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Dehydrooligopeptides. VIII. Convenient Syntheses of Various Dehydrotyrosine Derivatives Protected with Useful N, O-Protecting Groups via *N*-Carboxy Dehydrotyrosine Anhydrides[1)]

Chung-gi SHIN,* Yasuchika YONEZAWA, Takumi OBARA, and Hiroaki NISHIO
Laboratory of Organic Chemistry, Faculty of Technology, Kanagawa University, Rokkakubashi, Kanagawa-ku, Yokohama 221
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Various *N*-benzyloxycarbonyl (Cbz) O-protected dehydrotyrosine (*Δ*Tyr) esters have been successfully synthesized mainly via two routes, in which reactions of (diethoxyphosphinyl)glycine ester with *p*-substituted benzaldehyde were included. Subsequent hydrolyses of the esters under various alkaline conditions were carried out in order to produce corresponding Cbz-*Δ*Tyr-OH derivatives, which were further converted with thionyl chloride to give *N*-carboxy dehydrotyrosine anhydrides [*Δ*Tyr·NCA]. In addition to these topics, the transformation of *Δ*Tyr·NCA to various kinds of *Δ*Tyr derivatives and a discussion on the configurational determination of all the new compounds are presented.

In the course of our work on the syntheses of various α-dehydroamino acids (DHA), which seem to be important residues in naturally occurring[2-5)] and synthetic dehydropeptides (DHP),[6)] we reported on several versatile synthetic methods for DHA and DHP.[1,7-9)] Recently, such DHA and DHP derivatives have been utilized for studies on both structure-biological activity correlation[10)] and asymmetric hydrogenation.[11)] So far, the syntheses and reactions of various kinds of neutral aliphatic, aromatic, and acidic DHA and their DHP derivatives have been reported.[12,13)] In addition, we already reported that *N*-carboxy α-dehydroamino acid anhydrides (*Δ* NCA), derived from benzyloxycarbonyl (Cbz)-DHA and thionyl chloride, were very useful for syntheses of DHP and for transformations to other DHA derivatives.[8)] Consequently, the *Δ* NCAs and their derivatives became a very important synthon as the building block of DHP. However, the syntheses and properties of DHA and its *Δ* NCA derivatives, which have another functional group in their side chains, such as a hydroxyl group, have never been investigated in detail, except for our brief report.[12,14)] In particular, in the case of DHA as well as an α-amino acid ester possessing two functional groups, e.g., amino and hydroxyl, it is usually necessary to protect them with different protecting groups for peptide synthesis. Therefore, we thoroughly examined the syntheses of several dehydrotyrosine (*Δ* Tyr) and its *Δ* NCA derivatives (*Δ* Tyr·NCA) mainly concerning two routes; we also tried to protect their functional groups by various combinations of useful N,O-protecting groups.[12)]

Results and Discussion

Synthesis of Dehydrotyrosine Derivatives. Since it was found that the methoxymethyl (MOM) group is effective for the protection of the phenolic hydroxyl group,[15)] the starting *p*-methoxymethoxybenzaldehyde (**1b**), derived from *p*-hydroxybenzaldehyde and methoxymethyl chloride by the usual method, was used in the following type condensation. According to the Hemetsberger method,[16)] the condensation of ethyl 2-azidoacetate with **1b** in the presence of sodium ethoxide was performed in order to produce (*Z*)-2-azido-(*p*-MOM)oxycinnamate (**2**) in a 57% yield. Although the yield of **2** was slightly low, compound **2** was subsequently subjected to a reduction. The selective hydrogenolysis of the azido group of **2** with aluminum-amalgam (Al-Hg) was smoothly carried out to give (*O*-MOM)dehydrotyrosine ethyl ester [*Δ*Tyr(MOM)-OEt] (**3**) in an almost quantitative yield. Unfortunately, however, it was found that a subsequent acylation of **3** with Cbz-Cl in the presence of a base such as triethylamine (TEA) or sodium hydride in CH_2Cl_2 or tetrahydrofuran (THF), did not take place, whereas a similar treatment of aliphatic DHA with Cbz-Cl proceeded.[7)]

Furthermore, in the presence of pyridine, the analogous acylation of **3** took place to give Cbz-(*O*-MOM)dehydrotyrosine ester [Cbz-*Δ*Tyr(MOM)-OY] (**4b**; Y=Et) in only a 33% yield. In order to increase the yield of **4b**, phase-transfer catalyst, such as $[CH_3(CH_2)_3]_4NBr$ (TBAB), was added to a heterogeneous solution of **3** and Cbz-Cl in the presence of powdered NaOH in CH_2Cl_2 at room temperature. As a result, the yield of **4b** ultimately increased to a 63%.

