+0.95° (c 1.04, EtOH), $[\alpha]^{23}_D$ -10.67° (c 5.24, $CHCl_3$).

(R)-tert-Butyl (O-Tetrahydropyranyl)-γ-hydroxyundecanoate (14). This was prepared as **5** from 1.5 g (5.8 mmol) of hydroxy ester **13** in a quantitative yield, following the procedure used for compound **5**: IR (CCl_4) $\nu_{C=O}$ 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.7–1.7 (m, 30 aliphatic H), 2.10–2.8 (m, 2 H), 3.2–4.1 (m, 3 H), 4.60 (br s, 1 H).

(R)-3-(O-Tetrahydropyranyl)-1,3-undecanediol (15). This was prepared from 2 g (5.8 mmol) of ester **14** by the procedure used for **6**. The yield of crude product was 95%: IR (CCl_4) ν_{OH} 3500, 3620 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.8–2.0 (m, 23 aliphatic H), 3.2–4.10 (m, 6 H, 1 H exchanged with D_2O), 4.4–4.8 (m, 2 H).

(R)-γ-Hydroxydodecanonitrile (18). 1. To a solution of 1.2 g (4.2 mmol) of alcohol **15** in 25 mL of THF were added 0.9 mL (6.3 mmol) of triethylamine at 0 °C and 0.4 mL (4.2 mmol) of mesyl chloride over a period of 15 min. After complete disappearance of the starting material by TLC (15 min), the reaction mixture was diluted with 25 mL of ether and washed with cold water (2 × 50 mL). The organic layer was then washed twice with a saturated sodium bicarbonated solution 2 × 50 mL) and water and dried over sodium carbonate. The solvent was evaporated and the residue, the corresponding mesylate **16**, was used directly in the next step.

2. To a solution of the crude mesylate in 20 mL of THF and 15 mL of Me_2SO (freshly distilled over $CaCl_2$) was added 2 equiv (5.4 g, 8.2 mmol) of potassium cyanide and the mixture was heated at 70 °C for 4 h. Then 2 equiv of potassium cyanide was again added and the mixture was left overnight at 70 °C and then, after cooling, poured on a mixture of ice and water. The solution was finally extracted with methylene chloride. The organic layer was washed twice with a 20% hydrochloric acid solution and twice with water and then dried over sodium carbonate, and the solvent was evaporated. A rapid chromatography on silica gel (eluant, 50/50 ether/hexane) was used to purify the product, which was a mixture of nitriles **17** and **18**, the *O*-tetrahydropyranyl group being partly hydrolyzed during the workup.

3. This mixture of nitriles **17** and **18** was diluted with 50 mL of ethanol and heated under reflux for 3 h in the presence of a catalytic amount (70 mg) of pyridinium *p*-toluenesulfonate. The solution was then filtered over silica gel and the solvent was evaporated. The crude nitrile **18** was used directly in the next step: IR ($CHCl_3$) ν_{OH} 3200–3500, 3620 cm^{-1}, ν_{CN} 2230 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.9 (br t, 3 H), 1.0–2.2 (m, 17 H), 2.45 (t, 2 H, J = 7.8 Hz), 3.40–3.9 (m, 1 H).

(R)-(+)-γ-n-Dodecanolactone (19). The crude nitrile **18** (410 mg, 2 mmol) and 1.2 g of sodium hydroxide were dissolved in 50 mL of a 3:1 mixture of ethanol and water, and the mixture was heated overnight under reflux. After cooling, the solution was neutralized with a 10% hydrochloric acid solution and the ethanol was evaporated. The residue was extracted with ether (2 × 100 mL) and then with 100 mL of chloroform. The organic layer was dried over sodium sulfate and the solvent was evaporated. The residue, dissolved in 25 mL of benzene, was heated for 1 h in the presence of a catalytic amount of *p*-toluenesulfonic acid with azeotropic distillation of water in a Dean–Stark trap. The solvent was then evaporated and the residue was purified by column chromatography on silica gel (eluant, 25/75 ether/hexane) to yield 95% of **19**: IR (CCl_4) ν_{CO} 1775 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.9 (br t, 3 H), 1–2 (m, 16 H), 2.1–2.70 (m, 2 H), 4.10–4.70 (m, 1 H); $[\alpha]^{23}D$ +32.70° (c 0.71, CH_3OH) (lit.[1] $[\alpha]_D$ +33.3° (0.73, MeOH), lit.[3] $[\alpha]_D$ +37.7° (1, MeOH), lit.[15] $[\alpha]^{20}_D$ +41.1 (5, MeOH); circular dichroism, λ 215 nm ($\Delta\epsilon$ = −0.08) (0.3, EtOH). Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.73; H, 11.11. Found: C, 72.93; H, 11.03.

