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Synthetic Studies of Indoles and Related Compounds. XXVIII.[1] Intramolecular Vinylation of Pyrrole Derivatives Using Palladium: a New Synthetic Method for Substituted Indoles

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The cyclization of methyl (*E*)-6-oxo-6-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]-2-hexenoate (8a) using an equimolar amount of palladium chloride gave methyl 4-hydroxy-1-(phenylsulfonyl)-1*H*-indole-7-acetate (11a) in 33% yield. The similar cyclization of methyl (*E*)-6-acetoxy-6-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]-2-hexenoate (8c) proceeded smoothly to give methyl 1-(phenylsulfonyl)-1*H*-indole-7-acetate (11c) and 4-acetoxy-7-methoxycarbonylmethylidene-1-phenylsulfonyl-4,5,6,7-tetrahydro-1*H*-indole (10c) in 41% and 22% yields, respectively. Conversion of the tetrahydroindole (10c) to the indole (11c) was accomplished in 44% yield by treatment with *p*-toluenesulfonic acid in benzene. Methyl (*E*)-6-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]-2-hexenoate (8d) gave 11c and 7-methoxycarbonylmethylidene-1-phenylsulfonyl-4,5,6,7-tetrahydro-1*H*-indole (10d) in 27% and 40% yields, respectively. The cyclization of ethyl (*E*)-4-(5-methoxycarbonyl-4-pentenyl)-1*H*-pyrrole-2-carboxylate (18) also gave the corresponding indole-7-acetate (20) and 7-methoxycarbonylmethylidene-4,5,6,7-tetrahydro-1*H*-indole (21) in 16% and 49% yields, respectively.

Keywords intramolecular vinylation; palladation; synthesis; 4,7-disubstituted indole; 1-(phenylsulfonyl)pyrrole; Friedel–Crafts acylation

Recently, new synthetic methods for the indole nucleus starting from pyrrole derivatives have been reported.[2,3] An important characteristic of those routes is that indole derivatives which have variously functionalized alkyl side chains and/or hetero atoms on the benzene ring can be prepared regiospecifically.[2] Several indole alkaloids, such as teleocidin analogues,[3a,d] ergot alkaloids,[3b] and trikentrins,[3c] have been synthesized by utilizing those methods. We have reported the regioselective C_4-acylation of ethyl pyrrole-2-carboxylate by Friedel–Crafts (F–C) reaction,[4] and the direct regioselective vinylation of indoles at the C_3-position with α,β-unsaturated carbonyl compounds using a stoichiometric amount of palladium.[5] On the basis of those results, we report here a new methodology for the synthesis of 4,7-disubstituted or 7-substituted indole derivatives starting from pyrroles (**5**, **6**).

Chart 1 shows the synthetic plan, which consists of the following steps; i) regioselective synthesis of a β-substituted pyrrole (**2**) which has a side chain with a double bond at the appropriate position (step 1), ii) novel intramolecular vinylation of **2** at the α-position using an equimolar amount of palladium (step 2), and iii) aromatization of the cyclized product (**3**) to give the 4,7-disubstituted indole (**4**) (step 3).

Results and Discussion

Introduction of the Side Chain Regioselective introduction of the side chain is essential for accomplishment of the new synthesis. For this purpose, 1-(phenylsulfonyl)-1*H*-pyrrole (**5**) and ethyl 1*H*-pyrrole-2-carboxylate (**6**) were selected as starting pyrroles, since these compounds undergo regioselective F–C acylation at the 3- (or β-) position of **5**

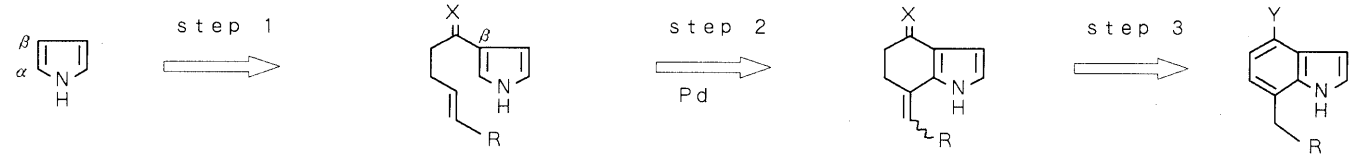

Chart 1

Chart 2

TABLE I. Cyclization of the *N*-Phenylsulfonylpyrrole Series (**8a—d**)

Run	Pyrrole (**8a—d**)	Conditions				Product (%)	SM[a] recovery (%)
		Solvent	Additive (4 eq)	Temperature	Time (h)		
1	**8a**	CH_3CN	$(CH_3COO)_2Cu$	Reflux	4	—	—
2	**8a**	CH_3COOH	CH_3COONa	Reflux	10	**11a** (13)	35
3	**8a**	CH_3COOH[b]	CH_3COONa	Reflux	4	**11a** (33)	40
4	**8b**	CH_3CN	CH_3COONa	60 °C	6	**10b** (20 and 5)	19
5	**8c**	CH_3COOH[b]	CH_3COONa	Reflux	1	**10c** (22), **11c** (41)	25
6	**8c**	CH_3CN	$(CH_3COO)_2Cu$	60 °C	4.5	**10c** (26), **11c** (9)	10
7	**8d**	CH_3COOH[b]	CH_3COONa[c]	Reflux	2.5	**10b** (40), **11c** (27)	—

a) Starting material. *b*) High dilution condition (**8**: 0.01 mol/l). *c*) Nine eq of AcONa was used.

