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New Synthetic Method for Dehydrotryptophan Derivatives. Synthetic Studies on Indoles and Related Compounds. XXXIV[1)]

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Dehydrotryptophans (9) having various substituents on the indole ring were synthesized by vinylation of the corresponding indole derivatives (6) with *N*-acetyldehydroalanine methyl ester (7a) by the use of a stoichiometric amount of palladium salt in acetic acid (stoichiometric condition). Although vinylation of 4-, 5-, and 7-bromoindoles (6b, g, l, m) with 7a occurred chemoselectively at the C_3-position to give the corresponding bromodehydrotryptophans (9b, g, l, m) under the stoichiometric condition, the palladium-catalyzed vinylation of 4-bromoindoles (6b, i) occurred at the bromine-bearing carbon at the C_4-position [0.1 eq $PdCl_2(PPh_3)_2$ in Et_3N–dimethylformamide]. Vinylation of 3-bromoindoles (17a, b) with 7a, or ethoxycarbonyl- (7b) or *tert*-butoxycarbonyldehydroalanine methyl ester (7c) also gave the dehydrotryptophan (18a—d) in good yields under catalytic conditions. One of two possible regioisomers of the vinylated products was isolated in all cases, and the geometry was determined as *Z* based on the coupling constant of the ester carbonyl carbon and the olefinic proton in the ^{13}C-NMR spectrum.

Keywords vinylation; palladium; dehydrotryptophan; indole; dehydroalanine

Tryptophan analogues (**1**) having various substituents on the indole ring are widely distributed in nature as free amino acids or as components of peptides,[2)] and play important roles in biological systems.[3)] Furthermore, 4-substituted tryptophans should be useful intermediates for the synthesis of indole alkaloids which have a tryptophan skeleton, such as clavicipitic acid (**3**), indolactam V (**4**), and echinuline (**5**). Several attempts to synthesize optically active **3** or **4** starting from L-tryptophan (**1**, X=H) have been reported,[4)] but satisfactory results have not been obtained because of difficulty in the cyclization of the α-carboxyl group of the side chain to its C_4-position without racemization or in the selective introduction of a functional group at the benzene ring, which is less reactive than the pyrrole ring.

Although such tryptophan analogues (**1**) are readily available in racemic form by applying the known synthetic method for tryptophan itself (**1**, X=H),[5)] access to optically active analogs has been difficult.[6)] Asymmetric reduction of dehydroamino acids is a well established method for obtaining optically active amino acids.[7)] Thus, the dehydrotryptophans (**2**) having a functional group on the indole ring, can be regarded as good starting materials for the synthesis of optically active tryptophan analogues (**1**).[8)] The dehydrotryptophan derivatives were synthesized in good yields from 3-formylindole by the condensation of glycine oxazolones or of glycine phosphonates, but this method was applicable to the synthesis of only a few indole derivatives, and gave a mixture of *E*, *Z*-isomers in most cases.[9)]

Recently several methods for the preparation of dehydroamino acids utilizing a palladium-catalyzed vinylation have been reported,[10)] and those reactions give the *Z*-isomers exclusively. We have also reported[11)] the one-step synthesis of 4-bromodehydrotryptophan (**8**) from 4-bromoindole (**6b**) and ethoxycarbonyldehydroalanine

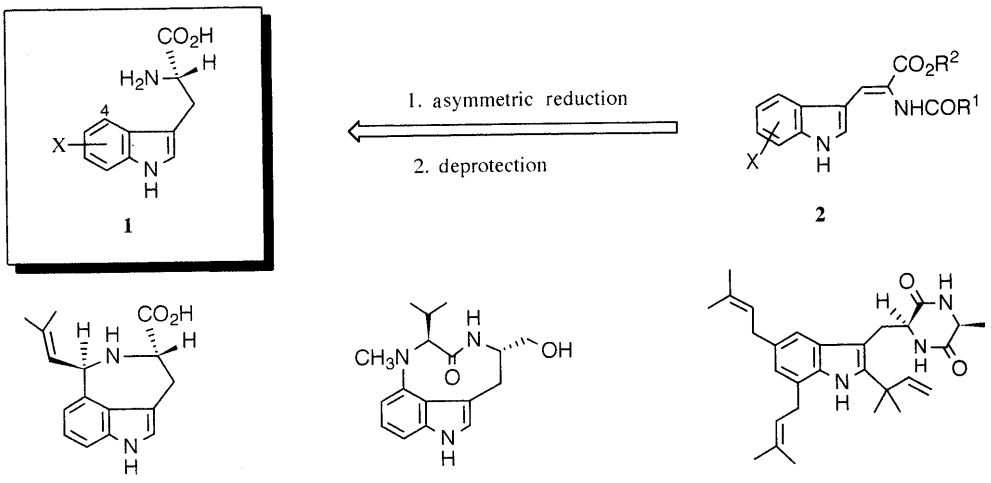


Chart 1

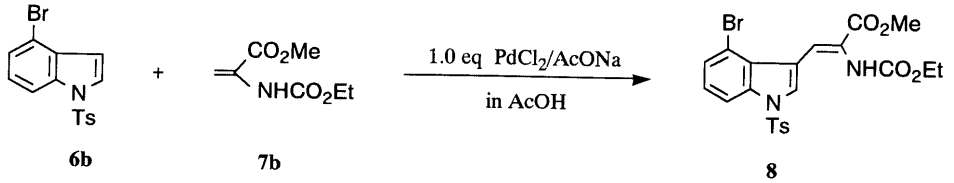


Chart 2

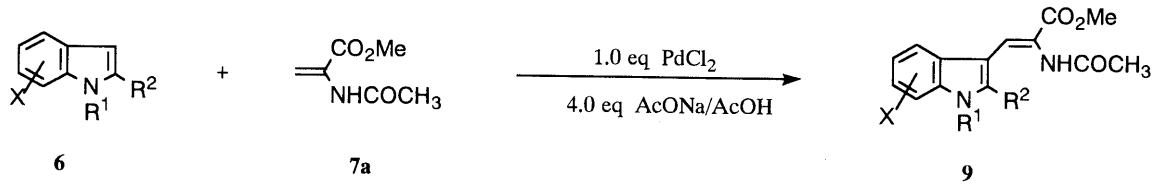


Chart 3

TABLE I. Vinylation of Various Indoles (**6a—m**) under the Stoichiometric Condition[a,b]

