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Strategies for the Total Synthesis of Fucoxanthin from a Commercial Perspective

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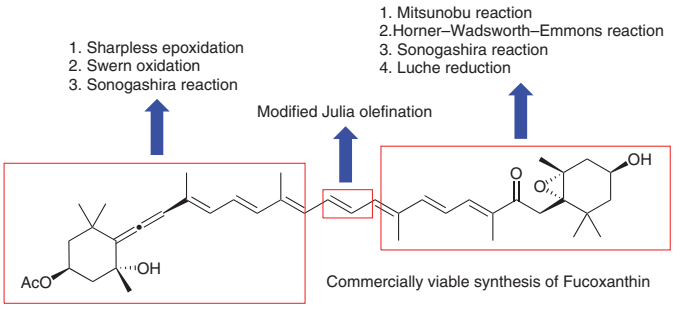

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Abstract Fucoxanthin, the light-harvesting pigment of various algae, has shown promising biological activity in pre-clinical and clinical models. It has also received marketing approval as a nutraceutical and cosmetic ingredient in the USA and other countries. The commercial synthesis of this natural ingredient assumes significance because of various drawbacks (low yield, patent infringement, longer duration of cultivation, etc.) associated with its extraction and isolation procedures. This review is intended to provide an appraisal of the total syntheses of fucoxanthin reported to date along with a detailed explanation of the commercially viable approach. Finally, we briefly discuss the future of research for the total synthesis of fucoxanthin.

Key words fucoxanthin, total synthesis, commercialization

1 Introduction

Fucoxanthin is the most abundant xanthophyll carotenoid, and it plays a pivotal role in photosynthesis and photoprotection in various types of algae. It has anti-cancer, anti-oxidant, anti-obesity, anti-diabetic and anti-inflammatory activity and it has received FDA approval as a nutritional supplement.[1,2] Furthermore, it has shown promising results in phase-II clinical trials to treat metabolic syndrome (MetS).[3] Besides its primary use as a medicinal agent, it holds a prominent space in cosmetics formulations such as anti-aging, skin brightening, and sunscreen products. The market for fucoxanthin in 2024 is valued at 31 million US dollars and is projected to grow with a compound annual growth rate (CAGR) of 3.9% from 2024–2032, ultimately reaching 41 million USD.[4]

The chemical synthesis of fucoxanthin assumes significance commercially because the yield from natural sources has not crossed 7%. Additionally, there are patent infringement issues with producing fucoxanthin from high-yielding species. Moreover, there are several other bottlenecks in the fucoxanthin extraction process such as limited evaluation of scale-up cultivation and extraction, a few unclear steps in its biosynthetic pathway, and conflict between biomass and fucoxanthin accumulation under high-light conditions.[5,6]

The present review summarizes the various total synthesis methodologies available for fucoxanthin. We also provide in-depth analyses of the methodologies that exhibit promising potential for commercial success and discuss their intricacies in detail.

2 Types of Synthetic Strategies

There are two synthetic procedures reported for producing fucoxanthin to date. The major challenge in its chemical synthesis is the extremely alkali-labile β,γ-epoxy keto moiety. This structural feature prevented the stereochemical control of both the epoxidation and polyene chain formation from being efficiently achieved in the first reported synthetic procedure, which involved 30 synthetic steps. Additionally, the synthetic yield of the method was 8% fucoxanthin in the final step.[7,8] The most promising method described to date was reported by Takayuki Kajikawa et al. in 2012,[9] wherein the stereochemical control of both the epoxidation and polyene chain formation was achieved successfully with a modest yield of 40% in the final step of the synthesis. The primary distinction between this

method and the first approach lies in the formation of the epoxide ring as an intermediate rather than in the final step of the synthesis (Scheme 1).

3 A Promising Synthetic Method: Takayuki Kajikawa's Total Synthesis

The most successful synthetic method for fucoxanthin involves the fusion of an allenic segment (**I**) and a hydroxy sulfone fragment (**II**) by the modified Julia olefination method to obtain an isomeric mixture **III**. It was not possible to estimate the ratio of isomers because of the mixture with the C8-epimer (of hydroxy sulfone part) on HPLC analysis. Hence, the mixture of isomers **III** was used in the next oxidation step with Dess–Martin periodinane (DMP), wherein the C8 hydroxy group is converted into a ketone (**IV**). This was followed by deprotection of the TES group to obtain *cis*/*trans* fucoxanthin isomers. Thereafter, the all-*trans* isomer **V** was obtained by keeping the mixture in benzene under fluorescent light in an argon atmosphere for three days (Scheme 2).[9]

