82	116—118[g]	6.54 d (10.0)	4.54 dt (8.0, 7.0)	−15.5

a) All compounds were analyzed for C, H, and N, and the results were within ±0.3% of theoretical values. b) Yield by acid chloride method. c) Yield by DCC-pyridine method. d) Colorless needles from chloroform-hexane. e) Colorless needles from benzene. f) Colorless needles from ethyl acetate-hexane. g) Pale yellow needles from diisopropyl ether. h) Measured in DMSO-d_6.

two kinds of C- and N-protected L-α-amino acids, respectively. Accordingly, the ⊿NCA method mentioned above was expected to facilitate the coupling of **2** with the above two kinds of α-amino acids in one-pot. At first the acylation of an equimolar **2** with chloride of Pht-L-AA-OH in the presence of triethylamine in THF at 5—10 °C for 1 h was performed, followed by a treatment with H-L-AA-OMe at room temperature for 1.5 h. As a result, it is interesting to note that the above successive reactions were also completely accomplished in only one-pot to give Pht-⊿^{2}-(L, Z, L)-dehydrotripeptide-OMe (**14**) in good yields.

Furthermore, instead of the acid chloride method, the usual DCC method was also utilized for the synthesis of ⊿^{2}-dehydrotripeptides using **2**. A similar coupling of **2** with Boc- or Cbz-L-AA-OH in the presence of DCC and pyridine in THF or CH_2Cl_2 and then with H-L-AA-OMe gave the expected Boc- and Cbz-⊿^{2}-(L, Z, L)-dehydrotripeptide-OMe (**15** and **16**) via Boc- and Cbz-L-AA-⊿NCA as intermediates in good yields, respectively, as illustrated in Scheme 4. On the other hand, on the contrary, after treating **2** with an amino acid ester in THF, the subsequent treatment of the resulting solution with a N-protected amino acid was found not to be effective. In addition, the simultaneous treatment of **2** with two kinds of C- and N-protected amino acids was also unsuccessful.



Scheme 4.

From the above versatile information, the ⊿NCA method can be firmly believed to be promising for the synthesis of antrimycins as well as the C-terminal ⊿^{2}-dehydrotripeptide moieties. The dehydrotripeptide sequences were composed of L-AA [Ala, Abu, nVal (normal valine), and Leu], DHA (⊿Val and ⊿Ile), and Ser residues in turn, which were variously combined to afford eight kinds of antrimycins. The syntheses of all the partial skeletons have already been briefly reported.[10] However, since the yields were comparatively low, here, the procedures were modified. Consequently, similar reactions of **2c** or **2f** with the four kinds of Boc-L-AA-OH listed above for 12 h (then in situ with H-L-Ser-OMe) were carried out to give the expected Boc-⊿^{2}-dehydrotri-

Table 4. Pht-⊿^{2}-Dehydrotripeptide Methyl Esters (**14**)

Compound[a]	Yield %	Mp[b] θ_m/°C	^{1}H NMR (δ, $CDCl_3$) R-CH= (J/Hz)	-NHCHCO- (J/Hz)		$[\alpha]_D^{25}$ (c 1.00°)[c]
Pht-Gly-⊿Abu-L-Phe-OMe	58	175—176	6.43 q (7.0)	4.74 dt (7.5, 7.0)	4.28 s	−24.9
Pht-Gly-⊿Abu-L-Leu-OMe	76	161—162	6.59 q (7.0)	4.52 dt (7.0, 7.0)	4.44 s	−42.8
Pht-Gly-⊿Leu-L-Val-OMe	74	204—205	6.33 d (10.0)	4.44 m		−24.6
Pht-Gly-⊿Phe-L-Phe-OMe	68	175—176	6.92—7.30 m	4.64 dt (7.5, 7.0)	4.24 s	−64.6 (c 0.50)
Pht-Gly-⊿Leu-L-Phe-OMe	78	193—194	6.25 d (10.0)	4.80 dt (7.5, 7.0)	4.40 s	−20.2
Pht-L-Ala-⊿Abu-L-Phe-OMe	55	161—162	6.48 q (7.0)	4.92 q (7.0)	4.62 dt (7.0, 6.5)	12.9
Pht-L-Leu-⊿Abu-L-Phe-OMe	71	151—152	6.46 q (7.0)	5.00 dd (11.0, 5.0)	4.66 dt (7.0, 7.0)	−4.5
Pht-Gly-⊿Phe-L-Val-OMe	77	215—216	7.17 s	4.26 dd (7.5, 7.0)	4.50 s	−20.5
Pht-Gly-⊿nVal-L-Phe-OMe	72	169—171	6.36 t (7.0)	4.80 dt (7.0, 7.0)	4.42 s	−18.9
Pht-L-Leu-⊿nLeu-L-Phe-OMe	56	53—55	6.46 t (7.0)	5.02 dd (11.0, 5.0)	4.72 dt (7.5, 6.0)	−7.0
Pht-L-Phe-⊿Abu-Gly-OMe	77	100—101	6.56 q (7.0)	5.20 dd (10.5, 5.5)	3.90 d (6.0)	−113.4
Pht-L-Phe-⊿Leu-L-Ser-OMe	58	179—180	6.21 d (10.0)	5.30 dd (11.0, 5.0)	4.38 m	−59.1

