Synthesis of 6-Alkoxy-3-(1-hydroxyalkyl)-5-nitro-4,5,6,7-tetrahydroindole-4-carboxylates

Ho Hyeon Kim, Yang Mo Goo,† and Youn Young Lee*

Department of Chemistry and †Department of Pharmacy, Seoul National University, Seoul 151-742, Korea
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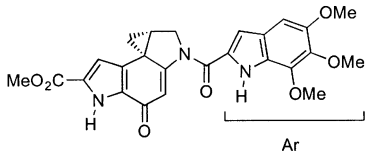
2-(β-Alkoxyvinyl)-4-(1-hydroxyalkyl)pyrroles (**14**) were synthesized from 4-acylpyrrole-2-carboxylates (**8**) by sequential reduction of their acyl and alkoxycarbonyl groups to give 4-(1-hydroxyalkyl)pyrrole-2-carbaldehydes (**13**) followed by Wittig reaction of the aldehydes with the ylide of alkoxymethylphosphonium chloride. Diels-Alder reaction of 2-(β-alkoxyvinyl)-4-(1-hydroxyalkyl)pyrroles with *trans*-methyl β-nitroacrylate gave 6-alkoxy-3-(1-hydroxyalkyl)-5-nitro-4,5,6,7-tetrahydroindole-4-carboxylates (**3**).

Introduction

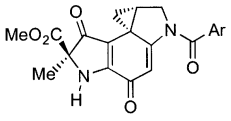
Duocarmycins (**1**) are novel antitumor and antibiotic agents isolated from the culture broth of *Streptomyces* spp.[1] Duocarmycin C_1 and C_2 are identical with pyrindamycin B and A, respectively, which were also isolated at the almost same time from the culture broth of a *Streptomyces* spp.[2] They have very similar structures with the potent antitumor antibiotic CC-1065 which was isolated from the culture broth of *Streptomyces zelensis*.[3]

The total synthesis of duocarmycins has been achieved through pyrrolo[3,2-*e*]indole (**PI**) skeletons. In the early synthesis of duocarmycin A by Terashima *et al.*,[4] and duocarmycin SA by Boger *et al.*,[5] the approach employed in the synthesis of CC-1065[6,7] is adapted, in which 4-chloro-3-nitroanisole and 2-amino-5-nitrophenol are used as the starting materials, respectively. The starting materials are converted to indole derivatives which are further transformed to pyrrolo[3,2-*e*]indole derivatives. For the synthesis of duocarmycins and their analogs, we have thought that pyrrolo[3,2-*e*]indole derivatives can be obtained from tetrahydroindole derivatives (**3**) which can be synthesized by Diels-Alder reaction of 2-(β-alkoxyvinyl)-4-hydroxymethylpyrrole (**2**) with β-nitroacrylate (Scheme 1).

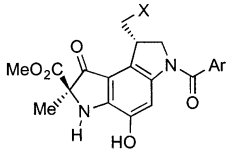
In the present paper, we wish to report the synthesis of 2-(β-alkoxyvinyl)-4-(1-hydroxyalkyl)-pyrroles and the use of Diels-Alder reactions of these compounds with β-nitroacrylates for the construction of tetrahydroindole derivatives.



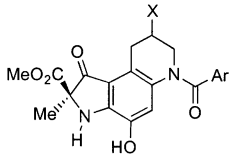
1a Duocarmycin SA



1b Duocarmycin A



1c Duocarmycin B_2 ; X = Br
1d Duocarmycin C_2 ; X = Cl
(Pyrindamycin A)



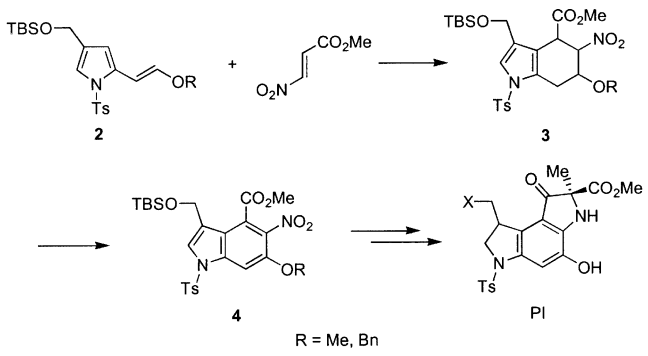
1e Duocarmycin B_1 ; X = Br
1f Duocarmycin C_1 ; X = Cl
(Pyindamycin B)

Figure 1

Results and Discussion

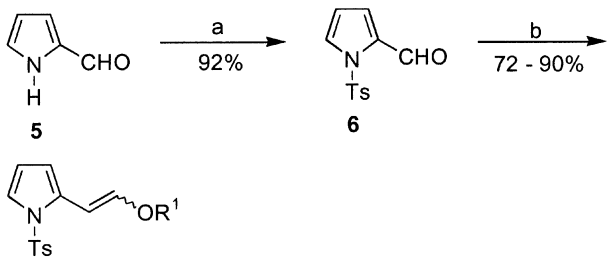
Synthesis of 2-(β-alkoxyvinyl)pyrroles. 2-(β-Alkoxyvinyl)pyrroles (**7**) were obtained by Wittig reaction of the ylides of alkoxymethyltriphenylphosphonium chloride with pyrrole-2-carbaldehyde (**5**) protected with a tosyl group (Scheme 2). The tosylation was done on compound **5** by treatment with NaH in DMF followed by tosyl chloride to give 1-tosylpyrrole-2-carbaldehyde (**6**) in 92% yield. The ylide of alkoxymethyltriphenylphosphonium chloride produced by treatment of LDA was reacted with **6** to give **7** in 72-90% yields.