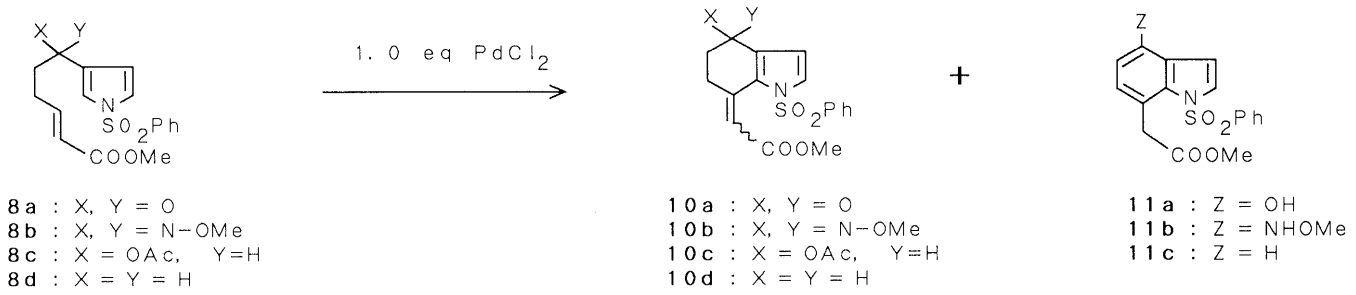

Chart 3

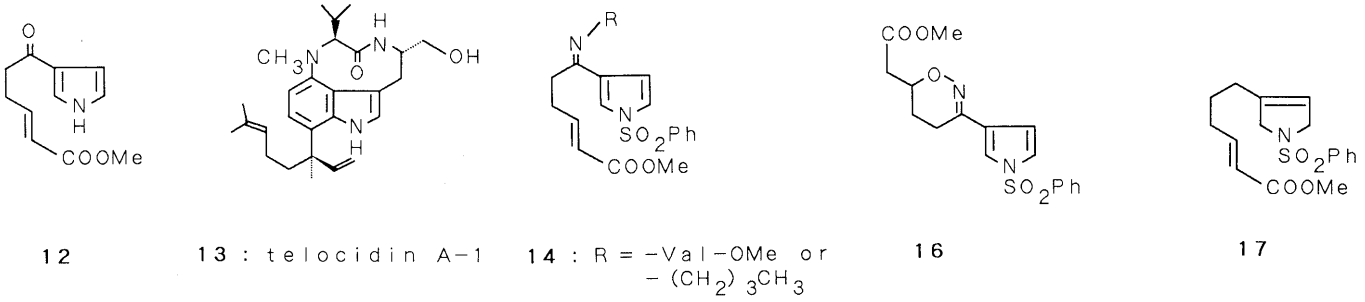

Chart 4

and the 4- (or β-) position of **6** as shown by Kakushima *et al.*[6] and ourselves.[4] Furthermore, those compounds should be stable under oxidative conditions (palladation) owing to the electron-withdrawing phenylsulfonyl or 2-ethoxycarbonyl group on the pyrrole ring.[7] The F–C acylation of the pyrroles (**5** and **6**) with the acid chloride (**7**) derived from (*E*)-5-methoxycarbonyl-4-pentenoic acid,[8] regioselectively gave the β-acylated products in good yields (73% for **8a**, 62% for **9a**) under the reported conditions.[4,6] If the ketone group in **8a** and **9a** is changed to other groups, various 4,7- or 7-substituted indoles should be obtained after cyclization.

Cyclization of the 1-(Phenylsulfonyl)-1*H*-pyrrole Series (8a—d) The cyclizations of the 1-(phenylsulfonyl)-1*H*-pyrrole series (**8a—d**) were examined in detail, and the results are summarized in Table I.

The cyclization of the ketone (**8a**) with 1.0 eq of $PdCl_2$ in the presence of 4.0 eq of $Cu(OAc)_2$ in CH_3CN gave no isolable product (run 1). So we changed the solvent and additive to AcOH and AcONa (run 2). The 4-hydroxy-7-alkylindole (**11a**) was obtained in low yield accompanied with the starting pyrrole (**8a**). The product (**11a**) should be formed by spontaneous isomerization of the double bond of the expected cyclized product (**10a**). This reaction was affected by the amount of solvent, since the yield was increased to 33% (with 40% recovery of starting material) by dilution about 10-fold with solvent (run 3). As the yield was still unsatisfactory, we tried to change the reactivity of the pyrrole ring towards palladation by deprotection of the phenylsulfonyl group. The deprotection of **8a** by Mg/MeOH[9] smoothly proceeded to give the NH-ketone (**12**) in good yield, but the cyclization of **12** was unsuccessful, giving only a tarry product accompanied with the starting material (49%) under the same conditions as those of run 2. The expected indole might be unstable under these conditions.

Next, we tried to synthesize 4-amino-7-alkylindole, which is potentially useful for the synthesis of teleocidines (**13** is a representative example). As the Schiff's base (**14**) could not be obtained by the reaction of the ketone (**8a**) with primary amines such as valine methyl ester (H–Val–OMe) or *n*-butylamine, preparation of the oxime (**15**) was examined. The reaction of **8a** with hydroxylamine gave the desired oxime (**15**) in only 35% yield as an unstable oil,

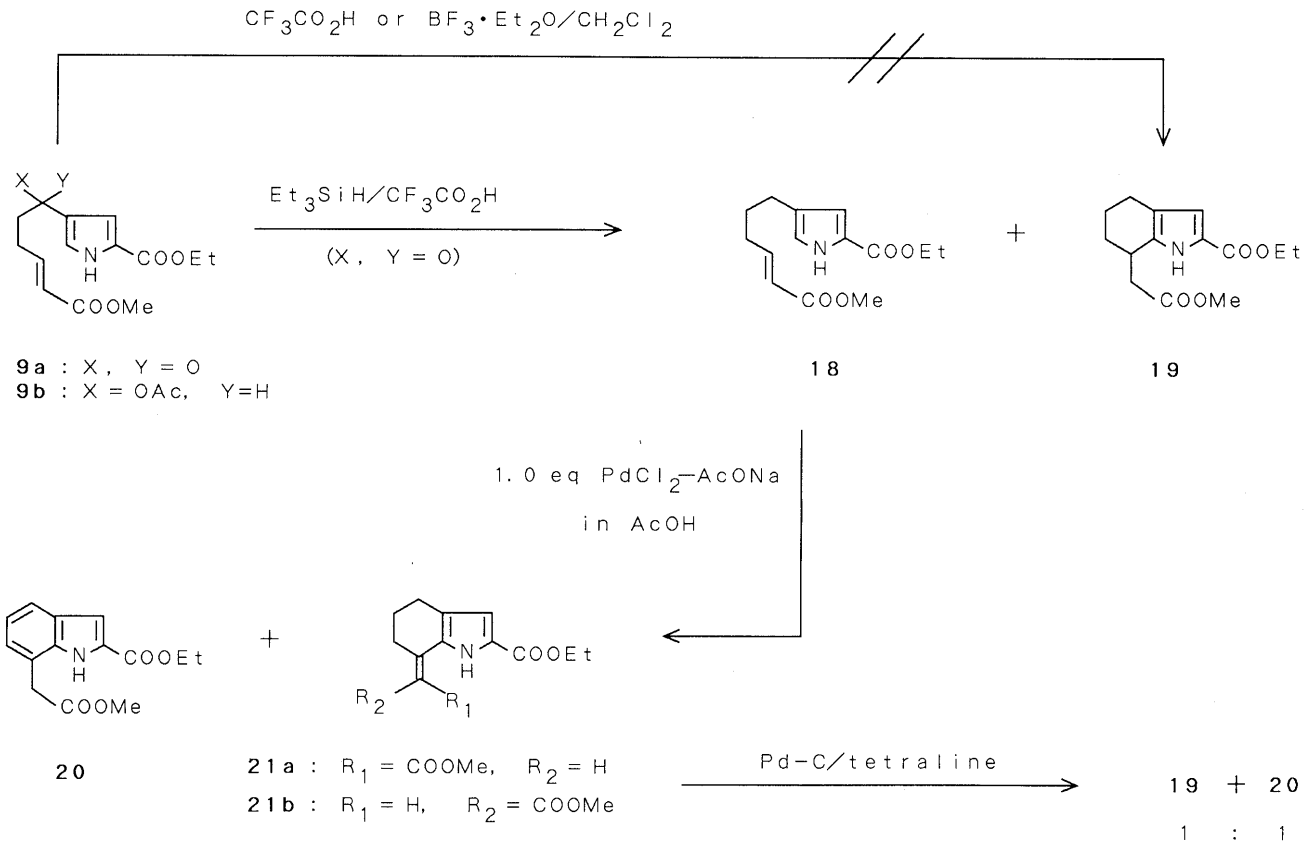

Chart 5

and the oxazole (**16**) in 62% yield as the major product. The oxazole (**16**) should be formed as a result of an intramolecular Michael addition of the hydroxyl group of the oxime (**15**). Thus, the methoxylamine was used in place of hydroxylamine to give the desired oxime (**8b**) in good yield as a mixture of *E*- and *Z*-isomers (91%). Both isomers were separable by silica gel chromatography, but the isomerization occurred very rapidly even in $CDCl_3$ during nuclear magnetic resonance (NMR) measurement. So a mixture of *E*- and *Z*-isomers was subjected directly to the cyclization. The cyclized product (**10b**) was obtained by using a combination of CH_3CN and AcONa in 25% yield as a mixture of two isomers out of four possible isomers (run 4). Each isomer was isolated as a pure form, but their structures could not be determined from the spectral data. Curiously, the desired indole (**11b**), which should be formed from **10b** by spontaneous isomerization of the double bond, was neither detected in the reaction mixture nor formed by heating **10b** with Pd–C or $RhCl(PPh_3)_3$.

