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Stereocontrolled Total Synthesis of Fucoxanthin and Its Polyene Chain-Modified Derivative

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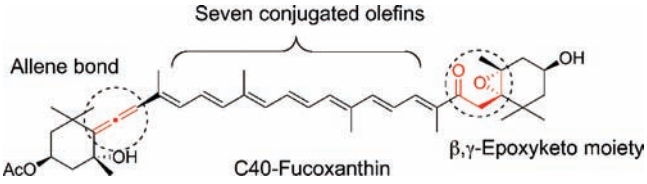
ABSTRACT



Fucoxanthin exhibits high energy transfer efficiencies to Chlorophyll a (Chl a) in photosynthesis in the sea. In order to reveal how each characteristic functional group, such as the length of the polyene chain, allene, and conjugated carbonyl groups, of this marine natural product are responsible for its remarkably efficient ability, the total synthesis of fucoxanthin by controlling the stereochemistry was achieved. The method established for fucoxanthin synthesis was successfully applied to the synthesis of the C42 longer chain analogue.

The allenic carotenoids possessing a conjugated carbonyl group, such as peridinin (**1**) and fucoxanthin (**2**), have been paid much attention as the main light-harvesting pigments in photosynthesis in the sea, because they exhibit high energy transfer efficiencies to Chlorophyll a (Chl a), reported as $>95\%$ in peridinin and $>80\%$ in fucoxanthin, and in the complexes constructed by these carotenoids with chlorophylls and a protein, the so-called PCP and FCP.[1,2] These energy transfer efficiencies are thought to be related to the intricate structures of these attractive carotenoids. In order to examine the relationship between their unique structures and excellent energy transfer ability, our attention first focused on peridinin. We achieved the highly efficient stereocontrolled synthesis of peridinin and then successfully carried out the syntheses of a series of allene-modified,[3] ylidenebutenolide-modified,[4] and π-electron chain length-modified[5] derivatives of peridinin. The measurements of the ultrafast time-resolved optical absorption and the Stark spectroscopy performed on these peridinin-modified derivatives have clearly revealed that an intramolecular charge transfer (ICT) state behaves independently from the S_1 state, and furthermore, the striking observation in the data is that the lifetime of the ICT state converges to a value of 10 ± 1 ps in methanol for all the peridinin analogues regardless of the extent of the

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π-electron conjugation.[6] This unique and noticeable observation can be regarded as an inherent characteristic of the ICT state. Moreover, the allene and unique C37 carbon skeleton of peridinin (**1**) contribute to the generation of a large dipole moment in the excited state of the molecule.[7] These unexpected findings are the first in particular in the field of molecular spectroscopy. Therefore, the next stage is to verify the generality and specificity of the remarkable results obtained in peridinin.

For the efficient synthesis of polyfunctional carotenoids, the stereocontrolled construction of the terminal oxidized cyclohexane moiety is very important along with the polyolefin chain construction (Figure 1). In the case of the peridinin synthesis reported by four groups,[8] all of them

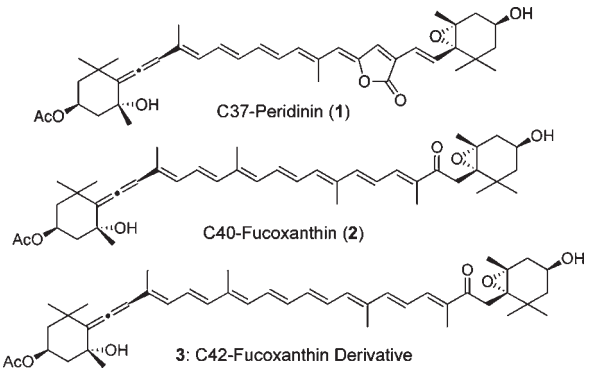

Figure 1. Structure of target molecules.

used the Sharpless asymmetric epoxidation of the corresponding allyl alcohol as a key step for the construction of the oxidized cyclohexane moiety.[9] However, for the stereocontrolled synthesis of fucoxanthin, the method established in the synthesis of peridinin cannot be applied, because this carotenoid possesses a β,γ-epoxyketo moiety, which is known to be extremely labile to alkali.[10] Although the synthesis of fucoxanthin was only reported by Ito's group, the stereochemical control of both the epoxidation and polyene chain formation were not achieved due to this labile moiety.[11] Therefore, the second synthesis of fucoxanthin must be a stereocontrolled one and should be applicable for the syntheses of various kinds of fucoxanthin modified derivatives. We now report the stereocontrolled total syntheses of fucoxanthin and the longer chain C42 derivative **3** based on the successful stereocontrolled construction of the terminal cyclohexane moiety.

