Dehydrooligopeptides. II. The Synthesis of Dehydrodehydrodipeptides by Direct Coupling and Base-catalyzed β-Elimination[1]

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(Received June 19, 1980)

The direct coupling between N-protected α-dehydroamino acid (**1**) and N-free α-dehydroamino acid ester (**2**) by the acid-chloride method was carried out to give several dehydrodehydrodipeptides (**7**). Furthermore, the two kinds of dehydrodipeptides with a hydroxyl group, obtained by the coupling of **1** with a serine or threonine ester, and that of N-protected serine or threonine with **2**, followed by mesylation and subsequent base-catalyzed β-elimination gave a number of **7** substances in good yields. The configurational structures of **7** obtained by both direct condensation and elimination were found to have (*Z,Z*)-geometry.

Much attention has been focused on the correlation between the structure and the bioactivity of dehydrooligopeptides containing one or more α-dehydroamino acid (DHA or ⊿AA)[2] residues.[3-7] Recently, antibiotic berninamycin A, a cyclodehydrodecapeptide with two dehydrodehydrodipeptide (⊿DHP) sequences and seven DHA moieties, has been isolated from a culture of *Streptomyces bernensis*, and the primary structure confirmed, by Liesch and Rinehart.[8] However, concerning the synthesis of ⊿DHP, few reports have been published on its preparation by means of the base-catalyzed β-elimination or by the direct coupling between two different DHA's, these being the indirect and restricted preparative methods from unsaturated azlactone.[9,10]

In a previous communication,[11] we briefly reported on the synthesis of the N-protected ⊿DHP ester by the coupling of benzyloxycarbonyl (Cbz)–DHA (**1**) with the N-free DHA ester (**2**) by the acid-chloride method. Here, we wish to report on a method of synthesis featuring the base-catalyzed β-elimination to dehydrodipeptide with a leaving group; we wish also to describe the direct method in detail.

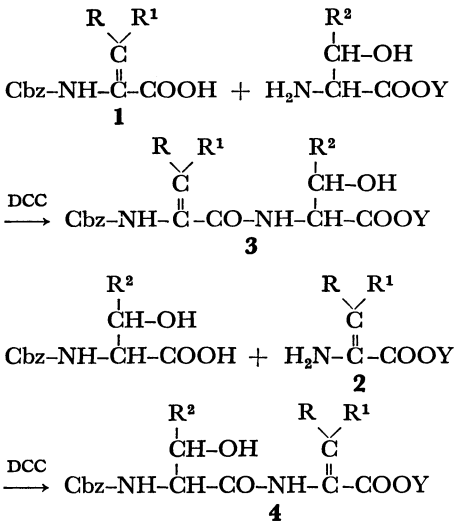
Results and Discussion

Coupling of (Z)-DHA with β-Hydroxy α-Amino Acid. In order to prepare a dehydrodipeptide containing a Ser or Thr residue at the C- or N-terminus according to the method previously reported by us,[1,12] first, the coupling of **1** with α-amino acid ester was performed. The (*Z*)-**1** compound, as a carboxyl component, readily reacted with a racemic Ser or Thr ester by the usual peptide synthetic method [mixed anhydride (MA), dicyclohexylcarbodiimide (DCC), acid chloride, and azide method] to give Cbz–(*Z*)-α-dehydroaminoacyl–Ser and –Thr esters (**3**) respectively, as a colorless syrup or crystals, in *ca.* 70% yields. Therefore, although the yield was not significantly different, the preparation of **3** by the DCC method was found to be superior to that by the other methods. In Table 1, the yield of **3** by the DCC method is listed.

On the other hand, N-protected Ser or Thr was also coupled with (*Z*)-**2** as an amine component by the similar DCC method to give Cbz–Ser– and –Thr–(*Z*)-α-dehydroamino acid esters (**4**) respectively as colorless crystals in *ca.* a 34% yield. However, because of the weak basicity of the amino group in the amine component, the yield was lower than that of **3**, and the coupling of the α-dehydrophenylalanine ester with Cbz–Ser or –Thr was found to proceed to only a very small degree.