2-(β-Alkoxyvinyl)-4-(1-hydroxyalkyl)pyrroles (**14**) were obtained from the esters **8**[9] by sequential reduction of their



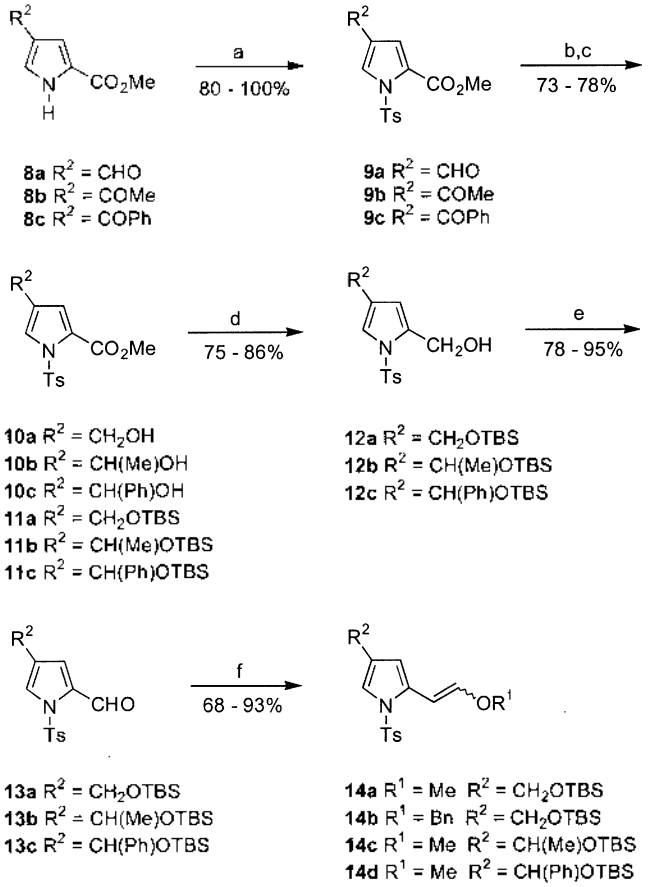
R = Me, Bn

Scheme 1



7a R^1 = Me
7b R^1 = Bn

Scheme 2. Reagents and conditions: a) DMF, NaH, TsCl, 0 °C, 1 h. b) LDA, −78 °C, $Ph_3P^+CH_2OCH_3Cl^-$ or $Ph_3P^+CH_2OCH_2PhCl^-$, 1 h.



8a R^2 = CHO
8b R^2 = COMe
8c R^2 = COPh

9a R^2 = CHO
9b R^2 = COMe
9c R^2 = COPh

10a R^2 = CH_2OH
10b R^2 = CH(Me)OH
10c R^2 = CH(Ph)OH
11a R^2 = CH_2OTBS
11b R^2 = CH(Me)OTBS
11c R^2 = CH(Ph)OTBS

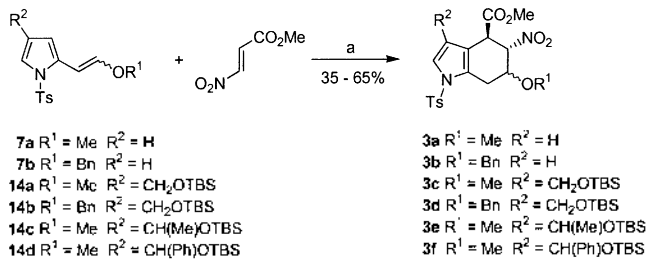
12a R^2 = CH_2OTBS
12b R^2 = CH(Me)OTBS
12c R^2 = CH(Ph)OTBS

13a R^2 = CH_2OTBS
13b R^2 = CH(Me)OTBS
13c R^2 = CH(Ph)OTBS

14a R^1 = Me R^2 = CH_2OTBS
14b R^1 = Bn R^2 = CH_2OTBS
14c R^1 = Me R^2 = CH(Me)OTBS
14d R^1 = Me R^2 = CH(Ph)OTBS

Scheme 3. Reagents and conditions: a) NaH, DMF, TsCl, 0 °C, 1 h b) 5 eq $NaBH_4$, EtOH - H_2O (3 : 1), 2 h. c) TBDMSCl, imidazole, DMF, 30 min. d) LAH, ether, −78 °C, 1 h. e) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, NEt_3, 30 min. f) LDA, THF, −78 °C, $Ph_3P^+CH_2OMeCl^-$ or $Ph_3P^+CH_2$-OCH_2PhCl^-, 1 h.

acyl and alkoxycarbonyl groups to give 4-(1-hydroxyalkyl)pyrrole-2-carbaldehydes (**13**) followed by Wittig reaction (Scheme 3). After tosylation of the amino groups of compounds **8** in 80-100% yields, their acyl groups were reduced with sodium borohydride to give 4-(1-hydroxyalkyl)pyrrole-2-carboxylates (**10**) in 73-78% yields. The compounds **11** obtained from **10** by protecting their hydroxy groups with a *t*-butyldimethylsilyl group (yields, 89-97%) were reduced with lithium aluminium hydride to give 2-hydroxymethylpyrroles (**12**) in 75-86% yields.



7a R^1 = Me R^2 = H
7b R^1 = Bn R^2 = H
14a R^1 = Me R^2 = CH_2OTBS
14b R^1 = Bn R^2 = CH_2OTBS
14c R^1 = Me R^2 = CH(Me)OTBS
14d R^1 = Me R^2 = CH(Ph)OTBS

3a R^1 = Me R^2 = H
3b R^1 = Bn R^2 = H
3c R^1 = Me R^2 = CH_2OTBS
3d R^1 = Bn R^2 = CH_2OTBS
3e R^1 = Me R^2 = CH(Me)OTBS
3f R^1 = Me R^2 = CH(Ph)OTBS

Scheme 4. Reagents and conditions: a) toluene, reflux, 9-12 h.

Swern oxidation of compounds **12** gave 4-(1-hydroxyalkyl)pyrrole-2-carbaldehydes (**13**) in 78-95% yields. After treatment of alkoxymethyltriphenylphosphonium chloride with LDA, it was reacted with compounds **13** to give 2-(β-alkoxyvinyl)pyrroles (**14**) in 68-93% yields. The products were composed of *cis* and *trans* isomers as shown in ^{1}H NMR spectra.

Diels-Alder reactions of 2-(β-alkoxyvinyl)pyrroles with β-nitroacrylates. Diels-Alder reactions of 2-vinylpyrrole,[10] 3-vinylpyrrole,[10] or 2-(β-nitrovinyl)pyrrole[11] with dienophiles have been reported to produce 4,5,6,7-tetrahydroindole or indole derivatives. In the present study, we employed Diels-Alder reaction to achieve synthesis of 6-alkoxy-5-nitro-4,5,6,7-tetrahydroindole-4-carboxylates (**3**) from 2-(β-alkoxyvinyl)pyrroles (**14**) and *trans*-methyl β-nitroacrylate. Heating 2-(β-alkoxyvinyl)pyrroles (**14**) and *trans*-methyl β-nitroacrylate in toluene at reflux for 9-12 h produced tetrahydroindole derivatives (**3**) in 35-65% yields (Scheme 4).