Run	Indole (**6**)				Product **9** (%)	Starting material recov. **6** (%)
	R_1	R_2	X			
1	Ts	H	H	(**6a**)	50 (**9a**)	35
2	Ts	H	4-Br	(**6b**)	17 (**9b**)	62
3	Ts	H	4-Me	(**6c**)	29 (**9c**)	51
4	Ts	H	4-CO_2Me	(**6d**)	14 (**9d**)	67
5	Ts	H	5-NO_2	(**6e**)	47 (**9e**)[c]	47
6	Ts	H	5-OMe	(**6f**)	53 (**9f**)[c]	35
7	Ts	H	5-Br	(**6g**)	51 (**9g**)[d]	35
8	H	CO_2Et	H	(**6h**)	59 (**9h**)[d]	8
9	H	CO_2Et	4-Br	(**6i**)	— (**9i**)	65
10	H	CO_2Et	5-NO_2	(**6j**)	36 (**9j**)[e]	21
11	H	CO_2Et	5-OMe	(**6k**)	42 (**9k**)[e]	13
12	H	CO_2Et	5-Br	(**6l**)	49 (**9l**)[e]	27
13	H	CO_2Et	7-Br	(**6m**)	45 (**9m**)[f]	39

a) Molar ratio; **6**: **7a**: $PdCl_2$: AcONa = 1 : 2 : 1 : 4. *b*) Reaction conditions: 130 °C, 2 h. *c*) 2.5 eq of **7a** was used. *d*) 1.2 eq of **7a** was used. *e*) 2.0 eq of AcONa was used. *f*) Reaction conditions: 100 °C, 3 h.

methyl ester (**7b**) by the use of a stoichiometric amount of $PdCl_2$ (Chart 2). This reaction might have wide applicability for the synthesis of dehydrotryptophan derivatives having various substituents on the indole ring, because the starting indoles having various substituents are easily prepared by known methods.[12] In the present report, we wish to describe a new synthesis of dehydrotryptophan having various substituents on the indole ring by applying the above palladium-mediated vinylation.

Results and Discussion

Various indoles (**6a—m**) were allowed to react with *N*-acetyldehydroalanine methyl ester (**7a**) in the presence of 1.0 eq of $PdCl_2$ and 4 eq of AcONa in AcOH at 120—130 °C, and the results are summarized in Table I (Chart 3). *N*-*p*-Toluenesulfonyl(tosyl)indole (**6a**) and ethyl indole-2-carboxylate (**6h**), which has been utilized as a stable synthetic equivalent of indole itself by our group,[13] gave the desired products (**9a**, **9h**) in 50% and 59% yields, respectively (runs 1 and 8). It is noteworthy that the protection of indole nitrogen was not necessary in the case of **6h**, whereas the protection of nitrogen on indole itself (**6**, $R^1 = R^2 = X = H$) was essential in the palladium-mediated vinylation.[14] Indoles with an electron-withdrawing or -donating group on the C_5- or C_7-positions (**6e—g** or **6j—m**) gave the products (**9e—g** or **9j—m**) in almost the same yields as unsubstituted indoles (**6a**, **6h**) (runs 5—7, 10—13). However, 4-substituted indoles (**6b—d**, **6i**) did not react smoothly, and the products were obtained in low yields or not at all (runs 2—4, 9). Those data show that this reaction was not affected by the electron density of the indole ring but was greatly influenced by steric hindrance.

The selective formation of bromodehydrotryptophan derivatives (**6b**, **g**, **l**, **m**) is especially interesting, because these results indicated that selective palladation occurred at the C_3-position to form the σ-complex (**10**) in spite of the presence of a carbon–bromine bond. It is well known[15] that the aryl palladium σ-complex (**14**) is formed either by direct palladation of an aromatic hydrocarbon (**12**) with Pd(II) salt or by the oxidative addition of Pd(0) species to an aryl halide (**13**) (Chart 4). The former process requires a stoichiometric amount of Pd(II) (stoichiometric condition) and the latter, known as Heck arylation,[16] requires a catalytic amount of Pd(0) (catalytic condition).

Since the vinylations under the stoichiometric condition were accomplished as above, we next tried vinylation of

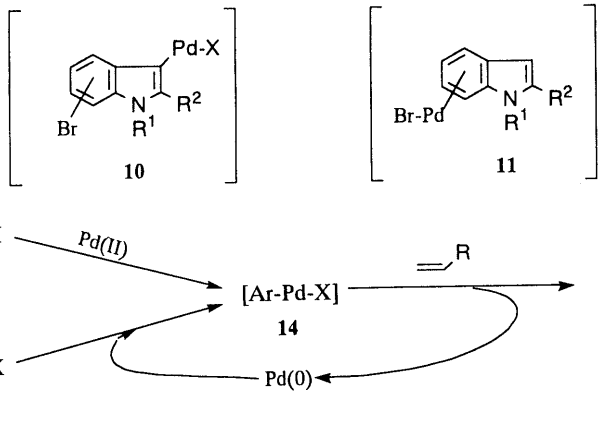
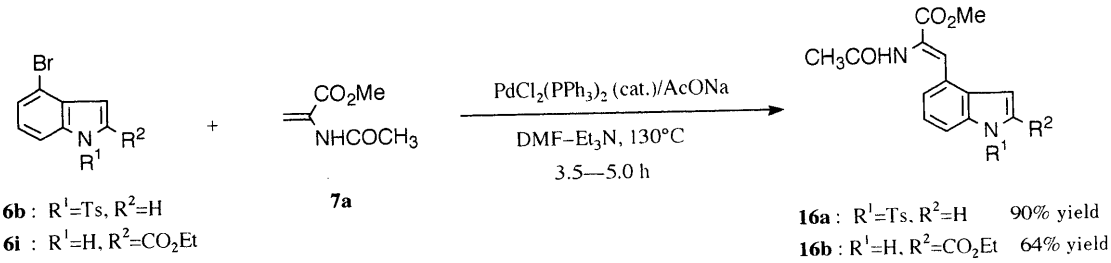


Chart 4

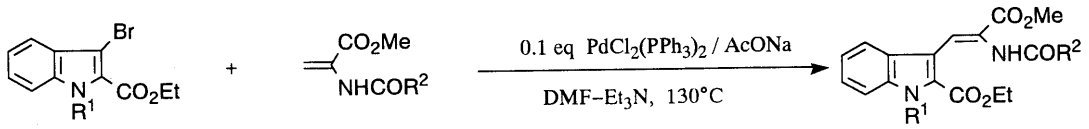


6b : R^1=Ts, R^2=H
6i : R^1=H, R^2=CO_2Et

7a

16a : R^1=Ts, R^2=H 90% yield
16b : R^1=H, R^2=CO_2Et 64% yield

Chart 5



17a : R^1=H,
17b : R^1=CH_2Ph

7a : R^2=CH_3
7b : R^2=OCH_2CH_3
7c : R^2=$OC(CH_3)_3$

18a : R^1=H, R^2=CH_3 (=**9h**)
18b : R^1=H, R^2=OEt
18c : R^1=H, R^2=$OC(CH_3)_3$
18d : R^1=CH_2Ph, R^2=CH_3

Chart 6

various bromoindoles under catalytic condition [0.1 eq $PdCl_2(PPh_3)_2$ in dimethylformamide (DMF)–Et_3N at 120 °C] in order to confirm the formation of the σ-complex (**11**) by oxidative addition of Pd(0) to the carbon–bromine bond. Vinylation of 4-bromoindoles (**6b**, **6i**) gave the C_4-vinylated products (**16a**, **16b**) in very good yields (Chart 5). It was interesting that the C_3-vinylated products (bromodehydrotryptophans, **9b**, **9i**) were not detected in the case of the catalytic condition. Vinylation of 5- or 7-bromoindoles (**6g** or **6m**) with **7a** did not give the C_5 or C_7-vinylated products but a mixture of starting material and debrominated product (**6**, X=H), while on vinylation of 3-bromoindole (**17a**, **17b**) with **7a** or alkoxycarbonyldehydroalanine (**7b**, **7c**), the dehydrotryptophans (**18a—d**) were obtained in good yields (Chart 6, Table II).

