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Dehydrooligopeptides. V.[1] Synthesis of *N*-Carboxy α-Dehydroamino Acid Anhydrides and Their Transformation to α-Dehydroamino Acid and Dehydrooligopeptide Derivatives

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The synthesis of *N*-carboxy α-dehydroamino acid anhydrides (*Δ*NCA) from benzyloxycarbonyl-α-dehydroamino acids and the subsequent conversion of these products into new α-dehydroamino acid and dehydrooligopeptide derivatives are described. It was found that the new *Δ*NCA derivatives were very useful synthons for dehydropeptides. The racemization behavior and configurational determination of all the new dehydrooligopeptides thus obtained are discussed.

Keywords——α-dehydroamino acid; *N*-carboxy α-dehydroamino acid anhydride; coupling; fragment condensation; dehydrooligopeptide; geometric configuration

In recent years, much attention has been paid to the correlation between the structure and the bioactivity of dehydropeptides (DHP) containing one or more α-dehydroamino acid (DHA) residues,[2-7] which are very important constituents or moieties of antibacterial, antibiotic, and phytotoxic DHP. Syntheses of DHA and DHP derivatives by several methods, *i.e.*, by the *β*-elimination of peptides having a leaving group,[8-11] by direct coupling of DHA with α-amino acids,[12,13] and by the ring cleavage of unsaturated azlactones,[14-17] have been reported by many workers.

Previously, we reported practical syntheses of *N*-benzyloxycarbonyl (Cbz)–DHA (**1**) and of dehydrooligopeptides by the stepwise elongation of **1** with α-amino acids or other DHAs.[18-22] Furthermore, in the preceding communications,[23-25] we have briefly reported the synthesis of *N*-carboxy α-dehydroamino acid anhydride (*Δ*NCA; **2**) from **1** and the application of **2** to DHP synthesis. Here, we wish to report the details of the *Δ*NCA synthesis, followed by conversion of the products to N-free DHA esters and various acetyl DHP derivatives without the use of any coupling reagent. The usefulness of *Δ*NCA derivatives as synthons for DHA and dehydrooligopeptide compounds is discussed.

Results and Discussion

Synthesis and Reactivity of *Δ*NCA

Sakakibara's method for the synthesis of *N*-carboxy dehydroalanine anhydride[26] was modified and a general synthesis of *Δ*NCA was accomplished here.

Treatment of the starting (*Z*)-Cbz–DHA (**1**)[18] with 3 mol of thionyl chloride in acetic acid gave the desired **2** in an almost quantitative yield, then acetylation with acetyl chloride at pH 4.0 in dry tetrahydrofuran (THF) gave *N*-acetyl-*Δ*NCA (**3**) in *ca.* 91% yield (see Tables I and II).

As summarized in Tables I and II, the infrared (IR) spectra of **2** and **3** showed characteristic acid anhydride carbonyl group (–CO–O–CO–) absorptions as two strong bands in the 1850—1820 and 1785—1750 cm^{-1} regions and that of the carbon–carbon double bond

TABLE I. *N*-Carboxy α-Dehydroamino Acid Anhydrides (**2**)

Compound No.	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)			IR (KBr) cm^{-1}			^{1}H-NMR (δ, $CDCl_3$)		
				C	H	N	NH	$O(CO)_2$	C=C	R-C<u>H</u>= (J, Hz)	<u>R</u>-CH=	NH
2a	95	136—138[a]	$C_5H_5NO_3$	47.25 (47.19	3.97 3.90	11.02 11.09)	3150	1820 1780	1695	5.80 q (7.5)	1.82 d	11.20
2b	90	97—98[a]	$C_6H_7NO_3$	51.06 (51.06	5.00 4.90	9.93 9.87)	3210	1820 1780	1690	5.28 t (8.0)	2.24 qu[d]	11.40
2c	92	145—146[b]	$C_6H_7NO_3$	51.06 (50.94	5.00 4.91	9.93 9.85)	3200	1820 1770	1680	—	1.92 2.16 s	11.00
2d	93	116—117[a]	$C_7H_9NO_3$	54.19 (54.12	5.85 5.71	9.03 8.83)	3210	1830 1770	1690	5.82 t (8.0)	2.23 q	11.24
2e	94	91—92[a]	$C_7H_9NO_3$	54.19 (54.00	5.85 5.78	9.03 8.92)	3240	1830 1770	1680	5.74 d (10.0)	2.70 m	11.26
2f	93	230—232[c]	$C_{10}H_7NO_3$	63.49 (63.49	3.73 3.73	7.41 7.38)	3200	1820 1750	1660	6.66 s	7.38—7.76 m	11.62

a) Colorless needles from cyclohexane.
b) Colorless needles from benzene.
c) Colorless needles from chloroform.
d) Quintet.