The regiochemistry of tetrahydroindoles **3** was assigned on the basis that the similar regioisomers were observed during the Diels-Alder reaction of 1-oxygenated butadienes with *trans*-methyl β-nitroacrylate.[12] We could not isolate regioisomers of **3**. Compounds **3a-3c** were found to be composed of two diastereomers having *cis* and *trans* configurations at C-5 and C-6 positions. The stereochemistry of two diastereomers of **3a-3c** can not be defined with certainty. We assigned tentatively their stereochemistry with the coupling constants between C-5 and C-6 protons on the basis of the literature.[13] Compound **3a** showed ^{1}H NMR signals corresponding to the *trans* and the *cis* isomers at the ratio of 3 : 2. The *trans* isomer showed a double doublet (J_{cd} – 10.0 Hz, J_{cc} – 1.4 Hz) at 4.42 ppm for the proton (H_c) of C-4 and also a double doublet (J_{dc} – 10.0 Hz, J_{dc} – 10.0 Hz) at the 5.04 ppm for the proton (H_d) at the C-5 position in ^{1}H NMR spectrum. Also, the isomer showed multiplets at 4.55 ppm for H_c at the C-6 position and a double double doublets (J_{ab} – 17.0 Hz, J_{bc} – 5.0 Hz, J_{bd} – 1.8 Hz) at 2.78 ppm for H_b, and a double doublet (J_{ab} – 17.0 Hz, J_{ac} – 5.8 Hz) at 3.63 ppm for H_a at the C-7 position. The *cis* isomer showed two double doublets at 4.31 (J_{cd} – 10.0 Hz, J_{cc} – 1.4 Hz) ppm and at 4.95 (J_{dc} – 10.0 Hz, J_{dc} – 2.0 Hz) ppm for H_c of C-4 and H_d of C-5, respectively in the ^{1}H NMR spectrum. The *cis* isomer also showed a multiplet at 4.04 ppm (H_c of C-6) and a double double doublet (J_{ab} – 17.0 Hz, J_{bc} – 2.0 Hz, J_{bd} – 2.0 Hz) and a double doublet (J_{ab} – 17.0 Hz, J_{ac} – 1.4 Hz) for the two protons of

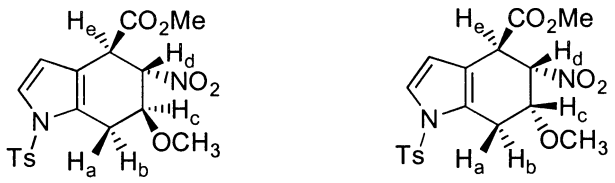


Figure 2

C-7 (Figure 2). Since aromatization of the tetrahydroindoles **3** to indole derivatives was necessary for the synthesis of duocarmycins and their analogs, we did not try to isolate these isomers.

Experimental Section

IR spectra were obtained with Perkin-Elmer 735-B IR spectrophotometer. ^{1}H NMR spectra were recorded with Bruker AC 80, Varian VXR-200S or Bruker DPX-300 NMR spectrometer with tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed as δ (ppm). Melting points were measured with Electrothermal digital melting point measurement apparatus without correction. THF was distilled in the presence of sodium and benzophenone. Xylene and toluene were used after distillation over P_2O_5. Other solvents and chemicals were used without further purification of commercially available first grade reagents.

1-Tosylpyrrole-2-carbaldehyde (6). Pyrrole-2-caraldehyde (2.20 g, 24 mmol) in DMF (30 mL) was treated with NaH (60% in mineral oil, 1.08 g, 26 mmol) and *p*-toluenesulfonyl chloride (4.58 g, 24 mmol) was added to the solution. After stirring 1 h at room temperature, saturated ammonium chloride solution (20 mL) was added. The reaction mixture was extracted with ethyl acetate (50 mL × 2). The extract was washed with water (100 mL) and dried over magnesium sulfate. Evaporation of the solvent gave a solid product. Yield, 5.30 g (92%); mp 89-90 °C; ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3H, CH_3), 6.50 (t, 1H, J = 4.0 Hz, H-4), 7.35 (m, 1H, H-3), 7.42 (d, 2H, J = 8.0 Hz, Ar), 7.75 (m, 1H, H-5), 7.95 (d, 2H, J = 8.0 Hz, Ar), 10.1 (s, 1H, CHO).

2-(-Methoxyvinyl)-1-tosylpyrrole (7a). Methoxymethyltriphenylphosphonium chloride (1.83 g, 5.30 mmol) in THF (30 mL) was treated wtih phenyllithium (cyclohexane-ether, 1.8 M, 2.9 mL, 5.3 mmol) at 0 °C for 15 min. Then, 1-tosylpyrrole-2-carbaldehyde (1.1 g, 4.4 mmol) in THF (5 mL) was added and the mixture was stirred for 1 h. After evaporation of the solvent, the residue was chromatographed over silica gel using hexane-ethyl acetate (9 : 1) as an eluent to give an oily product. Yield, 1.1 g (90%); ^{1}H NMR ($CDCl_3$) δ 2.47 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 6.10-6.40 (m, 3H, H-3, H-4, –C**H**OCH_3), 6.90 (d, 1H, J = 13.0, –C**H**Ar), 7.35-7.60 (m, 3H, Ar), 7.90 (d, 2H, J = 9.0 Hz, Ar); IR (neat) 2930, 1640, 1590, 815, 710 cm^{-1}; Anal. Caled for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.35; H, 5.53; N, 5.13.

2-(β-Benzyloxyvinyl)-1-tosylpyrrole (7b). Benzyloxymethyltriphenylphosphonium chloride (7.0 g, 16.0 mmol) was reacted with 1-tosylpyrrole-2-carbaldehyde (2.80 g, 11 mmol) following the same procedure as described for the synthesis of **7a** to give an oily product. Yield, 2.85 g (72%); ^{1}H NMR ($CDCl_3$), δ 2.33 (s, 3H, CH_3), 4.85 (s, 2H, CH_2), 6.00-6.40 (m, 3H, H-3, H-4, –C**H**OBn), 6.60-6.80 (m, 1H, –C**H**Ar), 7.10-7.60 (m, 10H, Ar); IR (neat) 1640, 1600, 810 cm^{-1}; Anal. Caled for $C_{20}H_{19}NO_3S$: C, 67.97; H, 5.42; N, 3.96. Found: C, 67.72; H, 5.24; N, 4.12.