3.1 Synthesis of Allenic Segment I

The allenic segment **I** was synthesized starting from 4-hydroxy-2,2,6-trimethylcyclohexane-1-one (Scheme 3). First, the hydroxy group was protected with TBS, followed by OTf conversion of the ketone group to afford the methyl ester under a carbon monoxide atmosphere using tetrakis-(triphenylphosphine)palladium catalyst.[10,11] The ester was then reduced to the alcohol with lithium aluminum hydride and submitted to Sharpless epoxidation using *t*-butyl hydroperoxide. The diastereomeric mixture **5** was subjected to Swern oxidation using oxalyl chloride to obtain the required 5*S*,6*R* aldehyde **6**.[11] This stereocontrolled epoxide formation in good yield is crucial for this synthetic procedure. The epoxide was converted into the corresponding acetylene derivative **7** by utilizing chloromethyl triphenylphosphonium chloride and *n*-BuLi. The intermediate crude vinyl chloride formed was subjected to elimination using potassium *t*-butoxide to obtain **7**.[11] The Pd- and Cu-catalyzed Sonogashira reaction between acetylene **7** and trienyl iodide proceeded smoothly to furnish the desired coupling product **8** in 81% yield with complete retention of stereochemistry.[12] The reduction of **8** with DIBAL for the construction of the allenic moiety **9** afforded the C20-allenic triol, which was oxidized to the corresponding aldehyde **10** with manganese dioxide.[9] The synthesis of the allenic segment **I** is depicted in Scheme 3. The crude aldehyde was used in the next acetylation step without further purification to obtain **10** (allenic segment I).

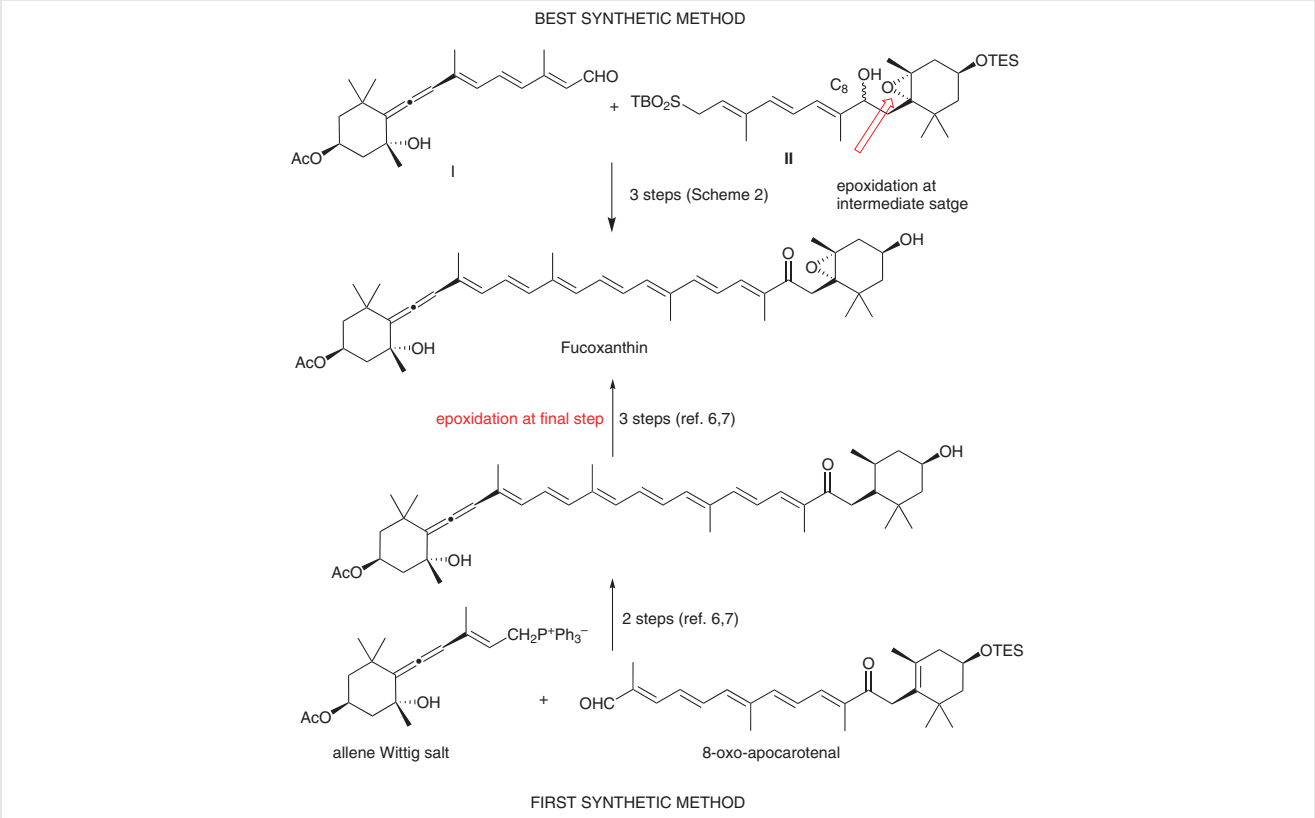
3.2 Synthesis of Hydroxy Sulfone Segment II

