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Straightforward synthesis of fucoxanthin short-chain derivatives via modified-Julia olefination

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ABSTRACT

Fucoxanthin is an essential pigment for the light-harvesting of aquatic algae. It exhibits high energy transfer efficiencies to Chl *a* (>80%) as well as peridinin (>95%). In order to verify the generality and specificity of the noticeable observation on the ICT excited energy state character, which was found in the study of peridinin, we achieved the straightforward synthesis of a series of fucoxanthin short-chain derivatives via the modified-Julia olefination with the aldehyde half segment possessing a β,γ -epoxyketone function. The established method was successfully applied to the synthesis of the epoxy olefin derivative as an allene modified fucoxanthin analogue.

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A marine carotenoid, fucoxanthin (**1**), exhibits high energy transfer efficiencies to chlorophyll *a* (Chl *a*) during the initial process of photosynthesis, reported as >80%, as well as peridinin, which is also one of the representative light-harvesting marine carotenoid and shows >95% energy transfer efficiencies, in the sea. During the course of our studies on the relationship between the structural features of these carbonyl-containing carotenoids and their propensity for carrying out the highly efficient energy transfer in the super-complex composed of these carotenoids and Chl *a* embedded in the protein complex,^{1,2} we have already reported the synthesis of a series of peridinin analogues, such as allene-modified,³ ylidenebutenolide-modified,⁴ and π -electron chain length-modified⁵ derivatives, and the results of their ultrafast time resolved optical absorption⁶ and the Stark spectroscopy analyses.⁷ The measurements of these spectroscopies have revealed that an intramolecular charge transfer (ICT) excited energy state, which is postulated to be closely associated with the highly efficient energy transfer, behaves independently from the S_1 state, and that the ICT state lifetime, which indicates the relative energy level from the ground state, converges the nearly same value in methanol for all π -electron chain length-modified derivatives regardless of the extent of the π -electron conjugation.⁶ Furthermore, the most recent measurements of these derivatives in the

most polar solvent, acetonitrile, demonstrated that the ICT state lifetime is present in the very narrow region slightly related with the extent of the π -electron conjugation.⁸ This unique and noticeable observation can be regarded as an inherent character of the ICT state. In addition, the allene and the position of the ylidenebutenolide functions of peridinin contribute to the generation of a large dipole moment in the excited state of the molecule.^{7,9} These unexpected findings are the first regarding the unique characteristics of the ICT state in the field of molecular spectroscopy.^{6,8} Then, the next stage is to verify the generality and specificity of the remarkable results obtained in peridinin. Our attention was then concentrated on fucoxanthin (**1**) and its derivatives, and we reported the stereocontrolled synthesis of both natural C40-fucoxanthin and its longer-chain derivative, C42-fucoxanthin, in a previous paper.¹⁰ Although the method of synthesis for these compounds would be applicable for the synthesis of the less-conjugated short-chain derivatives of fucoxanthin, we intended to develop a more concise and straightforward method for the synthesis of a series of the short-chain fucoxanthin derivatives (see Fig. 1).

We now describe the straightforward synthesis of the different π -electron chain length derivatives **2–4** and an allene modified derivative **5** possessing an epoxy olefin group instead of the hydroxyl allene moiety of fucoxanthin, by means of the modified-Julia olefination reaction of the corresponding sulfone segments with the aldehyde segments possessing a β,γ -epoxyketone function.

Fucoxanthin (**1**) and its derivatives possess a β,γ -epoxyketone moiety in a π -electron conjugated system along with the allene

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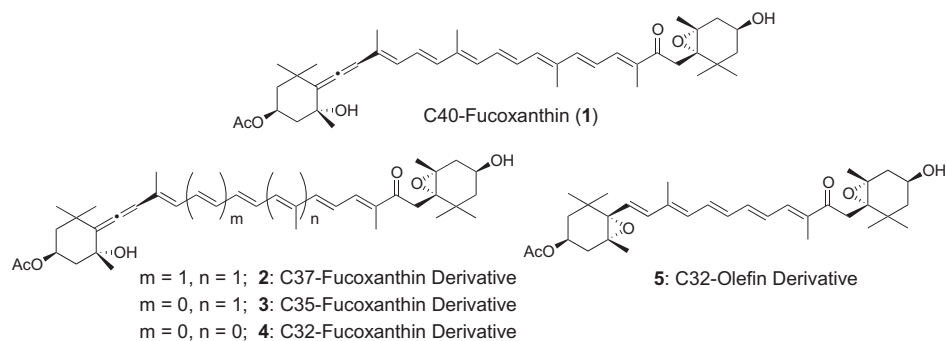


Figure 1. Structure of target molecules.