Registry No. (R)-(+)-**1**, 58059-08-8; **2**, 112-54-9; **3**, 79816-64-1; (R)-(+)-**4**, 79816-65-2; (R)-**5**, 79827-26-2; (R)-**6**, 79816-66-3; (R)-**7**, 79816-67-4; (R)-**8**, 79816-68-5; (R)-**9**, 79816-69-6; (R)-(+)-**10**, 59812-96-3; **11**, 124-19-6; **12**, 79816-70-9; (R)-(+)-**13**, 79816-71-0; (R)-**14**, 79816-72-1; (R)-**15**, 79816-73-2; (R)-**16**, 79816-74-3; (R)-**17**, 79816-75-4; (R)-**18**, 69830-97-3; (R)-(+)-**19**, 69830-91-7; *tert*-butyl acetate, 540-88-5; (R)-1-iodo-(O-tetrahydropyranyl)-3-tetradecanol, 79816-76-5.

Useful Synthesis of α,β-Dehydrotryptophan Derivatives[1]

Tamon Moriya, Naoto Yoneda, Muneji Miyoshi, and Kazuo Matsumoto*

Research Laboratory of Applied Biochemistry, Tanabe Seiyaku Co., Ltd., 16-89 Kashima-3-chome, Yodogawa-ku, Osaka 532, Japan

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N-Acyl-α,β-dehydrotryptophan (ΔTrp) esters **4a–h** were directly synthesized by the reaction of 3-[(1-pyrrolidinyl)methylene]-3*H*-indole (**2**) with *N*-acylglycinates **3a–h** in reasonable yields. Of these, *N*-formyl-substituted ΔTrp methyl ester (**4a**) was easily converted into ΔTrp methyl ester (**7**) in a high yield by acidolysis with dry methanol–hydrogen chloride. Furthermore, **7** was successfully used for the preparation of a dipeptide, *N*-alanyl-substituted ΔTrp methyl ester (**10**).

The synthesis of biologically active amino acids and peptides is of continuing interest in amino acid and peptide chemistry. In particular, the syntheses of α,β-dehydroamino acids have recently received increased attention in the preparation of biologically active compounds.[2] From this point of view, the synthesis of α,β-dehydrotryptophan (ΔTrp) which is a constituent of telomycine,[3] antibiotic A-128-OP,[4] etc. is also currently desired. Besides this, ΔTrp derivatives are useful starting materials for asymmetric syntheses of optically active tryptophan and its analogues. For example, Knowles et al. reported[5] an enantioselective synthesis of (*S*)-tryptophan in 93% ee using N,N'-Ac_2ΔTrp. In subsequent work, Hengartner et al.

(1) Synthesis of Amino Acids and Related Compounds. 24. For part 23 see ref 14.

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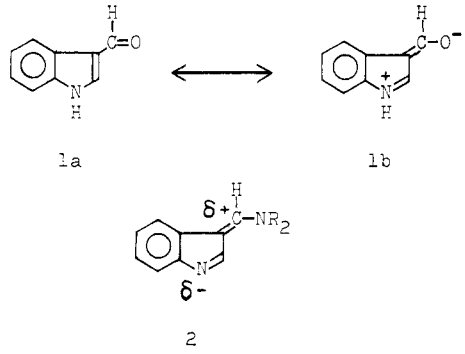
Scheme I



1a 1b

2

synthesized[6] (*R*)-6-methyltryptophan as a potential sweetening agent via an effective enantioselective hydrogenation of 6-MeΔTrp derivatives.

With regard to the synthesis of the ΔTrp derivatives,[7] the Erlenmeyer–Plöchl method using an azlactone is well-known:[8] however, the yield of *N*-AcΔTrp as a typical derivative of ΔTrp is poor.[8b-d] Additionally for the preparation of peptides containing ΔTrp, it is of significance to prepare N-protected ΔTrp in which the protecting group is more easily removed under mild conditions. Nevertheless, little is known about the synthesis of N-protected ΔTrp.[7,8]

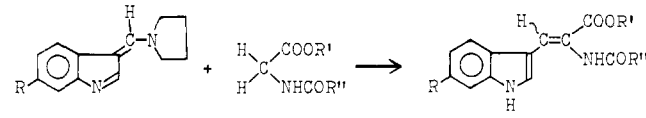
In this paper, we describe a facile synthesis of *N*-acyl-substituted ΔTrp esters by the reaction of *N*-acylglycinates with 3-(aminomethylene)-3*H*-indole,[9] and we have found that the method allows a synthesis of *N*-formyl-substituted ΔTrp ester which is easily converted into ΔTrp ester.

Results and Discussion

For the preparation of *N*-acyl-substituted ΔTrp derivatives, Knoevenagel condensation of 3-indolecarboxaldehyde (1) with an *N*-acylglycine derivative may be a general method. However, the yields of the condensation under basic conditions are generally poor, since the reactivity of **1** seems to be rather low owing to the significant contribution of canonical form **1b**[10] (Scheme I). In this connection, Hellmann and Piechota[11] reported that 1 was recovered quantitatively in a triethylamine-catalyzed decarboxylative aldol condensation with the ethyl half-ester of acetamidomalonic acid.