Although the 4,7-disubstituted indoles were regiospecifically obtained in only a few steps from *N*-phenylsulfonylpyrrole (**5**), the yields of the cyclization products were unsatisfactory for the practical use. The reactivity of the ketone (**8a**) was presumed to be insufficient for palladation owing to the presence of electron-withdrawing substituents (1-phenylsulfonyl and C_3-carbonyl groups), since it is known[10] that electron-rich aromatic compounds show higher reactivity for palladation. As deprotection of the phenylsulfonyl group of **8a** led to unsatisfactory results in the cyclization as described before, the electron-withdrawing carbonyl group was reduced to alcohol or methylene. At first, the cyclization of the acetate (**8c**), which was obtained by reduction of the ketone (**8a**) with $NaBH_4$ followed by acetylation, was carried out, expecting the formation of the 7-monosubstituted indole (**11c**) in one step by spontaneous elimination of AcOH from the cyclization product (**10c**). In practice, however, the cyclic acetate (**10c**) was also formed as a minor product in addition to the expected indole (**11c**) (run 5). The combination of CH_3CN and $Cu(OAc)_2$ gave a much worse result (run 6). Treatment of the cyclic acetate (**10c**) with *p*-toluenesulfonic acid (*p*-TsOH) in benzene gave the corresponding indole (**11c**) in 46% yield.

Next we tried cyclization of the methylene compound (**8d**), although spontaneous aromatization could not be expected in the cyclized product (**10d**). When the ketone (**8a**) was reduced with triethylsilane (Et_3SiH) in CF_3COOH, not only the carbonyl group but also the pyrrole ring was reduced to give the dihydropyrrole derivative (**17**). The position of the double bond was tentatively determined to be between the 3- and 4-position based on the NMR spectrum, which showed one broad singlet at 4.02 ppm derived from two sets of methylene protons in the pyrrole ring. The crude product (**17**) was directly dehydrogenated with MnO_2 to give the aromatized α,β-unsaturated ester (**8d**). The reaction of **8d** under palladation conditions gave the cyclized product (**10d**) and aromatized indole (**11c**) in 40 and 27% yields, respectively, contrary to our prediction (run 7). Aromatization of **10d**[11] was accomplished in a stepwise manner according to our reported method.[4] Thus, **10d** was treated with $CuBr_2$ in AcOEt followed by heating with $LiBr/Li_2CO_3$ in *N*,*N*-dimethylformamide (DMF) to give the indole (**11c**) in 48% overall yield from **10d**.

Cyclization of the Ethyl Pyrrole-2-carboxylate Series (9a, b and 18) Next we turned our attention to the cyclization

of the ethyl pyrrole-2-carboxylate series (**9a, b** and **18**). The steric effect of the 2-ethoxycarbonyl group on the cyclization should be much less than that of the 1-phenylsulfonyl group, while the pyrrole ring would be stabilized by a 2-ethoxycarbonyl group to about the same extent as by the 1-phenylsulfonyl group. Contrary to our prediction, the ketone (**9a**) did not give the cyclized product at all, and the acetate (**9b**), a relatively unstable oil, afforded a complex mixture. But the cyclization of the methylene compound (**18**), which was obtained by the reduction of the ketone (**9a**) with Et_3SiH in CF_3COOH (*vide infra*), proceeded smoothly to give the indole (**20**), and the *Z*- and *E*-form of the tetrahydroindole (**21a** and **21b**) in 16%, 32%, and 17% yields, respectively. The geometries of the double bond of **21a** and **21b** were estimated from the chemical shifts of hydrogen at the pyrrole nitrogen [12.66 ppm for the major product (**21a**) and 9.63 ppm for the minor product (**21b**)], since hydrogen bonding of NH with the ester carbonyl was possible in the *Z*-form. Disappointingly, conversion of the cyclized olefin (**21a** or **21b**) to the indole (**20**) by Pd–C in tetraline gave a 1 : 1 mixture of the desired indole (**20**) and hexahydro derivative (**19**) as a result of disproportionation. It is not clear why disproportionation occurred instead of simple dehydrogenation.

Reduction of the ketone (**9a**) with Et_3SiH in CF_3COOH (room temperature, overnight) afforded an unexpected cyclized product (**19**) as the major product (59% yield) accompanied with the desired methylene compound (**18**) as a minor product (26% yield). The cyclized product (**19**) should be formed by an intramolecular Michael addition of the aromatic ring to the conjugated double bond. The shorter reaction time (4.5 h) increased the yield of the desired product (**18**, 56%), which was accompanied with **19** in 11% yield. On the basis of those results, we attempted the acid catalyzed cyclization of the ketone (**9a**), but the cyclized product was not obtained on treatment with CF_3COOH or $BF_3 \cdot OEt_2$ in CH_2Cl_2.

Conclusion

The present investigation, which involves palladium-mediated cyclization from the α- to the β-position of the pyrrole ring, provides a new methodology of indole synthesis, although it does not represent a practical approach so far, owing to the unsatisfactory yield and the requirement for stoichiometric use of expensive palladium salt.

Experimental

All melting points were determined on a Yanagimoto micromelting hot-stage apparatus and are uncorrected. Infrared (IR) spectra were recorded in Nujol mulls (unless otherwise stated) on a Shimadzu IR-400 spectrometer. ^{1}H-Nuclear magnetic resonance (^{1}H-NMR) spectra were recorded in $CDCl_3$ (unless otherwise stated) on a Hitachi R-24B spectrometer (60 MHz) (unless otherwise stated) or a JEOL GX-400 (400 MHz) spectrometer with tetramethylsilane as an internal reference. Mass spectra (MS) were measured with JEOL JMS-D-300 and JMS-DX-303 spectrometers using a direct inlet system. For column chromatography, Kiesel gel 60 (70—230 mesh, Merck), and for thin layer chromatography (TLC), Kieselgel GF_{254}, were used. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; dt, double triplet; ddd, double double doublet; dddd, double double double doublet; ddt, double double triplet; ttt, triple triple triplet; q, quartet; m, multiplet; dif, diffused; br, broad; arom, aromatic.

Preparation of Methyl (*E*)-6-Oxo-6-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]-2-hexenoate (8a) Oxalyl chloride (12.8 ml, 0.15 mol) was added to a solution of (*E*)-5-methoxycarbonyl-4-pentenoic acid (15.82 g, 0.10 mol) in CH_2Cl_2 (50 ml) at room temperature under an Ar atmosphere. After refluxing of the mixture for 20 min, excess oxalyl chloride and solvent were removed under reduced pressure to give the crude acid chloride (**7**) as an oil. A solution of this crude oil in CH_2ClCH_2Cl (100 ml) was added to powdered $AlCl_3$ (27 g, 0.20 mol) at 0 °C under an Ar atmosphere. After 15 min, a solution of 1-(phenylsulfonyl)pyrrole[12] (10.36 g, 0.05 mol) in CH_2Cl_2 (50 ml) was slowly added to the above mixture under ice cooling and the whole was stirred for 30 min at room temperature. Then the reaction mixture was poured into ice water and extracted with CH_2Cl_2. The organic layer was washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, and dried over $MgSO_4$. Evaporation of the solvent gave a brown oil (25.0 g), which was purified by silica gel column chromatography (AcOEt : *n*-hexane = 1 : 2) to give **8a** as a pale yellow solid (12.63 g, 73%). This solid was recrystallized from AcOEt–hexane to give colorless prisms, mp 74.5—75.5 °C. *Anal.* Calcd for $C_{17}H_{17}NO_5S$: C, 58.78; H, 4.93; N, 4.03. Found: C, 58.65; H, 4.86; N, 4.05. IR ν_{max} cm^{-1}: 1702, 1675 (C=O). ^{1}H-NMR (400 MHz) δ: 2.59 (2H, dq, J=7.0, 1.6 Hz, C$\underline{H}_2$CH=CH), 2.91 (2H, t, J=7.0 Hz, COC$\underline{H}_2$CH$_2$), 3.72 (3H, s, OCH_3), 5.87 (1H, dt, J=15.5, 1.6 Hz, =C$\underline{H}$CO), 6.69 (1H, dd, J=3.4, 1.8 Hz, 4-H), 6.98 (1H, dt, J=15.5, 7.0 Hz, C$\underline{H}$=CHCO), 7.17 (1H, dd, J=3.4, 2.0 Hz, 5-H), 7.56 (2H, t, J=7.5 Hz, 2×3′-H), 7.67 (1H, dt, J=7.5, 1.3 Hz, 4′-H), 7.74 (1H, dd, J=2.0, 1.8 Hz, 2-H), 7.92 (2H, dd, J=7.5, 1.3 Hz, 2×2′-H). MS m/z (%): 234 (100), 347 (M^+, 3.9).