The synthesis of the hydroxy sulfone segment II started from 3-*epi*-actinol. First, the alcohol group was TES-protected for the introduction of the aldehyde group at C-5

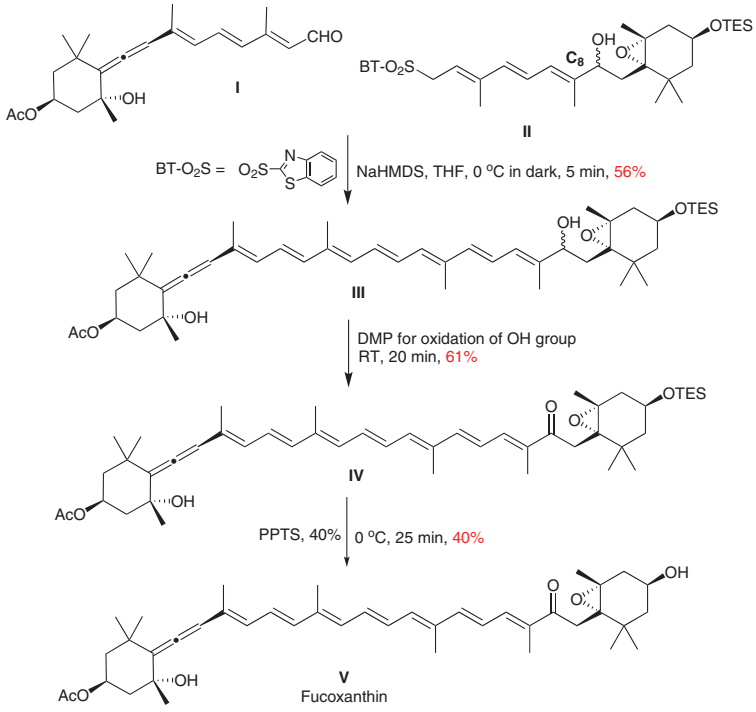
Biographical Sketches

Dr. Sayan Dutta Gupta received his Ph.D. in pharmaceutical chemistry from J.N.T.U., Hyderabad, India. He was awarded the prestigious Brain Pool Fellowship (formerly known as the Korea Research Fellowship) for carrying out anticancer research at KIST, Gangneung Institute of Natural Products. He is an accomplished drug discovery scientist with 18 years of experience in academia and industry. He established Dr. Sayan's Drug Discovery Solutions (DSDDS, https://dsdrugdiscoverysolutions.com/) in January 2024 after identifying gaps and opportunities in the drug discovery domain.

