A Novel Synthetic Approach toward Phycobilin Derivatives -A Total Synthesis of Phycocyanbilin Dimethyl Ester

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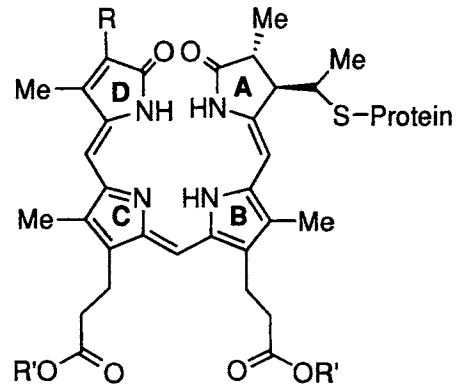
論文審査委員	（主査）　猪 股 勝 彦 （副査）　中 島　　正，木 下 英 樹 　　宇 梶　　裕，中 本 義 章

学位論文要旨

Abstract A convenient method for the preparation of A-, D- and C/D-rings components of phycobilins toward the total synthesis of phycocyanobilin dimethyl ester was developed. 3-Ethyl-4-methyl-5-tosyl-(1,5-dihydro-2*H*-pyrrol)-2-one and diethyl 4-ethyl-3-methyl-5-oxo-(1,5-dihydro-2*H*-pyrrol-2yl)phosphonate which are both related to D-ring, were readily synthesized regioselectively from the corresponding pyrrole derivatives by bromination and the subsequent acidic hydrolysis. These pyrrolinone derivatives underwent the coupling reaction with various aldehydes according to Wittig-type and Horner-Emmons-type reactions respectively to afford the corresponding 5-exomethylene derivatives in good yields. This method was successfully applied to the synthesis of C/D-rings component. Furthermore, a new synthetic approach to diethyl 4-ethyl-3-methyl-5-oxo-(1,5-dihydro-2*H*-pyrrol-2yl)phosphonate (D-ring) and 2-ethylidene-3-methyl-1-thiosuccinimide (A-ring) was investigated by using commercially available mucochloric acid as a starting material. The C/D-rings component and A-ring synthesized above were successfully employed for the total synthesis of phycocyanobilin dimethyl ester.

Biliproteins such as phycocyanin and phytochrome which exist in plants contain the chromophores, phycocyanobilin and phytochromobilin, known as tetrapyrrole pigments. They play an important role in the course of photosynthesis and photomorphogenesis. Even though the chromophoric units, bile pigments could be isolated from natural sources, the knowledge of the relationship between the structure of synthetic compounds and biochemical properties of the biliproteins obtained by combining them with an apoprotein is interesting and important to reveal the precise function of the phycobilins. Therefore the synthesis of the bile pigments and the study of their structural aspects became important for chemists.



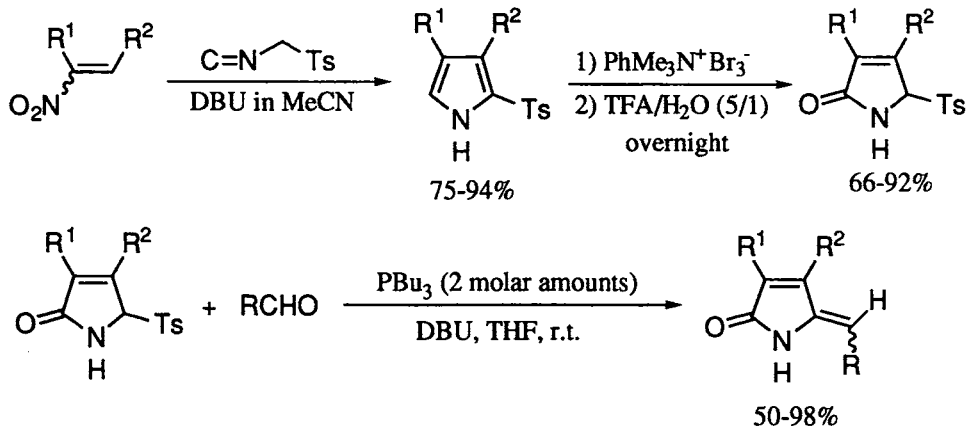
Phycocyanin (R = Ethyl, R' = H)
Phytochrome (R = Vinyl, R' = H)

Gossauer and his co-workers reported the total synthesis of phycocyanobilin and phytochromobilin derivatives. However, their methods required many steps and the yields for some steps were poor, or it was difficult to get the reproducible results. Therefore it was at first required to develop the new methodology for the synthesis of four pyrrole components toward the total syntheses of phycobilin derivatives.