On the other hand, recently, Schmidt and coworkers have reported an interesting and convenient synthetic method for DHA by using an *N*-acyl-2-(dialkoxyphosphinyl)glycine ester as a Wittig-Horner reagent to an arbitrary aldehyde.[17)] Using the above-mentioned method, *N*-Cbz-2-(diethoxyphosphinyl)-glycinemethyl ester was prepared and then reacted with several *p*-substituted benzaldehydes (**1**) in the presence of potassium *t*-butoxide in CH_2Cl_2 at room temperature to give the expected Cbz-*Δ*Tyr(R)-OMe [**4**: **a**; R=CH_3 (Me), **b**; R=CH_3OCH_2 (MOM), **c**; R=CH_3CO (Ac)] in ca. a 50% yield (summarized in

Table 1. Dehydrotyrosine Ester Derivatives **4**

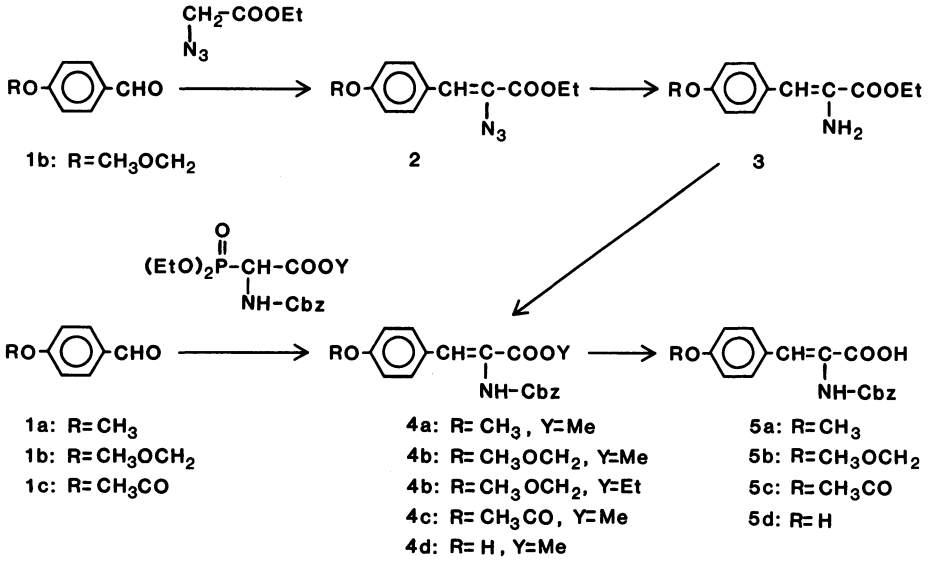
Compound No.	Y	Yield %	Mp θ_m/°C	Formula	Found (Calcd)/% C	H	N
4a	Me	42	syrup	$C_{19}H_{19}NO_5$	66.72 (66.85	5.45 5.61	4.25 4.10)
4b	Me	38	64—65[a]	$C_{20}H_{21}NO_6$	64.61 (64.68	5.77 5.70	3.70 3.77)
4b	Et	63	syrup	$C_{21}H_{23}NO_6$	65.64 (65.44	6.21 6.02	3.60 3.63)
4c	Me	69	126—128[b]	$C_{20}H_{19}NO_6$	65.21 (65.03	5.24 5.19	3.72 3.79)
4d	Me	85	156—158[c]	$C_{18}H_{17}NO_5$	66.18 (66.05	5.39 5.24	4.32 4.28)

a) Colorless needles from diisopropyl ether. b) Colorless prisms from ethyl acetate. c) Colorless needles from hexane–ethyl acetate.

Table 2. Properties of Dehydrotyrosine Ester Derivatives **4**

Compound No.	IR, ν/cm^{-1} in KBr NH	COO	C=C	^{1}H NMR, δ in $CDCl_3$ -CH=	-NH- (-OH)
4a	3300	1720	1640	7.32s	6.34bs
4b (Y=Me)	3310	1720	1640	7.16s	6.24bs
4b (Y=Et)	3310	1720	1640	7.28s	6.56bs
4c	3250	1762 1718	1640	7.30s	6.47s
4d	3270	1685	1632	7.20s	8.85bs[a] (9.90bs)

a) Measured in DMSO-d_6.



Scheme 1.

