Efficient Construction of A,B-Rings Component for Syntheses of Phycocyanobilin and Its Derivative

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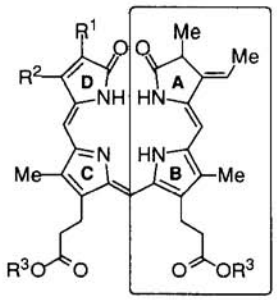
Total syntheses of phycocyanobilin and its photoactivatable derivative were accomplished by developing a new and versatile method for the construction of A,B-rings component, which consists of the Wittig-type new coupling reaction of 4-(1-methoxyethyl) -3-methyl -5-tosyl -1,5 -dihydro -2*H*-pyrrol-2-one and a 2-formyl pyrrole derivative in the presence of ^{n}Bu$_3$P and a base, followed by reduction with aluminum amalgam and subsequent acid treatment.

Biliproteins such as phycocyanin and phytochrome, which contain the bile pigments as chromophoric units, exist in plants. The chromophores of them, namely phycocyanobilin (**1**) and phytochromobilin (**2**) are linear tetrapyrrole derivatives and covalently bonded to their apoproteins at A-ring. Even though such bile pigments, phycobilins, could be isolated from natural sources, the knowledge of the relationship between the structure of synthetic pigments and biochemical properties of the biliproteins obtained by combining them with an apoprotein is quite interesting and important to reveal the precise function of the phycobilins. The recent development in gene technology have made it possible to assemble the chromophores such as **1** and **2** with the apoprotein obtained by the over-expression of the corresponding cDNA in bacteria and yeast.

For the structure/function analysis of phytochrome, we have been studying on the syntheses of phycobilin derivatives.[1] In this paper, we wish to report a new method for the construction of A,B-rings component applicable to the total syntheses of phycocyanobilin (**1**) and its photoactivatable derivative (**3**). Compound **1** has been often used as a substitute for the natural chromophore in phytochrome reconstitution experiments. Moreover, the photophysical and photochemical properties of wild type phytochrome are quite similar to those of the reconstituted chromoprotein containing phycocyanobilin (**1**).[2]



1; R^1 = Et, R^2 = Me, R^3 = H
Phycocyanobilin

2; R^1 = vinyl, R^2 = Me, R^3 = H
Phytochromobilin

3; R^1 = Et, R^2 =Ar, R^3 = H

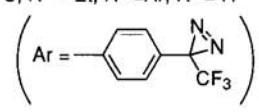


Figure 1.

Even though there are reports for the syntheses of phycobilin ester derivatives, most of the published works in this area for the synthesis of A,B-rings component have been carried out by utilizing either the Eschenmoser's sulfide contraction,[3] the thio-Wittig coupling,[4,5] or the photochemical rearrangement of N-pyrrolo enamide.[6] These methods provide viable routes to the required A,B-rings component, however, the former two usual methods require the removal of a meso-carboxylic ester group at the later stage in syntheses of phycobilins. Therefore, we developed an alternative route as illustrated in Figure 2 by retrosynthetic analyses of A,B- and C,D-rings components (**4** and **5**), both of which apply our original Wittig-type new coupling reaction between 5-tosyl pyrrolinones (**6** and **8**) and a common formyl pyrrole (**7**).[1b-d]

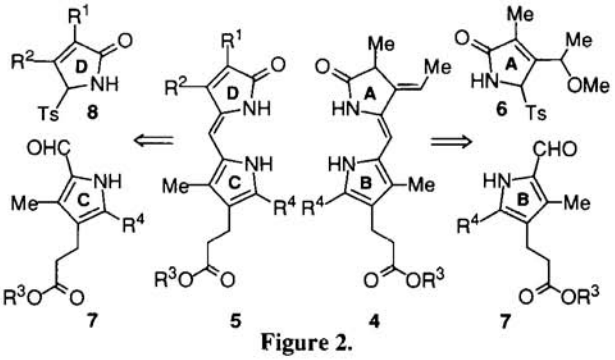
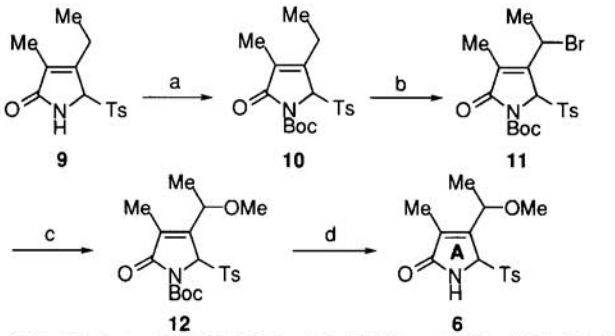