TABLE II. Acetyl *N*-Carboxy α-Dehydroamino Acid Anhydrides (**3**)

Compound No.	Yield (%)	mp[a] (°C)	Formula	Analysis (%) Calcd (Found)			IR (KBr) cm^{-1}			^{1}H-NMR (δ, $CDCl_3$)	
				C	H	N	–CO–O–CO–		C=C	–CH= (*J*, Hz)	CH_3CO–
3a	92	82—85	$C_7H_7NO_4$	49.71 (49.63	4.17 4.24	8.28 8.18)	1830	1780	1670	6.47 d (7.5)	2.54 s
3b	90	55—56	$C_8H_9NO_4$	52.46 (52.37	4.95 4.90	7.65 7.59)	1830	1780	1670	6.36 t (7.5)	2.54 s
3d	93	Syrup	$C_9H_{11}NO_4$	54.82 (55.11	5.62 5.87	7.10 6.89)	1830	1780	1675	6.40 t (7.5)	2.54 s
3e	90	82—84	$C_9H_{11}NO_4$	54.82 (54.69	5.62 5.73	7.10 7.09)	1850	1785	1680	6.18 d (10.0)	2.54 s
3f	87	105—108	$C_{12}H_9NO_4$	62.34 (62.28	3.92 3.84	6.06 5.98)	1830	1780	1645	7.17 s	2.52 s

a) Colorless needles after successive washings with water and ethyl ether.

TABLE III. Ethyl 2-Amino-2-alkenoates (**4**)

Compound No.	Yield (%)	bp[a] (°C/mmHg)
4a	70	40—41/1.5
4b	71	50—53/1.5
4c	81	50—52/1.5
4d	70	58—60/1.3
4e	76	55—58/1.0
4f	80	90—95/0.5

a) See refs. 29 and 30.

as a weak band in the 1695—1645 cm^{-1} region, confirming the formation of **2** and **3**. Furthermore, the disappearance of the ring amide NH stretching band of **2** at 3240—3150 cm^{-1} and the appearance of an acetyl carbonyl band at 1700—1600 cm^{-1} support the formation of N-acetylated **2** (**3**) and the retention of the oxazolidinedione ring during the acetylation. On the other hand, in the nuclear magnetic resonance (NMR) spectra of **2** and **3**, the shift of the olefinic proton signals (δ 5.28—7.17 region) and the disappearance of the signal of **2** at δ 11.00—11.62 due to the NH proton also unambiguously demonstrate the formation of **3**.

Interestingly, **2** thus obtained was found to be very stable, whereas the ordinary *N*-carboxy α-amino acid anhydrides (NCA) were extremely unstable in air at room temperature as well as in the presence of amines. On treatment with water in the presence of base, **2** was readily hydrolyzed to give the corresponding α-oxoalkanoic acid, but in the absence of base, the hydrolysis did not take place. However, it was found that **3** was quite unstable at room temperature.

In addition, the ethanolysis of **2** in the presence of a small amount of triethylamine

TABLE IV. Alkyl 2-Amino-2-alkenoates (**4**)

Compd. No.	Ester	Yield (%)	bp (°C/mmHg)	IR (KBr) cm^{-1}			^{1}H-NMR (δ, $CDCl_3$)	
				NH_2	COO	C=C	–CH= (*J*, Hz)	NH_2 (br s)
4a	Me	76	42—45/1.8	3450 3350	1710	1650	5.68 q (7.0)	3.54
4b	Me	75	50—52/1.7	3450 3350	1710	1650	5.52 t (7.0)	3.65
4c	Me	84	50—53/1.5	3450 3350	1750	1650	—	3.52
4d	Me	75	56—59/0.5	3450 3350	1715	1645	5.67 t (7.0)	3.80
4e	Me	79	53—56/1.0	3450 3350	1713	1645	5.48 d (10.0)	3.50
4f	Me	77	105—110/0.1	3430 3350	1710	1625	6.45 s	4.20
4f	Bz[a]	60	Syrup	3420 3340	1700	1620	6.52 s	4.20
4f	iso-Pr[b]	25	Syrup	3450 3360	1710	1630	6.45 s	4.70
4a	iso-Bu[c]	15	50—55/0.4	3420 3340	1720	1630	5.70 q (7.0)	3.56
4e	iso-Bu	17	53—57/0.2	3440 3350	1710	1630	5.52 d (9.0)	3.75

a) Benzyl. *b*) Isopropyl. *c*) Isobutyl.