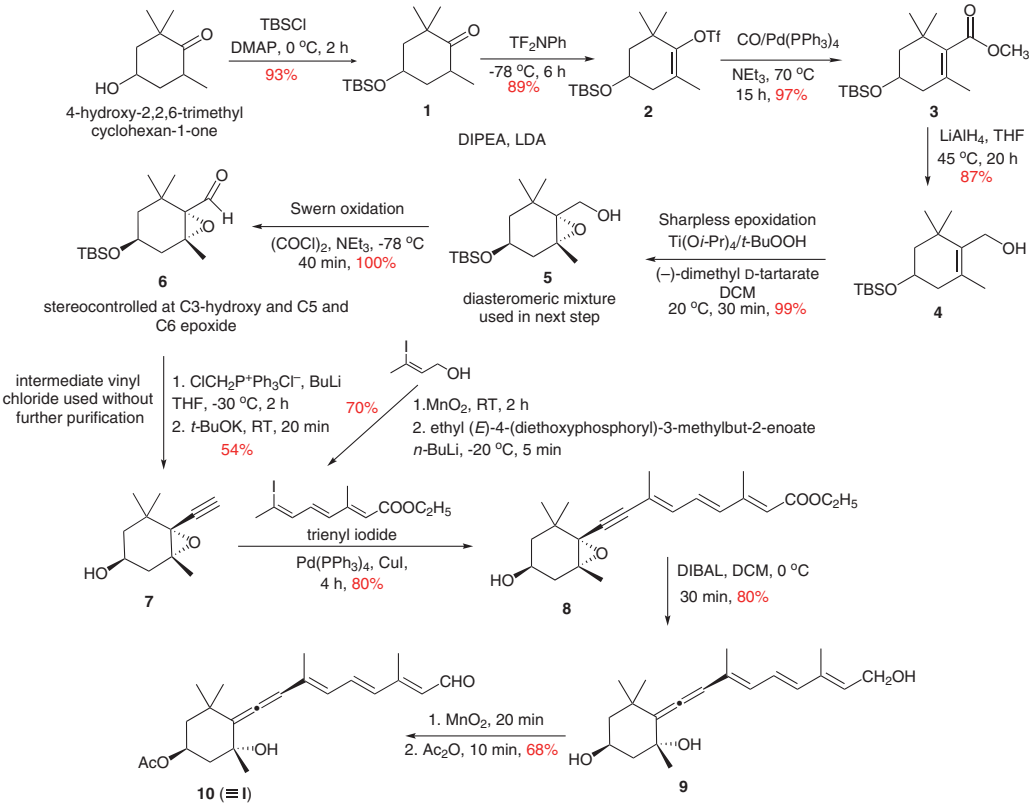
Dr. Cheol-Ho Pan received his Ph.D. in agricultural chemistry from Seoul National University in 2001. He is the principal research scientist at the Natural Product Informatics Research Center, KIST Gangneung Institute of Natural Products, South Korea. Additionally, he is CEO of Microalgae Ask US Co., Ltd. (http://maus2020.com/), a company involved in microalgae culture and extract manufacturing R & D service. He has about 30 years of research experience with more than 15 years in microalgae research. He has published 65 papers and has 14 patents to his credit.



Scheme 1 Comparison of the reported synthetic methodologies to access fucoxanthin



Scheme 2 Synthesis of fucoxanthin. NaHMDS = sodium bis(trimethylsilyl)amide. DMP = Dess–Martin periodinane, PPTS = pyridinium *p*-toluenesulfonate.

