A Novel Synthesis of C/D-Rings Component of Phytochromobilin Dimethyl Ester

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C/D-Rings component of phytochromobilin dimethyl ester was readily synthesized by employing our recent new preparative method for 3,4-disubstituted 1,5-dihydro-2*H*-pyrrol-2-ones and their coupling with a 2-formylpyrrole. A convenient method for the preparation of a substituted pyrrole common to B- and C-rings was also described.

Phytochrome is a photoreceptive chromoprotein existing in plants. Its structure interchanges reversibly by specific wavelengths between two geometrical isomers, P_R and P_{FR} (Fig. 1), and it is known to cause the photoreaction called "red–far red light reversible reaction". This photoreaction plays an important role which transmits environmental information about light to plants, and it is widely concerned in a variety of processes in plants, such as growth, development, morphogenesis etc.[1)]

The chromophore of phytochrome is phytochromobilin, which is a linear tetrapyrrole derivative and covalently bonded to an apoprotein. The total synthesis of phytochromobilin was reported by Weller and Gossauer for its dimethyl ester derivative (**1**), but the synthesis required many steps and the overall yield was not satisfactory.[2)] We wish to report here a versatile methods for the preparation of C/D-rings component of **1**, which successively employs our recent new preparative method for 3,4-disubstituted 1,5-dihydro-2*H*-pyrrol-2-ones[3)] and their coupling with a 2-formylpyrrole to pyrromethenone derivatives.[4)]

Results and Discussion

Toward the total synthesis of phytochromobilin dimethyl ester (**1**), we established here a new convenient method for the preparation of its left-half component, C/D-rings (**2**) illustrated in Fig. 2.

The substituted pyrrole derivative (**7**), which is common to B- and C-rings, was at first synthesized as shown in Scheme 1. Methyl 3-formylpropionate (**4**), prepared from methyl acrylate and carbon monooxide by a modified procedure of the reported method,[5)] was reacted with nitroethane to give the nitro alcohol (**5**) in quantitative yield, followed by dehydration[6)] with *N*,*N*′-dicyclohexylcarbodiimide (DCC) and CuCl to afford the nitroalkene (**6**) in 69% yield. The reaction of **6** with *t*-butyl isocyanoacetate[7)] gave the desired pyrrole derivative (**7**)[8)] in reasonable yield. This synthetic method of **7** is much simpler than the reported one.[9)] The pyrrole **7** was then formylated by Vilsmeier reaction to give C-ring (**8**)[10)] in 96% yield.

On the other hand, the synthesis of D-ring (**15**) was achieved through the substituted pyrrole derivative (**13**), which has 2-tosylethyl group at β-position, as illustrated in Scheme 2. The 2-tosylethyl group is potentially equivalent to vinyl group, since the β-elimination of *p*-toluenesulfinate can readily take place for the coupled compound **16** under basic conditions as will be seen later. Addition of nitromethane to tosylethene (**9**) under basic conditions afforded 3-nitro-1-tosylpropane (**10**), which was subsequently condensed with acetaldehyde to give nitro alcohol (**11**) in quantitative yield. Then **11** was dehydrated[6b,11)] with mesyl chloride and triethylamine to give nitroalkene (**12**) which reacts with tosylmethyl isocyanide (TosMIC)[12)] and 1,8-diazabicyclo[5.4.0.]undec-7-ene (DBU) to give the desired pyrrole (**13**) in high yield. The compound **13** was selectively converted to the corresponding pyrrolinone (**15**) by our original method[3)] through α-bromination and the subsequent acidic hydrolysis with aqueous trifluoroacetic acid in excellent yield.

So far, pyrromethenone has been usually synthesized via base-catalyzed condensation of an α-unsubstituted pyrrolinone and a 2-formylpyrrole, but the application of this method for **15** requires the elimination of tosyl group at its α-position. Therefore, the condensation of C-ring (**8**) and D-ring (**15**) was attempted by the novel method developed in our laboratory,[4)] and the expected pyrromethenone derivative (**16**) was obtained in good yield as shown in Scheme 3. The resulting mixture of (*E*)- and (*Z*)-**16** was treated with iodine to get only (*Z*)-**16**. Then, the **16** was reacted with potassium *t*-butoxide in order to convert the 2-tosylethyl group into vinyl group. The free carboxylic acid, which was partially formed by the attack of *p*-toluenesulfinate toward the methyl ester, was reesterified with diazomethane to afford the pyrromethenone derivative (**2**), C/D-rings component of phytochromobilin derivative, in high yield.