Figure 2.

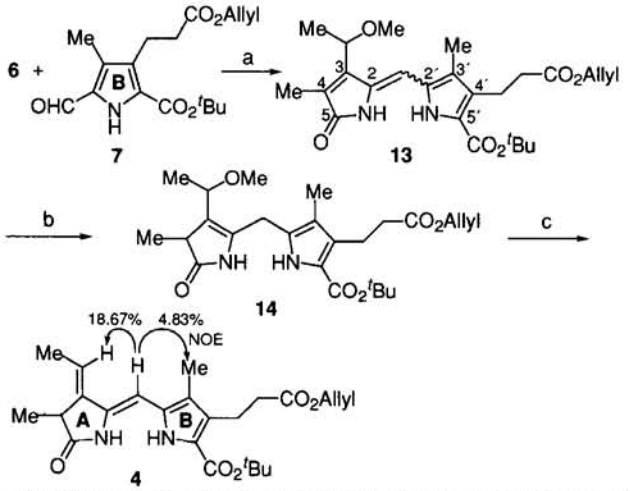
Preparation of A-ring **6** starting from the 5-tosylpyrrolinone **9**, which is readilly available by our previous method,[1a] was achieved through *N*-Boc-4-(1-methoxyethyl)-3-methyl-5-tosyl-1,5-dihydro-2*H*-pyrrol-2-one (**12**) as illustrated in Scheme 1. Namely, a nitrogen atom of **9** was protected with di-*t*-butyl dicarbonate and the resulting compound **10** was brominated with NBS to afford **11** regioselectively. Then treatment of **11** with NaOAc in MeOH followed by deprotection of Boc group with trifluoroacetic acid afforded the desired compound **6** in good yield.[7]



a) (Boc)$_2$O (1.5 eq.), DMAP (0.1 eq.) in MeCN at -40 °C - 0 °C, 1 h. **10** 91%. b) NBS (1.2 eq.) in benzene at rt, 2 d. **11** 70%. c) NaOAc (5 eq.) in refluxing MeOH, 1 h. **12** (not isolated). d) TFA at rt, 10 min. **6** 80% (from **11**).

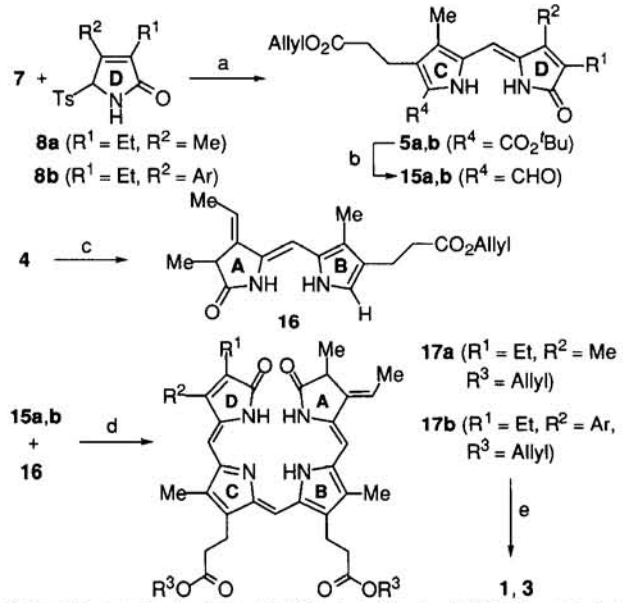
Scheme 1.