Methyl 4-formyl-1-tosylpyrrole-2-carboxylate (9a). Methyl 4-formylpyrrole-2-carboxylate (2.0 g, 13 mmol) in DMF (30 mL) was treated with NaH (60% in mineral oil, 0.62 g, 15 mmol). After the mixture was stirred for 10 min at 0 °C, tosyl chloride (2.80 g, 15 mmol) was added and stirred for 30 min at the same temperature. After saturated ammonium chloride solution was added, the reaction mixture was extracted with chloroform (50 mL × 3). Drying of the extract with magnesium sulfate and evaporation of solvent gave a solid product. Yield, 3.2 g (80%); ^{1}H NMR ($CDCl_3$), δ 2.93 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 7.33-8.00 (m, 6H, Ar), 9.83 (s, 1H, CHO); IR (KBr) 1720, 1690, 1340, 820, 730 cm^{-1}.

Methyl 4-acetyl-1-tosylpyrrole-2-carboxylate (9b). Methyl 4-acetylpyrrole-2-carboxylate (1.50 g, 8.9 mmol) was reacted with tosyl chloride (2.54 g, 13 mmol) by the same procedure as described for the synthesis of **9a** to give a solid product. Yield, 2.86 g (100%); mp 168 °C; ^{1}H NMR ($CDCl_3$), δ 2.46 (s, 3H, CH_3), 2.47 (s, 3H, $COCH_3$), 3.77 (s, 3H, OCH_3), 7.33 (d, 2H, J = 8.0 Hz, Ar), 7.40 (m, 1H, H-3), 8.00 (d, 2H, J = 8.0 Hz, Ar), 8.30 (m, 1H, H-5); IR (KBr) 2950, 1730, 1670, 1230, 1170, 1130 cm^{-1}.

Methyl 4-benzoyl-1-tosylpyrrole-2-carboxylate (9c). Methyl 4-benzoylpyrrole-2-carboxylate (2.52 g, 11 mmol) was reacted with tosyl chloride (3.0 g, 16 mmol) by the same procedure as described for the synthesis of **9a** to give a solid product. Yield, 4.0 g (95%); mp 162 °C; ^{1}H NMR ($CDCl_3$), δ 2.40 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 7.20-8.23 (m, 11H, Ar); IR (KBr) 2950, 1730, 1650, 1550, 1240, 1175, 725 cm^{-1}.

Methyl 4-hydroxymethyl-1-tosylpyrrole-2-carboxylate (10a). Compound **9a** (3.0 g, 9 mmol) was dissolved in aqueous ethanol (75%, 100 mL) and sodium borohydride (1.7 g, 48 mmol) dissolved in ethanol (40 mL) was added. The mixture was stirred for 12 h at room temperature. After evaporation of ethanol, the product was extracted with chloroform (50 mL × 3). The extract was dried over magnesium sulfate and evaporated to give a solid product. Yield, 2.20 g (73%); mp 112 °C; ^{1}H NMR ($CDCl_3$), δ 2.33 (s, 3H, CH_3), 2.35 (s, 1H, OH), 3.67 (s, 3H, OCH_3), 4.50 (s, 2H, CH_2), 7.00 (m, 1H, H-3), 7.23 (d, 2H, J = 8.0 Hz, Ar), 7.80 (m, 1H, H-5), 7.87 (d, 2H, J = 8.0 Hz, Ar); IR (KBr) 3500, 1730, 820 cm^{-1}.

Methyl 4-(1-hydroxyethyl)-1-tosylpyrrole-2-carboxylate (10b). Compound **9b** (2.86 g, 8.9 mmol) was reduced with sodium borohydride (1.68 g, 44 mmol) by the same procedure as described for the synthesis of **10a** to give a solid product. Yield, 2.20 g (76%); mp 115 °C; ^{1}H NMR ($CDCl_3$), δ 1.43 (d, 3H, J = 6.0 Hz, CH_3), 2.33 (s, 3H, CH_3),

2.60 (s, 1H, OH), 3.68 (s, 3H, OCH_3), 4.85 (m, 1H C**H**OH), 7.03 (d, 2H, J = 1.8 Hz, H-3), 7.28 (d, 2H, J = 8.0 Hz, Ar), 7.67 (d, 1H, J = 1.8 Hz, H-5), 7.88 (d, 2H, J = 8.0 Hz, Ar); IR (KBr) 3600-3200, 2960, 1725, 1370, 1230, 1175, 820 cm^{-1}.

Methyl 4-(-hydroxybenzyl)-1-tosylpyrrole-2-carboxylate (10c). Compound **9c** (4.20 g, 11 mmol) was reduced with sodium borohydride (2.0 g, 55 mmol) by the same procedure as described for the synthesis of **10a** to give a solid product. Yield, 3.30 g (78%); mp 125 °C; ^{1}H NMR ($CDCl_3$), δ 2.37 (s, 3H, CH_3), 2.60 (s, 1H, OH), 3.60 (s, 3H, OCH_3), 5.70 (s, 1H, CH), 6.90 (d, 1H, J = 1.8 Hz, H-3), 7.10-7.43 (m, 7H, Ar), 7.60 (m, 1H, H-5), 7.87 (d, 2H, J = 8.0 Hz, Ar); IR (KBr) 3600-3300, 1730, 1180, 820, 730 cm^{-1}.

Methyl 4-(*t*-butyldimethylsilyloxymethyl)-1-tosylpyrrole-2-carboxylate (11a). Compound **10a** (2.0 g, 6.0 mmol) in DMF (15 mL) was stirred with *t*-butyldimethylsilyl chloride (1.45 g, 9.0 mmol) and imidazole (1.2 g, 18.0 mmol) at room temperature for 1 h. The reaction mixture was diluted with water (100 mL) and extracted with diethyl ether (50 mL × 3). The extract was washed with saturated sodium bicarbonate solution (50 mL) and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a solid product. Yield 2.5 g (92%), mp 92 °C; ^{1}H NMR ($CDCl_3$), δ 0.11 (s, 6H, $Si(CH_3)_2$), 0.93 (s, 9H, SiBu-*t*), 2.47 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.67 (s, 2H, CH_2), 7.07 (m, 1H, H-3), 7.40 (d, 2H, J = 8.0 Hz, Ar), 7.73 (m, 1H, H-5), 8.00 (d, 2H, J = 8.0 Hz, Ar); IR (KBr) 2950, 1730 cm^{-1}.