As mentioned above, excellent result was obtained for the synthesis of the substituted pyrrole derivative (**8**) corresponding to C-ring of phytochromobilin dimethyl ester (**1**) and the pyrrolinone derivative (**15**) to D-ring, and also for the condensation of them into pyrromethenone (**16**) as a precursor of C/D-rings (**2**), respectively. The synthesis of phytochromobilin dimethyl ester (**1**) with the C/D-rings (**2**) prepared above and A/B-rings (**3**) prepared by the known manner is available in the literature.[2)]

Experimental

All the melting points were determined with a micro

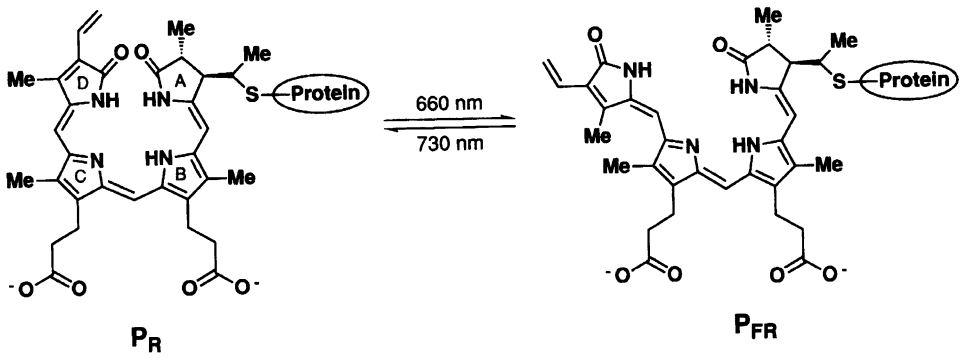


Fig. 1. Phytochrome.

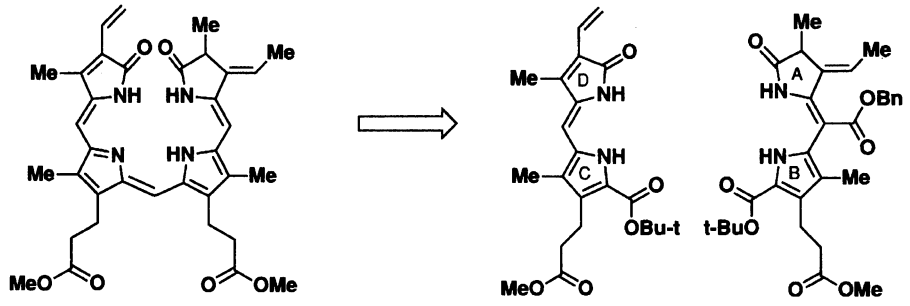
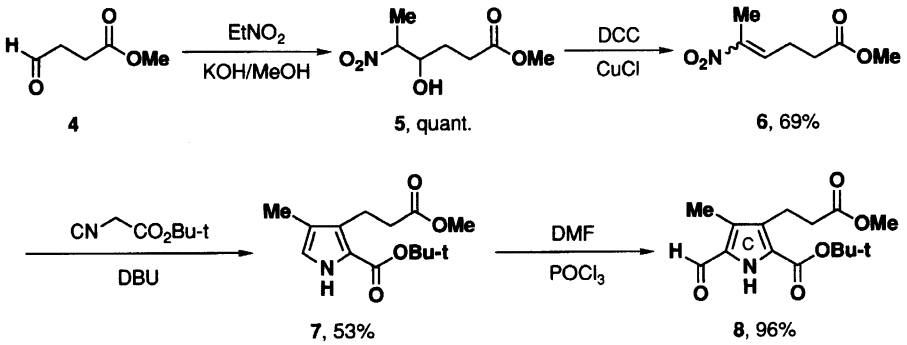


Fig. 2.

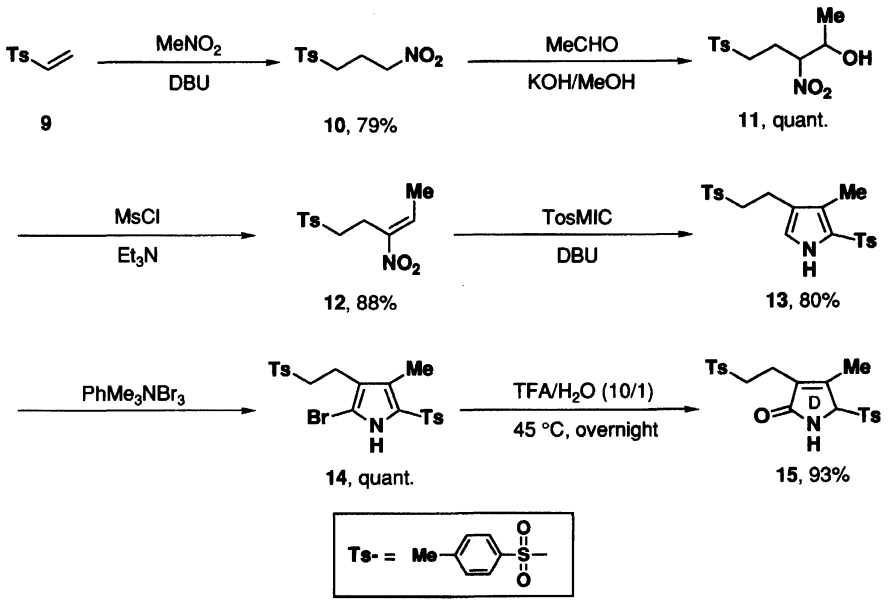


Scheme 1.