TABLE V. 2-Acetylamino-2-alkenoic Acids (**5**) and Their Ethyl Esters (**6**)

Compound No.	Yield (%)	Compound No.	Yield (%)
5a	91	**6a**	90
5b	82	**6b**	85
5c	90	**6c**	95
5d	85	**6d**	86
5e	90	**6e**	88
5f	95	**6f**	96

proceeded immediately to give a colorless oil. Surprisingly, the oily product was found to be the corresponding ethyl (*Z*)-2-amino-2-alkenoate (**4**) which was obtained in *ca.* 78% yield (Table III). Accordingly, in order to extend and generalize the new synthetic method for N-free DHA, **2** was subjected to alcoholysis with various alcohols under conditions similar to

TABLE VI. Alkylethanedioylamide Derivatives (7)

Compound R	Compound Y	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	IR (KBr) cm^{-1} C=O	IR (KBr) cm^{-1} NHCO	^{1}H-NMR (δ, $CDCl_3$) $-CH_2CO-$	^{1}H-NMR (δ, $CDCl_3$) $-NHCH-$ (J, Hz)	^{1}H-NMR (δ, $CDCl_3$) NH
CH_3	Cyclohexyl	45	63—65[a]	$C_{10}H_{17}NO_2$	65.54 (65.49	9.35 9.31	7.64 7.70)	1725	1675 1530	2.96 q (7.0)	3.73 m	6.90 br s
CH_3	Bz	47	79—81[b]	$C_{11}H_{13}NO_2$	69.09 (69.05	6.85 6.89	7.33 7.28)	1725	1655 1530	2.98 q (7.0)	4.50 d (6.0)	7.36 m (Ph+1)
CH_3	Phe–OEt	50	48—50[c]	$C_{15}H_{19}NO_4$	64.96 (64.91	6.91 6.88	5.05 5.07)	1720	1680 1515	2.85 q (7.0)	4.75 dt (8.2, 6.3)	7.34 br d (8.0)
C_2H_5	Phe–OEt	53	Syrup	$C_{16}H_{21}NO_4$	65.95 (65.67	7.27 7.19	4.81 4.85)	1720	1680 1510	2.60 t (7.0)	4.76 dt (8.2, 6.3)	7.42 br d (8.0)
n-C_3H_7	Phe–OEt	57	Syrup	$C_{17}H_{23}NO_4$	66.86 (66.49	7.59 7.54	4.59 4.62)	1720	1680 1510	2.84 t (7.0)	4.76 dt (8.2, 6.3)	7.44 br d (8.0)
iso-C_3H_7	Phe–ORt	51	Syrup	$C_{17}H_{23}NO_4$	66.86 (66.58	7.59 7.38	4.59 4.68)	1720	1680 1510	2.74 d (7.0)	4.78 dt (9.0, 6.7)	7.44 br d (8.0)
C_6H_5	Phe–OEt	65	126—127[d]	$C_{20}H_{21}NO_4$	70.78 (70.75	6.24 6.20	4.13 4.17)	1725	1680 1520	4.14 d (1.1)	4.75 dt (8.0, 6.2)	7.38 br d (8.0)

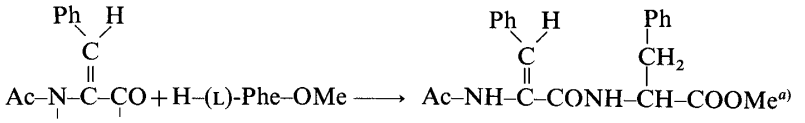
a) Colorless needles from cyclohexane.
b) Colorless needles from ethanol.
c) Colorless needles from hexane.
d) Colorless needles from CCl_4.