Cyclization of 8a A mixture of **8a** (100 mg, 0.29 mmol), $PdCl_2$ (51 mg, 0.29 mmol), and AcONa (95 mg, 1.2 mmol) in AcOH (30 ml) was refluxed for 4 h under an Ar atmosphere. Then the reaction mixture was poured into H_2O and extracted with benzene. The organic layer was washed with H_2O and saturated aqueous NaCl and dried over $MgSO_4$. After evaporation of the solvent, the resultant brown oil (94 mg) was chromatographed on silica gel with AcOEt–hexane (1 : 2) to give methyl 4-hydroxy-1-(phenylsulfonyl)-1*H*-indole-7-acetate (**11a**) as a brown solid (33 mg, 33%), accompanied with 40 mg of starting material (40% recovery). **11a** was recrystallized from AcOEt–hexane to give pale brown prisms, mp 152.5—153.5 °C. *Anal.* Calcd for $C_{17}H_{15}NO_5S$: C, 59.12; H, 4.38; N, 4.06. Found: C, 59.11; H, 4.38; N, 4.06. IR ν_{max} cm^{-1}: 3365 (OH), 1718 (C=O). ^{1}H-NMR (400 MHz) δ: 3.71 (3H, s, OCH_3), 4.01 (2H, s, arom-C$\underline{H}_2$), 5.76 (1H, s, OH), 6.43 (1H, d, J=8.0 Hz, 5- or 6-H), 6.71 (1H, d, J=4.0 Hz, 2- or 3-H), 6.83 (2H, d, J=8.0 Hz, 5- or 6-H), 7.41 (2H, t, J=8.0 Hz, 2×3′-H), 7.52 (1H, dif t, J=8.0 Hz, 4′-H), 7.52 (1H, d, J=4.0 Hz, 2- or 3-H), 7.63 (2H, dd, J=8.0, 1.5 Hz, 2×2′-H). MS m/z (%): 149 (100), 345 (M^+, 40.4).

Preparation of Methyl 6-Oxo-6-(1*H*-pyrrol-3-yl)-2-hexenoate (12) A mixture of **8a** (2.00 g, 5.8 mmol) and Mg powder (210 mg, 8.6 mmol), and 2 drops of AcOH in absolute MeOH (30 ml) was refluxed for 7.5 h. Since the reaction was not completed, further Mg powder (140 mg, 5.8 mmol) and 1 drop of AcOH were added to the reaction mixture. Refluxing was continued for 2 h, then the precipitates were removed by filtration through Celite and washed thoroughly with MeOH. The combined filtrate was concentrated by evaporation and H_2O was poured into the residue. The aqueous layer was extracted with CH_2Cl_2. The organic layer was washed successively with H_2O and saturated aqueous NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the resultant yellow oil (1.22 g) was chromatographed on silica gel with AcOEt–hexane (1 : 2) to give **12** as a pale yellow solid (734 mg, 62%), which was recrystallized from AcOEt–Et_2O to give colorless prisms, mp 64.0—66.0 °C. *Anal.* Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.62; H, 6.30; N, 6.80. IR ν_{max} cm^{-1}: 3340—3260 (NH), 1725 (C=O). ^{1}H-NMR δ: 2.22—3.10 (4H, m, CH_2CH_2), 3.67 (3H, s, $COOCH_3$), 5.82 (1H, d, J=16.0 Hz, =C$\underline{H}$CO$_2$CH$_3$), 6.5—7.1 (3H, m, C$\underline{H}$=CHCO and arom-H), 7.3—7.5 (1H, m, arom-H), 9.1—10.1 (1H, br s, NH). MS m/z (%): 94 (100), 207 (M^+, 6.5).

Preparation of Methyl 6-Hydroxyimino-6-[1-(phenylsulfonyl)-1*H*-pyrrol-2-yl]-2-hexenoate (15) A solution of hydroxylamine hydrochloride (63 mg, 0.91 mmol) and sodium acetate (123 mg, 1.50 mmol) in H_2O (0.8 ml) was added to a solution of **8a** (300 mg, 0.86 mmol) in MeOH (3 ml) at 0 °C. The mixture was stirred for 4 h at room temperature, then MeOH was removed by evaporation and the residue was extracted with benzene. The organic layer was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the resultant colorless oil (310 mg) was separated into two fractions by silica gel column chromatography using AcOEt–hexane as an eluent. The first fraction was an isomeric mixture of oximes (**15**), which was obtained as an unstable oil (111 mg, 35%). IR ν_{max} cm^{-1}: 3140 (OH), 1720 (C=O). ^{1}H-NMR δ: 2.1—3.1 (4H, m, –C$\underline{H}_2$C$\underline{H}_2$–), 3.69 (3H, s, $CO_2C\underline{H}_3$),

5.80 (1H, dif d, J=15 Hz, =CHCO), 6.51 (1H, dd, J=3, 1 Hz, 2- or 3-H), 6.6—8.0 (8H, m, arom-H and CH=CHCO), 8.2—8.8 (1H, br, O–H). MS m/z (%): 77 (100), 362 (M^+, 22). The second fraction was the oxazole (**16**), which was obtained as a colorless oil (188 mg, 60%). IR ν_{max} cm^{-1}: 1735 (C=O). ^{1}H-NMR δ: 1.7—3.5 (6H, m, aliphatic-H), 3.65 (3H, s, CO_2CH_3), 4.1—4.8 (1H, m, O–CH), 6.4—6.6 (1H, m, 2- or 3-H), 7.0—8.0 and 8.4—8.6 (7H, m, arom-H). MS m/z (%): 362 (M^+, 100). High-resolution MS m/z: Calcd for $C_{17}H_{18}N_2O_5S$: 362.0932. Found: 362.0923.

