A New Method for the Preparation of A- and D-Rings of Phycocyanobilin Using Mucochloric Acid as a Starting Material

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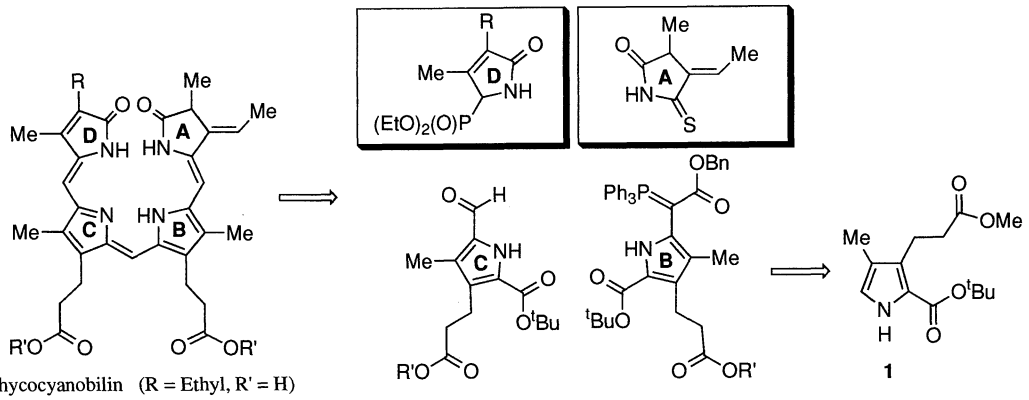
Diethyl 4-ethyl-1,5-dihydro-3-methyl-5-oxo-2*H*-pyrrol-2-yl-phosphonate and 2-ethylidene-3-methyl-1-thiosuccinimide as D-and A-rings of phycocyanobilin dimethyl ester could be synthesized by using commercially available mucochloric acid as a starting material in good yields.

Biliproteins such as phycocyanin, phytochrome which contain the bile pigments as the chromophoric units, exist in plants. They play an important role in the course of photo-synthesis and photomorphogenesis. Their chromophores are phycocyanobilin and phytochromobilin (Scheme 1), respectively, which are the linear tetrapyrrole derivatives and covalently bonded to their apoproteins.[1] The total synthesis of their dimethyl ester derivatives was reported by Gossauer and his co-workers, however, it required many steps and remained unsatisfied ones.[2,3] Therefore we targetted to develop a new methodology for their total synthesis. Recently, we have reported (1) the convenient method for the preparation of the pyrrole derivative (**1**)[4] as a precursor of B- and C-rings components; (2) the regioselective synthesis of 3,4-disubstituted 5-tosyl[5] or 5-(diethylphosphono)pyrrolin-2-ones[6] related to D-ring; (3) the synthesis of C/D-ring components of phycocyanobilin and phytochromobilin dimethyl esters in high yields[4,6]. However, in the synthesis of diethyl 3,4-disubstituted 1, 5-dihydro-2*H*-pyrrol-2-ylphosphonate related to D-ring, their yields were unsatisfactory. In addition, in the synthesis of A-ring according to the methods reported by Gossauer[2] and Rapopport[7], the former required many steps and both methods were found to be difficult to get the reproducible results. We wish to report herein a new method for the synthesis of D- and A-rings illustrated in Scheme 1 by using commercially available mucochloric acid as a starting material.

D-Ring (**7**) was synthesized via the sequence shown in Scheme 2. We first tried to replace both Cl atoms at C(3) and C(4) of the N-*p*-methoxybenzylpyrrolinone derivative **3** prepared from the mucochloric acid derivative **2**[8] to the corresponding alkyl groups, however, it was difficult to undergo the 1,4-addition by using the Grignard reagent or organocopper reagents. Ultimately it was found that when excess amounts of Me_2CuLi was used, 1,4-addition and the subsequent elimination and reduction took place to afford the compound **4** in 67% yield. Ethyl group was introduced to C(3) of the compound **4** by using ethyl iodide in the presence of potassium hydride in 56% yield together with its regioisomer ethylated at C(5) and diethylated compound at C(3). Methoxy group of the compound **5** could be replaced by diethyl phosphono group by treatment with triethyl phosphite in the presence of $TiCl_4$ to afford the compound **6** in 83% yield. Finally, N-*p*-methoxybenzyl protecting group was successfully removed by refluxing with an equimolar amount of anisole in TFA giving **7**[6] in 94% yield, which underwent the coupling reaction with α-formylpyrrole derivative (C-ring, **8**)[4] to afford the corresponding C/D-ring component of phycocyanobilin dimethyl ester **9**[6] in high yield as shown in Scheme 3.