TABLE VII. Ac-Δ^1-(*Z*, L)-dehydrodipeptide Ethyl Esters (**9**)

Compound No.	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (δ, $CDCl_3$) –CH=	–NHCH– (*J*, Hz)	$[\alpha]_D^{25}$ (*c*=0.5, MeOH)
9a	95	138—140[a]	$C_{17}H_{22}N_2O_4$	64.13 (64.10	6.97 6.91	8.80 8.75)	6.38 q (7.1)	4.76 dt (7.5, 6.0)	−5.4°
9b	97	162—163[a]	$C_{18}H_{24}N_2O_4$	65.04 (64.98	7.28 7.11	8.43 8.39)	6.38 t (7.0)	4.87 dt (7.5, 6.0)	−6.1°
9d	92	137—138[b]	$C_{19}H_{26}N_2O_4$	65.87 (65.93	7.57 7.62	8.09 8.03)	6.26 t (7.0)	4.82 dt (7.5, 6.0)	−7.5°
9e	94	150—152[b]	$C_{19}H_{26}N_2O_4$	65.87 (66.02	7.57 7.66	8.09 7.99)	6.10 d (10.0)	4.82 dt (7.5, 6.0)	−6.2°
9f	98	152—154[c]	$C_{28}H_{24}N_2O_4$	74.32 (74.28	5.35 5.40	6.19 6.15)	6.88 s	4.79 dt (7.5, 6.0)	−35.8°

a) Colorless needles from CCl_4.
b) Colorless needles from CCl_4–ethyl acetate.
c) Colorless needles from benzene–isopropyl alcohol.

TABLE VIII. The Young Test of Ac-ΔPhe-Phe-OMe Synthesized by Various Methods



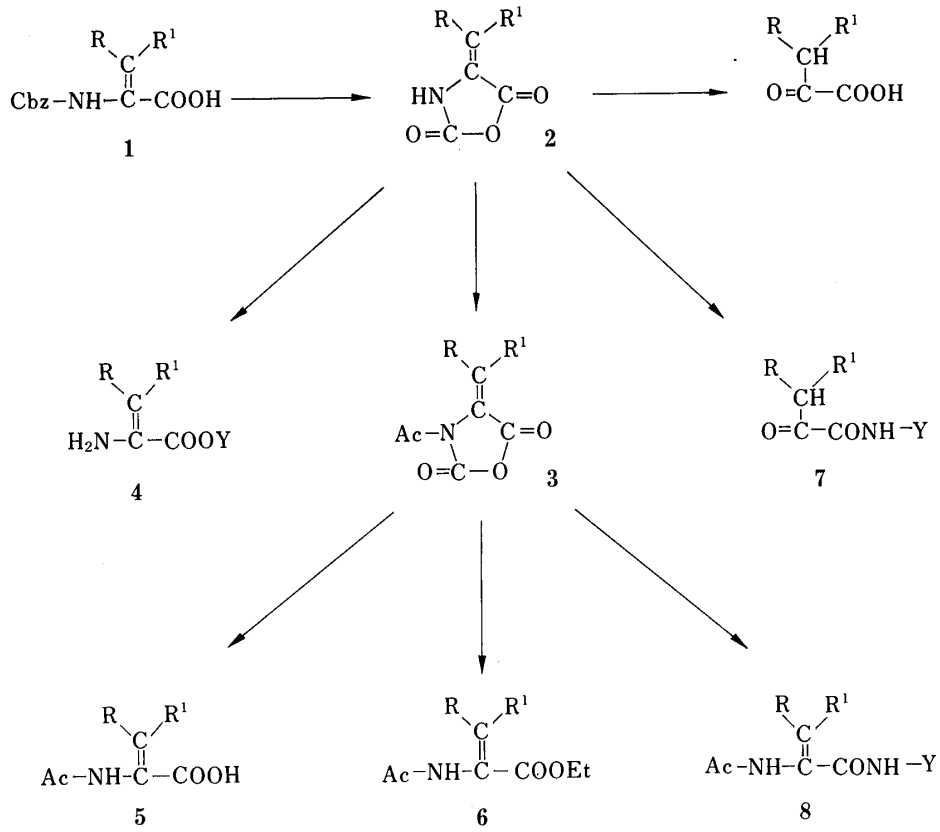
Method	Yield (%)	e.e. (%)	$[\alpha]_D^{25}$ (*c*=1.0, MeOH)
Azide	38	100	−36.5°
ΔNCA	95	99.0	−35.8°
WSCI-HOBT	66	97.4	−34.6°
MA	53	97.1	−34.4°
Azlactone	75	96.6	−34.0°
WSCI	43	96.4	−33.9°

a) mp 190.5—191.5 °C. *Anal.* Calcd for $C_{21}H_{22}N_2O_4$: C, 68.83; H, 6.05; N, 7.65. Found: C, 68.75; H, 6.09; N, 7.61. ^{1}H-NMR (DMSO-d_6) δ: 6.94 (1H, s, –CH=), 4.55 (1H, dt, *J*=7.5, 6.0 Hz), 8.25 (1H, d, –NH–), 9.34 (1H, br s, –NH–).

those mentioned above. As the alcohol used became bulkier (primary to secondary), the reactivity of **2** decreased gradually and the reaction with tertiary alcohol did not proceed at all (Table IV).

