An Efficient Method for the Conversion of 2-Bromo-5-tosylpyrroles to the Corresponding 5-Tosylpyrrolinones as the D-Ring of Phycocyanobilin Derivatives

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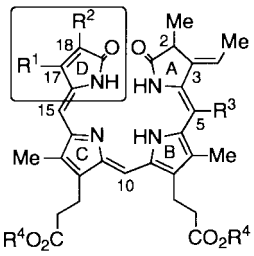
2-Bromo-5-tosylpyrroles were efficiently converted to the corresponding 5-tosylpyrrolinones as the D-ring of phycocyanobilin (PCB) derivatives by treating with DMSO and Zn in TFA in the presence of a catalytic amount of iodine. PCB derivatives modified at the D-ring were prepared in free acid forms employing the resulting 5-tosylpyrrolinones toward structure/function analysis of phytochrome.

Phytochrome, one of the best-characterized photoreceptors in plants, was discovered as chromoprotein controlling red/far-red reversible developmental responses.[1] The chromophore named phytochromobilin (PΦB, R^1 = Me, R^2 = vinyl, R^3 = R^4 = H in Figure 1) is a linear tetrapyrrole similar in structure to phycocyanobilin (PCB, **1**), which is a chromophore of the light-harvesting pigment phycocyanin and used as a substitute for PΦB to reconstitute with apoproteins. In order to analyze the structural requirements of the chromophore in phytochrome,[2] we have been studying on the syntheses of phycobilin derivatives and have recently succeeded to synthesize PΦB,[2d] PCB (**1**),[2b,c,e] and PCB derivatives modified at the A-,[2g] B-,[2f] and C-rings[2f] in free acid forms.

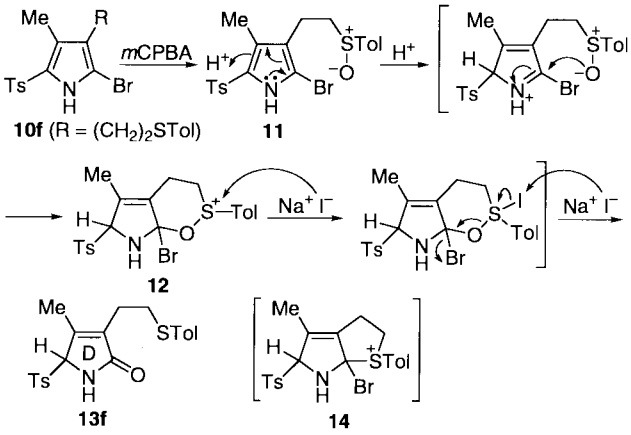
Modification of the D-ring is essential for analysis of photochromism, because the D-ring (C-15 position) is the site at which isomerization occurs during photoconversion of phytochrome.[3] In this paper, we wish to report an efficient synthetic method of various kinds of 5-tosylpyrrolinones as the D-ring to synthesize PCB (**1**) and its derivatives (**2–9**) modified at the C-17 and C-18 positions toward structure/function analysis of phytochrome.



1 (R^1 = Me; R^2 = Et; R^3, R^4 = H) (PCB)
2 (R^1 = Me; R^2 = ^{n}Pr; R^3, R^4 = H)
3 (R^1 = Me; R^2 = ^{n}Pen; R^3, R^4 = H)
4 (R^1 = Me; R^2 = ^{n}Oct; R^3, R^4 = H)
5 (R^1 = Me; R^2 = $(CH_2)_2OAc$; R^3, R^4 = H)
6 (R^1 = Me; R^2 = $(CH_2)_2STol$; R^3, R^4 = H)
7 (R^1 = ^{n}Pr; R^2 = Me; R^3, R^4 = H)
8 (R^1 = ^{n}Pen; R^2 = Me; R^3, R^4 = H)
9 (R^1 = ^{n}Oct; R^2 = Me; R^3, R^4 = H)

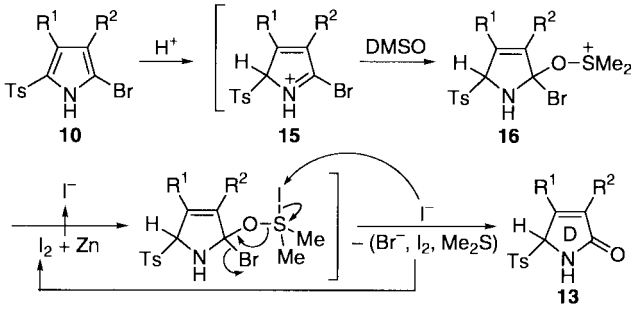
Figure 1.