Tables 1 and 2). From the results, in the case of *p*-acetoxybenzaldehyde (**1c**), the obtained yield of Cbz-⊿Tyr(Ac)-OMe (**4c**) was a 69%. Moreover, Cbz-⊿Tyr-(R)-OMe (**4d**; R=H) was independently derived by the hydrolysis of **4c** with K_2CO_3 (as mentioned later).

Furthermore, in order to synthesize for the first time various kinds of useful ⊿Tyr·NCA derivatives, compounds **4a—c** had to be submitted to ester hydrolysis under mild conditions. The conventional hydrolysis of **4a** with 2-M† NaOH (1.0 equiv mol) at room temperature, even for more than 24 h, proceeded to give Cbz-⊿Tyr(Me)-OH (**5a**) in an only 10% yield. On the other hand, as shown in Tables 3 and 4, when 1-M LiOH instead of NaOH was used in the

† 1 M=1 mol dm^{-3}.

Table 3. Hydrolysis of **4** with a Few Bases

Compound No.	Reaction condition			Yield/%			
	Base (equiv)		Time/h	**5a**	**5b**	**5d**	**4d**
4a	2 M NaOH	1.0	24	10			
4a	1 M LiOH	1.0	3.5	75			
4b (Y=Me)	1 M LiOH	1.2	4		92		
4b (Y=Et)	1 M LiOH	1.2	4		89		
4c	1 M K_2CO_3	2.0	4			0	85
4c	1 M NaOH	3.3	22			24	0
4c	1 M $Ba(OH)_2$	3.3	22			47	25
4c	1 M LiOH	3.3	22			59	20
4c	2 M LiOH	5.0	22			71	5

Table 4. Dehydrotyrosine Derivatives **5**

Compound No.	Mp θ_m/°C	Formula	Found (Calcd)/%			IR, ν/cm^{-1} in KBr			^{1}H NMR, δ in DMSO-d_6	
			C	H	N	NH	COOH	C=C	-CH=	-NH= (-OH)
5a	179—180[a]	$C_{18}H_{17}NO_5$	66.10 (66.05	5.19 5.24	4.30 4.28)	3250	1685	1630	7.36s	8.78bs
5b	148—149[a]	$C_{19}H_{19}NO_6$	63.92 (63.86	5.30 5.36	3.82 3.92)	3250	1700	1640	7.34s	9.84bs
5c	167—168[a]	$C_{19}H_{17}NO_6$	64.52 (64.22	4.82 4.82	4.12 3.94)	3275	1690	1645	7.40s	9.10bs
5d	168—170[b]	$C_{17}H_{15}NO_5$	64.97 (65.17	4.91 4.82	4.32 4.47)	3275	1685	1630	7.26s	8.72bs (9.90bs)

a) Colorless needles from benzene. b) Colorless prisms from ethyl acetate.

hydrolysis, the desired **5a** could be obtained within a short time of 3.5 h in ca. a 75% yield. In a similar manner, the hydrolysis of **4b** (Y=Me and Et) was also worked up to give Cbz-⊿Tyr(MOM)-OH (**5b**) almost quantitatively. However, when 1-M of LiOH or 1-M $Ba(OH)_2$ was used in the analogous hydrolysis of **4c**, two products, **4d** and Cbz-⊿Tyr-OH (**5d**), instead of expected Cbz-⊿Tyr(Ac)-OH (**5c**), were obtained in ca. a 76% overall yield (in about a 1:2 ratio) accompanying an elimination of the acetyl group.

In addition, in the case of 2-M LiOH (5.0 equiv mol) for 22 h, the ester hydrolysis and the elimination of the acetyl group of **4c** occurred simultaneously to give **5d** as the main product (71%). Consequently, a high-yield synthesis of **5c** was accomplished by the acetylation of **5d** with acetyl chloride by the usual method. On the other hand, when 1-M K_2CO_3 was used as a weak base, only a deacetylation of **4c** was found to take place to give **4d** in an 85% yield.

Eventually, in almost all the cases mentioned above, it was proved that the acetyl group as the O-protecting group of ⊿Tyr derivatives was always labile under alkaline conditions, while the ester was gradually hydrolyzed upon increasing the concentration of the base.

The yields, melting points, and spectral data (IR and ^{1}H NMR) of **4** and **5** are summarized in Tables 1, 2, and 4.

In the IR spectra of **4** and **5**, the characteristic absorption bands of NH, acid carbonyl, and carbon–carbon double bond functions appear at 3250—3310, 1685—1720, and 1632—1645 cm^{-1} regions, respectively. Furthermore, in the ^{1}H NMR spectra, all the olefin protons of **4** and **5** shift at the δ 7.40—7.16 region as a singlet. In particular based on the ^{1}H NMR spectral data, the configurations of **4** and **5** could be tentatively determined to be in the (*Z*)-geometry, since the chemical shifts and the spectral patterns of (*Z*)-configurational DHA derivatives, the olefin protons of which shifted at comparatively higher magnetic fields than those of (*E*)-isomer,[18] were quite similar to those of the ⊿Tyr derivatives. Accordingly, the configuration of **2** and **3** could be also confirmed to be (*Z*)-geometry.