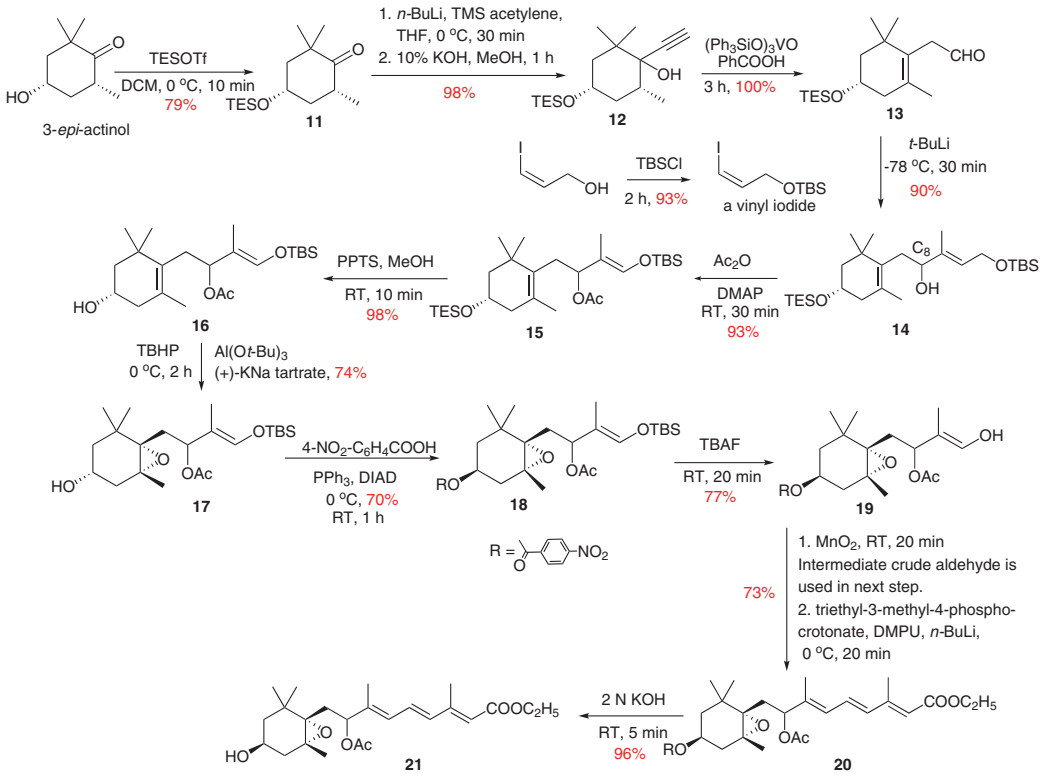


Scheme 3 Synthesis of allenic segment for preparing fucoxanthin

(**13**) via the formation of acetylene derivative **12**.[8,13] The carbon chain of aldehyde **13** was extended with the introduction of the C8 hydroxyl group by reacting **13** with vinyl iodide and *t*-BuLi to produce the desired alcohol **14** in high yield. Acetylation of the resulting alcohol **15** and subsequent chemoselective removal of the TES group led to the *R*-homoallylic alcohol **16**. Thereafter, the reaction of organoaluminum peroxide, prepared in situ from TBHP and (*t*-BuO)$_3$Al with **16**, exhibited complete stereocontrol and formed the desired compound **17** in 74% yield as a single diastereomer. Inversion of the resulting secondary hydroxyl group under Mitsunobu reaction conditions using 4-nitrobenzoic acid afforded diester **18** in 70% yield in a completely stereocontrolled manner. This was followed by TBAF treatment to deprotect the terminal OH group to obtain **19**. Thereafter, the alcohol group was oxidized with manganese dioxide and the crude aldehyde was used in the next subsequent Horner–Emmons reaction to obtain the *E*-isomer of triene ester **20** in excellent yield. Selective hydrolysis of the *p*-nitrobenzoyl group (to obtain **21**) and then TES protection of the resulting alcohol afforded the triene ester **22** in excellent yield (Scheme 4 and Scheme 5). The ester group of **22** was transformed into the sulfide **23** by DIBAL reduction followed by the Mitsunobu reaction with 2-mercapto benzothiazole. The C8 of compound **23** was oxidized to the keto group with Dess–Martin periodinane to obtain **24** in 70% yield. The oxidation of the sulfide to sulfone **25** was carried out with aluminum heptamolybdate and 30% aqueous hydrogen peroxide. Reprotection of the C3 hydroxyl group with TES followed by the Luche reduction afforded the desired hydroxyl sulfone **27** (Scheme 5).[9]

4 Future Perspectives

There are immense opportunities in the total synthesis of fucoxanthin because only two methods have been reported to date. One of them has the potential for commercialization and is discussed in detail in this review. However, researchers need to find novel ways to improve the total synthesis of fucoxanthin. One such example is the procedure reported by Satoshi Okumura and co-workers for the synthesis of C37 and C32 fucoxanthin.[14] The method employs a fusion of the allenic sulfone segment and aldehydic epoxy fragment by the Julia olefination method. It is the reverse of the promising method described in this review, wherein allenic aldehyde segment is fused with an epoxy sulfone fragment (Scheme 6). The yield for all the steps is 50–100% with a final step yield of 64%. The tedious step for the introduction of C-8 carbonyl group is reduced by two



Scheme 4 Synthesis of hydroxy sulfone segment for preparing fucoxanthin, Part I.

steps and overall there are 29 steps leading to the final product. It is 10 years since the modified synthetic procedure for C37 fucoxanthin was reported and it is yet to be reported for C42 fucoxanthin (marketed as fucoxanthin). Therefore, we are a little skeptical about this procedure. Nevertheless, this synthetic methodology provides another approach to fucoxanthin. Additionally, it can generate ideas for exploring structure-activity relationship studies of fucoxanthin derivatives.