Previously, we reported a general method for the preparation of 5-tosylpyrrolinones **13** by acid hydrolysis of the corresponding 2-bromo-5-tosylpyrroles **10**.[4] However, in the recent total synthesis of PΦB which possesses a vinyl group at the C-18 position,[2d] we could not apply the previous method to prepare 1,5-dihydro-4-methyl-3-[2-(tolylthio)ethyl]-5-tosyl-2*H*-pyrrol-2-one (**13f**) as a precursor of the D-ring from the 2-bromo-5-tosylpyrrole **10f**, because it gave a complicated mixture of by-products besides the formation of **13f** in poor yield [21%, TFA/H_2O (5/1, v/v), rt, 16 h]. This result seemed to be due to the neighboring effect of 2-(tolylthio)ethyl group to form the cyclic intermediate such as **14** to avoid the expected hydrolysis. Consequently, the 5-tosylpyrrolinone **13f** was synthesized from **10f** via sulfoxide **11** by treatment with NaI in acidic medium as shown in Scheme 1.



Scheme 1.

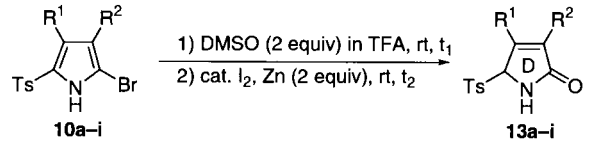
This successful redox method for the conversion of **10f** to **13f** prompted us to examine the use of dimethyl sulfoxide (DMSO) as an external nucleophile instead of the sulfoxide moiety in **11** to expand the method into the general 2-bromo-5-tosylpyrroles **10** without a thioether such as 2-(tolylthio)ethyl group. Though the expected reaction proceeded well to give the corresponding 5-tosylpyrrolinones **13** by employing DMSO and NaI in trifluoroacetic acid (TFA), the use of a large excess (5–7 equiv) of NaI was required to realize high yield, and besides, a lot of iodine liberated in progress of the reaction. After many attempts, it became possible to use only a catalytic amount of iodine together with zinc powder that reduces iodine in situ repeatedly as shown in Scheme 2.



Scheme 2.

The representative procedure for the conversion of 2-bromo-5-tosylpyrrole **10a** to the corresponding 5-tosylpyrrolinone **13a** was as follows: To a solution of 89 mg (0.26 mmol) of 2-bromo-3-ethyl-4-methyl-5-tosylpyrrole (**10a**) in 1 mL of TFA was added 0.74 ml of 0.705 M (= mol dm^{-3}) TFA solution of DMSO (0.52 mmol) at room temperature under nitrogen atmosphere. After stirring for 1 h, a catalytic amount (ca. 2 mg) of iodine and zinc powder (34 mg, 0.52 mmol) were added and the mixture was stirred for another 1 h at room temperature. After usual work-up, 3-ethyl-1,5-dihydro-4-methyl-5-tosyl-2*H*-pyrrol-2-one (**13a**) as the D-ring of PCB (**1**) was isolated by preparative TLC [SiO_2, hexane/AcOEt (3/1, v/v)] in 94% yield (68 mg) (Entry 1 in Table 1). In a similar manner, other 5-tosylpyrrolinones **13b–i** were prepared from the corresponding 2-bromo-5-tosylpyrroles **10b–i** in good yields as summarized in Table 1. Thus, the present method is much better than the previous one.[4]

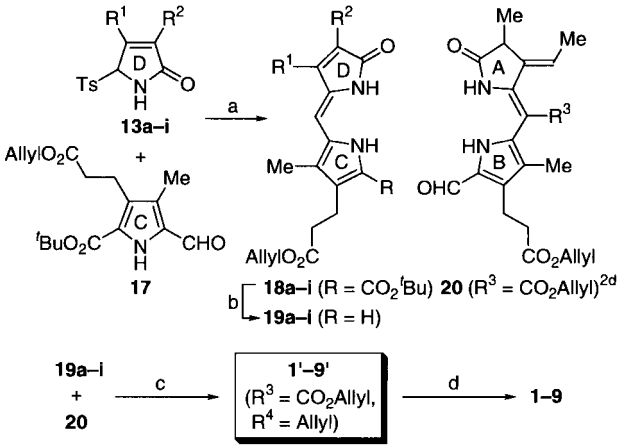
Table 1.