Synthesis and Conversion of ⊿Try·NCA to Various ⊿Tyr Derivatives. In order to synthesize *N*-carboxy dehydrotyrosine anhydride derivatives (⊿Tyr·NCA) (**6**), compounds **5a—d** (mentioned above) were subjected to cyclization of **5a** and **5c** with $SOCl_2$ in CH_2Cl_2 proceeded smoothly to give *N*-carboxy (*O*-Me)dehydrotyrosine anhydride [⊿Tyr(Me)·NCA] (**6a**) and *N*-carboxy (*O*-Ac)dehydrotyrosine anhydride [⊿Tyr(Ac)·NCA] (**6c**) in high yields, respectively, according to our previously reported technique.[12] On the other hand, the cyclization of **5b** also took place, but the O-protecting MOM group was found to behave interestingly under certain reaction conditions. In particular, when acetyl chloride or CH_2Cl_2 was used as the solvent, the cyclization and partial deprotection of **5b** readily proceeded to give only *N*-

Table 5. Conversion of **5** to *N*-Carboxy Dehydrotyrosine Anhydrides **6a—d**

Substrate[a] No.	Reaction condition Solvent–$SOCl_2$ (ml)		Time/h	Yield/% 6a	6b	6c	6d
5a	AcCl	1:1	1.0	76			
5b	AcCl	1:1	1.5				70
	CH_2Cl_2	1:1	1.5				93
	Et_2O	1:1	1.5		79		17
	Et_2O	2:1	1.5		98		
5c	CH_2Cl_2	1:1	1.5			93	
5d	CH_2Cl_2	1:1	1.5				86

a) 100 mg of **5** was used.

Table 6. *N*-Carboxy Dehydrotyrosine Anhydride Derivatives **6**

Compound No.	Yield %	Mp θ_m/°C	Formula	Found (Calcd)/% C	H	N	IR, $\tilde{\nu}$/cm^{-1} in KBr CO–O–CO	C=C	^1H NMR (δ, DMSO-d_6) –NH– (–OH)	–CH=
6a	76	197—198[a]	$C_{11}H_9NO_4$	60.19	4.18	6.33	1840	1670	11.39	6.66
				(60.27	4.14	6.39)	1770			
6b	98	148—149[b]	$C_{12}H_{11}NO_5$	57.77	4.51	5.58	1838	1670	11.30	6.68
				(57.85	4.45	5.62)	1780			
6c	93	192[c,e]	$C_{12}H_9NO_5$	58.41	3.55	5.47	1830	1680	7.40	6.76
				(58.30	3.69	5.67)	1780			
6d	86	196[d,e]	$C_{10}H_7NO_4$	58.15	3.49	6.78	1830	1662	10.05	6.70
				(58.54	3.44	6.83)	1770		(11.30)	

a) Colorless needles from ethyl acetate. b) Colorless needles from benzene. c) Colorless needles from chloroform. d) Colorless prisms from dioxane. e) Decomposition.

carboxy *O*-free-dehydrotyrosine anhydride [ΔTyr·NCA] (**6d**) almost quantitatively, instead of the desired *N*-carboxy (*O*-MOM)dehydrotyrosine anhydride [ΔTyr-(MOM)·NCA] (**6b**). However, interestingly, when diethyl ether was used as the solvent, a similar treatment of **5b** yielded another crystalline product in addition to a small amount of **6d** (17%). From the spectroscopic data and satisfactory elemental analytical results, the structure of the main isolated product was determined to be **6b**. As a result, the MOM protecting group was found to remain unchanged. Additionally, as shown in Tables 5 and 6, when the quantity of diethyl ether was doubled, only **6b** was obtained in an almost quantitative yield.