In the IR spectral data, the characteristic differences between **3** and **4** could not be recognized. The absorption bands of the hydroxyl and NH (3475—3175 cm^{-1}), ester carbonyl (1760—1720 cm^{-1}), secondary amide (1665—1625 cm^{-1}), and carbon-carbon double bond (1670—1620 cm^{-1}) functions are consistent with the assignment of the dehydrodipeptide structure.

The chemical shifts and the coupling constants of **3** and **4** were assigned as is shown in Tables 1 and 2. In the NMR spectrum of **3**, the signals at δ 4.56—4.76 as double doublets or double triplets, at δ 7.07—7.53 as doublets, and at δ 2.84—3.80 as broad singlets are attributable to methine, NH, and hydroxyl protons of the α-AA residue, respectively and the signals at δ 5.34—6.08, 6.37—7.10, and 6.76—7.52 regions as singlets, to vinyl, olefinic, and NH protons of the ⊿AA



DHA and DHA residues = ⊿Ala, ⊿But, ⊿norVal, ⊿Val, ⊿norLeu, ⊿Leu, and ⊿Phe; R^2 = H and CH_3; Y = CH_3 and C_2H_5.

Scheme 1.

residue respectively. On the other hand, in the case of **4**, the corresponding signals appeared at δ 4.30—4.35 (methine) as multiplets, at δ 6.01—6.19 (NH) as doublets, and at δ 3.40—3.88 (hydroxyl) as broad singlets of the α-AA residue, and at δ 6.55—6.81 and at δ 7.96—8.15 (vinyl and olefinic protons) regions as broad singlets of the ⊿AA residue. As a result, it was found that the IR and NMR spectral patterns of **3** were remarkably similar to those of **4**.

According to the method confirmed previously,[1] the configurations of **3** and **4** could be readily determined to have (*Z*)-geometry.

The yields, physical constants, and NMR spectral data of **3** and **4** are summarized in Tables 1 and 2.

Preparation of Dehydro-dehydrodipeptides. In order to carry out the following base-catalyzed β-elimination easily, the mesylation of the hydroxyl group in **3** and **4** was performed. We followed a procedure reported

Table 1. Cbz-(*Z*)-⊿AA-Ser- and -Thr-OY (**3**)