a) All compounds were analyzed for C, H, and N, and the results were within ±0.3% of theoretical values. b) Colorless needles from chloroform-hexane. c) Measured in methanol.

peptide-OMe (**15**). The yields reached to ca. 65% within 1 h. As a result, in the case of **2f**, even if a pure (E)-isomer was used, it was found that geometric isomerization took place during stepwise couplings to give a 3:2 mixture of the (Z)- and (E)-isomers of **15**.

The yields, physical constants, and the ^{1}H NMR spectral data of **14**—**16**, involving C-terminal dehydrotripeptides of antrimycins, are summarized in Tables 4—6. From the ^{1}H NMR spectra of the (E)-isomers of **15**, the chemical shifts of CH_3 (δ 1.75s) and $CH_3C\underline{H}_2$ (δ 2.42q) in ΔIle residue and of two CH_3 (δ 1.75s and 2.05s) in ΔVal residue were found to be very similar to those (δ 1.78s, 2.46q, 1.81s, and 2.10s, respectively) of antrimycins.[13] Consequently, the naturally occurring products could be unambiguously determined to have (E)-isomeric structures.

In conclusion, it is worth noting that not only the synthesis of all the C-terminal Δ^2-dehydrotripeptides of antrimycins in one pot but also the configuration of the DHA residues could be readily confirmed.

Table 5. Boc- and Cbz-Δ^2-Dehydrotripeptide Methyl Esters (**15** and **16**)

Compound[a]	Yield %	Mp[b] θ_m/°C	^{1}H NMR (δ, $CDCl_3$) R-CH=	-NHC$\underline{H}$CO- (J/Hz)		$[\alpha]_D^{25}$ (c 1.00°, MeOH)
Cbz-Gly-ΔPhe-L-Ser-OMe	60	Syrup	7.06 s	3.84 m	4.60 m	−21.9
Boc-L-Ala-ΔAbu-L-Ser-OMe	51	Syrup	6.63 q (7.0)	4.20 dd (7.0, 7.0)	4.61 dt (8.0, 4.0)	−31.9
Boc-L-Val-ΔAbu-L-Ser-OMe	52	Syrup	6.62 q (7.0)	4.02 m	4.62 m	−22.9
Boc-L-Ala-ΔnVal-L-Ser-OMe	56	Syrup	6.57 t (7.0)	4.20 dd (7.0, 7.0)	4.60 dt (8.0, 4.0)	−34.5
Boc-Gly-ΔPhe-L-Met-OMe	74	160—162	7.12 s	3.70 d (6.0)	4.51 dt (8.0, 7.0)	−50.9
Boc-Gly-ΔPhe-L-Leu-OMe	75	188—189	7.16 s	3.70 d (5.5)	4.40 dt (8.0, 4.5)	−26.2
Boc-L-Phe-ΔAbu-L-Ala-OMe	85	190—191	6.65 q (7.5)	4.36 dq (8.0, 5.5)	4.59 m	−26.4
Boc-L-Ala-ΔLeu-L-Phe-OMe	83	121—122	6.29 d (10.0)	4.21 m	4.86 dq (7.5, 5.0)	−35.8
Boc-L-Leu-ΔLeu-L-Ala-OMe	77	126—127	6.36 d (10.0)	4.19 m	4.62 dq (7.5, 5.0)	−60.8

a) All compounds were analyzed for C, H, and N, and the results were within ±0.3% of theoretical values.
b) Colorless needles from chloroform-diisopropyl ether.