Preparation of Methyl 6-Methoxyimino-6-[1-(phenylsulfonyl)-1*H*-pyrrol-2-yl)-2-hexenoate (8b) A solution of methoxylamine hydrochloride (264 mg, 3.2 mmol) and AcONa (425 mg, 5.2 mmol) in H_2O (2.5 ml) was added to a solution of **8a** (1.00 g, 2.9 mmol) in MeOH (20 ml) at room temperature. After refluxing of the mixture for 15.5 h, MeOH was removed by evaporation and the residue was extracted with benzene. The organic layer was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the resultant colorless oil (1.098 g) was chromatographed on silica gel with AcOEt–hexane (1 : 3) to give an isomeric mixture of **8b** as a colorless solid (985 mg, 91%). Each isomer was separated by careful silica gel column chromatography to give the pure isomers. The first fraction, the major isomer, was a colorless solid, mp 66.5—71.0 °C. IR ν_{max} cm^{-1}: 1710 (C=O), 1648 (C=N). ^{1}H-NMR (400 MHz) δ: 2.41 (2H, ddt, J=6.8, 1.6, 7.8 Hz, CH_2CH=), 2.67 (2H, t, J=7.8 Hz, N=CCH_2), 3.73 and 3.89 (2×3H, 2×s, 2×OCH_3), 5.83 (1H, dt, J=15.6, 1.6 Hz, =CHCO), 6.60 (1H, dd, J=3.3, 1.6 Hz, 4- or 5-H), 6.96 (1H, dt, J=15.6, 6.8 Hz, CH_2CH=CH), 7.13 (1H, dd, J=3.3, 2.1 Hz, 4- or 5-H), 7.30 (1H, dd, J=2.1, 1.6 Hz, 2-H), 7.52 (2H, t, J=7.7 Hz, 2×3′-H), 7.62 (1H, tt, J=7.7, 1.5 Hz, 4′-H), 7.87 (2H, dd, J=7.7, 1.5 Hz, 2×2′-H). MS m/z (%): 77 (100), 376 (M^+, 2.9). High-resolution MS m/z: Calcd for $C_{18}H_{20}N_2O_5S$: 376.1088. Found: 376.1090. The second fraction, the minor isomer, was a colorless oil. IR (film) ν_{max} cm^{-1}: 1710 (C=O), 1648 (C=N). ^{1}H-NMR (400 MHz) δ: 2.46—2.53 (2H, m, CH_2CH=), 2.63 (2H, t, J=7.9 Hz, N=CCH_2), 3.72 and 3.96 (2×3H, 2×s, 2×OCH_3), 5.84 (1H, dt, J=15.8, 1.7 Hz, =CHCO), 6.54 (1H, dd, J=3.4, 1.7 Hz, 4- or 5-H), 6.99 (1H, dt, J=15.8, 6.8 Hz), CH_2CH=CH), 7.15 (1H, dd, J=3.4, 2.2 Hz, 4- or 5-H), 7.53 (2H, t, J=7.5 Hz, 2×3′-H), 7.63 (1H, tt, J=7.5, 1.5 Hz, 4′-H), 7.90 (2H, dd, J=7.5, 1.5 Hz, 2×2′-H), 7.92 (1H, dd, J=2.2, 1.7 Hz, 2-H), MS m/z (%): 77 (100), 376 (M^+, 1.8). High-resolution MS m/z: Calcd for $C_{18}H_{20}N_2O_5S$: 376.1088. Found: 376.1091. These isomers were easily isomerized to each other during recrystallization or NMR measurement.

Cyclization of 8b A mixture of **8b** (100 mg, 0.27 mmol), $PdCl_2$ (47 mg, 0.27 mmol), and AcONa (87 mg, 1.1 mmol) in CH_3CN (3 ml) was heated at 60 °C for 25 h under an Ar atmosphere. Then the reaction mixture was poured into H_2O and extracted with AcOEt–benzene. The organic layer was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the resultant dark brown oil (71 mg) was chromatographed on silica gel with benzene–AcOEt (40 : 1) to give the two pure isomers of 7-methoxycarbonylmethylidene-4-methoxyimino-1-phenylsulfonyl-4,5,6,7-tetrahydro-1*H*-indole (**10b**). The first fraction was a pale yellow solid (20 mg, 20%), which was recrystallized from AcOEt–hexane to give colorless prisms, mp 131.5—133.0 °C. *Anal.* Calcd for $C_{18}H_{18}N_2O_5S$: C, 57.74; H, 4.85; N, 7.48. Found: C, 57.63; H, 4.83; N, 7.36. IR ν_{max} cm^{-1}: 1695 (C=O), 1615 (C=N). ^{1}H-NMR (400 MHz) δ: 2.67 (2H, t, J=6.9 Hz, N=CCH_2), 2.98 (2H, dt, J=6.9, 0.9 Hz, CH=CCH_2), 3.77 and 3.91 (2×3H, 2×s, 2×OCH_3), 6.58 (1H, br s, =$CHCO_2CH_3$), 6.65 (1H, d, J=3.5 Hz, 2- or 3-H), 7.44 (2H, t, J=8.0 Hz, 2×3′-H), 7.48 (1H, d, J=3.5 Hz, 2- or 3-H), 7.59 (1H, tt, J=8.0, 1.5 Hz, 4′-H), 7.65 (2H, dd, J=8.0, 1.5 Hz, 2×2′-H). MS m/z (%): 201 (100), 374 (M^+, 86.3). The second fraction was a pale yellow solid (5.3 mg, 5.3%), which was recrystallized from benzene to give colorless prisms, mp 160.5—161.5 °C. *Anal.* Calcd for $C_{18}H_{18}N_2O_5S$: C, 57.74; H, 4.85; N, 7.48. Found: C, 57.62; H, 4.82; N, 7.46. IR ν_{max} cm^{-1}: 1700 (C=O), 1615 (C=N). ^{1}H-NMR (400 MHz) δ: 2.73 (2H, t, J=6.9 Hz, N=CCH_2), 3.18 (2H, dt, J=6.9, 1.6 Hz, CH=CCH_2), 3.73, 3.92 (2×3H, 2×s, 2×OCH_3), 6.14 (1H, t, J=1.6 Hz, =$CHCO_2CH_3$), 7.41 (1H, d, J=2.2 Hz, 2- or 3-H), 7.52 (1H, d, J=2.2 Hz, 2- or 3-H), 7.54 (2H, t, J=7.5 Hz, 2×3′-H), 7.66 (1H, tt, J=7.5, 1.9 Hz, 4′-H), 7.93 (2H, dd, J=7.5, 1.9 Hz, 2×2′-H). MS m/z (%): 77 (100), 374 (M^+, 75.9). The third fraction was recovered starting material as a mixture of isomers (**8b**, 19 mg, 19%).

Preparation of Methyl 6-Acetoxy-6-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl)-2-hexanoate (8c) A) Reduction of the ketone (**8a**) with $NaBH_4$: $NaBH_4$ (109 mg, 2.88 mmol) was added to a solution of **8a** (1.00 g, 2.88 mmol) in MeOH (20 ml) at room temperature and the mixture was stirred for 30 min. Since the reaction was not completed, further $NaBH_4$ (15 mg, 0.40 mmol) was added. After 30 min, the reaction was quenched with H_2O and the mixture was extracted with Et_2O. The organic layer was washed successively with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, and dried over $MgSO_4$. Evaporation of the solvent gave a colorless oil (1.076 g), which was chromatographed on silica gel with AcOEt–benzene (1 : 4) to give methyl 6-hydroxy-6-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]-2-hexenoate as a a colorless oil (916 mg, 91%). IR (film) ν_{max} cm^{-1}: 1720 (C=O). ^{1}H-NMR δ: 1.5—2.5 (4H, m, CH_2CH_2), 2.30 (1H, br s, OH), 3.64 (3H, s, OCH_3), 4.53 (1H, t, J=6 Hz, CHOH), 5.71 (1H, d, J=16 Hz, CH=CHCO), 6.20 (1H, dd, J=4, 2 Hz, 4-H), 6.6—7.9 (8H, m, Ar-H and CH=CHCO). MS m/z (%): 236 (100), 349 (M^+, 1.6). High-resolution MS m/z: Calcd for $C_{17}H_{19}NO_5S$: 349.0979. Found: 349.0989. B) Acetylation of methyl 6-hydroxy-6-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]-2-hexenoate: Ac_2O (0.451 ml, 4.78 mmol) was added to a solution of the above alcohol (835 mg, 2.39 mmol) in pyridine (8 ml) and the mixture was stirred for 17 h. The reaction mixture was poured into ice water, stirred for 1 h, and extracted with Et_2O. The organic layer was washed successively with 10% aqueous HCl, saturated $NaHCO_3$, and saturated aqueous NaCl, and dried over $MgSO_4$. Evaporation of the solvent gave a pale yellow oil (0.924 g), which was chromatographed on silica gel with AcOEt–hexane (1 : 2) to give the title compound (**8c**) as a pale yellow oil (906 mg, 97%). *Anal.* Calcd for $C_{19}H_{21}NO_6S$: C, 58.30; H, 5.41; N, 3.58. Found: C, 58.26; H, 5.52; N, 3.64. IR (film) ν_{max} cm^{-1}: 1735, 1720 (C=O). ^{1}H-NMR δ: 1.6—2.5 (4H, m, CH_2CH_2), 2.00 (3H, s, $COCH_3$), 3.67 (3H, s, $COOCH_3$), 5.68 (1H, dif t, J=6 Hz, $CHOCOCH_3$), 5.71 (1H, dif d, J=16 Hz, =$CHCO_2CH_3$), 6.20 (1H, t, J=3 Hz, arom-H), 6.6—7.9 (8H, m, CH=CHCO and arom-H).