Cbz-⊿AA-AA(OH)-OY	Yield[a] %	Mp/°C	Formula	Found (Calcd), % C	H	N	NMR spectrum, δ in $CDCl_3$ Olefinic-proton(J_{Hz})	α-Proton[h] (J_{Hz})	NH	OH
Cbz-⊿Ala-Ser-OMe	67	syrup[b]								
Cbz-⊿But-Ser-OMe	64	syrup	$C_{16}H_{20}N_2O_6$	57.45 (57.13	6.12 5.99	8.15 8.33)	6.52q, (7.5)	4.62dt, (3.0, 7.0)	7.04s, 7.26d	3.72
Cbz-⊿norVal-Ser-OMe	70	syrup	$C_{17}H_{22}N_2O_6$	58.49 (58.27	6.45 6.33	8.03 8.00)	6.43t, (7.3)	4.62m,	7.01s, 7.26d	3.80
Cbz-⊿norLeu-Ser-OMe	65	syrup	$C_{18}H_{24}N_2O_6$	59.51 (59.33	6.82 6.64	7.68 7.69)	6.45t, (7.3)	4.66m,	6.82s, 7.20d	3.20
Cbz-⊿Leu-Ser-OMe	86	100—101[c]	$C_{18}H_{24}N_2O_6$	59.42 (59.33	6.58 6.64	7.71 7.69)	6.41d, (10.0)	4.66dt, (3.0, 7.0)	7.07s, 7.40d	3.69
Cbz-⊿Phe-Ser-OMe	65	107—108[d]	$C_{21}H_{22}N_2O_6$	63.23 (63.31	5.56 5.57	7.11 7.03)	7.10s,	4.67dt, (3.0, 8.0)	6.76s, 7.24d	3.26
Cbz-⊿Ala-Thr-OMe	45	syrup	$C_{16}H_{20}N_2O_6$	57.51 (57.13	6.23 5.99	8.19 8.33)	5.34t, 6.08d	4.56dd, (2.5, 9.0)	7.07s, 7.53d	2.94
Cbz-⊿But-Thr-OMe	67	62—64[e]	$C_{17}H_{22}N_2O_6$	58.21 (58.27	6.45 6.33	7.91 8.00)	6.56q, (7.3)	4.56dd, (3.0, 8.8)	7.00s, 7.07d	3.34
Cbz-⊿norVal-Thr-OEt	61	65—66[e]	$C_{19}H_{26}N_2O_6$	60.12 (60.30	7.02 6.93	7.44 7.40)	6.46t, (7.2)	4.57dd, (3.0, 8.8)	7.00s, 7.09d	3.25
Cbz-⊿norLeu-Thr-OEt	76	54—56[f]	$C_{20}H_{28}N_2O_6$	61.07 (61.21	7.28 7.19	7.19 7.14)	6.51t, (7.5)	4.58dd, (3.0, 8.8)	6.86s, 7.09d	3.20
Cbz-⊿Leu-Thr-OMe	77	58—60[f]	$C_{19}H_{26}N_2O_6$	60.51 (60.30	7.11 6.93	7.32 7.40)	6.37d, (10.8)	4.61dd, (2.8, 9.0)	6.79s, 7.09d	2.84
Cbz-⊿Phe-Thr-OEt	84	110—111[f]	$C_{23}H_{26}N_2O_6$	64.56 (64.77	6.32 6.15	6.86 6.57)	7.40—7.55[g],	4.76dd, (3.0, 9.0)	7.14s, 7.40—7.55[g]	3.27

a) Yield by the DCC method. b) Ref. 1. c) Colorless prisms from benzene. d) Colorless prisms from CCl_4. e) Colorless needles from propyl ether. f) Colorless needles from CCl_4. g) Overlapped with phenyl protons. h) α-Proton of α-AA residue.

Table 2. Cbz-Ser- and Thr-(*Z*)-⊿AA-OEt (**4**)

Cbz-AA(OH)-⊿AA-OEt	Yield[a] %	Mp/°C[b]	Formula	Found (Calcd), % C	H	N	NMR spectrum, δ in $CDCl_3$ Olefinic-proton(J_{Hz})	α-Proton[c]	NH	OH
Cbz-Ser-⊿Val-OEt	51	155—157	$C_{18}H_{24}N_2O_6$	59.39 (59.33	6.58 6.64	7.77 7.69)	—	4.30m,	6.10d, 7.96bs	3.40
Cbz-Ser-⊿norLeu-OEt	26	64—66	$C_{19}H_{26}N_2O_6$	60.25 (60.30	7.05 6.93	7.39 7.40)	6.72t, (7.0)	4.35m,	6.19d, 8.04bs	3.75
Cbz-Ser-⊿Leu-OEt	33	107—108	$C_{19}H_{26}N_2O_6$	60.51 (60.30	7.23 6.93	7.34 7.40)	6.55d, (10.0)	4.35m,	6.10d, 7.96bs	3.75
Cbz-Thr-⊿But-OEt	21	88—90	$C_{18}H_{24}N_2O_6$	59.32 (59.33	6.79 6.64	7.79 7.69)	6.81q, (7.0)	4.30m,	6.16d, 8.15bs	3.70
Cbz-Thr-⊿norVal-OEt	25	99—100	$C_{19}H_{26}N_2O_6$	60.51 (60.30	6.87 6.93	7.29 7.40)	6.68t, (7.0)	4.30m,	6.06d, 8.00bs	3.80
Cbz-Thr-⊿Val-OEt	50	159—161	$C_{19}H_{26}N_2O_6$	60.33 (60.30	7.11 6.93	7.23 7.40)	—	4.35m,	6.01d, 7.96bs	3.84
Cbz-Thr-⊿norLeu-OEt	28	95—97	$C_{20}H_{28}N_2O_6$	60.98 (61.21	7.32 7.19	7.19 7.14)	6.73t, (7.0)	4.30m,	6.08d, 8.10bs	3.88
Cbz-Thr-⊿Leu-OEt	38	100—101	$C_{20}H_{28}N_2O_6$	61.23 (61.21	6.89 7.19	7.22 7.14)	6.55d, (10.0)	4.30m,	6.06d, 7.96bs	3.88

