Controlled Synthesis of C/D-Ring Components of Phycobilin Derivatives Bearing a Photoreactive Group at D-Ring

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C/D-Ring components of phycobilin derivatives bearing a photoreactive group at D-ring were regioselectively synthesized by applying our original synthetic reactions such as acid-catalyzed rearrangement of 2-tosyl group of 3,4-disubstituted 2-tosylpyrroles to 5-position, regioselective preparation of 3,4-disubstituted 5-tosylpyrrolinones, and their Wittig-type new coupling reaction with 2-formyl pyrrole.

Phycocyanin and phytochrome are chromoproteins and these are widely concerned with some algal photosynthetic systems and a variety of processes such as growth, development, and morphogenesis etc. in higher plants. The chromophores of them, named phycocyanobilin (**1**) and phytochromobilin (**2**), are linear tetrapyrrole derivatives and covalently bound to their apoproteins at A-ring.[1] It is known that the structure of phytochrome interchanges reversibly by specific wavelengths between two geometrical isomers, Pr and Pfr, to cause the photoreaction referred to as "red/far-red light reversible reaction" (Figure 1; R^1 = vinyl, R^2 = Me).[2] On the other hand, recent developments in gene technology have made it possible to assemble the chromophores such as **1** and **2** with the apoproteins obtained by the over-expression of the corresponding cDNA in bacteria and yeast. Moreover, the photophysical and photochemical properties of wild type phytochrome are quite similar to those of the reconstituted chromoprotein.[1] For the structure/function analysis of phytochrome, we have so far been studying on the synthesis of phycobilin derivatives.[3] In this paper, we wish to report the first synthesis of the C/D-ring components of phycobilin derivatives bearing a photoreactive group, 4-[3-(trifluoromethyl)-3*H*-diazirin-3-yl]phenyl group,[4] at C-17 or C-18 on D-ring (**3** and **4** in Figure 2) to investigate the structural relationship between the chromophore and the apoprotein of the

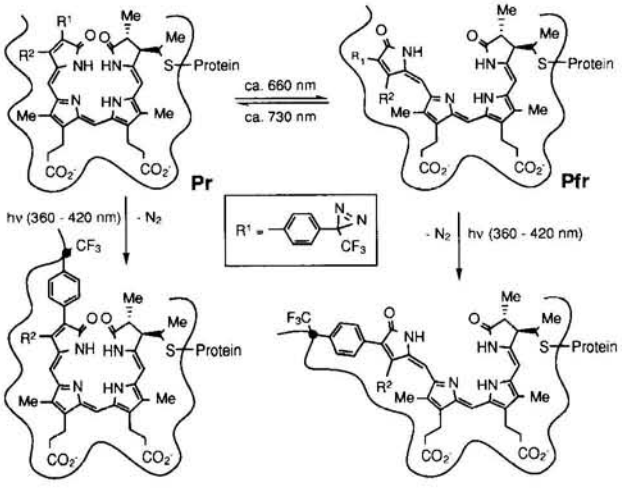


Figure 1.

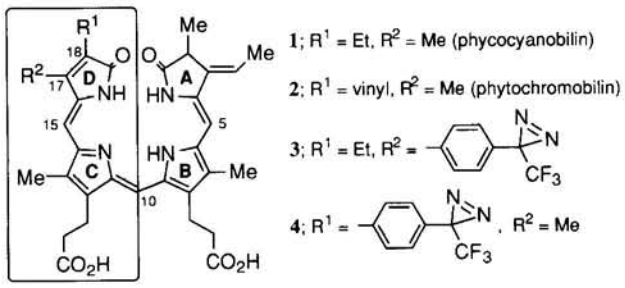
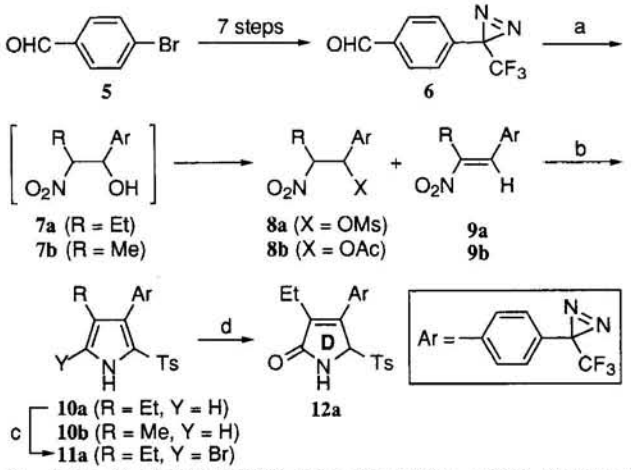