On the other hand, most recently we have reported[9] that 3-(aminomethylene)-3*H*-indole **2** is a useful 1,4-dipolar synthon of **1**: **2** reacts with a variety of nucleophiles and electrophiles to afford the corresponding 3-mono- and 1,3-disubstituted indole derivatives in excellent yields. In the present study, **2** was applied to the synthesis of the *N*-acyl-substituted ΔTrp derivatives by using *N*-acylglycine esters as the amino acid moiety.

Scheme II[a,b]



2, 5 3a-h 4a-h, 6d

[a] For 2 and 4, R = H; for 5 and 6, R = Me. [b] a, R′ = Me, R″ = H; b, R′ = Et; R″ = H; c, R′ = Bu; R″ = H; d, R′ = Me, R″ = Me; e, R′ = Et, R″ = Me; f, R′ = Bu, R″ = Me; g, R′ = Me, R″ = Ph; h, R′ = Et, R″ = Ph.

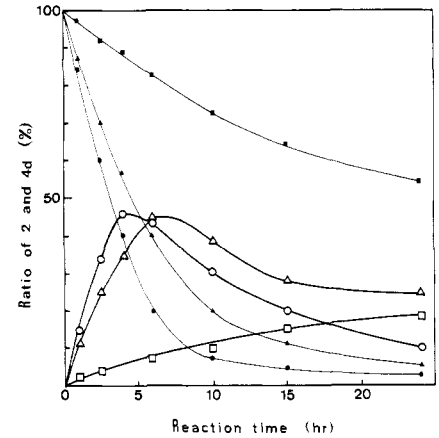


Figure 1. Temperature effect in the reaction of **2** with **3d** in DMF as the solvent: unreacted 2 (■) and **4d** (□) at 80 °C, unreacted 2 (▲) and **4d** (△) at 110 °C, unreacted 2 (●) and **4d** (○) at 120 °C.

Reaction of methyl *N*-acetylglycinate (**3d**) with 3-[(1-pyrrolidinyl)methylene]-3*H*-indole (**2**) as a typical example was carried out in *N*,*N*-dimethylformamide (DMF) at 120 °C for 4 h. As a result, the desired methyl 2-acetamido-3-[3(1*H*)-indolyl]acrylate, which is *N*-AcΔTrp methyl ester (**4d**), was obtained in 41% yield as a mixture of *E* and *Z* isomers. The ratio of the geometrical isomers (1:10 *E*/*Z*) of **4d** was determined by analytical high-pressure liquid chromatography (HPLC). The retention time (t_R) of the major *Z* isomer, which was thermodynamically favored, was shorter than that of the *E* isomer. In the ^{1}H NMR spectra, the methyl signal of acetyl group in the *Z* isomer appeared at δ 2.10, and that of *E* isomer was observed at δ 1.85. Additionally, the stereochemistry was further confirmed by the synthesis of *N*-Ac-6-MeΔTrp methyl ester (**6d**), the geometrical configuration of which was established by Hengartner et al;[6] i.e., we carried out a similar reaction on the 6-methyl derivative (**5**) of **2** with **3d** (Scheme II). As a result, **6d** was obtained in 50% yield as a mixture of geometrical isomers (1:10 *E*/*Z*), and a similar relationship between the two isomers of **6d** to that of **4d** was observed in the HPLC analysis and the ^{1}H NMR spectra.

Optimum conditions were explored for the formation of *N*-AcΔTrp methyl ester (**4d**). The yields of **4d** (a mixture of *E* and *Z* isomers) under various temperatures and times were measured by HPLC analysis in which the unreacted material (**2**) was determined as 3-indolecarboxaldehyde (**1**). The ratios of **4d** and **2** are plotted in Figure 1. Figure 1 shows that the reaction did not proceed smoothly at 80 °C, that a suitable temperature was 110–120 °C, that the maximum yield was about 46% after 4–6 h from the start of the reaction, and that afterward the content of **4d** was on the decrease. This suggested that thermal decomposition of **4d** took place on prolonged heating. To diminish decomposition of the product, the solvent effect was in-