Table 6. C-Terminal Dehydrotripeptide Sequences of Antrimycins (**15**)

Compound[a]	Yield[b] %	^{1}H NMR (δ, $CDCl_3$) $CH_3C\underline{H}_2$- [J=7.5 Hz]	CH_3-	-NHC$\underline{H}$CO- (J/Hz)	
Boc-L-Ala-ΔIle-L-Ser-OMe	84	(*E*) 2.40 q (*Z*) 2.10 q	1.72 s 2.04 s	4.16 dq (7.0, 7.0)	4.60 m
Boc-L-Abu-ΔIle-L-Ser-OMe	72	(*E*) 2.44 q (*Z*) 2.08 q	1.76 s 2.04 s	4.08 m	4.68 m
Boc-L-nVal-ΔIle-L-Ser-OMe	53	(*E*) 2.40 q (*Z*) 2.08 q	1.76 s 2.04 s	4.12 m	4.64 m
Boc-L-Leu-ΔIle-L-Ser-OMe	58	(*E*) 2.42 q (*Z*) 2.08 q	1.76 s 2.04 s	4.14 m	4.60 m
Boc-L-Ala-ΔVal-L-Ser-OMe	82		(*E*) 2.04 s (*Z*) 1.72 s	4.16 dq (7.0, 7.0)	4.58 m
Boc-L-Abu-ΔVal-L-Ser-OMe	61		(*E*) 2.06 s (*Z*) 1.76 s	4.08 m	4.68 m
Boc-L-nVal-ΔVal-L-Ser-OMe	59		(*E*) 2.04 s (*Z*) 1.76 s	4.12 m	4.64 m
Boc-L-Leu-ΔVal-L-Ser-OMe	53		(*E*) 2.04 s (*Z*) 1.74 s	4.20 m	4.64 m

a) All compounds were analyzed for C, H, and N, and the results were within ±0.3% of the theoretical values.
b) Colorless needles from ethyl acetate.

Experimental

General. Melting points were determined with a Yamato (Model Mp-21) micro melting-point apparatus, and were not corrected. IR spectra were recorded with a Hitachi EPI-G2 grating spectrometer. ^{1}H NMR spectra were measured with a JEOL JMN PS-100 spectrometer in a $CDCl_3$ solution with tetramethylsilane as the internal standard. The specific rotations were measured in a 0.5-dm tube using a JASCO DIP-4 polarimeter (Japan Spectroscopic Co., Ltd.).

Cbz-Dehydroisoleusine (1f). A solution of 3-methyl-2-oxopentanoic acid (0.50 mol) and benzyl carbamate (0.55 mol) in the presence of *p*-toluenesulfonic acid (0.10 mmol) in dry benzene (800 ml) was refluxed for 6 h, removing water by means of water-separator. The reaction solution was extracted three times with a saturated $NaHCO_3$ aqueous solution; then, the combined aqueous extracts were acidified to pH 1—2 with concentrated HCl. The deposited crystals were collected and then recrystallized from benzene to give Cbz-ΔIle-OH (**1f**) as colorless needles. Yield 60% as a mixture of (E)- and (Z)-isomers by 3:2 ratio, mp 141—142 °C. IR (KBr): 3280 (NH), 1700, 1520 (NHCO) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ=1.76 (s, 3H, CH_3–), 2.04 (s, 3H, CH_3–), 2.10 (q, 2H, J=7.0 Hz, $CH_3C\underline{H}_2$–), 2.42 (q, 2H, J=7.0 Hz, $CH_3C\underline{H}_2$–), 8.56 (bs, 1H, -NH-). Found: C, 68.02; H, 6.90; N, 5.61%. Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66%.