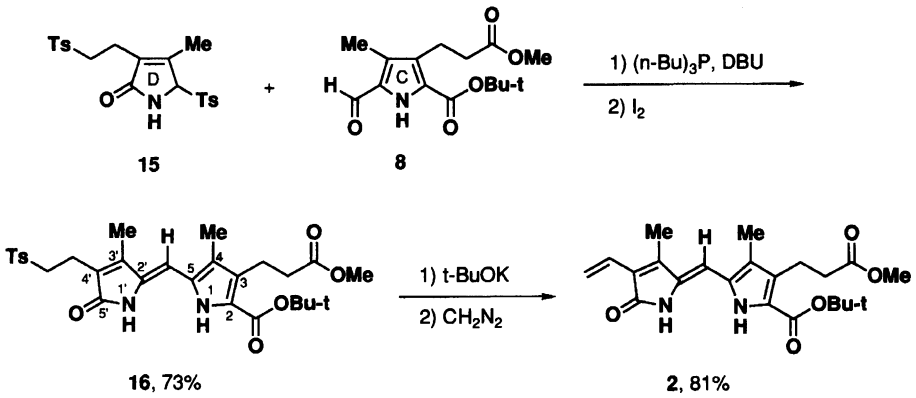
melting apparatus (Yanagimoto-Seisakusho) and were uncorrected. The ^{1}H NMR, IR, and MS spectra were recorded on JEOL JNM-GX 400 (400 MHz) FT-NMR spectrometer, JASCO IRA-1 diffraction grating infrared spectrometer and Hitachi M-80 mass spectrometer, respectively. The chemical shifts of NMR are reported in the δ-scale relative to TMS as an internal standard. All the solvents were distilled and stored over a drying agent. Thin-layer chromatography (TLC) and flash column chromatography were performed by the use of Merck's silica gel 60 PF_{254} (Art. 7749) and Wakogel C-300, respectively.

Methyl 3-Formylpropionate (4): Acetylacetonatodicarbonylrhodium(I) (60 mg, 0.23 mmol), methyl acrylate (3.96 g, 46 mmol), and triphenyl phosphite (356 mg, 1.15 mmol) were mixed with 5 ml of benzene under nitrogen atmosphere. This mixture was transferred to autoclave to give pressure up to 100 atm (H_2/CO=1/2) and stirred for 13 h at 40 °C. The solvent was removed in vacuo and the distillation of the residue under reduced pressure gave 4.06 g (76%) of **4** as a colorless oil. Bp 94 °C/40 Torr (1 Torr=133.322 Pa) (lit,[5] 69—70 °C/14 Torr); MS m/z 117 (M^++1, 12.69%), 116 (M^+, 38.50), 88 (100.00), 85 (84.51), 84 (33.72), 59 (33.52), 57 (56.00), 56 (94.13), 55 (46.72), 43 (49.71), 29 (88.27), 28 (43.43), 27 (56.57), 15 (42.34); IR (neat) 2960, 2840, 1735, 1440 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.61 (t, J=6.60 Hz, 2H), 2.78 (t, J=6.60 Hz, 2H), 3.69 (s, 3H), 9.80 (s, 1H).

Methyl 4-Hydroxy-5-nitro-hexanoate (5): To a mixture of **4** (3.48 g, 30 mmol) and nitroethane (3.83 g, 51 mmol) was added dropwise 3.0 ml of 1 mol dm^{-3}-KOH methanol solution at 0 °C, and the mixture was kept at this temperature for 2.5 h followed by dropwise addition of 2.0 ml of 0.9 mol dm^{-3}-H_2SO_4 methanol solution. The solvent was removed in vacuo, and the residue was partitioned between ethyl acetate and water. The organic layer was successively washed with water, a saturated aqueous solution of $NaHCO_3$, and brine, and dried over Na_2SO_4. Evaporation



Scheme 2.