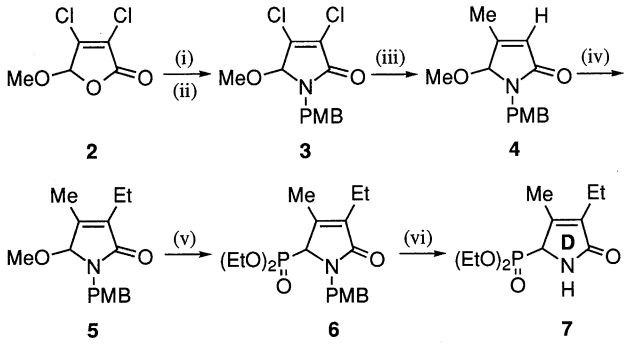
In order to synthesize the A-ring (**17**), the attempted introduction of ethyl group to C(4) of the compound **3** under various conditions was unsuccessful to generate the corresponding compound **11**. However, ethylation of the compound **2** with EtMgBr in the presence of $PdCl_2(PPh_3)_2$ catalyst proceeded readily to afford the compound **10** in 81% yield, and it was then converted to the corresponding N-*p*-methoxybenzylpyrrolinone derivative **11** (Scheme 4). Interestingly treatment of **11** with sodium alkoxide in alcohol created an acetal group at C(5) to afford the compound **13**[9] in high yield probably through the intermediate **12** produced by isomerization of **11** in the presence of alkoxide ion followed by S_N2' reaction. This observation prompted us to apply the compound **13** as a starting material for the synthesis of A-ring.

The synthesis of A-ring as a monothiosuccinimide (**17**) is illustrated in Scheme 5. It was found that the endo olefin of the compound **13** could be transfered to exo position by treatment with a base such as LDA, LHMDS etc. When methylation of



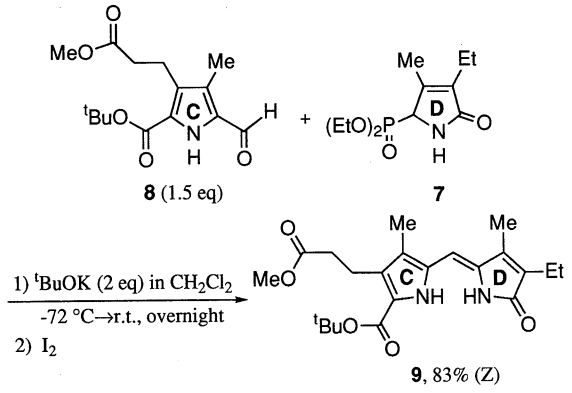
Scheme 1.

13 at C(3) was carried out with excess amounts of methyl iodide in the presence of 1.1 molar amounts of LHMDS at -50 °C, only the monomethylated compound **14** was selectively obtained in 97% yield. After acid hydrolysis of acetal group to afford the compound **15** followed by N-deprotection with CAN, the resulting compound **16** was reacted with an equimolar amount of Lawesson's reagent to afford the monothioamidated compound **17**[10] in 54% yield accompanied by unaffected **16** (39% yield).

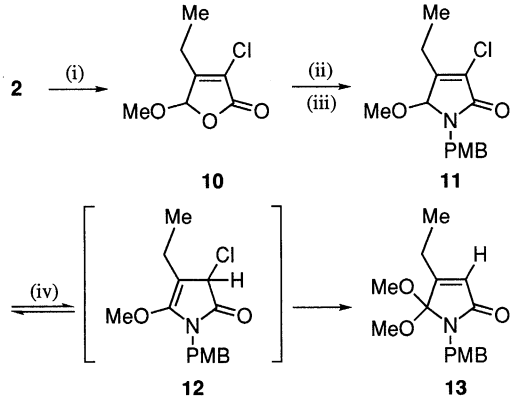


(i) *p*-$MeOC_6H_4CH_2NH_2$ ($PMBNH_2$, 1.5 eq) in Et_2O, r.t., 2h, 72%. (ii) H_2SO_4 in MeOH, reflux, 24 h, 84%. (iii) Me_2CuLi (6 eq), - 40 °C, 5 min, 67%. (iv) (1) KH (1.1 eq) in DME, r.t., 1 h; (2) EtI (1.25 eq), r.t., 5 min, 56%. (v) $P(OEt)_3$ (2 eq), $TiCl_4$ (1.2 eq) in CH_2Cl_2, r.t., 40 min, 83%. (vi) anisole (1 eq) in TFA, reflux, 6 h, 94%.