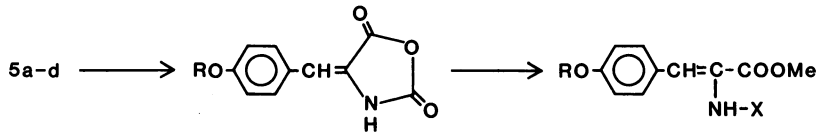
From the above results, it was found that diethyl ether used as the solvent behaved as a scavanger of the HCl gas that evolved during the reaction of **5b** with $SOCl_2$. Accordingly, in the former case in the absence of ether, it was clarified that the cyclization of **5b** initially formed **6b** as an intermediate, the MOM group of which was immediately eliminated with HCl to give **6d** in high yield. Consequently, it was clearly demonstrated that either compound **6b** or **6d** could be selectively prepared, according to the reaction conditions listed in Table 5. These results provide useful information for the dehydropeptide synthesis regarding the protection of side chain functional groups.

Furthermore, to be utilized in a wide variety of peptide syntheses, both the hydroxyl and amino groups of the ΔTyr derivatives must be easily and selectively protected with such groups as Cbz and *t*-butoxycarbonyl (Boc). In addition, we are interested in not only the protection but also the reactivity of the newly formed ΔNCA ring, itself. Thus, compound **6d** was chosen and directly applied for transformations to other DHA derivatives under various reaction conditions.

Compound **6d** was treated with di-*t*-butyl carbonate [$((CH_3)_3COCO)_2O$; $(Boc)_2O$] in the presence of a few drops of pyridine in THF; then, methanol was added. The resulting solution was made basic to pH 9 with *N*-methylmorpholine (NMM) in order to give *N*-free (*O*-Boc)dehydrotyrosine methyl ester [ΔTyr(Boc)-OMe] (**7a**) in an 80% yield. On the other hand, in the case of using Cbz-Cl instead of $(Boc)_2O$, a similar reaction was carried out to give the (*O*-Cbz)dehydrotyrosine methyl ester [ΔTyr(Cbz)-OMe] (**7b**) in an 84% yield (Scheme 2.)

From the above results and by a comparison with the reactivity of two reaction points of **6d**, the phenolic hydroxyl group was found to be acylated more easily than the imino group of the ΔNCA ring.

Furthermore, for one-pot syntheses of the ΔTyr



6a: R=CH_3
6b: R=CH_3OCH_2
6c: R=CH_3CO
6d: R=H

7a: R=Boc, X=H
7b: R=Cbz, X=H
7c: R=Boc, X=Cbz
7d: R=Cbz, X=Boc

Scheme 2.

Table 7. O-Protected Dehydrotyrosine Methyl Ester Derivatives **7**

Compound No.	Yield %	Mp θ_m/°C	Formula	Found (Calcd)/% C	H	N	IR, $\tilde{\nu}$/cm^{-1} in KBr $-NH_2$ (-NH-)	C=C	^{1}H NMR (δ, $CDCl_3$) -NH	-CH=
7a	80	113—115[a]	$C_{15}H_{19}NO_5$	61.82 (61.42	6.26 6.53	4.34 4.78)	3455 3380	1630	4.24bs	6.50s
7b	84	93—95[a]	$C_{18}H_{17}NO_5$	66.23 (66.05	5.19 5.24	4.22 4.28)	3480 3400	1630	4.24bs	6.48s
7c	46	97—98[b]	$C_{23}H_{25}NO_7$	64.38 (64.62	5.98 5.90	3.22 3.28)	(3325)	1645	6.48bs	7.12—7.52m (Ph+H)
7d	52	78—80[b]	$C_{23}H_{25}NO_7$	64.44 (64.62	5.95 5.90	3.19 3.28)	(3350)	1650	6.20bs	7.32s

a) Colorless prisms from hexane. b) Colorless needles from diisopropyl ether.

derivatives N,O-protected with different groups, a similar treatment of **6d** with $(Boc)_2O$ in THF was worked up, followed by consecutive treatments with TEA and Cbz-Cl. Finally, the reaction solution was treated further with MeOH to give the expected *N*-Cbz-(*O*-Boc)dehydrotyrosine methyl ester [Cbz-⊿Tyr-(Boc)-OMe] (**7c**) in ca. a 46% yield. Contrary to the above successive reactions, similar treatments of **6d** with Cbz-Cl, $(Boc)_2O$, and then MeOH were also performed to give *N*-Boc-(*O*-Cbz)dehydrotyrosine methyl ester [Boc-⊿Tyr(Cbz)-OMe] (**7d**) in ca. a 52% yield (Table 7).

In conclusion, facile syntheses of various kinds of ⊿Tyr and ⊿Tyr·NCA derivatives were accomplished in high yield; detailed knowledge concerning their protection and deprotection mechanisms were obtained. These results should be very useful regarding dehydropeptide synthesis.

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 spectrometer. ^{1}H NMR spectra were measured with a JEOL LMN PS-100 spectrometer in a $CDCl_3$ or DMSO-d_6 solution with tetramethylsilane as the internal standard.