Scheme 3.

of the solvent gave **5** in quantitative yield (5.76 g) as a colorless oil. The crude product as a mixture of diastereoisomers (M and m) was used for the preparation of methyl 5-nitro-4-hexenoate (**6**) without further purification. MS *m/z* 192 (M^++1, 3.09%), 160 (10.14), 117 (36.35), 113 (24.94), 107 (27.41), 88 (58.79), 86 (49.31), 85 (33.17), 79 (13.78), 58 (10.26), 57 (100.00), 56 (14.99), 43 (27.15), 32 (16.13), 29 (16.38), 28 (56.06), 18 (12.75); IR (neat) 3700—3000, 2960, 1720, 1540, 1350, cm^{-1}; ^1H NMR ($CDCl_3$) (M) δ=1.58 (d, J=6.84 Hz, 3H), 1.64—1.91 (m, 3H), 2.53 (t, J=7.08 Hz, 2H), 3.69 (s, 3H), 3.95 (d-d-d, J_1=2.93 Hz, J_2=7.08 Hz, J_3=10.01 Hz, 1H); (m) δ=1.58 (d, J=6.84 Hz, 3H), 1.64—1.91 (m, 3H), 2.53 (t, J=7.08 Hz, 2H), 3.69 (s, 3H), 4.15 (d-t, J_1=3.42 Hz, J_2=9.77 Hz, 1H); M/m=52/48.

Methyl 5-Nitro-4-hexenoate (6): A solution of **5** (0.69 g, 3.3 mmol), *N*,*N*′-dicyclohexylcarbodiimide (1.65 g, 8.0 mmol), and copper(I) chloride (52 mg, 0.53 mmol) in 5 ml of THF was refluxed overnight in the dark under nitrogen atmosphere.[6] After cooling to room temperature, 0.12 ml of acetic acid was added and the mixture was kept at this temperature for 1 h. The solvent was removed in vacuo, and the residue was taken up in ether. The organic layer was washed with water and brine, and dried over Na_2SO_4. Evaporation of the solvent and separation of the residue with a preparative TLC (Hex/AcOEt=5/1, v/v) gave 0.39 g (69%) of **6** as a yellowish oil. MS *m/z* 173 (M^+, 0.86%), 172 (M^+-1, 8.72), 157 (36.95), 126 (38.54), 125 (100.00), 108 (33.33), 98 (37.78), 80 (74.30), 43 (57.80), 42 (51.37), 39 (66.68), 15 (36.75); IR (neat) 2940, 1730, 1660, 1510, 1320, 860 cm^{-1}; ^1H NMR[6b] ($CDCl_3$) (*E*)-Isomer δ=2.21 (s, 3H), 2.48—2.55 (m, 4H), 3.70 (s, 3H), 7.02 (t, J=7.63 Hz, 1H); (*Z*)-Isomer δ=2.20 (s, 3H), 2.48—2.55 (m, 2H), 2.73 (q, J=6.92 Hz, 2H), 3.69 (s, 3H), 5.88 (t, J=6.92 Hz, 1H); *E*/*Z*=92/8.

Methyl 2-*t*-Butoxycarbonyl-4-methyl-3-pyrrolepropionate (7): To a mixed solution of *t*-butyl isocyanoacetate[7] (311 mg, 2.2 mmol) and DBU (304 mg, 2.2 mmol) in 3 ml of acetonitrile was added dropwise a solution of **6** (346 mg, 2.0 mmol) in 3 ml of acetonitrile over a period of 1 h at 0 °C in the dark under nitrogen atmosphere. The mixture was kept at the temperature for 30 min, then the solvent was removed in vacuo and the residue was partitioned between ethyl acetate and water. The organic layer was washed with water and brine, and dried over Na_2SO_4. Evaporation of

the solvent and separation of the residue by a preparative TLC (Hex/AcOEt=5/1, v/v) gave 281 mg (53%) of **7** as a colorless solid. Mp 36—38 °C (crude, not reported in lit[9]); MS *m/z* 267 (M^+, 4.74%), 180 (21.36), 167 (34.22), 166 (11.05), 165 (19.97), 152 (24.69), 151 (100.00), 138 (23.51), 134 (10.95), 133 (20.72), 120 (16.50), 108 (16.89), 94 (22.25); IR (KBr) 3320, 2960, 1730, 1660, 1580, 1560, 1460, 1420, 1390, 1355, 1265, 1235, 1210, 1160, 1120, 1100, 1050, 1000, 935, 835, 765, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.56 (s, 9H), 2.03 (s, 3H), 2.53 (t, J=8.06 Hz, 2H), 3.01 (t, J=8.06 Hz, 2H), 3.67 (s, 3H), 6.62 (d, J=2.44 Hz, 1H), 8.77 (s, 1H).

Methyl 2-*t*-Butoxycarbonyl-5-formyl-4-methyl-3-pyrrolepropionate (8): This compound was synthesized by the use of $POCl_3$ and **7** in DMF according to the method reported in the literature.[10] Mp 74.0—75.0 °C (from AcOEt) [lit,[10] 77 °C (from Et_2O/petroleum ether)].