The compound **6** thus obtained was coupled with formyl pyrrole **7**[8] (R^3 = allyl, R^4 = $CO_2{}^tBu$ in Figure 2) as B-ring by the Wittig-type coupling reaction in the presence of $^nBu_3P$ and ^tBuOK in CH_2Cl_2 to afford 5(1*H*)-pyrromethenone **13** as a mixture of *E*- and *Z*-isomers in good yield. The resulting compound **13** was reduced with aluminum amalgam to give 5(4*H*)-dipyrrylmethanone **14**.[9] This isolable intermediate **14**[10] was treated with pyridinium *p*-toluenesulfonate (PPTS) without further purification to give the desired A,B-rings component **4**[11] (R^3 = allyl, R^4 = $CO_2{}^tBu$ in Figure 2) via elimination of methoxy group as a single *Z*-isomer (confirmed by NOE measurement) in good yield as shown in Scheme 2.



a) A CH_2Cl_2 solution of **6** (1.3 eq.) was added dropwise over the period of 30 min to the mixed solution of **7** (1.0 eq.), $^nBu_3P$ (2.4 eq.), and ^tBuOK (1.2 eq.) in CH_2Cl_2 at -78 °C - rt, overnight at rt, **13** 84% (*E*/*Z* = 28/72). b) Al(Hg), in THF/H_2O (10/1, v/v) at rt, 2 h. **14** (not isolated in general). c) PPTS (0.1 eq.) in CH_2Cl_2 at 0 °C - rt, 30 min. **4** 72% (from **13**).

Scheme 2.



a) See reference 1e for **5a,b**. b) TFA at rt, 40 min, $HC(OMe)_3$ at rt, 1 h. **15a** 81%; **15b** 66%. c) TFA at rt, 1 h. **16** (not isolated). d) **17a** 36% (cat. conc. H_2SO_4 in EtOH at rt, 4 h); **17b** 32% (cat. $MeSO_3H$ in EtOH at rt, 2 h). e) See refeference 1f for **1** and **3**.

Scheme 3.

The C,D-rings components **5a,b** were also prepared from **7** and **8a,b** by our original Wittig-type coupling reaction as described previously,[1e] followed by decarboxylation and formylation to afford **15a,b**. Then, these components were reacted with A,B-rings component **16** obtained by acid treatment of **4** to construct the corresponding tetrapyrrole derivatives **17a,b**. The allyl ester groups were deprotected according to the method described in the previous paper[1f] to obtain the acid forms of phycocyanobilin and its derivative bearing a photoreactive group at D-ring for a photoaffinity study.[1f,12]

As described above, the Wittig-type coupling reaction proved to be useful not only for the preparation of the C,D-rings component but also for the construction of A,B-rings component by introducing an eliminating group like methoxy group into the precursor of A-ring.

References and Notes

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7 **6:** A mixture of two diastereomers (Major/Minor = 2/1); mp 161-162 °C (from EtOAc/Hexane); IR (KBr) 3170, 3068, 2979, 2925, 2824, 1704, 1597, 1437, 1378, 1339, 1314, 1288, 1212, 1170, 1147, 1114, 1082, 985, 904, 806, 786, 746, 704, 674 cm^{-1}; ^1H NMR ($CDCl_3$) Major δ = 1.44 (d, J = 6.71 Hz, 3H), 1.83 (s, 3H), 2.45 (s, 3H), 3.37 (s, 3H), 4.68 (q, J = 6.71 Hz, 1H), 5.01 (s, 1H), 6.24 (brs, 1H), 7.34 (d, J = 8.42 Hz, 2H), 7.74 (d, J = 8.42 Hz, 2H) ppm. Minor δ = 1.57 (d, J = 6.34 Hz, 3H), 1.87 (s, 3H), 2.45 (s, 3H), 3.31 (s, 3H), 4.45 (q, J = 6.34 Hz, 1H), 5.23 (s, 1H), 6.19 (brs, 1H), 7.34 (d, J = 8.42 Hz, 2H), 7.74 (d, J = 8.42 Hz, 2H) ppm. Found: C, 58.08; H, 6.17; N, 4.32%. Calcd for $C_{15}H_{19}NO_4S$: C, 58.23; H, 6.19; N, 4.53%.