On the other hand, the analogous hydrolysis and alcoholysis of **3** were also achieved to give the expected (*Z*)-2-acetylamino-2-alkenoic acids (**5**) and esters (**6**),[27] respectively, in almost quantitative yields (Table V).

Furthermore, although attempts to cleave the ring of **2** with primary amines gave the undesired α-oxoalkanamides (**7**; Y=alkyl) alone in *ca.* 50% yield (Table VI), the similar



a: R = CH_3, R^1 = H, **b**: R = C_2H_5, R^1 = H, **c**: R = R^1 = CH_3,
d: R = *n*-C_3H_7, R^1 = H, **e**: R = iso-C_3H_7, R^1 = H, **f**: R = C_6H_5, R^1 = H

Chart 1

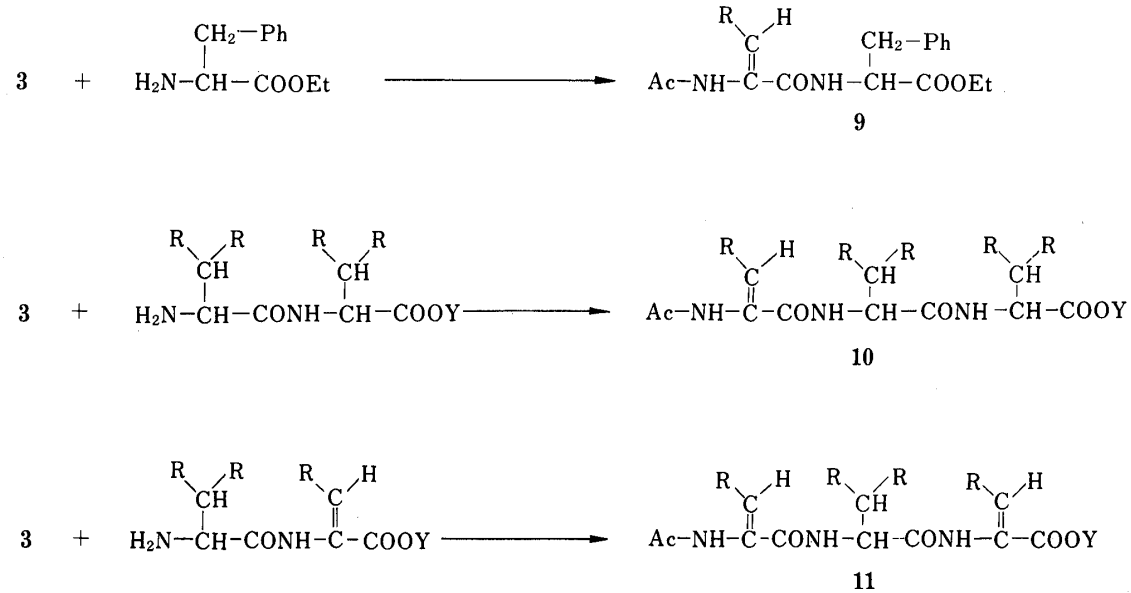


Chart 2

reaction of **3** with amines gave the expected (*Z*)-2-acetylamino-2-alkenamides (**8**) in fairly good yield. As a result of the facile amide formation, the formation of peptide bonding between ⊿NCA derivative and α-amino acids was expected. Accordingly, **2** and **3** were directly

TABLE IX. Ac–Δ^1-(*Z*, L, L)-Dehydrotripeptide Esters (**10**)