In our retrosynthetic analysis (Figure 2), the labile β,γ-epoxyketo moiety of fucoxanthin (**2**) would be formed in the final step. We bisected an allenic segment and a hydroxy sulfone segment to form a library of each half-segment in order to synthesize the various designed fucoxanthin derivatives. The allenic segment **4** would be synthesized from the optically homogeneous epoxyaldehyde derivative **6**,[12] which had been prepared from (−)-actinol **7**.[9] Therefore, the subject is how to synthesize the hydroxyl sulfone segment **5** under satisfactorily stereocontrolled conditions, in particular, the cyclohexane moiety possessing the hydroxyl and epoxy functions. We planned to construct **5** introducing the C8 oxygen function from the β,γ-unsaturated aldehyde **8**, which would be prepared from 3-epi actinol **9**[13] possessing an unnatural stereochemistry (carotenoid numbering). We thoroughly investigated the satisfactorily stereocontrolled introduction of the *cis*-epoxide to the C3-α-homoallylic alcohol by utilizing the Sharpless epoxidation, then followed by inversion of the resulting unnatural stereochemistry at the C3 hydroxyl group to the corrected one by the Mitsunobu reaction.

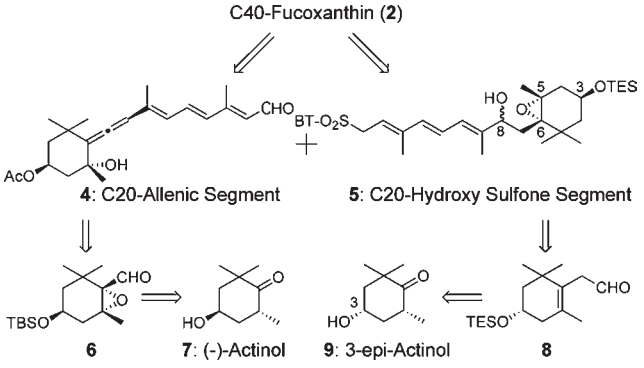

Figure 2. Retrosynthesis.

First, the synthesis of the hydroxyl sulfone segment **5** is described (Scheme 1). The β,γ-unsaturated aldehyde **8** was synthesized by the known method.[11,14] To extend the carbon chain of **8** accompanied by introducing the C8 hydroxyl group, the vinyl anion prepared from vinyl iodide **10** and *tert*-butyllithium was reacted with the aldehyde **8** to produce the desired alcohol in high yield. Acetylation of the resulting alcohol and then chemoselective removal of the TES group led to the α-homoallylic alcohol **11**. Next,

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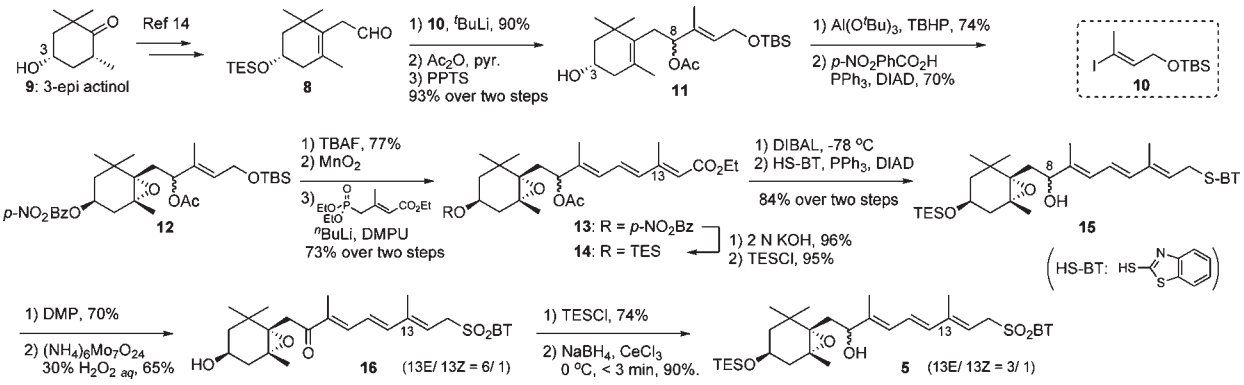
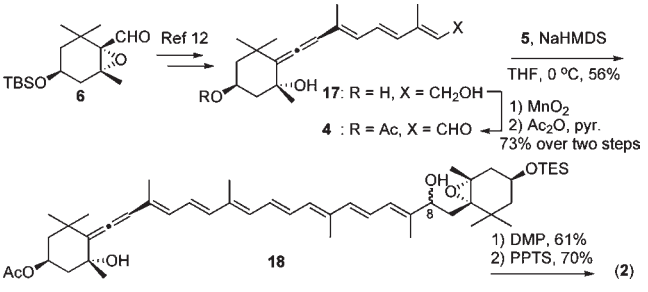
Scheme 1. Synthesis of Hydroxy Sulfone **5**