***N*-Carboxy-α-dehydroisoleusine Anhydride (2f).** A solution of **1f** (20 mmol) in acetyl chloride (3 ml) and thionyl chloride (9 ml) was stirred at room temperature for 2 h. After removal of the solvent under reduced pressure, dry carbon tetrachloride (30 ml) was added to the crystalline residue and then the resulting solution was concentrated. This procedure was repeated three times. The residual crystals were recrystallized from cyclohexane to give ΔIle·NCA (**2f**) as colorless needles. Yield 90% as a mixture of (E)- and (Z)-isomers by 3:2 ratio, mp 69—101 °C. The mixture was recrystallized repeatedly to give only (E)-isomer, which melting point was 122—123 °C. IR (KBr): 3200 (NH), 1820, 1780 (-O-C=O) cm^{-1}. ^{1}H NMR (DMSO-d_6): (E)-isomer; δ=1.96 (s, 3H, CH_3–), 2.70 (q, 2H, J=7.0 Hz, $CH_3C\underline{H}_2$–). 9.44 (s, 1H, -NH-). (Z)-isomer; δ= 2.24 (s, 3H, CH_3–), 2.26 (q, 2H, J=7.0 Hz, $CH_3C\underline{H}_2$–), 9.44 (s, 1H, -NH-). Found: C, 54.21; H, 5.88; N, 9.07%. Calcd for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03%.

Ac-Δ^1-Dehydrodipeptide Methyl Esters (6). To a solution of an appropriate **2** (10 mmol) in THF (5 ml) was added acetyl chloride (12 mmol). The resulting solution was approximately neutralized under cooling by adding triethylamine and then stirred at room temperature for 1 h. After concentrating the solution, the residue, thus obtained, was suspended in THF (5 ml) and then with a solution of an appropriate L-α-amino acid ester (12 mmol) in THF (5 ml). with stirring, at room temperature for 1 h. The solvent was removed and the obtained residue was dissolved in chloroform (50 ml); the resulting solution was successively washed twice with 1 M HCl (1 M=1 mol dm^{-1}) and water and then dried over anhydrous Na_2SO_4. After removing the chloroform, the residual crystals or syrup was purified by recrystallization from a mixture of chloroform–diisopropyl ether or hexane and by chromatography on a silica-gel column using a mixture of chloroform and acetone (20:1 v/v) as the eluent. See Table 1.

Tfa-Δ^1-Dehydrodipeptide Methyl Esters (7). To a solution of **2** (10 mmol) in CH_2Cl_2 (5 ml) trifluoroacetic acid anhydride (12 mmol) was added dropwise at 0 °C and the resulting prepared solution was made acidic to pH 5—6 by adding pyridine. After stirring at room temperature for 5 h, an appropriate L-α-amino acid methyl ester (11 mmol) was added to the resultant solution. After stirring continuously for 1 h, CH_2Cl_2 (50 ml) was further added to the reaction solution and then solution, thus prepared, was successively washed twice with 1 M HCl and water and then dried over anhydrous Na_2SO_4. The removal of the solvent gave a residual syrup, which was purified on a silica-gel column using a mixture of benzene and ethyl acetate (20:1 v/v) as the eluent to give **7** as a viscous syrup or as colorless needles from hexane. See Table 1.

Boc-Δ^1-Dehydrodipeptide Methyl Esters (8). To a solution of **2** (10 mmol) in THF (5 ml) was added $(Bu^tOCO)_2O$ (12 mmol) and a few drops of pyridine; the resulting solution was stirred at room temperature for 6 h. A solution of an appropriate L-α-amino acid methyl ester (11 mmol) in THF (5 ml) was added to the solution prepared above, which was then stirred continuously for 1 h. After removing the solvent, the residual syrup was dissolved in ethyl acetate (100 ml) and the resulting solution was successively washed twice with 10% citric acid, a saturated NaCl aqueous solution, and water and then dried over anhydrous $MgSO_4$. The concentration of the solution gave a viscous syrup, which was purified on a silica-gel column using a mixture of benzene and ethyl acetate (5; 1 v/v) as the eluent to give **8** as a colorless viscous syrup or as colorless needles from a mixture of chloroform and diisopropyl ether. See Table 2.

Pht-Δ^2-Dehydrodipeptides (10 and 11). To a solution of **2** (10 mmol) and chloride of phthaloyl-L-α-amino acid (11 mmol) in THF (5 ml) was added dropwise triethylamine until reaching pH 6 under cooling. After stirring at room temperature for 1 h, the resulting solution was treated with methanol or ethanol (10 ml) and then made basic to pH 8—9 by adding triethylamine. After further stirring for 1 h and then removing the solvent under reduced pressure, the residual syrup was dissolved in ethyl acetate (100 ml). The resultant solution was washed twice, successively, with 1 M HCl and water and then dried over anhydrous Na_2SO_4. The concentration of the solution gave a crude syrup which was then purified on a silica-gel column using a mixture of benzene and ethyl acetate (10:1 v/v) as the eluent to give **10** as a colorless viscous syrup or needles.