Cyclization of 8c A mixture of **8c** (100 mg, 0.26 mmol), $PdCl_2$ (46 mg, 0.26 mmol), and AcONa (84 mg, 1.0 mmol) in AcOH (30 ml) was refluxed for 1 h under an Ar atmosphere. Then most of the AcOH was removed by evaporation. The residue was diluted with H_2O and extracted with AcOEt. The organic layer was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the resultant dark brown tar (96 mg) was chromatographed on silica gel with benzene–AcOEt (30 : 1) to give the two cyclized products. The first fraction gave methyl 1-(phenylsulfonyl)-1*H*-indole-7-acetate (**11c**) as a colorless solid (34 mg, 41%), which was recrystallized from benzene–hexane to give colorless prisms, mp 104.0—105.5 °C. *Anal.* Calcd for $C_{17}H_{15}NO_4S$: C, 61.99; H, 4.59; N, 4.25. Found: C, 62.09; H, 4.55; N, 4.25. IR (film) ν_{max} cm^{-1}: 1735 (C=O). ^{1}H-NMR δ: 3.60 (3H, s, OCH_3), 4.10 (2H, s, arom-CH_2CO), 6.58 (1H, d, J=4 Hz, 2- or 3-H), 7.0—7.7 (9H, m, arom-H). MS m/z (%): 374 (M^+, 100). The second fraction gave 4-acetoxy-7-methoxycarbonylmethylidene-4,5,6,7-tetrahydro-1*H*-indole (**10c**) as a colorless oil (22 mg, 22%). IR ν_{max} cm^{-1}: 1733 and 1700 (C=O). ^{1}H-NMR (400 MHz) δ: 1.8—1.9, 2.0—2.1, 2.9—3.0, 3.1—3.2 (each 1H, 4×m, CH_2CH_2), 2.04 (3H, s, CH_3CO), 3.74 (3H, s, OCH_3), 5.78 (1H, t, J=5.5 Hz, $CHOCOCH_3$), 6.34 (1H, d, J=3.5 Hz, 2- or 3-H), 6.59 (1H, br s, =$CHCO_2CH_3$), 7.47 (2H, t, J=8.5 Hz, 2×3′-H), 7.53 (1H, d, J=3.5 Hz, 2- or 3-H), 7.61 (1H, tt, J=8.5, 1.2 Hz, 4′-H), 7.67 (2H, dd, J=8.5, 1.2 Hz, 2×2′-H). MS m/z (%): 188 (100), 389 (M^+, 12.7). High-resolution MS m/z: Calcd for $C_{19}H_{19}NO_6S$: 389.0934. Found: 389.0926. The third fraction gave recovered starting material (**8c**, 24.8 mg, 25% recovery).

Conversion of 10c to 11c A mixture of 4-acetoxy-7-carbomethoxymethylidene-4,5,6,7-tetrahydro-1*H*-indole (**10c**) (46.7 mg, 0.12 mmol) and *p*-toluenesulfonic acid (20 mg, 0.11 mmol) in benzene was heated at 60 °C for 10 min under an Ar atmosphere. Then the reaction mixture was poured into H_2O and extracted with benzene. The organic layer was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the resultant brown oil (39.2 mg) was chromatographed on silica gel with AcOEt–benzene (1 : 30) to give methyl 1-(phenylsulfonyl)-1*H*-indole-7-acetate (**11c**) as a solid (18.0 mg, 46%), whose IR and NMR spectra were identical with those of the product obtained from the cyclization of **8c** or **8d**.

Preparation of Methyl 6-[1-(Phenylsulfonyl)-1*H*-pyrrol-3-yl]-2-hexenoate (8d) A mixture of **8a** (1.39 g, 4.0 mmol) and Et_3SiH (2.1 ml, 13.2 mmol) in CF_3COOH (24 ml) was heated at 60 °C for 1 h. Then CF_3COOH was removed under reduced pressure below 40 °C and the residue was diluted with CH_2Cl_2. The organic layer was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the resultant oil (2.48 g) was chromatographed on silica gel with AcOEt–hexane (1 : 3) to give methyl 6-(1-phenylsulfonyl-2,5-dihydro-1*H*-pyrrol-3-yl)-2-hexenoate (**17**) as an unstable pale brown oil (0.992 g). IR (film) ν_{max} cm^{-1}: 1720 (C=O). ^{1}H-NMR δ: 1.3—1.8 (2H,

m, $CH_2C\underline{H}_2CH_2CH=$), 1.8—2.6 (4H, m, $C\underline{H}_2CH_2C\underline{H}_2CH=$), 3.70 (3H, s, OCH_3), 4.02 (4H, br s, $C\underline{H}_2NC\underline{H}_2$), 5.28 (1H, br s, $NCH_2C\underline{H}=$), 5.75 (1H, br d, $J=17$ Hz, $CH=C\underline{H}CO$), 6.5—7.2 (1H, m, $C\underline{H}=CHCO$), 7.3—7.6 (3H, m, $2\times3'$-H and 4′-H), 7.6—7.8 (2H, m, $2\times2'$-H).

A mixture of the above oil (**17**, 0.992 g) and MnO_2 (9.92 g) in benzene (99 ml) was refluxed for 1 h. MnO_2 was filtered off and washed thoroughly with hot benzene. After evaporation of the solvent, the title compound (**8d**) was obtained as a pale brown oil (0.607 g, 46% yield from **8a**). IR (film) ν_{max} cm^{-1}: 1730 (C=O). ^{1}H-NMR δ: 1.4—1.9 (2H, m, $CH_2C\underline{H}_2CH_2CH=$), 1.9—2.6 (4H, m, $C\underline{H}_2CH_2C\underline{H}_2CH=$), 3.67 (3H, s, OCH_3), 5.72 (1H, br d, $J=17$ Hz, $CH=C\underline{H}CO$), 6.0—6.2 (1H, m, 4-H), 6.6—7.2 (3H, m, $C\underline{H}=CHCO$, 2-H, and 5-H), 7.3—7.6 (3H, m, $2\times3'$-H and 4′-H), 7.6—8.1 (2H, m, $2\times2'$-H). MS *m/z* (%): 77 (100), 333 (M^+, 2.1). High-resolution MS *m/z*: Calcd for $C_{17}H_{19}NO_4S$: 333.1035. Found: 333.1020.