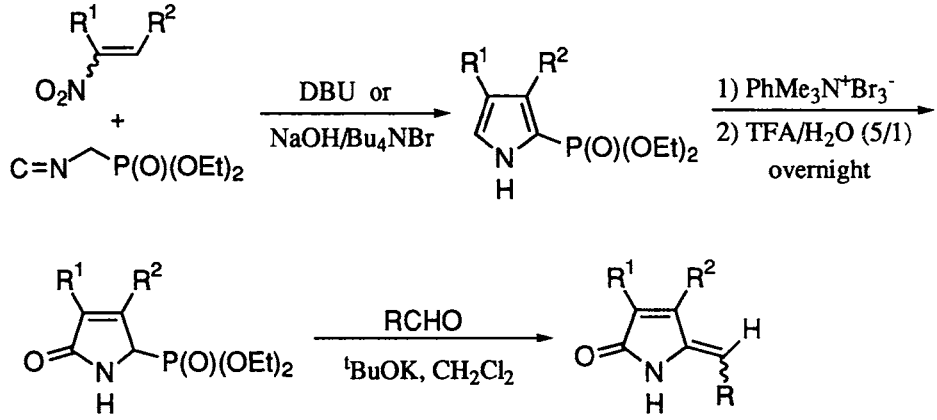
Recently, in our laboratory, a convenient method for the preparation of a pyrrole compound common to B- and C-rings of phycobilins and a new approach to the total synthesis of phycocyanobilin dimethyl ester and its derivative bearing a photolabelling group have been exploited.

In the present work, the syntheses of A-, D- and C/D-rings components of phycobilin derivatives and the total synthesis of phycocyanobilin dimethyl ester were achieved.

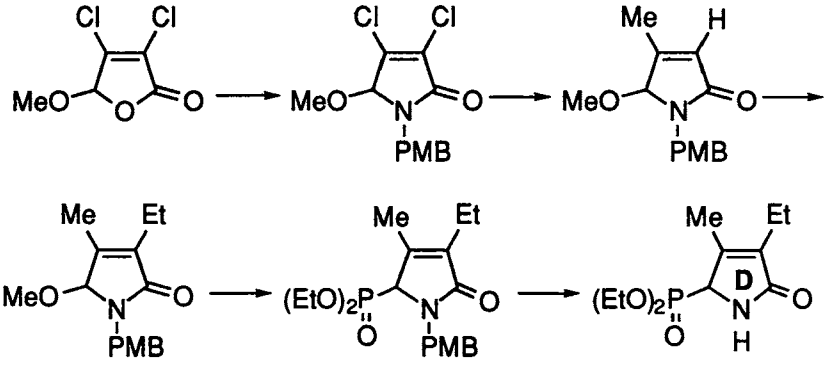
In Chapter 2, the preparation of 3,4-disubstituted 5-tosyl-(1,5-dihydro-2*H*-pyrrol)-2-ones related to D-ring of phycobilins and the C/D-rings components of phycocyanobilin dimethyl ester was described. The former pyrrolinone derivatives could be synthesized regioselectively by bromination and the subsequent acidic hydrolysis of the corresponding 3,4-disubstituted 2-tosylpyrrole derivatives which were obtained from nitroolefins and TosMIC in the presence of DBU according to Barton's method in good yields. The pyrrolinone derivatives thus obtained could be coupled with various aldehydes by Wittig-type reaction in the presence of tri(n-butyl)phosphine and a base to afford the corresponding 5-exomethylene compounds including pyrromethenone derivatives and C/D-rings component of the phycocyanobilin dimethyl ester in excellent yields. The 5-exomethylene compounds were formed as a mixture of (*Z*)- and (*E*)-isomers, however, the (*E*)-isomer was readily converted to thermodynamically more stable (*Z*)-one by treatment with a small amounts of iodine quantitatively.