a) Yield by the DCC method. b) Colorless fibrous from CCl_4. c) α-Proton of α-AA residue.

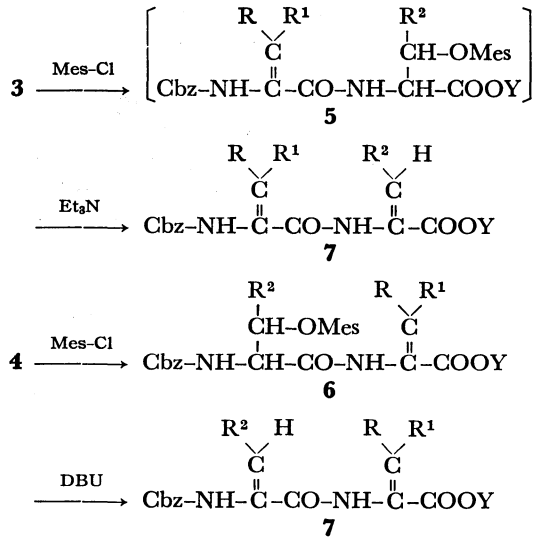
previously,[13] treating a solution of **3** and methanesulfonyl (mesyl) chloride in CH_2Cl_2 with excess triethylamine but, unexpectedly, ⊿DHP (**7**) as a colorless syrup or crystals was obtained directly in *ca.* a 74% yield, without any yield of the corresponding mesyloxy intermediates (**5**).

On the other hand, a similar treatment of **4** with mesyl chloride gave the corresponding stable mesyloxy derivative (**6**) as colorless crystals in *ca.* an 80% yield. The subsequent elimination reaction of the **6** isolated purely was attempted in the presence of triethylamine, but the reaction did not proceed at all. In consequence, the treatment of a solution of **6** in THF in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), a stronger base than triethylamine, was carried out successfully, and the desired **7** was obtained in *ca.* a 65% yield.

In the spectrum of **6**, the disappearance of the hydroxyl absorption and in the 3260—3300 cm^{-1} region and the appearance of characteristic strong sulfonyl function bands in the 1345—1360 and 1160—1190 cm^{-1} regions indicate unambiguously the formation of the mesyloxy derivative. Moreover, the IR spectrum of **7** showed bands in the 3280—3400 and 3200—3300 cm^{-1} regions due to the NH group, bands in the 1680—1728 and 1500—1540, and 1620—1650 and 1490—1500 cm^{-1} regions due to two secondary amide functions, and a weak band in the 1620—1670 cm^{-1} region due to the carbon-carbon double bond.

On the other hand, from the NMR spectral data of **7** listed in Tables 4 and 5, it was found that the signals in the δ 4.46—7.74 and 7.61—8.61 regions as broad singlets due to two NH protons, and the characteristic signals at δ 5.26—6.76 and at δ 6.30—7.24 due to vinyl and olefinic protons of the ⊿AA–⊿AA moeties respectively, are consistent with the assignment of the dehydrodehydrodipeptide structure. In consequence, it can be said that the appearance of two olefinic proton signals indicates unambiguously the formation of **7**.

As a result, it was found that the IR and NMR spectral patterns of **7** derived from **3** *via* **5** were in fairly good agreement with those of **7** from **4** *via* **6**.