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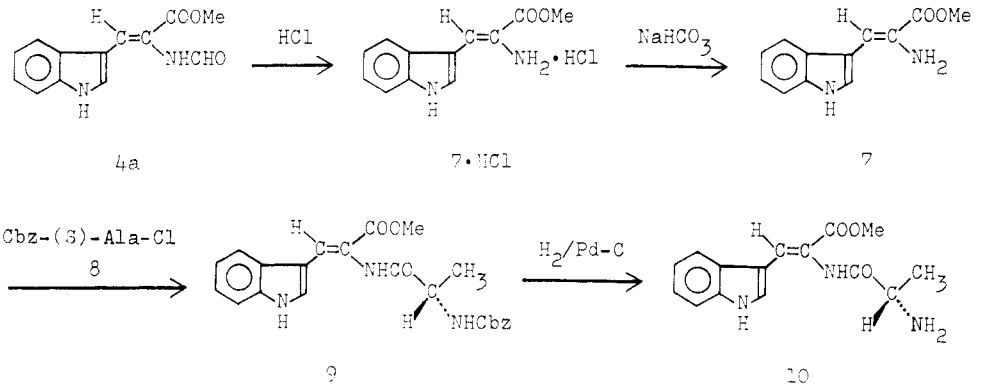
Table I. Synthesis of *N*-Acyl-Substituted ΔTrp Esters 4a-h and 6d

product no.	R	R′	R″	reaction conditions[a] solvent[b]	temp, °C	t_R,[c] min	*E*/*Z*[d] ratio	% yield[e]	mp,[f] °C
4a	H	Me	H	DMF-MeOH	110	9.61	*Z*	55	196-198[g]
4b	H	Et	H	DMF-EtOH	110	15.52	*Z*	50	168-170
4c	H	Bu	H	BuOH	118	58.17	*Z*	61	173-174
4d	H	Me	Me	DMF-MeOH	110	8.49 (9.63)	1/10	52	170-171 (167-170)
4e	H	Et	Me	DMF-EtOH	110	13.51 (15.30)	1/15	65	171-172[h] (162-172)
4f	H	Bu	Me	BuOH	118	47.26	*Z*	60	156-157
4g	H	Me	Ph	DMF-*t*-BuOH	120	12.62 (14.33)	1/4	72	244-246[i] (222-230)
4h	H	Et	Ph	DMF-EtOH	110	20.27 (23.00)	1/4	70	200-202 (179-185)
6d	6-Me	Me	Me	DMF-MeOH	110	13.84 (15.58)	1/10	50	182-183[j] (180-183)

[a] Reaction time 6 h. [b] DMF/ROH ratio of 10:1. [c] Retention time of *Z* isomer on HPLC analysis. The value in parentheses is that of *E* isomer. [d] Determined by HPLC analysis. [e] Isolated. [f] The melting point of *Z* isomer. The value in parentheses is that of the mixture of *E* and *Z* isomers. [g] Reference 9b, mp 196-198 °C. [h] Binograd, L. X.; Suborob, D. D. *Khim. Geterotsikl. Soedin.* **1974**, 1235; mp 171-172 °C. [i] Yamato, E.; Okumura, K. Japanese Kokai 75 58063; *Chem. Abstr.* **1975**, *83*, 193075. [j] Reference 6, mp 182-183 °C.

Scheme III



vestigated. Aprotic less polar solvents such as toluene or xylene promoted somewhat the formation of **4d** but also increased the decomposition of the product. Variations in the yield of **4d** in toluene are shown in Figure 2. On the other hand, mixtures of DMF with a protic solvent such as methanol or *tert*-butyl alcohol increased the yield of **4d** and fortunately decreased the deomposition of the product. Consequently, the reaction with methanol as a cosolvent of DMF afforded the maximum yield of **4d** up to 70% as shown in Figure 2.

Condensations of **2** with other *N*-acylglycine alkyl esters (**3a-c,e-h**) were similarly carried out in appropriate solvents to afford the corresponding *N*-acyl-substituted ΔTrp esters (**4a-c,e-h**) as shown in Table I. The HPLC analysis and ^{1}H NMR spectra[12] suggested that all of the *N*-formyl derivatives were single geometrical isomers. Among them, **4a**, having a methyl ester group, was identical with an authentic *Z* isomer[9b] which was synthesized by hydrolysis of methyl (*Z*)-2-isocyano-3-[3(1*H*)-indolyl]acrylate or methyl (*Z*)-2-[[(1-pyrrolidinyl)methylene]amino]-3-[3-(1*H*)-indolyl]acrylate. On the other hand, the bulkier the acyl group, the greater the formation of *E* isomers as minor products as shown in Table I (compare columns 1, 4, and 7). Contrary to this, an increase in the bulkiness of the ester group in the acetyl derivatives **4d-f** diminished formation of the *E* isomers (compare columns 4-6). This could be explained in terms of a steric effect between the indole moiety and the *N*-acyl or ester group.