Although the reactivities in the vinylation varied irregularly with the position of the bromine on the indole ring and with the reaction conditions (stoichiometric or catalytic), the reacted position was completely differentiated between the stoichiometric and catalytic conditions. The selective vinylation at the C_3-position of bromoindoles is considered to be synthetically useful, because bromine on an aromatic ring might be easily converted to carbon functionalities by various methods including organotransition metal-catalyzed reactions. We have reported[17] that such chemoselectivity appeared more clearly when vinylation of various bromoindoles or some bromobenzene derivatives was carried out by the use of ethyl acrylate instead of **7** as an olefin; Et_3N and PPh_3 played an important role in the appearance of such chemoselectivity.

Table II. Vinylation of 3-Bromoindoles (**17**) under the Catalytic Condition[a]

Run	Indole **17**	Olefin **7**	Reaction time (h)	Product yield (%)
1	**17a**	**7a**	5	66 (**18a**)
2	**17a**	**7b**	2.5	53 (**18b**)[b]
3	**17a**	**7c**	5	61 (**18c**)
4	**17b**	**7a**	5	53 (**18d**)

a) Molar ratio; **17**:**7**:$PdCl_2(PPh_3)_2$:AcONa=1:2:0.1:2. *b*) Molar ratio; **17**:**7**:$PdCl_2(PPh_3)_2$:AcONa=1:1.5:0.05:1.5.

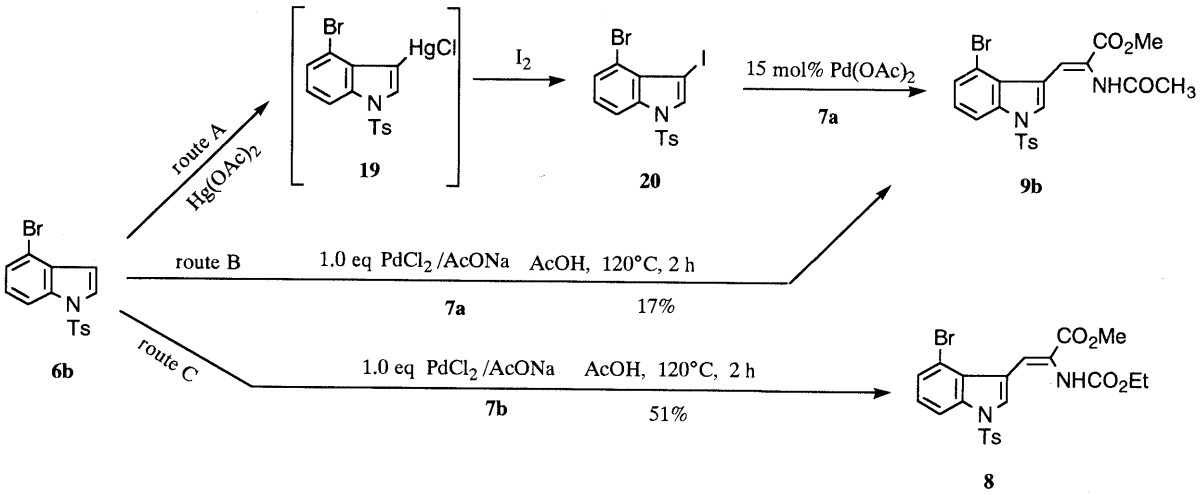


Chart 7

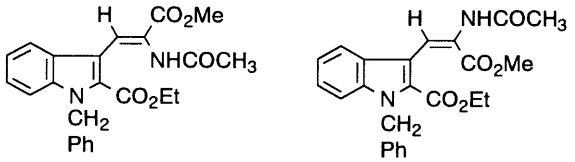


Chart 8

Hegedus[18] reported that the 4-bromodehydrotryptophan (**9b**), used as a key intermediate for the total synthesis of clavicipitic acid (**2**), was prepared from **6b** by a three-step sequence of reactions including a hazardous mercuration–iodination reaction and selective vinylation of the resultant 3-iodo-4-bromoindole (**20**) with **7a** (route A in Chart 7). Although we obtained the same compound (**9b**) in one step from the same starting material (**6b**), the yield was only 17% (route B in Chart 7). The reason for the low yield was considered to be that Pd(II) was consumed by the reaction with **7a** to produce Pd(0). So we tried to change the reactivity of **7a** toward Pd(II) by changing the protecting group on nitrogen from an acetyl group to an ethoxycarbonyl group. The reaction of **7b** with 4-bromoindole (**6b**) smoothly proceeded to give the desired product (**8**) in 51% yield (route C in Chart 7). Our method proved to be greatly superior to the reported method.[18] We are now trying to synthesize optically active indole alkaloids by using this compound as a starting material.

All of the dehydrotryptophans (**8**, **9**, **18**) and C_4-vinylated products (**16**) were isolated as single geometrical isomers from the present reaction, but a trace amount of the other isomer was sometimes detected in the reaction mixture on thin layer chromatography (TLC). Most of those minor isomers were not isolated in a pure form. However, in the case of the reaction of **17b** with **7a** under the catalytic condition, the minor isomer of **18d** was isolated as a pure form (*ca.* 2%). The determination of the geometry of those isomers was accomplished by consideration of the ^{13}C-NMR coupling constant of ester carbonyl carbon and olefinic hydrogen. It was reported[8a] that the *Z*-isomer has a larger coupling constant (*ca.* 10 Hz) than that of *E*-isomer (*ca.* 4 Hz). The coupling constants of both isomers were measured by low-power selective decoupling of the ester methyl protons and amide proton simultaneously to eliminate the effect of these protons. Since the major isomer had a smaller coupling constant (4.4 Hz) than that of the minor isomer (11.7 Hz), the former isomer was concluded to be the *Z*-isomer (*Z*-**18d**) while the latter was the *E*-isomer (*E*-**18d**). The coupling constants (4.4—5.1 Hz) observed for some analogous dehydrotryptophans (**8**, **9h**, **18b**) and C_4-vinylated products (**16a**, **b**) showed all these isomers to have *Z*-configuration. Since asymmetric reduction of *Z*-dehydroamino acids or esters was shown to give better results than that of *E*-isomer,[9] the present method has an advantage over other known methods for dehydrotryptophan synthesis.