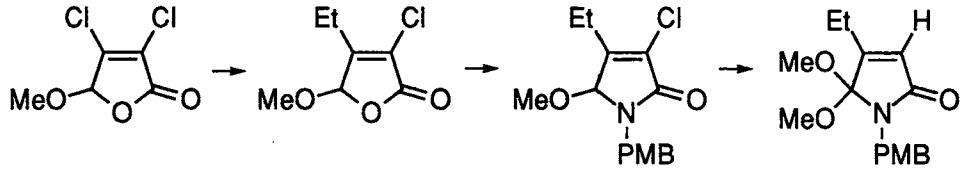
In Chapter 3, the preparation of diethyl 3,4-disubstituted 5-oxo-(1,5-dihydro-2*H*-pyrrol-2-yl) phosphonates and their coulping with various aldehydes were described. Diethyl 3,4-disubstituted 5-oxo-(1,5-dihydro-2*H*-pyrrol-2-yl)phosphonates could be prepared regio-selectively via diethyl 3,4-disubstituted 2-pyrrolylphosphonates, which were synthesized from nitroolefins and diethyl isocyanomethylphosphonate according to Barton's method, by bromination and the subsequent acidic hydrolysis in moderate yields. These diethyl 3,4-disubstituted 5-oxo-(1,5-dihydro-2*H*-pyrrol-2yl)phosphonates underwent the Horner-Emmons-type coupling reaction with various aldehydes in the presence of ^{t}BuOK to afford the corresponding 5-exomethylene derivatives including the C/D-rings component of phycocyanobilin dimethyl ester in good yields. Although the formation of C/D-rings component was successfully performed, the yield of the D-ring was unsatisfactory.



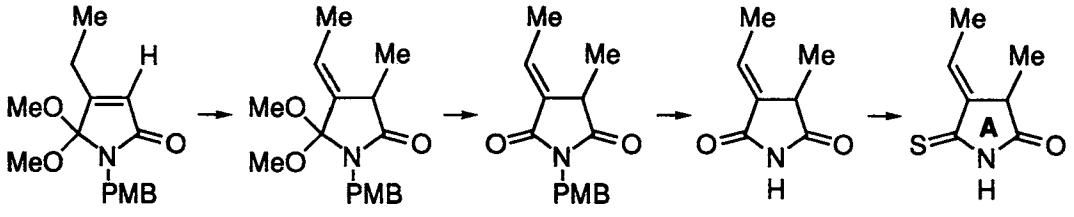
In Chapter 4, to improve the yield of the diethyl 4-ethyl-3-methyl-5-oxo-(1,5-dihydro-2*H*-pyrrol-2-yl)phosphonate (D-ring), the synthesis of D-ring starting from the commercially available mucochloric acid was investigated. A precursor, 3,4-dichloro-5-methoxy-1-(*p*-methoxybenzyl)-(1,5-dihydro-2*H*-pyrrol)-2-one derived from mucochloric acid could be converted to D-ring bearing diethyl phosphono group at C(5) by the following sequence; (1) methylation at C(4) with 6 molar amounts of Me_2CuLi, (2) ethylation at C(3) with ethyl iodide in the presence of KH, (3) phosphorylation at C(5) with triethyl phosphite in the presence of $TiCl_4$, and (4) deprotection of *p*-methoxybenzyl group with anisole in TFA.