5 Conclusions

The most promising synthesis of fucoxanthin reported to date comprises 32 steps, including the preparation of two intermediates. The advantage of this method is that the yield for the synthetic steps can be rated as moderate (50%) to excellent (99%). The final step in fucoxanthin production demonstrates a five-fold improvement in yield (40%) compared to the previous method. Furthermore, to our knowledge, this method does not pose any patent infringement issues. Hence, this synthetic method has the potential for commercial manufacture of fucoxanthin. The 32 synthetic steps give ample scope for process patents in the future, which can act as a good revenue source for companies engaged in the commercial manufacture of fucoxanthin. An initial assessment of the synthesis costs indicates that it is economically feasible to substitute traditional extraction methods, which are still not widely favored commercially. The primary drawback lies in the multitude of synthetic steps required, posing a potential challenge during scale-up operations. Nonetheless, we are confident that advancements in technology will enable us to gradually surmount these challenges.

Conflict of Interest

The authors declare no conflict of interest.

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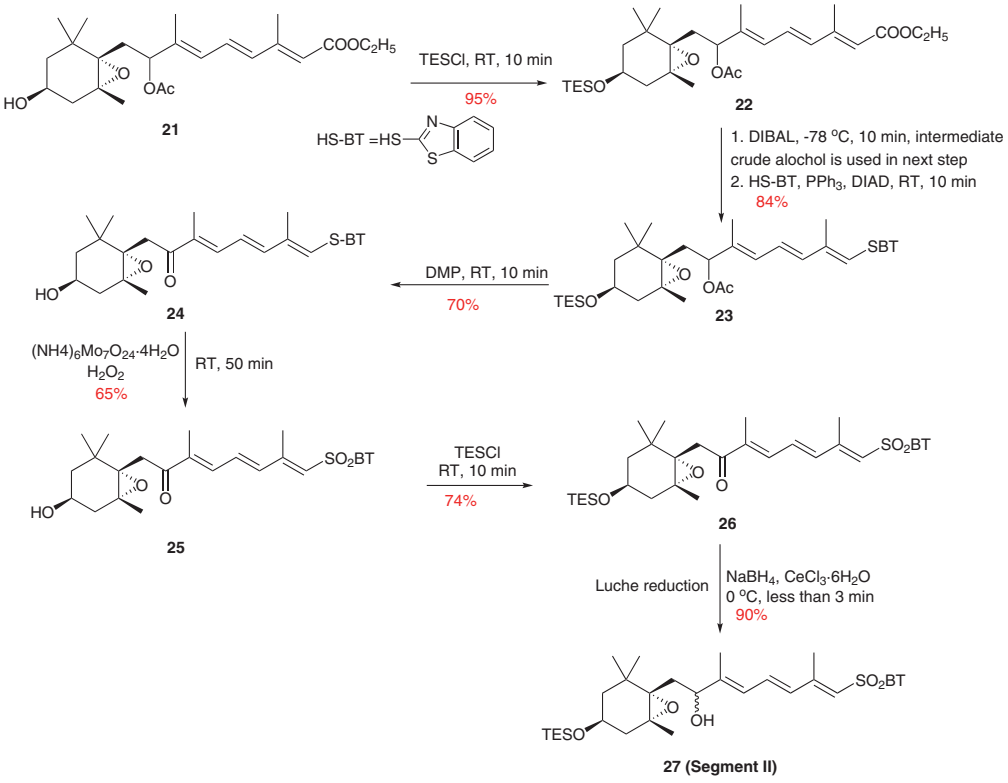
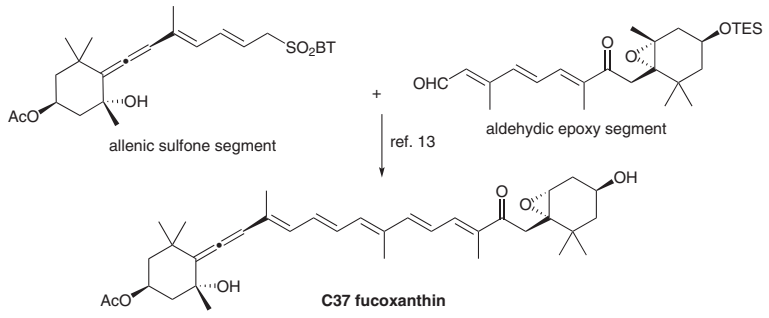


Scheme 5 Synthesis of hydroxy sulfone segment for preparing fucoxanthin, Part II. HSBT = 2-mercaptobenzothiazole.



Scheme 6 Synthesis of C37 fucoxanthin derivatives

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