In a similar manner, a treatment of **2** with Pht-L-AA-Cl in water instead of alcohol was worked up to give **11** as colorless needles. See Table 3.

Cbz- and Boc-Δ^2-Dehydrodipeptide Esters (12 and 13). To a solution of Cbz-L-α-amino acid (11 mmol) and **2** (10 mmol) in THF (5 ml) was added DCC (11 mmol) portionwise at −10 °C. After stirring for 20 min, the resulting solution was made acidic to pH 6 by adding pyridine and then stirred at 0 °C for 1 h. After cooling to stand at room temperature, the stirring was continued for 12 h.

The prepared solution was treated with alcohol (10 ml) and then made basic to pH 9 by adding *N*-methylmorpholine and stirred continuously for 1 h. After removing the solvent under reduced pressure, the residue, thus obtained, was dissolved in ethyl acetate (50 ml) and the resultant solution was allowed to stand under cooling for 1 h. The deposited *N,N'*-dicyclohexylurea was filtered off and the filtrate was further diluted in ethyl acetate (50 ml) and then successively washed twice with 10% citric acid and water and finally dried over anhydrous Na_2SO_4. The evaporation of the solvent gave a syrup or crystalline substance, which was purified on a silica-gel column using a mixture of chloroform and acetone (20:1 v/v) as the eluent to give **12** as a colorless viscous syrup or needles.

In a similar manner, the treatment of **2** with Boc-L-α-amino acid in alcohol was worked up to give **13** as a colorless viscous syrup or needles. See Table 3.

Pht-Δ^2-Dehydrotripeptide Methyl Esters (14). To a solution of **2** (10 mmol) and Pht-L-α-AA-Cl (11 mmol) in THF (5 ml) was added dropwise triethylamine under cooling. When the pH of the solution became to 6, the resulting solution was stirred at room temperature for 1 h and was then treated with an appropriate L-α-amino acid methyl ester (11 mmol) and finally made basic to pH 8—9 by adding triethylamine. After stirring for an additional 1 h and removing the solvent, the residual crystalline substance was dissolved in ethyl acetate (100 ml). The solution, thus obtained, was successively washed twice with 1 M HCl and water and then dried over anhydrous Na_2SO_4. The evaporation of the solvent gave crude crystalline materials, which were purified on a silica-gel column using a mixture of benzene and ethyl acetate (10:1 v/v) as the eluent to give **14** as colorless needles. See Table 4.

Boc- and Cbz-Δ^2-Dehydrotripeptide Methyl Esters (15 and 16). To a solution of Boc-L-α-amino acid (11 mmol) and **2** (10 mmol) in CH_2Cl_2 (5 ml) was added portionwise DCC (11 mmol) at −10 °C. After stirring for 20 min, the resultant solution was made slightly acidic to pH 6 by adding pyridine and then stirring below 0 °C for 1 h. The prepared solution was continuously stirred at room temperature for 12 h and treated with L-α-amino acid methyl ester (11 mmol) and then made basic to pH 9 by adding *N*-methylmorpholine, with stirring for 1 h. After removing the solvent under reduced pressure, the residue, thus obtained, was dissolved in ethyl acetate (50 ml) and the solution was allowed to stand under cooling for 1 h. Deposited *N,N'*-dicyclohexylurea was filtered off and the filtrate was further diluted in ethyl acetate (50 ml) and then successively washed twice with 10% citric acid and water and finally dried over anhydrous Na_2SO_4. The concentration of the solution gave a crystalline product, which was purified on a silica-gel column using a mixture of chloroform and acetone (20:1 v/v) as the eluent to give **15** as a colorless viscous syrup or needles. See Table 5.

In a similar manner, a treatment of **2** with Cbz-Gly-OH and H-L-Ser-OMe was worked up to give **16** as a colorless syrup.

In addition, a similar treatment of **2** with Boc-L-AA-OH and H-L-Ser-OMe gave C-terminal dehydrotripeptide sequences of antrimycins (**15**). See Table 6.

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