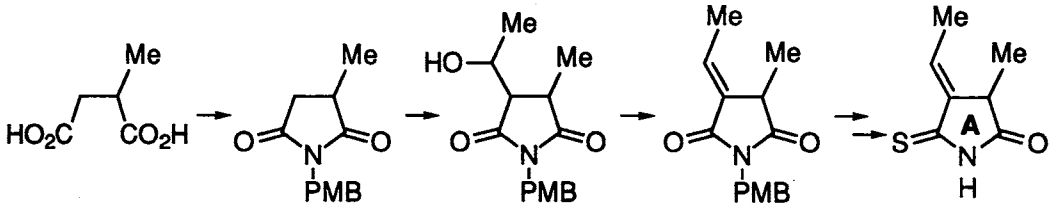
On the other hand, a synthesis of 4-ethyl-5,5-dimethoxy-1-(*p*-methoxybenzyl)-(1,5-dihydro-2*H*-pyrrol)-2-one as a precursor of A-ring was also described in this chapter. They could be obtained by the sequence; (1) regioselective ethylation at C(4) of a mucochloric acid ester using EtMgBr in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$, (2) conversion to the corresponding lactams using *p*-methoxybenzylamine followed by treatment with alcohol in the presence of conc. H_2SO_4, and (3) treatment with sodium alkoxide in alcohol to create an acetal functional group at C(5), in excellent yields.



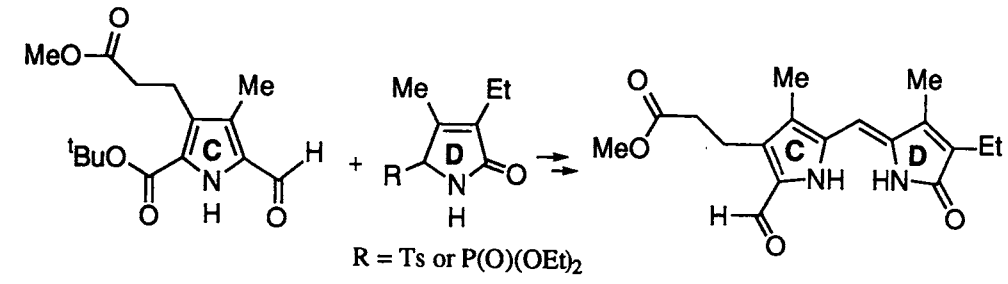
In Chapter 5, a new method for the preparation of A-ring as a monothiosuccinimide derivative was investigated using mucochloric acid as a starting material. It could be prepared by a series of (1) methylation at C(3) of 4-ethyl-5,5-dimethoxy-1-(*p*-methoxybenzyl)-(1,5-dihydro-2*H*-pyrrol)-2-one derived from mucochloric acid as described above, (2) hydrolysis of acetal group, (3) oxidative deprotection of N-*p*-methoxybenzyl group with CAN, (4) regioselective thiocarbonylation by the use of Lawesson's reagent.



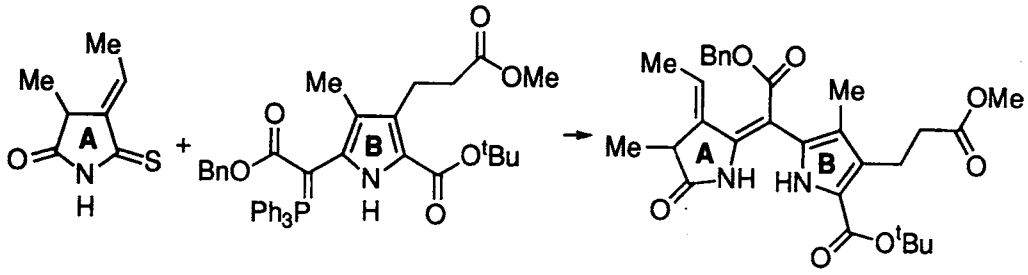
It is now tried to synthesize the A-ring with a few steps according to the following route.