For the projected synthesis of peptides containing ΔTrp, the methyl ester having a free amino group was envisioned as a useful key intermediate. Concerning the preparation of the ΔTrp esters, Babievskii et al.[13] reported briefly that

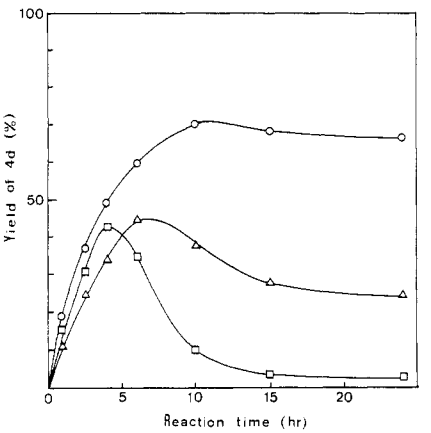


Figure 2. Solvent effect in reaction of **2** with **3d** at 110 °C: ○, DMF-MeOH (10:1); △, DMF; □, toluene.

the methyl ester was obtained in 35% yield as a byproduct in the catalytic reduction of methyl α-nitro-3-[3(1*H*)-indolyl]acrylate. Later, Hengartner et al. reported[6] a more efficient reductive method for the preparation of the 6-methyl derivative of the ΔTrp ester with stannous chloride. However, they stated that the overall yield and practicality of scale up was unsatisfactory. Thus, the development of a useful method for the synthesis of the ΔTrp ester is still required. For this purpose, a partial hydrolysis of the *N*-formyl derivative (**4a**) was tried according to our previous report,[14] which described a synthesis of α,β-dehydroamino acid esters by acidolysis of 2-(formylamino)acrylates. Treatment of **4a** with excess 20% dry

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methanolic hydrogen chloride was carried out at room temperature for 0.5 h to afford methyl (*Z*)-2-amino-3-[3-(1*H*)-indolyl]acrylate hydrochloride (Δ^ZTrp methyl ester hydrochloride, 7·HCl), in an excellent yield (Scheme III). Under these conditions, the corresponding keto acid which was generally considered as a byproduct did not form. Subsequently, the hydrochloride was converted successfully into free base **7** by treatment with aqueous sodium hydrogen carbonate in chloroform. The structures of these products were confirmed by IR, ^{1}H NMR, and mass spectra and by elemental analysis. The configuration of **7** was assumed to be *Z* from the configuration of the acylated products; a reaction of **7** with acetyl chloride in the presence of triethylamine afforded *N*-AcΔ^ZTrp methyl ester (**4d**) under mild conditions in good yields.

The Δ^ZTrp ester **7** thus obtained was used in the synthesis of the peptide. As a typical example, an attempt to synthesize (*S*)-alanyl-substituted Δ^ZTrp methyl ester **10** was achieved. Reaction of **7** with *N*-(benzyloxycarbonyl)-(*S*)-alanyl chloride (**8**), which was prepared from *N*-(benzyloxycarbonyl)-(*S*)-alanine in situ by an action of phosgene, afforded *N*-(benzyloxycarbonyl)-(*S*)-alanyl-substituted Δ^ZTrp methyl ester **9** in 58% yield.

Concerning the removal of *N*-(benzyloxycarbonyl) (Cbz) group of the α,β-dehydroamino acid derivative, Konno and Stammer reported[15] that the deprotection of Cbz-Gly-ΔPhe-OMe was successfully performed by treatment with hydrogen bromide in acetic acid, whereas hydrogenolysis of this compound afforded a mixture of Gly-ΔPhe-OMe and Gly-Phe-OMe. In contrast with their report, cleavage of the *N*-Cbz group of **9** by using hydrogen bromide under the same reaction conditions was not successful.

Fortunately, hydrogenolysis of the protecting group with 10% palladium on charcoal in methanol containing a small amount of hydrochloric acid afforded only the desired compound (**10**) in 95% yield. The structure of **10**·HCl was confirmed by its ^{1}H NMR spectrum in which the olefinic proton appeared at δ 7.76 as a sharp singlet, and aliphatic protons of the hydrogenated compound were not observed. Further evidence of the structure was supported by the UV spectrum having the characteristic absorption of 3-vinylindole derivatives at 341 nm. This selective hydrogenolysis might be due to the strong resonance interaction between the electron-releasing indole ring and the double bond.[10]

Thus, *N*-acyl-substituted ΔTrp esters, especially *N*-formyl derivatives, which had been difficult to synthesize by conventional methods were conveniently synthesized by the condensation of a reactive species, 3-(aminomethylene)-3*H*-indole **2**, with a poorly reactive *N*-acylglycinate. Regarding the preparation of α,β-dehydro amino acids, in more recent years a method using the anionic[16] or cationic[17] amino acid synthon has frequently been employed. Adding to this methodology, the present study provides a new method which involves activation of the group being introduced into the amino acid moiety. It has also been demonstrated that N-deprotection of the *N*-formyl-substituted ΔTrp ester proceeded smoothly by acidolysis to give an N-deblocked ΔTrp ester in good yield and that the resulting ΔTrp ester can be used as a key intermediate for the synthesis of peptides containing the ΔTrp moiety.