Scheme 2.

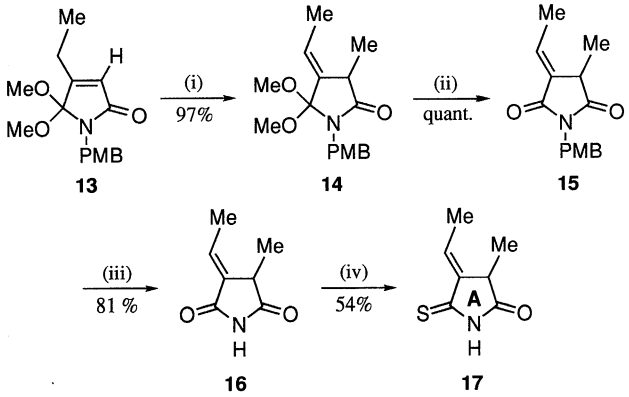


Scheme 3.



(i) EtMgBr (1.5 eq), $PdCl_2(PPh_3)_2$ (2.6 mol%) in THF, - 78 °C, 1 h, 81 %. (ii) *p*-$MeOC_6H_4CH_2NH_2$ (1.2 eq) in Et_2O, r.t., 6 h, 74%. (iii) H_2SO_4 in MeOH, reflux, 3 h, 82%. (iv) NaOMe (1.1 eq) in MeOH, r.t., 30 min, 90%.

Scheme 4.



(i) (1) LHMDS (1.1 eq) in THF, - 50 °C, 1 h; (2) MeI (5 eq), - 50 °C, 1 h. (ii) 6 M HCl in THF, 10 min. (iii) (1) CAN (4 eq) in MeCN / H_2O (3/1), 0 °C→r.t., 4 h; (2) H_2N-NH_2·H_2O (0.4 eq) in MeOH, r.t., 5 min. (iv) Lawesson's reagent (1 molar amount) in toluene, reflux, 30 min.

Scheme 5.

As mentioned above, the A- and D-rings of phycocyanobilin were both synthesized from mucochloric acid in reasonable yields. We are now investigating the new preparative method of A/B-ring component toward the total synthesis of phycocyanobilin dimethyl ester derivative.

References and Notes

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7 J. E. Bishop, S. A. Dagan, and H. Rapoport, *J. Org. Chem.*, **54**, 1876 (1989).
8 H. Simonis, *Chem. Ber.*, **34**, 509 (1899); **2:** Bp 114-119 °C/20 Torr (1 Torr = 133.322 Pa); MS m/z 182 (M^+, 23.34%), 155 (30.12), 153 (93.71), 151 (100.00), 147 (94.01), 103 (92.41), 87 (51.78), 75 (30.04); IR (neat) 2980, 2860, 1780, 1630, 1230, 1140, 1020, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 3.59 (3H, s), 5.76 (1H, s).
9 **13:** A colorless solid; Mp 57-58 °C (from Et_2O); IR (KBr) 3000, 2960, 2840, 1700, 1600, 1500, 1380, 1240, 1100, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.19 (3H, t, J=7.32 Hz), 2.16 (2H, dq, J=2.14, 7.32 Hz), 2.80 (6H, s), 3.78 (3H, s), 4.27 (2H, s), 5.99 (1H, t, J=2.14 Hz), 6.80 (2H, d, J=8.54 Hz), 7.39 (2H, d, J=8.96 Hz); Found: C, 66.21; H, 6.99; N, 4.90%. Calcd for $C_{16}H_{21}NO_4$: C, 65.95; H, 7.27; N, 4.81%.
10 **17:** Mp 113-114 °C (from Et_2O/Hexane) (lit. Mp 115 °C[2], 116-117 °C[7]).