Compound	Yield (%)	mp[c] (°C)	Formula	Analysis (%) Calcd (Found)			^{1}H-NMR (δ, $CDCl_3$)			$[\alpha]_D^{25}$ (*c* = 1.0, MeOH)
				C	H	N	–CH=	–NHCHCO–		
							(*J*, Hz)			
⊿But–Leu–Val–OMe[a]	80	153—154	$C_{18}H_{31}N_3O_5$	58.51	8.46	11.37	5.95	4.50	4.50	−71.6°
				(58.33	8.39	11.49)	q	m	m	
							(7.0)			
⊿n-Leu–Phe–Val–OEt[b]	80	114—115	$C_{24}H_{35}N_3O_5$	64.69	7.92	9.43	6.22	4.83	4.36	−36.8°
				(64.61	8.00	9.40)	t	m	dd	
							(7.0)		(7.7, 5.5)	
⊿n-Leu–Val–Val–OMe	91	103—104	$C_{19}H_{33}N_3O_5$	59.51	8.67	10.96	6.34	4.56	4.56	−57.6°
				(59.62	8.75	10.79)	t	m	m	
							(7.0)			
⊿Leu–Phe–Val–OEt	85	85—87	$C_{24}H_{35}N_3O_5$	64.69	7.92	9.43	6.00	4.84	4.35	−39.5°
				(64.78	8.03	9.56)	d	m	m	
							(10.0)			
⊿Phe–Leu–Val–OMe	82	193—194	$C_{23}H_{31}N_3O_5$	64.31	7.28	9.78	6.63	4.40	4.40	+16.2°
				(64.28	7.33	9.82)	s	m	m	
⊿Phe–Phe–Val–OMe	95	95—97	$C_{26}H_{31}N_3O_5$	67.08	6.71	9.03	6.72	4.74	4.32	−63.3°
				(67.05	6.78	8.98)	s	dt	dd	
								(7.5, 7.0)	(7.7, 5.5)	
⊿Leu–Ala–Val–OMe	80	180—181	$C_{17}H_{29}N_3O_5$	57.44	8.22	11.82	6.10	4.54	4.36	−22.2°
				(57.22	8.57	11.51)	d	m	m	
							(10.0)			
⊿But–Phe–Val–OMe	95	185—186	$C_{21}H_{29}N_3O_5$	62.51	7.25	10.42	6.26	4.83	4.40	−38.3°
				(62.26	7.11	10.37)	q	dt	dd	
							(7.0)	(7.0, 7.0)	(7.7, 5.5)	
⊿Phe–Met–Ala–OMe	83	194—196	$C_{20}H_{27}N_3O_5S$	57.00	6.46	9.97	6.63	4.28	4.50	−18.4°
				(56.92	6.67	10.03)	s	(7.5, 7.5)	m	

a) ⊿But = dehydro α-aminobutanoic acid residue. *b*) ⊿n-Leu = dehydronorleucine residue.
c) Colorless needles from isopropyl ether–chloroform.

coupled with appropriate α-amino acid esters. Although the reaction of **2** with (L)-α-amino acid esters gave only *N*-alkylethanedioyl-α-amino acid esters (**7**), the similar reaction of **3** gave the desired dehydrodipeptide esters (**9**)[13,19] in almost quantitative yield (Tables VII and VIII).

The structural and configurational confirmation of the products (**9**) thus obtained were accomplished by comparison with the acetyl (Ac)–Δ^1-(*Z*, L)-dehydrodipeptide esters,[28] prepared independently by the coupling of Ac–(*Z*)-**5** with (L)-α-amino acid esters by an usual peptide synthetic method.

To compare the usefulness of the new method with that of conventional peptide synthetic methods (Table VIII) from the viewpoints of both yield and racemization, Ac–(*Z*)-dehydrophenylalanyl-(L)-phenylalanine methyl ester [**9f**; Ac–(*Z*)-ΔPhe–(L)-Phe–OMe] chosen for the two examinations was prepared by the following routes: by the reaction of Ac–*N*–carboxy α-dehydrophenylalanine anhydride (**3f**) with (L)-Phe–OMe by the ΔNCA method, and by the stepwise elongation of Ac–(*Z*)-ΔPhe–OH with (L)–Phe–OMe by well-known methods.

As Table VIII shows, the ΔNCA method was found to be slightly inferior to the azide method. In this case, the enantiomer excess (e.e., %) obtained by the ΔNCA method reached 99.0%, whereas the azide method gave 100%. However, the product yield of the new method was the highest, reaching 95% in a short reaction time. Furthermore, the procedure is very simple.

Consequently, the ΔNCA method developed by us should be very useful for the synthesis of various kinds of DHP derivatives.

Synthesis of Acetyl Dehydrotripeptide Esters

In order to examine whether or not the ΔNCA method can be actually applied to the synthesis of DHP, **3** was subjected to coupling with dipeptide esters or dehydrodipeptide esters as amine components. The fragment condensation of **3** with equimolar (L, L)-dipeptide ester hydrochlorides in THF in the presence of *N*-methylmorpholine (NMM) under cooling for 1 h gave a crude solid residue, which was purified on a silica gel column. The colorless needles thus obtained in *ca.* 86% yield were identified as the corresponding Ac–Δ^1-(*Z*, L, L)-dehydrotripeptide esters (**10**). Furthermore, similar coupling of **3** with Δ^2-(L, *Z*)-dehydrodipeptide esters[19] gave Ac–$\Delta^{1,3}$-(*Z*, L, L)-dehydrotripeptide esters (**11**) as colorless needles in *ca.* 66% yield. As expected, it was found that the two kinds of dehydrotripeptides could be easily synthesized in good yields.