Experimental Section

Equipment. Melting points were measured by using the Yamato melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-27 infrared spectrophotometer. ^{1}H NMR spectra were obtained by using a Hitachi Perkin-Elmer R-20 high-resolution NMR spectrometer with tetramethylsilane as an internal standard. Mass spectra were taken on a Hitachi M-60 mass spectrometer. HPLC analyses were carried out by using a Waters Model 244 HPLC instrument: column, LS-410, 300 × 4 mm; mobile phase, MeOH–1% AcOH (1:1); flow rate, 0.8 mL/min; detector, 450 nm. Specific rotations were determined with a Perkin-Elmer Model 141 polarimeter.

Synthesis of *N*-Acyl-Substituted ΔTrp Esters 4a–h. Typical Procedure. A mixture of **2** (9.91 g, 0.05 mol) and **3d** (8.52 g, 0.065 mol) in a mixed solvent (DMF, 50 mL; MeOH, 5 mL) was stirred at 110 °C for 6 h. The reaction mixture was diluted with ethyl acetate (300 mL) and then poured into 1% hydrochloric acid (250 mL). The organic layer was washed with water, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was crystallized from methanol to give pale yellow prisms [8.00 g (62%), mp 167–170 °C) as a mixture of *E* and *Z*-isomers (1:10) of **4d**. Recrystallization of the mixture from methanol afforded the *Z* isomer of **4d**, mp 170–171 °C.

Similarly, the reaction of **2** and **5** with **3a–h** in appropriate solvents afforded **4a–c,e–h** and **6d**, respectively. The reaction conditions, isolated yields, and physical and spectral data are listed in Tables I and II.

Reaction Conditions of Condensation of 2 with 3d. Reaction of **2** with **3d** under various reaction conditions was carried out in a similar manner as described above, and the ratio of **2** and **4** was measured by HPLC analysis. The analytical samples (about 0.5 g) were taken from the reaction mixture with at different times. To each of the samples was added a 10 mL of 0.5 N methanolic hydrochloric acid (9:1 MeOH/H_2O), and they were allowed to stand overnight at room temperature. After dilution to 50 mL with methanol, they were subjected to the HPLC analysis. Three peaks corresponding to **1** (formed by hydrolysis of **2**), (*Z*)-**4d**, and (*E*)-**4d** appeared at t_R = 7.02, 8.49, and 9.63 min, respectively, and they were determined by the integrated intensity. The results are plotted in Figures 1 and 2.

Δ^ZTrp-OMe (7) and Its Hydrochloride (7·HCl). Dry methanolic hydrogen chloride (20%, 50 mL) was added to **4a** (2.44 g, 0.01 mol) at 0 °C, and the mixture was stirred at room temperature for 2 h. Ether (100 mL) was added to the reaction mixture to precipitate colorless fine crystals of 7·HCl: 2.40 g (95%); mp 194 °C dec; IR (Nujol) 3300 (νNH), 1710 (νC=O), 1660 cm^{-1} (δNH); ^{1}H NMR (Me_2SO-d_6) δ 3.87 (3 H, s, CH_3), 5.8 (3 H, br, D_2O exchangeable, NH_3^+), 7.67 (1 H, s, D_2O exchangeable, olefinic H), 7.0–7.9 (4 H, m, aromatic H), 8.20 (1 H, br d, *J* = 4 Hz, coalesced to a singlet on D_2O exchange, C-2 H), 12.3 (1 H, br s, D_2O exchangeable, indole NH); mass spectrum, *m/e* 216 (M^+ – HCl).

Anal. Calcd for $C_{12}H_{13}N_2ClO_2$: C, 57.04; H, 5.19; N, 11.09; Cl, 14.03. Found: C, 56.97; H, 5.34; N, 10.92; Cl, 13.74.

A suspension of 7·HCl (2.00 g, 0.008 mol) in chloroform was shaken with aqueous sodium hydrogen carbonate below 5 °C. The organic layer was dried over anhydrous magnesium sulfate, concentrated, and triturated with *i*-Pr_2O to afford **7** as yellow prims: 1.70 g (98%); mp 131–132 °C (*i*-Pr_2O): IR (Nujol) 3420 and 3350 (νNH), 1675 (νC=O), 1590 cm^{-1} (δNH); ^{1}H NMR ($CDCl_3$) δ 3.88 (5 H, s, among them 2 H were D_2O exchangeable, CH_3 and NH_2), 6.95 (1 H, s, olefinic H), 7.1–7.9 (4 H, m, C-4 to C-7 H), 7.40 (1 H, d, *J* = 3 Hz, coalesced to a singlet on D_2O exchange, C-2 H), 8.5 (1 H, br s, D_2O exchangeable, indole NH); mass spectrum, *m/e* 216 (M^+).

Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.63; H, 5.51; N, 12.90.