Ethyl (*Z*)-2-Azido-(*p*-MOM)oxycinnamate (2). Into a solution of ethyl 2-azidoacetate (5.12 g, 40 mmol) and **1b** (6.64 g, 40 mmol) in dry benzene (120 ml) was added sodium ethoxide (made from Na 0.9 g, 40 mmol) in dry ethanol (24 ml) drop by drop, with stirring, at 5—8 °C. After allowing the solution to stand at room temperature for 2 h, the reaction solution was diluted with benzene (100 ml) and washed with a saturated aqueous ammonium chloride solution and then with chilled water. The organic layer was dried over anhydrous sodium sulfate. After removing the solvent under reduced pressure, the residual syrup was purified on a silica-gel column using benzene as the eluent to give **2** as a colorless viscous syrup. Yield 57%. IR ν_{max}^{KBr} (cm^{-1}) 2153 (N_3), 1650 (C=C); ^{1}H NMR ($CDCl_3$) δ=6.86 (s, 1H, -CH=). Found: C, 56.48; H, 5.32; N, 15.33%. Calcd for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.16%.

(*Z*)-⊿Tyr(MOM)-OEt (3). A solution of **2** (6.0 g, 22 mmol) in ether (70 ml) was added to a suspension of Al-Hg (made from 9.94 g of Al and 9.94 g of $HgCl_2$) in ether (200 ml) with vigorous stirring at room temperature. After a few minutes, the ether began to reflux; this was maintained by the addition of a few drops of water at about 20 min intervals. After completing the addition of the solution, stirring was continued for 3 h. After removing on insoluble substance, the filtrate was washed several times with ice-water. The organic layer was dried over anhydrous sodium sulfate and then evaporated under reduced pressure. The residual syrup was purified on a silica-gel column using a mixture of benzene and ethyl acetate (10:1 v/v) as the eluent to give **3** as colorless viscous syrup. Yield 97%. IR ν_{max}^{KBr} (cm^{-1}) 3360, 3350 (NH_2), 1640 (C=C); ^{1}H NMR ($CDCl_3$) δ=6.48 (s, 1 H, -CH=), 4.16 (bs, 2H, $-NH_2$). Found: C, 61.87; H, 7.03; N, 5.81%. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57%.

(*Z*)-Cbz-⊿Tyr(MOM)-OY (4b; Y=Me and Et). a) Method A. Into a solution of **3** (5.0 g, 20 mmol) in pyridine (40 ml) was added slowly Cbz-Cl (6.4 g, 40 mmol), with stirring, at 5—8 °C. The resultant solution was allowed to stand at room temperature and then stirred continuously for 2 h.

After removing the solvent under reduced pressure, the residual syrup was dissolved in ethyl acetate (200 ml) and washed twice, successively, with a 10% citric acid solution and with water; it was then dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gave a viscous syrup, which was then purified on a silica-gel column using a mixture of hexane and ethyl acetate (20:1 v/v) as the eluent to give **4b** (Y=Et) as a colorless syrup. Yield 33%.

b) Method B. Into a suspension of **3** (5.0 g, 20 mmol) and powdered NaOH (2.0 g, 50 mmol) in the presence of TBAB (0.66 g, 2 mmol) in dry CH_2Cl_2 (50 ml) was added a solution of Cbz-Cl (4.8 g, 30 mmol) in CH_2Cl_2 (10 ml), with stirring, at 5—8 °C. The stirring was continued at room temperature for 8 h. An insoluble substance was filtered off and the filtrate was diluted with $CHCl_3$ (50 ml). The resultant solution was washed twice, successively, with a 10% citric acid solution and with water and then dried over anhydrous sodium sulfate. By removing the solvent under reduced pressure a crude syrup was obtained which could be similarly purified on a silica-gel column to give **4b** (Y=Et). Yield 63%.

c) Method C. Into a solution of potassium *t*-butoxide (3.1 g, 28 mmol) in dry CH_2Cl_2 (40 ml) was added a solution of *N*-Cbz-2-(diethoxyphosphinyl)glycine methyl ester (10 g, 28 mmol), with stirring, at −60 °C. After stirring for 15 min, the resulting solution was further stirred with an appropriate aldehyde (**1a**—**c**; 28 mmol) below −60 °C. After allowing this solution to stand at room temperature for 12 h, the reaction solution was concentrated under reduced pressure to give a residual syrup, which was dissolved in ethyl acetate (150 ml). The resultant solution was washed, successively, with a saturated aqueous ammonium chloride solution and water and finally dried over anhydrous sodium sulfate. The evaporation of the solvent under reduced pressure gave a viscous syrup, which was similarly worked up to give **4a**—**c** as a colorless syrup or crystals. (See Tables 1 and 2).