we surveyed the diastereoselective epoxidation of the tetrasubstituted olefin in the cyclohexene ring with the aid of the C3 homoallylic hydroxyl group.[15] For the combination of the rather general Mo and V catalysts with TBHP, an unknown compound was produced along with a small amount of the desired product. After a thorough investigation of the substrates and conditions, we found that the reaction of organoaluminum peroxide prepared *in situ* from TBHP and $(t\text{-BuO})_3Al$[16] to the acetate **11** resulted in the complete stereocontrol and gave the desired compound in 74% yield as a single diastereomer. The inversion of the resulting secondary hydroxyl group under the Mitsunobu reaction conditions using *p*-nitrobenzoic acid afforded the diester **12** in 70% yield in a completely stereocontrolled manner. This satisfactorily stereocontrolled introduction of the oxygen function to the terminal cyclohexene ring of carotenoids is the second example in addition to the natural peridinin synthesis.[8a] The obtained diester **12** was followed by the sequence of TBAF treatment, MnO_2 oxidation, and the Horner–Emmons reaction to produce **13** (13*E*/13*Z* = 15/1). Selective hydrolysis of the *p*-nitrobenzoyl group and then TES protection of the resulting alcohol afforded the triene ester **14** in excellent yield. The ester group of **14** was transformed into the sulfide **15** by DIBAL reduction followed by the Mitsunobu reaction. The successful oxidation of the sulfide **15** to the sulfone **16** to employ the modified-Julia olefination for coupling with the allenic segment proceeded in the limited substrate under restricted conditions. After an extensive investigation, we found that oxidation was successful only to the C8 carbonyl derivative; meanwhile the corresponding hydroxyl derivatives such as acetate and silyl ether gave no desired product. The reaction smoothly proceeded and afforded **16** in 65% yield. Reprotection of the C3 hydroxyl group with TES followed by the Luche reduction afforded the desired hydroxyl sulfone **5**. The corresponding Wittig salt and Horner–Emmons reagents could not be prepared.

The next step of the fucoxanthin synthesis was the coupling between segment **4** prepared from aldehyde **6** through **17**[12] and segment **5** (Scheme 2). The crucial reaction conditions of the modified Julia olefination were explored in detail, and the appropriate reaction conditions were found. At 0 °C, 4 equiv of NaHMDS was added to a mixture of the aldehyde **4** and sulfone **5** in THF. The reaction immediately proceeded in the dark to produce the desired coupling product **18** in 56% amount as a mixture of diastereomers. On the other hand, other bases (LHMDS, KHMDS), solvents (DMF), and temperature (−78 °C) did not give good results. On the basis of the previous experiments,[3−5,17] it is anticipated that the modified Julia olefination of **4** and **5** mainly produced the *Z*-isomer at the connected double bond, although we could not estimate the ratio of isomers for compound **18** because of the mixture with the C8-epimer on HPLC analysis. We then tried to estimate the ratio at the next step. For the coupling product **18**, oxidation of the secondary hydroxyl group

Scheme 2. Synthesis of C40 Fucoxanthin (**2**)



and removal of the TES group under mild acidic conditions produced the crude fucoxanthin. After Dess–Martin oxidation, we observed that the initially generated major peak is 45% (peak 1) based on HPLC as shown in Figure 3A.[18] Another oxidation (MnO_2 and TPAP) did not give the expected results. After deprotection of the TES group

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with PPTS, the isomerization to the desired all-*trans* **2** was then attempted in benzene at room temperature under fluorescent light in an argon atmosphere. After 3 days, the major peak 1 grew to 76% as shown in Figure 3C. We then isolated this peak and confirmed the structure to be the all-*trans* **2**. The ^{1}H and ^{13}C NMR spectra of the synthesized fucoxanthin were directly compared to those of the natural one, which were completely identical.[10a,10e] We thus achieved the stereocontrolled total synthesis of fucoxanthin.