DHA residues = ⊿Ala, ⊿But, ⊿norVal, ⊿Val, ⊿norLeu, ⊿Leu, and ⊿Phe; Y = CH_3 and C_2H_5

Scheme 2.

The yields, physical constants, and NMR spectral data of **6** and **7** are summarized in Tables 3, 4, and 5.

The geometric structure of **7** could be readily determined to have (*Z*,*Z*)-geometry, since the chemical shifts and the spectral patterns of the individual ⊿AA residue in **7** were quite similar to the starting, (*Z*)-configurational **1** and **2**.[13,14] The above determination was further confirmed independently by the following direct coupling between two different (*Z*)-DHA's.[11]

The equimolar coupling of (*Z*)-**1** as a carboxyl component with (*Z*)-**2** as an amine component by the usual acid-chloride method gave the desired ⊿DHP (**7**) in *ca.* a 50% yield; its structure was completely in agreement with that of **7** derived from **3** and **4** respectively. Therefore, it was further ascertained that the (*Z*)-geometry of the DHA and DHA residues was maintained during the peptide-formation reaction and the base-catalyzed β-elimination reaction.

TABLE 3. Cbz–Ser(Mes)– AND Thr(Mes)–(*Z*)-⊿AA–OEt (**6**)

Cbz–AA(Mes)–⊿AA–OEt	Yield %	Mp/°C[a]	Formula	Found (Calcd), % C	H	N	NMR spectrum, δ in $CDCl_3$ Olefinic-proton(J_{Hz})	α-Proton[b] (J_{Hz})	NH
Cbz–Ser(Mes)–Val–OEt	80	135—136	$C_{19}H_{26}N_2O_8S$	51.38 (51.58	6.12 5.92	6.38 6.33)	—	4.60m,	6.12d 7.90bs
Cbz–Ser(Mes)–⊿Leu–OEt	78	107—108	$C_{20}H_{28}N_2O_8S$	52.39 (52.62	6.17 6.19	6.23 6.14)	6.58d, (10.0)	4.60m,	6.00d 7.70bs
Cbz–Thr(Mes)–⊿But–OEt	75	131—132	$C_{19}H_{26}N_2O_8S$	51.45 (51.58	6.01 5.92	6.39 6.33)	6.88q, (7.0)	4.60dd, (3.5, 8.0)	6.00d 7.86bs
Cbz–Thr(Mes)–⊿norVal–OEt	85	130—131	$C_{20}H_{28}N_2O_8S$	52.71 (52.62	6.08 6.19	6.19 6.14)	6.74t, (7.0)	4.60dd, (3.5, 8.3)	6.04d 7.86bs
Cbz–Thr(Mes)–⊿Val–OEt	88	159—160	$C_{20}H_{28}N_2O_8S$	52.66 (52.62	6.38 6.19	6.24 6.14)	—	4.52dd, (3.5, 8.3)	5.86d 7.60bs
Cbz–Thr(Mes)–⊿norLeu–OEt	80	132—133	$C_{21}H_{30}N_2O_8S$	53.88 (53.61	6.39 6.43	5.99 5.95)	6.76t, (7.0)	4.60dd, (3.5, 8.3)	6.00d 7.86bs
Cbz–Thr(Mes)–⊿Leu–OEt	76	127—130	$C_{21}H_{30}N_2O_8S$	53.66 (53.61	6.51 6.43	6.12 5.95)	6.58d, (10.0)	4.54dd, (3.5, 8.3)	5.88d 7.61bs

a) Colorless needles from CCl_4. b) α-Proton of α-AA residue.