Ac-Δ^ZTrp-OMe (4d) by Acetylation of 7. To a solution of **7** (4.32 g, 0.02 mol) and triethylamine (7 mL, 0.05 mol) in THF

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Table II. Spectral Data of *N*-Acyl-Substituted Δ^ZTrp Esters 4b–d, f–h

compd[f]	MS, *m/e*[a]	IR (Nujol), cm^{-1} ν(N—H)	IR (Nujol), cm^{-1} ν(C=O)	^1H NMR (Me_2SO-d_6), δ
4b	258	3350, 3200	1670, 1630	1.27 (3 H, brt, J = 7 Hz, CH_2CH_3), 4.0–4.5 (2 H, m, CH_2CH_3), 7.0–8.1 (6 H, m, aromatic and olefinic H), 8.5 and 8.30 [1 H (1:4),[b] d (J = 12 Hz) and s, respectively, CHO], 9.61 and 9.50 [1 H (1:4),[b,c] brd, (J = 12 Hz) and brs, respectively, amide NH], 11.85 (1 H, brs,[c] indole NH)
4c	286	3340, 3200	1700, 1655	0.7–1.8 (7 H, m, CH_2-n-C_3H_7), 4.0–4.4 (2 H, m, CH_2-n-C_3H_7), 7.0–8.0 (6 H, m, aromatic and olefinic H), 8.04 and 8.25 [1 H (1:5),[b] d (J = 12 Hz) and s, respectively, CHO], 9.15 and 9.45 [1 H (1:5),[b,c] brd (J = 12 Hz) and brs, respectively, amide NH], 11.8 (1 H, brs,[c] indole NH)
4d	258	3280	1690, 1630	2.10 (3 H, s, $COCH_3$), 3.80 (3 H, s, OCH_3), 7.76 (1 H, brs,[d] olefinic H), 7.95 (1 H, d, J = 3 Hz,[e] C-2 H), 7.0–8.1 (4 H, m, C-4 to C-7 H), 9.4 (1 H, brs,[c] amide NH), 11.9 (1 H, brs,[c] indole NH)
4f	300	3280, 3250	1670, 1640	0.7–2.0 (7 H, m, CH_2-n-C_3H_7), 2.06 (3 H, s, $COCH_3$), 4.0–4.3 (2 H, m, CH_2-n-C_3H_7), 7.63 (1 H, brs,[d] olefinic H), 7.83 (1 H, brd, J = 3 Hz,[e] C-2 H), 7.0–8.0 (4 H, m, C-4 to C-7 H), 9.3 (1 H, brs,[c] amide NH), 11.7 (1 H, brs,[c] indole NH)
4g	320	3380, 3330	1690, 1660	3.76 (3 H, s, OCH_3), 7.0–8.2 (11 H, m, aromatic and olefinic H), 9.85 (1 H, brs,[c] amide NH), 11.7 (1 H, brs,[c] indole NH)
4h	334	3380, 3300	1680, 1660	1.29 (3 H, t, J = 7 Hz, CH_2CH_3), 4.23 (2 H, q, J = 7 Hz, CH_2CH_3), 7.0–8.2 (11 H, m, aromatic and olefinic H), 9.85 (1 H, brs,[c] indole NH)

[a] 30 eV, 160 °C, direct injection. [b] Ratio of rotational isomers with respect to the formamido group. The signals having large coupling constant are attributable to the cis isomer (the situation of each proton of NH and CHO is a trans relationship).[12] [c] D_2O exchangeable. [d] Sharpened on D_2O exchange. [e] Coalesced to singlet on D_2O exchange. [f] Satisfactory analytical data (±0.23% for C, H, and N) were submitted for review.

(100 mL) was added acetyl chloride (1.96 g, 0.025 mol) at 0 °C. After being stirred for 3 h at room temperature, the reaction mixture was diluted with ethyl acetate and then washed successively with water, 1% hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated to afford pale yellow prisms of **4d** [4.13 g (80%), mp 169–171 °C] identical with (*Z*)-**4d** prepared previously.

Similarly, **4g** was obtained from **7** by using benzoyl chloride and triethylamine in 73% yield (mp 242–243 °C) and was identical with (*Z*)-**4g** prepared previously.