Methyl 4-[1-(*t*-butyldimethylsilyloxy)ethyl]-1-tosylpyrrole-2-carboxylate (11b). Compound **10b** (2.0 g, 6.1 mmol) was reacted with *t*-butyldimethylsilyl chloride (1.40 g, 9.0 mmol) and imidazole (1.2 g, 18.0 mmol) by the same procedure as described for the synthesis of **11a** to give an oily product. Yield 2.40 g (89%); ^{1}H NMR ($CDCl_3$), δ 0.06 [s, 6H, $Si(CH_3)_2$], 0.93 (s, 9H, SiBu-*t*), 1.40 (d, 3H, J = 6.0 Hz, CH_3), 2.43 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 4.83 (q, 1H, J = 6.0 Hz, CH), 7.00 (d, 1H, J = 1.8 Hz, H-3), 7.30 (d, 2H, J = 8.0 Hz, Ar), 7.57 (d, 1H, J = 1.8 Hz, H-5), 7.87 (d, 2H, J = 8.0 Hz, Ar); IR (neat) 2950, 1730, 1600, 1380, 1180, 810 cm^{-1}.

Methyl 4-[α-(*t*-butyldimethylsilyloxy)benzyl]-1-tosylpyrrole-2-carboxylate (11c). Compound **10c** (3.0 g, 7.8 mmol) was reacted with *t*-butyldimethylsilyl chloride (1.80 g, 11.0 mmol) and imidazole (1.5 g, 22 mmol) by the same procedure as described for the synthesis of **11a** to give an oily product. Yield 3.75 g (97%); ^{1}H NMR ($CDCl_3$), δ 0.11 [s, 6H, $Si(CH_3)_2$], 0.96 (s, 9H, SiBu-*t*), 2.48 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 5.73 (s, 1H, CH), 6.93 (d, 1H, J = 1.8 Hz, H-3), 7.13-7.53 (m, 7H, Ar), 7.60 (m, 1H, H-5), 7.90 (d, 2H, J = 8.0 Hz, Ar); IR (neat) 3600-3300, 1730, 1600, 1470, 1370, 1250 cm^{-1}.

4-(*t*-Butyldimethylsilyloxymethyl)-2-hydroxymethyl-1-tosylpyrrole (12a). Compound **11a** (0.50 g, 1.1 mmol) in diethyl ether (3.0 mL) was added to the diethyl ether solution (15 mL) of $LiAlH_4$ (0.05 g, 1.4 mmol) which was cooled in dry ice-acetone bath, and the mixture was stirred for 30 min. After warming up the reaction mixture to room tempertature, ethyl acetate (4.0 mL) was added. The mixture was filtered through celite. Evaporation of the solvent gave an oily product. Yield, 0.4 g (86%); ^{1}H NMR ($CDCl_3$), δ 0.02 [s, 6H, $Si(CH_3)_2$], 0.84 (s, 9H, SiBu-*t*), 2.34 (s, 3H, CH_3), 2.36 (s, 1H, OH), 4.47 (s, 2H, CH_2), 4.51 (s, 2H, CH_2), 6.16 (d, 1H, J = 2.0 Hz, H-3), 7.09 (d, 1H, J = 2.0 Hz, H-5), 7.27 (d, 2H, J = 8.0 Hz, Ar), 7.60 (d, 2H, J = 8.0 Hz, Ar); IR (neat) 3550-3400, 2950, 1365, 1170, 1090, 840 cm^{-1}.

4-[1-(*t*-Butyldimethylsilyloxy)ethyl]-2-hydroxymethyl-1-tosylpyrrole (12b). Compound **11b** (2.40 g, 5.4 mmol) was reduced with $LiAlH_4$ (0.30 g, 8.0 mmol) by the same procedure as described for the synthesis of **12a** to give an oily product. Yield, 1.8 g (80%); ^{1}H NMR ($CDCl_3$), δ 0.10 [s, 6H, $Si(CH_3)_2$], 0.93 (s, 9H, SiBu-*t*), 1.43 (d, 3H, J = 6.0 Hz, CH_3), 2.47 (s, 3H, CH_3), 2.91 (br s, 1H, OH), 4.63 (s, 2H, CH_2), 4.83 (q, 1H, J = 6.0 Hz, CH), 6.30 (d, 1H, J = 1.8 Hz, H-3), 7.20 (m, 1H, H-5), 7.38 (d, 2H, J = 8.0 Hz, Ar), 7.87(d, 2H, J = 8.0 Hz, Ar); IR (neat) 3550-3300, 1600, 1380, 1250, 1175, 840 cm^{-1}.

4-[-(*t*-Butyldimethylsilyloxy)benzyl]-2-hydroxymethyl-1-tosylpyrrole (12c). Compound **11c** (3.70 g, 7.4 mmol) was reduced with $LiAlH_4$ (0.34 g, 7.4 mmol) by the same procedure as described for the synthesis of **12a** to give an oily product. Yield, 2.61 g (75%); ^{1}H NMR ($CDCl_3$), δ 0.06 [s, 6H, $Si(CH_3)_2$], 0.83 (s, 9H, SiBu-*t*), 2.37 (s, 3H, CH_3), 2.63 (s, 1H, OH), 4.47 (s, 2H, CH_2), 5.58 (s, 1H, CH), 6.08 (d, 1H, J = 1.8 Hz, H-3), 7.00-7.50 (m, 8H, Ar), 7.70 (d, 2H, J = 8.0 Hz, Ar); IR (neat) 3550-3400, 2940, 1595, 1460, 1250 cm^{-1}.

4-(*t*-Butyldimethylsilyloxymethyl)-1-tosylpyrrole-2-carbaldehyde (13a). Compound **12a** (0.17 g, 0.43 mmol) in methylene chloride (2 mL) was added to the methylene chloride solution (20 mL) of oxalyl chloride (0.10 g, 0.86 mmol) and DMSO (0.13 g, 1.70 mmol) at −78 °C and the mixture was stirred for 15 min at the same temperature. After addition of triethylamine (0.45 g, 4.3 mmol), the reaction mixture was warmed up to room temperature and water (5 mL) was added. After addition of additional water (100 mL), the reaction mixture was extracted with chloroform (50 mL × 3). The extract was dried over anhydrous magnesium sulfate and evaporated to give a solid product. Yield, 0.16 g (95%); mp 79-80 °C; ^{1}H NMR ($CDCl_3$), δ 0.03 [s, 6H, $Si(CH_3)_2$], 0.87 (s, 9H, SiBu-*t*), 2.37 (s, 3H, CH_3), 4.53 (s, 2H, CH_2), 7.07 (d, 1H, J = 2.0 Hz, H-3), 7.28 (d, 2H, J = 8.0 Hz, Ar), 7.47 (d, 1H, J = 2.0, Hz, H-5), 7.78 (d, 2H, J = 8.0 Hz, Ar), 9.95 (s, 1H, CHO); IR (KBr) 2950, 1180, 1090, 840 cm^{-1}.