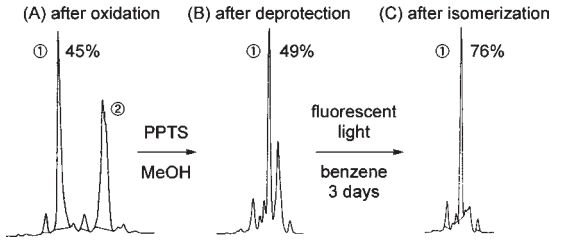


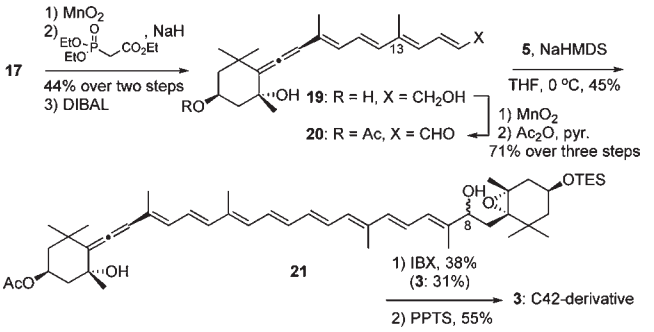
Figure 3. HPLC analysis of fucoxanthin (**2**).

Our next objective was the synthesis of the C42 fucoxanthin derivative **3** (Scheme 3). If the C42 derivative having a polyene chain longer than the natural product would stably exist, the expected modified Julia olefination between the sulfone **5** and aldehyde **20** would yield the desired coupling product according to the same synthetic strategy used for the fucoxanthin synthesis. The C22 allenic tetraenal **20** was prepared by the MnO_2 oxidation of **17** followed by the Horner–Emmons reaction and then DIBAL reduction without any isomerization of the double bond. Oxidation and acetylation of the resulting triol afforded the unstable allenic tetraenal segment **20** accompanied by a slight isomerization (13*E*/13*Z* = 6/1) in good yield. The modified Julia olefination between **5** and **20** fortunately proceeded under the same conditions as that of the fucoxanthin synthesis at 0 °C to produce the expected coupling compound **21** in 45% amount as a mixture of stereoisomers. The oxidation of the C8 secondary hydroxyl group, however, was problematic. Under the Dess–Martin oxidation condition, the product gradually decomposed. Another oxidation (TPAP, Swern, SO_3-pyr, and Pfitzner-Moffatt oxidation) did not give the expected results. However, we obtained the desired product by the successful IBX oxidation in 38% yield along with the deprotected C42-fucoxanthin derivative **3** in 31% yield. Removal of the TES group with PPTS achieved the synthesis of the C42 derivative **3**. It was estimated to be 62% based on the HPLC analysis after the isomerization under the same conditions as those of the fucoxanthin synthesis.[19] We then isolated the major peak and confirmed the structure by NMR (750 MHz).

(18) Peak 2 consists of two peaks; we presumed them to be the 15*Z*-isomer and 13*Z*-isomer based on a peak at around a 310 nm absorption of carotenoids, the *cis*-peak, in the UV spectra. For the *cis*-peak, see: Hu, Y.; Hashimoto, H.; Moine, G.; Hengartner, U.; Koyama, Y. *J. Chem. Soc., Perkin Trans. 2* **1997**, 2699.

(19) The data of the HPLC analysis of the fucoxanthin derivatives are provided in the Supporting Information.

Scheme 3. Synthesis of C42 Fucoxanthin Derivative **3**



In summary, we achieved the stereocontrolled total synthesis of fucoxanthin (**2**), which possesses an allene and a labile β,γ-epoxyketo moiety, by utilizing the stereocontrolled Sharpless epoxidation of a homoallylic alcohol as the key step. This synthesis includes a second example to have satisfactorily controlled the stereochemistry at the terminal cyclohexane moiety of polyfunctional carotenoids that is essentially important for the highly oxygenated carotenoid synthesis. The ultrafast time-resolved optical absorption measurements of the synthesized fucoxanthin derivative have revealed very interesting information on the relationship between the ICT energy level and the polyene chain length.[20] In addition, the syntheses of allene and the β,γ-epoxyketo moiety modified derivatives are currently in progress in our laboratory.

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Supporting Information Available. Experimental details and characterization data of **2**–**5**, **8**, **11**–**16**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

(20) The C35-fucoxanthin (fx) derivative **22** and C37-fx **23** were also synthesized by the similar synthetic method. Ultrafast time-resolved optical absorption measurements were performed on C42-fx **3**, C40-fx (**2**), C37-fx **23**, and C35-fx **22**, which possess 5–8 conjugated olefins. The obtained results showed that the S_1 lifetimes for fucoxanthin and its derivatives were similar to that of peridinin. Although the shorter polyene chain derivatives had the longer lifetime in hexane, the S_1 lifetime in methanol converged to a value of 15–22 ps. These results strongly support the unique characteristics of the ICT state that we have observed in peridinin. The detailed results will be reported in another specific journal.