Tosylethene (9): This compound was prepared by the general preparative method for vinylic sulfones developed in our laboratory[13] starting from ethene as follows: Sodium *p*-toluenesulfinate tetrahydrate (50.1 g, 200 mmol) and iodine (25.4 g, 100 mmol) were mixed in 200 ml of ethyl acetate and 150 ml of water under ethene atmosphere at room temperature. After stirring for 5 h, the organic layer was separated and the aqueous layer was further extracted with ethyl acetate. The combined organic layer was successively washed with a saturated aqueous solution of $NaHCO_3$, a saturated aqueous solution of $Na_2S_2O_3$, and brine, and dried over Na_2SO_4. The residue obtained by evaporation of the solvent was treated with triethylamine (15.3 ml, 110 mmol) in 100 ml of dichloromethane with stirring for 1 h at room temperature. The solvent was removed in vacuo, and the residue was partitioned between ethyl acetate and water. The organic layer was successively washed with a saturated aqueous solution of $NaHCO_3$, a saturated aqueous solution of $Na_2S_2O_3$, and brine, and dried over Na_2SO_4. Evaporation of the solvent and recrystallization from 2-propanol gave 14.7 g (81%) of **9** as a colorless solid. Mp 65.0—66.0 °C (from 2-PrOH) [lit,[14] 65—66 °C (from EtOH), lit,[15] 64—66 °C (from aqueous EtOH)]; IR (KBr) 3040, 1580, 1370, 1295, 1140, 1075, 980, 805, 703 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.45 (s, 3H), 6.00 (d, J=9.77 Hz, 1H), 6.43 (d, J=16.60 Hz, 1H), 6.65 (d-d, J_1=9.77 Hz, J_2=16.60 Hz, 1H), 7.35 (d, J=8.06 Hz, 2H), 7.78 (d, J=8.06 Hz, 2H). Found: C, 59.39; H, 5.48%. Calcd for $C_9H_{10}O_2S$: C, 59.32; H, 5.53%.

1-Nitro-3-tosylpropane (10): To a solution of 1-tosylethene (**9**) (2.2 g, 12.2 mmol) in 60 ml of nitromethane was added DBU (7.4 g, 48.6 mmol) all at once at −20 °C under nitrogen atmosphere, and the mixture was kept at this temperature for 1 h. The solvent was removed in vacuo, and the residue was taken up in ethyl acetate. The organic layer was successively washed with water, 1 mol dm^{-3} HCl, a saturated aqueous solution of $NaHCO_3$, and brine, and dried over Na_2SO_4. The solvent was removed in vacuo. The product was separated by flash column chromatography (CH_2Cl_2/AcOEt=100/1, v/v) to give 2.3 g (79%) of **10** as a colorless solid. Mp 49.5—50.5 °C (from AcOEt); MS *m/z* 243 (M^+, 24.63%), 155 (14.98), 91 (69.86), 88 (100.00), 60 (11.30), 28 (19.96); IR (KBr) 3000, 2950, 1592, 1535, 1488, 1430, 1370, 1340, 1300, 1279, 1253, 1222, 1140, 1078, 1040, 870, 802, 770, 745 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.40—2.47 (m, 2H), 2.47 (s, 3H), 3.21 (t, J=7.08 Hz, 2H), 4.57 (t, J=6.59 Hz, 2H), 7.39 (d, J=8.06 Hz, 2H), 7.79 (d, J=8.06 Hz, 2H). Found: C, 49.44; H, 5.47; N, 5.78%. Calcd for $C_{10}H_{13}NO_4S$: C, 49.37; H, 5.39; N, 5.76%.

3-Nitro-5-tosyl-2-pentanol (11): To a solution of **10** (2.0 g, 8.3 mmol) in 20 ml of methanol was added acetaldehyde (4.7 ml, 83 mmol) at 0 °C, followed by dropwise addition of 0.83 ml of 1 mol dm^{-3} methanolic solution of KOH. The mixture was kept at this temperature for 2 h, and acidified with 1 ml of 1 mol dm^{-3} HCl, then the solvent was removed in vacuo. The residue was partitioned between ethyl acetate and water. The organic layer was successively washed with water, a saturated aqueous solution of $NaHCO_3$, and brine, and dried over Na_2SO_4. Evaporation of the solvent gave **11** as a colorless solid in quantitative yield (2.8 g). The crude product was used for the preparation of 3-nitro-5-tosyl-2-pentene (**12**) without further purification. Mp 63.0—65.0 °C (from AcOEt, a mixture of diastereoisomers; M/m=57/43); MS *m/z* 288 (M^++1, 1.92%), 287 (M^+, 3.85), 157 (25.67), 155 (36.49), 140 (35.97), 139 (33.85), 132 (53.63), 92 (31.79), 91 (52.88), 88 (99.65), 85 (100.00), 83 (11.34), 43 (33.28), 32 (18.82), 28 (64.41); IR (KBr) 3600—3300, 3040, 1586, 1535, 1488, 1430, 1403, 1370, 1342, 1297, 1260, 1230, 1170, 1140, 1080, 1045, 1010, 935, 870, 850, 805, 790, 750, 720 cm^{-1}; ^1H NMR ($CDCl_3$) (M) δ=1.31 (d, J=6.35 Hz, 3H), 2.31—2.45 (m, 3H), 2.47 (s, 3H), 3.05—3.25 (m, 2H), 4.11—4.17 (m, 1H), 4.58—4.64 (m, 1H), 7.39 (d, J=8.30 Hz, 2H), 7.78 (d, J=8.30 Hz, 2H); (m) δ=1.29 (d, J=6.35 Hz, 3H), 2.31—2.45 (m, 3H), 2.47 (s, 3H), 3.05—3.25 (m, 2H), 4.32 (m, 1H), 4.58—4.64 (m, 1H), 7.39 (d, J=8.06 Hz, 2H), 7.78 (d, J=8.06 Hz, 2H). Found: C, 50.16; H, 6.07; N, 4.90%. Calcd for $C_{12}H_{17}NO_5S$: C, 50.16; H, 5.96; N, 4.87%.