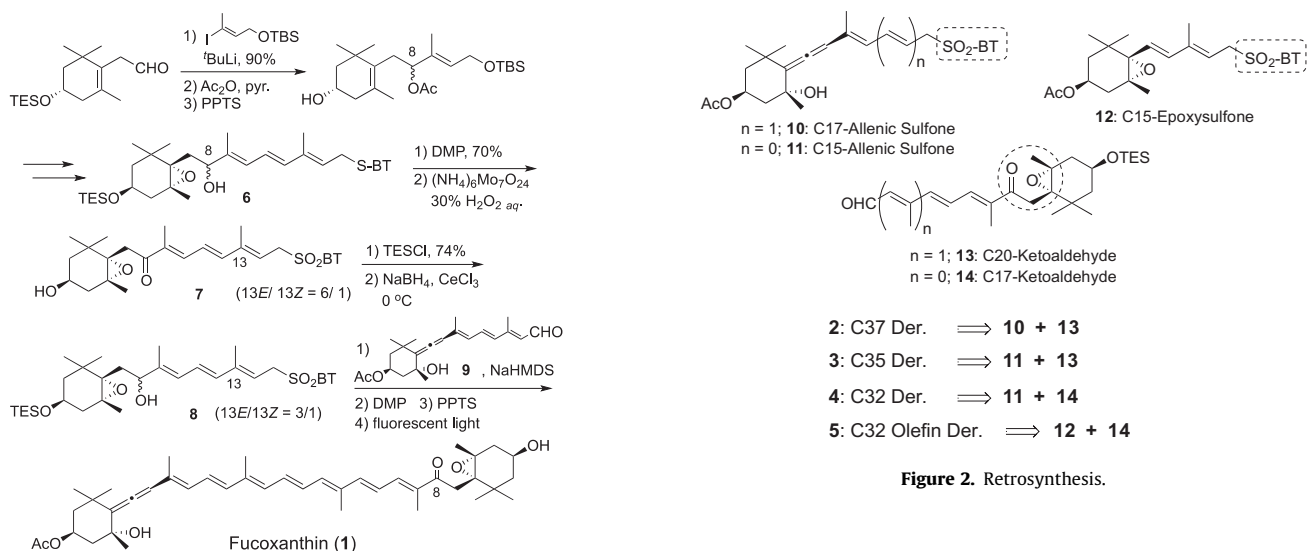


Figure 2. Retrosynthesis.

Scheme 1. Previous synthesis of fucoxanthin.

function at another terminal. Generally, the epoxide presented in such a functional moiety easily opens to give the γ -hydroxy- α , β -unsaturated ketone due to the high acidity of the α -proton of a carbonyl group. Actually, this moiety in fucoxanthin was reported to be labile to *alkali*, such as a 5% aqueous KOH solution, to give the corresponding cyclic hemi-acetal derivative along with the decomposed compounds.¹¹ Considering these problems, we succeeded in the stereocontrolled total synthesis of natural fucoxanthin (1) and its longer polyene chain C42-derivative by construction of this reactive moiety after the connection of the C20-allenic aldehyde 9 with the C20-hydroxy sulfone 8 (Scheme 1).¹⁰ This method, however, required tedious transformations for the preparation of the ketone moiety at the C-8 position of fucoxanthin (1). Thus, this function must be a carbonyl group for the transformation from the sulfide 6 to the corresponding sulfone 7, and a hydroxyl group for the modified Julia olefination reaction of the sulfone segment 8.¹⁰ In addition, the resulting hydroxyl group must be oxidized again to construct the β , γ -epoxyketone moiety of fucoxanthin (Scheme 1). We then decided to investigate the straightforward strategy for the synthesis of the short-conjugated chain and allene modified derivatives of fucoxanthin 2–5 by the direct coupling of the ketoaldehyde segments 13–14 possessing a β , γ -epoxyketone moiety with the sulfone segments 10–12 by the modified-Julia olefination coupling (Fig. 2).

Thus, the C37-fucoxanthin derivative 2 would be obtained by the coupling between the C17-allenic sulfone 10¹² and C20-ketoaldehyde 13. The coupling between the C15-allenic sulfone

11⁵ and C20-ketoaldehyde 13, and between the C15-allenic sulfone 11 and C17-ketoaldehyde 14 would produce the C35-fucoxanthin derivative 3 and C32-fucoxanthin derivative 4, respectively. Meanwhile, the coupling between the C15-epoxy sulfone 12 and C17-ketoaldehyde 14 would produce the allene modified C32-olefin derivative 5. The C20- and C17-ketoaldehyde segments 13 and 14 would be easily synthesized from the intermediates of the fucoxanthin synthesis.¹⁰

First, the syntheses of ketoaldehydes 13 and 14 are described (Scheme 2). The aldehyde 15, which was an intermediate in the fucoxanthin synthesis, was treated with an anion generated from the commercially available HWE reagents 16 and 19 to stereoselectively produce the desired triene ester 17 and diene ester 20 in good yields, respectively. Selective hydrolysis of the *p*-nitrobenzoyl group of the ester 17 and then protection of the resulting hydroxyl group afforded the diester 18¹⁰ in 91% yield for two steps. The obtained diester was transformed into the C20-ketoaldehyde 13 by the DIBAL reduction followed by the Dess–Martin oxidation in 56% yield for 2 steps. The same procedures also afforded the C17-ketoaldehyde 14 from 20. Thus, two kinds of aldehyde half-segments having a different conjugating chain were systematically easily synthesized.

With the C20-ketoaldehydes in hand, the crucial modified-Julia olefination between the known sulfone 11⁵ and ketoaldehyde 13 possessing the β , γ -epoxyketone moiety was investigated as a key step in the synthesis of the C35-fucoxanthin 3. The reaction conditions were explored in detail and the appropriate reaction conditions were finally determined. At -78 °C, three equivalents of NaHMDS were added to a mixture of the aldehyde 13 and sulfone 11 in THF. Gratifyingly, the reaction proceeded within 5 min to

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