8 This pyrrole **7** is readily available by our previous method.[1c,e]

9 A. Gossauer and M. Blacha-Puller, *Liebigs Ann. Chem.*, **1981**, 1492.

10 **14:** An oily mixture of two diastereomers (Major/Minor = 2/1); IR (neat) 3287, 3090, 2976, 2931, 1694, 1448, 1368, 1279, 1169, 1138, 1116, 1053, 990, 848, 777, 756 cm^{-1}; ^1H NMR ($CDCl_3$) Major δ = 1.36 (d, J = 7.65 Hz, 3H), 1.37 (d, J = 6.42 Hz, 3H), 1.53 (s, 9H), 1.98 (s, 3H), 2.53 (t, J = 8.02 Hz, 2H), 2.99 (t, J = 8.02 Hz, 2H), 3.10 (q, J = 7.65 Hz, 1H), 3.29 (s, 3H), 3.52-3.69 (m, 2H), 4.21 (q, J = 6.42 Hz, 1H), 4.58 (dt, J = 1.28, 5.69 Hz, 2H), 5.22 (dq, J = 1.28, 10.27 Hz, 1H), 5.29 (dq, J = 1.28, 17.24 Hz, 1H), 5.90 (ddt, J = 5.69, 10.27, 17.24 Hz, 1H), 7.96, (brs, 1H), 9.55 (brs, 1H) ppm. Minor δ = 1.35 (d, J = 7.56 Hz, 3H), 1.37 (d, J = 6.42 Hz, 3H), 1.53 (s, 9H), 1.99 (s, 3H), 2.53 (t, J = 8.02 Hz, 2H), 2.99 (t, J = 8.02 Hz, 2H), 3.04 (q, J = 7.65 Hz, 1H), 3.34 (s, 3H), 3.52-3.69 (m, 2H), 4.04 (q, J = 6.42 Hz, 1H), 4.58 (dt, J = 1.28, 5.69 Hz, 2H), 5.22 (dd, J = 1.28, 10.27 Hz, 1H), 5.29 (dd, J = 1.28, 17.24 Hz, 1H), 5.90 (ddt, J = 5.69, 10.27, 17.24 Hz, 1H), 7.81 (brs, 1H), 9.48 (brs, 1H) ppm. HRMS (FAB): (M^+), Found: m/z 460.2578. Calcd for $C_{25}H_{36}N_2O_6$: 460.2573.

11 **4:** Z-form; mp 112-113.5 °C (from Cyclohexane/Hexane) ; IR (KBr) 3369, 3169, 2979, 1732, 1699, 1681, 1640, 1442, 1364, 1318, 1278, 1250, 1156, 1127, 1053, 989, 934, 772, 712 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.39 (d, J = 7.43 Hz, 3H), 1.55 (s, 9H), 1.85 (d, J = 7.15 Hz, 3H), 1.98 (s, 3H), 2.54 (t, J = 8.07 Hz, 2H), 3.00 (t, J = 8.07 Hz, 2H), 3.23 (q, J = 7.43 Hz, 1H), 4.59 (dt, J = 1.23, 5.69 Hz, 2H), 5.23 (dq, J = 1.23, 10.27 Hz, 1H), 5.30 (dq, J = 1.23, 17.06 Hz, 1H), 5.68 (s, 1H), 5.92 (ddt, J = 5.69, 10.27, 17.06 Hz, 1H), 6.18 (dq, J = 2.30, 7.15 Hz, 1H), 8.20 (brs, 1H), 8.85 (brs, 1H) ppm. Found: C, 67.13; H, 7.61; N, 6.36%. Calcd for $C_{24}H_{32}N_2O_5$: C, 67.27; H, 7.53; N, 6.54%.

12 K. Inomata, *Kagaku (Chemistry)*, **51**, 730 (1996).