(*E*)-3-Nitro-5-tosyl-2-pentene (12): To a solution of **11** (408 mg, 1.4 mmol) in 5 ml of dichloromethane was added 0.22 ml (2.8 mmol) of methanesulfonyl chloride at 0 °C under nitrogen atmosphere, followed by dropwise addition of 0.79 ml (5.7 mmol) of triethylamine.[11] The mixture was kept at this temperature for 10 min, and 0.49 ml (8.5 mmol) of acetic acid was added dropwise, then the solvent was removed in vacuo. The residue was partitioned between ethyl acetate and water. The organic layer was successively washed with water, a saturated aqueous solution of $NaHCO_3$, and brine, and dried over Na_2SO_4. Evaporation of the solvent and separation of the residue with a preparative TLC (Hex/AcOEt=2/1, v/v) gave 337 mg (88%) of **12** as a colorless solid. Mp 97.8—99.5 °C (from AcOEt); MS *m/z* 270 (M^++1, 0.13%), 269 (M^+, 0.23), 224 (18.43), 223 (100.00), 157 (16.31), 139 (31.26), 91 (22.02), 67 (21.68), 32 (12.76), 28 (49.33); IR (KBr) 3040, 2960, 2920, 1650, 1580, 1505, 1420, 1370, 1320, 1280, 1240, 1180, 1140, 1125, 1080, 1025, 1005, 990, 935, 840, 800, 780, 750, 710 cm^{-1}; ^1H NMR[6b] ($CDCl_3$) δ=1.96 (d, J=7.32 Hz, 3H), 2.46 (s, 3H), 3.03 (t, J=7.82 Hz, 2H), 3.30 (t, J=7.57 Hz, 2H), 7.30 (q, J=7.57 Hz, 1H), 7.38 (d, J=8.30 Hz, 2H), 7.80 (d, J=8.30 Hz, 2H). Found: C, 53.31; H, 5.64; N, 5.19%. Calcd for $C_{12}H_{15}NO_4S$: C, 53.52; H, 5.61; N, 5.20%.

3-Methyl-2-tosyl-4-(2-tosylethyl)pyrrole (13): To a mixed solution of TosMIC[12] (234 mg, 1.2 mmol) and DBU (152 mg, 1.0 mmol) in 3 ml of acetonitrile was added dropwise a solution of **12** (269 mg, 1.0 mmol) in 2 ml of acetonitrile at 0 °C under nitrogen atmosphere.[8] The mixture was kept at the temperature for 30 min, and treated with a saturated aqueous solution of NH_4Cl, and the solvent was re-

moved in vacuo. The residue was partitioned between ethyl acetate and water. The organic layer was washed with water and brine, and dried over Na_2SO_4. Evaporation of the solvent and separation of the residue by a preparative TLC (CH_2Cl_2/AcOEt=15/1, v/v) gave 332 mg (80%) of **13** as a colorless solid. Mp 161.0—162.0 °C (from AcOEt); MS *m/z* 417 (M^+, 10.94%), 325 (13.57), 262 (27.52), 261 (100.00), 92 (54.70), 91 (19.61), 28 (32.80); IR (KBr) 3320, 2920, 1593, 1552, 1492, 1439, 1395, 1365, 1290, 1130, 1080, 1040, 1010, 800, 730, 700, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.07 (s, 3H), 2.40 (s, 3H), 2.45 (s, 3H), 2.76—2.80 (m, 2H), 3.17—3.21 (m, 2H), 6.65 (d, J=2.93 Hz, 1H), 7.27 (d, J=8.30 Hz, 2H), 7.34 (d, J=8.31 Hz, 2H), 7.72 (d, J=8.31 Hz, 2H), 7.77 (d, J=8.30 Hz, 2H), 8.86 (br s, 1H). Found: C, 60.49; H, 5.61; N, 3.40%. Calcd for $C_{21}H_{23}NO_4S_2$: C, 60.41; H, 5.55; N, 3.35%.