(*Z*)-Cbz-⊿Tyr(Me)-OH (5a). a) Method A. A solution of **4a** (1.71 g, 5 mmol) in dioxane (4 ml) and 2-M NaOH (2.5 ml) was stirred at room temperature for 24 h. After removing the solvent under reduced pressure, the residue was dissolved in water (20 ml). The resultant solution was washed twice with ethyl acetate and then the aqueous layer was made acidic to pH 2 with 3-M HCl. The acidic solution was extracted three times with ethyl acetate; the combined extracts were then washed with saturated aqueous NaCl solution and dried over anhydrous sodium sulfate. The concentration of the solution under reduced pressure gave crude crystals, which were recrystallized from a mixture of ethyl acetate and hexane to give **5a** as colorless prisms. Yield 10%.

b) Method B. In a similar manner, the treatment of **4a** (5 mmol) in dioxane (4 ml) with a 1-M LiOH solution (5 ml) was worked up at room temperature for 3.5 h to give **5a**. Yield 75%

(*Z*)-Cbz-⊿Tyr(MOM)-OH (5b). Treatment of **4b** (Y=Me; 4.5 g, 12 mmol) in dioxane (9 ml) with 1-M LiOH solution (14 ml) was similarly worked up for 4.5 h to give a crystalline substance. The residue was dissolved in water (40 ml) and then washed twice with ethyl acetate. The aqueous layer was made acidic to pH 2 with 3-M HCl. The acidic solution was extracted three times with ethyl acetate; the combined extracts were washed with a saturated aqueous NaCl solution and then dried over anhydrous sodium sulfate. Removing the solvent under reduced pressure gave crude crystals, which were recrystallized from a mixture of ethyl acetate and hexane or benzene alone to give **5b** as colorless prisms. Yield 92%.

In a similar manner, the treatment of **4b** (Y=Et) with 1-M LiOH was worked up to give **5b** in an 89% yield.

(*Z*)-Cbz-⊿Tyr-OH (5d) and (*Z*)-Cbz-⊿Tyr-OMe (4d). Into a solution of **4c** (1.85 g, 5 mmol) in dioxane (5 ml) was added a 2-M LiOH solution (12.5 ml), with stirring, at room temperature. The resulting solution was stirred continuously for 22 h. After removing dioxane under reduced pressure, water (30 ml) was added to the residual substance; the aqueous solution, thus obtained, was washed twice with ethyl acetate. The aqueous layer was made acidic to pH 2 with 3-M HCl and then extracted twice with ethyl acetate. The combined extracts were washed with a saturated aqueous NaCl solution and finally dried over anhydrous sodium sulfate. After removing the solvent under reduced pressure, a crystalline product was obtained as a mixture of **5d** and a small amount of **4d**. The mixture was washed well with benzene; the remaining crystals were then collected. Recrystallization from ethyl acetate gave only **5d** as colorless prisms.

In a similar manner, the treatment of **4c** (1.85 g, 5 mmol) in dioxane (5 ml) with a 1-M K_2CO_3 solution (10 ml) was worked up at room temperature for 4 h and then made acidic to pH 3 with 3-M HCl to give crude crystals. Recrystallization from CCl_4 gave only **4d** as colorless prisms.

Furthermore, the treatment of **4c** with 1-M NaOH, 1-M LiOH, or 1-M $Ba(OH)_2$ was similarly worked up to give a mixture of **4d** and **5d**, except for the case of 1-M NaOH (Table 3).

(*Z*)-Cbz-⊿Tyr(Ac)-OH (5). Into a suspension of **5d** (1.57 g, 5 mmol) and acetyl chloride (0.47 g, 6 mmol) in dry CH_2Cl_2 (10 ml) was added pyridine (0.47 g, 6 mmol), with stirring, at room temperature. After stirring for 2 h, chloroform (30 ml) was added to the reaction solution. The resulting solution was washed, successively, with 1-M HCl and three times with a saturated aqueous NaCl solution and then dried over anhydrous sodium sulfate. After removing the solvent, the residual syrup was crystallized with cyclohexane; the crystals collected were then recrystallized from benzene to give **5c** as colorless needles.