Table 4. Cbz-(*Z*)-⊿AA-(*Z*)-⊿AA-OY (**7**) from **3**

Cbz-⊿AA-⊿AA-OY	Yield %	Mp/°C[a]	Formula	Found (Calcd), % C	H	N	NMR spectrum, δ in $CDCl_3$ CH_2= Me-CH=(J_{Hz})	R-CH= (J_{Hz})	NH
Cbz-⊿Ala-⊿Ala-OMe	62	syrup	$C_{15}H_{16}N_2O_5$	59.41 (59.20)	5.23 (5.30)	9.13 (9.21)	5.26dd, 6.18d	5.94d[b] 6.58s	7.51bs 8.43bs
Cbz-⊿But-⊿Ala-OMe	63	61—62	$C_{16}H_{18}N_2O_5$	60.33 (60.37)	5.58 (5.70)	8.97 (8.80)	5.36t, 6.22d	6.88q[c] (7.4)	7.54bs 7.67bs
Cbz-⊿norVal-⊿Ala-OMe	62	87—88	$C_{17}H_{20}N_2O_5$	61.34 (61.43)	5.89 (6.07)	8.44 (8.43)	5.84d, 6.60s	6.43t, (7.2)	6.60bs 8.40bs
Cbz-⊿norLeu-⊿Ala-OMe	76	100—101	$C_{18}H_{22}N_2O_5$	62.42 (62.41)	6.56 (6.40)	7.89 (8.09)	5.86d, 6.60s	6.47t, (7.2)	6.63bs 8.60bs
Cbz-⊿Leu-⊿Ala-OMe	91	86—87	$C_{18}H_{22}N_2O_5$	62.56 (62.41)	6.32 (6.40)	7.97 (8.09)	6.01d, 6.76s	6.46d, (10.2)	6.85bs 8.61bs
Cbz-⊿Phe-⊿Ala-OMe	86	115—116	$C_{21}H_{20}N_2O_5$	66.23 (66.30)	5.12 (5.30)	7.25 (7.37)	5.95d, 6.70s	7.22s, —	6.67bs 8.61bs
Cbz-⊿Ala-⊿But-OMe	65	syrup	$C_{16}H_{18}N_2O_5$	60.54 (60.37)	5.81 (5.70)	8.97 (8.80)	6.68q, (7.2)	5.36t,[b] 6.22d	7.54bs 7.67bs
Cbz-⊿But-⊿But-OMe	71	syrup	$C_{17}H_{20}N_2O_5$	61.23 (61.43)	5.98 (6.07)	8.55 (8.43)	6.77q, (7.2)	6.55q,[c] (7.2)	6.96bs 7.78bs
Cbz-⊿norVal-⊿But-OEt	76	syrup	$C_{19}H_{24}N_2O_5$	63.11 (63.32)	6.79 (6.71)	7.59 (7.77)	6.77q, (7.2)	6.47t, (7.5)	6.93bs 7.78bs
Cbz-⊿norLeu-⊿But-OEt	69	syrup	$C_{20}H_{26}N_2O_5$	63.89 (64.15)	6.89 (7.00)	7.57 (7.48)	6.80q, (7.2)	6.52t, (7.2)	6.76bs 7.73bs
Cbz-⊿Leu-⊿But-OMe	86	89—90	$C_{20}H_{26}N_2O_5$	63.53 (64.15)	6.68 (7.00)	7.90 (7.48)	6.77q, (7.2)	6.30d, (10.2)	6.46bs 7.61bs
Cbz-⊿Phe-⊿But-OEt	79	79—81	$C_{23}H_{24}N_2O_5$	67.60 (67.63)	6.08 (5.92)	7.11 (6.86)	6.82q, (7.2)	7.24s, —	6.72bs 7.85bs

a) Colorless needles from CCl_4. b) Vinyl protons. c) 1-Propenyl protons.