10a–i **13a–i**

Entry	10a–i	R^1	R^2	t_1/h	t_2/h	Yield of 13a–i/%
1	**a**,	Me	Et	1	1	94
2	**b**,	Me	^{n}Pr	2	2	82
3	**c**,	Me	^{n}Pen	2	2	86
4	**d**,	Me	^{n}Oct	2	2	78
5	**e**,	Me	$(CH_2)_2OAc$	2.5	1	93
6	**f**,	Me	$(CH_2)_2STol$	2	2	81[a]
7	**g**,	^{n}Pr	Me	2	2	91
8	**h**,	^{n}Pen	Me	2	2	84
9	**i**,	^{n}Oct	Me	2	2	89

[a]When 2 equiv of DMSO was used, the yield was 65%. A large excess (20 equiv) of DMSO was required to realize the shown higher yield.



a) (1) **13a–i** (1.1–1.2 equiv), **17** (1.0 equiv), ^{n}Bu$_3$P (2–3 equiv), DBU (1.1–1.5 equiv) in THF, 0 °C, then rt, 4–6 h. (2) cat. I_2 in CH_2Cl_2, rt, 3–24 h. **18a** 88%[2b]; **18b** 80%; **18c** 83%; **18d** 84%; **18e** 73%; **18f** 79%; **18g** 79%; **18h** 84% **18i** 80%. b) TFA, rt, ca. 1 h. **19a–i** were not isolated. c) **19a–i** (from 1.1–1.2 equiv of **18a–i**), **20** (1.0 equiv), cat. $MeSO_3H$ in MeOH, rt, ca. 5 h, unless otherwise noted. **1'** 86% (cat. HBr/AcOH in MeOH, rt, 4 h)[2b]; **2'** 75%; **3'** 70%; **4'** 62%; **5'** 60%; **6'** 65%; **7'** 68%; **8'** 72%; **9'** 60%. d) (1) [$Pd(PPh_3)_4$] (0.1–0.2 equiv), morpholine (10 equiv) in THF, rt, 1 h. (2) TFA, rt, 1–3 h. **1** 96%[2b]; **2** 53%; **3** 51%; **4** 58%; **5** 60%; **6** 31%; **7** 63%; **8** 62%; **9** 51%.

Scheme 3.

In the case of **10f**, it was necessary to use a large excess of DMSO to get higher yield (Entry 6), probably due to the formation of the cyclic intermediate **14** in equilibrium with **15** and/or **16** in Scheme 2.

The 5-tosylpyrrolinoes **13a–i** thus obtained were used to synthesize various PCB derivatives **1–9** modified at the D-ring in free acid forms with all-*Z*, all-*syn* conformations (confirmed by NOESY) according to our previous method as shown in Scheme 3.[2] The resulting PCB derivatives **1–9**[5] were employed in assembly with phytochrome B apoprotein (PHYB) in vitro to reveal the structural requirement of the side-chain of the D-ring for the photoreversible spectral change of the adducts.[3]

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References and Notes

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5 Spectral data of the final products **1–9** are given for UV/Vis (MeOH) λ_{max} and HRMS (FAB) (M^++1) in the following. **1**: see ref 2b. **2**: 364 (40200), 621 (12600) nm; Calcd for $C_{34}H_{41}N_4O_6$: *m/z* 601.3026. Found: 601.3026. **3**: 364 (40600), 621 (13500) nm; Calcd for $C_{36}H_{45}N_4O_6$: *m/z* 629.3339. Found: 629.3340. **4**: 364 (49800), 621 (16000) nm; Calcd for $C_{39}H_{51}N_4O_6$: *m/z* 671.3808. Found: 671.3812. **5**: 364 (45200), 621 (14200) nm; Calcd for $C_{35}H_{41}N_4O_8$: *m/z* 645.2924. Found: 645.2921. **6**: 366 (61700), 621 (19100) nm; Calcd for $C_{40}H_{45}N_4O_6S$: *m/z* 709.3060. Found: 709.3063. **7**: 364 (43800), 621 (14400) nm; Calcd for $C_{34}H_{41}N_4O_6$: *m/z* 601.3026. Found: 601.3023. **8**: 364 (45100), 621 (14800) nm; Calcd for $C_{36}H_{45}N_4O_6$: *m/z* 629.3339. Found: 629.3333. **9**: 364 (54600), 621 (17300) nm; Calcd for $C_{39}H_{51}N_4O_6$: *m/z* 671.3808. Found: 671.3800.