⊿Tyr(Me)·NCA (6a). Into a suspension of **5a** (0.63 g, 2 mmol) in dry CH_2Cl_2 (6 ml) was added $SOCl_2$ (6 ml), with stirring, below 0 °C. The resulting solution was then stirred continuously at room temperature for 2 h. After removing the solvent and excess $SOCl_2$ under reduced pressure, the residual syrup was dissolved in CCl_4 (10 ml) and then concentrated under reduced pressure. This procedure was repeated three times; then, the crystals collected were recrystallized from ethyl acetate to give **6a** as colorless needles.

⊿Tyr(MOM)·NCA (6b) and ⊿Tyr·NCA (6d). A solution of **5b** (0.2 g, 0.56 mmol) and $SOCl_2$ (2 ml) in dry ethyl ehter (2 ml) was stirred below 0 °C for 1.5 h. The reaction solution was concentrated under reduced pressure and the residure, thus obtained, was dissolved in CCl_4 (6 ml) and again concentrated. This procedure was repeated three

times. Finally, the crude crystals collected were washed with warm chloroform and then recrystallized from dioxane to give **6d** as colorless prisms in a 17% yield. On the other hand, a chloroform filtrate was concentrated to give crude crystals, which were recrystallized from benzene to give **6b** as colorless needles in a 79% yield.

In a similar manner, the treatment of **5b** with $SOCl_2$ in dry ethyl ether (4 ml) was worked up to give only **6b** quantitatively. See Table 5.

⊿Tyr(Ac)·NCA (6c). Similarly, the treatment of **5c** with $SOCl_2$ in CH_2Cl_2 was worked up to give **6c** as colorless needles.

⊿Tyr·NCA (6d). In a similar manner, the treatment of **5d** with $SOCl_2$ was worked up to give crude crystals, which were recrystallized from dioxane to give **6d** as colorless prisms.

(*Z*)-⊿Tyr(Boc)-OMe (7a). To a solution of **6d** (0.2 g, 0.97 mmol) and $(Boc)_2O$ (0.23 g, 1.05 mmol) in THF (2 ml) was added pyridine (30 μl); the resulting solution was stirred continuously at room temperature for 12 h. After adding methanol (5 ml), the reaction solution was made basic to pH 9 with NMM and then stirred for 1 h. After removing the solvent under reduced pressure, the residue was dissolved in ethyl acetate (15 ml); the resultant solution was then washed with water and dried over anhydrous sodium sulfate. After concentrating the solution under reduced pressure, thus obtained, the residue was purified on a silica-gel column using a mixture of hexane and ethyl acetate (20:1 v/v) as the eluent. The fraction eluted was concentrated under reduced pressure to give residual crystals, which were recrystallized from hexane to give **7a** as colorless prisms.

(*Z*)-⊿Tyr(Cbz)-OMe (7b). To a solution of **6d** (0.2 g, 0.97 mmol) and pyridine (94 μl, 1.16 mmol) in THF (2 ml) was added, drop by drop, a solution of Cbz-Cl (0.17 ml, 1.06 mmol) in THF (1 ml) at room temperature. The reaction solution was similarly worked up to give **7b**.

(*Z*)-Boc-⊿Tyr(Cbz)-OMe (7c). A solution of **6d** (0.2 g, 0.97 mmol) and $(Boc)_2O$ (0.23 g, 1.05 mmol) in the presence of pyridine (30 μl) in THF (2 ml) was stirred at room temperature for 12 h. After first adding triethylamine (0.22 ml) and then a solution of Cbz-Cl (0.25 ml, 1.46 mmol) in THF (1 ml), the resulting solution was stirred for 4 h. Methanol (20 ml) was further added to the reaction solution, which was then made basic to pH 9—10 with NMM; stirring continued at room temperature for 3 h. After evaporating the solvent under reduced pressure, the residue was dissolved in ethyl acetate (20 ml); the resultant solution was then washed three times with water and finally dried over anhydrous sodium sulfate. After concentrating under reduced pressure, the residue, thus obtained, was purified on a silica-gel column using a mixture of hexane and ethyl acetate (20:1 v/v) as the eluent. The fraction eluted was concentrated to give residual crystals, which were recrystallized from diisopropyl ether to give **7c** as colorless needles.

(*Z*)-Cbz-⊿Tyr(Boc)-OMe (7d). To a solution of **6d** (0.2 g, 0.97 mmol) and pyridine (94 μl, 1.16 mmol) in THF (2 ml) was added, drop by drop, a solution of Cbz-Cl (0.17 ml, 1.06 mmol) in THF (1 ml) at room temperature. After stirring for 1.5 h, triethylamine (0.17 ml) and then $(Boc)_2O$ (0.27 g, 1.23 mmol) were added to the resulting solution. The reaction solution was similarly worked up at room temperature for 18 h to give **7d** as colorless needles.

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