Table 5. Cbz-(*Z*)-⊿But-(*Z*)-⊿AA-OEt (**7**) from **6**

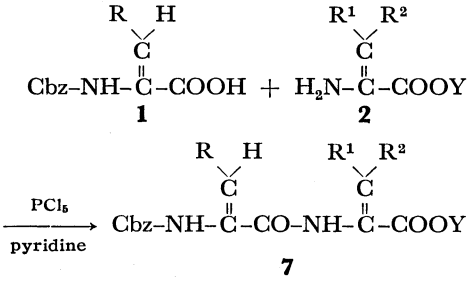
Cbz-⊿AA-⊿AA-OEt	Yield %	Mp/°C[a]	Formula	Found (Calcd), % C	H	N	NMR spectrum, δ in $CDCl_3$ CH_2= Me-CH(J_{Hz})	R-CH= (J_{Hz})	NH (bs)[b]
Cbz-⊿But-⊿But-OEt	61	syrup	$C_{18}H_{22}N_2O_5$	62.45 (62.41)	6.38 (6.40)	7.97 (8.09)	6.57q, (7.2)	6.77q, (7.2)	6.96 7.78
Cbz-⊿But-⊿norVal-OEt	65	syrup	$C_{19}H_{24}N_2O_5$	63.45 (63.32)	6.88 (6.71)	7.70 (7.77)	6.70q, (7.2)	6.77t, (7.5)	7.30 8.06
Cbz-⊿But-⊿Val-OEt	67	69—70	$C_{19}H_{24}N_2O_5$	63.22 (63.32)	6.89 (6.71)	7.98 (7.77)	6.56q, (7.2)	—	6.95 7.71
Cbz-⊿But-⊿norLeu-OEt	65	45—46	$C_{20}H_{26}N_2O_5$	63.98 (64.15)	6.09 (7.00)	7.48 (7.48)	6.60q, (7.2)	6.71t, (7.5)	6.90 7.75
Cbz-⊿But-⊿Leu-OEt	66	67—68	$C_{20}H_{26}N_2O_5$	64.33 (64.15)	6.89 (7.00)	7.37 (7.48)	6.70q, (7.5)	6.57d, (7.2)	6.96 7.78

a) Colorless needles from cyclohexane. b) Broad singlet.

Table 6. Cbz-(*Z*)-⊿AA-(*Z*)-⊿AA-OEt (**7**) from **1** and **2**

Cbz-⊿AA-⊿AA-OEt	Yield/%	Mp/°C
Cbz-⊿But-⊿But-OEt[a]	40	syrup
Cbz-⊿But-⊿norVal-OEt[a,b]	41	syrup
Cbz-⊿But-⊿Val-OEt[a]	68	69—70
Cbz-⊿Leu-⊿norVal-OEt[b]	43	syrup[c]
Cbz-⊿norVal-⊿norLeu-OEt[b]	51	syrup[d]
Cbz-⊿But-⊿Leu-OEt[a,b]	65	67—68

a) See Table 5. b) Ref. 11. c) Found: C, 65.15; H, 7.40; N, 7.09%. Calcd for $C_{21}H_{28}N_2O_5$: C, 64.93; H, 7.27; N, 7.21%. d) Found: C, 65.33; H, 7.41; N, 7.10%. Calcd for $C_{21}H_{28}N_2O_5$: C, 64.93; H, 7.27; N, 7.21%.



DHA residues = ⊿But, ⊿norVal, ⊿norLeu, ⊿Val, and ⊿Leu; Y = CH_3 and C_2H_5

Scheme 3.

The yields, physical constants, and NMR spectral data of **7** obtained by the direct coupling are summarized in Table 6.

Experimental

All the melting 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 Laboratory Co., Ltd.), using tetramethylsilane as the internal standard.

Starting Materials. The starting (*Z*)-**1** and (*Z*)-**2** were prepared by the methods reported previously.[1,11,12]

Preparation of **3**. Into a solution of (*Z*)-**1** (10 mmol) and the Ser or Thr ester (10 mmol) in DMF (10 ml), we stirred DCC (11 mmol) under cooling. After stirring at room temperature for 12 h, the dicyclohexylurea deposited was filtered off and washed well with ethyl acetate. The filtrate was poured into water (70 ml), and the aqueous solution was extracted twice with ethyl acetate (60 ml). The combined extracts were successively washed with 2% aqueous HCl, water, saturated aqueous $NaHCO_3$, and water, and finally dried over anhydrous Na_2CO_3. The subsequent evaporation of the ethyl acetate under reduced pressure gave crude crystals or a syrup, subsequently purified on a silica gel column using benzene–ethyl acetate (4 : 1 v/v) to give **3**. See Table 1.