Experimental

All melting points were determined on a Yanagimoto micro-melting point hot-stage apparatus and are uncorrected. IR spectra were recorded in Nujol mulls (unless otherwise stated) on a Shimadzu IR-400 spectrometer. NMR spectra were recorded in $CDCl_3$ on a Hitachi R-24B spectrometer (^1H-NMR, 60 MHz) (unless otherwise stated) or a JEOL GX-400 spectrometer (^1H-NMR, 400 MHz; ^{13}C-NMR, 100 MHz) with tetramethylsilane as an internal reference. Mass spectra were measured with a JEOL JMS-01-SG-2 spectrometer using a direct inlet system. For column chromatography, Kieselgel 60 (70—230 mesh, Merck), and for TLC, Kieselgel GF_{254}, were used. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; dt, double triplet; q, quartet; m, multiplet; br, broad; dif, diffused; Ar, aromatic.

General Procedure for the Synthesis of Dehydroalanine Derivatives (7a—c) According to the reported method[19] for the preparation of *N*-benzyloxycarbonyldehydroalanine methyl ester, a mixture of methyl pyruvate and 2.0 eq of acetamide for **7a** (1.0 eq of ethyl carbamate for **7b** or 0.5 eq of *tert*-butyl carbamate for **7c**) in benzene was refluxed for 2—5 h in the presence of a catalytic amount of *p*-toluenesulfonic acid (TsOH, 0.1 eq) and hydroquinone (0.05 eq) with a Dean–Stark apparatus for continuous removal of H_2O. After the reaction was completed, the solution was directly passed through a short dry Al_2O_3 column (benzene–AcOEt or benzene–hexane) without any work-up. Since the obtained dehydroalanines (**7a—c**) were relatively unstable and pure enough (checked by ^1H-NMR) to use for the next step, further purification was not carried out.

N-Acetyldehydroalanine Methyl Ester (**7a**): Yield 61%. Colorless needles, mp 49—51 °C. IR : 3330 (NH), 1695, 1660 (C=O) cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.11 (3H, s, $NHCOC\underline{H}_3$), 3.83 (3H, s, CO_2CH_3), 5.87 (1H, d, J=2 Hz, one of CH_2=C), 6.57 (1H, s, one of CH_2=C), 7.8 (1H, br s, NH). MS *m/z*: 143 (M^+, 84%), 101 (100%).

N-Ethoxycarbonyldehydroalanine Methyl Ester (**7b**): Yield 39%. Colorless oil. IR (neat): 3400 (NH), 1720 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J=6 Hz, $OCH_2C\underline{H}_3$), 3.80 (3H, s, CO_2CH_3), 4.17 (2H, d, J=6 Hz, $OC\underline{H}_2CH_3$), 5.70 (1H, d, J=2 Hz, one of CH_2=C), 6.15 (1H, s, one of CH_2=C), 7.08 (1H, br s, NH). MS *m/z*: 173 (M^+, 44%), 42 (100%).

tert-Butoxycarbonyldehydroalanine Methyl Ester (**7c**): Yield 68% yield, colorless oil. IR (neat): 3410 (NH), 1720 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.43 [9H, s, $C(CH_3)_3$], 3.77 (3H, s, CO_2CH_3), 5.65 (1H, d, J=2 Hz, one of CH_2=C), 6.08 (1H, s, one of CH_2=C), 6.9 (1H, br s, NH). MS *m/z*: 201 (M^+, 1.3%), 57 (100%).

General Procedure for the Vinylation of the Indoles (6) with *N*-Acetyldehydroalanine Methyl Ester (7a) under the Stoichiometric Condition A mixture of an indole (**6**, 0.50 mmol), *N*-acetyldehydroalanine methyl ester (**7a**, 1.0 mmol), $PdCl_2$ (0.50 mmol), and AcONa (2.0 mmol) in AcOH (2.5 ml) was heated at 130 °C for 2 h in a sealed tube. Then the reaction mixture was diluted with AcOEt and filtered through a Celite pad. The Celite pad was thoroughly washed with AcOEt and H_2O, and the separated aqueous layer was extracted with AcOEt. The combined organic layer was washed successively with 5% aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the residue was separated by silica gel column chromatography (benzene or benzene–AcOEt) to give the desired dehydrotryptophan derivative (**9a—m**) and the corresponding starting material. The yields of the products and the recoveries of the starting materials are listed in Table I, and the physical and spectral data are as follows.

(*Z*)-*N*-Acetyl-1-tosyldehydrotryptophan Methyl Ester (**9a**): Colorless needles (benzene–AcOEt–EtOH), mp 227—230 °C. *Anal.* Calcd for $C_{21}H_{20}N_2O_5S$: C, 61.16; H, 4.89; N, 6.79. Found: C, 61.10; H, 4.82; N, 6.80. IR: 3260 (NH), 1720 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.05 (3H, s, $COCH_3$), 2.30 (3H, s, $ArCH_3$), 3.71 (3H, s, CO_2CH_3), 7.1—8.0 (9H, m, Ar-H), 8.1 (1H, s, C=CH), 9.6 (1H, br s, NH). MS *m/z*: 412 (M^+, 100%).

(*Z*)-*N*-Acetyl-4-bromo-1-tosyldehydrotryptophan Methyl Ester (**9b**): Colorless needles (hexane–AcOEt), mp 198—201 °C. *Anal.* Calcd for $C_{21}H_{19}BrN_2O_5S$: C, 51.33; H, 3.90; N, 5.70. Found: C, 51.11; H, 3.88; N, 5.67. IR: 3280 (NH), 1720, 1655 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.17 (3H, s, $COCH_3$), 2.34 (3H, s, $ArCH_3$), 3.84 (3H, s, CO_2CH_3), 6.9—8.0 (8H, m, Ar-H), 8.1 (1H, s, C=CH), 8.39 (1H, s, NH). MS *m/z*: 492 (M^++2, 35%), 490 (M^+, 32%), 43 (100%).

(*Z*)-*N*-Acetyl-4-methyl-1-tosyldehydrotryptophan Methyl Ester (**9c**): Colorless needles (benzene), mp 171—173 °C. *Anal.* Calcd for $C_{22}H_{22}N_2O_5S$: C, 61.96; H, 5.20; N, 6.57. Found: C, 62.09; H, 5.23; N, 6.50. IR: 3300 (NH), 1725, 1675 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.11 (3H, s, $COCH_3$), 2.28 (3H, s, $ArCH_3$), 2.58 (3H, s, C_4-CH_3), 3.79 (3H, s, CO_2CH_3), 6.8—7.3, 7.6—7.9 (10H, m×2, Ar-H, CH=C, NH). MS *m/z*: 426 (M^+, 48%), 229 (100%).