TABLE X. Ac–$\Delta^{1,3}$-(*Z*, L, *Z*)-Dehydrotripeptide Ethyl Esters (**11**)

Compound	Yield (%)	mp[a] (°C)	Formula	Analysis (%) Calcd (Found)			^{1}H-NMR (δ, $CDCl_3$)			$[\alpha]_D^{25}$ (c=1.0)[b]
				C	H	N	–CH= (J, Hz)		–NHCHCO–	
ΔLeu–Phe–ΔLeu	60	109—110	$C_{25}H_{35}N_3O_5$	65.62 (65.41)	7.71 7.86	9.18 9.07)	6.45 d (10.0)	6.48 d (10.0)	4.78 dt	−45.9°
ΔPhe–Leu–ΔVal	55	198—200	$C_{24}H_{33}N_3O_5$	64.99 (64.52	7.50 7.10	9.47 9.38)	6.64 s		4.32 m	+28.3°
ΔLeu–Ala–ΔBut	71	Syrup	$C_{17}H_{27}N_3O_5$	57.77 (57.89	7.70 7.45	11.89 11.61)	6.16 d (10.0)	6.78 q (7.0)	4.61 m	−11.5°

a) Colorless needles from ethyl acetate–hexane.
b) Recorded in methanol.

The yields, physical constants, and spectral data of **10** and **11** are summarized in Tables IX and X. As Tables IX and X show, in the NMR spectra of **10** and **11**, the methine protons of α-amino acid residues resonate in the δ 4.84—4.28 region, at comparatively low magnetic field, and the olefin proton signal of the α-dehydroamino acid residue is shifted to the δ 6.97—5.95 region.

In conclusion, the *Δ*NCA method was found to be generally useful, and the acyl derivatives of *Δ*NCA represented efficient synthons for DHA and DHP.

Experimental

All the melting and boiling points are uncorrected. The IR spectra were recorded with a Hitachi EPI-G3 spectrometer. The NMR spectra were measured with a JNM-PS-100 spectrometer (Japan Electron Optics Laboratory Co., Ltd.), using tetramethylsilane as an internal standard. The specific rotations were measured in a 0.5 dm tube using a JASCO DIP-4 polarimeter (Japan Spectroscopic Co., Ltd.).

***N*-Carboxy α-Dehydroamino Acid Anhydrides (2)**——Thionyl chloride (100 mmol) was added to a solution of **1** (20 mmol) in acetyl chloride (15 ml) with stirring, and the mixture was stirred at room temperature for 4 h. The reaction solution was concentrated and the residual syrup was dissolved in chloroform (20 ml). Insoluble material was filtered off. After removal of the chloroform, residual colorless crystals were collected and recrystallized from cyclohexane to give colorless needles.

Acetylation of 2——Acetyl chloride (12 mmol) was added to a solution of **2** (10 mmol) in THF (5 ml) with stirring at room temperature. The resulting solution was adjusted to pH 6—7 by adding triethylamine with shaking under cooling. After standing at room temperature for 1 h, the reaction solution was concentrated under reduced pressure. The resulting colorless crystals were collected, and washed with water and ethyl ether to give the corresponding pure *N*-acetyl-*N*-carboxy α-dehydroamino acid anhydride (**3**).

Treatment of 2 with Base——A solution of **2** (10 mmol) in THF (10 ml) was treated with 5% NaOH (5 ml) in portions with stirring at room temperature for 30 min. After concentration of the reaction solution, the residual oil was adjusted to pH 2 with 1 M HCl and the resulting solution was extracted with ethyl acetate. The extract was washed with saturated aqueous NaCl solution and then dried over anhydrous Na_2SO_4. After removal of the solvent, the residual oil obtained was distilled under reduced pressure to give a colorless oil, which was identified as the corresponding α-oxocarboxylic acid. Yield *ca.* 95%.

Alcoholysis of 2——A small amount of triethylamine was added to a solution of **2** (20 ml) in an appropriate dry alcohol (10 ml) with stirring at room temperature for 1 h. The reaction solution was concentrated under reduced pressure and the residual oil was distilled *in vacuo* to give a colorless oil, which was identified as the corresponding alkyl 2-amino-2-alkenoate (**4**).