Preparation of **4**. Into a solution of (*Z*)-**2** (10 mmol) and Cbz–Ser or –Thr (10 mmol) in CH_2Cl_2 (10 ml), we vigorously stirred DCC (11 mmol), portion by portion, below 0 °C. After stirring at room temperature for 20 h, the reaction solution was worked-up exactly according to the above treatment procedure to give **4**. See Table 2.

Preparation of **6**. Into a solution of **4** (4 mmol) and mesyl chloride (5 mmol) in CH_2Cl_2 (20 ml) we stirred triethylamine (12 mmol), drop by drop, at 0 °C for 1 h, and then the stirring was continued at room temperature for 2 more h. The reaction solution was then poured into CH_2Cl_2 (50 ml), and the resulting solution was washed once with chilled 1 M HCl (50 ml) and twice with water and finally dried over anhydrous $MgSO_4$. The subsequent evaporation of the solvent gave a crude syrupy residue, which was crystallized with CCl_4 to give **6** as colorless needles. See Table 3.

Preparation of **7**. *From Ser Derivatives (3)*: Into a solution of **3** (4 mmol) and mesyl chloride (5 mmol) in CH_2Cl_2 (20 ml) we stirred triethylamine (12 mmol), drop by drop, at 0—2 °C for 0.5 h, and then the stirring was continued at room temperature for 1.5 more h. Dichloromethane (40 ml) was further added to the reaction solution, and the resulting solution was washed with chilled 1 M HCl till the washing solution reached pH 4 and twice with water, and finally dried over $MgSO_4$. The subsequent evaporation of the CH_2Cl_2 gave **7** as a colorless syrup or crystals. See Table 4.

From Thr Derivatives (3): Similarly, the treatment of **3** (4 mmol) with mesyl chloride (5 mmol) in the presence of triethylamine (20 mmol) was worked-up for 1 h; it was then stirred at room temperature for 12 h to give a crude syrupy substance, which was purified on a silica gel column using a mixture of benzene–ethyl acetate (3 : 1 v/v) as the eluent to give **7** as a colorless syrup or crystals. See Table 4.

From **6**: Into a solution of **6** (4 mmol) in THF (20 ml) we stirred DBU (4.5 mmol) under cooling. After stirring at the same temperature for 2 h, the evaporation of THF gave a crude reaction product; this product was dissolved in ethyl acetate (20 ml) and chilled 1 M HCl (40 ml), and then the residual solution was well shaked. The organic layer thus separated was washed with water and dried over anhydrous Na_2SO_4. After the removal of the ethyl acetate under reduced pressure, the residual syrup thus obtained was chromatographed on a silica-gel column, using a mixture of benzene–ethyl acetate (4 : 1 v/v) as the eluent, to give **7** from the second fraction. See Table 5.

From **1** *and* **2**: Into a solution of **1** (10 mmol) in dry THF (20 ml) we successively stirred PCl_5 (11 mmol), portion by portion, at 0 °C and then, after 20 min, a chilled solution of **2** (10 mmol) in dry pyridine (15 ml), drop by drop, all below 5 °C. The reaction mixture was continuously stirred at room temperature for 3 more h, and then the resulting solution was poured into ice water (100 ml). The resulting aqueous solution was extracted three times with ethyl acetate (180 ml). The extracts were washed once with 3 M HCl (50 ml) and three times with water (100 ml), and then dried over anhydrous Na_2SO_4. After the evaporation of the ethyl acetate under reduced pressure, the residual syrup thus obtained was purified on a silica-gel column, using a mixture of benzene–ethyl acetate (8 : 1 v/v) as the eluent, to give **7** as a pure colorless syrup or crystals. See Table 6.

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