Cbz-(*S*)-Ala-Δ^ZTrp-OMe (9). To a solution of Cbz-(*S*)-Ala-OH (2.23 g, 0.01 mol) in THF (30 mL) were successively added at −50 °C a solution of phosgene (0.99 g, 0.01 mol) in methylene chloride (3.4 mL) and tributylamine (1.85 g, 0.01 mol). After the mixture was stirred for 20 min at −20 °C, to the resulting Cbz-(*S*)-Ala-Cl (**8**) in situ was added a mixture of **7** (1.08 g, 0.005 mol) and tributylamine (1.85 g, 0.01 mol) in THF (5 mL) at the same temperature. Then the mixture was stirred at room temperature for an additional 1 h, was poured into ice–water, and was extracted with ethyl acetate. The organic layer was shaken with water, 1% hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine, successively. The extract was dried over anhydrous magnesium sulfate, concentrated in vacuo, and triturated with a mixed solvent of ethyl acetate and ether (1:1) to afford 1.23 g (58%) of **9**, mp 149–152 °C. A sample was recrystallized from methanol: Colorless fine crystals; mp 159–161 °C; $[\alpha]^{25}_D$ +127.7° (*c* 2, MeOH); IR (Nujol) 3300 (νNH), 1690, 1650, 1620 cm^{-1} (νC=O); UV max (MeOH) 226.5 nm (log ϵ 4.42), 277 (sh, 3.80), 340 (4.31); ^1H NMR (Me_2SO-d_6) δ 1.35 (3 H, d, J = 8 Hz, $CHCH_3$), 3.76 (3 H, s, OCH_3), 4.0–4.6 (1 H, m, coalesced to a quartet on D_2O exchange, $CHCH_3$), 5.10 (2 H, s, CH_2Ph), 7.0–8.2 (7 H, m, among them 1 H was D_2O exchangeable, olefinic and indole H and amide NH). 7.38 (5 H, s, Ph), 9.45 and 11.9 (1 H each, br s, D_2O exchangeable, NH protons of indole and amide); mass spectrum, *m/e* 421 (M^+).

Anal. Calcd for $C_{23}H_{23}N_3O_5$: C, 65.55; H, 5.50; N, 9.97. Found: C, 65.33; H, 5.64; N, 9.94.

(*S*)-Ala-Δ^ZTrp-OMe-HCl (10·HCl). Hydrogen gas was passed through a solution of **9** (3.00 g, 0.007 mol) in methanol (400 mL) containing concentrated HCl (1.0 mL) in the presence of 10% palladium on charcoal (0.5 g) at room temperature (ca. 20 °C) for 1.5 h with vigorous stirring. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was triturated with an ether–methanol (2:1) mixed solvent to afford a fine precipitate of **10**·HCl: 2.30 g (quantitative); mp 198–200 °C dec. A sample was recrystallized from methanol–THF: colorless fine crystals; mp 202–203 °C dec; PPC (BuOH/AcOH/H_2O, 4:1:1) R_f 0.78, single spot; $[\alpha]^{25}_D$ +103.0° (*c* 0.5, MeOH); IR (Nujol) 3200 (νNH), 1680 and 1630 cm^{-1} (νC=O); UV max (H_2O) 223 nm (log ϵ 4.36), 273 (sh, 3.88), 341 (4.24); ^1H NMR (Me_2SO-d_6) 1.55 δ 1.65 (3 H, d, J = 8 Hz, $CHCH_3$), 3.71 (3 H, s, OCH_3), 3.8–4.5 (1 H, m, coalesced to quartet on D_2O exchange, $CHCH_3$), 7.0–8.1 (4 H, m, C-4 to C-7 H), 7.76 (1 H, s, olefinic H), 8.08 (1 H, d, J = 3 Hz, coalesced to singlet on D_2O exchange, C-2 H), 8.4 (3 H, br, D_2O exchangeable, NH_3^+). 10.0 and 12.0 (1 H each, br s, D_2O-exchangeable, indole and amide NH).

Anal. Calcd for $C_{15}H_{18}N_3ClO_3$: C, 55.64; H, 5.60; N, 12.98; Cl, 10.95. Found; C, 55.67; H, 5.52; N, 12.88; Cl, 11.11.

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Registry No. **2**, 75629-45-7; **3a**, 3154-54-9; **3b**, 3154-51-6; **3c**, 79722-78-4; **3d**, 1117-77-7; **3e**, 1906-82-7; **3f**, 2743-44-4; **3g**, 1205-08-9; **3h**, 1499-53-2; (*Z*)-**4a**, 79722-79-5; (*Z*)-**4b**, 79722-80-8; (*Z*)-**4c**, 79722-81-9; (*E*)-**4d**, 79722-82-0; (*Z*)-**4d**, 79722-83-1; (*E*)-**4e**, 79722-84-2; (*Z*)-**4e**, 79722-85-3; (*Z*)-**4f**, 79722-86-4; (*E*)-**4g**, 79722-87-5; (*Z*)-**4g**, 79722-88-6; (*E*)-**4h**, 79722-89-7; (*Z*)-**4h**, 79722-90-0; **5**, 75629-47-9; (*E*)-**6d**, 71359-94-9; (*Z*)-**6d**, 71359-89-2; **7**, 79722-91-1; **7**·HCl, 79722-92-2; **8**, 49760-60-3; **9**, 79722-93-3; **10**·HCl, 79722-94-4; Cbz-(*S*)-Ala-OH, 1142-20-7.