Treatment of 4 with HCl——A solution of **4** (10 mmol) in methanol (7 ml) was treated with 1 M HCl (3 ml) at room temperature for 30 min. After removal of the solvent, the residual oil was distilled *in vacuo* to give the corresponding methyl α-oxoalkanoate as a colorless oil in *ca.* 95% yeild.

Preparation of α-Oxoalkanamides and *N*-Alkylethanedioyl-α-amino Acid Ester (7)——An amine or α-amino acid ester was added to a solution of **2** (10 mmol) in THF (7 ml) with stirring at room temperature for 30 min. After removal of the solvent, the residual syrup was purified on a silica gel column using a mixture of benzene and ethyl acetate (4 : 1, v/v) as the eluent. The eluate was concentrated under reduced pressure to give a colorless syrup or crystals.

Preparation of 2-Acetylamino-2-alkenoic Acids (5), Ethyl 2-Acetylamino-2-alkenoates (6), and 2-Acetylamino-2-alkenamides (8)——Acetyl chloride (12 mmol) was added to a solution of **2** (10 mmol) in THF (5 ml) with stirring at room temperature. Water (5 ml) was added to the resulting solution and then the reaction solution was made basic (pH 8—9) with triethylamine and left for 40 min. The mixture was concentrated, and the residue was acidified with 1 M HCl to give colorless crystals. Recrystallization from chloroform gave colorless needles (**5**).

In a similar manner, the reaction mixture of **3** (10 mmol) with ethanol (5 ml) was worked up to give a crude syrup, which was subsequently purified on a silica gel column using a mixture of benzene and ethyl acetate (7 : 1, v/v) as the eluent. The eluate was concentrated under reduced pressure and then the residue was distilled *in vacuo* to give a colorless syrup, which soon crystallized. Recrystallization from isopropyl ether gave colorless needles (**6**).

Furthermore, the reaction mixture of **2** (10 mmol) and acetyl chloride (12 mmol) in THF (5 ml) with a primary amine (11 mmol) was worked up to give colorless crystals, which were recrystallized from ethanol to give colorless needles (**8**). *N*-Acetyl-dehydrophenylalaninanilide, yield 95%, mp 184—185 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.10 (s, –CH=), 9.42 (br s, –NH–), 8.56 (br t, –NH–, J=6.0 Hz). *Anal.* Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.40; H, 6.19; N, 9.55. *N*-Acetyl-dehydrophenylalanine cyclohexylamide, yield 96%, mp 215—216 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.88 (s, –CH=), 9.28 (br s, –NH–), 7.69 (br d, –NH–, J=7.5 Hz). *Anal.* Calcd for $C_{17}H_{22}N_2O_2$: C, 71.31; H, 7.74; N, 9.78. Found: C, 71.25; H, 7.69; N, 9.82.

Preparation of Ac–Δ^1-(Z, L)-Dehydrodipeptide Ester——A solution of an α-amino acid ester hydrochloride (11 mmol) and triethylamine (12 mmol) in THF (10 ml) was added with stirring to a solution of **2** (10 mmol), acetyl chloride (12 mmol) and triethylamine (12 mmol) in THF (5 ml) at room temperature during 40 min. After removal of the salt that separated out, the filtrate was concentrated and the residual syrup was dissolved in ethyl acetate (50 ml). This solution was washed successively with saturated aqueous sodium hydrogen carbonate solution, 3 M HCl and water, then dried over anhydrous Na_2SO_4. After removal of the solvent, the residual crystalline product was recrystallized from CCl_4–ethyl acetate to give colorless needles.

Preparation of Ac–Δ^1-(Z, L, L)-Dehydrotripeptide Esters and Ac–$\Delta^{1,3}$-(Z, L, Z)-Dehydrotripeptide Esters——A dipeptide ester or dehydrodipeptide ester hydrochloride (10 mmol) was dissolved in THF (10 ml), and was added *N*-methylmorpholine (11 mmol), with stirring, under cooling. After 30 min, **3** (10 mmol) was added to the resulting solution with stirring at room temperature for 1 h. The whole was evaporated to dryness and chloroform (60 ml) was added to the residue. The resulting solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$ and concentrated. The residual crystalline product was purified on a silica gel column using a mixture of chloroform and acetone as the eluent. The eluate was concentrated under reduced pressure to give colorless crystals, which were recrystallized from isopropyl ether–chloroform (3 : 1, v/v) or from ethyl acetate–hexane (5 : 1, v/v) to give colorless needles.

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