Cyclization of 8d A mixture of **8d** (100 mg, 0.30 mmol), $PdCl_2$ (53 mg, 0.30 mmol), and AcONa (218 mg, 2.7 mmol) in AcOH (30 ml) was refluxed for 3 h under an Ar atmosphere. Then most of the AcOH was distilled off under reduced pressure. The residue was diluted with H_2O and extracted with AcOEt. The organic layer was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the resultant dark brown tar (97 mg) was chromatographed on silica gel with AcOEt–hexane (1 : 5) to give the two cyclized products. The first fraction gave 7-methoxycarbonylmethylidene-1-phenylsulfonyl-4,5,6,7-tetrahydro-1*H*-indole (**10d**) as a colorless solid (39 mg, 40%), which was recrystallized from benzene–hexane to give colorless prisms, mp 91.0—92.5 °C. *Anal.* Calcd for $C_{17}H_{17}NO_4S$: C, 61.62; H, 5.17; N, 4.23. Found: C, 61.57; H, 5.17; N, 4.22. IR ν_{max} cm^{-1}: 1700 (C=O). ^{1}H-NMR (400 MHz) δ: 1.72 (2H, quintet, $J=6.2$ Hz, $CH_2C\underline{H}_2CH_2$), 2.50 (2H, t, $J=6.2$ Hz, $CH_2C\underline{H}_2$-arom), 2.96 (2H, dt, $J=6.2$, 1.3 Hz, $CH_2C\underline{H}_2C=$), 3.72 (3H, s, OCH_3), 6.17 (1H, d, $J=3.3$ Hz, 2- or 3-H), 6.51 (1H, br s, $CH=C\underline{H}CO$), 7.43 (2H, t, $J=7.5$ Hz, 3′-H), 7.47 (1H, d, $J=3.3$ Hz, 2- or 3-H), 7.57 (1H, dif tt, $J=7.5$, 1.5 Hz, 4′-H), 7.64 (2H, dif dd, $J=7.5$, 1.5 Hz, 2′-H). MS *m/z* (%): 77 (100), 331 (M^+, 11.9). The second fraction gave methyl 1-(phenylsulfonyl)-1*H*-indole-7-acetate (**11c**, 27 mg, 27%), of which the IR and NMR spectra were identical with those of the product obtained by the cyclization of the acetate (**8c**).

Conversion of 10d to 11c A) Bromination: A mixture of **10d** (23.7 mg, 0.07 mmol) and $CuBr_2$ (31.9 mg, 0.14 mmol) in AcOEt (1 ml) was refluxed for 20 min under an Ar atmosphere. Then the precipitates were removed by filtration and washed with AcOEt. The combined organic layer was washed with H_2O and saturated aqueous NaCl, and dried over $MgSO_4$. Evaporation of the solvent gave dark a brown oil (30 mg), which was chromatographed on silica gel with benzene to give 6-bromo-7-methoxycarbonylmethylidene-1-phenylsulfonyl-4,5,6,7-tetrahydro-1*H*-indole as a colorless solid (18.1 mg, 62%), which was recrystallized from benzene–hexane to give a colorless prisms, mp 115—134 °C. IR ν_{max} cm^{-1}: 1700 (C=O). ^{1}H-NMR δ: 2.08 (1H, dddd, $J=14.5$, 11.0, 6.0, 3.1 Hz, 5-H_A), 2.21 (1H, dddd, $J=14.5$, 6.0, 3.1, 1.5 Hz, 5-H_B), 2.63 (1H, ddd, $J=17.0$, 6.0, 1.5 Hz, 4-H_A), 2.85 (1H, ddd, $J=17.0$, 11.0, 6.0 Hz, 4-H_B), 3.79 (3H, s, OCH_3), 6.22 (1H, d, $J=3.5$ Hz, 2- or 3-H), 6.60 (1H, t, $J=3.1$ Hz, 6-H), 6.66 (1H, s, C=CHCO), 7.42 (2H, dif t, $J=8.0$ Hz, 3′-H), 7.55 (1H, dif tt, $J=8.0$, 1.5 Hz 4′-H), 7.55 (1H, d, $J=3.5$ Hz, 2- or 3-H), 7.66 (2H, dif dd, $J=8.0$, 1.5 Hz, 2′-H). MS *m/z* (%): 188 (100), 409 (M^+, 18.7), 411 (M^++2, 18.7%). High-resolution MS *m/z*: Calcd for $C_{17}H_{16}BrNO_4S$: 408.9979. Found: 408.9979.

B) Aromatization: A mixture of the above bromide (11.0 mg, 0.027 mmol), LiBr (2.6 mg, 0.03 mmol), and $LiCO_3$ (2.2 mg, 0.03 mmol) in DMF (0.2 ml) was heated at 120 °C for 2 h under an Ar atmosphere. Then the reaction mixture was poured into H_2O and extracted with Et_2O. The organic layer was washed with H_2O and saturated aqueous NaCl, and dried over $MgSO_4$. Evaporation of the solvent gave a residue (9.6 mg), which was chromatographed on silica gel to give methyl 1-(phenylsulfonyl)-1*H*-indole-7-acetate (**11c**, 6.8 mg, 77%) as a colorless solid. The IR and NMR spectra of this compound were identical with those of the cyclization product obtained from **8c** or **8d**.

Preparation of Ethyl 4-(5-Methoxycarbonyl-1-oxo-4-pentenyl)-1*H*-pyrrole-2-carboxylate (9a) Oxalyl chloride (12.6 ml, 144 mmol) was added to a solution of (*E*)-5-methoxycarbonyl-4-pentenoic acid (15.37 g, 97 mmol) in CH_2Cl_2 (30 ml) at room temperature under an Ar atmosphere and the mixture was heated at 40 °C for 1.5 h. Then the solvent and excess oxalyl chloride were removed by evaporation to give the crude acid chloride (**7**) as an oil. A solution of this crude oil in $CHCl_3$ (100 ml) was added to $AlCl_3$ (25.72 g, 193 mmol) under Ar, then a solution of ethyl 1*H*-pyrrole-2-carboxylate (6.78 g, 49 mmol) in $CHCl_3$ (30 ml) was added to the above solution. The whole mixture was refluxed for 3 h, poured into ice water, and then extracted with AcOEt. The organic layer was washed successively with saturated $NaHCO_3$ and saturated NaCl and dried over $MgSO_4$. Evaporation of the solvent gave a brown oil (24.0 g), which was purified by silica gel chromatography (AcOEt–benzene) to give the desired compound (**9a**) as a pale yellow solid (8.47 g, 62%). This solid was recrystallized from benzene–hexane to give colorless prisms, mp 76—79 °C. *Anal.* Calcd for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14; N, 5.02. Found: C, 59.95; H, 6.09; N, 5.02. IR ν_{max} cm^{-1}: 1705, 1645 (C=O). ^{1}H-NMR δ: 1.37 (3H, t, $J=7.0$ Hz, $OCH_2C\underline{H}_3$), 2.4—3.2 [4H, m, $CO(C\underline{H}_2)_2CH=$], 3.69 (3H, s, OCH_3), 4.33 (2H, q, $J=7$ Hz, $OC\underline{H}_2CH_3$), 5.83 (1H, d, $J=16$ Hz, $=C\underline{H}CO_2CH_3$), 6.7—7.2 (1H, m, $C\underline{H}=CHCO$), 7.21 (1H, t, $J=2$ Hz, 3- or 5-H), 7.50 (1H, dd, $J=3$, 2 Hz, 3- or 5-H), 10.1 (1H, br s, NH). MS *m/z* (%): 120 (100), 279 (M^+, 11.7).