Figure 2.

reconstituted phytochrome in both Pr and Pfr forms as outlined in Figure 1.[5]

Especially, introduction of a photoreactive group to C-18 (see **4**) was achieved by applying the rearrangement of 2-tosyl group of 3,4-disubstituted 2-tosylpyrroles to 5-position,[3f] followed by transformation to 5-tosylpyrrolinones according to our original method.[3a]



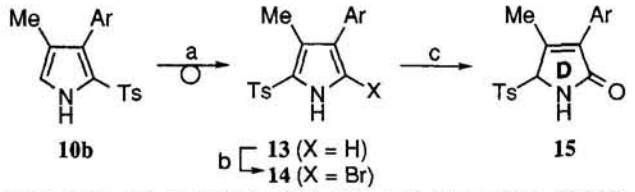
[a]For **8a,9a**: (1) 1 M KOH/MeOH (0.2 eq.) in ^{n}PrNO$_2$ at 0 °C, 18 h at r.t. (2) MsCl (2 eq.), Et_3N (4 eq.) in CH_2Cl_2 at 0 °C, 18 h at r.t. **8a** 62%, **9a** 27%. For **8b,9b**: (1)(2) Et_3N (0.4 eq.) in EtNO$_2$ at 0 °C, 53 h at r.t., 4-Me$_2$NPy (0.2 eq.), Ac_2O (2 eq.) at 0 °C, 1.3 h. **8b** 57%, **9b** 37%. [b]**8+9**, TosMIC (1.0-1.2 eq.), DBU (1.7-1.9 eq.) in MeCN at 0 °C, 16-21 h at r.t. **10a** quant., **10b** 80%. [c]PhMe$_3$N$^+$Br$_3^-$ (2.0 eq.) in CH_2Cl_2, 10 min at 0 °C. **11a** quant. [d]**11a**, TFA/H_2O (5/1, v/v) at 0 °C, 2 d at 25 °C. **12a** 72%.

Scheme 1.

At first, 2-tosylpyrroles **10a,b** were synthesized from 4-[3-(trifluoromethyl)-3*H*-diazirin-3-yl]benzaldehyde (**6**), which is available in 7 steps from 4-bromobenzaldehyde (**5**) by the improved procedure of the reported method,[4] according to Scheme 1. Namely, **6** was reacted with nitroalkanes in the presence of a base (KOH or Et_3N) to afford the corresponding nitroalcohols **7a,b**, which were subsequently converted to the

mesylate **8a** or the acetate **8b** and the nitroolefins **9a,b** by treatment with MsCl or Ac_2O and Et_3N, respectively. The mixtures of **8** and **9** were treated with tosylmethylisocyanide (TosMIC) to afford the 2-tosylpyrroles **10a,b** in high yields. The pyrrole **10a** was then brominated with $PhMe_3N^+Br_3^-$, followed by acidic hydrolysis to give **12a** as a D-ring of phycocyanobilin bearing a photoreactive group instead of methyl group at C-17.[3a]

Next, we attempted to introduce the same photoreactive group to C-18 of phytochromobilin (**2**) instead of vinyl group. Since it was difficult to prepare the corresponding nitro intermediate, we applied our acid-catalyzed rearrangement of 2-tosyl group of the 2-tosylpyrroles to 5-position, which has been reported previously,[3f] as shown in Scheme 2, to afford the pyrrole **13** in 82% yield. In a similar manner described above, pyrrolinone **15** was obtained from **13** via brominated intermediate **14** in reasonable yield.

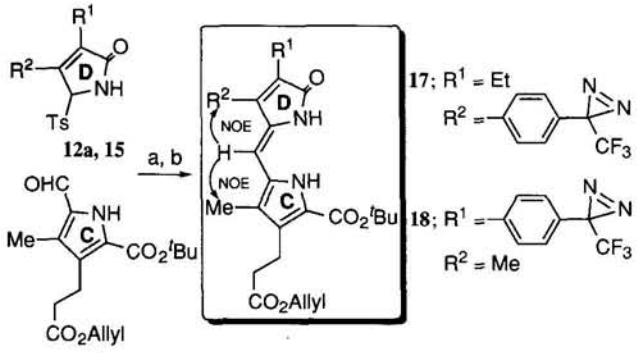


[a]TsNa (0.05 eq.), TFA/$CHCl_3$ (1/9, v/v) at 25 °C for 50 h. **13** 82%. [b]$PhMe_3N^+Br_3^-$ (1.2 eq.) in CH_2Cl_2, 30 min at 0 °C. **14** 81%. [c]**14**, TFA/H_2O (5/1, v/v) at r.t. for 5 d. **15** 58%.