4-[1-(*t*-Butyldimethylsilyloxy)ethyl]-1-tosylpyrrole-2-carbaldehyde (13b). Compound **12b** (1.80 g, 4.4 mmol) was oxidized with oxalyl chloride (1.1 g, 8.8 mmol) and DMSO (1.37 g, 17.6 mmol) by the same procedure as described for the synthesis of **13a** to give an oily product. Yield, 1.50 g (84%); ^{1}H NMR ($CDCl_3$), δ 0.10 [s, 6H, $Si(CH_3)_2$], 0.85 (s, 9H, SiBu-*t*), 1.40 (d, 3H, J = 6.0 Hz, CH_3), 2.40 (s, 3H, CH_3), 4.83 (q, 1H, J = 6.0 Hz, CH), 7.06 (d, 1H, J = 1.8 Hz, H-3), 7.31 (d, 2H, J = 8.0 Hz, Ar), 7.50 (d, 1H, J = 1.8 Hz, H-5), 7.80 (d, 2H, J = 8.0 Hz, Ar), 9.91 (s, 1H, CHO); IR

(neat) 2950, 1670, 1380, 1255, 1180, 840 cm $^{-1}$.

4-[α-(*t*-Butyldimethylsilyloxy)benzyl]-1-tosylpyrrole-2-carbaldehyde (13c). Compound **12c** (0.18 g, 3.8 mmol) was oxidized with oxalyl chloride (0.97 g, 7.6 mmol) and DMSO (1.20 g, 15 mmol) by the same procedure as described for the synthesis of **13a** to give an oily product. Yield, 1.40 g (78%); ^{1}H NMR ($CDCl_3$), δ 0.06 [s, 6H, $Si(CH_3)_2$], 0.96 (s, 9H, SiBu-*t*), 2.45 (s, 3H, CH_3), 5.80 (s, 1H, CH), 7.13 (m, 1H, H-3), 7.30-7.67 (m, 8H, Ar), 8.00 (d, 2H, J = 8.0 Hz, Ar), 10.11 (s, 1H, CHO); IR (neat) 2950, 1670, 1460, 1380, 1180, 840 cm $^{-1}$.

4-(*t*-Butyldimethylsilyloxymethyl)-2-(β-methoxyvinyl)-1-tosylpyrrole (14a). Compound **13a** (1.0 g, 2.5 mmol) in THF (5 mL) was added to the solution of methoxymethyltriphenylphosphonium bromide (1.50 g, 3.8 mmol) in THF (20 mL) which was treated for 15 min at 0 °C with phenyllithium (1.8 M in cyclohexane-diethyl ether, 2.1 mL, 3.8 mmol). After stirring the mixture for 1 h at the same temperature, the reaction mixture was treated with saturated ammonium chloride solution (10 mL), and extracted with ethyl acetate (50 mL × 3). The extract was dried over anhydrous magnesium sulfate and evaporated to give a deep red color residue which was chromatographed over silica gel using hexane-ethyl acetate (20 : 1) as an eluent to give an oily product. Yield, 1.0 g (93%); ^{1}H NMR ($CDCl_3$), δ 0.02 [s, 6H, $Si(CH_3)_2$], 0.88 (s, 9H, SiBu-*t*), 2.39 (s, 3H, CH_3), 3.65 and 3.72 (s, 3H, OCH_3), 4.52 and 4.53 (d, 2H, J = 0.8 Hz, CH_2), 5.93-6.17 (m, 2H, H-3, =CH-), 6.67-6.92 (m, 1H, =C**H**OCH_3), 7.15 (m, 1H, H-5), 7.24 (d, 2H, J = 8.0 Hz, Ar), 7.66 (d, 2H, J = 8.0 Hz, Ar); IR (neat) 2950, 1640, 1370, 1250, 1180, 840 cm $^{-1}$; Anal. Calcd for $C_{21}H_{31}NO_4SSi$: C, 59.82; H, 7.41; N, 3.32. Found: C, 60.12; H, 7.52; N, 3.21.

4-(*t*-Butyldimethylsilyloxymethyl)-2-(β-benzyloxyvinyl)-1-tosylpyrrole (14b). Compound **13a** (0.5 g, 1.3 mmol) was reacted with benzyloxymethyltriphenylphosphonium bromide (1.0 g, 2.5 mmol) by the same procedure as described for the synthesis of **14a** to give an oily product. Yield, 0.43 g (68%); ^{1}H NMR ($CDCl_3$), δ 0.02 [s, 6H, $Si(CH_3)_2$], 0.88 (s, 9H, SiBu-*t*), 2.39 (s, 3H, CH_3), 3.65 and 3.72 (s, 3H, OCH_3), 4.52 and 4.53 (d, 2H, J = 0.8 Hz, CH_2), 5.93-6.17 (m, 2H, J = 0.8 Hz, CH_2), 6.67-6.92 (m, 1H, =C**H**OCH_3), 7.15 (m, 1H, H-5), 7.24 (d, 2H, J = 8.0 Hz, Ar), 7.66 (d, 2H, J = 8.0 Hz, Ar); IR (neat) 2950, 1640, 1370, 1250, 1180, 840 cm $^{-1}$; Anal. Calcd for $C_{27}H_{35}NO_4SSi$: C, 65.16; H, 7.09; N, 2.81. Found: C, 65.45; H, 7.21; N, 3.03.

4-[1-(*t*-Butyldimethylsilyloxy)ethyl]-2-(β-methoxyvinyl)-1-tosylpyrrole (14c). Compound **13b** (1.5 g, 3.6 mmol) was reacted with methoxymethyltriphenylphosphonium bromide (2.1 g, 5.5 mmol) by the same procedure as described for the synthesis of **14a** to give an oily product. Yield, 1.30 g (81%); ^{1}H NMR ($CDCl_3$), δ 0.06 [s, 6H, $Si(CH_3)_2$], 0.90 (s, 9H, SiBu-*t*), 1.40 (d, 3H, J = 6.0 Hz, CH_3), 2.40 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 4.78 (m, 1H, CH), 6.00-6.20 (m, 2H, H-3, =CH-), 6.70-6.80 (m, 1H, =CH-), 7.00-7.80 (m, 5H, Ar); IR (neat) 2950, 1635, 1370, 1250, 1170, 830 cm $^{-1}$; Anal. Calcd for $C_{22}H_{33}NO_4SSi$: C, 60.65; H, 7.64; N, 3.22. Found: C, 60.42; H, 7.52; N, 3.31.