2-Bromo-4-methyl-5-tosyl-3-(2-tosylethyl)pyrrole (14): To a solution of **13** (506 mg, 1.2 mmol) in 20 ml of dichloromethane was added dropwise a solution of $PhMe_3NBr_3$ (910 mg, 2.4 mmol) in 20 ml of dichloromethane at 0 °C.[3] The mixture was kept at the temperature for 15 min, then the solvent was removed in vacuo. The residue was partitioned between ethyl acetate and water. The organic layer was successively washed with water, a saturated aqueous solution of $NaHCO_3$, a saturated aqueous solution of $Na_2S_2O_3$, and brine, and dried over Na_2SO_4. Evaporation of the solvent gave **14** as a grayish solid in quantitative yield (643 mg). The crude product was used for the preparation of 4-methyl-5-tosyl-3-(2-tosylethyl)-1,5-dihydro-2*H*-pyrrol-2-one(**15**) without further purification. Mp 200.5—201.5 °C (from AcOEt); MS *m/z* 498 (M^+ (^{81}Br)+1, 1.33%), 497 (M^+ (^{81}Br), 4.85), 496 (M^+(^{79}Br)+1, 1.17), 495 (M^+ (^{79}Br), 4.39), 341 (23.28), 339 (21.03), 64 (100.00), 32 (53.74), 18 (11.34); IR (KBr) 3300—3100, 2900, 1910, 1580, 1540, 1480, 1430, 1390, 1350, 1280, 1220, 1200, 1160, 1130, 1070, 1000, 800, 740, 700, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.09 (s, 3H), 2.41 (s, 3H), 2.45 (s, 3H), 2.73—2.77 (m, 2H), 3.11—3.15 (m, 2H), 7.29 (d, J=8.30 Hz, 2H), 7.34 (d, J=8.30 Hz, 2H), 7.74 (d, J=8.30 Hz, 2H), 7.77 (d, J=8.30 Hz, 2H), 8.97 (s, 1H). Found: C, 50.98; H, 4.49; N, 2.72%. Calcd for $C_{21}H_{22}BrNO_4S_2$: C, 50.81; H, 4.47; N, 2.82%.

4-Methyl-5-tosyl-3-(2-tosylethyl)-1,5-dihydro-2*H*-pyrrol-2-one (15): To a solution of **14** (496 mg, 1.0 mmol) in 20 ml of trifluoroacetic acid was added 2 ml of water at room temperature under nitrogen atmosphere.[3] The mixture was kept at 45 °C for 19 h, then the solvent was removed in vacuo, and the residue was taken up in ethyl acetate. The organic layer was successively washed with water, a saturated aqueous solution of $NaHCO_3$, a saturated aqueous solution of $Na_2S_2O_3$, and brine, and dried over Na_2SO_4. Evaporation of the solvent and separation of the residue by a preparative TLC (CH_2Cl_2/AcOEt=4/1, v/v) gave 404 mg (93%) of **15** as a colorless solid. Mp 148.5—149.5 °C (from 2-PrOH); MS *m/z* 434 (M^++1, 0.55%), 278 (77.04), 139 (55.34), 123 (52.70), 122 (100.00), 92 (46.44), 91 (91.15), 65 (37.79), 41 (29.16), 39 (39.99); IR (KBr) 3200, 3060, 2930, 1920, 1680, 1580, 1480, 1430, 1400, 1380, 1350, 1290, 1240, 1195, 1170, 1120, 1070, 1030, 1000, 945, 900, 800, 770, 735, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.18 (s, 3H), 2.36 (s, 3H), 2.40—2.49 (m, 3H), 2.44 (s, 3H), 2.95—3.04 (m, 1H), 5.02 (s, 1H), 6.87 (s, 1H), 7.30 (d, J=8.30 Hz, 2H), 7.35 (d, J=8.30 Hz, 2H), 7.64 (d, J=8.30 Hz, 2H), 7.72 (d, J=8.30 Hz, 2H). Found: C, 57.92; H, 5.29; N, 3.11%. Calcd for $C_{21}H_{23}NO_5S_2$: C, 58.18; H, 5.35; N, 3.23%.