(*Z*)-*N*-Acetyl-4-methoxycarbonyl-1-tosyldehydrotryptophan Methyl Ester (**9d**): Colorless needles (hexane–AcOEt), mp 182—184 °C. *Anal.* Calcd for $C_{23}H_{22}N_2O_7S$: C, 58.72; H, 4.71; N, 5.95. Found: C, 58.58; H, 4.82; N, 5.88. IR: 3290 (NH), 1710, 1675 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.08 (3H, s, $COCH_3$), 2.30 (3H, s, $ArCH_3$), 3.81, 3.87 (3H×2, s×2, CO_2CH_3×2), 6.9—8.0 (9H, m, Ar-H, CH=C, NH), 8.1 (1H, d, J=8 Hz, C_5-H). MS *m/z*: 470 (M^+, 61%), 241 (100%).

(*Z*)-*N*-Acetyl-5-nitro-1-tosyldehydrotryptophan Methyl Ester (**9e**): Pale brown needles (EtOH–AcOEt), mp 249—252 °C. *Anal.* Calcd for $C_{21}H_{19}N_3O_7S$: C, 55.14; H, 4.19; N, 9.19. Found: C, 55.27; H, 4.36; N, 8.73. IR: 3280 (NH), 1730, 1655 (C=O) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.26 (3H, s, $COCH_3$), 2.38 (3H, s, $ArCH_3$), 3.92 (3H, s, CO_2CH_3), 7.30 (2H, d, J=8 Hz, C_3'-H) 7.36 (1H, s, C_2-H), 7.63 (1H, br s, CH=C), 7.82 (2H, d, J=8 Hz, C_2'-H), 8.04 (1H, d, J=9.0 Hz, C_7-H), 8.23 (1H, dd, J=9.0, 1.5 Hz, C_6-H), 8.6 (1H, d, J=1.5 Hz, C_4-H), 9.73 (1H, s, NH). MS *m/z*: 457 (M^+, 34%), 260 (100%).

(*Z*)-*N*-Acetyl-5-methoxy-1-tosyldehydrotryptophan Methyl Ester (**9f**): Colorless needles (AcOEt), mp 191—193 °C. *Anal.* Calcd for $C_{22}H_{22}N_2O_6S$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.47; H, 5.03; N, 6.05. IR: 3250 (NH), 1715, 1655 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.14 (3H, s, $COCH_3$), 2.29 (3H, s, $ArCH_3$), 3.77, 3.80 (3H×2, s×2, OCH_3, CO_2CH_3), 6.8—7.8 (10H, m, Ar-H, CH=C, NH). MS *m/z*: 442 (M^+, 51%), 245 (100%).

(*Z*)-*N*-Acetyl-5-bromo-1-tosyldehydrotryptophan Methyl Ester (**9g**): Colorless needles (hexane–AcOEt), mp 217—225 °C. *Anal.* Calcd for $C_{21}H_{19}BrN_2O_5S$: C, 51.33; H, 4.00; N, 5.84. Found: C, 51.18; H, 3.92; N, 5.65. IR: 3250 (NH), 1710, 1660 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.19 (3H, s, $COCH_3$), 2.33 (3H, s, $ArCH_3$), 3.85 (3H, s, CO_2CH_3), 7.1—7.8 (10H, m, Ar-H, CH=C, NHCO). MS *m/z*: 492 (M^++2, 36%), 490 (M^+, 35%), 293 (100%).

(*Z*)-*N*-Acetyl-2-ethoxycarbonyldehydrotryptophan Methyl Ester (**9h**): Colorless needles (EtOH–AcOEt), mp 205—206 °C. *Anal.* Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.65; H, 5.47; N, 8.45. IR: 3310, 3250 (NH), 1710, 1680, 1670 (C=O) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.35 (3H, t, J=7.0 Hz, $OCH_2C\underline{H}_3$), 1.81 (3H, s, $COCH_3$), 3.73 (3H, s, CO_2CH_3), 4.37 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$). 7.11, 7.31 (1H×2, dt× 2, J=8.0, 1.5 Hz, C_5-, C_6-H), 7.38 (1H, d, J=8.0 Hz, C_7-H), 7.50 (1H, d, J=8.0 Hz, C_4-H) 7.66 (1H, s, C=CH), 9.42 (1H, s, NHCO), 12.21 (1H, br s, indole-NH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 14.1 ($CH_2\underline{C}H_3$), 22.2 ($CO\underline{C}H_3$), 51.6 ($CO_2\underline{C}H_3$), 60.4 ($O\underline{C}H_2CH_3$), 112.5, 114.8, 119.9, 121.3, 123.2, 123.8, 124.3, 125.1, 126.0, 135.9 (Ar-C, vinylic-C), 160.1 ($\underline{C}O_2CH_2CH_3$), 164.5 ($\underline{C}O_2CH_3$), 168.2 (NHCO). Low-power selective double irradiation of the amide proton at 9.42 ppm and the ester methyl at 3.73 ppm changed the signal of the ester carbon at 164.5 ppm from multiplet to doublet (J=5.1 Hz) in the ^{13}C-non-decoupling spectrum. MS *m/z*: 330 (M^+, 87%), 288 (100%).

(*Z*)-*N*-Acetyl-5-nitro-2-ethoxycarbonyldehydrotryptophan Methyl Ester (**9j**): Pale yellow needles (EtOH–AcOEt), mp > 300 °C. *Anal.* Calcd for $C_{17}H_{17}N_3O_7$: C, 54.40; H, 4.57; N, 11.20. Found: C, 54.02; H, 4.61; N, 10.93. IR: 3290, (NH), 1705, 1675 (C=O) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.36 (3H, t, J=7.0 Hz, $OCH_2C\underline{H}_3$), 1.82 (3H, s, $COCH_3$), 3.76 (3H, s, CO_2CH_3), 4.41 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$). 7.62 (1H, s, C=CH), 7.68 (1H, d, J=9.2 Hz, C_7-H), 8.19 (1H, dd, J=9.2, 2.2 Hz, C_6-H), 8.40 (1H, d, J=2.2 Hz, C_4-H), 9.67 (1H, s, NHCO) 12.89 (1H, br s, indole-NH). MS *m/z*: 375 (M^+, 44%), 333 (100%).