4-[α-(*t*-Butyldimethylsilyloxy)benzyl]-2-(β-methoxyvinyl)-1-tosylpyrrole (14d). Compound **13c** (1.20 g, 2.50 mmol) was reacted with methoxymethyltriphenylphosphonium bromide (1.50 g, 3.8 mmol) by the same procedure as described for the synthesis of **14a** to give an oily product. Yield, 1.10 g (87%); ^{1}H NMR ($CDCl_3$), δ 0.06 [s, 6H, $Si(CH_3)_2$], 0.91 (s, 9H, SiBu-*t*), 2.48 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 5.78 (s, 1H, CH), 6.11-6.37 (m, 2H, H-3, =CH-), 6.75-6.90 (m, 1H =CH-), 7.16-8.00 (m, 10H, Ar); IR (neat) 2950, 1640, 1370, 1250, 1175 cm $^{-1}$; Anal. Calcd for $C_{27}H_{35}NO_4SSi$: C, 65.16; H, 7.09; N, 2.81. Found: C, 64.98; H, 7.01; N, 2.96.

Methyl 6-methoxy-5-nitro-1-tosyl-4,5,6,7-tetrahydroindole-4-carboxylate (3a). Compound **7a** (0.58 g, 2.09 mmol) and methyl β-nitroacrylate (0.54 g, 4.09 mmol) were dissolved in toluene (20 mL). The mixture was refluxed for 9 h. The residue obtained after evaporation of solvent was chromatographed over silica gel using hexane-ethyl acetate (4 : 1) as an eluent to give a solid product. Yield, 0.47 g (55%); mp 151 °C; ^{1}H NMR ($CDCl_3$), (*trans*) δ 2.41 (s, 3H, CH_3), 2.78 (ddd, 1H, J = 17.0, 5.0, 1.8 Hz, H_b-7), 3.20 (s, 3H, OCH_3), 3.63 (dd, 1H, J = 17.0, 5.8 Hz, H_a-7), 3.82 (s, 3H, OCH_3), 4.42 (dd, J = 10.0, 1.4 Hz, H-4), 4.55 (m, 1H, H-6), 5.04 (dd, 1H, J = 10.0, 10.0 Hz, H-5), 6.25 (d, 1H, J = 3.4 Hz, H-3), 7.27-7.31 (m, 3H, Ar, H-2), 7.70 (m, 2H, Ar) and (*cis*) δ 2.43 (s, 3H, CH_3), 2.83 (ddd, 1H, J = 17.0, 2.0, 2.0 Hz, H_b-7), 3.39 (dd, 1H, J = 17.0, 1.4 Hz, H_a-7), 3.40 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.04 (m, 1H, H-6), 4.31 (dd, 1H, J = 10.0, 1.4 Hz, H-4), 4.95 (dd, 1H, J = 10.0, 2.0 Hz, H-5), 6.25 (d, 1H, J = 3.4 Hz, H-3), 7.27-7.31 (m, 3H, Ar, H-2), 7.70 (m, 2H, Ar); IR (KBr) 1740, 1550, 1370, 1180 cm $^{-1}$; Anal. Calcd for $C_{18}H_{20}N_2O_7S$: C, 52.93; H, 4.94; N, 6.86. Found: C, 52.72; H, 4.72; N, 6.92.

Methyl 6-benzyloxy-5-nitro-1-tosyl-4,5,6,7-tetrahydroindole-4-carboxylate (3b). Compound **7b** (1.70 g, 4.80 mmol) and methyl β-nitroacrylate (1.70 g, 12.9 mmol) were dissolved in toluene (40 mL). The mixture was refluxed for 10 h. The residue obtained after evaporation of solvent was chromatographed over silica gel using hexane-ethyl acetate (4 : 1) as an eluent to give an oily product. Yield, 1.50 g (65%); ^{1}H NMR ($CDCl_3$), (*trans*) δ 2.37 (s, 3H, CH_3), 2.58 (ddd, 1H, J = 16.7, 5.0, 1.7 Hz, H_b-7), 3.65 (dd, 1H, J = 16.7, 5.8 Hz, H_a-7), 3.74 (s, 3H, OCH_3), 4.50 (m, 1H, H-4), 4.58 (d, 2H, J = 9.7 Hz, CH_2Ph), 4.74 (m, 1H, H-6), 5.10 (dd, 1H, J = 9.6, 9.6 Hz, H-5), 6.20 (d, 1H, J = 3.4 Hz, H-3), 7.02 (m, 1H, H-2), 7.20-7.30 (m, 6H, Ar), 7.60 (m, 3H, Ar) and (*cis*) δ 2.35 (s, 3H, CH_3), 2.82 (ddd, 1H, J = 16.7, 2.0, 2.0 Hz, H_b-7), 3.40 (dm, 1H, J = 16.7 Hz, H_a-7), 3.80 (s, 3H, OCH_3), 4.21 (m, 1H, H-6), 4.25 (m, 1H, H-4), 4.32 (d, 2H, J = 9.7 Hz, CH_2Ph), 4.74 (dd, 1H, J = 9.9, 2.3 Hz, H-5), 6.23 (d, 1H, J = 3.4 Hz, H-3), 7.04 (m, 1H, H-2), 7.20-7.30 (m, 6H, Ar), 7.60 (m, 3H, Ar); Anal. Calcd for $C_{24}H_{24}N_2O_7S$: C, 59.49; H, 4.99; N, 5.78. Found: C, 59.62; H, 4.72; N, 5.82.

Methyl 3-(*t*-butyldimethylsilyloxymethyl)-6-methoxy-5-nitro-1-tosyl-4,5,6,7-tetrahydroindole-4-carboxylate (3c). Compound **14a** (0.50 g, 1.10 mmol) and methyl β-nitroacrylate (0.22 g, 1.60 mmol) were dissolved in toluene (20 mL).