Reduction of 9a Et_3SiH (0.31 ml, 1.9 mmol) was added to a solution of **9a** (140 mg, 0.50 mmol) in CF_3COOH (3.0 ml) at room temperature under an Ar atmosphere, and the mixture was stirred for 4.5 h, then poured into ice-water and extracted with AcOEt. The organic layer was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, and dried over $MgSO_4$. Evaporation of the solvent gave a residue (184 mg), which was chromatographed on silica gel with benzene–hexane to provide two products. The first fraction gave ethyl 7-methoxycarbonylmethyl-4,5,6,7-tetrahydro-1*H*-indole-2-carboxylate (**19**) (15 mg, 11% yield), which was recrystallized from benzene–hexane to give colorless needles, mp 89—94 °C. *Anal.* Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.31; H, 7.32; N, 5.27. IR ν_{max} cm^{-1}: 3300 (NH), 1735, 1670 (C=O). ^{1}H-NMR δ: 1.32 (3H, t, $J=7$ Hz, $OCH_2C\underline{H}_3$), 1.6—2.3 (4H, m, arom-$CH_2C\underline{H}_2C\underline{H}_2$), 2.2—2.8 (4H, m, arom-$CH_2$ and $C\underline{H}_2COOCH_3$), 3.0—3.4 (1H, m, $C\underline{H}CH_2CO$), 3.72 (3H, s, OCH_3), 4.27 (2H, q, $J=7$ Hz, $OC\underline{H}_2CH_3$), 6.62 (1H, d, $J=2$ Hz, 3-H), 9.62 (1H, br s, NH). MS *m/z* (%): 192 (100), 265 (M^+, 50.3). The second fraction gave ethyl 4-(5-methoxycarbonyl-4-pentenyl)-1*H*-pyrrole-2-carboxylate (**18**) as an yellow oil (75 mg, 56% yield). IR (film) ν_{max} cm^{-1}: 3300 (NH), 1705 (C=O). ^{1}H-NMR δ: 1.25 (3H, t, $J=7$ Hz, $OCH_2C\underline{H}_3$), 1.5—1.9 (2H, m, arom-$CH_2C\underline{H}_2CH_2$), 1.9—2.7 (4H, m, arom-$C\underline{H}_2$ and $C\underline{H}_2CH=CH$), 4.22 (2H, q, $J=7$ Hz, $OC\underline{H}_2CH_3$), 3.62 (3H, s, OCH_3), 5.71 (1H, d, $J=15$ Hz, $CH=C\underline{H}CO$), 6.5—6.8 (2H, m, 3-H and 5-H), 6.7—7.2 (1H, m, $C\underline{H}=CHCO$), 9.38 (1H, br s, NH). MS *m/z* (%): 106 (100), 265 (M^+, 27.0). High-resolution MS *m/z*: Calcd for $C_{14}H_{19}NO_4$: 265.1314. Found: 265.1306.

Cyclization of 18 A mixture of **18** (162 mg, 0.61 mmol), $PdCl_2$ (108 mg, 0.61 mmol), and AcONa (200 mg, 2.44 mmol) in AcOH (6 ml) was heated at 60 °C for 3 h under an Ar atmosphere. The reaction mixture was filtered through Celite and the residue was washed with hot AcOEt and water. The aqueous layer was extracted with AcOEt. The combined organic layer was washed with saturated aqueous NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the residue (171 mg) was chromatographed on silica gel with AcOEt–hexane to give four pure compounds as colorless solids. The first fraction gave ethyl (*Z*)-7-methoxycarbonylmethylidene-4,5,6,7-tetrahydro-1*H*-indole-2-carboxylate (**21a**, 51 mg, 32% yield), which was recrystallized from AcOEt–hexane to give colorless needles, mp 68—70 °C. *Anal.* Calcd for $C_{14}H_{17}NO_4$: C, 63.56; H, 6.51; N, 5.32. Found: C, 63.88; H, 6.59; N, 5.29. IR ν_{max} cm^{-1}: 3200 (NH), 1710, 1690, (C=O). ^{1}H-NMR δ: 1.37 (3H, t, $J=7$ Hz, $OCH_2C\underline{H}_3$), 1.89 (2H, q, $J=6$ Hz, arom-$CH_2C\underline{H}_2CH_2$), 2.56 and 2.65 (2×2H, $2\times$t, $J=6$ Hz, arom-$C\underline{H}_2$ and $C\underline{H}_2C=CH$), 3.73 (3H, s, OCH_3), 4.34 (2H, q, $J=7$ Hz, $OC\underline{H}_2CH_3$), 5.56 (1H, br s, $C=C\underline{H}CO$), 6.66 (1H, d, $J=3$ Hz, 3-H), 12.66 (1H, br s, NH). MS *m/z* (%): 263 (M^+, 100). The second fraction gave ethyl (*E*)-7-methoxycarbonylmethylidene-4,5,6,7-tetrahydro-1*H*-indole-2-carboxylate (**21b**, 28 mg, 17%), which was recrystallized from AcOEt–hexane to give colorless needles, mp 158—161 °C. *Anal.* Calcd for $C_{14}H_{17}NO_4$: C, 63.56; H, 6.51; N, 5.32. Found: C, 63.57; H, 6.57; N, 5.27. IR ν_{max} cm^{-1}: 3280 (NH), 1685 (C=O). ^{1}H-NMR δ: 1.33 (3H, t, $J=7$ Hz, $OCH_2C\underline{H}_3$), 1.6—2.2 (2H, m, arom-$CH_2C\underline{H}_2CH_2$), 2.61 (2H, t, $J=6$ Hz, $ArC\underline{H}_2$), 3.10 (2H, br t, $J=6$ Hz, $C\underline{H}_2C=CH$), 3.69 (3H, s, OCH_3), 4.34 (2H, q, $J=7$ Hz, $OC\underline{H}_2CH_3$), 6.03 (1H, br s, $C=C\underline{H}CO$), 6.66 (1H, d, $J=2$ Hz, 3-H), 9.63 (1H, br s, NH). MS *m/z* (%): 263 (M^+, 100). The third fraction gave ethyl 7-(methoxycarbonylmethyl)-1*H*-indole-2-carboxylate (**20**, 26 mg, 16%), which was recrystallized from AcOEt–hexane to give colorless needles, mp 100—101 °C. *Anal.* Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.37; H, 6.01; N, 5.09. IR ν_{max} cm^{-1}: 3340 (NH), 1725, 1685 (C=O). ^{1}H-NMR δ: 1.40 (3H, t, $J=7$ Hz, $OCH_2C\underline{H}_3$), 3.67 (3H, s, CO_2CH_3), 3.87 (2H, s, arom-CH_2CO), 4.41 (2H, q, $J=7$ Hz, $OC\underline{H}_2CH_3$), 7.0—7.4 (3H, m, arom-H), 7.59 (1H, dd, $J=6$, 3 Hz, 4-H), 9.50 (1H, br s, NH). MS *m/z* (%): 261 (M^+, 100). Fourth fraction gave unchanged starting material (20 mg, 12% recovery).

Dehydrogenation of 21 with Pd–C A mixture of **21** (a mixture of *E*- and *Z*-isomer, 76 mg, 0.29 mmol) and 10% Pd–C (20 mg) in tetralin (2 ml) was heated at 220 °C for 11.5 h. Then Pd–C was filtered off and washed thoroughly with AcOEt. The combined organic layer was evaporated and the residue was chromatographed on silica gel with AcOEt–benzene to give a colorless solid (62 mg), which was a mixture of **19** and **20** (1 : 1). The ratio of **19** and **20** was determined by NMR.

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References and Notes

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