Scheme 2.

5-Tosylpyrrolinones **12a** and **15** thus prepared were then coupled with a formyl pyrrole **16** as a C-ring by the Wittig-type coupling reaction developed by us[3b,c] using $^nBu_3P$ in the presence of base (^{t}BuOK or DBU) in CH_2Cl_2 in good yields. Subsequent treatment of the coupling products with a catalytic amount of iodine in CH_2Cl_2 afforded only thermodynamically more stable *Z*-isomers (**17** and **18**) quantitatively as shown in Scheme 3.

Structures of the resulting **17** and **18** were fully confirmed by spectral measurements (IR, NMR) and elementary analysis.[6]



[a]For **17**: ^{t}BuOK (1.2 eq.), **16** (1.1 eq.), **12a** (1 eq.), and $^nBu_3P$ (2.4 eq., dropwise) in CH_2Cl_2 at -78 °C - r.t., overnight at r.t., 73% (*E*/*Z* = 79/21); For **18**: a CH_2Cl_2 solution of **15** (1.4 eq.) was added dropwise over a period of 1.5 h to the mixed solution of **16** (1 eq.), nBu_3P (2 eq.), and DBU (1.5 eq.) in CH_2Cl_2 under refluxing, then 1 h, 87% (*E*/*Z* = 71/29). [b]cat. I_2 (ca. 0.1 eq.) in CH_2Cl_2 at r.t., overnight, quant.

Scheme 3.

Now, we have C/D-ring components (**17**, **18**) bearing a photoreactive group at D-ring in hand. We are now developing a new convenient method for the preparation of A/B-ring component[3e] toward the total synthesis of the phycobilin derivatives **3** and **4** in combination with **17** and **18** obtained above.

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6 **17** (*Z*-form): mp (decomp.) 203 °C (from EtOAc/hexane); IR (KBr) 3321, 3117, 2975, 1730, 1698, 1675, 1457, 1369, 1343, 1281, 1230, 1162, 1134, 1053, 987, 938, 848, 785, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.07 (t, J = 7.52 Hz, 3H), 1.56 (s, 9H), 1.94 (s, 3H), 2.43 (q, J = 7.52 Hz, 2H), 2.52 (t, J = 8.07 Hz, 2H), 2.98 (t, J = 8.07 Hz, 2H), 4.56 (dt, J = 5.69, 1.28 Hz, 2H), 5.22 (dq, J = 10.45, 1.47 Hz, 1H), 5.29 (dq, J = 17.24, 1.47 Hz, 1H), 5.71 (s, 1H), 5.90 (ddt, J = 17.24, 10.45, 5.69 Hz, 1H), 7.30 (d, J = 8.33 Hz, 2H), 7.38 (d, J = 8.33 Hz, 2H), 9.60 (brs, 1H), 9.79 (brs, 1H) ppm. NOE was observed for methyl protons (4.63%) at C-ring and phenyl ortho-protons (6.17%) at D-ring when methine bridge proton (5.71 ppm) was irradiated. Found: C, 62.33; H, 5.65; N, 9.16%. Calcd for $C_{31}H_{33}N_4O_5F_3$: C, 62.20; H, 5.56; N, 9.36%.
18 (*Z*-form): mp (decomp.) 135 °C (from cyclohexane); IR (KBr) 3286, 2980, 2930, 1742, 1691, 1670, 1458, 1369, 1344, 1290, 1235, 1154, 1052, 999, 938, 828, 714 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.50 (s, 9H), 2.13 (s, 3H), 2.29 (s, 3H), 2.57 (t, J = 7.93 Hz, 2H), 3.03 (t, J = 8.05 Hz, 2H), 4.60 (d, J = 5.61Hz, 2H), 5.23 (dd, J = 10.37, 1.46 Hz, 1H), 5.30 (dd, J = 17.20, 1.46 Hz, 1H), 5.92 (ddt, J = 17.20, 10.37, 5.61 Hz, 1H), 6.15 (s, 1H), 7.20 (d, J = 8.42 Hz, 2H), 7.58 (d, J = 8.42 Hz, 2H), 9.40 (brs, 1H), 9.58 (brs, 1H) ppm. NOE was observed for both methyl protons [7.08% (2.13 ppm) and 9.24% (2.29 ppm)] at C- and D-rings, respectively, when methine bridge proton (6.15 ppm) was irradiated. Found: C, 61.55; H, 5.29; N, 9.39%. Calcd for $C_{30}H_{31}N_4O_5F_3$: C, 61.64; H, 5.35; N, 9.58%.