(*Z*)-*N*-Acetyl-2-ethoxycarbonyl-5-methoxydehydrotryptophan Methyl Ester (**9k**): Colorless prisms (EtOH–AcOEt), mp 254—256 °C. *Anal.* Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 59.64; H, 5.72; N, 7.56. IR: 3270, 3210 (NH), 1720, 1680 (C=O) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.34 (3H, t, J=7.0 Hz, $OCH_2C\underline{H}_3$), 1.83 (3H, s, $COCH_3$), 3.70, 3.73 (3H×2, s×2, CO_2CH_3, OCH_3), 4.35 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$). 6.79 (1H, d, J=2.2 Hz, C_4-H), 6.95 (1H, dd, J=9.0, 2.2 Hz, C_6-H), 7.39 (1H, d, J=9.0 Hz, C_7-H), 7.67 (1H, s, C=CH), 9.44 (1H, s, NHCO) 12.13 (1H, br s, indole-NH). MS *m/z*: 360 (M^+, 100%), 272 (62%).

(*Z*)-*N*-Acetyl-5-bromo-2-ethoxycarbonyldehydrotryptophan Methyl Ester (**9l**): Pale yellow fine needles (EtOH–AcOEt), mp 254—258 °C. *Anal.* Calcd for $C_{17}H_{17}BrN_2O_5$: C, 49.89; H, 4.19; N, 6.85. Found: C, 49.54; H, 4.26; N, 6.77. IR: 3310, 3250 (NH), 1710, 1690 (C=O) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.35 (3H, t, J=7.1 Hz, $OCH_2C\underline{H}_3$), 1.85 (3H, s, $COCH_3$), 3.74 (3H, s, CO_2CH_3), 4.38 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 7.4—7.5 (2H m, C_6-, C_7-H), 7.52 (1H, d, J=0.9 Hz, C_4-H), 7.65 (1H, s, C=CH), 9.51 (1H, s, NHCO), 12.46 (1H, br s indole-NH). MS *m/z*: 410 (M^++2, 29%), 408 (M^+, 29%), 368, 366 (100%).

(*Z*)-*N*-Acetyl-7-bromo-2-ethoxycarbonyldehydrotryptophan Methyl Ester (**9m**): Colorless needles (hexane–AcOEt), mp 155—157 °C. *Anal.* Calcd for $C_{17}H_{17}BrN_2O_5$: C, 49.89; H, 4.19; N, 6.84. Found: C, 49.71; H, 4.25; N, 6.72. IR: 3300 (NH), 1710, 1690, 1660 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.87 (3H, s, $COCH_3$), 3.80 (3H, s, CO_2CH_3), 4.38 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 6.8—7.6 (3H, m, C_4-, C_5-, C_7-H), 7.69 (1H, s, C=CH), 9.10 (1H, br s, NH). MS *m/z*: 410 (M^++2, 89%), 408 (M^+, 86%), 366 (100%).

Vinylation of 4-Bromo-1-tosylindole (6b) with 7a under the Catalytic Condition A mixture of *N*-tosyl-4-bromoindole (**6b**, 88 mg, 0.25 mmol), *N*-acetyldehydroalanine methyl ester (**7a**, 91 mg, 0.64 mmol), $PdCl_2(PPh_3)_2$ (16 mg, 0.023 mmol), and AcONa (82 mg, 0.98 mmol) in Et_3N (0.8 ml)–DMF (0.4 ml) was heated at 120 °C for 2 h in a sealed tube. Then the reaction mixture was diluted with AcOEt and filtered through a Celite pad. The Celite pad was thoroughly washed with AcOEt and H_2O and the separated aqueous layer was extracted with AcOEt. The combined organic layer was washed successively with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the residue (147 mg) was separated by silica gel column chromatography (benzene : AcOEt = 10 : 1) to give methyl 2-(1-tosylindole-4-yl)acetamidoacrylate (**16a**) as a pale yellow solid (93 mg, 90% yield), which was recrystallized from benzene to give colorless needles, mp 171—173 °C. *Anal.* Calcd for $C_{21}H_{20}N_2O_5S$: C, 61.15; H, 4.89; N, 6.79. Found: C, 61.45; H, 4.98; N, 6.62. IR : 3260 (NH), 1720, 1660 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 1.91 (3H, s, $NHCOC\underline{H}_3$), 2.31 (3H, s, Ar-CH_3), 3.73 (3H, s, CO_2CH_3), 6.89

(1H, d, J= 3.7 Hz, C_3-H), 7.28—7.42, 7.82—7.87 (3H × 2, m × 2, C_2-H, C_6-H, $SO_2C_6\underline{H}_4CH_3$), 7.53 (1H, d, J=7.5 Hz, C_5-H), 7.92 (1H, d, J=8.5 Hz, C_7-H), 9.48 (1H, s, NHCO). ^{13}C-NMR (DMSO-d_6) δ: 20.9, 22.2 ($CO\underline{C}H_3$, Ar-$\underline{C}H_3$), 52.0 ($CO_2\underline{C}H_3$), 107.5, 113.5, 123.5, 124.6, 126.2, 126.6, 126.7, 127.4, 128.3, 129.9, 130.2, 134.28, 134.29, 145.5 (Ar-C, vinylic-C), 165.3 ($\underline{C}O_2CH_3$), 169.3 ($NH\underline{C}OCH_3$). MS m/z: 412 (M^+, 76%), 155 (100%). Low-power selective double irradiation of the amide proton at 9.48 ppm and the ester methyl at 3.73 ppm changed the signal of the ester carbon at 165.3 ppm from multiplet to doublet (J=5.1 Hz) in the ^{13}C-non-decoupling spectrum.