Methyl (*Z*)-2-(*t*-Butoxycarbonyl)-4-methyl-5-[3-methyl-5-oxo-4-(2-tosylethyl)-1,5-dihydro-2*H*-pyrrol-2-ylidene]methylpyrrole-3-propionate (16): To a mixed solution of **15** (86 mg, 0.2 mmol) and **8** (59 mg, 0.2 mmol) in 4 ml of THF was added tributylphosphine (81 mg, 0.4 mmol) followed by dropwise addition of a solution of DBU (30 mg, 0.2 mmol) in 1 ml of THF under nitrogen atmosphere.[4] The mixture was kept at room temperature for 3 h, then the solvent was removed in vacuo. The residue was treated with a solution of iodine (15 mg, 0.06 mmol) in 5 ml of dichloromethane at room temperature for 24 h, then the solvent was removed in vacuo, and the residue was taken up in ethyl acetate. The organic layer was successively washed with water, a saturated aqueous solution of $NaHCO_3$, a saturated aqueous solution of $Na_2S_2O_3$, and brine, and dried over Na_2SO_4. Evaporation of the solvent and separation of the residue by a preparative TLC (CH_2Cl_2/AcOEt=4/1, v/v) gave 81 mg (73%) of **16** as a yellowish solid. Mp 170.0—171.0 °C (from AcOEt); MS *m/z* 557 (M^++1, 13.41%), 556 (M^+, 37.27), 501 (31.13), 500 (100.00), 456 (47.00), 344 (55.62), 301 (58.03), 300 (45.57), 285 (24.44), 284 (20.78), 56 (25.02), 41 (40.29); IR (KBr) 3360—3100, 2960, 2900, 2850, 1725, 1675, 1650, 1580, 1430, 1390, 1355, 1270, 1120, 1070, 1040, 830, 795, 715 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.54 (s, 9H), 2.12 (s, 3H), 2.13 (s, 3H), 2.31 (s, 3H), 2.52 (t, J=8.06 Hz, 2H), 2.90 (t, J=7.08 Hz, 2H), 3.01 (t, J=8.06 Hz, 2H), 3.48 (t, J=7.08 Hz, 2H), 3.68 (s, 3H), 5.99 (s, 1H), 7.21 (d, J=8.06 Hz, 2H), 7.68 (d, J=8.06 Hz, 2H), 9.92 (s, 1H), 10.15 (s, 1H). When a proton of *meso*-position (5.99 ppm) was irradiated, 8.81% of NOE was observed for the six protons of both methyl groups (2.12 and 2.13 ppm, respectively) at 4- and 3′-positions. Found: C, 62.53; H, 6.63; N, 4.95%. Calcd for $C_{29}H_{36}N_2O_7S$: C, 62.57; H, 6.52; N, 5.03%.

Methyl (*Z*)-2-(*t*-Butoxycarbonyl)-4-methyl-5-(3-methyl-5-oxo-4-vinyl-1,5-dihydro-2*H*-pyrrol-2-ylidene)methylpyrrole-3-propionate (2): To a solution of potassium *t*-butoxide (45 mg, 0.4 mmol) in 4 ml of *t*-butyl alcohol was added a solution of **16** (22 mg, 0.04 mmol) in 2 ml of THF under nitrogen atmosphere. The mixture was refluxed for 1.5 h, then treated with a saturated aqueous solution of NH_4Cl, and the solvent was removed in vacuo. The residue was taken up in ethyl acetate, and the organic layer was washed with water and brine, and dried over Na_2SO_4, followed by evaporation of the solvent. The solution of the residue in methanol was treated with a solution of diazomethane in ether to esterify the carboxyl group partially formed in situ. Evaporation of the solvent and separation of the residue by a preparative TLC (CH_2Cl_2/AcOEt=4/1, v/v) gave 13 mg (81%) of **2** as a yellowish solid. Mp 197.0—198.2 °C [from AcOEt, lit,[2] 192 °C (from CH_2Cl_2/Et_2O/Hex)]; MS *m/z* 401 (M^++1, 6.47%), 400 (M^+, 23.25), 345 (22.36), 344 (100.00), 313 (7.99), 285 (10.69), 284 (36.53), 270 (8.18), 224 (5.59); IR (KBr) 3310, 3240, 2960, 2900, 2840, 1725, 1680, 1640, 1600, 1430, 1360, 1265, 1150, 1120, 1070, 1040, 1000, 890, 835, 800, 780, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.56 (s, 9H), 2.11 (s, 3H), 2.19 (s, 3H), 2.53 (t, J=8.06 Hz, 2H), 3.01 (t, J=8.06 Hz, 2H), 3.68 (s, 3H), 5.44 (d-d, J_1=1.95 Hz, J_2=11.23 Hz, 1H), 6.04 (s, 1H), 6.26 (d-d, J_1=1.96 Hz, J_2=17.58 Hz, 1H), 6.58 (d-d,

J_1=11.47 Hz, J_2=17.82 Hz, 1H), 9.25 (s, 1H), 9.53 (s, 1H). Found: C, 66.27; H, 7.12; N, 6.87%. Calcd for $C_{22}H_{28}N_2O_5$: C, 65.98; H, 7.05; N, 6.99%.

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