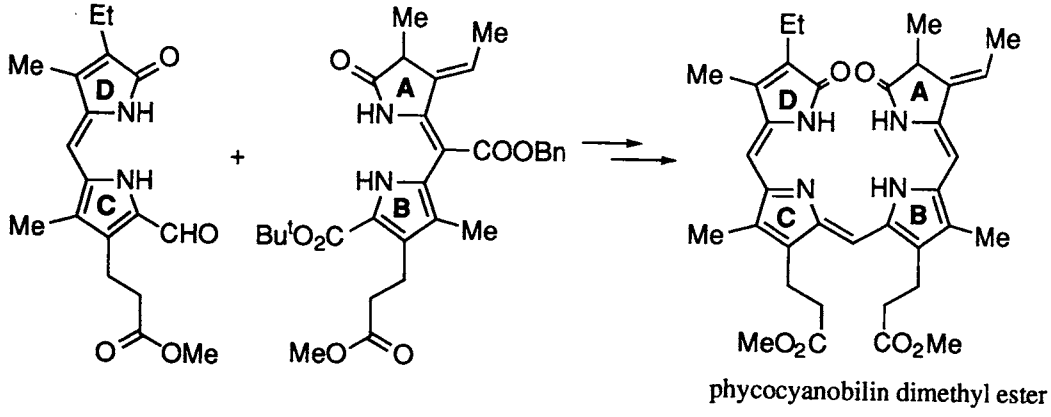
In Chapter 6, a total synthesis of phycocyanobilin dimethyl ester was achieved by employing the new coupling method of C- and D-rings described above (Eq. 1) and the known sequence for the coupling of A- and B-rings as follows; (1) condenstaion of A- and B-rings based on thio-Wittig-type reaction (Eq. 2), (2) coupling of the A/B- and C/D-rings under acidic conditions (Eq. 3).



(1)

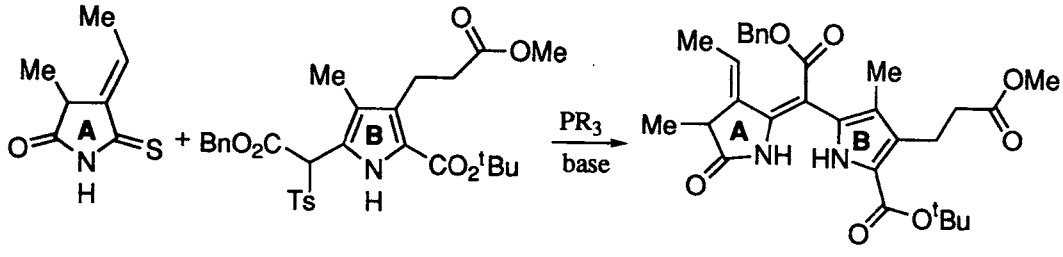


(2)



(3)

Further, a promising method for the synthesis of A/B-rings component shown in the following scheme is now attempted.



As mentioned above, the new methods for the syntheses of D-ring, A-ring and

C/D-rings components of the phycobilin derivatives could be developed in this work and these methods were successfully employed for the total synthesis of phycocyanobilin dimethyl ester.

学位論文の審査結果の要旨

提出された当該学位論文に対し，各審査委員が参考論文等の関連資料の検討を含めて審査を行い，さらに平成７年８月１日の口頭発表における質疑応答（最終試験に代える）の結果をふまえて，同日開催された審査委員会において最終審査を行い，以下の通り判定した。

本論文は，植物内に存在し，植物の発生や分化等の形態形成を調節する重要な役割を演じている光受容タンパク色素ーフィトクロムやフィコシアニンの色素成分でテトラピロール化合物の一種であるフィコビリン誘導体の新規合成法の開発を目的として研究を行い，(1) D環に相当する５-トシルおよび５-ジエチルホスホノピロリノン誘導体の簡便合成法の開発，(2) ここで得られたD環とα-ホルミルピロール骨格を有するC環との高効率的カップリング反応，(3) A環の新規合成法の開発，(4) A環とB環との新規カップリング反応，について注目すべき結果を得ている。また，これらの新規合成法およびカップリング反応を応用して，(5) フィコシアノビリンジメチルエステルの全合成にも成功している。これらの成果は今後，上述した極めて興味深い生理活性を有するビリタンパク質の色素部分の構造と機能の相関関係や，色素部分とアポタンパク質との相対的位置関係などを明らかにする上で，大きく貢献するものである。

以上のように，本研究では，フィコビリン誘導体の一般的合成法の検討を行い，関連分野ならびに新しい研究領域の発展に大きく寄与する成果を挙げており，博士（理学）の学位を受けるに充分値するものと判定した。