Vinylation of Ethyl 4-Bromoindole-2-carboxylate (6i) with *N*-Acetyldehydroalanine Methyl Ester (7a) under the Catalytic Condition A mixture of ethyl 4-bromoindole-2-carboxylate (**6i**, 137 mg, 0.51 mmol), *N*-acetyldehydroalanine methyl ester (**7a**, 145 mg, 1.0 mmol), $PdCl_2$-$(PPh_3)_2$ (26 mg, 0.037 mmol), and AcONa (87 mg, 1.1 mmol) in Et_3N (0.5 ml)–DMF (0.5 ml) was heated at 130 °C for 3.5 h in a sealed tube. Then the reaction mixture was diluted with AcOEt and filtered through a Celite pad. The Celite pad was thoroughly washed with AcOEt and H_2O, and the separated aqueous layer was extracted with AcOEt. The combined organic layer was washed successively with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the residue (191 mg) was triturated with benzene to give pure methyl 2-(2-ethoxycarbonylindole-4-yl)acetamidoacrylate (**16b**) as a pale yellow solid (105 mg, 62%), which was recrystallized from AcOEt–EtOH to give colorless needles, mp 229—232 °C. *Anal.* Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.55; H, 5.49; N, 8.46. IR: 3340 (NH), 1710, 1650 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 1.35 (3H, t, J=7.2 Hz, $OCH_2C\underline{H}_3$), 1.96 (3H, s, $NHCOC\underline{H}_3$), 3.74 (3H, s, CO_2CH_3), 4.36 (2H, q, J= 7.2 Hz, $OC\underline{H}_2CH_3$), 7.21 (1H, br s, C_3-H), 7.33 (1H, t, J=7.7 Hz, C_6-H), 7.45 (1H, s, C=CH), 7.47, 7.49 (1H × 2, d × 2, J=7.7 × 2, C_5-, C_7-H), 9.65 (1H, s, NHCO), 12.1 (1H, s, indole-H). ^{13}C-NMR (DMSO-d_6) δ: 14.2 ($CH_2\underline{C}H_3$), 22.3 ($CO\underline{C}H_3$), 52.0 ($CO_2\underline{C}H_3$), 60.5 ($OCH_2\underline{C}H_3$), 106.0, 113.6, 121.0, 124.5, 126.3, 126.6, 127.1, 127.4, 127.8, 137.4 (Ar-C, vinylic-C), 161.1 ($\underline{C}O_2CH_2CH_3$), 165.5 ($\underline{C}O_2CH_3$), 169.3 ($NH\underline{C}OCH_3$). Low-power selective double irradiation of the amide proton at 9.65 ppm and the ester methyl at 3.74 ppm changed the signal of the ester carbon at 161.1 ppm from multiplet to doublet (J=5.1 Hz) in the ^{13}C-non-decoupling spectrum. MS m/z: 330 (M^+, 60%), 288 (100%).

General Procedure for the Vinylation of Ethyl 3-Bromoindole-2-carboxylates (17a, b) with Dehydroalanine Methyl Esters (7a—c) under the Catalytic Condition A mixture of ethyl 3-bromoindole (**17a** or **b**), *N*-acetyl- or *N*-alkoxycarbonyldehydroalanine methyl ester (**7a—c**, 2.0 eq), $PdCl_2(PPh_3)_2$ (0.1 eq), and AcONa (4.0 eq) in Et_3N–DMF (2 : 1) in a sealed tube was heated at 130 °C for the time indicated in Table II. Then the reaction mixture was diluted with AcOEt and filtered through a Celite pad. The Celite pad was thoroughly washed with AcOEt and H_2O, and the separated aqueous layer was extracted with AcOEt. The combined organic layer was washed successively with 5% aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the residue was washed with benzene to give the pure *N*-acetyldehydrotryptophan methyl ester (**18a**) or separated by silica gel column chromatography (benzene or benzene–AcOEt) to give the *N*-alkoxycarbonyldehydrotryptophan methyl ester (**18b—d**). The yields are listed in Table II and physical and spectral data are given below.

(*Z*)-*N*-Ethoxycarbonyl-2-ethoxycarbonyldehydrotryptophan Methyl Ester (**18b**): Pale yellow prisms (benzene), mp 170-172°C. *Anal.* Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 60.23; H, 5.61; N, 7.87. IR: 3320, 3270 (NH), 1730, 1690 (C=O) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.07, 1.36 (3H × 2, t × 2, J=7.0, 7.0 Hz, $OCH_2C\underline{H}_3$ × 2), 3.77 (3H, s, CO_2CH_3), 3.97, 4.37 (2H × 2, q × 2, J=7.0, 7.1 Hz, $OC\underline{H}_2CH_3$ × 2). 7.07, 7.29 (1H × 2, t × 2, J=8 Hz × 2, C_5-, C_6-H), 7.51, 7.54 (1H × 2, d × 2, J=8.0 Hz × 2, C_4-, C_7-H), 7.78 (1H, s, C=CH), 8.56 (1H, s, NHCO), 12.0 (1H, br s, indole-NH). ^{13}C-NMR (DMSO-d_6) δ: 14.1, 14.4 ($CH_2\underline{C}H_3$ × 2), 52.0 ($CO_2\underline{C}H_3$), 60.2, 60.7 ($O\underline{C}H_2CH_3$ × 2), 112.9, 115.5, 120.5, 122.2, 124.5, 124.7, 124.9, 125.8, 125.9, 136.6 (Ar-C, vinyl-C), 154.4, 161.0 ($\underline{C}O_2CH_2CH_3$ × 2), 165.5 ($\underline{C}O_2CH_3$). Low-power selective double irradiation of the amide proton at 8.56 ppm and the ester methyl at 3.77 ppm changed the signal of the ester carbon at 165.5 ppm from multiplet to doublet (J=5.1 Hz) in the ^{13}C-non-decoupling spectrum. MS m/z: 360 (M^+, 100%).

(*Z*)-*N*-*tert*-Butoxycarbonyl-2-ethoxycarbonyldehydrotryptophan Methyl Ester (**18c**): Pale yellow prisms (benzene), mp 168—171 °C. *Anal.* Calcd for $C_{20}H_{24}N_2O_6$: C, 61.84; H, 6.23; N, 7.21. Found: C, 61.62; H, 6.29; N, 7.19. IR: 3380 (NH), 1690, 1680 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.28 [9H, s, $C(CH_3)_3$], 1.40 (3H, t, J=7.0 Hz, $OCH_2C\underline{H}_3$), 3.87 (3H, s, CO_2CH_3), 4.37 (2H, q, J= 7.0 Hz, $OC\underline{H}_2CH_3$). 6.46 (1H, s, NHCO), 6.9—7.7 (4H, m, Ar-H), 7.75 (1H, s, C=CH), 9.59 (1H, br s, indole-NH). MS m/z: 388 (M^+, 35%), 288 (100%).

(*Z*)-*N*-Acetyl-1-benzyl-2-ethoxycarbonyldehydrotryptophan Methyl Ester (**18d**): Colorless needles (AcOEt–EtOH), mp 180—183 °C. *Anal.* Calcd for $C_{24}H_{24}N_2O_5$: C, 68.56 H, 5.75; N, 6.66. Found: C, 68.49, H, 5.69; N, 6.64. IR: 3310, (NH), 1720, 1670, 1650 (C=O) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.30 (3H, t, J=8.0 Hz, $OCH_2C\underline{H}_3$), 1.89 (3H, s, $COCH_3$), 3.87 (3H, s, CO_2CH_3), 4.31 (2H, q, J=8.0 Hz, $OC\underline{H}_2CH_3$). 5.80 (2H, s, CH_2Ph), 6.7—7.4 (8H, m, Ar-H), 7.14 (1H, s, NHCO), 7.56 (1H, d, J=8.0 Hz, C_4-H), 7.77 (1H, s, C=CH). ^{13}C-NMR (DMSO-d_6) δ: 14.0 ($CH_2\underline{C}H_3$), 23.0 ($NHCO\underline{C}H_3$), 48.2 ($N\underline{C}H_2Ph$), 52.4 ($CO_2\underline{C}H_3$), 61.0 ($O\underline{C}H_2CH_3$), 110.7, 116.6, 121.1, 121.6, 123.4, 123.7, 125.3, 125.6, 125.9, 126.8, 128.0, 137.1, and 138.1 (Ar-C, vinyl-C), 160.9 ($\underline{C}O_2CH_2CH_3$), 164.6 ($\underline{C}O_2CH_3$), 167.8 ($NH\underline{C}OCH_3$). Low-power selective double irradiation of the amide proton at 7.14 ppm and the ester methyl at 3.87 ppm changed the signal of the ester carbon at 164.6 from multiplet to doublet (J=4.4 Hz) in the ^{13}C-non-decoupling spectrum. MS m/z: 420 (M^+, 73%), 91 (100%).