The mixture was refluxed for 12 h. The residue obtained after evaporation of solvent was chromatographed over silica gel using hexane-ethyl acetate (9 : 1) as an eluent to give an oily product, which was crystallized upon standing in refrigerator. Yield, 0.39 g (60%); mp 116 °C; ^{1}H NMR ($CDCl_3$), (*trans*) δ 0.02 [s, 6H, $Si(CH_3)_2$], 0.89 (s, 9H, SiBu-*t*), 2.40 (s, 3H, CH_3), 2.70 (ddm, 1H, J = 17.0, 7.0 Hz, H_b-7), 3.36 (s, 3H, OCH_3), 3.40 (ddm, 1H, J = 17.0, 5.0 Hz, H_a-7), 3.69 (s, 3H, OCH_3), 4.10 (ddd, 1H, J = 15.3, 8.0, 2.0 Hz, H-6), 4.38 (dd, 1H, J = 7.0, 0.98 Hz, H-4), 4.43 (dd, 2H, J = 4.0, 1.0 Hz, $SiOCH_2$), 4.95 (dd, 1H, J = 7.5, 7.0 Hz, H-5), 7.10 (s, 1H, H-2), 7.27 (d, 2H, J = 8.0 Hz, Ar), 7.63 (d, 2H J = 8.0 Hz, Ar) and (*cis*) δ 0.02 [s, 6H, $Si(CH_3)_2$], 0.89 (s, 9H, SiBu-*t*), 2.40 (s, 3H, CH_3), 2.70 (ddm, 1H, J = 17.0, 7.0 Hz, H_b-7), 3.24 (s, 3H, OCH_3), 3.40 (ddm, 1H, J = 17.0, 5.0 Hz, H_a-7), 3.76 (s, 3H, OCH_3), 4.10 (ddd, 1H, J = 15.3, 8.0, 2.0 Hz, H-6), 4.38 (dd, 1H, J = 7.0, 0.98 Hz, H-4), 4.43 (dd, 2H, J = 4.0, 1.0 Hz, $SiOCH_2$), 4.95 (dd, 1H, J = 7.5, 7.0 Hz, H-5), 7.10 (s, 1H, H-2), 7.27 (d, 2H, J = 8.0 Hz, Ar), 7.63 (d, 2H J = 8.0 Hz, Ar); IR(KBr) 2940, 1740, 1560, 1370 cm^{-1}; Anal. Calcd for $C_{25}H_{36}N_2O_8SSi$: C, 54.33; H, 6.57; N, 5.07. Found: C, 54.15; H, 6.32; N, 5.15.

Methyl 3-(*t*-butyldimethylsilyloxymethyl)-6-benzyloxy-5-nitro-1-tosyl-4,5,6,7-tetrahydroindole-4-carboxylate (3d). Compound **14b** (0.40 g, 0.80 mmol) was reacted with methyl β-nitroacrylate (0.21 g, 1.60 mmol) by the same procedure as described for the synthesis of **3a** to give an oily product. Yield, 0.29 g (58%); ^{1}H NMR ($CDCl_3$), δ 0.03 [s, 6H, $Si(CH_3)_2$], 0.88 (s, 9H, SiBu-*t*), 2.40 (s, 3H, CH_3), 2.80 (ddm, 1H, J = 17.3, 6.7 Hz, H_b-7), 3.26 (ddm, 1H, J = 17.3, 5.3 Hz, H_a-7), 3.61 (s, 3H, OCH_3), 4.30-4.55 (m, 6H, OCH_2, OCH_2Ph, H-4, H-6), 5.20 (m, 1H, H-5), 7.10-7.64 (10H, Ar); IR (neat) 2940, 1740, 1560, 1370 cm^{-1}; Anal. Calcd for $C_{31}H_{40}N_2O_8SSi$: C, 59.21; H, 6.41; N, 4.46. Found: C, 59.51; H, 6.23; N, 4.18.

Methyl 3-[1-(*t*-butyldimethylsilyloxy)ethyl]-6-methoxy-5-nitro-1-tosyl-4,5,6,7-tetrahydroindole-4-carboxylate (3e). Compound **14c** (1.10 g, 2.50 mmol) was reacted with methyl β-nitroacrylate (0.65 g, 5.0 mmol) by the same procedure as described for the synthesis of **3a** to give a solid product. Yield, 0.64 g (45%); mp 157 °C; ^{1}H NMR ($CDCl_3$), δ 0.02 [s, 6H, $Si(CH_3)_2$], 0.89 (s, 9H, SiBu-*t*), 1.28 (d, 3H, J = 6.0 Hz, CH_3), 2.47 (s, 3H, CH_3), 2.71 (ddm, 1H, J = 16.7, 7.0 Hz, H_b-7), 3.38 (s, 3H, OCH_3), 3.45 (dd, 1H, J = 16.7, 7.0 Hz, H_a-7), 3.71 (s, 3H, OCH_3), 4.12 (dd, 1H, J = 14.0, 6.7 Hz, H-6), 4.25 (dd, 1H, J = 7.0, 0.7 Hz, H-4), 4.62 (q, 1H, J = 6.0 Hz, CH), 4.96 (dd, 1H, J = 8.0, 8.0 Hz, H-5), 7.15 (s, 1H, H-2), 7.30 (d, 2H, J = 8.0 Hz, Ar), 7.62 (d, 2H, J = 8.0 Hz, Ar); IR (KBr) 2950, 1745, 1560, 1370, 1250, 1090, 830 cm^{-1}; Anal. Calcd for $C_{26}H_{38}N_2O_8SSi$: C, 55.10; H, 6.76; N, 4.94. Found: C, 54.92; H, 6.58; N, 5.06.

Methyl 3-[α-(*t*-butyldimethylsilyloxy)benzyl]-6-methoxy-5-nitro-1-tosyl-4,5,6,7-tetrahydroindole-4-carboxylate (3f). Compound **14d** (1.0 g, 2.0 mmol) was reacted with methyl β-nitroacrylate (0.52 g, 4.0 mmol) by the same procedure as described for the synthesis of **3a** to give an oily product. Yield, 0.44 g (35%); ^{1}H NMR ($CDCl_3$), δ 0.16 [s, 6H, $Si(CH_3)_2$], 0.89 (s, 9H, SiBu-*t*), 2.43 (s, 3H, CH_3), 2.73 (ddm, 1H, J = 17.0, 8.0 Hz, H_b-7), 3.26 (ddm, 1H, J = 17.0, 5.0 Hz, H_a-7), 3.29 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 3.68-4.12 (m, 2H, H-6, H-4), 4.89 (dd, 1H, J = 8.0, 5.3 Hz, H-5), 5.55 (d, 1H, J = 1.3 Hz, CHPh), 7.0-7.40 (m, 8H, Ar), 7.64 (d, 2H, J = 8.0 Hz, Ar); IR (neat) 2950, 1740, 1560, 1370, 1170 cm^{-1}; Anal. Calcd for $C_{31}H_{40}N_2O_8SSi$: C, 59.21; H, 6.41; N, 4.46. Found: C, 59.44; H, 6.21; N, 4.22.

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