Synthesis of (*Z*)-*N*-Ethoxycarbonyl-4-bromo-1-tosyldehydrotryptophan Methyl Ester (8) A mixture of *N*-tosyl-4-bromoindole (**6**, 356 mg, 1.0 mmol), 2-ethoxycarbonyldehydroalanine methyl ester (**7b**, 439 mg, 2.5 mmol), $PdCl_2$ (183 mg, 1.0 mmol), and AcONa (335 mg, 4.1 mmol) in AcOH (2.5 ml) was heated at 120 °C for 2 h in a sealed tube. Then the reaction mixture was diluted with AcOEt and filtered through a Celite pad. The Celite pad was thoroughly washed with AcOEt and H_2O, and the separated aqueous layer was extracted with AcOEt. The combined organic layer was washed successively with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl and dried over $MgSO_4$. After evaporation of the solvent, the residue was separated by silica gel column chromatography (benzene : AcOEt = 20 : 1) to give **8** as a pale yellow solid (270 mg, 51% yield), which was recrystallized from benzene to give colorless needles, mp 171—173 °C. *Anal.* Calcd for $C_{22}H_{21}BrN_2O_6S$: C, 50.68; H, 4.06; N, 5.37. Found: C, 50.90; H, 4.09; N, 5.32. IR: 3240 (NH), 1730, 1690 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 1.22 (3H, t, J=8.0 Hz, $NHCO_2CH_2C\underline{H}_3$), 2.33 (3H, s, Ar-$CH_3$), 3.78 (3H, s, CO_2CH_3), 4.11 (2H, q, J=8.0 Hz, $OC\underline{H}_2CH_3$), 7.31 (1H, t, J=8.2 Hz, C_6-H), 7.41 (2H, d, J=8.3 Hz, C'_3-H), 7.54 (1H, d, J=7.1 Hz, C_5- or C_7-H), 7.88 (2H, d, J=8.2 Hz, C'_2-H), 8.00 (1H, d, J=8.4 Hz, C_5- or C_7-H), 8.20, 8.35 (1H × 2, s × 2, C_2-H, CH=C), 8.99 (1H, s, NHCO). ^{13}C-NMR (DMSO-d_6) δ: 14.4 ($CH_2\underline{C}H_3$), 21.0 (Ar-$\underline{C}H_3$), 52.3 ($CO_2\underline{C}H_3$), 60.6 (OCH_2), 112.8, 113.5, 114.8, 123.0, 125.8, 126.5, 126.9, 128.2, 128.68, 128.72 130.4, 133.5, 135.0, 146.3 (Ar-C, vinyl-C), 154.5 ($NH\underline{C}O_2CH_2$), 165.2 ($\underline{C}O_2CH_3$). Low-power selective double irradiation of the amide proton at 8.99 ppm and the ester methyl at 3.78 ppm changed the signal of the ester carbon at 165.2 ppm from multiplet to doublet (J=5.1 Hz) in the ^{13}C-non-decoupling spectrum. MS m/z: 522 (M^+ +2, 66%), 520 (M^+, 60%), 91 (100%).

Isolation of (*E*)-*N*-Acetyl-1-benzyl-2-ethoxycarbonyldehydrotryptophan Methyl Ester (*E*-18d) A mixture of ethyl *N*-benzyl-3-bromoindole-2-carboxylate (**17b**, 354 mg, 0.99 mmol), *N*-acetyldehydroalanine methyl ester (**7a**, 274 mg, 1.92 mmol), $PdCl_2(PPh_3)_2$ (70 mg, 0.1 mmol), and AcONa (162 mg, 1.98 mmol) in Et_3N (1.0 ml)–DMF (0.5 ml) was heated at 130 °C for 5 h in a sealed tube. Then the reaction mixture was diluted with AcOEt and filtered through a Celite pad. The Celite pad was thoroughly washed with AcOEt and H_2O, and the separated aqueous layer was extracted with AcOEt. The combined organic layer was washed successively with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the residue was subjected to silica gel column chromatography (benzene : AcOEt = 10 : 1). The first fraction gave the title compound (**18**) as a yellow solid (26 mg, 6%), which was recrystallized from benzene to give colorless needles, mp 122—125 °C. IR: 3320, (NH), 1720, 1680 (C=O) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.27 (3H, t, J=7.1 Hz, $OCH_2C\underline{H}_3$), 2.18 (3H, s, $COCH_3$), 3.33 (3H, s, CO_2CH_3), 4.26 (2H, q, J=7.1 Hz, $OC\underline{H}_2CH_3$). 5.80 (2H, s, CH_2Ph), 6.9—7.3 (8H, m, Ar-H), 7.50 (1H, d, J=8.0 Hz, C_4-H), 7.81 (1H, s, NHCO), 8.42 (1H, s, C=CH). ^{13}C-NMR ($CDCl_3$) δ: 14.0 ($CH_2\underline{C}H_3$), 24.6 ($NHCO\underline{C}H_3$), 47.9 ($N\underline{C}H_2Ph$), 51.9 ($CO_2\underline{C}H_3$), 60.6 ($O\underline{C}H_2CH_3$), 110.2, 119.0, 119.1, 120.4, 120.7, 124.3, 124.8, 125.5, 125.6, 125.7, 126.5, 127.9, 137.7, 137.9 (Ar-C,

vinyl-C), 161.3 ($\underline{C}O_2CH_2CH_3$), 164.8 ($\underline{C}O_2CH_3$), 167.8 ($NH\underline{C}OCH_3$). Low-power selective double irradiation of the amide proton at 7.81 ppm and the ester methyl at 3.33 ppm changed the signal of the ester carbon 164.8 ppm from multiplet to doublet ($J=11.7$ Hz) in the ^{13}C-non-decoupling spectrum. MS *m/z*: 420 (M^+, 63%), 91 (100%). High-resolution-MS Found: 420.1721, Calcd for $C_{24}H_{24}N_2O_5$: 420.1686. The second fraction gave the *Z*-isomer (**18d**) as a pale yellow solid (221 mg, 53%).

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References and Notes

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